Health-Related Quality of Life with Sacituzumab Govitecan Versus Treatment of Physician's Choice in Previously Treated Hormone Receptor-Positive/HER2-Negative Metastatic Breast Cancer: A Meta-Analysis of TROPiCS-02 and EVER-132-002 Trials

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Conclusion

- SG significantly improved health-related quality of life (HRQoL) compared to TPC for 6/15 EORTC QLQ C-30 domains and for EQ-5D-5L VAS across the overall, CDK4/6i pre-treated, and fast-progressors population
- The HRQoL attributed to diarrhea, nausea, and vomiting worsened significantly with SG. To be noted, these symptoms are known part of SG's safety profile which can be managed easily by following established guidelines and were associated with lower rates of treatment discontinuations
- The consistency of these results across different patient populations and several time-to-event analyses enhances the generalizability of the individual trials and reinforces the HRQoL benefits associated with SG versus TPC

Plain language summary

- SG is an important option to treat patients with HR+/HER2- metastatic breast cancer who have developed resistance to endocrine drugs
- The current study evaluated TROPiCS-02 and EVER-132-002 and compared the HRQoL outcomes
- In the overall and prior CDK4/6i-treated populations, SG showed a statistically significant improvement in HRQoL over TPC on the EORTC QLQ-C30 domains including Global Health Status/QoL, physical & emotional functioning, fatigue, pain, and dyspnea
- Fast-progressors experienced significant improvement in HRQoL for all the above-mentioned domains in addition to financial difficulties
- HRQoL worsened significantly with SG due to diarrhea, nausea and vomiting across the three populations which are the commonly reported AEs of SG
- SG demonstrated a significantly better improvement in HRQoL over TPC for EQ-5D-5L VAS for all the patient subgroups
- The sensitivity analysis confirmed these results, thereby favoring SG over TPC

References:

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Introduction

- Two phase III randomized controlled trials (RCTs), TROPiCS-02[1] and EVER-132-002[2], compared the health-related quality of life (HRQoL) outcomes of sacituzumab govitecan (SG) versus chemotherapeutic treatment of physician's choice (TPC) in participants with hormone receptor-positive (HR+) and human epidermal growth factor receptor-2–negative (HER2– [IHC0, IHC1 positive, or IHC2 positive and ISH negative]) locally recurrent inoperable or metastatic breast cancer (MBC) who had progressed after 2-4 prior chemotherapy regimens

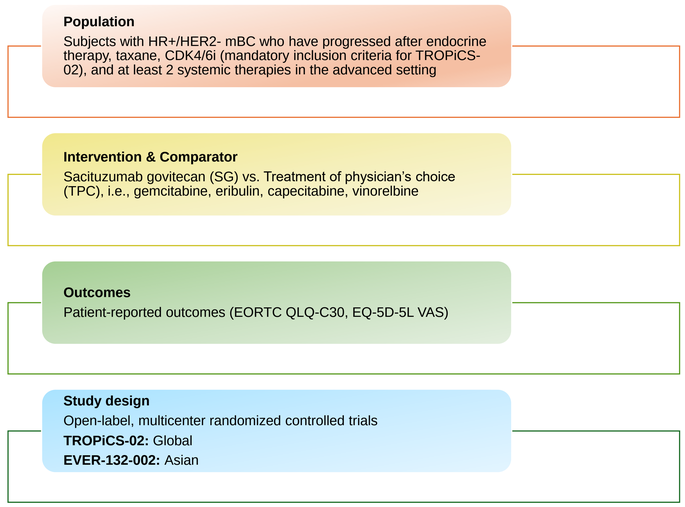
Objective

- This meta-analysis explored the HRQoL benefits of SG vs TPC in the overall population and determined if the results varied by prior CDK4/6i exposure and duration of prior CDK4/6i treatment

Methodology

- A meta-analysis based on individual patient-level data was performed according to the PRISMA-IPD[3] guidelines to compare time to first clinically meaningful deterioration (TTD) of SG vs TPC using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30) domains (≥10 points change) and EuroQol 5 Dimensions 5 Levels Visual Analog Scale (EQ-5D-5L VAS) (≥15 points change) **(Figure 1)**
- TTD assessment was performed in the EORTC QLQ-C30 and EQ-5D-5L evaluable population, which was defined as intention-to-treat (ITT) subjects who completed at least one domain/dimension at baseline and had at least one evaluable assessment post-baseline
- Base-case was performed by excluding death from the analysis and a sensitivity analysis was also conducted considering death as an event. HR and 95% CI were estimated for TTD outcomes using a stratified Cox proportional hazards regression analysis
- Further, a subgroup analysis was performed in the prior CDK4/6i-treated population and fast-progressors (prior CDK4/6i duration of treatment: ≤12 months) to explore the benefits of SG vs TPC

Figure 1: PICOS criteria for inclusion in the meta-analysis



CDK4/6i: CDK4/6 inhibitor; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; EQ-5D-5L VAS: EuroQol 5 Dimensions 5 Levels Visual Analog Scale; HER2-: Human epidermal growth factor receptor 2 negative; HR+: Hormone receptor-positive; mBC: metastatic breast cancer

Results

Base-case: Death as censored

- A statistically significant increase in TTD was observed with SG compared to TPC for six of 15 domains of EORTC QLQ C-30, including Global Health Status/QoL, physical functioning, emotional functioning, fatigue, pain, and dyspnea measures in the overall and prior CDK4/6i treated population while nausea & vomiting and diarrhea worsened significantly with SG **(Table 1A)**
- Subgroup results for fast-progressors revealed significant TTD findings for the above six domains favoring SG, with significant benefit also observed for the financial difficulties **(Table 1A)**

Sensitivity analysis: Death as an event

- In the sensitivity analyses, the findings remained largely consistent in the overall and prior CDK4/6i treated population, however statistical significance in TTD favoring SG was lost in pain and was gained in financial difficulties **(Table 1B)**
- Sensitivity results were broadly consistent in the fast-progressors subgroup with statistically significant longer TTD also observed with SG in insomnia **(Table 1B)**
- Furthermore, SG demonstrated significantly longer TTD over TPC for EQ-5D-5L VAS in all three populations **(Table 2)**

Table 1: TTD in the various scales of the EORTC QLQ-C30 questionnaire in both Death as Censored (A) and as Event (B) analysis

A) EORTC QLQ C-30 Subscale	Overall, HR (95% CI)	Prior CDK4/6i-treated, HR (95% CI)	Fast-progressors, HR (95% CI)
Global Health Status/QoL	0.76 (0.63, 0.92), p=0.005, n=756	0.69 (0.56, 0.86), p=0.001, n=592	0.62 (0.47, 0.82), p=0.001, n=366
Physical Functioning	0.72 (0.59, 0.88), p=0.001, n=762	0.74 (0.59, 0.93), p=0.009, n=597	0.69 (0.51, 0.92), p=0.010, n=371
Role Functioning	0.84 (0.70, 1.01), p=0.060, n=749	0.88 (0.71, 1.08), p=0.404, n=586	0.83 (0.64, 1.08), p=0.169, n=361
Emotional Functioning	0.73 (0.58, 0.91), p=0.006, n=752	0.64 (0.49, 0.83), p=0.001, n=588	0.53 (0.38, 0.74), p=0.000, n=365
Cognitive Functioning	0.83 (0.68, 1.02), p=0.071, n=760	0.87 (0.69, 1.10), p=0.230, n=596	0.77 (0.57, 1.03), p=0.079, n=370
Social Functioning	0.88 (0.72, 1.06), p=0.181, n=742	0.88 (0.71, 1.10), p=0.262, n=578	0.76 (0.58, 1.01), p=0.059, n=362
Fatigue	0.80 (0.67, 0.95), p=0.011, n=755	0.77 (0.63, 0.94), p=0.009, n=591	0.71 (0.55, 0.91), p=0.007, n=366
Nausea and Vomiting	1.48 (1.21, 1.79), p<0.001, n=762	1.33 (1.07, 1.65), p=0.011, n=597	1.22 (0.93, 1.60), p=0.154, n=372
Pain	0.82 (0.67, 0.99), p=0.042, n=744	0.77 (0.62, 0.96), p=0.021, n=580	0.72 (0.55, 0.96), p=0.024, n=357
Dyspnea	0.71 (0.57, 0.88), p=0.002, n=748	0.69 (0.54, 0.88), p=0.003, n=584	0.62 (0.45, 0.85), p=0.003, n=361
Insomnia	0.87 (0.69, 1.08), p=0.208, n=718	0.81 (0.63, 1.05), p=0.119, n=559	0.78 (0.56, 1.07), p=0.120, n=343
Appetite loss	1.13 (0.93, 1.39), p=216, n=739	1.00 (0.80, 1.26), p=0.978, n=575	0.86 (0.65, 1.16), p=0.325, n=359
Constipation	1.11 (0.89, 1.38), p=0.366, n=747	1.13 (0.89, 1.44), p=0.325, n=585	1.08 (0.79, 1.47), p=0.641, n=363
Diarrhoea	2.21 (1.77, 2.76), p<0.001, n=757	2.25 (1.76, 2.88), p<0.001, n=593	2.14 (1.57, 2.91), p<0.001, n=367
Financial difficulties	1.09 (0.83, 1.44), p=0.530, n=715	1.02 (0.73, 1.44), p=0.889, n=570	0.60 (0.39, 0.93), p=0.022, n=352
Summary score	0.89 (0.72, 1.09), p=0.259. n=764	0.87 (0.69, 1.11), p=0.265, n=599	0.84 (0.63, 1.14), p=0.264, n=372

B) EORTC QLQ C-30 Subscale	Overall, HR (95% CI)	Prior CDK4/6i-treated, HR (95% CI)	Fast-progressors, HR (95% CI)
Global Health Status/QoL	0.83 (0.71, 0.97), p=0.021, n=756	0.78 (0.66, 0.93), p=0.006, n=592	0.72 (0.58, 0.90), p=0.004, n=366
Physical Functioning	0.77 (0.66, 0.90), p=0.001, n=762	0.78 (0.66, 0.94), p=0.007, n=597	0.74 (0.59, 0.93), p=0.010, n=371
Role Functioning	0.90 (0.77, 1.05), p=0.200, n=749	0.93 (0.79, 1.11), p=0.426, n=586	0.87 (0.70, 1.09), p=0.223, n=361
Emotional Functioning	0.75 (0.64, 0.89), p=0.001, n=752	0.70 (0.58, 0.84), p<0.001, n=588	0.62 (0.49, 0.78), p<0.001, n=365
Cognitive Functioning	0.86 (0.73, 1.00), p=0.055, n=760	0.86 (0.72, 1.03), p=0.100, n=596	0.82 (0.66, 1.02), p=0.077, n=370
Social Functioning	0.89 (0.76, 1.05), p=0.160, n=742	0.88 (0.74, 1.05), p=0.162, n=578	0.80 (0.64, 1.00), p=0.047, n=362
Fatigue	0.83 (0.71, 0.97), p=0.019, n=755	0.81 (0.68, 0.96), p=0.015, n=591	0.75 (0.60, 0.93), p=0.010, n=366
Nausea and Vomiting	1.21 (1.03, 1.41), p=0.018, n=762	1.11 (0.93, 1.32), p=0.252, n=597	1.08 (0.86, 1.34), p=0.513, n=372
Pain	0.90 (0.77, 1.06), p=0.199, n=744	0.86 (0.73, 1.03), p=0.103, n=580	0.82 (0.65, 1.03), p=0.085, n=357
Dyspnea	0.74 (0.63, 0.87), p=0.000, n=748	0.72 (0.60, 0.86), p=0.000, n=584	0.66 (0.52, 0.83), p=0.000, n=361
Insomnia	0.87 (0.73, 1.02), p=0.088, n=718	0.85 (0.71, 1.02), p=0.074, n=559	0.79 (0.63, 1.00), p=0.050, n=343
Appetite loss	1.07 (0.91, 1.25), p=0.439, n=739	0.95 (0.80, 1.14), p=0.588, n=575	0.89 (0.71, 1.11), p=0.310, n=359
Constipation	1.03 (0.88, 1.22), p=0.681, n=747	1.04 (0.87, 1.24), p=0.697, n=585	0.94 (0.75, 1.18), p=0.615, n=363
Diarrhoea	1.47 (1.25, 1.72), p<0.001, n=757	1.41 (1.19, 1.68), p<0.001, n=593	1.33 (1.07, 1.66), p=0.012, n=367
Financial difficulties	0.83 (0.70, 0.99), p=0.035, n=715	0.78 (0.64, 0.94), p=0.008, n=570	0.63 (0.50, 0.80), p=0.000, n=352
Summary score	0.92 (0.79, 1.08), p=0.325, n=764	0.90 (0.76, 1.08), p=0.259, n=599	0.87 (0.70, 1.09), p=0.234, n=372

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; GHS: Global health status. *The 30-item EORTC QLQ-C30 questionnaire consisted of 5 functional scales (physical, role, cognitive, emotional, and social functioning), 3 symptom scales (fatigue, pain, nausea, and vomiting), a global health status/QOL scale (GHS/QoL), and 6 single items (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial difficulties). A summary score for the EORTC QLQ-C30 is also calculated as the mean of 13 out of the 15 domains, excluding the GHS/QoL and financial difficulties[1]; Significant improvement favoring SG vs. TPC; Significant improvement favoring TPC vs. SG

Table 2: Time to First HRQoL Worsening for EQ-5D-5L VAS Death as Censored and as Event in overall, prior CDK4/6 inhibitor-treated and fast-progressors population

SG vs TPC, EQ-5D-5L-VAS: HR (95% CI)	Overall population	Prior CDK4/6 inhibitor-treated	Fast-progressors
Death as censored	0.68 (0.53, 0.87) p=0.002; n=754	0.63 (0.48, 0.83) p=0.001; n=589	0.69 (0.48, 0.97) p=0.034; n=365
Death as event	0.76 (0.64, 0.90) p<0.001; n=754	0.73 (0.61, 0.87) p<0.001; n=589	0.74 (0.59, 0.94) p=0.012; n=365

EQ-5D-5L VAS: EuroQol 5 Dimensions 5 Levels Visual Analog Scale; HR: Hazards ratio; SG: Sacituzumab govetican; TPC: Treatment of physician's choice. * EQ-5D measure includes an EQ-5D-5L scale and a visual analog scale (VAS). The EQ-5D-5L assesses 5 dimensions of health including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[1]; Significant improvement favoring SG vs. TPC