

# Oncology Drug Development and Approval of Systemic Anticancer Therapy by the U.S. Food and Drug Administration

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**Key Words.** Drug therapy • Neoplasms • U.S. Food and Drug Administration • Biological markers • Clinical trial

## ABSTRACT

**Background.** Regulatory approval of oncology drugs is the cornerstone of the development process and approval characteristics shape eventual utilization. Approval trends and characteristics provide valuable information for drug developers and regulators and ultimately affect clinicians and patients.

**Methods.** Indication characteristics were tabulated for drugs approved by the U.S. Food and Drug Administration (FDA) for systemic therapy of malignancies from 1949 through October 2011. Variables included time to approval, initial/supplemental indication, tumor type, stage of disease, specification of protein expression or genetic information, drug class, trial design, concomitant agent, trial size, and endpoint.

**Results.** A total of 121 unique anticancer agents, including 242 unique indications, were approved. The number of trials for each indication has decreased; however, trial size has increased and more randomized controlled trials have been

performed. Trial designs have increasingly used time-to-event endpoints and rarely have used symptom-based primary endpoints. Approvals have been primarily single agent, with less emphasis on palliative treatments and increasing emphasis on advanced disease stages and requirements for prior therapy. Molecular specifications in labels have increased, but they are present in less than 30% of recent indications and are not associated with shorter approval times.

**Conclusion.** Approval of oncology agents is occurring in increasingly more challenging settings, suggesting gaps between eventual practice and development in potentially suboptimal indications. Molecular specifications promise to enhance development, yet widespread use in label indications has not yet been achieved. *The Oncologist* 2013;18:104–111

**Implications for Practice:** Regulatory approval of oncology drugs is the cornerstone of the development process and approval characteristics shape eventual utilization. Approval trends and characteristics provide valuable information for drug developers and regulators, and ultimately impact clinicians and patients. This review found that approval of oncology agents is occurring in increasingly more challenging settings, suggesting gaps between eventual practice and development in potentially sub-optimal indications. Molecular specifications promise to enhance development, yet widespread use in label indications has not yet been achieved.

## INTRODUCTION

Cancer continues to be a major cause of morbidity and mortality in our society. Although local interventions, including surgery, radiotherapy, and adjuvants are highly effective in early disease, there remains huge unmet need in more advanced stages. Pharmaceuticals make up the mainstay of therapy for advanced cancer. Yet, the ability to develop new anticancer agents is profoundly inefficient. With only 3%–25% of agents entering clinical Investigational New Drug (IND) development actually gaining regulatory approval, and the majority of development costs being spent on drugs that never become approved, there is a dire need to improve efficiency [1–5]. Regulatory approval of oncology drugs is the cornerstone of the development process and approval characteristics

shape eventual utilization. Approval trends and characteristics provide valuable information for drug developers and regulators and ultimately affect clinicians and patients. To understand characteristics of successful products, we performed a comprehensive review of approved systemic anticancer agents.

Key strategies to improve efficiency have made incremental advances, including predictive biomarkers [6–8], clinical trial design [9, 10], efficiency in regulatory approval [11, 12], accelerated approval, access to unapproved anticancer agents, membership and voting rights to patients and patient representatives on U.S. Food and Drug Administration (FDA) advisory committees, and reducing the need for IND applica-

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tions for investigator-initiated studies for marketed agents in nonlabeled cancer indications [13–17].

Cancer chemotherapy has evolved significantly over the past five decades. This evolution has involved many new classes of agents ranging from biologics to immune-stimulating agents to kinase inhibitors. During this time, the sophistication of clinical trial design and interpretation of data have also improved dramatically. A key paradigm currently emphasizes targeted agents and predictive/biomarkers. The current review tracks changes in aspects of drug development over the lifespan of chemotherapy and will give insight into future trends.

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## METHODS

### Drug Selection

This study includes all drugs approved by the FDA for systemic therapy of malignancies from 1949 through October 2011, including new drug applications, biologic licensing applications, and supplemental applications. Drugs that were initially approved for a noncancerous condition were also included. Indications for benign tumors or precancerous conditions were excluded from the analysis. In addition, only drugs that are used as systemic chemotherapy were included. Creams and other locally administered drugs were excluded. Generics were only included if they were approved for a unique cancer indication. Approvals for new formulations of a drug for a comparable indication were not included.

### Data Collection

Data were collected from drug labels using the FDA website and the Physician Desk Reference (PDR). When the original or new indication label was not available on the FDA website, data were obtained from the PDR of the corresponding year.

Each unique indication is counted for each drug, including indications approved at the same time as long as substantive data support each indication. Approvals for alternate formulations or generic forms of a particular active pharmaceutical ingredient (API) were not counted if the approval was for an existing indication for that API. If a drug was originally approved for a noncancerous condition, the first approval for cancer was counted as the initial indication; any additional indications for cancer were considered supplemental. Indications involving corticosteroids, adjunctive agents, or agents used primarily for local therapy were not included.

Tumor type represents the type of cancer specified in the indication. Indications that either did not specify a tumor type or listed several types, were classified as multiple unless the label included specific clinical studies that demonstrated efficacy for each. Tumor type classifications were initially captured exactly as written in the indication and were grouped into specified categories for the purpose of presentation.

Stage classification was based on the indication and was assigned to one of four categories: local/adjuvant, advanced/metastatic, palliative, or prophylactic. Leukemia and myelodysplastic syndrome indications were excluded from the stage classification analysis. The local/adjuvant category includes indications that specify the following: adjuvant therapy, local, early, locally or regionally advanced, and operable cancer. The palliative category includes all indications that specify palliative therapy or treatment, even if it also specifies metastatic disease.

Prior treatment data were based on the indication and assigned to one of three categories: chemotherapy, surgery or radiotherapy, or no prior therapy. Indications that specified adjuvant therapy were included in the surgery or radiotherapy category. Indications indicating both no prior therapy and prior therapy were included in the “no prior therapy” category. Indications that specify prior therapy without mentioning what type were assigned a category based on currently accepted treatments for that cancer. *Molecular specification* refers to indications that specify genetic or protein parameters that guide the use of the agent.

Data for the single-agent/combination category were based on specification within the indication of use of the drug as a single agent or in combination with other agents. Indications that did not specify use in combination therapy were classified as single-agent therapy. In situations where both single-agent and combination use was specified, this was counted as such, unless stand-alone clinical trial data were sufficient to designate two separate indications in this analysis.

Data on study size, design, and endpoints used for regulatory approval were obtained from the drug label. The studies considered in this analysis were those that were the basis of FDA approval for each indication. Information on clinical studies was not consistently presented in many pre-1990 labels, and therefore data during this period were not included in some of the analyses. For endpoint evaluation, only one trial (the largest or most relevant to the initial indication) was considered for each indication. Additionally, when the primary study endpoint was not clearly articulated and multiple endpoints met statistical criteria, the endpoint with highest priority was taken for this analysis, using the following hierarchy: survival (e.g., overall survival, median survival, 3-year survival), symptom (e.g., clinical benefit response), time-to-event (progression-free survival, time to progression, time to recurrence, incidence), and response rate (e.g., tumor or other surrogate response rate).

### Data Analysis

Data were analyzed to determine trends over time by categorizing the indications into the following periods: pre-1990; 1990–1999; 2000–2005; and 2006–2011. The pre-1990 data were grouped together for several reasons, including lower frequency of oncology drug approvals; granularity of trends during that period are less relevant now and data are less available on the FDA website.

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## RESULTS

### General Approval Characteristics

A total of 121 unique anticancer agents, including 242 unique indications, approved by the FDA for systemic therapy of cancer were evaluated, with approval dates ranging from 1949 to 2011 (Table 1). Considering multiple indications at the time of initial approval, 136 indications have been specified. Sixty-four agents received supplemental approvals, including 106 unique supplemental indications. The proportion of supplemental indications has increased in the most recent period (54% of all approved indications) versus 52% and 34% respectively for the next two most recent periods. Monotherapy approvals were found to be more common than combination

**Table 1.** Tabulation of indications and drug classes

<b>Overall tabulation of initial and supplemental approvals and indications</b>	<b>Pre-1990</b>	<b>1990–1999</b>	<b>2000–2005</b>	<b>2006–2011</b>	<b>Total</b>
Agents with initial approval	37	33	23	28	121
Initial approval unique indications	41	35	24	36	136
Agents with supplemental approval <sup>a</sup>	12	13	16	23	64
Supplemental approval unique indications	19	18	26	43	106
<b>Class (initial approval)</b>					
Alkylating	13	2		1	16
Angiogenesis inhibitor			2	1	3
Anthracycline	2	4			6
Antibiotic	2	1			3
Antibody		2	5	4	11
Antifolate	1		1	1	3
Antimetabolite	6	5	3	1	15
Antimicrotubule	2	3	1	3	9
Differentiation		2	1		3
Enzyme		2			2
Histone deacetylase inhibitor				2	2
Hormone	6	6	4	3	19
Immune/cytokine	1	3		2	6
Kinase inhibitor			4	10	14
Platinum	2		1		3
Proteasome Inhibitor			1		1
Topoisomerase inhibitor	2	3			5
<b>Total</b>	<b>37</b>	<b>33</b>	<b>23</b>	<b>28</b>	<b>121</b>
<b>Stage (initial and supplemental indications)</b>					
Palliative	18	3	4		25
Advanced/metastatic	40	41	37	70	188
Local/adjuvant	2	8	9	7	26
Prophylactic		1		2	3
<b>Total</b>	<b>60</b>	<b>53</b>	<b>50</b>	<b>79</b>	<b>242</b>

Bevacizumab is listed under angiogenesis inhibitor rather than antibody. Molecular or mechanistic class was determined for each molecule. The number of unique molecules in each drug class is indicated for each time period at the time of initial approval. Stage of cancer treatment was categorized into palliative, advanced/metastatic, local/adjuvant, and prophylactic. The number of indications in each stage is presented for each time period.

<sup>a</sup>After date of initial approval.

approvals, particularly in the initial indications but also in supplemental indications (Fig. 1). This finding has been maintained over time.

Review of the suggested first-line treatments from the National Comprehensive Cancer Network for the 12 most common malignancies in the U.S., including certain indication subsets, revealed that 14 of the 21 (67%) indications had combinations listed as the treatment of choice for good-performance status patients, yet only 8 of 18 (44%) of the drugs listed in these combinations were first approved in a combination [18, 19]. This discordance is primarily with older oncology agents and suggests that optimal use of many oncology agents is not articulated in the initial approval.

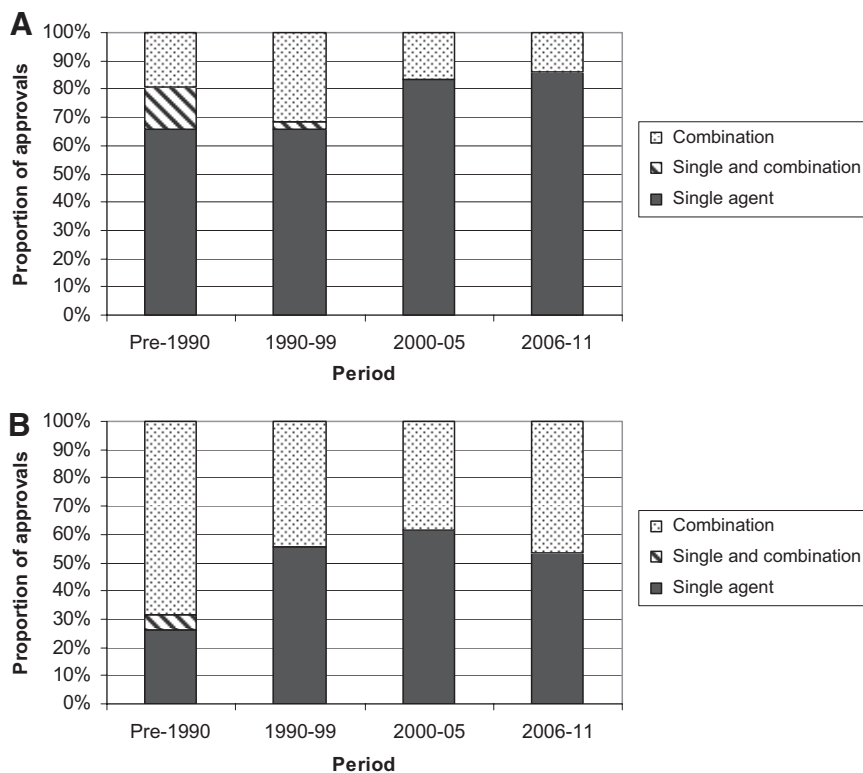
The proportion of approvals that were accelerated approvals peaked in the early 2000s and is now utilized in about a quarter of approvals (supplemental online Fig. 1A, 1B). There is a clear trend toward faster approval times, with the median plateauing at around 6 months (supplemental online Fig. 1C–

E). There was no clear association between faster approval times and use of accelerated approval (Table 2).

### Types of Agents and Malignancies

Initial approvals for alkylating agents, anthracyclines, and topoisomerase inhibitors have been declining over time, whereas antibodies and kinase inhibitors have increased in the past decade (Table 1), making up 15% and 36%, respectively, of all approved molecules in the most recent 6 years.

Breast, prostate, and hematologic malignancies are the most common indications (supplemental online Table 1). There has been a shift away from indications specifying multiple malignancies. Indications in certain malignancies peaked during different time periods; for example germ cell, central nervous system, and gynecologic malignancies peaked in the pre-1990s, breast in the 1990s, colon and lung in the 1990s and early 2000s, and renal and skin in the most recent period. The stage of disease was largely advanced/metastatic disease.



**Figure 1.** Single-agent and combination approvals. The proportion of approvals involving a single agent (black), combinations of more than one agents (grey), and both single-agent and combination use designated in the same indication (striped). Initial (A) and supplemental (B) approvals are presented. In situations where substantive data independently supported both single-agent and combination use, separate indications were designated.

**Table 2.** Correlation between development parameters and approval time

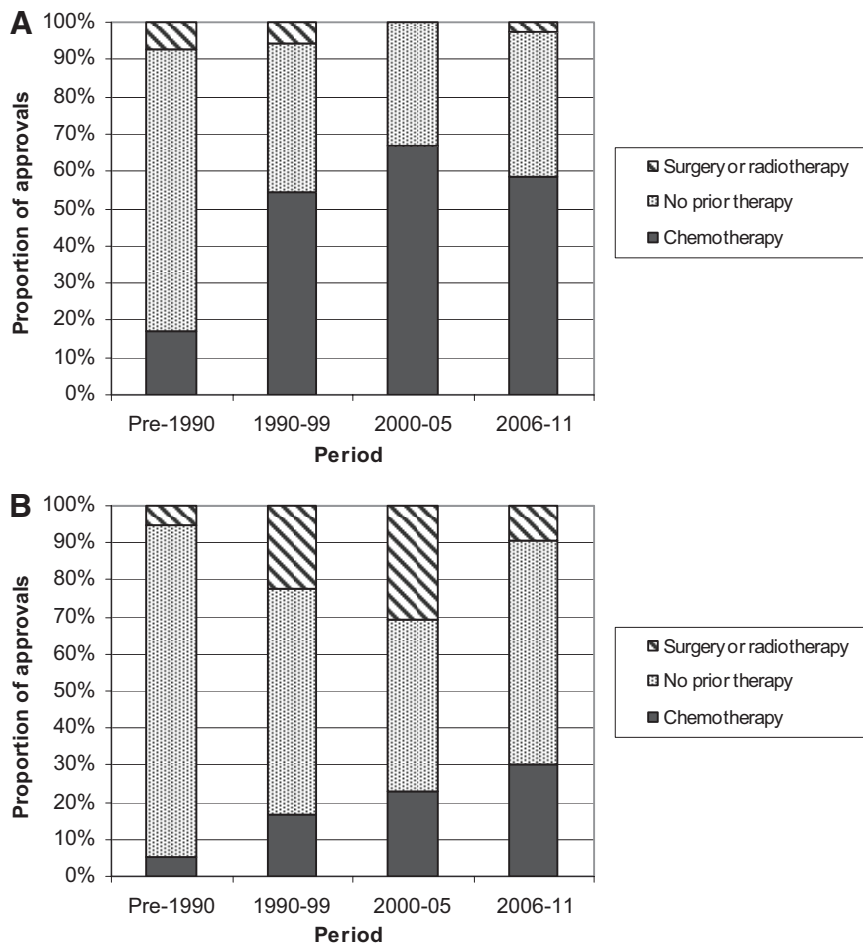
Parameter present	Time to approval (months)					
	No			Yes		
Quartile	25%	50%	75%	25%	50%	75%
Molecular specification	5.9	6.1	9.9	6.1	6.1	10.3
Accelerated approval	6.0	6.1	10.0	6.0	6.1	9.0
Randomized controlled trial	6.0	6.1	10.1	5.9	6.1	10.0

For each parameter, the approval time quartiles are presented both for the group of approvals where the parameter was not present (no) and the group of approvals where the parameter was present (yes). Molecular specification:  $n = 83$  for no and  $n = 46$  for yes; accelerated approval:  $n = 90$  for no and  $n = 39$  for yes; randomized controlled trial:  $n = 44$  for no and  $n = 85$  for yes.

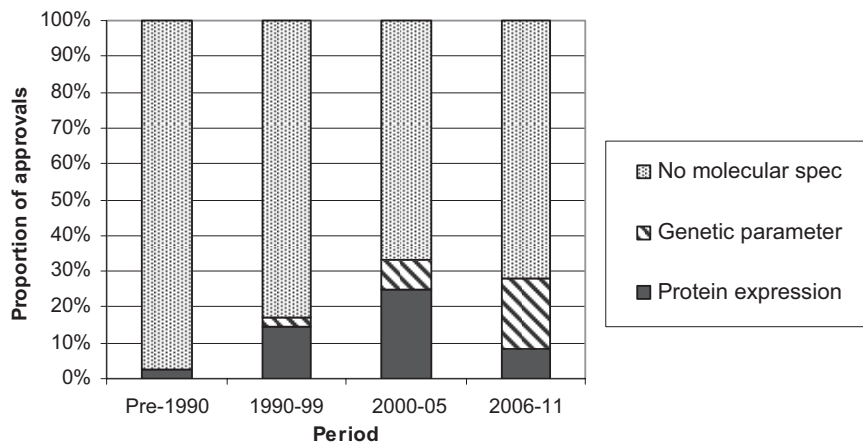
**Details of Indications**

Important aspects of indications have shifted over time. The requirement for prior treatment has increased recently (Fig. 2). Most pre-1990 initial indications do not specify any prior treatment as part of the approved indication; prior chemotherapy is specified in 67% and 58% of initial indications in the two most recent 6-year periods, respectively. Supplemental indications are much more likely to indicate no prior chemotherapy or an adjuvant setting. Likewise, considering tumor stage, the majority of indications involved advanced/metastatic disease; this increased over time, with 89% of all indications in the most recent 6 years specifying this requirement for prior therapy (Table 1). This trend reflects the fact that many drugs now are first studied in patients with an advanced disease process and where effective standard therapies have been available and have been exhausted.

Designation of indications as palliative was more common early in oncology drug development history, but it has not occurred recently. Prophylactic indications have primarily occurred recently but remain rare. With regard to tumor characteristics, there has been a significant rise in protein and genetic specifications over time, reflecting the advancing science of molecular classifications and the availability of well qualified in vitro diagnostics; however, the majority of indications still have no such specification (Fig. 3). Specification of genotypic information is increasing most rapidly, with 27% of initial approvals specifying this in the most recent 6 years, compared with 8% in the 6 years before that and only 3% in the preceding decade. Molecular specification did not appear to be associated with slower or faster approval time (Table 2).



**Figure 2.** Prior therapy. The proportion of initial (A) and supplemental (B) approvals listing no prior therapy (grey), prior chemotherapy (black), or prior surgery or radiotherapy (striped) for each time period is presented.



**Figure 3.** Molecular specification. The proportion of initial approvals listing protein expression (black), a genetic parameter (striped), or no specification of molecular phenotype or genotype (grey) in the indication is presented. Abbreviation: Spec, specification.

**Study Design**

The number of trials for each indication has decreased since 1990, with 83% of initial indications in the most recent 6 years being based on a single trial (supplemental online Fig. 2). In contrast, trial design has improved. Trial size has consistently increased, with a median of 356 patients in the most recent 6 years, 303 patients in the 6 years prior to that, and 229 patients in the decade prior to that (supplemental online Table 2).

Furthermore, slightly more randomized controlled trials (RCTs) have been performed, with 67% of approvals (initial and supplemental) in the most recent 6 years involving an RCT (supplemental online Fig. 2), compared with 65% in the 6 years prior to that and 61% in the preceding decade. The proportion of indications with RCTs that used placebo were as follows: 4/31 (13%) in 1990–1999, 6/32 (19%) in 2000–2005, and 14/53 (26%) in 2006–2011. There was not a clear relationship

Another example of oncology drug approval occurring in less-than-ideal situations is the observation that most drugs are initially approved in advanced disease, palliative settings, and/or in later lines of treatment when cancer is biologically much more difficult to treat. Reasons for this trend likely include the need for larger studies, longer time to endpoints, and the requirement that a new drug be superior or not inferior to existing drugs.

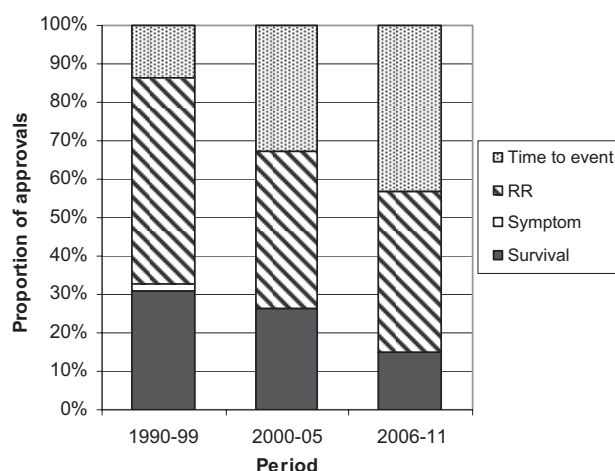
between use of RCTs and approval time (Table 2), although the complexity of RCTs, including design and use of active control arms, likely confounds this analysis.

The primary endpoints for studies supporting cancer indications usually involved time-to-event or response, while survival was less common and symptom palliation was rarely the endpoint of interest (Fig. 4). The use of time-to-event has increased over time, with 43% of recent approvals (2006–2011) using such an endpoint compared to 33% in the 6 years prior to that (2000–2005) and only 13% in the decade prior to that (1990–1999).

## DISCUSSION

Evaluation of FDA approval trends over the history of effective anticancer therapy reveals a number of notable findings, some of which are expected and others somewhat surprising. Approvals cover a broad range of indications and involve agents with a wide variety of mechanisms of action. Advancing technology and discovery of novel classes of drugs appear to correlate with shifts in approval trends. Significant trends included more cell signaling targets, more advanced disease, more prior therapy in the case of initial approvals, larger trials, more RCTs (but fewer numbers of trials), faster approval times, and greater use of molecular specification.

A concerning observation in this evaluation is that oncology drug approvals occur largely in clinical situations that may not be suited to the optimal application of a drug. This raises the question of whether potentially valuable drugs are being overlooked or are failing to achieve initial approval. From a biological perspective, one might expect many more drugs to have activity in situations where tumor burden is low, where treatment resistance is low, and when combined with other complementary agents. Yet, approval patterns are just the opposite. The majority of initial oncology drug approvals involve trials testing single agents in advanced-disease settings. Even in supplemental approvals, single-agent studies dominate. There are only a handful of examples where a drug is approved in a combination, but not as single agent. Such trials are more complex and typically require an active control comparator. This is despite numerous examples in oncology where combination studies demonstrate superior efficacy over single agents, perhaps due to the multiple derangements that are now recognized to exist in any given malignancy [20]. Reasons for the high rate of single-agent approvals include technical and regulatory challenges of demonstrating safety and efficacy of a drug when combined with other active agents.



**Figure 4.** Primary endpoints for indications. Primary endpoint categories of time to event (grey), response rate (striped), symptom based (white), and survival (black) are presented for time periods from 1990 through 2011. Abbreviation: RR, response rate.

Another example of oncology drug approval occurring in less-than-ideal situations is the observation that most drugs are initially approved in advanced disease, palliative settings, and/or in later lines of treatment when cancer is biologically much more difficult to treat. Reasons for this trend likely include the need for larger studies, longer time to endpoints, and the requirement that a new drug be superior or not inferior to existing drugs. Strategies to reduce the chance of overlooking a valuable drug might include novel study designs, better predictive models, and perhaps changes in regulatory approach. “Window” studies evaluating a new drug early in the sequence of treatments can allow safe initial assessment of clinical activity in such settings [21]. Increased use of small well-designed randomized studies may enhance early recognition of agents or combinations [9, 22–26]. The use of preclinical models designed to differentiate activity in various clinical settings has had relatively poor correlation with clinical utility, although ongoing efforts to improve predictability of preclinical evaluations may prove beneficial [27–31]. Finally, regulatory paradigms could be shifted, perhaps lowering the threshold for a drug to be considered efficacious, focusing more on individuals rather than large heterogeneous populations when assessing efficacy, and, upon lowering threshold for initial drug approval, shift resources to postmarketing setting to ensure safety and efficacy as experience grows. These changes would reduce the costs and technical hurdles for initial approval and allow a broader spectrum of oncology drugs to be approved.

As our understanding of cancer biology and the human genome expand, one approach to improving cancer treatment efficiency is to develop predictive biomarkers that allow selection of a sensitive patient population. This topic has received much attention from drug developers, academic researchers, and regulators, including significant work to facilitate incorporation of predictive biomarkers [8, 14, 32–34]. Although the incorporation of molecular specification into the label is clearly increasing, it is surprising to find that less than 30% of cancer drug approvals in the past 6 years mentioned genetic or protein expression in the labeled indication. One limitation may be

challenges in demonstrating clinical usefulness of companion diagnostics [35]. It is also interesting that molecular specification did not affect approval times, perhaps balancing greater complexity with improved definition of populations.

As recognition of the importance of well-designed clinical trials is increasing, the proportion of studies that are randomized and placebo-controlled is also increasing, as is the study size. However, a significant fraction of approvals continue to be based on nonrandomized studies. Potential drivers for this include FDA initiatives of accelerated approval [15], which accounted for a quarter of initial oncology drug approvals over the past decade, and the Orphan Drug Act [36, 37]. Such approvals appear to be robust, as Tsimberidou et al. evaluated 31 oncology drugs approved by single-arm studies and found that all but one retained marketing approval, and only one additional such drug was withdrawn since that report [38, 39]. Advancing further creative clinical trial design will continue to improve efficiency and accuracy of oncology drug development [9, 10, 23–26]. We also found a clear trend toward reduced approval time in more recent periods, possibly related

to implementation of the Prescription Drug User Fee Act first enacted in 1992 and perhaps to greater interaction during the design and implementation of trials between sponsors and FDA.

Our evaluation focuses on oncology drug approvals in the U.S. and the role of the FDA, so it should be noted that oncology approvals in other regulatory settings might reveal different results [40–43].

#### AUTHOR CONTRIBUTIONS

**Conception and design:** Robert E. Martell, David Sermer, Kenneth Getz, Kenneth I. Kaitin

**Collection and/or assembly of data:** Robert E. Martell, David Sermer, Kenneth Getz, Kenneth I. Kaitin

**Data analysis and interpretation:** Robert E. Martell, David Sermer, Kenneth Getz, Kenneth I. Kaitin

**Manuscript writing:** Robert E. Martell, David Sermer, Kenneth Getz, Kenneth I. Kaitin

**Final approval of manuscript:** Robert E. Martell, David Sermer, Kenneth Getz, Kenneth I. Kaitin

#### DISCLOSURES

The authors indicated no financial relationships.

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