CLINICAL UPDATE

Current Developments in the Management of Breast Cancer

New Data for Sacituzumab Govitecan-hziy in the Treatment of Metastatic Triple-Negative Breast Cancer

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H&O What data led the US Food and Drug Administration (FDA) to approve sacituzumab govitecan-hziy?

AB The antibody-drug conjugate sacituzumab govitecan-hziy (Trodelvy, Gilead) targets the human trophoblast cell-surface antigen 2 (Trop-2), which is expressed in most types of breast cancer. The phase 3 ASCENT trial demonstrated that the efficacy of sacituzumab govitecan-hziy is superior to standard chemotherapy in pretreated metastatic triple-negative breast cancer. The ASCENT study was an international, multicenter, randomized confirmatory trial that enrolled more than 500 patients with relapsed/refractory metastatic triple-negative breast cancer who had received at least 2 prior therapies for metastatic disease (1 of the required prior regimens could be from progression that occurred within a 12-month period after completion of [neo]adjuvant therapy). Patients were randomly assigned to receive either sacituzumab govitecan-hziy or chemotherapy chosen by their treating physicians. The primary endpoint of the study was progression-free survival (PFS) in patients without brain metastases at baseline. Secondary endpoints included PFS for the full study population, overall survival, objective response rate (ORR), duration of response, and time to response.

In the ASCENT study, patients receiving sacituzumab govitecan-hziy demonstrated a statistically significant and clinically meaningful 59% improvement in PFS, which was extended to 5.6 months vs 1.7 months with chemotherapy (hazard ratio [HR], 0.41; 95% CI, 0.32-0.52; *P*<.0001). Sacituzumab govitecan-hziy also extended overall survival to 12.1 months from 6.7 months (HR, 0.48; 95% CI, 0.38-0.59; *P*<.0001), which represents a 52% reduction in the risk of death. Similar results were seen in the intention-to-treat population. Sacituzumab govitecan-hziy improved the ORR (35% vs 5%) in patients without brain metastases, as well as in the intention-to-treat population (31% vs 4%).

Based on these data, in April 2021, the FDA granted full approval to sacituzumab govitecan-hziy for the treatment of adults with unresectable locally advanced or metastatic triple-negative breast cancer who have received 2 or more prior treatments, including at least 1 treatment for metastatic disease. In 2020, the FDA had granted accelerated approval of sacituzumab govitecan-hziy for adults with pretreated metastatic triple-negative breast cancer.

Among all patients evaluable for safety in the confirmatory study (n=482), sacituzumab govitecan-hziy had a safety profile consistent with the data submitted for the previously approved FDA label. The most frequent grade 3 or higher treatment-related key adverse events were neutropenia (51% with sacituzumab govitecan-hziy vs 33% with chemotherapy), diarrhea (11% vs <1%), leukopenia (10% vs 6%), anemia (8% vs 5%), and febrile neutropenia (5% vs 2%). Adverse events leading to treatment discontinuation were low and similar (4.7% vs 5.4%) in both treatment arms of the study.

H&O Has anything been learned about sacituzumab govitecan-hziy as it moved from trials to use in the clinic?

AB Overall, sacituzumab govitecan-hziy is well tolerated, with common adverse effects being neutropenia, diarrhea, and alopecia.

H&O Could you describe the recent subanalysis of the ASCENT trial that focused on use in the second-line setting?

AB In metastatic triple-negative breast cancer, poor response and survival outcomes have been reported with standard single-agent chemotherapy in the second-line setting and beyond. In addition, patients with localized triple-negative breast cancer treated with neoadjuvant chemotherapy have a higher risk of relapse and death within the first 3 years compared with other types of breast cancer. At the 2021 American Society of Clinical Oncology (ASCO) annual meeting, Carey and colleagues presented a subset analysis from the ASCENT trial that focused on patients treated with prior neoadjuvant or adjuvant chemotherapy who had received 1 line of therapy in the metastatic setting. Sacituzumab govitecan-hziy prolonged PFS (median, 5.7 months vs 1.5 months [HR, 0.41; 95% CI, 0.22-0.76]) and overall survival (median, 10.9 months vs 4.9 months [HR, 0.51; 95% CI, 0.28-0.91]) vs treatment of physician's choice, consistent with results seen in the overall population. Hematologic events/diarrhea were the most common treatment-related grade 3 or higher adverse events associated with sacituzumab govitecan-hziy. In the second-line setting, as with later-line therapy, sacituzumab govitecan-hziy improved survival over conventional chemotherapy among patients with metastatic triple-negative breast cancer.

H&O What was learned from the subanalysis of the ASCENT trial that focused on the performance of each agent in the control arm?

AB At the 2021 ASCO meeting, O'Shaughnessy and colleagues presented data for each of the treatments used in the control arm. The median PFS was 5.6 months with sacituzumab govitecan-hziy, 2.1 months with eribulin mesylate (Halaven, Eisai), 1.6 months with vinorelbine, 1.6 months with capecitabine, and 2.7 months with gemcitabine. The median overall survival was 12.1 months, 6.9 months, 5.9 months, 5.2 months, and 8.4 months, respectively. The efficacy benefit observed with sacituzumab govitecan-hziy over the treatment of physician's choice in patients with metastatic triple-negative breast cancer was retained regardless of the comparator chemotherapy agent, including eribulin.

H&O Were there any particularly notable findings from these analyses of the ASCENT trial?

AB The benefit with sacituzumab govitecan-hziy was seen in all subgroups.

H&O Do you anticipate that the latest subanalysis results of the ASCENT trial will impact clinical care?

AB The results confirm that sacituzumab govitecan-hziy should be considered as a new standard of care in patients with pretreated metastatic triple-negative breast cancer.

H&O What are the recommendations from the National Comprehensive Cancer Network (NCCN) for sacituzumab govitecan-hziy in metastatic triple-negative disease?

AB In September 2021, the NCCN guidelines (version 8.2021) were updated to recommend sacituzumab govitecan-hziy as a preferred regimen for patients with metastatic triple-negative breast cancer who have received at least 2 prior therapies, with at least 1 line for metastatic disease. This update is consistent with the FDA label. Updated guidelines from ASCO, which were posted online in July 2021, recommend that patients with metastatic triple-negative breast cancer who have received at least 2 prior therapies for metastatic breast cancer should be offered treatment with sacituzumab govitecan-hziy.

H&O Is sacituzumab govitecan-hziy an option for older patients?

AB In the ASCENT trial, patients ages 65 years and older who received sacituzumab govitecan-hziy had a significant survival benefit vs the treatment of physician's choice, similar to that seen in patients younger than 65 years. Among the older patients, the median PFS was 7.1 months in the sacituzumab govitecan-hziy arm vs 2.4 months in the control arm (HR, 0.22; 95% CI, 0.12-0.40; $P<.0001$). The median overall survival was 15.3 months vs 8.2 months, respectively (HR, 0.37; 95% CI, 0.22-0.64; $P=.0003$). The safety profile was tolerable.

H&O What do the data show concerning toxicities?

AB Grade 3 or higher treatment-related toxicity included febrile neutropenia, anemia, and diarrhea.

H&O What are the components of monitoring for toxicities and management of adverse events?

AB Sacituzumab govitecan-hziy is associated with well-defined and manageable adverse events, with similar toxicity in patients ages 65 years and older. Patients with the *UGT1A1**28/*28 genotype should be closely monitored because they could have a higher incidence of grade 3

toxicities, particularly febrile neutropenia. Proactive monitoring and management of adverse events allows optimal therapeutic exposure to sacituzumab govitecan-hziy.

> The ASCENT trial demonstrated that the efficacy of sacituzumab govitecan-hziy is superior to standard chemotherapy in pretreated metastatic triple-negative breast cancer.

H&O Will the use of sacituzumab govitecan-hziy undergo evaluation in other settings?

AB The ASCENT trial demonstrated that the efficacy of sacituzumab govitecan-hziy is superior to standard chemotherapy in pretreated metastatic triple-negative breast cancer. Moving forward, the drug needs to be evaluated in earlier lines, including first-line therapy for metastatic triple-negative breast cancer. In the ASCENT trial, patients who had received prior immunotherapy also benefited from sacituzumab govitecan-hziy, suggesting that there is no cross-resistance between sacituzumab govitecan-hziy and immunotherapy. The potential combination of sacituzumab govitecan-hziy with immunotherapy would be an attractive therapeutic option for patients with metastatic triple-negative breast cancer that is positive for programmed death ligand 1.

H&O Are there any ongoing studies of sacituzumab govitecan-hziy?

AB Trop-2 is overexpressed in triple-negative breast cancer, as well as in hormone receptor–positive breast cancer. Sacituzumab govitecan-hziy might therefore be an option for patients with hormone receptor–positive disease also. In a phase 1/2 basket clinical trial by Kalinsky and colleagues, clinical activity with sacituzumab govitecan-hziy was observed in patients with metastatic hormone receptor–positive breast cancer. The phase 3 TROPiCS-02 trial is evaluating the efficacy of sacituzumab govitecan-hziy compared with standard chemotherapy in hormone receptor–positive metastatic breast cancer. The NeoSTAR clinical trial is investigating sacituzumab govitecan-hziy as neoadjuvant therapy in patients with localized breast cancer.

Disclosure

Dr Bardia has performed consulting for and is a member of the advisory boards of Pfizer, Novartis, Genentech, Merck, Radius Health, Immunomedics, Taiho, Sanofi, Daiichi Pharma/AstraZeneca, Puma, Biotheranostics Inc., Phillips, Eli Lilly, and Foundation Medicine. He has performed contracted research and received grants (directed to his institution) from Genentech, Novartis, Pfizer, Merck, Sanofi, Radius Health, Immunomedics, Daiichi Pharma/Astra Zeneca, and Natera.

Suggested Readings

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