Efficacy and safety of disitamab vedotin combined with pyrotinib as neoadjuvant therapy for HER2-positive breast cancer: a phase II trial

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Abstract

Dual HER2 blockade with chemotherapy achieves responses but has toxicity risks. Disitamab vedotin (RC48), a HER2-targeting ADC, and pyrotinib, a pan-HER TKI, show synergy. This trial tests the first chemo-free neoadjuvant combo in operable or locally advanced HER2+ breast cancer. Patients received RC48 biweekly and daily pyrotinib (cycles 1-4). Post-surgery, they got adjuvant and maintenance therapy based on pCR status. Primary endpoint was pCR; secondary endpoints included OR, EFS, IDFS, and adverse events. At data cutoff (June 25, 2025), 17 evaluable women, mean age 51.9, BMI 21.8, all HR-negative/HER2+. Among 15 who had surgery, pCR was 53.3%; ORR 88.2%. No EFS events or deaths occurred. Hepatic dysfunction was the main grade ≥3 TRAE, lasting median 13 days; no treatments stopped. The study shows a promising chemo-free, effective, and manageable safety regimen, warranting further comparison with standard chemotherapy. Limited follow-up, pending biomarker data, and single-arm design are limitations.

Introduction

- Standard neoadjuvant therapy for HER2-positive breast cancer combines dual HER2 blockade (trastuzumab + pertuzumab) with chemotherapy, resulting in pCR rates of 50-70%, but it also involves significant chemotherapy-related toxicity.
- Disitamab vedotin (RC48) is a novel HER2-targeting antibody-drug conjugate with a cleavable linker and monomethyl auristatin E payload.
- Pyrotinib is an irreversible pan-HER tyrosine kinase inhibitor that blocks compensatory signaling pathways.
- This trial evaluates the first chemo-free neoadjuvant combination of HER2-ADC and TKI in operable or locally advanced HER2-positive breast cancer.

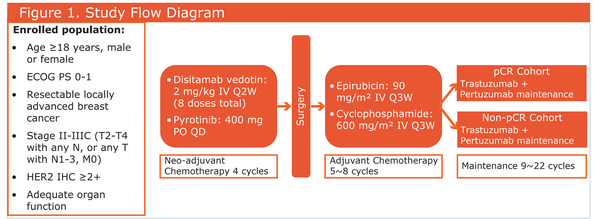
Objective

- To assess the efficacy, safety, and feasibility of disitamab vedotin combined with pyrotinib as neoadjuvant therapy for HER2-positive breast cancer.itive breast cancer.

Methods and Materials

- Multicenter, single-arm, phase II trial
- Primary endpoint: pCR (ypT0/is ypN0)
- Secondary endpoints: ORR, EFS, IDFS, safety
- Statistical analysis: Clopper-Pearson exact method for binary endpoints

Figure 1. Study Flow Diagram



Exclusion Criteria:
History of invasive breast cancer; Stage IV (metastatic) breast cancer, per AJCC 8th Edition; Prior malignancy within 3 years, except resected non-melanoma skin cancer or cured carcinoma in situ; DCIS history, except for those treated with mastectomy over 5 years ago; Any severe or uncontrolled systemic disease, as judged by the investigator, that might contraindicate study participation or affect compliance.

Table 1. Patient and disease characteristics

Characteristics	N=17
Age, mean (range), years	51.9 (29.0-67.0)
BMI, mean (range), kg/m²	21.9 (17.5-30.5)
HER2 IHC, n (%) 2+ 3+	 2 (11.8) 15 (88.2)
ER IHC, n (%) Positive	 0 (0)
PR IHS, n (%) Positive	 0 (0)
HER2-enriched, n (%)	17 (100)

Results

With a median follow-up of 5.2 months (range: 1.9-8.5).

EFFICACY OUTCOMES, n/N, rates (95% CI)

- pCR rate: 8/15, 53.3% (26.6-78.7%) (Table 2)
- ORR: 15/17, 88.2% (63.6-98.5%) (Figure 2, Table 2)
- No EFS events or deaths observed

SAFETY PROFILE (Table 3)

- Most common Grade ≥3 TRAE: Hepatic dysfunction (29.4%, 5/17), median 13 days
- No treatment-related deaths or treatment discontinuations

Figure 2. Waterfall plot of objective response

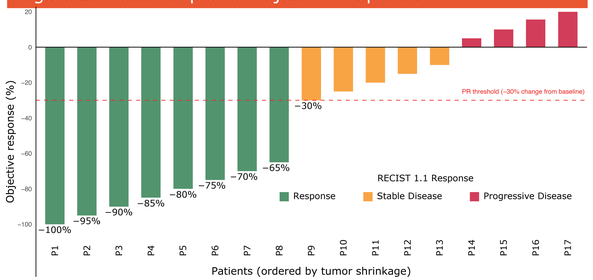


Table 2. Efficacy Outcomes

Outcomes	n/N, % (95% CI)
pCR	8/15, 53.3 (26.6-78.7)
ORR	15/17, 88.2 (63.6-98.5)
Clinical complete response	6/17, 35.3 (14.2-61.7)
Clinical partial response	9/17, 52.9 (27.8-77.0)

Table 3. Treatment Emergent Adverse Events (TEAEs) (N=17)

TEAEs	Any Grade, n (%)	Grade ≥3, n (%)
Hepatic function abnormal	16 (94.1)	5 (29.4)
Hypokalaemia	9 (52.9)	1 (5.9)
Hyperuricaemia	4 (23.5)	0 (0.0)
Blood creatinine increased	4 (23.5)	0 (0.0)
Abdominal pain upper	2 (11.8)	0 (0.0)

Discussion

This phase II trial shows a chemo-free regimen with disitamab vedotin (RC48) and pyrotinib achieving a 53.3% pCR rate in HER2-positive breast cancer, supporting efforts to improve efficacy and reduce chemo toxicities. Our results align with the principle that dual HER2 blockade is effective. Villacampa et al. (2023) reviewed 46 RCTs, recommending dual anti-HER2 therapy with chemo for better pCR than single-agent HER2 blockade. Our study advances this by replacing chemo with targeted agents: an ADC and a TKI for signaling. The 53.3% pCR rate is competitive, especially as it's chemo-free during neoadjuvant therapy. Gunasekara et al. (2022) meta-analysis showed dual HER2 blockade with chemo achieved high pCR, but TKI regimens were also effective. Our chemo-free combo offers targeted therapy. Safety is key; main grade ≥3 adverse event was manageable hepatic dysfunction, unlike traditional chemo. Chen et al. (2019) noted increased diarrhea, rash, and blood toxicities with chemo. Our regimen shifts toxicity to organ effects like hepatotoxicity with ADC/TKI. The 88.2% ORR indicates strong antitumor activity and better outcomes with newer HER2 treatments. Li et al. (2023) confirmed that trastuzumab with or without TKIs improves survival. Our study adds by examining a chemo-free combo in the neoadjuvant setting.

Conclusions

- Disitamab vedotin combined with pyrotinib demonstrates promising efficacy as a chemo-free neoadjuvant regimen in HER2-positive breast cancer, with a pCR rate of 53.3%.
- The combination shows a manageable safety profile, predominantly reversible hepatic toxicity.
- These results support further randomized evaluation against standard chemotherapy-containing regimens.
- This chemo-free approach may represent a new treatment paradigm for HER2-positive breast cancer, potentially reducing chemotherapy-related toxicity while maintaining efficacy.
- The follow-up period remains limited for EFS/IDFS assessment, and another limitation was the single-arm design.

Contact

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