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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

Continued on page 10

ASCO 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

Continued on page 25

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

Continued on page 11

REAL-WORLD DATA

continued from page 10

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. OT

Peggy Eastman is a contributing writer.

CLL & NHL

continued from page 1

for dose-limiting toxicities would not have been sufficient given the relatively late occurrence of pneumonitis. "We suggest that similar future studies enroll patients without dose escalating individual patients."

Combination Active

The study aim was to improve the depth of remission and durability of responses in CLL and NHL by combining idelalisib, a selective inhibitor of PI3-kinase (PI3K), with entospletinib, a small-molecule inhibitor specific to spleen tyrosine kinase that has been implicated in the pathobiology of B-cell lymphoid malignancies.

In vitro studies have shown that simultaneous inhibition of multiple kinases in the B-cell receptor signaling pathway can produce synergistic antitumor activity, suggesting the potential to improve the depth of clinical responses and to overcome treatment resistance.

In this study each patient underwent a relatively rapid dose escalation—idelalisib from 100 to 150 mg and entospletinib 200 to 800 mg twice daily—every 2-4 weeks.

The idelalisib/entospletinib combination was active. With median exposure to therapy of 10 weeks, overall response rates were 60 percent in the CLL cohort, 36 percent in the follicular lymphoma cohort, and 17 percent in patients with diffuse large B-cell lymphoma.

Exactly how related the various doses were to the pneumonitis is unclear, Barr said, because of the rapid intrapatient dose escalation and the delayed occurrence of pneumonitis.

Mean time to onset of pneumonitis was 12 weeks. Symptoms were characterized by acute-onset dyspnea, cough, hypoxia, and bilateral ground-glass infiltrates on CT scan, often accompanied by fever and chills.

The researchers reported most patients with pneumonitis recovered with supportive measures and systemic steroids. The noninfectious pneumonitis was accompanied by increases of cytokines/chemokines associated with immune-cell recruitment, including interferon-gamma and interleukins-6, -7, and -8. The increases started around week 4 and were most pronounced by week 12, long after the rapid dose escalations.

Researchers recommended future investigations prospectively evaluate plasma cytokine/chemokine levels in an attempt to validate biomarkers predictive of response and toxicity.

Other toxicities observed were treatment-emergent diarrhea, rash, and hepatic transaminase elevation, seen in 29 percent, 30 percent, and 23 percent of patients, respectively; but these were generally reversible with treatment discontinuation.

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to identify the implications of a study that aimed to improve the depth of remission and durability of responses in chronic lymphatic leukemia (CLL) and non-Hodgkin lymphoma (NHL) by combining idelalisib, a selective inhibitor of PI3-kinase (PI3K), with entospletinib.

FDA Alert

The FDA alerted health care professionals March 4 about reports of an increased rate of adverse events, including deaths, in clinical trials with idelalisib in combination with other cancer medicines. Six clinical trials in patients with CLL, small lymphocytic lymphoma, and indolent NHL have been stopped.

Idelalisib is currently FDA-approved by treatment of relapsed CLL in combination with rituximab in patients for whom rituximab alone would be considered appropriate; in relapsed follicular B-cell NHL in patients who have received at least two prior systemic therapies; and in relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies.

Idelalisib is not approved for previously untreated CLL.

Barr said his trial was not one of the six involved in this action. "Pneumonitis was known as a potential adverse event with idelalisib, as it is with most of the PI3K inhibitors, but it is rare, occurring in

Continued on page 13

Welcome to WKOncology.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, **WKOncology.com**. This debut content gateway is dedicated to renal cell carcinoma (RCC).

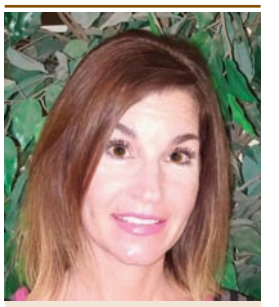
Available online now, you'll find regularly updated articles on topics such as "First-line Therapy for Treatment Naïve Patients," "Era36 Expression in Renal Tumors," and "Implications for the Classification of PEComas and the Differential Diagnosis With Metastatic Renal Cell Carcinoma," to name a few. 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, **WKOncology.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.

WKOncology.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 WKOncology 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 **WKOncology.com** often. We welcome input, feedback and comments on this exciting new initiative. OT



LYNN NACE
is Publisher of
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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 drugs through the pipeline. Second, it's important not only to monitor individual patients but also monitor the data sets very carefully."

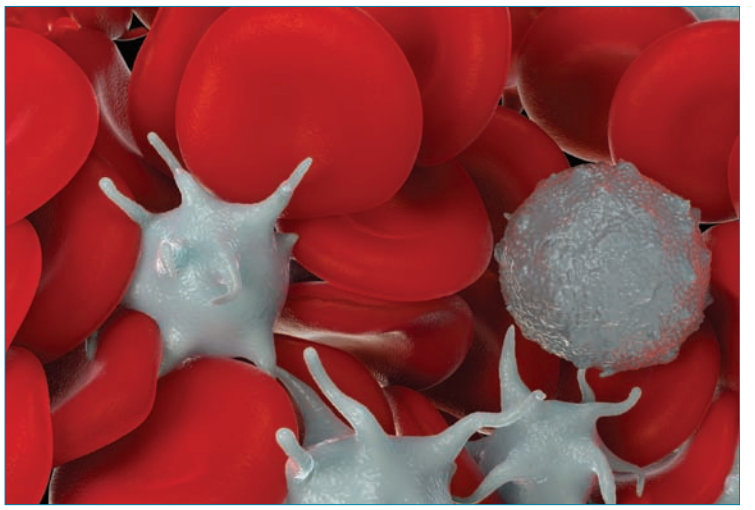
> Dose escalation has to be slow and careful despite the pressure to move drugs through the pipeline.

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. OT