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[1] indicated for patients with previously treated HER2+ LA/MBC, including patients with brain metastases[2-6]

- 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≤0.005 for all), respectively[3]

- The incidence of brain metastases in patients with HER2+ LA/MBC remains high[7-9]; combining HER2-directed therapies can improve patient outcomes in HER2+ LA/MBC[10,11]

- T-DM1 is a HER2-directed ADC approved for patients with HER2+ LA/MBC previously treated with trastuzumab and a taxane[12]

- Preclinical data have shown that the combination of tucatinib and T-DM1 results in enhanced antitumor activity compared with either agent alone[13]

- 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[14]

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

- HER2+ LA/MBC with progression after trastuzumab and taxane in any setting[a]
- ECOG PS ≤1
- Previously treated stable, progressing, or untreated brain metastases not requiring immediate local therapy

N≈460

R 1:1

Stratification factors:
- Line of treatment for metastatic disease (1L vs other)
- Hormone receptor status (positive vs negative)
- Presence or history of brain metastases (yes vs no)
- ECOG PS (0 vs 1)

T-DM1 + Tucatinib

T-DM1 3.6 mg/kg IV and tucatinib 300 mg PO BID

T-DM1 + Placebo

T-DM1 3.6 mg/kg IV and Placebo PO BID

Outcomes

Primary
- PFS by investigator assessment per RECIST v1.1

Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

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.[b]

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Demographics and Baseline Characteristics

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

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

[a]Includes 2 patients with missing brain metastases data.
[b]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)
Median prior lines of systemic therapy in metastatic setting (range)	1 (0-8)	1 (0-6)
Prior lines of systemic therapy in metastatic setting, n (%)		
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)
Received prior pertuzumab treatment, n (%)	202 (88.6)	214 (91.1)
Received prior anti-HER2 TKIs, n (%)	3 (1.3)	5 (2.1)

HER2: human epidermal growth factor receptor 2; **T-DM1**: trastuzumab emtansine; **TKIs**: tyrosine kinase inhibitors
Date of data cutoff: Jun 29, 2023.

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Progression-Free Survival

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
HR (95% CI): **0.76** (0.61, 0.95) P=0.0163		
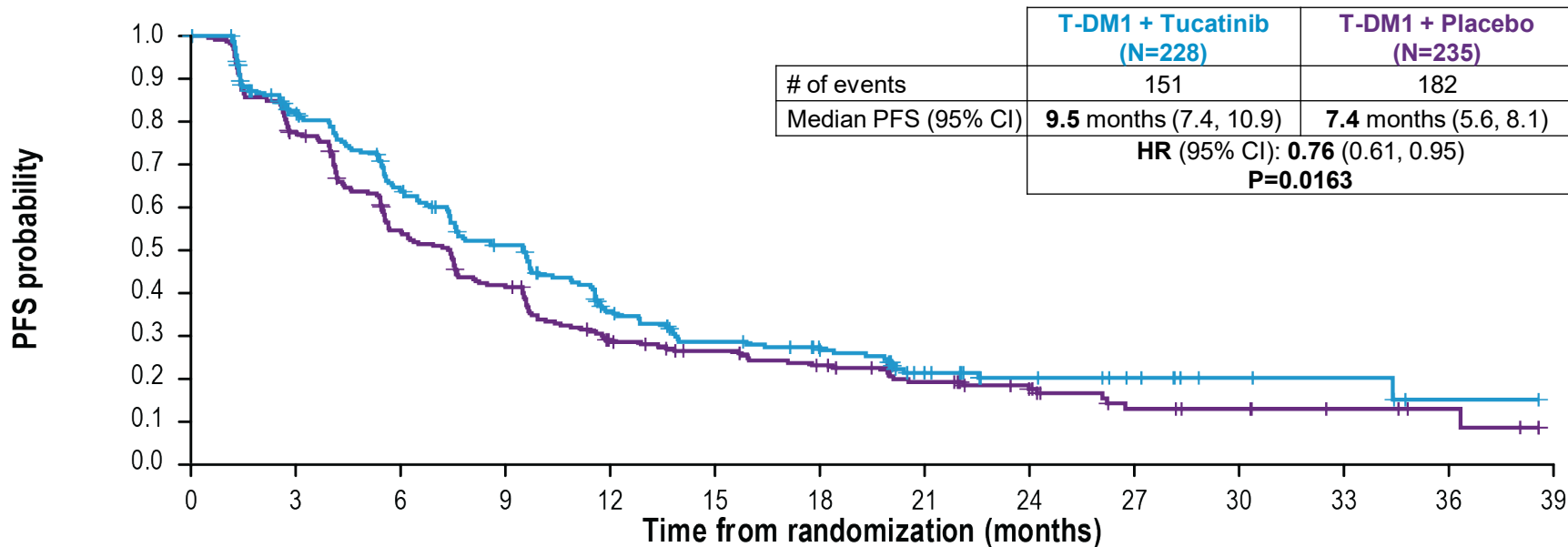
Patients at risk

T-DM1 + Tucatinib	228	165	126	96	62	47	40	22	14	10	5	4	1	0
T-DM1 + Placebo	235	177	120	91	58	48	40	29	19	10	8	5	3	0

CI: confidence interval; **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)

Scale: 0.01 0.1 1 10 100
Favors T-DM1 + Tucatinib ← → Favors T-DM1 + Placebo
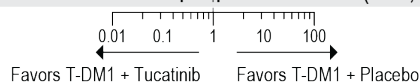
	T-DM1 + Tucatinib (N=228) Events/N	T-DM1 + Placebo (N=235) Events/N		Hazard Ratio with 95% CI
Age				
<65 years	126/186	155/201	⊢■⊣	0.80 (0.62, 1.02)
≥65 years	25/42	27/34	⊢■⊣	0.61 (0.33, 1.11)
Race				
White	68/101	76/102	⊢■⊣	0.79 (0.55, 1.13)
Asian	45/66	58/65	⊢■⊣	0.73 (0.49, 1.11)
Others	38/61	48/68	⊢■⊣	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)

Scale: 0.1 1 10
Favors T-DM1 + Tucatinib   Favors T-DM1 + Placebo
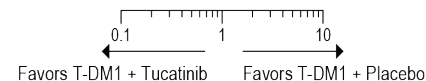
CI: confidence interval; **ECOG:** Eastern Cooperative Oncology Group; **ITT**: intention-to-treat; **PFS**: progression-free survival; **T-DM1:** trastuzumab emtansine
Date of data cutoff: Jun 29, 2023.

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PFS in Patients with Brain Metastases

	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
HR (95% CI)[a]: **0.64** (0.46, 0.89)		
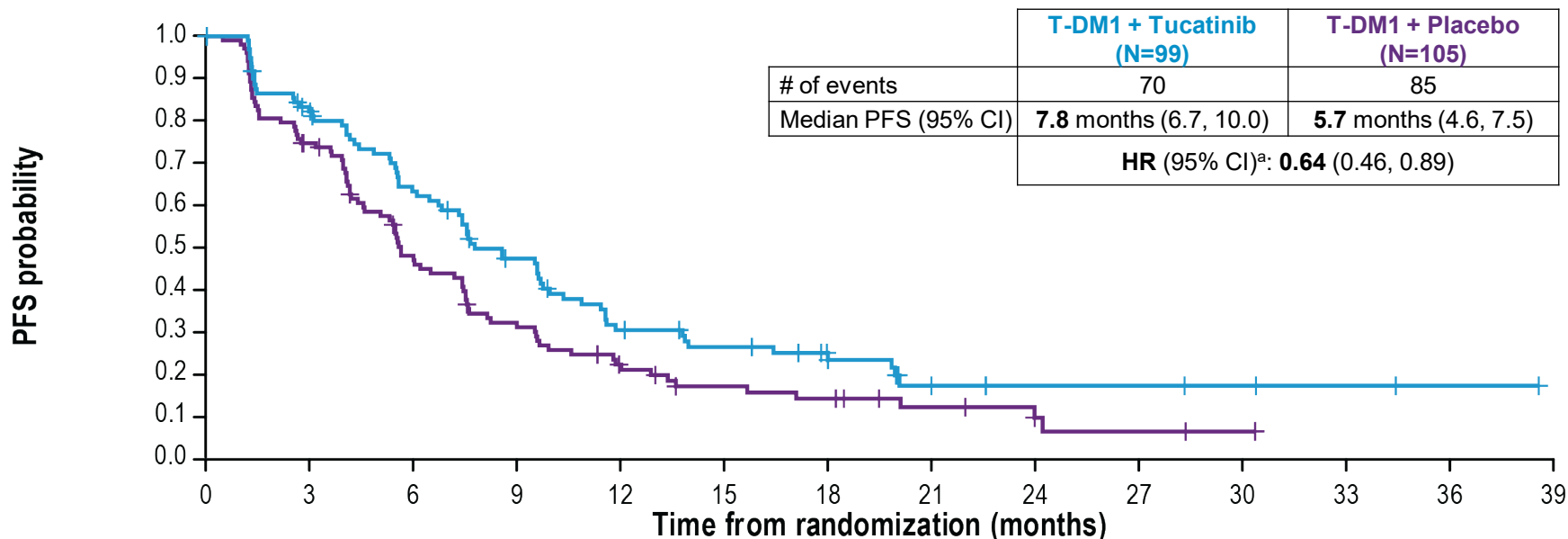
Patients at risk

T-DM1 + Tucatinib	99	76	57	40	25	20	15	6	4	4	3	2	1	0
T-DM1 + Placebo	105	75	46	30	18	12	10	6	3	2	1	0	0	0

CI: confidence interval; **HR**: hazard ratio; **PFS**: progression-free survival; **T-DM1**: trastuzumab emtansine
[a]The outcome was not formally tested.
Date of data cutoff: Jun 29, 2023.

Confirmed Objective Response Rate
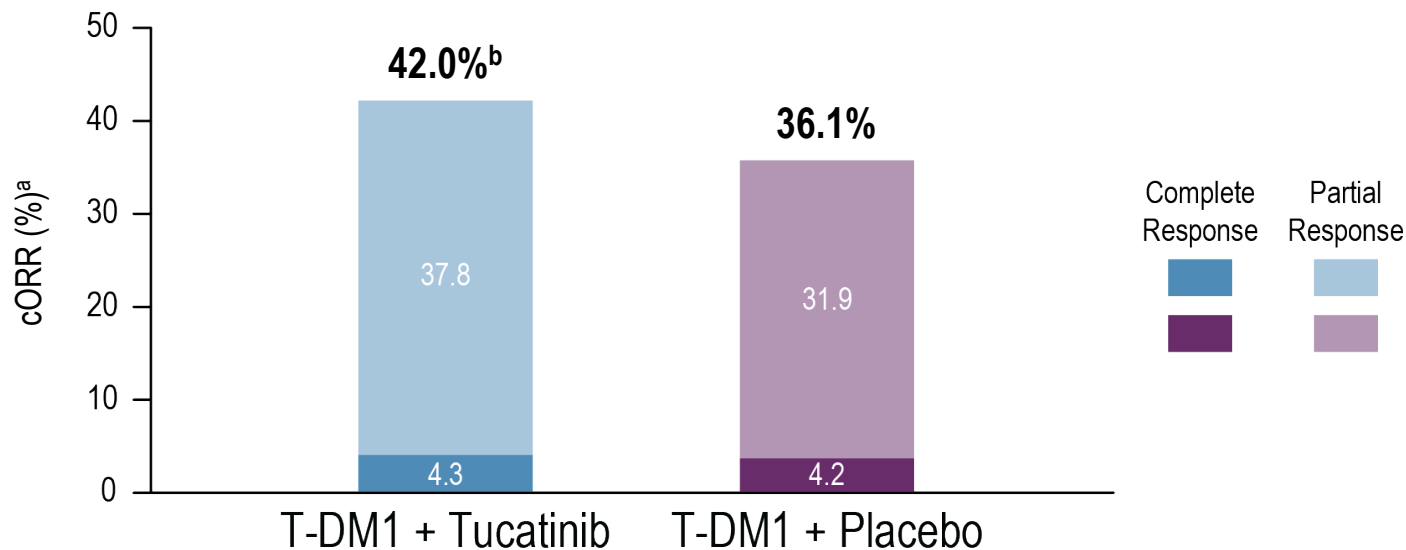
cORR: confirmed objective response rate; **T-DM1**: trastuzumab emtansine
[a]The outcome was not formally tested. Only patients with measurable disease were included in the analysis (N=188 for T-DM1 + Tucatinib arm and N=191 for T-DM1 + Placebo arm).
[b]Percentages for complete and partial response do not add up to the cORR due to rounding.
Date of data cutoff: Jun 29, 2023.

Subsequent Systemic Therapies

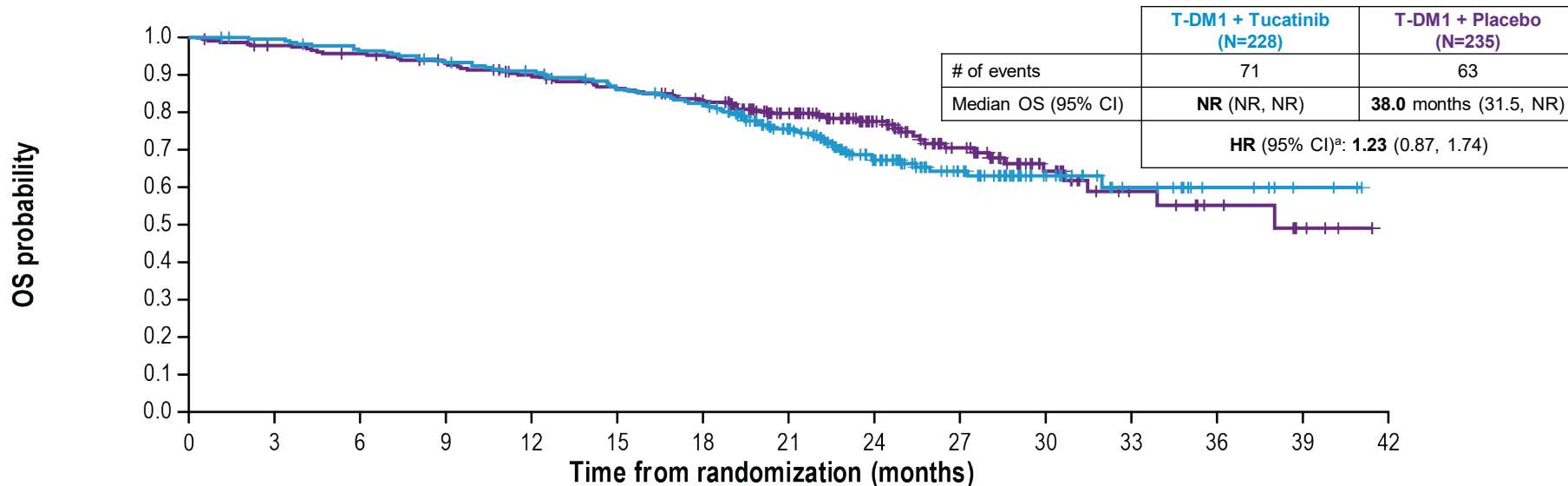|	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Patients who have discontinued or never received study treatment, n (%)	188 (82.5)	206 (87.7)
Patients who received ≥1 subsequent anticancer systemic therapy, n (%)[a]	150 (79.8)	168 (81.6)
Median subsequent lines of therapies (range)	2.0 (1-13)	2.0 (1-15)
Subsequent therapies, n (%)[a]		
T-DXd	93 (49.5)	101 (49.0)
Chemotherapy[b]	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)

T-DM1: trastuzumab emtansine; **T-DXd**: trastuzumab deruxtecan
[a]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.
[b]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.
Date of data cutoff: Jun 29, 2023.

Overall Survival

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	71	63
Median OS (95% CI)	**NR** (NR, NR)	**38.0** months (31.5, NR)
	HR (95% CI)[a]: **1.23** (0.87, 1.74)	

OS probability (y-axis: 0.0 to 1.0)

Time from randomization (months) (x-axis: 0 to 42)

Patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
T-DM1 + Tucatinib	228	225	217	209	202	189	180	132	89	55	30	16	7	3	0
T-DM1 + Placebo	235	227	221	212	201	191	180	135	90	58	32	16	10	4	0

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≤0.0041.

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

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Overall Safety Summary

	T-DM1 + Tucatinib (N=231) n (%)	T-DM1 + Placebo (N=233) n (%)
Any TEAE	230 (99.6)	233 (100)
Grade ≥3 TEAE	159 (68.8)	96 (41.2)
Any TESAE	70 (30.3)	52 (22.3)
TEAE leading to death	3 (1.3)	2 (0.9)
Discontinued tucatinib or placebo due to TEAE	40 (17.3)	16 (6.9)
Discontinued T-DM1 due to TEAE	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 (≥2%) leading to tucatinib or placebo discontinuation (T-DM1 + Tucatinib vs T-DM1 + Placebo):
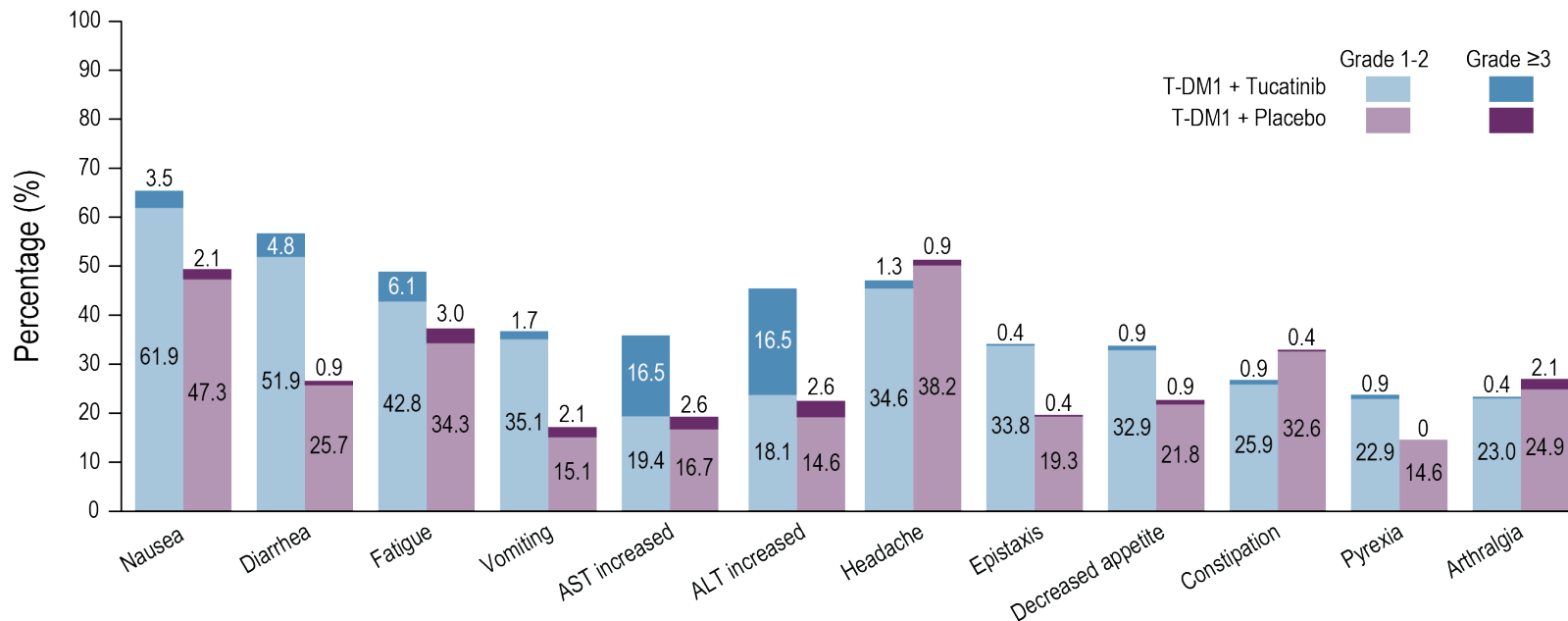- ALT increased (2.6% vs 0%)

Most common TEAEs (≥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 (≥20%)

Most common (≥5%) grade ≥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 ≥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 ≥3 hepatic TEAEs[a] 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[b]

- Diarrhea
  - Grade ≥3 events reported in 4.8% of T-DM1 + Tucatinib arm and 0.9% of T-DM1 + Placebo arm
  - No grade ≥4 events were reported in either arms

Dose Modifications Due to Hepatic TEAEs

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

Dose Modifications Due to Diarrhea

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

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

[a]Hepatic TEAEs refer to terms from the drug-related hepatic disorders - comprehensive search SMQ (narrow).

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

Date of data cutoff: Jun 29, 2023.

Author's 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 including patients with brain metastases demonstrating that a tucatinib-containing regimen delays disease progression in HER2+ LA/MBC

HER2: human epidermal growth factor receptor 2; **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

Acknowledgments

Plain Language Summary

- Why was this research needed?
    - HER2+ LA/MBC is hard to treat. While there are many approved treatment options, the disease often progresses. New treatment options are needed.
    - Tucatinib and T-DM1 are both approved for previously treated HER2+ LA/MBC. Patients with HER2+ LA/MBC who received T-DM1 plus tucatinib in a prior study had encouraging antitumor activity, including patients with brain metastases.
    - This study, HER2CLIMB-02, compared T-DM1 plus tucatinib to T-DM1 alone in patients with HER2+ LA/MBC who had been treated with trastuzumab and a taxane.

- What were the results and why are the findings meaningful?
    - T-DM1 plus tucatinib was significantly better at stopping disease progression compared to T-DM1 alone, including in patients with brain metastases.
    - In patients who received T-DM1 plus tucatinib, a higher number stopped the drugs because of side effects compared to T-DM1 alone. But no new side effects or risks were seen when using T-DM1 plus tucatinib.

- Where can I find more information?
    - https://www.clinicaltrials.gov/study/NCT03975647

HER2: human epidermal growth factor receptor 2; **LA/MBC**: locally advanced or metastatic breast cancer; **PFS**: progression-free survival; **T-DM1**: trastuzumab emtansine