



Positive Quality Intervention: Sacituzumab govitecan-hziy -hziy (Trodelvy®): Management of Neutropenia and Diarrhea

Description: Sacituzumab govitecan-hziy is an antibody drug conjugate (ADC) that is indicated in locally advanced or metastatic urothelial cancer (mUC), triple negative breast cancer, and most recently approved for use in HR(+) HER2(-) breast cancer.¹⁻³ The purpose of this PQI is to provide information on the management of common adverse events, follow-up with patients, and dose-modifications related to neutropenia and diarrhea.

Background: Sacituzumab govitecan-hziy is an ADC that consists of an anti-Trop-2 humanized monoclonal antibody, hRS7 IgGk, coupled to the topoisomerase I inhibitor SN38 via a hydrolyzable linker. Sacituzumab govitecan-hziy binds to Trop-2, a surface protein overexpressed in most epithelial cancer cells. Once internalized by the cancer cell, a cytotoxic payload (SN38) is released intracellularly leading to cell death. In addition, the hydrolyzable linker enables SN38 to be released into the tumor microenvironment resulting in death of adjacent tumor cells.⁴ The most common side effects leading to dose reduction or discontinuation of sacituzumab govitecan-hziy are neutropenia (63% all grade, 49% grade 3-4), diarrhea (59% all grade; 10% grade 3-4) and nausea/vomiting (57% all grade, 3% grade 3-4).⁴ 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, febrile neutropenia, and anemia following initiation of TRODELVY treatment. Proactive management of both neutropenia and diarrhea can prevent early discontinuation of sacituzumab govitecan-hziy.

PQI Process:

- Ensure proper dose of 10 mg/kg once weekly on Days 1 and 8 of continuous 21-day treatment cycles
- Patients with UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia; and may be at increased risk for other adverse reactions
 - This genetic test is not commonly performed prior to administration and is not required
- Neutropenia Prevention and Management⁵⁻⁷
 - Neutropenia (boxed warning) is the most common cause of dose-interruption or dose-delay alongside leukopenia and anemia
 - The median time to first onset of neutropenia (including febrile neutropenia) was 16 days
 - Obtain a CBC with Diff on Days 1 and 8 of each cycle
 - ANC cut-offs for treatment: Day 1 $\geq 1500/\text{mm}^3$ & Day 8 $\geq 1000/\text{mm}^3$
 - Patients may be initiated on GCSF secondary prophylaxis (allowed per protocol in mUC for those with high-risk features according to ASCO guidelines i.e. age > 65 years, poor renal or liver function, pre-existing neutropenia or BM involvement, previous chemo/RT, etc) including:
 - Pegfilgrastim OBI Day 8 or pegfilgrastim injection Day 9
 - Ensure proper timing between cycles; if Day 8 is delayed for any reason, ensure a minimum of 14 days between Day 8 and the next cycle's Day 1
 - Ongoing discussions with disease state experts have evaluated alternative approaches to preventing neutropenia to keep patients on-track and meeting treatment parameters, such as administering daily filgrastim between day 1 and day 8, in addition to post-day 8 pegfilgrastim, as well as defining patient risk-factors for empiric dose-reductions or omission of the day 8 dose⁶

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Neutropenia Dose Adjustment Table:

| Neutropenia Grade | Occurrence | Dose Modification |
|---|------------|--|
| Grade 4 Neutropenia ≥ 7 days OR Grade 3-4 Neutropenia OR At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2-3 weeks for recovery to Grade ≤ 1 | First | 25% dose-reduction Administer GCSF |
| | Second | 50% dose-reduction Administer GCSF |
| | Third | Discontinue treatment Administer GCSF |
| At time of scheduled treatment Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to Grade ≤ 1 | First | Discontinue treatment Administer GCSF |

- Diarrhea Prevention and Management⁹
 - Boxed warning: Severe diarrhea may occur
 - Evaluate for infectious cause at onset of diarrhea and provide treatment with antibiotics if clinically indicated
 - Loperamide (OTC)
 - Recommended for mild/moderate AND severe/persistent diarrhea
 - Take 2 tablets (4 mg) by mouth initially at onset of diarrhea, followed by 2 mg every 4 hours for mild/moderate diarrhea or every 2 hours for severe/persistent diarrhea or 4 mg every 4 hours overnight for severe/persistent diarrhea
 - Max 16 mg/day
 - Discontinue 12 hours after diarrhea resolves
 - If diarrhea is not resolved after 24 hours, the patient should contact their healthcare provider
 - May schedule loperamide around the clock before adding another agent
 - Additional anti-diarrheals to consider: diphenoxylate/atropine or octreotide
 - Diphenoxylate/atropine (Rx)
 - Take 2 tablets (5 mg) by mouth 3-4 times daily (max 8 tablets/day)
 - May alternate with loperamide to achieve around the clock coverage
 - Octreotide:
 - Inject 100-150 mcg subcutaneously three times daily
 - May not be conducive for patients unable to self-inject or are averse to needles
 - If patient exhibits excessive cholinergic response (similar to irinotecan - abdominal cramping, diarrhea, salivation, etc), they may receive pre-medications such as atropine with subsequent treatments
 - Bland diet, small frequent meals, adequate fluid intake of clear liquids to maintain hydration
 - Discontinuation of lactose-containing foods and drinks and alcohol

Dose Adjustment Table:

| Nonhematologic toxicity: | Occurrence | Dose Modification |
|--|------------|-----------------------|
| Grade 4 non-hematologic toxicity of any duration OR Any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with anti-emetics and anti-diarrheal agents OR Other Grade 3-4 non hematologic toxicity persisting > 48 hours despite optimal medical management OR At time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2-3 weeks for recovery to Grade ≤ 1 | First | 25% dose-reduction |
| | Second | 50% dose-reduction |
| | Third | Discontinue treatment |
| In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover within 3 weeks to Grade ≤ 1 | First | Discontinue treatment |

Patient-Centered Activities:

- Provide [Intravenous Cancer Treatment Education \(IVE\)](#) Sheet and [Supplemental Diarrhea Sheet](#)
- Provide upfront take-home medications, including anti-emetics and loperamide
- Ensure patient has a working thermometer at home prior to starting
 - Instruct patients to call their provider (or on-call provider) at first sign of fever ($\geq 100.4^{\circ}\text{F}/38^{\circ}\text{C}$)
- Explain median timeline to neutropenia is as early as 7-10 days
- Explain sacituzumab govitecan-hziy associated diarrhea may happen during the infusion or days to weeks after starting
 - Instruct patients to call their provider at first sign of diarrhea or black/bloody stools
 - Encourage patients to take loperamide at the onset of a loose, watery stool and every two hours until resolution of diarrhea
 - Provide OTC Loperamide education handouts
- Diet Recommendations
 - Bland diet, small frequent meals, adequate fluid intake of clear liquids to maintain hydration
 - Discontinuation of lactose-containing foods and drinks and alcohol

References:

1. Tagawa ST, Balar AV, Petrylak DP et al. TROPHY-U-01: A Phase II Open-Label Study of Sactuzumab in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. *J Clin Oncol.* 2021 Aug 1;39(22):2474-2485.
2. Bardia A, Mayer IA, Vahdat LT et al, Sacituzumab Govitecan-hziy -hziy in Refractory Metastatic Triple-Negative Breast Cancer. *N Engl J Med.* 2019 Feb 21;380(8):741-751.
3. Rugo HS, Bardia A, Tolaney SM et al, TROPiCS-02: A Phase III study investigating sacituzumab govitecan-hziy in the treatment of HR+/HER2- metastatic breast cancer. *Future Oncol.* 2020 Apr;16(12):705-715.
4. [Sacituzumab govitecan-hziy package insert. Revised 2/2023. Accessed March 9th, 2023.](#)
5. [Gilead MI: Trodelvey Trodelvy® \(sacituzumab govitecan-hziy -hziy\) Neutropenia and Growth Factor Support \(Pooled Safety\) \(askgileadmedical.com\).](#)
6. [Part 2: Managing Sacituzumab-Associated Neutropenia in TNBC \(targetedonc.com\).](#)
7. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Practice Guideline Update. *Vol 33, Issue 28, 2015.*
8. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol.* 2004 Jul 15;22(14):2919-26.