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APOIO



GERENCIAMENTO E PRODUÇÃO



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# HER2CLIMB-02: Primary Analysis of a Randomized, Double-blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-positive Metastatic Breast Cancer

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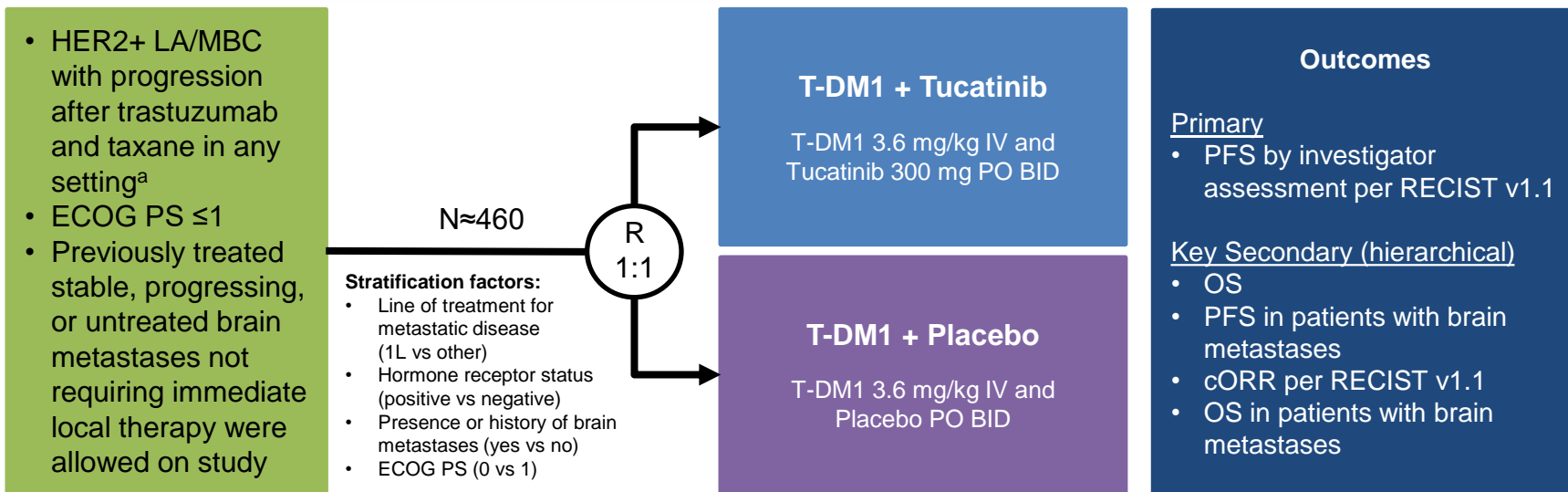
# Background

- Tucatinib is a highly selective HER2-directed TKI<sup>1</sup> indicated for patients with previously treated HER2+ LA/MBC, including patients with brain metastases<sup>2-6</sup>
- In HER2CLIMB, adding tucatinib to trastuzumab and capecitabine demonstrated HRs for PFS, OS, and PFS in patients with brain metastases of 0.54, 0.66, and 0.48 ( $P \leq 0.005$  for all), respectively<sup>3</sup>
- The incidence of brain metastases in patients with HER2+ LA/MBC remains high<sup>7-9</sup>; combining HER2-directed therapies can improve patient outcomes in HER2+ LA/MBC<sup>10,11</sup>
- T-DM1 is a HER2-directed ADC approved for patients with HER2+ LA/MBC previously treated with trastuzumab and a taxane<sup>12</sup>
- Preclinical data have shown that the combination of tucatinib and T-DM1 results in enhanced antitumor activity compared with either agent alone<sup>13</sup>
- In a phase 1b/2 study, the combination of tucatinib and T-DM1 demonstrated encouraging antitumor activity, including intracranial responses, with a manageable safety profile<sup>14</sup>

ADC, antibody-drug conjugate; HRs, hazard ratios; LA/MBC, locally advanced or metastatic breast cancer; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor.

1. Kulukian A et al. *Mol Cancer Ther*. 2020;19:976-87. 2. TUKYSA. Prescribing Information. Seagen Inc. Jan 2023. Accessed Oct 4, 2023. 3. Murthy RK et al. *N Engl J Med*. 2020;382:597-609. 4. Lin NU et al. *J Clin Oncol*. 2020;38:2610-9. 5. Curigliano G et al. *Ann Oncol*. 2022;33:321-9. 6. Lin NU et al. *JAMA Oncol*. 2023;9:197-205. 7. Clayton AJ et al. *Br J Cancer*. 2004;91:639-43. 8. Lin NU. *Lancet Oncol*. 2013;14:185-6. 9. Pestalozzi BC et al. *Lancet Oncol*. 2013;14:244-8. 10. Baselga J et al. *N Engl J Med*. 2012;366:109-19. 11. Baselga J et al. *Lancet*. 2012;379:633-40. 12. KADCYLA. Prescribing Information. Genentech Inc. Feb 2022. Accessed Oct 4, 2023. 13. Olson D et al. *Cancer Res Commun*. 2023;3:1927-39. 14. Borges VF et al. *JAMA Oncol*. 2018;4:1214-20.

# HER2CLIMB-02 Study Design



The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05. The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive.<sup>b</sup>

NCT03975647. <https://www.clinicaltrials.gov/study/NCT03975647>. Accessed Oct 5, 2023.

<sup>a</sup> Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were not eligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.

<sup>b</sup> Subsequent OS analyses are planned upon 80% and 100% of required events for the final OS analysis.

1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PO, orally; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors.

Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.

# Demographics and Baseline Characteristics

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
<b>Median age, years (range)</b>	55.0 (26-83)	53.0 (27-82)
<b>Female sex, n (%)</b>	226 (99.1)	235 (100)
<b>Geographic region, n (%)</b>		
North America	105 (46.1)	93 (39.6)
Europe/Israel	53 (23.2)	77 (32.8)
Asia-Pacific	70 (30.7)	65 (27.7)
<b>Hormone-receptor status, n (%)</b>		
Positive	137 (60.1)	140 (59.6)
Negative	91 (39.9)	95 (40.4)
<b>ECOG performance status score, n (%)</b>		
0	137 (60.1)	141 (60.0)
1	91 (39.9)	94 (40.0)

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
<b>Presence or history of brain metastases, n (%)</b>		
Yes	99 (43.4)	105 (44.7)
Active	50 (21.9)	57 (24.3)
Treated stable	49 (21.5)	48 (20.4)
No <sup>a</sup>	129 (56.6)	130 (55.3)
<b>Stage at initial diagnosis, n (%)<sup>b</sup></b>		
0-III	120 (52.6)	130 (55.3)
IV	103 (45.2)	98 (41.7)

<sup>a</sup> Includes 2 patients with missing brain metastases data.

<sup>b</sup> Five patients in T-DM1 + Tucatinib arm and 7 patients in T-DM1 + Placebo arm had unknown stage.

ECOG, Eastern Cooperative Oncology Group; T-DM1, trastuzumab emtansine.

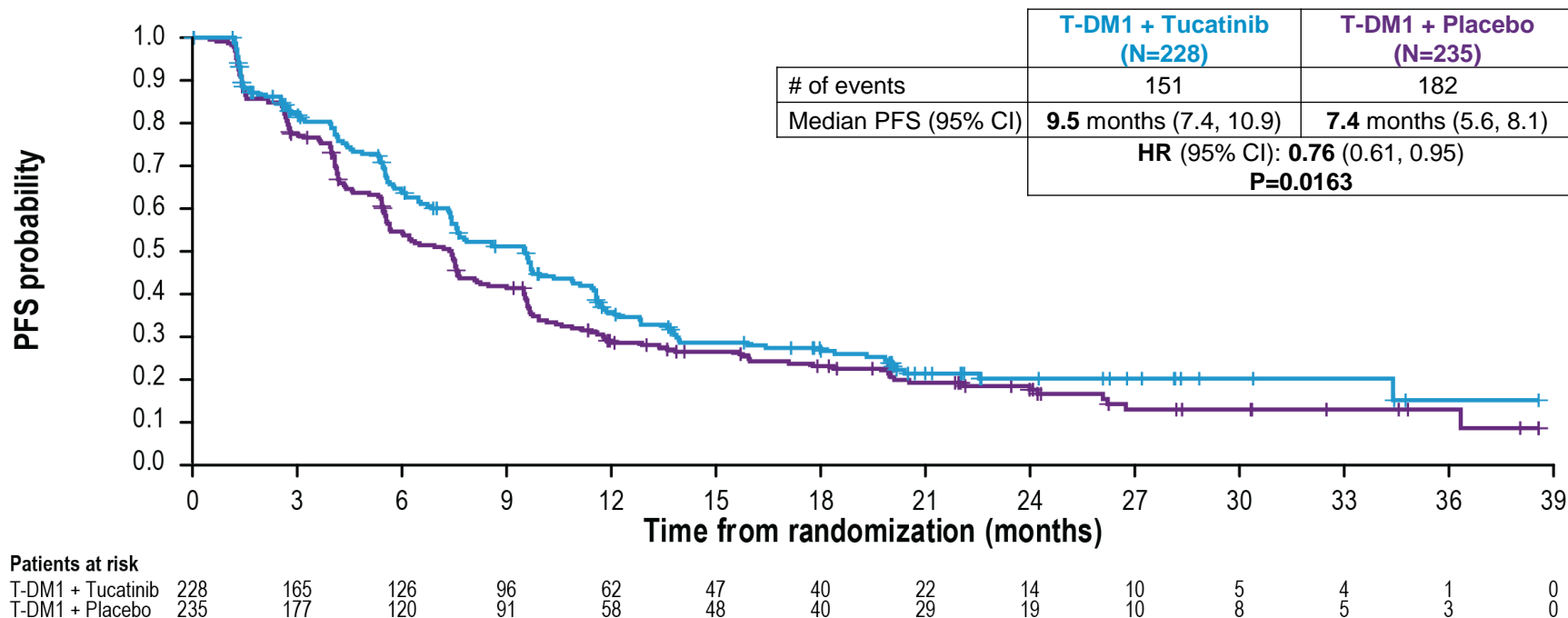
Date of data cutoff: Jun 29, 2023.

# Prior Systemic Therapies

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
<b>Median prior lines of systemic therapy in metastatic setting (range)</b>	1 (0-8)	1 (0-6)
<b>Prior lines of systemic therapy in metastatic setting, n (%)</b>		
0	29 (12.7)	33 (14.0)
1	146 (64.0)	150 (63.8)
2	36 (15.8)	31 (13.2)
≥3	17 (7.5)	21 (8.9)
<b>Received prior pertuzumab treatment, n (%)</b>	202 (88.6)	214 (91.1)
<b>Received prior anti-HER2 TKIs, n (%)</b>	3 (1.3)	5 (2.1)

T-DM1, trastuzumab emtansine.  
Date of data cutoff: Jun 29, 2023.

# Progression-Free Survival

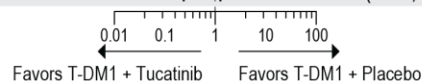


HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.  
Date of data cutoff: Jun 29, 2023.

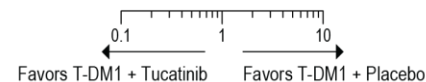


# PFS in Prespecified Subgroups

	T-DM1 + Tucatinib (N=228) Events/N	T-DM1 + Placebo (N=235) Events/N		Hazard Ratio with 95% CI
ITT Analysis	151/228	182/235		0.76 (0.61, 0.95)
Baseline brain metastasis				
Yes	70/99	85/105		0.64 (0.46, 0.89)
No	80/127	97/130		0.88 (0.65, 1.19)
Line of treatment for metastatic disease				
First	16/26	21/28		0.51 (0.23, 1.12)
Other	135/202	161/207		0.79 (0.63, 1.00)
ECOG performance status				
0	86/137	109/141		0.66 (0.49, 0.89)
1	65/91	73/94		0.91 (0.65, 1.28)
Hormone receptor status				
Positive	85/137	107/140		0.75 (0.56, 1.01)
Negative	66/91	75/95		0.82 (0.58, 1.15)
Region				
North America	68/105	69/93		0.88 (0.62, 1.26)
Europe/Israel	36/53	57/77		0.75 (0.46, 1.20)
Asia-Pacific	47/70	56/65		0.74 (0.49, 1.12)

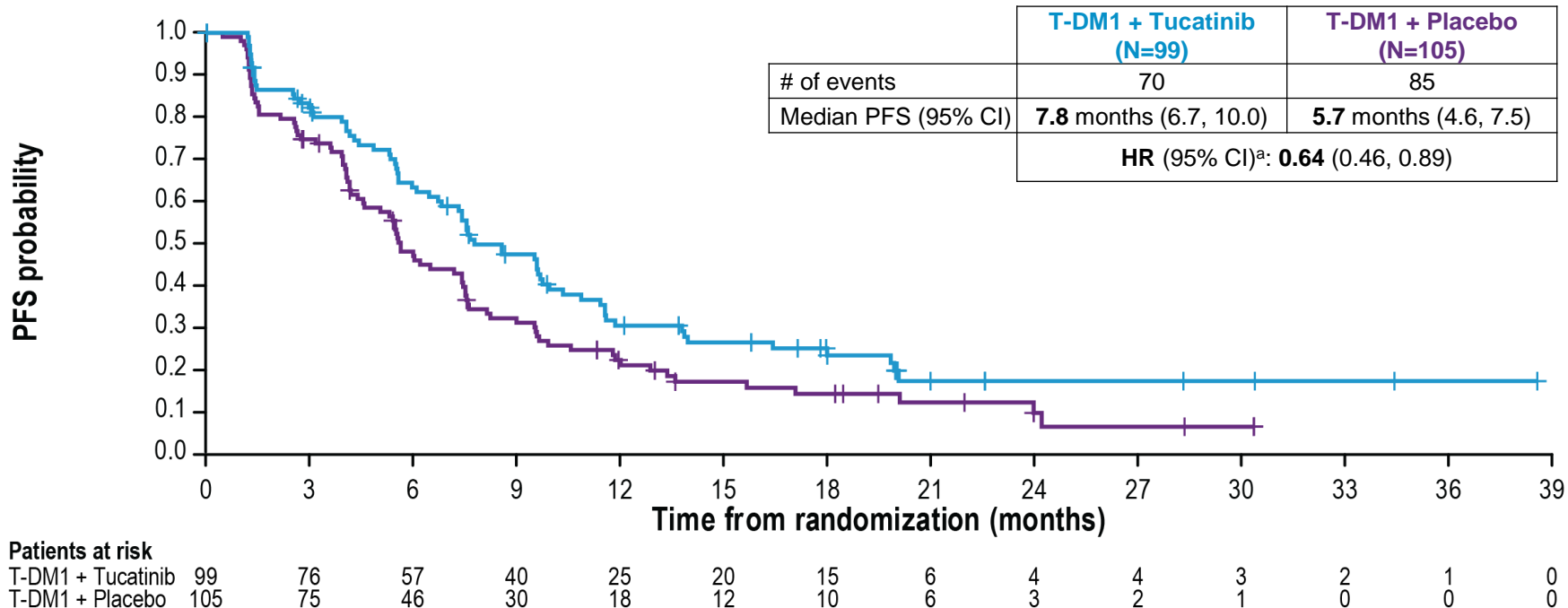


	T-DM1 + Tucatinib (N=228) Events/N	T-DM1 + Placebo (N=235) Events/N		Hazard Ratio with 95% CI
Age				
<65 years	126/186	155/201		0.80 (0.62, 1.02)
≥65 years	25/42	27/34		0.61 (0.33, 1.11)
Race				
White	68/101	76/102		0.79 (0.55, 1.13)
Asian	45/66	58/65		0.73 (0.49, 1.11)
Others	38/61	48/68		0.79 (0.48, 1.28)
Initial diagnosis				
0-III	81/120	100/130		0.72 (0.53, 0.99)
IV	67/103	79/98		0.77 (0.55, 1.08)
Prior pertuzumab				
Yes	137/203	166/214		0.78 (0.62, 0.99)
No	14/25	16/21		0.74 (0.29, 1.87)



ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PFS, progression-free survival; T-DM1, trastuzumab emtansine.  
Date of data cutoff: Jun 29, 2023.

# PFS in Patients with Brain Metastases

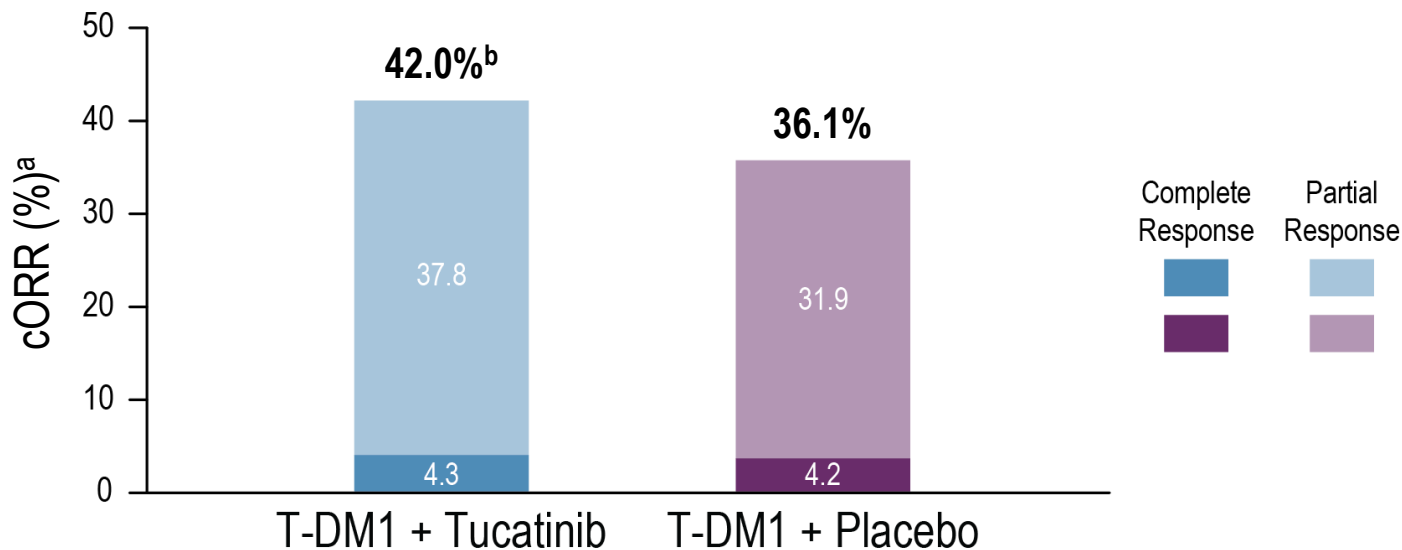


<sup>a</sup> The outcome was not formally tested.

HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.

Date of data cutoff: Jun 29, 2023.

# Confirmed Objective Response Rate



<sup>a</sup> The outcome was not formally tested. Only patients with measurable disease were included in the analysis (N=188 for T-DM1 + Tucatinib arm and N=191 for T-DM1 + Placebo arm).

<sup>b</sup> Percentages for complete and partial response do not add up to the cORR due to rounding.

cORR, confirmed objective response rate; T-DM1, trastuzumab emtansine.

Date of data cutoff: Jun 29, 2023.

# Subsequent Systemic Therapies

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
<b>Patients who have discontinued or never received study treatment, n (%)</b>	188 (82.5)	206 (87.7)
Patients who received ≥1 subsequent anticancer systemic therapy, n (%) <sup>a</sup>	150 (79.8)	168 (81.6)
<b>Median subsequent lines of therapies (range)</b>	2.0 (1-13)	2.0 (1-15)
<b>Subsequent therapies, n (%)<sup>a</sup></b>		
T-DXd	93 (49.5)	101 (49.0)
Chemotherapy <sup>b</sup>	76 (40.4)	81 (39.3)
Trastuzumab	60 (31.9)	51 (24.8)
Tucatinib	29 (15.4)	28 (13.6)
T-DM1	25 (13.3)	22 (10.7)

<sup>a</sup> Percentages were calculated using 188 or 206 (patients who have discontinued or never received study treatment) as denominators for T-DM1 + Tucatinib and T-DM1 + Placebo arms, respectively.

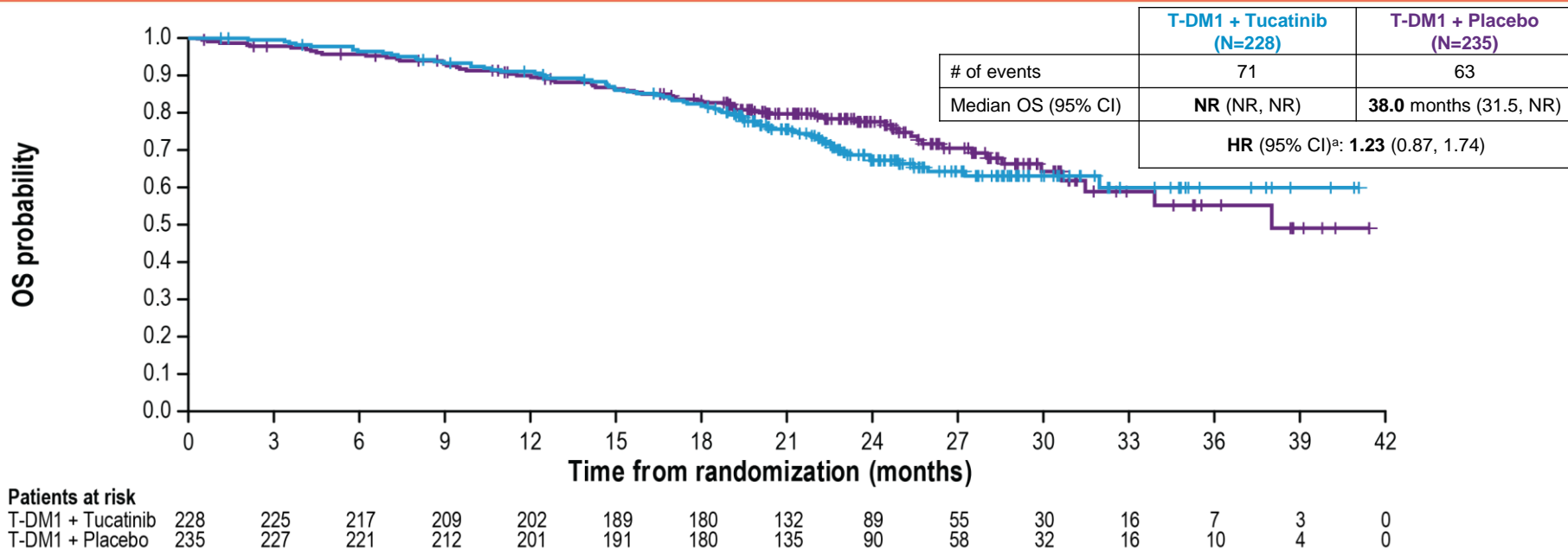
<sup>b</sup> Includes capecitabine, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, epirubicin, eribulin, fluorouracil, gemcitabine, methotrexate, nab-paclitaxel, paclitaxel, tegafur-gimeracil-oteracil potassium, topoisomerase I inhibitor, and vinorelbine.

These regimens may have been given in combination with HER2-directed therapy, and only a proportion of patients received chemotherapy alone.

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Date of data cutoff: Jun 29, 2023.

# Overall Survival



Median follow-up was 24.4 months. As of data cutoff, 134 out of 253 (53%) prespecified events for the OS final analysis were observed. Interim OS results did not meet the prespecified crossing boundary of  $P \leq 0.0041$ .

<sup>a</sup> The proportional hazard assumption was not maintained post-18 months, with extensive censoring on both arms. HR, hazard ratio; NR, not reached; OS, overall survival; T-DM1, trastuzumab emtansine. Date of data cutoff: Jun 29, 2023.

# Overall Safety Summary

	T-DM1 + Tucatinib (N=231) n (%)	T-DM1 + Placebo (N=233) n (%)
<b>Any TEAE</b>	230 (99.6)	233 (100)
<b>Grade <math>\geq</math>3 TEAE</b>	159 (68.8)	96 (41.2)
<b>Any TESAE</b>	70 (30.3)	52 (22.3)
<b>TEAE leading to death</b>	3 (1.3)	2 (0.9)
<b>Discontinued tucatinib or placebo due to TEAE</b>	40 (17.3)	16 (6.9)
<b>Discontinued T-DM1 due to TEAE</b>	47 (20.3)	26 (11.2)

Median duration of tucatinib or placebo treatment: 7.4 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo  
 Median duration of T-DM1 treatment: 7.5 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo

**Most common TEAEs ( $\geq$ 2%) leading to tucatinib or placebo discontinuation (T-DM1 + Tucatinib vs T-DM1 + Placebo):**

- ALT increased (2.6% vs 0%)

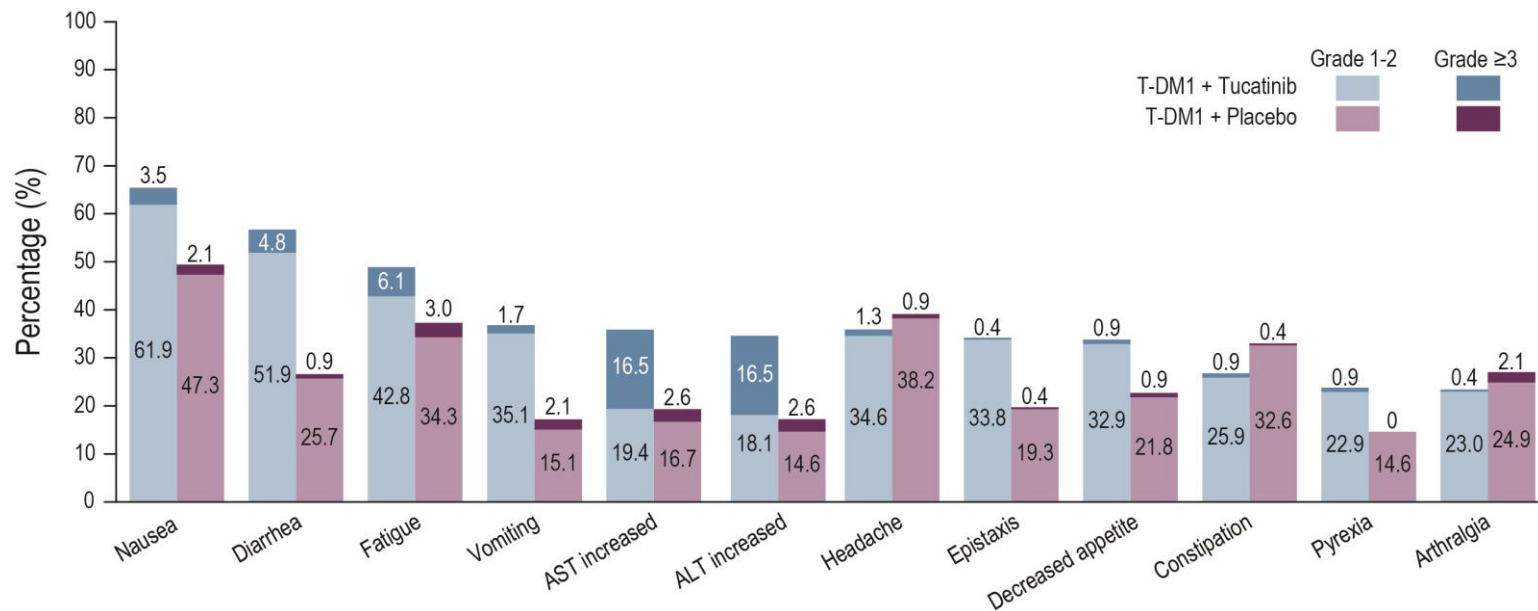
**Most common TEAEs ( $\geq$ 2%) leading to T-DM1 discontinuation (T-DM1 + Tucatinib vs T-DM1 + Placebo):**

- ALT increased (2.2% vs 0%)
- Thrombocytopenia (2.2% vs 0%)
- Interstitial lung disease (0% vs 2.1%)

ALT, alanine aminotransferase; T-DM1, trastuzumab emtansine; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Date of data cutoff: Jun 29, 2023.

# Most Common TEAEs ( $\geq 20\%$ )



**Most common ( $\geq 5\%$ ) grade  $\geq 3$  TEAEs (T-DM1 + Tucatinib vs T-DM1 + Placebo):** ALT increased (16.5% vs 2.6%), AST increased (16.5% vs 2.6%), anemia (8.2% vs 4.7%), thrombocytopenia (7.4% vs 2.1%), and fatigue (6.1% vs 3.0%)

TEAEs occurring in  $\geq 20\%$  of patients in T-DM1 + Tucatinib arm are shown.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-DM1, trastuzumab emtansine; TEAEs, treatment-emergent adverse events.

Date of data cutoff: Jun 29, 2023.

# Adverse Events of Interest

## • Hepatic TEAEs

- Grade  $\geq 3$  hepatic TEAEs<sup>a</sup> greater in T-DM1 + Tucatinib arm (28.6% vs 7.3%), primarily due to AST/ALT elevations
- No Hy's law cases were identified
- 85% of all-grade hepatic TEAEs in T-DM1 + Tucatinib arm resolved or returned to grade 1, with median of 22 days to resolution<sup>b</sup>

### Dose Modifications Due to Hepatic TEAEs

	T-DM1 + Tucatinib (N=231) n (%)	T-DM1 + Placebo (N=233) n (%)
<b>Tucatinib or placebo dose holds</b>	76 (32.9)	26 (11.2)
<b>Tucatinib or placebo dose reductions</b>	46 (19.9)	12 (5.2)
<b>Treatment discontinuation</b>		
Tucatinib or placebo	16 (6.9)	5 (2.1)
T-DM1	18 (7.8)	5 (2.1)

<sup>a</sup> Hepatic TEAEs refer to terms from the drug-related hepatic disorders - comprehensive search SMQ (narrow).

<sup>b</sup> For T-DM1 + Placebo arm, 75% of all-grade hepatic TEAEs resolved or returned to grade 1, with median of 22 days to resolution.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SMQ, standardized Medical Dictionary for Regulatory Activities Queries; T-DM1, trastuzumab emtansine; TEAEs, treatment-emergent adverse events.

Date of data cutoff: Jun 29, 2023.

## • Diarrhea

- Grade  $\geq 3$  events reported in 4.8% of T-DM1 + Tucatinib arm and 0.9% of T-DM1 + Placebo arm
- No grade  $\geq 4$  events were reported in either arm

### Dose Modifications Due to Diarrhea

	T-DM1 + Tucatinib (N=231) n (%)	T-DM1 + Placebo (N=233) n (%)
<b>Tucatinib or placebo dose holds</b>	9 (3.9)	2 (0.9)
<b>Tucatinib or placebo dose reductions</b>	9 (3.9)	1 (0.4)
<b>Treatment discontinuation</b>		
Tucatinib or placebo	1 (0.4)	0
T-DM1	0	0

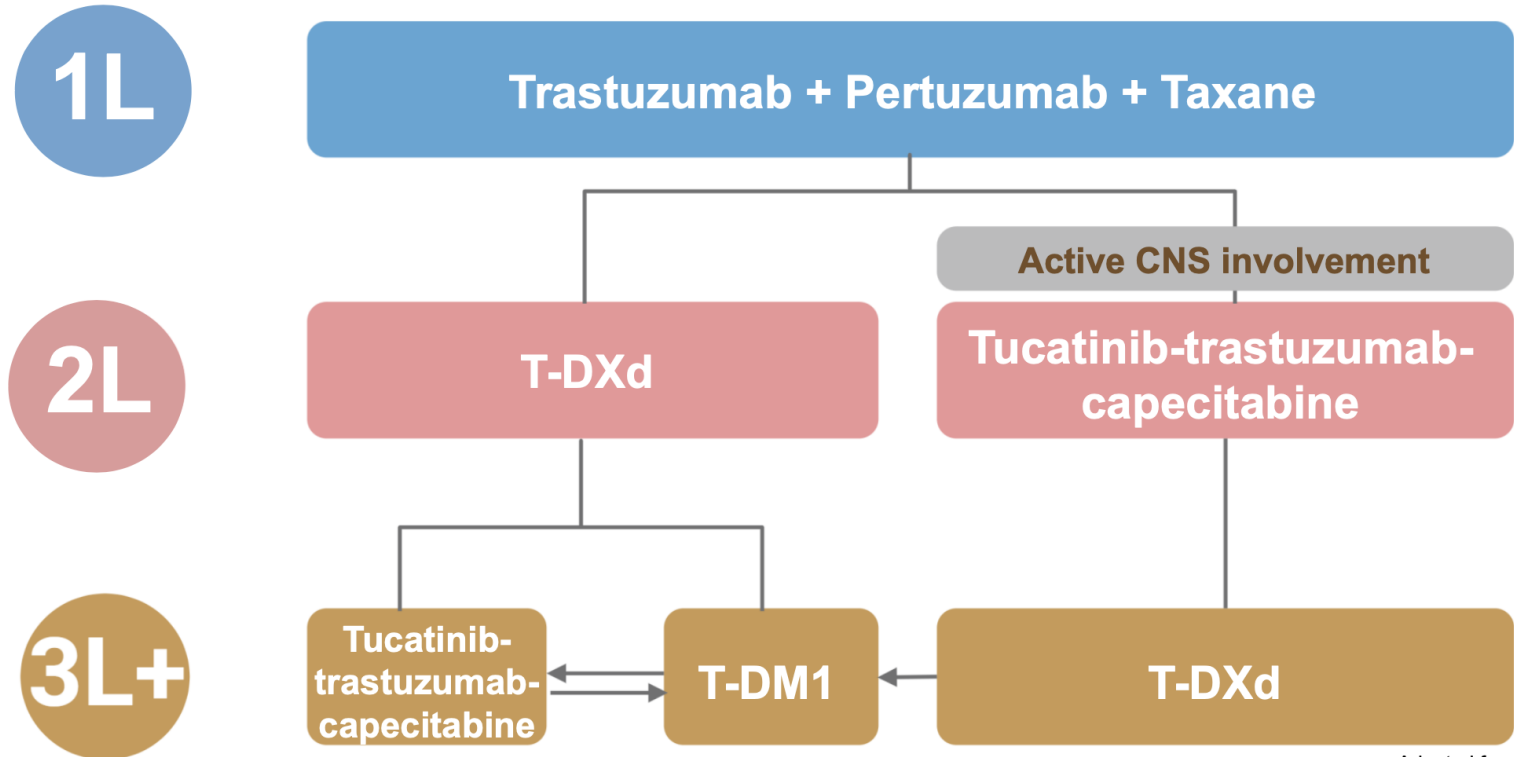


# Conclusions

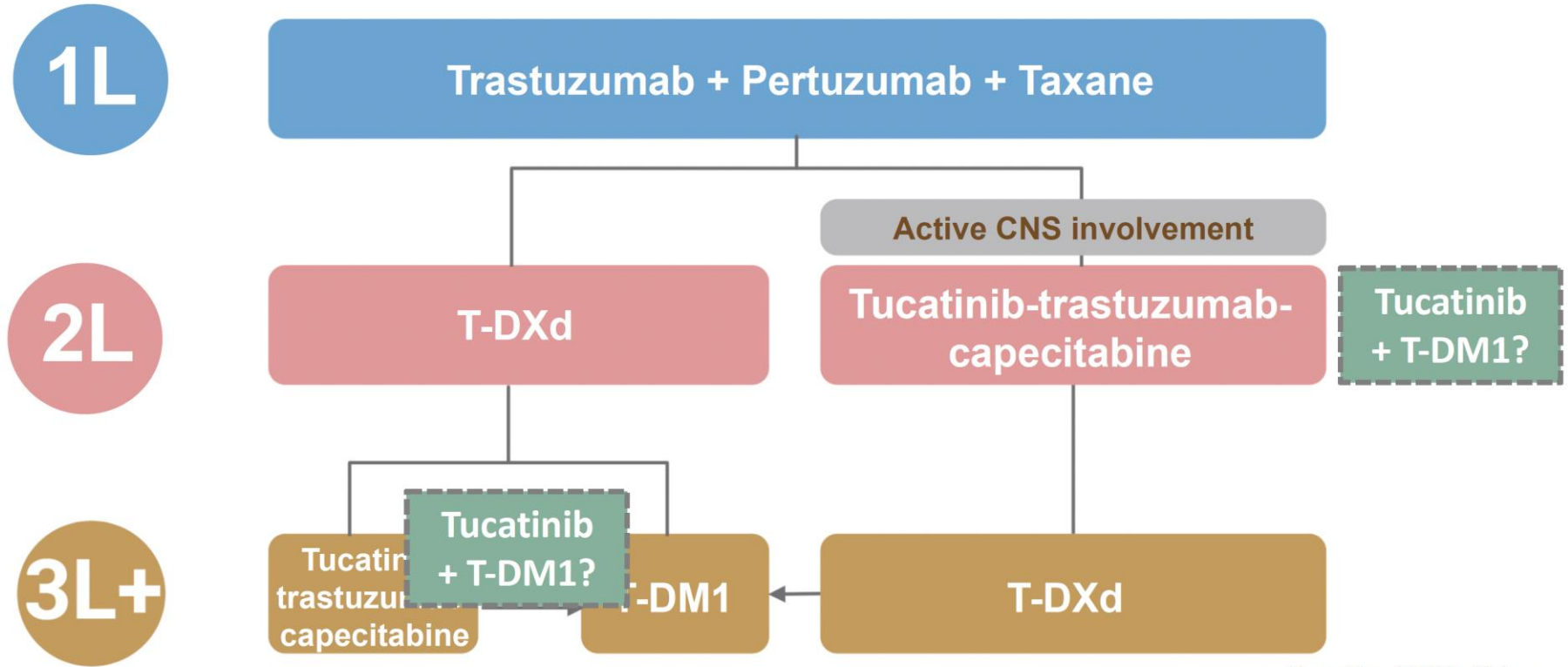
- Adding tucatinib to T-DM1 significantly improved PFS in patients with previously treated HER2+ LA/MBC
  - Median PFS was 9.5 vs 7.4 months (HR, 0.76; P=0.0163)
  - PFS HRs for prespecified subgroups were consistent with that of the overall population
  - Median PFS for patients with brain metastases was 7.8 vs 5.7 months (HR, 0.64)
  - OS data are immature
- Types of adverse events were consistent with those previously reported for tucatinib and T-DM1
  - Higher rate of hepatic events in the T-DM1 + Tucatinib arm; the events were generally transient, manageable, and reversible
- This is the second randomized study which included patients with brain metastases to demonstrate that a tucatinib-containing regimen delays disease progression in HER2+ LA/MBC

HR, hazard ratio; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TEAEs, treatment-emergent adverse events.

# HER2 Positive MBC: Current treatment algorithm



# Current algorithm: where will HER2CLIMB-02 fit in?



# Muito obrigado!



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