Genomic Alterations in DNA Damage Response Genes in HR+/HER2– Metastatic Breast Cancer and Impact on Clinical Efficacy With Sacituzumab Govitecan: Biomarker Results From TROPiCS-02 Study

Poster # 1075

TROPiCS-02
(NCT03901339)

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Conclusions

- Baseline characteristics, PFS, and OS were generally similar between patients with HR+/HER2– mBC in the ITT and BE populations
- In the BE population, SG benefit over TPC was observed in patients with wild type and mutant DDR genes
  - Numerically greater PFS, OS, and ORR benefits with SG over TPC were observed for patients with DDR-deficient tumors, suggesting a possible synergy between the DDR pathway and the antitumor effect of SG
- Genes in the DDR pathways that contributed to the observed efficacy benefit of SG over TPC were identified
- Further study of the synergistic effects of SG in combination with agents targeting the DDR pathway are warranted

Plain Language Summary

- Sacituzumab govitecan (SG) is a new treatment for HR+/HER2– breast cancer that has spread to other parts of the body
- SG works by damaging the DNA of tumor cells leading to their death; tumor cells that can repair these damages may be able to avoid death
- This analysis looked at whether SG worked better than chemotherapy in participants whose genes involved in the DNA damage repair pathway were defective in their tumors
- Participants receiving SG had improved survival compared with the participants receiving chemotherapy
  - Participants with certain mutations in DNA repair genes had even better results with SG treatment
- The researchers suggest that combining SG with treatments that disrupt the DNA damage repair pathway could provide even greater benefit in people with mutations in this pathway

References: **1.** Starodub AN, et al. *Clin Cancer Res*. 2015;21:3870-8. **2.** Rugo HS, et al. *Lancet*. 2023;402:1423-33. **3.** Goldenberg DM, et al. *Expert Opin Biol Ther*. 2020;20:871-85. **4.** Kanehisa M, et al. *Nucleic Acids Res*. 2023;51:D587-92. **5.** Human DNA Repair Genes. https://www.mdanderson.org/documents/Labs/Wood-Laboratory/human-dna-repair-genes.html. Accessed April 25, 2024.

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Introduction

- Sacituzumab govitecan (SG) is a Trop-2–directed antibody-drug conjugate coupled to SN-38 as the payload[1]
- In the phase 3 TROPiCS-02 study (NCT03901339), SG demonstrated clinically meaningful improvement in survival outcomes over chemotherapy in patients with pretreated HR+/HER2– metastatic breast cancer (mBC)[2]
  - Median overall survival (OS) was 14.4 months (95% CI, 13.0-15.7) and 11.2 months (10.1-12.7), respectively (hazard ratio [HR], 0.79; 95% CI, 0.65-0.96; *P* = .020)
- SN-38 leads to double-stranded DNA damage; therefore, we hypothesized that in tumors with defective DNA damage response (DDR) machinery, SG may provoke synthetic lethality[3]
- We report on a post hoc exploratory genomic analysis of DDR gene variants in patients from the TROPiCS-02 study and assess SG clinical efficacy by DDR status

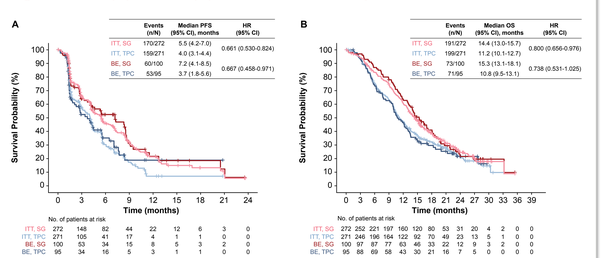
Methods

- Patients with previously treated HR+/HER2– mBC were randomized to receive SG or treatment of physician's choice (TPC) until disease progression or unacceptable toxicity[2]
- DDR gene deleterious variants were identified using whole exome sequencing (WES) on archival or screening tumor tissues based on 142 DDR pathway genes annotated in the Kyoto Encyclopedia Genes and Genomes database and Human DNA Repair Gene database[4,5]
- The association between DDR deleterious variants and clinical outcomes was evaluated using a Cox regression model as HR with 95% CI. Objective response rate (ORR) odds ratio was calculated using the Cochran-Mantel-Haenszel method

Results

- Of the 543 patients (intent-to-treat [ITT] population; SG, N = 272; TPC, N = 271) enrolled in TROPiCS-02, 195 (36%) patients (SG, n = 100; TPC, n = 95) were included in the WES biomarker-evaluable population, which will be referred to as the biomarker-evaluable (BE) population hereafter
- Overall, demographics and baseline characteristics were similar between the ITT and BE populations (median age, 57 vs 58 years for SG and 55 vs 55 years for TPC; prior lines of chemotherapy > 2 lines, 58% vs 57% for SG and 58% vs 55% for TPC)
  - A slightly higher proportion of patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (43% vs 48% for SG and 46% vs 51% for TPC) and who had received prior cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) for less than 12 months (60% vs 65% for SG and 62% vs 67% for TPC) were in the BE population
- Progression-free survival (PFS) and OS were similar in the ITT and BE populations and demonstrated improved efficacy with SG vs TPC in these populations (**Figure 1**)

Figure 1. PFS (A) and OS (B) in the ITT and BE Populations



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

- Out of the 195 patients in the BE population, 114 (58%) had at least 1 DDR gene with a deleterious mutation; baseline characteristics were generally similar between patients with mutant and wild type DDR in the SG and TPC arms (**Table 1**)

Results

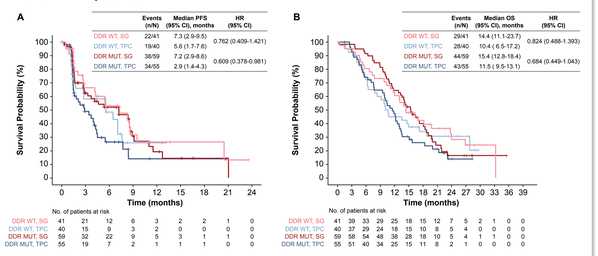
Table 1. Demographics and Baseline Characteristics Among Patients With or Without DDR Mutations in the BE Population

Characteristic	SG WT (n = 41)	SG MUT (n = 59)	TPC WT (n = 40)	TPC MUT (n = 55)
Median age (IQR), years	59 (53-70)	56 (49-62)	57 (47-65)	55 (48-61)
Race, n (%)				
White	26 (63)	39 (66)	33 (83)	33 (60)
Other	4 (10)	3 (5)	0	9 (16)
Not reported	11 (27)	17 (29)	7 (17)	13 (24)
ECOG performance status, n (%)				
0	20 (49)	28 (47)	22 (55)	26 (47)
1	21 (51)	31 (53)	18 (45)	29 (53)
Visceral metastasis, n (%)				
Yes	39 (95)	55 (93)	35 (88)	52 (95)
No	2 (5)	4 (7)	5 (12)	3 (5)
Prior CDK4/6i treatment duration, n (%)				
≤ 12 months	27 (66)	37 (65)	21 (54)	41 (76)
> 12 months	14 (34)	20 (35)	18 (46)	13 (24)
ET in the metastatic setting for ≥ 6 months, n (%)				
Yes	36 (88)	54 (92)	37 (93)	48 (87)
No	5 (12)	5 (8)	3 (7)	7 (13)
Estrogen receptor status, n (%)				
> 10%	39 (95)	57 (97)	37 (93)	47 (85)
Prior CT regimen in the metastatic setting, n (%)				
2	19 (46)	24 (41)	17 (42)	26 (47)
3-4	22 (54)	35 (59)	23 (58)	29 (53)
TPC, n (%)				
Capecitabine	-	-	7 (17)	1 (2)
Eribulin	-	-	15 (38)	24 (44)
Gemcitabine	-	-	8 (20)	13 (24)
Vinorelbine	-	-	10 (25)	17 (31)

BE, biomarker evaluable; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; DDR, DNA damage response; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; MUT, mutant; SG, sacituzumab govitecan; TPC, treatment of physician's choice; WT, wild type.

- Of the 142 DDR pathway genes evaluated, 87 were mutated in this patient population
- In the BE population, PFS (**Figure 2A**) and OS (**Figure 2B**) benefit of SG vs TPC was greater (as shown by smaller HRs) for patients with vs without DDR mutations
- A greater benefit in ORR was also observed as shown by the larger odds ratio for patients with vs without DDR mutations (**Table 2**)

Figure 2. PFS (A) and OS (B) of Patients With or Without DDR Mutations in the BE Population



BE, biomarker evaluable; DDR, DNA damage response; HR, hazard ratio; MUT, mutant; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; WT, wild type.

Table 2. ORR of Patients With or Without DDR Mutations in the BE Population

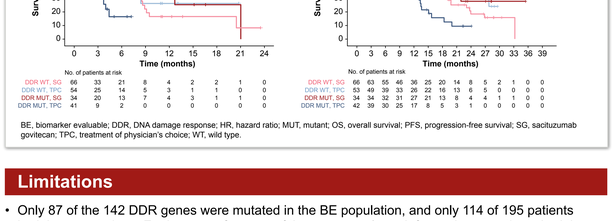
Treatment	DDR WT ORR n/N (%)	DDR WT ORR Odds Ratio	DDR MUT ORR n/N (%)	DDR MUT ORR Odds Ratio
SG	9/41 (22)	1.6 (0.5-5.0)	11/59 (19)	4.0 (1.0-15.1)
TPC	6/40 (15)		3/55 (5)	

BE, biomarker evaluable; DDR, DNA damage response; MUT, mutant; ORR, objective response rate; SG, sacituzumab govitecan; TPC, treatment of physician's choice; WT, wild type.

Full Interaction Model to Identify DDR Genes That Are Potentially Predictive of SG Benefit Over TPC

- To enrich for DDR genes that contribute to the predictive benefit of SG over TPC, each of the 87 mutated genes was omitted, 1 at a time, and genes for which the predictability was reduced were selected for further analyses (**Figure 3**)
  - By comparing the numeric HRs to the HR in the all-inclusive model (HR_0), the genes were separated out by their potential contribution to predictive effect in the full interaction model

Figure 3. Model to Identify DDR Genes With a Predictive Effect



[a]HRs were evaluated for predictive effect in the interaction model.
DDR, DNA damage response; HR, hazard ratio; MUT, mutant; SG, sacituzumab govitecan; TPC, treatment of physician's choice; WT, wild type.

- Among the DDR genes evaluated, 39 mutated genes contributed to the improved PFS with SG over TPC
  - These genes are: *APEX1*, *APEX2*, *ATM*, *ATRIP*, *BLM*, *BRCA2*, *CHEK2*, *CUL4A*, *CUL4B*, *DNTT*, *ERCC2*, *ERCC6*, *ERCC8*, *EXO1*, *FANCF*, *FANCM*, *GTF2H1*, *HMGB1*, *HMGB1P40*, *MDC1*, *MRE11*, *MUTYH*, *NBN*, *NEIL1*, *PALB2*, *PARP1*, *PARP4*, *POLD1*, *PRKDC*, *RAD17*, *RAD50*, *RECQL4*, *RFC5*, *SLX4*, *TOP3A*, *WRN*, *XPC*, *XRCC2*, *XRCC6*
- Mutations on 47 genes contributed to the improved OS with SG over TPC
  - These genes are: *APEX2*, *ATM*, *ATRIP*, *CHEK2*, *CUL4A*, *CUL4B*, *DNTT*, *ERCC2*, *ERCC8*, *FAAP100*, *FANCA*, *FANCD2*, *FANCE*, *FANCF*, *FANCI*, *FANCM*, *FEN1*, *GTF2H1*, *HMGB1*, *HMGB1P40*, *LIG1*, *MDC1*, *MLH3*, *MRE11*, *MUTYH*, *NBN*, *NEIL1*, *PARP4*, *PMS2*, *POLD1*, *POLD3*, *POLM*, *PRKDC*, *RAD17*, *RAD23B*, *RAD51D*, *RAD52*, *RAD54L*, *RFC1*, *RFC5*, *RPA2*, *TOP3A*, *TOPBP1*, *XPA*, *XPC*, *XRCC2*, *XRCC6*
- PFS and OS in patients with or without mutations in predictive DDR genes (based on the lists outlined above for each outcome) in the BE population are shown in **Figure 4**

Figure 4. PFS (A) and OS (B) in Patients With or Without Mutation in Predictive DDR Genes in the BE Population

BE, biomarker evaluable; DDR, DNA damage response; HR, hazard ratio; MUT, mutant; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; WT, wild type.

Limitations

- Only 87 of the 142 DDR genes were mutated in the BE population, and only 114 of 195 patients had these mutations. Furthermore, for most of the genes evaluated, fewer than 5 patients had the mutation in a given gene
- The current method did not consider co-mutations (which may include key mutations that are associated with survival); thus, it is hard to separate out the effect of other key mutations from DDR mutations
- The identified DDR genes that are potentially predictive of SG benefit over TPC might be overfitted to this study; validation of the predictive effect for greater SG benefit is needed