NeoSaci-IO: Neoadjuvant sacituzumab govitecan + pembrolizumab in patients with early-stage TNBC experiencing suboptimal response to KEYNOTE-522

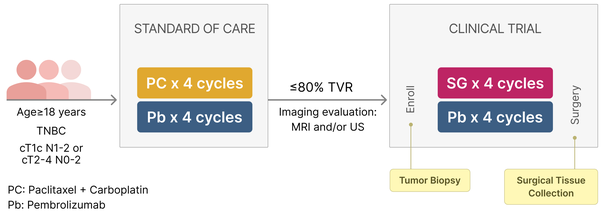
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Background

- In high-risk, early-stage triple-negative breast cancer (TNBC), residual disease (non-pCR) after the KEYNOTE-522 regimen is associated with a 30-40% risk of recurrence within the first 3 years.
- In preliminary studies, we observed that suboptimal tumor volume reduction (≤80%) after 4 cycles of paclitaxel+carboplatin+pembrolizumab was associated with low pCR rates (~20%) with continued standard therapy (doxorubicin+cyclophosphamide+pembrolizumab).
- Sacituzumab govitecan (SG) has demonstrated superior clinical efficacy over conventional chemotherapy in metastatic TNBC, and emerging data suggest that SG enhances anti-PD-(L)1 activity.
- We conducted the first trial of SG + pembrolizumab (Pb) as sequential neoadjuvant therapy in patients with high-risk, early-stage TNBC with suboptimal response to paclitaxel+carboplatin+ pembrolizumab (NCT05675579).

Methods



PC: Paclitaxel + Carboplatin
Pb: Pembrolizumab
SG: Sacituzumab govitecan

Eligibility: Patients with stage II-III TNBC and suboptimal response (≤80% tumor volume reduction) to paclitaxel+carboplatin+ pembrolizumab

Treatment: Patients received SG (10 mg/kg IV, D1 & 8) + Pembrolizumab (200 mg IV, D1) every 21 days x 4 cycles

Statistical design: Bayesian Optimal Phase II (BOP2) design

Null hypothesis: pCR rate=20%

Alternative hypothesis: pCR rate=45%

Threshold for success: pCR in 9 of 25 response evaluable patients (α=4.6%, power=85.8%)

Patients not evaluable for response were replaced to ensure N=25

Results

Table 1. Clinicopathological characteristics.

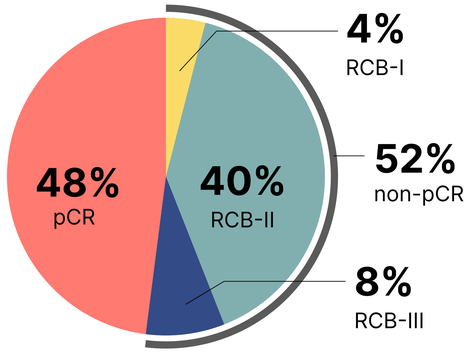
	pCR (n=12)	Non-pCR (n=13)	P value
Age at diagnosis - Median (range)	49.8 (28.6-71.1)	63.2 (38.8-77.1)	0.19
T stage - n(%)			
T1	1 (8)	0	0.65
T2	9 (75)	9 (69)	
T3	2 (17)	4 (31)	
T4	0	0	
Nodal involvement - n(%)			
Positive	5 (42)	4 (31)	0.69
Negative	7 (58)	9 (69)	
Germline BRCA mutation status - n(%)			
Mutant	2 (17)	1 (8)	0.59
Wild Type	9 (75)	11 (85)	
Wildtype	1 (8)	1 (8)	
Histology - n(%)			
Ductal	9 (75)	9 (69)	1.00
Metaplastic	3 (25)	3 (23)	
Lobular	0	1 (8)	
Histologic Grade - n(%)			
2	3 (25)	6 (46)	0.41
3	9 (75)	7 (54)	
Ki67 - n(%)			
≤35%	2 (17)	4 (31)	0.65
>35%	9 (75)	9 (69)	
Unknown	1 (8)	0	

Table 2. Adverse Events.

Adverse Event	Grade 4	Grade 3	Grade 2
Hematological			
Neutropenia – n (%)	4 (15)	12 (44)	5 (19)
Anemia – n (%)		1 (4)	6 (22)
Leukopenia – n (%)			8 (30)
Non-hematological			
Fatigue – n (%)			10 (37)

Treatment-Related Adverse Events (TRAEs) occurring in ≥20% of safety-evaluable patient (N = 27).

Figure 1. Pathologic response in 25 response-evaluable patients.



Clinical Trial Enrollment

- 27 patients were enrolled from 6/22/2023-5/23/2025.
- All 27 patients were evaluable for safety, and 25 patients were evaluable for response:
  - 1 patient completed <2 cycles of study treatment due to an unrelated adverse event
  - 1 patient had ineligible histology at the time of surgery

Efficacy (N=25)

- The pCR rate was 48% (95% CI: 28-69%).
- Among the 13 patients with non-pCR, residual cancer burden was distributed as follows: RCB-I (n=1), RCB-II (n=10), RCB-III (n=2).

Safety (N=27)

- 24 patients (89%) successfully completed all 4 cycles of SG+Pb.
- 9 patients (38%) required a dose reduction of SG.
- Only 3 patients discontinued study treatment early due to TRAEs (n=1), adverse events unrelated to study treatment (n=1), disease progression (n=1).
- TRAES (all grades) occurring in ≥20% pts included: neutropenia (78%), fatigue (37%), leukopenia (30%) and anemia (26%).
- 16 patients (59%) experienced Grade ≥3 neutropenia.

Conclusions

- SG+Pb is an effective treatment option in patients with high-risk, early-stage TNBC experiencing suboptimal response to paclitaxel+ carboplatin+ pembrolizumab.
- The pCR rate was 48% compared to 20% in historical controls, with no new safety signals.
- Correlative proteomic (including TROP2 IHC), genomic, and immunological studies are ongoing.
- Evaluation of SG+Pb in a larger, randomized study is warranted as a potential alternative to doxorubicin, cyclophosphamide, and pembrolizumab in patients with suboptimal response to paclitaxel, carboplatin, and pembrolizumab.

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References

Bardia, Aditya, et al. "Final results from the randomized phase III ASCENT clinical trial in metastatic triple-negative breast cancer and association of outcomes by human epidermal growth factor receptor 2 and trophoblast cell surface antigen 2 expression." Journal of Clinical Oncology 42.15 (2024): 1738-1744.
McKenzie, Jodi A., et al. "The effect of topoisomerase I inhibitors on the efficacy of T-cell-based cancer immunotherapy." JNCI: Journal of the National Cancer Institute 110.7 (2018): 777-786.
Iwai, Toshiki, et al. "Topoisomerase I inhibitor, irinotecan, depletes regulatory T cells and up-regulates MHC class I and PD-L1 expression, resulting in a supra-additive antitumor effect when combined with anti-PD-L1 antibodies." Oncotarget 9.59 (2018): 31411.
Schmid, Peter, et al. "Pembrolizumab for early triple-negative breast cancer." New England Journal of Medicine 382.9 (2020): 810-821.
Schmid, Peter, et al. "Event-free survival with pembrolizumab in early triple-negative breast cancer." New England Journal of Medicine 386.6 (2022): 556-567.
Symmans, W. Fraser, et al. "Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype." Journal of Clinical Oncology 35.10 (2017): 1049-1060.

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