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FDA's Breakthrough Therapy Designation: Update from Janet Woodcock

BY PEGGY EASTMAN

WASHINGTON—It's only two years old, but the U.S. Food and Drug Administration's Breakthrough Therapy designation has proven to be far more popular than anticipated with drug sponsors—potentially good news for cancer patients. Therapies granted this designation must show very early clinical evidence suggesting a substantial improvement over existing treatments for serious or life-threatening diseases.

At a Capitol Hill congressional briefing here hosted by the advocacy organization Friends of Cancer Research (FOCR), speakers hailed the novel regulatory pathway's ability to bring effective new therapies to cancer patients rapidly. The bill authorizing the breakthrough therapy designation was signed into law on July 9, 2012.

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Study Finds Disconcerting Trends in NSCLC Trials

BY HEATHER LINDSEY

Researchers have identified several unsettling developments in randomized, Phase III studies of systemic therapy for non-small-cell lung cancer (NSCLC) conducted during the past three decades.

"Our findings clearly point to a disquieting trend in NSCLC trials," said Adrian G. Sacher, MD, lead author of the study published in the May 10 issue of the *Journal of Clinical Oncology* (***2014;32:1407-1411***), which was conducted while he was a hematologist/oncologist at Princess Margaret Cancer Centre at the University of Toronto. "In general, they are larger, have less clinically meaningful endpoints, and are less effective in identifying clinically useful drugs."

Especially problematic are large trials in unselected populations that are powered to detect clinically insignificant differences, said Sacher, who is now at Dana-Farber Cancer Institute.

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PERIODICALS

Febrile Neutropenia: Good Results with Tigecycline Combos

BY KURT SAMSON

The broad-spectrum antibiotic tigecycline, when added to the standard of piperacillin or tazobactam, appears to improve the empiric treatment of febrile neutropenia in patients with leukemia and other hematologic malignancies.

In a study in the May 10 issue of the *Journal of Clinical Oncology (2014;32:1463-1471)*, a team led by Giampaolo Bucaneve, MD, of Hospital Policlinico Monteluce in Perugia, Italy, reported that favorable outcomes were 23 percent better for patients treated with the addition of tigecycline than with monotherapy with piperacillin/tazobactam.

Antibiotic monotherapy is currently the front-line empiric treatment for such patients, but increasingly resistant organisms have led to attempts to use antibiotic combinations to treat infections, he explained.

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DISCONCERTING TRENDS IN NSCLC TRIALS

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Still, some studies with promising methodologies do evaluate selected patients with specific biomarkers that may respond to targeted agents, he added.

David H. Johnson, MD, Professor and Chairman of the Department of Internal Medicine at the University of Texas Southwestern School of Medicine, who wrote an accompanying editorial (***JCO 2014;32:1389-1391***), said that some of what was characterized as

potentially bad news in this study is explainable by circumstances during the particular time period evaluated: For example, he said, NCI trials of the 1970s and 1980s were not well designed or able to discern small but meaningful differences in clinical outcomes—"The fact that studies got larger was in response to this, and that's a good thing."

Asked for his opinion for this article, Benjamin P. Levy, MD, an attending hematologist-oncologist in the Department of Medicine at Mount Sinai Beth Israel and Mount Sinai St. Luke's Roosevelt in New York, said that despite some of the findings of this paper, research in NSCLC is "heading in the right direction," and that with

ADRIAN SACHER, MD, said he hopes that future NSCLC trials are biomarker driven and attempt to match targeted drugs to selected patients. "Studying large, unselected populations for which investigators observe a very small benefit is not the way to go, and is a trend we have to work to change."

the identification of driver mutations and the development of targeted therapies, researchers are observing unprecedented response rates and survival times in this disease.

Study Details

Sacher and his colleagues Lisa W. Le, MSc, and Natasha B. Leighl, MD, MMSc, used PubMed to conduct a literature search of all Phase III, randomized, controlled clinical trials evaluating systemic treatment for advanced NSCLC conducted between 1980 and 2010. Of the 248 trials identified, 203 demonstrated several notable trends: Specifically, the number of NSCLC trials increased over time, from 32 conducted during the 1980s, to 53 studies in the 1990s, to 118 trials conducted between 2001 and 2010. The sample size also increased from a median of 152 patients in the 1980s, to 184 patients in the 1990s, to 413 in the most recent decade.

Treatment has also shifted from triplet chemotherapy in the 1980s to mostly doublet therapy in the 1990s, and then to a noticeable increase in targeted therapies from 2001 to 2010.

The team also found that the primary study endpoint was overall survival (OS) in most of the studies conducted before 2000, with 97 percent of trials reporting median OS in the 1980s and 96 percent reporting this outcome in the 1990s. Between 2001 and 2010, 81 percent of NSCLC trials used this endpoint. None of the trials used progression-free survival (PFS) as the primary endpoint between 1980 and 1990, and 13 percent used it in 2001 to 2010.

While 29 percent of trials from 1980 to 1990 and 31 percent from 2001 to 2010 met their primary statistical endpoints, the percentage of trials reporting a positive outcome without meeting that endpoint increased from 30 percent in 1980 to 1990 to 53 percent in 2001 to 2010.

In 60 of the studies reporting a statistically significant improvement in survival, there was a trend for an improved median net survival benefit of 3.9 months from 1981 to 1990, 2.4 months from 1991 to 2000, and 2.5 months from 2001 to 2010. When all trials deemed positive were evaluated, there was a statistically significant median net survival of 3.9 months, 2.0 months, and 0.9 months in the three respective decades.

Despite a declining net survival, the average median survival was 6.7 months from 1981 to 1990, 7.9 months from 1991 to 2000, and 9.5 months from 2001 to 2010, the data showed.

DAVID H. JOHNSON, MD: "Moving away from the traditional clinical development approach that is based on sequential, distinct phases toward a more integrated view that uses adaptive design tools to increase flexibility and maximize the use of accumulated knowledge could play an important role in improving the speed and cost-effectiveness of drug development."

Positive Trials

One of the more worrisome trends identified in the study, Johnson said, was that investigators of NSCLC tended to impart a positive spin on what were actually negative studies. Researchers may design a study to demonstrate improvement in PFS, OS, or another endpoint, but the research does not meet that endpoint, he explained. Instead, study investigators address trends such as improved survival or seemingly better control of symptoms.

Sacher speculated that one reason for an increasing number of trials being deemed positive may be that investigators are asserting noninferiority of a drug without using a noninferiority design in their trial. Another is that researchers may focus on secondary endpoints such as toxicity and progression-free survival in an attempt to create a paper thought to be more publishable.

Also asked for his opinion, Nathan Pennell, MD, PhD, of the Department of Solid Tumor Oncology at Cleveland Clinic, speculated that researchers may be under pressure from pharmaceutical companies and by academicians to produce positive studies. Still, the oncology community does do a good job of interpreting results appropriately, he added.

Sacher said that yes, while the pharmaceutical industry's influence on NSCLC research is not directly addressed in the paper, it may be worth investigating.

Also of note, Pennell said, is that Sacher et al defined a study as positive if the conclusion mentioned that a drug merited further evaluation. But, whether a drug should be entirely

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"A significant shift has occurred over the past three decades in the design and interpretation of Phase III trials in advanced NSCLC."

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abandoned because of one trial is not clear-cut, he said. For example, using the same agent in a different patient population may yield different results.

Levy said that a concern surrounding the increased number of trials reporting a positive outcome without meeting that endpoint is that they may lead to further costly and potentially futile studies. "This paper reminds all of us that we need to be cognizant and careful how we report and interpret studies that may demonstrate non-significant trends in outcomes or very small significant benefits," he said.

> "The use of survival as the primary measure of benefit is declining, as is the magnitude of benefit deemed clinically relevant."

Progression-Free Survival

Whether PFS is an appropriate primary endpoint is controversial in the oncology community, he added, explaining that PFS has limitations based on its subjectivity, lack of reproducibility, and questionable clinical relevance. As an endpoint, overall survival is not subject to these factors, he said.

Sacher said that evaluating PFS can potentially be problematic, especially if it is the primary endpoint in Phase III trials. Government agencies such as the FDA put the onus on investigators to demonstrate that PFS can be used as a surrogate for OS. Using PFS needs to be looked at critically, he said.

Progression-free survival is a reasonable endpoint in some solid tumors for which multiple systemic therapies may be available and benefit may be intermixed between multiple lines of therapy, said Jack Jacoub, MD, Director of Thoracic Oncology at MemorialCare Cancer Institute at Orange Coast Memorial Medical Center in California. As each of these therapies is added to a regimen, they may contribute to overall survival by PFS "blocks," he explained.

However, in cancers that don't have many effective therapeutics and where first-, and perhaps, second-line therapy is the best chance at improving survival, PFS is a questionable endpoint, he said.

Pennell said that for traditional chemotherapy, PFS is not a strong correlate for OS. However, for newer and more targeted therapies, though—for example, EGFR-inhibitors and ALK inhibitors—PFS is a reasonable endpoint because many patients undergoing chemotherapy may cross over to these agents.

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NATHAN PENNELL, MD: "Overall, the field is starting to move toward caring about the magnitude of clinical benefit and better-designed trials that incorporate molecular targets and effective inhibitors."

JACK JACOUB, MD: "We are making fairly small progress in lung cancer when considering the burden of the cost and morbidity associated with the treatment of the disease."

Levy added that demonstrating differences in overall survival for Phase III studies that allow for crossover of a potentially active drug in an enriched population may be exceedingly difficult, making PFS a useful outcome.

Survival Benefit and Targeted Therapies

While the studies showed that the survival of lung cancer patients increased by a small increment decade over decade, there is nonetheless only fairly small progress when considering the burden of the cost and morbidity associated with the treatment of lung cancer, Jacoub said.

A declining net survival benefit is to be expected, though, Pennell said. "At some point you're going to see diminishing returns." Survival results have plateaued with chemotherapy and targeted agents in unselected patient populations, he explained.

While chemotherapeutics have likely reached their maximum benefit, targeted therapies are being used in patients who have identifiable biomarkers to help improve response and OS, Jacoub said. In the near future, researchers will likely observe both a marked survival and clinical benefit based on the robust research and targeted therapies developed over the past decade and beyond, he said.

Checkpoint inhibitors, namely PD-1 and PDL-1, are especially promising, Levy said. "Researchers need to continue distancing themselves from the traditional approach of sequential-phase studies evaluating therapies in non-select patient populations to more biomarker-driven, genotype focused designs."

Sacher said he hopes that future NSCLC trials are biomarker driven and attempt to match targeted drugs to selected patients. Studying large, unselected populations for which investigators observe a very small benefit "is not the way to go, and is a trend we have to work to change."

More novel and adaptive trial designs, namely a Bayesian approach rather than a "frequentisit" approach, could be useful for accelerating new drug approval, Johnson said. "We may need to be more creative in how we design trials and think about them and use new statistical techniques," he said, adding that both the FDA and the European Medicines Agency support such methods.

Overall, the field is starting to move toward caring about the magnitude of clinical benefit and better-designed trials that incorporate molecular targets and effective inhibitors, Pennell concluded.