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Economics of Cancer Drugs: Development, Approval, Benefit, Trials, Innovation, Value, Price, and Competition

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Abbreviations

ASCO-VF	American Society of Clinical Oncology – Value Framework
ATC	Anatomical Therapeutic Chemical
BLA	Biologic License Application
BTD	Breakthrough Therapy Designation
CAR	Chimeric antigen receptor
CED	Coverage with evidence development
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CTLA-4	Cytotoxic T-lymphocyte-associated protein-4
CI	Confidence interval
CPI	Consumer price index
DALY	Disability-adjusted life year
DoR	Duration of Response
EMA	European Medicines Agency
ESMO-MCBS	European Society for Medical Oncology – Magnitude of Clinical Benefit Scale
GBD	Global Burden of Disease study, 2019
FDA	US Food and Drug Administration
GDP	Gross domestic product
HDAC	Histone deacetylase
HQ	Headquarter
HR	Hazard ratio
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IND	Investigational new drug application
IQR	Interquartile range
IPO	Initial public offering
IRA	Inflation Reduction Act of 2022
ISP	Indication-specific pricing
LY	Life year
M&A	Mergers and acquisitions
MEA	Managed entry agreement
mTOR	mammalian target of rapamycin
NASDAQ	National Association of Securities Dealers Automated Quotations
NCCN	National Comprehensive Cancer Network

NDA	New Drug Application
NICE	National Institute for Health and Care Excellence
NME	New molecular entity
NPV	Net present value
ODA	Orphan Drug Act of 1983
OOP	Out-of-pocket
OS	Overall survival
OR	Odds ratio
ORR	Objective response rate
PAS	Patient Access Scheme
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death ligand-1
PED	Price elasticity of demand
PFS	Progression-free survival
R&D	Research and development
RCTs	Randomized controlled trials
rNPV	risk-adjusted net present value
RR	Relative risk
SIC	Standard Industrial Classification
SMC	Scottish Medicines Consortium
TKI	Tyrosine kinase inhibitor
TNF-α	Tumor necrosis factor-α
UK	United Kingdom
US	United States
US SEC	United States Securities and Exchange Commission
USPTO	US Patent and Trademark Office
WHO	World Health Organization
WTP	Willingness-to-pay
YLD	Years lived with disability
YLL	Years of life lost

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1 Introduction

The US spent $388 billion on prescription drugs in 2019, representing 9.0% of total health expenditures and 1.6% of the gross domestic product (GDP), respectively.[1] Prescription drugs are not only a significant source of innovation for the economy but have also transformed the treatment and lives of many patients. However, over the past two decades, rising prices for new drugs that lead to high profit margins for pharmaceutical companies have sparked public debate about the development, approval, and pricing of new drugs.[2–4] In this introduction, we highlight and review current trends in drug development, approval, and pricing that contributed to this dissonance. Particular emphasis will be laid upon drugs that are used for the treatment of multiple diseases and indications.[1]

1.1 Research and development of drugs with multiple indications

Recently, scientists and consulting firms noted a worrying trend of declining efficiency in pharmaceutical research and development (R&D).[6,7] Scannell et al. observed that the costs of developing new drugs have risen exponentially since the 1950s (a phenomenon known as "Eroom's Law" – the inverted version of "Moore's Law"). They attributed this downward trend in R&D productivity to an expanding pool of available treatments, tighter regulations, operational overspending, and a focus on basic research and drug screening approaches. However, Eroom's Law was broken immediately after its discovery.[8] Advances in our understanding of diseases – thanks in particular to the Human Genome Project, relaxed regulatory requirements,

[1] The European Medicines Agency (2013, p. 1) defines an indication as "a medical condition that a medicine is used for".[5] The breadth of a drug's indication is typically defined by the regulatory agency in a drug's marketing authorization label. The breadth of an indication may vary. For example, diabetes is the indication for insuling. However, for cancer drugs, an indication is typically defined by the treated disease, line of therapy, biomarker status, combination treatments, and disease stage. If a medicine is prescribed for the indication defined in the drug label, the prescription is "in-label". In contrast, prescriptions that are outside of this label are called "off-label" indications. Whilst "in-label" prescriptions are (mostly) covered by health insurers, "off-label" uses have to be authorized by the insurer on a case-by-case basis.

and more prudent R&D spending drove a recovery in R&D productivity after 2010 (Figure 1 – A, C, E, G).

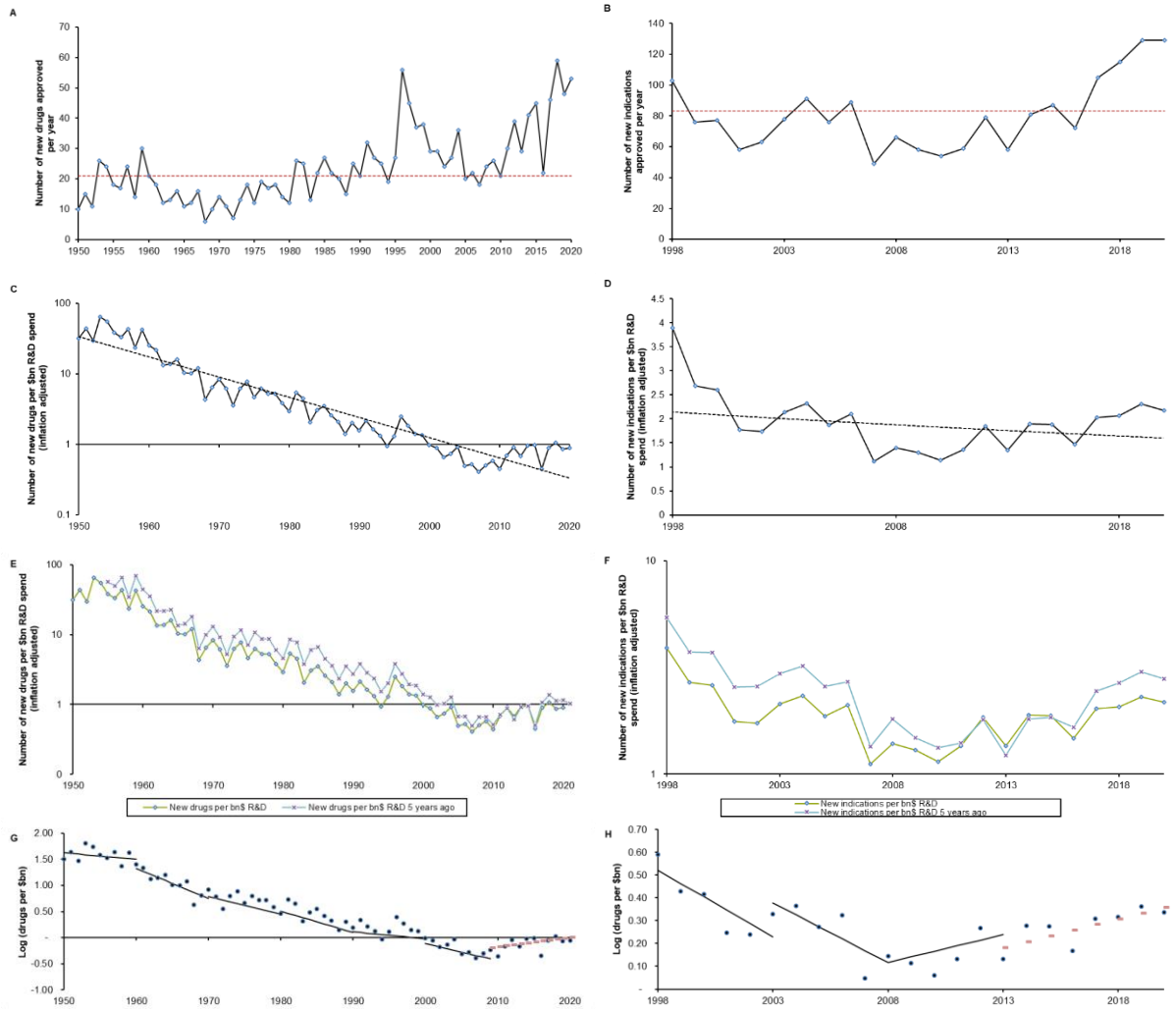

Figure 1: Pharmaceutical R&D efficiency for drugs and indications

Notes: The graphs on the left show the R&D efficiency of new drugs approved by the FDA from 1950 to 2020. The graphs on the right compare this to the R&D efficiency of FDA-approved new indications from 1998 to 2020. Data for these analyses were adapted from Scannell et al. and Ringel et al. and subsequently updated until 2020 with new inputs for the R&D efficiency of new indications.[6,8]

Abbreviations: FDA, US Food and Drug Administration; R&D, research and development.

Furthermore, the drug development process has become more complex over the past three decades. Instead of analyzing the R&D process at the drug level, we should examine the discovery and development of new indications to capture the full scope of pharmaceutical innovation. Figure 1 – B, D, F, H re-examines Scannell et al.'s and Ringel et al.'s analyses on an indication level. Since 2010, an increasing number of indications have been approved by the US Food and Drug Administration (FDA), resulting in improved R&D efficiency for new indications.

The Human Genome Project paved the way for modern, personalized medicine. Based on a newfound understanding of the genetic code, scientists began to specifically target genetic mutations that cause fatal diseases without any treatment options. New therapies were developed not only for rare metabolic and neurological diseases but also for genetically defined patient subpopulations of high-prevalence diseases. With this new arsenal of modern therapeutics, physicians are striving to personalize the treatment for each patient. Therefore, personalized medicine, enabled by targeted, immune, and gene therapies, has led to the development of drugs for "more focused indications within particular diseases" (Ringel et al., 2020, p. 834).[8] Most of these drugs are marketed for multiple therapeutic diseases and indications.

For instance, the immune-checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, cemiplimab, dostarlimab, and ipilimumab have been approved for multiple types of cancer, such as skin, lung, breast, bladder, or renal cancer. Some of these programmed cell death ligand-1 (PD-L1) / programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitors have even been approved for pan-tumor treatments. Similarly, tumor necrosis factor-α (TNF-α) inhibitors have been approved for a variety of immune disorders, including rheumatoid arthritis, psoriasis, ankylosing spondylitis, and juvenile idiopathic arthritis. Accordingly, the tyrosine kinase inhibitor (TKI) imatinib is not only approved for chronic myeloid leukemia, but also for acute lymphatic leukemia, gastrointestinal struma tumors, myelodysplastic/myeloproliferative diseases, aggressive systematic mastocytosis, hypereosinophilic syndrome/chronic eosinophilic leukemia, and dermatofibrosarcoma protuberans. All of these drugs target molecular or cellular signaling pathways that are involved in the underlying pathologies of various diseases.

Multi-indication drugs have become an integral part of pharmaceutical innovation. Between 2003 and 2014, 60% of new drugs approved by the FDA were used across multiple indications.[9] By 2020, the majority of anti-cancer drugs (75%) were approved for more than one indication.[10]

Accordingly, the mean number of indications of drugs under phase 1 development has increased to 2.8 (+73% from 2010 to 2018).[11] In 2019, all top ten selling drugs – "blockbuster drugs" – were commercialized for more than one indication.[12] Figure 2 further underlines the importance of multi-indication drugs based on an analysis of US Medicare and Medicaid spending on new anti-cancer drugs. In 2020, $1.8 billion was spent on single-indication drugs, compared to the $28.2 billion spent on cancer drugs approved across multiple indications. Average spending per drug was more than 10x higher for multi- than single-indication cancer drugs ($381 vs. $34 million). A total of 37,311 patients benefitted from single-indication drugs, whilst 350,386 patients received multi-indication drugs. Accordingly, the average number of beneficiaries was more than 6x higher for multi- than single-indication cancer drugs (4,735 vs. 777 patients).

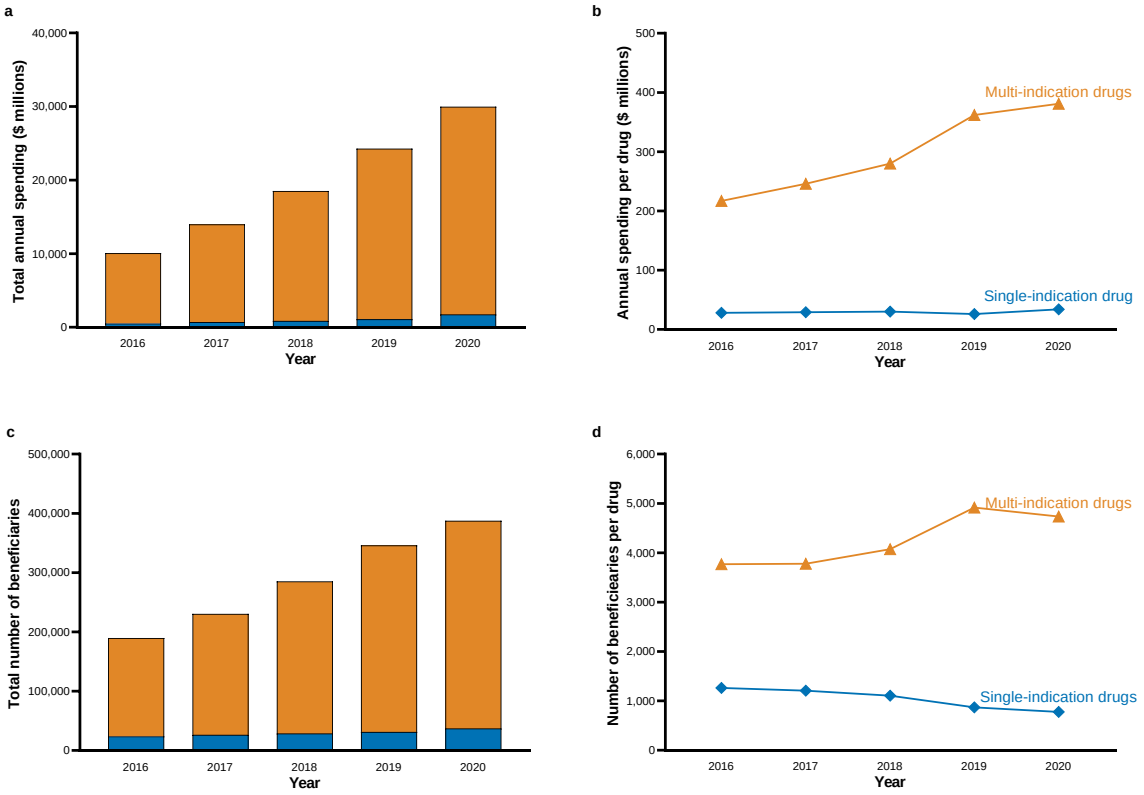

Figure 2: Estimated Medicare and Medicaid spending on and number of beneficiaries of single- and multi-indication cancer drugs, 2016-2020

Notes: For this analysis, a similar methodology described by Rome et al. was employed.[13] All cancer drugs and their supplemental indications that received FDA approval between 1st January 2000 and 1st January 2020 were identified. The Medicare and Medicaid database was then accessed to obtain data on drug spending and the number of beneficiaries for each drug. Spending and the number of beneficiaries were then stratified for on-patent cancer drugs with a single indication (single-indication drugs) vs. those approved for multiple indications (multi-indication drugs).

Abbreviations: FDA, US Food and Drug Administration.

In summary, there is a substantial number of patients receiving multi-indication drugs and a significant portion of healthcare expenditure is dedicated towards these drugs. However, researchers mostly focus on the first approved indication, commonly neglecting supplemental indication approvals (also referred to as indication extensions or supplementary indications). This is particularly concerning given that multi-indication drugs are swiftly approved for supplemental indications and most of these drugs are more frequently used for their supplemental than original indication.[13] Figure 3 highlights this phenomenon. In 2020, Medicare and Medicaid expenditure amounted to $1.1 billion for multi-indication drugs that were exclusively sold

in their original indication. However, $26.8 billion was spent on drugs that were already approved for more than one indication.

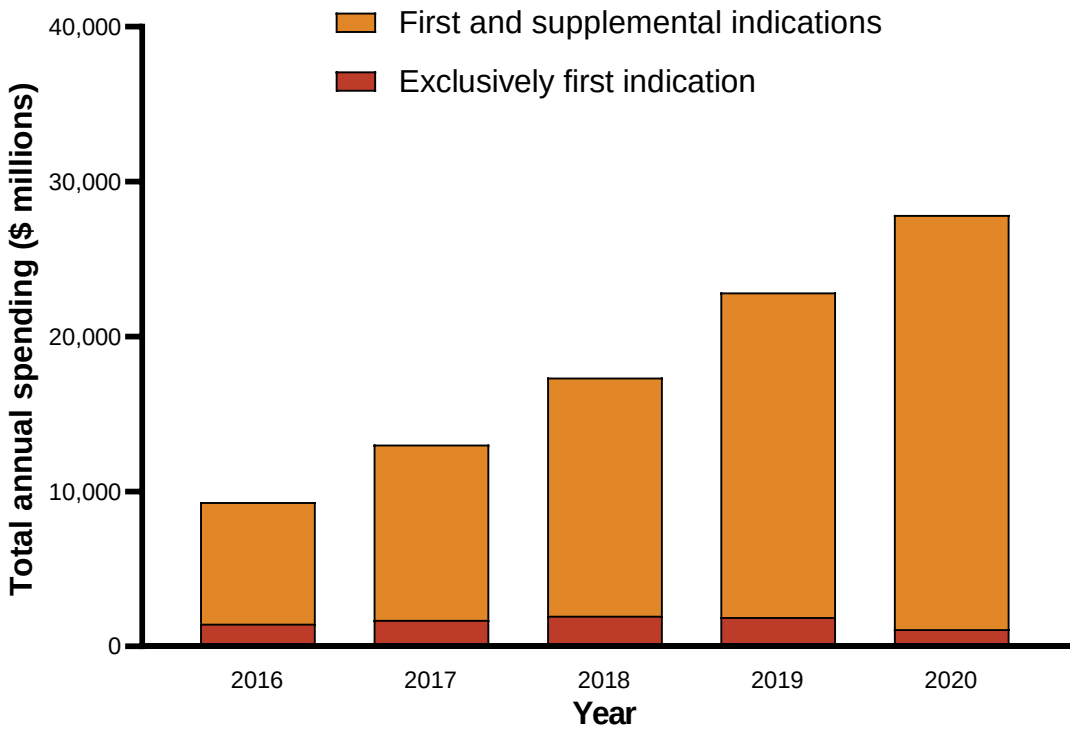

Figure 3: Estimated Medicare and Medicaid spending on cancer drugs with exclusively one or multiple indications, 2016-2020

Notes: The same methodology as described in Figure 2 was employed. Spending was stratified for periods when multi-indication cancer drugs were exclusively approved in a single indication vs. periods when a drug was approved in multiple indications. Annual spending estimates were prorated where necessary.

1.2 Drug prices in the US

The US is the country with the highest per capita spending on prescription medicines. For newly FDA-approved drugs, median annual net launch prices increased from $2,115 (2008) to $180,007 (2021).[2] After launch, net drug prices commonly increase by an average of 4.5% per year.[4] As a result, in 2019, an average of $1,126 per capita was spent on prescription drugs in the US, relative to $552 for an average Western country.[14] Of this spending, $963 was covered by private or public health insurers, whilst $164 was paid out-of-pocket (OOP). In contrast, the average citizen in other Western countries paid $88 OOP for prescription drugs.

These high prescription drug costs are a leading contributor to personal bankruptcy in the US.[15] Particularly drug prices exceeding an annual cost of $100,000 lead to catastrophic health expenditure and high OOP costs among the poor population given that the lack of universal health coverage.[15,16] Ultimately, adherence to required treatment regimens is challenged by this financial toxicity.[17]

Although rising cancer drug prices are continuously identified as a leading policy challenge, pharmaceutical companies rebut any systemic changes in the way drugs are priced in the US. Over the past three decades, they have argued that R&D costs over $2.8 billion are needed to bring a new drug to market.[18] Yet, more thorough and unbiased investigations of the R&D process concluded that the cost of developing new drugs is closer to $1.3 billion.[19,20] Considering that this success rate-adjusted cost estimate is substantially lower than the revenues generated by multi-indication blockbuster drugs, pharmaceutical companies realized high profit margins and returns for investors.[3,19–21] A recent study found that R&D costs are not even associated with drug prices; further questioning the validity of the pharmaceutical industry's justification for high drug prices.[22]

Most recently, the US government finally acknowledged this growing socio-economic problem and introduced the Inflation Reduction Act of 2022 (IRA), which will empower the Centers for Medicare and Medicaid Services (CMS) to directly negotiate prices with pharmaceutical companies for the 10 highest-spending prescription drugs by 2026. Until 2029 these negotiations will be extended to the 20 highest-spending drugs.[23] Rome et al. estimated that this new provision could have reduced Medicare and Medicaid drug spending by 5% or $26.5 billion from 2018 to 2020.[24] Furthermore, the IRA caps patients' cost sharing at $2,000 per year (for drugs covered under Medicare Part D) and provides rebates on list price hikes exceeding inflation.[25]

Currently, there is an ongoing debate on how the CMS will enact its new power to negotiate drug prices.[26] Health technology assessment (HTA) systems from other countries may inform

the calculation and negotiation of the maximum list and net prices in the US. In countries such as Germany, HTA agencies determine the clinical benefit of each new drug to then inform whether a drug should be priced at par, higher, or lower than the current standard of care. In countries like England or Scotland, HTA agencies evaluate each drug's cost-effectiveness based on its incremental benefit and cost relative to the current standard of care to calculate the incremental cost-effectiveness ratio (ICER). Typically, the ICER presents the incremental cost per incremental quality-adjusted life year (QALY) or life year (LY) gained. Countries usually define a maximum willingness-to-pay (WTP) threshold for the ICER. ICERs above this threshold are deemed "not cost-effective". ICERs below this threshold are judged "cost-effective". For drugs with an ICER above the WTP threshold, the HTA agency may negotiate a discount on a drug's (list) price, such that the ICER falls within the WTP threshold. In the UK, the WTP threshold is between 20,000 and 30,000 GBP per QALY, with a higher WTP threshold for end-of-life treatments such as cancer medicines.[27,28] In the US, studies frequently cite WTP thresholds of 50,000, 100,000, and 150,000 USD per QALY.[29,30] However, in the US, there currently is no HTA agency that conducts unbiased value assessments for new therapeutics. Furthermore, several countries that do not have the capacity, financial capital, and expertise to conduct these assessments simply rely on the cost-effective drug price from a basket of reference countries to calculate their national drug price (external reference pricing).[31] Directly or indirectly underlying all these mechanisms is the principle of value-based pricing. In the pharmaceutical context, value-based pricing is a strategy that sets drug prices primarily, but not exclusively, according to the benefits and harms of the new intervention.[32,33] Whilst aligning a single price to drugs that only treat one disease is already complex, aligning a single price to drugs with multiple uses and therefore value propositions poses a challenge for healthcare systems in the US and abroad.

1.3 Pricing drugs with multiple indications

The pricing, coverage, and reimbursement of drugs with multiple indications and value proposition remains complex. Currently, a drug is sold for a single list price in the US (one drug, one price). For drugs that are used across multiple indications, this uniform pricing distorts the value-price link that ought to be established under a value-based pricing policy. In most countries, current rigid HTA processes do not permit pharmaceutical policies that entail differential prices per indication, posing substantial barriers to market and patient access. Many European countries, including Denmark, Finland, Norway, Poland, and Netherlands, simply anchor drugs' list prices to the first indication.[11] The cost-effectiveness or cost-benefit of supplemental indications is then assessed relative to this initial drug price. Low-value indications deemed "not cost-effective" (e.g. indications with an ICER above the WTP thresholds) may not be reimbursed unless manufacturers agree to reduce the single list price such that the new indication becomes "cost-effective".

Economists, therefore, argue that under a single drug pricing systems, pharmaceutical companies are incentivized to sequence, delay, and even withhold the development of new indications (Figure 4).[11,34–37] In theory, a single drug pricing system creates a strong incentive for companies to first launch a drug in the indication that delivers the highest value for the smallest patient population. Thereby companies can set the highest possible list price for its drug which merely impacts the insurers' prescription drug budget as it is only sold to a few patients. Thereafter, companies are incentivized to extend a drug's use to other high-value indications, yet not low-value indications which would drive down prices. In practice, Michaeli et al. and Mills et al. found evidence in favor of this launch sequencing of indications based on a sample of 25 cancer drugs with approval for 100 indications from 2009 to 2019.[38,39] They showed that drugs are first approved for indications targeting rare diseases that deliver a substantial gain in QALYs and LYs. However, they also noted that this observed launch sequence is "influenced by multiple

factors throughout the discovery, development, approval, and pricing process. Scientists aim to address decision-makers' revealed preference and discover drugs for diseases with unmet medical needs, the FDA and other regulatory agencies provide incentives for orphan indications, whilst manufacturers seek to set the highest possible price (attained in indications with high QALYs gained) and thereby maximize revenue and profit streams" (Michaeli et al., 2022, p. 767).[38]

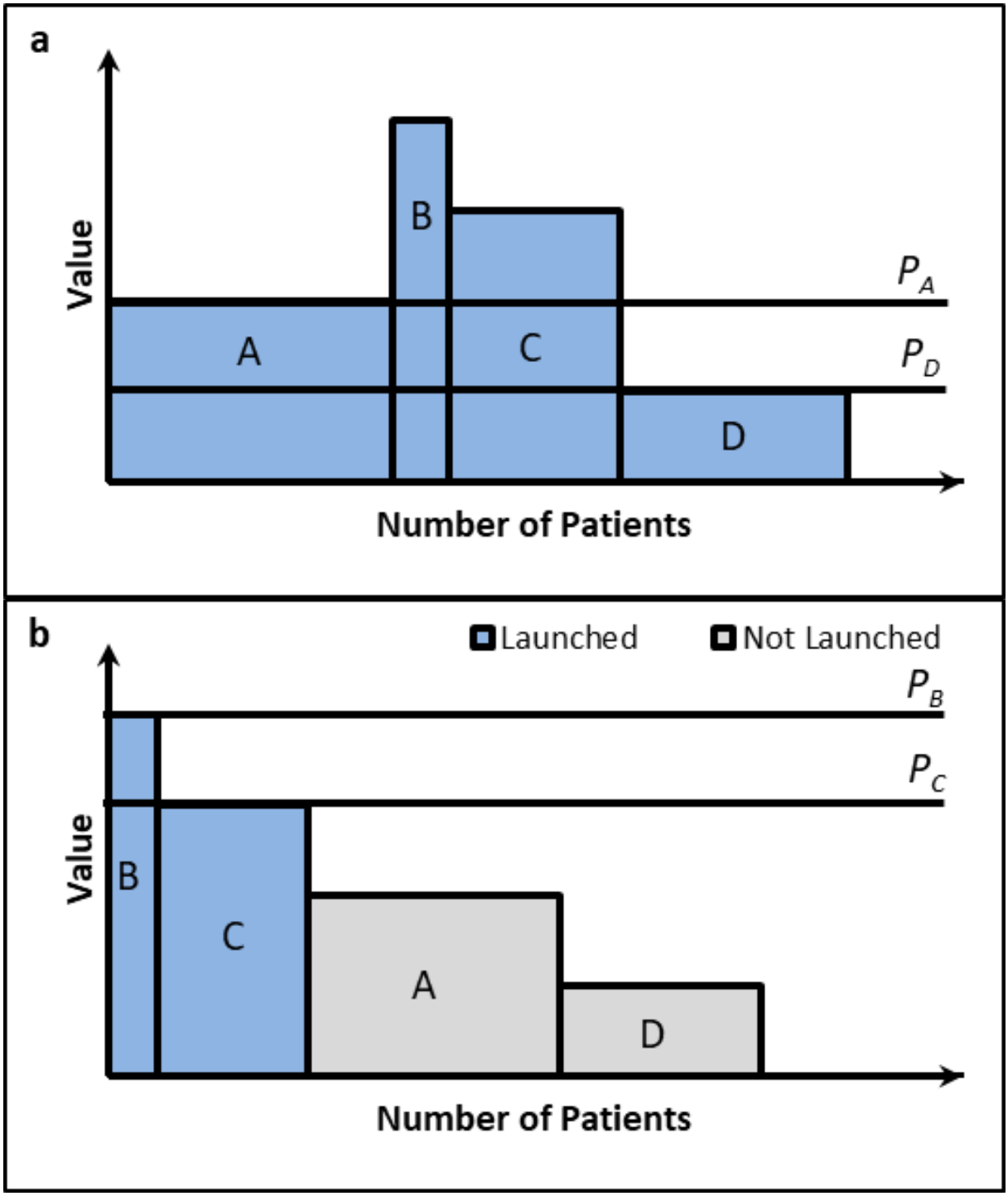

Figure 4: Indication development under single-lowest drug pricing

Notes: Assuming the natural development of indications occurs in the order: A, B, C, D. Each indication targets a separate disease with its distinct number of affected patients and the value it delivers to them. The natural development order of indications would disincentivize pharmaceutical companies to market the high-value, low-prevalence indications B and C (graph a). A single-lowest drug pricing system encourages companies to first approve a drug for the high-value, low-prevalence indications B and C. Thereafter, companies may delay or withhold the low-value, high-prevalence indications A and D if the launch of these indications drives down the price and profits that could be realized (graph b). Graphs adapted from Michaeli (2020).[34]

Besides the aforementioned three studies with limited sample size[38–40] and four case reports,[41–44] comprehensive evidence examining the consequences of uniform prices for drugs with multiple indications remains scarce. In Chapter 2, we conducted the most comprehensive analysis of the development, approval, and benefit of new drugs with multiple indications to date. This study confirms that original and supplemental indications differ in their clinical benefit, evidence, and approval. We find that a higher clinical benefit is measured in pivotal trials supporting the FDA approval of original relative to supplemental indications. However, original indications are also more frequently supported by smaller, non-robust clinical trials that could potentially overstate these efficacy estimates. Furthermore, we show and hypothesize that these discrepancies in a drug's clinical benefit could be explained by several factors throughout the drug life-cycle. After the original drug approval, pharmaceutical companies aim to "spread" their new drug to as many patients as possible to increase their revenues and, thereby, profits. One of these market expansion vectors is the line of therapy. New drugs tend to move up the therapeutic ladder from the advanced-line to first-line to adjuvant to neoadjuvant setting. However, this move up the therapeutic ladder also increases the number of potential competitors, the heterogeneity in the treated patient population, as well as the safety and efficacy requirements for robust randomized controlled trials (RCTs). All these variables could mediate the decline in clinical benefit measures. Similarly, we show that drugs are first developed for biomarker-positive and then extended to biomarker-negative patients, which of course lowers the observed pooled patient benefit (see the discussion in Chapters 2 and 5). In addition, after a new drug has proven its safety and efficacy as a monotherapy, pharmaceutical companies and academic research centers quickly try to use the new medicine together with other drugs, as combination treatments, especially to treat patients who are ineligible or did not respond to the gold standard of care. Finally, we show that drugs with efficacy for one cancer type are often repurposed for use in other cancer types with a similar pathomechanism. With the use of adaptive trial designs pharmaceutical companies can select the patient population with the greatest

tumor response and potential benefit early in the drug development process. In summary, Chapter 2 shows that the clinical evidence, clinical benefit, treated disease, and, therefore, value a drug offers to patients and health insurers varies across its indications. We hypothesize that the current US pricing policy does not reflect these succinct differences, e.g. prices for supplemental indications are not aligned with their value proposition.

In Chapter 3 we test and confirm this hypothesis. We find that original indications are aligned with the biotechnological innovation they achieve and the unmet medical needs they fill. However, prices are not aligned with the value proposition of the supplemental indication. In Chapter 4 we then tested whether supplemental indication's lower value is perhaps reflected in post-launch price changes, as suggested by previous studies.[45] Our results indicate that the approval of new supplemental indications for the same drug is associated with a marginal price decline of up to -2%. However, this decline is only marginal in comparison to the effect of differential pricing policies currently employed in Europe. For instance, at least a -5% price decline was observed in France and Germany following the market entry of new indications.[38]

In Chapters 5 and 6 we further highlight the unintended consequences of adopting an indication-specific rare disease policy, yet keeping a single drug pricing, coverage, and reimbursement policy across all other indications. The government and FDA offer financial incentives to pharmaceutical companies that develop drugs for rare indications. These incentives are specified in the Orphan Drug Act of 1982 (ODA). However, some companies were criticized for unfairly taking advantage of this orphan designation by developing drugs for rare and common diseases, so-called partial orphan drugs (Chapter 5).[46] Especially partial orphan drugs with indications that receive the orphan designation to treat a subgroup of common diseases (common orphans) and then extend their approval to non-orphan indications are slated to unfairly profit from the dissonance between the indication-specific orphan designation, yet drug-specific pricing, coverage, and reimbursement policies (Chapter 6).[47]

These financially lucrative unintended consequences and loopholes of the current single-price policy for drugs with multiple indications could be greatly valued by pharmaceutical companies and investors. In Chapters 9 and 10, we therefore evaluated whether pharmaceutical companies with multi-indication drugs are valued higher than those developing single-indication drugs. Using a sample of 311 mergers and acquisitions (M&As), we find that pharmaceutical companies paid a 8% (p=.210) acquisition valuation premium per additional indication for the lead drug. Coherently, we find higher expected returns for companies that developed multi- relative to single-indication drugs. Albeit current single-price policies could partially explain these financial profits for pharmaceutical companies and investors, there are further factors that financially encourage the development of multi-indication drugs. With each additional indication, companies increase the total addressable market for their product (and thereby revenues), whilst pre-clinical and phase 1 development costs typically only occur once per drug.[48] Thereby a drug's average cost per indication could decline as new indications receive FDA approval. Furthermore, a drug's fixed costs (e.g. administrative and general expenses that are only required once per drug) can be shared across multiple indications.

Within the new IRA, the CMS has the unique opportunity to reflect the differential value that each indication offers to patients by using differential pricing approaches. These differential pricing mechanisms must consider that multiple indications of the same drug may vary in their safety, efficacy, and efficiency. Academic literature describes several pricing systems that aim to reflect the value of multiple indications: pure indication-specific pricing (ISP) and indirect ISP, e.g. single weighted-average prices, single prices with differential discounts, managed entry agreements (MEAs) per indication, and different brands with distinct prices per indication. Several systematic reviews have theoretically evaluated the merits of these differential pricing methods.[11,35,49] However, besides several theoretical articles[35–37,49–56] and four case studies,[41–44] our knowledge of the potential impacts of adopting these pricing systems in the US remains

decimal. The following paragraphs will provide a concise overview of these pricing mechanisms and our current knowledge of their implications on drug development, healthcare budgets, and patient access. Furthermore, we highlight this dissertation's contribution to our understanding of the pricing of drugs with multiple indications.

1.3.1 Indication-specific pricing

The most rational option to price drugs with multiple indications is ISP (also referred to as indication-based pricing or multi-indication pricing).[41] Under ISP, a distinct price is assigned to the differential value a drug offers in each indication (one drug, multiple prices).[41] Thereby, higher prices are assigned to indications that offer substantial benefits to patients with significant unmet needs, whilst lower prices are aligned to indications that only offer an incremental benefit (Figure 5). However, the implications of ISP on healthcare budgets, pharmaceutical competition, and patient access remain debated.

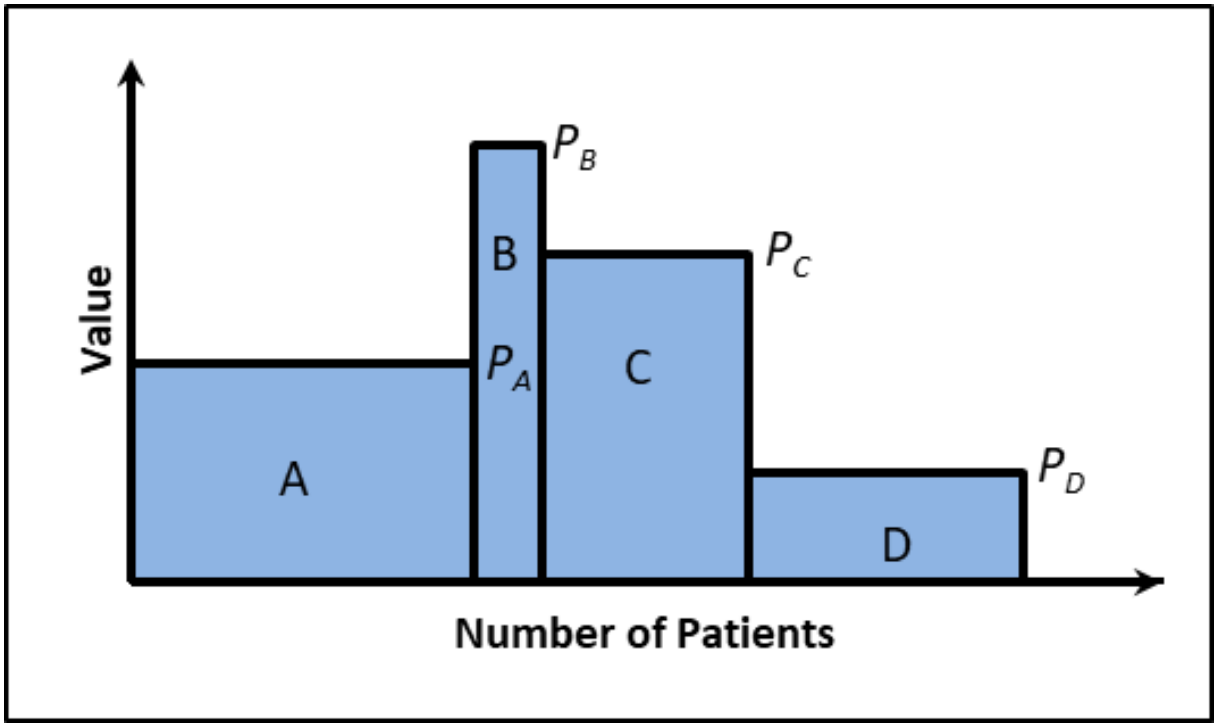

Figure 5: Indication development under pure indication-specific pricing

Notes: Under an indication-specific pricing policy, pharmaceutical companies are not incentivized to sequence their indication launches according to value and prevalence (at least from a pricing perspective). Indication A is sold for the price P_A, indication B for the price P_B, etc. This policy could not only increase revenues for pharmaceutical companies but also the number of available therapeutic options to patients. Graph adapted from Michaeli (2020).[34]

Bach noted that ISP could rationalize drug pricing and thereby reduce healthcare expenditure.[41] In contrast, Chandra & Garthwaite (2017, p.103-104) noted that ISP "will result in higher prices for patients who benefit the most from a given drug, higher utilization by patients who benefit least, higher overall spending, and higher manufacturer profits."[37] Although spending might be increased under ISP, the increased healthcare budget would be allocated to high-value indications that provide substantial benefit to patients rather than money being wasted on indications offering marginal benefit.[35] ISP encourages pharmaceutical companies to engage in pharmaceutical R&D for both high-value low-prevalence and low-value high-prevalence indications if ISP is implemented alongside a value-based pricing mechanism. Thereby ISP could not only increase the number of therapeutic options available to patients but also reduce incentives to delay or withhold indications (e.g. the sequencing of indication launches as illustrated in Figure 4), resulting in quicker access to these novel indications.[35,55] Cole et al. argue that this greater

number of available therapeutic alternatives will result in more competition that will dynamically reduce prices.[35] Hitherto, evidence demonstrates that greater brand-brand competition does not lead to reduced prescription drug prices.[57] Ultimately, ISP could benefit all stakeholders: expediting patient access to more therapeutic options, increasing revenues and profits for pharmaceutical companies, and reducing health insurers' spending on prescription drugs.

Although there are several benefits to indication-specific pricing, its challenges may be greater (Table 1). First, indication-specific pricing requires indication-specific monitoring of drug use. Whilst these systems exist and are warmly welcomed by healthcare workers,[58–60] their widespread implementation is associated with significant upfront costs.[41] Moreover, data sharing with pharmaceutical companies may pose a privacy concern for patients.[61] Payers must further hire administrative personnel that monitors drug use, conducts value assessments, negotiates prices, and facilitates payments for each indication.[49] Furthermore, pharmacies often purchase in bulk rather than ordering a drug for each patient (and indication).[41] Additionally, there are national legal barriers, such as Medicaid's best-price rule, that must be surmounted to pave the ground for indication-specific pricing.[50] In conclusion, the "political challenges [of ISP] may be greater than [its] technical challenges" (Towse, 2018, p. 5).[35]

Consequently, the challenges of pure ISP pose a significant barrier to its implementation in the US (and other countries). Despite a few pilot projects (of unknown outcome) a pure ISP policy has not yet been adopted in the US.[11,50] Payers have therefore turned to indirect ISP policies, including weighted-average pricing, differential discounts, and MEA, to capture the value of multiple indications for a single drug.[11,49,52] Meanwhile, manufacturers experimented with separate brands for the same drug to commercialize their product for a distinct price for each indication.

Benefits	Challenges
- Rationalizing drug prices	- Higher prices for high-value low-prevalence indications (e.g. ultra-rare orphan indications)
- Reducing payers' healthcare spending on pharmaceuticals	- National barriers (e.g. only one price per drug allowed in France or Medicaid's best-price rule)
- Access to more therapeutic options for patients	- IT infrastructure to track indication-specific use of drugs
- No incentive for launch sequencing of indications, resulting in expedited patient access	- Value assessment must be conducted for each indication
- Higher revenues and profits for pharmaceutical companies	- Patient privacy must be ensured whilst tracking drug use per indication
- Incentivizes the development of new indications	- Administrative burden and costs associated with the negotiation and payment of prices for each indication
- "Balance[s] affordability for payers, sustainability for manufacturers, and access for patients" (Towse, 2018, p. 2)[35]	- Reduces prices and incentives to develop low-value high-prevalence indications
- Indication-specific tracking of drug use would permit the collection of real-world outcome data for rare diseases	- Potential risk of arbitrage (buying drugs for low-value indications and using them for high-value indications)
- Improves transparency in drug use	
- Provides transparent policy frame for manufacturers to develop and prioritize the R&D of new indications	

Table 1: Benefits and challenges of indication-specific pricing

In Chapter 7 of this dissertation, we sought to clarify the impact of indication-specific pricing on healthcare budgets in the US. Using data from 170 drugs with 455 indications, we estimate that Medicare and Medicaid could have saved $3.4 billion (-12.1%) in spending in 2020 with the adoption of indication-specific pricing. We show that these savings were especially attributed to lower drug prices for supplemental indications. These findings are coherent with our previous observation in Chapter 2 that supplemental indications provide a lower clinical benefit to a broader patient population. Further, these findings resonate with Chapter 3, which shows that the current US single drug price policy does not reflect the value of supplemental indications. Assigning a value-based price to all, original and supplemental, indications could not

only align the value and price of new medicines but also reduce prices and spending for health insurers.

Chapter 7 confirms that under an indication-specific pricing policy, prices are reduced for drugs with a low-value proposition for a broad patient population, e.g. non-orphan drugs (spending: -9.9%) and partial orphans, e.g. drugs treating orphan and non-orphan diseases, (spending: -19%). The stratification between full, partial, and non-orphan drugs conducted in Chapter 7 shows that indication-specific pricing could help to resolve the potential overspending on indications treating common diseases from partial orphan drugs stemming from a disconnect between the indication-specific orphan drug designation and a drug-specific pricing policy.

However, Chapter 7 also finds that drug prices and spending on drugs with a high-value proposition for a smaller patient population would increase under indication-specific pricing. We find that prices for and consequently the spending on ultra-rare orphan drugs would increase by $70 million (+27%). This is particularly concerning given that ultra-rare orphan cancer drugs are sold for $70,128 – a price far exceeding non-orphan drug prices of $14,508 (Chapter 5). These results underline that the detailed implications and adverse effects of any new pharmaceutical policies must be thoroughly evaluated for all patients.

1.3.2 Weighted-average pricing

The simplest indirect ISP policy is weighted-average pricing. Under this policy, a single drug price is calculated reflecting the value and/or volume of different indications. This system requires the ex-ante estimation or ex-post monitoring of patients receiving the drug for each indication.[38] As for all drug pricing considerations, the operationalization of "value" remains subject to the national HTA process. Therefore, this calculation or monitoring imposes an additional administrative burden on manufacturers and payers. Moreover, given that drug prices are still anchored to the initial indication, there remains an incentive for drug sponsors to sequence

the development and launch of new indications. Particularly, low-value high-prevalence indications, which may substantially reduce the weighted-average price for the entire drug, may not be launched (Figure 6).[39] Weighted-average pricing is currently applied in Germany, France, Spain, Australia, Austria, and Belgium,[11,40,49] and was shown to effectively reduce list prices as new low-value high-prevalence indications enter the market.[38]

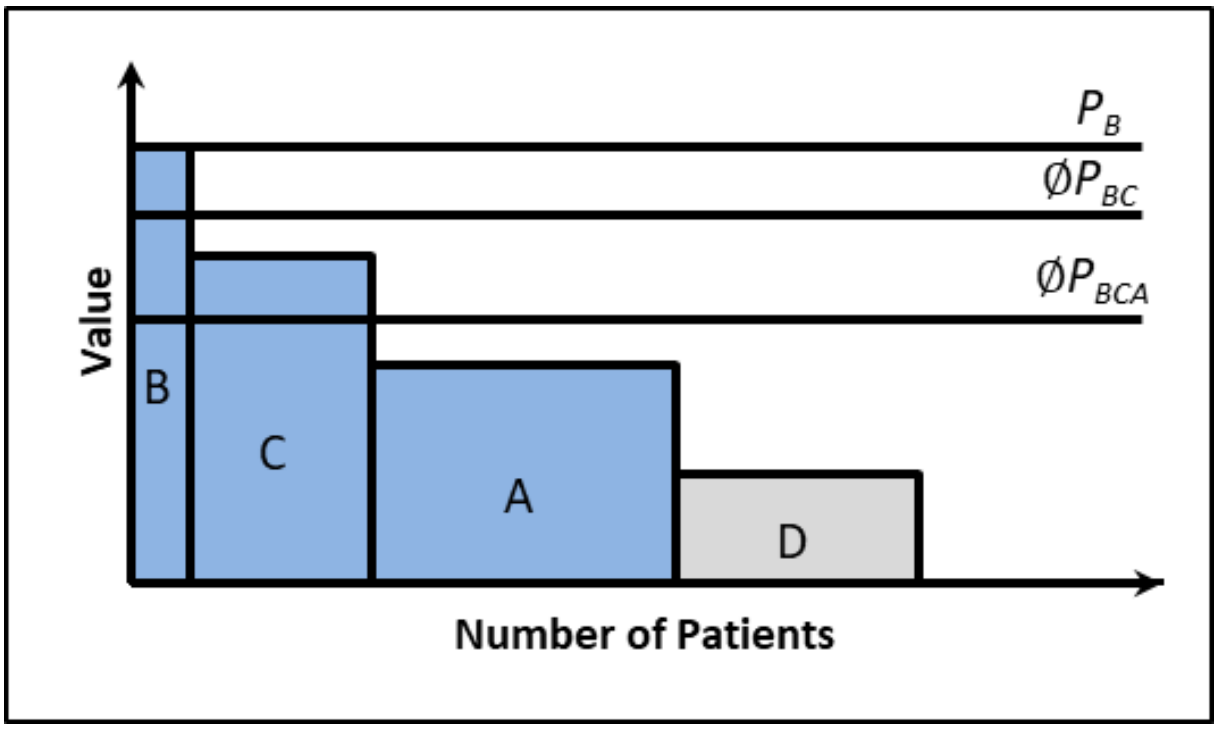

Figure 6: Indication development under weighted-average pricing

Notes: The graph visualizes drug pricing and indication development under a weighted-average pricing policy. The first indication that enters the market (B) is priced at P_B. Following the entry of a new indication (C), a single drug price ($\emptyset P_{BC}$) is calculated based on the weighted-average value and volume of indications B and C. Accordingly, the single drug price is recalculated to $\emptyset P_{BCA}$ as indication A enters the market. Similar to Figure 4, there remains an incentive for sponsors to sequence and withhold the launch of new indications according to value and disease prevalence. Graph adapted from Michaeli (2020).[34]

In Chapter 7, we estimated the potential savings of adopting weighted-average pricing in the US for Medicare and Medicaid. Similar to indication-specific pricing, the adoption of weighted-average pricing would result in cost savings of $3.4 billion (-12.1%) for Medicare and Medicaid in 2020. Prices declined with the approval of each new supplemental indication. The cost saving sources were similar to indication-specific pricing (see above). However, in contrast to indication-specific pricing, weighted-average pricing also resulted in lower prices for and spending

on drugs treating ultra-rare diseases. Combined with the potentially lower costs of implementing and operating a weighted-average than indication-specific pricing system, weighted-average pricing could, henceforth, be the preferred option to rationalize prices for drugs with multiple indications.

1.3.3 Single drug prices with differential discounts per indication

The second most prominent indirect ISP policy is single drug pricing with differential discounts per indication. Under this policy, a single list price is set for each drug's highest value indication (usually the first indication). Thereafter, drug sponsors and payers negotiate differential discounts (or premiums) for each new indication that enters the market (Figure 7). Albeit this policy results in a single constant list price across all indications,[38] the negotiated net price varies for each indication. Similar to weighted-average pricing, differential discounts are associated with additional administrative burdens as payers and sponsors have to conduct value assessments, negations, payments, and monitoring of drug use for each new indication.[49] Although this policy results in indication-specific net prices that are aligned to the value of each indication, sponsors are still incentivized to sequence indication launches. In theory, the incentives for this sequencing should be reduced if differential premiums for high-value indications were permitted. In practice, differential premiums have not been observed.[38]

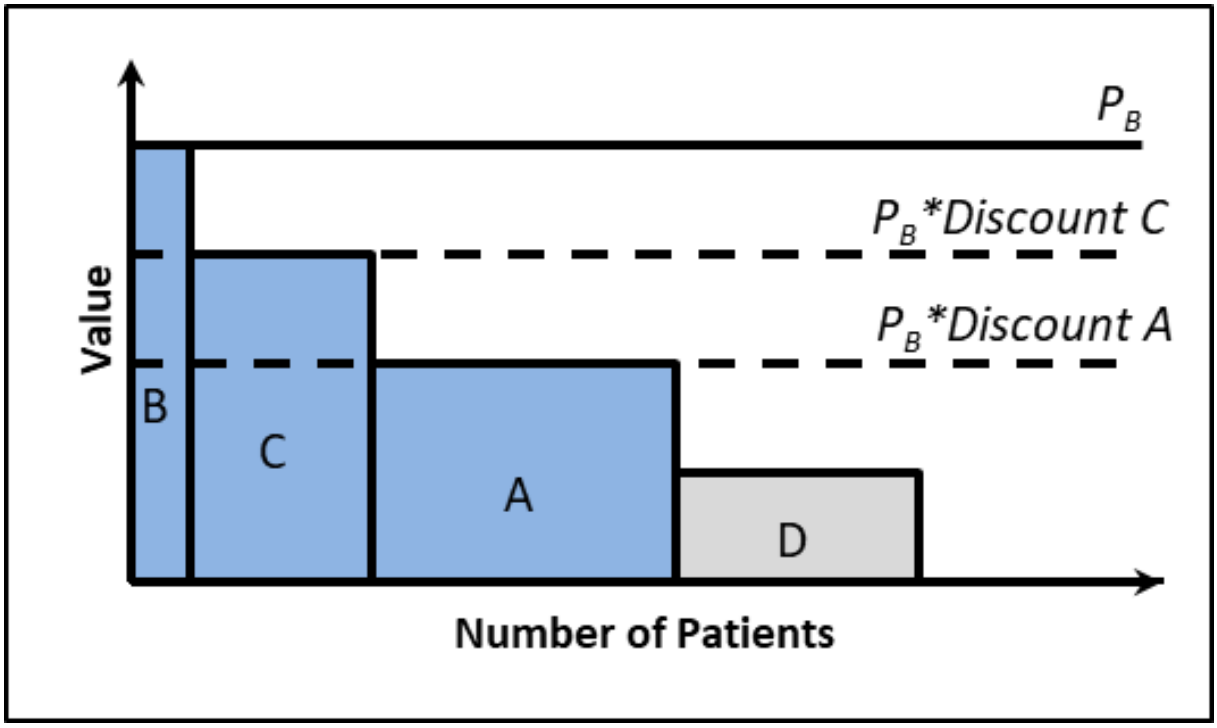

Figure 7: Indication development under single drug pricing with differential discounts per indication

Notes: The graph visualizes drug pricing and indication development under a single drug price with differential discounts per indication policy. The first indication that enters the market (B) is priced at P_B. For each new indication that enters the market, a differential discount is applied on this list price P_B. The resulting net price for indication C will be calculated as P_B times discount C and for indication A as P_B time discount A. Similar to Figure 4, there remains an incentive for sponsors to sequence and withhold the launch of new indications according to value and disease prevalence. Graph adapted from Michaeli (2020).[34]

Frequently, these differential discounts are applied in the form of MEAs. MEAs "are arrangements between firms and healthcare payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance" (Wenzl & Chapman, 2018, p. 4).[62] MEAs are a heterogeneous group of innovative coverage and reimbursement mechanisms. Their taxonomy can broadly be categorized into two groups: financial and performance-based/outcomes-based (Figure 8). Discounts fall under the category of financial MEAs. Although financial contracts were shown to be the dominant form of MEAs, performance-based MEAs may be particularly applied for therapies with an uncertain safety and efficacy profile that is based on non-robust clinical trials. For these performance-based MEAs, reimbursement of new therapies is conditional upon the achievement of a pre-defined outcome. For example,

new anti-cancer drugs are only fully reimbursed if the patient reaches a certain survival milestone (risk-sharing agreement).[52] However, for drugs approved based on small, non-randomized, single-arm phase 2 trials, reimbursement may also be conditional upon the enrollment of patients into confirmatory phase 3 or 4 trials (coverage with evidence development [CED]).

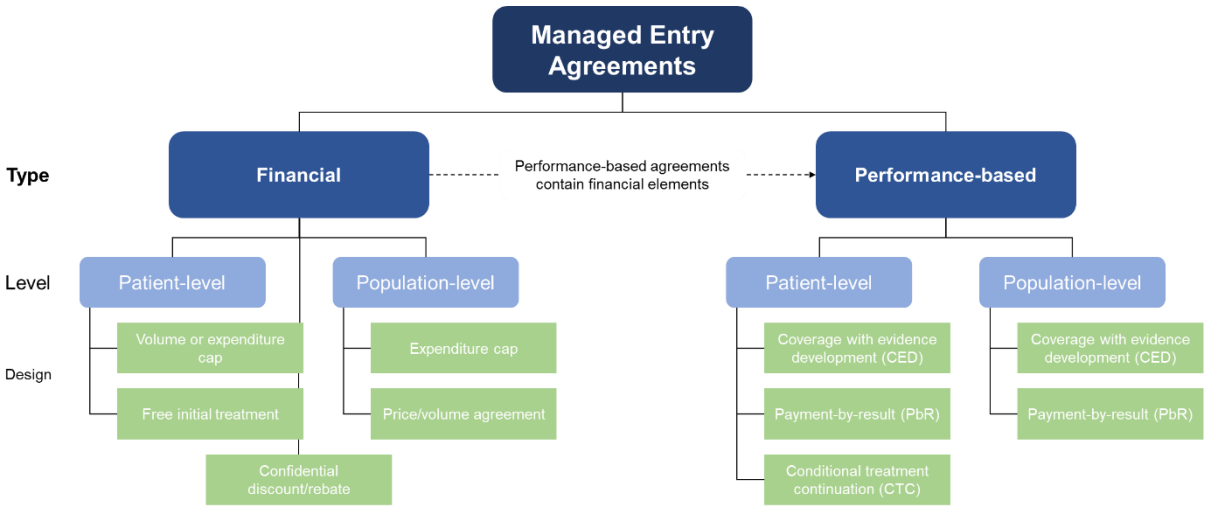

Figure 8: Taxonomy of managed entry agreements

Notes: Adapted from Wenzl & Chapman (2019).[62]

Given the heterogeneity in and continually evolving forms of MEAs, countries employ different types of MEAs for the coverage and reimbursement of drugs with multiple indications. In England and Scotland, drugs are sold for the same list price across all indications. Indication-specific Patient Access Schemes (PAS) are then negotiated for each new disease to achieve cost-effectiveness and not exceed the pre-defined WTP threshold of 20,000-30,000 GBP per QALY.[11,49] Alongside these financial MEAs, England and Scotland were shown to restrict the usage of drugs on an indication-specific level. Particularly clinical conditions that restrict drug usage to certain (sub-)populations are especially frequently applied for new indications.[38] In Spain, weighted-average prices are calculated on a national level.[11,49] However, differential discounts on these list prices may be negotiated on a regional or hospital level. The Italian pricing system is similarly complex. It permits the setting of unique list prices and discounts alongside

separate MEAs.[11,49] In the US, there are few examples of insurers applying differential discounts for new indications of the same drug.[11,32,49,63] For instance, Express Scripts and CVS Caremark negotiated with Novartis to sell the new chimeric antigen receptor (CAR) T-cell therapy, tisagenlecleucel (Kymriah®), for two different net prices for the indications acute lymphoblastic leukemia and large B-cell lymphoma. Similar to tisagenlecleucel, most of these pilot projects were conducted for drugs with excessively high prices for ultra-rare diseases. To the best of our knowledge, the outcome of these pilots has not been reported.[11]

For this dissertation, we did not have access to costly databases that estimate drugs' list and net prices. Therefore, we conducted our analyses for list prices. However, indication-specific discounts, as part of indication-specific MEAs, could help to resolve some of the unintended consequences of a single drug price across all indications. For example, in Chapters 5 and 6 we discuss that in the absence of indication-specific pricing, the indication-specific coverage and reimbursement of orphan indications could avoid the aforementioned consequences of partial orphan drugs and common orphan indications for patients of non-orphan diseases. Health insurers could selectively cover only high-value indications that prove in RCTs to extend patient survival. For low-value indications, insurers could demand indication-specific discounts, restrict reimbursement to certain biomarker-positive patient subpopulations that benefit the most from the drug, or require patients to enroll in post-marketing trials for drugs with an uncertain clinical benefit in pivotal clinical trials. The results of Chapters 2, 3, 4, and 7 suggest that these indication-specific coverage and reimbursement policies could be particularly useful throughout a product's life cycle as new indications are approved, new competitors enter the market, and new clinical trial evidence emerges. Guided by French, German, Swiss, and Japanese examples,[64–66] these chapters highlight that coverage and reimbursement policies should be re-evaluated in specified time-intervals to ensure that the price that US patients and insurers pay for a drug is aligned to its current, not past, value proposition. Nonetheless, future research must

thoroughly evaluate our propositions and assess the implications of indication-specific coverage and reimbursement on patient access as well as its potentially adverse implications on the R&D of novel indications.

1.3.4 Different brands with distinct prices per indication

In healthcare systems that do not adequately reflect the value an indication offers to patients, pharmaceutical companies may choose to set their differential prices by introducing different brands for the same medicine. Thereby companies can sell their drug for different prices, allowing them to charge a higher price for the first brand that is sold for high-value indications, whilst charging a lower price for the second brand that is sold for low-value indications (Figure 9). The most widely known example of this price discrimination is sildenafil. Pfizer first commercialized sildenafil for erectile dysfunction under the brand name Viagra® and then started to also sell sildenafil for pulmonary hypertension under the brand name Revatio®. Thereby Pfizer was able to set separate list prices for a drug that offered very different value propositions to two distinct patient populations.

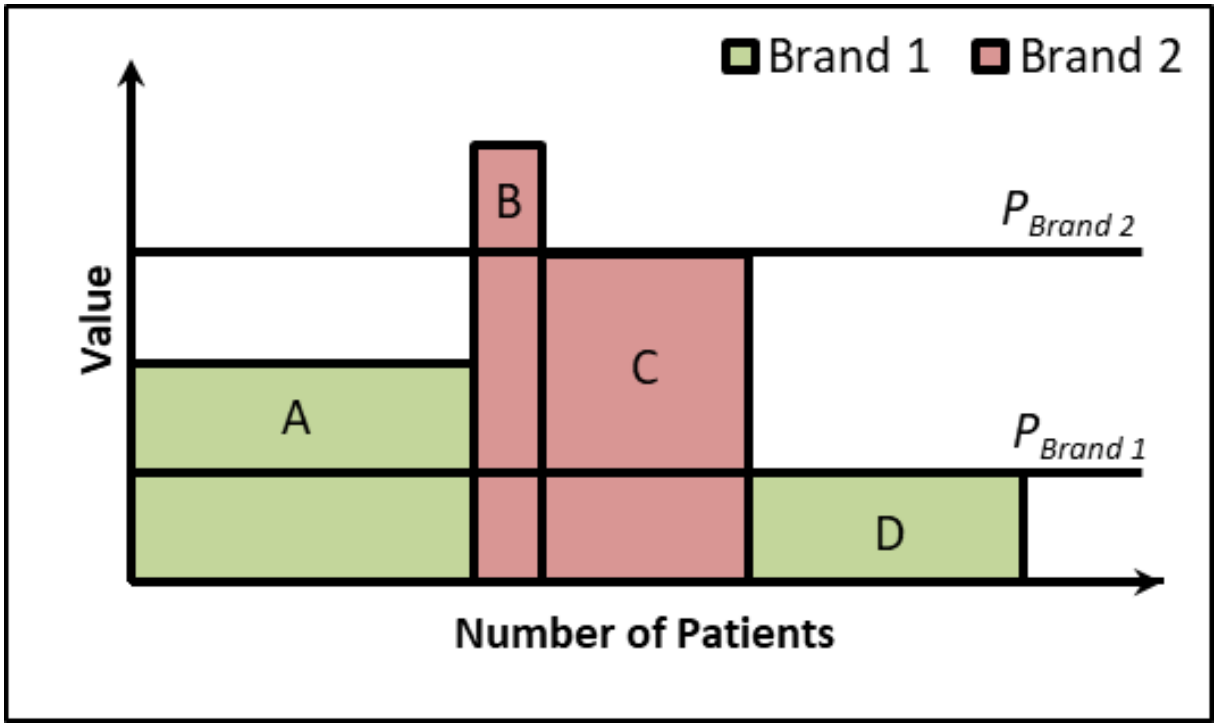

Figure 9: Indication development for drugs with different brands per indication

Notes: Assuming the natural development order displayed in Figure 4, companies are incentivized to commercialize their drug with distinct brand names without the introduction of adequate differential pricing policies. If the low-value high-prevalence indication A is already on the market, the manufacturer may increase its revenues by introducing a new brand for its high-value low-prevalence indications B and C. Thereby different brands could reduce incentives for sequencing indication launches. However, different brands are mostly applied for drugs with low-value indications that have already entered the market and high-value indications that are discovered thereafter; especially when these indications are for distinct therapeutic areas or require distinct formulations. Graph adapted from Michaeli (2020).[34]

In practice, different brands of the same drug are only rarely used. Among 170 cancer drugs with FDA approval, 94 were used in multiple indications. Of these, 12 (13%) were marketed with more than one brand (Table 2). On the one hand, manufacturers used distinct brands for drugs with different formulations. For example, ribociclib is sold as Kisqali®, containing only ribociclib, and as Kisqali femara co-pack®, containing ribociclib and letrozole. Similarly, pertuzumab is commercialized as Perjeta®, containing only pertuzumab, and Phesgo®, containing pertuzumab, trastuzumab, and hyaluronidase-zzxf. On the other hand, the predominant reason for distinct brand names for the same drug are separate indications, especially when these indications are in distinct therapeutic areas (e.g. oncology and neurology). For instance, ofatumumab is commercialized with distinct brands for chronic lymphatic leukemia (Arzerra®) and

multiple sclerosis (Kesimpta®). Similarly, lutetium Lu-177 dotatate is approved for neuroendocrine tumors under the brand name Lutathera® and prostate cancer under the brand name Pluvicto®. Different brand names for the same drug may be particularly beneficial for companies, healthcare professionals, and patients when they are used in indications of different therapeutic areas. As previously mentioned, companies can capitalize on the distinct value proposition that is associated with each indication. In contrast, healthcare professionals may welcome different brand names for separate therapeutic areas as they decrease the chance of prescription and dosing errors.[58–60] However, different brand names are regarded as a burden for healthcare professionals when they are used for indications in the same therapeutic area.[58–60] For example, if pembrolizumab was sold under a distinct brand name for all its cancer indications, pharmacists would have to keep more than fifteen different brand versions of the same medicine in stock. Moreover, physicians and patients are incentivized to use the lower-priced brand off-label in the higher-priced indication. Manufacturers can only prevent this off-label use when brands are sold for indications with different formulations, e.g. ruxolitinib or azacitidine.

Generic name	Brand names	Reason	Details
Lutetium Lu-177 dotatate	Lutathera, Pluvicto	Different indications	**Lutathera:** NET **Pluvicto:** prostate cancer
Pertuzumab	Perjeta, Phesgo	Different formulation	**Perjeta:** Pertuzumab **Phesgo:** Pertuzumab, Trastuzumab, Hyaluronidase-zzxf
Ruxolitinib	Jakafi, Opzelura	Different indication, different formulation	**Jakafi:** myelofibrosis, PV, GvHD (Tablet (oral)) **Opzelura:** atopic dermatitis, nonsegmental vitiligo (Cream (topical))
Cabozantinib	Cometriq, Cabometyx	Different indications	**Cometriq:** thyroid cancer **Cabometyx:** RCC, HCC, thyroid cancer
Ribociclib	Kisqali, Kisqali femara co-pack	Different formulation	**Kisqali:** Ribociclib **Kisqali femara co-pack:** Ribociclib, Letrozole
Aflibercept	Eylea, Zaltrap	Different indications	**Eylea:** neovascular (wet) AMD, macular edema following RVO, DME and DR, ROP **Zaltrap:** colorectal cancer
Ofatumumab	Arzerra, Kesimpta	Different indications	**Arzerra:** CLL **Kesimpta:** multiple sclerosis
Everolimus	Afinitor, Afinitor Disperz, Zortress	Different indications	**Afinitor:** breast cancer, NET, RCC, renal angiomyolipoma and TSC, TSC with SEGA **Afinitor Disperz:** TSC-associated partial-onset seizures **Zortress:** prophylaxis of organ rejection for kidney and liver transplants
Decitabine	Dacogen, Inqovi	Different formulation	**Dacogen:** Decitabine: injection (IV) **Inqovi:** Decitabine, Cedazuridine: tablet (oral)
Azacitidine	Onureg, Vidaza	Different indications, different formulation	**Onureg:** Myeloid leukemia (tablet (oral)) **Vidaza:** MDS, JMML (injection (IV))
Alpelisib	Piqray, Vijoice	Different indications	**Piqray:** Breast cancer **Vijoice:** PIK3CA-related Overgrowth Spectrum
Daratumumab	Darzalex, Darzalex faspro	Different formulation	**Darzalex:** Daratumumab **Darzalex faspro:** Daratumumab, Hyaluronidase-fihj

Table 2: Different brand names for cancer drugs with FDA approval between 2000 and 2022

Abbreviations: AMG, age-related macular degeneration; CLL, chronic lymphatic leukemia; DME, diabetic macular edema; DR, diabetic retinopathy; GvHD, graft-versus-host-disease; HCC, hepatocellular carcinoma; MDS, myelodysplastic syndrome; NET, neuroendocrine tumors; PV, polycythemia vera; RCC, renal cell carcinoma; ROP, retinopathy of prematurity; SEGA, subependymal giant cell astrocytoma; TSC, tuberoses sclerosis complex; RVO, retinal vein occlusion.

In conclusion, different brand names for the same drug cannot be viewed as the optimal solution for the pricing of drugs with multiple indications. Albeit they are used for drugs with indications across distinct therapeutic areas, different brand names are associated with an increased administrative burden for pharmaceutical companies, healthcare workers, and insurers.

1.4 Summary of this dissertation

The previous sections highlighted that drugs are increasingly developed and used for multiple indications. However, payers have not yet found the best solution how to adequately reflect the value that each indication offers to patients. Therefore, the pricing, coverage, and reimbursement of drugs with multiple clinical indications remain challenging. EU countries have adopted indirect differential pricing mechanisms, e.g. weighted-average prices and differential discounts with MEAs per indication. Meanwhile, in the US drugs are marketed under a single (highest) list price that is anchored to the original indication approval. The recent US drug pricing reform – IRA – offers the CMS a unique opportunity to not only adopt value-based pricing but to also create a price system that reflects the differential value of each indication. Therefore, this dissertation analyses the development, approval, clinical benefit, clinical trial evidence, epidemiology, and pricing of drugs in their original and supplemental indications. Figure 10 provides a brief overview of key aspects of the drug development process. This thesis' research articles' contributions to our understanding of the drug and indication development, approval, and pricing processes are highlighted in Figure 10.

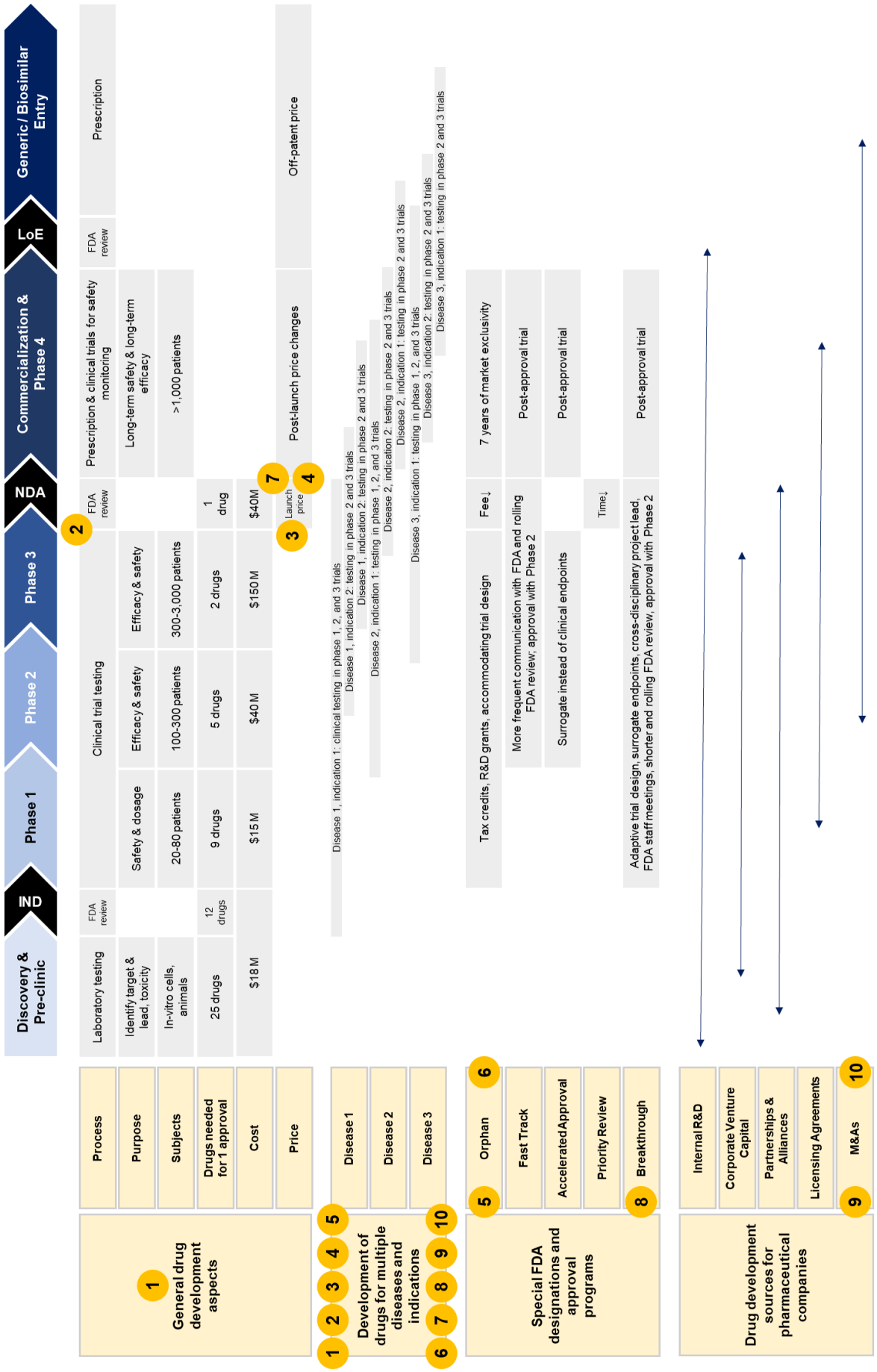

Figure 10: Aspects of the drug and indication development, approval, and pricing process covered in this thesis

Notes: The figure illustrates the drug and indication development process in a schematic overview. Aspects that are covered in this thesis are highlighted with orange circles. The number within the circle refers to the Chapter that examines the indicated aspect.

Abbreviations: FDA, US Food and Drug Administration; IND, investigational new drug applications; LoE, loss of exclusivity; M, million; M&A mergers and acquisitions; R&D research and development.

Based on a uniquely large dataset we highlight the succinct differences between original and supplemental indications and also discuss innovative pharmaceutical policies, including but not limited to indirect or direct indication-specific pricing, coverage, and reimbursement mechanisms. The dataset of anti-cancer drug approvals was then leveraged to conduct an in-depth analysis of the ODA with its current implications. Particularly highlighting how the trend towards personalized medicine for drugs with multiple indications has led to unintended consequences of the ODA. We then combined the results of these analyses to estimate the potential cost savings for Medicare and Medicaid if they were to adopt indication-specific pricing and weighted average pricing for cancer drugs, especially highlighting the consequences of these new pharmaceutical policies for patients with rare diseases.

Furthermore, we examined one of the most debated reforms of the FDA's approval process over the past 10 decades: The breakthrough therapy designation (BTD). Thereafter, we examined the drug and indication development process from the perspective of entrepreneurs and investors. For this purpose, financial acquisition data were combined with drug development data to identify and quantify factors associated with biopharma firm valuations. Thereafter, we estimated the returns that investors and bioentrepreneurs can expect from founding and investing in drug development companies. For both analyses, we especially focused on the valuation and return differences between multi-indication vs. single-indication drugs as well as orphan vs. non-orphan drugs.

This cumulative dissertation consists of nine original research articles. Most of these publications focus on anti-cancer drugs. Oncology drugs represent the single largest therapeutic area in drug development, accounting for 30% of new medicines approved by the FDA in 2021.[67]

Additionally, particularly high prices were observed for oncology drugs[2,4] and the majority of these drugs are developed for multiple cancer types and indications.[10] Furthermore, there are three coherent measures that physicians require to evaluate the clinical benefit of anti-cancer drugs: overall survival (OS), progression-free survival (PFS), and tumor response. Consequently, anti-cancer drugs represent the most interesting and relevant sample for an investigation and analysis of indication development, approval, and pricing. Furthermore, we focus on the US market for prescription drugs given that it is the single largest pharmaceutical market in the world; the FDA is frequently the first regulatory agency to approve new medicines; the US represents the largest geographic region for innovative biotechnology companies in terms of human, academic, and financial capital; most clinical trials are conducted within the US; and the US is the country with the highest prescription drug prices in the world.[68–71] Particular focus is laid upon orphan drugs given that they represent one-fifth of total prescription drug sales, regularly command prices over $100,000 per year, account for one-third of the pharmaceutical industry's value of assets under development, receive substantial government subsidies through the ODA, and are a "sandbox" for innovative treatment modalities such as gene and cell therapies, antibody-drug conjugates, and radionuclides.[72] The following paragraphs provide a summary of each article's key findings.

Chapter 2[73] entails the largest and most comprehensive analysis of the development, clinical benefit, and FDA approval of new anti-cancer drug indications to date. Whilst preceding research analyzed single aspects of the drug development process, they are typically limited to original indication approvals. Analyzing 124 novel cancer drugs FDA-approved for 374 indications, we find that new treatments with available data from RCTs (234 [63%]) reduced the risk of death by a mean of 27% (median: 2.80 months) and the risk of tumor progression by 43% (median: 3.30 months) compared with control. However, initial approvals prevented more

deaths and tumor progressions and provided a greater tumor response than indication extensions, yet were more frequently supported by non-randomized trials. In conclusion, new cancer drugs substantially reduce the risk of death and tumor progression, yet only marginally extend patient survival. From a health policy perspective, this article, therefore, highlights that the FDA, physicians, patients, and insurers must evaluate and decide on a drug's safety and efficacy approval, pricing, coverage, and reimbursement on an *indication-specific* level. Particular caution is warranted when assessing initial drug approvals with non-robust clinical evidence, which may overestimate efficacy outcomes.

Chapter 3[74] contains the first study to identify and quantify factors associated with cancer drug prices in the United States, distinctly analyzing original and supplementary indications. Based on a sample of 145 on-patent drugs with approval for 373 anti-cancer indications, we find that, for original indications, drug prices are not aligned with the survival benefit they offer to patients. Prices for new drugs are aligned with the unmet medical needs they fill and the biotechnological innovation they achieve. However, prices were not associated with the efficacy, clinical evidence, and epidemiology offered by supplementary indications, albeit the majority of cancer drugs are FDA-approved for multiple indications. In summary, cancer drug prices are set based on the original indication’s characteristics, thereby omitting the value of supplementary indications. The discussion of the article presents and evaluates differential pricing, coverage, and reimbursement policies, considering each indication’s safety, efficacy, innovativeness, and unmet needs, to reconcile this disconnect between a medicine’s cost and value.

In Chapter 4,[75] we identify and quantify factors associated with post-launch price changes of injectable cancer drugs from 2005 to 2023. We used the aforementioned dataset of new cancer drugs with FDA approval from 2000 to 2022 and combined it with quarterly price data from the CMS. The association of selected variables on post-launch price changes was evaluated in random-effects regression analyses. We found cancer drug prices regularly increased faster than

inflation. However, there was no evidence that post-launch price changes are aligned with the clinical benefit or innovativeness a drug offers to patients. The approval of new supplemental indications was associated with marginal price declines (up to -2%). Particularly patients suffering from rare and severe diseases experienced great price increases for their orphan drugs. There was no evidence that brand-brand competition results in drug price reductions.

In Chapter 5,[76] we conducted the first study to analyze the development, approval, clinical benefit, and price of cancer drugs for ultra-rare, rare, common, and non-orphan diseases. This analysis of 170 cancer drugs with 455 indications demonstrates that orphan indications fill significant unmet needs, yet their approval is supported by small, non-robust trials. For these orphan drugs manufacturers demand prices beyond $30,000 per month. Therefore, we present and discuss innovative pricing, coverage, and reimbursement policies (with a particular focus on differential pricing mechanisms) to ensure that US patients can access and afford orphan cancer drugs. The article furthermore shines light on three distinct groups of orphan drug indications: common (>200,000 US inhabitants), rare (6,600-200,000 US inhabitants), and ultra-rare (<6,600 US inhabitants) diseases. Although we show that it is more complex to develop and seek approval for ultra-rare and rare orphans, common orphans benefit from all of the ODA's incentives, higher drug prices, and expedited development timelines. We, therefore, present policy reforms to differentially incentivize drug development for common, rare, and ultra-rare orphan indications.

Chapter 6[77] contains the first study to thoroughly examine the development, approval, pricing, and spending on partial orphan drugs – drugs used to treat common and rare diseases. Using the aforementioned dataset of 170 cancer drugs with 455 indications, we show that the clinical benefit, trial characteristics, and epidemiology of partial orphan cancer drugs are more similar to non-orphan than full orphan drugs. However, partial orphans receive all of the ODA's incentives and are swiftly extended to new indications; resulting in greater prices for patients, more

beneficiaries, and higher spending for Medicare and Medicaid. Policymakers could reduce expenditure on top-selling partial orphan drugs by establishing a maximum revenue and/or patient threshold for the ODA's benefits alongside indication-specific pricing.

In Chapter 7,[78] we estimated price and cost savings if US Medicare and Medicaid were to adopt indication-specific pricing and weighted-average pricing. Using the aforementioned dataset of cancer drugs with price and spending data, we conducted a multivariate regression analysis of factors associated with prices for original indications (e.g. innovativeness, disease burden, R&D costs, disease incidence, disease severity, and other treatment options). This model was then used to predict indication-specific prices for supplemental indications. Based on these indication-specific prices, we calculated value- and population-weighted-average prices for each drug as new supplemental indications were approved. We assigned Medicare and Medicaid spending per drug proportionally to each indication based on their disease prevalence. We find that Medicare and Medicaid spent a total of $28.3 billion on new cancer drugs in 2020. This spending could be reduced by -12.1% with indication-specific pricing as well as weighted-average pricing. We show that these savings were especially realized by reducing prices for partial orphan drugs' low-value non-orphan supplemental indications. However, indication-specific pricing would also result in higher prices for patients with ultra-rare cancers, e.g. patients that benefit most from the new drug. This effect was not observed for weighted-average pricing. In conclusion, indication-specific and weighted-average pricing could reduce expenditure on new cancer drugs in the US by -12.1%. Nonetheless, the effects of any new pharmaceutical policy on all patient groups, especially those suffering from rare and severe diseases, must be thoroughly evaluated.

Chapter 8[79] entails the largest study to evaluate the efficacy, clinical trial evidence, epidemiology, and price of breakthrough and non-breakthrough cancer drugs and indications. In this study of 355 FDA-approved cancer indications over 10 years, breakthrough indications showed a

greater OS (4.8 vs. 3.2 months), PFS (5.4 vs. 3.3 months), and tumor response (8.7 vs. 4.7 months) benefit. Breakthrough indications were more frequently supported by smaller, open-label single-arm trials, approved 3.5 years faster, and priced at a premium of 73% (mean: $38,971 vs. $22,591) compared to non-breakthrough indications. In contrast to previous criticism, we henceforth conclude that the BTD expedites patient access to highly effective and innovative, yet also expensive, new medicines.

In Chapter 9,[80] we identify and quantify factors associated with the valuation of drug development companies in the EU and US. For this study, 311 biopharmaceutical M&As were identified between 2005 and 2020. We complemented financial acquisition data with variables characterizing the target's product portfolio extracted from clinicaltrials.gov, Drugs@FDA database, United States Securities and Exchange Commission (US SEC) filings, and transaction announcements. The association between firm valuations with extracted variables was assessed in a multivariable regression analysis. The following variables were significantly associated with firm valuations: development stage, number of products, product type, number of indications, headquarter location in the US, underlying market conditions, and acquirer market capitalization. However, there was no significant valuation difference between companies developing orphan vs. non-orphan designated lead products. This information offers entrepreneurs, regulators, and payers insights into the valuation of drug development companies and permits the design of targeted pricing and industrial policies to steer drug development toward diseases with high unmet needs.

In Chapter 10,[81] we estimate annual returns that bioentrepreneurs and investors can expect from founding and investing in drug development companies. The dataset of 311 biopharma M&As was combined with previously published clinical development periods alongside orphan-, indication-, and disease-specific success rates to estimate annual returns for investments in drug development companies. Results indicate that companies developing orphan, multi-indication,

and oncology drugs were valued significantly higher than their peers during later development stages. We also estimated significantly higher returns for shareholders of companies with orphan relative to non-orphan-designated lead drugs from Phase 1 to FDA approval (46% vs. 12%, $p<.001$). Furthermore, higher returns were estimated for oncology (compared to other therapeutic areas) and multi-indication (compared to single-indication) drugs. In conclusion, the clinical and economic conditions surrounding orphan-designated drugs translate to a favorable financial risk-return profile for bioentrepreneurs and investors. Furthermore, bioentrepreneurs must be aware of the upside real option value their multi-indication drug could offer when negotiating acquisition or licensing agreements.

1.5 Declarations

Authors' disclosers of potential conflicts of interest: Daniel Tobias Michaeli reported receiving external advisory fees from NB Capital ApS, Marwood Group, and LSE Consulting outside the work of this dissertation. Thomas Michaeli reported receiving external advisory fees from Amgen and Janssen outside the work of this dissertation.

Ethical approval: Not needed as no patients were directly involved in this dissertation.

Data availability statement: All data used in this study were in the public domain. All data relevant to the study are included in this dissertation.

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2 Development, approval, and benefit of cancer drugs with multiple indications

Summary: This study meta-analyzes the clinical benefit of innovative cancer drugs, comparing differences in original and supplementary FDA indication approvals.

2.1 Abstract

Purpose: Clinical trial evidence is routinely evaluated for initial drug approvals, yet the benefit of indication extensions remains uncertain. This study evaluates the clinical benefit supporting new cancer drugs' initial and supplemental FDA indication approval.

Patients and Methods: Clinical trial evidence supporting each indication's FDA approval was collected from the Drugs@FDA database between 2003 and 2021. Drug, indication, and clinical trial characteristics are described. Hazard ratios (HRs) for OS, PFS, and relative risk (RR) for tumor response were meta-analyzed.

Results: Out of 124 FDA-approved drugs, 78 were approved across multiple indications. Out of 374 indications, 141 were approved as combination therapies, 255 for solid cancers, 121 with biomarkers, and 182 for first-line therapy. Approval was mostly supported by open-label (267 [71%]) phase III (238 [64%]) concurrent randomized controlled trials (248 [66%]) with a median of 331 enrolled patients (interquartile range [IQR], 123-665 patients). Across 234 randomized controlled trials with available data, drugs' HRs were 0.73 (95% CI, 0.72 to 0.75; I^2=29.6%) for OS and 0.57 (95% CI, 0.54 to 0.60; I^2=90.6%) for PFS, whereas tumor response was 1.38 (95% CI, 1.33 to 1.42; I^2=80.7%). Novel pharmaceuticals increased patient survival by a median of 2.80 months (IQR, 1.97-4.60 months) for OS and 3.30 months (IQR, 1.50-5.58 months) for PFS. Initial indications more frequently received accelerated approval, supported

by single-arm trials for advanced-line monotherapies, than indication extensions. Initial approvals provided a higher PFS (HR, 0.48 *v* 0.58; P=.002) and tumor response (RR, 1.76 *v* 1.36; P<.001).

Conclusion: New cancer drugs substantially reduce the risk of death and tumor progression, yet only marginally extend patient survival. The FDA, physicians, patients, and insurers must evaluate and decide on a drug's safety and efficacy approval, pricing, coverage, and reimbursement on an *indication-specific* level.

2.2 Context

Key objective: Previous studies only investigated new drugs' initial FDA approval; yet, most cancer drugs are approved and used across multiple indications. This study describes and meta-analyzes the evidence and efficacy supporting new cancer drugs' initial FDA approval and indication extensions.

Knowledge generated: Among 124 novel cancer drugs approved across 374 indications, new treatments with available data from randomized controlled trials (234 [63%]) reduced the risk of death by a mean of 27% (median: 2.80 months) and the risk of tumor progression by 43% (median: 3.30 months) compared with control. Initial approvals prevented more deaths, tumor progressions, and provided a greater tumor response than indication extensions, yet were more frequently supported by nonrandomized trials.

Relevance: The OS and PFS benefit associated with new cancer drugs is marginal. The FDA and physicians must cautiously evaluate initial drug approvals with non-robust clinical evidence, which may overestimate efficacy outcomes.

2.3 Introduction

Rising prices have attracted public debate about the clinical benefit cancer drugs offer to patients in the United States. Before a drug is sold, the FDA must grant regulatory approval to ensure that the drug is safe and effective for its intended use.[82] Although a survey of 4,316 US inhabitants reported that 39% mistakenly believed that the FDA only approves *extremely effective* drugs,[83] previous meta-analyses demonstrated that novel cancer drugs marginally extend life by 2 to 3 months on average.[84–87] However, these meta-analyses are limited to initial drug approvals. Little is known about the clinical evidence and benefit of new drugs' indication extensions. This is especially concerning for drugs that are more frequently prescribed for the supplemental than the original indication.[13,88]

Previous studies investigated the clinical trial characteristics,[89–92] the clinical benefits, [84–87,93] the merits of expedited review programs,[94–99] and the validity and use of clinical end points[100] for new drug approvals in the United States and European Union. Preceding research analyzed differences in clinical trial design and FDA approval timelines between original drug approvals and indication extensions,[40,88,101,102] yet not treatment outcomes. The purpose of this study is to meta-analyze the clinical benefit of novel cancer drugs across all FDA-approved indications. We report drug, indication, and clinical trial characteristics and meta-analyze OS, PFS, and tumor response outcomes.

2.4 Patients and methods

2.4.1 Search strategy and selection criteria

We identified all new oncology drugs approved in the United States between January 1, 2003, and January 1, 2020, in the Drugs@FDA database. Before 2003 the FDA label structure was inconsistent with newer approvals.[103] NDAs and BLAs for anti-cancer agents were included, while excluding non-oncology, cancer care, and diagnostic drugs. For each newly approved

drug, we retrieved data on the first indication and all indication extensions until December 31, 2021.

2.4.2 Data collection

Within the FDA label, we collected variables on drug, indication, and clinical trial characteristics as well as endpoint performance according to peer-reviewed guidelines for evidence syntheses of FDA approval documents.[103,104] Data were independently extracted from FDA labels by one reviewer (D.T.M.) and then cross-checked with clinical trial data from clinicaltrials.gov and peer-reviewed publications linked to each trial's National Clinical Trial number by another reviewer (T.M.; Table 3). Disagreements were solved in consensus and by consulting an experienced oncologist.

Drug characteristics

Drugs were categorized by number of indications (single-indication *v* multi-indication), mechanism of action (cytotoxic chemotherapy *v* targeted agents *v* immune regulators), and product type (small molecule *v* others). Each drug's innovativeness was classified as first-in-class or not first-in-class based on the compound's target by accessing the anatomic therapeutic chemical classification.[105]

Source	Variable	Website
FDA label	Indication	https://www.accessdata.fda.gov/scripts/cder/daf/
	Indication approval date	
	Treatment type	
	Cancer type	
	Biomarker	
	Line of therapy	
	Drug dosing regimen	
FDA label and clinicaltrials.gov	Clinical trial enrolled patients	https://www.accessdata.fda.gov/scripts/cder/daf/
	Clinical trial design	
	Clinical trial phase [a]	
	Clinical trial blinding	https://clinicaltrials.gov/
	Clinical trial endpoint type	
	Clinical trial comparator	
	Clinical trial endpoint outcome	
WHO	Innovation status [b]	https://www.whocc.no/atc_ddd_index/
Drug Bank	Mechanism of action	https://go.drugbank.com/
	Product type	
Global Burden of Disease study	Disease incidence	http://ghdx.healthdata.org/gbd-results-tool
	Disease prevalence	
	DALYs including YLD and YLL	
National Cancer Institute	No. of available treatment options / competitors	https://www.cancer.gov/about-cancer/treatment/drugs/cancer-type
	5-year survival rate	https://seer.cancer.gov/
Medicare and Medicaid [c]	Prices Medicare Part B	https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice
	Prices Medicare Part D	https://www.medicare.gov/plan-compare/#/?lang=en&year=2022
	Spending & beneficiaries Medicare Part B	https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-b-spending-by-drug
	Spending & beneficiaries Medicare Part D	https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-d-spending-by-drug
	Spending & beneficiaries Medicaid	https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicaid-spending-by-drug
FDA label / Federal register	IND date [d]	https://www.federalregister.gov/
	FDA approval date	https://www.accessdata.fda.gov/scripts/cder/daf/
Federal Reserve Bank of St. Louis	Quarterly CPI inflation	https://fred.stlouisfed.org/series/USACPGRLE01IXOBSAQ
FDA	Orphan Designation	https://www.accessdata.fda.gov/scripts/opdlisting/oopd/
	Fast Track	https://www.fda.gov/drugs/nda-and-bla-approvals/fast-track-approvals
	Accelerated Approval	https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals
	Priority Review	https://www.fda.gov/drugs/nda-and-bla-approvals/priority-nda-and-bla-approvals
	Breakthrough Therapy	https://www.fda.gov/drugs/nda-and-bla-approvals/breakthrough-therapy-approvals

Table 3: Data sources

[a] Combined phase 1/2 trials were classified as phase 2, combined phase 2/3 as phase 3.
[b] Within each Anatomical Therapeutic Chemical (ATC) class, drugs connoted with a 1 were labeled as first-in-class, whilst subsequently approved drugs were labeled as not first-in-class. For drugs with ambiguous ATC clas-

sifications (e.g. ATC categories with a "X"), two reviewers independently assessed the drug's novelty. For instance, in the group "L01EF Cyclin-dependent kinase (CDK) inhibitors" palbociclib (L01EF01) is labeled as first-in-class, whilst ribociclib (L01EF02) and abemaciclib (L01EF03) are not first-in-class. This classification captures a drug's novelty in terms of the modulated target. However, this classification does not differentiate between novel mechanisms of action, clinical indications, or treated diseases.

[c] For drugs without available data from Medicare and Medicaid data sources, prices were retrieved from the drug abacus (https://www.drugpricinglab.org/).

[d] The date when the IND became effective was primarily obtained from "Determination of Regulatory Review Period for Purposes of Patent Extension" documents submitted by the FDA to the US Patent and Trademark Office (USPTO). For drugs without these documents, the date when the IND became effective was determined 30 days after the IND was submitted to the FDA as disclosed in FDA review documents.

Abbreviations: CPI, consumer price index; DALY, disability-adjusted life years; FDA, US Food and Drug Administration; IND, investigational new drug application; USPTO, US Patent and Trademark Office; WHO, World Health Organization; YLD, year lived with disability; YLL, years of life lost.

Indication characteristics

For each new indication, we extracted information on the treated cancer type, associated biomarkers, treatment type (combination *v* monotherapy), and line of treatment (first-line, second-line, or ≥ third-line). For each multi-indication drug, indications were classified as first, second, third, fourth, and ≥ fifth according to FDA approval date – indications approved on the same date were both classified as first; the next approved indication was then considered second.

Clinical trial characteristics

Clinical trial data informing each indication's FDA approval were extracted from the indication-specific label. Obtained data included the pivotal trial phase, design (randomized, nonrandomized, or single-arm), blinding (open-label, single-blind, or double-blind), number of trial arms, number of enrolled patients, comparator, and endpoint.

Clinical benefit

Endpoint performance was extracted for all RCTs. For OS and PFS endpoints, we obtained HRs with 95% CIs as well as the number of subjects and events in the control and experimental arms. For tumor response endpoints, we calculated the RR and OR based on the number of

responders. We calculated the median monthly OS and PFS gain and the median duration of response with IQR.

2.4.3 Statistical analysis

Descriptive statistics were used to examine drug, indication, regulatory, and clinical trial characteristics. Statistics were reported for the entire sample and separately for single- and multi-indication drugs. For multi-indication drugs, we compared the distribution of collected variables across first, second, third, fourth, and ≥ fifth approved indications using $\chi 2$-tests.

The performance of clinical trial endpoints was meta-analyzed with random-effects models in STATA 14.2 (StataCorp LLC, College Station, TX). Heterogeneity was reported based on the I^2 statistic. Subgroups were compared using Cochran's Q test. Differences in median survival gains were compared with Mann-Whitney U and Kruskal-Wallis tests. The association between clinical benefit and indication approval sequence was analyzed in meta-regressions.

2.5 Results

2.5.1 Sample overview

A total of 547 NDAs and Biologic License Applications (BLA) were screened to identify 124 new anticancer drugs between 2003 and 2020 (Figure 11). The sample includes two CAR-T-cell therapies. For these 124 drugs, we identified 374 anticancer indications in the Drugs@FDA database, excluding nine non-oncology indications. Of these 124 drugs, 78 drugs were approved for multiple indications with a total of 328 approved indications, and 46 drugs were approved for a single indication.

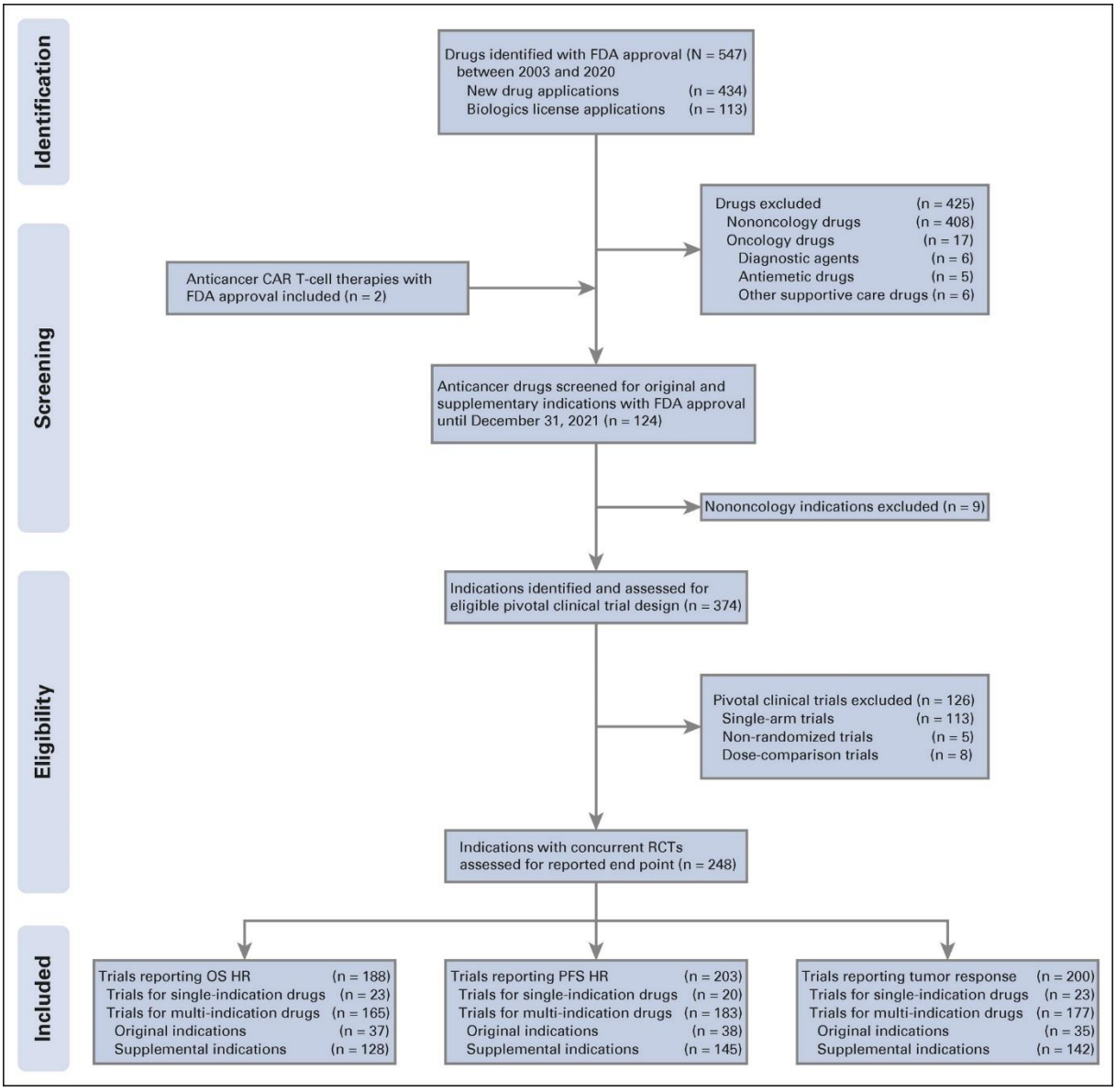


Figure 11: Flow diagram of new cancer drugs and indications with FDA approval included in the meta-analysis, 2003-2021

Notes: Out of 547 drugs with FDA approval between 2003 and 2020, 124 anticancer drugs (including two CAR T-cell therapies) were identified and screened for a total of 374 original and supplementary indication approvals. To accurately evaluate each drug's indication development, all FDA-approved indications – even those that were later withdrawn, amended, or retracted – were included in the analysis. Descriptive statistics in Table 4 are presented for the entire sample of FDA-approved indications. The meta-analysis and meta-regression only feature concurrent RCTs with OS, PFS, or tumor response outcomes.

Abbreviations: CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial.

Drug characteristics

Of 124 drugs, 47 (38%) were first-in-class, and 89 (72%) were small molecules. Eighty-four (68%) drugs acted via a targeted, 24 (19%) via a immune-regulatory, and 16 (13%) via a cytotoxic mechanism of action (Table 4). Multi-indication drugs were on average approved for 4.2 indications (median: 3; IQR, 2-4), with on average 7.3 (median: 4; IQR, 2-6) indications observed for immune regulators, 3.5 (median: 3; IQR, 2-4) for targeted, and 2.3 (median: 2; IQR, 2-2) for cytotoxic agents.

Variable	No.	(%)
Number of indications		
Single-indication	46	(37.1)
Multi-indication	78	(62.9)
Innovation status		
Not first-in-class	77	(62.1)
First-in-class	47	(37.9)
Mechanism of action		
Cytotoxic chemotherapy	16	(12.9)
Targeted agents [a]	84	(67.7)
Immune regulators [b]	24	(19.4)
Product type		
Small-molecule	89	(71.8)
Other [c]	35	(28.2)
Total	**124**	**(100.0)**

Table 4: Drug characteristics of the sample of FDA-approved cancer drugs

[a] Targeted agents include anti-hormonal compounds and therapeutics such as tyrosine kinase inhibitors.
[b] Immune regulators include immune modulators, CAR T-cell therapies, and immune antibodies, including immune checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 inhibitors.
[c] Other includes monoclonal antibodies, antibody-drug conjugates, enzymes, and radiotherapeutics.

Abbreviations: CAR, chimeric antigen receptor; CTLA4, cytotoxic T-lymphocyte-associated protein 4; FDA, US Food and Drug Administration; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1.

Indication characteristics

Out of the 328 approved indications for multi-indication drugs, 84 (26%) were first, 73 (22%) were second, 47 (14%) were third, 27 (8%) were fourth, and 97 (30%) were ≥ fifth according to FDA approval date (Table 5). Across 374 FDA-approved indications, 233 (62%) were mon-

otherapies, and 141 (38%) were combination treatments. Initial drug approvals were more frequently monotherapies than indication extensions (P<.001). Out of 374 indication approvals, 255 (68%) were developed for solid and 119 (32%) for hematologic cancers (Table 6). One hundred twenty-one out of 374 (32%) indications were approved with biomarkers (Table 7). The majority of indications were approved as first-line (182 [49%]) or second-line treatments (151 [40%]). Indication extensions were more frequently approved as first-line treatments than initial drug approvals (P<.001).

	No. (%)								
	Multi-Indication							Single-Indication	Overall
	Indication Approval Sequence [a]								
Characteristics	**1st**	**2nd**	**3rd**	**4th**	**≥5th**	**Overall**	***P Value*** [b]		
Indication Characteristics									
Treatment Type							*<.001*		
Monotherapy	69 (82.1)	50 (68.5)	26 (55.3)	13 (48.1)	44 (45.4)	202 (61.6)		31 (67.4)	233 (62.3)
Combination	15 (17.9)	23 (31.5)	21 (44.7)	14 (51.9)	53 (54.6)	126 (38.4)		15 (32.6)	141 (37.7)
Cancer Type							*0.012*		
Solid	49 (58.3)	50 (68.5)	33 (70.2)	18 (66.7)	80 (82.5)	230 (70.1)		25 (54.3)	255 (68.2)
Hematological	35 (41.7)	23 (31.5)	14 (29.8)	9 (33.3)	17 (17.5)	98 (29.9)		21 (45.7)	119 (31.8)
Biomarker							*0.856*		
No	53 (63.1)	46 (63.0)	32 (68.1)	19 (70.4)	67 (69.1)	217 (66.2)		36 (78.3)	253 (67.6)
Yes	31 (36.9)	27 (37.0)	15 (31.9)	8 (29.6)	30 (30.9)	111 (33.8)		10 (21.7)	121 (32.4)
Line of Therapy							*<.001*		
First-line	24 (28.6)	31 (42.5)	30 (63.8)	16 (59.3)	58 (59.8)	159 (48.5)		23 (50.0)	182 (48.7)
Second-line	43 (51.2)	33 (45.2)	15 (31.9)	11 (40.7)	34 (35.1)	136 (41.5)		15 (32.6)	151 (40.4)
≥Third-line	17 (20.2)	9 (12.3)	2 (4.3)	0 (0.0)	5 (5.2)	33 (10.1)		8 (17.4)	41 (11.0)
FDA Approval Characteristics									
FDA Approval Type							*0.003*		
Standard Approval	46 (54.8)	57 (78.1)	38 (80.9)	22 (81.5)	70 (72.2)	233 (71.0)		33 (71.7)	266 (71.1)
Accelerated Approval	38 (45.2)	16 (21.9)	9 (19.1)	5 (18.5)	27 (27.8)	95 (29.0)		13 (28.3)	108 (28.9)
Not Converted	3	1	2	0	4	10		2	12
Pending	7	4	3	1	14	29		9	38
Converted	28	11	4	4	9	56		2	58
Clinical Trial Characteristics									
Enrolled patients, median (IQR)	236 (119-508)	369 (153-602)	474 (155-847)	582 (119-707)	387 (154-709)	363 (133-670)	*0.109*	230 (104-431)	331 (123-665)
Trial Design							*0.003*		
Single-Arm	39 (46.4)	17 (23.3)	8 (17)	6 (22.2)	28 (28.9)	98 (29.9)		15 (32.6)	113 (30.2)
Non-Randomized	0 (0.0)	2 (2.7)	2 (4.3)	1 (3.7)	0 (0.0)	5 (1.5)		0 (0.0)	5 (1.3)
Concurrent RCT	41 (48.8)	53 (72.6)	37 (78.7)	20 (74.1)	68 (70.1)	219 (66.8)		29 (63.0)	248 (66.3)
Dose-Comparison RCT	4 (4.8)	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.0)	6 (1.8)		2 (4.3)	8 (2.1)
Clinical Trial Phase							*0.152*		
Phase 1	5 (6.0)	3 (4.1)	1 (2.1)	1 (3.7)	2 (2.1)	12 (3.7)		2 (4.3)	14 (3.7)
Phase 2	37 (44.0)	21 (28.8)	12 (25.5)	6 (22.2)	28 (28.9)	104 (31.7)		18 (39.1)	122 (32.6)
Phase 3	42 (50.0)	49 (67.1)	34 (72.3)	20 (74.1)	67 (69.1)	212 (64.6)		26 (56.5)	238 (63.6)
Type of Blinding							*0.905*		
Open-Label	60 (71.4)	52 (71.2)	33 (70.2)	18 (66.7)	71 (73.2)	234 (71.3)		33 (71.7)	267 (71.4)
Single-Blind	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)		0 (0.0)	1 (0.3)
Double-Blind	23 (27.4)	21 (28.8)	14 (29.8)	9 (33.3)	26 (26.8)	93 (28.4)		13 (28.3)	106 (28.3)
Clinical Trial Arms							*0.014*		
1 arm	39 (46.4)	16 (21.9)	8 (17)	6 (22.2)	28 (28.9)	97 (29.6)		15 (32.6)	112 (29.9)
2 arms	44 (52.4)	54 (74)	36 (76.6)	20 (74.1)	66 (68.0)	220 (67.1)		30 (65.2)	250 (66.8)
≥3 arms	1 (1.2)	3 (4.1)	3 (6.4)	1 (3.7)	3 (3.1)	11 (3.4)		1 (2.2)	12 (3.2)
Total Concurrent RCTs, No.	41	53	37	20	68	219		29	248
Endpoint for Concurrent RCTs							*0.926*		
Overall Survival	37 (90.2)	39 (73.6)	28 (75.7)	14 (70.0)	47 (69.1)	165 (75.3)		23 (79.3)	188 (75.8)
Progression-Free Survival	38 (92.7)	42 (79.2)	31 (83.8)	14 (70.0)	58 (85.3)	183 (83.6)		20 (69.0)	203 (81.9)
Tumor Response	35 (85.4)	44 (83.0)	29 (78.4)	13 (65.0)	56 (82.4)	177 (80.8)		23 (79.3)	200 (80.6)
Other	2 (4.9)	5 (9.4)	6 (16.2)	4 (20.0)	9 (13.2)	26 (11.9)		3 (10.3)	29 (11.7)
Comparator for Concurrent RCTs							*0.131*		
Placebo or No Treatment	31 (75.6)	32 (62.2)	23 (75.0)	15 (52.9)	36 (62.6)	137 (62.6)		18 (62.1)	155 (62.5)
Active Agent	10 (24.4)	21 (37.8)	14 (25.0)	5 (47.1)	32 (37.4)	82 (37.4)		11 (37.9)	93 (37.5)
Total No. of Indications	**84**	**73**	**47**	**27**	**97**	**328**		**46**	**374**

Table 5: Indication, FDA approval, and clinical trial characteristics compared across the indication approval sequence

[a] Indication approval sequence based on FDA approval date.
[b] P values comparing differences across the indication approval sequence calculated based on χ^2-and Kruskal-Wallis tests.

Abbreviations: FDA, US Food and Drug Administration, IQR, interquartile range; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial.

	No. (%)							
	Multi-Indication						Single-Indication	Overall
	Indication Approval Sequence [a]							
Disease	First	Second	Third	Fourth	≥Fifth	Overall		
Bladder cancer	3 (3.6)	2 (2.7)	1 (2.1)	1 (3.7)	5 (5.2)	12 (3.7)	1 (2.2)	13 (3.5)
Breast cancer	9 (10.7)	7 (9.6)	5 (10.6)	0 (0.0)	4 (4.1)	25 (7.6)	3 (6.5)	28 (7.5)
Cervical cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.1)	3 (0.9)	0 (0.0)	3 (0.8)
Colorectal cancer	5 (6.0)	2 (2.7)	1 (2.1)	3 (11.1)	4 (4.1)	15 (4.6)	1 (2.2)	16 (4.3)
Endometrial cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	1 (1.0)	2 (0.6)	0 (0.0)	2 (0.5)
Gastric cancer	2 (2.4)	4 (5.5)	0 (0.0)	0 (0.0)	7 (7.2)	13 (4.0)	0 (0.0)	13 (3.5)
Head and neck cancer	0 (0.0)	1 (1.4)	1 (2.1)	1 (3.7)	3 (3.1)	6 (1.8)	0 (0.0)	6 (1.6)
Hepatic cancer	0 (0.0)	1 (1.4)	2 (4.3)	1 (3.7)	7 (7.2)	11 (3.4)	0 (0.0)	11 (2.9)
Leukemia	14 (16.7)	10 (13.7)	5 (10.6)	3 (11.1)	5 (5.2)	37 (11.3)	9 (19.6)	46 (12.3)
Lung cancer	8 (9.5)	12 (16.4)	9 (19.1)	5 (18.5)	18 (18.6)	52 (15.9)	4 (8.7)	56 (15.0)
Lymphoma	10 (11.9)	8 (11.0)	5 (10.6)	2 (7.4)	8 (8.2)	33 (10.1)	7 (15.2)	40 (10.7)
Multiple myeloma	6 (7.1)	4 (5.5)	3 (6.4)	3 (11.1)	2 (2.1)	18 (5.5)	2 (4.3)	20 (5.3)
Other cancers	5 (6.0)	6 (8.2)	3 (6.4)	3 (11.1)	5 (5.2)	22 (6.7)	8 (17.4)	30 (8.0)
Ovarian cancer	3 (3.6)	3 (4.1)	1 (2.1)	1 (3.7)	4 (4.1)	12 (3.7)	0 (0.0)	12 (3.2)
Pancreatic cancer	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.0)	2 (0.6)	0 (0.0)	2 (0.5)
Prostate cancer	3 (3.6)	3 (4.1)	3 (6.4)	1 (3.7)	1 (1.0)	11 (3.4)	5 (10.9)	16 (4.3)
Renal cancer	5 (6.0)	3 (4.1)	5 (10.6)	0 (0.0)	9 (9.3)	22 (6.7)	1 (2.2)	23 (6.1)
Skin cancer	9 (10.7)	6 (8.2)	2 (4.3)	2 (7.4)	7 (7.2)	26 (7.9)	4 (8.7)	30 (8.0)
Thyroid cancer	2 (2.4)	0 (0.0)	1 (2.1)	0 (0.0)	3 (3.1)	6 (1.8)	1 (2.2)	7 (1.9)
Total no. of indications	**84**	**73**	**47**	**27**	**97**	**328**	**46**	**374**

Table 6: Diseases treated by new cancer drugs

[a] Indication approval sequence based on FDA approval date.

Abbreviations: FDA, US Food and Drug Administration.

Biomarker	No.	(%)
No	253	(67.6)
Yes		
BRAF mutation positivity	17	(4.5)
PD-L1 expression positivity	16	(4.3)
Philadelphia chromosome positivity	11	(2.9)
BRCA mutation positivity	10	(2.7)
HER2 expression positivity	10	(2.7)
ALK mutation positivity	10	(2.7)
EGFR expression positivity	9	(2.4)
Hormone receptor positivity	6	(1.6)
Microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) cancers	6	(1.6)
HRD mutation positivity	3	(0.8)
IDH1 mutation positivity	3	(0.8)
Estrogen receptor positivity	3	(0.8)
T790M mutation positivity	3	(0.8)
Other	14	(3.7)
Total	**374**	**(100.0)**

Table 7: Biomarkers used for the FDA approval of new cancer drugs

Abbreviations: FDA, US Food and Drug Administration.

FDA approval characteristics

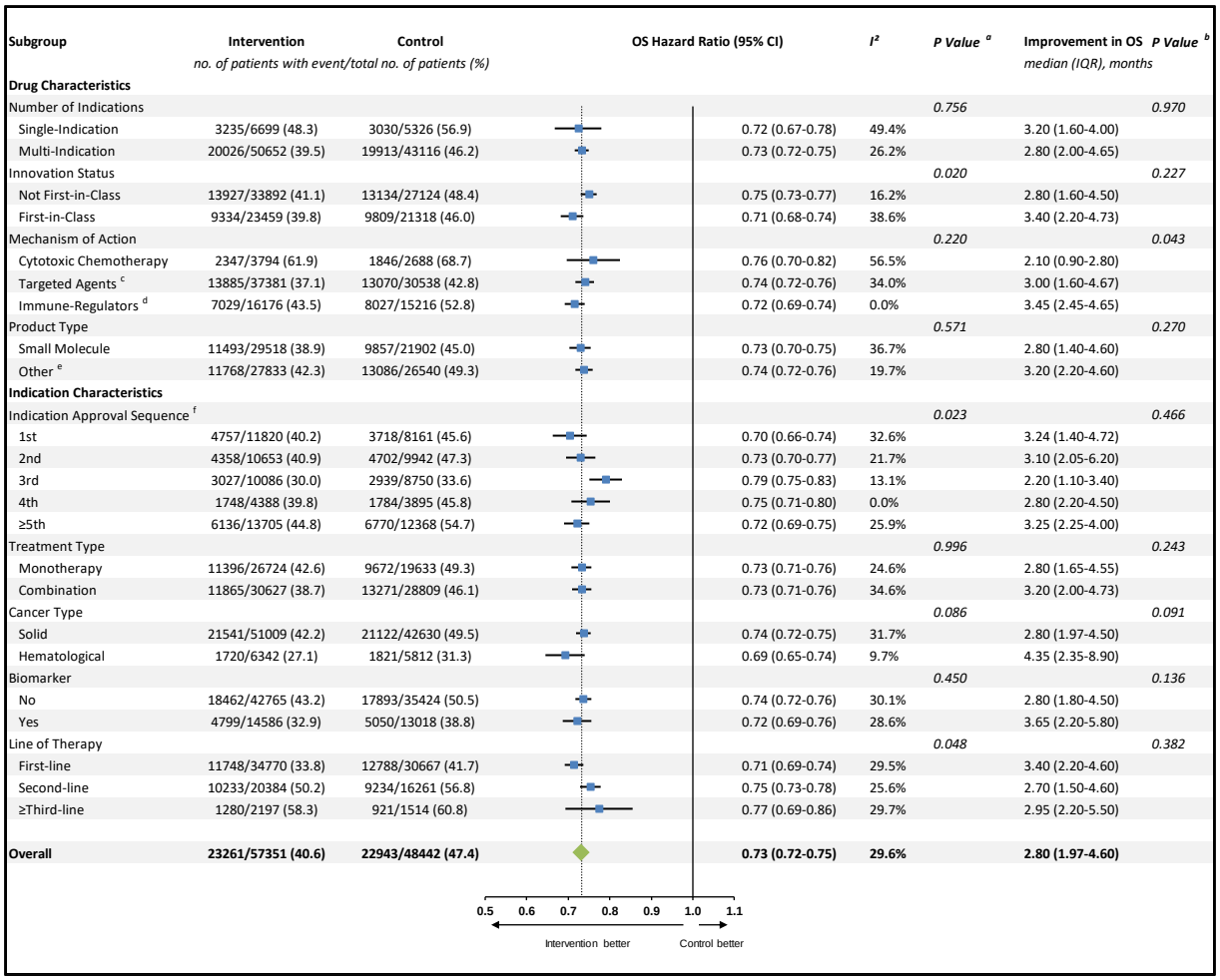
Out of 374 indications, 108 (29%) received accelerated approval. Of these, confirmatory trials were pending for 38 (35%) indications, 12 (11%) were withdrawn, and 58 (54%) received full approval until December 31, 2021. Accelerated approval was significantly more common for original than supplemental indications (45% *v* 23%; P=.003).

Clinical trial characteristics

FDA approval was mostly supported by open-label (267 [71%]) phase III (238 [64%]) concurrent RCTs (248 [66%]) with a median of 331 enrolled patients (IQR, 123-665). However, approximately one-third of indications were supported by single-arm phase II trials. Particularly original indications were more frequently approved based on single-arm trials than indication extensions. Out of 248 concurrent RCTs, 155 (63%) compared the new drug to placebo or no treatment.

2.5.2 Cancer drug indications' clinical benefit

Out of 248 eligible RCTs, 188 (76%) reported OS, 203 (82%) PFS, 200 (81%) tumor response, and 29 (12%) other endpoints (Fig 1). Novel cancer drugs reduced the risk of death by a mean of 27% compared with control (HR, 0.73; 95% CI, 0.72 to 0.75; I2=29.6%) and increased survival by a median of 2.80 months (IQR, 1.97-4.60 months; Figure 12). New drugs reduced the risk of cancer progression by a mean of 43% compared with control (HR, 0.57; 95% CI, 0.54 to 0.60; I^2=90.6%), increasing PFS by a median of 3.30 months (IQR, 1.50-5.58 months; Figure 13). Novel drugs provided a 1.38× (95% CI, 1.33 to 1.42; I^2=80.7) greater tumor response than control with a median duration of response of 5.00 months (IQR, 2.70-8.70 months; Figure 14). The full meta-analyses are enclosed in Figure 58, Figure 59, Figure 60, and Figure 61.

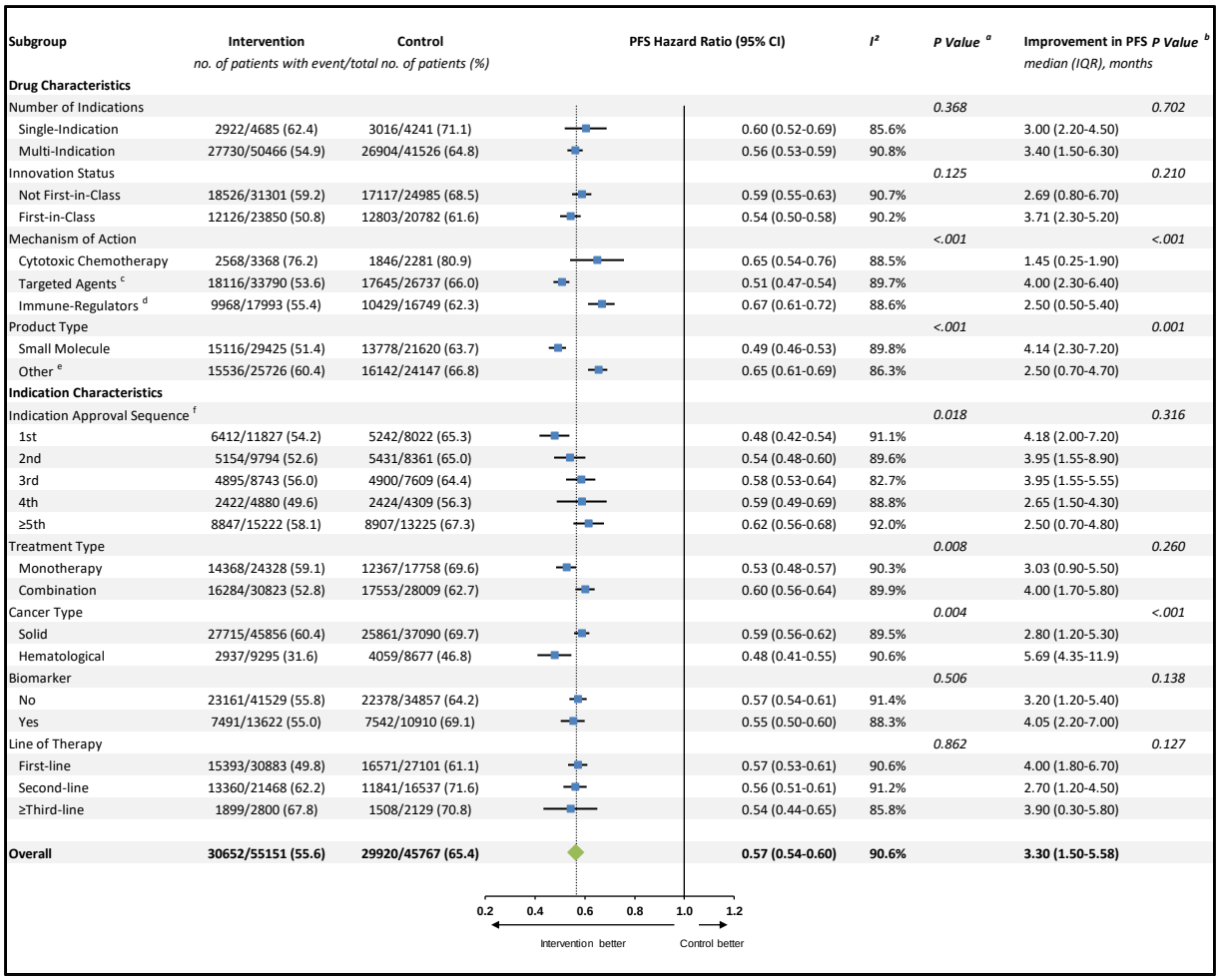


Subgroup	Intervention	Control	OS Hazard Ratio (95% CI)	I^2	*P Value* [a]	Improvement in OS	*P Value* [b]
	no. of patients with event/total no. of patients (%)					*median (IQR), months*	
Drug Characteristics							
Number of Indications					*0.756*		*0.970*
Single-Indication	3235/6699 (48.3)	3030/5326 (56.9)	0.72 (0.67-0.78)	49.4%		3.20 (1.60-4.00)	
Multi-Indication	20026/50652 (39.5)	19913/43116 (46.2)	0.73 (0.72-0.75)	26.2%		2.80 (2.00-4.65)	
Innovation Status					*0.020*		*0.227*
Not First-in-Class	13927/33892 (41.1)	13134/27124 (48.4)	0.75 (0.73-0.77)	16.2%		2.80 (1.60-4.50)	
First-in-Class	9334/23459 (39.8)	9809/21318 (46.0)	0.71 (0.68-0.74)	38.6%		3.40 (2.20-4.73)	
Mechanism of Action					*0.220*		*0.043*
Cytotoxic Chemotherapy	2347/3794 (61.9)	1846/2688 (68.7)	0.76 (0.70-0.82)	56.5%		2.10 (0.90-2.80)	
Targeted Agents [c]	13885/37381 (37.1)	13070/30538 (42.8)	0.74 (0.72-0.76)	34.0%		3.00 (1.60-4.67)	
Immune-Regulators [d]	7029/16176 (43.5)	8027/15216 (52.8)	0.72 (0.69-0.74)	0.0%		3.45 (2.45-4.65)	
Product Type					*0.571*		*0.270*
Small Molecule	11493/29518 (38.9)	9857/21902 (45.0)	0.73 (0.70-0.75)	36.7%		2.80 (1.40-4.60)	
Other [e]	11768/27833 (42.3)	13086/26540 (49.3)	0.74 (0.72-0.76)	19.7%		3.20 (2.20-4.60)	
Indication Characteristics							
Indication Approval Sequence [f]					*0.023*		*0.466*
1st	4757/11820 (40.2)	3718/8161 (45.6)	0.70 (0.66-0.74)	32.6%		3.24 (1.40-4.72)	
2nd	4358/10653 (40.9)	4702/9942 (47.3)	0.73 (0.70-0.77)	21.7%		3.10 (2.05-6.20)	
3rd	3027/10086 (30.0)	2939/8750 (33.6)	0.79 (0.75-0.83)	13.1%		2.20 (1.10-3.40)	
4th	1748/4388 (39.8)	1784/3895 (45.8)	0.75 (0.71-0.80)	0.0%		2.80 (2.20-4.50)	
≥5th	6136/13705 (44.8)	6770/12368 (54.7)	0.72 (0.69-0.75)	25.9%		3.25 (2.25-4.00)	
Treatment Type					*0.996*		*0.243*
Monotherapy	11396/26724 (42.6)	9672/19633 (49.3)	0.73 (0.71-0.76)	24.6%		2.80 (1.65-4.55)	
Combination	11865/30627 (38.7)	13271/28809 (46.1)	0.73 (0.71-0.76)	34.6%		3.20 (2.00-4.73)	
Cancer Type					*0.086*		*0.091*
Solid	21541/51009 (42.2)	21122/42630 (49.5)	0.74 (0.72-0.75)	31.7%		2.80 (1.97-4.50)	
Hematological	1720/6342 (27.1)	1821/5812 (31.3)	0.69 (0.65-0.74)	9.7%		4.35 (2.35-8.90)	
Biomarker					*0.450*		*0.136*
No	18462/42765 (43.2)	17893/35424 (50.5)	0.74 (0.72-0.76)	30.1%		2.80 (1.80-4.50)	
Yes	4799/14586 (32.9)	5050/13018 (38.8)	0.72 (0.69-0.76)	28.6%		3.65 (2.20-5.80)	
Line of Therapy					*0.048*		*0.382*
First-line	11748/34770 (33.8)	12788/30667 (41.7)	0.71 (0.69-0.74)	29.5%		3.40 (2.20-4.60)	
Second-line	10233/20384 (50.2)	9234/16261 (56.8)	0.75 (0.73-0.78)	25.6%		2.70 (1.50-4.60)	
≥Third-line	1280/2197 (58.3)	921/1514 (60.8)	0.77 (0.69-0.86)	29.7%		2.95 (2.20-5.50)	
Overall	**23261/57351 (40.6)**	**22943/48442 (47.4)**	**0.73 (0.72-0.75)**	**29.6%**		**2.80 (1.97-4.60)**	

Figure 12: Subgroup meta-analysis of all randomized controlled trials reporting OS used for the FDA approval of new cancer drugs, 2003-2021

[a]P values calculated based on Cochran's Q test for subgroup differences.
[b]P values calculated based on Mann-Whitney U and Kruskal-Wallis tests.
[c]Targeted agents include antihormonal compounds and therapeutics such as tyrosine kinase inhibitors.
[d]Immune regulators include immune modulators, chimeric antigen receptor T-cell therapies, and immune antibodies, including immune checkpoint inhibitors such as programmed cell death protein-1/programmed death ligand-1 and cytotoxic T-cell lymphocyte-4 inhibitors.
[e]Other includes monoclonal antibodies, antibody-drug conjugates, enzymes, and radiotherapeutics.
[f]Indication sequence according to FDA approval date. Includes only multi-indication cancer drugs.

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; IQR, interquartile range; OS, overall survival.



Subgroup	Intervention	Control	PFS Hazard Ratio (95% CI)	I^2	*P Value* [a]	Improvement in PFS median (IQR), months	*P Value* [b]
	no. of patients with event/total no. of patients (%)						
Drug Characteristics							
Number of Indications					*0.368*		*0.702*
Single-Indication	2922/4685 (62.4)	3016/4241 (71.1)	0.60 (0.52-0.69)	85.6%		3.00 (2.20-4.50)	
Multi-Indication	27730/50466 (54.9)	26904/41526 (64.8)	0.56 (0.53-0.59)	90.8%		3.40 (1.50-6.30)	
Innovation Status					*0.125*		*0.210*
Not First-in-Class	18526/31301 (59.2)	17117/24985 (68.5)	0.59 (0.55-0.63)	90.7%		2.69 (0.80-6.70)	
First-in-Class	12126/23850 (50.8)	12803/20782 (61.6)	0.54 (0.50-0.58)	90.2%		3.71 (2.30-5.20)	
Mechanism of Action					*<.001*		*<.001*
Cytotoxic Chemotherapy	2568/3368 (76.2)	1846/2281 (80.9)	0.65 (0.54-0.76)	88.5%		1.45 (0.25-1.90)	
Targeted Agents [c]	18116/33790 (53.6)	17645/26737 (66.0)	0.51 (0.47-0.54)	89.7%		4.00 (2.30-6.40)	
Immune-Regulators [d]	9968/17993 (55.4)	10429/16749 (62.3)	0.67 (0.61-0.72)	88.6%		2.50 (0.50-5.40)	
Product Type					*<.001*		*0.001*
Small Molecule	15116/29425 (51.4)	13778/21620 (63.7)	0.49 (0.46-0.53)	89.8%		4.14 (2.30-7.20)	
Other [e]	15536/25726 (60.4)	16142/24147 (66.8)	0.65 (0.61-0.69)	86.3%		2.50 (0.70-4.70)	
Indication Characteristics							
Indication Approval Sequence [f]					*0.018*		*0.316*
1st	6412/11827 (54.2)	5242/8022 (65.3)	0.48 (0.42-0.54)	91.1%		4.18 (2.00-7.20)	
2nd	5154/9794 (52.6)	5431/8361 (65.0)	0.54 (0.48-0.60)	89.6%		3.95 (1.55-8.90)	
3rd	4895/8743 (56.0)	4900/7609 (64.4)	0.58 (0.53-0.64)	82.7%		3.95 (1.55-5.55)	
4th	2422/4880 (49.6)	2424/4309 (56.3)	0.59 (0.49-0.69)	88.8%		2.65 (1.50-4.30)	
≥5th	8847/15222 (58.1)	8907/13225 (67.3)	0.62 (0.56-0.68)	92.0%		2.50 (0.70-4.80)	
Treatment Type					*0.008*		*0.260*
Monotherapy	14368/24328 (59.1)	12367/17758 (69.6)	0.53 (0.48-0.57)	90.3%		3.03 (0.90-5.50)	
Combination	16284/30823 (52.8)	17553/28009 (62.7)	0.60 (0.56-0.64)	89.9%		4.00 (1.70-5.80)	
Cancer Type					*0.004*		*<.001*
Solid	27715/45856 (60.4)	25861/37090 (69.7)	0.59 (0.56-0.62)	89.5%		2.80 (1.20-5.30)	
Hematological	2937/9295 (31.6)	4059/8677 (46.8)	0.48 (0.41-0.55)	90.6%		5.69 (4.35-11.9)	
Biomarker					*0.506*		*0.138*
No	23161/41529 (55.8)	22378/34857 (64.2)	0.57 (0.54-0.61)	91.4%		3.20 (1.20-5.40)	
Yes	7491/13622 (55.0)	7542/10910 (69.1)	0.55 (0.50-0.60)	88.3%		4.05 (2.20-7.00)	
Line of Therapy					*0.862*		*0.127*
First-line	15393/30883 (49.8)	16571/27101 (61.1)	0.57 (0.53-0.61)	90.6%		4.00 (1.80-6.70)	
Second-line	13360/21468 (62.2)	11841/16537 (71.6)	0.56 (0.51-0.61)	91.2%		2.70 (1.20-4.50)	
≥Third-line	1899/2800 (67.8)	1508/2129 (70.8)	0.54 (0.44-0.65)	85.8%		3.90 (0.30-5.80)	
Overall	**30652/55151 (55.6)**	**29920/45767 (65.4)**	**0.57 (0.54-0.60)**	**90.6%**		**3.30 (1.50-5.58)**	

Figure 13: Subgroup meta-analysis of all randomized controlled trials reporting PFS used for the FDA approval of new cancer drugs, 2003-2021

[a]P values calculated based on Cochran's Q test for subgroup differences.
[b]P values calculated based on Mann-Whitney U and Kruskal-Wallis tests.
[c]Targeted agents include antihormonal compounds and therapeutics such as tyrosine kinase inhibitors.
[d]Immune regulators include immune modulators, chimeric antigen receptor T-cell therapies, and immune antibodies, including immune checkpoint inhibitors such as programmed cell death protein-1/programmed death ligand-1 and cytotoxic T-cell lymphocyte-4 inhibitors.
[e]Other includes monoclonal antibodies, antibody-drug conjugates, enzymes, and radiotherapeutics.
[f]Indication sequence according to FDA approval date. Includes only multi-indication cancer drugs.

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; IQR, interquartile range; PFS, progression-free survival.

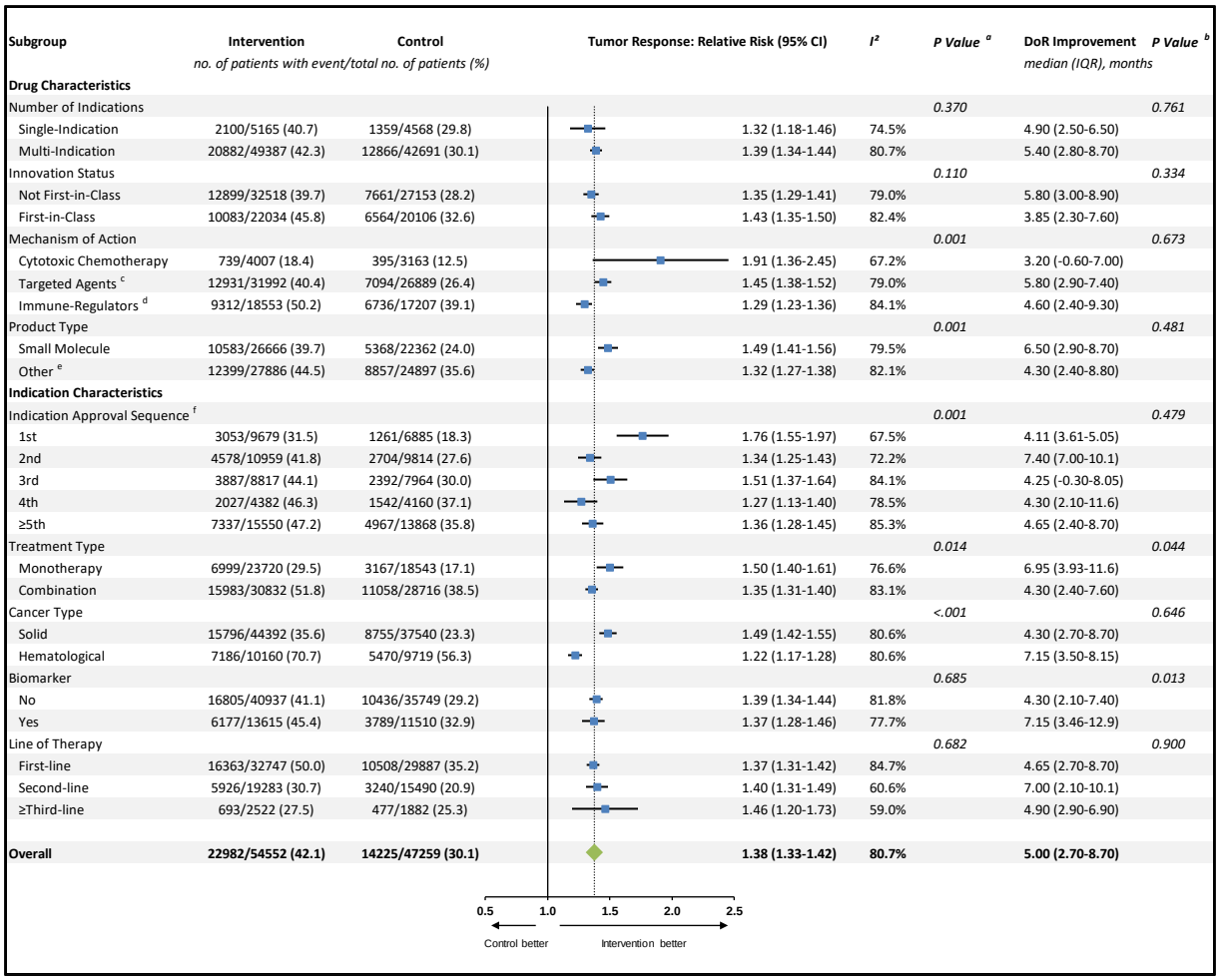


Figure 14: Subgroup meta-analysis of all randomized controlled trials reporting tumor response used for the FDA approval of new cancer drugs, 2003-2021

[a]P values calculated based on Cochran's Q test for subgroup differences.
[b]P values calculated based on Mann-Whitney U and Kruskal-Wallis tests.
[c]Targeted agents include antihormonal compounds and therapeutics such as tyrosine kinase inhibitors.
[d]Immune regulators include immune modulators, chimeric antigen receptor T-cell therapies, and immune antibodies, including immune checkpoint inhibitors such as programmed cell death protein-1/programmed death ligand-1 and cytotoxic T-cell lymphocyte-4 inhibitors.
[e]Other includes monoclonal antibodies, antibody-drug conjugates, enzymes, and radiotherapeutics.
[f]Indication sequence according to FDA approval date. Includes only multi-indication cancer drugs.

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; IQR, interquartile range; RR, relative risk.

Drug characteristics

OS was significantly higher for first-in-class (HR, 0.71; 95% CI, 0.68 to 0.74) relative to not first-in-class drugs (HR, 0.75; 95% CI, 0.73 to 0.77; P=.020). Immune regulators provided a higher OS (median: 3.45 months *v* 3.00 *v* 2.10; P=.043), yet a lower PFS (median: 2.50 months *v* 4.00 *v* 1.45; P<.001) benefit than targeted and cytotoxic agents. PFS was significantly higher

for small molecules (HR, 0.49; 95% CI, 0.46 to 0.53) relative to other drugs (HR, 0.65; 95% CI, 0.61 to 0.69; P<.001).

Indication characteristics

Original indications prevented more deaths (HR, 0.70; 95% CI, 0.66 to 0.74) than second (HR, 0.73; 95% CI, 0.70 to 0.77), third (HR, 0.79; 95% CI, 0.75 to 0.83), fourth (HR, 0.75; 95% CI, 0.71 to 0.80), and fifth (HR, 0.72; 95% CI, 0.69 to 0.75) indications (P=.023). Original indications provided a higher PFS gain (HR, 0.48; 95% CI, 0.42 to 0.54) than second (HR, 0.54; 95% CI, 0.48 to 0.60), third (HR, 0.58; 95% CI, 0.53 to 0.64), fourth (HR, 0.59; 95% CI, 0.49 to 0.69), and fifth (HR, 0.62; 95% CI, 0.56 to 0.68) indications (P=.018) and induced a greater tumor response.

In the meta-regression, OS HRs were not significantly correlated with the FDA indication approval sequence (Figure 15). By contrast, PFS HRs rose by 0.01 (95% CI, 0.00 to 0.01) with each indication extension (P<.001). Tumor response declined by –0.21 (95% CI, –0.38 to –0.04) for RR (P=.018) and –0.32 (95% CI, –0.61 to –0.03) for odds ratio (P=.030) per new indication approval. The results were confirmed in regression analyses of median survival benefits on indication approval sequence (Figure 16).

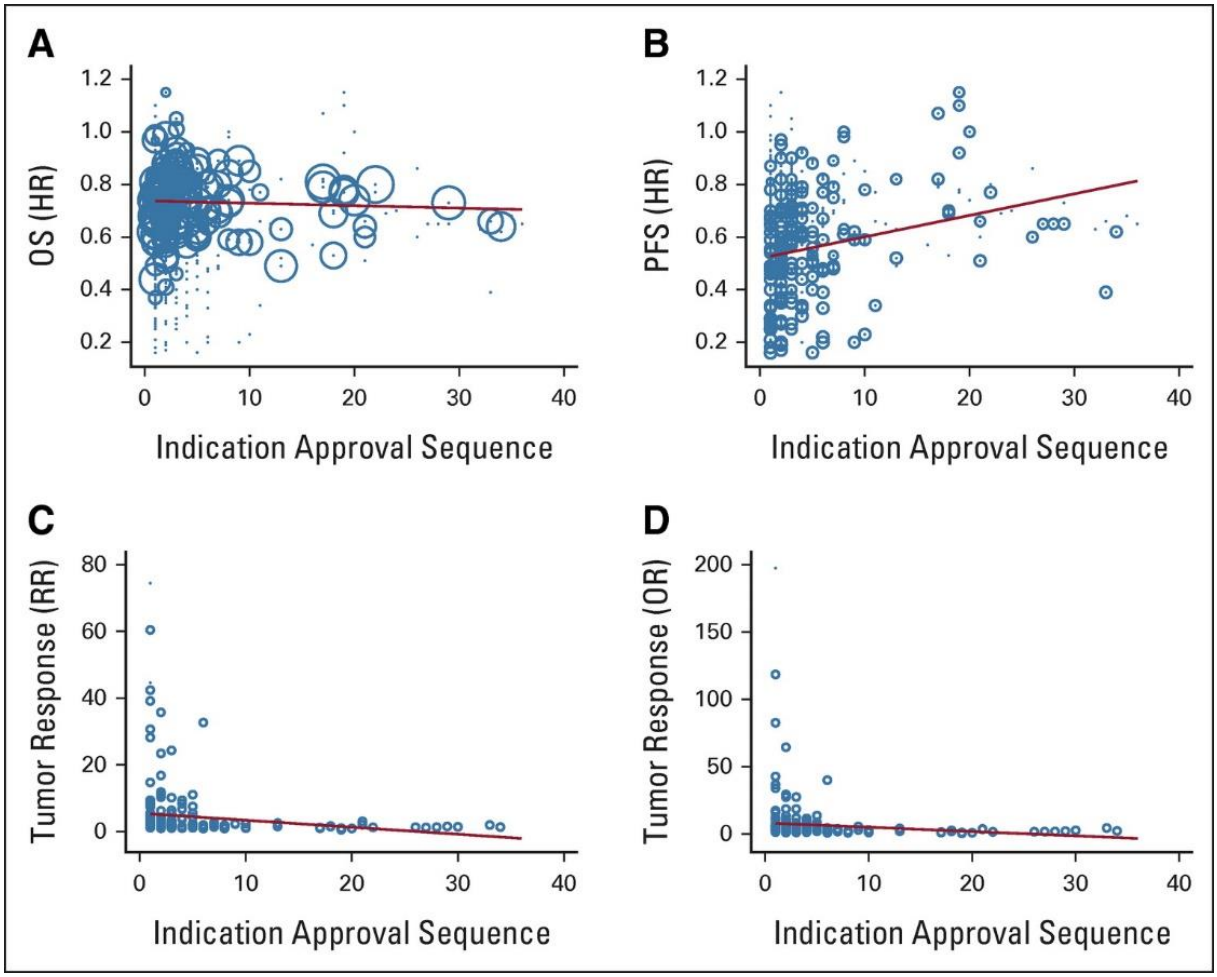


Figure 15: Meta-regression of overall survival, progression-free survival, and tumor response on FDA indication approval sequence

Notes: (A) Each indication's overall survival HR (y-axis) is mapped against the FDA approval sequence (x-axis). The approval sequence was determined according to each indication's FDA approval date: Initial indication approvals are classified as 1, second indication approvals as 2, third indication approvals as 3, etc. Accordingly, (B) maps each indication's progression-free survival HR against the FDA indication approval sequence. (C and D) Map tumor response, in terms of RR and OR, against the indication approval sequence. Within the graphs, the red line presents fitted treatment outcomes of the random-effects meta-regression. Circle sizes are subject to the precision of each treatment outcome, the inverse of their within-study variance. The meta-regression includes multi-indication cancer drugs approved between 2003 and 2021 with OS, PFS, and/or tumor response treatment outcome, single-indication drugs were excluded. Meta-regression coefficients: OS=−0.0009 (95% CI, −0.0036 to 0.0018, P=.497); PFS=0.0082 (95% CI, 0.0036 to 0.0127, P<.001); RR=−0.2099 (95% CI, −0.3838 to −0.0360, P=.018); and OR=−0.3204 (95% CI, −0.6095 to −0.0312, P=.030).

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk.

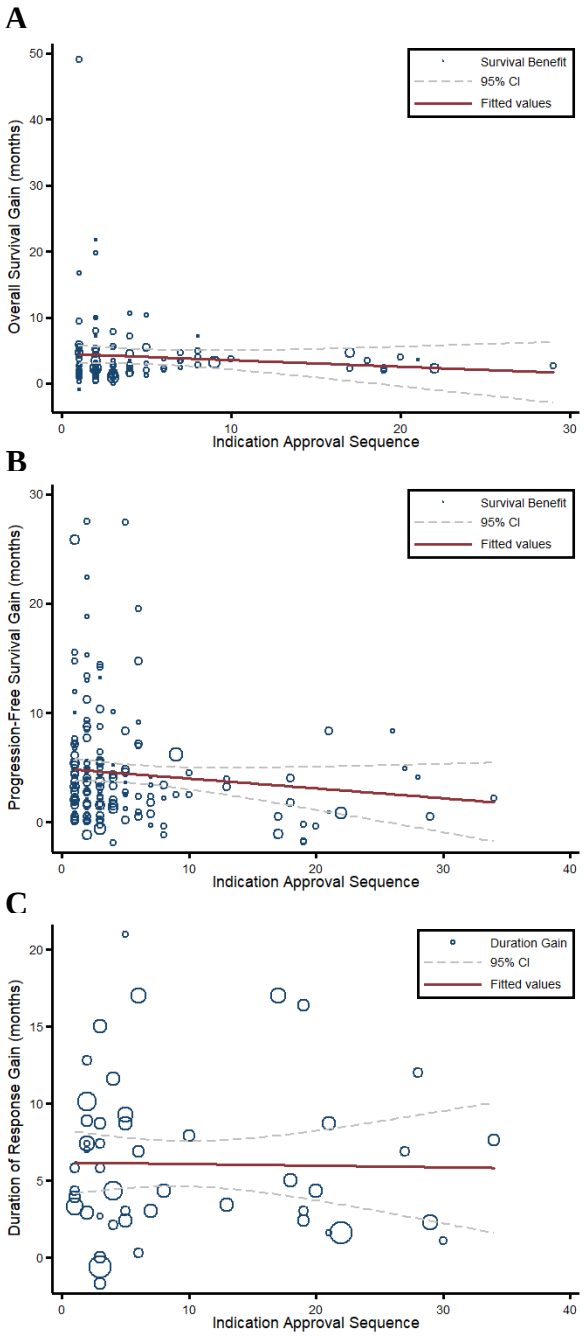


Figure 16: Weighted regression of median monthly overall survival (A), progression-free survival (B), and duration of response (C) gain on FDA indication approval sequence

Notes: In graph A, each indication's overall survival benefit (y-axis) is mapped against the FDA approval sequence (x-axis). The approval sequence was determined according to each indication's FDA approval date: Initial indication approvals are classified as 1, second indication approvals as 2, third indications as 3, etc. Accordingly, graph B maps each indication's progression-free survival benefit against the FDA indication approval sequence. Graph C and C maps the duration of response against the indication approval sequence. Within the graphs, the red line presents fitted treatment outcomes of the weighted regression. Circle sizes are subject to the number of enrolled patients in each trial. The regression includes multi-indication cancer drugs approved between 2003 and 2021 with OS, PFS, and/or tumor response treatment outcome, single-indication drugs were excluded. Weighted regression coefficients: OS=-0.10 (95% CI -0.23 to 0.03, P =.139); PFS=-0.16 (95% CI -0.29 to -0.03, P =.017); and duration of response=-0.01 (95% CI -0.17 to 0.15, P =.899).

Abbreviations: FDA, US Food and Drug Administration; OS, overall survival; PFS, progression-free survival.

Patients' PFS benefit was higher for monotherapies (HR, 0.53; 95% CI, 0.48 to 0.57) than combination treatments (HR, 0.60; 95% CI, 0.56 to 0.64; P=.008). Drugs treating hematologic tumors exerted a greater PFS benefit (HR, 0.48; 95% CI, 0.41 to 0.55) than those treating solid cancers (HR, 0.59; 95% CI, 0.56 to 0.62; P=.004). Except for a greater duration of response (median: 7.15 *v* 4.30; P=.013), drugs approved with biomarkers did not provide superior treatment outcomes. OS HRs were 0.71 (95% CI, 0.69 to 0.74) for first-line, 0.75 (95% CI, 0.73 to 0.78) for second-line, and 0.77 (95% CI, 0.69 to 0.86) for third-line therapies (P=.048).

2.5.3 Sensitivity analysis

The results were robust under sensitivity analyses with different meta-analysis models and when restricting the data set to phase III, double-blind, or two-arm trials (Table 8). PFS and tumor response outcomes were subject to the trial's comparator and the drug's mechanism of action. Lower OS and higher RR were observed for confirmatory trials required by the FDA for accelerated approvals leading to a new indication. Heterogeneity between trial outcomes was low for OS (I^2=29.6%) and high for PFS (I^2=90.6%) and tumor response (I^2=80.7).

	OS		PFS		Tumor response		Tumor response	
	HR (95% CI)	I^2	HR (95% CI)	I^2	RR (95% CI)	I^2	OR (95% CI)	I^2
Model sensitivity								
Random-effects model	0.73 (0.72-0.75)	*29.6%*	0.57 (0.54-0.60)	*90.6%*	1.38 (1.33-1.42)	*80.7%*	2.02 (1.89-2.16)	*72.9%*
Fixed-effects model	0.74 (0.72-0.75)	*29.6%*	0.50 (0.50-0.51)	*90.6%*	1.13 (1.11-1.14)	*80.7%*	1.44 (1.39-1.50)	*72.9%*
Hartung-makambi model	0.73 (0.71-0.75)	*29.6%*	0.57 (0.54-0.59)	*90.6%*	1.37 (1.33-1.41)	*80.7%*	2.00 (1.87-2.13)	*72.9%*
With effects extrapolation [a]	0.74 (0.72-0.76)	*49.6%*	0.57 (0.54-0.60)	*90.5%*				
Without continuity adjustment [b]					1.38 (1.33-1.43)	*82.0%*	2.03 (1.89-2.17)	*74.6%*
Indication and drug sensitivity								
Indication approval sequence								
First indication	0.70 (0.66-0.74)	*32.6%*	0.48 (0.42-0.54)	*91.1%*	1.76 (1.55-1.97)	*67.5%*	2.52 (2.08-2.96)	*45.2%*
Subsequent indications	0.74 (0.72-0.76)	*21.6%*	0.58 (0.55-0.62)	*89.9%*	1.36 (1.31-1.41)	*82.0%*	1.99 (1.84-2.14)	*76.5%*
Without checkpoint inhibitors	0.74 (0.72-0.77)	*54.3%*	0.52 (0.49-0.55)	*89.7%*	1.37 (1.32-1.42)	*79.5%*	2.12 (1.96-2.28)	*61.3%*
Targeted drugs								
Without biomarker	0.76 (0.73-0.79)	*31.2%*	0.51 (0.47-0.56)	*91.7%*	1.48 (1.39-1.57)	*73.1%*	2.23 (1.99-2.48)	*57.4%*
With biomarker	0.72 (0.67-0.76)	*36.7%*	0.50 (0.45-0.55)	*84.6%*	1.43 (1.32-1.53)	*74.0%*	1.94 (1.71-2.18)	*54.1%*
Without non-metastatic cancers	0.73 (0.72-0.75)	*33.2%*	0.57 (0.54-0.60)	*90.4%*	1.38 (1.33-1.42)	*80.8%*	2.02 (1.89-2.16)	*73.0%*
Clinical trial sensitivity								
Only double-blind trials	0.73 (0.71-0.76)	*16.5%*	0.51 (0.47-0.55)	*89.7%*	1.37 (1.28-1.45)	*67.4%*	1.87 (1.65-2.08)	*52.5%*
Only phase 3 trials	0.74 (0.72-0.75)	*28.3%*	0.57 (0.54-0.60)	*90.9%*	1.37 (1.33-1.42)	*81.4%*	2.01 (1.87-2.15)	*74.0%*
Only trials with 2 arms	0.73 (0.72-0.75)	*30.1%*	0.57 (0.54-0.60)	*90.6%*	1.37 (1.33-1.42)	*80.8%*	2.01 (1.87-2.15)	*73.2%*
Comparator								
Active agent	0.72 (0.69-0.75)	*39.4%*	0.61 (0.56-0.66)	*91.8%*	1.44 (1.36-1.51)	*86.1%*	2.08 (1.86-2.29)	*81.1%*
Placebo or no treatment	0.74 (0.72-0.76)	*22.2%*	0.54 (0.50-0.57)	*89.4%*	1.33 (1.28-1.39)	*71.9%*	1.94 (1.79-2.10)	*54.3%*
FDA approval sensitivity								
Approval trial [c]								
Standard trial	0.73 (0.71-0.75)	*32.3%*	0.57 (0.54-0.60)	*90.7%*	1.40 (1.35-1.45)	*81.1%*	2.02 (1.87-2.16)	*73.3%*
Confirmatory trial	0.75 (0.70-0.80)	*29.6%*	0.53 (0.45-0.61)	*89.6%*	1.27 (1.20-1.35)	*62.2%*	2.08 (1.71-2.45)	*66.8%*
Base case	**0.73 (0.72-0.75)**	***29.6%***	**0.57 (0.54-0.60)**	***90.6%***	**1.38 (1.33-1.42)**	***80.7%***	**2.02 (1.89-2.16)**	***72.9%***

Table 8: Sensitivity analyses

[a] For this scenario, treatment outcomes without 95% confidence intervals were extrapolated based on the number of events and subjects in the control and treatment group. Thereby 5 confidence intervals for OS and 1 for PFS were extrapolated.
[b] Continuity adjustment of 0.5 for control arms with 0 responders was applied in the base case. This scenario calculates tumor response without continuity adjustment.
[c] Confirmatory trials may be required by the FDA for indications receiving accelerated approval. This scenario compares treatment outcomes for indications supported by standard trials and those approved based on confirmatory trials after accelerated approval (n=28).

Abbreviations: HR, hazard ratio; RR, relative risk; OR, odds ratio, OS, overall survival; PFS, progression-free survival.

The drug-level fixed-effects regression analyses further confirm the robustness of previous results (Table 9). In the fixed-effects model, the PFS HR increased by 0.02 (95% CI: 0.00 to 0.05, p=0.030) for each additional indication approval. Accordingly, the RR of tumor response declined (-1.99, 95% CI: -3.46 to -0.52, p=0.008). Consistent with results from the meta-analysis and meta-regression, there was no association between OS HR and the FDA indication approval sequence.

	OS (HR)			PFS (HR)			Tumor Response (RR)		
	Coef.	**(95% CI)**	***P-Value***	**Coef.**	**(95% CI)**	***P-Value***	**Coef.**	**(95% CI)**	***P-Value***
FDA Indication Approval Sequence	-0.01	(-0.03 to 0.01)	*0.466*	0.02	(0.00 to 0.05)	*0.030*	-1.99	(-3.46 to -0.52)	*0.008*
Constant	0.75	(0.70 to 0.80)	*0.000*	0.49	(0.44 to 0.55)	*0.000*	10.05	(6.46 to 13.63)	*0.000*
Observations		172			193			185	
R^2 Within		0.74%			4.34%			8.61%	
R^2 Between		1.46%			0.57%			2.08%	
R^2 Overall		0.76%			0.80%			3.74%	

Table 9: Fixed-effects panel regression analyses

The table presents the results of the fixed-effects regression analyses. The indication approval sequence was the only independent variable. OS, PFS, and tumor response outcomes were specified as the depdendent variables of interest. Each drug molecule was specified as a distinct panel. The approval sequence was determined according to each indication's FDA approval date: Initial indication approvals are classified as 1, second indication approvals as 2, third indications as 3, etc., until ≥5 indications).

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; RR, relative risk; OS, overall survival; PFS, progression-free survival.

2.6 Discussion

This study analyzed the clinical trial evidence and efficacy supporting the initial and supplemental FDA approval of 124 cancer drugs across a total of 374 indications.

2.6.1 Cancer drugs' overall benefit

We find that new cancer drugs significantly reduced the risk of death by 27% and of tumor progression by 43% compared with control. However, OS and PFS were only prolonged by a median of 2.80 and 3.30 months, respectively. These results are within the range of previous meta-analyses. Ladanie et al[85] calculated an OS benefit of 2.4 months and a PFS benefit of 2.7 months. However, their sample is limited to 92 initial indication approvals (2000-2016). Fojo et al[86] reported an OS gain of 2.1 months and a PFS gain of 2.5 months for 71 novel cancer drugs approved against solid cancers (2002-2014). Davis et al[87] observed a median OS benefit of 2.7 months on the basis of a sample of 48 European Medicines Agency–approved cancer drugs across 68 indications (2009-2013). Salas-Vega et al[84] estimated an OS gain of 3.43 months for 53 cancer drugs that underwent health technology assessment in France, England, or Australia (2003-2013). Similar to previous studies, we conclude that novel cancer drugs only marginally extend patient life.

2.6.2 Cancer indications' clinical evidence and benefit

We observed a progressive loss of clinical benefit across indication extensions. This diluted benefit could be subject to the new indications' line of therapy, clinical trial evidence, selected patient population, and treated disease.

Cancer drugs are first approved as monotherapies in the second- or third-line setting and then extended to first-line combination regimens. First approving drugs for advanced-line treatments results in biased efficacy estimates as these studies select heavily pre-treated patients with more indolent diseases. The observed higher clinical benefit for initial indications could therefore be partially attributed to selecting patients who have exhausted standard treatments.[106]

The FDA quickly approves new drugs for indications targeting serious conditions with an unmet need on the basis of the accelerated approval pathway.[94] However, initial approval is often only supported by single-arm trials. Even initial indications that are supported by concurrent RCTs lack adequate comparators[101] – merely 24% of RCTs for initial indications assess the new drug to an active comparator. By contrast, supplemental indications are more frequently supported by phase III RCTs with active comparators. The lower OS and tumor response benefits observed in confirmatory trials highlight that poorly designed trials may overestimate efficacy outcomes. Consequently, original indications' nonrandomized, open-label trials cast doubt on the certainty and external validity of efficacy estimates. Yet, investors hype initial indications by posting esthetic Kaplan-Meier curves and astonishing HRs, which are interpreted by patients – often without reviewing a trial's robustness – who pressure the FDA to swiftly approve the new treatment.

Furthermore, the selected patient population influences efficacy estimates. Drugs are frequently approved in specific patient subgroups, for example, those with positive biomarkers, and then expanded to the broader population regardless of biomarker status to increase a drug's market

size. However, pooling efficacy data from high, low, and negative biomarker patients results in a diluted overall benefit. For example, pembrolizumab was first approved for the treatment of patients with ≥ 50% and then extended to ≥ 1% programmed death ligand-1–positive non–small-cell lung cancer (OS HR, 0.60 *v* 0.81).[43,107] The FDA must critically review pooled efficacy data to identify patient subgroups that stand to benefit most from a new treatment. Addressing areas of unmet need should be achieved through patient selection on the basis of validated biomarkers, not more and more drugs.

Coherent with previous studies,[38,40] the market access pattern of immune checkpoint inhibitors (Figure 17) highlights that drugs are first approved for rare diseases with unmet needs and then expanded to less serious conditions. This indication prioritization is incentivized by the FDA's special designations (e.g., orphan or breakthrough therapy), enabled by innovative clinical trial designs (e.g. basket trials), and motivated by a single drug pricing policy.[40] First approving a drug for orphan diseases enables pharmaceutical companies to set the highest possible list price.[37,38,40] These high prices are maintained while drugs are expanded to non-orphan diseases with a high prescription volume, yet a potentially lower clinical benefit to patients, under current US policies.[11,37,49]

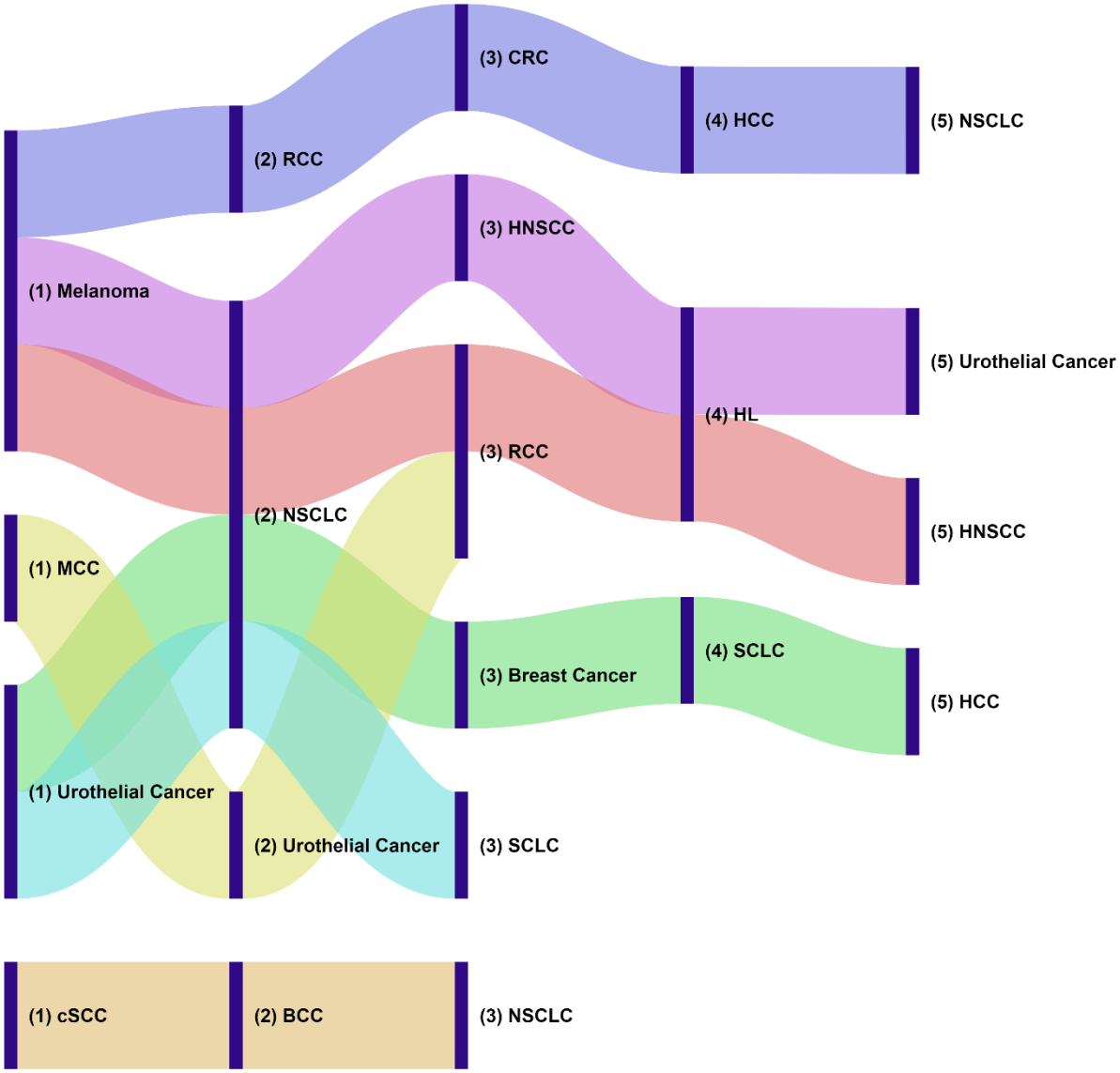


Figure 17: Sankey diagram of diseases treated by immunotherapy checkpoint inhibitors

Notes: Nodes present diseases that are treated by immunotherapy checkpoint inhibitors. The number in brackets refers to the order in which the drug was approved by the FDA. Colors visualize the FDA approval pathway for each checkpoint inhibitor: Ipilimumab (dark blue), pembrolizumab (purple), nivolumab (red), atezolizumab (yellow), avelumab (green), durvalumab (turquoise), cemiplimab-rwlc (orange).

Abbreviations: BCC, basal cell carcinoma; CRC, colorectal cancer; cSCC, cutaneous squamous cell carcinoma; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; HNSCC, head and neck squamous cell carcinoma; MCC, merkel cell carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

2.6.3 Indication-specific pharmaceutical policies

This study highlights that initial drug approvals rely on non-robust evidence, which may overestimate treatment outcomes. This differential evidence and efficacy a drug offers to patients

and insurers across indications should be reflected in pricing, coverage, and reimbursement policies.[55,108]

In the United States, drugs are sold on the basis of a single drug price across all indications. For multi-indication drugs with varying clinical benefits per indication, this policy causes a misalignment between value and price.[37,38,40,55,108] Therefore, Bach[41] proposed an indication-specific pricing (ISP) mechanism, which prices each indication according to its distinct safety and efficacy profile. Although no such policy has been implemented to date, several countries adopted indirect ISP policies. For instance, Germany and France evaluate each new indication's evidence, safety, and efficacy and then (re)calculate a weighted-average price across all indications to bill drugs.[11,38,49] Coherent with the diluted clinical benefit, these countries were shown to effectively reduce list prices with each indication extension. To adopt similar policies in the United States, legislators must empower Medicare to directly negotiate prices with manufacturers.[50]

For indication approvals encircling a broad population without adequate (biomarker-) selection by the FDA, US payers should evaluate restricting coverage to patient subgroups that benefit most from the new treatment. The FDA's special review processes, especially accelerated approvals, are criticized to nurture the approval of potentially unsafe and ineffective, yet expensive drugs.[13] Although the FDA mandates post-marketing trials that prove a drug's safety and efficacy, these often take years to complete – with some not even initiated – and fail to verify clinical benefit.[94] For debated FDA approvals, US payers could restrict coverage to patients enrolled in post-marketing trials with clinical endpoints. Medicare's decision to only cover aducanumab for beneficiaries enrolled in clinical trials established the first precedence for this policy.[109] Price negotiations and coverage decisions should be informed by indication-specific cost-effectiveness analyses conducted by independent health technology assessment institutes.

If insurers restricted coverage to drug indications that prove to increase patient survival, perhaps there would be more of them.[110]

US insurers should further explore indication-specific reimbursement. Performance- and financial-based MEAs could help to incentivize evidence development for and control expenditure on expensive drug indications with uncertain evidence.[38] However, the implementation of indication-specific pricing, coverage, and reimbursement policies in the United States remains debated. Political opposition, structural investments, and a payers' system oriented toward unmet needs must be surmounted to innovate pharmaceutical policies.

2.6.4 Limitations

This study is prone to several limitations. First, the analyses are limited to clinical trial evidence disclosed on FDA labels. Other clinical trials evaluating a drug for the respective indication may exist. Furthermore, our analyses only considered data present at the time of FDA approval. Although long-term data are scarce, 5- or 10-year follow-up outcomes could offer more precise treatment outcomes. Second, sample selection bias of only including successful FDA reviews and clinical trials may overestimate results. Third, similar to previous studies,[84–87] clinical outcomes were meta-analyzed across a variety of tumor entities with low to high heterogeneity between effect sizes. “However, it is reasonable to pool outcome data, even in the case of high heterogeneity,” (Ladanie et al., 2020, p. 11) with previous meta-analyses demonstrating coherent interpretations of treatment outcomes across tumor types.[104,111] Fourth, at the time of our study, indication development is still ongoing for certain drugs. Fifth, non-proportional hazard models may be a possible source of misestimation in the grouped estimates as the sensitivity analysis for immune checkpoint inhibitors illustrates.

2.7 Conclusion

In conclusion, pharmaceutical innovation in oncology is driven by the development and use of drugs for multiple rather than one cancer entity. This study showed that novel cancer drugs reduce the risk of death by 27% and tumor progression by 43%; however, the quality of evidence and patient benefit vary across indications. Patients and physicians must be able to rely on the FDA's competence to decide that a drug is safe and effective for all approved cancer entities. Patients and insurers should only pay for the clinical benefit a drug delivers in their cancer treatment. We consequently advise policymakers to explore *indication-specific* pricing, coverage, and reimbursement policies.

2.8 Author contributions

Conception and design: All authors. Administrative support: Daniel Tobias Michaeli. Provision of study materials or patients: Daniel Tobias Michaeli. Collection and assembly of data: All authors. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors. Accountable for all aspects of the work: All authors.

3 Prices for cancer drugs with multiple indications

Summary: This cross-sectional study identifies and quantifies factors associated with cancer drug prices in the United States, distinctly analysing original and supplementary indications.

3.1 Abstract

Objectives: Rising cancer drug prices challenge patients and healthcare systems. Whilst prices are routinely assigned to original drug indications receiving FDA approval, the pricing of supplemental indication approvals remains uncertain. This study identifies and quantifies factors associated with cancer drug prices, distinctly analyzing original and supplemental indications.

Methods: Clinical trial evidence and epidemiologic data supporting new indications' FDA approval (2003-2022) were collected from the Drugs@FDA database, clinicaltrials.gov, and the Global Burden of Disease study. Indication-specific monthly treatment costs were calculated for Medicare patients. The association between log-prices and collected variables was assessed in regression analyses.

Results: We identified 145 drugs approved across 373 cancer indications. Drugs were priced at $24,444 per month on average (median=$16,013). For original indications, prices were significantly associated with improvements in OS (β=0.28, p=0.037) and PFS (β=0.16, p=0.001). Original indications' prices were: (i) negatively associated with disease incidence (β=-0.21, p<0.001) and prevalence; (ii) positively associated with first-in-class drugs (26%, p=0.057), gene and cell therapies (176%, p<0.001), hematologic cancers (62%, p<0.001), and severe diseases with substantial unmet needs (6% per disability-adjusted life year [DALY], p<0.001); and (iii) negatively associated with indications supported by phase 3 RCTs. Prices were poorly associated with supplemental indications' efficacy, clinical evidence, and epidemiology.

Conclusions: Cancer drug prices are set based on the original indication's characteristics, thereby omitting the value of supplemental indications. *Indication-specific* pricing, coverage, and reimbursement policies considering each indication's safety, efficacy, innovativeness, and unmet needs are necessary to align a drug's value and price.

3.2 Highlights

- Cancer drug prices are a leading contributor to growing healthcare expenditure in the US with unaffordable drugs' financial toxicity adversely affecting treatment adherence. Previous studies found cancer drug prices are not aligned with the clinical benefit they offer; however, these studies are limited to *original* drug approvals. After the FDA first approves a drug in its original indication, sponsors submit additional evidence to extend a drug's use to *supplemental* indications.
- For *original* indications, drug prices are poorly aligned with the survival benefit they offer to patients. Drug prices are significantly aligned with the unmet medical needs they fill and the biotechnological innovation they achieve. Albeit the majority of cancer drugs are FDA-approved for multiple indications, drug prices were not associated with the efficacy, clinical evidence, and epidemiology offered by *supplemental* indications.
- In summary, cancer drug prices are set based on the *original* indication's characteristics, thereby omitting the value of *supplemental* indications. *Indication-specific* pricing, coverage, and reimbursement policies considering each indication's safety, efficacy, innovativeness, and unmet needs, are necessary to reconcile the disconnect between a medicine's costs and value.

3.3 Introduction

Medical expenditure has been identified as the leading cause of personal bankruptcy in the US.[15] Particularly drug prices over $100,000 per year contribute to catastrophic health expenditure among the low-and middle-income population.[112] In Europe, universal health coverage effectively protects patients from this financial risk of ill health; however, in the US, insured patients typically bear 20-30% of treatment costs OOP.[15,16] The financial toxicity resulting from these OOP expenditures adversely affects treatment adherence specifically for the poor; ultimately increasing inequity and mortality rates.[17] Meanwhile, the pharmaceutical industry argues high prices are necessary to fund innovative R&D projects as it costs beyond $2.8 billion to bring a new drug to market.[18] However, this argument stands in contrast to revised R&D estimates of $1.3 billion, which are not even linked to a drug's price and are often substantially lower than its revenues; thereby generating excess profit margins for pharmaceutical companies.[3,20–22] Furthermore, there is substantial uncertainty around a link between high prices and truly innovative medicines.[112,113]

Although this public debate has been ongoing for more than 20 years in the US, there remains a lack of transparency and regulation in the pricing of novel drugs. Only recently, US Congress passed the IRA, which – for the first time in US history – grants the government the power to negotiate prices directly with manufacturers for the 10 highest spending prescription drugs starting in 2025.[23] The negotiation will be extended to a total of 60 drugs until 2029.

Drug pricing is further complicated by considering the value of multiple clinical indications. The FDA first approves a drug in its *original* indication. Thereafter, a company may submit additional evidence to extend a drug's marketing authorization to *supplemental* indications. These supplemental approvals are particularly important given that all top ten grossing drugs (2019) were sold across more than one indication and especially oncology drugs are regularly

commercialized across multiple indications.[10,73] Supplemental indications have, therefore, become an important source of pharmaceutical innovation. Patients benefit from the extension of drug patents to new indications and uses by increasing the availability of treatment options. However, the clinical benefit, clinical trial evidence, regulatory approval, and clinical development timelines differ for original and supplemental indications.[38,40,73,101,102] Oncology drugs were shown to first receive approval for "rare diseases that offer significant QALY gains and [are] then extended to indications that deliver lower QALY gains to more eligible patients" (Michaeli et al., 2022, p. 767).[38] This "orphan-first" strategy permits pharmaceutical companies to anchor drug prices to orphan indications and then transfer these high prices to non-orphan diseases. As a result of single drug prices across all indications, yet lower QALY gains for supplemental than original indications, supplemental indications' are often assessed to be not cost-effective. In the US, increasing ICERs were observed for original relative to second and third indications (188,382 vs. 513,249 vs. 515,144 USD per QALY).[38] Consequently, Bach proposed an indication-specific pricing methodology that distinctly prices a drug based on each indication's differential value.[41] Whilst European countries account for a drug's indication-specific value through volume-weighted-average prices, differential discounts, MEAs, and/or by restricting coverage,[11,36,38,40,49] to date no such policy has been implemented in the US.[11,50] Therefore, we hypothesize that in the US drug prices are currently anchored to the original FDA-approved indication and thereby do not adequately reflect the value, unmet needs, and innovation offered by supplemental indications.

Previous studies routinely described treatment costs of cancer drug prices, correlated prices to efficacy, safety, and quality of evidence,[110,112–118] evaluated price changes over time,[114,119–122] compared prices across countries,[113,117,118,120] and correlated prices to disease prevalence.[123–125] However, comprehensive evidence evaluating the relation between drug prices and efficacy,

clinical trial evidence, and epidemiology data is missing. The objective of this study is to identify drug-, indication-, clinical trial-, and epidemiology-specific factors associated with cancer drug prices in the US. This is also the first study that distinctly analyzes drug prices for original and supplementary FDA-approved indications.

3.4 Data and methods

3.4.1 Sample selection

All new cancer drugs with initial FDA approval between 1st January 2003 and 1st January 2022 were identified in the Drugs@FDA database. Both NDAs and BLAs were included. The sample was then restricted to on-patent anti-cancer drugs, thereby excluding generics, biosimilars, supportive cancer treatments, and diagnostic agents. Gene and cell therapies were included. For each drug, we then identified all supplemental New Drug Applications (sNDA) and supplemental Biologic License Applications (sBLA) anti-cancer indications approved by the FDA until 1st January 2022 in the Drugs@FDA database (Figure 18). 1st January 2022 was the cut-off date since data collection was conducted in 2022.

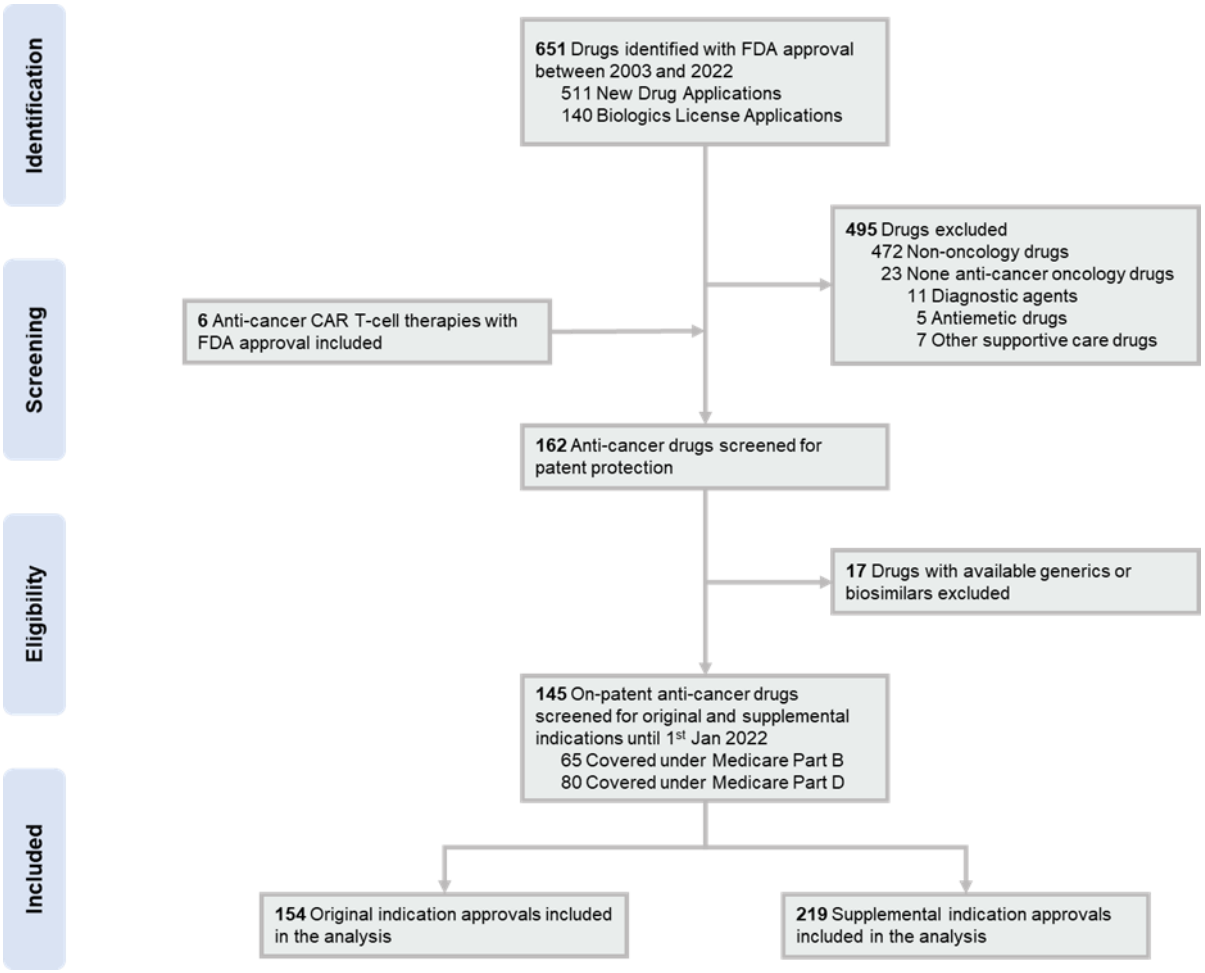


Figure 18: Flow diagram of new cancer drugs and their original and supplemental indications included in the analysis

Notes: We identified all FDA drug approvals between 1st January 2003 and 1st January 2022 in the Drugs@FDA database. Thereafter, the sample was restricted to on-patent anti-cancer drugs, thereby excluding generics, biosimilars, supportive cancer treatments, and diagnostic agents. CAR T-cell therapies were included. For each drug, we further identified all supplemental indications approved by the FDA until 1st January 2022. Consequently, approved treatments were categorized into original and supplemental indications.

Abbreviations: CAR, chimeric antigen receptor; FDA, US Food and Drug Administration.

3.4.2 Data collection

Data on drug, indication, clinical trial, and epidemiologic characteristics were collected by two independent reviewers (Table 3). Data collection adhered to peer-reviewed guidelines for evidence synthesis from FDA approval documents.[103,104] The first reviewer (D.T.M.) extracted drug, indication, and clinical trial evidence from FDA labels. The extracted information was cross-checked by the second reviewer (T.M.) based on data found on clinicaltrial.gov and peer-

reviewed publications associated with each trial's NCT. Reviewers solved any inconsistencies in consensus or by consulting an independent experienced oncologist (T.B).

Drug characteristics

Data on drug, indication, and clinical trial evidence were obtained from FDA labels, clinicaltrials.gov, and associated peer-reviewed publications.[126,127] Drugs were categorized by their number of indications, innovativeness/novelty, mechanism of action, and molecule type. Each drug's innovativeness/novelty was assessed based on the World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) code. Drugs with an ATC code ending in 1 were considered "first-in-class", all others being "not-first-in-class". For drugs with ambiguous ATC codes (e.g. ATC categories with a "X"), two independent reviewers (D.T.M. and T.M.) assessed the drug's novelty. Drugs were classified by mechanism of action (cytotoxic chemotherapy vs. targeted therapy vs. immune-regulators) according to information found on the Drug Bank. Targeted agents include anti-hormonal compounds and therapeutics such as TKIs, whilst immune-regulators include immune-modulators, CAR T-cell therapies, and immune-antibodies, comprising immune-checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 inhibitors. The Drug Bank was further accessed to categorize each drug's product type (small molecules vs. antibodies vs. antibody-drug conjugates vs. others).

Indication characteristics

For each indication, we obtained information on the FDA approval date, treatment type (monotherapy vs. combination therapy), disease type (solid vs. hematologic), companion biomarker status, and line of therapy (first-line vs. advanced-line). We differentiated indications according to FDA approval type (standard vs. accelerated approval). For accelerated approvals final FDA decisions (conversion/verified benefit vs. pending assessment vs. not converted/withdrawn indication) were traced until 31st March 2023.

Clinical trial characteristics

We noted the pivotal trial's number of enrolled patients, phase (phase 1 or 2 vs. phase 3), design (RCTs vs. other), blinding (open-label/single-blind vs. double-blind), and treatment outcomes for each indication. For indications supported by multiple clinical trials, we selected the trial that was of the highest phase or with the most number of enrolled patients. The pivotal trial design category "other" includes single-arm trials, dose-comparison trials, and non-randomized trials.

Clinical benefit

For RCTs, we noted each drug's clinical benefit in relation to the control arm. First, we extracted the absolute benefit in OS/PFS. Then, we calculated the drug's relative benefit in relation to the control arm expressed as OS/PFS percentage. Lastly, as an alternative measure for clinical benefit, we noted HRs for OS/PFS.

Cancer epidemiology

Epidemiologic data associated with each indication were obtained from two separate sources. The annual disease incidence, disease prevalence, and DALYs comprised of years lived with disability (YLD) and years of life lost (YLL) were retrieved from the Global Burden of Disease study for the US population in 2019.[128] DALYs, alongside YLD and YLL, were considered as a measurement for the disease burden. We calculated DALYs, YLD, and YLL per person to prevent confounding by disease incidence, e.g. the influence of rare diseases. Epidemiologic data were obtained for cancer entities, e.g. breast cancer or melanoma. Therefore, these data did not differentiate between distinct tumor subgroups and lines of therapy.

We accessed the National Cancer Institute's cancer drug list to identify the number of available treatment options for each indication as a proxy for competition on the treatment level.[129] For

each cancer entity data on 5-year survival rates were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.[130] 5-year survival rates were considered as a measurement of disease severity.

Drug prices

Drug prices were collected from two distinct data sources coherent with a methodology employed in previous studies.[116,119,131] For drugs covered by Medicare Part B, prices were extracted from the CMS files for the first quarter of 2023. For drugs covered by Medicare Part D, prices were obtained from Medicare's plan finder tool in January 2023. To ensure comparability with prior studies,[116,131] we collected Part D price data using the following steps. First, we searched the plan finder tool for each drug's name. For each indication, we then selected the appropriate dosing regimen (see below). Thereafter, we selected the lowest-cost pharmacy for patients living in New York City (ZIP code 10065). We then chose the "Humana Basic Rx Plan (PDP)" and noted the "Full Cost of Drug", e.g. the retail price. For drugs covered under both Medicare Part B and D, we used Part B prices. The collected treatment costs are an approximation of drug list prices. Patients' OOP resulting from deductibles, premiums, co-payments, and coverage gaps may vary depending on the insurance plan.

For each indication, monthly treatment costs were calculated for an average adult with a body surface area of 1.7 m^2 weighing 70 kg with normal renal and hepatic function.[115–117,119,131] The average monthly treatment costs of indication regimens were calculated based on indication-specific dosing schedules. Dosing schedules were obtained from each drug indication's FDA label. For regimens entailing different drug doses for initiation, consolidation, and/or maintenance treatment, average monthly costs were calculated for the median treatment duration defined in the respective pivotal trial. For indications with multiple dosing schedules, the dosing schedule resulting in the lowest treatment costs was selected. Calculated treatment costs therefore only include a drug's price without any supportive treatment, doctor's fees, administrative

costs, or delivery expenses. The assumptions and two examples for the monthly treatment cost calculations are detailed in Table 54.

Monthly instead of episode treatment costs were calculated for several medical and economic reasons. First, in previous literature, most articles calculated monthly treatment costs[112,113,115,116,119,120,122,132] rather than episode treatment costs.[110,117] Among articles with episode treatment costs, one article[110] found a significant relationship between drugs' benefits and episode treatment costs for several following reasons. The timeframe to calculate episode treatment costs is clinically defined by the DoR or the time until tumor progression. Both measures vary widely based on the underlying tumor disease, e.g. patients with pancreatic cancer may only receive a new agent for a few weeks up to months, whereas patients with multiple myeloma or prostate cancer may receive the new drug for several months or even years. Accordingly, a larger absolute benefit for new drugs is measured for drugs treating prostate cancer or multiple myeloma rather than pancreatic cancer given that these cancers have distinct and greatly varying pathologic growth and progression rates. Further, the new agent, therefore, also has more time to exert its anti-cancer effect on the tumor. Out of these reasons, the relationship between episode treatment costs and new drugs' clinical benefit is confounded by the underlying disease. Second, in the previous chapter we showed that large heterogeneity exists between trials and, even more concerningly, between patients in tumor response and tumor progression. This is particularly highlighted by the clinical trial's Kaplan-Meier survival curves. Although one may measure a median PFS or DoR benefit, the benefit for each patient is represented by the underlying survival curve. Furthermore, the length of the clinical drug use may vary from clinical trial results, particularly given that the introduction of prior-line/later-line treatments influences the examined drug's clinical benefit and treatment duration. In addition, physicians usually prescribe time-unlimited anti-cancer agents for a pre-defined period of 2-3 months. Thereafter, stagings are performed with computed tomography or magnetic resonance imaging scans to

decide if the treatment should be continued or changed. Henceforth, in clinical practice, monthly rather than episode treatment costs are considered as the relevant measure to evaluate drug prices.

3.4.3 Statistical analysis

Descriptive statistics examine the sample's baseline characteristics. Thereafter, the association between collected variables and monthly treatment costs was analyzed in a series of linear univariate ordinary least squares (OLS) regression analyses reporting coefficients (β), 95% confidence intervals (CI), and R^2. For all regression models, indication-specific monthly treatment costs were defined as the dependent variable.

We evaluated the association between the dependent variable and the following independent variables in separate univariate OLS regressions: clinical benefit, number of indications, innovativeness/novelty, mechanism of action, molecule type, treatment type, cancer disease, companion biomarker, line of therapy, as well as the pivotal trial's number of enrolled patients, trial phase, trial design, trial blinding, as well as the treated disease's incidence, prevalence, DALYs, YLD, YLL, and number of competitors. Treatment costs, the pivotal trial's number of enrolled patients, and disease incidence were transformed with the natural logarithm to account for their right-skewed distribution (Table 10). Distinct regressions were conducted for original and supplemental indication approvals. For regressions analyzing supplemental indications, standard errors are corrected for clustering at the drug level.

Variable	N	Mean	Median	P25	P75	SD	Skewness
Monthly treatment cost, $	372	24,444	16,013	14,648	22,348	30,671	564
Improvement in median OS, %	95	0.35	0.26	0.16	0.38	0.32	-0.15
Improvement in median PFS, %	155	0.83	0.61	0.27	1.04	0.91	-0.50
No. patients enrolled in pivotal trial	373	395	270	106	565	431	9
Incidence per 100,000 US inhabitants	366	40.0	9.8	3.9	67.6	99.5	0.0
Prevalence per 100,000 US inhabitants	365	165.4	67.3	13.2	117.8	260.4	0.1
DALY per person	359	10.1	10.0	5.5	16.4	5.8	0.0
YLD per person	359	0.5	0.5	0.3	0.7	0.2	0.0
YLL per person	359	9.6	9.3	4.8	16.2	5.9	0.0
5-year survival rate, %	367	0.65	0.72	0.36	0.91	0.27	0.07
No. of available treatment options	359	10.1	10.0	5.5	16.4	5.8	0.0

Table 10: Distribution of interval-scaled variables

Abbreviations: DALYs, disability-adjusted life years; OS, overall survival; PFS, progression-free survival; SD, standard deviation; YLD, year lived with disability; YLL, years of life lost.

We conducted a variety of sensitivity analyses to scrutinize the robustness of our results. First, we considered different measures of clinical benefit (e.g. relative benefit, absolute monthly benefit, and HRs). Second, all regression analyses were re-conducted with models adjusting for FDA approval year. Third, median monthly treatment costs were compared across the afore-mentioned variables.

Furthermore, we calculated the price per LY gained for original and supplemental indications based on OS and PFS trial data. A higher price per LY gained indicates a worse cost-to-benefit ratio for indications. We hypothesize that supplemental indications have a higher cost-to-benefit ratio, e.g. a higher price per LY gained, than original indications. This hypothesis was tested by comparing indications price per LY gained using medians and in a fixed-effects regression analysis.

Data were stored in Microsoft Excel (Microsoft Corp) and analyzed with Stata software, version 14.2 (StataCorp LLC, College Station, TX). Two-tailed p-values below 0.05 were considered significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline when applicable.[133]

3.5 Results

3.5.1 Sample overview

The analyses entail 145 new cancer drugs approved by the FDA across a total of 373 indications. Of these, 154 were original and 219 supplemental indication approvals. Drugs were priced at $24,444 per month on average (median $16,013; IQR 14,648 to 22,348). We observed rising drug prices for more recent FDA-approved indications (Figure 19). Out of 145 drugs, 54 (37%) were first-in-class, and 95 (66%) were small molecules (Table 11). Fourteen (10%) drugs acted via a cytotoxic, 96 (66%) via a targeted, and 35 (24%) via a immune-regulatory mechanism of action. Seventy-four (51%) drugs were approved across multiple indications. Only 206 (55%) indications were approved on the basis of phase 3 trials. Clinical trials were mostly open-label or single-blind (287 [77%]) and enrolled a median of 270 (IQR 106 to 565) patients. Across indications with available data from RCT (216 [58%]), new cancer drugs improved OS by a median of 2.80 months (IQR, 1.97 to 4.60 months) and PFS by 3.30 months (IQR, 1.50 to 5.58 months) or by 26% (IQR 16 to 38) and 61% (IQR 27 to 104) compared to control, respectively.

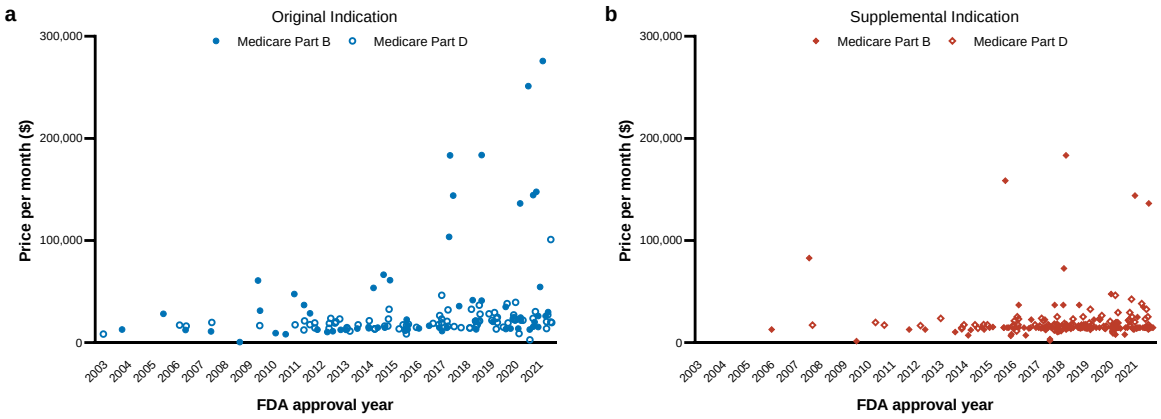


Figure 19: Drug prices for original (a) and supplementary (b) cancer indications approved by the FDA

Notes: The analysis entails all new cancer drugs with FDA approval for original and supplemental indications between 2003 and 2022. Drug prices were obtained from CMS files for drugs covered under Medicare Part B and from the publicly available plan finder tool for drugs covered under Medicare Part D. Monthly treatment costs were calculated using indication-specific dosing regimens retrieved from each drug's FDA label. All costs were calculated for January 2023.

Abbreviations: CMS, Centers for Medicare and Medicaid Services; FDA, US Food and Drug Administration.

Variable	No.	(%)
(A) Drug characteristics		
No. of indications		
Single-indication	71	(49.0)
Multi-indication	74	(51.0)
Innovation status		
Not-first-in-class	91	(62.8)
First-in-class	54	(37.2)
Mechanism of action		
Cytotoxic chemotherapy	14	(9.7)
Targeted agents	96	(66.2)
Immune-regulators	35	(24.1)
Molecule Type		
Small-molecule	95	(65.5)
Antibody	29	(20.0)
Other	21	(14.5)
Total no. of drugs	**145**	**(100.0)**
(B) Indication characteristics		
Treatment type		
Combination	127	(34.0)
Monotherapy	246	(66.0)
Disease		
Solid	248	(66.5)
Hematologic	125	(33.5)
Biomarker		
No	230	(61.7)
Yes	143	(38.3)
Line of therapy		
First-line	170	(45.6)
Advanced-line	203	(54.4)
Accelerated approval		
No	247	(66.2)
Yes	126	(33.8)
Converted	55	(43.7)
Pending	54	(42.9)
Not converted / withdrawn	17	(13.5)
(C) Pivotal clinical trial characteristics		
No. enrolled patients, median (IQR)	270.0	(106-565)
Trial Phase		
Phase 1	21	(5.6)
Phase 2	146	(39.1)
Phase 3	206	(55.2)
Trial design		
Other	157	(42.1)
Randomized-controlled trial	216	(57.9)
Trial blinding		
Open label or single-blind	287	(76.9)
Double blind	86	(23.1)
(D) Cancer epidemiology		
Incidence per 100,000 US inhabitants, median (IQR)	9.8	(3.9-67.6)
Prevalence per 100,000 US inhabitants, median (IQR)	67.3	(13.2-117.8)
DALY per person, median (IQR)	10.0	(5.5-16.4)
YLD per person, median (IQR)	0.5	(0.3-0.7)
YLL per person, median (IQR)	9.3	(4.8-16.2)
5-year survival rate, percentage (IQR)	72.2	(36.0-90.7)
Available treatment options, median (IQR)	10.0	(5.5-16.4)
Total no. of indications	**373**	**(100.0)**

Table 11: Descriptive statistics for the entire sample

Abbreviations: DALYs, disability-adjusted life years; IQR, interquartile range; YLD, year lived with disability; YLL, years of life lost.

3.5.2 Clinical benefit

Drug prices were associated to improvements in OS for original (β=0.28, 95%CI 0.02 to 0.54, p=0.037), yet not for supplemental indications (β=0.13, 95%CI -0.46 to 0.72, p=0.656) (Figure 20). Accordingly, prices were associated with improvements in PFS for original (β=0.16, 95%CI 0.07 to 0.25, p=0.001) and supplemental indications (β=0.12, 95%CI 0.04 to 0.21, p=0.006). No consistent significant association was observed when measuring OS and PFS benefit in absolute months, as hazard ratios, and as a binary variable (Figure 21, Figure 22, and Table 12).

Across all indications, the median price per LY gained amounted to $176,807 (IQR: $154,439 to 209,799) and the median price per PFS year gained amounted $177,095 (IQR: $162,591 to 231,415). There was no significant difference in the median price per LY gained ($193,534 vs. 176,807, p=0.092) or median price per PFS gained ($187,766 vs. 177,095, p=0.628) for original relative to supplemental indications.

Table 13 shows the fixed-effects regression analysis of indication approval type on the price per LY gained. Similar to Howard et al., LYs gained were calculated based on OS and PFS data with a separate dummy variable for the reported endpoint. There was no significant association between the FDA indication approval type, e.g. original or supplemental, and the price per LY gained (ß=-0.13, 95%CI -0.35 to 0.09, p=0.256).

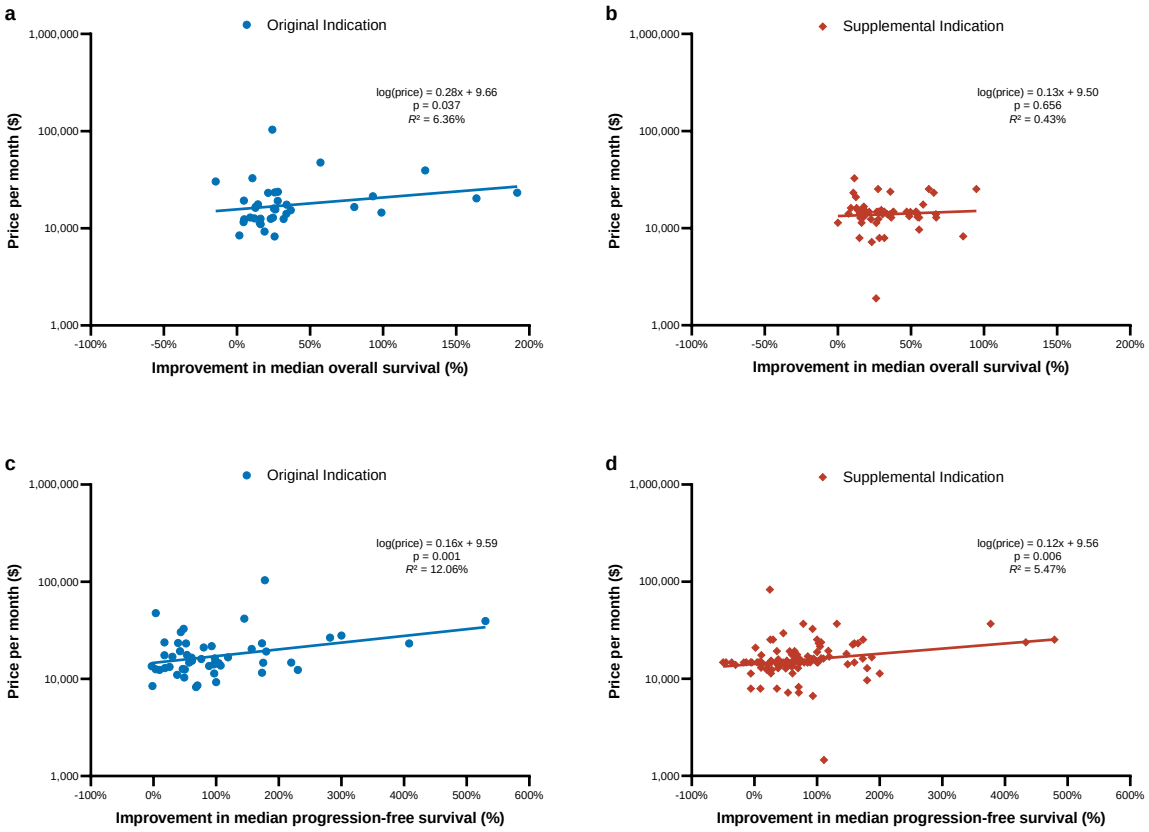


Figure 20: Association between OS/PFS improvement (%) and drug prices for original and supplementary FDA indication approvals

Notes: Graphs a and c illustrate the regression analyses of cancer drugs' overall / progression-free survival benefit and prices for original FDA approvals. In contrast, graphs b and d conduct the same analyses considering only supplemental indications. Monthly treatment costs were calculated for January 2023 based on Medicare Part B and D prices using indication-specific dosing regimens retrieved from each drug's FDA label.

Abbreviations: FDA, US Food and Drug Administration; OS, overall survival; PFS, progression-free survival.

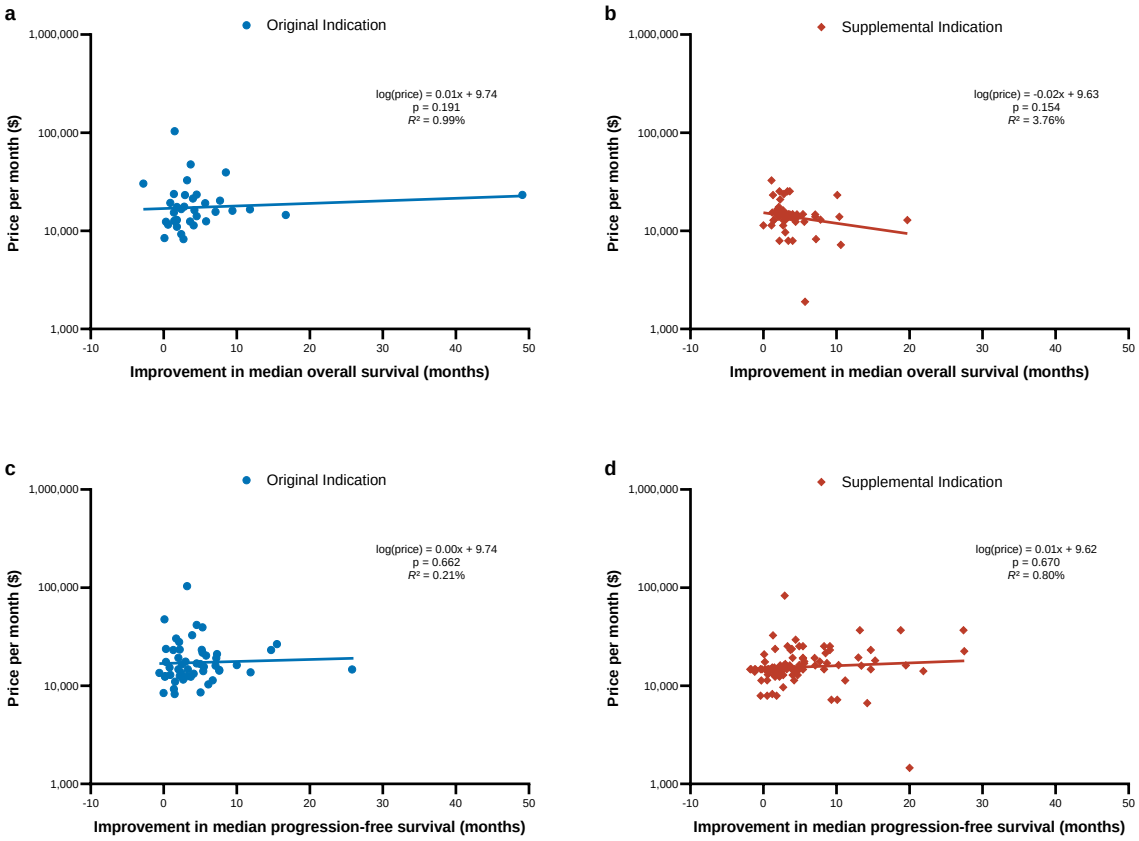


Figure 21: Association between OS/PFS improvement (months) and drug prices for original and supplementary FDA indication approvals

Notes: Graph a and c illustrate the regression analyses of cancer drugs' OS/PFS benefit and prices for original FDA approvals. In contrast, graphs b and d conduct the same analyses considering only supplementary indications. Monthly treatment costs were calculated for January 2022 based on Medicare Part B and D prices using indication-specific dosing regimens retrieved from each drug's FDA label.

Abbreviations: FDA, US Food and Drug Administration; OS, overall survival; PFS, progression-free survival.

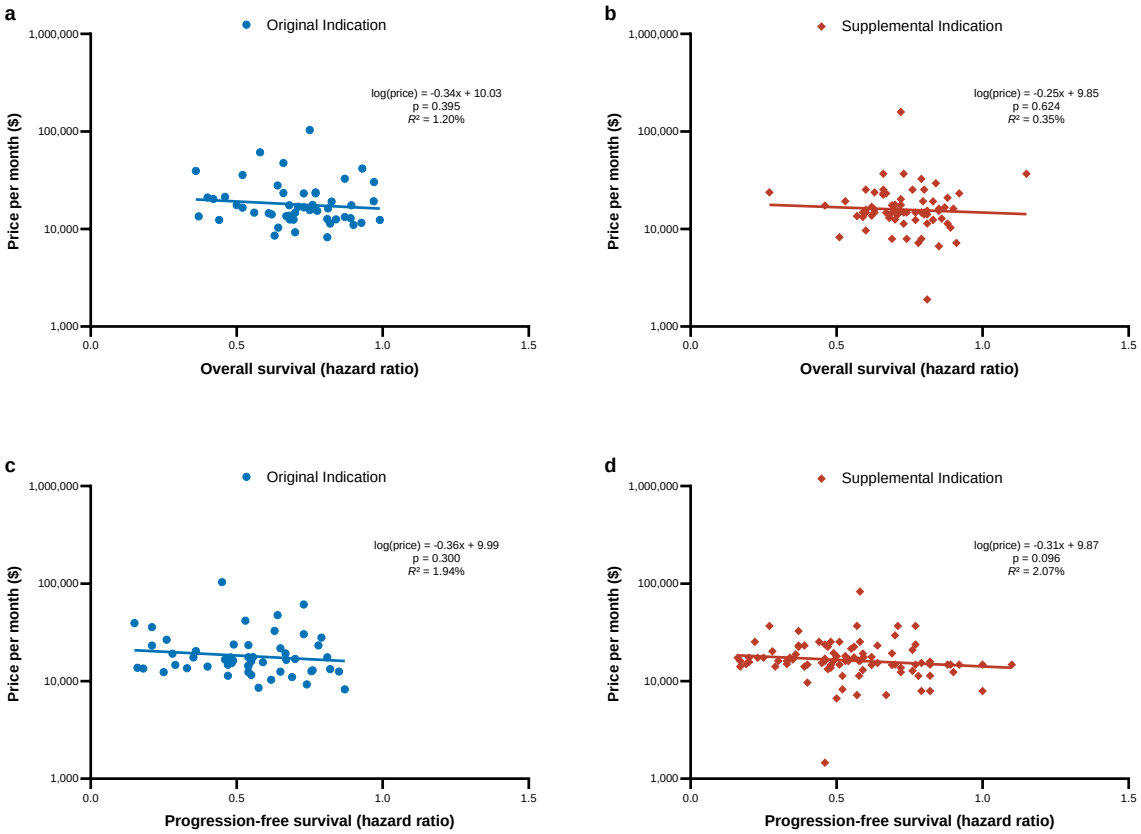


Figure 22: Association between OS/PFS benefit (hazard ratios) and drug prices for original and supplementary FDA indication approvals

Notes: Graph a and c illustrate the regression analyses of cancer drugs' OS/PFS benefit and prices for original FDA approvals. In contrast, graphs b and d conduct the same analyses considering only supplementary indications. Monthly treatment costs were calculated for January 2022 based on Medicare Part B and D prices using indication-specific dosing regimens retrieved from each drug's FDA label.

Abbreviations: FDA, US Food and Drug Administration; OS, overall survival; PFS, progression-free survival.

	Original Indication				Supplemental Indication			
	β [a]	[95% CI]	*P*	R^2	β [a]	[95% CI]	*P*	R^2
Improvement in median survival, %								
OS	0.28	[0.02 to 0.54]	*0.037*	6.36%	0.13	[-0.46 to 0.72]	*0.656*	0.43%
PFS	0.16	[0.07 to 0.25]	*0.001*	12.06%	0.12	[0.04 to 0.21]	*0.006*	5.47%
Improvement in median survival, months								
OS	0.01	[0.00 to 0.02]	*0.191*	0.99%	-0.02	[-0.06 to 0.01]	*0.154*	3.76%
PFS	0.00	[-0.02 to 0.03]	*0.662*	0.21%	0.01	[-0.02 to 0.04]	*0.670*	0.80%
Hazard ratio								
OS	-0.34	[-1.14 to 0.46]	*0.395*	1.20%	-0.25	[-1.27 to 0.77]	*0.624*	0.35%
PFS	-0.36	[-1.04 to 0.33]	*0.300*	1.94%	-0.31	[-0.68 to 0.06]	*0.096*	2.07%
Significant improvement in OS?								
No	Ref.				Ref.			
Yes	0.23	[0.00 to 0.46]	*0.050*	1.70%	0.05	[-0.10 to 0.20]	*0.488*	0.17%

Table 12: Series of univariate regression analysis of survival benefit on cancer drug prices

[a] For the analysis of supplementary indications, standard errors are corrected for clustering at the molecule level.

Abbreviations: OS, overall survival; PFS, progression-free survival.

	Log(Price per LY gained)		
	ß	**[95% CI]**	***P Value***
FDA approval type			
Original indication	Ref.		
Supplemental indication	-0.13	[-0.35 to 0.09]	*0.256*
Endpoint type			
OS	Ref.		
PFS	-0.05	[-0.12 to 0.02]	*0.182*
N	160		
Within R^2	7.52%		
Between R^2	1.16%		
Overall R^2	2.41%		

Table 13: Fixed-effects regression of FDA approval type on price per life years gained

Notes: The table presents the results of a fixed-effects regression analysis of the FDA indication approval type on the price per LY gained. LY gained were calculated based on OS and PFS data. To account for the differential nature of these endpoints and additional dummy variable indication the measured trial endpoint was included in the model. The model accounts for heteroskedastic standard errors. Results suggest that supplemental indications do not have a higher price per LY gained.

Abbreviations: FDA, US Food and Drug Administration; LY, life year; OS, overall survival; PFS, progression-free survival.

3.5.3 Drug characteristics

Initial indication's prices were 26% (95%CI -1 to 60, p=0.057) non-significantly higher for first-in-class compared to not-first-in-class drugs and 176% (95%CI 79 to 324, p<0.001) greater for gene and cell therapies, radionuclides, and enzymes relative to small-molecules (Table 14). The observed associations were of smaller magnitude and lower explanatory power for supplemental indication prices.

	Original Indication				Supplemental Indication			
	β [a]	[95% CI]	*P*	R^2	β [a]	[95% CI]	*P*	R^2
(A) Drug characteristics								
No. of indications								
Single-indication	Ref.							
Multi-indication	-10.81%	[-30.52 to 14.48]	*0.367*	0.58%				
Innovation status								
Not-first-in-class	Ref.				Ref.			
First-in-class	25.91%	[-0.71 to 59.68]	*0.057*	2.23%	13.25%	[-7.94 to 39.33]	*0.235*	1.47%
Mechanism of action								
Cytotoxic chemotherapy	Ref.				Ref.			
Targeted agents [b]	-6.83%	[-44.08 to 55.25]	*0.785*	8.93%	41.96%	[-17.68 to 144.79]	*0.204*	
Immune-regulators [c]	59.45%	[-10.4 to 183.77]	*0.112*		37.96%	[-21.38 to 142.09]	*0.258*	0.46%
Molecule Type								
Small-molecule	Ref.				Ref.			
Antibody	12.97%	[-15.13 to 50.37]	*0.401*		-19.68%	[-28.96 to -9.19]	*0.001*	
Other [d]	175.83%	[79.3 to 324.31]	*0.000*	21.14%	52.44%	[-38.75 to 279.39]	*0.360*	10.51%
(B) Indication characteristics								
FDA approval year	5.61%	[2.38 to 8.95]	*0.001*	9.33%	2.40%	[-1.95 to 6.94]	*0.280*	1.57%
Treatment type								
Combination	Ref.				Ref.			
Monotherapy	7.99%	[-16.79 to 40.14]	*0.561*	0.18%	16.34%	[-0.36 to 35.83]	*0.055*	2.13%
Disease								
Solid	Ref.				Ref.			
Hematologic	62.04%	[27.68 to 105.66]	*0.000*	10.18%	19.96%	[-7.75 to 55.99]	*0.171*	2.53%
Biomarker								
No	Ref.				Ref.			
Yes	-11.77%	[-28.63 to 9.07]	*0.245*	0.67%	-14.07%	[-27.88 to 2.39]	*0.089*	2.06%
Line of therapy								
First-line	Ref.				Ref.			
Advanced-line	31.35%	[1.57 to 69.85]	*0.038*	2.99%	9.20%	[-3.81 to 23.98]	*0.171*	0.73%
Accelerated approval								
No	Ref.				Ref.			
Yes	3.54%	[-18.05 to 30.81]	*0.769*	0.05%	1.55%	[-12.3 to 17.57]	*0.835*	0.02%
Converted	Ref.				Ref.			
Pending	30.88%	[-1.85 to 74.53]	*0.066*		24.96%	[0.37 to 55.57]	*0.047*	
Not converted / Withdrawn	-23.81%	[-40.51 to -2.44]	*0.032*	12.33%	-5.49%	[-13.68 to 3.48]	*0.211*	12.54%
(C) Pivotal clinical trial characteristics								
Log(Enrolled patients) [e]	-0.3136	[-0.4388 to -0.1884]	*0.000*	15.14%	-0.0959	[-0.1669 to -0.025]	*0.009*	4.04%
Trial Phase								
Phase 1 or 2	Ref.				Ref.			
Phase 3	-30.68%	[-45.49 to -11.86]	*0.003*	5.87%	-17.03%	[-30.63 to -0.77]	*0.041*	3.04%
Trial design								
Other [f]	Ref.				Ref.			
Randomized controlled	-35.03%	[-48.33 to -18.31]	*0.000*	8.16%	-19.16%	[-33.74 to -1.37]	*0.036*	3.71%
Trial blinding								
Open-label/single-blind	Ref.				Ref.			
Double-blind	-21.59%	[-35.80 to -4.24]	*0.017*	1.76%	3.93%	[-10.62 to 20.83]	*0.612*	0.10%
(D) Cancer epidemiology								
Log(Incidence) [e,g]	-0.2055	[-0.2786 to -0.1325]	*0.000*	23.30%	-0.0604	[-0.1069 to -0.0138]	*0.012*	3.81%
Log(Prevalence) [e,g]	-0.2118	[-0.2851 to -0.1386]	*0.000*	26.43%	-0.0420	[-0.091 to 0.007]	*0.092*	1.85%
DALYs per person	5.67%	[3.41 to 7.99]	*0.000*	18.17%	0.21%	[-1.27 to 1.72]	*0.777*	0.06%
YLD per person	-14.11%	[-51.02 to 50.61]	*0.593*	0.14%	35.67%	[-15.41 to 117.62]	*0.202*	1.26%
YLL per person	5.58%	[3.33 to 7.87]	*0.000*	17.92%	0.17%	[-1.29 to 1.66]	*0.813*	0.04%
5-year survival	-45.00%	[-64.71 to -14.28]	*0.009*	3.99%	22.51%	[-7.85 to 62.89]	*0.159*	1.27%
No. of competitors	-0.24%	[-0.98 to 0.50]	*0.671*	0.21%	-0.01%	[-0.59 to 0.57]	*0.967*	0.00%

Table 14: Series of univariate regression analyses of collected variables on cancer drug prices

[a] For the analysis of supplementary indications, standard errors are corrected for clustering at the molecule level.
[b] Targeted agents include anti-hormonal compounds and therapeutics such as tyrosine kinase inhibitors.
[c] Immune-regulators include immune-modulators, CAR T-cell therapies, and immune-antibodies, including immune-checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 inhibitors.
[d] The category "other" includes antibody-drug conjugates, enzymes, radio-therapeutics, gene therapies, and cell therapies.
[e] For the number of enrolled patients and disease incidence/prevalence, coefficients should be interpreted as elasticities. For example, a 1% increase in disease incidence corresponds to a -0.21% decrease in drug prices for original indications.
[f] The category "other" includes single-arm, non-randomized, and dose comparison trials.
[g] Disease incidence/prevalence rate per 100,000 US inhabitants.

Abbreviations: CAR, chimeric antigen receptor; CTLA-1, cytotoxic T-lymphocyte-associated protein 4; DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; YLD, years lived with disability; YLL, years of life lost.

Indication characteristics

Figure 19 shows that original indications' prices in 2023 were significantly associated with the year of FDA approval (6% per year, 95%CI 2 to 9, p=0.001). Original indications treating hematologic cancers were priced 62% (95%CI 28 to 106, p<0.001) higher than those treating solid cancers. We observed 31% (95%CI 2 to 70, p=0.036) greater treatment costs for advanced-line compared to first-line treatments. However, the association with disease type (20%, 95%CI -8 to 56, p=0.171) and line of therapy (9%, 95%CI 4 to 24, p=0.171) for supplemental indications were not significant.

Out of 373 indications, 247 (66%) received standard and 126 (34%) received accelerated approval by the FDA. There was no difference in prices of drugs receiving standard relative to accelerated approval. Out of the 126 accelerated approvals, 55 (44%) were converted to full approvals, 54 (43%) have pending confirmatory trials, and 17 (14%) were not converted/withdrawn. For original indications, withdrawn indications were priced -24% (95%CI -41 to -2, p=0.032) lower than those converted to full approvals. This association was not consistent for supplemental indications.

Clinical trial evidence

The pivotal trial's number of enrolled patients was significantly associated with the original indications' cost (Figure 23). A 1% increase in the number of enrolled patients corresponds to a -0.31% (95%CI -0.44 to -0.19, p<0.001) decrease in drug prices. The elasticity was -0.10 for supplemental indications (95%CI -0.17 to -0.03, p=0.009). Original indications supported by phase 3 trials cost -31% (95%CI -45 to -12, p=0.003) less than those approved based on phase 1 or 2 trials. Similarly, prices were -35% (95%CI -48 to -18, p<0.001) lower for original indications approved based on RCTs. Both associations were of smaller magnitude and had lower explanatory power for supplemental indications.

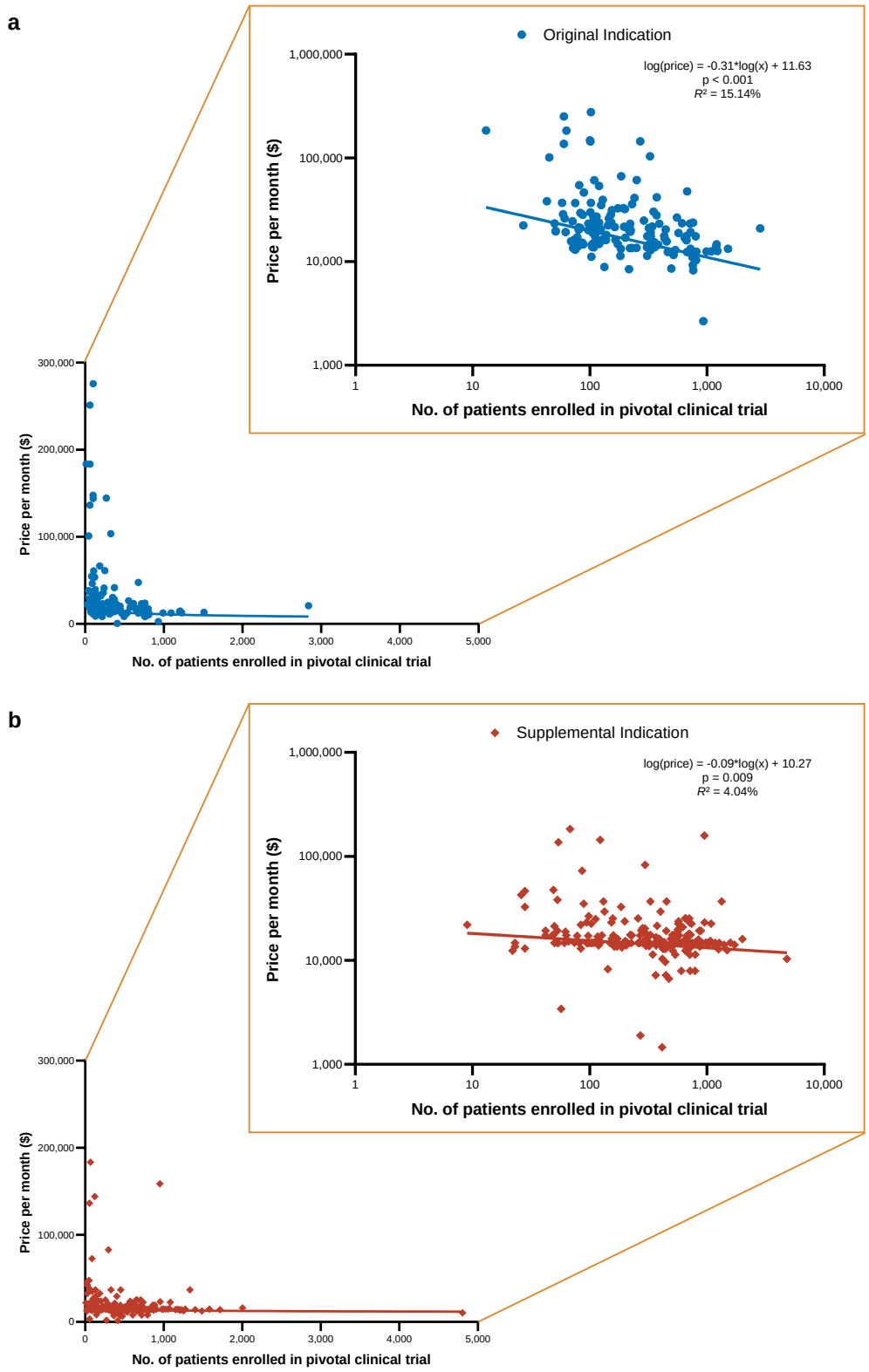


Figure 23: Association between the number of patients enrolled in the pivotal trial and drug prices for original (a) and supplementary (b) FDA indication approvals

Notes: The number of enrolled patients in the pivotal trial leading to FDA approval was obtained from FDA drug labels for each indication. Monthly treatment costs were calculated for January 2022 based on Medicare Part B and D prices using indication-specific dosing regimens retrieved from each drug's FDA label.

Abbreviations: FDA, US Food and Drug Administration.

Cancer epidemiology

Drug prices were negatively associated with disease incidence (Figure 24) and prevalence rates (Figure 25). A 1% increase in disease incidence corresponds to a -0.21% (95%CI -0.28 to -0.13, $p<0.001$) decrease in drug prices. The disease prevalence elasticity was -0.21 (95%CI -0.29 to -0.14, $p<0.001$). These elasticities were of smaller magnitude, had lower explanatory power, and were not significant for supplemental indications.

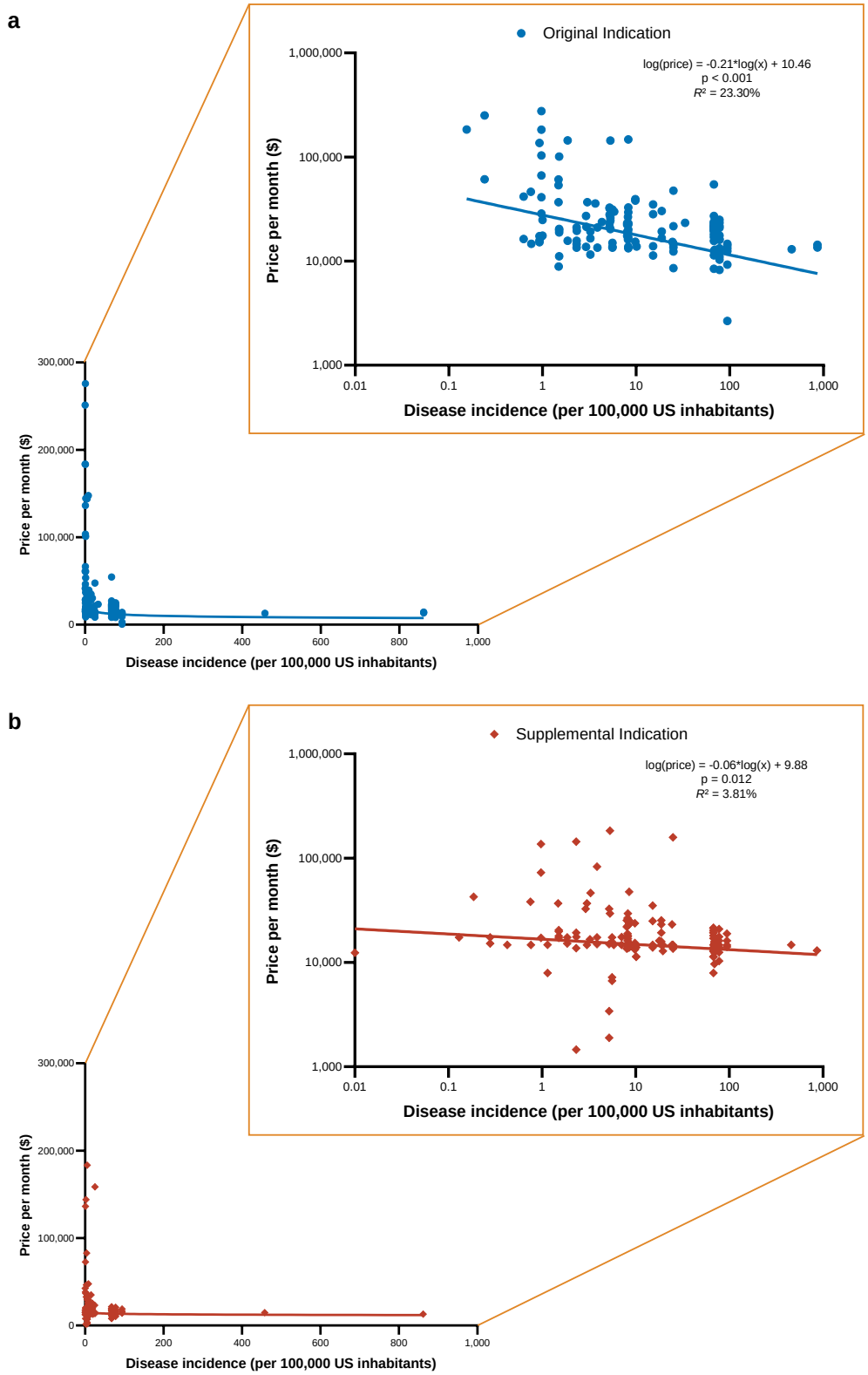


Figure 24: Association between disease incidence and drug prices for original (a) and supplementary (b) FDA indication approvals

Notes: Disease incidence rates for the 2019 US population were retrieved from the Global Burden of Disease study and matched to indications based on FDA labels. Monthly treatment costs were calculated for January 2022 based on Medicare Part B and D prices using indication-specific dosing regimens retrieved from each drug's FDA label.

Abbreviations: FDA, US Food and Drug Administration.

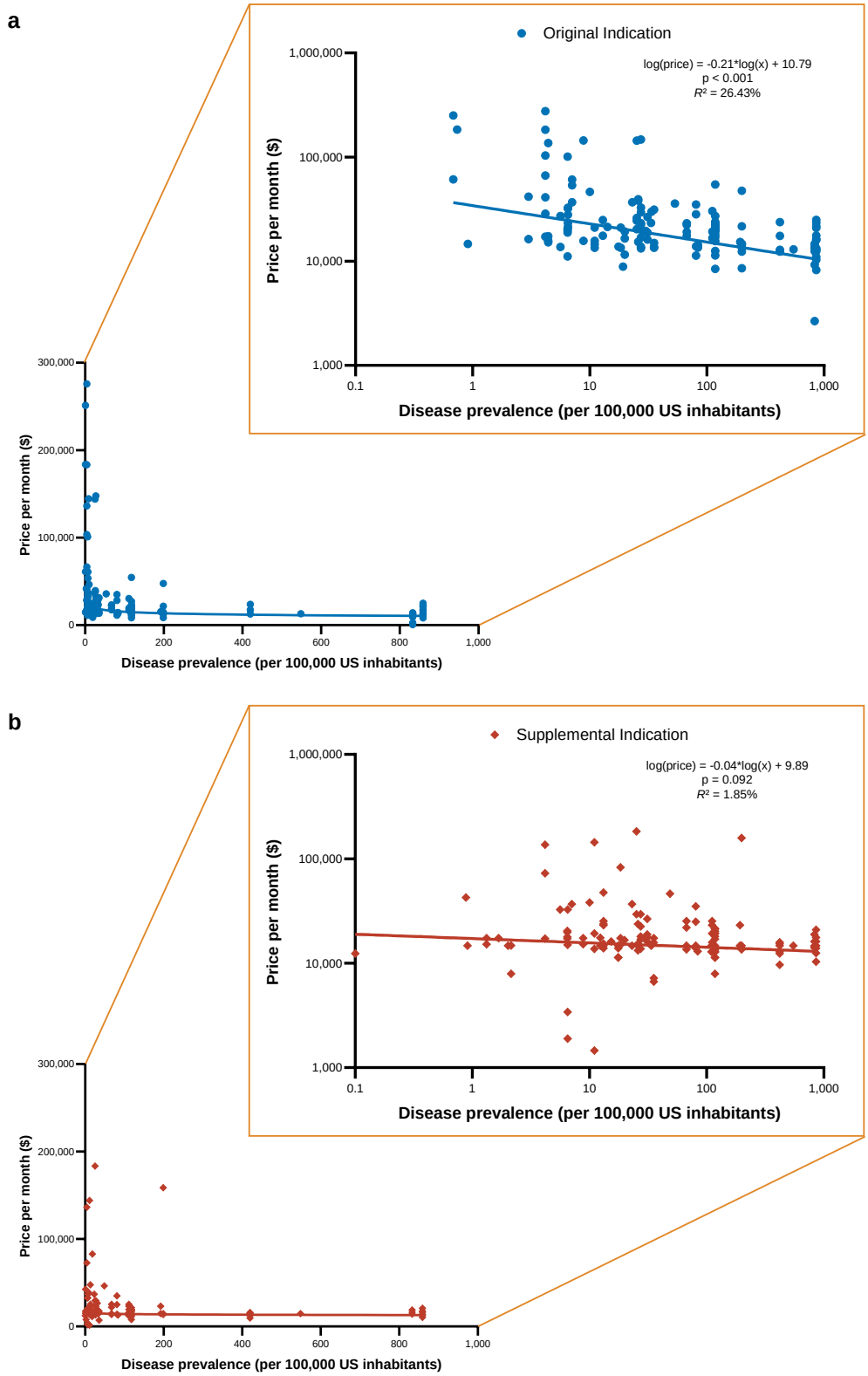


Figure 25: Association between disease prevalence and drug prices for original (a) and supplementary (b) FDA indication approvals

Notes: Disease prevalence rates for the 2019 US population were retrieved from the Global Burden of Disease study and matched to indications based on FDA labels. Monthly treatment costs were calculated for January 2022 based on Medicare Part B and D prices using indication-specific dosing regimens retrieved from each drug's FDA label.

Abbreviations: FDA, US Food and Drug Administration.

Drugs treating diseases with a greater burden and severity were priced higher (Figure 26). Prices increased by an average of 6% (95%CI 3 to 8, p<0.001) per additional DALY. Figure 27 demonstrates that this association is mainly driven by an association between drug prices and YLL (6% per additional YLL, 95%CI 3 to 8, p<0.001). For supplemental indication approvals, none of these associations were observed. Prices were significantly associated with the treated disease's 5-year survival rate for original indications (-45%; 95%CI -104% to -15%; p=0.009), yet not supplemental indications (20%; 95%CI -8% to 49%; p=0.159). Neither original nor supplemental indication prices were associated with the number of competitors.

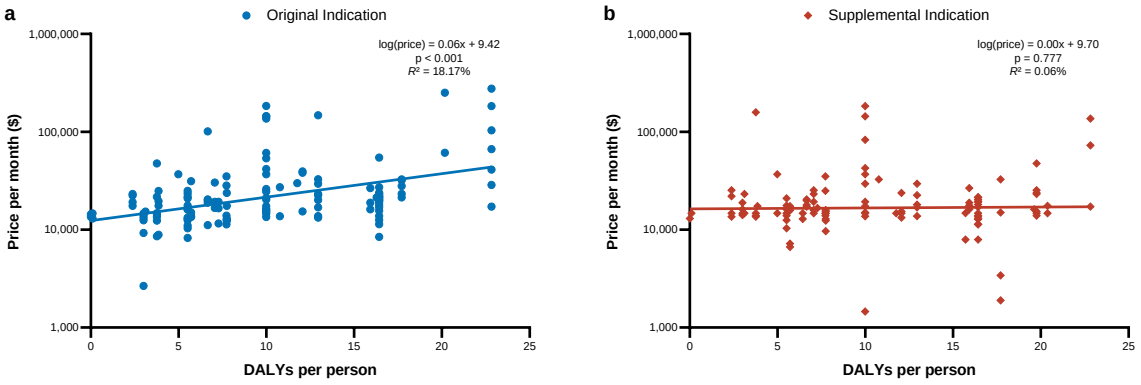


Figure 26: Association between DALYs and drug prices for original (a) and supplementary (b) FDA indication approvals

Notes: DALYs for the 2019 US population were retrieved from the Global Burden of Disease study and matched to indications based on FDA labels. Monthly treatment costs were calculated for January 2023 based on Medicare Part B and D prices using indication-specific dosing regimens retrieved from each drug's FDA label.

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration.

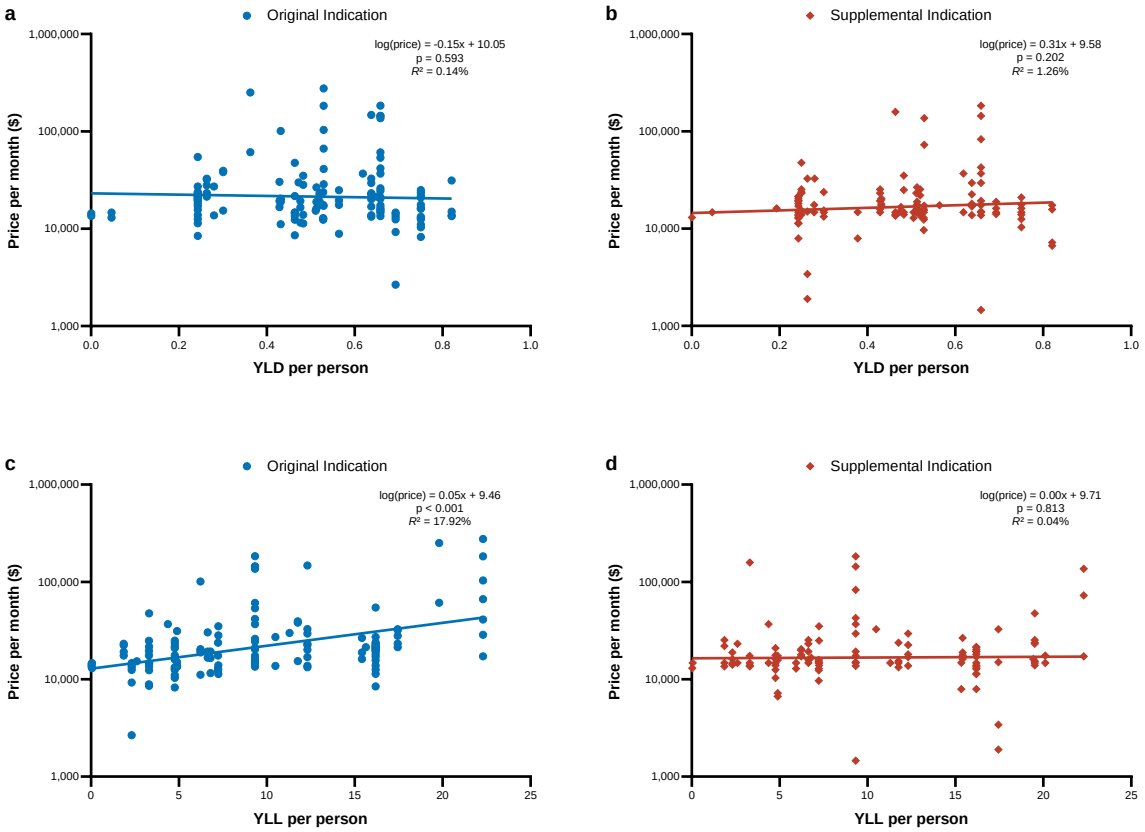


Figure 27: Association between YLD / YLL and drug prices for original and supplementary FDA indication approvals

Notes: YLD and YLL for the 2019 US population were retrieved from the Global Burden of Disease study and matched to indications based on FDA labels. Monthly treatment costs were calculated for January 2023 based on Medicare Part B and D prices using indication-specific dosing regimens retrieved from each drug's FDA label.

Abbreviations: FDA, US Food and Drug Administration; YLD, years lived with disability; YLL, years of life lost.

Results were robust when regression models were adjusted for the FDA approval year (Table 15) and when comparing median drug prices (Table 16).

	Original Indication				Supplemental Indication			
	β [a]	[95% CI]	*P*	R^2	β [a]	[95% CI]	*P*	R^2
(A) Drug characteristics								
No. of indications								
Single-indication	Ref.							
Multi-indication	-0.02	[-0.28 to 0.23]	*0.865*	9.35%				
Innovation status								
Not-first-in-class	Ref.				Ref.			
First-in-class	0.30	[0.07 to 0.53]	*0.010*	13.10%	0.12	[-0.09 to 0.33]	*0.257*	2.97%
Mechanism of action								
Cytotoxic chemotherapy	Ref.				Ref.			
Targeted agents [b]	-0.25	[-0.79 to 0.29]	*0.356*		0.35	[-0.14 to 0.84]	*0.158*	
Immune-regulators [c]	0.25	[-0.35 to 0.86]	*0.407*	17.44%	0.30	[-0.22 to 0.82]	*0.252*	2.18%
Molecule Type								
Small-molecule	Ref.				Ref.			
Antibody	0.15	[-0.13 to 0.44]	*0.296*		-0.22	[-0.34 to -0.1]	*0.001*	
Other [d]	0.93	[0.51 to 1.34]	*<.001*	26.45%	0.40	[-0.51 to 1.32]	*0.384*	11.62%
(B) Indication characteristics								
Treatment type								
Combination	Ref.				Ref.			
Monotherapy	0.09	[-0.15 to 0.33]	*0.464*	9.59%	0.16	[0.01 to 0.31]	*0.032*	3.98%
Disease								
Solid	Ref.				Ref.			
Hematologic	0.48	[0.26 to 0.71]	*<.001*	19.58%	0.22	[-0.04 to 0.47]	*0.093*	4.99%
Biomarker								
No	Ref.				Ref.			
Yes	-0.19	[-0.39 to 0.02]	*0.072*	10.82%	-0.15	[-0.33 to 0.02]	*0.080*	3.70%
Line of therapy								
First-line	Ref.				Ref.			
Advanced-line	0.32	[0.07 to 0.57]	*0.013*	13.41%	0.09	[-0.03 to 0.22]	*0.135*	2.40%
Accelerated approval								
No	Ref.				Ref.			
Yes	0.01	[-0.21 to 0.24]	*0.917*	9.34%	0.02	[-0.12 to 0.16]	*0.789*	1.59%
Converted	Ref.				Ref.			
Pending	0.23	[-0.08 to 0.55]	*0.142*	0.00%	0.21	[-0.06 to 0.49]	*0.126*	0.00%
Not converted / Withdrawn	-0.29	[-0.54 to -0.04]	*0.026*	12.63%	-0.06	[-0.18 to 0.05]	*0.270*	12.58%
(C) Pivotal clinical trial characteristics								
Log(Enrolled patients) [e]	-0.26	[-0.39 to -0.14]	*<.001*	19.16%	-0.09	[-0.16 to -0.03]	*0.007*	5.28%
Trial Phase								
Phase 1 or 2	Ref.				Ref.			
Phase 3	-0.30	[-0.53 to -0.07]	*0.010*	13.21%	-0.18	[-0.35 to -0.02]	*0.032*	4.54%
Trial design								
Other [f]	Ref.				Ref.			
Randomized controlled	-0.37	[-0.58 to -0.16]	*0.001*	15.10%	-0.21	[-0.39 to -0.02]	*0.030*	5.02%
Trial blinding								
Open-label/single-blind	Ref.				Ref.			
Double-blind	-0.16	[-0.35 to 0.04]	*0.117*	10.03%	0.03	[-0.12 to 0.19]	*0.666*	1.65%
(D) Cancer epidemiology								
Log(Incidence) [e,g]	-0.20	[-0.27 to -0.13]	*<.001*	30.89%	-0.06	[-0.11 to -0.02]	*0.007*	5.75%
Log(Prevalence) [e,g]	-0.20	[-0.27 to -0.13]	*<.001*	32.91%	-0.04	[-0.09 to 0.01]	*0.082*	3.41%
DALYs per person	0.05	[0.03 to 0.07]	*<.001*	25.08%	0.00	[-0.01 to 0.02]	*0.855*	1.22%
YLD per person	-0.03	[-0.55 to 0.49]	*0.902*	9.02%	0.36	[-0.09 to 0.81]	*0.117*	2.91%
YLL per person	0.05	[0.03 to 0.07]	*<.001*	24.79%	0.00	[-0.01 to 0.02]	*0.896*	1.20%
5-year survival	-0.45	[-0.86 to -0.03]	*0.034*	11.42%	0.23	[-0.05 to 0.51]	*0.103*	2.92%
No. of competitors	0.00	[-0.01 to 0.01]	*0.568*	9.50%	0.00	[-0.01 to 0.01]	*0.960*	1.57%

Table 15: Series of univariate regression analyses of collected variables on cancer drug prices adjusted for FDA approval year

[a] For the analysis of supplementary indications, standard errors are corrected for clustering at the molecule level.
[b] Targeted agents include anti-hormonal compounds and therapeutics such as tyrosine kinase inhibitors.
[c] Immune-regulators include immune-modulators, CAR T-cell therapies, and immune-antibodies, including immune-checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 inhibitors.
[d] Biologics include monoclonal antibodies, antibody-drug conjugates, enzymes, and radio-therapeutics.
[e] For the number of enrolled patients and disease incidence/prevalence, coefficients should be interpreted as elasticities. For example, a 1% increase in disease incidence corresponds to a -0.2042% decrease in drug prices for original indications.
[f] The category "other" includes single-arm, non-randomized, and dose comparison trials.
[g] Disease incidence/prevalence rate per 100,000 US inhabitants.

Abbreviations: CAR, chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; YLD, years lived with disability; YLL, years of life lost.

	Original Indication			Supplemental Indication		
	Median	[IQR]	*P* [a]	Median	[IQR]	*P* [a]
(A) Drug characteristics						
No. of indications						
Single-indication	21,708	[13825 to 30359]				
Multi-indication	17,624	[14674 to 22544]	*0.135*			
Innovation status						
Me-too	17,847	[13868 to 23315]		14,758	[13911 to 17335]	
First-in-class	21,654	[16146 to 35047]	*0.031*	15,000	[14734 to 19285]	*0.031*
Mechanism of action						
Cytotoxic chemotherapy	15,054	[11024 to 28679]		12,859	[8236 to 17482]	
Targeted agents [b]	18,990	[14439 to 23564]		17,188	[14711 to 19387]	
Immune-regulators [c]	23,151	[14758 to 61058]	*0.011*	14,734	[14648 to 14758]	*<.001*
Molecule Type						
Small-molecule	19,137	[14509 to 23302]		17,385	[15864 to 21092]	
Antibody	14,758	[13023 to 24523]		14,734	[13911 to 14758]	
Other [d]	36,785	[24932 to 143933]	*<.001*	36,785	[13284 to 36785]	*<.001*
(B) Indication characteristics						
Treatment type						
Combination	17,254	[13485 to 24523]		14,734	[13911 to 16243]	
Monotherapy	19,723	[14674 to 27137]	*0.364*	15,325	[14734 to 19387]	*0.001*
Disease						
Solid	17,482	[13520 to 23223]		14,734	[14103 to 16243]	
Hematologic	21,506	[16000 to 36785]	*0.003*	17,385	[15000 to 22544]	*<.001*
Biomarker						
No	19,252	[13911 to 30359]		14,758	[14734 to 19268]	
Yes	19,993	[15151 to 23606]	*0.849*	14,758	[13911 to 17385]	*0.114*
Line of therapy						
First-line	17,592	[13636 to 23262]		14,734	[14103 to 17385]	
Advanced-line	20,260	[14758 to 28679]	*0.111*	15,092	[14734 to 20405]	*0.046*
Accelerated Approval						
No	17,610	[13520 to 27957]		14,758	[14103 to 18035]	
Yes	20,298	[15487 to 26590]	*0.256*	14,758	[14734 to 17385]	*0.965*
Converted	20,196	[16146 to 23223]		14,734	[14734 to 15000]	
Pending	22,348	[18318 to 29027]		15,243	[14734 to 21933]	
Not converted / Withdrawn	15,672	[13485 to 21009]	*0.014*	14,734	[13911 to 14758]	*0.012*
(C) Pivotal clinical trial characteristics						
Trial Phase						
Phase 1 or 2	21,357	[15716 to 29480]		14,758	[14734 to 21273]	
Phase 3	16,337	[12767 to 23164]	*<.001*	14,758	[13911 to 17482]	*0.106*
Trial design						
Other [e]	21,392	[15672 to 30543]		14,758	[14734 to 21273]	
Randomized controlled	16,536	[13293 to 23122]	*<.001*	14,758	[13911 to 17482]	*0.035*
Trial blinding						
Open-label/single-blind	20,196	[14648 to 28679]		14,758	[14648 to 18844]	
Double-blind	17,487	[13502 to 23306]	*0.103*	15,349	[14734 to 17385]	*0.568*

Table 16: Median cancer drug prices compared across drug, indication, and clinical trial characteristics

[a] P-Values calculated based on Mann-Whitney-U tests and Kruskal-Wallis tests.
[b] Targeted agents include anti-hormonal compounds and therapeutics such as tyrosine kinase inhibitors.
[c] Immune-regulators include immune-modulators, CAR T-cell therapies, and immune-antibodies, including immune-checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 inhibitors.
[d] The category "other" includes monoclonal antibody-drug conjugates, enzymes, radio-therapeutics, gene therapies, and cell therapies.
[e] The category "other" includes single-arm, non-randomized, and dose comparison trials.

Abbreviations: CAR, chimeric antigen receptor; CTLA-1, cytotoxic T-lymphocyte-associated protein 4; FDA, US Food and Drug Administration; IQR: interquartile range; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1.

3.6 Discussion

This study analyzed factors associated with anti-cancer drug prices in the US based on a sample of 145 drugs with FDA approval across 373 indications. In 2023, average drug prices amounted to $24,444 per month. For original indications, median OS improvement of 26% and PFS improvement of 61% were significantly associated with drug prices. Original indications' prices were: (i) negatively associated with disease incidence/prevalence and the pivotal trial's number of enrolled patients; (ii) positively associated with first-in-class drugs, gene and cell therapies, hematologic cancers, and severe diseases with high unmet needs; and (iii) negatively associated with double-blinded phase 3 RCTs. However, prices are only poorly associated with supplemental indications' efficacy, clinical evidence, or cancer epidemiology.

3.6.1 Pricing the original indication

Clinical benefit

In our sample of 373 cancer indications with FDA approval (2003-2022), treatment costs were significantly associated with improvements in OS and PFS. However, this association was of low magnitude. Similarly, Mailankody & Prasad only observed a weak insignificant association between OS/PFS and treatment costs based on 51 FDA-approved cancer drugs (2009-2013).[112] Accordingly, four other studies could not confirm any association between cancer drug prices and clinical benefit.[113–118] In contrast, Howard et al. found prices increased by 120% (95% CI 74 to 166%) for each additional LY gained based on 58 FDA-approved cancer drugs (1995-2013).[110] However, their regression analysis includes modeled outcomes and does not distinguish between OS and PFS benefit. Unlike the aforementioned studies, they calculated each disease episode's treatment costs instead of mean monthly drug prices.

For supplemental indications, the association between prices and clinical benefit were of lower maginute or insignificant. However, the conducted comparison of prices per life LY gained

could not confirm our hypothesis that supplemental indications have a lower cost-to-benefit ratio than original indications. Nonetheless, OS and PFS data from RCTs for this analysis was only available for a total of 160 out of 373 drug indications. Furthermore, many original high-value indications are approved based on single-arm phase 1/2 trials without available OS and PFS data. Recent studies highlight that original indications are of higher clinical value than supplemental indications.[38,40,73,134] A similar analysis to ours, with benefit data available for all indications, should compare QALYs and ICERs across original and supplemental indications. A study of 25 cancer drugs with FDA approval across 100 indications showed ICERs increased from original to second to third approved indications in the US, France, and Canada.[38]

We conclude that cancer drug prices are (at best) only poorly aligned to the marginal benefit they offer to patients. If the US implemented value-based pricing, coverage, and reimbursement policies that incentivized manufacturers to only develop drugs that offer a meaningful survival benefit, "perhaps there would be more of them" (Howard et al., 2015, p. 158).[110]

Clinical trial evidence

The US drug market seemingly offers a price premium to medicines supported by poor evidence, which are often also those targeting rare diseases. The approval of drugs with limited safety and efficacy evidence was progressively enabled by the introduction of special FDA review processes, especially the accelerated approval pathway. These processes expedite the approval of drugs treating severe conditions with significant unmet needs. However, drugs with special designations are not more effective or innovative and lack evidence from RCTs.[73,135] As a result of limited trial experience, expedited approvals are associated with more unknown side-effects; yet, the required post-marketing trials are often deferred or not even commenced.[136,137] Expedited approvals are nonetheless swiftly incorporated in clinical guidelines and prescribed for patients across multiple indications,[138] thereby causing a significant economic burden for the US healthcare system.[13,99] A drug price and coverage system *with evidence development*

could reconcile the disconnect between high prices and poor clinical evidence:[139] If payers negotiated discounts for or restricted coverage of indications supported by low-quality trials, perhaps there would be more indications supported by robust RCTs.

Our findings provide evidence that the US drug market already incorporates clinical trial evidence for new cancer drugs. Drugs that are approved based on early clinical trials, yet fail to convert this accelerated approval to full approval in confirmatory trials, are sold for a 25% discount.

Innovation

We observed significantly higher prices for innovative – "first-in-class" – cancer drugs. First-in-class drugs were priced higher than not-first-in-class drugs ($21,654 vs. $17,847, p=0.031). Gene and cell therapies, enzymes, and radionuclides were priced higher than antibodies and small molecules ($36,785 vs. $14,758 vs. 19,137, p<0.001). These results were consistent for original and supplemental indications. These findings suggest that the US drug market encourages the development of new agents with an innovative molecular target, mechanism of action, and/or product type. Some authors criticize US patients are paying for the world's pharmaceutical inventions as foreign countries "freeload off American medical innovations" (Pitts, 2017, p. 1).[140] A global approach to harmonizing drug development efforts across nations is encouraged to equitably distribute the cost of biotechnological innovation across patients. Meanwhile, US policymakers must balance the affordability, access, and innovativeness of new cancer drugs – "a drug that cannot be purchased offers no value to patients" (Prasad, 2020, p. 167).[141]

Cancer epidemiology

Results demonstrate that cancer drug prices are negatively associated with disease incidence and prevalence. For every -1% decrease in disease incidence, drug prices increased by 0.21%. These results are coherent with previous studies from Europe.[123–125] Accordingly, particularly

high drug prices were observed for orphan drugs in previous research.[123–125] Alongside special approval procedures, tax credits, waiver of fees, research grants, and extended marketing exclusivity periods, high prices aim to incentivize the development of drugs for rare diseases.[142] Orphan drug development has, henceforth, emerged as an "economically viable strategy" (Meekings et al., 2012, p. 660) that increases manufacturers' returns and company valuations.[80,81,143] However, high orphan drug prices "pose significant barriers to patient access" (Gammie, 2015, p. 20) especially when patients have to pay OOP for co-payments.[142]

Results furthermore demonstrate that drug prices are significantly associated to disease burden, measured by DALYs, and disease severity, measured by 5-year survival rates, respectively. A one-point increase in DALYs was associated with a 5.7% increase in drug prices. A 1% decrease in the 5-year survival rate was associated with a 0.45% increase in drug prices. DALYs are a composite measure considering the burden and duration of physical impairment (YLD) as well as premature death (YLL) caused by a disease.[144] Consequently, higher prices are paid for drugs treating more severe diseases with a significant burden for patients, e.g. diseases that substantially reduce life expectancy.[110] This was particularly driven by the association between prices and YLL. This result indicates that drugs targeting pediatric cancers, which cause a high burden of premature mortality, are priced higher than those targeting tumors of the elderly.

The regression analysis could not confirm any significant relationship between prices and a drug's number of competitors. Accordingly, Gordon et al. found that drug price changes were not influenced by the introduction of new competitors.[119] In contrast, Howard et al. observed lower prices for diseases with many competitors.[110] Similar to Howard et al., we collected the number of available treatment options per cancer site from the National Cancer Institute. However, measuring available treatment options, and thereby competition, remains complex as "drugs are often used in a complementary manner" (Howard et al., 2015, p. 152) in addition to their use as single treatments for certain indications.[110]

Unmet medical need is characterized by three aspects according to a comprehensive global literature review: (1) disease incidence/prevalence, (2) disease burden/severity, and (3) available treatment options.[145] Our analysis demonstrates that (1) and (2), yet not (3), are significantly associated with cancer drug prices. We, therefore, conclude that cancer drug prices in the US are not priced based on the benefits they deliver to patients; prices are rather based on the unmet medical needs they fill. The alignment between unmet needs and drug prices could be improved by reassessing drug pricing and coverage as new treatment alternatives, e.g. competitors, are introduced to the market.

3.6.2 Pricing supplementary indications

Previous research highlighted that the clinical benefit, quality of evidence, regulatory approval, and clinical development timelines differ for original and supplemental indications.[38,40,73,101,102] However, drugs are currently commercialized for the same price across all indications in the US. Consequently, results from the regression analyses show that these uniform (single) drug prices are only poorly associated with the supplemental indications' efficacy, clinical trial evidence, and unmet needs. Without considering the specific characteristics of supplemental indications a drug's value and price are delinked. Policymakers in the US should explore *indication-specific* pricing, coverage, and reimbursement policies to realign a drug's clinical benefit, innovativeness, and unmet needs with its cost. Ideally, the following pricing and coverage policies should be evaluated and implemented in conjunction with each other, rather than viewing them as isolated regulations.

Indication-specific pricing

Indication-specific pricing distinctly prices a drug according to each indication's differential value.[41] A pure indication-specific pricing system – "one drug, different prices" – faces several

barriers to implementation, including a costly IT infrastructure to track indication-specific usage.[49] Therefore, Germany and France introduced an indirect indication-specific pricing mechanism: volume-weighted-average drug prices.[11,38,49] Under this policy, health technology agencies evaluate and weigh the value and eligible patient population for each indication. Michaeli et al. observed cancer drugs' list prices declined with the introduction of new indications in Germany and France.[38] If indication-specific pricing were to be implemented, it would likely result in cost-savings for payers and patients.[11,38,49] Both policies could reduce ICERs for supplemental indications with a lower QALY gains. Whilst critiques argue that indication-specific pricing may disincentivize the development of clinical trials for "low-value" indications, e.g. indications with decimale QALY gains and high ICERs, (especially with few patients), proponents welcome the dynamic competitive pressure that is introduced by a multi-price system.[11,38,49] In this context, the recently passed IRA offers the CMS the power to negotiate drug prices with pharmaceutical companies and, thereby, the potential to adopt similar indication-specific pricing policies in the US.[23]

Indication-specific coverage

As long as direct nor indirect indication-specific pricing are not implemented in the US, payers should explore the indication-specific assessment and coverage of new drugs. For indications that are deemed not cost-effective at a drug's current list price, payers may restrict coverage to patient subgroups that stand to benefit most from the new treatment. New US policies could be guided by the French, Australian, British, or Canadian examples.[11,38,49] These countries employ indication-specific coverage restrictions to effectively control the use of drugs in supplementary indications with low clinical value, e.g. few quality-adjusted life years gained.[38] Similarly, the CMS could only cover drugs for indications and patient subgroups that prove to extend quality of life or patient survival. CMS' recent decision to restrict aducanumab's coverage sets the first

precedence for such a policy.[109] In this context, the CMS' existing CED program, which requires sponsors of drugs without a proven clinical benefit to enroll beneficiaries in post-approval trials,[146] is a pre-requisite for most indication-specific coverage and reimbursement policies.

Indication-specific reimbursement

Payers may also choose to reimburse drugs on an indication-specific level based on their distinct evidence, efficacy, and epidemiology. Previous studies showed that especially trials supporting original indications' accelerated approvals are of poor design, suffer from selection bias, and lack adequate sample size and follow-up, thereby potentially overestimating efficacy results.[40,73] Therefore, payers in Europe increasingly implement indication-specific MEAs.[11,38,49] Countries such as Italy, England, Spain, and Scotland employ financial or outcome-based MEAs and negotiate indication-specific discounts on drugs to contain spending on new drugs. All proposed policies must be tailored to the US insurance and pharmaceutical market. Therefore, the feasibility of implementing new indication-specific drug policies in the US remains difficult compared to the EU, given the fragmented system of public and private health insurers, pharmaceutical benefit managers mediating drug procurement, and the lack of federal health technology assessments.[50]

3.6.3 Limitations

There are several limitations inherent to this study. First, drug prices were extracted for Medicare and Medicaid patients – drug prices for other insurance systems may vary. Second, we analyzed average sales prices, which do not capture confidential discounts and rebates negotiated between manufacturers and insurers/health systems. Third, epidemiologic variables were obtained for cancer entities and matched to each indication. However, within cancer entities

prognosis, incidence/prevalence, and the number of available treatments differ by tumor histology, biomarker, stage, and line of therapy. Fourth, although this study is unique in its breadth of analyzed variables, further data characterizing an indication's safety profile, patients' quality of life, or special regulatory approval pathways could help to explain variations in drug prices. To include these data points, future studies could therefore employ the European Society for Medical Oncology – Magnitude of Clinical Benefit Scale (ESMO-MCBS), American Society of Clinical Oncology – Value Framework (ASCO-VF), or National Comprehensive Cancer Network (NCCN) Evidence Blocks to assess cancer drugs' clinical benefit and price across indications. Fifth, efficacy and clinical trial evidence were collected from data disclosed on FDA labels at the time of approval. Therefore, our analysis is biased to only successful FDA reviews which may overestimate a drug's efficacy. Moreover, clinical trial evidence reported after FDA approval with longer follow-up periods could offer more precise efficacy measures.

3.7 Conclusion

This study finds that new cancer drugs are not affordable to US patients, with 95% of drugs costing more than $10,000 per month and patients' with a median household income of $5,899 have to cover 20-30% of these prices OOP. Drug prices are (at best) only poorly aligned with the survival benefit they offer. Drug prices are significantly aligned with the unmet medical needs they fill and the biotechnological innovation they achieve. US policymakers should explore *value-based* pricing and coverage policies *with evidence development* to incentivize the development of drugs that prove to increase patient survival in RCTs.

Although the majority of drugs are approved for multiple indications, US prices are pre-dominantly set based on the original indication's characteristics. Thereby the value of supplemental indications is omitted. Policy reforms are necessary to reflect a drug's clinical benefit, innovativeness, and unmet needs across all approved indications. The authors, therefore, recommend

US decision-makers explore the adoption of *indication-specific* pricing, coverage, and reimbursement policies.

3.8 Author contributions

Daniel Tobias Michaeli and Thomas Michaeli had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Daniel Tobias Michaeli. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Daniel Tobias Michaeli. Administrative, technical, or material support: All authors. Study supervision: All authors.

4 Launch and post-launch prices of injectable cancer drugs in the US

Summary: This longitudinal study identifies and quantifies factors associated with launch prices and post-launch price changes of injectable cancer drugs in the United States.

4.1 Abstract

Background: Rising cancer drug prices adversely affect patients' adherence and survival.

Objective: To identify and quantify factors associated with launch prices and post-launch price changes of injectable cancer drugs in the US from 2005 to 2023.

Data and methods: All anti-cancer drugs with FDA approval between 2000 and 2022 were identified in the Drugs@FDA database. The sample was then restricted to cancer drugs covered under Medicare Part B (injectable drugs). Data characterizing each drug's clinical benefits, disease epidemiology, approved indications, competition, and price were obtained from FDA labels, the Global Burden of Disease study, and the CMS. The association between launch/post-launch prices and collected variables was assessed in random-effects regressions.

Results: Of 170 cancer drugs with FDA approval between 2000 and 2022, we identified 66 (39%) injectable cancer drugs with available quarterly price data from 2005 to 2023. In 2023, mean prices amounted to $27,688 per month with an average price increase of 94% from 2005 to 2023. Launch and post-launch price changes were significantly associated with the treated disease epidemiology. A 1% decline in disease incidence was associated with a 0.2511% (p=0.008) increase in launch prices and a 0.0086% (p=0.032) annual increase in post-launch prices, respectively. Accordingly, launch prices were 120% (p=0.051) higher for orphan than non-orphan drugs, with 3% (p=0.008) greater annual post-launch price increases. Post-launch prices declined by up to -2% annually as new supplemental indications were approved for the same drug. We found no consistent association between launch/post-launch prices and drugs'

clinical benefit in terms of OS, PFS, and tumor response. The market entry of new competitors was not associated with price reductions. 28 of 33 drug pairs within the same class had positive correlation coefficients. Pearson correlation coefficients were high (>0.80) for PD-1/PD-L1 inhibitors, CD38 antibodies, CD20 antibodies, HER2 antibodies, and mTOR inhibitors.

Conclusions: Cancer drug prices regularly increase faster than inflation. However, there is no evidence that launch prices and post-launch price changes are aligned with the clinical benefit a drug offers to patients. In particular, patients with rare diseases experienced greater price increases for their orphan drugs. There is no evidence that brand-brand competition results in drug price reductions.

4.2 Key Points

- From 2005 to 2023, US injectable cancer drug prices increased faster than inflation.
- Launch prices and post-launch price increases are not aligned with the clinical benefit a drug offers to patients.
- In particular, great price increases were observed for orphan drugs.
- There is no evidence that brand-brand competition results in drug price reductions.

4.3 Introduction

From 2020 to 2021, US launch prices for half of all new medicines approved by the FDA exceeded $150,000 per year.[2] In particular, high prices were observed for oncology drugs, with 95% of new anti-cancer drugs in the US priced beyond $100,000 per year in 2023.[74] For cancer patients in the US, who typically bear 20-30% of treatment costs OOP, these high prices are a major cause of financial distress and financial toxicity.[16] High drug prices contribute to catastrophic healthcare expenditure, which ultimately leads to personal bankruptcy.[15] Particularly cancer patients are at 2.7-times greater risk of personal bankruptcy than non-cancer patients in the US.[147] This financial toxicity results in non-adherence to recommended treatment regimens[148] and, therefore, higher mortality rates.[149]

High prescription drug prices are not only caused by high launch prices. Contributing to the economic burden of prescription drug costs are post-launch price changes. Price changes exceeding inflation were identified as a major contributor to rising treatment costs and patients' OOP, particularly for cancer drugs in the US.[4,120,150] For instance, the annual price for the TKI imatinib, a scientific breakthrough for patients with chronic myeloid leukemia, more than tripled in price from $30,000 to $92,000 in merely 10 years.[16] This price increase occurred despite the introduction of new second-generation TKIs, such as dasatinib and nilotinib. Although these competitors are similar in their mechanism of action and treat similar diseases, they were commercialized for launch prices beyond $110,000 per year.

Previous studies analyzed the association between launch prices and R&D costs, competition, drug safety and efficacy, disease incidence and burden, and special FDA review procedures.[22,74,110,112–118,123–125] Further studies investigated the correlation between post-launch price changes and new competitors, new indication approvals, new off-label uses, and safety and efficacy measures.[57,110,119,120,122,151–155] However, these studies are limited in their sample size, analyzed time horizon, and statistical analysis. Therefore, in this longitudinal study, we identify

and quantify factors associated with launch prices and post-launch price changes of injectable cancer drugs. We evaluate the association between launch/post-launch prices and time-dependent and time-independent variables, characterizing each drug's innovativeness, efficacy, disease epidemiology, and competition.

4.4 Data and methods

4.4.1 Sample identification

We identified all new drugs that received FDA approval between 1st January 2000 and 1st January 2022. The sample was then restricted to include only anti-cancer medicines, excluding those for supportive cancer care, diagnostic agents, and anti-emetics. For these anti-cancer drugs, we identified all original and supplemental anti-cancer indication approvals until 1st January 2022. In our analyses, we only included drugs covered under Medicare Part B given that no longitudinal price data are available for drugs covered under Medicare Part D from the CMS. In general, Medicare Part B covers injectable cancer drugs (typically drugs that are administered at a hospital or doctor's office), whilst Medicare Part D covers oral cancer drugs (typically self-administered drugs). Certain drugs with multiple routes of administration are covered by Medicare Part B and D, for example, everolimus.

4.4.2 Data collection

For all identified cancer agents, we collected price data and information characterizing each drug's characteristics, disease epidemiology, and market dynamics (Table 17).

Variable	Type	Time-Varying	Definition	Source	Link
Drug prices	Interval	Yes	Monthly treatment costs for the average patient insured under Medicare	Centers for Medicare and Medicaid Services (CMS)	https://www.cms.gov/medicare/medicare-fee-for-service-part-b-drugs/mcrpartbdrugavg-salesprice
Clinical benefit:					
Overall survival (HRs)	Interval	No	Overall survival benefit in terms of hazard ratios reported in RCTs	FDA documents	https://www.accessdata.fda.gov/
Overall survival (median improvement)	Interval	No	Median overall survival benefit between treatment and control arm in RCTs	FDA documents	https://www.accessdata.fda.gov/
Progression-free survival (HRs)	Interval	No	Progression-free survival benefit in terms of hazard ratios reported in RCTs	FDA documents	https://www.accessdata.fda.gov/
Progression-free survival (median improvement)	Interval	No	Median progression-free survival benefit between treatment and control arm in RCTs	FDA documents	https://www.accessdata.fda.gov/
Tumor response (RRs)	Interval	No	Tumor response benefit in terms of relative risk rate reported in RCTs	FDA documents	https://www.accessdata.fda.gov/
Duration of response (median improvement)	Interval	No	Median tumor response benefit between treatment and control arm in RCTs	FDA documents	https://www.accessdata.fda.gov/
Innovativeness	Binary	No	0: next-in-class 1: first-in-class	WHO ATC code	https://www.whocc.no/atc_ddd_index/
Molecule Type	Binary	No	0: small-molecule 1: other [a]	DrugBank	https://go.drugbank.com/
Biomarker	Binary	No	0: no companion biomarker 1: companion biomarker	FDA documents	https://www.accessdata.fda.gov/
Orphan designation	Binary	No	0: Non-orphan 1: Orphan	FDA Orphan Drug Designations and Approvals database	https://www.accessdata.fda.gov/scripts/opdlisting/oopd/
Accelerated approval	Binary	No	0: Standard Approval 1: Accelerated Approval	FDA Accelerated Approvals List	https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals
Fast track status	Binary	No	0: Not Fast Track 1: Fast Track	FDA Fast Track Approvals List	https://www.fda.gov/drugs/nda-and-bla-approvals/fast-track-approvals
Priority review	Binary	No	0: Standard Review 1: Priority Review	FDA Priority Review Approvals List	https://www.fda.gov/drugs/nda-and-bla-approvals/priority-nda-and-bla-approvals
Breakthrough therapy [b]	Binary	No	0: Not Breakthrough Therapy Designation 1: Breakthrough Therapy Designation	FDA Breakthrough Therapy Designation Approvals List	https://www.accessdata.fda.gov/scripts/cder/daf/
Disease incidence	Interval	No	Disease incidence rate per 100,000 US inhabitants in 2019	Global Burden of Disease study, 2019	https://www.healthdata.org/gbd
DALYs	Interval	No	DALYs per person for the US population in 2019	Global Burden of Disease study, 2019	https://www.healthdata.org/gbd
New supplemental indications	Interval	Yes	Number of new supplemental indications with FDA approval for each drug	FDA documents	https://www.accessdata.fda.gov/
New competitors (broad)	Interval	Yes	Number of new competitors defined as new anticancer indications with FDA approval for the same disease	FDA documents	https://www.accessdata.fda.gov/
New competitors (narrow)	Interval	Yes	Number of new competitors defined as new anticancer indications with FDA approval for the same disease in the same line of therapy for the same treatment setting with the same biomarker	FDA documents	https://www.accessdata.fda.gov/

Table 17: Variable definition and data sources

[a] The category other includes biologics, antibody-drug conjugates, enzymes, cell therapies, gene therapies, and radionuclides.
[b] Only cancer drugs with FDA approval after 2012 were included to compare breakthrough and non-breakthrough therapy drugs.

Abbreviations: ATC, Anatomical Therapeutic Chemical; DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; WHO, World Health Organization.

Drug characteristics

First, we characterized each drug's innovativeness. Two reviewers assessed the novelty of the underlying drug target based on the WHO's ATC code. Drugs with novel targets were considered first-in-class, whereas those with known targets were considered next-in-class. Second, the University of Alabama's drug database – "Drug Bank" – was accessed to determine each drug's product type. Drugs were categorized as small molecules and others, which entail biological agents, antibody-drug conjugates, gene therapies, cell therapies, enzymes, and radionuclides. Third, we obtained information on the approval of companion biomarkers from FDA labels. Finally, we obtained data from FDA websites to determine if special FDA designations were

associated with each drug, e.g. orphan designation, accelerated approval, fast track, priority review, and BTD.

Clinical benefit

The clinical benefit of new cancer drugs was measured by their benefit in OS, PFS, and tumor response rates. We accessed FDA labels and clinicaltrials.gov to collect data on OS and PFS hazard ratios and tumor response rates from RCTs. Furthermore, we extracted median improvements in OS, PFS, and duration of response. The absolute median improvement in OS/PFS was calculated as the difference between median OS/PFS in the treatment relative to the control arm. The percentage improvement in OS/PFS was then calculated as the quotient of the absolute median OS/PFS improvement relative to the absolute median OS/PFS in the control arm. Although multiple analyses evaluated the association between new drugs' clinical benefit and launch prices,[22,74,112–118] evidence scrutinizing the association between new drugs' clinical benefit and post-launch price changes remains scarce.[120] Most European countries introduced regulations to limit drug price increases exceeding inflation and even reduce drug prices to control expenditure on new drugs. For instance, drug price increases are re-evaluated in Switzerland every 3 years, controlled by the government in England, and re-evaluated for drugs with new indications in Germany and France.[38,64,65] Given that over the study period, there was no value-based pricing policy in the US that regulates launch prices and post-launch price changes, we hypothesize that there is no association between launch/post-launch prices and drugs' clinical benefit.

Disease epidemiology

We obtained epidemiologic data for the US population in 2019 from the Global Burden of Disease study to describe the disease treated by each drug.[128] First, we collected disease incidence rates (per 100,000 US inhabitants) as a measure of disease rarity. Second, we collected

DALYs per person as a measure of disease burden. DALYs are calculated as the sum of YLD and YLL. Therefore, DALYs not only capture the forgone lifetime but also the reduced quality of life that is caused by diseases. The disease-specific epidemiologic data were matched to each drug according to the treated disease specified in FDA labels.

Market dynamics

Market dynamics were captured in two variables. We tracked the FDA approval of new supplemental indications for each drug. Given that these supplemental indications are often for non-orphan diseases supported by robust clinical trials with a relatively low clinical benefit ("low-value indications"), we expect drug prices to decline following the introduction of new indications for the same drug.[38,40,73]

We then monitored the number of new competitors entering the market for each drug. We used two alternative measures of new competitors. First, we counted the number of new cancer drug indications receiving FDA approval within the same disease during each quarter. This represents a broad measure of competition in the market of anti-cancer drugs (variable: new competitors (broad)). Second, we counted the number of new anti-cancer drug indications receiving FDA approval within the same disease in the same line of therapy for the same treatment setting with the same biomarker during each quarter. This represents a narrow measure of competition in the market of anti-cancer drugs (variable: new competitors (narrow)). The narrow measure of competition might be more reflective of the underlying market dynamics in the cancer drug market, given that each drug and indication often fills a distinct therapeutic niche that is defined by the therapeutic setting (neoadjuvant vs. adjuvant vs. metastatic), line of therapy (first-line vs. second-line vs. advanced-line), and biomarker profile (for example differentiated by driver mutations for non-small cell lung cancer: KRAS vs. EGFR vs. ALK vs. BRAF vs. MET vs.

ROS1 vs. HER2 (ERBB2) vs. NTRK). For both measures of competition, we included the market entry of all new drug indications with FDA approval regardless of insurance states, e.g. we included drug indications covered under Part B and D.

Drug prices

Drug prices were calculated according to a methodology that has been described in prior articles.[74,116,119,131] First, we accessed the CMS' quarterly average sales price (ASP) data files to obtain drug pricing data from 2005 to 2023. For each drug, we then calculated monthly treatment costs based on the dosing regimen defined in FDA labels for the average US patient with a body weight of 70 kg and a body surface area of 1.7 m².[74,115–117,131] As a result, these treatment costs only include the drug price and do not consider any additional charges for doctor's fees, delivery expenses, administrative fees, or supportive care that may be necessary for the treatment of cancer patients.

4.4.3 Statistical analysis

We used descriptive statistics to describe the sample's baseline characteristics. Then, we conducted random-effects regression models to evaluate the association between post-launch price changes and collected variables. Random-effects effects regressions were performed to examine the association between time-varying and time-invariant variables on drug prices. The use of random-effects rather than fixed-effects models was confirmed by performing the Hausman test (χ^2=12.47, p=0.0861) and the Lagrange Multiplier test ($\overline{\chi^2}$=42,858.22, p<0.001). All models account for drug-level clustered standard errors to adjust for heteroscedasticity and autocorrelation. Drug prices, disease incidence, and disease prevalence were transformed with the natural logarithm to account for their skewed distribution.

For all models, the dependent variable (y_{dt}) is the inflation-adjusted log-price for each drug (d). First, we evaluated the association between each independent variable and launch prices as

well as post-launch drug price changes in a series of separate univariate regression analyses. In these models, each independent time-invariant variable (x_d) was included alongside an interaction term between the time-invariant variable and the time since launch (q_{dt}) (Equation 1). We defined drug launch as the first time a drug's price was listed in CMS files. Coefficients of the independent variable (β_d) can be interpreted as the association between the independent variable of interest and launch prices. The coefficient of the interaction term (β_{dq}) can be interpreted as the association between the independent variable of interest and post-launch price changes. Product type, innovativeness, companion biomarkers, special FDA designations, disease incidence, and DALYs per person were included as time-independent variables. Across all models, v_d represents the drug-specific error and ε_{dt} represents the idiosyncratic error.

$$y_{dt} = \alpha + q_{dt}\beta_0 + x_d\beta_1 + q_{dt}x_d\beta_{q1} + v_d + \varepsilon_{dt}$$

Equation 1

Among models with time-varying variables, the variable of interest (x_{dt}) was the only independent variable and its coefficient can be interpreted as the post-launch price change (Equation 2). The number of new competitors and new supplemental indications were included as time-varying variables.

$$y_{dt} = \alpha + q_{dt}\beta_0 + x_{dt}\beta_1 + v_d + \varepsilon_{dt}$$

Equation 2

Thereafter, a multivariate regression model was conducted (Equation 3). Special FDA designations, except for the orphan designation were excluded, as they are often granted concurrently.

$$y_{dt} = \alpha + q_{dt}\beta_0 + \sum_{i=1}^{I}(x_{di}\beta_i + q_{dti}x_{di}\beta_{qi}) + \sum_{j=1}^{J}(x_{dtj}\beta_j) + v_d + \varepsilon_{dt}$$

Equation 3

Sensitivity analysis was conducted using two-step fixed-effects mondels rather than random-effects regression models. First, we constructed a fixed-effects panel regression including all time-varying variables. Based on this model we predicted log-prices at launch. Thereafter, an

OLS regression including all time-invariant variables on predicted log-prices at launch was performed.

Coherent with previous studies, we examined the cancer drug market within drug classes based on the correlation of prices.[151,153–156] The relationship between 9 drug classes with a total of 25 injectable cancer agents was analyzed and visualized using a Pearson correlation matrix. Stigler & Sherwin (1985) suggest that price movements between two products can be used to define the extent of a market.[157] A positive correlation coefficient close to 1 indicates that two products are competing in the same market, whereas a low correlation coefficient suggests that the two products are competing in separate markets.[158] We tested for causality between each drug pair's logarithmic first difference of prices using the Granger causality test.[159]

Data were stored in Microsoft Excel (Microsoft Corp) and analyzed with Stata software, version 14.2 (StataCorp LLC). Two-tailed p-values below 0.05 were considered significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines where applicable.[133]

4.5 Results

4.5.1 Sample overview

We identified a total of 720 new drugs that received FDA approval between 2000 and 2022. Among these, we identified 170 anti-cancer agents with FDA approval for a total of 455 indications. 104 of these drugs were covered under Medicare Part D and, therefore, excluded from our analysis. The final sample consists of 66 cancer drugs with quarterly price data from 2005 to 2023 (Figure 28).

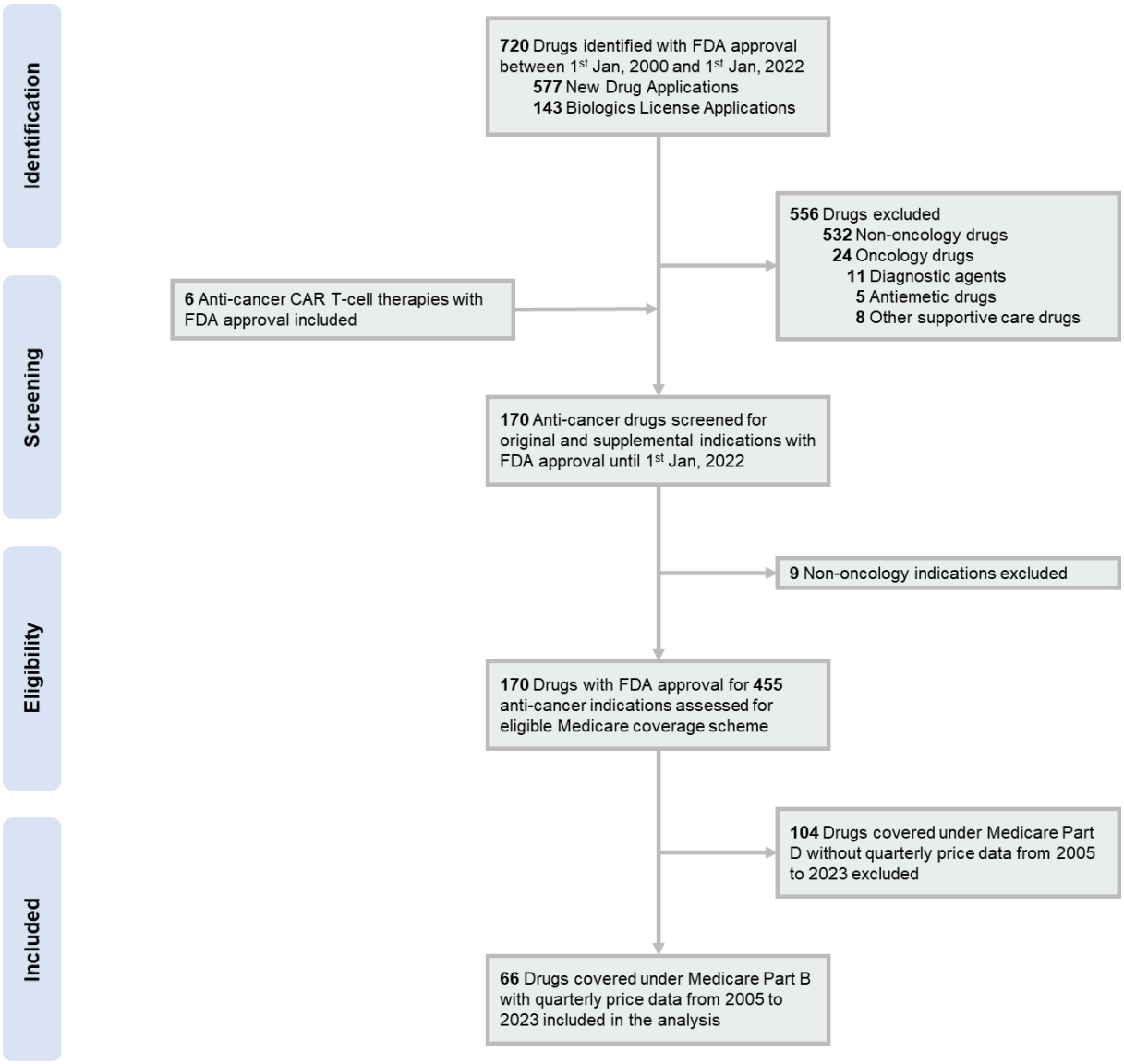


Figure 28: Flow chart of FDA-approved injectable cancer drugs included in the analysis, 2000-2023

Abbreviations: CAR, chimeric antigen receptor; FDA, US Food and Drug Administration.

For these 66 drugs, mean prices amounted to $27,688 per month in 2023. Higher prices were observed for on-patent than generic drugs (mean: $33,988 vs. $7,529, Student's t-test p=0.008). Figure 29 illustrates the post-launch price trajectory of cancer drugs in our sample. For on-patent drugs, prices increased by an average of 94% from 2005 to 2023. For drugs that lost their exclusivity, prices declined by an average of -94% (Figure 30).

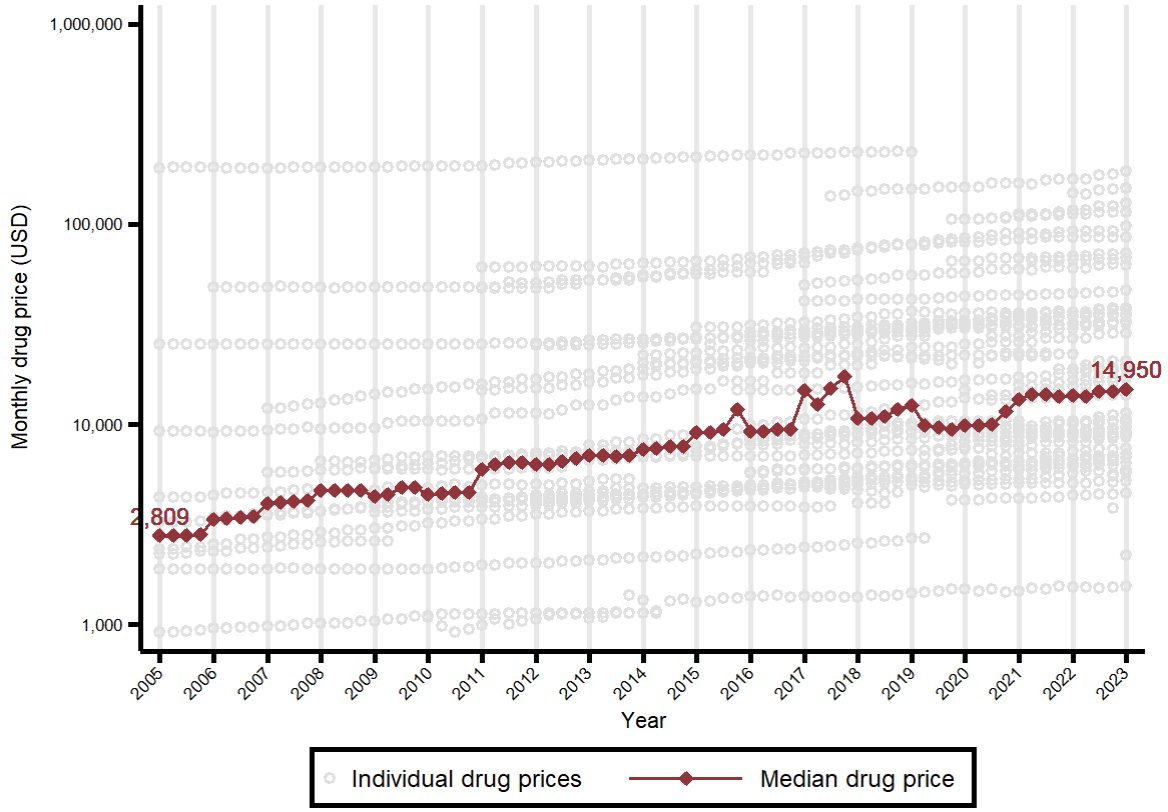


Figure 29: Prices of injectable cancer drugs from 2005 to 2023

Notes: The graph shows individual and median prices for injectable cancer drugs (covered under Medicare Part B) from 2005 and 2023. Prices were calculated for the average patient's monthly treatment cost for the first indication with FDA approval. The median monthly drug price amounted to USD 2,809 in 2005 and rose to USD 14,950 in 2023. We only included on-patent periods, whilst excluding periods after patent expiry. The outlier triptorelin pamoate was excluded for visualization. All prices are presented in US dollars.

Abbreviations: FDA, US Food and Drug Administration.

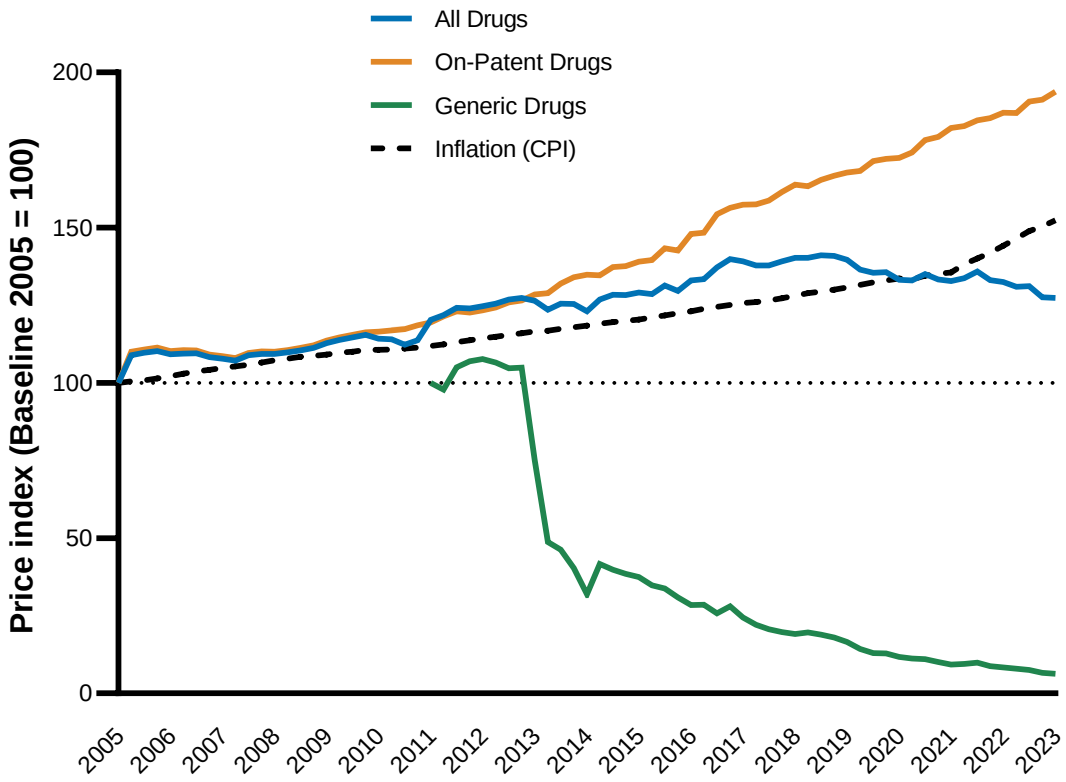


Figure 30: Post-launch price changes for injectable cancer drugs, 2005-2023

Notes: The graph shows the mean price development of cancer drugs since 2005 stratified by patent status. The price development was calculated as an index with a baseline of 100 in the first quarter of 2005, which changes each quarter according to the mean change in drug prices over the next quarter. The price development is illustrated for all drugs (blue), on-patent drugs (orange), and off-patent drugs with an available generic or biosimilar (green).

Abbreviations: CPI, consumer inflation index; FDA, US Food and Drug Administration.

Out of the 66 included drugs, 42% were first-in-class agents and 41% were small molecules (Table 18). There were 12 drugs (18%) that were approved with a companion biomarker. Cancer drugs frequently received the orphan designation (62%), accelerated approval (50%), fast track (44%), priority review (80%), and BTD (63%). Median disease incidence per 100,000 US inhabitants was 8.3 (IQR: 3.2 to 69.3) and median DALYs per person were 7.7 (IQR: 5.5 to 12.9). A median of 1 (IQR: 0 to 3) supplemental indication was approved by the FDA for each drug. On a broad level, a median of 14 (IQR: 6 to 23) new competitors entered the market and on a narrow level a median of 3 (IQR: 1 to 6) new competitors entered the market during the study period.

	No.	(%)
Clinical benefit		
OS (HRs), median (IQR)	0.76	(0.68-0.9)
OS (median improvement), median (IQR)	2.2	(1.5-3.7)
OS (% improvement), median (IQR)	24	(10-30)
PFS (HRs), median (IQR)	0.64	(0.48-0.7)
PFS (median improvement), median (IQR)	2.4	(1.4-4.3)
PFS (% improvement), median (IQR)	62	(40-110)
Tumor response (RRs)	2.37	(1.37-5.78)
Innovativeness		
Next-in-class	38	(57.6%)
First-in-class	28	(42.4%)
Molecule Type		
Small-molecule	27	(40.9%)
Other [a]	39	(59.1%)
Biomarker		
No	54	(81.8%)
Yes	12	(18.2%)
Orphan designation		
No	25	(37.9%)
Yes	41	(62.1%)
Accelerated approval		
No	33	(50.0%)
Yes	33	(50.0%)
Fast track status		
No	37	(56.1%)
Yes	29	(43.9%)
Priority review		
No	13	(19.7%)
Yes	53	(80.3%)
Breakthrough therapy [b]		
No	13	(37.1%)
Yes	22	(62.9%)
Disease incidence, median (IQR) [c]	8.3	(3.2-69.3)
DALYs per person, median (IQR)	7.7	(5.5-12.9)
New supplemental indications, median (IQR) [d]	1	(0-3)
New competitors (broad), median (IQR) [d]	14	(6-23)
New competitors (narrow), median (IQR) [d]	3	(1-6)
Total	**66**	**100.0%**

Table 18: Sample overview

[a] The category other includes biologics, antibody-drug conjugates, enzymes, cell therapies, gene therapies, and radionuclides.
[b] Only cancer drugs with FDA approval after 2012 were included to compare breakthrough and non-breakthrough therapy drugs.
[c] Disease incidence rate per 100,000 US inhabitants.
[d] New supplemental indications and competitors were tracked until 2022.

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; HR, hazard ratio; IQR, interquartile range; OS, overall survival; PFS, progression-free survival; RR, relative risk.

4.5.2 Univariate regression analysis

Results of the univariate regression analyses are exhibited in Table 19. OS hazard ratios were not significantly correlated to launch prices (ß=1.12, p=0.441) or post-launch price changes (ß=-0.0097, p=0.651). Accordingly, there was no meaningful association between PFS HRs, and launch (ß=0.11, p=0.945) or post-launch prices (ß=0.0071, p=0.729).

In the univariate random-effects models, there was a non-significant trend that launch / post-launch prices are 50% (p=0.220) / 2% per year (p=0.183) higher for first-in-class and 55% (p=0.191) / 2% (p=0.283) higher for biologic agents. There was no relevant association between launch / post-launch prices and a drug's biomarker status. The price elasticity between launch prices and disease incidence was -0.26 (p=0.006) and between annual post-launch price changes and disease incidence -0.0065 (p=0.028). Accordingly, 73% (p=0.108) higher launch prices and 2% (p=0.037) higher price increases per year post-launch were observed for orphan than non-orphan drugs. The approval of new supplemental indications (ß=-0.0082, p=0.097) and the market entry of new competitors were only marginally and non-significantly associated with post-launch price changes (ß=-0.0064, p=0.076).

	Univariate analyses		
	ß	[95% CI]	*P*
Clinical Benefit			
OS (HRs)			
OS (HRs)	1.1207	[-1.7291 to 3.9706]	*0.441*
Δ Time since launch X OS (HRs)	-0.0097	[-0.0517 to 0.0323]	*0.651*
OS (median improvement)			
OS (median improvement)	-0.0448	[-0.1383 to 0.0487]	*0.348*
Δ Time since launch X OS (median improvement)	0.0001	[-0.0031 to 0.0033]	*0.935*
OS (% improvement)			
OS (% improvement)	-0.0704	[-0.7945 to 0.6538]	*0.849*
Δ Time since launch X OS (% improvement)	0.0072	[-0.0296 to 0.0440]	*0.701*
PFS (HRs)			
PFS (HRs)	0.1127	[-3.0821 to 3.3075]	*0.945*
Δ Time since launch X PFS (HRs)	0.0071	[-0.0332 to 0.0475]	*0.729*
PFS (median improvement)			
PFS (median improvement)	0.0545	[-0.0697 to 0.1787]	*0.390*
Δ Time since launch X PFS (median improvement)	-0.0015	[-0.0026 to -0.0004]	*0.006*
PFS (% improvement)			
PFS (% improvement)	0.2214	[-0.5773 to 1.0200]	*0.587*
Δ Time since launch X PFS (% improvement)	-0.0068	[-0.0167 to 0.0032]	*0.182*
Tumor response (RRs)			
Tumor response (RRs)	-0.0234	[-0.0481 to 0.0013]	*0.063*
Δ Time since launch X Tumor response (RRs)	0.0003	[0.0000 to 0.0005]	*0.023*
Drug Characteristics			
Innovativeness			
First-in-Class	0.4058	[-0.2432 to 1.0548]	*0.220*
Δ Time since launch X First-in-Class	0.0196	[-0.0092 to 0.0483]	*0.183*
Product Type			
Biologic	0.4396	[-0.2186 to 1.0979]	*0.191*
Δ Time since launch X Biologic	0.0171	[-0.0141 to 0.0482]	*0.283*
Biomarker Status			
Biomarker	0.0199	[-0.907 to 0.9468]	*0.966*
Δ Time since launch X Biomarker	0.0017	[-0.034 to 0.0375]	*0.924*
Disease Epidemiology			
Disease Incidence [a]			
Log(Disease Incidence)	-0.2608	[-0.4451 to -0.0765]	*0.006*
Δ Time since launch X Log(Disease Incidence)	-0.0065	[-0.0124 to -0.0007]	*0.028*
Disease Burden			
DALYs per Person	0.0640	[0.0059 to 0.1221]	*0.031*
Δ Time since launch X DALYs per Person	0.0016	[-0.0003 to 0.0035]	*0.094*
Special FDA Designations			
Orphan Designation			
Orphan Designation	0.5492	[-0.1213 to 1.2197]	*0.108*
Δ Time since launch X Orphan Designation	0.0240	[0.0014 to 0.0465]	*0.037*
Fast Track			
Fast Track	-0.3499	[-0.9393 to 0.2395]	*0.245*
Δ Time since launch X Fast Track	-0.0226	[-0.0476 to 0.0024]	*0.077*
Accelerated Approval			
Accelerated Approval	0.1817	[-0.4472 to 0.8106]	*0.571*
Δ Time since launch X Accelerated Approval	0.0244	[-0.0025 to 0.0512]	*0.075*
Priority Review			
Priority Review	0.4409	[-0.4970 to 1.3788]	*0.357*
Δ Time since launch X Priority Review	-0.0148	[-0.0521 to 0.0225]	*0.436*
Breakthrough Therapy [b]			
Breakthrough Therapy	0.4189	[-0.1635 to 1.0013]	*0.159*
Δ Time since launch X Breakthrough Therapy	-0.0083	[-0.0171 to 0.0004]	*0.062*
Market Dynamics [c]			
Δ New Supplemental Indications	-0.0082	[-0.0180 to 0.0015]	*0.097*
Δ New Competitors (broad)	-0.0064	[-0.0135 to 0.0007]	*0.076*
Δ New Competitors (narrow)	-0.0114	[-0.0249 to 0.0021]	*0.099*

Table 19: Univariate random-effects regression analyses of collected variables on prices for FDA-approved injectable cancer drugs from 2005 to 2023

Notes: Each row represents a separate random-effects regression. Time-variant variables are marked with a Δ and their coefficients can be interpreted as associations with drugs' post-launch price changes. Coefficients of all other

variables are time-invariant and can be interpreted as associations with drugs' launch prices. All models were adjusted for heteroskedastic standard errors.

[a] The category other includes biologics, antibody-drug conjugates, enzymes, cell therapies, gene therapies, and radionuclides. [b] Only cancer drugs with FDA approval after 2012 were included to compare breakthrough and non-breakthrough therapy drugs. [c] Disease incidence rate per 100,000 US inhabitants. [d] Only includes price data until the fourth quarter of 2021, given that indication and competition data was not collected for 2022.

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk.

4.5.3 Multivariate regression analysis

In the multivariate random-effects model, special FDA pathways (e.g. fast track, priority review, accelerated approval, BTD) other than the orphan designation were excluded given that these are often granted concurrently to medicines with substantial benefits in treating serious conditions with significant unmet needs, e.g. orphan conditions.[76] We conducted three different multivariate random-effects models (Table 20). The first model included all variables, the second model excluded the orphan designation, and the third model excluded disease incidence and DALYs per person, given that these three variables are collinear. The second model shows that launch and post-launch price changes were negatively associated with disease incidence, yet not disease burden. The elasticity between launch / post-launch price changes and disease incidence was -0.25 (p=0.008) / -0.0086 (p=0.032), respectively. The third model highlights that launch prices were 120% (p=0.051) higher for orphan than non-orphan drugs, with 3% (p=0.008) greater annual post-launch price increases.

	Model 1			Model 2			Model 3		
	ß	[95% CI]	*P*	ß	[95% CI]	*P*	ß	[95% CI]	*P*
Time invariant variables									
First-in-class	0.0890	[-0.4655 to 0.6436]	*0.753*	0.0903	[-0.4685 to 0.6491]	*0.751*	0.2119	[-0.3614 to 0.7851]	*0.469*
Biologic	0.4951	[-0.1823 to 1.1725]	*0.152*	0.4794	[-0.2084 to 1.1673]	*0.172*	0.3171	[-0.3208 to 0.9550]	*0.330*
Biomarker	0.3190	[-1.0338 to 1.6718]	*0.644*	0.3320	[-0.9269 to 1.5910]	*0.605*	0.3708	[-0.9687 to 1.7102]	*0.587*
Orphan Designation	-0.1120	[-0.9321 to 0.7082]	*0.789*				0.7870	[-0.0045 to 1.5784]	*0.051*
Log(disease incidence) [a]	-0.2748	[-0.4700 to -0.0797]	*0.006*	-0.2511	[-0.4357 to -0.0666]	*0.008*			
DALYs per person	0.0291	[-0.0243 to 0.0825]	*0.285*	0.0288	[-0.0269 to 0.0845]	*0.311*			
Time variant variables									
Δ Time since launch	-0.0105	[-0.0649 to 0.0439]	*0.704*	0.0402	[0.0027 to 0.0777]	*0.036*	0.0001	[-0.0209 to 0.0210]	*0.995*
Δ Time since launch X First-in-class	0.0069	[-0.0115 to 0.0254]	*0.462*	0.0111	[-0.0085 to 0.0307]	*0.268*	0.0071	[-0.0092 to 0.0234]	*0.391*
Δ Time since launch X Biologic	0.0174	[-0.0037 to 0.0386]	*0.106*	0.0182	[-0.0040 to 0.0404]	*0.108*	0.0183	[-0.0049 to 0.0415]	*0.123*
Δ Time since launch X Biomarker	0.0017	[-0.0225 to 0.0258]	*0.893*	0.0032	[-0.0264 to 0.0328]	*0.832*	0.0020	[-0.0238 to 0.0277]	*0.881*
Δ Time since launch X Orphan Designation	0.0388	[0.0000 to 0.0776]	*0.050*				0.0301	[0.0079 to 0.0523]	*0.008*
Δ Time since launch X Log(disease incidence)	0.0029	[-0.0070 to 0.0128]	*0.566*	-0.0086	[-0.0165 to -0.0007]	*0.032*			
Δ Time since launch X DALYs per person	0.0000	[-0.0021 to 0.0021]	*0.988*	-0.0004	[-0.0028 to 0.0019]	*0.716*			
Δ New supplemental indications	-0.0164	[-0.0317 to -0.0012]	*0.034*	-0.0136	[-0.0290 to 0.0018]	*0.083*	-0.0158	[-0.0306 to -0.0010]	*0.037*
Δ New competitors (broad)	-0.0002	[-0.0077 to 0.0074]	*0.964*	0.0012	[-0.0073 to 0.0097]	*0.789*	0.0006	[-0.0075 to 0.0088]	*0.876*
Constant	4.6105	[3.3516 to 5.8694]	*<0.001*	4.4835	[3.6062 to 5.3607]	*<0.001*	3.6663	[2.7965 to 4.5360]	*<0.001*
Observations		1733			1733			1744	
R^2 Within		47.6%			45.0%			47.5%	
R^2 Between		21.4%			22.0%			12.5%	
R^2 Overall		13.1%			13.8%			9.0%	

Table 20: Multivariate random-effects regression analyses of collected variables on prices for FDA-approved injectable cancer drugs from 2005 to 2022

Notes: Three distinct models were constructed. Whilst Model 1 includes all variables, Model 2 excludes the orphan designation status and Model 3 excludes disease incidence rates and DALYs per person, given their collinearity.

[a] The category other includes biologics, antibody-drug conjugates, enzymes, cell therapies, gene therapies, and radionuclides.
[b] Disease incidence rate per 100,000 US inhabitants.

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration.

In all three models, post-launch prices declined by up to -2% as the FDA approved new supplemental indications for the same drug. Prices did not significantly decline as new competitors for the same disease entered the market.

4.5.4 Sensitivity analysis

Results remain robust under sensitivity analysis. Regression coefficients and significance levels were robust when using a two-step fixed-effects approach to evaluate the association between collected variables and launch / post-launch price changes (Table 21). Furthermore, there was also no association between post-launch price changes and the narrow measure of competition (Table 22).

A) Fixed-Effects Panel Regression

	Model 1			Model 2			Model 3		
	ß	[95% CI]	*P*	ß	[95% CI]	*P*	ß	[95% CI]	*P*
Time variant variables									
Δ Time since launch	-0.0108	[-0.0663 to 0.0447]	*0.699*	0.0401	[0.0019 to 0.0783]	*0.040*	0.0002	[-0.0212 to 0.0216]	*0.987*
Δ Time since launch X First-in-class	0.0069	[-0.0119 to 0.0258]	*0.465*	0.0111	[-0.0089 to 0.0311]	*0.272*	0.0072	[-0.0095 to 0.0238]	*0.392*
Δ Time since launch X Biologic	0.0175	[-0.0041 to 0.0390]	*0.110*	0.0182	[-0.0044 to 0.0409]	*0.112*	0.0183	[-0.0054 to 0.0419]	*0.127*
Δ Time since launch X Biomarker	0.0015	[-0.0231 to 0.0261]	*0.902*	0.0031	[-0.0271 to 0.0332]	*0.839*	0.0019	[-0.0244 to 0.0282]	*0.885*
Δ Time since launch X Orphan Designation	0.0389	[-0.0007 to 0.0785]	*0.054*				0.0300	[0.0074 to 0.0527]	*0.010*
Δ Time since launch X Log(disease incidence)	0.0030	[-0.0071 to 0.0131]	*0.556*	-0.0086	[-0.0166 to -0.0005]	*0.037*			
Δ Time since launch X DALYs per person	0.0000	[-0.0022 to 0.0022]	*0.995*	-0.0004	[-0.0028 to 0.0020]	*0.722*			
Δ New supplemental indications	-0.0164	[-0.0320 to -0.0009]	*0.038*	-0.0136	[-0.0293 to 0.0021]	*0.089*	-0.0157	[-0.0308 to -0.0006]	*0.042*
Δ New competitors (broad)	-0.0003	[-0.0080 to 0.0074]	*0.935*	0.0010	[-0.0077 to 0.0097]	*0.814*	0.0006	[-0.0077 to 0.0088]	*0.890*
Observations		1733			1733			1744	
R² Within		47.6%			45.0%			47.5%	
R² Between		0.0%			0.5%			0.2%	
R² Overall		0.8%			1.9%			1.4%	

B) OLS Regression at Launch

	Model 1			Model 2			Model 3		
	ß	[95% CI]	*P*	ß	[95% CI]	*P*	ß	[95% CI]	*P*
Time invariant variables									
First-in-class	0.0889	[-0.4952 to 0.6729]	*0.761*	0.0902	[-0.4865 to 0.6669]	*0.755*	0.2119	[-0.3782 to 0.8021]	*0.475*
Biologic	0.4959	[-0.2205 to 1.2124]	*0.171*	0.4803	[-0.2270 to 1.1877]	*0.179*	0.3175	[-0.3428 to 0.9779]	*0.340*
Biomarker	0.3191	[-1.0666 to 1.7048]	*0.646*	0.3319	[-0.9337 to 1.5975]	*0.601*	0.3708	[-0.9563 to 1.6979]	*0.578*
Orphan Designation	-0.1112	[-0.9394 to 0.7170]	*0.789*				0.7871	[-0.0006 to 1.5749]	*0.050*
Log(disease incidence) [a]	-0.2746	[-0.4802 to -0.0690]	*0.010*	-0.2510	[-0.4467 to -0.0553]	*0.013*			
DALYs per person	0.0292	[-0.0259 to 0.0842]	*0.293*	0.0288	[-0.0273 to 0.0849]	*0.308*			
Observations		60			60			61	
R² Between		21.5%			21.4%			12.2%	

Table 21: Multivariate fixed-effects regression analyses of collected variables on prices for FDA-approved injectable cancer drugs from 2005 to 2022

Notes: First, we constructed a fixed-effects panel regression including all time-varying variables (A). Based on this model we predicted log-prices at launch. Thereafter, we conducted an OLS regression including all time-invariant variables on predicted log-prices at launch was performed (B). Three distinct models were constructed. Whilst Model 1 includes all variables, Model 2 excludes the orphan designation status, and Model 3 excludes disease incidence rates and DALYs per person, given their collinearity. Coefficients of the time-invariant variables can be interpreted as associations with drugs' launch prices. Coefficients of the time-variant variables can be interpreted as associations with drugs' post-launch prices. All models were adjusted for heteroskedastic standard errors. The time since launch was measured in years.

[a] Disease incidence rate per 100,000 US inhabitants.

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; OLS, ordinary least squares.

	Model 1			Model 2			Model 3		
	ß	[95% CI]	*P*	ß	[95% CI]	*P*	ß	[95% CI]	*P*
Time invariant variables									
First-in-class	0.0840	[-0.4702 to 0.6381]	*0.767*	0.0883	[-0.4694 to 0.6459]	*0.756*	0.2097	[-0.3647 to 0.7841]	*0.474*
Biologic	0.5068	[-0.1629 to 1.1766]	*0.138*	0.4865	[-0.1908 to 1.1638]	*0.159*	0.3251	[-0.3075 to 0.9578]	*0.314*
Biomarker	0.3095	[-1.0382 to 1.6573]	*0.653*	0.3348	[-0.9169 to 1.5864]	*0.600*	0.3717	[-0.9604 to 1.7037]	*0.584*
Orphan Designation	-0.1159	[-0.927 to 0.6951]	*0.779*				0.7870	[-0.0072 to 1.5812]	*0.052*
Log(disease incidence) [a]	-0.2741	[-0.4671 to -0.081]	*0.005*	-0.2498	[-0.4361 to -0.0635]	*0.009*			
DALYs per person	0.0301	[-0.0234 to 0.0836]	*0.270*	0.0290	[-0.0268 to 0.0849]	*0.308*			
Time variant variables									
Δ Time since launch	-0.0129	[-0.0646 to 0.0388]	*0.625*	0.0403	[0.0028 to 0.0778]	*0.035*	0.0019	[-0.0166 to 0.0204]	*0.839*
Δ Time since launch X First-in-class	0.0062	[-0.0122 to 0.0245]	*0.510*	0.0111	[-0.0083 to 0.0306]	*0.261*	0.0070	[-0.0093 to 0.0232]	*0.402*
Δ Time since launch X Biologic	0.0179	[-0.0037 to 0.0394]	*0.104*	0.0181	[-0.0044 to 0.0407]	*0.115*	0.0185	[-0.0051 to 0.0421]	*0.124*
Δ Time since launch X Biomarker	0.0013	[-0.0229 to 0.0255]	*0.916*	0.0030	[-0.0269 to 0.0328]	*0.846*	0.0018	[-0.024 to 0.0276]	*0.890*
Δ Time since launch X Orphan Designation	0.0409	[0.0029 to 0.0789]	*0.035*				0.0290	[0.0086 to 0.0494]	*0.005*
Δ Time since launch X Log(disease incidence)	0.0040	[-0.0056 to 0.0137]	*0.413*	-0.0083	[-0.0158 to -0.0008]	*0.029*			
Δ Time since launch X DALYs per person	0.0000	[-0.0021 to 0.0021]	*0.997*	-0.0004	[-0.0028 to 0.002]	*0.726*			
Δ New supplemental indications	-0.0169	[-0.0325 to -0.0013]	*0.033*	-0.0134	[-0.0292 to 0.0024]	*0.097*	-0.0157	[-0.0305 to -0.0008]	*0.039*
Δ New competitors (broad)	-0.0040	[-0.0179 to 0.0099]	*0.571*	0.0003	[-0.0132 to 0.0138]	*0.961*	-0.0015	[-0.0156 to 0.0126]	*0.833*
Constant	4.6085	[3.3607 to 5.8564]	*<.001*	4.4813	[3.6028 to 5.3598]	*0.000*	3.6703	[2.7929 to 4.5477]	*0.000*
Observations		1733			1733			1744	
R² Within		47.8%			45.0%			47.5%	
R² Between		21.0%			21.7%			12.3%	
R² Overall		12.7%			13.6%			8.8%	

Table 22: Multivariate random-effects regression analyses with the narrow measure of new competitors

Notes: Three distinct model were constructed. Whilst Model 1 includes all variables, Model 2 excludes the orphan designation status and Model 3 excludes disease incidence rates and DALYs per person, given their collinearity.

[a] The category other includes biologics, antibody-drug conjugates, enzymes, cell therapies, gene therapies, and radionuclides. [b] Disease incidence rate per 100,000 US inhabitants.

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration.

4.5.5 Pairwise Pearson correlation coefficients

Figure 31 shows pairwise Pearson correlation coefficients of inflation-adjusted prices for drugs within a class. Price changes for PD-1/PD-L1 inhibitors were closely aligned with Pearson correlation coefficients between 0.8 and 1.0 (only coefficients for dostarlimab, which was only recently approved by the FDA, were lower). The Granger causality test suggests that for most PD-1/PD-L1 inhibitor drug pairs' prices (at least) univariate causality exists (Figure 32). Similarly, coefficients were approaching 1.0, suggesting a very strong positive correlation between prices of drugs within the same class, for CD20 antibodies (r=0.68 (no causality), 0.93 (bidirectional causality), and 0.97 (unidirectional causality)), CD38 antibodies (r=0.91, no causality), HER2 antibodies (r=0.88, unidirectional causality), and mTOR inhibitors (r=0.98, bidirectional causality). In contrast, correlation coefficients were negative for VEGFR antibodies (r=-0.24, unidirectional causality), proteasome inhibitors (r=-0.83, no causality), and HDAC inhibitors (r=-0.31, no causality). For EGFR antibodies, we observed positive (r=0.20 to 0.72) and negative (r=-0.45) correlation coefficients with mixed causality test results.

PD-1/PD-L1 antibodies | CD20 antibodies | CD38 antibodies | mTOR inhibitors | HDAC inhibitors
EGFR antibodies | VEGFR antibodies | HER2 antibodies | Proteasom inhibitors

	Pembrolizumab	Nivolumab	Durvalumab	Avelumab	Atezolizumab	Cemiplimab	Dostarlimab	Cetuximab	Panitumumab	Necitumumab	Rituximab	Ofatumumab	Obinutuzumab	Bevacizumab	Ramucirumab	Daratumumab	Isatuximab	Trastuzumab	Pertuzumab	Temsirolimus	Everolimus	Bortezomib	Carfilzomib	Romidepsin	Belinostat
Pembrolizumab																									
Nivolumab	0.88																								
Durvalumab	0.89	0.98																							
Avelumab	0.88	0.99	0.98																						
Atezolizumab	0.82	0.91	0.95	0.86																					
Cemiplimab	0.87	0.97	0.97	0.97	0.93																				
Dostarlimab	-0.39	0.86	0.83	0.81	0.83	0.59																			
Cetuximib	0.17	0.17	0.65	0.46	0.11	0.69	0.97																		
Panitumumab	-0.25	-0.32	-0.46	-0.49	-0.67	-0.53	-0.13	0.72																	
Necitumumab	0.83	0.93	0.98	0.95	0.88	0.99	0.68	0.20	-0.45																
Rituximab	0.64	0.72	-1.00	0.19	-0.04	NE	NE	-0.44	0.91	0.85															
Ofatumumab	0.38	0.36	0.84	0.77	0.51	0.87	0.68	0.93	0.92	0.52	0.93														
Obinutuzumab	0.72	0.76	0.90	0.83	0.96	0.90	0.24	0.55	0.28	0.86	0.97	0.68													
Bevacizumab	0.61	0.69	-1.00	0.20	-0.01	NE	NE	0.20	0.93	0.87	0.75	0.93	0.97												
Ramucirumab	0.40	0.55	0.66	0.64	0.43	0.66	0.87	0.34	0.03	0.46	-0.23	0.28	0.27	-0.24											
Daratumumab	0.19	0.25	0.75	0.50	0.19	0.74	0.67	0.91	0.70	0.29	0.90	0.89	0.33	0.89	0.28										
Isatuximab	0.68	0.97	0.92	0.95	0.94	0.90	0.99	0.93	0.04	0.92	NE	0.88	0.90	NE	0.92	0.91									
Trastuzumab	0.61	0.73	-0.50	-0.02	0.11	1.00	NE	-0.38	0.91	0.80	1.00	0.91	0.96	0.77	-0.23	0.86	.								
Pertuzumab	-0.09	-0.16	-0.06	-0.21	-0.46	-0.06	-0.04	0.94	0.89	-0.19	0.92	0.87	0.40	0.89	0.05	0.83	0.43	0.88							
Temsirolimus	0.76	0.82	NE	0.20	0.85	NE	NE	0.44	0.95	0.69	0.98	0.90	0.91	0.99	0.25	0.82	NE	0.97	0.78						
Everolimus	0.62	0.77	0.56	0.50	-0.71	0.97	NE	0.83	0.98	0.88	0.96	0.95	0.87	0.97	-0.06	0.95	NE	0.98	0.88	0.98					
Bortezomib	-0.73	-0.83	NE	-0.79	-0.17	NE	NE	-0.91	0.31	-0.35	0.82	-0.57	-0.83	0.20	-0.37	-0.71	NE	0.82	-0.81	0.39	-0.53				
Carfilzomib	-0.17	-0.24	-0.37	-0.33	-0.59	-0.43	-0.16	0.89	0.93	-0.25	0.93	0.85	0.30	0.92	-0.07	0.81	0.17	0.90	0.96	0.83	0.88	-0.83			
Romidepsin	0.03	-0.06	-0.21	-0.24	0.19	-0.47	NE	0.34	0.65	-0.47	0.86	0.52	-0.03	0.88	0.05	-0.30	0.82	0.67	-0.04	0.97	0.54	-0.04	0.00		
Belinostat	0.07	0.02	0.59	0.17	-0.26	0.72	0.56	0.94	0.87	0.04	0.98	0.87	0.29	0.98	0.18	0.88	0.90	0.91	0.95	0.98	0.95	-0.92	0.91	-0.31	

Figure 31: Pairwise Pearson correlation coefficients among injectable cancer drugs

Notes: This matrix presents pairwise correlation coefficients for 9 injectable cancer classes entailing 25 distinct drugs. We included cancer drugs with FDA approval between 2000 and 2022. To accurately analyze the competitive dynamics of the HER2 and CD20 antibodies, we further included rituximab and trastuzumab. We only included price data for drugs before patent expiry.

Abbreviations: CAR, chimeric antigen receptor; CD20, cluster of differentiation 20; CD38, cluster of differentiation 38; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; NE, no estimates; VEGFR, vascular endothelial growth factor receptor.

PD-1/PD-L1 antibodies | CD20 antibodies | CD38 antibodies | mTOR inhibitors | HDAC inhibitors
EGFR antibodies | VEGFR antibodies | HER2 antibodies | Proteasom inhibitors

	Pembrolizumab	Nivolumab	Durvalumab	Avelumab	Atezolizumab	Cemiplimab	Dostarlimab	Cetuximab	Panitumumab	Necitumumab	Rituximab	Ofatumumab	Obinutuzumab	Bevacizumab	Ramucirumab	Daratumumab	Isatuximab	Trastuzumab	Pertuzumab	Temsirolimus	Everolimus	Bortezomib	Carfilzomib	Romidepsin	Belinostat
Pembrolizumab		0.23	0.41	0.05	0.03	0.94	NE																		
Nivolumab	0.00		0.20	0.04	0.61	0.51	NE																		
Durvalumab	0.00	0.37		0.21	0.19	0.65	NE																		
Avelumab	0.00	0.40	0.65		0.75	0.91	NE																		
Atezolizumab	0.00	0.11	0.10	0.02		0.01	NE																		
Cemiplimab	0.00	0.00	0.00	0.00	0.02		NE																		
Dostarlimab	NE	NE	NE	NE	NE	NE																			
Cetuximib									0.00	0.21															
Panitumumab								0.96		0.66															
Necitumumab								0.18	0.55																
Rituximab												0.02	0.05												
Ofatumumab											0.69		0.26												
Obinutuzumab											0.01	0.40													
Bevacizumab															0.02										
Ramucirumab														0.45											
Daratumumab																	0.49								
Isatuximab																0.10									
Trastuzumab																			0.01						
Pertuzumab																		0.29							
Temsirolimus																				0.00					
Everolimus																					0.02				
Bortezomib																							0.67		
Carfilzomib																						0.84			
Romidepsin																									0.56
Belinostat																								0.62	

Figure 32: Granger causality test for the first difference of log prices of injectable cancer drugs

Notes: This matrix presents p-values for the Granger causality test for the first difference of log prices of 9 injectable cancer classes entailing 25 distinct drugs. We included cancer drugs with FDA approval between 2000 and

2022. We further included rituximab and trastuzumab to accurately analyze the competitive dynamics of the HER2 and CD20 antibodies. We only included price data for drugs before patent expiry. For each drug pair, bidirectional causality was tested, resulting in two p-values.

Abbreviations: CAR, chimeric antigen receptor; CD20, cluster of differentiation 20; CD38, cluster of differentiation 38; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; NE, no estimates; VEGFR, vascular endothelial growth factor receptor.

Figure 33 suggests that the number of overlapping FDA-approved indications was positively associated with the measured correlation coefficient for each drug pair. For example, the CD38 antibodies daratumumab and isatuximab were both only approved to treat multiple myeloma (100% overlapping indications). Their price correlation coefficient was 0.91. In contrast, the price correlation coefficient was -0.45 for panitumumab and necitumumab, EGFR antibodies that were separately approved for colorectal cancer and NSCLC, respectively (0% overlapping indications).

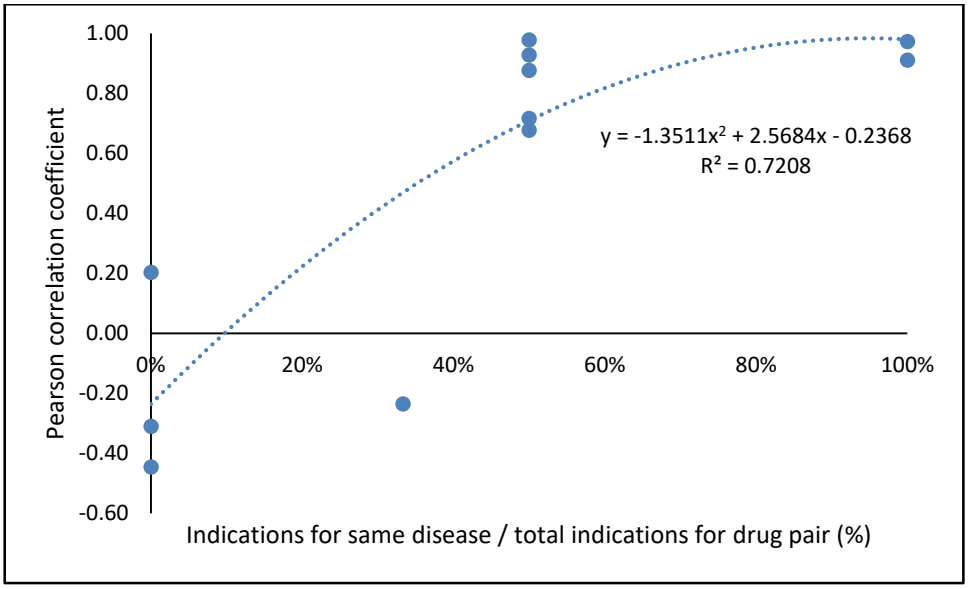


Figure 33: Scatterplot of pairwise correlation coefficients and the share of overlapping indications

Notes: The graph plots the share of overlapping indication against pairwise correlation coefficients for each drug pair within a class. The share of overlapping FDA-approved indications was determined by the quotient of the number of common indications and the number of total indications for each drug pair. PD-1/PD-L1 inhibitors were excluded. Further, the drug pair "bortezomib-carfilzomib" was excluded given that carfilzomib, a second generation proteasome inhibitor, replaced bortezomib, a first generation proteasome inhibitor, for most multiple myeloma patients.

Abbreviations: FDA, US Food and Drug Administration.

4.6 Discussion

This longitudinal study analyzed factors associated with launch prices and post-launch price changes of injectable cancer drugs in the US. Over the study period from 2005 to 2023, prices for on-patent cancer drugs increased by an average of 94%. We found that launch prices were non-significantly higher for innovative first-in-class drugs. Post-launch price changes were positively associated with the orphan designation and negatively associated with disease incidence and the approval of new supplemental indications. We found no consistent association between launch/post-launch prices and drugs' clinical benefit. The market entry of new competitors was not associated with price reductions. 28 of 33 drug pairs within the same class had positive correlation coefficients.

4.6.1 Clinical benefit

We found that post-launch price changes were not significantly associated with new cancer drugs' clinical benefit in terms of OS, PFS, or tumor response benefit. Similarly, Vokinger et al. could not identify any association between post-launch price changes and drugs' clinical benefit, as measured by the ASCO-VF and the ESMO-MCBS.[120] We observed a positive association between launch prices and drugs' PFS, yet not OS and tumor response. This positive association between launch prices could be explained by the orphan drugs' greater PFS benefit that is measured in non-robust clinical trials.[76,160] These findings are coherent with prior studies that could not confirm a consistent link between drugs' benefits and launch prices.[22,74,112–118] In summary, there is little evidence that launch and post-launch prices are aligned with the clinical benefit a drug offers to patients in the US.

US policymakers could implement value-based pricing policies that regularly re-examine drug prices following initial market entry to better align launch prices and post-launch price changes with drugs' clinical benefits. Thereby new drug prices could better reflect each drug's clinical

benefit as new evidence is generated. This is particularly relevant for cancer drugs.[26] Most cancer drugs are initially approved based on small, non-robust, single-arm trials testing the new drug for rare diseases in a heavily pre-treated patient population and reporting surrogate endpoints, e.g. PFS or tumor response.[73] Over time more robust post-approval trials are conducted for the first-line setting evaluating clinical endpoints, e.g. OS. Evidence from European countries highlights that the resulting lower benefit is associated with price reductions.[38]

4.6.2 Cancer epidemiology

Greater post-launch price increases were observed for orphan drugs. Accordingly, post-launch price changes were negatively associated with disease incidence. A 1% decline in disease incidence was associated with a 0.2511% (p=0.008) increase in launch prices and a 0.0086% annual increase in post-launch prices, respectively. These findings are coherent with previous studies highlighting that sponsors of specialty drugs, in particular those for rare diseases, demand a launch price premium and further increase prices at more than double the pace of non-orphan drugs.[74,76,123–125] Orphan drugs often offer significant therapeutic advances for patients.[76,160] However, their high launch and rising post-launch prices pose a barrier for patients to access these medicines.[142] Insured patients do not only have to pay their insurance premium but also have to bear the insurance plans' deductible and co-payment. Given that co-payments are calculated as a percentage of a drug's list price, rising post-launch list prices result in rising OOP expenditure for patients. The Orphan Drug Act of 1983 effectively grants drugs for rare diseases 7 years of market exclusivity. Sponsors often use this monopoly position to raise prices,[76] which results in excess profits and returns for pharmaceutical firms.[80,81] The recently introduced IRA contains an OOP cost cap of $2,000 per year for Medicare Part D drugs. A similar provision would be necessary to limit patients' OOP expenditures of Medicare Part B drugs, particularly those with rare diseases.

4.6.3 Competition

In our study, the market entry of new competitors for the same disease was not associated with post-launch price declines. These findings are coherent with previous literature finding no or weak evidence for price competition. Sarpatwari et al. systematically reviewed ten studies and found little evidence and no evidence that launch and post-launch prices are affected by competition, respectively.[57] Howard et al. found launch prices for anti-cancer drugs to be negatively associated with the number of competitors.[110] Bennette et al. analyzed the market for oral anti-cancer drugs from 2007 to 2013 using pharmacy claims data and found that the market entrance of new competitors resulted in a 2% price reduction.[45] In contrast, Gordon et al. did not observe any change in anti-cancer post-launch prices as new competitors entered the market between 2005 and 2012. In conclusion, there is little to no evidence of brand-brand price competition in the drug market.

Several factors could help to explain the special competitive dynamics in branded pharmaceutical product markets. First, higher prices could signal greater safety and efficacy, e.g., high-quality products. Acting as a Veblen good, highly-priced drugs could be viewed as superior and thereby induce demand, especially when safety and efficacy data are not available or not accessible (which is often the case for newly approved cancer drugs).[161,162] Second, anti-cancer drugs may often fill niche market segments within a disease. Given only a subset of biomarker-positive patients are eligible to receive targeted agents, from the pool of all available medicines for a disease, only a few products can be perceived as close substitutes. Moreover, the market for anti-cancer drugs is further convoluted by the use of drugs in different lines of therapy and a complementary manner.[45] Next-in-class drugs may enter market segments for the advanced-line but not first-line therapy within the same disease, and thereby do not affect the pricing of

the first-in-class agent. Nonetheless, our narrow measure of competition, which adjusts for disease type, line of therapy, therapeutic setting, and biomarker profile, did not show any significant price reductions following the entry of new competitors.

Prior studies inappropriately evaluated the competitive dynamics of the pharmaceutical market based on a price correlation analysis.[151,153–156] They assumed that drugs of the same class compete within the same market. Although cancer drugs within the same class are typically not approved for the same indications, authors assumed that high correlation coefficients (>0.80) can be interpreted as a lack of within-class competition, given that drug pairs' prices rise at the same pace. However, correlation coefficients approaching 1 may also indicate competitive pressure if drug pairs' prices simultaneously decline. In economics, price correlations are used to define and differentiate markets.[157,158,163] A positive correlation indicates that two products compete in the same market, whereas a low correlation suggests that they belong to two separate markets. This study observed positive correlation coefficients beyond 0.80 for 25 of 33 evaluated drug pairs (without PD-1/PD-L1 inhibitors: 6 of 12). Excluding PD-1/PD-L1 inhibitors, we found the percentage of overlapping indications to be positively associated with drug pairs' correlation coefficients. This result suggests that the drug's class, which represents a biochemical classification of a drug's target, may not be the sole adequate measure to define the competitive market for cancer drugs. Instead, a clinical, patient-centered approach for a cancer drug's competitive market should also entail its FDA-approved indications which legally define the eligible patient population. In other words, physicians can only interchangeably prescribe new drugs of the same class to cancer patients (and thereby create a competitive market environment) if both drugs receive approval for the same diseases and line of therapy. Therefore, future studies analyzing competition among cancer drugs must adequately define the competitive market for each drug based on the eligible patient population, and employ appropriate economic methodology to analyze competition.

4.6.4 Supplemental indications

Results show a marginal reduction in prices (up to -2%) as new supplemental indications were approved for the same drug. In contrast, Gordon et al. did not observe any association between price changes and new supplemental indications or off-label uses,[119] whilst Bennette et al. found a positive correlation between price changes and new supplemental indications.[45] However, Gordon et al.'s analysis is based on multivariate OLS models and limited to 24 injectable anti-cancer drugs with price data from 2005 to 2017. In our analysis, we performed random-effects panel regressions entailing price data from 66 drugs from 2005 to 2023. Further, Bennette et al. examined the market for oral cancer drugs from 2007 to 2013, whilst we analyzed the market for injectable cancer drugs. The dynamics for these two markets appear to differ. Furthermore, the result that new supplemental indication approvals are associated with marginal price declines was expected given that pharmaceutical companies were shown to first approve cancer drugs for orphan indications and then extend FDA approval to non-orphan diseases with a greater patient population for which the drug often offers a lower clinical benefit.[38,40,73] Pharmaceutical companies seem to account for the FDA label extension to more patients with a lower benefit by marginally reducing drug prices.

4.6.5 Inflation Reduction Act of 2022

US Congress recently passed the IRA in 2022,[164] which contains three key elements to reduce the financial burden of prescription drug prices for patients and the healthcare system. Regarding drugs covered under Medicare Part B, there are two important IRA provisions. First, the CMS is now, for the first time in US history, permitted to directly negotiate prices of the 10/20 top-grossing prescription drugs with manufacturers, beginning in 2026/2029.[26] For Medicare Part B drugs, these negotiations may start in 2028, excluding orphan drugs (with only a single approved indication). Given the significantly higher prices of orphan than non-orphan drugs that generate substantial revenues for pharmaceutical companies,[46,76] top-grossing orphan drugs

should be included in price negotiations. Second, the CMS sets discounts on post-launch drug price increases exceeding inflation beginning in 2023. Although this provision will limit post-launch net price increases for patients and insurers, pharmaceutical companies will likely continue to raise list prices as certain countries, e.g. Canada, South Korea, or Japan, include US drug prices in their basket of countries to calculate their national price (external reference pricing).[165] For these countries and for patients' OOP expneses, limiting the post-launch list, instead of net, price increases in the US would be the more effective pharmaceutical policy.

4.6.6 Limitations

There are several limitations inherent to our analysis. First, we only assessed prices for drugs covered under Medicare Part B. Medicare Part B covers only injectable drugs that are typically administered at a hospital or doctor's office. Therefore, our sample is restricted to 66 out of 170 drugs (39%) with FDA approval between 2000 and 2022. The distinction between injectable (Part B) and oral (Part D) drugs is particularly important given that these two markets could be subject to different pricing dynamics.[45] These different dynamics may be caused by separate price regulations for Medicare Part B and D drugs. For Part B drugs, the Medicare payment limit is defined as lesser of 106% of the ASP or 106% of the wholesale acquisition cost for the drug. Whilst this provision effectively limits the reimbursement of Part B drugs, the reimbursement and post-launch price changes for Part D drugs have remained largely unregulated until the introduction of the IRA. Furthermore, our analysis of Pearson correlation coefficients is also limited to Part B drugs. Future research should conduct a similar analysis with Part B and D drug prices to fully capture the market dynamics of new competitors. Second, we analyzed list prices for patients covered under Medicare. Net prices and net price changes may vary, particularly for patients covered by private insurers whose plans may offer a distinct set of co-payments, deductibles, and discounts. Third, our analysis was conducted before the IRA's provision to limit price increases exceeding inflation became effective in 2023. This provision may

distort the competitive dynamics of branded pharmaceutical products, thereby limiting the generalizability of our findings for the future. Fourth, the pairwise correlation analysis could be subject to omitted variable bias and spurious correlation.[158] Furthermore, our analysis is limited to price data. Price changes caused by differential changes in the number of units sold for a drug pair could yield too-low correlation coefficients. Moreover, the price correlation analysis does not capture drugs' differential quality. Finally, given that our findings rely on cancer drug prices, results, and policy implications should be confirmed for non-oncology drugs.

4.7 Conclusion

Using Medicare and Medicaid data, we observed substantial increases in the post-launch prices of injectable cancer drugs from 2005 to 2023. Launch prices and post-launch price changes were not aligned with the clinical benefit a drug offers to patients. Greater launch prices and post-launch price changes were observed for orphan drugs, whilst the introduction of new supplemental indications was associated with a -2% price reduction. We show that the competitive market for each drug is defined by the eligible patient population (e.g. FDA-approved indications). In our analysis, the market entry of new competitors was not associated with price declines. Similar to European countries, US policymakers should not only negotiate drug prices at launch but also reassess their initial negotiations several years post-launch to limit the rising cost of cancer drugs for health insurers and patients.

4.8 Author contributions

Daniel Tobias Michaeli and Thomas Michaeli had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Daniel Tobias Michaeli. Administrative, technical, or material support: All authors. Study supervision: All authors.

5 Ultra-rare, rare, common, and non-orphan cancer drug indications

Summary: This cross-sectional study compares the FDA approval, clinical trial evidence, efficacy, epidemiology, and price of ultra-rare, rare, common, and non-orphan cancer drug indications.

5.1 Abstract

Objective: To analyze the FDA approval, trials, unmet needs, benefits, and pricing of ultra-rare (<6,600 affected US inhabitants), rare (6,600-200,000 US inhabitants), common (>200,000 US inhabitants), and non-orphan cancer drug indications.

Design: Cross-sectional analysis.

Setting: Data from Drugs@FDA, FDA labels, Global Burden of Disease study, and Medicare and Medicaid.

Population: 170 FDA-approved drugs across 455 cancer indications between 2000 and 2022.

Main outcome measures: Comparison of ultra-rare, rare, common, and non-orphan indications regarding regulatory approval, trials, epidemiology, and price. HRs for OS and PFS survival were meta-analyzed.

Results: 161 non-orphan and 294 orphan cancer drug indications were identified, of which 25 were approved for ultra-rare diseases, 205 for rare diseases, and 64 for common diseases. Drugs for ultra-rare orphan indications were more frequently first-in-class (76% v 48% v 38% v 42%; P<0.001), monotherapies (88% v 69% v 72% v 55%; P=0.001), for hematologic cancers (76% v 66% v 0% v 0%; P<0.001), and supported by smaller trials (median 85 v 199 v 286 v 521 patients; P<0.001), of single arm (84% v 44% v 28% v 21%; P<0.001) phase 1/2 design (88% v 45% v 45% v 27%; P<0.001) compared with rare, common, and non-orphan indications.

Drugs for common orphan indications were more often biomarker-directed (69% v 26% v 12%; P<0.001), first-line (77% v 39% v 20%; P<0.001), small molecules (80% v 62% v 48%; P<0.001) benefiting from quicker time to first FDA approval (median 5.7 v 7.1 v 8.9 years; P=0.02) than those for rare and ultra-rare orphan indications. Drugs for ultra-rare, rare, and common orphan indications offered a significantly greater PFS benefit (HR: 0.53 v 0.51 v 0.49 v 0.64; P<0.001), but not OS benefit (HR: 0.50 v 0.73 v 0.71 v 0.74; P=0.06), than non-orphans. In single-arm trials, tumor response rates were greater for drugs for ultra-rare orphan indications than for rare, common, or non-orphan indications (ORR: 57% v 48% v 55% v 33%; P<0.001). Disease incidence/prevalence, five-year survival, and the number of available treatments were lower, whereas DALY per patient were higher, for ultra-rare orphan indications compared with rare, common, and non-orphan indications. For 147 on-patent drugs with available data in 2023, monthly prices were higher for ultra-rare orphan indications than for rare, common, and non-orphan indications ($70 128 (£55 971; €63 370) v $33 313 v $16 484 v $14 508; P<0.001). For 48 on-patent drugs with available longitudinal data from 2005 to 2023, prices increased by 94% for drugs for orphan indications and 50% for drugs for non-orphan indications on average.

Conclusions: The ODA incentivizes drug development not only for rare diseases but also for ultra-rare diseases and subsets of common diseases. These orphan indications fill significant unmet needs, yet their approval is based on small, non-robust trials that could overestimate efficacy outcomes. A distinct ultra-orphan designation with greater financial incentives could encourage and expedite drug development for ultra-rare diseases.

5.2 Summary box

What is already known on this topic:

- The ODA of 1983 incentivizes drug development for serious conditions affecting fewer than 200,000 US inhabitants.
- Orphan drugs are often supported by small, single-arm, non-randomized trials measuring surrogate rather than clinical endpoints.
- Orphan drug prices are a leading contributor to growing healthcare expenditure in the US, with unaffordable drugs' financial toxicity adversely affecting adherence to treatment.

What this study adds:

- Orphan drugs fill significant unmet needs, but their approval is supported by small, non-robust trials. For these orphan drugs manufacturers demand prices beyond $30 000 per month.
- The ODA incentivizes drug development not only for rare diseases but also for ultra-rare diseases and subsets of common diseases.
- Common orphan drugs benefit from all of the ODA's incentives, although developing and seeking approval for ultra-rare and rare orphan drugs is more complex.

5.3 Introduction

The ODA, passed in 1983, aims to facilitate and financially incentivize the R&D of drugs for rare diseases with fewer than 200,000 affected inhabitants.[166] The ODA incentives include research grants for conducting clinical trials, tax credits of 25%, exemption from FDA user fees, and enhanced marketing exclusivity of up to seven years after regulatory approval.[166]

Celebrated as (potentially) the best healthcare legislation of the 20th century, the ODA encouraged the development of 6,144 drug indications, of which 1,035 received FDA approval since 1983 (Figure 34). However, voices calling for reform of the ODA to keep pace with the biotechnological innovation and commercialization strategies of the 21st century are growing.[125,167–171]

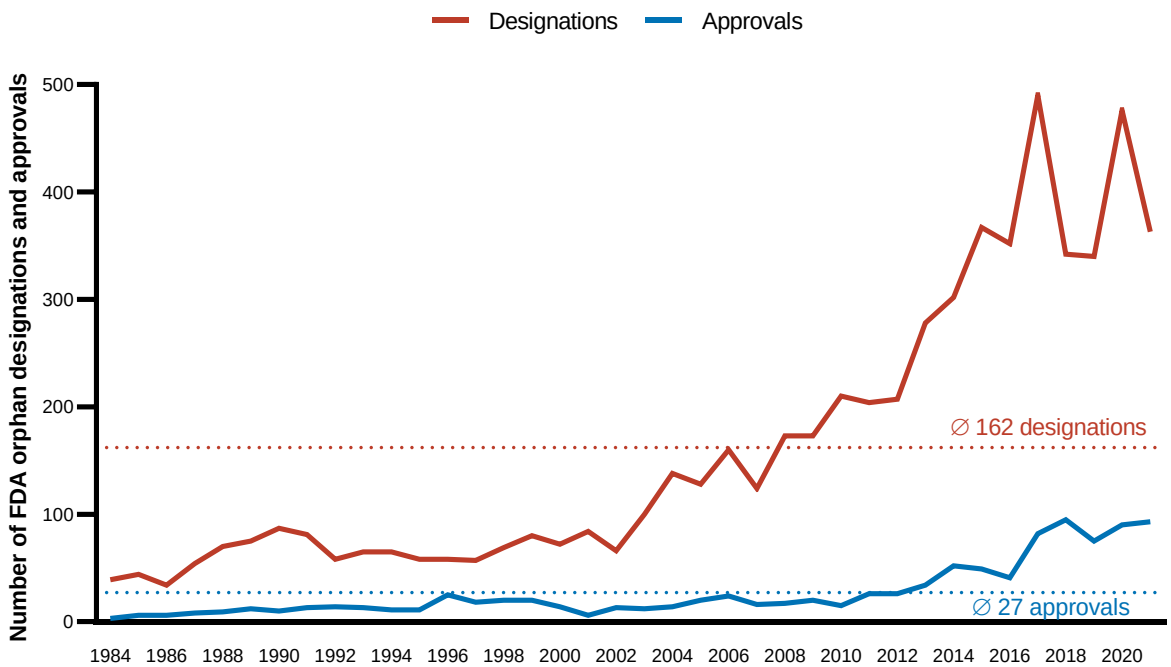


Figure 34: Orphan drug designations and approvals by the FDA from 1983 to 2021

Notes: The graph illustrates the total number of orphan designations granted and approved by the FDA since the ODA was passed in 1983 until 2021. Data was obtained and analyzed as presented in the FDA's Orphan Drug Designations and Approvals database.

Abbreviations: FDA, US Food and Drug Administration; ODA, Orphan Drug Act.

Advances in precision medicine enabled drug companies to develop targeted treatments for rare diseases. With the rise of this personalized medicine, companies also began to "slice" common diseases into multiple narrow indications. According to the FDA's interpretation, "orphan subset[s] of a non-rare disease" (21 U.S. Code § Sec. 316.3 Definitions (b) (13)) are eligible to receive the orphan designation.[172] The FDA has the power to grant the orphan designation not only to drugs treating rare diseases with fewer than 200,000 affected US inhabitants but also to drugs treating common diseases "for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (21 U.S. Code § 360bb - Designation of drugs for rare diseases or conditions (a) (2)).[166] However, biomarker-defined subsets of common diseases were especially identified as a misfit to the ODA's intention.[47,171,173] These orphan drugs for common diseases are criticized as benefiting from expedited development timelines and swift expansion to non-orphan indications, resulting in considerable revenues for manufacturers,[47,173] while shifting the FDA's and taxpayers' resources away from truly rare or even ultra-rare diseases.

A public debate surrounds the safety, efficacy, and affordability of orphan drugs. Orphan drugs are frequently supported by small, non-randomized clinical trials assessing surrogate endpoints,[124,174,175] as competent investigators, sufficient funding, and the right patients for trials of orphan drugs are lacking.[176] However, biased and small trials were found to overstate efficacy outcomes and lead to unknown side effects at the time of FDA approval.[177–179] Drug companies pursue orphan drugs as "an economically viable strategy" (Meekings et al., 2012, p. 660) with high profit margins and firm valuations resulting from governmental incentives, smaller and shorter clinical trials, and higher success rates,[80,81,143,180] but insurers are often reluctant to

reimburse highly priced orphan drugs with an uncertain efficacy.[181] Trapped between corporates' financial interests, patients are too often denied access to promising, yet unaffordable, new treatments.

The purpose of this study was to compare orphan and non-orphan cancer drug indications (original and supplemental) regarding their FDA approval, trial evidence, unmet needs, and pricing. We defined and compared subsets of common, rare, and ultra-rare orphan indications to refine the ODA.

5.4 Data and methods

5.4.1 Sample identification

We accessed the Drugs@FDA database to identify all new drugs, including NDAs and BLAs, with FDA approval between 1 January 2000 and 1 January 2022. Before 2000, the FDA label structure was inconsistent with newer approvals. We then restricted the sample to include only anticancer drugs, excluding non-oncology, supportive care, and diagnostic agents, but including CAR T-cell therapies. For each drug, we accessed the Drugs@FDA database to identify all original and supplemental anti-cancer indications approved until 1 January 2022.

We used the FDA's orphan drug database to link the orphan designation status to each indication (Table 3). We stratified orphan indications according to the number of affected US inhabitants into common (>200,000), rare (6,600-200,000), or ultra-rare (<6,600). Coherent with health technology assessment agencies in the UK (Scottish Medicines Consortium (SMC) and National Institute for Health and Care Excellence (NICE)),[182,183] we defined the threshold for ultra-rare diseases based on a prevalence rate of 1 in 50,000 US inhabitants.

5.4.2 Data collection

We accessed public data sources to collect information characterizing each drug indication's FDA approval, clinical trial evidence, cancer epidemiology, and price (Table 3).

FDA approval

We reviewed FDA labels for each anti-cancer indication to collect data on drug, indication, and clinical trial characteristics. The first reviewer (D.T.M.) independently retrieved data from FDA labels, which the second reviewer (T.M.) then cross-checked with data found on clinicaltrials.gov and associated peer-reviewed publications. Disagreements were resolved in consensus or by consulting an experienced oncologist. Full details of the data extraction method have been described elsewhere,[73] adhering to peer-reviewed guidelines for evidence synthesis from FDA documents.[103,104]

We categorized drugs by their number of indications (single-indication versus multi-indication), innovativeness (first-in-class versus not-first-in-class), mechanism of action (cytotoxic chemotherapy versus targeted agents versus immune regulators), and product type (small molecule versus antibody versus antibody-drug conjugate versus other). For multi-indication drugs, we classified FDA approvals as original and supplemental indications. We then categorized indications by treatment regimen (monotherapy versus combination), cancer type (solid versus hematologic), biomarker status, and line of therapy (first-line versus second-line versus third-line or higher). We characterized each indication's pivotal trial by the number of enrolled patients, phase, design (randomized concurrent versus randomized dose comparison versus non-randomized versus single-arm), blinding (open-label versus single-blind versus double-blind), number of arms, comparator (no treatment or placebo versus active comparator), and endpoint. For indications supported by multiple clinical trials, we retrieved data for the largest and highest

phase trial. Among RCTs, we extracted HRs for OS and/or PFS and/or the RR of tumor response with 95% confidence intervals. We noted the number of participants and events for the control and intervention arms. We calculated median improvements in OS, PFS, and duration of tumor response with IQR. For single-arm trials, we noted the objective response rate (ORR) based on the number of responders and enrolled patients.

Cancer epidemiology

For each indication, we retrieved data on the treated cancer's incidence, prevalence, and DALYs, comprising YLD and YLL, from the Global Burden of Disease study.[128] Five-year survival rates and the number of available treatment options per cancer entity came from the National Cancer Institute.

Drug prices

We retrieved drug prices in January 2023 from the CMS and Medicare's plan finder tool for an average patient covered under Medicare Part B and D. Coherent with previous studies,[115–117,119,131] we estimated monthly treatment costs for the average adult living in New York (ZIP code 10065) covered under the "Humana Basic Rx Plan" with a body surface area of 1.7 m^2 weighing 70 kg based on the dosing regimen defined in the respective FDA label. Full details of the drug price calculation have been described elsewhere.[74]

5.4.3 Statistical analysis

We compared ultra-rare, rare, common, and non-orphan cancer drug indications regarding their time to approval, drug, indication, clinical trial and epidemiologic characteristics, and efficacy, as well as price. Similar to prior studies,[135] we compared the time to approval, calculated as the difference between IND to NDA/BLA approval, in a Cox regression model. We used Fisher's exact tests to compare the distribution of categorical variables. We compared medians with

Kruskal-Wallis tests. We meta-analyzed OS, PFS, and RR outcomes in random effects regressions for RCTs and ORR outcomes for single-arm trials. We compared differences between orphan and non-orphan indications with Cochran's Q test. For on-patent drugs with available data, we compared mean monthly prices in January 2023 by using Student's t-test and analysis of variance. We calculated the compounded annual growth rate (CAGR) of drug prices from 2005 to 2023. We stored data in Microsoft Excel and analyzed data with Stata 14.2. We considered two-tailed P values below 0.05 to be significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline when applicable.[133]

5.4.4 Patient involvement statement

Owing to a lack of funding, no patients or members of the public were directly involved in the design, conduct, or reporting of this study. A member of the public was, however, asked to read the manuscript after submission.

5.5 Results

The FDA approved 720 new drugs from 2000 until 2022, 170 of which were anti-cancer treatments (Figure 35). For these 170 anticancer drugs, we identified 455 original and supplemental indication approvals until 2022 (Table 55). Of these, the FDA granted the orphan designation to 294 (65%) indications: 64 (15%) for common diseases, 205 (48%) for rare diseases, and 25 (6%) for ultra-rare diseases.

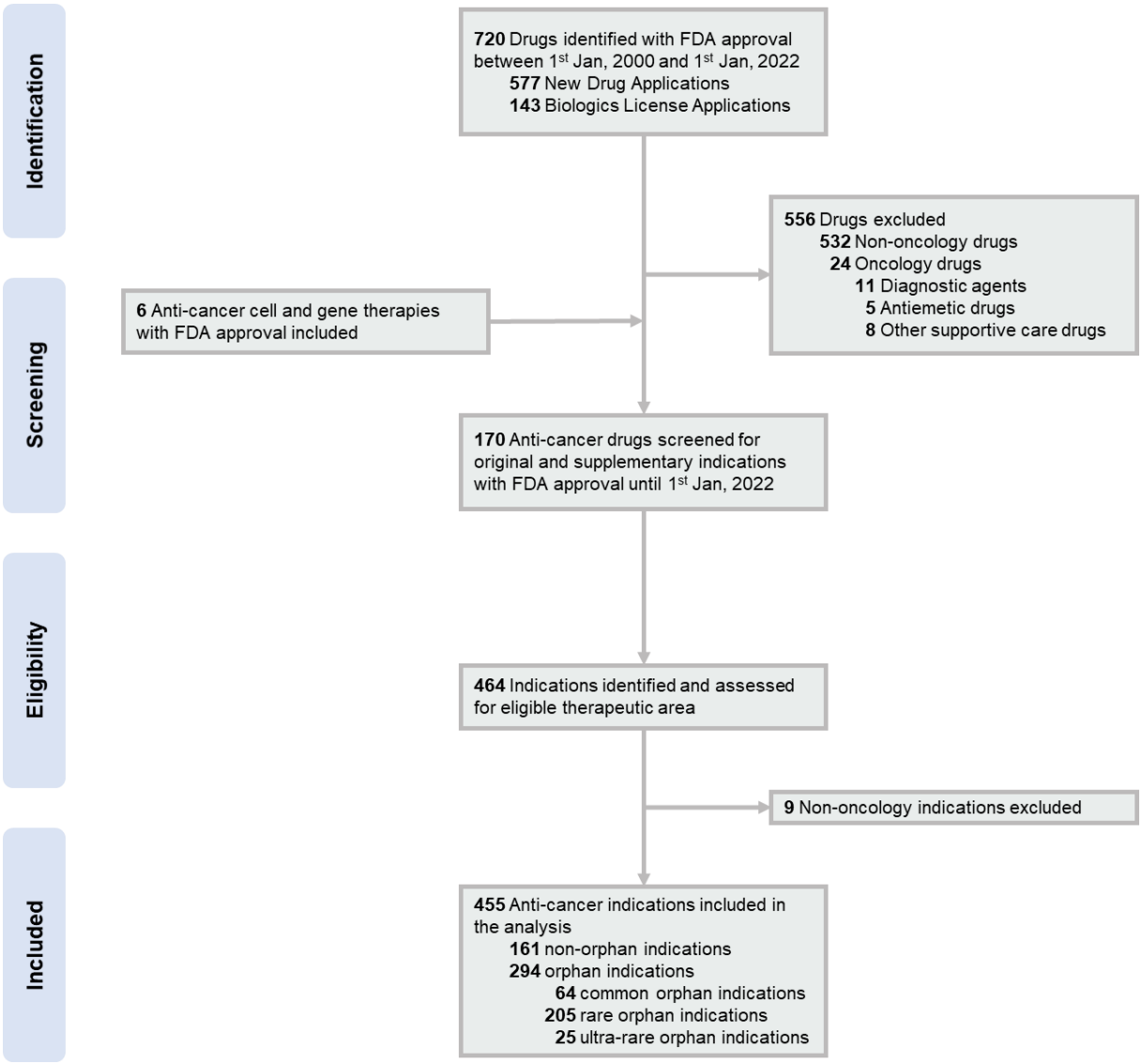


Figure 35: Flow diagram of ultra-rare, rare, common, and non-orphan cancer drug indications included in the analysis, 2000-2022

Notes: All drugs that received FDA approval between 1st January 2000 and 1st January 2022 were identified in the Drugs@FDA database. We then limited the sample to anti-cancer drugs by excluding non-oncology drugs and oncology drugs indicated for diagnostic, supportive care, or antiemetic treatments. For each drug, we identified all original and supplementary indications with FDA approval until 1st January, 2022, excluding approvals for non-oncology indications. Orphan indications were stratified according to the number of affected US inhabitants into common (>200,000), rare (200,000-6,600), or ultra-rare (<6,600).

Abbreviations: FDA, US Food and Drug Administration.

5.5.1 Time to approval

The time from IND to first FDA approval was similar for orphan and non-orphan drugs (median: 7.0 vs. 7.0 years, p=.292; Figure 36). Orphan drugs for common diseases were approved earlier than those for rare and ultra-rare diseases (median: 5.7 vs. 7.1 vs. 8.9 years).

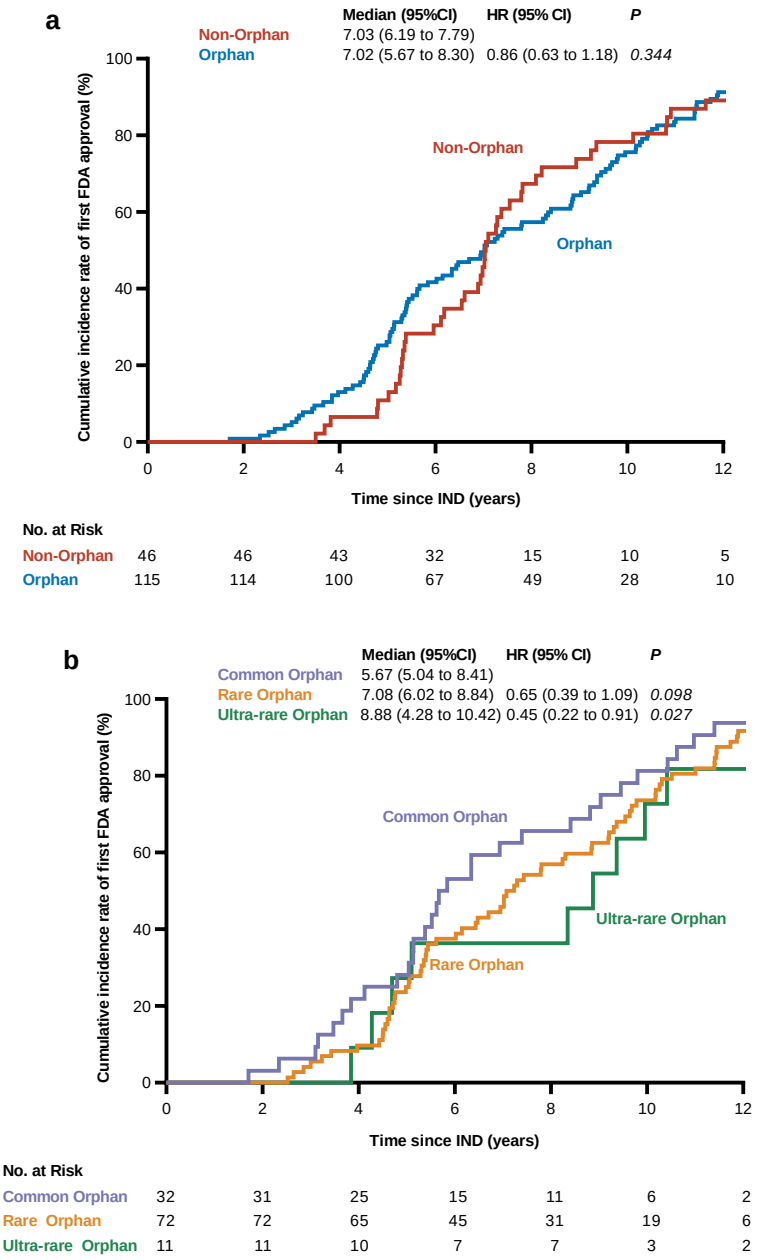


Figure 36: Time from IND to first FDA approval for ultra-rare, rare, common, and non-orphan cancer drugs

Notes: Graph a illustrates the cumulative incidence of first FDA approval for cancer drugs with an orphan (blue curve) and non-orphan designation (red curve) for the first indication. Graph b portrays the cumulative incidence of first FDA approval for cancer drugs with rare (golden curve) and common (purple curve) orphan designations for the first indication. Orphan indications were stratified according to the number of affected US inhabitants into common (>200,000), rare (200,000-6,600), or ultra-rare (<6,600). Only drugs receiving their FDA approval within 12 years of the IND are illustrated.

Abbreviations: FDA, US Food and Drug Administration; IND, investigational new drug application.

5.5.2 Drug characteristics

Drugs for orphan and non-orphan indications did not differ significantly in their innovativeness or mechanism of action (Table 23). However, the orphan designation was more frequently granted to small molecules (64% v 45%; p<0.001). In particular, drugs for common orphan indications were predominantly small molecules (80% v 62% v 48%; p<0.001) acting via a targeted mechanism of action (84% v 56% v 52%; p<0.001) relative to those for rare and ultra-rare orphan indications, respectively (Table 24). Drugs for ultra-rare orphan indications were more innovative than those for rare and common orphan indications, given the higher percentage of first-in-class molecules (76% vs. 48% vs. 38%, p=.006).

No. (%)			
	Orphan designation		
Variables	**No**	**Yes**	***P Value*** [a]
Drug characteristics			
Number of indications			*0.036*
Single-indication	19 (11.8)	58 (19.7)	
Multi-indication	142 (88.2)	236 (80.3)	
Innovativeness			*0.238*
Me-too	93 (57.8)	152 (51.7)	
First-in-class	68 (42.2)	142 (48.3)	
Mechanism of action			*0.474*
Cytotoxic chemotherapy	11 (6.8)	21 (7.1)	
Targeted agents	91 (56.5)	182 (61.9)	
Immune-regulators	59 (36.6)	91 (31.0)	
Product type			*<.001*
Small-molecule	73 (45.3)	189 (64.3)	
Antibody	79 (49.1)	76 (25.9)	
Antibody-drug conjugate	8 (5.0)	15 (5.1)	
Other [b]	1 (0.6)	14 (4.8)	
Indication characteristics			
FDA approval type			*0.007*
Original indication	50 (31.1)	130 (44.2)	
Supplemental indication	111 (68.9)	164 (55.8)	
Treatment type			*<.001*
Combination	73 (45.3)	84 (28.6)	
Monotherapy	88 (54.7)	210 (71.4)	
Cancer type			*<.001*
Hematological	0 (0.0)	154 (52.4)	
Solid	161 (100.0)	140 (47.6)	
Biomarker			*0.186*
No	95 (59.0)	193 (65.6)	
Yes	66 (41.0)	101 (34.4)	
Line of therapy			*0.001*
First-line	84 (52.2)	133 (45.2)	
Second-line	69 (42.9)	114 (38.8)	
≥Third-line	8 (5.0)	47 (16.0)	
Clinical trial characteristics			
Enrolled patients, median (IQR)	521 (219-793)	187 (97-424)	*<.001*
Clinical trial phase			*<.001*
Phase 1	6 (3.7)	15 (5.1)	
Phase 2	38 (23.6)	130 (44.2)	
Phase 3	117 (72.7)	149 (50.7)	
Trial design			*<.001*
Single-arm	34 (21.1)	129 (43.9)	
Non-randomized	1 (0.6)	7 (2.4)	
Concurrent RCT	122 (75.8)	152 (51.7)	
Dose-comparison RCT	4 (2.5)	6 (2.0)	
Type of blinding			*0.023*
Open-label	109 (67.7)	229 (77.9)	
Single-blind	0 (0.0)	1 (0.3)	
Double-blind	52 (32.3)	64 (21.8)	
Clinical trial arms			*<.001*
1 arm	34 (21.1)	129 (43.9)	
2 arms	121 (75.2)	156 (53.1)	
≥3 arms	6 (3.7)	9 (3.1)	
Total concurrent RCTs, no.	122	152	
Endpoint for concurrent RCTs			
Overall survival	104 (85.2)	100 (65.8)	*<.001*
Progression-free survival	102 (83.6)	120 (78.9)	*0.328*
Tumor response	96 (78.7)	123 (80.9)	*0.647*
Other	17 (13.9)	17 (11.2)	*0.493*
Comparator			*0.261*
Active agent	51 (41.8)	53 (34.9)	
Placebo/No treatment	71 (58.2)	99 (65.1)	
Cancer epidemiology			
Disease incidence, median (IQR) [c]	67.6 (18.8-77.6)	7.1 (2.3-9.8)	*<.001*
Disease prevalence, median (IQR) [c]	117.8 (111.2-832.8)	24.2 (7.1-35.4)	*<.001*
DALYs per person, median (IQR)	7.1 (5.5-7.7)	10.8 (6.4-16.4)	*<.001*
YLL per person, median (IQR)	6.6 (4.8-7.2)	10.5 (5.9-16.2)	*<.001*
YLD per person, median (IQR)	0.5 (0.2-0.7)	0.5 (0.3-0.6)	*0.606*
5-year survival rate in %, median (IQR)	76.4 (66.2-91.4)	66.1 (30.5-88.9)	*<.001*
No. of available treatments, median (IQR)	18 (12-38)	14 (11-22)	*0.026*
Total no. of indications	**161 (35.4)**	**294 (64.6)**	

Table 23: Characteristics of orphan and non-orphan cancer drug indications approved by the FDA from 2000 to 2022

[a] P Values calculated based on Fisher's-exact tests or Kruskal-Wallis tests. [b] Other includes gene therapies, cell therapies, enzymes, and radionuclides. [c] Disease incidence and prevalence rates per 100,000 US inhabitants. Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; IQR, interquartile range; RCTs, randomized controlled trials; YLD, years of healthy life lost due to disability; YLL, years of life lost due to premature death.

No. (%)

	Non-orphan	Orphan			*P Value* [a]
		Common	Rare	Ultra-rare	
Drug characteristics					
Number of indications					*0.077*
Single-indication	19 (11.8)	14 (21.9)	37 (18.0)	7 (28.0)	
Multi-indication	142 (88.2)	50 (78.1)	168 (82.0)	18 (72.0)	
Innovativeness					*0.006*
Not-first-in-class	93 (57.8)	40 (62.5)	106 (51.7)	6 (24.0)	
First-in-class	68 (42.2)	24 (37.5)	99 (48.3)	19 (76.0)	
Mechanism of action					*<.001*
Cytotoxic chemotherapy	11 (6.8)	0 (0.0)	21 (10.2)	0 (0.0)	
Targeted agents	91 (56.5)	54 (84.4)	115 (56.1)	13 (52.0)	
Immune-regulators	59 (36.6)	10 (15.6)	69 (33.7)	12 (48.0)	
Product type					*<.001*
Small-molecule	73 (45.3)	51 (79.7)	126 (61.5)	12 (48.0)	
Antibody	79 (49.1)	12 (18.8)	57 (27.8)	7 (28.0)	
Antibody-drug conjugate	8 (5.0)	0 (0.0)	12 (5.9)	3 (12.0)	
Other [b]	1 (0.6)	1 (1.6)	10 (4.9)	3 (12.0)	
Indication characteristics					
FDA approval type					*0.005*
Original indication	50 (31.1)	35 (54.7)	82 (40.0)	13 (52.0)	
Supplemental indication	111 (68.9)	29 (45.3)	123 (60.0)	12 (48.0)	
Treatment type					*0.001*
Combination	73 (45.3)	18 (28.1)	63 (30.7)	3 (12.0)	
Monotherapy	88 (54.7)	46 (71.9)	142 (69.3)	22 (88.0)	
Cancer type					*<.001*
Hematological	0 (0.0)	0 (0.0)	135 (65.9)	19 (76.0)	
Solid	161 (100.0)	64 (100.0)	70 (34.1)	6 (24.0)	
Biomarker					*<.001*
No	95 (59.0)	20 (31.3)	151 (73.7)	22 (88.0)	
Yes	66 (41.0)	44 (68.8)	54 (26.3)	3 (12.0)	
Line of therapy					*<.001*
First-line	84 (52.2)	49 (76.6)	79 (38.5)	5 (20.0)	
Second-line	69 (42.9)	15 (23.4)	84 (41.0)	15 (60.0)	
≥Third-line	8 (5.0)	0 (0.0)	42 (20.5)	5 (20.0)	
Clinical trial characteristics					
Enrolled patients, median (IQR)	521 (219-793)	286 (122-505)	199 (98-447)	85 (53-124)	*<.001*
Clinical trial phase					*<.001*
Phase 1	6 (3.7)	5 (7.8)	9 (4.4)	1 (4.0)	
Phase 2	38 (23.6)	24 (37.5)	85 (41.5)	21 (84.0)	
Phase 3	117 (72.7)	35 (54.7)	111 (54.1)	3 (12.0)	
Trial design					*<.001*
Single-arm	34 (21.1)	18 (28.1)	90 (43.9)	21 (84.0)	
Non-randomized	1 (0.6)	6 (9.4)	1 (0.5)	0 (0.0)	
Concurrent RCT	122 (75.8)	38 (59.4)	110 (53.7)	4 (16.0)	
Dose-comparison RCT	4 (2.5)	2 (3.1)	4 (2.0)	0 (0.0)	
Type of blinding					*0.002*
Open-label	109 (67.7)	43 (67.2)	162 (79.0)	24 (96.0)	
Single-blind	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	
Double-blind	52 (32.3)	21 (32.8)	42 (20.5)	1 (4.0)	
Clinical trial arms					*<.001*
1 arm	34 (21.1)	18 (28.1)	90 (43.9)	21 (84.0)	
2 arms	121 (75.2)	41 (64.1)	111 (54.1)	4 (16.0)	
≥3 arms	6 (3.7)	5 (7.8)	4 (2.0)	0 (0.0)	
Total concurrent RCTs, no.	122	38	110	4	
Comparator					*0.615*
Active agent	51 (41.8)	15 (39.5)	37 (33.6)	1 (25.0)	
Placebo/No treatment	71 (58.2)	23 (60.5)	73 (66.4)	3 (75.0)	
Endpoint for concurrent RCTs					
Overall survival	104 (85.2)	25 (65.8)	73 (66.4)	2 (50.0)	*0.003*
Progression-free survival	102 (83.6)	29 (76.3)	89 (80.9)	2 (50.0)	*0.297*
Tumor response	96 (78.7)	31 (81.6)	89 (80.9)	3 (75.0)	*0.958*
Other	17 (13.9)	6 (15.8)	11 (10.0)	0 (0.0)	*0.615*
Cancer epidemiology					
Disease incidence, median (IQR) [c]	68.4 (18.8-77.6)	25 (19.5-67.6)	5.2 (1.5-8.2)	0.9 (0.2-4.3)	*<.001*
Disease prevalence, median (IQR) [c]	117.8 (111.2-832.8)	117.8 (111.2-198.6)	15.3 (6.5-27.3)	3.2 (0.9-15)	*<.001*
DALYs per person, median (IQR)	7.1 (5.5-7.7)	5.5 (3.8-16.4)	12.1 (7.3-17.7)	10 (10-10)	*<.001*
YLL per person, median (IQR)	6.6 (4.8-7.2)	4.8 (3.3-16.2)	11.8 (6.8-17.4)	9.3 (9.3-9.3)	*<.001*
YLD per person, median (IQR)	0.5 (0.4-0.7)	0.5 (0.2-0.5)	0.5 (0.3-0.7)	0.7 (0.7-0.7)	*<.001*
5-year survival rate in %, median (IQR)	76.4 (66.2-91.4)	91.4 (25-95)	65 (32.7-75.2)	66.1 (50-75.2)	*<.001*
No. of available treatments, median (IQR)	18 (12-38)	14 (14-38)	15 (11-22)	8 (7-17)	*<.001*
Total no. of indications	**161 (37.4)**	**64 (14.9)**	**205 (47.7)**	**25 (5.8)**	

Table 24: Characteristics of ultra-rare, rare, common, and non-orphan cancer drug indications approved by the FDA from 2000 to 2022

Notes: Orphan indications were stratified according to the number of affected US inhabitants into common (>200,000), rare (200,000-6,600), or ultra-rare (<6,600). [a] P Values calculated based on Fisher's-exact-tests or Kruskal-Wallis-tests. [b] Other includes gene therapies, cell therapies, enzymes, and radionuclides. [c] Disease incidence and prevalence rates per 100,000 US inhabitants. Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; IQR, interquartile range; RCTs, randomized controlled trials; YLD, years lived with disability; YLL, years of life lost due to premature death.

5.5.3 Indication characteristics

Original FDA drug approvals were more likely to receive the orphan designation than supplemental indications (44% vs. 31%, p=.007). The FDA more frequently granted the orphan designation to monotherapy treatments (71% vs. 55%, p<.001) for hematologic cancers (52% vs. 0%, p<.001) in the third-line setting (16% vs. 5%, p<.001). The proportion of monotherapy treatments (55% vs. 72% vs. 69% vs. 88%, p=.001) for hematologic cancers (0% vs. 0% vs. 66% vs. 76%, p<.001) in the third-line of therapy (5% vs. 0% vs. 21% vs. 20%, p<.001) increased from non-orphan to common, rare, and ultra-rare orphan indications, respectively. Drugs for ultra-rare orphan indications were predominantly approved for treating lymphoma or skin cancer, whereas those for common orphan indications were mostly approved for subsets of lung or skin cancer (Table 25). Biomarker-based approvals were frequently observed for common orphan (69%) and non-orphan indications (41%) but not for rare (26%) or ultra-rare (12%, p<.001) orphan indications.

No.

	Non-orphan	**Orphan**			**Total**
		Common	**Rare**	**Ultra-rare**	
Bladder	14	0	0	0	14
Brain	0	0	0	3	3
Breast	35	1	0	0	36
Cervical	4	0	0	0	4
Colorectal	19	0	0	0	19
Endometrial	3	0	0	0	3
Gastric	1	0	16	0	17
Head and Neck	5	1	0	0	6
Hepatic	0	0	11	0	11
Leukemia	0	0	62	0	62
Lung	30	26	9	0	65
Lymphoma	0	0	63	13	76
Other	4	2	28	6	40
Ovarian	0	0	12	0	12
Pancreatic	0	0	2	0	2
Prostate	18	0	0	0	18
Renal	21	3	0	0	24
Skin	7	20	2	3	32
Thyroid	0	11	0	0	11
Total	**161**	**64**	**205**	**25**	**455**

Table 25: Tumor entities treated by ultra-rare, rare, common, and non-orphan cancer drugs

5.5.4 Clinical trial characteristics

Clinical trials enrolled a median of 187 patients (IQR: 97-424) for orphan indications compared to 521 patients (IQR: 219-793, p<.001) for non-orphan indications. The median trial size was 521, 286, 199, and 85 patients for non-, common, rare, and ultra-rare orphan indications (p<.001). Orphan indications were less often supported by concurrent RCTs (52% vs. 76%, p<.001) of phase 3 design (51% vs. 73%, p<.001). The share of double-blind (32% vs. 33% vs. 21% vs. 4%, p=.002) concurrent RCTs (76% vs. 59% vs. 54% vs. 16%, p<.001) of phase 3 (73% vs. 55% vs. 54% vs. 12%, p<.001) design declined from non-orphan to common, rare, and ultra-rare orphan indications, respectively. Concurrent RCTs for orphan indications less frequently included an assessment of OS (85% vs. 66%, p<.001).

5.5.5 Cancer epidemiology

Drugs for orphan indications treated diseases with a lower prevalence (median: 24 vs. 118 per 100,000 US inhabitants, p<.001) compared with non-orphan indications. Orphan diseases were more severe, as measured by DALYs (median: 10 vs. 7 DALYs per patient, p<.001) and five-year survival (median: 67% vs. 76%, p<.001). The median prevalence per 100,000 was similar for non- (118) and common orphans (118) but significantly lower for rare (15) and ultra-rare orphans (3, p<.001). Accordingly, DALYs were higher and five-survival lower for rare and ultra-rare compared to non- and common orphan indications. Fewer treatment options were available for ultra-rare than non-orphan indications (8 vs. 18, p<.001).

5.5.6 Special FDA review

A total of 105 (23%), 358 (78%), 147 (32%), and 137 (39%) indications received fast track, priority review, accelerated approval, and breakthrough therapy designation, respectively (Table 26). Orphan indications were significantly more likely than non-orphan indications to receive fast track review (26% vs. 17%, p=.036). Ultra-rare and common orphan indications were

significantly more likely than rare and non-orphan indications to receive the breakthrough therapy designation (77% vs. 57% vs. 30% vs. 34%, p<.001).

a

No. (%)

	Orphan designation		
	No	**Yes**	***P Value***
Fast Track	28/161 (17.4)	77/294 (26.2)	*0.036*
Priority Review	123/161 (76.4)	235/294 (79.9)	*0.403*
Accelerated Approval	44/161 (27.3)	103/294 (35.0)	*0.095*
Breakthrough Therapy [b]	42/122 (34.4)	95/233 (40.8)	*0.253*

b

No. (%)

	Non-orphan	**Orphan**			***P Value*** [a]
		Common	**Rare**	**Ultra-rare**	
Fast Track	28/161 (17.4)	19/64 (29.7)	52/205 (25.4)	6/25 (24.0)	*0.147*
Priority Review	123/161 (76.4)	52/64 (81.3)	161/205 (78.5)	22/25 (88.0)	*0.614*
Accelerated Approval	44/161 (27.3)	23/64 (35.9)	67/205 (32.7)	13/25 (52.0)	*0.088*
Breakthrough Therapy [b]	42/122 (34.4)	31/54 (57.4)	47/157 (29.9)	17/22 (77.3)	*<.001*

Table 26: Special review pathways used for the FDA approval of orphan drugs: fast track, priority review, accelerated approval, and breakthrough therapy

Notes: Orphan indications were stratified according to the number of affected US inhabitants into common (>200,000), rare (200,000-6,600), or ultra-rare (<6,600).

[a] P Values calculated based on Fisher's-exact-test.
[b] Includes only indications approved in 2013 and thereafter.

Abbreviations: FDA, US Food and Drug Administration.

5.5.7 OS, PFS, and Tumor Response

Drugs for orphan indications did not prevent more deaths than those for non-orphan indications (HR: 0.72 vs. 0.74, p=.178) and did not provide a superior survival benefit (median 3.3 vs. 2.8 months, p=.382) (Figure 37). PFS was 13% greater for orphan than non-orphan indications (HR: 0.51 vs. 0.64, p<.001) with a 1.5 months greater survival benefit (median: 4.2 vs. 2.7, p=.011). Accordingly, ultra-rare, rare, and common orphan indications offered a significantly greater PFS benefit (HR: 0.53 vs. 0.51 vs. 0.49 vs. 0.64, p<.001), but not OS (HR: 0.50 vs. 0.73 vs. 0.71 vs. 0.74, p=.055), than those for non-orphan indications. By contrast, tumor response rates among RCTs were lower for orphan compared to non-orphan indications (RR: 1.29 vs. 1.53, p<.001). However, mean tumor response rates in single-arm trials were greater for orphan than non-orphan indications (ORR: 51% vs. 33%, p<.001). Similarly, tumor response rates were

greater for ultra-rare orphan indications than for rare or common orphan indications and non-orphan indications in single-arm trials (ORR: 57% vs. 48% vs. 55% vs. 33%, p<.001). Details of the full meta-analyses, including individual effect sizes for each trial, can be found in Figure 62, Figure 63, and Figure 64.

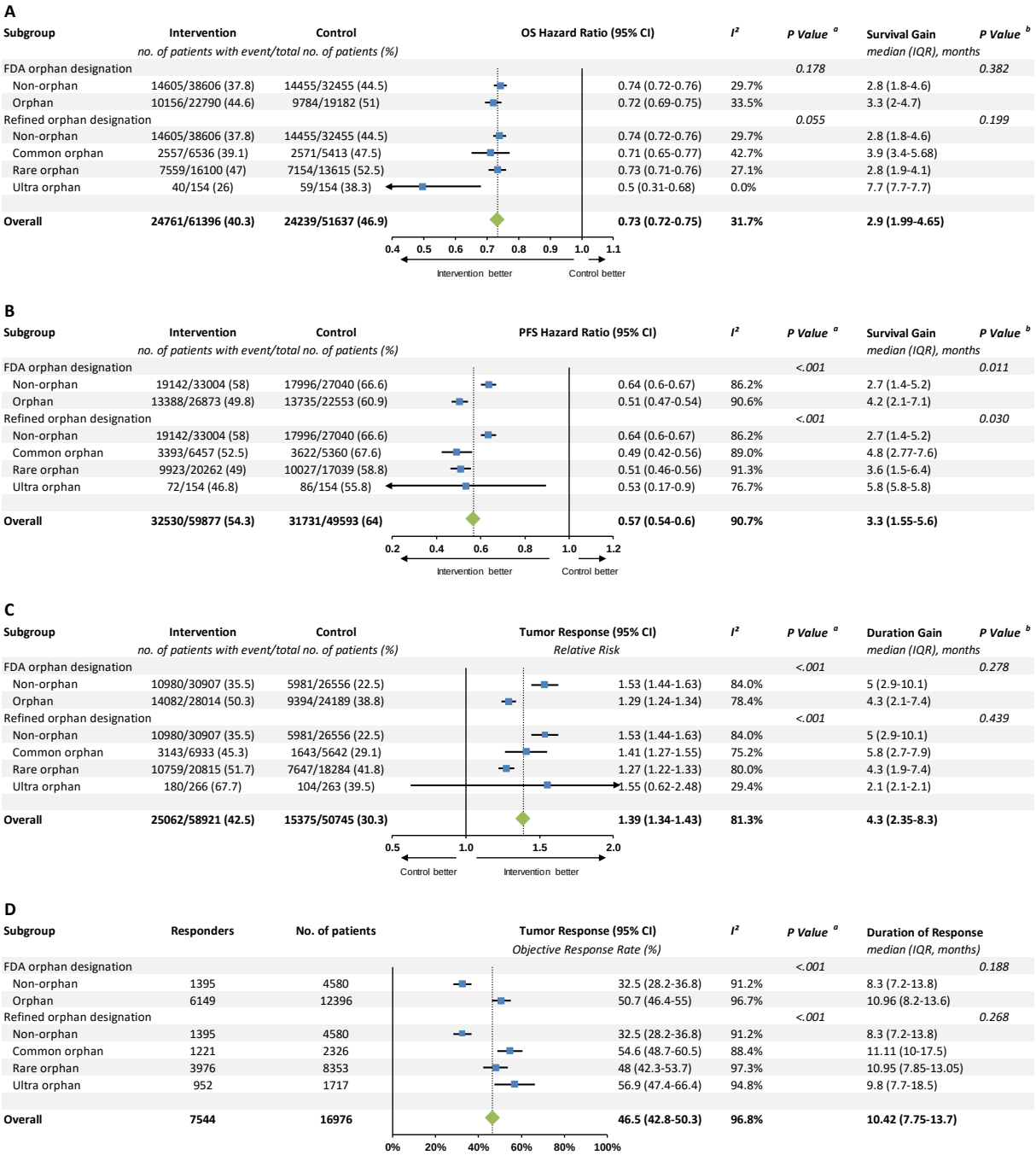


Figure 37: Meta-analyses of overall survival, progression-free survival, and tumor response for ultra-rare, rare, common, and non-orphan cancer drug indications approved by the FDA from 2000 to 2022

Notes: In graphs A, B, and C, treatment outcomes were meta-analyzed for RCTs. Graph D shows average tumor response rates measured in single-arm trials. Orphan indications were stratified according to the number of affected

US inhabitants into common (>200,000), rare (200,000-6,600), or ultra-rare (<6,600). For tumor responses, a continuity adjustment of 0.5 for control arms with 0 responders was applied.

Abbreviations: FDA, US Food and Drug Administration; IQR, interquartile range; OS, overall survival; PFS, progression-free survival.

5.5.8 Drug prices

Of 170 drugs approved by the FDA, 22 lost their exclusivity by the first quarter of 2023 and price data were not available for one drug. For the resulting sample of 147 on-patent drugs with available data, we compared prices across original indication approvals. Mean monthly prices were 128% higher for drugs with orphan indications ($33,070 (£26 438; €29 935); 95%CI: $24,048-42,091) relative to those for non-orphan indications ($14 508; 95%CI: $11,494-17,522; p=.02) (Figure 38). Mean monthly prices were $70,128 for ultra-rare, $33,313 for rare, $16,484 for common orphan indications, and $14,508 for non-orphan indications (p<.001).

Quarterly drug price data were available for 48 drugs covered under Medicare Part B. From 2005 to 2023, drug prices increased by an average of 94% for orphans and 50% for non-orphans. Prices for rare orphans rose by 102% relative to 49% for common orphans. Whilst inflation amounted to 2.2% per quarter, drug prices increased by a CAGR of 3.5% for orphan (rare orphans: 3.7%, common orphans: 2.1%) and 2.2% for non-orphan drugs.

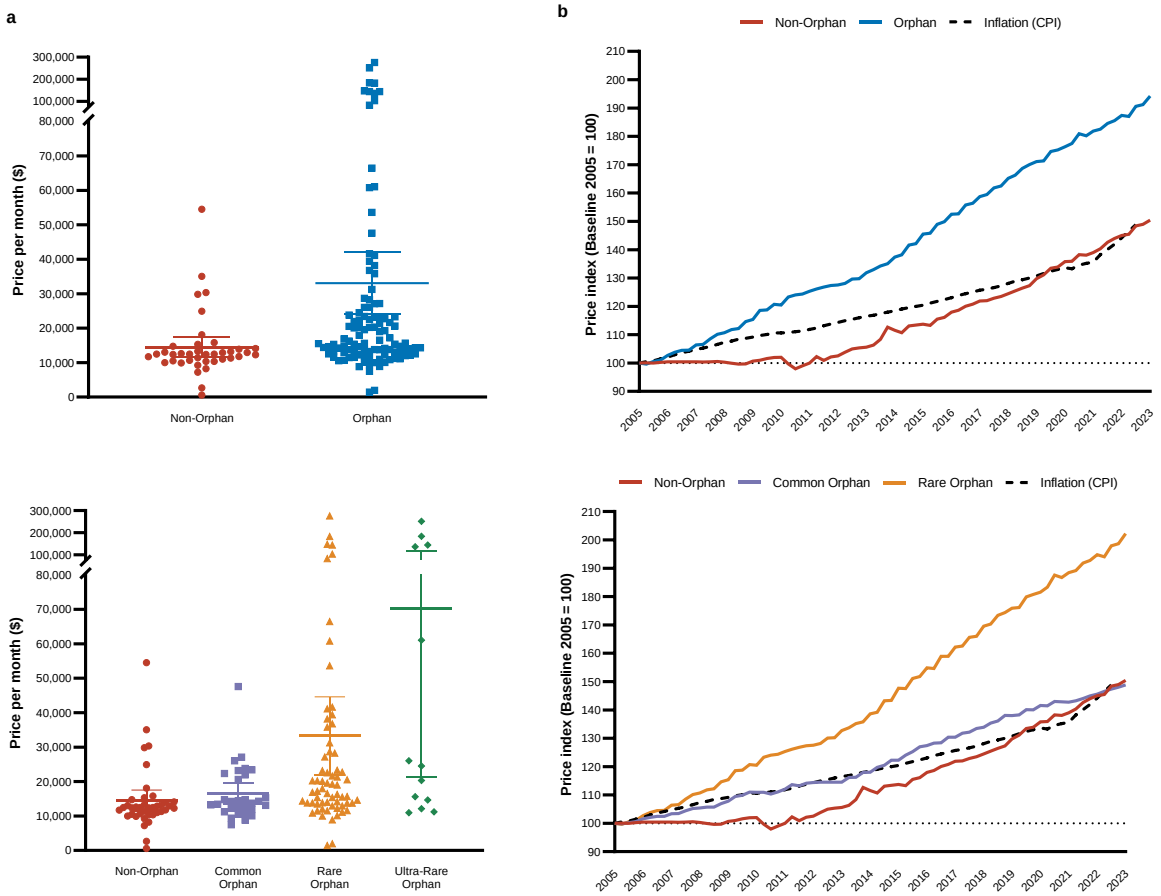


Figure 38: Prices for ultra-rare, rare, common, and non-orphan cancer drugs from 2005 to 2023

Notes: In graph a monthly prices of drugs with and without an orphan designation for the original FDA indication are compared in the year 2023. Graph c compares monthly prices for ultra-rare, rare, common, and non-orphan cancer in 2023. Bars represent means with 95% confidence intervals. In graph b the mean price change of orphan and non-orphan drugs is compared from 2005 until 2023. Graph d compares mean price changes for ultra-rare, common, rare, and non-orphan drugs from 2005 until 2023. Lines illustrate price indices with the baseline set in the year 2005. Inflation was measured by the consumer price index. Orphan indications were stratified according to the number of affected US inhabitants into common (>200,000), rare (200,000-6,600), or ultra-rare (<6,600).

Abbreviations: CPI, consumer price index; FDA, US Food and Drug Administration.

5.5.9 Temporal differences in the development of orphan indications

Table 27 shows that from 2000 to 2022, the orphan designation was increasingly granted to immune-regulators targeting hematologic cancers as combination therapies.

No (%)

	Time Period			*P Value* [a]
	2000-2012	**2013-2017**	**2017-2022**	
Orphan subgroup				*0.415*
Common orphan	10 (16.4)	24 (25.5)	30 (21.6)	
Rare orphan	48 (78.7)	63 (67.0)	94 (67.6)	
Ultra-rare orphan	3 (4.9)	7 (7.5)	15 (10.8)	
Drug characteristics				
Number of indications				*0.085*
Single-indication	10 (16.4)	13 (13.8)	35 (25.2)	
Multi-indication	51 (83.6)	81 (86.2)	104 (74.8)	
Innovativeness				*0.330*
Me-too	28 (45.9)	46 (48.9)	78 (56.1)	
First-in-class	33 (54.1)	48 (51.1)	61 (43.9)	
Mechanism of action				*<.001*
Cytotoxic chemotherapy	12 (19.7)	2 (2.1)	7 (5.0)	
Targeted agents	42 (68.9)	58 (61.7)	82 (59.0)	
Immune-regulators	7 (11.5)	34 (36.2)	50 (36.0)	
Product type				*0.098*
Small-molecule	48 (78.7)	55 (58.5)	86 (61.9)	
Antibody	9 (14.8)	31 (33.0)	36 (25.9)	
Antibody-drug conjugate	3 (4.9)	5 (5.3)	7 (5.0)	
Other [b]	1 (1.6)	3 (3.2)	10 (7.2)	
Indication characteristics				
FDA approval type				*0.132*
Original indication	33 (54.1)	43 (45.7)	54 (38.8)	
Supplemental indication	28 (45.9)	51 (54.3)	85 (61.2)	
Treatment type				*<.001*
Combination	5 (8.2)	30 (31.9)	49 (35.3)	
Monotherapy	56 (91.8)	64 (68.1)	90 (64.7)	
Cancer type				*0.040*
Hematological	40 (65.6)	50 (53.2)	64 (46.0)	
Solid	21 (34.4)	44 (46.8)	75 (54.0)	
Biomarker				*0.840*
No	40 (65.6)	64 (68.1)	89 (64.0)	
Yes	21 (34.4)	30 (31.9)	50 (36.0)	
Line of therapy				*0.519*
First-line	28 (45.9)	36 (38.3)	69 (49.6)	
Second-line	24 (39.3)	42 (44.7)	48 (34.5)	
≥Third-line	9 (14.8)	16 (17.0)	22 (15.8)	
Clinical trial characteristics				
Enrolled patients, median (IQR)	170 (100-456)	215 (11-417)	162 (80-403)	*0.276*
Clinical trial phase				*0.388*
Phase 1	1 (1.6)	4 (4.3)	10 (7.2)	
Phase 2	32 (52.5)	39 (41.5)	59 (42.4)	
Phase 3	28 (45.9)	51 (54.3)	70 (50.4)	
Trial design				*0.245*
Single-arm	32 (52.5)	35 (37.2)	62 (44.6)	
Non-randomized	0 (0.0)	3 (3.2)	4 (2.9)	
Concurrent RCT	27 (44.3)	53 (56.4)	72 (51.8)	
Dose-comparison RCT	2 (3.3)	3 (3.2)	1 (0.7)	
Type of blinding				*0.624*
Open-label	47 (77)	73 (77.7)	109 (78.4)	
Single-blind	1 (1.6)	0 (0.0)	0 (0.0)	
Double-blind	13 (21.3)	21 (22.3)	30 (21.6)	
Clinical trial arms				*0.244*
1 arm	32 (52.5)	35 (37.2)	62 (44.6)	
2 arms	26 (42.6)	56 (59.6)	74 (53.2)	
≥3 arms	3 (4.9)	3 (3.2)	3 (2.2)	
Total concurrent RCTs, no.	27	53	72	
Comparator				*0.502*
Active agent	7 (25.9)	18 (34)	28 (38.9)	
Placebo/No treatment	20 (74.1)	35 (66)	44 (61.1)	
Endpoint for concurrent RCTs				
Overall survival	20 (74.1)	39 (73.6)	41 (56.9)	*0.093*
Progression-free survival	20 (74.1)	45 (84.9)	55 (76.4)	*0.406*
Tumor response	22 (81.5)	45 (84.9)	56 (77.8)	*0.603*
Other	3 (11.1)	4 (7.5)	10 (13.9)	*0.539*
Total no. of indications	**61 (20.7)**	**94 (32)**	**139 (47.3)**	

Table 27: Temporal differences in the FDA approval of orphan cancer drugs from 2000 to 2022

Notes: In this table orphan cancer drug indications are compared across their FDA approval year to identify temporal differences in drug development over the past two decades. Non-orphan cancer drugs are excluded.

[a] P Values calculated based on Fisher's-exact tests or Kruskal-Wallis tests.
[b] Other includes gene therapies, cell therapies, enzymes, and radionuclides.

Abbreviations: FDA, US Food and Drug Administration; IQR, interquartile range; RCTs, randomized controlled trials.

5.6 Discussion

This review of 170 anticancer drugs approved across 455 indications from 2000 to 2022 identified significant differences in the FDA approval, treatment characteristics, efficacy, clinical trial design, and pricing of drugs for orphan and non-orphan cancer indications. We shine light on three distinct groups of orphan drug indications: common, rare, and ultra-rare orphan indications.

5.6.1 Orphan vs. non-orphan cancer drugs and indications

US Congress introduced the ODA to incentivize drug development for rare diseases with limited sales potential. Unsurprisingly, we found that the orphan designation was granted to rare diseases with substantial unmet needs. However, the ODA enabled the FDA to approve drugs for orphan indications on the basis of small, non-randomized, open-label trials. This flexibility in clinical trial design accommodates the complexity of conducting trials for rare diseases. Yet, small non-randomized trials are likely a cause for unobserved side effects among drugs for orphan indications.[179] Moreover, meta-epidemiologic studies found that non-robust and small trial designs could overestimate and, thereby, bias efficacy outcomes.[177,178] The higher proportion of open-label RCTs comparing the new drug with an inactive comparator could, henceforth, partially explain the greater PFS outcomes of drugs for orphan than for non-orphan indications. Testing orphan drugs on a large population is difficult, but the FDA, drug manufacturers, and investigators should strive to adhere to the hallmarks of high-quality trials: randomization, active comparators, and blinding.[174]

5.6.2 Common orphan indications

In this study, we defined common orphan drug indications as those that treat diseases or subgroups of diseases with more than 200,000 affected US inhabitants. Similar to previous studies, we found that these subgroups were often defined by biomarker-directed targeted therapies for

solid cancers.[47,171] We showed that conducting clinical trials is less complex for common than rare orphan indications. With the widespread adoption of biomarker screening programs for highly prevalent cancers, such as lung or skin cancer, manufacturers have less difficulty recruiting a sufficient number of patients to conduct large randomized double-blinded trials for common orphan indications, which may ultimately lead to the observed shortened development timelines. However, drugs for common orphan indications secure all of the ODA's advantages, including the FDA's $3.1m user fee waiver. Critiques argue that "salami slicing" common diseases into orphan indications with faster clinical development times and rapid expansion to non-orphan use makes them "ill suited" for the ODA.[47,125,170]

This study highlights that the clinical, epidemiologic, and economic characteristics of biomarker-defined subgroups of common diseases are distinctly different from truly rare cancers or metabolic disorders. Therefore, the ODA's current definition and implementation of rare diseases should be re-evaluated. Instead of defining orphan indications based on the number of patients who are biomarker-positive for a single cancer type, the entire number of biomarker-positive patients across all cancers represents a drug's true potential market.[47] For instance, drugs treating the BRAF mutation would be considered orphan only if fewer than 200,000 cancer patients harboured the BRAF mutation across all tumor entities, not just skin cancer. Thereby, fewer resources would be wasted on drugs not intended for the orphan designation – for example, those that effortlessly recover their R&D cost with multi-million dollar revenues through commercialization across multiple indications.

5.6.3 Ultra-rare orphan indications

In England and Scotland, ultra-rare indications are defined as diseases affecting a population of 1 in 50,000 (approximately 6,600 inhabitants in the US).[182,183] In this study only 25 (6%) drugs for cancer indications were approved to treat ultra-rare diseases. Although the ODA was impressively effective at incentivizing drug development for rare diseases, conducting clinical

trials and commercializing drugs for ultra-rare diseases remain challenging.[184] A median of merely 85 patients were enrolled in trials for ultra-rare diseases, with most of these being single-arm, open-label phase 2 trials. Conducting randomized, blinded trials is not feasible for most ultra-rare diseases owing to the hurdles in recruiting the right and adequate numbers of investigators and patients. These challenges in patient accrual result in delayed development timelines for ultra-rare compared with rare diseases (median 8.9 v 7.1 years). As a result, thousands of patients continue to suffer from ultra-rare diseases without adequate treatment options.[185]

Policymakers in the US and EU could overcome these unmet medical needs with policies that encourage drug development for ultra-rare diseases. Firstly, a definition of ultra-rare diseases is essential. The US could adopt the UK's current prevalence threshold of 1 in 50,000 inhabitants[182] or set an arbitrary threshold of 10,000 affected US inhabitants.[186] Secondly, on the basis of this coherent definition, US Congress could create a distinct ultra-orphan designation entailing greater direct and indirect financial incentives for eligible drugs. For example, the ODA's R&D tax credit of 25% could be increased to 50% (or even 75%) and the market exclusivity period from seven to 10 years to boost the economic viability and account for longer trial accrual rates of ultra-rare orphan indications, respectively. This will likely encourage manufacturers to sponsor more and riskier clinical trials, but direct federal funding of pre-clinical drug development is also needed to incentivize early-stage research projects for ultra-rare diseases. Over the past years, public-private partnerships were particularly successful in guiding pre-clinical development efforts. For instance, the Bespoke Gene Therapy Consortium, a partnership between the National Institutes of Health, FDA, academia, and manufacturers, was initiated in 2021 to tackle challenges in developing gene therapies for ultra-rare diseases.[187] Finally, the use of every available tool – for example, synthetic control arms or natural history studies – should be encouraged when trials for ultra-rare diseases with few alternative treatment options are designed, particularly when accrual is challenging and endpoints may be difficult to meet.

5.6.4 Pricing, coverage, and reimbursement policies

This study highlights the significant financial burden of orphan anticancer drugs for payers and patients. Although pharmaceutical companies argue that high prices are necessary to incentivize drug development for rare diseases, monthly prices of $33,070 with 20-30% paid out of pocket are not affordable for the average US patient with a median household income of $5,899.[16] Patients must wonder why orphan drug prices increased by 3.5% per quarter, far exceeding inflation and prices of non-orphan drugs. The following paragraphs, therefore, explore innovative pricing, coverage, and reimbursement policies to ensure that orphan drugs remain accessible and affordable to US patients.

Recently, US Congress granted the CMS the power to directly negotiate prescription drug prices with pharmaceutical companies by passing the IRA.[164] The CMS could thereby not only mandate drug prices to be aligned to their clinical benefit and unmet needs (value-based pricing) but also limit price increases exceeding inflation. Independent non-governmental health technology assessment agencies, such as the Institute for Clinical and Economic Review, could conduct cost-effectiveness analyses to inform price negotiations. Although proponents would welcome pricing to be informed by cost-effectiveness analyses, similar to the UK, recent guidance by the CMS states that QALYs and ICERs will not inform price negoatiations.[188] The CMS will not use QALYs as this approach assigns a lower value to the lives of the elderly, disabled, and terminally ill patients. Although this study highlights particularly high prices for orphan drugs, the IRA is limited to drugs for non-orphan indications.[23,164] The next pharmaceutical policy reform should, therefore, extend the CMS' power to negotiate value-based prices for top-selling orphan drugs.

Guided by examples from Europe, this value-based pricing could entail a special assessment pathway for ultra-rare diseases. Similarly to the UK's NICE, the CMS could set a higher cost-effectiveness or clinical benefit threshold, and thereby price premium, for ultra-rare diseases to

account for the smaller eligible patient population or exclude ultra-rare diseases from price negotiations until a pre-defined annual revenue threshold is surpassed.[123] Both options would likely increase access to and stimulate the development of drugs treating ultra-rare diseases. Most importantly, the CMS should always mandate manufacturers to engage in their existing CED program,[146] such that outcome data are collected to reassess each ultra-rare orphan indication's benefit after a pre-defined period (for example, three years).

The ODA was intended to incentivize drug development for rare diseases, but drugs for common orphan indications in particular often turn into top-selling blockbusters.[46] Moreover, the usage and economic spending patterns of drugs for common orphan indications are more similar to those of drugs for non-orphan indications than those that are for truly rare diseases.[189] After an orphan drug has reached a maximum revenue threshold (for example, $750m) or surpassed the orphan prevalence threshold of 200,000 affected inhabitants, the FDA could revoke or reduce the ODA's benefits received by the pharmaceutical company, such as tax credits, R&D grants, and exclusivity period.[173,181] Finally, payers could tackle the swift extension of biomarker-defined orphan indications to biomarker-negative non-orphan indications based on pooled efficacy data[73] by using indication-specific pricing.[41] By setting a distinct price for each indication, rather than each drug, payers would be able to pay a higher price for and thus incentivize the development of highly effective biomarker-positive orphan indications.[41] Although indication-specific pricing is challenging to implement,[38,40] it could help to realign the value and price for (non)-orphan indications.

5.6.5 Weaknesses of this study

This study has certain limitations. We analyzed only clinical trial evidence supporting the FDA approval of cancer drug indications. Consequently, the sample includes only successful trials, which may bias (overstate) efficacy outcomes. Secondly, our analyses are limited to trial data available at the time of FDA approval. Thirdly, we calculated prices for the average patient

insured by Medicare. With more than 60 million enrollees, Medicare is the largest US insurer, but the affordability and pricing for privately insured patients may vary. Fourthly, we meta-analyzed efficacy outcomes across a variety of tumor entities with low to high heterogeneity between effect sizes, in line with previous studies.[84–87] Fifthly, epidemiologic data underlying to our analyses were collected for broad cancer entities. Calculating epidemiologic data that considers each indication's line of therapy, biomarker status, cancer subgroup as well as tumor histology and stadium may provide more precise insights. Sixtly, this study is limited to cancer indications. Results and policy implications must be confirmed for other therapeutic areas.

5.7 Conclusion

The ODA incentivized the development of more than 6,000 drug indications. Among anti-cancer drugs, these orphan indications fill significant unmet needs; however, their approval is based on small, non-robust trials, which could overestimate efficacy outcomes. We identified three groups of orphan drug indications with distinct clinical, epidemiologic, and economic characteristics: common, rare, and ultra-rare orphan indications. Policy reforms could help to differentially incentivize and rigorously evaluate the development of these orphan drug groups. For common orphan indications, the genomic drug target across all, rather than a single, cancer type should build the prevalence basis of the orphan designation. By contrast, a distinct ultra-orphan designation with greater financial incentives could encourage drug development for ultra-rare diseases. The recent IRA, which empowers the CMS to directly negotiate drug prices and price increases with manufacturers, should be extended to all drugs with orphan indications to ensure that US patients can access and afford the treatment they need.

5.8 Author contributions

Daniel Tobias Michaeli and Thomas Michaeli had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Concept and design: Daniel Tobias Michaeli and Thomas Michaeli. Acquisition, analysis, or interpretation of data: Daniel Tobias Michaeli and Thomas Michaeli. Drafting of the manuscript: Thomas Michaeli. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Daniel Tobias Michaeli. Administrative, technical, or material support: All authors. Study supervision: All authors.

6 Partial orphan cancer drugs

Summary: This cross-sectional study compares the FDA approval, clinical benefit, trials, epidemiology, price, beneficiaries, and spending of full, partial, and non-orphan cancer drugs.

6.1 Abstract

Background: The ODA incentivizes drug development for rare diseases with limited sales potential. However, orphan drugs frequently turn into multi-billion dollar blockbusters, particularly those used to treat rare and common diseases: “partial orphans”.

Objective: To analyze the development, FDA approval, epidemiology, and economics of full, partial, and non-orphan cancer drugs.

Patients and Methods: 170 drugs with FDA approval for 455 cancer indications were identified between 2000-2022. Full, partial, and non-orphan drugs were compared regarding their regulatory approval, clinical benefit, trials, epidemiology, price, beneficiaries, and spending with data extracted from FDA documents, Global Burden of Disease study, and Medicare and Medicaid.

Results: We identified 110 full, 22 partial, and 38 non-orphan cancer drugs. The time from first to second FDA approval was shorter for partial than non- and full orphans (median: 1.3 vs. 1.6 vs. 2.3 years). Full orphans, relative to partial and non-orphans, were more frequently third-line (17% vs. 8% vs. 7%, p=.025) monotherapies (74% vs. 58% vs. 58%, p=.002) for hematologic cancers (66% vs. 4% vs. 0%, p<.001) supported by smaller (median: 154 patients vs. 416 vs. 536, p<.001) open-label (87%vs. 64% vs. 56%, p<.001) single-arm trials (50% vs. 23% vs. 19%, p<.001). Disease incidence was lower and disease burden/severity higher for full than partial and non-orphans. Full orphans offered a significantly greater OS (median: 4.0 vs. 2.8 vs. 2.8, p<.001) and PFS benefit (median: 5.1 vs. 2.5 vs. 3.6, p<.001). Monthly prices were higher

for full and partial than non-orphan drugs (median: $17,177 vs. $13,284 vs. $12,457, p<.001). Medicare and Medicaid beneficiaries (8,790 vs. 4,390 vs. 1,730) and spending ($570 vs. $305 vs. $156 million) per drug were greater for partial than non-and full orphans.

Conclusions: The clinical benefit, trials, and epidemiology of partial orphan cancer drugs are more similar to non-orphans than full orphans. However, partial orphans receive all of the ODA's incentives and are swiftly extended to new indications; resulting in greater prices, beneficiaries, and spending. Establishing a maximum revenue threshold for the ODA's benefits alongside indication-specific pricing could reduce expenditure on partial orphan drugs.

6.2 Key points

Question: What are the benefits, clinical trial evidence, epidemiology, price, beneficiaries, and spending of cancer drugs with FDA approval to treat orphan and non-orphan diseases – "partial orphans"?

Findings: The clinical benefit, trial characteristics, and epidemiology of partial orphan cancer drugs are more similar to non-orphan than full orphan drugs. However, partial orphans receive all of the ODA's incentives and are swiftly extended to new indications; resulting in greater prices for patients, more beneficiaries, and higher spending for Medicare and Medicaid.

Meaning: Establishing a maximum revenue and/or patient threshold for the ODA's benefits alongside indication-specific pricing could help to reduce expenditure on top-selling partial orphan drugs.

6.3 Introduction

The ODA incentivizes drug development for rare diseases with limited sales potential.[166] However, orphan drugs frequently turn into multi-billion dollar blockbusters, particularly those approved for rare and common diseases – "partial orphan drugs".[72] In 2019, seven of the top-ten selling drugs were partial orphans, generating revenues of $67 billion.[12] Yet, partial orphan drugs are more frequently used in and sold for their non-orphan (71%) than orphan (21%) indications.[46] For many top-selling partial orphan drugs, only a small fraction is spent on the orphan indications: pegfilgrastim (1%), etanercept (1%), trastuzumab (2%), denosumab (6%), and adalimumab (8%). Nonetheless, the ODA currently provides the same incentives to sponsors of full and partial orphans, including "research grants for conducting clinical trials, tax credits of 25%, exemption from FDA user fees, and an enhanced marketing exclusivity of up to 7 years after regulatory approval" (Michaeli et al., 2023, p. 1-2).[76,166] Patients and policymakers are therefore debating whether partial orphan drugs fit the ODA's intention and should receive all of the ODA's benefits.[46,173,181,190]

This debate is especially prominent for partial orphan drugs that are first approved for rare and then used for common diseases. Critiques argue that this "*orphan-first*" strategy permits sponsors to establish high launch prices for patient populations suffering from rare diseases with few treatment alternatives based on non-robust evidence.[46] Thereafter, sponsors swiftly transfer these high prices to patients suffering from common diseases.[38–40] Concerns were particularly raised that sponsors "game" the ODA by slicing common diseases into biomarker-defined subsets to receive the orphan designation and then extend these "*common orphans*" approvals to non-orphan diseases.[47,76,173] Whilst European countries, Canada, and Australia encounter this sequencing of indication launches with indication-specific pricing policies,[38–40] the US has not yet introduced any new differential pricing policy.[50]

The debate surrounding partial orphan drugs that are first approved for common and then rare diseases is more complex. Albeit patients benefit from the indication extension of these "*non-orphan-first*" drugs to rare diseases, policymakers question whether all the ODA's benefits are needed to incentivize sponsors to conduct this repurposing.[46] Moreover, this non-orphan-first strategy could unreasonably increase spending on non-orphan indications because orphan drugs do not have to provide the 340B Price Program's discounts[191] and are more frequently covered by health insurers.[192]

Although previous analyses investigated the spending on and use of partial orphan drugs,[46,190,193] little is known about the FDA approval, epidemiology, and economics of partial orphan drugs. This is the first study to analyze the regulatory approval, clinical benefit, trials, epidemiology, price, beneficiaries, and spending of partial orphan drugs. We used a sample of 170 drugs with FDA approval in 455 anti-cancer indications between 2000-2022 to compare full, partial, and non-orphan drugs. We focused on cancer drugs because they represent the largest therapeutic area of drug development and spending.

6.4 Data and methods

6.4.1 Sample identification

We identified all new medicines with FDA approval between 1st January 2000 and 1st January 2022 (Figure 39). The sample was then restricted to anti-cancer drugs, excluding non-oncology, supportive care, and diagnostic agents, including gene and cell therapies. For these medicines, we then identified all original and supplemental anti-cancer indications in the Drugs@FDA database until 1st January 2022.

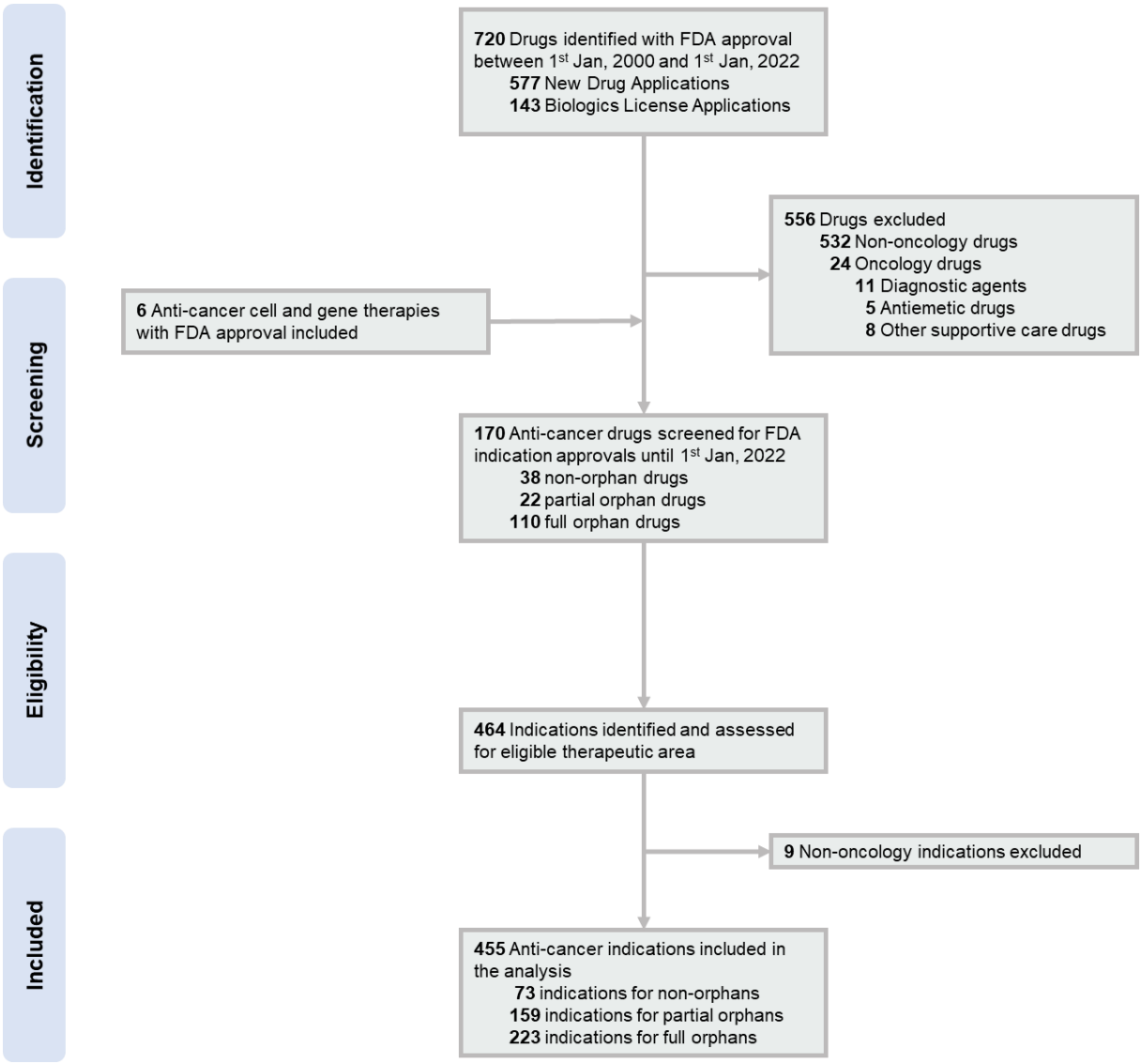


Figure 39: Flow diagram of full, partial, and non-orphan cancer drug indications included in the analysis, 2000-2022

Notes: All drugs that received FDA approval between 1st January 2000 and 1st January 2022 were identified in the Drugs@FDA database. We then limited the sample to anti-cancer drugs by excluding non-oncology drugs and oncology drugs indicated for diagnostic, supportive care, or antiemetic treatments. For each drug, we identified all original and supplementary indications with FDA approval until 1st January 2022, excluding approvals for non-oncology indications. Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).

Abbreviations: FDA, US Food and Drug Administration.

The FDA's orphan drug database was accessed to link the orphan designation status to each indication (Table 3). Orphan drugs were then classified as full orphans (only orphan indications), partial orphans (orphan and non-orphan indications), and non-orphans (only non-orphan indications).

6.4.2 Data collection

Two independent reviewers (D.T.M. and T.M.) retrieved and cross-checked data characterizing each indication from public sources including FDA labels, clinicaltrials.gov, associated publications, the Global Burden of Disease study, and Medicare and Medicaid websites (Table 3). Details of the data collection and synthesis methodology are described elsewhere.[73]

FDA approval

For each drug, we collected the number of indications, innovativeness, mechanism of action, and product type. For each indication, we retrieved data describing its treatment regimen, cancer type, companion biomarkers, and line of therapy. Clinical trials supporting each approval were described by their phase, enrolled patients, blinding, design, arms, comparator, and endpoint. For RCTs, HRs were noted for OS and PFS and RR rates were calculated for tumor response. The ORR was retrieved for single-arm trials. Improvements in OS, PFS, and duration of response were characterized by medians with IQR.

Epidemiology

Data describing each indication's cancer incidence, prevalence, and DALYs, calculated as the sum of YLD and YLL, were obtained from the Global Burden of Disease study for the US population in 2019.[128]

Prices

Medicare and Medicaid websites were accessed in 2023 to collect drug price data for the average US patient covered by Medicare Part B and D. The average monthly cost of treating an adult patient (weight: 70 kg, surface area:1.7 m^2) living in New York (ZIP:10065) covered by the "Humana Basic Rx Plan" was then estimated based on each indication's dosing regimen. Full details of this methodology are described elsewhere.[74]

Beneficiaries and spending

Medicare and Medicaid drug beneficiaries and gross spending were obtained from CMS websites with separate reports for Medicare Part D and B and Medicaid (Table 3). Beneficiary and spending data were retrieved for all on-patent drugs in our sample. We then calculated the total and average spending on new anti-cancer drugs with FDA approval for full, partial, and non-orphans.

6.4.3 Statistical analysis

We compared the development times, indication characteristics, pivotal trials, epidemiology, benefit, price, beneficiaries, and spending of full, partial, and non-orphan cancer drugs. Fisher's-exact-tests and Kruskal-Wallis-tests were used to compare the distribution of categorical variables and medians of interval-scaled variables, respectively. Similar to prior studies,[135] the time to approval, calculated as the difference between investigational new drug (IND) application to NDA/BLA approval, and the time to second approval, calculated as the difference between first and second NDA/BLA approval, were compared in Cox regression models. For RCTs, we conducted random-effects meta-analyses of HRs for OS and PFS and of RRs for tumor response. For single-arm trials, we meta-analyzed ORRs for tumor response. Cochran's Q-tests were used to compare differences in patient outcomes. Beneficiaries of and spending on full, partial, and non-orphan drugs were compared using three-way ANOVA, adjusting for the FDA approval year.

Data were stored in Microsoft EXCEL and analyzed with STATA 14.2 (StataCorp LLC, College Station, TX). Two-tailed p-values below 0.05 were considered significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline when applicable.[133]

6.5 Results

170 drugs with FDA approval in 455 indications were identified between 2000-2022 (Figure 39). Of these, 110 were full (65%), 22 partial (13%), and 38 non-orphan (22%) drugs. An equal share of partial orphans pursued an orphan-first (50%) and a non-orphan-first (50%) strategy (Table 28).

Generic name	First orphan approval	First non-orphan approval	Orphan indications	Non-orphan indications	Orphan-First [a]
Olaparib	19.12.2014	12.01.2018	5	2	Yes
Lenvatinib	13.02.2015	13.05.2016	2	3	Yes
Rucaparib	19.12.2016	15.05.2020	2	1	Yes
Cabozantinib	29.11.2012	25.04.2016	3	3	Yes
Trifluridine; Tipiracil	22.02.2019	22.09.2015	1	1	No
Regorafenib	25.02.2013	27.09.2012	2	1	No
Eribulin	28.01.2016	15.11.2010	1	1	No
Ipilimumab	25.03.2011	16.04.2018	4	4	Yes
Ramucirumab	21.04.2014	12.12.2014	3	3	Yes
Atezolizumab	18.03.2019	18.05.2016	3	8	No
Pembrolizumab	04.09.2014	02.10.2015	14	24	Yes
Avelumab	23.03.2017	09.05.2017	1	3	Yes
Durvalumab	27.03.2020	01.05.2017	1	2	No
Encorafenib	27.06.2018	08.04.2020	1	1	Yes
Everolimus	29.10.2010	30.03.2009	5	2	No
Pazopanib	26.04.2012	19.10.2009	1	1	No
Nivolumab	22.12.2014	04.03.2015	12	12	Yes
Erlotinib	11.02.2005	18.11.2004	1	3	No
Cetuximab	01.03.2006	12.02.2004	1	4	No
Pemetrexed	04.02.2004	19.08.2004	1	4	Yes
Bevacizumab	05.05.2009	26.02.2004	6	4	No
Fam-trastuzumab deruxtecan-nxki	15.02.2021	20.12.2019	1	1	No
Total			**71**	**88**	**11**

Table 28: Partial orphan cancer drugs approved by the FDA from 2000 to 2022

Notes: Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).

[a] Orphan-first refers to drugs with FDA approval in an orphan before a non-orphan indication.

Abbreviations: FDA, US Food and Drug Administration; NA, not applicable.

6.5.1 Clinical development time

The time from IND to first FDA approval was similar for full, partial, and non-orphans (Figure 40). The time from first to second FDA approval was shorter for partial than non- and full orphans (median: 1.3 vs. 1.6 vs. 2.3 years).

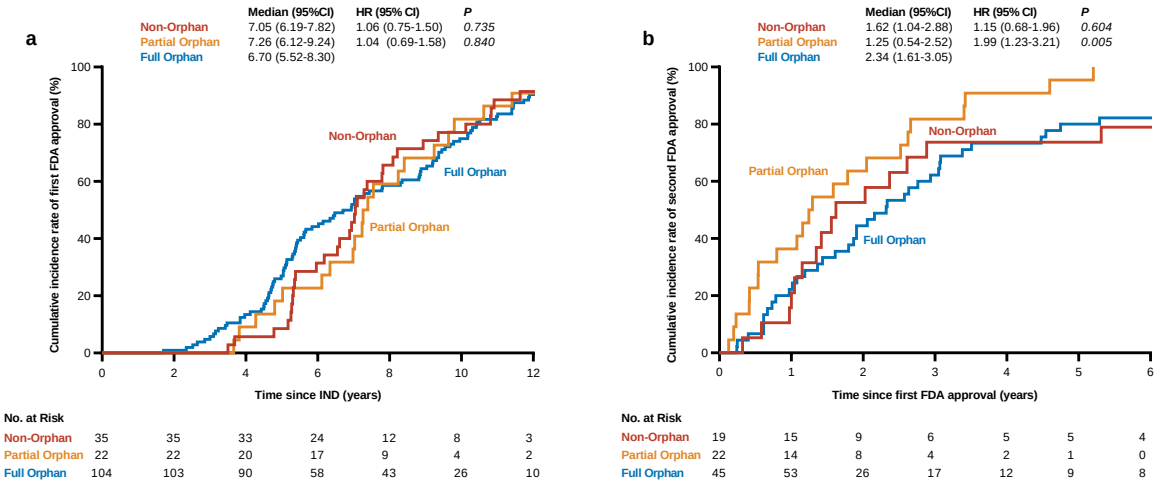


Figure 40: Time from IND to first and second FDA approval for full, partial, and non-orphan cancer drugs

Notes: Graph a illustrates the cumulative incidence of first FDA approval since IND for full (blue curve), partial (orange curve), and non-orphan (red curve) cancer drugs. Graph b portrays the cumulative incidence of second FDA approval since the first FDA indication approval for full (blue curve), partial (orange curve), and non-orphan (red curve) cancer drugs. Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications). P values calculated based on Cox-proportional hazard models.

Abbreviations: FDA, US Food and Drug Administration; IND, investigational new drug application.

6.5.2 FDA approval

Partial orphans were approved for more indications than full and non-orphan drugs (median: 5 vs. 1 vs. 2, p<.001; Table 29; Table 30). Indications of partial orphans more closely resembled non-orphans than full orphans regarding the share of monotherapies (58% vs. 58% vs. 74%, p=.002), hematologic cancers (4% vs. 0% vs. 66%, p<.001), and third-line therapies (8% vs. 7% vs. 17%, p=.025). Full orphans more frequently received the breakthrough therapy (46% vs. 32% vs. 32%, p=.031) and fast track (31% vs. 13% vs. 22%, p<.001) designations compared to partial and non-orphans (Table 31). Partial orphan drugs were predominantly approved for the treatment of lung, renal, skin, colorectal, and gastric cancers (Table 32).

No. (%)	Orphan Designation			*P Value* [a]
	Non-Orphan	**Partial Orphan**	**Full Orphan**	
Indication characteristics				
Number of indications, median (IQR)	2 (1-3)	5 (3-7)	1 (1-2)	*<.001*
FDA approval type				*<.001*
Original indication	39 (53.4)	22 (13.8)	119 (53.4)	
Supplemental indication	34 (46.6)	137 (86.2)	104 (46.6)	
Treatment type				*0.002*
Combination	31 (42.5)	67 (42.1)	59 (26.5)	
Monotherapy	42 (57.5)	92 (57.9)	164 (73.5)	
Cancer type				*<.001*
Hematological	0 (0.0)	7 (4.4)	147 (65.9)	
Solid	73 (100.0)	152 (95.6)	76 (34.1)	
Biomarker				*0.008*
No	39 (53.4)	115 (72.3)	134 (60.1)	
Yes	34 (46.6)	44 (27.7)	89 (39.9)	
Line of therapy				*0.025*
First-line	40 (54.8)	75 (47.2)	102 (45.7)	
Second-line	28 (38.4)	72 (45.3)	83 (37.2)	
≥Third-line	5 (6.8)	12 (7.5)	38 (17)	
Clinical trial characteristics				
Enrolled patients, median (IQR)	536 (230-886)	416 (173-709)	154 (83-365)	*<.001*
Clinical trial phase				*<.001*
Phase 1	4 (5.5)	4 (2.5)	13 (5.8)	
Phase 2	14 (19.2)	43 (27.0)	111 (49.8)	
Phase 3	55 (75.3)	112 (70.4)	99 (44.4)	
Trial design				*<.001*
Single-arm	14 (19.2)	37 (23.3)	112 (50.2)	
Non-randomized	0 (0.0)	1 (0.6)	7 (3.1)	
Concurrent RCT	57 (78.1)	118 (74.2)	99 (44.4)	
Dose-comparison RCT	2 (2.7)	3 (1.9)	5 (2.2)	
Type of blinding				*<.001*
Open-label	41 (56.2)	102 (64.2)	195 (87.4)	
Single-blind	0 (0.0)	1 (0.6)	0 (0.0)	
Double-blind	32 (43.8)	56 (35.2)	28 (12.6)	
Clinical trial arms				*<.001*
1 arm	14 (19.2)	37 (23.3)	112 (50.2)	
2 arms	55 (75.3)	116 (73.0)	106 (47.5)	
≥3 arms	4 (5.5)	6 (3.8)	5 (2.2)	
Total concurrent RCTs, no.	57	118	99	
Comparator				*0.375*
Active agent	17 (29.8)	47 (39.8)	40 (40.4)	
Placebo/No treatment	40 (70.2)	71 (60.2)	59 (59.6)	
Endpoint for concurrent RCTs				
Overall survival	45 (78.9)	98 (83.1)	61 (61.6)	*0.001*
Progression-free survival	41 (71.9)	105 (89.0)	76 (76.8)	*0.011*
Tumor response	38 (66.7)	100 (84.7)	81 (81.8)	*0.017*
Other	12 (21.1)	10 (8.5)	12 (12.1)	*0.061*
Cancer epidemiology				
Disease incidence, median (IQR) [b]	77.6 (69.3-94.1)	18.8 (8.5-67.6)	5.2 (1.5-8.2)	*<.001*
Disease prevalence, median (IQR) [b]	832.8 (117.8-859.2)	111.2 (25.9-117.8)	19.9 (6.5-35.4)	*<.001*
DALYs per person, median (IQR)	5.5 (3-7.1)	7.7 (6.4-16.4)	10 (6.7-16.4)	*<.001*
YLL per person, median (IQR)	4.8 (2.3-6.6)	7.2 (5.9-16.2)	9.3 (6.2-16.2)	*<.001*
YLD per person, median (IQR)	0.7 (0.5-0.8)	0.4 (0.2-0.5)	0.5 (0.4-0.7)	*<.001*
Total no. of indications	**73 (16.0)**	**159 (34.9)**	**223 (49.0)**	

Table 29: Characteristics of full, partial, and non-orphan cancer indications approved by the FDA from 2000 to 2022

Notes: Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (no orphan indications).

[a] P Values calculated based on Fisher's-exact-tests or Kruskal-Wallis-tests.
[b] Disease incidence and prevalence rates per 100,000 US inhabitants.

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; IQR, interquartile range; RCTs, randomized controlled trials; YLD, years lived with disability; YLL, years of life lost due to premature death.

No. (%)

	Orphan Designation			*P Value* [a]
	Non-Orphan	**Partial Orphan**	**Full Orphan**	
Drug characteristics				
Innovativeness				*0.730*
Not-first-in-class	25 (65.8)	15 (68.2)	66 (60.0)	
First-in-class	13 (34.2)	7 (31.8)	44 (40.0)	
Mechanism of action				*0.021*
Cytotoxic chemotherapy	3 (7.9)	3 (13.6)	15 (13.6)	
Targeted agents	33 (86.8)	13 (59.1)	66 (60.0)	
Immune-regulators	2 (5.3)	6 (27.3)	29 (26.4)	
Product type				*0.084*
Small-molecule	26 (68.4)	12 (54.5)	76 (69.1)	
Antibody	7 (18.4)	9 (40.9)	16 (14.5)	
Antibody-drug conjugate	4 (10.5)	1 (4.5)	7 (6.4)	
Other [b]	1 (2.6)	0 (0.0)	11 (10.0)	
Total number of drugs	**38 (22.4)**	**22 (12.9)**	**110 (64.7)**	

Table 30: Characteristics of full, partial, and non-orphan cancer drugs approved by the FDA from 2000 to 2022

Notes: Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).

[a] P Values calculated based on Fisher's-exact-tests.
[b] Other includes gene therapies, cell therapies, enzymes, and radionuclides.

Abbreviations: FDA, US Food and Drug Administration

No. (%)

	Orphan Designation			*P Value* [a]
	Non-Orphan	**Partial**	**Full**	
Fast Track	16/73 (21.9)	21/159 (13.2)	68/223 (30.5)	*<.001*
Priority Review	53/73 (72.6)	127/159 (79.9)	178/223 (79.8)	*0.400*
Accelerated Approval	17/73 (23.3)	49/159 (30.8)	81/223 (36.3)	*0.103*
Breakthrough Therapy [b]	16/50 (32.0)	42/132 (31.8)	79/173 (45.7)	*0.031*

Table 31: Special review pathways used for the FDA approval of full, partial, and non-orphan cancer drugs: fast track, priority review, accelerated approval, and breakthrough therapy

Notes: Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).

[a] P Values calculated based on Fisher's-exact-test.
[b] Includes only indications approved in 2013 and thereafter.

Abbreviations: FDA, US Food and Drug Administration.

No.

	Orphan Designation			Total
	Non-orphan	**Partial**	**Full**	
Bladder	4	10	0	14
Brain	0	1	2	3
Breast	27	8	1	36
Cervical	1	3	0	4
Colorectal	7	12	0	19
Endometrial	1	2	0	3
Gastric	1	12	4	17
Head and Neck	0	6	0	6
Hepatic	0	10	1	11
Leukemia	0	0	62	62
Lung	3	34	28	65
Lymphoma	0	5	71	76
Other	2	9	29	40
Ovarian	0	9	3	12
Pancreatic	0	2	0	2
Prostate	16	2	0	18
Renal	6	16	2	24
Skin	5	15	12	32
Thyroid	0	3	8	11
Total	**73**	**159**	**223**	**455**

Table 32: Tumor entities treated by full, partial, and non-orphan cancer drugs

Notes: Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).

6.5.3 Clinical trials

Clinical trials supporting full orphan indications enrolled fewer patients than those for partial and non-orphans (median: 154 vs. 416 vs. 536, p<.001). Full orphan indications were less frequently supported by double-blind (13% vs. 35% vs. 44%, p<.001) concurrent RCTs (44% vs. 74% vs. 78%, p<.001) assessing OS (62% vs. 83% vs. 79%, p<.001) than partial and non-orphan indications.

6.5.4 Epidemiology

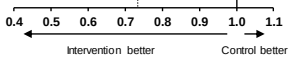
Full orphan indications exhibited a lower disease incidence (median: 5.2 vs. 18.8 vs. 77.6, p<.001) and higher DALYs (median: 10.0 vs. 7.7 vs. 5.5, p<.001) than indications of partial and non-orphan drugs.

6.5.5 Clinical benefit

Indications of full orphan drugs did not prevent significantly more deaths (HR: 0.69 vs. 0.74 vs. 0.75, p=.064), yet provided a greater OS benefit (median: 4.0 vs. 2.8 vs. 2.8, p<.001) than those of partial and non-orphan drugs (Figure 41). Full orphans prevented more tumor progressions (HR: 0.48 vs. 0.61 vs. 0.62, p<.001) with a greater PFS benefit (median: 5.1 vs. 2.5 vs. 3.6, p<.001) than partial and non-orphans. However, tumor response in RCTs was lower for full than partial and non-orphan drugs (RR: 1.28 vs. 1.50 vs. 1.52, p<.001). Nevertheless, more tumor responses were observed for full than partial and non-orphans in single-arm trials (ORR: 54% vs. 33% vs. 34%, p<.001).

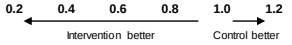
A

Subgroup	Intervention	Control	OS Hazard Ratio (95% CI)	I^2	*P Value* [a]	Survival Gain	*P Value* [b]
	no. of patients with event/total no. of patients (%)					*median (IQR), months*	
Indication-level					*0.178*		*0.382*
Non-orphan	14605/38606 (37.8)	14455/32455 (44.5)	0.74 (0.72-0.76)	29.7%		2.8 (1.8-4.6)	
Orphan	10156/22790 (44.6)	9784/19182 (51)	0.72 (0.69-0.75)	33.5%		3.3 (2-4.7)	
Drug-level					*0.064*		*<.001*
Non-orphan	6017/20433 (29.4)	5711/16785 (34)	0.75 (0.72-0.79)	33.1%		2.8 (1.8-4.8)	
Partial orphan	14234/28024 (50.8)	14056/23782 (59.1)	0.74 (0.72-0.76)	24.0%		2.8 (2-4)	
Full orphan	4510/12939 (34.9)	4472/11070 (40.4)	0.69 (0.65-0.73)	36.9%		4 (1.5-7.7)	
Overall	**24761/61396 (40.3)**	**24239/51637 (46.9)**	**0.73 (0.72-0.75)**	**31.7%**		**2.9 (1.99-4.65)**	



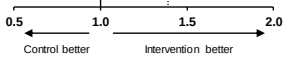
B

Subgroup	Intervention	Control	PFS Hazard Ratio (95% CI)	I^2	*P Value* [a]	Survival Gain	*P Value* [b]
	no. of patients with event/total no. of patients (%)					*median (IQR), months*	
Indication-level					*<.001*		*0.011*
Non-orphan	19142/33004 (58)	17996/27040 (66.6)	0.64 (0.6-0.67)	86.2%		2.7 (1.4-5.2)	
Orphan	13388/26873 (49.8)	13735/22553 (60.9)	0.51 (0.47-0.54)	90.6%		4.2 (2.1-7.1)	
Drug-level					*<.001*		*<.001*
Non-orphan	6983/14405 (48.5)	6731/11310 (59.5)	0.62 (0.57-0.67)	83.7%		3.6 (1.8-7.1)	
Partial orphan	19305/29081 (66.4)	17565/23818 (73.7)	0.61 (0.57-0.64)	90.3%		2.5 (0.7-4.55)	
Full orphan	6242/16391 (38.1)	7435/14465 (51.4)	0.48 (0.43-0.53)	89.8%		5.06 (2.83-9)	
Overall	**32530/59877 (54.3)**	**31731/49593 (64)**	**0.57 (0.54-0.6)**	**90.7%**		**3.3 (1.55-5.6)**	



C

Subgroup	Intervention	Control	Tumor Response (95% CI)	I^2	*P Value* [a]	Duration Gain	*P Value* [b]
	no. of patients with event/total no. of patients (%)		*Relative Risk*			*median (IQR), months*	
Indication-level					*<.001*		*0.278*
Non-orphan	10980/30907 (35.5)	5981/26556 (22.5)	1.53 (1.44-1.63)	84.0%		5 (2.9-10.1)	
Orphan	14082/28014 (50.3)	9394/24189 (38.8)	1.29 (1.24-1.34)	78.4%		4.3 (2.1-7.4)	
Drug-level					*<.001*		*0.543*
Non-orphan	4697/11864 (39.6)	2376/10101 (23.5)	1.52 (1.38-1.65)	83.3%		2.9 (0.1-6.8)	
Partial orphan	9818/29310 (33.5)	5681/24688 (23)	1.5 (1.4-1.59)	78.7%		4.3 (2.4-8.7)	
Full orphan	10547/17747 (59.4)	7318/15956 (45.9)	1.28 (1.23-1.34)	81.4%		5.8 (2.2-7.4)	
Overall	**25062/58921 (42.5)**	**15375/50745 (30.3)**	**1.39 (1.34-1.43)**	**81.3%**		**4.3 (2.35-8.3)**	



D

Subgroup	Responders	No. of patients	Tumor Response (95% CI)	I^2	*P Value* [a]	Duration of Response
			Objective Response Rate (%)			*median (IQR, months)*
Indication-level					*<.001*	*0.188*
Non-orphan	1395	4580	32.5 (28.2-36.8)	91.2%		8.3 (7.2-13.8)
Orphan	6597	13106	50.7 (46.4-55)	96.7%		10.96 (8.2-13.6)
Drug-level					*<.001*	*0.098*
Non-orphan	553	1649	33.5 (27.8-39.2)	85.0%		7.65 (6.73-9.85)
Partial orphan	1596	4873	33.4 (27.6-39.2)	95.8%		10.3 (7.9-14.8)
Full orphan	5843	11164	53.5 (49.1-57.9)	96.5%		11.1 (8.2-14.3)
Overall	**7992**	**17686**	**46.5 (42.8-50.3)**	**96.8%**		**10.42 (7.75-13.7)**

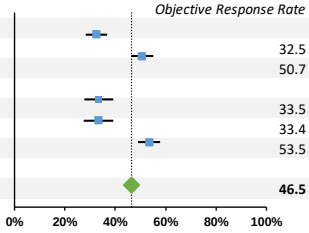


Figure 41: Meta-analyses of overall survival, progression-free survival, and tumor response for full, partial, and non-orphan cancer drugs approved by the FDA from 2000 to 2022

Notes: In graphs A, B, and C, treatment outcomes were meta-analyzed for RCTs. Graph D shows average tumor response rates measured in single-arm trials. For tumor responses, a continuity adjustment of 0.5 for control arms with 0 responders was applied. Cancer indications were stratified by their orphan designation status into orphan and non-orphan. Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).

Abbreviations: FDA, US Food and Drug Administration; IQR, interquartile range; OS, overall survival; PFS, progression-free survival.

6.5.6 Prices

Monthly prices were higher for full than partial and non-orphan drugs (median: $17,177 vs. $13,284 vs. $12,457, p<.001; Figure 42). Particularly partial orphans pursuing an orphan-first strategy were priced at a premium compared to those pursuing a non-orphan-first strategy (median: $14,734 vs. $12,624).

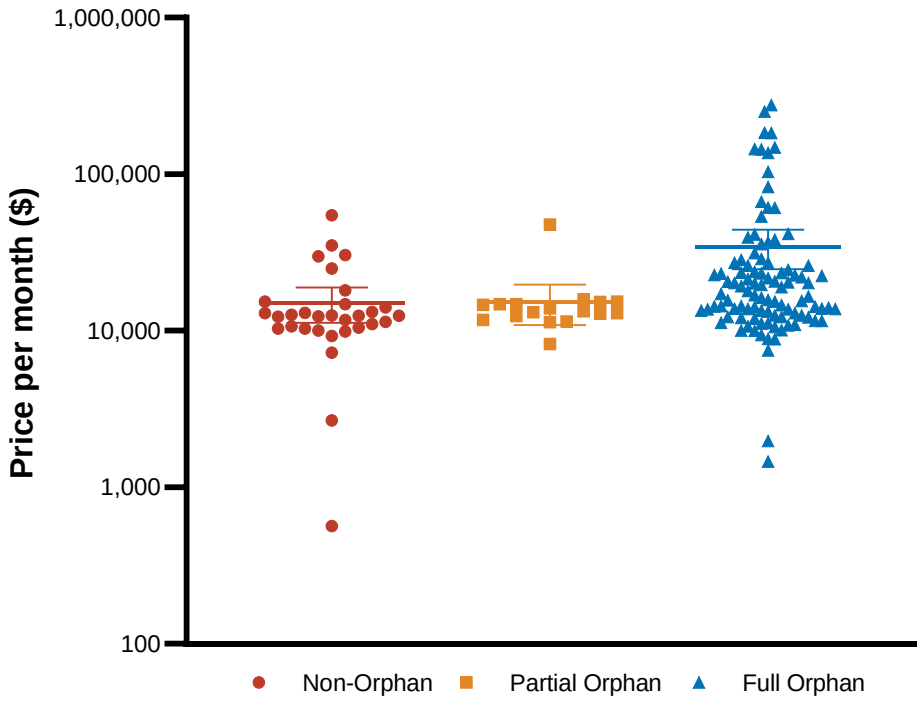


Figure 42: Prices for full, partial, and non-orphan cancer drugs in 2023

Notes: Monthly prices are compared for full, partial, and non-orphan cancer drugs. Bars represent means with 95% confidence intervals. Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).

6.5.7 Beneficiaries and spending

In 2020, Medicare and Medicaid gross spending on our sample of FDA-approved cancer drugs amounted to $30 billion (Figure 43). Of this, 44% ($13.2 billion) was spent on full, 30% ($9.1 billion) on partial, and 25% ($7.6 billion) on non-orphan drugs. Average gross spending per drug was higher for partial than non- and full orphan drugs ($570 vs. $305 vs. $156 million).

Spending per indication was higher for non-orphans than full and partial orphans ($162 vs. $83 vs. $72 million).

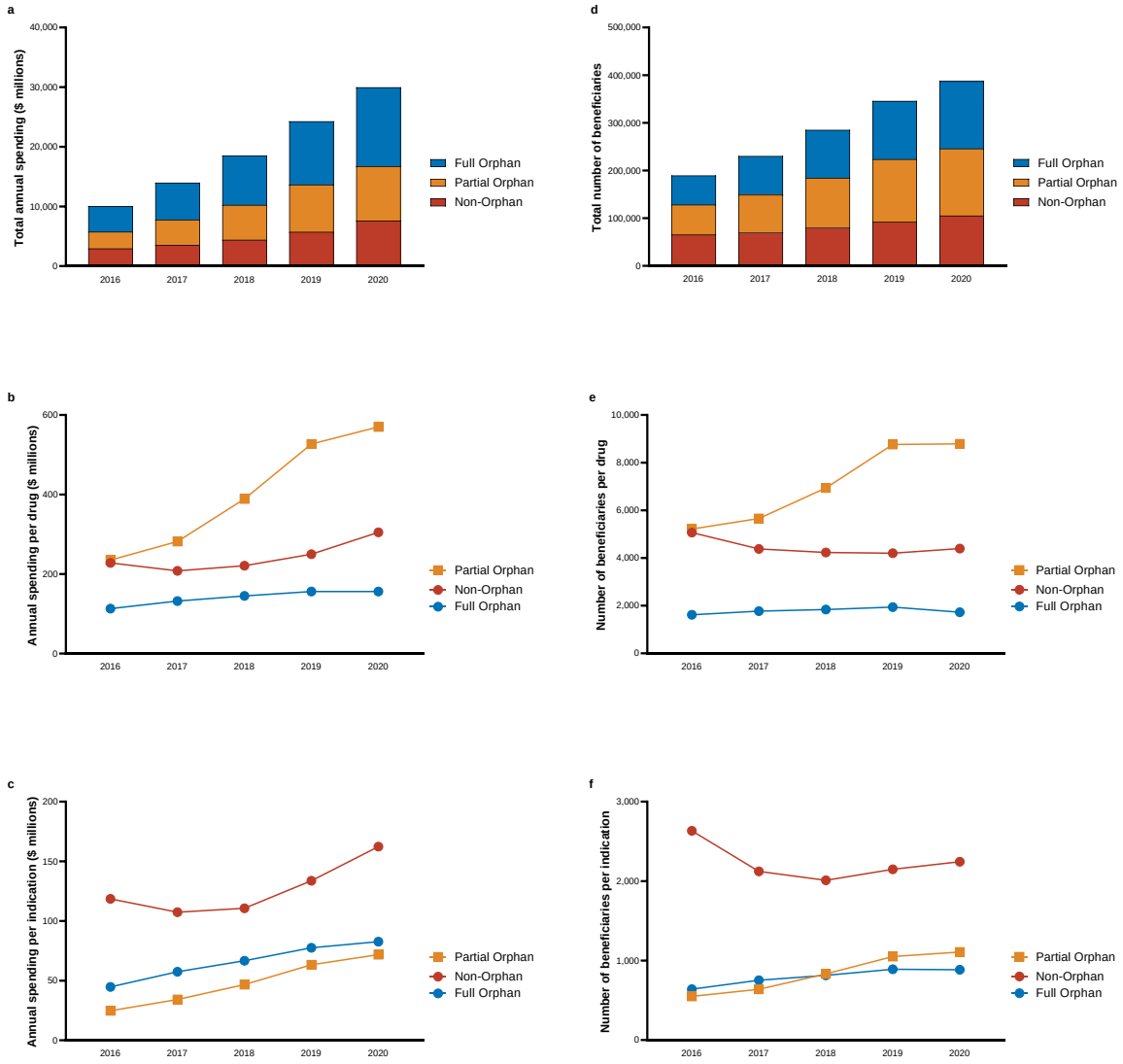


Figure 43: Medicare and Medicaid spending on and beneficiaries of full, partial, and non-orphan cancer drugs from 2016 to 2020

Notes: Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).

In 2020, a total of 387,700 beneficiaries received new FDA-approved anti-cancer drugs covered under Medicare and Medicaid. Of these, 37% (141,600) received full, 36% (140,600) partial, and 27% (105,500) non-orphan drugs. Consequently, the mean number of beneficiaries was substantially higher for partial than non- and full orphan drugs (8,790 vs. 4,390 vs. 1,730). On

an indication level, the average number of beneficiaries was higher for non- and partial orphans than full orphans (2,244 vs. 1,107 vs. 885).

6.6 Discussion

In this study of 170 drugs with 455 anti-cancer indications, we compared the characteristics of full, partial, and non-orphan drugs. Albeit there were only 22 (13%) partial orphan drugs approved between 2000-2022, they were a major driver of pharmaceutical innovation, accounting for 35% of indication approvals; yet, also a major source of Medicare and Medicaid expenditure, accounting for 30% of spending.

6.6.1 Partial orphans and the Orphan Drug Act

The ODA was introduced to encourage the R&D of drugs treating rare diseases for which clinical trials are difficult to conduct and sales are unlikely to recoup development costs. In this study, we showed that partial orphans were distinctly different from drugs that only treat rare diseases and on average do not fulfill the ODA's underlying intention. Relative to full orphans, partial orphans were more likely to be combination treatments for solid cancers supported by larger, randomized, double-blind phase 3 trials assessing OS rather than surrogate endpoints. Although partial orphans were swiftly approved for follow-on indications, on average, they did not treat rare diseases as exhibited by higher disease incidence rates and lower disease severity. The average OS, PFS, and tumor response benefit was lower for partial than full orphan drugs. However, the average partial orphan drug was more frequently prescribed and exhibited greater Medicare and Medicaid gross spending than full or non-orphan drugs. Policy reforms are necessary to reflect partial orphans' distinct characteristics in the ODA.

Policymakers could amend the ODA benefits for partial orphan drugs. The ODA benefits could be lowered or even revoked for partial orphans that surpass a pre-defined revenue (e.g. $200 million) and/or total patient threshold (e.g. 200,000 affected US inhabitants).[46,181] For example,

partial orphans exceeding these thresholds need to repay half of the ODA's tax credits and user fees and only benefit from a market exclusivity period of 5 instead of 7 years. Similar provisions are observed in European and Japanese orphan drug policies.[194,195] The EU's orphan drug policy entails a "*clawback*" clause that allows the EMA to reduce the period of market exclusivity from 10 to 6 years for drugs that were shown to generate sufficient revenues; yet, this clause has never been enacted.[190] While these thresholds ensure that the ODA benefits are only granted to drugs with limited sales potential for rare diseases, it would also discourage sponsors to pursue the development of orphan follow-on indications.

6.6.2 Pricing, usage, and spending of partial orphans

In 2020, average Medicare and Medicaid spending was 3.6x and 1.8x greater for partial than full and non-orphan cancer drugs, respectively. Coherent with theory, our results confirm that partial orphans are priced slightly higher than non-orphans. Yet, spending on partial orphans is mainly driven by drug usage, particularly for common disease indications.[46,190,193] As a result, we observed 5.1x and 2.0x more beneficiaries for partial than full and non-orphan drugs, respectively. The greater number of beneficiaries for partial orphan drugs is mainly driven by the expansion of partial orphan drugs to new indications and uses. At an indication level, there were only 1.3x more beneficiaries per indication for partial than full orphan drugs, whilst there were more beneficiaries for non-orphan than partial orphan drugs. There are several policy options to control the expenditure on and usage of partial orphans for non-orphan indications.

In this study, prices were especially high for drugs that were first-approved for orphan and then extended to non-orphan indications. Indication-specific pricing – aligning a distinct price to each indication rather than a drug – could help to decrease incentives for this orphan-first strategy.[41] Thereby sponsors could charge a lower price for common and a higher price for rare diseases treated by the same drug. Essential to this policy is the monitoring of drugs for their intended indication. Physicians and pharmacists would have to note the intended usage of each

drug that is prescribed and dispensed. Albeit patients, physicians, and pharmacists welcome indication-specific prescriptions, monetary investments for a clinically well-integrated IT system and political resistance of key stakeholders must be overcome for its widespread adoption in clinical practice.[58–60] Besides rationalizing drug prices, this novel system permits the collection and analysis of real-world outcomes data, especially for orphan indications with an uncertain safety and efficacy profile at the time of FDA approval.[41] Furthermore, indication-specific tracking of drug usage is fundamental to encourage generic competition for partial orphans. Generic "skinny labels" of partial orphans could lower prices for off-patent non-orphan indications, whilst protecting on-patent orphan indications with a prolonged period of market exclusivity.[196–198]

Given that a *pure* ISP system will likely not be implemented in the short-term,[50] US policymakers can explore *indirect* ISP policies currently used in other countries.[11,38,40,49] For instance, Germany and France calculate a weighted-average drug price based on each indication's benefit and patient population. This policy was shown to effectively reduce drugs' list prices as new non-orphan indications entered the market.[38] England, Scotland, and Canada demand indication-specific discounts for drug indications that are deemed not cost-effective based on the original indication's list price. Insurance systems in Australia, England, and Scotland were also shown to restrict the coverage and reimbursement of low-value indications; e.g. non-orphan indications were more frequently restricted to subpopulations with a greater observed benefit.[38] The CMS' existing CED policy could be amended to a similar extent.[146]

This study showed that half of the partial orphan drugs pursued a non-orphan-first strategy. Among these drugs, more than 80% of spending is attributable to non-orphan indications.[46] There are three options to control the usage of and expenditure on partial orphans' indications for common diseases. First, partial orphans should not be exempted from the 340B Price Program as proposed by the recently introduced "Closing Loopholes for Orphan Drugs Act".[199]

The 340B Price Program mandates sponsors to sell outpatient drugs at a 23% discount to healthcare providers serving uninsured and low-income patients.[181] Second, insurers should create indication-specific formulary lists rather than drug-specific formularies.[46] Thereby insurers could exclude partial orphans' indications for common diseases with a low benefit from formularies, whilst granting patients access to indications for rare diseases with a high benefit. Finally, top-selling partial orphans are eligible to be included in the new IRA's price negotiations.[164] Thereby, the CMS could demand price discounts for top-selling partial orphan drugs that are predominantly used for common diseases.

6.6.3 Balancing the benefits and affordability of partial orphan drugs

All the proposed policies could reduce the cost of and expenditure on non-orphan indications; yet, these changes could also deter sponsors from investing in and developing orphan indications. Whilst pharmaceutical companies pursue indications for economic profits, there is a benefit to testing a drug in a defined rare disease population. For example, pembrolizumab was not only approved for common cancer entities but was also successfully tested in and approved for rare cancers, including Merkel cell carcinoma, Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, and cervical cancer. Imatinib was first approved for chronic myeloid leukemia and later received regulatory approval for rare and ultra-rare tumors such as gastrointestinal struma tumor, chronic eosinophilic leukemia, and aggressive systemic mastocytosis. Therefore, the pursuit of orphan indications for blockbuster drugs that have proven their efficacy in non-orphan diseases can have substantial benefits for patients suffering from rare diseases. Moreover, the extension of non-orphan drugs to orphan indications is associated with lower R&D spending for pharmaceutical companies as pre-clinical development and phase 1 and 2 trials may only be necessary once in each therapeutic area.[48] Whilst this analysis suggests that partial orphan drug prices could be slightly higher than those for non-orphan drugs, they are not close

to the highly-priced full orphan drugs. Therefore, partial orphan drugs also offer important therapeutic gains to patients suffering from rare diseases without available treatment options.

As a consequence, any changes to the ODA in its current form and to the pricing, coverage, and reimbursement of orphan drugs must be thoroughly evaluated. For example, scholars are concerned that the IRA will deter pharmaceutical sponsors from testing full orphan drugs in common diseases, yet not partial orphans, since full orphan drugs are excluded from the IRA's price negotiations.[200] Any novel policy must balance the risk of undermining investments in orphan drug development, particularly the pursuit of novel indications, with the benefit of increasing the affordability of drugs that are not (or only partially) deserving of the ODA.

6.6.4 Partial orphan drugs beyond oncology

In this study only anti-cancer drugs were analyzed. Two prior studies assessed the spending on partial orphan drugs across all therapeutic areas in the US. Using a sample of 315 drugs, Tu et al. showed that sales of drugs with an orphan designation in the first indication was just as high as sales for those without the designation in the first indication.[201] Chua et al. showed among the top fifteen selling partial orphan drugs in the US, 21% was spent on orphan and 71% on non-orphan indications.[46] However, pharmaceutical companies' commercialization strategies may differ across therapeutic areas.[202] In oncology, an orphan-first strategy generates high prices that are transferred across indications. In contrast, in rheumatology, the non-orphan-first strategy permits pharmaceutical companies to quickly gain market share for high-prevalence diseases to then roll out their medicine to rare diseases. This strategy maximizes early revenue potential for pharmaceutical companies but requires robust, certain outcomes data. Future research should confirm our results and policy implications for non-cancer medicines.

6.6.5 Limitations

This study has certain limitations. First, we only examined drugs and indications with FDA approval. Therefore, the efficacy analysis is upward-biased to only successful trials, whilst the spending analysis does not distinguish between approved and off-label indication uses. Second, drugs' list prices and gross spending were calculated for the average patient covered under Medicare & Medicaid – net prices, co-payments, deductibles, rebates, and net spending may vary for patients covered with private health insurers. Third, in the absence of nationwide claims data, we were not able to calculate the number of beneficiaries of and spending on orphan and non-orphan indications for the same drug.[46]

6.7 Conclusion

This study showed that partial orphan cancer drugs are more similar to non-orphan than fully orphan drugs regarding their clinical benefit, trial evidence, and epidemiology. However, partial orphans receive all of the ODA's incentives and are swiftly extended to new indications; resulting in greater prices, more beneficiaries, and higher gross spending on partial than non-orphan drugs. We, therefore, propose to reduce the ODA benefits for top-selling partial orphans that exceed pre-defined revenue and/or patient thresholds. Policymakers should explore indication-specific prescription, pricing, coverage, and reimbursement systems as well as deleting partial orphans' exemptions from the 340B Pricing Program to ensure that US patients can access and afford their required medicines.

6.8 Author contributions

Daniel Tobias Michaeli and Thomas Michaeli had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: All authors. Administrative, technical, or material support: All authors. Study supervision: All authors.

7 Cost savings of indication-specific and weighted-average pricing

Summary: This study estimates that Medicare and Medicaid could reduce spending on cancer drugs by 15.5% with the adoption of indication-specific pricing or weighted-average pricing.

7.1 Abstract

Background: In the US single drug prices do not reflect the value of supplemental indications approvals. Therefore, indication-specific and weighted-average pricing were suggested for drugs with multiple indications. Under indication-specific pricing, a distinct price is assigned to the differential value a drug offers in each indication. Under weighted-average pricing, a single drug price is calculated reflecting the value and/or volume of each indication.

Objective: To estimate potential price reductions and resulting cost savings for cancer drugs under indication-specific pricing or weighted-average pricing.

Data and methods: All anti-cancer drugs and their original and supplemental indications with FDA approval between 2003 and 2022 were identified in the Drugs@FDA database. Data on each indication's innovativeness, disease, trial, price, and spending were collected from FDA labels, the Global Burden of Disease study, clinicaltrials.gov, and the CMS. A multivariate regression analysis, informed by original indications' innovativeness, disease, and trial characteristics, was used to predict indication-specific prices for supplemental indications. These indication-specific prices were combined with each indication's prevalence data to estimate weighted-average prices and potential cost savings for both policies.

Results: The FDA approved 162 anti-cancer drugs with 373 indications between 2003-2022. Of these, price data were available for 149 on-patent drugs. On these drugs, Medicare and Medicaid spent a total of $28.3 billion in 2020. Adopting indication-specific pricing reduced drug

prices by an average of -2.9% with cost savings of -$4.4 billion (-15.5%). Spending was particularly reduced on orphan drugs treating rare and common diseases, e.g. partial orphans (-10.0%). However, higher prices for ultra-rare diseases increased spending by 16.8% (+$44 million). Adopting weighted-average pricing also reduced spending by -$4.4 billion (-15.5%). Weighted-average pricing reduced prices for and spending on ultra-rare diseases by -21.3%.

Conclusion: Indication-specific and weighted-average pricing could help to align new indications' value and price; thereby reducing Medicare and Medicaid's expenditure on cancer drugs with multiple indications.

7.2 Introduction

Cancer drugs are increasingly approved and used for multiple indications. Between 2000 and 2022, 55% of cancer drugs received FDA approval for more than one indication; with an average of four indications per drug.[73] However, in the US, a single (uniform) drug price is set based on the original indication's unmet needs and innovativeness.[74] These uniform drug prices neglect the value of supplemental indications. This is particularly concerning for partial orphan drugs pursuing an "orphan-first" strategy – drugs that are initially approved for rare and then extended for use in common diseases.[46,76,77,189,201] Under uniform prices, this strategy was shown to unfairly boost revenues for drug sponsors by transferring high orphan prices to non-orphan indications.[77] Indication-specific pricing or weighted-average pricing could help to better align prices with each indication's value and, thereby, resolve the current loopholes created under uniform drug prices.[76,77]

Systematic reviews have theoretically evaluated the merits of these differential pricing methods.[11,35,49] However, besides several theoretical articles[35–37,49–56] and four case studies,[41–44] our knowledge of the potential impacts of adopting these pricing systems in the US remains decimal. Therefore, we estimated prices and Medicare and Medicaid spending if indication-specific or weighted-average pricing was adopted in the US for a sample of anti-cancer drugs.

7.2.1 Indication-specific pricing

Indication-specific pricing, also referred to as indication-based pricing or multi-indication pricing, is the most rational option to price drugs with multiple indications.[41] Under indication-specific pricing, a distinct price is assigned to the differential value a drug offers in each indication ("one drug, multiple prices").[41] Thereby, higher prices are assigned to indications that offer substantial benefits (high QALY gains) to patients with significant unmet needs, while a lower price is aligned to indications that only offer an incremental benefit (low QALY gains).

However, the implications of ISP on healthcare budgets, pharmaceutical competition, and patient access remain debated.

Bach noted that indication-specific pricing could rationalize drug pricing and thereby reduce healthcare expenditure.[41] In contrast, Chandra & Garthwaite (2017, p.103-104) noted that indication-specific pricing "will result in higher prices for patients who benefit the most from a given drug, higher utilization by patients who benefit least, higher overall spending, and higher manufacturer profits."[37] Although spending might be increased under indication-specific pricing, the increased healthcare budget would be allocated to high-value indications that provide substantial benefit to patients rather than money being wasted on indications offering marginal benefit.[35] Indication-specific pricing encourages pharmaceutical companies to engage in pharmaceutical R&D for both high-value low-prevalence and low-value high-prevalence indications if indication-specific pricing is implemented alongside a value-based pricing mechanism. Thereby indication-specific pricing could not only increase the number of therapeutic options available to patients but also reduce incentives to delay or withhold indications (e.g. the sequencing of indication launches), resulting in quicker access to these novel indications.[35,55] Cole et al. argue that this greater number of available therapeutic alternatives will result in more competition that will dynamically reduce prices.[35] Hitherto, evidence from a systematic review suggests that greater brand-brand competition does not lead to reduced prescription drug prices.[57] Ultimately, indication-specific pricing could benefit all stakeholders: expediting patient access to more therapeutic options, increasing revenues and profits for pharmaceutical companies, and reducing health insurers' spending on prescription drugs.

7.2.2 Weighted-average pricing

Weighted-average pricing is an indirect differential pricing policy. Under this policy, a single drug price is calculated reflecting the value and/or volume of each indication. This system re-

quires the ex-ante estimation or ex-post monitoring of patients receiving the drug for each indication.[38] As for all drug pricing considerations, the operationalization of "value" remains subject to the national HTA process. Therefore, this calculation or monitoring imposes an additional administrative burden on manufacturers and payers. Moreover, given that drug prices are still anchored to the initial indication, there remains an incentive for drug sponsors to sequence the development and launch of new indications. Particularly, low-value high-prevalence indications, which may substantially reduce the weighted-average price for the entire drug, may not be launched (Figure 6).[39] Weighted-average pricing is currently applied in Germany, France, Spain, Australia, Austria, and Belgium,[11,40,49] and was shown to be associated with declining list prices as new low-value high-prevalence indications enter the pharmaceutical market.[38]

7.3 Data and methods

First, we collected data on all cancer drugs with FDA approval from 2000 to 2022. Then, we used these data to calculate indication-specific and weighted-average prices. First, we conducted a regression analysis of prices for original approvals informed by each indication's innovativeness, R&D costs, disease incidence, disease severity, and the number of available treatment options. This model was then used to predict indication-specific prices for all supplemental indications. Based on these indication-specific prices, we calculated value- and population-weighted-average prices for each drug as new indications enter the market. Medicare and Medicaid drug spending was proportionally assigned to each indication based on disease prevalence rates published by the Global Burden of Disease study. The current uniform pricing policy was compared to indication-specific and weighted-average pricing regarding monthly treatment costs and total Medicare and Medicaid spending.

7.3.1 Data collection

We identified all cancer drugs receiving FDA approval between 2000-2022 in the Drugs@FDA database.[73] Then, we collected data from marketing authorization labels and clinicaltrials.gov on all anti-cancer drugs, including their original and supplemental indications, with FDA approval between 2000 and 2022. Epidemiologic data, including estimates for disease incidence, DALYs, and number of available treatment options, were retrieved for all indications from the Global Burden of Disease study and the National Institute of Health.[128,129] Monthly drug prices were then calculated based on data retrieved from the CMS for an average adult US patient (weight: 70 kg, surface area: 1.7 m^2) living in New York (ZIP: 10065) covered under Medicare Part B and D. Drug prices were obtained from the CMS and the Medicare's plan finder tool. For each cancer drug, Medicare Part B and D as well as Medicaid spending was downloaded from the CMS website. We have previously described details for the data collection methodology elsewhere.[73,74]

7.3.2 Estimating indication-specific prices

US drug prices are set based on the original indication's characteristics and then transferred to following supplemental indication approvals, regardless of their unmet needs, innovativeness, and R&D costs.[74] We sought to estimate indication-specific prices for these supplemental indications, based on the original indication's characteristics. First, we conducted a multivariable regression analysis of original indication prices informed by variables relevant to the pricing of new cancer drugs/indications (selection of these variables was informed by previous studies)[74,110,203]:

- Disease burden: Disease burden was measured by each disease's incidence rate per 100,000 US inhabitants in 2019 as published by the Global Burden of Disease study.[128]

- Disease severity: Disease severity was estimated based on DALYs per patient as published by the Global Burden of Disease study.[128] DALYs are a composite measure of YLL and YLD.
- Number of treatment alternatives: Besides disease rarity and burden, the number of treatment alternatives represents the last domain of unmet medical needs.[145] The number of available treatment options was obtained from the National Cancer Institute for each cancer entity.[129]
- R&D costs: The number of patients enrolled in the pivotal trial supporting the new indication's FDA approval was used as a proxy for pharmaceutical companies' R&D costs. Although this proxy may be imperfect, R&D costs were shown to be positively correlated to clinical trial size.[204]
- Innovation/Novelty: A drug's innovativeness/novelty may be judged from different aspects. The industry perspective has long focused on new drugs' biotechnological aspects: mechanism of action, target, and/or delivery method.[110,203,205] However, these biotechnological aspects may not be meaningful to patients and physicians. From a clinical perspective, innovativeness is better determined by combining the novelty of a drug's target as well as the medical novelty of the treated disease. Patients benefit from next-in-class drugs if they treat a novel disease. For instance, avelumab was not the first PD-L1 inhibitor to receive FDA approval; yet, it is the first (and only) PD-L1 inhibitor to treat Merkel Cell Carcinoma. We consequently adopted Lanthier et al.'s methodology of determining new drugs' innovativeness[205] and modified it for the classification of new indications' innovativeness. We differentiated drugs for new indications (first-in-indication), drugs for known indications with a major benefit as exhibited by FDA priority review (advance-in-indication), and drugs for known indications without FDA pri-

ority review (addition-to-indication). Furthermore, this novel methodology of determining innovativeness fits the purpose of calculating indication-specific prices as it allows for varying levels of innovation across a drug's indications.

The results of the log-linear regression analysis with robust standard errors are presented in Table 33. This model was then used to predict prices for all supplemental indications adjusting for smearing. These indication-specific prices were then used to calculate weighted-average prices. Following the French and German examples, we estimated a single drug price weighted by each indication's value and prevalence.[11,49] This single drug price was then re-calculated as new indications were approved for the same drug.[38] We present prices as a percentage of the original indication's price, given that under the current uniform pricing policy, the prices of drugs with two, three, or four indications vary.

	Log(drug price for first indication)		
	ß	**[95% CI]**	***P value***
Clinical innovativeness			
First-in-indication	0.000	[Reference]	
Advance-in-indication	-0.035	[-0.572,0.502]	*0.899*
Addition-to-indication	0.108	[-0.443,0.658]	*0.699*
Log(patients enrolled in pivotal trial)	-0.222	[-0.337,-0.106]	*<.001*
Log(disease incidence)	-0.125	[-0.207,-0.044]	*0.003*
DALYs per person	0.002	[0.001,0.003]	*0.002*
No. of treatment options	0.003	[-0.006,0.013]	*0.484*
Constant	11.103	[10.194,12.012]	*<.001*
N		149	
F value		8.99	
R^2		32.47%	
Prob > F		<.001	

Table 33: Multivariate regression analysis of selected variables on monthly prices for original cancer indications

Abbreviations: DALYs, disability-adjusted life-years.

7.3.3 Estimating Medicare and Medicaid spending

Finally, we combined CMS' drug spending data and our estimated prices to calculate the spending on and cost savings of adopting indication-specific and weighted-average pricing policies

in the US. For this purpose, we proportionally assigned drug usage to each indication based on the treated disease's prevalence rate in the US. Ideally, indication-specific usage would be tracked based on indication-specific monitoring of drug use, yet IT systems with this capability have not yet been adopted across the entire nation.[41] Under the assumption that demand for anti-cancer drugs is inelastic to marginal changes in prices, we estimated spending under an indication-specific and weighted-average pricing policy by combining the previously calculated drug prices and drug usage.

7.3.4 Comparison across indications and orphan drugs

We examined where savings were realized under the aforementioned novel pharmaceutical policies by comparing subgroups of indications and drugs. First, spending was compared across original and supplemental indication approvals (first vs. second vs. third vs. fourth vs. fifth approved indications). Second, drugs were compared across their orphan designation status. Drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).[77] Third, indications were compared across their orphan designation status. Orphan indications were stratified according to the number of affected US inhabitants into ultra-rare (<6,600), rare (6,600-200,000), and common (>200,000).[76]

Data were stored in Microsoft EXCEL and analyzed with STATA 14.2 (StataCorp LLC, College Station, TX). Two-tailed p-values below 0.05 were considered significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline when applicable.[133]

7.3.5 Sensitivity analysis

We conducted various sensitivity analyses to check the robustness of our model and its input parameters. First, we re-calculated cost savings under different price elasticity of demand inputs

given that the published estimates range from 0.10 to 0.74.[206–210] Second, we re-calculated prices and associated cost savings using different input parameters for the multivariable regression model. For instance, we used the established definition of drug novelty rather than our novel definition of indication novelty and exchanged the number of available treatment options for the 5-year survival rates for each cancer as one of the pillars for unmet needs.[145]

7.4 Results

The FDA approved 162 anti-cancer drugs with 373 indications between 2003-2022. Of these, price data were available for 149 on-patent drugs. Across all indications, monthly drug prices amounted to a median of $12,140 (IQR: 14,648-16,885) and a mean of $17,331 (95%CI: 9,493-25,169) under the current uniform pricing policy. On these drugs, Medicare and Medicaid spent a total of $28.3 billion in 2020.

7.4.1 Indication-specific pricing

Adopting an indication-specific pricing policy would result in an increase of drug prices by +5.8% across all indications (Figure 44 and Table 34). However, Medicare and Medicaid spending would be reduced by a total of -$4.4 billion or -15.5%.

Prices for original indications would increase by +1.6%, prices for the second (+2.0%), third (+4.7%), fourth (-7.5%), and ≥fifth approvals (+16.6%) would mostly increase. Spending on original indications remained unchanged (-0.2%), whilst spending on second (-23.5%), third (-18.4%), fourth (-10.5%), and ≥fifth (-20.1%) indications was reduced.

Spending was particularly reduced on full orphan drugs (-24.6%), partial orphan drugs (-10.0%), and non-orphan drugs (-7.6%). On an indication level, savings were particularly high for common diseases (-26.1%), whilst lower savings were realized for rare diseases (-8.6%) and

non-orphan diseases (-9.8%). In contrast, high prices for ultra-rare diseases increased spending by 16.8% ($44 million).

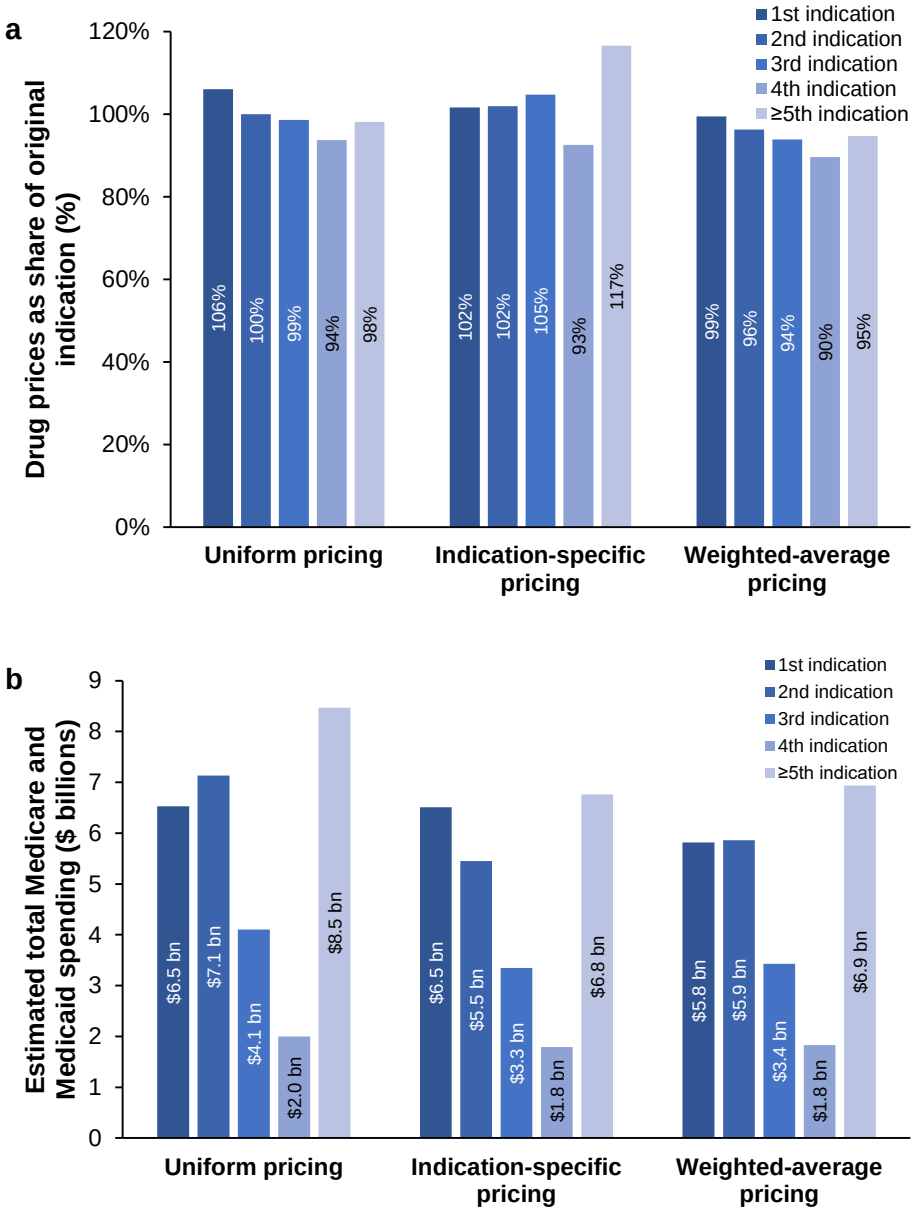


Figure 44: Estimated cancer drug prices (a) and spending (b) under uniform, indication-specific, and weighted-average pricing

Notes: Uniform pricing represents the current policy under which a single price is assigned to drugs in the US. We estimated prices and Medicare and Medicaid spending for our sample of anti-cancer drugs if an indication-specific or weighted-average pricing policy were to be adopted in the US. Drug prices are presented as a percentage of the original indication's cost.

in $ million

	Uniform pricing	Indication-specific pricing			Weighted-average pricing		
	Total spending	Total spending	Cost savings (absolute)	*Cost savings (%)*	Total spending	Cost savings (absolute)	*Cost savings (%)*
Indication launch sequence							
1st indication	6,528	6,511	-16	*-0.2%*	5,815	-712	*-10.9%*
2nd indication	7,130	5,453	-1,678	*-23.5%*	5,858	-1,272	*-17.8%*
3rd indication	4,101	3,345	-756	*-18.4%*	3,429	-672	*-16.4%*
4th indication	2,000	1,790	-210	*-10.5%*	1,829	-171	*-8.6%*
≥5th indication	8,469	6,764	-1,705	*-20.1%*	6,934	-1,535	*-18.1%*
Orphan drug type [a]							
Non-orphan drug	6,970	6,442	-527	*-7.6%*	6,442	-527	*-7.6%*
Partial orphan drug	9,525	8,577	-948	*-10.0%*	8,579	-946	*-9.9%*
Full orphan drug	11,733	8,843	-2,890	*-24.6%*	8,844	-2,889	*-24.6%*
Orphan disease type [b]							
Non-orphan disease	14,867	13,405	-1,462	*-9.8%*	13,473	-1,393	*-9.4%*
Common orphan disease	10,427	7,709	-2,718	*-26.1%*	7,644	-2,783	*-26.7%*
Rare orphan disease	2,674	2,445	-230	*-8.6%*	2,543	-131	*-4.9%*
Ultra-rare orphan disease	259	303	44	*16.8%*	204	-55	*-21.3%*
Total	**28,227**	**23,862**	**-4,365**	*-15.5%*	**23,865**	**-4,363**	*-15.5%*

Table 34: Estimated Medicare and Medicaid spending and cost savings on cancer drugs under uniform, indication-specific, and weighted-average pricing in 2020

Notes: Uniform pricing represents the current base case scenario under which a single price is assigned to each drug in the US. We estimated Medicare and Medicaid spending on and cost savings for anti-cancer drugs if an indication-specific or weighted-average pricing policy was adopted in the US.

[a] Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications).
[b] Orphan indications were stratified according to the number of affected US inhabitants into common (>200,000), rare (200,000-6,600), or ultra-rare (<6,600).

7.4.2 Weighted-average pricing

Implementing a weighted-average pricing policy would lower drug prices by -4.1% across all indications. These price discounts would reduce Medicare and Medicaid spending by a total of -$4.4 billion or -15.5%. Although the reduction in spending is similar between weighted-average and indication-specific pricing, savings arose for different indications.

With the introduction of new indications, prices declined by -3.7%, -6.1%, -10.4%, and 5.3% for second, third, fourth, and ≥fifth approvals, respectively. These price reductions resulted in lower spendings of -10.9%, -17.8%, -16.4%, -8.6%, and -18.1% for first, second, third, fourth, and ≥fifth approvals, respectively.

Spending on partial orphan drugs declined by -9.9%, non-orphan drugs by -7.4%, and full orphan drugs by -24.6%. Savings were realized for non-orphan diseases (-9.4%), rare orphan diseases (-4.9%), and common orphan diseases (-26.7%). In contrast to indication-specific pricing, adopting weighted-average pricing would reduce spending on ultra-rare diseases by -21.3%.

7.4.3 Sensitivity analysis

Results remained robust under sensitivity analyses with different input variables for the regression analysis and different price elasticities of demand (Table 35). Using drug instead of indication novelty resulted in savings of -12.0% for indication-specific and weighted-average pricing. Using the trial phase instead of the number of enrolled patients resulted in savings of -17.3% for both policies. Results were marginally impacted by using prevalence instead of incidence rates, 5-year survival instead of number of available treatment options, or YLL instead of DALYs for the multivariate regression analysis.

In our base case scenario, we assumed a PED of 0, indicating that drug usage is inelastic to price changes. However, the sensitivity analysis highlights that elasticity inputs above 0 diminish expected cost savings as drug usage increases with lower prices. At a PED of 1, indication-specific pricing would result in cost savings of -10.0% and weighted-average pricing in cost savings of -6.2%.

in $ millions

	Uniform pricing	Indication-specific pricing			Weighted-average pricing		
	Total spending	**Total spending**	**Cost savings (absolute)**	***Cost savings (%)***	**Total spending**	**Cost savings (absolute)**	***Cost savings (%)***
Regression input variables							
Base case	28,227	23,862	-4,365	*-15.5%*	23,865	-4,363	*-15.5%*
Drug instead of indication novelty	28,227	24,846	-3,382	*-12.0%*	24,843	-3,385	*-12.0%*
5-yr survival instead of treatment options	28,227	23,575	-4,652	*-16.5%*	23,579	-4,649	*-16.5%*
YLL instead of DALYs	28,227	23,865	-4,363	*-15.5%*	23,868	-4,360	*-15.4%*
Trial phase instead of size	28,227	23,352	-4,876	*-17.3%*	23,354	-4,873	*-17.3%*
Prevalence instead of incidence	28,227	24,367	-3,860	*-13.7%*	24,369	-3,858	*-13.7%*
Price elasticity of demand (PED)							
Base case (PED=0)	28,227	23,862	-4,365	*-15.5%*	23,865	-4,363	*-15.5%*
PED=0.1	28,227	24,016	-4,212	*-14.9%*	24,126	-4,102	*-14.5%*
PED=0.2	28,227	24,170	-4,058	*-14.4%*	24,386	-3,841	*-13.6%*
PED=0.3	28,227	24,324	-3,904	*-13.8%*	24,647	-3,580	*-12.7%*
PED=0.4	28,227	24,477	-3,750	*-13.3%*	24,908	-3,320	*-11.8%*
PED=0.5	28,227	24,631	-3,596	*-12.7%*	25,168	-3,059	*-10.8%*
PED=0.6	28,227	24,785	-3,442	*-12.2%*	25,429	-2,798	*-9.9%*
PED=0.7	28,227	24,939	-3,288	*-11.6%*	25,690	-2,538	*-9.0%*
PED=0.8	28,227	25,093	-3,135	*-11.1%*	25,950	-2,277	*-8.1%*
PED=0.9	28,227	25,247	-2,981	*-10.6%*	26,211	-2,016	*-7.1%*
PED=1.0	28,227	25,401	-2,827	*-10.0%*	26,472	-1,756	*-6.2%*

Table 35: Sensitivity analysis

Notes: Cost savings were re-calculated for scenarios with different input variables for the regression analysis and different PED values.

Abbreviations: DALYs, disability-adjusted life years; PED, price elasticity of demand; YLL, years of life lost.

7.5 Discussion

We estimate that Medicare and Medicaid could have realized cost savings of -$4.4 billion (-15.5%) with both indication-specific or weighted-average pricing in 2020. These savings were especially realized by reducing prices for partial orphan drugs' low-value non-orphan follow-on indications.

7.5.1 Indication-specific pricing

We estimated that indication-specific pricing reduces Medicare and Medicaid spending on supplemental indication approvals, particularly for non-orphan indications of partial orphan drugs. This is especially desirable given that supplemental indications were shown to be of lower value to patients and insurers.[38,39,73] Furthermore, partial orphan drugs were criticized for benefiting from high orphan drug prices for their non-orphan indications, resulting in substantial revenues and profit streams for manufacturers.[46,77,201] Indication-specific pricing could resolve these disputes. However, confirming Chandra & Garthwaite's theoretical expectations,[37] indication-specific pricing would also result in higher prices for patients that benefit most from new drugs, e.g. patients with ultra-rare diseases. On the upside, pharmaceutical companies are thereby encouraged to especially develop high-value treatments for ultra-rare diseases. On the downside, this could adversely lead to increased pharmaceutical expenditure in the long-term.[76] Moreover, the implementation of indication-specific pricing remains challenging. It requires the tracking of drug usage across indications, which is currently not available across the entire US. Due to its technical challenges alongside opposition from key stakeholders, authors previously concluded that indication-specific pricing is not feasible to implement (at least in the short-term).

7.5.2 Weighted-average pricing

Similar to indication-specific pricing, the adoption of weighted-average pricing would reduce Medicare and Medicaid's expenditure on cancer drugs by -15.5%. These cost savings are realized by sequentially lowering the drug's initial list price as new supplemental indications receive FDA approval. These results are consistent with a prior study that showed cancer drug prices declined with the introduction of each new indication in Germany and France (countries that employ weighted-average pricing).[38] In contrast to indication-specific pricing, the adoption of weighted-average pricing does not increase but reduces prices for drugs treating patients with ultra-rare diseases. Thereby weighted-average pricing could help to improve the financial sustainability of costly ultra-orphan drugs.

The CMS should, therefore, carefully examine the mechanisms of a weighted-average pricing system for its price negotiations as part of the IRA.[23,24,164] Given that the CMS will be allowed to directly negotiate prices of the top-grossing drugs with manufacturers, weighted average-pricing considerations could support the CMS to justify its price proposition for top-selling drugs with multiple indications, especially partial orphans.

Nonetheless, there are several barriers to implementing weighted-average pricing across the entire US.[11,49,55,56] First, it requires an understanding that drug prices can be negotiated between insurers and manufacturers based on their value proposition for patients (value-based pricing). Second, value or benefit assessments must be conducted for each additional indication that receives FDA approval. Thereafter, payers and insurers must set or negotiate a price for each indication. These indication prices are then combined with the anticipated or monitored indication usage to calculate a single drug price. Given that drugs are still sold for a single price under weighted-average pricing, it is more feasible than indication-specific pricing to implement in the current US healthcare system. However, similar to indication-specific pricing, politicians

must propose changes to the current US drug price system and overcome opposition from pharmaceutical benefit managers, pharmaceutical companies, and other stakeholders that stand to lose with a new pricing policy.

7.5.3 Short- and long-term effects of indication-specific pricing

In this study, we estimated static short-term price and cost savings for weighted-average and indication-specific pricing. However, economists previously debated that the dynamic long-term economic effects of indication-specific pricing on social welfare, consumer surplus, and producer surplus may differ (Figure 45).[37,41,211] Bach, who considered that US prices are set based on the first high-value indication (single-highest price), argued that indication-specific pricing increases patient access to new treatments, reduces prices for low-value indications, and, thereby, increases social welfare, payers' spending, and producer surplus (Figure 45a).[41] In contrast, Chandra & Garthwaite, who considered US prices are set based on the lowest value indication (single-lowest price), argued that (overall) indication-specific pricing increases drug prices for high-value indications, increases payers' spending, and transfers consumer surplus to producers whilst social welfare remains constant (Figure 45b).[37]

We previously showed that US drug prices are set based on the first, high-value indication (single-highest price).[74] This supports Bach's single-highest price scenario (Figure 45a). Under a single-highest drug price system, the adoption of indication-specific pricing encourages pharmaceutical companies to launch new low-value indications (Figure 45c). Without indication-specific pricing companies would be incentivized to withhold these indications as they would deteriorate the single-highest list price.[38–40] These additional new indication launches increase patient access to new therapeutic options. This expanded access will, of course, increase consumer surplus, increase producer surplus, and thereby maximize social welfare. In the short-term, the additional approval of new indications will also increase payers' spending. Nonethe-

less, this additional spending will increase enrollees' health benefits, if indication-specific pricing is adopted as part of a formal HTA process that uses value-based pricing. In a system with a formal HTA process, payers only reimburse new cost-effective indications, e.g. indications with an ICER below the nation's WTP threshold. A formal HTA process essentially ensures that pharmaceutical companies are only incentivized to develop new indications that are worthwhile for patients and the health system.

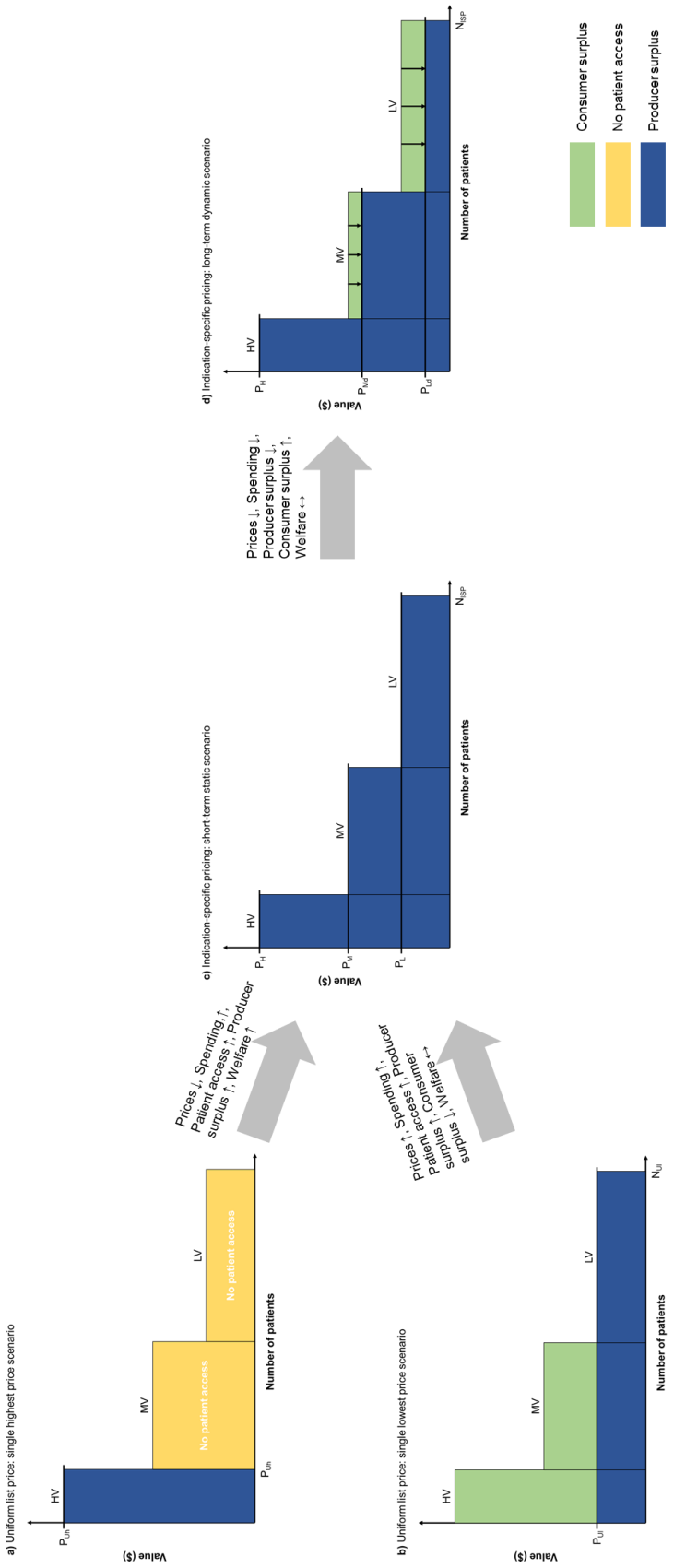


Figure 45: Short- and long-term effects of indication-specific pricing on consumer surplus, producer surplus, prices, spending, and social welfare

Notes: Under a single highest list price scenario, producers only sell their drug at price P_{Uh} for the HV indication to N_{Ul} patients. Patients in the MV and LV indication do not have access to the drug. In the short term, adopting ISP would reduce prices, increase spending, increase patient access, increase producer surplus, and thereby increase welfare. Under a single lowest list price scenario, producers sell their drug at price P_{Ul} to N_{Ul} patients with indications HV, MV, and LV. Adopting ISP would increase prices, increase spending, increase producer surplus, and increase welfare while patient access remains unchanged. In the long term, ISP encourages the development of new MV and LV indications. The dynamic market entry of new indications under this scenario with fierce competition between these new indications would lower prices for the MV and LV indications to P_{MVd} and P_{LVd}. Graphs adapted from Towse (2018).[211]

Abbreviations: HV, high value; ISP, indication-specific pricing; LV, low value; MV, medium value.

The long-term effects of indication-specific pricing are more complex (Figure 45d). As previously explained, pharmaceutical companies are incentivized to research, develop, and launch more indications under indication-specific pricing. The increased number of new indications will likely intensify competition at the indication level. Economic theory suggests that the market entry of new competitors will drive down prices, even below the national WTP threshold.[211] These dynamic competitive effects of indication-specific pricing could, thereby, increase consumer surplus, whilst reducing producer surplus and payers' spending. However, previous studies analyzing brand-brand competition in the pharmaceutical market could not confirm that the entry of new competitors resulted in a reduction in drug prices.[57,75,151,153] Furthermore, our sensitivity analysis highlighted that the estimated cost savings are subject to consumers' underlying PED. As a consequence, price reductions for low-value indications could increase consumer demand and thereby increase payers' overall spending in the long-term. On the other hand, a positive PED also implies that higher prices for high-value indications could pose a barrier for consumers to purchase drugs that deliver substantial value to them and, therefore, reduce spending (especially in the US). Our analysis suggests that because low-value indications are typically for diseases with a higher prevalence and high-value indications are typically for diseases with a lower prevalence, the effects of a positive PED will likely diminish the estimated cost-saving potential.

Given that weighted-average pricing is an indirect form of differential pricing, the considerations of this subchapter also apply to weighted-average pricing, yet are likely of smaller magnitude.

7.5.4 Limitations

There are several limitations inherent to our analysis. First, our model did not capture the upfront investments and ongoing administrative costs of introducing indication-specific or weighted-average pricing. Presumably, the cost of introducing weighted-average pricing is lower than indication specific-pricing, given that the latter requires the introduction of new IT and prescription systems across healthcare providers in the US, whilst the former only entails a novel way to calculate, negotiate, and assign single drug prices. Furthermore, we only calculated cost savings for anti-cancer drugs. Adopting a new pricing policy would, of course, also reduce costs for drugs of other therapeutic areas. This would also mean that upfront investments in introducing these novel pricing systems could be shared (and are likely easily covered by the savings realized) across all therapeutic areas. Second, we conducted a retrospective analysis. Cost savings that Medicare and Medicaid may realize in the future may differ. Nonetheless, our model highlights the mechanism of indication-specific and weighted-average pricing policies, particularly underlining their effects on partial orphan drugs and indications for ultra-rare diseases. Third, there are other differential pricing mechanisms, such as indication-specific discounts on drug prices or indication-specific MEAs, that are currently employed in countries but not included in our analysis.[11,49] Although these policies impact drug spending and usage, they do not affect list prices – the underlying main variable of our model.

7.6 Conclusion

In this study, we estimated that Medicare and Medicaid could have reduced expenditure on new FDA-approved cancer drugs by -15.5% with the adoption of indication-specific pricing or

weighted-average pricing. However, prices for ultra-rare orphan drugs increased under indication-specific pricing. Furthermore, there are several barriers to adopting indication-specific pricing in the US. In contrast, weighted-average pricing also reduces prices for ultra-rare orphan drugs and is more compatible with the current US pricing system. In conclusion, indication-specific and weighted-average pricing could help to limit the growing burden of rising cancer drug prices on the US healthcare system.

7.7 Author contributions

Daniel Tobias Michaeli and Thomas Michaeli had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: All authors. Administrative, technical, or material support: All authors. Study supervision: All authors.

8 Breakthrough therapy cancer drugs and indications

Summary: This cross-sectional study compares the FDA approval, innovativeness, efficacy, clinical trial evidence, epidemiology, and price of breakthrough and non-breakthrough cancer drugs and indications.

8.1 Abstract

Background: The breakthrough therapy designation facilitates the development of drugs with a large preliminary benefit in treating serious or life-threatening diseases.

Objective: To analyze the FDA approval, trials, benefits, unmet needs, and pricing of breakthrough and non-breakthrough therapy cancer drugs and indications.

Patients and Methods: We analyzed 355 cancer indications with FDA approval (2012-2022). Breakthrough and non-breakthrough indications were compared regarding their FDA approval, innovativeness, trials, epidemiology, and price with data extracted from FDA labels, Global Burden of Disease study, and Medicare and Medicaid. HRs for OS and PFS and RR for tumor response were meta-analyzed across RCTs. ORRs were meta-analyzed for single-arm trials.

Results: We identified 137 breakthrough and 218 non-breakthrough cancer indications. The median clinical development time was 3.2 years shorter for breakthrough drugs (5.6 vs. 8.8 years, p=.002). The breakthrough designation was more frequently granted to biomarker-directed indications (46% vs. 34%, p=.025) supported by smaller trials (median: 149 vs. 326 patients, p<.001) of single-arm (53% vs. 27%, p<.001) phase 1/2 design (61% vs. 31%, p<.001). Breakthrough indications offered a greater OS (HR: 0.69 vs. 0.74, p=.031) and tumor response (RR: 1.48 vs. 1.32, p=.006; ORR: 52% vs. 40%, p=.004), yet not PFS benefit (HR: 0.53 vs. 0.58, p=.212). Median improvements in OS (4.8 vs. 3.2 months, p=.004) and PFS (5.4 vs. 3.3 months, p=.005), yet not duration of response (8.7 vs. 4.7 months, p=.245) were higher for

breakthrough than non-breakthrough indications. The breakthrough designation was more frequently granted to first-in-class drugs (42% vs. 28%, p=.001) and first-in-indication treatments (43% vs. 29%, p<.001). There was no difference in the treatment and epidemiologic characteristics between breakthrough and non-breakthrough drugs. Breakthrough drugs were more expensive than non-breakthrough drugs (mean monthly price: $38,971 vs. $22,591, p=.0592).

Conclusion: The breakthrough therapy designation expedites patient access to effective and innovative, yet also expensive, new cancer drugs and indications.

8.2 Key points

Question: What is the efficacy, clinical trial evidence, epidemiology, and price of breakthrough and non-breakthrough cancer drugs and indications approved by the FDA?

Findings: In this study of 355 FDA-approved cancer indications over 10 years, breakthrough indications were associated with a lower likelihood of death than non-breakthrough indications (hazard ratio: 0.69 vs. 0.74, p=.031) and offered significantly greater improvements in median overall survival (4.8 vs. 3.2 months, p=.004). Breakthrough drugs and indications were more innovative, more frequently supported by smaller, open-label single-arm trials, approved 3.2 years faster, and priced at a premium of 73% (mean: $38,971 vs. $22,591, p=.0592) compared to non-breakthrough drugs and indications.

Meaning: The breakthrough therapy designation expedites patient access to innovative and effective, yet also expensive, new cancer drugs and indications.

8.3 Introduction

In 2012, US Congress introduced the BTD under section 902 of the FDA Safety and Innovation Act. To keep pace with the biotechnological advances of the 21st century, US Congress aimed to facilitate the development of and expedite patient access to highly innovative drugs.[212] Particularly patients with serious or life-threatening diseases should be granted access to therapies whose preliminary large benefit can already be observed in phase 1 or 2 trials.[212,213] Therefore, the BTD permits the FDA to allocate resources to these promising breakthrough drugs by providing pharmaceutical companies with "intensive guidance on efficient drug development" (US Department of Health and Human Services, 2014, p. 8); entailing shorter response timelines, close collaboration with senior FDA officials, and a rolling review of clinical evidence.[214,215] Moreover, the BDT justifies the use of historical controls as control groups and smaller less time-intense trials.[215,216]

Ten years after its inception, the BTD has been vividly lauded by patients, the pharmaceutical industry, and the FDA itself.[212,214] From 2012 until 2022, the FDA received 1,289 BTD requests; of which 506 (39%) were granted (Figure 46). This led to the approval of 157 breakthrough drugs. The BTD has become an integral part of the FDA's expedited review process, including priority review and fast track.[217] However, the new BTD program has been heavily criticized by physicians and academics to nurture the development of potentially unsafe drugs that are approved based on small, non-randomized, unblinded trials.[212,216,218]

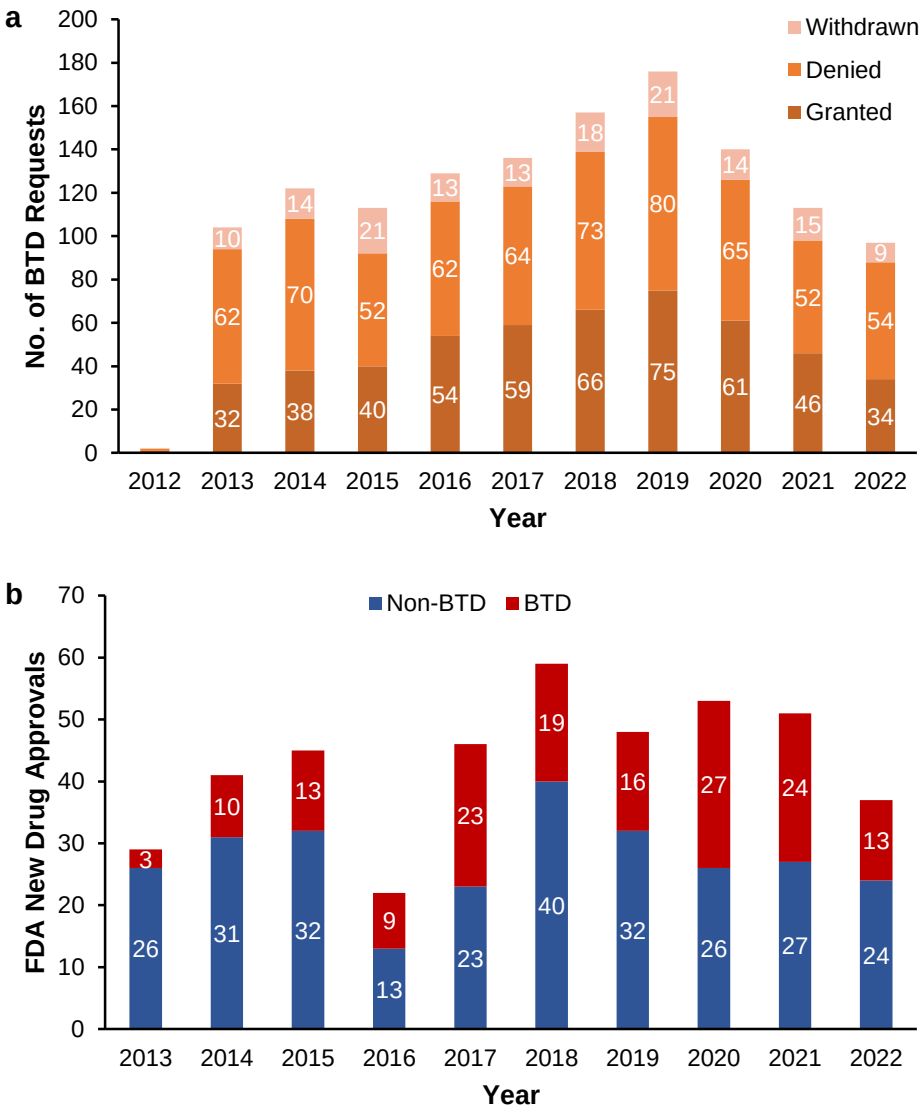


Figure 46: Breakthrough therapy designation requests and new FDA drug approvals

Notes: In graph **a,** the yearly development of the number of BTD requests with subsequent approval, denial, or withdrawal for new drug indications is displayed from 2012 to 2022. Pending BTD requests are excluded. Graph **b** compares yearly FDA new drug approvals for BTD vs non-BTD drugs from 2013 until 2022.

Abbreviations: BTD, breakthrough therapy designation; FDA, US Food and Drug Administration.

Moreover, the efficacy of breakthrough drugs remains disputed. Patients and physicians associate the term *breakthrough* with a major scientific disruption. Consequently, three surveys demonstrated that physicians are more inclined to prescribe a breakthrough-designated drug rather than a similarly effective alternative.[219–221] Yet, previous studies analyzing the first five years of the BTD could not confirm a consistent superior clinical benefit of breakthrough compared to non-breakthrough drugs.[95,135,222] Nonetheless, pharmaceutical companies demand 25%

higher list prices for breakthrough drugs.[222] Although these studies are limited in sample size and analyzed time horizon, some authors criticize the "laudatory [breakthrough] labels that promote the use of new drugs that frequently offer limited additional benefits" (Darrow et al., 2018, p. 1451).[218]

This study clarifies the role of the BTD in drug development and clinical practice by analyzing a uniquely large sample of 114 cancer drugs and 355 indications with FDA approval over 10 years. Breakthrough and non-breakthrough cancer drugs and indications are compared regarding their clinical development time, clinical trial evidence, efficacy, innovativeness, epidemiology, and pricing.

8.4 Data and methods

8.4.1 Sample identification

We accessed the Drugs@FDA database to identify all new drugs, including NDAs and BLAs, with FDA approval between 1st January 2000 and 1st January 2022 (Figure 47). The sample was then restricted to include only anti-cancer drugs, excluding non-oncology, supportive care, and diagnostic agents, whilst including gene and cell therapies. For each drug, we identified all anti-cancer indications, including original and supplemental indications, approved until 1st January 2022. The sample was then restricted to include only drugs and indications approved after 1st January 2013. The breakthrough therapy designation status was linked to each indication using the FDA's breakthrough drug database (Table 3).

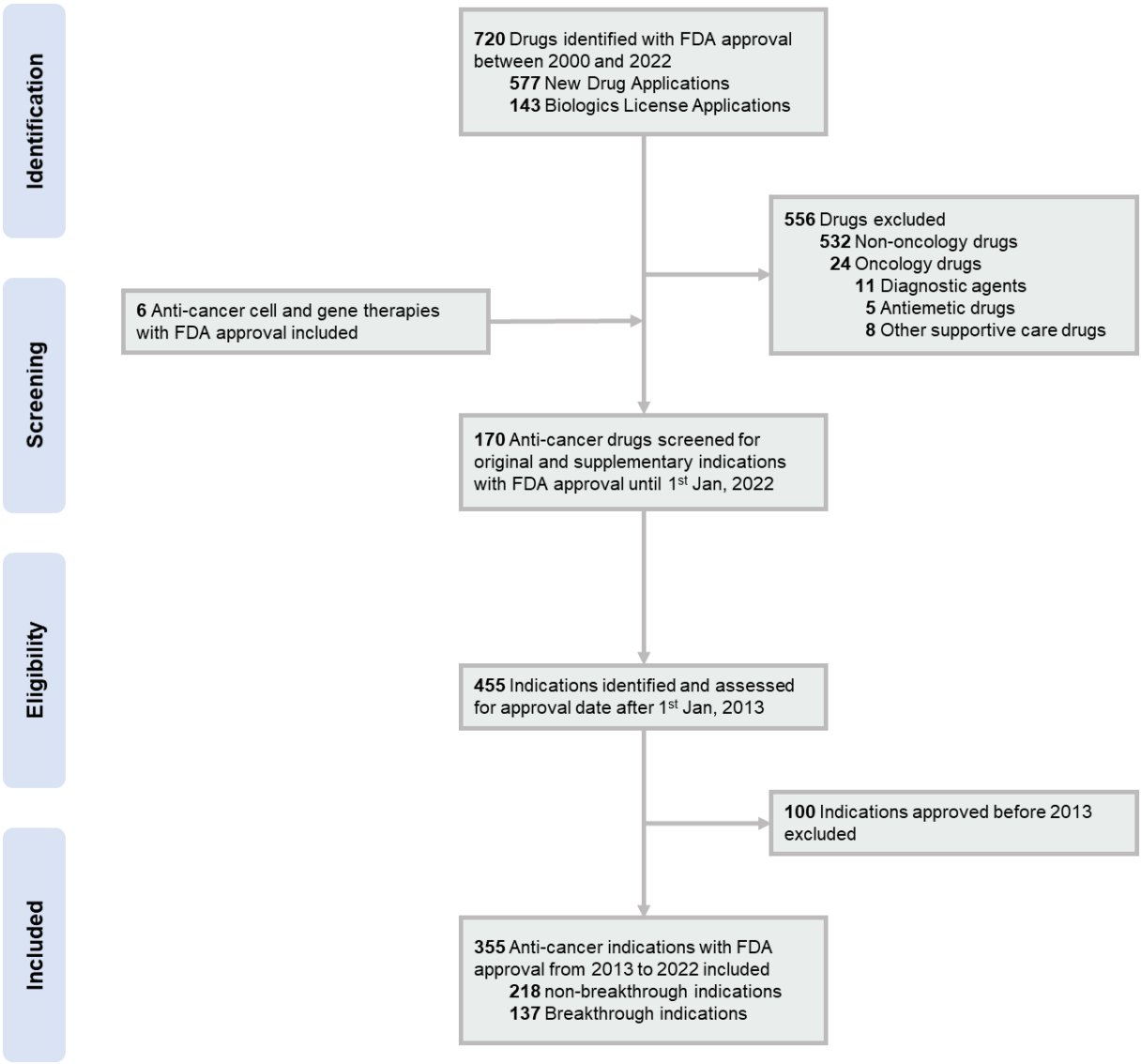


Figure 47: Flow diagram of breakthrough and non-breakthrough therapy cancer drug indications included in the analysis, 2013-2022

Notes: All drugs that received FDA approval between 1st January 2000 and 1st January 2022 were identified in the Drugs@FDA database. We then limited the sample to anti-cancer drugs by excluding non-oncology drugs and oncology drugs indicated for diagnostic, supportive care, or anti-emetic treatments. For each drug, we identified all original and supplementary indications with FDA approval until 1st January 2022, excluding approvals for non-oncology indications. For this analysis, we then restricted the dataset to include only indications that were approved after 1st January 2013.

Abbreviations: FDA, US Food and Drug Administration.

8.4.2 Data collection

We collected data on the FDA approval, clinical trial evidence, cancer epidemiology, and price for each cancer drug and indication from publically available sources (Table 3).

FDA approval

For each anti-cancer indication, FDA labels were accessed to gather data on drug, indication, and clinical trial characteristics. The first reviewer (D.T.M.) independently retrieved data from FDA labels, which was then cross-checked by the second reviewer (T.M.) with data found on clinicaltrials.gov and associated peer-reviewed publications. Disagreements were resolved in consensus or by consulting an experienced oncologist. Full details of the data extraction method have been described elsewhere.[73]

Drugs were categorized by their number of indications, innovativeness, mechanism of action, and product type. Biotechnological innovation was determined on a drug level based on each compound's target according to the definition provided by Lanthier et al. (first-in-class vs. advance-in-class vs. addition-to-class).[205] For multi-indication drugs, FDA approvals were classified as original and supplemental indications. For all original indications, we collected data on the date the IND became effective and the FDA approval date from FDA documents or the USPTO.

Indications were then categorized by clinical novelty, approval type, treatment regimen, cancer type, biomarker status, and line of therapy. Clinical novelty was determined on an indication level based on each indication's target and treated disease (first-in-indication vs. advance-in-indication vs. addition-to-indication).

Each indication's pivotal trial was characterized by the number of enrolled patients, phase, design, blinding, number of arms, comparator, and primary endpoint. For RCTs, we extracted HRs for OS and/or PFS and/or the RR of tumor response with 95% CI. The number of subjects and events was noted for the control and intervention arms. For single-arm trials, we obtained the ORR. Furthermore, we extracted median improvements in OS, PFS, and duration of tumor response with IQR for each indication.

Cancer epidemiology

For each indication, we retrieved data on the treated cancer's incidence, prevalence, and DALYs, composed of YLD and YLL from the Global Burden of Disease study.[128] Five-year survival rates and the number of available treatment options per cancer entity were extracted from the National Cancer Institute.[129]

Drug prices

Drug prices were retrieved in January 2023 from the CMS and Medicare's plan finder tool for patients covered under Medicare Part B and D, respectively. Coherent with previous studies,[115–117,119,131] monthly treatment costs were estimated for an average adult with a body surface area of 1.7 m² weighing 70 kg based on the dosing regimen in the FDA label. Full details of the drug price calculation have been described elsewhere.[74]

8.4.3 Statistical analysis

Breakthrough and non-breakthrough therapy cancer drugs and indications were compared regarding their clinical development time, drug, indication, clinical trial, epidemiologic characteristics, efficacy, and price.

First, clinical development times, calculated as the difference between IND to NDA/BLA approval for original indications, were compared using Kaplan-Meier survival curves, log-rank tests, and a Cox proportional hazard model, coherent with prior analyses.[135] Second, the distribution of categorical variables describing breakthrough and non-breakthrough designations' drug, indication, clinical trial, and epidemiology characteristics were compared with Fisher's-exact-tests. Medians were compared with Kruskal-Wallis-tests. Third, a series of random-effects meta-analyses was conducted for clinical trials with available outcome data. HRs for OS and PFS were meta-analyzed in all RCTs. RRs for tumor response were meta-analyzed in all

RCTs. ORRs were meta-analyzed in all single-arm trials. Differences between breakthrough and non-breakthrough therapy indications' HRs, RRs, and ORRs were compared with Cochran's Q-test. Fourth, mean monthly drug prices were compared in January 2023. Mean monthly prices were further calculated for all drugs covered under Medicare Part B from 2015 to 2023. The CAGR of drug prices was calculated from 2015 to 2023. Then, we reevaluated the comparison of breakthrough and non-breakthrough drugs by stratification between full and accelerated approvals. Finally, we conducted a logistic regression analysis of drug, indication, and epidemiology characteristics on the BTD to comprehend which variables the FDA considers when granting the BTD. In this analysis, we did not include clinical trial characteristics given that the clinical trial design is influenced by the BTD itself, e.g. after receiving the BTD, the indication may receive approval based on less robust trial designs.

Data were stored in Microsoft Excel (Microsoft Corp) and analyzed with Stata software, version 14.2 (StataCorp LLC). Two-tailed p-values below 0.05 were considered significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines where applicable.[133]

8.5 Results

The FDA approved 720 new drugs from 2000 until 2022, with 170 anti-cancer drugs with FDA approval in 455 indications. After 2012, a total of 114 drugs and 355 indications received approval and were include in the final sample for analysis. Of these 355 indications, the FDA granted the breakthrough therapy designation to 137 (39%) indications (Figure 47).

8.5.1 Clincal development time

For all original drug approvals, we measured clinical development times as the difference between the IND date and the first FDA indication approval. The IND date was available for 106 out of 114 (93%) drugs in our sample. The clinical development time was significantly shorter

for breakthrough vs. non-breakthrough drugs (median: 5.6 vs. 8.8 years, p=.002; HR: 1.82, p=.003) (Figure 48).

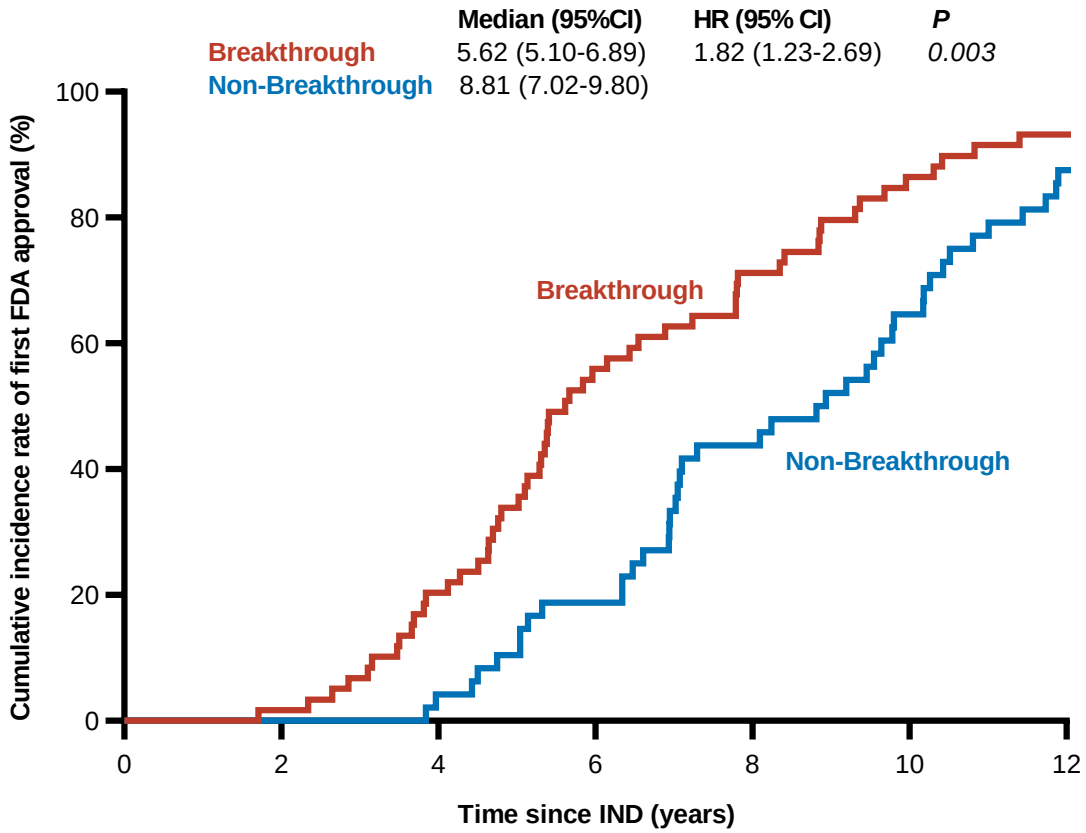


Figure 48: Time from IND to first FDA approval for breakthrough and non-breakthrough therapy cancer drugs

Notes: The graph illustrates the cumulative incidence of the first FDA approval for cancer drugs with a breakthrough (red curve) and non-breakthrough therapy designation (blue curve) for the first indication. P values were calculated based on Cox-proportional hazard models.

Abbreviations: FDA, US Food and Drug Administration; IND, investigational new drug application.

8.5.2 Drug characteristics

There were 60 (17%) and 54 (15%) drugs with and without the breakthrough designation for the original FDA indication approval (Table 36). Breakthrough drugs were more innovative than non-breakthrough drugs. On a biotechnological level, more breakthrough than non-breakthrough drugs were first-in-class (42% vs. 28%, p<.001). Accordingly, breakthrough drugs more frequently acted via a novel mechanism of action: immune-regulatory (37% vs. 19%),

targeted (63% vs. 70%), cytotoxic (0% vs. 11%, p=.004). There was a tendency for breakthrough drugs to more frequently be antibodies (27% vs. 13%) or antibody-drug conjugates (12% vs. 6%, p=.147).

No. (%)			
	Breakthrough Therapy		
Variables	**No**	**Yes**	***P Value*** [a]
Drug characteristics			
Number of indications			*0.001*
Single-indication	37 (68.5)	22 (36.7)	
Multi-indication	17 (31.5)	38 (63.3)	
Biotechnological Innovativeness			*0.001*
Addition-to-class	12 (22.2)	1 (1.7)	
Advance-in-class	27 (50.0)	34 (56.7)	
First-in-class	15 (27.8)	25 (41.7)	
Mechanism of action			*0.004*
Cytotoxic chemotherapy	6 (11.1)	0 (0.0)	
Targeted agents	38 (70.4)	38 (63.3)	
Immune-regulators	10 (18.5)	22 (36.7)	
Product type			*0.147*
Small-molecule	38 (70.4)	32 (53.3)	
Antibody	7 (13.0)	16 (26.7)	
Antibody-drug conjugate	3 (5.6)	7 (11.7)	
Other [b]	6 (11.1)	5 (8.3)	
Total no. of drugs	**54 (47.4)**	**60 (52.6)**	

Table 36: Characteristics of breakthrough and non-breakthrough therapy cancer drugs approved by the FDA from 2012 to 2022

[a] P Values calculated based on Fisher's-exact-tests.
[b] Other includes biologics, gene therapies, cell therapies, enzymes, and radionuclides.

Abbreviations: FDA, US Food and Drug Administration; RCTs, randomized controlled trials.

8.5.3 Indication characteristics

On an indication level, the BTD was more often granted to first-in-indication treatments (43% vs. 29%, p<.001) (Table 37). Breakthrough indications were more likely to be original than supplemental FDA approvals (47% vs. 26%, p<.001). Breakthrough and non-breakthrough indications did not significantly differ in treatment type, cancer type, or line of therapy. The FDA more frequently granted the breakthrough designation to biomarker-based indications (46% vs. 34%, p=.025). The breakthrough designation was particularly often granted to treatments for

lung (18% vs. 15%), breast (10% vs. 6%), thyroid (5% vs. 1%), and endometrial cancer (2% vs. 0%) (Table 38).

No. (%)			
	Breakthrough Therapy		
Variables	**No**	**Yes**	***P Value*** [a]
Indication characteristics			
Clinical novelty			*<.001*
Addition-to-indication	43 (19.7)	5 (3.6)	
Advance-in-indication	112 (51.4)	73 (53.3)	
First-in-indication	63 (28.9)	59 (43.1)	
Indication approval sequence			*<.001*
Original indication approval	161 (73.9)	72 (52.6)	
Supplemental indication approval	57 (26.1)	65 (47.4)	
Treatment type			*0.178*
Combination	90 (41.3)	46 (33.6)	
Monotherapy	128 (58.7)	91 (66.4)	
Cancer type			*0.486*
Hematological	67 (30.7)	47 (34.3)	
Solid	151 (69.3)	90 (65.7)	
Biomarker			*0.025*
No	144 (66.1)	74 (54.0)	
Yes	74 (33.9)	63 (46.0)	
Line of therapy			*0.135*
First-line	112 (51.4)	60 (43.8)	
Second-line	77 (35.3)	63 (46.0)	
≥Third-line	29 (13.3)	14 (10.2)	
Special FDA designations			
Orphan designation	138 (63.3)	95 (69.3)	*0.253*
Fast Track	44 (20.2)	25 (18.2)	*0.682*
Accelerated Approval	52 (23.9)	60 (43.8)	*<.001*
Converted	16	27	
Pending	26	27	
Withdrawn / not converted	10	6	
Clinical trial characteristics			
Enrolled patients, median (IQR)	326 (137-616)	149 (84-521)	*<.001*
Clinical trial phase			*<.001*
Phase 1	9 (4.1)	11 (8.0)	
Phase 2	59 (27.1)	73 (53.3)	
Phase 3	150 (68.8)	53 (38.7)	
Trial design			*<.001*
Single-arm trial	61 (28)	68 (49.6)	
Non-randomized controlled trial	2 (0.9)	6 (4.4)	
Randomized controlled trial	152 (69.7)	60 (43.8)	
Dose-comparison randomized trial	3 (1.4)	3 (2.2)	
Type of blinding			*0.022*
Open-label	156 (71.6)	113 (82.5)	
Double-blind	62 (28.4)	24 (17.5)	
Clinical trial arms			*<.001*
1 arm	61 (28)	68 (49.6)	
2 arms	152 (69.7)	65 (47.4)	
≥3 arms	5 (2.3)	4 (2.9)	
Primary Endpoint			
Overall survival	43 (19.7)	12 (8.8)	*0.006*
Progression-free survival	83 (38.1)	40 (29.2)	*0.109*
Tumor response	67 (30.7)	78 (56.9)	*<.001*
Cancer epidemiology			
Disease incidence, median (IQR) [b,c]	8.5 (5.2-67.6)	15.2 (3.9-67.6)	*0.559*
Disease prevalence, median (IQR) [b,c]	33.7 (17.6-117.8)	74 (13.2-117.8)	*0.710*
DALYs per person, median (IQR) [b]	10 (5.5-16.4)	8.9 (5.5-16.4)	*0.111*
YLL per person, median (IQR) [b]	9.3 (4.8-16.2)	8.3 (4.8-16.2)	*0.127*
YLD per person, median (IQR) [b]	0.5 (0.3-0.6)	0.5 (0.3-0.7)	*0.514*
5-year survival rate in %, median (IQR) [b]	66.2 (30.5-90.7)	75.2 (32.7-90.7)	*0.207*
No. of available treatments, median (IQR) [b]	16 (11-38)	16 (11-38)	*0.484*
Total no. of indications	**218 (61.4)**	**137 (38.6)**	

Table 37: Characteristics of breakthrough and non-breakthrough therapy cancer indications approved by the FDA from 2012 to 2022

Notes: In this table, the breakthrough designation was analyzed on an indication level. All cancer indications with FDA approval between 2012 and 2022 were included in the analysis. We compared the characteristics of breakthrough relative to non-breakthrough indications.

[a] P Values calculated based on Fisher's-exact-tests. [b] P Values calculated based on Kruskal-Wallis-tests. [c] Disease incidence and prevalence rates (per 100,000) for the US population in 2019.

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; IQR, interquartile range; RCTs, randomized controlled trials; YLD, years lived with disability; YLL, years of life lost.

No. (%)			
	Breakthrough Therapy		
Cancer Type	**No**	**Yes**	**Total**
Bladder	8 (3.7)	6 (4.4)	14 (3.9)
Brain	1 (0.5)	1 (0.7)	2 (0.6)
Breast	14 (6.4)	14 (10.2)	28 (7.9)
Cervical	4 (1.9)	0 (0.0)	1 (1.2)
Colorectal	8 (3.7)	2 (1.5)	10 (2.8)
Endometrial	0 (0.0)	3 (2.2)	3 (0.8)
Gastric	11 (5.0)	3 (2.2)	14 (3.9)
Head and Neck	3 (1.4)	1 (0.7)	4 (1.1)
Hepatic	6 (2.8)	4 (2.9)	10 (2.8)
Leukemia	25 (11.5)	15 (10.9)	40 (11.3)
Lung	32 (14.7)	24 (17.5)	56 (15.8)
Lymphoma	37 (17)	26 (19)	63 (17.7)
Other	18 (8.3)	10 (7.3)	28 (7.9)
Ovarian	10 (4.6)	2 (1.5)	12 (3.4)
Pancreatic	1 (0.5)	0 (0.0)	1 (0.3)
Prostate	10 (4.6)	1 (0.7)	11 (3.1)
Renal	9 (4.1)	8 (5.8)	17 (4.8)
Skin	19 (8.7)	10 (7.3)	29 (8.2)
Thyroid	2 (0.9)	7 (5.1)	9 (2.5)
Total	**218 (100.0)**	**137 (100.0)**	**355 (100.0)**

Table 38: Tumor entities treated by breakthrough therapy cancer drug indications

A total of 69 (19%), 112 (32%), and 233 (66%) indications received fast track review, accelerated approval, and the orphan designation, respectively. Breakthrough indications were significantly more likely than non-breakthroughs to receive accelerated approval (44% vs. 24%, p<.001). Among these accelerated approvals, there was no difference in the rate of withdrawals between breakthrough and non-breakthrough indications until 31st March 2023 (10% vs. 19%, p=.199).

8.5.4 Pivotal clinical trial characteristics

A median of 149 patients (IQR: 84-521) were enrolled in the pivotal clinical trials for breakthrough compared to 326 patients (IQR: 137-616, p<.001) for non-breakthrough indications.

Breakthrough indications were less frequently supported by double-blind (18% vs. 28%, p=.022) concurrent RCTs (44% vs. 70%, p<.001) of phase 3 design (39% vs. 69%, p<.001). Instead, clinical evidence for breakthrough indications was commonly gathered in phase 2 (53% vs. 27%, p<.001) single-arm trials (50% vs. 28%, p<.001). The primary endpoint for pivotal clinical trials supporting breakthrough relative to non-breakthrough indications less frequently involved an assessment of OS (9% vs. 20%, p=.006), whilst more frequently assessing tumor response (57% vs. 31%, p<.001).

8.5.5 Cancer epidemiology

Breakthrough and non-breakthrough indications did not significantly differ in disease incidence or prevalence. Disease severity as measured by DALYs, five-year survival, and the number of available treatments were the same for non-breakthrough and breakthrough indications.

8.5.6 Clinical benefit

Breakthrough indications were associated with a lower likelihood of death than non-breakthrough indications (HR: 0.69, [95%CI:0.66-0.73] vs. 0.74 [95%CI:0.71-0.76], p=.031) and offered significantly greater improvements in OS (median: 4.8 [IQR:3.5-9.5] vs 3.2 [IQR:2.2-4.4] months, p=.002) (Figure 49). Breakthrough indications were not associated with a lower likelihood of tumor progression (HR: 0.53 [95%CI:0.47-0.60] vs. 0.58 [95%CI:0.54-0.62], p=.212), but provided significantly greater improvements in PFS (median: 5.4 [IQR:2.5-9.7] vs. 3.30 [IQR:1.3-5.4] months, p=.005). Tumor response rates were higher for breakthrough compared to non-breakthrough indications (RR: 1.48 [95%CI:1.38-1.58] vs. 1.32 [95%CI:1.27-1.37], p=.006). The median duration of response was not significantly longer for breakthrough indications (median: 8.70 [IQR:2.7-10.1] vs. 4.65 [IQR:2.5-7.6] months, p=.245). Consistently, more patients responded to treatment with breakthrough than non-breakthrough indications in single-arm trials (ORR: 52% [95%CI:47-57] vs. 40% [95%CI:33-46], p=.004). Figure 50 shows

single-arm trials with higher tumor response rates, expressed as ORR, were at a significantly higher likelihood of receiving the BTD (OR: 4.29, 95%CI:1.85-6.74, p=.001). The direction and significance of results were confirmed in a series of meta-regression analyses of the BTD on OS, PFS, and tumor response outcomes (Table 39).

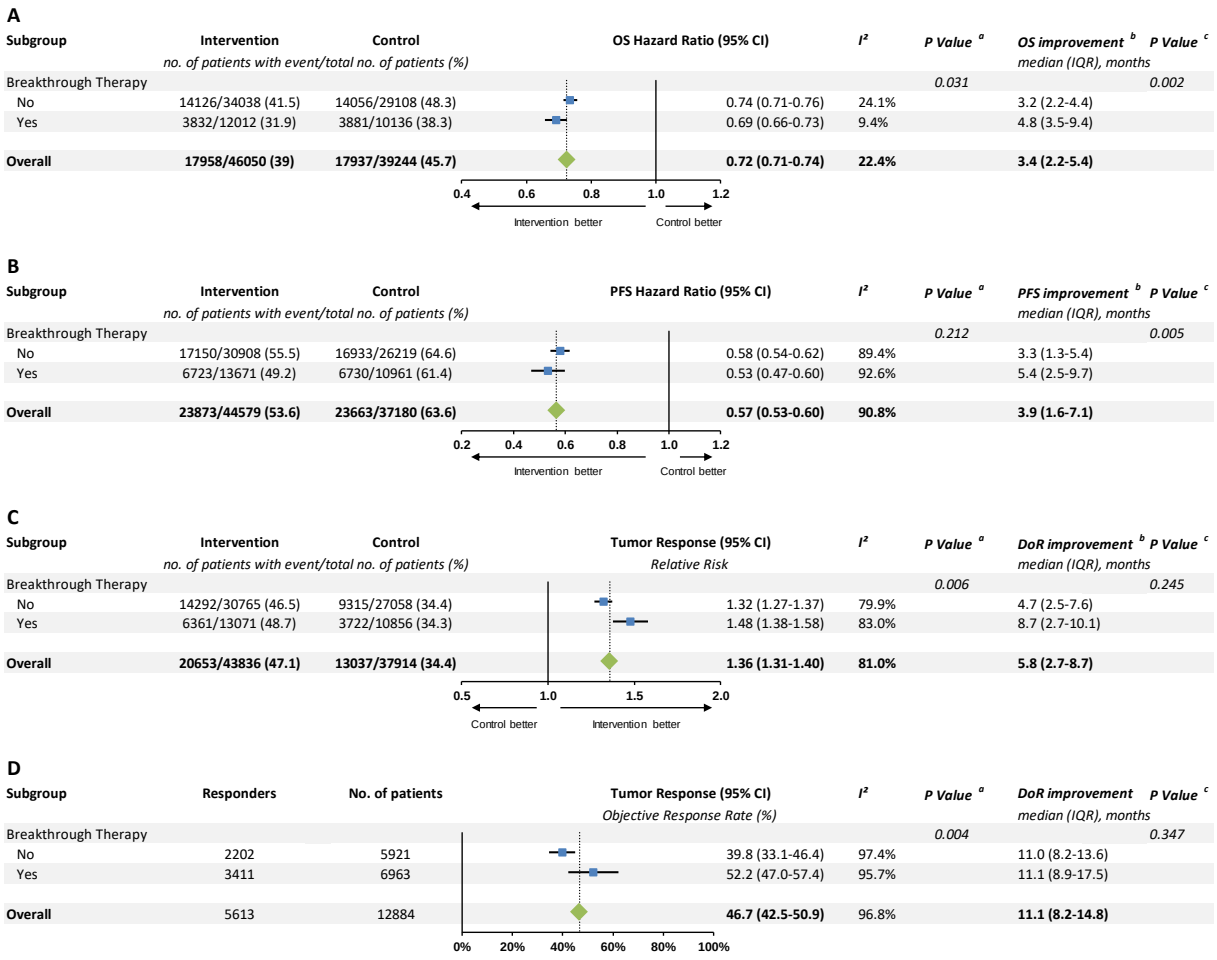


Figure 49: Meta-analyses of overall survival, progression-free survival, and tumor response for breakthrough and non-breakthrough therapy cancer drug indications approved by the FDA from 2012 to 2022

Notes: For randomized controlled trials with available outcome data, hazard ratios for OS (A) and PFS (B) and RR for tumor response (C) were meta-analyzed. For single-arm trials with available outcome data, ORR (D) were meta-analyzed. For tumor responses, a continuity adjustment of 0.5 for control arms with 0 responders was applied.

[a] P values calculated based on Cochran's-Q-tests.
[b] Improvements in OS, PFS, and DoR were calculated as the difference in median OS/PFS/DoR between the treatment and control arm.
[c] P values calculated based on Kruskal-Wallis-tests.

Abbreviations: DoR, duration of response; FDA, US Food and Drug Administration; IQR, interquartile range; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RR, relative risk.

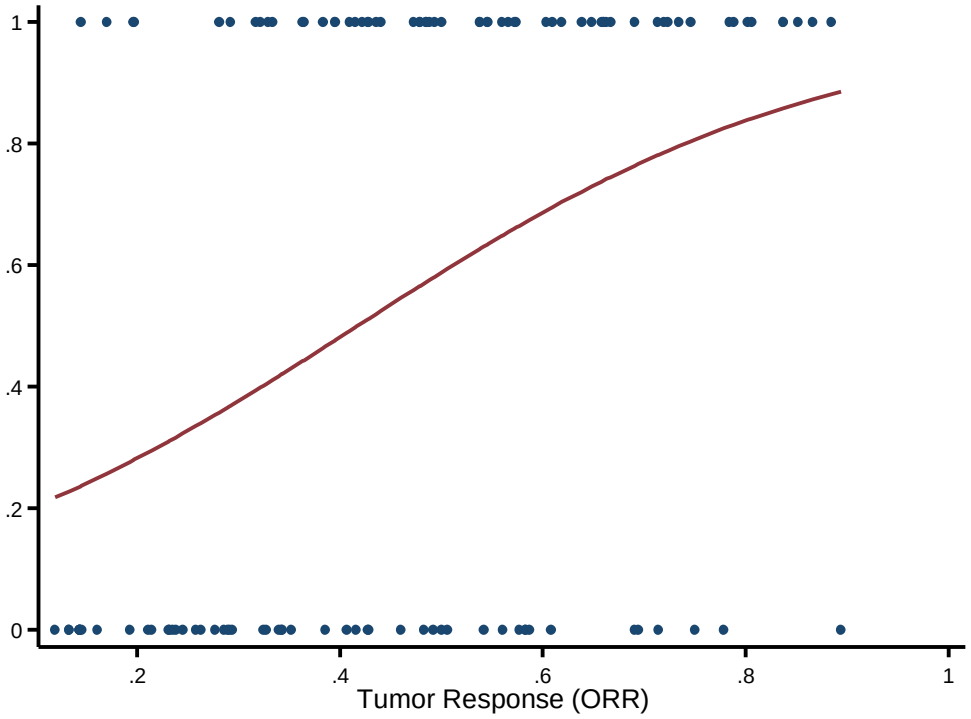


Figure 50: Association of Breakthrough Therapy Designation with tumor response in single-arm trials

Notes: A logistic regression quantifies the association between the probability of indications receiving the BTD and tumor response in single-arm trials for monotherapies. The odds ratio of the logistic regression was 4.29 (95%CI: 1.85-6.74, p=.001).

Abbreviations: BTD, Breakthrough Therapy Designation; FDA, US Food and Drug Administration; ORR, objective response rate.

	Dependent variable: BTD			
Independent variable	**Coef.**	**95%CI**		***P Value***
Overall survival				
Hazard Ratio	-0.06	-0.12	-0.01	*0.033*
Improvement in median OS	0.61	0.17	1.06	*0.007*
Progression-free survival				
Hazard Ratio	-0.11	-0.24	0.02	*0.110*
Improvement in median PFS	0.72	0.24	1.21	*0.004*
Tumor response				
Relative Risk	-0.57	-0.64	-0.50	*<.001*
Improvement in median DoR	0.46	-0.07	0.99	*0.090*

Table 39: Series of meta-regression analyses of breakthrough therapy designation on overall survival, progression-free survival, and tumor response outcomes

Notes: This table presents the results of a series of meta-regression analyses. Across all conducted regression models the breakthrough therapy designation was defined as the independent variable. Each row presents results for a distinct meta-regression of the breakthrough therapy designation on each outcome presented in the first column. OS, PFS, and tumor response outcomes were log-transformed given their skewed distribution. Only randomized controlled trials were included in the analyses.

Abbreviations: BTD, breakthrough therapy designation; DoR; duration of response, OS, overall survival; PFS, progression-free survival.

8.5.7 Drug prices

Mean monthly prices were 73% higher for breakthrough ($38,971 [95%CI: 25,547-52,394]) relative to non-breakthrough drugs ($22,591 [95%CI:12,387-32,795], p=.0592) (Figure 51). Quarterly drug price data was available for 48 drugs covered under Medicare Part B. From 2015 to 2023, drug prices increased by an average of 125% for breakthrough and 138% for non-breakthrough drugs. Whilst inflation amounted to 2.77% per quarter, drug prices increased by a quarterly CAGR of 2.67% for breakthrough and 4.08% for non-breakthrough drugs.

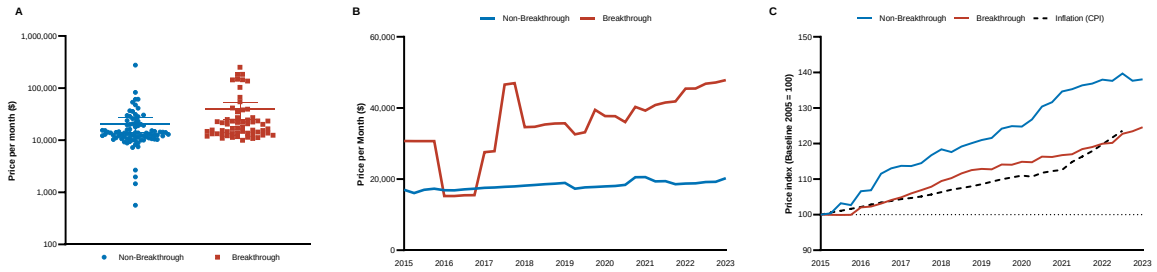


Figure 51: Prices for breakthrough and non-breakthrough cancer drugs from 2015 to 2023

Notes: In graph **a**, monthly prices of drugs with and without a breakthrough therapy designation for the original FDA indication are compared in the year 2023. In graph **a**, bars represent means with 95% confidence intervals. Graph **b** compares monthly prices for breakthrough vs non-breakthrough therapy cancer drugs from 2015 until 2023. In graph **c,** the mean price change of breakthrough vs. non-breakthrough therapy drugs is compared from 2015 until 2023. Lines illustrate price indices with the baseline set in the year 2015. Inflation was measured by the consumer price index.

Abbreviations: CPI, consumer price index; FDA, US Food and Drug Administration.

8.5.8 Predictors of the breakthrough therapy designation

Table 40 presents the results of the conducted logistic regression analyses. Among trials with available tumor response data (n=121), the tumor response rate was the greatest predictor of the breakthrough therapy designation (OR: 1.03, 95%CI: 1.01-1.06, p=0.018). Across all trials, a companion biomarker was associated with a 2.39-times (95%CI: 1.39-4.13, p=0.002) and second-line therapy with a 1.92-times (95%CI: 1.11-3.32, p=0.020) higher likelihood for the BTD. There was a tendency for novel product classes to be associated with the BTD; yet, this was not

significant at the 5% level. Coherent with previous results, epidemiologic characteristics were not meaningfully associated with the BTD.

	Logit(Breakthrough Therapy Designation)					
	Single-arm trials			All trials		
	Odds Ratio	**[95% CI]**	**P-Value**	**Odds Ratio**	**[95% CI]**	**P-Value**
Tumor response (ORR)[a]	1.03	[1.01-1.06]	*0.018*			
Mechanism of action						
Cytotoxic chemotherapy	1.00	[Reference]		1.00	[Reference]	
Targeted agents	6.64	[0.84-52.68]	*0.073*	0.56	[0.24-1.30]	*0.178*
Immune regulatory	1.00	[Omitted]		1.00	[Omitted]	
Product class						
Small molecule	1.00	[Reference]				
Antibody	10.77	[1.31-88.72]	*0.027*	0.64	[0.27-1.52]	*0.316*
Antibody-drug conjugate	2.05	[0.42-10.06]	*0.376*	1.79	[0.59-5.41]	*0.305*
Other	35.86	[1.56-825.04]	*0.025*	2.64	[0.59-11.78]	*0.205*
First-in-indication						
No	1.00	[Reference]		1.00	[Reference]	
Yes	1.00	[0.41-2.48]	*0.993*	1.27	[0.75-2.16]	*0.375*
Treatment type						
Combination	1.00	[Reference]		1.00	[Reference]	
Monotherapy	0.34	[0.06-1.8]	*0.203*	0.96	[0.57-1.61]	*0.871*
Disease						
Hematologic	1.00	[Reference]		1.00	[Reference]	
Solid	1.44	[0.32-6.49]	*0.638*	0.91	[0.42-1.97]	*0.818*
Biomarker						
No	1.00	[Reference]		1.00	[Reference]	
Yes	4.08	[1.46-11.41]	*0.007*	2.39	[1.39-4.13]	*0.002*
Line of therapy						
First-line	1.00	[Reference]		1.00	[Reference]	
Second-line	0.74	[0.23-2.38]	*0.619*	1.92	[1.11-3.32]	*0.020*
≥Third-line	0.29	[0.06-1.43]	*0.129*	0.73	[0.33-1.65]	*0.453*
Log(disease incidence)	0.89	[0.64-1.24]	*0.496*	0.92	[0.75-1.14]	*0.443*
DALYs per person	0.96	[0.89-1.03]	*0.222*	0.96	[0.92-1.00]	*0.045*
Constant	0.12	[0.01-2.80]	*0.188*	1.05	[0.35-3.14]	*0.930*
Observations	121			332		
Pseudo-R^2	19.15%			1.44%		

Table 40: Logistic regression analyses of breakthrough therapy designation on collected variables

Notes: This table presents the results the logistic regression models. Across all conducted regression models the breakthrough therapy designation was defined as the independent variable. The regression on the left side only includes single-arm trials with available tumor response outcome data. The regression on the right side includes all indications.

[a] Tumor response measured per 1% ORR.

Abbreviations: OR, odds ratio; ORR, objective response rate.

8.5.9 Full approval vs. accelerated approval

The previous analyses were re-evaluated in the subgroups of drugs and indications receiving full and accelerated approval. Figure 52b shows that in the subgroup of drugs with accelerated

approval, breakthrough drugs had shorter clinical development times (median: 5.4 vs. 8.3 years, p=.009). Figure 52a shows that this association was not significant in the sample of drugs with full approval due to a limited sample size (median: 6.6 vs. 8.9 years, p=.362). Across both subgroups, most drug characteristics did not significantly differ due to the small sample sizes (Table 41). In the full approval subgroup, there was a trend for breakthrough drugs to more frequently be first-in-class (50% vs. 24%, p=.053) and breakthrough indications to be first-in-indication (34% vs. 24%, p=.001). These associations were not significant for the accelerated approval subgroup. In the accelerated approval group, a higher rate of biomarker-directed therapies was observed for breakthrough than non-breakthrough indications (53% vs. 29%, p=.012). In the accelerated approval subgroup, pivotal trial characteristics did not differ between the breakthrough and non-breakthrough indications (Table 42). However, for the full approval subgroup, breakthrough indications were more often supported by single-arm (26% vs. 13%, p=.012) phase 1 or 2 trials (34% vs. 14%, p=.002) evaluating tumor response (88% vs. 82%, p=.008) instead of OS (13% vs. 25%, p=.042) as the primary endpoint.

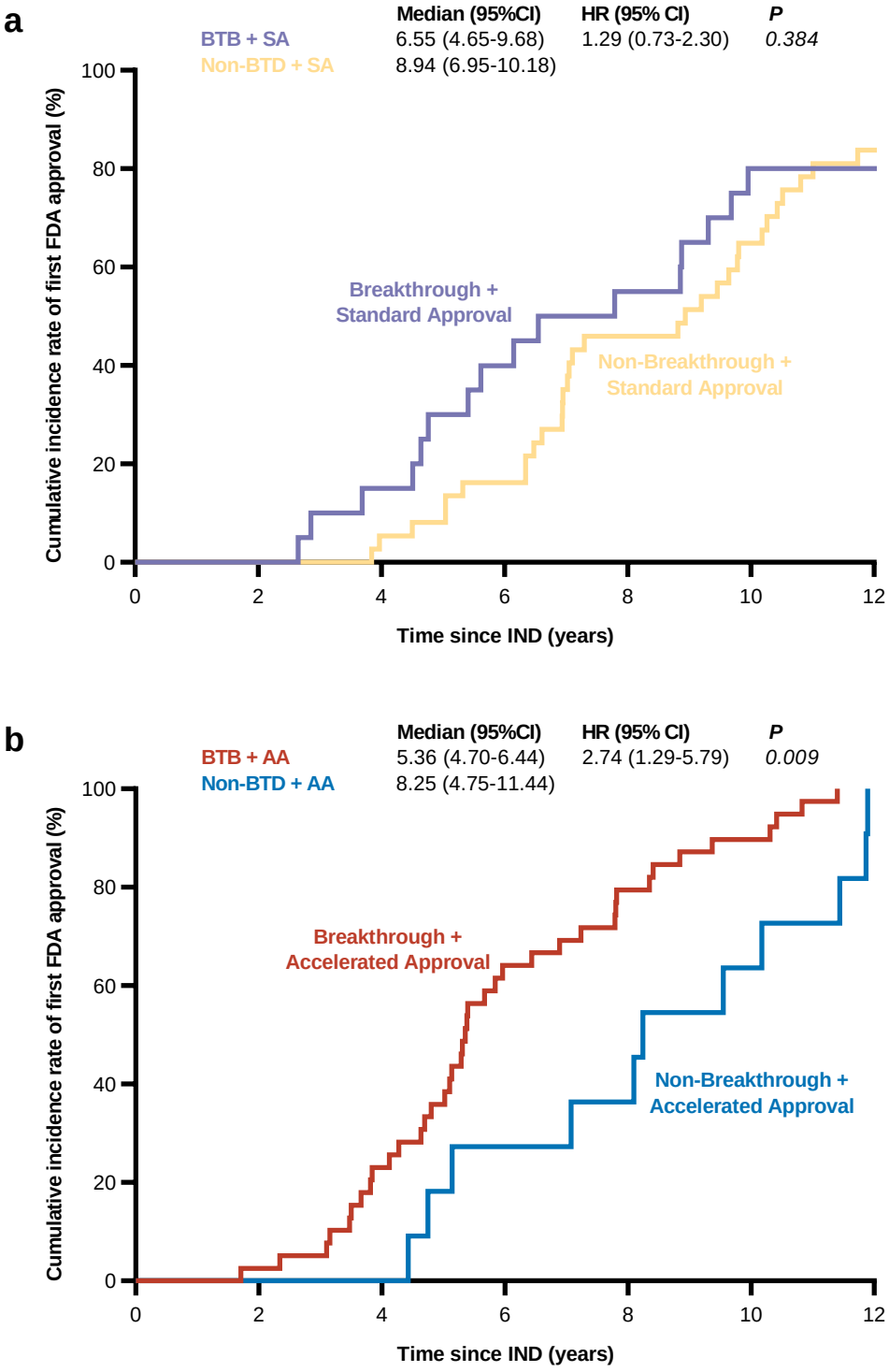


Figure 52: Time from IND to first FDA approval for breakthrough and non-breakthrough therapy cancer drugs stratified by accelerated approval

Notes: The graphs illustrate the cumulative incidence of the first FDA approval. In graph a, breakthrough (purple) and non-breakthrough (yellow) drugs were compared in the sample of drugs receiving standard/full FDA approval. In graph b, breakthrough (red) and non-breakthrough (blue) drugs were compared in the sample of drugs receiving accelerated approval. P values are calculated based on Cox-proportional hazard models.

Abbreviations: AA, accelerated approval; BTD, breakthrough therapy designation; FDA, US Food and Drug Administration; IND, investigational new drug application; SA, standard approval.

No. (%)

	Accelerated Approval					
	No			Yes		
	Breakthrough Therapy			Breakthrough Therapy		
Variables	**No**	**Yes**	***P Value*** [a]	**No**	**Yes**	***P Value*** [a]
Drug characteristics						
Number of indications			*0.099*			*0.026*
Single-indication	28 (68.3)	9 (45.0)		9 (69.2)	13 (32.5)	
Multi-indication	13 (31.7)	11 (55.0)		4 (30.8)	27 (67.5)	
Biotechnological Innovativeness			*0.053*			*0.319*
Addition-to-class	11 (26.8)	1 (5.0)		1 (7.7)	0 (0.0)	
Advance-in-class	20 (48.8)	9 (45.0)		7 (53.8)	25 (62.5)	
First-in-class	10 (24.4)	10 (50.0)		5 (38.5)	15 (37.5)	
Mechanism of action			*0.008*			*0.305*
Cytotoxic chemotherapy	5 (12.2)	0 (0.0)		1 (7.7)	0 (0.0)	
Targeted agents	30 (73.2)	10 (50.0)		8 (61.5)	28 (70.0)	
Immune-regulators	6 (14.6)	10 (50.0)		4 (30.8)	12 (30.0)	
Product type			*0.459*			*0.065*
Small-molecule	27 (65.9)	10 (50.0)		11 (84.6)	22 (55.0)	
Antibody	7 (17.1)	4 (20.0)		0 (0.0)	12 (30.0)	
Antibody-drug conjugate	1 (2.4)	2 (10.0)		2 (15.4)	5 (12.5)	
Other [b]	6 (14.6)	4 (20.0)		0 (0.0)	1 (2.5)	
Total no. of drugs	**41 (67.2)**	**20 (32.8)**		**13 (24.5)**	**40 (75.5)**	

Table 41: Characteristics of breakthrough and non-breakthrough therapy cancer drugs approved by the FDA from 2012 to 2022 stratified by accelerated approval

Notes: In this table, the breakthrough designation was analyzed on a drug level stratified by accelerated approval. All cancer drugs with FDA approval between 2012 and 2022 were included in the analysis. We compared the characteristics of breakthrough relative to non-breakthrough drugs in the subgroups of drugs receiving full approval and drugs receiving accelerated approval.

[a] P Values were calculated based on Fisher's-exact tests.
[b] Other includes biologics, gene therapies, cell therapies, enzymes, and radionuclides.

Abbreviations: FDA, US Food and Drug Administration.

No. (%)

	Accelerated Approval					
	No			Yes		
	Breakthrough Therapy			Breakthrough Therapy		
Variables	**No**	**Yes**	***P Value*** [a]	**No**	**Yes**	***P Value*** [a]
Indication characteristics						
Clinical Novelty			*0.001*			*0.165*
Addition-to-indication	38 (22.9)	4 (5.2)		5 (9.6)	1 (1.7)	
Advance-in-indication	89 (53.6)	47 (61.0)		23 (44.2)	26 (43.3)	
First-in-indication	39 (23.5)	26 (33.8)		24 (46.2)	33 (55.0)	
Indication approval sequence			*0.532*			*<.001*
Original indication approval	125 (75.3)	55 (71.4)		36 (69.2)	17 (28.3)	
Supplemental indication approval	41 (24.7)	22 (28.6)		16 (30.8)	43 (71.7)	
Treatment type			*1.000*			*0.490*
Combination	77 (46.4)	35 (45.5)		13 (25.0)	11 (18.3)	
Monotherapy	89 (53.6)	42 (54.5)		39 (75.0)	49 (81.7)	
Cancer type			*0.376*			*1.000*
Hematological	50 (30.1)	28 (36.4)		17 (32.7)	19 (31.7)	
Solid	116 (69.9)	49 (63.6)		35 (67.3)	41 (68.3)	
Biomarker			*0.480*			*0.012*
No	107 (64.5)	46 (59.7)		37 (71.2)	28 (46.7)	
Yes	59 (35.5)	31 (40.3)		15 (28.8)	32 (53.3)	
Line of therapy			*0.808*			*0.240*
First-line	99 (59.3)	46 (59.7)		13 (25.0)	14 (23.3)	
Second-line	53 (31.7)	26 (33.8)		25 (48.1)	37 (61.7)	
≥Third-line	15 (9.0)	5 (6.5)		14 (26.9)	9 (15.0)	
Special FDA designations						
Orphan designation	104 (62.7)	52 (67.5)	*0.476*	34 (65.4)	43 (71.7)	*0.542*
Fast Track	29 (17.5)	13 (16.9)	*1.000*	15 (28.8)	12 (20.0)	*0.376*
Pivotal clinical trial characteristics						
Enrolled patients, median (IQR)	439 (251-719)	447 (120-669)	*0.154*	109 (83-168)	107 (78-146)	*0.327*
Clinical trial phase			*0.002*			*0.240*
Phase 1	4 (2.4)	5 (6.5)		13 (25.0)	14 (23.3)	
Phase 2	20 (12.0)	21 (27.3)		25 (48.1)	37 (61.7)	
Phase 3	142 (85.5)	51 (66.2)		14 (26.9)	9 (15.0)	
Trial design			*0.012*			*0.406*
Single-arm trial	21 (12.7)	20 (26.0)		40 (76.9)	48 (80.0)	
Non-randomized controlled trial	0 (0.0)	1 (1.3)		2 (3.8)	5 (8.3)	
Randomized controlled trial	144 (86.7)	56 (72.7)		8 (15.4)	4 (6.7)	
Dose-comparison randomized trial	1 (0.6)	0 (0.0)		2 (3.8)	3 (5.0)	
Type of blinding			*0.663*			*0.019*
Open-label	109 (65.7)	53 (68.8)		47 (90.4)	60 (100.0)	
Double-blind	57 (34.3)	24 (31.2)		5 (9.6)	0 (0.0)	
Clinical trial arms			*0.011*			*0.808*
1 arm	21 (12.7)	20 (26)		40 (76.9)	48 (80.0)	
2 arms	141 (84.9)	53 (68.8)		11 (21.2)	12 (20.0)	
≥3 arms	4 (2.4)	4 (5.2)		1 (1.9)	0 (0.0)	
Primary Endpoint						
Overall survival	41 (24.7)	10 (13.0)	*0.042*	2 (3.8)	2 (3.3)	*1.000*
Progression-free survival	120 (83.3)	51 (91.1)	*0.783*	9 (17.3)	4 (6.7)	*0.137*
Tumor response	118 (81.9)	49 (87.5)	*0.008*	39 (75.0)	53 (88.3)	*0.085*
Cancer epidemiology						
Disease incidence, median (IQR) [b,c]	9.8 (5.6-67.6)	9.8 (5.2-67.6)	*0.510*	8.4 (3.2-25)	15.2 (3-67.6)	*0.725*
Disease prevalence, median (IQR) [b,c]	35.4 (17.6-117.8)	67.3 (18.4-117.8)	*0.914*	27.3 (13.2-83.7)	80.8 (13.2-117.8)	*0.384*
DALYs per person, median (IQR) [b]	10.8 (5.5-16.4)	7.4 (5.5-14.4)	*0.157*	10 (6.7-12.9)	10 (5-16.4)	*0.689*
YLL per person, median (IQR) [b]	10.5 (4.8-16.2)	6.9 (4.8-13.9)	*0.169*	9.3 (6.2-12.3)	9.3 (4.4-16.2)	*0.678*
YLD per person, median (IQR) [b]	0.5 (0.3-0.6)	0.5 (0.4-0.7)	*0.107*	0.5 (0.3-0.7)	0.5 (0.2-0.6)	*0.503*
5-year survival in %, median (IQR) [b]	65.5 (30.5-90.4)	76.4 (56.5-91.4)	*0.045*	71.9 (56.5-91.4)	71.9 (25-85)	*0.719*
No. of treatments, median (IQR) [b]	16 (12-22)	18 (13.5-38)	*0.055*	14 (10-38)	14 (9-38)	*0.482*
Total no. of indications	**167 (68.4)**	**77 (31.6)**		**52 (46.4)**	**60 (53.6)**	

Table 42: Characteristics of breakthrough and non-breakthrough therapy cancer indications approved by the FDA from 2012 to 2022 stratified by accelerated approval

Notes: In this table, the breakthrough designation was analyzed on an indication-level stratified by accelerated approval. All cancer indications with FDA approval between 2012 and 2022 were included in the analysis. We compared the characteristics of breakthrough relative to non-breakthrough indications in the subgroups of indications receiving full approval and indications receiving accelerated approval.

[a] P Values were calculated based on Fisher's-exact tests.
[b] P Values were calculated based on Kruskal-Wallis tests.
[c] Disease incidence and prevalence rates (per 100,000) for the US population in 2019.

Abbreviations: DALYs, disability-adjusted life years; FDA, US Food and Drug Administration; RCTs, randomized controlled trials; YLD, Years of healthy life lost due to disability.

8.6 Discussion

In this study of 355 FDA-approved cancer indications (2012-2022), we identified significant differences in the FDA approval, efficacy, clinical trial design, and pricing of breakthrough and non-breakthrough cancer indications. However, the treatment characteristics and epidemiology of diseases treated by breakthrough and non-breakthrough drugs did not significantly differ.

8.6.1 Clinical benefit

In contrast to previous studies,[135,222] our analyses revealed a substantially greater clinical benefit for breakthrough than non-breakthrough cancer indications in 5 out of 8 evaluated benefit measures. Most importantly breakthrough indications were associated with a greater efficacy in OS in terms of HRs (0.69 vs. 0.74, p=.031) and median improvement in OS (4.8 vs. 3.2 months, p=.002). The studies from Hwang et al. and Molto et al. are limited in their sample size, employed methodology, and analyzed time horizons. Precisely, these studies were not able to evaluate the full breadth of the BTD, given their focus on the first five years after the program was signed into law – many of the analyzed therapeutics receiving the BTD in late clinical development could not benefit from all of the program's advantages. Further, Hwang et al. only focused on original drug approvals as supplemental approvals were neglected. Therefore, Hwang et al., who examined 58 original FDA drug approvals from 2012 to 2017, found no significant difference between breakthrough and non-breakthrough cancer drugs' PFS and tumor response benefit.[135] Molto et al., who evaluated the same timeframe, only found significant differences between breakthrough and non-breakthrough drugs' benefit in two out of four evaluated value scores.[222] Our study, which comprises data from 355 original and supplemental FDA indication approvals, offers the largest assessment of breakthrough cancer drugs' clinical benefits. These results could be explained by the observation that supplemental approvals are less frequently breakthrough indications and are more often supported by larger and more robust clinical trials for first-line treatments,[73] which results in lower efficacy estimates for non-

breakthrough indications. In conclusion, breakthrough indications offered a greater clinical efficacy in 5 out of 8 evaluated measures than non-breakthrough indications. However, this greater clinical benefit could be partially caused by differences in the design characteristics of the underlying clinical trials (see below).

With our new comprehensive findings on breakthrough cancer drugs' clinical benefit, patients and physicians can adequately manage their optimistic expectations for drugs marketed as innovative promising "breakthroughs".[219–221] Nonetheless, US Congress could rename the designation from "breakthrough" to "high potential" to avoid invoking misleading hopes among patients.[218] The EU and Japan have arguably found more neutral wordings of their analogous approval pathways, naming them Priority Medicines (PRIME) and Sakigake (Japanese for "pioneer" or "pathfinder"), respectively.[223,224]

8.6.2 Expedited clinical development timelines

US Congress introduced the BTD to facilitate and accelerate the FDA's pre-marketing approval process for promising drugs treating serious diseases. Coherent with previous studies,[135,225] we find the BTD expedites drug development. These faster clinical development timelines were also observed for drugs receiving accelerated approval. This observation suggests that the BTD is non-redundant to the existing FDA's accelerated approval program. However, we also find that the BTD facilitated FDA approval via smaller single-arm trials. For patients, this flexibility in clinical trial design may represent a trade-off between earlier access to innovative medicines vs. robust safety and efficacy evidence. Smaller and shorter trials were not only shown to be more frequently associated with unobserved side effects but are also a source of bias for efficacy outcomes measured in randomized controlled and single-arm trials.[136,177,178] As a result, our study identified a tendency that breakthrough indications with accelerated approval are more frequently withdrawn than non-BTD with accelerated approval (19% vs. 10%, p=.199), although this result was not a significant at a 5% level. Balancing these competing goals, the FDA

should encourage sponsors and investigators of breakthrough drugs to conduct high-quality trials with sufficient enrollment and randomization whenever possible. For indications with an uncertain safety and efficacy profile, post-marketing requirements and commitments encouraging additional data collection should be mandated as time-dependent conditions to keep the breakthrough designation.

8.6.3 Innovation

Over the past two decades, biotechnological advances resulted in the discovery and development of new classes of medicinal products. Particularly the rise of personalized therapies, immune-therapies, and gene and cell therapeutics opened new therapeutic options for otherwise fatal conditions. These targeted therapies are often developed for biomarker-defined patient subgroups of the larger disease population, whose benefit is frequently already apparent in early phase 1 or 2 trials. The BTD was intended to expedite patient access and encourage the development of these promising and innovative new treatments. This study confirms that the BTD was especially granted to innovative cancer drugs and indications. Breakthrough drugs more frequently affected a novel target (first-in-class) using a novel mechanism of action to treat a novel disease (first-in-indication) and also displayed a tendency to be of a novel product class (antibody-drug conjugates, gene and cell therapies, or radionuclides). In contrast to prior studies,[135] we, therefore, conclude that the BTD did fulfill its intention and probably enabled US drug development to keep pace with and facilitate the biopharmaceutical innovation of the 21st century.

The BTD introduced more flexibility in the conduct of clinical trials for these novel therapeutics. To account for genomically homogenous patient populations across diseases, the BTD specifically accommodates novel trial designs, such as master protocols, umbrella trials, or basket trials. For instance, vemurafenib, a targeted agent that received the BTD, was approved for BRAF V600+ Erdheim-Chester disease, an ultra-rare blood disorder, based on a basket study

enrolling 24 patients with different forms of glioma.[226] The BTD likely also paved the way for the approval of tumor-agnostic treatments. For instance, pembrolizumab was the first treatment approved for metastatic solid tumors with mismatch-repair deficiency based on a basket study enrolling 41 patients with colorectal and non-colorectal cancer.[227] However, companion diagnostics for these biomarker-directed therapies currently need to be approved by the FDA through a separate review process.[228] Legislative action is necessary to combine and harmonize the expedited approval of biomarker therapies and their companion diagnostics to ensure early access for patients.

8.6.4 Treatment and epidemiologic characteristics

Over the past four decades, US Congress provided the FDA with a vast set of special designations and approval pathways to expedite the development and approval of new medicines.[217] For instance, the orphan designation financially incentivizes drug development for rare diseases.[76] The accelerated approval program permits early marketing authorization based on surrogate endpoints for medicines treating serious conditions and filling unmet medical needs. Similarly, the BTD is supposed to expedite the development of serious conditions with a preliminary large clinical benefit. Yet, in our study, we could not confirm that the BTD is more frequently granted to serious diseases given that there was no significant difference in DALYs and 5-year survival rates for BTD and non-BTD indications. Furthermore, there was no evidence that the BTD is more often granted to advanced-line patients, e.g. patients with serious diseases that have progressed or are ineligible for standard first-line therapy regimens. Combined with the aforementioned results, these findings suggest that the FDA's decision to grant the BTD is mainly based on biotechnological innovativeness, clinical novelty, and clinical efficacy rather than disease epidemiology. In other words, this study shows that the FDA seeks out the most innovative and promising drugs within each disease for the breakthrough designation.

8.6.5 Limitations

There are certain limitations inherent to our analyses. First, we only included successful trials which led to the FDA approval of new cancer drug indications. Second, drug price data were assessed for patients covered under Medicare Part B and D. Albeit Medicare and Medicaid is the leading health insurance scheme in the US, drug prices, rebates, co-payments, and deductibles may vary for patients covered in private insurance schemes. Third, to compare breakthrough and non-breakthrough indications, we meta-analyzed the efficacy outcomes of clinical trials for multiple tumor entities, which may be a source of high heterogeneity in calculated effect sizes.[84–87] Fourth, in our meta-analyses Cochran's-Q-tests were used to compare differences in efficacy outcomes for breakthrough and non-breakthrough indications. Cochran's-Q-tests examine sources of heterogeneity across subgroups. Yet, these tests are limited in statistical power and risk increasing alpha errors.[229] Nonetheless, our findings were consistent in magnitude and statistical significance for the comparison of median improvements in OS and PFS. Sixth, merely 9% breakthrough and 20% of non-breakthrough indications were supported by trials measuring OS as the primary endpoint. Therefore, the meta-analysis of OS is limited to a subset of the overall cohort of cancer drugs. Fifth, albeit we observed significantly greater RR in RCTs and ORR in single-arm trials for breakthrough relative to non-breakthrough indications, the clinical benefit of these tumor responses must be confirmed in well-designed, robust post-marketing trials assessing OS. Finally, we only evaluated cancer drug indications in our analysis. The results and policy implications of this study should be confirmed for other therapeutic areas.

8.7 Conclusion

The BTD encouraged the development of more than 1,100 indications. Over the past 10 years, breakthrough cancer drugs have been associated with faster development and approval timelines. Compared to their peers, breakthrough drugs more often affected a novel target using a

novel mechanism of action to treat a novel disease. Breakthrough indications displayed a substantially higher clinical benefit in 5 out of 8 evaluated efficacy measures. Most importantly breakthrough indications were associated with a greater benefit in OS in terms of HRs (0.69 vs. 0.74, p=.031) and median improvement in OS (4.8 vs. 3.2 months, p=.002). However, breakthrough indications were more frequently supported by small, non-robust single-arm trials that could partially explain the observed greater efficacy. No difference in treatment and epidemiologic characteristics was observed. In brief, the FDA primarily grants the breakthrough designation based on biotechnological innovativeness, clinical novelty, and clinical efficacy rather than disease epidemiology. In contrast to previous criticism, we, therefore, conclude that the BTD expedites patient access to innovative and effective, yet also expensive, new medicines.

8.8 Author contributions

Daniel Tobias Michaeli and Thomas Michaeli had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: All authors. Administrative, technical, or material support: All authors. Study supervision: All authors.

9 Value drivers of development stage biopharma companies

Summary: This cross-sectional study identifies and quantifies factors associated with the valuation of drug development companies in the EU and the US.

9.1 Abstract

Objective: Scholars previously estimated the R&D costs of the internal drug development process. However, little is known about the costs and value arising from externally acquired therapeutics. This study identifies and estimates the magnitude of factors associated with Biopharma acquisition value.

Methods: SDC Thomson Reuters and S&P Capital IQ were screened for majority acquisitions of US and EU Biopharma companies developing new molecular entities (NME) for prescription use (Standard Industrial Classification [SIC] code: 2834) from 2005 to 2020. Financial acquisition data were complemented with variables characterizing the target's product portfolio extracted from clinicaltrials.gov, Drugs@FDA database, US SEC filings, and transaction announcements. A multivariate regression assesses the association of firm value with extracted variables.

Results: 311 acquisitions of companies developing prescription drugs were identified over the study period. Acquirers paid 40% ($p<.05$) more for companies with biologics and gene therapeutics than small-molecule lead drugs. The total transaction value non-significantly increased by 8% with the lead product's number of indications ($p=.210$). No significant valuation difference between companies developing orphan and non-orphan designated lead products was observed (19%, $p=.244$). Acquisition value was positively associated with the total number of further products, headquarter location in the US, underlying market conditions, and acquirer market capitalization ($p<.05$).

Conclusions: Internal and external drug development consumes many financial and human resources, yet entrepreneurs, regulators, and payers need to understand their precise magnitude and value drivers. This information permits the design of targeted pricing and industrial policies that incentivize the development of novel drugs in areas with high unmet needs.

9.2 Introduction

Rising drug prices recently sparked controversy about the high profit margins of pharmaceutical companies.[3,230] Crucial to this dispute are the costs associated with developing new drugs.[231] While scholars previously estimated R&D costs of the internal drug development process,[18,20,232] little is known about the value and costs associated with externally developed therapeutics.[233]

Estimates show that the share of revenues from novel drugs developed externally surged to 50% in 2016.[233] External innovation sources include partnerships with academic institutions, licensing agreements, and M&As of disruptive start-ups. Acquisitions may be especially advantageous for strategic Biopharma companies when internal R&D pipelines must be replenished quickly due to patent expiry.[234,235] Furthermore, partnerships and acquisitions combine leading technological advances from risk-tolerant incumbent biotechnology start-ups with established commercialization capabilities of large pharmaceutical companies.[236] These synergies do not only create direct value for acquired start-ups, venture capital investors, and large pharmaceutical corporations but could ultimately benefit patients by permitting timely access to innovative medicines. Concisely, acquisitions fuel the development of medicines with financial, human, and technological capital which eventually advances available therapeutic options.

Innovation combined with a high risk-return profile has long sparked the interest of venture capitalists in the Biopharma industry. After several funding stages successful start-ups either debut on a public stock exchange through an initial public offering (IPO) or are sold directly to strategic or financial investors. Despite available economic valuation methodologies, e.g., net present value (NPV), risk-adjusted NPV (rNPV), real options, or the venture capital method, the valuation of Biopharma companies remains challenging due to the absence of solid financial metrics.[237–239] Even though there are some attempts to account for the intangible value of phar-

maceutical companies arising from technological firm capabilities or patents,[240,241] such approaches are still imperfect. Greater knowledge of external Biopharma innovation sources can inform the design of pricing and industrial policies that effectively reward the development of novel drugs in areas with high unmet needs.[242–245]

Biopharma firm valuation is mainly subject to the lead product's development stage.[81,236,246–248] However, knowledge of factors that explain the valuation dispersion within development stages is scarce. Yearly Biopharma deal reviews often focus on multi-billion-dollar acquisitions.[236,246] Thereby, early-stage pre-clinical and clinical-stage acquisitions, which drive pharmaceutical innovation, are neglected. A regression analysis of 122 US Biopharma IPOs (1991–2000) found a significant positive association between firm value and the products' development stage, R&D expenditure, market conditions, ownership retention, as well as a company's number of total products, alliances, and patents.[247] A cross-sectional study of 98 M&As (2008–2012) revealed no significant valuation difference between companies with FDA orphan and non-orphan designated lead products.[249] Valuations were also identified to be higher for US, large-cap pharma-backed, and oncology companies.[250,251] Surveys with 16 financial and strategic investors in 2002 qualitatively identified market size, development stage, strategic fit to the acquirer, competition, reputation, patents, and product novelty – in this order – as the most important value drivers in Biopharma licensing deals.[248]

Previous studies are, therefore, limited in sample size, geographic scope, and breadth of examined variables. Our study fills this gap by quantitatively assessing Biopharma company valuations based on a sample of 311 M&As across 23 collected variables in the US and EU between 2005 and 2020. We specifically aim to examine the relationship between the company acquisition value and the lead product's development stage (Pre-Clinic to FDA Approval), additional lead products, other products, and transition variables using multivariate regression analyses.

To the best of our knowledge, this is the first study that identifies and quantifies key financial and non-financial value drivers of private and public Biopharma corporations.

9.3 Data and methods

9.3.1 Sample selection

SDC Thomson Reuters and S&P Capital IQ were screened for majority acquisitions of Biopharma companies developing NME for therapeutic use (SIC code: 2834) from 1st January 2005 to 1st January 2020. Corporations developing generics, reformulations, medical devices, diagnostic substances, over-the-counter medicines, cannabis products, animal therapeutics as well as active pharmaceutical ingredients producers and sales of manufacturing sites were excluded. Only acquisitions with a total transaction value beyond $10 million were considered. To exclude mega-mergers, the sample was limited to targets with a portfolio of less than 10 NME. The geographic location was restricted to targets headquartered in the US or developed European markets. The sample contains both private and public targets.

9.3.2 Data collection

Variables were collected across four distinct areas: valuation, lead product, further products, and acquisition characteristics (Table 43). The selection was based on previous quantitative and qualitative studies that identified variables associated with Biopharma firm value.[247–251] Financial variables and acquisition characteristics were extracted from SDC Thomson Reuters and S&P Capital IQ. Subsequently, variables characterizing the target's product portfolio were obtained from US Securities and Exchange Commission (SEC) filings, clinicaltrials.gov, transaction announcements, and company websites at the time of the acquisition announcement.

	Unit	N	Mean	Median	SD	Min.	Max.	Skewness	Sum
A) Valuation									
Up-front Payment (USD)	Millions	303	958	257	2,270	0	22,434	5.02	290,417
Milestone Payment (USD)	Millions	290	159	0	330	0	2,945	3.89	46,144
Total Transaction Value (USD)	Millions	300	1,119	458	2,285	12	22,434	4.86	335,662
B) Lead Drug									
Development Stage									
Pre-Clinic	Binary	311	0.15	0.00	0.36	0	1		46
Phase 1	Binary	311	0.13	0.00	0.34	0	1		40
Phase 2	Binary	311	0.33	0.00	0.47	0	1		103
Phase 3	Binary	311	0.19	0.00	0.39	0	1		59
Approved	Binary	311	0.20	0.00	0.40	0	1		63
No. of Indications	Number	311	1.83	1.00	1.88	1	16	4.20	569
Biologic / Gene Therapy	Binary	311	0.21	0.00	0.41	0	1		66
Disease Area									
Oncology	Binary	311	0.30	0.00	0.46	0	1		93
CNS	Binary	311	0.16	0.00	0.37	0	1		51
Anti-Viral / Anti-Biotic	Binary	311	0.11	0.00	0.32	0	1		35
Others	Binary	311	0.42	0.00	0.50	0	1		132
FDA Orphan Designation	Binary	311	0.16	0.00	0.37	0	1		51
C) Other Products									
Total No. of Drugs	Number	311	2.96	2.00	2.19	1	10	1.31	921
Average Development Score [a]	Number	311	6.38	5.67	3.67	2	14	0.76	1,984
Average No. of Indications [b]	Number	311	1.46	1.00	1.09	1	12	5.00	455
D) Acquisition Characteristics									
Target Headquarter US	Binary	311	0.76	1.00	0.43	0	1		235
Target Public Ownership	Binary	311	0.37	0.00	0.48	0	1		114
Acquirer Market Cap ≥ $10 Bn	Binary	311	0.47	0.00	0.50	0	1		147
Market Conditions	Number	311	0.12	0.10	0.21	-0.24	0.69	0.47	38
Spin-Off / Single Drug Acquisition	Binary	311	0.11	0.00	0.31	0	1		34

Table 43: Descriptive statistics for the entire sample

Notes: All valuation metrics are inflation-adjusted.

[a] The average development score represents the number of years required to reach each development stage.
[b] The average number of indications refers to all products excluding the lead product.

Abbreviations: SD, standard deviation; CNS, central nervous system; FDA, US Food and Drug Administration; HQ, headquarter.

Valuation metrics

Up-front payments, maximum milestone payments (both regulatory and sales), and the total transaction value were obtained from SDC Thomson Reuters and S&P Capital IQ in US dollars at the time of the acquisition. To ensure data validity, all company valuations were cross-checked with US SEC filings and transaction announcements, if available. Valuation metrics were adjusted for inflation to 2020 values.

Lead product characteristics

We obtained multiple variables characterizing the target's lead product. For clinical phase products, the development stage was extracted from clinicaltrials.gov. Therapeutics in parallel Phase 1/2 trials were categorized within the Phase 2 development stage. For approved products, the

development stage was derived from publically available marketing authorization reports issued by the FDA. For pre-clinical products, the development stage was derived from US SEC filings or transaction announcements. The same methodology was applied to identify and categorize the lead product's number of indications (single indication vs. multi-indication), treatment type (small-molecule vs. biologic/gene and cell therapy), and disease area (oncology, central nervous system (CNS), infectious diseases, and others) according to the most advanced indication.

Further products

The same methodology was employed to obtain the target's total number of medicines alongside their development stage, and number of indications. We applied a similar concept proposed by Guo et al. to calculate the remaining portfolio's average development stage.[247,252] The stage score represents the number of years required to reach each development stage. Consistently, the average number of indications of all further products was assessed.

Acquisition characteristics

Target ownership status (private vs. public) and headquarter location (Europe vs. US) were extracted. We further identified the asset type (company acquisitions vs. spin-off/single drug transactions). The market condition variable represents the dividend and stock-split adjusted return of the NASDAQ Biotech – an index capturing the market capitalization of NASDAQ-listed Biopharma companies according to the SIC code – 12 months before the transaction announcement.

9.3.3 Methods and statistical analysis

Data were stored in Microsoft EXCEL and then analyzed using STATA SE Version 14.2. We calculated mean acquisition values and payment structures across our sample. Data were expressed as means with 95% CI. Company valuations were compared across development stages using ANOVA with Turkey's multiple comparison test. A two-tailed probability value < 0.05 was considered significant.

Thereafter, valuation metrics were examined in a sequence of multivariate regression models. First, valuation metrics were transformed with the natural logarithm to account for the right-skewed data distribution. Several regressions are presented in a consistent stepwise structure to examine the association of collected variables with company valuation. Model 1 only includes the lead product's development stage as an explanatory variable. Model 2 further includes all lead product characteristics. Model 3 considers all lead product and further product variables. Model 4 entails all lead product, further product, and acquisition variables (Table 44 and Table 45). This sequence of regression models permits to assess the explanatory value, measured by R^2, of the different variable categories. Mathematical equations for all regression models are attached in Table 46. Post-regression tests were conducted, as shown in Table 47, to evaluate omitted variable bias (Ramsey's test), model specification errors (Link test), as well as heteroscedasticity, skewness, and kurtosis (Cameron and Trivedi's test).

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
(1) Log(total transaction value)	1																
(2) Log(up-front payment)	0.89***	1															
(3) Lead development phase	0.66***	0.68***	1														
(4) Lead no. of indications	0.31***	0.29***	0.25***	1													
(5) Biologic/gene therapy	0.10	0.14*	-0.04	0.08	1												
(6) Oncology	0.03	0.02	-0.12*	0.19***	0.14*	1											
(7) CNS	-0.1	-0.09	0.00	-0.11*	-0.06	-0.29***	1										
(8) Anti-viral/anti-biotic	-0.05	-0.02	-0.07	-0.08	-0.09	-0.23***	-0.16**	1									
(9) FDA orphan designation	0.25***	0.23***	0.26***	0.24***	0.05	0.09	-0.08	-0.13*	1								
(10) Total no. of drugs	0.34***	0.39***	0.13*	0.09	0.02	0.06	-0.01	-0.05	0.11*	1							
(11) Mean development score [a]	0.44***	0.44***	0.83***	0.12*	-0.03	-0.15**	0.04	-0.06	0.19***	-0.26***	1						
(12) Mean no. of indications [b]	0.24***	0.20***	0.22***	0.82***	0.16**	0.13*	-0.1	-0.06	0.23***	-0.11*	0.24***	1					
(13) Target HQ US	0.22***	0.15*	0.10	-0.06	0.00	0.06	0.01	0.06	0.01	-0.13*	0.14*	-0.01	1				
(14) Target public	0.39***	0.46***	0.40***	0.15**	0.05	0.00	-0.01	0.00	0.08	0.29***	0.24***	0.06	0.15**	1			
(15) Acquirer market cap ≥ $10 Bn	0.44***	0.43***	0.22***	0.05	0.06	-0.06	0.00	-0.05	0.02	0.17**	0.1	-0.06	0.10	0.12*	1		
(16) Market condition	0.20***	0.19*	0.08	0.07	0.03	-0.07	-0.02	0.09	0.02	0.03	0.09	0.06	0.06	0.00	0.07	1	
(17) Spin-off/single drug deal	-0.09	-0.08	0.10	0.00	0.05	-0.05	-0.04	0.07	0.01	-0.13*	0.21***	0.11*	-0.04	0.05	-0.02	-0.07	1

Table 44: Pearson correlation matrix for the sample of collected biopharma acquisitions

Notes: P values: * p<.05; **p<.01; *** p<.001. [a] The average development score represents the number of years required to reach each development stage. [b] The average number of indications refers to all products excluding the lead product. Abbreviations: CNS, central nervous system; FDA, US Food and Drug Administration; HQ, head-quarter.

	Model 1	Model 2	Model 3	Model 4
Dependent variable: natural logarithm of total transaction value				
(**A**) Lead product				
Phase 1	1.61	1.66	1.98	2.05
Phase 2	2.15	2.24	4.07	4.28
Phase 3	1.81	1.92	5.24	5.64
Approved	1.89	2.14	11.35	12.04
No. of indications		1.17	3.79	3.89
Biologic/gene therapy		1.96	1.08	1.10
Oncology		1.35	1.35	1.40
CNS		1.20	1.21	1.22
Anti-viral/anti-biotic		1.17	1.17	1.20
FDA orphan designation		1.13	1.15	1.16
(**B**) Other products				
Total no. of drugs			2.02	2.13
Average development score [a]			7.36	7.56
Average no. of indications [b]			3.64	3.73
(**C**) Acquisition characteristics				
Target HQ US				1.13
Target public ownership				1.44
Acquirer market cap ≥ $10 Bn				1.17
Market conditions				1.06
Spin-off/single drug acquisition				1.12
Mean VIF	**1.87**	**1.50**	**3.49**	**2.96**

Table 45: Variance inflation factors for the regression of total transaction value on collected variables

Notes: The Table presents VIF for each model of the conducted regression. VIF beyond 10 indicated multicollinearity between independent variables.

[a] The average development score represents the number of years required to reach each development stage.
[b] The average number of indications refers to all products excluding the lead product.

Abbreviations: CNS, central nervous system; FDA, US Food and Drug Administration; HQ, headquarter; VIF, variance inflation factors.

The dependent variable (Y) was defined as company acquisition value (total acquisition value or up-front payment). The summary characteristics of the independent variables (x_i) are presented in Table 43. The association of independent variables with the dependent variable was examined in a sequence of regression models:

Model 1

Model 1 includes the lead product's development stages as the sole explanatory variables. Coefficients are presented as α_k.

$$Log(Y = Company\ Valuation \mid X_i = x_i) = \alpha_0 + x_1\alpha_{Phase\ 1} + x_2\alpha_{Phase\ 2} + x_3\alpha_{Phase\ 3} + x_4\alpha_{Approved}$$

Equation 4

Model 2

Model 2 includes all lead product characteristics as explanatory variables.

$$Log(Y = Company\ Valuation \mid X_i = x_i) = \alpha_0 + x_1\alpha_{Phase\ 1} + x_2\alpha_{Phase\ 2} + x_3\alpha_{Phase\ 3} + x_4\alpha_{Approved} + x_5\alpha_{No.\ of\ Indications} + x_6\alpha_{Biologic/Gene\ Therapy} + x_7\alpha_{Oncology} + x_8\alpha_{CNS} + x_9\alpha_{Anti-Viral/Anti-Biotic} + x_{10}\alpha_{Orphan\ Designation}$$

Equation 5

Model 2

Model 3 includes all lead and other product characteristics as explanatory variables.

$$Log(Y = Company\ Valuation \mid X_i = x_i) = \alpha_0 + x_1\alpha_{Phase\ 1} + x_2\alpha_{Phase\ 2} + x_3\alpha_{Phase\ 3} + x_4\alpha_{Approved} + x_5\alpha_{No.\ of\ Indications} + x_6\alpha_{Biologic/Gene\ Therapy} + x_7\alpha_{Oncology} + x_8\alpha_{CNS} + x_9\alpha_{Anti-Viral/Anti-Biotic} + x_{10}\alpha_{Orphan\ Designation} + x_{11}ß_{Total\ No.\ of\ Drugs} + x_{12}ß_{Average\ Development\ Score} + x_{13}ß_{Average\ No.\ of\ Indications}$$

Equation 6

Model 4

Model 4 includes all lead product, other product, and acquisition characteristics as explanatory variables.

$$Log(Y = Company\ Valuation \mid X_i = x_i) = \alpha_0 + x_1\alpha_{Phase\ 1} + x_2\alpha_{Phase\ 2} + x_3\alpha_{Phase\ 3} + x_4\alpha_{Approved} + x_5\alpha_{No.\ of\ Indications} + x_6\alpha_{Biologic/Gene\ Therapy} + x_7\alpha_{Oncology} + x_8\alpha_{CNS} + x_9\alpha_{Anti-Viral/Anti-Biotic} + x_{10}\alpha_{Orphan\ Designation} + x_{11}ß_{Total\ No.\ of\ Drugs} + x_{12}ß_{Average\ Development\ Score} + x_{13}ß_{Average\ No.\ of\ Indications} + x_{14}\gamma_{Target\ HQ\ in\ US} + x_{15}\gamma_{Target\ Public\ Ownership} + x_{16}\gamma_{Acquirer\ Market\ Cap \geq \$10\ Bn} + x_{17}\gamma_{Market\ Conditions} + x_{18}\gamma_{Spin-Off/Single\ Drug\ Deal}$$

Equation 7

Regression coefficients are presented as α_k for lead product, $ß_k$ for other product, and γ_k for acquisition characteristics.

Table 46: Mathematical equations for the regression analysis of acquisition value on collected variables

Abbreviations: CNS, central nervous system; FDA, US Food and Drug Administration; HQ, headquarter.

	Model 1	Model 2	Model 3	Model 4
Ramsey's-test				
p value	NA	0.0468	0.3188	0.6531
F value	NA	2.69	1.18	0.54
Link-test				
hat	0.122	0.003	0.001	0.005
hat²	1.000	0.391	0.405	0.481
Cameron & Trivedi's-test				
Heteroscedasticity	0.8356	0.4851	0.0747	0.3070
Skewness	0.8445	0.1954	0.894	0.7163
Kurtosis	0.9589	0.7828	0.5081	0.1362
Total	**0.9699**	**0.3917**	**0.0391**	**0.3640**

Table 47: Omitted variable, model specification, heteroscedasticity, skewness, and kurtosis tests for the total acquisition value analysis

Notes: The Ramsey's-test was performed to detect omitted variables in the regression model (H0: model has no omitted variables). The Link-test was conducted to identify model specification errors (H0 of hat²: model has no specification errors). Cameron & Trivedi's-test was executed to identify heteroscedasticity, skewness, and kurtosis in our model (H0: model has no heteroscedasticity, skewness, or kurtosis).

9.4 Results

Overall, we identified 2106 unique Biopharma acquisitions in the SDC Thomson Reuters (n = 1427) and S&P Capital IQ (n = 679) databases between 1st January 2005 and 1st January 2020 with valuation metrics (Figure 53). Further restricting the search to companies developing NME for human prescription use led to a final sample of 311 Biopharma M&As.

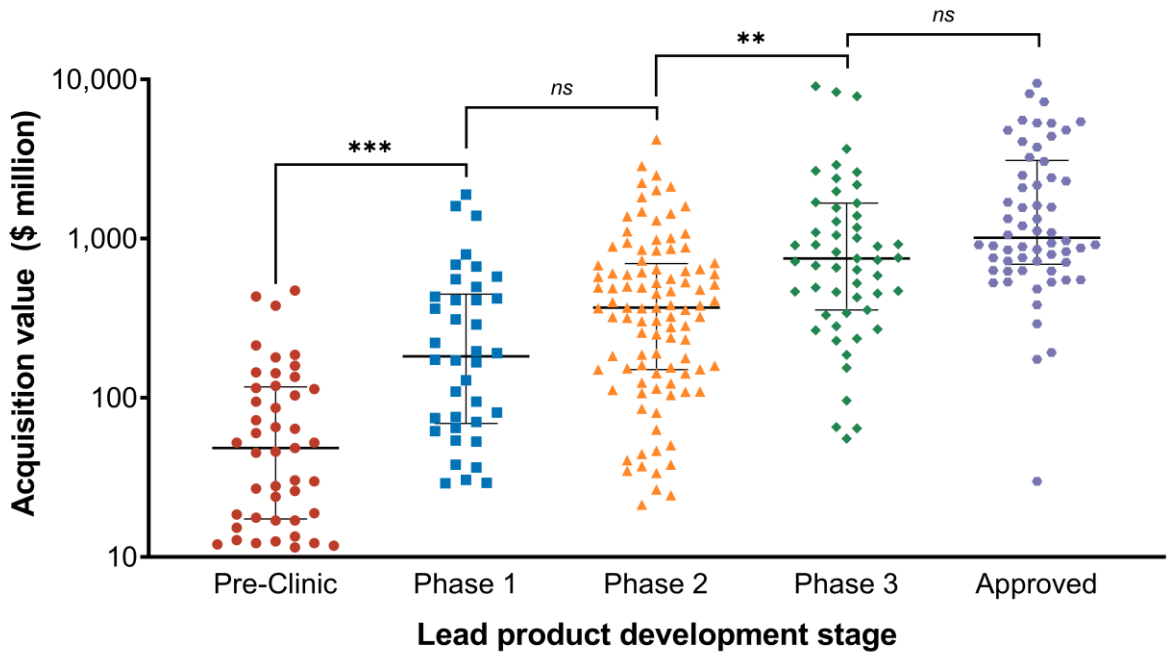


Figure 53: Acquisition value of Biopharma companies by lead product development stage

Notes: All values were inflation-adjusted to 2020. For visualization purposes, five observations with an acquistion value beyond $10,000 million are not shown in this graph. p values calculated based on ANOVA with Turkey's multiple comparison test: * p<.05; **p<.01; *** p<.001; ns, not significant.

9.4.1 Descriptive statistics

Overall, the entire acquisition volume cumulated to $336 billion over the 15 years period (Figure 54). On average, firms were acquired for a total transaction value of $1119 million (up-front payment: $958 million; milestone payment: $159 million). Valuation metrics were not reported for the entire sample (total transaction value: 300; up-front payment: 303; milestone payment: 290).

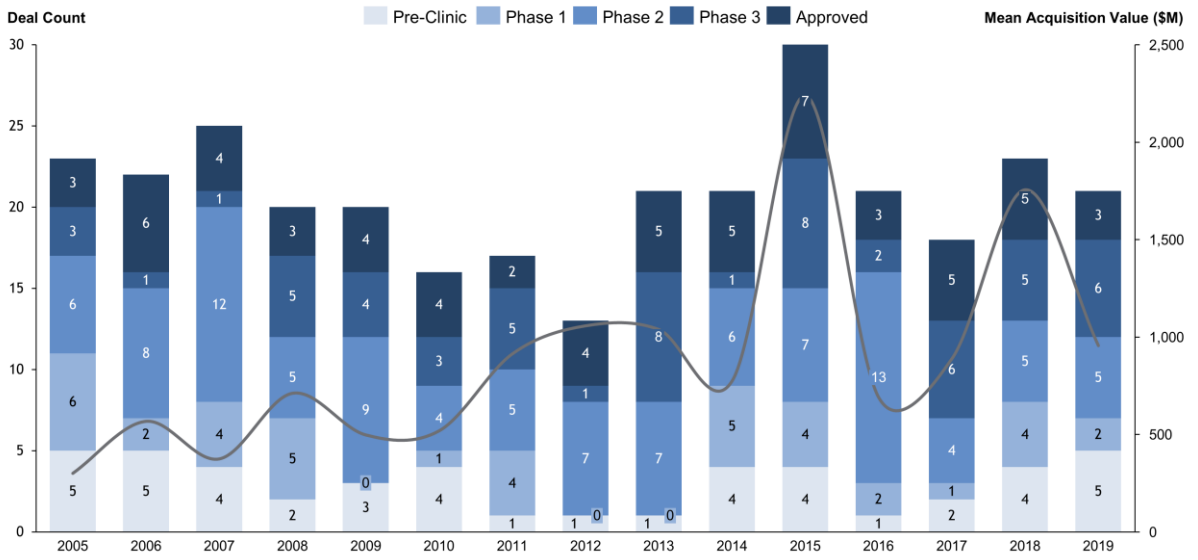


Figure 54: Number and deal value of development-stage Biopharma acquisitions from 2005 to 2020

Notes: The deal count represents the number of acquisitions by development stage. Mean acquisition values are inflation-adjusted to 2020.

Most acquired corporations were developing a lead product in Phase 2 (33%) or already commercialized the lead product (20%). Approximately one-third of lead products were developed across multiple indications (Table 43). 21% were classified as biologics or gene therapy and 16% received an orphan designation from the FDA. Most acquisitions focused on oncology (30%), CNS (16%), and infectious disease therapies (11%).

On average, acquired companies had a product portfolio of approximately 3 medicines. Yet, one-third of companies only pursued the development of one product. The average development score of these further products was 4.18, indicating that the average portfolio of the further products was between the Pre-Clinical and Phase 1 development stages. Only 18% of further products under development were tested across several indications.

Target companies were mostly headquartered in the US (76%) and under private ownership (37%). Furthermore, 47% of corporations were acquired by companies with a total market capitalization of more than $10 billion. The sample also includes acquisitions of single drugs or

spin-offs (11%). Acquisitions were predominantly struck under favorable market conditions, with the NASDAQ Biotech index posting an average 12-month return of approximately 12% before the transaction announcement.

Valuation by development stage

On average, companies with lead products in pre-clinical development were acquired for a total transaction value of $88 million (95% CI $56–120 million). Mean valuations rose to $354 million (95% CI $211–498 million) for Phase 1, $683 million (95% CI $436–930 million) for Phase 2, $1761 million (95% CI $996–2527 million) for Phase 3, and $2469 million (95% CI $1582–3355 million) for Approved lead products. However, the acquisition value displayed a high dispersion within the development stages. Therefore, only the transitions from Pre-Clinic to Phase 1 ($p<.001$) and from Phase 2 to Phase 3 ($p<.01$) significantly differed.

Payment structure

Acquisitions of companies with lead products under Pre-clinic and Phase 1 development included a mean up-front component of 51% (95% CI 49–75%) and 43% (95% CI 51–74%), respectively. Consequently, approximately half of the early-stage company transaction value was a deferred component (milestone payment). However, this deferred component decreased while the up-front component increased throughout clinical development. The mean up-front payment amounted to 72% (95% CI 56–71%) for Phase 2, 80% (95% CI 69–86%) for Phase 3, and 95% (95% CI 85–95%) for approved lead products.

9.4.2 Multivariate regression

The association between total transaction value and collected variables is evaluated in a sequence of multivariate regression models. Lead product, further product, and transaction characteristics are separately examined in a sequence of stepwise regressions (Table 48).

	Model 1	Model 2	Model 3	Model 4
Dependent Variable: Natural Logarithm of Total Transaction Value				
A) Lead Product				
Phase 1	1.338 (0.000)	1.281 (0.000)	1.102 (0.000)	0.861 (0.000)
Phase 2	1.914 (0.000)	1.928 (0.000)	1.652 (0.000)	1.302 (0.000)
Phase 3	2.788 (0.000)	2.776 (0.000)	2.483 (0.000)	1.918 (0.000)
Approved	3.302 (0.000)	3.092 (0.000)	2.637 (0.000)	1.987 (0.000)
No. of Indications		0.128 (0.000)	0.131 (0.099)	0.080 (0.210)
Biologic / Gene Therapy		0.474 (0.009)	0.452 (0.007)	0.340 (0.022)
Oncology		0.110 (0.509)	0.085 (0.601)	0.058 (0.675)
CNS		-0.270 (0.160)	-0.284 (0.133)	-0.306 (0.068)
Anti-Viral / Anti-Biotic		0.092 (0.689)	0.120 (0.575)	0.058 (0.762)
FDA Orphan Designation		0.192 (0.306)	0.098 (0.578)	0.172 (0.244)
B) Other Products				
Total No. of Drugs			0.184 (0.000)	0.1740 (0.000)
Average Development Score [a]			0.028 (0.490)	0.043 (0.234)
Average No. of Indications [b]			-0.016 (0.905)	0.106 (0.350)
C) Acquisition Characteristics				
Target Headquarter US				0.593 (0.000)
Target Public Ownership				0.189 (0.182)
Acquirer Market Cap ≥ $10 Bn				0.761 (0.000)
Market Conditions				0.780 (0.003)
Spin-Off / Single Drug Acquisition				-0.404 (0.050)
Constant	3.890 (0.000)	3.579 (0.000)	3.153 (0.000)	2.493 (0.000)
No. of Observations	300	300	300	300
R^2	44.9%	50.2%	55.5%	66.7%
Adjusted-R^2	44.1%	48.5%	53.4%	64.5%
F-Test:				
Pre-Clinic to Phase 1	1.338 (0.000)	1.281 (0.000)	1.102 (0.000)	0.861 (0.000)
Phase 1 to 2	0.576 (0.012)	0.647 (0.004)	0.550 (0.013)	0.441 (0.026)
Phase 2 to 3	0.875 (0.000)	0.848 (0.000)	0.831 (0.000)	0.616 (0.002)
Phase 3 to Approved	0.514 (0.201)	0.316 (0.156)	0.154 (0.547)	0.069 (0.767)

Table 48: Multivariate regression of total transaction value on (A) lead product's, (B) other products', and (C) acquisition characteristics

Notes: P-value in brackets.

[a] The average development score represents the number of years required to reach each development stage.
[b] The average number of indications refers to all products excluding the lead product.

Abbreviations: CNS, central nervous system; FDA, US Food and Drug Administration; HQ, headquarter.

Lead product characteristics

The lead product's development stage is the major highly significant value driver, explaining approximately 44.9% of firm valuation (Model 1). The total transaction value non-significantly increased by 8% with the lead product's number of indications (p=.210). Companies developing biologics or gene therapeutics were sold for a 40% (p<.05) premium relative to small molecules

(all coefficients were interpreted from Model 4). While regression suggests that firms developing CNS lead products were acquired for a -26% discount relative to other disease areas, this was not significant (p=.153). Similarly, companies with orphan-designated lead medicines were valued 19% higher, yet not significantly (p=.244). Overall, lead product characteristics explain 50.2% of value variation (Model 2).

Valuing further products

On average, company valuations increased by 19% (p<.001) for each additional product under development. In contrast, the average development score and the average number of indications do not seem to impact transaction value. Considering the high association of these insignificant variables with the lead product's stage and indications, this result was expected. In conclusion, the further product characteristics improved R^2 by 5.3% (Model 3).

Transaction characteristics

Valuations were 81% (p<.001) higher for target companies located in the US relative to Europe, but not significantly higher for public targets (21%, p=.175). Furthermore, the acquirer's market capitalization was identified as a major value driver, given that large-cap corporations purchased Biopharma companies for an 114% (p<.001) premium compared to medium- and small-cap acquirers. The average market condition for acquisitions was favorable in the sample. Yet, better market conditions were considerably positively associated with company valuations (p<.01). Lastly, spin-offs and single drug acquisitions were valued at a -33% (p<.05) discount relative to acquisitions of entire corporations. In summary, considering acquisition characteristics raised the R^2 by 11.2% (Model 4).

Further considerations

We conducted a cross-validation lasso regression analysis to verify that Model 4 presents the regression model that minimizes the mean squared prediction error. It is furthermore noteworthy that several independent variables display low, yet statistically significant, Pearson correlation coefficients (Table 44). Transitions in-between development stages, e.g., Pre-Clinic to Phase 1 or Phases 2–3, differed significantly – solely the transition between Phase 3 to Approved was insignificant (p=.175).

A similar multivariate regression model for up-front payments can be found in Table 49. The overall model fit is similar, yet slightly higher than the total transaction value model (R^2 of 69.2%). Variable signs, magnitude, and significance levels follow the same concept explained for the total transaction value regression. Solely, the lead product's number of indications and market conditions variables are slightly insignificant, while the spin-off variable turned significant.

	Model 1	Model 2	Model 3	Model 4
Dependent variable: natural logarithm of up-front payment				
(**A**) Lead product				
Phase 1	1.504 (0.000)	1.482 (0.000)	1.328 (0.000)	0.871 (0.002)
Phase 2	2.144 (0.000)	2.218 (0.000)	1.976 (0.000)	1.339 (0.000)
Phase 3	3.251 (0.000)	3.324 (0.000)	3.170 (0.000)	2.138 (0.000)
Approved	4.108 (0.000)	3.977 (0.000)	3.711 (0.000)	2.376 (0.000)
No. of indications		0.0994 (0.023)	0.090 (0.049)	0.047 (0.542)
Biologic/gene therapy		0.687 (0.000)	0.678 (0.000)	0.555 (0.000)
Oncology		0.217 (0.025)	0.140 (0.416)	0.184 (0.236)
CNS		-0.277 (0.241)	-0.295 (0.178)	-0.286 (0.155)
Anti-viral/anti-biotic		0.341 (0.207)	0.357 (0.135)	0.363 (0.112)
FDA orphan designation		0.153 (0.497)	0.061 (0.756)	0.143 (0.396)
(**B**) Other products				
Total no. of drugs			0.251 (0.000)	0.236 (0.000)
Average development score [a]			0.031 (0.512)	0.065 (0.113)
Average no. of indications [b]			-0.067 (0.607)	0.105 (0.342)
(**C**) Acquisition characteristics				
Target HQ US				0.251 (0.088)
Target public ownership				0.537 (0.001)
Acquirer market cap ≥ $10 Bn				0.901 (0.000)
Market conditions				0.625 (0.066)
Spin-off/single drug acquisition				-0.691 (0.007)
Constant	2.938 (0.000)	2.517 (0.000)	2.018 (0.000)	1.500 (0.000)
No. of observations	301	301	301	301
R^2	46.7%	51.7%	60.0%	69.2%
Adjusted-R^2	45.9%	50.0%	58.2%	67.2%
F test				
Pre-Clinic to Phase 1	1.504 (0.000)	1.482 (0.000)	1.263 (0.000)	0.871 (0.002)
Phase 1 to 2	0.640 (0.009)	0.736 (0.002)	0.597 (0.010)	0.468 (0.023)
Phase 2 to 3	1.106 (0.000)	1.106 (0.000)	1.116 (0.000)	0.799 (0.000)
Phase 3 to Approved	0.857 (0.000)	0.653 (0.010)	0.429 (0.151)	0.238 (0.367)

Table 49: Multivariate regression of up-front payment on (A) lead product's, (B) other products', and (C) acquisition characteristics

Notes: P-values in brackets.

[a] The average development score represents the number of years required to reach each development stage.
[b] The average number of indications refers to all products excluding the lead product.

Abbreviations: CNS, central nervous system; FDA, US Food and Drug Administration; HQ, headquarter.

9.5 Discussion

Based on a sample of 311 Biopharma acquisitions from 2005 to 2020, mean valuations significantly rose for corporations with lead products in Pre-Clinic ($88 million), Phase 1 ($354 million), Phase 2 ($683 million), Phase 3 ($1761 million), and FDA Approved ($2469 million)

development. Approximately, half of the agreed company valuation was deferred through regulatory and sales milestone payments for early development stages (Pre-Clinic and Phase 1). The lead drug's molecule type and number of indications were positively associated with company valuations. In addition, the total number of further products, targets headquartered in the US, underlying market conditions, and acquirer market capitalization were estimated to have a significant positive impact on valuations.

These figures are in line with mean Biopharma acquisition valuations found in annually published M&A reports.[236,246] The additional information gained about new drugs by conducting clinical trials is priced in by investors. In contrast, licensing agreements were more frequent than acquisitions in the examined period, yet their contract value – ranging from $20 million (Pre-Clinic) to $140 million (Phase 3) – was lower. Licensing agreements incur reduced valuations because contracts only incorporate distinct drug candidates, are subject to regional restrictions, and vary according to milestone thresholds and revenue distributions.[253]

Similar to Rooswinkel et al.,[249] we did not find a significant valuation difference between companies developing orphan and non-orphan lead products. Nonetheless, several factors positively affect the economics of orphan drugs: shorter development and approval timelines, additional financial R&D incentives, higher clinical trial and FDA success rates, stricter and extended market exclusivity, lower marketing costs, faster uptake, and high reimbursed prices.[143,180,254] Arguably, these factors could only significantly impact valuation in later development stages. Additionally, the orphans' market niche limits the number of strategic acquirers and restricts the eligible patient population. Combined with increasing pricing pressure,[255] these factors could partially offset the favorable economics of orphan drugs.

In 2019, all top ten grossing drugs were approved across several indications. Especially, treatments targeting molecular pathways that are inherent to multiple diseases, e.g., cancer or autoimmune diseases, may offer therapeutic benefits across several indications. Consequently,

multi-indication drugs target an expanded patient group. However, early drug development timelines and costs of multi-indication drugs can be dynamically reduced as they only occur once per drug.[38,40] Additionally, the sequencing of indication launches permits higher pricing and revenues under single-price policies.[38,40,41] These financial factors offer explanations as to why Biopharma acquirers displayed a tendency to pay an 8% (p=.210) premium per additional indication for firms with multi-indication products.

Oncology, CNS, and anti-infective drugs were previously identified as key focus areas of large Biopharma companies with higher multiples.[246,251] However, after adjusting for further covariates, the lead product's disease area did not significantly impact company valuations. An orphan designation status and the number of indications might already account for the most important drug characteristics implicitly impacting its economic properties, such as price and target patient population. Additionally, the strategic fit between the acquirer's and the target's product portfolio could impact acquisition values more than the underlying disease area.

Equivalent to Guo et al.,[247] the sample demonstrates that valuation is positively associated with the company's drug portfolio size. They ran a regression on 114 Biopharma IPOs (1991–2000) and identified that the number of total products and their patent protection are associated with company valuations. Consequently, Biopharma valuation can be regarded as the sum of all products, each with its distinct clinical and economic characteristics, within a company's R&D portfolio.[238]

Results reveal higher valuations for companies with biologic or gene therapy lead products relative to small molecules. Biologics and gene therapies often offer enhanced clinical safety and efficacy, higher clinical and FDA success rates, and target diseases previously considered untreatable.[180,256–258] However, greater drug prices resulting from increased development and production costs alongside impractical administration routes and reimbursement barriers hinder

widespread commercialization.[259,260] Besides the enhanced therapeutic benefits, strategic acquirers are seemingly willing to pay a premium for the scientific technology inherent to biologics and gene therapeutics.[235]

In line with previous research,[250,261] we found more and higher valued acquisitions of US companies relative to their European peers. Arguably, US Biopharma clusters in San Francisco, Cambridge (US), and San Diego provide start-ups with better access to human, technological, financial, and social capital to foster scientific innovation than their European counterparts in Zurich, Cambridge (UK), and Munich.[250] Moreover, stricter legal barriers to conducting laboratory research and clinical trials in European countries could ultimately impact Biopharma's operating costs, and thereby company valuations.[262]

The results of this study permit policymakers to design incentives for corporations to steer drug development into areas of interest. Neurodegenerative disorders cause a significant burden of disease in the US and Europe, yet drug development in this area is lagging. In our analysis, we also observed lower company valuations for CNS drug development companies. This "troublesome disconnect" between patients' needs and lagging drug development may be overcome by providing higher research grants, regulatory submission support, and patent term expansions for CNS drugs – similar to regulations incentivizing orphan drug development (The Lancet Neurology, 2021, p. 81).[263] Results also demonstrate that anti-biotic and anti-viral drugs are not valued significantly higher than their peers, even though recent policies aimed to incentivize drug development in this area.[264] Consequently, novel approaches beyond financial incentives that de-link drug prices from commercial success such as health impact bonds or pooled funds could be explored. The dataset also demonstrated that the valuation gap between companies with Phase 1 and 2 drugs is only marginal. Targeted financial and regulatory support programs may help to overcome this pharmaceutical "valley of death" (Dorey, 2009, p. 678).[265] Governments should also explore anti-cyclical industrial policies as results demonstrate that valuation

and thereby available capital for drug development companies is scarce during economic downturns.

9.5.1 Limitations

This study has several limitations. First, undisclosed information may impact results. Undisclosed acquisition valuations in the examined period may result in an over- or underestimation of company valuations. Especially, acquisitions of small pre-clinical biotechnology companies may not be released, which could overestimate valuations at this development stage. Additionally, unnamed pre-clinical drug candidates could overestimate the impact of the total number of products on firm valuation.

Second, the geographic scope of our analyses is limited to European and US Biopharma companies. Further studies investigating Biopharma company valuations in Asia, Africa, and South America are of interest. The therapeutic scope of the analyses is limited to companies developing NME for therapeutic use. Value drivers of medical technology, generic, and over-the-counter companies are subject to future research. The dataset is limited to a cross-section of Biopharma company valuations. Future panel studies should therefore examine the impact of time-varying variables on firm value.

Third, further variables are necessary to fully explain the valuation of Biopharma companies. Even though the regression explains approximately 65% of the variation in company valuation, 35% remains unexplained. Variables distinctly describing each drug's clinical benefit, anticipated competition, and population size are missing. A drug's peak sales volume is a key, yet difficult to estimate, variable combining all named elements.

Fourth, company valuation is furthermore subject to negotiations between acquirers and targets/backers. Therefore, bargaining power, negotiation skills, soft skills, as well as personal and inter-firm networks may influence company valuations in an up- or downward manner.[266–268]

The applied valuation methodology – NPV, rNPV, real options, venture capital methods – could furthermore influence company valuations.[237–239]

Fifth, some FDA-approved products have already been marketed for several years and could be close to patent expiry. Therefore, the observed marginal increase in company valuation might stem from the difference in the lead product's remaining exclusivity period.

9.6 Conclusion

Greater transparency throughout the R&D process is necessary to unravel and optimize the timelines and costs associated with introducing new drugs to the market. Internal and external drug development consume many financial and human resources, yet entrepreneurs, regulators, and payers need to understand their exact magnitude and value drivers. This research revealed that Biopharma company valuation is significantly associated with the lead product's development stage, number of indications, treatment type, product portfolio size, headquarters location, acquirer market capitalization, and market conditions. Policymakers are encouraged to design targeted pricing and industrial policies that incentivize the development of novel drugs in areas with high unmet needs.

9.7 Author contributions

Daniel Tobias Michaeli: data collection, statistical analysis, visualization, writing, editing. Hasan Basri Yagmur: data collection, statistical analysis, supervision, review. Timur Achmadeev: data collection, editing. Thomas Michaeli: supervision, editing, review.

10 Valuation and returns of drug development companies

Summary: This cross-sectional study estimates annual returns that bioentrepreneurs can expect from founding and investing in drug development companies.

10.1 Abstract

Objectives: This study evaluates the association of Biopharma company valuation with the lead drug's development stage, orphan status, number of indications, and disease area. We also estimated the annual returns Bioentrepreneurs and investors can expect from founding and investing in drug development ventures.

Methods: SDC Thomson Reuters and S&P Capital IQ were screened for majority acquisitions of US and EU Biopharma companies developing NME for prescription use (SIC code: 2834). Acquisition data were complemented with drug characteristics extracted from clinicaltrials.gov, the FDA, and deal announcements. Thereafter, company valuations were combined with previously published clinical development periods alongside orphan-, indication-, and disease-specific success rates to estimate annual returns for investments in drug-developing companies.

Results: Based on a sample of 311 Biopharma acquisitions from 2005 to 2020, companies developing orphan, multi-indication, and oncology drugs were valued significantly higher than their peers during later development stages ($p<.05$). We also estimated significantly higher returns for shareholders of companies with orphan relative to non-orphan-designated lead drugs from Phase 1 to FDA approval (46% vs. 12%, $p<.001$). Drugs developed across multiple indications also provided higher returns than single-indication agents from Pre-Clinic to FDA approval (21% vs. 11%, $p<.001$). Returns for oncology drugs exceeded other disease areas (26% vs. 8%, $p<.001$).

Conclusions: Clinical and economic conditions surrounding orphan-designated drugs translate to a favorable financial risk-return profile for Bioentrepreneurs and investors. Bioentrepreneurs must be aware of the upside real option value their multi-indication drug could offer when negotiating acquisition or licensing agreements.

10.2 Introduction

Large Biopharma firms are often in the spotlight of public media for bringing novel pharmaceuticals to the market. However, more than half of new drug approvals are developed externally by start-ups or research institutes.[233] While previously published literature focuses on the costs and timelines of the internal R&D process,[231] in this article, we concentrate on the dynamics of the external drug development process.

A common path for a Biopharma venture to emerge is for scientists to build a business around their novel scientific discovery. These scientists are often subject matter experts in their field. Yet for their venture to succeed they also require managerial competencies that extend beyond their scientific work. Specifically, soft skills coupled with managerial principles are crucial to scale a Biopharma venture.[269,270] Early-on Bioentrepreneurs will face the challenge of securing funding for their venture from academic institutions, research grants, and investors. In other words, founders must be able to evaluate both the scientific and financial merits of their discovery. Consequently, in this study, we aim to identify key value drivers of Biopharma ventures based on a cross-sectional sample of 311 Biopharma acquisitions. While it is established that Biopharma firm value is mainly dependent on the lead drug's development stage,[80,236,246–248] we also evaluate the association of firm valuation with the lead drug's FDA orphan designation status, number of indications, molecule type, and disease area.

On the other side, investors and large Biopharma companies must continuously find new ventures to deploy their fund's capital and commercialize new drugs.[271] They too evaluate both the scientific and financial merits of an investment proposal. Ideally, the investment would yield excess – better than average – financial returns. Consequently, the second aim of this paper is to model the risk-return characteristics of the drug development process. We will combine extracted company valuations with success rates and timelines of the drug development process to estimate financial returns. While these are not real returns from a longitudinal dataset of

investments, our model permits the identification of industry trends. We will particularly evaluate whether orphan-designated, multi-indication, biologic, and oncology drugs provide excess returns for Bioentrepreneurs and investors.

10.3 Materials and methods

10.3.1 Data collection

SDC Thomson Reuters and S&P Capital IQ were screened for majority acquisitions of Biopharma companies developing NME for therapeutic use (SIC code: 2834) from 1st January 2005 to 1st January 2020. Corporations developing generics, reformulations, medical devices, diagnostic substances, over-the-counter medicines, cannabis products, animal therapeutics as well as active pharmaceutical ingredients producers and sales of manufacturing sites were excluded. Only acquisitions with a total deal value beyond $10 million were considered. To exclude mega-mergers, the sample was limited to targets with a portfolio of less than 10 NME. The geographic location was restricted to targets headquartered in the US or developed European markets. The sample contains both private and public targets.

Financial variables and acquisition characteristics were extracted from SDC Thomson Reuters and S&P Capital IQ. Subsequently, the target's lead product's development stage, orphan designation status, number of indications, molecule type, and disease area were obtained from the US FDA database, US SEC filings, clinicaltrials.gov, and deal announcements.

Valuation metrics

Up-front payments, maximum milestone payments (both regulatory and sales), and the overall deal value were obtained from SDC Thomson Reuters and S&P Capital IQ in US dollars at the time of the acquisition. To ensure data validity, all company valuations were cross-checked

with US SEC filings and deal announcements, if available. Valuation metrics were adjusted for inflation to 2020 values.

Development stage

The development of human pharmaceutical products can be categorized into five distinct stages: Pre-Clinic, Phase 1, Phase 2, Phase 3, and Approved. We extracted and cross-checked the lead product's development phase from FDA marketing authorization reports, clinicaltrials.gov, US SEC filings, and deal announcements. Therapeutics in parallel Phase 1/2 (2/3) trials were categorized within the Phase 2 (3) development stage.

Orphan designation

All therapeutics were checked for orphan designations issued by the FDA. Thereby therapeutics were classified as "orphan" and "non-orphan".

Number of indications

We also extracted the number of indications a therapeutic is being developed for using clinicaltrials.gov. Consequently, therapeutics developed for one disease were categorized as "single-indication" and therapeutics developed for more than one disease were classified as "multi-indication".

Molecule type

The lead therapeutics molecule type was furthermore classified into "small-molecule" and "biologics or gene/cell therapies".

Disease area

Lead therapeutics were furthermore classified into disease areas according to the most advanced indication. Categories include oncology, CNS, and others (immunology, infectious disease, cardiovascular, dermatology, internal medicine, ophthalmology).

10.3.2 Statistical analysis

First, the mean company valuations' 95% CI for orphan designation status, disease area, number of indications, and molecule type were calculated within each development stage. A non-parametric bootstrapped resampling with replacement (1,000 iterations) was conducted to calculate mean company valuations and their respective 95% CI in our sample. Thereafter, investment multiples and returns were estimated based on mean company valuations, development stage success rates, and development periods (Table 50).

	Mean	95% CI	Source	σ	α	β	Distribution
Company Valuation (*$ millions*)							
Pre-Clinic	88	(57-119)	[a]	15.65	31.54	2.79	Gamma
Phase 1	399	(211-498)	[a]	66.78	28.17	12.58	Gamma
Phase 2	734	(436-930)	[a]	112.14	31.28	21.84	Gamma
Phase 3	1,656	(996-2,527)	[a]	369.13	22.77	77.36	Gamma
Approved	2,496	(1,582-3,355)	[a]	432.58	32.57	75.80	Gamma
Success Rate (*%*)							
Pre-Clinic to Phase 1	32.0	(28.8-35.2)	[272]	1.60	271.68	577.32	Beta
Phase 1 to Phase 2	75.8	(68.2-83.4)	[273]	3.79	96.04	30.66	Beta
Phase 2 to Phase 3	55.6	(50.0-61.2)	[273]	2.78	177.04	141.38	Beta
Phase 3 to Approved	67.7	(60.9-74.5)	[273]	3.39	128.52	61.32	Beta
Development Period (*years*)							
Pre-Clinic to Phase 1	1.00	(0.75-1.25)	[274]	0.13	64	0.016	Gamma
Phase 1 to Phase 2	1.50	(1.13-1.88)	[274]	0.19	64	0.023	Gamma
Phase 2 to Phase 3	2.50	(1.88-3.13)	[274]	0.31	64	0.039	Gamma
Phase 3 to Approved	2.50	(1.88-3.13)	[274]	0.31	64	0.039	Gamma

Table 50: Input parameters for the estimation of investment multiples and returns

Notes: Distinct company valuations by orphan designation status, number of indications, molecule type, and disease area are enclosed in Table 51. Company valuations include up-front and milestone payments and were inflation-adjusted to 2020 values.

[a] Mean company valuations were calculated from our dataset of 311 biopharma acquisitions.

Company valuation

Mean company valuations were compared by orphan designation status, disease area, number of indications, and molecule type within development stages based on non-parametric bootstrapped t-tests (resampling of 1,000 iterations with replacement). Company valuations were calculated as the sum of the up-front payments and all future milestone payments. Valuations were visualized using beeswarm plots.

Data on company valuations were available for 300 of the 311 collected acquisitions. The analysis of mean valuations and the multiple and return calculations consequently excluded 11 observations to arrive at a final sample of 300 Biopharma acquisitions. No missing data were observed for lead product characteristics, e.g., FDA orphan status, number of indications, molecule type, and disease area.

Estimating investment multiples

We subsequently estimated multiples Bioentrepreneurs and investors could expect from investments in development stage Biopharma ventures. In the finance industry, investment multiples compare a company's valuation at the time of sale to a company's valuation at the time of purchase. Consequently, we estimated investment multiples in the Biopharma context by dividing the mean company valuation of development stage Phase j by the mean company valuation of development stage Phase i (Equation 8). To account for clinical trial failures, investment multiples were adjusted for development stage-specific success rates. Clinical success rates were extracted from Wong et al.,[273] given that they use the largest sample size, overlap with our study period, and employ the most relevant path-by-path methods – in contrast to other estimations which follow a phase-by-phase methodology.[180,275,276] Pre-Clinic to clinic success rates were extracted from Takebe et al. who analyzed 798 drug discovery projects in the US.[272] For example, the mean valuation of biopharmaceutical companies with Phase 2 therapeutics ($683 million) was divided by the mean valuation of companies with Phase 1 products ($354 million). This quotient was thereafter adjusted by the success rate to progress from Phase 1 to 2 (75.8%) to arrive at the investment multiple (1.5x).

$$Multiple_{Phase\ i\ to\ j} = \frac{Company\ Valuation_{Phase\ j}}{Company\ Valuation_{Phase\ i}} * Success\ Rate_{Phase\ i\ to\ j}$$

Equation 8

Stage-, indication-, biologic-, disease-, and orphan-specific means for company valuations and success rates were applied to estimate and compare investment multiples and returns within the respective categories. For instance, distinct Phase 1 to 2 (96.1% vs. 75.8%), Phase 2 to 3 (86.1% vs. 55.6%), and Phase 3 to Approved (63.5% vs. 67.7%) success rates were used for orphan vs. non-orphan-designated therapeutics. Similarly, distinct Phase 1 ($227 vs. $370 million), Phase 2 ($744 vs. $673 million), Phase 3 ($2166 vs. $1648 million), and Approved ($3703 vs. $1964

million) company valuations were used for orphan vs. non-orphan therapeutics. Employed company valuations are enclosed in Table 51.

	Pre-Clinic		Phase 1		Phase 2		Phase 3		Approved	
	Mean	*P* Value	Mean	*P* Value	Mean	*P* Value	Mean	*P* Value	Mean	*P* Value
FDA orphan designation status										
Orphan	NA[a]	*NA [a]*	227	*p=.257*	744	*p=.373*	2,166	*p=.317*	3,703	*p<.05*
Non-orphan	88		370		673		1,648		1,964	
No. of indications										
Multi-indication	87	*p=.484*	594	*p<.05*	1,058	*p<.05*	2,249	*p=.208*	3,438	*p<.01*
Single-indication	88		230		522		1,578		1,670	
Molecule type										
Small-molecule	71	*p<.05*	325	*p=.139*	517	*p<.05*	1,536	*p=.103*	2,105	*p=.161*
Biologic OR gene/cell therapy	109		341		811		3,759		2,088	
Disease area										
Oncology	70	*p=.176*	403	*p=.242*	1,068	*p<.05*	1,747	*p=.490*	4,561	*p<.01*
CNS	67	*p=.346*	233	*p=.204*	314	*p<.001*	1,740	*p=.490*	2,066	*p=.372*
Other [b]	104		343		607		1,775		1,747	
Mean	**99**		**479**		**856**		**2,255**		**1,964**	

Table 51: Stage-specific Biopharma company valuation (in million US dollars) by FDA orphan status, number of indications, molecule type, and disease area

Notes: All valuation metrics are inflation-adjusted to 2020. P Values were calculated based on nonparametric bootstrapped *t*-tests (resampling of 1,000 iterations with replacement).

[a] No valuation data exists for the Pre-Clinic orphan category given that the FDA only issues the orphan designation status after IND approval.
[b] The disease category "other" includes immunology, infectious disease, cardiovascular, dermatology, internal medicine, and ophthalmology.

Notes: CNS, central nervous system; FDA US Food and Drug Administration; IND, investigational new drug application; NA not applicable.

Estimating investment returns

Finally, the annual returns Bioentrepreneurs and investors can expect from investments in development-stage Biopharma companies were estimated by linking the previously calculated investment multiple to the mean development time of the respective development stage (Equation 9). Mean development periods were extracted for Pre-Clinic to Phase 1 (1.0 years), Phase 1 to 2 (1.5 years), Phase 2 to 3 (2.5 years), and Phase 3 to Approved (2.5 years) from previous literature.[274]

$$Investment\ Return_{Phase\ i\ to\ j} = (Multiple_{Phase\ i\ to\ j})^{Mean\ Development\ Time_{Phase\ i}} - 1$$

Equation 9

Sensitivity analysis

We conducted a probabilistic sensitivity analysis in Microsoft EXCEL to account for uncertainty surrounding point estimates of company valuation, success rates, and development stage length. Therefore, input parameters for the calculation of investment multiples and returns were drawn by random sampling iterations from their defined distribution displayed in Table 50. Thereby this sampling method permitted simultaneous variations in considered input parameters. This probabilistic analysis features the simulation of 1,000 investments per variable category.

In more detail, we first defined each variable's underlying distribution. Success rates were modeled using a beta function given that the point estimate value may vary between 0 and 1. Company valuations were modeled using a gamma function given that the right-skewed data distributions suggest outliers exist with high company values. Accordingly, development times were also approximated with a gamma function as development timelines for a few drugs stretch beyond 10 or even 15 years.[277] For each variable of interest and development stage, the specified distribution function was informed by calculating alpha and beta values based on the variable's underlying point estimate and standard deviation. We then conducted 1,000 iterations to calculate multiples and returns. For each iteration, the probabilistic point estimate for the company valuation, success rate, and development time is drawn by random sampling from the previously defined distribution function that was populated with alpha, beta, and the deterministic point estimates. Across these 1,000 iterations that distinctly calculate a probabilistic value for each multiple and return of interest, we calculated means with 95% confidence intervals.

Data were stored in Microsoft EXCEL and analyzed using STATA SE Version 14.2. For the two-factorial analysis of variance, ANOVA with Dunnett's/Sidak's test was applied. A two-tailed probability value < 0.05 was considered significant.

10.4 Results

A total of 2106 unique Biopharma acquisitions were identified in the SDC Thomson Reuters (n = 1427) and S&P Capital IQ (n = 679) databases between 1st January 2005 and 1st January 2020. Further restricting the search to companies developing NME for human prescription use led to a final sample of 311 Biopharma company valuations. Most acquired companies were developing a lead product in Phase 2 (33%) or already commercialized the lead product (20%). Approximately one-third of lead products were developed across multiple indications, 21% were classified as biologics or gene/cell therapy, and 21% received FDA orphan designation status. Most acquisitions focused on oncology (30%), CNS (16%), and infectious disease therapies (11%). More detailed descriptive statistics for the entire sample can be found in Table 43. Overall, downward-sloping annual returns for advanced drug development stages could be observed for the entire sample (Figure 55).

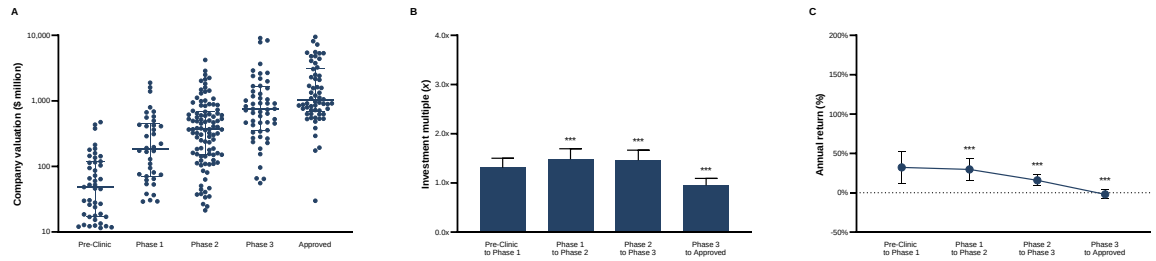


Figure 55: Company valuation (A), investment multiples (B), and annual returns (C) by development stage for the entire sample

Notes: All valuation metrics are inflation-adjusted to 2020. For visualization purposes, five observations with an acquistion value beyond $10,000 million are not shown in this graph A. P Values calculated based on ANOVA with Dunnett's test compared to Pre-Clinic to Phase 1: *p<.05, **p<.01, ***p<.001.

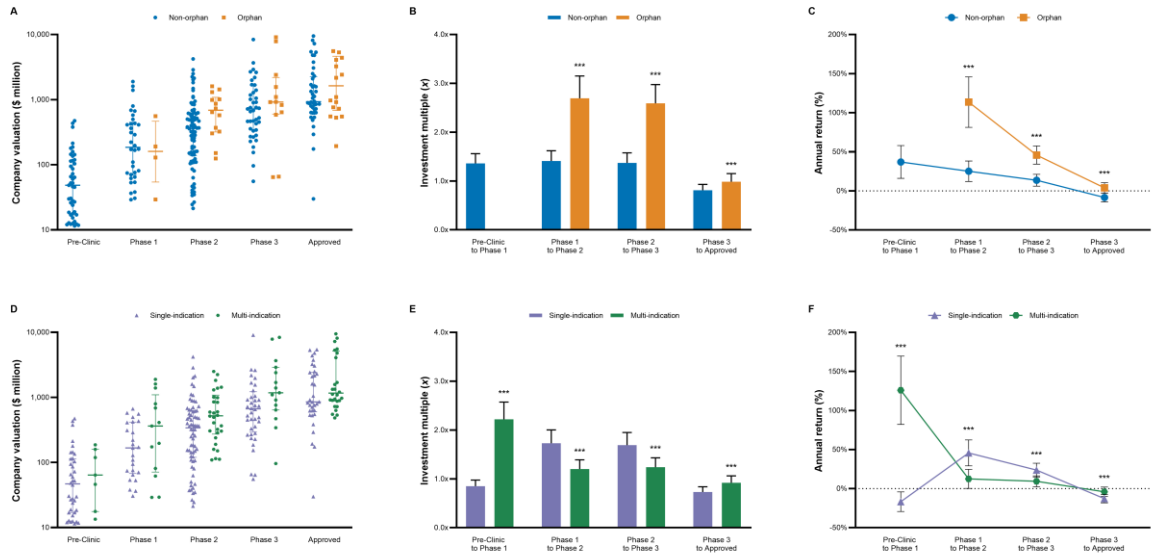


Figure 56: Company valuation, investment multiples, and annual returns by lead drug's FDA orphan designation status and number of indications

Notes: Graphs in the first row compare the valuation (A), investment multiples (B), and annual returns (C) for companies with orphan- and non-orphan-designated lead drugs by development stage. Graphs in the second row compare the valuation (D), investment multiples (E), and returns (F) for companies with multi-indication and single-indication lead drugs by development stage. Valuation data from our sample of 311 Biopharma acquisitions (2005-2020) were inflation-adjusted to 2020 values and combined with previously published success rates and development periods to calculate multiples and returns.[273,274] No valuation data exist for the Pre-Clinic orphan category given that the FDA only issues the orphan designation status after IND approval. For visualization purposes, five observations with an acquistion value beyond $10,000 million are not shown in this graphs A and D. P values were calculated based on ANOVA with Dunnett's test: *p<.05; **p<.01; ***p<.001.

Abbreviations: FDA, US Food and Drug Administration; IND, investigational new drug application.

Bioentrepreneurs and investors that keep their equity stake in a company with an orphan-designated product from Phase 1 until FDA approval can expect to increase their initial capital by 7.2x (95%CI 5.6–9.0) which translates to annual returns of 46% (95%CI 37–56) after adjusting for drug failures (Table 52). In contrast, a similar investment in companies developing non-orphan-designated products would increase the initial capital by only 2.1x (95%CI 1.6–2.6, p<.001) at annual returns of 12% (95%CI 8–16, p<.001).

	Investment Multiple (x)			Annual Return (%)		
	Value	95% CI [a]	*P-Value*	Value	95% CI [a]	*P-Value*
FDA Orphan Designation Status						
Orphan	7.2x	(5.6-9.0)	*<.001*	46%	(37-56)	*<.001*
Non-Orphan	2.1x	(1.6-2.6)		12%	(8-16)	
Number of Indications						
Multi-Indication	2.9x	(2.3-3.7)	*<.001*	21%	(15-29)	*<.001*
Single-Indication	1.7x	(1.3-2.2)		11%	(7-14)	
Molecule Type						
Biologic or Gene/Cell Therapy	1.8x	(1.4-2.2)	*<.001*	16%	(11-21)	*<.001*
Small-Molecule	3.6x	(2.8-4.5)		19%	(15-25)	
Disease Area						
Oncology	4.3x	(3.5-5.4)	*<.001*	26%	(21-33)	*<.001*
CNS	2.6x	(2.0-3.2)		17%	(13-22)	
Other [b]	1.5x	(1.2-1.9)		8%	(4-11)	
Overall	**2.6x**	**(2.0-3.3)**		**15%**	**(11-19)**	

Table 52: Estimated multiples and returns for investment in drug development Biopharma companies

Notes: Multiples and annual returns were estimated assuming an investment horizon from Pre-Clinic until FDA approval. Valuation data from our sample of 311 biopharma acquisitions (2005-2020) was inflation-adjusted to 2020 values and combined with previously published success rates and development periods to calculate multiples and returns.[273,274]

[a] 95% confidence intervals were calculated based on empirical 2.5th and 97.5th percentiles from the conducted sensitivity analysis.
[b] The disease category other includes immunology, infectious disease, cardiovascular, dermatology, internal medicine, and ophthalmology.

Abbreviations: FDA, US Food and Drug Administration; CNS, Central nervous system.

10.4.1 Number of indications

Valuations of companies developing multi-indication relative to single-indication lead drugs were significantly higher for Phase 1 ($594 vs. $230 million, p<.05), Phase 2 ($1058 vs. $522 million, p<.05), and Approved ($3438 vs. $1670 million, p<.01), yet not Pre-Clinic ($87 vs. $88 million, p=.484) and Phase 3 ($2249 vs. $1578 million, p=.208) development stages. However, estimated multiples of investments in companies with multi-indication relative to single-indication therapeutics were only higher for Pre-Clinic to Phase 1 and Phase 3 to Approved investments periods (p<.001). For Phase 1 to 2 and Phase 2 to 3, investment multiples of companies with single-indication therapeutics outpace multi-indication products (p<.001). Similarly, estimated returns were higher for investments in companies with multi-indication relative to single-indication therapeutics for Pre-Clinic to Phase 1 (126% vs. -16%, p<.001) and Phase

3 to Approved (-4% vs. -12%, p<.001), yet not for Phase 1 to 2 (12% vs. 45%, p<.001), Phase 2 to 3 (9% vs. 24%, p<.001).

Equity stakes in Biopharma companies with multi-indication lead products increased by 2.9x (95%CI 2.3–3.7) yielding annualized returns of 21% (95%CI 15–29) – assuming shareholders keep their stakes from Pre-Clinic to FDA approval (Table 52). In contrast, single-indication lead products only provided an overall investment multiple of 1.7x (95%CI 1.3–2.2, p<.001) and annualized returns of 11% (95%CI 7–14, p<.001).

10.4.2 Molecule type

Companies developing biologics or gene and cell therapies were valued higher relative to small-molecules during Pre-Clinic ($109 vs. $71 million, p<.05), Phase 1 ($341 vs. $325 million, p=.139), Phase 2 ($811 vs. $517 million, p<.05), and Phase 3 ($2,249 vs. $1,578 million, p=.103) yet not Approved development stages ($2088 vs. $2105 million, p=.161). However, estimated returns for investments in companies with biologics or gene and cell therapies were lower for Pre-Clinic to Phase 1 (18% vs. 46%, p<.001), higher for Phase 1 to 2 (93% vs. 23%, p<.001), the same for Phase 2 to 3 (14% vs. 15%, p=.53), and lower for Phase 3 to Approved (-29% vs. 11%, p<.001) development stages relative to small molecules (Figure 57).

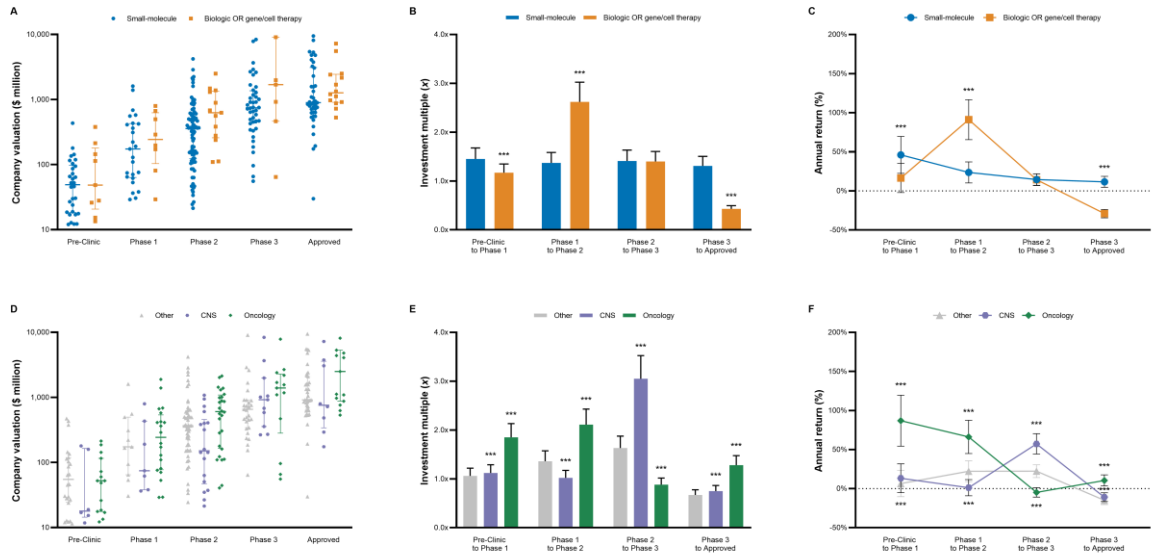


Figure 57: Company valuation, investment multiples, and annual returns by lead drug's molecule type and disease area

Notes: Graphs in the first row compare the valuation (A), investment multiples (B), and annual returns (C) for companies with biologics or gene/cell therapies and small-molecule lead drugs by development stage. Graphs in the second row compare the valuation (D), investment multiples (E), and returns (F) for companies with lead drugs in oncology, CNS, and other disease areas by development stage. Valuation data from our sample of 311 Biopharma acquisitions (2005-2020) were inflation-adjusted to 2020 values and combined with previously published success rates and development periods to calculate multiples and returns.[273,274] The disease category other includes immunology, infectious disease, cardiovascular, dermatology, internal medicine, and ophthalmology. For visualization purposes, five observations with an acquistion value beyond $10,000 million are not shown in this graphs A and D. P values were calculated based on ANOVA with Dunnett's test (Sidak's test for disease area): *p<.05; **p<.01; ***p<.001.

Abbreviations: CNS, central nervous system.

Bioentrepreneurs and investors that keep their equity stake in a company with a biologic or gene therapeutic lead product from Phase 1 until FDA approval can expect to increase their initial capital by 1.8x (95%CI 1.4–2.2) which translates to annual returns of 16% (95%CI 11–21) after adjusting for drug failures (Table 52). In contrast, a similar investment in companies developing small-molecule drugs would see their capital grow by 3.6x (95%CI 2.8–4.5, p<.001) at annual returns of 19% (95%CI 15–25, p<.001).

10.4.3 Disease area

Companies with oncology drugs were valued significantly higher during Phase 2 development ($1068, p<.05), while companies with CNS lead drugs ($314 million, p<.001) were valued

lower than other companies ($607 million). Simulated returns of investments into oncology relative to CNS lead drugs were significantly higher for Pre-Clinic to Phase 1 (89% vs. 13%, p<.001), Phase 1 to Phase 2 (66% vs. 2%, p<.001), Phase 3 to Approved (10% vs. -11%, p<.001), yet not Phase 2 to 3 (-5% vs. 57%, p<.001).

Assuming an investment horizon from Pre-Clinic to FDA approval, founders and capital providers of Biopharma companies with oncology therapeutics can expect to increase their invested capital to a greater extent compared to companies developing CNS and other therapeutic agents (p<.001). Estimated annual returns from Pre-Clinic to FDA approval were 26% (95%CI 21–33) for oncology, 17% (95%CI 13–22) for CNS, and 8% (95%CI 4–11) for other lead therapeutics (Table 52).

10.5 Discussion and conclusion

This study first assessed the association of Biopharma company valuation with development stage, FDA orphan designation status, number of indications, molecule type, and disease area based on a sample of 311 Biopharma acquisitions from 2005 to 2020. Thereafter, company valuations were combined with previously published clinical development periods and success rates to estimate investment multiples and annual returns. Orphan-designated (46%), oncology (26%), CNS (17%), multi-indication (21%), and small-molecule (19%) drugs were projected to provide significantly higher than average (15%) annual returns to company shareholders holding equity stakes from Pre-Clinic to FDA approval (p<.001). These results provide Bioentrepreneurs with first insights into the valuation and potential of their ventures. On the other side, results educate financial and strategic financiers on investment opportunities with favorable risk-return profiles.

Our dataset illustrates that Biopharma company valuation is mainly driven by the lead product's development stage. This is in line with previous studies investigating Biopharma acquisitions

and therapeutic licensing agreements.[236,246,253] Our calculations also demonstrate downward-sloping annual returns for advanced drug development stages (Figure 55). Assuming annual returns are correlated to an investment's risk, this result implies risk is unequally distributed across the drug development process. This observation is coherent with expectations given that the pre-clinical drug discovery process and early clinical development are associated with several unknown factors and incur higher attrition rates than late-stage clinical development.[273,274] The more pre-clinical and clinical data are available on a drug, the lower the uncertainty and also the risk of failure, resulting in diminished returns. Overall, we calculated annual returns of 15% throughout the drug development process. This is slightly higher than previous estimates of mean industry returns for new drug introductions of 11.5%.[278] These estimates are based on new drug launches from the 1990s in large, publically listed Biopharma companies, whereas our estimate is derived from riskier acquisitions of private and public small to medium-sized Biopharma ventures from 2005 to 2020.

In contrast to Rooswinkel et al.,[249] our dataset of 311 Biopharma acquisitions demonstrates that late-stage valuations were significantly higher for companies developing orphan relative to non-orphan lead products. Accordingly, we also estimated higher investment multiples and returns for shareholders of companies with orphan relative non-orphan-designated lead products from Phase 1 to FDA approval (46% vs. 12%, $p<.001$). Several reasons may help to explain this observation. Orphan drugs possess favorable economics given the lower clinical and FDA attrition rates, firmer and prolonged market exclusivity periods, financial R&D incentives, expedited development and FDA approval periods, swift market penetration, and greater reimbursement prices.[143,180,254] Particularly the higher success rates for orphan drugs may explain why we observed higher returns for orphan than non-orphan drugs; yet, we did not observe significantly higher company valuations in Chapter 9. Furthermore, the comparison of firm value by orphan vs. non-orphan drugs in development stages may be biased as orphan drugs more frequently

receive approval based on early clinical evidence from phase 1 or 2 trials rather than large phase 3 trials.[76,174] This bias could help to explain why the valuation difference was only significant after the lead drug received FDA approval. Consequently, Bioentrepreneurs developing orphan-designated products can negotiate higher company valuations with financial investors. On the other side, investors may particularly seek to invest in orphan drugs as their unique economics translate to a favorable financial risk-return profile.

In 2019, the ten highest-grossing drugs were all authorized and commercialized across more than one therapeutic indication. Accordingly, results demonstrate that late-stage valuations were significantly higher for companies developing multi-indication relative to single-indication lead products. Similarly, we calculated that an investment in pre-clinical companies with multi-indication lead products yields annual returns of 21% until FDA approval, whereas single-indication products only provide a return of 11% per year. Multi-indication therapeutics provide companies with an upside option to develop and commercialize the drug across several diseases if it proves to be safe and efficacious in initial trials. Additionally, early drug discovery efforts and timelines can be dynamically offset as they are only undertaken once per drug.[38,40,48] Furthermore, companies may engage in the sequencing of indications according to clinical benefit and patient population to establish higher drug prices and revenues under prevailing single-price policies.[38,39,41] Consequently, Bioentrepreneurs must be aware of the upside real option value their therapeutic could offer to large Biopharma corporations when engaging in acquisition or licensing deals. Oppositely, strategic investors can benefit from the large market potential and favorable risk-return profile of multi-indication products.

The collected dataset of 311 Biopharma acquisitions did not reveal any significant valuation difference for companies with small molecules compared to biologic or gene/cell therapy lead products. Nonetheless, we estimated that shareholders of Biopharma companies developing small molecules can expect higher returns than companies developing biologics or gene/cell

therapies (19% vs. 16%, p<.001). This result is surprising as one might expect that the often superior clinical safety and efficacy profile of biologics and gene/cell therapeutics – which frequently permit the treatment or even cure of previously untreatable disease – would translate into a greater economic and financial benefit.[180,256–258] Nonetheless, these clinical benefits could be offset by large initial investment outlay, higher production costs, inconvenient administration routes, and reimbursement hurdles often faced by biologics and gene/cell therapies.[259,260] Consequently, purely financial investors should be cautious about venture opportunities in biologics and gene/cell therapies. On the contrary, large Biopharma corporations could potentially benefit from strategic investments into such technologies as this provides them access to the capabilities and human capital of the innovative venture.[235]

Small and large Biopharma ventures alike frequently focus their R&D efforts on disease areas with high unmet patient needs – oncology and CNS.[246,251] However, our dataset did not exhibit a significant difference in company valuation according to therapeutic area. Nonetheless, our calculations show higher returns for shareholders with oncology (26%) and CNS (17%) products relative to other (8%) therapeutic areas (p<.001) from Pre-Clinic to FDA approval. This discrepancy might have multifactorial reasons. From a clinical perspective, oncology drugs offer a survival benefit for patients and often also improve quality of life.[73,85] In contrast, drugs in other areas mostly improve patients' quality of life without a proven effect on overall survival. Consequently, higher annual treatment costs and drug prices are observed for cancer drugs.[122] While some authors argue that these high prices are justified by providing clinical value to patients in areas of high unmet, Prasad et al. argue that the observed prices cannot be explained by rational arguments such as R&D costs and the absence of treatment alternatives.[279] As a result, Biopharma companies stand to make a profit on this mismatch between high prices yet arguably marginal benefit for patients.[86] Additionally, many cancer drugs are launched for

rare diseases, whereby Biopharma companies realize the previously discussed favorable economics of the FDA orphan designation status. Moreover, Biopharma companies could profit from launching me-too drugs that are priced similarly to first-in-class agents yet consume less R&D resources.[112] A combination of all these factors helps to explain the estimated higher returns of investments in companies developing oncology drugs.

10.5.1 Strengths and limitations

Strengths of this study include its large sample size, uniquely detailed drug characteristics, and employed modeling technique. However, this study also has several limitations. First, non-disclosed information may bias results. Specifically, undisclosed acquisitions of very early-stage pre-clinical corporations may not be released and thereby overestimate company valuations of the pre-clinical development stage, which in turn causes returns to be underestimated.

Second, investment multiples and returns were estimated based on a cross-section of company valuations. Detailed longitudinal data entailing a company's valuation alongside its drug's development stage and characteristics would be necessary to correctly evaluate real returns received by Bioentrepreneurs and investors. However, given that this information is not publicly disclosed our employed methodology of combining company valuation with success rates and development periods may offer first insights into the investment characteristics of this industry. Particularly, we calculated mean valuations per development stage to then estimate multiples and returns for the transition between stages. Mathematically this methodology may yield different results than calculating multiples and returns of several companies that are observed across all development stages in a longitudinal panel dataset to then calculate mean estimates. Especially outliers may bias our results. Extremely high valuations in the later development stage and extremely low valuations in the early development stage would result in greater estimates for multiples and returns, and vice versa. Given the breadth of our dataset, the present

sample, nonetheless, offers the closest feasible approximation for multiples and returns and allows to conclude investment trends for drug development companies.

Third, our analysis only captures value arising from the lead product. Biopharma companies in our sample frequently develop numerous drugs at the same time. Therefore, a more detailed modeling technique capturing the further product portfolio's value is necessary to more realistically estimate investment multiples and returns. However, our assumption of only considering the development stage of the lead product may account for most of a company's value given that products usually share a similar technology or mechanism of action. Consequently, if the lead product fails a development stage, the likelihood of the other products failing could be similarly high. Moreover, early-stage developments of additional indications for a company's lead drug may not be disclosed. Therefore, data on the total number of indications may have been missing and could consequently bias results. Nevertheless, this effect is assumed to be minor given that a company's main value driver remains the lead drug's first (most advanced) indication.

Finally, our methodology projected overall negative returns for the Phase 3 to FDA approval investment period. Valuation of companies in the Approved development stage also includes products that have already been on the market for some years and could consequently face loss of exclusivity. As a result, our sample may underestimate the Biopharma company valuation right after FDA approval, which thereby also underestimates returns.

10.6 Authors contributions

Daniel Tobias Michaeli: data collection, statistical analysis, visualization, writing, and editing. Hasan Basri Yagmur: data collection, statistical analysis, supervision, and review. Timur Achmadeev: data collection and editing. Thomas Michaeli: supervision, editing, and review.

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Appendix

Drug	Indication			Hazard Ratio (95% CI)	Weight (%)
	Approval Date	*Treatment Line*	*Disease*	*Overall Survival*	
Idelalisib	23.07.2014	2nd line	CLL/SLL	0.37 (0.14-0.98)	0.14
Sunitinib	20.05.2011	1st line	NET	0.41 (0.19-0.89)	0.20
Polatuzumab vedotin-piiq	10.06.2019	≥3rd line	DLBCL	0.42 (0.24-0.75)	0.35
Vemurafenib	17.08.2011	1st line	Melanoma	0.44 (0.33-0.59)	0.91
Glasdegib	21.11.2018	1st line	AML	0.46 (0.3-0.71)	0.50
Ibrutinib	28.07.2014	1st line	CLL	0.46 (0.2-1.07)	0.14
Pembrolizumab	30.10.2018	1st line	NSCLC	0.49 (0.38-0.64)	0.91
Sunitinib	26.01.2006	2nd line	GIST	0.49 (0.29-0.83)	0.32
Eribulin Mesylate	28.01.2016	2nd line	Liposarcoma	0.51 (0.35-0.75)	0.51
Lutetium Lu 177 dotatate	16.01.2018	1st line	NET	0.52 (0.32-0.84)	0.34
Olaratumab	19.10.2016	1st line	STS	0.52 (0.34-0.79)	0.43
Axitinib	19.04.2019	1st line	RCC	0.53 (0.38-0.74)	0.60
Pembrolizumab	19.04.2019	1st line	RCC	0.53 (0.38-0.74)	0.60
Trametinib	29.05.2013	1st line	Melanoma	0.56 (0.33-0.95)	0.25
Bortezomib	25.03.2005	2nd line	Multiple Myeloma	0.57 (0.4-0.81)	0.50
Dabrafenib	30.04.2018	1st line	Melanoma	0.57 (0.42-0.79)	0.58
Azacitidine	19.05.2004	1st line	MDS	0.58 (0.43-0.77)	0.65
Bevacizumab	29.05.2020	1st line	HCC	0.58 (0.42-0.79)	0.58
Dinutuximab	10.03.2015	2nd line	Neuroblastoma	0.58 (0.37-0.91)	0.32
Atezolizumab	29.05.2020	1st line	HCC	0.58 (0.42-0.79)	0.58
Fam-trastuzumab deruxtecan-nxki	15.02.2021	1st line	Gastric Cancer	0.59 (0.39-0.88)	0.37
Nivolumab	04.03.2015	2nd line	NSCLC	0.59 (0.44-0.79)	0.62
Atezolizumab	18.05.2020	1st line	NSCLC	0.59 (0.4-0.89)	0.37
Cabozantinib	22.01.2021	1st line	RCC	0.6 (0.4-0.89)	0.37
Encorafenib	08.04.2020	2nd line	Colorectal Cancer	0.6 (0.45-0.79)	0.65
Acalabrutinib	21.11.2019	1st line	CLL	0.6 (0.28-1.27)	0.11
Cetuximab	24.09.2021	2nd line	Colorectal Cancer	0.6 (0.45-0.79)	0.65
Pembrolizumab	24.10.2016	1st line	NSCLC	0.6 (0.41-0.89)	0.39
Nivolumab	22.01.2021	1st line	RCC	0.6 (0.4-0.89)	0.37
Encorafenib	27.06.2018	1st line	Melanoma	0.61 (0.47-0.79)	0.70
Enzalutamide	31.08.2012	2nd line	Prostate Cancer	0.62 (0.52-0.73)	1.13
Atezolizumab	08.03.2019	1st line	Breast Cancer	0.62 (0.45-0.86)	0.50
Obinutuzumab	26.02.2016	2nd line	Follicular Lymphoma	0.62 (0.39-0.98)	0.27
Elotuzumab	06.11.2018	≥3rd line	Multiple Myeloma	0.62 (0.3-1.28)	0.11
Abiraterone	07.02.2018	1st line	Prostate Cancer	0.62 (0.51-0.76)	0.96
Cobimetinib	10.11.2015	1st line	Melanoma	0.63 (0.47-0.85)	0.56
Regorafenib	27.04.2017	2nd line	HCC	0.63 (0.5-0.79)	0.80
Ipilimumab	16.04.2018	1st line	RCC	0.63 (0.44-0.89)	0.43
Nivolumab	16.04.2018	1st line	RCC	0.63 (0.44-0.89)	0.43
Everolimus	26.02.2016	1st line	NET	0.64 (0.4-1.05)	0.23
Gilteritinib	28.11.2018	2nd line	AML	0.64 (0.49-0.83)	0.65
Pembrolizumab	30.07.2019	2nd line	Esophageal Cancer	0.64 (0.46-0.9)	0.44
Pembrolizumab	13.10.2021	1st line	Cervical Cancer	0.64 (0.5-0.81)	0.73
Pertuzumab	06.08.2012	1st line	Breast Cancer	0.64 (0.47-0.88)	0.50
Bortezomib	08.10.2014	1st line	Multiple Myeloma	0.65 (0.51-0.84)	0.68
Lenvatinib	10.08.2021	1st line	RCC	0.66 (0.49-0.88)	0.53
Cabozantinib	25.04.2016	2nd line	RCC	0.66 (0.53-0.83)	0.77
Bevacizumab	26.02.2004	1st line	Colorectal Cancer	0.66 (0.54-0.81)	0.87
Ipilimumab	25.03.2011	1st line	Melanoma	0.66 (0.51-0.87)	0.60
Brentuximab vedotin	16.11.2018	1st line	T-cell Lymphoma	0.66 (0.46-0.95)	0.37
Pembrolizumab	10.08.2021	1st line	RCC	0.66 (0.49-0.88)	0.53
Dabrafenib	29.05.2013	1st line	Melanoma	0.67 (0.28-1.58)	0.06
Lenvatinib	13.05.2016	2nd line	RCC	0.67 (0.42-1.08)	0.22
Apalutamide	14.02.2019	1st line	Prostate Cancer	0.67 (0.51-0.89)	0.56
Trifluridine; Tipiracil	22.09.2015	2nd line	Colorectal Cancer	0.68 (0.58-0.81)	1.03
Cemiplimab-rwlc	22.02.2021	1st line	NSCLC	0.68 (0.53-0.87)	0.65
Obinutuzumab	01.11.2013	1st line	CLL/SLL	0.68 (0.29-1.6)	0.06
Trastuzumab Emtansine	22.02.2013	2nd line	Breast Cancer	0.68 (0.55-0.85)	0.76
Azacitidine	01.09.2020	2nd line	AML	0.69 (0.55-0.86)	0.73
Trifluridine; Tipiracil	22.02.2019	≥3rd line	metastatic GEJ cancer	0.69 (0.56-0.85)	0.80
Sorafenib	16.11.2007	1st line	HCC	0.69 (0.55-0.87)	0.70
Darolutamide	30.07.2019	1st line	Prostate Cancer	0.69 (0.53-0.88)	0.62
Avelumab	30.06.2020	1st line	Urothelial Cancer	0.69 (0.56-0.86)	0.77
Ipilimumab	26.05.2020	1st line	NSCLC	0.69 (0.55-0.87)	0.70
Nivolumab	26.05.2020	1st line	NSCLC	0.69 (0.55-0.87)	0.70
Radium Ra 223 dichloride	15.05.2013	1st line	Prostate Cancer	0.7 (0.58-0.83)	0.94
Cabazitaxel	17.06.2010	2nd line	Prostate Cancer	0.7 (0.59-0.83)	0.99
Trastuzumab Emtansine	03.05.2019	2nd line	Breast Cancer	0.7 (0.47-1.05)	0.28
Niraparib	29.04.2020	1st line	Ovarian Cancer	0.7 (0.44-1.11)	0.22
Apalutamide	14.02.2018	1st line	Prostate Cancer	0.7 (0.48-1.04)	0.30
Atezolizumab	18.03.2019	1st line	SCLC	0.7 (0.54-0.91)	0.58
Nivolumab	10.11.2016	1st line	HNSCC	0.7 (0.53-0.92)	0.53
Enzalutamide	10.09.2014	1st line	Prostate Cancer	0.71 (0.6-0.84)	0.99
Bevacizumab	14.08.2014	1st line	Cervical Cancer	0.71 (0.54-0.95)	0.50
Ramucirumab	10.05.2019	2nd line	HCC	0.71 (0.53-0.95)	0.48
Elotuzumab	30.11.2015	2nd line	Multiple Myeloma	0.71 (0.54-0.93)	0.53
Ribociclib	18.07.2018	1st line	Breast Cancer	0.72 (0.57-0.92)	0.62
Lorlatinib	03.03.2021	1st line	NSCLC	0.72 (0.41-1.25)	0.14
Sorafenib	20.12.2005	1st line	RCC	0.72 (0.55-0.95)	0.51
Ipilimumab	28.10.2015	1st line	Melanoma	0.72 (0.58-0.88)	0.77
Erlotinib	18.11.2004	2nd line	NSCLC	0.73 (0.61-0.86)	0.95
Temsirolimus	30.05.2007	1st line	RCC	0.73 (0.58-0.92)	0.65
Pazopanib	19.10.2009	1st line	RCC	0.73 (0.53-1)	0.40
Lenvatinib	13.02.2015	2nd line	Thyroid Cancer	0.73 (0.5-1.07)	0.29
Durvalumab	27.03.2020	1st line	SCLC	0.73 (0.59-0.91)	0.70
Pembrolizumab	22.03.2021	1st line	Esophageal Cancer	0.73 (0.62-0.86)	0.99
Pembrolizumab	18.05.2017	2nd line	Urothelial Cancer	0.73 (0.59-0.91)	0.70
Brentuximab vedotin	20.03.2018	1st line	Hodgkin Lymphoma	0.73 (0.6-0.98)	0.56
Nivolumab	23.11.2015	2nd line	RCC	0.73 (0.6-0.89)	0.80
Nivolumab	09.10.2015	2nd line	NSCLC	0.73 (0.6-0.89)	0.80
Cetuximab	01.03.2006	2nd line	HNSCC	0.74 (0.57-0.97)	0.51
Lapatinib	29.01.2010	1st line	Breast Cancer	0.74 (0.5-1.1)	0.27
Abiraterone	28.04.2011	2nd line	Prostate Cancer	0.74 (0.64-0.86)	1.08
Ipilimumab	02.10.2020	1st line	Pleura Mesothelioma	0.74 (0.61-0.89)	0.83
Nivolumab	02.10.2020	1st line	Pleura Mesothelioma	0.74 (0.61-0.89)	0.83
Dacomitinib	27.09.2018	1st line	NSCLC	0.75 (0.59-0.95)	0.61
Carfilzomib	20.08.2020	2nd line	Multiple Myeloma	0.75 (0.49-1.13)	0.24
Inotuzumab ozogamicin	17.08.2017	2nd line	ALL	0.75 (0.57-0.99)	0.48

Abemaciclib	28.07.2017	2nd line	Breast Cancer	0.76 (0.61-0.95)	0.65
Talazoparib	16.10.2018	1st line	Breast Cancer	0.76 (0.55-1.06)	0.35
Cabozantinib	14.01.2019	2nd line	HCC	0.76 (0.63-0.92)	0.80
Pemetrexed	04.02.2004	1st line	Mesothelioma	0.77 (0.61-0.96)	0.62
Regorafenib	27.09.2012	≥3rd line	Colorectal Cancer	0.77 (0.64-0.94)	0.77
Midostaurin	28.04.2017	1st line	AML	0.77 (0.63-0.95)	0.69
Regorafenib	25.02.2013	2nd line	GIST	0.77 (0.42-1.41)	0.11
Panitumumab	29.06.2017	1st line	Colorectal Cancer	0.77 (0.64-0.94)	0.77
Atezolizumab	15.10.2021	2nd line	NSCLC	0.77 (0.51-1.17)	0.22
Pembrolizumab	10.06.2019	1st line	HNSCC	0.77 (0.63-0.93)	0.77
Nivolumab	10.06.2020	2nd line	Esophageal Cancer	0.77 (0.62-0.96)	0.65
Ramucirumab	21.04.2014	2nd line	Gastric Cancer	0.78 (0.6-1)	0.52
Lapatinib	13.03.2007	2nd line	Breast Cancer	0.78 (0.55-1.12)	0.29
Pembrolizumab	10.06.2019	1st line	HNSCC	0.78 (0.64-0.96)	0.70
Ofatumumab	31.08.2016	2nd line	CLL/SLL	0.78 (0.56-1.09)	0.33
Atezolizumab	06.12.2018	1st line	NSCLC	0.78 (0.64-0.96)	0.70
Pemetrexed	02.07.2009	2nd line	NSCLC	0.79 (0.65-0.95)	0.77
Ivosidenib	25.08.2021	2nd line	Cholangiocarcinoma	0.79 (0.56-1.12)	0.30
Bevacizumab	11.10.2006	1st line	NSCLC	0.79 (0.68-0.94)	0.91
Carfilzomib	21.01.2016	2nd line	Multiple Myeloma	0.79 (0.67-0.95)	0.83
Nivolumab	15.05.2020	1st line	NSCLC	0.79 (0.67-0.94)	0.87
Ipilimumab	15.05.2020	1st line	NSCLC	0.79 (0.67-0.94)	0.87
Atezolizumab	18.10.2016	2nd line	NSCLC	0.79 (0.69-0.91)	1.08
Abiraterone	10.12.2012	1st line	Prostate Cancer	0.79 (0.66-0.96)	0.76
Axitinib	04.06.2020	1st line	RCC	0.8 (0.62-1.03)	0.49
Avelumab	14.05.2019	1st line	RCC	0.8 (0.62-1.03)	0.49
Enzalutamide	13.07.2018	1st line	Prostate Cancer	0.8 (0.58-1.09)	0.35
Cetuximab	06.07.2012	1st line	Colorectal Cancer	0.8 (0.67-0.94)	0.87
Cabozantinib	19.12.2017	1st line	RCC	0.8 (0.53-1.21)	0.21
Cetuximab	07.11.2011	2nd line	HNSCC	0.8 (0.64-0.98)	0.65
Atezolizumab	03.12.2019	1st line	NSCLC	0.8 (0.64-0.99)	0.62
Nivolumab	16.04.2021	2nd line	metastatic GEJ cancer	0.8 (0.71-0.9)	1.23
Eribulin Mesylate	15.11.2010	≥3rd line	Breast Cancer	0.81 (0.68-0.96)	0.83
Erlotinib	16.04.2010	2nd line	NSCLC	0.81 (0.7-0.95)	0.95
Erlotinib	11.02.2005	1st line	Pancreatic Cancer	0.81 (0.68-0.97)	0.80
Afatinib	15.04.2016	2nd line	SCLC	0.81 (0.69-0.95)	0.91
Ramucirumab	05.11.2014	2nd line	Gastric Cancer	0.81 (0.68-0.96)	0.83
Aflibercept	08.03.2012	2nd line	Colorectal Cancer	0.81 (0.71-0.93)	1.08
Enzalutamide	16.12.2019	1st line	Prostate Cancer	0.81 (0.53-1.25)	0.19
Pembrolizumab	11.04.2019	1st line	NSCLC	0.81 (0.71-0.93)	1.08
Palbociclib	03.02.2015	1st line	Breast Cancer	0.81 (0.49-1.35)	0.14
Everolimus	30.03.2009	2nd line	RCC	0.82 (0.57-1.17)	0.27
Cabozantinib	29.11.2012	2nd line	Thyroid Cancer	0.83 (0.6-1.14)	0.32
Panitumumab	23.05.2014	1st line	Colorectal Cancer	0.83 (0.7-0.98)	0.83
Ramucirumab	29.05.2020	1st line	NSCLC	0.83 (0.53-1.3)	0.17
Pemetrexed	26.09.2008	1st line	NSCLC	0.84 (0.74-0.96)	1.08
Necitumumab	24.11.2015	1st line	NSCLC	0.84 (0.74-0.96)	1.08
Selinexor	18.12.2020	2nd line	Multiple Myeloma	0.84 (0.57-1.23)	0.22
Bevacizumab	06.12.2016	2nd line	Ovarian Cancer	0.84 (0.69-1.01)	0.70
Ramucirumab	24.04.2015	2nd line	Colorectal Cancer	0.85 (0.73-0.98)	0.95
Olaparib	17.08.2017	≥≥3rd line	Ovarian Cancer	0.85 (0.48-1.51)	0.10
Ofatumumab	19.01.2016	≥3rd line	CLL/SLL	0.85 (0.52-1.37)	0.14
Atezolizumab	30.07.2020	1st line	Melanoma	0.85 (0.64-1.11)	0.40
Bevacizumab	31.07.2009	1st line	RCC	0.86 (0.72-1.04)	0.70
Ramucirumab	12.12.2014	2nd line	NSCLC	0.86 (0.75-0.98)	1.03
Pazopanib	26.04.2012	2nd line	Sarcoma	0.87 (0.67-1.12)	0.43
Ixazomib	20.11.2015	2nd line	Multiple Myeloma	0.87 (0.64-1.18)	0.32
Panobinostat	23.02.2015	≥3rd line	Multiple Myeloma	0.87 (0.69-1.1)	0.50
Bevacizumab	22.02.2008	1st line	Breast Cancer	0.87 (0.72-1.05)	0.68
Neratinib	25.02.2020	≥3rd line	Breast Cancer	0.88 (0.72-1.07)	0.62
Afatinib	12.01.2018	1st line	NSCLC	0.88 (0.66-1.17)	0.35
Everolimus	20.07.2012	2nd line	Breast Cancer	0.89 (0.73-1.1)	0.58
Bevacizumab	13.06.2018	1st line	Ovarian Cancer	0.89 (0.76-1.05)	0.80
Pertuzumab	20.12.2017	1st line	Breast Cancer	0.89 (0.66-1.21)	0.31
Bevacizumab	14.11.2014	≥3rd line	Ovarian Cancer	0.89 (0.69-1.14)	0.43
Vandetanib	06.04.2011	1st line	Thyroid Cancer	0.89 (0.49-1.63)	0.08
Ixabepilone	16.10.2007	2nd line	Breast Cancer	0.9 (0.77-1.05)	0.83
Olaparib	12.01.2018	2nd line	Breast Cancer	0.9 (0.66-1.23)	0.29
Ofatumumab	17.04.2014	1st line	CLL/SLL	0.91 (0.51-1.43)	0.12
Lenvatinib	15.08.2018	1st line	HCC	0.92 (0.79-1.06)	0.87
Sorafenib	22.11.2013	1st line	Thyroid Cancer	0.92 (0.71-1.21)	0.36
Trabectedin	23.10.2015	2nd line	STS	0.93 (0.75-1.15)	0.51
Erlotinib	14.05.2013	1st line	NSCLC	0.93 (0.64-1.35)	0.20
Mogamulizumab-kpkc	08.08.2018	2nd line	T-cell Lymphoma	0.93 (0.61-1.43)	0.15
Bendamustine	20.03.2008	1st line	CLL/SLL	0.97 (0.47-2.01)	0.04
Axitinib	27.01.2012	2nd line	RCC	0.97 (0.8-1.17)	0.57
Panitumumab	27.09.2006	2nd line	Colorectal Cancer	0.99 (0.77-1.27)	0.36
Pemetrexed	19.08.2004	2nd line	NSCLC	0.99 (0.82-1.2)	0.56
Sunitinib	16.11.2017	1st line	RCC	1.01 (0.72-1.44)	0.19
Everolimus	05.05.2011	1st line	PNET	1.05 (0.71-1.55)	0.14
Brentuximab vedotin	17.05.2016	2nd line	Hodgkin Lymphoma	1.15 (0.67-1.97)	0.06
Overall				0.73 (0.72-0.75)	**100.00**

Test for Overall Effect Size = 0: z=86.685, p<.001

Tests for Heterogeneity: I^2=29.6% (95% CI: 12.0-42.5), Q=252.97 (p<.001), tau^2=0.0035

Figure 58: Meta-analysis of all randomized controlled trials reporting overall survival used for FDA approval of new cancer drugs, 2003-2021

Abbreviations: CI, confidence interval; FDA, US Food and Drug Administration.

Drug	Indication			Hazard Ratio (95% CI)	Weight (%)
	Approval Date	*Treatment Line*	*Disease*	*Progression-Free Survival*	
Obinutuzumab	01.11.2013	1st line	CLL/SLL	0.16 (0.11-0.24)	0.56
Ibrutinib	04.03.2016	1st line	CLL	0.16 (0.09-0.28)	0.55
Olaparib	17.08.2017	≥3rd line	Ovarian Cancer	0.17 (0.09-0.32)	0.53
Idelalisib	23.07.2014	2nd line	CLL/SLL	0.18 (0.1-0.31)	0.54
Venetoclax	08.06.2018	2nd line	CLL/SLL	0.19 (0.13-0.28)	0.56
Ibrutinib	24.08.2018	1st line	Morbus Waldenström	0.2 (0.11-0.38)	0.56
Acalabrutinib	21.11.2019	1st line	CLL	0.2 (0.13-0.3)	0.52
Ibrutinib	06.05.2016	1st line	SLL	0.2 (0.15-0.28)	0.55
Lenvatinib	13.02.2015	2nd line	Thyroid Cancer	0.21 (0.16-0.28)	0.57
Lutetium Lu 177 dotatate	16.01.2018	1st line	NET	0.21 (0.13-0.32)	0.55
Cabozantinib	17.09.2021	2nd line	Thyroid Cancer	0.22 (0.15-0.31)	0.54
Ibrutinib	25.01.2019	1st line	CLL/SLL	0.23 (0.15-0.37)	0.50
Vemurafenib	17.08.2011	1st line	Melanoma	0.25 (0.2-0.32)	0.57
Ibrutinib	28.07.2014	1st line	CLL	0.25 (0.14-0.45)	0.53
Niraparib	27.03.2017	2nd line	Ovarian Cancer	0.26 (0.17-0.41)	0.54
Bendamustine	20.03.2008	1st line	CLL/SLL	0.27 (0.17-0.43)	0.52
Regorafenib	25.02.2013	2nd line	GIST	0.27 (0.19-0.39)	0.52
Brentuximab vedotin	09.11.2017	2nd line	T-cell Lymphoma	0.27 (0.17-0.43)	0.54
Lorlatinib	03.03.2021	1st line	NSCLC	0.28 (0.19-0.41)	0.54
Cabozantinib	29.11.2012	2nd line	Thyroid Cancer	0.28 (0.19-0.4)	0.57
Apalutamide	14.02.2018	1st line	Prostate Cancer	0.29 (0.24-0.36)	0.55
Olaparib	19.12.2018	1st line	Ovarian Cancer	0.3 (0.23-0.41)	0.54
Venetoclax	15.05.2019	1st line	CLL/SLL	0.33 (0.22-0.51)	0.51
Dabrafenib	29.05.2013	1st line	Melanoma	0.33 (0.2-0.55)	0.48
Olaparib	08.05.2020	1st line	Ovarian Cancer	0.33 (0.25-0.45)	0.54
Sunitinib	26.01.2006	2nd line	GIST	0.33 (0.24-0.47)	0.51
Everolimus	30.03.2009	2nd line	RCC	0.34 (0.26-0.44)	0.55
Erlotinib	14.05.2013	1st line	NSCLC	0.34 (0.23-0.49)	0.52
Ibrutinib	21.04.2020	1st line	CLL	0.34 (0.22-0.52)	0.55
Pazopanib	26.04.2012	2nd line	Sarcoma	0.35 (0.26-0.48)	0.54
Everolimus	05.05.2011	1st line	PNET	0.35 (0.27-0.45)	0.51
Vandetanib	06.04.2011	1st line	Thyroid Cancer	0.35 (0.24-0.53)	0.56
Rucaparib	06.04.2018	2nd line	Ovarian Cancer	0.36 (0.3-0.45)	0.45
Polatuzumab vedotin-piiq	10.06.2019	≥3rd line	DLBCL	0.36 (0.21-0.63)	0.46
Lenvatinib	13.05.2016	2nd line	RCC	0.37 (0.22-0.62)	0.53
Ivosidenib	25.08.2021	2nd line	Cholangiocarcinoma	0.37 (0.25-0.54)	0.55
Daratumumab	21.11.2016	2nd line	Multiple Myeloma	0.37 (0.27-0.52)	0.54
Lenvatinib	10.08.2021	1st line	RCC	0.39 (0.32-0.49)	0.50
Pembrolizumab	10.08.2021	1st line	RCC	0.39 (0.32-0.49)	0.42
Cetuximab	24.09.2021	2nd line	Colorectal Cancer	0.4 (0.31-0.52)	0.46
Enzalutamide	31.08.2012	2nd line	Prostate Cancer	0.4 (0.32-0.5)	0.56
Encorafenib	08.04.2020	2nd line	Colorectal Cancer	0.4 (0.31-0.52)	0.54
Nivolumab	30.09.2015	1st line	Melanoma	0.4 (0.22-0.71)	0.52
Sunitinib	20.05.2011	1st line	NET	0.43 (0.27-0.67)	0.52
Sorafenib	20.12.2005	1st line	RCC	0.44 (0.35-0.55)	0.56
Cabozantinib	14.01.2019	2nd line	HCC	0.44 (0.36-0.52)	0.54
Ramucirumab	10.05.2019	2nd line	HCC	0.45 (0.34-0.6)	0.55
Everolimus	20.07.2012	2nd line	Breast Cancer	0.45 (0.38-0.54)	0.51
Inotuzumab ozogamicin	17.08.2017	2nd line	ALL	0.45 (0.34-0.61)	0.53
Pazopanib	19.10.2009	1st line	RCC	0.46 (0.34-0.62)	0.50
Osimertinib	18.04.2018	1st line	NSCLC	0.46 (0.37-0.57)	0.46
Regorafenib	27.04.2017	2nd line	HCC	0.46 (0.37-0.56)	0.49
Palbociclib	19.02.2016	2nd line	Breast Cancer	0.46 (0.36-0.59)	0.45
Trametinib	29.05.2013	1st line	Melanoma	0.47 (0.34-0.65)	0.56
Fam-trastuzumab deruxtecan-nxki	15.02.2021	1st line	Gastric Cancer	0.47 (0.31-0.71)	0.49
Afatinib	12.07.2013	1st line	NSCLC	0.47 (0.34-0.65)	0.54
Daratumumab	26.09.2019	1st line	Multiple Myeloma	0.47 (0.33-0.67)	0.50
Trifluridine; Tipiracil	22.09.2015	2nd line	Colorectal Cancer	0.48 (0.41-0.57)	0.54
Cabozantinib	19.12.2017	1st line	RCC	0.48 (0.31-0.74)	0.54
Bevacizumab	22.02.2008	1st line	Breast Cancer	0.48 (0.39-0.61)	0.53
Apalutamide	14.02.2019	1st line	Prostate Cancer	0.48 (0.39-0.6)	0.45
Everolimus	26.02.2016	1st line	NET	0.48 (0.35-0.67)	0.53
Bevacizumab	14.11.2014	≥3rd line	Ovarian Cancer	0.48 (0.38-0.6)	0.56
Obinutuzumab	26.02.2016	2nd line	Follicular Lymphoma	0.48 (0.34-0.68)	0.49
Ramucirumab	21.04.2014	2nd line	Gastric Cancer	0.48 (0.38-0.62)	0.53
Palbociclib	03.02.2015	1st line	Breast Cancer	0.49 (0.32-0.75)	0.50
Olaparib	19.05.2020	2nd line	Prostate Cancer	0.49 (0.38-0.63)	0.51
Regorafenib	27.09.2012	≥3rd line	Colorectal Cancer	0.49 (0.42-0.58)	0.52
Brigatinib	22.05.2020	1st line	NSCLC	0.49 (0.35-0.68)	0.53
Daratumumab	07.05.2018	1st line	Multiple Myeloma	0.5 (0.38-0.65)	0.53
Ofatumumab	19.01.2016	≥3rd line	CLL/SLL	0.5 (0.38-0.66)	0.45
Pembrolizumab	24.10.2016	1st line	NSCLC	0.5 (0.37-0.68)	0.54
Pembrolizumab	18.12.2015	1st line	Melanoma	0.5 (0.39-0.64)	0.53
Cabozantinib	22.01.2021	1st line	RCC	0.51 (0.41-0.64)	0.43
Nivolumab	22.01.2021	1st line	RCC	0.51 (0.41-0.64)	0.48
Eribulin Mesylate	28.01.2016	2nd line	Liposarcoma	0.52 (0.35-0.78)	0.37
Durvalumab	16.02.2018	2nd line	NSCLC	0.52 (0.42-0.65)	0.51
Pembrolizumab	30.10.2018	1st line	NSCLC	0.52 (0.43-0.64)	0.40
Olaparib	01.07.2019	2nd line	Pancreatic Cancer	0.53 (0.35-0.81)	0.51
Alectinib	06.11.2017	1st line	NSCLC	0.53 (0.38-0.73)	0.51
Mogamulizumab-kpkc	08.08.2018	2nd line	T-cell Lymphoma	0.53 (0.41-0.69)	0.51
Pembrolizumab	10.05.2017	1st line	NSCLC	0.53 (0.31-0.91)	0.54
Abemaciclib	26.02.2018	1st line	Breast Cancer	0.54 (0.42-0.7)	0.54
Encorafenib	27.06.2018	1st line	Melanoma	0.54 (0.41-0.71)	0.50
Talazoparib	16.10.2018	1st line	Breast Cancer	0.54 (0.41-0.71)	0.52
Elotuzumab	06.11.2018	≥3rd line	Multiple Myeloma	0.54 (0.34-0.86)	0.49
Panitumumab	27.09.2006	2nd line	Colorectal Cancer	0.54 (0.45-0.67)	0.53
Bevacizumab	26.02.2004	1st line	Colorectal Cancer	0.54 (0.45-0.66)	0.53
Trabectedin	23.10.2015	2nd line	STS	0.55 (0.44-0.7)	0.51
Lapatinib	13.03.2007	2nd line	Breast Cancer	0.55 (0.41-0.74)	0.54
Bortezomib	25.03.2005	2nd line	Multiple Myeloma	0.55 (0.44-0.69)	0.51
Ceritinib	26.05.2017	1st line	NSCLC	0.55 (0.42-0.73)	0.45
Abemaciclib	28.07.2017	2nd line	Breast Cancer	0.55 (0.45-0.68)	0.52
Ribociclib	13.03.2017	1st line	Breast Cancer	0.56 (0.43-0.72)	0.52
Trifluridine; Tipiracil	22.02.2019	≥3rd line	metastatic GEJ cancer	0.56 (0.46-0.68)	0.52
Daratumumab	27.06.2019	1st line	Multiple Myeloma	0.56 (0.43-0.73)	0.52
Cetuximab	07.11.2011	2nd line	HNSCC	0.57 (0.46-0.72)	0.48
Brentuximab vedotin	17.05.2016	2nd line	Hodgkin Lymphoma	0.57 (0.4-0.81)	0.47

Ofatumumab	17.04.2014	1st line	CLL/SLL	0.57 (0.45-0.72)	0.51
Cobimetinib	10.11.2015	1st line	Melanoma	0.58 (0.46-0.72)	0.51
Palbociclib	31.03.2017	1st line	Breast Cancer	0.58 (0.46-0.72)	0.51
Afatinib	12.01.2018	1st line	NSCLC	0.58 (0.43-0.78)	0.51
Cabozantinib	25.04.2016	2nd line	RCC	0.58 (0.45-0.74)	0.52
Olaparib	12.01.2018	2nd line	Breast Cancer	0.58 (0.43-0.8)	0.53
Sorafenib	16.11.2007	1st line	HCC	0.58 (0.45-0.74)	0.51
Erlotinib	18.11.2004	2nd line	NSCLC	0.59 (0.5-0.7)	0.54
Ramucirumab	29.05.2020	1st line	NSCLC	0.59 (0.46-0.76)	0.51
Sorafenib	22.11.2013	1st line	Thyroid Cancer	0.59 (0.46-0.76)	0.53
Bevacizumab	29.05.2020	1st line	HCC	0.59 (0.47-0.76)	0.48
Dacomitinib	27.09.2018	1st line	NSCLC	0.59 (0.48-0.74)	0.53
Cemiplimab-rwlc	22.02.2021	1st line	NSCLC	0.59 (0.49-0.72)	0.53
Atezolizumab	29.05.2020	1st line	HCC	0.59 (0.47-0.76)	0.54
Ribociclib	18.07.2018	1st line	Breast Cancer	0.59 (0.48-0.73)	0.52
Pemetrexed	02.07.2009	2nd line	NSCLC	0.6 (0.49-0.73)	0.53
Bevacizumab	31.07.2009	1st line	RCC	0.6 (0.49-0.72)	0.51
Pembrolizumab	29.06.2020	1st line	Colorectal Cancer	0.6 (0.45-0.8)	0.53
Bevacizumab	06.12.2016	2nd line	Ovarian Cancer	0.61 (0.51-0.72)	0.52
Bortezomib	08.10.2014	1st line	Multiple Myeloma	0.61 (0.49-0.76)	0.49
Pertuzumab	06.08.2012	1st line	Breast Cancer	0.62 (0.51-0.75)	0.53
Bevacizumab	13.06.2018	1st line	Ovarian Cancer	0.62 (0.52-0.75)	0.53
Niraparib	29.04.2020	1st line	Ovarian Cancer	0.62 (0.5-0.76)	0.46
Pembrolizumab	13.10.2021	1st line	Cervical Cancer	0.62 (0.5-0.77)	0.45
Avelumab	30.06.2020	1st line	Urothelial Cancer	0.62 (0.52-0.75)	0.54
Nivolumab	04.03.2015	2nd line	NSCLC	0.62 (0.47-0.81)	0.49
Atezolizumab	08.03.2019	1st line	Breast Cancer	0.62 (0.49-0.78)	0.54
Panobinostat	23.02.2015	≥3rd line	Multiple Myeloma	0.63 (0.52-0.76)	0.54
Carfilzomib	20.08.2020	2nd line	Multiple Myeloma	0.63 (0.46-0.85)	0.46
Atezolizumab	18.05.2020	1st line	NSCLC	0.63 (0.45-0.88)	0.47
Ramucirumab	05.11.2014	2nd line	Gastric Cancer	0.64 (0.54-0.75)	0.54
Lenvatinib	15.08.2018	1st line	HCC	0.64 (0.55-0.75)	0.48
Ipilimumab	25.03.2011	1st line	Melanoma	0.64 (0.5-0.83)	0.44
Alpelisib	24.05.2019	1st line	Breast Cancer	0.65 (0.5-0.85)	0.51
Trastuzumab Emtansine	22.02.2013	2nd line	Breast Cancer	0.65 (0.55-0.77)	0.54
Pembrolizumab	22.03.2021	1st line	Esophageal Cancer	0.65 (0.55-0.76)	0.52
Pembrolizumab	13.11.2020	2nd line	Breast Cancer	0.65 (0.49-0.86)	0.37
Pembrolizumab	14.10.2020	≥3rd line	Hodgkin Lymphoma	0.65 (0.48-0.88)	0.47
Temsirolimus	30.05.2007	1st line	RCC	0.66 (0.53-0.81)	0.51
Bevacizumab	11.10.2006	1st line	NSCLC	0.66 (0.57-0.77)	0.55
Pembrolizumab	30.07.2019	2nd line	Esophageal Cancer	0.66 (0.48-0.92)	0.51
Axitinib	27.01.2012	2nd line	RCC	0.67 (0.55-0.81)	0.52
Olaratumab	19.10.2016	1st line	STS	0.67 (0.44-1.02)	0.51
Bevacizumab	14.08.2014	1st line	Cervical Cancer	0.67 (0.54-0.82)	0.52
Ofatumumab	31.08.2016	2nd line	CLL/SLL	0.67 (0.51-0.88)	0.52
Abiraterone	28.04.2011	2nd line	Prostate Cancer	0.67 (0.59-0.78)	0.51
Pemetrexed	04.02.2004	1st line	Mesothelioma	0.68 (0.59-0.87)	0.53
Ixabepilone	16.10.2007	2nd line	Breast Cancer	0.69 (0.58-0.83)	0.51
Axitinib	19.04.2019	1st line	RCC	0.69 (0.57-0.84)	0.51
Carfilzomib	21.01.2016	2nd line	Multiple Myeloma	0.69 (0.57-0.83)	0.48
Axitinib	04.06.2020	1st line	RCC	0.69 (0.56-0.84)	0.51
Pembrolizumab	19.04.2019	1st line	RCC	0.69 (0.57-0.84)	0.46
Avelumab	14.05.2019	1st line	RCC	0.69 (0.56-0.84)	0.46
Selinexor	18.12.2020	2nd line	Multiple Myeloma	0.7 (0.53-0.93)	0.52
Cetuximab	06.07.2012	1st line	Colorectal Cancer	0.7 (0.57-0.86)	0.45
Cetuximab	01.03.2006	2nd line	HNSCC	0.7 (0.54-0.9)	0.54
Elotuzumab	30.11.2015	2nd line	Multiple Myeloma	0.7 (0.57-0.85)	0.47
Nivolumab	26.05.2020	1st line	NSCLC	0.7 (0.57-0.86)	0.50
Lapatinib	29.01.2010	1st line	Breast Cancer	0.71 (0.53-0.96)	0.38
Erlotinib	16.04.2010	2nd line	NSCLC	0.71 (0.62-0.82)	0.54
Atezolizumab	06.12.2018	1st line	NSCLC	0.71 (0.59-0.85)	0.45
Brentuximab vedotin	16.11.2018	1st line	T-cell Lymphoma	0.71 (0.54-0.93)	0.51
Panitumumab	29.06.2017	1st line	Colorectal Cancer	0.72 (0.58-0.9)	0.54
Obinutuzumab	16.11.2017	1st line	Follicular Lymphoma	0.72 (0.56-0.93)	0.55
Dinutuximab	10.03.2015	2nd line	Neuroblastoma	0.73 (0.5-1.06)	0.51
Cabazitaxel	17.06.2010	2nd line	Prostate Cancer	0.74 (0.64-0.86)	0.46
Atezolizumab	03.12.2019	1st line	NSCLC	0.75 (0.63-0.91)	0.51
Aflibercept	08.03.2012	2nd line	Colorectal Cancer	0.76 (0.66-0.88)	0.47
Erlotinib	11.02.2005	1st line	Pancreatic Cancer	0.76 (0.64-0.92)	0.49
Ramucirumab	12.12.2014	2nd line	NSCLC	0.76 (0.68-0.86)	0.55
Neratinib	25.02.2020	≥3rd line	Breast Cancer	0.76 (0.63-0.93)	0.49
Sunitinib	16.11.2017	1st line	RCC	0.76 (0.59-0.98)	0.52
Brentuximab vedotin	20.03.2018	1st line	Hodgkin Lymphoma	0.77 (0.6-0.98)	0.51
Atezolizumab	18.03.2019	1st line	SCLC	0.77 (0.62-0.96)	0.51
Nivolumab	16.04.2021	2nd line	metastatic GEJ cancer	0.77 (0.68-0.87)	0.54
Midostaurin	28.04.2017	1st line	AML	0.78 (0.66-0.93)	0.41
Durvalumab	27.03.2020	1st line	SCLC	0.78 (0.65-0.94)	0.24
Atezolizumab	30.07.2020	1st line	Melanoma	0.78 (0.63-0.97)	0.49
Gilteritinib	28.11.2018	2nd line	AML	0.79 (0.58-1.09)	0.45
Ramucirumab	24.04.2015	2nd line	Colorectal Cancer	0.79 (0.7-0.9)	0.51
Ipilimumab	26.05.2020	1st line	NSCLC	0.79 (0.57-0.86)	0.50
Ruxolitinib	16.11.2011	1st line	Myelofibrosis	0.81 (0.47-1.39)	0.45
Afatinib	15.04.2016	2nd line	SCLC	0.82 (0.68-1)	0.51
Ixazomib	20.11.2015	2nd line	Multiple Myeloma	0.82 (0.67-1)	0.53
Ipilimumab	15.05.2020	1st line	NSCLC	0.82 (0.69-0.97)	0.49
Nivolumab	16.04.2018	1st line	RCC	0.82 (0.64-1.05)	0.51
Ipilimumab	16.04.2018	1st line	RCC	0.82 (0.64-1.05)	0.45
Nivolumab	15.05.2020	1st line	NSCLC	0.82 (0.69-0.97)	0.50
Necitumumab	24.11.2015	1st line	NSCLC	0.85 (0.74-0.98)	0.49
Eribulin Mesylate	15.11.2010	≥3rd line	Breast Cancer	0.87 (0.71-1.05)	0.49
Nivolumab	23.11.2015	2nd line	RCC	0.88 (0.75-1.03)	0.51
Nivolumab	10.11.2016	1st line	HNSCC	0.89 (0.7-1.13)	0.48
Pemetrexed	26.09.2008	1st line	NSCLC	0.9 (0.79-1.02)	0.47
Panitumumab	23.05.2014	1st line	Colorectal Cancer	0.9 (0.66-0.97)	0.46
Nivolumab	09.10.2015	2nd line	NSCLC	0.92 (0.77-1.11)	0.46
Pembrolizumab	10.06.2019	1st line	HNSCC	0.92 (0.77-1.1)	0.54
Atezolizumab	18.10.2016	2nd line	NSCLC	0.95 (0.82-1.1)	0.52
Pemetrexed	19.08.2004	2nd line	NSCLC	0.97 (0.82-1.17)	0.46
Pembrolizumab	18.05.2017	2nd line	Urothelial Cancer	0.98 (0.81-1.19)	0.45
Nivolumab	02.10.2020	1st line	Pleura Mesothelioma	1 (0.82-1.21)	0.05

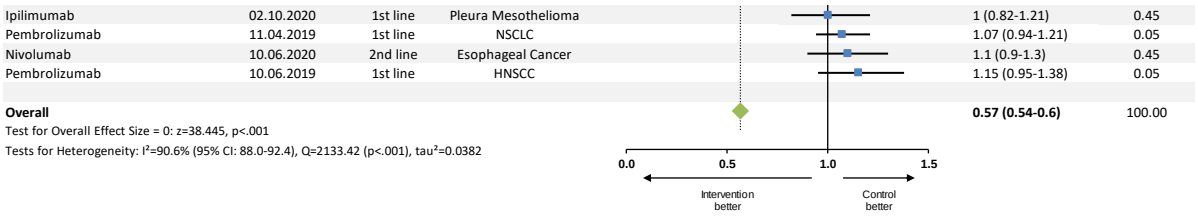

Figure 59: Meta-analysis of all randomized controlled trials reporting progression-free survival used for the FDA approval of new cancer drugs, 2003-2021

Abbreviations: CI, confidence interval; FDA, US Food and Drug Administration.

Drug	Indication			Tumor Response (95% CI)	Weight (%)
	Approval Date	*Treatment Line*	*Disease*	*Relative Risk*	
Pembrolizumab	10.06.2019	1st line	HNSCC	0.55 (0.4-0.74)	1.11
Ipilimumab	02.10.2020	1st line	Pleura Mesothelioma	0.93 (0.77-1.12)	1.08
Nivolumab	02.10.2020	1st line	Pleura Mesothelioma	0.93 (0.77-1.12)	1.09
Atezolizumab	18.03.2019	1st line	SCLC	0.94 (0.8-1.09)	1.15
Nivolumab	10.06.2020	2nd line	Esophageal Cancer	0.97 (0.62-1.5)	0.58
Zanubrutinib	31.08.2021	1st line	Morbus Waldenström	1 (0.86-1.16)	1.14
Pembrolizumab	10.06.2019	1st line	HNSCC	1 (0.8-1.25)	0.99
Pembrolizumab	11.04.2019	1st line	NSCLC	1 (0.84-1.2)	1.08
Degarelix	24.12.2008	1st line	Prostate Cancer	1.01 (0.98-1.05)	1.30
Atezolizumab	18.10.2016	2nd line	NSCLC	1.02 (0.72-1.43)	0.72
Atezolizumab	30.07.2020	1st line	Melanoma	1.02 (0.9-1.16)	1.18
Ramucirumab	29.05.2020	1st line	NSCLC	1.02 (0.92-1.14)	1.22
Daratumumab	26.09.2019	1st line	Multiple Myeloma	1.03 (0.99-1.07)	1.30
Obinutuzumab	16.11.2017	1st line	Follicular Lymphoma	1.03 (1-1.08)	1.29
Brentuximab vedotin	20.03.2018	1st line	Hodgkin Lymphoma	1.04 (0.99-1.09)	1.29
Osimertinib	18.04.2018	1st line	NSCLC	1.04 (0.95-1.13)	1.24
Dacomitinib	27.09.2018	1st line	NSCLC	1.04 (0.93-1.16)	1.20
Erlotinib	11.02.2005	1st line	Pancreatic Cancer	1.04 (0.59-1.85)	0.37
Obinutuzumab	26.02.2016	2nd line	Follicular Lymphoma	1.05 (0.93-1.19)	1.18
Pemetrexed	19.08.2004	2nd line	NSCLC	1.06 (0.63-1.79)	0.41
Necitumumab	24.11.2015	1st line	NSCLC	1.08 (0.9-1.3)	1.04
Acalabrutinib	21.11.2019	1st line	CLL	1.09 (0.99-1.2)	1.22
Alectinib	06.11.2017	1st line	NSCLC	1.09 (0.96-1.24)	1.16
Ixazomib	20.11.2015	2nd line	Multiple Myeloma	1.1 (1.01-1.19)	1.24
Pemetrexed	26.09.2008	1st line	NSCLC	1.1 (0.94-1.29)	1.09
Panobinostat	23.02.2015	≥3rd line	Multiple Myeloma	1.11 (0.99-1.26)	1.17
Carfilzomib	20.08.2020	2nd line	Multiple Myeloma	1.13 (1.02-1.25)	1.20
Daratumumab	27.06.2019	1st line	Multiple Myeloma	1.14 (1.08-1.21)	1.27
Panitumumab	23.05.2014	1st line	Colorectal Cancer	1.15 (0.99-1.34)	1.09
Brentuximab vedotin	16.11.2018	1st line	T-cell Lymphoma	1.15 (1.04-1.28)	1.20
Pertuzumab	06.08.2012	1st line	Breast Cancer	1.16 (1.06-1.26)	1.22
Cetuximab	01.03.2006	2nd line	HNSCC	1.16 (1.02-1.32)	1.14
Durvalumab	27.03.2020	1st line	SCLC	1.17 (1.03-1.34)	1.13
Venetoclax	15.05.2019	1st line	CLL/SLL	1.19 (1.07-1.32)	1.19
Brigatinib	22.05.2020	1st line	NSCLC	1.2 (1.01-1.41)	1.04
Elotuzumab	30.11.2015	2nd line	Multiple Myeloma	1.2 (1.09-1.32)	1.20
Ofatumumab	17.04.2014	1st line	CLL/SLL	1.2 (1.08-1.34)	1.18
Nivolumab	15.05.2020	1st line	NSCLC	1.21 (0.99-1.47)	0.95
Ibrutinib	25.01.2019	1st line	CLL/SLL	1.21 (1.06-1.37)	1.13
Ibrutinib	06.05.2016	1st line	SLL	1.22 (1.11-1.34)	1.20
Pembrolizumab	14.10.2020	≥3rd line	Hodgkin Lymphoma	1.22 (1.02-1.47)	0.98
Daratumumab	21.11.2016	2nd line	Multiple Myeloma	1.22 (1.13-1.32)	1.24
Selinexor	18.12.2020	2nd line	Multiple Myeloma	1.23 (1.08-1.4)	1.12
Ruxolitinib	22.09.2021	2nd line	GVHD	1.23 (1.04-1.45)	1.03
Neratinib	25.02.2020	≥3rd line	Breast Cancer	1.23 (0.97-1.57)	0.82
Daratumumab	07.05.2018	1st line	Multiple Myeloma	1.23 (1.15-1.32)	1.25
Palbociclib	31.03.2017	1st line	Breast Cancer	1.25 (1.03-1.51)	0.95
Nivolumab	16.04.2021	2nd line	metastatic GEJ cancer	1.27 (1.13-1.43)	1.14
Everolimus	26.02.2016	1st line	NET	1.27 (1.08-1.49)	1.03
Enzalutamide	16.12.2019	1st line	Prostate Cancer	1.27 (1.03-1.58)	0.88
Venetoclax	08.06.2018	2nd line	CLL/SLL	1.28 (1.16-1.41)	1.19
Bosutinib	19.12.2017	1st line	CML	1.28 (1.03-1.58)	0.88
Panitumumab	29.06.2017	1st line	Colorectal Cancer	1.29 (1.08-1.53)	0.99
Bevacizumab	26.02.2004	1st line	Colorectal Cancer	1.29 (1.09-1.53)	0.99
Atezolizumab	06.12.2018	1st line	NSCLC	1.3 (1.11-1.52)	1.03
Carfilzomib	21.01.2016	2nd line	Multiple Myeloma	1.31 (1.21-1.42)	1.22
Ramucirumab	21.04.2014	2nd line	Gastric Cancer	1.31 (0.35-4.85)	0.04
Lorlatinib	03.03.2021	1st line	NSCLC	1.31 (1.11-1.55)	1.00
Pembrolizumab	29.06.2020	1st line	Colorectal Cancer	1.32 (0.99-1.76)	0.67
Atezolizumab	18.05.2020	1st line	NSCLC	1.33 (0.93-1.91)	0.51
Bevacizumab	06.12.2016	2nd line	Ovarian Cancer	1.34 (1.16-1.54)	1.07
Pembrolizumab	13.11.2020	2nd line	Breast Cancer	1.34 (1.02-1.75)	0.71
Gilteritinib	28.11.2018	2nd line	AML	1.35 (0.74-2.46)	0.23
Pembrolizumab	13.10.2021	1st line	Cervical Cancer	1.36 (1.18-1.57)	1.05
Bevacizumab	14.08.2014	1st line	Cervical Cancer	1.36 (1.09-1.69)	0.83
Abemaciclib	26.02.2018	1st line	Breast Cancer	1.38 (1.09-1.75)	0.77
Atezolizumab	03.12.2019	1st line	NSCLC	1.41 (1.14-1.74)	0.82
Trastuzumab Emtansine	22.02.2013	2nd line	Breast Cancer	1.41 (1.17-1.7)	0.90
Ribociclib	13.03.2017	1st line	Breast Cancer	1.42 (1.19-1.69)	0.94
Pembrolizumab	05.05.2021	1st line	Gastric Cancer	1.42 (1.17-1.72)	0.87
Trabectedin	23.10.2015	2nd line	STS	1.42 (0.76-2.67)	0.19
Afatinib	15.04.2016	2nd line	SCLC	1.42 (0.55-3.7)	0.08
Ribociclib	18.07.2018	1st line	Breast Cancer	1.44 (1.14-1.8)	0.77
Cetuximab	06.07.2012	1st line	Colorectal Cancer	1.46 (1.24-1.71)	0.96
Ipilimumab	26.05.2020	1st line	NSCLC	1.5 (1.2-1.87)	0.75
Nivolumab	26.05.2020	1st line	NSCLC	1.51 (1.21-1.89)	0.75
Cobimetinib	10.11.2015	1st line	Melanoma	1.51 (1.28-1.78)	0.94
Olaratumab	19.10.2016	1st line	STS	1.52 (0.67-3.48)	0.09
Nivolumab	09.10.2015	2nd line	NSCLC	1.55 (1.05-2.27)	0.38
Pembrolizumab	22.03.2021	1st line	Esophageal Cancer	1.55 (1.28-1.89)	0.82
Ipilimumab	16.04.2018	1st line	RCC	1.57 (1.29-1.91)	0.81
Nivolumab	16.04.2018	1st line	RCC	1.57 (1.29-1.91)	0.81
Encorafenib	27.06.2018	1st line	Melanoma	1.58 (1.29-1.95)	0.77
Cabozantinib	19.12.2017	1st line	RCC	1.6 (1.24-2.04)	0.64
Pembrolizumab	24.10.2016	1st line	NSCLC	1.61 (1.18-2.2)	0.49
Atezolizumab	08.03.2019	1st line	Breast Cancer	1.63 (1.27-2.08)	0.63
Ramucirumab	12.12.2014	2nd line	NSCLC	1.63 (1.28-2.07)	0.65
Axitinib	19.04.2019	1st line	RCC	1.64 (1.42-1.91)	0.94
Pembrolizumab	19.04.2019	1st line	RCC	1.64 (1.42-1.91)	0.94
Lapatinib	13.03.2007	2nd line	Breast Cancer	1.7 (1.11-2.61)	0.28
Ramucirumab	05.11.2014	2nd line	Gastric Cancer	1.73 (1.28-2.33)	0.47
Bevacizumab	22.02.2008	1st line	Breast Cancer	1.74 (1.37-2.22)	0.60
Cemiplimab-rwlc	22.02.2021	1st line	NSCLC	1.77 (1.39-2.26)	0.59
Aflibercept	08.03.2012	2nd line	Colorectal Cancer	1.78 (1.32-2.39)	0.46
Temsirolimus	30.05.2007	1st line	RCC	1.78 (0.84-3.77)	0.09
Cetuximab	07.11.2011	2nd line	HNSCC	1.82 (1.32-2.51)	0.40
Pertuzumab	30.09.2013	1st line	Breast Cancer	1.83 (1.19-2.81)	0.25
Durvalumab	16.02.2018	2nd line	NSCLC	1.87 (1.32-2.66)	0.33

Lapatinib	29.01.2010	1st line	Breast Cancer	1.89 (1.1-3.24)	0.15
Pembrolizumab	18.05.2017	2nd line	Urothelial Cancer	1.91 (1.27-2.88)	0.25
Pembrolizumab	10.05.2017	1st line	NSCLC	1.93 (1.22-3.03)	0.21
Lenvatinib	10.08.2021	1st line	RCC	1.96 (1.69-2.29)	0.82
Pembrolizumab	10.08.2021	1st line	RCC	1.96 (1.69-2.29)	0.82
Axitinib	04.06.2020	1st line	RCC	2 (1.67-2.4)	0.70
Avelumab	14.05.2019	1st line	RCC	2 (1.67-2.4)	0.70
Nilotinib	17.06.2010	1st line	CML	2.01 (1.55-2.59)	0.47
Duvelisib	24.09.2018	≥3rd line	CLL/SLL	2.02 (1.54-2.64)	0.44
Olaparib	01.07.2019	2nd line	Pancreatic Cancer	2.02 (0.92-4.47)	0.06
Elotuzumab	06.11.2018	≥3rd line	Multiple Myeloma	2.03 (1.24-3.32)	0.16
Cabozantinib	22.01.2021	1st line	RCC	2.05 (1.68-2.51)	0.61
Nivolumab	22.01.2021	1st line	RCC	2.05 (1.68-2.51)	0.61
Axitinib	27.01.2012	2nd line	RCC	2.07 (1.41-3.03)	0.25
Bevacizumab	14.11.2014	≥3rd line	Ovarian Cancer	2.12 (1.36-3.29)	0.19
Trifluridine; Tipiracil	22.02.2019	≥3rd line	metastatic GEJ cancer	2.17 (0.63-7.48)	0.02
Bortezomib	25.03.2005	2nd line	Multiple Myeloma	2.18 (1.65-2.88)	0.38
Alpelisib	24.05.2019	1st line	Breast Cancer	2.21 (1.41-3.46)	0.17
Erlotinib	16.04.2010	2nd line	NSCLC	2.23 (1.4-3.55)	0.15
Ibrutinib	24.08.2018	1st line	Morbus Waldenström	2.25 (1.57-3.22)	0.24
Abemaciclib	28.07.2017	2nd line	Breast Cancer	2.25 (1.65-3.09)	0.30
Nivolumab	04.03.2015	2nd line	NSCLC	2.28 (1.21-4.32)	0.08
Bendamustine	20.03.2008	1st line	CLL/SLL	2.29 (1.69-3.11)	0.31
Olaparib	12.01.2018	2nd line	Breast Cancer	2.3 (1.56-3.4)	0.20
Nivolumab	10.11.2016	1st line	HNSCC	2.31 (1.05-5.07)	0.05
Trametinib	22.06.2017	1st line	NSCLC	2.32 (1.56-3.45)	0.19
Ibrutinib	04.03.2016	1st line	CLL	2.33 (1.83-2.97)	0.42
Bevacizumab	11.10.2006	1st line	NSCLC	2.33 (1.8-3.02)	0.38
Obinutuzumab	01.11.2013	1st line	CLL/SLL	2.37 (1.78-3.16)	0.32
Bevacizumab	31.07.2009	1st line	RCC	2.37 (1.71-3.28)	0.26
Atezolizumab	29.05.2020	1st line	HCC	2.4 (1.52-3.8)	0.14
Bevacizumab	29.05.2020	1st line	HCC	2.4 (1.52-3.8)	0.14
Ixabepilone	16.10.2007	2nd line	Breast Cancer	2.42 (1.82-3.21)	0.32
Everolimus	05.05.2011	1st line	PNET	2.45 (0.78-7.69)	0.02
Regorafenib	27.09.2012	≥3rd line	Colorectal Cancer	2.53 (0.3-21.5)	0.00
Pembrolizumab	30.10.2018	1st line	NSCLC	2.54 (1.88-3.43)	0.27
Polatuzumab vedotin-piiq	10.06.2019	≥3rd line	DLBCL	2.6 (1.45-4.66)	0.07
Trametinib	29.05.2013	1st line	Melanoma	2.64 (1.34-5.17)	0.05
Afatinib	12.01.2018	1st line	NSCLC	2.64 (1.77-3.92)	0.15
Everolimus	10.04.2018	1st line	TSC	2.64 (1.65-4.25)	0.11
Regorafenib	27.04.2017	2nd line	HCC	2.69 (1.29-5.61)	0.04
Ceritinib	26.05.2017	1st line	NSCLC	2.71 (2.11-3.49)	0.32
Talazoparib	16.10.2018	1st line	Breast Cancer	2.73 (1.81-4.1)	0.14
Inotuzumab ozogamicin	17.08.2017	2nd line	ALL	2.75 (2.03-3.73)	0.23
Afatinib	12.07.2013	1st line	NSCLC	2.8 (1.84-4.26)	0.12
Eribulin Mesylate	15.11.2010	≥3rd line	Breast Cancer	2.85 (1.48-5.49)	0.05
Pemetrexed	04.02.2004	1st line	Mesothelioma	2.91 (2.02-4.2)	0.15
Lutetium Lu 177 dotatate	16.01.2018	1st line	NET	2.92 (1.1-7.77)	0.02
Dabrafenib	29.05.2013	1st line	Melanoma	2.97 (1.71-5.17)	0.06
Regorafenib	25.02.2013	2nd line	GIST	2.98 (0.37-24.23)	0.00
Eribulin Mesylate	28.01.2016	2nd line	Liposarcoma	3.04 (0.13-73.44)	0.00
Pembrolizumab	30.07.2019	2nd line	Esophageal Cancer	3.06 (1.29-7.27)	0.02
Cabazitaxel	17.06.2010	2nd line	Prostate Cancer	3.27 (1.59-6.73)	0.03
Lenvatinib	15.08.2018	1st line	HCC	3.27 (2.52-4.26)	0.22
Brentuximab vedotin	09.11.2017	2nd line	T-cell Lymphoma	3.31 (1.98-5.53)	0.06
Ivosidenib	25.08.2021	2nd line	Cholangiocarcinoma	3.46 (0.18-65.9)	0.00
Sorafenib	16.11.2007	1st line	HCC	3.55 (0.74-16.94)	0.00
Fam-trastuzumab deruxtecan-nxki	15.02.2021	1st line	Gastric Cancer	3.59 (1.73-7.43)	0.02
Ofatumumab	31.08.2016	2nd line	CLL/SLL	3.75 (2.11-6.67)	0.04
Trifluridine; Tipiracil	22.09.2015	2nd line	Colorectal Cancer	3.99 (0.5-31.7)	0.00
Erlotinib	14.05.2013	1st line	NSCLC	4.09 (2.47-6.78)	0.04
Cabozantinib	25.04.2016	2nd line	RCC	4.29 (2.54-7.22)	0.04
Ramucirumab	10.05.2019	2nd line	HCC	4.34 (0.56-33.76)	0.00
Abiraterone	28.04.2011	2nd line	Prostate Cancer	5.07 (2.06-12.44)	0.01
Idelalisib	23.07.2014	2nd line	CLL/SLL	5.13 (3.22-8.17)	0.03
Nivolumab	30.09.2015	1st line	Melanoma	5.38 (2.09-13.8)	0.01
Nivolumab	23.11.2015	2nd line	RCC	5.51 (3.3-9.23)	0.02
Everolimus	30.03.2009	2nd line	RCC	5.53 (0.31-99.3)	0.00
Sorafenib	20.12.2005	1st line	RCC	5.53 (2.65-11.57)	0.01
Mogamulizumab-kpkc	08.08.2018	2nd line	T-cell Lymphoma	5.78 (2.93-11.38)	0.01
Lenvatinib	13.05.2016	2nd line	RCC	6.21 (1.96-19.68)	0.00
Pembrolizumab	18.12.2015	1st line	Melanoma	6.36 (2.95-13.72)	0.01
Avelumab	30.06.2020	1st line	Urothelial Cancer	6.8 (2.69-17.18)	0.00
Glasdegib	21.11.2018	1st line	AML	6.91 (0.94-50.61)	0.00
Ipilimumab	25.03.2011	1st line	Melanoma	7.45 (1.74-31.94)	0.00
Everolimus	20.07.2012	2nd line	Breast Cancer	7.52 (2.77-20.42)	0.00
Enzalutamide	31.08.2012	2nd line	Prostate Cancer	7.99 (3.99-15.98)	0.01
Bortezomib	08.10.2014	1st line	Multiple Myeloma	8.35 (4.68-14.9)	0.01
Pazopanib	19.10.2009	1st line	RCC	8.8 (3.66-21.19)	0.00
Vemurafenib	17.08.2011	1st line	Melanoma	8.87 (5.03-15.64)	0.01
Erlotinib	18.11.2004	2nd line	NSCLC	9.39 (2.29-38.55)	0.00
Cabozantinib	14.01.2019	2nd line	HCC	9.4 (1.27-69.8)	0.00
Siltuximab	23.04.2014	1st line	Castleman's disease	9.81 (1.39-69.15)	0.00
Ibrutinib	28.07.2014	1st line	CLL	10.16 (3.27-31.6)	0.00
Pazopanib	26.04.2012	2nd line	Sarcoma	10.34 (0.62-171.99)	0.00
Encorafenib	08.04.2020	2nd line	Colorectal Cancer	11.05 (4.04-30.23)	0.00
Cetuximab	24.09.2021	2nd line	Colorectal Cancer	11.05 (4.04-30.23)	0.00
Enzalutamide	10.09.2014	1st line	Prostate Cancer	11.82 (8.69-16.07)	0.01
Sunitinib	26.01.2006	2nd line	GIST	14.75 (0.89-244.78)	0.00
Sunitinib	20.05.2011	1st line	NET	16.8 (0.99-286.6)	0.00
Ruxolitinib	04.12.2014	2nd line	Polycythemia Vera	23.42 (3.22-170.43)	0.00
Sorafenib	22.11.2013	1st line	Thyroid Cancer	24.35 (3.32-178.33)	0.00
Decitabine	02.05.2006	1st line	MDS	28.23 (1.72-464.3)	0.00
Azacitidine	19.05.2004	1st line	MDS	30.68 (1.87-504.13)	0.00
Cabozantinib	17.09.2021	2nd line	Thyroid Cancer	32.7 (2.03-528.13)	0.00
Everolimus	29.10.2010	1st line	SEGA	35.73 (2.25-567.3)	0.00
Panitumumab	27.09.2006	2nd line	Colorectal Cancer	39.17 (2.38-644.93)	0.00
Lenvatinib	13.02.2015	2nd line	Thyroid Cancer	42.41 (10.69-168.28)	0.00
Vandetanib	06.04.2011	1st line	Thyroid Cancer	44.59 (6.31-315.12)	0.00
Cabozantinib	29.11.2012	2nd line	Thyroid Cancer	60.45 (3.77-968.67)	0.00

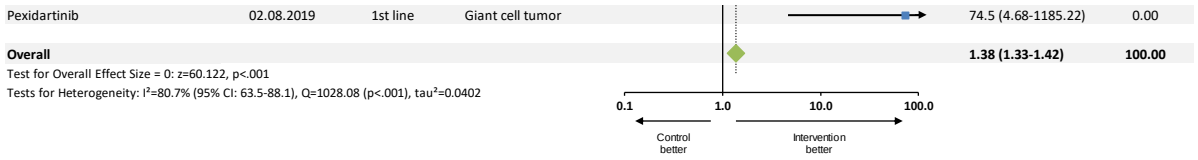

Figure 60: Meta-analysis of all randomized controlled trials reporting tumor response (relative risk) used for the FDA approval of new cancer drugs, 2003-2021

Abbreviations: CI, confidence interval; FDA, US Food and Drug Administration.

Drug	Indication			Tumor Response (95% CI)	Weight (%)
	Approval Date	*Treatment Line*	*Disease*	*Odds Ratio*	
Pembrolizumab	10.06.2019	1st line	HNSCC	0.44 (0.29-0.66)	1.14
Atezolizumab	18.03.2019	1st line	SCLC	0.84 (0.56-1.25)	1.08
Ipilimumab	02.10.2020	1st line	Pleura Mesothelioma	0.88 (0.64-1.22)	1.10
Nivolumab	02.10.2020	1st line	Pleura Mesothelioma	0.88 (0.64-1.22)	1.10
Nivolumab	10.06.2020	2nd line	Esophageal Cancer	0.96 (0.57-1.62)	0.99
Zanubrutinib	31.08.2021	1st line	Morbus Waldenström	0.98 (0.51-1.91)	0.89
Pembrolizumab	10.06.2019	1st line	HNSCC	1 (0.71-1.41)	1.08
Pembrolizumab	11.04.2019	1st line	NSCLC	1 (0.78-1.28)	1.12
Atezolizumab	18.10.2016	2nd line	NSCLC	1.02 (0.69-1.51)	1.05
Erlotinib	11.02.2005	1st line	Pancreatic Cancer	1.05 (0.56-1.96)	0.89
Atezolizumab	30.07.2020	1st line	Melanoma	1.06 (0.74-1.53)	1.06
Pemetrexed	19.08.2004	2nd line	NSCLC	1.06 (0.6-1.89)	0.92
Ramucirumab	29.05.2020	1st line	NSCLC	1.1 (0.71-1.68)	1.01
Necitumumab	24.11.2015	1st line	NSCLC	1.12 (0.86-1.45)	1.10
Pemetrexed	26.09.2008	1st line	NSCLC	1.14 (0.92-1.41)	1.12
Dacomitinib	27.09.2018	1st line	NSCLC	1.16 (0.76-1.76)	1.00
Osimertinib	18.04.2018	1st line	NSCLC	1.2 (0.8-1.79)	1.00
Obinutuzumab	26.02.2016	2nd line	Follicular Lymphoma	1.25 (0.74-2.11)	0.90
Brentuximab vedotin	20.03.2018	1st line	Hodgkin Lymphoma	1.27 (0.94-1.7)	1.06
Panobinostat	23.02.2015	≥3rd line	Multiple Myeloma	1.29 (0.97-1.71)	1.07
Nivolumab	15.05.2020	1st line	NSCLC	1.32 (0.98-1.78)	1.05
Ramucirumab	21.04.2014	2nd line	Gastric Cancer	1.32 (0.34-5.08)	0.26
Panitumumab	23.05.2014	1st line	Colorectal Cancer	1.33 (0.98-1.8)	1.05
Neratinib	25.02.2020	≥3rd line	Breast Cancer	1.34 (0.95-1.9)	1.02
Enzalutamide	16.12.2019	1st line	Prostate Cancer	1.37 (1.04-1.8)	1.06
Obinutuzumab	16.11.2017	1st line	Follicular Lymphoma	1.38 (0.95-2)	0.99
Gilteritinib	28.11.2018	2nd line	AML	1.41 (0.72-2.77)	0.70
Daratumumab	26.09.2019	1st line	Multiple Myeloma	1.42 (0.93-2.17)	0.93
Afatinib	15.04.2016	2nd line	SCLC	1.44 (0.54-3.82)	0.43
Ixazomib	20.11.2015	2nd line	Multiple Myeloma	1.44 (1.02-2.02)	1.00
Alectinib	06.11.2017	1st line	NSCLC	1.45 (0.85-2.45)	0.83
Degarelix	24.12.2008	1st line	Prostate Cancer	1.46 (0.46-4.67)	0.31
Trabectedin	23.10.2015	2nd line	STS	1.47 (0.74-2.91)	0.67
Nivolumab	16.04.2021	2nd line	metastatic GEJ cancer	1.5 (1.23-1.84)	1.10
Bevacizumab	26.02.2004	1st line	Colorectal Cancer	1.52 (1.15-2.02)	1.04
Bosutinib	19.12.2017	1st line	CML	1.52 (1.06-2.19)	0.97
Durvalumab	27.03.2020	1st line	SCLC	1.53 (1.08-2.18)	0.97
Atezolizumab	18.05.2020	1st line	NSCLC	1.54 (0.91-2.6)	0.80
Palbociclib	31.03.2017	1st line	Breast Cancer	1.55 (1.07-2.24)	0.95
Pembrolizumab	29.06.2020	1st line	Colorectal Cancer	1.57 (0.99-2.5)	0.85
Cetuximab	01.03.2006	2nd line	HNSCC	1.61 (1.06-2.43)	0.89
Acalabrutinib	21.11.2019	1st line	CLL	1.61 (0.93-2.79)	0.75
Olaratumab	19.10.2016	1st line	STS	1.64 (0.62-4.31)	0.37
Atezolizumab	06.12.2018	1st line	NSCLC	1.65 (1.22-2.23)	1.00
Pembrolizumab	14.10.2020	≥3rd line	Hodgkin Lymphoma	1.65 (1.04-2.63)	0.83
Nivolumab	09.10.2015	2nd line	NSCLC	1.67 (1.06-2.64)	0.83
Panitumumab	29.06.2017	1st line	Colorectal Cancer	1.68 (1.18-2.38)	0.95
Bevacizumab	14.08.2014	1st line	Cervical Cancer	1.7 (1.17-2.48)	0.91
Pembrolizumab	13.11.2020	2nd line	Breast Cancer	1.72 (1.07-2.76)	0.80
Trastuzumab Emtansine	22.02.2013	2nd line	Breast Cancer	1.73 (1.29-2.32)	0.99
Ribociclib	18.07.2018	1st line	Breast Cancer	1.74 (1.24-2.42)	0.95
Brigatinib	22.05.2020	1st line	NSCLC	1.75 (1.05-2.92)	0.75
Atezolizumab	03.12.2019	1st line	NSCLC	1.75 (1.26-2.44)	0.95
Ruxolitinib	22.09.2021	2nd line	GVHD	1.76 (1.12-2.78)	0.81
Pertuzumab	06.08.2012	1st line	Breast Cancer	1.79 (1.26-2.54)	0.92
Ipilimumab	26.05.2020	1st line	NSCLC	1.8 (1.31-2.48)	0.95
Ramucirumab	12.12.2014	2nd line	NSCLC	1.82 (1.36-2.43)	0.98
Carfilzomib	20.08.2020	2nd line	Multiple Myeloma	1.82 (1.13-2.93)	0.77
Nivolumab	26.05.2020	1st line	NSCLC	1.82 (1.32-2.51)	0.95
Abemaciclib	26.02.2018	1st line	Breast Cancer	1.85 (1.21-2.83)	0.82
Temsirolimus	30.05.2007	1st line	RCC	1.86 (0.84-4.13)	0.43
Ribociclib	13.03.2017	1st line	Breast Cancer	1.89 (1.39-2.57)	0.95
Brentuximab vedotin	16.11.2018	1st line	T-cell Lymphoma	1.91 (1.21-3.01)	0.77
Bevacizumab	06.12.2016	2nd line	Ovarian Cancer	1.91 (1.41-2.6)	0.95
Elotuzumab	30.11.2015	2nd line	Multiple Myeloma	1.92 (1.35-2.73)	0.89
Lapatinib	13.03.2007	2nd line	Breast Cancer	1.92 (1.15-3.22)	0.69
Selinexor	18.12.2020	2nd line	Multiple Myeloma	1.96 (1.27-3.02)	0.78
Aflibercept	08.03.2012	2nd line	Colorectal Cancer	1.97 (1.39-2.78)	0.89
Ipilimumab	16.04.2018	1st line	RCC	1.98 (1.48-2.64)	0.96
Nivolumab	16.04.2018	1st line	RCC	1.98 (1.48-2.64)	0.96
Pembrolizumab	22.03.2021	1st line	Esophageal Cancer	2.01 (1.48-2.72)	0.94
Ramucirumab	05.11.2014	2nd line	Gastric Cancer	2.01 (1.38-2.94)	0.84
Cetuximab	06.07.2012	1st line	Colorectal Cancer	2.06 (1.52-2.8)	0.92
Pembrolizumab	24.10.2016	1st line	NSCLC	2.11 (1.31-3.4)	0.69
Pembrolizumab	13.10.2021	1st line	Cervical Cancer	2.12 (1.5-3)	0.85
Ofatumumab	17.04.2014	1st line	CLL/SLL	2.14 (1.37-3.34)	0.72
Pembrolizumab	18.05.2017	2nd line	Urothelial Cancer	2.16 (1.34-3.49)	0.67
Durvalumab	16.02.2018	2nd line	NSCLC	2.18 (1.43-3.32)	0.74
Bevacizumab	22.02.2008	1st line	Breast Cancer	2.18 (1.57-3.04)	0.86
Trifluridine; Tipiracil	22.02.2019	≥3rd line	metastatic GEJ cancer	2.22 (0.62-7.92)	0.12
Lapatinib	29.01.2010	1st line	Breast Cancer	2.23 (1.14-4.37)	0.44
Cemiplimab-rwlc	22.02.2021	1st line	NSCLC	2.23 (1.6-3.12)	0.85
Venetoclax	15.05.2019	1st line	CLL/SLL	2.23 (1.39-3.59)	0.66
Ibrutinib	06.05.2016	1st line	SLL	2.27 (1.53-3.36)	0.76
Cetuximab	07.11.2011	2nd line	HNSCC	2.27 (1.48-3.5)	0.70
Lorlatinib	03.03.2021	1st line	NSCLC	2.29 (1.39-3.77)	0.61
Axitinib	27.01.2012	2nd line	RCC	2.32 (1.5-3.6)	0.68
Olaparib	01.07.2019	2nd line	Pancreatic Cancer	2.32 (0.92-5.86)	0.24
Atezolizumab	08.03.2019	1st line	Breast Cancer	2.33 (1.53-3.55)	0.70
Pertuzumab	30.09.2013	1st line	Breast Cancer	2.36 (1.29-4.31)	0.48
Erlotinib	16.04.2010	2nd line	NSCLC	2.4 (1.45-3.96)	0.58
Nivolumab	10.11.2016	1st line	HNSCC	2.51 (1.07-5.86)	0.25
Everolimus	05.05.2011	1st line	PNET	2.53 (0.78-8.19)	0.12
Everolimus	26.02.2016	1st line	NET	2.53 (1.46-4.4)	0.49
Regorafenib	27.09.2012	≥3rd line	Colorectal Cancer	2.54 (0.3-21.86)	0.02
Bevacizumab	14.11.2014	≥3rd line	Ovarian Cancer	2.55 (1.49-4.38)	0.50
Axitinib	19.04.2019	1st line	RCC	2.57 (1.95-3.39)	0.88
Pembrolizumab	19.04.2019	1st line	RCC	2.57 (1.95-3.39)	0.88

Cobimetinib	10.11.2015	1st line	Melanoma	2.58 (1.79-3.71)	0.73
Encorafenib	27.06.2018	1st line	Melanoma	2.58 (1.71-3.89)	0.66
Pembrolizumab	05.05.2021	1st line	Gastric Cancer	2.59 (1.55-4.35)	0.52
Nivolumab	04.03.2015	2nd line	NSCLC	2.6 (1.26-5.39)	0.31
Nilotinib	17.06.2010	1st line	CML	2.8 (1.94-4.04)	0.68
Ibrutinib	25.01.2019	1st line	CLL/SLL	2.81 (1.38-5.7)	0.29
Bortezomib	25.03.2005	2nd line	Multiple Myeloma	2.85 (1.98-4.11)	0.68
Alpelisib	24.05.2019	1st line	Breast Cancer	2.88 (1.61-5.16)	0.39
Regorafenib	27.04.2017	2nd line	HCC	2.9 (1.33-6.3)	0.24
Atezolizumab	29.05.2020	1st line	HCC	2.94 (1.72-5.02)	0.43
Bevacizumab	29.05.2020	1st line	HCC	2.94 (1.72-5.02)	0.43
Bevacizumab	31.07.2009	1st line	RCC	2.98 (2-4.45)	0.60
Daratumumab	27.06.2019	1st line	Multiple Myeloma	3.03 (1.88-4.87)	0.48
Bevacizumab	11.10.2006	1st line	NSCLC	3.05 (2.19-4.25)	0.69
Pembrolizumab	10.05.2017	1st line	NSCLC	3.06 (1.45-6.45)	0.23
Axitinib	04.06.2020	1st line	RCC	3.06 (2.3-4.06)	0.78
Avelumab	14.05.2019	1st line	RCC	3.06 (2.3-4.06)	0.78
Regorafenib	25.02.2013	2nd line	GIST	3.07 (0.36-26.05)	0.01
Eribulin Mesylate	15.11.2010	≥3rd line	Breast Cancer	3.08 (1.55-6.15)	0.27
Eribulin Mesylate	28.01.2016	2nd line	Liposarcoma	3.09 (0.12-77.04)	0.00
Trametinib	29.05.2013	1st line	Melanoma	3.1 (1.46-6.59)	0.23
Ixabepilone	16.10.2007	2nd line	Breast Cancer	3.17 (2.22-4.54)	0.63
Elotuzumab	06.11.2018	≥3rd line	Multiple Myeloma	3.2 (1.47-6.97)	0.20
Lutetium Lu 177 dotatate	16.01.2018	1st line	NET	3.21 (1.13-9.15)	0.10
Cabozantinib	22.01.2021	1st line	RCC	3.38 (2.44-4.69)	0.64
Nivolumab	22.01.2021	1st line	RCC	3.38 (2.44-4.69)	0.64
Carfilzomib	21.01.2016	2nd line	Multiple Myeloma	3.38 (2.36-4.85)	0.59
Abemaciclib	28.07.2017	2nd line	Breast Cancer	3.42 (2.22-5.27)	0.47
Daratumumab	07.05.2018	1st line	Multiple Myeloma	3.51 (2.28-5.42)	0.45
Ivosidenib	25.08.2021	2nd line	Cholangiocarcinoma	3.53 (0.18-69.42)	0.00
Daratumumab	21.11.2016	2nd line	Multiple Myeloma	3.56 (2.18-5.81)	0.38
Sorafenib	16.11.2007	1st line	HCC	3.61 (0.74-17.51)	0.03
Pembrolizumab	30.07.2019	2nd line	Esophageal Cancer	3.65 (1.38-9.67)	0.10
Cabazitaxel	17.06.2010	2nd line	Prostate Cancer	3.65 (1.68-7.93)	0.16
Olaparib	12.01.2018	2nd line	Breast Cancer	3.72 (2.15-6.44)	0.30
Everolimus	10.04.2018	1st line	TSC	3.74 (2.03-6.9)	0.24
Cabozantinib	19.12.2017	1st line	RCC	3.94 (1.94-7.98)	0.17
Pembrolizumab	30.10.2018	1st line	NSCLC	3.96 (2.66-5.9)	0.44
Trifluridine; Tipiracil	22.09.2015	2nd line	Colorectal Cancer	4.03 (0.5-32.4)	0.01
Bendamustine	20.03.2008	1st line	CLL/SLL	4.14 (2.54-6.75)	0.31
Afatinib	12.01.2018	1st line	NSCLC	4.3 (2.53-7.32)	0.25
Lenvatinib	10.08.2021	1st line	RCC	4.32 (3.16-5.93)	0.53
Pembrolizumab	10.08.2021	1st line	RCC	4.32 (3.16-5.93)	0.53
Pemetrexed	04.02.2004	1st line	Mesothelioma	4.39 (2.72-7.09)	0.29
Talazoparib	16.10.2018	1st line	Breast Cancer	4.47 (2.6-7.69)	0.23
Trametinib	22.06.2017	1st line	NSCLC	4.5 (2.34-8.64)	0.16
Ramucirumab	10.05.2019	2nd line	HCC	4.5 (0.56-36.05)	0.01
Afatinib	12.07.2013	1st line	NSCLC	4.51 (2.61-7.79)	0.22
Venetoclax	08.06.2018	2nd line	CLL/SLL	4.57 (2.48-8.44)	0.18
Ofatumumab	31.08.2016	2nd line	CLL/SLL	4.75 (2.48-9.13)	0.15
Lenvatinib	15.08.2018	1st line	HCC	4.83 (3.48-6.7)	0.44
Dabrafenib	29.05.2013	1st line	Melanoma	5.1 (2.5-10.37)	0.11
Cabozantinib	25.04.2016	2nd line	RCC	5.16 (2.92-9.1)	0.17
Fam-trastuzumab deruxtecan-nxki	15.02.2021	1st line	Gastric Cancer	5.34 (2.25-12.67)	0.06
Ibrutinib	24.08.2018	1st line	Morbus Waldenström	5.46 (2.72-11)	0.10
Polatuzumab vedotin-piiq	10.06.2019	≥3rd line	DLBCL	5.57 (2.12-14.65)	0.05
Duvelisib	24.09.2018	≥3rd line	CLL/SLL	5.6 (2.99-10.51)	0.12
Everolimus	30.03.2009	2nd line	RCC	5.62 (0.31-102.4)	0.00
Abiraterone	28.04.2011	2nd line	Prostate Cancer	5.73 (2.25-14.57)	0.05
Sorafenib	20.12.2005	1st line	RCC	6.22 (2.88-13.43)	0.06
Obinutuzumab	01.11.2013	1st line	CLL/SLL	6.69 (3.99-11.19)	0.13
Nivolumab	23.11.2015	2nd line	RCC	6.75 (3.88-11.73)	0.11
Ceritinib	26.05.2017	1st line	NSCLC	7.22 (4.58-11.38)	0.14
Avelumab	30.06.2020	1st line	Urothelial Cancer	7.42 (2.87-19.22)	0.03
Mogamulizumab-kpkc	08.08.2018	2nd line	T-cell Lymphoma	7.63 (3.63-16.03)	0.05
Brentuximab vedotin	09.11.2017	2nd line	T-cell Lymphoma	8.03 (3.6-17.91)	0.03
Pembrolizumab	18.12.2015	1st line	Melanoma	8.13 (3.55-18.6)	0.03
Glasdegib	21.11.2018	1st line	AML	8.22 (1.04-65.1)	0.00
Ipilimumab	25.03.2011	1st line	Melanoma	8.24 (1.85-36.76)	0.01
Everolimus	20.07.2012	2nd line	Breast Cancer	8.45 (3.04-23.54)	0.02
Ibrutinib	04.03.2016	1st line	CLL	8.54 (4.85-15.05)	0.07
Lenvatinib	13.05.2016	2nd line	RCC	9.3 (2.54-34.06)	0.01
Cabozantinib	14.01.2019	2nd line	HCC	9.75 (1.3-73.27)	0.00
Erlotinib	14.05.2013	1st line	NSCLC	9.87 (4.79-20.34)	0.03
Inotuzumab ozogamicin	17.08.2017	2nd line	ALL	10.08 (5.37-18.93)	0.04
Erlotinib	18.11.2004	2nd line	NSCLC	10.21 (2.44-42.74)	0.00
Pazopanib	26.04.2012	2nd line	Sarcoma	10.74 (0.64-181.49)	0.00
Enzalutamide	31.08.2012	2nd line	Prostate Cancer	11.08 (5.32-23.11)	0.02
Bortezomib	08.10.2014	1st line	Multiple Myeloma	11.45 (6.15-21.3)	0.03
Nivolumab	30.09.2015	1st line	Melanoma	11.86 (3.79-37.13)	0.01
Pazopanib	19.10.2009	1st line	RCC	12.2 (4.83-30.81)	0.01
Encorafenib	08.04.2020	2nd line	Colorectal Cancer	13.56 (4.78-38.48)	0.01
Cetuximab	24.09.2021	2nd line	Colorectal Cancer	13.56 (4.78-38.48)	0.01
Siltuximab	23.04.2014	1st line	Castleman's disease	15.15 (1.9-120.62)	0.00
Sunitinib	26.01.2006	2nd line	GIST	15.78 (0.93-267.15)	0.00
Vemurafenib	17.08.2011	1st line	Melanoma	16.26 (8.58-30.82)	0.01
Idelalisib	23.07.2014	2nd line	CLL/SLL	17.21 (8.7-34.03)	0.01
Ibrutinib	28.07.2014	1st line	CLL	18.49 (5.24-65.18)	0.00
Sunitinib	20.05.2011	1st line	NET	18.53 (1.05-326.32)	0.00
Enzalutamide	10.09.2014	1st line	Prostate Cancer	27.39 (19.37-38.74)	0.02
Sorafenib	22.11.2013	1st line	Thyroid Cancer	27.41 (3.67-204.62)	0.00
Ruxolitinib	04.12.2014	2nd line	Polycythemia Vera	29.35 (3.89-221.59)	0.00
Decitabine	02.05.2006	1st line	MDS	33.93 (2-577.19)	0.00
Azacitidine	19.05.2004	1st line	MDS	36.58 (2.16-619.31)	0.00
Cabozantinib	17.09.2021	2nd line	Thyroid Cancer	39.89 (2.41-660.17)	0.00
Panitumumab	27.09.2006	2nd line	Colorectal Cancer	42.68 (2.56-711.27)	0.00
Everolimus	29.10.2010	1st line	SEGA	64.4 (3.82-1085.5)	0.00
Vandetanib	06.04.2011	1st line	Thyroid Cancer	79.66 (10.92-580.97)	0.00
Cabozantinib	29.11.2012	2nd line	Thyroid Cancer	82.56 (5.05-1349.47)	0.00
Lenvatinib	13.02.2015	2nd line	Thyroid Cancer	118.48 (28.65-489.95]	0.00

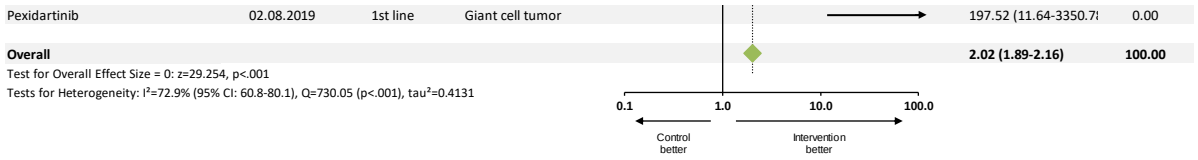

Figure 61: Meta-analysis of all randomized controlled trials reporting tumor response (odds ratio) used for the FDA approval of new cancer drugs, 2003-2021

Abbreviations: CI, confidence interval; FDA, US Food and Drug Administration.

	Variable	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)
(1)	Log(Monthly treatment cost)	1.00																						
(2)	Improvement in OS, %	0.19	1.00																					
(3)	Improvement in PFS, %	0.29*	0.38*	1.00																				
(4)	Multi-indication	-0.18*	-0.02	-0.06	1.00																			
(5)	First-in-class	0.10*	0.18	0.03	0.06	1.00																		
(6)	Targeted	0.05	0.04	-0.22*	0.26*	0.16*	1.00																	
(7)	Biologics	0.02	-0.01	-0.35*	0.13*	0.12*	0.73*	1.00																
(8)	Monotherapy	0.13*	-0.12	0.21*	-0.05	-0.03	-0.10	-0.17*	1.00															
(9)	Hematologic	0.26*	0.33*	0.14	-0.08	0.13*	0.06	-0.03	0.05	1.00														
(10)	Biomarker	-0.11*	-0.03	0.00	0.09	-0.09	-0.22*	-0.26*	0.04	-0.29*	1.00													
(11)	2nd, 3rd, 3+4th line	0.16*	-0.07	0.20*	-0.02	0.00	-0.01	0.08	0.27*	0.19*	-0.16*	1.00												
(12)	Accelerated approval	0.06	0.09	-0.07	-0.02	0.00	0.07	0.02	0.24*	0.06	0.08	0.32*	1.00											
(13)	Log(Enrolled patients in trial)	-0.31*	-0.35*	-0.31*	0.13*	-0.15*	0.02	0.10	-0.33*	-0.27*	-0.04	-0.24*	-0.51*	1.00										
(14)	Phase 3 trial	-0.24*	-0.22*	0.05	0.09	-0.11*	-0.02	0.02	-0.29*	-0.17*	-0.07	-0.27*	-0.65*	0.76*	1.00									
(15)	Randomized controlled trial	-0.28*	0.11	0.10	0.09	-0.05	-0.01	0.04	-0.38*	-0.22*	-0.05	-0.33*	-0.67*	0.77*	0.87*	1.00								
(16)	Double-blind trial	-0.06	-0.01	0.22*	0.03	-0.08	-0.11*	-0.12*	-0.13*	-0.24*	-0.04	-0.15*	-0.31*	0.41*	0.42*	0.44*	1.00							
(17)	Log(Incidence)	-0.34*	-0.22*	-0.26*	0.05	-0.16*	0.02	0.07	-0.14*	-0.68*	0.28*	-0.18*	-0.07	0.38*	0.19*	0.25*	0.19*	1.00						
(18)	Log(Prevalence)	-0.33*	-0.32*	-0.16*	0.07	-0.13*	-0.04	0.02	-0.20*	-0.64*	0.28*	-0.19*	-0.10	0.44*	0.26*	0.31*	0.24*	0.90*	1.00					
(19)	DALYs per person	0.21*	0.04	-0.10	-0.05	-0.04	0.04	0.09	0.02	0.07	0.06	0.12*	-0.01	-0.08	-0.05	-0.06	-0.11*	-0.18*	-0.42*	1.00				
(20)	YLD per person	0.06	-0.10	0.08	-0.02	0.09	-0.11*	-0.09	-0.15*	0.39*	-0.10*	0.11*	-0.04	0.09	0.11*	0.09	0.05	-0.25*	0.11*	-0.41*	1.00			
(21)	YLL per person	0.21*	0.05	-0.10	-0.05	-0.04	0.04	0.09	0.02	0.06	0.06	0.11*	-0.01	-0.08	-0.06	-0.06	-0.11*	-0.17*	-0.42*	1.00*	-0.43*	1.00		
(22)	5-year survival rate	-0.01	0.02	0.23*	0.01	0.04	-0.08	-0.08	-0.03	0.14*	-0.12*	-0.01	0.01	0.03	0.02	0.00	0.08	0.01	0.29*	-0.77*	0.65*	-0.78*	1.00	
(23)	No. of competitors	-0.01	-0.16	-0.11	-0.03	-0.06	-0.12*	-0.11*	-0.10*	0.10	0.18*	-0.04	-0.03	0.16*	0.11*	0.11*	-0.02	0.21*	0.20*	0.20*	0.21*	0.19*	-0.03	1.00

Table 53: Pearson correlation coefficients

Notes: P-values: * $p<.05$.

Abbreviations: DALYs, disability-adjusted life years; OS, overall survival; PFS, progression-free survival.

Assumptions

Patient age:	adult
Patient weight:	70 kg
Patient body surface area:	1.7 m²
Liver function:	normal (not impaired)
Kidney function:	normal (not impaired)
Patient location:	New York City (ZIP code: 10065)
Part D plan:	Human Basic Rx Plan (PDP)
Average days per month:	365 days/12 months = 30.4167 days per month
Medicare payment limit:	106% of average sales price (ASP)

Medicare Part B example: Belinostat (®Beleodaq)

FDA-approved indication:	peripheral t-cell lymphoma (pTCL)
Dosing schedule:	= 1,000 mg/m² once daily on days 1-5 of a 21-day cycle
	= 1,000 mg/m² * 1.7 m² * 5 days per 21-day cycle
Medicare payment limit Q1 2023:	= 46.15 $ per 10 mg
Treatment cost formula:	= Medicare payment limit * dosing schedule * (1/1.06)
	* (average number of days per month/treatment cycle length)
Treatment cost calculation:	= 4,615 $/1,000 mg * 1,000 mg/m² * 1.7 m² * 5 days per cycle * (1/1.06)
	* (30.42 days per month/21-day cycle)
	= **$53,606 per month**

Medicare Part D example: Ixazomib (®Ninlaro)

FDA-approved indication:	multiple myeloma
Dosing schedule:	= 4 mg taken orally on Days 1, 8, and 15 of a 28-day cycle
	= 4 mg/day * 3 days per 28-day cycle
Retail cost in Q1 2023:	= 12,240 $ per 28-day cycle
Treatment cost formula:	= retail cost * (average number of days per month/treatment cycle length)
Treatment cost calculation:	= 12,240 $ per 28-day cycle * (30.42 days per month/28-day cycle)
	= **$13,296 per month**

Table 54: Assumptions and examples for the calculation of monthly treatment costs

Date	Molecule Name	Disease	OD	NCT	P	Blind	Design	Article or FDA Link
17.05.2000	Gemtuzumab ozogamicin	AML	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21174_Mylotorg.cfm
15.06.2000	Triptorelin	Prostate Cancer	No	NA	3	OL	RCT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20715lbl.pdf
25.09.2000	Arsenic trioxide	AML	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021248s013lbl.pdf
07.05.2001	Alemtuzumab	CLL/SLL	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103948s5167lbl.pdf
10.05.2001	Imatinib	CML	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21335lbl.pdf
01.02.2002	Imatinib	GIST	Yes	NA	2	OL	DRCT	https://pubmed.ncbi.nlm.nih.gov/12181401/
19.02.2002	Ibritumomab-Tiuxetan	Follicular Lymphoma	Yes	NA	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/12011122/
25.04.2002	Fulvestrant	Breast Cancer	No	NA	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/12177099/
09.08.2002	Oxaliplatin	Colorectal Cancer	No	00008281	3	OL	RCT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21492lbl.pdf
20.12.2002	Imatinib	CML	Yes	NA	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/12181401/
05.05.2003	Gefitinib	NSCLC	No	NA	2	DB	DRCT	https://pubmed.ncbi.nlm.nih.gov/14570950/
13.05.2003	Bortezomib	Multiple Myeloma	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/021602lbl.pdf
20.05.2003	Imatinib	CML	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/021588s001lbl.pdf
25.11.2003	Abarelix	Prostate Cancer	No	NA	3	OL	RCT	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-320_Plenaxis.cfm
09.01.2004	Oxaliplatin	Colorectal Cancer	No	NA	3	OL	RCT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21492se1-002_eloxatin_lbl.pdf
04.02.2004	Pemetrexed	Pleura Mesothelioma	Yes	NA	3	Single-blind	RCT	https://pubmed.ncbi.nlm.nih.gov/12860938/
12.02.2004	Cetuximab	Colorectal Cancer	No	NA	2	OL	DRCT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125084lbl.pdf
26.02.2004	Bevacizumab	Colorectal Cancer	No	00109070	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/15175435/
19.05.2004	Azacitidine	MDS	Yes	NA	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/12011120/
19.08.2004	Pemetrexed	NSCLC	No	NA	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/15117980/
04.11.2004	Oxaliplatin	Colorectal Cancer	No	NA	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/15175436/
18.11.2004	Erlotinib	NSCLC	No	NA	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/16014882/
28.12.2004	Clofarabine	ALL	Yes	00042341	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/16622268/
11.02.2005	Erlotinib	Pancreatic Cancer	Yes	NA	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/17452677/
25.03.2005	Bortezomib	Multiple Myeloma	Yes	00048230	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/15958804/
28.10.2005	Nelarabine	ALL	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021877lbl.pdf
20.12.2005	Sorafenib	RCC	Yes	00073307	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/17215530/
26.01.2006	Sunitinib	GIST	No	00075218	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/17046465/
26.01.2006	Sunitinib	RCC	No	00077974	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/16757724/
01.03.2006	Cetuximab	HNSCC	Yes	00004227	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/16467544/
02.05.2006	Decitabine	MDS	Yes	00043381	3	OL	RCT	https://ashpublications.org/blood/article/104/11/67/75732
28.06.2006	Dasatinib	ALL	Yes	NA	2	OL	SAT	https://ashpublications.org/blood/article/106/11/42/122702/A-Phase-II-Study-of-Dasatinib-in-Patients-with
27.09.2006	Panitumumab	Colorectal Cancer	No	00113763	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/17470858/
27.09.2006	Imatinib	CML	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021588s016lbl.pdf
06.10.2006	Vorinostat	cTCL	Yes	00091559	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/17577020/
11.10.2006	Bevacizumab	NSCLC	No	00021060	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/17167137/
19.10.2006	Imatinib	Dermatofibrosarcoma protuberans	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021588s011s012s013s014s017lbl.pdf
19.10.2006	Imatinib	Hypereosinophilic Syndrome / Chronic Eosinophilic Leukemia	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021588s011s012s013s014s017lbl.pdf
19.10.2006	Imatinib	aggressive systemic mastocytosis	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021588s011s012s013s014s017lbl.pdf
19.10.2006	Imatinib	MDS	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021588s011s012s013s014s017lbl.pdf
19.10.2006	Imatinib	ALL	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021588s011s012s013s014s017lbl.pdf
08.12.2006	Bortezomib	Mantle Cell Lymphoma	Yes	00063713	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/17001068/
13.03.2007	Lapatinib	Breast Cancer	No	00078572	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/17192538/
30.05.2007	Temsirolimus	RCC	Yes	00065468	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/17538086/
19.09.2007	Alemtuzumab	CLL/SLL	Yes	00046683	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/17984186/
16.10.2007	Ixabepilone	Breast Cancer	No	00082433	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/20530276/
29.10.2007	Nilotinib	CML	Yes	00109707	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/16775235/
08.11.2007	Dasatinib	ALL	Yes	00123474	3	OL	DRCT	https://pubmed.ncbi.nlm.nih.gov/18541900/

16.11.2007	Sorafenib	HCC	Yes	00105443	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/18650514/
22.02.2008	Bevacizumab	Breast Cancer	No	00028990	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/18160686/
20.03.2008	Bendamustine	CLL	Yes	NA	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/19652068/
26.09.2008	Pemetrexed	NSCLC	No	00087711	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/18506025/
31.10.2008	Bendamustine	indolent B-NHL	Yes	01570049	3	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022303lbl.pdf
19.12.2008	Imatinib	GIST	Yes	00041197	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/19303137/
24.12.2008	Degarelix	Prostate Cancer	No	00295750	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/19035858/
30.03.2009	Everolimus	RCC	No	00410124	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/18653228/
05.05.2009	Bevacizumab	Glioblastoma	Yes	00345163	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/19720927/
02.07.2009	Pemetrexed	NSCLC	No	00102804	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/19767093/
31.07.2009	Bevacizumab	RCC	Yes	00738530	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/18156031/
03.09.2009	Ibritumomab-Tiuxetan	Follicular Lymphoma	Yes	NA	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/18854568/
24.09.2009	Pralatrexate	pTCL	Yes	00364923	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/21245435/
19.10.2009	Pazopanib	RCC	No	00334282	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/20100962/
26.10.2009	Ofatumumab	CLL	Yes	00349349	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/20194866/
05.11.2009	Romidepsin	cTCL	Yes	00106431	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27637428/
29.01.2010	Lapatinib	Breast Cancer	No	00073528	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/19786658/
16.04.2010	Erlotinib	NSCLC	No	00556712	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/20493771/
17.06.2010	Cabazitaxel	Prostate Cancer	No	00417079	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/20888992/
17.06.2010	Nilotinib	CML	Yes	00471497	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/20525993/
28.10.2010	Dasatinib	CML	Yes	00481247	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/20525995/
29.10.2010	Everolimus	SEGA	Yes	00789828	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/23158522/
15.11.2010	Eribulin Mesylate	Breast Cancer	No	00388726	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/21376385/
25.03.2011	Ipilimumab	Melanoma	Yes	00094653	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/20525992/
06.04.2011	Vandetanib	Thyroid Cancer	Yes	00410761	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/22025146/
28.04.2011	Abiraterone	Prostate Cancer	No	00638690	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/22995653/
05.05.2011	Everolimus	NET	Yes	00510068	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/21306238/
20.05.2011	Sunitinib	NET	No	00428597	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/21306237/
16.06.2011	Romidepsin	pTCL	Yes	00007345	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/21355097/
17.08.2011	Vemurafenib	Melanoma	Yes	01006980	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/21639808/
19.08.2011	Brentuximab vedotin	Hodgkin Lymphoma	Yes	00848926	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/22454421/
19.08.2011	Brentuximab vedotin	pTCL	Yes	00866047	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/22614995/
26.08.2011	Crizotinib	NSCLC	Yes	00585195	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/20979469/
07.11.2011	Cetuximab	HNSCC	No	00122460	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/18784101/
16.11.2011	Ruxolitinib	Myelofibrosis	Yes	00952289	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/22375971/
18.11.2011	Asparaginase Erwinia chrysanthemi	ALL	Yes	00537030	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/23741010/
27.01.2012	Axitinib	RCC	No	00678392	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/22056247/
30.01.2012	Vismodegib	BCC	No	00833417	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/22670903/
08.03.2012	Aflibercept	Colorectal Cancer	No	00561470	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/22949147/
26.04.2012	Everolimus	Renal Angiomyolipoma	Yes	00790400	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/23312829/
26.04.2012	Pazopanib	STS	Yes	00753688	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/22595799/
06.07.2012	Cetuximab	Colorectal Cancer	No	00154102	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/19339720/
20.07.2012	Carfilzomib	Multiple Myeloma	Yes	00511238	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/22833546/
20.07.2012	Everolimus	Breast Cancer	No	00863655	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/22149876/
06.08.2012	Pertuzumab	Breast Cancer	No	00567190	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/23602601/
31.08.2012	Enzalutamide	Prostate Cancer	No	00974311	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/22894553/
04.09.2012	Bosutinib	CML	Yes	00261846	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/21865346/
27.09.2012	Regorafenib	Colorectal Cancer	No	01103323	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/23177514/
26.10.2012	Omacetaxine mepesuccinate	CML	Yes	00375219	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/22896000/
29.11.2012	Cabozantinib	Thyroid Cancer	Yes	00704730	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/29045520/
10.12.2012	Abiraterone	Prostate Cancer	No	00887198	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/23228172/
14.12.2012	Ponatinib	CML	Yes	01207440	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/24180494/
25.01.2013	Imatinib	ALL	Yes	00022737	3	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/19805687/
08.02.2013	Pomalidomide	Multiple Myeloma	Yes	00833833	2	OL	DRCT	https://pubmed.ncbi.nlm.nih.gov/24421329/
22.02.2013	Trastuzumab Emtansine	Breast Cancer	No	00829166	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/23020162/
25.02.2013	Regorafenib	GIST	Yes	01271712	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/23177515/
14.05.2013	Erlotinib	NSCLC	No	00446225	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/22285168/
15.05.2013	Radium Ra 223 dichloride	Prostate Cancer	No	00699751	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/23863050/
29.05.2013	Trametinib	Melanoma	Yes	01245062	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/22663011/
29.05.2013	Dabrafenib	Melanoma	Yes	01227889	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/22735384/
12.07.2013	Afatinib	NSCLC	Yes	00949650	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/23816960/
30.09.2013	Pertuzumab	Breast Cancer	No	00545688	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/22153890/
01.11.2013	Obinutuzumab	CLL	Yes	01010061	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/24401022/
13.11.2013	Ibrutinib	Mantle Cell Lymphoma	Yes	01236391	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/23782157/
22.11.2013	Sorafenib	Thyroid Cancer	Yes	00984282	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/24768112/
08.01.2014	Trametinib	Melanoma	Yes	01072175	2	OL	NRT	https://pubmed.ncbi.nlm.nih.gov/23020132/
09.01.2014	Dabrafenib	Melanoma	Yes	01072175	2	OL	NRT	https://pubmed.ncbi.nlm.nih.gov/25287827/
12.02.2014	Ibrutinib	CLL	Yes	01105247	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/23782158/
17.04.2014	Ofatumumab	CLL	Yes	00748189	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/25882396/
21.04.2014	Ramucirumab	Gastric Cancer	Yes	00917384	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/24094768/

23.04.2014	Siltuximab	Castleman's disease	Yes	01024036	2	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/25042199/
29.04.2014	Ceritinib	NSCLC	Yes	01283516	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/24670165/
23.05.2014	Panitumumab	Colorectal Cancer	No	00364013	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/20921465/
03.07.2014	Belinostat	pTCL	Yes	00865969	3	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/26101246/
23.07.2014	Idelalisib	CLL	Yes	01539512	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/24450857/
23.07.2014	Idelalisib	Follicular Lymphoma	Yes	01282424	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/24450858/
23.07.2014	Idelalisib	CLL/SLL	Yes	01282424	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/24450858/
28.07.2014	Ibrutinib	CLL	Yes	01578707	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/24881631/
14.08.2014	Bevacizumab	Cervical Cancer	No	00803062	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/24552320/
04.09.2014	Pembrolizumab	Melanoma	Yes	01295827	1	OL	DRCT	https://pubmed.ncbi.nlm.nih.gov/23724846/
10.09.2014	Enzalutamide	Prostate Cancer	No	01212991	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/24881730/
08.10.2014	Bortezomib	Multiple Myeloma	Yes	00111319	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/18753647/
05.11.2014	Ramucirumab	Gastric Cancer	Yes	01170663	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/25240821/
14.11.2014	Bevacizumab	Ovarian Cancer	Yes	00976911	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/24637997/
03.12.2014	Blinatumomab	ALL	Yes	01466179	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/25524800/
04.12.2014	Ruxolitinib	Polycythemia Vera	Yes	01243944	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/25629741/
12.12.2014	Ramucirumab	NSCLC	No	01168973	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/24933332/
19.12.2014	Olaparib	Ovarian Cancer	Yes	01078662	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/26723501/
22.12.2014	Nivolumab	Melanoma	Yes	01721746	3	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/25795410/
29.01.2015	Ibrutinib	Morbus Waldenström	Yes	01614821	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/25853747/
03.02.2015	Palbociclib	Breast Cancer	No	00721409	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/25524798/
13.02.2015	Lenvatinib	Thyroid Cancer	Yes	01321554	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/25671254/
23.02.2015	Panobinostat	Multiple Myeloma	Yes	01023308	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27751707/
04.03.2015	Nivolumab	NSCLC	No	01642004	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26028407/
10.03.2015	Dinutuximab	Neuroblastoma	Yes	00026312	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/20879881/
24.04.2015	Ramucirumab	Colorectal Cancer	No	01183780	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/25877855/
24.07.2015	Sonidegib	BCC	No	01327053	2	DB	DRCT	https://pubmed.ncbi.nlm.nih.gov/25981810/
22.09.2015	Trifluridine; Tipiracil	Colorectal Cancer	No	01607957	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/25970050/
30.09.2015	Nivolumab	Melanoma	Yes	01844505	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/26027431/
02.10.2015	Pembrolizumab	NSCLC	No	01905657	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/26712084/
09.10.2015	Nivolumab	NSCLC	No	01673867	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26412456/
23.10.2015	Trabectedin	STS	Yes	01343277	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26371143/
27.10.2015	Talimogene laherparepvec	Melanoma	Yes	00769704	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26014293/
28.10.2015	Ipilimumab	Melanoma	Yes	00636168	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/25840693/
10.11.2015	Cobimetinib	Melanoma	Yes	01689519	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/25265494/
13.11.2015	Osimertinib	NSCLC	Yes	01802632	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28221867/
16.11.2015	Daratumumab	Multiple Myeloma	Yes	01985126	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/26778538/
20.11.2015	Ixazomib	Multiple Myeloma	Yes	01564537	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27119237/
23.11.2015	Nivolumab	RCC	No	01668784	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26406148/
24.11.2015	Necitumumab	NSCLC	Yes	00981058	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26045340/
30.11.2015	Elotuzumab	Multiple Myeloma	Yes	01239797	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26035255/
11.12.2015	Alectinib	NSCLC	Yes	01801111	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27863201/
18.12.2015	Pembrolizumab	Melanoma	Yes	01704287	2	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/26115796/
19.01.2016	Ofatumumab	CLL	Yes	01039376	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26377300/
21.01.2016	Carfilzomib	Multiple Myeloma	Yes	01080391	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/25482145/
28.01.2016	Eribulin Mesylate	Liposarcoma	Yes	01327885	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26874885/
19.02.2016	Palbociclib	Breast Cancer	No	01942135	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/35552673/
26.02.2016	Obinutuzumab	Follicular Lymphoma	Yes	01059630	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27345636/
26.02.2016	Everolimus	NET	Yes	01524783	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/26703889/
02.03.2016	Fulvestrant	Breast Cancer	No	01942135	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/30345905/
04.03.2016	Ibrutinib	CLL	Yes	01722487	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26639149/
11.03.2016	Crizotinib	NSCLC	Yes	00585195	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/20979469/
11.04.2016	Venetoclax	CLL	Yes	01889186	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27178240/
15.04.2016	Afatinib	SCLC	Yes	01523587	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26156651/
25.04.2016	Cabozantinib	RCC	No	01865747	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26406150/
06.05.2016	Ibrutinib	CLL/SLL	Yes	01611090	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/26655421/
13.05.2016	Lenvatinib	RCC	No	01136733	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/26482279/
17.05.2016	Brentuximab vedotin	Hodgkin Lymphoma	Yes	01100502	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/25796459/
17.05.2016	Nivolumab	Hodgkin Lymphoma	Yes	02181738	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27451390/
18.05.2016	Atezolizumab	Urothelial Cancer	No	02108652	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/26952546/
05.08.2016	Pembrolizumab	HNSCC	No	01848834	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27646946/
31.08.2016	Ofatumumab	CLL	Yes	00824265	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27731748/
18.10.2016	Atezolizumab	NSCLC	No	02008227	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27979383/
19.10.2016	Olaratumab	STS	Yes	01185964	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27291997/
24.10.2016	Pembrolizumab	NSCLC	No	02142738	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27718847/
10.11.2016	Nivolumab	HNSCC	No	02105636	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27718784/
21.11.2016	Daratumumab	Multiple Myeloma	Yes	02076009	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27705267/
06.12.2016	Bevacizumab	Ovarian Cancer	Yes	00565851	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28438473/

19.12.2016	Rucaparib	Ovarian Cancer	Yes	01891344, 01482715	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27908594/
18.01.2017	Ibrutinib	Marginal cell lymphoma	Yes	01980628	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28167659/
02.02.2017	Nivolumab	Urothelial Cancer	No	02387996	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28131785/
13.03.2017	Ribociclib	Breast Cancer	No	01958021	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27717303/
14.03.2017	Pembrolizumab	Hodgkin Lymphoma	Yes	02453594	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28441111/
23.03.2017	Avelumab	Merkel Cell Carcinoma	Yes	02155647	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27592805/
27.03.2017	Niraparib	Ovarian Cancer	Yes	01847274	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27717299/
31.03.2017	Palbociclib	Breast Cancer	No	01740427	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27959613/
17.04.2017	Atezolizumab	Urothelial Cancer	No	02951767	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30929841/
25.04.2017	Nivolumab	Hodgkin Lymphoma	Yes	02181738	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27451390/
27.04.2017	Regorafenib	HCC	Yes	01774344	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27932229/
28.04.2017	Brigatinib	NSCLC	Yes	02094573	2	OL	DRCT	https://pubmed.ncbi.nlm.nih.gov/29768119/
28.04.2017	Midostaurin	AML	Yes	00651261	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28644114/
28.04.2017	Midostaurin	Systemic Mastocytosis	Yes	00782067	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27355533/
01.05.2017	Durvalumab	Urothelial Cancer	No	01693562	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28817753/
09.05.2017	Avelumab	Urothelial Cancer	No	01772004	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28375787/
10.05.2017	Pembrolizumab	NSCLC	No	02039674	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27745820/
18.05.2017	Pembrolizumab	Urothelial Cancer	No	02335424	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28967485/
18.05.2017	Pembrolizumab	Urothelial Cancer	No	02256436	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28212060/
23.05.2017	Pembrolizumab	Mismatch	No	01876511	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/26028255/
26.05.2017	Ceritinib	NSCLC	Yes	01828099	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28126333/
16.06.2017	Daratumumab	Multiple Myeloma	Yes	01998971	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28637662/
22.06.2017	Trametinib	NSCLC	Yes	01336634	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27080216/
22.06.2017	Dabrafenib	NSCLC	Yes	01336634	2	OL	NRT	https://pubmed.ncbi.nlm.nih.gov/27080216/
29.06.2017	Panitumumab	Colorectal Cancer	No	00364013	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/20921465/
14.07.2017	Copanlisib	Follicular Lymphoma	Yes	01660451	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28633365/
17.07.2017	Neratinib	Breast Cancer	No	00878709	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/26874901/
28.07.2017	Abemaciclib	Breast Cancer	No	02107703	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28580882/
31.07.2017	Nivolumab	Colorectal Cancer	No	02060188	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28734759/
01.08.2017	Enasidenib	AML	Yes	01915498	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28588020/
02.08.2017	Ibrutinib	GVHD	Yes	02195869	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28924018/
17.08.2017	Olaparib	Ovarian Cancer	Yes	00753545	2	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/22452356/
17.08.2017	Inotuzumab ozogamicin	ALL	Yes	01564784	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/27292104/
25.08.2017	Fulvestrant	Breast Cancer	No	01602380	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27908454/
30.08.2017	Tisagenlecleucel	ALL	Yes	02228096	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29385370/
01.09.2017	Gemtuzumab ozogamicin	AML	Yes	00927498	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/22482940/
01.09.2017	Gemtuzumab ozogamicin	AML	Yes	NA	2	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf
22.09.2017	Pembrolizumab	Gastric Cancer	Yes	02335411	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29543932/
22.09.2017	Nivolumab	HCC	Yes	01658878	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28434648/
18.10.2017	Axicabtagene ciloleucel	DLBCL	Yes	02348216	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29226797/
31.10.2017	Acalabrutinib	Mantle Cell Lymphoma	Yes	02213926	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29241979/
06.11.2017	Alectinib	NSCLC	Yes	02075840	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28586279/
06.11.2017	Vemurafenib	Erdheim-Chester Disease	Yes	01524978	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/26287849/
09.11.2017	Brentuximab vedotin	pTCL	Yes	01578499	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28600132/
10.11.2017	Dasatinib	CML	Yes	00306202	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29498925/
14.11.2017	Fulvestrant	Breast Cancer	No	02107703	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28580882/
16.11.2017	Obinutuzumab	Follicular Lymphoma	Yes	01332968	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28976863/
16.11.2017	Sunitinib	RCC	No	00375674	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27718781/
19.12.2017	Cabozantinib	RCC	No	01835158	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28199818/
19.12.2017	Bosutinib	CML	Yes	02130557	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29091516/
20.12.2017	Pertuzumab	Breast Cancer	No	01358877	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28581356/
20.12.2017	Nivolumab	Melanoma	Yes	02388906	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28891423/
12.01.2018	Olaparib	Breast Cancer	No	02000622	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28578601/
12.01.2018	Afatinib	NSCLC	Yes	00949650	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/23816960/
12.01.2018	Arsenic trioxide	AML	Yes	00482833	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/23841729/
16.01.2018	Lutetium Lu 177 dotatate	NET	Yes	01578239	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28076709/
07.02.2018	Abiraterone	Prostate Cancer	No	01715285	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28578607/
14.02.2018	Apalutamide	Prostate Cancer	No	01946204	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/29420164/
16.02.2018	Durvalumab	NSCLC	No	02125461	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28885881/
26.02.2018	Abemaciclib	Breast Cancer	No	02246621	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28968163/
20.03.2018	Brentuximab vedotin	Hodgkin Lymphoma	Yes	01712490	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29224502/
29.03.2018	Blinatumomab	ALL	Yes	01207388	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29358182/

06.04.2018	Rucaparib	Ovarian Cancer	Yes	01968213	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28916367/
10.04.2018	Everolimus	TSC	Yes	01713946	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27613521/
16.04.2018	Ipilimumab	RCC	No	02231749	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29562145/
16.04.2018	Nivolumab	RCC	No	02231749	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29562145/
18.04.2018	Osimertinib	NSCLC	Yes	02296125	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/29151359/
30.04.2018	Trametinib	Melanoma	Yes	01682083	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28891408/
30.04.2018	Dabrafenib	Melanoma	Yes	01682083	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/28891408/
01.05.2018	Tisagenlecleucel	DLBCL	Yes	02445248	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30501490/
04.05.2018	Trametinib	Thyroid Cancer	Yes	02034110	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29072975/
04.05.2018	Dabrafenib	Thyroid Cancer	Yes	02034110	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29072975/
07.05.2018	Daratumumab	Multiple Myeloma	Yes	02185479	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29231133/
04.06.2018	Pemetrexed	NSCLC	No	02039674	2	OL	DRCT	https://pubmed.ncbi.nlm.nih.gov/27745820/
08.06.2018	Venetoclax	CLL/SLL	Yes	02005471	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29562156/
12.06.2018	Pembrolizumab	Cervical Cancer	No	02628067	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30943124/
13.06.2018	Pembrolizumab	PMBCL	Yes	02576990	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/31609651/
13.06.2018	Bevacizumab	Ovarian Cancer	Yes	00262847	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/22204724/
27.06.2018	Encorafenib	Melanoma	Yes	01909453	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29573941/
27.06.2018	Binimetinib	Melanoma	Yes	01909453	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29573941/
10.07.2018	Ipilimumab	Colorectal Cancer	No	02060188	2	OL	NRT	https://pubmed.ncbi.nlm.nih.gov/28734759/
10.07.2018	Nivolumab	Colorectal Cancer	No	02060188	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29355075/
13.07.2018	Enzalutamide	Prostate Cancer	No	02003924	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/29949494/
18.07.2018	Ribociclib	Breast Cancer	No	02422615	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31826360/
20.07.2018	Ivosidenib	AML	Yes	02074839	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29860938/
08.08.2018	Mogamulizumab-kpkc	cTCL	Yes	01728805	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30100375/
15.08.2018	Lenvatinib	HCC	Yes	01761266	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29433850/
16.08.2018	Nivolumab	SCLC	Yes	01928394	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27269741/
24.08.2018	Ibrutinib	Morbus Waldenström	Yes	02165397	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/27956157/
13.09.2018	Moxetumomab pasudotox-tdfk	Hairy Cell Leukemia	Yes	01829711	3	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30030507/
24.09.2018	Duvelisib	CLL/SLL	Yes	02004522	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30287523/
24.09.2018	Duvelisib	Follicular Lymphoma	Yes	02204982	3	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf
27.09.2018	Dacomitinib	NSCLC	Yes	01774721	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/28958502/
28.09.2018	Cemiplimab-rwlc	cSCC	No	02383212	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29863979/
16.10.2018	Talazoparib	Breast Cancer	No	01945775	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30110579/
30.10.2018	Pembrolizumab	NSCLC	No	02578680	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/29658856/
02.11.2018	Lorlatinib	NSCLC	Yes	01970865	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/31669155/
06.11.2018	Elotuzumab	Multiple Myeloma	Yes	02654132	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30403938/
09.11.2018	Pembrolizumab	HCC	Yes	02702414	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29875066/
16.11.2018	Brentuximab vedotin	pTCL	Yes	01777152	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/30522922/
16.11.2018	Larotrectinib	Solid Tumors	Yes	02122913	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29466156/
21.11.2018	Venetoclax	AML	Yes	02203773	2	OL	NRT	https://pubmed.ncbi.nlm.nih.gov/29339097/
21.11.2018	Glasdegib	AML	Yes	01546038	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30074259/
28.11.2018	Gilteritinib	AML	Yes	02421939	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31665578/
06.12.2018	Atezolizumab	NSCLC	No	02366143	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29863955/
19.12.2018	Olaparib	Ovarian Cancer	Yes	01844986	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/30345884/
19.12.2018	Pembrolizumab	Merkel Cell Carcinoma	Yes	02267603	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30726175/
20.12.2018	Calaspargase pegol-mknl	ALL	Yes	01574274	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33026184/
21.12.2018	Tagraxofusp-erzs	BPDCN	Yes	02113982	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/31018069/
21.12.2018	Dasatinib	ALL	Yes	01460160	1	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021986s021lbl.pdf
08.01.2019	Pembrolizumab	Urothelial Cancer	No	02625961	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34051177/
14.01.2019	Cabozantinib	HCC	Yes	01908426	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/29972759/
25.01.2019	Ibrutinib	CLL/SLL	Yes	02264574	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30522969/
14.02.2019	Apalutamide	Prostate Cancer	No	02489318	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31150574/
15.02.2019	Pembrolizumab	Melanoma	Yes	02362594	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/29658430/
22.02.2019	Trifluridine; Tipiracil	metastatic GEJ cancer	Yes	02500043	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/30355453/
08.03.2019	Atezolizumab	Breast Cancer	No	02425891	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/30345906/
11.03.2019	Fulvestrant	Breast Cancer	No	02422615	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31826360/
18.03.2019	Atezolizumab	SCLC	Yes	02763579	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/30280641/
11.04.2019	Pembrolizumab	NSCLC	No	02220894	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30955977/
12.04.2019	Erdafitinib	Urothelial Cancer	No	02365597	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/31340094/
19.04.2019	Axitinib	RCC	No	02853331	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30779529/
19.04.2019	Pembrolizumab	RCC	No	02853331	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30779529/
02.05.2019	Ivosidenib	AML	Yes	02074839	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29860938/
03.05.2019	Trastuzumab Emtansine	Breast Cancer	No	01772472	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30516102/
10.05.2019	Ramucirumab	HCC	Yes	02435433	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/30665869/
14.05.2019	Avelumab	RCC	No	02684006	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30779531/
15.05.2019	Venetoclax	CLL/SLL	Yes	02242942	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31166681/
24.05.2019	Ruxolitinib	GVHD	Yes	02953678	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32160294/
24.05.2019	Alpelisib	Breast Cancer	No	02437318	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31340094/
10.06.2019	Pembrolizumab	HNSCC	No	02358031	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31679945/
10.06.2019	Pembrolizumab	HNSCC	No	02358031	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31679945/
10.06.2019	Polatuzumab vedotin-piiq	DLBCL	Yes	02257567	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31693429/

17.06.2019	Pembrolizumab	SCLC	Yes	02054806	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/28813164/
27.06.2019	Daratumumab	Multiple Myeloma	Yes	02252172	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31141632/
03.07.2019	Selinexor	Multiple Myeloma	Yes	02336815	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29381435/
30.07.2019	Pembrolizumab	Esophageal Cancer	Yes	02564263	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33026938/
30.07.2019	Darolutamide	Prostate Cancer	No	02200614	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/30763142/
02.08.2019	Pexidartinib	Giant cell tumor	Yes	02371369	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31229240/
15.08.2019	Entrectinib	NSCLC	Yes	02568267	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/31838015/
16.08.2019	Fedratinib	Myelofibrosis	Yes	01437787	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/26181658/
17.09.2019	Lenvatinib	Endometrial Carcinoma	No	02501096	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30922731/
17.09.2019	Pembrolizumab	Endometrial Carcinoma	No	02501096	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30922731/
26.09.2019	Daratumumab	Multiple Myeloma	Yes	02541383	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31171419/
23.10.2019	Niraparib	Ovarian Cancer	Yes	02354586	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30948273/
14.11.2019	Zanubrutinib	Mantle Cell Lymphoma	Yes	03206970	2	OL	SAT	https://ashpublications.org/blood/article/132/Supplement%201/148/273151/Safety-and-Activity-of-the-Investigational-Bruton
21.11.2019	Acalabrutinib	CLL	Yes	02475681	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32305093/
03.12.2019	Atezolizumab	NSCLC	No	02367781	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31122901/
16.12.2019	Enzalutamide	Prostate Cancer	No	02677896	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31329516/
18.12.2019	Enfortumab vedotin-ejfv	Urothelial Cancer	No	03219333	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/31356140/
20.12.2019	Fam-trastuzumab deruxtecan-nxki	Breast Cancer	No	03248492	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/31825192/
27.12.2019	Olaparib	Pancreatic Cancer	Yes	02184195	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31157963/
09.01.2020	Avapritinib	GIST	Yes	02508532	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32615108/
23.01.2020	Tazemetostat	Epithelioid Sarcoma	Yes	02601950	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33035459/
25.02.2020	Neratinib	Breast Cancer	No	01808573	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32678716/
02.03.2020	Isatuximab-irfc	Multiple Myeloma	Yes	02990338	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31735560/
10.03.2020	Ipilimumab	HCC	Yes	01658878	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33001135/
10.03.2020	Nivolumab	HCC	Yes	01658878	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33001135/
27.03.2020	Durvalumab	SCLC	Yes	03043872	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31590988/
08.04.2020	Encorafenib	Colorectal Cancer	No	02928224	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31566309/
10.04.2020	Selumetinib	Nerofibromatose	Yes	01362803	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32187457/
17.04.2020	Tucatinib	Breast Cancer	Yes	02614794	2	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31825569/
17.04.2020	Pemigatinib	Cholangiocarcinoma	Yes	02924376	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32203698/
21.04.2020	Ibrutinib	CLL	Yes	02048813	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31365801/
22.04.2020	Sacituzumab govitecan-hziy	Breast Cancer	No	01631552	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30786188/
29.04.2020	Niraparib	Ovarian Cancer	Yes	02655016	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31562799/
06.05.2020	Capmatinib	NSCLC	Yes	02414139	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32877583/
08.05.2020	Olaparib	Ovarian Cancer	Yes	02477644	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31851799/
08.05.2020	Selpercatinib	NSCLC	Yes	03157128	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32846060/
08.05.2020	Selpercatinib	Medullary Thyroid Cancer	Yes	03157128	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32846060/
08.05.2020	Selpercatinib	Thyroid Cancer	Yes	03157128	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32846060/
14.05.2020	Pomalidomide	Kaposi Sarcoma	Yes	01495598	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/27863194/
15.05.2020	Rucaparib	Prostate Cancer	No	02952534	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32795228/
15.05.2020	Ipilimumab	NSCLC	No	02477826	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29658845/
15.05.2020	Nivolumab	NSCLC	No	02477826	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/29658845/
15.05.2020	Ripretinib	GIST	Yes	03353753	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/32511981/
18.05.2020	Atezolizumab	NSCLC	No	02409342	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32997907/
19.05.2020	Olaparib	Prostate Cancer	No	02987543	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32343890/
22.05.2020	Brigatinib	NSCLC	Yes	02737501	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30280657/
26.05.2020	Ipilimumab	NSCLC	No	03215706	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33476593/
26.05.2020	Nivolumab	NSCLC	No	03215706	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33476593/
29.05.2020	Ramucirumab	NSCLC	No	02411448	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/31591063/
29.05.2020	Atezolizumab	HCC	Yes	03434379	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32402160/
29.05.2020	Bevacizumab	HCC	Yes	03434379	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32402160/
04.06.2020	Axitinib	RCC	No	02684006	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/30779531/
10.06.2020	Nivolumab	Esophageal Cancer	Yes	02569242	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31582355/
16.06.2020	Pembrolizumab	TMB-H Cancer	No	02628067	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32919526/
18.06.2020	Tazemetostat	Follicular Lymphoma	Yes	01897571	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33035457/
18.06.2020	Tazemetostat	Follicular Lymphoma	Yes	01897571	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33035457/
22.06.2020	Selinexor	DLBCL	Yes	02227251	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32589977/
24.06.2020	Pembrolizumab	sSCC	No	03284424	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32673170/
25.06.2020	Lurbinectedin	SCLC	Yes	02454972	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32224306/
29.06.2020	Pembrolizumab	Colorectal Cancer	No	02563002	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33264544/
30.06.2020	Avelumab	Urothelial Cancer	No	02603432	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32945632/
07.07.2020	Decitabine and Cedazuridine	MDS	Yes	02103478	3	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/30926081/
24.07.2020	Brexucabtagene autoleucel	Mantle Cell Lymphoma	Yes	02601313	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32242358/

30.07.2020	Atezolizumab	Melanoma	Yes	02908672	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/32534646/
31.07.2020	Tafasitamab-cxix	DLBCL	Yes	02399085	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32511983/
05.08.2020	Belantamab mafodotin-blmf	Multiple Myeloma	Yes	03525678	2	OL	DRCT	https://pubmed.ncbi.nlm.nih.gov/31859245/
20.08.2020	Carfilzomib	Multiple Myeloma	Yes	03158688	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32682484/
01.09.2020	Azacitidine	AML	Yes	01757535	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/33369355/
04.09.2020	Pralsetinib	NSCLC	Yes	03037385	2	OL	NRT	https://pubmed.ncbi.nlm.nih.gov/34118197/
02.10.2020	Ipilimumab	Pleura Mesothelioma	Yes	02899299	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33485464/
02.10.2020	Nivolumab	Pleura Mesothelioma	Yes	02899299	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33485464/
14.10.2020	Pembrolizumab	Hodgkin Lymphoma	Yes	02684292	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33721562/
13.11.2020	Pembrolizumab	Breast Cancer	No	02819518	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/33278935/
25.11.2020	Naxitamab-gqgk	Neuroblastoma	Yes	03363373	2	OL	SAT	https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.10022
01.12.2020	Pralsetinib	Medullary Thyroid Cancer	Yes	03037385	2	OL	NRT	https://pubmed.ncbi.nlm.nih.gov/34118197/
01.12.2020	Pralsetinib	Thyroid Cancer	Yes	03037385	2	OL	NRT	https://pubmed.ncbi.nlm.nih.gov/34118198/
16.12.2020	Margetuximab-cmkb	Breast Cancer	No	02492711	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33480963/
18.12.2020	Osimertinib	NSCLC	Yes	02511106	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/32955177/
18.12.2020	Ponatinib	CML	Yes	02467270	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34407543/
18.12.2020	Selinexor	Multiple Myeloma	Yes	03110562	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33189178/
18.12.2020	Relugolix	Prostate Cancer	No	03085095	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32469183/
14.01.2021	Crizotinib	ALCL	Yes	00939770	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/23598171/
22.01.2021	Cabozantinib	RCC	No	03141177	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33657295/
22.01.2021	Nivolumab	RCC	No	03141177	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33657295/
03.02.2021	Tepotinib	NSCLC	Yes	02864992	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32469185/
05.02.2021	Umbralisib	Marginal cell lymphoma	Yes	02793583	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33683917/
05.02.2021	Umbralisib	Follicular Lymphoma	Yes	02793583	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33683917/
05.02.2021	Lisocabtagene maraleucel	Large B-cell lymphoma	Yes	02631044	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32888407/
09.02.2021	Cemiplimab-rwlc	BCC	No	03132636	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34000246/
09.02.2021	Cemiplimab-rwlc	BCC	No	03132636	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34000246/
15.02.2021	Fam-trastuzumab deruxtecan-nxki	Gastric Cancer	Yes	03329690	2	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32469182/
22.02.2021	Cemiplimab-rwlc	NSCLC	No	03088540	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33581821/
26.02.2021	Melphalan flufenamide	Multiple Myeloma	Yes	02963493	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33296242/
03.03.2021	Lorlatinib	NSCLC	Yes	03052608	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33207094/
05.03.2021	Axicabtagene ciloleucel	Follicular Lymphoma	Yes	03105336	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34895487/
10.03.2021	Tivozanib	RCC	No	02627963	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31810797/
22.03.2021	Pembrolizumab	Esophageal Cancer	Yes	03189719	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/34454674/
26.03.2021	Idecabtagene vicleucel	Multiple Myeloma	Yes	03361748	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33626253/
31.03.2021	Isatuximab-irfc	Multiple Myeloma	Yes	03275285	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/34097854/
13.04.2021	Sacituzumab govitecan-hziy	Urothelial Cancer	No	03547973	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33929895/
16.04.2021	Nivolumab	metastatic GEJ cancer	Yes	02872116	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/34102137/
22.04.2021	Dostarlimab-gxly	Endometrial Carcinoma	No	02715284	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33001143/
23.04.2021	Loncastuximab tesirine-lpyl	DLBCL	Yes	03589469	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33989558/
05.05.2021	Pembrolizumab	Gastric Cancer	Yes	03615326	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/34912120/
20.05.2021	Nivolumab	Esophageal Cancer	Yes	02743494	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/33789008/
21.05.2021	Amivantamab-vmjw	NSCLC	No	02609776	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34339292/
16.06.2021	Avapritinib	Advanced Systemic Mastocytosis	Yes	03580655	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34873347/
30.06.2021	Asparaginase erwinia chrysanthemi (recombinant)-rywn	ALL	Yes	04145531	3	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761179s000lbledt.pdf
06.07.2021	Pembrolizumab	cSCC	No	03284424	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/32673170/
09.07.2021	Enfortumab vedotin-ejfv	Urothelial Cancer	No	03219333	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/31356140/
26.07.2021	Pembrolizumab	Breast Cancer	No	03036488	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/32101663/
10.08.2021	Lenvatinib	RCC	No	02811861	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33616314/
10.08.2021	Pembrolizumab	RCC	No	02811861	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/33616314/
13.08.2021	Belzutifan	VHL disease	Yes	03401788	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34818478/
17.08.2021	Dostarlimab-gxly	Solid Tumors	No	02715284	1	OL	SAT	https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761223s000lbl.pdf
19.08.2021	Nivolumab	Urothelial Cancer	No	02632409	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/34437799/
25.08.2021	Ivosidenib	Cholangiocarcinoma	Yes	02989857	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/32416072/
25.08.2021	Sotorasib	NSCLC	Yes	03600883	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34096690/

25.08.2021	Infigratinib	Cholangiocarcinoma	Yes	02150967	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/29182496/
31.08.2021	Zanubrutinib	Morbus Waldenström	Yes	03053440	3	OL	RCT	https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.8007
14.09.2021	Zanubrutinib	Marginal cell lymphoma	Yes	03846427	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34526366/
15.09.2021	Mobocertinib	NSCLC	Yes	02716116	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34647988/
17.09.2021	Cabozantinib	Thyroid Cancer	Yes	03690388	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/34237250/
20.09.2021	Tisotumab vedotin-tftv	Cervical Cancer	No	03438396	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33845034/
22.09.2021	Ruxolitinib	GVHD	Yes	03112603	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/34260836/
24.09.2021	Cetuximab	Colorectal Cancer	No	02928224	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/31566309/
01.10.2021	Brexucabtagene autoleucel	ALL	Yes	02614066	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/34097852/
12.10.2021	Abemaciclib	Breast Cancer	No	03155997	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/32954927/
13.10.2021	Pembrolizumab	Cervical Cancer	No	03635567	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/34534429/
15.10.2021	Atezolizumab	NSCLC	No	02486718	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/34555333/
29.10.2021	Asciminib	CML	Yes	03106779	3	OL	RCT	https://pubmed.ncbi.nlm.nih.gov/34407542/
29.10.2021	Asciminib	CML	Yes	02081378	1	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/31826340/
12.11.2021	Ropeginterferon alfa-2b-njft	Polycythemia Vera	Yes	01193699	2	OL	SAT	https://ashpublications.org/blood/article/132/Supplement%201/3030/263686/Long-Term-Efficacy-and-Safety-of-Ropeginterferon
17.11.2021	Pembrolizumab	RCC	No	03142334	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/34407342/
30.11.2021	Carfilzomib	Multiple Myeloma	Yes	03412565	2	OL	SAT	https://pubmed.ncbi.nlm.nih.gov/33216361/
03.12.2021	Pembrolizumab	Melanoma	Yes	03553836	3	DB	RCT	https://pubmed.ncbi.nlm.nih.gov/35367007/

Table 55: Overview of included indications and clinical trials, 2000-2022

Notes: NCT identifiers were not available for most clinical trials that were initiated before 2005.

Abbreviations: DB, double blind; dRCT, dose-comparison randomized trial; FDA, US Food and Drug Administration; NA, not applicable; NRT, non-randomized trial; OL, open-label; RCT, randomized controlled trial; SAT, single-arm trial.

Drug	Indication			Hazard Ratio (95% CI)	Weight (%)
	Treatment Line	*Disease*	*Orphan*	*Overall Survival*	
Daratumumab	1st line	Multiple Myeloma	Yes	0.36 (0.21-0.62)	0.47
Idelalisib	2nd line	CLL	Yes	0.37 (0.14-0.98)	0.14
Sunitinib	1st line	NET	No	0.41 (0.19-0.89)	0.20
Polatuzumab vedotin-piiq	≥3rd line	DLBCL	Yes	0.42 (0.24-0.75)	0.34
Vemurafenib	1st line	Melanoma	Yes	0.44 (0.33-0.59)	0.84
Ibrutinib	1st line	CLL	Yes	0.46 (0.2-1.07)	0.13
Glasdegib	1st line	AML	Yes	0.46 (0.3-0.71)	0.47
Pembrolizumab	1st line	NSCLC	No	0.49 (0.38-0.64)	0.84
Sunitinib	2nd line	GIST	No	0.49 (0.29-0.83)	0.30
Eribulin Mesylate	2nd line	Liposarcoma	Yes	0.51 (0.35-0.75)	0.49
Olaratumab	1st line	STS	Yes	0.52 (0.34-0.79)	0.41
Lutetium Lu 177 dotatate	1st line	NET	Yes	0.52 (0.32-0.84)	0.32
Axitinib	1st line	RCC	No	0.53 (0.38-0.74)	0.57
Pembrolizumab	1st line	RCC	No	0.53 (0.38-0.74)	0.57
Trametinib	1st line	Melanoma	Yes	0.56 (0.33-0.95)	0.24
Dabrafenib	1st line	Melanoma	Yes	0.57 (0.42-0.79)	0.55
Bortezomib	2nd line	Multiple Myeloma	Yes	0.57 (0.4-0.81)	0.47
Dinutuximab	2nd line	Neuroblastoma	Yes	0.58 (0.37-0.91)	0.31
Atezolizumab	1st line	HCC	Yes	0.58 (0.42-0.79)	0.55
Azacitidine	1st line	MDS	Yes	0.58 (0.43-0.77)	0.61
Bevacizumab	1st line	HCC	Yes	0.58 (0.42-0.79)	0.55
Atezolizumab	1st line	NSCLC	No	0.59 (0.4-0.89)	0.36
Nivolumab	2nd line	NSCLC	No	0.59 (0.44-0.79)	0.59
Fam-trastuzumab deruxtecan-nxki	1st line	Gastric Cancer	Yes	0.59 (0.39-0.88)	0.36
Cabozantinib	1st line	RCC	No	0.6 (0.4-0.89)	0.36
Pembrolizumab	1st line	NSCLC	No	0.6 (0.41-0.89)	0.37
Acalabrutinib	1st line	CLL	Yes	0.6 (0.28-1.27)	0.10
Encorafenib	2nd line	Colorectal Cancer	No	0.6 (0.45-0.79)	0.61
Nivolumab	1st line	RCC	No	0.6 (0.4-0.89)	0.36
Cetuximab	2nd line	Colorectal Cancer	No	0.6 (0.45-0.79)	0.61
Encorafenib	1st line	Melanoma	Yes	0.61 (0.47-0.79)	0.66
Elotuzumab	≥3rd line	Multiple Myeloma	Yes	0.62 (0.3-1.28)	0.11
Enzalutamide	2nd line	Prostate Cancer	No	0.62 (0.52-0.73)	1.03
Obinutuzumab	2nd line	Follicular Lymphoma	Yes	0.62 (0.39-0.98)	0.26
Atezolizumab	1st line	Breast Cancer	No	0.62 (0.45-0.86)	0.47
Abiraterone	1st line	Prostate Cancer	No	0.62 (0.51-0.76)	0.89
Cobimetinib	1st line	Melanoma	Yes	0.63 (0.47-0.85)	0.53
Regorafenib	2nd line	HCC	Yes	0.63 (0.5-0.79)	0.75
Ipilimumab	1st line	RCC	No	0.63 (0.44-0.89)	0.41
Nivolumab	1st line	RCC	No	0.63 (0.44-0.89)	0.41
Pembrolizumab	2nd line	Esophageal Cancer	Yes	0.64 (0.46-0.9)	0.42
Pembrolizumab	1st line	Cervical Cancer	No	0.64 (0.5-0.81)	0.69
Gilteritinib	2nd line	AML	Yes	0.64 (0.49-0.83)	0.61
Everolimus	1st line	NET	Yes	0.64 (0.4-1.05)	0.22
Pertuzumab	1st line	Breast Cancer	No	0.64 (0.47-0.88)	0.48
Bortezomib	1st line	Multiple Myeloma	Yes	0.65 (0.51-0.84)	0.64
Daratumumab	1st line	Multiple Myeloma	Yes	0.65 (0.53-0.8)	0.81
Lenvatinib	1st line	RCC	No	0.66 (0.49-0.88)	0.51
Cabozantinib	2nd line	RCC	No	0.66 (0.53-0.83)	0.72
Ipilimumab	1st line	Melanoma	Yes	0.66 (0.51-0.87)	0.57
Brentuximab vedotin	1st line	pTCL	Yes	0.66 (0.46-0.95)	0.36
Pembrolizumab	1st line	RCC	No	0.66 (0.49-0.88)	0.51
Bevacizumab	1st line	Colorectal Cancer	No	0.66 (0.54-0.81)	0.81
Daratumumab	1st line	Multiple Myeloma	Yes	0.66 (0.5-0.87)	0.55
Daratumumab	1st line	Multiple Myeloma	Yes	0.66 (0.22-2.03)	0.03
Lenvatinib	2nd line	RCC	No	0.67 (0.42-1.08)	0.22
Dabrafenib	1st line	Melanoma	Yes	0.67 (0.28-1.58)	0.06
Apalutamide	1st line	Prostate Cancer	No	0.67 (0.51-0.89)	0.53
Trifluridine; Tipiracil	2nd line	Colorectal Cancer	No	0.68 (0.58-0.81)	0.95
Obinutuzumab	1st line	CLL	Yes	0.68 (0.29-1.6)	0.06
Cemiplimab-rwlc	1st line	NSCLC	No	0.68 (0.53-0.87)	0.61
Trastuzumab Emtansine	2nd line	Breast Cancer	No	0.68 (0.55-0.85)	0.71
Daratumumab	1st line	Multiple Myeloma	Yes	0.69 (0.46-1.02)	0.29
Trifluridine; Tipiracil	≥3rd line	metastatic GEJ cancer	Yes	0.69 (0.56-0.85)	0.75
Ipilimumab	1st line	NSCLC	No	0.69 (0.55-0.87)	0.66
Avelumab	1st line	Urothelial Cancer	No	0.69 (0.56-0.86)	0.72
Sorafenib	1st line	HCC	Yes	0.69 (0.55-0.87)	0.66
Nivolumab	1st line	NSCLC	No	0.69 (0.55-0.87)	0.66
Azacitidine	2nd line	AML	Yes	0.69 (0.55-0.86)	0.69
Darolutamide	1st line	Prostate Cancer	No	0.69 (0.53-0.88)	0.59
Radium Ra 223 dichloride	1st line	Prostate Cancer	No	0.7 (0.58-0.83)	0.87
Cabazitaxel	2nd line	Prostate Cancer	No	0.7 (0.59-0.83)	0.91
Trastuzumab Emtansine	2nd line	Breast Cancer	No	0.7 (0.47-1.05)	0.27
Atezolizumab	1st line	SCLC	Yes	0.7 (0.54-0.91)	0.55
Niraparib	1st line	Ovarian Cancer	Yes	0.7 (0.44-1.11)	0.21
Apalutamide	1st line	Prostate Cancer	No	0.7 (0.48-1.04)	0.29
Nivolumab	1st line	HNSCC	No	0.7 (0.53-0.92)	0.51
Elotuzumab	2nd line	Multiple Myeloma	Yes	0.71 (0.54-0.93)	0.51
Enzalutamide	1st line	Prostate Cancer	No	0.71 (0.6-0.84)	0.91
Ramucirumab	2nd line	HCC	Yes	0.71 (0.53-0.95)	0.45
Bevacizumab	1st line	Cervical Cancer	No	0.71 (0.54-0.95)	0.47
Ipilimumab	1st line	Melanoma	Yes	0.72 (0.58-0.88)	0.72
Ribociclib	1st line	Breast Cancer	No	0.72 (0.57-0.92)	0.59

Lorlatinib	1st line	NSCLC	Yes	0.72 (0.41-1.25)	0.14
Sorafenib	1st line	RCC	Yes	0.72 (0.55-0.95)	0.49
Daratumumab	1st line	Multiple Myeloma	Yes	0.72 (0.57-0.92)	0.59
Erlotinib	2nd line	NSCLC	No	0.73 (0.61-0.86)	0.88
Lenvatinib	2nd line	Thyroid Cancer	Yes	0.73 (0.5-1.07)	0.28
Brentuximab vedotin	1st line	Hodgkin Lymphoma	Yes	0.73 (0.6-0.98)	0.53
Pembrolizumab	2nd line	Urothelial Cancer	No	0.73 (0.59-0.91)	0.66
Pembrolizumab	1st line	Esophageal Cancer	Yes	0.73 (0.62-0.86)	0.91
Durvalumab	1st line	SCLC	Yes	0.73 (0.59-0.91)	0.66
Pazopanib	1st line	RCC	No	0.73 (0.53-1)	0.38
Temsirolimus	1st line	RCC	Yes	0.73 (0.58-0.92)	0.61
Nivolumab	2nd line	NSCLC	No	0.73 (0.6-0.89)	0.75
Nivolumab	2nd line	RCC	No	0.73 (0.6-0.89)	0.75
Abiraterone	2nd line	Prostate Cancer	No	0.74 (0.64-0.86)	0.99
Ipilimumab	1st line	Pleura Mesothelioma	Yes	0.74 (0.61-0.89)	0.78
Lapatinib	1st line	Breast Cancer	No	0.74 (0.5-1.1)	0.26
Nivolumab	1st line	Pleura Mesothelioma	Yes	0.74 (0.61-0.89)	0.78
Cetuximab	2nd line	HNSCC	Yes	0.74 (0.57-0.97)	0.49
Dacomitinib	1st line	NSCLC	Yes	0.75 (0.59-0.95)	0.58
Carfilzomib	2nd line	Multiple Myeloma	Yes	0.75 (0.49-1.13)	0.23
Inotuzumab ozogamicin	2nd line	ALL	Yes	0.75 (0.57-0.99)	0.45
Abemaciclib	2nd line	Breast Cancer	No	0.76 (0.61-0.95)	0.61
Daratumumab	1st line	Multiple Myeloma	Yes	0.76 (0.61-0.95)	0.61
Cabozantinib	2nd line	HCC	Yes	0.76 (0.63-0.92)	0.75
Talazoparib	1st line	Breast Cancer	No	0.76 (0.55-1.06)	0.34
Pemetrexed	1st line	Pleura Mesothelioma	Yes	0.77 (0.61-0.96)	0.59
Regorafenib	≥3rd line	Colorectal Cancer	No	0.77 (0.64-0.94)	0.72
Regorafenib	2nd line	GIST	Yes	0.77 (0.42-1.41)	0.10
Atezolizumab	2nd line	NSCLC	No	0.77 (0.51-1.17)	0.22
Pembrolizumab	1st line	HNSCC	No	0.77 (0.63-0.93)	0.72
Midostaurin	1st line	AML	Yes	0.77 (0.63-0.95)	0.65
Panitumumab	1st line	Colorectal Cancer	No	0.77 (0.64-0.94)	0.72
Nivolumab	2nd line	Esophageal Cancer	Yes	0.77 (0.62-0.96)	0.61
Ramucirumab	2nd line	Gastric Cancer	Yes	0.78 (0.6-1)	0.50
Atezolizumab	1st line	NSCLC	No	0.78 (0.64-0.96)	0.66
Pembrolizumab	1st line	HNSCC	No	0.78 (0.64-0.96)	0.66
Ofatumumab	2nd line	CLL	Yes	0.78 (0.56-1.09)	0.31
Lapatinib	2nd line	Breast Cancer	No	0.78 (0.55-1.12)	0.28
Ipilimumab	1st line	NSCLC	No	0.79 (0.67-0.94)	0.81
Carfilzomib	2nd line	Multiple Myeloma	Yes	0.79 (0.67-0.95)	0.78
Atezolizumab	2nd line	NSCLC	No	0.79 (0.69-0.91)	0.99
Ivosidenib	2nd line	Cholangiocarcinoma	Yes	0.79 (0.56-1.12)	0.29
Nivolumab	1st line	NSCLC	No	0.79 (0.67-0.94)	0.81
Pemetrexed	2nd line	NSCLC	No	0.79 (0.65-0.95)	0.72
Bevacizumab	1st line	NSCLC	No	0.79 (0.68-0.94)	0.84
Daratumumab	1st line	Multiple Myeloma	Yes	0.79 (0.62-1)	0.53
Abiraterone	1st line	Prostate Cancer	No	0.79 (0.66-0.96)	0.71
Axitinib	1st line	RCC	No	0.8 (0.62-1.03)	0.47
Avelumab	1st line	RCC	No	0.8 (0.62-1.03)	0.47
Cabozantinib	1st line	RCC	No	0.8 (0.53-1.21)	0.21
Enzalutamide	1st line	Prostate Cancer	No	0.8 (0.58-1.09)	0.34
Atezolizumab	1st line	NSCLC	No	0.8 (0.64-0.99)	0.59
Nivolumab	2nd line	metastatic GEJ cancer	Yes	0.8 (0.71-0.9)	1.12
Cetuximab	2nd line	HNSCC	No	0.8 (0.64-0.98)	0.61
Cetuximab	1st line	Colorectal Cancer	No	0.8 (0.67-0.94)	0.81
Enzalutamide	1st line	Prostate Cancer	No	0.81 (0.53-1.25)	0.19
Eribulin Mesylate	≥3rd line	Breast Cancer	No	0.81 (0.68-0.96)	0.78
Afatinib	2nd line	SCLC	Yes	0.81 (0.69-0.95)	0.84
Ramucirumab	2nd line	Gastric Cancer	Yes	0.81 (0.68-0.96)	0.78
Pembrolizumab	1st line	NSCLC	No	0.81 (0.71-0.93)	0.99
Aflibercept	2nd line	Colorectal Cancer	No	0.81 (0.71-0.93)	0.99
Erlotinib	1st line	Pancreatic Cancer	Yes	0.81 (0.68-0.97)	0.75
Erlotinib	2nd line	NSCLC	No	0.81 (0.7-0.95)	0.88
Daratumumab	1st line	Multiple Myeloma	Yes	0.81 (0.6-1.09)	0.36
Palbociclib	1st line	Breast Cancer	No	0.81 (0.49-1.35)	0.14
Everolimus	2nd line	RCC	No	0.82 (0.57-1.17)	0.26
Cabozantinib	2nd line	Thyroid Cancer	Yes	0.83 (0.6-1.14)	0.30
Ramucirumab	1st line	NSCLC	No	0.83 (0.53-1.3)	0.16
Panitumumab	1st line	Colorectal Cancer	No	0.83 (0.7-0.98)	0.78
Necitumumab	1st line	NSCLC	Yes	0.84 (0.74-0.96)	0.99
Pemetrexed	1st line	NSCLC	No	0.84 (0.74-0.96)	0.99
Bevacizumab	2nd line	Ovarian Cancer	Yes	0.84 (0.69-1.01)	0.66
Selinexor	2nd line	Multiple Myeloma	Yes	0.84 (0.57-1.23)	0.22
Olaparib	≥3rd line	Ovarian Cancer	Yes	0.85 (0.48-1.51)	0.10
Ramucirumab	2nd line	Colorectal Cancer	No	0.85 (0.73-0.98)	0.88
Atezolizumab	1st line	Melanoma	Yes	0.85 (0.64-1.11)	0.38
Ofatumumab	≥3rd line	CLL	Yes	0.85 (0.52-1.37)	0.14
Ramucirumab	2nd line	NSCLC	No	0.86 (0.75-0.98)	0.95
Bevacizumab	1st line	RCC	Yes	0.86 (0.72-1.04)	0.66
Daratumumab	1st line	Multiple Myeloma	Yes	0.86 (0.68-1.08)	0.49
Panobinostat	≥3rd line	Multiple Myeloma	Yes	0.87 (0.69-1.1)	0.47
Ixazomib	2nd line	Multiple Myeloma	Yes	0.87 (0.64-1.18)	0.31
Pazopanib	2nd line	STS	Yes	0.87 (0.67-1.12)	0.41
Bevacizumab	1st line	Breast Cancer	No	0.87 (0.72-1.05)	0.64
Daratumumab	1st line	Multiple Myeloma	Yes	0.87 (0.63-1.22)	0.27

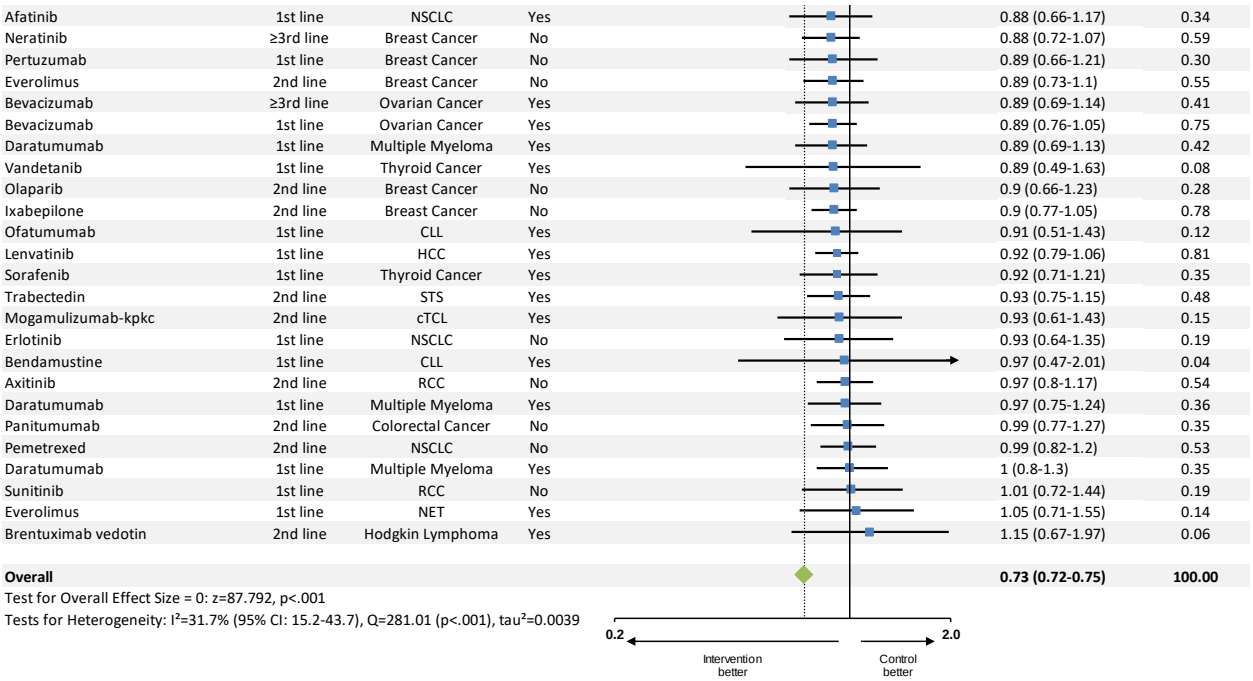

Figure 62: Meta-analysis of overall survival in randomized controlled trials supporting the FDA approval of orphan and non-orphan cancer drugs, 2000-2022

Abbreviations: CI, confidence interval; FDA, US Food and Drug Administration.

Drug	Indication			Hazard Ratio (95% CI)	Weight (%)
	Treatment Line	*Disease*	*Orphan*	*Progression-Free Survival*	
Daratumumab	1st line	Multiple Myeloma	Yes	0.15 (0.09-0.25)	0.50
Obinutuzumab	1st line	CLL	Yes	0.16 (0.11-0.24)	0.51
Ibrutinib	1st line	CLL	Yes	0.16 (0.09-0.28)	0.49
Olaparib	≥3rd line	Ovarian Cancer	Yes	0.17 (0.09-0.32)	0.48
Idelalisib	2nd line	CLL	Yes	0.18 (0.1-0.31)	0.49
Daratumumab	1st line	Multiple Myeloma	Yes	0.18 (0.12-0.29)	0.50
Venetoclax	2nd line	CLL/SLL	Yes	0.19 (0.13-0.28)	0.50
Ibrutinib	1st line	CLL/SLL	Yes	0.2 (0.15-0.28)	0.51
Ibrutinib	1st line	Morbus Waldenström	Yes	0.2 (0.11-0.38)	0.47
Acalabrutinib	1st line	CLL	Yes	0.2 (0.13-0.3)	0.50
Lenvatinib	2nd line	Thyroid Cancer	Yes	0.21 (0.16-0.28)	0.51
Lutetium Lu 177 dotatate	1st line	NET	Yes	0.21 (0.13-0.32)	0.49
Cabozantinib	2nd line	Thyroid Cancer	Yes	0.22 (0.15-0.31)	0.50
Ibrutinib	1st line	CLL/SLL	Yes	0.23 (0.15-0.37)	0.48
Ibrutinib	1st line	CLL	Yes	0.25 (0.14-0.45)	0.45
Vemurafenib	1st line	Melanoma	Yes	0.25 (0.2-0.32)	0.51
Niraparib	2nd line	Ovarian Cancer	Yes	0.26 (0.17-0.41)	0.48
Regorafenib	2nd line	GIST	Yes	0.27 (0.19-0.39)	0.49
Brentuximab vedotin	2nd line	pTCL	Yes	0.27 (0.17-0.43)	0.47
Bendamustine	1st line	CLL	Yes	0.27 (0.17-0.43)	0.47
Cabozantinib	2nd line	Thyroid Cancer	Yes	0.28 (0.19-0.4)	0.49
Lorlatinib	1st line	NSCLC	Yes	0.28 (0.19-0.41)	0.48
Apalutamide	1st line	Prostate Cancer	No	0.29 (0.24-0.36)	0.51
Olaparib	1st line	Ovarian Cancer	Yes	0.3 (0.23-0.41)	0.50
Olaparib	1st line	Ovarian Cancer	Yes	0.33 (0.25-0.45)	0.49
Venetoclax	1st line	CLL/SLL	Yes	0.33 (0.22-0.51)	0.46
Dabrafenib	1st line	Melanoma	Yes	0.33 (0.2-0.55)	0.43
Sunitinib	2nd line	GIST	No	0.33 (0.24-0.47)	0.48
Ibrutinib	1st line	CLL	Yes	0.34 (0.22-0.52)	0.45
Everolimus	2nd line	RCC	No	0.34 (0.26-0.44)	0.50
Erlotinib	1st line	NSCLC	No	0.34 (0.23-0.49)	0.47
Everolimus	1st line	NET	Yes	0.35 (0.27-0.45)	0.50
Pazopanib	2nd line	STS	Yes	0.35 (0.26-0.48)	0.48
Vandetanib	1st line	Thyroid Cancer	Yes	0.35 (0.24-0.53)	0.46
Rucaparib	2nd line	Ovarian Cancer	Yes	0.36 (0.3-0.45)	0.50
Polatuzumab vedotin-piiq	≥3rd line	DLBCL	Yes	0.36 (0.21-0.63)	0.40
Lenvatinib	2nd line	RCC	No	0.37 (0.22-0.62)	0.41
Ivosidenib	2nd line	Cholangiocarcinoma	Yes	0.37 (0.25-0.54)	0.46
Daratumumab	2nd line	Multiple Myeloma	Yes	0.37 (0.27-0.52)	0.47
Lenvatinib	1st line	RCC	No	0.39 (0.32-0.49)	0.50
Pembrolizumab	1st line	RCC	No	0.39 (0.32-0.49)	0.50
Enzalutamide	2nd line	Prostate Cancer	No	0.4 (0.32-0.5)	0.50
Encorafenib	2nd line	Colorectal Cancer	No	0.4 (0.31-0.52)	0.49
Nivolumab	1st line	Melanoma	Yes	0.4 (0.22-0.71)	0.37
Cetuximab	2nd line	Colorectal Cancer	No	0.4 (0.31-0.52)	0.49
Sunitinib	1st line	NET	No	0.43 (0.27-0.67)	0.41
Cabozantinib	2nd line	HCC	Yes	0.44 (0.36-0.52)	0.50
Sorafenib	1st line	RCC	Yes	0.44 (0.35-0.55)	0.49
Ramucirumab	2nd line	HCC	Yes	0.45 (0.34-0.6)	0.47
Inotuzumab ozogamicin	2nd line	ALL	Yes	0.45 (0.34-0.61)	0.47
Everolimus	2nd line	Breast Cancer	No	0.45 (0.38-0.54)	0.50
Osimertinib	1st line	NSCLC	Yes	0.46 (0.37-0.57)	0.49
Regorafenib	2nd line	HCC	Yes	0.46 (0.37-0.56)	0.49
Pazopanib	1st line	RCC	No	0.46 (0.34-0.62)	0.46
Daratumumab	1st line	Multiple Myeloma	Yes	0.46 (0.35-0.6)	0.47
Palbociclib	2nd line	Breast Cancer	No	0.46 (0.36-0.59)	0.48
Daratumumab	1st line	Multiple Myeloma	Yes	0.46 (0.36-0.59)	0.48
Trametinib	1st line	Melanoma	Yes	0.47 (0.34-0.65)	0.45
Afatinib	1st line	NSCLC	Yes	0.47 (0.34-0.65)	0.45
Fam-trastuzumab deruxtecan-nxki	1st line	Gastric Cancer	Yes	0.47 (0.31-0.71)	0.41
Daratumumab	1st line	Multiple Myeloma	Yes	0.47 (0.33-0.67)	0.44
Cabozantinib	1st line	RCC	No	0.48 (0.31-0.74)	0.40
Trifluridine; Tipiracil	2nd line	Colorectal Cancer	No	0.48 (0.41-0.57)	0.50
Obinutuzumab	2nd line	Follicular Lymphoma	Yes	0.48 (0.34-0.68)	0.44
Apalutamide	1st line	Prostate Cancer	No	0.48 (0.39-0.6)	0.49
Everolimus	1st line	NET	Yes	0.48 (0.35-0.67)	0.45
Bevacizumab	1st line	Breast Cancer	No	0.48 (0.39-0.61)	0.48
Bevacizumab	≥3rd line	Ovarian Cancer	Yes	0.48 (0.38-0.6)	0.48
Ramucirumab	2nd line	Gastric Cancer	Yes	0.48 (0.38-0.62)	0.48
Palbociclib	1st line	Breast Cancer	No	0.49 (0.32-0.75)	0.40
Olaparib	2nd line	Prostate Cancer	No	0.49 (0.38-0.63)	0.47
Regorafenib	≥3rd line	Colorectal Cancer	No	0.49 (0.42-0.58)	0.50
Brigatinib	1st line	NSCLC	Yes	0.49 (0.35-0.68)	0.44
Pembrolizumab	1st line	Melanoma	Yes	0.5 (0.39-0.64)	0.47
Pembrolizumab	1st line	NSCLC	No	0.5 (0.37-0.68)	0.45
Ofatumumab	≥3rd line	CLL	Yes	0.5 (0.38-0.66)	0.46
Daratumumab	1st line	Multiple Myeloma	Yes	0.5 (0.38-0.65)	0.47
Cabozantinib	1st line	RCC	No	0.51 (0.41-0.64)	0.48
Nivolumab	1st line	RCC	No	0.51 (0.41-0.64)	0.48
Eribulin Mesylate	2nd line	Liposarcoma	Yes	0.52 (0.35-0.78)	0.40
Pembrolizumab	1st line	NSCLC	No	0.52 (0.43-0.64)	0.49
Durvalumab	2nd line	NSCLC	No	0.52 (0.42-0.65)	0.48
Olaparib	2nd line	Pancreatic Cancer	Yes	0.53 (0.35-0.81)	0.39

Alectinib	1st line	NSCLC	Yes	0.53 (0.38-0.73)	0.43
Pembrolizumab	1st line	NSCLC	No	0.53 (0.31-0.91)	0.33
Mogamulizumab-kpkc	2nd line	cTCL	Yes	0.53 (0.41-0.69)	0.46
Elotuzumab	≥3rd line	Multiple Myeloma	Yes	0.54 (0.34-0.86)	0.36
Abemaciclib	1st line	Breast Cancer	No	0.54 (0.42-0.7)	0.46
Encorafenib	1st line	Melanoma	Yes	0.54 (0.41-0.71)	0.45
Talazoparib	1st line	Breast Cancer	No	0.54 (0.41-0.71)	0.45
Daratumumab	1st line	Multiple Myeloma	Yes	0.54 (0.42-0.71)	0.46
Daratumumab	1st line	Multiple Myeloma	Yes	0.54 (0.41-0.71)	0.45
Panitumumab	2nd line	Colorectal Cancer	No	0.54 (0.45-0.67)	0.48
Bevacizumab	1st line	Colorectal Cancer	No	0.54 (0.45-0.66)	0.49
Daratumumab	1st line	Multiple Myeloma	Yes	0.55 (0.37-0.82)	0.39
Ceritinib	1st line	NSCLC	Yes	0.55 (0.42-0.73)	0.45
Trabectedin	2nd line	STS	Yes	0.55 (0.44-0.7)	0.47
Lapatinib	2nd line	Breast Cancer	No	0.55 (0.41-0.74)	0.44
Bortezomib	2nd line	Multiple Myeloma	Yes	0.55 (0.44-0.69)	0.47
Abemaciclib	2nd line	Breast Cancer	No	0.55 (0.45-0.68)	0.48
Daratumumab	1st line	Multiple Myeloma	Yes	0.55 (0.45-0.68)	0.48
Ribociclib	1st line	Breast Cancer	No	0.56 (0.43-0.72)	0.46
Trifluridine; Tipiracil	≥3rd line	metastatic GEJ cancer	Yes	0.56 (0.46-0.68)	0.48
Daratumumab	1st line	Multiple Myeloma	Yes	0.56 (0.43-0.73)	0.45
Brentuximab vedotin	2nd line	Hodgkin Lymphoma	Yes	0.57 (0.4-0.81)	0.41
Ofatumumab	1st line	CLL	Yes	0.57 (0.45-0.72)	0.47
Cetuximab	2nd line	HNSCC	No	0.57 (0.46-0.72)	0.47
Cobimetinib	1st line	Melanoma	Yes	0.58 (0.46-0.72)	0.47
Palbociclib	1st line	Breast Cancer	No	0.58 (0.46-0.72)	0.47
Afatinib	1st line	NSCLC	Yes	0.58 (0.43-0.78)	0.43
Olaparib	2nd line	Breast Cancer	No	0.58 (0.43-0.8)	0.43
Cabozantinib	2nd line	RCC	No	0.58 (0.45-0.74)	0.46
Sorafenib	1st line	HCC	Yes	0.58 (0.45-0.74)	0.46
Daratumumab	1st line	Multiple Myeloma	Yes	0.58 (0.43-0.77)	0.44
Ramucirumab	1st line	NSCLC	No	0.59 (0.46-0.76)	0.45
Atezolizumab	1st line	HCC	Yes	0.59 (0.47-0.76)	0.46
Dacomitinib	1st line	NSCLC	Yes	0.59 (0.48-0.74)	0.47
Cemiplimab-rwlc	1st line	NSCLC	No	0.59 (0.49-0.72)	0.48
Sorafenib	1st line	Thyroid Cancer	Yes	0.59 (0.46-0.76)	0.45
Erlotinib	2nd line	NSCLC	No	0.59 (0.5-0.7)	0.49
Bevacizumab	1st line	HCC	Yes	0.59 (0.47-0.76)	0.46
Ribociclib	1st line	Breast Cancer	No	0.59 (0.48-0.73)	0.47
Daratumumab	1st line	Multiple Myeloma	Yes	0.59 (0.48-0.73)	0.47
Daratumumab	1st line	Multiple Myeloma	Yes	0.6 (0.44-0.81)	0.43
Pembrolizumab	1st line	Colorectal Cancer	No	0.6 (0.45-0.8)	0.43
Pemetrexed	2nd line	NSCLC	No	0.6 (0.49-0.73)	0.48
Bevacizumab	1st line	RCC	Yes	0.6 (0.49-0.72)	0.48
Bevacizumab	2nd line	Ovarian Cancer	Yes	0.61 (0.51-0.72)	0.49
Bortezomib	1st line	Multiple Myeloma	Yes	0.61 (0.49-0.76)	0.47
Pertuzumab	1st line	Breast Cancer	No	0.62 (0.51-0.75)	0.48
Atezolizumab	1st line	Breast Cancer	No	0.62 (0.49-0.78)	0.46
Pembrolizumab	1st line	Cervical Cancer	No	0.62 (0.5-0.77)	0.47
Avelumab	1st line	Urothelial Cancer	No	0.62 (0.52-0.75)	0.48
Niraparib	1st line	Ovarian Cancer	Yes	0.62 (0.5-0.76)	0.47
Nivolumab	2nd line	NSCLC	No	0.62 (0.47-0.81)	0.44
Bevacizumab	1st line	Ovarian Cancer	Yes	0.62 (0.52-0.75)	0.48
Panobinostat	≥3rd line	Multiple Myeloma	Yes	0.63 (0.52-0.76)	0.48
Carfilzomib	2nd line	Multiple Myeloma	Yes	0.63 (0.46-0.85)	0.42
Atezolizumab	1st line	NSCLC	No	0.63 (0.45-0.88)	0.40
Lenvatinib	1st line	HCC	Yes	0.64 (0.55-0.75)	0.49
Ipilimumab	1st line	Melanoma	Yes	0.64 (0.5-0.83)	0.44
Ramucirumab	2nd line	Gastric Cancer	Yes	0.64 (0.54-0.75)	0.49
Trastuzumab Emtansine	2nd line	Breast Cancer	No	0.65 (0.55-0.77)	0.48
Pembrolizumab	≥3rd line	Hodgkin Lymphoma	Yes	0.65 (0.48-0.88)	0.41
Pembrolizumab	2nd line	Breast Cancer	No	0.65 (0.49-0.86)	0.43
Pembrolizumab	1st line	Esophageal Cancer	Yes	0.65 (0.55-0.76)	0.49
Alpelisib	1st line	Breast Cancer	No	0.65 (0.5-0.85)	0.43
Pembrolizumab	2nd line	Esophageal Cancer	Yes	0.66 (0.48-0.92)	0.40
Temsirolimus	1st line	RCC	Yes	0.66 (0.53-0.81)	0.46
Bevacizumab	1st line	NSCLC	No	0.66 (0.57-0.77)	0.49
Axitinib	2nd line	RCC	No	0.67 (0.55-0.81)	0.47
Olaratumab	1st line	STS	Yes	0.67 (0.44-1.02)	0.33
Ofatumumab	2nd line	CLL	Yes	0.67 (0.51-0.88)	0.43
Bevacizumab	1st line	Cervical Cancer	No	0.67 (0.54-0.82)	0.46
Abiraterone	2nd line	Prostate Cancer	No	0.67 (0.59-0.78)	0.49
Pemetrexed	1st line	Pleura Mesothelioma	Yes	0.68 (0.59-0.87)	0.46
Axitinib	1st line	RCC	No	0.69 (0.57-0.84)	0.47
Axitinib	1st line	RCC	No	0.69 (0.56-0.84)	0.46
Carfilzomib	2nd line	Multiple Myeloma	Yes	0.69 (0.57-0.83)	0.47
Pembrolizumab	1st line	RCC	No	0.69 (0.57-0.84)	0.47
Avelumab	1st line	RCC	No	0.69 (0.56-0.84)	0.46
Ixabepilone	2nd line	Breast Cancer	No	0.69 (0.58-0.83)	0.47
Elotuzumab	2nd line	Multiple Myeloma	Yes	0.7 (0.57-0.85)	0.46
Nivolumab	1st line	NSCLC	No	0.7 (0.57-0.86)	0.46
Cetuximab	2nd line	HNSCC	Yes	0.7 (0.54-0.9)	0.43
Cetuximab	1st line	Colorectal Cancer	No	0.7 (0.57-0.86)	0.46
Selinexor	2nd line	Multiple Myeloma	Yes	0.7 (0.53-0.93)	0.41
Brentuximab vedotin	1st line	pTCL	Yes	0.71 (0.54-0.93)	0.42

Atezolizumab	1st line	NSCLC	No	0.71 (0.59-0.85)	0.47
Lapatinib	1st line	Breast Cancer	No	0.71 (0.53-0.96)	0.40
Erlotinib	2nd line	NSCLC	No	0.71 (0.62-0.82)	0.49
Obinutuzumab	1st line	Follicular Lymphoma	Yes	0.72 (0.56-0.93)	0.43
Panitumumab	1st line	Colorectal Cancer	No	0.72 (0.58-0.9)	0.45
Dinutuximab	2nd line	Neuroblastoma	Yes	0.73 (0.5-1.06)	0.34
Daratumumab	1st line	Multiple Myeloma	Yes	0.73 (0.56-0.95)	0.42
Cabazitaxel	2nd line	Prostate Cancer	No	0.74 (0.64-0.86)	0.48
Daratumumab	1st line	Multiple Myeloma	Yes	0.74 (0.61-0.89)	0.46
Atezolizumab	1st line	NSCLC	No	0.75 (0.63-0.91)	0.46
Aflibercept	2nd line	Colorectal Cancer	No	0.76 (0.66-0.88)	0.48
Ramucirumab	2nd line	NSCLC	No	0.76 (0.68-0.86)	0.50
Neratinib	≥3rd line	Breast Cancer	No	0.76 (0.63-0.93)	0.45
Sunitinib	1st line	RCC	No	0.76 (0.59-0.98)	0.42
Erlotinib	1st line	Pancreatic Cancer	Yes	0.76 (0.64-0.92)	0.46
Daratumumab	1st line	Multiple Myeloma	Yes	0.76 (0.59-0.98)	0.42
Daratumumab	1st line	Multiple Myeloma	Yes	0.76 (0.65-0.9)	0.47
Brentuximab vedotin	1st line	Hodgkin Lymphoma	Yes	0.77 (0.6-0.98)	0.42
Atezolizumab	1st line	SCLC	Yes	0.77 (0.62-0.96)	0.44
Nivolumab	2nd line	metastatic GEJ cancer	Yes	0.77 (0.68-0.87)	0.49
Atezolizumab	1st line	Melanoma	Yes	0.78 (0.63-0.97)	0.44
Midostaurin	1st line	AML	Yes	0.78 (0.66-0.93)	0.47
Durvalumab	1st line	SCLC	Yes	0.78 (0.65-0.94)	0.46
Ipilimumab	1st line	NSCLC	No	0.79 (0.57-0.86)	0.46
Ramucirumab	2nd line	Colorectal Cancer	No	0.79 (0.7-0.9)	0.49
Gilteritinib	2nd line	AML	Yes	0.79 (0.58-1.09)	0.36
Daratumumab	1st line	Multiple Myeloma	Yes	0.8 (0.64-1)	0.43
Ruxolitinib	1st line	Myelofibrosis	Yes	0.81 (0.47-1.39)	0.22
Ixazomib	2nd line	Multiple Myeloma	Yes	0.82 (0.67-1)	0.44
Ipilimumab	1st line	RCC	No	0.82 (0.64-1.05)	0.41
Ipilimumab	1st line	NSCLC	No	0.82 (0.69-0.97)	0.46
Afatinib	2nd line	SCLC	Yes	0.82 (0.68-1)	0.45
Nivolumab	1st line	RCC	No	0.82 (0.64-1.05)	0.41
Nivolumab	1st line	NSCLC	No	0.82 (0.69-0.97)	0.46
Necitumumab	1st line	NSCLC	Yes	0.85 (0.74-0.98)	0.48
Eribulin Mesylate	≥3rd line	Breast Cancer	No	0.87 (0.71-1.05)	0.44
Nivolumab	2nd line	RCC	No	0.88 (0.75-1.03)	0.46
Nivolumab	1st line	HNSCC	No	0.89 (0.7-1.13)	0.40
Panitumumab	1st line	Colorectal Cancer	No	0.9 (0.66-0.97)	0.45
Pemetrexed	1st line	NSCLC	No	0.9 (0.79-1.02)	0.48
Pembrolizumab	1st line	HNSCC	No	0.92 (0.77-1.1)	0.44
Nivolumab	2nd line	NSCLC	No	0.92 (0.77-1.11)	0.44
Atezolizumab	2nd line	NSCLC	No	0.95 (0.82-1.1)	0.46
Pemetrexed	2nd line	NSCLC	No	0.97 (0.82-1.17)	0.43
Pembrolizumab	2nd line	Urothelial Cancer	No	0.98 (0.81-1.19)	0.42
Ipilimumab	1st line	Pleura Mesothelioma	Yes	1 (0.82-1.21)	0.42
Nivolumab	1st line	Pleura Mesothelioma	Yes	1 (0.82-1.21)	0.42
Daratumumab	1st line	Multiple Myeloma	Yes	1 (0.8-1.26)	0.39
Pembrolizumab	1st line	NSCLC	No	1.07 (0.94-1.21)	0.47
Nivolumab	2nd line	Esophageal Cancer	Yes	1.1 (0.9-1.3)	0.41
Pembrolizumab	1st line	HNSCC	No	1.15 (0.95-1.38)	0.40
Overall				**0.57 (0.54-0.6)**	**100.00**

Test for Overall Effect Size = 0: z=39.698, p<.001

Tests for Heterogeneity: I^2=90.7% (95% CI: 88.2-92.4), Q=2337.14 (p<.001), tau^2=0.0390

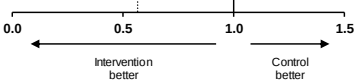

Figure 63: Meta-analysis of progression-free survival in randomized controlled trials supporting the FDA approval of orphan and non-orphan cancer drugs, 2000-2022

Abbreviations: CI, confidence interval; FDA, US Food and Drug Administration.

Drug	Indication			Tumor Response (95% CI)	Weight (%)
	Treatment Line	*Disease*	*Orphan*	*Relative Risk*	
Pembrolizumab	1st line	HNSCC	No	0.55 (0.4-0.74)	0.99
Ipilimumab	1st line	Pleura Mesothelioma	Yes	0.93 (0.77-1.12)	0.97
Nivolumab	1st line	Pleura Mesothelioma	Yes	0.93 (0.77-1.12)	0.97
Atezolizumab	1st line	SCLC	Yes	0.94 (0.8-1.09)	1.03
Nivolumab	2nd line	Esophageal Cancer	Yes	0.97 (0.62-1.5)	0.54
Zanubrutinib	1st line	Morbus Waldenström	Yes	1 (0.86-1.16)	1.02
Pembrolizumab	1st line	HNSCC	No	1 (0.8-1.25)	0.89
Pembrolizumab	1st line	NSCLC	No	1 (0.84-1.2)	0.97
Degarelix	1st line	Prostate Cancer	No	1.01 (0.98-1.05)	1.15
Atezolizumab	2nd line	NSCLC	No	1.02 (0.72-1.43)	0.66
Atezolizumab	1st line	Melanoma	Yes	1.02 (0.9-1.16)	1.05
Ramucirumab	1st line	NSCLC	No	1.02 (0.92-1.14)	1.08
Daratumumab	1st line	Multiple Myeloma	Yes	1.03 (0.84-1.26)	0.92
Daratumumab	1st line	Multiple Myeloma	Yes	1.03 (0.99-1.07)	1.15
Obinutuzumab	1st line	Follicular Lymphoma	Yes	1.03 (1-1.08)	1.15
Brentuximab vedotin	1st line	Hodgkin Lymphoma	Yes	1.04 (0.99-1.09)	1.14
Osimertinib	1st line	NSCLC	Yes	1.04 (0.95-1.13)	1.10
Dacomitinib	1st line	NSCLC	Yes	1.04 (0.93-1.16)	1.07
Erlotinib	1st line	Pancreatic Cancer	Yes	1.04 (0.59-1.85)	0.34
Daratumumab	1st line	Multiple Myeloma	Yes	1.04 (0.95-1.15)	1.09
Obinutuzumab	2nd line	Follicular Lymphoma	Yes	1.05 (0.93-1.19)	1.05
Pemetrexed	2nd line	NSCLC	No	1.06 (0.63-1.79)	0.38
Daratumumab	1st line	Multiple Myeloma	Yes	1.08 (0.95-1.22)	1.04
Necitumumab	1st line	NSCLC	Yes	1.08 (0.9-1.3)	0.94
Acalabrutinib	1st line	CLL	Yes	1.09 (0.99-1.2)	1.08
Alectinib	1st line	NSCLC	Yes	1.09 (0.96-1.24)	1.03
Ixazomib	2nd line	Multiple Myeloma	Yes	1.1 (1.01-1.19)	1.10
Pemetrexed	1st line	NSCLC	No	1.1 (0.94-1.29)	0.97
Panobinostat	≥3rd line	Multiple Myeloma	Yes	1.11 (0.99-1.26)	1.04
Carfilzomib	2nd line	Multiple Myeloma	Yes	1.13 (1.02-1.25)	1.07
Daratumumab	1st line	Multiple Myeloma	Yes	1.14 (1.08-1.21)	1.13
Panitumumab	1st line	Colorectal Cancer	No	1.15 (0.99-1.34)	0.98
Brentuximab vedotin	1st line	pTCL	Yes	1.15 (1.04-1.28)	1.07
Pertuzumab	1st line	Breast Cancer	No	1.16 (1.06-1.26)	1.09
Cetuximab	2nd line	HNSCC	Yes	1.16 (1.02-1.32)	1.02
Durvalumab	1st line	SCLC	Yes	1.17 (1.03-1.34)	1.01
Venetoclax	1st line	CLL/SLL	Yes	1.19 (1.07-1.32)	1.06
Brigatinib	1st line	NSCLC	Yes	1.2 (1.01-1.41)	0.93
Elotuzumab	2nd line	Multiple Myeloma	Yes	1.2 (1.09-1.32)	1.07
Ofatumumab	1st line	CLL	Yes	1.2 (1.08-1.34)	1.05
Nivolumab	1st line	NSCLC	No	1.21 (0.99-1.47)	0.86
Ibrutinib	1st line	CLL/SLL	Yes	1.21 (1.06-1.37)	1.01
Ibrutinib	1st line	CLL/SLL	Yes	1.22 (1.11-1.34)	1.07
Pembrolizumab	≥3rd line	Hodgkin Lymphoma	Yes	1.22 (1.02-1.47)	0.88
Daratumumab	2nd line	Multiple Myeloma	Yes	1.22 (1.13-1.32)	1.10
Selinexor	2nd line	Multiple Myeloma	Yes	1.23 (1.08-1.4)	1.00
Ruxolitinib	2nd line	GVHD	Yes	1.23 (1.04-1.45)	0.93
Neratinib	≥3rd line	Breast Cancer	No	1.23 (0.97-1.57)	0.75
Daratumumab	1st line	Multiple Myeloma	Yes	1.23 (1.15-1.32)	1.11
Palbociclib	1st line	Breast Cancer	No	1.25 (1.03-1.51)	0.86
Nivolumab	2nd line	metastatic GEJ cancer	Yes	1.27 (1.13-1.43)	1.02
Everolimus	1st line	NET	Yes	1.27 (1.08-1.49)	0.93
Enzalutamide	1st line	Prostate Cancer	No	1.27 (1.03-1.58)	0.80
Venetoclax	2nd line	CLL/SLL	Yes	1.28 (1.16-1.41)	1.06
Bosutinib	1st line	CML	Yes	1.28 (1.03-1.58)	0.80
Panitumumab	1st line	Colorectal Cancer	No	1.29 (1.08-1.53)	0.89
Bevacizumab	1st line	Colorectal Cancer	No	1.29 (1.09-1.53)	0.89
Atezolizumab	1st line	NSCLC	No	1.3 (1.11-1.52)	0.93
Carfilzomib	2nd line	Multiple Myeloma	Yes	1.31 (1.21-1.42)	1.09
Ramucirumab	2nd line	Gastric Cancer	Yes	1.31 (0.35-4.85)	0.04
Lorlatinib	1st line	NSCLC	Yes	1.31 (1.11-1.55)	0.90
Pembrolizumab	1st line	Colorectal Cancer	No	1.32 (0.99-1.76)	0.61
Atezolizumab	1st line	NSCLC	No	1.33 (0.93-1.91)	0.47
Bevacizumab	2nd line	Ovarian Cancer	Yes	1.34 (1.16-1.54)	0.96
Pembrolizumab	2nd line	Breast Cancer	No	1.34 (1.02-1.75)	0.65
Gilteritinib	2nd line	AML	Yes	1.35 (0.74-2.46)	0.21
Pembrolizumab	1st line	Cervical Cancer	No	1.36 (1.18-1.57)	0.94
Bevacizumab	1st line	Cervical Cancer	No	1.36 (1.09-1.69)	0.75
Daratumumab	1st line	Multiple Myeloma	Yes	1.37 (0.91-2.05)	0.39
Abemaciclib	1st line	Breast Cancer	No	1.38 (1.09-1.75)	0.70
Daratumumab	1st line	Multiple Myeloma	Yes	1.39 (1.09-1.78)	0.68
Daratumumab	1st line	Multiple Myeloma	Yes	1.4 (0.75-2.6)	0.19
Atezolizumab	1st line	NSCLC	No	1.41 (1.14-1.74)	0.75
Trastuzumab Emtansine	2nd line	Breast Cancer	No	1.41 (1.17-1.7)	0.81
Ribociclib	1st line	Breast Cancer	No	1.42 (1.19-1.69)	0.85
Pembrolizumab	1st line	Gastric Cancer	Yes	1.42 (1.17-1.72)	0.79
Trabectedin	2nd line	STS	Yes	1.42 (0.76-2.67)	0.18
Afatinib	2nd line	SCLC	Yes	1.42 (0.55-3.7)	0.07
Daratumumab	1st line	Multiple Myeloma	Yes	1.43 (1.12-1.81)	0.67
Ribociclib	1st line	Breast Cancer	No	1.44 (1.14-1.8)	0.70
Daratumumab	1st line	Multiple Myeloma	Yes	1.44 (1.14-1.8)	0.70
Cetuximab	1st line	Colorectal Cancer	No	1.46 (1.24-1.71)	0.87
Ipilimumab	1st line	NSCLC	No	1.5 (1.2-1.87)	0.69

Daratumumab	1st line	Multiple Myeloma	Yes	1.5 (1.28-1.77)	0.85
Nivolumab	1st line	NSCLC	No	1.51 (1.21-1.89)	0.68
Cobimetinib	1st line	Melanoma	Yes	1.51 (1.28-1.78)	0.85
Olaratumab	1st line	STS	Yes	1.52 (0.67-3.48)	0.09
Nivolumab	2nd line	NSCLC	No	1.55 (1.05-2.27)	0.36
Pembrolizumab	1st line	Esophageal Cancer	Yes	1.55 (1.28-1.89)	0.74
Ipilimumab	1st line	RCC	No	1.57 (1.29-1.91)	0.74
Nivolumab	1st line	RCC	No	1.57 (1.29-1.91)	0.74
Encorafenib	1st line	Melanoma	Yes	1.58 (1.29-1.95)	0.70
Daratumumab	1st line	Multiple Myeloma	Yes	1.58 (1.29-1.95)	0.70
Cabozantinib	1st line	RCC	No	1.6 (1.24-2.04)	0.59
Pembrolizumab	1st line	NSCLC	No	1.61 (1.18-2.2)	0.45
Atezolizumab	1st line	Breast Cancer	No	1.63 (1.27-2.08)	0.58
Ramucirumab	2nd line	NSCLC	No	1.63 (1.28-2.07)	0.59
Axitinib	1st line	RCC	No	1.64 (1.42-1.91)	0.85
Pembrolizumab	1st line	RCC	No	1.64 (1.42-1.91)	0.85
Lapatinib	2nd line	Breast Cancer	No	1.7 (1.11-2.61)	0.27
Daratumumab	1st line	Multiple Myeloma	Yes	1.71 (1.33-2.2)	0.54
Daratumumab	1st line	Multiple Myeloma	Yes	1.73 (1.6-1.87)	1.04
Ramucirumab	2nd line	Gastric Cancer	Yes	1.73 (1.28-2.33)	0.43
Bevacizumab	1st line	Breast Cancer	No	1.74 (1.37-2.22)	0.55
Cemiplimab-rwlc	1st line	NSCLC	No	1.77 (1.39-2.26)	0.54
Aflibercept	2nd line	Colorectal Cancer	No	1.78 (1.32-2.39)	0.43
Daratumumab	1st line	Multiple Myeloma	Yes	1.78 (1.31-2.41)	0.41
Temsirolimus	1st line	RCC	Yes	1.78 (0.84-3.77)	0.08
Cetuximab	2nd line	HNSCC	No	1.82 (1.32-2.51)	0.37
Pertuzumab	1st line	Breast Cancer	No	1.83 (1.19-2.81)	0.23
Durvalumab	2nd line	NSCLC	No	1.87 (1.32-2.66)	0.31
Lapatinib	1st line	Breast Cancer	No	1.89 (1.1-3.24)	0.15
Daratumumab	1st line	Multiple Myeloma	Yes	1.89 (1-3.58)	0.10
Pembrolizumab	2nd line	Urothelial Cancer	No	1.91 (1.27-2.88)	0.24
Pembrolizumab	1st line	NSCLC	No	1.93 (1.22-3.03)	0.20
Lenvatinib	1st line	RCC	No	1.96 (1.69-2.29)	0.75
Pembrolizumab	1st line	RCC	No	1.96 (1.69-2.29)	0.75
Axitinib	1st line	RCC	No	2 (1.67-2.4)	0.64
Avelumab	1st line	RCC	No	2 (1.67-2.4)	0.64
Nilotinib	1st line	CML	Yes	2.01 (1.55-2.59)	0.44
Duvelisib	≥3rd line	CLL/SLL	Yes	2.02 (1.54-2.64)	0.41
Olaparib	2nd line	Pancreatic Cancer	Yes	2.02 (0.92-4.47)	0.06
Elotuzumab	≥3rd line	Multiple Myeloma	Yes	2.03 (1.24-3.32)	0.15
Cabozantinib	1st line	RCC	No	2.05 (1.68-2.51)	0.56
Nivolumab	1st line	RCC	No	2.05 (1.68-2.51)	0.56
Axitinib	2nd line	RCC	No	2.07 (1.41-3.03)	0.23
Bevacizumab	≥3rd line	Ovarian Cancer	Yes	2.12 (1.36-3.29)	0.18
Trifluridine; Tipiracil	≥3rd line	metastatic GEJ cancer	Yes	2.17 (0.63-7.48)	0.02
Bortezomib	2nd line	Multiple Myeloma	Yes	2.18 (1.65-2.88)	0.35
Alpelisib	1st line	Breast Cancer	No	2.21 (1.41-3.46)	0.16
Erlotinib	2nd line	NSCLC	No	2.23 (1.4-3.55)	0.14
Ibrutinib	1st line	Morbus Waldenström	Yes	2.25 (1.57-3.22)	0.23
Abemaciclib	2nd line	Breast Cancer	No	2.25 (1.65-3.09)	0.28
Daratumumab	1st line	Multiple Myeloma	Yes	2.25 (1.65-3.09)	0.28
Nivolumab	2nd line	NSCLC	No	2.28 (1.21-4.32)	0.07
Daratumumab	1st line	Multiple Myeloma	Yes	2.29 (1.26-4.13)	0.09
Bendamustine	1st line	CLL	Yes	2.29 (1.69-3.11)	0.29
Olaparib	2nd line	Breast Cancer	No	2.3 (1.56-3.4)	0.19
Nivolumab	1st line	HNSCC	No	2.31 (1.05-5.07)	0.05
Trametinib	1st line	NSCLC	Yes	2.32 (1.56-3.45)	0.18
Ibrutinib	1st line	CLL	Yes	2.33 (1.83-2.97)	0.39
Bevacizumab	1st line	NSCLC	No	2.33 (1.8-3.02)	0.35
Obinutuzumab	1st line	CLL	Yes	2.37 (1.78-3.16)	0.30
Bevacizumab	1st line	RCC	Yes	2.37 (1.71-3.28)	0.25
Atezolizumab	1st line	HCC	Yes	2.4 (1.52-3.8)	0.13
Bevacizumab	1st line	HCC	Yes	2.4 (1.52-3.8)	0.13
Ixabepilone	2nd line	Breast Cancer	No	2.42 (1.82-3.21)	0.30
Everolimus	1st line	NET	Yes	2.45 (0.78-7.69)	0.02
Regorafenib	≥3rd line	Colorectal Cancer	No	2.53 (0.3-21.5)	0.00
Pembrolizumab	1st line	NSCLC	No	2.54 (1.88-3.43)	0.25
Polatuzumab vedotin-piiq	≥3rd line	DLBCL	Yes	2.6 (1.45-4.66)	0.07
Trametinib	1st line	Melanoma	Yes	2.64 (1.34-5.17)	0.05
Afatinib	1st line	NSCLC	Yes	2.64 (1.77-3.92)	0.15
Everolimus	1st line	TSC	Yes	2.64 (1.65-4.25)	0.10
Regorafenib	2nd line	HCC	Yes	2.69 (1.29-5.61)	0.04
Ceritinib	1st line	NSCLC	Yes	2.71 (2.11-3.49)	0.30
Talazoparib	1st line	Breast Cancer	No	2.73 (1.81-4.1)	0.13
Inotuzumab ozogamicin	2nd line	ALL	Yes	2.75 (2.03-3.73)	0.21
Afatinib	1st line	NSCLC	Yes	2.8 (1.84-4.26)	0.12
Eribulin Mesylate	≥3rd line	Breast Cancer	No	2.85 (1.48-5.49)	0.05
Pemetrexed	1st line	Pleura Mesothelioma	Yes	2.91 (2.02-4.2)	0.14
Lutetium Lu 177 dotatate	1st line	NET	Yes	2.92 (1.1-7.77)	0.02
Dabrafenib	1st line	Melanoma	Yes	2.97 (1.71-5.17)	0.06
Regorafenib	2nd line	GIST	Yes	2.98 (0.37-24.23)	0.00
Eribulin Mesylate	2nd line	Liposarcoma	Yes	3.04 (0.13-73.44)	0.00
Pembrolizumab	2nd line	Esophageal Cancer	Yes	3.06 (1.29-7.27)	0.02
Cabazitaxel	2nd line	Prostate Cancer	No	3.27 (1.59-6.73)	0.03
Lenvatinib	1st line	HCC	Yes	3.27 (2.52-4.26)	0.21

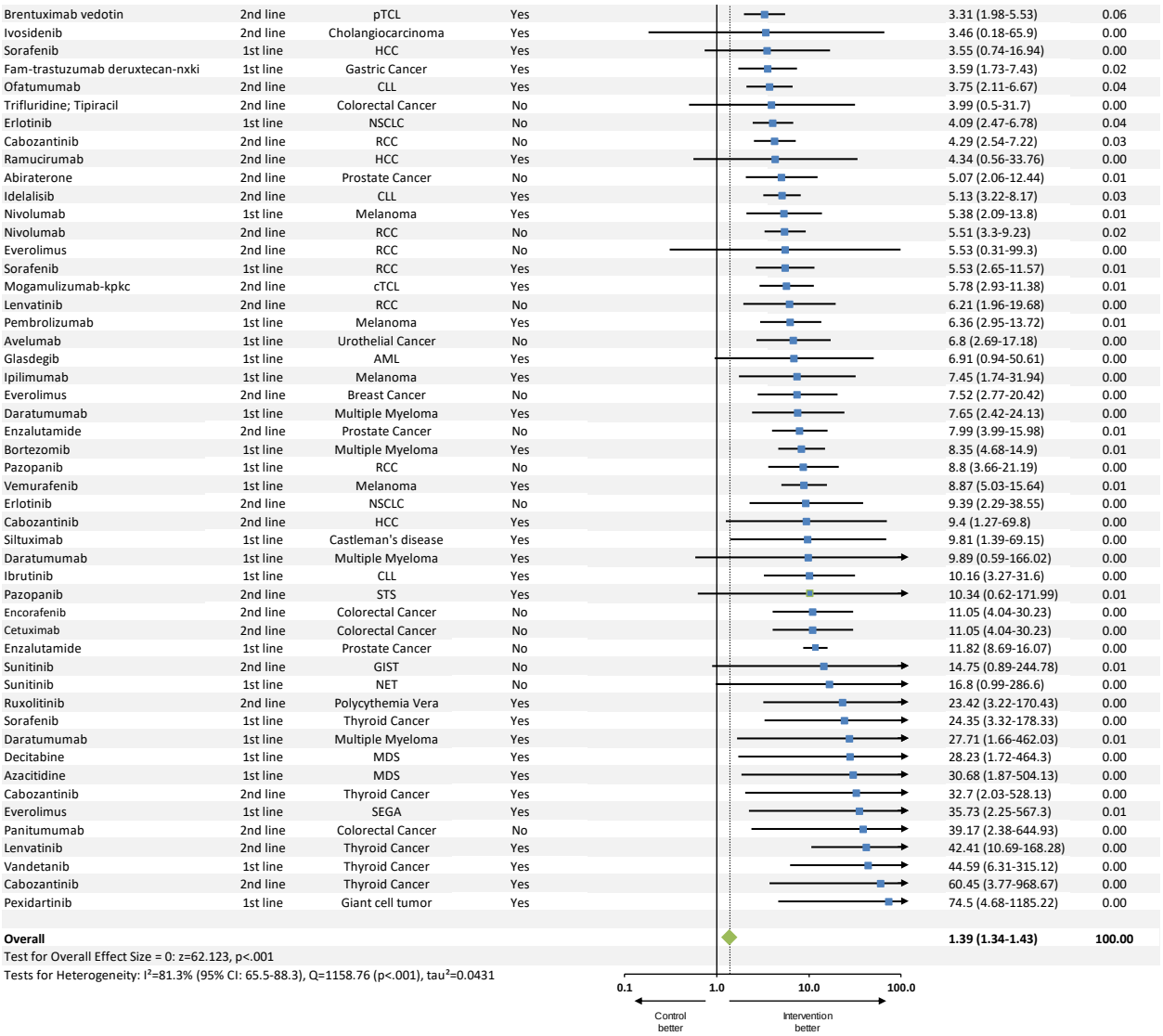

Figure 64: Meta-analysis of tumor response (relative risk) in randomized controlled trials supporting the FDA approval of orphan and non-orphan cancer drugs, 2000-2022

Abbreviations: CI, confidence interval; FDA, US Food and Drug Administration.

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