HER2 Targeted Therapies: Recent Advances

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UCDAVIS COMPREHENSIVE CANCER CENTER

Today's Talk

- Advance stage
- Early stage
- Future directions

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HER2-positive MBC

Setting	Regimen	Trial
1st-line	Taxane + trastuzumab and pertuzumab	CLEOPATRA
2nd-line	Trastuzumab deruxtecan	DESTINY 03
3rd-line	Tucatinib, trastuzumab + capecitabine	HER2CLIMB
	Trastuzumab emtansine	EMILIA
4th line and beyond	Trastuzumab + chemotherapy	
	Lapatinib + capecitabine	
	Trastuzumab + lapatinib	
	Neratinib + capecitabine	NALA
	Margetuximab + chemotherapy	SOPHIA

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AACR American Association for Cancer Research

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

Sara A. Hurvitz, MD

Fred Hutchinson Cancer Center, Seattle, WA, USA

Sherene Loi, Joyce O'Shaughnessy, Alicia F. C. Okines, Sara M. Tolaney, Joohyuk Sohn, Cristina Saura, Xiaofu Zhu, David Cameron, Thomas Bachelot, Erika P. Hamilton, Giuseppe Curigliano, Antonio C. Wolff, Nadia Harbeck, Norikazu Masuda, Linda Vahdat, Khalil Zaman, Frances Valdes-Albini, Margaret Block, Timothy Pluard, Tira J. Tan, Chelsea D. Gawryletz, Arlene Chan, Philippe L. Bedard, Rinat Yerushalmi, Binghe Xu, Konstantinos Tryfonidis, Michael Schmitt, Diqiong Xie, Virginia F. Borges

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]

NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Accessed Oct 5, 2023.
a 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.
b 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)
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.

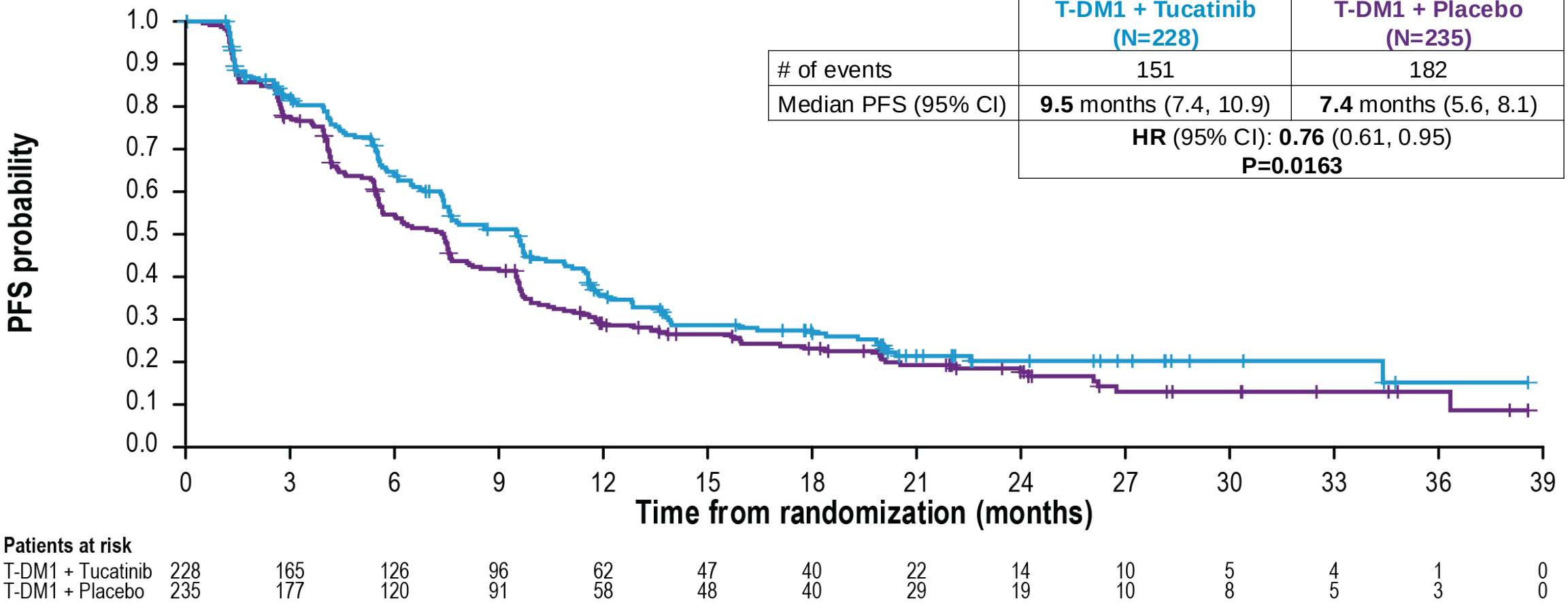
Prior Systemic Therapies

	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)

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

Progression-Free Survival

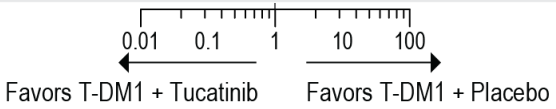
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
	HR (95% CI): **0.76** (0.61, 0.95) **P=0.0163**	



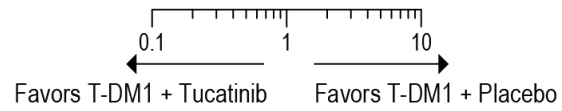
HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

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)



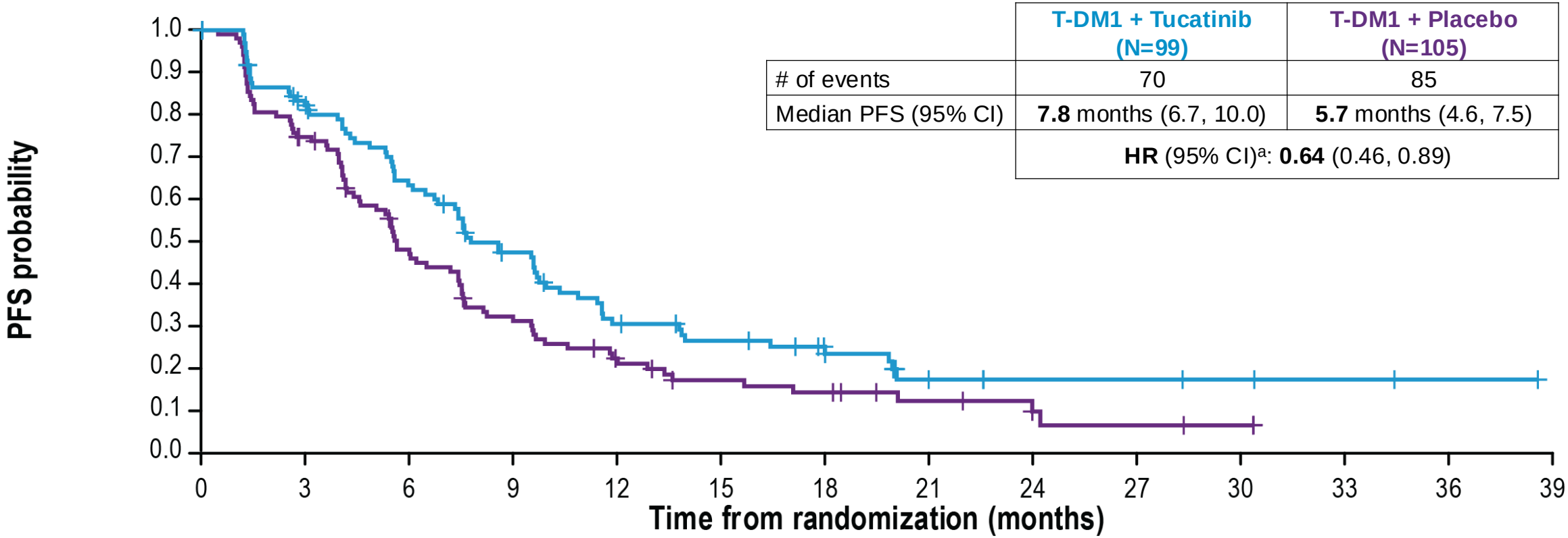
	T-DM1 + Tucatinib (N=228) Events/N	T-DM1 + Placebo (N=235) Events/N	Hazard Ratio with 95% CI
Age			
<65 years	126/186	155/201	0.80 (0.62, 1.02)
≥65 years	25/42	27/34	0.61 (0.33, 1.11)
Race			
White	68/101	76/102	0.79 (0.55, 1.13)
Asian	45/66	58/65	0.73 (0.49, 1.11)
Others	38/61	48/68	0.79 (0.48, 1.28)
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

	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)	



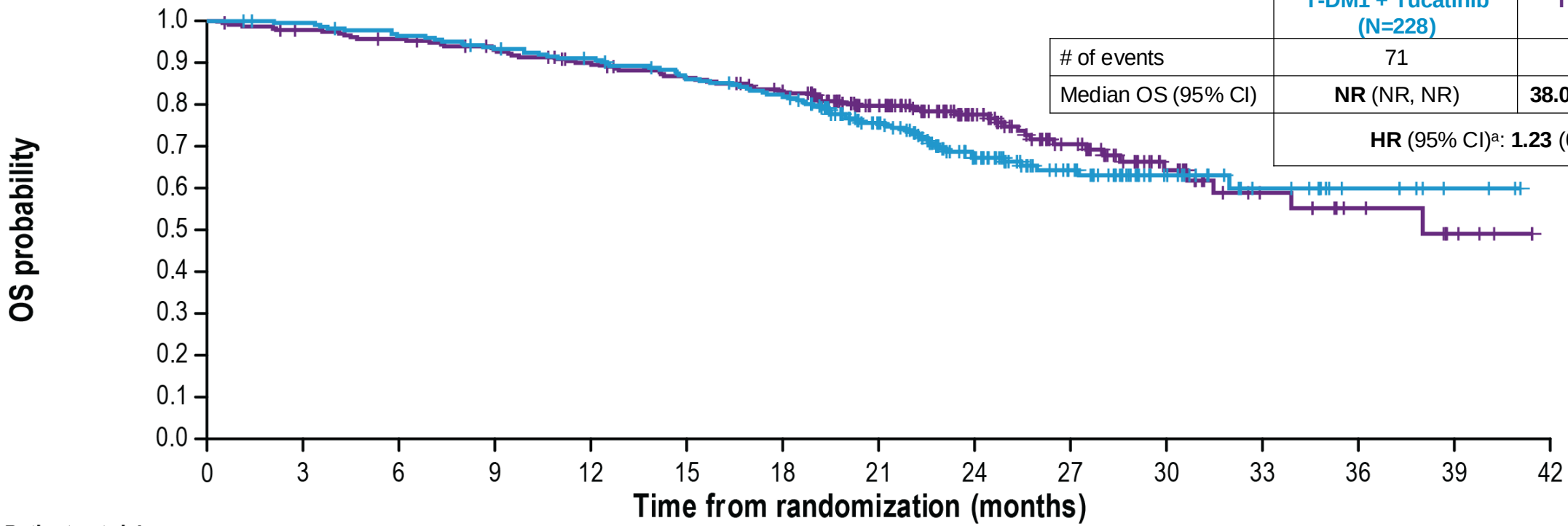
Patients at risk

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

a The outcome was not formally tested.
HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
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)	



Patients at risk

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.

a 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 (%)
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)

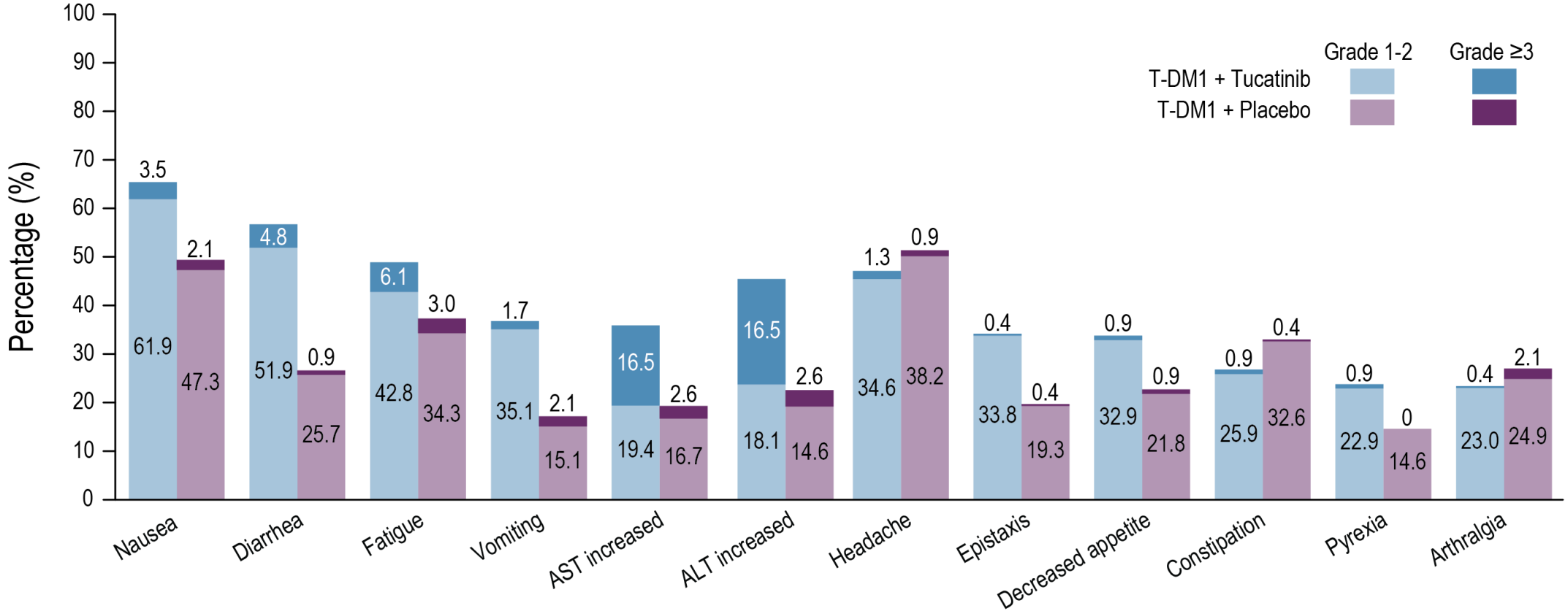
Median duration of tucatinib or placebo treatment: 7.4 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo
Median duration of T-DM1 treatment: 7.5 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo

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.

HER2CLIMB-02

- Improvement in PFS (9.5 vs 7.4 months) but at increased toxicity

- Tucatinib continued to improve PFS in the CNS

2024 ASCO ANNUAL MEETING

Japan Breast Cancer Research Group

Trastuzumab and pertuzumab in combination with eribulin mesylate or a taxane as first-line chemotherapeutic treatment for HER2-positive, locally advanced or metastatic breast cancer: results of a multicenter, randomized, non-inferiority phase 3 trial in Japan (JBCRG-M06/EMERALD)

Toshinari Yamashita MD, PhD, Kanagawa Cancer Center, Kanagawa, Japan

Shigehira Saji, Toshimi Takano, Yoichi Naito, Michiko Tsuneizumi, Akiyo Yoshimura, Masato Takahashi, Junji Tsurutani, Tsuguo Iwatani, Masahiro Kitada, Hiroshi Tada, Natsuko Mori, Toru Higuchi, Tsutomu Iwasa, Kazuhiro Araki, Kazuko Sakai, Hiroki Hasegawa, Yohei Uchida, Satoshi Morita, Norikazu Masuda

Study design

Patients with HER2+ LABC or MBC

- Age 20–70 years
- No prior use of chemotherapy (excluding T-DM1) for LABC/MBC
- Hormonal or anti-HER2 therapy alone, or their combination as treatment for recurrence, were allowed
- ECOG performance status score 0/1
- Left ventricular ejection fraction (LVEF) ≥50%
- Major organ function preserved
- At least 6 months since prior neoadjuvant or adjuvant cytotoxic chemotherapy

R 1:1

Eribulin group (21-day cycle)

Eribulin 1.4 mg/m^2
days 1, 8
+
H + P[a] day 1

Taxane group (21-day cycle)

Docetaxel 75 mg/m^2 day 1 or
Paclitaxel 80 mg/m^2 days 1, 8, 15
+
H + P[a] day 1

Docetaxel =186
Paclitaxel = 36

Primary endpoint :

- Progression-free survival (PFS), investigator-assessed

Secondary endpoints

- Objective response rate (ORR)
- Duration of response
- Overall survival (OS)
- Patient-reported outcomes (QoL and neuropathy)
- Safety and biomarker
- New metastases−free survival
- Duration of next treatment

Translational research

- Search for biomarker to improve individual precision therapy

Stratification factors for randomization

- History of perioperative use of taxane
- Prior treatment with HER2-targeting antibody-drug conjugate after recurrence
- Presence of visceral metastases

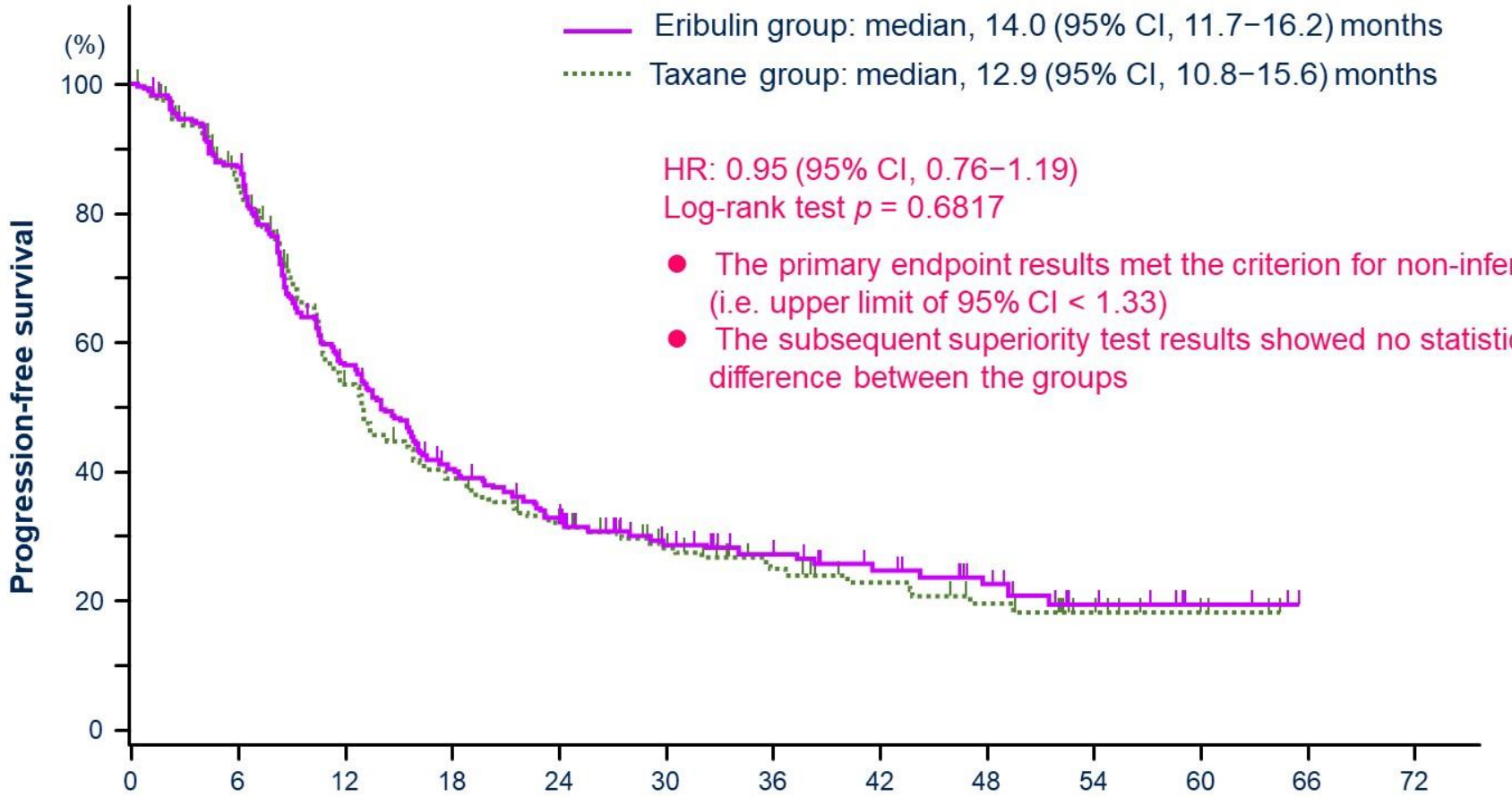
[a]Trastuzumab (H) : 8 mg/kg loading dose, 6 mg/kg subsequent doses + pertuzumab (P): 840 mg/body loading dose, 420 mg/body subsequent doses
Treatment continued to disease progression or unmanageable toxicity

JBCRG-M06/EMERALD: A multicenter, randomized, non-inferiority phase 3 trial
(UMIN000027938; ClinicalTrials.gov identifier, NCT03264547)

Sample size and non-inferiority testing

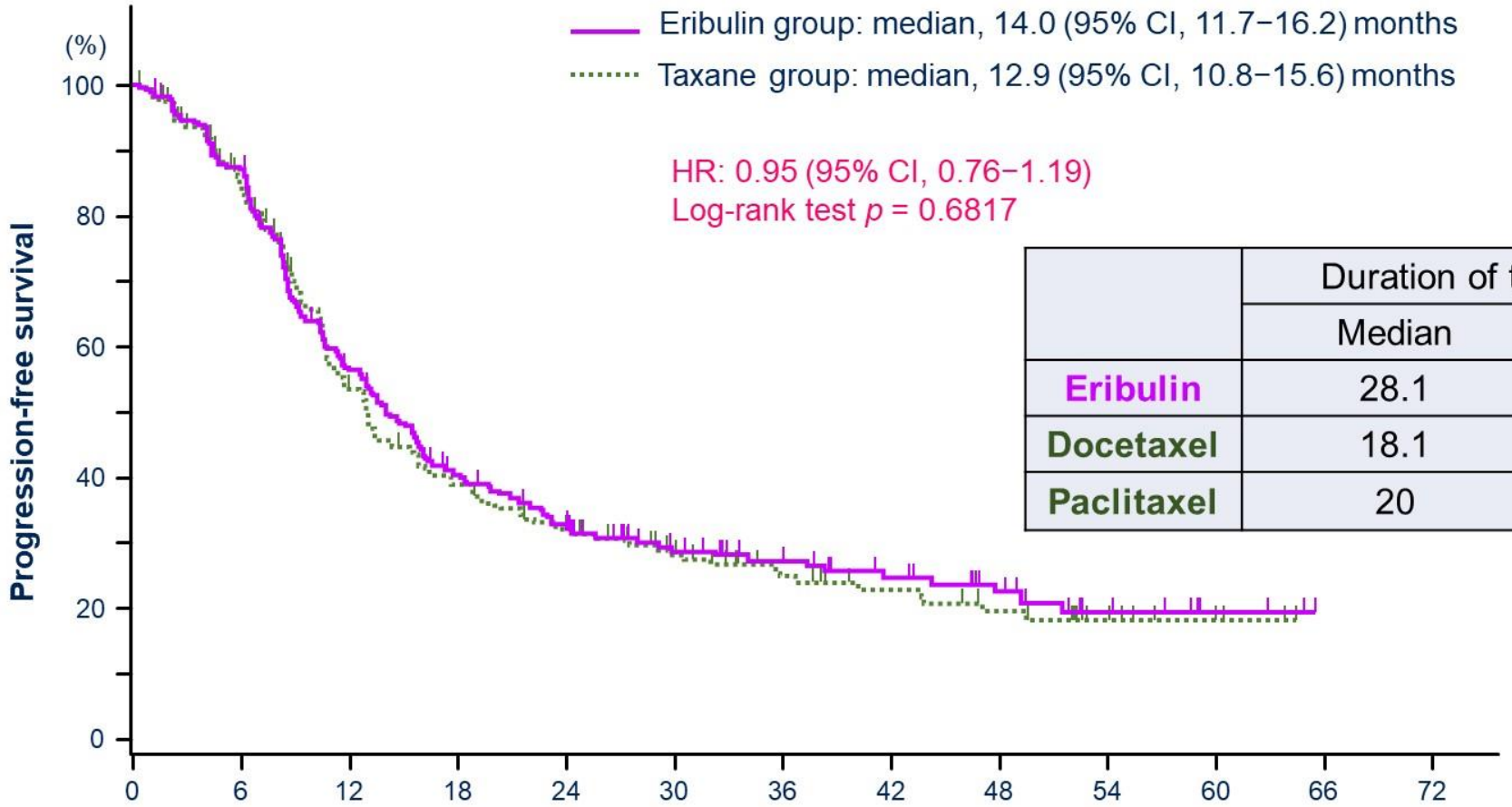
- Sample size was calculated for a statistical power of 80%, a significance level of 0.05 (two-sided), and an expected median PFS in the control group of 14.2 months
- Non-inferiority was tested using the Cox proportional hazards model to estimate hazard ratios (HRs) for PFS events
- The upper limit of acceptance of non-inferiority HR margins (1.33 and 1.25) was tested in a stepwise manner, and superiority was to be tested if the upper limit of the 95% CI of HR was < 1.25

PFS (primary endpoint)



No. at risk													
Eribulin group	224	191	119	81	64	43	34	26	17	8	3	0	0
Taxane group	222	173	105	75	59	39	28	21	16	9	3	0	0

PFS (primary endpoint)

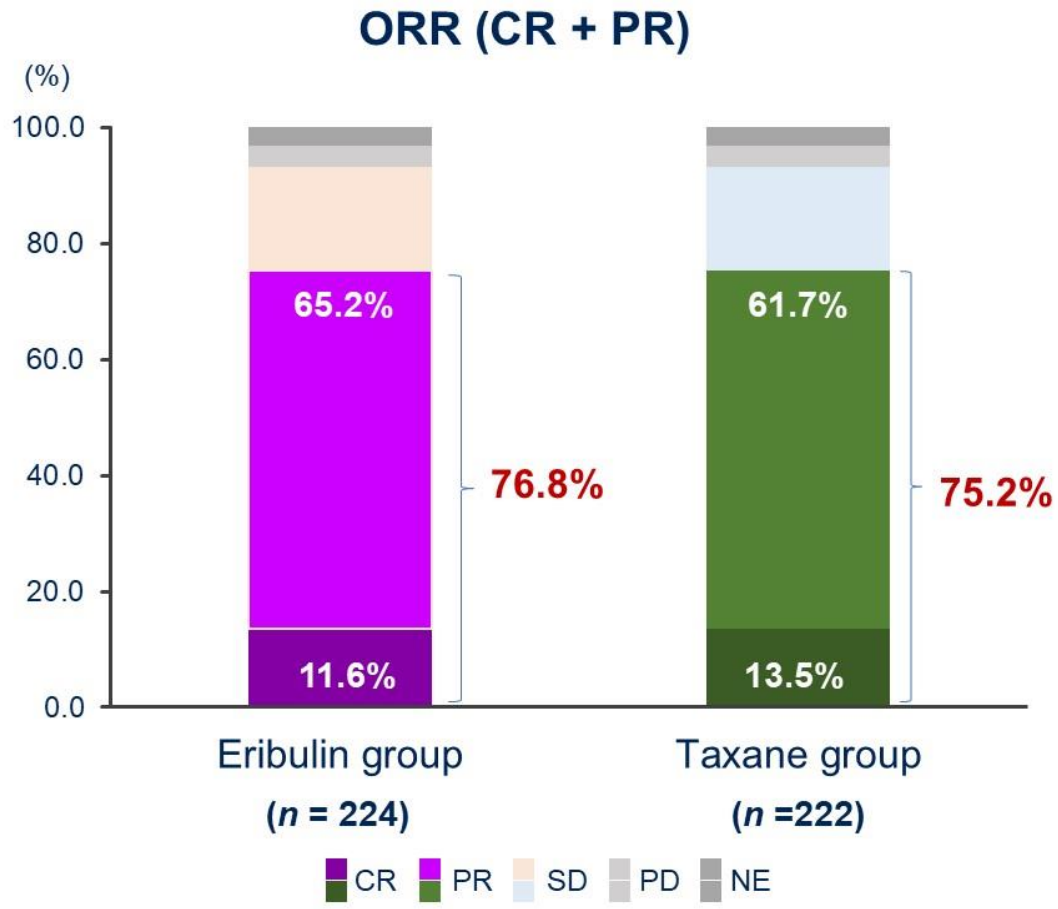


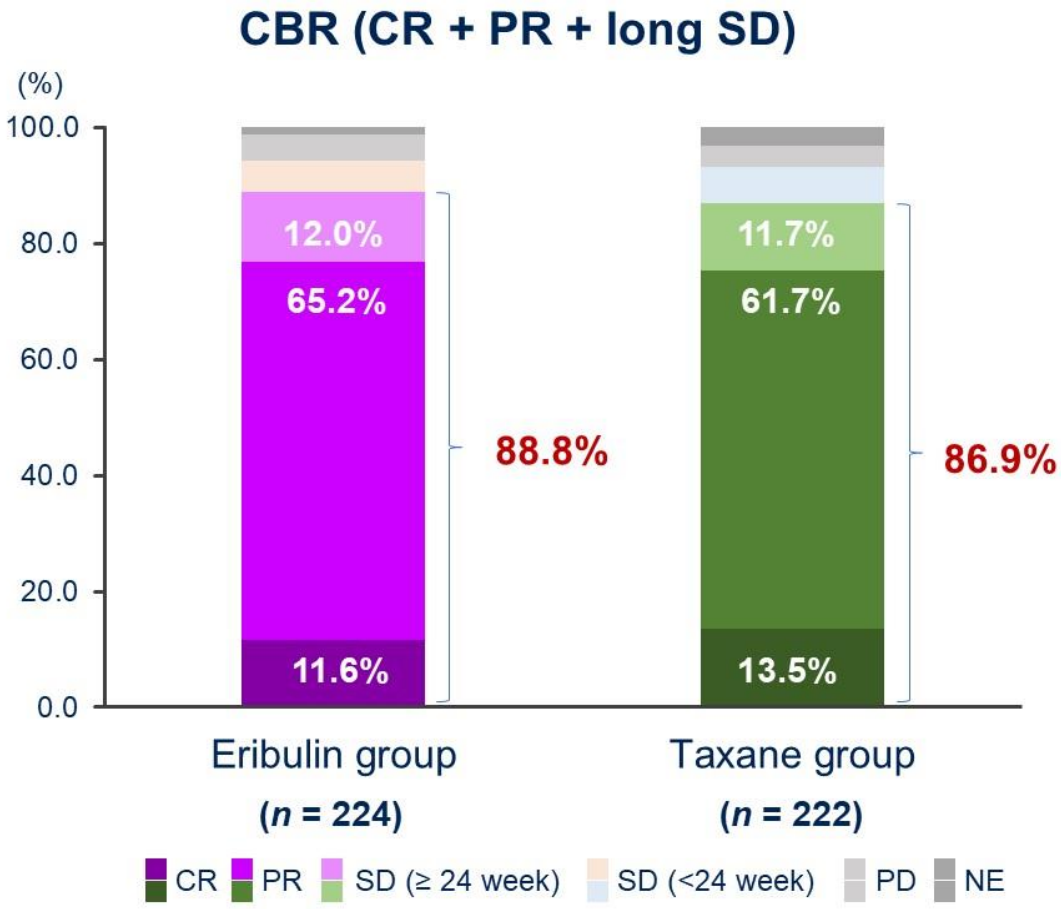
	Duration of treatment (weeks)	
	Median	Mean
Eribulin	28.1	37.9
Docetaxel	18.1	20.7
Paclitaxel	20	24.7

No. at risk

Eribulin group	224	191	119	81	64	43	34	26	17	8	3	0	0
Taxane group	222	173	105	75	59	39	28	21	16	9	3	0	0

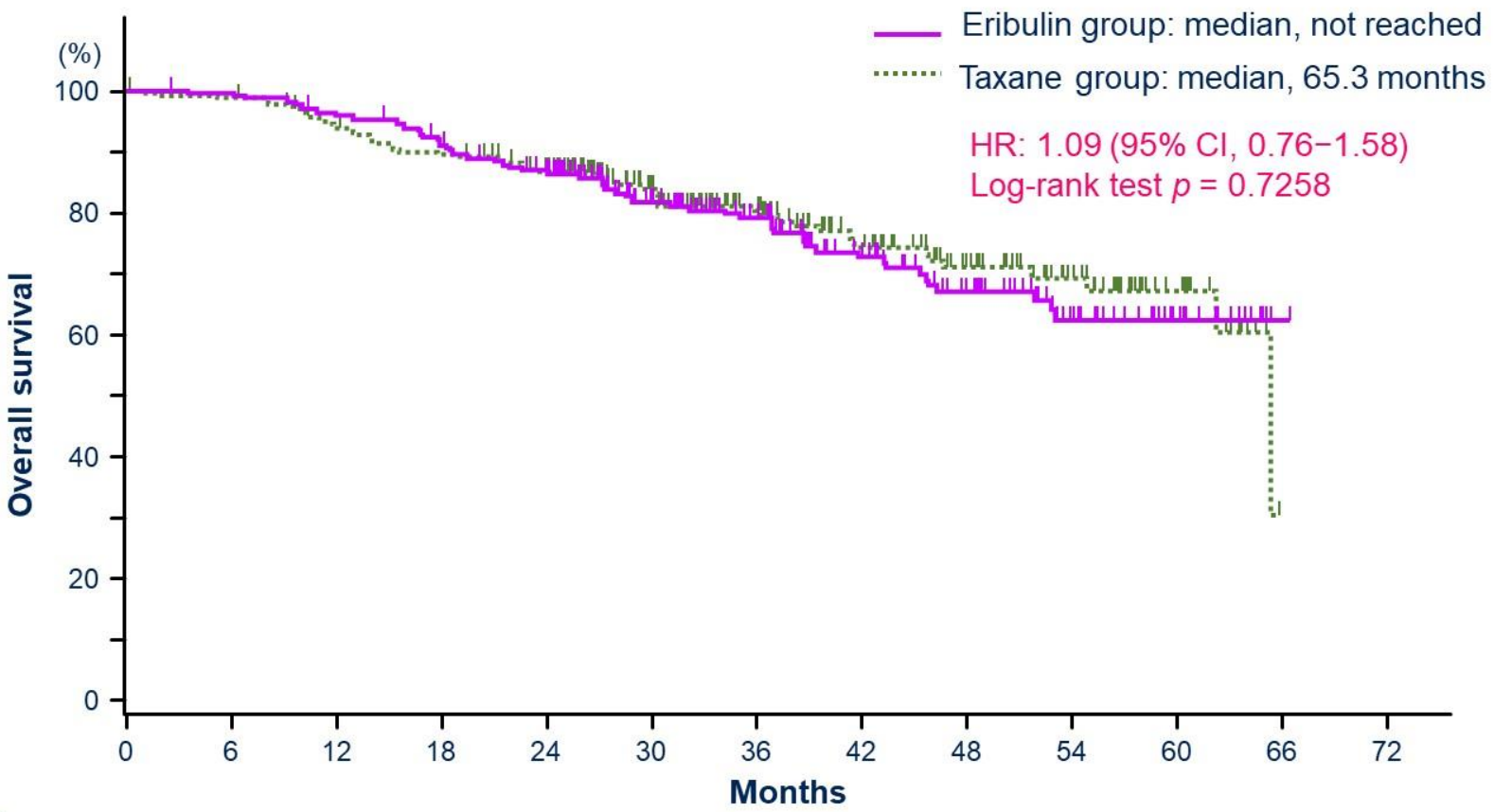
Response rate





ORR, Objective response rate; CBR, clinical benefit rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, non-evaluable

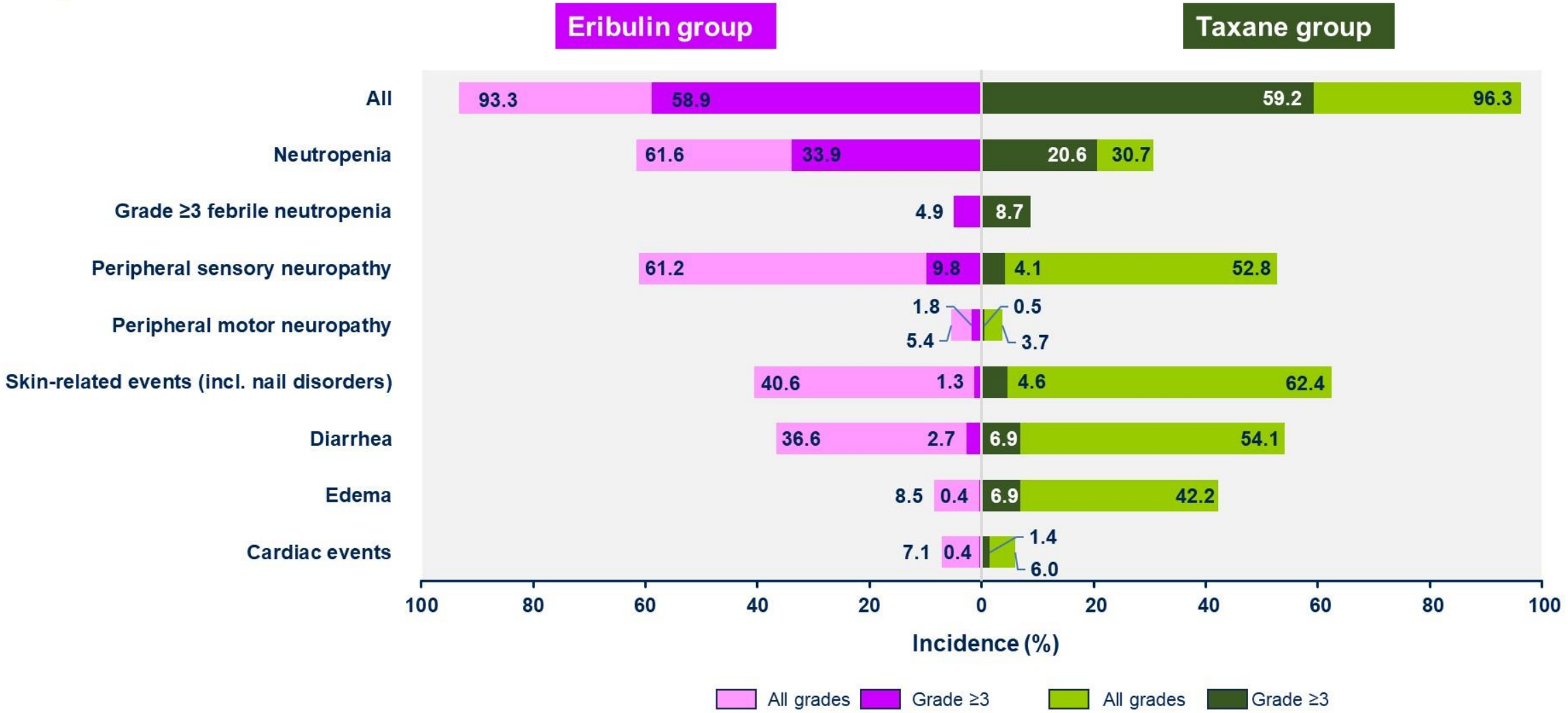
OS



No. at risk

Eribulin group	224	222	214	200	187	141	112	83	64	37	17	2	0
Taxane group	222	218	203	193	180	141	109	81	57	37	16	0	0

Drug-related treatment-emergent adverse events
Special interest



JBCRG-m06 EMERALD

- First-line eribulin was noninferior to taxane in combination with HP

- Similar (vs less toxic??) side effect profile

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AACR American Association for Cancer Research

A phase III study comparing trastuzumab emtansine with trastuzumab, pertuzumab, and docetaxel in older patients with advanced-stage HER2-positive breast cancer. (JCOG1607 HERB TEA study)

Akihiko Shimomura, Kenji Tamura, Keita Sasaki, Ryo Sadachi, Akihiko Suto, Masataka Sawaki, Yasuaki Sagara, Naohito Yamamoto, Tomoyuki Yoshiyama, Takako Hayashi, Eriko Tokunaga, Takashi Yamanaka, Chikako Shimizu, Tadahiko Shien, Hiroji Iwata

Department of Breast and Medical Oncology, National Center for Global Health and Medicine, Tokyo, Japan, Department of Medical Oncology, Shimane University Hospital, Shimane, Japan, JCOG Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan, Department of Breast Surgery, National Cancer Center Hospital, Tokyo, Japan, Department of Breast Oncology, Aichi Cancer Center, Aichi, Japan, Department of Breast and Thyroid Surgical Oncology, Sagara Hospital, Kagoshima, Japan, Division of Breast Surgery, Chiba Cancer Center, Chiba, Japan, Department of Breast Surgery, NHO Kure Medical Center and Chugoku Cancer Center, Hiroshima, Japan, Department of Breast Surgery, NHO Nagoya Medical Center, Aichi, Japan, Department of Breast Oncology, NHO Kyushu Cancer Center, Fukuoka, Japan, Department of Breast Surgery and Oncology, Kanagawa Cancer Center, Kanagawa, Japan, Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan

JCOG Japan Clinical Oncology Group

HERBTEA study

Study Design

Primary endpoint:
Overall survival (OS)
Secondary endpoints:
Progression-free survival, Cumulative breast cancer specific survival, Response rate, Adverse events, Serious adverse events, Proportion of non-deteriorating of instrumental activities of daily living

- Older patients with advanced HER2-positive breast cancer
- No prior chemotherapy for MBC
- Over 65 years and old
- PS 0 to 2 (0 to 1 for over 75 y.o.)

R

N=148

Arm A: HPD arm (N=75)

Trastuzumab (6 mg/kg, loading dose 8 mg/kg)
+ Pertuzumab (420 mg, loading dose 840 mg)
+ Docetaxel (60 mg/m^2) q3w
until PD

The dose up of Docetaxel (75 mg/m^2) from the second cycle was allowed based on the data regarding safety during the first cycle.

Arm B: T-DM1 arm (N=73)

T-DM1 (3.6 mg/kg) q3w
until PD

*Planned sample size: 250 Pts. Terminated early at 148 Pts by interim analysis because the OS hazard ratio estimate exceeded the non-inferiority margin (data cutoff 12/22/2022).
The data cutoff for this presentation is 6/15/2023.

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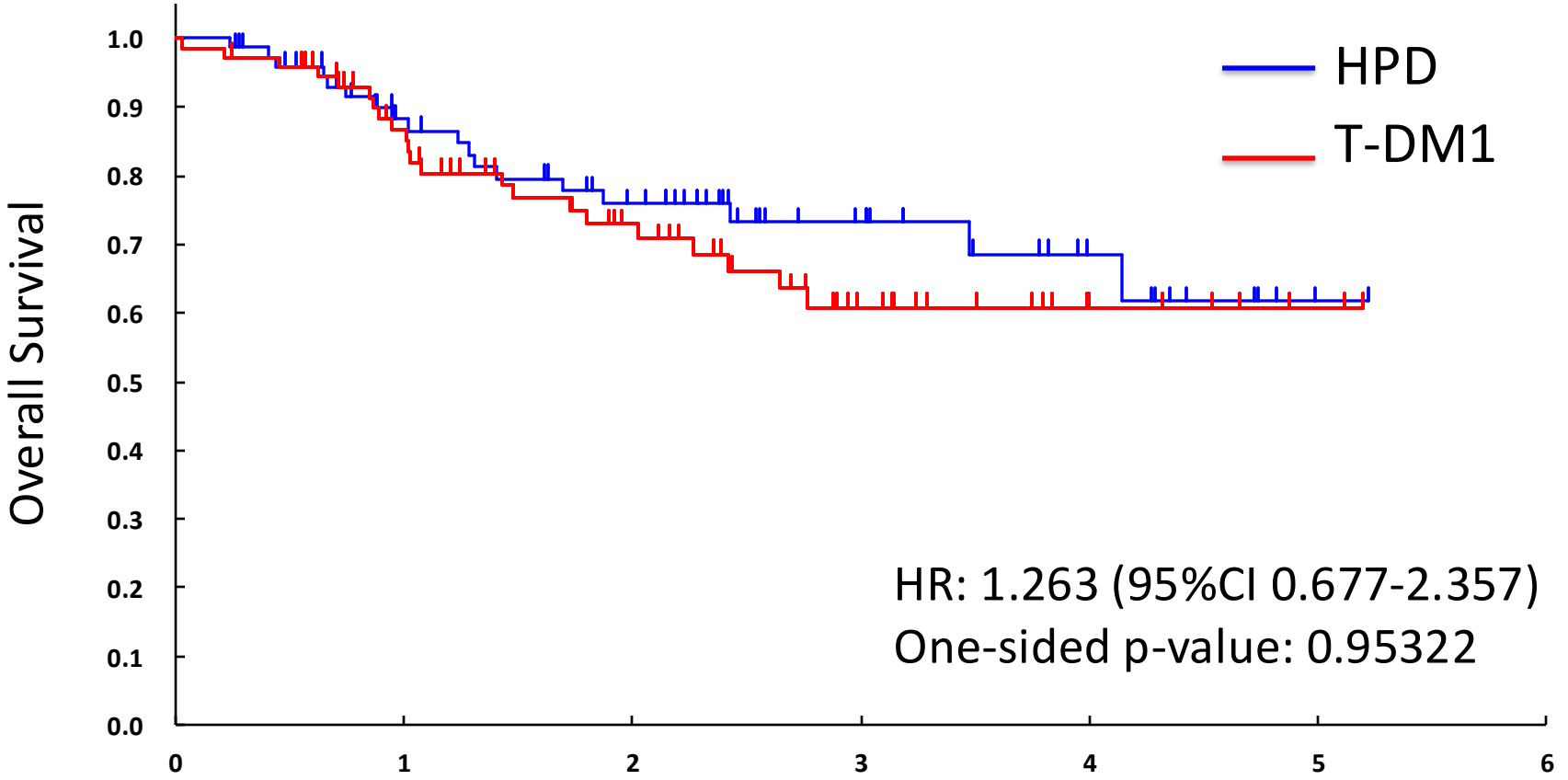
UMIN-CTR:UMIN000030783

Overall Survival



Number at risk							
HPD	75	52	39	21	10	1	0
T-DM1	73	55	35	18	6	2	0

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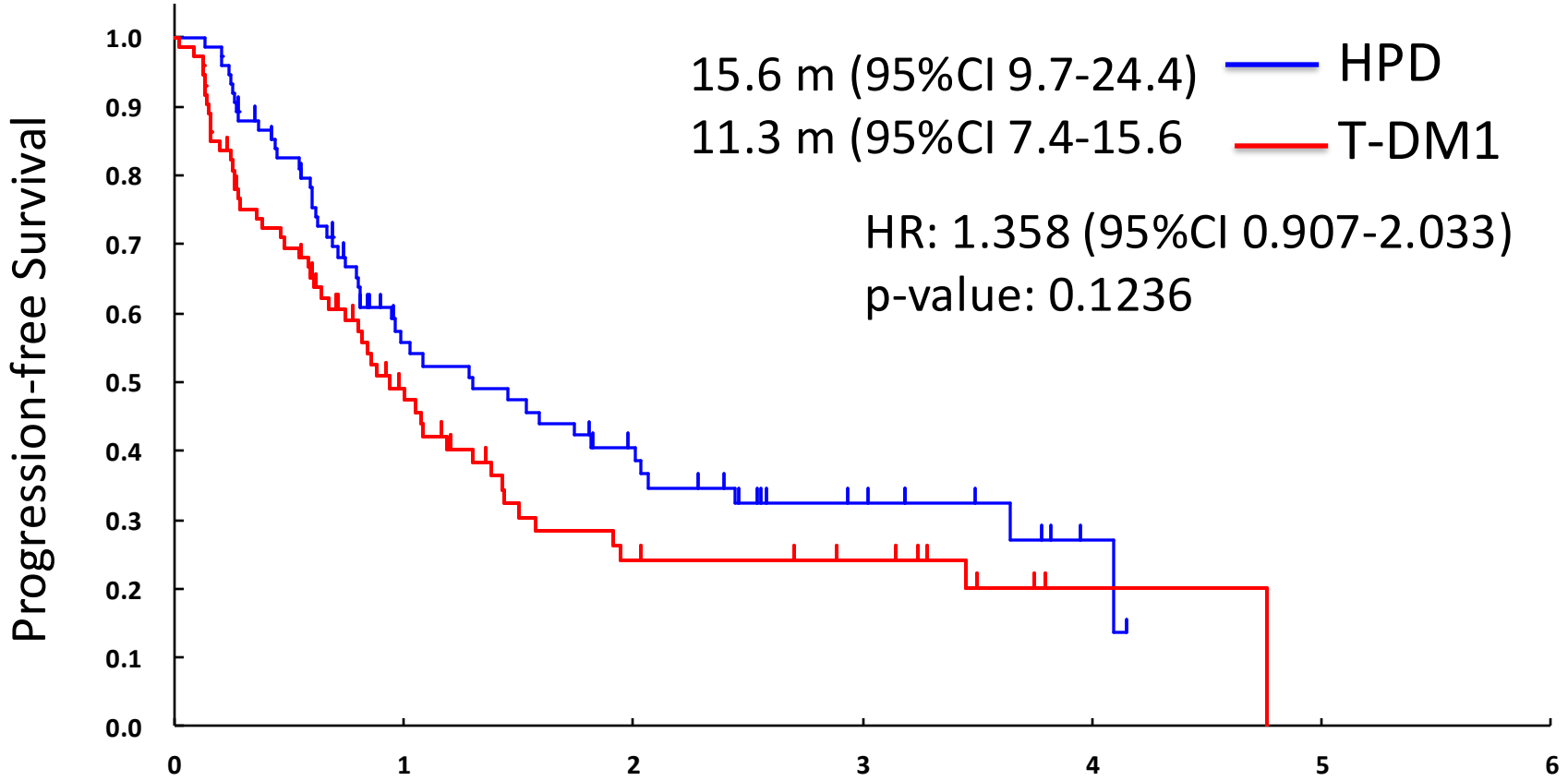
Progression-free Survival



Number at risk							
HPD	75	33	21	10	2	0	0
T-DM1	73	28	12	9	1	0	0

JCOG Japan Clinical Oncology Group

Safety (adverse events reported in at least 10% of patients in either arm)

		HPD		T-DM1	
		Grade ≧ 3	Grade 4	Grade ≧ 3	Grade 4
Any AE		56.8%	0%	34.7%	1.4%
Hematologic	Leukopenia	26.0%	8.2%	0%	0%
	Neutropenia	30.1%	21.9%	0%	0%
	Thrombocytopenia	0%	0%	16.7%	0%
Non-Hematologic	AST increased	0%	0%	15.3%	0%
	ALT increased	2.7%	0%	16.7%	0%
	Diarrhea	12.2%	0%	0%	0%
	Fatigue	21.6%	0%	5.6%	0%
	Appetite loss	10.8%	0%	8.3%	0%

JCOG
Japan Clinical Oncology Group

HERCTEA study

HERB TEA

- TDM-1 failed to demonstrate noninferiority to HPD in OS and PFS in the elderly population

2024 ASCO ANNUAL MEETING

SOLTI

Primary results from PATRICIA Cohort C (SOLTI-1303), a randomized phase II study evaluating palbociclib with trastuzumab and endocrine therapy in pretreated HER2-positive and PAM50 luminal advanced breast cancer.

Eva Ciruelos, Tomás Pascual, Guillermo Villacampa, Sonia Pernas, Rodrigo Sanchez Bayona, José Ponce, Blanca Cantos, Santiago Escrivá-de-Romaní, Antonia Perelló, Alvaro Montaño, Eduardo Martínez, Ana Lopez, Mireia Mele, Juan de la Haba, Javier Cortés, Mafalda Oliveira, Lorea Villanueva, Xavier Gonzalez, Patricia Villagrasa and Aleix Prat

Presenter: Eva M Ciruelos MD, PhD.

Medical Oncology Dpt

University Hospital 12 de Octubre

HM Hospitals

Background

- The incorporation of novel anti-HER2 drugs has changed the treatment landscape of HER2+ advanced breast cancer, but new treatment options are still needed.

- In advanced HR+/HER2+ breast cancer, the combination of the **CDK4/6 inhibitor abemaciclib** with **fulvestrant** and **trastuzumab** showed **improved PFS** versus standard of care chemotherapy plus trastuzumab (MonarcHER, NCT02675231)[1].

- **SOLTI-1303 PATRICIA cohorts A and B** (NCT02448420) evaluated palbociclib plus trastuzumab +/- letrozole in postmenopausal patients with advanced HER2+ breast cancer[2].
  - Combination was feasible and safe.
  - **PAM50 LumA or LumB subtypes** had **superior PFS** compared to non-luminal subtypes: 10.6 vs 4.2 months, adjusted hazard ratio 0.40 (p 0.003).

- **Cohort C of PATRICIA** has prospectively enrolled patients with HR+/HER2+ and PAM50 Luminal A or B tumors to further explore the strategy of using a chemotherapy-free regimen.

[1] Tolaney S (2020). Lancet Oncol, 21(6):763-775
[2] Ciruelos E. et al. (2020). Clin Cancer Res. 26(22):5820-5829

PATRICIA Cohort C: Study design

Open-label, multicenter, randomized phase II trial

- ✓ Male or Pre and postmenopausal women
- ✓ **HR+/HER2+ ABC**
- ✓ **PAM50 Luminal A or B subtype** by Prosigna® (research use only)
- ✓ **At least 1L for ABC**[1]
- ✓ **Baseline LVEF ≥ 50%**
- ✓ **Stable CNS metastasis allowed**[2]
- ✓ **No prior CDK4/6i**

Pre-screening

PAM50 Luminal A/B[3]

R 1:1

Palbociclib 125 mg QD 3W + Trastuzumab* + Endocrine therapy**

Treatment of physician's choice (TPC)***

Re-randomization[4]

R 1:1

Stratification factors:

- Number of previous regimens (1-2 vs ≥ 3)
- Visceral disease (yes vs no)

* Trastuzumab: loading dose of 8mg/kg followed by 6 mg/kg IV or 600 mg SC administration.
** Aromatase inhibitor, fulvestrant or tamoxifen +/- gonadal suppression
*** T-DM1, any endocrine therapy or chemotherapy (gemcitabine, vinorelbine, capecitabine, eribulin, paclitaxel or docetaxel) plus trastuzumab.

Primary endpoint

- Investigator-assessed PFS (RECIST 1.1)

Secondary endpoints

- Overall response rate (ORR)
- Disease control rate (DCR)
- Duration of response
- Safety profile

(1) Including trastuzumab and/or anti-HER2 ADC for ABC ;or recurrence during or within 12 months after completing adjuvant trastuzumab and/or anti-HER2 ADCs and metastatic disease diagnosis.
(2) No evidence of progression, ≥3 wks between completion of local therapy study treatment initiation, and stable doses or no need of corticosteroids.
(3) Evaluated in primary or metastatic (preferred) sample.
(4) Patients that are initially allocated in the TPC i) have a documented disease progression and ii) meet inclusion criteria after progression, can be re-randomized to receive the experimental or control treatment.

PRESENTED BY: Eva M Ciruelos MD, PhD.

Statistical considerations

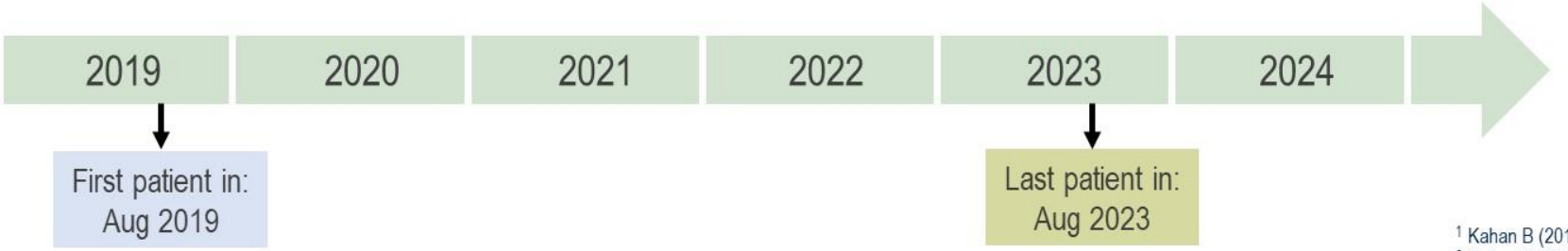
Protocol assumptions

- **Sample size** of **102** patients
- One-sided stratified log-rank test (0.1 alpha)
- **Target** PFS **hazard ratio (HR)**: **0.62**
- To achieve **80% statistical power**, 80 PFS events were needed

Feb 2021: Re-randomization design

- **Patients allocated** in the **TPC arm** could be **re-randomized** after disease progression if the inclusion criteria were met
- **Mixed effects Cox** models were used to adjust for intra-patient correlation
- The re-randomization approach led to unbiased treatment estimation, correct type I error and **potentially reduce number of patients** to be pre-screened[1-2]. **Overall survival** was not assessed as a trial endpoint.

- The trial was **closed earlier** after 73 patients were randomized due to **low recruitment**. At data cut-off, 51 PFS events were observed. The study was **underpowered** based on the protocol assumptions (64% statistical power)



[1] Kahan B (2015). BMC Med Res Methodol
[2] Kahan B (2016). Trials

Patient´s disposition

Assessed for elegibility (N=264)

Excluded (N= 150)
Insufficient sample quality=26
HER2E/basal like =124

Excluded (n= 48)
Exclusion criteria=13
Withdrawal of consent=1
Refuses to participate =1
Death=1
Finalization of study=32

Luminal A/B (N=114)

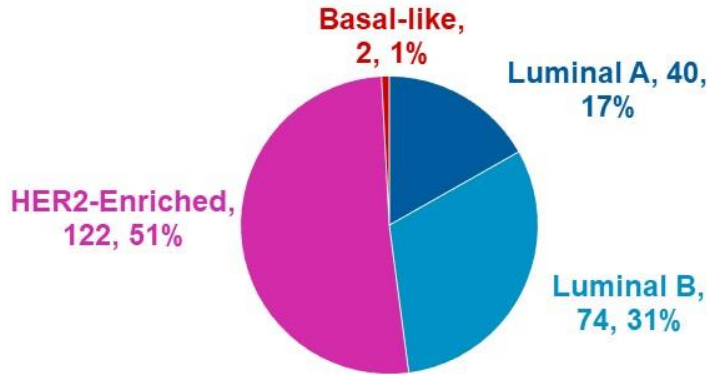
Allocated patients (N=73) ↔ Re-randomized (n=7)

Palbociclib + T + ET (N=38)*	TPC (N=35)
38 received allocated intervention of Trastuzumab + Palbociclib plus: • Aromatase inhibitor: 19 (50%) • Fulvestrant :19 (50%)	2 patients: consent withdrawal (5.7%) 33 received allocated intervention of: • TDM-1: 13 (37.1%) • Trastuzumab plus CT: Vinorelbine (N=6, 17.1%), Capecitabine (N=5, 14.3%), Eribulin (N=5, 14.3%) • Trastuzumab plus ET: 4 (11.4%)
12 patient on treatment 26 discontinued all treatments **25 disease progression** 1 consent withdrawal	1 patient on treatment 34 discontinued all treatments **25 disease progression** **6 consent withdrawal** 2 adverse event 1 physician decision

* 1 patient randomized to TPC received P+T+ET

PAM50 subtype distribution

Pre-screened tumors (N = 238)
Tissue type: primary tumor 54.8%; metastatic 45.2%

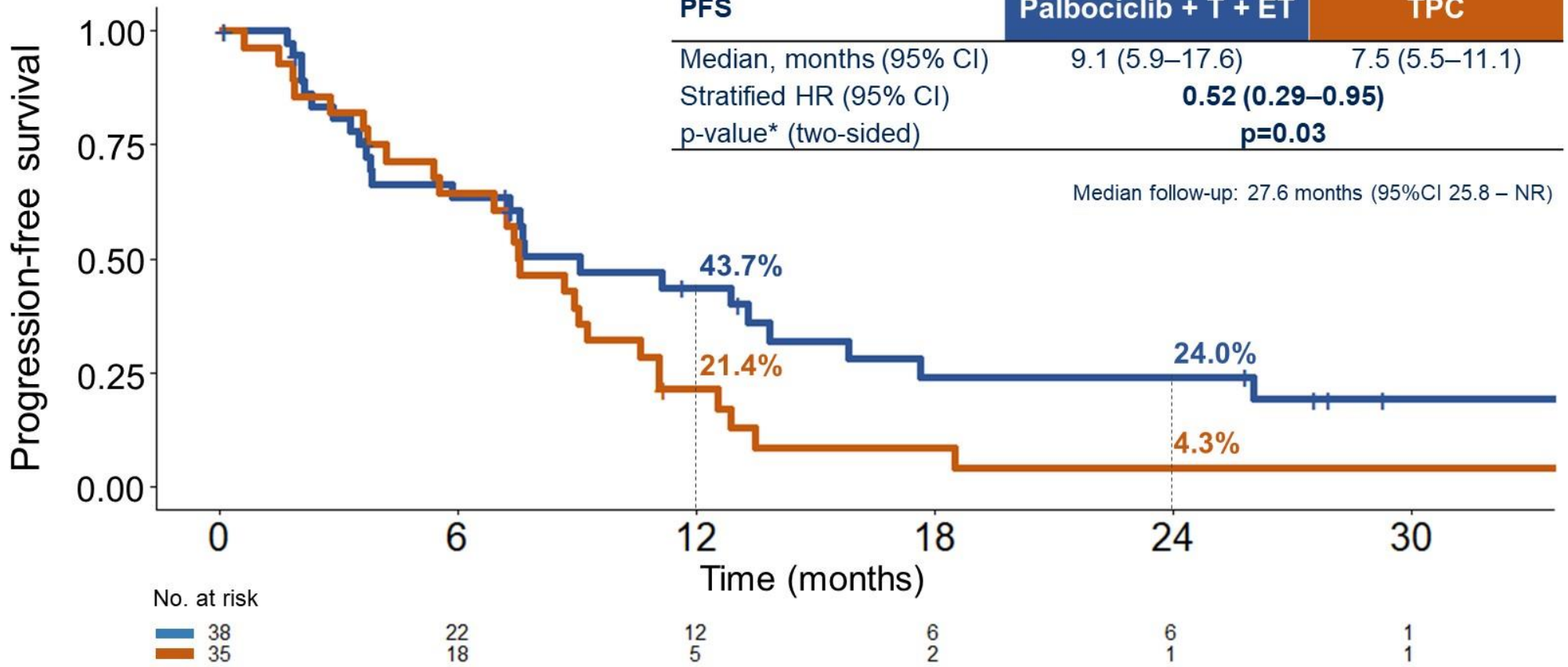


Molecular screening failure rate: 52.1%

Primary objective: Investigator-assessed PFS

PFS	Palbociclib + T + ET	TPC
Median, months (95% CI)	9.1 (5.9–17.6)	7.5 (5.5–11.1)
Stratified HR (95% CI)	**0.52 (0.29–0.95)**	
p-value* (two-sided)	**p=0.03**	

Median follow-up: 27.6 months (95%CI 25.8 – NR)



*p-value was estimated using a stratified mixed effect Cox model

Summary of AEs

AE, n (%)	Palbociclib + T + ET (N=39)*	TPC (N=32)
Any AE	36 (92.3)	28 (87.5)
Grade ≥3	24 (61.6)	16 (50.1)
Any TRAE	34 (87.2)	30 (93.8)
Grade ≥3	**20 (51.3)**	**9 (28.1)**
Dose reductions	13 (33.3)[a]	9 (28.1)
AE leading to permanent discontinuation due to toxicity	0	2 (6.3)[b]
Deaths due to adverse events	0	0

AE, adverse event; TRAE, treatment-related adverse event.
*1 patient randomized to TPC received P+T+ET
[a] 76.9% of dose reductions associated with neutropenia
[b] 1 patient due to recurrent grade 3 neutropenia; 1 patient due to heart failure

PATRICIA

- In advanced HR+ and HER2+ breast cancer and PAM50 luminal A or B intrinsic subtypes, the combination of trastuzumab, ET and palbociclib was feasible

- Hard to draw conclusions from small, underpowered, randomized phase II study

HER2-positive MBC

Setting	Regimen	Trial
1st-line	Taxane + trastuzumab and pertuzumab	CLEOPATRA
2nd-line	Trastuzumab deruxtecan	DESTINY 03
3rd-line	Tucatinib, trastuzumab + capecitabine	HER2CLIMB
	Trastuzumab emtansine	EMILIA
4th line and beyond	Trastuzumab + chemotherapy	
	Lapatinib + capecitabine	
	Trastuzumab + lapatinib	
	Neratinib + capecitabine	NALA
	Margetuximab + chemotherapy	SOPHIA

Eribulin?

TDM-1 + tucatinib?

Today's Talk

- Advance stage
- Early stage
- Future directions

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AACR American Association for Cancer Research

Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis

Sibylle Loibl, Max S. Mano, Michael Untch, Chiun-Sheng Huang, Eleftherios P. Mamounas, Norman Wolmark, Adam Knott, Asna Siddiqui, Thomas Boulet, Beatrice Nyawira, Eleonora Restuccia, Charles E. Geyer, Jr.

Presenting author: Prof. Dr. Sibylle Loibl, M.D., Ph.D

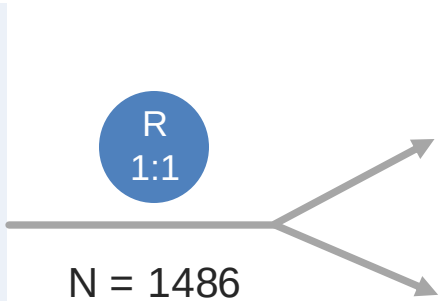
German Breast Group, Neu-Isenburg; Centre for Haematology and Oncology Bethanien, Goethe University, Frankfurt, Germany

GBG GERMAN BREAST GROUP
NSABP Foundation, Inc.

IDFS, invasive disease-free survival; OS, overall survival.

KATHERINE study design

- Prior neoadjuvant therapy consisting of:
  - Minimum 6 cycles of chemotherapy
  - Minimum 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

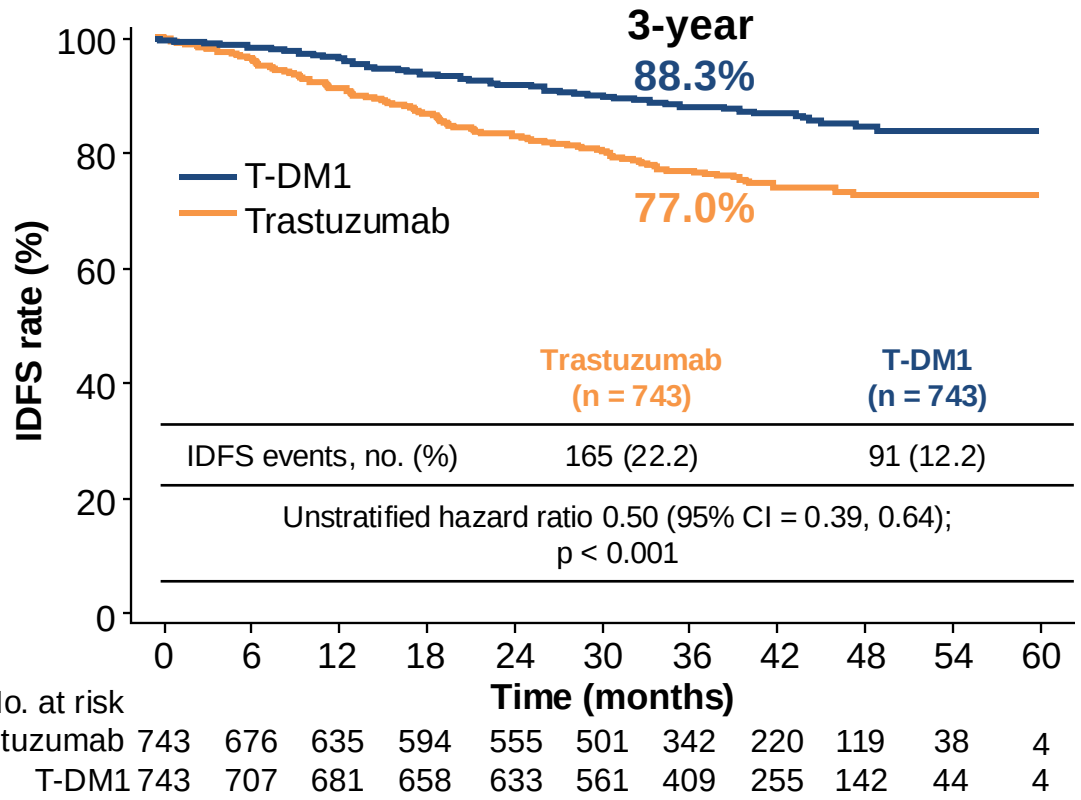
- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL
- **Stratification factors:** Clinical stage at presentation (inoperable vs operable), HR status, preoperative HER2-directed therapy, pathologic nodal status after preoperative therapy

AE, adverse event; DFS, disease-free survival; DRFI, distant recurrence-free interval; HR, hormone receptor; IDFS, invasive disease-free survival; IV, intravenous; OS, overall survival; Q3W, every 3 weeks; QoL, quality of life; R, randomized; T-DM1, ado-trastuzumab emtansine.

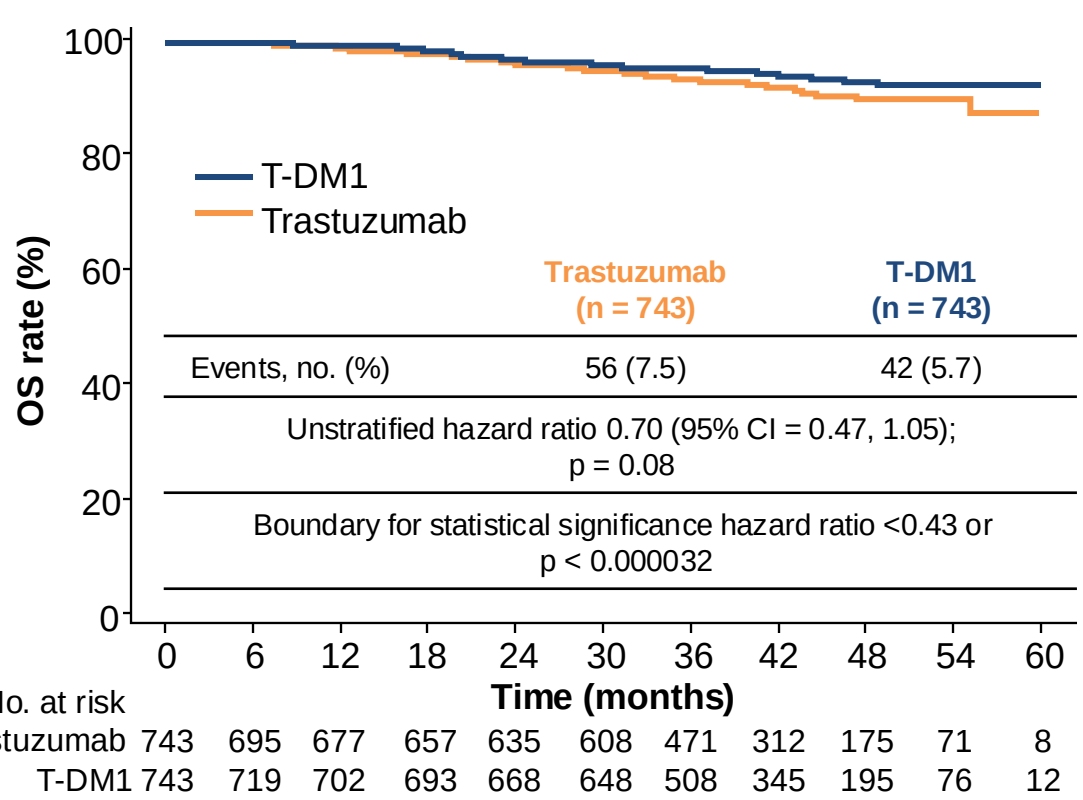
Adapted from *N Engl J Med*, von Minckwitz *et al.*, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

KATHERINE primary analysis (2018)

IDFS



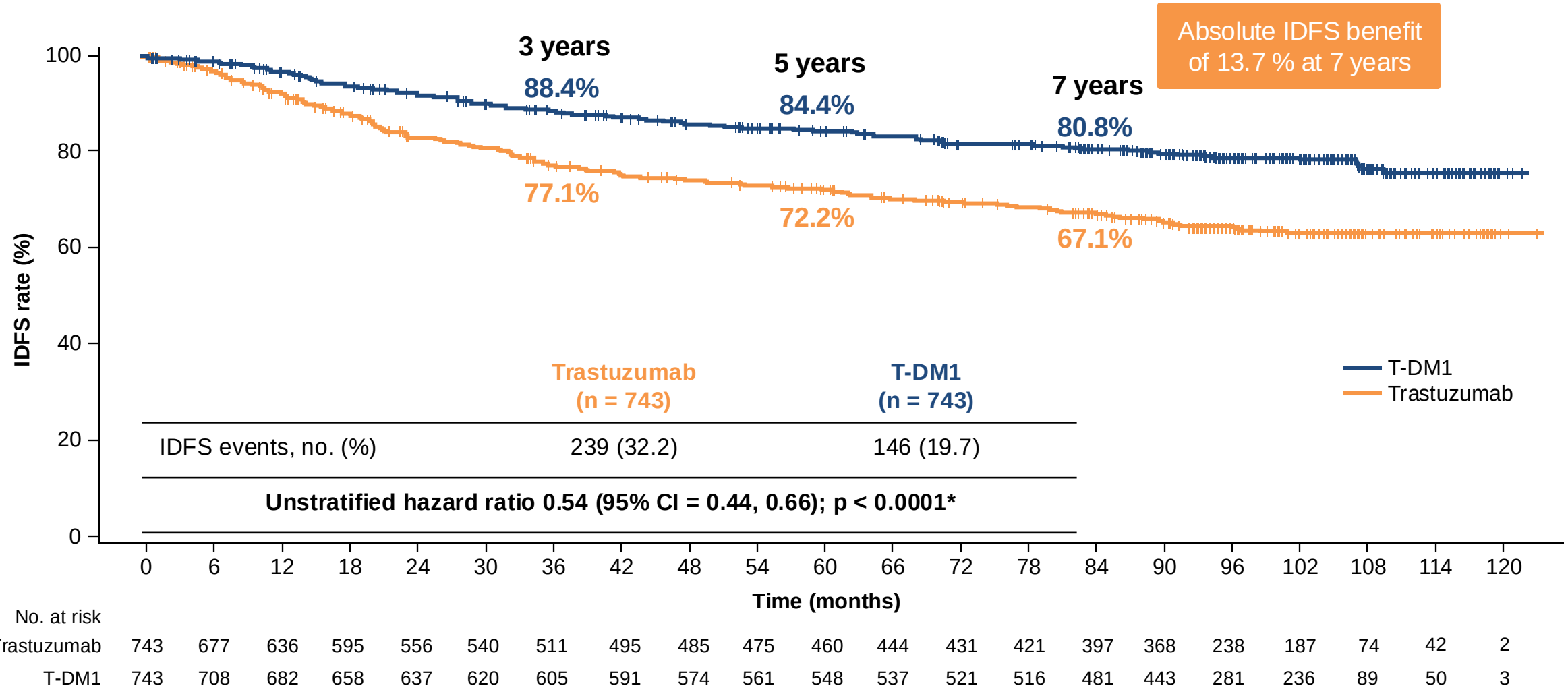
OS



CCOD: July 25, 2018; median follow-up: 41.4 months (T-DM1) and 40.9 months (trastuzumab).
CCOD, clinical cutoff date; CI, confidence interval; IDFS, invasive disease-free survival; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

Adapted from *N Engl J Med*, von Minckwitz *et al.*, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

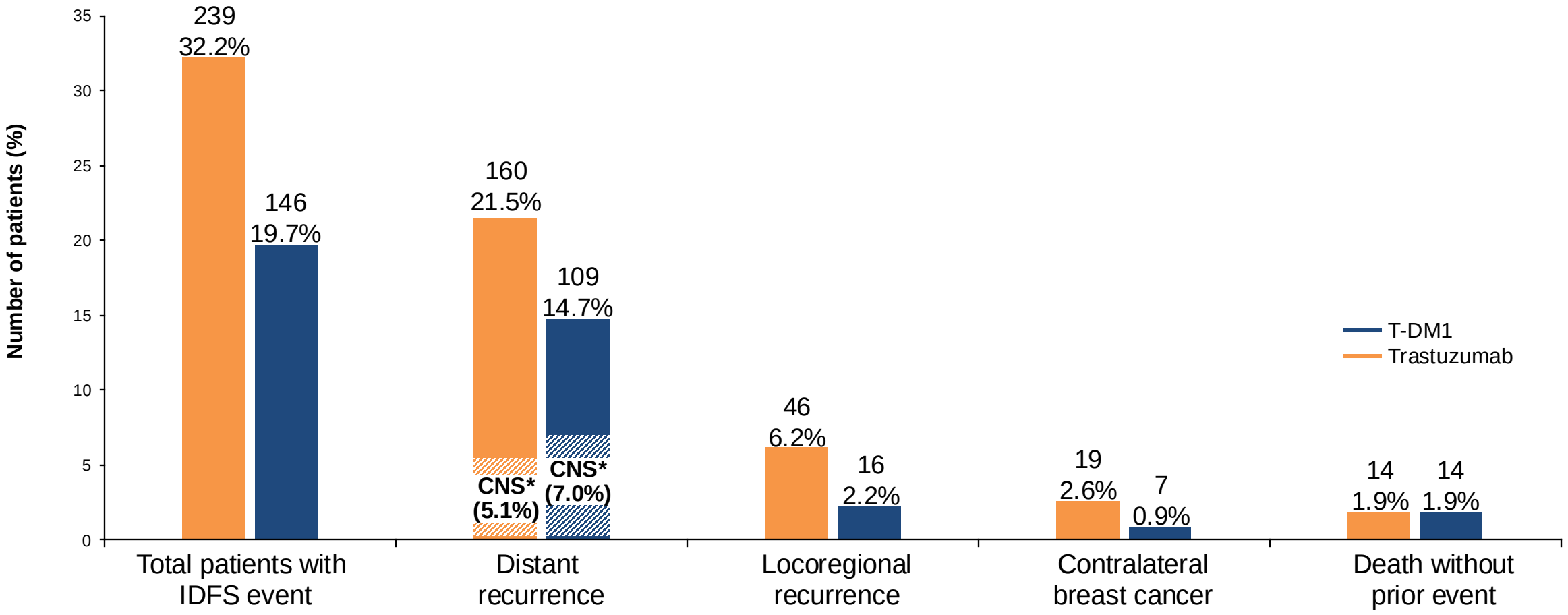
KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)



No. at risk																					
Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
T-DM1	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3

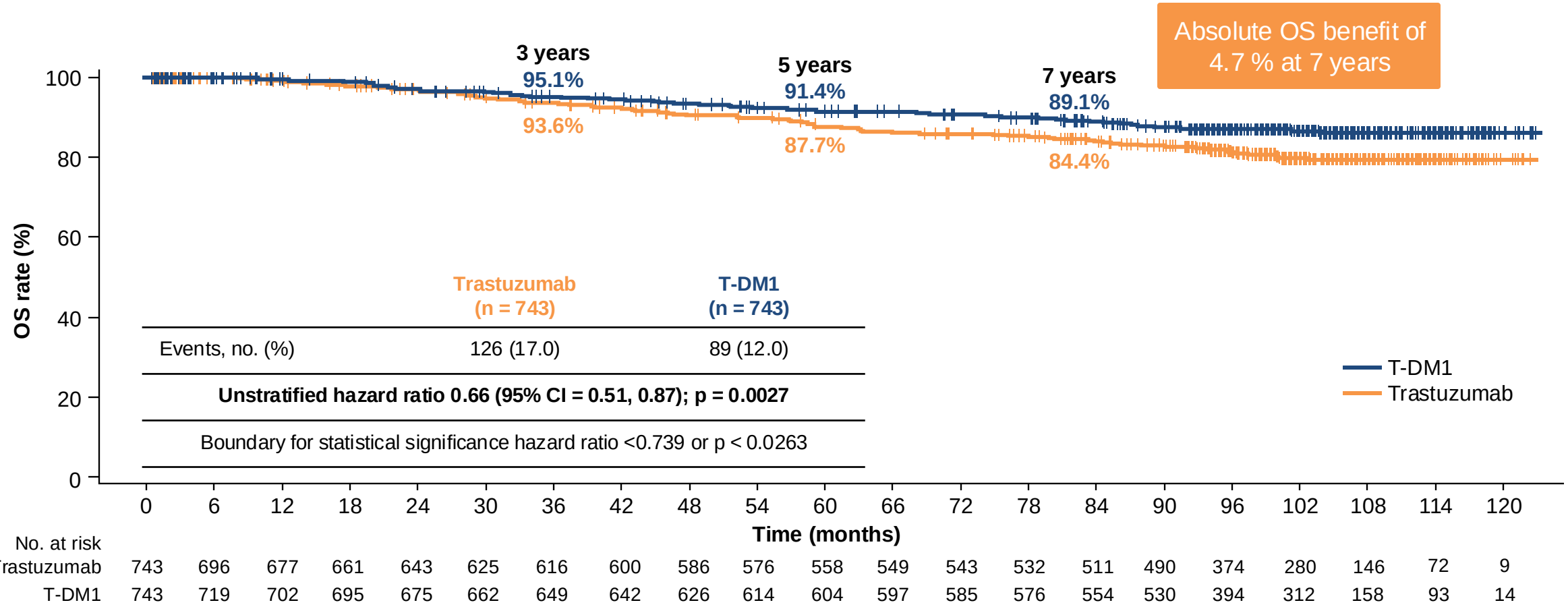
* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Site of first occurrence of an IDFS event



* **CNS metastases as component of distant recurrence (isolated or with other sites).**
CNS recurrence after first IDFS event: 19 patients (2.6%) in the trastuzumab arm and four patients (0.5%) in the T-DM1 arm.
CNS, central nervous system; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



Significant reduction in risk of death by 34% with T-DM1

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

KATHERINE

- Reassuring OS data on a regimen that has been FDA-approved since 2019.
- Although small numbers, patients who received pertuzumab and those with small volume residual disease benefitted.
- More toxicities with TDM-1 so the approach should be individualized and monitored.

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Future Directions

- DB-09: THP vs T-Dxd vs T-Dxd + P in first-line HER2-positive breast cancer

- PATINA: H +/-P + ET after induction chemo vs H +/-P + ET + palbociclib

Thank you!

Questions?

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