An Exploratory Clinical Study for Neoadjuvant Treatment of HER2-low Expressing, Stage II-III Breast Cancer with Disitamab Vedotin in Combination with Penpulimab

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Introduction

- HER2-low breast cancer lacks effective targeted options in the curative setting.
- Disitamab vedotin, a novel HER2-targeted antibody-drug conjugate (ADC), and Penpulimab, an anti-PD-1 monoclonal antibody, have both shown promise in different contexts of cancer treatment.

Methods

- We evaluated the efficacy, safety, and exploratory biomarker correlates of neoadjuvant disitamab vedotin (HER2-targeted antibody–drug conjugate) plus penpulimab (PD-1 inhibitor) in stage Ⅱ–Ⅲ disease (NCT05726175).
- The overall design of the study are as follows (Fig 1). The primary end point was pathologic complete response (pCR). Secondary end points included objective response rate (ORR) and safety. Exploratory analyses incorporated multi-omic profiling and integrative modeling to derive predictive biomarkers.

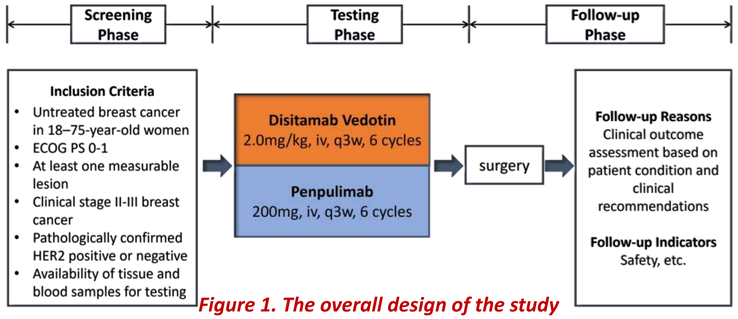


Figure 1. The overall design of the study

Results

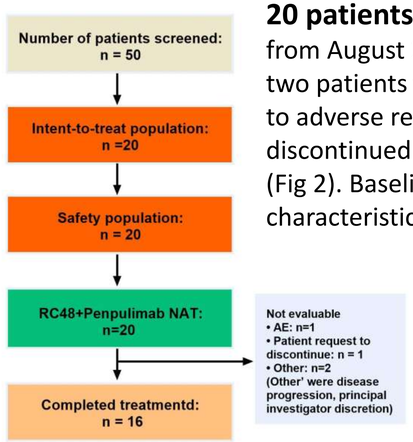


Figure 2. Patient disposition Of 50 screened patients

20 patients were enrolled in the study from August 2023 to August 2024, with two patients withdrawn due to intolerance to adverse reactions and two others discontinued due to disease progression (Fig 2). Baseline demographic and disease characteristics are shown in Table 1.

Table 1. Baseline Patient Characteristics

Patient Characteristic	All ITT Patients (N=20)
Median age, years	43.5 (33, 68)
Female, n (%)	20 (100)
ECOG-PS , n (%)	
0	20(100)
1	0
HER2, n (%)	
IHC 1+	10 (50.0)
IHC 2+/FISH-	10 (50.0)
KI-67 score, n (%)	
≤20%	4 (20.0)
> 20%	16 (80.0)
HR , n (%)	
ER+	18 (90.0)
PR+	17 (85.0)
T stage, n (%)	
T1	2 (10.0)
T2	13(74.5)
T3	1 (5.0)
T4	4 (20.0)
N stage, n (%)	
N0	3 (15.0)
N1	14 (70.0)
N2	3 (15.0)
N3	0
Stage, n (%)	
Ⅱ	13(65.0)
Ⅲ	7(35.0)
PD-L1, n (%)	
CPS≥1	11 (55.0)
CPS<1	9 (45.0)

Safety analysis

- Treatment was generally well tolerated: grade ≥3 events occurred in 25%, with no treatment-related deaths.
- Adverse events considered ADC-related were frequent, led by alopecia 18 (90%), with paresthesia 8 (40%), insomnia 5 (25%), and allergic dermatitis 1 (5%).

Efficacy outcomes

- At the end of the treatment, total pCR (ypT0/is ypN0) rate was 25.0% (4/16). ORR reached 56.3% (9/16) by the clinical response assessment at the end of neoadjuvant treatment (Fig 3). The PD-L1 positive subgroup demonstrated a higher tpCR rate compared to the PD-L1 negative subgroup (33.3% vs. 14.3%). Additionally, the IHC 1+ subgroup exhibited a lower tpCR rate than the IHC 2+ subgroup without amplification by FISH (12.5% vs. 37.5%).

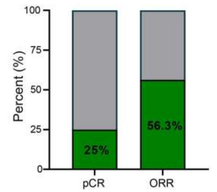


Figure 3. Efficacy Outcomes in the Evaluable Cohort

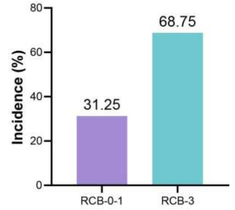


Figure 4. RCB distribution at surgery

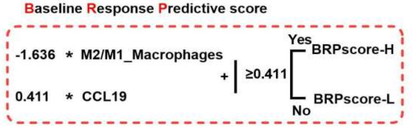


Figure 5. Formula of the BRPscore

Exploratory multi-omics yielded a baseline response prediction model (BRPscore; CCL19 + M2/M1 macrophage ratio) that correctly discriminated all pCR cases with strong discriminatory capacity (AUC 0.89) (Fig 5), and identified MCP-1 as the most consistent biomarker across timepoints(Fig 6)

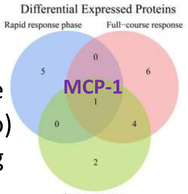


Figure 6. Screening cross-proteins

Conclusions

Neoadjuvant disitamab vedotin plus penpulimab produced a 25% pCR with manageable safety in stage II–III HER2-low breast cancer. The integration of a BRPscore with MCP-1 as a dynamic biomarker provides proof-of-concept for biomarker-driven patient selection and adaptive monitoring, supporting further randomized evaluation of ADC–ICI combinations.

The authors state that they have no conflicts of interest to report concerning publication of this abstract, or authorship.

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