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COMPARISON OF RESPONSE TO TREATMENT IN LINES SUBSEQUENT TO T-DM1 IN PATIENTS WITH METASTATIC HER2 POSITIVE BREAST CANCER

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Abstract: Introduction: Breast cancer has a strong epidemiological impact. Approximately 20% of them are HER-2 positive. In the metastatic setting, first-line treatment with pertuzumab, trastuzumab and taxane is consolidated by the CLEOPATRA study and second-line treatment, until recently, with trastuzumab-emtansine (T-DM1) by the EMILIA study. Sequencing after using T-DM1 lacks consistent information. **Objectives**: the primary outcome was the comparison of the response rate of patients undergoing subsequent line to T-DM1, in HER2-positive metastatic breast cancer. Secondary objectives were to compare Overall Survival (OS), Progression-Free Survival to T-DM1 (PFS), Progression-Free Survival to subsequent line (PFS2), Time to Treatment Failure (TFT) and adverse events. **Methods**: Retrospective, single-center study, including 67 patients with HER2-positive metastatic breast cancer exposed to T-DM1 between August 2013 and December 2021. Of the 67 patients, 38 received subsequent lines of treatment, with a median follow-up of 34 months. Treatments subsequent to T-DM1 were divided into 3 groups: Group 1 = capecitabine + lapatinib (21 patients); Group 2 = trastuzumab-deruxtecan (5 patients) and Group 3 = anti-HER2 associated with chemotherapy (12 patients). **Results**: The response rate was 19% in group 1, 60% in group 2 and patients in group 3 showed disease stability. The DFS was 15 months. The median OS of T-DM1 was 47 months. No patient in Group 2 experienced progression or death. There was no significant difference in PFS between groups 1 and 3. **Conclusion:** The response rate varied according to the subsequent line, being favorable to trastuzumab-deruxtecan, which also had lower toxicity. Comparison of OS between groups was not possible due to the number of patients included and events.

Keywords: breast cancer; HER2; trastuzumab-emtansine

INTRODUCTION

Breast cancer has a strong epidemiological impact. Excluding non-melanoma skin tumors, breast cancer is the neoplasm with the highest incidence in Brazilian women, according to INCA estimates in 2022.(1)

It is a heterogeneous disease at the molecular level, being defined from a practical point of view, by immunohistochemistry, five subtypes: luminal tumors (with expression of estrogen and progesterone receptors), subdivided into Luminal A and Luminal B, HER-2 positive (with expression of hormonal receptors - luminal HER2 positive or without hormonal expression - pure HER2) and triple negative (absence of expression of estrogen, progesterone receptors and overexpression of HER-2).(2) Approximately 15 to 20% of breast tumors are HER -2 positive, which is associated with worse survival when compared to HER-2 negative luminal tumors.(3)

The standard first line of treatment for patients with metastatic HER-2 positive breast cancer with trastuzumab, pertuzumab and taxane was consolidated with the CLEOPATRA study. This study showed that the addition of pertuzumab to trastuzumab and taxane, compared with the addition of placebo, significantly improved overall survival to 56 months. (4) The PERUSE study demonstrated that paclitaxel is an alternative to docetaxel.(5)

The phase 3 study, EMILIA, demonstrated that trastuzumab-emtansine (T-DM1) promoted an increase in overall survival in the population of metastatic HER-2 positive patients with disease progression on taxane and trastuzumab, until recently being the treatment option for second line of treatment.(6,7)

In March 2022, the DESTINY-BREAST03 study was published, which changed the clinical practice of second-line treatment of patients who progressed to trastuzmab and taxane. The study compared trastuzumab-

derutecan (T-Dxd) with trastuzumab-emtansine. Patients in the T-Dxd arm had gains in disease-free survival and overall survival. The use of T-Dxd was approved in Brazil for treatment after progression with taxane and trastuzumab in June 2022.(8).

For later lines there are therapeutic options, such as those addressed in the studies: EGF104900 with the use of lapatinib and trastuzumab (9), EFG100151, which evaluated the use of lapatinib with capecitabine (10), Th3resa with the use of T-DM1 after 2 or more lines of treatment (11), HER-2CLIMB with tucatinib, trastuzumab and capecitabine (12), NALA with neratinib and capecitabine compared with lapatinib and capecitabine (13), SOPHIA, comparing margetuximab associated with chemotherapy against trastuzumab and chemotherapy (14), and DESTINY DESTINY-BREAST01, with trastuzumab-deruxtecan after 2 or more lines of treatment for metastatic disease.(15)

This study aims to compare the effectiveness of subsequent lines to T-DM1 in patients with HER-2 positive metastatic breast cancer in clinical practice ("real world data") in patients treated at a Brazilian Cancer Center.

METHODS

This is an analytical, observational/non-interventional, retrospective, single-center study. The study evaluated the response rate and other secondary endpoints (Progression-Free Survival, Overall Survival, Adverse Event, Time to Treatment Failure) in patients with HER-2 positive metastatic breast cancer who underwent systemic treatment subsequent to T-DM1 in A.C. Camargo Cancer Center from August 2013 to December 2021. The data analyzed were collected exclusively from an institutional database with data entered between the period from January 2019 to December 2021, previously established and anonymized.

INCLUSION AND EXCLUSION CRITERIA

Patients who met the following criteria were included in the study: (1) Female or male; (2) Age over eighteen years old; (3) Diagnosis of HER-2 positive breast cancer by anatomopathological evaluation, immunohistochemistry and, when necessary, by *in situ* hybridization; (4) Staging I-IV; (5) Development of distant metastases at any site and at any time; (6) Exposure to T-DM1 in the metastatic setting in any line of treatment; (7) Exposure to at least one line of systemic treatment subsequent to T-DM1; (8) For secondary analysis of treatment with T-DM1, the inclusion of patients who did not undergo subsequent treatments was also allowed.

STATISTICAL ANALYSIS

All patients who underwent T-DM1 and subsequent treatment in the metastatic setting between 08/01/2013 and 12/31/2021 and met the inclusion criteria were included in the study. Therefore, there is no sample size calculation for the study.

Descriptive statistics were used to evaluate the characteristics of the population.

Categorical variables were described using frequencies and percentages. The numerical variables were described by measures of central tendency (means and medians) and central dispersion (percentiles and standard deviation). The assessment of associations between categorical variables was performed using the chi-square or Fisher tests, when appropriate.

The time-to-event variables were analyzed using Kaplan Meier curves and the comparison between them was performed using the Log Rank test and Cox regression. Univariate and multivariate analyzes using Cox regression were performed to define the predictive factors associated with SLP, TFT and SG. P values < 0.2 in univariate analyzes were included

in multivariate analyses, with the exception of stage and volume of disease, which were included in multivariate analyses. Univariate and multivariate analyzes were performed using conditional logistic regression.

Schoenfeld residual tests were used to test the proportionality of the *hazard* assumed in the Cox model. In case the proportionality of the Cox model was not accepted, the restricted mean survival time was used.

The significance level considered was 5% and the software used was SPSS version 25 and the free software R version 3.6.2.

RESULTS

POPULATION OF PATIENTS WITH HER-2 POSITIVE METASTATIC BREAST CANCER TREATED WITH T-DM1

We identified 118 patients who received TDM1 during the studied period and included 67 with a median follow-up time of 34 months who fulfilled the scope of the study (95%CI 30.7-37.3). 51 patients who used T-DM1 in the adjuvant setting were excluded.

The median age of patients who received T-DM1 in the metastatic setting was 49 (29-66) years. Regarding the line of treatment: 10 patients received T-DM1 in the 1st line, 48 patients in the 2nd line, 7 patients in the 3rd line, 1 patient in the 4th line and 1 patient in the 6th line. The other clinicopathological characteristics are described in table 1.

Thirty-eight patients received some subsequent line of treatment for metastatic HER 2 disease.

Regarding treatments prior to T-DM1, 67 patients received taxane and trastuzumab, 54 patients received prior pertuzumab. Results described in table 2.

POPULATION CHARACTERISTICS

All patients were female, 18 (26.9%) were in menopause at the start of treatment and 37 (55.2%) had some comorbidity, 49 (73.1%) had T staging ≤ 2, 45 (67.2%) had lymph node involvement, 23 (34.3%) were metastatic, 43 (64.2%) had a luminal component, patients were between ECOG 0 and 2, 21 patients had CNS metastasis before starting T- DM1 and 44 with visceral metastasis. Table 1.

General Characteristics	
Gender	
Masculine	0
Feminine	67 (100%)
Comorbidity	
Not	30 (44,8%)
Yes	37 (55,2%)
Menopause	
Not	49 (73,1%)
Yes	18 (26,9%)
Tumor size	
T1-2	43 (64,2%)
T3-4	18 (26,9%)
Missing	06 (9%)
Lymph node involvement	
Not	15 (22,4%)
Yes	45 (67,2%)
Missing	07 (10,4 %)
Metastasis at Diagnosis	
Not	44 (65,7)
Yes	23 (34,3%)
Luminal	
Not	24 (35,8%)
Yes	43 (64,2%)
HER2 (Immunohistochemistry)	
++	06 (9%)
+++	61 (91%)
ECOG before TDM1	
0	23 (34,3%)
1	39 (58,2%)
2	05 (7,5%)
CNS metastasis before T-DM1	
Not	46 (68,7%)
Yes	21 (31,3%)
Visceral metastasis before T-DM1	
Not	23 (34,3%)
Yes	44 (65,7%)

Table 1 – General Characteristics

PREVIOUS TREATMENTS

The number of patients who received neoadjuvant treatment was 28 (41.8%), with 7 patients showing complete response and 33 receiving adjuvant treatment, no adjuvant treatment included T-DM1. All received taxane and trastuzumab prior to T-DM1 and 54 (80.6%) received pertuzumab. Table 2.

Treatments Prior to T-DM1	
Neoadjuvance	
Not	39 (58,2%)
Yes	28 (41,8%)
Complete Response after Neoadjuvantage	
Not	60 (89,5%)
Yes	07 (10,4%)
Adjuvance	
Not	34 (50,7%)
Yes	33 (48,7%)
Taxane prior to TDM1	
Not	0
Yes	67 (100%)
Trastuzumab prior to T-DM1	
It did not receive	0
It received	67 (100%)
Pertuzumab prior to T-DM1	
It did not receive	13 (19,4%)
It received	54 (80,6%)
T-DM1	
1st line	10 (15%)
2nd row and subsequent rows	57 (85%)

Table 2 – Treatments prior to T-DM1

* **Adjuvance**: patients who were treated with "upfront" surgery or maintained HER-2 blockade initiated in neoadjuvant treatment.

OUTCOMES

RESPONSE RATE TO T-DM1

In patients treated with T-DM1 there was 10.4% partial response and 38.8% stable disease. None of them provided a complete response. The clinical benefit was 49.2%. Figure 1.

PROGRESSION-FREE SURVIVAL (PFS) AND OVERALL SURVIVAL (OS)

The median PFS was 15 months (8-21 months), the factors associated with statistical significance: absence of visceral metastasis at diagnosis, HER2 3+ on immunohistochemistry and ECOG 0 and 1. As described in tables 3, 4 and in figure 1.

The median OS was 47 months (24-69 months), the factors associated with significance were: ECOG 0 or 1, HER2 3+, absence of serious AE, absence of previous pertuzumab use. As described in tables 3, 4 and figure 2.

When comparing the use of T-DM1 in patients with HER2 positive luminal tumors versus HER2 pure, 43 (64.1%) were luminal and 24 (35.8%) HER2 pure. The median PFS in luminal patients was 11 months (8-13 months) versus 20 months (16-23 months), despite the difference, there was no statistical significance. As for overall survival, it was 47 months (18-75 months) versus 37 months (17-58 months) respectively, also without statistical significance. The results showed a trend towards lower PFS in luminal tumors, but with higher OS. According to Table 1 (studied population) and Table 3 (outcome).

When comparing patients who received T-DM1 in the 1st line versus the 2nd line, the PFS was 19 months (8-29 months) in the 1st line and 11 months (2-19 months) in the second line with a p value = 0.009. The OS was 47 months (25-68 months) versus 74 months (17-130 months) respectively, but without statistical significance. Table 3.

When comparing the use of T-DM1 in patients previously treated with pertuzumab versus those not treated with pertuzumab, the PFS was 17 months (7-22 months) versus 11 months (2-19 months), there was no statistical significance. OS was 74 months (24-69 months) versus 74 months (35-112 months) respectively, with p = 0.15. Table 3.

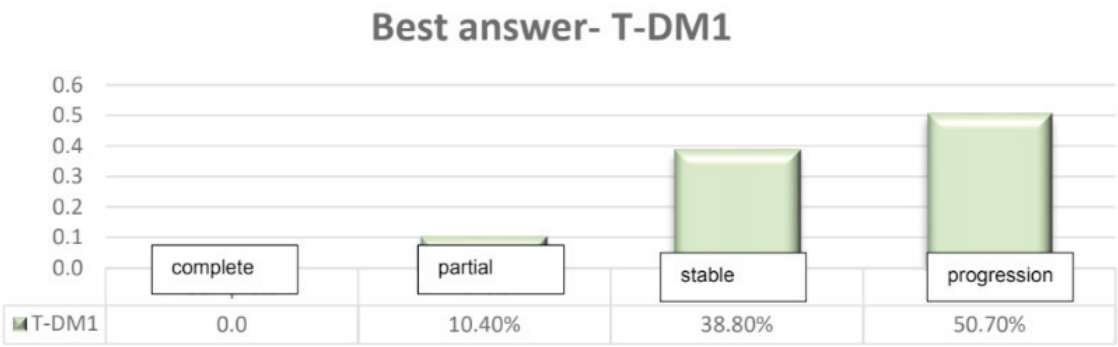

Figure 1

	SLP			SG		
Characteristics	*Median (95%IC)*	*p-value*	*HR (95%IC)*	*Median (95%IC)*	Value p	HR (95%IC)
Survival Time	15 (8,4-21,5)	-	-	47 (24,1-69,8)	-	-
Comorbidity						
Not	11 (6,3-15,6)		1	74 (10,6-137,3)		-
Yes	19 (6,4-31,5)	0,191	-	47 (19,7-74,2)	0,37	
Menopause						
Not	11 (6,4-15,5)		1	30 (10,4-49,5)		-
Yes	22(2,4 - 41,5)	0,029	2,1 (1,0-4,5)	71 (34,2-107,7)	0,05	
ECOG						
0 and 1	17 (9,6-24,3)		1	47 (30,6-63,3)		
2	4 (1,8-6,1)	0,000	0,16 (0,05-0,50	11 (0-23,8)	0,0	0,140
Size						
1 e 2	19 (8,6-29,3)		1	-	-	-
3 e 4	11 (4,5-17,4)	0,345	-	-		
N+						
Not	8 (0,0-21,5)		1	24 (13,8-34-14)		-
Yes	17 (9,1-24,8)	0,815	-	38	0,86	
Metastasis						
Not	13 (1,9-24,0)		1	38 (17,5 -58,1)		-
Yes	17(5,4-28,5)	0,202	-	53 (22,6-83,3)	0,54	
MT SNC*						
Not	19 (8,5-29,4)		1	47 (24,1-69,8)	0,26	-
Yes	11 (2,9-19)	0,716	-	20 (0-43)		
MT Visceral*						
Not	-		1	38 (16,1-59,8)		-
Yes	11(8,5-13,4)	0,004	0,32 (0,14-0,73)	47 (23,7-70,2)	0,53	
Luminal						
Not	20 (16-23,9)		1	38 (17,5-58,4)		-
Yes	11 (8,2-13,7)	0,082	-	47 (18-75,9)	0,76	
HER2						
++	8 (0,0-17,8)		1	6 (0-20,4)		-
+++	17 (10,9-23,0)	0,041	2,5 (0,9-6,7)	47 (30,5-63,4)	0,1	
RCp						
Not	13 (6,7-19,2)		1	47 (24,8-69,17)		-
Yes	-	0,178	-	-	0,76	

Pertuzumab						
Prior						
Not	11(2,5-19,4)		1	74 (35,5-112,4)		-
Yes	17(7,5-22,4)	0,692	-	47 (24,3-69,6)	0,15	
TDM1 lines						
1	19 (8,5-29,4)		1	47 (25,8-68,1)		-
2 ou +	11 (2,9-19,0)	0,009	0,3 (0,19-0,83)	74 (17-130,9)	0,96	
EA seriously						
Not	13 (8,1-17,8)	,309	1	53 (29,7-76,2)		
Yes	20 (5,7-34,2)		-	19 (10,1-27,8)	0,00	0,359

Table 3 – Univariate analysis of PFS and OS of all patients who received T-DM1

* MT CNS: metastasis in the central nervous system before the use of T-DM1

* Visceral MT: visceral metastasis before the use of T-DM1

	SLP		**SG**	
Characteristics	HR (95%IC)	Value p	HR (95%IC)	Value p
Menopause				
Not	-	-	1	
Yes			3,0 (0,874-10,7)	0,08
HER2				
++	1		-	-
+++	3,0 (1,1-8,0)	0,026		
MT Visceral				
Yes	1		-	-
Not	0,30(0,134-0,696)	0,005		
ECGOG				
1	1		1	
2	0,069 (0,55-0,522)	0,002	0,059 (0,015-0,232)	0,000
Prior Pertuzumab				
Not	-	-	1	
Yes			0,26 (0,07-0,89)	0,032
EA Serious				
Not	-	-	1	
Yes			0,17 (0,07-0,41)	0,000

Table 4 – Multivariate analysis of PFS and OS of all patients who received T-DM1 – Variables with significance

Comorbidities			
	Group 1	Group 2	Group 3
Not	7	3	7
Yes	14	2	5
Comorbidity was not a statistically significant factor.			
Menopause			
	Group 1	Group 2	Group 3
Not	16	3	10
Yes	5	2	2
Menopause was not a statistically significant factor.			
ECOG			
	Group 1	Group 2	Group 3
0 and 1	8	5	7

2	13	0	5
Lower ECOG was a significant factor by the chi-square test, with a significance of 0.04			
Tumor Size			
	Group 1	Group 2	Group 3
T1 and T2	7	5	8
T3 and T4	8	0	4
Tumor size was not a statistically significant factor			
N+			
	Group 1	Group 2	Group 3
Not	3	1	3
Yes	11	4	9
Lymph node involvement was not a statistically significant factor			
Metastasis			
	Group 1	Group 2	Group 3
Not	11	4	8
Yes	10	1	4
Metastasis was not a factor with statistical significance			
CNS metastasis			
	Group 1	Group 2	Group 3
Not	10	5	5
Yes	11	0	7
CNS metastasis was not a statistically significant factor			
Visceral metastasis			
	Group 1	Group 2	Group 3
Not	2	2	6
Yes	19	3	6
Visceral metastasis was significantly favored by the chi-square test, with a significance of 0.030			
Luminal			
	Group 1	Group 2	Group 3
Not	6	1	3
Yes	15	4	9
Luminal component was not a factor with statistical significance			
HER2			
	Group 1	Group 2	Group 3
++	0	0	4
+++	21	5	8
HER2 +++ was a significant favor by the chi-square test, with a significance of 0.008			
Prior pertuzumab			
	Group 1	Group 2	Group 3
Not	5	0	3
Yes	16	5	9
Previous use of pertuzumab was not a statistically significant factor			

Table 10 – Characteristics of patients who received treatment subsequent to T-DM1

TREATMENT FAILURE TIME

The time to treatment failure (TFT) of patients who received T-DM1 was 10 months, with a range of 5.6 to 14.3 months. Figure 2.

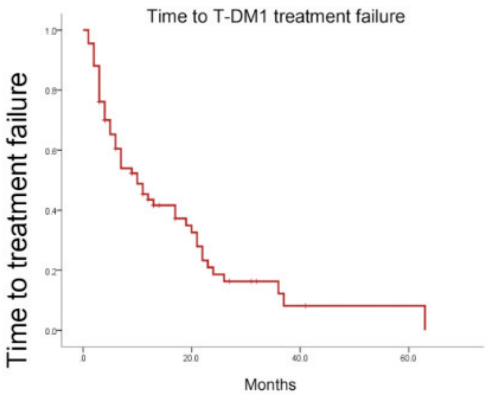

Figure 2

TIME FROM METASTASIS TO ONSET OF T-DM1 (TIME BETWEEN DIAGNOSIS OF METASTATIC DISEASE AND ONSET OF TDM1)

The median time from metastasis to the onset of T-DM1 was 17 months (12.5-21.4).

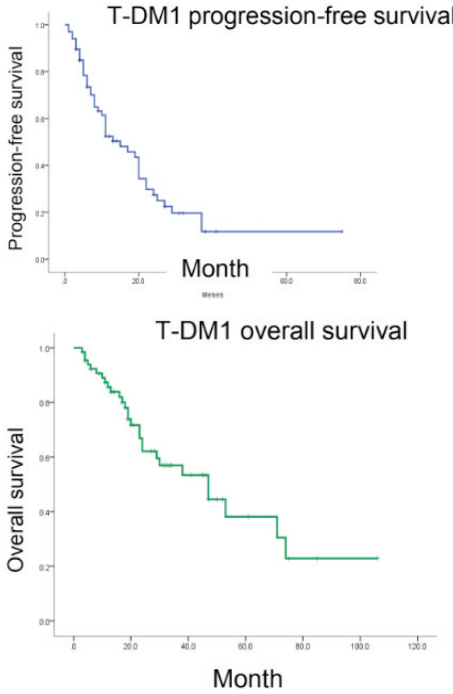

Figure 3

T-DM1 ADVERSE EVENTS

Of the 67 patients who received T-DM1: 17 (25.4%) had a serious adverse event, 15 (22.3%) had to postpone treatment due to toxicity, 17 (25.4%) had T-DM1 suspended due to limiting toxicity and 5 (7.5%) required dose reduction due to toxicity. A serious adverse event was defined as any unfavorable occurrence since the start of treatment with T-DM1 that resulted in one of the following: death; life-threatening condition; hospitalization ≥ 24 hours or prolonged hospitalization. Adverse events described in table 5.

Adverse events to TDM1	
EA seriously*	
Not	50 (74,6%)
Yes	17 (25,4%)
Postponement due to toxicity	
Not	52 (77,6%)
Yes	15 (22,3%)
Suspension due to toxicity	
Not	50 (74,6%)
Yes	17 (25,4%)
Dose reduction due to toxicity	
Not	62 (92,5%)
Yes	05 (7,5%)

Table 5 – Adverse Events to T-DM1

* **serious adverse event** was defined as any unfavorable occurrence since the start of treatment with T-DM1 that resulted in one of the following: death; life-threatening condition; hospitalization ≥ 24 hours or prolonged hospitalization.

POPULATION THAT RECEIVED TREATMENT SUBSEQUENT TO T-DM1

Of the 67 patients included in this study, 38 patients received treatment subsequent to TDM 1, with a median follow-up time of 21 months (11.5-30.4). The characteristics of this population are detailed in table 9. Previous treatments for this subpopulation are described in table 7.

CHARACTERISTICS OF THE POPULATION THAT RECEIVED TREATMENT SUBSEQUENT TO T-DM1

Table 6 shows the characteristics of the population that received treatment subsequent to T-DM1.

Lines after T-DM1	
Median age at diagnosis	46 years old (28-64)
Median age at metastasis	49.5 years (29-66)
Gender	
Masculine	0
Feminine	38
Comorbidity	
Not	17 (44,7%)
Yes	21 (55,3%)
Menopause	
Not	29 (76,3%)
Yes	09 (23,7%)
Size	
1	04 (10,5%)
2	16 (42,1%)
3	06 (15,8%)
4	06 (15,8%)
Missing	06 (15,8%)
N+	
Not	07 (18,4%)
Yes	24 (63,2%)
Metastasis	
Not	23 (60,5%)
Yes	15 (39,5%)
Luminal	
Not	10 (26,3%)
Yes	28 (73,7%)
HER2	
++	04 (10,5%)
+++	34 (89,5%)

Table 6 – Characteristics – Treatment lines subsequent to T-DM1

PREVIOUS TREATMENTS IN THE POPULATION THAT RECEIVED TREATMENT SUBSEQUENT TO T-DM1

In the population that received treatment subsequent to T-DM1: 15 (39.5%) received neoadjuvant treatment, with 3 (7.9%) showing a complete response after neoadjuvant treatment and 16 (42.1%) receiving adjuvant treatment. All patients had previously received taxane and herceptin and 30 (78.9%) had previously received pertuzumab. Table 7.

Previous Treatments	
Neoadjuvance	
Not	23 (60,5%)
Yes	15 (39,5%)
Adjuvance	
Not	22 (57,9%)
Yes	16 (42,1%)
Complete response after neoadjuvant treatment	
Not	35 (92,1%)
Yes	03 (7,9 %)
Prior taxane	
Not	0
Yes	38 (100%)
Prior pertuzumab	
Not	08 (21,1%)
Yes	30 (78,9%)
Prior Herceptin	
Not	0
Yes	38 (100%)

Table 7 – Treatments prior to T-DM1

CLINICAL EVOLUTION OF THE POPULATION AFTER T-DM1 – BEFORE STARTING SUBSEQUENT TREATMENT

Prior to subsequent treatment for T-DM1, 47% of patients had CNS metastasis, 73% visceral metastasis, 47% were ECOG 2. Table 8.

Clinical Evolution after T-DM1	
CNS metastasis after T-DM1	
Not	10 (26,3%)
Yes	18 (47,4%)
Visceral metastasis after T-DM1	
Not	10 (26,3%)
Yes	28 (73,7%)
ECOG after TDM1	
0 and 1	20 (52,6%)
2	18 (47,3%)
ECOG after Treatment Subsequent to T-DM1	
0 and 1	20 (52,6%)
2	18 (47,3%)

Table 8 – Clinical evolution after T-DM1

SUBGROUP ANALYSIS

Patients were divided into three groups, according to the treatment received, being GROUP 1: lapatinib + capecitabine; GROUP 2: trastuzumab-deruxtecan; GROUP 3: anti-HER2 ± chemotherapy/endocrine therapy. Table 9.

Post-T-DM1 treatment	
GROUP 1: Lapatinib + Capecitabine	21 (55,3%)
GROUP 2: Trastuzumab-deruxtecan	05 (13,2%)
GROUP 3: anti-HER2 ± chemotherapy/endocrine therapy	12 (31,6%)

Table 9 – Subsequent treatments – subgroups evaluated

In GROUP 3, patients received a combination of the following agents:

- trastuzumab + abemaciclib;
- trastuzumab + carboplatin + gemzar;
- trastuzumab + cisplatin + gemzar;
- trastuzumab + pertuzumab + aromasin;
- trastuzumab + taxol;
- trastuzumab + pertuzumab;
- trastuzumab + pertuzumab + taxol;
- trastuzumab + lapatinib;
- trastuzumab + capecitabine;
- lapatinib + fulvestrant;
- lapatinib + exemestane.

CHARACTERISTICS OF PATIENTS WHO RECEIVED SUBSEQUENT T-DM1 TREATMENT

The characteristics are shown in table 10. ECOG 0 and 1, HER2 +++ and absence of visceral metastasis were factors with statistical significance.

OUTCOMES – SUBGROUP ANALYSIS

RESPONSE TO TREATMENT ACCORDING TO SUBGROUP

Comparing the clinical response between the subgroups, in GROUP 1 there was 1 complete response, 3 partial responses, 16 patients with stable disease and 1 patient with progression at the first reevaluation. Totaling 19% response. In GROUP 2 there was no complete response, 3 patients had a partial response and 2 patients had stable disease. Totaling 60% response. In GROUP 3 there was no complete response or partial response, 11 patients had stable disease as their best response and 1 progressed on the first reevaluation. There was no response, just disease control. Tables 11 and 12. Figure 5.

Response			
	Group 1	Group 2	Group 3
Complete	1	0	0
Partial	3	3	0
Stable disease	16	2	11
Progression	1	0	1

Table 11 – Response to subsequent treatment

No statistical significance

Response to Subsequent Treatment			
	Group 1	Group 2	Group 3
Not	17	2	12
Yes	4	3	0

Table 12 – Best response to treatment subsequent to T-DM1

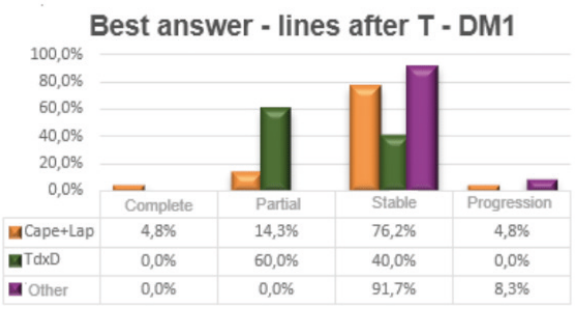

Figure 5.

PROGRESSION-FREE SURVIVAL

The median progression-free survival for patients receiving treatment subsequent to T-DM1 was 12 months (4.2-19.7). Table 13. Graph shown in figure 6.

In group 1 the median PFS was 6 months (1.7-10.2), in group 2 there was no disease progression and in group 3 the median PFS was 13 months (11.6-14.4). Table 13.

Median SLP		
Group 1	**Group 2**	**Group 3**
6 months (1.7-10.2)	There was no progression or deaths	13 months (11.6-14.4)

Table 13 – Median SLP – Subgroup Analysis

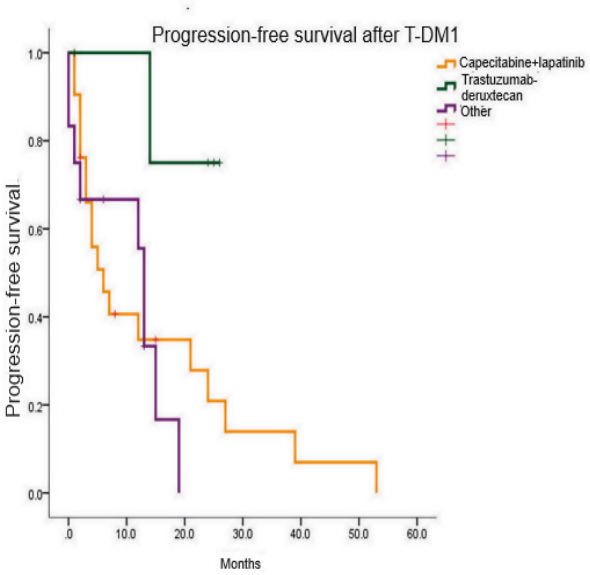

Figure 6

OVERALL SURVIVAL

The median overall survival was 47 months (23.9-70). In the subgroup analysis, there were no deaths in GROUP 2.

The OS was not reached, since in the three groups there were patients who had not yet died.

In group 1 there were 13 deaths (61%), in group 2 there were no deaths and in group 3 there were 4 deaths (33%). Figure 7.

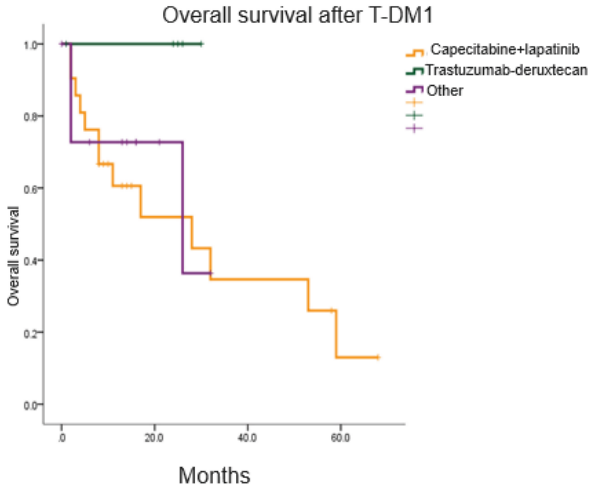

Figure 7

ADVERSE EVENTS ACCORDING TO SUBGROUP

In GROUP 1 there were 6 serious AEs (28.6%), in GROUP 2 there were no serious AEs and in GROUP 3 there were 3 serious AEs (25%).

In GROUP 1, 4 patients (19%) needed to postpone treatment due to limiting toxicity, in GROUP 2, 1 patient (20%), in GROUP 3, 3 patients (25%).

Suspension of treatment was necessary in 6 patients in GROUP 1 (28.6%), there was no suspension of treatment in GROUP 2 and in group 3, 2 patients (16.7%). Table 14.

Serious Adverse Event			
	Group 1	Group 2	Group 3
Not	15	5	9
Yes	6	0	3
Postponement due to toxicity			
	Group 1	Group 2	Group 3
Not	17	4	9
Yes	4	1	3
Suspension due to toxicity			
	Group 1	Group 2	Group 3
Not	15	5	10
Yes	6	0	2
Dose reduction due to toxicity			
	Group 1	Group 2	Group 3
Not	21	4	12
Yes	0	1	0

Table 14 – AE - Patients who received treatment subsequent to T-DM1

DISCUSSION

Based on the therapeutic options available in Brazil, for patients who progressed after previous use of taxane and trastuzumab, the treatment of choice was based on the EMILIA study, with the use of T-DM1. However, in June 2022, the treatment of choice in this scenario became T-Dxd with the DESTINY-BREAST03 study, which demonstrated greater overall survival, progression-free survival and greater objective response.

Treatment of HER2-positive metastatic breast cancer in later lines is challenging. As already mentioned in the introduction, there are several studies and therapeutic options, which must be interpreted according to the previous treatments used (anti her2 antibody (trastuzumab/pertuzumab/lapatinib), chemotherapy and conjugated antibody (T-DM1/T-Dxd).

Analyzing all patients in this study who received T-DM1 compared to the EMILIA study, the population characteristics were similar in terms of population age, performance status and percentage of visceral metastases.

The response rate was quite divergent, being 10% in this study and 40% in the EMILIA study. OS was higher despite the lower response rate 47 (24-69) months versus 29 (36-34) months, PFS was also higher in this study 15 months versus 9.6 months. Occurrence of serious adverse event was 25% versus 40%. Table 15.

This difference could possibly be attributed to a population profile with a more aggressive tumor. In the present study, 78.9% received pertuzumab prior to the use of T-DM1. Firstly, we attribute this to a population with a higher initial risk and secondly, a greater selection of tumor clones with resistance, as they were subjected to double HER2 blockade (trastuzumab + pertuzumab) unlike the EMILIA study whose selection criterion was previous use of trastuzumab and taxane.

	TCC (all T-DM1)	**EMILIA Study**
Population		
Age	49 years old (28-64)	53 years old (25-84)
ECOG 0 and 1	92,5%	99%
Visceral metastasis	65%	67%
Answer rate (complete or partial)	10%	43%
SG	47 months (24-69)	29 months (26-34)
SLP	15 months (8-21)	9.6 months
EA seriously	25,4%	40%
Dose reduction	7,5%	16,3%

Table 15 - CBT versus Emília Study

The time to treatment failure (TFT) of patients who received T-DM1 was 10 months, range 5.6 to 14.3 months.

In the multivariate analysis of PFS, there were 3 variables with statistical significance, namely: absence of visceral metastasis, her-2 +++ in immunohistochemistry, and ECOG <2. These characteristics were associated with higher PFS.

In the multivariate analysis of OS,

there were 4 variables with statistical significance, namely: ECOG <2, HER2 +++ in immunohistochemistry, absence of adverse effects, absence of use of pertuzumab. These characteristics were associated with higher OS.

Patients in better clinical conditions (absence of visceral metastasis and ECOG <2) showed a better response to T-DM1, possibly due to better tolerance to treatment.

The higher the expression of HER2 in immunohistochemistry, the greater the effectiveness of T-DM1, as expected due to its mechanism of action.

The association of lower OS in patients who used pertuzumab corroborates the article published by Ethier J-L et. Al. Suggesting that the population that received pertuzumab had more aggressive disease.

In the subgroup analysis, the main point of this work, where the primary outcome was evaluated, the line subsequent to T-DM1 with the highest response rate was the group that received trastuzumab-deruxtecan, with 60% (3 patients with partial response and 2 patients with stable disease) which proved to be a promising drug despite the limited number of patients evaluated, with a response rate much higher than that of the other groups. The use of lapatinib associated with capecitabine also proved to be an option for subsequent treatment of T-DM1 in the unavailability of T-Dxd, with a response rate of 19%. In the group that received chemotherapy associated with trastuzumab, there was only disease control.

In the PFS analysis, there was no disease progression in the group that used T-Dxd, once again showing its greater effectiveness. In the Lapatinib group associated with capecitabine the median PFS was 6 months, with an interval between 1.7 and 10.2 months and in GROUP 3 the median was 13 months, with an interval between 11.6 and 14.3 months.

Regarding OS in the group that received T-Dxd there were no deaths, and it was not possible to perform a statistical analysis of overall survival (OS) with the other groups. The absence of death after T-Dxd was attributed to the short follow-up period, which varied from 1 month to 26 months. In this group there were also no serious AEs. However, 1 patient (20%) needed to postpone treatment, there was no suspension of treatment in any patient in this group.

The group that received lapatinib and capecitabine was the largest represented due to it being the therapy with the greatest evidence of benefit in the subsequent line up to the start date of this study and greater ease of access. Follow-up was between 2 months and 68 months, with 12 deaths out of a total of 21 patients. In this group there were 6 serious AEs (28.6%), 4 patients (19%) needed to postpone treatment due to limiting toxicity. Treatment suspension was necessary in 6 patients (28.6%).

The group that received chemotherapy and trastuzumab involved a heterogeneous number of cases due to a small representative number of patients receiving the same treatment who could be compared in a separate group. The characteristic of anti-her2 therapy/chemotherapy was maintained, excluding deruxtecan and/or the combination of lapatinib with capecitabine. In this group, 12 patients were evaluated, with a follow-up period of 2 months to 32 months, with 4 deaths in the analyzed period, there were 3 serious AEs (25%), 3 patients (25%) needed to postpone treatment, 8 patients (16, 7%) had treatment suspended. The group that received lapatinib had a worse toxicity profile, probably due to the difference in the mechanism of action, as lapatinib is a dual tyrosine kinase inhibitor targeting EGFR and HER2, while trastuzumab targets only HER2.

The result was numerically superior with

the use of trastuzumab-deruxtecan (T-Dxd), with a better toxicity profile. As already defined by phase 3 study, DESTINY-BREAST01. The response rate of this study was the same as that demonstrated in the DESTINY-BREAST01 study, being 60%.

The group that received lapatinib associated with capecitabine showed a response rate, while group 3 only had disease control. The toxicity profile was similar between the two, being between 20 and 30%.

Repeat chemotherapy with *trastuzumab versus* exposure to a new agent (lapatinib) favored the tyrosine kinase inhibitor in this sample.

In the analysis of all patients who received T-DM1, the response rate was only 10% and almost 40% controlled disease. This shows a very significant action of T-Dxd, which in a subsequent line showed a response rate of 60%, as well as a significant action of lapatinib associated with capecitabine with a response rate of 19%;

Furthermore, T-Dxd, even in a subsequent line, presented a better toxicity profile compared to T-DM1. The toxicity of T-DM1, lapatinib + capecitabine and trastuzumab + chemotherapy was similar, ranging from 20 to 30%.

The limitations of the study were that it was retrospective, therefore generating hypotheses.

T-Dxd was shown to be superior even to T-DM1 in the DESTINY-BREAST03 study, being the standard treatment in the 2nd line in Brazil since July 2022 (date after the start of this study).

Strengths infer outcomes from useful treatment options when T-Dxd is not accessible. In the absence of T-Dxd, lapatinib and capecitabine was superior to continuing chemotherapy and trastuzumab, and can be taken into consideration in situations without access to T-Dxd.

CONCLUSION

In this unicentric analysis, the result tends to infer greater benefit for the use of trastuzumab-deruxtecan in the subsequent treatment of T-DM1, with a better toxicity profile.

The use of lapatinib + capecitabine showed a response rate, while subgroup 3 only had disease control. However, no significance in relation to PFS. The toxicity profile of the 2 subgroups was similar, being less than 30%.

Therefore, the treatment preference in progressions after T-DM1 falls on T-Dxd. This treatment sequence has been undergoing modifications, due to the superior results of T-Dxd and even in earlier lines, showing that the sequence of treatment for HER2 positive tumors is under construction and continues to evolve. New agents have been developed, contributing to this line of sequencing.

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