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CCR Perspectives in Drug Approval

Clinical Cancer Research

Use of Multiple Endpoints and Approval Paths Depicts a Decade of FDA Oncology Drug Approvals

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Abstract

This study explores the historic use of different endpoints to support regular and accelerated approval of cancer drugs between 2002 and 2012. In the past 10 years, two thirds of oncology regular approvals were based on endpoints other than overall survival. More than three quarters of accelerated approvals were based on response rates. The accelerated approval program has been heavily used over this time period, with one third of all approved oncology indications receiving accelerated approval. At times, critics have characterized the agency as rigid and unpredictable. This research describes the degree of regulatory flexibility that U.S. Food and Drug Administration and drug sponsors have used over the past decade in the development of new treatments for cancer. *Clin Cancer Res; 19(14); 3722–31. ©2013 AACR.*

Introduction

Drug development is a long and costly process, typically requiring up to 15 years and more than $1 billion to shepherd a drug through initial discovery, clinical testing, and regulatory approval (1). Despite advances in basic research, the pharmaceutical industry is widely considered to be in an innovation crisis; although research and development costs have increased drastically, the rate of new drug output has remained relatively constant since the 1950s (2). This crisis has been attributed to many factors, including the exhaustion of "easy" drug targets, overuse of molecular screening strategies for drug discovery, increased attention to high-risk, targeted therapeutics, and, in particular, an overcautious U.S. Food and Drug Administration (FDA; refs. 3–5). A 2011 report released by the National Venture Capital Association's Medical Innovation and Competitiveness Coalition, *Vital Signs: The Threat to Investment in U.S. Medical Innovation and the Imperative of FDA Reform*, described a significant decrease in investment in biopharmaceutical and medical device companies by U.S. venture capitalists and cited FDA regulatory rigidity and unpredictability as the key drivers for this decrease (6).

While the impact of the regulatory environment on drug development is important in every therapeutic area, it is especially so for cancer, the second leading cause of death in the United States. Although recent studies have found that the FDA reviews new oncology drug applications relatively quickly, concerns remain about the long timelines in oncology drug development, in part due to the high hurdles required to meet regulatory approval (7–9). Some have voiced concern that the FDA is increasingly requiring sponsors to conduct large, randomized trials that measure overall survival (OS) benefit to be granted regular approval (10). Others have questioned the willingness of the FDA to consider novel anticancer medicines for accelerated approval (11).

Many of these concerns have stemmed from recent high-profile events, such as the FDA-initiated withdrawal of the breast cancer indication for bevacizumab in November 2011 (12). Bevacizumab originally received accelerated approval for first-line treatment of metastatic breast cancer in 2008 based on the results of a small randomized trial (E2100) in which bevacizumab combined with paclitaxel showed a 5.5-month improvement in progression-free survival (PFS) compared with paclitaxel alone (13). In two large randomized confirmatory trials (AVADO and RIBBON-1), bevacizumab failed to show an OS benefit (14). Furthermore, these trials were unable to reproduce the originally observed effect on PFS. The AVADO trial, in which patients were randomized to docetaxel combined with either bevacizumab or placebo, showed only a 0.8-month improvement in PFS. The RIBBON-1 trial examined bevacizumab in combination with two different chemotherapy backbones: capecitabine or anthracycline/taxane. In the capecitabine cohort, bevacizumab showed a 2.9-month improvement in PFS, while in the anthracycline/taxane cohort, only a 1.2-month improvement in PFS was observed. The magnitude of these PFS results was not considered clinically meaningful by the FDA, particularly in light of the drug's adverse effects, and ultimately the breast cancer indication was withdrawn (15). However, because a statistically significant, if not clinically significant, improvement in PFS was observed in these trials, this withdrawal prompted worries that the FDA would no longer accept drugs without a survival benefit (16).

Another controversial event occurred in February 2011, when the FDA convened its Oncologic Drugs Advisory

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Committee (ODAC) to discuss possible changes to the accelerated approval pathway. The meeting focused on two key issues: the use of single-arm trials to support accelerated approval and requirements for confirmatory trials (17). FDA officials expressed their concerns that too many sponsors were pursuing accelerated approval through single-arm trials, the results of which can be difficult to interpret, as well as their concerns that sponsors were not completing confirmatory trials with due diligence (17). In a publication later that year, FDA officials noted that the majority of accelerated approvals were pursued in heavily pretreated patient populations, which may not be representative of the cancer type being studied (18). These incidents raised skepticism about the future use of accelerated approval in oncology.

To investigate whether the FDA approval process has in fact become more demanding in recent years, we have reviewed a decade of FDA oncology approvals from 2002 to 2012. This study examines the endpoints accepted for regular and accelerated approval and the FDA's utilization of the accelerated approval program.

Materials and Methods

Study data

Information was collected about all initial and supplemental oncology drug approvals from January 1, 2002, to December 31, 2012. We collected data for antineoplastic agents only; drugs for supportive or palliative care were not included. Supplemental approvals for new dosing regimens were also not included; data are limited to approvals for new indications. All data presented were collected from publicly available documents stored on the CDER database Drugs@FDA (19). Drug labels were viewed to identify clinical trial information including trial size, trial type (randomized or single-arm), and primary efficacy endpoints. Press releases published by the Office of Hematology and Oncology Products (OHOP) were used to confirm information collected on Drugs@FDA (20).

Approval dates and types

Several supplemental indications included in the data were preceded by initial approvals granted before January 1, 2002. These pre-2002 approvals were not included in our analysis because they did not fall into the specified date range of this study. In some cases, a new molecular entity received approval for two indications simultaneously. For example, on January 26, 2006, sunitinib was approved for both gastrointestinal stromal tumors (GIST) and advanced renal cell carcinoma (RCC), and on August 19, 2011, brentuximab vedotin was approved for both Hodgkin lymphoma and systemic anaplastic large-cell lymphoma (21, 22). In these cases, both indications were considered initial approvals due to the fact that they share the status as the first approved indication of a particular drug. In some cases, multiple supplemental indications were granted approval in the same approval letter. These indications were considered separate, even if data from the same study were used to approve the indications. For example, on October 19, 2006, imatinib was approved for five indications, all based on findings from one open-label, phase II study (23).

Approvals were classified as either "first-line" or "second-line or later." Adjuvant therapies were viewed as first-line if they were part of a regimen that was the first treatment option following cancer diagnosis. For example, the December 19, 2008, approval of imatinib for treatment of adult patients following complete gross resection of cKit-positive GIST was considered part of the first therapeutic regimen for that disease (24).

Endpoint classification

The majority of drug labels name a commonly used endpoint such as OS, PFS, response rate (RR), time to progression (TTP), or disease-free survival (DFS). Some labels specify less common endpoints that could reasonably be categorized with one of those just mentioned. For example, the label for bosutinib, approved September 4,2012, cites "rate of major cytogenetic response" and "rate of complete hematologic response" as primary endpoints (25). These were categorized as RRs.

Many efficacy studies involve multiple or coprimary endpoints. To identify the primary outcome measure of each study, we erred on the side of the most rigorous endpoint recorded on each label: (i) if OS and an intermediate endpoint such as PFS or RR were listed as coprimary endpoints, we classified OS as the basis for approval; (ii) if PFS and RR were listed as coprimary endpoints, we classified PFS as the basis for approval because its measurement necessitates a controlled trial; and (iii) if PFS and TTP were listed as coprimary endpoints, we classified PFS as the basis for approval because PFS does not involve censoring and is considered by the FDA to be preferable to TTP (26).

Results

Approval statistics

Between January 1, 2002, and December 31, 2012, the FDA granted approval to 65 oncology products for 127 indications (Table 1). Fifty-four of these products were either new molecular entities or new biologic products. The remaining 11 products were initially approved before 2002 but were approved for supplemental indications between 2002 and 2012. During this time period, the agency granted accelerated approval to 30 oncology products for 42 new indications and regular approval to 49 products for 85 new indications. Of the indications granted accelerated approval, 18 were converted to regular approval following confirmatory trials, 2 were revoked after failing to confirm clinical benefit, 1 was released from its postmarketing commitment, and 22 have yet to complete confirmatory trials.

Endpoint utilization

We examined the endpoints used as the basis of accelerated and regular approval in the past decade. We found that OS was the most frequently used endpoint

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Table 1. FDA oncology drug approvals (January 2002–December 2012)

Product	Approval date	Approval type[a]	Indication(s)	Primary endpoint	AA?	Single-arm vs. randomized trial	Trial size
Imatinib[b]	2/1/2002	S	First-line GIST	RR	Yes	Randomized	74
	12/20/2002	S	First-line Ph^+ CML	PFS	Yes	Randomized	1,106
	5/20/2003	S	Second-line pediatric Ph^+ CML	RR	Yes	Extrapolated from 2 single-arm studies	39
	9/27/2006	S	First-line pediatric Ph^+ CML	RR	Yes	Single-arm	51
	10/19/2006	S	Dermafibrosarcoma protuberans	RR	No	Single-arm	12
	10/19/2006	S	Myelodysplastic syndrome	RR	No	Single-arm	7
	10/19/2006	S	Adult Ph^+ ALL	RR	No	Single-arm	48
	10/19/2006	S	Adult aggressive systemic mastocytosis	RR	No	Single-arm	5
	10/19/2006	S	Hypereosinophilic syndrome	RR	No	Single-arm	14
	12/19/2008	S	Adjuvant therapy for GIST	DFS	Yes	Randomized	713
Ibritumomab	2/19/2002	I	Relapsed follicular lymphoma	RR	Yes	Randomized	143
	9/3/2009	S	First-line NHL	PFS	No	Randomized	414
Fulvestrant	4/25/2002	I	Second-line breast cancer	TTP	No	2 Randomized	400; 451
Oxaliplatin	8/9/2002	I	Second-line metastatic CRC	RR	Yes	Randomized	463
	1/9/2004	S	First-line advanced CRC	OS	No	Randomized	531
	11/4/2004	S	Adjuvant stage III CRC	DFS	No	Randomized	2,246
Anastrozole[b]	9/5/2002	S	Adjuvant HER^+ breast cancer	DFS	Yes	Randomized	9,366
Docetaxel[b]	11/27/2002	S	NSCLC combination therapy	OS	No	Randomized	1,218
	5/19/2004	S	Metastatic prostate cancer	OS	No	Randomized	1,006
	8/18/2004	S	Adjuvant node + breast cancer	DFS	No	Randomized	1,491
	3/22/2006	S	Gastric cancer	OS	No	Randomized	457
	10/17/2006	S	Inoperable SCCHN	PFS	No	Randomized	358
	9/28/2007	S	Induction treatment of SCCHN	OS	No	Randomized	501
Gefitinib	5/5/2003	I[c]	Third-line NSCLC	RR	Yes	Single-arm	142
Bortezomib	5/13/2003	I	Third-line multiple myeloma	RR	Yes	Single-arm	202
	3/25/2005	S	Second-line multiple myeloma	OS	No	Randomized	669
	12/8/2006	S	Second-line mantle cell lymphoma	RR	No	Single-arm	155
	6/20/2008	S	First-line multiple myeloma	TTP	No	Randomized	682
Tositumomab	6/27/2003	I[c]	Relapsed NHL	RR	No	2 Single-arm	40; 60
	12/22/2004	S	Refractory low-grade lymphoma	RR	Yes	Single-arm	60
Pemetrexed	2/4/2004	I	Malignant pleural mesothelioma	OS	No	Randomized	456
	8/19/2004	S[c]	Second-line NSCLC	RR	Yes	Randomized	571
	9/26/2008	S	First-line NSCLC combination therapy	RR	Yes	Randomized	1,725
	7/2/2009	S	Maintenance NSCLC	OS	No	Randomized	663

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Product	Approval date	Approval type[a]	Indication(s)	Primary endpoint	AA?	Single-arm vs. randomized trial	Trial size
Cetuximab	2/12/2004	I	Single agent for second-line CRC	RR	Yes	1 Randomized, 1 Single-arm	329; 57
	2/12/2004	I	Second-line CRC combination therapy	RR	Yes	1 Randomized, 1 Single-arm	329; 138
	3/1/2006	S	SCCHN combination therapy	OS	No	Randomized	424
	3/1/2006	S	Second-line SCCHN as single agent	RR	No	Single-arm	103
	11/7/2011	S	First-line SCCHN combination therapy	OS	No	Randomized	442
	7/6/2012	S	First-line mCRC	OS	No	3 Randomized	1,217; 453; 315
Bevacizumab	2/26/2004	I	First-line mCRC	OS	No	Randomized	813
	6/20/2006	S	Second-line mCRC	OS	No	Randomized	829
	10/11/2006	S	First-line NSCLC	OS	No	Randomized	878
	2/22/2008	S[d]	First-line HER2$^-$ breast cancer	PFS	Yes	Randomized	712
	5/5/2009	S[c]	Glioblastoma	RR	Yes	2 Single-arm	85; 56
	7/31/2009	S	Metastatic RCC	PFS	No	Randomized	649
Gemcitabine[b]	5/19/2004	S	First-line metastatic breast cancer combination therapy	TTP	No	Randomized	529
	7/14/2006	S[d]	Second-line ovarian cancer combination therapy	PFS	No	Randomized	356
Azacitidine	5/19/2004	I	Myelodysplastic syndrome	RR	No	1 Randomized, 2 Single-arm	191; 120
Letrozole[b]	10/29/2004	S	Extended adjuvant breast cancer	DFS	Yes	Randomized	5,187
	12/28/2005	S	Adjuvant breast cancer	DFS	Yes	Randomized	8,000+
Erlotinib	11/18/2004	I	Second-line NSCLC	OS	No	Randomized	731
	11/2/2005	S[c]	Metastatic pancreatic cancer	OS	No	Randomized	569
	4/16/2010	S[d]	Maintenance therapy for NSCLC	OS	No	Randomized	889
Clofarabine	12/28/2004	I[c]	Relapsed pediatric ALL	RR	Yes	Single-arm	49
Paclitaxel	1/7/2005	I	Second-line breast cancer	RR	No	Randomized	460
	10/11/2012	S	First-line locally advanced NSCLC	RR	No	Randomized	1,052
Nelarabine	10/28/2005	I[c]	T-cell ALL or T-cell lymphoblastic lymphoma	RR	Yes	2 Single-arm	39; 28
Sorafenib	12/20/2005	I	Advanced RCC	PFS	No	Randomized	769
	11/16/2007	S	Hepatocellular carcinoma	OS	No	Randomized	602
Lenalidomide	12/27/2005	I[c]	Myelodysplastic syndromes	RR	No	Single-arm	148
	6/29/2006	S	Second-line multiple myeloma	TTP	No	2 Randomized	341; 351
Pegaspargase[b]	7/24/2006	S	First-line ALL	DR	No	Randomized	118
Topotecan[b]	6/14/2006	S	Carcinoma of the cervix	OS	No	Randomized	293
Rituximab[b]	2/10/2006	S	Diffuse large B-cell, CD20$^+$, NHL	OS	No	3 Randomized	632; 399; 823
	9/29/2006	S	NHL combination therapy	PFS	No	Randomized	322
	9/29/2006	S	NHL following chemotherapy	PFS	No	Randomized	322
	2/18/2010	S	First-line CLL combination therapy	PFS	No	2 Randomized	817; 522
	1/28/2011	S	Maintenance therapy for NHL	PFS	No	Randomized	1,018

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Thalidomide[b]	5/26/2006	S	Multiple myeloma	ORR	Yes	Randomized	207
Trastuzumab[b]	11/16/2006	S	Adjuvant node$^+$ breast cancer	DFS	No	2 Randomized	(Total) 3,752
	10/20/2010	S	Adenocarcinoma	OS	No	Randomized	594
Vorinostat	1/6/2006	I	Third-line CTCL	RR	No	Single-arm	74
Sunitinib	1/26/2006	I	Second-line GIST	TTP	No	Randomized	312
	1/26/2006	I	Advanced RCC	RR	Yes	Randomized	750
	5/20/2011	S[c]	Advanced pNET tumors	PFS	No	Randomized	171
Decitabine	5/2/2006	I	Myelodysplastic syndromes	RR	No	Randomized	170
Dasatinib	6/28/2006	I[c]	Second-line CML	RR	Yes	3 Single-arm	186; 107; 74
	6/28/2006	I[c]	Second-line Ph$^+$ ALL	RR	No	Single-arm	78
	10/28/2010	S	First-line Ph$^+$ CML	RR	Yes	Randomized	519
Panitumumab	9/27/2006	I	Second-line CRC	PFS	Yes	Randomized	463
Lapatinib	3/13/2007	I	Second-line HER2$^+$ metastatic breast cancer combination therapy	TTP	No	Randomized	399
	1/29/2010	S	First-line HER2$^+$ metastatic breast cancer combination therapy	PFS	Yes	Randomized	1,286
Doxorubicin[b]	5/17/2007	S	Multiple myeloma combination therapy	TTP	No	Randomized	646
Temsirolumus	5/30/2007	I	Advanced RCC	OS	No	Randomized	626
Ixabepilone	10/16/2007	I	Second-line metastatic breast cancer combination therapy	PFS	No	Randomized	752
	10/16/2007	S	Second-line breast cancer monotherapy	RR	No	Single-arm	126
Nilotinib	10/29/2007	I	Second-line Ph$^+$ CML	RR	Yes	Single-arm	105
	6/17/2010	S	Newly diagnosed Ph$^+$ CML	RR	Yes	Randomized	846
Bendamustine	3/20/2008	I	Second-line CLL	PFS	No	Randomized	301
	10/31/2008	S	Indolent B-cell NHL	RR	No	Single-arm	100
Fludarabine	12/18/2008	I	Second-line B-cell CLL	RR	Yes	Single-arm	78
Degarelix	12/24/2008	I	Advanced prostate cancer	DR	No	Randomized	620
Everolimus	3/30/2009	I	Second-line advanced RCC	PFS	No	Randomized	416
	10/29/2010	S	SEGA with tuberous sclerosis	RR	Yes	Single-arm	28
	5/5/2011	S[c]	pNET tumors	PFS	No	Randomized	410
	4/26/2012	S	Renal angiomyolipoma with tuberous sclerosis	RR	Yes	Randomized	118
	7/20/2012	S	HER2$^+$ breast cancer	PFS	No	Randomized	724
Romidepsin	9/5/2009	I[c]	Second-line CTCL	RR	No	2 Single-arm	96; 71
	6/16/2011	S	PTCL	RR	Yes	Single-arm	130
Eribulin	11/15/2010	I	Third-line metastatic breast cancer	OS	No	Randomized	762
Pralatrexate	9/24/2009	I[c]	Relapsed or refractory PTCL	RR	Yes	Single-arm	115
Pazopanib	10/19/2009	I[c]	Advanced RCC	PFS	No	Randomized	435
	4/26/2012	S[c]	Second-line soft-tissue sarcoma	PFS	No	Randomized	369
Ofatumumab	10/26/2009	I[c]	Refractory CLL	RR	Yes	Single-arm	154
Cabazitaxel	6/17/2010	I	Second-line prostate cancer	OS	No	Randomized	755

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Table 1. FDA oncology drug approvals (January 2002–December 2012) (Cont'd)

Product	Approval date	Approval type[a]	Indication(s)	Primary endpoint	AA?	Single-arm vs. randomized trial	Trial size
Ipilimumab	3/25/2011	I	Melanoma	OS	No	Randomized	676
Peginterferon alfa-2b[b]	3/29/2011	S[c]	Melanoma	DFS	No	Randomized	1,256
Vandetanib	4/6/2011	I[e]	Medullary thyroid cancer	PFS	No	Randomized	331
Abiraterone	4/28/2011	I	Second-line prostate cancer	OS	No	Randomized	1,195
	12/10/2012	S	Metastatic prostate cancer	PFS	No	Randomized	1,088
Vemurafenib	8/17/2011	I	Melanoma with BRAF mutation	OS	No	Randomized	675
Brentuximab	8/19/2011	I[c]	Third-line Hodgkin lymphoma	RR	Yes	Single-arm	102
	8/19/2011	I[c]	Second-line ALCL	RR	Yes	Single-arm	58
Crizotinib	8/26/2011	I	NSCLC ALK$^+$	RR	Yes	2 Single-arm	136; 119
Asparaginase	11/18/2011	I	ALL combination therapy	DR	No	Single-arm	58
Axitinib	1/27/2012	I[c]	Second-line RCC	PFS	No	Randomized	723
Vismodegib	1/30/2012	I	Metastatic basal cell carcinoma	RR	No	Single-arm	104
Pertuzumab	6/8/2012	I	HER2$^+$ metastatic breast cancer	PFS	No	Randomized	808
Carfilzomib	7/20/2012	I[c]	Relapsed multiple myeloma	RR	Yes	Single-arm	266
Ziv-aflibercept	8/3/2012	I	Second-line mCRC	OS	No	Randomized	1,226
Vincristine sulfate	8/9/2012	I[c]	Third-line adult Ph$^-$ ALL	CR	Yes	Single-arm	65
Enzalutamide	8/31/2012	I	Castration-resistant prostate cancer	OS	No	Randomized	1,199
Bosutinib	9/4/2012	I	Second-line Ph$^+$ CML	RR	No	Single-arm	546
Regorafenib	9/27/2012	I	Refractory mCRC	OS	No	Randomized	760
Omacetaxine mepesuccinate	10/26/2012	I[f]	Third-line CML	RR	Yes	2 Single-arm	73; 35
Cabozantinib	11/29/2012	I	Medullary thyroid cancer	PFS	No	Randomized	330
Ponatinib	12/14/2012	I	Second-line chronic, accelerated, or blast-phase CML	RR	Yes	Single-arm	449

Abbreviations: AA, accelerated approval; ALCL, anaplastic large-cell lymphoma; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; CRC, colorectal cancer; CTCL, cutaneous T-cell lymphoma; DR, durable response; NHL, non–Hodgkin lymphoma; NSCLC, non–small cell lung cancer; Ph, Philadelphia chromosome; pNET, pancreatic neuroendocrine tumors; PTCL, peripheral T-cell lymphoma; SCCHN, squamous cell carcinoma of the head and neck; SEGA, subependymal giant cell astrocytoma.

[a]I, initial approval; S, supplemental approval.

[b]Initial approval granted before January 1, 2002.

[c]ODAC recommended approval.

[d]ODAC did not recommend approval.

[e]ODAC convened to discuss postmarketing safety studies.

[f]ODAC did not recommend approval, and the drug was subsequently approved under a different new drug application.

for regular approval, serving as the basis for 36% (31/85 indications) of regular approvals. However, 64% (54/85 indications) of regular approvals between 2002 and 2012 were approved on the basis of endpoints other than OS.

Of the 54 indications that were granted regular approval on the basis of endpoints other than OS, 28 indications were based on improvements in time to event endpoints (PFS or TTP). We found that 14 of these 28 approvals were reported as not statistically significant OS results at the time of approval. For some drugs, such as sorafenib for RCC (2005), statistically significant OS findings were not reported at the time of approval, but subsequent follow-up analyses did achieve significant OS results after post–cross-over placebo survival data were censored (27). For other drugs, such as abiraterone for prostate cancer (2012), favorable but not statistically significant OS results were reported. For the remaining 14 non–survival-based indications, survival data were not reported at the time of

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approval, either because the data were not mature or because the data were not measured. For example, ixabepilone for second-line metastatic breast cancer (2007) did not report OS results at the time of approval, but an analysis of OS was planned once a predetermined number of patients had died (28).

For indications granted accelerated approval, we found that 79% (33/42) were approved on the basis of RRs. While the majority of confirmatory trials for products granted accelerated approval have not yet been completed, 18 of the 42 indications granted accelerated approval between 2002 and 2012 have been converted to regular approval. Thirty-nine percent of these conversions were based on OS. The remaining 61% were based on PFS, DFS, or RR.

Use of OS over time

The number of indications approved based on OS has increased in recent years; however, that increase has been accompanied by an increase in total regular approvals. As a percentage of approvals per year, OS indications have not increased. In 2010, 80% of regular approvals were based on OS; in 2011 and 2012, OS indications were reduced to 40% and 38%, respectively (Fig. 1A). We did not detect a trend indicating that approvals based on overall survival, relative to total yearly approvals, have increased.

Accelerated approval over time

We examined the number of accelerated approvals and regular approvals in oncology from 2002 to 2012 (Fig. 1B).

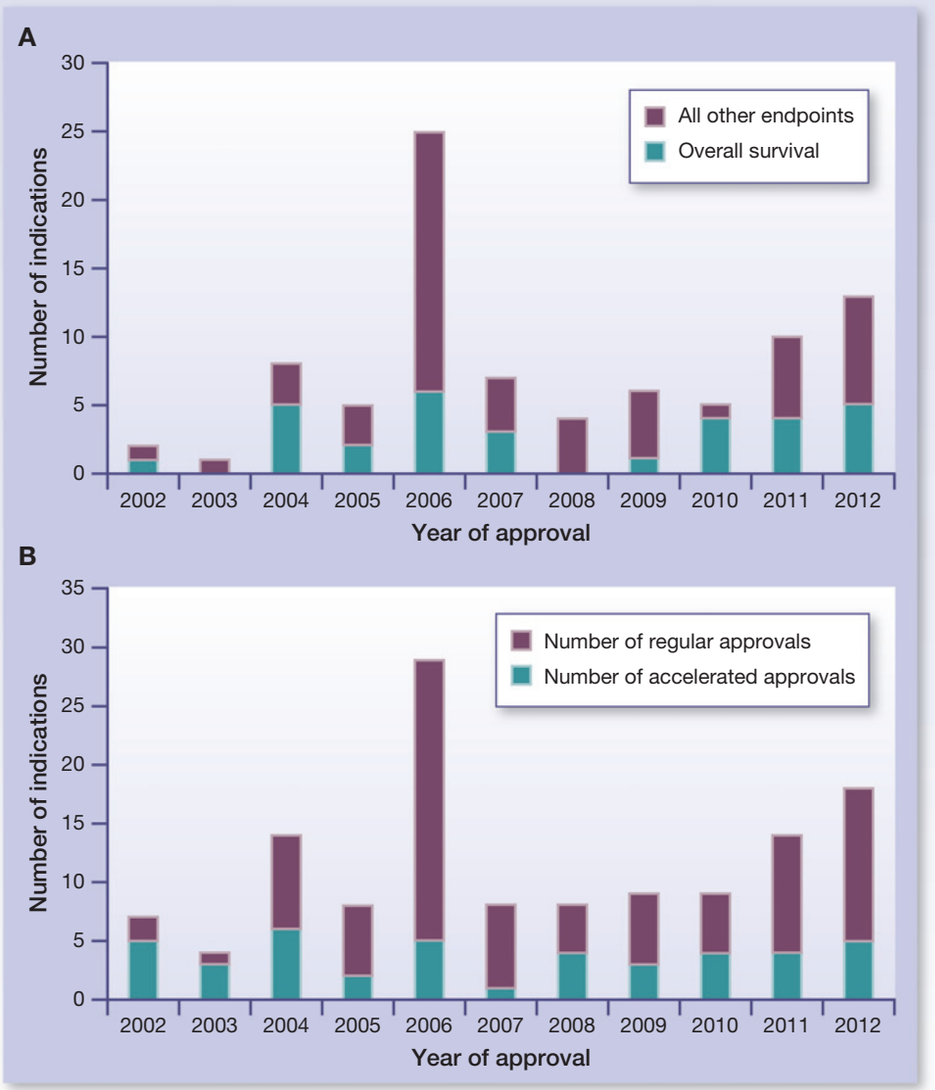

Figure 1. Approval trends between 2002 and 2012. A, the use of OS to support regular approval is compared with all other endpoints supporting regular approval. B, the number of accelerated approvals is compared with the number of regular approvals per year.

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These numbers include both initial and supplemental indications. We did not detect any trend indicating a decrease in accelerated approvals in oncology. Although there is variation from year to year, the absolute number of accelerated approvals has remained relatively constant in this time period. There is a slight decrease in the percentage of accelerated approvals per year following the 2007 reauthorization of the Prescription Drug User Fee Act, but this difference is not statistically significant (43% per year, 2002–2007, vs. 38% per year, 2008–2012) and is likely reflective of a slight increase in the number of regular approvals in this time period.

Accelerated approval by line of therapy

We found a noticeable pattern in the way the accelerated approval pathway has been used in the past decade: All but one (21/22) of the new drugs entering the market that received accelerated approval were indicated for second-line or later therapy (Fig. 2). In contrast, 70% (14/20) of supplemental indications were for first-line disease.

Discussion

Our research indicates that the FDA has exercised considerable flexibility in the approval of oncology drugs over the past decade. We found that the accelerated approval program has been used consistently in this time period, showing that sponsors' interest in the program and the FDA's willingness to grant accelerated approvals have not waned. Indeed, in 2012, the FDA granted accelerated approval to five oncology drugs, matching its second-highest single-year total in the past 10 years. We also found that extension of OS, while still considered the gold standard by the FDA, is by no means required for approval in oncology. Even the conversion of accelerated approval to regular approval has frequently taken place without demonstration of an improvement in OS. Our research is consistent with a 2003 study conducted by the FDA, which found that 68% of drugs were approved on the basis of endpoints other than survival (29), as well as with a 2011 study that showed the FDA's flexibility in approving orphan drugs (30).

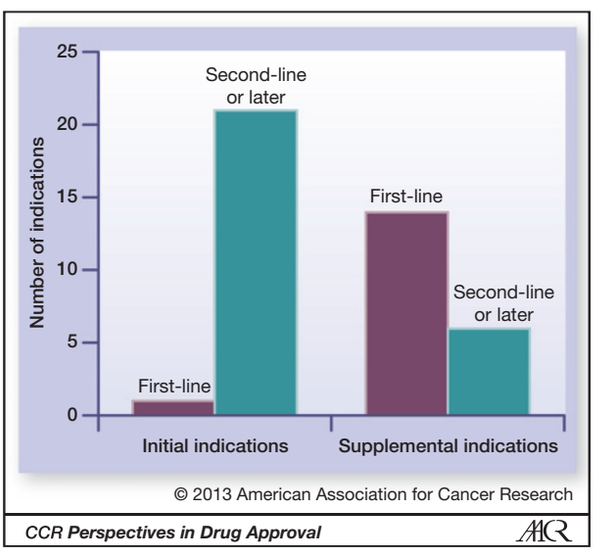

Figure 2. The use of accelerated approval in first-line treatment settings is compared with use of accelerated approval in pretreated settings for initial and supplemental indications from 2002 to 2012.

It is reasonable to expect that as our understanding of cancer improves, new cancer therapies may be more likely to significantly extend and improve survival and perhaps should be held to higher standards than cancer therapies of the past. However, problems remain with measuring OS (31). First, measuring an OS benefit requires large numbers of patients and can take several years, delaying access to new drugs for very sick patients who lack effective options. Second, clinical trials often permit control-arm patients to cross over to the investigational agent after disease progression, confounding analysis of the impact of the investigational agent on survival. Third, as improved therapies become the standard of care, showing a survival benefit compared with these therapies becomes increasingly difficult. Our research shows that the FDA understands these limitations and is willing to accept notable improvements in intermediate endpoints in place of a demonstrated OS benefit. In fact, as experience is gained with an intermediate endpoint in a specific disease, the FDA may become more willing to accept that endpoint as the basis for full approval in that disease. For example, PFS is now routinely accepted as the basis for full approval in RCC (18).

This study has some limitations. First, our data do not include drugs that were submitted for approval but were rejected by the FDA. Unfortunately, information about failed submissions is not made public by the FDA. Without knowledge of drugs that failed to obtain approval, we can assert only what the FDA deems acceptable and not what it deems unacceptable. Second, because of the confidentiality of prenew drug application meetings between sponsors and the FDA, we cannot determine the motivations of sponsors when designing drug development programs. For example, sponsors may choose to design a clinical trial to measure an OS benefit not because the FDA has required it, but because they wish the drug to be more competitive with other drugs already on the market, or because an OS benefit is needed to secure reimbursement in Europe. Third, it may be too soon to make a judgment about the ramifications of the February 2011 ODAC on the approval of drugs based on single-arm trials. For example, any drugs granted accelerated approval after February 2011 that enjoyed Special Protocol Assessments (SPA) would have been exempt from any new FDA expectations. SPAs are agreements between the FDA and trial sponsors regarding the protocol design, size, and endpoints of a particular trial. Our research revealed that, of the eight drugs granted accelerated approval between February 2011 ODAC and the end of 2012, two

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(romidepsin for peripheral T-cell lymphoma and brentuximab vedotin for Hodgkin lymphoma) were approved under SPAs. Both were approved on the basis of the results of single-arm trials using RR as an endpoint. However, five of the six remaining drugs were also approved on the basis of single-arm trials without predetermined trial designs, suggesting that the FDA has continued, of its own accord, to grant accelerated approvals based on single-arm trials.

A major trend in our data is that 95% of accelerated approvals for new oncology drugs were indicated for disease that has failed to respond to other therapeutic options or progressed after prior treatment. The high incidence of pretreated disease among accelerated approvals is, in part, an unintended consequence of the requirement that a drug must show improvement over available therapy to be considered for accelerated approval. Sponsors seeking accelerated approval in early disease settings must show superiority over existing therapies, whereas those seeking accelerated approval in late-line disease settings must show only that they provide a therapy where none exists. Sponsors seeking accelerated approval in late-line disease settings are thus able to conduct single-arm trials using historical controls that measure RR as an intermediate endpoint (18, 26). Although the FDA has expressed concern about the tendency to pursue accelerated approval in pretreated or refractory disease, our research shows that the agency continues to grant accelerated approval in these settings, perhaps because it recognizes the significant unmet need in these patient populations, as well as the barriers to conducting randomized trials in earlier settings.

Although 95% of drugs first entering the market that receive accelerated approval are indicated for late-stage disease, 70% of supplemental accelerated approvals are approved in the first-line setting. A major risk in granting accelerated approval to a new agent is that there is a limited safety database. This risk is at least somewhat mitigated when the drug is already in use in some disease setting, which may help to explain why supplemental accelerated approvals are more likely to be in first-line settings. Furthermore, sponsors often seek to expand the label of a drug by studying its use in an entirely different disease than the original indication, and in some cases these supplemental approvals are in very rare diseases with no effective therapies. In other cases, these supplemental approvals represent label expansions to earlier settings of the originally indicated disease. The FDA encourages sponsors to conduct confirmatory trials in earlier settings of a disease than that for which accelerated approval was granted. In some cases, this leads to full approval in both settings, while in others, approval in the earlier setting is accelerated. For example, the confirmatory studies for the 2003 accelerated approval of imatinib for second-line chronic myelocytic leukemia (CML) were conducted in patients with CML who had not received prior therapy. Those studies led to the accelerated approval of imatinib for first-line CML in 2006 (18).

While the finding that the vast majority of new drugs obtain accelerated approval through studies in pretreated patients is not surprising, it is concerning and is not beneficial for patients, drug sponsors, or regulators. The intent of the accelerated approval program is to expedite patient access to improved therapies for very serious diseases. This program, as it is currently being used in oncology, is not providing expedited access to new and potentially beneficial therapies for patients who have not already been heavily pretreated. These patients, still relatively healthy, may stand to benefit the most from novel therapies. Furthermore, by pursuing accelerated approval in heavily pretreated patients, sponsors decrease the pool of eligible patients that may participate in a clinical trial, thus increasing the challenge of accrual. Finally, trials in refractory patient populations often yield marginal results, making regulatory review difficult. Finding ways to promote the use of accelerated approval in earlier-disease settings should be a priority for all stakeholders. In a recent article, Wilson and colleagues propose a revised approach to accelerated approval to accomplish this goal (32). In their proposal, the authors argue for a mechanistic-based approach to defining what constitutes "available therapy" in any given disease setting and for a more structured approach to accelerated approval. If such a proposal were to be adopted, this might enable sponsors of truly novel therapeutics to pursue accelerated approval in earlier patient populations.

Our research shows that recent criticism of the FDA's regulatory policy in oncology has been overstated. Approval trends over the past decade reveal that the agency has widely accepted the use of intermediate endpoints in the place of overall survival, consistently granted accelerated approvals, and, despite its outspoken resistance to single-arm trials in refractory populations, continued to grant accelerated approval to late-line therapies. The findings presented here indicate that the recent FDA statements about the accelerated approval pathway should not be taken to signal a more restrictive stance but rather as a call for rethinking drug development strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.A. Roberts, J. Allen, E.V. Sigal
Development of methodology: M.B. Shea, S.A. Roberts, J. Allen
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.B. Shea
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.B. Shea, S.A. Roberts, J. Allen
Writing, review, and/or revision of the manuscript: MB. Shea, S.A. Roberts, J. Allen
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.B. Shea
Study supervision: J. Allen, E.V. Sigal

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