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EDITORIAL

Exploring a Novel Approach to Spare Classic Chemotherapy in HER2-Low, ER-Positive Breast Cancer Based on Trastuzumab Deruxtecan Combined with Endocrine Therapy

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ABSTRACT

Background: Breast cancer presents diverse molecular subtypes affecting treatment strategies. Human epidermal growth factor receptor 2 (HER2)-low, hormone receptor-positive (HR+) breast cancer poses a challenge due to limited targeted therapies. Current neoadjuvant treatment primarily utilizes chemotherapy, with conflicting results regarding efficacy in patients with HER2-low breast cancer. Trastuzumab deruxtecan (T-DXd) shows promise in HER2-low metastatic disease, and preliminary evidence suggests synergy with endocrine therapy.

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***Objective*:** This editorial explores the hypothesis that neoadjuvant T-DXd with or without endocrine therapy offers efficacy in the clinical management of HR+/HER2-low breast cancer.
***Methods*:** We propose a phase II study with two treatment arms: T-DXd + letrozole and T-DXd alone. The primary endpoint is the radiological complete response rate. Secondary endpoints include pathological complete response rate, safety, event-free survival, and overall survival. Exploratory analyses will compare the arms to identify potential for optimizing treatment efficacy and minimizing side effects.
***Conclusions*:** This study design allows for initial assessment of T-DXd with or without endocrine therapy in the treatment of HER2-low breast cancer. The findings may pave the way for personalized treatment strategies and inform future research, potentially leading to a chemotherapy-sparing approach.

Keywords: Breast cancer; HER2-low; Estrogen receptor-positive; Neoadjuvant therapy; Trastuzumab deruxtecan

Key Summary Points

Why carry out this study?
Breast cancer remains a significant global health challenge, particularly in human epidermal growth factor receptor 2 (HER2)-low, hormone receptor-positive (HR+) subtypes, necessitating exploration of novel treatment strategies.
This proposed study will aim to investigate the efficacy and safety of neoadjuvant T-DXd with and without endocrine therapy in cancer patients with HER2-low, endocrine-positive breast.
The question to be asked is: Does the combination of neoadjuvant T-DXd with and without endocrine therapy improve treatment outcomes in patients with HER2-low, endocrine-positive breast cancer?
What will be learned from the study?
The study may demonstrate promising outcomes with neoadjuvant T-DXd with and without endocrine therapy, indicating potential for a classic chemotherapy-sparing approach in treatment regimens for HER2-low, endocrine-positive breast cancer.
The expected results may suggest that T-DXd with or without endocrine therapy could offer an effective treatment option with manageable toxicity for this patient population.
In addition to evaluating treatment efficacy and safety, the study will explore the potential of identifying novel biomarkers predictive of response to T-DXd with or without endocrine therapy. This could lead to the development of personalized treatment approaches for patients with HER2-low, endocrine-positive breast cancer.
Given the parallel phase II design, the study is primarily exploratory and not intended for direct comparison between the treatment arms.

BACKGROUND

Breast cancer (BC) affects over 2 million women annually worldwide and is characterized by diverse molecular subtypes, each requiring unique treatment strategies. BC remains a challenge to global healthcare systems, with its incidence continuing to rise worldwide [1]. Among its heterogeneous subtypes, human epidermal growth factor receptor 2 (HER2)-low BC presents a unique clinical entity characterized by a possible distinct molecular profile [2]. Notably, HER2-low, endocrine-positive BC presents a distinct challenge due to limited targeted therapeutic options [3]. While advances in treatment modalities have significantly improved outcomes for patients with BC, the clinical management of estrogen receptor (ER)-positive/HER2-low (ER+/HER2-low) disease remains complex. Neoadjuvant therapy plays a crucial role in the management of localized BC, providing the means to

downstage tumors, assess treatment response, and facilitate breast-conserving surgery, while informing adjuvant treatment modulation and prognosis. Current guidelines primarily advocate for a combination of chemotherapy and endocrine therapy, with chemotherapy being the cornerstone of neoadjuvant treatment for ER-positive, HER2-negative disease, including HER2-low (ER+/HER2-low) disease [4].

However, conflicting results have emerged regarding the potential variability in the efficacy of neoadjuvant chemotherapy (NACT) among patients with ER+/HER2-low disease. In particular, Wang et al. [5] recently reviewed the results of 178 patients with BC who underwent NACT at a single hospital between January 2018 and July 2022. Among these patients, 112 tumors were classified as HER2 score 0 by immunohistochemistry (IHC), while 66 were categorized as HER2-low, having HER2 IHC score 1+ or 2+ with non-amplified ERBB2 oncogene (*ERBB2*). Comparison of baseline characteristics revealed a significantly higher progesterone receptor-positive rate in the HER2-low group compared to the HER2-0 group (60.6% vs. 46.4%; $p<0.05$). Additionally, the local treatment response, assessed through tumor size reduction and pathological complete response rates, was notably worse in the HER2-low group compared to the HER2-0 group ($p<0.05$). Conversely, in another recently conducted study [6], a total of 855 patients with HER2-negative BC who underwent NACT between January 2007 and December 2018 at a single cancer center were retrospectively reviewed. Among these patients, 285 (33.3%) were classified as HER2-low, characterized by IHC classification +1 or +2 with non-amplified in situ hybridization (ISH), while the remaining patients were categorized as HER2-0 (IHC 0). The median follow-up period was 59 months, with most patients presenting locally advanced tumors. Pathological complete response (pCR) rates and relapse-free survival (RFS) were assessed between luminal/HER2-low versus luminal/HER2-0 and triple-negative (TNBC)/HER2-low versus TNBC/HER2-0 populations. For patients with luminal BC, pCR rates were 13% in HER2-low tumors compared to 9.5% in HER2-0 tumors ($p=0.27$). Similarly, no significant difference in pCR rates was observed among patients with TNBC: 51% in HER2-low versus 47% in HER2-0 ($p=0.64$). Moreover, HER2-low status did not show prognostic value for RFS in either luminal-like or TNBC subtypes.

Another treatment strategy in the setting of localized endocrine-responsive BC is with neoadjuvant endocrine therapy (NET). In their landmark systematic review and meta-analysis, Spring et al. [7] analyzed data from 20 prospective, randomized neoadjuvant clinical trials involving a total of 3490 unique patients. The results indicated that compared to combination chemotherapy, NET involving aromatase inhibitors used as single agents showed similar clinical response rates (odds ratio [OR] 1.08, 95% confidence interval [CI] 0.50–2.35), radiological response rates (OR 1.38, 95% CI .92–2.07), and breast conservation surgery (BCS) rates (OR 0.65, 95% CI 0.41–1.03), in a subset of 378 patients.

On the other hand, trastuzumab-deruxetan (T-DXd) demonstrates significant promise in HER2-low disease, supported by emerging evidence from clinical trials highlighting its efficacy in HER2-low metastatic BC. In the phase 3 DESTINY-Breast04 trial [8] involving patients with HER2-low metastatic BC who had previously undergone one or two lines of chemotherapy, 557 patients were randomized, with 494 having hormone receptor-positive (HR+) disease and 63 hormone receptor-negative (HR–) disease. Among all patients, the median progression-free survival was 9.9 months in the T-DXd group compared to 5.1 months in the physician's choice group, with hazard ratios of 0.50 ($p<0.001$) for disease progression or death and 0.64 ($p=0.001$) for overall survival. Notably, even more favorable outcomes were observed in the HR+ cohort, with a median progression-free survival of 10.1 months in the T-DXd group compared to 5.4 months in the physician's choice group, and hazard ratios of 0.51 ($p<0.001$) for disease progression or death and 0.64 ($p=0.003$) for overall survival.

Preliminary clinical evidence intriguingly suggests that T-DXd synergizes with endocrine therapy. T-DXd was investigated in the DESTINY-Breast08 (DB-08) trial to evaluate its safety, tolerability, and initial efficacy when combined with standard therapies for HER2-low, HR+ metastatic BC (mBC). In this Phase

1b multicenter, open-label trial, patients with centrally confirmed HER2-low advanced/mBC received T-DXd in combination with either anastrozole or fulvestrant. As of 20 February 2023, 21 patients in the T-DXd + anastrozole arm and 20 in the T-DXd + fulvestrant arm had undergone treatment. The confirmed objective response rate (ORR) was 71.4% in the T-DXd + anastrozole arm and 40.0% in the T-DXd + fulvestrant arm [9]. Additionally, T-DXd has showed to be feasible in the neoadjuvant setting. In the phase 2 neoadjuvant clinical trial TRIO-US B-12 TALENT, the use of T-DXd with or without endocrine therapy resulted in clinical responses in two-thirds of the patients treated, with a pCR rate of 5.3%. [10] Perhaps, adapting treatments to the ongoing treatment response based on more dynamic biomarkers is a key step to enhancing treatment responses and achieving higher rates of pCR.

Based on the available evidence, the combination of NET with T-DXd represents an intriguing avenue for investigation, with the possibility that endocrine manipulation may enhance HER2 expression. In particular, recent findings from a single-arm, interventional phase II clinical trial shed light on the effects of short-term NET in patients with early-stage HR+/HER2-negative (HR+/HER2–) BC. A total of 37 patients with cT1-T3, cN0, and HR+/HER2– BC were enrolled. Following NET, HER2 protein was upregulated in 48.6% (17 of 35 evaluable tumors), with statistical significance ($p = 0.025$). Notably, three patients developed HER2-positive status (IHC 3+ or fluorescent in situ hybridization [FISH]-amplified testing), detected at surgery, leading to a recommendation for adjuvant trastuzumab-based therapy. Furthermore, downregulation of HER3 and/or HER4 protein was observed in 54.2% of tumors. However, HER1 protein levels remained low and unchanged in all cases. Although radiographic imaging did not show significant volumetric reduction post-NET, there was a significant reduction in tumor proliferation rates. Despite comprehensive analysis, no significant associations were identified between any clinicopathologic covariates and changes in HER1-4 protein expression [11].

STUDY DESIGN

This editorial explores the hypothesis that neoadjuvant treatment with T-DXd, with or without the addition of endocrine therapy, demonstrates efficacy in patients with HR+/HER2-low BC. Continued investigation of T-DXd in the perioperative setting is evidenced by ongoing trials, as outlined in Table 1. Based on the protocol outlined in the SHAMROCK study, we propose a similar approach utilizing T-DXd with and without endocrine therapy for the treatment of HER2-low BC. The SHAMROCK study investigates neoadjuvant T-DXd in early-stage HER2-positive BC, aiming to achieve a high pCR rate while minimizing treatment-associated toxicity. [12]. The key difference between our proposed trial and the SHAMROCK study lies in their patient selection criteria and the scope of biomarker exploration. While the SHAMROCK study does not select patients based on hormonal status and also explores translational biomarkers to direct therapy, our study specifically focuses on patients with HR+ BC. Our primary objective is to delve deeper into the potential synergy between hormonal therapy and T-DXd, providing a more comprehensive understanding of this combined treatment approach. To this end, we have designed this trial as a parallel two-arm phase II study, following a novel approach conducive to exploratory analyses with a reasonable required sample size at this stage of investigation. Importantly, the authors of this editorial are affiliated with tertial referral centers with units specialized in BC that can effectively enroll patients as required.

While this paper focuses on the potential research design, ethical considerations are paramount for any future study. Should this research progress, obtaining informed consent, ensuring participant confidentiality and securing Institutional Review Board (IRB) approval will be essential. The research will also adhere to the principles outlined in the Declaration of Helsinki of 1964 and its later amendments and be registered with a relevant clinical trial registry.

In one arm, patients eligible for neoadjuvant treatment will receive T-DXd in combination

Table 1 Ongoing neoadjuvant clinical trials of trastuzumab deruxtecan in patients with human epidermal growth factor receptor 2-positive breast cancer

Neoadjuvant T-DXd clinical trials	Inclusion criteria	Description	Status
T-DXd alone or in sequence with THP, versus standard treatment (ddAC-THP), in HER2-positive early breast cancer	RECRUITING Participants must have a histological or cytological diagnosis of invasive breast cancer All histologic subtypes are eligible Participants must have a clinical diagnosis of stage III inflammatory breast cancer within the past 6 months HER2-positive status as determined locally by the current ASCO/CAP guidelines or HER2-low tumor expression (IHC 2+/ISH-, IHC 1+/ISH-, or IHC 1+/ISH untested) (note: ISH may be determined by either FISH or DISH] Any ER and PR expressions are permitted but must be known Participants must be treatment-naïve	Phase 3 open-label Trial of neoadjuvant T-DXd monotherapy or T-DXd followed by THP compared to ddAC-THP (DESTINY-Breast11)	RECRUITING
A study of T-DXd versus T-DM1 in high-risk HER2-positive participants with residual invasive breast cancer following neoadjuvant therapy (DESTINY-Breast05)	ACTIVE: NOT RECRUITING Women or men aged ≥ 18 years Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations Histologically confirmed breast cancer with an invasive component measuring ≥ 20 mm and/or with morphologically confirmed spread to regional lymph nodes (stage cT2-cT4 with any cN, or cN1-cN3 with any cT) ECOG performance status 0 or 1 at the time of randomization Known ER and/or PR status, as assessed locally by IHC. The cut-off for positivity for ER/PR for this study is at least 10% of cell nuclei staining for ER or PR, respectively	Phase 3, multicenter, randomized, open-label, study of T-DXd versus T-DM1	

Table 1 continued

Neoadjuvant T-DXd clinical trials	Inclusion criteria	Description	Status
TRUDI: T-DXd + durvalumab in HER2+/low-IBC (TRUDI)	RECRUITING Patients must be at least 18 years of age Histologically documented HER2-positive early breast cancer participants, including clinical stage at presentation (based on mammogram or breast MRI assessment): T0-4 (inclusive of inflammatory breast cancer), N1-3, M0 or ≥ T3, N0, M0 as determined by the AJCC staging system, 8th edition ECOG performance status of 0 or 1 at randomization Adequate organ and bone marrow function LVEF ≥ 50% within 28 days before randomization	Phase 2 open-label study of neoadjuvant T-DXd plus durvalumab	
Neoadjuvant therapy with T-DXd versus chemotherapy + trastuzumab + pertuzumab in HER2+ early breast cancer (ADAPTHER2-IV)	Patients eligible for inclusion in this study must meet all the following criteria: 1. Female patients with invasive, untreated HER2+ breast cancer (as assessed by local pathology) maximum 6 weeks before registration (standard-of-care diagnostic biopsy according to current AGO guidelines) 2. Age ≥ 18 years. 3a. Cohort 1: low- to intermediate-risk for recurrence as per investigator´s decision (recommendation: *c*T1c–*c*T2 (1 to ≤ 3 cm), cN0; *c*T1a/b excluded), OR 3b. Cohort 2: intermediate- to high-risk for recurrence as per investigator´s decision (recommendation: *c*T2 (> 3 to ≤ 5cm), cN0). 3c. Elderly patients (≥ 65 years) may be assigned to any cohort as per investigator's decision 4. Written informed consent 5. LVEF ≥ 50% within 28 days before randomization 6. ECOG performance status 0–17	Phase 2 study, ADAPT-HER2-IV is planned as a superiority trial to demonstrate higher pCR rates	NOT YET RECRUITING

Table 1 continued

Neoadjuvant T-DXd clinical trials	Inclusion criteria	Description	Status
Neoadjuvant T-DXd therapy with response-directed definitive therapy in early-stage HER2+ breast cancer (SHAMROCK study)	RECRUITING Adult women and men aged ≥ 18 years Histologically confirmed HER2-positive breast cancer: Documented HER2 overexpression by local laboratory (IHC 3+ or FISH- or CISH-positive on diagnostic breast biopsy) Newly diagnosed breast cancer, planned for neoadjuvant therapy prior to surgery Stages 2–3 breast cancer Patients should not have received any prior therapy for breast cancer	Phase 2 open-label study, single-arm, adaptive multi-center trial, with T-DXd for up to 6 cycles	
T-DXd alone or in combination with anastrozole for the treatment of early-stage HER2-low, HR+ breast cancer	RECRUITING Previously untreated operable invasive carcinoma of the breast > 2.0 cm (cT2) in size based on physical exam or imaging. Patients with clinical node-negative disease or clinical node (cN1/cN2)-positive disease are allowed, provided they are deemed to have operable disease at study entry Participants with clinically involved lymph nodes should not have radiological evidence of distant disease per standard of care staging prior to PICF signature In the USA, tumor is HER2-low by IHC, defined as 1+ or 2+, confirmed by central testing (central testing results not required for enrollment, unless no local results available). If HER2 is 2+ by IHC, FISH must be performed (per standard of care) and the FISH result must be HER2 non-amplified per 2018 ASCO CAP guidelines Tumor is HR+ per ASCO CAP guidelines with known ER and PR status, locally defined ECOG performance status of 0 or 1	Phase 2 trial investigating how T-DXd works alone or in combination with anastrozole, based on pCR rate	

Table 1 continued

Neoadjuvant T-DXd clinical trials	Inclusion criteria	Description	Status
T-TXd versus standard neoadjuvant treatment for HER2-positive breast cancer (ARIADNE)	RECRUITING Adults ≥ 18 years (local regulatory requirements will apply if the legal age of consent for study participation is > 18 years) Pathologically documented HER2+ breast cancer HER2+ expression defined as an IHC score of 3+ and/or positive by ISH confirmed prior to study randomization Histologically confirmed invasive breast carcinoma Clinical stage at disease presentation: T1–4, N0–-3, M0; patients presenting with T1N0 tumors are not eligible	Phase 2 clinical trial comparing T-DXd to standard preoperative treatment	

AGO German Gynecological Oncology Group, *AJCC* American Joint Committee on Cancer, *ASCO CAP* American Society of Clinical Oncology College of American Pathologists, *CISH* chromogenic in situ hybridization, *DDAC* didecyldimethylammonium chloride, *DISH* dual in situ hybridization, *ECOG* Eastern Cooperative Oncology Group, *ER* estrogen receptor, *FISH* fluorescence in situ hybridization, *HER2* human epidermal growth factor receptor 2, *HER2+* HER2-positive, *HR* hormone receptor, *IBC* iron-binding capacity, *ICH/GCP* International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use–Good Clinical Practice, *ISH* in situ hybridization, *LVEF* left ventricular ejection fraction, *MRI* magnetic resonance imaging, *pCR* pathological complete response, *PICF* patient informed consent form, *PR* progesterone receptor, *T-DM1* trastuzumab emtansine, *T-DXd* trastuzumab deruxtecan, *THP* docetaxel/trastuzumab/ pertuzumab chemotherapy regimen

with letrozole, while the other arm will receive T-DXd alone. TDXd will be administered at a dose of 5.4 mg/kg every 3 weeks for a maximum of 8 cycles. Endocrine therapy will be based on letrozole at a dosage of 2.5 mg orally once daily. Men and pre/peri-menopausal women will also receive a gonadotropin hormone-releasing hormone (GnRH) agonist. Although patients will be randomized to one of the two arms, each arm essentially represents an independent phase II trial. The primary endpoint for both arms is the complete radiological response rate. Patients demonstrating a favorable response, evidenced by imaging complete response (iCR) after a predetermined number of treatment cycles, will proceed to definitive therapy. This may include surgery, with or without radiotherapy in accordance with current guidelines, along with continued endocrine therapy. Patients who do not achieve iCR may be offered salvage systemic chemotherapy based on their individual response and clinical judgment. The trial employs a minimax sample size design for two separate phase II single-arm clinical arms, each investigating T-DXd. One arm will test T-DXd combined with an aromatase inhibitor, letrozole, while the other arm will test T-DXd alone. The total sample size required across both arms is 52 participants, with 29 participants in the initial stage and an additional 23 participants in the second stage. Stopping rules are predefined for each stage based on response rates: the trial may stop early for futility or if strong efficacy is observed. The trial aims to maintain a Type I error rate of 0.05 and a power of 0.8, with response probabilities set at 0.05 for a poor drug response and 0.15 for a good drug response. Our proposed study will primarily focus on evaluating the radiological complete response rate as the primary endpoint for each of the two separate Phase II arms. Secondary endpoints will include assessing changes in Ki-67 expression, evaluation of the pathologic complete response (pCR) rate, toxicity profile, event-free survival, and overall survival. Explorative analyses will further allow for comparisons between the two arms, seeking to optimize treatment efficacy while minimizing treatment-related adverse effects and ultimately improving outcomes for this patient population. Descriptive statistics, including means, medians, ranges, and frequencies, will be used to summarize patient characteristics, treatment adherence, and safety data. Furthermore, additional analyses will leverage exploratory techniques to delve deeper into potential differences between the two treatment arms. These techniques may involve comparisons of response rates, toxicity profiles, and other clinical outcomes using methods, such as Chi-square tests or logistic regression (depending on the data distribution). The goal of these exploratory analyses is to identify trends or relationships that could inform the design of future, larger studies.

This study explores the potential of neoadjuvant trastuzumab deruxtecan (T-DXd) with or without endocrine therapy for HER2-low, HR+ breast cancer. The proposed phase II design allows for initial assessment of safety, efficacy, and potential for a chemotherapy-sparing approach. Given the parallel phase II design, the study is primarily exploratory and not intended for direct comparison between the treatment arms. While the study may provide valuable insights into the efficacy of T-DXd with or without endocrine therapy, definitive conclusions regarding the superiority of one arm over the other may not be drawn. Nevertheless, the findings from this study, along with the exploration of novel biomarkers, could pave the way for personalized treatment strategies in this patient population. Future research, particularly a confirmatory randomized controlled trial, is necessary to definitively determine the role of T-DXd and endocrine therapy to optimize treatment regimens for patients with HER2-low breast cancer.

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Declarations

Conflict of Interest. Luca Scafuri and Carlo Buonerba have received honoraria as speakers from Genetic Spa. Vincenzo Di Lauro has received speaker's honoraria from Amgen, Seagen, Wavepharma, Genetic, Veracyte, Novartis, and Accord. Paolo Tarantino reports research funding (to institution) from AstraZeneca and has served as advisor/consultant for AstraZeneca, Daiichi-Sankyo, Gilead, Novartis, Roche, Genentech and Lilly. Giuseppe Di Lorenzo is an Editorial Board member of *Oncology and Therapy*; he was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Antonio Marra has received honoraria as a consultant, advisor or speaker from Roche and Menarini/Stemline; and has received travel and accommodation support from AstraZeneca. Vincenzo Tortora, Marco Cascella, Luigi Liguori, Antonella Sciarra, Francesco Sabbatino, Anna Diana, Dario Trapani, Mario Giuliano, Grazia Arpino and Giuseppe Curigliano have nothing to disclose.

Ethical Approval. While this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, ethical considerations are paramount for any future study. Should this research progress, obtaining informed consent, ensuring participant confidentiality, and securing Institutional Review Board (IRB) approval will be essential. The research will also adhere to the principles outlined in the Declaration of Helsinki and be registered with a relevant clinical trial registry.

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