Biomarkers of response and resistance to Sacituzumab Govitecan in HR+/HER2– advanced breast cancer: interim results from the phase II SOLTI ACROSS-TROP2 Trial

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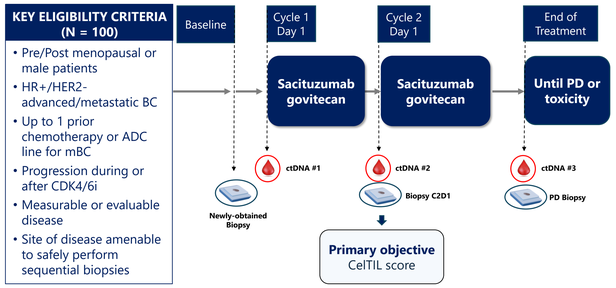
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1. RATIONALE

- Sacituzumab Govitecan (SG) is an antibody-drug conjugate (ADC) containing a TROP2-directed antibody bound to a topoisomerase I inhibitor payload (SN-38) through a chemically hydrolysable CL2A linker.
- SG has shown significant clinical benefit and is approved for metastatic triple negative breast cancer (mTNBC) after at least two prior systemic therapies, including one in the metastatic setting; and for HR+ /HER2- metastatic breast cancer (MBC) after endocrine therapy (including CDK4/6 inhibitors) and at least two prior systemic treatments, based on results from the ASCENT and TROPiCS-02 trials, respectively [1,2].
- Both trials showed a manageable safety profile, and benefit from SG was consistent across a wide range of TROP2 expression levels, although higher efficacy outcomes were observed in high and medium TROP2 H-score [3-5].
- Technical limitations with the IHC-based assays used for TROP2-detection (such as different antibody sensitivities, interobserver variability and lack of standardized measurement methods and cutoffs) may limit its interpretability [6].
- To date, no biomarkers have shown a standardized clinical utility to predict anti-TROP2 treatment benefit.

2. STUDY DESIGN

Figure 1. Trial Design.



What does ACROSS-TROP2 add?

- Aims to **identify predictive biomarkers of SG benefit** and understanding the key resistance mechanisms and how they longitudinally emerge.
- Collects **tissue biopsies before, during and after treatment** which will allow:
  - the exploration of **reproducible predictive biomarkers** to refine patient selection
  - a more comprehensive understanding of **primary and acquired resistance mechanisms**
  - the characterization of **SG-induced tumor and tumor microenvironment (TME) modulation to inform future potential treatment combinations**
- Looks at the value of **CelTIL score as a surrogate of treatment response** to SG.

3. ENDPOINTS

Primary objective

- To evaluate the change in the CelTIL score after one cycle of SG in paired baseline and C2D1 tumor samples in the overall population.

CelTIL score is a metric for quantifying changes in tumor cellularity and the number of tumor infiltrating lymphocytes (TILs)[7]. An increase in CelTIL score associates with a favorable response to treatment [8,9].

The minimum and maximum unscaled CelTIL scores are −80 and 130. This unscaled CelTIL score is subsequently scaled to reflect a range from 0 to 100 points.

Secondary and exploratory objectives

- Overall response rate (ORR), clinical benefit rate (CBR), progression-free survival (PFS), duration of response (DoR), and time to response (TtR)
- Associations between TROP2 mRNA/IHC expression and CelTIL score variation and clinical benefit
- Correlate CelTIL score at C2D1 with long-term outcome
- To assess safety and tolerability of SG
- Integrate biological findings with clinicopathological data
- Investigate early changes in ctDNA and CTCs in response to treatment

4. INTERIM ANALYSIS METHODS

An exploratory interim analysis was carried out after the first 50 enrolled patients completed the second tumor assessment. CelTIL score change, PFS and ORR along with safety outcomes are reported in this analysis. No formal hypothesis testing was conducted to control the overall type I error of the study.

5. RESULTS

a. Patient disposition and baseline characteristics

Figure 2. Patient disposition.

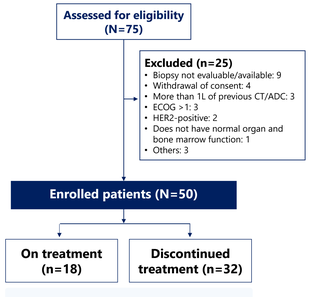


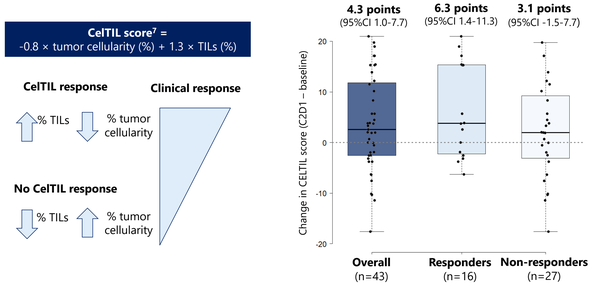
Table 1. Baseline characteristics.

Patients' characteristics (N=50)	N (%)
Age, median (range)	58 (30-79)
Female	
Pre/Perimenopausal	11 (22)
Postmenopausal	39 (78)
ECOG	
0	29 (58)
1	21 (42)
Visceral metastasis	42 (84)
Previous Chemotherapy or ADC in the metastatic setting	35 (70)
Previous Chemotherapy	33 (66)
Previous T-DXd	2 (4)
Measurable disease	47 (94)
CelTIL evaluable*	**43 (86)**

**7 patients were not evaluable for CelTIL - C2D1 sample was not collected or sample did not meet minimal criteria for analysis.*

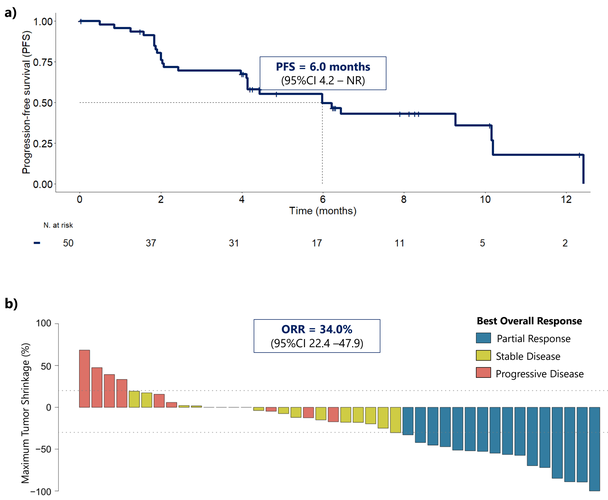
b. CelTIL score change after one cycle of SG

Figure 3. Change in CelTIL score. The mean increase in CelTIL score from baseline to C2D1 was 4.33 points (95% CI 1.0-7.7), indicating an overall change, with a greater increase in patients that achieved radiological response (6.3 vs 3.1 points).



c. Efficacy

Figure 4. Efficacy outcomes. (a) Progression-free survival (PFS) and **(b)** Maximum tumor shrinkage. Median follow-up was 8.6 months. PFS events occurred in 28/50 pts (maturity 56%). Median PFS was 6 months (4.2-NR) both overall and among patients treated in second line for mBC. Overall Response Rate (ORR) was 34.0% in overall population and 38.2% among patients treated in second line for mBC respectively.



d. Safety

Table 2. Treatment-related adverse events (TRAEs).

TRAEs occurring in ≥10% of patients	Overall N (%)	Grade ≥ 3 N (%)
Any AE	**48 (96)**	**24 (48)**
Fatigue	29 (58)	5 (10)
Anemia	29 (58)	2 (4)
Neutropenia	27 (54)	13 (26)
Nausea	23 (46)	1 (2)
Diarrhea	23 (46)	6 (12)
Alopecia	15 (30)	0 (0)
Stomatitis	11 (22)	0 (0)
Transaminases increased	9 (18)	0 (0)
Rash	7 (14)	0 (0)
Vomiting	6 (12)	1 (2)
Abdominal pain	6 (12)	1 (2)
Gamma-glutamyltransferase increased	5 (10)	0 (0)
Leukopenia	5 (10)	0 (0)
Decreased appetite	5 (10)	0 (0)

Table 3. SG dose modifications.

Dose modifications resulting from TEAE	N (%)
Dose reductions	**10 (20%)**
Related to SG	10 (20%)
Dose interruptions	**29 (58%)**
Related to SG	20 (40%)
Permanent discontinuation	**6 (12%)**
Related to SG	4 (8%)

- 15 (30%) SAEs we reported, of which 8 (16%) were related to SG
- 3 patients experienced SG-related febrile-neutropenia and were treated with granulocyte-colony-stimulating factor (G-CSF)*.
- 2 SG-unrelated deaths were reported

**In November 2024, a protocol amendment was approved to include additional guidance for neutropenia management, recommending primary prophylaxis with G-CSF starting in the first treatment cycle for patients at increased risk of febrile neutropenia.*

6. CONCLUSIONS

- In this interim analysis of SOLTI ACROSS-TROP2, one cycle of SG led to an increase in CelTIL score, particularly among patients who achieved a radiological response (complete or partial response according to RECIST v1.1).
- Efficacy results are immature at this time.
- The safety profile of SG was consistent with previously reported data.
- The final results from the full cohort of 100 patients, along with a comprehensive translational analysis of paired pre- and on-treatment biopsies, are expected to provide further insights into biomarkers of response and mechanisms of resistance to SG in HR+/HER2– mBC.

7. ACKNOWLEDGEMENTS

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8. FUNDING

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9. RESOURCES

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