Primary Results From TROPiCS-02: A Randomized Phase 3 Study of Sacituzumab Govitecan Vs Treatment of Physician's Choice in Patients With Hormone Receptor-Positive/HER2-Negative Advanced Breast Cancer

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Background

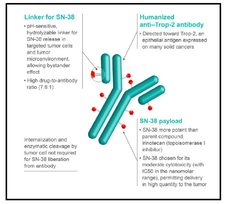
HR+/HER2− Breast Cancer

- Breast cancer is the second leading cause of cancer deaths in women; HR+/HER2- disease is the most common subset, accounting for ~70% of breast cancers[1,2]
- Sequential endocrine therapy (ET) combined with targeted agents is the recommended option for metastatic HR+/HER2- breast cancer[3-5]
  - International guidelines recommend first-line ET in combination with CDK4/6 inhibitors (CDK4/6i)[3-5]
  - The optimal sequencing of therapeutic agents following progression on ET + CDK4/6i remains unclear[3-5]
- For ET resistant disease, sequential single-agent chemotherapy is the standard of care; however, it is associated with declining response rates, disease control, and QoL, and increased toxicity[3,5-9]
- Few chemotherapy options are available in later lines and there remains a high unmet clinical need

TROPiCS-02 is a phase 3 study evaluating sacituzumab govitecan (SG) therapy for heavily pre-treated patients with HR+/HER2- metastatic disease who have received prior endocrine therapy, CDK4/6 inhibitor, and prior chemotherapy

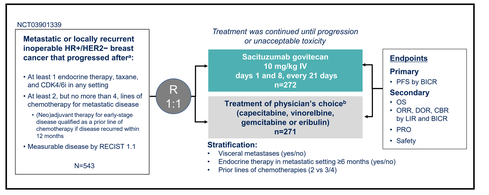
Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed Antibody-Drug Conjugate (ADC)[10-14]

- Trop-2, a transmembrane calcium signal transducer linked to tumor progression and poor prognosis, is highly expressed in approximately 80% of breast cancers regardless of subtype[15,16]
- SG is approved for patients with mTNBC with ≥2 prior therapies (≥1 in the metastatic setting)[17,18]
- In the IMMU-132-01 phase 1/2 study, SG showed encouraging clinical activity in patients with previously treated metastatic HR+/HER2- breast cancer (N=54)[19]
- ORR by investigator assessment: 31.5% (prior CDK4/6i use subgroup, 25%)
- Median PFS by investigator assessment: 5.5 months (95% CI, 3.6-7.6)
- Median OS: 12 months (95% CI, 9.0-18.2)
- A manageable safety profile consistent with that in other studies of SG[20]



Methods

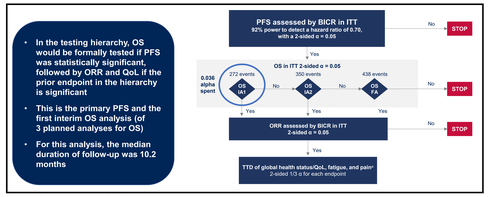
TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer



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

Methods

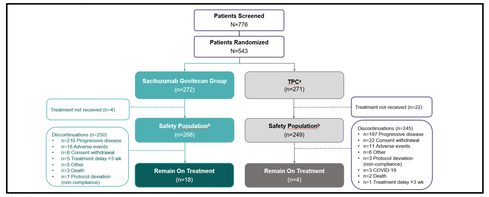
Statistical Analysis



Data cutoff date was January 3, 2022.
[c]The 3 QoL endpoints are measured by EORTC QLQ-C30 and will be tested using a graphical approach of Maurer and Bretz to control multiplicity.

Results

Patient Disposition



No patients discontinued treatment due to being lost to follow-up.
[a]Patients in the chemotherapy group were randomized to eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22).
[b]All patients who received ≥1 dose of study treatment.
Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.* 2022. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology.

Demographics and Baseline Characteristics

	SG (n=272)	TPC (n=271)
Female, n (%)	270 (99)	268 (99)
Median age, y (range)	57 (29-86)	55 (27-78)
<65 y, n (%)	199 (73)	204 (75)
≥65 y, n (%)	73 (27)	67 (25)
Race or ethnic group, n (%)		
White	184 (68)	178 (66)
Black	8 (3)	13 (5)
Asian	11 (4)	5 (2)
Other[a] / Not reported[b]	69 (25)	75 (28)
ECOG PS, n (%)		
0	116 (43)	126 (46)
1	156 (57)	145 (54)
Visceral metastases at baseline, n (%)	259 (95)	258 (95)
Liver metastases,[c] n (%)	229 (84)	237 (87)
De novo metastatic breast cancer, n (%)	78 (29)	60 (22)

	SG (n=272)	TPC (n=271)
Median time from initial metastatic diagnosis to randomization, mo (range)	48.5 (1.2- 243.8)	46.6 (3.0- 248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)	173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 mo, n (%)	235 (86)	234 (86)
Prior CDK4/6 inhibitor use, n (%)		
≤12 months	161 (59)	166 (61)
>12 months	106 (39)	102 (38)
Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting, n (range)[d]	3 (0-8)	3 (1-5)

[a]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander. [b]Not reported indicates local regulators did not allow collection of race or ethnicity information. [c]Presence of baseline target/non-target liver metastases per RECIST 1.1 by local investigator review. [d]The reported number of prior therapies were miscounted at screening for some patients; 9 patients received prior chemotherapy regimens in the metastatic setting outside the per protocol range for inclusion criteria and were included in the intent-to-treat population.

Prior Therapies

Setting of prior anticancer regimens, n (%)	SG (n=272)	TPC (n=271)
Neoadjuvant	67 (25)	62 (23)
Adjuvant	186 (68)	206 (76)
Advanced/Metastatic	272 (100)	271 (100)
Other/Unknown	12 (4)	9 (3)

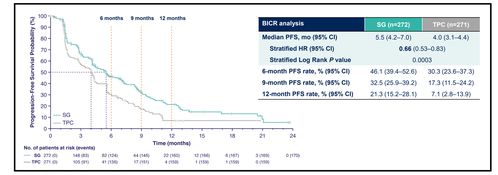
Most common prior anticancer therapy in the metastatic setting[a], by class, n (%)	SG (n=272)	TPC (n=271)
Endocrine therapy[b]	268 (99)	269 (99)
CDK4/6 inhibitor[b]	267 (98)	270 (>99)
Targeted agent[c]	181 (67)	172 (63)
Immunotherapy	21 (8)	15 (6)
Chemotherapy	271 (>99)	271 (100)
Capecitabine	221 (81)	232 (86)
Paclitaxel	174 (64)	147 (54)
Eribulin	95 (35)	88 (33)

[a]Includes any treatment used either as single agent or in combination. [b]The remaining patients were treated with these agents in early-stage disease. [c]Targeted agents include PARP, mTOR, PI3K, BET, AKT, AAK, and other kinase inhibitors, antibody-drug conjugates, and other targeted agents.

Results

Primary Endpoint: BICR-Assessed PFS per RECIST v1.1 in the ITT Population

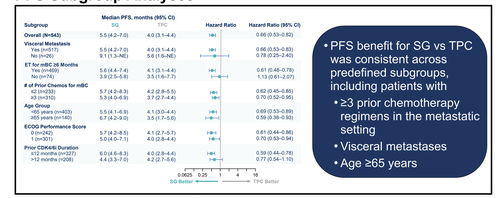
SG demonstrated a statistically significant improvement in PFS vs TPC with a 34% reduction in the risk of disease progression/death; a higher proportion of patients were alive and progression-free at all landmark timepoints



BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	0.66 (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)

Median follow-up was 10.2 months.
Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.* 2022. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology.

PFS Subgroup Analyses



- PFS benefit for SG vs TPC was consistent across predefined subgroups, including patients with
  - ≥3 prior chemotherapy regimens in the metastatic setting
  - Visceral metastases
  - Age ≥65 years

PFS subgroup analyses by race, geographic region, TPC arm agents, and early relapse were assessed but not included in this figure.
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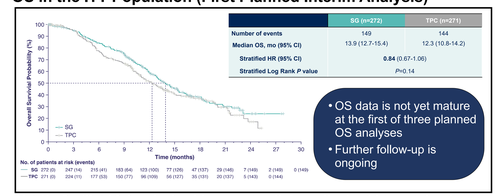
OS in the ITT Population (First Planned Interim Analysis)



	SG (n=272)	TPC (n=271)
Number of events	149	144
Median OS, mo (95% CI)	13.9 (12.7-15.4)	12.3 (10.8-14.2)
Stratified HR (95% CI)	0.84 (0.67-1.06)	
Stratified Log Rank *P* value	*P*=0.14	

- OS data is not yet mature at the first of three planned OS analyses
- Further follow-up is ongoing

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Response Rates

BICR analysis	SG (n=272)	TPC (n=271)
ORR, n (%)	57 (21)	38 (14)
Odds ratio, nominal *P* value[a]	1.63, *P*=0.03	
Best overall response, n (%)		
CR	2 (1)	0
PR	55 (20)	38 (14)
SD	142 (52)	106 (39)
SD ≥6 mo	35 (13)	21 (8)
PD	58 (21)	76 (28)
NE	15 (6)	51 (19)
CBR,[b] n (%)	92 (34)	59 (22)
Odds ratio, nominal *P* value[a]	1.84, *P*=0.002	
Median DOR, mo (95% CI)	7.4 (6.5-8.6)	5.6 (3.8-7.9)

ORR (21% vs 14%) and CBR (34% vs 22%) were higher with SG vs TPC

[a]Not formally tested because OS at IA1 was not statistically significant.
[b]CBR is defined as the percentage of patients with a confirmed best overall response of CR, PR, and SD ≥6 months.

Safety Summary

n (%)	SG (n=268)	TPC (n=249)
Grade ≥3 TEAE	198 (74)	149 (60)
TEAEs leading to treatment discontinuation	17 (6)	11 (4)
TEAEs leading to dose delay	178 (66)	109 (44)
TEAEs leading to dose reductions	89 (33)	82 (33)
TE SAEs	74 (28)	47 (19)
TEAEs leading to death[a]	6 (2)	0
Treatment-related	1 (<1)	0

- The most common TE SAEs (≥2% incidence) in this study were
  - SG: diarrhea (5%), febrile neutropenia (4%), neutropenia (3%), and neutropenic colitis (2%)
  - TPC: febrile neutropenia (4%), pneumonia (2%), nausea (2%), and dyspnea (2%)

Overall, the safety profile of SG in this study was consistent with that observed in previous studies of SG[20]

[a]Of 6 TEAEs leading to death, only 1 was considered by the investigator as treatment-related (septic shock due to neutropenic colitis). The other 5 were: COVID-19 pneumonia, pulmonary embolism, pneumonia, nervous system disorder, and arrhythmia.
Upon detailed review of the TEAEs leading to death, there were no patterns identified.
TEAEs defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug.

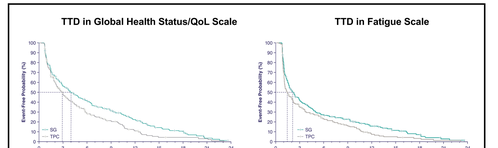
Key All Grade and Grade ≥3 Treatment-Related Adverse Events[a]

		SG (n=268)		TPC (n=249)	
TRAEs, n (%)		All grade	Grade ≥3	All grade	Grade ≥3
Hematologic	**Neutropenia[b]**	188 (70)	**136 (51)**	134 (54)	**94 (38)**
	Anemia[c]	91 (34)	17 (6)	62 (25)	8 (3)
	Leukopenia[c]	37 (14)	23 (9)	23 (9)	13 (5)
	Lymphopenia[c]	31 (12)	10 (4)	25 (10)	8 (3)
	Febrile neutropenia	**14 (5)**	**14 (5)**	**11 (4)**	**11 (4)**
Gastrointestinal	**Diarrhea**	152 (57)	**25 (9)**	41 (16)	**3 (1)**
	Nausea	148 (55)	3 (1)	77 (31)	7 (3)
	Vomiting	50 (19)	1 (<1)	30 (12)	4 (2)
	Constipation	49 (18)	0	36 (14)	0
	Abdominal pain	34 (13)	2 (1)	17 (7)	0
Other	Alopecia	123 (46)	0	41 (16)	0
	Fatigue	100 (37)	15 (6)	73 (29)	6 (2)
	Asthenia	53 (20)	5 (2)	37 (15)	2 (1)
	Decreased appetite	41 (15)	1 (<1)	34 (14)	1 (<1)
	Neuropathy[c]	23 (9)	3 (1)	38 (15)	6 (2)

- There were no events of interstitial lung disease in the SG arm (vs 1% in the TPC arm) and no TRAEs of cardiac failure or left ventricular dysfunction in either arm

Assessed in the safety population of patients who received ≥1 dose of study treatment. Patients may report more than one event per preferred term. [a]Any All Grade and Grade ≥3 TRAEs defined as those occurring in ≥10% and ≥5% of patients in one arm, respectively. [b]Combined preferred terms of 'neutropenia' and 'neutrophil count decreased.' [c]Combined preferred terms of 'anemia,' 'hemoglobin decreased,' and 'red blood cell count decreased.' [d]Combined preferred terms of 'leukopenia' and 'white blood cell count decreased.' [e]Combined preferred terms of 'lymphopenia' and 'lymphocyte count decreased.' [f]Combined preferred terms of 'gait disturbance', 'hypoesthesia', 'muscular weakness', 'neuropathy peripheral', 'paraesthesia', and 'peripheral sensory neuropathy'.

EORTC QLQ-C30 Time to Deterioration Endpoint



TTD	Patients SG/TPC, n/n	SG median TTD, mo (95% CI)	TPC median TTD, mo (95% CI)	Stratified HR (95% CI)	Nominal *P* value[a]
Global Health Status/QoL	234/207	4.0 (3.0-5.4)	2.9 (2.3-3.6)	0.74 (0.59-0.91)	0.005
Fatigue	234/205	2.1 (1.6-2.8)	1.4 (1.1-1.9)	0.76 (0.62-0.93)	0.007
Pain	229/202	3.7 (2.8-4.9)	3.4 (2.7-4.6)	0.92 (0.74-1.14)	0.45

Assessed in all patients in the intent-to-treat population who had an evaluable assessment of the health-related QoL at baseline and at least one evaluable assessment at post-baseline visits. [a]Not formally tested because OS at IA1 was not statistically significant.

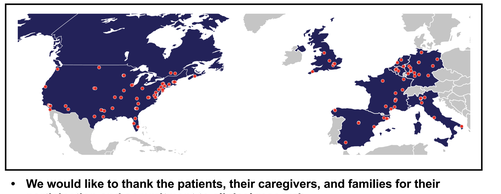
Conclusions

- In patients with heavily pretreated HR+/HER2- advanced breast cancer who have received prior endocrine-based therapy, including prior CDK4/6i therapy, and at least 2 prior chemotherapy regimens for metastatic disease, SG demonstrated a statistically significant PFS benefit over TPC
  - The primary endpoint of PFS by BICR was met, with a 34% reduction in risk of disease progression or death (HR, 0.66; P<0.001)
  - A higher proportion of patients were alive and progression-free at all landmark timepoints, with three times as many patients progression-free at the one-year mark when treated with SG compared to those who received TPC (21% vs 7%)
- At the first planned interim analysis of OS, a numeric trend for improvement for SG vs TPC was observed; results are not yet mature, and further follow-up for OS is ongoing
- SG also demonstrated an overall HRQoL benefit over TPC, with delayed deterioration in fatigue and global health status/QoL scales in EORTC QLQ-C30
- The safety profile of SG was manageable and consistent with that in previous studies[19-21]; no new safety concerns were identified

SG demonstrated statistically significant and clinically meaningful benefit and should be considered a potential treatment option in this heavily pre-treated patient population with limited treatment options

Acknowledgments

Participating Study Sites



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Abbreviations: AAK, aurora A kinase; **ADC**, antibody-drug conjugate; **ASCO/CAP**, American Society of Clinical Oncology/College of American Pathologists; **BET,** bromodomain and extra-terminal motif; **BICR**, blinded independent central review; **CBR**, clinical benefit rate; **CDK4/6**, cyclin-dependent kinase 4/6; **CDK4/6i**, cyclin-dependent kinase 4/6 inhibitor; **CR**, complete response; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EORTC QLQ-C30**, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; **ET,** endocrine therapy; **FA,** final analysis; **HER2-**, human epidermal growth factor receptor 2-negative; **HR+**, hormonal receptor-positive; **HRQoL**, health-related quality of life; **IA**, interim analysis; **IA1**, interim analysis 1; **ITT,** intent-to-treat; **IV**, intravenously; **LIR**, local investigator review; **mBC**, metastatic breast cancer; **mTNBC**, metastatic triple-negative breast cancer; **mTOR**, mammalian target of rapamycin; **NE,** not evaluable; **(neo)adjuvant**, neoadjuvant or adjuvant; **ORR**, objective response rate; **OS**, overall survival; **PARP**, poly (ADP-ribose) polymerase; **PD**, progressive disease; **PFS**, progression-free survival; **PI3K**, phosphatidylinositol 3-kinase; **PR**, partial response; **PRO**, patient-reported outcomes; **QoL**, quality of life; **R**, randomized; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SD**, stable disease; **SG**, sacituzumab govitecan; **TPC**, treatment of physician's choice; **TRAE**, treatment-related adverse event; **TTD**, time-to-deterioration.

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