End Points and United States Food and Drug Administration Approval of Oncology Drugs

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Purpose: **To summarize the end points used by the United States Food and Drug Administration (FDA) to approve new cancer drug applications over the last 13 years.**

Materials and Methods: **The FDA granted marketing approval to 71 oncology drug applications between January 1, 1990, and November 1, 2002. The end points used as the approval basis for each application are presented, and the rationale for each end point is discussed.**

Results: **The FDA grants either regular marketing approval or accelerated marketing approval for oncology drug applications. Regular approval is based on end points that demonstrate that the drug provides a longer life, a better life, or a favorable effect on an established surrogate for a longer life or a better life. Accelerated approval (AA) is based on a surrogate end point that is less well established but that is reasonably likely to predict a longer or a better life. Tumor response was the approval basis in 26 of 57 regular approvals, supported by relief of tumor-specific symptoms in nine of these 26 regular approvals. Relief of tumor-specific symptoms provided critical support for approval in 13 of 57 regular approvals. Approval was based on tumor response in 12 of 14 AAs.**

Conclusion: **End points other than survival were the approval basis for 68% (39 of 57) of oncology drug marketing applications granted regular approval and for all 14 applications granted accelerated approval from January 1, 1990, to November 1, 2002.**

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THERE IS a common misperception that the United States Food and Drug Administration (FDA) requires a survival improvement for approval of oncology drug marketing applications.[1] This article reviews the marketing applications for oncology drugs approved by the FDA's Division of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER) from January 1, 1990, to November 1, 2002. The end points used as the approval basis for each application are presented, and the rationale for end-point selection is discussed.

Regular marketing approval of oncology drugs requires substantial evidence of efficacy from adequate and well-controlled investigations. The attributes of adequate and well-controlled investigations are described in the regulations.[2] Studies must allow a valid comparison to a control and must provide a quantitative assessment of the drug's effect. Guidance promulgated in the 1980s indicated that efficacy should be demonstrated by prolongation of life, a better life, or an established surrogate for at least one of these. Drugs must also be safe for their intended use. The safety requirement comes from the Federal Food Drug and Cosmetic Act of 1938. A 1962 amendment to that Act codifies the efficacy requirement.

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The views expressed are the result of independent work and do not necessarily represent the views and findings of the United States Food and Drug Administration.

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In 1992, Subpart H was added to the new drug application (NDA) regulations to allow accelerated approval (AA) for diseases that are serious or life-threatening when the new drug appears to provide benefit over available therapy, but under situations when the demonstrated benefit did not yet meet the standard for regular approval. For instance, AA can be granted on the basis of a surrogate end point that is reasonably likely to predict clinical benefit (Table 1) but that is not established to the level that would support regular approval. After AA, the applicant is required to perform a postmarketing study to demonstrate that treatment with the drug is indeed associated with clinical benefit. If the postmarketing study fails to demonstrate clinical benefit or if the applicant does not demonstrate due diligence in conducting the required study, the regulations describe a process for rapidly removing the drug from the market.[3] The AA regulations provide drugs that are promising on the basis of surrogates that are reasonably likely to predict clinical benefit to patients with serious or life-threatening diseases. Drugs that are only similar to available therapy on the basis of such a surrogate would not appear to be especially promising and would not provide benefit over available therapy. If the drug showed clinical benefit, it would be granted regular approval and would not need to provide benefit over available therapy.

In the early 1980s, the FDA approved oncology drugs based on tumor response rate alone. In the mid-1980s, on the advice of the Oncologic Drugs Advisory Committee (ODAC), the FDA determined that response rate generally should not be the sole basis for approval. The potential benefit associated with a partial response did not necessarily outweigh the substantial toxicity of oncology drugs, and the correlation between response rate and survival or clinical benefit was not well established. The new FDA position called for an improvement in survival or patient symptoms for regular approval.[4]

In subsequent years, the FDA stated that under selected circumstances, impressive tumor-related outcomes could be

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Table 1. Surrogate End Point Status and Marketing Approval

End Point Status	Example	Type of Approval
Established surrogate	Response rate in breast cancer with hormonal treatments	Regular approval
Reasonably likely surrogate	Response rate in refractory solid tumors	Accelerated approval
Not reasonably likely surrogate	Tumor markers	Not approvable

considered clinical benefit. In 1991, the FDA and National Cancer Institute examined end points that potentially demonstrated clinical benefit. An improvement in disease-free survival (DFS) was proposed as a valid end point for an adjuvant setting if a large proportion of recurrences are symptomatic. Complete responses of reasonable duration may also represent evidence of clinical effectiveness. For example, complete responses in acute leukemia may correlate with improved survival and clinical benefits of reduced infections and transfusion requirements. Evaluation of response rates should take into consideration the response duration, the drug toxicity, and relief of tumor-related symptoms.[5]

MATERIALS AND METHODS

Information available to the public under the Freedom of Information Act was surveyed for new oncology drug applications and supplements for new uses approved by the Division of Oncology Drug Products from January 1, 1990, to November 1, 2002. This survey does not include oncology drug applications approved by other CDER divisions, including drugs for skin cancer, hormone treatments for prostate cancer, or radiopharmaceuticals, and does not include biologic drug products, which are reviewed by the Center for Biologics Evaluation and Research. The primary source for this analysis was the package insert. When multiple end points were identified in the package insert and questions existed regarding the approval basis, other sources were consulted (medical officer review documents and ODAC meeting transcripts). The final arbiter in these cases was the approving official.

End-point definitions were those used in the applications submitted to the FDA and can be found in approved labeling. The following general definitions were commonly used: complete response was complete disappearance of all tumor and all manifestations of tumor for at least 1 month; partial response was a 50% decrease from baseline in the sum of the cross-products of all bidimensionally measurable tumors lasting at least 1 month; progression was a 25% increase in the sum of cross-products of all bidimensionally measurable lesions from the nadir value, the occurrence of new lesions, or obvious progression in evaluable disease. Disease-free survival was assessed from date of randomization until first recurrence or death. Survival was assessed from date of randomization to death. Skeletal-related events (SREs) formed a composite end point of pathologic fractures, radiation therapy, surgery to bone, or spinal cord compression. Statistical significance for time-to-event end points was determined by the log-rank test at a two-sided significance level of 0.05. Additional assessments of clinical benefit were descriptive or used end points described here.

RESULTS

End Points Used for Regular Approval

Table 2 shows the end points that were the basis for the FDA marketing approval of oncology drug applications approved from January 1, 1990, to November 1, 2002. In addition to conventional anticancer drugs, this analysis includes approvals of four chemoprotectant and three bisphosphonate applications. Seventy-one marketing applications for oncology drugs were approved. Fifty-seven applications were granted regular approval, and 14 applications were granted AA. Marketing approval in 39 of the 57 applications granted regular approval was based on end points other than survival. Excluding chemoprotectant and bisphosphonate applications, 34 of 52 regular approvals were based on nonsurvival end points. Table 3 tabulates the number of regular approvals using each end point.

Survival. Survival was the primary approval basis for 18 applications. This finding does not necessarily mean that only survival benefit could have led to approval in these cases. Whenever a survival benefit was demonstrated, it was designated as the primary approval basis.

Tumor response, response duration, and time-to-tumor progression. The FDA oncology drug approval record shown in Table 2 demonstrates that tumor response rate and time-to-progression were important end points in regular approval of oncology drugs. Forty-seven percent (27 of 57) of the regular oncology drug approvals had response rate or time-to-tumor progression (TTP) as the primary or coprimary end point in the trials supporting approval. Ten of these 27 approvals were based solely on tumor response, nine were based on both tumor response and relief of tumor-specific symptoms (see section on Relief of Tumor-Specific Symptoms or Improvement in Laboratory Findings), seven were based on both tumor response and TTP, and one was based on TTP alone.

Regular approval of oncology drug applications based on tumor response or TTP indicates that these end points were considered surrogates for a better life and possibly improved survival in selected clinical settings. Considerations include efficacy of other available therapy, drug toxicity, type of response (complete or partial), response duration, and supportive data on disease-specific symptom improvement. A discussion of the rationale for these approvals follows. Further information can be found in the package inserts of the oncology drugs listed in Table 2.

Anastrazole, exemestane, letrozole, toremifene, and fulvestrant were granted regular approval for treatment of advanced breast cancer in postmenopausal women on the basis of randomized controlled trials (RCTs) comparing each with tamoxifen or another approved hormonal agent. Given the favorable toxicity profile associated with hormonal drugs compared with conventional cytotoxic agents, tamoxifen's well-accepted therapeutic role, and the lack of a demonstrated survival effect with any hormonal drugs, response rate and TTP are considered adequate surrogates for a better life in hormonal drug trials in advanced metastatic breast cancer and have been the primary end points for comparing efficacy.[6,7] At the time of approval in each case, a preliminary survival analysis was performed and showed no disadvantage compared with the control. Final survival data were assessed after approval.

Tumor response was judged to represent clinical benefit in several other regular approvals. Durable complete responses are considered an established surrogate for a better life in refractory

Table 2. End Points for Approval of Oncology Drug Marketing Applications January 1, 1990 to November 1, 2002

Drug (year, application type)	Indication	Approval Type	End Points Supporting Approval	Trial Design
Altretamine (1990, N)	Refractory ovarian cancer	Regular	RR	SAT
Altretinoin gel (1999, N)	Kaposi's sarcoma, cutaneous lesions	Regular	RR, cosmesis	RCT
Amifostine				
(1995, N)	To decrease cisplatin-induced renal toxicity in refractory ovarian cancer	Regular	Creatinine clearance, CR and TTP to assess potential tumor protection	RCT
(1996, S)	To decrease cisplatin-induced renal toxicity in lung cancer	AA	Creatinine clearance, RR to assess tumor protection	SAT
(1999, S)	To decrease xerostomia after radiation therapy for head and neck cancer	Regular	Salivary production and xerostomia scores	RCT
Anastrozole				
(1995, N)	Breast cancer, second-line treatment	Regular	RR, TTP	DB RCT
(2000, S)	Breast cancer, first-line treatment	Regular	RR, TTP	DB RCT
(2002, S)	Breast cancer, adjuvant therapy of postmenopausal patients with ER-positive tumors	AA	DFS	DB RCT
Arsenic trioxide (2000, N)	Acute promyelocytic leukemia, second-line treatment	Regular	CR and CR duration	SAT
Bexarotene capsules (1999, N)	Cutaneous T-cell lymphoma, skin lesions	Regular	RR, composite assessment of index lesion severity	SAT
Bexarotene gel (2000, N)	Cutaneous T-cell lymphoma, skin lesions	Regular	RR, composite assessment of index lesion severity	SAT
Bleomycin (1996, S)	Malignant pleural effusions	Regular	Recurrence of effusion	RCT
Busulfan injection (1999, S)	CML, conditioning regimen for stem-cell transplantation	Regular	DFS, time to engraftment	RCT
Capecitabine				
(1998, N)	Breast cancer, refractory	AA	RR	SAT
(2001, S)	Colon cancer, first-line treatment	Regular	Survival	RCT
(2001, S)	Breast cancer, with docetaxel after failed anthracycline treatment	Regular	Survival	RCT
Carboplatin (1991, S)	Ovarian cancer, first-line treatment	Regular	Pathologic CR, PFS, survival	RCT
Carmustine wafer (1996, N)	Recurrent glioblastoma multiforme	Regular	Survival	Placebo RCT
Cladribine (1993, N)	Hairy cell leukemia	Regular	CR and CR duration	SAT
Dexrazoxane (1995, N)	To decrease doxorubicin-induced cardiotoxicity	AA	Cardiotoxicity (clinical and MUGA scans), RR to assess potential tumor protection	Placebo RCT
Docetaxel				
(1996, N)	Breast cancer, second-line treatment	AA	RR	SAT
(1996, S)	Breast cancer, second-line treatment	Regular	RR, TTP, survival	RCT
(1999, S)	NSCLC, second-line treatment	Regular	TTP and survival	RCT
Epirubicin (1999, N)	Breast cancer, adjuvant treatment	Regular	DFS and survival	RCT
Exemestane (1999, N)	Breast cancer, second-line treatment	Regular	RR and TTP	DB RCT
Fludarabine (1991, N)	Refractory chronic lymphocytic leukemia	Regular	CR and PR, improvement in anemia and thrombocytopenia	SAT
Fulvestrant (2002, N)	Breast cancer, second-line treatment	Regular	RR and TTP	DB RCT
Gemcitabine				
(1996, N)	Pancreatic cancer	Regular	Survival, clinical benefit response (composite end point including pain, performance status, and weight gain)	RCT
(1998, S)	NSCLC	Regular	RR, TTP, survival	RCT
Gemtuzumab ozogamicin (2000, N)	Acute myelogenous leukemia, second-line treatment in elderly patients	AA	CR and CRp (CR with decreased platelets)	SAT
Idarubicin (1990, N)	Acute myelogenous leukemia	Regular	CR and survival	RCT
Imatinib mesylate				
(2001, N)	CML, blast phase, accelerated phase, and failing interferon	AA	Hematologic response and cytogenetic response	SAT
(2002, S)	Gastrointestinal stromal tumors (GISTs)	AA	RR	SAT
Irinotecan				
(1996, N)	Colon cancer, second-line treatment	AA	RR	SAT
(1998, S)	Colon cancer, second-line treatment	Regular	Survival	RCT
(2000, S)	Colon cancer, first-line treatment	Regular	Survival	RCT
Letrozole				
(1997, N)	Breast cancer, second-line treatment	Regular	RR, TTP	DB RCT
(2001, S)	Breast cancer, first-line treatment	Regular	RR, TTP	DB RCT
Leucovorin (1991, S)	In combination with FU for metastatic colon cancer	Regular	Survival	RCT
Liposomal cytarabine (1999, N)	Lymphomatous meningitis	AA	Cytologic response	RCT
Liposomal daunorubicin (1996, N)	Kaposi's sarcoma	Regular	RR, TTP, cosmesis	RCT
Liposomal doxorubicin				
(1995, N)	Kaposi's sarcoma, second-line treatment	AA	RR	SAT
(1999, S)	Ovarian cancer, refractory	AA	RR	SAT
Methoxsalen (1999, N)	Cutaneous T-cell lymphoma, skin lesions	Regular	RR based on overall skin scores, improvement in edema and scaling, and fissure resolution	SAT

Table 2. End Points for Approval of Oncology Drug Marketing Applications January 1, 1990 to November 1, 2002 (Continued)

Drug (year, application type)	Indication	Approval Type	End Points Supporting Approval	Trial Design
Mitoxantrone (1996, S)	Patients with pain from hormone-refractory advanced prostate cancer	Regular	Decrease in pain	RCT
Oxaliplatin (2002, N)	Colon cancer progressing after bolus 5 FU/LV and irinotecan	AA	RR and TTP	RCT
Paclitaxel				
(1992, N)	Refractory ovarian cancer	Regular	Durable PRs in bulky tumors	SAT
(1994, S)	Breast cancer, second-line treatment	Regular	TTP	Dose-response RCT
(1997, S)	Kaposi's sarcoma	Regular	RR and clinical benefit (assessed by evaluating photographs)	SAT
(1998, S)	Ovarian, first-line	Regular	Survival	RCT
(1998, S)	NSCLC	Regular	TTP and survival	RCT
(1999, S)	Breast cancer, adjuvant therapy	Regular	DFS and survival	RCT
Pamidronate				
(1995, N)	Skeletal morbidity of osteolytic bone metastases of myeloma	Regular	SRE	Placebo RCT
(1996, S)	Skeletal morbidity of osteolytic bone metastases of breast cancer	Regular	SRE	Placebo RCT
Pentostatin				
(1991, N)	Hairy cell leukemia, second-line treatment	Regular	CR and CR duration, improvement in hemoglobin, WBC, platelets	SAT
(1993, S)	Hairy cell leukemia, first-line treatment	Regular	CR and CR duration	RCT
Porfimer sodium				
(1995, N)	For PDT in completely obstructed esophageal cancer	Regular	Luminal response and palliative response	SAT
(1998, S)	For PDT of CIS and microinvasive NSCLC	Regular	CR and CR duration	SAT
(1998, S)	For PDT of completely or partially obstructing endobronchial NSCLC	Regular	Luminal response and pulmonary symptom severity scale	RCT
Talc (1997, N)	To prevent recurrence of malignant pleural effusion	Regular	Recurrence of effusion	RCT
Tamoxifen				
(1990, S)	Node-negative breast cancer, adjuvant therapy	Regular	DFS	Placebo RCT
(1998, S)	To reduce the incidence of breast cancer in women at high risk	Regular	Occurrence of breast cancer	Placebo RCT
(2000, S)	To reduce the incidence of breast cancer after treatment of DCIS	Regular	Occurrence of breast cancer	Placebo RCT
Temozolomide (1999, N)	Anaplastic astrocytoma, refractory	AA	RR	SAT
Teniposide (1992, N)	Refractory childhood acute lymphoplastic leukemia	Regular	CR and CR duration	SAT
Topotecan				
(1996, N)	Ovarian cancer, second-line treatment	Regular	RR, TTP, survival	RCT
(1998, S)	Small cell lung cancer, second-line treatment	Regular	RR and response duration, symptom improvement	RCT
Toremifene (1997, N)	Breast cancer, first-line treatment	Regular	RR, TTP	RCT
Tretinoin (1995, N)	Acute promyelocytic leukemia, second-line treatment	Regular	CR	SAT
Vinorelbine (1994, N)	NSCLC	Regular	Survival	RCT
Zoledronic acid (2002, N)	Multiple myeloma and bone metastases from solid tumors	Regular	SRE	

Abbreviations: N, new drug application; RR, response rate; SAT, single-arm trial; RCT, randomized controlled trial; S, supplement; CR, complete response; TTP, time to progression; AA, accelerated approval; DB, double blind; ER, estrogen receptor; DFS, disease-free survival; CML, chronic myelogenous leukemia; PFS, progression-free survival; MUGA, multiple-gated acquisition; FU, fluorouracil; LV, leucovorin; PDT, photodynamic therapy; CIS, carcinoma-in-situ; NSCLC, non–small-cell lung cancer; DCIS, ductal carcinoma-in-situ; SRE, skeletal-related event.

ovarian cancer. Altretamine was approved on the basis of a small number of durable complete responses in patients with refractory ovarian cancer. Before the AA regulations, paclitaxel was approved on the basis of durable partial responses in refractory ovarian cancer.

Pentostatin, cladribine, tretinoin, and arsenic trioxide were granted regular approval for treatment of hematologic malignancies on the basis of durable complete responses, many lasting 6 months or longer. In these settings, durable complete responses were considered an established surrogate for a better life and possibly a longer life. Fludarabine was approved for refractory chronic lymphocytic leukemia on durable complete and partial responses associated with improvements in anemia and thrombocytopenia.

Regular approval of topotecan in refractory small-cell lung cancer was based on both response rate and symptom benefit. The ODAC indicated that the topotecan tumor response (20% with median response duration of 14 weeks) was associated with decreased morbidity and mortality in this disease setting of rapid clinical progression and short survival.[8]

A randomized controlled trial comparing two doses of paclitaxel and demonstrating an advantage in TTP with the higher dose was the approval basis for paclitaxel for second-line treatment of advanced metastatic breast cancer. Bleomy-

Table 3. Summary of End Points for Regular Approval of Oncology Drug Marketing Applications January 1, 1990 to November 1, 2002

Total	57
Survival	18
RR	26
RR alone	10
RR + decreased tumor-specific symptoms	9
RR + TTP	7
Decreased tumor-specific symptoms	4
DFS	2
TTP	1
Recurrence of malignant pleural effusion	2
Occurrence of breast cancer	2
Decreased impairment of creatinine clearance	1
Decreased xerostomia	1

Abbreviations: RR, response rate; TTP, time to progression; DFS, disease-free survival.

cin and talc were approved for treatment of malignant pleural effusions on the basis of time-to-recurrence of malignant pleural effusion, an end point closely related to TTP and symptom development.

DFS. DFS may be the approval basis in the adjuvant setting if a high proportion of symptomatic recurrences is present or if a strong correlation with survival exists. A relatively long interval between recurrence and death also supports the use of DFS. DFS has supported approval of applications for adjuvant therapy for breast cancer and the use of busulfan in the transplant setting for chronic myelogenous leukemia. In the anastrozole application for adjuvant treatment of breast cancer in postmenopausal women, DFS supported AA rather than regular approval because the follow-up duration was insufficient for the latter type of approval.

Time to treatment failure. No approvals were based on time to treatment failure (TTF). TTF is usually defined as the time from randomization to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death. TTF is a composite end point that is seldom useful for regulatory purposes. Discontinuance because of toxicity, for example, has no direct relevance to effectiveness. Because the FDA must determine that approved drugs are both safe and effective, separate analyses of the efficacy and safety components of TTF (TTP, survival, and toxicity) are required for oncology drug marketing application approval.

Relief of tumor-specific symptoms or improvement in laboratory findings. Relief of tumor-specific symptoms alone was the basis for regular approval in four of 57 applications and provided support for regular approval in nine other applications. Mitoxantrone's approval for treatment of hormone-refractory prostate cancer was based solely on pain relief. In a randomized controlled trial, the approval end point was a two-point decrease on a six-point pain scale lasting at least 6 weeks. Pamidronate and zoledronate were approved for prevention of morbidity from bone lesions of multiple myeloma and solid tumors on the basis of a composite symptom benefit end point described in the section on Composite Clinical Benefit End Points.

Several applications for treatment of cutaneous manifestations of malignancy were approved on response rates augmented by descriptions of clinical benefit in responding individual patients. Alitretinoin gel was approved for treatment of cutaneous Kaposi's sarcoma (KS) on the basis of cutaneous tumor responses. Cutaneous tumor responses were considered a clinical benefit because symptomatic skin lesions of the hands, feet, groin, and other areas responded with symptomatic relief. Cosmetic improvement of disfiguring lesions was also considered evidence of clinical benefit. Paclitaxel was approved for second-line treatment of KS on the basis of response rate and retrospective collection of symptom relief information; for example, improved ambulation with KS involving the feet, healing of cutaneous ulcers, and resolution of disfiguring facial lesions.

In first-line treatment of KS, liposomal daunorubicin was approved on the basis of a randomized controlled trial comparing it with standard combination chemotherapy using the end points of response rate, TTP, and photographic evidence of cosmesis and other clinical benefit. Liposomal doxorubicin received AA rather than full approval on the basis of tumor response rates that were not accompanied by clinical benefit data. Bexarotene capsules and bexarotene gel received regular approval for treatment of cutaneous manifestations of cutaneous T-cell lymphoma on the basis of a composite assessment of index lesion severity that assessed erythema, scaling, elevation, and lesion pigmentation. Methoxsalen solution was approved for use in a photopheresis system for treatment of skin manifestations of cutaneous T-cell lymphoma on the basis of overall skin score responses and improvement in edema, scaling, and resolution of fissures.

Tumor responses plus a diversity of evidence of clinical benefit supported the regular approval of several applications. Luminal tumor responses supported by relief of obstructive symptoms were the basis for regular approval of porfirmer sodium for photodynamic therapy in patients with completely obstructing esophageal cancer and completely or partially obstructing endobronchial non–small-cell lung cancer. Palliation of obstructing esophageal cancer was defined as a two-point change on a five-point dysphagia scale. In endobronchial cancer, palliation was defined as a two-point change on five-point pulmonary symptom severity scales for dyspnea, cough, or hemoptysis. Amifostine, a protectant to decrease xerostomia after radiation therapy of head and neck cancer, was approved on xerostomia scores with support from measurements of salivary production. Maintenance of normal creatinine clearance was the approval basis for amifostine to decrease the incidence of cisplatin-induced renal function impairment.

Composite Clinical Benefit End Points. A composite end point may be appropriate when the drug's benefit is multifaceted. The end-point components should be related and generally of similar clinical importance. Pamidronate was the first bisphosphonate drug approved to decrease morbidity of skeletal metastases; it was initially approved for myeloma and, subsequently, for breast cancer. The applicant developed the end-point SREs, which included one or more of the following: pathologic fractures, radiation therapy for local pain, surgery to stabilize near-fractures, or spinal cord compression. In the applicant's myeloma and breast cancer trials, treatment with pamidronate resulted in both a decrease in the proportion of patients with at least one SRE and an increase in time to first SRE. Recently, a

second bisphosphonate, zoledronate, was approved on the basis of similar end points. Composite end points can also be constructed from symptoms. Clinical benefit response—a composite end point of pain, performance status, and weight gain—was supportive of regular approval of gemcitabine for treatment of pancreatic cancer, although a small, statistically significant survival improvement was the primary approval basis.

Quality of life. Although many of the 53 marketing application approvals that were based on nonsurvival end points used surrogate end points for a better life, no approvals were based on instruments measuring health-related quality of life. Although quality-of-life (QOL) assessments using global QOL instruments often have been submitted in oncology drug applications, this aspect of the clinical trials has generally not been well conducted. Problems have usually included unblinded assessment, large amounts of missing data, and poorly defined prospective analytic plans. Applications including QOL claims should use QOL instruments validated for the intended purpose: to measure QOL differences in randomized studies of patients with a specific cancer type. Changes in QOL scores should be defined in clinically meaningful terms. QOL data are most credible when patients and investigators are blinded to treatment assignment, when QOL findings are duplicated in trials using the same instrument, and when QOL analytic plans are prospectively detailed.[9]

Tumor markers. The FDA has not accepted changes in tumor markers alone as a basis for marketing approval of oncology drugs. Although tumor markers have not been used alone as a basis for marketing approval, the FDA has permitted applicants to include tumor markers as elements in composite end points. For instance, women with ovarian cancer often show clinical deterioration from progression of nonmeasured tumor. In blinded RCTs in advanced refractory ovarian cancer, the FDA has recently allowed use of a composite end point that includes CA-125 levels. The occurrence of certain clinical events (a significant decrease in performance status or bowel obstruction) coupled with a sustained increase in CA-125 levels is considered disease progression.

End Points Used for AA

The 14 AAs of oncology drugs between January 1, 1990, and November 1, 2002, and the surrogate end points that were the basis of the AAs are listed in Table 4. None of the drugs has been removed from the market. Four AA applications subsequently received regular approval. Two applications subsequently have been converted to regular approval in the same patient population. Ten of the 14 AAs were based on tumor responses in single-arm phase II studies in refractory cancers. The AA for liposomal cytarabine was based on cytologic tumor response in a small RCT in patients without prior drug treatment. Oxaliplatin in combination with fluorouracil/leucovorin (FU/LV) received AA on the basis of superior response rate and TTP compared to FU/LV in an RCT. The AA for dexrazoxane was based on cardiac protection demonstrated in RCTs. Although cardiac protection would qualify a drug for regular approval, dexrazoxane received AA because its potential for tumor protection was not adequately investigated. The AA of anastrozole as adjuvant therapy of postmenopausal women with estrogen receptor–positive breast cancer was based on DFS. DFS would ordinarily support regular approval for this indication, but follow-up was inadequate for regular approval.

DISCUSSION

This report documents the FDA's acceptance of a variety of end points for oncology drug approval over the last 13 years. An improvement in overall survival is the gold standard end point

Table 4. End Points for Accelerated Approval of Oncology Drug Marketing Applications January 1, 1990 to November 1, 2002

Drug	Indication	Surrogate End Point	Trial Design	Year	NDA or S
Liposomal doxorubicin	Kaposi sarcoma, second-line treatment	Response	SAT	1995	NDA
Dexrazoxane	Cardiac protection, anthracycline	Cardiac ejection fraction, CHF, Response	Placebo RCT	1995	NDA
Docetaxel	Breast cancer, second-line treatment	Response	SAT	1996	NDA
Irinotecan	Colon cancer, second-line treatment	Response	SAT	1996	NDA
Amifostine	To decrease cisplatin-induced renal toxicity, NSCLC	Response	SAT	1996	S
Capecitabine	Breast cancer, refractory	Response	SAT	1998	NDA
Liposomal cytarabine	Lymphomatis meningitis	Cytologic response	RCT	1999	NDA
Temozolomide	Anaplastic astrocytoma, refractory	Response	SAT	1999	NDA
Liposomal doxorubicin	Ovarian cancer, refractory	Response	SAT	1999	S
Gemtuzumab ozogamicin	AML, second-line treatment, elderly	CR and CRp (CR with decreased platelets)	SAT	2000	NDA
Imatinib mesylate	CML, blast phase, accel. phase, and failing interferon	Hematologic and cytogenetic response	SAT	2001	NDA
Imatinib mesylate	GIST	Response	SAT	2002	S
Oxaliplatin	Colon cancer after bolus 5 FU/LV and irinotecan	Response and TTP	RCT	2002	NDA
Anastrozole	Adjuvant therapy of postmenopausal breast cancer	Disease-free survival	RCT	2002	S

Abbreviations: NDA, new drug application; S, supplement; SAT, single-arm trial; RCT, randomized controlled trial; CR, complete response; TTP, time to progression; CHF, congestive heart failure; NSCLC, non–small-cell lung cancer; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor; FU, fluorouracil; LV, leucovorin.

for a new oncology drug. The importance of a clinically meaningful survival improvement is unquestioned. Survival can be assessed with 100% accuracy for the event and with nearly 100% accuracy for the time of the event. Despite its importance, 68% (39 of 57) of the regular approvals and all of the 14 AAs for oncology drugs were based on end points other than survival (January 1, 1990 to November 1, 2002). Excluding the seven applications for either chemoprotectants or bisphosphonates, 68% (34 of 50) of the regular approvals and 12 AAs were based on nonsurvival end points. Including all oncology drugs and both regular approvals and AAs, nonsurvival end points were the basis for 75% (53 of 71) of oncology drug approvals.

Objective tumor response rate has been the approval basis in 46% (26 of 57) of oncology drug regular approvals. Objective tumor response has been the approval basis for three general categories of indications. One category is complete responses of adequate duration in refractory hematologic malignancies and in refractory ovarian cancer. The second category is partial responses in advanced breast cancer achieved with hormonal drugs, which are considered to be less toxic than conventional cytotoxic anticancer drugs. The third category is partial responses supported by tumor-specific symptom relief.

Objective tumor response became a widely accepted measure of cancer chemotherapy activity in the early 1980s after Miller et al[10] established standard response criteria on the basis of bidimensional tumor measurements. More recently, response criteria on the basis of unidimensional measurements have been widely adopted by investigators and have been used in protocols intended to support drug approval.[11] Because objective responses are infrequent in the absence of treatment, response rates are accepted as a valid measure of antitumor activity in single-arm phase II studies. However, response rates are probably seldom true surrogates for clinical benefit; true surrogates should capture the full effect of treatment benefit, and there is no evidence that response rates do so.[12] Some patients with nonresponding tumors may benefit from delay in tumor progression, which explains survival benefits sometimes observed despite relatively low response rates.[13]

Partial tumor response has been the approval basis in 10 of 14 applications given AA. Irinotecan and docetaxel, single agents for second-line treatment of metastatic colorectal cancer and metastatic breast cancer, respectively, were granted AA on partial tumor responses in refractory tumors in single-arm trials. These single agents each subsequently demonstrated improved survival in RCTs in the same indication initially awarded AA. These are the only AA applications for which this has occurred.

TTP, unlike survival, is documented before patients change therapies, and results cannot be obscured by subsequent or cross-over therapies. TTP may be a preferred end point for evaluating cytostatic agents because it does not require tumor size reduction. Progression occurs months to years before death, and smaller patient numbers are required to show improved TTP than to show improved survival. Delaying cancer progression may be of direct benefit because cancer progression is inevitably followed by morbidity and/or death. TTP is measured in all patients (not just responders) and may be a better predictor of overall benefit than response rate.

Because historic estimates of TTP are unreliable, TTP must be evaluated in randomized controlled trials. Careful assessment of progression at frequent intervals is labor intensive and expensive. Small incremental improvements in TTP may be of questionable clinical value, and unblinded trials may introduce assessment bias.[14] Unequal time interval ascertainment of progression between treatment arms may occur, and asymmetry of censoring may introduce additional bias. Patients who die without documentation of disease progression often have the date of death recorded as the progression date, thereby inappropriately crediting an unknown amount of additional progression-free time.

Studies using symptom end points have been successful in selected indications, but present difficulties. Frequently, clinical trial eligibility criteria discriminate against entry of symptomatic patients on the basis of poor performance status. Tumor-related symptoms may be evidence of advanced disease and predict poor clinical outcomes and rapid demise. Symptomatic patients are difficult to accrue and often prematurely discontinue studies, complicating interpretation of results. Problems with missing data are often uncorrectable.[15] The FDA strongly encourages the development of additional end points to describe symptom-based clinical benefit in cancer patients and will work with sponsors and investigators to explore possibilities.

The AA regulations were initially applied to the approval of AIDS drugs. These early AAs used a different drug approval paradigm than that commonly implemented in oncology. AA was based on an interim analysis of a surrogate end point evaluated in randomized controlled trials. Subsequent demonstration of clinical benefit and regular drug approval usually were based on final analyses of a nonsurrogate or established surrogate end point in the same trials. In contrast, AA in oncology has usually relied on response rate as the surrogate end point in patients with highly refractory cancer without available therapies, usually determined in nonrandomized trials with limited patient numbers. Clinical benefit is to be subsequently demonstrated in randomized trials after drug approval, usually in patients with less refractory tumors.

The use of results in highly refractory tumors as the basis for drug approval is potentially problematic. These tumors are composed of heterogeneous refractory cell populations that approach the plateau of the sigmoidal growth curve.[16] Potentially effective therapies could be overlooked in such populations with marginal response rates, and demonstrating survival benefits in refractory patient populations may be difficult.[17] Nonrandomized phase II studies also present problems. After AA on the basis of nonrandomized phase II trials, the required confirmatory RCT in the approved population may not be feasible because of the drug's commercial availability outside of the trial. Small phase II studies provide only limited safety data.

An alternative to the nonrandomized trial in refractory patients is to implement the paradigm used in AIDS. AA is based on an interim analysis of a surrogate end point (eg, response rate and TTP) in a randomized trial, with the ultimate clinical benefit (eg, survival) demonstrated at the trial's completion. The randomized trial design allows use of AA in less refractory populations, can detect an advantage compared to available therapy, and can assess time-to-event end points that are not interpretable in a

single-arm trial. Single-arm studies are generally useful for AA only when no therapy is available. The randomized study also allows evaluation of drug combinations; for example, standard drug versus standard drug plus investigational drug. This design led to the recent AA of oxaliplatin in combination with FU/LV for advanced colorectal cancer.

The FDA has used several end points other than survival for approval of oncology drug marketing applications. These end points have included tumor response, TTP, DFS, recurrence of malignant pleural effusion, occurrence of breast cancer, decreased morbidity of bone metastases, and pain relief. Improvement in anemia, thrombocytopenia, and cosmesis; palliation of dysphagia and pulmonary symptoms; and decreased chemotherapy toxicities have also served as primary approval end points. The selection of an end point should attempt to minimize subjectivity and bias and preserve clinical benefit observed in earlier drug approvals for the indication. Blinding of treatment arms is frequently difficult to implement in oncology trials because of the different treatment toxicities and schedules in randomized trials. Findings that may ensure the assessment of true treatment effects include duplication of trial results, consistency of treatment effects in patient subsets, highly statistically persuasive results, and consistency between primary and secondary end points.

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