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REVIEW ARTICLE

Ultimate Fate of Oncology Drugs Approved by the US Food and Drug Administration Without a Randomized Trial

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ABSTRACT

Purpose
To approve a new anticancer drug, the US Food and Drug Administration often requires randomized trials. However, several oncology drugs have been approved on the basis of objective end points without a randomized trial. We reviewed the long-term safety and efficacy of such agents.

Methods
We searched the Web site of the US Food and Drug Administration's Center for Drug Evaluation and Research and MEDLINE for initial applications of investigational anticancer drugs from 1973 through 2006.

Results
Overall, 68 oncology drugs, excluding hormone therapy and supportive care, were approved, including 31 without a randomized trial. For these 31 drugs, a median of two clinical trials (range, one to seven) and 79 patients (range, 40 to 413) were used per approval. Objective response was the most common end point used for approval; median response rate was 33% (range, 11% to 90%). Thirty drugs are still fully approved. United States marketing authorization for one drug, gefitinib (an epidermal growth factor receptor [EGFR] inhibitor), was rescinded after a randomized trial showed no survival improvement; however, this trial was performed in unselected patients, and it was subsequently demonstrated that patients with EGFR mutation are more likely to respond. Nineteen of the 31 drugs have additional uses (per National Comprehensive Cancer Network or National Cancer Institute Physician Data Query guidelines), and subsequent formal US Food and Drug Administration approvals were obtained for 11 of these (range, one to 18 new indications). No drug has demonstrated safety concerns.

Conclusion
Nonrandomized clinical trials with definitive end points can yield US Food and Drug Administration approvals, and these drugs have a reassuring record of long-term safety and efficacy.

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INTRODUCTION

The United States Food and Drug Administration has several mandates for developing oncology treatments, including the approval of claims made about the use of a particular drug.[1] To approve a new product, the US Food and Drug Administration requires adequate and well-controlled trials in support of marketing claims, in addition to proof of efficacy and safety. Randomized clinical trials demonstrating a statistically significant improvement in survival are considered the "gold standard" for approval of anticancer drugs by the US Food and Drug Administration.[2] However, using the randomized trial approach, several oncology drugs have been US Food and Drug Administration-approved on the basis of relatively small differences (ie, weeks to 2 to 3 months of survival or relapse-free survival).[3-12]

Several anticancer drugs have been approved with no randomized trial employing a comparator arm consisting of an established therapy, best supportive care, or a placebo. The argument against nonrandomized trials is that the data obtained from them may be biased,[2] leading to the approval of drugs that, in the long run, are not beneficial because of unforeseen toxicities or because response and/or survival are not as robust as inferred from the nonrandomized trial results.

Most notably, randomized trials reduce bias that might skew results in nonrandomized trials because[13,14] they allow unbiased random allocation to intervention groups; patients are normally analyzed within the group to which they are allocated, irrespective of whether they experienced the intended intervention (intention-to-treat analysis); the analysis is focused on estimating the size of the difference

in predefined outcomes among intervention groups; the randomized groups have balanced characteristics; and blinding enhances objectivity.[13-15] In contrast, randomized, controlled trials are disadvantaged by several features[16]: the requirement for a large number of patients, making them expensive and time consuming; the tendency to ignore genotypic differences in patients and to look for small survival differences; the ethical questions raised when one arm is suspected to have inferior response[17]; and their propensity to exclude certain groups of patients, such as those with comorbidities, which later may limit the generalizability of the research.[15] In addition, randomized trials are not free from selection bias, as a result of differential loss to follow-up or patient dropout after random assignment.[18]

However, some investigators believe that the large number of patients is not an inherent disadvantage of randomized trials, as the sample size is driven by the magnitude of difference in effect that the trial is designed to detect. A randomized trial designed to detect a large difference in effect might not require many more patients than a nonrandomized trial. Oncology has been at the forefront of incorporating genotypic differences when justified by the prevailing science. One example is the recent amendment of all National Cancer Institute–sponsored trials of anti-EGFR antibodies in colorectal cancer to exclude patients with *KRas* mutations. Ethical questions that could be raised "when one arm is suspected to be inferior" constitute the entire basis of equipoise as a fundamental requirement in randomized trials, and the exclusion of certain patient groups, such as those with comorbidities, is not a feature unique to randomized trials and is even more likely to occur in phase II (nonrandomized) studies of investigational agents.

The question then arises as to whether it is reasonable to approve a drug for cancer without a randomized trial, and if so, under what conditions. This article reviews the experience with anticancer drugs that have been approved by the US Food and Drug Administration without randomized trials employing a comparator arm consisting of standard therapy, supportive care, or a placebo. Our review suggests that anticancer drugs approved without randomized trials have proven to be safe and efficacious in the long-term.

METHODS

We searched the Web site of the Center for Drug Evaluation and Research, US Food and Drug Administration,[19] and MEDLINE for all initial applications of investigational new anticancer drugs seeking US Food and Drug Administration approval. We analyzed approvals for a period of 34 years, from January 1973 through December 2006, providing follow-up data for analysis for 2+ to 35+ years. We selected 1973 as the initial year of our search because reporting of detailed drug information on the Web site of the US Food and Drug Administration begins with that year. Hormone therapy and supportive agents were excluded. Specifically, we identified US Food and Drug Administration–approved new applications for anticancer agents based on studies other than randomized controlled trials that employed a comparator arm with standard therapy, supportive care, or a placebo.

We reviewed the use of each of these agents and compared initially approved indications to current clinical indications. To define current indication guidelines, we queried two major guideline sources for cancer treatment. We accessed the National Comprehensive Cancer Network (NCCN) Web site for the 2008 guidelines[20] and examined the use of each agent in the current treatment regimen of choice for each specific cancer. For diseases not outlined in this guideline, such as chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL), we consulted the National Cancer Institute comprehensive cancer database Physician Data Query (PDQ). The PDQ provides comprehensive, peer-reviewed, evidence-based information about the treatment of these leukemias. We identified the current clinical usage of these drugs, as extracted from the NCCN Clinical Practice Guidelines in Oncology, the NCCN Drugs and Biologics Compendium, and the National Cancer Institute Physician Document Query.[21]

RESULTS

Thirty-one new molecules were approved as anticancer drugs or biologics from January 1973 through December 2006, without randomized clinical trials that used a comparator arm with a different therapy, supportive care, or a placebo (Table 1), including 23 drugs that did not have accelerated approval.[22-36] During this period, a total of 68 drugs that were not hormone therapy or supportive care were approved for cancer. Nearly half of the drugs approved on the basis of nonrandomized trial data were initially approved for leukemias (n = 13; 42%; Table 2).[37-40]

Figure 1 is a summary of all approved "new molecules" and "claims for new indications" of available molecules from 1949 to 2007.[41] The number of approved new molecules increased significantly after 1995. This increase appears to be, at least in part, due to the introduction of the US Food and Drug Administration's accelerated approval program in 1992, with the first anticancer drug (liposomal doxorubicin) being approved under this program in 1995.[36] From 1992 to 2007, a total of 19 new molecules received accelerated approval. Eight (42%) of these 19 drugs were approved in the absence of randomized, controlled trials having a therapeutic, supportive care, or placebo arm: liposomal doxorubicin, irinotecan, temozolamide, tositumomab, clofarabine, nelarabine, bortezomib, and gefitinib.[21] The remaining 11 drugs were docetaxel, capecitabine, denileukin diftitox, liposomal cytarabine, alemtuzumab, imatinib,[42,43] oxaliplatin, pemetrexed, cetuximab,[12] thalidomide, and sunitinib.[21]

Of the 31 drugs initially approved without a randomized clinical trial that used a comparator therapeutic, supportive care, or placebo arm, all except one are still fully approved. One drug, gefitinib, had its approval partially rescinded due to efficacy concerns.[44] Only three additional drugs (liposomal doxorubicin for Kaposi's sarcoma, mitomycin for pancreatic carcinoma, and doxorubicin for ovarian cancer) are no longer recommended for use, per NCCN guidelines, for their initial US Food and Drug Administration indications, because the discovery of more efficacious drugs supplanted their use.[44-47] However, these three drugs have new uses (Table 2), and liposomal doxorubicin is still utilized for rapidly progressive or widely disseminated Kaposi's sarcoma.[20,48] In no case was a drug's approval revoked due to a safety concern.

Overall, 19 of 31 drugs have additional uses (per NCCN or NCI PDQ guidelines; Table 2). Subsequent formal US Food and Drug Administration approvals were obtained for 11 of the drugs, with a range of 1 to 18 new uses. In some cases, new indications or uses included noncancer conditions, such as rheumatoid arthritis (rituximab), and hepatitis B and C (interferon alfa).

For drugs the US Food and Drug Administration approved without a randomized, controlled trial from 1973 through 2006, a median of two clinical studies per drug were conducted to obtain approval (range, one to seven clinical trials; Table 1). The median number of patients studied per drug approval was 79 (range, 40 to 413 patients). For most of the drugs, response rate was the primary end point, although other end points, such as disease-free survival, were used for

Table 1. New Anticancer Molecules Approved by the FDA From 1973 to 2006 (excluding hormone therapy) Without Randomized Controlled Trials That Used a Comparator Treatment Arm

Drug	Year of Approval	Indication	Main Mechanism	Pharmacologic Class	Phase	End Point
Bleomycin[22]	1973	Testicular cancer	Antibiotic, DNA and RNA synthesis, DNA repair, alkylating agent	Cytotoxic	II	RR
Mitomycin[23]	1974	Stomach, pancreas	Antibiotic, DNA and RNA synthesis, DNA repair, alkylating agent	Cytotoxic	II	RR
Doxorubicin[24,25]	1974	Ovarian cancer	Anthracycline	Cytotoxic	II	RR
Cisplatin[26]	1978	Testicular cancer	Alkylating agent, production of intrastrand crosslinks, and formation of DNA adducts	Cytotoxic	II	RR
Asparaginase[27]	1978	ALL	Antimetabolite, enzyme, depletion of asparagine, cell cycle arrest in G1	Cytotoxic	III*	RR
Etoposide[19]	1983	Testicular cancer	Topoisomerase II inhibitor	Cytotoxic	II	RR
Interferon alfa 2b[28-30]	1986	HCL	Biologic response modifier	Cytokine	II	Reduction of hairy cell index and increased time to relapse
Ifosfamide	1988	Germ cell testicular cancer	Alkylating agent crosslinking DNA strands	Cytotoxic	II	DFS
Altretamine	1990	Ovarian cancer	Antineoplastic s-triazine derivative DNA and RNA synthesis	Cytotoxic	II	RR
Fludarabine	1991	B-cell lymphocytic leukemia	Antimetabolite, nucleoside analog DNA polymerase alpha, ribonucleotide reductase and DNA primase	Cytotoxic	I/II	RR
Pentostatin	1991	HCL	Adenosine deaminase inhibitor	Cytotoxic	II	RR and duration of response
Aldesleukin	1992	Renal cell carcinoma	Recombinant interleukin-2, multiple immunologic effects	Cytokine	II	RR
Cladribine[31]	1993	HCL	Antimetabolite, nucleoside analog resistant to adenosine deaminase	Cytotoxic	II	RR
Pegaspargase	1994	ALL	Antimetabolite, enzyme, depletion of asparagine, cell cycle arrest in G1	Cytotoxic	II	RR
Liposomal doxorubicin	1995	AIDS-related Kaposi's sarcoma	Anthracycline	Cytotoxic	II	RR
Tretinoin, ATRA	1995	APL	Interacts with retinoic acid receptors	Retinoid	II	RR
Irinotecan[32]	1996	Colon or rectum	Topoisomerase I inhibitor	Cytotoxic	II	RR
Rituximab	1997	CD20 (+) non-Hodgkin's lymphoma	Binds to CD20 antigen	mAb	II	RR
Busulfan IV[33]	1999	Allogeneic HSCT for CML	Alkylating agent	Cytotoxic	II	Myeloablation, engraftment
Methoxsalen	1999	CTCL	Tricyclic furocoumarin inhibits DNA synthesis	Photosensitizing agent	II	RR
Bexarotene capsules	1999	CTCL	Selective retinoid X receptor ligand	Retinoid	II	RR
Temozolomide	1999	Anaplastic astrocytoma	Alkylating agent	Cytotoxic	II	PFS, RR
Arsenic trioxide	2000	APL	DNA fragmentation and degradation of PML-RAR alpha, multiple targets	Retinoid	II	RR

(continued on following page)

Table 1. New Anticancer Molecules Approved by the FDA From 1973 to 2006 (excluding hormone therapy) Without Randomized Controlled Trials That Used a Comparator Treatment Arm (continued)

Drug	Year of Approval	Indication	Main Mechanism	Pharmacologic Class	Phase	End Point
Gemtuzumab ozogamicin	2000	CD33 (+) AML	Binds to CD33	mAb conjugated with calicheamicin	II	RR
Tositumomab[26]	2003	CD20+, follicular, non-Hodgkin's lymphoma	Binds to CD20	Radioimmunotherapeutic mAb	II	RR, TTP
Bortezomib	2003	Myeloma	Proteasome inhibitor	Targeted	II	RR
Gefitinib[34,35]	2003	Non–small-cell lung cancer	EGFR tyrosine kinase inhibitor	Small molecule TKI	II†	RR, symptoms
Clofarabine[26]	2004	ALL	Anti-metabolite (purine antagonist)	Cytotoxic	II	RR
Lenalidomide[26]	2005	Low- or intermediate-1-risk MDS with a del(5q)	Immunodulator	Immunomodulatory	II	RBC transfusion independence
Nelarabine[26]	2005	T-cell ALL and T-cell lymphoblastic lymphoma	Anti-metabolite (prodrug or ara-G)	Cytotoxic	II	RR
Vorinostat	2006	CTCL	Epigenetic	HDAC inhibitor	I and II	RR

Abbreviations: FDA, US Food and Drug Administration; RR, response rate; ALL, acute lymphocytic leukemia; HCL, hairy cell leukemia; APL, acute promyelocytic leukemia; DFS, disease-free survival; mAb, monoclonal antibody; HSCT, hematopoietic stem cell transplantation; CML, chronic myelogenous leukemia; CTCL, cutaneous T-cell lymphoma; PFS, progression-free survival; PML-RARA, promyelocytic leukemia-retinoic acid receptor α; TTP, time to progression; AML, acute myelogenous leukemia; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; MDS, myelodysplastic syndrome; RBC, red blood cell; HDAC, histone deacetylase.

*Phase III open-label, double arm (randomly assigned to several dosages of asparginase, no comparator).

†Third line: two randomized, double-blind, phase II, multicenter studies comparing two doses of gefitinib tablets (250 *v* 500 mg/day) two of 216 patients.

individual agents. The median objective response rate was 33% (range, 11% to 90%).

The median response rate and the median number of patients with hematologic malignancies were 39% and 128 patients, respectively, and in solid tumors 26% and 120 patients, respectively.

DISCUSSION

This review identified anticancer drugs approved by the US Food and Drug Administration without randomized, controlled comparisons to a reasonable alternative (eg, standard of care, placebo, or best supportive care). Cancer is now the leading cause of death in persons under the age of 85 years in the United States,[49] and worldwide, almost 11 million people are diagnosed with cancer annually.[50] Because more than 40% of people in the United States develop cancer during their lifetimes, and more than half a million Americans succumb to this illness each year, there is a great sense of urgency in the quest to identify and approve new treatments.[49]

Of the 31 drugs approved without a randomized clinical trial from 1973 through 2006, gefitinib is the only drug whose approval was later rescinded after the completion of a randomized, controlled trial.[51] The initial trial that led to gefitinib's approval examined gefitinib monotherapy for the treatment of advanced non–small-cell lung cancer (NSCLC) after failure or intolerance of platinum-containing and docetaxel chemotherapies.[34,35] The overall response rate was 10.6% (median duration, 7 months) and, hence, gefitinib monotherapy was recommended in the setting of third-line therapy for lung cancer.[34] After initial approval, the Iressa Survival Evaluation in Lung Cancer phase III double-blind, multicenter study compared gefitinib with placebo in 1,692 unselected patients with refractory advanced NSCLC at a 2:1 ratio. Gefitinib therapy was associated with a significant prolongation of progression-free survival and with a numerically longer median overall survival than placebo, but the results for overall survival did not reach statistical significance ($P = .087$).[51] Twenty-six of 1,692 patients had detectable epidermal growth factor receptor (*EGFR*) mutations (21 were randomly assigned to gefitinib and five to placebo). The small number of *EGFR* mutation–positive patients randomly assigned precluded a meaningful statistical analysis.[51] Consequently, the US Food and Drug Administration restricted the use of gefitinib to patients already receiving it and to patients who enrolled in clinical trials approved by an institutional review board before June 17, 2005. A subsequent analysis of this randomized study demonstrated that patients with *EGFR* mutations had higher response rates than patients without *EGFR* mutations (37.5% *v* 2.6%).[52]

Furthermore, it was shown that the basis for EGFR inhibitor response in NSCLC was mainly due to *EGFR* mutation.[53] A randomized study of a different EGFR inhibitor, erlotinib, demonstrated a survival advantage compared with placebo, albeit a small one (6.7 *v* 4.7 months, respectively; $P < .001$), in favor of erlotinib, further supporting the concept of benefit for EGFR inhibition therapy in lung cancer.[54,55] These data suggest that the gefitinib failure may not have been due to its being ineffective, but rather due to the fact that the postapproval randomized study was done in an unselected patient population. The experience with other agents (eg, trastuzumab in patients with HER2-*neu*–positive breast cancer[55]) further illustrates the importance of appropriate patient selection. At no time were there any major safety concerns with gefitinib.

Of the other 30 drugs approved without a randomized trial with a comparator arm, only three drugs are no longer listed in the NCCN guidelines for use for their initial US Food and Drug Administration

Table 2. Initial Indications and Current Uses of Anticancer Drugs (nonhormone) Approved by the FDA As per NCCN Guidelines

Drug Name	Year of FDA Approval	Initial FDA Cancer Indication	Current FDA Labeled Anticancer Indications	Current Clinical Use*
Bleomycin	1973	Testicular	Head and neck; HL; NHL; nasopharynx; neoplastic pleural effusion; squamous cell carcinoma of cervix, penis, and vulva; testicular	Head and neck, HL, ovarian, testicular
Mitomycin	1974	Gastric, pancreatic	Gastric; pancreatic	Anal, bladder, cervical, NSCLC, upper GU tract
Doxorubicin	1974	Ovarian	ALL, AML, AIDS-related Kaposi's sarcoma, bladder, breast, CLL, gastric, HL, prostate, thyroid, NHL, multiple myeloma, CTCL, nephroblastoma, neuroblastoma, lung (NSCLC, SCLC), ovarian, sarcoma (bone, soft tissue)	Bladder, breast, HL, kidney, islet cell tumors, NHL, Merkel cell, lung (NSCLC; SCLC), thymus, plasmacytoma, multiple myeloma, sarcoma (bone, soft tissue), uterus (endometrial and sarcoma)
Cisplatin	1978	Testicular	Testicular, ovarian, bladder	Anal, bladder, bone, breast, cervical, esophageal, gastric, head and neck, HL, melanoma, plasmacytoma, multiple myeloma, Waldenström's macroglobulinemia, NHL, Merkel cell, lung (NSCLC, SCLC), unknown primary, ovarian, pancreatic, prostate, testicular, thymus, endometrial
Asparaginase	1978	ALL	ALL	ALL, NHL
Interferon alfa 2b	1986	HCL[37]	AIDS-related Kaposi's sarcoma, NHL, HCL, melanoma (adjuvant), *Condyloma acuminatum* involving external surfaces of the genital and perianal areas, hepatitis C, hepatitis B	CML, HCL, hepatocellular, kidney, melanoma, multiple myeloma, carcinoid tumors, islet cell tumors, CTCL, desmoid tumors, plasmacytoma
Etoposide	1983	Testicular	SCLC, testicular	Brain, breast, HL, lung (NSCLC, SCLC), Merkel cell, multiple myeloma, NHL, thymus, ovarian, plasmacytoma, sarcoma (bone), testicular, unknown primary
Ifosfamide	1988	Testicular	Testicular	Cervical, head and neck, HL, lung (NSCLC, SCLC), NHL, ovarian, sarcoma (bone, soft tissue), testicular, thymus, endometrial
Altretamine	1990	Ovarian	Ovarian	Ovarian
Fludarabine	1991	CLL	CLL	CLL, multiple myeloma, NHL, Waldenström's macroglobulinemia
Pentostatin	1991	HCL[38]	HCL	HCL, NHL, *Mycosis fungoides* and Sezary syndrome
Aldesleukin	1992	Kidney	Kidney, melanoma	Kidney, melanoma
Cladribine	1993	HCL[39]	HCL	HCL, multiple myeloma, NHL, Waldenström's macroglobulinemia
Pegaspargase	1994	ALL[40]	ALL, AML	ALL, AML
Liposomal doxorubicin	1995	AIDS-related Kaposi's sarcoma[37]	AIDS-related Kaposi's sarcoma, multiple myeloma, ovarian	Breast, HL, CTCL, multiple myeloma, NHL, ovarian, plasmacytoma, sarcoma (soft tissue)
Tretinoin, ATRA	1995	APL	APL	APL, CTCL
Irinotecan	1996	Colorectal	Colorectal	Brain, cervical, colorectal, esophageal, gastric, lung (NSCLC, SCLC), ovarian
Rituximab	1997	NHL CD20 (+)	NHL CD20 (+), rheumatoid arthritis	Brain, HL, multiple myeloma, NHL CD20(+), Waldenström's macroglobulinemia
Busulfan intravenous	1999	CML; stem cell conditioning	CML, stem cell conditioning	CML, stem cell conditioning
Methoxsalen	1999	CTCL	CTCL	CTCL
Bexarotene capsules	1999	CTCL	CTCL	CTCL
Temozolomide	1999	Anaplastic astrocytoma	Brain (anaplastic astrocytoma, glioblastoma multiforme)	Brain, brain metastasis, melanoma, neuroendocrine, NHL, CTCL, unknown primary

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Table 2. Initial Indications and Current Uses of Anticancer Drugs (nonhormone) Approved by the FDA As per NCCN Guidelines (continued)

Drug Name	Year of FDA Approval	Initial FDA Cancer Indication	Current FDA Labeled Anticancer Indications	Current Clinical Use*
Arsenic trioxide	2000	APL	APL	APL
Gemtuzumab ozogamicin	2000	AML CD33 (+)	AML CD33 (+)	AML CD33 (+), APL
Tositumomab	2003	NHL CD20(+)	NHL CD20 (+)	NHL CD20 (+)
Bortezomib	2003	Myeloma	Mantle cell lymphoma, multiple myeloma	Mantle cell lymphoma, multiple myeloma, Waldenström's macroglobulinemia, systemic light chain amyloidosis, peripheral T-cell lymphoma, plasmacytoma
Gefitinib	2003	Lung (NSCLC)	Lung (NSCLC)	Not in NCCN
Clofarabine	2004	ALL	ALL	ALL
Lenalidomide	2005	Low- or intermediate-risk MDS del(5q)	MDS del(5q), multiple myeloma	MDS, multiple myeloma, plasmacytoma
Nelarabine	2005	T-cell ALL; T-cell lymphoblastic lymphoma		T-cell ALL, T-cell lymphoblastic lymphoma
Vorinostat	2006	CTCL	CTCL	CTCL

Abbreviations: FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; GU, genitourinary; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; SCLC, small-cell lung cancer; HCL, hairy cell leukemia; CML, chronic myelogenous leukemia; APL, acute promyelocytic leukemia; MDS, myelodysplastic syndrome.

*As per the NCCN Clinical Practice Guidelines in Oncology, the NCCN Drugs and Biologics Compendium, and the National Cancer institute Physician Document Query.

indication. In all three cases, the discovery of better drugs supplanted the use of these drugs in the cancers for which they were initially approved. However, these three drugs have found new uses (Table 2). Overall, 19 drugs have additional uses per NCCN or National Cancer Institute PDQ guidelines, and 11 drugs have additional US Food and Drug Administration approvals, including approvals for nononcologic diseases (eg, interferon for condyloma acuminatum and hepatitis B and C, and rituximab for rheumatoid arthritis), further supporting their safety.

The experience to date with accelerated approval strategies, which may or may not include a randomized trial, suggests that this approach for the identification of useful new therapies is valid and that it is meant to reduce the time required to make a new therapy available to patients with life-threatening illnesses. However, the accelerated approval process is concentrated on eliminating procedural delays. Our review suggests favorable long-term experience with several drugs approved without a randomized trial using a comparator arm with standard therapy, supportive care, or placebo. The median number of patients needed for approval was 79 in these trials, and the most common parameter used was response rate, with the median objective response rate being 33%. In contrast, randomized trials for approval of new drugs often require more than 500 patients.[3]

It is commonly perceived that the US Food and Drug Administration requires survival as an end point for drug approval. Indeed,

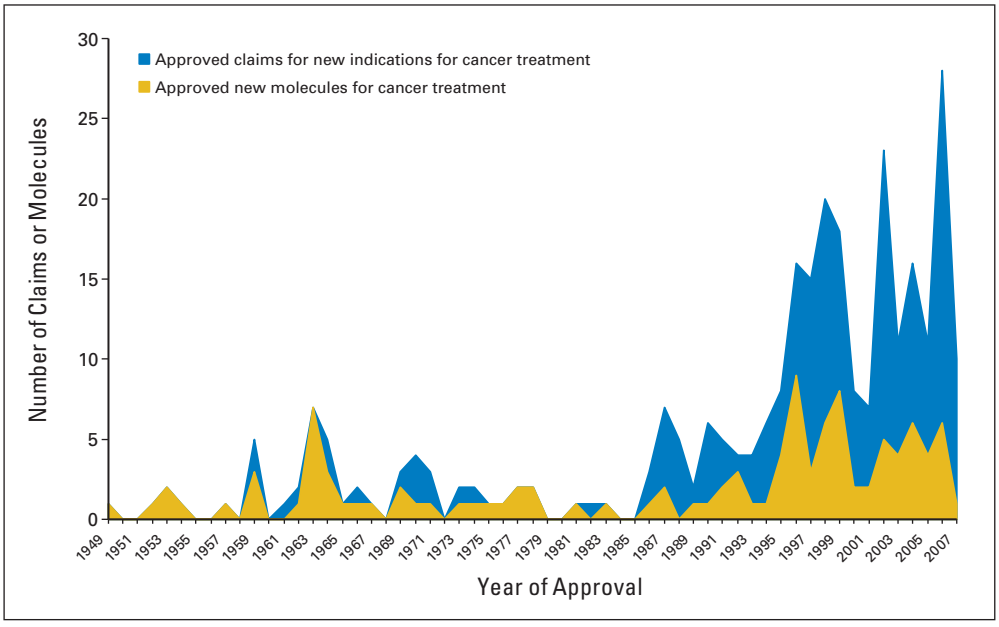

Fig 1. Approved claims (blue) and initially approved new molecules (gold) for anticancer therapy: significant increase in approval was noted after 1995 (Subpart H was introduced in 1992).

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. However, there are significant disadvantages to the survival end point, including the long time it may take to reach it, and the effect of subsequent therapies on survival. Of interest in this regard, end points other than survival have been the basis for US Food and Drug Administration approval for 68% of oncology drug marketing applications granted regular approval and for 14 applications granted accelerated approval from 1990 through 2002.[56] The objective tumor response rate has been the approval basis in 46% of oncology drug regular approvals (26 of 57). Other end points have included time to progression, disease-free survival, and symptom improvement. The selection of an end point should attempt to minimize subjectivity and bias. The ability to reproduce the findings and highly persuasive results are desirable.[56]

There are several strong arguments for the use of randomized trials in oncology.[2,57-61] Certainly, randomized trials lend substantial credibility to a research study because they reduce bias. For instance, patients in an uncontrolled trial may have less serious comorbidities or better supportive care than a historical control group, and these factors, rather than treatment benefit, could lead to the inference of superior survival.[2,57-61] Biased selection of patients may therefore result in erroneous conclusions, though a counterargument could be that one could control for parameters known to influence outcome. This type of control does not, however, eliminate the possibility that unknown covariates exist, and only a randomized trial would address such a possibility.[62] Finally, randomized trials have proven that certain treatments are ineffective despite the expert consensus belief to the contrary. The classic example is the use of high-dose chemotherapy and autologous stem-cell transplantation in patients with breast cancer, which required a randomized trial to demonstrate that patients treated with conventional therapy had comparable survival rates.[63] Therefore, the main argument against bypassing time consuming and expensive, but well-designed, randomized trials is that ineffective or even damaging approaches will be designated as standard of care.

However, randomized trials also have drawbacks, including the difficulty in generalizing the results of research done in such well-controlled populations. Furthermore, some authors have claimed that when clear superiority is noted for an agent or modality, the equipoise standard cannot be met in a trial, and in those cases, a randomized trial would be improper or even unethical.[17] As an example, Goitein et al[17] refute the argument that proton beam therapy requires a randomized trial before it can be promulgated, based on the claim that there is exhaustive evidence supporting the superiority of proton beams over x-rays, and that, therefore, a randomized trial is at best unnecessary and at worst improper. It should also be kept in mind that there are biases, even in randomized trials. For instance, Booth et al[64] in a comprehensive review of 321 randomized oncology trials concluded that these trials have become larger with time and more likely to be sponsored by industry. Further, for-profit sponsorship was independently associated with endorsement of the experimental arm.

In conclusion, while randomized controlled trials remain the gold standard for obtaining definitive answers, these trials incur substantial expense, may take a prolonged time period to complete, and are not free of flaws. Importantly, our review of oncology drugs suggests that phase II trials with definitive end points can yield US Food and Drug Administration approval and that the long-term experience with drugs approved in such a way is that they remain safe and effective. Based on these data, and the emerging knowledge regarding molecular pathophysiology in cancer, as well as the identification of more reliable biomarkers with the potential to personalize anticancer therapies, the question arises whether large randomized trials or carefully designed smaller phase II studies with biomarker selection would optimize the use of resources, given that resources are not unlimited.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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