ICARUS-BREAST02: A phase Ib/II, Multicenter, Open-label, Modular Study to Explore the Safety, Tolerability, and Activity of Patritumab Deruxtecan (HER3- DXd) Monotherapy and Combinations in Patients with Advanced Breast Cancer (ABC) after Progression on T-DXd

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PLAIN LANGUAGE SUMMARY

Why is this study being conducted ?

HER3 is a protein overexpressed in 50%-70% of breast cancers, playing a significant role in cancer growth, spread, and treatment resistance. Patritumab Deruxtecan (HER3-DXd) is a new antibody-drug conjugate (ADC) combining a HER3-directed antibody with a chemotherapy agent. It has shown promising effects in patients with ABC particularly those who have already been treated with multiple therapies. Since resistance to HER2-directed therapies can be sometimes mediated by HER3, our study aims to evaluate whether HER3-DXd works and is tolerated in patients whose cancers have become resistant to Trastuzumab Deruxtecan (T-DXd).

How is this study being conducted and who are the patients that can participate ?

The ICARUS-BREAST02 study is designed to test HER3-DXd as a single drug or in combination with other cancer treatments in patients with advanced HER2-positive or HER2-low breast cancer who have already been treated with T-DXd. The study currently has two parts:

- ***Module 0:*** *HER3-DXd alone in HER2-low ABC*
- ***Module 1:*** *HER3-DXd in combination with olaparib (a cancer drug shown to enhance HER3-DXd activity in lab studies) in HER2-positive ABC initially, and then both HER2-low and HER2-positive ABC in the later part.*

Patients will receive treatment until their cancer worsens or unacceptable side effects occur. HER3-DXd is given through an IV every three weeks, while olaparib is an oral treatment. This study started in May 2024, with the first patients receiving HER3-DXd alone to assess safety after prior T-DXd exposure, before adding olaparib in another part of the study.
The study main goal is to determine safety and efficacy of HER3-DXd as single agent or in combination after progression on T-DXd. To better understand how HER3-DXd works, blood and tumor samples will be collected at the beginning, during, and after stopping the treatment. Additional treatment combinations may be tested in the future.

STUDY RATIONALE

- HER3, part of the ErbB family, is overexpressed in 50%-70% of breast cancers and contributes to cancer progression and therapy resistance[1-10].
- HER3-DXd is an antibody-drug conjugate 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[11-14].
- HER3-DXd has shown promising activity in patients with heavily pretreated ABC, across different subtypes and a wide range of HER3 expression[15].
- Recently, in ICARUS-BREAST01 phase-2 study, we observed a clinically meaningful activity and manageable safety profile of HER3-DXd in patients with HR+/HER2- ABC progressing after 2 or more lines of therapy, including CDK4/6inh: ORR 53.5% [95%CI, 43.2; 63.6]; mDoR 8.7 months [8.1; 12.5]; mPFS 9.4 months [95%CI 8.1; 13.4][16] .

- Despite T-DXd's efficacy in HER2-positive and HER2-low ABC, strategies post-T-DXd remain undefined.
- **As HER3 expression has been associated with resistance to HER2-directed therapies and that topoisomerase-I inhibitors and PARP-inhibitors showed synergistic efficacy in preclinical models[17,18], ICARUS-BREAST02 study aims to assess the efficacy and safety of HER3-DXd, either as single agent or in combination with olaparib (or other agents) following progression on T-DXd.**

References

1. Papa F et al, Cancer Treat Rev 2024; 2.Jura N, et al, Proc Natl Acad Sci USA 2009; 3.Hynes NE et al, Nat Rev Cancer 2005; 4.Ocana et al, J Natl Cancer Inst 2013; 5.Chandarlapaty S et al, Cancer Cell, 2011; 6. Rodrik-Outmezguine VS et al, Cancer Discov 2011; 7.Chakrabarty A et al, Proc Natl Acad Sci U S A 2012; 8. Huang X et al, Cancer Res 2010; 9.Liu B et al, Int J Cancer 2007; 10. Morrison MM et al, Oncogene 2016; 11.Hashimoto Y, et al. Clin Cancer Res. 2019; 12. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019; 13. OgitaniY, et al. Clin Cancer Res. 2016; 14. KoganemaruS, et al. Mol Cancer Ther. 2019; 15. Krop I et al, JCO 2023, 16. Pistilli B et al, ESMO 2024; 17. Boerner et al, PLoS One 2015; 18. Murai et al, J Pharmacol Exp Ther. 2014

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STUDY DESIGN

ICARUS-BREAST02 (NCT06298084)

- **Phase Ib/II Multicenter, Open-label, Platform Study, currently composed of 2 modules:**
- **Module 0: HER3-DXd as single agent in patients with HER2-low ABC (cohort 2) in the safety run-in (part 1a) and dose-expansion part (part 2)**
- **Module 1: HER3-DXd in combination with olaparib in patients with HER2-positive ABC (cohort 1) in the dose-finding part (part 1b) and in patients with HER2-positive or HER2-low ABC (cohort 1 and cohort 2) in the dose-expansion part (part 2)**

KEY ELIGIBILITY CRITERIA

MAIN INCLUSION CRITERIA:

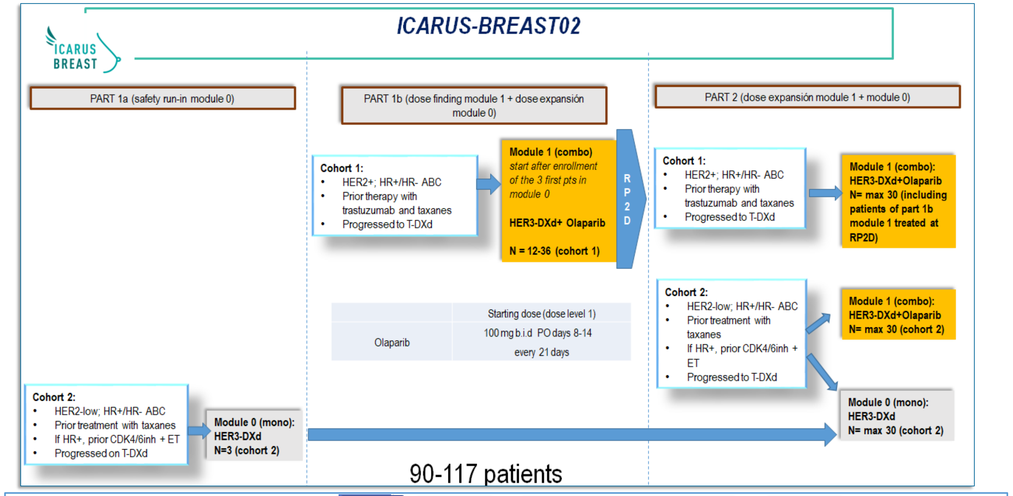
- ❑ All patients must have disease progression while on T-DXd or within 2 months from discontinuation
- ❑ Patients are included in **2 cohorts:**
  - **Cohort 1:** patients with HER2-positive (IHC 3+ or IHC2+/ISH positive), HR+/HR- ABC, must have received prior therapy with trastuzumab and taxanes
  - **Cohort 2:** patients with HER2-low (IHC 2+/ISH negative or IHC 1+), HR+/HR-ABC; patients with HR-positive ABC must have received ET and CDK4/6 inhibitors; may have received prior treatment with Sacituzumab Govitecan
- ❑ Female or male patient aged ≥18 years
- ❑ ECOG PS ≤1
- ❑ Patients must have a tumor site easily accessible to biopsy and must have accepted to perform pre-treatment, on-treatment, and end-of-treatment biopsies
- ❑ Patients must have at least one radiologically measurable lesion (different from the biopsy site) according to RECIST V1.1 criteria

MAIN EXCLUSION CRITERIA:

- ❑ Patients with any history of ILD (including pulmonary fibrosis or radiation pneumonitis), current ILD, or suspected to have ILD as assessed by imaging during screening
- ❑ Spinal cord compression or active brain metastases, patients with clinically inactive or treated brain metastases who are asymptomatic are eligible
- ❑ Patients with leptomeningeal disease
- ❑ Patients with clinically significant corneal disease

CURRENT STUDY STATUS

- Enrollment is terminated in the Safety Run-In part (part 1a) with no dose limiting toxicities (DLT) detected
- The study is currently enrolling in Dose-finding part (part 1b) for module 1 and Dose-expansion part (part 2) for module 0
- **New combination treatment modules could be added, via protocol amendment**



TUMOR AND BLOOD SAMPLE COLLECTION: BASELINE | On-treatment (C1D3/C1D7 for tumor) | EOT

KEY STUDY ENDPOINTS

PRIMARY ENDPOINTS:

- **Part 1a and 1b:** Safety as measured by DLTs, frequency and severity of any AEs, TEAEs, SAEs, AESIs graded by NCI-CTCAE v5.0;
- **Part 2:** Anti-tumor activity of HER3-DXd single agent and combinations as measured by investigator assessed ORR per RECIST 1.1

SECONDARY ENDPOINTS:

- **Part 1a and 1b:** Anti-tumor activity of HER3-DXd single agent and combinations as measured by investigator assessed ORR per RECIST 1.1
- **Part 2:** Safety as measured by DLTs, frequency and severity of any AEs, TEAEs, SAEs, AESIs graded by NCI-CTCAE v5.0

EXPLORATORY ENDPOINTS:

- Mechanism of action of HER3-DXd monotherapy and in combination with olaparib or other agents
- DXd uptake and target antigens modulation
- Modulation of immune tumor microenvironment
- Genomic alterations and gene expression modulation associated with response/resistance

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