Quality-Adjusted Time Without Symptoms of Disease Progression or Toxicity of Treatment (Q-TWiST) Analysis to Assess Benefit-Risk of Sacituzumab Govitecan in Previously Treated Patients With Metastatic Triple-Negative Breast Cancer

Adam Brufsky[1], Aditya Bardia[2], Mina S Sedrak[2,3], Sibylle Loibl[4], Sara M Tolaney[5], Kevin Punie[6,7], Sara A Hurvitz[8], Kevin Kalinsky[9], Javier Cortés[10], Joyce A O'Shaughnessy[11], Véronique Dieras[12], Martine J Piccart-Gebhart[13], Anandaroop Dasgupta[14], Ankita Kaushik[14], Catherine Lai[15], Ling Shi[16], Hope S Rugo[17]

[1]Department of Hematology/Oncology, Magee-Womens Hospital and the Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [2]Division of Medical Oncology, UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [3]Cancer and Aging Program, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA; [4]German Breast Group, Forschungs, Germany; Neu-Isenburg and Centre for Haematology and Oncology Bethanien, Frankfurt, Germany; [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [6]Department of General Medical Oncology and Multidisciplinary Breast Centre, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium; [7]Laboratory of Experimental Oncology, Department of Oncology, KU Leuven, Leuven, Belgium; [8]Division of Hematology and Oncology, Department of Medicine, University of Washington Medicine, Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA, USA; [9]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [10]International Breast Cancer Center, Quironsalud Group, Barcelona, Spain; [11]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA; [12]Centre Eugene Marquis UNICANCER, Rennes Cedex, France; [13]Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; [14]Department of Health Economics Outcomes Research, Gilead Sciences Inc., Foster City, CA, USA; [15]Department of Clinical Development, Gilead Sciences Inc., Foster City, CA, USA; [16]Department of Patient Centered Research, Evidera Inc, Bethesda, MD, USA; [17]Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

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Conclusions

- Q-TWiST analysis supports a positive benefit-risk ratio for SG compared with chemotherapy in patients with previously treated mTNBC in the ASCENT study, and the net benefits of SG continued to accrue over time
- SG demonstrated statistically significant Q-TWiST improvement vs chemotherapy, and this improvement met the externally validated threshold for clinical importance in quality-adjusted survival
- Q-TWiST analysis showed that the long-term survival benefit of SG over chemotherapy in mTNBC was not at the expense of quality of life or unmanageable toxicities
- In summary, Q-TWiST provides a useful adjunct in clinical decision-making

Plain Language Summary

- Sacituzumab govitecan is a drug that is approved for use in previously treated triple-negative breast cancer (TNBC) that has spread to other parts of the body (metastatic TNBC)
- Cancer treatment may affect a person's sense of well-being and ability to perform daily activities, which is referred to as quality of life
- Q-TWiST is a measure to determine the benefit of a cancer treatment while taking into account the preferences and quality of life of people with metastatic TNBC
- This analysis used data from the ASCENT study to show that sacituzumab govitecan treatment provided longer Q-TWiST than chemotherapy, which indicates that sacituzumab govitecan improved the duration of survival without compromising quality of life of participants who were being treated with sacituzumab govitecan for metastatic TNBC

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Correspondence: brufskyam@upmc.edu

Introduction

- Triple-negative breast cancer (TNBC) accounts for 15%-20% of breast cancers. TNBC is defined as low (< 1%) estrogen and/or progesterone receptor expression with no overexpression of human epidermal growth factor receptor 2[1]
- Sacituzumab govitecan (SG) is an antibody-drug conjugate directed to Trop-2, which is commonly expressed in breast cancers[2]; SG is approved for the treatment of unresectable locally advanced or metastatic TNBC (mTNBC) in patients who have received 2 or more prior systemic therapies, at least 1 of them for metastatic disease[3]
- The ASCENT study demonstrated significantly prolonged overall survival (OS) and progression-free survival (PFS) with SG vs chemotherapy, with higher rates of treatment-related adverse events in the SG group compared with the chemotherapy group[4]
- Quality of life is a humanistic outcome associated with treatment, and Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment (Q-TWiST) is an established framework to evaluate quality of life regarding a treatment in the context of its clinical benefits and associated toxicities[5]

Objective

- To assess the benefit-risk profile of SG vs chemotherapy for previously treated mTNBC while accounting for patient quality of life in the intention-to-treat (ITT) population of the ASCENT study using Q-TWiST methodology

Methods

- ASCENT is a randomized, phase 3 study of SG vs chemotherapy in patients with pretreated mTNBC, as previously described[4]
- Our study evaluated the ITT population of the ASCENT study
- Toxicities were defined as treatment-emergent adverse events (TEAEs)

Description of Q-TWiST Framework

- Survival time was partitioned into 3 health states:
  - **TOX**: Time with toxicity (TEAE) until the earliest of TEAE resolving, disease progression, death, or end of follow-up
  - **REL**: Time from disease progression until death or end of follow-up, whichever was first
  - **TWiST**: Time spent without toxicity before disease progression
- The base case analysis was performed using grade ≥ 3 TEAEs
- Partitioned survival plots were generated with restricted means for TOX, PFS, and OS
- Restricted mean survival time (95% CI using a non-parametric bootstrapping approach with replacement; 1000 replications) in TOX, TWiST, REL, PFS, and OS states was calculated up to maximum patient follow-up time observed
- Health state utilities were derived from published literature: u_{TOX} = 0.605 (= 0.715 – 0.11), u_{REL} = 0.443 (= 0.715 – 0.272), u_{TWiST} = 0.715[6]
- Q-TWiST was calculated as utility-weighted sum of mean health state durations: Q-TWiST = u_{TOX} x TOX + u_{REL} x REL + u_{TWiST} x TWiST
- Difference (95% CI and *P*-value, using a non-parametric bootstrapping approach) in restricted mean survival times was calculated between SG and chemotherapy groups
- Relative gains (%) in Q-TWiST (difference in mean Q-TWiST between SG and chemotherapy groups divided by restricted mean OS of chemotherapy group) were calculated
- The prevalidated thresholds for relative Q-TWiST gain were ≥ 10% for clinically important difference and ≥ 15% for clearly clinically important difference, as established by Revicki et al[7]

Sensitivity Analyses

- Variation in TOX: Q-TWiST was re-evaluated with grade ≥ 2 TEAEs measured in the TOX state
- Two-way utility analysis: TOX and REL utility values were adjusted (from 0-1) with u_{TWiST} = 0.715 (stable disease with no TEAE) and 1 (best overall health state)
- Variation in follow-up: The base-case analysis was adjusted by available follow-up

Results

- Based on maximum follow-up of 31 months (mo), SG was associated with a statistically significant improvement in OS (difference 5.3 mo; *P* < .0001) and PFS (difference 4.5 mo; *P* < .0001) compared with chemotherapy (**Table 1**)
- SG had significantly longer TWiST (difference 4.4 mo; *P* < .0001) and Q-TWiST (difference 3.5 mo; *P* < .0001) than chemotherapy (**Table 1**)
- Relative Q-TWiST gain with SG (39.5%) exceeded the clearly clinically important threshold

Table 1. Q-TWiST Analysis (TEAE ≥ 3, Base Case)

Duration (mo)	SG (n = 267)	Chemotherapy (n = 262)	Difference	*P*-value
OS (95% CI)	14.2 (13.1 to 15.4)	9.0 (8.1 to 9.9)	5.3 (3.8 to 6.6)	< .0001
PFS (95% CI)	7.7 (6.5 to 8.9)	3.1 (2.7 to 4.6)	4.5 (2.8 to 5.8)	< .0001
TOX (95% CI)[a]	0.7 (0.6 to 0.9)	0.6 (0.5 to 0.7)	0.2 (< −0.1 to 0.4)	.0778
REL (95% CI)[b]	6.5 (5.4 to 7.6)	5.8 (4.3 to 6.6)	0.7 (−0.6 to 2.6)	.3939
TWiST (95% CI)[c]	7.0 (5.8 to 8.2)	2.6 (2.2 to 4.1)	4.4 (2.6 to 5.7)	< .0001
Q-TWiST (95% CI)	8.3 (7.6 to 9.1)	4.8 (4.3 to 5.4)	3.5 (2.6 to 4.4)	< .0001

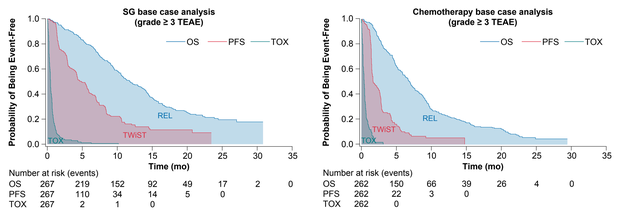
Data cut February 25, 2021. Restricted means evaluated at maximum follow-up time (30.8 mo). Number of patients in TOX, REL, and TWiST analyses are the number of patients with time > 0 in that health state.
[a]SG, n = 174; chemotherapy, n = 115. [b]SG, n = 248; chemotherapy, n = 225. [c]SG, n = 267; chemotherapy, n = 262.
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; TWiST, Time Without Symptoms of disease progression or Toxicity of treatment.

- Time spent in TOX, REL, and TWiST was numerically longer for SG than for chemotherapy in the base case (grade ≥ 3 TEAE) and sensitivity analysis (grade ≥ 2 TEAE); this difference was significant for the TWiST health state (**Figure 1**)

Sensitivity Analysis (Grade ≥ 2 TEAE) Results

- SG had significantly longer median Q-TWiST vs chemotherapy, a difference of 3.3 mo (*P* < .0001)
- Patients in the SG group had 1.9 mo longer TWiST and 2.6 mo longer TOX vs chemotherapy
- Relative Q-TWiST gain with SG (36.5%) exceeded the clearly clinically important threshold

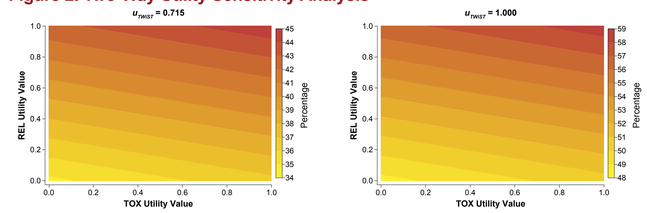
Figure 1. Partitioned Survival Plots



mo, months; OS, overall survival; PFS, progression-free survival; REL, relapse; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event; TOX, toxicity; TWiST, Time Without Symptoms of disease progression or Toxicity of treatment.

- Relative Q-TWiST gain was mainly dependent on u_{REL} values; for the same u_{TOX}, relative Q-TWiST gains varied substantially with u_{REL} value, while for the same u_{REL}, relative Q-TWiST gains did not substantially vary with u_{TOX} value (**Figure 2**)
- Relative Q-TWiST gain was higher than the threshold (15%) for clearly clinically important improvement in quality-adjusted survival for all u_{REL} and u_{TOX} values
- With u_{TWiST} = 0.715, relative Q-TWiST gain ranged from 34.8% to 44.7%; with u_{TWiST} = 1.000, relative Q-TWiST gain ranged from 48.7% to 58.6%; all relative Q-TWiST gains in these ranges were statistically significant

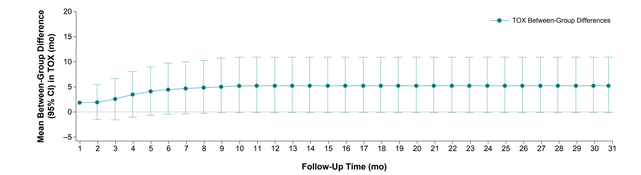
Figure 2. Two-Way Utility Sensitivity Analysis



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

- The difference in time spent in TOX between SG and chemotherapy stabilized over time and was shown to be nonsignificant throughout the follow-up period (**Figure 3**)

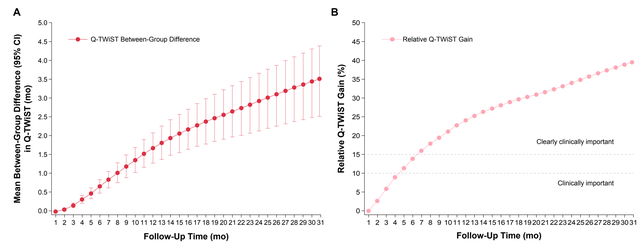
Figure 3. Between-Group Difference in Toxicity Over Time



Time scale of toxicity difference vs time has been truncated to the upper limit of the PFS value of the SG group.
mo, months; PFS, progression-free survival; SG, sacituzumab govitecan; TOX, toxicity.

- The Q-TWiST benefit of SG over chemotherapy increased over time to month 31 (**Figure 4A**)
- Relative Q-TWiST gain also increased over time; the clinically important threshold was exceeded at ~4.5 mo, and the clearly clinically important threshold was exceeded at ~6.5 mo (**Figure 4B**)

Figure 4. 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.