Quality-Adjusted Time Without Symptoms of Disease Progression or Toxicity of Treatment (Q-TWiST) Analysis of Sacituzumab Govitecan vs Chemotherapy in Previously Treated Patients With HR+/HER2– Metastatic Breast Cancer

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Conclusions

- Results from this Q-TWiST analysis show that SG was associated with an incremental gain in quality-adjusted survival vs TPC in patients with pretreated HR+/HER2– mBC enrolled in TROPiCS-02; the gain exceeded the 10% threshold for a clinically important treatment difference
- Although time spent with toxicity (grade ≥ 3 TEAEs) was initially longer for SG vs TPC, this difference was not statistically significant and diminished with longer follow-up
- Therefore, long-term survival benefit with SG over TPC was not at the expense of QOL or unmanageable toxicities, and the net benefit of SG continued to accrue over time; however, there is a need for further research to refine our understanding of the utility values that can be attributed to different health states

Plain Language Summary

- Sacituzumab govitecan (SG) is a drug approved for previously treated hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (mBC), which is the most common subtype of breast cancer
- Q-TWiST is an established way to determine the benefit:risk of a cancer treatment; it incorporates survival, quality of life, participant preferences, and any side effects of treatment into a single measure of overall well-being
- This analysis used data from a pivotal study (TROPiCS-02) to show that SG had a better Q-TWiST value than chemotherapy, indicating that SG improved both the duration and quality of survival in participants with HR+/HER2– mBC

References: **1.** International Agency for Research on Cancer. Global Cancer Observatory, GLOBOCAN 2022, World Fact Sheet. 2022. https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf. **2.** American Cancer Society. Female Breast Cancer Subtypes. https://seer.cancer.gov/statfacts/html/breast-subtypes.html. **3.** Starodub AN, et al. *Clin Cancer Res*. 2015;21:3870-8. **4.** TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc., February 2023. **5.** Rugo HS, et al. *J Clin Oncol*. 2022;40:3365-76. **6.** Rugo HS, et al. *Lancet*. 2023;402:1423-33. **7.** Rugo HS, et al. *Oncologist*. 2024;29:768-79. **8.** Glasziou PP, et al. *Stat Med*. 1990;9:1259-76. **9.** Lloyd A, et al. *Br J Cancer*. 2006;95:683-90. **10.** Revicki DA, et al. *Qual Life Res*. 2006;15:411-23.

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Introduction

- Breast cancer (BC) is the most common cancer in women globally, with nearly 2.3 million new cases in 2022,[1] and hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2– [immunohistochemistry 0, 1+, or 2+/in situ hybridization-negative]) BC is the most common type, accounting for ~70% of cases[2]
- Sacituzumab govitecan (SG) is a Trop-2–directed antibody-drug conjugate that delivers SN-38, a cytotoxic payload, to cancer cells[3]
- SG is approved for HR+/HER2– metastatic BC (mBC) in patients who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting.[4] This approval was primarily based on TROPiCS-02, a phase 3, randomized study in which SG demonstrated statistically significant and clinically meaningful survival benefit and improved quality of life (QOL) over chemotherapy treatment of physician's choice (TPC) with a manageable safety profile[5-7]

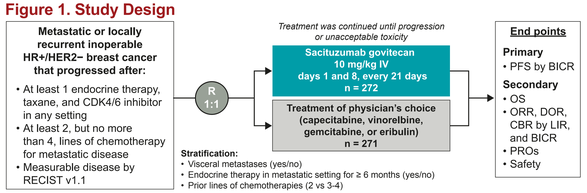
Objective

- To evaluate both survival time and QOL associated with SG vs TPC in patients with HR+/HER2– mBC from the TROPiCS-02 study using Q-TWiST analysis

Methods

- This analysis included the intent-to-treat population (all participants who were randomized, regardless of whether they received study treatment) from TROPiCS-02 (**Figure 1**)

Figure 1. Study Design



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, intravenous; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

Description of Q-TWiST Framework

- Q-TWiST is an established method to compare 2 treatments by incorporating benefit (survival) vs risk (toxicity) adjusted for QOL utilities (patient preferences)[8]
- For this Q-TWiST analysis, we divided survival time into 3 health states:
  - **TOX:** time with treatment-emergent adverse events (TEAEs; grade ≥ 3 TEAEs in the base case) before disease progression, death, or follow-up (whichever came first)
  - **REL:** time from disease progression until death or end of follow-up (whichever came first)
  - **TWiST:** time without toxicity before disease progression
- Utility weights were assigned to each heath state based on published values[9]; the base state (stable disease on treatment with no toxicities) had a utility value of 0.715. Moving to the progressive disease state resulted in a utility decrement (–0.272). The toxicity health state had a utility value of –0.11. Thus, the utility weights were:
  - U_{TOX} = 0.605 (0.715–0.11); U_{REL} = 0.443 (0.715–0.272); U_{TWiST} = 0.715
- To estimate (restricted mean) duration spent in each health state for each treatment, survival curves that corresponded to progression-free survival (PFS), overall survival (OS), and TOX were developed using the Kaplan–Meier method. These health state durations were adjusted for the utility weights to provide Q-TWiST:
  - **Q-TWiST** = U_{TOX} × TOX + U_{TWiST} × TWiST + U_{REL} × REL

Methods

- Difference (95% CI and *P*-value, using a nonparametric bootstrapping approach) in restricted mean survival times were calculated between SG and TPC groups
- **Relative gain in Q-TWiST** (%) for SG was then calculated as difference in mean Q-TWiST between SG and TPC divided by restricted mean OS of the TPC group
  - This measure provided the incremental gain in quality-adjusted survival associated with SG over TPC
  - Published estimates indicate that a relative Q-TWiST gain > 10% is clinically important[10]

Sensitivity Analyses

- To further examine the utility and treatment duration, the following sensitivity analyses were performed:
  - **Two-way utility analysis:** U_{TOX} and U_{REL} were adjusted from 0 to 1 with U_{TWiST} = 0.715 (stable disease, no side effects) and 1.000 (best overall health state)
  - **Variation in follow-up:** base case analysis was adjusted by available follow-up

Results

- Based on a maximum follow-up of 38 months, SG was associated with statistically significant improvements in OS (difference 2.3 months; *P* = .0168), PFS (difference 2.3 months; *P* = .0289), TWiST (difference 2.1 months; *P* = .0417), and Q-TWiST (difference 1.6 months; *P* = .0067) vs TPC (**Table 1**)
- Relative Q-TWiST gain with SG (10.8%) exceeded the threshold for clinical importance

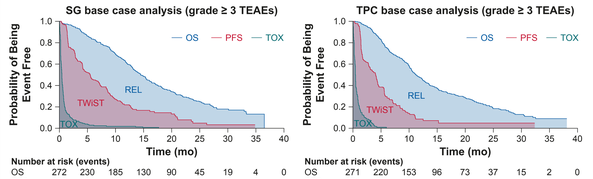
Table 1. Mean Duration of Health States and Q-TWiST (TEAE ≥ 3, Base Case)

Duration (mo)	SG (n = 272)	TPC (n = 271)	Difference	*P*-value
OS (95% CI)	17.0 (15.8 to 18.4)	14.8 (13.4 to 16.2)	2.3 (0.5 to 4.3)	.0168
PFS (95% CI)	8.3 (7.0 to 9.7)	6.0 (4.6 to 7.7)	2.3 (0.1 to 4.2)	.0289
TOX (95% CI)[a]	1.0 (0.8 to 1.4)	0.8 (0.7 to 1.0)	0.2 (−0.1 to 0.6)	.2590
REL (95% CI)[b]	8.8 (7.5 to 10.1)	8.7 (7.1 to 10.4)	< 0.1 (−2.0 to 2.3)	.9937
TWiST (95% CI)[c]	7.3 (6.1 to 8.6)	5.2 (3.8 to 6.8)	2.1 (0.1 to 3.9)	.0417
Q-TWiST (95% CI)	9.7 (8.9 to 10.5)	8.1 (7.3 to 9.0)	1.6 (0.5 to 2.7)	.0067

Data cut December 1, 2022. Restricted means evaluated at maximum follow-up time (38.0 mo). Number of patients in TOX, REL, and TWiST analyses were the number of patients with time > 0 in that health state.
[a]SG, n = 183; TPC, n = 130. [b]SG, n = 239; TPC, n = 241. [c]SG, n = 272; TPC, n = 271.
mo, months; OS, overall survival; PFS, progression-free survival; Q-TWiST, Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment; REL, relapse; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event; TOX, toxicity; TPC, treatment of physician's choice; TWiST, Time Without Symptoms of disease progression or Toxicity of treatment.

- Survival plots showed that patients treated with SG remained in the TOX and TWiST states longer than those treated with TPC (**Figure 2**)
- Although time spent with toxicity (grade ≥ 3 TEAEs) was initially longer for SG vs TPC (**Figure 2**), this difference was not statistically significant and stabilized over time (**Figure 3**)

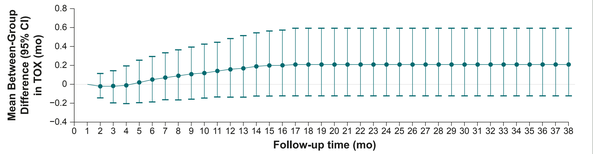
Figure 2. Partitioned Survival Plots



mo, months; OS, overall survival; PFS, progression-free survival; REL, relapse; SG, sacituzumab govitecan; TOX, toxicity; TPC, treatment of physician's choice; TWiST, Time without Symptoms of disease progression or toxicity of treatment.

Results

Figure 3. Between-Group Difference in TOX Over Time

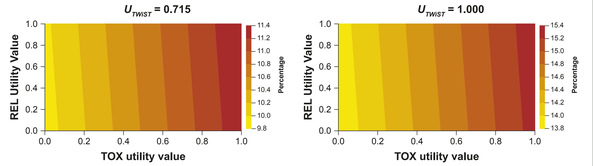


mo, months; TOX, toxicity.

Sensitivity Analyses

- Relative Q-TWiST gains were primarily driven by U_{TOX}; for a given value of U_{REL}, relative Q-TWiST gain varied substantially based on U_{TOX}, while for a given value of U_{TOX}, relative Q-TWiST gains did not vary substantially by U_{REL} values (**Figure 4**)
- With U_{TWiST} set to 0.715, relative Q-TWiST gain exceeded the 10% threshold for clinical importance for all U_{TOX} values > 0.07, and relative Q-TWiST gains varied from 9.9% to 11.4%
- With U_{TWiST} set to 1.000, relative Q-TWiST gain exceeded the 10% threshold for all U_{TOX} and U_{REL} values, with relative Q-TWiST gain ranging from 13.9% to 15.3%
- All relative Q-TWiST gains in this sensitivity analysis were statistically significant across U_{TOX} and U_{REL} ranges for both U_{TWiST} = 0.715 and U_{TWiST} = 1.000

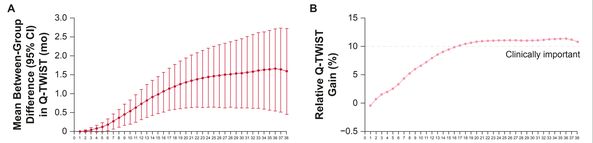
Figure 4. Two-Way Utility Sensitivity Analysis



Threshold utility analysis was performed to assess the impact of assumptions regarding health state utilities on the between-treatment Q-TWiST comparisons.
REL, relapse; TOX, toxicity; TWiST, Time without Symptoms of disease progression or toxicity of treatment.

- When Q-TWiST was varied by follow-up time, the benefits of SG over TPC increased and then stabilized over time up to month 38 (**Figure 5A**)
- Similar findings were observed with relative Q-TWiST gains; the clinically important difference threshold was exceeded at 17 months with SG and remained above this threshold up to month 38 (**Figure 5B**)

Figure 5. Q-TWiST Difference by Follow-Up Time (Sensitivity Analysis)



mo, months; Q-TWiST, Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment.