Cemiplimab in High-risk or Locally Advanced Luminal and Triple Negative Breast Cancer (CemiHALT)

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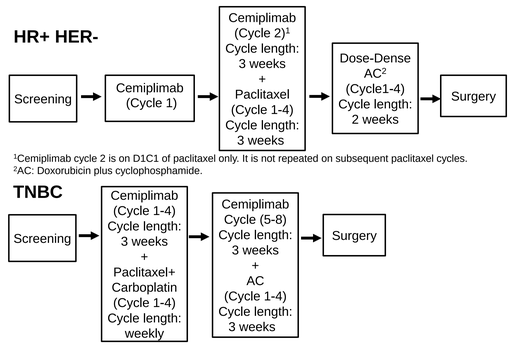
INTRODUCTION

- PD-1 inhibitors (PD-1i) are associated with significantly higher pathological complete responses (pCR) in patients (pts) with triple-negative breast cancer (TNBC) as well as luminal/hormone receptor-positive (HR+) breast cancer (BC), particularly in PD-L1-positive pts.
- Most clinical trials of PD-1i have thus far focused on PD-L1 expression for pt eligibility. The alternative PD-1 ligand, PD-L2, with reported ~3-fold greater affinity for PD-1, remains understudied.
- We recently reported that high levels of PD-L2 in pts with treatment-naïve HR+ BC were an independent predictor of shorter progression-free survival[1]. We therefore sought to assess the correlation of PD-L1 and PD-L2 with pCR in TNBC and HR+/HER2-negative BC treated with PD-1i and neoadjuvant chemotherapy (NACT).

METHODS

- CemiHALT (NCT04243616) is a single-arm, open-label phase II study of PD-1i cemiplimab (Regeneron Pharmaceuticals) and NACT in pts with high-risk TNBC or locally advanced HR+/HER2-negative BC with positive PD-L1 and/or PD-L2 tumor expression (≥1% baseline protein expression in cancer cells or stromal cells). Primary objective was to assess pCR rates with NACT and cemiplimab.
- First dose of cemiplimab (350mg) was given as monotherapy to prime the immune microenvironment and 2nd dose concurrently with NACT start. The trial was later amended to incorporate cemiplimab concurrently with NACT for TNBC pts after FDA approval of pembrolizumab per KEYNOTE-522 in July 2021 (Figure 1).
- Wilcoxon paired analyses and Spearman correlation were used to correlate PD-L1 and PD-L2 protein expression with pCR rates and radiographic responses, respectively. Fisher's test and McNemar's tests were used for comparison of variables and PD-L1/PD-L2 expression between HR+ and TNBC subtypes. Primary analyses were planned with 80% power and a significance level of 0.05.

Fig 1. Study Schema



[1]Cemiplimab cycle 2 is on D1C1 of paclitaxel only. It is not repeated on subsequent paclitaxel cycles.
[2]AC: Doxorubicin plus cyclophosphamide.

Fig 2. pCR rates, PD-L1 and PD-L2 status by subtype

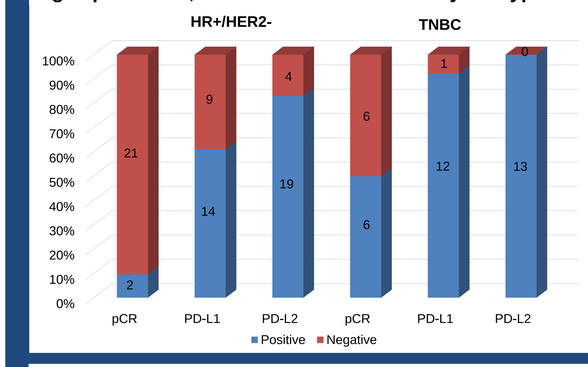
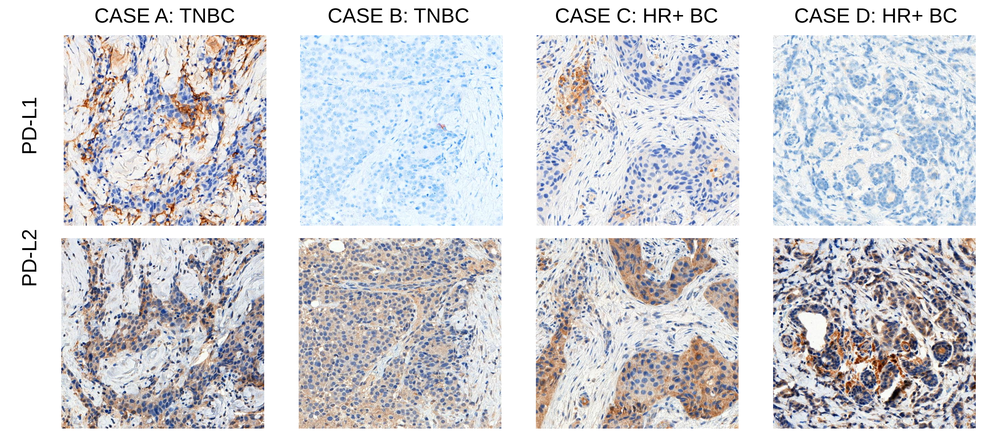


Table 1. Patient characteristics

Characteristics	Overall N= 36	HR+ N= 23	TNBC N=13	P-value
Age				**0.041**
Median (range)	49 (26-70)	45 (26-69)	58 (40-70)	
Race				**0.002**
White	29 (81%)	22 (96%)	7 (54%)	
Black	5 (14%)	0 (0%)	5 (38%)	
Other	2 (5.6%)	1 (4.3%)	1 (7.7%)	
cT size				0.157
T1	5 (14%)	3 (13%)	2 (15%)	
T2	19 (53%)	10 (43%)	9 (69%)	
T3	11 (31%)	9 (39%)	2 (15%)	
Missing*	1 (2.8%)	1 (4.3%)	0 (0%)	
cN				**0.016**
N0	10 (28%)	3 (13%)	7 (54%)	
N1	23 (64%)	18 (78%)	5 (38%)	
N2	1 (2.8%)	1 (4.3%)	0 (0%)	
N3	2 (5.6%)	1 (4.3%)	1 (7.7%)	
PD-L1 status				0.060
Negative	10 (28%)	9 (39%)	1 (7.7%)	
Positive	26 (72%)	14 (61%)	12 (92%)	
PD-L1 in CCs				0.958
Median (range)	0.5 (0-10)	0.5 (0-10)	0.5 (0-10)	
PD-L1 in stroma				**0.003**
Median (range)	5 (0-50)	1 (0-30)	25 (0-50)	
PD-L2 status				0.274
Negative	4 (11%)	4 (17%)	0 (0%)	
Positive	32 (89%)	19 (83%)	13 (100%)	
PD-L2 in CCs				0.427
Median (range)	50 (0-100)	50 (1-95)	50 (01-100)	
PD-L2 in stroma				0.178
Median (range)	8 (0-60)	5 (0-60)	15 (1-60)	

cT=clinical tumor size, cN= clinical nodal stage, *one patient with node+ without primary tumor, CCs= cancer cells

Fig 3. Distinct cellular PD-L1 and PD-L2 expression patterns



RESULTS

- Thirty-six pts were enrolled between June 2020 and January 2025, with 23 HR+/HER2-negative and 13 TNBC pts (5 with 2 doses, 8 with 8 doses).
- Median age and proportion of AA women were higher in the TNBC cohort, while LN+ disease was more common in the HR+ cohort (Table 1).
- More TNBC pts had positive PD-L1 and PD-L2 status (92% and 100%) than HR+ pts. Among HR+ pts, positivity for PD-L2 (83%) was higher than PD-L1 (61%) (Fig 2).
- Of the evaluable 33 pts, the pCR rate was 24% (all grade 3 tumors) in the overall cohort with a significantly higher pCR seen in TNBC compared to HR+/HER2-negative pts [50% (6/12) vs 9.5% (2/21), p=0.007] and no differences seen by doses of cemiplimab in TNBC pts.
- Higher proportion of TNBC pts had complete and partial responses radiographically (25% and 58% respectively) while HR+/HER2- pts had more stable disease (42%).
- Baseline PD-L1 and/or PD-L2 expression was not significantly associated with pCR rates or radiographic responses. Treatment-related adverse events were not higher than expected.

CONCLUSIONS

- Addition of cemiplimab to NACT resulted in 24% pCR rate in the overall cohort with a significantly higher pCR of 50% in TNBC pts. This study incorporated only 2 doses of cemiplimab for HR+ pts which could explain the low pCR rates in this cohort.
- Given the discordance in PD-L1 and PD-L2 expression with a higher prevalence of PD-L2 in HR+ pts, further studies exploring PD-L1/PD-L2 as a combined marker for PD-1i use are warranted. To our knowledge, this is the first clinical trial with PD-L2 status as an eligibility criterion for PD-1i treatment.

ACKNOWLEDGEMENTS

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Reference: 1. JCO Precis Oncol. 2023 Jan:7:e2100498