Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer

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The Orphan Drug Act of 1983 provides special incentives to manufacturers who develop drugs to treat rare diseases (affecting <200,000 people in the United States), including grants to perform clinical trials, a 50% tax credit for clinical testing costs, and an exclusive right to market the drug for 7 years after regulatory approval. Orphan drug manufacturers also receive waivers of drug application fees and may be eligible for faster review by the US Food and Drug Administration (FDA). Through 2010, 362 orphan designations have led to approvals, with oncology representing the largest clinical subcategory.

While the Orphan Drug Act has been lauded as highly effective policy making, there has been some debate about how its incentives are implemented. For example, a recent study suggested that the Orphan Drug Act encourages manufacturers to define subdivisions of nonrare conditions, such as subpopulations in whom existing therapies have failed or who have a more severe or progressed form of a disease. Recent developments have also raised concerns about the safety and efficacy of some approved orphan drugs. For example, gemtuzumab ozogamicin, an orphan drug approved in 2000 for acute myeloid leukemia, was removed from the market in 2010 when a confirmatory postmarketing trial (initiated in 2004) showed no improvement in outcome and a greater number of deaths in the gemtuzumab group. The drug was originally approved after an open-label study in 142 patients with no control group, using the surrogate end point of response rate. Similar concerns have been raised about other orphan drugs.

The Orphan Drug Act incentivizes medication development for rare diseases, offering substantial financial benefits to the manufacturer. Orphan products constitute most new drug approvals in oncology, but safety and efficacy questions have emerged about some of these agents.

Objectives To define characteristics of orphan cancer drugs and their pivotal clinical trials and to compare these with nonorphan drugs.

Design and Setting We identified all new orphan and nonorphan drugs approved between 2004 and 2010 to treat cancer. We then collected data on key development variables from publicly available information on the US Food and Drug Administration’s Web site and in the Code of Federal Regulations.

Main Outcome Measures We assessed clinical testing dates, approved indications, and regulatory characteristics (regular vs accelerated review, advisory committee review, postmarketing commitments). We then compared design features (randomization, blinding, primary end point) of pivotal trials supporting approval of orphan and nonorphan drugs and rates of adverse safety outcomes (deaths not attributed to disease progression, serious adverse events, dropouts) in pivotal trials.

Results Fifteen orphan and 12 nonorphan drugs were approved between January 1, 2004, and December 31, 2010. Pivotal trials of orphan drugs had smaller participant numbers (median, 96 [interquartile range (IQR), 66-152] vs 290 [IQR, 185-394] patients exposed to the drug; P < .001) and were less likely to be randomized (30% vs 80%; P = .007). Orphan and nonorphan pivotal trials varied in their blinding (P = .04), with orphan trials less likely to be double-blind (4% vs 33%). Primary study outcomes also varied (P = .04), with orphan trials more likely to assess disease response (68% vs 27%) rather than overall survival (8% vs 27%). More treated patients had serious adverse events in trials of orphan drugs vs trials of nonorphan drugs (48% vs 36%; odds ratio, 1.72; 95% confidence interval, 1.02-2.92; P = .04).

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point of complete remission.8 In early 2010, the United Kingdom’s National Institute for Clinical Excellence recommended against use of 2 orphan drugs also approved in the United States—nilotinib and dasatinib for chronic myelogenous leukemia—because evidence to support their effectiveness was “very poor” and their cost was “extremely high.”9

The FDA must approve prescription drugs on the basis of adequate studies, which, according to the Code of Federal Regulations, requires a “design that permits a valid comparison with a control.”10 However, such requirements may be relaxed at the discretion of the FDA,11 and orphan drugs are likely to qualify for lower approval standards because they are designed for small populations in which organization of controlled trials may be difficult.12,13 In 2009, Mitsumoto et al14 evaluated 3 characteristics—blinding, control groups, and randomization—in the pivotal clinical trials used to approve orphan drugs for neurological conditions and found that a substantial minority of trials for orphan drugs lacked these qualities.

We hypothesized that we would find similar differences in the basis of approval for newly approved orphan vs nonorphan drugs used in oncology. We also sought to identify whether those differences were associated with signals of safety concerns in the approved drugs. Therefore, we identified characteristics of the core preapproval clinical trials, as well as the efficacy and safety outcomes of the trials, for recently approved orphan and nonorphan cancer drugs.

METHODS

Sample Identification

We first identified the names of all new orphan drugs approved by the FDA to treat cancer-related indications between January 1, 2004, and December 31, 2010, a period when comprehensive data needed for this study were accessible. The cohort was derived from a public domain master list of all orphan product approvals and their approved indications published by the FDA Office of Orphan Product Development.15 We selected those indicated to treat a form of cancer, as defined in a complete cancer directory published by the National Cancer Institute.16

For a comparator group of drugs, we used the FDA Web site to identify all nonorphan drugs approved during the same period to treat cancer-related indications.17 For both groups, we excluded drugs already on the market that received a supplemental approval for a cancer-related condition during this period.

Data Collection

The FDA publishes summary reports of the basis of approval and makes them publicly available on the Drugs@FDA Web site. This document provides (1) an overview of the drug development process, including a description of the administrative characteristics of the FDA review and (2) a detailed description of clinical data collection. Data were collected independently by 2 of us (A.S.K. and J.A.M.), with differences reconciled by consensus.

First, we noted the characteristics of first approval mentioned in the FDA reports, including indication, dates, drug class, and alternative therapies available at the time of approval. We then extracted when possible the important administrative and drug development dates corresponding to the approval of the Investigational New Drug (IND) application (beginning of human trials), the orphan drug designation (if applicable), and the filing of the New Drug Application (NDA). Dates were checked for 17 products from drug-specific Determinations of Regulatory Review Period for Purposes of Patent Extension published in the Code of Federal Regulations. For 2 orphan drugs for which IND dates could not be located (decitabine and temsirolimus), we used the earliest reported date of communication with the FDA, while for 1 orphan drug (azacitidine) for which the original IND was reportedly set more than 30 years ago, we used the more recent date of initiation of contact between the FDA and the manufacturer regarding trials in the patient population for which the drug was approved. Next, we identified whether an FDA advisory committee was convened to consider the drug’s efficacy and safety and whether the drug underwent regular or accelerated review. Finally, we noted postmarketing commitments required at the time of approval by examining the formal Letter of Approval for each drug (available on the FDA Web site) and a special database published by the FDA that lists all postmarketing requirements for approved drugs.18

We next focused on the trials leading to each drug’s approval. The Clinical Review provides detailed information on the methods and results of the trial(s) deemed by the FDA to be most important in providing support for the indication(s) for which a drug is approved; these are usually labeled as “pivotal” trials. The Clinical Review also provides more limited information about so-called supportive studies that supplemented the efficacy data presented in the pivotal trials. In 1 case in which the Clinical Review provided a detailed report about a trial but did not specify whether it was pivotal or supportive (for the orphan drug dasatinib), we considered this trial to be pivotal. For all pivotal trials, we identified basic features of their design: whether participants were randomized, the extent of blinding (double-blind, single-blind, or open-label), the number of participants (defined as the number randomized to active treatment in randomized controlled trials and the total number of enrollees in single-group studies), and the existence (if any) of a comparator. The primary end point was recorded as relating to overall survival or 1 of 2 general types of surrogate end points recognized by the FDA: disease response (including hemato logical response, cytogenetic response, or change in tumor burden) or a temporal measure of disease progression (including time to tumor progression and progression-free survival). If trials included open-label extensions,
we defined the features of the trial based on the controlled segment.

We also collected the results of pivotal trials, including reported rates of any serious adverse events, deaths not related to progression of disease, and dropouts due to adverse events. Although we sought to focus on pivotal trials, safety data were occasionally reported in aggregate with nonpivotal trials; if so, we adjusted the denominator accordingly. If any details were not extractable from the Clinical Review, we sought copies of published articles related to the pivotal studies and checked the data reported in that source. We were unable to identify rates of death for 1 trial of the nonpharmaceutical drug sunitinib and serious adverse events for 2 trials of the orphan drug nilotinib.

**Statistical Analysis**

We used the Fisher exact test to compare the distributions of categorical attributes (randomization, blinding, etc) between orphan and nonorphan trials and between orphan and nonorphan approval processes. A nonparametric Wilcoxon rank sum test was used to compare the development times and the number of patients treated with the study drug between orphan and nonorphan trials. To compare relative rates of serious adverse events, deaths, and dropouts, we used patient-level random-effects logistic regression models for each of these outcomes, with a random intercept for each trial and a fixed effect for orphan status. From these models, we estimated the odds ratio (OR) of a given trial characteristic comparing orphan trials with nonorphan trials.

We also used the Simes procedure (a modified Bonferroni correction) to test the null hypothesis of no differences between orphan and nonorphan approval characteristics. This procedure allows evidence to be combined across many hypothesis tests of varying type. Rejecting the null hypothesis at the .05 level of significance indicates that at least 1 of the individual

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**Table 1. New Drug and Biologic Agents Approved to Treat Cancer, 2004-2010**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Year Approved</th>
<th>Original Indication(s)</th>
<th>Orphan Drugs</th>
<th>Drug Class (Other Similar Drugs)a</th>
<th>Alternative Therapies Available at Time of Approvala</th>
<th>Clinical Testing Duration (IND to NDA), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>2004</td>
<td>Malignant pleural mesothelioma</td>
<td>Antifolate (methotrexate)</td>
<td>None approved for this indication</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td>Clofarabine</td>
<td>2004</td>
<td>Pediatric patients with ALL after at least 2 prior treatments</td>
<td>Purine antagonist (fludarabine, cladribine)</td>
<td>Numerous</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Nelarabine</td>
<td>2005</td>
<td>Adult patients with T-cell lymphoblastic lymphoma and ALL after at least 2 prior treatments, pediatric patients with same conditions</td>
<td>Purine antagonist (fludarabine, cladribine)</td>
<td>None approved for this indication</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>2005</td>
<td>Advanced renal cell carcinoma</td>
<td>Multiple tyrosine kinase inhibitor (none)</td>
<td>Interleukin 2</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>2005</td>
<td>Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a 5q deletion cytogenetic abnormality</td>
<td>Immunomodulator (thalidomide)</td>
<td>Azacitidine</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Decitabine</td>
<td>2006</td>
<td>Myelodysplastic syndrome previously treated and untreated, de novo and secondary, of all F-A-B subtypes</td>
<td>DNA methylation inhibitor (azacitidine)</td>
<td>Azacitidine</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Dasatinib</td>
<td>2006</td>
<td>Chronic-phase, accelerated-phase, or myeloid or lymphoid blast-phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib; Philadelphia chromosome-positive ALL with resistance or intolerance to prior therapy</td>
<td>BCR-ABL tyrosine kinase inhibitor (imatinib)</td>
<td>None approved for this indication</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Vorinostat</td>
<td>2006</td>
<td>Cutaneous T-cell lymphoma on or following 2 systemic therapies</td>
<td>Histone deacetylase inhibitor (none)</td>
<td>None approved for this indication</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>2007</td>
<td>Advanced renal cell carcinoma</td>
<td>mTOR kinase inhibitor (sirolimus)</td>
<td>Sorafenib, sunitinib, interleukin 2</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Nilotinib</td>
<td>2007</td>
<td>Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase and accelerated phase in adults resistant or intolerant to prior therapy that included imatinib</td>
<td>BCR-ABL tyrosine kinase inhibitor (imatinib, dasatinib)</td>
<td>Dasatinib</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Bendamustine</td>
<td>2008</td>
<td>Chronic lymphocytic leukemia</td>
<td>Alkylation agent (carmustine, others)</td>
<td>Chlorambucil, rituximab, fludarabine</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>P препараты</td>
<td>2009</td>
<td>Relapsed or refractory peripheral T-cell lymphoma</td>
<td>Antifolate (methotrexate)</td>
<td>None approved for this indication</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>2009</td>
<td>Chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab</td>
<td>CD20 monoclonal antibody (rituximab)</td>
<td>Chlorambucil, bendamustine, cyclophosphamide</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Romidepsin</td>
<td>2009</td>
<td>Cutaneous T-cell lymphoma after ≥1 prior systemic therapy</td>
<td>Histone deacetylase inhibitor (vorinostat)</td>
<td>Bexarotene, vorinostat</td>
<td>6.6</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
differences tested is nonzero with a global type I error of .05. The statistical analysis was conducted using R software, version 2.12.2, with a 2-sided \( \alpha = .05 \).

**RESULTS**

Our sample included 15 orphan drugs (56%) and 12 nonorphan drugs (44%) approved to treat oncologic diseases (Table 1). Twenty-three (83%) were approved under an NDA, while 4 (15%) were approved under a Biologics Licensing Application. The indications covered 14 different general categories of cancer, led by renal cell carcinoma (5 drugs), acute lymphoblastic leukemia in pediatric and adult patients (3 drugs), myelodysplastic syndrome (3 drugs), breast cancer (3 drugs), and colorectal cancer (3 drugs). Among the drugs approved for renal cell cancer, 3 were orphan drugs and 2 were nonorphan drugs. Three of the orphan drugs (20%) and 5 nonorphan drugs (42%) were novel compounds not closely related to previously FDA-approved drugs, while 6 orphan drugs (40%) and 4 nonorphan drugs (33%) were approved for at least 1 condition with no alternative approved chemotherapeutic agents (Table 1).

**Regulatory Characteristics**

The median total clinical testing phase (IND approval to NDA submission) for orphan drugs was 5.1 years (interquartile range [IQR], 4.5-7.0 years), shorter than that for nonorphan drugs (6.9 years [IQR, 6.5-8.0 years]), although it was not a statistically significant difference \( (P = .07) \). The median FDA review time—from submission of the NDA to final approval—was nearly identical: 6.2 months (IQR, 5.8-8.9 months) for orphan drugs and 6.1 months (IQR, 5.4-8.0 months) for nonorphan drugs \( (P = .45) \). The orphan drugs received their orphan designa-
Table 2. Characteristics of Pivotal Preapproval Trials of Orphan and Nonorphan Cancer Drugs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Orphan Drug Pivotal Trials (n = 23)</th>
<th>Nonorphan Drug Pivotal Trials (n = 15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollies, median (interquartile range)</td>
<td>96 (66-152)</td>
<td>290 (185-394)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Randomized, multigroup</td>
<td>7 (30)</td>
<td>12 (80)</td>
<td>.007</td>
</tr>
<tr>
<td>Comparator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>4 (17)</td>
<td>7 (47)</td>
<td>.007</td>
</tr>
<tr>
<td>Supportive care</td>
<td>2 (9)</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1 (4)</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>16 (70)</td>
<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>Blinding</td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Double-blind</td>
<td>1 (4)</td>
<td>5 (33)</td>
<td></td>
</tr>
<tr>
<td>Single-blind</td>
<td>1 (4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Open-label</td>
<td>21 (91)</td>
<td>10 (67)</td>
<td></td>
</tr>
<tr>
<td>Primary trial end point reported</td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Disease response</td>
<td>17 (68)</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>4 (16)</td>
<td>6 (40)</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>2 (8)</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (8)</td>
<td>1 (7)</td>
<td></td>
</tr>
</tbody>
</table>

a Data are reported as No. (%) unless otherwise indicated.

b Two orphan trials included co-primary end points of disease response and disease progression.

c Disease response included hematologic response (6 pivotal trials of orphan drugs), cytogenetic response (3 pivotal trials of orphan drugs), or change in tumor burden (8 pivotal trials of orphan drugs and 4 pivotal trials of nonorphan drugs).

d Disease progression end points include time to tumor progression (4 pivotal trials of nonorphan drugs) and progression-free survival (4 pivotal trials of orphan drugs and 2 pivotal trials of nonorphan drugs).

Pivotal Trial Characteristics and Patient Outcomes

The FDA approvals for the 27 drugs in this sample were based on 38 pivotal and 19 supportive trials. Among the 38 pivotal trials, 23 were conducted for the 15 orphan drugs and 15 were conducted for the 12 nonorphan drugs. Pivotal trials for orphan drugs enrolled fewer patients exposed to the drug per study than those for nonorphan drugs (median, 96 [IQR, 66-152] vs 290 [IQR, 185-394]; P < .001). Table 2 presents the characteristics of these trials.

The pivotal trials on which approval of orphan drugs was based were significantly less likely to be randomized than the pivotal trials of nonorphan drugs (30% vs 80%; P = .007). Among the 7 orphan drug pivotal trials that were randomized, the drug was compared with an active comparator in 4, a placebo in 1, and supportive care in 2. Among the 12 randomized pivotal trials for nonorphan drugs, 7 included testing against an active comparator, 4 against a placebo, and 1 against supportive care.

Adequate masking (blinding) of study group assignment was significantly less common for orphan drug studies (P = .04). Of the 23 orphan drug pivotal trials, only 1 was double-blind (4%) and 1 was single-blind (4%). In contrast, 5 of 15 nonorphan drugs studies (33%) were double-blind.

The distributions of the primary outcomes studied also varied by orphan status (P = .04). Most pivotal trials of orphan drugs used a surrogate measure of disease response as the primary trial end point (17/23 [68%]), while pivotal trials for nonorphan drugs most commonly used a measure of disease progression (6/15 [40%]). In total, 21 of the 27 drugs (78%) were approved on the basis of data on surrogate end points; the exceptions were 4 nonorphan drugs—bevacizumab for advanced colorectal cancer, erlotinib for advanced non-small cell lung cancer, eribulin for advanced breast cancer, and cabazitaxel for advanced prostate cancer—and 2 orphan drugs: temsirolimus for advanced renal cell carcinoma and pemetrexed for malignant pleural mesothelioma. Further details of the pivotal studies of the orphan cancer drugs in our study are presented in the eTable.

Patients participating in preapproval studies of orphan drugs had a higher rate of serious adverse events than those in studies of nonorphan products. A total of 1358 serious adverse events were reported in 2806 treated patients in orphan drug pivotal trials (48%), significantly more than in nonorphan drug pivotal trials, where there were 1666 serious adverse events in 4621 patients (36%; OR, 1.72; 95% confidence interval [CI], 1.02-2.92; P = .04). There was a higher death rate among patients in the orphan drug studies, although the difference did not reach statistical significance (129/3105 [4.2%] vs 135/4534 [3.0%]; OR, 1.61; 95% CI, 0.89-2.91; P = .12). The proportion of dropouts (316/2940 [10.7%] vs 658/4745 [13.9%]; OR, 0.78; 95% CI, 0.51-1.20; P = .26) also did not differ significantly between the 2 cohorts.

Combining information from all the comparisons reported above, the Simes procedure rejects the null hypothesis of no differences between orphan and nonorphan drugs.


tions a median of 2.4 years (IQR, 1.2-2.7 years) before the date of approval.

With regard to the FDA review process, 7 orphan drugs (47%) were reviewed by an FDA advisory committee compared with only 1 nonorphan drug (8%; P = .04). There was no difference in the distribution of usual vs accelerated review (P = .70): 5 (33%) of the orphan drugs and 2 (17%) of the nonorphan drugs underwent accelerated review, with 1 orphan and 1 nonorphan drug receiving both regular and accelerated review for different indications.

As reflected in documents made public by the FDA, all drugs except 1 (the orphan drug pemetrexed) were approved with postmarketing “commitments” and “recommendations” of various types, although the agency’s capacity to require the completion of such studies is limited, especially for the years studied. For most drugs, the FDA asked manufacturers to complete a controlled trial assessing efficacy (including overall survival); we could not identify such requirements for 6 orphan drugs (40%) and 1 nonorphan drug (8%).
COMMENT

A review of all new drug approvals from 2004 through 2010 in oncology reveals several important differences in the preapproval evaluation of orphan vs nonorphan drugs for patients with cancer. The Orphan Drug Act has made available considerable resources to encourage manufacturers to develop new drugs for rare conditions. In evaluating such products, the FDA has approved alternative trial designs that allowed most orphan cancer drugs to be approved on the basis of single-group, nonrandomized trials that enrolled comparatively small numbers of patients. These pivotal trials tended to be unblinded and relied on surrogate markers of disease response to assess efficacy. Perhaps because of more limited preapproval testing, drugs designated as orphan products had shorter clinical testing phases than nonorphan products, although this difference did not reach statistical significance.

There can be several reasons for approving some cancer drugs—including orphan drugs in particular—on the basis of trials with limitations in their design. Organizing a randomized clinical trial of a new cancer drug might not be feasible if the disease is exceedingly rare or might encounter resistance if a reasonable therapeutic alternative does not exist. Using surrogate end points for the pivotal trials leading to drug approval is a common practice in oncology, and many drugs approved on this basis remain useful and on the market. Preapproval trials that are single-group or that use surrogate end points can be completed and analyzed more rapidly than large randomized trials, which can expedite drug availability to patients with life-threatening disease. However, while the complexity of performing clinical trials in orphan populations should be acknowledged, methodological designs should still strive to include blinded and randomization, which are among the hallmarks of high-quality clinical trial design.

The higher frequency of nonblinded, nonrandomized trials of orphan drugs raises concerns about the robustness of the findings of such trials. While the FDA permitted surrogate end points to be the basis for approval of many of the orphan drugs (and some nonorphan drugs) in our study, these efficacy data can later turn out to be unfounded, as in the cases of gemcitabine and the approval of bevacizumab for breast cancer. In addition, although both newly approved orphan and nonorphan cancer drugs in our sample were tested in relatively small numbers of patients prior to approval, we found a suggestion of safety concerns associated with the orphan drugs. No new drug's safety can be completely assessed on the basis of prospective clinical trials. The FDA has recently announced a commitment to comprehensive and timely follow-up testing and postmarketing surveillance of cancer drugs granted accelerated approval, and our findings support extending this policy to orphan drugs as well. Notably, manufacturers of orphan drugs receive substantial additional financial benefits during the drug development process, including tax breaks, additional market exclusivity, and research grants. One way to encourage timely completion of such studies would be to amend the Orphan Drug Act to withdraw exclusivity for drugs or require reimbursement of public grant funding if the required studies have not been satisfactorily completed after 3 years on the market.

Our study shines a light on other aspects of drug development and evaluation related to the Orphan Drug Act. First, while there are about 6000 unique rare diseases affecting about 25 million Americans, including many malignant conditions, most orphan drug innovation in our sample occurred for a limited number of diseases and drug classes (eg, tyrosine kinase inhibitors). These results suggest that the orphan drug incentives may not encourage transformative drug innovation that affects a diverse range of conditions. Furthermore, although patients benefit from having multiple treatment options, there may be less compelling justification for rapid approval of follow-on drugs, even if they treat a rare disease. It should be possible for orphan drugs that are not first-in-class compounds or that do not address an important unmet clinical need to be subjected to higher standards of clinical evaluation, more similar to that expected of nonorphan cancer drugs.

We found some variability in the way orphan drug designation was applied. For example, drugs approved to treat advanced renal cell cancer were evaluated as both orphan and nonorphan products, even though disease prevalence has not changed substantially over the past decade. Sunitinib was approved to treat gastrointestinal stromal tumor as a nonorphan product, even though this is an extremely rare condition that would qualify for orphan drug status. Orphan designation occurred relatively late in the product life cycle for many drugs, well into the clinical testing phase. If a product was initially designed solely for a particular orphan disease, one might predict that orphan designation would occur close to the time of the initiation of clinical trials. One potential explanation is that manufacturers may delay the administrative mechanism required for orphan product designation until the early clinical results suggest that a product will be marketable. Another possibility is that manufacturers identify whether their product will be useful in an orphan disease relatively late in the process, which also leads to questions about the role of the statutory incentives in driving drug development.

This study has certain limitations. It is restricted to recently approved cancer drugs and so may not be generalizable to orphan drugs for other diseases. However, our results are consistent with the findings of Mitsu moto et al, who studied this question in neurology. In addition, our study is limited to pivotal trials and we did...
not examine the entire range of data presented to the FDA. For example, the FDA commonly evaluates the safety of cancer drugs under review by taking into account results from all phase I trials and experiences of patients who receive the product for compassionate use, neither of which were included in our analysis. We do not conclude that the FDA erred in its decision to approve any of the products in our sample.

Our results may also reflect that most orphan drugs in our sample relate to hematologic malignancies, for which the clinical trial designs observed and use of surrogate end points such as disease response may be appropriate, at least for initial evaluation of the drugs’ efficacy. In nearly all circumstances, the design of pivotal studies for potential new cancer drugs is prospectively agreed on after discussions between the sponsoring pharmaceutical manufacturer and the FDA. Worse safety outcomes for orphan drugs may also be related to the patient population in which these drugs were tested, rather than the drugs themselves, although many orphan and nonorphan drugs in this sample were tested in patients with advanced disease who had received 1 or more prior chemotherapy regimens.

The Orphan Drug Act is widely regarded as a watershed piece of legislation that has helped spur the development of numerous useful drugs for rare medical conditions. However, given the limited evidentiary basis on which orphan cancer drugs are approved, the act may need to be amended so that its resources can be more selectively guided to first-in-class drugs or those that treat a condition for which no other treatments are available, and to ensure that orphan products are rigorously evaluated and closely followed up once they are approved.

Author Contributions: Dr Kesselheim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kesselheim, Avorn.

Acquisition of data: Kesselheim, Myers.

Analysis and interpretation of data: Kesselheim, Myers, Avorn.

Drafting of the manuscript: Kesselheim, Avorn.

Critical revision of the manuscript for important intellectual content: Kesselheim, Avorn.

Statistical analysis: Myers.

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Study supervision: Avorn.

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