BARCELONA 2024 ESMO congress

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

B. Pistilli[1,15], L. Pierotti[2], M. Lacroix-Triki[3], C. Vicier[4], J.S. Frenel[5], V. D'Hondt[6], F. Dalenc[7], T. Bachelot[8], A. Ducoulombier[9], M.A Benderra[10], D. Loirat[11], D. Mayeur[12], G. Nachabeh[13], A. Sporchia[14], F.Suto[14], S.Michiels[2], N. Corcos[15], F. Mosele[1,16], F. André[1,16,17], G. Montagnac[15]

[1]Department of Medical Oncology, Gustave Roussy, Villejuif, France; [2]Department of Biostatistics and Epidemiology, Gustave Roussy, Villejuif, France; [3]Department of Pathology, Gustave Roussy, Villejuif, France; [4]Department of Medical Oncology, Institut Paoli Calmettes, Marseille, France; [5]Department of Medical Oncology, Institut de Cancerologie de l'Ouest; Saint Herblain, France; [6]Department of Medical Oncology, Institut Régional du Cancer de Montpellier, Montpellier, France; [7]Department of Medical Oncology; Oncopole Claudius Regaud, Toulouse, France; [8]Department of Medical Oncology, Centre Léon Bérard, Lyon, [9]Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France; [10]Department of Medical Oncology, Tenon Hospital, Paris, France; France; [11]Clinical Investigation Unit, Curie Hospital, Paris, France; [12]Department of Medical Oncology, Centre Georges François Leclerc, Dijon, France; [13]Projects and Promotion Division, Gustave Roussy, Villejuif, France; [14]Daiichi Sankyo Inc, NJ, USA; [15]INSERM 1279, Gustave Roussy, Villejuif, France; [16]INSERM U981, Gustave Roussy, Villejuif, France; [17]Université Paris Saclay, Gif Sur Yvette, France

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

ICARUS

DECLARATION OF INTERESTS

Barbara Pistilli, MD

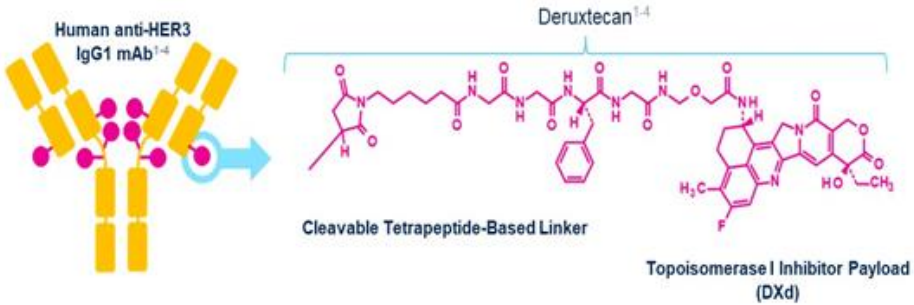
Consulting fees: Astra Zeneca (institutional), Seagen (institutional), Gilead (institutional), Novartis (institutional), Lilly (institutional), MSD (institutional), Pierre Fabre (personal), Daiichi Sankyo (institutional/personal)

Research funding (to my institution): Astra Zeneca, Daiichi Sankyo, Gilead, Seagen, MSD

Travel support: Astra Zeneca; Pierre Fabre; MSD; Daiichi Sankyo, Pfizer

Background

- Despite the improved clinical outcomes achieved with endocrine therapy + CDK4/6 inh in HR+/HER2- advanced breast cancer, effective therapeutic options are limited after disease progression[1-3]
- **High expression of Human Epidermal Growth Factor Receptor-3 (HER3)** is associated with **poor prognosis** and plays a key role in **resistance to PI3K/AKT/mTOR inh, 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 inh by a cleavable peptide linker[13-16]
- Prior phase I and II studies showed **promising activity of HER3-DXd** across breast cancer subtypes and across a range of HER3 membrane expression[17-20]



BARCELONA 2024 ESMO congress

1. Gennari A, et al. *Ann Oncol* 2021;32:1475-1495; 2. Wolff AC, et al. *J Clin Oncol* 2023;41:3867–72;3. Moy B, et al. *J Clin Oncol* 2023;41:1318–20; 4..Jura N, et al, Proc Natl Acad Sci USA 2009, 106:21608-13; 5.Hynes NE et al, Nat Rev Cancer 2005, 5(5): 341-354; 6.Ocana et al, J Natl Cancer Inst 2013, 105:266–273; 7.Chandarlapaty S et al, Cancer Cell, 2011, 19:58-71; 8. Rodrik-Outmezguine VS et al, Cancer Discov 2011, 1:248-59; 9.Chakrabarty A et al, Proc Natl Acad Sci U S A 2012;109: 2718–23; 10. Huang X et al, Cancer Res 2010, 70:1204-14; 11.Liu B et al, Int J Cancer 2007;120:1874-82.; 12. Morrison MM et al, Oncogene (2016) 35, 1143–1152; 13.Hashimoto Y, et al. Clin Cancer Res. 2019;25(23):7151-7161; 14. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185; 15. OgitaniY, et al. Clin Cancer Res. 2016;22(20):5097-5108; 16. KoganemaruS, et al. Mol Cancer Ther. 2019;18(11):2043-2050. 17; Krop I et al, JCO 2023, 18.Hamilton E et al, ASCO 2023.; 19 Oliveira M et al, Ann Oncol 2023; 20. Braso-Maristany et al, Nature Communications 2024

Background

UNLOCK BY GUSTAVE ROUSSY

Ph1/2 translationnal studies

Biopsies timepoints

Mechanisms of action and resistance of innovative drugs
Current portfolio: platform of 10 phase II dedicated trials and 9 phase I trials

ICARUS

Mechanisms of actions and resistance to Dato-DXd and HER3-DXd

Dato-DXd

ICARUS LUNG

ICARUS BREAST

HER3-DXd

ICARUS BREAST01: Study Design

Multi-center, single-arm, phase 2 study (NCT04965766)

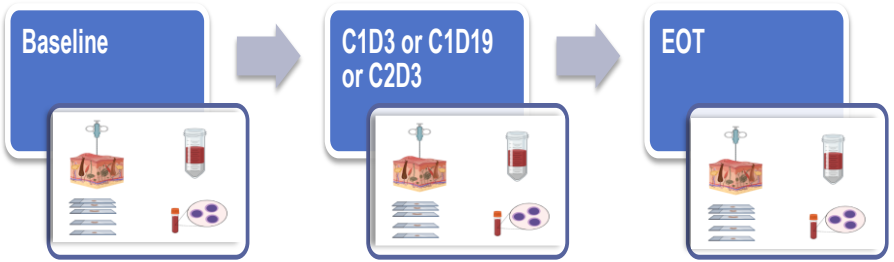
KEY ELIGIBILITY CRITERIA*:
-unresectable locally advanced/metastatic BC
-HR+/HER2-neg[a]
-progression on CDK4/6inh + ET
-progression on 1 prior chemotherapy for ABC
-prior PI3K/AKT/mTORinh allowed
-no prior T-DXd

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

Primary Endpoint:
- Investigator-assessed confirmed ORR

Secondary Endpoints:
- DOR, PFS, CBR, OS
- Safety and tolerability

Mandatory:
-tumor biopsy (1 frozen + 3 FFPE)
-blood (whole blood + serum)



Exploratory Endpoints:
- Predictors of response/resistance
- Dynamics of HER3 expression before and after treatment
- CTCs levels during treatment

***HER3-expression prescreening (75% of membrane positivity at 10x) was removed by amendment on April 21st 2022[b]**

BARCELONA 2024 ESMO congress

a. Either IHC2+ and in situ hybridization [ISH] negative, or IHC1+ or IHC0+; b. The study was initially designed to include only patients with HER3-membrane expression ≥ 75% with 10x in tumor biopsies at baseline, however this inclusion criterion was deleted by amendment on 21st of April, 2022, after including the first 29 patients, and afterwards recruitment proceeded regardless of HER3 expression. This decision was taken because of the lack of a clear correlation between HER3 expression and response in other datasets. ABC: advanced breast cancer; CBR: clinical benefit rate; CTC: circulating tumor cells; DOR: duration of response; ET: endocrine therapy, T-DXd: Trastuzumab deruxtecan; ORR: objective response rate; OS: overall survival; PFS: progression-free survival;

Statistical considerations and methods

Investigator-initiated, multi-center trial in 11 French sites

Primary endpoint: confirmed ORR according to the investigator

Evaluation RECIST (V1.1) every 6 weeks (±7 days) for the first 12 months and then every 12 weeks (±7 days)

Confirmation of response had to be demonstrated with an assessment 4 weeks or later from the initial response

Sample size: ***99 patients required to provide 85% power to test H0: ORR ≤ 12% at a one-sided 5% significance level, assuming ORR = 23% under the alternative***

Data cut-off: Apr 16th, 2024; median follow-up: 15.3 months [95%CI 13.0;17.2]

Demographics and baseline characteristics

PATIENTS N=99

Age	
Median [range], years	57.0 (48.0;66.0)
Sex, n (%)	
Female	99 (100.0)
HR status, n (%)[a]	
ER+	94 (94.9)
PR+	42 (42.4)
HER2 expression, n (%)[b]	
IHC 0*	39 (39.4)
IHC 1+	22 (22.2)
IHC 2+	7 (7.1)
IHC 3+	1 (1.0)
Unknown	30 (30.3)[c]
HER3 expression[b]	
Membrane H-score, median (IQR)	180 (144;215)
Overall membrane positivity at 10x, n (%):	
<25%	16 (16.2)
25-74%	7 (7.1)
≥75%	49 (49.4)
Unknown	27 (27.3)
Median number of systemic therapies for ABC, n [range]	2 [1;4]
Prior treatment with CDK4/6inh, n (%)	98 (99.0)[d]
Median duration, months [range]	13.7 [6.5;19.7][e]
Prior PI3K/AKT/mTOR inh for ABC, n (%)	35 (35.4)
Prior chemotherapy for ABC, n (%)[f]	99 (100.0)

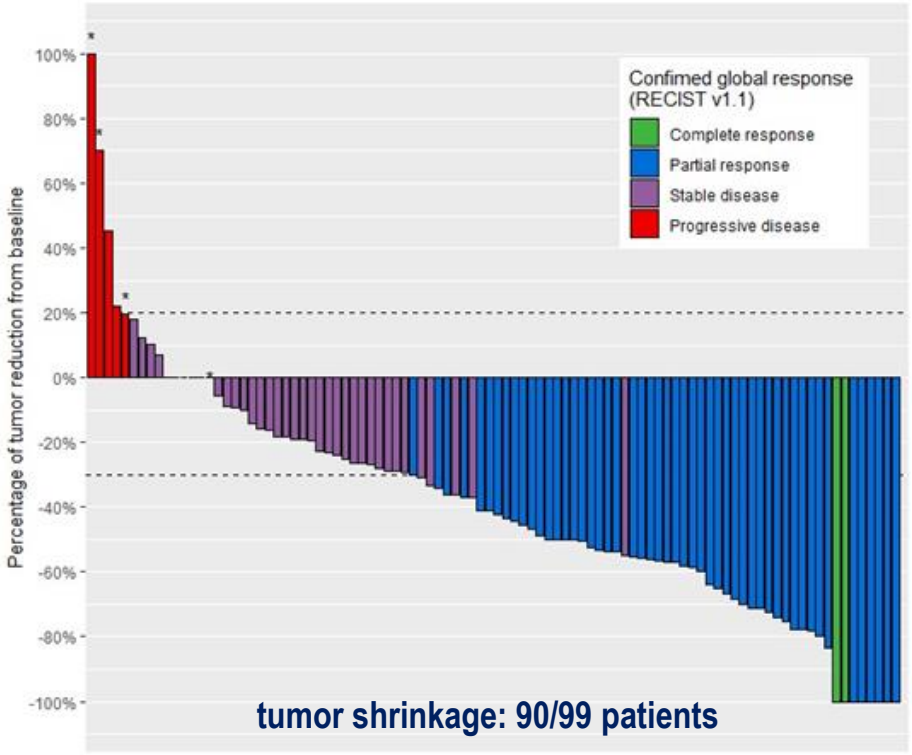
a. As assessed on initial tumor biopsy at diagnosis; b. Centrally assessed on tumor biopsy at study entry; c. Insufficient tumor sample available; d. 96 patients had CDK4/6inh for ABC, 2 patients for early breast cancer; 1 patient was enrolled by mistake as did not receive any prior treatment with CDK4/6inh;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

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)
Number of HER3-DXd cycles, median [IQR]	11.0 [6.0;18.0]
Median treatment duration, days [IQR]	251.0 [144.5;402.0]
At least one dose modification, n (%)	
No	67 (67.7)
Yes	32 (32.3)

a.n=2 adjudicated HER3-DXd-related grade 1 ILD, n=2 grade 3 nausea/vomiting; n=1 grade 3 fatigue; n=1 grade 3 thrombocytopenia, n=1 grade 3 hepatic fibrosis; n=1 patient died from concurrent medical condition, with last tumor assessment showing PR

Confirmed Objective Response Rate



	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]

No significant association between HER2 expression and ORR (*p-value 0.8*)[e]

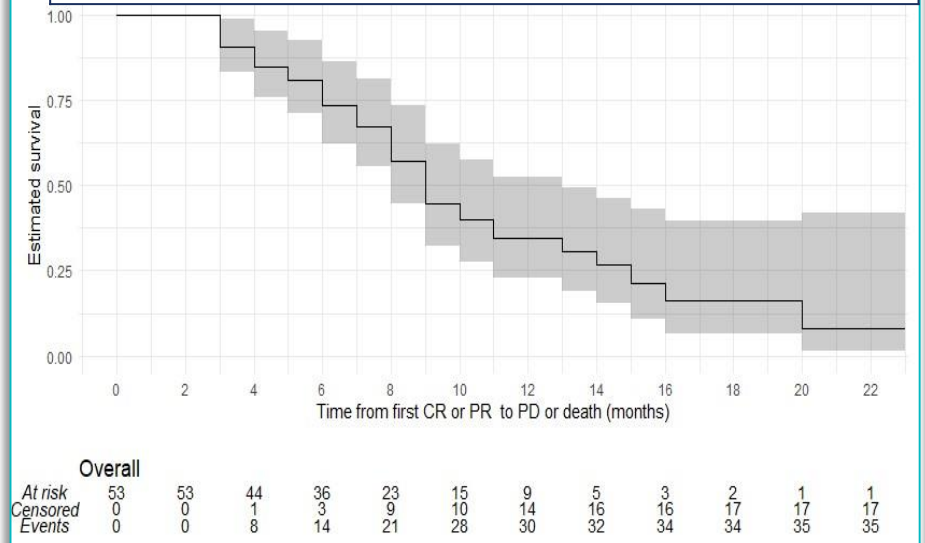
BARCELONA 2024 ESMO congress

a. Clopper-Pearson (Exact) method was used for confidence interval; b. Confirmation of response must be demonstrated with a new tumor assessment 4 weeks or later from the initial response; c. 2 patients were not evaluable for ORR: one patient had only one tumor assessment with PR and then treatment discontinued due to clinical progression, a second patient had not evaluable as global response of target lesions. d. CBR is defined as the presence of at least a confirmed PR or CR, or a stable disease (SD) >6 months; e. logistic regression model was performed to estimate association between HER2 expression and ORR

Duration of Response and Progression-free Survival

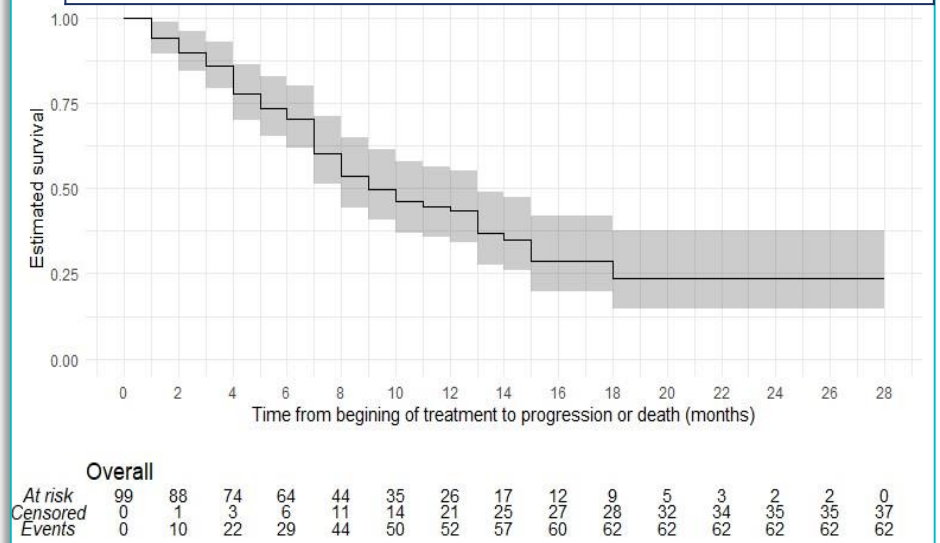
DOR

Median, months [95% CI] **8.7** [8.1; 12.5]



PFS

Median, months [95% CI] **9.4** [8.1; 13.4]



Median follow-up: 15.3 months [95%CI 13.0;17.2]

No significant association between HER2 expression and PFS (*p-value 0.6*)[a]

a. Cox regression model was performed to estimate association between HER2 expression and PFS

Overall safety data

ICARUS BREAST

Overall safety profile, n (%)

• **Patients with any grade TEAEs**	**97 (98.0)**
Grade ≥3 TEAEs	**54 (54.5)**
• **Patients with 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

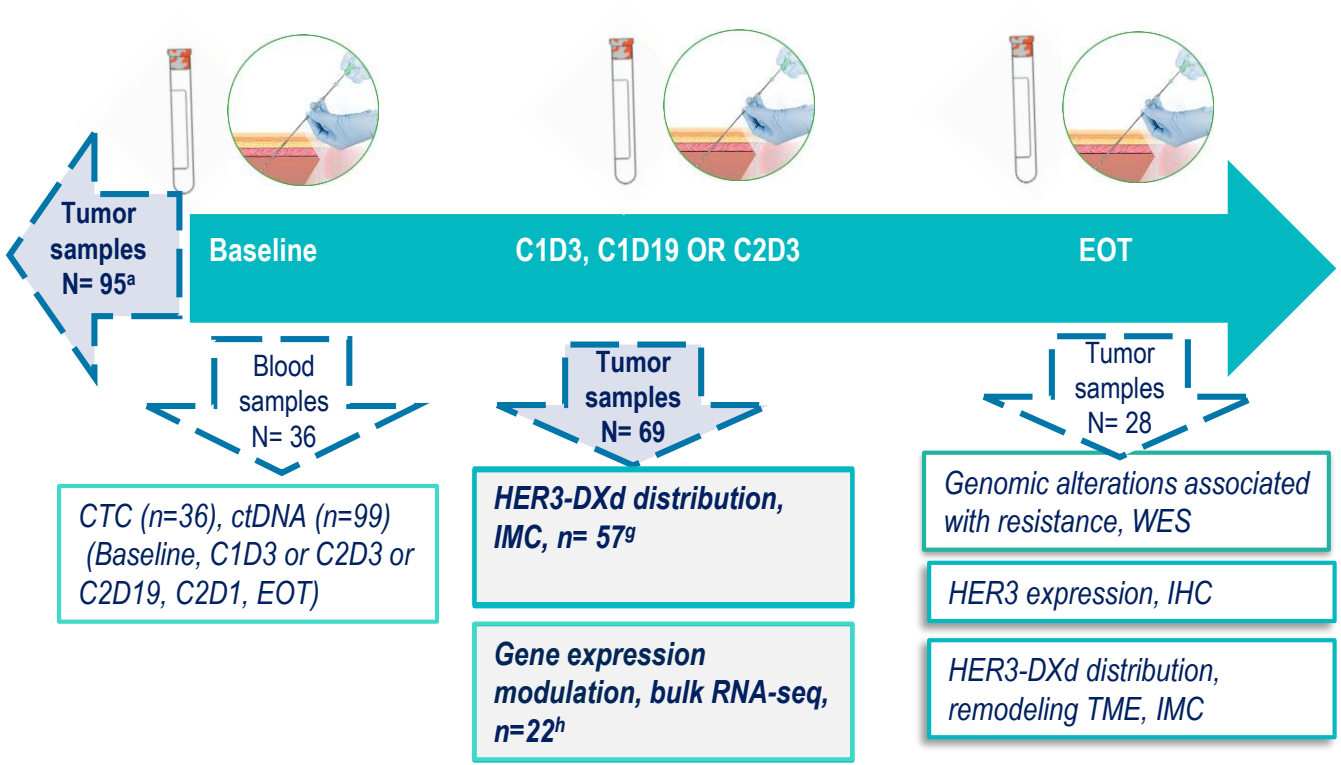
TRAEs occurring in ≥ 10% of patients

	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 decrease	14 (14.1)	12 (12.1)
Abdominal pain	11 (11.1)	0
Stomatitis	10 (10.1)	0
Anemia	10 (10.1)	0

TEAEs: Treatment-Emergent Adverse Events; ILD: Interstitial Lung Disease ; a. one patient died due to a massive pleural effusion not related to study treatment; b.Among the 13 cases identified as suspected during the treatment period, 7 case was adjudicated as HER3-DXd-related ILD, 2 of them led to treatment discontinuation

Exploratory biomarker analysis

- ***HER3 expression by IHC, n=72[b]***
- ***HER3 spatial distribution, ML, n=69[c]***
- ***Genomic alterations associated with response/resistance WES, n= 43[d]***
- ***Gene expression modulation, bulk RNA-seq, n=22[e]***
- ***Characterization of tumor/TME IMC, n=61[f]***

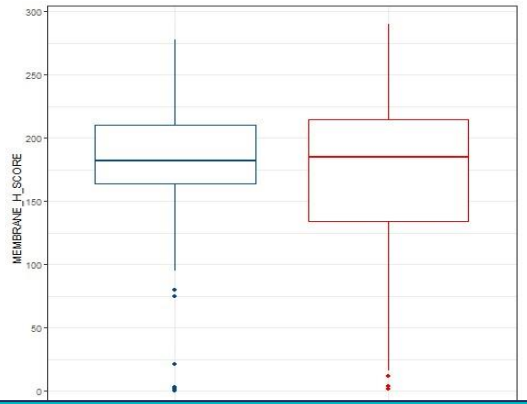


a.4 biopsies not performed/collected; b. 23 samples < 10%; c.25 excluded after pathologist's review; d. 15 fresh biopsies not collected/provided by centers, 28 < 200 ng DNA or < 10% tumor cell; 13 failed quality control; e. 15 fresh biopsies not provided by centers, 28 < 200 ng RNA or < 30% tumor cell, 5 failed quality control, 29 did not have the matched on-T sample; f. 15 fresh biopsies were not provided centers, 28 < 200 ng RNA or < 30% tumor cell, 5 failed the quality control, 29 did not have matched on-T sample; g. 12 samples inadequate staining; h. 22 fresh biopsies not provided by centers, 39 < 200 ng RNA or < 30% tumor cell, 1 sample failed the quality control, 15 did not have matched BL sample;
IHC: Immunohistochemistry, RNAseq: RNA Sequencing, IMC: Imaging Mass Cytometry, WES: Whole Exome Sequencing; ML: machine learning; HER3 IHC: clone SP438

HER3 expression and outcome

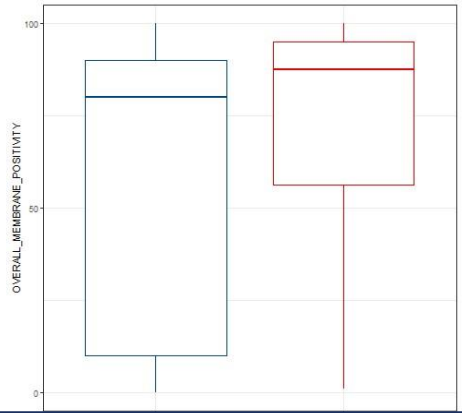
IHC analysis on tumor samples at baseline

HER3 membrane H-score



Non-responders (SD, PD) Median, [IQR]; n=34	Responders (CR,PR) Median, [IQR]. n=38
180.0 [165.0;210.0]	185.0 [134.0; 215.0]

HER3 membrane positivity 10x



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

No significant difference in HER3-membrane expression between responders and non-responders

(*p-value 0.8 and 0.4*, respectively with HER3 H-score and 10x membrane positivity) *

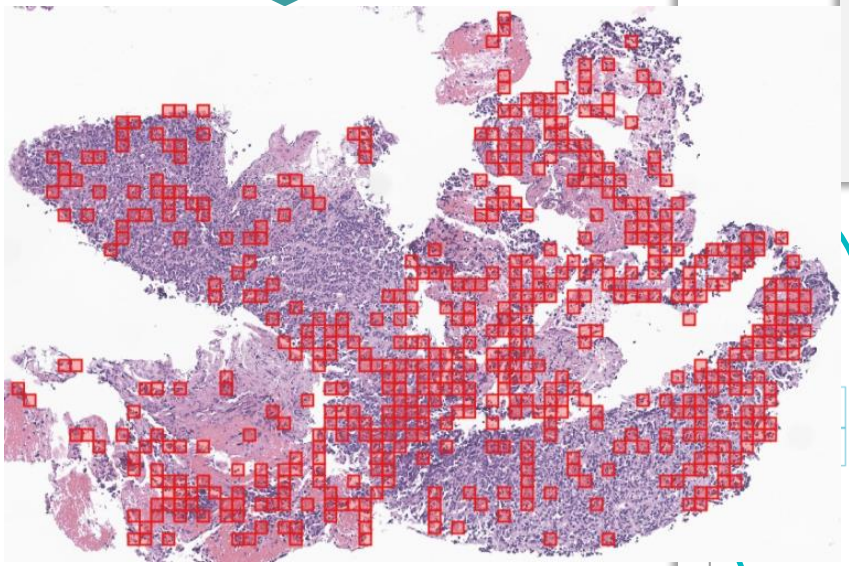
BARCELONA 2024 ESMO

72 patients at baseline, of whom 29 enrollment before study amendment ; *Logistic regression models were used to estimate the association of ORR and HER3 expression as continuous or categorical variable; HER3 assessment made by Roche CDx CAP/CLIA Laboratory (Tucson) using clone SP438

HER3 spatial distribution relative to neighboring cells and outcome

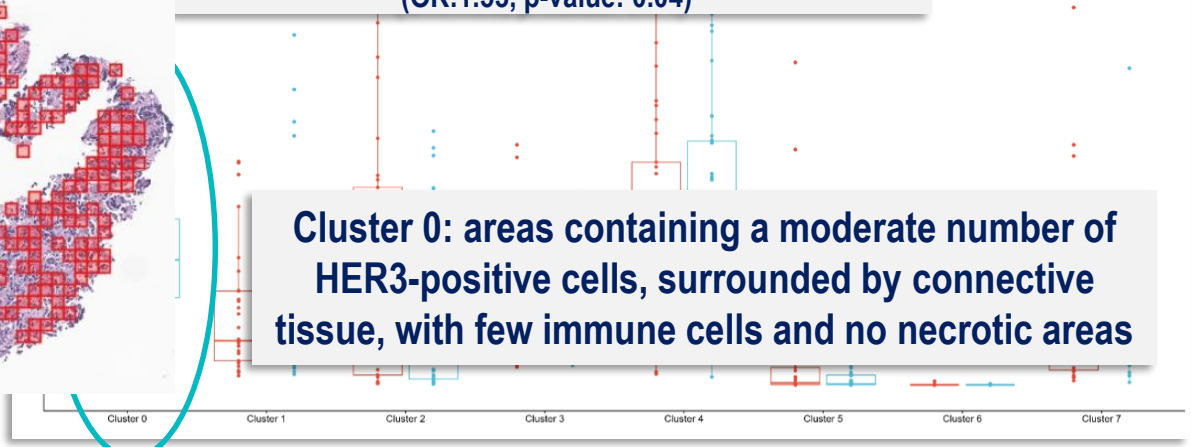
AI-digital pathology analysis on tumor samples at baseline

1. HER3 (DAB) stained slides overlapped with H&E slide



Tumors containing a higher proportion of clusters 0 had a higher likelihood of responding to the treatment

(OR:1.53, p-value: 0.04)*



Cluster 0: areas containing a moderate number of HER3-positive cells, surrounded by connective tissue, with few immune cells and no necrotic areas

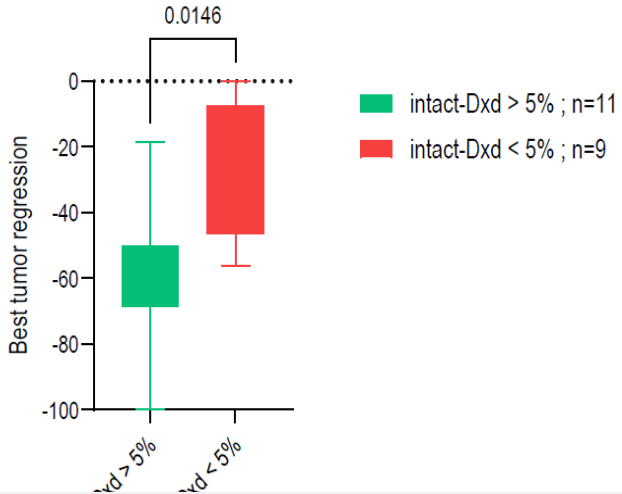
BARCELONA 2024 ESMO congress

*63 samples at baseline, upon pathologist's review and exclusion of samples with non-optimal registration quality control ; . For all these analysis, using R version 4.1.2, we applied Dirichlet regression to identify which clusters were significantly associated with the objective response to treatment, and logistic regression to obtain odds ratios. 1. Hörst F, Rempe M, Heine L, et al. CellViT: Vision Transformers for precise cell segmentation and classification. Medical Image Analysis 2024;94:103143

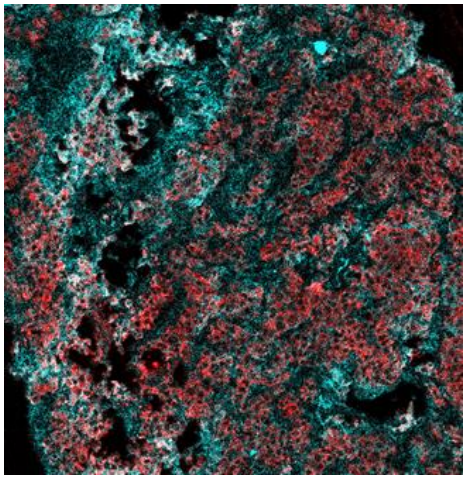
HER3-DXd distribution and treatment response

Imaging Mass Cytometry on tumor samples on-treatment

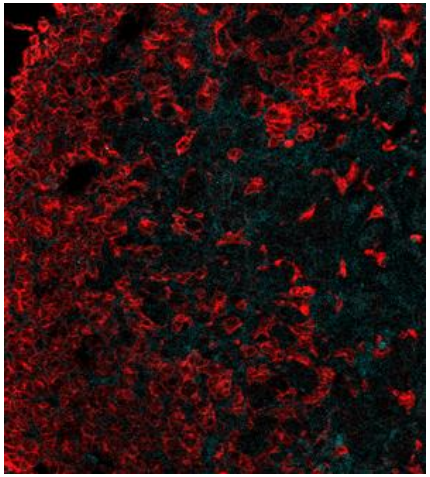
Tumor shrinkage/HER3-DXd-positive cells



HER3-DXd staining > 5% of tumor cells at C1D3; Tumor shrinkage: -52.5%



HER3-DXd staining < 5% of tumor cells at C1D3; Tumor shrinkage: -26.0%



Greater tumor shrinkage in patients with HER3-DXd-positive cells > 5% (n=11) compared to HER3-DXd-positive cells <5% (n=9) at Cycle 1 Day 3 (t-test, *p-value 0.0146*)

Results to be interpreted with cautions due to the small sample size

was 3.75%, likely due to background noise

Genomic alterations and treatment response

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

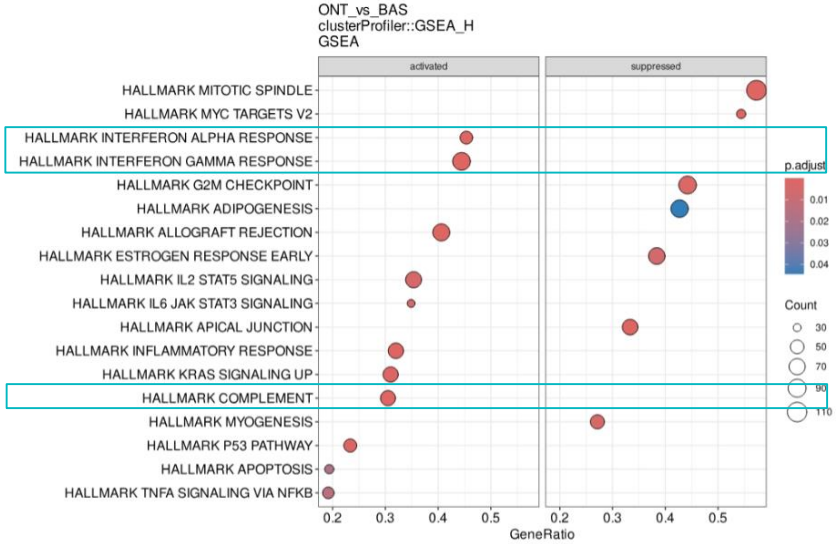
Gene alterations	Responders (CR, PR) n= 26 (%)	Non-responders (PD, SD) n=17 (%)
TP53	14 (53.8)	5 (29.4)
PIK3CA	10 (38.5)	3 (17.6)
ESR1	6 (23.1)	9 (52.9)
ERBB3	3 (11.5)	1 (5.9)

43 frozen tumor biopsies at baseline were analyzed for WES. Forty-three blood samples were used as germline control. Overall, at baseline, 15 fresh biopsies were either not collected or not provided by the participating centers, 28 were excluded due to < 200 ng DNA or < 10% tumor cell and 13 failed the quality control. Point muts. and indels were identified with Mutect2 following best practices while CNAs were called with FACETS.

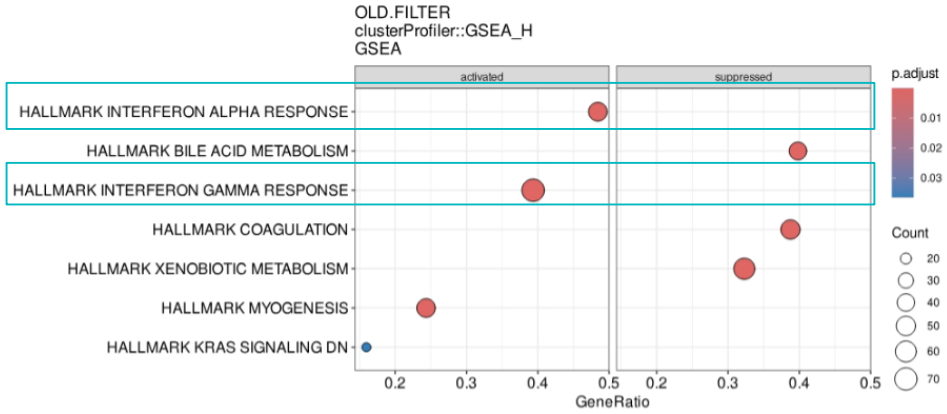
Gene expression modulation by HER3-DXd

- **22 pairs of baseline/on-treatment biopsies from <u>all analyzable samples</u>**
- Gene Set Enrichment Analysis (GSEA) using the Gene Sets “Hallmarks”*

Regardless of treatment response (n=22)



Responders (n=14)



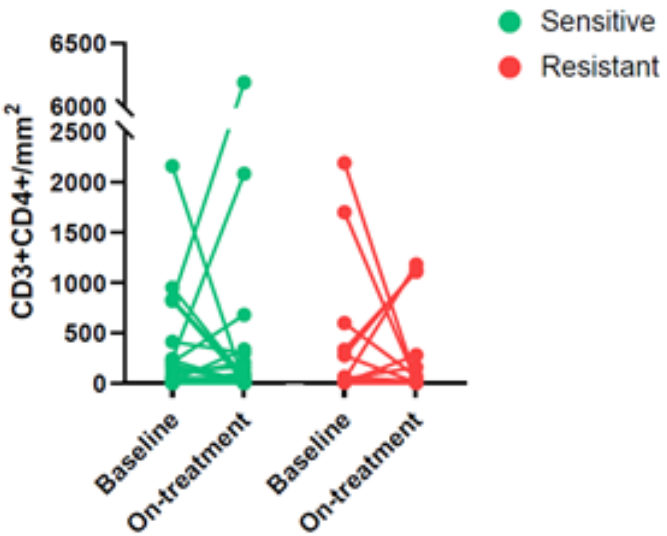
Up-regulation of pathways involved in immune response, interferon alpha and gamma and complement signaling, enriched in the whole cohort and in responders (*adj p-value ≤0.05*)

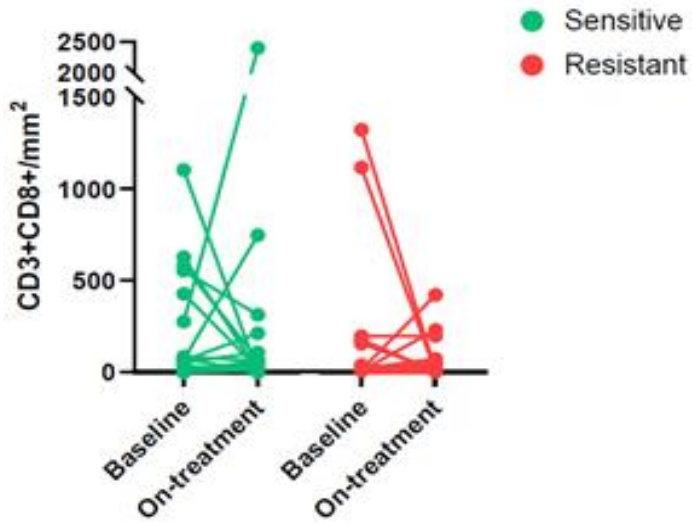
BARCELONA 2024 ESMO congress

At baseline, 15 fresh biopsies not provided by centers, 28 were excluded due to < 200 ng RNA or < 30% tumor cell, 5 failed the quality control, 29 did not have the matched on-T sample. On-treatment (n=12 at C1D3, n=4 at C1D19, n=6 at C2D3), 22 fresh biopsies not provided by centers, 39 were excluded due to < 200 ng RNA or < 30% tumor cell, 1 sample failed the quality control, and 15 did not have the matched BL sample; ”P_Value_Adj” by Benjamini-Hochberg method

Immune-modulation of TME

Imaging Mass Cytometry on tumor samples at baseline and on-treatment





IMC analysis on paired tumor samples at baseline and on-treatment showed a notable T-cell expansion and activation (increase of CD4+, CD8+, CD8+GzmB+ and CD8+CD107a+) at C1D3 in two patients who responded to the treatment

Conclusion and perspectives

- HER3-DXd showed clinically meaningful activity and manageable safety profile 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 [8.1; 12.5]; mPFS 9.4 mos [95%CI 8.1; 13.4]

- Activity of HER3-DXd was observed **across a range of tumor HER3 and HER2 membrane expression by IHC**

- Although with the limitations of the small sample size, exploratory biomarker analysis suggest that:
  -distribution of HER3-DXd in the tumor may play a role in determining a better treatment response
  -up-regulation of genes involved in immune response, particularly interferon alpha and gamma were significantly enriched in the entire cohort and among responders

- **Efficacy and safety profile of HER3-DXd make this ADC an optimal candidate for further larger trials in patients with HR+/HER2- ABC after failure of CDK4/6 inhibitors**

Acknowledgements

- We thank the patients who participated in the study, their families and caregivers
- We thank all the investigators and study members
- This study is sponsored by Gustave Roussy Cancer Center and supported by Daiichi-Sankyo

BARCELONA 2024 ESMO congress

barbara.pistilli@gustaveroussy.fr

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org