Introduction

Rare cancers are rare diseases and pose particular challenges to programs of drug development. By definition, the relevant patient populations are geographically dispersed, and the paucity of patients is frequently exacerbated by limited access to experienced oncologists who specialize in these cancers. Rare cancers are further problematic owing to their poorly understood natural histories, their phenotypic heterogeneity, and to a range of manifestations that, even if their poorly understood natural histories, their phenotypic heterogeneity, and to a range of manifestations that, even within a given phenotype, can be diverse. Rare cancers thus represent a particular unmet need in clinical oncology.


definition of rare cancer can be useful for the analysis of trial data and for the path toward harmonizing the terminology in the area of clinical research on rare cancers. Clin Cancer Res; 1–8. ©2012 AACR.

The U.S. Food and Drug Administration (FDA) has recognized the importance of addressing unmet needs by instituting programs to facilitate the research, development, regulation, and approval of therapeutic agents for rare disorders and serious diseases. One such initiative is the Orphan Drug Act (ODA), which provides incentives to make the development of drugs for patients with orphan disease financially viable (1). The Secretary of Health and Human Services designates an orphan disease as a condition that affects less than 200,000 persons in the United States (or one that affects >200,000 people, but where there is "no reasonable expectation that the cost of development" of the drug will be recovered from sales in the United States; ref. 2). Under the ODA, orphan disease designation qualifies the drug's sponsor for 7 years of market exclusivity (3), certain tax credits (4), and waiver of fees that otherwise would be due under the Prescription Drug User Fee Act (PDUFA; ref. 5).

The approval of an orphan designation request, however, does not obviate existing legal and regulatory requirements for drug approval (6). Accordingly, the safety and effectiveness of the orphan product must be established, before market approval, through adequate and well-controlled studies (4). In addition, the FDA maintains initiatives such as fast-track drug development, priority review, and accelerated approval. (See Supplementary Textbox for definitions of selected regulatory terms). Furthermore, the FDA's


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**Translational Relevance**

Absence of clear definition for "rare" cancers and lack of comprehensive trial information on rare cancers can hinder their drug development. Stakeholders might benefit from a systematic analysis of clinical trials that supported the approval of drugs for the treatment of rare cancers. Our results presented in the manuscript identified valuable concepts and terms that can inform the effective design of prospective clinical trials for rare cancers. In addition, an operational definition of rare cancer can be useful for the analysis of trial data and for the path toward harmonizing the terminology in the area of clinical research on rare cancers. Therefore, we believe that our results are important, not only to researchers in clinical cancer research, but also to oncology drug developers in general. Furthermore, with successful identification of molecular targets, the coming era of personalized medicine may usher in familiar challenges that had previously been associated with therapeutic approaches to "rare cancer." The results presented in our manuscript thus provided timely information to meeting these challenges in terms of adequate patient recruitment, trial design, and choice of trial endpoints.

Center for Drug Evaluation and Research has recently established a rare diseases program to facilitate and support the research, development, regulation, and approval of drug and biologic products for the treatment of rare disorders (7).

The challenges of conducting clinical trials to investigate drugs for rare cancers include the appropriate use of endpoints. Oncology trials are often designed using surrogate endpoints, such as overall tumor response rate, which are not necessarily direct metrics of survival or irreversible morbidity. The accelerated approval (AA) regulation was established so that the unmet medical needs could be addressed through the use of surrogate endpoints that are reasonably likely to predict clinical benefit (8, 9). Sponsors of drugs granted accelerated approval are required to conduct postapproval clinical trials to verify clinical benefit and thereby prevent the drug from being removed from the market (10, 11).

Under the current version of 21 C.F.R. 316.20(b)(6), orphan drug designation may also be granted for a drug intended for a narrow indication, encompassing a specific, medically plausible disease subset or "orphan subset" (12). FDA has recently proposed a rule that would clarify this portion of the regulation (12). One ramification of this proposed rule, should it become final, could be that common cancers may comprise subsets which, by virtue of expressing specific molecular markers, could become orphan subsets. For example, tumors of 4% to 7% patients with non–small cell lung cancer (NSCLC; a common cancer) overexpress anaplastic lymphoma kinase (ALK; refs. 13, 14). The drug crizotinib has been specifically developed for patients with ALK-positive tumors and was granted orphan status.

In the absence of a clear definition for "rare" cancers, regulatory recommendations with regard to drug development can be problematic, as evidenced in 2011 at an Oncologic Drug Advisory Committee (ODAC) meeting that focused on the discussion of potential trial designs for the consideration of accelerated approval for oncologic drugs (15). Although committee members agreed that accelerated approvals of oncology products in general would be better served through randomized trials, rather than single-arm trials, they commented that owing to challenges of patient recruitment in rare disease trials, single-arm trials might be considered for trials involving rare cancers. However, a reasonable working definition for a rare cancer has yet to be established. These and many other discussions have suggested to us that stakeholders in drug development—particularly, those who are tasked with the design of prospective trials in oncology—might benefit from a systematic analysis of clinical trials that have led to the approval of drugs for the treatment of rare cancers.

Here, we report a retrospective analysis of FDA drug approvals associated with rare cancers, according to our operational definition of 6 cases per 100,000 persons per year. We relied on FDA internal databases pertaining to trial data, collected between December 1987 and May 2011, as described below.

**Materials and Methods**

Figure 1 outlines the steps used in generating the database for our analyses, pertaining to 45 drugs for 68 approved rare cancer indications that were supported by a total of 99 trials (Supplementary Table S1). The information of this database was independently verified by 4 staff members of Office of Hematology and Oncology Products (OHOP), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), FDA who were not associated with this research. For purposes of our analysis, we define "rare cancer" by an incidence rate of ≤6 new cases per population of 100,000 per year. This incidence rate was first suggested by the Surveillance of Rare Cancers in Europe project (funded by the European Commission; ref. 16), based on the assumption that it would be difficult to conduct a randomized trial below this threshold. This definition would predict approximately 18,000 new patients per year in the United States, based on recent U.S. population census data (~308 million in 2010). According to this criterion, we estimated the incidence rate for any given selected indication on the basis of the published information from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI; ref. 17), the National Comprehensive Cancer Network (NCCN; ref. 18), and UpToDate (19). It should be noted that incidence rates for specific cancer stages are generally not available, so that any given indication used in our analyses stands without regard for cancer stage. For example, in April 2011,
vandetanib was approved for patients with symptomatic or progressive medullary thyroid cancer, a subset of patients with unresectable locally advanced or metastatic disease. Because the annual incidence of this subset is unknown, we estimated the incidence rate for vandetanib’s indication at 2,000 cases per 100,000 per year on the basis of all stages of medullary thyroid cancer instead of the subset of symptomatic or progressive medullary thyroid cancer. However, one exception to this rule is the incidence of non–Hodgkin lymphoma (NHL) where the incidence rate was estimated on the basis of the subtypes. Although as a whole, the incidence for NHL is greater than 6 per 100,000 per year, NHL subtypes represent clinically distinct diseases with respect to their biology, natural history, and treatment.

For each of the 68 rare cancer indications, we analyzed the characteristics of the corresponding trial(s) that supported the indication’s approval in terms of the number of trials conducted, study design, sample size, primary efficacy endpoints, and statistical analysis. We also tracked whether approval was accelerated or regular, whether the approved product was a new molecular entity (NME), proposed mechanism of action, approval date, and whether the review type was priority review or standard review. For drugs granted accelerated approval, the status of their postmarketing commitments was also reviewed, and we ascertained whether any important postmarketing safety findings resulted in the revision of the “Warnings and Precautions” section of the product package insert.

The statistics we present throughout our retrospective analyses of the trials are descriptive and not hypothesis-driven.

**Results**

Between December 1987 and May 2011, a total of 45 oncology products were approved for 68 rare cancer indications.
indications (i.e., incidence rates ≤6 per 100,000 per year; see Supplementary Table S1). Thirty-three drugs were approved for a single indication each; 8 were approved for 2 indications; one drug was approved for 3 indications; 2 drugs were approved for 4 indications; and one drug, imatinib, was approved for a total of 8 different indications.

Over the time period inspected, there was a marked increase in number of indications approved for rare cancers (Fig. 2B). Whereas 7 new indications were approved in the time leading up to 1993, 33 new indications were approved from 2006 to 2011. Forty-eight of the 68 indications (70%) were approved for hematologic malignancies (Fig. 2A), 37 (54%) for NMEs, and 28 (41%) as efficacy supplements for new indications, one (1%) for a new formulation of an existing drug, and 2 (3%) for new manufacturing methods.

**Trial design and endpoints**

Of the total 99 trials involved in our analysis of FDA-approved rare cancer indications, one third were randomized controlled (Fig. 3A). Of these 33 randomized trials, 32 were multicenter trials and 15 were blinded in some fashion: 12 were double-blinded (6 placebo-controlled and 6 controlled by active comparator), and 3 were single-blinded. The remaining 18 randomized trials were open-label. The most common primary efficacy endpoint, used for 69% of the approvals, was overall objective response rate (ORR; complete and partial responses); the high use of ORR correlates with the preponderance of single-arm design among the trials. Less frequently used endpoints included time to progression (TTP; 7%), progression-free survival (PFS; 10%), and overall survival (OS; 6%; Fig. 3C).
Number of trials and trial size

The average number of trials conducted per indication was 1.5 (99 trials for 68 rare cancer indications). Only 25 indications (37%) were approved on the basis of the results from more than one trial: 20 indications from 2 clinical trials; 4 indications from 3 trials; and one indication from 4 small trials in aggregate. The mean sample size was 174 patients with a median of 94 patients (range, 5–846 patients). For the 66 single-arm trials, median sample size was 54 patients; among the 33 randomized trials, the median sample size was 301 patients.

Regulatory characteristics and postmarketing safety issues

The majority of the 68 indications (60%; see Supplementary Table S1) were granted after a priority review, typically within 6 months of submission (Fig. 3B); of the indications reviewed after 1992, when standard and priority review tiers were established under the PDUFA (20), the fraction of priority reviews is 64%. Twenty-four of the 68 indications (35%) were granted through accelerated approval (Fig. 3D); of the indications approved after introduction of the accelerated approval regulation in 1992 (20), 37% were approved under accelerated approval. Of the 24 indications granted accelerated approval, 11 (46%) have completed postmarketing commitments to date.

Postmarketing safety issues related to the approved rare cancer products are tabulated in Supplementary Table S2. Only one drug, gemtuzumab, initially approved for the indication for the treatment of elderly patients with acute myeloid leukemia, was removed from the market in June 2010, due to unacceptable toxicity, mortality, and lack of clinical benefit (21).

Of the 19 products granted accelerated approval for 24 indications, 8 products (42%) were associated with new important toxicity findings identified from the postmarketing experience and led to a revision of the "Warning and Precautions" section of the product labeling. In contrast, 7 (27%) of 26 products that were given regular approval for 44 indications had postmarketing toxicity issues. Indications approved through accelerated approval were less likely to have relied upon randomized trial design than those indications approved through regular approval (21% vs. 43%, respectively). Trials associated with accelerated approval were also less likely to depend on endpoints of PFS, TTP, and symptomatic improvement (SI) or OS than the trials that supported the regular approval (13% vs. 35%, respectively).
Characterization of trials as a function of incidence rate for defining rare cancers

To explore whether our choice of incidence rate (≤6 per 100,000 per year) in selecting data might have biased assessment of the feasibility and value of conducting randomized controlled clinical trials, we further characterized trials as a function of incidence rate. By applying arbitrary incidence rates of ≤1, ≤2, ≤3, ≤4, ≤5, and ≤6 new cases per 100,000 per year to our trial data, we were able to determine whether the selected incidence rate had any effect on trial characteristics such as median sample size, percentage of randomized trials, and use of response rate as primary endpoint. As shown in Table 1, the choice of different lower incidence rates for analyzing the 99 trials had no apparent effect upon these trial characteristics.

Discussion

The importance of applying effective trial design is especially underscored in the context of rare diseases. In particular, recent discussions have questioned the practicality of applying randomized trial designs to evaluations of rare conditions (22, 23). We undertook the present study to offer a comprehensive analysis of drug approvals specifically in the context of rare cancer.

The primary goal of the analysis presented here is to provide heuristic profiles of those clinical trials that have supported FDA drug approvals for rare cancer. We hope that such profiles will prove useful to stakeholders involved in various aspects of drug development and drug approval. Specifically, we have analyzed the characteristics of 99 clinical trials that supported the approval of 45 products, between December 1987 and May 2011, for 68 indications of "rare" cancer, defined by an incidence threshold of no more than 6 new cases per 100,000 people per year. We believe that this incidence threshold as an operational definition can prove to be of value. Although this threshold is not to be construed as an exact definition for a rare cancer and does not reflect a standard expressed by the FDA, we expect that it can be of practical use for researchers in the analysis of trial data and for the path toward harmonizing the terminology in the area of clinical research on rare cancers.

One of three trials in our retrospective analysis proves to have been randomized controlled (Fig. 3A). This considerable proportion of randomized trials appears to be a relatively rigorous statistic; it does not appear to be a function of the specific threshold of incidence rate chosen for analysis (Table 1). It must be noted, however, that the small number of clinical trials defined by any of the given thresholds of incidence rate (Table 1) precludes highly rigorous hypothesis-driven statistical analyses. Nevertheless, our results clearly indicate that randomized controlled trials provide feasible avenues for evaluating the efficacy and safety of therapeutics in many rare cancer indications. This finding has important implications for sponsors as they consider trial design and invest in the development of drugs for rare cancer indications.

An additional finding in our study is that the products that were granted accelerated approval for rare cancers indications appear, relative to those approved under regular approval, to manifest a higher incidence of postmarketing safety issues (42% vs. 27%, respectively). It should be pointed out that accelerated approval drugs, like those approved via the regular approval process, must still be shown to be safe; the difference in rates of postmarketing safety issues becomes usually apparent only because a much larger patient population is exposed to the given product after its approval. In any event, the higher incidence of postmarketing safety issues associated with products approved under accelerated approval is not surprising, given the fact that accelerated approval can be based on small sample sizes and endpoints other than survival or irreversible morbidity. It is for this reason that safety information, including OS, should be continuously assessed postapproval. In our analysis, 46% of rare cancer indications that had been granted accelerated approval fulfilled their postmarketing commitments. This percentage appears to be lower than the 55% reported by Johnson and colleagues for all oncology products which were granted accelerated approval and had fulfilled their postmarketing commitments (24). The reason for this relatively small discrepancy is unknown, although it may reflect the inherent challenges in conducting clinical trials for rare cancers (e.g., difficulty in adequate patient recruitment).

Table 1. Trial characteristics as a function of incidence rates

<table>
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<th>Incidence rate (number of new cases per 100,000 per year)</th>
<th>Number of trials</th>
<th>Median sample size (number of patients enrolled)</th>
<th>Percentage of trials using response rate as primary endpoint</th>
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It should be noted that of the 68 rare cancer indications that we discuss here (see Supplementary Table S1), 43 (63%) were based on results from a single, pivotal trial. This result indicates FDA’s flexibility in making products that address unmet need available to patients as early as possible. The reliance on the results from one trial for approval is consistent with section 115(a) of the Food and Drug Administration Modernization Act of 1997, which states that the Secretary of Health and Human Services may consider “data from one adequate and well controlled clinical investigation and confirmatory evidence” to constitute “substantial evidence” for purposes of subsections 505(d) and (e) of the Federal Food, Drug, and Cosmetics Act if the Secretary determines that such data and evidence are “sufficient to establish effectiveness” (25).

With respect to trial endpoints that supported the approvals discussed here, ORR was the primary efficacy endpoint used for 69% of the approvals, which correlates with the prevalence of single-arm design among the trials. In the remainder of the trials, OS, PFS, TTP, time to graftenfrment (TTE) and SI were generally used as primary endpoints, which is consistent with published FDA guidance that in the randomized trial setting, time-to-event endpoints, rather than response rate, should be preferred endpoints (26).

We expect that the trend toward increasing numbers of rare cancer drug approvals (Fig. 2B) will continue in the foreseeable future, especially given the improvements in target identification that are underpinning cancer biology. As novel targets are identified, subsets of common cancers may be defined as “rare cancers” according to their unique molecular profiles and meeting arbitrary criteria. With successful identification of molecular targets, the coming era of personalized medicine may thus usher in familiar challenges, in terms of adequate patient recruitment, trial design, and choice of trial endpoints, that had previously been associated with therapeutic approaches to “rare cancer.” Our continued commitment to foster disease awareness, advocacy, and research is crucial, as are our efforts to elucidate those trial design parameters upon which efficient drug development will best flourish.

Disclosure of Potential Conflicts of Interest

Results of this manuscript have not been previously presented or published. The opinions expressed in this article do not necessarily reflect those of the U.S. Food and Drug Administration and the U.S. government. No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: H. Gaddipati, K. Liu, A. Pariser. Development of methodology: H. Gaddipati, K. Liu. Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H. Gaddipati, K. Liu, R. Pazdur. Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Gaddipati, K. Liu. Writing, review, and/or revision of the manuscript: H. Gaddipati, K. Liu, A. Pariser, R. Pazdur. Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H. Gaddipati, K. Liu. Study supervision: K. Liu.

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# Rare Cancer Trial Design: Lessons from FDA Approvals

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