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ORIGINAL ARTICLE

Patritumab deruxtecan in untreated hormone receptor-positive/HER2-negative early breast cancer: final results from part A of the window-of-opportunity SOLTI TOT-HER3 pre-operative study

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Background: Patritumab deruxtecan (HER3-DXd) is a human epidermal growth factor receptor 3 (HER3)-directed antibody—drug conjugate composed of a fully human anti-HER3 monoclonal antibody (patritumab) covalently linked to a topoisomerase I inhibitor payload via a stable, tumor-selective, tetrapeptide-based cleavable linker. TOT-HER3 is a window-of-opportunity study designed to assess the biological activity, measured by CelTIL score [$= -0.8 \times$ tumor cellularity (in %) $+ 1.3 \times$ tumor-infiltrating lymphocytes (TILs) (in %)], and clinical activity of HER3-DXd during short-term (21 days) pre-operative treatment in patients with primary operable HER2-negative early breast cancer.

Patients and methods: Patients with previously untreated hormone receptor-positive/HER2-negative tumors were allocated to one of four cohorts according to baseline *ERBB3* messenger RNA expression. All patients received one dose of HER3-DXd 6.4 mg/kg. The primary objective was to evaluate change from baseline in CelTIL score.

Results: Seventy-seven patients were evaluated for efficacy. A significant change in CelTIL score was observed, with a median increase from baseline of 3.5 (interquartile range, −3.8 to 12.7; $P = 0.003$). Among patients assessable for clinical response ($n = 62$), an overall response rate of 45% was observed (tumor measurement by caliper), with a trend toward an increase in CelTIL score among responders compared with non-responders (mean difference, +11.9 versus +1.9). Change in CelTIL score was independent of baseline *ERBB3* messenger RNA and HER3 protein levels. Genomic changes occurred, including switching toward a less proliferative tumor phenotype based on PAM50 subtypes, suppression of cell proliferation genes, and induction of genes associated with immunity. Treatment-emergent adverse events were observed in 96% of patients (14% grade ≥3); most common were nausea, fatigue, alopecia, diarrhea, vomiting, abdominal pain, and neutrophil count decrease.

Conclusions: A single dose of HER3-DXd was associated with clinical response, increased immune infiltration, suppression of proliferation in hormone receptor-positive/HER2-negative early breast cancer, and a tolerable safety profile consistent with previously reported results. These findings support further study of HER3-DXd in early breast cancer.

Key words: CelTIL score, HER3-DXd, patritumab deruxtecan, HER3, *ERBB3*, breast cancer

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INTRODUCTION

Human epidermal growth factor receptor 3 (HER3) is an ERBB receptor expressed at higher levels in luminal than in basal mammary cells and has been associated with poor prognosis in many tumor types, making it a compelling molecular target for the development of anticancer therapies.[1-4] Patritumab deruxtecan (U3-1402; HER3-DXd) is a first-in-class HER3-directed antibody–drug conjugate (ADC) composed of a fully human anti-HER3 monoclonal antibody (patritumab) covalently linked to a topoisomerase I inhibitor payload (MAAA-1181a, an exatecan derivative) via a stable, selective, tetrapeptide-based cleavable linker.[5-7] Results from a phase I/II study in patients diagnosed with heavily pretreated metastatic breast cancer demonstrated that treatment with HER3-DXd was associated with durable responses across breast cancer subtypes and a wide range of HER2 and HER3 membrane expression levels.[8-10]

Window-of-opportunity studies use paired biopsies to evaluate novel compounds in several clinical scenarios. These studies may help identify biomarkers to improve patient selection, provide a molecular landscape absent of acquired mutations associated with resistance in treatment-naive patients, and allow for the evaluations of *in vivo* changes within the tumor microenvironment after drug exposure.[11,12]

The CelTIL score combines information on tumor cellularity and stromal tumor-infiltrating lymphocytes (TILs). CelTIL score measured early after the start of neoadjuvant treatment is a practical and easily assessable surrogate biomarker of response to neoadjuvant therapy, with a demonstrated independent predictive value of pathological complete response (pCR) rate across all breast cancer subtypes.[13,14] The SOLTI-1805 TOT-HER3 trial (NCT04610528) is a window-of-opportunity study designed to assess the biological activity, measured by CelTIL score, of a single dose of neoadjuvant HER3-DXd in patients with primary operable early breast cancer.[15,16] Here we report the results from part A of the study, which evaluated HER3-DXd in hormone receptor (HR)-positive/HER2-negative breast cancer.

METHODS

Trial design and patients

The SOLTI-1805 TOT-HER3 study is a prospective, multicenter, single-arm, window-of-opportunity study evaluating the biological effects of a single dose of preoperative HER3-DXd in treatment-naive patients with early breast cancer. Part A was planned to recruit until the accrual of 80 patients with HR-positive/HER2-negative tumors, allocated to one of four cohorts ($n = 20$) according to baseline *ERBB3* messenger RNA (mRNA) expression analyzed using the nCounter platform (NanoString Technologies, Seattle, WA) (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.05.004). The cutoffs of *ERBB3* mRNA used for patient allocation into cohorts were prespecified and derived as previously described.[15,16] Briefly, *ERBB3* mRNA levels from an in-house cohort composed of 1600 formalin-fixed, paraffin-embedded (FFPE) breast cancer samples were explored across immunohistochemistry (IHC) and PAM50-based subtypes. A statistically significant variability in *ERBB3* mRNA expression between and within IHC or molecular subtypes was observed. Using quartiles to categorize tumor samples as high, medium, low, and ultra-low based on *ERBB3* mRNA expression, the proportion of high-*ERBB3* tumors ranged from 4% in triple-negative to 36% in HR-positive/HER2-negative tumors. The quartile-based cutoffs were then validated in two external independent cohorts (i.e. the METABRIC and TCGA datasets).[15,16]

A safety-only interim analysis in 10 patients was carried out to assess available safety data and inform study continuation. A pre-planned second interim analysis in 30 patients was carried out to provide safety and efficacy data to the study steering committee to enable a decision on study continuation. No interruption in study accrual was planned during the interim analyses, as the safety of HER3-DXd had been previously evaluated in the metastatic setting.[8-10]

Patients must have had previously untreated, histologically confirmed, non-metastatic, operable, HR-positive/HER2-negative invasive adenocarcinoma of the breast, with primary tumor $\geq$1 cm by ultrasound or magnetic resonance imaging (MRI). Eligible participants were men or pre/postmenopausal women aged $\geq$18 years, with an Eastern Cooperative Oncology Group performance status of 0 or 1. Ki67 expression $\geq$10% by local assessment was also required. Estrogen and progesterone receptor and HER2 statuses were locally assessed and defined according to the most recent American Society of Clinical Oncology–College of American Pathologists guidelines.[17,18] Written informed consent was obtained from all study participants before the initiation of any study-specific assessments. This trial was conducted in compliance with the protocol, regulatory requirements, an independent ethics committee in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for Good Clinical Practice, and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association and approved by the Spanish Agency for Medicines and Health Products.

Procedures

Baseline assessments to confirm eligibility included a physical examination and radiological assessment by ultrasound (or alternatively by MRI) of the breast and axillary lymph nodes, central assessment of *ERBB3* mRNA expression, and laboratory assessments. A tumor biopsy or archival tissue was required at baseline.

All patients received a single dose of HER3-DXd 6.4 mg/kg intravenously on day 1 of the treatment cycle. A mandatory biopsy was carried out at the end of treatment (day 21 $\pm$ 3 days) to assess the primary endpoint of CelTIL score. At the same time point, clinical response was also assessed by tumor measurement with a caliper. Mandatory blood samples for biomarker analyses were collected on day 1,

between days 3 and 10, on day 21, and on day 49 after treatment administration. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Following study treatment, patients received subsequent treatment at the investigator's discretion, which could include additional neoadjuvant systemic therapy and/or surgical resection. Post-operative locoregional and systemic treatment was administered according to local guidelines.

Objectives and endpoints

The primary objective of part A was to evaluate the change in CelTIL score between baseline and C1D21 tumor samples. Secondary objectives included (i) overall response rate (ORR) measured at C1D21 by clinical palpation using a caliper, (ii) change in CelTIL score according to baseline expression levels of *ERBB3* mRNA and HER3 IHC-based protein, (iii) association between HER3 IHC-based expression and *ERBB3* mRNA expression, (iv) variation in CelTIL score across PAM50-based signatures, (v) differential expression of a custom 67-gene panel, and (vi) change in expression of centrally assessed biomarkers between baseline and post-treatment tumor samples. Safety and tolerability were also included as secondary objectives.

Translational and biomarker analyses

FFPE tumor samples were obtained from all patients and used for CelTIL score and other biomarker assessments. Baseline and C1D21 tumor samples were used to assess the primary endpoint of change in CelTIL score. TILs and tumor cellularity were centrally determined from FFPE hematoxylin and eosin staining of tumor tissues. TILs were quantified according to the 2014 guidelines developed by the International TILs Working Group.[19]

RNA was extracted from these tissue samples and analyzed for gene expression using the nCounter platform. A minimum of approximately 100 ng of total RNA was used to measure the expression of 67 genes, including PAM50 genes, and 5 housekeeping genes (*ACTB*, *MRPL19*, *PSMC4*, *RPLP0*, and *SF3A1*). Data were log base 2 transformed and normalized. All tumors were assigned to an intrinsic molecular subtype (luminal A, luminal B, HER2-enriched, basal-like) or the normal-like group using the research-based PAM50 subtype predictor.[20] The PAM50 risk of recurrence (ROR) was calculated using weighted coefficients for the four subtypes and a proliferation score using a previously reported and validated formula.[21]

HER3 membrane expression was determined by IHC in baseline and C1D21 tumor samples by Roche Tissue Diagnostics (Tucson, AZ). HER3 IHC was carried out on FFPE tissue using the BenchMark ULTRA IHC/ISH system (Roche Diagnostics, Tucson, AZ). Staining was conducted with an anti-HER3 recombinant rabbit monoclonal antibody (clone SP438) after antigen retrieval in CC1 buffer followed by detection with the OptiView DAB IHC Detection Kit (Ventana Medical Systems, Tucson, AZ). HER3 membrane expression (overall percentage of membrane staining at $\times$10 magnification) was used for assessment of the study's secondary endpoints according to Krop et al.[8,9] and was classified as negative ($<$25%), low ($\geq$25% to $\leq$74%), or high ($\geq$75% to $\leq$100%).

Statistical analysis

The sample size was based on the primary endpoint. The analysis was planned for 72 patients with paired samples (baseline and C1D21) providing 80% power at the 5% significance level (two-sided) to detect a mean CelTIL score change of 13 points from baseline and a standard deviation of 38.6 (based on internal data). Considering a 10% dropout rate or lack of a C1D21 tumor sample, a target sample size of 80 patients was planned.

The CelTIL score was calculated using the following formula:[21]

[CelTIL score $= -0.8 \times$ tumor cellularity (in %) $+ 1.3 \times$ TILs (in %)] and scaled to reflect a range from 0 to 100 points. As the assumption of normal distribution of the CelTIL score was rejected (Shapiro test; $P < 0.05$), the Wilcoxon signed-rank test was used to assess whether the median change in CelTIL score between paired biopsies was statistically different from zero. Median change values and interquartile range (IQR) were reported. This analysis was carried out in the intent-to-treat population, which included all eligible and assessable patients enrolled in the study.

Exploratory analyses of change in CelTIL score across subpopulations (i.e. *ERBB3* mRNA cohorts and PAM50-based intrinsic subtypes) were carried out. Correlation coefficients were estimated using the Spearman rank correlation test. A paired two-class significance analysis of microarrays with a false discovery rate of 5% was carried out to identify genes that were significantly up-regulated or down-regulated at C1D21 compared with the baseline biopsy.[22,23] No data imputation was used, all *P* values were two-sided, and all analyses were undertaken using R statistical software version 4.2.1.

RESULTS

Patients

A total of 139 patients were screened, 120 had samples available for central assessment of *ERBB3* mRNA expression, and 78 (instead of the planned 80) were enrolled in the study due to slow accrual in the ultra-low cohort (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.05.004).

The mean age of the study population ($n = 78$) was 52 years (range, 29-78 years); 44 patients (56%) were premenopausal, and most patients presented with histological grade 2 tumors (57%) and invasive ductal carcinoma (75%) (Table 1). Grade 3 tumors were present in 15 patients (18%) and lobular carcinoma was reported in 18 (23%). Median tumor size was 21 mm, with a range of 10-100 mm (Table 1).

Patient tumors were distributed across *ERBB3* mRNA groups, with 15 in the ultra-low and 21 each in the low, medium, and high mRNA cohorts (Figure 1). A 4.6-fold

Table 1. Patient demographics and baseline characteristics

	(*n* = 78)
Age, mean (range), years	52 (29-78)
Ethnicity, *n* (%)	
White	77 (99)
Hispanic	1 (1)
Sex, *n* (%)	
Female	78 (100)
Menopausal status, *n* (%)	
Premenopausal	44 (56)
Postmenopausal	34 (44)
Histological type, *n* (%)	
Ductal	58 (75)
Lobular	18 (23)
Other	2 (2)
Histological grade, *n* (%)	
1	9 (12)
2	44 (57)
3	15 (18)
Unknown	10 (13)
Ki67 expression by central assessment, %	
Mean (range)	27 (5-90)
Median	21
Tumor size by ultrasonography, mm	
Median (range)	21 (10-100)
cT stage, *n* (%)	
cT1	26 (33)
cT2	42 (53)
cT3	9 (12)
cT4	1 (2)
cN stage, *n* (%)	
cN0	56 (71)
cN1	18 (23)
cN2	4 (6)
ER expression, *n* (%)	
0%	1 (2)
<10%	5 (6)
≥10%	72 (92)
PR expression	
0%	8 (10)
<10%	8 (10)
≥10%	62 (80)
HER2 status, *n* (%)	
0	26 (32)
1+	29 (38)
2+[a]	23 (30)
PAM50 subtype at baseline	
Luminal A	40 (52)
Luminal B	33 (42)
Basal-like	3 (4)
HER2-Enriched	2 (3)

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
[a]All negative by *in situ* hybridization.

difference in *ERBB3* mRNA expression was measured between tumor samples collected from patients in the ultra-low mRNA cohort and patients in the high mRNA cohort. HER3 IHC protein expression was evaluable in 67 patients (86%). Patients primarily demonstrated high overall HER3 membrane expression [80.6% (*n* = 45) (Figure 1)]. Low (≥25% to ≤74%) HER3 expression was reported in 12 assessable patients (17.9%) and negative HER3 expression (<25%) was reported in 1 patient (1.5%). A weak correlation (Spearman coefficient = 0.36) was observed between *ERBB3* mRNA and HER3 membrane expression. Baseline characteristics of patients for whom HER3 IHC was available are comparable with those of the overall trial population (data not shown).

Variation in CelTIL score for all patients and based on clinical response

As CelTIL score was not evaluable in the C1D21 biopsy from one patient, the primary efficacy analysis was carried out in a total of 77 individuals.

Overall, a median increase in CelTIL score of 3.5 (IQR, −3.8 to 12.7; Wilcoxon signed-rank test $P = 0.003$), corresponding to a mean increase of 6.9 [95% confidence interval (CI), 3.40-10.19), was detected (Figure 2A). Of the 77 patients, 62 were assessable for clinical response (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.05.004). The clinical ORR was 45.2% (95% CI 32.7% to 58.2%), with 14 complete responses (22.6%) and 14 partial responses (22.6%) (Figure 3). Change in CelTIL score was associated with a higher odd of response [odds ratio, 1.05 (95% CI 1.02-1.10) for a one-unit change in CelTIL score]. A more pronounced increase in CelTIL score from baseline was observed among responders (*n* = 28; median increase, +11.9; IQR, −0.2 to 25.5) than among patients experiencing stable disease at C1D21 (*n* = 34; median increase, +1.9; IQR, −2.5 to 9.3) (Figure 2B).

Change in CelTIL score and clinical response according to baseline ERBB3 mRNA levels, HER3 protein expression, and PAM50-based signatures

Changes in CelTIL score and clinical response were evaluated and correlated with baseline *ERBB3* mRNA and HER3 protein expression levels. Overall, changes in CelTIL score and clinical response were not associated with baseline *ERBB3* mRNA or HER3 levels (Figure 4 and Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2023.05.004).

Distribution of PAM50-based subtypes in baseline samples was as follows: luminal A, 51.9% (*n* = 40); luminal B, 41.6% (*n* = 32); basal-like, 3.9% (*n* = 3); and HER2-enriched, 2.6% (*n* = 2) (Figure 5A). After treatment, a switch in PAM50 subtypes occurred in 29 patients (37.7%): 21 luminal B tumors switched to luminal A (*n* = 20) and HER2-enriched (*n* = 1); 6 luminal A tumors switched to luminal B (*n* = 2) and normal-like (*n* = 4); 1 HER2-enriched tumor switched to luminal A; and one basal-like tumor switched to luminal B. No residual tumor could be identified in the post-treatment biopsy from three patients, whose baseline samples were luminal A (*n* = 1), luminal B (*n* = 1), and HER2-enriched (*n* = 1) (Figure 5A). Non-luminal subtype (basal-like and HER2-enriched) and high ROR score at baseline were associated with a greater increase in CelTIL score at day 21 compared with luminal subtype and low/medium ROR score, respectively (Figure 5B).

The percentage changes from baseline in tumor size based on PAM50 subtypes, *ERBB3* mRNA cohorts, and CelTIL variations are reported in Figure 3. Changes in CelTIL score based on clinical response, baseline *ERBB3* mRNA levels, and PAM50 subtypes are summarized in

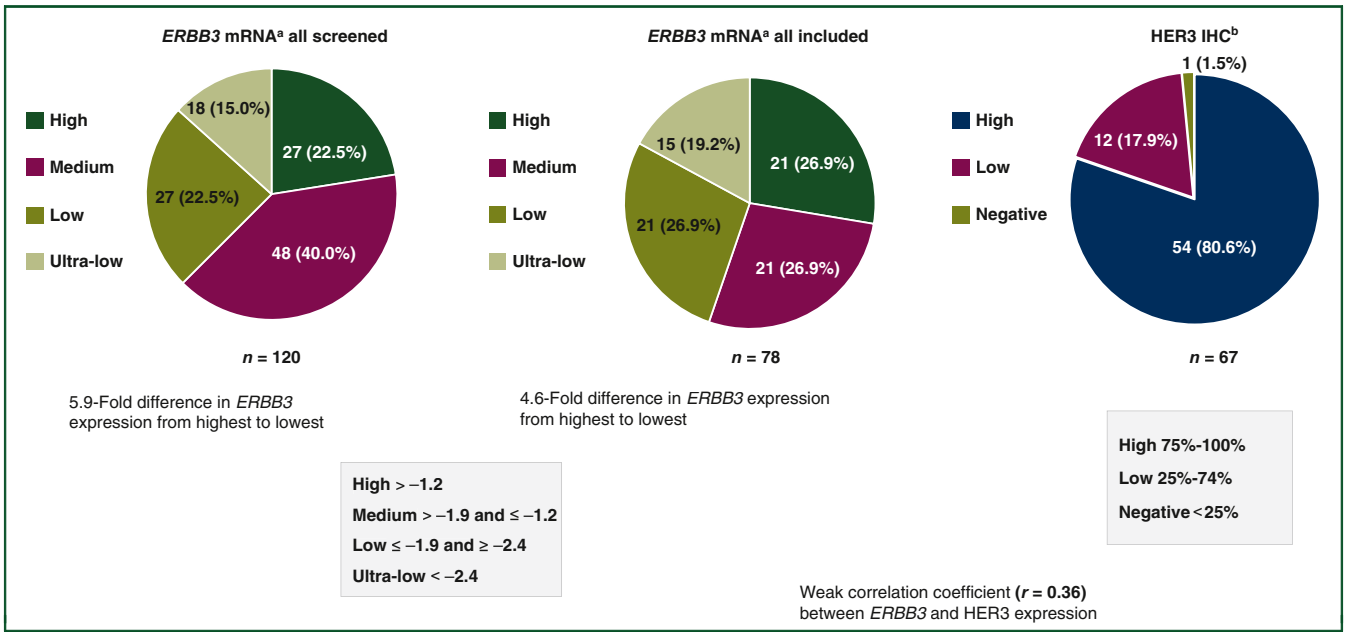

Figure 1. Distribution of *ERBB3* mRNA[a] and baseline HER3 membrane[b] expression in all screened patients and in those who entered the trial.
HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry; mRNA, messenger RNA.
[a]The *ERBB3* mRNA cut-offs used for patient allocation to high, medium, low, and ultra-low cohorts were prespecified and determined according to Pascual T. et al., *Front Oncol* 2021.[15]
[b]HER3 IHC was assessed as overall HER3 membrane positivity at 10× (%) and high, low, and negative categories identified per Krop et al. *J Clin Oncol*. 2022.[9]

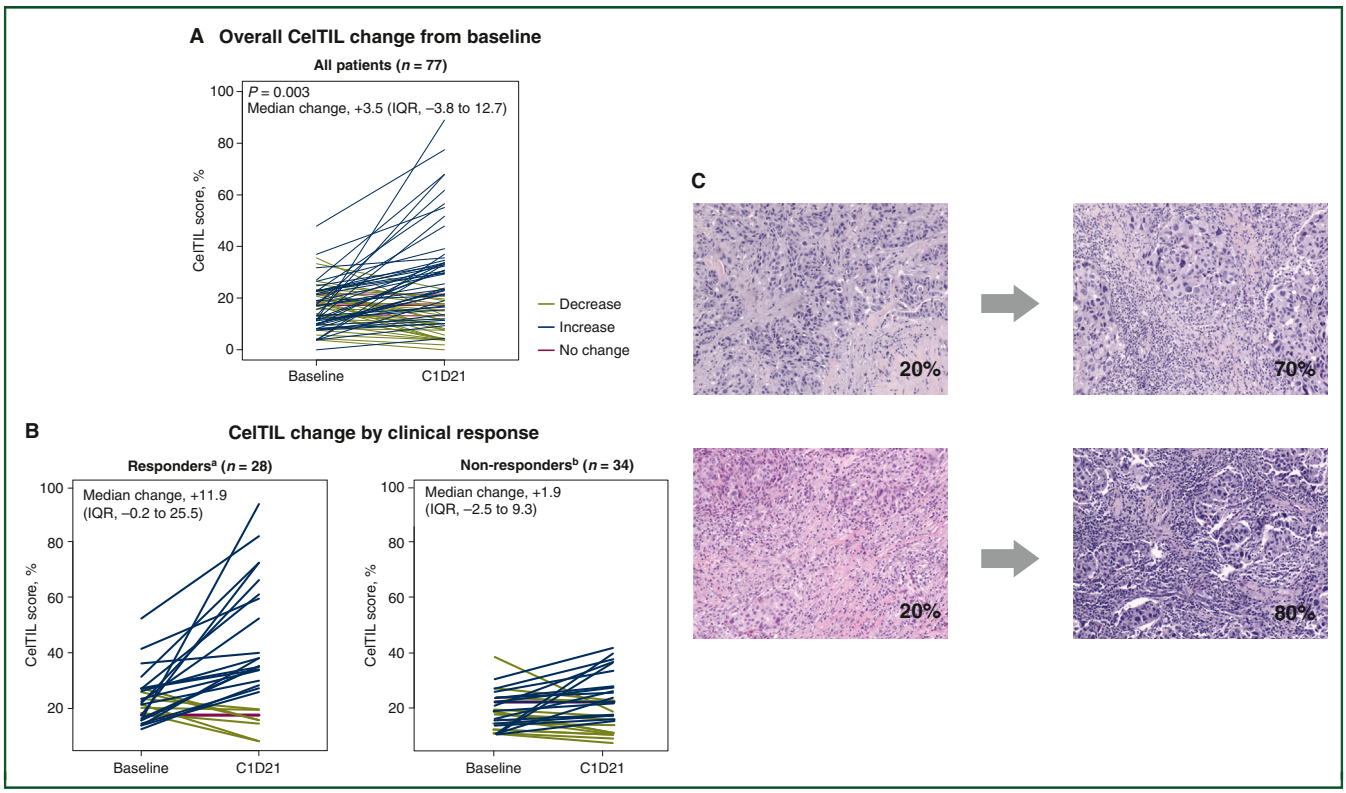

Figure 2. Change in CelTIL score for all patients (A) and based on clinical response (B). (C) Microscope images of tumor-infiltrating lymphocytes in baseline and day 21 biopsies from two selected cases; complete response by clinical palpation was reported in both cases.
C, cycle; CelTIL, tumor cellularity and stromal tumor infiltrating lymphocytes; D, day; IQR, interquartile range.
[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).

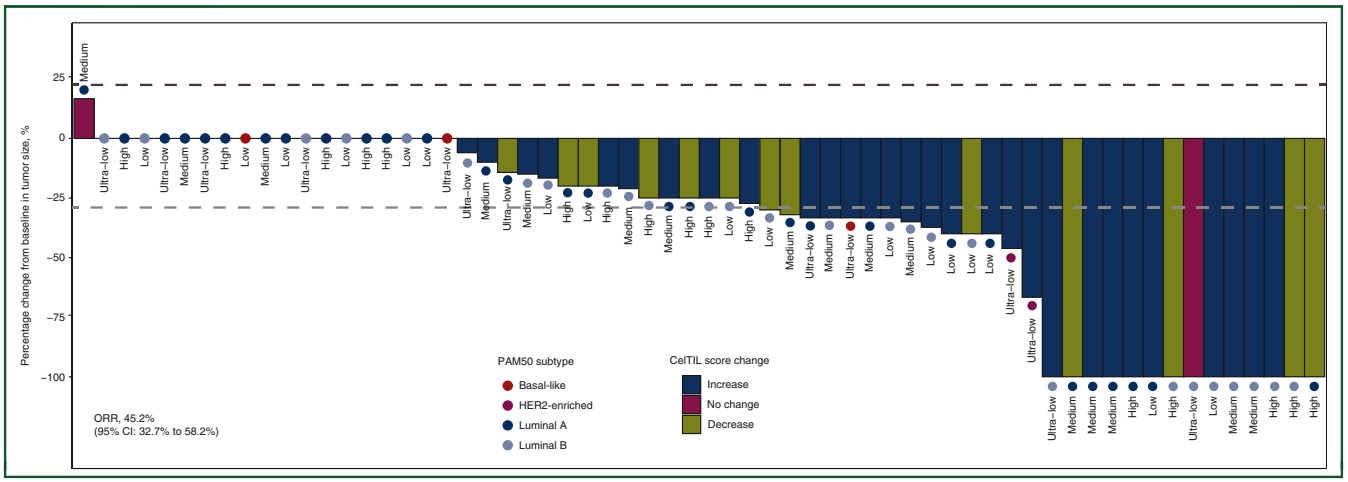

Figure 3. Percentage change from baseline in tumor size measured at day 21 by caliper and based on PAM50 intrinsic subtype, *ERBB3* mRNA cohort and CelTIL score variation.

CelTIL, tumor cellularity and stromal tumor infiltrating lymphocytes; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mRNA, messenger RNA; ORR, overall response rate.

High, medium, low, and ultra-low refer to *ERBB3* mRNA cohorts.

Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2023.05.004.

Differential gene expression and biomarker changes from baseline to C1D21

With a false discovery rate of 5%, analysis of 74 paired tumor samples showed that 23 genes were up-regulated (including immune-related genes such as *CD8A*, *CD4*, and *PDCD1*) and 44 genes (including proliferation-associated genes such as *MELK*, *MKI67*, and *UBE2T*) were down-regulated at C1D21 in comparison with the baseline biopsy (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2023.05.004).

Paired pre- and post-treatment *ERBB3* mRNA and HER3 IHC was available from 74 and 54 patients, respectively. Overall, the median expression of *ERBB3* mRNA decreased by −0.2 points (IQR, −5.9 to 7.5) whereas a median decrease of −5.0 points (IQR, −27.5 to 10.0) was reported for HER3 IHC (Supplementary Figure S6A and B, available at https://doi.org/10.1016/j.annonc.2023.05.004).

Change in centrally assessed Ki67 expression was also explored. Among 53 evaluable paired tumor samples, a median four-point decrease (IQR, −10.0 to 0) from baseline

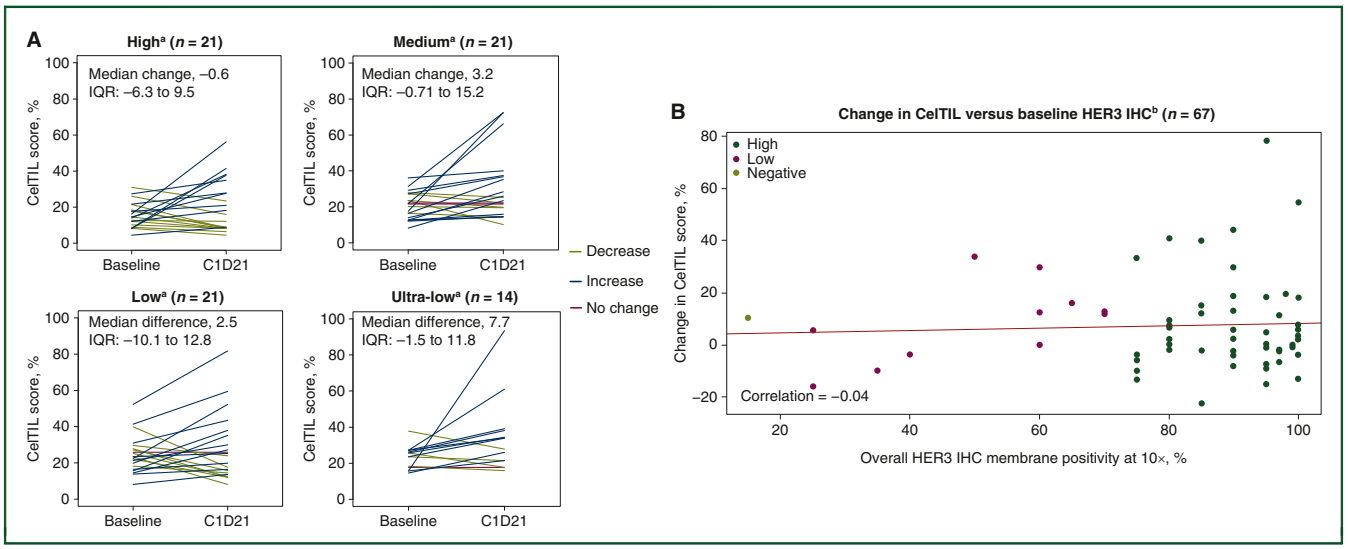

Figure 4. Change in CelTIL score according to (A) *ERBB3* mRNA-based cohorts[a] and (B) baseline HER3 membrane expression[b].

C, cycle; CelTIL, tumor cellularity and stromal tumor infiltrating lymphocytes; D, day; HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry; IQR, interquartile range; mRNA, messenger RNA.

[a]Based on prespecified cut-off of *ERBB3* mRNA derived as per Pascual T. et al., *Frontiers in Oncology* 2021.[15]

[b]Assessed as overall HER3 membrane positivity at 10× (%) per Krop et al. *J Clin Oncol*. 2022.[9]

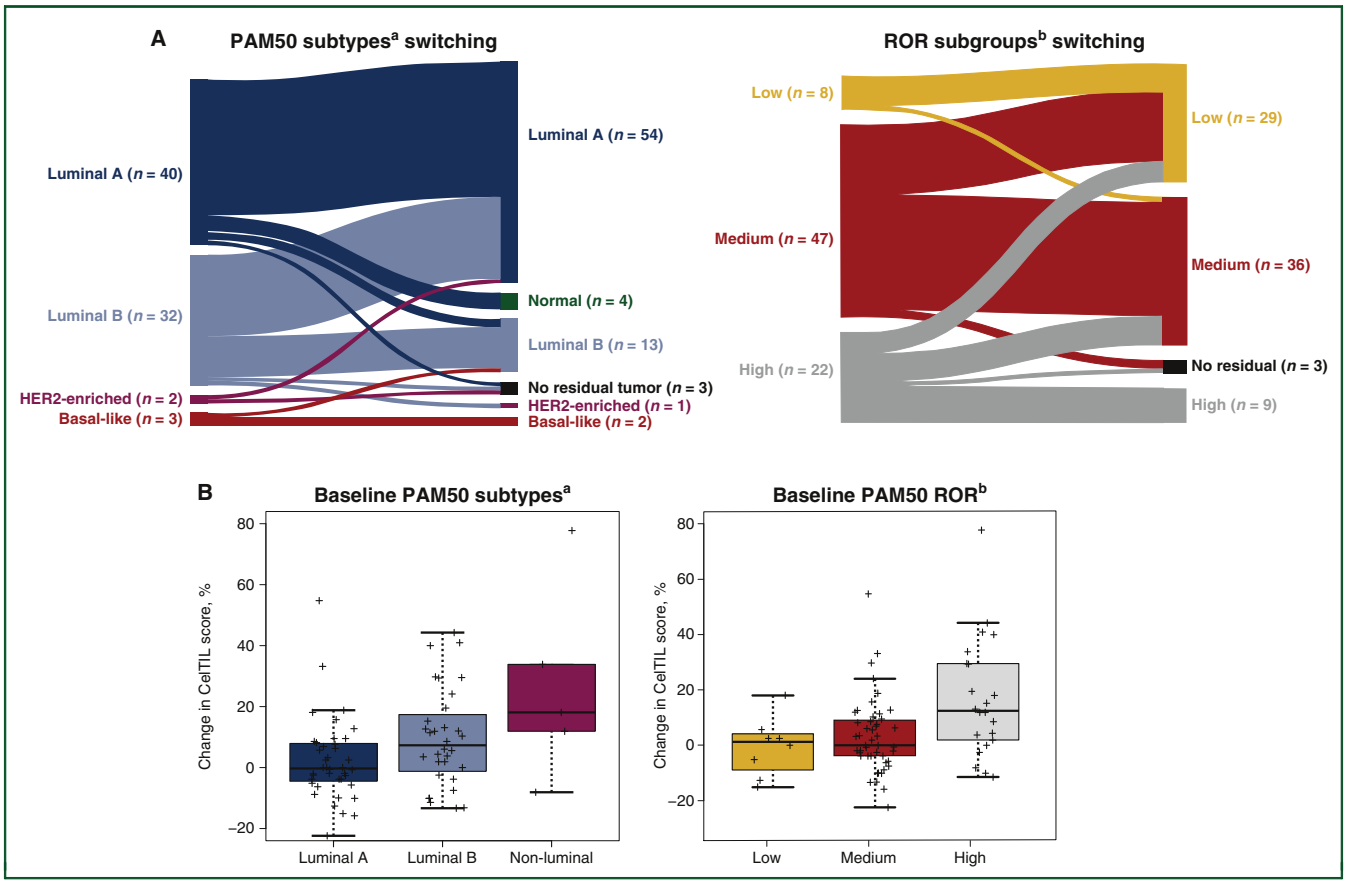

Figure 5. (A) PAM50 and ROR switching from baseline to day 21 biopsies and (B) CelTIL changes according to baseline PAM50 and ROR score.
CelTIL, tumor cellularity and stromal tumor infiltrating lymphocytes; HER2, human epidermal growth factor receptor 2; ROR, risk of recurrence.
[a]Intrinsic molecular subtypes of breast cancer based on the PAM50 gene signature panel.
[b]Risk of recurrence based on PAM50 subtype and proliferation using the following predefined cut-off values: high risk (>53), medium risk (12-53), low risk (<12).

was observed (Supplementary Figure S6C, available at https://doi.org/10.1016/j.annonc.2023.05.004).

Safety

The incidence of treatment-emergent adverse events (TEAEs), irrespective of causality, was 96.2%, and TEAEs were observed in 75 patients. TEAEs were primarily grade 1 or 2 (grade 1, 91.0%; grade 2, 57.7%; grade 3, 12.8%; grade 4, 5.1%; Table 2). The most common drug-related adverse events of any grade that were reported were nausea (67%), fatigue (41%), alopecia (36%), diarrhea (24%), abdominal pain (22%), vomiting (20%), neutrophil count decreased (19%), constipation (13%), and increased alanine aminotransferase and aspartate aminotransferase levels (12% and 8%, respectively).

Grade 3 or higher TEAEs occurred in 14 patients (17.9%) and were all reversible; the most common were decreased neutrophil count (7.7%), increased alanine aminotransferase level (2.6%), and diarrhea (1.3%) (Table 2). No cases of interstitial lung disease were observed, and no deaths occurred during the study.

DISCUSSION

In part A of the window-of-opportunity SOLTI-TOT HER3 trial, a single dose of HER3-DXd increased immune infiltration and suppressed proliferation across a wide range of *ERBB3* mRNA and HER3 protein expression levels and induced a switch to a less proliferative tumor phenotype.

Table 2. Treatment-emergent adverse events

	(*n* = 78)	
TEAEs (all cause), *n* (%)[a]	75 (96.2)	
Grade 4	4 (5.1)	
Grade 3	10 (12.8)	
Grade 2	45 (57.7)	
Grade 1	71 (91.0)	
Treatment-emergent SAEs	4 (5.1)	
Grade ≥3	3 (3.8)	
TEAEs in >5% of patients, *n* (%)[a]	**All grades**	**Grade ≥3**
Nausea	53 (67.9)	0
Fatigue	31 (39.7)	0
Alopecia	28 (35.9)	NA
Diarrhea	19 (24.4)	1 (1.3)
Vomiting	20 (25.6)	0
Abdominal pain	17 (21.8)	0
Neutrophil count decreased	15 (19.2)	6 (7.7)
Constipation	10 (12.8)	0
ALT level increased	9 (11.5)	2 (2.6)
AST level increased	6 (7.7)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Patients could experience ≥1 adverse event.

Patritumab deruxtecan (HER3-DXd) was associated with a 45.2% ORR. A more pronounced immune infiltration was observed among patients experiencing a complete or partial clinical response after one dose of HER3-DXd than in those experiencing stable disease. Subgroup analyses revealed that non-luminal tumor subtype or high baseline PAM50 ROR score was associated with greater CelTIL response than luminal tumors or medium/low ROR scores.

ADCs represent a new paradigm in the treatment landscape of breast cancer across all tumor subtypes. ADCs that target HER2 or TROP2 (Trophoblast cell-surface antigen 2) have been shown to improve clinical outcomes versus standard-of-care treatment in previously treated metastatic HR-positive breast cancer with low or no expression of the HER2 protein,[24-27] and are currently being studied in the early disease setting [SASCIA (NCT04595565), TALENT (NCT04553770)]. Similarly, HER3-DXd has demonstrated highly encouraging efficacy and a tolerable safety profile across subtypes in advanced breast cancer motivating further investigation in the early disease setting.[9]

TOT-HER3 is the first study demonstrating clinical and biological activity of an HER3-directed ADC in HR-positive/HER2-negative early breast cancer. This tumor phenotype represents the most common breast cancer phenotype and requires special attention, especially considering features of the subgroups with lower endocrine responsiveness (i.e. low expression of estrogen and/or progesterone receptor, high tumor proliferation, high histologic grade, non-luminal tumor) and/or high tumor burden that result in low sensitivity to endocrine therapy and suboptimal 7% to 16% rates of pCR, following standard neoadjuvant polychemotherapy.[28-31] Clinically and biologically relevant responses after one dose of pre-operative treatment with HER3-DXd were reported in the TOT-HER3 trial, which includes a heterogeneous group of clinically and/or genomically low- to high-risk patients with a more aggressive, less endocrine-sensitive baseline tumor biology. Strikingly, an unprecedented 45.2% ORR was reported, suggesting that HER3-DXd might be particularly active for the treatment of patients with HR-positive/HER2-negative early breast cancer for whom the currently available neoadjuvant chemotherapy options are associated with low pCR rates.

HER3 is a compelling molecular target for cancer treatment. No standardized IHC-based HER3 assay is currently available, however, due to the inherent technical and analytical limitations of the tested assays (i.e. different antibody sensitivity, lack of agreement in scoring methods, and different HER3 expression cut-offs). A more robust and reproducible mRNA-based *ERBB3* assay was developed by our group using the nCounter platform[15] and prospectively validated in the TOT-HER3 trial. Consistent with previous investigations in the metastatic breast cancer setting,[9] the antitumor activity of HER3-DXd in TOT-HER3 spanned a wide range of *ERBB3* mRNA and HER3 protein expression levels, suggesting limited treatment predictive value. Alternative putative biomarkers of response, such as heregulin expression,[32] epidermal growth factor receptore (EGFR)-HER3 score,[33] and the dynamics of HER3 expression during treatment, represent an interesting area of future research. Preclinical evidence from patient-derived xenograft models suggests that *TP53* mutations and basal-like intrinsic subtype are potential biomarkers of response to HER3-DXd.[34] Further correlative studies to identify biomarkers of response to HER3-DXd in TOT-HER3 are ongoing.[35]

In this study, we found that several immune-related genes, including the *PD-1* gene, were overexpressed after just one dose of HER3-DXd, corroborating preclinical evidence suggesting that HER3-DXd elicits potent antitumor immunity through a massive infiltration of innate and adaptive immune cells and the reinvigoration of TILs from a previous state of functional exhaustion. This suggests that HER3-DXd may synergize with blockade by programmed cell death protein 1/programmed death-ligand 1 inhibitors and may allow for novel treatment combinations in an otherwise cold tumor microenvironment.[36]

During neoadjuvant chemotherapy, high baseline levels of tumor TILs positively correlate with an increased rate of pCR across all breast cancer subtypes.[37] Change in CelTIL score in on-treatment biopsies correlates with pCR rate and with long-term survival in HER2-positive early breast cancer.[14,38] In HR-positive/HER2-negative breast cancer, an early increase in CelTIL score during neoadjuvant chemotherapy was significantly associated with tumor shrinkage at surgery.[13,39] The surrogacy of CelTIL to predict survival outcomes in HR-positive/HER2-negative breast cancer is an issue that remains to be elucidated at this time, however, and we will study that in the ongoing Valentine trial. Compared with triple-negative breast cancer and HER2-positive breast cancer, HR-positive/HER2-negative tumors appear to be associated with a less immunogenic and more exhausted CD8+ T-cell phenotype; furthermore, the prognostic role of TILs in HR-positive/HER2-negative breast cancer is controversial.[37,40] In TOT-HER3, whereas a significant increase in CelTIL score was observed for all patients after a single dose of HER3-DXd, a trend toward a higher increase in CelTIL score was observed among responders versus non-responders. Understanding how a change in CelTIL score correlates with pCR rate and long-term survival was not within the scope of TOT-HER3, but the ongoing SOLTI-VALENTINE (NCT05569811) trial testing neoadjuvant HER3-DXd as monotherapy or in combination with endocrine therapy is addressing this issue.

The safety results from these analyses were similar to those previously reported in the metastatic setting.[8-10] The incidence of grade $\geq$3 TEAEs in TOT-HER3 was lower than that observed in the advanced or metastatic setting, as patients received just one dose of HER3-DXd. Although this is reassuring, TOT-HER3 is currently enrolling an additional cohort of patients using a reduced dose of HER3-DXd (5.6 mg/kg), which resulted in similar efficacy in the metastatic setting and with a more favorable benefit—risk balance.

Our study has several limitations that should be acknowledged. First, IHC data for HER3 expression was not available for all specimens at baseline, with 14.1% of samples not being evaluable for HER3, and only one tumor

sample was classified as HER3-negative. This may have contributed to the weak correlation observed between baseline *ERBB3* mRNA and HER3 membrane expression, as well as the absence of correlation between HER3 membrane positivity and change in CelTIL score. Second, ORR was assessed by clinical palpation or measurement by a caliper, which is a less sensitive method than breast ultrasonography and MRI. In part B of TOT-HER3, breast ultrasonography has been carried out to assess treatment responses. Third, only a small number of genes were evaluated in the gene expression analysis. Lastly, it is difficult to speculate whether longer treatment may increase clinical benefit or to estimate disease-free survival in the high-risk patient population enrolled in this study, since the trial design only evaluated a single dose of HER3-DXd.

In conclusion, the SOLTI TOT-HER3 window-of-opportunity study testing one dose of HER3-DXd found no correlation between *ERBB3* mRNA or HER3 IHC expression and change in CelTIL score. The changes in the tumor microenvironment and promising clinical response rates that were observed, however, may translate into increased response rates in the neoadjuvant setting and improved long-term outcomes. In addition, the safety profile was tolerable and consistent with previously reported results. Overall, these findings support further study of HER3-DXd in high-risk early breast cancer and provide additional evidence for the role of CelTIL score as an early biomarker of response in the pre-operative setting. The VALENTINE trial (NCT05569811) has been launched to further investigate these findings.

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