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An Overview of Cancer Drugs Approved by the US Food and Drug Administration Based on the Surrogate End Point of Response Rate

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IMPORTANCE Approximately one-third of cancer drugs are approved based on response rate (RR)—the percentage of patients whose tumors shrink beyond an arbitrary threshold—typically assessed in a single-arm study.

OBJECTIVE To characterize RR end points used by the US Food and Drug Administration (FDA) for cancer drug approval.

DESIGN, SETTING, AND PARTICIPANTS A retrospective review of FDA-approved drug indications in oncology from 2006 to 2018.

EXPOSURES Data related to cancer type, line of therapy (first-line, second-line, or third-or-later-line treatment for advanced/metastatic disease), type of FDA approval pathway, trial design, sample size, and level of innovation were extracted.

MAIN OUTCOMES AND MEASURES The primary outcome was the RR used as the basis for FDA approval. The secondary outcome was rate of complete response.

RESULTS Eighty-five indications for 59 cancer drugs were identified, 32 (38%) received regular approval, and 53 (62%) were granted accelerated approval. Twenty-nine (55%) accelerated approvals were later converted to regular approval. Of these, 6 (21%) approvals showed overall survival benefit, 16 (55%) later established progression-free survival benefit, and 7 (24%) continued to use RR but gained regular approval. The median RR among the 85 indications was 41% (interquartile range [IQR], 27%-58%). Among them, 14 of 85 (16%) had an RR less than 20%, 28 of 85 (33%) had an RR less than 30%, and 40 of 85 (47%) had an RR less than 40%. The median complete RR for 81 participants was 6% (IQR, 2%-22%). The median sample size among studies leading to approval was 117 (IQR, 76-182; range, 18-1052 participants). Drugs with accelerated approval pending confirmatory data had lower RR compared with drugs that have completed most postmarketing efficacy requirements (median, 28%; IQR, 15%-50% vs median, 42%; IQR, 31%-58%; *P* = .02).

CONCLUSIONS AND RELEVANCE Many cancer drugs approved on the basis of response rate offer numerically low or modest response rates. Most premarket studies accrue more than 100 patients. Some of these drugs could potentially be tested in premarket randomized clinical trials measuring directly end points that demonstrate clinical benefit.

Invited Commentary
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Supplemental content

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The US Food and Drug Administration (FDA) approves cancer drugs based on (1) overall survival (OS) or patient reported outcomes, (2) progression-free survival, ie, the time until cancer recurs or worsens, or (3) response rate (RR), ie, the percent of patients experiencing tumor shrinkage.[1,2] Response rate and complete response rate are typically ascertained in uncontrolled, nonrandomized studies. Because these trials have no comparator arm, drug-related adverse events may be missed among symptomatic patients because they may be mistakenly attributed to their underlying cancer. There is also uncertainty about whether and to what degree these drugs improve survival or quality of life.[3]

The FDA has noted that a high RR in early phase trials justifies granting expedited approval. The agency has stated, "for drugs demonstrating unprecedented activity in early clinical development in cancers with few effective options, the ability to randomly allocate patients to either an agent with markedly improved durable response rates or to a tox-ic and marginally effective comparator may not be feasible because equipoise may not exist."[4] The FDA has used response rate to justify both accelerated and regular (traditional) approval. The accelerated approval program is often based on response rate and duration of response in a single-arm study. For accelerated approval, the FDA generally mandates postmarketing efficacy requirements be fulfilled by subsequent randomized clinical trials in the same treatment setting or in an earlier disease course setting, but the agency has also accepted larger single-arm studies using RR.[5] This is different from the regular approval pathway where postmarketing commitments generally only address drug-drug interactions, dosing based on hepatic and renal impairment, short-term and long-term drug safety, and efficacy in special or subgroup populations, and not further evidence of general efficacy. The European Medicines Agency (EMA) echoes a similar perspective that "outstanding activity from a new drug in early development in high unmet need situations with no therapeutic alternatives might obviate the need for the large confirmatory trials."[6] There is no specific definition of "unprecedented" or "outstanding," and this determination is made at the discretion of the agency. Adding to the complexity, although regular approvals do not typically require further demonstration of efficacy, accelerated approvals may be converted to regular approvals based solely on impact on a surrogate end point.

For most nonhematologic cancers, the RR is defined as the percentage of patients with 30% or more tumor shrinkage, and the complete response rate is the percentage of patients with no visible disease and normalization of lymph nodes. The use of 30% shrinkage is an arbi-trary cutoff and does not mean that symptoms or longevity are improved.[7] Similarly, approvals for drugs for hematologic malignant diseases use various criteria of blood-based and imaging-based RRs that do not necessarily predict survival.[8-10] This investigation aims to describe FDA drug approvals made on the basis of RRs.

Key Points

Question When the US Food and Drug Administration approves cancer drugs based on response rate (RR) (ie, the percentage of patients whose cancer shrinks beyond an arbitrary threshold), what is the RR?

Findings In this review of 85 cancer drug indications approved on the basis of RR, the median RR was 41%. Of the 85 approvals, 14 (16%) had RR less than 20%, 28 (33%) had an RR less than 30%, and 40 (47%) had an RR less than 40%.

Meaning Many cancer drugs are approved on the basis of low or modest RRs, typically in single-arm studies.

Methods

Overview

We studied all drugs approved on the basis of RR, ie, a measure of the percent of cancer patients whose tumor shrinks beyond an accepted threshold. We sought to characterize the RR end point used for approval, the frequency of regular or accelerated approval, the end points used for subsequent conversion from accelerated to regular approval, and the number of indications that had been studied in randomized clinical trials during the approval process.

Data Set

We performed a comprehensive review of available package inserts for all oncology drugs that were FDA approved on the basis of RR end points for any adult malignant disease from January 1, 2006, to September 30, 2018. The public FDA website was accessed via https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm to collect data from publicly available package inserts and FDA approval documents. Additional data with respect to complete response rate was collected from the subsequent published clinical trials to complement the respective package inserts.[11-15] Supplemental data was also verified using https://clinicaltrials.gov/. Every oncology drug and any subsequent new indication in a distinct cancer type were counted as separate entries. Both accelerated and regular approvals were included in the data set. This study excluded drug indications of which the primary basis for first drug approval was end points other than RR: progression-free survival (PFS), overall survival (OS), or patient reported outcomes (PRO). Drug indications in the neoadjuvant and adjuvant treatment setting were also excluded (ex. pertuzumab was initially approved for *HER-2* amplified early-stage breast cancer on the basis of pathologic complete response on the surgical specimen). This retrospective study of publicly available medication package inserts involved no protected health information and enrolled no study participants and was therefore not submitted for institutional review board approval.

Response Rate Outcome

For each indication in our data set, we used the corresponding tumor-specific RR criteria that were used to justify FDA approval. Objective overall RR using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, a widely used but still arbitrary method

to measure tumor diameter shrinkage down to 30% (partial response) or growth to 20% (disease progression), has been adopted in many solid tumor trials to systemically measure the growth and shrinkage of solid tumors.[16,17] With respect to hematologic malignant diseases, response rate based on PET scan results, clinical assessment, complete blood counts (eg, hematologic complete response), serological testing (eg, multiple myeloma response criteria), cytogenetic testing (eg, major cytogenetic response), and molecular response (eg, major molecular response) have all been used for FDA drug approval.[18]

Data Collection

The main outcome of interest was RR as defined by each clinical trial used as the basis for first drug approval. Complete response rate was also specifically collected, if available, as the secondary outcome of interest.

In addition, we collected data related to the oncology drug, mechanism of action, cancer type, line of treatment setting, year of first drug approval, type of drug approval, subsequent conversion to regular approval, efficacy end points used for drug approval, and study design used for initial drug approval and postmarketing confirmation.

With regard to the oncology drug, we categorized each drug approval by "level of innovation" described by Lanthier and colleagues[19] with modification pertaining to oncology drug approval: (1) "first-in-class" (new molecular or biologic entity), (2) "first-in-indication" (FDA-approved drug or drug class used in a new cancer type), (3) "advance-in-class" (similar drug but promising improvement deemed by FDA to warrant priority review), and (4) "addition-to-class" (similar drug that did not warrant priority review). With regard to the cancer type, we categorized each disease setting by rarity of the indication based on incidence and mortality data from the American Cancer Society[20] and published estimates, all detailed in eMethods in the Supplement to assess feasibility of randomized clinical trials. "Rare" was defined by fewer than 100 cases or deaths per year, "uncommon" by fewer than 1000 cases or deaths per year, and "common" by 1000 or greater cases and deaths per year. Our study was primarily conducted between July 25, 2018, and October 25, 2018, with data cutoff on September 30, 2018.

Statistical Analysis

Descriptive statistics were completed for all collected data. The main outcome, RR, was tabulated individually and in quintiles. Response rate was compared by FDA approval type, such as first accelerated vs first regular approval (2 groups) and accelerated approval thus far vs regular approval at any time (2 groups), by using the Mann-Whitney test. They were also compared by subcategories of FDA approval type, accelerated only vs accelerated followed by regular vs regular approval only (3 groups), by using the Kruskal-Wallis test. They were additionally compared by study design, randomized clinical trials ever completed thus far vs never completed yet (2 groups), by using the Mann-Whitney test. *P* values were not adjusted for multiple hypothesis testing. We used SAS statistical software (version 9.4; SAS Institute, Inc) for all comparison analyses.

Results

There were 59 oncology drugs with 85 unique marketing authorizations approved by the FDA for advanced-stage or metastatic cancer on the basis of an RR end point from 2006 to 2018. Thirty-two of 85 (38%) were granted regular approval immediately with limited postmarketing efficacy requirements, and 29 of 85 were granted accelerated approval followed by regular approval. Of the 53 (62%) granted accelerated approval, 6 later established OS advantage, 16 later established PFS advantage, 7 continued to use only RR end point results, and 24 of 85 (28%) have not yet been converted to regular approval (**Table 1**).

Eight of 85 (9%) initial drug registration trials were randomized clinical trials, whereas 77 of 85 (91%) trials used a single-arm, nonrandomized multicohort, or randomized multidose study design (no standard-of-care control arm). Including subsequent trials done to fulfill postmarketing requirements, 34 of 85 (40%) have had randomized clinical trials. Twenty-six of 59 accelerated approvals have completed randomized clinical trials to fulfill their postmarketing requirement. Characteristics of all 85 indications receiving approval on the basis of RR end points show that most drugs were through the accelerated approval pathway, were first-in-class or first-in-indication, and were not conventional chemotherapy (Table 1).

The median RR for all 85 indications was 41% (IQR, 27%-58%), and occurred in trials with median sample size of 117 (IQR, 76-182) participants. The median complete response rate for the available 81 drug indications was 6% (IQR, 2%-22%), as complete response data were not reported for 4 drug indications. Most studies reported median duration of response (among patients who respond) greater than 6 months. Among all approvals, 14 of 85 (16%) had RR less than 20%, 28 of 85 (33%) had an RR less than 30%, and 40 of 85 (47%) had an RR less than 40%. Most approved drugs had RR ranging from 20% to 59% (**Table 2**).

There was no difference in the RR between drugs granted accelerated approval and drugs granted regular approval (median, 41%; IQR, 26%-54% vs median, 43%; IQR, 30%-61%; *P* = .21) (**Figure 1** and **Figure 2**). Each oncology drug indication and its level of innovation are listed in eTable 1 in the Supplement, which links the details of each data entry to the labeled column in the Figures. All 85 drug indications also exhibit wide range of sample size and disease settings detailed in eTable 2 in the Supplement. The RR among drugs granted accelerated approval pending confirmation, however, was lower than the RR for those converted to regular approval and those initially granted regular approval (median, 28%; IQR, 15%-50% vs median, 42%; IQR, 32%-54% vs median, 43%; IQR, 30%-61%; *P* = .048) (**Table 3**). There was a difference in the RR between drugs granted accelerated approval pending confirmation and drugs that had obtained regular approval, either initially or subsequently (median, 28%; IQR, 15%-50% vs median, 42%; IQR, 31%-58%; *P* = .02) (Table 3). There was also no difference in the RR of indications with available randomized clinical trial results vs those with no such results (median, 41%; IQR, 30%-52% vs median, 41%; IQR, 25%-61%; *P* = .85).

Table 1. Characteristics of 85 FDA-Approved Drug Indications in Oncology From 2006 to 2018 on the Basis of Response Rate End Point

FDA Approval Type	No. (%)
No.	85
First approval	
Regular	32 (38)
Accelerated	53 (62)
Accelerated converted to regular approval	
Owing to OS benefit	6 (7)
Owing to PFS benefit	16 (19)
Owing to response rate benefit	7 (8)
Accelerated approval only	24 (28)
Line of therapy	
First-line advanced or metastatic	23 (27)
Second-line advanced or metastatic	38 (45)
Third-or-later-line advanced or metastatic	24 (28)
Use of randomized clinical trials for first approval	
Yes	8 (9)
No	77 (91)
Use of randomized clinical trials ever	
Yes	34 (40)
No	51 (60)
Drug innovation	
First-in-class	19 (22)
First-in-indication	32 (38)
Advance-in-class	23 (27)
Addition-to-class	11 (13)
Drug mechanism class	
Cytotoxic chemotherapy	5 (6)
Biologic therapy	8 (9)
Small molecule targeted agent	44 (52)
Immunotherapy	20 (24)
Miscellaneous (radiation, cellular, etc)	8 (9)
Rarity of disease indication	
Rare (fewer than 100 cases per year)	9 (11)
Uncommon (100 to 999 cases per year)	12 (14)
Common (>1000 cases per year)	64 (75)
Most common cancer types	
B cell non-Hodgkin lymphoma	13 (15)
Lung cancer	12 (14)
Myeloproliferative disorder/chronic myelogenous leukemia	8 (9)
Acute lymphoid leukemia	6 (7)
Melanoma	4 (5)
Multiple myeloma	4 (5)
T-cell non-Hodgkin lymphoma	4 (5)
Urothelial cancer	4 (5)
Nonmelanoma cutaneous cancers	4 (5)
Acute myeloid leukemia/myelodysplastic syndrome	3 (3.5)
Chronic lymphocytic leukemia	3 (3.5)
Colorectal cancer	3 (3.5)
Hodgkin lymphoma	3 (3.5)
Other cancers	14 (16)
Response rate end point leading to approval, median (IQR) [range], %	41 (27-58) [12-86]
Reported median duration of response (N = 46), median (IQR) [range], mo	9 (7-12) [2-37]
Complete response rate only (N = 81), median (IQR) [range], %	6 (2-22) [0-83]
Sample size of initial drug registration trial, median (IQR) [range], persons	117 (76-182) [18-1052]

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

Regarding complete response, 51 of 81 (63%) had complete response rate of less than 10%, 60 of 81 (74%) had complete response rate of less than 20%, 63 of 81 (78%) had complete response rate of less than 30%, and 70 of 81 (86%) had complete response rate of less than 40%. Most complete response rates were below 10% among 81 available drugs (eFigure in the Supplement). Complete response rate was higher in drugs granted regular approval compared with drugs granted accelerated approval (median, 12%; IQR, 4%-33% vs median, 4%; IQR, 1%-11%; $P = .02$). Comparison of complete response rate by FDA approval type shows the complete response is low across approval types (eTable 3 in the Supplement).

Currently 24 of 85 (28%) drug indications have not received regular approval. The initial approval dates and the requested deadlines for all of these accelerated approvals are listed in eTable 4 in the Supplement. Only 12 of 24 indications specifically required randomized clinical trials and OS as the efficacy end point in the postmarketing requirements, as noted in eTable 4 in the Supplement.

Discussion

Our investigation of drug approvals made on the basis of RR—a measure of the percentage of cancer patients whose tumor shrinks beyond an arbitrary threshold—reveals several points. First, many drugs that are approved based on RR do not have substantial drug activity, with median RR of 41% (and 16% of indications had RR of less than 20%). Although high response rates (>60%) could justify approval based on RR, we found just 18 (21%) indications have such a response rate. Notably imatinib, a truly transformational drug, had a 98% rate of complete hematologic response in its phase 1 trial and eventually also had confirmed survival benefit.[21,22] In contrast, we find the median complete RR to be 6% (and 74% of indications had complete response of less than 20%). Our current drug approval process based on response rate suggests that most drugs have less than transformational response rates and unconfirmed clinical benefit, with only 6 of 85 establishing OS advantage in postmarketing studies. Although, in specific settings, achieving a response has shown prognostic value regarding OS,[23,24] the ability of RR to serve as a validated surrogate for OS varies among cancer types, and is generally poor.[3,25,26]

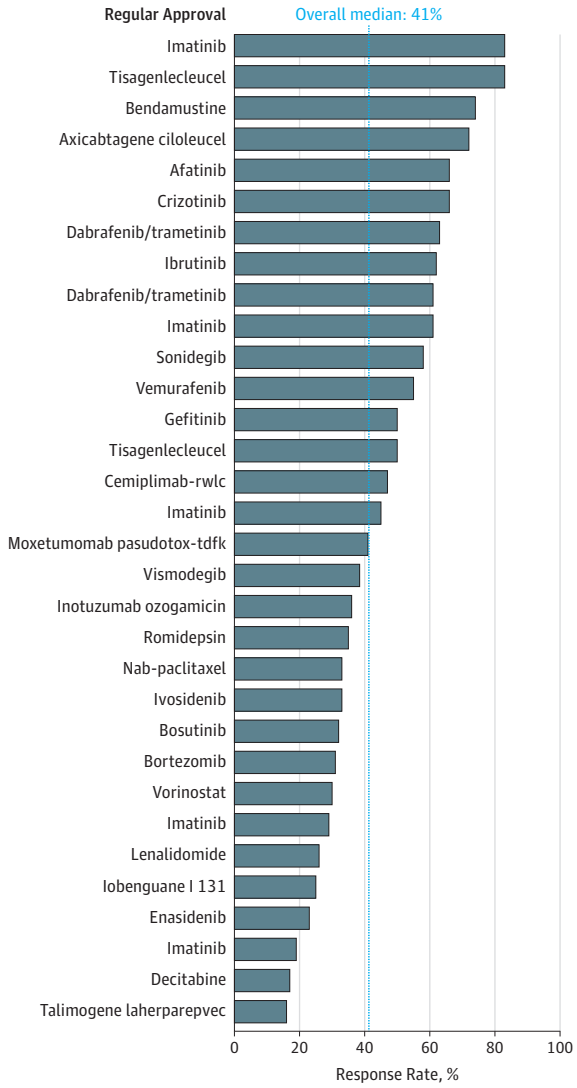
Second, the sample size of studies ascertaining RR is substantial (median, 117; IQR, 76-182 participants). Combining these observations—modest response rate and reasonable sample sizes—suggests that randomized clinical trials may be feasible for many of these indications, yet 60% of these indications do not yet have randomized clinical trials. We do note some of these indications were in patients with rare cancers or rare subtypes of cancers and randomized clinical trials may be challenging. In oncology, we have randomized trials for conditions with incidence of 0.7 to 2.0 per 1 000 000 patients.[27] Randomized clinical trials measuring clinical end points such as OS and health-related quality of life have the advantage of assessing direct clinical benefits, and may be needed to identify important safety signals or even exclude modest decrements in OS.[28]

Table 2. Drug Response Rate in Quintiles by FDA Approval Status

Variable	Drug Response Rate in Quintiles, No. (%)					
	80-100	60-79	40-59	20-39	0-19	Totals
Regular approval	2 (6)	8 (25)	7 (22)	12 (38)	3 (9)	32
Accelerated then OS approval	0	1 (17)	3 (50)	2 (33)	0	6
Accelerated then PFS approval	2 (13)	1 (6)	7 (44)	6 (38)	0	16
Accelerated then RR approval	0	0	5 (71)	1 (14)	1 (14)	7
Accelerated only	1 (4)	3 (13)	5 (21)	5 (21)	10 (42)	24
Total	5 (6)	13 (15)	27 (32)	26 (31)	14 (16)	85

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

Figure 1. Median and Range of Response Rate of 32 Oncology Drug Indications Granted Regular Approval as First Approval



Third, the rate of complete response—complete disappearance of tumor and normalization of lymph nodes—among these drugs is low, with a median rate of 6% (IQR, 2%-22%). Although there was a statistical difference between drugs granted regular vs accelerated approvals, both groups had low complete response rates and are unlikely to be curative therapies for most patients.

Finally, many of these drugs have remained on the market for years without subsequent confirmatory data. When accelerated approvals based on RR were converted to full approval, 23 of 29 were made on the basis of surrogate end points (PFS or RR), 7 of 29 were made on the basis of RR, and only 6 of 29 were made on the basis of OS, an end point of clinical benefit. In summary, our analysis of drugs approved on the basis of RR end points suggests marked flexibility on behalf of the FDA to use this surrogate end point in the absence of randomized clinical trials.

Limitations

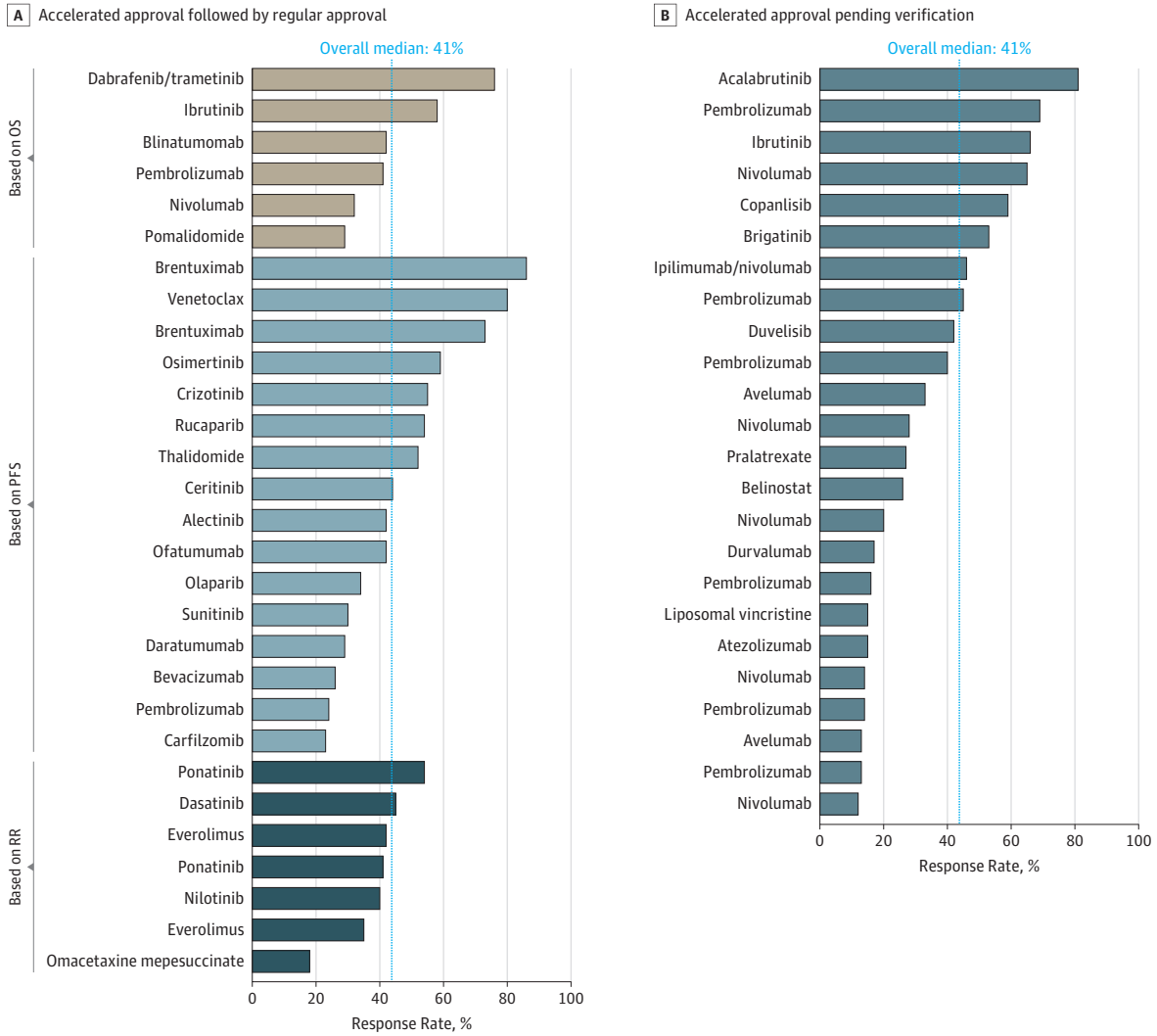
Our study has several limitations. First, we note that not all FDA label updates may be completely available on the FDA website, but we examined all publicly available package inserts on the FDA website. We also made every effort to minimize missing data by reviewing FDA approval letters and published drug registration trials that were referenced in the package insert. Even so, 4 drug indications did not have known CR rate data. In addition, median duration of response may not have been available or may not yet be reached.

Second, we recognize there is a high level of heterogeneity among the cancer types. We therefore used level of innovation and rarity of indication to address feasibility of conducting randomized clinical trials testing OS or patient-reported outcomes.

Third, we acknowledge some RR end points have components of patient-oriented benefit, such as cutaneous lymphoma and nonmelanoma skin cancers because treatment response is assessed with close visual inspection. At the same time, symptomatic benefit can be directly assessed through patient-reported outcomes and health-related quality of life scales.

Fourth, we recognize there may be other relevant clinical trials with RR as the primary end point that have not been submitted to the FDA or have been rejected by the FDA. We recognize that although some of these data are systemically tracked by the FDA, they cannot be made publicly available under current US law. There may also be trials prior to 2006 that are not well publicized on the FDA website.

Figure 2. Median and Range of Response Rate (RR) of 53 Oncology Drug Indications Granted Accelerated Approval as First Approval



OS Indicates overall survival; PFS, progression-free survival.

Table 3. Response Rate of 85 Drugs Categorized by FDA Approval Type

Approval Type	Median (IQR) [Range]	No.	*P* Value
Drugs granted regular approval first	43 (30-61) [16-83]	32	.21
Drugs granted accelerated approval first	41 (26-54) [12-86]	53	
Drugs granted regular approval first	43 (30-61) [16-83]	32	
Drugs granted accelerated followed by regular approval	42 (32-54) [18-86]	29	.048
Drugs granted only accelerated approval thus far	28 (15-50) [12-81]	24	
Drugs already granted regular approval thus far	42 (31-58) [16-86]	61	.02
Drugs granted only accelerated approval thus far	28 (15-50) [12-81]	24	

Abbreviations: FDA, US Food and Drug Administration; IQR, interquartile range.

Fifth, the definition of RR outcome varied by year of FDA approval and cancer types, especially apparent among hematologic malignant diseases, and thus the clinical validity of each RR end point was heterogeneous among some of the drug indications. However, each efficacy end point used for FDA approval was generally accepted by the field at the time of approval.

Finally, we are unable to account for subsequent trials not submitted to or tracked by the FDA, which may have further supported some of the oncology drug indications in our study using more robust clinical end points. Perhaps all subsequent phase 3 trials could be systemically tracked by the FDA for long-term safety and efficacy reporting.

Conclusions

Many cancer drugs come to market based on single-arm studies with modest RRs. Most of these drugs are tested in studies of over 100 patients prior to approval. Most (60%) of these approvals lack randomized clinical trials during the lifecycle of the product. Our findings suggest greater room for the role of randomization in the assessment of novel anticancer drugs that exhibit low levels of innovation or treat common cancer types.

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Study concept and design: Chen, Prasad.
Acquisition, analysis, or interpretation of data: Chen, Raghunathan.
Drafting of the manuscript: Chen, Prasad.
Critical revision of the manuscript for important intellectual content: Chen, Raghunathan.
Statistical analysis: Chen.
Study supervision: Prasad.

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