HER3 expression and overall survival (OS) in ICARUS-BREAST01: a phase 2 study of Patritumab Deruxtecan (HER3-DXd) in patients with HR+/HER2- advanced breast cancer

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PLAIN LANGUAGE SUMMARY

What was this study about?

This study examined a new antibody drug conjugate (ADC) called HER3-DXd in patients with advanced breast cancer (ABC) (HR-positive, HER2-negative) whose disease had already progressed after standard treatments (including CDK4/6 inhibitors and chemotherapy).

What did we find ?

The objective response rate (ORR) was 53.5%.The median duration of response (DOR) was 9.3 months, indicating prolonged disease control. The median overall survival (OS) was 27.9 months.

Did HER3 expression matter?

Higher HER3 expression was associated with a trend towards an improved OS (28.8 vs 21.9 months). A trend towards improved PFS was also observed in tumors with higher HER3 expression levels. However, the study was not powered to evaluate whether this difference is statistically significant.

What does this mean?

HER3-DXd shows promising effectiveness in pretreated patients. Higher HER3 levels may be linked to better outcomes and more research is needed to confirm this.

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INTRODUCTION

- The human epidermal growth factor receptor 3 (HER3) is a member of the ErbB family overexpressed in 50%-70% of breast cancers [1]
- HER3 overexpression is linked to poor prognosis[2,8] and has been associated with resistance to PI3K/AKT/mTOR inhibitors and HER2-targeting therapies [3,4]
- HER3-DXd is an ADC containing a human anti- HER3 immunoglobulin G1 monoclonal antibody conjugated via a cleavable peptide linker to an exatecan derivative (topoisomerase-I inhibitor) payload, with a drug to antibody ratio of 8:1. [5,6]
- HER3-DXd has shown encouraging antitumor activity in patients with heavily pretreated ABC, independently of HER3 level expression.[7]
- This trial evaluated safety and efficacy of HER3-DXd in patients with HR+/HER2-negative ABC progressing on CDK4/6 inhibitors and one prior chemotherapy.
- **We reported previously that the study met its primary point with an ORR of 53.5% [90% CI, 44.8;62.1] and median PFS of 9.4 [95%CI, 8.1; 13.4] [5] In light of these results, further analyses have been conducted of which results are reported here.**

METHODS

From May 27th, 2021 to March 9th, 2023, 99 pts received HER3-DXd 5.6 mg/kg IV every 3 weeks until progression or unacceptable toxicity. HER3 staining was centrally performed, using an IHC antibody for HER3 (SP438) (Roche Diagnostics), and scored for % HER3-membrane IHC at 0, 1+, 2+, and 3+. Kaplan-Meier estimations and curves were used to describe OS in the overall population and by HER3 expression level. As of the June 12th 2025 data cutoff, 4 pts were still on treatment. Being a post-hoc analysis, all reported p-values should be considered nominal and interpreted as exploratory.

CURRENT STUDY STATUS

The study is currently enrolling in an expansion cohort of 40 additional patients to further explore the relationship between HER3 expression and clinical outcomes (ORR, PFS).

STUDY DESIGN

ICARUS-BREAST01 (NCT04965766)

- **Phase II academic, multicenter, non-randomized, single-arm study, evaluating efficacy and safety of HER3-DXd in patients with HR+/HER2- ABC, following progressing on a prior CDK4/6 inhibitor and one line chemotherapy in the metastatic setting**

N= 99 patients pathologically confirmed HER2- and HR+ ABC
- Resistant to ET + CDK 4/6 inh (+/- more lines of ET + targeted therapies)
- Prior 1 line of chemotherapy for ABC

→ HER3-DXd 5.6 mg/kg every 3 weeks until progression or unacceptable toxicity

PRIMARY OBJECTIVES: ORR per investigator assessment

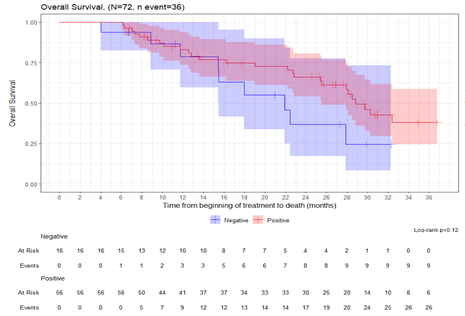
SECONDARY OBJECTIVES: CBR , PFS , DOR , OS Safety

TUMOR AND BLOOD SAMPLES COLLECTION

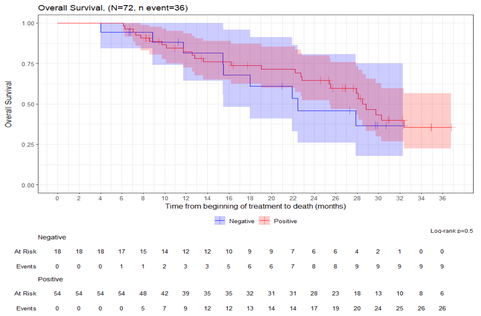
BASELINE	ON-TREATMENT	EOT
Tumor ctDNA, CTC, PBMC	• C1D3 or C1D19: *Tumor, ctDNA, CTC* • Other pre-defined cycles: *PK, ctDNA, CTC, PBMC*	Tumor ctDNA, CTC, PBMC

RESULTS

HER3 Positivity: Membrane 2+/3+ ≥ 50% for HER3



HER3 Positivity: Membrane 1+/2+/3+ ≥ 75% for HER3



❑ **Efficacy results**

- HER3 expression was evaluable in 72 baseline tumor biopsies. Using an IHC 2+/3+ ≥50% cutoff, 56 patients (77.8%) had high HER3 expression (IHC 2+/3+ in ≥50% of tumor cells), while 16 (22.2%) had low expression (<50%). Using an alternative 1+/2+/3+ ≥75% cutoff, 54 patients (75.0%) had high HER3 expression (IHC 1+/2+/3+ in ≥75% of tumor cells) and 18 (25.0%) low (<75%).
- At a median follow-up of 29.6 months [95%CI, 26.8; 32.2], mOS in all patients was 27.9 mos [95%CI, 22.7; 32.4]. Using the cutoff IHC 2+/3+ in ≥50% of tumor cells: mOS was 28.8 mos [95%CI, 25.5; NA] and 21.9 mos [95% CI, 15.5; NA] (p=0.122) in the high and low group, respectively. Similarly, using the cutoff IHC 1+/2+/3+ in ≥75% of tumor cells, mOS was 28.8 [25.4; NA] and 22.4 [15.5; NA] in the high and low group, respectively (p=0.504).

❑ **Safety results**

Grade ≥3 treatment-emergent adverse events occurred in 55 (55.6%) patients; fatigue (89.0%; G3 11.0%), nausea (81.0%; G3 6.0%) and diarrhea (61.0%; G3 3.0%) were the most frequent adverse events reported. Centrally adjudicated (G1-G2) treatment-related interstitial lung disease was reported in 8 pts.

CONCLUSIONS

HER3-DXd demonstrated clinically meaningful and durable antitumor activity, with a median OS of 27.9 months, in heavily pretreated patients with HR+/HER2− advanced breast cancer. These results complement the previously reported ORR and PFS benefit and support the therapeutic potential of HER3-DXd in earlier-line settings, including ongoing studies such as HERTHENA-Breast04.

A trend towards a longer OS was observed in patients with higher HER3 expression, consistent with prior trend seen for PFS. However, the study was underpowered to formally assess the statistical significance of this difference. These findings suggest a potential association between HER3 expression and clinical outcomes, warranting further investigation.

The safety profile remained manageable and consistent with prior reports, with no new safety signals identified, including a low incidence of adjudicated interstitial lung disease.

Overall, these data support HER3-DXd as a promising treatment option in this population and highlight the need for further analyses to better define the predictive role of HER3 expression and to optimize patient selection through biomarker-driven strategies.

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ABBREVIATIONS: CBR: Clinical Benefit Rate, ctDNA: Circulating Tumor DNA, DOCR: Duration of Confirmed Response, DOR: Duration of Response, ILD: Interstitial Lung Disease, PFS: Progression-Free Survival, ORR: Objective Response Rate, OS: Overall Survival

The presenter declares no conflict of interest