Characteristics of pre-approval and post-approval studies for drugs granted accelerated approval by the US food and drug administration

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Characteristics of Pre-Approval and Post-Approval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration

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Key points

Question: What are the characteristics and findings of pre-approval and post-approval trials of drugs granted FDA Accelerated Approval between 2009 and 2013?

Findings: Clinical trials conducted before and after Accelerated Approval have similar design characteristics such as lack of blinding, randomization, and comparator groups. While most post-approval confirmatory studies showed some benefit, they rely on surrogate measures rather than clinical outcomes.

Meaning: Although many drugs granted Accelerated Approval by the FDA from 2009-2013 had had their efficacy confirmed in post-approval trials, there may be limitations in the study designs and endpoints used.

Abstract

Importance: Drugs treating serious conditions can receive US Food and Drug Administration (FDA) Accelerated Approval based on showing an effect in surrogate measures that are only reasonably likely to predict clinical benefit. Confirmatory trials are then required to determine whether these effects translate to clinical improvements.

Objective: To characterize pre-approval and confirmatory clinical trials of drugs granted Accelerated Approval.

Design and Setting: Publicly available FDA documents were surveyed to evaluate the pre-approval trials leading to Accelerated Approval between 2009 and 2013. Information on the status and findings of required confirmatory studies was extracted from the FDA's database of postmarketing requirements and commitments, ClinicalTrials.gov, and matched publications. End date of follow up was 7 April 2017.

Exposure: Granting of Accelerated Approval.

Main Outcomes and Measures: Characteristics of pre-approval and confirmatory studies were compared in terms of study design features (randomization, blinding, comparator, primary endpoint) and indications. Subsequent regulatory decisions and estimated time between Accelerated Approval and fulfillment of regulatory requirements were reviewed.

Results: FDA granted Accelerated Approval to 22 drugs for 24 indications in the study period. At a minimum 3 years of follow-up, 19 of 38 required confirmatory studies were completed (50%). The proportion of studies with randomized designs did not differ before and after Accelerated Approval (16%, 95% confidence interval [CI]: -15%-46%; P=0.31). Post-approval requirements were completed and demonstrated efficacy in 10 indications (42%) on the basis of trials that evaluated surrogate measures alone. Among the 14 indications (58%) that had not yet completed requirements, confirmatory studies failed to demonstrate clinical benefit in 2 (8%) indications; were terminated in 2 (8%); and were

delayed by more than one year in 3 (13%) with no regulatory action. Studies were progressing according to target timelines for the remaining 7 indications (29%). Clinical benefit had not yet been confirmed for 7 indications that had been initially approved 5 or more years prior.

Conclusions and Relevance: Many drugs recently granted Accelerated Approval had had their efficacy confirmed in post-approval trials, although confirmatory trials have similar design elements to pre-approval trials, including reliance on surrogate measures as outcomes. Delays in completing post-approval confirmatory trials persisted for a minority of drugs.

Introduction

The US Food and Drug Administration (FDA) has several pathways aimed at expediting the development and approval of drugs that address serious or life-threatening conditions.[1] The Accelerated Approval pathway permits the FDA to grant marketing authorization on the basis of surrogate measures—biomarkers, laboratory values, or other physical measures that may serve as indicators of clinical outcomes such as symptom control or mortality—that are only "reasonably likely" to predict clinical benefit.[2] Once Accelerated Approval drugs are granted marketing authorization, the FDA requires that the sponsors complete confirmatory trials to describe and verify clinical efficacy.[3] When these requirements are fulfilled, the drug's label may be updated to account for the new information.

While special pathways like Accelerated Approval can be highly effective in facilitating the testing of certain new drugs,[4,5] they have also been a source of controversy. Drugs approved via expedited pathways may have greater safety risks to patients.[6,7] There is also uncertainty about whether observed effects on surrogate measures will materialize into clinical improvements.[8] In a review of drugs approved by the FDA between 2005 and 2012 on the basis of limited evidence, only a minority showed efficacy in controlled trials in the post-approval period.[9] Confirmatory trials evaluating the clinical benefit of drugs in the Accelerated Approval pathway can also be substantially delayed.[10] In a previous evaluation of Accelerated Approval of oncology products, clinical benefit was demonstrated in confirmatory studies for approximately half of new indications,[11] but drugs granted Accelerated Approval quickly become standard of care despite the tenuous evidence on which they were approved.[12]

The implementation of the Accelerated Approval pathway in recent years has not been characterized. We sought to compare the evidence gathered on qualifying drugs before

and after approval, including the extent to which confirmatory studies were completed and determined whether they demonstrated clinically meaningful benefits.[13] We also reviewed the time between Accelerated Approval and fulfillment of post-approval requirements.

Methods

Sample Identification

Two investigators (H.N., K.R.S.) reviewed publicly available FDA documents ("CDER Drug and Biologic Accelerated Approvals as of 30 June 2016" and "Novel Drug Approvals" for 2011-2013) to identify drugs granted Accelerated Approval over 5 years between 1 January 2009 and 31 December 2013.[1] The CDER Drug and Biologic Accelerated Approvals list is compiled by the FDA's Center for Drug Evaluation and Research. The Novel Drug Approvals report is an annual catalog of approved new molecular entities. Our sample included drugs that received Accelerated Approval as new therapeutic agents and as supplemental approvals (products already approved for other indications). Drugs that received original marketing authorization prior to 2009 were also included if they received a supplemental Accelerated Approval for a new indication during our study period. Accelerated Approvals for new formulations (e.g., tablet vs. injection) of already-approved agents were excluded (n=1). We confirmed the consistency of our sample with a previously published report on FDA approvals.[14] Our study period ended in 2013, allowing at least 3 years for the completion and publication of confirmatory clinical studies, and a median of 5 years.

Identification of Pre-approval Studies

We identified and characterized the clinical studies underlying Accelerated Approval. For all drugs in our sample, we examined medical review reports and product labels from the Drugs@FDA database to identify pre-approval studies that established the drug's efficacy. Drugs@FDA is a publicly available database of all FDA-approved products and contains the approval history for each product, including links to communications from the FDA to the sponsor, and product label updates.[15] When available, we used the medical review reports to

gather information about pre-approval trial characteristics. Medical review reports provide a comprehensive overview of drugs' efficacy and safety. When medical reviews were not available (as can be the case for supplemental approvals), we used the product labels that describe the key clinical studies that supported the Accelerated Approval for a new indication.

Identification of Post-approval Confirmatory Studies

We systematically examined the FDA's approval letters available on the Drugs@FDA database to identify the confirmatory study requirements at the time of Accelerated Approval.[16] We excluded postmarketing study requirements focusing on safety evaluations alone under FDAAA Section 505(o)(3) regulations.[17] We relied on information reported in product labels and FDA's approval letters to summarize how the FDA characterized the main limitation of the available data at the time of Accelerated Approval and whether required postmarketing studies assessed efficacy, safety, or long-term follow-up.

We then reviewed two sources to determine the status of post-approval study requirements. First, we first searched the FDA's publicly available database of postmarketing requirements and commitments.[18] This database specifies the clinical studies that satisfy postmarketing requirements and commitments to gather additional information about a product's safety, efficacy, or optimal use. For the agents with confirmatory studies, we noted whether the study was ongoing, delayed, submitted, or fulfilled. Consistent with previous reports,[19,20] a substantial proportion (n=18, 47%) of indications did not have matching postmarketing requirements listed in the FDA database. Second, we screened ClinicalTrials.gov for all confirmatory study requirements. ClinicalTrials.gov is a publicly available clinical study registry and results database developed and maintained by the U.S. National Library of Medicine.[3] Since 2007, Section 801 of the FDA Amendments Act has

required the registration of clinical studies subject to FDA regulation, including studies that satisfy postmarketing requirements. For each registered study, ClinicalTrials.gov specifies the status (e.g., still recruiting, ongoing but no longer recruiting, completed), as well as start and end date. We noted whether the confirmatory study was completed or ongoing per specified timelines in the FDA's approval letters. Studies were considered to be delayed if the estimated primary completion date in ClinicalTrials.gov was at least one year later than that specified in the FDA approval letters. When there was a discrepancy between the FDA's public database and ClinicalTrials.gov, we relied on ClinicalTrials.gov to determine the status of post-approval study requirements.

Identification of Published Reports

Using a step-wise approach,[21,22] we searched for the published reports of completed confirmatory studies. First, we checked if there was a publication link available on the ClinicalTrials.gov file for each study. ClinicalTrials.gov periodically searches Pubmed to identify corresponding publications; investigators of studies can also add publication links manually. Second, we searched Pubmed using the ClinicalTrials.gov identification number. Third, we searched Pubmed and Google using the name of the principal investigator of the study (when available in ClinicalTrials.gov) in combination with the condition and drug name. Identified publications were matched to the corresponding postmarketing study based on the condition, comparator(s), enrollment, and primary and secondary outcome measures.

Data Extraction

We extracted the following data from each pre-approval and confirmatory study: design (randomized vs. nonrandomized), indication, comparator(s), participant enrollment, and primary endpoint. Comparators were classified as active (in trials comparing drugs A vs.

B), add-on (in trials comparing drugs A + B vs. drug B alone), placebo, or none. Drugs tested in single-arm trials were classified as having no comparators. We also noted the type of blinding (double-blinded vs. open-label). Study findings were summarized in terms of the specified primary endpoint. In confirmatory studies, we assessed whether the findings demonstrated verification of clinical benefit. All data extraction was performed independently by two investigators (H.N., K.R.S.) and disagreements resolved by consensus.

Assessment of Regulatory Outcomes

To determine whether drugs granted Accelerated Approvals later had their labels updated, we examined changes to product labels and the accompanying regulatory letters. The FDA's correspondence with product sponsors on topics related to the approval and changes in status of their products is publicly available on the Drugs@FDA database. We systematically screened the regulatory letters for either confirmation of the fulfillment of the requirements,[23] or the lack of regulatory action as of the end of our data collection (April 7, 2017). We estimated the time between the granting of Accelerated Approval and the associated label update.

Statistical Analysis

Using descriptive statistics, we characterized the clinical studies supporting the Accelerated Approval of drugs included in our sample. Next, Wilcoxon-Mann-Whitney and t-tests were used, as appropriate, to examine differences in study features between pre-approval and confirmatory studies, including enrollment, design, comparator(s), and primary endpoints. Two-tailed p values <0.008 were considered statistically significant, taking into account the 6 comparisons made between the two groups of studies. All analyses were performed using STATA (version 14, Stata Corp, College Station, Texas, USA).

Results

Between 2009 and 2013, the FDA granted Accelerated Approval to 22 drugs for 24 indications, with two products granted the designation for two indications (**Table 1**). Fourteen approvals were for novel therapeutic agents and 10 were for supplemental indications for previously-approved drugs. Cancer accounted for 19 of the indications. The remaining covered a range of conditions including transfusion and non-transfusion dependent iron overload, multi-drug resistant tuberculosis, and Hunter syndrome.

Features of Pre-approval Studies

Thirty pre-approval studies supported the 24 indications of interest. Twelve studies were randomized (40%) and 6 were double-blinded (20%) (**Table 2**). A minority of pre-approval studies used placebo controls (n=6, 20%), 2 (7%) used an active comparator, another 2 evaluated the active agent as an add-on to a standard treatment regimen, and more than half had no comparators (n=18, 60 %). Eight studies (27%) included fewer than 100 participants and 20 (67%) included fewer than 200. The median number of participants enrolled in the pre-approval studies was 132 (interquartile range [IQR]: 89-224).

The most common surrogate measure used in the pre-approval studies was a measure of disease response, such as response rate (n=21), consistent with the fact that most were oncology drugs. Other surrogate measures included time-to-event outcomes (e.g., time-to-sputum culture conversion, progression-free survival), change in baseline biomarker levels (e.g., liver iron concentration), and acceptable safety (**Table 2**).

Nonrandomized, noncomparative single-arm studies formed the exclusive basis of Accelerated Approval for 14 indications (47%), and pre-approval studies with fewer than 200 participants supported the Accelerated Approval of 12 indications (40%).

Status of Required Post-approval Confirmatory Studies

At the time of Accelerated Approval, the FDA labels emphasized the limitations of the available data (**Figure**). The majority of labels highlighted the lack of evidence demonstrating an improvement in disease-related symptoms or survival (n=19, 79%) (**eTable 1**). To address these limitations, the FDA required the completion of 38 post-approval confirmatory trials for the 24 indications. Twenty-five (66%) examined clinical efficacy, 7 (18%) evaluated longer follow-up and 6 (16%) focused on safety (**Figure**).

Most requirements were for randomized controlled trials (n=25, 66%). The remaining 13 requirements (34%) were for single-arm studies (**eTable 2**). Prespecified primary endpoints were reported in approximately one-third (n=13, 34%) of the required confirmatory studies from publicly available documents. Among this sample, the most common prespecified endpoint was progression-free survival (n=9), followed by overall survival (n=3) (**eTable 2**).

Nineteen (50%) confirmatory study requirements had been fulfilled as of April 7, 2017. Of the remaining 19, 11 were underway according to planned timelines, 6 were reported to be delayed by more than 12 months, and 2 had been terminated (**Figure**). In most cases, recruitment challenges were cited as the primary reason for reported delays (**eTable 2**).

Features of Completed and Published Post-approval Confirmatory Studies

Published reports were available for 18 out of 20 completed confirmatory studies. Ten (56%) of the completed and published post-approval confirmatory studies were randomized and 1 (6%) was double-blinded (**Table 3**). One study included a placebo comparator, 2 evaluated the Accelerated Approval agent as an add-on to a standard

treatment regimen, 7 (39%) had active comparators, and 8 (44%) had no comparators (single-arm). The majority of completed confirmatory studies included more than 100 participants, while the median number of participants enrolled in post-approval studies was 345 (IQR: 111-619).

Surrogate measures were the primary endpoints in 17 of the 18 studies. Disease response was the most common surrogate (n=9, 50%), followed by progression-free survival (n=6, 33%) and pharmacokinetic measures (n=2, 11%). The only confirmatory study that did not test a surrogate had co-primary endpoints of overall survival and progression-free survival.

Most completed post-approval studies showed that the drug had some benefit on the surrogate measure (n=15, 83%), including 2 trials that evaluated pharmacokinetics (**Table 3**). The remaining 3 studies (18%) either failed to demonstrate efficacy or were terminated early. In a randomized controlled trial, the addition of bevacizumab to radiotherapy improved progression-free survival, but did not extend overall survival in patients with glioblastoma multiforme.[18] Lapatinib combined with taxane showed shorter progression-free survival compared with trastuzumab as first-line therapy for HER2-positive metastatic breast cancer.[24] One of the required confirmatory studies of ponatinib among previously untreated patients with chronic myeloid leukemia was terminated early due to higher rates of arterial occlusive events observed in patients receiving ponatinib in other trials.[25]

Table 4 shows the comparison of pre-approval and published post-approval trial characteristics. The proportion with randomized designs was not statistically significantly different before and after Accelerated Approval (16%, 95% CI -15% to 46%; P=0.305). The confirmatory studies were more likely to use the surrogate measure of progression-free survival as the primary trial endpoint (36%, 95% CI 15% to 56%; P=0.001).

Regulatory Outcomes for Accelerated Approval Drugs

Of 24 indications treated by the drugs granted Accelerated Approval between 2009 and 2013, 10 (42%) fulfilled their postmarketing requirements and had their labels updated (**Figure**). All of the label updates were based on postmarketing studies evaluating surrogate measures. Label changes were supported by response rate in 6 (25%) indications, progression-free survival in 3 (13%) and changes in subependymal giant cell astrocytoma volume in 1 (4%) case. The completed confirmatory studies had no comparators in 4 cases, including 2 confirmatory trials that were single-arm open-label extensions of pre-approval randomized trials.

Among the remaining 14 indications with no label updates, confirmatory studies failed to demonstrate clinical benefit in 2 (8%) indications and studies were terminated in 2 (8%) indications. Studies for the remaining 10 indications remained ongoing, with 7 progressing according to target timelines and 3 reported to be delayed by more than one year.

Figure shows the duration of time elapsed between Accelerated Approval and follow-up actions by our study end date. Time from Accelerated Approval to fulfillment of requirements ranged from 1.3 years to 5.3 years among the 10 indications for which the requirements were fulfilled. Time elapsed since Accelerated Approval was 5 years or more for 7 indications.

Discussion

The clinical trial evidence on therapeutic agents granted Accelerated Approval by the FDA between 2009 and 2013 shows that 14 of 24 indications entered the market on the basis of single-arm studies enrolling small numbers of patients. After approval, half of required confirmatory studies were completed within at least 3 years on the market. The quality and quantity of postmarketing studies required by the FDA to confirm clinical benefit varied widely across indications. There were few statistically detectable differences in the key design features of trials conducted before and after approval. Nonrandomized studies were common in the Accelerated Approval pathway both before and after market entry. While the majority of completed studies showed positive results in the postmarketing period, all completed confirmatory studies demonstrating drug benefit evaluated surrogate measures of disease activity rather than clinical outcomes.

Drugs granted Accelerated Approval receive market authorization on the basis of fewer studies, smaller patient populations, shorter follow-up and less established surrogate measures than drugs approved via the traditional pathway.[26] In these cases, post-approval confirmation of clinical benefit is essential. For the 10 Accelerated Approvals between 2009 and 2013 that have since had their requirements fulfilled and labels updated, all of which were for cancer indications, the studies used to confirm clinical benefit tested surrogate measures. FDA senior scientists consider overall survival to be the most dependable endpoint in clinical trials of cancer drugs.[27] Yet, overall survival was among the prespecified primary endpoints in only a small fraction of required confirmatory studies. Disease response was the most common endpoint in post-approval trials, and although disease response may be an appropriate surrogate measure in hematological malignancies, its adequacy depends on several factors such as the magnitude and duration of effect.[28] In the remaining cases, postmarketing requirements were fulfilled based on improvements in progression-free

survival, which may not be a statistically validated surrogate for survival in all settings.[28] Our findings are aligned with previous research showing that cancer drugs approved on the basis of surrogate measures may not show survival benefit in the postmarketing period.[29]

Another finding from our data is the slow progression of some post-approval studies. A recent Government Accountability Office report criticized the FDA's oversight of drugs approved on the basis of surrogate measures.[19] Although the fulfillment of postmarketing commitments and requirements improved overall from 2009 to 2011, the number of studies with delays doubled during the same period.[20] For 14 of 24 indications granted Accelerated Approval from 2009 to 2013, results from required confirmatory studies were not available after several years of follow-up, and 8 of 19 incomplete confirmatory studies were either terminated or delayed by more than one year.

Confirmatory studies failed to demonstrate clinical benefit in 2 indications granted Accelerated Approval between 2009 and 2013. According to the Code of Federal Regulations, the FDA may withdraw a therapeutic agent if confirmatory studies fail to verify its clinical benefit. However, according to publicly available documents, the FDA has neither rescinded its approval nor imposed additional requirements for these 2 indications. Historically, the FDA has withdrawn an indication only once during the 25 years since the Accelerated Approval pathway was established. For bevacizumab (Avastin), which received Accelerated Approval in 2008 on the basis of progression-free survival for patients with metastatic breast cancer, the FDA later rescinded its approval for this indication after multiple postmarketing trials revealed no improvement in survival and increased toxicity.[30]

This study has several limitations. First, it was limited to the pre-approval and confirmatory studies presented to the FDA. There may be other studies that evaluated the clinical benefit of therapeutic agents granted Accelerated Approvals, but if those studies were rigorous and reflected strongly on the utility of the product, it is likely that the manufacturer

would have presented them to the FDA and used them to contribute to any label updates.[31] When safety-related postmarketing requirements under FDAAA Section 505(o)(3) generated efficacy data, we captured this information if it was used to inform label changes. Our findings are supported by another large investigation of drugs approved on the basis of a surrogate measures or single trials, which showed that post-approval studies rarely evaluate efficacy using clinical outcomes.[32] Second, we did not examine the adequacy of the confirmatory studies in addressing questions about the drugs that the FDA considered to be unresolved, because such insights are not available from the FDA documents.

Third, we examined a recent cohort of approvals, and the minimum 3 years of follow-up may not be adequate for completing some post-approval studies. However, our findings were consistent with a previous review of Accelerated Approvals in oncology, which showed a similar proportion of incomplete confirmatory studies.[10] Restricting our sample to Accelerated Approvals between 2009 and 2012 did not change our findings (data not shown). Fourth, our assessment focused on the trials' sample size, comparators, endpoints, and findings. Data on other important characteristics, including risk of bias and trial duration, were not consistently reported in FDA documents and published reports. Fifth, the comparisons between pre-approval and post-approval study characteristics may be underpowered to detect statistically significant differences.

Conclusions

Many drugs recently granted Accelerated Approval between 2009 and 2013 have had their efficacy confirmed in post-approval trials, although confirmatory trials have similar design elements to pre-approval trials, including reliance on surrogate measures. Delays in completing post-approval confirmatory trials were observed for a minority of drugs.

Author Contributions:

Dr Naci had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Naci, Kesselheim.

Acquisition of data: Naci, Smalley.

Analysis and interpretation of data: Naci.

Drafting of the manuscript: Naci.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Naci.

Obtained funding: No funding was received.

Administrative, technical, or material support: Smalley.

Study supervision: Kesselheim.

Conflict of Interest Disclosures:

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Kesselheim reported receiving unrelated grants from the FDA Office of Generic Drugs and Division of Health Communication. Other authors have no potential or actual conflicts of interest to report.

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Additional contributions:

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Figure legends

Figure 1. Key data limitations at the time of Accelerated Approval, objectives of postmarketing requirements, and timelines for completion.

Tables

Table 1. Drugs and Accelerated Approval Indications, 2009-2013.

Agent	**Year approved**	**Indication at the time of Accelerated Approval**
Bevacizumab	2009	Treatment of glioblastoma, as a single agent for patients with progressive disease following prior therapy
Ofatumumab	2009	Treatment of patients with CLL refractory to fludarabine and alemtuzumab
Pralatrexate	2009	Treatment of patients with relapsed or refractory PTCL
Dasatinib	2010	Treatment of newly diagnosed adults with Ph+ CML in chronic phase
Everolimus	2010	Treatment of SEGA associated with TS who require therapeutic intervention but are not candidates for curative surgical resection
Lapatinib	2010	In combination with letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated
Nilotinib	2010	Treatment of newly diagnosed adult patients with Ph+ CML in chronic phase
Brentuximab vedotin	2011	The treatment of patients with Hodgkin lymphoma after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates
Brentuximab vedotin	2011	The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen
Crizotinib	2011	Treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test
Deferiprone	2011	Treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Hydroxyprogesterone caproate	2011	To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
Romidepsin	2011	Treatment of PTCL in patients who have received at least one prior therapy
Bedaquiline	2012	Indicated as part of combination therapy in adults (≥ 18 years) with pulmonary

		MDR-TB
Carfilzomib	2012	Treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy
Everolimus	2012	Treatment of adults with renal angiomyolipoma and TSC, not requiring immediate surgery
Omacetaxine mepesuccinate	2012	Treatment of adult patients with chronic or accelerated phase CML with resistance and/or intolerance to two or more TKIs
Ponatinib	2012	Treatment of adult patients with chronic phase, accelerated phase, or blast phase CML that is resistant or intolerant to prior TKI therapy or Ph+ALL that is resistant or intolerant to prior TKI therapy
Vincristine sulfate liposome	2012	Treatment of adult patients with Ph- ALL in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies
Pomalidomide	2013	Patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy
Ibrutinib	2013	Treatment of patients with MCL who have received at least one prior therapy
Deferasirox	2013	Treatment of chronic iron overload in patients 10 years of age and older with non-transfusion dependent thalassemia syndromes and with a LIC of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L
Idursulfase	2013	Patients between 16 months to 5 years of age with Hunter syndrome (Mucopolysaccharidosis II)
Pertuzumab	2013	Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer

ALK: anaplastic lymphoma kinase; **ALL**: acute lymphoblastic leukemia; **ASCT**: autologous stem cell transplant; **CLL**: chronic lymphocytic leukemia; **CML**: chronic myeloid leukemia; **LIC**: liver iron concentration; **MCL**: mantle cell lymphoma; **MDR-TB**: multi-drug resistant tuberculosis; **NSCLC**: non-small cell lung cancer; **Ph+**: Philadelphia chromosome-positive; **Ph-**: Philadelphia chromosome-negative; **PTCL**: peripheral T-cell lymphoma; **SEGA**: subependymal giant cell astrocytoma; **TKI**: tyrosine kinase inhibitors; **TS**: tuberous sclerosis; **TSC**: tuberous sclerosis complex.

Table 2. Characteristics of pre-approval studies of drugs receiving Accelerated Approval.

Agent	Participant population	Design	Comparators	Enrollment	Primary endpoint
Bevacizumab	Glioblastoma after prior therapy	Randomized non-comparative study	None	85	Objective response rate
	Glioblastoma after prior therapy	Single-arm trial	None	56	Objective response rate
Pralatrexate	PTCL after prior therapy	Single-arm trial	None	115	Overall response rate
Ofatumumab	CLL after prior therapy	Single-arm trial	None	154	Objective response rate
Lapatinib	Postmenopausal women with HER2-positive metastatic breast cancer with no prior therapy for whom hormonal therapy is indicated	Placebo-controlled, double-blind randomized trial	*Arm 1*: lapatinib + letrozole *Arm 2*: letrozole + placebo	219	PFS
Nilotinib	Newly diagnosed Ph+ CP CML	Active-comparator, open-label randomized trial	*Arm 1*: nilotinib *Arm 2*: imatinib	846	Major molecular response
Dasatinib	Newly diagnosed CP CML	Active-comparator, open-label randomized trial	*Arm 1*: dasatinib *Arm 2*: imatinib	519	Complete cytogenetic response
Everolimus[a]	SEGA associated with TS	Single-arm trial	None	28	Change in SEGA volume

Hydroxy-progesterone caproate	Women with previous singleton spontaneous preterm birth	Placebo-controlled, double-blind randomized trial	*Arm 1*: hydroxyprogesterone *Arm 2*: placebo	463	Proportion of deliveries at <37 weeks of gestation
Romidepsin	PTCL after one or more prior therapy	Single-arm trial	None	131	Complete response rate
	PTCL after one or more prior therapy	Single-arm trial	None	47	Complete response rate
Brentuximab vedotin[b]	Hodgkin lymphoma after ASCT of after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates	Single-arm trial	None	102	Objective response rate
Brentuximab vedotin[c]	Systemic anaplastic large cell lymphoma after prior therapy	Single-arm trial	None	58	Objective response rate
Crizotinib	Locally advanced or metastatic ALK+ NSCLC after prior therapy	Single-arm trial	None	136	Objective response rate
	Locally advanced or metastatic ALK+ NSCLC	Single-arm trial	None	119	Objective response rate

	after prior therapy				
Deferiprone	Transfusion-dependent iron overload after prior therapy	Single-arm trial (pooled analysis of 12 studies)	None	236	≥20% decline in ferritin
Everolimus[d]	Renal angiomyolipoma as a feature of TSC or sporadic lymphangio-leimyomatosis	Placebo-controlled, double-blind randomized trial	*Arm 1*: everolimus *Arm 2*: placebo	118	Angiomyolipoma response rate
Carfilzomib	Multiple myeloma after two or more prior therapies	Single-arm trial	None	266	Overall response rate
Vincristine sulfate liposome	Ph- ALL after two or more prior therapies	Single-arm trial	None	65	Complete remission and complete remission with incomplete blood count recovery
Omacetaxine mepessucinate	CP and AP CML after two or more TKIs	Single-arm trial (pooled analysis of 2 studies)	None	111	Major cytogenetic and hematologic response
Ponatinib	CP, AP and BP CML and Ph+ ALL after prior TKI	Single-arm trial	None	449	Major cytogenetic and hematologic response
Bedaquiline	Newly diagnosed patients with MDR-TB	Placebo-controlled, double-blind	*Arm 1*: bedaquiline + other drugs used to treat MDR-TB	160	Proportion with sputum culture conversion

		randomized trial	*Arm 2*: placebo + other drugs used to treat MDR-TB *Other drugs: thionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone or available alternative*		
	Newly diagnosed patients with MDR-TB	Placebo-controlled, double-blind randomized trial	*Arm 1*: bedaquiline + other drugs used to treat MDR-TB *Arm 2*: placebo + other drugs used to treat MDR-TB	47	Proportion with sputum culture conversion
Deferasirox	Non-transfusion-dependent thalassemia syndromes and iron overload	Placebo-controlled, double-blind randomized trial	*Arm 1*: deferasirox 5 mg/kg/day *Arm 2*: deferasirox 10 mg/kg/day *Arm 3*: placebo	166	Mean change in liver iron concentration from baseline (mg Fe/g dry weight)
	Non-transfusion-dependent thalassemia syndromes and iron overload	Single-arm extension of randomized trial	None	133	Proportion achieving liver iron concentration <5 mg Fe/g dry weight
Pomalidomide	Refractory multiple myeloma after receiving lenalidomide and bortezomib	Randomized non-comparative study	*Arm 1*: pomalidomide *Arm 2*: pomalidomide + low-dose dexamethasone	221	Overall response rate
Idursulfase	Patients with Hunter	Single-arm trial	None	28	Adverse reactions (safety

	syndrome between ages of 16 months and 7.5 years				trial)
Pertuzumab	Patients with operable, locally advanced, or inflammatory HER2-positive breast cancer	Add-on comparator, open-label randomized controlled trial	*Arm 1*: pertuzumab + trastuzumab + docetaxel *Arm 2*: trastuzumab + docetaxel	417	Pathological complete response rate
	Patients with operable, locally advanced, or inflammatory HER2-positive breast cancer	Add-on comparator, open-label randomized controlled trial	*Arm 1*: Pertuzumab + trastuzumab + FEC followed by pertuzumab + trastuzumab + docetaxel *Arm 2*: pertuzumab + trastuzumab + docetaxel following FEC *Arm 3*: pertuzumab + TCH	225	Cardiac safety (Pathological complete response rate is secondary endpoint)
Ibrutinib	Mantle-cell lymphoma after one or more therapy	Single-arm trial	None	111	Overall response rate

[a] TS indication
[b] Hodgkin lymphoma indication
[c] Systemic anaplastic large cell lymphoma indication
[d] Renal angiomyolipoma and TSC indication
ALK+: anaplastic lymphoma kinase positive; **ALL**: acute lymphoblastic leukemia; **ASCT**: autologous stem cell transplant; **AP**: accelerated phase; **BP**: blast phase; **CI**: confidence interval; **CLL**: chronic lymphocytic leukemia; **CML**: chronic myeloid leukemia; **CP**: chronic phase; **FEC**: fluorouracil, epirubicin, and cyclophosphamide; **HER2**: human epidermal growth factor; **HR**: hazard ratio; **MDR**: multi-drug resistant; **NSCLC**: non-small cell lung cancer; **PFS**: progression-free survival; **Ph+**: Philadelphia chromosome positive; **Ph-**: Philadelphia chromosome negative; **PTCL**: peripheral T-cell lymphoma; **SEGA**: subependymal giant cell astrocytoma; **TB**: tuberculosis; **TCH**: docetaxel, carboplatin, and trastuzumab; **TS**: tuberous sclerosis; **TKI**: tyrosine kinase inhibitor; **TSC**: tuberous sclerosis complex.

Table 3. Characteristics and findings of completed and published post-approval, confirmatory studies of drugs receiving Accelerated Approval.

Agent	**Participant population**	**Design**	**Comparators**	**Enrollment**	**Primary endpoint**	**Magnitude of benefit[c]**
Bevacizumab	Newly diagnosed glioblastoma [e1]	Double-blind, placebo-controlled randomized trial	*Arm 1*: bevacizumab + radiotherapy-temozolomide *Arm 2*: placebo + radiotherapy-temozolomide	921	PFS and overall survival (co-primary endpoints)	Median PFS *Arm 1*: 10.6 months *Arm 2*: 6.2 months *HR: 0.64, 95% CI: 0.55-0.74, p<0.001* Median overall survival *Arm 1*: 16.8 months *Arm 2*: 16.7 months *HR: 0.88, 95% CI: 0.76-1.02, p=0.10*
Ofatumumab	Untreated patients with CLL [e2]	Add-on comparator, open-label randomized trial	*Arm 1*: ofatumumab + chlorambucil *Arm 2*: chrorambucil	447	PFS	*Arm 1*: 22.4 months *Arm 2*: 13.1 months *HR: 0.57, 95% CI: 0.45-0.72, p<0.0001*
Lapatinib	HER2-positive metastatic breast cancer [e3]	Active-comparator, open-label randomized trial	*Arm 1*: lapatinib + taxane *Arm 2*: trastuzumab + taxane	652	PFS	*Arm 1*: 9.0 months *Arm 2*: 11.3 months *HR: 1.33, 95% CI: 1.06-1.67, p=0.01* *More deaths occurred with lapatinib compared to trastuzumab: 102 vs. 82*

						HR: 1.28, 95% CI: 0.95-1.72, p=0.11
Nilotinib	Newly diagnosed CP CML [e4]	Active-comparator, open-label randomized trial *Long-term extension of pre-approval study*	*Arm 1*: nilotinib 300 mg twice daily *Arm 2*: nilotinib 400 mg twice daily *Arm 2*: imatinib 400 mg once daily	846	Major molecular response	*Arm 1*: 217 (77.0%) *Arm 2*: 217 (77.2%) *Arm 3*: 171 (60.4%)
Dasatinib	Newly diagnosed CP CML [e5]	Active-comparator, open-label randomized trial *Long-term extension of pre-approval study*	*Arm 1*: dasatinib *Arm 2*: imatinib	519	Complete cytogenetic response	*Arm 1*: 28.0% *Arm 2*: 26.0% (frequency data not reported)
Everolimus[a]	TSC-related SEGA [e6]	Single-arm extension of trial *Long-term extension of pre-approval study*	None	111	Response	64 (57.7%)

	TSC-related SEGA [e7]	Single-arm trial	None	27	Change in SEGA volume	0.50 (range = −0.74 to 9.84) cm^3
Crizotinib	Locally advanced or metastatic ALK-positive lung cancer following one prior platinum-based regimen [e8]	Active-comparator, open-label randomized trial	*Arm 1*: crizotinib *Arm 2*: chemotherapy (pemetrexed or docetaxel)	347	PFS	*Arm 1*: 7.7 months *Arm 2*: 3.0 months *HR: 0.49, 95% CI: 0.37-0.64, p<0.001*
	Advanced ALK-positive nonsquamous NSCLC without previous systemic treatment for advanced disease [e9]	Active-comparator, open-label randomized trial	*Arm 1*: crizotinib *Arm 2*: chemotherapy (pemetrexed + cisplatin or carboplatin)	343	PFS	*Arm 1*: 10.9 months *Arm 2*: 7.0 months *HR: 0.45, 95% CI: 0.35-0.60, p<0.001*
Everolimus[b]	Renal angiomyolipoma and diagnosis of TSC or LAM [e10]	Single-arm extension of trial *Long-term extension of pre-approval study*	None	112	Response	60 (54.0%)

Carfilzomib	Relapsed multiple myeloma following one to three prior treatments [e11]	Add-on comparator, open-label randomized trial	*Arm 1*: carfilzomib + lenalidomide + dexamethasone *Arm 2*: lenalidomide + dexamethasone	792	PFS	*Arm 1*: 26.3 months *Arm 2*: 17.6 months *HR: 0.69, 95% CI: 0.57-0.83, p=0.0001*
	Relapsed or refractory multiple myeloma following one to three prior treatments [e12]	Active-comparator, open-label randomized trial	*Arm 1*: carfilzomib + dexamethasone *Arm 2*: bortezomib + dexamethasone	929	PFS	*Arm 1*: 18.7 months *Arm 2*: 9.4 months *HR: 0.53, 95% CI: 0.44-0.64, p<0.0001*
Omacetaxine	CML who had received 2 or more approved TKI therapy [e13]	*Post-hoc* pooled analysis of 2 single-arm trials *Long-term extension of pre-approval study*	None	111	Major cytogenetic response and major hematologic response	CP CML: 14 (18.0%) AP CML: 5 (14.0%)
Ponatinib	Newly diagnosed patients with CP CML previously untreated patients [e14]	Active-comparator, open-label randomized trial	*Arm 1*: ponatinib *Arm 2*: imatinib	307 (22 remained on study at 12 months had had a molecular	Major molecular response	*Arm 1*: 8 (80.0%) *Arm 2*: 5 (38.0%) *Trial was terminated early following concerns about vascular adverse events observed in patients given ponatinib in other trials*

				assessment)		
	Healthy adults [e15]	Single-arm cross-over study	None	20	Pharmacokinetics	*Statistically significant interaction with rifampin*
	Healthy adults [e16]	Single-arm cross-over study	None	20	Pharmacokinetics	*Modest reduction in ponatinib concentration*
	CML and Ph+ ALL after prior therapy [e17]	Single-arm trial *Long-term extension of pre-approval study*	None	449	Major cytogenetic response and major hematologic response	CP CML: 158 (59.0%) AP CML: 51 (61.0%) BP CML: 19 (31.0%) Ph+ ALL: 13 (41.0%)
Ibrutinib	Relapsed or refractory mantle cell lymphoma [e18]	Single-arm trial *Long-term extension of pre-approval study*	None	111	Overall response rate	67.0% (frequency data not reported)

[a] TS indication
[b] Renal angiomyolipoma and TSC indication
[c] As reported in primary analysis in publication
ALK+: anaplastic lymphoma kinase positive; **ALL**: acute lymphoblastic leukemia; **AP**: accelerated phase; **BP**: blast phase; **CI**: confidence interval; **CLL**: chronic lymphocytic leukemia; **CML**: chronic myeloid leukemia; **CP**: chronic phase; **FEC**: fluorouracil, epirubicin, and cyclophosphamide; **HER2**: human epidermal growth factor; **HR**: hazard ratio; **LAM**: Lymphangioleimyomatosis; **MDR**: multi-drug resistant; **NSCLC**: non-small cell lung cancer; **PFS**: progression-free survival; **Ph+**: Philadelphia chromosome positive; **Ph-**: Philadelphia chromosome negative; **PTCL**: peripheral T-cell lymphoma; **SEGA**: subependymal giant cell astrocytoma; **TB**: tuberculosis; **TCH**: docetaxel, carboplatin, and trastuzumab; **TS**: tuberous sclerosis; **TKI**: tyrosine kinase inhibitor; **TSC**: tuberous sclerosis complex.

Table 4. Comparison of pre-approval and post-approval study characteristics.

Characteristics	Pre-approval studies (n=30)	Post-approval studies (n=18)	Difference in proportions (95% CI)	P value for difference
Enrollment, median (IQR)	132 (89-224)	345 (111-619)	-	0.37
Randomized, no. (%)	12 (40)	10 (56)	16 (-15 to 46)	0.31
Includes comparator, no. (%)	11 (37)	10 (56)	19 (-11 to 49)	0.21
Primary endpoint[a]				
Disease response, no. (%)	21 (70)	9 (50)	-20 (-49 to 9)	0.17
Progression-free survival, no. (%)	1 (3)	7 (39)	36 (15 to 56)	0.001
Overall survival, no. (%)	0 (0)	1* (6)	6 (0 to 142)	0.20
Other, no. (%)	8 (27)	2 (11)	-16 (-40 to 89)	0.21

a Primary endpoints do not add up to total number of post-approval studies: one study included two primary endpoints.
* Co-primary endpoint with progression-free survival.