ASCO 2023/ESMO BC 2023 Presentation Materials (vol.2)

ENHERTU®

- **DESTINY-PanTumor02**
  - Meric-Bernstam, FM. et al., ASCO 2023 #3000 Oral
- **HERALD/EPOC1806 study**
  - Taniguchi et al., ASCO 2023, #3014 Poster

Dato-DXd

- **TROPION-Lung02**
  - Goto, Y. et al., ASCO 2023 #9004 Oral

HER3-DXd

- **BRE-354 study**
  - Hamilton, E. et al., ASCO 2023 #1004 Oral
- **ICARUS-Breast01 study**
  - Pistilli et al., ESMO Breast 2023, #189O Oral
- **SOLTI TOT-HER3 study**
  - Oliveira et al. ESMO Breast 2023 #124O Oral
  - Brasó-Maristany et al. ESMO Breast 2023 #3MO Oral
  - Oliveira et al. ESMO Breast 2023 #155TiP Poster

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

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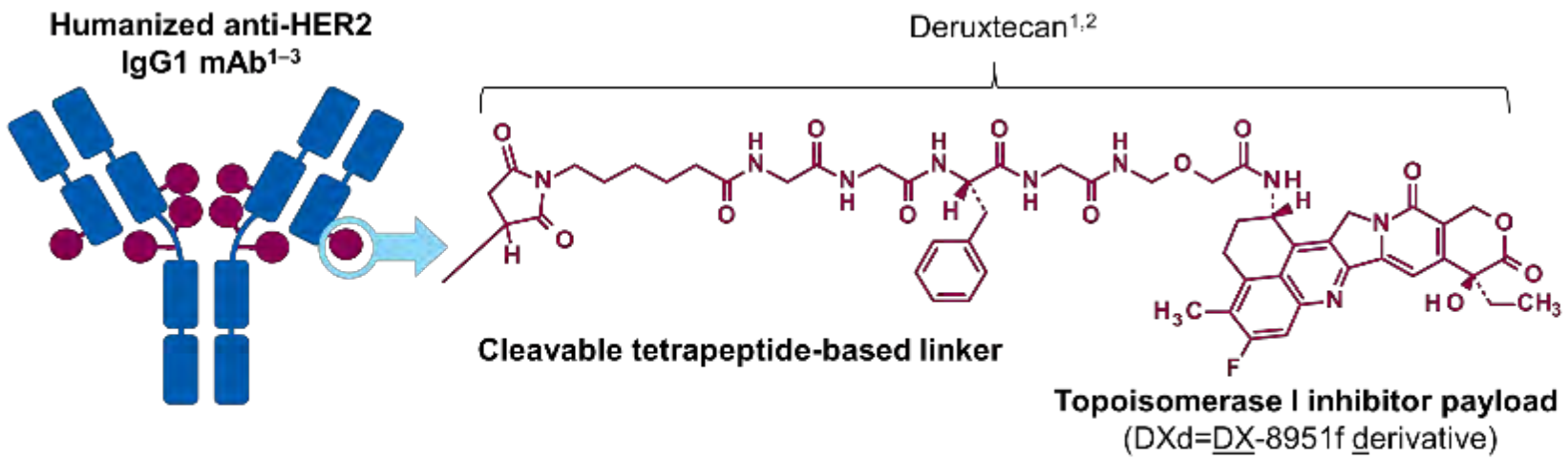
Trastuzumab Deruxtecan (T-DXd) was Designed with Seven Key Attributes

Daiichi-Sankyo

T-DXd is an ADC with three components:

1. A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
2. A topoisomerase I inhibitor payload, an exatecan derivative
3. A tetrapeptide-based cleavable linker



Seven Key Attributes[a,1–5]
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug-to-antibody ratio ≈8
Payload with short systemic half-life
Stable linker payload
Tumor-selective cleavable linker
Bystander antitumor effect

[a]The clinical relevance of these features is under investigation.

ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.
1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173–185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097–5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126–142.
4. Okamoto H, et al. *Xenobiotica*. 2020;50(10):1242–1250. 5. Nagai Y, et al. *Xenobiotica*. 2019;49(9):1086–1096.

Unmet Need in HER2-Expressing Tumors

- T-DXd has become a standard of care in HER2-expressing unresectable/metastatic breast cancer, HER2-positive locally advanced/metastatic gastric/GEJ cancer and HER2 (*ERBB2*)-mutant unresectable/metastatic NSCLC[1–4]
- Although testing is not routine, HER2 expression (IHC 3+ or IHC 2+) is seen in a wide range of other solid tumors and is associated with a biologically aggressive phenotype[5,6]
  - For HER2-expressing tumors without approved HER2-targeted treatments, there is an unmet need for effective therapies, particularly for patients with disease refractory to standard-of-care therapies
- In early-phase studies, T-DXd has demonstrated antitumor activity in other HER2-expressing malignancies, including colorectal, salivary gland, biliary tract, and endometrial cancers[7,8]

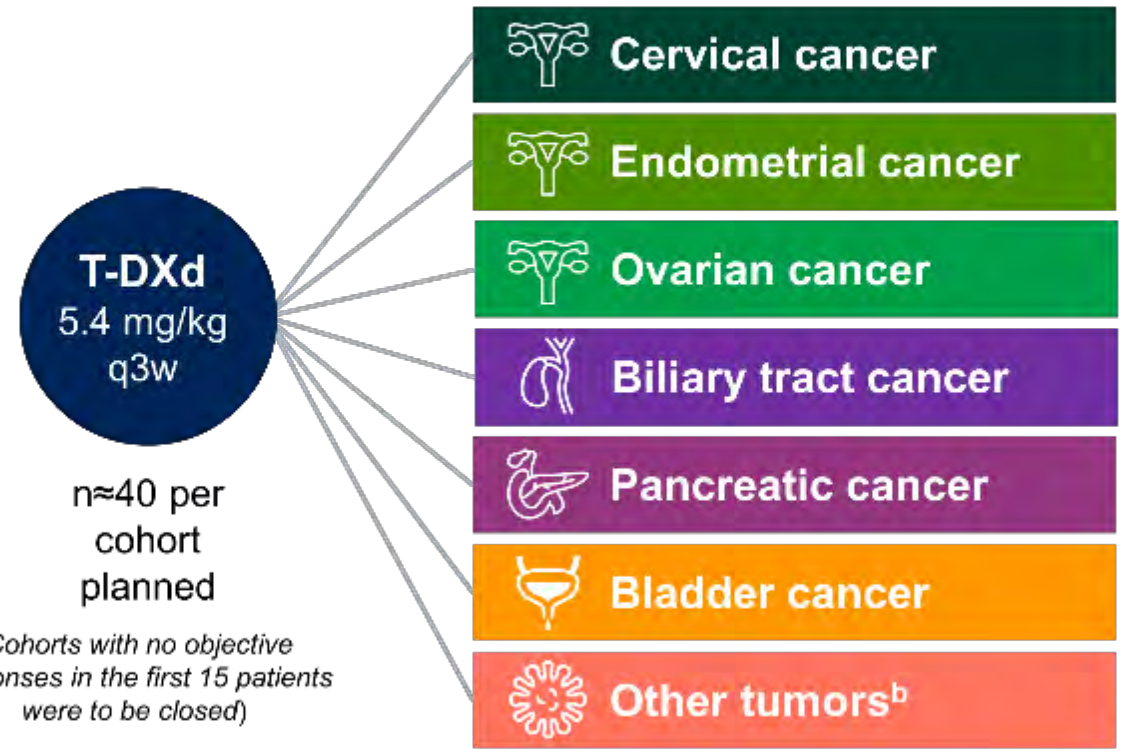
GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

1. ENHERTU® (fam-trastuzumab deruxtecan-nxki). Prescribing information. Daiichi Sankyo, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s024lbl.pdf. Accessed March 13, 2023.
2. Shah MA, et al. *J Clin Oncol.* 2023;41(7):1470–1491. 3. Giordano SH, et al. J *Clin Oncol.* 2022;40(23):2612–2635. 4. Jaiyesimi IA, et al. *J Clin Oncol.* 2023;41(11):e21–e30.
5. Yan M, et al. *Cancer Metastasis Rev.* 2015;34(1):157–164. 6. Li Z, et al. *EBioMedicine.* 2020;62:103074. 7. Yoshino T, et al. Presented at ASCO GI 2022; January 20–22, 2022 [abstract 119].
8. Tsurutami J, et al. *Cancer Discov* 2020;10(5):688–701.

DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Herceptest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



n≈40 per cohort planned

(*Cohorts with no objective responses in the first 15 patients were to be closed*)

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. [c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.

2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. *Histopathology* 2008;52(7):797–805.

Patient Disposition

	Cervical	Endometrial	Ovarian	BTC	Pancreatic	Bladder	Other[a]	All patients
Patients treated, n	40	40	40	41	25	41	40	267
Ongoing treatment at DCO, n (%)	**10 (25.0)**	**14 (35.0)**	**6 (15.0)**	**3 (7.3)**	**1 (4.0)**	**5 (12.2)**	**5 (12.5)**	**44 (16.5)**
Discontinued treatment, n (%)	30 (75.0)	26 (65.0)	34 (85.0)	38 (92.7)	24 (96.0)	36 (87.8)	35 (87.5)	223 (83.5)
Disease progression	21 (52.5)	18 (45.0)	29 (72.5)	22 (53.7)	17 (68.0)	26 (63.4)	23 (57.5)	156 (58.4)
Adverse event	4 (10.0)	2 (5.0)	3 (7.5)	8 (19.5)	3 (12.0)	4 (9.8)	6 (15.0)	30 (11.2)
Other[b]	5 (12.5)	6 (15.0)	2 (5.0)	8 (19.5)	4 (16.0)	6 (14.6)	6 (15.0)	37 (13.9)
Median follow up at DCO, months (range)	7.2 (0.9–23.0)	14.6 (0.8–24.2)	12.7 (0.7–23.7)	6.0 (0.7–20.0)	4.9 (1.1–19.8)	12.0 (0.4–21.2)	12.0 (0.7–23.9)	9.7 (0.4–24.2)
Median duration of treatment at DCO, months (range)	5.5 (0.7–19.8)	9.0 (0.7–24.4)	5.9 (0.7–23.0)	3.5 (0.7–20.1)	2.1 (0.7–11.0)	6.2 (0.4–18.0)	6.9 (0.7–19.9)	5.5 (0.4–24.4)

[a]Includes salivary gland cancer (n=19), malignant neoplasm of unknown primary site (n=5), extramammary Paget's disease (n=3), melanoma (n=2), oropharyngeal neoplasm (n=2), adenoid cystic carcinoma, adenocarcinoid tumor of the appendix, head and neck, intestinal adenocarcinoma, lip and/or oral cavity, oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, testis and vulva (all n=1).
[b]Includes patients who were lost to follow-up (n=1) and patients who discontinued for unknown reasons (n=3), patient decision (n=10), investigator decision (n=5), and other reasons (n=22; n=16 of which died while on treatment).
BTC, biliary tract cancer; DCO, data cut-off (Nov 16, 2022).

Baseline Characteristics

Characteristic			All patients (N=267)
Age, median (range), years			62 (23–85)
Female, n (%)			178 (66.7)
Race, n (%)	White		163 (61.0)
	Asian		87 (32.6)
	Other		6 (2.25)
	Not reported		5 (1.9)
Prior lines of therapy	Median (range)		2 (0–13)
	n (%)	0	3 (1.1)
		1	70 (26.2)
		2	84 (31.5)
		≥3	107 (40.1)
		Unknown	3 (1.1)
Prior HER2 therapy, n (%)	Monoclonal antibody		34 (12.7)
	Tyrosine kinase inhibitor		1 (0.4)
ECOG PS, n (%)	0		127 (47.6)
	1		139 (52.1)
	2		1 (0.4)

		All patients (N=267)
HER2 testing for eligibility, n (%)[a]	Local	205 (76.8)
	Central	61 (22.8)
	Unknown[b]	1 (0.4)
HER2-expression for eligibility, n (%)[a]	IHC 3+	108 (40.4)
	IHC 2+	153 (57.3)
	IHC 1+[c]	5 (1.9)
	Unknown[b]	1 (0.4)
Centrally confirmed HER2 status for efficacy evaluation, n (%)	IHC 3+	75 (28.1)
	IHC 2+	125 (46.8)
	IHC 1+	25 (9.4)
	IHC 0	30 (11.2)
	Unknown[d]	12 (4.5)

[a]HER2 expression for eligibility was based on local assessment, based on any HER2 test, where available. [b]Patient had missing IHC status (pancreatic cancer cohort) at data cut-off but was confirmed IHC3+ by local testing post-data cut-off.
[c]In the cervical cohort, 5 patients with IHC 1+ status were included per protocol. [d]Includes patients whose samples were not evaluable and may have included patients who did not provide a sample for central testing.
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

Efficacy endpoints: ORR, DCR and DOR

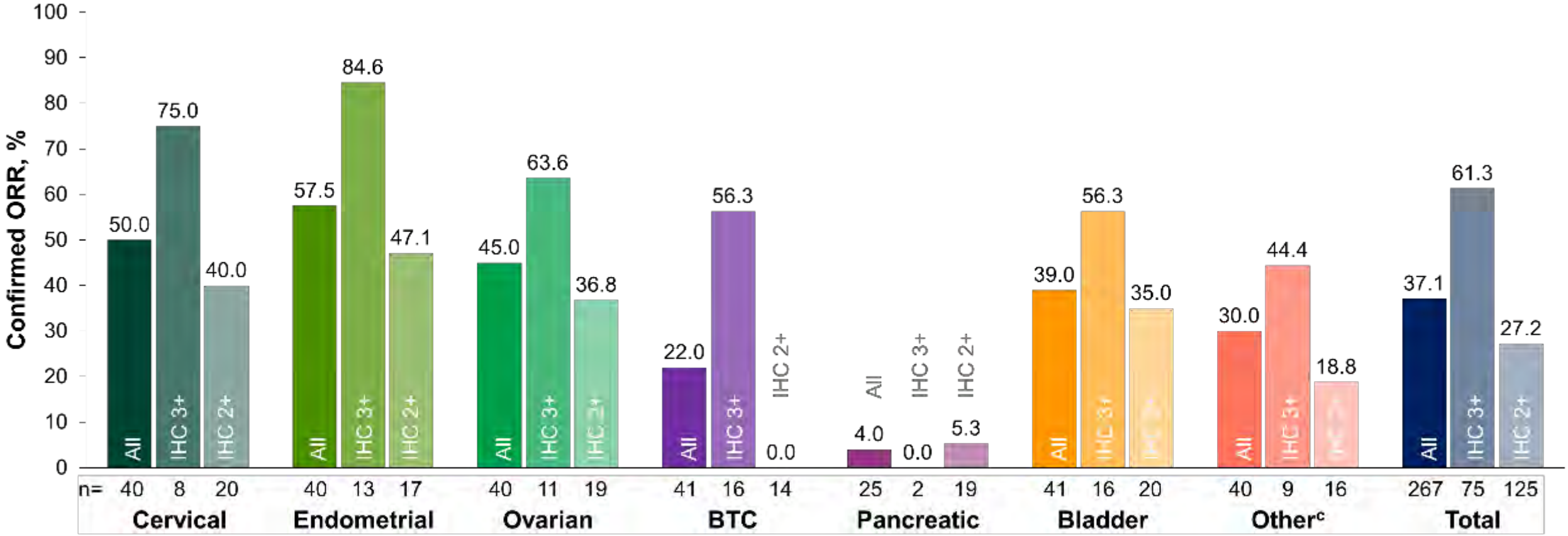
		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**	**9 (22.0)**	**1 (4.0)**	**16 (39.0)**	**12 (30.0)**	**99 (37.1)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)	25 (61.0)	17 (68.0)	18 (43.9)	24 (60.0)	123 (46.1)
	PD	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).

[a]Confirmed complete response, confirmed partial response or stable disease.

BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease.

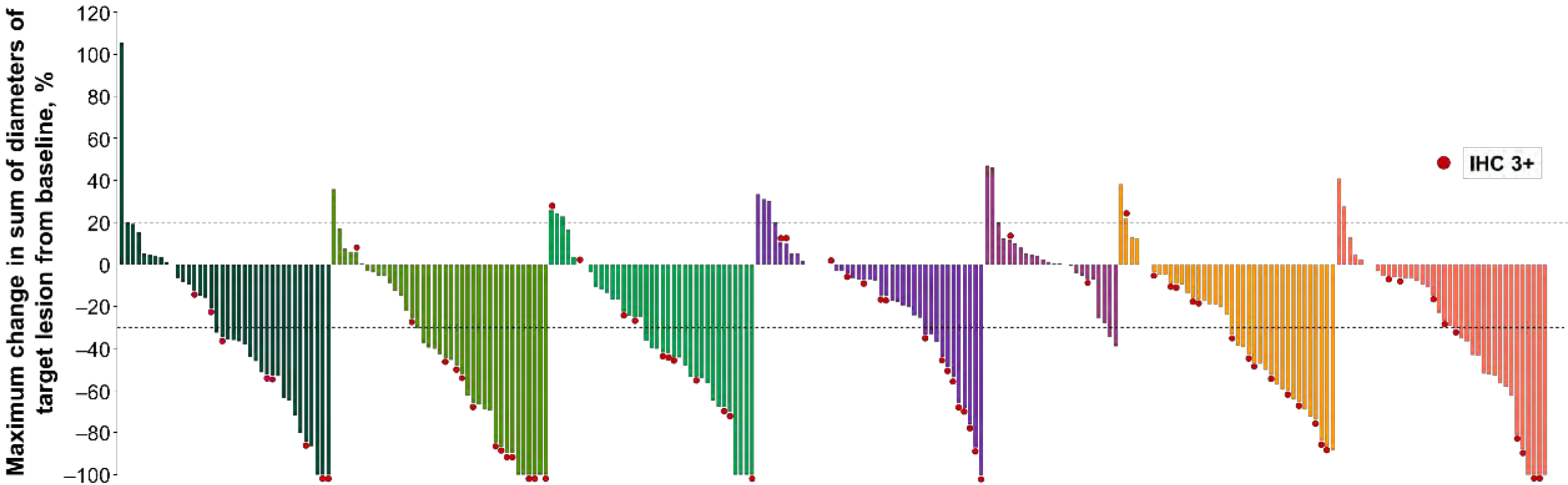
Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

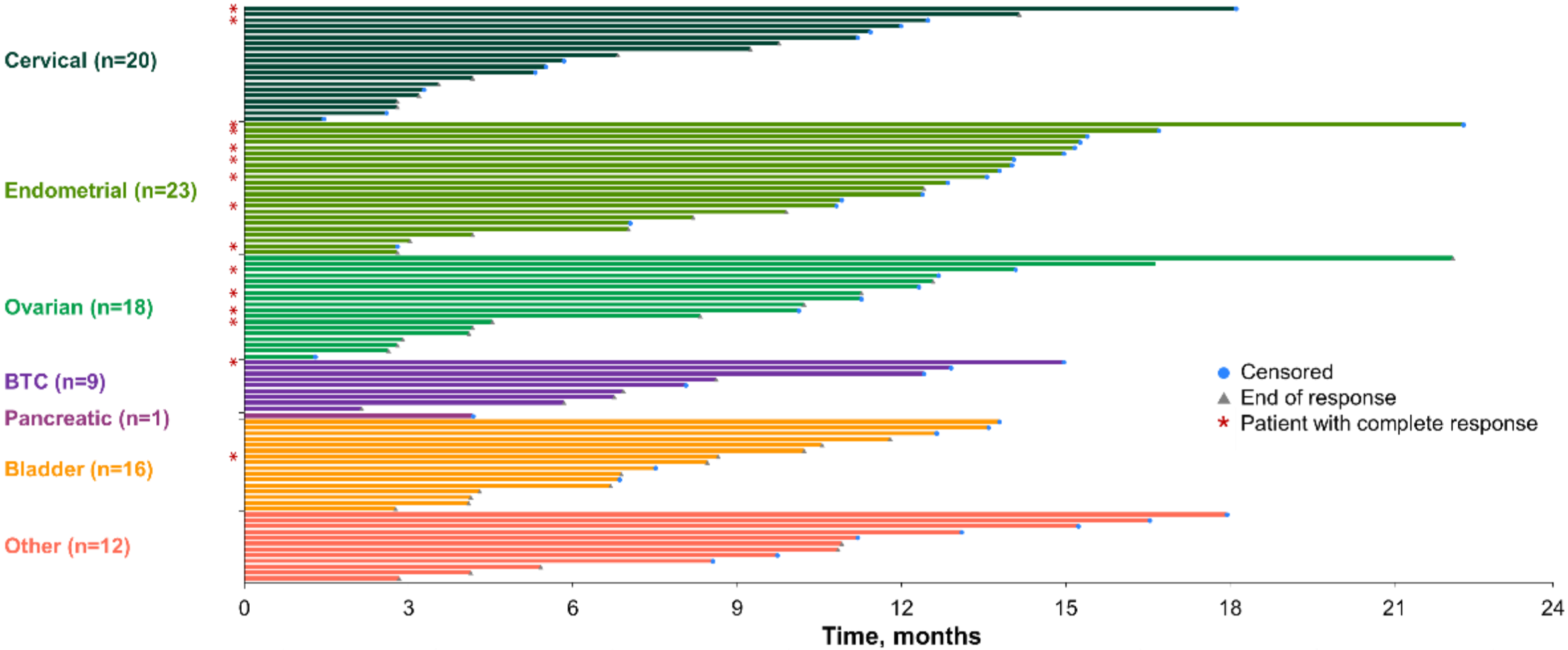
Best Percentage Change in Target Lesion From Baseline



ORR in IHC 3+	Cervical (n=8)	Endometrial (n=13)	Ovarian (n=11)	BTC (n=16)	Pancreatic (n=2)	Bladder (n=16)	Other[a] (n=9)
n (%)	6 (75.0)	11 (84.6)	7 (63.6)	9 (56.3)	0	9 (56.3)	4 (44.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of ORR in IHC 3+ was performed in patients with centrally confirmed HER2 status (n=75).
[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; IHC, immunohistochemistry; ORR, objective response rate.

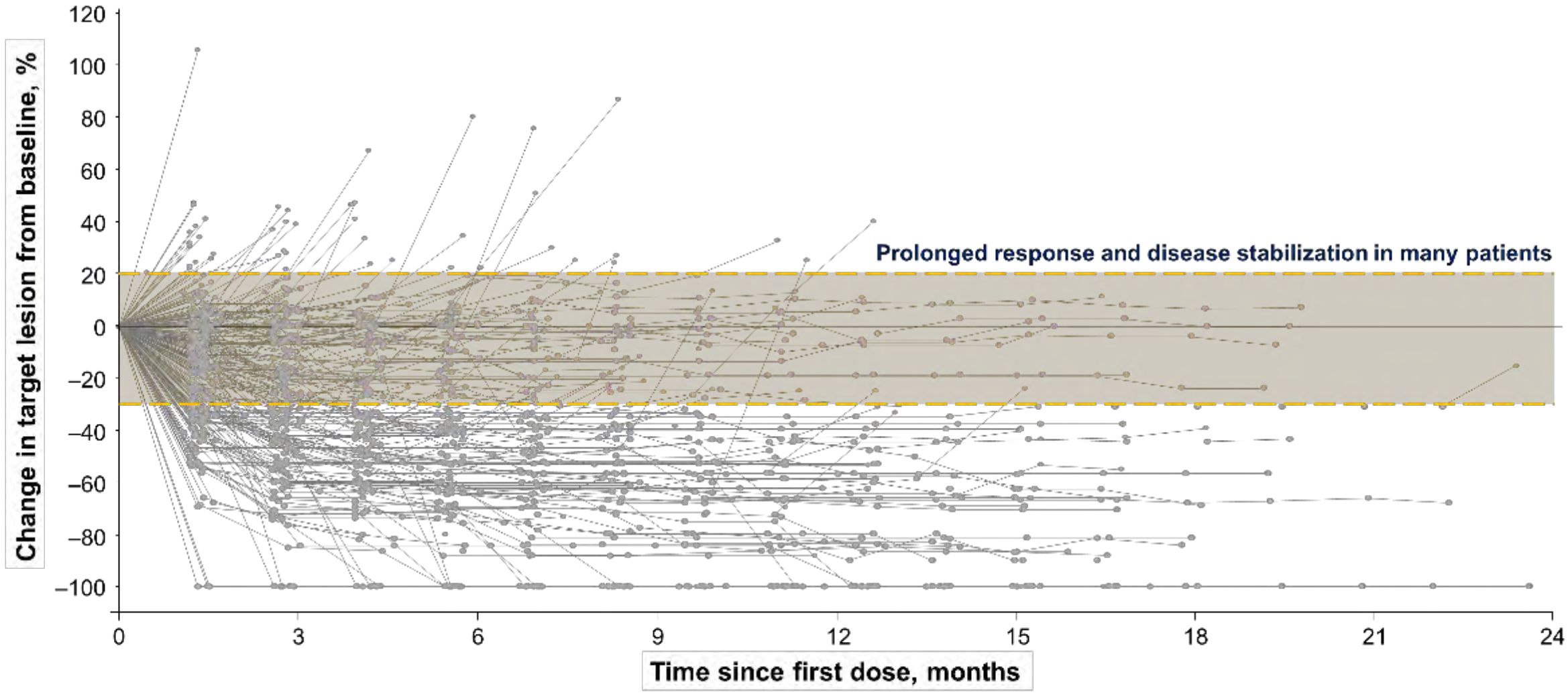
Duration of Objective Response



Kaplan-Meier estimate of response at 12 months (%)	Cervical	Endometrial	Ovarian	BTC	Pancreatic	Bladder	Other	All
	47.6	72.3	45.8	41.7	0	23.2	53.6	49.6

Analyses were performed in patients with objective response who received ≥1 dose of T-DXd (n=99). At data cut-off, 44 patients (16.5%) are still ongoing treatment, and 128 patients (47.9%) remain in the study. BTC, biliary tract cancer.

Percentage Change in Target Lesions Over Time



Analyses were performed in patients who received ≥1 dose of T-DXd (n=267).

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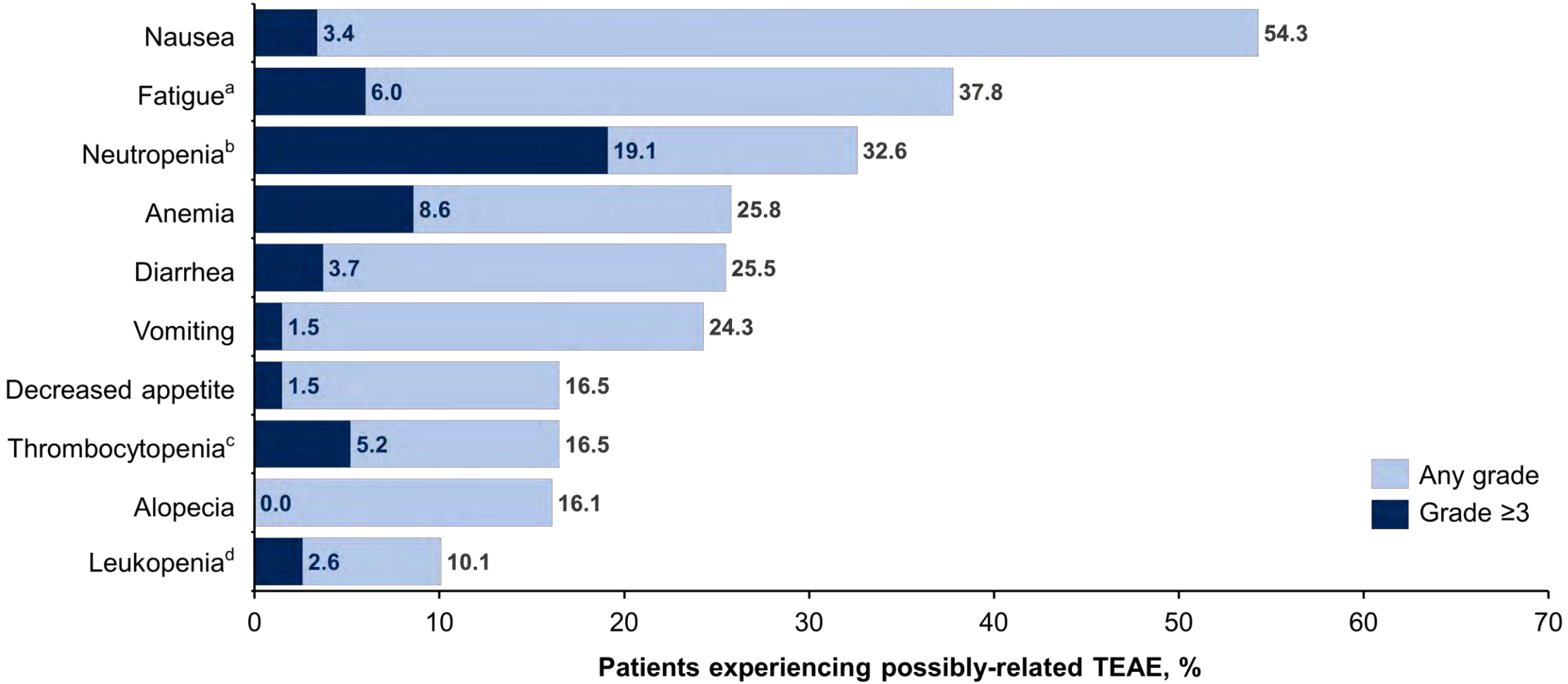
Overall Safety Summary

n (%)	All patients (N=267)
Any drug-related TEAEs	225 (84.3)
Drug-related TEAEs Grade ≥3	103 (38.6)
Serious drug-related TEAEs	32 (12.0)
Drug-related TEAEs associated with dose discontinuations	22 (8.2)
Drug-related TEAEs associated with dose interruptions	49 (18.4)
Drug-related TEAEs associated with dose reductions	50 (18.7)
Drug-related TEAEs associated with deaths	2 (0.7)[a]

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). [a]Included neutropenic sepsis (n=1) and pneumonia (n=1).
TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan.

Drug-Related TEAEs in ≥10% of Patients



Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). [a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms platelet count decreased and thrombocytopenia. [d]This category includes the preferred terms white blood cell count decreased and leukopenia.
TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan.

Adverse Events of Special Interest

ILD/pneumonitis adjudicated as T-DXd–related

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	6 (2.2)	12 (4.5)	1 (0.4)	0	1 (0.4)	20 (7.5)

Left ventricular dysfunction[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
All patients (N=267)	1 (0.4)	4 (1.5)	1 (0.4)	0	0	7 (2.6)[b]
Cardiac failure						
All patients (N=267)	0	0	1 (0.4)	0	0	1 (0.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267).
[a]Left ventricular dysfunction was reported in a total of 12 (4.5%) patients, of which 8 (3.0%) were considered possibly T-DXd–related. [b]One patient had unknown grade of ejection fraction decrease.
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

Conclusions

- T-DXd demonstrated clinically meaningful activity across a broad range of HER2-expressing solid tumors, including those that are hard to treat:
  - Encouraging ORR: 37.1% in all patients and 61.3% in patients with IHC 3+
  - Durable responses: median DOR 11.8 months in all patients and 22.1 months in patients with IHC 3+
- This trial is ongoing; OS and PFS will be analyzed with additional follow-up
- The safety profile of T-DXd was consistent with the known profile
- DESTINY-PanTumor02 shows T-DXd to be a potential new treatment option for patients with HER2-expressing solid tumors

DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

#3014 Tissue-agnostic efficacy of trastuzumab deruxtecan (T-DXd) in advanced solid tumors with *HER2* amplification identified by plasma cell-free DNA (cfDNA) testing: Results from a phase 2 basket trial (HERALD/EPOC1806)

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METHODS

HERALD/EPOC1806 was a multicenter, investigator-initiated phase 2 trial of T-DXd for patients with *HER2 (ERBB2)*-amplified advanced solid tumors identified in cfDNA by Guardant360 (G360) as a part of the Nationwide Cancer Genome Screening Project (GOZILA study) in Japan.

Study design

1) Patients with unresectable solid tumors* refractory or intolerant to standard of care (SoC) or no SoC available
2) *HER2* amplification by G360 within 8 weeks
3) Age ≥ 20 years
4) ECOG PS 0-1
5) Measurable lesion per RECIST version 1.1

- Esophagus
- Pancreas
- Urothelium
- Cervix
- Endometrium
- Ovary
- Salivary gland
- Head and neck
- Others

Trastuzumab deruxtecan (T-DXd) 5.4 mg/kg Q3W

Funding:
Japan AMED
Daiichi Sankyo Co., Ltd.

Study identifier:
JapicCTI-194707

*Excluding gastric cancer, breast cancer, colorectal cancer, lung cancer, biliary tract cancer or uterine carcinosarcoma, which have already been confirmed to have HER2 overexpression in tumor tissue. For gastric cancer and breast cancer, tissue HER2 testing is mandatory.

- Primary endpoint : ORR by Investigator's assessment
- Secondary endpoints : PFS, DoR, DCR, OS, ORR by ICR and TEAEs

ORR: objective response rate, PFS: progression free survival, DoR: duration of response, DCR: disease control rate, OS: overall survival, ICR: independent central review, TEAE: treatment emerged adverse event

HERALD study at a glance

- **Participants**: Solid tumors — *Refractory or intolerant to SoC or no SoC is available*
- **Screening**: *HER2 amp identified by* cfDNA *test*
- **Dosage**: T-DXd 5.4 *mg/kg Q3W*
- **Study period**: Recruitment *05Dec2019–17Jan2022*; Median follow-up time *8.9 months [range, 0.2–28.8]*
- **Enrollment**: 62 *participants*, 16 *cancer types*, 7 *Japan sites*
- **Efficacy**: ORR 56.5% [95% CI; 43.3%–69.0%] *58.1% by Independent Central Review*
- **Safety**: *Safety profile was consistent with those of Japanese populations in previous studies*
- **Biomarker**: *HER2* clearance in cfDNA *was early predictor of ORR*

RESULTS

N=4734 GOZILA screening
252 *HER2* amp
62 Participants enrolled
62 ITT efficacy analysis
62 FAS efficacy analysis
62 Safety analysis

Recruitment: 05Dec2019–17Jan2022
Data cutoff: 17Jul2022
ITT, intention to treat; FAS, full analysis set

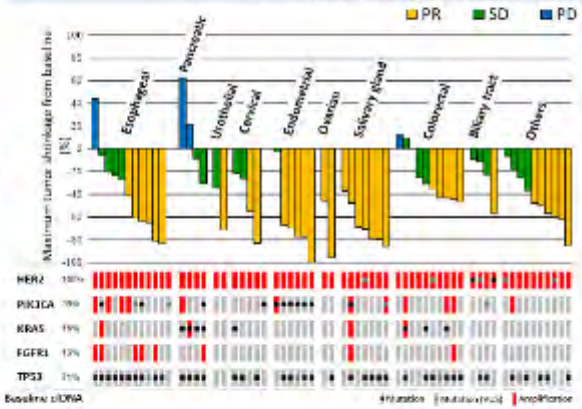
- Median age [range] : 63 years [32–80]
- Gender: Male (48.4%), Female (51.6%)
- ECOG PS: 0 (58.1%), 1 (41.9%)
- Median number of prior treatment regimens: 3 [0-8]

Type	n	%
Esophageal	12	19.4
Pancreatic	4	6.5
Urothelial	2	3.2
Cervical	5	8.1
Endometrial	6	9.7
Ovarian	2	3.2
Salivary gland	7	11.3
Head and neck	0	0.0
Others*	24	38.7
All	62	

Others*	n	%
	24	38.7
Colorectal	10	16.1
Biliary tract	4	6.5
Non-small cell lung	2	3.2
Gastric (Tissue HER2 negative)	2	3.2
Small bowel	2	3.2
Extramammary Paget's disease	1	1.6
Melanoma	1	1.6
Prostate	1	1.6
Unknown primary	1	1.6

*Mainly squamous cell carcinoma

Best tumor response

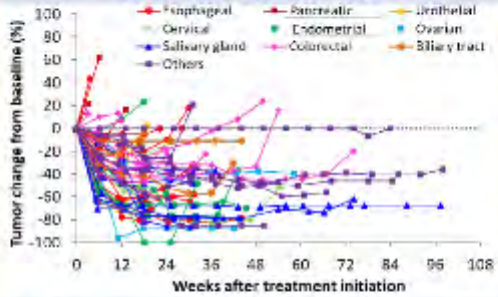


Best tumor response assessed by investigator (n=62)	
ORR [95% CI]	56.5%* [43.3–69.0]
CR	0 (0%)
PR	35 (56.5%)
SD	21 (33.9%)
PD	5 (8.1%)
NE	1 (1.6%)
DCR [95% CI]	90.3% [80.1–96.4]

*Lower limit of 95%CI exceeded the pre-determined threshold value of 5%

ORR by ICR was 58.1% (44.8-70.5) with 1 CR and 35 PR.

Tumor response over time



DoR, PFS and OS

	n=62
Median DoR* [95% CI]	8.8 months [5.8–11.2]
Median PFS* [95% CI]	7.0 months [4.9–9.7]
Median OS [95% CI]	14.6 months [10.8–22.3]

*Assessed by investigator

median follow-up time 8.9 months [range, 0.2–28.8]

Summary of TEAEs

	n=62
Treatment duration median, [range]	181.5 days [6–700]
TEAEs	62 (100.0)
TEAEs with ≥Grade 3	39 (62.9)
drug withdrawn	12 (19.4)
dose reduced	23 (37.1)
drug interrupted	37 (59.7)
TEAE-related death	1 (1.6)*

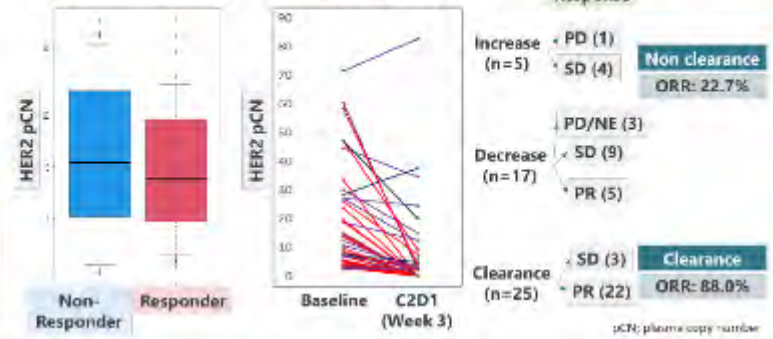
*Cause of death was DIC and sepsis.

Common TEAEs (≥ 20% in all patients)

Adverse event, n (%)	Any Grade	≥Grade 3
Nausea	37 (59.7)	1 (1.6)
Decreased appetite	34 (54.8)	4 (6.5)
Malaise	26 (41.9)	0
Anemia	25 (40.3)	14 (22.6)
Neutrophil count decreased	20 (32.3)	12 (19.4)
WBC count decreased	20 (32.3)	8 (12.9)
Constipation	17 (27.4)	0
ILD/pneumonitis*	16 (25.8)	1 (1.6)
Pyrexia	15 (24.2)	1 (1.6)
Platelet count decreased	15 (24.2)	5 (8.1)
Stomatitis	14 (22.6)	0
Diarrhea	13 (21.0)	1 (1.6)

ILD: interstitial lung disease, TEAE: treatment emergent adverse event, *Investigator assessment without ILD adjudication committee.

Relationship between plasma HER2 copy number and response



CONCLUSIONS

T-DXd achieved a high ORR and durable response with a manageable safety profile in patients with advanced solid tumors and *HER2* amplification detected in cfDNA

TROPION-Lung02: Datopotamab Deruxtecan (Dato-DXd) Plus Pembrolizumab With or Without Platinum Chemotherapy in Advanced Non-Small Cell Lung Cancer

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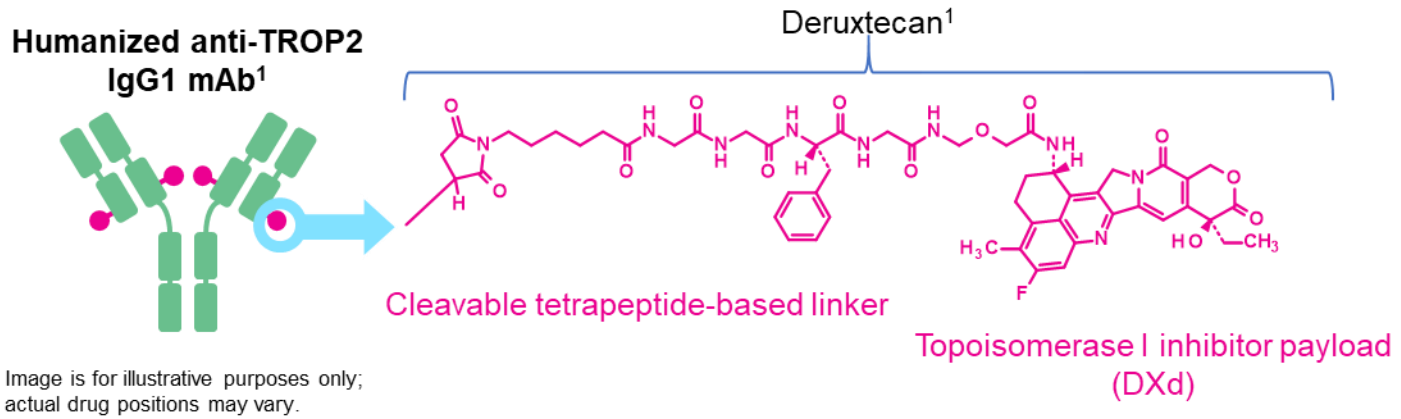
Introduction

- Dato-DXd is an antibody-drug conjugate composed of a TROP2-directed monoclonal antibody covalently linked to a highly potent cytotoxic payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1-5]
- Dato-DXd 6-mg/kg monotherapy demonstrated encouraging antitumor activity, with an ORR of 28% and a median DOR of 10.5 months, in patients with heavily pretreated advanced/metastatic NSCLC[6]



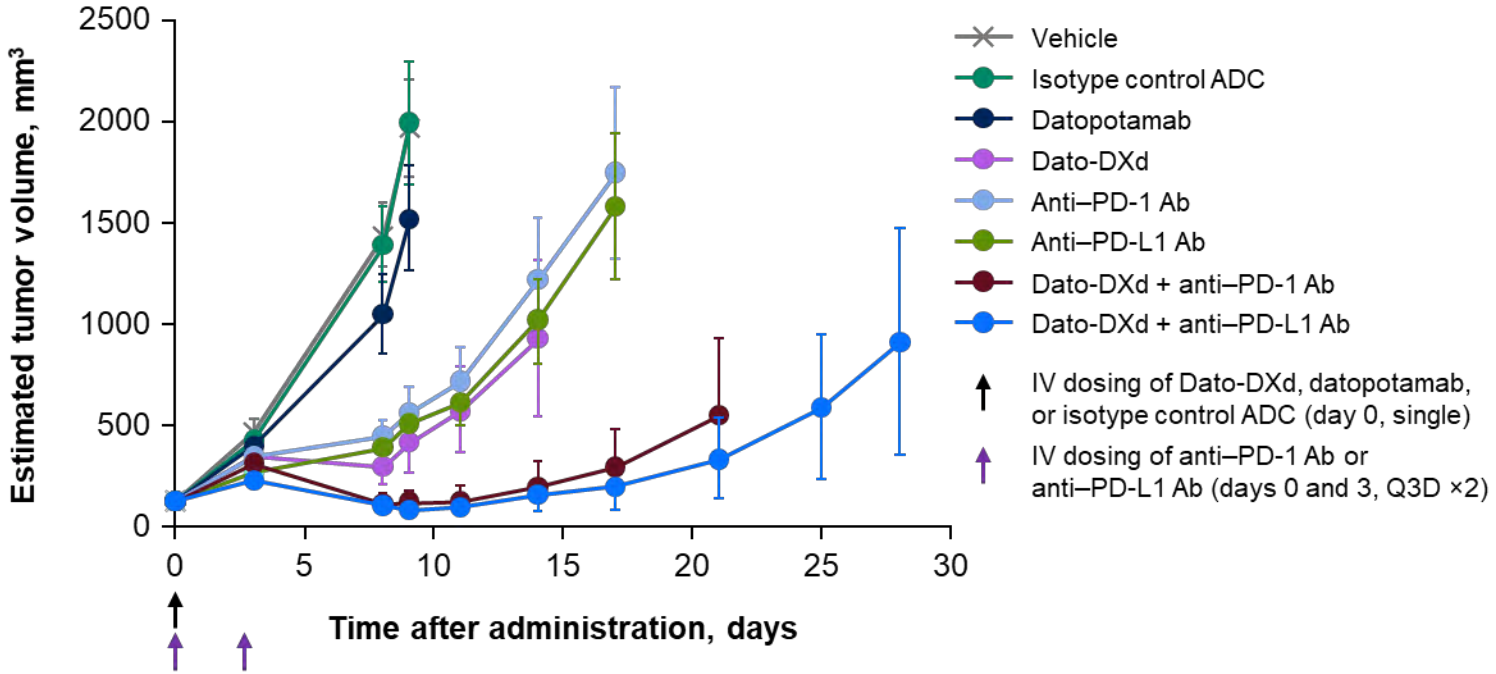
Dato-DXd, datopotamab deruxtecan; DOR, duration of response; IgG1, immunoglobulin G1; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; TROP2, trophoblast cell-surface antigen 2.

1. Okajima D, et al. *Mol Cancer Ther*. 2021;20(12):2329-2340. **2.** Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. **3.** Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. **4.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046. **5.** Shiose Y, et al. *Biol Pharm Bull*. 2007;30(12):2365-2370. **6.** Garon EB, et al. IASLC WCLC 2021. Abstract MA03.02.

Preclinical Rationale for TROPION-Lung02

- Preclinical data showed more potent antitumor activity of combinations of Dato-DXd and anti–PD-(L)1 antibodies than either agent alone, supporting their clinical investigation[1]
- The phase 1b/2 BEGONIA trial (NCT03742102) showed the promising clinical activity of 1L Dato-DXd + durvalumab in patients with advanced/metastatic TNBC (confirmed ORR, 74%; confirmed CR rate, 8%; patients remaining in response at data cutoff, 82%)[2]

hTROP2-MC38 tumor volume in C57BL/6 mice[1]



1L, first line; Ab, antibody; ADC, antibody-drug conjugate; CR, complete response; Dato-DXd, datopotamab deruxtecan; hTROP2, human trophoblast cell-surface antigen 2; IV, intravenous; ORR, objective response rate; PD-(L)1, programmed death (ligand) 1; Q3D, every 3 days; TNBC, triple-negative breast cancer.
Figure reproduced with permission from the presenting author.[1]

1. Okajima D, et al. AACR 2023. Poster 2932. **2.** Schmid P, et al. SABCS 2022. Poster PD11-09.

TROPION-Lung02: Phase 1b Study

- TROPION-Lung02 is the first study evaluating Dato-DXd + pembrolizumab ± platinum CT[a] in advanced NSCLC without actionable genomic alterations[b] (NCT04526691)
  - The safety of the Dato-DXd + pembrolizumab doublet was established prior to evaluation of the platinum-containing triplet
  - The safety of Dato-DXd 4-mg/kg combinations was established prior to evaluation of 6-mg/kg combinations

Key eligibility criteria

- **Advanced/metastatic NSCLC**
- **Dose escalation**[c]: ≤2 lines of prior therapy[d]
- **Dose expansion**
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[d]
  - Treatment naive (cohort 2; enrollment after Jun 30, 2022)[d]
  - Treatment naive (cohorts 3-6)[d]

	Dato-DXd IV Q3W	+	pembro IV Q3W	+	platinum CT IV Q3W	
Cohort 1 (n=20):	4 mg/kg	+	200 mg			Doublet
Cohort 2 (n=44):	6 mg/kg	+	200 mg			Doublet
Cohort 3 (n=20):	4 mg/kg	+	200 mg	+	carboplatin AUC 5	Triplet
Cohort 4 (n=30):	6 mg/kg	+	200 mg	+	carboplatin AUC 5	Triplet
Cohort 5 (n=12):	4 mg/kg	+	200 mg	+	cisplatin 75 mg/m^2	Triplet
Cohort 6 (n=10):	6 mg/kg	+	200 mg	+	cisplatin 75 mg/m^2	Triplet

- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, and antidrug antibodies

Data cutoff: April 7, 2023.

AUC, area under the curve; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DLT, dose-limiting toxicity; IV, intravenous; NSCLC, non-small cell lung cancer; pembro, pembrolizumab; Q3W, every 3 weeks.

[a] Administered sequentially at the same visit. [b] Patients with known actionable *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *RET*, or *MET* mutations or alterations in other actionable oncogenic driver kinases were not eligible for this study. Testing for *EGFR* and *ALK* alterations was not required for patients with squamous histology who were smokers or ≥40 years of age. [c] The first 3 to 6 patients in each cohort were enrolled to confirm acceptable safety/DLT rate; the remaining patients are considered part of dose expansion (for which enrollment was ongoing at the time of data cutoff). [d] Prior therapy requirements are for treatment in the advanced/metastatic setting.

Patient Baseline Characteristics

Characteristic	Doublet (n=64)	Triplet (n=72)
Age, median (range), years	65 (44-83)	64 (33-84)
Male, n (%)	48 (75)	48 (67)
Histology, n (%)		
Adenocarcinoma	45 (70)	49 (68)
Squamous	16 (25)	15 (21)
History of brain metastases, n (%)	11 (17)	14 (19)
PD-L1 expression, n (%)[a]		
<1%	23 (36)	29 (40)
1%-49%	28 (44)	24 (33)
≥50%	13 (20)	18 (25)
Prior lines of therapy, median (range)[b]	0 (0-4)[c]	0 (0-3)[c]
Previous systemic treatment, n (%)		
Immunotherapy	12 (19)	18 (25)
Platinum chemotherapy	24 (38)	17 (24)
Dato-DXd combination line of therapy, n (%)[d]		
1L	37 (58)	54 (75)
2L+	27 (42)	18 (25)

Data cutoff: April 7, 2023.
1L, first line; 2L+, second line and later; Dato-DXd, datopotamab deruxtecan; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1.
[a] PD-L1 expression testing was not performed in 1 patient (1%) receiving triplet therapy. [b] Prior therapy for advanced/metastatic NSCLC. [c] Additional prior lines of therapy were permitted under earlier versions of the protocol.
[d] In the advanced/metastatic setting.

- Of patients receiving doublet or triplet therapy, 58% and 75%, respectively, were treated in the 1L setting
- Immunotherapy was previously given in 19% of patients receiving doublet therapy and 25% of patients receiving triplet therapy

Patient Disposition

Disposition	Doublet (n=64)	Triplet (n=72)
Study duration, median (range), months	14.8 (1-30.2)	12.9 (2.6-23.4)
Treatment status		
Ongoing on study treatment, n (%)	23 (36)	33 (46)
Discontinued from study treatment, n (%)	41 (64)	39 (54)
Duration of treatment, median (range), months	4.2 (0.7-18.5)	5.7 (0.7-23.2)
No. of cycles received, median (range)		
Dato-DXd	6 (1-24)	7 (1-29)
Pembrolizumab	6 (1-25)	7 (1-29)
Cisplatin	NA	3.5 (1-4)
Carboplatin	NA	4 (1-5)
Primary reason for treatment discontinuation, n (%)		
Adverse event	11 (17)	11 (15)
Progressive disease	22 (34)	23 (32)
Patient withdrawal	5 (8)	0
Physician decision	0	3 (4)
Death	3 (5)	0

Data cutoff: April 7, 2023.
Dato-DXd, datopotamab deruxtecan; NA, not applicable.

- At the time of data cutoff, 36% of patients receiving doublet therapy and 46% of those receiving triplet therapy were still receiving study treatment
- Progressive disease was the primary reason for treatment discontinuation in both groups

Antitumor Activity

Response[a]	All patients		Patients in 1L	
	Doublet (n=61)[b]	Triplet (n=71)[b]	Doublet (n=34)[b]	Triplet (n=53)[b]
Confirmed + pending ORR, n (%)[c,d]	23 (38)	35 (49)	17 (50)	30 (57)
[95% CI]	[26-51]	[37-61]	[32-68]	[42-70]
Confirmed + pending BOR, n (%)[d,e]				
Confirmed CR	0	1 (1)	0	1 (2)
Pending CR[d]	0	0	0	0
Confirmed PR	21 (34)	34 (48)	15 (44)	29 (55)
Pending PR[d]	2 (3)	0	2 (6)	0
SD, n (%)[f]	30 (49)	27 (38)	16 (47)	18 (34)
DCR, n (%)[g]	51 (84)	62 (87)	31 (91)	48 (91)
Median DOR, months	NE	NE	NE	NE
[95% CI]	[8.8-NE]	[5.8-NE]	[5.5-NE]	[5.7-NE]

- In the 1L setting, the ORR (confirmed and pending)[d] was 50% in patients receiving doublet therapy and 57% in those receiving triplet therapy
- Among all patients, the DCR was 84% (doublet) and 87% (triplet); in the 1L setting, the DCR was 91% in both therapy subgroups

Preliminary PFS in all patients, median (95% CI), months: doublet, 8.3 (6.8-11.8); triplet 7.8 (5.6-11.1)[h]

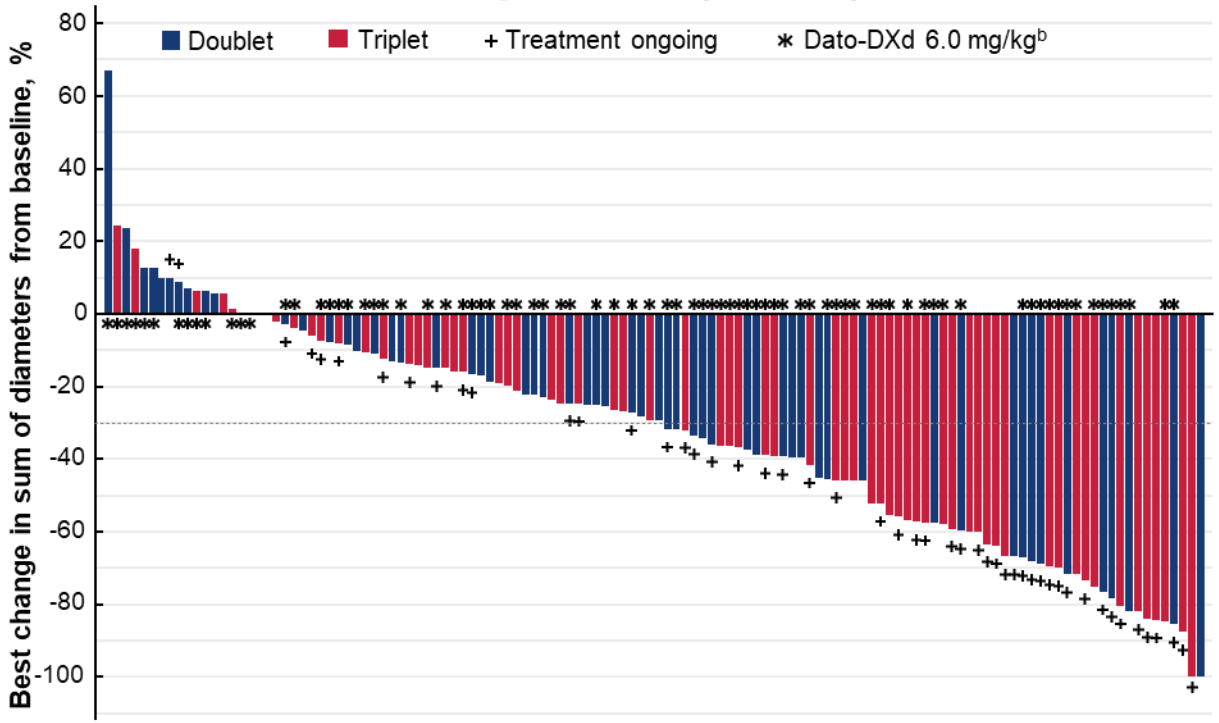
Data cutoff: April 7, 2023.

1L, first line; 2L+, second line and later; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

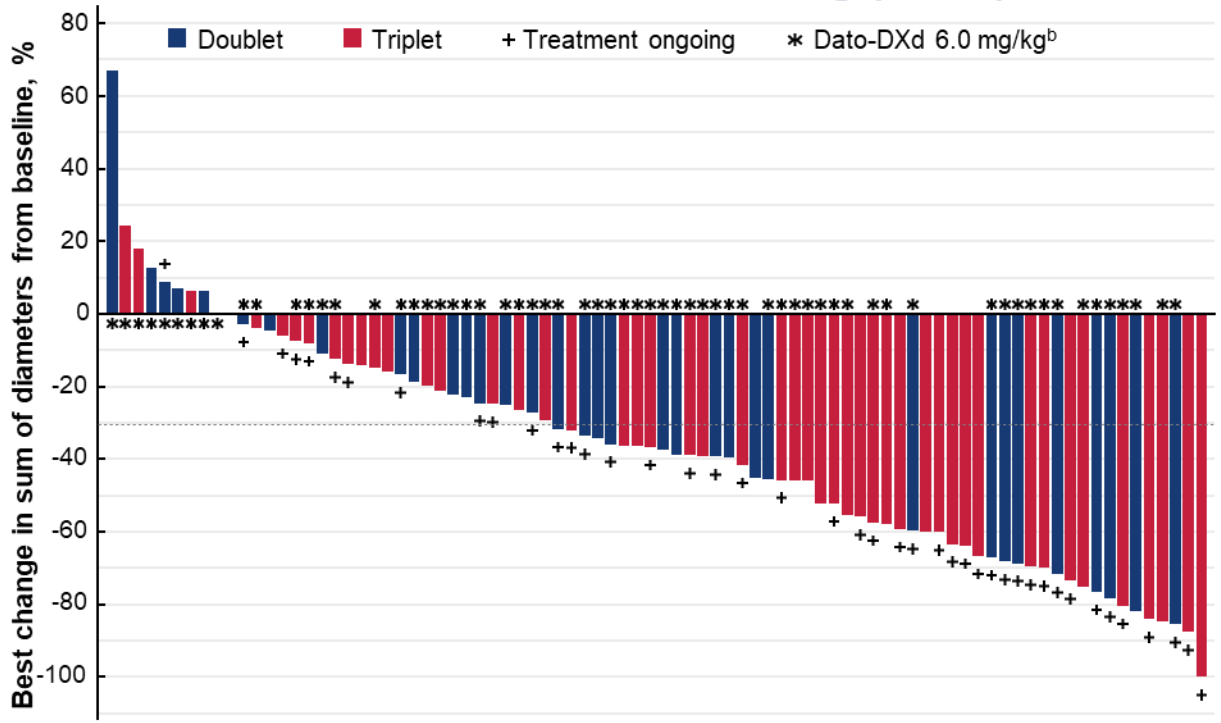
[a] By investigator. [b] Response-evaluable patients, which includes patients with ≥1 postbaseline overall response and those who discontinued without a postbaseline overall response. [c] ORR defined as BOR of CR + PR. [d] Responses pending confirmation. [e] BOR was determined using tumor assessments at different evaluation time points from the date of the first dose of study treatment until documented disease progression or the start of the next line of nonpalliative anticancer therapy (inclusive), whichever was earlier. [f] SD defined as ≥1 SD assessment (or better) ≥5 weeks after starting treatment and before progression without qualification for CR or PR (includes pending responses). [g] DCR defined as BOR of confirmed CR + confirmed PR + SD. [h] Preliminary PFS is limited by immature duration of follow-up.

Best Overall Tumor Change From Baseline

All patients (n=124)[a]



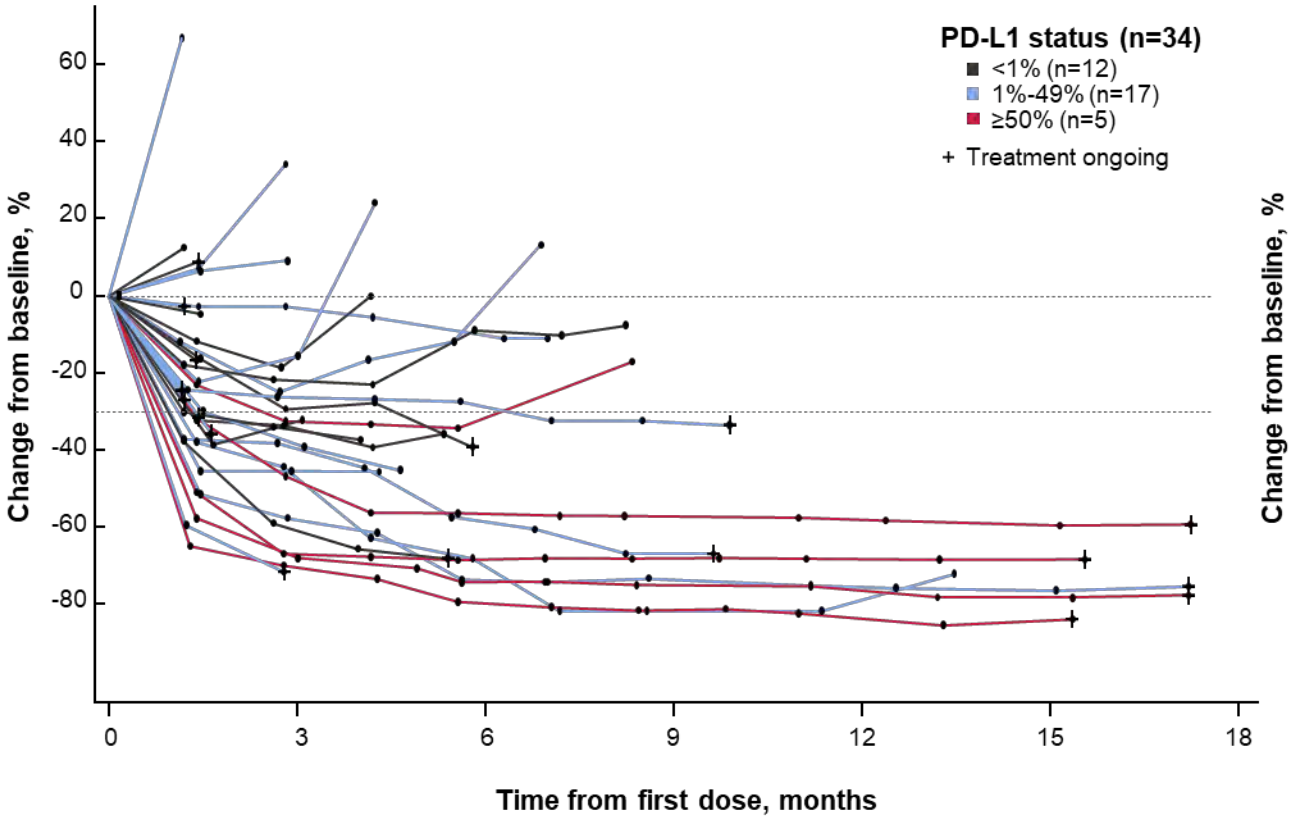
Patients in the 1L setting (n=84)[a]



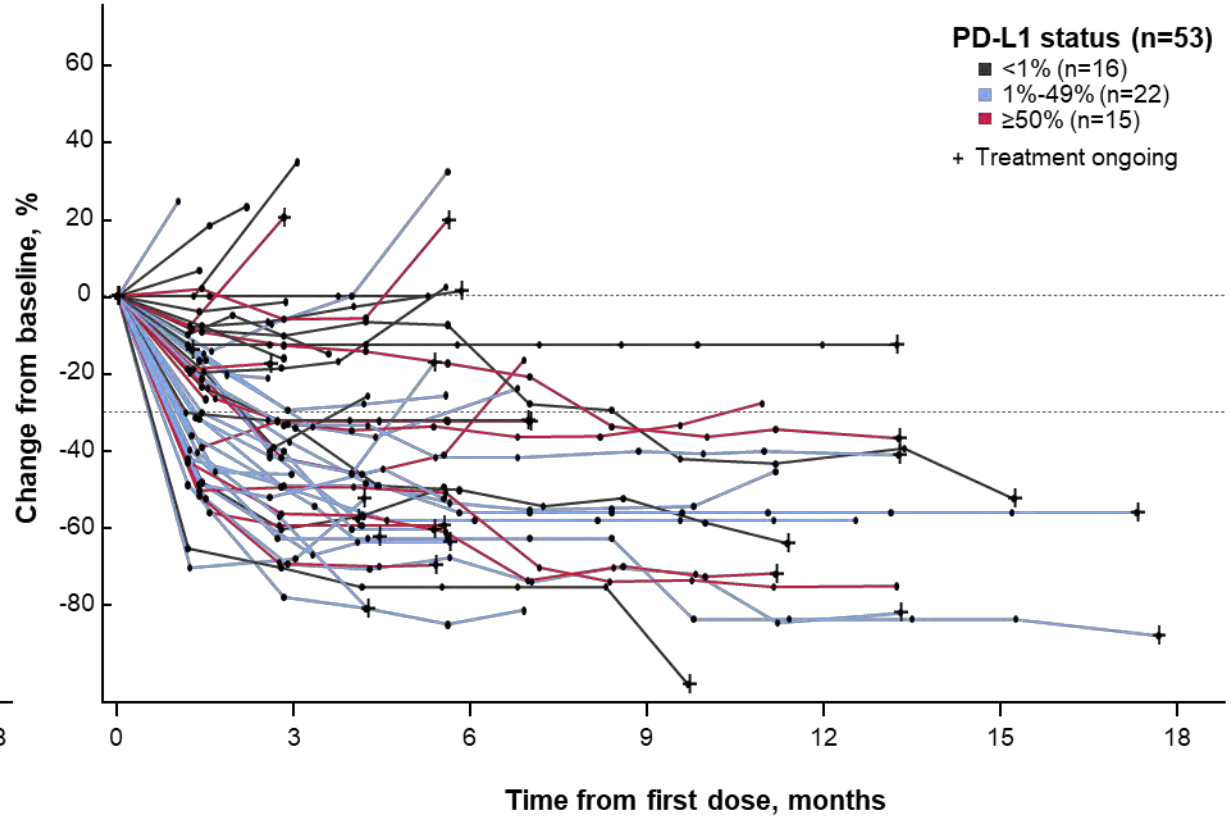
Data cutoff: April 7, 2023.
1L, first line.
[a] Patients with no baseline target lesions or no postbaseline tumor assessments were excluded from the waterfall plots. [b] Planned dose level.

Depth and Duration of Response

Doublet therapy, 1L subgroup



Triplet therapy, 1L subgroup



Data cutoff: April 7, 2023.
1L, first line; NE, not estimable; PD-L1, programmed death ligand 1.

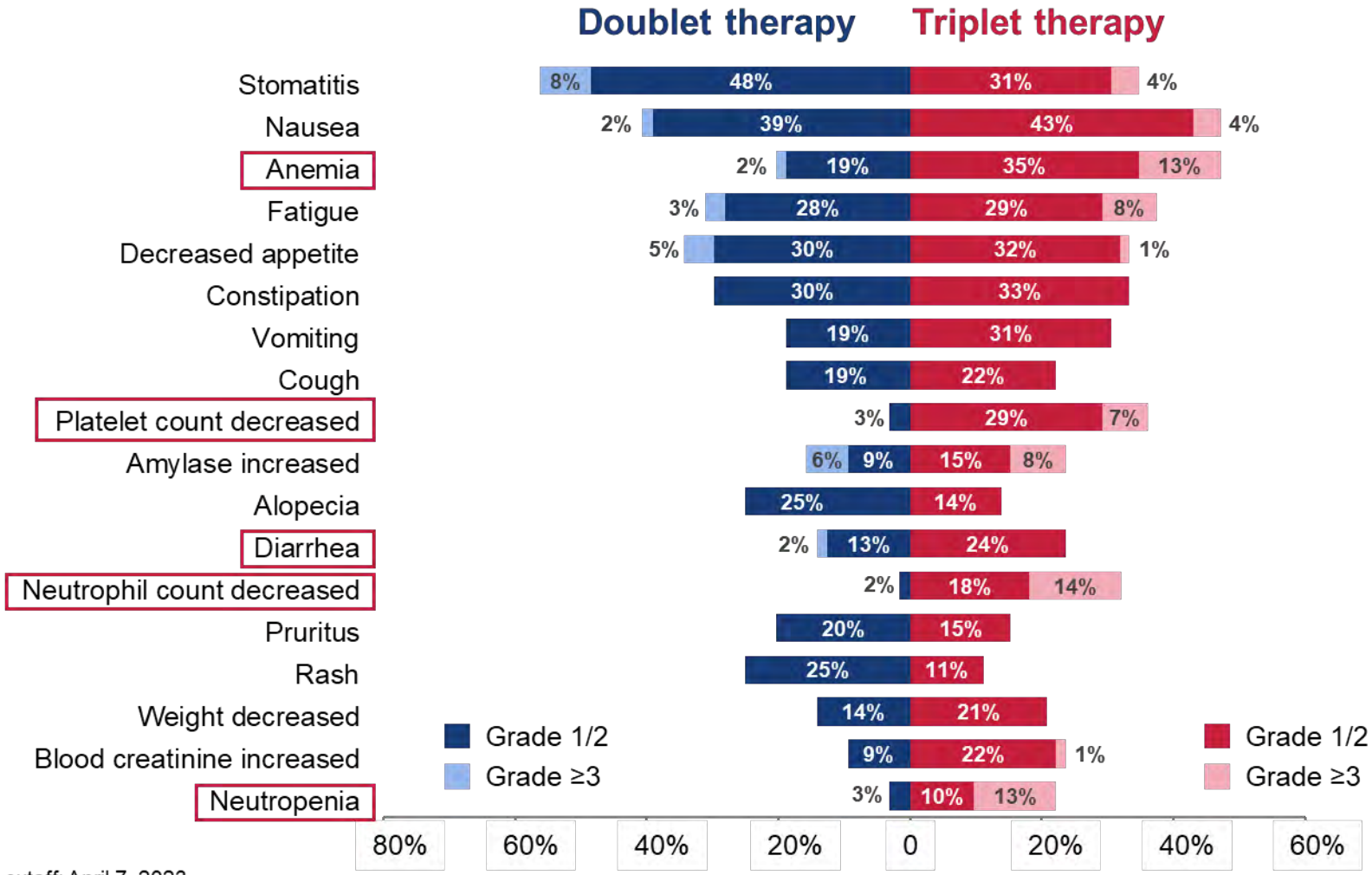
Safety Summary

Event, n (%)	Doublet (n=64)	Triplet (n=72)
TEAEs[a]	62 (97)	72 (100)
Study treatment related[b]	58 (91)	72 (100)
Grade ≥3 TEAEs	34 (53)	55 (76)
Study treatment related[b]	20 (31)	42 (58)
Serious TEAEs	20 (31)	29 (40)
Study treatment related	6 (9)	16 (22)
TEAEs associated with:		
Death[f]	3 (5)	5 (7)
Dose reduction of any drug	14 (22)	14 (19)
Dose reduction of Dato-DXd	14 (22)	11 (15)
Discontinuation of any drug	18 (28)	27 (38)
Discontinuation of Dato-DXd[g]	15 (23)	20 (28)

- During the dose-finding phase, 2 patients receiving Dato-DXd + pembrolizumab + platinum CT had DLTs[c,d,e]
- TEAEs (treatment-emergent adverse events) associated with discontinuation of Dato-DXd occurred in 23% of patients receiving the doublet regimen and in 28% of patients receiving the triplet regimen

Data cutoff: April 7, 2023.
CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DLT, dose-limiting toxicity; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event; TMG, toxicity management guideline.
[a] TEAEs were defined as AEs with a start or worsening date on or after the start of study treatment until 37 days after the end date of study treatment. [b] Drug-related TEAEs may be associated with any component of the study treatment: Dato-DXd, pembrolizumab, cisplatin, or carboplatin. [c] DLT defined as any TEAE not attributable to disease or any disease-related process that occurs during the DLT evaluation period (days 1-21 in cycle 1) and is grade ≥3 according to NCI CTCAE version 5.0, with certain exceptions. [d] Two grade 4 platelet count decreased, and 1 grade 4 neutrophil count decreased. [e] One additional patient was incorrectly reported as having a DLT and is not included here. [f] All TEAEs associated with death were considered by the investigator to be unrelated to study treatment, except for 1 case of grade 5 pneumonitis, which was ultimately adjudicated as not ILD.
[g] Twenty of these 35 events (11 in doublet cohorts and 9 in triplet cohorts) were due to ILD/pneumonitis events, and TMGs necessitate drug discontinuation for grade 2 events and grade 1 events lasting >49 days.

TEAEs Occurring in ≥20% of Patients



- The most frequent TEAEs of any grade were stomatitis, nausea, anemia, and fatigue
- In general, hematologic TEAEs, particularly those of grade ≥3, were more frequently observed with triplet therapy than with doublet therapy

Data cutoff: April 7, 2023.
TEAE, treatment-emergent adverse event.

Adverse Events of Special Interest

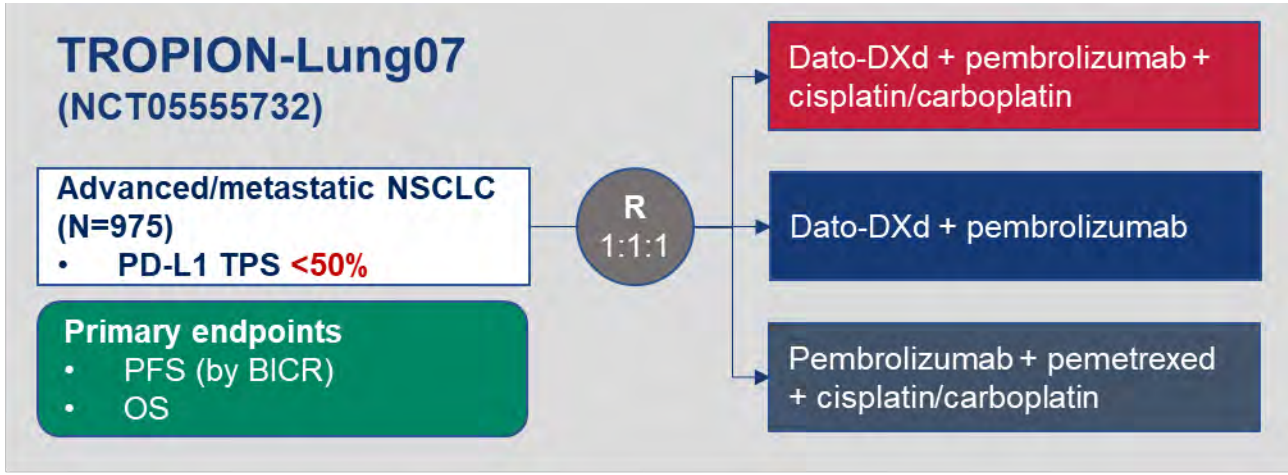
AESI, n (%)[a,b]	Doublet (n=64)		Triplet (n=72)	
	All grades	Grade ≥3	All grades	Grade ≥3
Oral mucositis/stomatitis	37 (58)	5 (8)	31 (43)	4 (6)
ILD/pneumonitis adjudicated as drug related[c]	11 (17)	2 (3)	16 (22)	2 (3)
Ocular surface toxicity[d]	10 (16)	1 (2)	17 (24)	2 (3)
IRR[e]	15 (23)	0	10 (14)	0

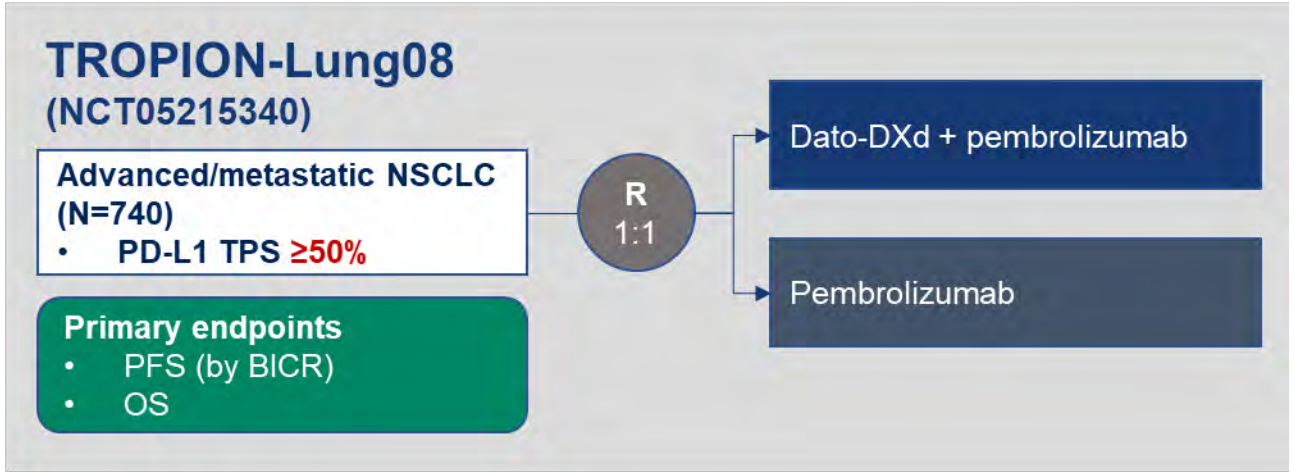
- Oral mucositis/stomatitis was the most common AESI and was predominantly grade 1/2
- No grade 5 AESIs have occurred
- There were no grade 4 or 5 adjudicated ILD/pneumonitis events[f]

Data cutoff: April 7, 2023.
AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction.
[a] AESIs listed in this slide include all preferred terms that define the medical concept. [b] No cases of mucosal inflammation occurred in patients receiving doublet or triplet therapy. [c] Five ILD cases are pending adjudication.
[d] The majority of these events were cases of dry eye (n=12 patients) and lacrimation increased (n=8 patients); grade ≥3 events were keratitis (n=2 patients) and dry eye (n=1 patient). [e] IRR refers to all IRR events that occurred in a patient who experienced any of the preselected preferred terms within the same day of Dato-DXd infusion. [f] There was 1 grade 5 event initially adjudicated as drug-related ILD in a patient receiving triplet therapy; this event was ultimately readjudicated to be grade 2.

Conclusions and Ongoing Studies With Pembrolizumab

- In this study, Dato-DXd + pembrolizumab ± platinum chemotherapy demonstrated encouraging antitumor activity in patients with NSCLC in the 1L and 2L+ settings
- No new safety signals were observed
  - The most frequent TEAEs of any grade were stomatitis, nausea, anemia, and fatigue
- Dato-DXd + pembrolizumab ± chemotherapy is being compared with SOC therapies in the 1L setting in the pivotal phase 3 TROPION-Lung07 and TROPION-Lung08 studies





1L, first line; 2L+, second line and later; BICR, blinded independent central review; Dato-DXd, datopotamab deruxtecan; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; R, randomized; SOC, standard of care; TEAE, treatment-emergent adverse event; TPS, tumor proportion score.

A Phase II Study of HER3-DXd in Patients with Metastatic Breast Cancer

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ASCO 2023 #1004 Oral

On behalf of the investigators

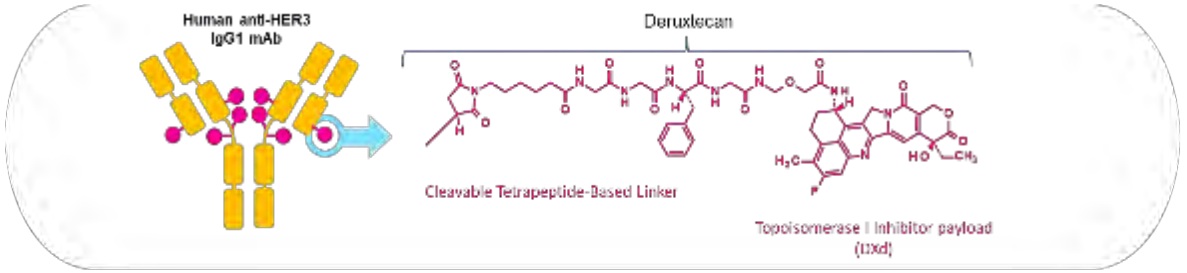
Background

Overexpression of HER3, a member of the HER receptor tyrosine kinase (RTK) family, is associated with disease progression and increased invasion of cancer cells into the vessels in many solid tumors.[1,2]

HER3 forms heterodimers with other RTKs (most notably HER2) to promote tumorigenesis and metastasis via downstream signaling.[3,4,5]

Higher HER3 expression is found in metastatic breast cancer (MBC) samples compared with primary breast tumor samples.[2]

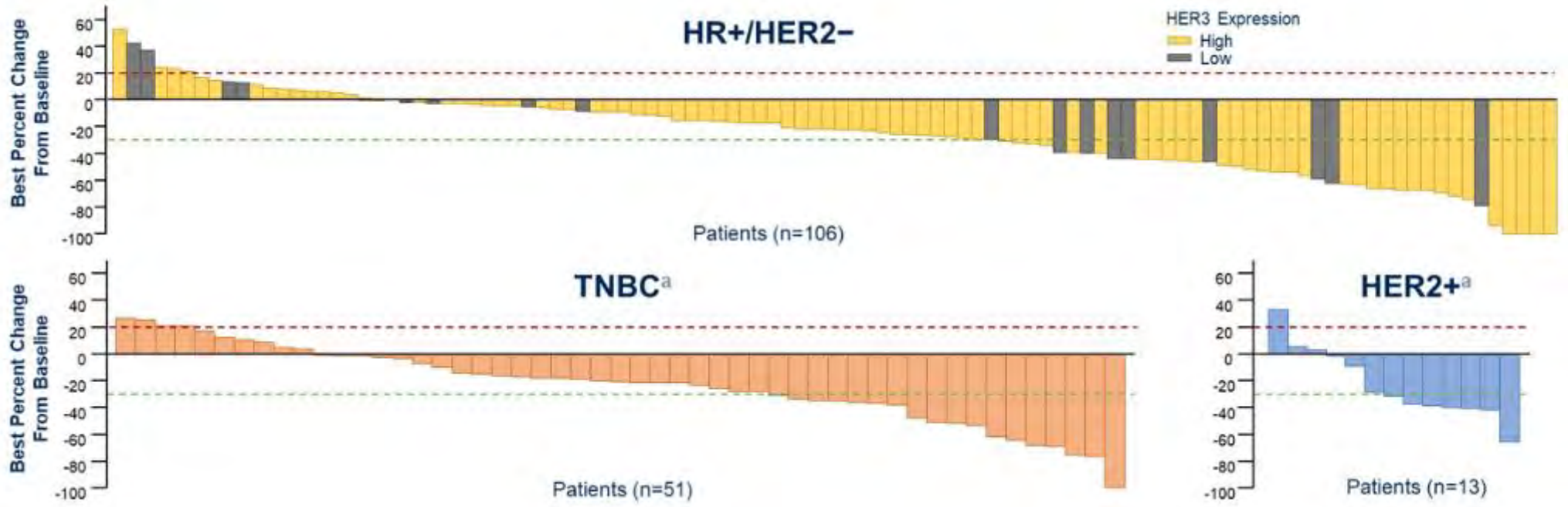
HER3-DXd (patritumab deruxtecan) is an antibody-drug conjugate (ADC) comprising a fully human anti-HER3 IgG1 monoclonal antibody (patritumab) covalently linked to a topoisomerase I inhibitor payload, an exatecan derivative (DXd), via a tetrapeptide-based cleavable linker.



1. Ocana A et al. *J Natl Cancer Inst*. 2013;105(4):266-73. 2. Xue C et al. *Cancer Res*. 2006;66(3):1418-26. 3. Lyu H et al. *Acta Pharm Sin B*. 2018;8:503-10. 4. Mishra R et al. *Oncol Rev*. 2018;12(1):355. 5. Mota JM et al. *Oncotarget*. 2017;8(51):89284-306.

Background

- A previous Phase I/II study (NCT02980341) that evaluated patritumab deruxtecan in patients with heavily pretreated MBC demonstrated decreased tumor size irrespective of BC subtype and HER3 expression.

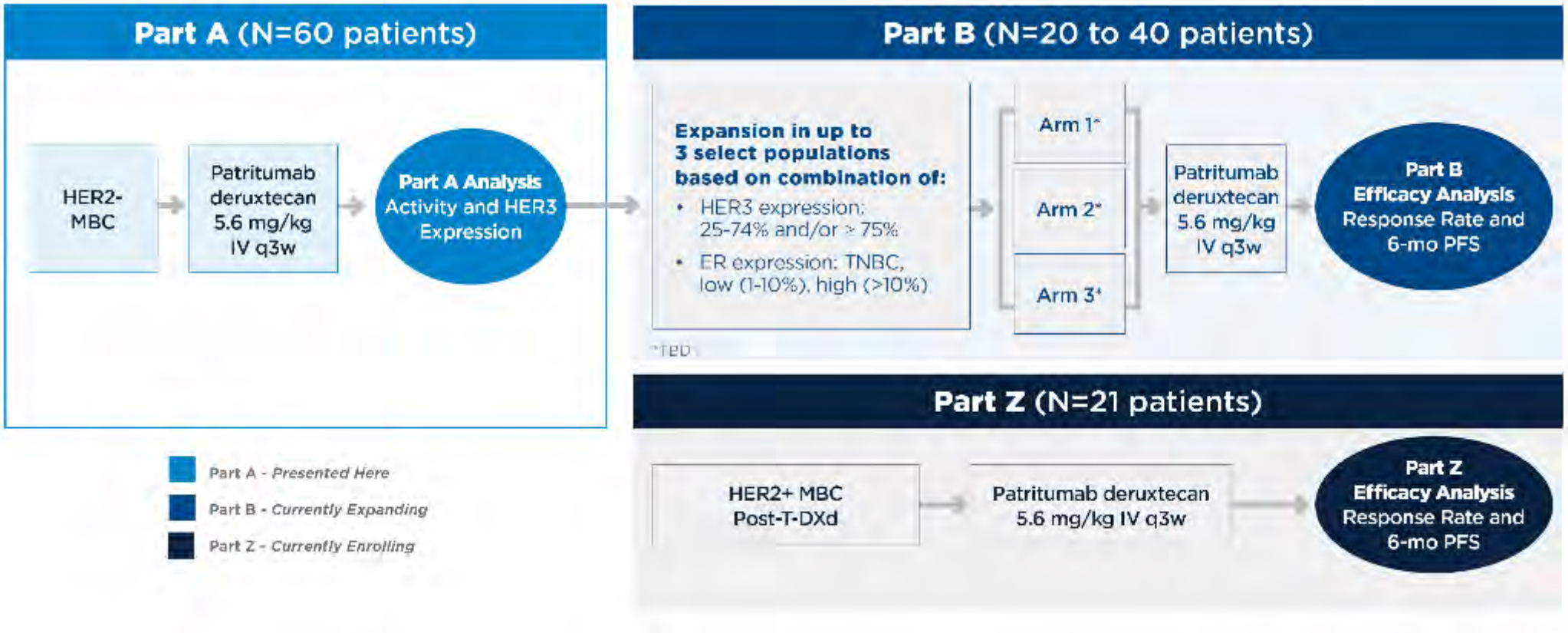


[a] Membrane positivity for all patients with TNBC or HER2+ BC was ≥75%.
HER3 expression: high, ≥75%; low, 25-74%. Efficacy data includes patients treated at all dose levels.

Figure reproduced with permission from: Krop IE et al. 2022 ASCO Annual Meeting.

Study Design

- This Phase II study (NCT04699630) examines the efficacy and safety of patritumab deruxtecan administered in patients with locally advanced or metastatic BC.
- Here, we present data for Part A.



HER3 expression was not an enrollment criterion for Part A; HER3 expression was retrospectively assessed using immunohistochemistry.

Study Objectives

Primary Objective

Evaluate objective response rate (ORR) and 6-month progression-free survival ($PFS_{6\ month}$) of single-agent patritumab deruxtecan in patients with HER2-negative MBC

Secondary Objectives

Assess safety and tolerability of patritumab deruxtecan in patients with HER2-negative and HER2-positive MBC

Estimate the duration of response (DoR), PFS, and clinical benefit rate (CBR) in patients with HER2-negative and HER2-positive MBC

Key Enrollment Criteria (Part A)

Women and men ≥18 years of age and ECOG status of 0 or 1

Locally advanced or metastatic BC with ≥1 measurable lesion

HER2-negative per ASCO-CAP guidelines (by immunohistochemistry) (includes zero and low expression)

Hormone receptor positive (HR+) or negative (HR-)

- **Patients (Pts) with HR+ BC**
  - Unlimited lines of endocrine therapy; prior CDK4/6 inhibitor required
  - ≤2 prior lines of chemotherapy in the metastatic setting
- **Pts with HR- (triple negative) BC**
  - 1-3 prior lines of chemotherapy in the metastatic setting

- Willingness to undergo pre-treatment and on-treatment biopsies
- No prior treatment with any HER3-targeting agent or any ADC that contains an exatecan derivative
- No prior history of interstitial lung disease (including pulmonary fibrosis or radiation pneumonitis)

ASCO 2023 #1004 Oral

Patient Disposition

	(N=60) n (%)
Patients Enrolled*	61
Patients Treated (Safety Set)	60
Treatment Status	
Receiving study treatment	21 (35.0)
Discontinued from study treatment	39 (65.0)
Primary reason for discontinuation from study treatment	
Adverse event**	8 (13.1)
Clinical progression/objective disease progression	25 (41.7)
Death†	2 (3.3)
Physician/patient decision	4 (6.7)
Duration on Study (Months)	
Median (range)	5.9 (0.2, 14.5)

*1 pt was enrolled but did not receive treatment. Pt was discontinued due to "Withdrawal by Pt."
**Pneumonitis, 3 pts; Interstitial Lung Disease (ILD), 1 pt; Muscular Weakness, 1 pt; Fatigue, 1 pt; Nausea, 1 pt; AST/ALT Increased, 1 pt. ILD adjudication of ILD/pneumonitis events is ongoing as of data cutoff.
†*Pneumocystis* pneumonia, 1 pt; Dyspnea, 1 pt. Neither death was treatment related.

Data cutoff: September 6, 2022.

Demographics and Prior Systemic Therapies

	(N=60) n (%)
Sex/Age (Years)	
Male	1 (1.7)
Female	59 (98.3)
>18 to <65	43 (71.7)
≥65 to <75	10 (16.7)
≥75	6 (10.0)
Race	
Asian	6 (10.0)
Black or African American	6 (10.0)
White	46 (76.7)
Other/not reported	2 (3.4)
ECOG	
0	31 (51.7)
1	29 (48.3)
Stage IV at Diagnosis	13 (21.7)
BRCA1	
Positive (mutated)	2 (3.3)
BRCA2	
Positive (mutated)	1 (1.7)

	(N=60) n (%)
Number of Prior Systemic Regimens in Metastatic Setting	
1-2 prior regimens	24 (40.0)
3 or more prior regimens	36 (60.0)
Median (range)	**3 (1, 9)**
Type of Prior Regimens in the Metastatic Setting*	
Chemotherapy	54 (90.0)
PARP inhibitors	3 (5.0)
Immunotherapy	12 (20.0)
Sacituzumab govitecan	5 (8.3)

*100% of the 29 patients with HR+ BC received prior therapy with CDK4/6 inhibitor.

Data cutoff: September 6, 2022.

Tumor Characteristics

- Of the 60 patients who received treatment, 48 patients (80%) had baseline results available for both estrogen receptor (ER) and progesterone receptor (PR), and 47 patients (78.3%) had baseline results available for HER3.

	(N=48) n (%)
Baseline ER	
High (>10% expression)	24 (50.0)
Low (1-10% expression)	1 (2.1)
Negative	23 (47.9)
Baseline PR	
High (>10% expression)	22 (45.8)
Low (1-10% expression)	3 (6.3)
Negative	23 (47.9)
Baseline Triple-Negative	19 (39.6)

	(N=47) n (%)
Baseline HER3 Expression*	
≥75%	30 (63.8)
25% to 74%	13 (27.7)
<25%	4 (8.5)

*Membrane HER3 expression measured at 10X objective.

Data cutoff: September 6, 2022.

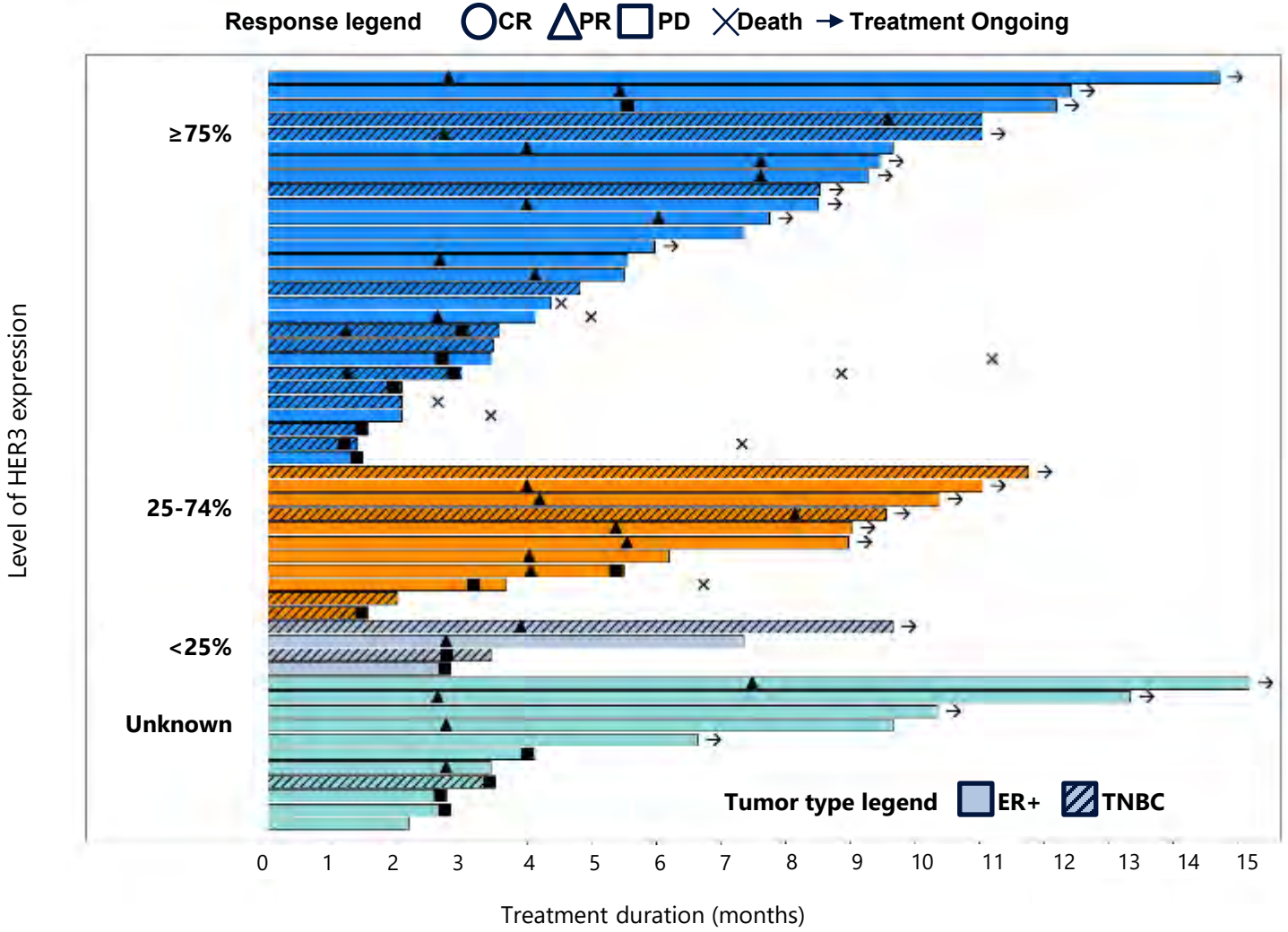
Treatment Received and Dose Modifications

	(N=60)
Treatment Duration (Months)	
Median (range)	5.2 (0.7, 15.2)
Patients with Treatment Duration ≥ 6 Months on Patritumab Deruxtecan, n (%)	26 (43.3)
Dose Reduced, n (%)	9 (15.0)
Adverse event*	9 (15.0)
Number of Dose Reductions, n (%)	
1 reduction	8 (13.3)
2 reductions	1 (1.7)
Dose Interrupted, n (%)	20 (33.3)
Adverse event	14 (23.3)
Other	7 (11.7)

*Gastrointestinal Disorders, 4 pts; Thrombocytopenia, 2 pts; Fatigue, 1 pt; Dyspnea, 1 pt; Pruritus, 1 pt

Data cutoff: September 6, 2022.

Duration on Study Treatment by HER3 Membrane Expression



Data cutoff: September 6, 2022.

Response – Investigator Assessment

	Membrane HER3 ≥75% (N=30)	Membrane HER3 25%- 74% (N=13)	Membrane HER3 <25% (N=4)	Unknown Membrane HER3 Expression* (N=13)	Total (N=60) N (%)
Best Overall Response, n (%)					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
Stable disease (SD)	13 (43.3)	4 (30.8)	1 (25.0)	8 (61.5)	26 (43.3)
Progressive disease (PD)	5 (16.7)	1 (7.7)	1 (25.0)	0	7 (11.7)
Missing/no post baseline	2 (6.7)	2 (15.4)	0	2 (15.4)	6 (10.0)
ORR, n (%)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
95% CI	(17.3, 52.8)	(19.2, 74.9)	(6.8, 93.2)	(5.0, 53.8)	(23.1, 48.4)
CBR, n (%)**	**12 (40.0)**	**7 (53.8)**	**2 (50.0)**	**5 (38.5)**	**26 (43.3)**
95% CI	(22.7, 59.4)	(25.1, 80.8)	(6.8, 93.2)	(13.9, 68.4)	(30.6, 56.8)
DoR ≥6 months, n (%)†	4 (40.0)	2 (33.3)	2 (100)	2 (66.7)	10 (47.6)

*HER3 results available for 47 pts. Remaining 13 pts had tissue not available/testing result unevaluable.
**CBR=CR, PR, or SD ≥180 days
†Percentage calculation uses the number of pts who responded as the denominator.

Among patients with heavily pretreated BC, all-comer ORR was 35%, overall CBR was 43%, and DoR was at least 6 months in nearly half of all patients who responded.

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; ORR, objective response rate.

Data cutoff: September 6, 2022.

Response by HER3 Expression Level and Clinical Subtype

HER3 Membrane Expression ≥75%

	ER+ (N=16)	TNBC (N=11)
ORR, n (%)	**6 (37.5)**	**2 (18.2)**
95% CI	(15.2, 64.6)	(2.3, 51.8)
CBR, n (%)	**8 (50.0)**	**2 (18.2)**
95% CI	(24.7, 75.3)	(2.3, 51.8)
DoR ≥ 6 months, n (%)	**3 (50.0)**	**1 (50.0)**

There are 30 total pts with HER3 ≥75%. 2 pts were ER-/PR+, and 1 pt did not have ER/PR testing results; therefore, they are not included in the table.

HER3 Membrane Expression 25% to 74%

	ER+ (N=5)	TNBC (N=5)
ORR, n (%)	**3 (60.0)**	**1 (20.0)**
95% CI	(14.7, 94.7)	(0.5, 71.6)
CBR, n (%)	**3 (60.0)**	**2 (40.0)**
95% CI	(14.7, 94.7)	(5.3, 85.3)
DoR ≥ 6 months, n (%)	**1 (33.3)**	**0**

There are 13 total pts with HER3 25% to 74%. 2 pts were ER-/PR+, and 1 pt did not have ER/PR testing results; therefore, they are not included in the table.

ORR and CBR were not higher for patients with HER3 expression ≥75% compared with patients with HER3 expression 25% to 74%.

Response Summary Irrespective of HER3 Membrane Expression

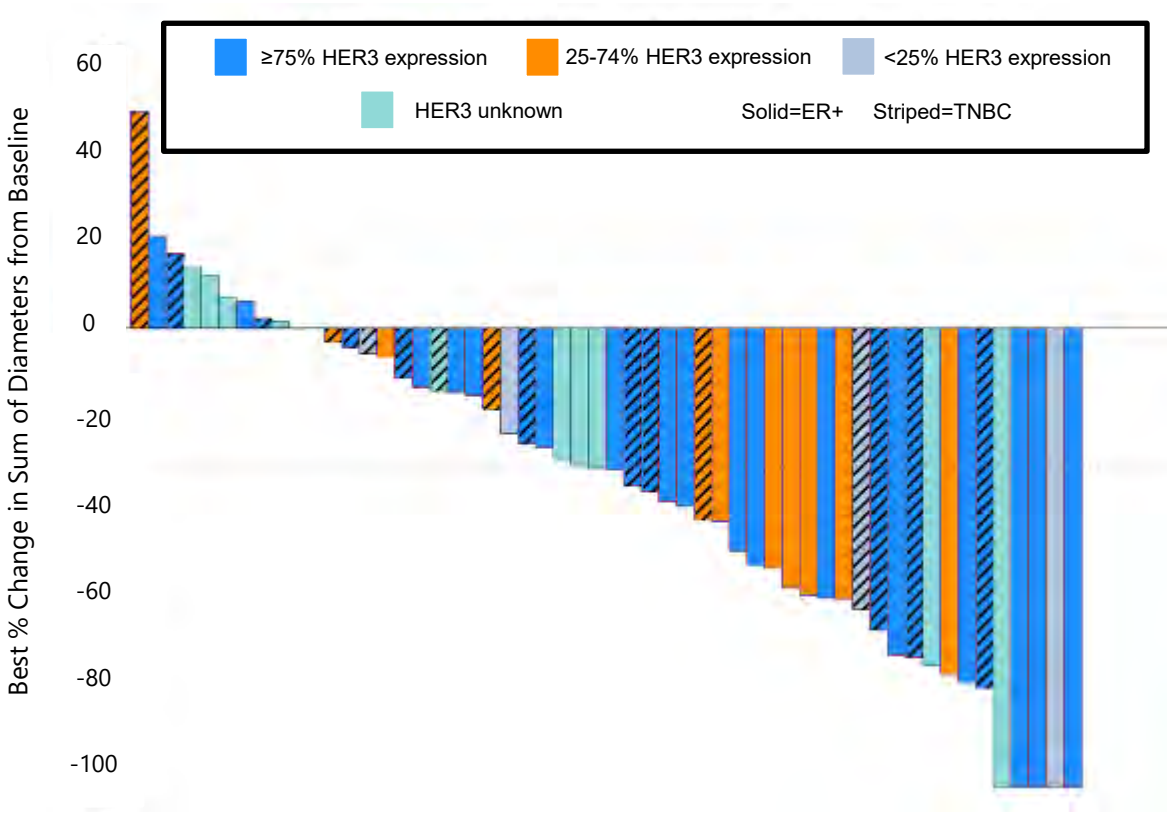
	HR+ (N=29)	TNBC (N=19)
ORR, n (%)	**12 (41.4)**	**4 (21.1)**
95% CI	(23.5, 61.1)	(6.1, 45.6)

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; ORR, overall response rate.

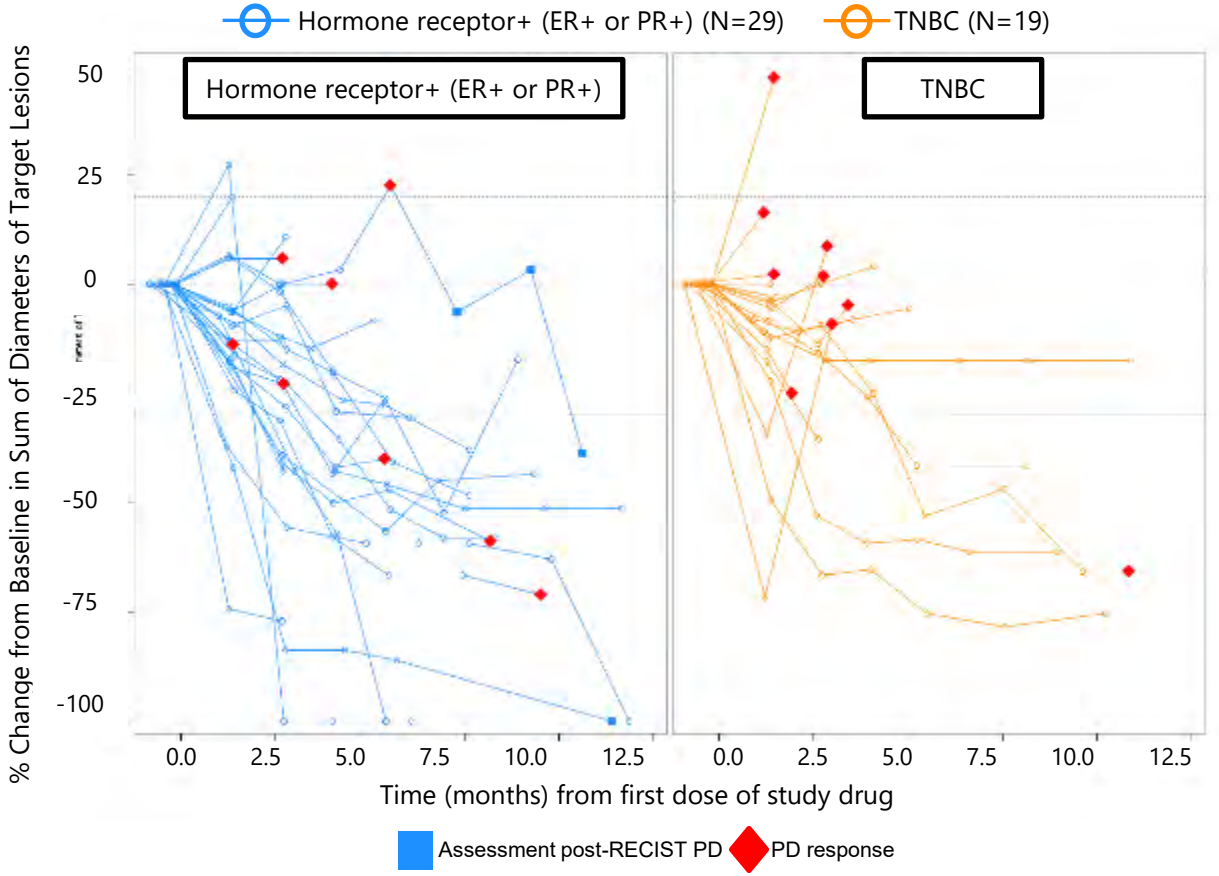
Data cutoff: September 6, 2022.

Majority of Patients Had Tumor Shrinkage

Best Percent Change in Sum of Diameters from Baseline in Target Lesions



Percent Change from Baseline in Sum of Diameters of Target Lesions HR+ vs TNBC



Data cutoff: September 6, 2022.

Safety

Treatment-Related Adverse Events Occurring in ≥10% of Patients by Highest Reported Grade*

	Any grade (N=60) n (%)	Grade 3/4 (N=60) n (%)
Any Adverse Event (AE)	56 (93.3)	19 (31.7)
Nausea	30 (50.0)	2 (3.3)
Fatigue	27 (45.0)	4 (6.7)
Diarrhea	22 (36.7)	3 (5.0)
Vomiting	19 (31.7)	1 (1.7)
Anemia	18 (30.0)	0
Alopecia	17 (28.3)	N/A
Hypokalemia	9 (15.0)	1 (1.7)
Decreased Appetite	8 (13.3)	0
Neutrophil Count Decreased**	7 (11.7)	3 (5.0)
White Blood Cell Count Decreased**	7 (11.7)	1 (1.7)

*No Grade 5 treatment-related adverse events had occurred prior to data cutoff.
**More than 1 adverse event could be reported per pt.

Treatment-Emergent Serious Adverse Events

Treatment-related SAEs	(N=60), n (%)
Interstitial Lung Disease†	1 (1.7)
Nausea/Vomiting	1 (1.7)
Pneumonitis	1 (1.7)
Thrombocytopenia	1 (1.7)
Unrelated SAEs	
Dyspnea	1 (1.7)
Pneumocystis jirovecii pneumonia	1 (1.7)
Pneumothorax	1 (1.7)

†Interstitial Lung Disease (ILD) adjudication of ILD/pneumonitis events ongoing as of data cutoff.

- **The most common adverse events were nausea, fatigue, and diarrhea.**
- **The majority of adverse events were Grades 1 and 2. No single Grade 3/4 adverse event occurred in more than 7% of patients.**

Data cutoff: September 6, 2022.

Conclusions

Clinical activity of patritumab deruxtecan was observed across a broad range of HER3 membrane expression levels in patients with heavily pretreated ER+ and TN metastatic breast cancers.

- This is consistent with emerging data:
  - SOLTI-TOT-HER3 reported an ORR of 30% irrespective of HR status in patients with early-stage HER2-negative BC (Oliviera M et al. ESMO BC 2023)
  - ICARUS-Breast01 reported an ORR of 29% in patients with HR+ MBC irrespective of level of HER3 expression (preliminary data) (Pistilli B et al. ESMO BC 2023)

The safety profile of patritumab deruxtecan was manageable, with very low rates of Grade 3/4 adverse events.

Data from this analysis supports the potential entry of patritumab deruxtecan into the therapeutic paradigm across MBC subtypes.

Part B (currently expanding) and Part Z (HER2+ MBC after progression on T-DXd) are both enrolling patients irrespective of HER3 expression.

ICARUS-BREAST01
A phase 2 Study of Patritumab Deruxtecan (HER3-DXd) in patients with advanced breast cancer:
AN EXPLORATORY BIOMARKER ANALYSIS

B. Pistilli, N. Ibrahimi, M. Lacroix-Triki, V. D'Hondt, C. Vicier, J.S. Frenel, F. Dalenc, T. Bachelot, M.A. Benderra, D. Loirat, A. Ducoulombier, D. Mayeur, G. Nachabeh, K. Serhal, N. Corcos, D. Sellami, S. Michiels, F. André, F. Mosele, G. Montagnac

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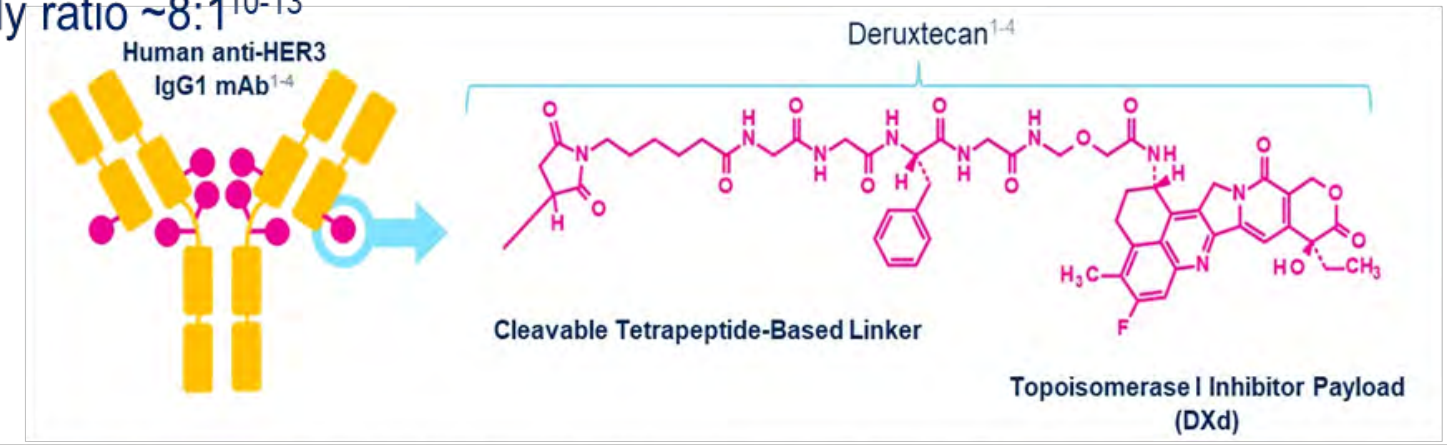
DECLARATION OF INTERESTS

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

BACKGROUND-I

- **Human epidermal growth factor receptor 3 (HER3)** is a key member of the ErbB family that lacks intrinsic protein tyrosine kinase activity and generally forms dimers with other HER family receptors (eg.HER2-HER3)[1,2]
- **HER3 overexpression** is associated with **worse prognosis across different solid tumors, including breast cancer**[3]
- In breast cancer, HER3 upregulation is a **key player in resistance to PI3K/AKT/mTOR inhibitors**[4-6]**, HER2-targeting therapies**[7] **and endocrine therapy** [8,9]
- **Patritumab deruxtecan (U3-1402; HER3-DXd)** is a novel ADC, composed of a fully human anti-HER3 IgG1 monoclonal antibody coupled via a cleavable linker to a topoisomerase I inhibitor payload, a derivative of exatecan (DX-8951f), with a drug to antibody ratio ~8:1[10-13]



1.Jura N, et al, Proc Natl Acad Sci USA 2009, 106:21608-13; 2. Hynes NE et al, Nat Rev Cancer 2005, 5(5): 341-354; 3. Ocana et al, J Natl Cancer Inst 2013, 105:266–273; 4.Chandarlapaty S et al, Cancer Cell, 2011, 19:58-71; 5.Rodrik-Outmezguine VS et al, Cancer Discov 2011, 1:248-59; 6.Chakrabarty A et al, Proc Natl Acad Sci U S A 2012;109: 2718–23; 7. Huang X et al, Cancer Res 2010, 70:1204-14; 8. Liu B et al, Int J Cancer 2007;120:1874-82.; 9; Morrison MM et al, Oncogene (2016) 35, 1143–1152; 10.Hashimoto Y, et al. Clin Cancer Res. 2019;25(23):7151-7161; 11. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185; 12. OgitaniY, et al. Clin Cancer Res. 2016;22(20):5097-5108; 13. KoganemaruS, et al. Mol Cancer Ther. 2019;18(11):2043-2050

BACKGROUND-II

- In the phase I/II U3-1402-J101 study, HER3-DXd showed promising activity in patients with heavily pretreated HER3-expressing advanced breast cancer (HR+/HER2-, TNBC, and HER2+); **efficacy was observed across a broad range of HER3-positive expression levels**[1]

- **Biomarkers of response and resistance to HER3-DXd are unknown**

- **ICARUS-BREAST01** (NCT04965766) is a phase II study aiming to determine **predictors of response and resistance to HER3-DXd** in patients with HR+/HER2- advanced breast cancer, who progressed on prior CDK4/6inhibitors, endocrine therapy +/- any target therapy and 1 line of chemotherapy; **study enrollment on HER3 IHC expression level (≥75% of membrane positivity at 10x) was removed by amendment on Apr 21st, 2022**

TNBC: triple negative breast cancer
IHC: immunohistochemistry

1. Krop et al, J Clin Oncol 40, 2022 (suppl 16; abstr 1002)

ICARUS-PROGRAM

Different **clinical, basic/translational research teams** to decipher **mechanisms of action** and the **multiple parallel mechanisms of resistance to ADCs**

100 patients with HR+/HER2- ABC → HER3-DXd 5.6 mg/kg every 3 weeks until PD or unacceptable toxicity

100 patients with NSCLC → DATO-DXd 6.0 mg/kg every 3 weeks until PD or unacceptable toxicity

WP1: Clinical trials

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Daiichi-Sankyo

ICARUS

cnrs Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

Clinical Axes

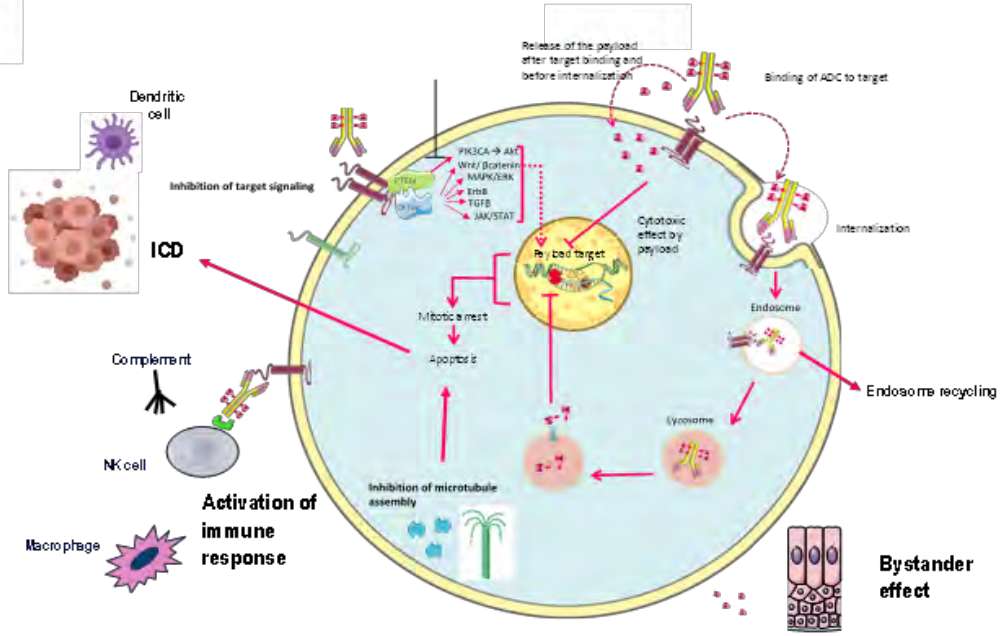
Phl/II trials across solid tumors

Scientific axes

Analyses of the different mechanisms of action and resistance

WP2: Tumor alterations associated with response/resistance

WP3: ADC Trafficking



WP4/5: Immune modulation and ICD

WP6: Payload efficiency

Modified from Rassy, et al Breast. 2022 Dec;66:217-226

ICARUS-BREAST01 STUDY DESIGN

Prospective, multicenter, single-arm study with multiple biomarker analyses

KEY ELIGIBILITY CRITERIA*:
-unresectable locally advanced/metastatic BC
-HR+/HER2-neg/ HER2-low
-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 ORR

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

Mandatory:
-tumor biopsy (1 frozen + 3 FFPE)
-blood (30 ml)

Exploratory Endpoints:
Predictors of response/resistance

5.6 mg/kg dose is based on prior exposure-response analysis of efficacy in NSCLC; 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; PK: Pharmacokinetics; PD: pharmacokynamics;

EXPLORATORY BIOMARKER ANALYSIS

QUESTION: Can we identify potential markers of early treatment response (3-mos RR)* ?

- Total and HER3+ CTCs count at baseline and after 1st HER3-DXd dose
- Gene alterations/expression at baseline/on-treatment

Baseline	C1D3 or C1D19 or C2D3	EOT
CTCs, HER3+CTCs (planned in 35 patients)	CTCs, HER3+CTCs (planned in 35 patients)	CTCs, HER3+CTCs (planned in 35 patients)
WES/RNAseq	RNAseq	WES/RNAseq
IHC/AI-digital pathology; Spectral cytometry; Hyperion IMC	IHC/AI-digital pathology; Spectral cytometry; Hyperion IMC	IHC/AI-digital pathology; Spectral cytometry; Hyperion IMC

*3-mos RR: response rate by 3 months from 1st cycle

BASELINE CHARACTERISTICS

Patients, N = 56	
Median age, years [range]	56 [28;82]
Sex, n (%)	
Female	56 (100.0)
HR status, n (%)	
ER-neg; PR-neg	1 (1.8); 12 (21.4)
HER2 expression, n (%)§	
IHC 0	35 (62.5)
IHC 1+	8 (14.3)
IHC 2+, ISH-	5 (8.9)
IHC 2+, ISH+	1 (1.8)
Unknown	7 (12.5)
HER3 expression, n (%) §§	
≥75% membrane positivity at 10x	29 (51.8)
Unknown	27 (48.2)

Prior (neo)adjuvant chemotherapy, n (%) *	35 (64.8)
Median number of systemic therapies for ABC, n [range]**	2 [1;4]
Prior treatment with CDK4/6inh, n (%) ***	56 (100.0)
Median duration of therapy with CDK4/6inh, months [range]	12.2 [1.9; 43.5]
Prior PI3K/AKT/mTOR inh for ABC, n (%)	
Everolimus	18 (32.1)
Prior chemotherapy for ABC, n (%)	56 (100.0)
Capecitabine	26 (52.0)
Paclitaxel	13 (26.0)
Anthracyclines	5 (8.9)

Data cut-off: Feb 15th, 2023

§ § HER3-expression prescreening was removed by amendment on April 21st, 2022

§ on archival tumor samples; *on 54 patients; ** on 52 patients; *** 3 patients received more than 1 CDK4/6inh

ISH: in situ hybridization

PATIENT DISPOSITION

Patients, N = 56	
HER3-DXd treatment status, n (%)	
Ongoing	24 (42.9)
Discontinued	32 (57.1)
Primary reason for discontinuation, n (%)	
Disease progression	23 (41.1)
Adverse events	4 (7.1)
Investigator's decision	2 (3.6)
Withdrawal by patient	2 (3.6)
Other	1 (1.7)
Median number of HER3-DXd cycles, n (%)	8 (1;20)
Dose reduction, n (%)	**21 (37.5)**

data cut-off: Feb 15th, 2023
all patients received ≥ 1 cycle

SAFETY RESULTS

Overall safety profile, n (%)*	
Any grade TEAE	56 (100.0)
Grade ≥ 3	27 (48.2)
• Leading to HER3-DXd discontinuation	7 (12.5)*
• Leading to HER3-DXd interruption	9 (16.0)
• Leading to HER3-DXd dose reduction	13 (23.2)
• Leading to death	0 (0)
Adjudicated treatment related ILD	**1 (1.8)****

TEAEs ≥ 25% of all patients, n (%)	All grades	Grade≥ 3
Fatigue	50 (89.3)	8 (14.3)
Nausea	42 (75.0)	2 (3.6)
Diarrhea	26 (46.4)	2 (3.6)
Alopecia	25 (44.6)	NA
Constipation	15 (26.8)	3 (5.3)

Fatigue and gastrointestinal toxicity were the most common adverse events
All grade and grade ≥3 neutropenia occurred in 8 (14.0%) and 6 (10.0%) patients, respectively
All grade and grade ≥3 thrombocytopenia occurred in 4 (8.0%) and 2 (4.0%) patients, respectively

*grade ≥3 TEAEs associated with treatment discontinuation were: worsening clinical conditions (n=2); vomiting (n=2); grade 3 thrombocytopenia (n=1); decompensation of chronic open-angle glaucoma (n=1); liver fibrosis (n=1)

data cut-off: Feb 15th, 2023; all patients received ≥ 1 cycle *safety data up to Nov 4th, 2022
TEAEs: treatment emergent adverse events **grade 1 interstitial lung disease

EXPLORATORY BIOMARKERS OF EARLY TREATMENT RESPONSE

Tumor response by 3 months from treatment initiation, n (%)	
Partial response*	16 (28.6)*
Stable Disease	30 (53.6)
Progressive Disease	10 (17.8)

BASELINE	ON-TREATMENT (C1D3/C1D19/C2D3)
CTCs, HER3+CTCs (planned in 35 patients)	CTCs, HER3+CTCs (planned in 35 patients)
WES/RNAseq	RNAseq

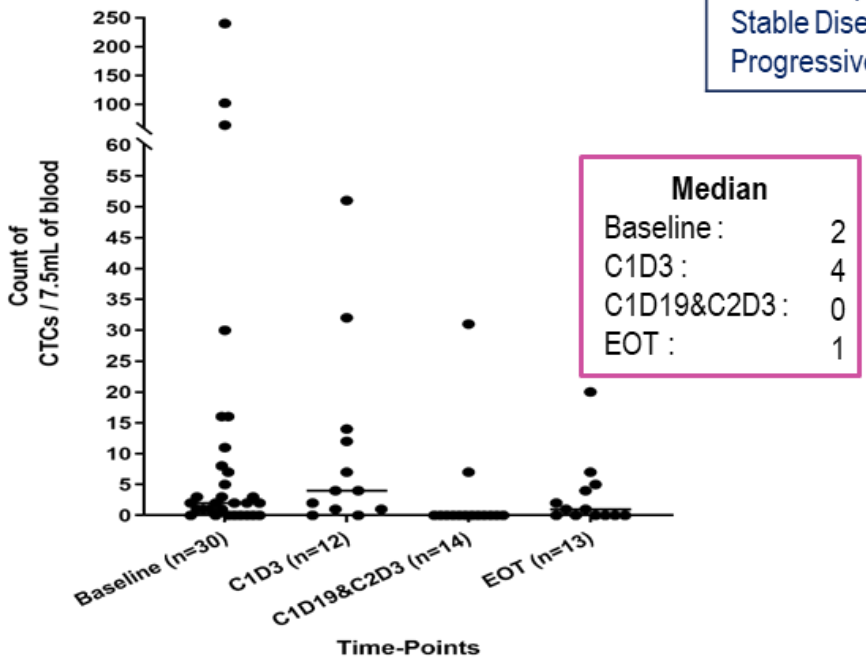
data cut-off: Feb 15th, 2023; no patients had complete response
Only patients enrolled before Sep 15th, 2022 were included in the analyses; *9 patients included before the study amendment

CTC COUNT AFTER FIRST HER3-DXD CYCLE

CTC counts by CellSearch

(31 patients, 69 blood samples)

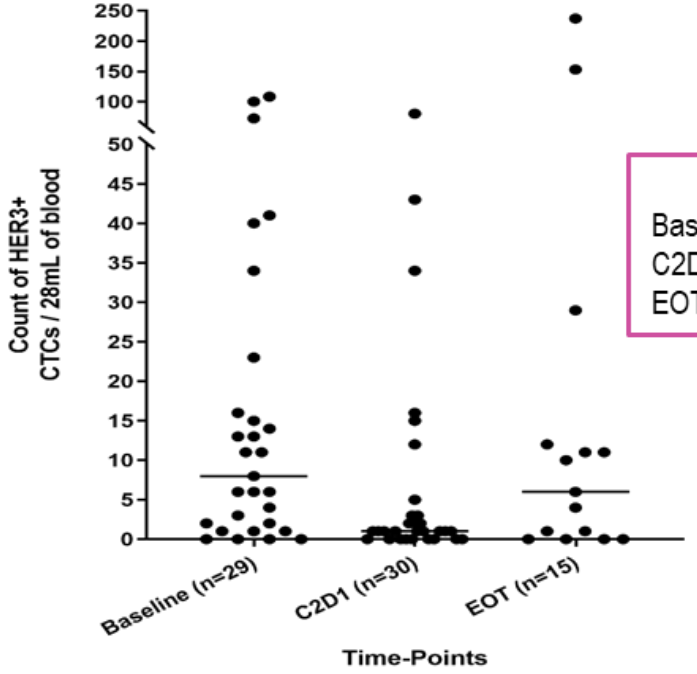
31 pts with evaluable CTC samples, n (%)	
Partial response	9 (29.0)
Stable Disease	16 (51.6)
Progressive Disease	6 (19.3)



Median	
Baseline :	2
C1D3 :	4
C1D19&C2D3 :	0
EOT :	1

HER3+ (cytokeratins+/-) CTCs by FACS*

(31 patients, 74 blood samples)



Median	
Baseline :	8
C2D1 :	1
EOT :	6

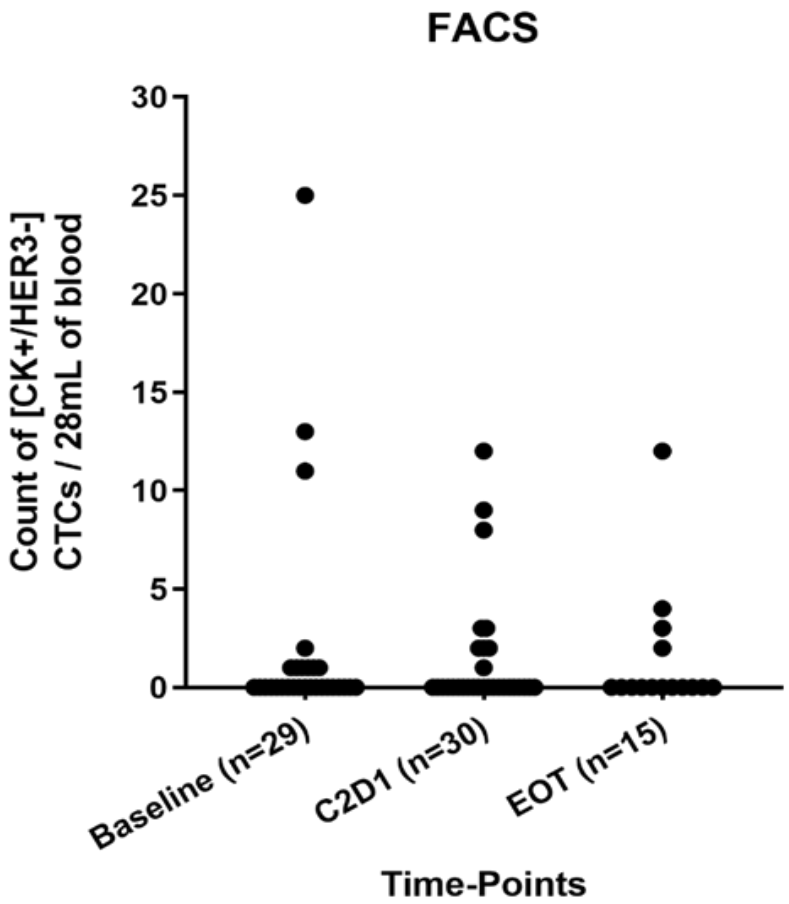
The median number of CTCs decreased after one to two cycles of HER3-DXd, mainly HER3+CTCs

*By FACS (Fluorescent Activated Cell Sorting) almost all detectable HER3+ CTCs were CK+
HER3, Thermofisher clone RTJ2 (ref MA1-860)
19 patients with assessable CTC were HER3+++ at baseline (included before the study amendment)

CTC COUNT AFTER FIRST HER3-DXD CYCLE

HER3- (cytokeratins+/-) CTCs by FACS*

(31 patients, 74 blood samples)



Median	
Baseline :	0
C2D1 :	0
EOT :	0

No substantial impact of the treatment on HER3- CTC count
No increase of HER3- CTC count at progression

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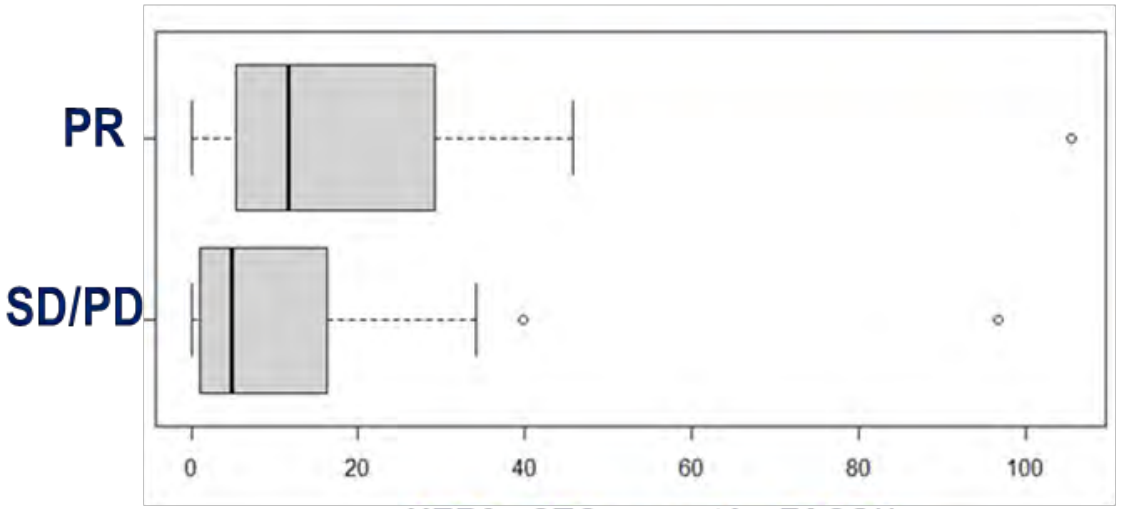
HER3+ CTCs DYNAMICS AND TREATMENT RESPONSE

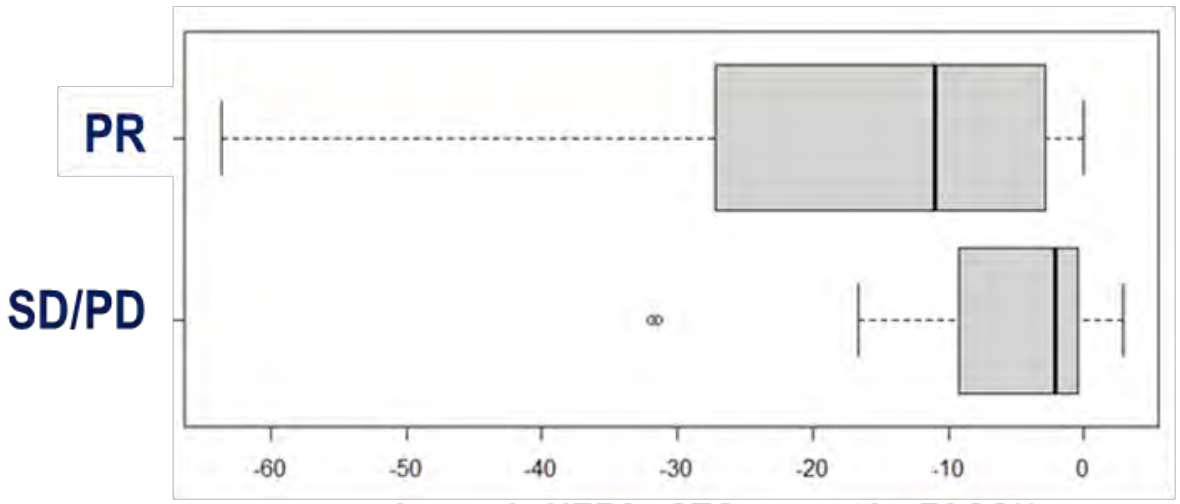
Daiichi-Sankyo

HER3+ CTCs AT BASELINE



OR 1.07 [95%CI 0.92-1.26] (p=0.335)

HER3+ CTCs DECREASE FROM BASELINE TO C2D1



OR 0.78 [95%CI 0.54; 1.02] (p=0.102)

Patients with higher HER3+CTCs count at baseline or greater HER3+ CTCs decrease after the 1st HER3-DXd cycle were more likely to have a early treatment response, although the association was not statistically significant

**CTC count as continuous variable

Univariable logistic models were performed to evaluate the relation between the response status and the CTC count. PR: partial response; SD:stable disease; PD: progressive disease

TUMOR GENOMIC ALTERATIONS AND TREATMENT RESPONSE

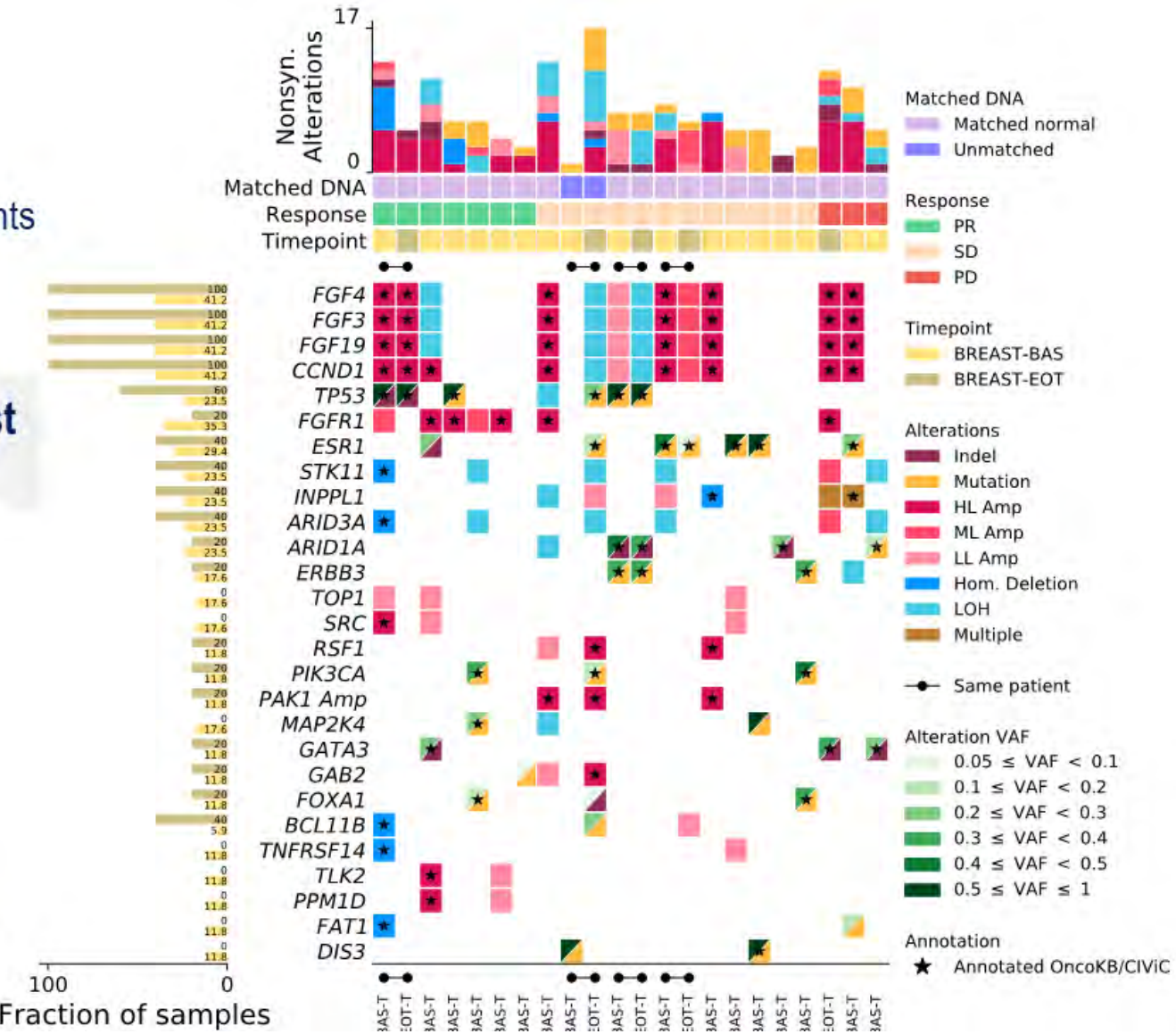
Whole-exome sequencing from frozen samples of 18 patients
-> 17 baseline samples
-> 5 samples at progression, 4/5 matched with baseline

HER3-DXd seems to be active regardless of most frequent breast cancer genomic alterations

The type of the somatic alterations are coded according to the legend.

Somatic mutations were filtered to exclude
1. non-exonic variants;
2. variants from positions with shallow coverage (< 20 tumor reads or < 10 normal reads);
3. variants with a VAF < 5% ;
4. variants seen in wild-type populations at MAF > 0.04% (gnomAD);
5. synonymous variants

Somatic copy-number alterations (CNAs) were filtered to include only
1. focal copy-number segments (< 10Mb in size)
2. Homozygous deletions (Hom. Del), losses-of-heterozygosity (LOH), high- (6+ copies), medium- (4,5 copies), and low-level (3 copies) amplifications



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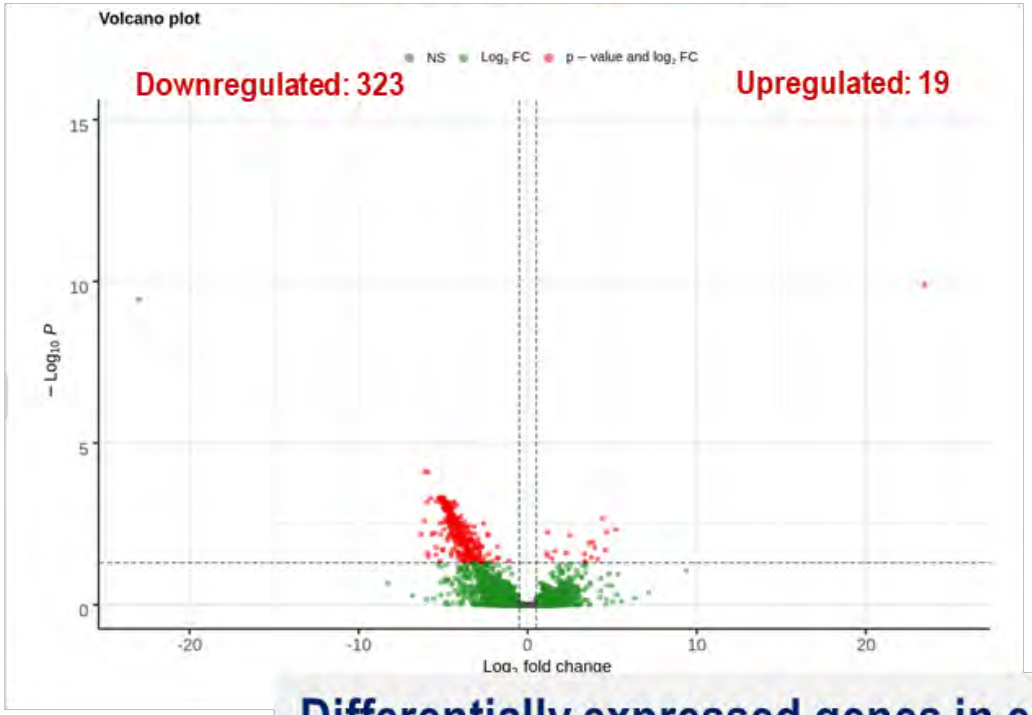
TRANSCRIPTOMIC RESPONSE TO HER3-DXD IN EARLY RESPONDERS

RNAseq from frozen samples of 24 patients -> 24 baseline samples and
->14 matched on-treatment samples (C1D3/C1D19/C2D1)

RESPONDERS (n=7)



NON-RESPONDERS (n=17)

Differentially expressed genes in early responders and non-responders

RNAseq: RNA sequencing

Volcano plot of differentially expressed genes between on-treatment and baseline in responders (PR at 3 mos) and non-responders (SD/PD at 3 mos). The red dots indicate genes with a adjusted *p*-value <0.05. The red dots on the right quadrant of the figures are up-regulated the ones on the left are down-regulated. The green dots represent the genes that did not reach the *adjusted p*-value <0.05

KEY FINDINGS AND PERSPECTIVES

- **HER3-DXd showed a manageable safety profile and early signs of clinical activity in patients who progressed on CDK4/6inh and further lines of endocrine therapy +/- target therapies;** these data are consistent with prior results of HER3-DXd in advanced breast cancer

- **Total and HER3+ CTCs count decreased after the first cycle of HER3-DXd; although not statistically significant, patients with higher HER3+ CTCs count at baseline and patients with greater HER3+CTCs decrease were more likely to have an early treatment response (3-mos RR)**
  - Further analysis will be performed to evaluate the association between HER3+CTCs count and dynamics and main treatment outcomes (ORR, PFS), to determine whether HER3+CTCs can help to better select patients who can benefit of HER3-DXd

- **RNAseq showed a higher modulation of gene expression in early responders as compared to non-responders: is primary resistance more related to reduced ADC internalization/binding ?**

- **ICARUS BREAST01 study is still ongoing and further efficacy and biomarker analysis will be presented**

PATRITUMAB DERUXTECAN (HER3-DXD) IN HR+/HER2- AND TNBC: RESULTS OF PART B OF SOLTI TOT-HER3 WINDOW OF OPPORTUNITY TRIAL

Mafalda Oliveira, T. Pascual, P. Tolosa, M. Margelí, J.M. Cejalvo, J. Cruz, F.J. Salvador Bofill, M. A. Arumi de Dios, M. Vidal, S. Pernas, S. Esker, P.-D. Fan, A. Santhanagopal, O. Martínez-Sáez, F. Brasó-Maristany, G. Villacampa, R. Sanchez-Bayona, J. M. Ferrero-Cafiero, C. Falato and A. Prat

ESMO 2023 #124O Oral

On behalf of the investigators

DECLARATION OF INTERESTS

Mafalda Oliveira MD, PhD

Grant/Research Support (to the Institution): AstraZeneca, Ayala Pharmaceuticals, Boehringer-Ingelheim, Genentech, Gilead, GSK, Novartis, Roche, Seagen, Zenith Epigenetics

Consultant: AstraZeneca, Daiichi-Sankyo / AstraZeneca, Gilead, iTEOS, MSD, Pierre-Fabre, Relay Therapeutics, Roche, Seagen

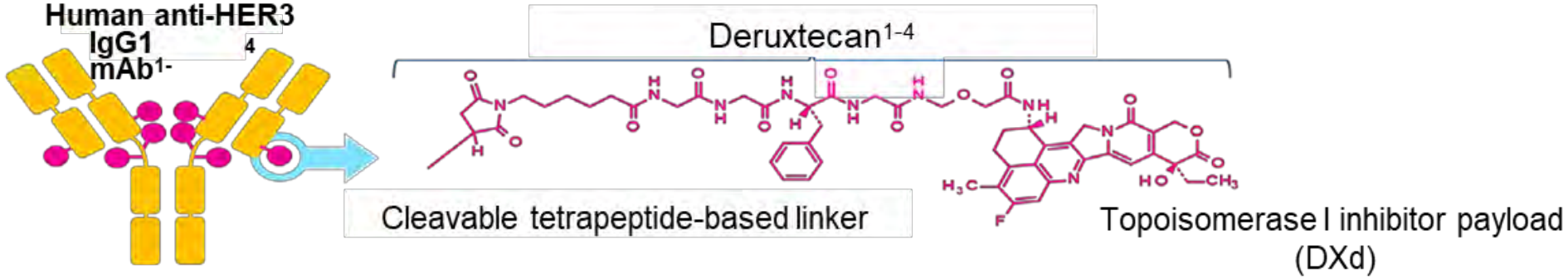
Honoraria: AstraZeneca, Eisai, Gilead, MSD, Novartis, Pfizer, Roche, Seagen

Travel Grants from AstraZeneca, Eisai, Gilead, Pierre-Fabre

Non-financial disclosure: member of the SOLTI Executive Board and Scientific Committee

BACKGROUND

- Patritumab deruxtecan (HER3-DXd; U3-1402) is a novel HER3-directed ADC composed of a human anti-HER3 mAb covalently linked to a topoisomerase I inhibitor payload via a stable, tumor selected, tetrapeptide-based, cleavable linker[1-4]
- HER3-DXd has demonstrated antitumor activity and an acceptable safety profile in heavily pretreated patients with metastatic breast cancer with varying levels of HER3 protein expression[5,6]
- The SOLTI TOT-HER3 study (NCT04610528) previously reported the biologic and clinical activity of a single dose of HER3-DXd in Part A of the trial[7]



HER3; human epidermal growth factor receptor 3; mAb, monoclonal antibody.

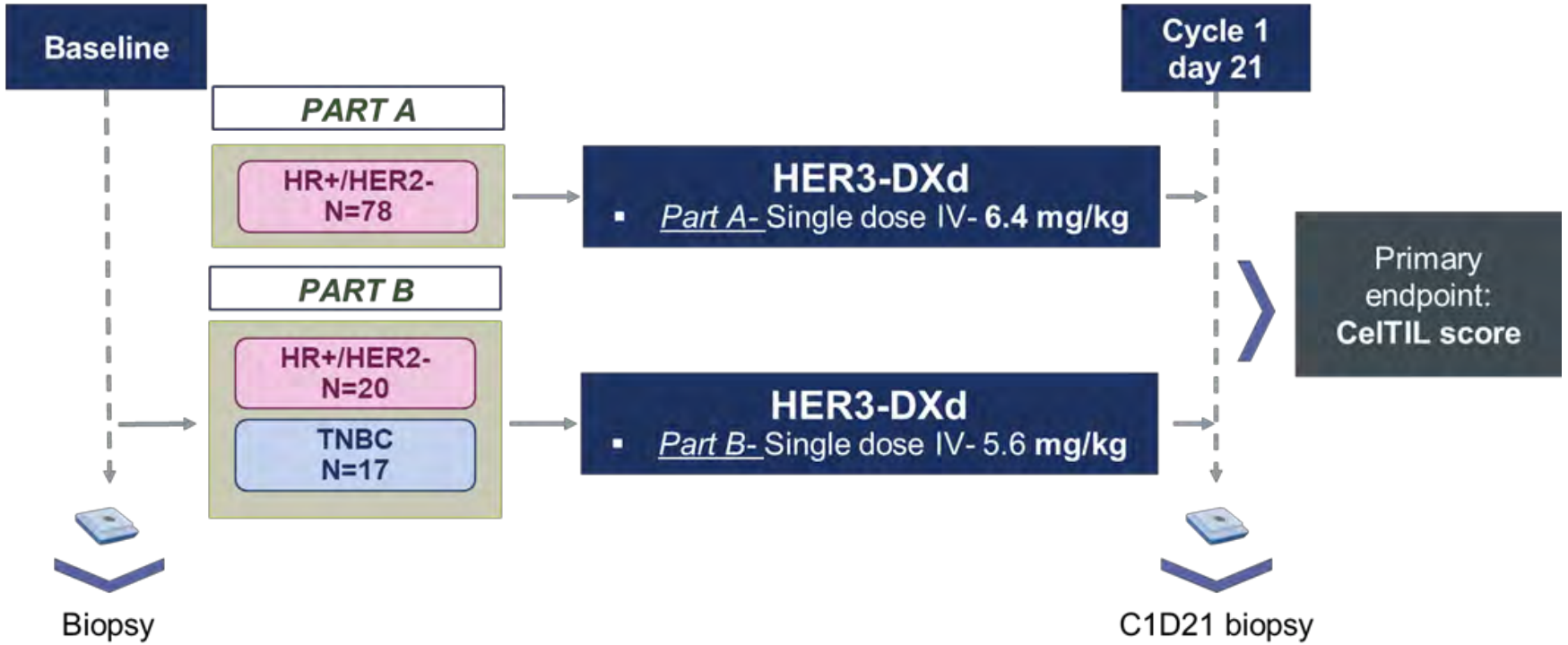
1. Hashimoto Y, et al. *Clin Cancer Res*. 2019;25(23):7151-7161; 2. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185; 3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108; 4. Koganemaru S, et al. *Mol Cancer Ther*. 2019;18(11):2043-2050. 5. Masuda N, et al. SABCS 2018. Abstract PD1-03; 6. Krop et al. SABCS 2020. Poster PD1-09; 7. Prat A, et al. ESMO Breast 2022. Proffered paper LBA3 and Oliveira M. et al, Ann Oncology, in press.

TOT-HER3 STUDY DESIGN

- Prospective, multicenter, window of opportunity trial

Key eligibility criteria

- Pre- and post-menopausal women, or men
- Primary operable breast cancer ≥1 cm by US or MRI
- HR-positive[a]/HER2-negative OR TNBC by local assessment
- Ki67 ≥10% by local assessment
- No previous anticancer treatment for the current diagnosis of breast cancer
- Available pre-treatment FFPE core-needle biopsy

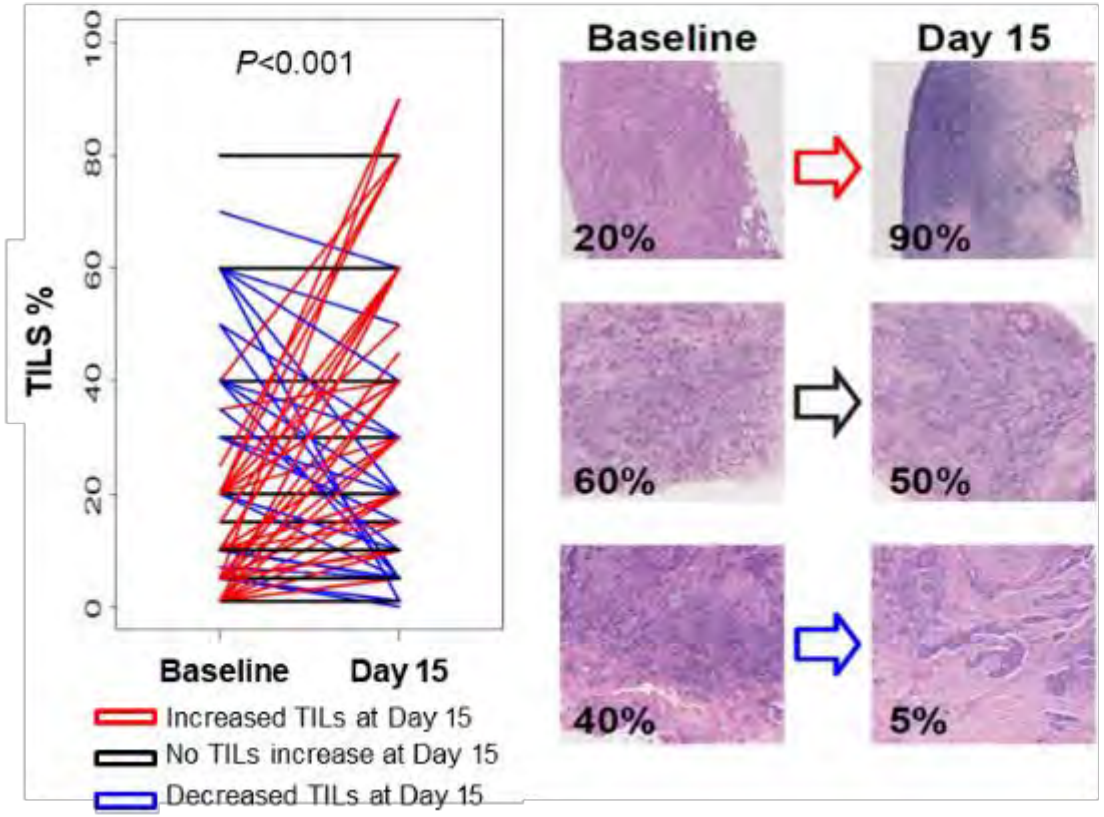


[a]Nuciforo et al. Ann Oncol. 2018

FFPE, formalin fixed paraffin embedded; HR, hormone receptor; US, ultrasonography; MRI, magnetic resonance imaging. [a] HR-positive status was defined as estrogen receptor and/or progesterone receptor positive status.

PRIMARY ENDPOINT: CELTIL SCORE

- CelTIL score correlates with pCR across breast cancer subtypes[1-4]
- Retrospective Analysis from PAMELA trial



CelTIL score[1] =
-0.8 × tumor cellularity (%) +
1.3 × TILs (%)

TILs, tumor infiltrating lymphocytes; pCR, pathological complete response.

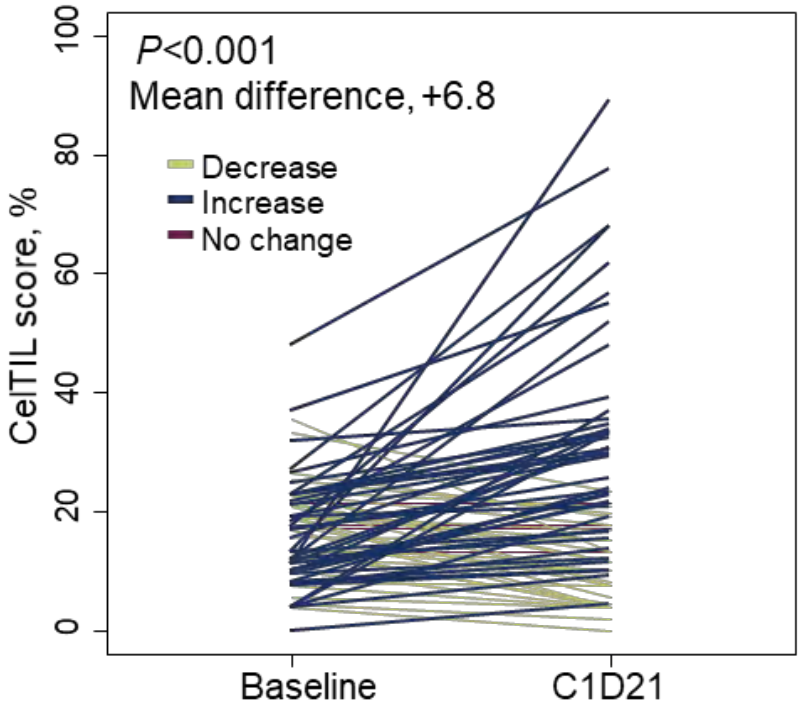
1. Nuciforo P, et al. Ann Oncol. 2018;29(1):170-177; 2. Chic N, et al. J Natl Cancer Inst. 2022;114(3):467-470; 3. González-Farré B, et al. Ann Oncol. 2020;31(suppl 2). Abstract 15P; 4. Manso L et al. Ann Oncol. 2020;31(suppl2). Abstract 41P.

PART A: CELTIL INCREASE AFTER 1 DOSE OF HER3-DXD

Daiichi-Sankyo

Overall CelTIL Change from Baseline

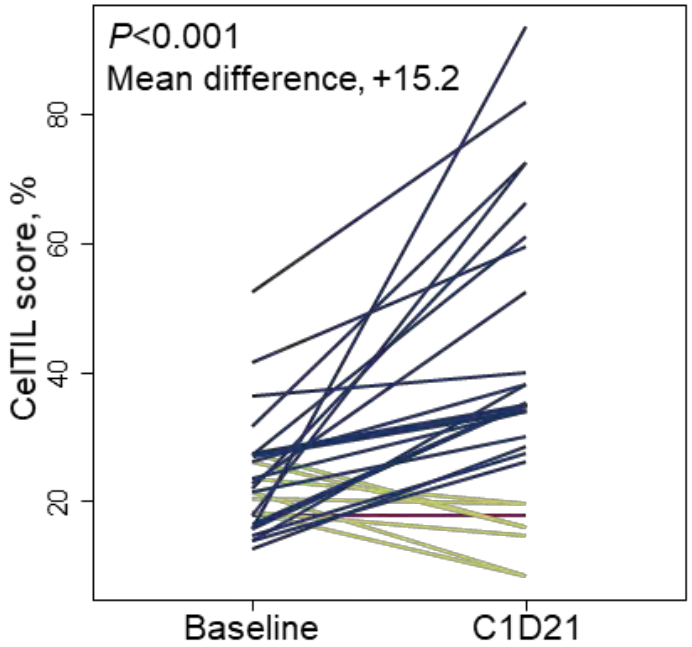
All patients (N=77)



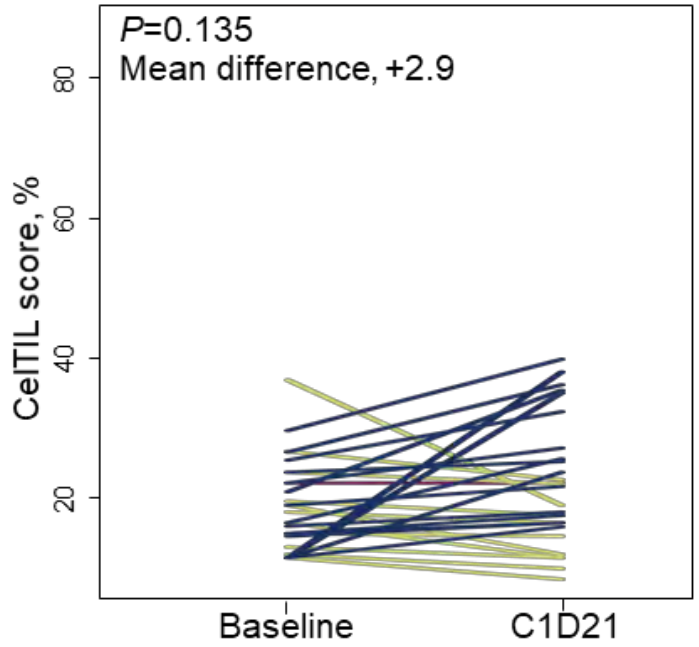
CelTIL Change by Clinical Response

ORR by **physical exam** at C1D21 was 45%

Responders[a] (N=28)



Non-responders[b] (N=34)



[a] Complete responses (N=14); partial responses (N=14); [b] Non-responders include patients with stable disease (no progressive disease was observed in the trial).

Prat A, et al. ESMO Breast 2022. Proffered paper LBA3 and Oliveira M. et al, Ann Oncology, in press.

STUDY OBJECTIVES – PART B

- Variation in CelTIL score between baseline and post-treatment (C1D21) tumor samples after 1 dose of HER3-DXd
- Overall response rate (ORR) measured at C1D21 by ultrasound
- Change in CelTIL score according to baseline expression levels of *ERBB3* mRNA
- Switch in PAM50 subtypes
- Differential expression of 67 genes at C1D21
- Safety and tolerability

Part B of TOT-HER3

1. Lower dose: 5.6mg/Kg
2. Response rate assessed by breast US
3. Inclusion of a small subset of TNBC to assess preliminary efficacy in this subtype

BASELINE CHARACTERISTICS

Assessed for eligibility (N=44)

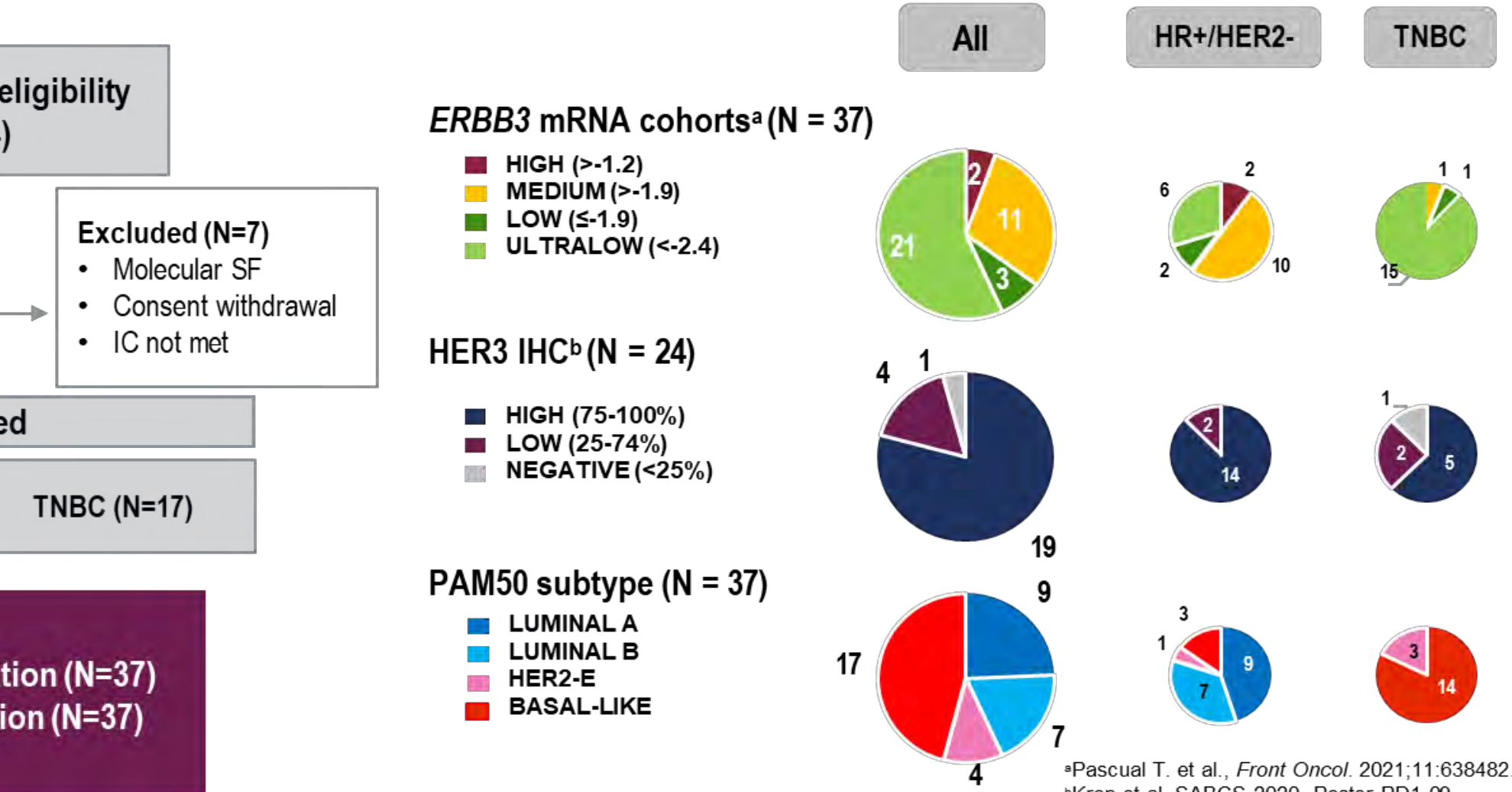
Excluded (N=7)
- Molecular SF
- Consent withdrawal
- IC not met

Included

HR+/HER2- (N=20)

TNBC (N=17)

Efficacy population (N=37)
Safety population (N=37)



[a]Pascual T. et al., *Front Oncol*. 2021;11:638482.
[b]Krop et al. SABCS 2020. Poster PD1-09.

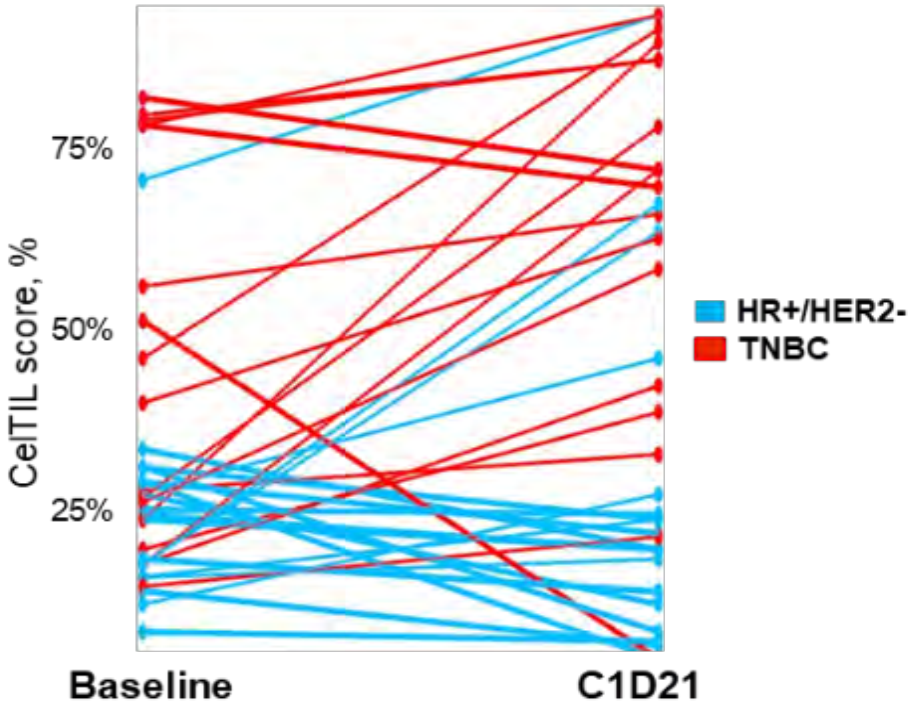
PATIENTS' CHARACTERISTICS

	ALL N= 37	HR+/HER2- N = 20	TNBC N = 17
Age			
Median (Range)	51 (30-81)	51 (30-65)	50 (30-81)
Race N (%)			
Caucasian	34 (92)	17 (85)	17 (100)
Other	3 (8)	3 (15)	0
Menopausal status N (%)			
Premenopausal	20 (54)	12 (60)	8 (47)
Postmenopausal	17 (46)	8 (40)	9 (53)
Histology N (%)			
Ductal	33 (89)	18 (90)	15 (88)
Lobular	2 (5)	2 (10)	0
Other	2 (5)	0	2 (12)
Tumor size by US			
Median, mm (range)	21 (10-80)	21.5 (10-32)	26 (11-80)
T size N (%)			
cT1	7 (19)	5 (25)	2 (12)
cT2	25 (68)	13 (65)	12 (71)
cT3	5 (14)	2 (10)	3 (18)

	ALL N= 37	HR+/HER2- N = 20	TNBC N = 17
Nodal status N (%)			
cN0	28 (76)	17 (85)	11 (65)
cN1	9 (24)	3 (15)	6 (35)
KI67 local			
Median, % (range)	30 (12-95)	20 (12-90)	70 (15-95)
Grade N (%)			
G1	2 (5)	2 (10)	0
G2	11 (30)	10 (50)	1 (6)
G3	19 (51)	6 (30)	13 (77)
NR	5 (14)	2 (10)	3 (18)
ER IHC N (%)			
0	17 (46)	0	17 (100)
1-10%	5 (14)	5 (25)	0
90-100%	15 (41)	15 (75)	0
PR IHC N (%)			
0	23 (62)	6 (30)	17 (100)
0-10%	3 (8)	3 (15)	0
60-100%	11 (30)	11 (55)	0
HER2 IHC N (%)			
0	20 (54)	6 (30)	14 (82)
1+	10 (27)	7 (35)	3 (18)
2+	7 (19)	7 (35)	0

PRIMARY ENDPOINT: CELTIL CHANGE AFTER 1 DOSE

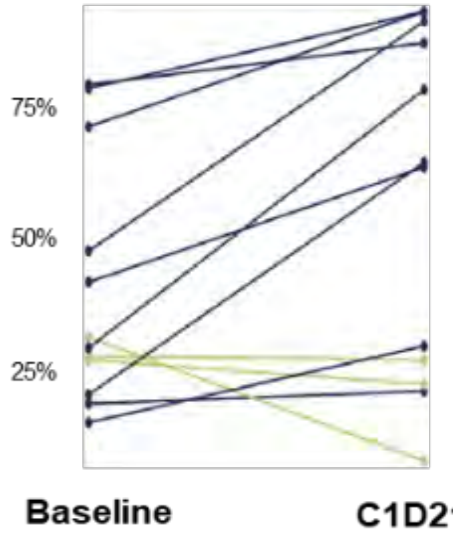
ALL (N =37)
Mean difference = +9.4, *p=0.046*



HR+/HER2- (N =20): Mean diff.= +2.2
TNBC (N =17): Mean diff. = +17.9

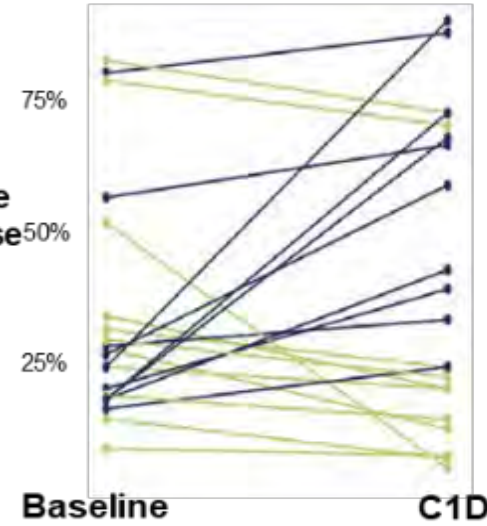
*The ORR **by Ultrasound** at C1D21 was 32% (35% in TNBC and 30% in HR+/HER2-)*

Responder
N =12
Mean difference = +23.9



p= 0.043

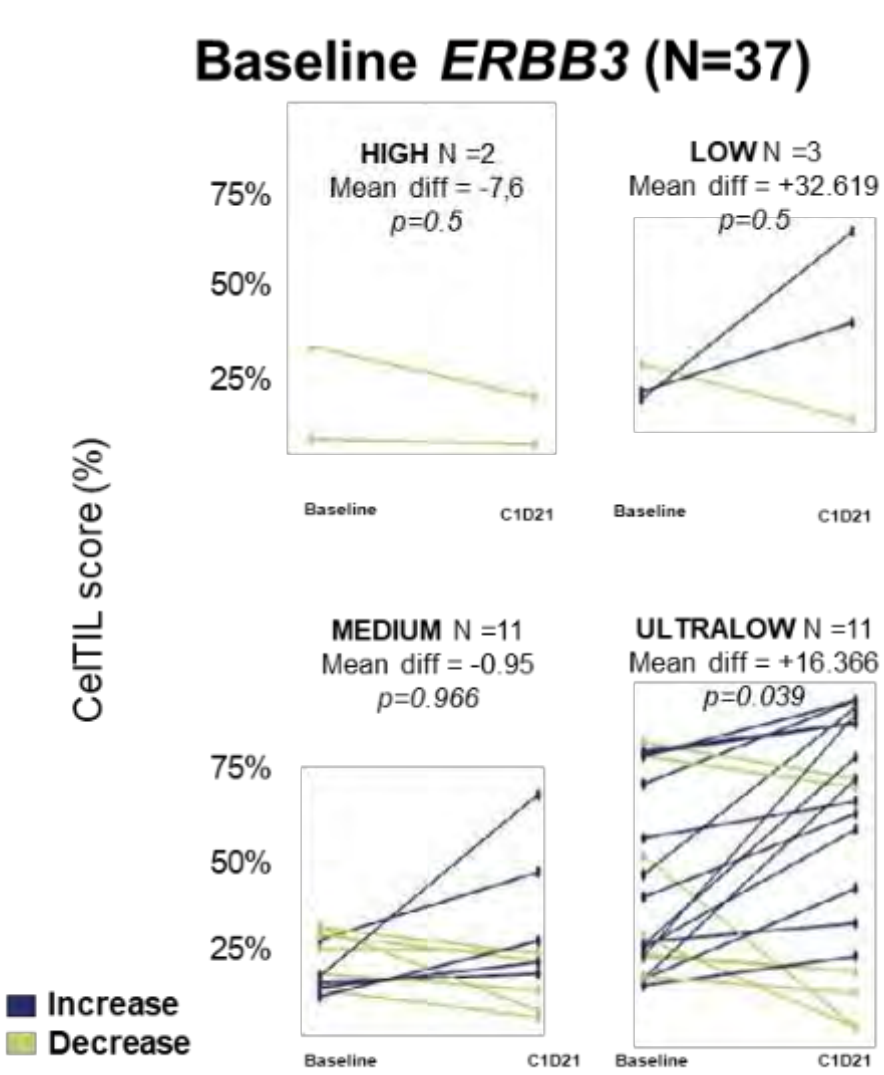
Non-responder
N =22
Mean difference = +4.77

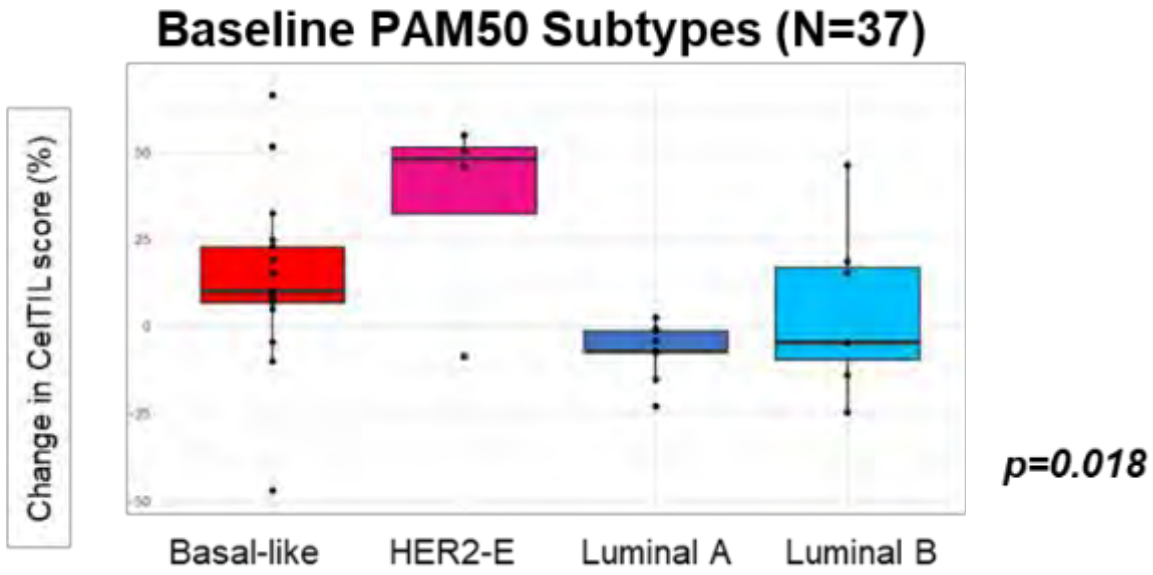


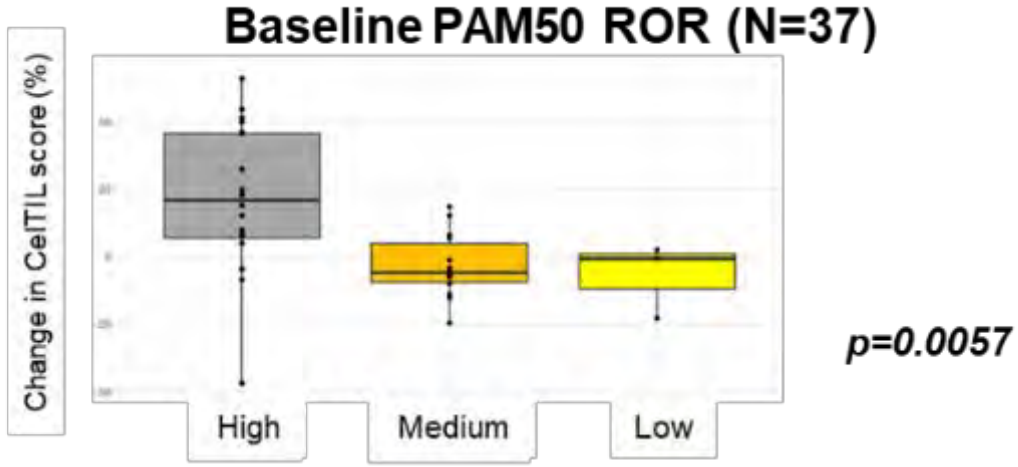
p = 0.445

The absolute change in CelTIL was associated with ORR (AUC=0.693; p=0.049)

CELTIL VARIATION BY *ERBB3* COHORT, PAM50 SUBTYPE AND ROR







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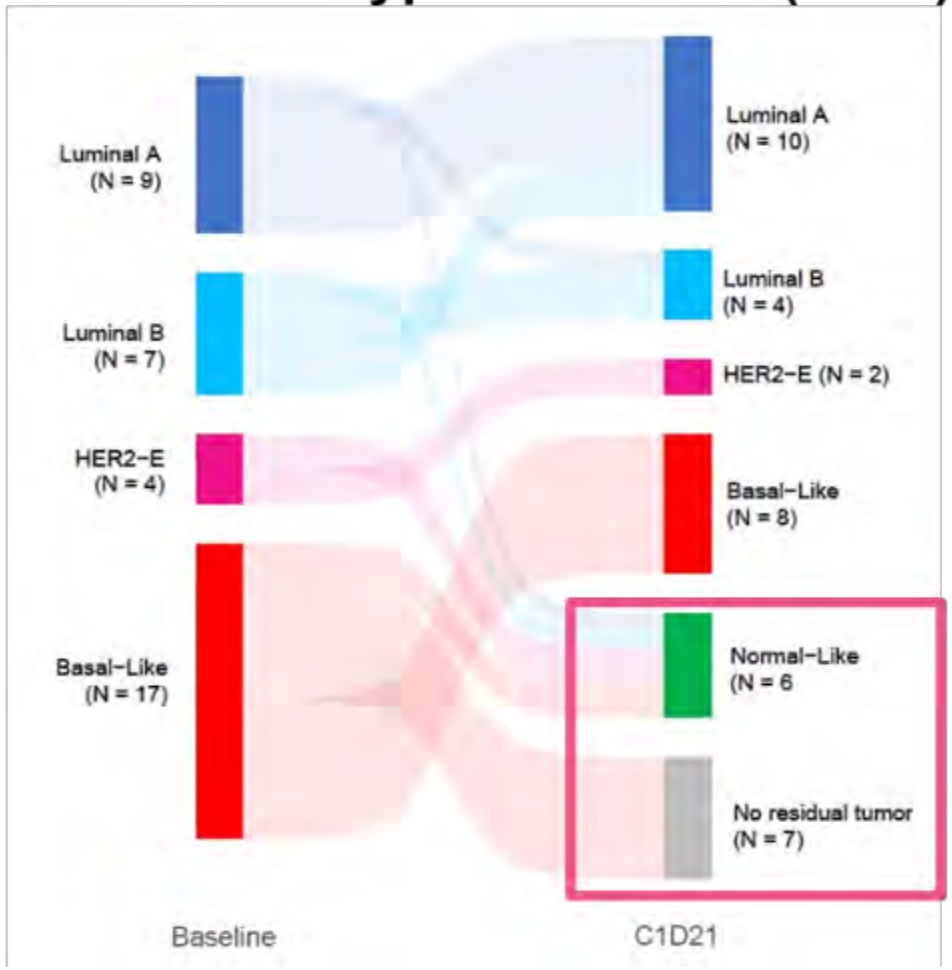
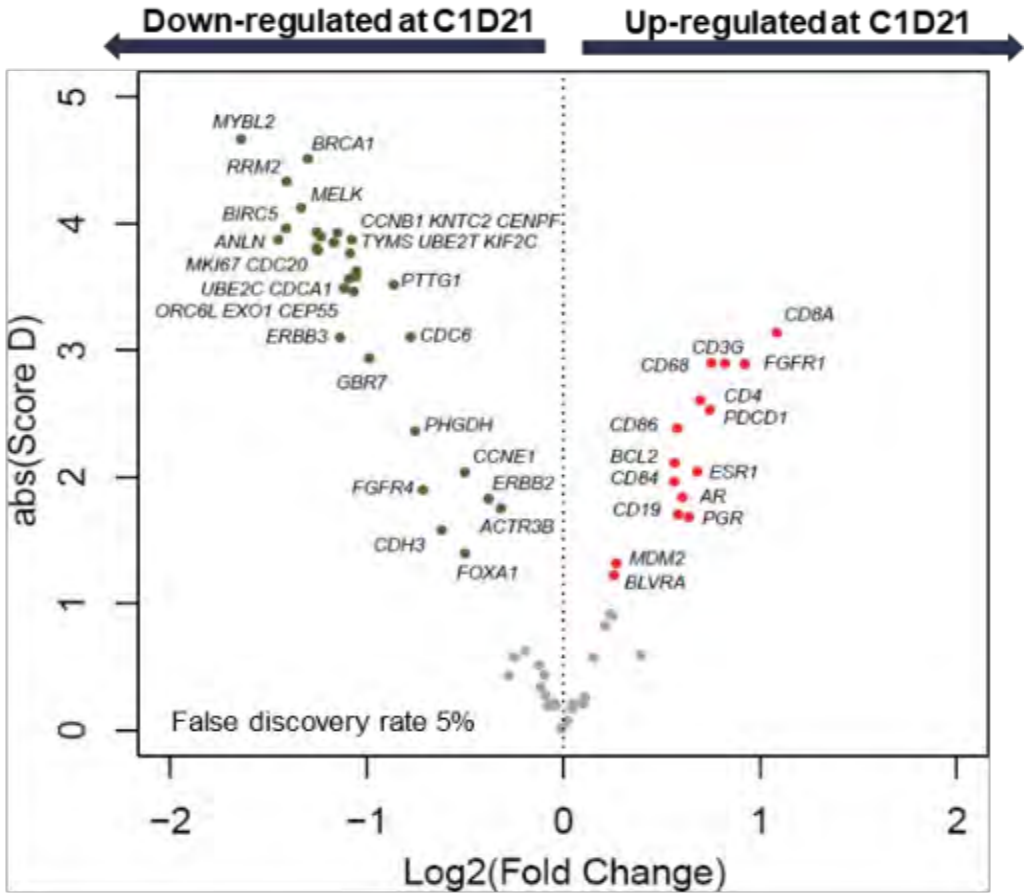
PAM50 SWITCH AND GENE EXPRESSION CHANGES

Daiichi-Sankyo

PAM50 Subtypes Switched (N=37)



Gene Expression Changes (N=37)



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SAFETY SUMMARY

TEAEs N (%)[a]	Part B 5.6 mg/kg N=37	Part A 6.4 mg/kg N=78
All grades	**31 (84)**	**74 (96)**
Grade 4	0	4 (5)
Grade 3	2 (5)	10 (13)
Grade 2	15 (41)	45 (58)
Grade 1	31 (84)	71 (91)
SAEs, all grades	**2 (5)**	**4 (5)**
Grade 3	1 (3)	3 (4)

- Lower incidence of hematological and hepatic toxicity compared to Part A (6.4 mg/kg)
- No ILD events were observed
- No Grade 4/5 events

TEAEs in >5% of patients, N (%)	Part B 5.6 mg/kg N=37		Part A 6.4 mg/kg N=78	
	All grades	Grade 3	All grades	Grade ≥ 3
Nausea	24 (65)	1 (3)	52 (67)	0
Fatigue	17 (46)	0	32 (41)	0
Alopecia	10 (27)	NA	28 (36)	NA
Diarrhea	8 (22)	0	19 (24)	1 (1)
Constipation	5 (14)	0	10 (13)	0
Headache	5 (14)	0	2 (3)	0
Transaminitis	5 (14)	0	15(19)	2(3)
Vomiting	4 (11)	0	20 (26)	0
Abdominal pain	3 (8)	0	17 (22)	0
Anemia	3 (8)	0	3 (4)	0
Erythema	3 (8)	0	3 (4)	0
Neutrophil count decrease	0	0	15 (19)	6 (8)

ILD, interstitial lung disease; SAEs, serious adverse events; TEAE, treatment-emergent adverse event.

[a] Patients could experience ≥1 adverse event

KEY FINDINGS

- In untreated HER2-negative early-stage breast cancer, a significant increase in CelTIL score is observed after one dose of HER3-DXd at 5.6 mg/kg
- A single dose of HER3-DXd induced a ~30% ORR (measured by breast US), independently of HR status
- A lower incidence of hematological and hepatic toxicity was observed with 5.6 mg/kg of HER3-DXd (Part B) compared with 6.4 mg/kg (Part A)
- SOLTI-2103 VALENTINE (NCT05569811) neoadjuvant phase II trial (n=120) is currently testing 6 cycles of HER3-DXd at 5.6 mg/kg in HR+/HER2- breast cancer

HER2 expression and early response to patritumab deruxtecan (HER3-DXd) in early-stage HR+/HER2- breast cancer: A correlative analysis from TOT-HER3 trial

Fara Brasó-Maristany, Mafalda Oliveira, Pablo Tolosa, Mireia Margelí, Josefina Cruz, Salvador Bofill, Juan Miguel Cejalvo, Miriam Arumí de Dios, Maria Vidal, Sònia Pernas, Stephen Esker, Pang-Dian Fan, Anu Santhanagopal, Olga Martínez-Sáez, Guillermo Villacampa, Rodrigo Sánchez-Bayona, Juan M Ferrero-Cafiero, Claudette Falato, Tomás Pascual and Aleix Prat

DECLARATION OF INTERESTS

Consultancy/speaker: Reveal Genomics

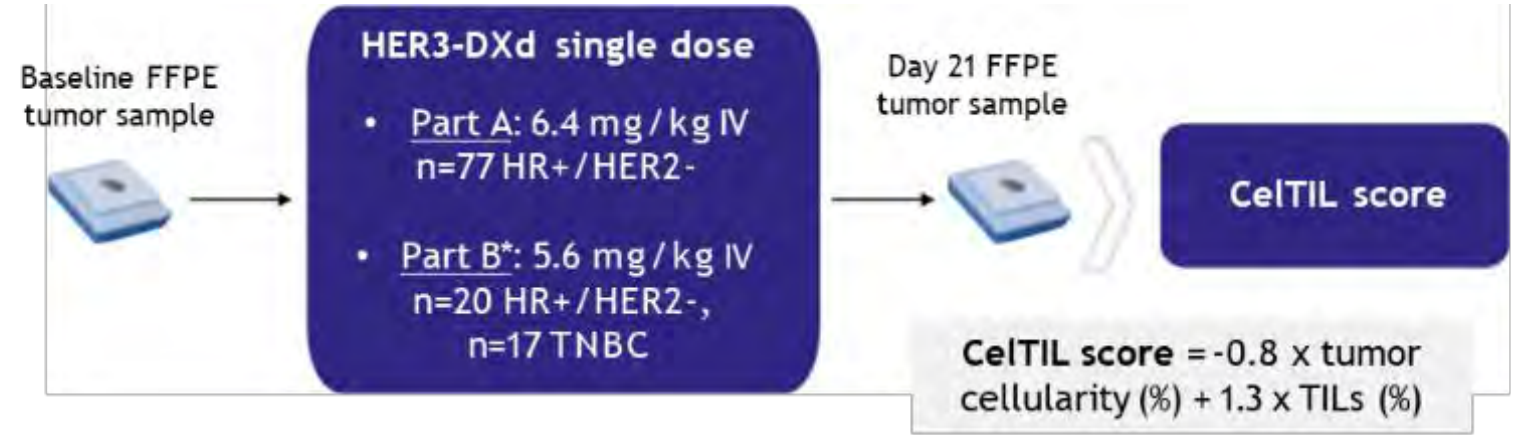
Research funding (my institution): Novartis, Roche, AstraZeneca, Daiichi-Sankyo, PUMA

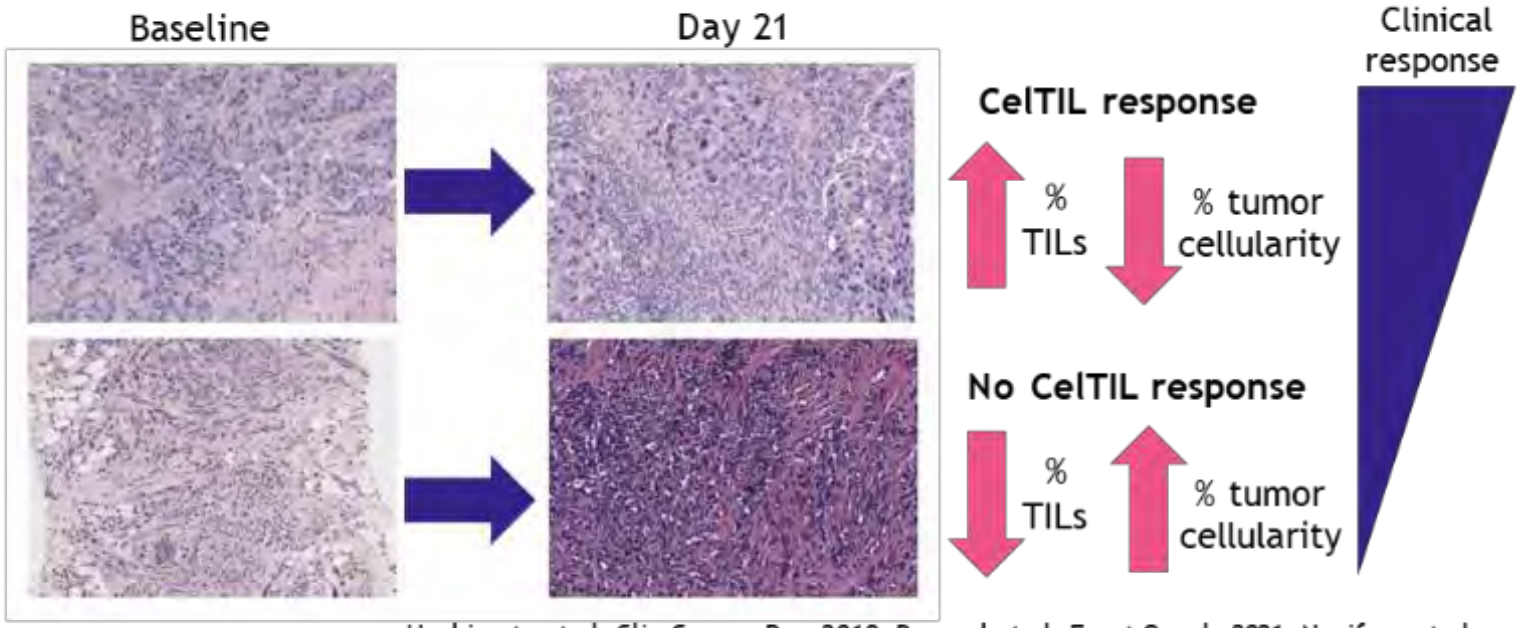
Patents: HER2DX (filed), DNADX (filed)

BACKGROUND (I)

- ✓ Patritumab deruxtecan (HER3-DXd) is a HER3-directed ADC composed of a human anti-HER3 mAb covalently linked to a topoisomerase I inhibitor payload via a cleavable linker.
- ✓ TOT-HER3 window-of-opportunity trial evaluated a single dose of HER3-DXd in untreated early-stage breast cancer.
- ✓ The primary endpoint was CelTIL score at day 21. CelTIL score is an early read-out of drug activity.
- ✓ In TOT-HER3 Part A, CelTIL score increased in most patients and was associated with clinical response at day 21.

*Oral session - 12th May 16.45





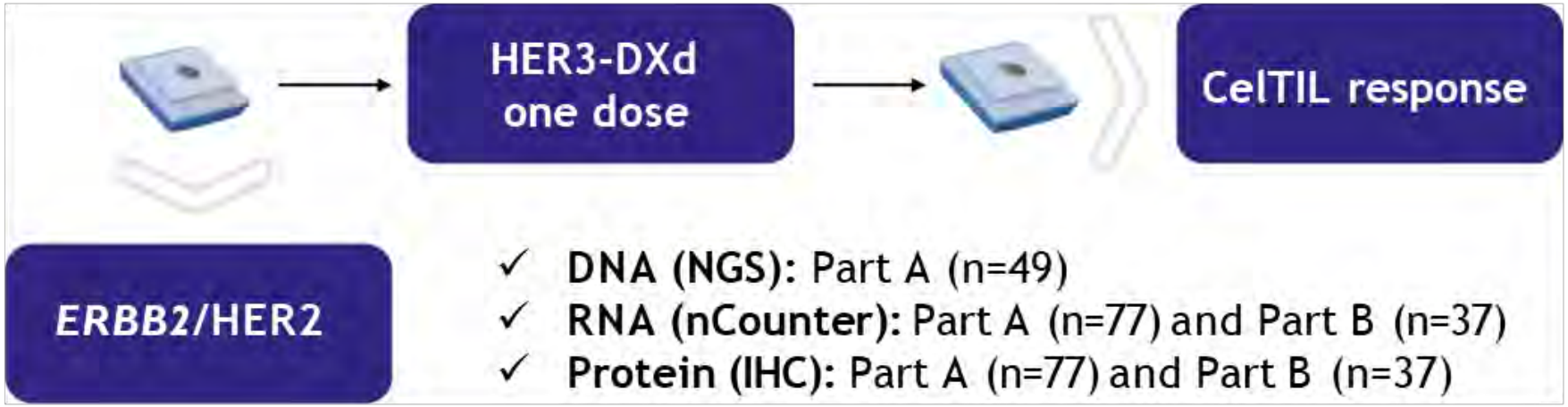
Hashimoto et al. Clin Cancer Res 2019. Pascual et al. Front Oncol. 2021. Nuciforo et al. Ann Oncol. 2018. Chic et al. JNCI 2022. Prat et al. ESMO Breast Cancer 2022.

BACKGROUND (II)

- ✓ In our previous preliminary correlative analysis (n=45) of TOT-HER3 Part A*:
  - ✓ *ERBB3*/HER3 levels **were not associated** with CelTIL response
  - ✓ High proliferation and non-luminal features
  - ✓ Intriguingly, low *ERBB2* mRNA levels

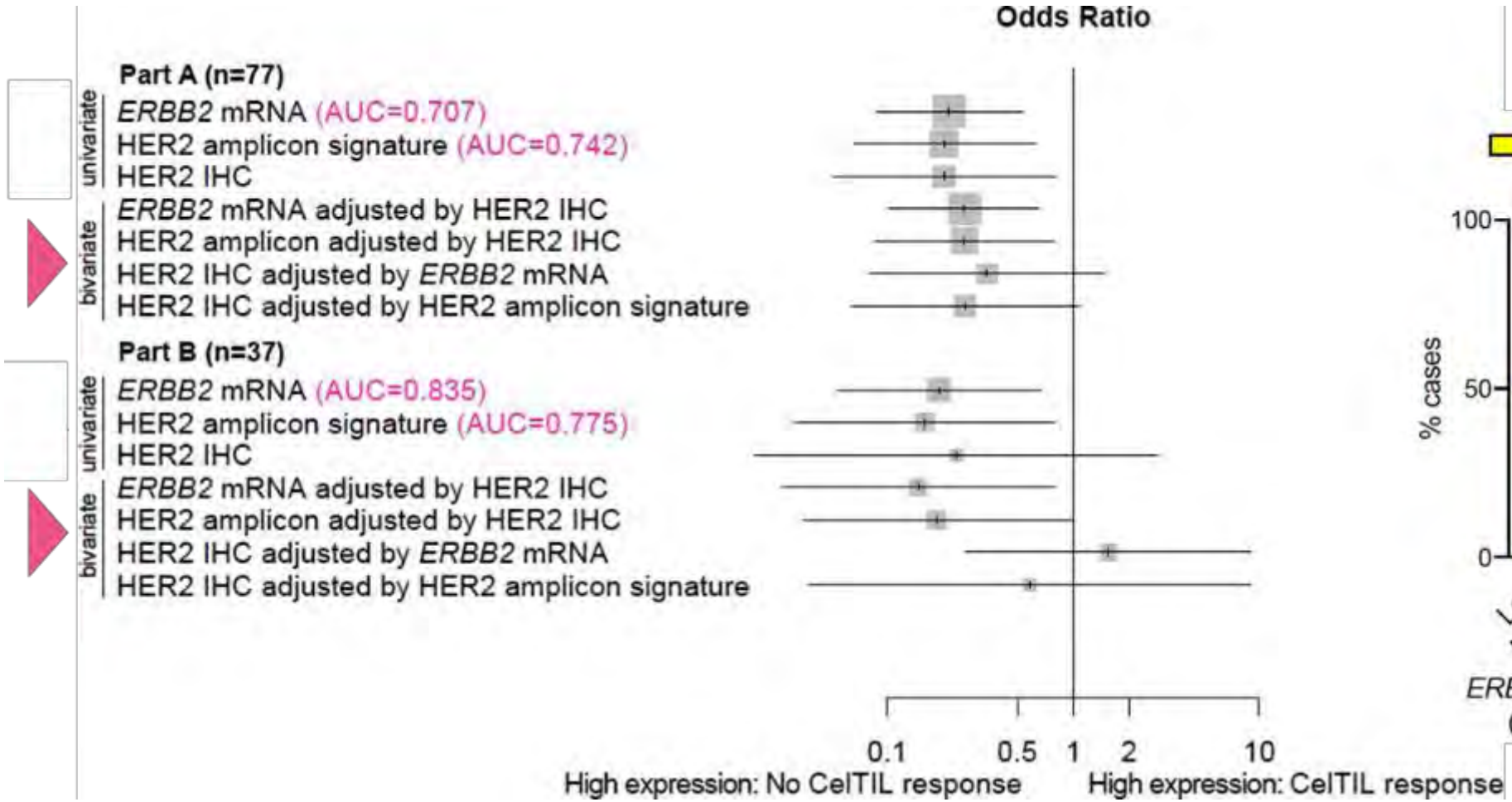
  } **were associated** with CelTIL response

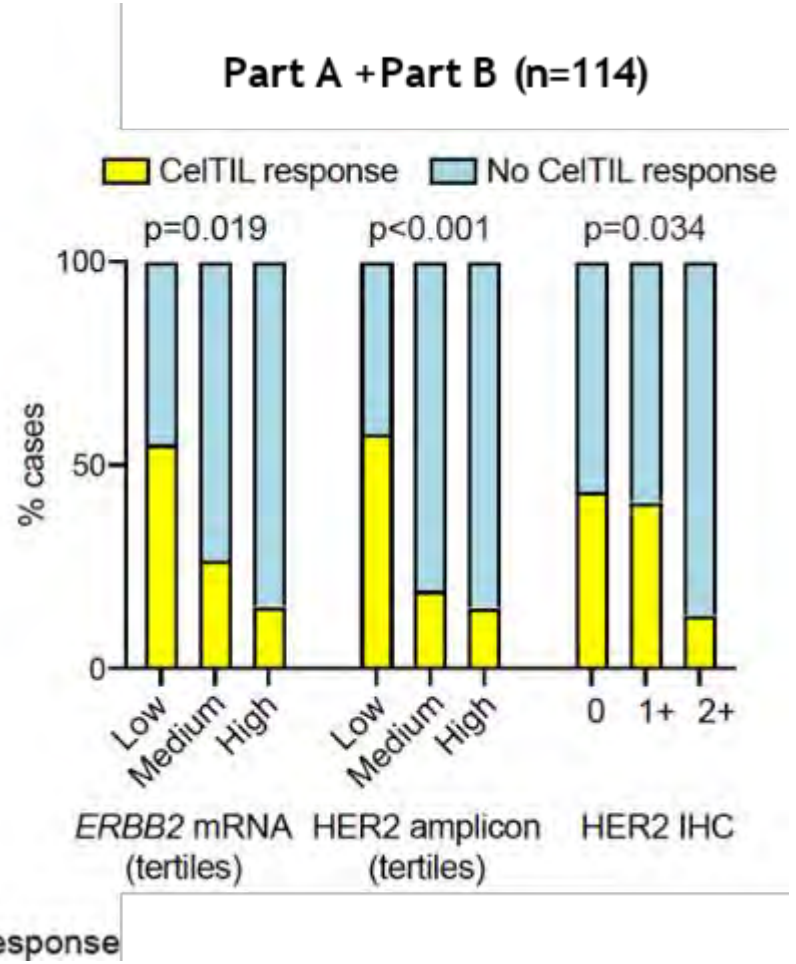
Do *ERBB2*/HER2 levels predict early response to HER3-DXd?



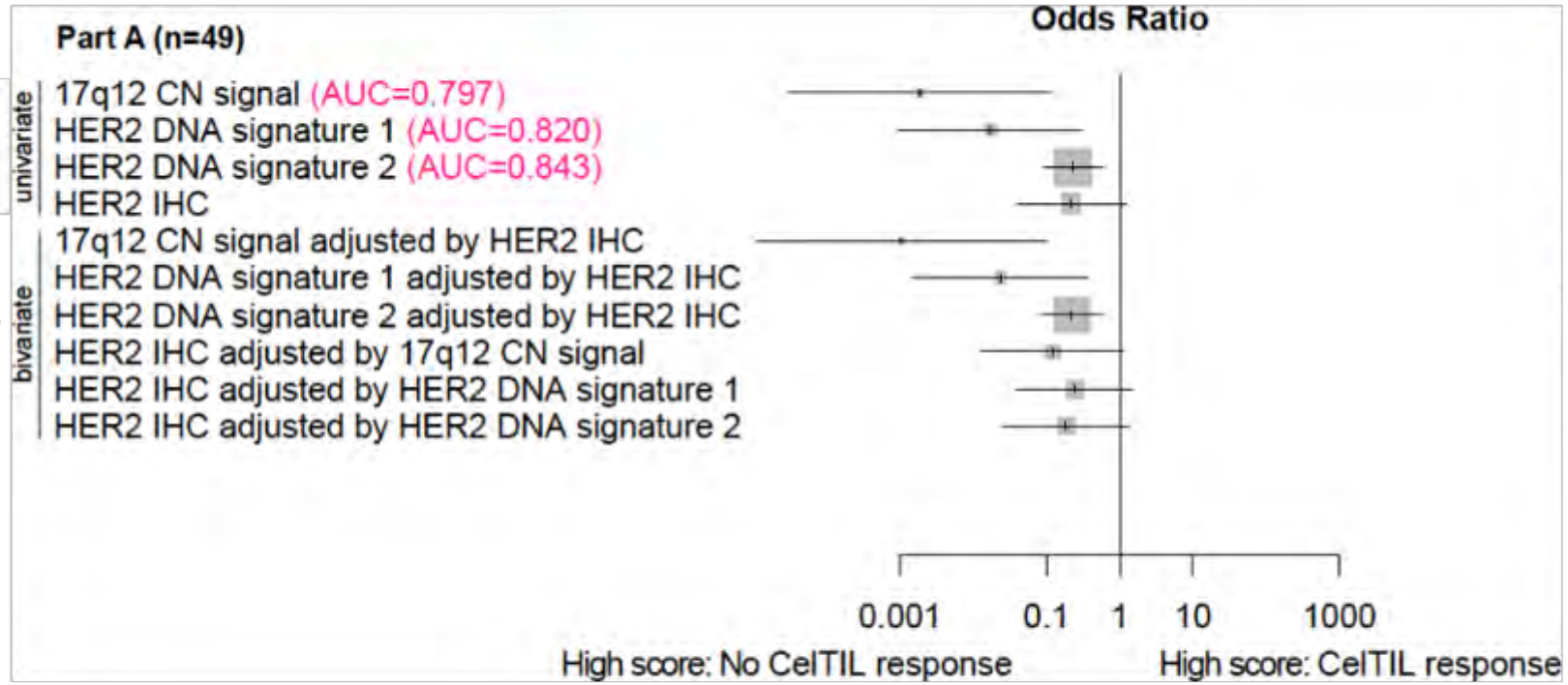
*Brasó-Maristany et al. SABCS 2022

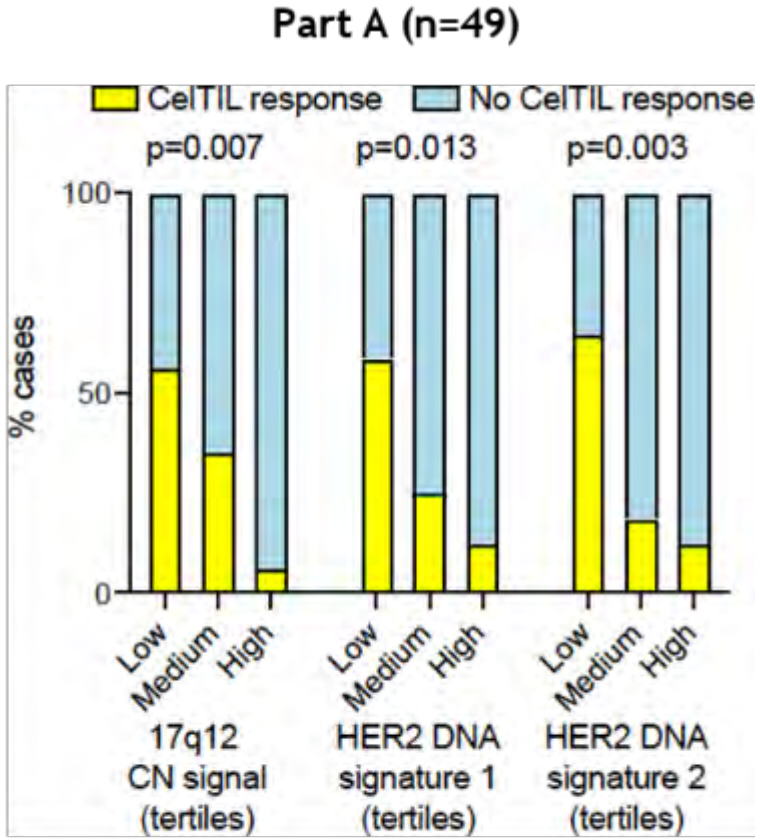
Higher CelTIL response to HER3-DXd in tumors with low *ERBB2* mRNA/HER2 protein expression





Higher CelTIL response to HER3-DXd in tumors with low HER2 DNA copy-number signal





17q12: CN signal of 1 segment
HER2 DNA signature 1: CN signal of 15 segments
HER2 DNA signature 2: CN signal of 33 segments

Xia et al. Nat Comm. 2019. Prat et al. Nat Comm. 2023

CONCLUSIONS

- ✓ In pre-treatment HER2-negative tumors, low levels of HER2 IHC, *ERBB2* mRNA and *ERBB2* DNA copy-number signal are associated with early response to HER3-DXd.
- ✓ Genomic tools may be better suited than IHC to capture HER2 expression levels which in turn can help better inform responses to HER3-DXd.
- ✓ Further analyses are needed to understand the mechanistic explanation behind this finding.
- ✓ Further validation in SOLTI-2103 VALENTINE (NCT05569811).

A randomized phase 2 trial of neoadjuvant multi-agent chemotherapy or patritumab deruxtecan (HER3-DXd; U3-1402) +/- endocrine therapy for high-risk hormone receptor positive (HR+/HER2-) early breast cancer: SOLTI-2103 VALENTINE trial

VALENTINE

SOLTI

Daiichi-Sankyo

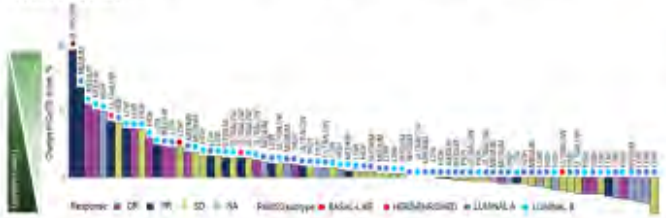
Mafalda Oliveira[1], T. Pascual[2], O. Villacampa[3], M. Morera[4], A. Peralta[5], M.E. Perez Lopez[6], K. Arribas Fernandez[7], E. Gonzalez-Farre[8], C. Martinez Vila[9], P. Tolosa Ortega[10], M. Borrell Poyet[11], M. Margelí[12], J.M. Cejalvo[13], Y. Zhukovskaya[14], D. W. Sternberg[15], P.D. Finn[16], A. Santhanagopal[16], R. Sanchez-Bayona[16], J. M. Ferrero-Gallego[17], A. Prat[18]

Abstract 155TiP

Background

- The decision regarding neoadjuvant treatment for high-risk HR+/HER2- EBC remains a challenge.
- Despite the availability of both chemotherapy and endocrine therapy, the risk of recurrence persists over time, highlighting the need for additional therapeutic strategies.
- In the TOT-HER3 trial, we have shown that a single dose of HER3-DXd, a first-in-class HER3 directed antibody drug conjugate, is associated with clinical response, increased immune infiltration and proliferation suppression, as well as a consistent and manageable safety profile in patients with HR+/HER2-negative early breast cancer[1]

Figure 1. ORR, Subtype and *ERBB3* Groups by Percent Change in CelTIL Score From Baseline



These data have informed the design of the VALENTINE trial of HER3-DXd in the neoadjuvant setting.

What does VALENTINE add?

- First trial testing a full course of neoadjuvant HER3-DXd treatment in patients with early stage breast cancer
- Evaluates the clinical benefit and biological effects of HER3-DXd with or without letrozole, measured by ability to achieve a pCR at surgery.
- Looks at the value of HER3-DXd in long-term efficacy outcomes i.e. iDFS
- Explores a wide range of biomarkers including gene expression, TILs, PKs, and immunohistochemistry (IHC) assays such as DXd, γH2AX, TROP2, HER3 and HER2.
- Translational data will be generated to support the development of biomarkers for HER3-DXd

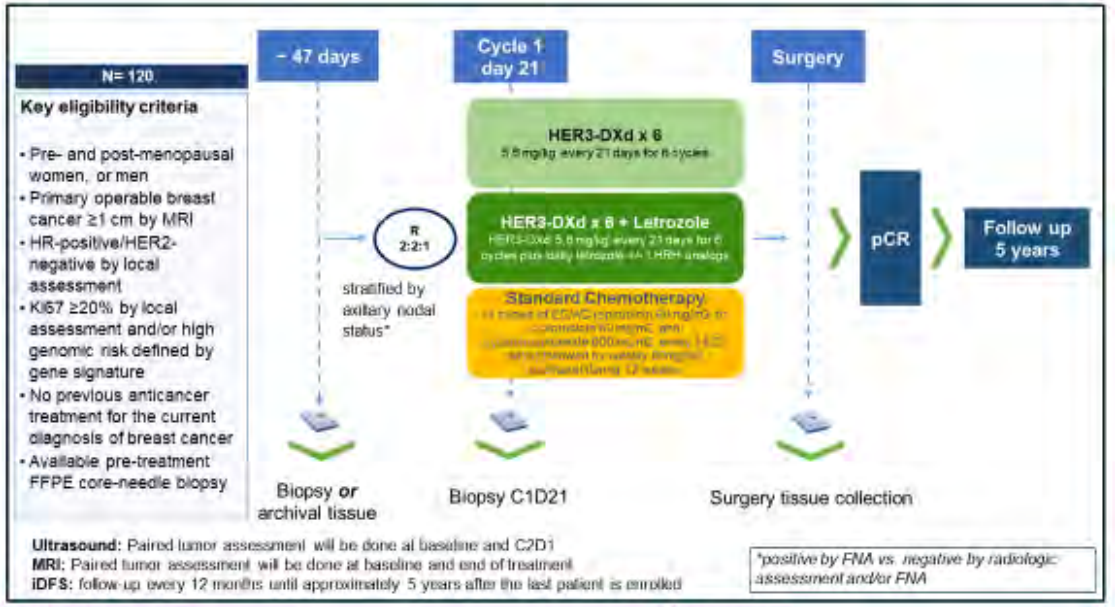
Methods and design

- VALENTINE is a parallel, three-arm, randomized, open-label, exploratory study of neoadjuvant HER3-DXd in patients with primary operable HR+/HER2-negative breast cancer with Ki67 ≥ 20% and/or high genomic risk (defined by gene signature)
- A total of 120 treatment naive pts will be randomly assigned in a 2:2:1 to each of the three arms (see right: study design)
- After completion of the assigned neoadjuvant treatment, patients will undergo surgery
- Adjuvant endocrine therapy, radiotherapy and/or chemotherapy after study end of treatment will be administered as per investigator's choice.
- All patients will be followed for iDFS status every 12 months for 5 years after the last patient is enrolled
- Baseline, C2D1 and post-treatment primary breast tumor tissue samples will be used for molecular characterization as well as serial blood samples across the study (see table 1).
- An interim analysis and final analysis is planned (see Statistical analysis section)

Table 1. Biomarker and PK Assays (timepoints)

- **Locally assessed Ki67, ER, PgR, HER2 (SCR)**
- **TILs, Tumor Cellularity and CelTIL (SCR, C2D1, SUR).**
- **Gene expression including *ERBB3* and research-based PAM50 intrinsic subtype (SCR, C2D1, SUR).**
- **DNAseq (SCR, C2D1, SUR)**
- **HER3 IHC (SCR, C2D1, SUR)**
- **Serum drug concentration - PK (C1D1, C2D1)**
- **DXd IHC (SCR, C2D1, SUR).**
- **γH2AX IHC (SCR, C2D1, SUR).**
- **ctDNA (SCR, C2D1, SUR, FUP).**

Sampling timepoints: Screening (SCR); Cycle 1 day 1: (C1 D1); Cycle 2 day 1 (C2D1); Surgery (SUR); Follow-up (FUP)



Endpoints

Primary endpoint

- **Rate of pCR_{BL} (ypT0/Is ypN0) at surgery**

Secondary endpoints

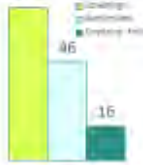
- Rate of residual cancer burden locally assessed by MD Anderson criteria
- pCR_b defined as complete absence of invasive carcinoma in the breast
- Tumor overall objective response rate (ORR) by Modified RECIST 1.1
- iDFS rate at 3 years and 5 years follow up[2]
- Change in CelTIL score[3] (CelTIL = −0.8 × tumor cellularity (in %) + 1.3 × TILs (in %) from baseline to C2D1 and its correlation with pCR, RCB, ORR and iDFS.
- Correlation of pCR with baseline levels of both HER3 receptor expression by IHC and *ERBB3* mRNA expression and with changes between baseline and C2D1.
- Change in Ki67 IHC from baseline to C2D1 and its correlation with: pCR RCB, ORR and iDFS.
- Type, incidence, severity (as graded by the NCI CTCAE v. 5.0), seriousness, moment of onset, duration and attribution to the study medications of TEAEs, AESI and any laboratory abnormalities.
- Change from baseline in EORTC QLQ-C30 and EORTC QLQ BR23 scores

Statistical analysis

- The selected sample size has been calculated based on precision analysis rather than power analysis.
- The study will estimate the percentage of pCR_{BL} in each treatment arm, but there will be **no formal comparison** between the three treatment arms
- **Safety and efficacy interim analysis** when 30 patients are available for local pCR and radiological response evaluation

Current status

- FPI December 2022
- As of 03th of May 2023:
  - 71 pts screened
  - **46 pts enrolled**



Interim analysis Q4 2023

Final analysis Q2 2025

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1. Prat A, Falato C, Pare Brunet L, et al. *Ann Oncol* **33**, S165–S174 (2022).
2. Hudis, C. A. *et al. J. Clin. Oncol.* **25**, 2127–2132 (2007).
3. Nuciforo P. et al, *Annals Oncol.*; 29:170-7. (2018)

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