

## A Closer Look at Sacituzumab Govitecan-hziy



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Sacituzumab govitecan-hziy (Trodelyv, Immunomedics) is an antibody-drug conjugate indicated for the treatment of adult patients with metastatic triple-negative breast cancer who have received at least 2 prior therapies for metastatic disease. The US Food and Drug Administration granted sacituzumab govitecan-hziy accelerated approval in April 2020. Sacituzumab govitecan-hziy targets Trop-2, an antigen expressed in the majority of breast cancers. This agent delivers high doses of the antineoplastic drug SN-38 to cancer cells, while relatively sparing noncancerous cells. Sacituzumab govitecan-hziy should be considered a new standard of care in patients with pretreated, metastatic triple-negative breast cancer.

### H&O What type of drug is sacituzumab govitecan-hziy?

**AB** Sacituzumab govitecan-hziy (Trodelyv, Immunomedics) is a novel antibody-drug conjugate that consists of 3 components: the antibody that targets the surface protein Trop-2; a hydrolysable linker; and SN-38, the toxic payload. SN-38 is an active metabolite of irinotecan and a topoisomerase 1 (TOP1) inhibitor. The rationale for targeting Trop-2 is that the antigen is expressed in the majority of breast cancers, including triple-negative breast cancer.

As compared with other antibody-drug conjugates, sacituzumab govitecan-hziy has 3 unique properties. First, sacituzumab govitecan-hziy is a first-in-class antibody-drug conjugate targeted against Trop-2. Second, the drug-to-antibody ratio is high, at 7.6 to 1. Third, hydrolysis of the linker can release SN-38 extracellularly into the tumor microenvironment, providing a bystander effect that could impact cells that have low or even no expression of Trop-2.

### H&O What trial data led to the approval of sacituzumab govitecan-hziy?

**AB** In April 2020, sacituzumab govitecan-hziy was granted accelerated approval by the US Food and Drug Administration (FDA) for patients with metastatic triple-negative breast cancer who had received 2 or more prior lines of therapy. Approval was based on IMMU-132-01, a basket

phase 1/2 trial. The trial enrolled 108 patients with metastatic triple-negative breast cancer who had received at least 2 prior lines of therapy for advanced metastatic disease. In this setting, the response rate expected with standard chemotherapy would be approximately 5% to 10%. In the trial of sacituzumab govitecan-hziy, the confirmed objective response rate was 33%. Another important finding is that sacituzumab govitecan-hziy produced durable responses. The median duration of response was 7.7 months, which is much higher than that reported with standard chemotherapy.

Finally, in the IMMU-132-01 trial, the median progression-free survival was 5.5 months. In comparison, the median progression-free survival is approximately 2 months with standard chemotherapy.

### H&O What were the adverse events in the trial?

**AB** The adverse events were related to the toxic payload—meaning the SN-38 backbone—and consisted of neutropenia, anemia, nausea, and diarrhea. Sacituzumab govitecan-hziy can also cause hair loss, another adverse event associated with SN-38.

### H&O Could you discuss data from the recent phase 3 ASCENT trial?

**AB** The phase 3 ASCENT trial compared sacituzumab govitecan-hziy vs standard chemotherapy in patients with advanced metastatic triple-negative breast cancer. In the

control arm, patients were treated with standard chemotherapy—capecitabine, eribulin mesylate (Halaven, Eisai), vinorelbine, or gemcitabine—as selected by their physician. The trial enrolled 468 patients throughout the United States, Canada, and Europe. The primary endpoint was progression-free survival as assessed by central review.

I reported results from the trial as a late-breaking abstract at the European Society for Medical Oncology Virtual Congress 2020. The median progression-free survival was 5.6 months with sacituzumab govitecan-hziy vs 1.7 months with treatment of the physician's choice (hazard ratio [HR], 0.41;  $P < .0001$ ). The objective response rate was 35% vs 5%, respectively ( $P < .0001$ ). The overall survival was more than double that typically reported with standard chemotherapy. The median overall survival was 12.1 months with sacituzumab govitecan-hziy vs 6.7 months with standard chemotherapy (HR, 0.48;  $P < .0001$ ).

Neutropenia was the most common grade 3 or higher treatment-related adverse event, occurring in 51% of the sacituzumab govitecan-hziy arm vs 33% of the control arm. Grade 3 or higher treatment-related diarrhea occurred in 10% vs less than 1%, respectively. Other grade 3 or higher treatment-related adverse events included leukopenia (10% vs 5%) and febrile neutropenia (6% vs 2%).

### **H&O** Do the adverse events reported in trials match your clinical experience?

**AB** The package insert contains warnings about severe neutropenia and diarrhea, events that occurred in the phase 3 trial. These reports reflect what we see in the clinic. The most common side effects include neutropenia and diarrhea, which are related to the SN-38 payload. In general, the neutropenia is manageable with dose reductions and interruptions. Sometimes the use of granulocyte colony-stimulating factor is needed for severe neutropenia. Prophylaxis with loperamide can usually control the diarrhea. The diarrhea typically occurs within the first few days of therapy. The neutropenia is usually seen in the first couple of cycles, as well. Thus, early during treatment, indications of whether a patient will develop significant problems with neutropenia and diarrhea usually become apparent, and it is then possible to institute appropriate measures, including secondary prophylaxis.

### **H&O** How is sacituzumab govitecan-hziy administered, and is premedication needed?

**AB** Sacituzumab govitecan-hziy is administered intravenously on days 1 to 8 every 21 days. We have seen that the

drug is well-tolerated. Infusion-related reactions are low. For most patients, we recommend premedication with antihistamines and antipyretics, as well as an antiemetic regimen consisting of 2 or 3 drugs. This recommendation follows that in the label.

Sacituzumab govitecan-hziy provides a way to administer high doses of toxic chemotherapy to cancer cells while relatively sparing normal cells.

### **H&O** What is the procedure for monitoring patients treated with sacituzumab govitecan-hziy?

**AB** We recommend restaging scans every 2 to 3 months to ensure that the patient is on the right track with the treatment. In the metastatic setting, therapies are continued until the patient develops disease progression or unacceptable toxicity. The same principle applies to sacituzumab govitecan-hziy.

### **H&O** How do you describe sacituzumab govitecan-hziy to your patients?

**AB** I tell patients that sacituzumab govitecan-hziy is a targeted chemotherapy. It has an antibody that targets an antigen present in breast cancer, which is attached to a chemotherapeutic agent. Sacituzumab govitecan-hziy provides a way to administer high doses of toxic chemotherapy to cancer cells while relatively sparing normal cells.

### **H&O** Do you have any other observations regarding the use of sacituzumab govitecan-hziy?

**AB** Sacituzumab govitecan-hziy is a very active agent, with clear evidence of activity in heavily pretreated patients with triple-negative breast cancer. This activity was seen in the phase 1/2 trial and then confirmed in the phase 3 ASCENT study. Sacituzumab govitecan-hziy is associated with toxicities such as gastrointestinal events and myelosuppression, which can be managed with dose-reduction, dose interruption, or the use of supportive medications.

## H&O Do you anticipate that the use of sacituzumab govitecan-hziy will evolve?

**AB** Sacituzumab govitecan-hziy is currently approved by the FDA for metastatic triple-negative breast cancer in the third-line setting and beyond. This treatment is now the standard of care for these patients. There is interest in evaluating sacituzumab govitecan-hziy as first- or second-line treatment in triple-negative breast cancer and as neoadjuvant or adjuvant therapy in localized breast cancers. It will be interesting to see the activity of this agent in earlier lines of therapy. Trop-2 is also expressed in hormone receptor-positive breast cancer, so sacituzumab govitecan-hziy is undergoing evaluation in this setting.

The other strategy to consider is building combination therapy with sacituzumab govitecan-hziy. There is a rationale for combining sacituzumab govitecan-hziy with immunotherapy or poly(ADP-ribose) polymerase (PARP) inhibitors. There is the potential to combine sacituzumab govitecan-hziy with immunotherapy, as well as other chemotherapies, particularly those agents that do not cause much myelosuppression. Hopefully, these combinatorial strategies can further improve the outcomes of patients with breast cancer.

## H&O Are there any ongoing clinical trials of sacituzumab govitecan-hziy?

**AB** The registrational, phase 3 TROPiCS-02 trial is comparing sacituzumab govitecan-hziy vs standard chemotherapy in patients with hormone receptor-positive metastatic breast cancer. Several studies are currently evaluating sacituzumab govitecan-hziy in combination

with immunotherapy in patients with metastatic triple-negative breast cancer. My institution has initiated a phase 2 study, known as NEOSTAR, which is evaluating sacituzumab govitecan-hziy as neoadjuvant therapy for patients with localized triple-negative breast cancer.

### Disclosure

*Dr Bardia has performed consulting for and/or is a member of the advisory boards of Pfizer, Novartis, Genentech, Merck, Radius Health, Immunomedics/Gilead, Taiho, Sanofi, Daiichi Sankyo/AstraZeneca, Puma, Biotheranostics, Phillips, Eli Lilly, and Foundation Medicine. He has received contracted research/grant support (directed to his institution) from Genentech, Novartis, Pfizer, Merck, Sanofi, Radius Health, Immunomedics, and Daiichi Sankyo/AstraZeneca.*

### Suggested Readings

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