Circulating Tumor DNA Mutation Analysis at Baseline and End of Treatment With Sacituzumab Govitecan and Clinical Impact on Efficacy in Patients With HR+/HER2– Metastatic Breast Cancer: Biomarker Results From TROPiCS-02

Poster #2043

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Conclusions

- Progression-free survival (PFS) and overall survival (OS) benefit were observed with sacituzumab govitecan (SG) vs chemotherapy treatment of physician's choice (TPC) for hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (mBC) in patients regardless of mutations in *PIK3CA* and *TP53*, and benefit was generally comparable with the intent-to-treat (ITT) population
- Mutations in *TOP1* and *TACSTD2* were rare and did not appear to be key mechanisms of acquired resistance to SG
- No clear expansion, clearance, or reversion of individual DNA damage repair (DDR) genes or variants were observed from baseline (BSL) to end of treatment (EOT)
- In an unbiased analysis, no individual genes or variants emerged as clear indicators of major mechanisms of resistance to SG, and high levels of data heterogeneity were observed
- Overall, resistance to SG is likely heterogeneous. We were not able to identify any pathways or genes as key mechanisms of acquired resistance to SG in our analysis of circulating tumor DNA (ctDNA) samples

Plain Language Summary

- Sacituzumab govitecan (SG) is a treatment for HR+/HER2– breast cancer that has spread to other parts of the body, and in the TROPiCS-02 clinical study, 21% of participants had their tumors shrink with SG treatment
- Not all people benefit from SG treatment, and some people may have their tumors shrink but not totally disappear (partial response) and start growing again
- To find out how tumors might resist SG, we looked at whether specific genes were mutated at the beginning of treatment (baseline) or at the end of treatment; mutations that appear during SG treatment could suggest that a specific gene might be involved in SG resistance
- We took blood samples at baseline and at the end of treatment during the TROPiCS-02 clinical study, which compared SG to chemotherapy in participants with HR+/HER2– breast cancer, and analyzed tumor DNA found in those blood samples
- We analyzed specific genes that we thought might be related to SG resistance, but none of those genes appeared to be responsible for SG resistance
- We also looked for any other genes that might show differences between the SG and chemotherapy treatment arms, but no genes showed clear signs of being related to SG resistance

References: **1.** TRODELVY® (sacituzumab govitecan-hziy) [prescribing information] Foster City, CA: Gilead Sciences, Inc., November 2024. **2.** TRODELVY® (sacituzumab govitecan-hziy) [summary of product characteristics]. County Cork, Ireland: Gilead Sciences Ireland UC; August 2023. **3.** Rugo HS, et al. *J Clin Oncol*. 2022;40:3365-76. **4.** Rugo HS, et al. *Lancet*. 2023;402:1423-33. **5.** Alqahtani A, et al. *Cancers (Basel)*. 2019;12:93. **6.** Schon K, et al. *Breast Cancer Res Treat*. 2018;167:417-23. **7.** Mosele F, et al. *Ann Oncol*. 2020;31:377-86. **8.** Varna M, et al. *J Biomed Biotechnol*. 2011;2011:284584. **9.** Coates JT, et al. *Cancer Discov*. 2021;11:2436-45

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Introduction

- SG is an antibody-drug conjugate approved for pretreated HR+/HER2– mBC based on the TROPiCS-02 study, which showed that SG provided significant PFS and OS benefit vs chemotherapy TPC, with a manageable safety profile[1-4]
- Mutations in *PIK3CA* and *TP53* are often oncogenic,[5,6] and have been associated with resistance or differences in response to chemotherapy[7,8]
- Both the trophoblast cell-surface antigen 2 (gene *TACSTD2*) and topoisomerase-1 (gene *TOP1*) proteins are targets of SG; mutations in these genes could impair the ability of the SN-38 payload to induce cytotoxicity. A case study showed parallel mutations of these genes associated with disease progression, potentially indicating acquired SG resistance[9]
- We analyzed mutations at BSL and EOT in TROPiCS-02 to identify genes that may be involved in acquired SG resistance

Methods

- Patients were randomized to receive SG (10 mg/kg intravenously, days 1 and 8 per 21-day cycle) or TPC (1:1) as previously described[3]
- Longitudinal plasma samples were collected at BSL and at EOT to obtain ctDNA, which was analyzed using the Guardant Health Infinity RUO ctDNA panel
- Frequently detected *PIK3CA* mutations in breast cancer with known functional impact were analyzed: N345K, C420R, E542K, E545K/A/D/G, Q546R/E, H1047R/L/Y
- Mutations in the DDR genes from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database were analyzed for association with acquired SG resistance
- Unbiased analysis was performed at EOT to identify other genes potentially associated with SG resistance
  - Filtering criteria of mean variant allele frequency (meanVAF) ≥ 0.1% at BSL or EOT, and change of meanVAF ≥ 0.3% (increases) or change of meanVAF ≤ –0.3% (decreases) were applied

Results

Analyses of BSL *PIK3CA* and *TP53* Mutations and SG Efficacy

- BSL characteristics in the ITT population (N = 543) were previously described for TROPiCS-02[3,4]; BSL characteristics in the ctDNA-evaluable population (46% of ITT) were comparable (data not shown)
- BSL characteristics were similar between wild-type (WT) and mutant populations for *PIK3CA* and *TP53* in both the SG and TPC arms, aside from differences in the proportion of White patients and differences in Eastern Cooperative Oncology Group performance status of 0 or 1 (data not shown)
- PFS and OS benefit were observed with SG over TPC in the ITT and ctDNA-evaluable populations (**Table 1**)
- PFS and OS benefit were also observed with SG vs TPC for patients in both the WT and mutant populations for both *PIK3CA* and *TP53* (**Figures 1 and 2**)

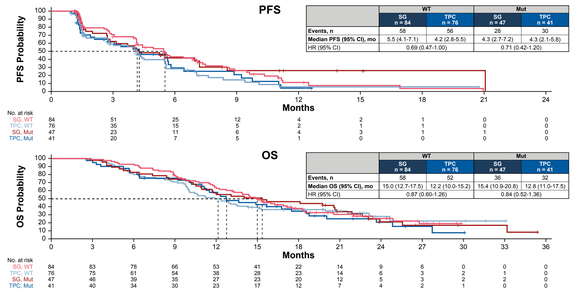
Table 1. PFS and OS in the ITT and ctDNA-Evaluable Populations

Median Survival, mo	ITT		ctDNA[a]	
	SG n = 272	TPC n = 271	SG n = 132	TPC n = 118
PFS (95% CI)	5.5 (4.2-7.0)	4.0 (3.1-4.4)	5.3 (4.1-6.9)	4.2 (3.0-5.6)
HR (95% CI)	0.66 (0.53-0.83)		0.71 (0.52-0.96)	
OS (95% CI)	14.4 (13.0-15.7)	11.2 (10.1-12.7)	15.0 (12.3-17.5)	12.4 (10.7-14.9)
HR (95% CI)	0.79 (0.65-0.96)		0.89 (0.66-1.19)	

[a]Includes patients with ctDNA data that passed quality control from at least 1 time point (n = 250).
ctDNA, circulating tumor DNA; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

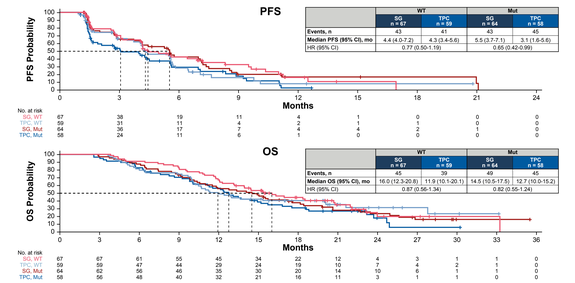
Results

Figure 1. PFS and OS by BSL *PIK3CA* Status



Includes patients with ctDNA data that passed quality control at BSL (n = 248).
BSL, baseline; ctDNA, circulating tumor DNA; HR, hazard ratio; ITT, intent-to-treat; mo, months; Mut, mutation; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; WT, wild type.

Figure 2. PFS and OS by BSL *TP53* Status

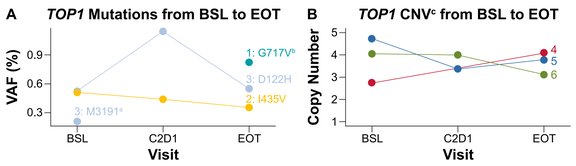


Includes patients with ctDNA data that passed quality control at BSL (n = 248).
BSL, baseline; ctDNA, circulating tumor DNA; HR, hazard ratio; ITT, intent-to-treat; mo, months; Mut, mutation; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; WT, wild type.

Analyses to Identify Potential Mechanisms of SG Resistance

- At BSL, there was 1 *TACSTD2* mutation in a patient in the TPC arm, and no new *TACSTD2* mutations were detected at any other time point or in the SG arm
- At BSL, 3 *TOP1* mutations were detected in 2 patients in the SG arm; at EOT, 1 new *TOP1* mutation was detected in the SG arm in a new patient; all mutations at BSL and EOT had very low VAF of < 1% (**Figure 3A**)
- There was 1 patient with increased *TOP1* copy number variation (CNV) from BSL to EOT, and 2 patients with decreased CNV (**Figure 3B**)

Figure 3. *TOP1* Mutations and CNV in Patients Treated With SG



[a]M319I *TOP1* mutation was not observed at C2D1 or EOT. [b]G717V *TOP1* mutation was not observed at BSL or C2D1. [c]CNV is shown for samples with focal amplification detected at any time point and does not include aneuploid amplification. BSL, baseline; C2D1, cycle 2 day 1; CNV, copy number variation; EOT, end of treatment; SG, sacituzumab govitecan; VAF, variant allele frequency.

- Efficacy outcomes for patients in **Figure 3** are listed in **Table 2**, with corresponding patient numbers

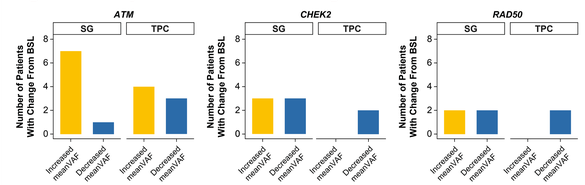
Table 2. SG Efficacy in Patients With *TOP1* Mutations and CNV

	Patient					
	1	2	3	4	5	6
PFS, mo	5.5	2.7	1.35	3.7	4.0	1.35
OS, mo	17.5	7.4	10.9	3.7	4.0	11.7
BOR	PR	SD	PD	SD	SD	SD

BOR, best overall response; CNV, copy number variation; mo, months; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SG, sacituzumab govitecan.

- The ctDNA panel included 69 DDR genes from the KEGG database. 63% of BSL samples had at least 1 deleterious variant in these DDR genes
- We analyzed change in meanVAF of these genes from BSL to EOT to assess their involvement in acquired SG resistance
- Several genes showed an increase in meanVAF from BSL to EOT in the SG and TPC groups. However, these genes also showed a decrease in meanVAF in other patients. Only a very small number of patients showed these changes
- The 3 representative genes with the greatest difference in number of patients with increased meanVAF in SG vs TPC are shown in **Figure 4**
- Overall, no clear expansion or clearance of individual DDR genes or variants was observed at EOT

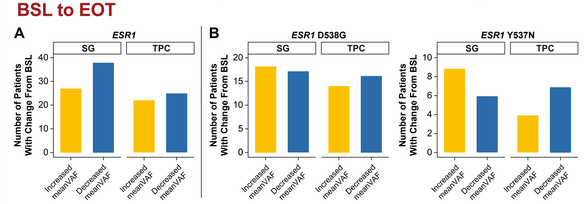
Figure 4. Analysis of DDR Gene Changes From BSL to EOT



BSL, baseline; EOT, end of treatment; SG, sacituzumab govitecan; TPC, chemotherapy treatment of physician's choice; VAF, variant allele frequency

- We analyzed all genes at BSL and EOT in an unbiased analysis to identify genes potentially related to SG resistance
- Several genes and variants showed increased meanVAF from BSL to EOT in both the SG and TPC groups in a small subset of patients. However, these genes and variants also showed decreased meanVAF in other patients
- The gene (*ESR1*) and variants of that gene with the greatest number of patients showing the changes are shown in **Figure 5A** and **Figure 5B**, respectively
- Overall, no clear expansion or clearance of potential resistance genes or variants was observed; however, interpretation of this result is limited due to small sample size and the restricted number of detected mutations

Figure 5. Unbiased Analysis of Gene and Variant Changes From BSL to EOT



BSL, baseline; SG, sacituzumab govitecan; TPC, treatment of physician's choice; VAF, variant allele frequency.

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