



Dana-Farber
Cancer Institute

Susan F. Smith Center
for Women's Cancers

Dana-Farber Breast Oncology Center

Consensus Statement Regarding Use of Trastuzumab Deruxtecan (T-DXd) in Patients with Metastatic, HER2-low Breast Cancer

Consensus: Obtained at Breast Oncology Center meetings on 7/1/2022 and 7/8/2022.

Acknowledgments: Paolo Tarantino, MD, for his leadership in the consensus discussions and in writing of the statements. Coordination and editorial support were performed by Mr. Scorzoni and Ms. Bak.

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Synopsis

Consensus statements regarding use of trastuzumab deruxtecan (T-DXd) in patients with metastatic, HER2-low breast cancer

Clinical Question	Consensus Statement
Q1. Which HER2-negative breast cancer patients should receive T-DXd?	<p>The following considerations, including a) HER2 status, b) hormone receptor status, c) history of prior treatments and d) medical history and history of central nervous system (CNS) involvement, for recommendations on the use of T-DXd are detailed below.</p> <p><u>a) HER2 status:</u></p> <ul style="list-style-type: none"> • Patients who had a HER2-low status (IHC 1+ or 2+/ISH negative) on any prior biopsy or surgery, including on the primary tumor. • Patients who never had a prior biopsy scored HER2-low. The collection of a fresh biopsy to re-test HER2 status could be considered to offer T-DXd in case of a HER2-low score <p>- Pathologic reassessment of prior samples scored IHC 0 is reasonable, particularly if these were read at an outside institution</p> <p>Importantly, given the relevance of the HER2 IHC score for treatment decisions (and clinical trials enrollment), the Breast Oncology Center (BOC) consensus group stressed the need to always report the HER2 IHC score in pathologic reports and clinical notes, both for tumors classified as HER2-positive as well as for those classified as HER2-negative.</p> <p><u>b) Hormone receptor status and c) history of prior treatments</u></p> <p>The BOC group convened that it is acceptable to use T-DXd in patients that have progressed to prior endocrine treatment, CDK4/6 inhibitors, and chemotherapy.</p> <p>Use of prior alpelisib, everolimus, PARP-inhibitors, and immunotherapy is also acceptable, although the small (or unknown) number of patients pretreated with these regimens in DESTINY-Breast04 warrants caution for the sequential use in clinical practice.</p> <p><u>d) Medical history and history of central nervous system (CNS) involvement.</u></p> <p>It is reasonable to exclude from treatment with T-DXd patients with significant cardiovascular disease, as well as patients with history of non-infectious ILD that required steroids or with ongoing ILD.</p> <p>Use of T-DXd in patients experimenting prior everolimus-related ILD can be considered, but only if this was mild and completely resolved at the time of using T-DXd.</p> <p>Given the promising data and the relevant unmet need represented by patients with CNS involvement, it is reasonable to use T-DXd for HER2-low breast cancer patients with either stable or active CNS disease at baseline.</p>

<p>Q2. How should T-DXd be sequenced with other available treatments?</p>	<p><u>a) HR-positive HER2-low breast cancer</u></p> <p>The BOC consensus group agreed to adopt T-DXd after exhaustion of endocrine-based treatment strategies and after prior treatment with at least one prior line of chemotherapy.</p> <p>Use of T-DXd immediately after exhaustion of endocrine-based treatment options can be considered in selected cases (i.e., for patients that have been previously treated with several chemotherapy agents in the neoadjuvant or adjuvant setting)</p> <p>It is also reasonable to use T-DXd after multiple prior lines of chemotherapy, as it has shown to be superior to most of the drugs commonly used in highly pretreated settings</p> <p>T-DXd should be prioritized over sacituzumab govitecan in HR-positive disease</p> <p>For patients with a germline <i>BRCA</i> pathogenic variant, the group agreed that any sequence of PARP-inhibitors and T-DXd is acceptable, although most of the panel would endorse prioritization of PARP-inhibitors in this setting.</p> <p><u>b) - HR-negative disease (i.e., TNBC)</u></p> <p>The use of T-DXd can be considered in HR-negative (i.e., TNBC) HER2-low breast cancer patients after at least one prior line of chemotherapy (with or without immunotherapy, depending on PD-L1 status)</p> <p>Treatment with T-DXd can be also considered for selected HR-negative (i.e., TNBC) HER2-low patients experiencing rapid recurrence after (neo)adjuvant chemotherapy</p> <p>Given strong efficacy data with both agents, and no available head-to-head comparison, any sequence of T-DXd and sacituzumab govitecan is acceptable for HR-negative (i.e., TNBC) HER2-low breast cancer patients</p> <p>For patients with a germline <i>BRCA</i> pathogenic variant, the group agreed that any sequence of PARP-inhibitors and T-DXd is acceptable, although most of the panel would endorse prioritization of PARP-inhibitors in this setting.</p>
<p>Q3. How should the toxicities of T-DXd be monitored and managed?</p>	<p>It is extremely important to adopt the following strategies to proactively detect and manage side effects of T-DXd:</p> <p>Proactive monitoring for ILD/pneumonitis: patients in DESTINY-Breast04 received tumor assessments with CT scans every 6 weeks, which concomitantly allowed for the early detection of radiological signs of ILD. The BOC group agreed that, for the purpose of following patients in clinical practice, a reasonable timing for CT scans would be 6-12 weeks.</p> <p>In addition, pulse oximetry and history of respiratory signs/symptoms should be carefully collected and reviewed at each visit. In case of signs/symptoms suspect for ILD/pneumonitis, T-DXd should be discontinued (temporarily if grade 1/asymptomatic, permanently discontinued in case of grade ≥2/symptomatic) and the dedicated guidelines should be followed to manage the event.</p> <p>Prevention of nausea and vomiting: Current guidelines categorize T-DXd as moderately emetogenic, although these may evolve with the accumulation of experience with the drug. Recommendations should be prophylactic anti-emetics with a two-drug regimen including dexamethasone and 5-HT3 receptor antagonist for all patients (i.e., decadron + ondansetron or palonosetron), with consideration for adding a NK1 inhibitor (e.g. emend) and thus administer a three-drug regimen.</p>

	<p>This can be considered upfront, based on patient-related factors, or as escalation in patients experiencing anything less than an optimal control of nausea and vomit with any cycle of T-DXd. For delayed nausea, Zofran +/- olanzapine can be effective management strategies</p> <p>Risk of alopecia: although this was observed in 38% of the patients treated with T-DXd in DESTINY-Breast04, it is not currently known what part of these events were grade 1 (<50%) or grade 2 (>50%). However, prior experiences suggest a rate of about 10% for grade 2 alopecia with T-DXd. At present, there is no data on the effectiveness of scalp cooling to prevent or mitigate alopecia. A clinical trial is currently enrolling at Dana-Farber Cancer Institute and will inform future practice once the data is available. The group was divided, but half of the panellists would consider use of scalp cooling to try preventing alopecia with T-DXd.</p> <p>Monitoring of cardiac function: patients in DESTINY-Breast04 were monitored with ECHO or MUGA every 4 cycles (q12 weeks). The consensus group agreed that, in clinical practice, it is reasonable to monitor cardiac function at baseline and then every 6-12 months.</p> <p>Drug dose: The recommended dosage of T-DXd is 5.4 mg/kg given as an intravenous infusion once every 3 weeks. Dose reductions should follow the drug FDA label, included below in this document. The consensus group, however, agreed that the adoption of a lower dose upfront for frail patients is reasonable.</p>
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Additional considerations:

- Potential toxicities and benefits of T-DXd should be discussed with the patient ahead of initiating treatment. Particular attention should be dedicated to the risk of interstitial lung disease (ILD)⁷, of which all patients should be aware ahead of initiating treatment and during treatment with T-DXd.
- Guidelines are subject to change with evolution of data from existing and future trials. The BOC will plan to reconvene in 12 months to review patterns of care for metastatic, HER2-low breast cancer.

Introduction

About half of all breast cancers have human epidermal growth factor receptor 2 (HER2)-low expression, defined as a HER2 immunohistochemical (IHC) score of 1+ or 2+ with negative in situ hybridization (ISH) assay¹. These tumors, traditionally classified as HER2-negative per American Society of Clinical Oncology (ASCO)/ College of American Pathologists (CAP) 2018 Guidelines on HER2 scoring, have been recently shown to respond to treatment with novel anti-HER2 antibody-drug conjugates (ADCs)²⁻⁴. Of note, the rate of HER2-low expression (vs HER2-0) varies depending on the expression of hormone receptors (HR), with about 60% of HR-positive HER2-negative tumors being HER2-low, compared with approximately 40% of triple-negative breast cancers (TNBC)⁵.

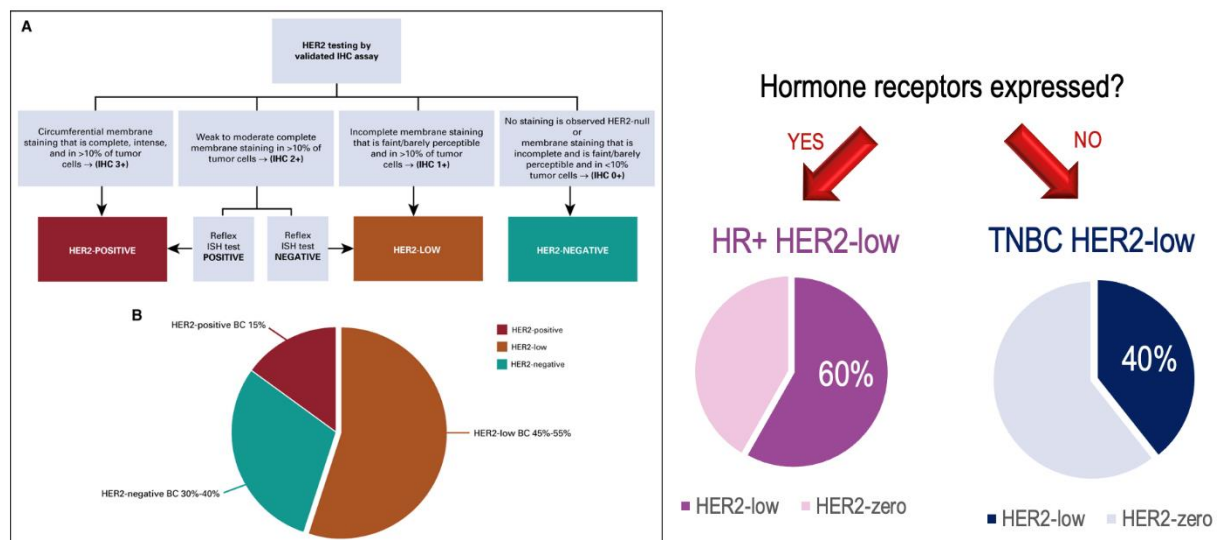


Figure 1 – Current definition of HER2-low breast cancer and rate of HER2-low tumors depending on HR-expression^{1,5}

Source: Image A is reprinted with permission from Tarantino, P., et al. *HER2-Low Breast Cancer: Pathological and Clinical Landscape. J Clin Oncol* 2020;38:1951-1962

<https://pubmed.ncbi.nlm.nih.gov/32330069/> The second image was created by the author.

The DESTINY-Breast04 trial has demonstrated the benefit of treating patients with metastatic HER2-low breast cancer with the anti-HER2 ADC trastuzumab deruxtecan (T-DXd)⁶. In this population, treatment with T-DXd resulted in a statistically significant and clinically meaningful improvement in both progression-free survival (PFS) and overall survival (OS) over physician's choice of chemotherapy.⁶

Development of the Consensus Statements

The Dana-Farber Cancer Institute's Breast Oncology Center (BOC) held multidisciplinary meetings on 07/01/2022 and 07/08/2022 to discuss recommendations for the use of T-DXd in patients with metastatic, HER2-low breast cancer. Data were reviewed from the DESTINY-Breast04 phase 3 trial, the TROPiCS-02 phase 3 trial, from the ASCENT phase 3 trial, from the OlympiAD phase 3 trial and from the EMBRACA phase 3 trial. Additional relevant data were reviewed to address the questions in this document as noted below. The gathered evidence was presented for discussion to a multidisciplinary group, which included physicians, nurses, clinical investigators, lab investigators, translational researchers, administrators, and patient advocates. The discussion and suggestions for improvements continued via email exchanges following the meeting. The final consensus statements were consolidated in August of 2022.

The consensus statements can be subject to future variations and periodic updates, based on emerging evidence and new reports from ongoing clinical studies. Therefore, the information provided in this document should not be considered as being complete or inclusive of all proper assessments, treatments or methods of care or as a statement of the standard of care. This information does not mandate any particular course of medical care and is not intended to be a substitute for the independent professional judgment of a health care provider. The document is based on the opinion of a multidisciplinary team at Dana-Farber but does not represent the official institutional position, and overall must be considered as a consensus based on the positions and ideas of the Dana-Farber providers.

DESTINY-Breast04 trial

DESTINY-Breast04 trial was a randomized phase 3 trial comparing the activity of T-DXd to physician's choice of chemotherapy (capecitabine, gemcitabine, eribulin, paclitaxel, or nab-paclitaxel) among patients with HER2-low metastatic breast cancer pretreated with endocrine treatment (if HR+) and 1 to 2 lines of chemotherapy. The study randomized 557 patients in a 2:1 ratio to receive T-DXd or chemotherapy.⁶

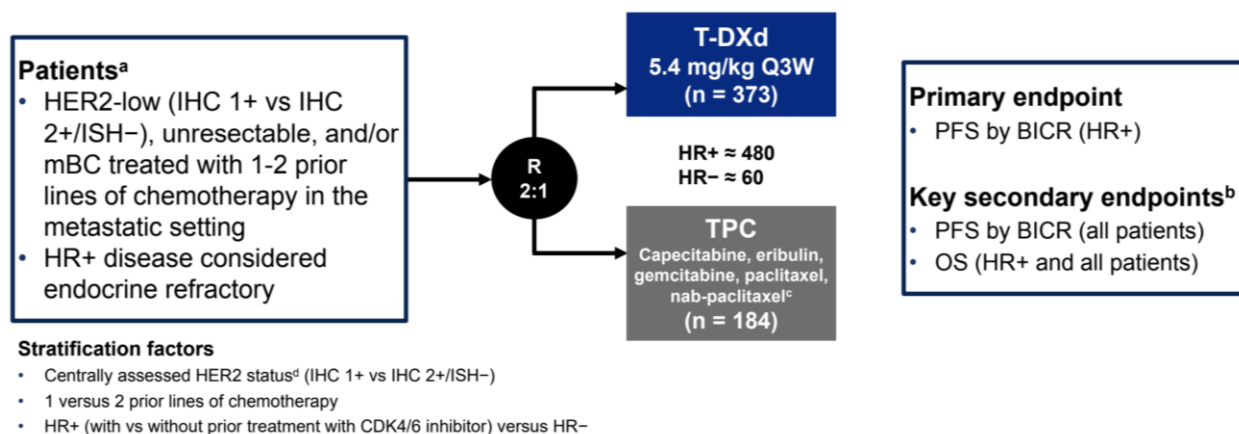


Figure 2 – DESTINY-Breast04 phase 3 trial design

Source: ASCO 2022 presentation by S. Modi, reprinted with permission from author.

A) Outcomes with T-DXd in HR+ patients and in ITT (HR+ and TNBC)

At the first analysis of the study results, T-DXd demonstrated an improvement in PFS compared with chemotherapy among HR-positive patients (primary endpoint, 10.1 vs 5.4 months, hazard ratio 0.51, $p < 0.001$), as well as in the overall study population (9.9 vs 5.1 months, hazard ratio 0.50, $p < 0.001$). OS was also improved among HR-positive patients (23.9 vs 17.5 months, hazard ratio 0.64, $p = 0.003$) and in the overall study population (23.4 vs 16.8 months, hazard ratio 0.64, $p = 0.001$). Response rate favored the study drug, with 52.6% of HR-positive breast cancer patients having an objective response with T-DXd compared with 16.3% of the patients receiving chemotherapy.

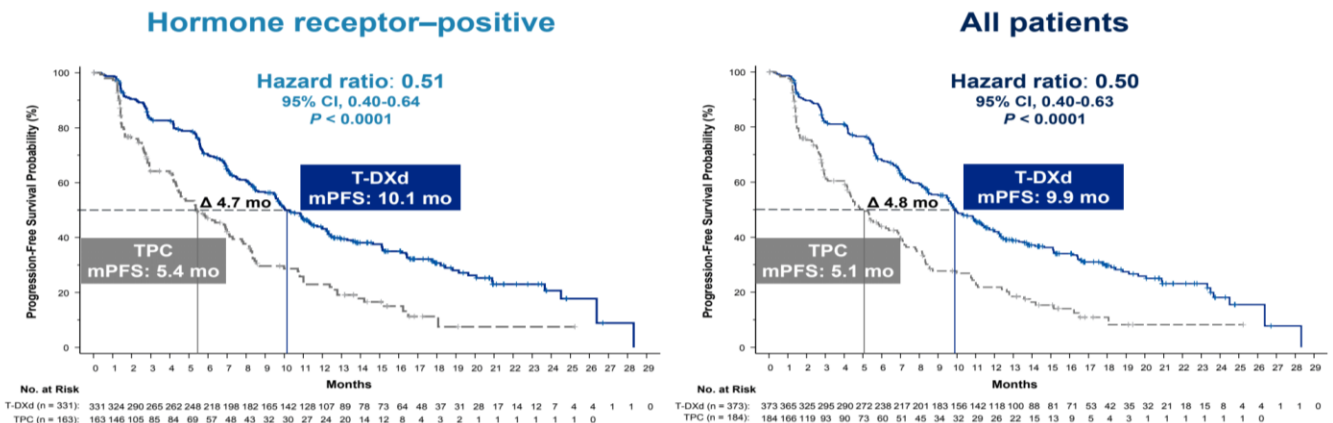


Figure 3 – PFS results with T-DXd vs chemotherapy among HR+ patients and in the overall study population

Source: ASCO 2022 presentation by S. Modi, reprinted with permission from author.

B) Outcomes with T-DXd in TNBC patients

In an exploratory analysis restricted at the TNBC patients enrolled in DESTINY-Breast04 (n=58) results were consistent with the primary analysis, with improved PFS (8.5 vs 2.9 months, hazard ratio 0.46) and OS (18.2 vs 8.3 months, hazard ratio 0.48) with T-DXd compared with chemotherapy. Response rate also favored T-DXd, with 50% of patients with HER2-low TNBC having an objective response with T-DXd compared with 16.7% of the patients receiving chemotherapy.

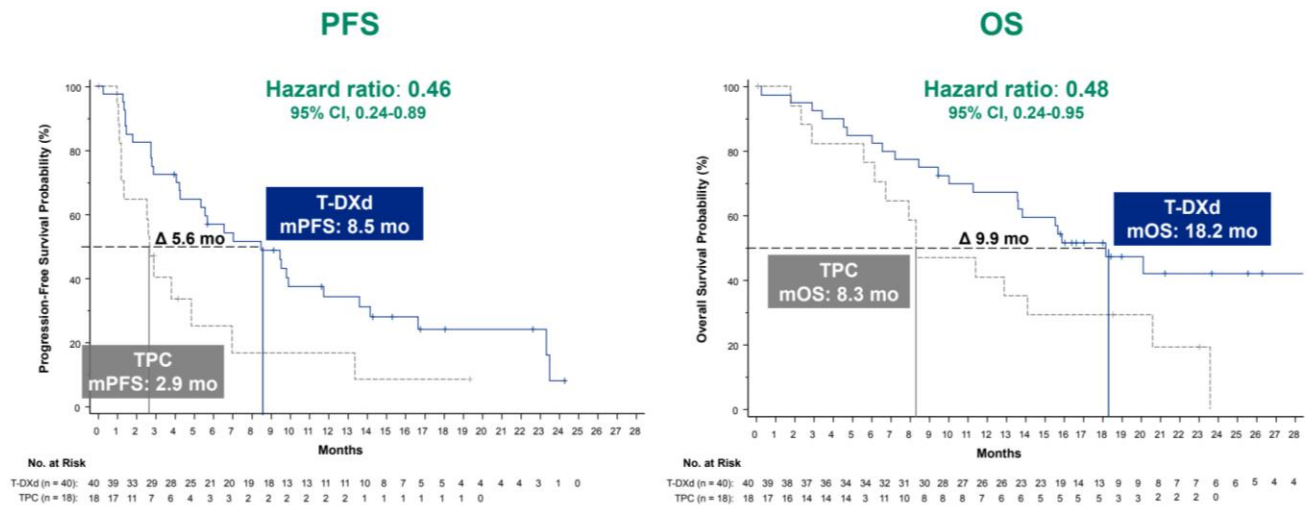


Figure 4 – Exploratory analysis of PFS and OS with T-DXd vs chemotherapy among HER2-low TNBC patients

Source: ASCO 2022 presentation by S. Modi, reprinted with permission from author.

Clinical Questions

This document summarizes the discussions and consensus among the Dana-Farber BOC group regarding the following clinical questions:

- Which HER2-negative breast cancer patients should receive T-DXd?
- How should T-DXd be sequenced with other available treatments?
- How should the toxicities of T-DXd be monitored and managed?

Additional considerations:

- Potential toxicities and benefits of T-DXd should be discussed with the patient ahead of initiating treatment. Particular attention should be dedicated to the risk of interstitial lung disease (ILD)⁷, of which all patients should be aware ahead of initiating treatment and during treatment with T-DXd.
- Guidelines are subject to change with evolution of data from existing and future trials. The BOC group will plan to reconvene in 12 months to review patterns of care for metastatic, HER2-low breast cancer

1. Which HER2-negative breast cancer patients should receive T-DXd?

The following considerations, including a) HER2 status, b) hormone receptor status, c) history of prior treatments and d) medical history and history of central nervous system (CNS) involvement, for recommendations on the use of T-DXd are detailed below.

A) HER2 status:

For the purpose of enrollment in the DESTINY-Breast04 trial, **HER2-low** was defined as a HER2 IHC score of 2+ with a negative ISH assay or an IHC score of 1+ with ISH untested or negative.¹ Scores were based on the latest ASCO/CAP Guidelines for HER2 testing.⁸ HER2 status was required to be confirmed at a centralized reanalysis (with the VENTANA 4B5 IHC assay) of the most recent archival tumor tissue sample, or a fresh tumor biopsy collected at baseline. If the most recent biopsy sample was unavailable, a prior tissue specimen was also acceptable. Patients were excluded from the trial if testing HER2-positive on prior pathology testing, or if they had received any prior anti-HER2 treatment. The presence of prior samples testing HER2 IHC 0 was instead not an exclusion criterion for the study.

It is important to stress that the current testing methods for HER2 were never developed to accurately distinguish an IHC score of 1+ from 0, but rather to identify tumors overexpressing HER2, thus potentially deriving benefit from trastuzumab. Several studies have shown the low concordance among pathologists in scoring HER2 in the low range^{9,10}, highlighting the risk of misassignment of patients to one of the two categories, potentially excluding patients with HER2-expressing breast tumors from treatment with T-DXd.

To further add complexity, it was recently demonstrated that HER2-low expression is a dynamic feature, with a relevant percentage of HER2-low tumors turning HER2-0 and vice versa after re-biopsy, either upon relapse^{11,12} or on residual disease after neoadjuvant treatment¹³. Although we still have no data regarding the stability of HER2-low scores in serial metastatic biopsies, empirical observations suggest that the same instability could be observed in this setting. This dynamism is likely multifactorial, related to both pre-analytical and analytical aspects, to the heterogeneity of HER2 expression, as well as to potential biological and treatment-related factors.¹ Regardless of the specific reason leading to HER2-low dynamism, this observation raises the opportunity to re-biopsy the tumor even when it was scored 0 on a prior sample, in order to potentially identify a HER2-low expression which could allow access to treatment with T-DXd.



		HER2 recurrence/metastasis N,%			Total
		0	Low	Positive	
HER2 primary BC N,%	0	132 (24.1)	83 (15.2)	13 (2.4)	228 (41.7)
	Low	77 (14.1)	101 (18.5)	9 (1.6)	187 (34.2)
	Positive	6 (1.1)	20 (3.7)	106 (19.4)	132 (24.1)
Total		215 (39.3)	204 (37.3)	128 (23.4)	547 (100)

Figure 5 – Evolution of HER2 expression from primary to recurrent breast cancer¹³

Source: Miglietta, F., et al. Evolution of HER2-low expression from primary to recurrent breast cancer. *NPJ Breast Cancer* 7, 137 (2021). Use permitted under [creative commons](https://creativecommons.org/licenses/by/4.0/) license.

Based on the abovementioned considerations, the BOC group came to the following consensus:

Consensus Statement

It is recommended that the following HER2-negative breast cancer patients should receive T-DXd:

- **Patients who had a HER2-low status (IHC 1+ or 2+/ISH negative) on any prior biopsy or surgery, including on the primary tumor.**
- Patients who never had a prior biopsy scored HER2-low. The collection of a fresh biopsy to re-test HER2 status could be considered to offer T-DXd in case of a HER2-low score

Pathologic reassessment of prior samples scored IHC 0 is reasonable, particularly if these were read at an outside institution

Importantly, given the relevance of the HER2 IHC score for treatment decisions (and clinical trials enrollment), the BOC consensus group stressed the need to **always report the HER2 IHC score in pathologic reports and clinical notes**, both for tumors classified as HER2-positive as well as for those classified as HER2-negative.

B) Hormone receptor status:

DESTINY-Breast04 included both HR-positive and HR-negative (i.e., TNBC) patients.⁶ Based on its statistical design, the study was able to confirm a benefit of T-DXd over chemotherapy both among HR-positive patients and among the overall study population (HR-positive plus HR-negative). However, the study wasn't powered to assess outcomes in the TNBC subgroup, highlighting the need for distinct considerations for the two HR-expressing subgroups.

The **HR-positive cohort** included 494 patients, among which T-DXd resulted in a statistically significant and clinically meaningful benefit in PFS and OS. Given the large sample size, the statistical design of the trial and the relevant magnitude of the benefit observed, the group convened to adopt T-DXd for the treatment of patients with HR-positive HER2-low breast cancer.

The **HR-negative** (i.e., TNBC) cohort included 58 patients, among which T-DXd also resulted in a meaningful benefit in PFS and OS. This was an exploratory analysis, which did not include formal hypothesis testing. Nonetheless, given the poor prognosis of this disease, the group convened to adopt T-DXd for the treatment of patients with HR-negative HER2-low breast cancer (i.e., TNBC HER2-low) based on the robust benefit seen in this subgroup.

C) History of prior treatments

Enrollment in DESTINY-Breast04 required prior treatment with at least one prior line of endocrine treatment (if HR-positive), allowed use of prior CDK4/6 inhibitors (received by 70% of the HR-positive study population) and required determination by the investigator that no further endocrine treatment would be beneficial for the patients.

In addition, for the purpose of enrollment, patients had to have received at least one and at most two prior lines of chemotherapy in the recurrent or metastatic setting. If recurrence had occurred within 6 months of adjuvant chemotherapy, adjuvant therapy would count as one line of chemotherapy. Prior treatment with DXd-based ADCs was an exclusion criterion.

Approximately 6% of the patients in the trial had also received prior immunotherapy. The percentage of patients receiving prior treatment with alpelisib, everolimus, PARP inhibitors, and/or other biologic treatments is unknown, as these were included in the 40% of "other" treatments received by the patients.

Consensus Statement

On the basis of these criteria, the group convened that it is acceptable to use T-DXd in patients that have progressed to prior endocrine treatment, CDK4/6 inhibitors and chemotherapy.

Use of prior alpelisib, everolimus, PARP-inhibitors, and immunotherapy is also acceptable, although the small (or unknown) number of patients pretreated with these regimens in DESTINY-Breast04 warrants caution for the sequential use in clinical practice.

D) *Medical history and CNS involvement*

Patients were excluded from enrollment in DESTINY-Breast04 if having uncontrolled or significant cardiovascular diseases, or if they had a history of (noninfectious) ILD/pneumonitis that required steroids, ongoing ILD/pneumonitis at baseline, or where suspected ILD/pneumonitis could not be ruled out by imaging at baseline.

History of clinically inactive brain metastases was allowed, whereas patients were excluded if they had spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.

It is thus reasonable to exclude from treatment with T-DXd patients with significant cardiovascular disease, as well as patients with history of non-infectious ILD that required steroids or with ongoing ILD. Use of T-DXd in patients experimenting prior everolimus-related ILD can be considered, but only if this was mild and completely resolved at the time of using T-DXd.

Finally, although the intracranial activity of T-DXd for HER2-low breast cancer remains to be defined, the compound has shown impressive intracranial activity for the HER2-positive disease, with 64% intracranial ORR among patients with stable brain metastases enrolled in DESTINY-Breast03¹⁴, and 73% intracranial ORR in the TUXEDO-1 trial enrolling patients with active brain metastases¹⁵. Given these promising data and the relevant unmet need represented by patients with CNS involvement, it is reasonable to use T-DXd for HER2-low breast cancer patients with either stable or active CNS disease at baseline.

Consensus Statement

It is reasonable to exclude from treatment with T-DXd patients with significant cardiovascular disease, as well as patients with history of non-infectious ILD that required steroids or with ongoing ILD.

Use of T-DXd in patients experimenting prior everolimus-related ILD can be considered, but only if this was mild and completely resolved at the time of using T-DXd.

Given the promising data and the relevant unmet need represented by patients with CNS involvement, it is reasonable to use T-DXd for HER2-low breast cancer patients with either stable or active CNS disease at baseline.

2. How should T-DXd be sequenced with other available treatments?

Defining the optimal treatment sequencing for T-DXd requires distinct considerations based on the HR status.

A) HR-positive disease

For **HR-positive HER2-low breast cancer**, treatment strategies after exhaustion of endocrine-based treatments commonly rely on subsequent lines of single-agent chemotherapy, with capecitabine, taxanes, anthracyclines, and eribulin being common choices in this setting.¹⁶ PARP-inhibitors (olaparib or talazoparib) are often considered in patients having a germline *BRCA* mutation, given the PFS advantage demonstrated over single-agent chemotherapy in randomized trials, although none of the approved PARP inhibitors has yet demonstrated an OS advantage in this setting.¹⁶ Of note, the phase 3 TROPiCS-02 study has recently shown the superiority in terms of PFS of the anti-TROP2 sacituzumab govitecan over chemotherapy (median PFS 5.5 vs 4.0 months; hazard ratio, 0.66, $p=0.0003$), although no significant benefits in terms of OS were yet reported.¹⁷

In DESTINY-Breast04, all patients needed to have received prior endocrine treatment and chemotherapy. However, if metastatic recurrence occurred within 6 months of adjuvant chemotherapy, adjuvant therapy was counted as one line of chemotherapy.

Consensus Statement

Based on the considerations above, the BOC consensus group agreed to adopt T-DXd after exhaustion of endocrine-based treatment strategies and after prior treatment with at least one prior line of chemotherapy.

Use of T-DXd immediately after exhaustion of endocrine-based treatment options can be considered in selected cases (i.e., for patients that have been previously treated with several chemotherapy agents in the neoadjuvant or adjuvant setting).

It is also reasonable to use T-DXd after multiple prior lines of chemotherapy, as it has shown to be superior to most of the drugs commonly used in highly pretreated settings.

T-DXd should be prioritized over sacituzumab govitecan in HR-positive disease.

For patients with a germline *BRCA* pathogenic variant, the group agreed that any sequence of PARP-inhibitors and T-DXd is acceptable, although **most of the panel would endorse prioritization of PARP-inhibitors in this setting.**

B) HR-negative disease (i.e., TNBC)

For **HR-negative (i.e., TNBC) HER2-low breast cancer**, treatment commonly involves first-line chemotherapy (plus immunotherapy if PD-L1 positive), followed by sequential lines of single-agent chemotherapy.¹⁶ PARP-inhibitors (olaparib or talazoparib) are often considered in patients having a germline *BRCA* mutation, given the PFS advantage demonstrated over single-agent chemotherapy in randomized trials, although none of the approved PARP inhibitors has yet demonstrated an OS advantage in this setting.¹⁶ Additionally, for patients that have received ≥ 1 prior lines of treatment, sacituzumab govitecan is an approved treatment regimen, and has demonstrated to improve both PFS and OS compared with chemotherapy in the randomized phase 3 ASCENT trial, that enrolled 529 patients with TNBC. At the final analysis of the study results, median PFS and OS with sacituzumab govitecan were 5.6 months and 12.1 months, respectively.¹⁸

As previously mentioned, DESTINY-Breast04 allowed enrollment if the patient had recurred rapidly (< 6 months) after adjuvant chemotherapy, even in the absence of any further treatment administered in the metastatic setting.

Consensus Statement

Based on the considerations discussed above, the consensus group convened that:

The use of T-DXd can be considered in HR-negative (i.e., TNBC) HER2-low breast cancer patients after at least one prior line of chemotherapy (with or without immunotherapy, depending on PD-L1 status).

Treatment with T-DXd can be also considered for selected HR-negative (i.e., TNBC) HER2-low patients experiencing rapid recurrence after (neo)adjuvant chemotherapy.

Given strong efficacy data with both agents, and no available head-to-head comparison, **any sequence of T-DXd and sacituzumab govitecan is acceptable for HR-negative (i.e., TNBC) HER2-low breast cancer patients.**

For patients with a germline *BRCA* pathogenic variant, the group agreed that any sequence of PARP-inhibitors and T-DXd is acceptable, although **most of the panel would endorse prioritization of PARP-inhibitors in this setting.**

3. How should the toxicities of T-DXd be monitored and managed?

The toxicity profile observed with T-DXd in the DESTINY-Breast04 trial was consistent with that observed in other breast cancer studies. The most common drug-related adverse events of any grade included nausea (in 73.0% of the patients), fatigue (in 47.7%), and alopecia (in 37.7%). The most common adverse events of grade 3 or higher were neutropenia (in 13.7% of the patients), anemia (in 8.1%), and fatigue (in 7.5%).⁶

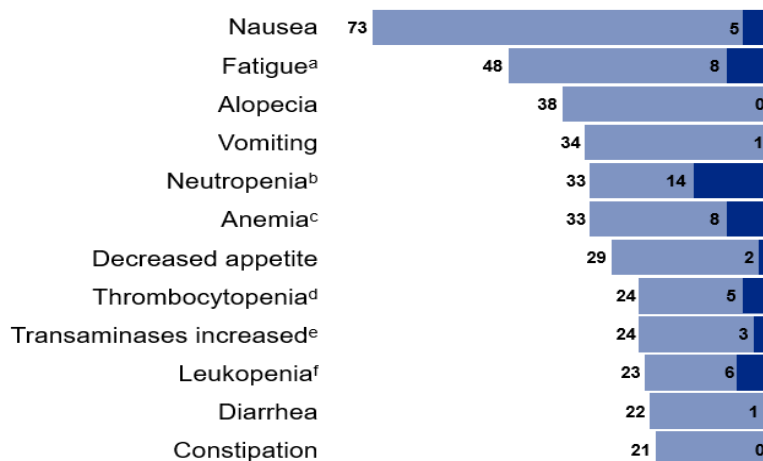


Figure 6 – Rates of drug-related adverse events observed in 20% or more of the patients with T-DXd in DESTINY-Breast04. Dark blue: grade 3 or higher; light blue: any-grade.

Source: ASCO 2022 presentation by S. Modi, reprinted with permission from author.

Drug-related interstitial lung disease (ILD) or pneumonitis occurred in 45 patients (12.1%) receiving T-DXd, including 13 (3.5%) with a grade 1 event, 24 (6.5%) with a grade 2 event, 5 (1.3%) with a grade 3 event, and 3 (0.8%) with a fatal event (grade 5). The median time to onset of ILD was 129 days (range, 26 to 710).

Left ventricular dysfunction was reported in 17 patients (4.6%) (decreased ejection fraction of grade 1 in 1 patient, of grade 2 in 14 patients, and of grade 3 in 1 patient and cardiac failure of grade 2 in 1 patient and of grade 3 in 1 patient). On the basis of laboratory values of the left ventricular ejection fraction, grade 2 events (10 to 19% decrease from baseline) were observed in 44 of 371 patients (11.9%) receiving T-DXd, whereas grade 3 events (>20% decrease from baseline) were observed in 5 patients (1.5%).

Consensus Statement

Based on the above-mentioned considerations, it is extremely important to adopt the following strategies to proactively detect and manage side effects of T-DXd:

Proactive monitoring for ILD/pneumonitis: patients in DESTINY-Breast04 received tumor assessments with CT scans every 6 weeks, which concomitantly allowed for the early detection of radiological signs of ILD. **The BOC group agreed that, for the purpose of following patients in clinical practice, a reasonable timing for CT scans would be 6-12 weeks.**

In addition, pulse oximetry and history of respiratory signs/symptoms should be carefully collected and reviewed at each visit. In case of signs/symptoms suspect for ILD/pneumonitis, T-DXd should be discontinued (temporarily if grade 1/asymptomatic, permanently discontinued in case of grade ≥2/symptomatic) and the following guidelines should be used to manage the event.

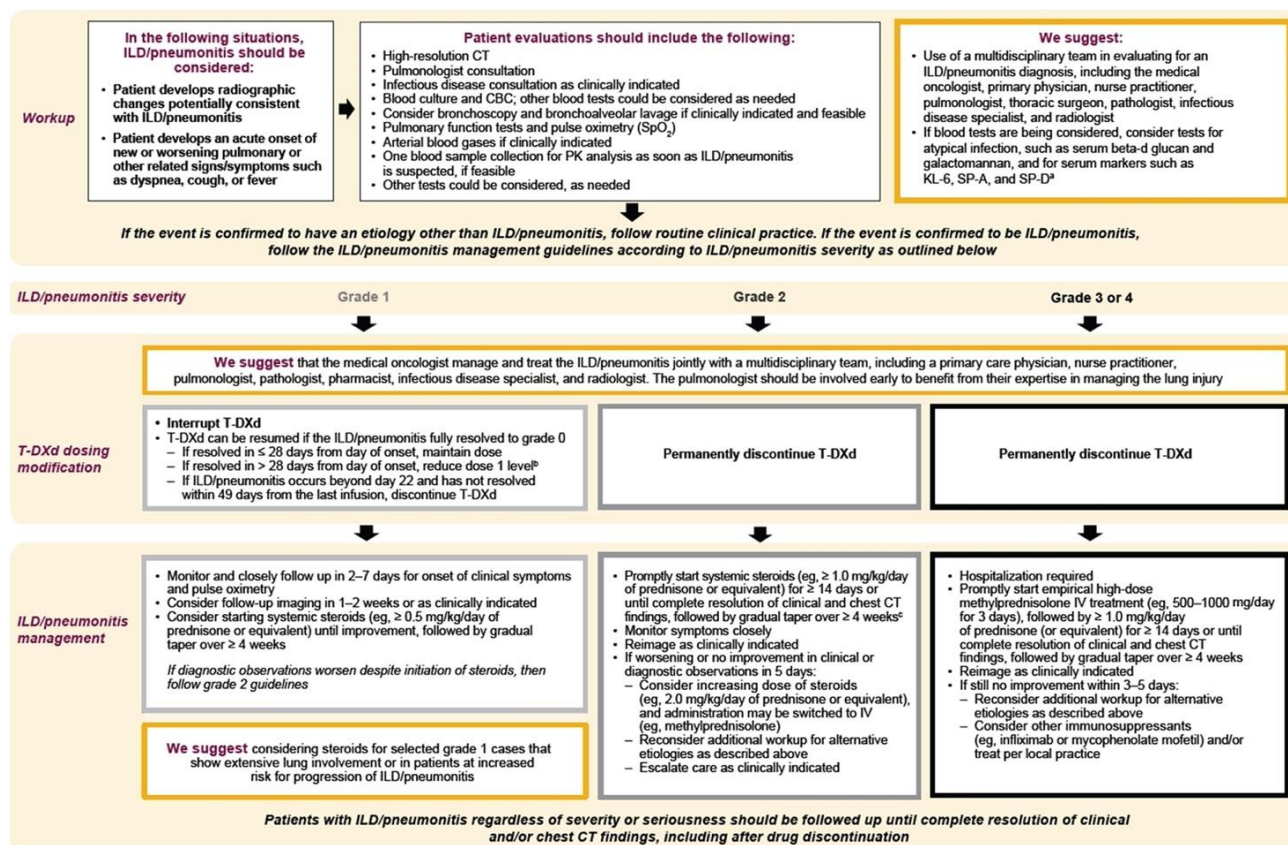


Figure 7 – Guidelines and recommendations for the multidisciplinary diagnosis and management of interstitial lung disease/pneumonitis in patients receiving T-DXd¹⁹

Source: Swain, S.M., et al. Multidisciplinary clinical guidance on trastuzumab deruxtecan (T-DXd)-related interstitial lung disease/pneumonitis—Focus on proactive monitoring, diagnosis, and management. *Cancer Treatment Reviews* 106, 102378 (2022). Reprinted under the [Creative Commons CC-BY-NC-ND](#) license.

Consensus Statements

Prevention of nausea and vomiting: Current guidelines categorize T-DXd as moderately emetogenic, although these may evolve with the accumulation of experience with the drug. Recommendations should be prophylactic anti-emetics with a **two-drug regimen** including dexamethasone and 5-HT₃ receptor antagonist for all patients (i.e., decadron + ondansetron or palonosetron), with consideration for adding a NK1 inhibitor (e.g. emend) and thus administer a **three-drug regimen**. This can be considered up front, based on patient-related factors, or as escalation in patients experiencing anything less than an optimal control of nausea and vomit with any cycle of T-DXd. For delayed nausea, Zofran +/- olanzapine can be effective management strategies

Risk of alopecia: although this was observed in 38% of the patients treated with T-DXd in DESTINY-Breast04, it is not currently known what part of these events were grade 1 (<50%) or grade 2 (>50%). However, prior experiences suggest a rate of about 10% for grade 2 alopecia with T-DXd. At present, there is no data on the effectiveness of scalp cooling to prevent or mitigate alopecia. A clinical trial is currently enrolling at Dana-Farber and will inform future practice once the data is available. **The group was divided, but half of the panelists would consider use of scalp cooling to try preventing alopecia with T-DXd. –**

Monitoring of cardiac function: patients in DESTINY-Breast04 were monitored with ECHO or MUGA every 4 cycles (q12 weeks). **The consensus group agreed that, in clinical practice, it is reasonable to monitor cardiac function at baseline and then every 6-12 months.**

Drug dose: The recommended dosage of T-DXd is 5.4 mg/kg given as an intravenous infusion once every 3 weeks. Dose reductions should follow the drug FDA label, included below in this document. **The consensus group, however, agreed that the adoption of a lower dose upfront for frail patients is reasonable.**

Adverse Reaction	Severity	Treatment Modification
Interstitial Lung Disease (ILD)/Pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)	Interrupt ENHERTU until resolved to Grade 0, then: <ul style="list-style-type: none"> if resolved in 28 days or less from date of onset, maintain dose. if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). consider corticosteroid treatment as soon as ILD/pneumonitis is suspected [see Warnings and Precautions (5.1)].
	Symptomatic ILD/pneumonitis (Grade 2 or greater)	<ul style="list-style-type: none"> Permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected [see Warnings and Precautions (5.1)].
Neutropenia	Grade 3 (less than 1.0 to $0.5 \times 10^9/L$)	<ul style="list-style-type: none"> Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose.
	Grade 4 (less than $0.5 \times 10^9/L$)	<ul style="list-style-type: none"> Interrupt ENHERTU until resolved to Grade 2 or less. Reduce dose by one level (see Table 1).
Febrile Neutropenia	Absolute neutrophil count of less than $1.0 \times 10^9/L$ and temperature	<ul style="list-style-type: none"> Interrupt ENHERTU until resolved. Reduce dose by one level (see

Adverse Reaction	Severity		Treatment Modification
Thrombocytopenia	Grade 3 (platelets less than 50 to 25 x 10 ⁹ /L)		<ul style="list-style-type: none"> Interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose.
	Grade 4 (platelets less than 25 x 10 ⁹ /L)		<ul style="list-style-type: none"> Interrupt ENHERTU until resolved to Grade 1 or less. Reduce dose by one level (see Table 1).
Left Ventricular Dysfunction	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		<ul style="list-style-type: none"> Continue treatment with ENHERTU.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	<ul style="list-style-type: none"> Continue treatment with ENHERTU. Repeat LVEF assessment within 3 weeks.
		And absolute decrease from baseline is 10% to 20%	<ul style="list-style-type: none"> Interrupt ENHERTU. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose.
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		<ul style="list-style-type: none"> Interrupt ENHERTU. Repeat LVEF assessment within 3 weeks. If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue ENHERTU.
	Symptomatic congestive heart failure (CHF)		<ul style="list-style-type: none"> Permanently discontinue ENHERTU.

Table 1 – Dose modifications for T-DXd in case of side effects

Dose Reduction Schedule	Breast Cancer	Gastric Cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment.	Discontinue treatment.

Table 2 – Dose reduction schedule

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