RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	Trodelvy™
Generic Name	sacituzumab govitecan-hziy
Drug Manufacturer	Immunomedics, Inc

New Drug Approval

FDA Approval Date: April 22, 2020
Review Designation: Orphan Drug; Biologic Data Exclusivity
Type of Review: Biologics License Application 761115

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Metastatic breast cancer is a cancer that has spread to parts of the body away from the breast, such as the bones or liver.Triple-negative breast cancer (TNBC) is a term that has historically been applied to cancers that lack expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBC tends to behave more aggressively than other types of breast cancer. Unlike other breast cancer subtypes (ie, ER-positive, HER2-positive subtypes), there are no approved targeted treatments available, although immunotherapy (in combination with chemotherapy) is available for those with advanced TNBC that expresses programmed cell death ligand 1 (PD-L1). For purposes of this review, we consider "triple-negative" to mean cancers that have ≤1 percent expression of ER and PR as determined by immunohistochemistry (IHC), and that are, for HER2, either 0 to 1+ y IHC, or IHC 2+ and fluorescence in situ hybridization (FISH) negative (not amplified), according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. Although the basic principles of diagnosis and management of TNBC are similar to those of breast cancer in general, many aspects, including risk factors, molecular and pathologic characteristics, natural history, and chemotherapy sensitivity, are unique to TNBC.

TNBC accounts for approximately 15 percent of breast cancers diagnosed worldwide, which amounts to almost 200,000 cases each year. Compared with hormone receptor-positive breast cancer, TNBC is more commonly diagnosed in women younger than 40 years. In one study, there was a twofold higher attributable risk of TNBC in women under 40 years compared with women over 50 years (odds ratio [OR] 2.13, 95% CI 1.34-3.39). In addition, TNBC appears to be relatively more common among black women compared with white women (OR 2.41, 95% CI 1.81-3.21).

Risk factors associated with the diagnosis of TNBC include:

- **Positive BRCA mutation status**: Up to 20 percent of patients with TNBC harbor a breast cancer susceptibility gene (BRCA*)* mutation, particularly in BRCA1. By contrast, less than 6 percent of all breast cancers are associated with a BRCA mutation. Given this finding, any patient with triple-negative disease should be offered a referral to a genetic counselor to discuss BRCA germline testing. Moreover, any patient age 60 years or younger with TNBC should undergo BRCA germline testing.
- **Race**: Several population-based studies have found that African American women have a higher risk of TNBC compared with non-African American women. However, African American women can certainly have ER-positive and/or HER2-positive disease, and testing their tumors for these markers is essential.
- **Premenopausal status**: Premenopausal status has been associated with increased incidence of TNBC diagnosis as compared with postmenopausal status. As with African American women, premenopausal

women can frequently have ER-positive and/or HER2-positive disease, and testing their tumors for these markers is essential.

- **Other factors**: Studies have suggested relationships between other factors such as obesity and a young age of first pregnancy with an increased risk of TNBC, while breastfeeding and parity may be associated with lower risks. However, these factors are less well validated and rarely factor into clinical considerations.

Efficacy

The efficacy of Trodelvy was evaluated in study IMMU-132-01 (NCT01631552), a multicenter, single-arm, trial that enrolled 108 patients with metastatic triple-negative breast cancer (mTNBC) who had received at least two prior treatments for metastatic disease. Patients with bulky disease, defined as a mass >7 cm, were not eligible. Patients with treated brain metastases not receiving high dose steroids (>20 mg prednisone or equivalent) for at least four weeks were eligible. Patients with known Gilbert's disease were excluded.Patients received Trodelvy 10 mg/kg intravenously on Days 1 and 8 of a 21-day treatment cycle. Patients were treated with Trodelvy until disease progression or intolerance to the therapy. Tumor imaging was obtained every 8 weeks, with confirmatory CT/MRI scans obtained 4-6 weeks after an initial partial or complete response, until progression requiring treatment discontinuation. Major efficacy outcome measures were investigator assessed overall response rate (ORR) using RECIST 1.1 and duration of response.The median age was 55 years (range: 31 – 80 years); 87% of patients were younger than 65 years. The majority of patients were female (99%), and White (76%). At study entry, all patients had an ECOG performance status of 0 (29%) or 1 (71%). Seventy-six percent had visceral disease, 42% had hepatic metastases, 56% had lung/pleura metastases, and 2% had brain metastases. Twelve patients (11%) had Stage IV disease at the time of initial diagnosis.The median number of prior systemic therapies received in the metastatic setting was 3 (range: 2 - 10). Prior chemotherapies in the metastatic setting included carboplatin or cisplatin (69%), gemcitabine (55%), paclitaxel or docetaxel (53%), capecitabine (51%), eribulin (45%), doxorubicin (24%), vinorelbine (16%), cyclophosphamide (19%), and ixabepilone (8%).Overall, 98% of patients had received prior taxanes and 86% had received prior anthracyclines either in the (neo)adjuvant or metastatic setting.

Efficacy results for patients with mTNBC in IMMU-132-01

	TRODELVY (N=108)
Overall Response Rate i	
ORR (95% CI)	33.3% (24.6, 43.1)
Complete response	2.8%
Partial response	30.6%
Response duration i	
Number of responders	36
Median, Months (95% CI)	7.7 (4.9, 10.8)
Range, Months	1.9+, 30.4+
% with duration ≥ 6 months	55.6%
% with duration ≥ 12 months	16.7%

i: investigator assessment; CI: confidence interval; +: denotes ongoing

NEW DRUG APPROVAL

Safety

ADVERSE EVENTS

Most common adverse reactions (incidence >25%) in patients with mTNBC are nausea, neutropenia, diarrhea, fatigue, anemia, vomiting, alopecia, constipation, rash, decreased appetite, and abdominal pain.

WARNINGS & PRECAUTIONS

- Hypersensitivity: Hypersensitivity reactions including severe anaphylactic reactions have been observed. Monitor patients for infusion-related reactions. Permanently discontinue Trodelvy if severe or lifethreatening reactions occur.
- Nausea/Vomiting: Use antiemetic preventive treatment and withhold Trodelvy for patients with Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment.
- Patients with Reduced UGT1A1 Activity: Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia following initiation of Trodelvy treatment.
- Embryo-Fetal Toxicity: Trodelvy can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

Trodelvy is contraindicated in patients who have experienced a severe hypersensitivity reaction to it.

Clinical Pharmacology

MECHANISMS OF ACTION

Sacituzumab govitecan-hziy is a Trop-2-directed antibody-drug conjugate. Sacituzumab is a humanized antibody that recognizes Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. Pharmacology data suggest that sacituzumab govitecan-hziy binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death. Sacituzumab govitecan-hziy decreased tumor growth in mouse xenograft models of triple-negative breast cancer.

Dose & Administration

ADULTS

10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles.

Premedication: Prior to each dose of Trodelvy, premedication for prevention of infusion reactions and prevention of chemotherapy induced nausea and vomiting (CINV) is recommended.

- Premedicate with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions.
- Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated).

PEDIATRICS

Safety and effectiveness of Trodelvy have not been established in pediatric patients.

GERIATRICS

Of the patients who received Trodelvy, 19/108 (18%) patients with mTNBC and 144/408 (35%) of all patients were 65 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

The safety of Trodelvy in patients with moderate or severe hepatic impairment has not been established.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection:

- 180 mg lyophilized powder in single-dose vials for reconstitution.