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Real-World Evidence May Find A Home On Breakthrough Pathway

by Sue Sutter

Industry, patient advocates seek to use data collected outside traditional clinical trials to confirm benefit or broaden labeling, but FDA officials say large drug effects would be needed to overcome 'noise' from more loosely structured studies.

Breakthrough-type drugs for which effect sizes are expected to be large may provide a potential avenue for using real-world evidence to confirm clinical benefit or expand labeled indications.

Industry representatives and patient advocates are eyeing opportunities for using real-world evidence in lieu of confirmatory trials for accelerated approval drugs and to broaden labeling for approved treatments. However, FDA officials caution that drug effects would need to be robust to ensure that efficacy can be detected in studies less rigidly controlled than clinical trials.

Real-world data can inform FDA regulatory actions beyond product approval, including risk management plans and labeling warnings.

Even if real-world data are not sufficient to form the basis for approval or labeling expansion, they can inform other FDA regulatory actions, including risk management plans and label warnings and precautions, agency officials said.

There is increasing interest among industry, FDA, patients and other stakeholders in leveraging real-world data – such as electronic health records, pragmatic clinical trials and other types of

information generated outside of the traditional controlled, clinical trial setting – to speed the development of new drugs or expand labeled indications while also reducing the costs of development.

However, there are a host of regulatory, technical and practical hurdles standing in the way of greater development and reliance on real-world evidence (Also see "*Real-World Evidence: Efficacy Assessments Await FDA Clarity, Pilot Projects*" - Pink Sheet, 14 Mar, 2016.).

There also is a recognition that collaboration is needed among all stakeholders – including data providers, practitioners, industry and the agency – to truly leverage real-world evidence.

"There are multiple foreseeable steps that we're going to have to go through and each party is going to have to do some things," Center for Drug Evaluation and Research Director Janet Woodcock said at a recent conference on real-world evidence.

"At FDA we are thinking and we will put out guidance and different things like that on how you could use evidence from nontraditional clinical trials. Hopefully that will cheer people up and think we can do this for regulatory purposes. [That] may be necessary, but is no means sufficient. There are so many additional things that have to be done to make this reality."

Confirmatory Evidence For Accelerated Approval

The June 16 conference, "A Blueprint for Breakthrough: Exploring Utility of Real-World Evidence," was sponsored by Friends of Cancer Research and Alexandria Summit. The multi-stakeholder meeting was convened with the goal of developing consensus toward potential use of real-world evidence in the regulatory setting.

The issue brief for the meeting states that real-world evidence may have utility in certain situations, such as in the case of breakthrough-designated products, "where the effect size is likely to be significantly larger than any confounding factors that might occur and where confidence in the original efficacy data is relatively high."

"While there may be concerns regarding data quality, owing to factors such as missing information and non-systematic data collection, information gathered from [electronic health records] can allow for data to be collected on more patients, in an unselected patient population and more rapidly than traditional Phase IV trials designed to meet post-market requirement and commitments," the brief states.

The paper includes case studies illustrating possible uses for real-world evidence collection, including fulfillment of confirmatory trial requirements under accelerated approval.

Pfizer Inc.'s kinase inhibitor *Xalkori* (crizotinib) received accelerated approval in August 2011 for

treatment of patients with locally advanced or metastatic non-small cell lung cancer that is anaplastic lymphoma kinase (ALK)-positive. Initial approval, which was based on response rate, predated the breakthrough therapy program created through the 2012 FDA Safety and Innovation Act.

Under accelerated approval, Pfizer was required to complete confirmatory trials in treatment-naïve and previously treated patients. Crizotinib received full approval in November 2013 based upon progression-free survival results in the trial of treatment-naïve patients.

A retrospective medical record review for 212 patients showed results that were supportive of the Phase III data on crizotinib.

The drug subsequently received a breakthrough therapy designation for ROS1-positive advanced NSCLC. An sNDA in this population was approved in March.

A retrospective medical record review for 212 patients in the US and Canada who initiated crizotinib as first- or later-line therapy showed results that were supportive of the Phase III data. "Response rates seen in the real-world cohort study (66% overall; 69% in first line and 60% in second- or later-line) were similar to the response rates seen in treatment-naïve patients (74%) and previously treated patients (65%) in the clinical studies," the issue brief states. "One-year survival rates in first-line patients (85%) from the real-world chart review was also similar to the one-year survival rate seen in the clinical study of treatment-naïve patients (84%)."

This retrospective evaluation begs the question of whether the confirmatory data required under accelerated approval could be satisfied through, or supplemented with, real-world evidence.

"We are proposing that … in breakthrough-type drugs the confirmatory studies could be indeed done, hopefully, as real-world studies," said Maria Koehler, Pfizer VP-oncology strategy, innovation and collaborations. "The type of the real-world evidence needs to be obviously discussed and agreed with FDA, but it could be either a pragmatic randomized trial, it could be contemporaneous historical controlled data, it could be registries. It could be many, many things."

When asked for his view of the crizotinib case study, Sean Khozin, senior medical officer in FDA's Office of Hematology and Oncology Products, said that at the time of the drug's original approval

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targeted therapy based on ALK mutation status was a new concept. However, had there been high-quality repositories or registries of genomic sequencing data on ALK-positive patients at that time, they might have been explored as a means for confirming efficacy, he said.

"That's why it's really important to start sequencing patients as part of routine care even for mutations that may not be actionable today, because tomorrow we may want to interrogate these real-world data repositories to get prognostic information for these rare mutations," Khozin said.

Khozin is heading up an OHOP initiative aimed at standardizing existing clinical trial datasets and integrating those with real-world data streams (*see sidebar*).

Discerning Treatment Effects From 'Noise'

However, FDA's Woodcock expressed some skepticism about using real-world evidence as the basis for labeling expansions for breakthrough-designated drugs.

"It's useful to start with something you can get your arms around, so that's probably why people have proposed it," she said. "But you know it doesn't follow that if it's a breakthrough in one tumor type it's going to be in another tumor type." In addition, "outside of cancer most of the breakthroughs are very targeted, and so they probably won't work elsewhere necessarily."

One reason for conducting randomized, controlled trials with rigid parameters is so that small treatment effects can be discerned from "noise," Woodcock said. "The underlying hypothesis here would be this has a very large treatment effect, we can tolerate a lot of heterogeneity, and we can tolerate a looser structure and if it's real we'll still discern it."

Similarly, OHOP Director Richard Pazdur said that in the era of breakthrough therapies with large effect sizes, strict enrollment criteria in controlled clinical trials are not needed to make a drug look better, as would be necessary when a drug has only marginal effects.

Pazdur talked about one real-world study idea that the agency has pitched to sponsors of PD-1 inhibitors, the breakthrough-designated, immuno-oncology agents that have demonstrated large treatment effects in multiple cancer populations (*see sidebar*).

A Role Beyond Approval

Pazdur, however, noted that there are other potential regulatory uses for real-world evidence outside of the decision on approval of a new drug or expanded indication.

Real-world data can help detect safety signals not seen in clinical trials and can provide information on how a drug compares to the standard of care actually used in clinical practice versus the comparator tested in a trial, he said. The agency also might be able to learn important lessons about how label warnings, precautions and Risk Evaluation and Mitigation Strategies are

implemented in clinical practice.

In addition, real-world data also can inform how well a drug works at controlling or ameliorating symptoms (*see related story,* (Also see "*Clinical Trial Endpoints May Not Fit Real-World Studies*" - Pink Sheet, 27 Jun, 2016.)). This, in turn, could lead to confirmation of clinical benefit for an accelerated approval drug, Pazdur said.

Pazdur also echoed remarks by Commissioner Robert Califf that randomized controlled trials and real-world evidence should be viewed as complementary, not polar opposites (Also see "*FDA's Califf On Real World Evidence: 'Use It For The Right Purposes'*" - Pink Sheet, 17 Jun, 2016.).

"There doesn't have to be this ... alpha and omega type of thing here," Pazdur said. "They could be merged and looked at in getting data reliably to us."