ASCO Updates- Breast Oncology

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Disclosures

I have no relevant relationships to disclose.

Early-Stage Breast Cancer Updates

2022 ASCO® ANNUAL MEETING

Adding ovarian function suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or resume menstruation after chemotherapy : 8-year follow-up of the randomized ASTRRA trial (KBCSG-05, 20 Trial)

Soo Yeon Baek[1], Woo Chul Noh[2], Sei-Hyun Ahn[1], Hyun-Ah Kim[3], Jai Min Ryu[4], Seung Il Kim[5], Eun-Gyeong Lee[6], Seock-Ah Im[7], Yongsik Jung[8], Min Ho Park[9], Kyong Hwa Park[10], Su Hwan Kang[11], Joon Jeong[12], Eunhwa Park[13], Sung Yong Kim[14], Min Hyuk Lee[15], Lee Su Kim[16], Woosung Lim[17], Seonok Kim[18], Hee Jeong Kim[1]

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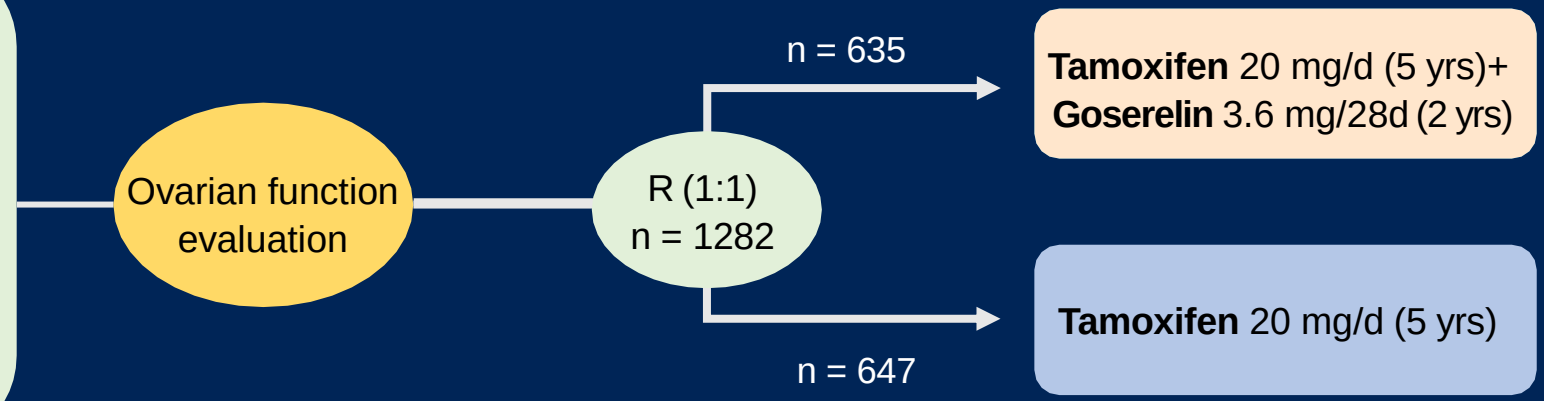
PRESENTED BY: Corresponding Author

Hee Jeong Kim MD, PhD
Professor, Asan Medical Center

ASTRRA study design

Inclusion criteria

- Premenopausal women
- Age ≤ **45** years
- ER+ stage I–III primary breast cancer
- Had been treated with definitive surgery and **chemotherapy**
- WHO performance status of 0–2



Ovarian function evaluation

- Serum FSH level ≥ 30 mIU/mL, menstruation
  - Evaluated every 6 months for 2 years
- Amenorrhea for 2 years
  - Permanent menopause group
    Excluded from the survival analysis

Endpoints

- Primary: Disease Free Survival (DFS)
- Secondary: Overall survival (OS)

Kim HA and Noh WC et al, JCO 2019

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Comparisons between ASTRRA and SOFT trial

	ASTRRA	SOFT-chemotherapy
Age	45 or less	Premenopausal
Median age	40	40
Lymph node positivity	55%	57%
HER2 over expression	14%	19%
Periods of ovarian function evauation for randomization	2 years	8 month
Treatment durations of OFS	2 years	5 years

Francis PA et al, NEJM 2015
Kim HA and Noh WC et al, JCO 2019

SOFT study: The Suppression of Ovarian Function Trial
OFS; Ovarian Function Suppression

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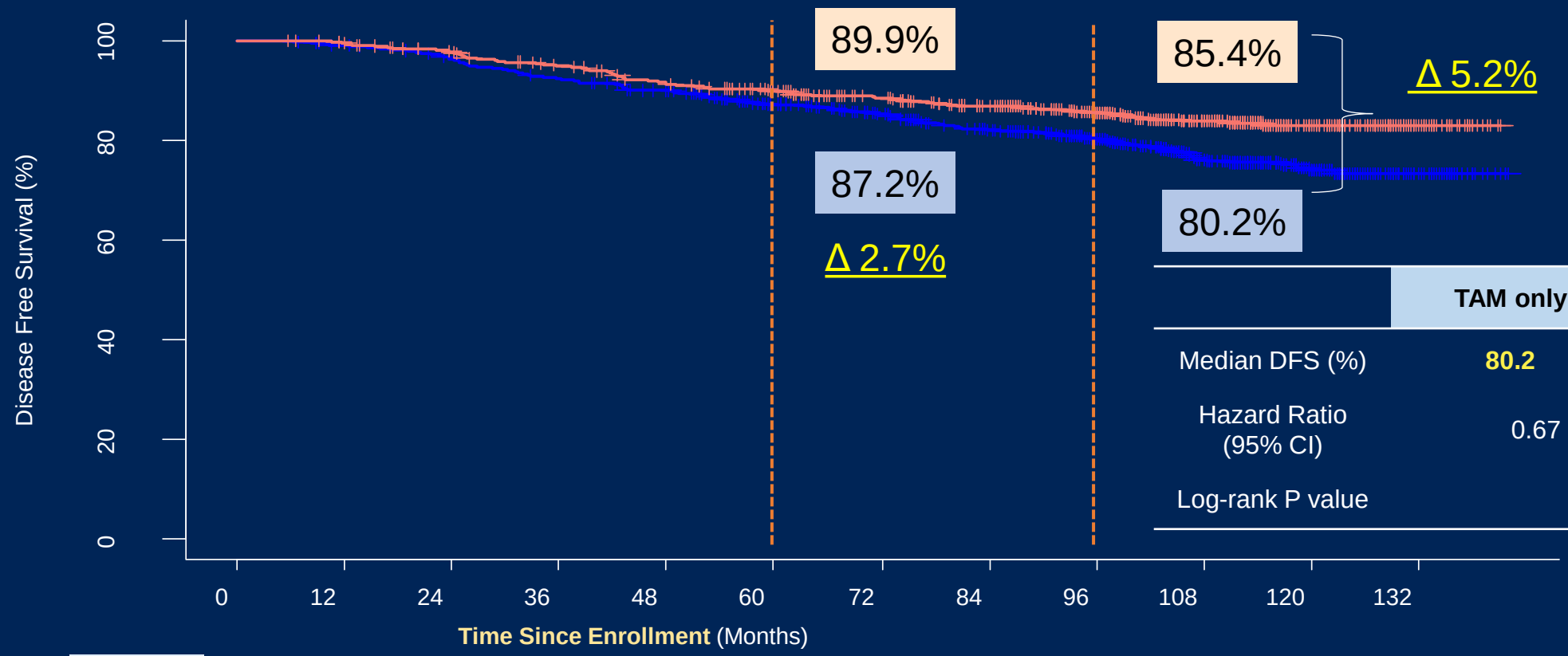
Primary Endpoint – Disease Free Survival



	TAM only	TAM + OFS
Median DFS (%)	80.2	85.4
Hazard Ratio (95% CI)	0.67 (0.514 to 0.869)	
Log-rank P value	0.0027	

TAM only	647	634	612	586	563	511	472	427	356	242	127	42
TAM+OFS	635	626	604	579	551	519	480	443	368	253	124	36

TAM only, Tamoxifen only group
TAM+OFS, Tamoxifen plus ovarian function suppression group

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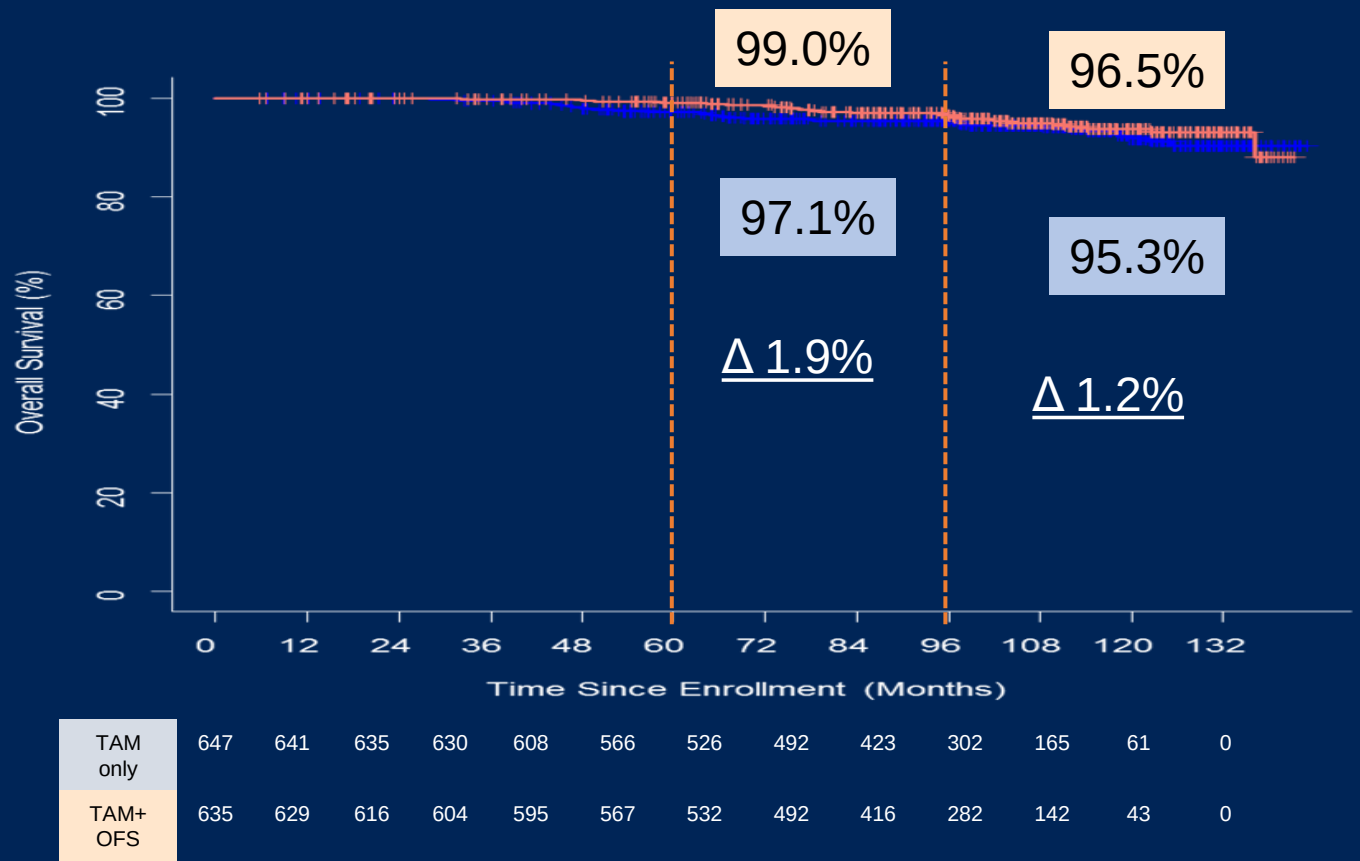
Secondary Endpoint – Overall Survival



	TAM only	TAM + OFS
Median OS (%)	95.3	96.5
Hazard Ratio (95% CI)	0.78 (0.486 to 1.253)	
Log-rank P value	0.3	

TAM only, Tamoxifen only group
TAM+OFS, Tamoxifen plus ovarian function suppression group

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Implication

- These updated data from the ASTRRA trial demonstrate a relatively large benefit for 2 years of ovarian function suppression in premenopausal women with ER+ breast cancer
- Findings suggest that a limited duration of ovarian function suppression in selected patients may be optimal given the risks and side effects of this therapy, and further study is needed

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2022 ASCO® ANNUAL MEETING

ABCSG AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP

Long-term outcomes of adjuvant denosumab in breast cancer

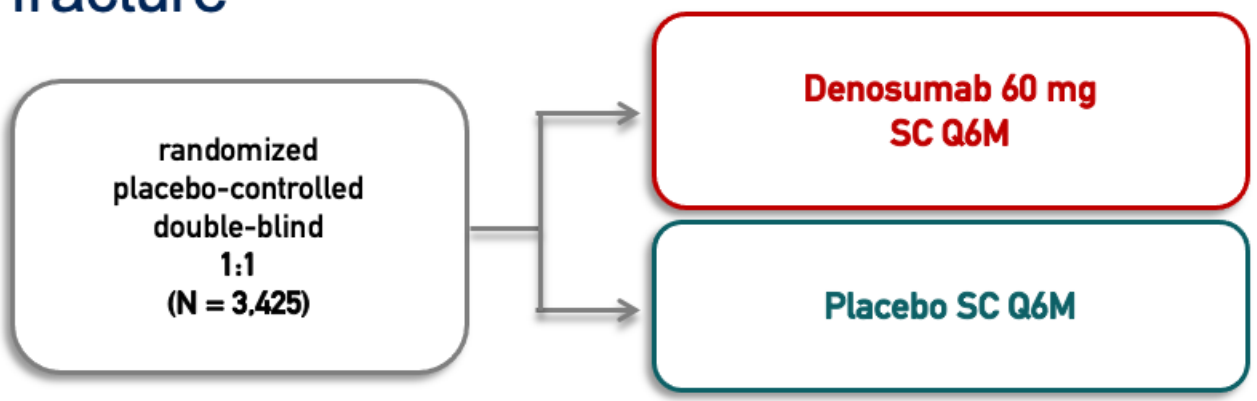
Fracture reduction and survival results from 3,425 patients in the randomised, double-blind, placebo-controlled ABCSG-18 trial

Michael Gnant, MD FACS FEBS

and S Frantal, G Pfeiler, GG Steger, D Egle, R Greil, F Fitzal, V Wette, M Balic, F Haslbauer, E Melbinger-Zeinitzer, V Bjelic-Radisic, C Brunner, S Artner-Matuschek, G Rinnerthaler, K Wimmer, J Bergh, C Fesl, CF Singer, on behalf of the ABCSG

ABCSG-18: Trial Design

- Prospective randomized placebo-controlled double-blind multicenter phase-3 trial
- Recruitment 2006 – 2013 (3,425 postmenopausal patients)
- Primary end point: Time to first clinical fracture
- Inclusion criteria:
  - Postmenopausal women with early breast cancer
  - ER+ and/ or PR+
  - adjuvant non-steroidal aromatase inhibitor therapy



- Exclusion criteria:
  - Prior or concurrent treatment with Selective Estrogen Receptor Modulators (SERMs)
  - Current or prior IV bisphosphonate administration
  - Recent use of oral bisphosphonates
  - Known history of: Paget's disease, Cushing's disease, hyperprolactinaemia, hypercalcaemia or hypocalcaemia, other active metabolic bone disease

Gnant M, et al. Lancet 2015; 386: 433-43

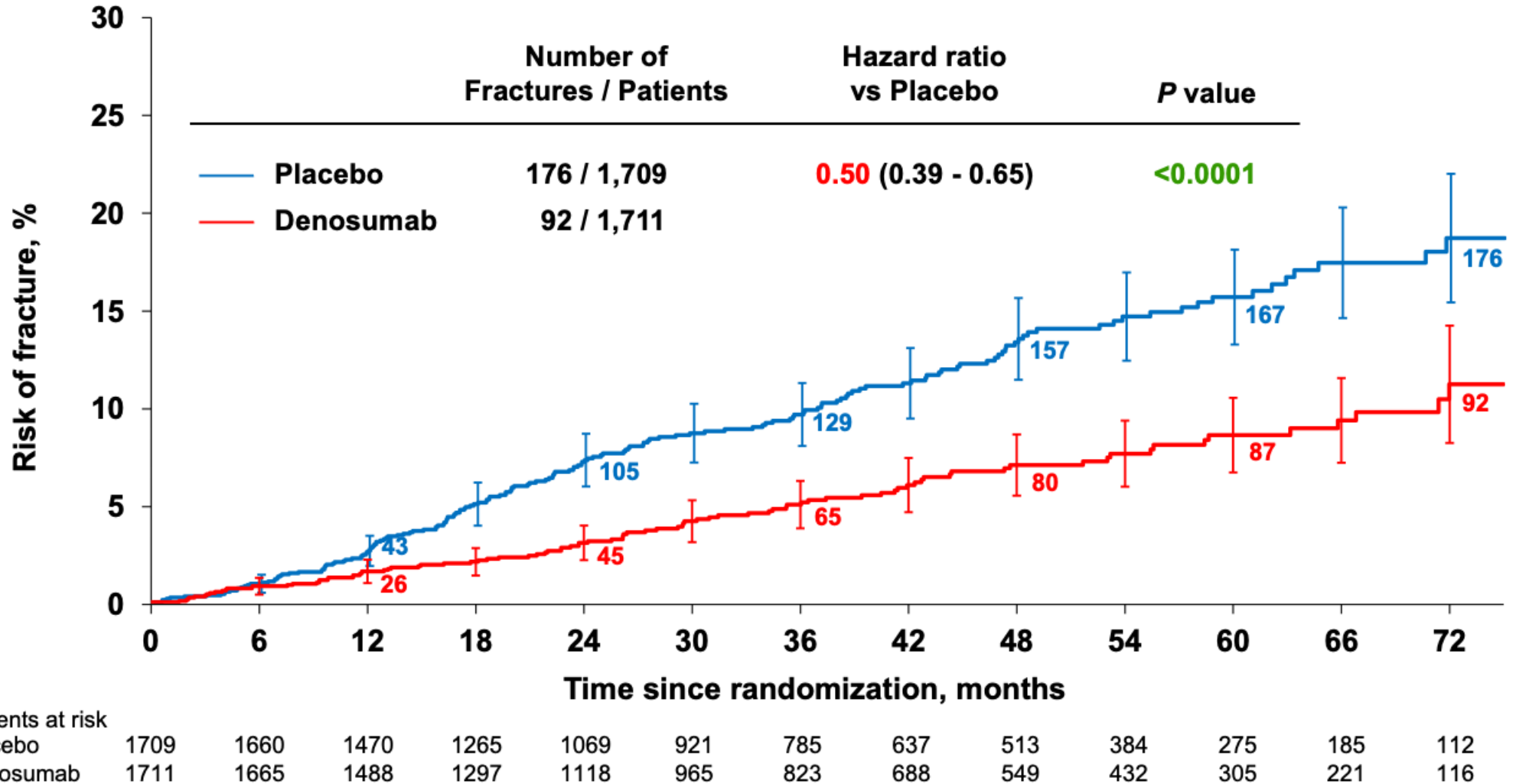
ABCSG-18: Trial End Points and Statistics

End Points		Sample size	Analysis time point: Planned	Analysis time point: Actual
Hierarchical test strategy				
Primary endpoint 1 **Time to first clinical fracture**	Bone	N=3,400; **Events=247**; HR=0.70; 80% power; 2-sided alpha=0.05	**Primary analysis (247 events)**	**Primary analysis (247 events)**
Secondary endpoints 2 **% change in BMD** 3 **Vertebral fractures**	Bone	N=204; Δ=1.8% (SD=3.9%) @12mo; 90% power; 2-sided alpha=0.05		
4 **Disease-free survival (DFS)**	Outcome		**Final analysis (Long-term Follow-Up)**	**Early analysis DFS - IDMC recommended**
5 **Bone metastasis-free survival (BMFS)**	Outcome			**Final analysis (Long-term Follow-Up)**
6 **Overall survival (OS)**	Outcome			

Gnant M, et al. Lancet 2015; 386: 433-43 Gnant M, et al. Lancet Oncol 2019; 20: 339-351

PRESENTED BY:
Michael Gnant, MD, FACS, FEBS

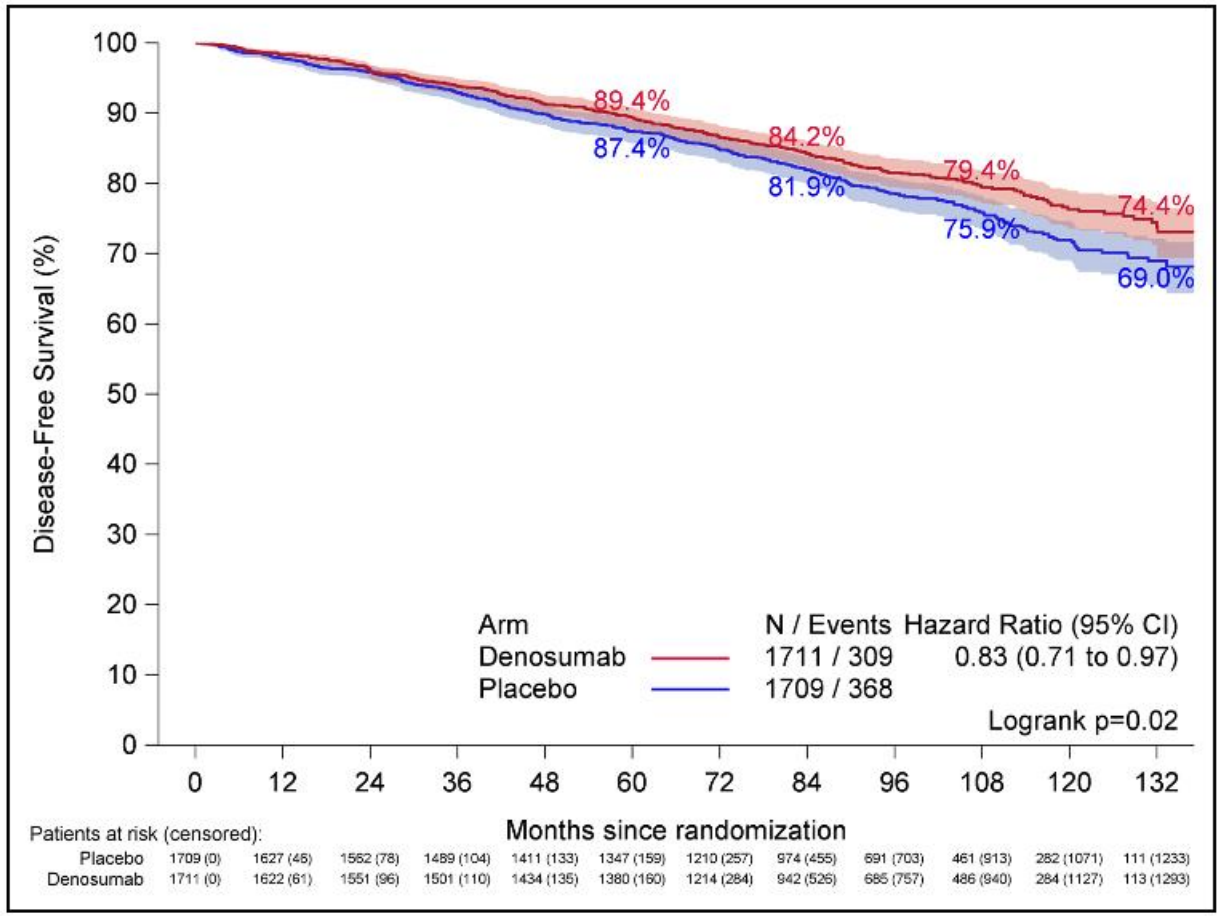
Primary End Point Results



Patients at risk													
Placebo	1709	1660	1470	1265	1069	921	785	637	513	384	275	185	112
Denosumab	1711	1665	1488	1297	1118	965	823	688	549	432	305	221	116

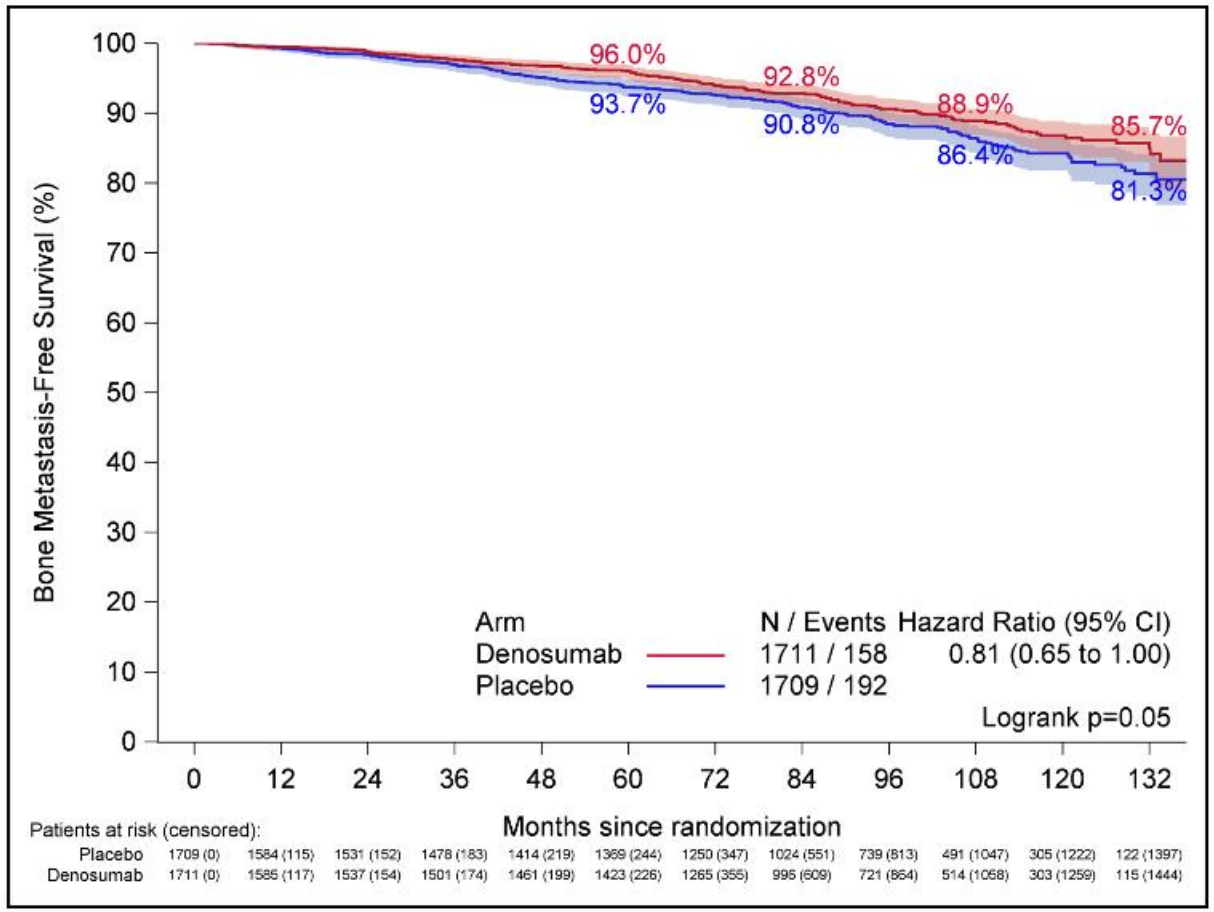
Gnant M, et al. Lancet 2015; 386: 433-43

ABCSG-18: Disease-free survival



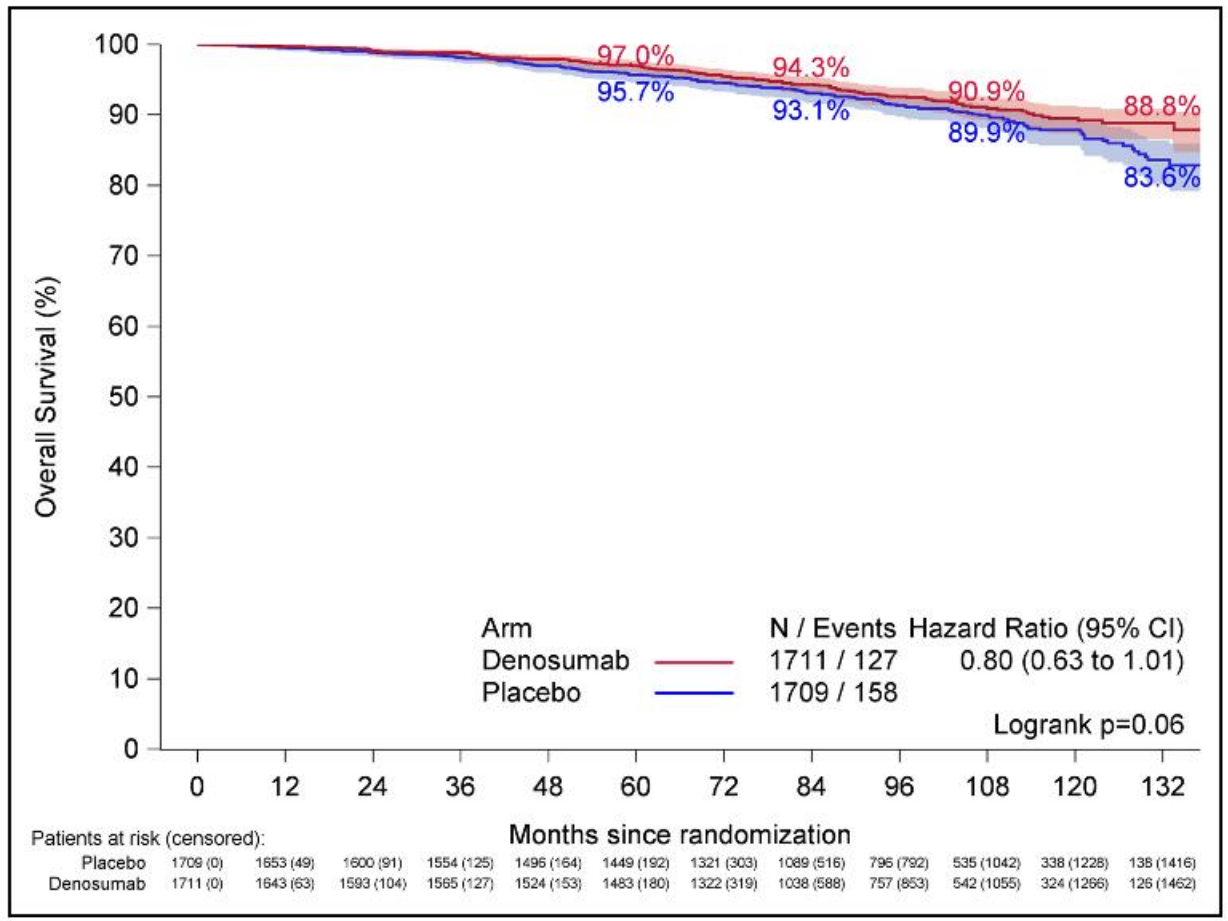
Model	HR Cox	CI Cox	P Cox	P Log-rank
Main	**0.83**	(0.71, 0.97)	0.02	0.02
RPSFTM	0.82	(0.70, 0.96)	0.02	0.02
Cens CO	0.82	(0.70, 0.96)	0.01	0.01
Cens BISDmab	0.83	(0.71, 0.97)	0.02	0.02
Cens BISDmab CO	0.82	(0.70, 0.95)	0.01	0.01

ABCSG-18: Bone metastasis-free survival



Model	HR Cox	CI Cox	P Cox	P Log-rank
Main	**0.81**	(0.65, 1.00)	0.05	0.05
RPSFTM	0.80	(0.64, 1.00)	0.05	0.05
Cens CO	0.77	(0.62, 0.95)	0.01	0.01
Cens BISDmab	0.80	(0.65, 0.99)	0.04	0.04
Cens BISDmab CO	0.76	(0.61, 0.94)	0.01	0.01

ABCSG-18: Overall survival



Model	HR Cox	CI Cox	P Cox	P Log-rank
Main	**0.80**	(0.64, 1.01)	0.06	0.06
RPSFTM	0.80	(0.62, 1.02)	0.06	0.06
Cens CO	0.75	(0.59, 0.95)	0.02	0.02
Cens BISDmab	0.79	(0.63, 1.00)	0.05	0.05
Cens BISDmab CO	0.74	(0.58, 0.94)	0.01	0.01

Conclusions

- Adjuvant denosumab 60mg every 6 months during AI therapy is safe, and markedly reduces treatment-induced clinical fractures, even in the long-term.
- DFS, BMFS, and OS are improved in this descriptive final long-term analysis of ABCSG-18.
- Adjuvant denosumab should be considered for routine clinical use in postmenopausal patients with HR+ breast cancer on AI treatment.

Metastatic Breast Cancer Updates

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

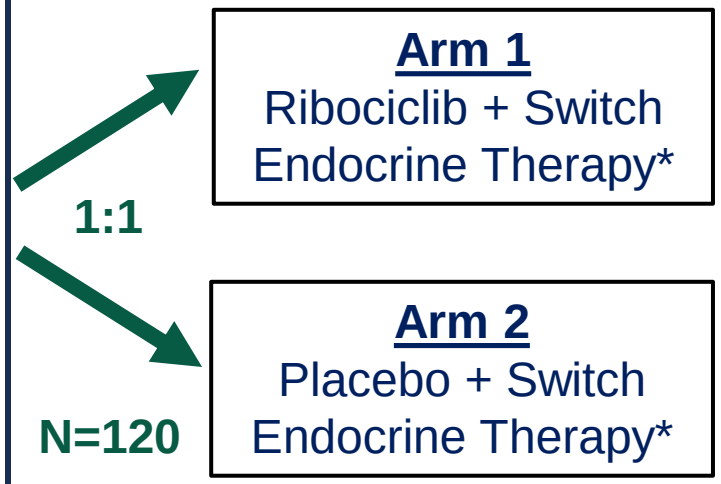
Kevin Kalinsky, Melissa K Accordino, Cody Chiuzan, Prabhjot Mundi, Meghna S Trivedi, Yelena Novik, Amy Tiersten, Amelia Zelnak, George Raptis, Lea Baer, Sun Y Oh, Erica Stringer-Reasor, Sonya Reid, Eleni Andreopoulou, William Gradishar, Kari B Wisinski, Anne O'Dea, Ruth O'Regan, Katherine D Crew, Dawn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

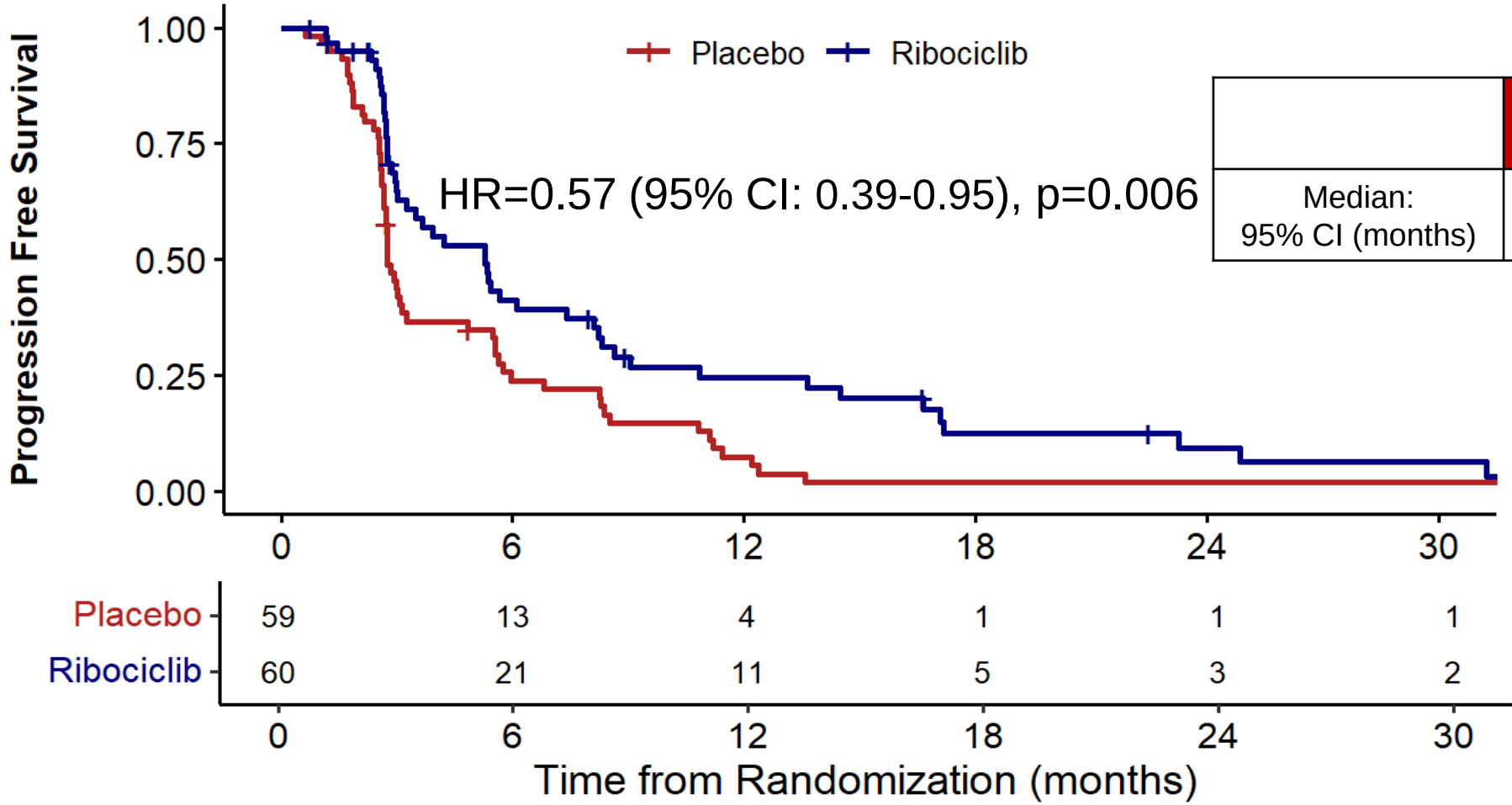
Patient Characteristics and Prior Treatment

	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%)

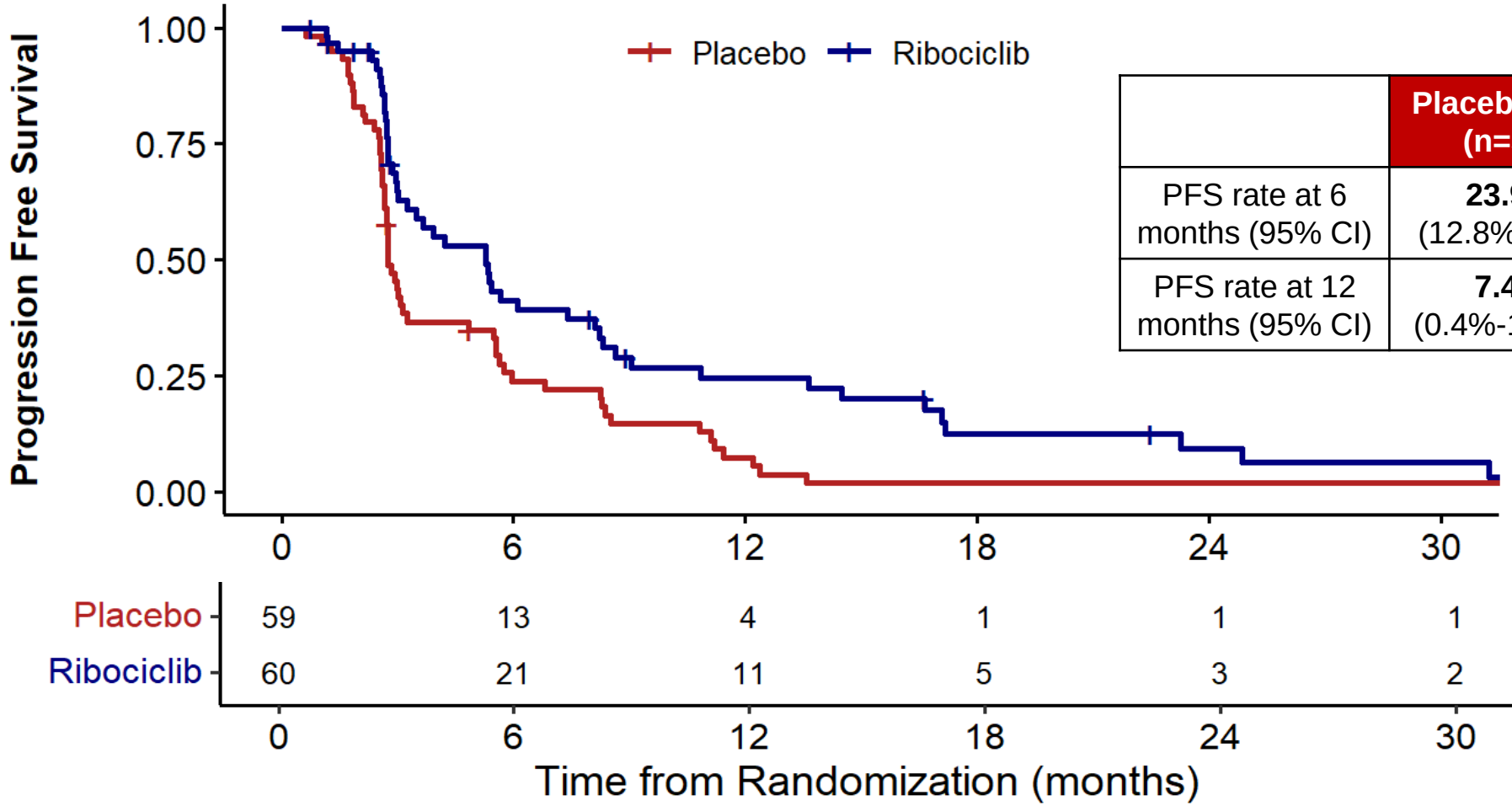
* Includes 1 pt who did not tolerate prior abemaciclib and 2 pts with insurance issues with ribociclib; ** Includes 1 pt who did not tolerate prior palbociclib; ***p=0.035; **** 10 pts (17%) in placebo arm and 7 pts (12%) pts in ribociclib arm on prior CDK4/6 inhibitor ≤ 6 months; IQR = interquartile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

Progression Free Survival at 6 and 12 months



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
PFS rate at 6 months (95% CI)	**23.9%** (12.8%-35%)	**41.2%** (27.8%-54.6%)
PFS rate at 12 months (95% CI)	**7.4%** (0.4%-14.3%)	**24.6%** (12.5%-36.7%)

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

Primary Results From TROPiCS-02: A Randomized Phase 3 Study of Sacituzumab Govitecan Vs Treatment of Physician's Choice in Patients With Hormone Receptor-Positive/HER2-Negative Advanced 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] Rosemary Delaney,[12] Olivia Fu,[12] Lanjia Lin,[12] Wendy Verret,[12] Sara M. Tolaney[13]

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Speaker: Hope S. Rugo

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

NCT03901339

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

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- 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

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

Endpoints

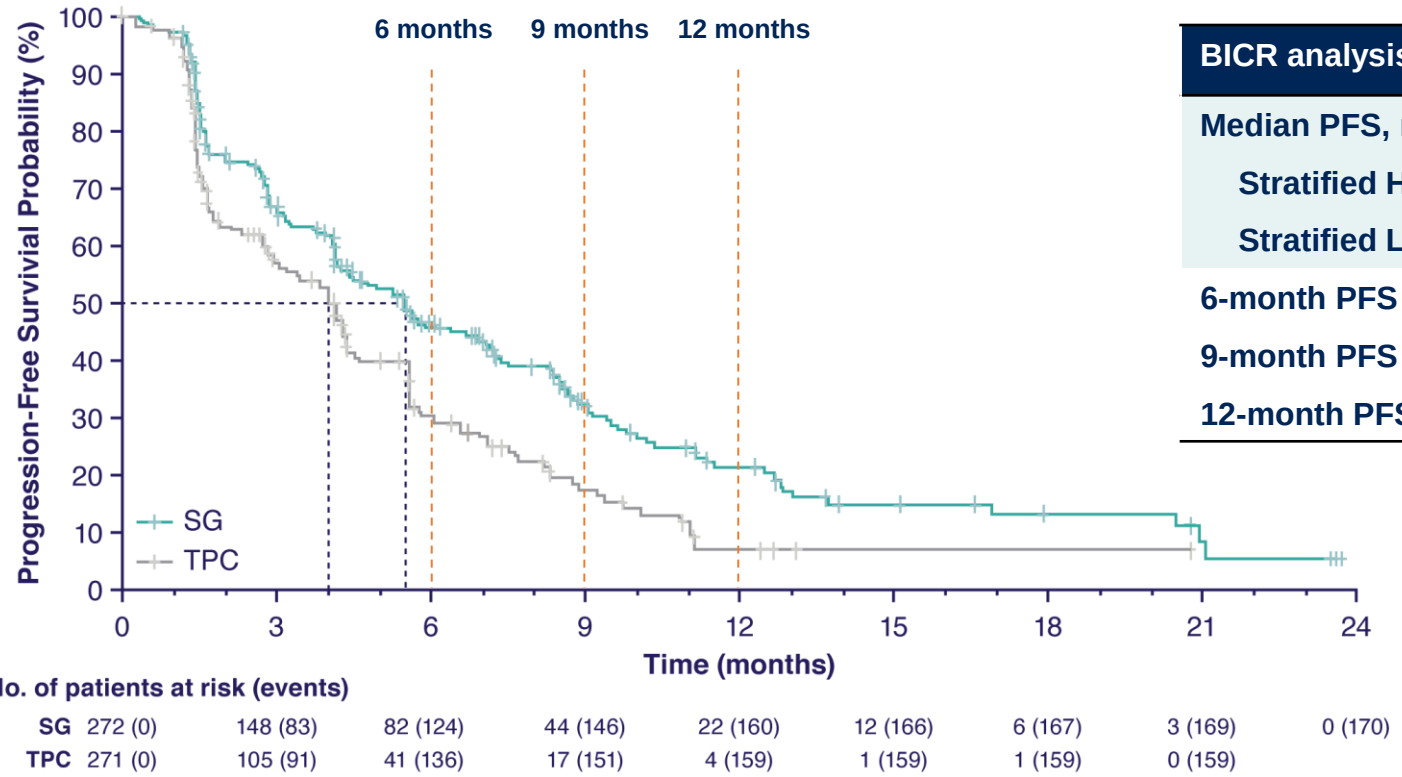
Primary
- PFS by BICR

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

[a]Disease histology based on the 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; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; 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.

Primary Endpoint: BICR-Assessed PFS per RECIST v1.1 in the ITT Population

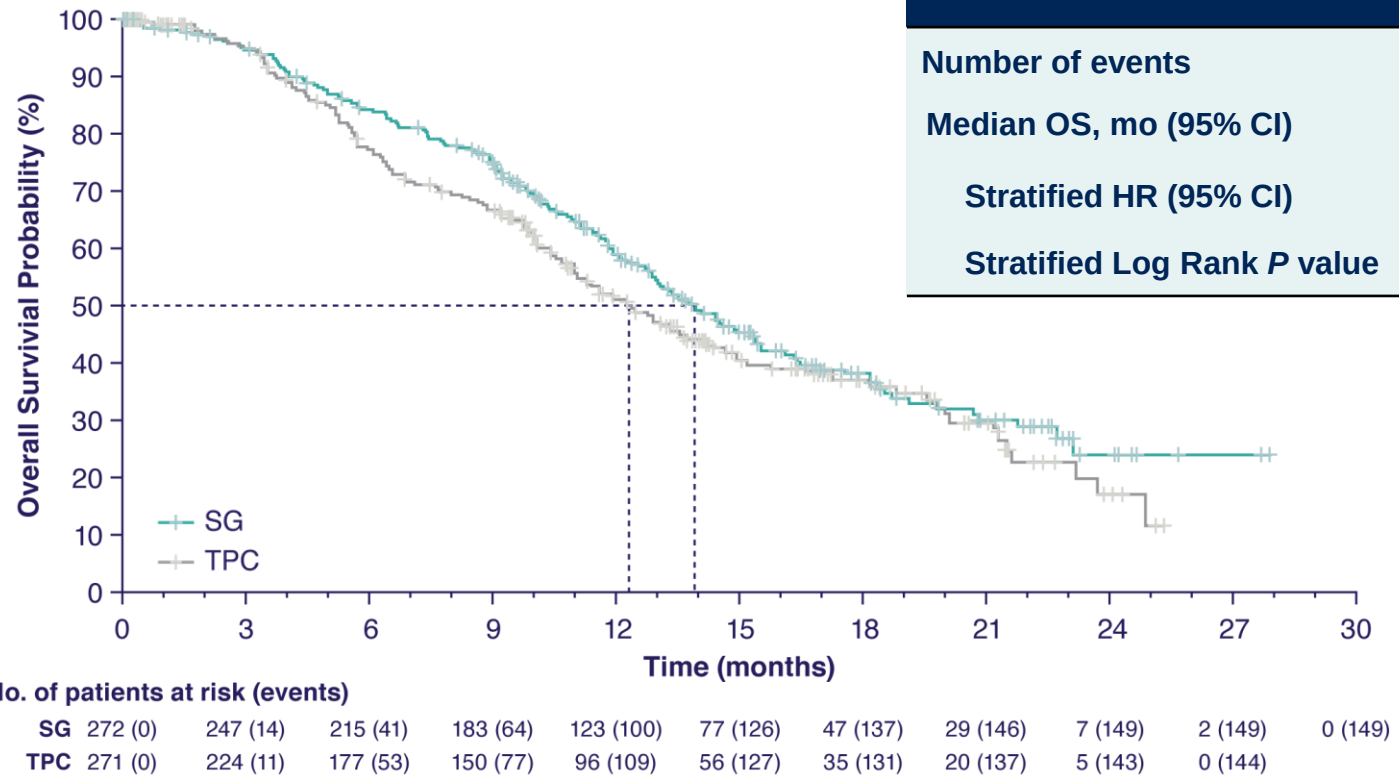
SG demonstrated a statistically significant improvement in PFS vs TPC with a 34% reduction in the risk of disease progression/death; a higher proportion of patients were alive and progression-free at all landmark timepoints



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	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

OS in the ITT Population (First Planned Interim Analysis)



	SG (n=272)	TPC (n=271)
Number of events	149	144
Median OS, mo (95% CI)	13.9 (12.7-15.4)	12.3 (10.8-14.2)
Stratified HR (95% CI)	**0.84** (0.67-1.06)	
Stratified Log Rank *P* value	*P*=0.14	

- **OS data is not yet mature at the first of three planned OS analyses**
- **Further follow-up is ongoing**

ITT, intent-to-treat; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Conclusions

- In patients with heavily pretreated HR+/HER2- advanced breast cancer who have received prior endocrine-based therapy, including prior CDK4/6i therapy, and at least 2 prior chemotherapy regimens for metastatic disease, SG demonstrated a statistically significant PFS benefit over TPC
  - The primary endpoint of PFS by BICR was met, with a 34% reduction in risk of disease progression or death (HR, 0.66; *P*<0.001)
  - A higher proportion of patients were alive and progression-free at all landmark timepoints, with three times as many patients progression-free at the one-year mark when treated with SG compared to those who received TPC (21% vs 7%)
- At the first planned interim analysis of OS, a numeric trend for improvement for SG vs TPC was observed; results are not yet mature, and further follow-up for OS is ongoing
- SG also demonstrated an overall HRQoL benefit over TPC, with delayed deterioration in fatigue and global health status/QoL scales in EORTC QLQ-C30
- The safety profile of SG was manageable and consistent with that in previous studies;[1-3] no new safety concerns were identified

SG demonstrated statistically significant and clinically meaningful benefit and should be considered a potential treatment option in this heavily pre-treated patient population with limited treatment options

BICR, blind independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related adverse event.

1. Bardia A, et al. *Ann Oncol*. 2021;32::746-756. 2. Kalinsky K, et al. *Ann Oncol.* 2020;31(12):1709-1718. 3. Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541.

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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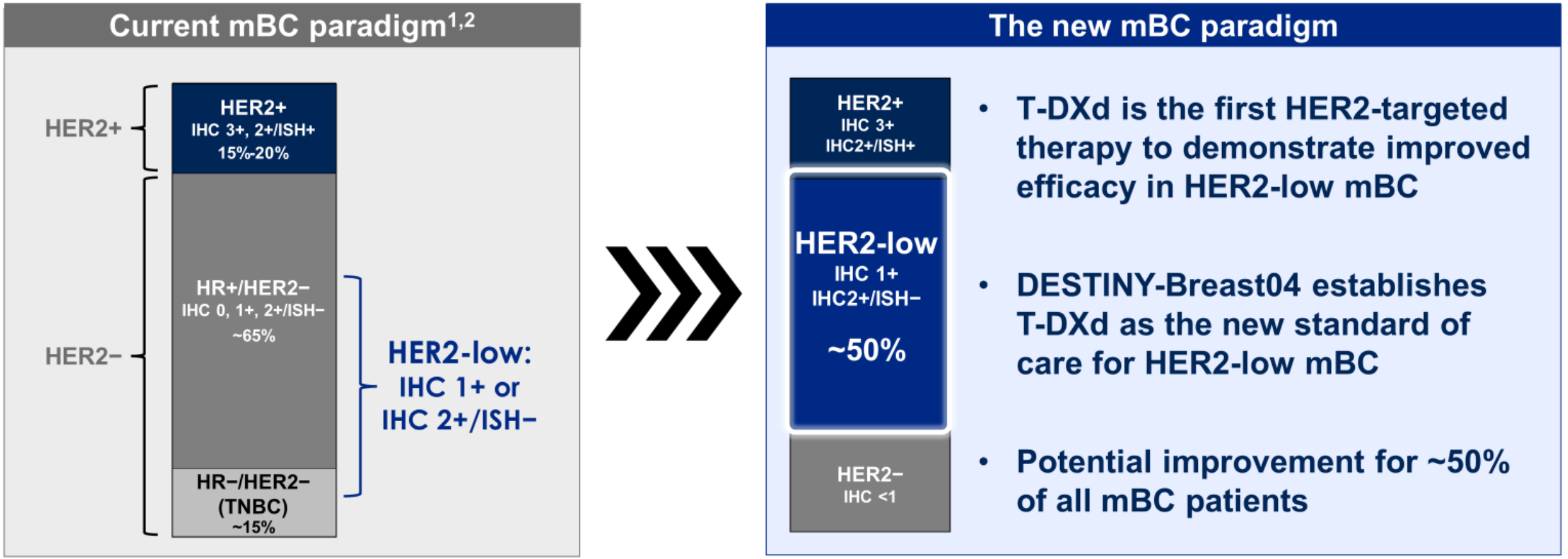
On behalf of the DESTINY-Breast04 investigators

DESTINY-Breast04 Summary and Impact

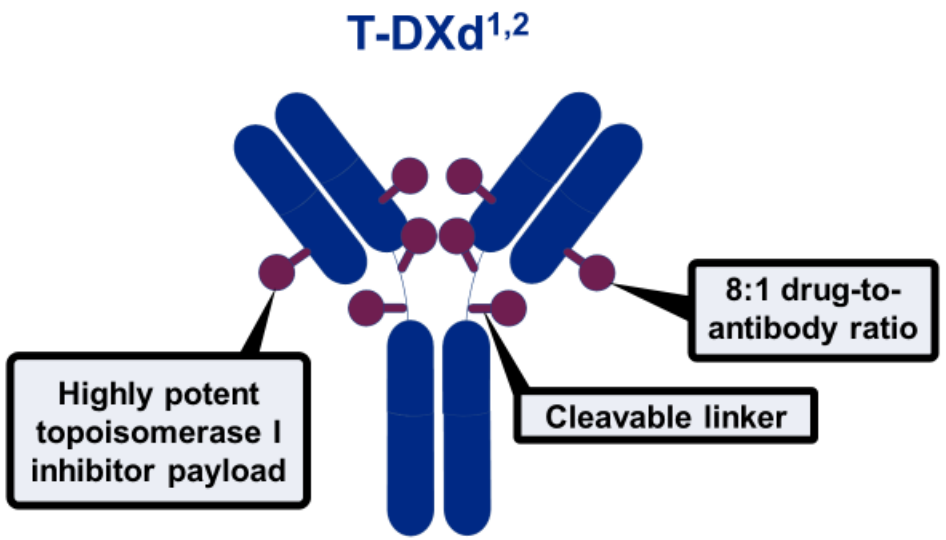
T-DXd treatment showed unprecedented improvement in efficacy for patients with HER2-low mBC



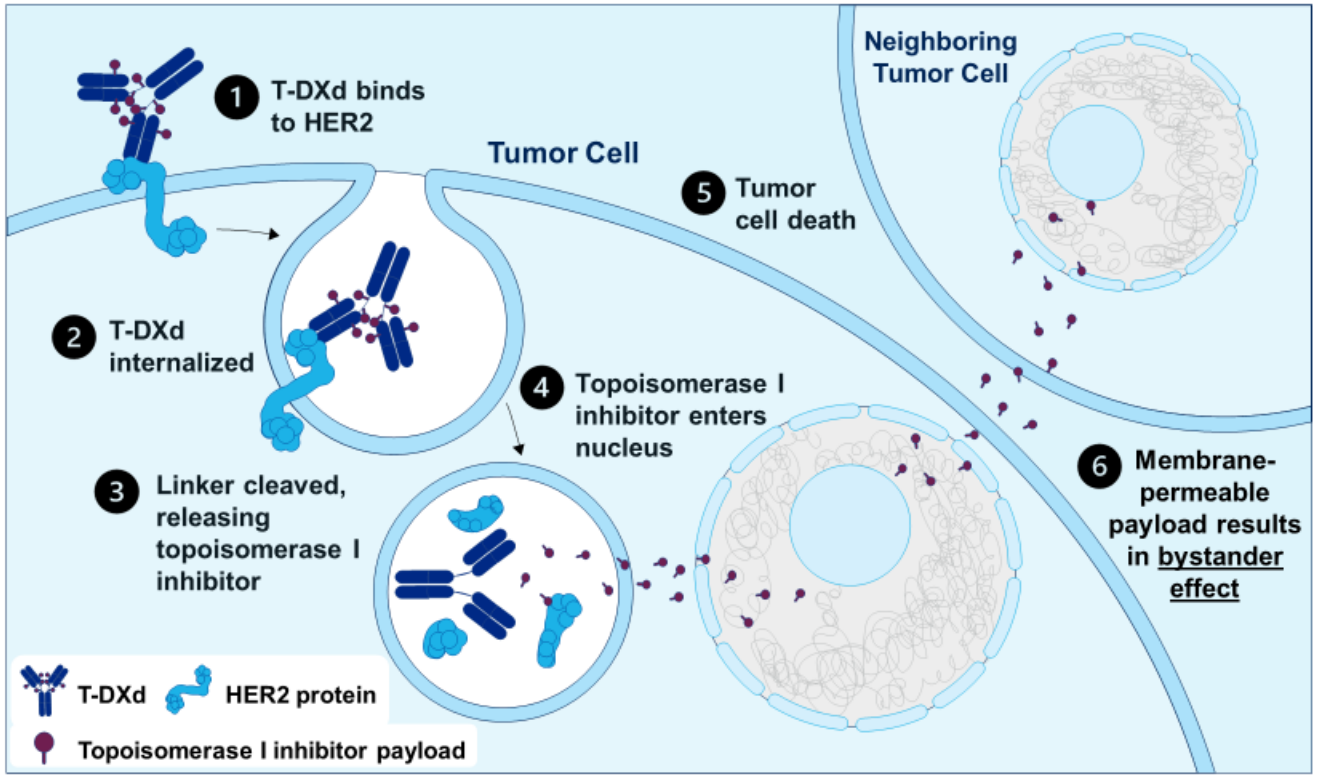
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

1. Schettini F, et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962.

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]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

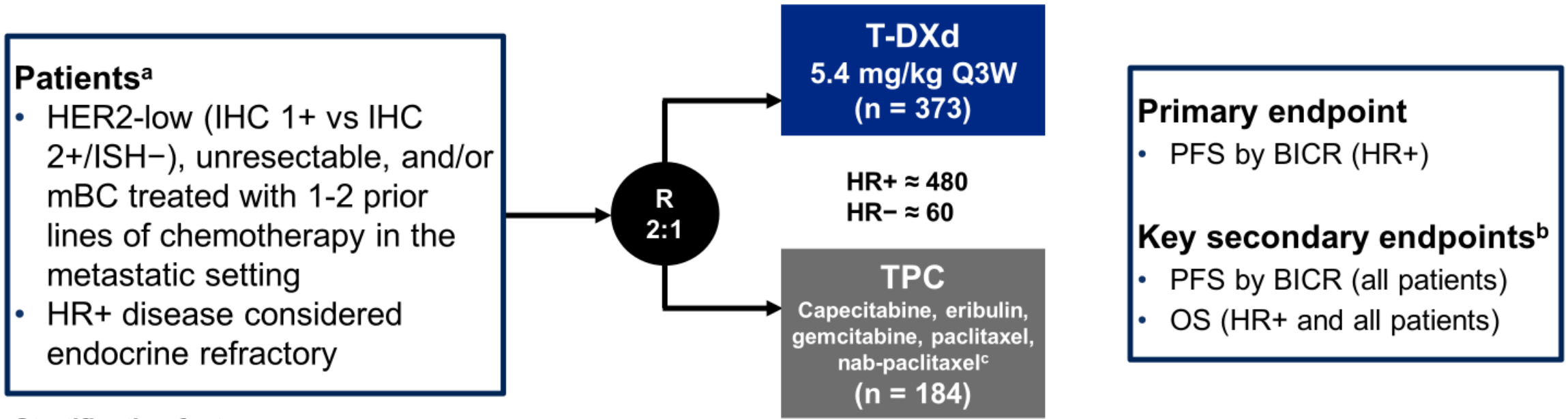
- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

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

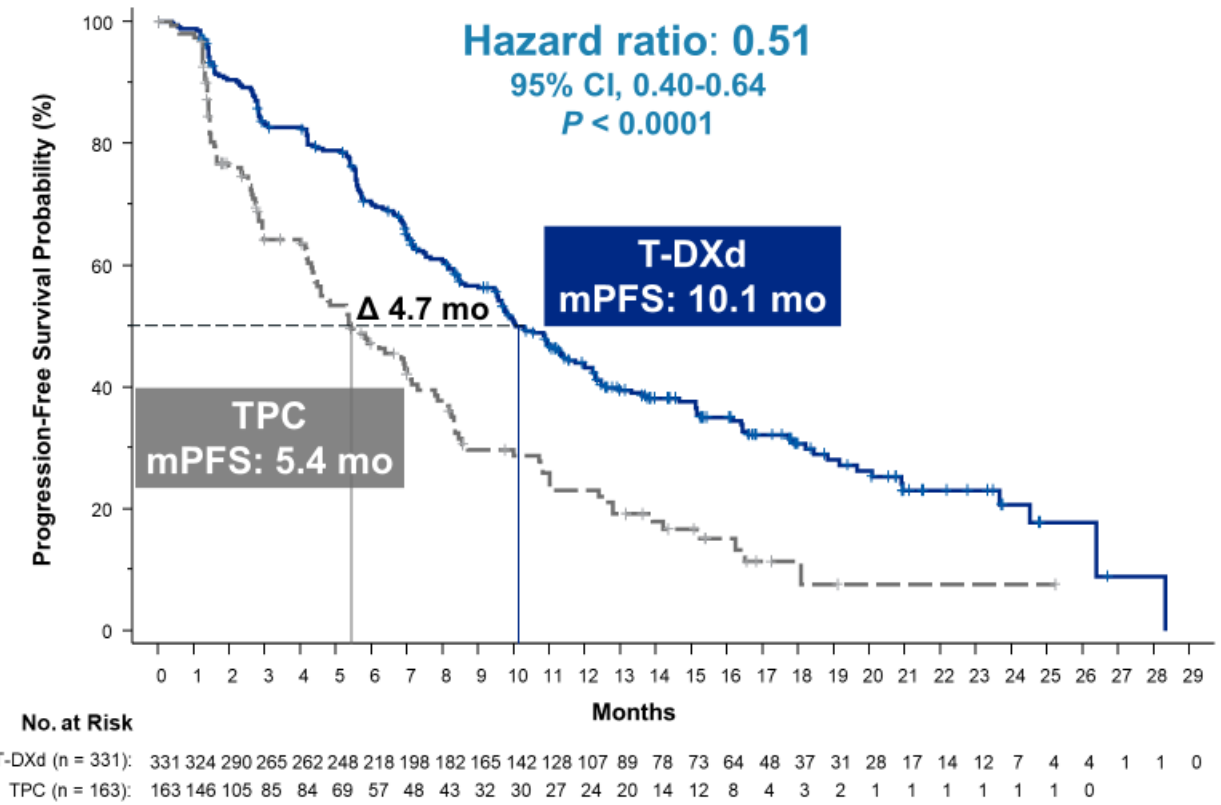
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

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.

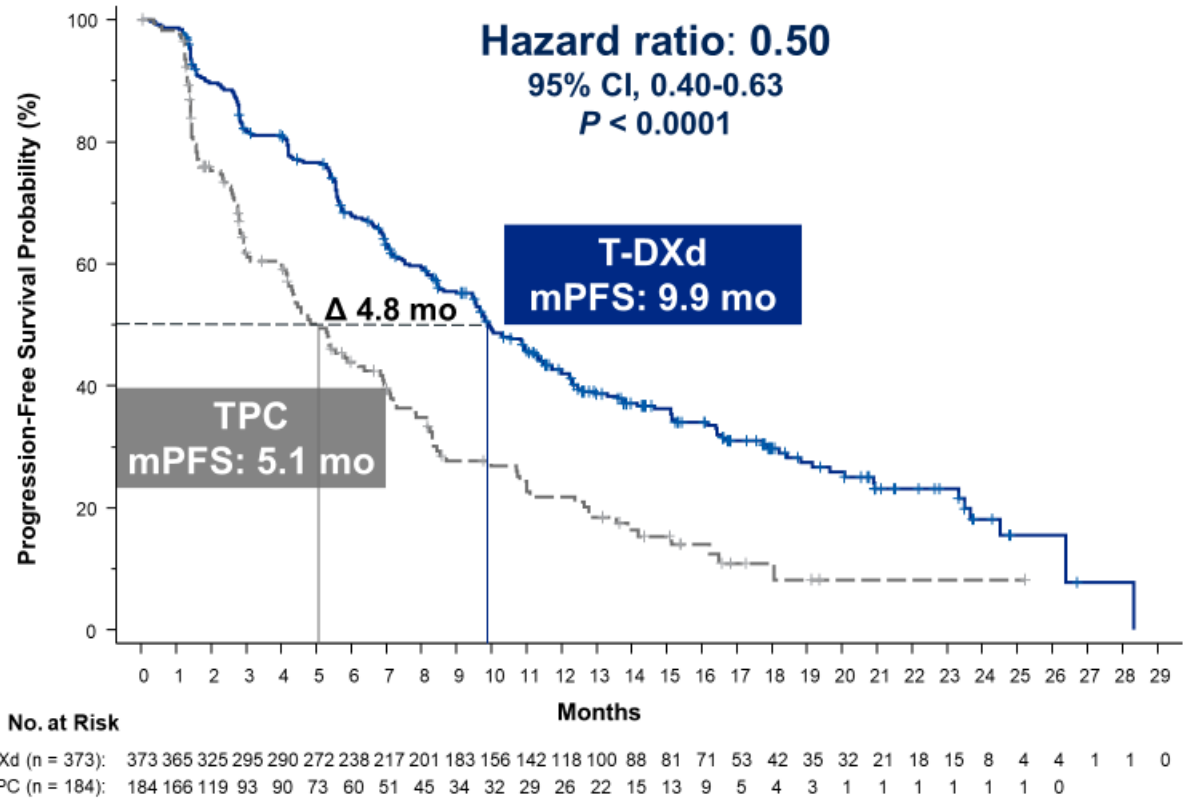
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate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

PFS in HR+ and All Patients

Hormone receptor–positive



All patients

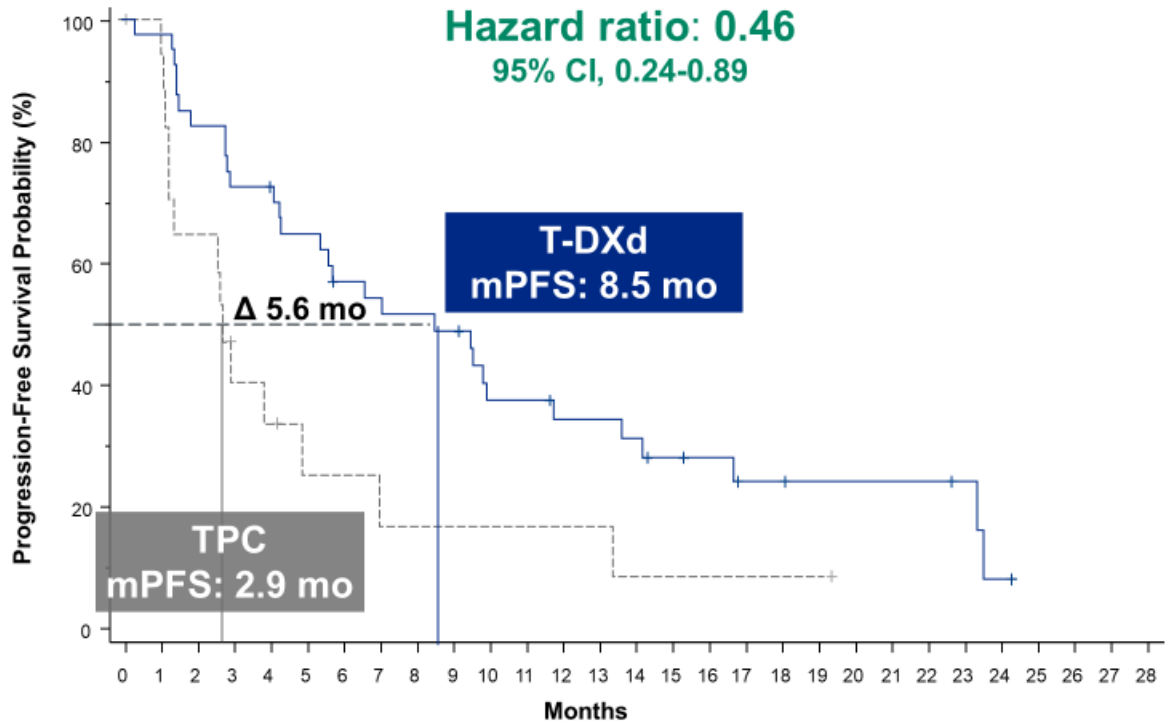


PFS by blinded independent central review.

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

PFS and OS in HR− (Exploratory Endpoints)

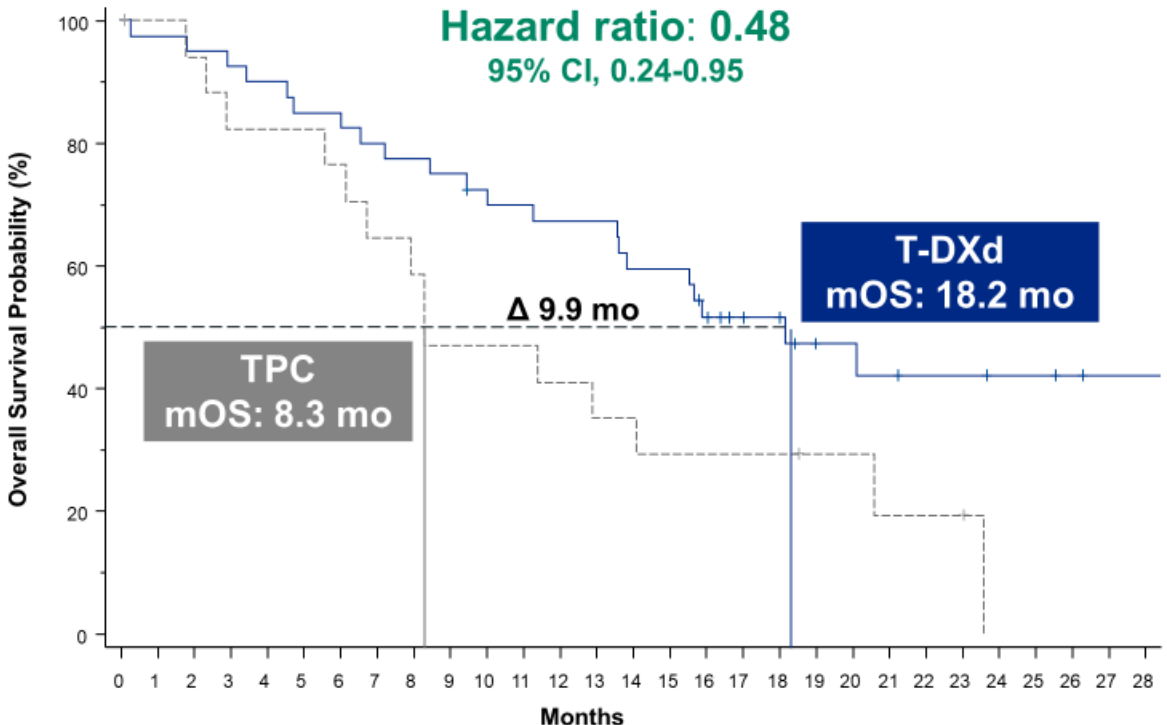
PFS



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

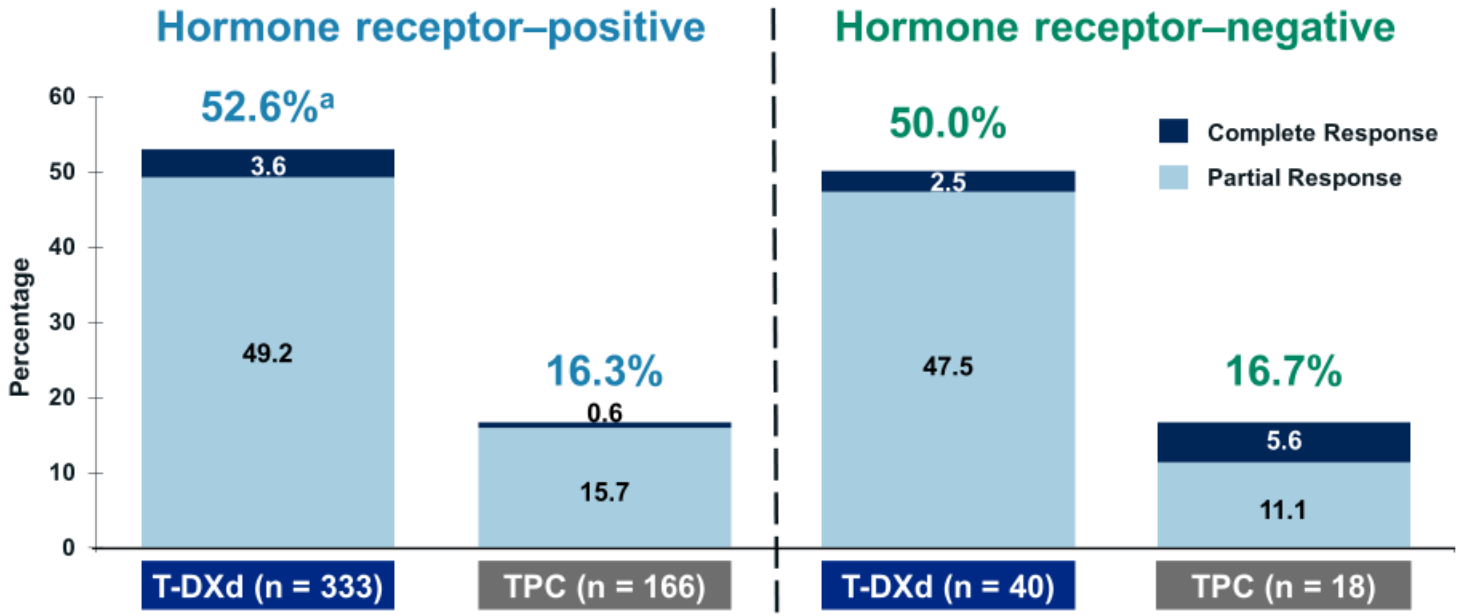
T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

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.

PRESENTED BY:
Shanu Modi, MD

Confirmed ORR

Confirmed Objective Response Rate

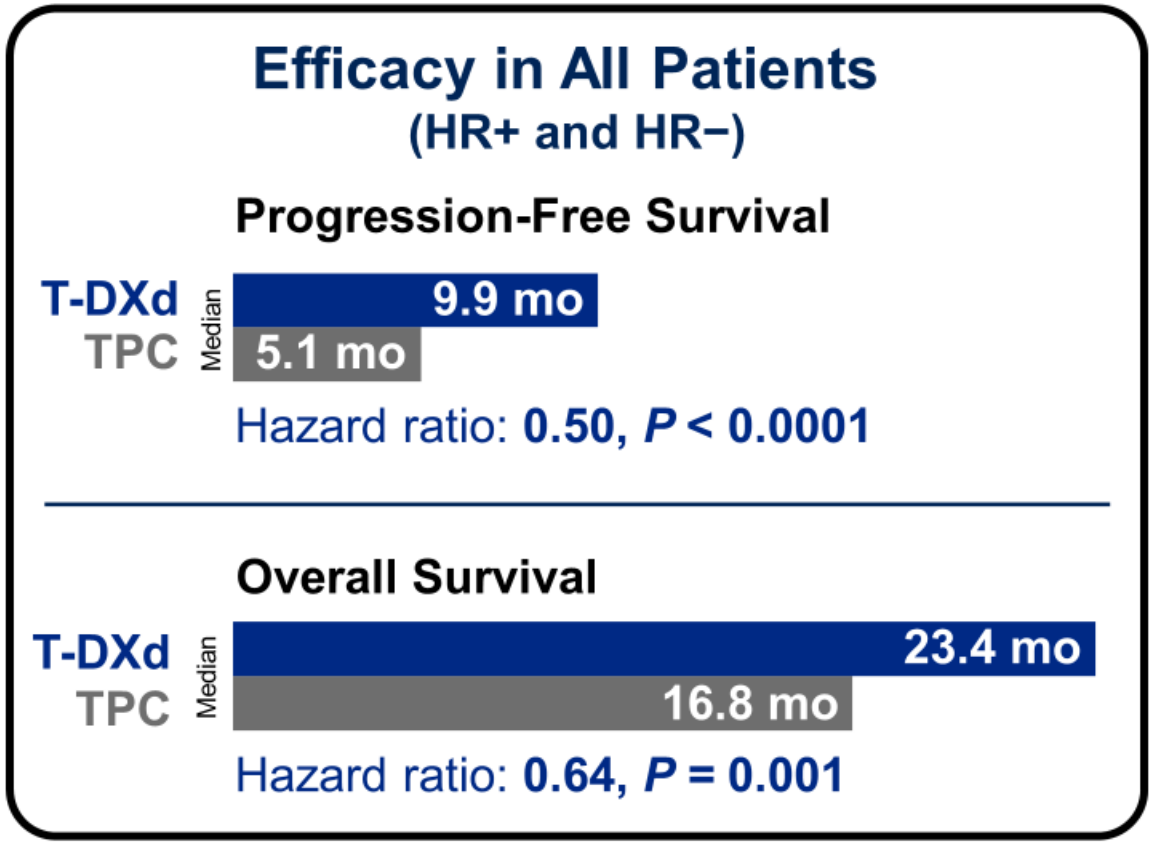


	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

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.

Thank you!

Questions?