

New benchmarks are needed: The experience with completing confirmatory trials for cancer drug indications that received accelerated approval by the Food and Drug Administration (1992- 2007)

Abstract

Background: Accelerated approval (AA) for oncology drugs was established in 1992 by the Food and Drug Administration (FDA) as a means of expeditiously providing new drugs to patients with life-threatening illnesses. After AA is granted, sponsors are required to complete larger trials, generally phase III studies, confirming clinical efficacy - termed Subpart H commitments. In 2003 and 2005, the Oncologic Drugs Advisory Committee (ODAC) provided guidance to drug sponsors for 13 cancer indications who were behind schedule in completing confirmatory clinical trials. We review the experience with fulfilling Subpart H commitments, focusing on activities since the 2005 ODAC meeting.

Methods: Information on approval status and the clinical trials which form the basis of AA was obtained from the FDA website, product inserts, medical literature reviews, and transcripts from the ODAC meetings in 2003 and 2005. Indications were categorized as those affecting small numbers of cancer patients (<25,000 estimated new cases in 2007) versus larger numbers of cancer patients (>25,000 estimated new cases in 2007).

Results: Since the adoption of AA in 1992, 13 drugs for 18 indications affecting smaller numbers of cancer patients and 12 drugs for 12 indications affecting larger numbers of cancer patients have received AA, primarily based on results from phase II trials (83% versus 50%, respectively). Since January 2005, AA has been granted for only two new cancer indications. Overall, 15 cancer indications have pending subpart H commitments. The hazard ratio for completing required confirmatory trials was 4.3 for high-incidence versus low-incidence cancer indications (95% Confidence Interval 1.4, 13.5) and the median time for conversion from AA to regular approval for relevant indications was 4.3 versus 2.7 years, respectively. Of the 9 cancer drug indications discussed at the 2003 and 2005 ODAC meetings, 8 indications affect small numbers of patients (<25,000 annually). Subpart H commitments are still pending for five of eight sponsors who attended the 2003 ODAC meeting and five of six sponsors who attended the 2005 ODAC meeting.

Conclusions: Confirmatory clinical trials are difficult to complete for sponsors of AA drugs, particularly those drugs used to treat cancers that affect small numbers of patients. The FDA should allow sponsors of drugs for these cancer indications the option of conducting additional phase II trials and establishing comprehensive safety registries as an alternative means of fulfilling Subpart H commitments.

Introduction

Accelerated approval (AA) regulations were established in 1992 in an effort to allow patients with life-threatening diseases rapid access to therapeutics. Unlike Fast Track and Priority Review Subpart E designations that affect time to review by the Federal Drug Administration (FDA), AA allows pharmaceutical marketing based on surrogate outcomes that show meaningful therapeutic benefit, often established by single-arm phase II trials (**Table 1**).¹ Subpart H regulations require that sponsors conduct confirmatory phase III studies to verify clinical benefit. Between 1995 and 2005, about one third of all cancer drug indications received approval via the AA mechanism.² Since 2005, only two cancer drug indications received AA and five new applications for AA have been rejected.³

At a meeting in 2003, the Oncologic Drug Advisory Committee (ODAC) of the FDA identified several obstacles to timely completion of confirmatory phase III studies for sponsors of drugs used to treat eight cancer indications.⁴ Dagher et al. of the FDA subsequently summarized the discussion at this meeting, advising sponsors who experience difficulties with enrollment to subpart H trials to consider adding new accrual sites in the United States or in countries where access to new cancer drugs is limited.⁵ In 2005, ODAC again met with six sponsors who were experiencing difficulties fulfilling Subpart H commitments, five of whom had also presented at the 2003 meeting (**Table 2**).⁶ The consensus from the 2005 meeting was that Subpart H commitments remain difficult to complete despite committed efforts from drug sponsors. In an attempt to remedy this obstacle, the FDA proposed that accrual to confirmatory trials be initiated at the time of AA and that interim analyses of Phase III studies should preferentially serve as the basis for AA in the future.^{6,7} After the meeting, Representative Ed Markey of Massachusetts issued a report entitled “Conspiracy of silence: How the FDA Allows Drug Companies to Abuse the Accelerated Approval Process.”⁸ He proposed that sponsors who fail to complete confirmatory trials should be fined and AA status for drugs should be withdrawn if Subpart H commitments remain incomplete. In 2007, legislation passed by Congress now allows the FDA to impose fines on drug sponsors and limit drug distribution if post-marketing commitments are not completed (FDA Revitalization Act S.1082).⁹

Herein, we review the experience to date with the AA process since its inception, focusing on the status of Subpart H commitments for sponsors of cancer drug indications since the last ODAC meeting in 2005. We also present an alternative to the current post-marketing requirements for cancer indications affecting small numbers of patients.

Methods

Clinical trial reports available under the Freedom of Information Act for new drug applications and supplements approved by the FDA, transcripts of ODAC meetings from 2003 and 2005, and efficacy and safety information included on the FDA website and package inserts were reviewed for information on cancer drugs that received AA between 1992 and 2007.^{4,6,10,11} If a particular drug received AA for multiple cancer indications, then all clinical indications were included in the analysis. Details of trials that supported AA approval or conversion from AA to regular approval since 2005 are reported herein. (For details of drug indications that received AA or converted from AA to regular approval prior to 2005, the reader is referred to the article by

Dagher et al.⁵) Cancer indications were grouped into two categories, termed smaller or low-incidence indications and larger or high-incidence indications, based on the estimated number of new cases in 2007. A cut-point of 25,000 new diagnoses in 2007 for the relevant indication was used, based on statistics reported by the American Cancer Society.¹² Statistical analyses involved comparisons of median values for various characteristics of trials that formed the basis of AA and confirmatory trials for indications that affected smaller versus larger numbers of cancer patients in 2007. We also derived a Cox-proportional hazards model that evaluated time to fulfillment of Subpart H requirements for high and low-incidence indications. Statistical analyses were completed using Stata version 10.0 (College Station, Texas). For trials that form the basis for AA, the absolute number of responders in the relevant studies was identified (Figure 3). For confirmatory trials, the absolute number of responders is also determined for studies in which response rate is reported; if response rate is not reported, then the absolute number of overall survivors, disease-free survivors, or progression-free survivors is reported where feasible.

Results

Since the adoption of AA in 1992, 25 drugs have received AA for a total of 30 indications (27 cancer treatment indications, 2 supportive care indications, and 1 cancer prevention indication). The number of new cancer-related indications receiving AA was highest in 1999, 2002, and 2004 (5 drugs received AA each year). In 1999, all 5 new AAs were for indications affecting smaller numbers of patients, while a total of 5 low-incidence indications received AA in 2002 and 2004 combined. In 2005, 2006, and 2007, 1, 1, and 0 drugs, respectively, received AA for a cancer-related indication. (**Figure 1**)

Clinical trials that serve in part as the basis for AA were predominantly phase I or phase II in design (83% of indications); results from phase III trials served as part of the basis for 30% of AA indications, and AA was based solely upon interim analyses of Phase III studies in 13% of AA indications. (**Table 3, Figure 1**) Categorizing by tumor type, phase III studies served in part as the basis for AA in 50% of high-incidence indications and 17% of low-incidence indications. The median number of patients included in clinical trials that formed the basis for AA was 124 for indications affecting smaller patient populations and 384 for indications affecting larger patient populations. Response rate was the relevant surrogate endpoint for 94% of AA indications affecting smaller patient populations and 75% for AA indications affecting larger patient populations; the median number of patients who experienced a response in clinical trials that formed the basis for AA was similar (median of 35 versus 32 patients).

To date, 50% of the cancer indications receiving AA no longer have pending Subpart H commitments. Thirteen AA's have converted to regular approval, the approval of gefitinib was restricted after the confirmatory study failed to show a survival benefit, and the sponsor for amifostine withdrew the AA for prevention of renal toxicity among cisplatin treated lung cancer patients. The odds of converting AA to regular approval were 4.3-fold greater for drug indications that affected larger versus smaller numbers of cancer patients (95% Confidence Interval 1.4, 13.5). Of AA cancer drug indications subsequently receiving regular approval, the median time to granting regular approval was 2.7 years for high-incidence drug indications versus 4.3 years for low-incidence drug indications. (**Figure 2**) Overall, the median number of patients who experienced an improvement in response or survival evaluated in completed

confirmatory clinical trials was similar for AA indications that affected smaller versus larger patient populations (median of 121 versus 103), roughly 3.5-fold higher than the median numbers of responders in trials that form the basis for AA. (**Figure 3**)

New Accelerated Approval Indications (January 2005-present)

In October 2005, nelarabine received AA by the FDA for refractory T cell acute lymphoblastic leukemia/lymphoblastic lymphoma on the basis of 2 single-arm Phase II studies.^{10, 13} Among 39 pediatric patients treated in the first study, response to therapy was seen in 23% of patients (complete response (CR) + complete response with incomplete bone marrow recovery (CR*)). Of the 28 treated adult patients treated in the second study, a 21% response rate was seen (CR + CR*). The confirmatory clinical trial is a planned randomized Phase III study of 1380 newly diagnosed patients with T cell ALL. This study will assess event-free survival at 4 years (COG-AALL0434).¹¹ This confirmatory trial was initiated in January 2007, nearly 2 years after AA was granted, and is open for patient recruitment.

In January 2006, sunitinib received AA for the treatment of advanced renal cell carcinoma based on results from 2 multicenter, single-arm Phase II studies with 106 and 63 patients respectively; responses were seen in 25.5% and 36.5% of treated patients respectively, with response durations of 27.1 and 54 weeks.¹⁴ In February 2007, AA was converted to regular approval based on findings from a Phase III study of 750 patients comparing sunitinib versus interferon alpha.¹⁵ In this study, sunitinib was associated with an improved progression free survival (11 months vs. 5 months, HR 0.42, p<0.001) and response rate (31% vs. 6%, p<0.001) compared with interferon alpha. Of note, this confirmatory Phase III study completed accrual in October 2005, three months prior to AA being granted.

Subpart H confirmatory trials completed for cancer indications that previously received accelerated approval (January 2005- present)

Temozolamide received AA in August 1999 based on a Phase II, single-arm study of 162 patients with relapsed anaplastic astrocytoma in which a 22% response rate (and 9% complete response rate) was identified in the subset of 54 patients with disease progression after both nitrosurea and procarbazine.^{16, 17} In a subsequent randomized, open-label, multicenter Phase III study of 573 patients with newly diagnosed glioblastoma multiformae, median survival was longer with temozolamide combined with radiation when compared with radiation therapy alone (14.6 versus 12.1 months, p<0.05).¹⁸

For the treatment of women with advanced relapsed or refractory ovarian carcinoma, liposomal doxorubicin received AA in June 1999 based on results from three Phase II studies with 176 patients demonstrating a combined response rate of 13.8%.^{6, 10} In February 2005, conversion to regular approval was based on a Phase III study of 474 ovarian cancer patients randomized to liposomal doxorubicin versus topotecan after progression on a platinum-based regimen. In the subgroup of platinum-refractory patients, improvement in overall survival was seen in the liposomal doxorubicin group (108 vs. 71.1 weeks, p=0.008).¹⁹

Anastrozole received AA in September 2002 for the adjuvant therapy of early stage breast cancer in postmenopausal women. AA was granted on the basis of an interim analysis of a randomized, double-blind, Phase III study of 9366 women that showed an improved recurrence-free survival of anastrozole-treated patients compared with tamoxifen-treated patients at a 33 month follow up (89.4% vs. 87.4%, $p=0.013$).²⁰ Longer-term follow up formed the basis of regular approval, granted in September 2005. At 68 month follow-up, anastrozole significantly prolonged disease-free survival compared with tamoxifen (575 vs 651 events, HR 0.87, $p=0.01$), reduced distant metastases (324 vs. 375 events, HR 0.86, $p=0.04$) and reduced contralateral breast cancers (35 vs. 59 events, $p=0.01$).^{21, 22}

In 2001, the monoclonal antibody alemtuzumab was approved as a treatment of B-cell chronic lymphocytic leukemia (B-CLL) which had failed treatment with alkylating agents and fludarabine based on results from a Phase II study of 93 patients in which an overall response rate of 33% was seen.^{6, 23} In September 2007, alemtuzumab received regular approval as single-agent therapy for B-CLL. In the confirmatory study, 297 previously untreated B-CLL patients were randomized to alemtuzumab vs. chlorambucil; patients in the alemtuzumab arm had an improvement in progression-free survival (14.6 vs. 11.7 months, HR 0.58, $p=0.0001$) as well as an improved overall response rate (83% vs. 55%, $p<0.0001$) compared with chlorambucil.¹¹

Accelerated approval was withdrawn (January 2005- present)

Amifostine initially received AA in March 1996 for the reduction of cisplatin-related renal toxicity among non-small cell lung cancer patients on the basis of a Phase II trial of 25 patients which demonstrated a 64% objective response rate and 12% reversible grade 3 nephrotoxicity rate.²⁴ Amifostine had previously received regular approval for reduction of renal toxicity in cisplatin-treated ovarian cancer patients in December 1995 and in June 1999 it received regular approval for reduction of xerostomia in head and neck cancer patients undergoing radiation. Due to difficulty in completing post-marketing commitments, the drug sponsor forfeited the AA of amifostine as a chemoprotectant for cisplatin-treated non-small cell lung cancer patients in March 2006.⁴

Discussion

In the late 1990s and early part of this decade, the AA program facilitated early access to clinically beneficial cancer therapeutics largely on the basis of improved response rates seen in Phase II studies. Unfortunately, the AA process has become stagnant in recent years. Since 2005, only two novel cancer agents have received AA, five novel cancer agents have had their application for AA rejected by the FDA, and subpart H commitments that verify the clinical benefits of these drugs remain unfulfilled for half of the 30 AA cancer-related indications.^{3, 10} These concerns are especially prominent for AA indications that affect smaller numbers of cancer patients. The hazard ratio of converting to regular approval is more than 4-fold lower and the median time to conversion is 60% longer for low-incidence indications. Subpart H commitments remain incomplete for five of eight AA cancer indications discussed at a 2003 ODAC meeting and five of six AA cancer indications discussed at a 2005 ODAC meeting that reviewed barriers to completing AA; all but 1 of the 9 total indications discussed at both meetings affected smaller numbers of cancer patients. These findings raise concern that, fifteen

years after initiating the AA program, reassessment of its benchmarks is warranted, particular for drugs developed to treat low-incidence malignancies.

Several reasons help explain the low rate of completion of confirmatory trials in low-incidence indications (13% fulfilled Subpart H commitments). Patients with these cancers are reluctant to enroll in phase III subpart H commitment trials where there is a high probability that they will not receive a drug that has recently received AA from the FDA. Similarly, after a novel drug is commercially available, physicians often view confirmatory trials as violations of equipoise, and are therefore reluctant to advise their patients to enroll on these studies.^{25, 26} Moreover, the bar for completing subpart H commitments may be set too high. For example, subpart H commitment studies for imatinib as an initial treatment for chronic myeloid leukemia (CML) have been pending since it received AA for this indication in December 2002. The agreed upon subpart H commitment is eight-year outcome data among the 1,106 patients enrolled in the phase III trial that evaluated imatinib versus interferon and low-dose cytarabine for newly diagnosed chronic-phase CML. Five-year follow-up data, reported in December 2006, identified 7% of imatinib-treated patients had progressed to accelerated-phase CML or blast crisis, and the estimated overall survival of patients who received imatinib as initial therapy was 89% at 60 months.²⁷ While five -year follow-up information demonstrating durable responses in a large proportion of CML patients has recently been submitted to the FDA, completion of the subpart H commitment study for this indication is not expected until 2008, six years after AA for this indication was granted.

At the 2003 and 2005 ODAC meetings, FDA officials outlined strategies designed to improve completion rates for subpart H commitment studies for sponsors of drugs used to treat rare cancers.⁴⁻⁷ One recommendation was to add clinical trial sites in countries where the study drugs have not received regulatory approval - an option that is not economically viable for small biotechnology and pharmaceutical companies. A second recommendation was to develop plans for subpart H confirmatory studies in collaboration with the FDA prior to applying for AA, and subsequently to enroll patients in these studies prior to the time that AA is granted. The use of interim analyses of Phase III trials as a basis for AA was also felt to be preferable. This strategy has been pursued in four indications, the majority of which affect larger number of patients. This approach is less tenable for sponsors of drugs used to treat small numbers of patients, where design and accrual to large Phase III studies may markedly delay the approval process.

Congressman Ed Markey and new legislation passed by the Congress in 2007 outline a punitive approach - fining pharmaceutical sponsors and withdrawing AA for drug indications that have not been evaluated with post-approval commitment studies.⁸ Such an approach would represent a disservice to patients, particularly those with less common cancers who benefit from novel therapies which have already shown clinical benefit in single-arm studies.

Alternative strategies to improve the AA process should be considered. It should be noted that a median of 40 and 120 cancer patients benefited from AA drugs in trials that supported AA and corresponding subpart H confirmatory trials, respectively. As suggested by some ODAC committee members following the 2005 meeting on AA, given the limited experience that the oncology community has with drugs shortly after they receive AA, drug sponsors should be allowed the option of fulfilling subpart H commitments by conducting long-term single-arm

phase II studies and establishing comprehensive safety registries, rather than pursuing obligatory short-term Phase III efficacy trials.^{7, 28} Better characterization of safety and efficacy profiles requires years of experience when thousands of patients receive novel cancer drugs, often in off-label clinical settings. Our review suggests that consideration of these options is especially important for sponsors of drugs used to treat cancers that affect small numbers of patients in which the current Subpart H requirement of completing a phase III trial may be insurmountable. Rather than waiting indefinitely for preliminary safety data from a Phase III trial, real-time drug registries allow proactive assessment of adverse events and provide data for assessment of clinical benefit. Moreover, drug registries represent a more effective use of finances for small companies that may experience significant financial burden in attempting to complete larger Phase III studies which are plagued by logistical difficulties. For both low-incidence and high-incidence cancer indications, the absolute numbers of patients shown to benefit in the initial trials that support AA as well as the confirmatory trials which support conversion to regular approval are small. As such, complete characterization of safety and efficacy profiles requires rigorous clinical observation and experience with therapies in the off-label setting. A structured pharmacovigilance program in the post-AA setting is likely to uncover safety and efficacy issues in a more timely fashion than randomized trials. Of note, establishing long-term registries is consistent with requirements outlined in the 2007 re-authorization of the Pharmaceutical Drug Utilization Fees Act. Specifically, the legislation requires pharmaceutical sponsors to establish registries in settings where uncertainty about the benefits and risks of a drug arise.

Our findings have practical and policy implications. ODAC members report that, in recent years, difficulty with completing confirmatory trials has led to a more cautious approach granting AA for new indications.⁷ A fear of increased numbers of languishing Subpart H commitments seems to have led to more stringent requirements for future AA applications, including an increased emphasis on phase III trials to support AA and accrual to phase III trials before granting AA.^{3, 29, 30} The end-result is that the bar to achieve AA has been raised in recent years to a level which favors the phase III trial design over the phase II design. This shift may account in part for the observation that only two cancer drugs have received AA since 2005 and several recent AA applications for novel cancer drugs have been rejected. Ultimately, these changes have resulted in fewer available drugs to patients with rare diseases who have few treatment options at baseline.

In summary, we found that Subpart H commitments are especially difficult to complete for sponsors of AA drugs used to treat cancer indications that affect small numbers of patients. After AA is granted, sponsors of these drugs should not uniformly be mandated to complete randomized phase III clinical trials to fulfill their subpart H requirements. Instead, drug sponsors should be encouraged to maintain rigorous drug safety registries. This policy change would facilitate early access to novel drugs for patients who have less common cancers, allow for AA to be granted for these indications on the basis of phase II studies rather than interim analyses of phase III studies, and facilitate earlier detection of adverse drug effects in the post-approval setting.

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Table 1: Summary of fast track review, priority review, and accelerated approval programs established under the Prescription Drug User Fee Act of 1992 (PDUFA) and the Food and Drug Administration Modernization Act of 1997 (FDAMA).¹

FDA Process	Eligibility Requirements	Effect on Approval Process
Fast Track (FDAMA 1997)	Drugs must concern a medical need that has not been previously addressed by a product or claim before.	Allows pharmaceutical companies to seek FDA input into development plan, allows the company to submit a New Drug Application or Biologic Licensing Application in sections and allows the companies to study drugs through surrogate endpoints.
Priority Review Subpart E (PDUFA 1992)	Drugs must “address unmet medical needs”	Reduces the drug review process from ten months to six months.
Accelerated Approval for Drugs (1992 as Subpart H in 21 CFR Sec. 314.510)	This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).	Request for accelerated approval consideration does not necessarily affect the actual length of the review process but allows for approval based on a surrogate endpoint likely to predict clinical benefit or a product may be approved with restrictions to assure safe use.
Accelerated approval for Biologics (Subpart E in CFR Sec 601.41)	This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).	Request for accelerated approval consideration does not necessarily affect the actual length of the review process but allows for approval based on a surrogate endpoint likely to predict clinical benefit or a product may be approved with restrictions to assure safe use.

Table 2: Status of Subpart H commitments for indications discussed at 2003 and 2005 ODAC meetings ^{4, 6, 11}

Pending Subpart H Commitments							
Drug/Indication	Presented at ODAC 2003	Presented at ODAC 2005	Date AA granted (Years lapsed)	Confirmatory trial initiated?	Confirmatory trial accrual/goal accrual	Expansion to international sites?	Subpart H Commitment Status/Accrual status
Liposomal Doxorubicin/AIDS-related Kaposi's sarcoma	Yes	Yes	November 1995 (12)	Completed in 2001	71	No	Study completed – drug not granted regular approval due to interim introduction of HAART therapy
Denileukin Diftitox/Cutaneous T Cell Lymphoma (CTCL)	Yes	Yes	February 1999 (8.8)	Yes	195	Yes	Accrual slow and recruitment ratio changed due to patient disinterest in placebo. Results recently reported – Denileukin diftiox showed improved response rate compared to placebo for 2 doses: 18mcg/kg/day and 9mcg/kg/day. ⁵¹
Liposomal cytarabine/Lymphomatous meningitis	Yes	Yes	April 1999 (8.6)	Yes – initiated enrollment in 2001 and completed in 2004	100	Yes – 2 Canadian sites	Pending.
Celecoxib/Familial adenomatous polyposis	Yes	Yes	December 1999 (7.9)	Yes – initiated in 2004	200	No	Pending. Slow, particularly since cardiovascular concerns were raised in 2004. Also required completion of a Phase I study in pediatrics prior to enrollment
Gemtuzumab/Acute Myeloid Leukemia (AML)	Yes	Yes	May 2000 (7.5)	Yes – initiated in 2004	684	Yes	Pending. Anticipated accrual over 4.5 years
Fulfilled Subpart H Commitments							
Drug/Indication	Presented at ODAC 2003	Presented at ODAC 2005	Date AA granted (Years to fulfillment)	Confirmatory trial design	Confirmatory trial accrual	Expansion to international sites?	Subpart H Commitment Status
Amifostine/Cisplatin toxicity in non-small cell lung cancer (NSCLC)	Yes	No	March 1996 (N/A)	N/A	N/A	No	No longer pending – accelerated approval status withdrawn by drug sponsor
Liposomal Doxorubicin/Refractory ovarian carcinoma	Yes	No	June 1999 (5.5)	Phase III	474	No	Fulfilled – conversion to regular approval January 2005
Temozolamide/Anaplastic astrocytoma, Glioblastoma multiformae	Yes	No	August 1999 (5.5)	Phase III	573	Yes	Fulfilled – conversion to regular approval March 2005
Alemtuzumab/ Chronic Lymphocytic Leukemia	No	Yes	May 2001 (6.3)	Phase III	297	Yes	Fulfilled – conversion to regular approval September 2007

Table 3: Drugs receiving accelerated approval (AA)

Drug Name	AA Indication	Date of AA (Years since AA)	Annual incidence of tumor type*	Type of study/studies on which AA was based	Primary outcome of study/studies on which AA was based	Date of fulfilled Subpart H commitment (years to fulfillment)	Confirmatory trials – type of study and number of patients enrolled	Confirmatory trial: Primary endpoint and results
Indications which Affect Fewer than 25,000 Patients Annually								
Nelarabine ^{10,13}	T Cell Acute Lymphoblastic Leukemia/Lymphoma	October 2005 (2.00)	9,478	2 Phase II studies (n=67) <i>Study 1 (n=39)</i> <i>Study 2 (n=28)</i>	RR (CR+CR*) <i>Study 1: 23%</i> <i>Study 2: 21%</i>	Pending	Pending	Pending
Clofarabine ³²	Pediatric acute lymphocytic leukemia	December 2004 (2.92)	2,790	Phase II and Phase I studies (n=86) <i>Study 1 (Phase II, n=61)</i> <i>Study 2 (Phase I, n=25)</i>	CR (CR + CRp) <i>Study 1: 20%</i> <i>Study 2: 32%</i>	Pending	Pending	Pending
Tositumomab ^{10,33,34}	Indication expanded to include rituximab-naïve follicular non-Hodgkin's lymphoma	December 2004 (2.92)	15,798	Phase II study (n=60)	ORR: 47%	Pending	Pending	Pending
Tositumomab ^{10,33,34}	Rituximab-refractory non-Hodgkin's lymphoma	June 2003 (4.33)	15,798	5 single arm studies (n=250) <i>1 Phase II multicenter study (n=40) and 4 additional single-arm studies (3 Phase II, 1 Phase I) (n=210)</i>	ORR: <i>Phase II: 68%</i> <i>4 additional studies: 47%-64%</i>	Pending	Pending	Pending
Bortezomib ³⁵	Refractory multiple myeloma	May 2003 (4.5)	19,900	2 Phase II studies (n=256) <i>Study 1 (n=202)</i> <i>Study 2 (n=54)</i>	ORR: <i>Study 1: 28%</i> <i>Study 2: 38%</i>	March 2005 (1.83)	Phase III study (n=669)³⁶ – Bortezomib vs. High-dose dexamethasone	Primary Endpoint = TTP: 6.22 vs. 3.49 months (HR 0.55, p<0.001)
Imatinib ^{10,37}	Pediatric Ph+ chronic myeloid leukemia refractory to interferon alpha or with disease recurrence after stem cell transplant	May 2003 (4.5)	~200	1 Phase II study and 2 Phase I dose-escalation studies (n=68) <i>Study 1 (Phase II, n=51)</i> <i>Study 2 (Phase I, n=14)</i>	RR (HR and CyR): <i>Study 1: 78% HR, 65% CCyR, 16% PCyR</i> <i>Study 2: 78% PCyR or CCyR</i> <i>Study 3: 66% CCyR</i>	Pending	Pending	Pending

				<i>Study 3</i> (Phase I, n=3)				
Imatinib ^{10, 38}	Initial treatment of newly diagnosed Ph+ chronic myeloid leukemia	December 2002 (4.92)	4,570	Randomized Phase III study (n=1,106): Imatinib vs. interferon alpha/cytarabine	RR: <i>HR:</i> 94% vs. 55% <i>MCyR:</i> 76% vs. 12% <i>CCyR:</i> 54% vs. 3%	Pending	Pending	Pending
Imatinib ^{10, 39, 40}	Metastatic or unresectable gastrointestinal stromal tumor	February 2002 (5.67)	6,000	Phase II study (n=147)	RR: PR in 38%	Pending	Pending	Pending
Ibritumomab ^{10, 41}	Relapsed, refractory low grade follicular or transformed non-Hodgkin's lymphoma	February 2002 (5.67)	15,798	Phase III study and Phase II study (n=197) <i>Study 1:</i> Phase III (n=143, ibritumomab vs. rituximab) <i>Study 2:</i> Phase II (n=54)	ORR: <i>Study 1:</i> 80% (ibritumomab) vs. 56% (rituximab) <i>Study 2:</i> 74%	Pending	Pending	Pending
Imatinib ^{10, 39, 40}	Ph+ chronic myeloid leukemia in chronic phase after failure of interferon-alpha, accelerated phase, or blast crisis	May 2001 (6.5)	4,570	3 Phase II studies (n=1,027) Chronic phase: n=532 Accelerated phase: n=235 Blast crisis: n=260	RR (HR): <i>Chronic phase:</i> 88% <i>Accelerated phase (600mg dose):</i> 72% <i>Blast crisis (600mg dose):</i> 31%	December 2003 (2.50)	3 Phase II studies (n=1,085) – longer follow up (2 year)	Primary Endpoints = RR and OS: <i>Chronic phase:</i> 85.4% HR, 90.8% OS <i>Accelerated phase (600mg dose):</i> 61%, 66% 2-year OS <i>Blast phase (600mg dose):</i> 33% HR and 18.3% 2-year OS
Alemtuzumab ^{6, 10, 23}	Chronic lymphocytic leukemia	May 2001 (6.5)	15,340	Phase II study (n=93)	ORR: 33%	September 2005 (4.33)	Phase III study (n=297)¹¹: Alemtuzumab vs. Chlorambucil (CAM307 NCT00046683) (NCI website)	Primary Endpoint = PFS: 14.6 vs. 11.7 months (p=0.0001)

Gemtuzumab ^{10, 42}	CD33+ Acute myeloid leukemia	May 2000 (7.5)	13,410	3 Phase II studies (n=142)	ORR (CR): 30% (combination of 3 studies)	Pending	Pending	Pending
Celecoxib ^{6, 10, 45}	Reduction of polyps in familial adenomatous polyposis	December 1999	<1,000	Randomized Phase II study (n=77): comparing 2 doses of drug	Reduction in colonic polyps: <i>400mg dose</i> – 28% vs. 5% compared with placebo (p=0.003) <i>100mg dose</i> – 12% vs. 5% compared with placebo (p=0.33)	Pending	Pending	Celecoxib ^{6, 10, 45}
Temozolamide ^{16, 17}	Anaplastic astrocytoma/high grade glioma in conjunction with radiation therapy	August 1999 (8.10)	10,000	Phase II study (n=162)	RR: 22% in subset of 54 patients who had progressed after both procarbazine and nitrosourea	March 2005 (4.50)	Phase III study (n=573)¹⁸ Radiotherapy (RT) alone vs. RT + Temozolamide	Primary Endpoint = OS: 26.5% vs. 10.4% (HR 0.63 [0.52-0.75] (p<0.001)) at 28 months
Liposomal doxorubicin ^{6, 10}	Refractory ovarian carcinoma	June 1999 (8.33)	22,430	3 Phase II studies (n=176)	RR: 14% (combination of 3 studies)	January 2005 (5.58)	Phase III study (n=474)¹⁹ Liposomal doxorubicin vs. Topotecan	Primary Endpoint = OS: 108 weeks vs. 71.1 weeks (p=0.008)
Liposomal cytarabine ^{10, 43}	Lymphomatous meningitis	April 1999 (8.58)	1,053	Randomized Phase II study (n=28)	RR: 71% liposomal cytarabine vs. 15% cytarabine (p=0.006)	Pending	Pending	Pending
Denileukin difitox ^{4, 6, 44}	Cutaneous T cell lymphoma	February 1999 (8.75)	<3,160	Phase III study and Phase I/II study (n=106) <i>Study 1:</i> Phase III (n=71) – comparing 2 doses of drug <i>Study 2:</i> Phase I/II (n=35)	RR: <i>Study 1:</i> 30% <i>Study 2:</i> 38%	Pending	Pending	Pending
Liposomal doxorubicin ^{6, 10}	AIDS-related Kaposi's sarcoma	November 1995 (12.00)	<1,000	Subanalysis of Phase II study (n=77) – cohort of patients refractory to multiple previous therapies identified	RR: 27% in 34 evaluable patients	Pending	Sponsor requested that Subpart H requirement be waived	Sponsor requested that Subpart H requirement be waived

Indications which Affect Greater than 25,000 Patients Annually

Sunitinib ¹⁴	Advanced renal cell carcinoma	January 2006 (1.83)	51,190	2 Phase II studies (n=169) <i>Study 1</i> (n=106) <i>Study 2</i> (n=63)	RR: <i>Study 1:</i> 26% <i>Study 2:</i> 37%	February 2007 (1.08)	Phase III randomized trial (n=750)¹⁵ Sunitinib vs. interferon alpha	Primary Endpoint = PFS: 11 vs. 5 months HR 0.42 [0.32-0.54] (p<0.001)
Letrozole ^{10, 45, 46}	Extended adjuvant hormonal therapy for postmenopausal women with breast cancer	October 2004 (3.00)	180,510	Phase III double-blind randomized study (n=5,187)	DFS (interim analysis): 122 events on letrozole vs. 193 events on placebo (p=0.00003)	Pending	Pending	Pending
Premetrexed ⁴⁷	Non small cell lung cancer	August 2004 (3.10)	185,641	Phase III study (n=571): comparison of premetrexed to docetaxel	OS (primary endpoint): 8.3 months (premetrexed) vs. 7.9 months (docetaxel), p=0.93 (not significant) RR (secondary endpoint): 9% (premetrexed) vs. 9% (docetaxel), not significant Safety profile favors premetrexed	Pending	Pending	Pending
Cetuximab ^{10, 48, 49}	EGFR+ metastatic colorectal cancer as second line therapy in combination with irinotecan	February 2004 (3.75)	153,760	2 Phase II studies and 1 randomized Phase III study (n =524) <i>Study 1:</i> Phase III (n=329) <i>Study 2:</i> Phase II (n=138) <i>Study 3:</i> Phase II (n=57)	RR: <i>Study 1:</i> 23% (cetuximab + irinotecan) vs. 11% (irinotecan) p=0.007 <i>Study 2:</i> 15% <i>Study 3:</i> 9% PR and 37% minor response or stable disease	October 2007 (3.67)	Phase III randomized trial (n=572) Cetuximab vs. Best supportive care	Primary Endpoint = OS: 6.1 vs. 4.6 months (HR 0.766, p=0.0048)
Gefitinib ^{50, 51}	Single agent therapy for refractory non small cell lung cancer	May 2003 (4.50)	185,641	Phase II study (n=142)	RR: 11%	June 2005 (4.33)	Randomized Phase III study (n=1,692)⁵² Gefitinib vs. Best supportive care	Primary Endpoint = OS: 5.6 vs. 5.1 months HR 0.89 [0.77-1.02], p=0.087
Anastrozole ^{20, 21}	Adjuvant hormonal treatment of early stage breast cancer in postmenopausal	September 2002 (5.08)	180,510	Phase III randomized study (interim analysis at 31 months) (n=9,366)	DFS: 89% (anastrozole) vs. 88% (tamoxifen), p=0.013	September 2005 (3.00)	Longer-term follow up of Phase III study (n=9,366)²²	Primary Endpoint = DFS: 575 vs. 671

	women						Anastrozole vs. Tamoxifen vs. combination	events HR 0.87 [0.78-0.97] p=0.01
Oxaliplatin ⁵³	Metastatic colorectal cancer	August 2002 (5.10)	153,760	Phase III randomized trial (n=463)	RR: 9% (oxaliplatin-containing arm) vs. 0% (5-FU/leucovorin alone) (p=0.0002) TTP (interim analysis): 4.6 vs. 2.7 months (p<0.0001)	January 2004 (1.42)	Phase III trial (n=795)⁵⁴ IFL vs. FOLFOX vs. IROX regimens	Primary Endpoint = TTP: 8.7 FOLFOX vs. 6.9 months IFL p=0.0014, HR 0.74 [0.61-0.89]
Capecitabine ^{10, 55}	Metastatic breast cancer	April 1998 (9.58)	180,510	Phase II study (n=163)	RR: 20% (29% in subgroup of 42 patients resistant to paclitaxel and doxorubicin)	September 2001 (3.42)	Phase III trial (n=511)⁵⁶ Docetaxel + capecitabine vs. Docetaxel alone	Primary Endpoint = TTP: 6.1 vs. 4.2 months HR 0.652 [0.545-0.780], p=0.0001
Irinotecan ¹⁰	Metastatic colorectal cancer	June 1996 (11.42)	153,760	3 Phase II studies (n=304) <i>Study 1 (n=48)</i> <i>Study 2 (n=90)</i> <i>Study 3 (n=166)</i>	RR: 13% (combination of 3 studies)	October 1998 (2.33)	2 Phase III studies (n=535)^{48, 57} Study 1 (n=279) Irinotecan vs. Best supportive care Study 2 (n=256)⁵⁸ Irinotecan vs. 5-FU continuous infusion	Study 1 Primary Endpoint = OS: 36% vs. 14% at 1 year (p=0.001) Study 2 Primary endpoint = OS: 45% vs. 32% alive at 1 year p=0.035
Docetaxel ¹⁰	Metastatic breast cancer	May 1996 (11.50)	180,510	3 Phase II trials (n=134)	RR: 41% (combination of 3 studies)	June 1998 (2.08)	2 Phase III studies (n=515)⁵⁹ Study 1 (n=326) Docetaxel vs. Doxorubicin Study 2 (n=392)	Study 1 Primary Endpoint = RR: 48% vs. 33% Study 2 Primary Endpoint =

							Docetaxel vs. Mitomycin C + Vinblastine	PFS: 11.4 vs. 8.7 months
Amifostine ^{6, 10, 24}	Reduction of platinum toxicity in non small cell lung cancer patients	March 1996 (11.58)	185,641	Phase II study (n=25)	RR and Development of Nephrotoxicity: 64% RR and 12% reversible grade 3 nephrotoxicity	Accelerated approval forfeited by sponsor	N/A	N/A
Dexrazoxane ¹⁰	Prevention of doxorubicin-associated cardiomyopathy	May 1995 (12.50)	N/A	2 identical Phase III studies (n=1,008)	Decrease in cardiac events: HR 3.5 significant decrease in cardiac events in dexrazoxane-treated patients (p<0.001)	October 2002 (7.42)	Literature review, including meta-analysis of 5 studies	N/A

* **Abbreviations:** **RR** (Response Rate); **ORR** (Overall Response Rate); **CR** (Complete Remission); **CR*** (Complete Remission with incomplete bone marrow recovery); **CRp** (Complete Remission without platelet recovery); **TTP** (Time to Progression); **HR** (Hematologic Response); **CyR** (Cytogenetic Response); **MCyR** (Major Cytogenetic Response); **CCyR** (Complete Cytogenetic Response); **PCyR** (Partial Cytogenetic Response); **PR** (Partial Response); **PFS** (Performance Free Survival); **OS** (Overall Survival)

Shaded rows indicate indications for which Subpart H commitment is no longer pending.

Figure 1: Cancer indications receiving accelerated approval (AA) stratified by frequency of disease and by the granting of AA solely or partially on the basis of phase III studies

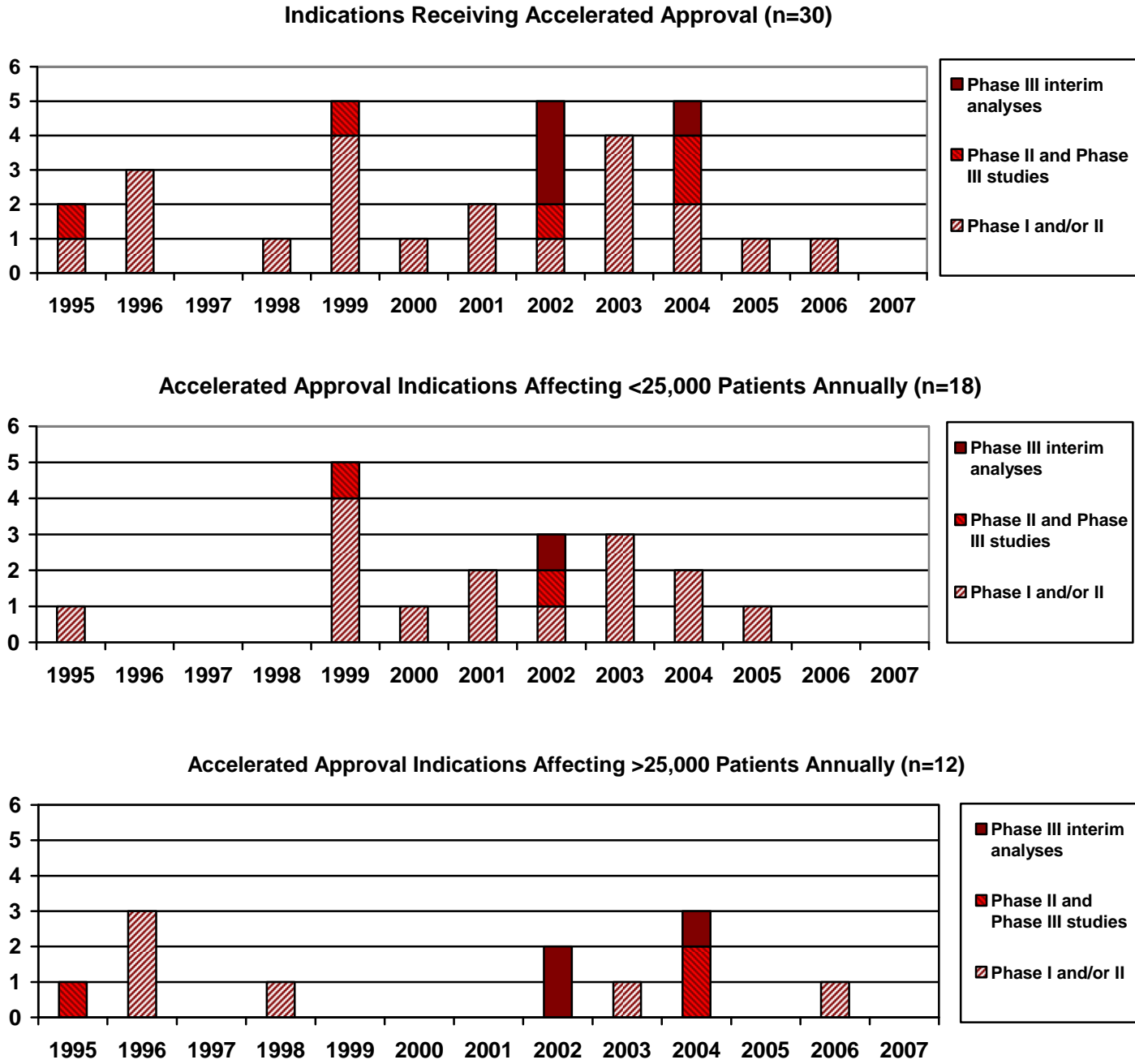


Figure 2: Cox proportional hazards model for Subpart H fulfillment for cancer indications affecting <25,000 and >25,000 patients annually

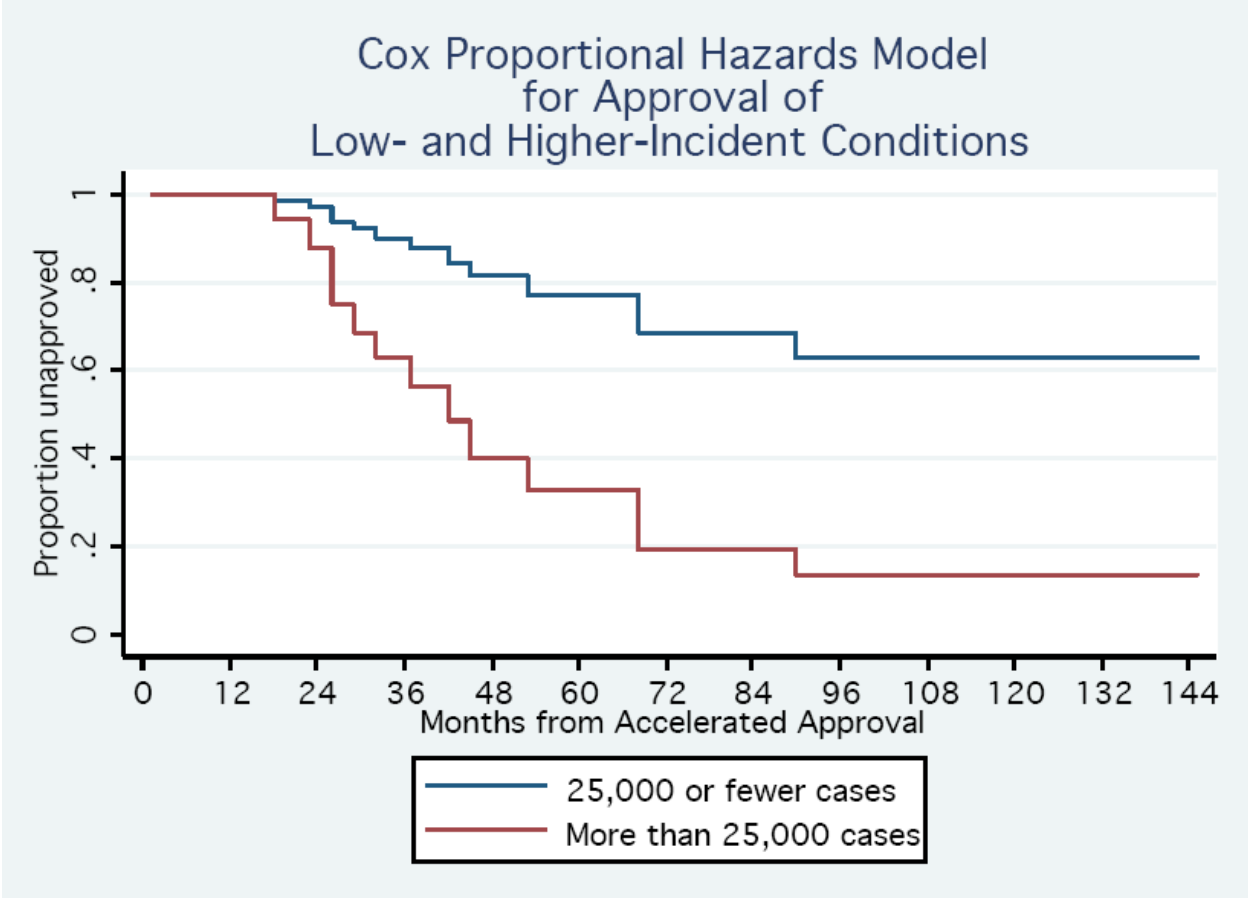
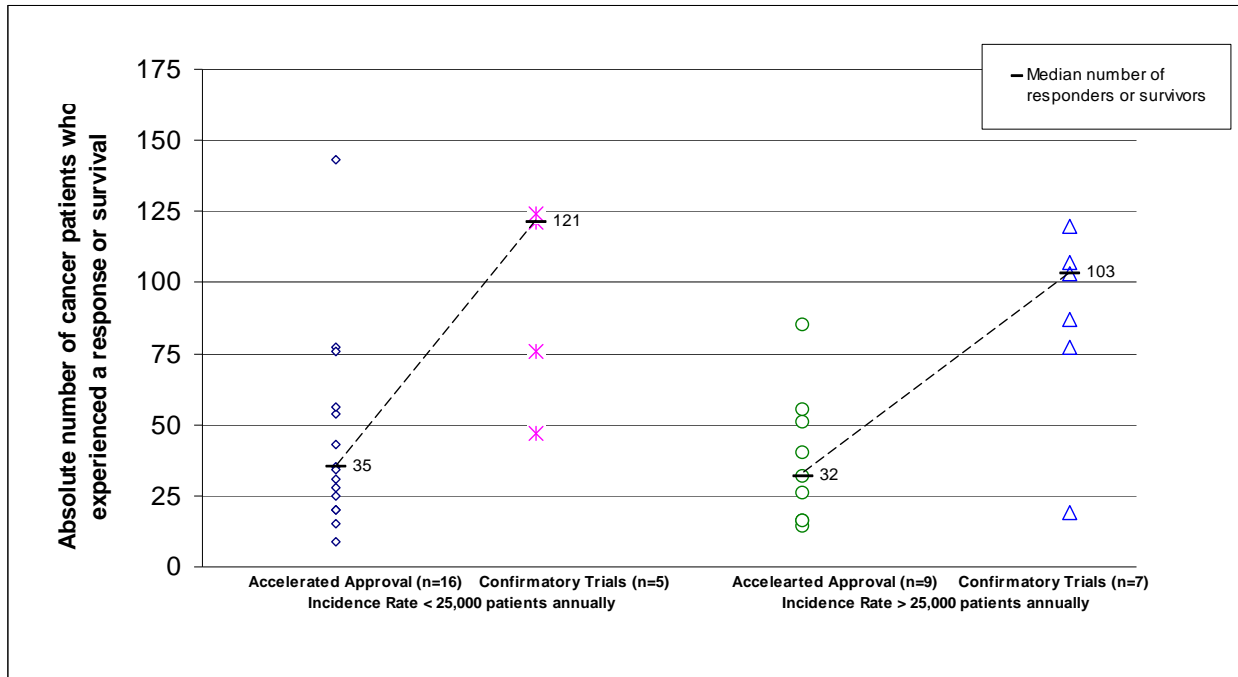


Figure 3: Absolute number of responders or survivors during clinical trials used for designation of accelerated approval and confirmatory trials for Subpart H fulfillment



Three outlying data points with absolute number of responders or survivors greater than 400 are not shown on the graph, but were included in calculations of median number of respondents or survivors.