Poster 194P

# Safety Outcomes by *UGT1A1* Status in the Phase 3 TROPiCS-02 Study of Sacituzumab Govitecan in HR+/HER2– Metastatic Breast Cancer


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## CONCLUSIONS

**SG had a manageable safety profile (consistent with previous reports[5,11]) regardless of *UGT1A1* status (including neutropenia, diarrhea, and febrile neutropenia, which typically resolved within 10 days) in patients with HR+/HER2– mBC**

**Patients who were homozygous for *UGT1A1* *28/*28 experienced numerically higher rates of grade ≥ 3 TEAEs, TEAEs leading to discontinuation, any-grade anemia, and grade ≥ 3 diarrhea and neutropenia, although sample sizes were small**

**Because patients treated with SG are closely monitored for adverse events according to the prescribing information and per standard practice regardless of *UGT1A1* genotype, *UGT1A1* testing is not needed for SG use in pretreated HR+/HER2– mBC**

**Active monitoring and early intervention with routine strategies for AE management (and G-CSF treatment) is recommended for all patients being treated with SG**



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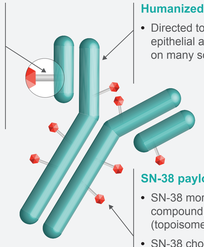
## BACKGROUND

- Breast cancer is the second leading cause of cancer death in women,[1] and hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2–) cancers make up approximately 70% of breast cancers[2]
- Sacituzumab govitecan (SG) is a trophoblast cell surface antigen 2 (Trop-2)–directed antibody-drug conjugate (ADC) (**Figure 1**) approved for triple-negative breast cancer (TNBC) in multiple countries and HR+/HER2– metastatic breast cancer (mBC) in the US[3,4]
- In the phase 3 randomized TROPiCS-02 study, SG versus treatment of physician's choice (TPC) demonstrated significantly improved median progression-free survival (PFS; 5.5 vs 4.0 months; hazard ratio [HR], 0.66; *P* = .0003) and median overall survival (OS; 14.4 vs 11.2 mo; HR, 0.79; *P* = .020), with a manageable safety profile in patients with pretreated, endocrine-resistant HR+/HER2– mBC[5]
- Polymorphisms in uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) have been associated with increased incidence of known adverse events, such as neutropenia, febrile neutropenia, anemia, and diarrhea, following treatment with some systemic anticancer agents, including SG, irinotecan, pazopanib, sunitinib, and nilotinib due to reduced rate of SN-38 glucuronidation[6-10]
- We present safety analyses of SG versus TPC by *UGT1A1* genotype status from TROPiCS-02

**Figure 1**. Sacituzumab govitecan antibody-drug conjugate



**Linker for SN-38**
- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)
- Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody

**Humanized anti–Trop-2 antibody**
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

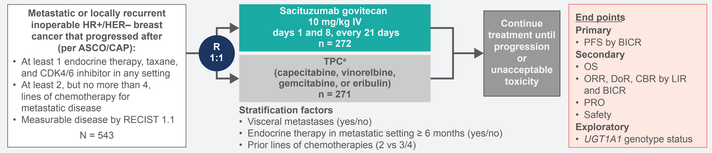
**SN-38 payload**
- SN-38 more potent than parent compound, irinotecan (topoisomerase I inhibitor)
- SN-38 chosen for its moderate cytotoxicity (with $IC_{50}$ in the nanomolar range), permitting delivery in high quantity to the tumor

$IC_{50}$, half maximal inhibitory concentration; Trop-2, trophoblast cell surface antigen 2.

## METHODS

- TROPiCS-02 is a phase 3, randomized, open-label study of SG versus TPC (**Figure 2**)
- Exploratory safety analyses by *UGT1A1* status were performed
- The data cutoff for the analysis was July 1, 2022

**Figure 2**. TROPiCS-02 (NCT03901339): A phase 3 study of SG in HR+/HER2– locally recurrent inoperable or metastatic breast cancer[11]




ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormonal receptor–positive; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors; TPC, treatment of physician's choice.
[a]Single-agent standard-of-care TPC was specified prior to randomization by the investigator.

# Results

## Patients

- Baseline characteristics were balanced between the treatment arms (**Table 1**)
- Of 543 patients enrolled, 517 were included in the safety population (SG, n = 268; TPC, n = 249)
  - 9 patients (3%) in the SG arm and 2 (1%) in the TPC arm remained on treatment at data cutoff
  - The most common reason for treatment discontinuation was progressive disease (SG, 80%; TPC, 73%)

**Table 1**. Demographics and baseline characteristics

| | SG (n = 272) | TPC (n = 271) |
|---|---|---|
| **Female, n (%)** | 270 (99) | 268 (99) |
| **Median age at study entry (range), y** | 57.0 (29-86) | 55.0 (27-78) |
| **Race,[a] n (%)** | | |
| White | 184 (68) | 178 (66) |
| Asian | 11 (4) | 5 (2) |
| Black | 8 (3) | 13 (5) |
| **ECOG performance status, n (%)** | | |
| 0 | 115 (42) | 126 (46) |
| 1 | 157 (58) | 145 (54) |
| **Metastatic disease, n (%)** | 262 (96) | 264 (97) |
| **Number of prior chemotherapies, n (%)** | | |
| 2-3 | 127 (47) | 119 (44) |
| > 3 | 144 (53) | 152 (56) |
| **Median prior systemic regimens,[b] n (range)** | 7.0 (3-17) | 7.0 (3-16) |
| **Setting of prior systemic therapies,[c] n (%)** | | |
| Adjuvant | 186 (68) | 206 (76) |
| Neoadjuvant | 67 (25) | 62 (23) |
| Metastatic | 272 (100) | 271 (100) |
| Other | 8 (3) | 7 (3) |
| ***BRCA1/2* mutational status, n (%)** | | |
| Negative | 109 (40) | 114 (42) |
| Positive | 21 (8) | 11 (4) |
| Unknown | 142 (52) | 146 (54) |

*BRCA*, breast cancer gene; ECOG, Eastern Cooperative Oncology Group; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.
[a]Race was not reported for 69 (25%) patients in the SG arm and 70 (26%) patients in the TPC arm, and 5 (2%) patients in the TPC arm were reported as other.
[b]Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting.
[c]Patients may have received prior systemic therapy in more than 1 setting.

- Of patients treated with SG, 38% had wild-type, 44% had heterozygous, and 9% had homozygous *UGT1A1* genotypes (**Table 2**)
- The number of patients with a homozygous genotype was low, potentially limiting interpretation of these analyses

**Table 2**. Summary of *UGT1A1* status

| | SG[a] (n = 268) | | |
|---|---|---|---|
| | *1/*1 Wild-type | *1/*28 Heterozygous | *28/*28 Homozygous |
| **Total, n (%)[b]** | 103 (38) | 119 (44) | 25 (9) |
| White | 71 (39) | 82 (45) | 16 (9) |
| Asian | 7 (64) | 2 (18) | 0 |
| Black | 2 (29) | 3 (43) | 1 (14) |

SG, sacituzumab govitecan.
[a]3 patients (1%) treated with SG had other genotypes, one each of *1/*36, *1/*37, and *28/*36; 2 of these patients were white, and 1 did not have race reported.
[b]Racial subgroups were calculated as percentage of total racial group in each genotype category.

## Safety

- Median relative dose intensity (cumulative dosage received divided by total assigned dosage) was 99%, 98%, and 94% for patients with wild-type, heterozygous, and homozygous *UGT1A1* genotypes, respectively
  - Median duration of exposure was 3.9, 4.8, and 2.8 months, respectively
- Compared with patients with wild-type or heterozygous genotypes, those with homozygous genotypes had higher rates of grade ≥ 3 treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation; patients with heterozygous or homozygous genotypes had higher rates of TEAEs leading to dose reduction versus patients with wild-type genotypes (**Table 3**)

**Table 3**. TEAEs by *UGT1A1* status

| | SG (n = 268) | | |
|---|---|---|---|
| | *1/*1 Wild-type (n = 103) | *1/*28 Heterozygous (n = 119) | *28/*28 Homozygous (n = 25) |
| **All TEAEs,[a] n (%)** | 103 (100) | 119 (100) | 25 (100) |
| Grade ≥ 3, n (%) | 69 (67) | 89 (75) | 23 (92) |
| **TEAEs leading to dose reduction, n (%)** | 26 (25) | 49 (41) | 10 (40) |
| **TEAEs leading to treatment interruption, n (%)** | 70 (68) | 76 (64) | 19 (76) |
| **TEAEs leading to treatment discontinuation, n (%)** | 5 (5) | 7 (6) | 3 (12) |

SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.
[a]TEAEs were defined as any AEs that started on or after first dose date and up 30 days after last dose date. Severity grades were defined using Common Terminology Criteria for Adverse Events v5.0.

- Grade ≥ 3 TEAEs of interest in patients treated with SG included neutropenia (51%), diarrhea (10%), anemia (7%), and febrile neutropenia (6%)
- Patients with homozygous genotypes had higher rates of grade ≥ 3 neutropenia and diarrhea, and higher rates of any-grade (but not grade ≥ 3) anemia compared to those with wild-type or heterozygous genotypes (**Table 4**)
- Rates of febrile neutropenia were similar across subgroups (**Table 4**)

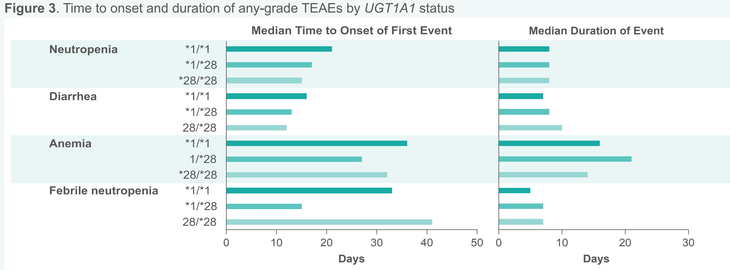
**Table 4**. TEAEs of special interest by *UGT1A1* status

| | SG (n = 268) | | | | | |
|---|---|---|---|---|---|---|
| | *1/*1 Wild-type (n = 103) | | *1/*28 Heterozygous (n = 119) | | *28/*28 Homozygous (n = 25) | |
| | Any grade | Grade ≥ 3 | Any grade | Grade ≥ 3 | Any grade | Grade ≥ 3 |
| **TEAEs of special interest, n (%)** | | | | | | |
| Neutropenia | 73 (71) | 46 (45) | 86 (72) | 68 (57) | 19 (76) | 16 (64) |
| Diarrhea | 60 (58) | 6 (6) | 77 (65) | 15 (13) | 17 (68) | 6 (24) |
| Anemia | 34 (33) | 6 (6) | 43 (36) | 10 (8) | 12 (48) | 2 (8) |
| Febrile neutropenia | 6 (6) | 6 (6) | 8 (7) | 8 (7) | 1 (4) | 1 (4) |

SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

- Patients with homozygous genotypes had shorter time to onset of neutropenia and diarrhea than those with wild-type genotypes, and patients with heterozygous genotypes had shorter time to onset of febrile neutropenia (**Figure 3**)
- Patients with heterozygous genotypes had longer duration of anemia than patients with wild-type or homozygous genotypes; duration was similar across groups for neutropenia, diarrhea, and febrile neutropenia (**Figure 3**)

**Figure 3**. Time to onset and duration of any-grade TEAEs by *UGT1A1* status




SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.
In patients treated with SG. Assessed in the safety population.

- Granulocyte colony-stimulating factor (G-CSF) was initiated for management of neutropenia for 54% of patients treated with SG; G-CSF treatment was initiated less frequently in wild-type patients and median time to G-CSF initiation was shortest in heterozygous patients (**Table 5**)

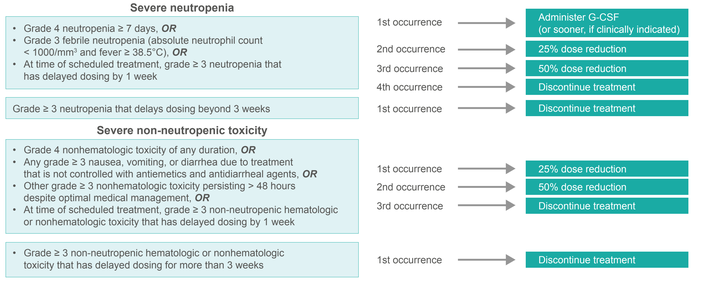
**Table 5**. G-CSF initiation

| | SG (n = 268) | | | |
|---|---|---|---|---|
| | *1/*1 Wild-type (n = 103) | *1/*28 Heterozygous (n = 119) | *28/*28 Homozygous (n = 25) | Total (n = 268) |
| **G-CSF initiated, n (%)** | 48 (47) | 71 (60) | 16 (64) | 144 (54) |
| **Median time to initiation of G-CSF,[a] mo** | 0.69 | 0.49 | 0.62 | 0.61 |

G-CSF, granulocyte colony-stimulating factor; SG, sacituzumab govitecan.
[a]Date of G-CSF initiation was defined as the first date of G-CSF medication that started from first SG dose date to 30 days after last SG dose date.

- Severe TEAEs were managed using a well-defined treatment algorithm (**Figure 4**)

**Figure 4**. TEAE management strategies[3]




G-CSF, granulocyte colony-stimulating factor; TEAE, treatment-emergent adverse event.

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## DISCLOSURES

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