

# First clinical experience with trastuzumab deruxtecan in Switzerland

## An online survey among oncologists

URS BREITENSTEIN<sup>A\*</sup>, BASIL BÄTTIG<sup>BC</sup>, BARBARA BOLLIGER<sup>D</sup>, MICHELE CIRIOLO<sup>E</sup>, MATTHIAS EGGER<sup>F</sup>,  
URSULA HASLER-STRUB<sup>G</sup>, JENS HUOBER<sup>H</sup>, CATRINA UHLMANN NUSSBAUM<sup>I</sup>, MARCUS VETTER<sup>J</sup>, KHALIL ZAMAN<sup>K\*</sup>

### Background

Breast cancer is the most common type of cancer worldwide (1). In Switzerland, more than 6000 women are diagnosed every year (2). In 15–20 % of all breast cancers, the human epidermal growth factor receptor 2 (HER2) gene is amplified, overexpressed, or both (3). In these patients, the risk of metastases and recurrence is higher and outcomes have historically been poor, until HER2-targeted therapies including monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and antibody-drug conjugates (ADCs) have revolutionized patients' treatment and improved survival rates (3). As first-line regimen for patients with newly diagnosed metastatic HER2-positive breast cancer, current guidelines recommend dual HER2-blockade with the monoclonal antibodies trastuzumab and pertuzumab in combination with a taxane, based on the results of the CLEOPATRA trial (4). As an advancement of anti-HER2 antibodies, ADCs offer a combination of tumor-antigen specificity and the potent cytotoxicity of chemotherapeutic agents, allowing for increased activity at tumor sites. The ADC trastuzumab emtansine (T-DM1) combines HER2-targeting with the cytotoxic microtubule inhibitor maytansine. Until now, it was standard practice for second-line treatment based on a significant improvement of progression free survival (PFS) and overall survival (OS) compared with lapatinib/capecitabine in the pivotal phase III trial EMILIA (5).

Beyond second line treatment, however, an universal consensus on best practice does not exist due to lack of randomized controlled trial data. Understanding resistance mechanisms remains a major challenge in defining optimal treatment sequences, especially with more effective agents becoming available. Currently, in later therapeutic lines, HER2-blockade with trastuzumab beyond progression or TKIs are often maintained in combination with chemotherapy or endocrine therapy, with limited benefit in this advanced setting (6). In hormone receptor-positive (HR+) cases, endocrine treatment in combination with trastuzumab is an additional option.

Trastuzumab deruxtecan (T-DXd) is a next-generation ADC with different characteristics, including a higher antibody-to-drug ratio as compared to older ADCs. It combines HER2-targeting and the cytotoxic topoisomerase I inhibitor deruxtecan with a tumor-specific, cleavable linker (7). Deruxtecan is cell membrane permeable, allowing it to reach neighboring cancer cells, even if they do not express HER2 (bystander effect). In the multicenter open-label phase II trial DESTINY-Breast01 with 184 heavily pretreated patients with HER2-positive metastatic breast cancer, who had progressed under T-DM1, T-DXd achieved unprecedented response rates (8). Based on the results of this trial, T-DXd was approved for the treatment of unresectable or metastatic HER2-positive breast cancer after at least two prior lines of HER2-targeted therapies in December 2019 in the United States and in January 2021 in Europe. At the time of the survey (November 2021), the drug was approved in Switzerland for the treatment of adult patients with unresectable locally advanced or metastatic HER2-positive breast cancer who have received at least two HER2-directed treatment regimens, including trastuzumab, and have had disease progression during or after therapy with T-DM1.<sup>†</sup> Further clinical trials are investigating T-DXd in earlier lines of therapy. The open-label, randomized phase III trial DESTINY-Breast03 (NCT03529110) evaluated T-DXd in a head-to-head comparison versus T-DM1 in 524 patients previously treated with trastuzumab and taxane in second or later therapy lines.

In this trial, T-DXd showed a significant improvement in PFS: while the median PFS was not reached in the T-DXd group (95% CI: 18.5–not estimable), PFS in the T-DM1 group was 6.8 months (95% CI: 5.6–8.2) (9). OS data are currently not mature. At 12 months, the percentage of patients who were alive without disease progression was 75.8% (95% CI: 69.8–80.7) in patients who received T-DXd and 34.1% (95% CI: 27.7–40.5) in patients who received T-DM1.

<sup>a</sup> Brust-Zentrum Zürich, <sup>b</sup> Practice Onkologie Bellevue, Zürich, <sup>c</sup> Oncology Department, Spital Zollikerberg, Zürich, <sup>d</sup> Tumor- und Brustzentrum ZeTuP, St. Gallen, <sup>e</sup> Bürgerspital Solothurn, <sup>f</sup> Tumorzentrum ZeTuP, Rapperswil-Jona, <sup>g</sup> Kantonsspital Graubünden, Chur, <sup>h</sup> Kantonsspital St. Gallen, St. Gallen, <sup>i</sup> Kantonsspital Olten, Olten, <sup>j</sup> Kantonsspital Baselland, Liestal, <sup>k</sup> Lausanne University Hospital CHUV, Lausanne, \* Contributed equally to this study

## Abstract

### Summary

**BACKGROUND:** HER2 is a prime example of how discovering and targeting oncogenic drivers can revolutionize clinical practice and achieve unprecedented outcomes. A new generation of HER2-targeted agents is now tackling the inherent challenges of drug resistance and lack of treatment options in later therapeutic lines in HER2-positive and HER2-low breast cancer. One of these agents is the antibody-drug conjugate trastuzumab deruxtecan, which has been approved in Switzerland in November 2021.

**OBJECTIVES:** Selected patients in Switzerland had access to trastuzumab deruxtecan before its approval. The aim of this survey was to document the first clinical experiences and insights that treating oncologists obtained with trastuzumab deruxtecan therapy and management. These data could be informative for the future prescribers.

**METHODS:** An online survey with 25 questions was distributed to 17 breast oncologists across Switzerland, whose patients either had early access to trastuzumab deruxtecan by participating in a compassionate use program, a clinical trial with trastuzumab deruxtecan, or upon agreement of the patient's health insurance. The survey was open for 17 days, from November 12<sup>th</sup> to November 29<sup>th</sup>, 2021.

**RESULTS:** 11 oncologists completed the survey (response rate: 64.7%), representing a total of 25 patients treated in private practices, regional hospitals, university hospitals, as well as certified breast cancer centers. Seventeen patients (68%) received trastuzumab deruxtecan in a compassionate use program. Four patients (16%) with HER2-low expressing metastatic breast cancer (IHC 1+ or 2+, ISH negative) were enrolled in the phase III trial DESTINY-Breast04. Four patients (16%) obtained access to trastuzumab deruxtecan via request to their health insurances. T-DXd was most commonly (40%) administered as third-line treatment. Prior to trastuzumab deruxtecan, all patients with HER-2-positive disease (IHC 3+ or ISH-confirmed) had been exposed to a HER2-targeting monoclonal antibody, i.e., trastuzumab, pertuzumab or both. 80% of them were exposed to trastuzumab emtansine and 80% had been exposed to a tyrosine kinase inhibitor. Adverse events specified most were hematotoxicity (32%), alopecia (28%), nausea (24%), and fatigue (20%). Treatment-emergent interstitial lung disease occurred in 8% of the patients and required treatment discontinuation. 44% discontinued treatment, mainly due to progressive disease and interstitial lung disease.

**CONCLUSION:** The first patients who have been treated with trastuzumab Deruxtecan in Switzerland and are represented in this survey differed from the participants of the pivotal clinical trials DESTINY-Breast01 and DESTINY-Breast03 with regards to various baseline characteristics including age, performance status, comorbidities, and expression levels of HER2 and hormone receptors. Yet, the treatment experience with trastuzumab deruxtecan was largely consistent with the findings obtained in the pivotal clinical trials DESTINY-Breast01 and DESTINY-Breast03 with regards to side effects and therapy management. The treatment strategy for HER2-positive metastatic breast cancer specified by the participating oncologists reflects that of international guidelines, i.e., initial dual HER2-blockade combined with chemotherapy in the first line of treatment, followed by trastuzumab emtansine in the second line and a tyrosine kinase inhibitor, or, if accessible, trastuzumab deruxtecan in the third line of treatment.

Selected patients in Switzerland had access to T-DXd before its approval, typically through clinical trials and compassionate use programs. In this report, we share the first clinical experiences and insights that we and other treating oncologists have acquired with T-DXd, as well as the challenges that were encountered with regards to T-DXd management.

## Methods

### Survey design and study sample

To obtain numerically evaluable data, a survey with 25 questions was distributed via e-mail to 17 breast oncologists across Switzerland, whose patients either had early access to T-DXd by participating in a compassionate use program, a clinical trial with T-DXd, or upon agreement of the patient's health insurance.

### Questionnaire

The questionnaire was developed by the medical communication agency IACULIS GmbH in collaboration with the authors UB and KZ. The survey consisted of 25 questions in English language and required 15–20 minutes to complete. The survey comprised both multiple choice and free text questions (see supplementary Appendix). The setup and analysis of the survey provided for physician and patient anonymity.

### Analysis

Results are presented either as total values or as percentage of total patients or a subset of patients, as indicated. The survey was neither designed nor intended to enable statistical evaluations on T-DXd's efficacy and safety. Hence, statistical means of analysis were not applied.

## Results

### Response rate and background information on treating oncologists

By the data cut-off on November 29<sup>th</sup>, 2021, 11 oncologists had completed the questionnaire (response rate 64.7%), representing a total of 25 patients. Nine of the responding oncologists administered T-DXd in the setting of a compassionate use program (17 patients, 68%). One reported that their patients (n = 4, 16%) were enrolled in the phase III trial DESTINY-Breast04 (NCT03734029), which examines the efficacy of T-DXd in HER2-low expressing metastatic breast cancer (HER2 IHC 1+

or 2+). One oncologist obtained access to T-DXd via request to the patients' (n = 4, 16%) health insurances. Responding oncologists were practicing in private practices (30.8%), certified breast cancer centers (46.2%), university hospitals (23.1%), and regional hospitals (28.1%) across Switzerland (multiple answers were possible).

### Baseline characteristics of patients represented in this survey

All baseline characteristic and comorbidities assessed in this survey are summarized in Table 1. The patients treated in Switzerland were at least 30 years of age, with the majority being 50–60 (32%) and 60–70 (32%) years old. 32% of the patients (n=8) had an amplification of HER2 demonstrated by in situ hybridization (ISH). In those patients, information on the immunohistochemistry (IHC) status was not covered by the survey. Among the 17 patients whose HER2-status was specified via IHC scores, 10 had a score of 3+ (40% of all patients, 58.8% of IHC-assessed patients), none had a score of 2+, and 7 patients had a score of 1+ (28% of all patients, 41.2% of IHC-assessed patients).

### Comorbidities

32% of the patients represented in this survey have a history of brain metastases and one patient (4%) had active brain metastases during T-DXd therapy (Table 1). None of the patients suffered from significant cardiac dysfunction. Liver dysfunction affected 16% and renal dysfunction affected 4% of the patients. Other comorbidities specified via free text answers in this survey included diabetes, hypertension, psychiatric disease and pulmonary embolism.

### T-DXd was mainly used in the third treatment line, after trastuzumab, pertuzumab and T-DM1

The patients represented in this survey received T-DXd mainly in the third treatment line (40.0%), followed by the fourth (24.0%) (Figure 1). Specific information on first-line treatment is available for 16 patients. Three of those had HER2-low expressing disease (IHC 1+) and 13 had HER2-positive disease as confirmed by IHC 3+ or ISH. In 61.5% of the 13 patients with HER2-positive disease, first-line treatment was dual HER2-blockade with trastuzumab and pertuzumab, in 23.1% trastuzumab monotherapy, and 15.4% received pertuzumab monotherapy (Figure 2A). For 9 HER2-positive patients, second-line treatment information is available. Among those, 77.8% received T-DM1 (Figure 2B). The remaining patients received either second-line endocrine therapy (11.1%) or pertuzumab (11.1%).

Table 1  
BASELINE CHARACTERISTICS

	patients represented in this survey (n = 25)	DESTINY-Breast01 (n = 184) (8)	DESTINY-Breast03, T-DXd arm (n = 261) (9)
Median age, years	median span <sup>†</sup> : 60–70	55	54.3
female	100%	100%	99.6%
Race			
White	100%	54.9%	n/s
Asian	0.0%	38.0%	n/s
Other or missing data	0.0%	7.1%	n/s
HR+ disease	68.0%	53.0%	50.2%
HER2 expression			
IHC 3+	≥40%*	83.7%	89.7%
IHC 1+	≥28%*	15%**	0.4%
ECOG performance status			
0	54.2%	55.4%	59.0%
1	33.3%	44.0%	40.6%
2	12.5%	0.2%±	0%±
Comorbidities			
Brain metastases			
treated, asymptomatic	32.0%	13.0%	23.8%
active	4.0%	0.0%±	0.0%±
visceral disease	92.0%	91.8%	70.5%
cardiac dysfunction	0.0%	n/s	n/s
liver dysfunction	16.0%	n/s	n/s
renal dysfunction	4.0%	n/s	n/s

Baseline characteristics of patients represented in this survey (answers from 11 oncologists, representing 25 patients) and participants of the DESTINY-Breast01 trial and the T-DXd-arm of the DESTINY-Breast03 trial.

\* age options in this survey: <20, 20–30, 30–40, 40–50, 50–60, 70–80, >80; IHC information on 8 patients with ISH+ disease is missing. Therefore, percentages might be higher. \*\*patients with IHC 1+ or IHC2+ and ISH+ disease. ECOG: Eastern Cooperative Oncology Group scale; HR+: hormone receptor-positive; IHC: immunohistochemistry; ISH: in situ hybridization; n/s: not specified.

Third-line treatment has been specified for 7 patients with HER2-positive disease. These patients mainly received HER2-directed TKIs (62.5%), T-DM1 (14.3%) or a combination of both (14.3%) (Figure 2C). For 5 HER2-positive metastatic breast cancer patients, the complete regimen of previous treatment lines prior to T-DXd is available: All these patients received trastuzumab, pertuzumab or both (Figure 2D). 80% were exposed to T-DM1, and 80% were exposed to an anti-HER2 TKI prior to T-DXd therapy.

Patients with HER2-low expressing metastatic breast cancer (IHC 1+) received chemotherapy without HER2-targeting as first-line therapy (n = 2), followed by endocrine therapy (n = 1) prior to T-DXd therapy. Another patient with IHC 1+ disease was treated with trastuzumab as first-line therapy, followed by T-DM1 and a TKI, before she received T-DXd. For the other 4 patients with HER2-low disease in this survey, no information on previous therapies was specified.

**Most common adverse events were hematotoxicity, alopecia, nausea, and fatigue**

Treatment-emergent adverse events (TEAEs) of any grade as specified by free text answers were hematotoxicity (not further specified), alopecia, nausea, fatigue, asthenia, weight loss, and diarrhea (Table 2). Five patients (20%) did not experience any side effects during T-DXd therapy. T-DXd therapy is associated with a 0.5–15% risk of interstitial lung disease (10), which also occurred in 8% of the patients represented in this survey and required treatment discontinuation. TEAEs required dose reductions in 20% of patients and treatment discontinuation in 12%.

Most patients (88%) started T-DXd treatment with the recommended starting dose of 5.4 mg/kg administered in the pivotal T-DXd trials (8, 9). For three patients (12%), lower starting doses were administered, due to bone marrow toxicity of a prior therapy, impaired liver function, and limited availability of the drug, respectively, as specified by free text answers.

**Treatment discontinuation rate and disease progression**

Upon data cut-off on November 29, 2021, responding oncologists indicated that 44% of the patients (n = 11) had discontinued T-DXd treatment (Figure 3A). The majority of the respondents specified the time to treatment discontinuation as 3–6 months or more than 6 months (both 45.5% of patients who discontinued T-DXd). For 36% of all patients (n = 9), disease progression under T-DXd therapy was reported. All of them discontinued treatment. Of the 9 patients who suffered from disease progression

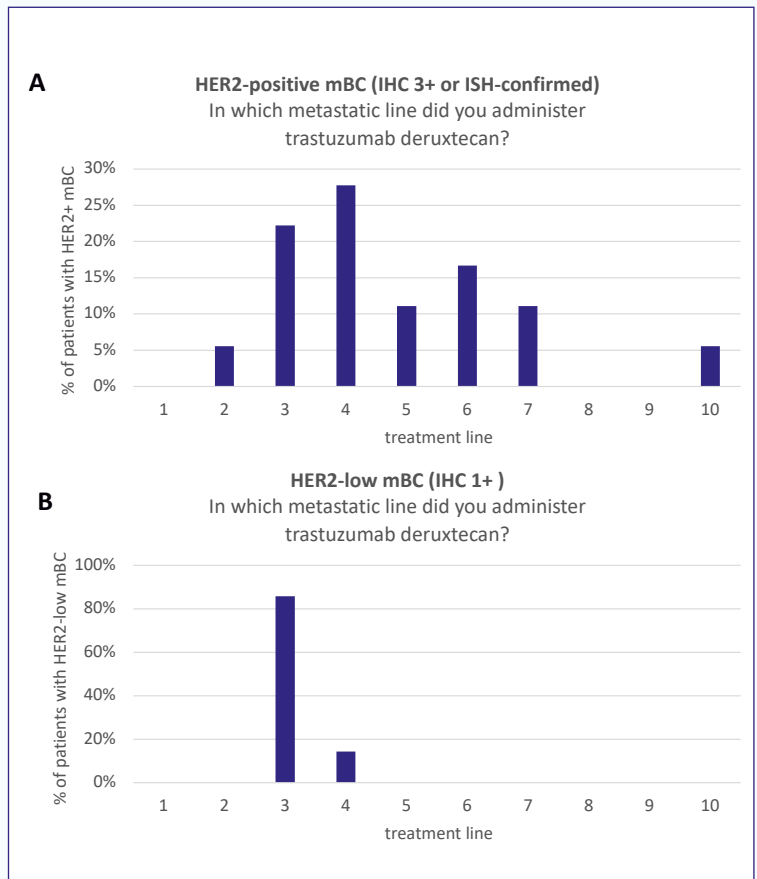


Figure 1: T-DXd administration by treatment line in patients with HER2-positive and HER2-low expressing disease, respectively. Graphs show percentage of (A) 18 patients with HER2-positive disease (IHC 3+ or ISH-confirmed) and (B) 7 patients with HER2-low disease (IHC 1+). ISH: in situ hybridization; mBC: metastatic breast cancer.

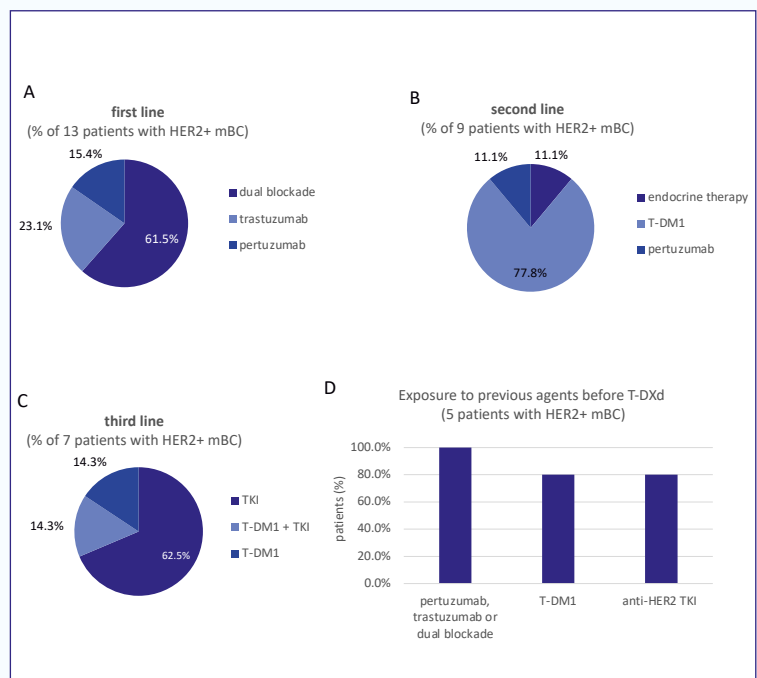


Figure 2: Previous systemic therapies in HER2-positive metastatic breast cancer patients represented in this survey (IHC 3+ or ISH-confirmed). A-C: Graphs show percentage of patients for whom first to third line regimens were specified by the responding oncologists. D: Complete regimens for all treatment lines prior to T-DXd were available for 5 patients. HER2+: HER2-positive; mBC: metastatic breast cancer; T-DM1: trastuzumab emtansine; T-DXd: trastuzumab deruxtecan; TKI: tyrosine kinase inhibitor.

Table 2  
Treatment-emergent Adverse Events

	patients represented in this survey (n = 25)	DESTINY-Breast01 (n = 184) (8)	DESTINY-Breast03, T-DXd arm (n = 257) (9)
<b>TEAEs, all grades</b>			
Hematological toxicity	32%	n/s*	n/s*
Alopecia	28%	48.4%	36.2%
Nausea	24%	77.3%	72.8%
Fatigue	20%	49.5%	44.7%
Asthenia	12%	14.1%	n/s
Weight loss	8%	n/s	n/s
Diarrhea	8%	29.2%	23.7%
Dysphagia	4%	n/s	n/s
Decreased appetite	4%	31.0%	26.1%
Constipation	4%	35.9%	22.6%
<b>TEAEs of special interest</b>			
Interstitial lung disease	8%	13.6%	10.5%
<b>TEAEs leading to dose reduction</b>			
Hematological toxicity Gr. 3	8%	n/a	n/a
Hematological toxicity Gr.3 and nausea Gr. 3	4%	n/a	n/a
Asthenia	4%	n/a	n/a
Not further specified	4%	n/a	n/a
<b>TEAEs leading to treatment discontinuation</b>			
Interstitial lung disease	8%	2.7%	8.2%
Not further specified	4%	n/a	n/a

Treatment-emergent Adverse Events (TEAEs) in patients represented in this survey (answers from 11 oncologists, representing 25 patients) and participants of the DESTINY-Breast01 trial and the T-DXd-arm of the DESTINY-Breast03 trial.

\*Only specific hematological toxicities were assessed. Gr.: Grade; n/a: not applicable; n/s: not specified.

under T-DXd therapy, 56% progressed within 3–6 months of T-DXd therapy and 33% progressed within more than 6 months. In the DESTINY-Breast01 trial, 28.8% of the patients discontinued due to progressive disease (median follow-up: 11.1 months). In the DESTINY-Breast03 trial, 25.3% of the T-DXd-treated patients discontinued treatment due to progressive disease after a median follow-up of 16.2 months.

**Safety monitoring is considered manageable, with exceptions**

The patients represented in this survey were monitored weekly during the first 2–3 cycles and every 3 weeks, once the dose was stably adjusted and no additional adverse events occurred. For over two thirds of the patients (68%), the questioned physicians described the required amount of safety monitoring as manageable and rated the corresponding survey question with a score of 5, the best score on a scale from 1 (burdensome) to 5 (manageable) (data not shown). For the great majority of the responding oncologists (82.8%), the safety profile they observed in their own patients reflects the findings from the two clinical trials DESTINY-Breast01 and DESTINY-Breast03.

Overall, physicians as well as the patients (as reported by the physicians) were satisfied with the tolerability of T-DXd (Figure 4). However, adverse events compromised the tolerability of T-DXd in some cases of severe nausea and hematological toxicities (both grade 3), ILD and asthenia.

**Discussion**

Novel HER2-targeted TKIs and ADCs provide promising new therapeutic options for patients with HER2-

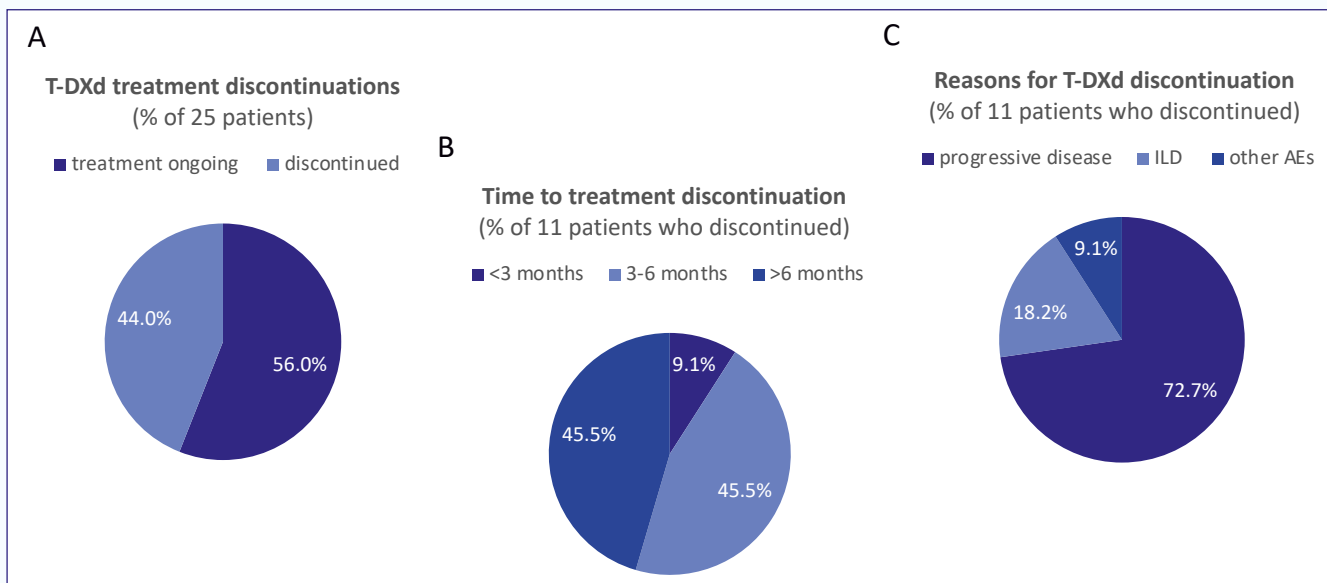


Figure 3: Treatment discontinuation among the patients represented in this survey at the cut-off date on November 29<sup>th</sup>, 2021. AE: adverse events; ILD: interstitial lung disease; T-DXd: trastuzumab deruxtecan.

positive and HER2-low metastatic breast cancer in different clinical settings and treatment lines. The next-generation ADC trastuzumab deruxtecan has shown impressive outcomes in second line therapy and later lines. This report summarizes the first experiences made with T-DXd management in Switzerland.

**Baseline characteristics differ from those of clinical trial populations**

As compared to the participants of the pivotal T-DXd trials DESTINY-Breast01 and DESTINY-Breast03, the first patients treated with T-DXd in Switzerland covered by this survey are less diverse with regards to their ethnicity. While the patients represented in the survey were exclusively white, the DESTINY-Breast01 trial comprised 38% of patients of Asian origin (8). In the DESTINY-Breast03 trial, 57.1% of the participants received T-DXd treatment in Asia (race not specified) (9).

Further, the patients represented in this survey show a greater burden of comorbidities and are more restricted in their functional status as compared to the participants of the DESTINY-Breast01 and -03 trials (8, 9). Specifically, 32% of the survey patients have a history of brain metastases, which is in line with the overall prevalence of brain metastases of 30–55% in patients with HER2-positive metastatic breast cancer (3). The percentage of patients with treated, asymptomatic brain metastases in the DESTINY-Breast01 and DESTINY-Breast03 trials was 13.0% and 23.8% (T-DXd arm), respectively (8, 9). While these trials excluded patients with active brain metastases, the patient population of the survey includes one individual (4%) with active brain metastases. Similarly, while patients with a performance status score above 1 on the ECOG scale were not eligible to participate in these trials, 12.5% of the patients in this survey had an ECOG performance score of 2. In addition, the patients in the survey were older and the prevalence of confirmed HER2-low expressing disease (IHC 1+) as well as the prevalence of hormone receptor (HR)-positive disease was higher as compared to the patients treated with T-DXd in the DESTINY-Breast01 and DESTINY-Breast03 trials (8, 9). The higher prevalence of confirmed HER2-low cases is, however, not surprising, given that the pivotal trials DESTINY-Breast01 and DESTINY-Breast03 excluded patients with HER2-low cancers, while this survey specifically addressed oncologists whose patients participated in the DESTINY-Breast04 trial with HER2-low expressing metastatic breast cancer patients.

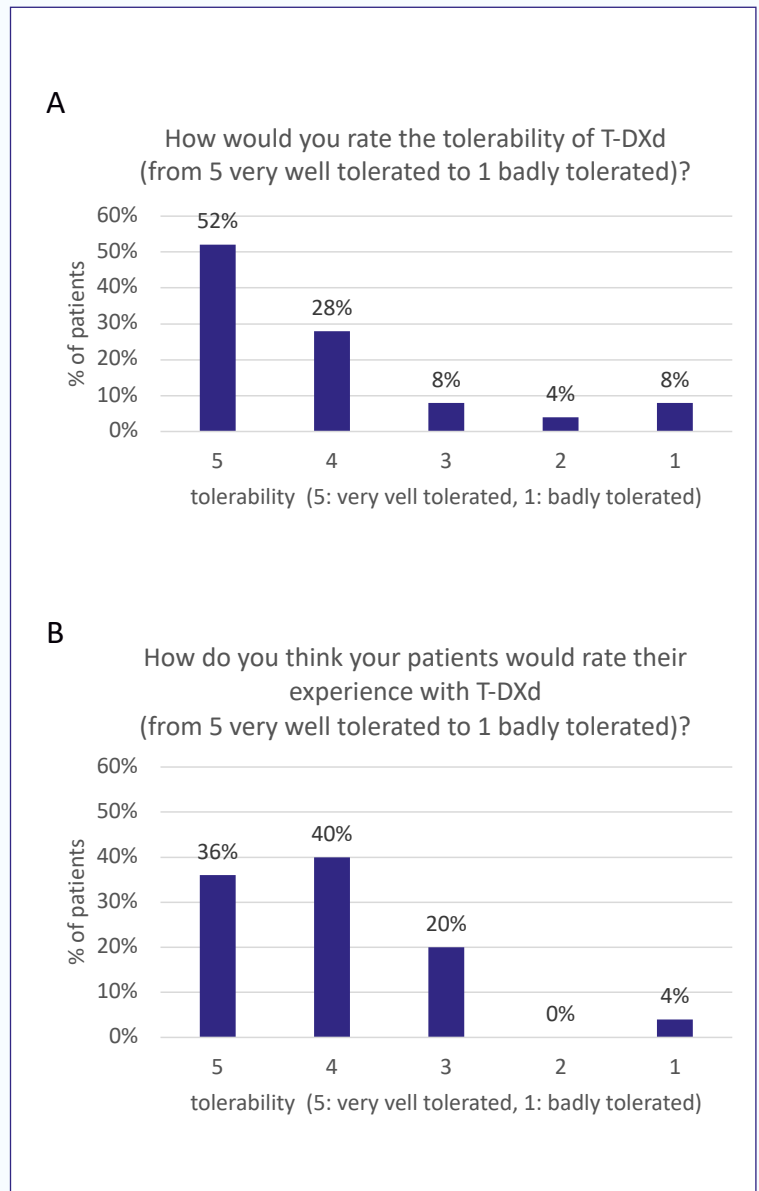


Figure 4: Physician-assessed tolerability of T-DXd. Graphs show percentage values of answers from 11 oncologists, representing 25 patients. T-DXd: trastuzumab deruxtecan.

**First patients received T-DXd in later lines, while previous exposure is comparable to trial population**

In the DESTINY-Breast01 trial, patients had a median of six (range 2–27) previous cancer regimens, while most of the participants of the DESTINY-Breast03 trial received T-DXd in the second (49.8%) or third (21.5%) treatment line (8, 9). The patients represented in this survey received T-DXd mainly in the third treatment line (40.0%), followed by the fourth (24.0%).

In the trials DESTINY-Breast01 and DESTINY-Breast03, all patients (100% and 99.6%, respectively) have been previously exposed to trastuzumab. Comparably, all HER2-positive patients represented in this survey have also been exposed to a HER2-targeting antibody. In the HER2-positive

population of this survey, the most common second-line treatment was T-DM1, followed by a HER2-targeting TKIs in the third line. Hence, the HER2-targeted approaches pursued by the participating physicians in Switzerland conforms with international guidelines. These recommend initial dual HER2-blockade combined with chemotherapy in the first line, followed by T-DM1 in the second line and a TKI, or, if accessible, T-DXd in the third line of treatment (4). These sequences can be modified for the patients having received some of these drugs in the adjuvant setting.

### **Distribution of adverse events is similar, although with lower overall prevalence**

Overall, the types of adverse events as well as the frequency of dose reductions specified in this survey are consistent with those observed in the DESTINY-Breast01 trial and the T-DXd arm of the DESTINY-Breast03 trial (8, 9). Specifically, hematotoxicity, nausea, fatigue, and alopecia were specified most in free text answers in this survey and were also the most abundant adverse events in the trials DESTINY-Breast01 and -03 (8, 9). Of note, hematological adverse events reported in these trials were specified and categorized into lymphopenia, neutropenia, and thrombocytopenia, while the responses of this survey were not specified beyond the term «hematotoxicity».

### **Interstitial lung disease is a notable risk**

ILD is a critical risk for patients treated with T-DXd, requiring active surveillance and management. In the DESTINY-Breast01 and DESTINY-Breast03 trials, patients with a history of noninfectious ILD or pneumonitis requiring the use of glucocorticoids, or a current or suspected ILD or pneumonitis were excluded. 13.6% of the participants of the DESTINY-Breast01 trial developed ILD, which led to death in 16% of these patients (2.2% of the total patient population) (8). In the DESTINY-Breast03 trial, 10.5% of the patients who received T-DXd developed a drug-related ILD, with no ILD-related deaths reported (cut-off date: May 21, 2021) (9). In the patient population represented in this survey, 2 patients (8%) developed ILD, requiring for treatment discontinuation. Early diagnosis and intervention are key for optimal ILD management. Patients must be counseled and

educated to monitor and report respiratory symptoms such as cough, dyspnea, or even fever promptly.

### **Conclusion**

Although patients represented in this survey differed from the participants in T-DXd clinical trials with regards to various baseline criteria, the first experiences oncologists obtained with T-DXd therapy in Switzerland are in accordance with the reports from the two pivotal T-DXd trials DESTINY-Breast01 and DESTINY-Breast03. While nausea, hematotoxicity, and ILD need to be monitored carefully and handled diligently, T-DXd was generally rated well tolerated. The overall safety profile was considered manageable by the respondents of this survey.

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### **Corresponding author**

Dr. Khalil Zaman  
Medical director Breast Center  
University Hospital CHUV, Lausanne  
khalil.zaman@chuv.ch

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\*Since June 2022, trastuzumab deruxtecan is approved in Switzerland for Monotherapy treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least one HER2-directed treatment regimen, including trastuzumab and a taxane, and have had disease progressive either at the metastatic stage or within 6 months of the end of adjuvant or neoadjuvant therapy.

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