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Efficacy of second- or third-line Tucatinib, Trastuzumab, and Capecitabine (TTC) following trastuzumab deruxtecan (T-DXd) in HER2-positive metastatic breast cancer: A multicenter French cohort study.

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Background

Trastuzumab deruxtecan (T-DXd) is currently established as the standard second-line therapy for HER2-positive metastatic breast cancer (MBC). Recent findings from the DESTINY-Breast09 (DB-09) trial indicate that it may soon be adopted as a first-line treatment option. However, the optimal sequencing of therapies following T-DXd remains uncertain. At present, evidence on the efficacy of the tucatinib, trastuzumab, and capecitabine (TTC) combination when used as a second- or third-line regimen after T-DXd is limited.

We conducted a cohort study across 20 French cancer centers, encompassing a range of clinical settings, including comprehensive cancer centers, university hospitals, and private practice hospitals to assess the efficacy of TTC in this context.

Methods

- **Retrospective Study in 20 French hospitals**

- **Main Inclusion criteria:**
  - HER2+ MBC treated with TTC between 06/2021 and 06/2025 as second or third line therapy
  - Pretreatment with T-DXd (stopped for progression or toxicity)

- **Enpoints**
  - Progression free survival (PFS) (RECIST 1.1) by local investigators in the whole population and in subgroups
  - Time to next treatment (TTNT)
  - Overall survival (OS) in the whole population and in subgroups
  - Response rate by local investigators

- **Statistics**
  - Survival curves were estimated by the Kaplan-Meier method with 95% confidence interval (CI)
  - PFS was computed from initiation of TTC to progression or death; patients who started a new treatment without progression and patients with ongoing TTC treatment were censored, respectively at the start date of new molecule and date of last follow-up
  - OS was computed from initiation of TTC to death ; patients alive were censored at the date of last follow-up

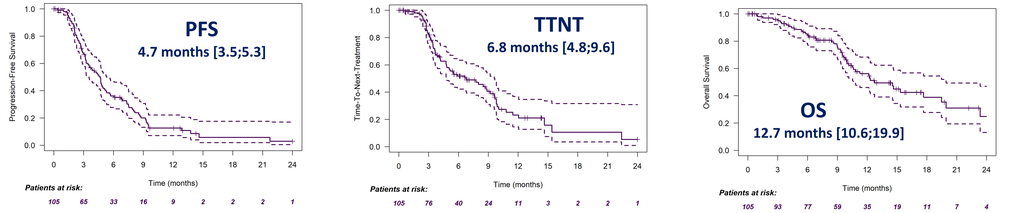
Patients Characteristics

	N = 105 (%)
Median Age (range) (years)	55.1 (21.0 - 86.0)
Stage IV at initial diagnosis	43 (41.0%)
Hormone receptor status	
ER- and/or PR-positive	53 (50.5%)
ER- and PR-negative	52 (49.5%)
HER2 status (1 unknown)	
3+	76 (73.1%)
2+ CISH amplified	28 (26.9%)
Prior lines of chemotherapy, n (%)	
(Neo)adjuvant setting	58 (55.2%)
Metastatic setting, one line	9 (8.6%)
Metastatic setting, two lines	96 (91.4%)
Previous therapies for metastatic breast cancer	
Trastuzumab	93 (88.6%)
Pertuzumab	93 (88.6%)
T-DM1	2 (1.9%)
Lapatinib	1 (1.0%)
T-DXd	105 (100.0%)
T-DXd treatment	
1st line	9 (8.6%)
2nd line	96 (91.4%)
Median (range) duration of T-DXd (months)	8.0 (0.7 - 37.2)
Reason for T-DXd discontinuation	
Progression	96 (91.4%)
Toxicity	8 (7.6%)
Unknown	1 (1.0%)
TTC immediately after T-DXd	105 (100.0%)
Brain metastases prior to TTC	
Yes	58 (55.2%)
No	47 (44.8%)
Visceral metastases at initial metastastic disease	
Yes	76 (72.4%)
No	29 (27.6%)
Classification of brain metastases (7 unknown)	
Previous local treatment and progressive BM prior to TTC	17 (33.3%)
No previous local treatment and progressive BM prior to TTC	31 (60.8%)
stable BM prior to TTC	3 (5.9%)

TTC treatment

	Data Cut of 1st of July 2025
Median follow-up (months)	14.2 [11.5;15.9]
Median duration of TTC (months	3.4 [0.4;21.2]
TTC ongoing	
Yes	27/105 (25.7%)
No	78/105 (74.3%)
Reason for TTC discontinuation	
Progression	74/78 (94.9%)
Toxicity	3/78 (3.8%)
Unknown	1/78 (1.3%)

Efficacy in the whole population (median follow-up: 14.2 months [11.5;15.9])



Efficacy in subgroups

		PFS		OS		TTNT
	N	Median (months) [95% CI]	6-months rate [95% CI]	Median (months) [95% CI]	6-months rate [95% CI]	Median (months) [95% CI]
Whole population						
	105	4.7 [3.5;5.3]	36.2% [27.6;47.3]	12.7 [10.6;19.9]	85.2% [78.4;92.7]	6.8 [4.8;9.6]
T-DXd discontinuation reason						
Toxicity	8	5.0 [3.3;NR]	37.5% [15.3;91.7]	10.6 [9.8;NR]	100.0% [100.0;100.0]	11.1 [3.3;NR]
Progression	96	4.5 [3.4;5.7]	36.5% [27.6;48.3]	14.6 [10.8;23.4]	83.7% [76.2;91.9]	6.6 [4.8;9.7]
Duration of previous T-DXd in patients stopping for progression						
≤18 months	82	3.9 [3.2;5.3]	34.3% [25.1;46.9]	12.3 [10.2;19.9]	82.7% [74.6;91.7]	5.5 [4.2;9.7]
>18 months	14	6.9 [4.4;NR]	50.5% [27.3;93.3]	23.4 [NR;NR]	90.0% [73.2;100.0]	7.8 [5.9;NR]
No. chemotherapy lines prior to TTC (including (Neo)adjuvant)						
1-2	55	4.8 [3.8;6.0]	35.5% [24.3;51.8]	12.3 [9.3;NR]	81.5% [71.3;93.2]	6.6 [4.8;10.1]
3	50	4.4 [2.8;7.3]	36.9% [25.2;54.1]	14.7 [10.8;NR]	89.1% [80.6;98.6]	7.8 [3.7;9.9]
Hormone Receptor expression						
ER and/or PR+	53	4.7 [3.8;7.4]	40.0% [28.0;57.0]	17.7 [12.7;NR]	87.1% [78.0;97.3]	6.8 [4.8;NR]
ER and PR -	52	4.1 [3.2;5.7]	32.6% [21.7;49.1]	10.8 [9.5;NR]	83.5% [73.6;94.7]	5.5 [4.2;9.9]
Brain metastases						
Yes	58	5.0 [3.9;7.3]	39.1% [27.9;54.9]	15.3 [12.7;NR]	86.7% [77.9;96.4]	8.8 [6.6;14.7]
No	47	3.2 [2.7;6.8]	32.6% [21.1;50.4]	10.5 [9.5;NR]	83.6% [73.1;95.5]	4.8 [3.4;9.6]
Type of brain metastases						
Active, treated	17	4.6 [3.6;7.4]	25.0% [10.7;58.4]	10.6 [9.1;NR]	81.2% [64.2;100.0]	9.8 [4.2;NR]
Active, not treated	31	5.3 [3.3;8.1]	46.4% [31.5;68.5]	19.5 [17.7;NR]	90.0% [79.8;100.0]	7.8 [5.5;NR]
Stable	3	-	-	-	-	-

Response rate with TTC (RECIST 1.1)

	Tumor response (RECIST 1.1)			Brain tumor response (RECIST 1.1)
	Overall population	Patients progressing on T-DXd	Patients stopping T-DXd for toxicity	Patients with active BM prior TTC initiation
	N = 105	N = 96	N = 8	N = 48
Complete response, n (%)	9 (9.2%)	8 (9.0%)	1 (12.5%)	2 (4.4%)
Partial response, n (%)	20 (20.4%)	19 (21.3%)	1 (12.5%)	12 (26.7%)
Stable disease, n (%)	27 (27.6%)	22 (24.7%)	5 (62.5%)	15 (33.3%)
Progressive disease, n (%)	42 (42.9%)	40 (44.9%)	1 (12.5%)	16 (35.6%)
Not available	7 (-)	7 (-)	0 (-)	3 (-)
Overall response rate, n (%)	29 (29.6%)	27 (30.3%)	2 (25.0%)	14 (31.1%)
Disease control rate, n (%)	56 (57.1%)	49 (55.1%)	7 (87.5%)	29 (64.4%)

Conclusion

In this multicenter retrospective cohort of HER2-positive MBC patients who received T-DXd followed by second- or third-line TTC, TTC appeared to retain clinically significant activity. The short median duration of prior T-DXd treatment reflects the specific characteristics of the population studied.

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