Clinical benefit, development, innovativeness, trials, epidemiology, and price for cancer drugs and indications with multiple special FDA designations

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Article information:

Article Type: Original research article

Short Title: Cancer drugs with multiple special FDA designations

Summary: This cross-sectional study compares the clinical benefit, development, innovativeness, trials, epidemiology, and price across cancer drugs and indications with multiple special FDA designations in the US.

Abstract word count: 414
Text word count: 5575
Number of figures: 3
Number of tables: 2
Number of references: 60
Online supplement: 5 tables, 2 figures

ABSTRACT

Background: Over the past decades, US Congress enabled the US Food and Drug Administration (FDA) to facilitate and expedite drug development for serious conditions filling unmet medical needs with five special designations: orphan, fast track, accelerated approval, priority review, and breakthrough therapy. Previous studies separately analyzed these special FDA processes; yet, drugs often receive multiple special designations.

Objective: To analyze cancer drugs with multiple special designations regarding their clinical development, benefit, innovativeness, trial evidence, epidemiology, and price.

Data and methods: All anti-cancer drugs and their supplemental indication approvals were identified in the Drugs@FDA database from 2012 to 2022. For each drug and indication, clinical trial evidence, epidemiologic data, and prices were collected from FDA labels, the Global Burden of Disease Study, and Medicare & Medicaid Part B and D, respectively. The association between hazard ratios (HR) for overall survival (OS) / progression-free survival (PFS), as well as relative risk (RR) for tumor response and indications' cumulative number of special designations, were compared in meta-analyses.

Results: We identified 355 FDA-approved cancer indications that received a total of 841 special designations. Median clinical development times were 7.3 months, 7.8 months (HR: 1.23, p=0.444), and 5.4 months (HR: 1.92, p=0.027) for drugs with 0-1, 2-3, and 4-5 special designations, respectively. Drugs and indications with multiple special designations were more innovative and novel. The median number of patients enrolled in the pivotal clinical trial decreased from 615 to 471, 398, 168, 104, and 120 (p<0.001) for indications with no, one, two, three, four, and five special FDA designations, respectively. Indications with more special designations were more frequently granted to rare diseases supported by smaller open-label phase 1/2 trials of single-arm design assessing tumor response rather than OS as the primary endpoint. In RCTs, HRs for OS (0.80 vs. 0.73 vs. 0.73 vs. 0.69 vs. 0.56 vs. 0.52, p=0.003) and PFS (0.70 vs. 0.61 vs. 0.59 vs. 0.44 vs. 0.37 vs. 0.67, p<0.001) substantially declined, whilst tumor response rates (RR: 1.21 vs. 1.61 vs. 1.28 vs. 1.39 vs. 1.97 vs. 1.72, p=0.002) increased with more special designations. Mean drug prices increased with more special designations ($21596 vs. $14753 vs. $32410 vs. $41240 vs. $38703 vs. $19184) with no, one, two, three, four, and five special FDA designations, respectively.

Conclusions: Drugs and indications with multiple special designations are associated with faster approval times and a greater clinical benefit for patients with high unmet needs. However, multiple special designations are also associated with less robust trial evidence and higher drug prices.

Keywords: *cancer drugs; orphan; breakthrough; accelerated approval; fast track; priority review; overall survival; progression-free survival; clinical trial; unmet need; drug price*

KEY POINTS

- Cancer drugs are frequently granted multiple special FDA designations.
- The cumulative number of special designations is associated with faster clinical development timelines, greater efficacy estimates, and greater unmet medical needs.
- However, more special designations are also associated with smaller, non-robust clinical trials and greater treatment costs.
- The FDA should only grant special designations and expedited clinical development processes to first-in-class drugs. To better inform clinical decision-making for physicians and patients, "me-too" drugs should be tested in large, robust, randomized-controlled head-to-head trials (compared to the first-in-class drug).

INTRODUCTION

Over the past four decades, US Congress provided the US Food and Drug Administration (FDA) with several special designations and approval pathways to facilitate, expedite, and encourage the development of certain drugs. The FDA's most prominent special designations are the orphan designation, fast track, accelerated approval, priority review, and breakthrough therapy designation. The orphan designation (1983) facilitates and financially incentivizes the development of drugs for rare diseases with fewer than 200,000 affected US citizens. Besides more flexibility in the design and conduct of clinical trials for rare diseases, the orphan designation provides drug sponsors with R&D grants, tax credits of 25% on qualified R&D expenditures, and an enhanced period of market exclusivity of up to 7 years. The fast track program (1988) expedites the development of drugs for serious and life-threatening diseases by enabling the FDA to grant approval based on Phase 2 instead of Phase 3 trials. Accordingly, the accelerated approval program (1992) expedites the development of drugs for serious and life-threatening diseases by permitting the use of surrogate, instead of clinical, endpoint measures for FDA approval. The priority review program (1992) reduces the FDA's review timelines for drugs with significant improvements in safety and efficacy measures from 12 to 6 months. The breakthrough therapy designation (2012) facilitates and expedites the development of drugs for serious conditions that have preliminary evidence indicating substantial improvements over the existing treatment options. Details of all five special designations are summarized in Table e1 and can be accessed in existing literature reviews.[1–3]

Interestingly, drugs can receive multiple of these special designations. Yet, there is little research on simultaneous or "stacked" FDA designations. Most authors present the co-occurrence of special designations in their sample set, whilst only rarely reporting distinct outcome measures for each designation.[4–9] Wang et al. and Liberti et al. showed that the combination of special approval pathways is not redundant – each additional designation further expedites the clinical development time of new drugs.[7, 9] This result was confirmed by Hwang et al. who reported shorter development periods for cancer drugs with the breakthrough therapy designation and accelerated approval.[4] Similarly, Rodriguez et al. found that the number of special designations is correlated to quicker inclusion in clinical guidelines.[5] Based on a sample of 138 indications approved between 1999 and 2012, Chambers et al. observed that patient health benefit, measured by incremental quality-adjusted life years (QALYs), increases with the cumulative number of FDA designations.[6] Median incremental QALYs were 0.003 for none, 0.126 for one, 0.182 for two, and 0.389 for three out of three tracked designations (priority review, accelerated approval, and fast track). In contrast, Miller et al. showed that there is no difference in equities' cumulative abnormal returns for stacked and unstacked designations.[8] However, their sample only included the orphan and fast track designations. In 2018, 48 out of 59 (81%) NDA benefited from at least one special FDA designation (Figure e1).[2] To the best of our knowledge, there has been no study that coherently evaluates the clinical benefit and prices for drugs with stacked FDA designations.

This study fills these gaps in research by analyzing the clinical development timelines, FDA approval, trials, clinical benefit, epidemiology, and prices of cancer drugs with cumulative special FDA designations. Oncology represents the therapeutic area with most drug approvals in the US,[10] which results in the largest possible sample size. Cancer drugs were further selected to ensure comparability of clinical evidence and efficacy within the sample and with previous studies.

DATA AND METHODS

Sample selection

We identified all drugs with FDA approval from 1st January 2000 and 1st January 2022 in the Drugs@FDA database (Figure e2). Then, we excluded all non-oncology drugs and oncology drugs

for supportive care, anti-emetics, and diagnostic agents. For the remaining sample of anti-cancer drugs, we screened the Drugs@FDA database for original and supplemental indications with FDA approval between 1st January 2000 and 1st January 2022. Finally, the sample was restricted to include only anti-cancer indications with FDA approval after 1st January 2013 given that the Breakthrough Therapy Designation was signed into law in 2012.

Data collection

Data on drug, indication, and clinical trial details were collected by two independent medical doctors from marketing authorization documents, clinicaltrials.gov, and scientific publications associated with each drug's NCT.[11] The data collection strategy adhered to peer-reviewed guidelines of data synthesis from FDA documents.[12, 13] The Global Burden of Disease (GBD) study and the National Cancer Institute at the National Institutes of Health (NIH) were curated for cancer epidemiology data. Monthly drug prices were calculated based on an established methodology.[14–17] Finally, special designations were retrieved from publically accessible FDA lists. Data sources are presented in Table e2 with collected variables specified in Table e3.

Drug characteristics

For each drug, all FDA-approved indications were identified in the Drugs@FDA database. Accordingly, drugs were classified as *multi-indication* in case of more than one approved indication per drug, whilst those with just one approved indication were labeled as *single-indication*. A drug's innovativeness was determined according to Lanthier et al.'s methodology (*first-in-class* vs. *advance-in-class* vs. *addition-to-class*).[18] Information on a drug's mechanism of action (MoA) and product type were retrieved from the Drug Bank, a publicly accessible database from the University of Alabama containing biologic and chemical information on investigational new molecules. We distinguished between drugs with *cytotoxic chemotherapy*, *targeted agents*, and *immune-regulatory* MoA. The product type differentiates *small-molecule* drugs from *antibodies*, *antibody-drug conjugates*, and *others* (e.g. cell therapies, gene therapies, radionuclides, enzymes).

Indication characteristics

For new indication approvals, the date and text defining the indication and its medical use were retrieved from the FDA label. First, indications were labeled as *original* and *supplemental* approvals according to their FDA approval date. The distinction between indications matters as previous studies highlight differences in clinical evidence,[19, 20] efficacy, marketing authorizations,[21] development timelines,[22] and pricing[23] across new indication launches. Second, an indication's treatment type was defined based on the number of involved drugs. Indications comprising only one drug were classified as *monotherapy*, whilst those entailing several drugs were labeled as *combination* treatments. Third, the indication's targeted cancer entity was noted. Diseases were grouped as *hematologic* or *solid* tumor types. Fourth, indications were categorized by biomarker status. The biomarker status was defined as a binary variable differentiating indications that are restricted to the use in a disease with a positive or negative biomarker status (*Yes*), e.g. programmed cell death ligand 1 positivity, from those without a biomarker (*No*). Finally, indications were characterized by the line of treatment. *First-line* treatments are generally accepted as the best available therapeutic option. *Second-line* and *≥third-line* treatments are used – in that order – if a patient has intolerable side effects or allergies to the prior-line treatment or when the prior-line treatment failed or the disease is progressing despite treatment under the prior-line regimen.

Pivotal clinical trial

Clinical trial evidence supporting the approval for the respective indication was retrieved from the FDA label. First, the clinical trial's number of enrolled patients was collected. Clinical trials were categorized according to their phase, e.g. *phase 1*, *phase 2*, or *phase 3*, their design, e.g. *single-arm*, *non-randomized*, *concurrent RCTs*, and *dose comparison RCTs*, their blinding, e.g. *open-label*/*single-blind* and *double-blind*, and number of arms. Second, the dataset entails a variable characterizing each trial's primary endpoint, differentiating between OS, PFS, and tumor response. For each endpoint, we collected the number of events, e.g. deaths for OS, tumor progression for PFS, responders for tumor response, and the number of subjects in the treatment and control arm. In the trial's treatment arm, subjects are exposed to the new cancer drug, whilst those in the control arm are exposed to a placebo, best available care, or an active comparator. For RCTs, we extracted hazard ratios for OS and PFS endpoints as well as the relative risk (RR) of tumor response. For single-arm trials, we calculated the objective response rate (ORR) based on the number of responders and subjects.

Disease epidemiology

For each disease, seven distinct variables depicting its epidemiologic characteristics were obtained from the GBD study and the National Cancer Institute. First, the GBD study's results tool was accessed to retrieve disease incidence, disease prevalence, and disability-adjusted life years (DALYs) data for the US population in 2019. DALYs are a composite measure of a disease's severity, comprising years lived with disability (YLD) and years of life lost (YLL). Second, 5-year survival rates were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program for each cancer entity. The number of therapeutic alternatives was retrieved from the National Cancer Institute's website listing all FDA-approved drugs per cancer entity. From a medical perspective, this can be interpreted as a measure of unmet needs, suggesting that cancer entities with few available therapeutic options have high unmet needs.[17, 24] From an economic perspective, this measure can be interpreted as competition within a cancer entity, indicating high competition for tumor types with a large number of treatment options.[25]

Drug prices

Drug prices were retrieved from two distinct sources. Payment limits covered under Medicare Part B (injectable drugs) were collected from files published by the Centers for Medicare & Medicaid Services (CMS). In line with previous studies,[14–17, 26] a drug's average sales price was then calculated by dividing the payment limit by 1.06. This is necessary given that Medicare's payment limit reflects 106% of a drug's average sales price. In contrast, the drug price for drugs covered under Medicare Part D was retrieved from Medicare's plan finder tool. Similar to previous studies,[14, 16, 17] prices were collected for a patient covered under the Medicare Advantage Plan "Humana Basic Rx Plan (PDP)" in New York, NY (ZIP: 10065) for a drug's full cost, including monthly premiums and deductibles. Therefore, *pure* prices are assessed, which do not entail expenses for combination therapeutics, administration, supportive care, or delivery.

However, until now this information only presents prices per unit, e.g. per 1 ml or 1 tablet. The FDA label was again accessed to retrieve each indication's treatment regimen. Based on this indication-specific dosing regimen, average monthly drug prices were then calculated for an average adult patient with a weight of 70 kg and a body surface area of 1.7 m^2.

Special FDA designations

Furthermore, we obtained data on each indication's special FDA designation. All five designations – orphan designation, fast-track, priority review, accelerated approval, and breakthrough therapy designation – were tracked based on information found on publically available FDA websites. The FDA's Orphan Drug Designations and Approvals database was searched to identify all orphan indications in the sample of cancer drugs.

Statistical analysis

We compared the cumulative number of special FDA designations cancer drugs and indications received regarding their time to approval, drug, indication, pivotal clinical trial, epidemiologic characteristics, clinical benefit, and price.

First, a survival analysis entailing a Kaplan-Meier curve and a Cox proportional hazard regression model was employed to compare the clinical development time, calculated as the difference between investigational new drug (IND) application to new drug application (NDA)/biologics license application (BLA) approval.

Second, the distribution and medians of drug, indication, pivotal clinical trial, and epidemiologic characteristics across the cumulative number of special designations were compared with Fisher's-exact-tests and Kruskal-Wallis tests, respectively.

Third, OS, PFS, and RR outcomes were meta-analyzed in random-effect models. Differences between the cumulative number of special FDA designations were compared with Cochran's Q test. Further, we conducted sensitivity analyses with meta-regressions to quantify the correlation between drugs' HRs/RRs/ORRs and each special designation. Accordingly, we conducted sensitivity analyses and weighted-least squares regressions to evaluate the association between indications' survival benefit and each special designation.

Fourth, for on-patent drugs with available data, prices in 2023 were compared across the number of special designations using one-way ANOVA and Kruskal-Wallis-tests.

Data were stored in Microsoft Excel (2016; Microsoft Corporation, Redmond, WA, USA) and then analyzed in STATA Version 14.0 (2015; StataCorp LLC, College Station, TX, USA). 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 were applicable.[27]

RESULTS

Sample overview

We identified a total of 355 cancer indications with FDA approval between 2013 and 2022. The FDA granted a total of 841 special designations. Each indication received an average of 2.4 special designations (median: 2, IQR: 2 to 3); yet, the number of designations varied substantially. 17 (5%) indications received no, 66 (19%) received one, 116 (33%) received two, 92 (26%) received three, 53 (15%) received four, and 11 (3%) received five special designations. Priority review was granted to 290 (82%), the orphan designation to 233 (66%), the breakthrough therapy designation to 137 (39%), accelerated approval to 112 (32%), and fast track to 69 (19%) indications. Pairwise correlation coefficients in Table e4 show that the following designations coincided: fast track and orphan (0.13, p=0.0138), breakthrough and accelerated approval (0.21, p<0.001), and breakthrough and priority review (0.24, p<0.001).

Clinical development time

The median clinical development time, defined as the time from IND to FDA approval, was significantly lower for drugs with multiple special designations (Figure 1). Median clinical development times were 7.3 months, 7.8 months (HR: 1.23, p=0.444), and 5.4 months (HR: 1.92, p=0.027) for drugs with 0-1, 2-3, and 4-5 special designations, respectively.

[Figure 1]

Drug characteristics

There was a significant association between the number of special designations and drug innovativeness (Table 1). The share of drugs rated first-in-class or advance-in-class increased with the number of special designations (0% vs. 40% vs. 83% vs. 97% vs. 100% vs. 100%, p<0.001). There were no significant associations between the number of special designations and a drug's number of indications, mechanism of action, or product type.

[Table 1]

Indication characteristics

The frequency of truly novel indications, rated as first-in-indication, increased with the total number of special designations (0% vs. 20% vs. 28% vs. 49% vs. 49% vs. 55%, p<0.001). More special designations were granted to original indications (18% vs. 15% vs. 20% vs. 39% vs. 74% vs. 100%, p<0.001), monotherapies (41% vs. 50% vs. 53% vs. 72% vs. 79% vs. 82%, p<0.001), hematologic cancers (0% vs. 17% vs. 30% vs. 39% vs. 49% vs. 55%, p<0.001), and advanced-line treatments (35% vs. 38% vs. 41% vs. 60% vs. 74% vs. 91%, p<0.001). The number of special designations was not associated with biomarker status (Table 2).

[Table 2]

Pivotal clinical trial

The median number of patients enrolled in the pivotal clinical trial decreased from 615 to 471, 398, 168, 104, and 120 (p<0.001) for indications with no, one, two, three, four, and five special FDA designations, respectively (Table 2). Accordingly, the share of phase 1/2 trials (12% vs. 21% vs. 23% vs. 69% vs. 87% vs. 82%, p<0.001) of single-arm design (6% vs. 17% vs. 20% vs. 51% vs. 72% vs. 82%, p<0.001) with open-label masking (59% vs. 67% vs. 71% vs. 80% vs. 91% vs. 100%) increased with more special designations. The share of trials assessing OS or PFS declined, whilst the share of trials assessing tumor response as the primary endpoint increased with the total number of designations. Concurrent RCTs with more special designations increasingly evaluated the new treatment relative to an inactive, e.g. placebo or no treatment, (65% vs. 64% vs. 68% vs. 76% vs. 100% vs. 91%, p<0.001).

Cancer epidemiology

Table 2 highlights that indications with multiple special designations treated rarer cancers with fewer treatment options. For indications with more special designations, median disease incidence (69 vs. 19 vs. 8 vs. 8 vs. 7 vs. 5, p<0.001) and prevalence (420 vs. 111 vs. 35 vs. 27 vs. 26 vs. 25, p<0.001) rates per 100,000 US citizens significantly declined. There were non-significant tendencies for indications with multiple special FDA designations to treat more severe diseases, e.g. those with higher DALYs and lower 5-year survival rates, with fewer available treatment options.

Clinical benefit

Indications' clinical benefit was significantly associated with the cumulative number of special FDA designations. HRs for OS (0.80 vs. 0.73 vs. 0.73 vs. 0.69 vs. 0.56 vs. 0.52, p=0.003) and PFS

(0.70 vs. 0.61 vs. 0.59 vs. 0.44 vs. 0.37 vs. 0.67, p<0.001) substantially declined, whilst tumor response rates (RR: 1.21 vs. 1.61 vs. 1.28 vs. 1.39 vs. 1.97 vs. 1.72, p=0.002) increased with more special designations (Figure 2). Accordingly, the improvement in OS (3.7 vs. 2.2 vs. 3.6 vs. 3.7 vs. 8.1 vs. 11.8 months, p=0.016), yet not PFS (2.0 vs. 3.3 vs. 4.1 vs. 4.5 vs. 5.6 vs. 2.5 months, p=0.077), increased with multiple special designations. Albeit ORR in single-arm trials was not significantly associated with the number of special designations, the median duration of response increased (NR vs. 15.3 vs. 8.3 vs. 10.6 vs. 12.0 vs. 17.5, p<0.012).

[Figure 2]

Results were robust in the conducted meta-regression and weighted-least squares regression analyses (Table e5). Each additional special FDA designation was correlated with a -0.04 (95%CI: -0.06 to -0.02, p<0.001) and -0.08 (95%CI: -0.11 to -0.05, p<0.001) decline in OS and PFS hazard ratios, respectively. Median improvements in OS and PFS increased by 3.0 months (95%CI: -1.1 to 7.1, p=0.150) and 1.8 months (0.6 to 2.9, p=0.004), respectively.

Drug prices

Average drug prices per month amounted to $21596, $14753, $32410, $41240, $38703, and $19184 for drugs with no, one, two, three, four, and five special FDA designations, respectively (Figure 3). Albeit mean drug prices did not significantly differ in the one-way ANOVA test (p=0.4923), median drug prices significantly differed in the Kruskal-Wallis test (p=0.029).

[Figure 3]

DISCUSSION

This study analyzed the efficacy, clinical evidence, cancer epidemiology, and price of drugs and indications with special FDA designations based on a sample of 355 cancer drug indications with FDA approval between 2012 and 2022. The FDA's special designations and review pathways are intended to facilitate and expedite the development of treatments for serious conditions filling unmet medical needs. We find that the cumulative number of special indications was associated with faster clinical development timelines, greater efficacy estimates, non-robust clinical trial designs, lower disease incidence, and higher monthly treatment costs.

Drug and indication characteristics

Drugs with multiple special designations were more innovative, as measured by biotechnological innovation and clinical novelty. Therefore, the FDA's special approval processes indeed expedite the development of highly innovative drugs. However, some addition-to-class and addition-to-indication treatments still received several special designations. Prasad, therefore, argues that expedited FDA review and special incentives should only be granted to the first – truly novel – drug that comes to market.[28] All drugs "that are not first-in-class compounds or that do not address an important unmet clinical need to be subjected to higher standards of clinical evaluation."[29] The FDA should especially encourage a head-to-head trial design testing addition-to-indication or advance-in-indication treatments compared to first-in-indication treatments. Perhaps with these head-to-head trials, patients and clinicians would have better evidence to find out which drug within a given class and indication offers the best treatment outcomes, instead of relying on non-robust statistical comparisons from network meta-analyses.

Indication characteristics were significantly associated with the number of special designations. More designations were granted to drug indications treating hematologic cancers as second- or third-line monotherapies. This is coherent with expectations since hematologic cancers are generally more severe, have a lower disease incidence/prevalence, have fewer treatment options,

and thereby (at least in the past) had greater unmet medical needs than solid tumors. Ultimately, this results in more special designations. Advanced-line treatments are indicated for patients that are refractory to first-line treatments. By definition, there are fewer available therapeutic options in the advanced-line setting, resulting in greater unmet needs than in the first-line setting. Accordingly, advanced-line treatments restrict an indications' eligible patient population to a subset of the disease population targeted by the first-line treatment. This is consistent with preceding studies finding combination regimens to be the preferred option for diseases with multiple available therapeutics on the market, e.g. non-orphans.[21] In summary, we conclude that drugs and indications with special designations are considered "special" due to their innovativeness, the patient population they treat, and the setting they are used in.

Clinical benefit

Drug indications' efficacy was significantly associated with each indication's number of special designations. More special designations were correlated with better treatment outcomes. Strikingly, indications with five out of five special designations prolonged patient life by 11.8 months compared to 3.7 months for those without any designation. Accordingly, there was a 28% difference in OS HRs for indications with five compared to no special designations (HR: 0.52 vs. 0.80). This association was consistent for PFS and tumor response outcomes and across all conducted analyses, e.g. meta-analysis, meta-regression, and weighted-least squares regression. Coherent with our results, Chambers et al. showed more special designations per indication were associated with higher incremental QALYs gained.[6]

At first glance, it seems like the FDA is terrific in seeking out the best drugs and indications with the highest benefit for patients. However, before we can draw this conclusion, we must also thoroughly evaluate the pivotal clinical trial design and epidemiology of special-designated indications. Special-designated indications with non-robust and biased clinical trial design may overestimate efficacy outcomes.[11, 30–32]

Pivotal clinical trial

Results demonstrate that indications with multiple special designations are more frequently supported by smaller single-arm open-label phase 1 or 2 trials compared to those with fewer designations. Moreover, trials less frequently assessed OS or PFS as the primary endpoint. This is coherent with previous studies.[29, 33–35] Multiple reasons could explain this difference in clinical trial design.[3] First, certain special designations were passed to enable the approval of indications based on phase 1 or 2 trials, e.g. the fast track program or the breakthrough therapy designation. Second, the accelerated approval program and the breakthrough therapy designation permit the FDA to approve indications based on PFS or tumor response outcomes (surrogate endpoints), rather than OS (clinical endpoint). Surrogate endpoints, which can be observed quicker than clinical endpoints, are commonly used in oncology to expedite drug development. Yet, their validity has not been proven across all cancer entities, even for surrogate endpoints used in the FDA approval of new cancer drugs.[36, 37] Clinical endpoints remain the gold standard to evaluate a cancer drug's efficacy. Third, for orphan-designated indications, it is more difficult to recruit a sufficient number of patients suffering from rare diseases.[38–41] Therefore, the FDA is more accommodating in the size and design of pivotal trials for drugs treating rare and severe conditions.

Although testing drugs for rare and severe conditions is challenging,[38–40] randomization and blinding "are among the hallmarks of high-quality clinical trial design."[29] However, it is necessary to spur innovation and expedite the development of first-in-class drugs by permitting more flexibility in clinical trial design. Yet, the authors believe that at least "me-too" drugs should be required to adhere to the evidentiary quality of randomization, blinding, and clinical endpoints, given that the first-in-class drug is already on the market and accessible to patients in need. This

is particularly important since several meta-epidemiological studies identified an upward bias in efficacy and safety outcomes among poorly randomized, open-label, and small trials measuring subjective outcomes.[30–32] Moreover, smaller trial sizes and shorter development periods could partially explain the high rates of post-marketing safety events for drugs approved under expedited review.[33, 42]

In summary, special review procedures gave the FDA more flexibility in the clinical trial design and approval of new drugs.[3] However, these legal changes resulted in the approval of drugs based on poor clinical trial design. In other words, "the FDA has continuously lowered its evidentiary standards." In this study, only two-thirds of all cancer indications were approved based on RCTs – this number dropped below 18% for indications with four or five special designations. Even among indications supported by RCTs, 75% of these trials compared the new drug to placebo or no treatment. Strikingly, all RCTs supporting indications with four or five special designations compared the new drug to an inactive comparator. Several studies show that such inadequate clinical trial comparators result in an overestimation of efficacy outcomes.[11, 32, 43, 44] In other words, comparing a new drug to no treatment only rarely reflects clinical practice.[28] These trials do not expand the scientific knowledge by much – barely that the new drug is better than not treating a patient at all. This could be one possible explanation for the observed association between the number of special designations and efficacy outcomes.

The FDA currently is not a *comparative effectiveness* authority, meaning that it does not have the power to force pharmaceutical companies to compare their drug to the clinically appropriate standard of care.[28] Pharmaceutical companies spend millions of dollars every year to lobby against such reforms of the FDA by the US Congress.[45] If US policymakers were to finally grant the FDA the authority to review and amend the design of clinical trials before they are conducted and submitted to the FDA, perhaps there would be more robust clinical trials that inform patients and physicians whether a new drug is superior to the standard of care.

Cancer epidemiology

A common requirement for accelerated approval, fast track, and breakthrough therapy programs is that they treat serious conditions and thereby fill an unmet medical need. Unmet medical need is defined by three factors: (1) the quantity and quality of available therapeutic options, (2) the burden of disease, and (3) the disease incidence.[24] This study indeed finds that indications with at least one special designation fill an unmet medical need. There were fewer therapeutic options, a greater burden of disease (although these two factors were not significant at the 5% level), and a smaller disease incidence/prevalence for drugs with special designations. Of course, the lower disease incidence could be particularly driven by the orphan designation.

These epidemiologic characteristics may also explain that indications with multiple special designations exert a greater clinical benefit. These indications target diseases with few treatment options. It is easier for new drugs to significantly improve patient life as monotherapy for rare diseases which have one, two, or three outdated alternatives compared to common malignancies, e.g. breast cancer, which have more than thirty treatment options. Moreover, there may be substantial *within-tumor heterogeneity* among patients with common cancers.[46] Therefore, only certain patient subgroups sharing a genetic alteration may benefit from a targeted new drug. In contrast, the within-tumor heterogeneity is narrower for rare cancers, resulting in more patients benefiting from highly effective targeted new drugs.[46]

In summary, the FDA indeed grants more special designations to drugs and indications that treat serious conditions with significant unmet medical needs. By their epidemiologic and histologic characteristics, drugs can attain a greater benefit for these serious conditions. The authors conclude that special designations help to allocate resources toward patient groups with few treatment

options that would otherwise not receive attention from pharmaceutical companies and investors. Developing drugs for rare and serious conditions has even become a very profitable and "economically viable" business strategy for many companies.[47–49] However, to fill the unmet medical needs that they were developed for, new drugs ought to be affordable. "A drug that cannot be purchased offers no value to patients."[28]

Drug prices

Results highlight that prices are positively correlated to a drug's cumulative number of special designations. Given that drug indications with multiple special designations are particularly developed for rare and serious conditions, the observed high drug prices are inequitably burdened onto patients with the greatest unmet needs. Overall, 95% of cancer drugs cost more than $10,000 per month.[23] This is far beyond the median American's monthly income of $4,012 per month. Even if assumed that the patient is insured (which is not the case for every American), approximately 20-30% of the drug price (=$3,000 per month) has to be paid out-of-pocket (OOP) in addition to health insurance costs which could easily amount to $500 to $1,000 per month.[50] For these treatments, pharmaceutical companies seem to not only benefit from the swift approval of the FDA's expedited review processes but also realize a price premium based on the associated "laudatory labels", which invoke unwarranted optimism about a drug's safety and efficacy among patients and physicians.[51–53] Particularly, the orphan designation was identified as a driving factor for this association.[23, 26, 39, 40, 54] However, drug prices are not transparent in the US. Albeit pharmaceutical companies claim to recoup the millions of dollars spent in researching and developing new drugs, there is no association between drugs' R&D costs and prices.[55, 56] Accordingly, prices are not aligned with their clinical benefit, but rather with the biotechnological innovation they achieve and the unmet medical needs they serve.[23, 26, 57] In summary, cancer drugs are not affordable for the majority of US citizens, and new pharmaceutical policies are needed to ensure that patients can access their required treatment. The authors are hopeful that the recent Inflation Reduction Act of 2022 will be a first step towards transparent drug price regulation in the US.

Limitations

This study has certain limitations. First, conclusions drawn from clinical trial data submitted to the FDA suffer from selection bias. The analyses only included successful clinical trials and indication approvals. However, a drug may have been tested in undisclosed clinical trials with a negative outcome. Similarly, the same drug could be developed across multiple indications, whilst this study only captures the ones with successful trial evidence leading to FDA approval. Ultimately, this selection bias of only successful trials may overestimate efficacy outcomes. Nevertheless, this study evaluated the evidence that is presented to the FDA, physicians, and patients at the time of approval. Based on this evidence, physicians prescribe new drugs to patients, drug prices are determined, coverage decisions are made, and reimbursement rates are paid.

Second, the results and conclusions of this study are limited to anti-cancer drugs. The generalizability of results beyond cancer drugs for other therapeutic areas is uncertain and has to be confirmed in future studies. It would be of particular interest to all stakeholders to compare and contrast the requirements, utilization, and implications of special approval processes across therapeutic areas.

Third, OS, PFS, and tumor response outcomes in this study entail trial data across different cancer entities. This may cause heterogeneity statistics (I^2) of PFS and tumor response outcomes to be low to high in the meta-analyses. Nonetheless, previous studies highlighted that meta-analysis of cancer drug outcomes should be conducted even in case of high heterogeneity as the interpretation of results remains consistent.[58, 59] For this study, it is crucial to include all cancer types as the

objective is to compare the efficacy of drugs with special designations across different cancer diseases.

Fourth, pharmaceutical companies need to actively apply for special FDA designations (except for priority review). If companies do not apply for these designations, the FDA does not grant them. Therefore, drugs that fulfill the requirements to be reviewed under a special program, may just be reviewed under a standard pathway. Ultimately, this could underestimate the association between the number of special designations and clinical benefit as well as price.

Fifth, drug prices were analyzed for the average US patient insured by Medicare in New York. The collected data only represents average sales prices, e.g. a drug's total acquisition costs. Patients and insurers must furthermore pay for supportive care agents, physician and nursing costs, travel expenditures, and other associated costs to receive a drug. Drug prices may vary for privately insured patients and across insurance plans.[60] Moreover, no discounts on drug prices, which are often confidentially negotiated between manufacturers and insurers via pharmaceutical benefit managers, are included in this analysis.[25] Nevertheless, Medicare and Medicare is the largest insurance scheme in the US with more than 80 million enrolled citizens. Therefore, this study captured drug prices for the largest insurer in the US and represents a benchmark for other insurance schemes. Future studies should evaluate the effectiveness of pricing, coverage, and reimbursement policies employed by other US insurers.

CONCLUSION

Drug development is a complex, tightly regulated, iterative, lengthy, and costly process. Within this process the FDA must balance all stakeholders' competing interests by (1) incentivizing investors and pharmaceutical companies to invest in and develop drugs for serious conditions with unmet medical needs; (2) expediting patient access to promising new drugs; (3) ensuring efficient and ethical clinical trial designs; whilst (4) safeguarding that all FDA-approved drugs are safe and effective. Over the past decades, US Congress passed new laws and special FDA review processes to incentivize pharmaceutical companies to develop and expedite patient access to promising drugs with a large benefit in treating serious conditions with unmet medical needs. These special FDA review processes have led to the development and approval of numerous drugs for diseases that were considered to be a death sentence beforehand.

Using a sample of 355 FDA-approved cancer indications, we find that the cumulative number of these special FDA designations was associated with faster clinical development times, greater efficacy, and greater unmet medical needs in the treated patient population. However, the cumulative number of special designations was also associated with non-robust, small, single-arm clinical trial designs and greater treatment costs. Whilst this flexibility in trial design is necessary to expedite patient access to promising first-in-class drugs, the safety and efficacy of "me-too" drugs should be tested in well-designed large, robust head-to-head trials assessing OS as the primary endpoint. To enforce these head-to-head trials, the US Congress should grant the FDA the authority to review a drug's clinical trial design and comparator agent before it is conducted (*comparative effectiveness authority*). In summary, the FDA must balance all stakeholders' competing interests as patients demand swift access to promising treatments, physicians require robust clinical trials, insurers mandate affordable prices, whilst investors and pharmaceutical companies seek to increase their revenues and profits. Over the past decades, this balance has shifted too far towards corporates', rather than patients', best interest.

DECLARATIONS

Author Contributions: D.T.M. and T.M. 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:* D.T.M. *Acquisition, analysis, or interpretation of data:* D.T.M. *Drafting of the manuscript:* D.T.M. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* D.T.M. *Administrative, technical, or material support:* D.T.M. *Study supervision:* D.T.M.

Funding/Support: No funding was received for conducting this study.

Conflict of Interest Disclosures: The authors declare that they have no conflicts of interest.

Data Sharing Statement: All data used in this study were in the public domain. All data relevant to the study are included in the article or uploaded as supplementary information.

Additional Contributions: Not applicable.

Patient Consent for Publication: Not applicable.

Ethics Approval: None needed.

Provenance and peer review: Not commissioned; externally peer-reviewed.

Patient and Public Involvement: No patients were involved in the conduct of this study.

Transparency Statement: D.T.M. (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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Tables and Figures

Clinical benefit, development, innovativeness, trials, epidemiology, and price for cancer drugs and indications with multiple special FDA designations: orphan, fast track, priority review, accelerated approval, and breakthrough therapy

No. (%)

Variables	No. of special FDA designations						*P Value* [a]	Overall
	0	**1**	**2**	**3**	**4**	**5**		
Drug characteristics								
Number of indications							*0.193*	
Single-indication	2 (66.7)	6 (60)	16 (69.6)	19 (54.3)	12 (37.5)	4 (36.4)		59 (51.8)
Multi-indication	1 (33.3)	4 (40)	7 (30.4)	16 (45.7)	20 (62.5)	7 (63.6)		55 (48.2)
Drug innovativeness							*<.001*	
Addition-to-class	3 (100)	6 (60)	3 (13)	1 (2.9)	0 (0)	0 (0)		13 (11.4)
Advance-in-class	0 (0)	3 (30)	12 (52.2)	17 (48.6)	23 (71.9)	6 (54.5)		61 (53.5)
First-in-class	0 (0)	1 (10)	8 (34.8)	17 (48.6)	9 (28.1)	5 (45.5)		40 (35.1)
Mechanism of action							*0.068*	
Cytotoxic chemotherapy	0 (0)	1 (10)	4 (17.4)	1 (2.9)	0 (0)	0 (0)		6 (5.3)
Targeted agents	3 (100)	6 (60)	16 (69.6)	19 (54.3)	25 (78.1)	7 (63.6)		76 (66.7)
Immune-regulators	0 (0)	3 (30)	3 (13)	15 (42.9)	7 (21.9)	4 (36.4)		32 (28.1)
Product type							*0.459*	
Small-molecule	3 (100)	6 (60)	13 (56.5)	18 (51.4)	24 (75)	6 (54.5)		70 (61.4)
Antibody	0 (0)	3 (30)	3 (13)	9 (25.7)	3 (9.4)	5 (45.5)		23 (20.2)
Antibody-drug conjugate	0 (0)	0 (0)	3 (13)	4 (11.4)	3 (9.4)	0 (0)		10 (8.8)
Other [b]	0 (0)	1 (10)	4 (17.4)	4 (11.4)	2 (6.3)	0 (0)		11 (9.6)
Total no. of drugs	**3 (100)**	**10 (100)**	**23 (100)**	**35 (100)**	**32 (100)**	**11 (100)**		**114 (100)**

Table 1. Characteristics of new cancer drugs by the cumulative number of special FDA designations

Notes: In this table, the cumulative number of special FDA designations were analyzed on a drug level. Drug characteristics were compared across drugs with no, one, two, three, four, and five special FDA designations for the first indication with FDA approval. The following five special FDA designations were considered in the analysis: orphan designation, fast track, accelerated approval, priority review, and breakthrough designations.

[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. (%)								
	No. of special FDA designations							Overall
Variables	**0**	**1**	**2**	**3**	**4**	**5**	***P Value*** [a]	
Indication characteristics								
Indication approval sequence							*<.001*	
Original indication approval	3 (17.6)	10 (15.2)	23 (19.8)	36 (39.1)	39 (73.6)	11 (100)		233 (65.6)
Supplemental indication approval	14 (82.4)	56 (84.8)	93 (80.2)	56 (60.9)	14 (26.4)	0 (0)		122 (34.4)
Indication novelty							*<.001*	
Addition-to-indication	17 (100)	23 (34.8)	6 (5.2)	2 (2.2)	0 (0)	0 (0)		48 (13.5)
Advance-in-indication	0 (0)	30 (45.5)	78 (67.2)	45 (48.9)	27 (50.9)	5 (45.5)		185 (52.1)
First-in-indication	0 (0)	13 (19.7)	32 (27.6)	45 (48.9)	26 (49.1)	6 (54.5)		122 (34.4)
Treatment type							*<.001*	
Combination	10 (58.8)	33 (50)	54 (46.6)	26 (28.3)	11 (20.8)	2 (18.2)		136 (38.3)
Monotherapy	7 (41.2)	33 (50)	62 (53.4)	66 (71.7)	42 (79.2)	9 (81.8)		219 (61.7)
Cancer type							*<.001*	
Hematological	0 (0)	11 (16.7)	35 (30.2)	36 (39.1)	26 (49.1)	6 (54.5)		114 (32.1)
Solid	17 (100)	55 (83.3)	81 (69.8)	56 (60.9)	27 (50.9)	5 (45.5)		241 (67.9)
Biomarker							*0.287*	
No	7 (41.2)	44 (66.7)	77 (66.4)	54 (58.7)	29 (54.7)	7 (63.6)		218 (61.4)
Yes	10 (58.8)	22 (33.3)	39 (33.6)	38 (41.3)	24 (45.3)	4 (36.4)		137 (38.6)
Line of therapy							*<.001*	
First-line	11 (64.7)	41 (62.1)	68 (58.6)	37 (40.2)	14 (26.4)	1 (9.1)		172 (48.5)
Second-line	4 (23.5)	21 (31.8)	41 (35.3)	41 (44.6)	25 (47.2)	8 (72.7)		140 (39.4)
≥Third-line	2 (11.8)	4 (6.1)	7 (6)	14 (15.2)	14 (26.4)	2 (18.2)		43 (12.1)
Pivotal clinical trial characteristics								
Enrolled patients, median (IQR)	615 (441-1072)	471 (226-800)	398 (173-712)	168 (84-356)	104 (72-162)	120 (106-130)	*<.001*	269 (106-564)
Clinical trial phase							*<.001*	
Phase 1	0 (0)	5 (7.6)	2 (1.7)	7 (7.6)	6 (11.3)	0 (0)		20 (5.6)
Phase 2	2 (11.8)	9 (13.6)	25 (21.6)	47 (51.1)	40 (75.5)	9 (81.8)		132 (37.2)
Phase 3	15 (88.2)	52 (78.8)	89 (76.7)	38 (41.3)	7 (13.2)	2 (18.2)		203 (57.2)
Trial design							*<.001*	
Single-arm	1 (5.9)	11 (16.7)	23 (19.8)	47 (51.1)	38 (71.7)	9 (81.8)		129 (36.3)
Non-randomized	0 (0)	0 (0)	0 (0)	3 (3.3)	5 (9.4)	0 (0)		8 (2.3)
Concurrent RCT	15 (88.2)	54 (81.8)	93 (80.2)	41 (44.6)	7 (13.2)	2 (18.2)		212 (59.7)
Dose-comparison RCT	1 (5.9)	1 (1.5)	0 (0)	1 (1.1)	3 (5.7)	0 (0)		6 (1.7)
Type of blinding							*0.003*	
Open-label/single-blind	10 (58.8)	44 (66.7)	82 (70.7)	74 (80.4)	48 (90.6)	11 (100)		269 (75.8)
Double-blind	7 (41.2)	22 (33.3)	34 (29.3)	18 (19.6)	5 (9.4)	0 (0)		86 (24.2)
Clinical trial arms							*<.001*	
1 arm	1 (5.9)	11 (16.7)	23 (19.8)	47 (51.1)	38 (71.7)	9 (81.8)		129 (36.3)
2 arms	15 (88.2)	52 (78.8)	91 (78.4)	42 (45.7)	15 (28.3)	2 (18.2)		217 (61.1)
≥3 arms	1 (5.9)	3 (4.5)	2 (1.7)	3 (3.3)	0 (0)	0 (0)		9 (2.5)
Primary Endpoint								212
Overall survival	2 (11.8)	18 (27.3)	24 (20.7)	9 (9.8)	2 (3.8)	0 (0)	*0.001*	55 (15.5)
Progression-free survival	9 (52.9)	27 (40.9)	47 (40.5)	31 (33.7)	8 (15.1)	1 (9.1)	*0.002*	123 (34.6)
Tumor response	2 (11.8)	10 (15.2)	36 (31)	46 (50)	41 (77.4)	10 (90.9)	*<.001*	145 (40.8)
Total concurrent RCTs, no.	15	54	93	41	7	2		
Comparator							*<.001*	
Active	6 (35.3)	24 (36.4)	37 (31.9)	22 (23.9)	0 (0)	1 (9.1)		90 (25.4)
Placebo/No treatment	11 (64.7)	42 (63.6)	79 (68.1)	70 (76.1)	53 (100)	10 (90.9)		265 (74.6)
Cancer epidemiology								
Disease incidence, median (IQR) [b]	69 (68-78)	19 (9-69)	8 (5-68)	8 (3-25)	7 (3-25)	5 (1-68)	*<.001*	10 (5-68)
Disease prevalence, median (IQR) [b]	420 (118-859)	111 (27-420)	35 (13-118)	27 (13-118)	26 (10-118)	25 (4-118)	*<.001*	35 (18-118)
DALYs per person, median (IQR)	7.1 (5.5-7.7)	7.7 (5.5-15.9)	10 (5.5-16.4)	10 (5.7-16.4)	10 (5.7-16.4)	10 (6.7-16.4)	*0.5172*	10 (5.5-16.4)
YLL per person, median (IQR)	6.6 (4.8-7.2)	7.2 (4.8-15.4)	9.3 (4.8-16.2)	9.3 (4.9-16.2)	9.3 (4.9-16.2)	9.3 (6.2-16.2)	*0.4586*	9.3 (4.8-16.2)
YLD per person, median (IQR)	0.5 (0.2-0.8)	0.5 (0.3-0.6)	0.5 (0.3-0.6)	0.5 (0.3-0.7)	0.5 (0.3-0.7)	0.5 (0.2-0.7)	*0.8236*	0.5 (0.3-0.7)
The 5-year survival rate, % (IQR)	76 (66-91)	71 (49-91)	67 (31-91)	72 (33-89)	75 (28-91)	66 (25-75)	*0.8165*	72 (33-91)
No. of available treatments, median (IQR)	38 (12-42)	16 (12-21)	16 (12-38)	14 (10-38)	20 (11-38)	14 (7-38)	*0.5747*	16 (11-38)
Total no. of indications	**17 (100)**	**66 (100)**	**116 (100)**	**92 (100)**	**53 (100)**	**11 (100)**		**355 (100)**

Table 2. Characteristics of new cancer indications by the cumulative number of special FDA designations

Notes: In this table, the cumulative number of special FDA designations were analyzed on an indication level. Indication, pivotal clinical trial, and epidemiologic characteristics were compared across indications with no, one, two, three, four, and five special FDA designations. The following five special FDA designations were considered in the analysis: orphan designation, fast track, accelerated approval, priority review, and breakthrough designations.

[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.

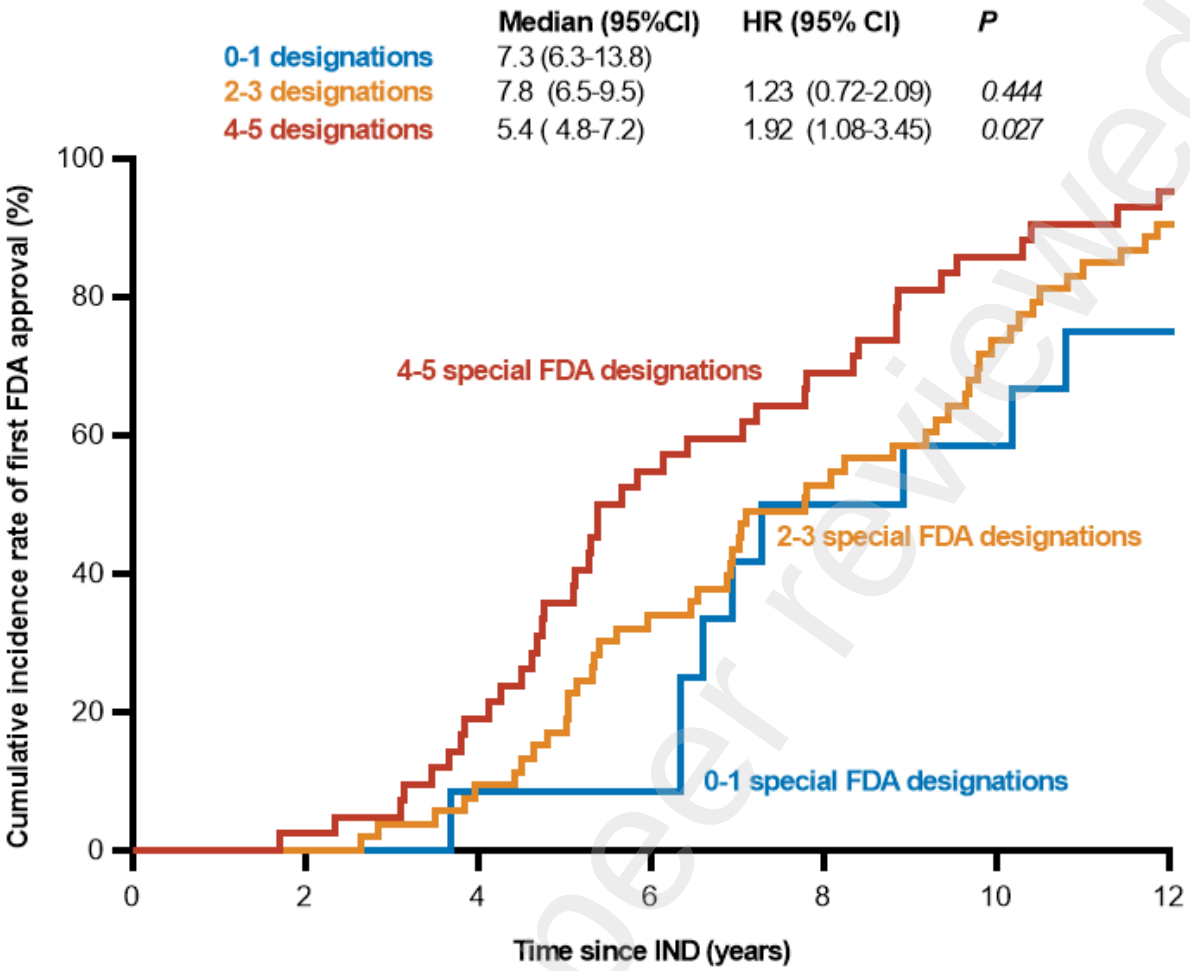


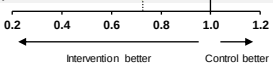
Figure 1. Time from IND to first FDA approval for new cancer drugs by the cumulative number of special FDA designations

Notes: The graph illustrates the cumulative incidence of the first FDA approval for cancer drugs with a 0-1 (blue curve), 2-3 (orange curve), and 4-5 special FDA designations for the first indication. P values calculated based on Cox-proportional hazard models. The following five special FDA designations were considered in the analysis: orphan designation, fast track, accelerated approval, priority review, and breakthrough designations.

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

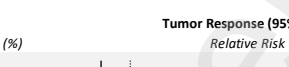
A

Subgroup	Intervention	Control	OS Hazard Ratio (95% CI)	I^2	*p value* [a]	OS improvement	*p value* [b]
	no. of patients with event/total no. of patients (%)					*median (IQR), months*	
No. of special FDA designations					*0.003*		*0.016*
0	1481/5367 (27.6)	1517/5129 (29.6)	0.8 (0.75-0.86)	11.8%		3.7 (1.95-4.6)	
1	6031/14491 (41.6)	6261/12701 (49.3)	0.73 (0.7-0.77)	40.7%		2.2 (1.9-3.55)	
2	8059/18708 (43.1)	8194/15779 (51.9)	0.73 (0.71-0.76)	0.0%		3.6 (2.7-5.4)	
3	2129/6127 (34.7)	1728/4642 (37.2)	0.69 (0.65-0.74)	0.0%		3.7 (2.7-4.2)	
4	219/1291 (17)	185/926 (20)	0.56 (0.41-0.72)	61.9%		8.1 (6.1-28.8)	
5	39/66 (59.1)	52/67 (77.6)	0.52 (0.3-0.75)	NA		11.8 (11.8-11.8)	
Overall	**17958/46050 (39)**	**17937/39244 (45.7)**	**0.73 (0.71-0.74)**	**23.1%**		**3.4 (2.2-5.4)**	



B

Subgroup	Intervention	Control	PFS Hazard Ratio (95% CI)	I^2	*p value* [a]	PFS improvement	*p value* [b]
	no. of patients with event/total no. of patients (%)					*median (IQR), months*	
No. of special FDA designations					*<.001*		*0.077*
0	1970/2967 (66.4)	1976/2725 (72.5)	0.7 (0.61-0.79)	78.5%		1.95 (1.35-3.55)	
1	6270/10868 (57.7)	6023/9459 (63.7)	0.61 (0.57-0.65)	75.3%		3.3 (1.5-5.3)	
2	11789/22494 (52.4)	11814/18630 (63.4)	0.59 (0.54-0.65)	92.0%		4.1 (0.85-7.7)	
3	3468/7343 (47.2)	3524/5772 (61.1)	0.44 (0.38-0.5)	88.0%		4.5 (2.5-8.5)	
4	321/841 (38.2)	278/527 (52.8)	0.37 (0.21-0.54)	92.4%		5.55 (5.2-15.5)	
5	55/66 (83.3)	48/67 (71.6)	0.67 (0.38-0.96)	NA		2.5 (2.5-2.5)	
Overall	**23873/44579 (53.6)**	**23663/37180 (63.6)**	**0.56 (0.53-0.6)**	**90.8%**		**3.9 (1.6-7.1)**	



C

Subgroup	Intervention	Control	Tumor Response (95% CI)	I^2	*p value* [a]	DoR improvement	*p value* [b]
	no. of patients with event/total no. of patients (%)		*Relative Risk*			*median (IQR), months*	
No. of special FDA designations					*0.002*		*0.319*
0	1252/2706 (46.3)	902/2467 (36.6)	1.21 (1.09-1.34)	56.9%		4.3 (3-6.8)	
1	4760/11946 (39.8)	2421/10556 (22.9)	1.61 (1.45-1.77)	86.2%		7.5 (2.95-15.7)	
2	10022/20228 (49.5)	6895/17845 (38.6)	1.28 (1.22-1.34)	79.3%		4.65 (2.3-7.4)	
3	4052/7872 (51.5)	2525/6255 (40.4)	1.39 (1.28-1.5)	78.7%		7.4 (4.9-8.9)	
4	516/861 (59.9)	276/648 (42.6)	1.97 (1.16-2.78)	75.1%		2 (2-2)	
5	51/223 (22.9)	18/143 (12.6)	1.72 (0.77-2.67)	0.0%		NR	
Overall	**20653/43836 (47.1)**	**13037/37914 (34.4)**	**1.36 (1.31-1.4)**	**81.0%**		**5.8 (2.7-8.7)**	

D

Subgroup	Responders	No. of patients	Tumor Response (95% CI)	I^2	*P Value* [a]	DoR	*p value* [b]
			Objective Response Rate (%)			*median (IQR), months*	
No. of special FDA designations					*0.197*		*0.012*
0	27	54	50 (36.7-63.3)	NR		NR	
1	492	1121	51 (35.4-66.6)	97.2%		15.25 (13.8-28)	
2	728	2103	36.8 (23.8-49.7)	98.2%		8.3 (7.6-8.3)	
3	1959	4983	44.4 (38-50.8)	96.4%		10.6 (7.9-12.1)	
4	1977	3776	53.4 (47.3-59.5)	94.2%		12 (9.2-14.8)	
5	630	1269	47.9 (35.9-59.8)	95.3%		17.5 (10-17.5)	
Overall	5813	13306	**46.7 (42.6-50.9)**	96.8%		**11.1 (8.2-14.8)**	

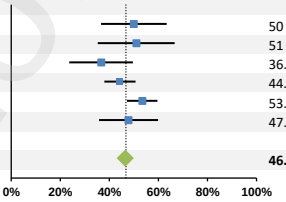


Figure 2. Meta-analysis of new cancer indications' overall survival, progression-free survival, and tumor response benefit by the cumulative number of special FDA designations

Notes: For randomized controlled trials with available outcome data, hazard ratios for OS (A) and PFS (B) and relative risk rates for tumor response (C) were meta-analyzed. For single-arm trials with available outcome data, objective response rates (D) were meta-analyzed. For tumor responses, a continuity adjustment of 0.5 for control arms with 0 responders was applied. The following five special FDA designations were considered in the analysis: orphan designation, fast track, accelerated approval, priority review, and breakthrough designations.

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

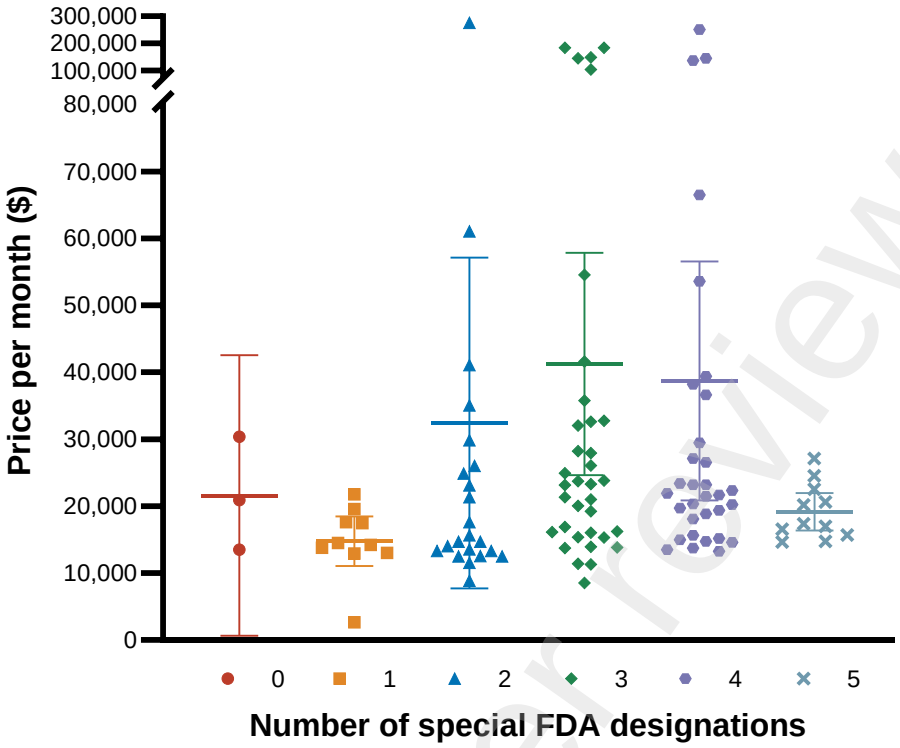


Figure 3. Drug prices by the cumulative number of special FDA designations

Notes: This graph illustrates monthly drug prices for cancer drugs with no, one, two, three, four, and five special FDA designations. The following five special FDA designations were considered in the analysis: orphan designation, fast track, accelerated approval, priority review, and breakthrough designations. Bars represent means with 95% confidence intervals. Prices in 2023 USD.

Abbreviations: FDA, US Food and Drug Administration.

Supplementary Online Content

Clinical benefit, development, innovativeness, trials, epidemiology, and price for cancer drugs and indications with multiple special FDA designations: orphan, fast track, priority review, accelerated approval, and breakthrough therapy

This supplementary material has been provided by the authors to give readers additional information about their work.

	Orphan Designation	Fast Track	Accelerated Approval	Priority Review	Breakthrough Therapy
Year	1983	1988	1992	1992	2012
Eligibility	Drugs for diseases with fewer than 200,000 affected US citizens or drugs with limited sales potential	Drugs which treat serious conditions and thereby fill an unmet medical need	Drugs which treat serious conditions and thereby fill an unmet medical need	Drugs with "significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications"	Drugs which treat a serious condition and first evidence indicates "substantial improvement" compared to other therapies
Benefit	-Tax credit (25%) [a] -R&D grants -User fee waiver -More collaboration with and guidance by the FDA -Extend period of market exclusivity (7 years) [b]	-More frequent communication with the FDA -Approval based on phase 2 trial -Potential for rolling review	-Approval based on surrogate or intermediate clinical [c] endpoint	-The FDA must review the NDA within 6 instead of 10 months [d]	-All fast track benefits -Communication with the FDA as soon as phase 1 -Meetings with senior FDA staff -Cross-disciplinary project lead -Adaptive and efficient trial design
Conditions	-	FDA may request a phase 4 trial	FDA may request a phase 4 trial	-	FDA may request a phase 4 trial
Effect on	Drug development and market exclusivity	Trial design and FDA review	Trial design and FDA review	FDA review	Trial design and FDA review

Table e1. An overview of the FDA's special review pathways and designations

[a] The tax credit was reduced from 50% to 25% in 2017.
[b] Extended from a market exclusivity period of 5 years.
[c] In 2012, congress amended that the FDA may also use the accelerated approval pathway for drugs with an intermediate clinical endpoint.
[d] The standard review timelines were reduced from 12 to 10 months in 2002.

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

Notes: Adapted from Kesselheim & Darrow and Darrow et al.*[1, 2]*

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/ https://clinicaltrials.gov/
	Clinical trial design	
	Clinical trial phase [a]	
	Clinical trial blinding	
	Clinical trial primary endpoint	
	Clinical trial comparator	
	Clinical trial endpoint outcome	
WHO	Drug innovation and indication novelty [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 [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
FDA label / Federal register	IND date [d]	https://www.federalregister.gov/ https://www.accessdata.fda.gov/scripts/cder/daf/
	FDA approval date	
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.accessdata.fda.gov/scripts/cder/daf/

Table e2. Data sources

[a] Combined phase 1/2 trials were classified as phase 2, combined phase 2/3 as phase 3.
[b] Drugs were categorized as "first-in-class", "advance-in-class", and "addition-to-class" according to Lanthier et al.'s methodology of defining drug innovation. Further, indication novelty was accordingly assessed to define indications' as "first-in-indication", "advance-in-indication", and "addition-to-indication".
[c] For drugs without available data from Medicare 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.

Group	Variable	Type	Definition
Drug characteristics	Number of indications	Binary	0 for single-indication drugs 1 for multi-indication drugs
	Drug Innovativeness	Ordinal	0 for addition-to-class drugs 1 for advance-in-class drugs 2 for first-in-class drugs
	Mechanism of action	Nominal	0 for cytotoxic chemotherapy 1 for targeted agents 2 for immune-regulators
	Product type	Binary	0 for small-molecules 1 for antibodies 2 for antibody-drug conjugates 3 for others
Indication characteristics	Indication approval sequence	Binary	0 for original indication approvals 1 for supplemental indication approvals
	Indication Novelty	Ordinal	0 for addition-to-indication 1 for advance-in-indication 2 for first-in-indication
	Treatment type	Binary	0 for combination treatments 1 for monotherapies
	Cancer type	Binary	0 for hematologic cancers 1 for solid cancers
	Biomarker	Binary	0 for indications without biomarker 1 for indications with biomarker
	Line of therapy	Binary	1 for fist-line therapies 2 for second-line therapies 3 for ≥third-line therapies
Clinical trial characteristics	Enrolled patients	Interval	Number of patients enrolled in the clinical trial
	Trial phase	Ordinal	1 for phase 1 trials 2 for phase 2 and phase 1/2 trials 3 for phase 3 and phase 2/3 trials
	Trial design	Nominal	0 for single-arm trials 1 for non-randomized trials 2 for concurrent RCTs 3 for dose-comparison RCTs
	Type of blinding	Nominal	0 for trials with open-label/single-blind masking 1 for trials with double-blind masking
	Clinical trial arms	Ordinal	1 for trials with 1 arm 2 for trials with 2 arms 3 for trials with ≥3 arms
	Primary endpoint	Nominal	Primary endpoints categorized in OS, PFS, tumor response
	Comparator for concurrent RCTs	Binary	0 for placebo or no treatment 1 for active comparator
	Hazard ratio	Interval	Hazard ratio reported by the clinical trial for OS or PFS
	RR or ORR	Interval	For RCTs: Tumor response calculated as RR based on each trial's number of responders and subjects in the treatment and control arm For single-arm trials: Tumor response calculated as ORR based on the number of responders and subjects
	Median survival benefit	Interval	Median survival benefit between treatment and control arm for OS, PFS, and duration of response
Cancer epidemiology	Disease incidence	Interval	Disease incidence rate per 100,000 US citizens in 2019
	Disease prevalence	Interval	Disease prevalence rate per 100,000 US citizens in 2019
	DALY	Interval	DALYs per person for the US population in 2019
	YLD	Interval	YLD per person for the US population in 2019
	YLL	Interval	YLL per person for the US population in 2019
	5-year survival rate	Interval	5-year survival rate (in %)
	No. of available treatment options	Interval	Number of drugs available per cancer entity in 2022
Drug prices	Price per month in 2023	Interval	Monthly price for Medicare Part B and D drugs
Special FDA designation	Orphan designation	Binary	0 for non-orphan indications 1 for orphan indications
	Fast track	Binary	0 for indications not approved under fast track review 1 for indications approved under fast track review
	Accelerated approval	Binary	0 for indications without accelerated approval 1 for indications with accelerated approval
	Priority review	Binary	0 for indications not approved under priority review 1 for indications approved under priority review
	Breakthrough therapy designation	Binary	0 for non-breakthrough therapy indications 1 for breakthrough therapy indications
	Number of special designations	Interval	Cumulative number of special FDA designations received by each indication

Table e3. Variables included in the dataset

Abbreviations: DALYs, disability-adjusted life years; DoR, duration of response; FDA, US Food and Drug Administration; HR, hazard ratio; IQR, interquartile range; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RR, relative risk; RCTs, randomized controlled trials; YLD, years lived with disability; YLL, years of life lost.

	Orphan Designation	Fast Track	Accelerated Approval	Priority Review	Breakthrough Therapy
Orphan Designation	1.00				
Fast Track	0.13*	1.00			
Accelerated Approval	0.05	0.08	1.00		
Priority Review	0.06	0.03	0.16**	1.00	
Breakthrough Therapy	0.06	-0.02	0.21***	0.24***	1.00

Table e4. Pearson correlation coefficients between special FDA designations

Notes: In this table pairwise Personal correlation coefficients are presented for each special FDA designation.

Abbreviations: FDA, US Food and Drug Administration, * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

	Coef.	95% CI	*P Value*
OS			
OS HR	-0.04	[-0.06 to -0.02]	*<.001*
Median improvement in OS	2.99	[-1.11 to 7.10]	*0.150*
PFS			
PFS HR	-0.08	[-0.11 to -0.05]	*<.001*
Median improvement in PFS	1.75	[0.58 to 2.92]	*0.004*
Tumour response			
RR	0.77	[-0.40 to 1.95]	*0.195*
Median Improvement in DoR	-0.30	[-1.91 to 1.31]	*0.710*

Table e5. Meta-regressions and weighted-least squares regressions of efficacy measures on the cumulative number of special FDA designations

Notes: Meta-regressions were conducted of OS/PFS HRs and tumour response RRs on the cumulative number of special FDA designations. For median improvements in OS, PFS, and duration of response, WLS regressions were conducted. The WLS models were weighted by the number of patients enrolled in each indication's pivotal clinical trial. The following five special FDA designations were considered in the analysis: orphan designation, fast track, accelerated approval, priority review, and breakthrough designations.

Abbreviations: DoR, duration of response; FDA, US Food and Drug Administrations; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk; WLS, weighted-least squares.

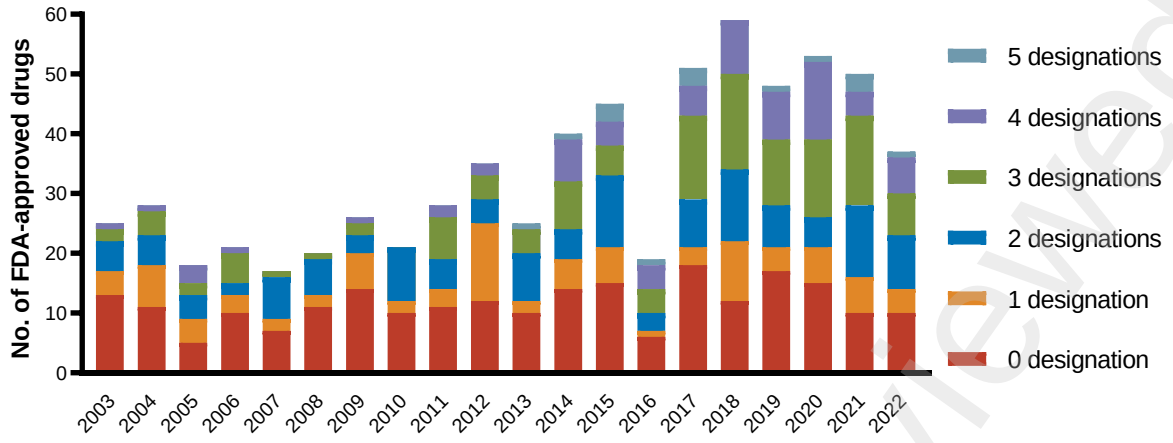


Figure e1. New FDA drug approvals with multiple special designations from 2003 until 2022

Not Abbreviations: FDA, US Food and Drug Administration.

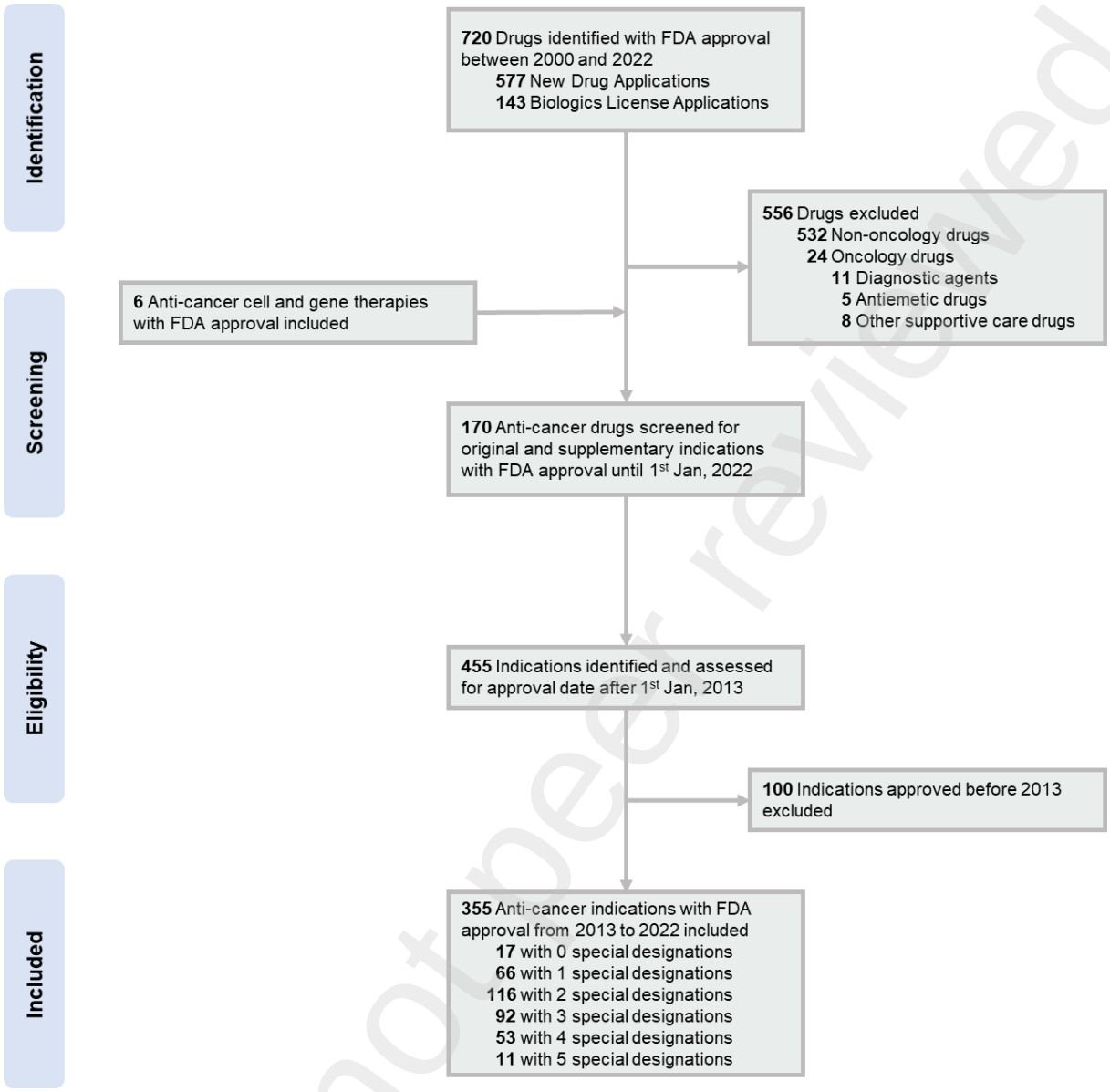


Figure e2. Flow chart of cancer drugs and indications with FDA approval included in the analysis

Notes: All new drugs and biologics, including cell therapies, with FDA approval from 1st January, 2000 and 1st January, 2022 were identified in the Drugs@FDA database. Then, we excluded all non-oncology drugs and oncology drugs for supportive care, anti-emetics, and diagnostic agents. For the remaining sample of anti-cancer drugs, we screened the Drugs@FDA database for original and supplemental indications with FDA approval between 1st January, 2000 and 1st January, 2022. Finally, the sample was restricted to include only anti-cancer indications with FDA approval after 1st January, 2013 given that the Breakthrough Therapy Designation was signed into law in 2012. For final set of anti-cancer indications, we identified the cumulative number of special FDA designation, considering the following special FDA designations and approval pathways: orphan designation, fast track, accelerated approval, priority review, and breakthrough designations.

Abbreviations: FDA, US Food and Drug Administration.