JAMA Oncology | Review

A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics
A Review

Julia A. Beaver, MD; Lynn J. Howie, MD; Lorraine Pelosof, MD, PhD; Tamy Kim, PharmD; Jinzhong Liu, MD; Kirsten B. Goldberg, MA; Rajeshwari Sridhara, PhD; Gideon M. Blumenthal, MD; Ann T. Farrell, MD; Patricia Keegan, MD; Richard Pazdur, MD; Paul G. Kluetz, MD

IMPORTANCE Accelerated approval (AA) is a US Food and Drug Administration (FDA) expedited program intended to speed the approval of drugs and biologics that may demonstrate a meaningful advantage over available therapies for diseases that are serious or life-threatening.

OBSERVATIONS This review describes all malignant hematology and oncology AAs from inception of the program on December 11, 1992, to May 31, 2017. During this period, the FDA granted AA to 64 malignant hematology and oncology products for 93 new indications. Of these AAs, 53 were for new molecular entities. Overall, the end point of response rate, including hematologic response rates, accounted for most AAs (81 [87%]), followed by time-to-event end points of progression-free survival or time to progression (8 [9%]) and disease-free survival or recurrence-free survival (4 [4%]). Single-arm trial designs provided the data for 67 (72%) of the initial AA indications. Of the 93 AAs, 51 (55%) have fulfilled their postmarketing requirement and verified benefit in a median of 3.4 years after their initial AA. Thirty-seven (40%) indications have not yet completed confirmatory trial(s) or verified benefit, and 5 indications receiving AA (5%) have been withdrawn from the market.

CONCLUSIONS AND RELEVANCE The use of the AA program during the past 25 years has increased over time, and only a small portion of indications under the AA program fail to verify clinical benefit. For patients with serious or life-threatening oncologic diseases, AA brings products to the market years before confirmatory trials are typically completed.

JAMA Oncol. 2018;4(6):849-856. doi:10.1001/jamaoncol.2017.5618
Published online March 1, 2018.

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 894

Author Affiliations: Office of Hematology and Oncology Products, US Food and Drug Administration, Silver Spring, Maryland (Beaver, Howie, Pelosof, Liu, Goldberg, Blumenthal, Farrell, Keegan); Office of Translational Sciences, US Food and Drug Administration, Silver Spring, Maryland (Sridhara); Center for Drug Evaluation and Research and Oncology Center of Excellence, US Food and Drug Administration, Silver Spring, Maryland (Kim, Pazdur, Kluetz).

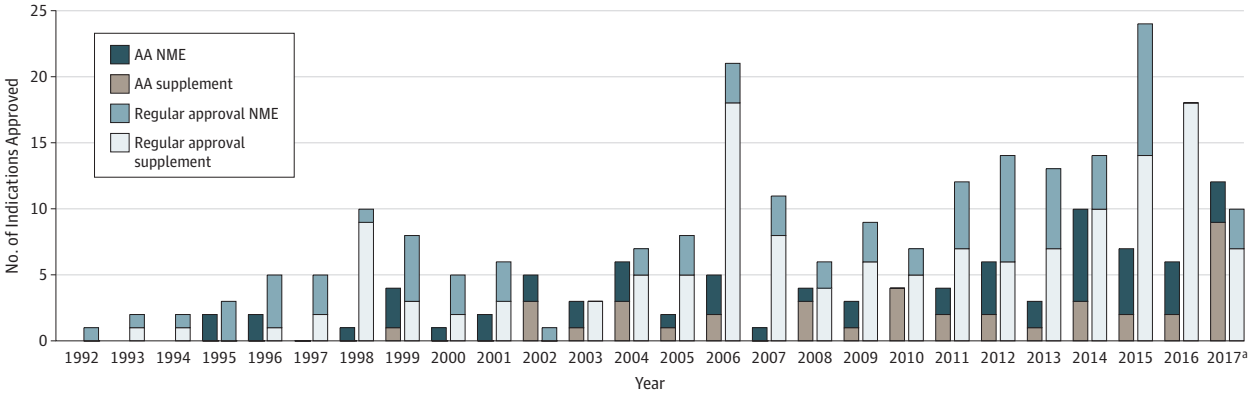
Corresponding Author: Julia A. Beaver, MD, Office of Hematology and Oncology Products, US Food and Drug Administration, 10903 New Hampshire Ave, Building 22, Room 2100, Silver Spring, MD 20993 (julia.beaver@fda.hhs.gov).

Marketing approval of drug products granted by the US Food and Drug Administration (FDA) requires substantial evidence of safety and therapeutic effectiveness based on adequate and well-controlled studies.[1] Regular approval was the only FDA approval pathway until 1992, when in the midst of the HIV crisis, Subpart H was added to federal regulations detailing accelerated approval (AA) as an alternative approval pathway.[2] Authorization of the AA program was also included in biologic product regulations, and the AA provisions were further clarified and broadened in the FDA Safety and Innovation Act.[3,4]

Accelerated approval is an expedited program that provides an alternative approval pathway to regular approval for drug and biologic products (subsequently referred to collectively as drugs) that treat serious or life-threatening conditions.[5] To qualify for AA, drugs must demonstrate an effect on an end point that is reasonably likely to predict clinical benefit or on a clinical end point that can be measured earlier than irreversible morbidity or mortality and demonstrate that the drug provides meaningful advantage over available therapies.[5] The improvement over available therapies can be demonstrated using efficacy end points and other potential mechanisms, such as improvements in safety or tolerability with similar efficacy, superior adherence, or efficacy in an outcome not known to be influenced by available therapy. *Available therapy* is defined as drugs that are approved under regular approval for the intended population at the time of the AA action and generally reflect the current standard of care for the indication. Thus, a drug approved under the AA program is not considered to be available therapy, and this definition allows for multiple drug approvals within an indication under the AA program. Oncologic diseases are considered to be serious or life-threatening; therefore, many of the AAs during the past 25 years have been for oncology drugs.

Given the uncertainty that the surrogate end point used to support AA is predictive of meaningful clinical benefit, drugs

Figure 1. Malignant Hematology and Oncology Approvals by Year



Malignant hematology and oncology accelerated approvals (AAs) and regular approvals by year from first approval in 1995 to May 31, 2017. NME indicates new molecular entity.

[a] Up to May 31, 2017.

approved through this program must be further studied in postapproval trials to verify the drug's clinical benefit. These postmarketing trials should be conducted with due diligence, or the drug may be removed from the market. To maximize the likelihood of trial accrual and timely completion, a confirmatory trial(s) should be under way, if not fully enrolled, at the time of AA.[6] The confirmatory trial(s) may be in a different line of therapy than the initial AA, allowing for multiple choices of clinical trial design and improved feasibility.

The FDA experience with AA of oncology drugs was first published in 2004 (detailing experience to 2004) and again in 2011 (detailing experience to 2010).[7,8] This article updates these reports to May 31, 2017, and provides new information regarding the maturation of the AA pathway in oncology, including trends in end points used, timelines for verification of benefit, and other key aspects of this important expedited program.

Methods

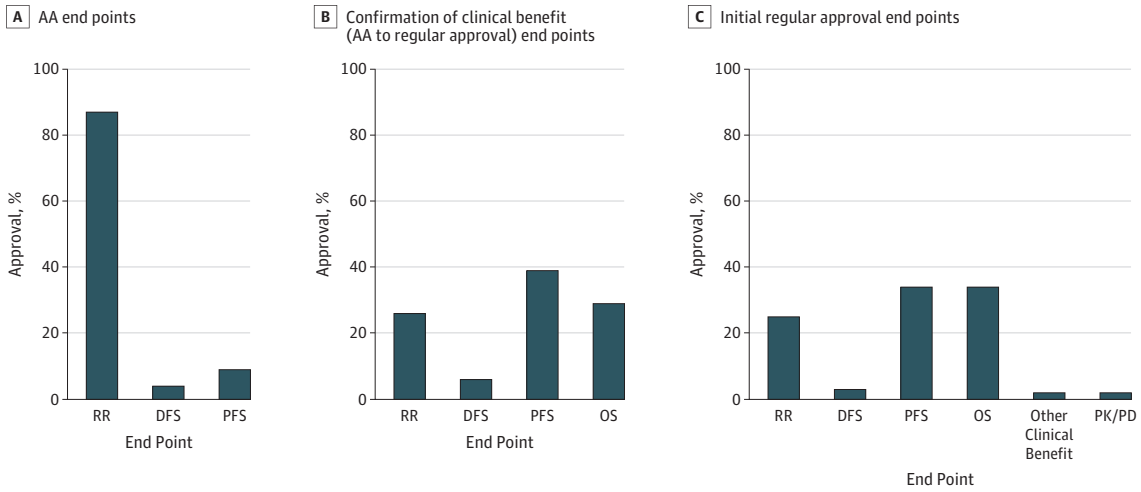
We searched the FDA databases to identify all drugs approved under the AA program with malignant hematology and oncology indications from inception of the program on December 11, 1992, to May 31, 2017. Data sources included approval letters, prescribing information, and review documents from the FDA's electronic record system.[9] The following information was collected: date of approval, indication, date of confirmation of clinical benefit and regular approval, size of the safety and efficacy database supportive of AA, type of trial design for both the accelerated and (if applicable) the confirmatory trial, end points used for these trials, and class of drug. The safety database for drugs encompassed the reported numbers of patients treated with a drug regardless of age or condition being treated or of healthy volunteer status. Data regarding confirmatory trials were collected from the supplemental efficacy submission. When the confirmatory trial was not complete, milestones were captured from multiple sources, including the AA letter, clinical review of available FDA documents, and clinicaltrials.gov. Information regarding whether the confirmatory trial was open and actively accruing patients at the time of the AA was also collected when available. For applications with more than 1 confirmatory trial or end point, the earliest of the dates was designated the trial completion date. When multiple end points were used to support approval, for end point description, we selected the end point with the clearest association with clinical benefit. For example, if a trial demonstrated a statistically significant improvement in both progression-free survival (PFS) and overall survival (OS), we reported this approval as being based on OS. Regular approvals were identified using a previous publication and databases available on the FDA website.[9,10] Approvals for cellular and gene therapies, vaccines, blood products, and nonmalignant hematology or supportive care indications were not included.

Results

AAs of Oncology Products

From December 11, 1992, to May 31, 2017, the FDA granted AA for 64 malignant hematology and oncology drugs for 93 new indications. Of these AAs, 53 were for new molecular entities. During this same period, 174 oncology drug indications were approved under regular approval, as were 51 indications that were initially approved under the AA program and verified clinical benefit, resulting in regular approval. Approved malignant hematology and oncology drug indications by year and approval pathway are shown in **Figure 1**. Of the AA indications, by mechanism of action, 29 were indications for tyrosine kinase inhibitors, 29 for monoclonal antibodies (including 16 anti–programmed cell death 1 or anti–programmed cell death 1 ligand antibodies), 15 for cytotoxic therapies, 5 for antibody drug conjugates, and 4 for hormonal therapies. Two drugs, pembrolizumab and imatinib, have received AA for 6 indications each. Nivolumab has received AA for 4 indications and for an additional indication in combination with ipilimumab. Atezolizumab, bevacizumab, brentuximab vedotin, cetuximab, dasatinib, everolimus, ibrutinib, letrozole, liposomal doxorubicin, nilotinib, avelumab, and pemetrexed have each received AA for 2 indications.

Figure 2. Malignant Hematology and Oncology Approval End Points



End points resulting in approvals of malignant hematology and oncology indications from December 11, 1992, to May 31, 2017. In A, n = 93; B, n = 51; C, n = 174. AA indicates accelerated approval; DFS, disease-free survival; OS, overall survival; PFS, progression-free survival (incuding time to progression); PK/PD, pharmacokinetic/pharmacodynamic; and RR, response rate.

End Points and Verification of Benefit

Randomized comparative trials supported 26 (28%) of these indications, and single-arm trials accounted for 67 (72%). Of the randomized clinical trials, 13 were supported by a primary end point of response rate (RR) (one of which also had time to progression [TTP] as an end point), 7 had PFS as the primary end point, 4 had disease-free survival (DFS) or recurrence-free survival (RFS), 1 had TTP, and 1 had pathologic complete response as the primary end point supporting AA. Of the single-arm trials, all had RR as the primary end point (one had duration of response as a coprimary end point, and some hematologic indications used hematologic response end points, such as complete response or major cytogenic response). Overall, the end point of RR, including pathologic complete response (n = 1) and hematologic response end points, accounted for most AAs (81 [87%]), followed by time-to-event end points of PFS or TTP (8 [9%]) and DFS or RFS (4 [4%]) (**Figure 2**A).

For the 51 drugs that were initially approved under the AA program and verified clinical benefit, the end point used to primarily support the verification of clinical benefit for regular approval was most frequently PFS or TTP (20 [39%]), followed by OS (15 [29%]), RR with supportive duration of response (including hematologic end points) (13 [26%]), and DFS or RFS (3 [6%]) (Figure 2B).

In addition, during the 25-year period, 174 new indications were approved through regular approval. Overall survival (60 [35%]) was the most commonly used end point, followed by PFS or TTP (59 [34%]), RR with supportive duration of response (including hematologic end points) (43 [25%]), DFS or RFS (6 [3%]), other clinical benefit (such as symptom reduction or reduction in transfusions) (3 [2%]), and other end points, such as pharmacokinetic end points for new drug formulations (3 [2%]) (Figure 2C).

Size of AA Efficacy and Safety Database

Trials that supported an AA had a median efficacy population of 143 patients, with a range of 17 (liposomal cytarabine for lymphomatous meningitis) to 9366 patients (anastrozole for adjuvant breast cancer) (eFigure 1 in the Supplement). Twenty-nine AAs had efficacy populations of less than 100, with 6 having sample sizes less than 50. The safety population was evaluated in the trials that supported the 54 AA indications for drugs that were not already approved. This finding demonstrated a median safety population size of 418 patients (range, 48-2098). Only 3 studies had a safety population of less than 100: lipocytarabine for lymphomatous meningitis in 2007 (n = 48), vincristine for acute lymphocytic leukemia in second relapse or greater in 2012 (n = 83), and alemtuzumab as third-line B-cell chronic lymphocytic leukemia in 2001 (n = 93).

Current Status of AA Indications

Of the 93 AAs, 51 (55%) have fulfilled their postmarketing requirement and verified benefit (**Table 1**). Thirty-seven indications (40%) have not yet completed confirmatory trial(s) or verified benefit (eTable in the Supplement). Five indications receiving AA (5%) have been withdrawn from the market (**Table 2**). Of the 51 that satisfied their postmarketing requirement(s) and verified benefit, the median time from AA to verification of benefit was 3.4 years (range, 0.5-12.6 years), with most of these having confirmatory trial(s) ongoing at the time of approval (eFigure 2 in the Supplement). For those that had ongoing confirmatory trials at the time of AA, the median time to verification of benefit was 3.1 years; for the 9 indications without ongoing trials, the median time to verification of benefit was 5.5 years.

Of the 37 indications that have ongoing confirmatory trials or have otherwise not yet verified benefit, the median time from AA to the cutoff date of May 31, 2017, was less than 2 years (18.5 months), with a range of less than 1 month to 149 months (12.4 years). Of these indications, 26 (70%) have been on the market for less than 3 years, and 20 (54%) have been marketed for less than 2 years. Eight indications that have not yet verified benefit have been on the market for more than 5 years, with several of these indications being for rare patient populations.

Table 1. AAs for Malignant Hematology and Oncology Products That Verified Benefit

Product	NME or Novel Biologic	Date of AA	Date of Verification of Benefit	AA End Point	Original AA Indication	Confirmatory Trial End Point	Time From Approval to Verification, y
Bicalutamide (Casodex)	Yes	Oct 4, 1995	Dec 12, 1997	TTP	Metastatic prostate cancer in combination with an LHRH analogue	TTP	2.2
Liposomal doxorubicin (Doxil)	Yes	Nov 17, 1995	Jun 10, 2008	RR	AIDS-related Kaposi sarcoma after progression or intolerance to prior chemotherapy	RR	12.6
Docetaxel (Taxotere)	Yes	May 14, 1996	Jun 22, 1998	RR	Advanced or metastatic breast cancer after prior chemotherapy	OS	2.1
Irinotecan (Camptosar)	Yes	Jun 14, 1996	Oct 22, 1998	RR	Metastatic colon or rectal cancer that has progressed after fluorouracil-based therapy	OS	2.4
Capecitabine (Xeloda)	Yes	Apr 30, 1998	Sep 7, 2001	RR	Metastatic breast cancer that is refractory to paclitaxel and to an anthracycline-containing regimen	OS	3.4
Denileukin (Ontak)	Yes	Feb 5, 1999	Oct 15, 2008	RR	Recurrent or persistent CTCL that expresses the CD25 component of the IL-2 receptor	RR	9.7
Lipocytarabine (DepoCyt)	Yes	Apr 1, 1999	Apr 19, 2007	RR	Intrathecal treatment for lymphomatous meningitis	RR	8.1
Liposomal doxorubicin (Doxil)	No	Jun 28, 1999	Jan 28, 2005	RR	Metastatic ovarian cancer that is refractory to paclitaxel- and platinum-based regimens	TTP	5.6
Temozolomide (Temodar)	Yes	Aug 11, 1999	Mar 15, 2005	RR	Refractory anaplastic astrocytoma after progression on a regimen that contains a nitrosourea and procarbazine	OS	5.6
Alemtuzumab (Campath)	Yes	May 7, 2001	Aug 19, 2007	RR	B-cell CLL that has been treated with alkylating agents and fludarabine	PFS	6.4
Imatinib (Gleevec)	Yes	May 10, 2001	Dec 8, 2003	RR	CML in BC, AP, or CP after failure of interferon alfa therapy	PFS	2.6
Imatinib (Gleevec)	No	Feb 1, 2002	Sep 26, 2008	RR	Kit (CD117)-positive unresectable and/or metastatic malignant GIST	PFS	6.7
Ibritumomab (Zevalin)	Yes	Feb 19, 2002	Sep 3, 2009	RR	As part of a regimen for relapsed or refractory low-grade, follicular, or transformed B-cell NHL	PFS	7.5
Oxaliplatin (Eloxatin)	Yes	Aug 9, 2002	Jan 9, 2004	RR	In combination with fluorouracil and leucovorin for mCRC that has recurred or progressed with fluorouracil and leucovorin plus irinotecan	OS	1.4
Anastrazole (Arimidex)	No	Sep 5, 2002	Sep 16, 2005	DFS	Adjuvant, postmenopausal, HR-positive early breast cancer	DFS	3
Imatinib (Gleevec)	No	Dec 20, 2002	May 27, 2009	PFS	Newly diagnosed, Ph-positive CML	PFS	6.4
Bortezomib (Velcade)	Yes	May 13, 2003	Mar 25, 2005	RR	MM with at least 2 prior therapies	OS	1.9
Imatinib (Gleevec)	No	May 20, 2003	Sep 27, 2006	RR	Pediatric, Ph-positive CP CML resistant to interferon or recurrent after SCT	RR	3.4
Cetuximab (Erbitux)	Yes	Feb 12, 2004	Oct 2, 2007	RR	Single agent for EGFR-positive mCRC intolerant to irinotecan-based chemotherapy	OS	3.6
Cetuximab (Erbitux)	No	Feb 12, 2004	Jul 6, 2012	RR	With irinotecan in EGFR-positive mCRC refractory to irinotecan-based chemotherapy	PFS	8.4
Pemetrexed (Alimta)	No	Aug 19, 2004	Jul 2, 2009	RR	Locally advanced or metastatic NSCLC after previous chemotherapy	OS	4.9
Letrozole (Femara)	No	Oct 29, 2004	Apr 30, 2010	DFS	Extended adjuvant postmenopausal breast cancer after 5 years of tamoxifen therapy	DFS	5.5
Letrozole (Femara)	No	Dec 28, 2005	Mar 2, 2010	DFS	Adjuvant, post-menopausal, HR-positive breast cancer	DFS	4.2
Sunitinib (Sutent)	Yes	Jan 26, 2006	Feb 2, 2007	RR	Advanced RCC	PFS	1
Dasatinib (Sprycel)	Yes	Jun 28, 2006	May 21, 2009	RR	CML that is resistant or intolerant to prior therapy, including imatinib	RR	2.9
Panitumumab (Vectibix)	Yes	Sep 27, 2006	May 23, 2014	PFS	EGFR expressing mCRC after fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens	OS	7.7
Imatinib (Gleevec)	No	Sep 27, 2006	Apr 1, 2011	RR	Newly diagnosed, pediatric, Ph-positive CML	RR	4.5
Nilotinib (Tasigna)	Yes	Oct 29, 2007	Jan 14, 2011	RR	Ph-positive CML CP or AP resistant or intolerant to imatinib	RR	3.2
Pemetrexed (Alimta)	No	Sep 26, 2008	Jul 2, 2009	RR	Locally advanced or metastatic NSCLC with cisplatin	OS	0.8

(continued)

Table 1. AAs for Malignant Hematology and Oncology Products That Verified Benefit (continued)

Product	NME or Novel Biologic	Date of AA	Date of Verification of Benefit	AA End Point	Original AA Indication	Confirmatory Trial End Point	Time From Approval to Verification, y
Imatinib (Gleevec)	No	Dec 19, 2008	Jan 31, 2012	RFS	Adjuvant treatment after complete gross resection of Kit (CD117)-positive GIST	OS	3.1
Ofatumumab (Arzerra)	Yes	Oct 26, 2009	Apr 17, 2014	RR	CLL refractory to fludarabine and alemtuzumab	PFS	4.5
Nilotinib (Tasigna)	No	Jun 17, 2010	Jan 22, 2014	RR	Newly diagnosed, Ph-positive CML in CP	RR	3.6
Dasatinib (Sprycel)	No	Oct 28, 2010	Aug 12, 2015	RR	Newly diagnosed, Ph-positive CML in CP	RR	4.8
Everolimus (Afinitor)	No	Oct 29, 2010	Jan 29, 2016	RR	SEGA associated with TSC that is not a resection candidate	RR	5.3
Brentuximab vedotin (Adcetris)	Yes	Aug 19, 2011	Aug 17, 2015	RR	HL after failure of ASCT or at least 2 prior multiagent chemo regimens in patients not ASCT candidates	PFS	4
Crizotinib (Xalkori)	Yes	Aug 26, 2011	Nov 20, 2013	RR	Locally advanced or metastatic *ALK* mutation-positive NSCLC	PFS	2.2
Everolimus (Afinitor)	No	Apr 26, 2012	Feb 18, 2016	RR	Renal angiomyolipoma associated with TSC who do not require immediate surgery	PFS	3.8
Carfilzomib (Kyprolis)	Yes	Jun 20, 2012	Jan 21, 2016	RR	MM after at least 2 prior therapies, including bortezomib and an immunomodulatory agent	PFS	3.5
Everolimus tablets for oral suspension (Afinitor Disperz)	No	Aug 29, 2012	Jan 29, 2016	RR	Pediatric and adult patients with TSC who have SEGA that requires therapeutic intervention but cannot be curatively resected	RR	3.4
Omacetaxine (Synribo)	Yes	Oct 26, 2012	Feb 10, 2014	RR	Chronic or accelerated CML after resistance or intolerance to 2 or more TKIs	RR	1.3
Ponatinib (Iclusig)	Yes	Dec 14, 2012	Nov 28, 2016	RR	CP, AP, or BC CML resistant or intolerant to prior TKI or Ph-positive ALL resistant or intolerant to prior TKIs	RR	4
Pomalidomide (Pomalyst)	Yes	Feb 8, 2013	Apr 23, 2015	RR	MM after at least 2 prior therapies, including lenalidomide and bortezomib	PFS	2.2
Trametinib (Mekinist)	No	Jan 8, 2014	Nov 20, 2015	RR	In combination with dabrafenib for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations	OS	1.9
Dabrafenib (Tafinlar)	No	Jan 9, 2014	Nov 20, 2015	RR	In combination with trametinib for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations	OS	1.9
Ibrutinib (Imbruvica)	No	Feb 12, 2014	Jul 28, 2014	RR	Treatment of CLL after 1 prior therapy	OS	0.5
Ceritinib (Zykadia)	Yes	Apr 29, 2014	May 26, 2017	RR	Treatment of *ALK* mutation-positive metastatic NSCLC after progression or intolerance to crizotinib	PFS	3.1
Pembrolizumab (Keytruda)	Yes	Sep 4, 2014	Dec 18, 2015	RR	Unresectable or metastatic melanoma after ipilimumab and a *BRAF* inhibitor if *BRAF* mutation positive	PFS	1.3
Palbociclib (Ibrance)	Yes	Feb 3, 2015	Mar 31, 2017	PFS	In combination with letrozole for postmenopausal, ER-positive *HER2* metastatic breast cancer as initial endocrine therapy	PFS	2.2
Pembrolizumab (Keytruda)	No	Oct 2, 2015	Oct 24, 2016	RR	PDL1-positive metastatic NSCLC after platinum-containing chemotherapy	OS	1.1
Osimertinib (Tagrisso)	Yes	Nov 13, 2015	Mar 30, 2017	RR	Metastatic *EGFR* T790M mutation-positive NSCLC after progression on or after an EGFR TKI	PFS	1.4
Daratumumab (Darzalex)	Yes	Nov 16, 2015	Nov 21, 2016	RR	MM after at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug or are double refractory	PFS	1

Abbreviations: AA, accelerated approval; ALK, anaplastic lymphoma receptor tyrosine kinase; ALL, acute lymphocytic leukemia; AP, accelerated phase; ASCT, autologous stem cell transplant; BC, blast crisis; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CP, chronic phase; CTCL, cutaneous T-cell lymphoma; DFS, disease-free survival; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; GIST, gastrointestinal stromal tumor; *HER2*, human epidermal growth factor receptor 2; HL, Hodgkin lymphoma; HR, hormone receptor; IL, interleukin; LHRH, luteinizing hormone–releasing hormone; mCRC, metastatic colorectal cancer; MM, multiple myeloma; NA, not applicable; NHL, non-Hodgkin lymphoma; NME, new molecular entity; NSCLC, non–small cell lung cancer; OS, overall survival; PDL1, programmed death-ligand 1; PFS, progression-free survival; Ph, Philadelphia chromosome; RCC, renal cell carcinoma; RFS, recurrence-free survival; RR, response rate (including hematologic response rates for the hematologic indications); SCT, stem cell transplant; SEGA, subependymal giant cell astrocytoma; TKI, tyrosine kinase inhibitor; TSC, tuberous sclerosis complex; TTP, time to progression.

Table 2. AAs for Malignant Hematology and Oncology Products That Were Withdrawn

Product	NME or Novel Biologic	Date of AA	Date of Withdrawal	AA End Point	Original AA Indication	Confirmatory Trial End Point	Time From Approval to Withdrawal, y
Gemtuzumab (Mylotarg)	Yes	May 17, 2000	Nov 28, 2011	RR	CD33-positive AML in first relapse in patients ≥60 y of age who are not candidates for cytotoxic chemotherapy	NA; confirmatory trial failed to confirm clinical benefit and raised safety concerns; another submission with lower dose, different patient population, and new schedule was approved 9/1/2017	11.5
Gefitinib (Iressa)	Yes	May 5, 2003	Apr 25, 2012	RR	Monotherapy for locally advanced or metastatic NSCLC after platinum-based and docetaxel therapies	NA; confirmatory trials failed to verify clinical benefit and voluntarily withdrawn by company; patients currently receiving gefitinib could continue treatment under expanded access program; subsequently approved (7/13/2015) in first-line NSCLC with EGFR exon 19 deletions or exon 21 substitution mutations	9
Tositumomab (Bexxar)	Yes	Dec 22, 2004	Oct 23, 2013	RR	Relapsed or refractory low-grade follicular not treated with rituximab	NA; confirmatory trial not completed and voluntarily withdrawn by company	8.8
Bevacizumab (Avastin)	No	Dec 22, 2008	Nov 18, 2011	PFS	First line in combination with paclitaxel for metastatic, *HER2*-negative breast cancer	NA; confirmatory trial(s) did not verify benefit; sponsor did not voluntarily withdraw, prompting public hearings; FDA commissioner issued final decision withdrawing approval	4
Fludarabine (Oforta)	Yes	Dec 18, 2008	Dec 31, 2011	RR	B-cell CLL after at least 1 standard alkylating agent–containing regimen	NA; failure to complete confirmatory trial and lack of commercial demand; company voluntarily withdrew	3.4

Abbreviations: AA, accelerated approval; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; *HER2*, human epidermal growth factor receptor 2; NA, not applicable; NME, new molecular entity; NSCLC, non–small cell lung cancer.

Discussion

The 25 years of experience with the AA program has demonstrated that it can be used successfully to expedite the approval of safe and effective cancer therapies. The AA program balances uncertainty associated with smaller sample sizes and earlier clinical trial end points with providing faster access to promising agents for those with serious or life-threatening disease. Completion of postmarketing trials in a timely manner is critical to provide the data to verify overall clinical benefit. Efficient postmarketing trial completion relies on careful planning. The benefit of having the postmarketing trial actively accruing at the time of AA is illustrated by the more than 2-year median difference in confirmatory trial completion and verification of benefit for indications that had confirmatory trials under way compared with those that did not. Moving forward, it may also be useful to begin to explore the utility of real-world data or pragmatic clinical trial designs to improve our ability to accrue patients and complement data from controlled postmarketing clinical trial information.

Some have criticized surrogate end points based on tumor measurement in oncology, suggesting that the postmarketing trials for verification of clinical benefit should focus on improvement in OS or health-related quality of life.[11] For multiple reasons, the feasibility of OS or health-related quality of life as primary end points can be problematic, and the complexity of FDA regulations and review can be challenging to convey to the public.[12,13] Regardless of the primary end point used, survival and patient experience data are included where available as part of the totality of the data in an FDA review. In addition, the FDA is actively identifying ways to better communicate the complex data and analyses leading to a regulatory decision through its clinical and statistical reviews, the FDA label, and other venues so that clinicians and patients can make informed choices about treatment options.

Oncology is a unique therapeutic area because our most common AA end points (RR and PFS) reflect direct measures of the disease and have been considered suitable for regular approval or AA depending on the magnitude of effect, safety profile, and disease context.[14] The FDA has recognized that substantial and durable tumor size reduction or delay in tumor progression frequently drives clinical decision making and may be of benefit to patients if the overall benefit-risk profile is favorable, particularly for diseases with limited treatment options.[15,16] Thus, although not directly measuring symptoms, function, or survival, measures of tumor burden (RR) and disease control (PFS) are commonly used as both the AA end point and the postmarketing clinical trial end point to verify benefit by verifying the initial magnitude of effect and further characterizing safety. Increasingly, many researchers working in drug development have noted that, for some drugs approved under AA, requiring OS as the end point to verify clinical benefit may not be ethical or practical.[17]

In particular, some targeted therapies and immunotherapies demonstrate substantial improvement in durable objective RRs with a differing toxicity profile compared with standard therapy. For example, the AA of crizotinib for treatment of anaplastic lymphoma kinase–positive locally advanced or metastatic non–small cell lung cancer was based on a durable RR in more than half (range, 50%-61%) of the patients treated. The randomized confirmatory trial compared single-agent crizotinib with cytotoxic chemotherapy, with more than 60% of patients crossing over from chemotherapy to crizotinib.[18] In these cases, it is unlikely

that patients would participate in a trial in which they could be randomized to the control arm without the opportunity to cross over to investigational therapy on disease progression. For many diseases, PFS is considered to be a clinically relevant end point for postmarketing trials, and crossover does not confound this end point assessment. Randomization may not be feasible in rare malignant tumors, such as those that have been reclassified based on molecular or genomic markers, particularly when a drug shows unprecedented activity early in clinical development. For these reasons, OS may not be a feasible end point to verify clinical benefit for many of the drugs approved under the AA program; therefore, less than half of the planned confirmatory trials used OS as a primary or coprimary end point. The FDA will continue to take advantage of all available efficacy data, including objective tumor-based end points and OS, either as supportive data or as the primary end point when appropriate. In addition, the FDA is proactively engaging the scientific community to advance measurement of health-related quality of life, symptom, and functional measures through patient-reported outcomes and other clinical outcome assessments to further complement safety and efficacy from existing tumor and survival measures.[19,20]

An additional criticism of the AA pathway is that there may be significantly fewer safety data at the time of approval. Although the FDA generally has fewer safety data for a new molecular entity granted AA compared with a drug granted regular approval, this safety database is usually larger than the efficacy database supporting AA. Our data reveal that, on average, there are approximately twice the number of patients with safety data than there are for the efficacy-evaluable population for AA applications supporting new molecular entities. In addition, many of the AA indications are efficacy supplements of already-approved drugs with large safety information and postmarketing safety data. There is only one case of a drug under AA being withdrawn for a combination of failure to verify clinical benefit and safety issues (gemtuzumab ozogamicin); however, this drug was recently approved after the dosing strategy and intended patient population were optimized.[21] There are no safety-related withdrawals of indications approved under regular approval; however, indications may have been withdrawn for other (eg, business) reasons. In the case of ponatinib, safety signals emerged after approval that caused a temporary suspension of marketing and sales with subsequent change in the presentation of safety information and intended population, allowing for continued marketing and continued favorable benefit-risk profile. The case of ponatinib highlights the importance of postmarketing safety review and the rapid identification and mitigation of a postmarketing safety finding.

Finally, this review reiterates that AA brings products to the market years before confirmatory trials are typically completed. The time on the market before verification reflects earlier access to safe and effective cancer drugs but also may reflect the period during which an ineffective drug may be marketed. The time between AA and verification of clinical benefit is the the accepted tradeoff for the AA program and highlights the importance of completing trials with due diligence. We encourage companies to meet with the FDA early in the drug development process to discuss the possibility of AA and the appropriate supportive and confirmatory trials to generate data necessary for AA and subsequent regular approval. The FDA will evaluate the AA submission in the context of the overall development of the drug and recommends that the confirmatory trial be ongoing at the time of AA to ensure rapid and complete trial enrollment.

Since the initiation of AA more than 25 years ago, this program has been used frequently to expedite oncology drug approvals. Our analysis indicates that use of the AA program has increased over time, and clinical benefit was not verified in only 5% of the indications approved. Thus, AA balances risk, accounts for uncertainty, and allows for regulatory flexibility to make safe and effective oncology drugs available to patients sooner than permitted through the regular approval pathway.

ARTICLE INFORMATION

Accepted for Publication: November 28, 2017.

Published Online: March 1, 2018. doi:10.1001/jamaoncol.2017.5618

Author Contributions: Drs Beaver, Howie, and Pelosof contributed equally to this work. Drs Beaver and Kluetz 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 analysis.
Study concept and design: Beaver, Kim, Blumenthal, Pazdur, Kluetz.
Acquisition, analysis, or interpretation of data: Beaver, Howie, Pelosof, Kim, Liu, Goldberg, Sridhara, Blumenthal, Farrell, Keegan, Kluetz.
Drafting of the manuscript: Beaver, Howie, Pelosof, Liu, Blumenthal, Farrell, Pazdur, Kluetz.
Critical revision of the manuscript for important intellectual content: Beaver, Howie, Pelosof, Kim, Goldberg, Sridhara, Blumenthal, Farrell, Keegan, Kluetz.
Statistical analysis: Howie, Liu.
Administrative, technical, or material support: Beaver, Howie, Kim, Goldberg, Sridhara, Keegan, Pazdur.
Study supervision: Beaver, Kim, Blumenthal, Farrell, Pazdur, Kluetz.

Conflict of Interest Disclosures: The authors conducted all work on the manuscript during their work at the US Food and Drug Administration. No additional funds were used for this activity.

REFERENCES

1. Code of Federal Regulations. §21-314.126. https://www.ecfr.gov/cgi-bin/text-idx?SID=8eea61dec0ef9b17f1fa0d0d3a7736c6&mc=true&node=se21.5.314_1126&rgn=div8. March 4, 2002. Accessed September 13, 2017.

2. Code of Federal Regulations. §314.510. https://www.ecfr.gov/cgi-bin/text-idx?SID=7e3afa31ba9326a86c1c08ca7cb22f4c&mc=true&node=se21.5.314_1510&rgn=div8. December 11, 1992. Accessed September 13, 2017.

3. Code of Federal Regulations. §601.41. https://www.ecfr.gov/cgi-bin/text-idx?SID=c03234aa22abbed0380923a4cc6ab001&mc=true&node=se21.7.601_141&rgn=div8. December 11, 1992. Accessed September 13, 2017.

4. Food and Drug Administration Safety and Innovation Act, 21 USC §301. https://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf. July 9, 2012. Accessed September 13, 2017.

5. US Food and Drug Administration. Guidance for Industry: Expedited Programs for Serious Conditions–Drugs and Biologics. May 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf. Accessed September 13, 2017.

6. US Food and Drug Administration. Center for Drug Evaluation and Research, Oncologic Drugs Advisory Committee (ODAC) [meeting transcript]. February 8, 2011. https://wayback.archive-it.org/7993/20170404153747/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf. Accessed September 13, 2017.

7. Dagher R, Johnson J, Williams G, Keegan P, Pazdur R. Accelerated approval of oncology products: a decade of experience. *J Natl Cancer Inst*. 2004;96(20):1500-1509.

8. Johnson JR, Ning YM, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of oncology products: the Food and Drug Administration experience. *J Natl Cancer Inst*. 2011;103(8):636-644.

9. US Food and Drug Administration. Drugs@FDA: FDA approved drug products. http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed March 15, 2017.

10. Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of oncology drugs. *J Clin Oncol*. 2003;21(7):1404-1411.

11. Naci H, Smalley KR, Kesselheim AS. Characteristics of preapproval and postapproval studies for drugs granted accelerated approval by the US Food and Drug Administration. *JAMA*. 2017;318(7):626-636.

12. Kesselheim AS, Woloshin S, Eddings W, Franklin JM, Ross KM, Schwartz LM. Physicians' knowledge about FDA approval standards and perceptions of the "breakthrough therapy" designation. *JAMA*. 2016;315(14):1516-1518.

13. Schwartz LM, Woloshin S. Communicating uncertainties about prescription drugs to the public: a national randomized trial. *Arch Intern Med*. 2011;171(16):1463-1468.

14. US Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. May 2007. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071590.pdf. Accessed September 13, 2017.

15. Blumenthal GM, Kluetz PG, Schneider J, Goldberg KB, McKee AE, Pazdur R. Oncology drug approvals: evaluating endpoints and evidence in an era of breakthrough therapies. *Oncologist*. 2017;22(7):762-767.

16. Blumenthal GM, Pazdur R. Response rate as an approval end point in oncology: back to the future. *JAMA Oncol*. 2016;2(6):780-781.

17. Califf RM. Balancing the need for access with the imperative for empirical evidence of benefit and risk. *JAMA*. 2017;318(7):614-616.

18. Kazandjian D, Blumenthal GM, Chen HY, et al. FDA approval summary: crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. *Oncologist*. 2014;19(10):e5-e11.

19. Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-reported outcomes in cancer clinical trials: measuring symptomatic adverse events with the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Am Soc Clin Oncol Educ Book*. 2016;35:67-73.

20. Kluetz PG, Papadopoulos EJ, Johnson LL, et al. Focusing on core patient-reported outcomes in cancer clinical trials: response. *Clin Cancer Res*. 2016;22(22):5618.

21. FDA approves Mylotarg for treatment of acute myeloid leukemia [press release]. Silver Spring, MD: US Food and Drug Administration; September 1, 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574507.htm. Accessed September 25, 2017.