Antibody-Drug Conjugate Provides Better Results for Triple-Negative Breast Cancer

Studies show that Trodelvy could be a potential first-line therapy option for hard-to-treat TNBC.

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Antibody-Drug Conjugate Provides Better Results Even After Subsequent Therapy for Advanced Triple-Negative Breast Cancer

A shift in the way advanced triple-negative breast cancer is treated may be on the horizon with mounting evidence that moving sacituzumab govitecan [Trodelvy], an antibody-drug conjugate (ADC), to the first line of treatment confers long-term benefit compared to standard therapy, including continued benefit even after subsequent therapy.

The evidence comes from two clinical trials, ASCENT-04, led by Sara Tolaney, MD, MPH, chief of the Division of Breast Oncology at Dana-Farber Cancer Institute, as well as the ASCENT-03 study where Tolaney served as the senior author, presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago on June 2 in Chicago.

These findings strengthen the case for approval of sacituzumab govitecan as first-line treatment of patients with advanced triple-negative breast cancer who are not eligible for immunotherapy, which was evaluated in ASCENT-03, and of sacituzumab govitecan plus pembrolizumab [Keytruda] as first-line treatment of patients whose tumors are positive for the immune checkpoint PD-L1, evaluated in ASCENT-04.

“We’re very excited about these results because this is a challenging disease to treat,” says Tolaney. “Changing a patient’s first line treatment to something much more effective is very meaningful. A change in this setting, if approved, would hopefully shift the needle for patients with advanced triple negative breast cancer and help them to live longer and better.”

Triple-negative breast cancer is an aggressive and difficult to treat form of breast cancer that accounts for about 15% of all breast cancer cases. The five-year survival rate for patients with metastatic triple-negative breast cancer is just 12%.

Sacituzumab govitecan is an antibody-drug conjugate designed to direct a potent chemotherapy drug into cancer cells by targeting a protein called TROP-2 that is found on triple-negative breast cancer cells. It is currently approved as second-line or later therapy for advanced triple-negative breast cancer, though approximately half of the patients who receive the current standard first-line treatment for disease do not go on to receive a second line of therapy.

The global, open-label ASCENT-03 study enrolled 558 patients who were randomized to receive either sacituzumab govitecan or chemotherapy as a first-line treatment. Eligible patients had locally advanced or unresectable triple-negative breast cancer and were not candidates for immune checkpoint inhibitors. Earlier this year, Tolaney published results from the study showing that first-line sacituzumab govitecan led to prolonged progression free survival.

The global, open-label ASCENT-04 study enrolled 443 patients who were randomized to receive either sacituzumab govitecan plus pembrolizumab, an immune checkpoint inhibitor, or chemotherapy plus pembrolizumab. Eligible patients had locally advanced or unresectable triple-negative breast cancer that tested positive for the immune checkpoint PD-L1. Earlier this year, Tolaney published results from the study showing that first-line sacituzumab govitecan plus pembrolizumab led prolonged progression-free survival.

In the abstracts presented at ASCO today, overall survival was immature. To assess long term clinical benefit of the study therapies, the team evaluated progression-free survival after a subsequent line of treatment, a measure called PFS2.

PFS2 helps investigators learn more about whether getting the ADC in the first line is better than getting it later, as second-line therapy. This question is particularly relevant in these two studies where most patients crossed over to receive the study therapy after progression on the control therapy. In ASCENT-03, 79% of patients who received first line chemotherapy crossed over to receive sacituzumab govetecan, and in ASCENT-04, 77% crossed over.

“Getting sacituzumab govitecan in the first-line setting was associated with much longer PFS2, despite the very high crossover rate in both studies,” says Tolaney. “This data is informative and suggests that first-line sacituzumab govitecan may have impact on longer term outcomes for patients.”

In the ASCENT-03 study, at the time of data cut off, 27% of patients remained on sacituzumab govitecan, and 14% on chemotherapy. Among patients who received the ADC as first-line treatment and progressed, the median time to the first subsequent therapy was 18.2 months, compared to 14 months for those who received chemotherapy first. Treatment with first-line sacituzumab govitecan reduced the risk of a second progression by 30%.

In the ASCENT-04 study, at a median of 14 months of follow up, 43% of patients remained on sacituzumab govitecan plus pembrolizumab, and 23% remained on chemotherapy. Among patients who received the ADC combination as first-line treatment and progressed, the median

time to the first subsequent therapy was 17.3 months, compared to 9.8 months for those who received chemotherapy first. Treatment with first-line sacituzumab govitecan plus pembrolizumab reduced the risk of a second progression by 33%.

Tolaney also presented results of a subgroup analysis of the ASCENT-04 study based on biomarkers including TROP-2 expression, tumor BRCA mutation status, and HER2 expression. Patients were grouped into categories including four TROP-2 expression level categories, BRCA wild-type or mutant, and HER2 zero or low. Across all subgroups, patients who received sacituzumab govitecan plus pembrolizumab as first-line therapy had longer progression free-survival compared to chemotherapy plus pembrolizumab. Similar findings were presented by a study collaborator for ASCENT-03.

“These data are reassuring and suggest that there isn’t a biomarker that you need to look at to choose which patient should get sacituzumab govitecan,” says Tolaney. “The ADC always did better than chemotherapy.”

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