Trop-2 mRNA Expression and Association With Clinical Outcomes With Sacituzumab Govitecan (SG) in Patients With HR+/HER2– Metastatic Breast Cancer (mBC): Biomarker Results From the Phase 3 TROPiCS-02 Study

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Key Findings

- **SG demonstrated efficacy benefit versus TPC regardless of *TACSTD2* mRNA expression**
- **SG should be considered as a therapeutic option in the endocrine-resistant setting, regardless of Trop-2 expression**

Conclusions

Similar to the previously published Trop-2 IHC correlative analysis,[5] SG demonstrated PFS and OS benefit versus TPC regardless of *TACSTD2* mRNA expression in patients with pretreated, endocrine-resistant HR+/HER2– mBC

SG benefit with ORR, CBR, and DoR versus TPC was seen regardless of *TACSTD2* expression

TACSTD2 expression was not correlated with ERBB2 expression or with HER2 expression by IHC

Regardless of Trop-2 and HER2-negative status, SG improved PFS and OS versus TPC

Additional studies are needed to determine whether *TACSTD2* mRNA expression has a prognostic role in mBC

Introduction

- Breast cancer is the second leading cause of cancer death in women,[1] and hormone receptor-positive (HR+)/human epidermal growth factor-negative (HER2–)[a] cancers represent approximately 70% of breast cancers[2]
- Sacituzumab govitecan (SG) is a trophoblast cell surface antigen 2 (Trop-2)–directed antibody-drug conjugate (ADC) that has been approved in multiple countries for patients with triple-negative breast cancer after at least 1 prior therapy and in the US also for patients with pretreated HR+/HER2– mBC[3]
- 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 [mo]; hazard ratio [HR], 0.66; *P* = .0003) and median overall survival (OS; 14.4 vs 11.2 mo; HR, 0.79; *P* = .020), and a manageable safety profile in patients with pretreated, endocrine-resistant HR+/HER2– mBC[4]
- SG improved PFS and OS regardless of Trop-2 expression by immunohistochemistry (IHC) in a post hoc analysis[5]
  - Median PFS with SG versus TPC was 5.3 versus 4.0 mo (HR, 0.77; 95% CI, 0.54-1.09) in patients with H-score < 100, and 6.4 versus 4.1 mo (HR, 0.60; 95% CI, 0.44-0.81) in patients with H-score ≥ 100[5]
  - Median OS with SG versus TPC was 14.6 versus 11.3 mo (HR, 0.75; 95% CI, 0.54-1.04) in patients with H-score < 100, and 14.4 versus 11.2 mo (HR, 0.83; 95% CI, 0.62-1.11) in patients with H-score ≥ 100[5]

[a]IHC 0, IHC 1+, or IHC2+ and in situ hybridization-negative (ISH-).

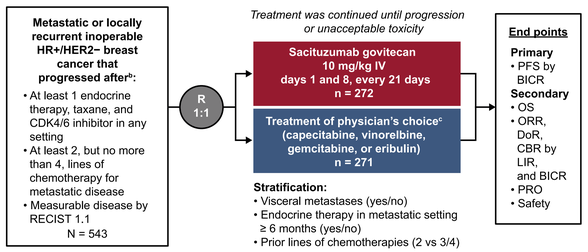
Objective

- We present a post hoc analysis using an orthogonal assay of Trop-2 gene expression (*TACSTD2*), with wider dynamic range than prior assays, to correlate with efficacy outcomes and other biomarkers

Methods

- TROPiCS-02 is a randomized, open-label, phase 3 study of SG, a first-in-class Trop-2–directed ADC consisting of a humanized anti-Trop-2 monoclonal antibody conjugated to an active metabolite of irinotecan (SN-38) via a hydrolysable CL2A linker (Figure 1)[4]
- Archival formalin-fixed paraffin-embedded primary or metastatic tumor tissue samples were collected at the start of the study. The samples were scraped from slides for RNA extraction; samples with less than 50% viable tumors were macro-dissected. RNA was isolated from the samples, and libraries were prepared with TruSeq RNA Exome Prep Kit (Illumina) and sequenced with an Illumina NovaSeq Sequencer (2 x 150bp)
  - RNAseq data were available from 197 tumor samples in the intent-to-treat (ITT) population (36% of ITT)
  - Gene expression was quantitated using Salmon[6]
- *TACSTD2* low and high mRNA expression were defined as expression below the median (10.5 transcripts per million [TPM]) and above the median, respectively
- Membrane Trop-2 expression was determined using a fit-for-purpose validated IHC research assay at a College of American Pathologists/Clinical Laboratory Improvement Amendments central laboratory
  - H-score was calculated (0-300), representing the sum of percent staining weighted by staining intensity
  - Trop-2 H-score cutoffs were set at < 100 and ≥ 100[5]
- Local IHC and in situ hybridization (ISH) results were utilized for HER2 status determination
  - HER2-low status was defined as an IHC score of 1+, or 2+ with negative ISH result
  - HER2 IHC0 status was defined as an IHC score of 0

Figure 1. TROPiCS-02: A phase 3 study of SG in HR+/HER2– locally recurrent inoperable or metastatic breast cancer[a]



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.
[a]ClinicalTrials.gov. NCT03901339. [b]Disease histology based on the ASCO/CAP criteria. [c]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.

Results

- Baseline characteristics were generally consistent between patients evaluable for *TACSTD2* expression and the ITT population (Table 1)

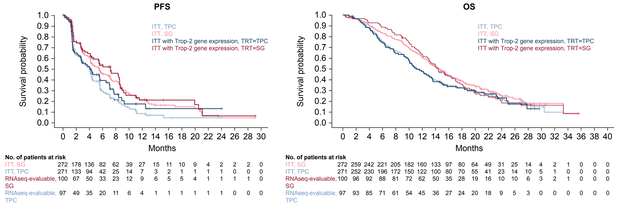
Table 1. Demographics and baseline characteristics

	ITT		*TACSTD2* expression		*TACSTD2* < 10.5 TPM		*TACSTD2* ≥ 10.5 TPM	
	SG (n = 272)	TPC (n = 271)	SG (n = 100)	TPC (n = 97)	SG (n = 47)	TPC (n = 51)	SG (n = 53)	TPC (n = 46)
Female, n (%)	270 (99)	268 (99)	100 (100)	96 (99)	47 (100)	50 (98)	53 (100)	46 (100)
Median age, (IQR) y	57 (49-65)	55 (48-63)	59 (50-65)	54 (47-63)	58 (50-64)	56 (50-63)	59 (51-66)	53 (44-65)
Median baseline BMI, (IQR) kg/m²	25 (22-29)	24 (21-29)	26 (23-29)	23 (21-29)	26 (23-27)	25 (22-29)	26 (23-31)	22 (20-26)
Race or ethnic group, n (%)[a]								
White	184 (68)	178 (66)	62 (62)	65 (67)	31 (66)	32 (63)	31 (58)	33 (72)
Non-white	19 (7)	23 (8)	9 (9)	10 (10)	7 (15)	6 (12)	2 (4)	4 (9)
Not reported	69 (25)	70 (26)	29 (29)	22 (23)	9 (19)	13 (25)	20 (38)	9 (20)
ECOG PS, n (%)								
0	116 (43)	126 (46)	45 (45)	52 (54)	26 (55)	27 (53)	19 (36)	25 (54)
1	156 (57)	145 (54)	55 (55)	45 (46)	21 (45)	24 (47)	34 (64)	21 (46)
Lines of prior chemotherapy, n (%)								
2	113 (42)	113 (42)	42 (42)	41 (42)	21 (45)	20 (39)	21 (40)	21 (46)
3/4	159 (58)	158 (58)	58 (58)	56 (58)	26 (55)	31 (61)	32 (60)	25 (54)
Prior CDK4/6 inhibitor use, n (%)								
≤ 12 months	161 (60)	166 (62)	62 (63)	62 (65)	23 (51)	35 (71)	39 (74)	27 (59)
> 12 months	106 (40)	102 (38)	36 (37)	33 (35)	22 (49)	14 (29)	14 (26)	19 (41)
Unknown	5	3	2	2	2	2	0	0

BMI, body mass index; CDK, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; ITT, intent-to-treat; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Percentages may not add up to 100 due to rounding.

- PFS and OS were comparable in the ITT population and in the RNAseq-evaluable population (Figure 2)

Figure 2. PFS and OS in the ITT and RNAseq-evaluable populations



ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

- Moderate positive concordance was observed between *TACSTD2* mRNA expression (median 10.5 TPM) and Trop-2 IHC (median H-score 115)
- Concordance by H-score was 71% (Cohen's kappa = 0.41) (Table 2)

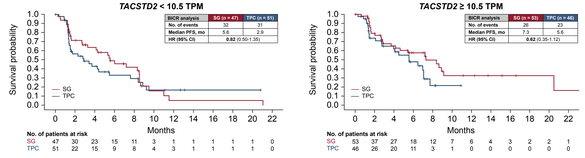
Table 2. Concordance scores between *TACSTD2* mRNA expression and Trop-2 IHC

Total (N = 194)		*TACSTD2* mRNA	
		Below median	Above median
Trop-2 IHC	**Below median**	71	33
H-score	**Above median**	24	66

IHC, immunohistochemistry; Trop-2, trophoblast cell surface antigen 2.

- PFS favored SG over TPC regardless of *TACSTD2* mRNA expression (Figure 3)

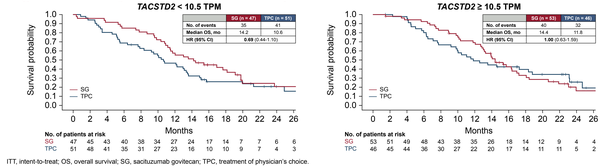
Figure 3. PFS by *TACSTD2* mRNA expression



BICR, blinded independent central review; HR, hazard ratio; H-score, histogram score; IHC, immunohistochemistry; ITT, intent-to-treat; mo, months; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

- Median OS favored SG over TPC regardless of *TACSTD2* mRNA expression despite the smaller sample size (36% of the ITT population) compared with prior Trop-2 IHC correlative analyses with H-score < 100 and ≥ 100[5] (Figure 4)

Figure 4. OS by *TACSTD2* mRNA expression



ITT, intent-to-treat; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

- SG versus TPC exhibited improvement of objective response rate (ORR) in the *TACSTD2* < 10.5 TPM (odds ratio [OR], 1.27 [95% CI, 0.45-3.63) and ≥ 10.5 TPM subgroups (OR, 2.75 [95% CI, 0.81-9.33]), and ORR in these subgroups was comparable to the ORR observed in the ITT population (Table 3)[7]
- CBR and median duration of response (DoR) were improved with SG versus TPC in the ITT population[7] and in the *TACSTD2* < 10.5 TPM and ≥ 10.5 TPM subgroups (Table 3)

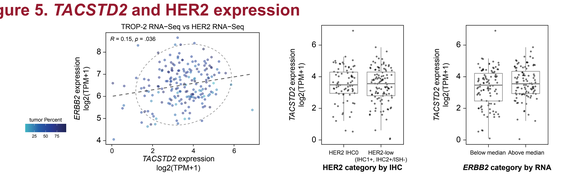
Table 3. Responses by *TACSTD2* mRNA expression

BICR analysis	ITT[7]		*TACSTD2* < 10.5 TPM		*TACSTD2* ≥ 10.5 TPM	
	SG (n = 272)	TPC (n = 271)	SG (n = 47)	TPC (n = 51)	SG (n = 53)	TPC (n = 46)
Best overall response, n (%)	57 (21)	38 (14)	9 (19)	8 (16)	11 (21)	4 (9)
Odds ratio (95% CI)	1.63 (1.03-2.56)		1.27 (0.45-3.63)		2.75 (0.81-9.33)	
Best overall response, n (%)						
CR	2 (1)	0	1 (2)	0	0	0
PR	55 (20)	38 (14)	8 (17)	8 (16)	11 (21)	4 (9)
SD	142 (52)	106 (39)	25 (53)	16 (31)	29 (55)	25 (54)
SD ≥ 6 mo	35 (13)	22 (8)	7 (15)	2 (4)	9 (17)	7 (15)
PD	58 (21)	76 (28)	11 (23)	16 (31)	10 (19)	10 (22)
NE	15 (6)	51 (19)	2 (4)	11 (22)	3 (6)	7 (15)
CBR,[a] n (%)	92 (34)	60 (22)	16 (34)	10 (20)	20 (38)	11 (24)
Odds ratio (95% CI)	1.80 (1.23-2.63)		2.12 (0.85-5.30)		1.93 (0.80-4.63)	
Median DoR, mo (95% CI)	8.1 (6.7-9.1)	5.6 (3.8-7.9)	7.4 (2.8-NR)	6.8 (4.1-NR)	18.6 (5.8-NR)	4.3 (4.3-NR)

CBR, clinical benefit rate; CR, complete response; DoR, duration of response; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]CBR is defined as the percentage of patients with a confirmed best overall response of CR, PR, and SD ≥ 6 months.

- *TACSTD2* mRNA expression was not associated with *ERBB2* mRNA (HER2 gene) expression (Figure 5)
- *TACSTD2* mRNA expression was similar across HER2 IHC subgroups and *ERBB2* mRNA expression (Figure 5)
  - *TACSTD2* log2 TPM, HER2 IHC0 3.36 (IQR, 2.76-4.22) and HER2-low (IHC1+, IHC2+/ISH-) 3.44 (IQR, 2.59-4.22)

Figure 5. *TACSTD2* and HER2 expression



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; Trop-2, trophoblast cell surface antigen 2.

- Median PFS and OS were higher with SG versus TPC across Trop-2 IHC subgroups for HER2-low (IHC1+, IHC2+/ISH-) and HER2 IHC0 patients, although sample sizes were low (Table 4)

Table 4. PFS and OS by Trop-2 and HER2 IHC subgroup[a]

	Trop-2 IHC below median		Trop-2 IHC above median	
HER2-low (IHC1+, IHC2+/ISH-)	SG (n = 47)	TPC (n = 45)	SG (n = 82)	TPC (n = 72)
No. of events, PFS	25	25	53	44
Median PFS, mo (95% CI)	5.5 (3.1-8.5)	4.6 (1.7-7.7)	7.0 (4.0-8.6)	4.0 (1.7-4.5)
HR (95% CI)	0.74 (0.42-1.29)		0.47 (0.30-0.73)	
No. of events, OS	33	37	56	50
Median OS, mo (95% CI)	16.3 (11.5-20.6)	12.3 (8.7-13.3)	14.9 (11.6-18.4)	11.3 (9.5-13.5)
HR (95% CI)	0.63 (0.39-1.01)		0.80 (0.55-1.18)	
HER2 IHC0	SG (n = 38)	TPC (n = 46)	SG (n = 52)	TPC (n = 44)
No. of events, PFS	28	31	30	33
Median PFS, mo (95% CI)	5.0 (3.9-8.5)	2.8 (1.4-5.4)	5.6 (2.8-7.5)	3.4 (1.5-5.6)
HR (95% CI)	0.77 (0.46-1.29)		0.63 (0.39-1.04)	
No. of events, OS	24	34	37	30
Median OS, mo (95% CI)	14.6 (10.5-21.9)	11.0 (8.8-19.5)	13.6 (11.4-17.0)	10.4 (6.1-13.6)
HR (95% CI)	0.86 (0.51-1.46)		0.82 (0.51-1.34)	

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.
[a]In patients for whom both Trop-2 IHC and HER2 IHC/ISH data were available.

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