Editorial Commentary

DESTINY-Breast01 trial: trastuzumab deruxtecan in previously treated HER2 positive breast cancer

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Introduction

Approximately 20% of metastatic breast cancers (MBC) overexpress human epidermal growth factor receptor 2 (HER2). HER2 overexpression is associated with a more aggressive disease biology and historically poorer outcomes (1,2). The human epidermal growth factor family includes four receptors (EGFR1, HER2, HER3, HER4) that regulate cell migration, adhesion, proliferation, and survival.

Since the revolutionary development of trastuzumab, many anti-HER2 medications have continued to dramatically improve outcomes for patients with HER2 positive breast cancers in both the neo/adjuvant and metastatic settings. The initial studies of trastuzumab in early breast cancer dramatically changed the survival of this aggressive subtype. In the metastatic setting the use of anti-HER2 agents has not only improved survival but also quality of life.

Antibody-drug conjugates (ADCs) represent a relatively novel class of HER2 directed therapy. While the research leading to the development of ADCs was initially proposed over 100 years ago by Paul Ehrlich, this class of anti-neoplastic agents has only recently emerged. These medications are comprised of a monoclonal anti-HER2 antibody linked to a cytotoxic payload. Trastuzumab emtansine (T-DM1) is the most extensively studied and has been in widespread use since its approval in 2013. Based on results of the EMILIA clinical trial, T-DM1 has been established as standard of care in HER2+ MBC patients with progression on HER2 directed therapy. T-DM1 is associated with a 43.6% objective response rate and a median duration of progression free survival (PFS) of 9.6 months when used after trastuzumab plus taxane (3), and overall survival of 29.9 months. The technology that led to its development was revolutionary and opened the doors for other such agents to be developed. Most of the research in this area has focused on hematologic malignancies and HER2 positive breast cancer.

Trastuzumab deruxtecan (T-DXd) is an ADC composed of a humanized monoclonal antibody with the same amino acid sequence as trastuzumab, joined via a cleavable peptide linker to a potent topoisomerase 1 inhibitor. Despite similar principles in structure and development, there are also many key differences between ADCs currently available and under-study.

T-DXd was designed to deliver a higher drug-to-antibody ratio than T-DM1, approximately 8:1 with T-DXd versus 3–4:1 with T-DM1 (4). This allows more efficient delivery of cytotoxic payload to target cells. Additionally, the payload in T-DXd can more easily cross cell membranes to exert effects on neighbouring cells regardless of their HER2 expression (termed bystander effect). T-DM1 uses a microtubule inhibitor cytotoxic payload, where T-DXd delivers a topoisomerase 1 inhibitor, which is a relatively unique compared to the mechanism of action of commonly used systemic chemotherapeutic agents in the treatment of breast cancer. Fortunately, this topoisomerase 1 inhibitor payload maintains a short half-life which limits potential for systemic toxicities with this agent. The peptide linker between antibody and drug in T-DXd is also unique. It is stable in plasma, but selectively

cleaved by cathepsins that are up-regulated within cancer cells to release the topoisomerase 1 inhibitor (4). The linker in T-DM1 is non-cleavable, and so DM1 release relies on proteolytic degradation of the antibody within the lysosome intracellularly. Together, these unique characteristics of T-DXd potentially explain the robust response rates and efficacy seen in HER2 positive MBC clinical trials to date (4). Additionally, early clinical data suggesting activity in lower HER2 expressing tumours is attributed to the potent cytotoxic payload and bystander effect seen with T-DXd (5).

DESTINY-Breast01 clinical trial

The DESTINY-Breast01 clinical trial was an open-label, single-arm, multicentre, phase 2 study of T-DXd in patients with unresectable or metastatic HER2 positive breast cancer [3+ on immunohistochemistry (IHC) or positive by fluorescent *in situ* hybridization (FISH)] (6). This trial included a heavily pretreated population, the median number of previous lines of therapy for metastatic disease was 6. All patients had been previously treated with both trastuzumab and T-DM1, and the majority (65.8%) of patients had also previously received pertuzumab. Patients with untreated or symptomatic brain metastases, and patients with current or prior interstitial lung disease (ILD) requiring glucocorticoids were excluded.

Although registered as a Phase 2 study the design resembles a phase IB/2. Part 1 of this two-part study included pharmacokinetics and dose finding analyses, administering doses at 5.4, 5.4 and 7.4 mg/kg. Exposure-efficacy and exposure-safety modeling showed a significant relationship between dose and both response rate and key adverse events respectively. To balance safety and efficacy ultimately, 5.4 mg/kg was identified as the recommended dose of T-DXd. Part 2 of the trial evaluated efficacy and safety parameters of T-DXd in 184 patients. The primary endpoint of part 2 was overall response (complete response plus partial response). Secondary endpoints were response duration, PFS, overall survival, response rate, best percentage change in the sum of diameter of measurable tumours, disease control rate (response rate plus stable disease rate), clinical benefit rate (disease control rate with stable disease lasting ≥6 months), safety and pharmacokinetics.

Among the 184 patients included in the part 2 analysis at median duration of follow-up of 11.1 months, overall response was 60.9% (95% CI: 53.4% to 68.0%), with 6% complete response and 54.9% partial response. It should be noted that this overall response rate has not been seen previously in metastatic HER2 positive breast cancer treatments. Only 3 patients (1.6%) experienced disease progression on T-DXd. Disease control rate was 97.3% (95% CI: 93.8% to 99.1%), and clinical benefit rate was 76.1% (95% CI: 69.3% to 82.1%). Efficacy results were consistent across key demographic and prognostic subgroups. Median PFS was 16.4 months (95% CI: 12.7 months to not reached). Median OS was not reached in the original published analysis. An updated analysis at 35% maturity (119 patients censored), estimated median OS at 24.6 months (95% CI: 23.1 months to not reached). This is similar to median OS reported in the original studies of first line HER2 directed therapy with trastuzumab and chemotherapy published in 2001 in the pivotal trial by Slamon *et al.* (7). Seeing these survival rates in such a heavily pre-treated population is revolutionary.

However, it is important that we temper our excitement. There were several key toxicities of note in this study. 99.5% of the 184 patients who received the recommended dose of T-DXd experienced an adverse event, 57.1% of grade 3 severity or higher. The most common grade 3 or higher events were decreased neutrophil count (19.6%), anemia (8.2%), and nausea (7.6%). Importantly, 25 patients (13.6%) developed ILD from T-DXd treatment. Twenty of the ILD diagnoses were grade 1 or 2 severity, one was grade 3, and four patients died from ILD related to treatment.

Widespread applicability of results from DESTINY-Breast01 are limited by the early phase II single-arm non-randomized nature of the study. While the robust and impressive results from this trial are very encouraging, further study is warranted and underway to ensure that these results retain validity in randomized controlled trials DESTINY-Breast02 and DESTINY-Breast03. The magnitude of benefit of T-DXd in a randomized trial is highly anticipated and speculated. There has been a recent press release on DESTINY-Breast03 that reported a significant improvement in PFS and trend towards improvement in OS of T-DXd compared to T-DM1 but we need to see the manuscript and full data.

Current treatment paradigms of metastatic HER2-positive breast cancer

Over the past 20 years immense effort and resources have been dedicated to drug development for HER2 positive MBC (8). Standard first- and second-line treatments are

Table 1 Summary of major trials for HER2 directed therapy in the metastatic setting discussed within

Trial	Population	Intervention	Results	Toxicities
CLEOPATRA (Phase III)	808 patients (pts), no prior therapy for MBC. Only 11% had trastuzumab in early setting	Pertuzumab *vs.* placebo plus trastuzumab and docetaxel	PFS: HR 0.68 (95% CI, 0.58–0.8) 18.7 *vs.* 12.4 months OS: HR 0.68 (95% CI, 0.56–0.84) 56.5 *vs.* 40.8 months	Diarrhea, rash, headache, nausea, fatigue, upper respiratory tract infection
EMILIA (Phase III)	978 pts, all with prior trastuzumab exposure	T-DM1 *vs.* lapatinib + capecitabine (L+C)	PFS: HR 0.65 (95% CI, 0.55–0.77) 9.6 *vs.* 6.4 months OS: HR 0.75 (95% CI, 0.64–0.88) 29.9 *vs.* 25.9 months	Thrombocytopenia, transaminitis
NALA (Phase III)	621 pts, 2+ lines prior HER2 therapy for MBC	Neratinib + capecitabine (N+C) *vs.* L+C	PFS: HR 0.76 (95% CI, 0.63–0.93) OS: HR 0.88 (95% CI, 0.72–1.07) Less intervention for CNS metastases with N+C (29.2% *vs.* 22.8%)	Diarrhea, nausea, hand-foot syndrome, fatigue
HER2CLIMB (Phase III)	480 pts, all had prior trastuzumab, pertuzumab, T-DM1. Progressive CNS metastases included	Tucatinib *vs.* placebo plus trastuzumab and capecitabine	PFS: HR 0.54 (95% CI, 0.42–0.71) 7.8 *vs.* 5.6 months OS: HR 0.66 (95% CI, 0.50–0.88) 21.9 *vs.* 17.4 months	Diarrhea, transaminitis, hand-foot syndrome, fatigue
SOPHIA (Phase III)	536 pts, 2+ lines prior HER2 therapy, 100% prior pertuzumab, 91% prior T-DM1	Margetuximab *vs.* trastuzumab	PFS: HR 0.76 (95% CI, 0.59–0.98) 5.8 *vs.* 4.9 months OS 0.89 (95% CI, 0.69–1.13) 21.6 *vs.* 19.8 months	Infusion reactions, otherwise comparable safety
DESTINY-Breast01 (Phase II)	184 pts, all prior T-DM1, median 6 prior lines therapy	All pts received trastuzumab deruxtecan	Overall response rate: 60.9% (95% CI, 53.4–68) PFS: 16.4 months (95% CI, 12.7 to not reached)	Interstitial lung disease, neutropenia, anemia, nausea

well established and globally accepted based on results from the CLEOPATRA and EMILIA clinical trials. Treatment options in the third-line setting and beyond are numerous, and ideal sequencing based on efficacy and toxicities remains undetermined. *Table 1* summarizes the major studies which have led to our current treatment guidelines.

The practice changing CLEOPATRA trial evaluated trastuzumab and pertuzumab *vs.* placebo, plus docetaxel included for a recommended minimum initial 6 cycles (median 8) (9). The addition of pertuzumab improved PFS to 18.7 months, compared to 12.4 months with placebo (HR 0.68, 95% CI: 0.58–0.8, P<0.001). OS benefit was shown as well with the addition of pertuzumab, demonstrating 56.5 months with pertuzumab versus 40.8 months with placebo (HR 0.68, 95% CI: 0.56–0.84, P<0.001). In CLEOPATRA, only 11% of included patients had been exposed to prior adjuvant or neoadjuvant trastuzumab.

The EMILIA clinical trial randomized patients with HER2 positive advanced breast cancer who had previously all received trastuzumab in the metastatic setting or who had progressed while on adjuvant trastuzumab or within 6 months of completion of adjuvant trastuzumab (3). Patients were randomized to T-DM1 versus lapatinib and capecitabine. Median PFS was improved to 9.6 months with T-DM1 versus 6.4 months with lapatinib and capecitabine. Median overall survival was also significantly increased in patients receiving T-DM1 (30.9 *vs.* 25.1 months). Patients treated with T-DM1 had a higher objective response rate (43.6% *vs.* 30.8%). The results of EMILIA established T-DM1 as standard of care for advanced HER2 positive breast cancer that has progressed on prior HER2 directed therapy.

Treatment sequencing beyond progression on T-DM1

The results of the DESTINY-Breast01 phase II trial yield encouraging results, demonstrating impressive response rates and PFS in an extensively pretreated patient population with advanced HER2 positive breast cancer.

Depending on results from future phase III trials, T-DXd may claim an emerging role vying for a position as standard third-line therapy. There were important safety concerns however, and as more patients are receiving trastuzumab, pertuzumab and T-DM1 in the neoadjuvant and adjuvant settings T-DXd may move into earlier lines of therapy and expose even greater numbers of patients to its toxicities. It is important to interpret the results of the DESTINY-Breast01 study in the context of other trials conducted in similar populations of patients, of which the HER2CLIMB, NALA, and SOPHIA trials are the most notable.

The phase III HER2CLIMB study established tucatinib [highly selective HER2 tyrosine kinase inhibitor (TKI)] plus trastuzumab and capecitabine as a novel third-line option for patients with advanced HER2 positive breast cancer all previously treated with trastuzumab, pertuzumab and T-DM1 (10). Median previous line of treatment for metastatic disease was 3. Median PFS among the first 480 randomized patients was 7.8 months with tucatinib, versus 5.6 months with placebo. Median OS among the total trial population of 612 patients was 21.9 months with tucatinib and 17.4 months with placebo. Patients with brain metastases were included so long as they did not require immediate intervention. Median PFS in patients with brain metastases was similar to the total trial population, 7.6 months with tucatinib and 5.4 months with placebo. Most common adverse events were diarrhea, hand-foot syndrome, and elevation in aminotransferases with tucatinib. It is important to note that only 6% of enrolled patients in HER2CLIMB had previously been exposed to lapatinib—raising the question whether the comparator arm should have been lapatinib instead of placebo. Key differences between HER2CLIMB and DESTINY-Breast01 are the phase II versus III maturity, inclusion of patients with progressive brain metastases in HER2CLIMB, and the more heavily pre-treated population enrolled in DESTINY.

The phase III NALA clinical trial evaluated neratinib (an irreversible pan-HER TKI) and capecitabine versus lapatinib and capecitabine in 621 patients with HER2 positive MBC (11). All patients had received at least 2 prior lines of HER2 directed therapy for MBC, but only about one third of patients in each arm had received trastuzumab, pertuzumab and T-DM1. Mean PFS, but not median PFS, was improved from 6.6 months with lapatinib and capecitabine to 8.8 months with neratinib and capecitabine. OS was not statistically significantly improved. Asymptomatic or stable brain metastases were not exclusions. Treatment with neratinib also delayed time to intervention for CNS metastases. The primary grade 3+ toxicity with neratinib was diarrhea in 24.4% patients, compared to 12.5% of patients in the lapatinib group. Key differences between NALA and DESTINY-Breast01 are the phase II versus III design, the more heavily pre-treated population enrolled in DESTINY, and the majority of patients enrolled in NALA had not received what is now considered standard first- and second-line therapies.

The phase III Sophia clinical trial randomized 536 patients with HER2 positive MBC to margetuximab versus trastuzumab, both combined with chemotherapy (12). Both drugs bind to the same epitope on HER2, but margetuximab has an optimized Fc domain with increased affinity for its activating receptor, triggering enhanced antibody-dependent cellular toxicity. All patients had previously progressed on at least 2 prior lines of HER2 directed therapy. The majority of patients had received prior trastuzumab, pertuzumab and T-DM1. Patients with stable treated brain metastases were included. There was a modest improvement in median PFS from 4.9 months with trastuzumab to 5.8 months with margetuximab. Median OS was immature at time of publication but not significantly different between the groups. Patients had more infusion reactions with margetuximab, but otherwise safety profiles were equivalent. The modest PFS difference is not clinically significant in a less heavily pretreated population, limiting the impact of this study.

Future directions

Selecting treatment for patients with HER2 positive MBC beyond second line is increasingly complex as the broad array of therapeutic options continue to rapidly evolve. To date, of the completed Phase III trials, only tucatinib has demonstrated a significant OS benefit of 4.5 months compared to trastuzumab and capecitabine. Importantly, the patient population in HER2CLIMB closely represents the modern clinical context as all patients had previously received treatment with trastuzumab, pertuzumab and T-DM1. The consistent benefit amongst patients with active brain metastases is encouraging for this notoriously difficult to treat condition.

T-DXd received accelerated FDA approval based on the results from the DESTINY-Breast01, with a boxed warning to monitor for ILD associated symptoms and prompt management with glucocorticoids if suspected. Certainly, this is a promising option for heavily pre-treated patients but there is caution as these are Phase II results. The phase

III trial DESTINY-Breast02 is underway (NCT03523585), randomizing patients whose disease previously progressed on T-DM1 to T-DXd or investigators choice (trastuzumab/capecitabine or lapatinib/capecitabine). Studies combining T-DXd with other agents are also ongoing. The DESTINY03- Breast trial has reported a 12 month PFS% of 75.8 months for T-DXd compared to 34.1% for T-DM1 in advanced breast cancer with a HR of 0.2840 and $P=7.8\times10^{-22}$. OS was trending but not yet significant. T-DXd appears to be set to replace T-DM1 in second line therapy and is being compared in earlier lines as well as the adjuvant and neoadjuvant settings (13).

In addition, there is an ongoing phase III study evaluating efficacy of T-DXd in HER2-low (IHC 1+/2+ and FISH negative) hormone receptor positive MBC (DESTINY-Breast06, NCT04494425). An earlier phase IB trial demonstrated 37% objective response rate (95% CI: 24.3–51.3%) with 10.4 months median duration of response in a heavily pretreated population (7.5 median lines of prior therapy) (14). Results from this ongoing study have the potential to revolutionize how we conceptualize HER2 status.

With this area of drug development finally hitting its stride over 100 years after initial proposals by Ehrlich, new HER2 directed ADCs continue to be developed. Trastuzumab duocarmazine (SYD985) is another second-generation ADC with a potent cytotoxic payload and cleavable linker (like T-DXd) currently being evaluated in an ongoing phase III TULIP trial (NCT03262935). Eligible patients have progressed after at least 2 prior lines of HER2 therapy, or progressed on T-DM1, and are being randomized 2:1 to receive either trastuzumab duocarmazine or physician's choice. An earlier phase I study of trastuzumab duocarmazine in HER2-positive and HER2-low MBC showed an overall response rate of 33% and median PFS of 9.4 months.

Fortunately, advanced lines of treatment options for MBC continue to expand. Optimal sequencing of available therapies is still unknown, as no direct comparisons exist. But the ongoing DESTINY-Breast03 clinical trial randomizing patients with HER2 positive MBC to T-DXd versus T-DM1 after progression on trastuzumab and a taxane will hopefully start to answer some of these questions.

Conclusions

T-DXd is a second-generation antibody drug conjugate with unique and potent characteristics. DESTINY-Breast01, a recent phase II single arm study, demonstrated impressive response rates and PFS with T-DXd in a heavily pretreated population with metastatic HER2 positive breast cancer. Important safety concerns were seen in the T-DXd population, with 13.6% of patients developing ILD and 2.2% of those cases being fatal. Results from continuing research with T-DXd in the HER2 positive and HER2 low expressing MBC population are eagerly awaited including the intriguing early results from DESTINY03-Breast.

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