Exploratory Circulating Tumor DNA Analysis in HR+/HER2– Metastatic Breast Cancer and Impact on Clinical Efficacy With Sacituzumab Govitecan in TROPiCS-02

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Conclusions

- In patients with pretreated HR+/HER2– mBC, ctDNA at baseline as measured by meanVAF was highly prognostic; lower baseline meanVAF correlated with longer PFS and OS in both the SG and chemotherapy groups
- MeanVAF reduction ≥ 50% during treatment was also associated with longer PFS and OS and higher rates of PR in both treatment arms
- Patients with high baseline meanVAF and < 50% ctDNA reduction had the worst PFS and OS outcomes with SG and chemotherapy

Plain Language Summary

- Sacituzumab govitecan is a drug approved for use in previously treated hormone receptor-positive/ human epidermal growth factor receptor-negative (HR+/HER2–) breast cancer that has spread to other parts of the body (metastatic breast cancer, mBC)
- Circulating tumor DNA (ctDNA) is DNA from a tumor that is found in the bloodstream of a person with cancer and has been shown to help predict the outcome of cancer treatment
- This analysis measured ctDNA at study entry (baseline) and at a specific time point during treatment (cycle 2 day 1, C2D1) to determine if the amount of ctDNA affected the prognosis (the likely course and outcome of a disease) in patients with HR+/HER2– mBC from the TROPiCS-02 study
- This analysis showed that patients with lower baseline ctDNA and those who had larger reductions in ctDNA from baseline to C2D1 lived longer without their disease getting worse and lived longer overall, and this was true for those treated with both SG and chemotherapy

References: **1.** Starodub AN, et al. *Clin Cancer Res*. 2015;21:3870-8. **2.** Rugo HS, et al. *Lancet*. 2023;402:1423-33. **3.** Rugo HS, et al. *J Clin Oncol*. 2022;40:3365-3376. **4.** Dawson S-J, et al. *N Engl J Med*. 2013;368:1199-209. **5.** Pascual J, et al. *Clin Cancer Res*. 2023;29:4166-4177. **6.** Martens GA, et al. *ESMO Open*. 2024;9:102235. **7.** Martínez-Sáez O, et al. *NPJ Breast Cancer*. 2021;7:8.

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Introduction

- Sacituzumab govitecan (SG) is a Trop-2–directed antibody-drug conjugate that delivers a potent payload, SN-38, into tumor cells[1]
- The phase 3, open-label, randomized TROPiCS-02 study (NCT03901339) demonstrated significant improvement of progression-free survival (PFS; HR, 0.66; 95% CI, 0.53-0.83; *P* = .0003) and overall survival (OS; HR for death, 0.79; 95% CI, 0.65-0.96; *P* = .020) with SG over chemotherapy in patients with pretreated hormone receptor-positive/human epidermal growth factor receptor-negative (HR+/HER2– [HER2 immunohistochemistry 0, 1+, or 2+/in situ hybridization-negative]) locally recurrent inoperable or metastatic breast cancer (mBC)[2,3]
- Circulating tumor DNA (ctDNA) is an indicator of treatment outcome and risk of progression in mBC[4-7]

Objective

- To assess the prognostic value of ctDNA in an exploratory analysis from the TROPiCS-02 study

Methods

- Patients were randomized 1:1 to receive SG or physician's choice of chemotherapy until disease progression, unacceptable toxicity, consent withdrawal, or per investigator's decision as previously described[2]
- Longitudinal plasma samples were collected at baseline and cycle 2 day 1 (C2D1), and samples were tested at Guardant Health using Infinity RUO ctDNA panel
- Variant allele fraction (VAF) for each detected ctDNA variant was determined by ratio of variant allele reads to total reads at that position; meanVAF for each sample was computed by averaging somatic single nucleotide variants (SNVs), indels, and fusions that met variant inclusion criteria: % reduction in meanVAF = ($meanVAF_{C2D1}$ – $meanVAF_{Baseline}$)/$meanVAF_{Baseline}$
- Baseline meanVAF and percent reduction of meanVAF from baseline to C2D1 were analyzed to determine their association with clinical outcomes, including PFS, OS, and best overall response

Results

Baseline Characteristics in the ITT and ctDNA Populations

- Baseline characteristics were comparable in the intent-to-treat (ITT) population and the population with available ctDNA data (**Table 1**)
- Chemotherapy regimens used in the chemotherapy group were balanced between the ITT and ctDNA populations

PFS and OS Outcomes in the ITT and ctDNA Populations

- PFS and OS were similar in the ITT and ctDNA populations, respectively
  - Median PFS: 5.5 months (mo; 95% CI, 4.2-7.0) vs 5.3 mo (95% CI, 4.1-6.9) for SG and 4.0 mo (95% CI, 3.1-4.4) vs 4.1 mo (95% CI, 2.8-5.6) for chemotherapy
  - Median OS: 14.4 mo (95% CI, 13.0-15.7) vs 14.5 mo (95% CI, 11.9-17.5) for SG and 11.2 mo (95% CI, 10.1-12.7) vs 12.1 mo (95% CI, 10.1-13.6) for chemotherapy

Efficacy by Baseline MeanVAF

- When patients were separated into subgroups by median meanVAF value ≥ 5.4% and < 5.4%, lower baseline meanVAF correlated with longer median PFS and OS with both SG and chemotherapy (**Figure 1**)

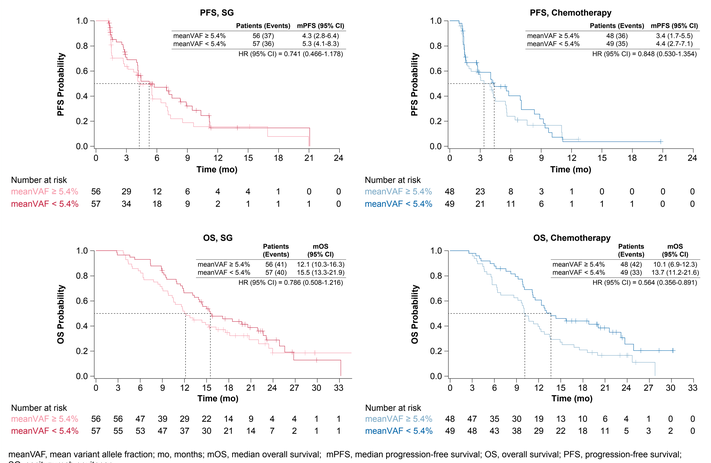
Results

Table 1. Baseline Characteristics

	ITT		ctDNA	
	SG (n = 272)	Chemotherapy (n = 271)	SG (n = 113)	Chemotherapy (n = 97)
Female, n (%)	270 (99)	268 (99)	112 (99)	95 (98)
Median age (IQR), years	57 (49-65)	55 (48-63)	58 (50-65)	56 (48-65)
Median BMI (IQR), kg/m²	24.8 (21.8-28.7)	24.2 (21.4-28.5)	25.5 (21.8-28.7)	23.7 (20.9-28.7)
Race, n (%)[a]				
White	184 (68)	178 (66)	71 (63)	55 (57)
Asian	11 (4)	5 (2)	5 (4)	1 (1)
Black or African American	8 (3)	13 (5)	3 (3)	7 (7)
ECOG PS, n (%)				
0	116 (43)	126 (46)	48 (42)	45 (46)
1	156 (57)	145 (54)	65 (58)	52 (54)
Prior lines of chemotherapy, n (%)				
2	113 (42)	113 (42)	47 (42)	45 (46)
3-4	159 (58)	158 (58)	66 (58)	52 (54)
Prior CDK4/6i treatment duration, n (%)[b]				
≤ 12 mo	161 (59)	166 (61)	62 (55)	63 (65)
> 12 mo	106 (39)	102 (38)	51 (45)	33 (34)

[a]Not reported in ITT, SG, n = 69; chemotherapy, n = 70; in ctDNA, SG, n = 34; chemotherapy, n = 32. Other race in ITT, chemotherapy, n = 5; in ctDNA, chemotherapy, n = 2.
[b]Missing in ITT, SG, n = 5; chemotherapy, n = 3; in ctDNA, SG, n = 0; chemotherapy, n = 1.
BMI, body mass index; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; mo, months; SG, sacituzumab govitecan.

Figure 1. PFS and OS by Baseline MeanVAF

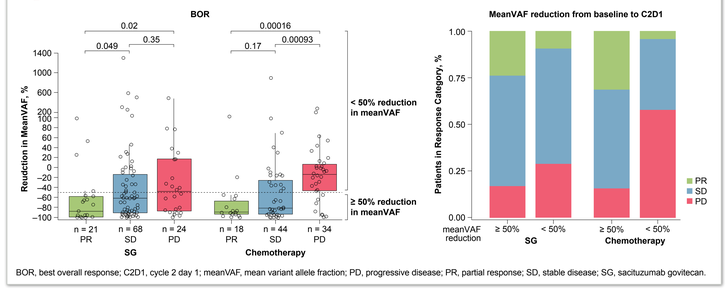


meanVAF, mean variant allele fraction; mo, months; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

Efficacy by Reduction in MeanVAF

- Most patients exhibited decreased meanVAF from baseline to C2D1 in the SG and chemotherapy groups
- Patients with partial response (PR) had the largest decrease in meanVAF; those with progressive disease had the smallest decrease. This association was consistent in the chemotherapy and SG arms (**Figure 2**)

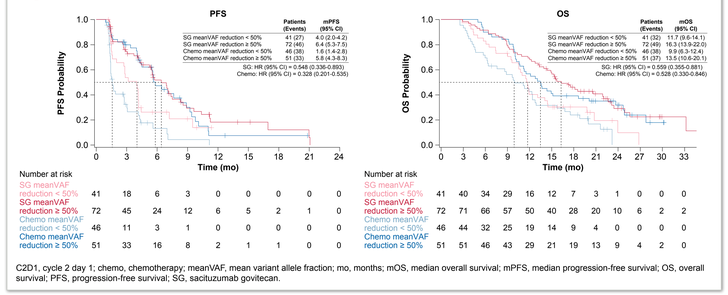
Figure 2. Association of BOR With Reduction in MeanVAF From Baseline to C2D1



BOR, best overall response; C2D1, cycle 2 day 1; meanVAF, mean variant allele fraction; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan.

- Patients with ≥ 50% ctDNA reduction at C2D1 had numerically higher PFS and OS (**Figure 3**)

Figure 3. Association of PFS and OS With Reduction in MeanVAF From Baseline to C2D1

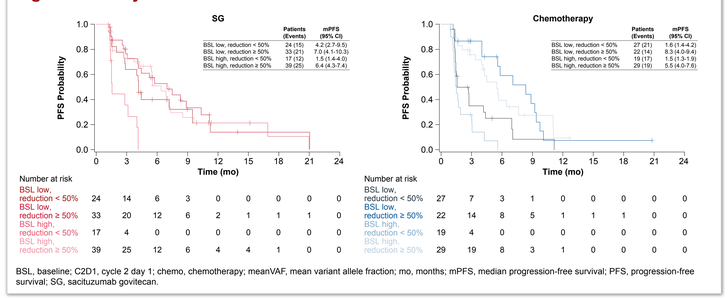


C2D1, cycle 2 day 1; chemo, chemotherapy; meanVAF, mean variant allele fraction; mo, months; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

Efficacy by Baseline MeanVAF and Reduction in MeanVAF Subgroups

- Patients with high meanVAF at baseline and < 50% ctDNA reduction at C2D1 had the worst PFS outcomes; this was consistent in the SG and chemotherapy groups (**Figure 4**)
- Patterns in OS outcomes were similar to those for PFS

Figure 4. PFS by Baseline MeanVAF and MeanVAF Reduction Levels From Baseline to C2D1



BSL, baseline; C2D1, cycle 2 day 1; chemo, chemotherapy; meanVAF, mean variant allele fraction; mo, months; mPFS, median progression-free survival; PFS, progression-free survival; SG, sacituzumab govitecan.