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Sacituzumab Govitecan for Metastatic Triple-Negative Breast Cancer

By: Maggie Segovia, Pharm.D.

Background: Triple-negative breast cancer is a specific type of breast cancer, characterized by a lack of tumor-cell expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor 2.[1] Triple-negative breast cancer is associated with a poor prognosis, especially for those with metastatic disease, with the current 5-year survival rate being 12%. Current treatment guidelines from the National Comprehensive Cancer Network recommend single-agent chemotherapy as the preferred regimen for recurrent, metastatic triple-negative breast cancer.[2] However, outcomes following treatment with chemotherapy remain poor.[1] Sacituzumab govitecan-hziy (Trodelvy®; Gilead Sciences, Inc.) is a unique and promising new treatment that combines immunotherapy and chemotherapy as a single agent.[3] Sacituzumab govitecan received accelerated approval from the Food and Drug Administration in April 2020 for the treatment of metastatic triple-negative breast cancer in adult patients who have received at least two prior therapies for metastatic disease.

Mechanism of Action: Trophoblast cell-surface antigen 2 (Trop-2) is a transmembrane calcium signal transducer that is present in several different types of tumors, including breast cancer.[1,4] Sacituzumab govitecan is composed of a humanized anti-Trop-2 monoclonal antibody that is linked to SN-38, the active metabolite of irinotecan, an antineoplastic agent. Sacituzumab govitecan targets and binds to Trop-2 expressing cancer cells allowing for the targeted delivery of SN-38.

Clinical Trial: The safety and efficacy of sacituzumab govitecan were evaluated in ASCENT, a randomized phase 3 trial, comparing sacituzumab govitecan to single-agent chemotherapy in

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Nexviazyme™ for Pompe Disease

By: Mitchell Blewett, Pharm.D.

What is Pompe Disease? Pompe disease, also referred to as glycogen storage disease type II, is an inherited disorder of glycogen metabolism caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA), which results in intralysosomal accumulation of glycogen in various tissues.[1] This accumulation of glycogen causes progressive muscle weakness throughout the body, most notably the heart, skeletal muscles, liver, and nervous system. Pompe disease is divided into two subtypes: infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD).[2] The subtypes differ based on whether symptoms occur before or after the age of 12 months.[3]

What agents are currently available to treat Pompe Disease? There are two agents available in the United States approved by the Food and Drug Administration (FDA) to treat Pompe disease. Avalglucosidase alfa-ngpt (Nexviazyme™; Sanofi Genzyme)

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patients with refractory/relapsed metastatic triple-negative breast cancer.[1] Patients were included if they had metastatic triple-negative breast cancer that had relapsed or was refractory to two or more previous standard chemotherapy regimens. Prior therapy had to include a taxane. Although included in the trial, patients with stable brain metastases were excluded from the primary endpoint analysis. Five-hundred twenty-nine patients were randomized in a 1:1 ratio to receive sacituzumab govitecan 10 mg/kg intravenously (IV) on days 1 and 8 of each 21-day cycle (n=235), or single-agent chemotherapy with one of the following agents: eribulin, vinorelbine, capecitabine, or gemcitabine (n=233). Sixty-one of the 529 randomized patients had brain metastases at baseline. Treatment was continued until disease progression, unacceptable toxic effects, withdrawal from the trial, or death, whichever occurred first. The primary endpoint was progression-free survival among patients without known baseline brain metastases. Progression-free survival among those with brain metastases was reported separately. Key secondary endpoints included overall survival and safety. Patient demographics were similar between groups. Most patients were white females, with a median age of 54 years old in the sacituzumab govitecan group and 53 years old in the chemotherapy group. Approximately 70% of patients were diagnosed with triple-negative breast cancer at initial diagnosis. About 30% of the patients had received more than three previous chemotherapy regimens. In patients without brain metastases, the median progression-free survival was 5.6 months with sacituzumab govitecan (95% confidence interval [CI], 4.2 to 6.3) compared to 1.7 months with chemotherapy (95% CI, 1.5 to 2.6). The median overall survival was 12.1 months with sacituzumab govitecan (95% CI, 10.7 to 14.0) compared to 6.7 months with chemotherapy (95% CI, 5.8 to 7.7). In the entire population (including those with and without brain metastases), the median progression-free survival was 4.8 months with sacituzumab govitecan (95% CI, 4.1 to 5.8) and 1.7 months with chemotherapy (95% CI, 1.5 to 2.5). The median overall survival was 11.8 months with sacituzumab govitecan (95% CI, 10.5 to 13.8) compared to 6.9 months with chemotherapy (95% CI, 5.9 to 7.7). Therefore, the investigators concluded that sacituzumab govitecan provided a significant benefit over single-agent chemotherapy in progression-free and overall survival.

Safety: In the ASCENT trial, adverse events of any severity level were reported in 98% of sacituzumab govitecan patients and in 86% of chemotherapy patients.[1] Neutropenia was commonly reported in both groups (63% with sacituzumab govitecan, 43% with chemotherapy). Febrile neutropenia was reported in 6% of patients in the sacituzumab govitecan group, compared to 2% in the chemotherapy group. Diarrhea, nausea, and vomiting occurred more frequently in the sacituzumab govitecan group (59%, 57%, and 29%, respectively) compared to the chemotherapy group (12%, 26%, and 10%, respectively). Serious treatment-related adverse events were reported in 39 (15%) patients in the sacituzumab govitecan group and 19 (8%) patients in the chemotherapy group. Six patients (three patients in each group) died due to adverse events. Only one of these deaths, a patient in the chemotherapy group, was considered treatment-related.

Dosing and Administration: The recommended dose of sacituzumab govitecan is 10 mg/kg IV once weekly on days 1 and 8 of a 21-day treatment cycle.[3] The first infusion should be given over 3 hours. Subsequent infusions may be given over 1-2 hours, if tolerated. Patients should be pre-medicated with antipyretics, histamine-receptor antagonists, and corticosteroids to prevent infusion-related reactions, as well as a two- or three-drug combination regimen to prevent chemotherapy-induced nausea and vomiting. Patients should be monitored during the infusion, and for at least 30 minutes afterward. Treatment interruption, dose reduction or both may be required to manage adverse effects. There are no dosage adjustments for decreased renal or hepatic function.[3,4]

Cost and Availability: Sacituzumab govitecan is available as 180 mg vials (NDC 55135-0132-01) and has an average wholesale price of $2,626 per vial.[4] The estimated cost of therapy per 21-day cycle for a 70 kg patient is approximately $20,497.

Formulary Status: Sacituzumab govitecan is currently on the CCHS Formulary restricted to the Department of Hematology and Oncology for outpatient use in patients with metastatic triple-negative breast cancer who have received at least two prior therapies or in patients with metastatic urothelial cancer who previously received a platinum-containing chemotherapy and either a programmed death receptor-1 or programmed death-ligand 1 inhibitor.

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was recently approved by the FDA on August 6, 2021, for the treatment of patients 1 year of age and older with LOPD.[4] Alglucosidase alfa (Lumizyme® ;Sanofi Genzyme) received FDA approval on August 1, 2014 for use in all patients with Pompe disease.[5]

Who should receive Lumizyme® as opposed to Nexviazyme™? Patients with IOP should receive Lumizyme®, since Nexviazyme™ is not yet FDA-approved for this indication.[4] Additionally, pregnant patients should receive Lumizyme®, since more safety data support its use in this patient population.[6]

What is the mechanism of action of Nexviazyme™ and how does it differ from Lumizyme®? Nexviazyme™ is an exogenous source of the enzyme GAA which is required for glycogen cleavage.[1,7] The Nexviazyme™ molecule is conjugated with mannose-6-phosphate (M6P) which mediates high-affinity binding to the M6P receptor. The proposed benefit of Nexviazyme™ over Lumizyme® is that by specifically targeting the M6P receptor, enzyme uptake into muscle cells is increased approximately five-fold, potentially resulting in improved glycogen cleavage in target tissues.[1]

What clinical trial led to the FDA approval of Nexviazyme™? Nexviazyme™ was evaluated in the Phase 3 COMET study, a randomized, double-blind, multinational study directly comparing it to alglucosidase alfa in treatment-naïve patients with LOPD.[8] Patients received an intravenous (IV) infusion of either Nexviazyme™ 20 mg/kg (n=51) or alglucosidase alfa 20 mg/kg (n=49) every 2 weeks for 49 weeks. The study's primary outcome was to determine the effect of Nexviazyme™ compared with alglucosidase alfa on the percent predicted forced vital capacity (FVC) while in an upright position from baseline to week 49. The key secondary objective was the effect on functional endurance measured by utilizing the 6-minute walk test (6MWT) during that same period. Comparative adverse effects were also assessed during the trial. Baseline characteristics for the study participants were 48 years old, 52% male, 94% white, and a percent predicted FVC in upright position of 62.1. The mean percent change from baseline to week 49 of the FVC for the Nexviazyme™ versus the alglucosidase alfa groups was 2.89% and 0.46%, respectively. The between-group difference was 2.43% (95%Cl: -0.13 to 4.99) meeting non-inferiority requirements. However, the primary objective failed to meet the threshold for superiority (p=0.0626). A statistically significant improvement was seen with Nexviazyme™ in the 6MWT compared to alglucosidase alfa. The least-square mean change from baseline to week 49 in 6MWT of those who received Nexviazyme™ compared to alglucosidase alfa was 32.21 meters versus 2.19 meters, respectively (p=0.04). Patients receiving Nexviazyme™ had a lower frequency of potential treatment-emergent adverse events than those receiving alglucosidase alfa, 45% versus 49%, respectively. The authors concluded that compared to alglucosidase alfa, Nexviazyme™ produced clinically meaningful improvements in respiratory function, ambulation, and functional endurance with a better safety profile.

What is the recommended dose and administration of Nexviazyme™? Nexviazyme™ is administered as an IV infusion every 2 weeks at a dose of 40 mg/kg for patients < 30 kg and 20 mg/kg for patients ≥ 30 kg.[4] Actual body weight should be used when calculating the dose. The initial infusion rate is 1 mg/kg/hour and may be increased every 30 minutes if no signs of infusion-associated reactions (IARS) occur. Antihistamines, antipyretics, and corticosteroids can be given prior to administration to reduce the risk of IARS. Details about dosage and administration modifications due hypersensitivity reactions and/or IARS are provided in the package insert. There are no dosage adjustments for renal or hepatic dysfunction.

What are the side effects of Nexviazyme™? Nexviazyme™ has three black box warnings as follows: 1) hypersensitivity reactions including anaphylaxis, 2) IARS, and 3) risk of acute cardiorespiratory failure in susceptible patients.[4] Common side effects reported in >10% of patients were IARS, headache, fatigue, diarrhea, nausea, arthralgia, dizziness, and myalgia.

What is the cost and availability of Nexviazyme™? Nexviazyme™ is available as a 100 mg vial with an average wholesale price of $2,058 per vial.[7] The estimated annual cost of Nexviazyme™ for a 100 kg patient is $1,070,098.

What is the formulary status of Nexviazyme™? Nexviazyme™ was added to the Adult and Pediatric CCHS Formularies with restrictions to Geneticists and the Department of Hematology and Oncology for outpatient use only.

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