FDA Requirements for New Molecular Entities for the Treatment of Cancer

By Edward Tabor, MD

New products for cancer indications are often approved by the US Food and Drug Administration (FDA) based on fewer and smaller clinical studies containing a smaller percentage of US patients than treatments for other diseases. For most products used to treat other diseases, FDA usually requires that New Drug Applications (NDAs) have at least two controlled clinical trials.

The more flexible requirements for cancer treatment may be explained by the fact that the treatment of many cancers is still an “unmet medical need,” and many are low-prevalence diseases. In addition, the trend toward targeting cancer treatment for particular stages of a cancer, or for “first-” or “second-line” treatment, adds to the difficulty of conducting large clinical trials.

New Cancer Treatments Approved in 2009 and 2010

The present analysis of FDA’s review and approval of New Molecular Entities (NMEs) for cancer treatments, conducted using publicly available review documents, showed that only four NDAs for NMEs for cancer were approved during 2009 and only two during 2010 (Table 1). These were for the treatment of cutaneous or peripheral T-cell lymphoma (two products), renal cell carcinoma (two products), breast cancer and prostate cancer.

One (Folotyn) was approved under accelerated approval (“Subpart H”), a process that permits the use of surrogate endpoints in clinical trials followed by postapproval studies to verify the effect on clinical endpoints. In addition, three non-NME products were approved for cancer treatment during the same years: two non-NME NDAs (one for glioblastoma in 2009 and one for prostate cancer in 2010) and one Biologics License Application (BLA) (for chronic lymphocytic leukemia in 2009).

Four of these six NME NDAs were approved on the basis of one Phase III controlled study each, of which two were placebo-controlled studies (these were “pure placebo” controlled studies with best supportive care) and two were active-controlled studies. The number of patients in the experimental drug arm of each study ranged from 277 to 508.

The two other NME NDAs were approved for cancer treatment on the basis of single-arm studies. One had two single-arm studies of 96 and 71 patients each. The other had one single-arm study of 111 patients, which FDA agreed to beforehand and designated as a Phase II study of “at least 100 patients.”

Study endpoints varied among the six NME NDAs approved for cancer in 2009 and 2010. For the two products with one Phase III study each with an active-treatment control, the endpoint was Overall Survival and the differences between test drug and comparator were 2.5 months (13.1 vs. 10.6 months), and 2.4 months (15.1 vs. 12.7 months). For the two approved with one placebo-controlled study each, the endpoint was Progression Free Survival, and the differences between test drug and placebo were 5.2 months (9.4 vs. 4.2 months), and 3.0 months (4.9 vs. 1.9 months). For the two approved based on one or two single-arm studies, endpoints were Overall Response Rates by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and were found to be 27%, 34% and 35% each.

Only one of these six oncology NMEs (Votrient) was required to have a Risk Evaluation and Mitigation Strategy (REMS), and that REMS consisted only of a Medication Guide. For each of the other five NMEs, however, some postmarketing study commitments were required, although not under a REMS.

The Pediatric Research Equity Act (PREA) requirements were waived for all six NMEs for cancer treatment. Four were waived on the basis of the diseases not occurring in pediatric age groups. Two others were waived because the NMEs had orphan product designation, which exempts a product from PREA requirements.

Clinical Trials “Applicable to the US Population”

Inclusion of sufficient numbers of US patients in a clinical trial to meet stated or perceived FDA expectations is often a challenge for study sponsors. In fact, FDA regulations only require that each NDA be supported by clinical studies whose “data are applicable to the US population and US medical practice,” and these regulations even permit the approval of an NDA based solely on studies...
conducted outside the US if certain criteria are met. In practice, study sponsors often meet these requirements by inclusion of a sufficient number of US patients in at least one of the clinical trials.

In the six NDAs for NME cancer treatments approved in 2009 and 2010, the percentage of US patients in individual pivotal studies ranged from 0–68%. In some of these six, the FDA reviewer specified that the study had included a certain number of Canadian patients in conjunction with the number of US patients, indicating that some FDA reviewers might accept the inclusion of Canadian patients to compensate for fewer US patients, due to the similarities in the US and Canadian populations and standards of medical care.

However, one of the NDAs was approved without having included any US patients in the one pivotal study (that study also had no Canadian patients), and two were approved with each having only 19% of patients from the US. In situations where a non-US study population is thought to be reasonably representative of the US patient population, FDA regulations urge the study sponsor to seek a discussion with FDA to justify this conclusion.

### Table 1. Review and Approval of New Molecular Entities

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Generic Name</th>
<th>Labelled indication in initial approval</th>
<th>Design of pivotal studies</th>
<th>Number of patients per arm</th>
<th>Number of patients in US</th>
<th>Primary endpoint</th>
<th>REMS</th>
<th>PREA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2009 Approvals</strong></td>
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<tr>
<td>Istodax</td>
<td>Romidepsin</td>
<td>Cutaneous T-cell lymphoma, 2nd line</td>
<td>Two single-arm studies, designated “1.” and “2.”</td>
<td>1. Istodax 96</td>
<td>1. 18 (19%)</td>
<td>1.0RR (CR+PR) = 34%</td>
<td>No</td>
<td>Waived because orphan drug</td>
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<td></td>
<td>2. Istodax 71</td>
<td>2. 56 (79%)</td>
<td>2.0RR (CR+PR) = 35%</td>
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<td>Votrient</td>
<td>Pazopanib</td>
<td>Advanced renal cell cancer</td>
<td>One Phase III randomized placebo-controlled; with or without prior Rx</td>
<td>Votrient 290</td>
<td>US: 0</td>
<td>PFS Votrient = 9.2 months; Placebo = 4.2 months</td>
<td>Yes</td>
<td>Waived because not disease of pediatric population</td>
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<td></td>
<td></td>
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<td>Placebo 145</td>
<td>Canada: 0</td>
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<td>Folotyn</td>
<td>Pralatrexate</td>
<td>Refractory peripheral T-cell lymphoma</td>
<td>One single-arm open label Phase 2 of “at least 100 pts” agreed</td>
<td>Folotyn 111</td>
<td>76 (68%)</td>
<td>ORR = 76/109 (27%)</td>
<td>No</td>
<td>Waived because orphan drug</td>
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<tr>
<td>Afinitor</td>
<td>Everolimus</td>
<td>Advanced renal cell cancer after sorafenib or sunitinib</td>
<td>One Phase III randomized placebo-controlled</td>
<td>Afinitor 277</td>
<td>US: 111 (27%) [68 Afinitor; 43 placebo]</td>
<td>PFS Afinitor = 4.9 months; Placebo = 1.9 months</td>
<td>No</td>
<td>Waived because not disease of pediatric population</td>
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<td><strong>2010 Approvals</strong></td>
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<td>Halaven</td>
<td>Eribulin</td>
<td>Metastatic breast cancer, 2nd line</td>
<td>One Phase III randomized two-arm “physician’s choice” active control</td>
<td>Halaven 508</td>
<td>US: 146 (19%) [100 Halaven; 46 control]</td>
<td>OS Halaven = 13.1 months; Control = 10.6 months</td>
<td>No</td>
<td>Waived because not disease of pediatric population</td>
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<td></td>
<td></td>
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<td></td>
<td>Control 254</td>
<td></td>
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<tr>
<td>Jevtana Kit</td>
<td>Cabazitaxel</td>
<td>Hormone-refractory prostate cancer, 2nd line</td>
<td>One Phase III open-label active control</td>
<td>Jevtana + prednisone 378; Mitoxantrone + prednisone 377</td>
<td>Some but not stated how many</td>
<td>OS Jevtana = 15.1 months; Control = 12.7 months</td>
<td>No</td>
<td>Waived because not disease of pediatric population</td>
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Approval of NDAs Based on Single-arm Studies

In 2009 and 2010, FDA approved two NDAs for NMEs for the treatment of cancer on the basis of single-arm studies. One was approved under accelerated approval and the other was not. It is interesting that more than half of the 49 oncology drugs granted accelerated approval by FDA between the inception of the accelerated approval process in 1992 and the year 2011 were approved based on single-arm studies. However, the FDA Oncologic Drugs Advisory Committee (ODAC) recently recommended that “the bar for accelerated approvals should not be lowered to move products onto the market faster through single arm trials, but rather single arm trials should only be used in certain situations,” which it defined as trials for treating rare diseases or trials of products that are known to have a high level of activity. It is not known whether FDA will follow the ODAC suggestions.

Conclusions

In 2009 and 2010, FDA approved NMEs for cancer treatment based on smaller numbers of studies, smaller numbers of patients and a smaller percentage of US patients compared with NMEs for many other diseases, and even approved two of these NMEs based on single-arm studies. FDA’s willingness to approve NMEs for cancer on the basis of fewer and smaller studies, including sometimes on the basis of studies conducted entirely outside the US, reflects the urgent need for safer and more effective treatments for uncommon cancers, as well as the increasing specificity of oncology drugs and the increased targeting of oncology indications in labeling for use as first- or second-line treatment for a specific cancer.

References


4. Ibid.


Author

Edward Tabor, MD, is vice president of global regulatory affairs and head of regulatory affairs for North America at Quintiles. He was formerly an FDA division director in both the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. He can be reached at edward.tabor@quintiles.com.