Efficacy, Safety, and Biomarker Analysis of ICARUS-BREAST01: A Phase 2 Study of Patritumab Deruxtecan (HER3-DXd) in Patients With HR+/HER2− Advanced Breast Cancer

#82

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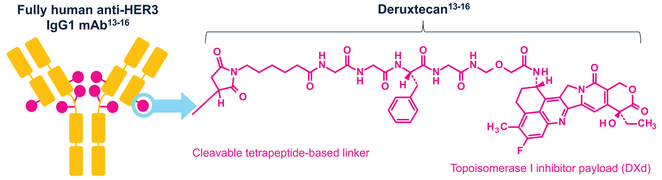
BACKGROUND

- Despite the improved clinical outcomes achieved with endocrine therapy + a CDK4/6 inhibitor in HR+/HER2− advanced breast cancer, effective therapeutic options are limited after disease progression[1-3]
- **High expression of human epidermal growth factor receptor (HER) 3** is associated with **poor prognosis** and plays a key role in **resistance to PI3K/AKT/mTOR inhibitors, HER2-targeting therapies, and endocrine therapy**[4-12]
- **HER3-DXd** is an antibody-drug conjugate composed of an anti-HER3 monoclonal antibody conjugated to a topoisomerase I inhibitor by a cleavable peptide linker[13-16]
- Prior phase 1 and 2 studies showed **promising activity of HER3-DXd** across breast cancer subtypes and across a range of HER3 membrane expression[17-20]



ICARUS-BREAST01: STUDY DESIGN

Multicenter, single-arm, phase 2 study (NCT04965766)

KEY ELIGIBILITY CRITERIA

- Unresectable locally advanced/metastatic BC
- HR+/HER2−[a]
- Progression on CDK4/6 inhibitor + ET
- Progression on 1 prior chemotherapy for ABC
- Prior PI3K/AKT/mTOR inhibitor allowed
- No prior T-DXd

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

Mandatory

- Tumor biopsy (1 frozen + 3 FFPE)
- Blood (whole blood + serum)

Primary endpoint

- Confirmed ORR per investigator

Secondary endpoints

- DOR, PFS, CBR, OS
- Safety and tolerability

Exploratory endpoints

- Predictors of response/resistance
- Dynamics of HER3 expression before and after treatment
- CTC levels during treatment

HER3 expression prescreening (75% of membrane positivity at 10× magnification) was removed by amendment on 21 April 2022[b]

[a] Either IHC 2+ and in situ hybridization negative, or IHC 1+ or IHC 0+. [b] The study was initially designed to include only patients with HER3 membrane expression ≥75% at 10× magnification in tumor biopsies at baseline; however, this inclusion criterion was deleted by amendment on 21 April 2022 after including the first 29 patients, and afterwards recruitment proceeded regardless of HER3 expression. This decision was made because of the lack of a clear correlation between HER3 expression and response in other datasets.

STATISTICAL CONSIDERATIONS AND METHODS

Investigator-initiated, multicenter trial at 11 French sites

Primary endpoint: confirmed ORR according to the investigator

- Evaluation per RECIST version 1.1 every 6 weeks (±7 days) for the first 12 months and then every 12 weeks (±7 days)
- Confirmation of response must be demonstrated with an assessment ≥4 weeks from the initial response

Sample size: 99 patients required to provide 85% power to test the null hypothesis: ORR ≤12% at a 1-sided 5% significance level, assuming that ORR = 23% under the alternative

Data cutoff: 16 April 2024; median follow-up: 15.3 (95% CI, 13.0-17.2) months

This study is sponsored by Gustave Roussy Cancer Center and supported by Daiichi Sankyo

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CONCLUSIONS AND PERSPECTIVES

ICARUS-BREAST01 (NCT04965766)

- HER3-DXd showed clinically meaningful activity and a manageable safety profile in patients with HR+/HER2− ABC who progressed after ≥2 lines of therapy, including a CDK4/6 inhibitor:
  - **ORR, 53.5% (95% CI, 43.2%-63.6%); mDOR, 8.7 (8.1-12.5) months; mPFS, 9.4 (95% CI, 8.1-13.4) months**
- HER3-DXd activity was observed **across a range of tumor HER3 and HER2 membrane expression in tumors by IHC**
- Despite the limitations of the small sample size, exploratory biomarker analysis suggests that:
  - Further evaluation is warranted to determine if the distribution of HER3-DXd in the tumor may play a role in determining a better treatment response
  - Following HER3-DXd treatment, upregulation of genes involved in the immune response, particularly interferon α and γ, was significantly enriched in the entire cohort and among responders

The efficacy and safety profile of HER3-DXd makes this antibody-drug conjugate an optimal candidate for further, larger trials in patients with HR+/HER2− ABC after failure of CDK4/6 inhibitors

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Patients (N=99)			
Age		**HER3 expression[b]**	
Median (range), years	57.0 (48.0-66.0)	Membrane H-score, median (IQR)	180 (144-215)
Sex, n (%)		**Overall membrane positivity at 10× magnification, n (%)**	
Female	99 (100.0)	<25%	16 (16.2)
HR status, n (%)[a]		25%-74%	7 (7.1)
ER+	94 (94.9)	≥75%	49 (49.4)
PgR+	42 (42.4)	Unknown	27 (27.3)
HER2 expression, n (%)[b]		**Median no. of systemic therapies for ABC (range)**	2 (1-4)
IHC 0[c]	39 (39.4)	**Prior treatment with CDK4/6 inhibitor, n (%)**	98 (99.0)[e]
IHC 1+	22 (22.2)	Median duration (range), months	13.7 (6.5-19.7)[f]
IHC 2+	7 (7.1)	**Prior PI3K/AKT/mTOR inhibitor for ABC, n (%)**	35 (35.4)
IHC 3+	1 (1.0)	**Prior chemotherapy for ABC, n (%)[g]**	99 (100.0)
Unknown	30 (30.3)[d]		

High levels of baseline HER3 membrane expression were observed
Most patients had HER2 IHC 0/1+ BC, with <10% of patients reporting IHC ≥2+

[a] As assessed on initial tumor biopsy at diagnosis. [b] Centrally assessed on tumor biopsy at study entry. [c] 20 patients with HER2 membrane staining of 1%-10%. [d] Insufficient tumor sample available. [e] 96 patients had received a CDK4/6 inhibitor for ABC, 2 patients for early breast cancer; 1 patient was enrolled by mistake as they did not receive any prior treatment with a CDK4/6 inhibitor. [f] Assessed in 73 patients. [g] Only 1 line of chemotherapy allowed.

PATIENT DISPOSITION AND TREATMENT EXPOSURE

Patients (N=99)	
HER3-DXd treatment status, n (%)	
Ongoing	19 (19.2)
Discontinued	80 (80.8)
Primary reason for discontinuation, n (%)	
Disease progression	64 (64.6)
Adverse events	8 (8.1)[a]
Other	7 (7.1)
No. of HER3-DXd cycles, median (IQR)	11.0 (6.0-18.0)
Median treatment duration (IQR), days	251.0 (144.5-402.0)
≥1 dose modification, n (%)	
No	67 (67.7)
Yes	32 (32.3)

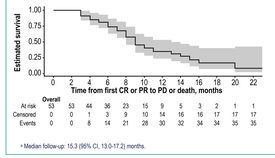
Disease progression was the primary reason for treatment discontinuation

[a] Adjudicated HER3-DXd–related grade 1 ILD (n=2), grade 3 nausea/vomiting (n=2), grade 3 fatigue (n=1), grade 3 thrombocytopenia (n=1), grade 3 hepatic fibrosis (n=1), grade 5 concurrent medical condition, with the last tumor assessment showing PR (n=1).

DURATION OF RESPONSE AND PROGRESSION-FREE SURVIVAL

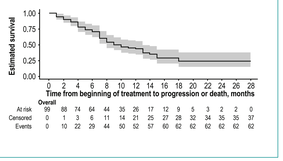
DOR[a]

Median (95% CI): **8.7** (8.1-12.5) months



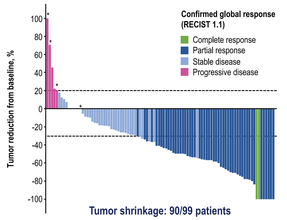
PFS[a]

Median (95% CI): **9.4** (8.1-13.4) months



[a] Median follow-up: 15.3 (95% CI, 13.0-17.2) months.

CONFIRMED OBJECTIVE RESPONSE RATE



Tumor shrinkage: 90/99 patients

	N=99	
	n	% (95% CI)[a]
Confirmed ORR[b]	**53**	**53.5** (43.2-63.6)
CR	2	2.0 (0.2-7.1)
PR	51	51.5 (41.3-61.7)
SD	37	37.4 (27.8-47.7)
PD	7	7.1 (2.9-14.0)
NE[c]	2	2.0 (0.2-7.1)
CBR[d]	**62**	**62.6** (52.3-72.1)

[a] Asterisks represent the appearance of new lesions.
[b] Clopper-Pearson (exact) method was used for CI. [c] Confirmation of response must be demonstrated with a new tumor assessment ≥4 weeks from the initial response. [c] 2 patients were not evaluable for ORR: 1 patient had only 1 tumor assessment with partial response and then treatment discontinued due to clinical progression; a second patient had "not evaluable" as global response of target lesions. [d] CBR was defined as the presence of at least a confirmed partial response or complete response, or stable disease >6 months.

OVERALL SAFETY

Overall safety profile, n (%)	
Any-grade TEAEs	**97 (98.0)**
Grade ≥3 TEAEs	54 (54.5)
Any-grade TRAEs	**97 (98.0)**
Grade ≥3 TRAEs	50 (50.1)
TEAEs leading to HER3-DXd discontinuation	11 (11.1)
TEAEs leading to HER3-DXd interruption	26 (26.3)
TEAEs leading to HER3-DXd dose reduction	20 (20.2)
TEAEs leading to death	1 (1.0)[a]
Adjudicated treatment-related ILD	**7 (7.1)[b]**
Grade 1	7

TRAEs occurring in ≥10% of patients		
	Any grade, n (%)	Grade ≥3, n (%)
Fatigue	82 (82.8)	10 (10.1)
Nausea	74 (74.7)	14 (14.1)
Diarrhea	52 (52.5)	10 (10.1)
Alopecia	40 (40.4)	0
Constipation	21 (21.2)	0
Vomiting	18 (18.2)	3 (3.0)
Anorexia	16 (16.2)	1 (1.0)
Neutrophil count decreased	14 (14.1)	12 (12.1)
Abdominal pain	11 (11.1)	0
Stomatitis	10 (10.1)	0
Anemia	10 (10.1)	0

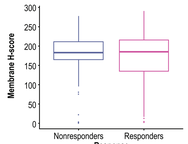
HER3-DXd showed a manageable safety profile, with low rates of TEAEs leading to treatment discontinuation

[a] One patient died of a massive pleural effusion, deemed not related to study treatment. [b] Among the 13 ILD cases identified as suspected during the treatment period, 7 cases were adjudicated as HER3-DXd–related ILD, 2 of which led to treatment discontinuation.

HER3 EXPRESSION AND OUTCOME

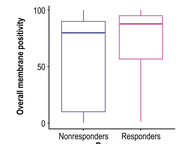
IHC analysis on tumor samples at baseline

HER3 membrane H-score[a]



Nonresponders (SD, PD)	Responders (CR, PR)
Median (IQR); n=34	Median (IQR); n=38
180.0 (165.0-210.0)	185.0 (134.0-215.0)

HER3 membrane positivity at 10× magnification



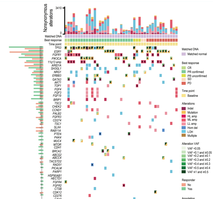
Nonresponders (SD, PD)	Responders (CR, PR)
Median (IQR); n=34	Median (IQR); n=38
80.0 (16.2-90.0)	87.5 (56.2-95.0)

No significant difference was found in HER3 membrane expression between responders and nonresponders (P=0.8 and 0.4 with HER3 H-score and membrane positivity at 10× magnification, respectively)[b]

[a] 72 patients at baseline, 29 of whom enrolled before study amendment. [b] Logistic regression models were performed centrally to estimate the association between ORR and HER3 expression as a continuous or categorical variable.

GENOMIC ALTERATIONS AND TREATMENT RESPONSE

WES on 43 tumor samples at baseline; 73 genes of interest (selected before study initiation)



Gene alterations, n (%)	Responders (CR, PR) n=26	Nonresponders (PD, SD) n=17
TP53	14 (53.8)	5 (29.4)
PIK3CA	10 (38.5)	3 (17.6)
ESR1	6 (23.1)	9 (52.9)
ERBB3	3 (11.5)	1 (5.9)

TP53, *PIK3CA*, and *ERBB3* alterations were more common in HER3-DXd responders
A higher proportion of *ESR1* mutations were observed in nonresponders

Forty-three frozen tumor biopsies at baseline were analyzed for WES; 43 blood samples were used as germline control. Overall, at baseline, 15 fresh biopsies were either not collected or not provided by the participating centers, 26 were excluded due to DNA <200 ng or tumor cells <10%, and 13 failed the quality control. Point mutations and indels were identified with Mutect2 following best practices, while CNAs were called with FACETS.

Acknowledgments

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- We thank all the investigators and study members

Abbreviations

ABC, advanced breast cancer; **AKT**, AKT serine/threonine kinase; **BC**, breast cancer; **C**, cycle; **CBR**, clinical benefit rate; **CDK**, cyclin-dependent kinase; **CNA**, copy number alteration; **CR**, complete response; **CTC**, circulating tumor cell; **D**, day; **DOR**, duration of response; **EOT**, end of treatment; **ER+**, estrogen receptor positive; **ERBB3**, erb-b2 receptor tyrosine kinase 3; **ESR1**, estrogen receptor 1; **ET**, endocrine therapy; **FFPE**, formalin fixed, paraffin embedded; **HER**, human epidermal growth factor receptor; **HL**, high-level; **HR**, hormone receptor; **Ig**, immunoglobulin; **IHC**, immunohistochemistry; **ILD**, interstitial lung disease; **IQR**, interquartile range; **LL**, low-level; **m**, median; **mAb**, monoclonal antibody; **ML**, medium-level; **mTOR**, mechanistic target of rapamycin kinase; **NE**, not evaluable; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PgR+**, progesterone receptor positive; **PI3K**, phosphatidylinositol 3-kinase; **PIK3CA**, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SD**, stable disease; **T-DXd**, trastuzumab deruxtecan; **TEAE**, treatment-emergent adverse event; **TP53**, tumor protein p53; **TRAE**, treatment-related adverse event; **WES**, whole-exome sequencing.

Declaration of Interests

Barbara Pistilli, MD
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