Trio of biosimilars have good showing

Susan London

Biosimilars for three widely used oncology drugs showed efficacy and safety in lung cancer and breast cancer similar to those of the reference products, according to findings reported at the 2018 annual meeting of the American Society of Clinical Oncology in Chicago.

Oncology biosimilars for bevacizumab (Avastin), trastuzumab (Herceptin), and filgrastim (Neupogen and others) have yielded positive results in various patient populations and clinical settings, investigators reported at the annual ASCO meeting. The findings advance the promise of new agents that have no clinically meaningful differences in efficacy and safety when compared with their reference drugs but have substantially lower cost.

"Biosimilars are here," said Michael A Thompson, MD, PhD, of Aurora Health Care in Milwaukee, Wisconsin, "[although] issues remain, including clinical decision support and pathway adoption, naming differences across the world, competition and lower prices versus the illusion of a free market, and adoption to decrease costs and increase value to our patients." Dr Thompson was commenting during an invited discussion at the meeting. He is the medical director of the Early Phase Cancer Research Program and the Oncology Precision Medicine Program at Aurora Health (also see Commentary, p. e292).

Bevacizumab biosimilar

The REFLECTIONS trial (NCT02364999) was a multinational, first-line, randomized, controlled trial among 719 patients with advanced nonsquamous non–small-cell lung cancer (NSCLC). Patients were randomized to paclitaxel and carboplatin chemotherapy plus either bevacizumab (sourced from the European Union) or the candidate bevacizumab biosimilar PF-06439535 on a double-blind basis, followed by monotherapy with the same assigned agent.

DR SOCINSKI

The overall response rate by week 19, confirmed by week 25 – the trial's primary endpoint – was 45.3% with the biosimilar and 44.6% with bevacizumab, reported lead author Mark A Socinski, MD, executive medical director of the Florida Hospital Cancer Institute in Orlando. The confidence interval (CI) for the risk difference fell within the equivalence margins set by European Union regulators (-13% and +13% for the 95% CI). And the confidence interval for the risk ratio fell within the equivalence margins set by the US Food and Drug Administration (0.73 and 1.37 for the 90% CI) and Japanese regulators (0.729 and 1.371 for the 95% CI).

Median progression-free survival (PFS) was 9.0 months with the biosimilar and 7.7 months with bevacizumab (hazard ratio [HR], 0.974; P = .814), and corresponding 1-year rates were 30.8% and

Study takeaways

Key clinical points Biosimilars for bevacizumab, trastuzumab, and filgrastim showed similar efficacy and safety compared with their reference drugs. **Major findings** *Bevacizumab* In patients with advanced nonsquamous NSCLC, the ORR was 45.3% with a candidate bevacizumab biosimilar and 44.6% with bevacizumab. *Trastuzumab* In patients with HER2+ advanced breast cancer, 48-week median PFS was 11.1 months for both trastuzumab-dkst and trastuzumab. *Filgrastim* The rate of chemotherapy-induced febrile neutropenia among breast cancer patients given a biosimilar for filgrastim was 5.1% in a trial population and 6.2% in a real-world population. **Study details** Randomized, controlled trials of first-line therapy among 719 patients with advanced nonsquamous NSCLC (REFLECTIONS trial with bevacizumab) and among 458 patients with HER2+ advanced breast cancer (HERITAGE trial with trastuzumab). Comparison of outcomes in a randomized, controlled trial among 217 patients with nonmetastatic breast cancer (PIONEER trial with filgrastim) and a real-world cohort study of 466 patients with any-stage breast cancer (MONITOR-GCSF with filgrastim). **Disclosures and sources** See pp. e291 and e293.

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29.3%, respectively, Dr Socinski reported. Median overall survival was 18.4 months and 17.8 months (HR, 1.001; *P* = .991), and corresponding 1-year rates were 66.4% and 68.8%.

Rates of grade 3 or higher hypertension, cardiac disorders, and bleeding did not differ significantly with the 2 agents. Patients also had similar rates of grade 3 or higher serious adverse events (AEs) and of fatal (grade 5) serious AEs with the biosimilar and bevacizumab (5.3% and 5.9%, respectively).

"Similarity between PF-06439535 and bevacizumab-EU was demonstrated for the primary efficacy endpoint of overall response rate. ... There were no clinically meaningful differences in safety profile shown in this trial, and similar pharmacokinetic and immunogenicity results were seen across treatment groups," Dr Socinski summarized. "These results confirm the similarity demonstrated in earlier analytical, nonclinical, and clinical studies of PF-06439535 with bevacizumab-EU."

Funding Pfizer sponsored the REFLECTIONS trial. **Disclosures** Dr Socinski disclosed that his institution receives research funding from Pfizer. **Source** Socinski MA et al. A comparative clinical study of PF-06439535, a candidate bevacizumab biosimilar, and reference bevacizumab, in patients with advanced non-squamous non-small cell lung cancer. ASCO 2018, Abstract 109. https://meetinglibrary.asco.org/record/161702/abstract. **Clinical trial registry number** NCT02364999 https://clinicaltrials.gov/ct2/show/NCT02364999

Trastuzumab biosimilar

The phase 3 HERITAGE trial was a first-line, randomized, controlled trial that compared biosimilar trastuzumab-dkst (Ogivri) with trastuzumab in combination with taxane chemotherapy and then as maintenance monotherapy in 458 patients with HER2+ advanced breast cancer. The 24-week results, previously reported (JAMA. 2017 Jan 3;317[1]:37-47), showed a similar overall response rate with each agent when combined with chemotherapy. Rates of various AEs were essentially the same.

The 48-week results showed a median PFS of 11.1 months with trastuzumab-dkst and 11.1 months with trastuzumab (HR, 0.95; *P* = .842), reported senior investigator Hope S Rugo, MD, a clinical professor of medicine and director of the Breast Oncology Clinical Trials Program at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center. "The overall survival is immature but is impressive at over 80% at 52 weeks," she noted.

Presence of overall response at 24 weeks correlated with duration of PFS at 48 weeks (biserial r = .752). "Additional patients achieved a response during the monotherapy portion of the treatment, which is intriguing and clearly emphasizes the importance of monotherapy, as well as the importance of having alternate agents at lower cost available," Dr Rugo commented.

Common AEs through week 48 were much the same as those seen at week 24, with few additional [events] occurring during monotherapy. "No new safety issues were observed, and in fact, toxicity during monotherapy was quite minor," she noted. "One thing that's interesting here is that there was more arthralgia during the first 24 weeks with trastuzumab-dkst than with trastuzumab, but in monotherapy, this fell to a very low number and was identical between the 2 arms. Paclitaxel, which people stayed on for longer [with the biosimilar], may have been the cause of this."


DR RUGO

The 48-week rates of AEs of special interest – respiratory events, cardiac disorders, and infusion-related AEs – and of serious AEs were similar for the 2 agents.

"We didn't see any additional serious cardiac events during monotherapy," Dr Rugo noted. Mean and median left ventricular ejection fraction over 48 weeks were similar, as was the rate of LVEF, which dropped below 50% (4.0% with trastuzumab-dkst and 3.3% with trastuzumab). The incidences of antidrug antibody and neutralizing antibody were also comparably low in both groups.

"HERITAGE data, now at week 48, supports trastuzumab-dkst as a biosimilar to trastuzumab in all approved indications," Dr Rugo said. "Final overall survival will be assessed after 36 months or after 240 deaths, whichever occurs first. Based on current data, this is predicted to conclude by the end of 2018, with final overall survival data available next year."

Dr Rugo emphasized that trastuzumab-dkst provides "an additional high-quality treatment option for patients with HER2+ breast cancers in any setting. This study shows that biosimilars offer the potential for worldwide cost savings and improved access to life-saving therapies. It's sobering to think that the patients enrolled in this study would not otherwise have had access to continued trastuzumab therapy, and so many of them are still alive with longer follow-up."

Funding Mylan sponsored the HERITAGE trial. **Disclosures** Dr Rugo disclosed that she receives travel, accommodations, and/or expenses from Mylan. **Source** Manikhas A et al. Biosimilar trastuzumab-dkst monotherapy versus trastuzumab monotherapy after combination therapy: Toxicity, efficacy, and immunogenicity from the phase 3 Heritage trial. ASCO 2018, Abstract 110. https://meetinglibrary.asco.org/record/161572/abstract. **Clinical trial registry number** NCT02472964 https://clinicaltrials.gov/ct2/show/NCT02472964

Incorporating biosimilars into cancer care

A variety of issues are influencing whether and how clinicians incorporate biosimilars into cancer care, according to Michael A Thompson, MD, PhD, of Aurora Health Care in Milwaukee, Wisconsin.

"Competition is highly relevant to biosimilars," Dr Thompson said at the ASCO annual meeting, with questions being raised about whether the oncology drug market is a free market, whether competition lowers drug prices, who owns the biosimilar companies, and whether, if biosimilars don't decrease drug cost, we should bother pursuing them. "We are seeing examples in which the biosimilars have been developed, they appear to work, they appear safe, and really the proof will be [to what extent that] is pushing the market to decrease cost," he noted.

Real-world data provide some insight into how biosimilars are being incorporated into oncology care. For example, in patients with non-Hodgkin lymphoma, hematologists tend to use rituximab (Rituxan) biosimilars in later lines of therapy, in patients with a better performance status and fewer comorbidities, and in cases of indolent or incurable disease (J Clin Oncol. 2018;36[suppl; abstr 112]). "So it appears that prescribers are acting tentatively to cautiously test the waters," Dr Thompson said.

Use will be influenced by clinical decision support and pathways, whether those are developed by institutions or insurers. These tools generally look at efficacy first, safety second, and cost third.

The relevance of patient choice (especially when physicians decreasingly have a choice) and perception of biosimilars may, or may not, be important, according to Dr Thompson. In some areas of medicine, there is evidence of a nocebo effect: Patients perceive worsening of symptoms when they believe they are getting a nonbranded medication, although that might not be valid in oncology, where many older chemotherapy drugs, the generics, are already being used, he said.

DR THOMPSON

ASCO recently published a statement on the use of biosimilars and related issues, such as safety and efficacy; naming and labeling; interchangeability, switching, and substitution; and the value proposition of those agents (J Clin Oncol. 2018 Apr 20;36[12]:1260-5).

One concern about the uptake of biosimilars is the possibility of an actual increase in patient cost related to single sources and potentially differing reimbursement rates, which could diminish the financial benefit of these drugs. Technically, if biosimilars have similar efficacy and safety, and lower cost, they provide greater value than the reference drugs.

But there may still be reasons for not using a higher-value drug, according to Dr Thompson. Clinicians may have lingering questions about efficacy and safety despite trial data, a situation that is being addressed in Europe by postmarketing pharmacovigilance. Other issues include delays in pathway implementation and pharmacies contracting with companies. "These are all minor but potential barriers to as fast an implementation as possible," he said.

— Dr Michael A Thompson is the medical director of the Early Phase Cancer Research Program and the Oncology Precision Medicine Program at Aurora Health Care in Milwaukee, Wisconsin.

Filgrastim biosimilar

Investigators led by Nadia Harbeck, MD, PhD, head of the Breast Center and chair for Conservative Oncology in the department of OB&GYN at the University of Munich (Germany), compared efficacy of filgrastim-sndz (Zarxio), a biosimilar of filgrastim (recombinant granulocyte colony-stimulating factor, or G-CSF), in a trial population with that of a real-world population of women receiving chemotherapy for breast cancer.

DR HARBECK

Data for the former came from PIONEER, a phase 3, randomized, controlled trial among patients with nonmetastatic breast cancer undergoing docetaxel, doxorubicin, and cyclophosphamide (TAC) chemotherapy in the neoadjuvant or adjuvant setting (Ann Oncol. 2015;26[9]:1948-53). Data for the latter came from MONITOR-GCSF, a postmarketing, open-label, observational cohort study among patients from 12 European countries receiving chemotherapy for various solid and hematologic malignancies (Support Care Cancer. 2016;24[2]:911-25).

Dr Harbeck and her colleagues compared 217 women who had nonmetastatic breast cancer from the trial with 466 women who had any-stage breast cancer (42% metastatic) from the real-world cohort.

Results showed that the 6.2% rate of chemotherapy-induced febrile neutropenia in any cycle seen in the real-world population was much the same as the 5.1% rate seen previously in the trial/biosimilar population. Findings were similar for temperature exceeding 38.5°C in any cycle: 3.4% and 5.6%, respectively. The real-world population had a lower rate of severe neutropenia than did the trial population (19.5% and 74.3%) and higher rates of infection (15.5% and 7.9%) and hospitalization caused by febrile neutropenia (3.9% and 1.8%). Findings were essentially the same in cycle-level analyses.

The real-world cohort had many fewer any-severity safety events of special interest than did the trial cohort, such as musculoskeletal/connective tissue disorders (20 and 261 events, respectively) and skin/subcutaneous tissue disorders (5 and 258 events). "Seeing these data, you have

to keep in mind that the patients received totally different chemotherapy. TAC chemotherapy has a lot of chemotherapy-associated side effects," Dr Harbeck noted. "The other thing is that MONITOR was a real-world database, and one could assume that there is some underreporting of events that are not directly correlated to the events that are of particular interest."

Additional results available only from the trial showed that no patients developed binding or neutralizing antibodies against G-CSF.

"From a clinician's point of view, it is very reassuring that we did not see any other safety signals in the real-world data than we saw in the randomized controlled trial and the efficacy was very, very similar," Dr Harbeck commented. "Having seen the discrepancies in the data, I think it's important to have randomized controlled trials to assess and monitor AEs for registration purposes and real-world evidence to reflect the daily clinical routine," she concluded.

Funding Sandoz sponsored the PIONEER and MONITOR-GCSF trials. **Disclosures** Dr Harbeck disclosed that she has a consulting or advisory role with Sandoz. **Source** Harbeck N et al. Comparison of efficacy and safety of biosimilar filgrastim in a RCT (PIONEER) and real-world practice (MONITOR-GCSF). ASCO 2018, Abstract 111. https://meetinglibrary.asco.org/record/161688/abstract. **Clinical trial registry number** NCT01519700 https://clinicaltrials.gov/ct2/show/NCT01519700

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