Blueprint Proposes Using Real-World Data to Speed Drug Approvals

BY PEGGY EASTMAN

In an effort to bring new drugs to cancer patients faster, the Friends of Cancer Research (FOCR) and Alexandria Summit collaborated in a meeting in Washington, D.C., to consider how real-world evidence can be used along with data collected from traditional randomized, controlled clinical trials in the approval of new drugs. The organizations presented a draft document called Blueprint for Breakthrough: Exploring the Utility of Real World Evidence.

“These are real-world patients who are suffering,” said FOCR Chair and Founder Ellen V. Sigal, PhD. Real-world evidence, as defined by FOCR, is evidence derived from the use, benefits, and risks of medicines that fall outside the bounds of the classic clinical trial settings, including use of data routinely collected in the daily practice of medicine, and thus reflects the heterogeneous

ASCOC 2016: Hematological Malignancies

BY RAVI VIJ, MD, MBA

The 2016 American Society of Clinical Oncology Annual Meeting had more than its fair share of breaking news about advances in a variety of hematological malignancies. There were a lot more sessions dedicated to blood cancers this year and hematological neoplasms were well-represented right from the plenary session to individual tracks on plasma cell dyscrasia to leukemia, myelodysplastic syndromes and allogeneic transplant to lymphoma and chronic lymphocytic leukemia. It is worthwhile to review some of the seminar abstractions and salient findings.

Multiple Myeloma

Monoclonal Antibodies: Daratumumab
Palumbo et al (Abstract LBA4) presented results of the phase III randomized controlled study of daratumumab, bortezomib and dexamethasone versus

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Novel Drug Development in CLL & HNL

BY ROBERT H. CARLSON

The results of a trial combining two novel agents in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) should serve as a cautionary tale to researchers developing novel agents.

The phase II dose-escalation study of idelalisib and entospletinib in 66 patients with relapsed/refractory CLL or NHL had to be terminated because of severe treatment-emergent pneumonitis in 12 patients (18%), including two who died. The study was published recently in Blood (2016;127:2411-2415).

The researchers pointed to the study design’s rapid intrapatient dose escalation schedule and consequent short window for dose-limiting toxicity to explain the pneumonitis, which was life-threatening in 11 of the 12 patients.

They recommend future clinical trials with novel agents be designed with an increased focus on safety, and thoroughly incorporate pharmacodynamics and other biomarker monitoring to predict unique toxicities.

“This clinical trial is a cautionary tale of why the classic manner in how we develop novel agents needs to remain as it has been, proceeding in a very conservative, cautious manner, where safety is our first priority,” said lead author Paul M. Barr, MD, Associate Professor of Medicine and Director of the Clinical Trials Office, James P. Wilmot Cancer Center, University of Rochester Medical Center in New York. “Future studies really need to keep this experience in mind.”

Barr said that, even without the trial’s short dose-limiting toxicity window, the traditional monitoring period

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progression-free survival as an endpoint, into the use of real-world data “may not be appropriate.”

On the other hand, what may be especially useful, said Pazdur, is using real-world data to focus on patients’ symptoms and to build health-related quality-of-life data into real-world evidence. Pazdur noted toxicity issues may not always surface in a clinical trial, but they could surface if real-world evidence is collected. As an example, he cited osteonecrosis of the jaw, a toxic side effect of the use of bisphosphonates in some patients that might have surfaced earlier if real-world EHR data had been collected and looked at systematically.

“We are still very tied to the clinical trial,” said Jeff Helterbrand, PhD, Senior Vice President and Global Head of Biometrics at Roche. But, he said, “I think oncology is getting to the point where we can’t always do a clinical trial.” That, he noted, is because the standard of care in oncology is changing very rapidly, and—agreeing with Woodcock—because “clinical trials take too long.” Helterbrand emphasized that “we need to open up the window beyond the clinical trial.”

Helterbrand praised the Targeted Agent and Profiling Utilization Registry (TAPUR) study launched in March 2016 by ASCO as an example of leveraging real-world evidence from clinical practice. TAPUR is a nonrandomized pragmatic trial whose goal is to collect data on the safety and efficacy of approved therapies in other disease settings. TAPUR, like other pragmatic trials, is a prospective intervention that leverages the existing clinical infrastructure to test therapies in everyday clinical settings to maximize their therapeutic applicability and generalizability.

On the whole, payers are “very supportive” of the idea of using real-world data as another pipeline in evaluating a new therapy, said Roy Beveridge, MD, a medical oncologist who is Chief Medical Officer and Senior Vice President at Humana. Beveridge noted that most of the cancer patients who are Humana beneficiaries are of Medicare age and are taking a number of medications for multiple conditions. Therefore, “we struggle trying to find out what is cost-effective and safe” for these patients, he said. Real-world evidence could help in making treatment decisions for this population.

Peggy Eastman is a contributing writer.
Welcome to WK Oncology.com

BY LYNN NACE

As we continue our mission of delivering high-quality oncology news, analysis, and updates, we’re pleased to present a new interactive and educational resource center, WK Oncology.com. This debut content gateway is dedicated to renal cell carcinoma (RCC).

Available online now, you’ll find regularly updated articles on topics such as “First-line Therapy for Treatment Naïve Patients,” “Era of Expression in Renal Tumors,” and “Implications for the Classification of PEComas and the Differential Diagnosis With Metastatic Renal Cell Carcinoma,” to name a few. And of course the latest FDA updates are included, such as the recent approval of cabozantinib (Cabometyx) for the treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy.

What’s more, WK Oncology.com features expert video commentary from renowned RCC authorities who share perspective on game changers in RCC developments, research and funding activities, and more. And Michael Harrison, MD, Assistant Professor of Medicine, Duke Cancer Institute, provides an exclusive and timely blog on the latest RCC trends.

WK Oncology.com also provides you invaluable access to the Renal Cell Carcinoma 5 Minute Consult as well as information you can share with your patients, the “Understanding Kidney Cancer” anatomical chart. We invite you to test your RCC knowledge with the interactive Expert Q&A. Simply read the scenario, select from a list of possible responses, and the correct answer (with explanation) will appear.

To complete the package and take the WK Oncology Renal Cell Carcinoma Resource Center one step further, we’ll also include four digital magazine editions. An easily identified icon for this traditional magazine in a digital format will be an option on the homepage. The first digital edition includes the latest RCC information and study results garnered from the American Society of Clinical Oncology meeting in June.

As the content and features will be updated weekly, we encourage you to visit WK Oncology.com often. We welcome input, feedback and comments on this exciting new initiative. 01

Dose escalation has to be slow and careful despite the pressure to move drugs through the pipeline. Second, it’s important not only to monitor individual patients but also monitor the data sets very carefully.

**What Appears Safe Is Sometimes Not**

An editorial accompanying this report in Blood summarized the balance researchers have to maintain in developing new treatments:

- **Wants:** maximizing dose for best response, and moving drugs quickly through the pipeline;
- **Musts:** more frequent and rigorous monitoring for toxicity, and increased use of biomarkers to predict toxicity (*Blood* 2016;127:2367-2368).

“A harmony between ‘musts’ and ‘wants’ in clinical trials is essential to ultimately increase survival,” said the authors, Spencer H. Bachow, MD, a fellow in oncology at Columbia University, and Nicole Lamanna, MD, Associate Professor of Medicine, Columbia University Medical Center.

This trial report “is an eye opener,” said Lamanna, the senior author, told Oncology Times. “It’s a warning of what to be careful of with these exciting new agents.”

As anticancer treatment enters the new territory of novel targets, particularly with those agents that harness the power of the immune system, researchers are just now learning that these drugs can stimulate the immune system in a different manner from the traditional chemo-immunotherapy approaches used for decades, she said.

“And when we try to combine some of these, we realize we have to be more careful how we design clinical trials to allow more time to watch for possible unanticipated side effects that may develop, particularly some of these inflammatory mediated responses such as pneumonitis.”

Lamanna noted pneumonitis has been seen with this class of drugs, “but clearly the combination for some reason enhanced the side effect. We don’t know the true mechanism.”

Dose escalations were allowed every 2-4 weeks, which might not have been enough time between escalations to observe side effects and begin to intervene soon enough, she explained.

Lamanna said there is another side to this balancing act—protecting patients, but not in a way that prevents a potentially active drug from being studied. “We’ve lost some good drugs that might have shown activity against a certain cancer, but they were nixed because they had side effects that we had to learn to deal with,” she concluded. 07

**CLL & NHL continued from page 11**

approximately 2-4 percent of patients,” he said. “But in this trial, it was 18 percent, a big surprise.”

Barr said that, interestingly, pneumonitis is now recognized as a complication across the PI3K inhibitors as well as in other classes of drugs, such as those that target the PD-1/PD-L1 axis.

“In fact, a lot of our novel agents that have pleiotropic effects on the immune system can cause such toxicities, another example of how we’re learning as we develop these drugs,” he said.

Barr said two lessons can be learned from this trial:

“First, drug development is not for the faint of heart and we have to do it in a very safe and cautious manner, whether it’s studying novel agents or using certain agents early on in the disease course. Dose escalation has to be slow and careful despite the pressure to move