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Real-World Effectiveness and Safety of Tucatinib, Trastuzumab, and Capecitabine in HER2-Positive Advanced Breast Cancer: A Multicenter Portuguese Study

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ABSTRACT

Objective: The HER2CLIMB trial demonstrated the benefit of tucatinib, trastuzumab and capecitabine (TTC) in human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer (ABC). However, it predated the clinical use of trastuzumab deruxtecan (T-DXd), leaving limited evidence for TTC after T-DXd exposure. This national multicenter study assessed the real-world effectiveness and safety of TTC in patients, including those previously treated with T-DXd.

Materials and Methods: This retrospective, non-interventional study included patients with HER2-positive ABC treated with TTC across 17 centers in Portugal (October 2021-May 2025). Outcomes included overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.

Results: Eighty-one patients were included (median age 54 years). Of the patients, 39.5% (n = 32) had brain metastases, and 61.7% (n = 50) had prior T-DXd exposure. Median follow-up was 21.0 months; ORR and DCR were 24.4% and 64.1%, respectively. Median PFS (mPFS) was 9.0 months (m) [95% confidence interval (CI): 5.9–12.1], and median OS (mOS) was 14.0 months (m) (95% CI: 10.5–17.5). In patients previously treated with T-DXd, the median mPFS 7.0 m (95% CI: 3.6–10.4) and 13.0 m (95% CI: 9.3–16.7), respectively. Among patients with brain metastases, mPFS was 12.0 m (95% CI: 6.7–17.3) and mOS was 17.0 m (95% CI: 12.9–21.1). The most frequent all grade adverse events were fatigue (58.0%) and diarrhea (56.8%); CTCAE grade ≥3 events occurred in 16.0%. Treatment discontinuation due to toxicity occurred in 7.4% of participants; there were no treatment-related deaths.

Conclusion: In this national real-world cohort, TTC demonstrated clinically meaningful activity and was not associated with any new safety signals in HER2-positive ABC, including patients previously exposed to T-Dxd and those with brain metastases.

Keywords: Breast cancer, HER2 protein, tucatinib, real-world data, survival analysis

KEY POINTS

- There is limited real-world evidence and a lack of prospective trial data specifically addressing the efficacy and safety of tucatinib, trastuzumab, and capecitabine (TTC) after trastuzumab deruxtecan (T-DXd) in HER2-positive advanced breast cancer.
- This national, multicenter, real-world study evaluated TTC in 81 patients who were treated at 17 oncology centers in Portugal.
- In the cohort, TTC achieved an overall response rate of 24.4%, a median progression-free survival of 9.0 months, and a median overall survival of 14.0 months.
- Clinical activity was maintained in patients previously treated with T-DXd and patients with central nervous system (CNS) metastases, including active CNS disease.
- TTC was generally well tolerated, with low rates of grade ≥3 adverse events and no treatment-related deaths.
- These findings provide real-world evidence supporting the effectiveness and safety of TTC in contemporary practice, including the post–T-DXd setting.

Introduction

Breast cancer (BC) is a major public health concern and the leading cause of cancer-related death among women worldwide, accounting for nearly one in four cancer diagnoses and one in six cancer deaths (1). In Portugal, approximately 8,950 new cases were diagnosed in 2022 (2). Although most BC are diagnosed at an early stage, 5–8% of patients present with metastatic disease at diagnosis (3).

The human epidermal growth factor receptor 2 (HER2) is encoded by the *ERBB2* gene and is a transmembrane tyrosine kinase (TK) receptor that activates multiple intracellular signaling pathways involved in cell growth and development (4). HER2 gene amplification and/or protein overexpression occurs in approximately 15–20% of BC cases (5), and is associated with a more aggressive phenotype, characterized by a higher risk of metastases—particularly to visceral organs and the central nervous system (CNS) (3).

Over the past two decades, the HER2 receptor has emerged as an effective therapeutic target, with the development of several targeted therapies. The introduction of HER2-targeted therapies, such as trastuzumab and pertuzumab, has significantly redefined the treatment of HER2-positive advanced BC (ABC), providing substantial improvements in clinical outcomes and patient survival. Nevertheless, as patients live longer, the incidence of CNS metastases has been rising, affecting up to 50% of individuals with HER2+ BC (6, 7), and it is generally associated with poor prognosis (8). Therapeutic options in this setting remain limited, largely because most HER2-targeted agents and chemotherapy demonstrate suboptimal intracranial activity (9).

Tucatinib is an oral TK inhibitor highly selective for the HER2 receptor kinase domain (10).

The pivotal phase II HER2CLIMB trial evaluated the efficacy and safety of tucatinib versus placebo, each combined with trastuzumab and capecitabine, in patients with HER2-positive ABC who had previously been treated with trastuzumab,

pertuzumab, and trastuzumab emtansine (T-DM1) (11). The study notably included patients with stable and active CNS metastases demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) in the tucatinib, trastuzumab and capecitabine (TTC) arm, including in patients with active CNS metastases. The combination was generally well tolerated, with serious adverse events (AEs) mainly related to palmar-plantar erythrodysesthesia (PPE) and diarrhea.

Given the substantial cohort of patients with CNS involvement in the HER2CLIMB trial, tucatinib has emerged as a pivotal, albeit not exclusive, therapeutic option for this patient subgroup. According to the European Society for Medical Oncology guidelines, second-line treatment for HER2-positive ABC primarily includes trastuzumab deruxtecan (T-DXd), with TTC also listed as an option, particularly for patients with CNS metastases; otherwise, it is mainly recommended in the third-line setting (12).

While the HER2CLIMB trial established the tucatinib regimen as an effective option, limited evidence exists on its real-world efficacy and safety. Furthermore, because the study predated widespread T-DXd use, there is a critical need for data on tucatinib's effectiveness in patients previously treated with T-DXd, which would better reflect current clinical practice.

This study aims to evaluate TTC therapy in a real-world setting and to provide data on its efficacy and safety in patients treated at national centers. To our knowledge, there are no previous similar studies in the Portuguese population.

Materials and Methods

Study Design and Population

This retrospective, multicenter, non-interventional study was conducted at 17 oncology centers in Portugal. It included patients aged ≥18 years with HER2-positive ABC who received at least one cycle of the TTC regimen for advanced disease until 31 May 2025. Eligibility was not restricted by Eastern Cooperative Oncology Group (ECOG) performance status (PS) or prior lines of therapy. Patients were excluded if they had not received systemic therapy for advanced disease, or if they had a history of another malignancy within 6 months before the diagnosis of ABC.

HER2 positivity was determined at each participating center and defined as either 3+ immunohistochemical (IHC) staining or 2+ IHC staining with positive fluorescence *in situ* hybridization or silver-enhanced *in situ* hybridization.

The TTC regimen comprised tucatinib (300 mg orally twice daily throughout the treatment period), trastuzumab (6 mg/kg intravenously once every 21 days, or 600 mg subcutaneously once every 21 days), and capecitabine (1,000 mg/m² orally twice daily on days 1 to 14 of each 21-day cycle). The TTC regimen was administered until disease progression, unacceptable toxicity, or patient preference.

Data Collection

Eligible patients were identified at participating centers through electronic medical records, and demographic and clinicopathological data were pseudonymized prior to analysis.

The collected baseline variables included age, ECOG (PS, metastatic sites, number of involved organs, and prior lines of therapy. CNS metastases were categorized as active—defined as untreated lesions or previously treated lesions showing progression immediately before starting TTC, without requiring urgent local intervention—or stable. Ongoing use of corticosteroids was permitted.

Histopathological characteristics were also recorded, including the BC subtype and hormone receptor (HR) status (estrogen and progesterone receptors). TTC treatment duration, clinical response, and AEs were also recorded.

Efficacy Assessment

Tumor response was assessed according to local clinical practice, based on imaging studies and clinical evaluation; radiologic response and disease progression at each center were evaluated using response evaluation criteria in solid tumors (RECIST v1.1) and response assessment in neuro-oncology brain metastases (RANO-BM). Patients who discontinued treatment or died before the first radiological assessment were considered non-evaluable for response.

Efficacy outcomes included OS, defined as the time from TTC treatment initiation to death from any cause; PFS, defined as the time from TTC treatment initiation to disease progression or death from any cause; overall response rate (ORR), defined as the proportion of patients achieving complete response (CR) or partial response (PR); and disease control rate (DCR), defined as the proportion of patients with stable disease (SD) in addition to those with an objective response. Patients who had not experienced an event by the data cut-off were censored on the date of their last documented follow-up.

Outcomes were evaluated across the overall cohort, and additional subgroup analyses were performed to explore treatment outcomes in patients with CNS metastases and in those previously treated with T-DXd.

Safety Assessment

AEs were extracted from medical records and graded on the Common Terminology Criteria for Adverse Events (CTCAE), version

5.0 (13). Safety outcomes included the incidence of grade ≥3 AEs and treatment discontinuation due to toxicity.

Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics® version 25.0. Continuous variables are presented as medians with 95% confidence intervals (CIs) and interquartile ranges (IQRs); categorical variables are presented as absolute and relative frequencies. Survival outcomes (OS and PFS) were estimated using the Kaplan-Meier method, with group comparisons performed using the log-rank test, and hazard ratios (HRs) with 95% CIs were estimated using Cox proportional hazards regression. A *p*-value <0.05 was considered statistically significant.

Ethics Approval

This study was approved by the Ethics Committee of the Local Health Unit of São José (approval number: 1728/2025_MJH/MAB/NO, date: 10.10.2025).

Results

Patient Characteristics

A total of 81 patients with HER2-positive ABC were enrolled at 17 oncology centers in Portugal and received TTC. All patients were female, with a median age of 54 years (IQR 48–62); fourteen patients (17.3%) were older than 65 years. The majority (n = 76, 93.8%) had an ECOG PS of 0 or 1. Regarding tumor biology, 72.8% (n = 59) had HR–positive disease, and invasive carcinoma of no special type was the most common histologic subtype (n = 73, 90.1%). At diagnosis, approximately one- third of patients (n = 29, 35.8%) presented with metastatic disease. The most frequent metastatic sites were bone (n = 53, 65.4%), liver (n = 37, 45.7%), and lung (n = 37, 45.7%). Thirty-two patients (39.5%) had CNS metastases, of whom 62.5% (n = 20) were active. The median number of prior treatment lines for metastatic disease was 3 (IQR 2–3, range 2–8). TTC was third-line therapy in 37.0% (n = 30) and fourth-line therapy in 48.1% (n = 39) of patients. Prior exposure to anti-HER2 agents included trastuzumab in 79 patients (97.5%), pertuzumab in 71 patients (87.7%), trastuzumab emtansine (T-DM1) in 76 patients (93.8%), and trastuzumab deruxtecan (T-DXd) in 50 patients (61.7%). Additionally, 77 patients (95.1%) had previously received chemotherapy.

Among patients previously treated with T-DXd, 86.0% (n = 43) initiated TTC immediately after disease progression. In this subgroup, the median age at TTC initiation was 53.5 years (IQR 48–62), and 94.0% (n = 47) had an ECOG PS of 0 or 1. CNS metastases were present in 28.0% (n = 14), of which 57.1% (n = 8) were active. Table 1 summarizes patient characteristics.

Table 1. Baseline demographics and clinical characteristics of patients with HER2 + MBC receiving TTC

Characteristics	Overall cohort (n = 81)	Patients previously treated with T-DXd (n = 50)
Female sex, n (%)	81 (100)	50 (100)
Age at TTC initiation, median (IQR), years	54.0 (48–62)	53.5 (48–62)
ECOG Performance Status score, n (%)		
0	30 (37.0)	21 (42.0)
1	46 (56.8)	26 (52.0)
2	5 (6.2)	3 (6.0)
Hormone-receptor status, n (%)		
Positive for ER, PR, or both	59 (72.8)	38 (76.0)
Negative for ER and PR	22 (27.2)	12 (24.0)
Histology, n (%)		
No special type	73 (90.1)	44 (88.0)
Lobular	6 (7.4)	5 (10.0)
Other	2 (2.5)	1 (2.0)
Stage IV at initial diagnosis, n (%)	29 (35.8)	18 (36.0)
Sites of metastasis, n (%)[a]		
Bone	53 (65.4)	35 (70.0)
Liver	37 (45.7)	21 (42.0)
Lung	37 (45.7)	27 (54.0)
CNS	32 (39.5)	14 (28.0)
Cutaneous	16 (19.8)	9 (18.0)
Other	19 (23.5)	10 (20.0)
Previous therapies in metastatic setting, n (%)		
Trastuzumab	79 (97.5)	48 (96.0)
Pertuzumab	71 (87.7)	44 (88.0)
T-DM1	76 (93.8)	45 (90.0)
T-DXd	50 (61.7)	50 (100)
Lapatinib	8 (9.9)	6 (12.0)
Chemotherapy	77 (95.1)	49 (98.0)
Metastatic treatment line at TTC initiation, n (%)		
Third line	30 (37.0)	5 (10.0)
Fourth line	39 (48.1)	37 (54.0)
Others	12 (14.8)	8 (16.0)

ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; IQR: Interquartile range; PR: Progesterone receptor; T-DM1: Ado-trastuzumab emtansine; T-DXd: Trastuzumab deruxtecan; TTC: Tucatinib, trastuzumab andcapecitabine; IQR: Interquartile range; HER2: Human epidermal growth factor receptor 2; MBC: Metastatic breast cancer, a: Not mutually exclusive

Efficacy Outcomes

All patients received TTC according to the approved dosing schedule and were October 1, 2021 and May 31, 2025. The median follow-up was 21.0 months, with patients receiving a median of 7 cycles of TTC (range, 1–36). At the data cut-off (December 2025), 9 patients (11.1%) remained on active treatment, while 65 patients (80.2%) discontinued TTC due to disease progression, and 7 patients (8.6%) discontinued due to toxicity. Seventy-eight of 81 patients were evaluable for response according to RECIST v1.1 and RANO-BM. Three patients were not evaluable for response: one died from a non–treatment-related cause before the first assessment; one discontinued treatment due to toxicity; and one discontinued due to clinical deterioration.

In the overall cohort, the ORR was 24.4%, including 2 CR (2.6%) and 17 PR (21.8%). An additional 31 patients (39.7%) experienced SD, resulting in a DCR of 64.1%. Thirty-one patients (39.7%) had disease progression as their best response. Median OS (mOS) was 14.0 months (95% CI: 10.5–17.5) (Figure 1), with a 12-month OS rate of 59.1%. Median PFS (mPFS) was 9.0 months (95% CI: 5.9–12.1; Figure 2), and the 12-month PFS rate was 38.0%. Response and survival outcomes are summarized in Tables 2 and 3.

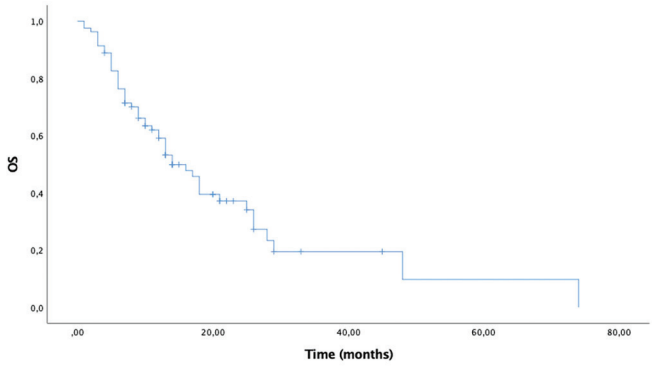

Figure 1. Kaplan-Meier curves for overall survival (OS) in the overall cohort

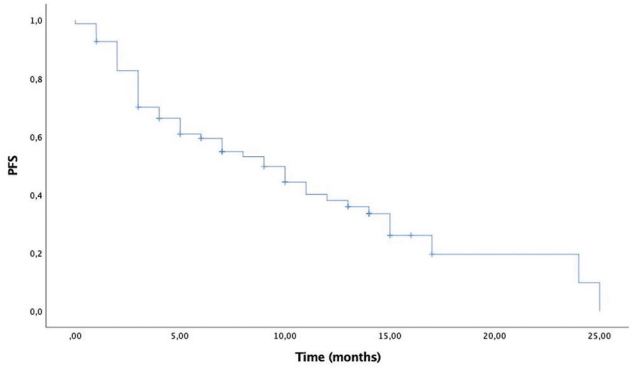

Figure 2. Kaplan-Meier curves for progression-free survival (PFS) in the overall cohort

Among patients previously treated with T-DXd, the ORR was 23.4%, including 9 patients (19.1%) with PR and 2 patients (4.3%) with CR, yielding a DCR of 61.7%. In this subgroup, mPFS was 7.0 months (95% CI: 3.6–10.4), and mOS was 13.0 months (95% CI: 9.3–16.7). In the subgroup of 31 patients who had not received T-DXd prior to TTC, the ORR was 25.8% and the DCR was 67.7%. The mOS was 28.0 months (95% CI: 11.5–44.5), and the mPFS was 12.0 months (95% CI: 6.8–17.2). The mOS was significantly longer in T-DXd–naïve patients compared with those previously treated with T-DXd ($p = 0.032$; HR: 0.52; 95% CI: 0.28–0.97) (Figure 3), whereas no statistically significant difference was detected in mPFS ($p = 0.104$; HR: 0.63; 95% CI: 0.35–1.13) (Figure 4).

Among the 32 patients with CNS metastases, the ORR was 15.6% (4 PR, 1 CR), and the DCR was 71.9%. The mPFS in patients with CNS involvement was 12.0 months (95% CI: 6.7–17.3), and the mOS was 17.0 months (95% CI: 12.9–21.1). In patients with active CNS metastases ($n = 20$), mPFS was 10.0 months (95% CI: 4.0–16.0); in those with stable CNS metastases ($n = 12$), mPFS was 14.0 months (95% CI: 4.3–23.7). The mOSs were 13.0 months (95% CI: 4.9–21.1) and 18.0 months (95% CI: 8.7–27.3), respectively.

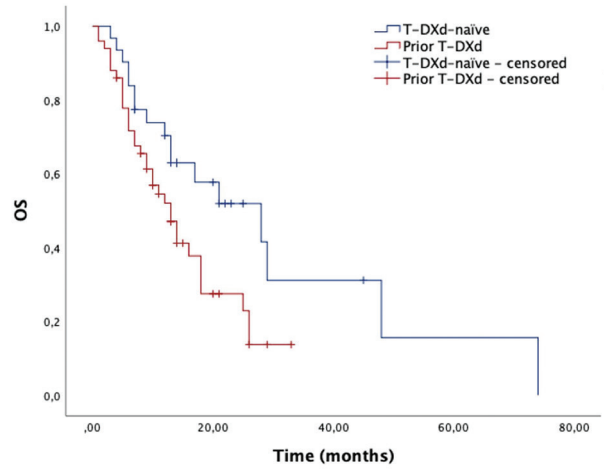

Figure 3. Kaplan-Meier curves for overall survival (OS) according to prior exposure to trastuzumab deruxtecan (T-DXd). Median OS was 28.0 months in T-DXd–naïve patients and 13.0 months in those previously treated with T-DXd (log-rank $p = 0.032$; HR: 0.52; 95% CI: 0.28–0.97)

HR: Hazard ratio; CI: Confidence interval

Table 2. Best overall response to tucatinib in combination with trastuzumab and capecitabine according to RECIST v1.1 in the overall cohort and key subgroups

Efficacy measures	Overall cohort (*n* = 81)	Patients previously treated with T-DXd (*n* = 50)	Patients with CNS metastasis (*n* = 32)
Best overall response according to RECIST v1.1[a], n (%)			
Complete response	2 (2.6)	2 (4.3)	1 (3.1)
Partial response	17 (21.8)	9 (19.1)	4 (12.5)
Stable disease	31 (39.7)	18 (38.3)	18 (56.3)
Progressive disease	31 (39.7)	21 (44.7)	9 (28.1)
Not available	3	3	0
Rate of response, (%)			
Overall response rate	24.4	23.4	15.6
Disease control rate	64.1	61.7	71.9

CNS: Central nervous system; RECIST: Response Evaluation Criteria in Solid Tumors; T-DXd: Trastuzumab deruxtecan

[a]: Responses were assessed by local investigators according to RECIST version 1.1

Table 3. Progression-free survival and overall survival outcomes in the overall cohort and predefined subgroups treated with tucatinib, trastuzumab, and capecitabine

	No of patients	PFS		OS	
		Median (95% CI), months	12-month rate (%)	Median (95% CI), months	12-month rate (%)
Overall cohort	81	9.0 (5.9–12.1)	38.0	14.0 (10.5–17.5)	59.1
Patients with no prior exposure to T-DXd	31	12.0 (6.8–17.2)	67.2	28.0 (11.5–44.5)	70.4
Patients previously treated with T-DXd	50	7.0 (3.6–10.4)	30.7	13.0 (9.3–16.7)	52.1
Duration of previous T-DXd treatment (months)					
<6	10	6.0 (2.0–10.0)	36.0	16.0 (8.8–23.2)	68.6
≥6 to ≤12	13	5.0 (0.0–11.5)	46.2	10 (1.7–18.3)	44.9
>12	27	8.0 (3.4–12.6)	28.7	12 (8.1–15.9)	49.9
TTC immediately after T-DXd treatment					
Yes	43	7.0 (3.9–10.1)	31.5	14 (11.5–16.5)	56.2
No	7	3.0 (2.2–3.8)	28.6	6.0 (3.4–8.6)	28.6
Population with CNS metastases	32	12.0 (6.7–17.3)	46.2	17.0 (12.9–21.1)	61.8
Type					
Active	20	10.0 (4.0–16.0)	41.1	13.0 (4.9–21.1)	55.0
Stable	12	14.0 (4.3–23.7)	54.7	18.0 (8.7–27.3)	72.2

CNS: Central nervous system; T-DXd: Trastuzumab deruxtecan; TTC: Tucatinib, trastuzumab and capecitabine; CI: Confidence interval; OS: Overal survival; PFS: Progression-free survival

Safety

Seventy-four patients (91.4%) experienced treatment-related AEs of any grade. The most frequent AEs were fatigue (*n* = 47, 58.0%), diarrhea (*n* = 46, 56.8%), PPE (*n* = 35, 43.2%), nausea (*n* = 29, 35.8%), and elevated liver enzymes (*n* = 23, 28.4%). Ten patients (12.3%) experienced grade 3 AEs, mainly dermatologic and gastrointestinal: the most common were PPE (*n* = 5, 6.2%) and diarrhea (*n* = 3, 3.7%). In total, 13 grade-3 events occurred, as some patients experienced multiple severe AEs. There were no grade 4 events. In patients aged ≥65 years (*n* = 14), 13 (92.9%) experienced treatment-related AEs of any grade with fatigue and PPE being the most common; 3 patients (21.4%) experienced grade 3 AEs including PPE (*n* = 2) and hyperbilirubinemia (*n* = 1).

Thirty-three patients (40.7%) received prophylaxis. Twenty-seven patients (33.3%) required dose modifications due to toxicity

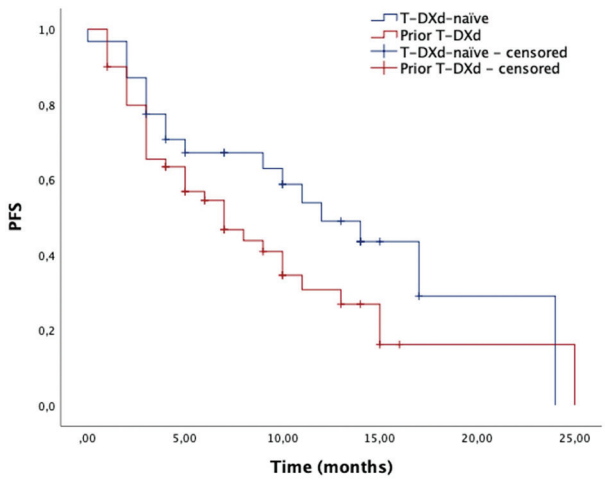

Figure 4. Kaplan-Meier curves for progression-free survival (PFS) according to prior exposure to trastuzumab deruxtecan (T-DXd). Median PFS was 12.0 months in T-DXd–naïve patients and 7.0 months in patients previously treated with T-DXd (log-rank $p = 0.104$; HR: 0.63; 95% CI: 0.35–1.13)

HR: Hazard ratio; CI: Confidence interval

and 36 (44.4%) required temporary treatment interruptions. Six patients (7.4%) discontinued treatment due to grade 3 PPE ($n = 2$), grade 3 diarrhe a ($n = 1$), grade 3 stomatitis ($n = 1$), grade 3 elevation of aspartate aminotransferase ($n = 1$), and grade 2 vomiting and diarrhea ($n = 1$). No treatment-related deaths occurred. Table 4 summarizes overall and grade 3 AEs according to CTCAE.

Discussion and Conclusion

The therapeutic landscape of HER2-positive ABC is rapidly evolving, with the emergence of multiple anti-HER2 therapies, including the TTC combination. This multicenter, real-world Portuguese study evaluated TTC in 81 patients with HER2-positive ABC at 17 oncology centers nationwide. It–expands–current evidence on the effectiveness of TTC in patients previously treated with T-DXd, now established as the standard first- or second-line therapy (14, 15). Importantly, it provides contemporary data in the post–T-DXd setting, where prospective trial evidence remains limited, and enables a pragmatic assessment of TTC sequencing after antibody–drug conjugate therapy.

Several baseline characteristics distinguish our real-world population from those in the HER2CLIMB trial and should be considered when interpreting the results. Compared with the trial population, our cohort reflects broader eligibility criteria and the heterogeneity typically seen in routine practice, including patients with ECOG PS 2 and a higher burden of visceral disease, particularly liver metastases. Conversely,

Table 4. Incidence of treatment-related adverse events of any grade and grade 3 among patients treated with tucatinib, trastuzumab, and capecitabine in the overall cohort

Adverse events	Any grade[a] n (%)	Grade 3[a] n (%)
Any adverse event	74 (91.4)	13 (16.0)
Fatigue	47 (58.0)	0 (0)
Diarrhea	46 (56.8)	3 (3.7)
PPE syndrome	35 (43.2)	5 (6.2)
Nausea	29 (35.8)	0 (0)
Aspartate aminotransferase increased	21 (25.9)	0 (0)
Alanine aminotransferase increased	20 (24.7)	2 (2.5)
Vomiting	17 (21.0)	0 (0)
Stomatitis	12 (14.8)	1 (1.2)
Decreased appetite	4 (4.9)	0 (0)
Decreased ejection fraction	4 (4.9)	0 (0)
Onycholysis	3 (3.7)	1 (1.2)
Dysgeusia	3 (3.7)	0 (0)
Neutropenia	2 (2.5)	0 (0)
Blood bilirubin increased	2 (2.5)	1 (1.2)
Anemia	1 (1.2)	0 (0)

PPE: Palmar-plantar erythrodysesthesia

[a]: Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 5.0

our cohort included a lower proportion of patients with CNS metastases and fewer active CNS lesions at treatment initiation. This may reflect differences in imaging strategies: routine brain imaging was mandatory in HER2CLIMB, whereas in routine practice imaging is often symptom-driven, potentially leading to underdiagnosis of asymptomatic disease. An additional distinguishing feature of this study is the high proportion of patients previously treated with. At the time of HER2CLIMB enrollment, T-DXd was not part of the therapeutic landscape, leaving uncertainty regarding the efficacy and safety of TTC after prior exposure, an issue addressed by this real-world analysis.

Despite these differences, TTC demonstrated clinically meaningful efficacy in this real-world cohort. When focusing on the subgroup of patients not previously exposed to T-DXd—more closely reflecting the HER2CLIMB population—both mOS and mPFS were numerically longer than those reported in the pivotal trial (mOS 28.0 *vs.* 21.9 months; mPFS 12.0 *vs.* 7.8 months), suggesting that TTC retains clinical activity in routine practice in this setting.

In the overall cohort, PFS was comparable to that observed in HER2CLIMB, with a modestly longer median PFS and 12-month PFS rate This difference likely reflects variations in prior treatment exposure—particularly the inclusion of patients previously treated with T-DXd—and a less-selective patient population. When considered alongside other real-world series, the survival outcomes in our study fall within the range reported in contemporary cohorts, including a French real-world series that enrolled patients treated with TTC after prior T-DXd exposure, despite differences in sample size, follow-up duration, and treatment sequencing (16).

Within the population previously treated with T-DXd, TTC retained clinically meaningful activity, with an mOS of 13.0 months and an mPFS of 7.0 months. These outcomes align with those reported in other real-world cohorts evaluating TTC after prior T-DXd exposure, including the aforementioned French cohort and two American real-world analyses (17, 18). In those studies, median PFS ranged from 4.7 to 5.5 months among patients receiving tucatinib-based regimens after T-DXd, with a median of three to four prior lines of therapy, reflecting that these patients were more heavily pretreated than those in our cohort. Together, these findings indicate that TTC retains activity after T-DXd exposure across different clinical settings, despite variations in cohort size, prior treatment burden, follow-up duration, and treatment sequencing. In our study, prior exposure to T-DXd was associated with worse overall survival, whereas T-DXd–naïve patients exhibited a lower risk of death (HR: 0.52; 95% CI: 0.28–0.97). Although no statistically significant difference in mPFS was detected between the two subgroups, given the limitations of the sample size ($p = 0.104$), the approximately 5-month difference in median PFS favoring T-DXd-naïve patients may still be clinically meaningful. Emerging evidence suggests that prior exposure to antibody–drug conjugates such as T-DXd, beyond representing a more heavily pretreated population, may induce biological changes—including loss of HER2 expression, altered HER2 binding, and increased drug efflux—that could attenuate, but not eliminate, sensitivity to subsequent HER2-directed therapies. These mechanisms may contribute to the reduced magnitude and durability of responses observed in the post–T-DXd setting (19-21). Given the recent shift toward the earlier use of T-DXd, the post–T-DXd subgroup in our cohort likely reflects early real-world experience following its integration into routine practice. Consequently, outcomes with TTC in this subgroup should be interpreted in the context of this evolving therapeutic landscape. In addition, survival comparisons by prior T-DXd exposure were based on univariate analyses, and multivariable adjustment was not performed due to the limited sample size and the number of events. Therefore, the observed differences in survival outcomes may have been influenced by baseline imbalances in prognostic factors, such as prior lines of therapy or disease burden, rather than representing independent treatment effects. These findings should therefore be interpreted as descriptive and hypothesis-generating.

Notably, most patients (86.0%) initiated TTC immediately after progression on T-DXd. Direct sequencing of TTC after T-DXd was associated with numerically longer mPFS and higher 12-month OS rates than in patients who received other systemic therapies between T-DXd and TTC (Table 3). The observed differences in outcomes could be due to the sequence of treatments or to a greater cumulative treatment burden among patients.

The TTC activity in CNS metastases was particularly noteworthy. In our study, mPFS among patients with CNS involvement reached 12 months, exceeding results reported in HER2CLIMB and other real-world cohorts (16, 17), and further supporting the intracranial activity of TTC. As expected, patients with stable CNS disease experienced more favorable outcomes than those with active CNS metastases. These findings support the role of TTC as a relevant therapeutic option for patients with CNS involvement, a population with historically limited therapeutic alternatives.

To our knowledge, real-world data specifically addressing the safety of TTC after T-DXd exposure remain limited. In this cohort, the tolerability of TTC was consistent with the safety profile reported in HER2CLIMB. As in the HER2CLIMB trial, the most common AEs associated with TTC were diarrhea, PPE, nausea, fatigue, and elevations in hepatic transaminases. AEs of any grade were reported in 91.4% of patients in our cohort, which is comparable to the rate reported in HER2CLIMB. Regarding grade ≥3 AEs, the reported frequency in the present cohort was 16%, which was lower than that observed in the HER2CLIMB trial (55.5%). While this difference should be interpreted with caution, the overall toxicity profile was consistent with that reported in HER2CLIMB, with grade ≥3 events predominantly consisting of PPE, diarrhea, and elevations in hepatic transaminases. Although prophylactic antidiarrheal therapy was not mandated in HER2CLIMB, 40.7% of patients in our cohort received loperamide prophylaxis, which may have contributed to a lower incidence of any-grade diarrhea compared with HER2CLIMB. No new safety signals were identified, and AEs were generally manageable with supportive care measures, dose reductions, and temporary treatment interruptions. Conversely, compared with HER2CLIMB, our study observed slightly higher rates of dose modifications and treatment discontinuation due to AEs, likely reflecting differences in patient selection, comorbidity burden, and toxicity management strategies in routine clinical practice. In HER2CLIMB, capecitabine discontinuation for treatment-related toxicity was permitted while continuing tucatinib and trastuzumab. Although not reported in our cohort, this pragmatic approach could help mitigate toxicity

and prevent premature treatment discontinuation in routine practice.

Study Limitations

Some limitations of this real-world study include inherent challenges of routine clinical practice, in which less-standardized protocols may cause clinicians to inconsistently report treatment-related AEs, potentially underestimating toxicity. In addition, heterogeneity in the timing of radiological response assessments across centers represents a significant limitation compared with centralized imaging evaluation. Survival comparisons by prior T-DXd exposure were based on univariate analyses, as the limited sample size precluded multivariable adjustment; therefore, residual confounding cannot be excluded. The retrospective nature of the study should be considered when interpreting these findings.

This national real-world cohort demonstrates that the TTC regimen has clinically meaningful activity and no unexpected safety signals in patients with HER2-positive ABC, including those with CNS metastases and prior exposure to T-DXd. These findings reinforce the clinical utility of TTC in contemporary practice, including in patients previously treated with T-DXd.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Local Health Unit of São José (approval number: 1728/2025_MJH/MAB/NO, date: 10.10.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.Q.F., C.B.M., A.C.D., F.A., B.D., M.J.O., I.A., J.C., A.F., R.F., D.A.C., M.T.M., T.P.C., F.A., S.B., C.L.F., M.S., B.S., M.A.M., D.C.S., L.F., S.D.O.; Concept: R.Q.F., M.A.M., D.C.S., L.F., S.D.O.; Design: R.Q.F., M.A.M., D.C.S., L.F., S.D.O., Data Collection or Processing: R.Q.F., C.B.M., A.C.D., F.A., B.D., M.J.O., I.A., J.C., A.F., R.F., D.A.C., M.T.M., T.P.C., F.A., S.B., C.L.F., M.S., B.S.; Analysis or Interpretation: R.Q.F., M.A.M., D.C.S., L.F., S.D.O.; Literature Search: R.Q.F., C.B.M., A.C.D., F.A., B.D., M.J.O., I.A., J.C., A.F., R.F., D.A.C., M.T.M., T.P.C., F.A., S.B., C.L.F., M.S., B.S., M.A.M., D.C.S., L.F., S.D.O.; Writing: R.Q.F., C.B.M., A.C.D., F.A., B.D., M.J.O., I.A., J.C., A.F., R.F., D.A.C., M.T.M., T.P.C., F.A., S.B., C.L.F., M.S., B.S., M.A.M., D.C.S., L.F., S.D.O.

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