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ONCOLOGY PROs: Limited Use Due To Small Trials, Fast Drug Development

By Kate Rawson, 27 April 2016

The success of the Breakthrough Therapy designation is nowhere better demonstrated than in oncology drug development.

Breakthrough emerged from the oncology drug review process at the Food & Drug Administration, and the “all-hands-on-deck” approach to development and application review has been enthusiastically adopted by review teams in the Office of Hematology & Oncology Products. Since the start of the designation in 2012, more than half of the Breakthrough approvals have been in oncology and hematology.

For treatments that have a big response rate in under-treated cancers, FDA has many tools at its disposal: single-arm trials, open-label studies, approvals based on Phase I/II data, and reviews that can be completed in just a few months. That’s all made possible by a solid understanding of cancer biology and the development of targeted therapies that can show big response rates. (“FDA Outlines “Expedited” Review For Breakthrough Therapies; “Hyper-Fast” Reviews, Beyond Oncology” —The RPM Report, March 2015)

The speed and efficiency of recent oncology reviews, however, may have a downside to another emerging trend in drug approval reviews: consideration of the patient experience in clinical trials.

FDA and drug sponsors rely on clinical endpoints like overall survival and tumor growth when assessing the efficacy of a new oncologic – and rightly so. But the degree to which a drug or biologic improves symptoms or increases toxicities are also important to patients. Accelerated drug development pathways – while critical to quickly getting new cancer treatments on the market quickly – mean sponsors don’t always have time to measure patient-reported outcomes, or design the kind of trials optimal for their use.

Patient-reported outcomes, or PROs, are growing in importance in drug development, because they help inform patients on how they may react to a treatment regimen. FDA’s patient-focused drug development initiative has pushed that agenda, but oncology has lagged behind other areas of pharmaceutical R&D in prioritizing the patient experience by including PROs in clinical trials – and including them in approved labeling. Without PROs, advocates say, a critical piece of drug development is lost.

Drug development pathways like Breakthrough and Accelerated Approval allow sponsors to conduct clinical trials in a small number of patients that might be open-label or have a single treatment arm. But those design features also make it difficult to include validated patient outcomes, because of the risk of bias. Furthermore, abbreviated development programs don’t always give sponsors enough time to consider PROs – or design quality measures that have a chance of making it into labeling.

The research bears that out. Of the 40 drugs approved by FDA’s Office of Hematology & Oncology Products between January 2010 and December 2014, just three (7.5%) included patient-reported outcomes in the label, according to a study published online by Ari Gnanasakthy, MD, et al. in the Journal of Clinical Oncology on April 11. Gnanasakthy is the head of patient reported outcomes at RTI Health Solutions, and a former Novartis AG exec.

That is significantly less than the 24% rate of PRO labeling reported for all novel drugs and biologics in a similar review between 2006 and 2010. (“Getting With The PRO-gram: Making Patient-Reported Outcomes Work” —The RPM Report, November 2014) FDA review divisions like Neurology and Gastrointestinal are far more likely to discuss patient-reported outcomes with sponsors, while other divisions, like Oncology, historically are not. That’s due in part to the design of oncology clinical trials, and...
the fact that oncology indications are far more likely to use abbreviated development pathways.

There are signs that things may be starting to change. FDA reviewers are increasingly sensitive to the importance of PROs, and have taken steps to encourage sponsors to better capture patient outcomes in the label. (“PRO-ving Ground: FDA Review Teams Commit to Patient-Reported Outcomes” — The RPM Report, May 2015)

Officials in the Office for Hematology & Oncology Products are now acknowledging a need for “flexibility” on the development and use of patient-reported outcomes for cancer products, and a willingness to reexamine PRO tools that can be used by sponsors. That’s a far better environment for PROs than the historical landscape.

Not an Ideal Setting for PROs

It’s well understood that certain clinical trial designs are more amenable than others to supporting the inclusion patient-reported outcomes. The most ideal setting, as Gnanasakthy et al. note, are randomized, double-blind, placebo-controlled studies – and the larger the patient population studied, the better. But that’s not the typical design for oncology products.

Based on a sample of the 160 new molecular entities and novel biologics approved between 2011 and 2014, pivotal trials for oncology products, when compared to non-oncology, were far more likely to be single-arm (37.5% vs. 8.3%) and open-label (67.5% vs. 8.3%), and far less likely to be double-blind, randomized-controlled trials (35% vs. 87.5%). Furthermore, 35% of the oncology trials had fewer than 200 patients in registration trials, versus 15.8% of non-oncology products.

That is not the ideal setting to assess patient-reported outcomes. As FDA notes in its 2009 guidance document on PROs, “open-label clinical trials, where patients and investigators are aware of assigned therapy, are rarely adequate to support labeling claims based on PRO instruments.” Patients who know they are in an active treatment group may over-estimate the benefit, the guidance says, whereas patients who know they are not on active treatment may under-report any actual improvement.

Gnanasakthy and his colleagues, however, argue that even open-label designs can yield beneficial insight into the patient experience. “Despite fears of potential bias, PRO findings from single-arm, open-label studies can provide useful data to patients and physicians who may want to compare experience with supportive care or standard of care. These studies can be useful for reviewers who may want to study the experience of patients during progression-free survival.”

That point came up during the 2011 advisory committee review of Seattle Genetics Inc.’s Adcetris (brentuximab). The high response rates in progression-free survival in the treatment of Hodgkin’s lymphoma led the advisory committee to call Adcetris the “poster child” for single-armed accelerated approval. But one committee member who supported the approval, Mikkael Sekeres, MD (Cleveland Clinic), said that without patient-reported outcomes, “progression-free survival alone is a Pyrrhic victory.” (“Adcetris Review Adds Some Clarity To Principles For Accelerated Approval” — “The Pink Sheet,” Jul. 25, 2011)

A more recent example is Clovis Oncology Inc.’s Xegafri (rociletinib) in EGFR T790M non-small cell lung cancer. The application was up for FDA advisory committee consideration on April 12, based on a single-arm trial for accelerated approval.

Clovis argued that, while FDA had concerns about potential long-term side effects (represented by QT prolongation and elevated blood sugar levels), the product offered substantial benefits in short-term quality of life degradation compared to other treatments (which have side effects like severe rashes). Based on the seriousness of the disease, the company said, less risk of short-term side effects might be much more meaningful to patients.

The suggested side effect benefits, however, were undercut by Clovis’ inability to collect data effectively from the single-armed trial that was the basis of the accelerated approval pathway. After discussing the potential benefits, the committee voted strongly (12-1) that Clovis first submit an ongoing Phase III randomized trial prior to approval. (“Clovis’ Rociletinib Facing Three-Year Delay If FDA Follows Panel’s Lead” — “The Pink Sheet” DAILY, Apr. 12, 2016)

Examples of oncology/hematology products approved with PROs in the label are few and far between. (See Exhibit 1.)

Gnanasakthy et al. cite three during the 2010-2014 study period: Pfizer Inc.’s Xalkori (crizotinib), Incyte Corp.’s Jakafi (ruxolitinib) and Janssen Biotech Inc.’s Zytiga (abiraterone). Jakafi treats myelofibrosis, which is a hematological malignancy that is often treated with chemother-
**SCARCE USE OF PROS IN ONCOLOGY LABELING**

<table>
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<th>Year</th>
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<th>No. of Nononcology NMEs and BLAs Approved</th>
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Abbreviations: BLA, biologic license application; FDA, US Food and Drug Administration; NME, new molecular entity; CHOP, Office of Hematology and Oncology Products; PRO, patient-reported outcome.


Final labeling included a PRO reported in the adverse event section of labeling: a higher incidence of “visual disturbances” as measured by the Visual Symptom Assessment Questionnaire-Anaplastic Lymphoma Kinase.

So while patient-reported outcomes are more often used by sponsors to demonstrate a quality of life benefit of a new therapy, Xalkori is an example of a side effect added to labeling as a PRO.

“Visual disturbances” was among the most common adverse event reported by patients in Xalkori registration trials, and while initial reports were mild (including floaters and blurred vision), FDA later added a 0.2% incidence of “severe vision loss” to the Warnings and Precautions section of labeling based on additional studies and post-marketing reports. Pfizer will further explore the vision loss side effect with a pharmacovigilence study to be completed in 2021.

Xalkori was a relatively rare example of an oncology drug approved with a PRO in labeling. But because the patient-reported outcome of vision disturbances was a safety issue – and not an attempt by Pfizer to show increased benefit – FDA was more likely to push to include the finding in labeling. Understandably, the agency tends to have a higher bar with patient-reported outcomes when the results show a benefit versus an increased risk with the drug.

Indeed, Pfizer included three other patient-reported measures in Xalkori’s early clinical program that were not added to the FDA-approved label, Gnanasakthy et al. note. Those three are more general health quality measures, they say, and may have been included to satisfy European regulators, who are more likely than FDA to approve labeling with PROs.

A second patient-reported outcome did make it into Xalkori labeling as part of a September 2015 labeling revision. An open-label, randomized, two-arm Phase III study comparing Xalkori versus chemotherapy included the patient-reported outcome of “lung cancer symptoms.”

“Lung cancer symptoms” was an exploratory patient-reported measure of dyspnea, cough, and chest pain, which suggested a delay in time to development or
worsening of dyspnea, but not cough or chest pain, in patients treated with Xalkori as compared to chemotherapy, labeling says.

Of note, the revised label also states that “the patient-reported delay in onset or worsening of dyspnea may be an overestimation, because patients were not blinded to treatment assignment.”

A More “Flexible” FDA

There were a number of other incidences (13) of products approved by the FDA’s Office of Hematology & Oncology Drug Products during 2010-2014 for which sponsors included PROs in clinical trials, but the results did not end up in labeling. In some cases, PROs were poorly designed from the start, or had too many missing values or protocol deviations. In others, the results are simple not reported to FDA. (See Exhibit 2.)

Gnanasakthy et al. suggest that the various regulatory pathways designed to speed up the development and review of high-need oncology products may lead sponsors to lower the priority for PROs. The researchers found that between 2011 and 2014, oncology products were far more likely to be approved using fast track (65.8% vs. 30%), priority review (78.9% vs. 36%) or accelerated approval (36.8% vs. 3%) than non-oncology products approved during the same time frame.

Low on time and careful on research budgets, sponsors may be more likely to use standard, “off-the-shelf” measures rather than develop those that are product-specific, Gnanasakthy et al. say. The product-specific measures could provide data that is more useful to patients – and more likely for FDA to agree to include in final labeling.

Stakeholders have also long-complained that under FDA’s 2009 guidance document on patient-reported outcomes, many legacy PRO measures no longer qualify and it is exceedingly difficult to develop and validate new ones. Those issues may prompt sponsors to push PROs into a long list of other secondary endpoints – or be

PROBLEM PROS: ONCOLOGY MEASURES THAT MISSED
included as an exploratory endpoint, the paper says. That often leads to “protocol violations and missing values, which often result in data that cannot be analyzed.”

On that point, however, FDA has acknowledged that sponsors need a bit more flexibility to address the specific challenges of oncology clinical trials.

Paul Kluetz, MD, a senior official in FDA’s Office of Hematology & Oncology Products and a thought leader on patient-reported outcomes, was the lead author on an article published online in Clinical Cancer Research on January 12, 2016 that gave new advice to sponsors interested in incorporating PROs oncology clinical studies. The article was co-authored by FDA officials in OHOP and the Office of Biostatistics.

FDA’s guidance on PRO development may have outlined the “optimal” path to developing new measures and incorporating them into clinical trials, Kluetz et. al note, but “flexibility” will be needed on the part of the agency in implementing the guidance for oncology products, given the unique challenges encountered with many clinical trials in cancer – open-label, single-arm designs.

“Continued efforts must be undertaken to identify the optimal PRO strategy for single-arm trials and to characterize and mitigate effects of open-label trial designs,” the FDA officials say.

Recognizing that the current focus on endpoints such as response rate, progression-free survival and overall survival, Kluetz et. al acknowledge a “need to reexamine the measurement tools available to assess key health-related contributors to the quality of life of patients in oncology clinical trials.” The researchers then outline in detail a PRO strategy that focuses on separate measures of three key elements of a patient’s health-related quality of life: symptomatic adverse events, physical function, and disease-related symptoms.

Perhaps example of a new flexibility was the review and approval of Amgen Inc.’s oncolytic virus therapy Imlygic (talimogene laherparepvec) for melanoma. (The application was handled by FDA’s Center for Biologics Evaluation & Research, not the CDER OHOP group – which may also be a factor.)

According to recently released review documents, a key element to FDA offering full approval to Imlygic was advisory committee testimony from patients about the psychological advantages of witnessing their melanoma lesions shrink. Those sentiments ultimately swayed FDA, despite concerns about the clinical meaning of the pivotal trial’s durable response rate endpoint. (“Patient Voices Swayed FDA’s Imlygic Review Team” — “The Pink Sheet,” Apr. 25, 2016)

Kluetz et.al also have advice for how to improve the use of current measures. “Regardless of the instruments used or concepts being measured, conveying the importance of the completion of PRO measures to patients, investigators, and research staff may reduce missing data and improve data quality,” they say. “Additional areas that will require collaborative work include the standardization of both data analysis and presentation of PRO information.”

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