Recent Advances In The Treatment Of Metastatic Breast Cancer

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Disclosures

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ER+ HER2 negative

- CDK 4/6 inhibitors
- Antibody Drug Conjugates
- Oral Selective Estrogen Downregulators

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Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy

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Background

- Chemotherapy (CT) is the standard of care in ABC with clinically aggressive disease features that include rapidly progressing or highly symptomatic disease and life-threatening visceral crisis, which requires rapid disease control[1]
- Combination CT is associated with a higher ORR and longer PFS than single-agent CT and may be preferred for those who have a critical disease condition and may tolerate potentially toxic treatment[2]
- Ribociclib (RIB) + endocrine therapy (ET) demonstrated statistically significant PFS and OS benefits over ET alone in 3 Phase III clinical trials (MONALEESA-2, -3, and -7) in patients with HR+/HER2− ABC, including patients with visceral metastases and a high tumor burden[3-11]
- No data on a head-to-head comparison of CDK4/6 inhibitor + ET vs combination CT in the patient population with aggressive HR+/HER2− disease have been published
- Here we report the prespecified primary analysis of PFS and key secondary endpoints from the randomized, open-label, multinational, Phase II RIGHT Choice trial

ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinases 4 and 6; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. Cardoso F, et al. *Ann Oncol.* 2020;31:1623-1649. 2. O'Shaughnessy J. *Oncologist.* 2005;10 Suppl 3:20-9. 3. Tripathy D, et al. *Lancet Oncol.* 2018;19:904-915. 4. Slamon DJ, et al. *J Clin Oncol.* 2018;36:2465-2472. 5. Hortobagyi GN, et al. *N Engl J Med.* 2016;375:1738-1748. 6. Im SA, et al. *N Engl J Med.* 2019;381:307-316. 7. Slamon DJ, et al. *N Engl J Med.* 2020;382:514-524. 8. Hortobagyi GN, et al. *N Engl J Med.* 2022;386:942-950. 9. Hortobagyi GN, et al. ESMO 2021. Oral LBA17_PR. 10. Tripathy D, et al. SABCS 2020. Poster PD2-04. 11. Slamon DJ, et al. ASCO 2021. Oral 1001.

RIGHT Choice study design

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2[b]
- Total bilirubin ≤ 1.5 ULN
- N = 222[c]

Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

R 1:1

Ribociclib
(600 mg, 3 weeks on/1 week off)
+
Letrozole or anastrozole + goserelin

Investigators' choice of combination CT[e]

Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]

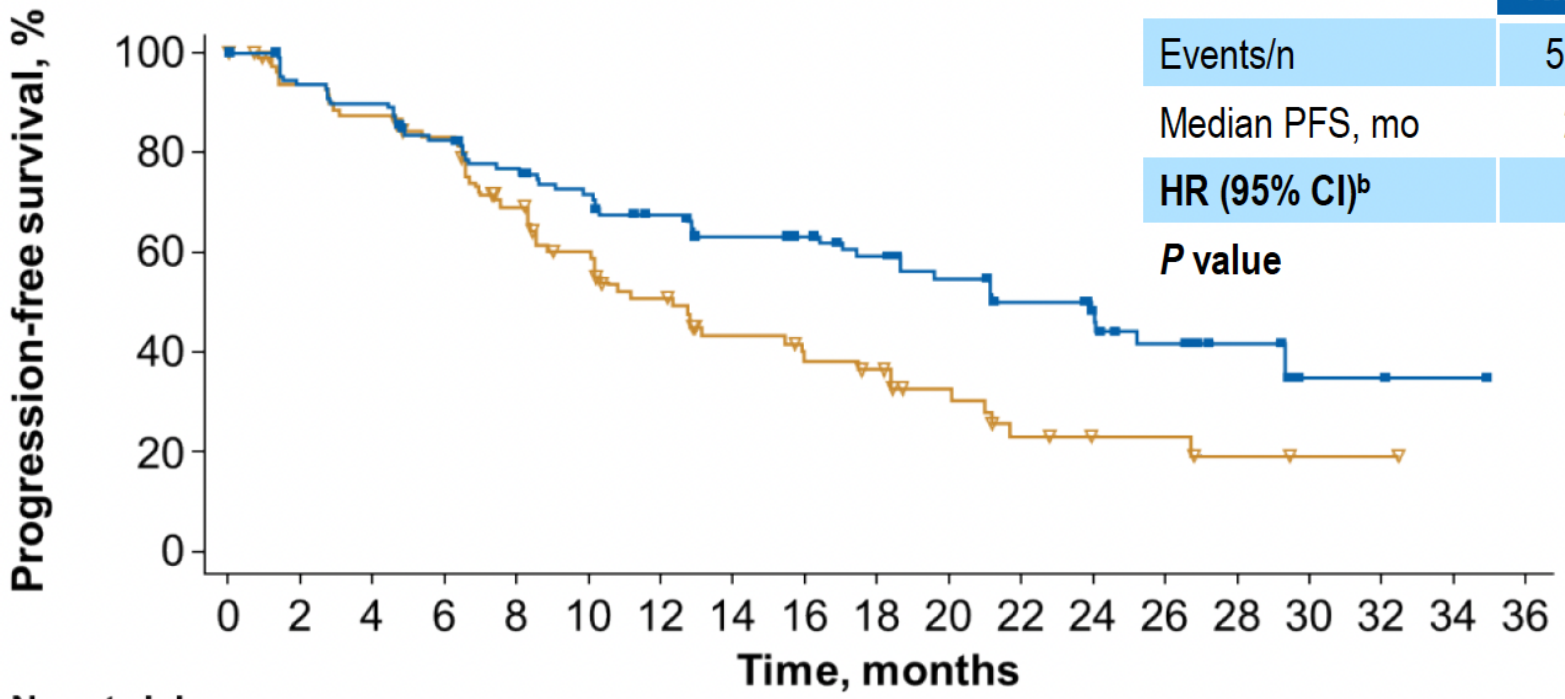
Primary endpoint
- PFS (locally assessed per RECIST 1.1)

Secondary endpoints
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor positive; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response; ULN, upper limit of normal.
[a] Where combination CT is clinically indicated by physician's judgment; [b] For patients with ECOG 2, the poor performance status should be due to breast cancer; [c] Patients were enrolled from Feb 2019 to Nov 2021; [d] Disease-free interval is defined as the duration from date of complete tumor resection for primary breast cancer lesion to the date of documented disease recurrence; [e] If one of the combination CT drugs had to be stopped because of toxicity, the patient was allowed to continue on the other, better-tolerated CT drug (monotherapy); [f] Until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision, and at end of treatment.

First-line RIB + ET achieved a statistically significant PFS benefit of ≈ 1 year over combination CT in aggressive HR+/HER2– ABC

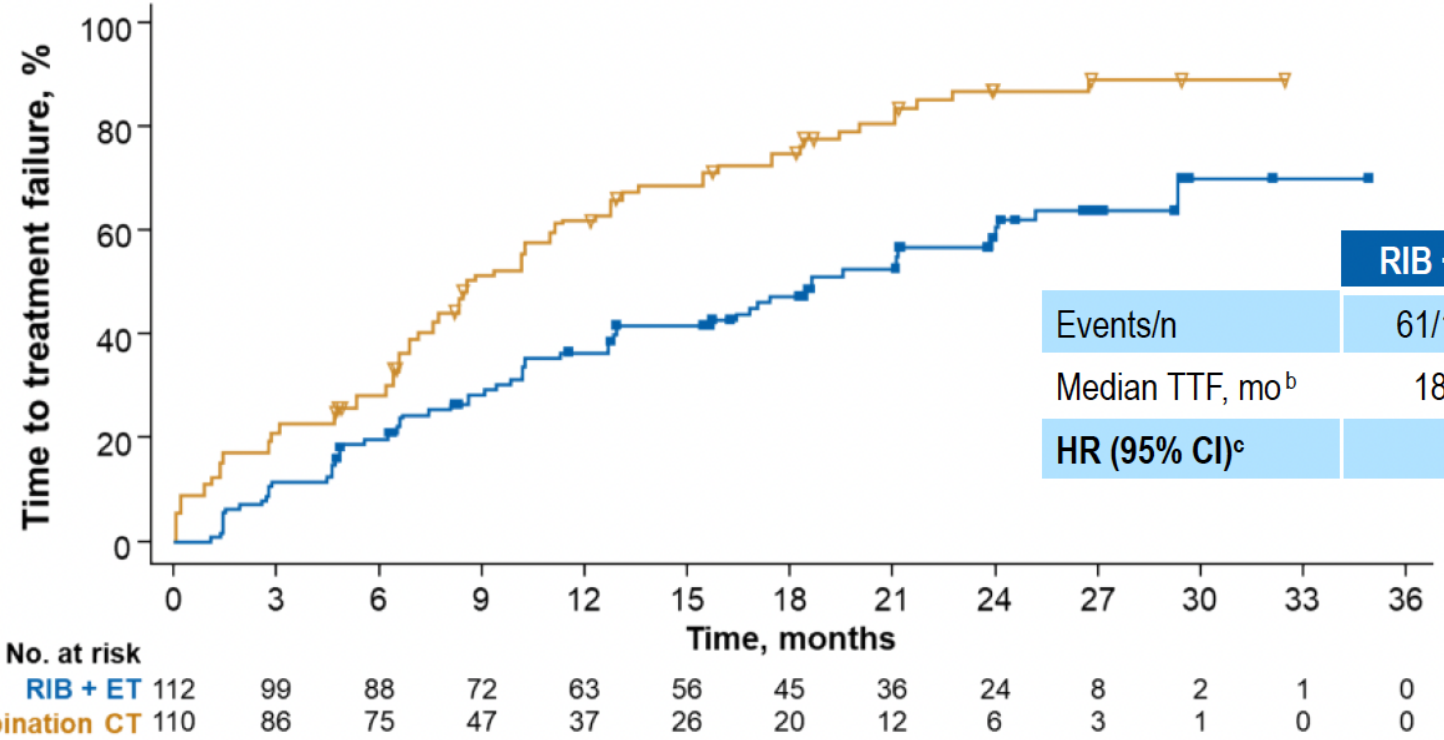


	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HR, hazard ratio; IRT, interactive response technology; PFS, progression-free survival; RIB, ribociclib.

[a] Ten patients in CT arm did not receive any treatment; [b] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT.

Median time to treatment failure (TTF) was longer with RIB + ET vs combination CT

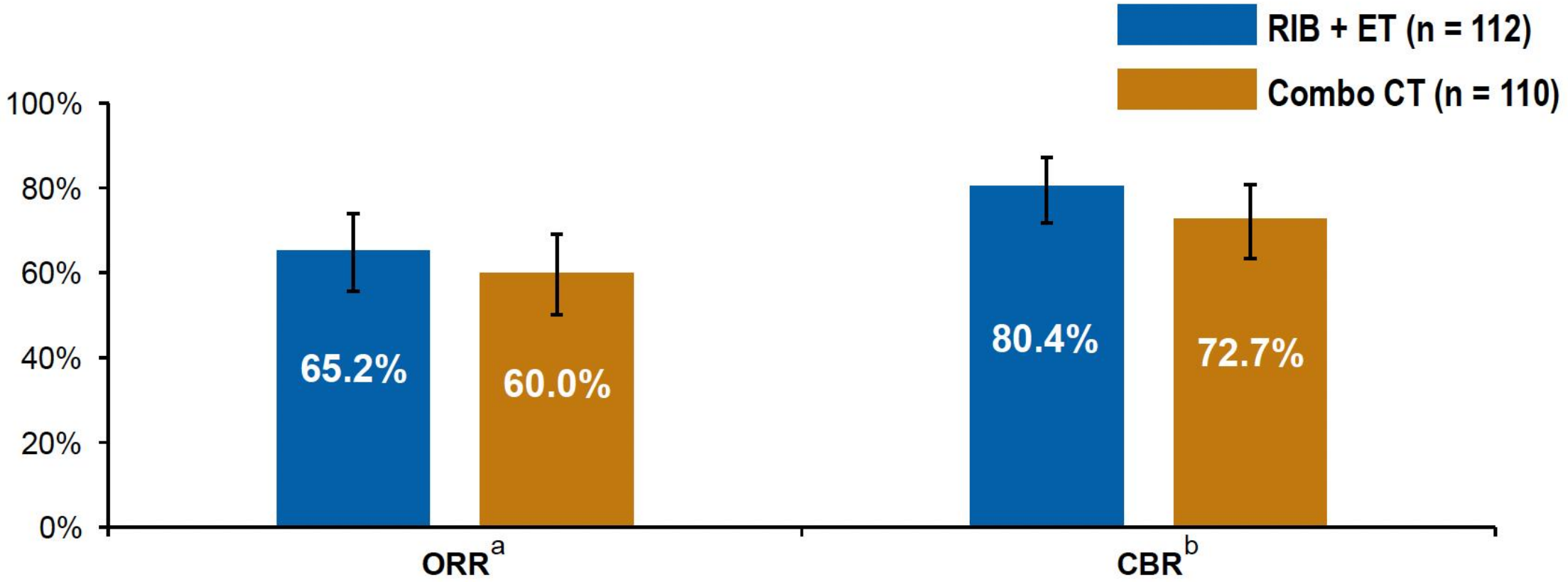


	RIB + ET	Combo CT
Events/n	61/112	84/110[a]
Median TTF, mo[b]	18.6	8.5
HR (95% CI)[c]	**0.45 (0.32-0.63)**	

- A sensitivity analysis[d] confirmed the TTF findings in the safety set
- The 3-month treatment failure rate[e] in the RIB arm was approximately half (n = 13; 11.6%; 95% CI, 6.3%-19.0%) that in the combination CT arm (n = 24; 21.8%; 95% CI, 14.5%-30.7%)

Combo CT, combination chemotherapy; ET, endocrine therapy; HR, hazard ratio; IRT, interactive response technology; RIB, ribociclib.
[a] Ten patients in CT arm did not receive any treatment; [b] Defined as the time from randomization to progression, death, change to other anticancer therapy, or discontinuation; [c] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT; [d] The sensitivity analysis excluded the 10 patients in the CT arm who did not receive any treatment; [e] The proportion of patients who discontinued study treatment due to progressive disease, death, change to other anticancer therapy, or discontinuation due to reasons other than protocol violation.

ORR and CBR were similar between RIB + ET and combination CT

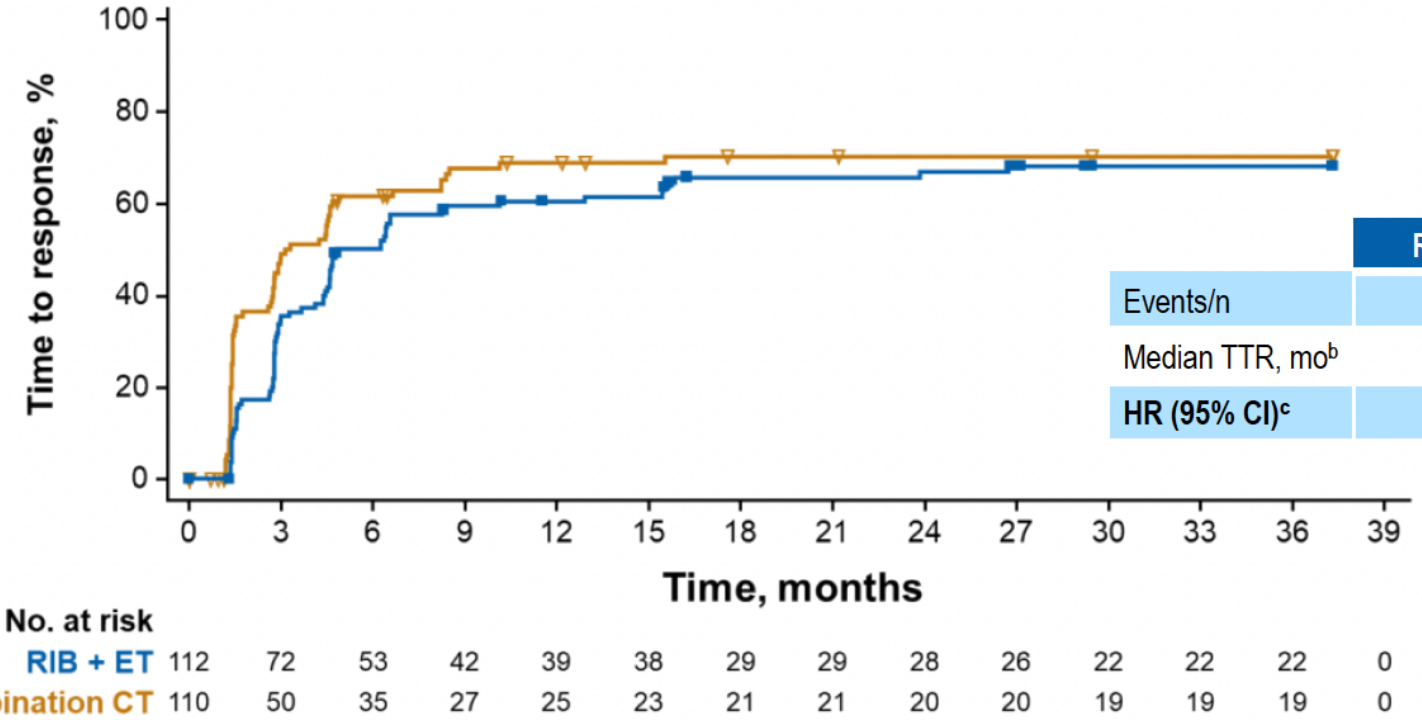


- A sensitivity analysis[c] confirmed the ORR and CBR findings in the safety set

CBR, clinical benefit rate; Combo CT, combination chemotherapy; CR, complete response; ET, endocrine therapy; ORR, overall response rate; PD, progressive disease; PR, partial response, RIB, ribociclib; SD, stable disease.

[a] Proportion of patients with CR or PR without confirmation (confirmation imaging was not mandatory according to study protocol); [b] Proportion of patients with CR or PR without confirmation or SD or non-CR/non-PD ≥24 weeks; [c] This analysis included all patients who received ≥1 dose of any component of the study treatment (safety set).

Time to onset of response (TTR) for RIB + ET was similar to combination CT



	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	**0.78 (0.56-1.09)**	

- A sensitivity analysis[d] confirmed the TTR findings in the safety set

Combo CT, combination chemotherapy; CR, complete response, ET, endocrine therapy; HR, hazard ratio; IRT, interactive response technology; PR, partial response; RIB, ribociclib.
[a] Ten patients in CT arm did not receive any treatment; [b] TTR is defined as the time from the date of randomization to the first documented response of either CR or PR without confirmation (confirmation imaging was not required according to study protocol); [c] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT; [d] The sensitivity analysis excluded the 10 patients in the CT arm who did not receive any treatment and were removed from the denominator for the CT arm.

Conclusions

- RIGHT Choice is the first prospective study comparing a CDK4/6 inhibitor + ET with combination CT and demonstrating the PFS superiority of RIB + ET over combination CT in patients with HR+/HER2− ABC with aggressive clinical features of rapidly progressing or highly symptomatic disease, including visceral crisis
  - First-line RIB + ET demonstrated a statistically significant PFS benefit (≈1 year longer) vs combination CT (24.0 vs 12.3 months; HR, 0.54) in pre/perimenopausal patients with aggressive HR+/HER2− ABC
- RIB + ET also showed longer TTF than combination CT with similar TTR and ORR between the two treatment groups, matching the high tumor response rate seen with combination CT
- No new safety signals were observed with RIB + ET
  - Compared with RIB +ET, combination CT was associated with higher rates of treatment-related AEs, many that impact QOL
- First-line RIB + ET offers an efficacious, clinically meaningful treatment option for patients with aggressive HR+/HER2− ABC, obviating the need for combination CT and related toxicities

ABC, advanced breast cancer; AE, adverse event; CDK4/6, cyclin-dependent kinases 4 and 6; CT, chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; QOL, quality of life; RIB, ribociclib; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response.

2022 ASCO® ANNUAL MEETING

A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer: MAINTAIN Trial

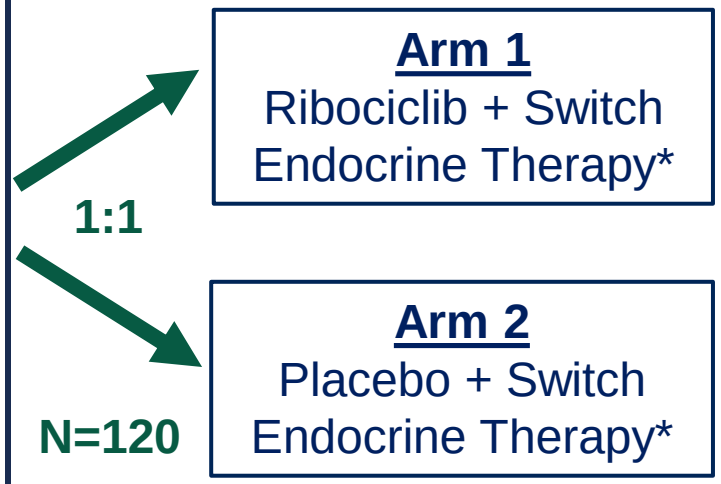
Kevin Kalinsky, Melissa K Accordino, Cody Chiuzan, Prabhjot Mundi, Meghna S Trivedi, Yelena Novik, Amy Tiersten, Amelia Zelnak, George Raptis, Lea Baer, Sun Y Oh, Erica Stringer-Reasor, Sonya Reid, Eleni Andreopoulou, William Gradishar, Kari B Wisinski, Anne O'Dea, Ruth O'Regan, Katherine D Crew, Dawn L Hershman

PRESENTED BY:
Kevin Kalinsky, MD, MS

Schema

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed



Primary Endpoint

- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints

- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

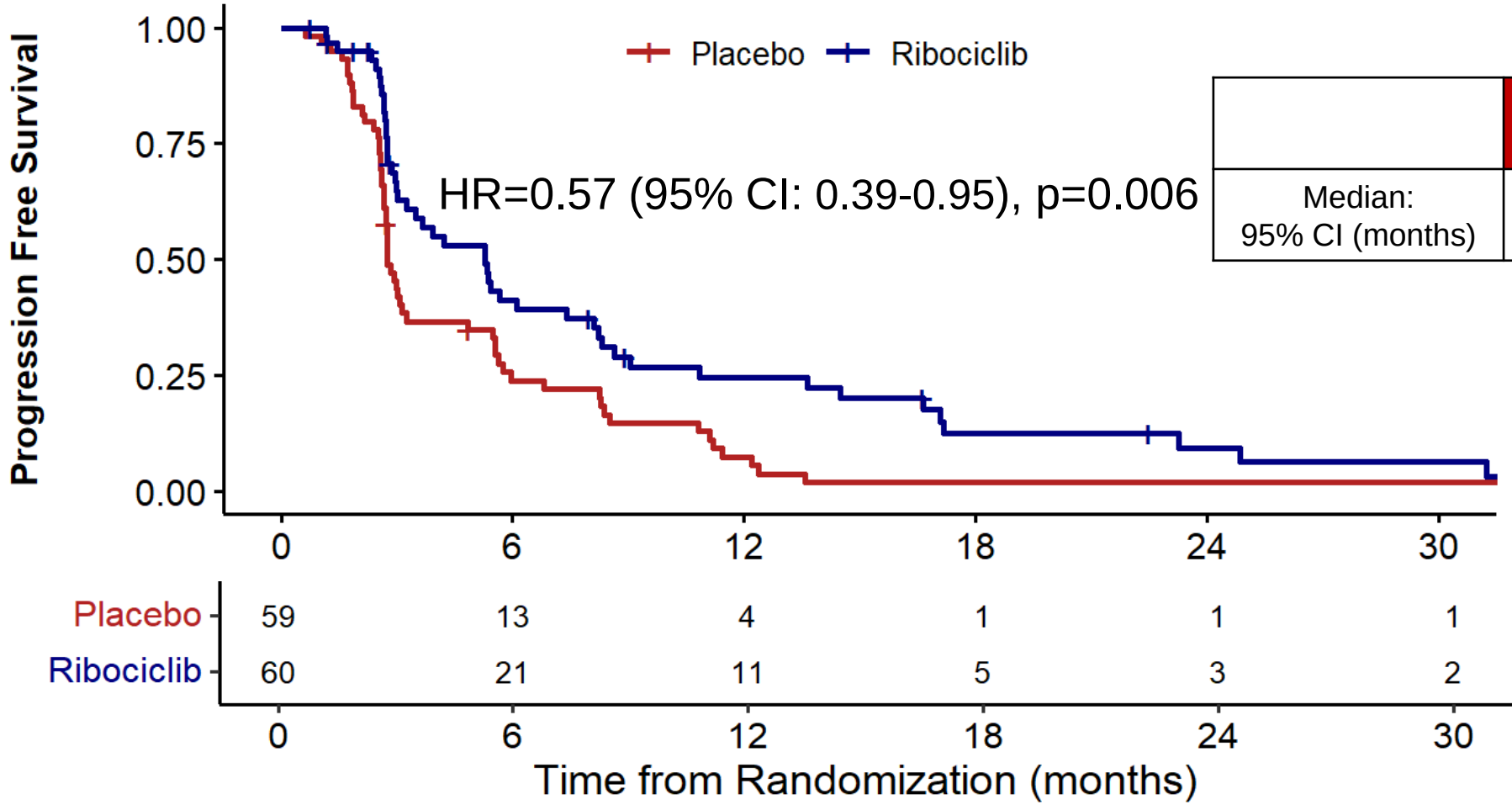
Patient Characteristics and Prior Treatment

	Placebo (n=59)	Ribociclib (n=60)
Female - no. (%)	58 (99%)	60 (100%)
Median age – years (IQR)	59 (52-65)	55 (48-67)
Race or ethnic group – no. (%)		
White	42 (71%)	46 (77%)
Black	8 (14%)	5 (8%)
Asian	2 (3%)	5 (8%)
Other or not specified	7 (12%)	4 (7%)
ECOG PS – no. (%)		
0	38 (64%)	40 (67%)
1	21 (36%)	20 (33%)
De Novo Metastasis at Dx - no. (%)* **	32 (54%)	21 (35%)
Visceral Metastasis – no. (%)	35 (59%)	36 (60%)
Bone-Only Disease – no. (%)	9 (15%)	13 (22%)
≥ 2 prior ET for MBC – no. (%)	11 (19%)	11 (18%)
Chemotherapy for MBC – no. (%)	7 (12%)	4 (7%)

	Placebo (n=59)	Ribociclib (n=60)
Prior CDK 4/6 inhibitor – no. (%)		
Palbociclib*	51 (86%)	52 (87%)
Ribociclib**	8 (14%)	6 (10%)
Abemaciclib	0 (0%)	2 (3%)
Median duration of prior CDK 4/6 inhibitor - months (IQR)	17 (11-23.5)	15.5 (12-21)
Prior CDK 4/6 inhibitor duration– no. (%)**		
≤ 12 months	21 (36%)	18 (30%)
> 12 months	38 (64%)	42 (70%)
Prior CDK 4/6 inhibitor in metastatic setting - no. (%)	59 (100%)	60 (100%)
Intervening treatment after progression on prior CDK 4/6 inhibitor - no. (%)	6 (10%)	1 (2%)

* Includes 1 pt who did not tolerate prior abemaciclib and 2 pts with insurance issues with ribociclib; ** Includes 1 pt who did not tolerate prior palbociclib; ***p=0.035; **** 10 pts (17%) in placebo arm and 7 pts (12%) pts in ribociclib arm on prior CDK4/6 inhibitor ≤ 6 months; IQR = interquartile range

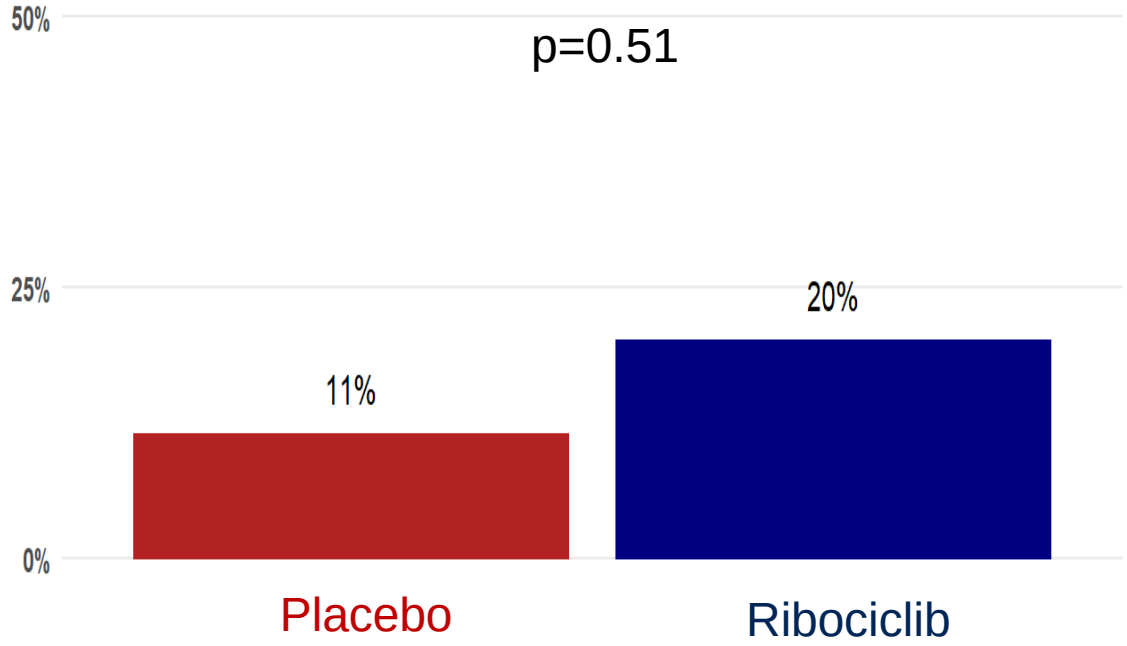
Primary Endpoint: Progression Free Survival (PFS)



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

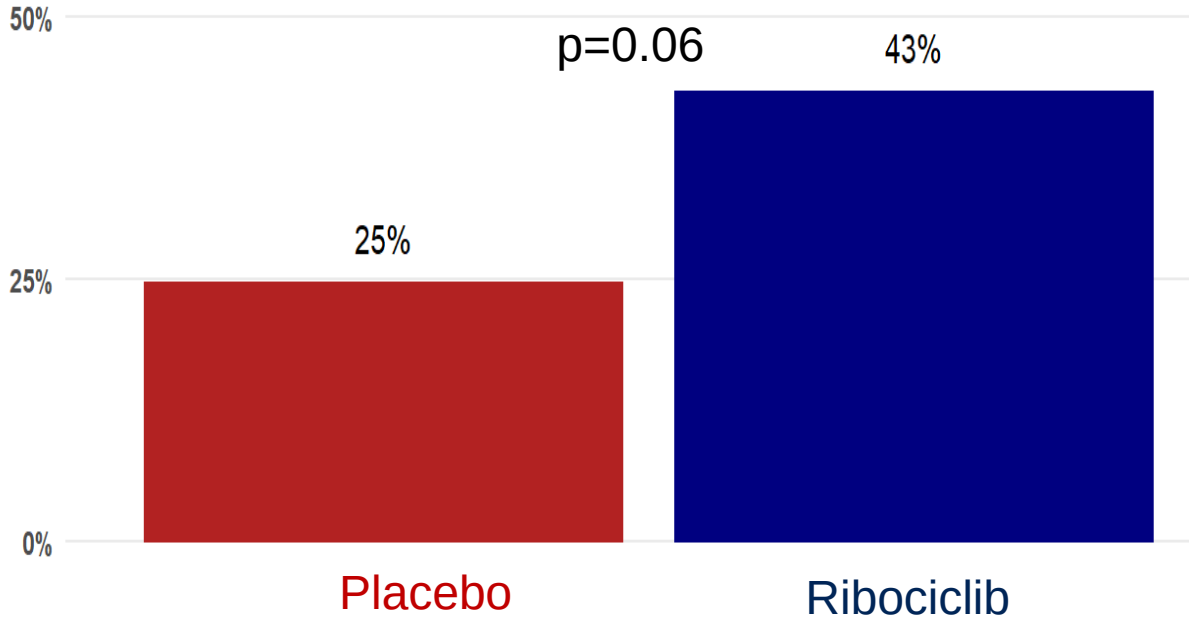
Overall Response and Clinical Benefit Rate

Overall Response Rate (n=70)



	Placebo + ET (n=35)	Ribociclib + ET (n=35)
CR	0 (0%)	2 (6%)
PR	4 (11%)	5 (14%)
Median DOR (IQR) (mos)	14.8 (6.7-21.3)	18.8 (11.4-50.2)

Clinical Benefit Rate (n=105)



	Placebo + ET (n=57)	Ribociclib + ET (n=49)
CR, PR, or SD ≥ 24 weeks	14 (25%)	21 (43%)

IQR = Interquartile Range, CR = Complete response, PR = Partial Response, DOR = Duration of Response, SD = Stable Disease

PRESENTED BY:
Kevin Kalinsky, MD, MS

Conclusion

- **First randomized trial to show the benefit of ribociclib and switching ET after CDK 4/6 inhibitor progression**
  - Ribociclib + ET led to a statistically significant improvement in PFS compared to placebo + ET in pts with tumor progression following prior CDK 4/6 inhibitor
  - Palbociclib was the prior CDK4/6 inhibitor in 87% of pts
  - 43% risk reduction of progression or death with ribociclib vs. placebo in ITT population
  - Higher PFS rate at 6 months and 12 months, as well as improved clinical benefit rate, with ribociclib vs. placebo
  - Ribociclib + ET demonstrated a manageable safety profile

2022 ASCO® ANNUAL MEETING

DESTINY-Breast04

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

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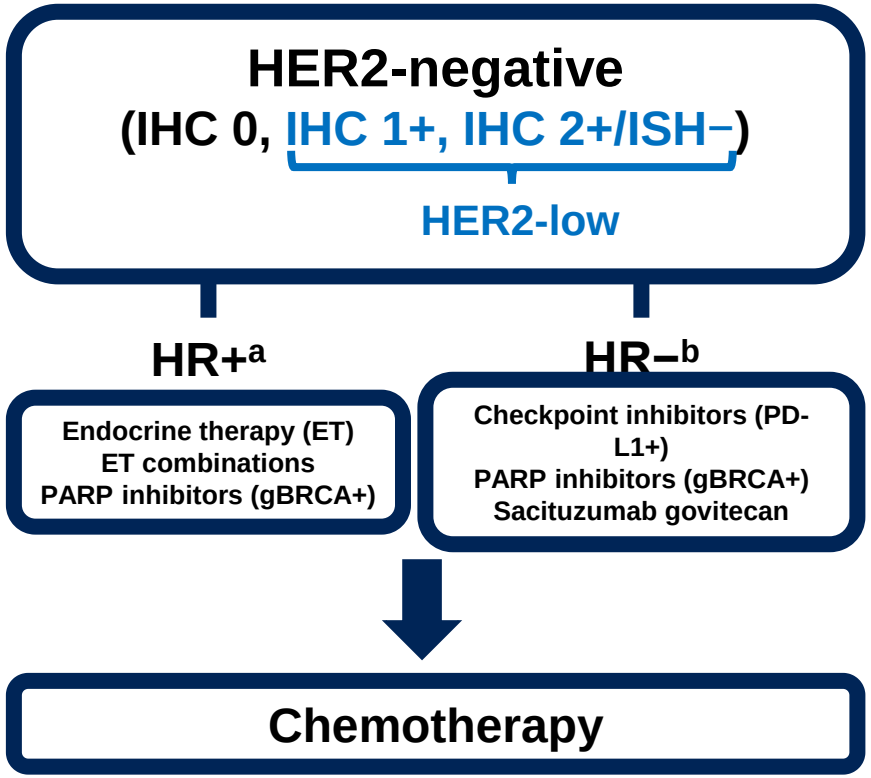
June 5, 2022

Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

On behalf of the DESTINY-Breast04 investigators

HER2-low mBC: Unmet Clinical Need

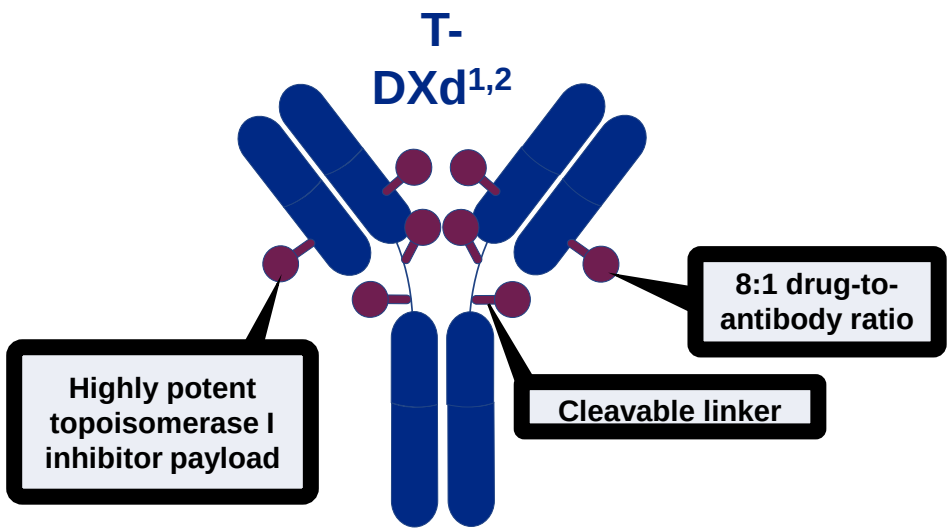
Current Standard of Care



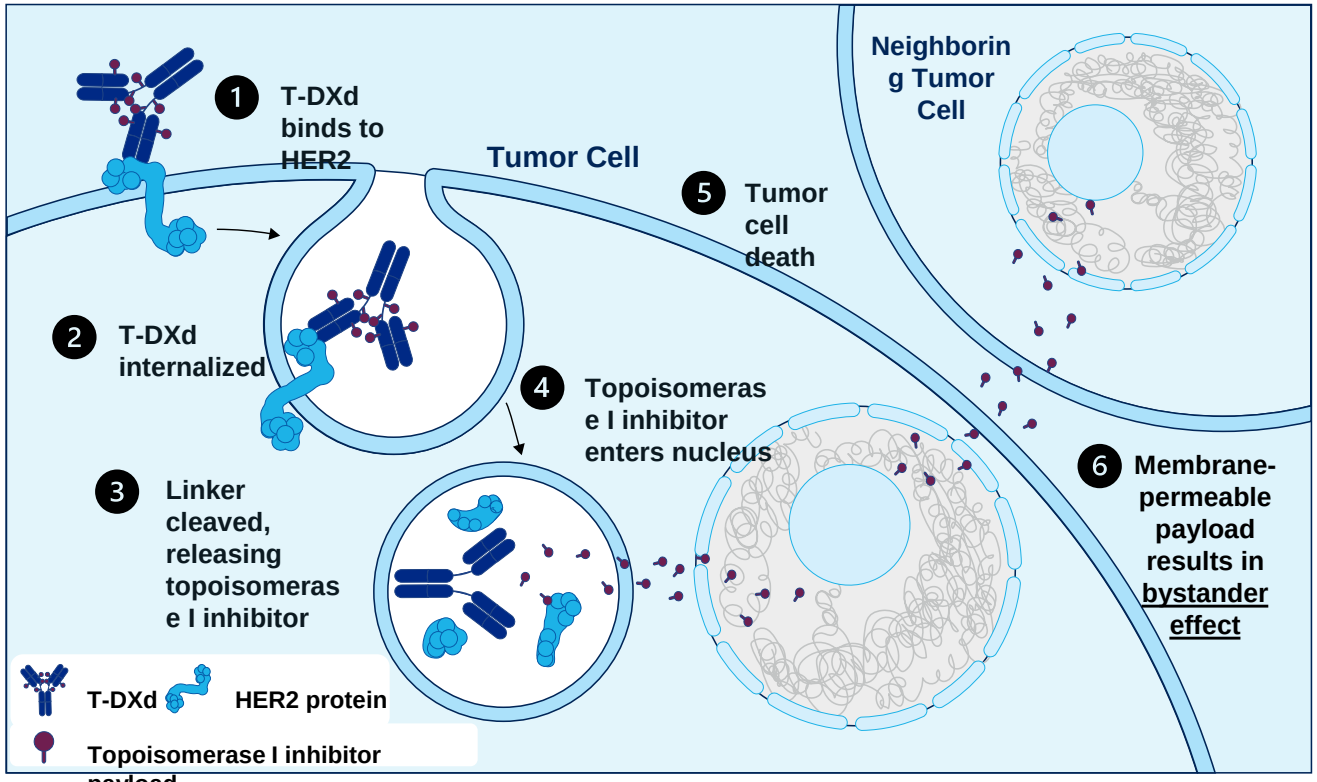
- **HER2-low mBC is defined by IHC scores of 1+ or 2+/ISH−**
  - This is a heterogenous population with a high prevalence of HR coexpression and without a distinct biology
- **HER2-low mBC is treated as HER2− mBC, with limited options for later lines of therapy[1-4]**
  - Current HER2-targeted therapies are not effective for patients with tumors that express lower levels of HER2
- **Therapeutic options for patients with HR+/HER2− mBC after CDK4/6i progression have limited efficacy**
  - Real-world studies suggest a PFS of <4 months after progressive disease with CDK4/6i[5]
- **Limited benefit exists for patients who progress after multiple lines of chemotherapy**
  - In a pooled analysis of patients with HER2− mBC, eribulin and capecitabine provide minimal benefit, with a mPFS of ~4 months and mOS of ~15 months[6]

CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; gBRCA+, germline breast cancer gene positive; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; mOS, median overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death ligand 1; mPFS, median progression-free survival; T-DXd, trastuzumab deruxtecan.
[a]Immunoreactive for estrogen or progesterone receptor in ≥1% tumor cell nuclei. [b]Immunoreactive for estrogen or progesterone receptor in <1% tumor cell nuclei.
1. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962. 2. Aogi K, et al. *Ann Oncol.* 2012;23:1441-1448. 3. Eiger D, et al. *Cancers (Basel).* 2021;13(5):1015. 4. Fehrenbacher L, et al. *J Clin Oncol.* 2019;38(5):444-453. 5. Mo H, et al. *Clin Breast Cancer.* 2022;22:143-148. 6. Kaufman PA, et al. *J Clin Oncol.* 2015;33:594-601.

T-DXd MOA, Bystander Effect, and Rationale for Targeting HER2-low mBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



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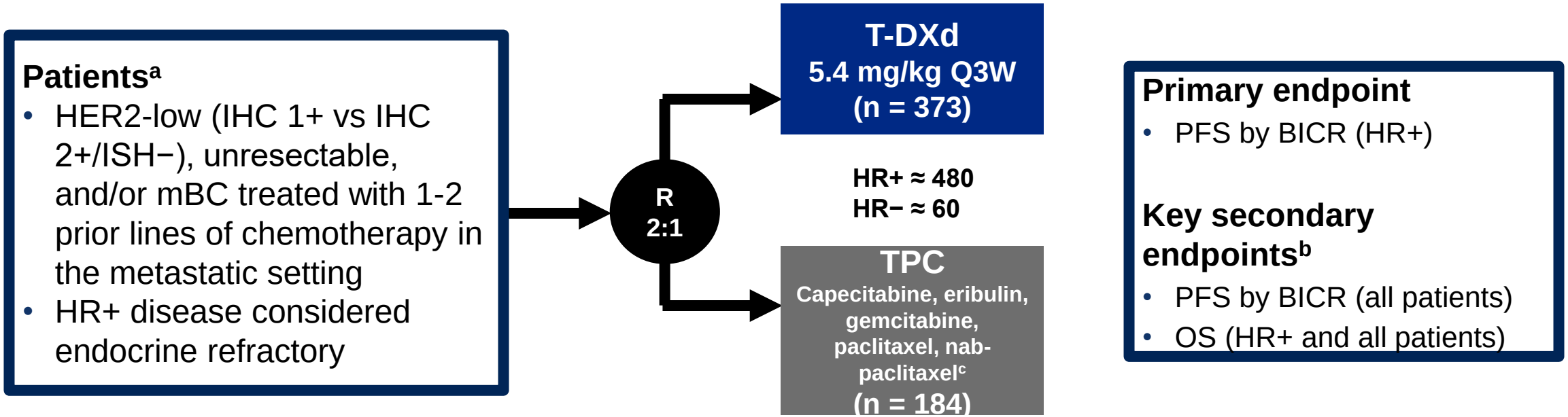
HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Modi S, et al. *J Clin Oncol.* 2020;38:1887-1896.

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

Baseline Characteristics

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]Hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes misstratified patients.

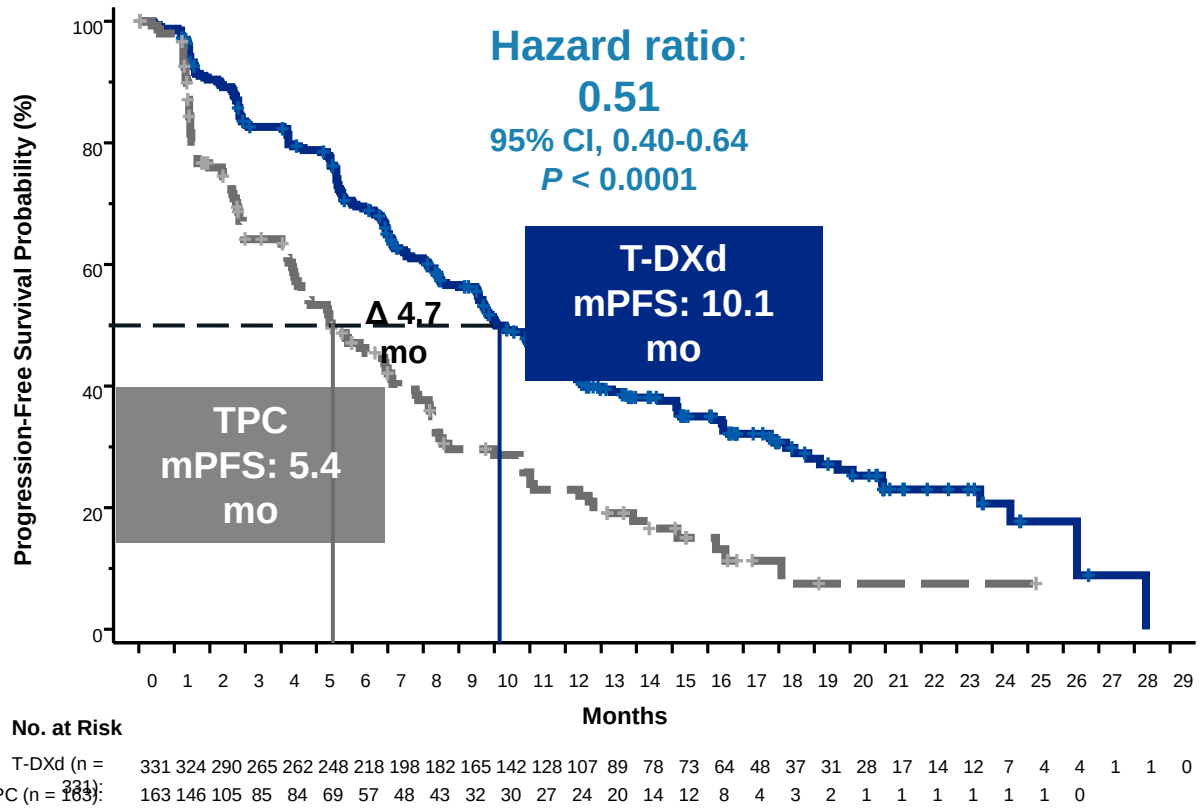
Prior Therapies

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

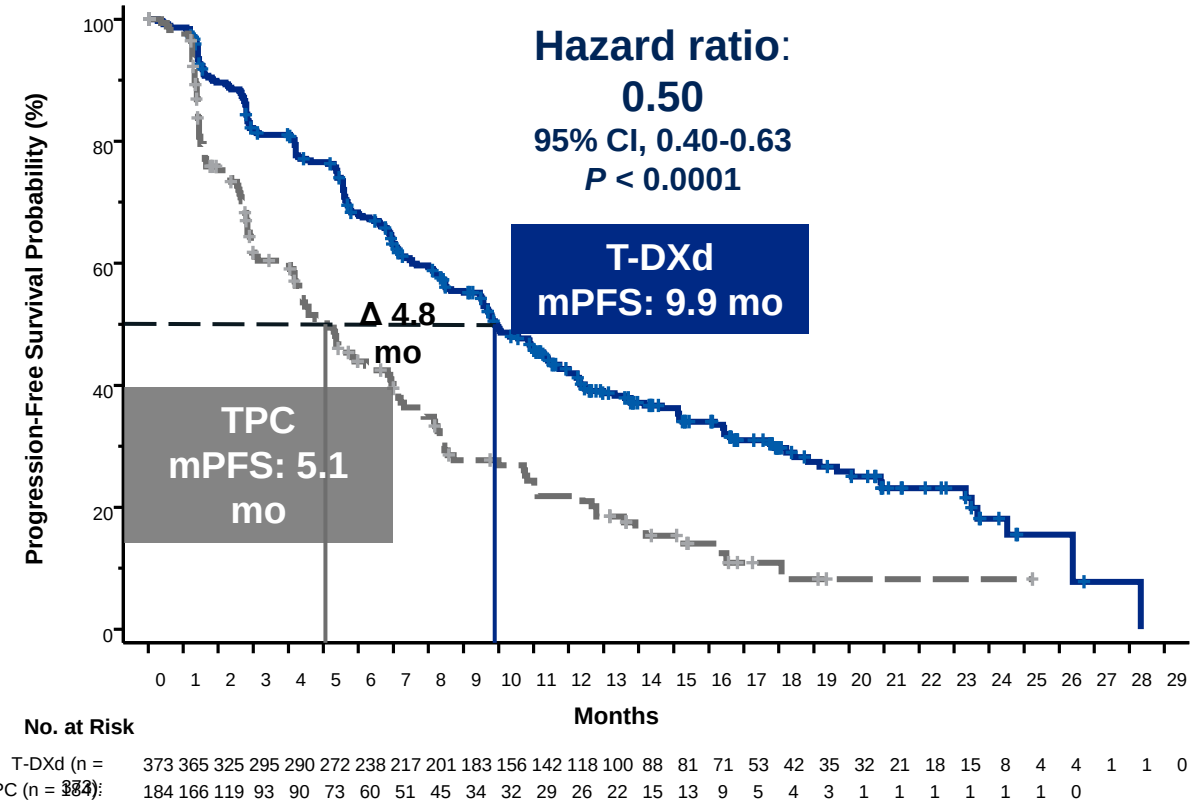
Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS in HR+ and All Patients

Hormone receptor–positive



All patients

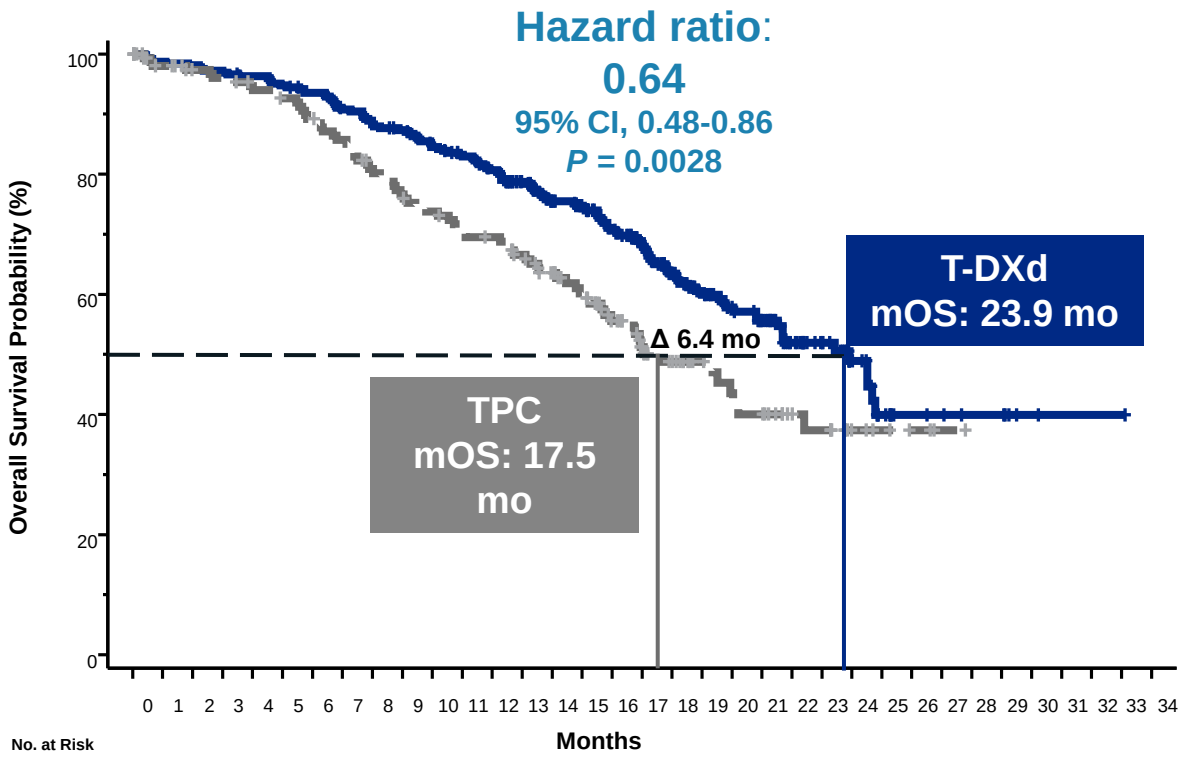


PFS by blinded independent central review.

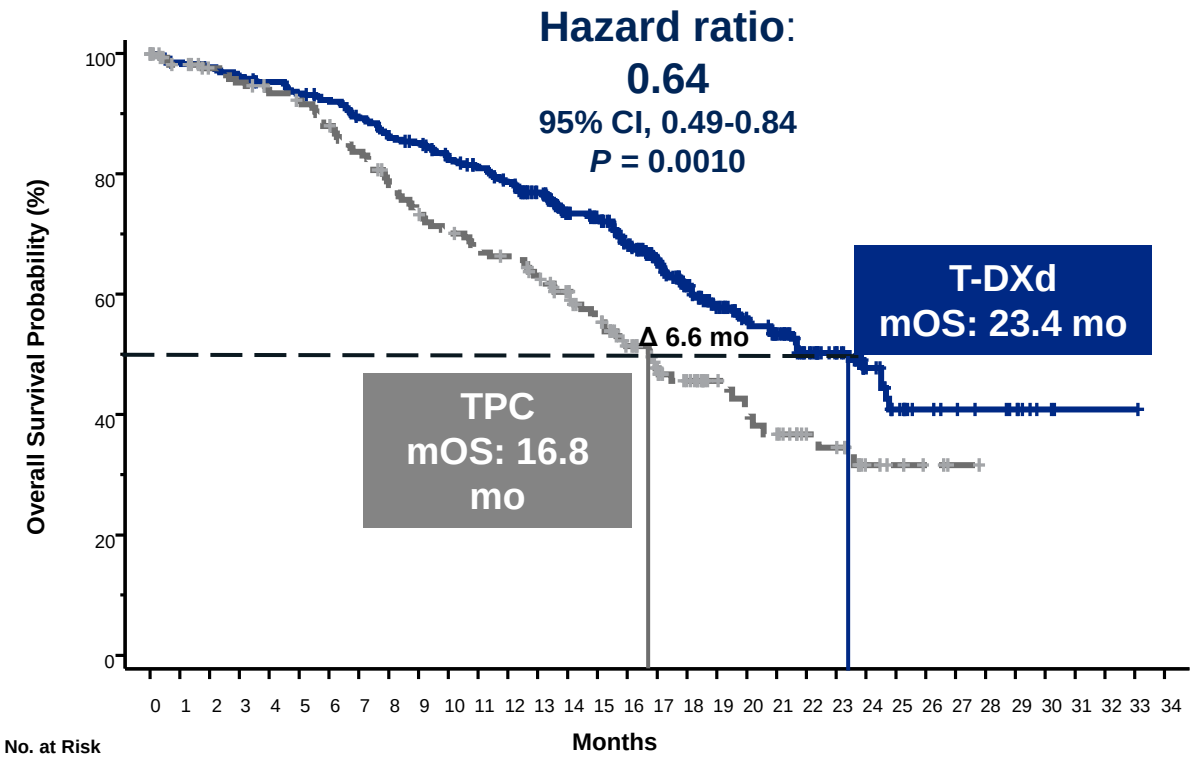
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



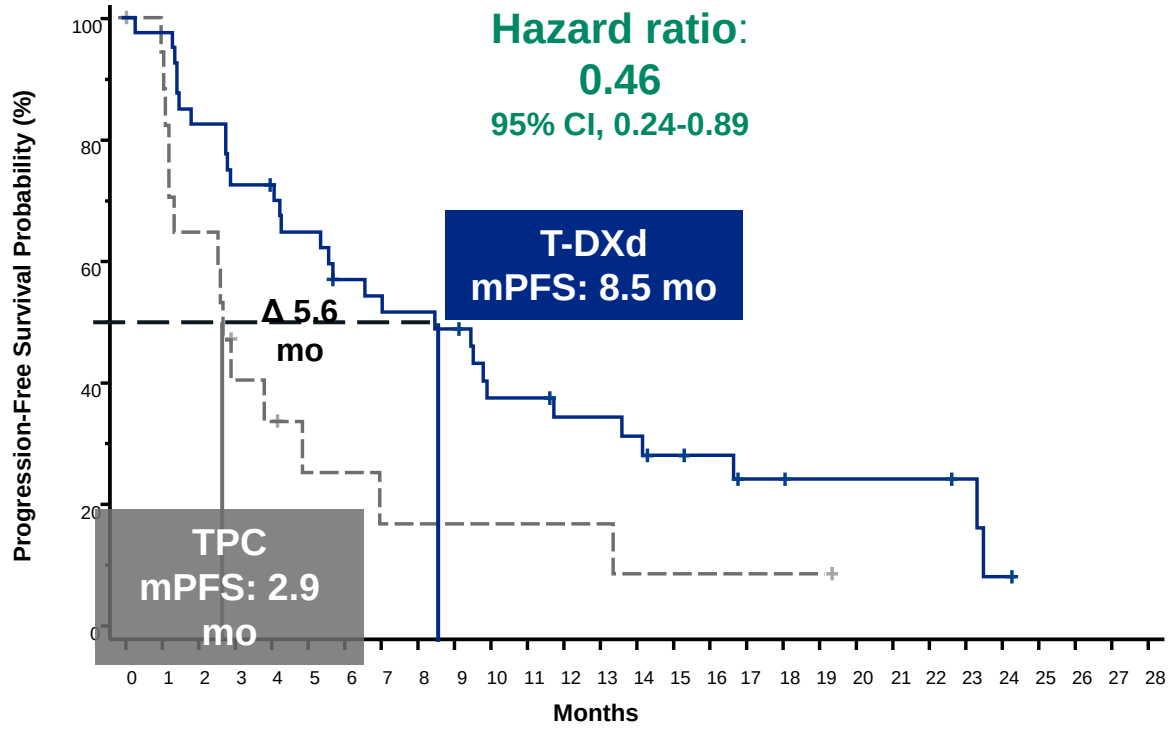
All patients



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS and OS in HR− (Exploratory Endpoints)

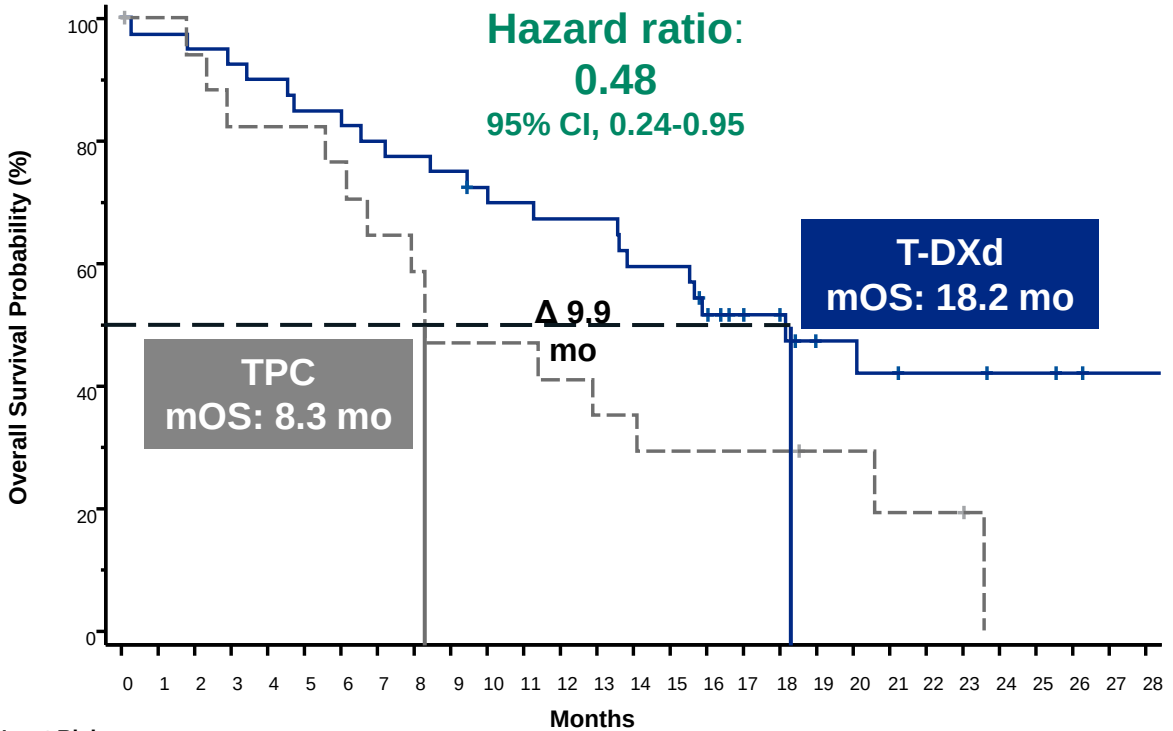
PFS



No. at Risk

T-DXd (n = 40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	4	3	1	0	
TPC (n = 18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0						

OS



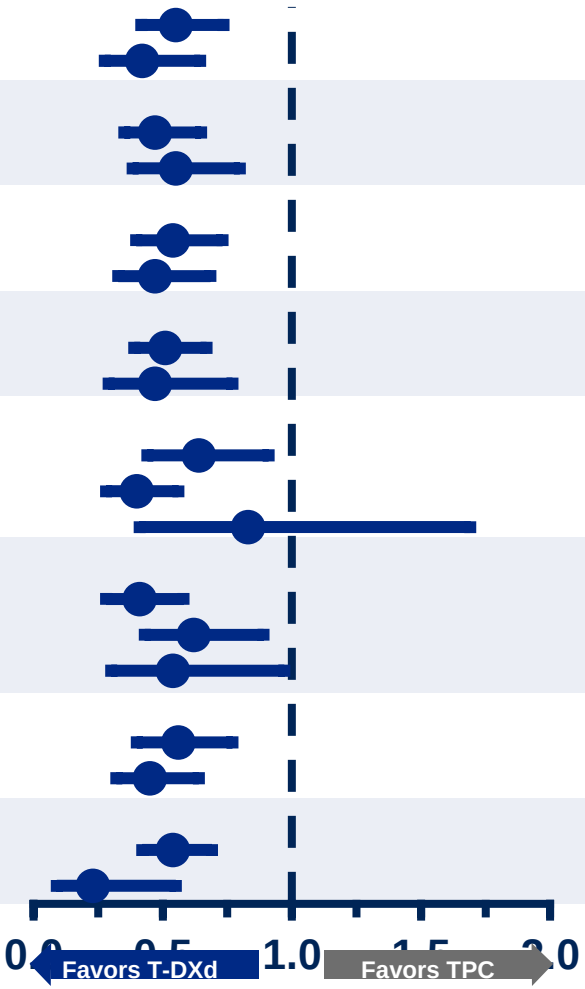
No. at Risk

T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

Subgroup Analysis: PFS in HR+

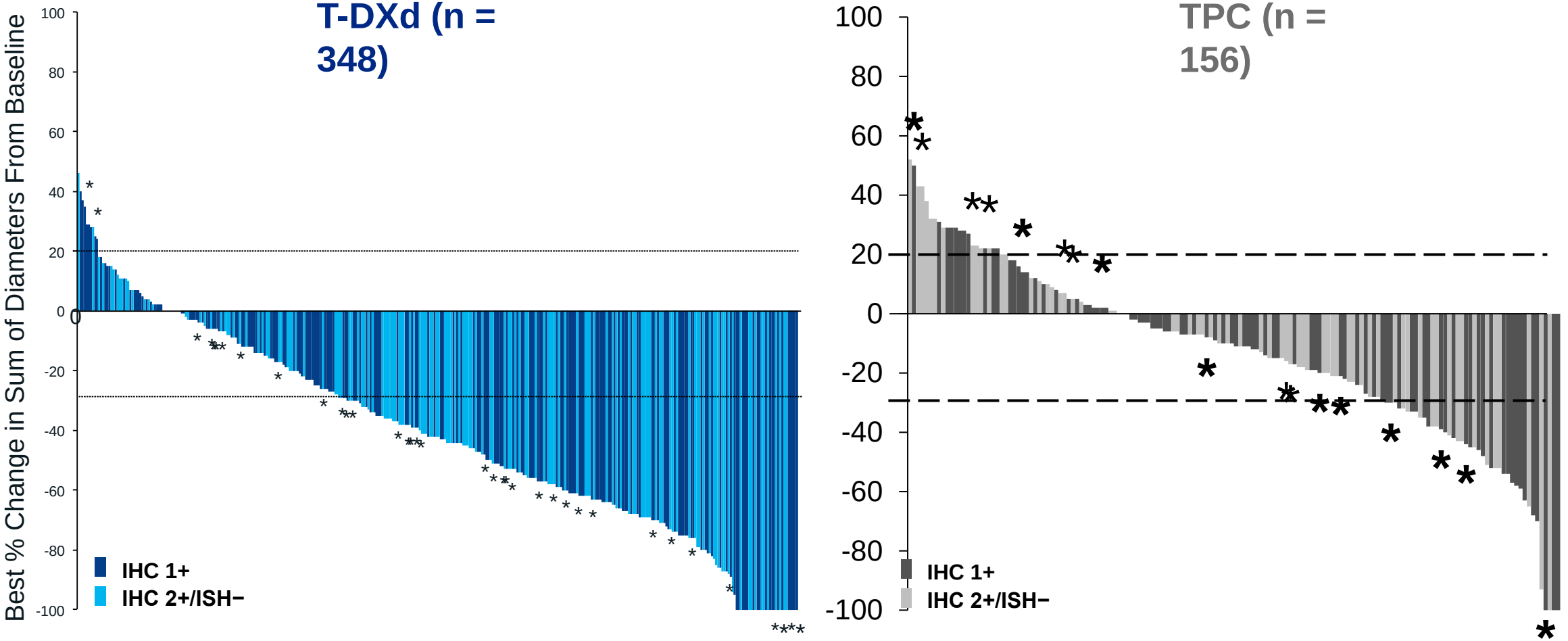
	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy					
1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
<65 years	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
≥65 years	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
Asian	83/131	54/66	11.0 (8.4-13.8)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
Other	25/37	11/16	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.28-0.58)
Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30-0.97)
ECOG performance status					
0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
1	95/144	55/68	9.7 (7.3-11.5)	4.6 (2.9-6.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)



PFS by blinded independent central review. Based on derived data, which include protocol deviations.

CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Best Change in Target Lesions (All Patients)

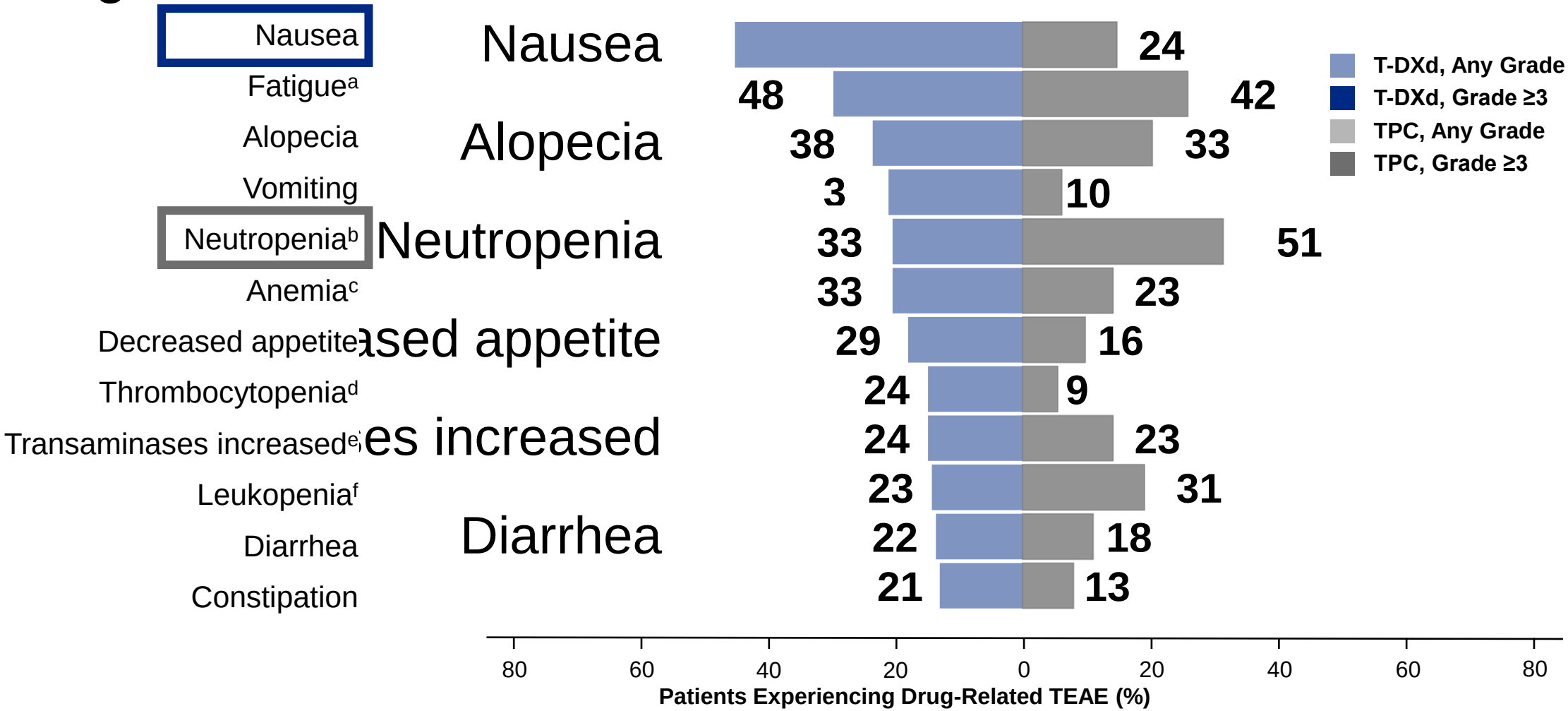


⁎Patients with HR− disease

Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumors in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression, and the lower dashed line indicates a 30% decrease in tumor size (partial response).

HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Drug-Related TEAEs in ≥20% of Patients



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Overall Safety Summary

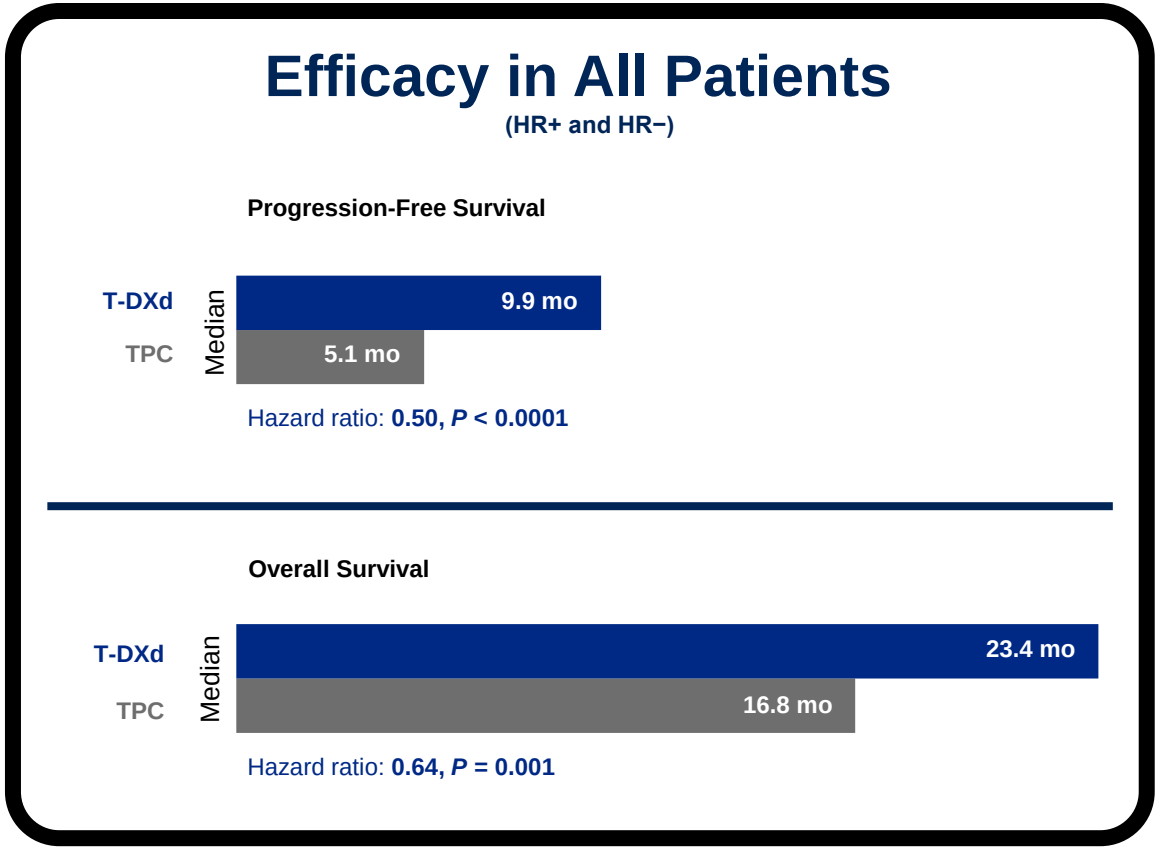
n (%)	Safety analysis set[a]	
	T-DXd (n = 371)	TPC (n = 172)
Total patient-years of exposure, years[b]	283.55	63.59
TEAEs	369 (99)	169 (98)
Grade ≥3	195 (53)	116 (67)
Serious TEAEs	103 (28)	43 (25)
TEAEs associated with dose discontinuations	60 (16)	14 (8)
TEAEs associated with dose interruptions	143 (39)	72 (42)
TEAEs associated with dose reductions	84 (23)	66 (38)
TEAEs associated with deaths	14 (4)	5 (3)

- **Median treatment duration**
  - **T-DXd: 8.2 months (range, 0.2-33.3)**
  - **TPC: 3.5 months (range, 0.3-17.6)**
- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue[d]
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]Patient-years of exposure are the treatment duration with year as unit. [c]Grouped term. [d]Fatigue includes the preferred terms fatigue, malaise, and asthenia; neutropenia included the preferred terms of neutropenia and neutrophil count decreased. [e]On-treatment death was defined as any death that occurred from the date of the first dose to 47 days after the last dose of study drug irrespective of the cause; the TEAEs associated with deaths represent a subset of on-treatment deaths reported by the investigators as adverse events.

DESTINY-Breast04 establishes T-DXd as the new standard of care in HER2-low, HR+/HR− mBC

- T-DXd is the first HER2-targeted therapy to demonstrate unprecedented statistically significant and clinically meaningful improvement in PFS and OS versus TPC
- Similar magnitude of benefit across all subgroups, including HER2 IHC status and prior CDK4/6i use
- Safety is consistent with the known safety profile and showed an overall positive benefit-risk
- DESTINY-Breast04 establishes HER2-low (IHC 1+, IHC 2+/ISH−) mBC as a new targetable patient population, with T-DXd as a new standard of care



CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Sacituzumab Govitecan vs Treatment of Physician's Choice: Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients With HR+/HER2– Metastatic Breast Cancer

Hope S. Rugo,[1] Aditya Bardia,[2] Frederik Marmé,[3] Javier Cortes,[4] Peter Schmid,[5] Delphine Loirat,[6] Olivier Trédan,[7] Eva Ciruelos,[8] Florence Dalenc,[9] Patricia Gómez Pardo,[10] Komal L. Jhaveri,[11] Monica Motwani,[12] Oh Kyu Yoon,[12] Hao Wang,[12] Wendy Verret,[12] Sara M. Tolaney[13]

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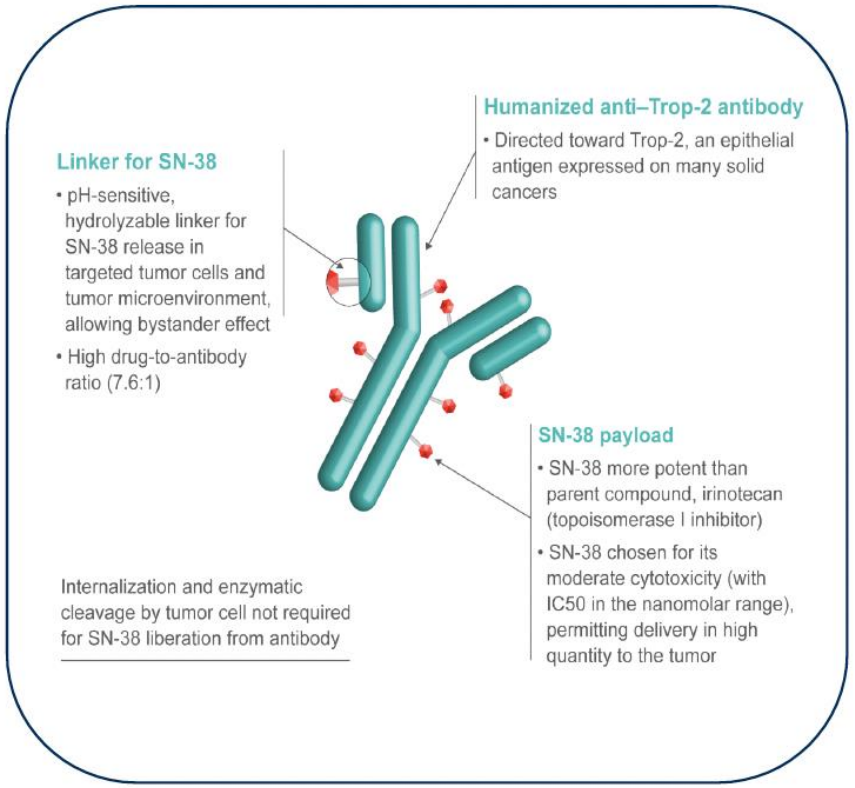
Sacituzumab Govitecan Is a First-in-Class Trop-2–Directed Antibody-Drug Conjugate[1-5]

- Trop-2 is an epithelial antigen that is highly expressed in ~85-90% of all subtypes of breast cancer, including HR+ breast cancer[6,7]
- SG is approved for patients with mTNBC with ≥2 prior therapies (≥1 in the metastatic setting)[8,9]
- In the TROPiCS-02 study, in patients with pretreated, endocrine-resistant HR+/HER2– mBC, SG demonstrated:
  - Statistically significant improvement in PFS, with a 34% reduction in the risk of disease progression or death (HR, 0.66; *P*=0.0003; median 5.5 vs 4.0 mo)[10]
  - Statistically significant improvement in OS at the second planned interim analysis (14.4 vs 11.2 mo; HR, 0.79; *P*=0.020)[11]
- SG demonstrated clinical benefit versus TPC in previously treated mTNBC, irrespective of level of Trop-2 expression[12]

Here, we compare clinical outcomes for SG versus TPC by Trop-2 expression in TROPiCS-02



HER2–, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

1. Goldenberg DM, et al. *Expert Opin Biol Ther*. 2020;20:871-885. 2. Nagayama A, et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 3. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496-22512. 4. Cardillo TM, et al. *Bioconjugate Chem*. 2015;26:919-931. 5. Govindan SV, et al. *Mol Cancer Ther*. 2013;12:968-978. 6. Coates JT et al. *Cancer Discov*. 2021;11:2436-2445. 7. Vidula N et al. *Breast Cancer Res and Treat*. 2022;194:569-575. 8. TRODELVY (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; 2022. 9. European Medicines Agency: Trodelvy, INN-sacituzumab govitecan. https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf. March 2022. Accessed November 23, 2022. 10. Rugo HS, et al. *J Clin Oncol*. 2022;40:3365-3376. 11. Rugo HS, et al. ESMO 2022. Oral LBA76. 12. Bardia A, et al. *Ann Oncol*. 2021;32:1148-1156.

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2− Locally Recurrent Inoperable or Metastatic Breast Cancer

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

Treatment of physician's choice[b]
(capecitabine, vinorelbine, gemcitabine, or eribulin)
n=271

Endpoints

Primary
- PFS by BICR

Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

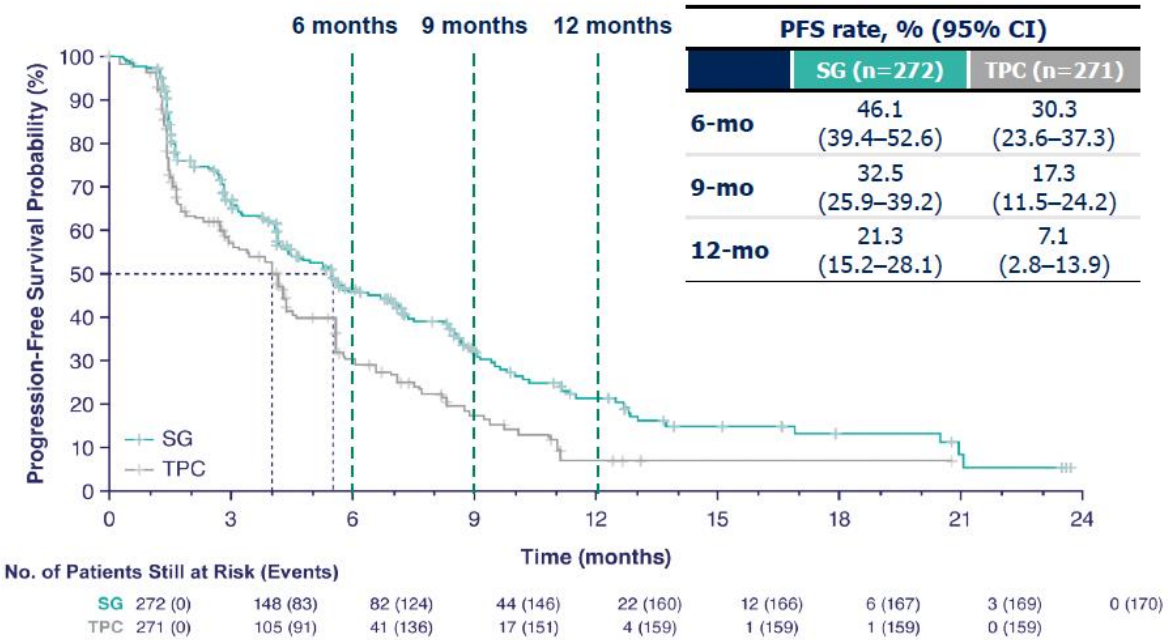
Stratification
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

[a]Disease histology based on ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DOR, duration of response; HER2− , human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IV, intravenously; LIR, local investigator review; (neo)adjuvant, neoadjuvant or adjuvant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

PFS & OS in the ITT Population

PFS[1]

BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



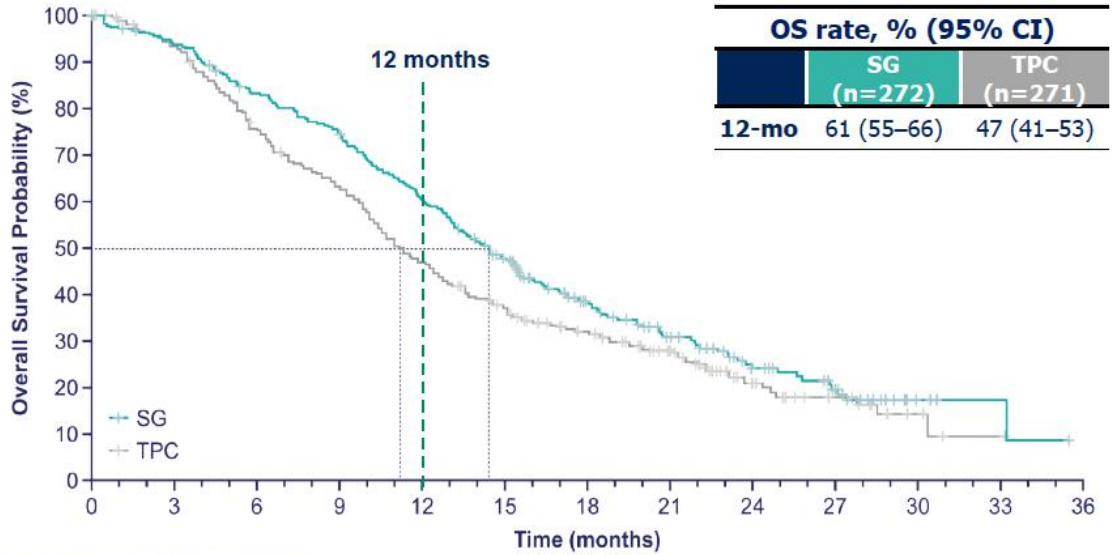
PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

No. of Patients Still at Risk (Events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

OS[2]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

No. of Patients Still at Risk (Events)

SG	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (158)	53 (173)	31 (183)	20 (188)	4 (190)	2 (190)	0 (191)
TPC	271 (0)	246 (16)	196 (64)	164 (95)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)

SG demonstrated a statistically significant improvement in PFS and OS vs TPC

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol. 2022.* doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76.

Methods: Trop-2 Subgroup Analysis

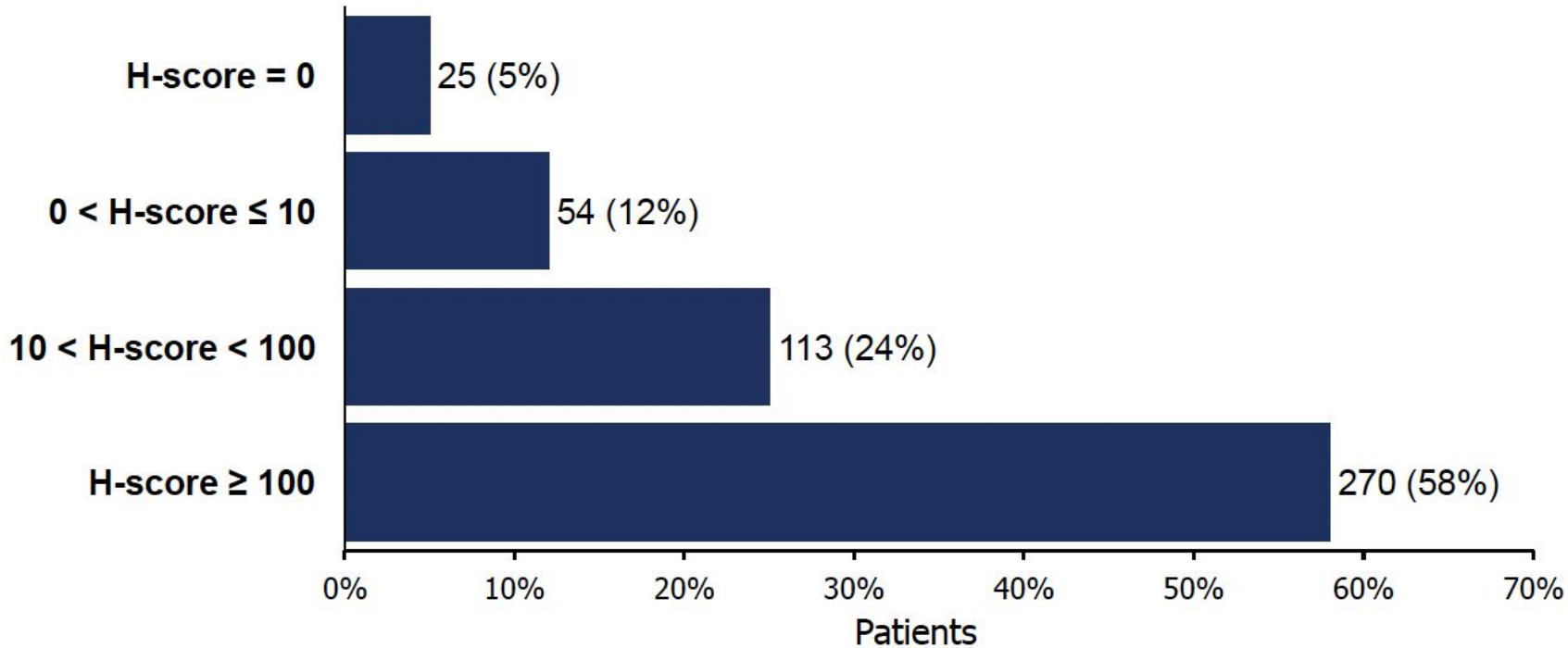
- We conducted an exploratory analysis to evaluate the potential impact of Trop-2 expression on efficacy outcomes in TROPICS-02[1]
  - Trop-2 expression was not required to determine patient eligibility and was not a stratification factor in TROPICS-02
- Trop-2 expression was determined on primary or metastatic archival tumor tissue requested at study entry
  - Median time from tumor tissue collection to study entry was 7.7 months (range, 0.03-177.9)
- Membrane Trop-2 expression was assessed by a validated research IHC assay at a CAP/CLIA central laboratory
  - Data was categorized based on an H-score (range, 0-300), representing a summation of percent staining weighted by staining intensity
  - Efficacy outcomes (PFS and OS) were assessed in H-score <100 and ≥100 groups; this cutoff resulted in 40-60% patients in each subgroup
  - The H-score <100 group was further divided into H-score ≤10 and >10 to <100 subgroups to assess the activity of SG in patients with very low tumor Trop-2 expression

1. Data cutoff dates for analysis were January 3, 2022 (PFS analysis) and July 1, 2022 (OS analysis)

CAP/CLIA, College of American Pathologists & Clinical Laboratory Improvement Amendment; H-score, histochemical score; OS, overall survival; PFS, progression-free survival; Trop-2, trophoblast cell surface antigen 2.

TROPiCS-02: Trop-2 Expression in Tumor Tissue Samples

- In total, 238 patients (88%) in the SG and 224 patients (83%) in the TPC group had samples evaluable for Trop-2 expression



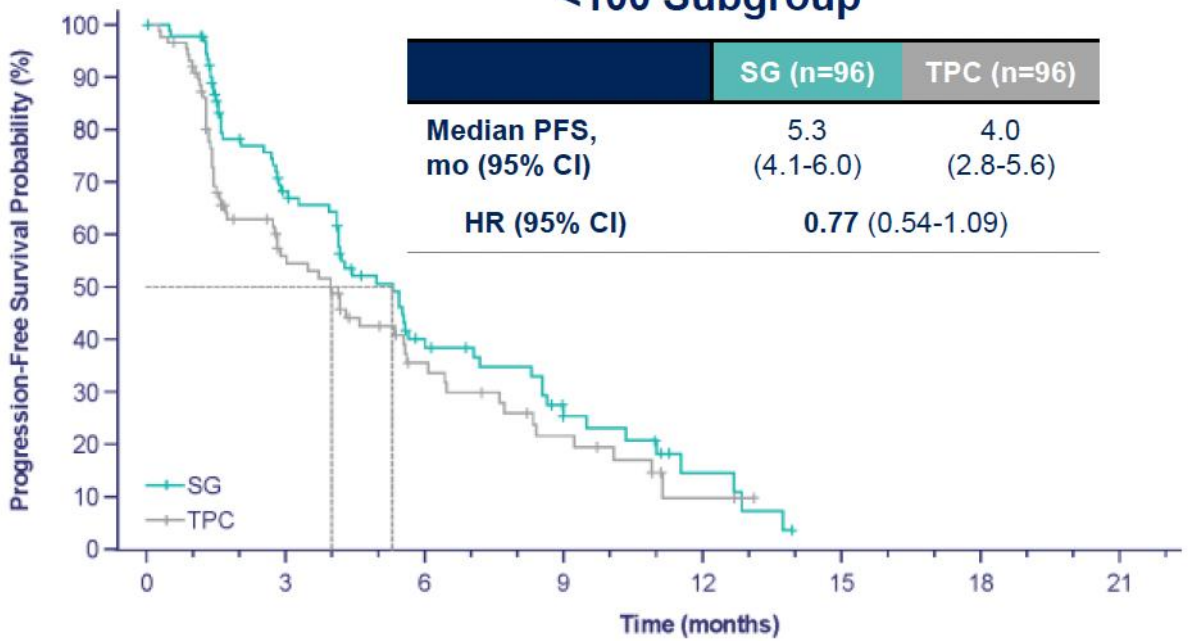
Trop-2 expression was observed in ~95% of patients with evaluable samples

H-score, histochemical score; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

Progression-free Survival: Trop-2 H-Score Cutoff of 100

<100 Subgroup

	SG (n=96)	TPC (n=96)
Median PFS, mo (95% CI)	5.3 (4.1-6.0)	4.0 (2.8-5.6)
HR (95% CI)	**0.77** (0.54-1.09)	

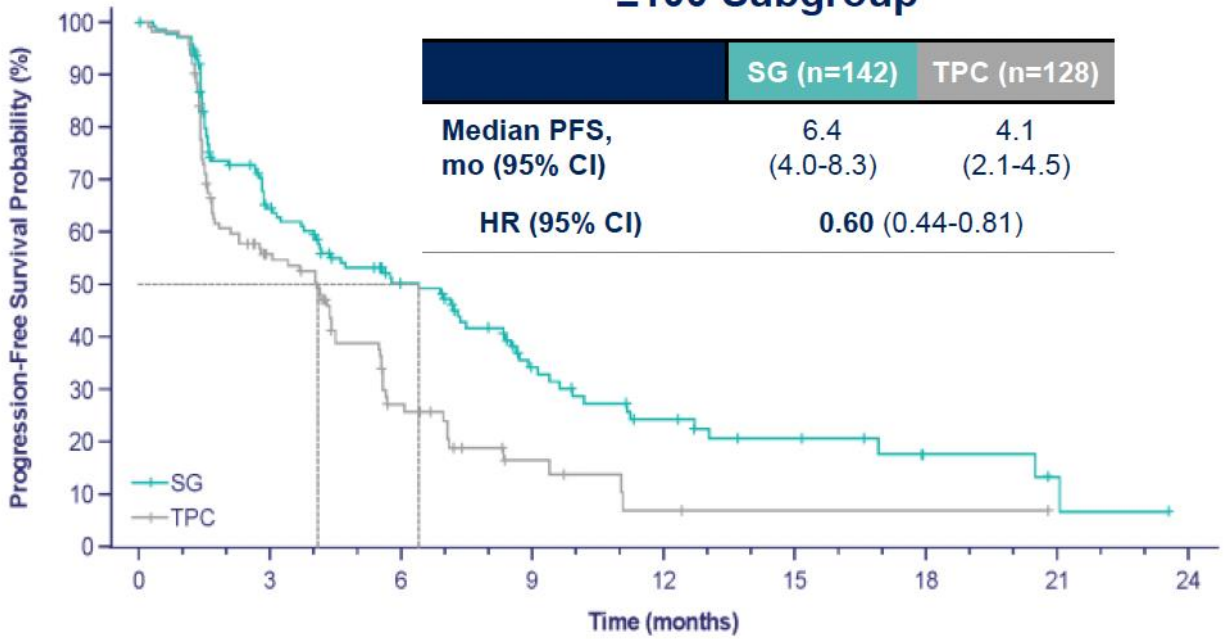


No. of Patients Still at Risk (Events)

SG	96 (0)	53 (27)	24 (47)	13 (54)	4 (59)	0 (62)
TPC	96 (0)	39 (36)	19 (49)	10 (56)	2 (60)	0 (60)

≥100 Subgroup

	SG (n=142)	TPC (n=128)
Median PFS, mo (95% CI)	6.4 (4.0-8.3)	4.1 (2.1-4.5)
HR (95% CI)	**0.60** (0.44-0.81)	



No. of Patients Still at Risk (Events)

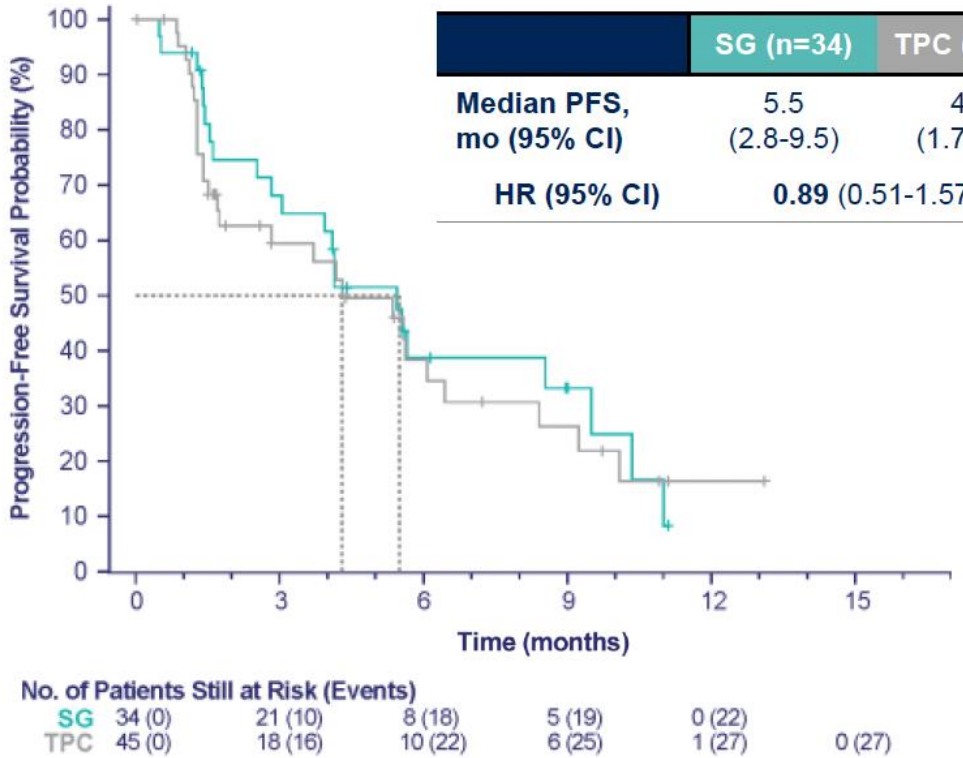
SG	142 (0)	77 (46)	50 (62)	25 (76)	15 (83)	10 (85)	4 (86)	2 (87)	0 (88)
TPC	128 (0)	52 (48)	18 (72)	6 (78)	2 (81)	1 (81)	1 (81)	0 (81)	

PFS outcome favored SG over TPC in both Trop-2 H-score <100 and ≥100

Hazard ratio is from an unstratified Cox Regression analysis.
H-score; histochemical score; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

Progression-free Survival: Trop-2 H-Score Cutoff of 10

≤10 Subgroup

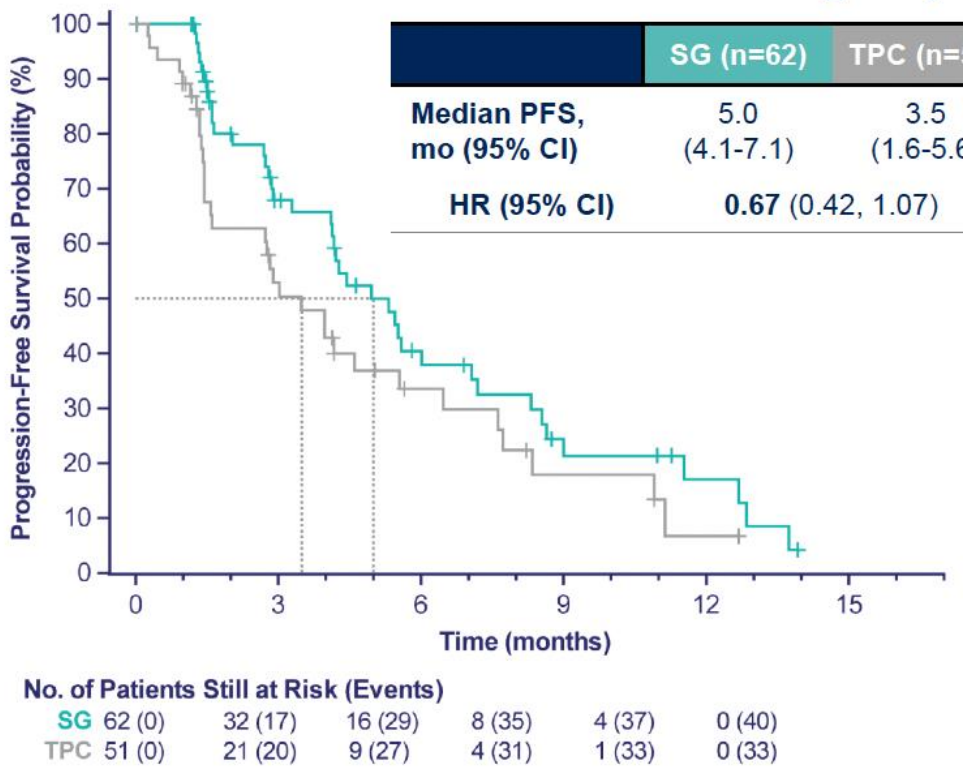


	SG (n=34)	TPC (n=45)
Median PFS, mo (95% CI)	5.5 (2.8-9.5)	4.3 (1.7-6.4)
HR (95% CI)	**0.89** (0.51-1.57)	

No. of Patients Still at Risk (Events)

SG	34 (0)	21 (10)	8 (18)	5 (19)	0 (22)	
TPC	45 (0)	18 (16)	10 (22)	6 (25)	1 (27)	0 (27)

>10 to <100 Subgroup



	SG (n=62)	TPC (n=51)
Median PFS, mo (95% CI)	5.0 (4.1-7.1)	3.5 (1.6-5.6)
HR (95% CI)	**0.67** (0.42, 1.07)	

No. of Patients Still at Risk (Events)

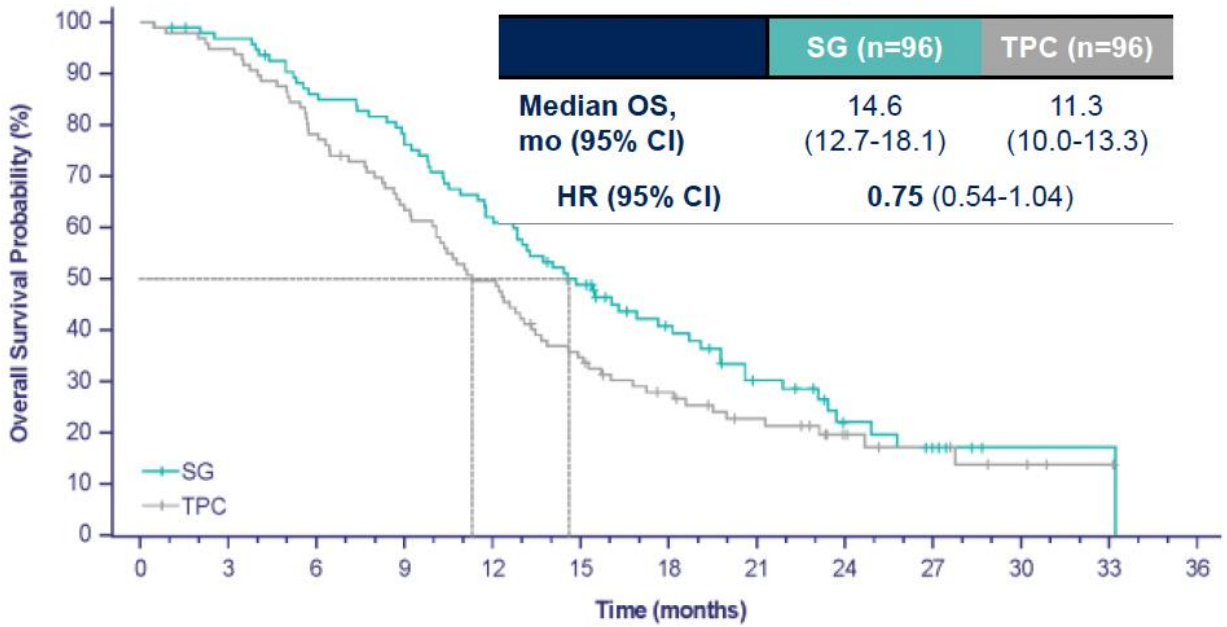
SG	62 (0)	32 (17)	16 (29)	8 (35)	4 (37)	0 (40)
TPC	51 (0)	21 (20)	9 (27)	4 (31)	1 (33)	0 (33)

PFS outcome favored SG over TPC across all Trop-2 H-score subgroups, including those with very low Trop-2 expression (H-score ≤10), though caution should be exercised in data interpretation given the small sample size

Hazard ratio is from an unstratified Cox Regression analysis.
H-score, histochemical score; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

Overall Survival: Trop-2 H-Score Cutoff of 100

<100 Subgroup

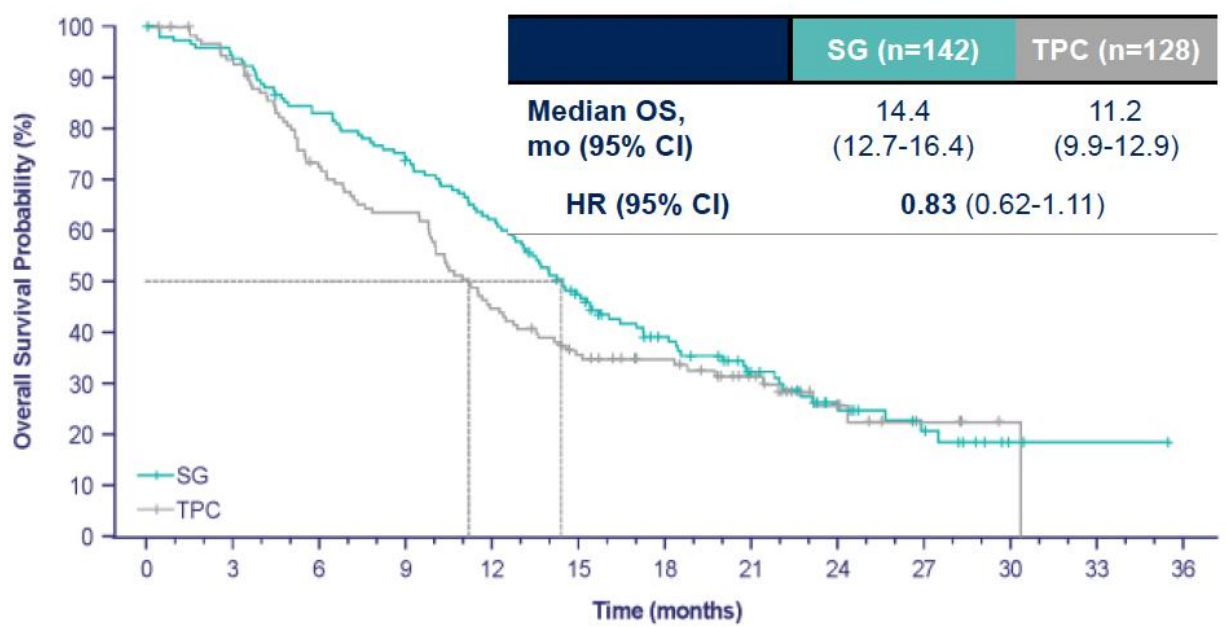


	SG (n=96)	TPC (n=96)
Median OS, mo (95% CI)	14.6 (12.7-18.1)	11.3 (10.0-13.3)
HR (95% CI)	**0.75** (0.54-1.04)	

No. of Patients Still at Risk (Events)

SG	96 (0)	90 (3)	79 (13)	72 (20)	57 (35)	43 (47)	28 (53)	18 (60)	9 (64)	5 (66)	1 (66)	1 (66)	0 (67)
TPC	96 (0)	91 (5)	75 (21)	61 (34)	47 (48)	32 (62)	23 (68)	16 (72)	9 (74)	6 (75)	3 (76)	1 (76)	0 (76)

≥100 Subgroup



	SG (n=142)	TPC (n=128)
Median OS, mo (95% CI)	14.4 (12.7-16.4)	11.2 (9.9-12.9)
HR (95% CI)	**0.83** (0.62-1.11)	

No. of Patients Still at Risk (Events)

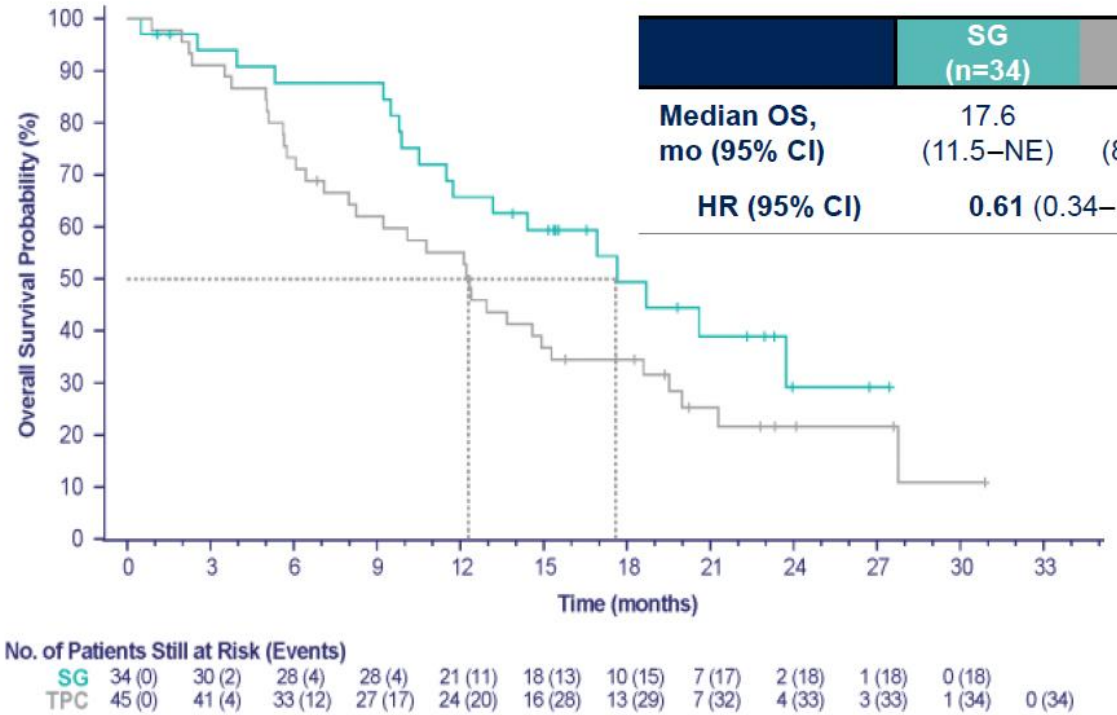
SG	142 (0)	132 (9)	116 (24)	102 (37)	86 (53)	61 (73)	42 (83)	28 (90)	16 (96)	10 (98)	2 (99)	1 (99)	0 (99)
TPC	128 (0)	117 (8)	89 (34)	78 (45)	55 (68)	41 (79)	32 (80)	22 (83)	9 (86)	4 (87)	1 (87)	0 (88)	

OS benefit with SG over TPC observed in subgroups with Trop-2 H-score <100 and ≥100

Hazard ratio is from an unstratified Cox Regression analysis.
H-score; histochemical score; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

Overall Survival: Trop-2 H-Score Cutoff of 10

≤10 Subgroup

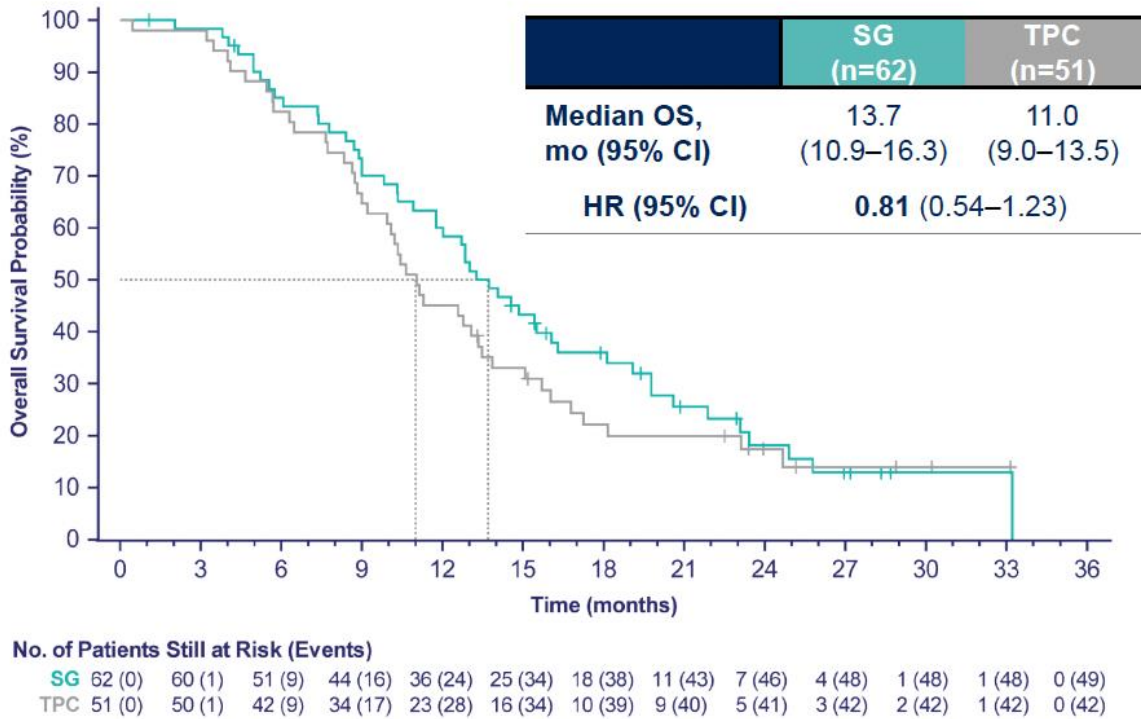


	SG (n=34)	TPC (n=45)
Median OS, mo (95% CI)	17.6 (11.5–NE)	12.3 (8.0–15.3)
HR (95% CI)	**0.61** (0.34–1.08)	

No. of Patients Still at Risk (Events)

SG	34 (0)	30 (2)	28 (4)	28 (4)	21 (11)	18 (13)	10 (15)	7 (17)	2 (18)	1 (18)	0 (18)
TPC	45 (0)	41 (4)	33 (12)	27 (17)	24 (20)	16 (26)	13 (29)	7 (32)	4 (33)	3 (33)	1 (34)	0 (34)

>10 to <100 Subgroup



	SG (n=62)	TPC (n=51)
Median OS, mo (95% CI)	13.7 (10.9–16.3)	11.0 (9.0–13.5)
HR (95% CI)	**0.81** (0.54–1.23)	

No. of Patients Still at Risk (Events)

SG	62 (0)	60 (1)	51 (9)	44 (16)	36 (24)	25 (34)	18 (38)	11 (43)	7 (46)	4 (48)	1 (48)	1 (48)	0 (49)
TPC	51 (0)	50 (1)	42 (9)	34 (17)	23 (28)	16 (34)	10 (39)	9 (40)	5 (41)	3 (42)	2 (42)	1 (42)	0 (42)

OS benefit with SG over TPC was consistently observed across all Trop-2 H-score subgroups, including those with very low Trop-2 expression (H-score ≤10), though caution should be exercised in data interpretation given the small sample size

Hazard ratio is from an unstratified Cox regression analysis.
H-score, histochemical score; NE, not evaluable; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

Conclusions

- In TROPiCS-02, treatment with SG improved PFS and OS compared to TPC in patients with pretreated, endocrine-resistant HR+/HER2– mBC
- In this post hoc analysis, SG improved efficacy across Trop-2 expression levels
  - Trop-2 expression was observed in ~95% of evaluable tumor samples
  - PFS and OS benefit of SG over TPC was observed across Trop-2 subgroups (H-score <100 and ≥100)
  - Benefit from SG was also observed in patients whose tumors had very low Trop-2 expression, including those with H-score ≤10
    - Caution should be exercised in data interpretation given the small sample size in this Trop-2 subgroup
- SG demonstrated a manageable safety profile, which was not impacted by Trop-2 expression

This post-hoc analysis demonstrated that SG improves outcomes in patients with pretreated, endocrine-resistant HR+/HER2– mBC regardless of Trop-2 expression; Trop-2 testing is not required for SG treatment

HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; H-score, histochemical score; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: updated results by duration of prior CDK4/6i in metastatic setting

Bardia A,[1*] Bidard FC,[2*] Neven P,[3] Streich G,[4] Montero AJ,[5] Forget F,[6] Mouret-Reynier MA,[7] Sohn JH,[8] Taylor D,[9] Harnden KK,[10] Khong H,[11] Kocsis J,[12] Dalenc F,[13] Dillon P,[14] Babu S,[15] Waters S,[16] Deleu I,[17] Garcia-Saenz J,[18] Bria E,[19] Cazzaniga M,[20] Aftimos P,[21] Cortes J,[22] Tonini G,[23] Tarek Sahmoud,[24] Habboubi N,[24] Grzegorzewski KJ,[24] **Kaklamani V[25]****

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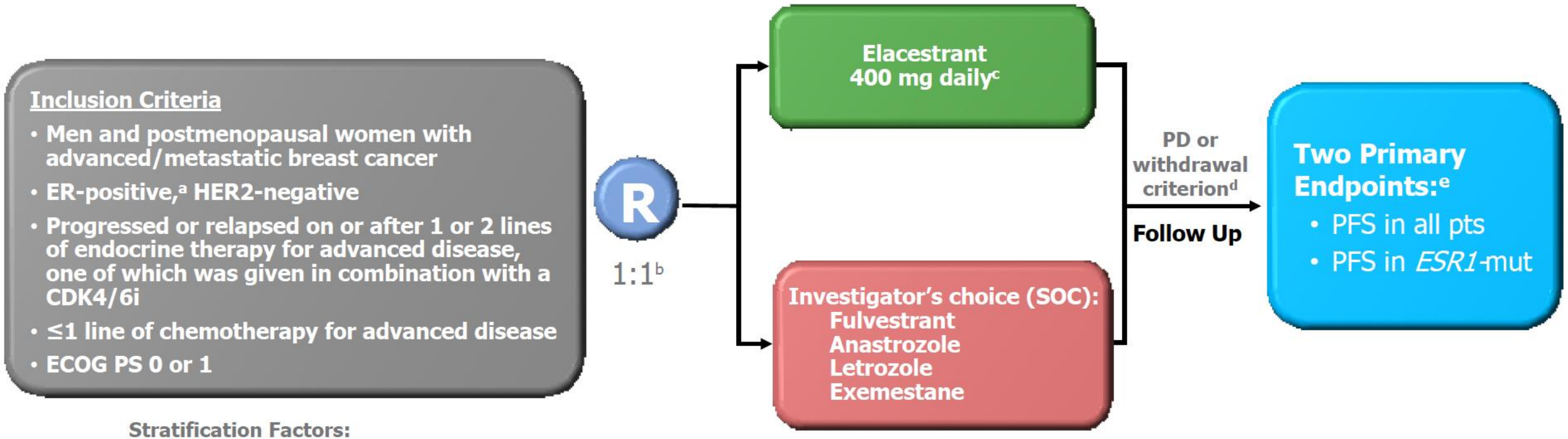
Introduction

- **Endocrine therapy plus CDK4/6i is the mainstay** for the management of ER+/HER2- mBC as 1st-line therapy.[1]
- However, **tumors eventually develop hormonal resistance**, mainly through the development of *ESR1* mutations.
- In current practice, sequential endocrine monotherapy or combination therapies are used in the 2nd/3rd line.
- **Sequential endocrine monotherapy is associated with low PFS after CDK4/6i** (1.94 months).[2] In addition, fulvestrant has low bioavailability and an IM injection burden.
- Main **combinations such as everolimus + exemestane and alpelisib + fulvestrant can be associated with significant toxicity** with discontinuation rates around 25%.[3,4]
- In this context, there is **a significant need for potent oral SERDS for monotherapy use** and for enabling oral-oral combinations.
- Elacestrant is a next-generation oral SERD, which has demonstrated a statistically significant improvement in PFS compared with single-agent endocrine therapy in the EMERALD trial, including in patients with *ESR1* mutated tumors. Emerald is the only pivotal oral SERD trial where prior CDK 4/6i usage was mandated.[5]
- Here we examine the impact of the duration of prior CDK4/6i on PFS and share updated safety results.

1. Moy B, et al. *J Clin Oncol.* 2021:JCO2101374; 2. Lindeman GJ et al. J Clin Oncol 2021,39(suppl 15):1004-1004; 3. Everolimus US Prescribing Information; 4. Alpelisib US Prescribing Information
5. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256.

EMERALD Phase 3 Study Design



[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

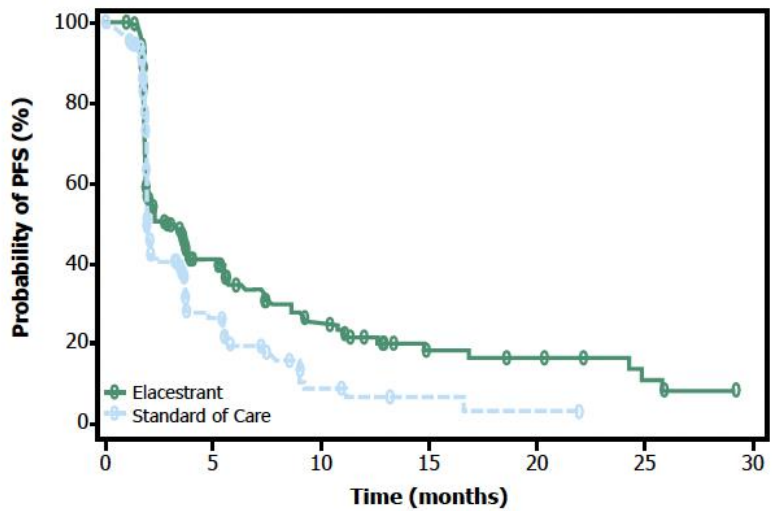
Baseline Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.0 (32-83)	63.0 (32-83)
Gender, n (%) Female Male	 233 (97.5) 6 (2.5)	 115 (100) 0	 238 (99.6) 1 (0.4)	 113 (100) 0
ECOG PS, n (%) 0 1 >1	 143 (59.8) 96 (40.2) 0	 67 (58.3) 48 (41.7) 0	 135 (56.5) 103 (43.1) 1 (0.4)	 62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6i, n (%)	239 (100)	115 (100)	239 (100)	113 (100)
Number of prior lines of endocrine therapy,** n (%) 1 2	 129 (54.0) 110 (46.0)	 73 (63.5) 42 (36.5)	 142 (59.4) 97 (40.6)	 69 (61.1) 44 (38.9)
Type of prior endocrine therapy,** n (%) Fulvestrant AI Tamoxifen	 70 (29.3) 193 (80.8) 19 (7.9)	 27 (23.5) 101 (87.8) 9 (7.8)	 75 (31.4) 194 (81.2) 15 (6.3)	 28 (24.8) 96 (85.0) 9 (8.0)
Number of prior lines of chemotherapy,** n (%) 0 1	 191 (79.9) 48 (20.1)	 89 (77.4) 26 (22.6)	 180 (75.3) 59 (24.7)	 81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

All Patients: PFS by Duration of CDK4/6i

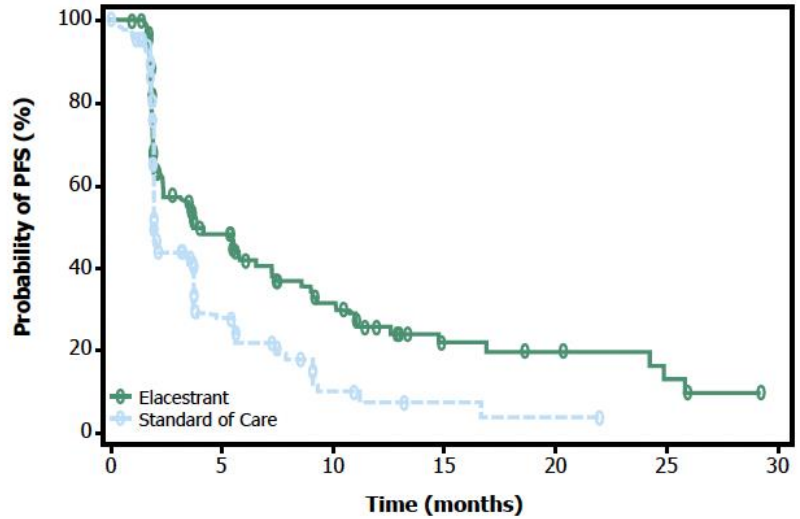
At least 6 mo CDK4/6i



Elacestrant	202	90	53	37	29	24	16	12	10	9	8	7	6	1	1	0
SOC	205	71	32	20	13	6	3	2	2	1	1	0				

	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

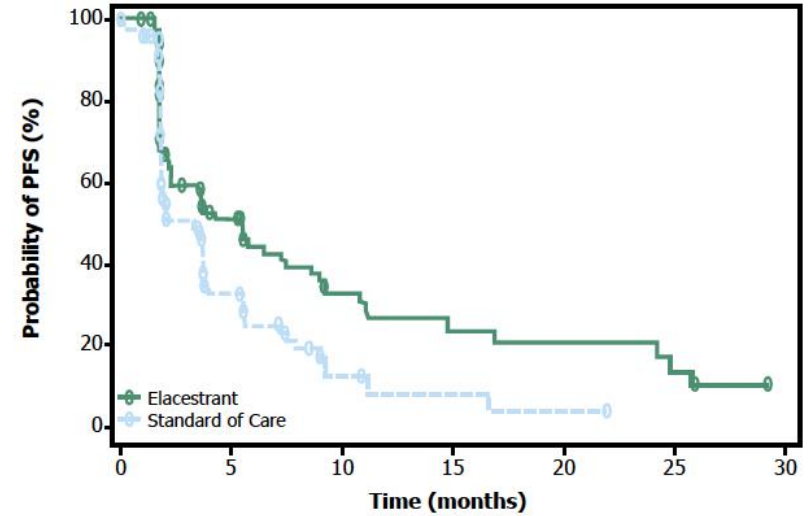
At least 12 mo CDK4/6i



Elacestrant	150	76	48	35	28	23	15	11	9	8	7	6	6	1	1	0
SOC	160	55	26	18	13	6	3	2	2	1	1	0				

	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)
PFS rate at 12 months, % (95% CI)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)
Hazard ratio (95% CI)	**0.613** (0.453 - 0.828)	

At least 18 mo CDK4/6i

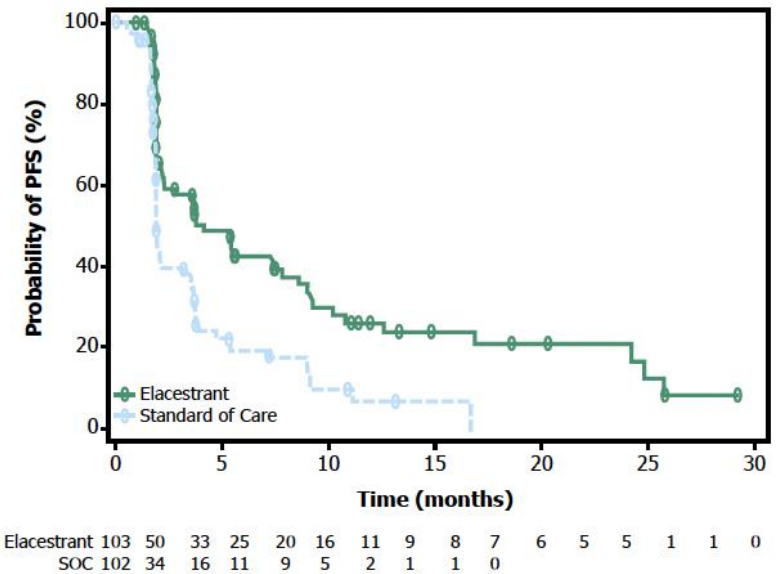


Elacestrant	98	51	35	26	23	18	11	10	8	7	7	6	6	1	1	0
SOC	119	47	22	15	10	5	2	2	2	1	1	0				

	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 12 months, % (95% CI)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
Hazard ratio (95% CI)	**0.703** (0.482 - 1.019)	

Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

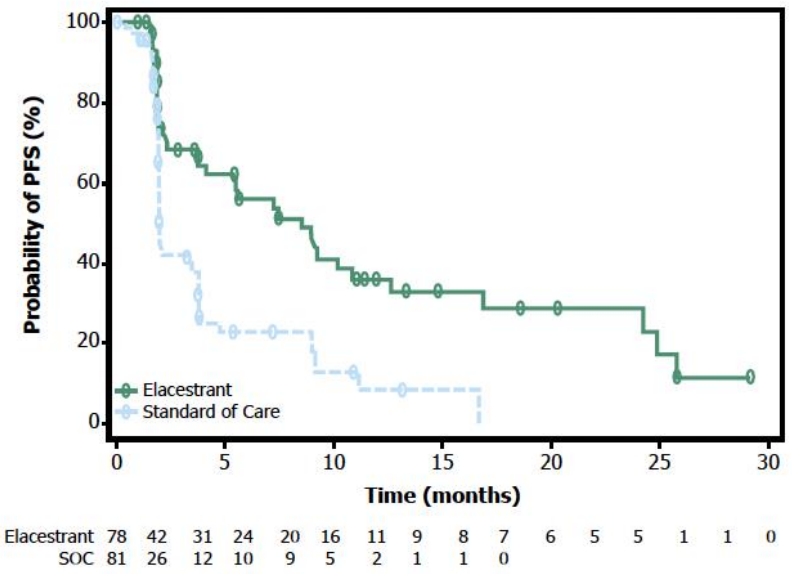
At least 6 mo CDK4/6i



Elacestrant	103	50	33	25	20	16	11	9	8	7	6	5	5	1	1	0
SOC	102	34	16	11	9	5	2	1	1	0						

	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

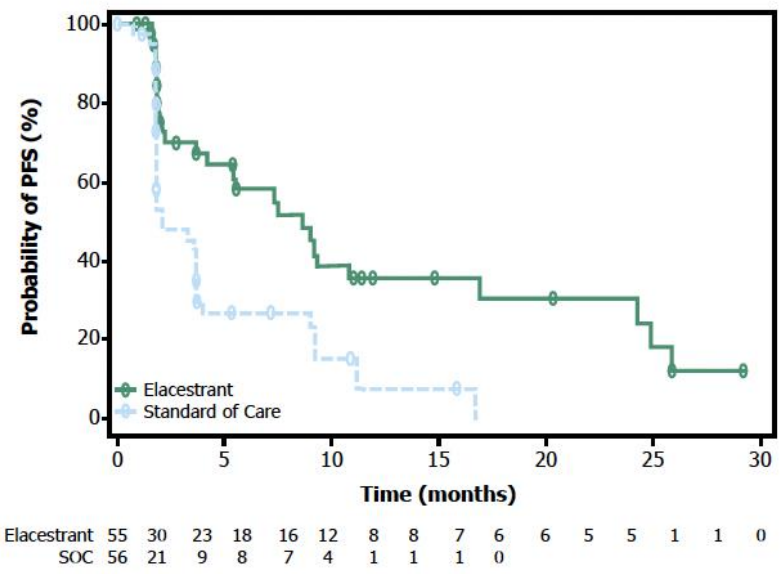
At least 12 mo CDK4/6i



Elacestrant	78	42	31	24	20	16	11	9	8	7	6	5	5	1	1	0
SOC	81	26	12	10	9	5	2	1	1	0						

	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



Elacestrant	55	30	23	18	16	12	8	8	7	6	6	5	5	1	1	0
SOC	56	21	9	8	7	4	1	1	1	0						

	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Conclusions

- EMERALD is the only pivotal trial in 2nd/3rd-line mBC with 100% prior CDK4/6i usage.
- Duration of CDK4/6i was associated with PFS in the EMERALD trial. The longer the duration of prior CDK4/6i, the longer PFS on elacestrant as compared with SOC.
- This was even more pronounced in patients with *ESR1*-mut tumors, where patients who had at least 12 months of prior CDK4/6i duration achieved a mPFS of 8.6 months with elacestrant vs 2.1 months mPFS with SOC.
- No new safety signals were identified. Low-grade nausea was common in both treatment arms, but antiemetic usage was low with both oral drugs: 8% on elacestrant and 10.3% on AIs. There was no incidence of bradycardia.
- These results showed that elacestrant significantly prolongs PFS vs SOC with a low rate of adverse events.
- Elacestrant can become an important oral endocrine monotherapy agent in 2nd/3rd line as an alternative to combination therapies that are associated with challenging safety profiles.

FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer

On January 27, 2023, the Food and Drug Administration (FDA) approved elacestrant (Orserdu, Stemline Therapeutics, Inc.) for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

FDA also approved the Guardant360 CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with elacestrant.

Future Directions

More trials and research regarding CDK 4/6 inhibitor use upon progression and mechanisms of resistance

- Pace trial

Multiple trials investigating oral SERDs in HR+ MBC

- SERENA-2 trial, EMBER-3 trial

Sequencing of these agents

Awaiting approval for Sacituzumab govitecan in HR+ MBC

HER2+ Breast Cancer

- Destiny Breast 02
- Destiny Breast 03

Trastuzumab deruxtecan vs physician's choice in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: Primary results of the randomized phase 3 study DESTINY-Breast02

Presentation ID: GS2-01

Ian Krop,[a] Yeon Hee Park, Sung-Bae Kim, Giuliano Borges, Sercan Aksoy, Joaquin Gavila Gregori, Rebecca Roylance, Elgene Lim, Rinat Yerushalmi, Flora Zagouri, Francois P. Duhoux, Tanja Fehm, Toshimi Takano, Anton Egorov, Iris Wu, Jillian Cathcart, Changan Chu, Fabrice André

On behalf of the DESTINY-Breast02 investigators

[a]Yale Cancer Center, New Haven, CT, USA

Evolution of Treatments for HER2+ Metastatic Breast Cancer

2L+

T-DM1, EMILIA:
mPFS 9.6 months vs 6.4 months with lapatinib + capecitabine
HR, 0.65 (95% CI, 0.55-0.77; *P* < 0.001)[1]

T-DXd, DESTINY-Breast03:
mPFS not reached vs 6.8 months with T-DM1;
HR, 0.28 (95% CI, 0.22-0.37; *P* < 0.001)[2]

- Prior to DESTINY-Breast03, the EMILIA trial established T-DM1 as 2L+ standard of care[1]
- Based on the strength of the DESTINY-Breast03 trial efficacy and safety data, T-DXd is now the recommended option in the 2L setting[2]

3L+

T-DXd, DESTINY-Breast01:
mPFS = 19.4 months[3,4]

- T-DXd demonstrated robust activity in a post-TDM1 phase 2 single arm study, DESTINY-Breast01, leading to regulatory approvals globally[3-5]

DESTINY-Breast02 is a randomized, multicenter, open-label, phase 3 trial comparing the efficacy and safety of T-DXd vs TPC in patients with HER2+ mBC previously treated with T-DM1

DESTINY-Breast02 is a confirmatory trial for DESTINY-Breast01. Results of the primary analysis are presented

2L, second-line; 3L, third-line; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Verma S et al. *N Engl J Med*. 2012;367:1783-1791. 2. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 3. Perez J et al. *Expert Opin Biol Ther*. 2021;21:811-824. 4. Saura C et al. Presented at ESMO 2021. Poster 279P.
5. Modi S et al. *N Engl J Med* 2020;382:610-621.

2022 ASCO® ANNUAL MEETING

Trastuzumab Deruxtecan vs Trastuzumab Emtansine in Patients With HER2-Positive Unresectable and/or Metastatic Breast Cancer: Safety Follow-up of the Randomized, Phase 3 Study DESTINY-Breast03

Erika Hamilton, MD,[a] Vanessa Petry, Winnie Yeo, Sung-Bae Kim, Giampaolo Bianchini, Toshinari Yamashita, Kan Yonemori, Kenichi Inoue, Giuseppe Curigliano, Sara A. Hurvitz, Javier Cortés, Hiroji Iwata, Jillian Cathcart, Yali Liu, Caleb Lee, Emarjola Bako, Rachel Kim, Seock-Ah Im
On behalf of the DESTINY-Breast03 investigators

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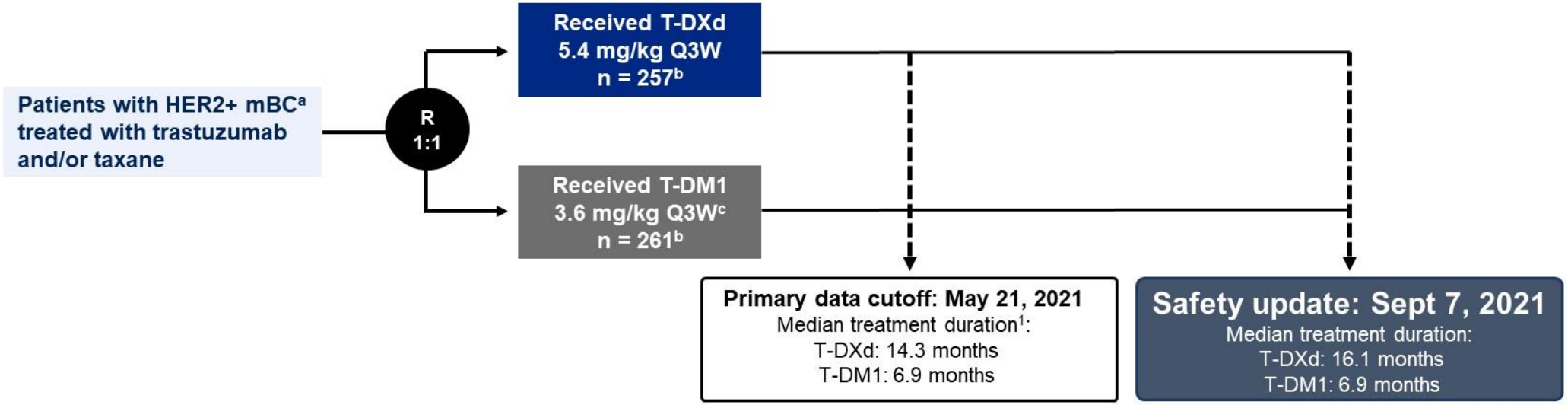
DESTINY-Breast03 Study Design



Objective of the study was to provide updated safety data with additional analyses in patients with HER2+ mBC treated with T-DXd or T-DM1 in DESTINY-Breast03

EAIRs, exposure-adjusted incidence rates; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; mBC, metastatic breast cancer; Q3W, every 3 weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

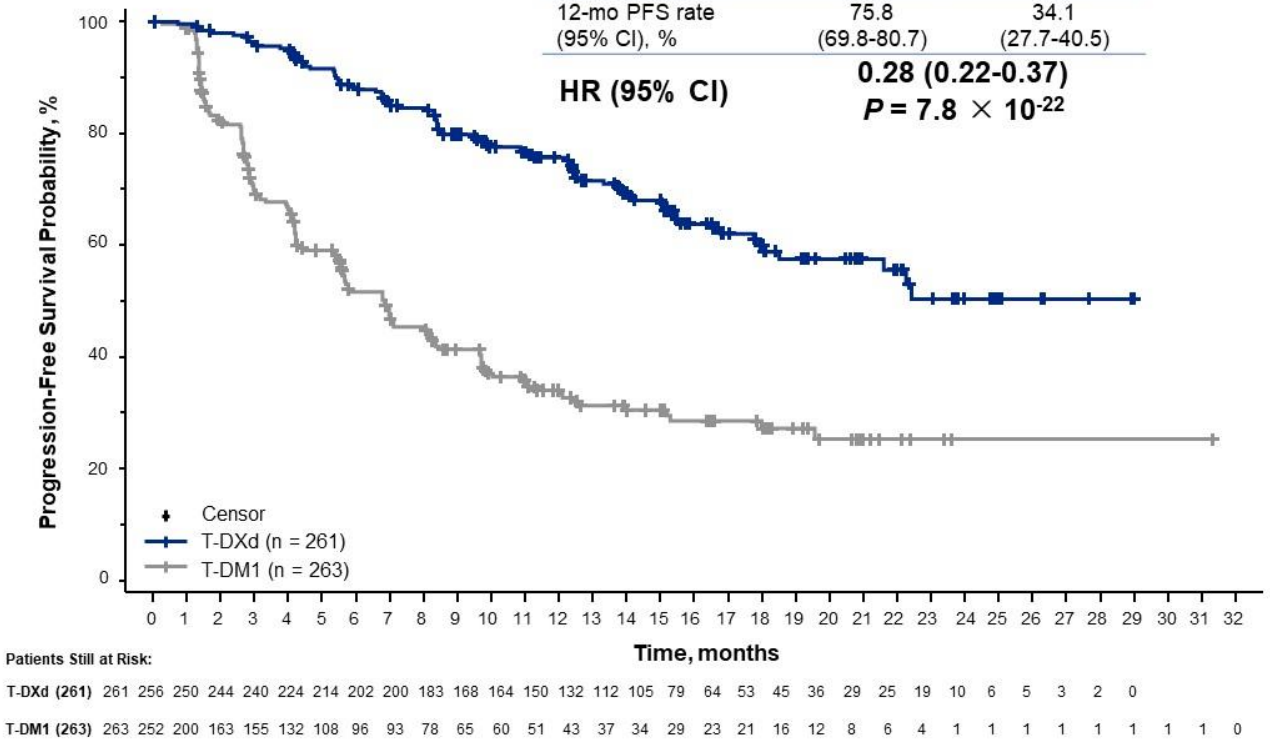
[a]Central testing of archived sample for HER2 status. [b]Number of treated patients (not the randomized number of patients). [c]Or in accordance with the local label.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

Background

PFS by BICR[1,a]

	T-DXd	T-DM1
mPFS (95% CI), mo	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate (95% CI), %	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

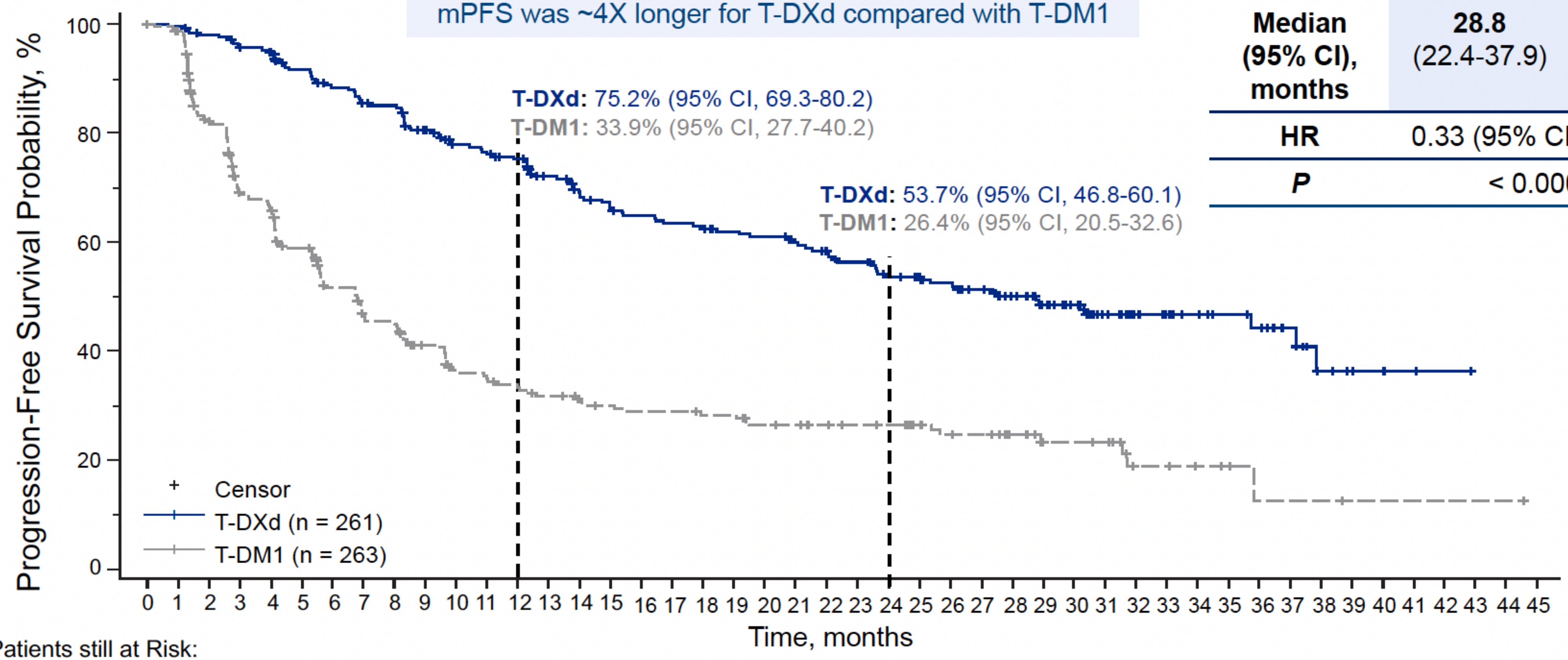


- T-DXd, a HER2-targeted ADC, was approved for the treatment of patients with HER2+ unresectable or mBC who have received a prior anti-HER2 therapy in the metastatic or neoadjuvant/adjuvant setting and had recurrence during or within 6 months after therapy[2]
- DESTINY-Breast03 (NCT03529110) investigated T-DXd vs T-DM1 in patients with HER2+ unresectable or mBC
  - In the primary analysis (May 21, 2021), T-DXd was superior to T-DM1 for PFS by BICR (primary endpoint)[1]
  - Overall health status and QoL was maintained with T-DXd and numerically favored T-DXd over T-DM1[3]

ADC, antibody-drug conjugate; BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median progression-free survival; PFS, progression-free survival; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. 1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Enhertu (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Daiichi Sankyo, Inc; 2022. 3. Curigliano G et al. Presented at ESMO Breast Cancer meeting; May 3-5, 2022; Berlin, Germany. Presentation 1630. [a]From *New England Journal of Medicine*, Cortés J et al, Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer, Vol. 386, Pages 1143-1154. Copyright © 2022 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Updated Primary Endpoint: PFS by BICR

mPFS was ~4X longer for T-DXd compared with T-DM1



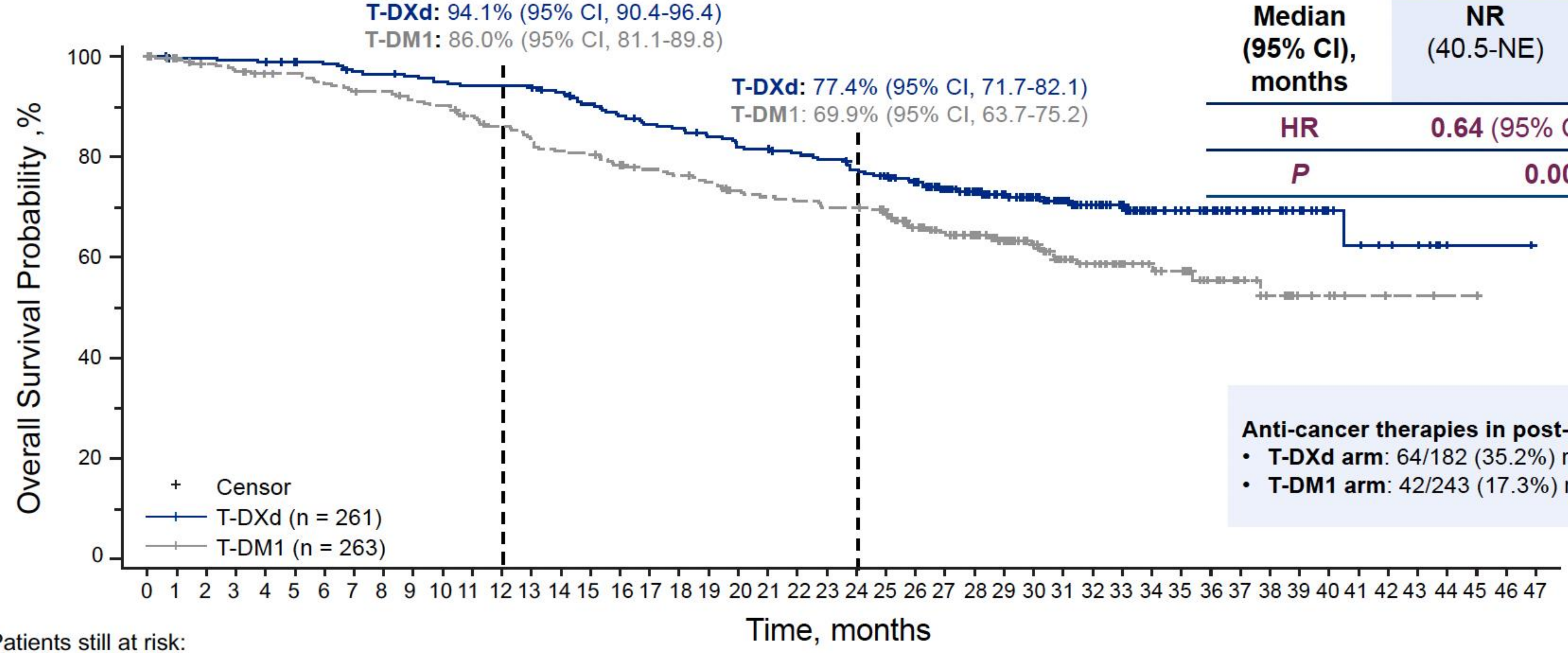
	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

Patients still at Risk:

T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Two-sided, from stratified log rank test. [b]Nominal *P* value.

Key Secondary Endpoint: Overall Survival



	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	

Anti-cancer therapies in post-trial setting:

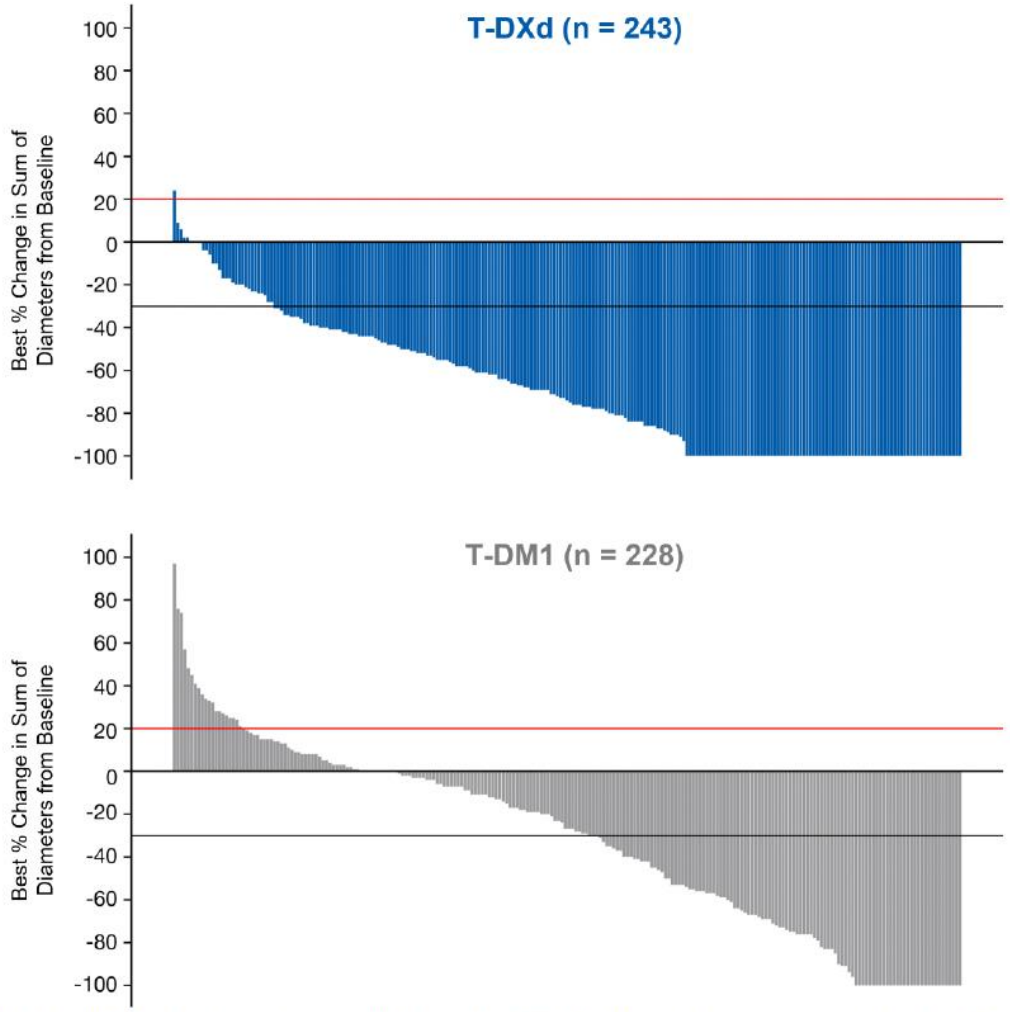
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Patients still at risk:

T-DXd	261	256	256	255	254	251	249	244	243	241	238	236	236	236	231	224	218	213	211	206	201	200	196	193	187	182	173	156	142	124	109	91	73	64	51	44	38	30	22	18	11	9	7	6	1	1	1	0
T-DM1	263	257	252	248	243	242	237	233	232	227	224	217	211	203	199	197	191	186	183	179	172	169	167	164	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = 0.013) and was statistically significant. [b]Two-sided from stratified log-rank test.

Confirmed ORR and Other Efficacy Endpoints



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	
mDoR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDoR, median duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Red line at 20% indicates progressive disease; black line at −30% indicates partial response.
[a]Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included.

Exposure-Adjusted Incidence Rates (EAIRs)[a]

	Exposure-adjusted incidence per total patient-years of exposure	
	T-DXd n = 257	T-DM1 n = 261
Patients remaining on treatment, n (%)	116 (45.1)	39 (14.9)
Treatment duration, median (range), months	**16.1 (0.7-33.0)**	**6.9 (0.7-28.5)**
Exposure, patient-years[b]	327.2	186.3
EAIR, grade ≥3 TEAE	0.42	0.70
EAIR, any grade serious TEAE	0.17	0.27
EAIR, grade ≥3 serious TEAE	0.12	0.20
EAIR, TEAE associated with drug discontinuation	0.12	0.10
EAIR, TEAE associated with dose reduction	0.18	0.19

- EAIRs were measured to account for differences in treatment duration exposure between T-DXd and T-DM1 and provide a more meaningful comparison
- EAIRs per patient-year were lower in the T-DXd arm than the T-DM1 arm except for TEAEs associated with drug discontinuation, which were primarily associated with ILD/pneumonitis in the T-DXd arm
  - EAIR for grade ≥3 TEAEs was 0.42 for T-DXd and 0.70 for T-DM1
  - EAIR for any grade serious TEAEs was 0.17 for T-DXd and 0.27 for T-DM1

EAIRs, exposure-adjusted incidence rates; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]EAIR was the number of patients with at least 1 event incidence divided by the sum of patient-years of exposure over patients in the safety analysis set (total patient-years of exposure). [b]Patient years of exposure were the treatment duration with year as unit.

Conclusions

- **No new safety signals were observed for T-DXd in patients with HER2+ mBC in this safety update,[1-3] and in-depth analysis demonstrated that:**
  - Most TEAEs were grade 1 or 2, and exposure-adjusted incidence rates of grade ≥3 TEAEs and serious TEAEs were lower with T-DXd than T-DM1
  - Risk of nausea, vomiting, fatigue, and alopecia was higher for T-DXd in the initial treatment cycles
  - Prevalence of nausea and vomiting was higher for T-DXd in the initial treatment cycles and was consistent over time for alopecia and fatigue
    - In the T-DXd arm, the increased risk and higher prevalence of these events that persisted throughout treatment duration necessitates ongoing supportive care
  - There were no additional grade 3 adjudicated ILD/pneumonitis events with T-DXd (overall rate = 0.8%), and no grade 4 or 5 events overall

These data reinforce the established favorable benefit/risk profile of T-DXd over T-DM1 in HER2+ mBC

HER2, human epidermal growth factor receptor-2; ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

1. Modi S et al. *J Clin Oncol*. 2020;38:1887-1896. 2. Modi S et al. *N Engl J Med*. 2020;382:610-621. 3. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]

- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
  or
- Lapatinib / Capecitabine

Primary endpoint

- PFS (BICR[b])

Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints

- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:

- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

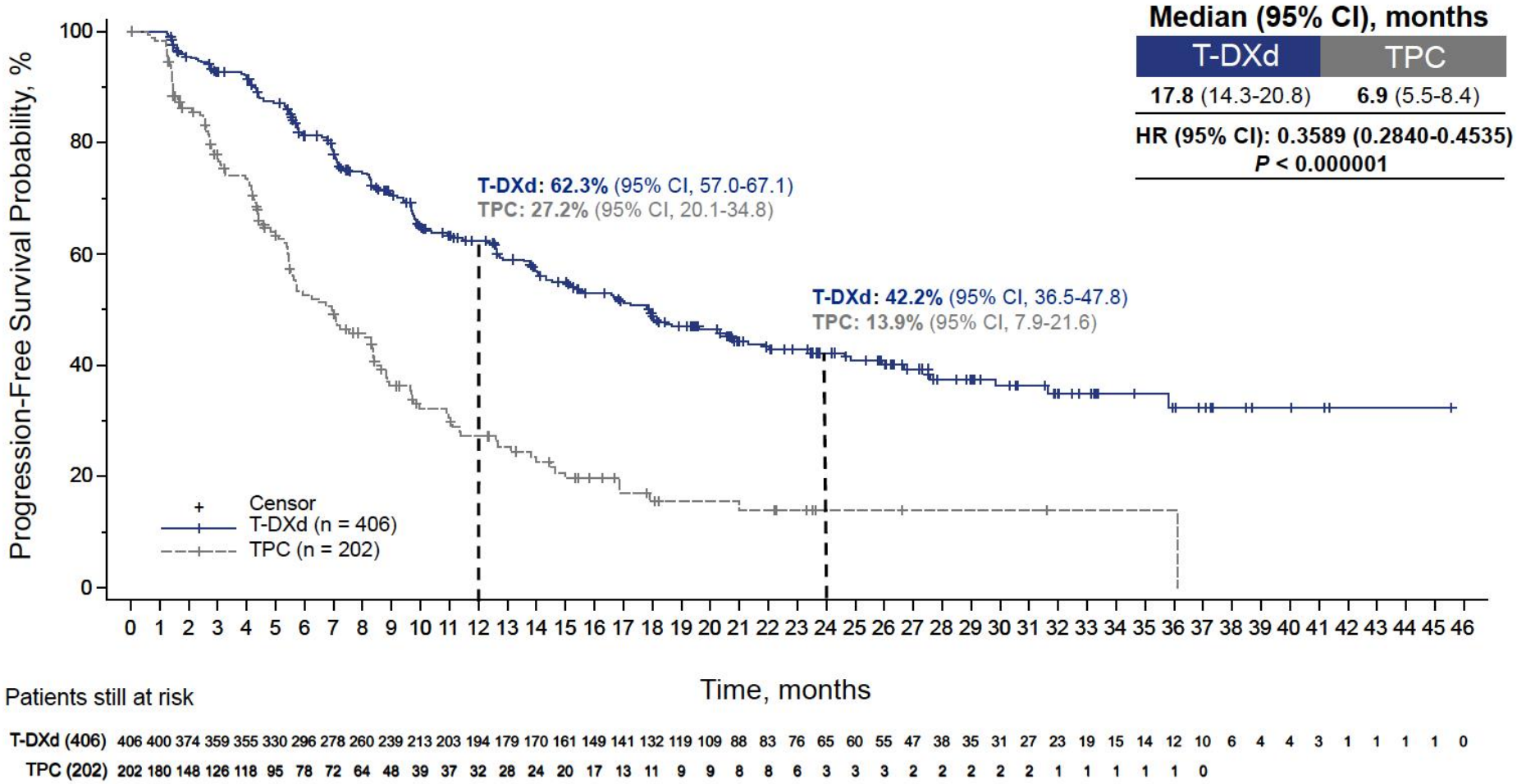
Protocol-prespecified statistical analysis plan

- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

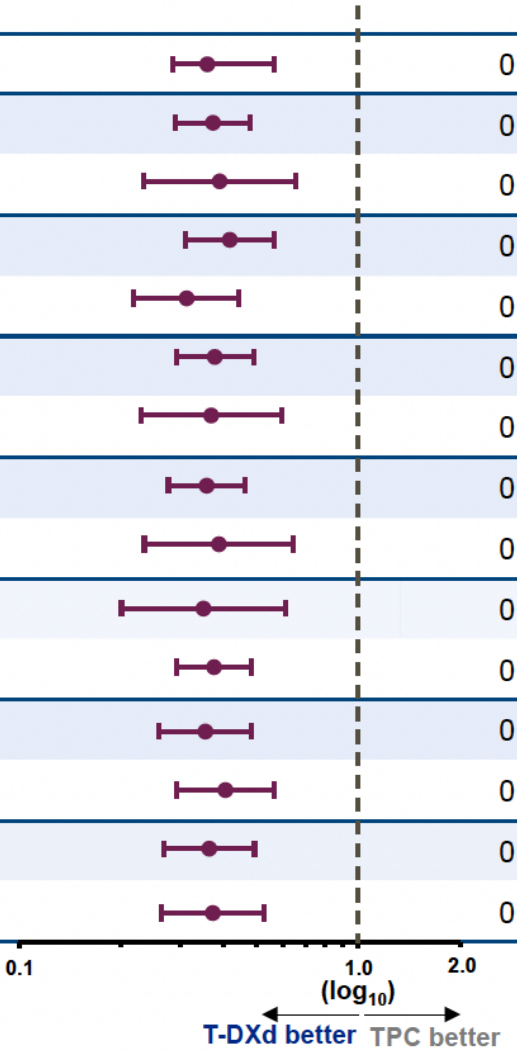
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

Primary Endpoint: PFS by BICR



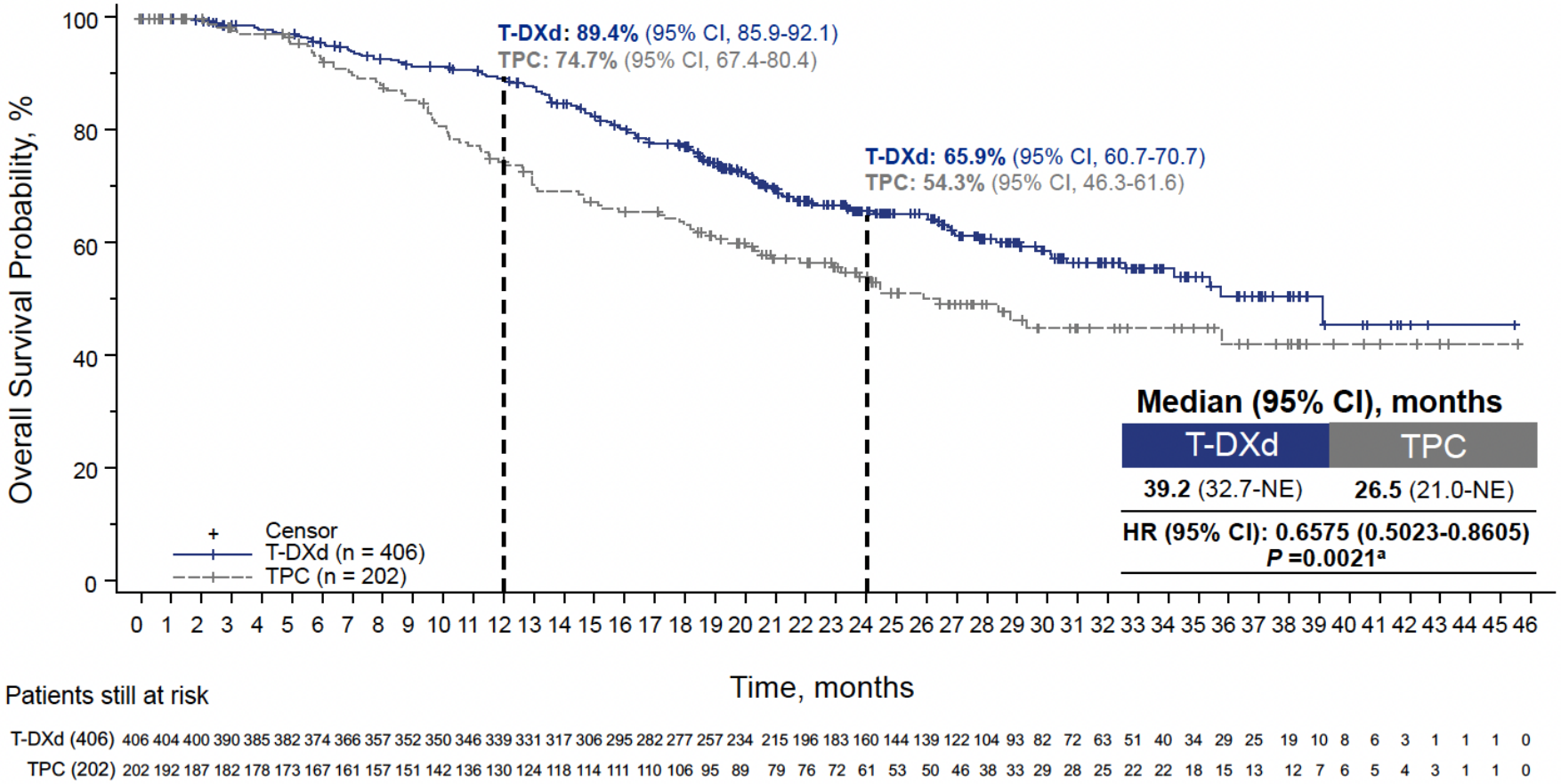
PFS in Key Subgroups

		Number of Events		Median PFS, mo (95% CI)		HR (95% CI)
		T-DXd	TPC	T-DXd	TPC	
All patients		200/406	125/202	17.8 (14.3-20.8)	6.9 (5.5-8.4)	0.36 (0.28-0.45)
Age	<65	160/321	101/164	17.9 (14.1-20.8)	7.1 (5.5-8.6)	0.37 (0.29-0.48)
	≥65	40/85	24/38	16.8 (12.7-NE)	6.7 (4.3-8.4)	0.39 (0.23-0.65)
Hormone receptor status	Positive	115/238	71/118	18.0 (15.1-21.3)	8.5 (6.5-10.0)	0.42 (0.31-0.57)
	Negative	84/165	53/83	17.0 (12.3-24.6)	5.3 (4.3-6.7)	0.31 (0.22-0.45)
Prior pertuzumab treatment[a]	Yes	155/318	95/156	17.8 (14.0-20.8)	6.2 (5.0-8.4)	0.38 (0.29-0.49)
	No	45/88	30/46	18.0 (13.9-26.7)	8.3 (5.5-12.6)	0.37 (0.23-0.60)
Visceral disease[a]	Yes	164/316	98/160	15.6 (12.8-20.3)	5.7 (5.3-7.2)	0.36 (0.28-0.46)
	No	36/90	27/42	29.8 (16.8-NE)	9.8 (6.2-12.6)	0.39 (0.23-0.64)
Baseline brain metastases	Yes	44/74	20/36	13.9 (11.1-18.0)	5.6 (3.3-8.1)	0.35 (0.20-0.61)
	No	156/332	105/166	18.7 (15.1-24.8)	7.1 (5.5-8.6)	0.38 (0.29-0.48)
Prior lines of therapy[b]	<3	105/212	66/104	16.6 (13.8-24.6)	7.0 (4.6-8.6)	0.35 (0.26-0.49)
	≥3	95/194	59/98	18.2 (14.3-22.0)	6.9 (5.5-8.8)	0.41 (0.29-0.57)
ECOG PS	0	101/228	75/121	24.6 (15.3-31.6)	8.1 (5.7-9.7)	0.36 (0.27-0.50)
	1	98/177	50/81	15.1 (11.5-18.0)	5.4 (4.3-7.5)	0.37 (0.26-0.53)



ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mo, months; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Subgroup values are derived from baseline. [b]Lines of prior systemic therapy not including hormone therapy.

Key Secondary Endpoint: OS



In the TPC arm

- **69.3% (140/202) of patients received a new systemic anticancer treatment**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

[a]The boundary for statistical significance is 0.0040. HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Conclusions

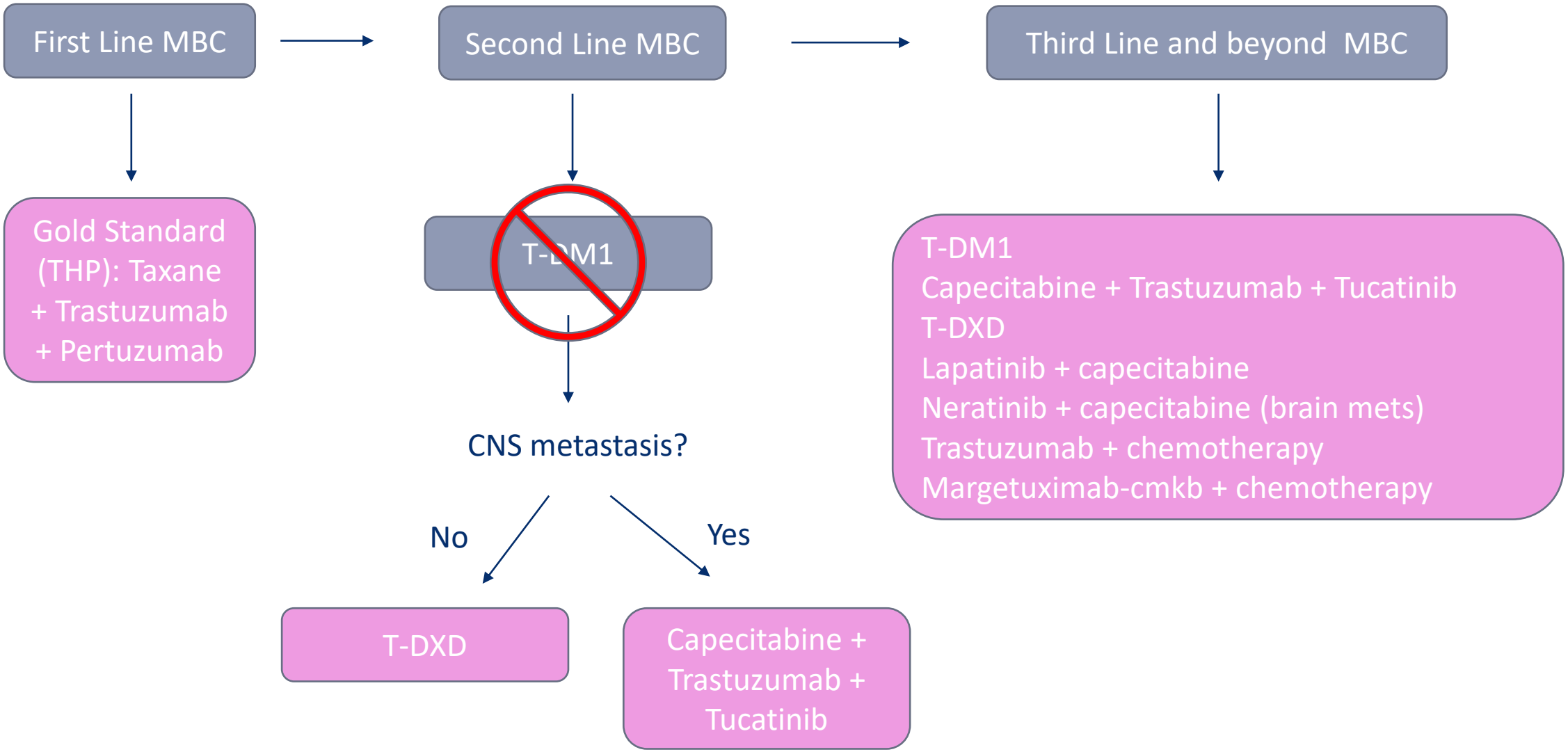
- **In DESTINY-Breast02, T-DXd demonstrated statistically significant and clinically meaningful improvement in PFS and OS vs TPC for patients with HER2+ mBC previously treated with T-DM1**
  - mPFS results showed T-DXd reduced the risk of progression or death compared with TPC (mPFS of 17.8 and 6.9 months, respectively; HR, 0.3589; 95% CI, 0.2840-0.4535; $P < 0.000001$)
  - mOS results showed T-DXd reduced the risk of death compared with TPC (mOS of 39.2 and 26.5 months, respectively; HR, 0.6575; 95% CI; 0.5023-0.8605; $P = 0.0021$)
- **The overall safety profile was consistent with the established safety of T-DXd, with no new safety signals observed**
  - Overall incidence of ILD for T-DXd in DESTINY-Breast02 was 10.4% (grade 1/2 events, 9.2%)
  - Fewer grade 5 ILD events were observed in DESTINY-Breast02 (0.5%) compared with DESTINY-Breast01 (2.7%)[1-2]

DESTINY-Breast02 confirms the favorable benefit/risk profile of T-DXd in patients with advanced HER2+ mBC, as previously demonstrated by DESTINY-Breast01

HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ILD, interstitial lung disease; mBC, metastatic breast cancer; mOS, median overall survival; mPFS, median progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi S et al. *Cancer Res.* 2021:81(4_suppl):PD3-06. 2. Saura C et al. Presented at: European Society for Medical Oncology; September 16-21, 2021. Poster 279P.

Treatment Algorithm for HER2+ MBC



Future Directions

Sequencing therapy

Novel Combinations of anti-HER2 therapies

Emerging therapies

- New ADCs (trastuzumab duocarmazine)
- Immune checkpoint inhibitor combinations
- Bispecific antibodies
- HER3 ADCs (patritumumab deruxtecan)

Questions?

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