Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Metastatic Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

Thursday, December 12, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Ian E Krop, MD, PhD
Joyce O'Shaughnessy, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Dr Love — Disclosures

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Save The Date

Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with

Florida Cancer Specialists & Research Institute

Friday to Sunday, February 28 to March 2, 2025

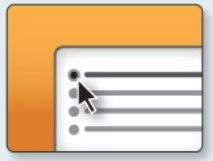
Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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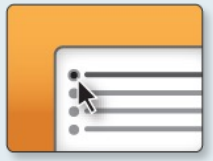
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
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Agenda

Module 1: Optimizing the Care of Patients with HER2-Positive Metastatic Breast Cancer (mBC) – Dr Krop

Module 2: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer – Dr Tolaney

Module 3: Integrating Novel Agents and Approaches into the Management of Endocrine-Resistant Hormone Receptor-Positive mBC – Dr Kalinsky

Module 4: Tolerability Considerations with Approved and Investigational Antibody-Drug Conjugates – Dr O'Shaughnessy

Module 5: Other Important Care Considerations for Patients with mBC – Dr Hamilton

Oncology Q&A: Addressing Common Questions Posed by Patients with Metastatic Triple-Negative Breast Cancer

A Live Webinar for Patients, Developed in Partnership with the Triple Negative Breast Cancer Foundation

Wednesday, November 13, 2024
6:00 PM – 7:00 PM ET

Faculty

Lisa A Carey, MD, ScM, FASCO
Rita Nanda, MD

Moderator

Neil Love, MD

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Agenda

Module 1: Optimizing the Care of Patients with HER2-Positive Metastatic Breast Cancer (mBC) – Dr Krop

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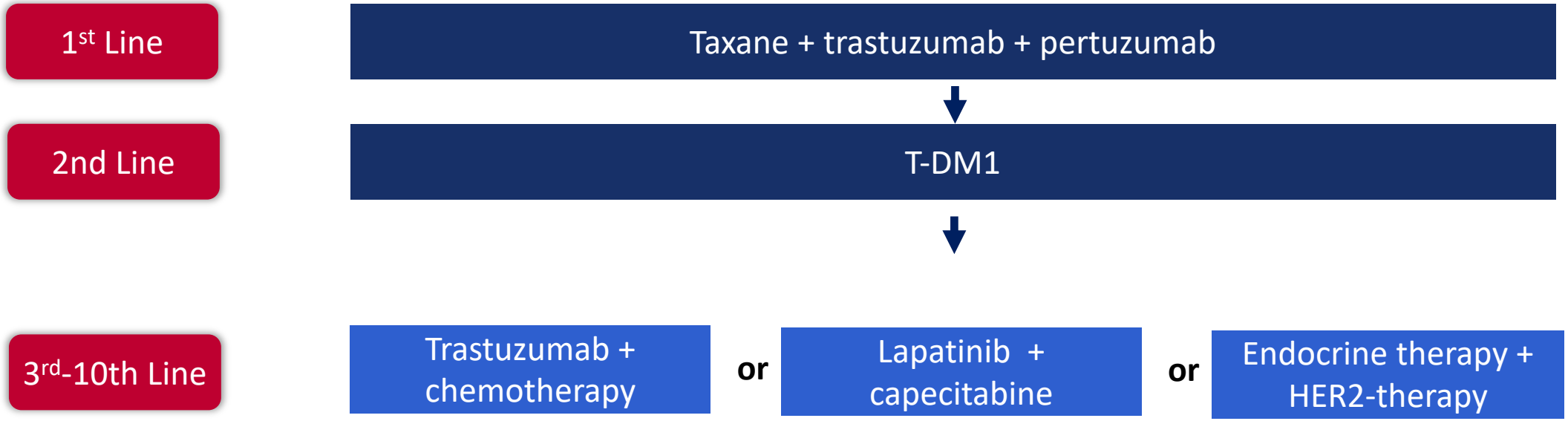
Module 5: Other Important Care Considerations for Patients with mBC – Dr Hamilton

Optimizing Management of HER2-Positive Advanced Breast Cancer

Ian Krop MD PhD

December 2024

Treatment Paradigm for Metastatic HER2+ Breast Cancer (Circa 2019)



Efficacy of Chemotherapy + Trastuzumab is limited in ≥3rd line*

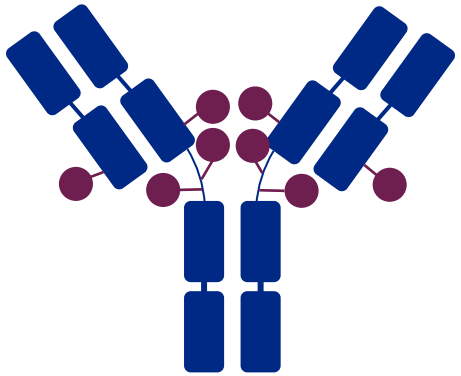
– PFS ≈ 5 months

– ORR ≈ 20%

* Ie control arms of SOPHIA and HER2CLIMB

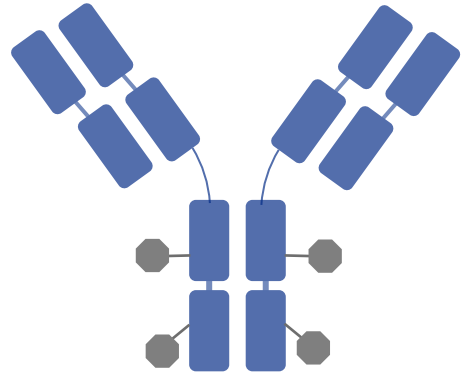
Trastuzumab deruxtecan: a 2nd generation HER2-targeted ADC

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



Adapted from J Cortes et al, ESMO 2021

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

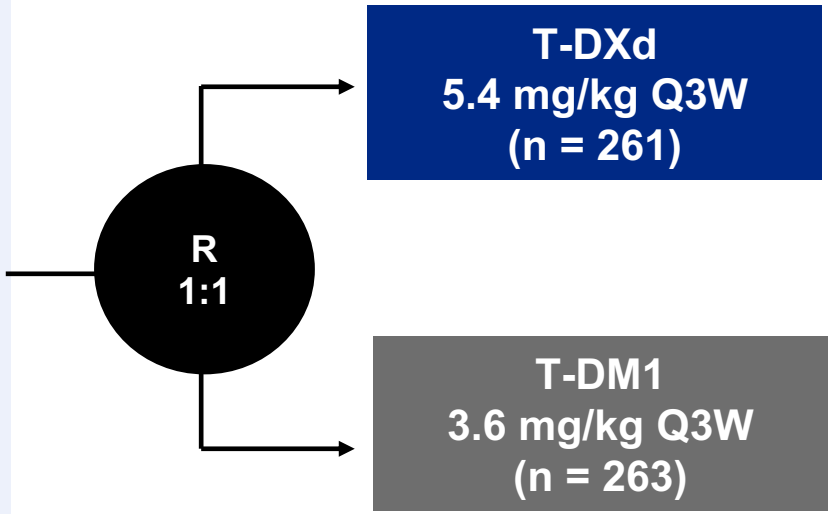
An open-label, multicenter study (NCT03529110)

Patients

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors

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



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)

- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

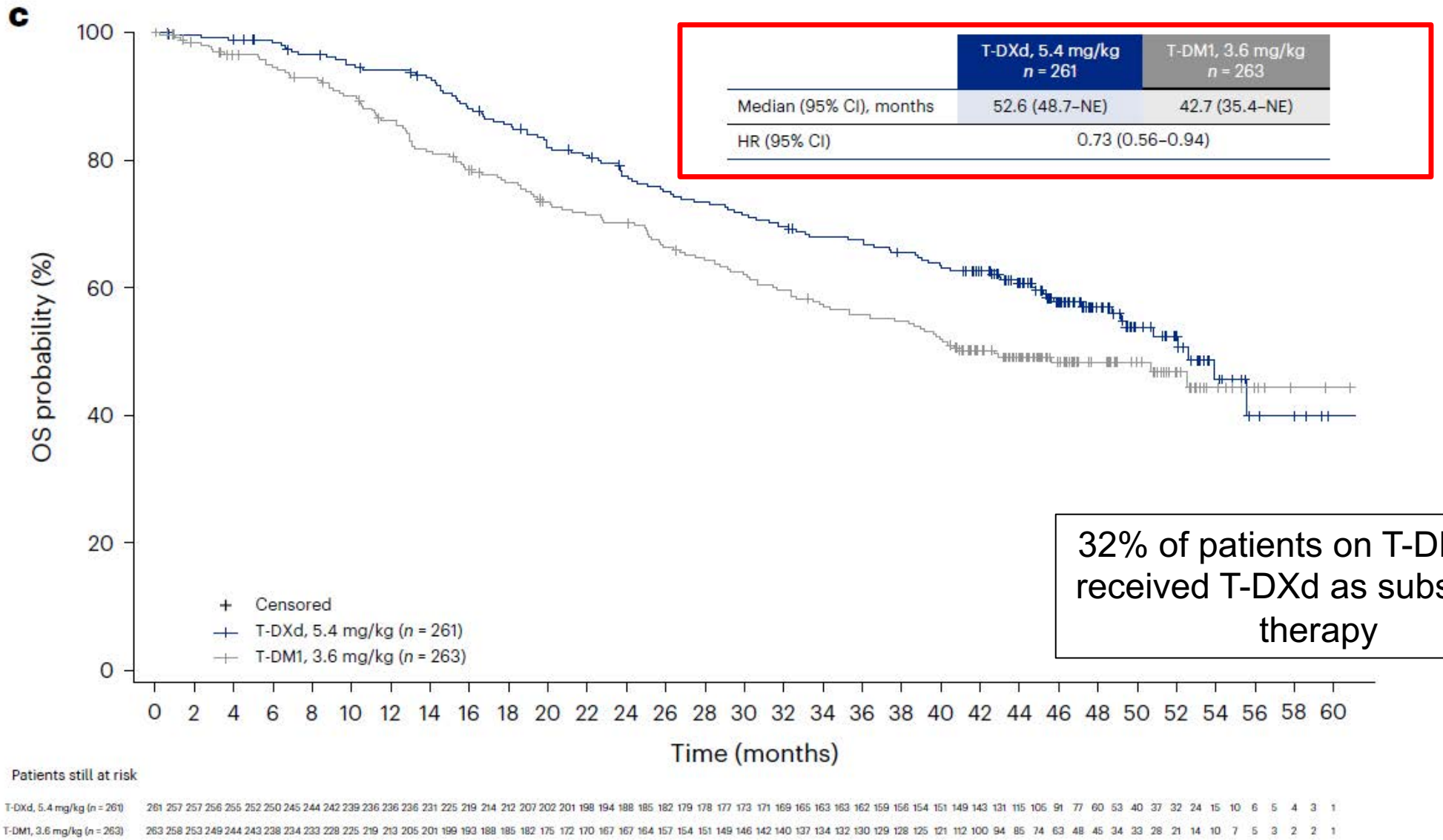
2021 ESMO congress

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.

[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

DESTINY-Breast03 Long Term OS results

43-month median follow-up



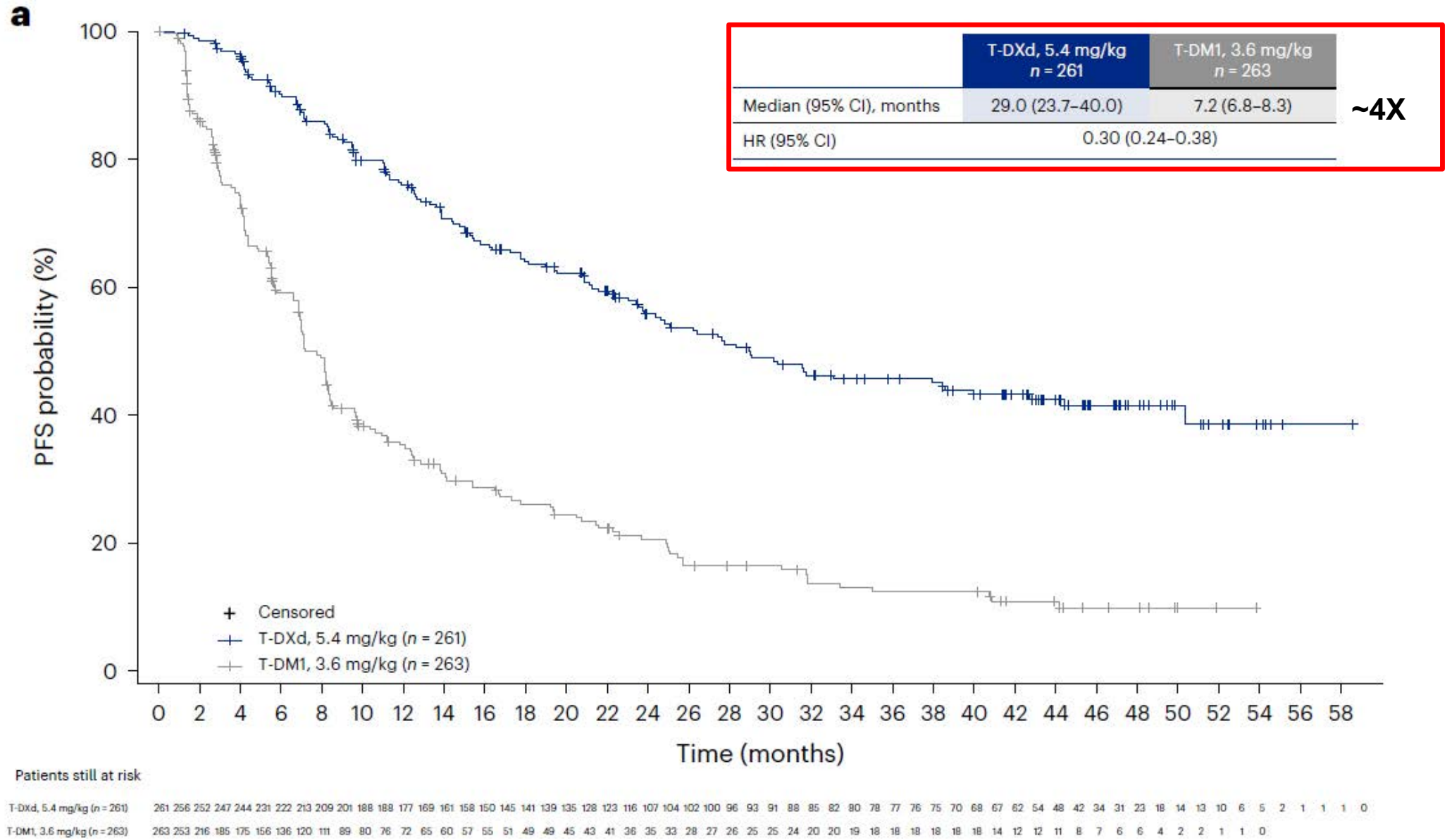
	T-DXd, 5.4 mg/kg *n* = 261	T-DM1, 3.6 mg/kg *n* = 263
Median (95% CI), months	52.6 (48.7–NE)	42.7 (35.4–NE)
HR (95% CI)	0.73 (0.56–0.94)	

32% of patients on T-DM1 arm received T-DXd as subsequent therapy

Cortes et al, Nat Med **30**, 2208 (2024)

DESTINY-Breast03 Long Term PFS results

43-month median follow-up



	T-DXd, 5.4 mg/kg *n* = 261	T-DM1, 3.6 mg/kg *n* = 263
Median (95% CI), months	29.0 (23.7–40.0)	7.2 (6.8–8.3)
HR (95% CI)	0.30 (0.24–0.38)	

~4X

Cortes et al, Nat Med **30**, 2208 (2024)

DESTINY-Breast03 Updated ORR Results

(Investigator Assessment)

	T-DXd n = 261	T-DM1 n = 263
cORR, n (%) (95% CI)[a]	206 (78.9) (73.5-83.7)	97 (36.9) (31.0-43.0)
CR, n (%)	33 (12.6)	11 (4.2)
PR, n (%)	173 (66.3)	86 (32.7)
SD, n (%)	48 (18.4)	119 (45.2)
PD, n (%)	2 (0.8)	34 (12.9)
NE, n (%)	5 (1.9)	13 (4.9)
DoR,[b] median (95% CI), months	30.5 (23.0-NE)	17.0 (14.1-23.7)
DoR rate at 36 months (95% CI), %	48.9 (41.3-56.1)	28.7 (18.9-39.2)

Hamilton et al, ASCO 2024

DESTINY-Breast03 Long Term Adverse Event Results

43-month median follow-up

n (%)	T-DXd 5.4 mg/kg Q3W *n* = 257	T-DM1 3.6 mg/kg Q3W *n* = 261
Any TEAEs	256 (99.6)	249 (95.4)
Blood and lymphatic system disorders		
Neutropenia[a]	117 (45.5)	38 (14.6)
Anemia[b]	98 (38.1)	53 (20.3)
Leukopenia[c]	88 (34.2)	25 (9.6)
Thrombocytopenia[d]	81 (31.5)	146 (55.9)
Gastrointestinal disorders		
Nausea	198 (77.0)	79 (30.3)
Vomiting	136 (52.9)	28 (10.7)
Constipation	97 (37.7)	51 (19.5)
Diarrhea	86 (33.5)	21 (8.0)
Abdominal pain[e]	64 (24.9)	25 (9.6)
Stomatitis[f]	60 (23.3)	14 (5.4)
General disorders		
Fatigue[g]	137 (53.3)	92 (35.2)
Infections and infestations		
Upper respiratory tract infection[h]	76 (29.6)	41 (15.7)
Investigations		
Transaminases increased[i]	89 (34.6)	124 (47.5)
Metabolism and nutrition disorders		
Decreased appetite	80 (31.1)	46 (17.6)
Weight decreased	61 (23.7)	24 (9.2)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[j]	88 (34.2)	65 (24.9)
Nervous system disorders		
Headache[k]	69 (26.8)	47 (18.0)
Skin and subcutaneous disorders		
Alopecia	103 (40.1)	10 (3.8)

Cortes et al, Nat Med **30**, 2208 (2024)

DESTINY-Breast03 Updated ILD Results

Adjudicated drug-related ILD/pneumonitis events for the entire study period through November 20, 2023 (DCO)						
n (%)[a]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)[b]	11 (4.3)	30 (11.7)	2 (0.8)	0	0	43 (16.7)
T-DM1 (n = 261)[b]	5 (1.9)	3 (1.1)	1 (0.4)	0	0	9 (3.4)
Time to first adjudicated drug-related ILD/pneumonitis[c] in the T-DXd group by CTCAE grade at the time of diagnosis						
≤6 months	3 (1.1)	10 (3.8)	1 (0.4)	0	0	14 (5.4)
>6 to ≤12 months	5 (1.9)	7 (2.7)	0	0	0	12 (4.6)
>12 to ≤24 months	5 (1.9)	5 (1.9)	1 (0.4)	0	0	11 (4.2)
>24 months	1 (0.4)	5 (1.9)	0	0	0	6 (2.3)

Hamilton et al, ASCO 2024

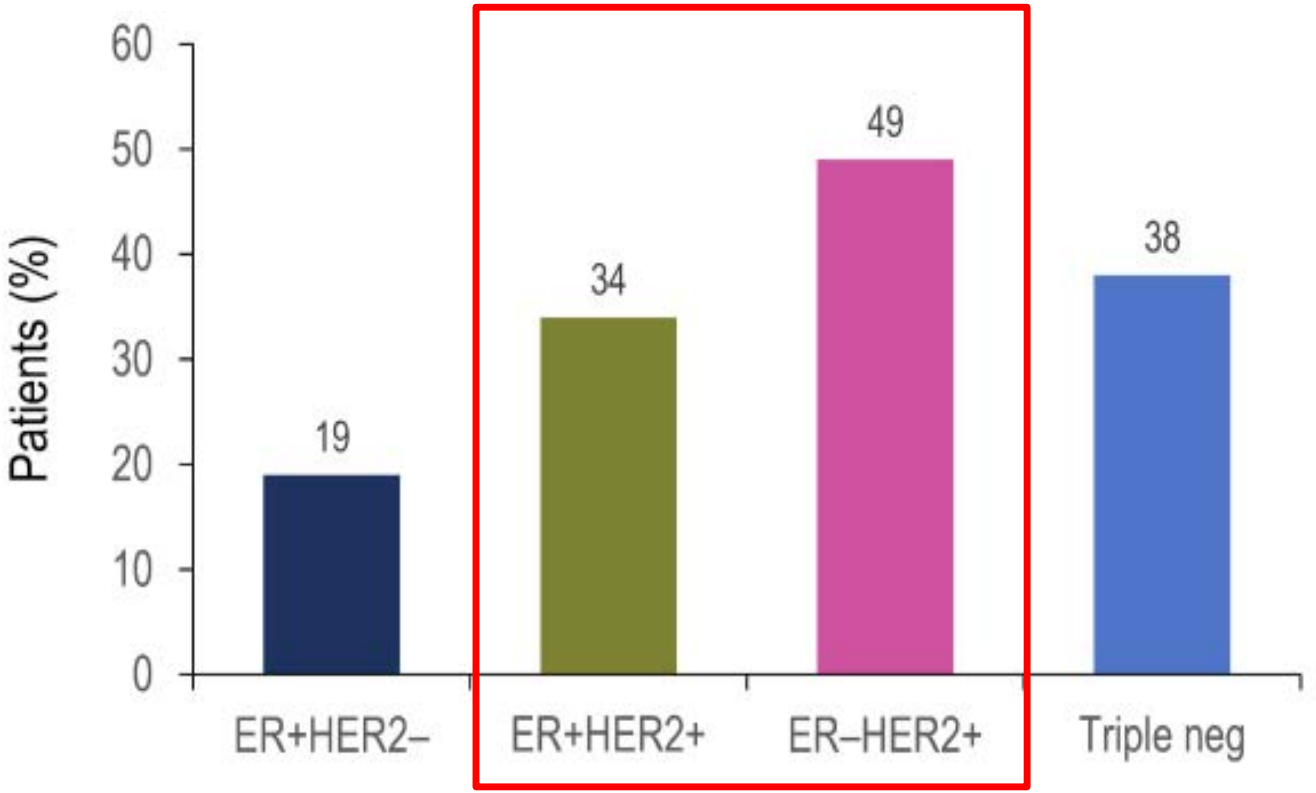
DESTINY-Breast03 Summary

- Establishes T-DXd role as preferred 2nd line SOC for most patients
  - Unprecedented levels of activity and reassuring ILD data

- What about pts with active CNS metastases?

Brain Metastases in HER2+ Breast Cancer

% BM at any time during their metastatic disease (in the absence of screening)



Prevalence of BM occurrence during mBC history is higher for HER2+ BC, especially in the HR- subgroup

Darlix A, Br J Cancer 2020; Pasquier D, et al. Eur J Cancer 2020; Le Rhun et al, Ann Oncol 2021

HER2CLIMB Trial Design

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

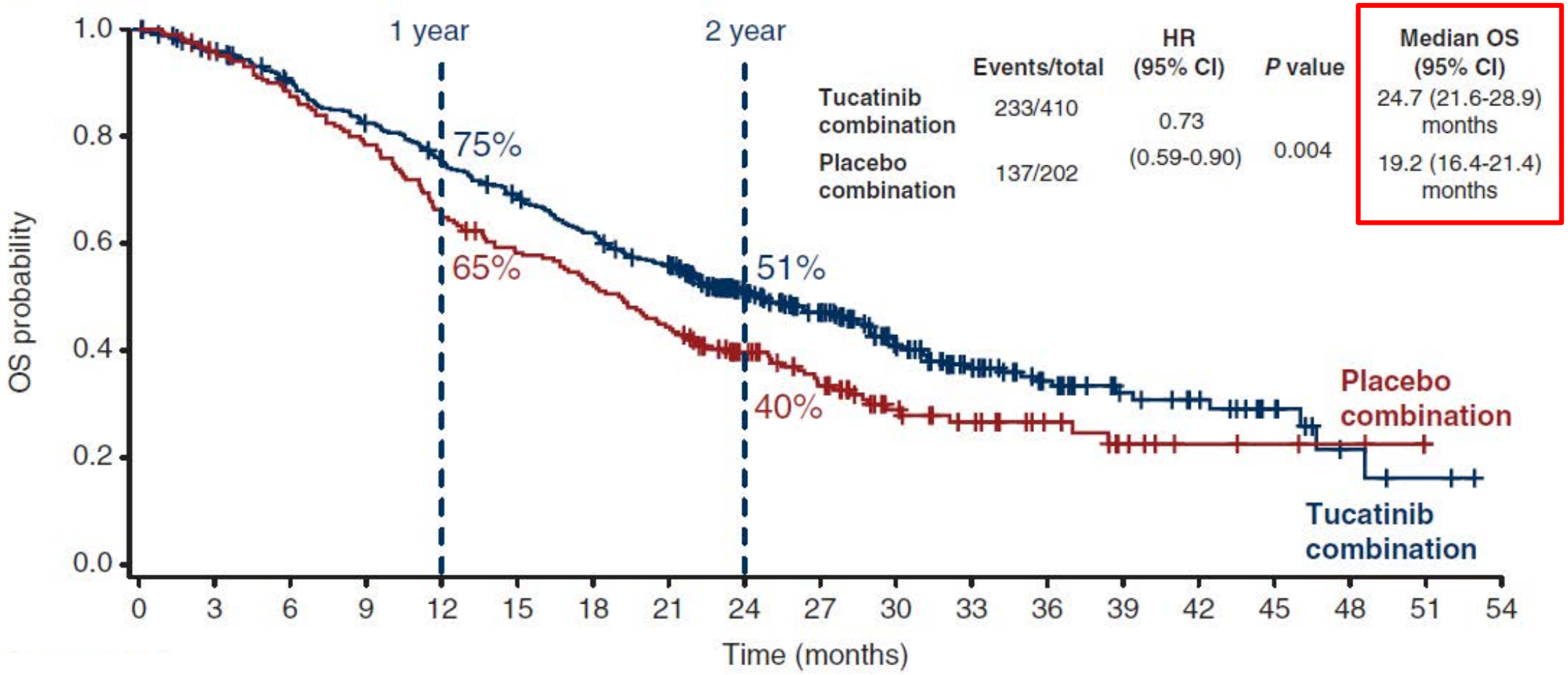
Placebo + Trastuzumab + Capecitabine
(21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

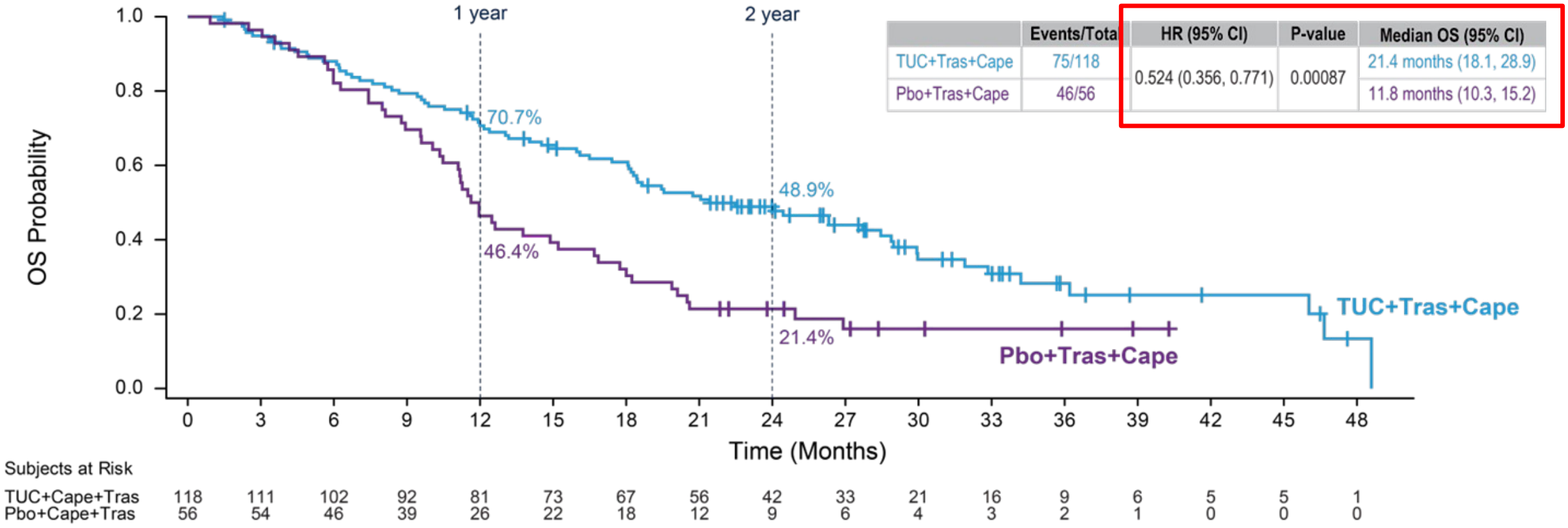
https://clinicaltrials.gov/ct2/show/NCT02614794

HER2CLIMB Updated OS results



Curigliano et al, Annals Oncology 2022 33:321

HER2CLIMB Updated OS results in patients with active brain metastases



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	75/118	0.524 (0.356, 0.771)	0.00087	21.4 months (18.1, 28.9)
Pbo+Tras+Cape	46/56			11.8 months (10.3, 15.2)

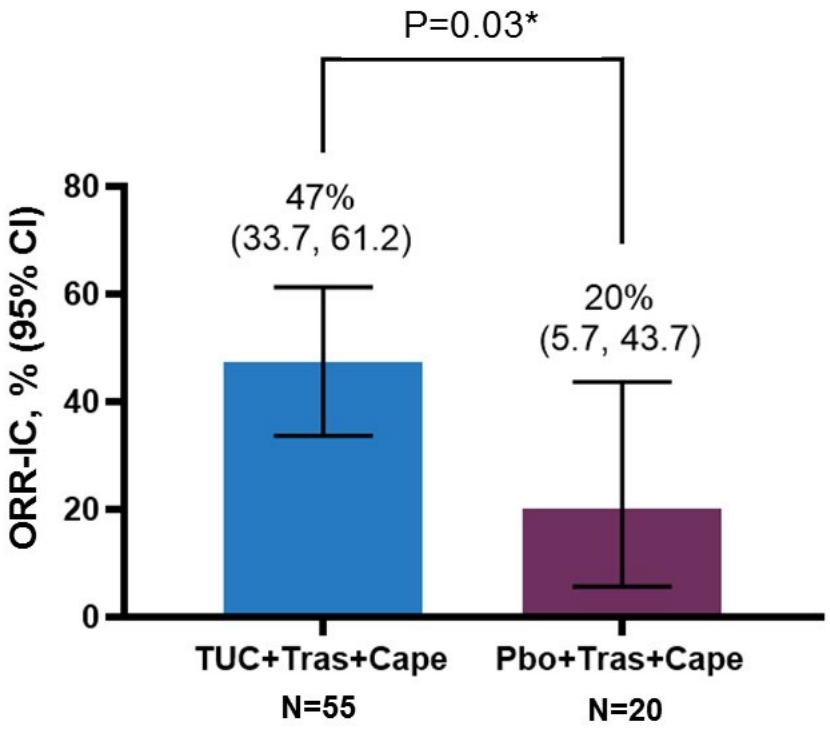
Subjects at Risk

TUC+Cape+Tras	118	111	102	92	81	73	67	56	42	33	21	16	9	6	5	5	1
Pbo+Cape+Tras	56	54	46	39	26	22	18	12	9	6	4	3	2	1	0	0	0

NU Lin et al, SABCS 2021
JAMA Oncol. 2023;9(2):197

Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Confirmed Objective Response Rate (RECIST 1.1)

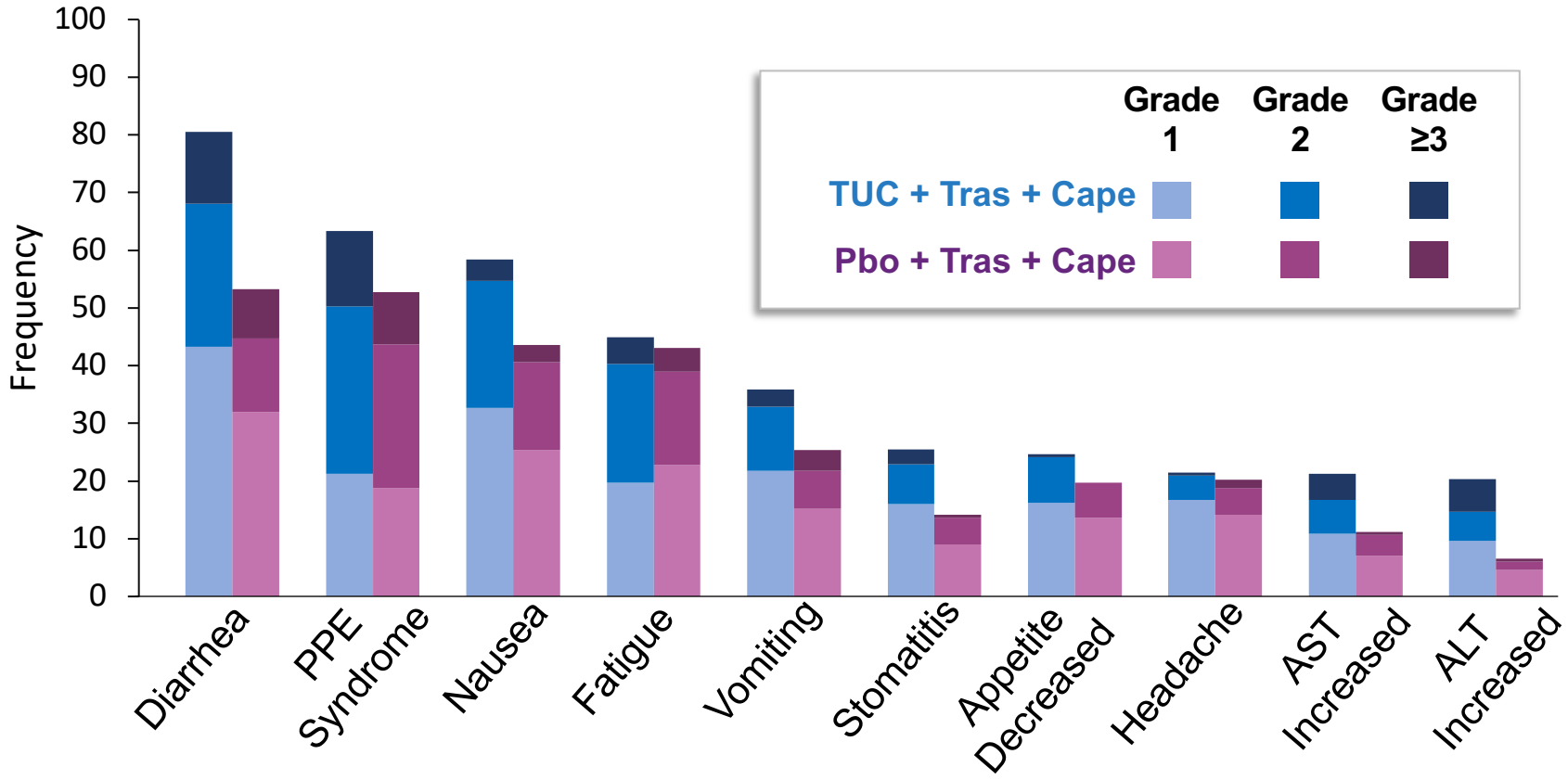


*Stratified Cochran-Mantel-Haenszel P value

	TUC+Tras+Cape (N=55)	Pbo+Tras+Cape (N=20)
Best Overall Intracranial Response[a], n (%)		
Complete Response (CR)	3 (5.5)	1 (5.0)
Partial Response (PR)	23 (41.8)	3 (15.0)
Stable Disease (SD)	24 (43.6)	16 (80.0)
Progressive Disease (PD)	2 (3.6)	0
Not Available[b]	3 (5.5)	0
Subjects with Objective Response of Confirmed CR or PR, n	26	4
Duration of Intracranial Response (DOR-IC)[e] (95% CI)[f], months	6.8 (5.5, 16.4)	3.0 (3.0, 10.3)

(a) Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).

Most Common Adverse Events (≥20% in the Tucatinib Arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

- Does trastuzumab deruxtecan have activity in HER2+ brain metastases?

MADRID 2023 ESMO congress

A Pooled Analysis of Trastuzumab Deruxtecan in Patients With HER2-Positive Metastatic Breast Cancer With Brain Metastases (BMs) from DESTINY-Breast01, -02, and -03

Presentation 3770

Sara A. Hurvitz[1], Shanu Modi, Wei Li, Yeon Hee Park, Wei-Pang Chung, Sung-Bae Kim, Javier Cortes, Toshinari Yamashita, Jose Luiz Pedrini, Seock-Ah Im, Ling-Ming Tseng, Nadia Harbeck, Ian Krop, Giuseppe Curigliano, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Shahid Ashfaque, Anton Egorov, Fabrice André

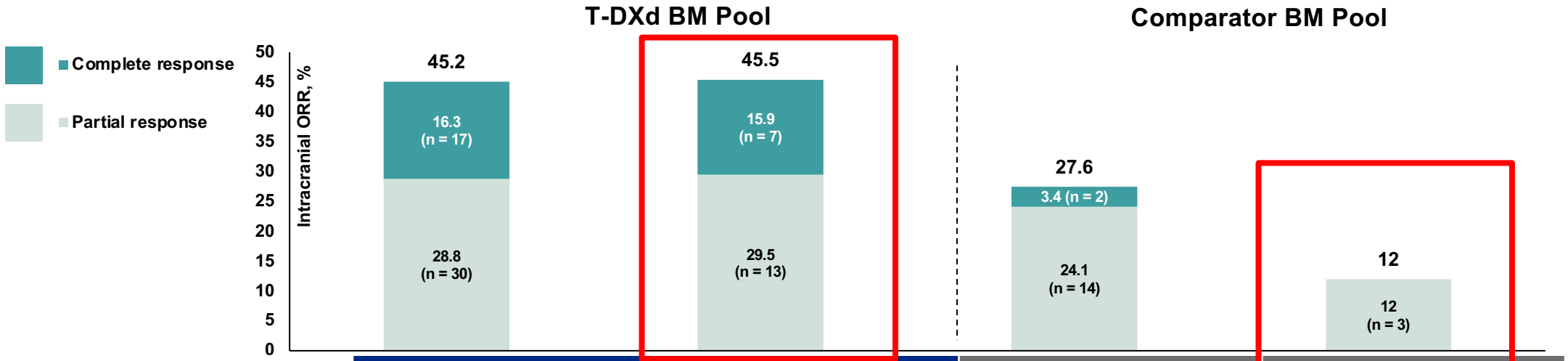
On behalf of the DESTINY-Breast01, -02, and -03 pooled investigators

[1]Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA

Madrid, Spain, October 20-24, 2023

Exploratory Best IC Response, ORR, and DoR per BICR

Intracranial ORR[a]



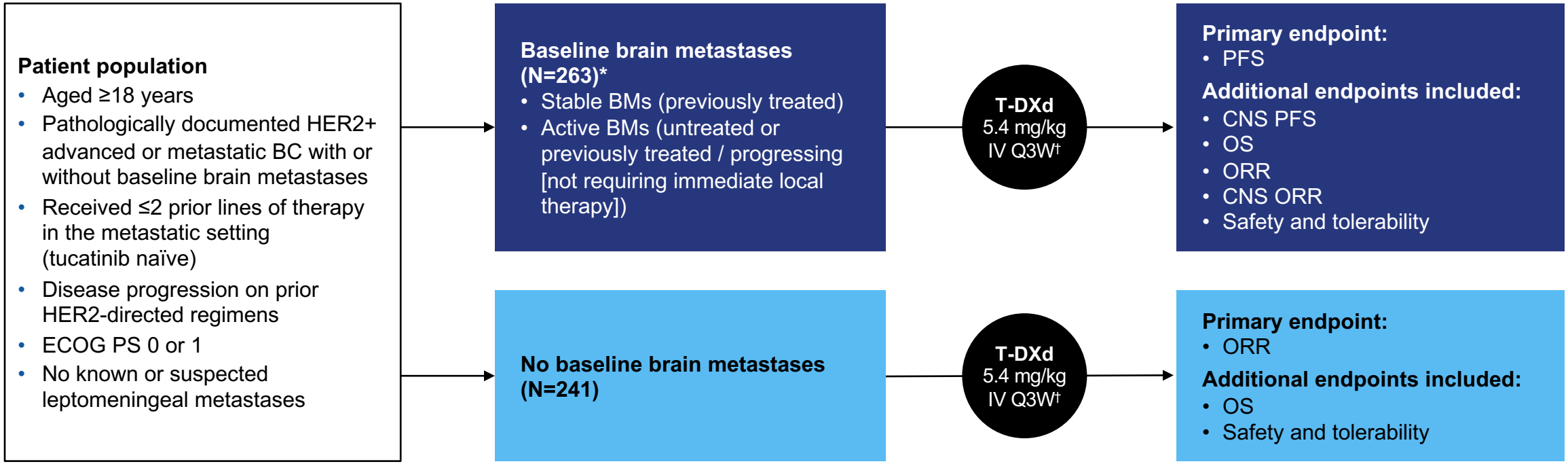
	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall IC response, n (%)				
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
Not evaluable/Missing	6 (5.8)	8 (18.2)	7 (12.1)	2 (8.0)
IC-DoR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	NA[b]

- **T-DXd consistently demonstrated superior rates of IC responses over comparator in patients with treated/stable and untreated/active BMs**
- **A trend in prolonged median IC-DoR was most pronounced in the untreated/active BMs subgroup**

BM, brain metastasis; BICR, blinded independent central review; DoR, duration of response; IC, intracranial; NA, not available; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.
This table considers both target and non-target lesions at baseline. Lesions in previously irradiated areas were not considered measurable target lesions unless there was demonstrated progression in the lesion.
[a]IC-ORR was assessed per RESIST v1.1. [b]IC-DoR NA due to small number of responders (n < 10).

DESTINY-Breast12 study design

Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs



Data reported for the full analysis set (all patients enrolled in the study who received at least one treatment dose) and safety analysis set (identical to full analysis set). No hypothesis testing or comparison of cohorts. Response and progression assessed by ICR per RECIST 1.1 in both cohorts. Patients were enrolled from Australia, Canada, Europe, Japan, and United States

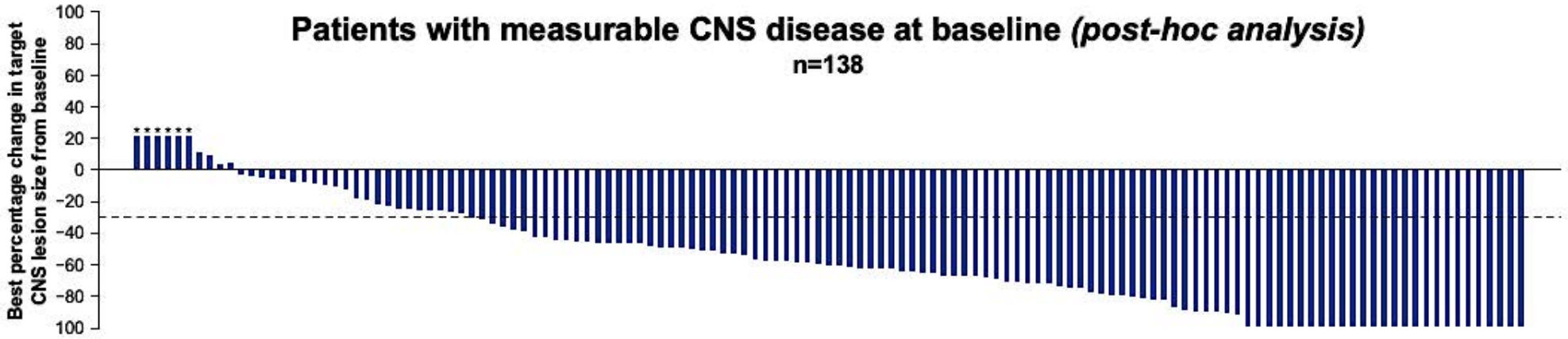
***Concomitant use of ≤3 mg of dexamethasone daily or equivalent allowed for symptom control of BMs (baseline BMs cohort only)**; †until RECIST 1.1-defined disease progression outside the CNS

BC, breast cancer; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; ICR, independent central review; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

NCT04739761. Updated. July 19, 2024. Available from: https://www.clinicaltrials.gov/study/NCT04739761 (Accessed September 9, 2024)

DESTINY-Breast12

CNS-ORR in patients with measurable BM at baseline



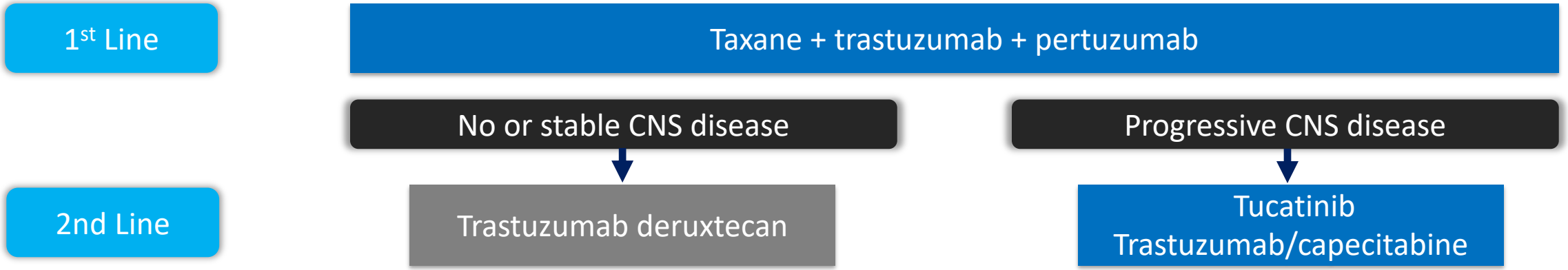
Measurable CNS disease at baseline	All patients (n=138)	Active BM subgroups: Stable BMs (n=77)	Active BMs (n=61)	Untreated (n=23) *Post-hoc analysis*	Previously treated / progressing (n=38) *Post-hoc analysis*
Confirmed CNS ORR, % (95% CI)	**71.7 (64.2, 79.3)**	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

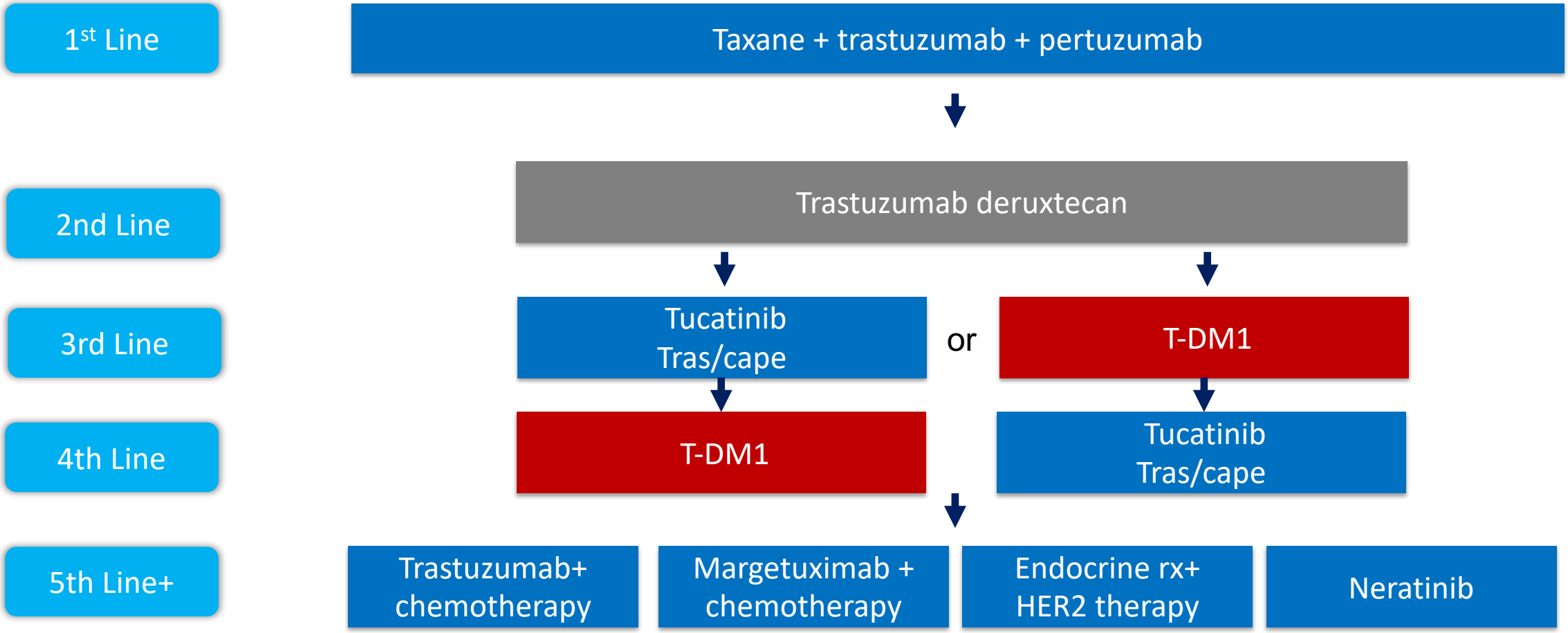
Dashed line indicates a 30% decrease in target tumor size (PR)
*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD
BM, brain metastasis; CI, confidence interval; CNS, central nervous system; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan

Lin et al, ESMO 2024

Approach to Therapy for Metastatic HER2+ disease



Approach to Therapy for Metastatic HER2+ disease



HER2CLIMB-02 Study Design

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

N≈460

R 1:1

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

T-DM1 + Tucatinib

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

T-DM1 + Placebo

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

Outcomes

Primary
- PFS by investigator assessment per RECIST v1.1

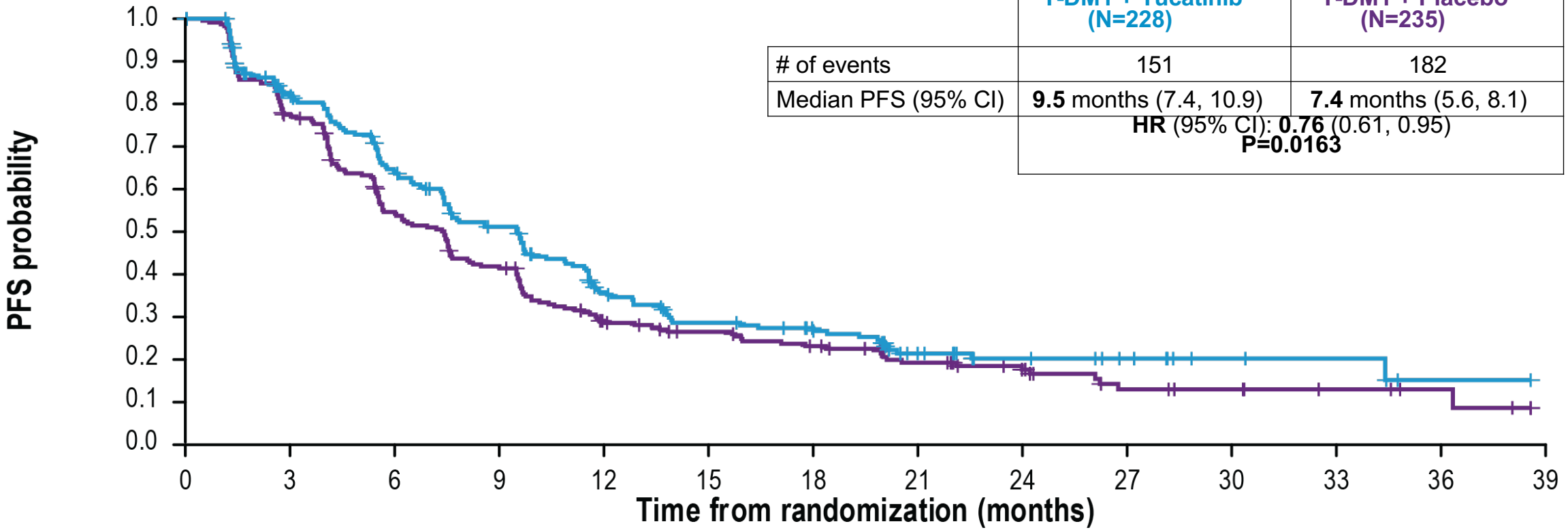
Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

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

NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Accessed Oct 5, 2023.
a Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were not eligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.
b Subsequent OS analyses are planned upon 80% and 100% of required events for the final OS analysis.
1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PO, orally; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors.
Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.

Progression-Free Survival

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



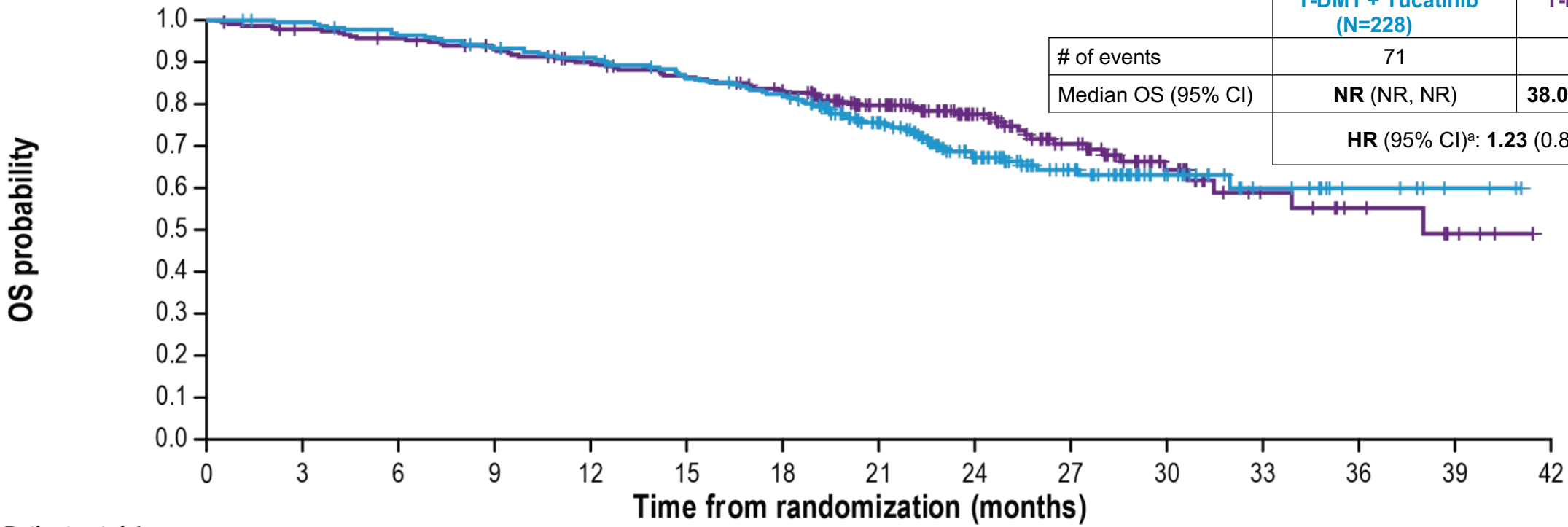
Patients at risk

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

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

Overall Survival

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



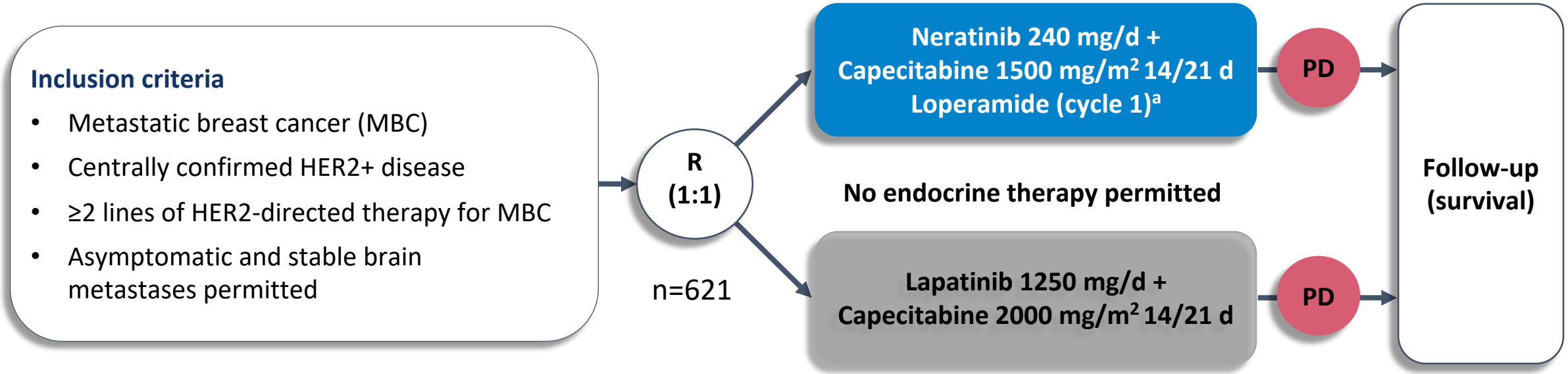
Patients at risk

T-DM1 + Tucatinib	228	225	217	209	202	189	180	132	89	55	30	16	7	3	0
T-DM1 + Placebo	235	227	221	212	201	191	180	135	90	58	32	16	10	4	0

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

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

NALA study design



Stratification variables

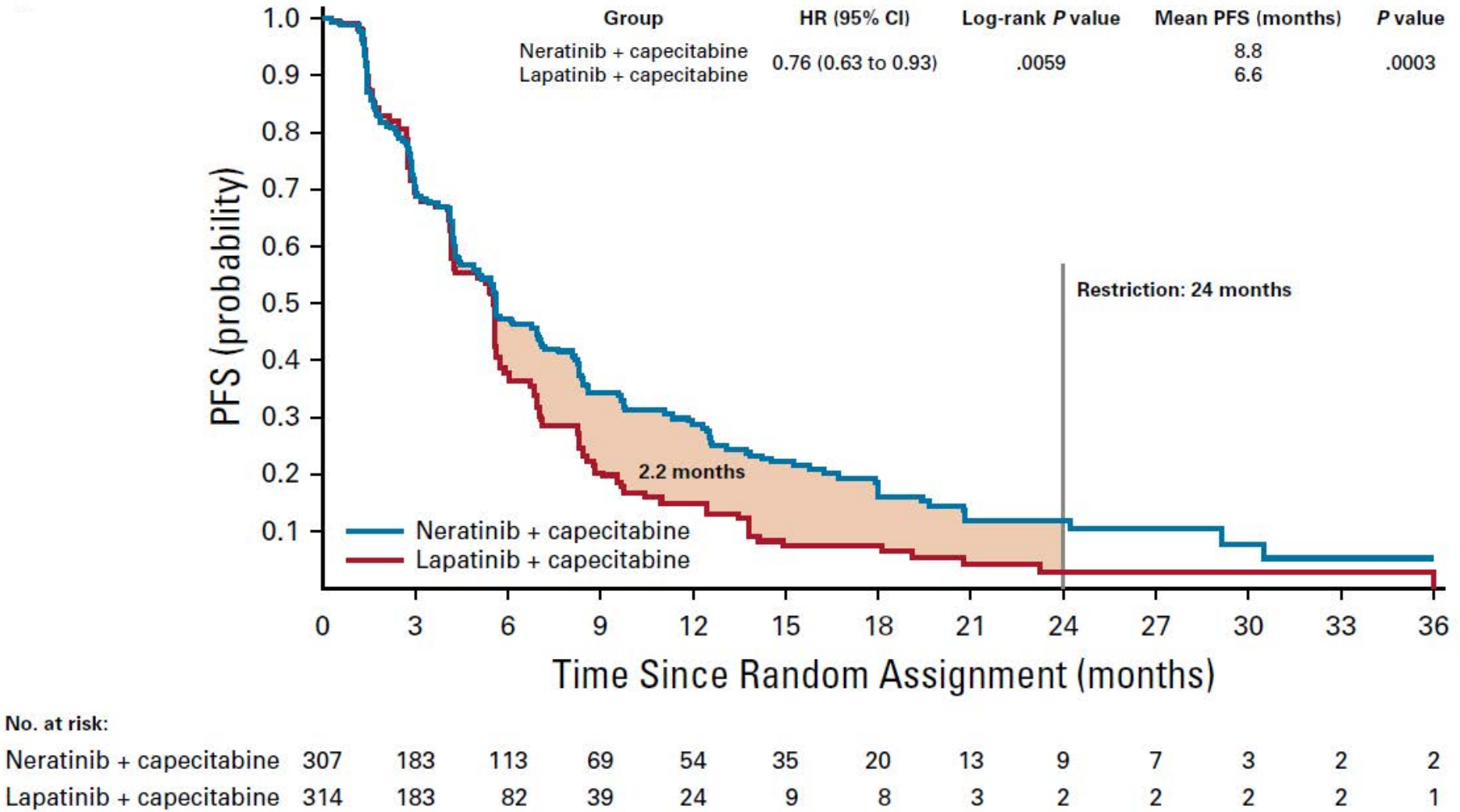
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

NALA Centrally Confirmed PFS



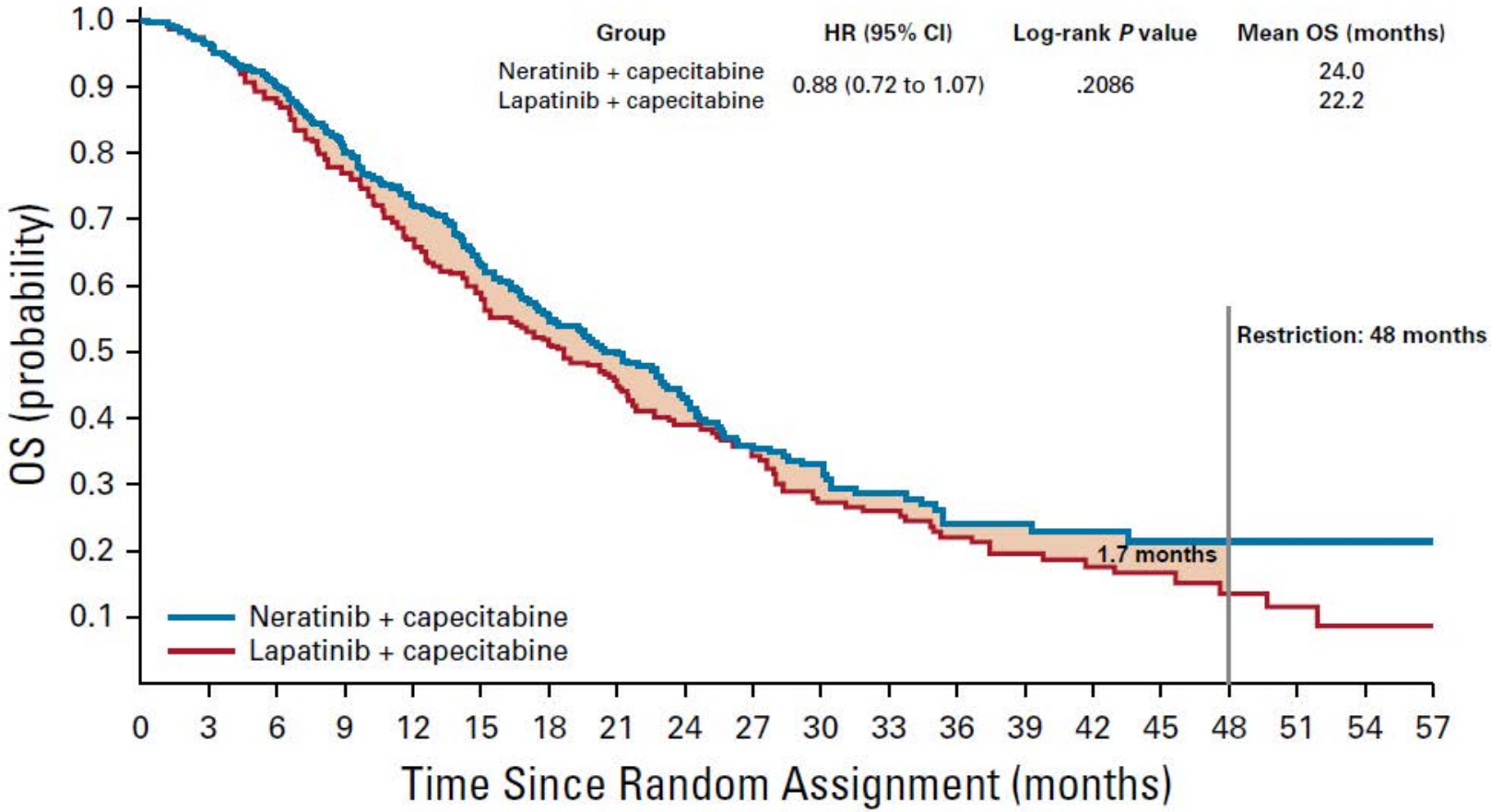
No. at risk:

Neratinib + capecitabine	307	183	113	69	54	35	20	13	9	7	3	2	2
Lapatinib + capecitabine	314	183	82	39	24	9	8	3	2	2	2	2	1

Saura et al, JCO 2020 38:3138

NALA Overall Survival Analysis

24% Gr3 Diarrhea



No. at risk:

Neratinib + capecitabine	307	294	275	244	220	182	142	112	82	64	47	34	28	18	15	13	6	4	2	1
Lapatinib + capecitabine	314	303	273	240	208	170	132	107	84	67	47	36	27	22	17	12	8	4	3	1

Saura et al, JCO 2020 38:3138

Unanswered questions in HER2+ MBC

- What is the efficacy of T-DM1 after trastuzumab deruxtecan?
- Is there a role for neratinib or pyrotinib?
  - Important to have data in patients who previously received tucatinib
- Can we improve upon THP in the first line?

AFT-38 PATINA Study Design

Pre-Study

- Histologically confirmed HR+,HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

Key eligibility criteria

- Completion of induction chemotherapy and no evidence of disease progression (ie, CR, PR, or SD)

N=518

R 1:1

Palbociclib (125 mg PO QD D1-D21)
Trastuzumab ± pertuzumab + endocrine therapy*

Trastuzumab ± pertuzumab + endocrine therapy*

Until PD or toxicity

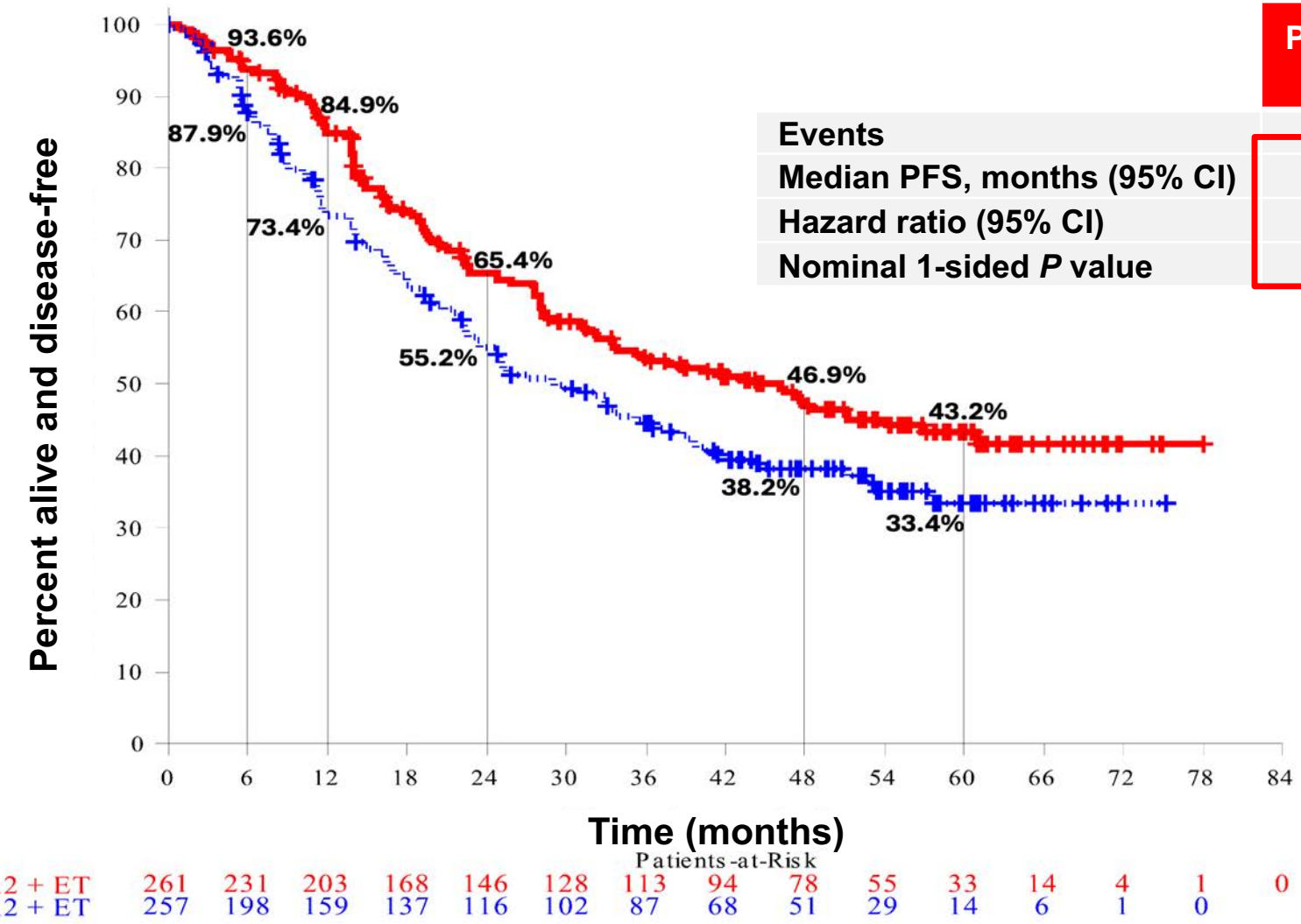
SURVIVAL FOLLOW-UP

Stratification factors

- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)†
- Response to induction therapy (CR or PR vs SD) by investigator assessment†
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

*Trastuzumab and pertuzumab were administered per SOC. Endocrine therapy options include an aromatase inhibitor or fulvestrant. †Factors used in stratified analyses.
CR=complete response; D=day; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; PD=progressive disease; PO=orally; PR=partial response; QD=once a day; R=randomized; SD=stable disease; SOC=standard of care.

Primary Endpoint: PFS (Investigator-Assessed)

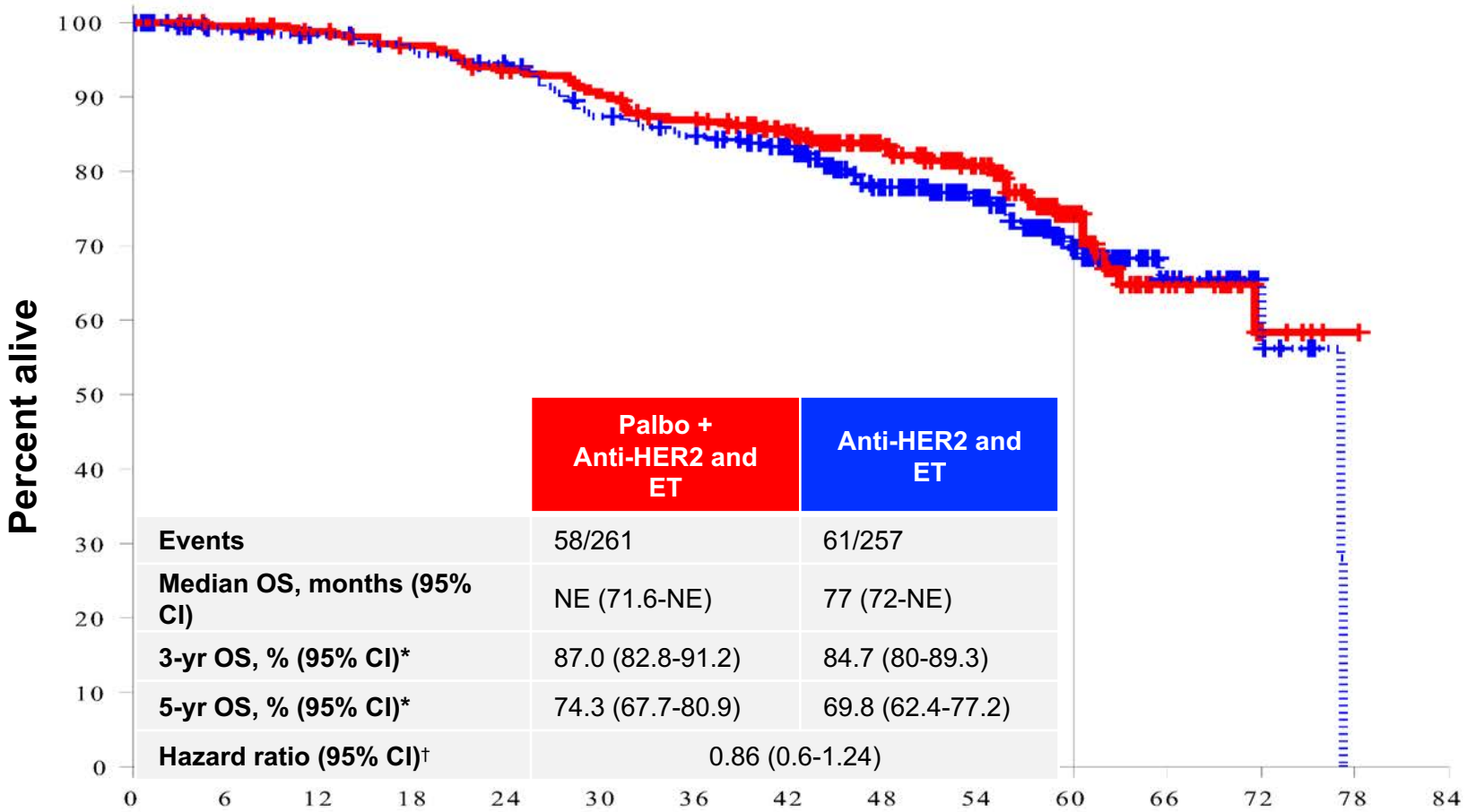


	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

Median f/u 53mo

CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.

Secondary Endpoint: Overall Survival (Interim Analysis)



	Palbo + Anti-HER2 and ET	Anti-HER2 and ET
Events	58/261	61/257
Median OS, months (95% CI)	NE (71.6-NE)	77 (72-NE)
3-yr OS, % (95% CI)*	87.0 (82.8-91.2)	84.7 (80-89.3)
5-yr OS, % (95% CI)*	74.3 (67.7-80.9)	69.8 (62.4-77.2)
Hazard ratio (95% CI)†	0.86 (0.6-1.24)	

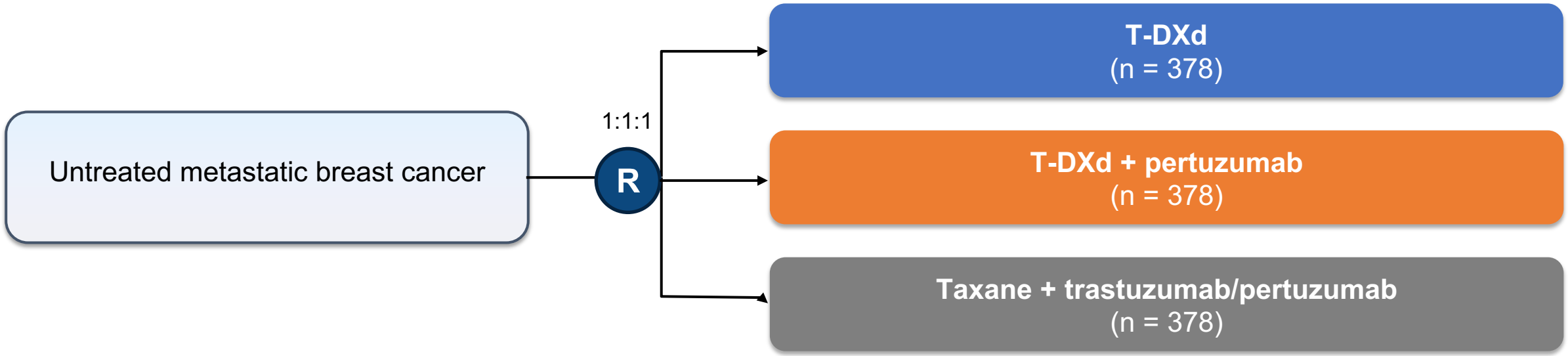
*Kaplan-Meier method.
†Unstratified Cox model.
CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; NE=not evaluable; OS=overall survival; palbo=palbociclib.

Adverse Events (Grade ≥2 in ≥10% of Patients)

Adverse Events, n (%)*	**Palbociclib + anti-HER2 and ET (N=261)**			**Anti-HER2 and ET (N=248)**		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	52 (19.9)	165 (63.2)	12 (4.6)	10 (4.0)	11 (4.4)	0 (0.0)
White blood cell count decreased	30 (11.5)	30 (11.5)	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)
Fatigue	60 (22.9)	14 (5.4)	0 (0.0)	32 (12.9)	0 (0.0)	0 (0.0)
Stomatitis	45 (17.2)	11 (4.2)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)
Diarrhea	69 (26.4)	29 (11.1)	0 (0.0)	26 (10.5)	4 (1.6)	0 (0.0)
Upper respiratory tract infection	30 (11.5)	1 (0.4)	0 (0.0)	16 (6.5)	0 (0.0)	0 (0.0)
Urinary tract infection	26 (10.0)	2 (0.8)	0 (0.0)	19 (7.7)	1 (0.4)	0 (0.0)
Arthralgia	23 (8.8)	4 (1.5)	0 (0.0)	44 (17.7)	3 (1.2)	0 (0.0)
Ejection fraction decreased	22 (8.4)	1 (0.4)	0 (0.0)	21 (8.5)	8 (3.2)	0 (0.0)
Cardiac heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)

*Adverse events were assessed per Common Terminology Criteria for Adverse Events, version 4.0 regardless of treatment attribution. Stomatitis, mouth ulceration, mucosal inflammation, and mucositis were assessed as medical concepts using grouped terms. Fatigue and asthenia were assessed as medical concepts using grouped terms. Cardiac safety data were also included in the table above. AE=adverse events.

DESTINY-Breast09: Is T-DXd superior to THP in first-line setting?

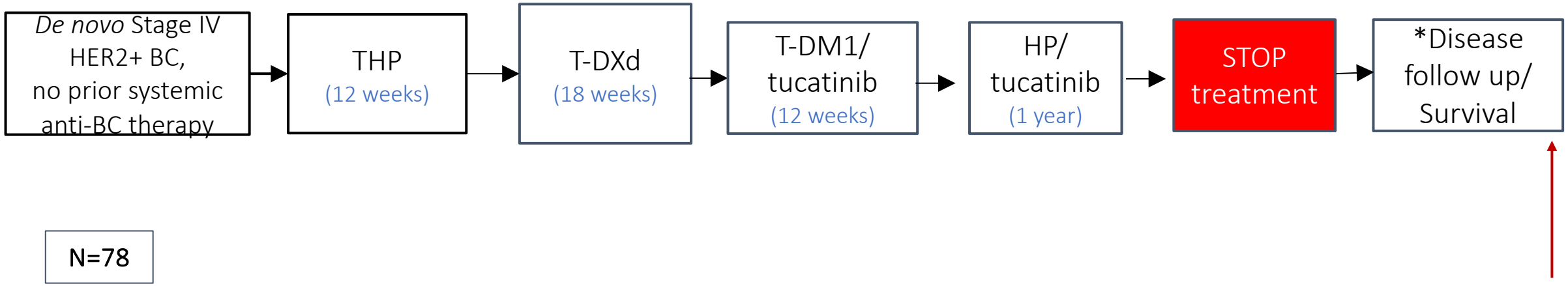


How will QOL on T-DXd compare to maintenance HP?

NCT04784715.

Primary endpoint: PFS

SAPPHO: Phase II Trial of Sequential HER2 Therapies for HER2+ Advanced Disease



N=78

Primary endpoint: Percentage of patients progression-free at 4yrs

*(ER+ BC continues on HR tx)

PI: Heather Parsons

tbcrc Translational Breast Cancer Research Consortium

Faculty Case Presentations

Case Presentation – Dr Hamilton

37 yo F with 1 child aged 10 years

- **Initially diagnosed with a 4.3 cm ER 10%+/PR 0%+, HER2+ (FISH ratio 5.4), SLN + invasive cancer**
- **Received neoadjuvant TCHP**
- **pCR achieved after lumpectomy, received XRT and adjuvant trastuzumab/pertuzumab to complete 1 year of anti-HER2 therapy**
- **Developed metastatic disease in liver and nodes after DFI of 5 years**
- **Enrolled in a clinical trial evaluating T-DXd as 1L therapy**
- **Starting emetic premeds of steroids, NK1, and 5-HT3**
  - Experiences 8-9 days of moderate nausea w/ vomiting, comes in for IV fluid twice
- **Cycle #2, add olanzapine 2.5 mg qhs**
  - Tolerates much better w/ maximal G1 nausea, no fluid support needed
- **C3 scans show 27% decrease in lesions**
- **C5 scans show 43% decrease**

Case Presentation – Dr Hamilton (Continued)

- Continued treatment with T-DXd for 20+ months
- Recent CT abdomen/pelvis scans show signs of progression, results of brain MRI pending
- Patient discussion: Next course of treatment Tucatinib+cape+trastuzumab or clinical trial?

Case Presentation – Dr O'Shaughnessy

- 32 yo Latina woman presented with Stage IIIA T3N1M1 ER- PR- HER2+ de novo MBC with a solitary liver metastasis, biopsy-positive, ER- PR- HER2+; germline testing was negative
- She was treated with 6 cycles of docetaxel/H/P and had a clinical complete response in breast/axilla and a near CR in the liver
- She continued maintenance H/P and underwent left breast lumpectomy and SLN biopsy (pCR in both) followed by breast and locoregional radiation and SBRT to the area of the liver metastasis. Her menses resumed
- After 9 mos on H/P she presented with seizures and underwent resection of a large cerebellar met (ER- PR- HER2+ AR++) , followed by SRS to the cavity and to a small frontal lobe mass. Staging was negative for other recurrence
- Her therapy was changed to full dose capecitabine, tucatinib, trastuzumab which she tolerated very well
- After 18 mos on TTC, brain MRI showed a new metastasis 1.5cm. Staging was otherwise negative
- Her therapy was switched to T-DXd by her outside oncologist and the brain metastasis responded and she has remained on T-DXd for 16+ mos with no progression of disease

Agenda

Module 1: Optimizing the Care of Patients with HER2-Positive Metastatic Breast Cancer (mBC) – Dr Krop

Module 2: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer – Dr Tolaney

Module 3: Integrating Novel Agents and Approaches into the Management of Endocrine-Resistant Hormone Receptor-Positive mBC – Dr Kalinsky

Module 4: Tolerability Considerations with Approved and Investigational Antibody-Drug Conjugates – Dr O'Shaughnessy

Module 5: Other Important Care Considerations for Patients with mBC – Dr Hamilton

Metastatic Triple-negative Breast Cancer (mTNBC)

Sara M. Tolaney, MD, MPH

Division of Breast Oncology,
Dana-Farber Cancer Institute

Dana-Farber Cancer Institute

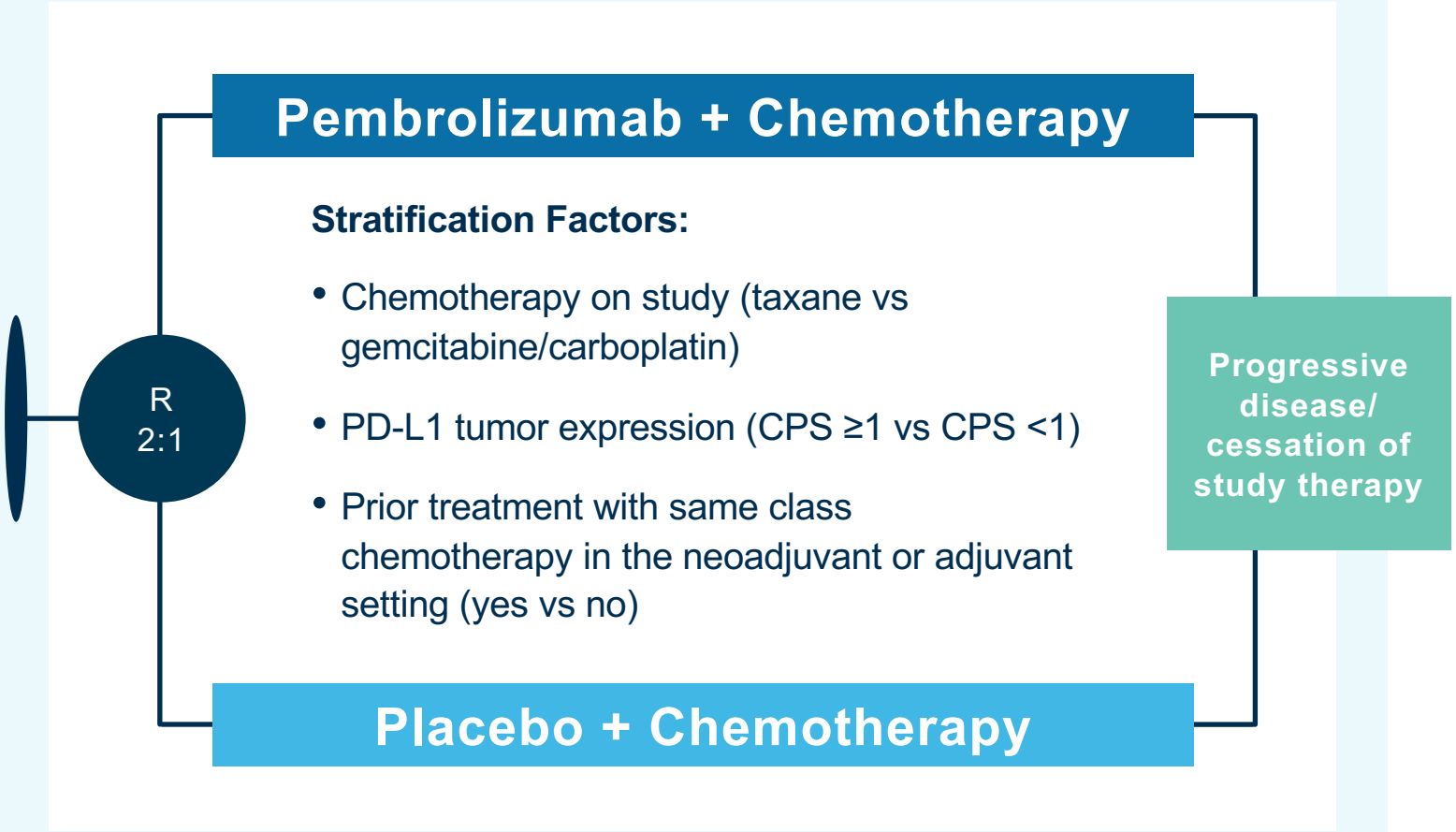
HARVARD MEDICAL SCHOOL

KEYNOTE-355: Study Design

Pembrolizumab + chemotherapy for advanced, metastatic TNBC

Patient Eligibility Criteria:

- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

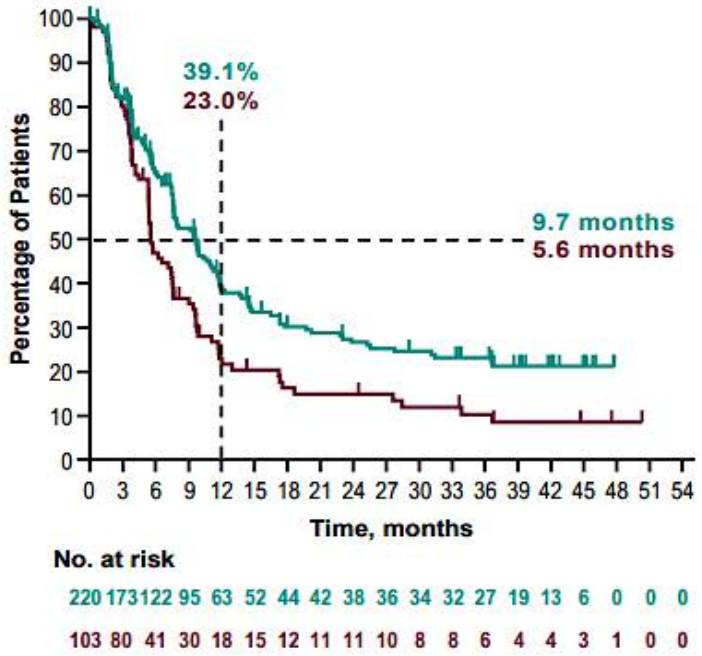


Cortes J, et al. Lancet. 2020;396:1817-1828.

KEYNOTE-355: PFS Analysis

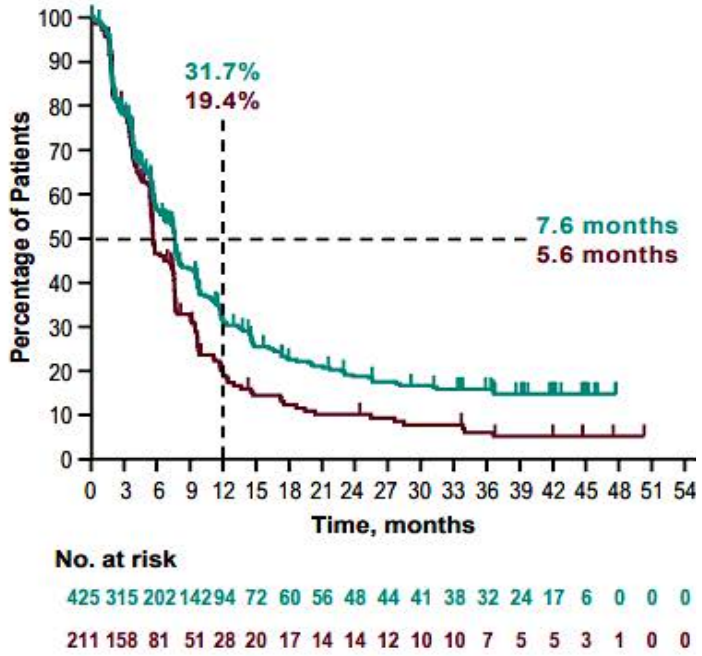
PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)
Pembro + Chemo	144/220	65.5%	0.66 (0.50-0.88)
Placebo + Chemo	81/103	78.6%	



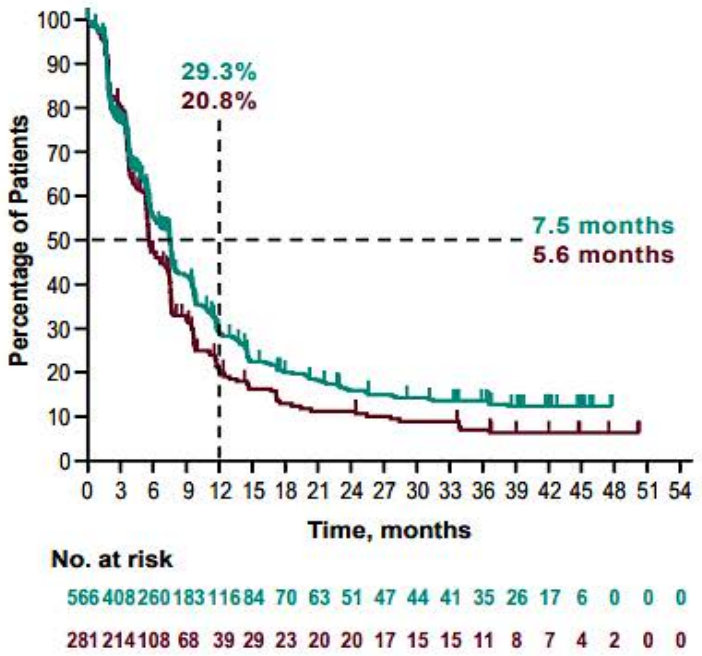
PD-L1 CPS ≥1

	n/N	Events	HR (95% CI)
Pembro + Chemo	299/425	70.4%	0.75 (0.62-0.91)
Placebo + Chemo	166/211	78.7%	



ITT

	n/N	Events	HR (95% CI)
Pembro + Chemo	406/566	71.7%	0.82 (0.70-0.98)
Placebo + Chemo	217/281	77.2%	

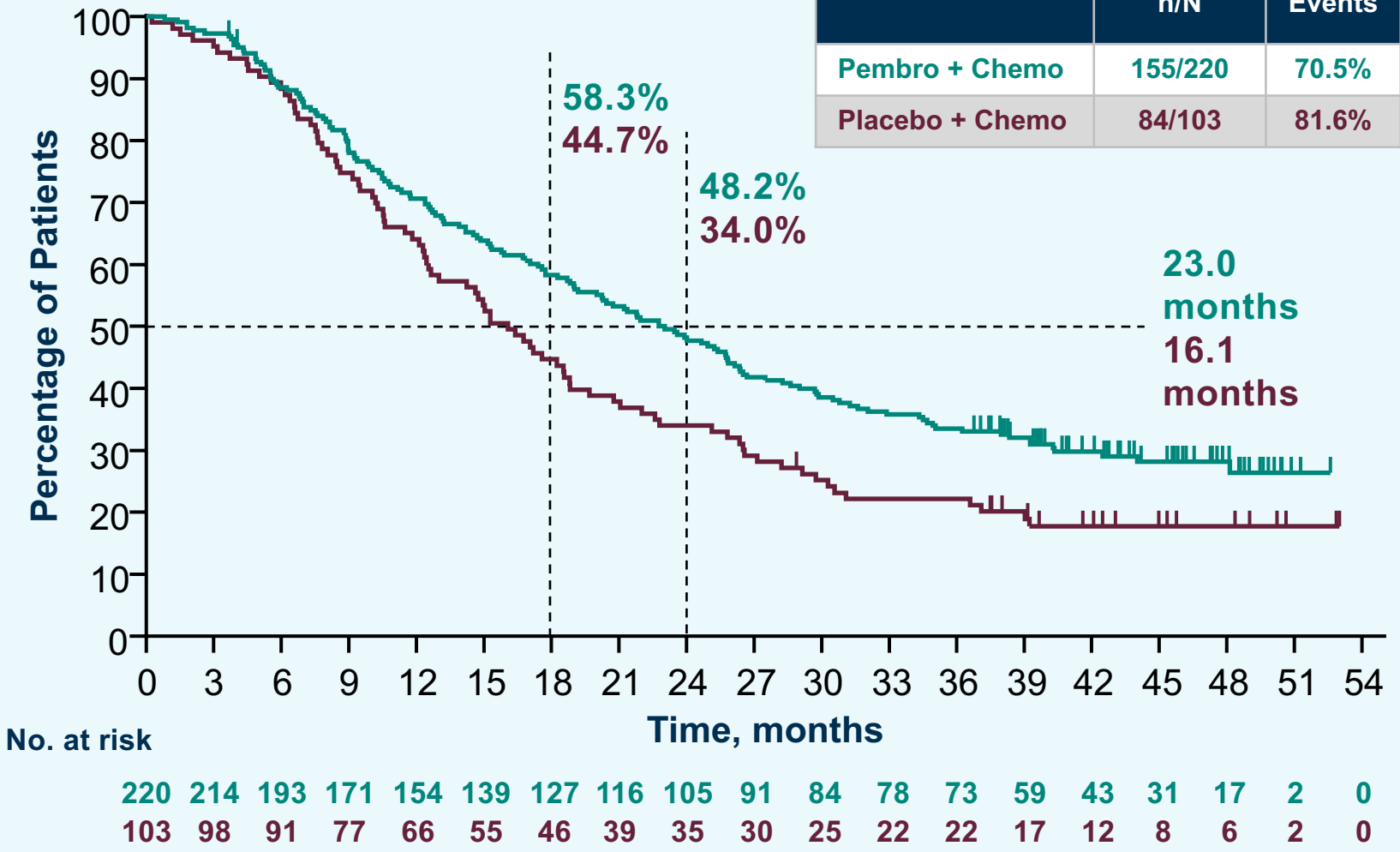


Data cutoff: June 15, 2021

Rugo HS, et al. ESMO 2021. Abstract LBA16.

KEYNOTE-355: Overall Survival at PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093*
Placebo + Chemo	84/103	81.6%		



*Prespecified P value boundary of 0.0113 met. Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors.
Data cutoff: June 15, 2021.

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Rugo HS, et al. ESMO 2021. Abstract LBA16.

What About Other Strategies? Targeting DNA Repair

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

Efficacy of PARP Inhibitors in Patients with mBC with gBRCA Mutations

	OlympiAD Olaparib vs. TPC	**EMBRACA** Talazoparib vs. TPC
PFS	**5.6 mos** vs. 2.9 mos **HR = 0.43** 95% CI (0.29, 0.63)	**5.8 mos** vs. 2.9 mos **HR= 0.60** 95% CI (0.41, 0.87)
ORR	**51.8%** vs. 5.4% (n=83) (n=37) *Investigator assessment*	**61.8%** vs. 12.5% (n=102) (n=48) *Investigator assessment*

Critical to obtain germline testing on all metastatic breast cancer patients to see if they could be a candidate for PARPi

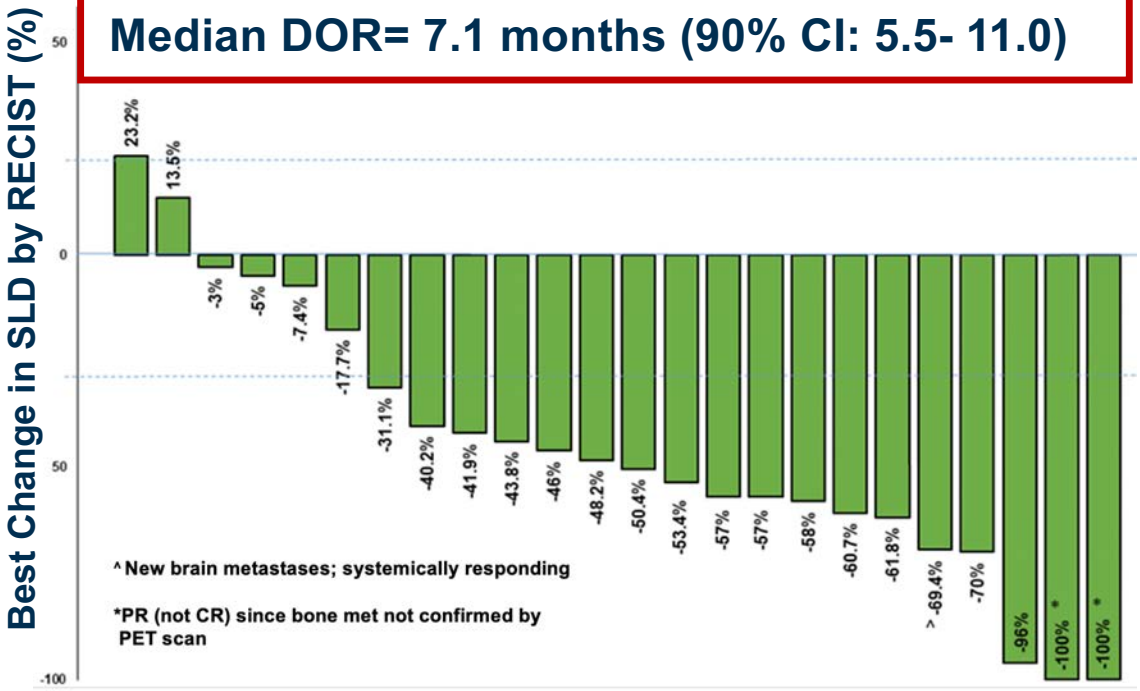
Robson et al, NEJM 2017; Litton et a, NEJM 2018; Dieras et al, Lancet Oncol 2020

Olaparib Expanded: Responses for g*PALB2*

g*PALB2* N=24	
Best Response	**Responses (rate, %)**
Complete Response (CR)	1 (4%)
Partial Response (PR)	17 (71%)
Stable Disease (SD)	5 (21%)
Progressive Disease (PD)	1 (4%)
ORR = 75% (18/24, 80%-CI: 60%-86%)	
CBR (18 wks) = 83% (20/24, 90%-CI: 66%-94%)	

Datacut May 3, 2024

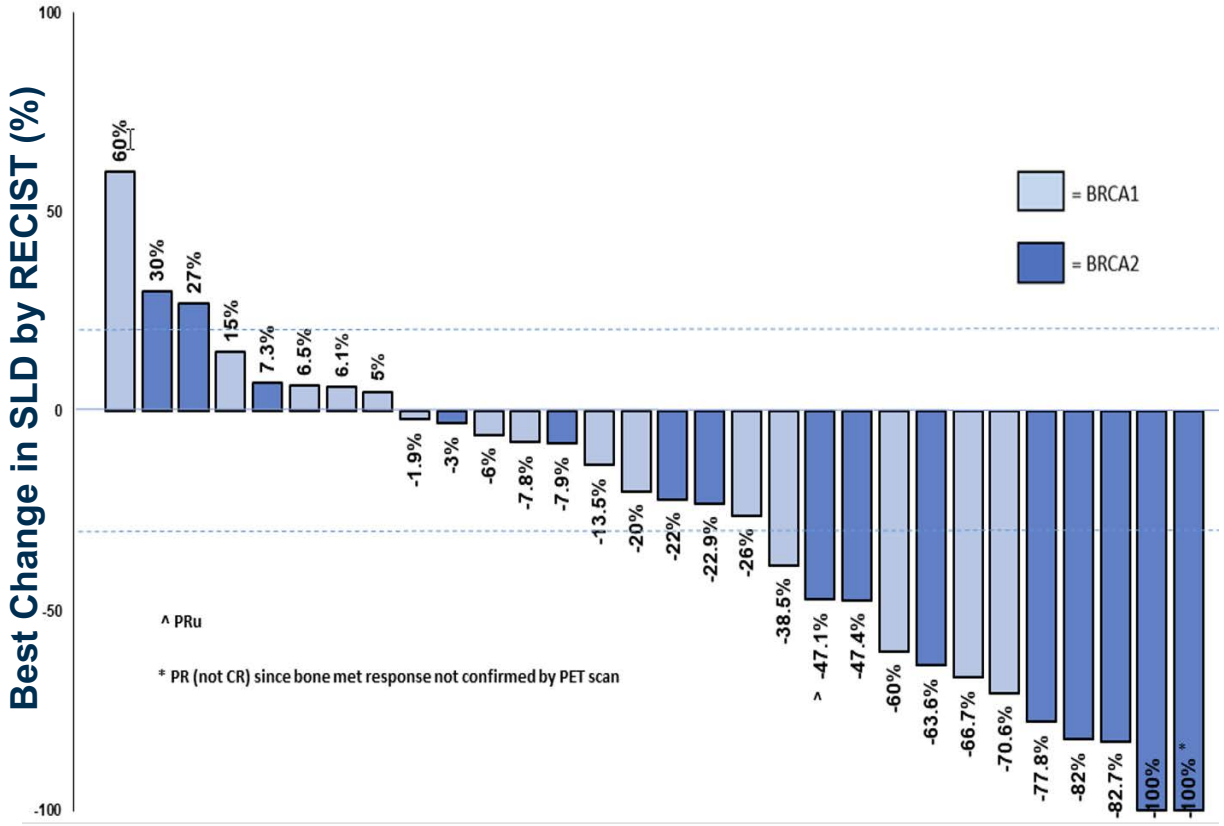
Median PFS= 9.6 months (90%-CI: 8.3- 12.4)
Median DOR= 7.1 months (90% CI: 5.5- 11.0)



Tumor Subtype	Responses
TNBC	2/2
ER+/HER2-neg	13/19
HER2+	3/3

Olaparib Expanded: Responses for s*BRCA1/2*

sBRCA1/2 N=30	
Best Response	**Responses, (rate, %)**
Complete Response (CR)	1 (3%)
Partial Response (PR)^	10 (33%)
Stable Disease (SD)	13 (43%)
Progressive Disease (PD)	6 (20%)
ORR = 37% (11/30, 80%-CI: 25%-50%)	
CBR (18 wks) = 53% (16/30, 90%-CI: 37%-69%)	



^ 1 unconfirmed PR did not count for ORR or CBR

Median PFS= 7.2 months (90% - CI: 3.9- 13.6)

Median DOR= 12.4 months (90% CI: 4.3- Not reached)

What About Antibody Drug Conjugates?

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

TROP2-directed ADCs

	Sacituzumab govitecan (IMMU-132)	Datopotamab deruxtecan (DS-1062a)	Sacituzumab tirumotecan (MK-2870)
Antibody	hRS7 Humanized IgG1 mAb	MAAP-9001a Humanized IgG1 mAb	hRS7 Humanized IgG1 mAb
Payload	SN38 (DNA Topoisomerase I inhibitor)	DXd (DNA Topoisomerase I inhibitor)	KL610023 (DNA Topoisomerase I inhibitor)
Linker Cleavage	Enzymatic and pH-dependent	Enzymatic	Enzymatic and pH-dependent
Bystander Effect	Yes	Yes	Yes
DAR	7.6	4	7.4
Half-life	11-14h	~5 days	57h
Dosing	D1, D8 of Q3W schedule	Q3W	Q2W

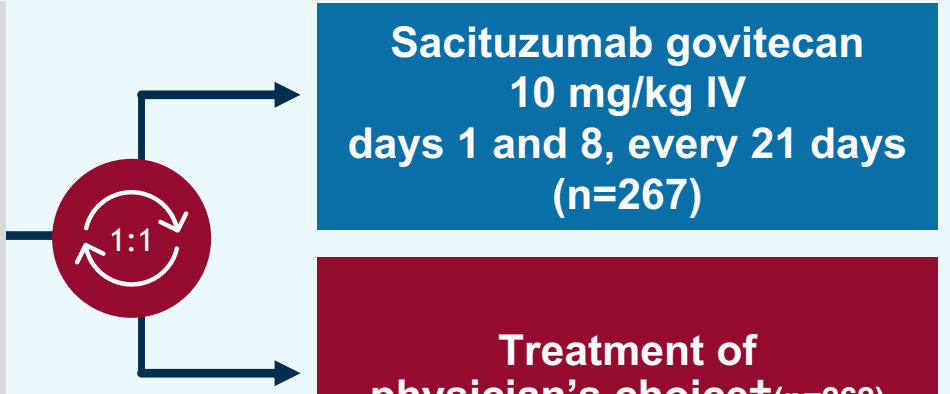
Sands J et al. ASCO 2018; Okajima D et al. ASCO 2018; Bardia A et al. ESMO Breast Cancer 2021; Cheng Y et al. Front Oncol 2022.

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in 2L and Later mTNBC[1-3*]

Metastatic TNBC

- ≥2 chemotherapies – one of which could be in neo/adjuvant setting provided progression occurred within a 12-month period
- Patients with stable brain metastases were allowed

(N=529)



Stratification Factors

- Number of prior chemotherapies (2 or 3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (Yes/No)

Continue treatment until progression or unacceptable toxicity

Endpoints

Primary

- PFS‡

Secondary

- PFS for the ITT population, § OS, ORR, DOR, TTR, QoL, safety

NCT02574455

*ASCENT was an international, Phase 3, multicentre, open-label, randomised trial of patients with unresectable locally advanced or metastatic TNBC (N=529). †Treatment of physician's choice: eribulin, vinorelbine, gemcitabine, or capecitabine; ‡PFS measured by an independent centralised and blinded group of radiology experts who assessed tumour response using RECIST 1.1 criteria in patients without brain metastasis; §The full population or intention-to-treat population includes all randomised patients (with and without brain metastases).

DOR, duration of response; IV, intravenous; ITT, intention-to-treat; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours; TNBC, triple-negative breast cancer; TTR, time to response; QoL, quality of life.

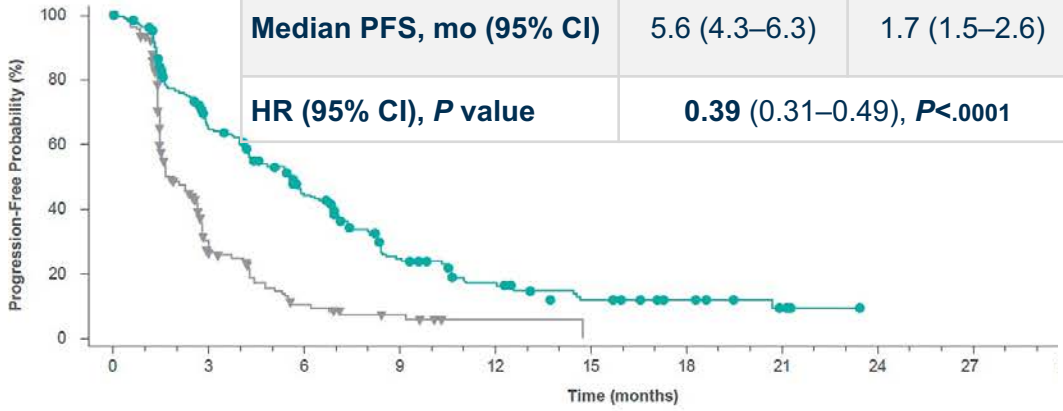
1. Bardia A, et al. *N Engl J Med.* 2021;384(16):1529-1541; 2. Bardia A, et al. ESMO 2020. Abstract LBA17; 3. ClinicalTrials.gov website. Available at: https://clinicaltrials.gov/ct2/show/NCT02574455. Accessed March 2022.

ASCENT: Statistically Significant and Clinically Meaningful Improvement in PFS and OS (BMNeg Population)

The ASCENT trial demonstrated statistically significant improvement in PFS and OS over single-agent chemotherapy in the primary study population

Progression-free survival (BICR Analysis)

BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	167	150
Median PFS, mo (95% CI)	5.6 (4.3–6.3)	1.7 (1.5–2.6)
HR (95% CI), *P* value	**0.39** (0.31–0.49), ***P*<.0001**	

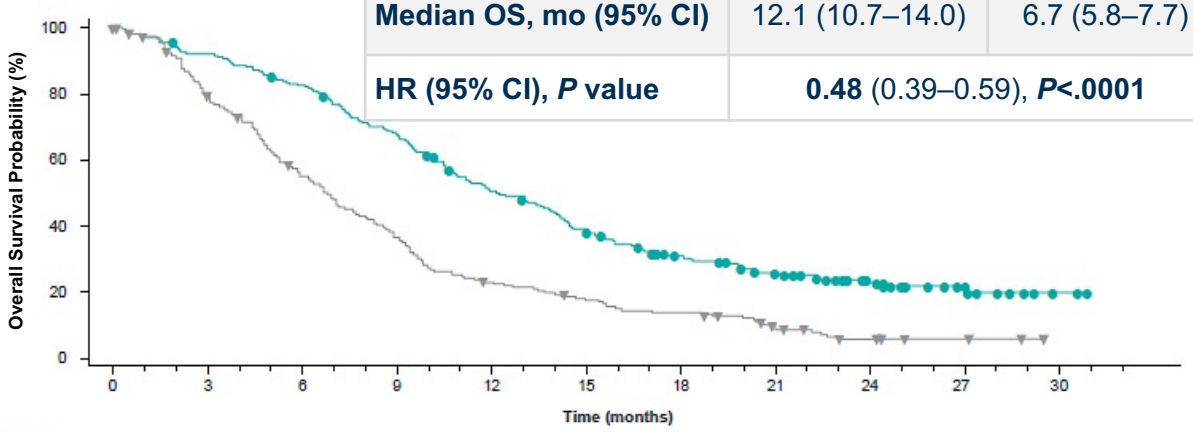


No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
IMMU-132	235	222	166	134	127	104	81	63	54	37	33	24	22	17	16	13	11	10	8	6	5	3	1	1	0
SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0		
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0		

Overall survival

	SG (n=235)	TPC (n=233)
No. of events	173	199
Median OS, mo (95% CI)	12.1 (10.7–14.0)	6.7 (5.8–7.7)
HR (95% CI), *P* value	**0.48** (0.39–0.59), ***P*<.0001**	



No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
IMMU-132	235	228	220	214	206	197	191	177	164	156	140	122	113	105	97	85	74	65	59	56	46	40	35	30	25	17	14	11	7	4	2
TPC	233	214	200	173	156	134	117	101	90	77	58	53	47	44	40	35	30	28	27	24	22	13	11	7	6	4	3	3	2	1	0

Analysis based on final database lock confirmed the improvement in clinical outcomes over TPC:

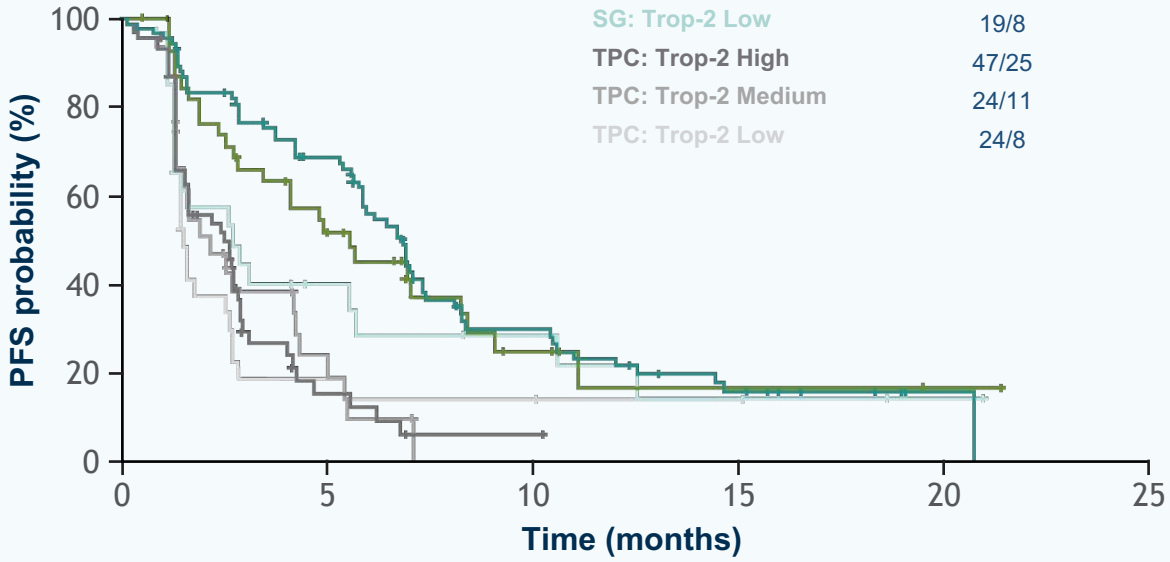
- **Median PFS of 5.6 vs 1.7 months (HR 0.39, P<0.0001)**
- Median OS of 12.1 vs 6.7 months (HR 0.48, P<0.0001)
- **OS rate at 24 months of 22.4% (95% CI, 16.8-28.5) vs 5.2% (95% CI, 2.5-9.4)**

Dana-Farber Cancer Institute

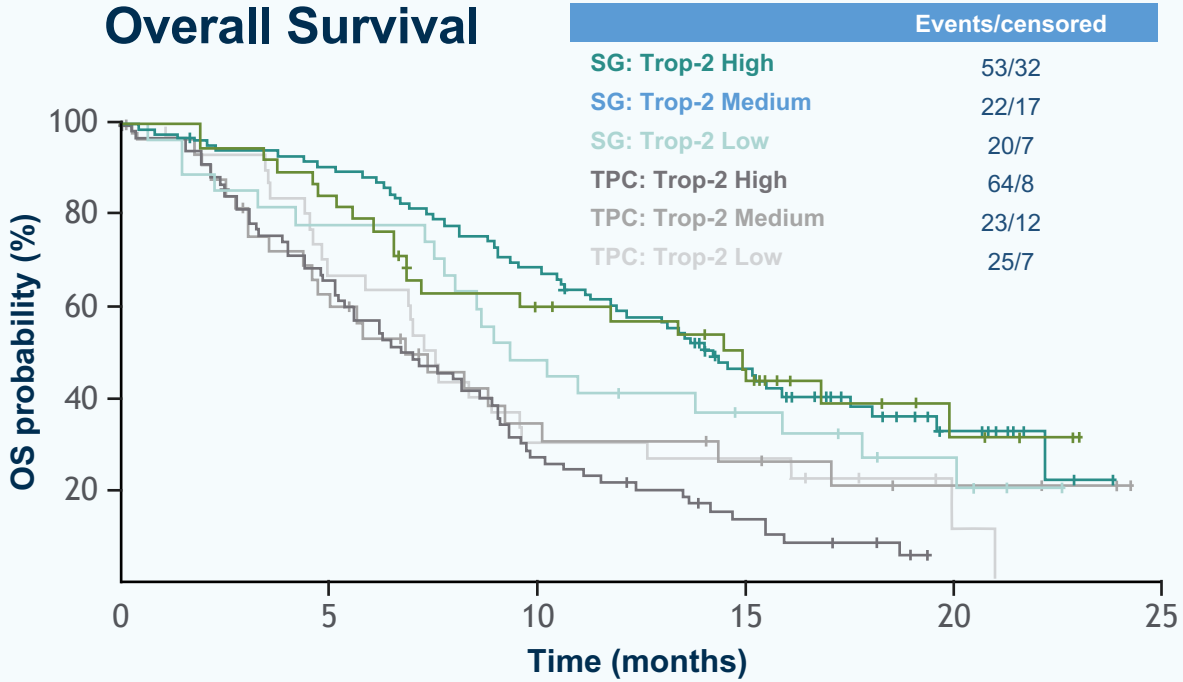
1. Bardia A, et al. J Clin Oncol. 2022;40(suppl 16):1071

Clinical Benefit with SG vs TPC is Irrespective of Level of Trop-2 Expression, in Previously Treated mTNBC

Progression-free Survival



Overall Survival



	Trop-2 High; H-score: 200–300		Trop-2 Medium; H-score: 100–200		Trop-2 Low; H-score: <100	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
Median PFS, mo (95% CI)	6.9 (5.8–7.4)	2.5 (1.5–2.9)	5.6 (2.9–8.2)	2.2 (1.4–4.3)	2.7 (1.4–5.8)	1.6 (1.4–2.7)
Median OS, mo (95% CI)	14.2 (11.3–17.5)	6.9 (5.3–8.9)	14.9 (6.9–NE)	6.9 (4.6–10.1)	9.3 (7.5–17.8)	7.6 (5.0–9.6)

Assessed in brain-metastases-negative population. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
H-score, histochemical score; NE, not estimable; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.

1. Hurvitz SA, et al. Oral presentation. SABCS [Virtual meeting] 2020. (Abstract GS3-06).

ASCENT-03:
Sacituzumab govitecan vs TPC in 1L PD-L1– mTNBC

1L mTNBC PD-L1–

- Previously untreated, inoperable, locally advanced, or metastatic TNBC
- PD-L1− tumors (CPS <10, IHC 22C3 assay) OR PD-L1+ tumors (CPS ≥10, IHC 22C3 assay) if treated with anti-PD-(L)1 agent in the curative setting
- ≥6 months since treatment in curative setting
- Prior anti-PD-(L)1 agent allowed in the curative setting
- PD-L1 and TNBC status centrally confirmed

1:1

N=540
(≤25% *de novo*)

Stratification Factors:
- *De novo* vs recurrent disease within 6-12 months of treatment in the curative setting vs recurrent disease >12 months after treatment in the curative setting
- Geographic region

Sacituzumab govitecan
10 mg/kg IV on
days 1 and 8 of 21-day cycles

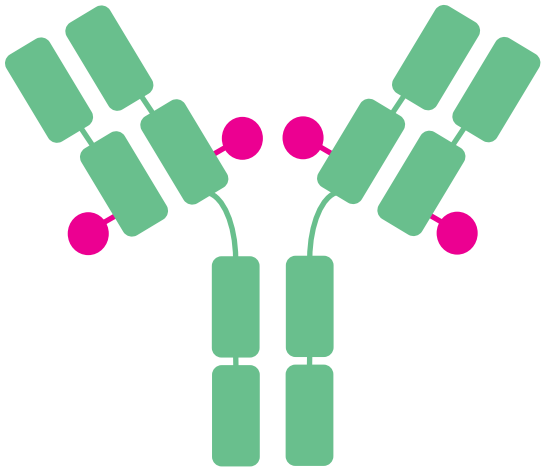
TPC Chemotherapy

- **Gem + carbo:** gem 1000 mg/m2 with carbo AUC 2 IV on days 1 and 8 of 21-day cycles
- **Paclitaxel:** 90 mg/m2 IV on days 1, 8, and 15 of 28-day cycles
- **Nab-paclitaxel:** 100 mg/m2 IV on days 1, 8, and 15 of 28-day cycles

Crossover to SG allowed after BICR-verified disease progression

BICR, blinded independent central review; CPS, combined positive score; IHC, immunohistochemistry; mTNBC, metastatic triple negative breast cancer; PD-L1, programmed death ligand 1; R, randomized; SG, sacituzumab govitecan; TPC, treatment of physician's choice. 1. EU Clinical trial register: EudraCT: 2021-005743-79. https://www.clinicaltrialsregister.eu/ctr-search/search/ Accessed April 2022.

Datopotamab Deruxtecan (Dato-DXd): TROP2 ADC in Development

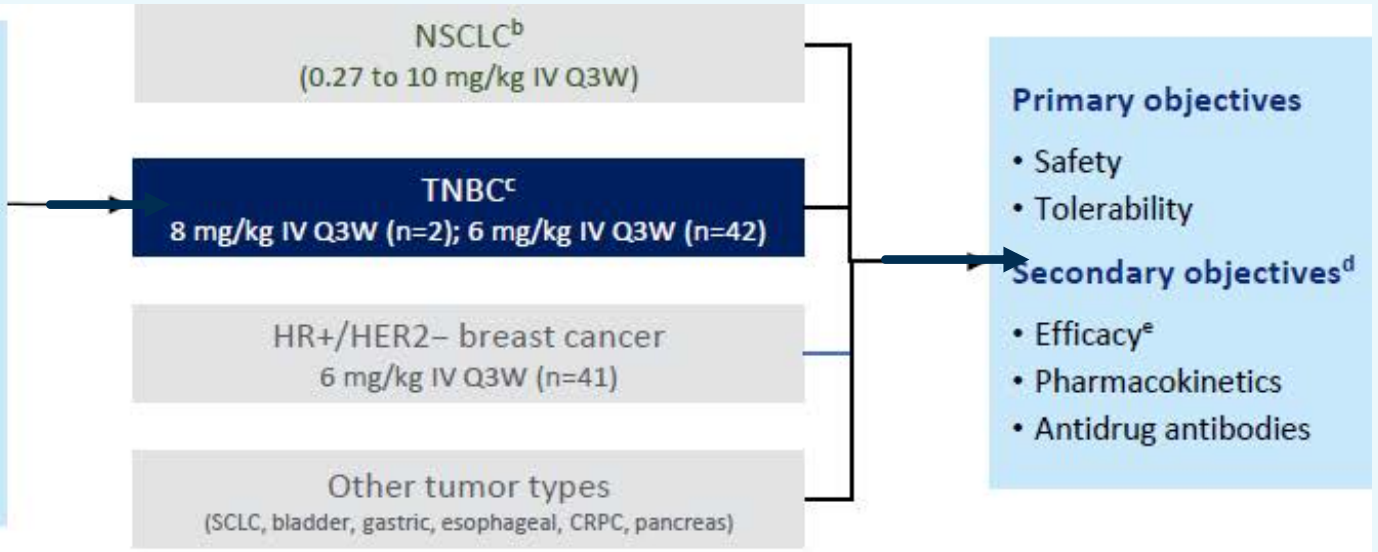


- Circulating free payload is negligible due to high stability of the linker, thereby limiting systemic exposure or nontargeted delivery of the payload[1]
- High-potency membrane-permeable payload (DXd) that requires TROP2-mediated internalization for release[2]
- DS-1062 has a DAR of 4 for optimized therapeutic index[2]
- DS-1062 has a substantially **longer half-life** than SG (≈ 5 days vs 11-14 hours), enabling a more optimal dosing regimen[3]
- SG's DLT is neutropenia, while DS-1062's DLTs are maculopapular rash and stomatitis/mucosal inflammation[4-6]

Dato-DXd in Advanced TNBC
TROPION-PanTumor01 Study

Study Design

- Advanced/unresectable or metastatic HR−/HER2− (IHC 0/1+ or IHC2+/ISH-) breast cancer
- Relapsed or progressed after local standard treatments
- Unselected for TROP2 expression[a]
- Age ≥18 years (US) or ≥20 years (Japan)
- ECOG PS 0-1
- Measurable disease per RECIST 1.1
- Stable, treated brain metastases allowed



Bardia A, et al. SABCS 2022. P6-10-03.

TROPION-PanTumor01 Study: Dato-DXd *Efficacy*

ORR by BICR:
- All patients: **32%**
- Topo I inhibitor-naive patients: **44%**

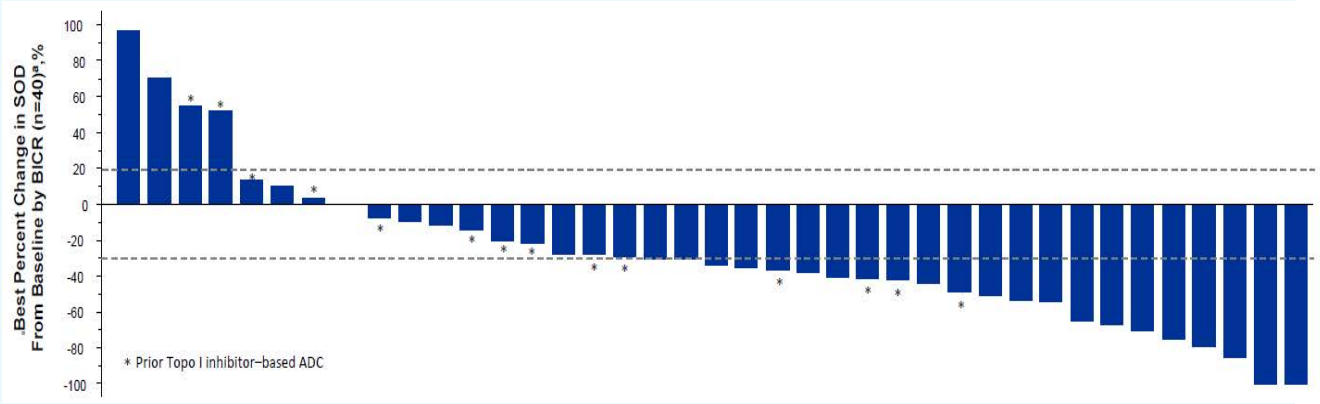
mDOR: 16.8 months in both groups

mPFS:
- All patients: 4.4 months
- Topo I inhibitor-naive patients: 7.3 months

mOS:
- All patients: 13.5 months
- Topo I inhibitor-naive patients: 14.3 months

AEs: Most common TEAEs: stomatitis (73%), nausea (66%), vomiting (39%)

Antitumor Tumor Responses by BICR



Ongoing Phase 3 Clinical Trials with Dato-DXd in 1L

TROPION-Breast02[1]

Key Eligibility Criteria:

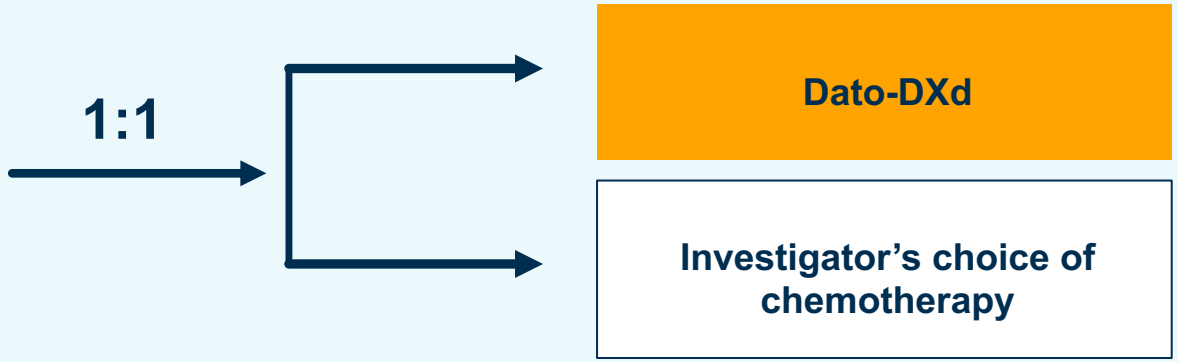
- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1/PDL1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification Factors:

- Geographic location
- DFI (de novo vs DFI ≤ 12 months vs DFI >12 months)

Dual Primary Endpoint:
PFS (BICR) and OS

Secondary Endpoints:
PFS (inv), ORR, DoR, Safety



- **1st line therapy for TNBC**
- **OD-L1 negative**

1. https://clinicaltrials.gov/study/NCT05374512

Design of Sacituzumab Tirumotecan (sac-TMT)

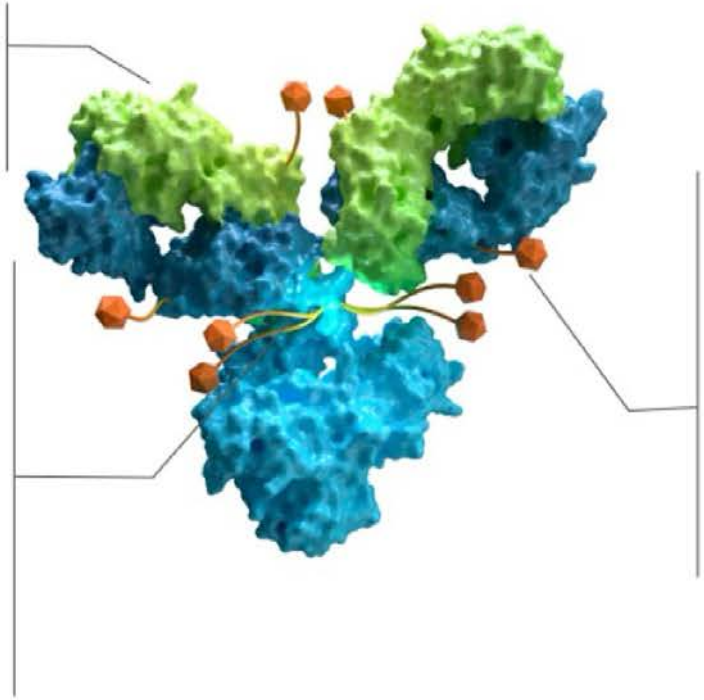
Sac-TMT is a TROP2 ADC developed with a proprietary (pyrimidine-thiol) linker conjugated to a novel topoisomerase I inhibitor at DAR 7.4. The feature of sac-TMT lead to release of the payload both in the tumor microenvironment (TME) and inside tumor cells, achieving a balance between safety and efficacy.

Antibody

- hRS7, a recombinant humanized anti-TROP2 antibody with high affinity

Linker

- **Kthiol conjugation:** irreversible coupling to improve stability of ADC
- **Payload release:** intracellular cleavage and extracellular hydrolysis in TME
- **Balanced stability:** balance between efficacy and safety to expand therapeutic window

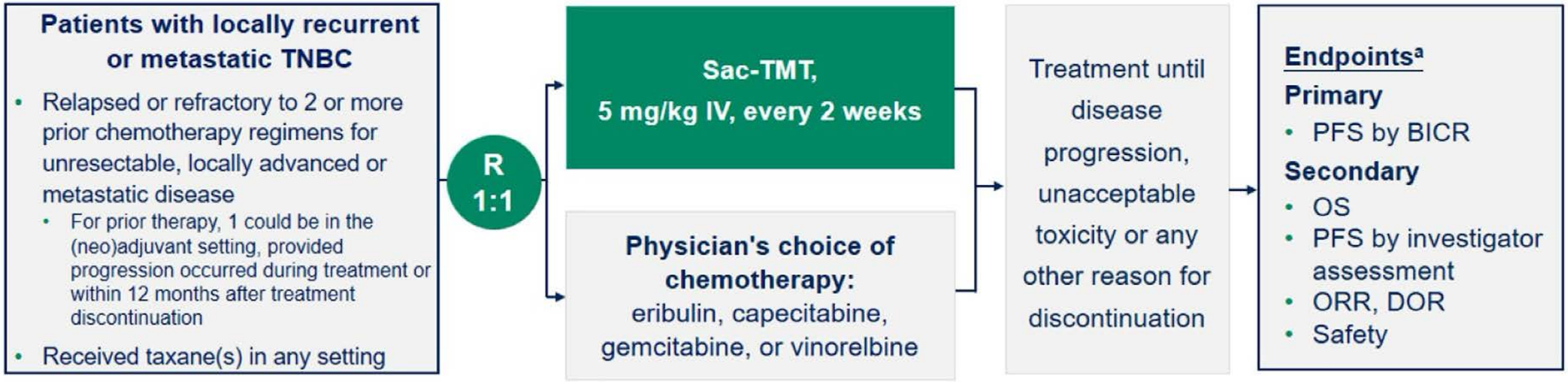


Payload

- **Novel topo I inhibitor** (a belotecan derivative), highly active
- Average **DAR: 7.4** (range: 7–8)
- **Bystander effect**
- Methylsulfonyl derivatization enhances linker stability and toxin permeability

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; TME, tumor microenvironment; TROP2, trophoblast cell surface antigen 2.

OptiTROP-Breast01: Randomized, Controlled, Open-Label Phase III Study (NCT05347134)



Stratification factors

- Line of prior therapy (2–3 vs >3)
- Presence of liver metastases (yes vs no)

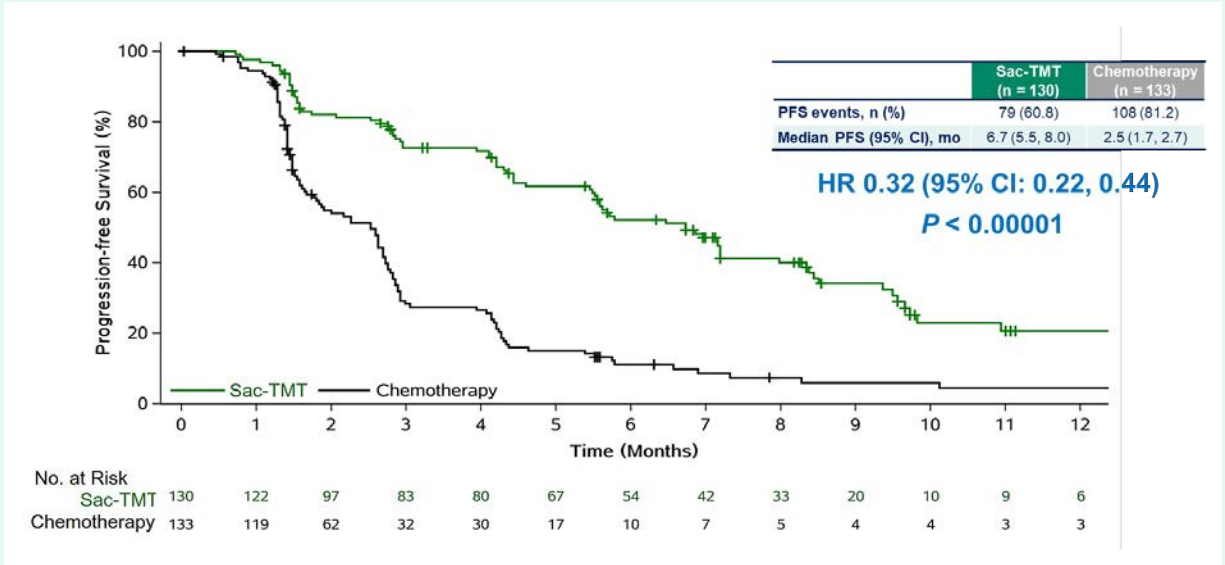
Tumor assessment

- Every 6 weeks for the first year and every 12 weeks afterward.

[a]Tumor response was assessed using RECIST version 1.1.
BICR, blinded independent central review; DOR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer.

OptiTROP-Breast01: Sac-TMT vs TPC in 2L+ mTNBC

PFS

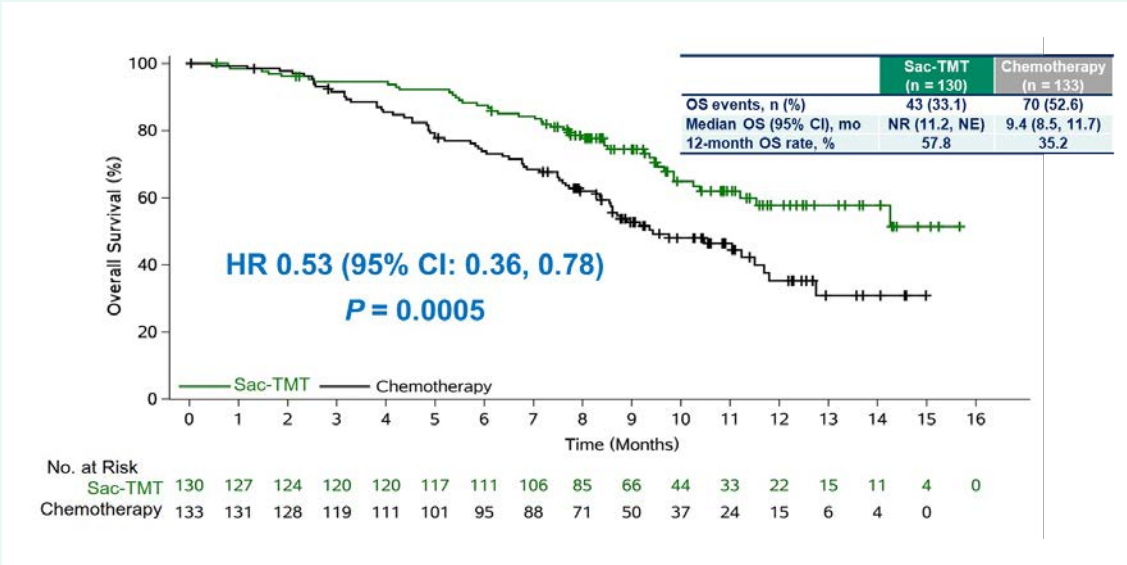


	Sac-TMT (n = 130)	Chemotherapy (n = 133)
PFS events, n (%)	79 (60.8)	108 (81.2)
Median PFS (95% CI), mo	6.7 (5.5, 8.0)	2.5 (1.7, 2.7)

HR 0.32 (95% CI: 0.22, 0.44)

P < 0.00001

OS



	Sac-TMT (n = 130)	Chemotherapy (n = 133)
OS events, n (%)	43 (33.1)	70 (52.6)
Median OS (95% CI), mo	NR (11.2, NE)	9.4 (8.5, 11.7)
12-month OS rate, %	57.8	35.2

HR 0.53 (95% CI: 0.36, 0.78)

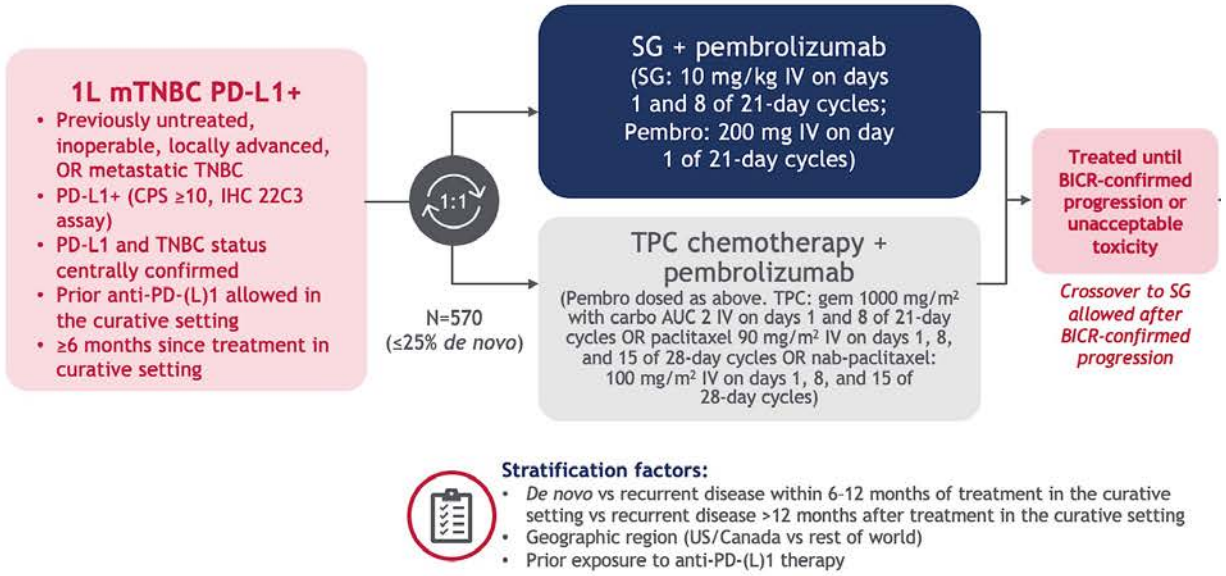
P = 0.0005

Fan Y et al. ASCO 2024. Zu B et al. J Clin Oncol. 2024;42(16_suppl).

Will ADC + IO Become the New 1L SOC for mTNBC?

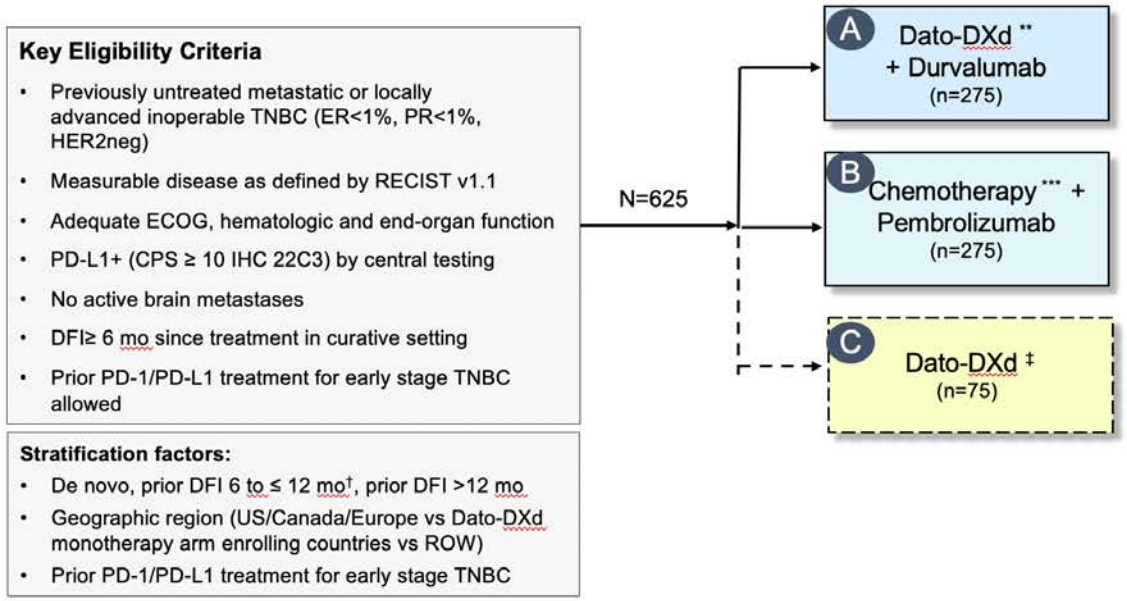
ASCENT-04

SG+ pembro vs TPC+ pembro in 1L PD-L1+ mTNBC



TROPION-Breast05

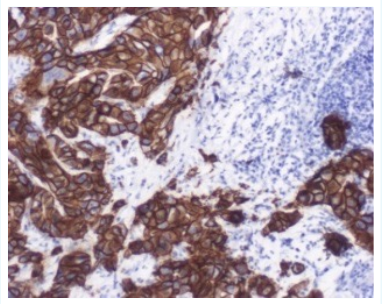
Dato-DXd +/- durva vs TPC + pembro in 1L PD-L1+ mTNBC



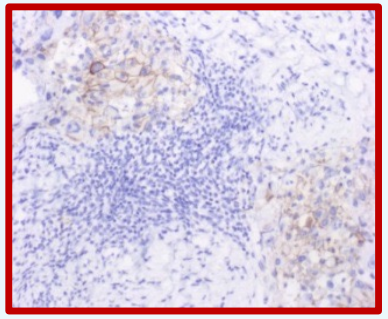
Prevalence of HER2-low by HR status

HER2 IHC Examples

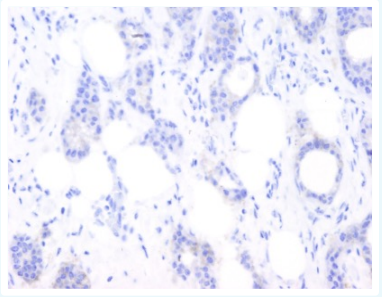
HER2+



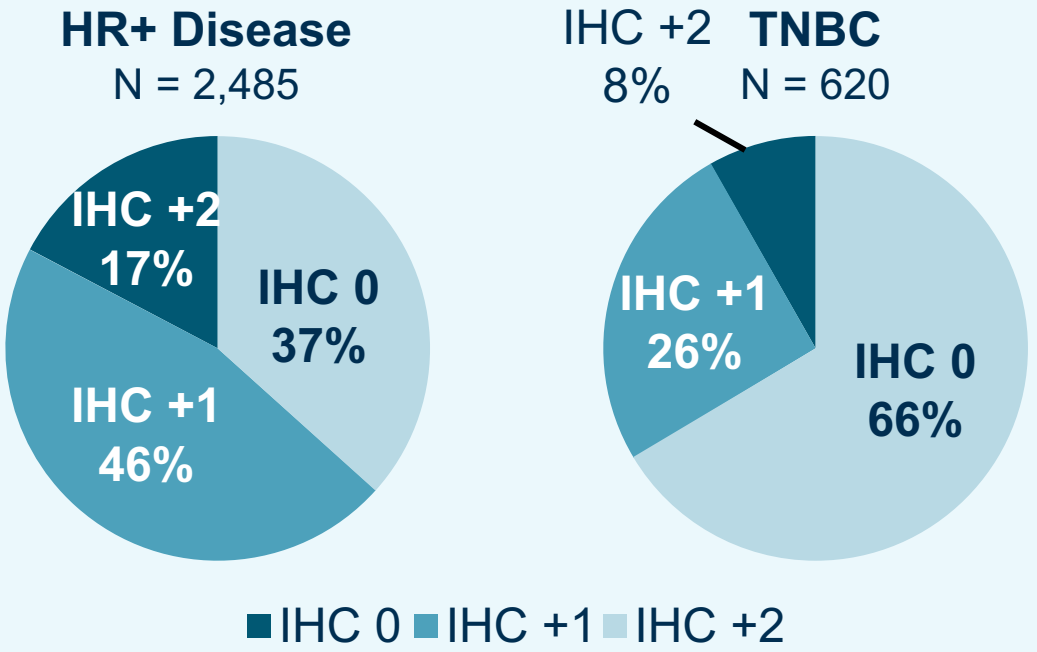
HER2-low



HER2-



HER2-negative



34% to **63%** of breast cancer patients considered HER2-negative under current guidelines express low levels of HER2

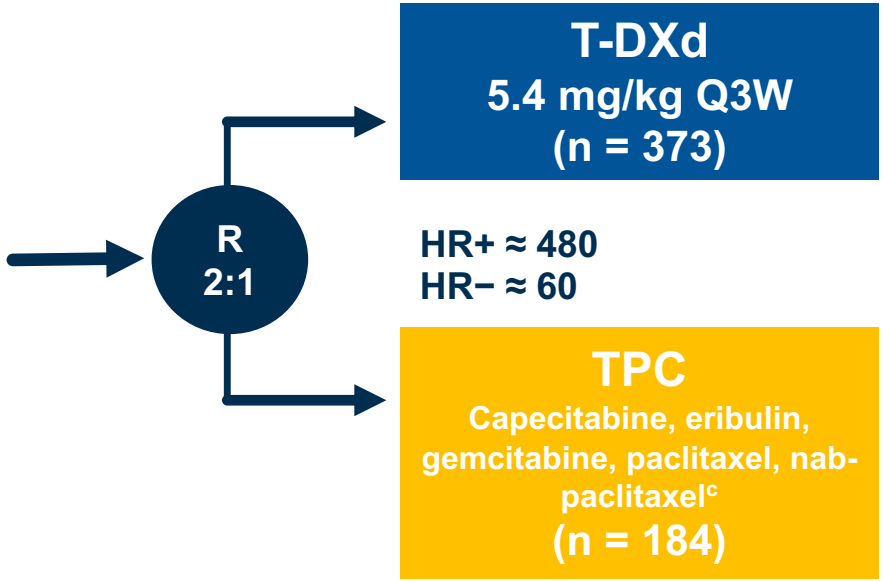
Schettini. ESMO Breast Cancer Virtual Meeting 2020. Abstr 23P. Slide courtesy of Aleix Prat.

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

An open-label, multicenter study (NCT03734029)

Patients[a]

- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory



Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints[b]

- PFS by BICR (all patients)
- OS (HR+ and all patients)

Stratification Factors

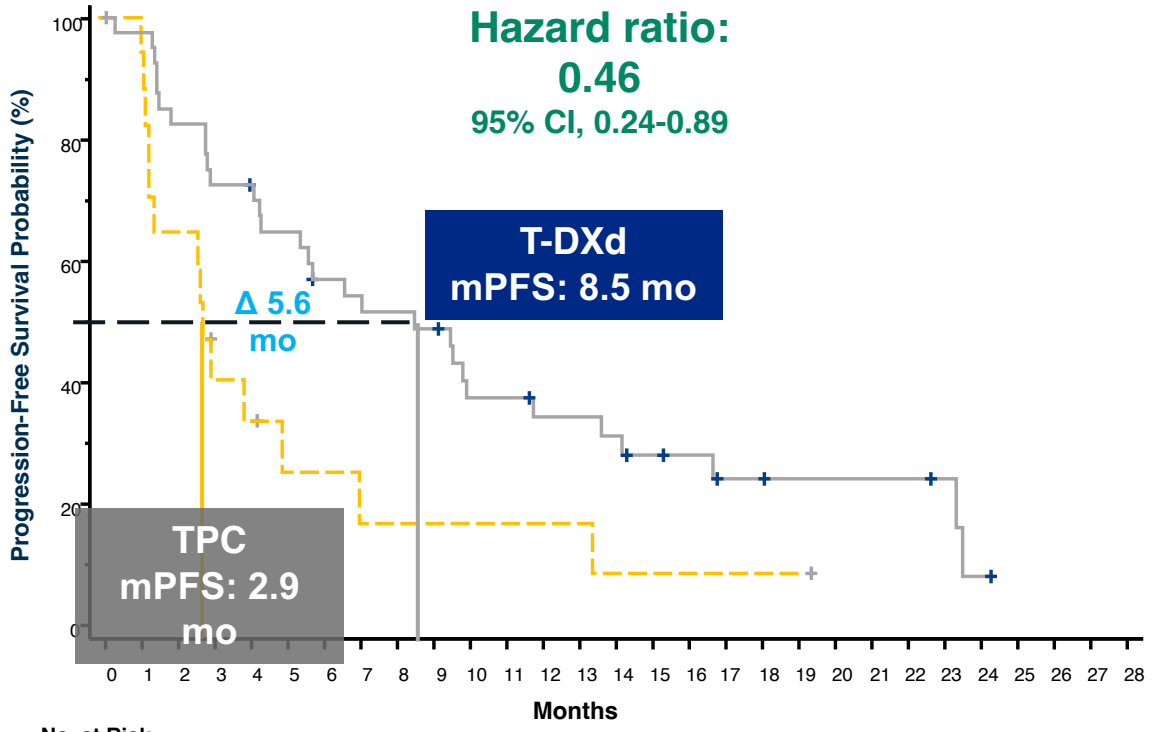
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

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 and OS in HR− (Exploratory Endpoints)

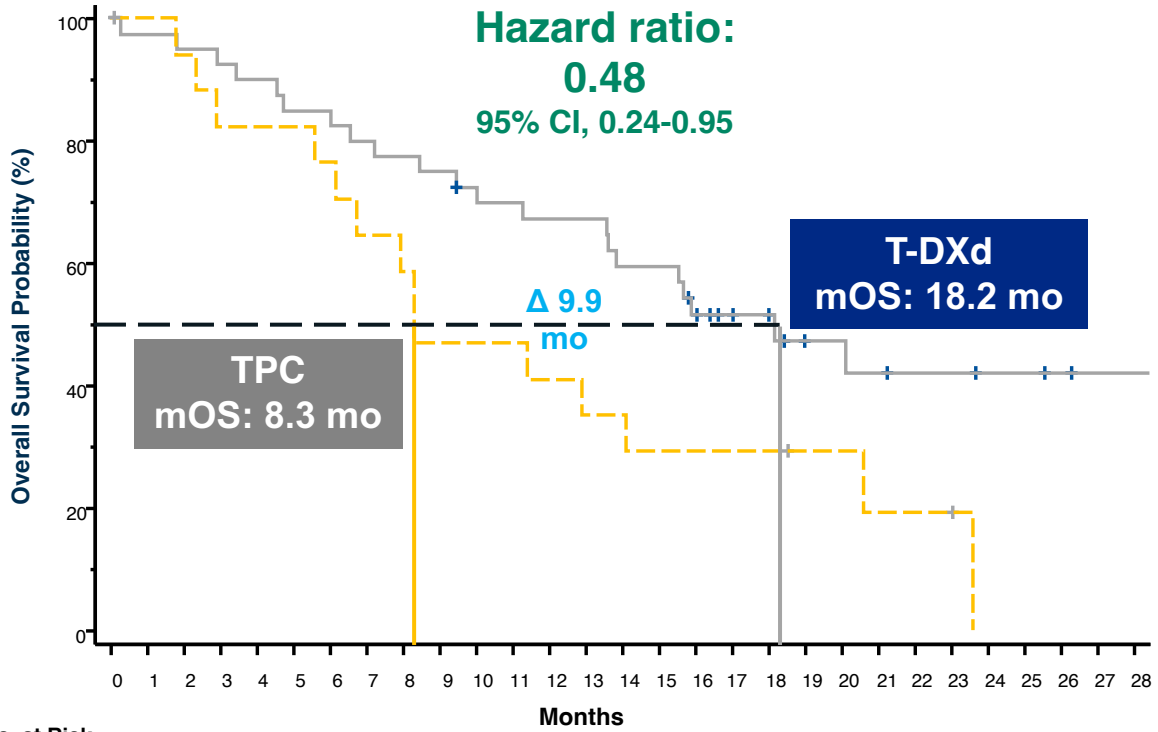
PFS



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



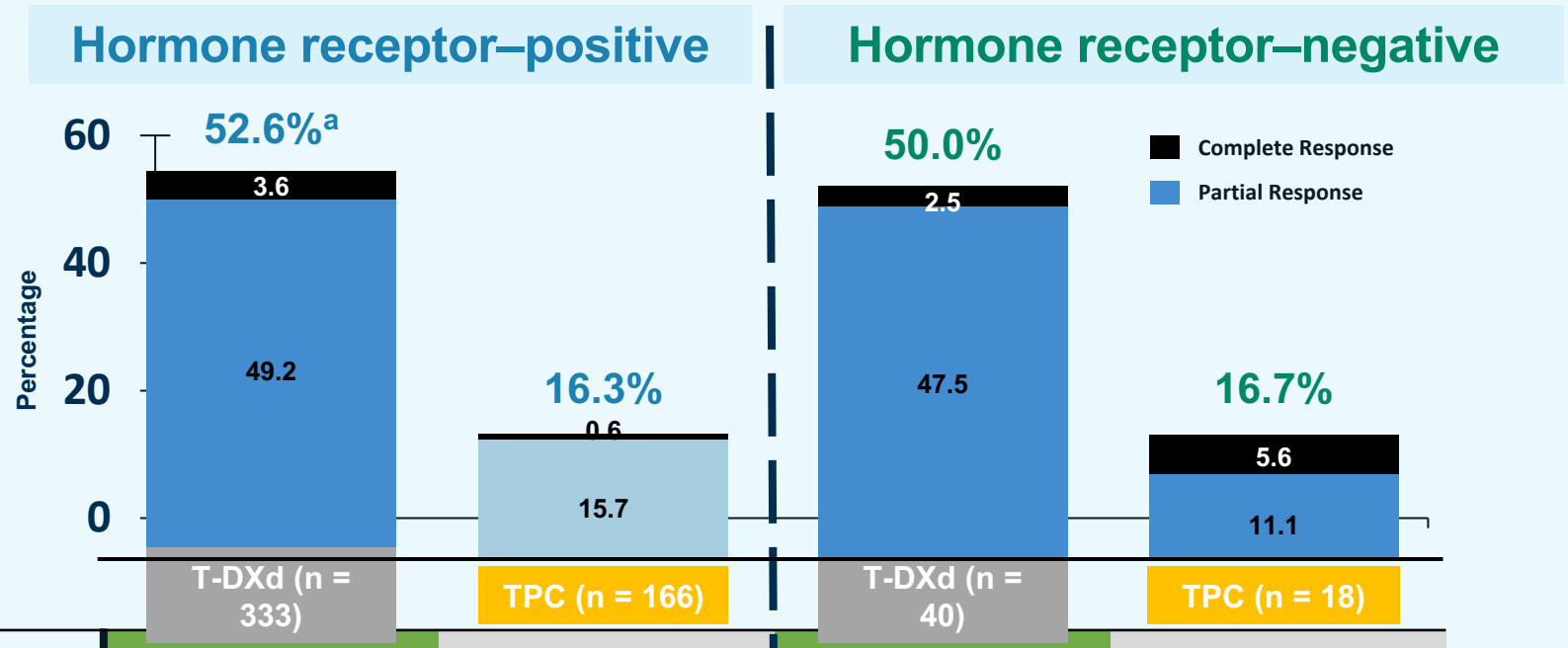
No. at Risk

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.

Confirmed ORR

Confirmed Objective Response Rate



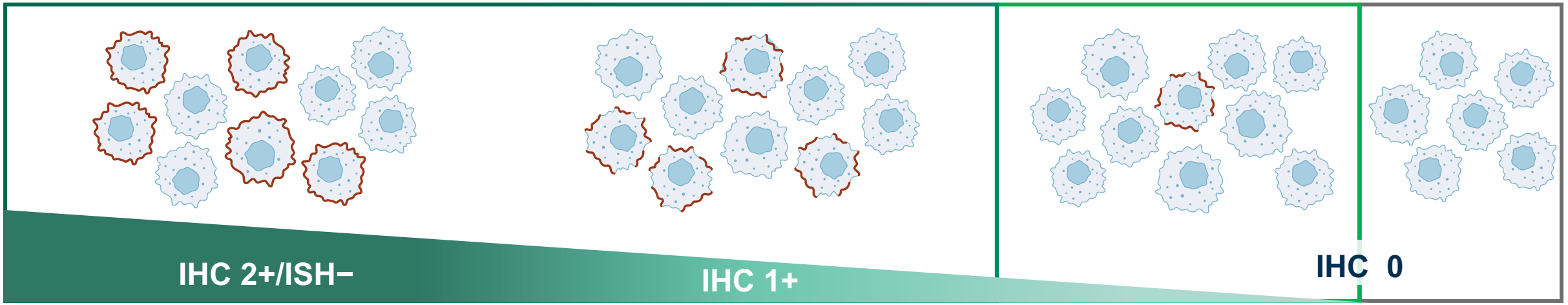
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

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.

What About HER2-ultralow in mTNBC?

HER2-low
~60–65%[2,3]

HER2-ultralow
~20–25%[2–4]



Weak-to-moderate complete membrane staining in >10% tumor cells

Faint, incomplete membrane staining in >10% tumor cells

Faint, incomplete membrane staining in ≤10% tumor cells

Absent / no observable membrane staining

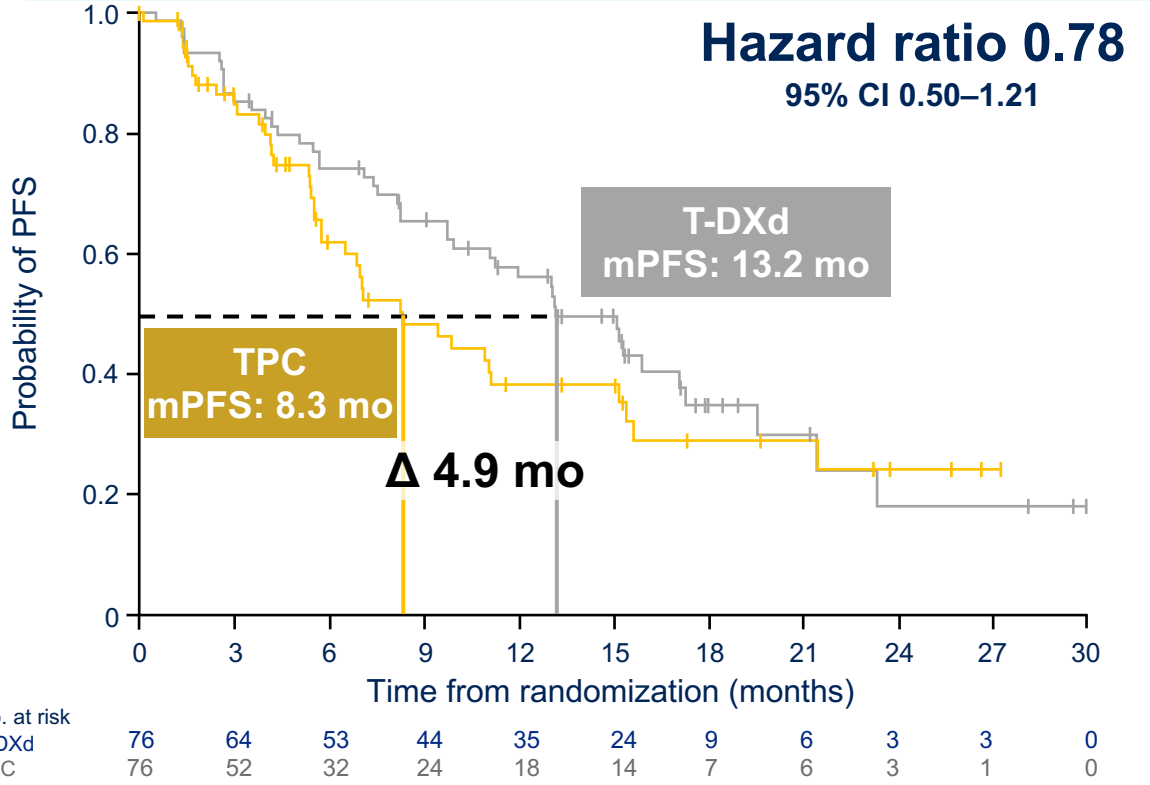
Patients with a HER2-low classification at any stage of the disease may be considered eligible for T-DXd

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry. Curigliano G, et al. Presented at ASCO Breast Annual Meeting 2024, 31 May–4 June. Chicago, IL. Abstract #LBA1000.

DESTINY-Breast06 Demonstrated Benefit for T-DXd in HR+ HER2-Ultralow

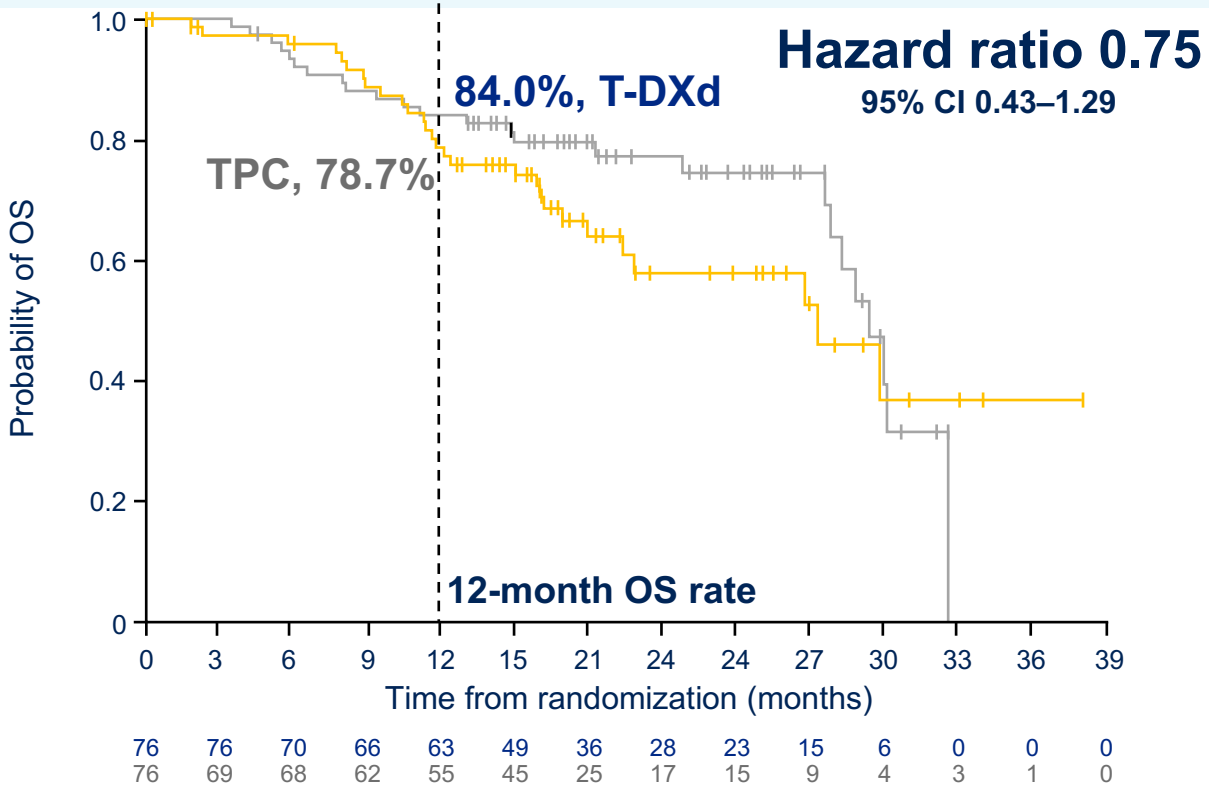
PFS (BICR)

n=152



OS*

n=152



PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

DESTINY-Breast15 Study Design (NCT05950945)

Patient Population

All Patients:

- mBC
- HER2 status
  - IHC 0
  - HER2-low: IHC 1+; IHC 2+/ISH–
- Up to 2 pLOT in metastatic setting
- Inclusion to ensure ethnic diverse population

HR+ (Early Progressors) = Cohort 3

- Recurrent disease <2 years from initiation of adjuvant endocrine therapy **OR**
- Progression within 12 months of completion of adjuvant CDK4/6i
- Progression within the first 12 months of CDK4/6i in the first line metastatic setting

HR–

- 2 pLOT capped at 25% of cohort and only allowed if one of the lines included SG

Cohort 1: HR-/HER2-low mBC (n = 100)

Cohort 2: HR-/HER2 IHC0 mBC (n = 50)

Cohort 3: HR+/HER2-low mBC (n = 50)

Cohort 4: HR+/HER2 IHC0 mBC (n = 50)

Primary Endpoint: TTNT

Key Secondary: rwPFS

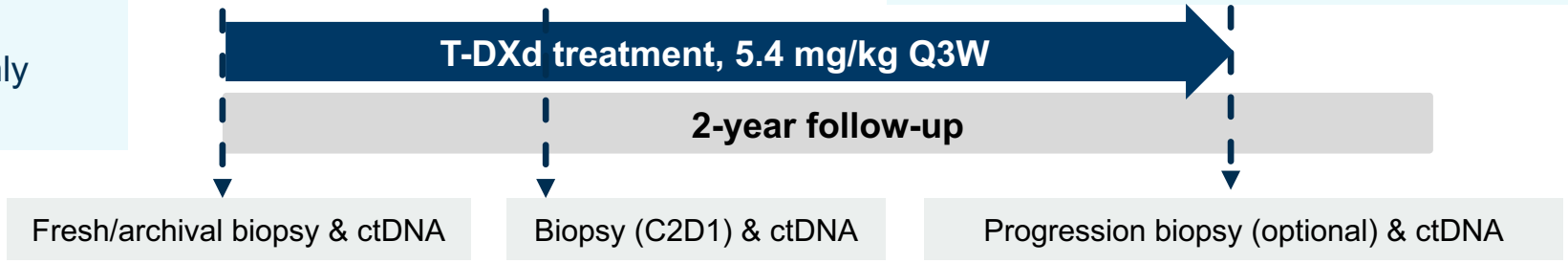
Secondary Endpoints:

- TTD
- QoL/PROs
- Tolerability
- ORR

Exploratory Endpoints: pathology/ translational research plan

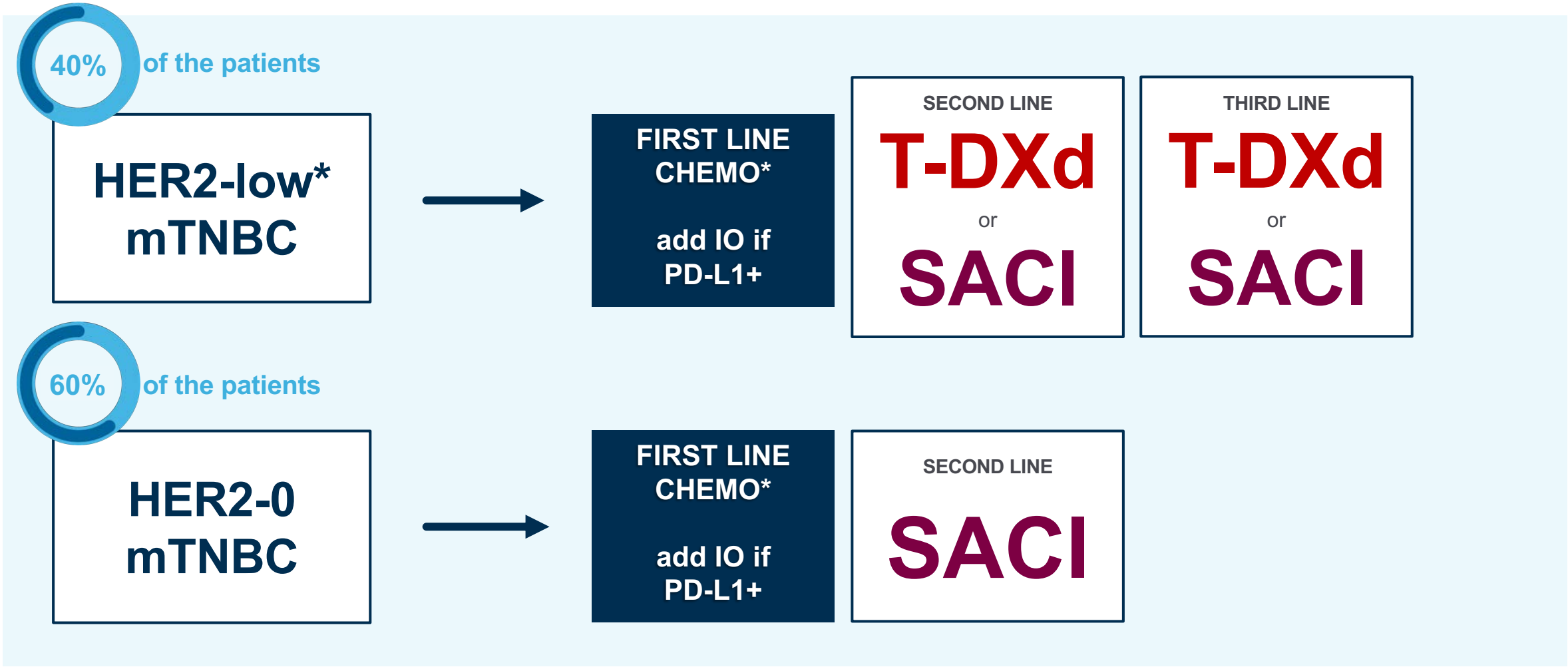
Descriptive stats of primary endpoint for FAS in subgroups:

- Brain mets
- Prior IO use
- Prior sacituzumab govitecan
- Bone metastases only



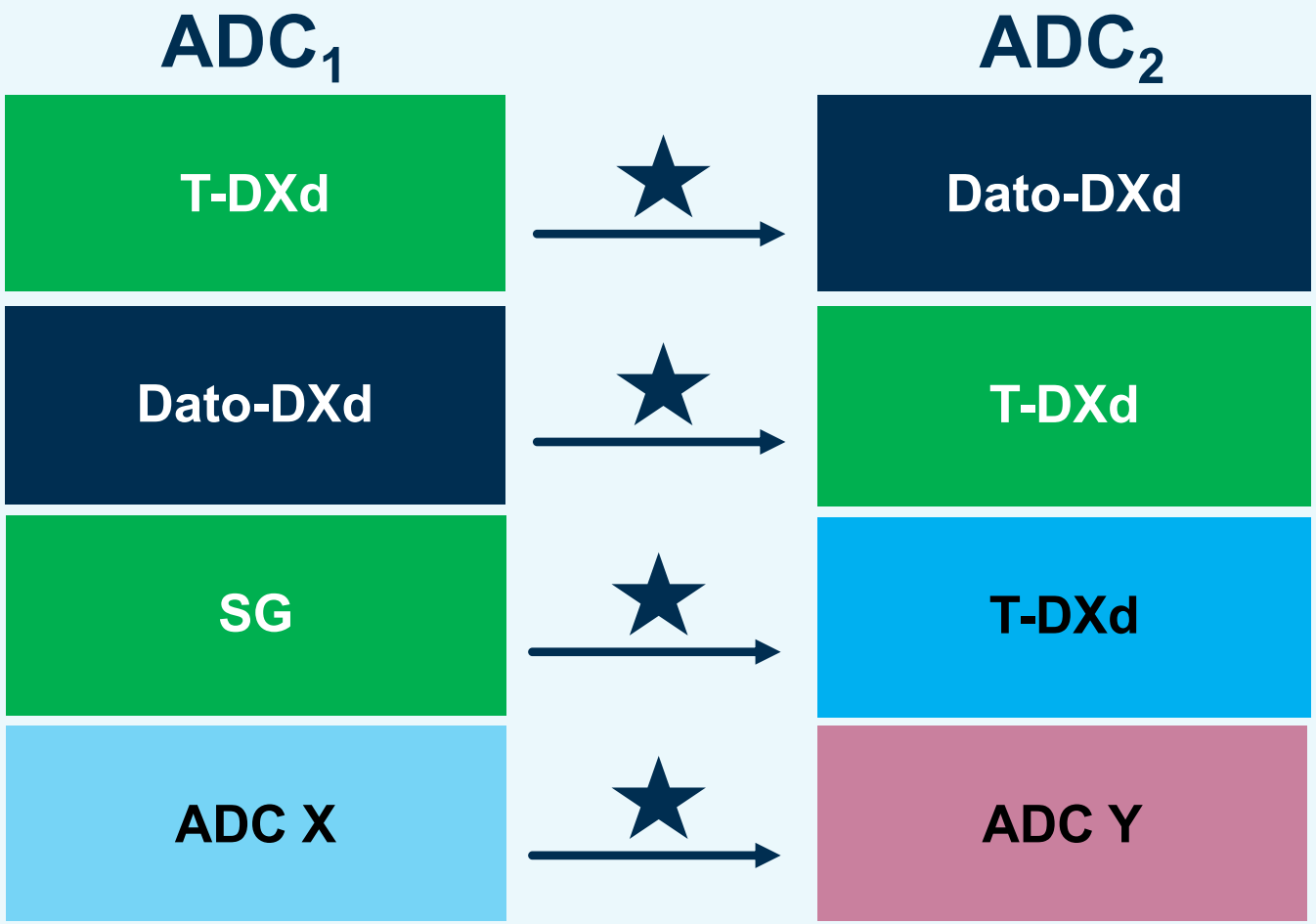
ctDNA, circulating tumor deoxyribonucleic acid; FAS, full analysis set; ISH, in situ hybridization; IO, immuno-oncology; ORR, objective response rate; pLOT, prior line of therapy; PROs, patient-reported outcomes; Q3W, every 3 weeks; QoL, quality of life; rwPFS, real-world progression-free survival; SG, sacituzumab govitecan; TTD, time to treatment discontinuation; TTNT, time to next treatment.

Treatment of mTNBC with ADCs



*PARP inhibitors can be considered in the first through third line setting for BRCAm patients

Critical Question: How will ADCs Work in Sequence?



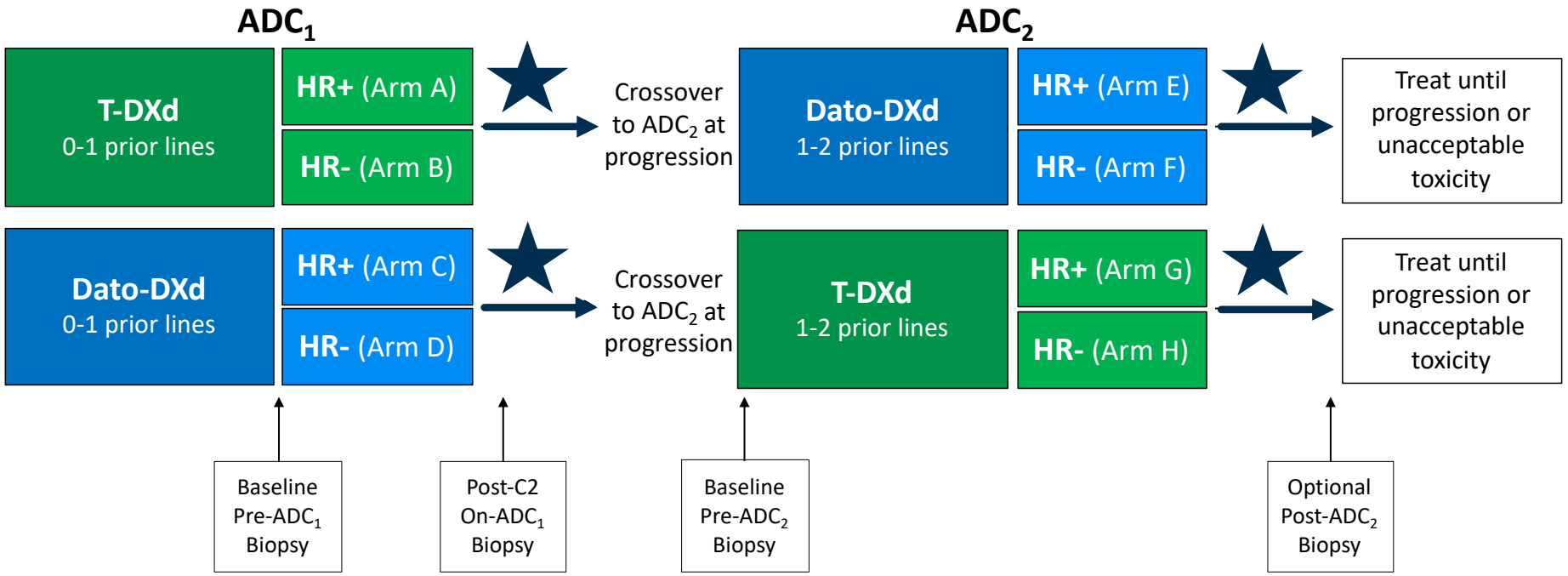
TReatment of ADC-Refractory Breast CancEr with Dato-**DXd** or T-**DXd**: TRADE DXd

Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low breast cancer (any prior primary or metastatic tumor) defined as IHC 1+ or 2+/ISH non-amplified
- Most recent pathology: HER2 IHC 0 or HER2-low
- Measurable disease
- No prior topo-I inhibitor-based therapy

Allocation 1:1 to T-DXd or Dato-DXd as ADC_1

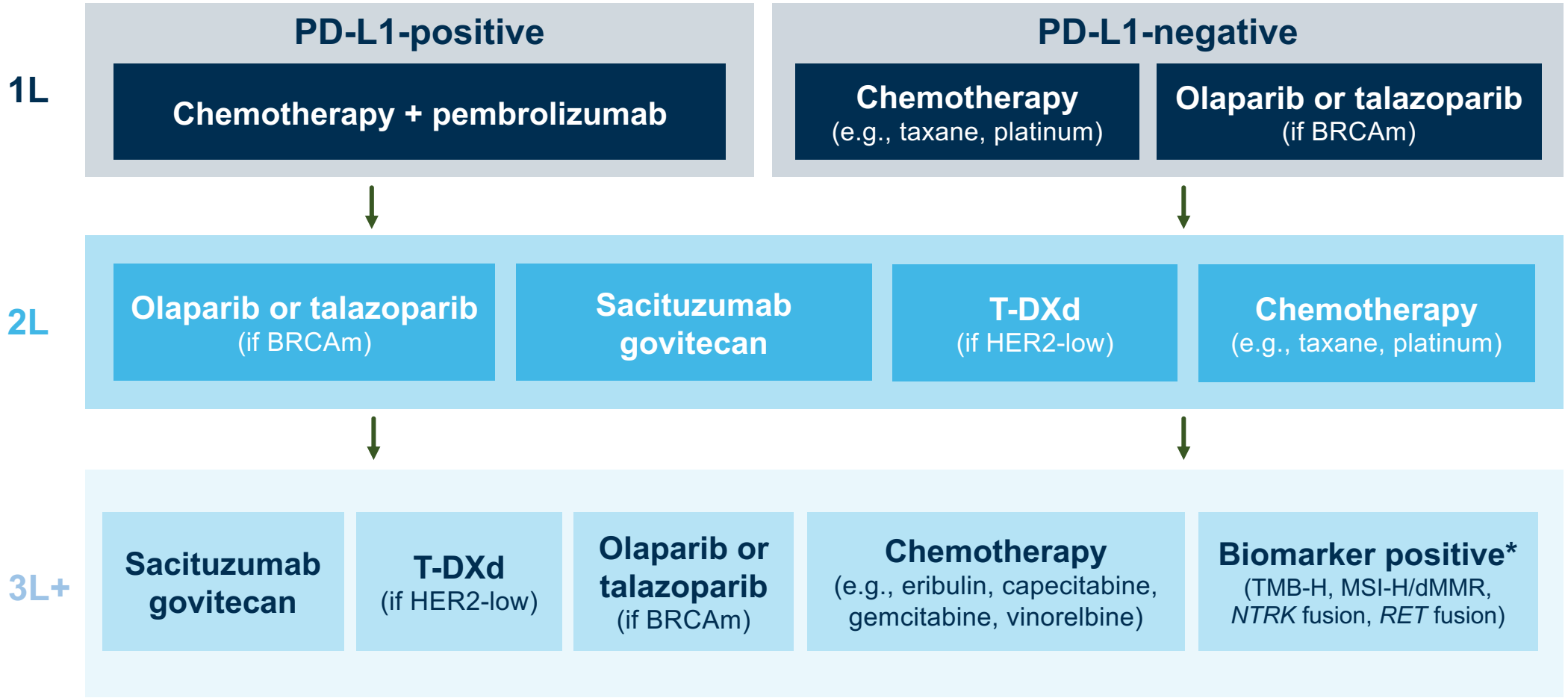
Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR



Tumor assessments + Blood collection q9w

*Patients who received T-DXd/Dato-DXd as ADC_1 off-study allowed to enroll on ADC_2 cohorts.

Treatment Algorithm for Metastatic TNBC



*TMB-H: Pembrolizumab; MSI-H: Pembrolizumab, Dostarlimab; *NTRK* fusion: Larotrectinib, Entrectinib; *RET* fusion: Selpercatinib

Faculty Case Presentation

Case Presentation – Dr Krop

- 56yo insurance saleswoman with hx/o HTN
  - FHx of breast cancer in paternal aunt (41y) and paternal grandmother (55y)

- Screening MMG identifies R breast mass
  - u/s: 1.1 cm spiculated R breast mass, no adenopathy
  - Bx: poorly differentiated Invasive ductal CA, triple negative
  - Found to have BRCA1 frameshift mutation
  - Bilateral mastectomy
    - 1.0 cm Gr3 TNBC, SLNBx: 0/2

- Adjuvant docetaxel/cyclophosphamide (TC) x4

Case Presentation – Dr Krop (Continued)

- Did well for 22 months, then presents with cough x6 weeks
  - CAP CT: two pulmonary nodules, largest 2.8 cm
- Bx of lung nodule – metastatic carcinoma, ER-PR-HER2-
  - PD-L1 CPS negative (1%)
- Started Olaparib
  - Initially had gr 2 nausea
    - Did not tolerate odansetron, metoclopramide, prochlorperazine
    - Did well on olanzapine
  - Cough resolved
  - Restaging CAP CT after 8 weeks demonstrated 70% reduction in lung lesions
- Continued on Olaparib for 9 months until PD

Case Presentation – Dr Krop (Take-Home Message)

- OlympiAD demonstrated superior PFS, ORR, and QOL with Olaparib compared with chemotherapy
  - No significant OS benefit
  - Subgroup analysis suggests OS benefit in patients without prior chemotherapy for MBC
  - Preferred 1st line therapy for PD-L1 negative BRCAmut TNBC

- In patients with PD-L1 positive BRCAmut TNBC, consider use of chemotherapy + pembrolizumab as 1st line therapy given clear OS benefit compared with chemotherapy in this population
  - Olaparib use in 2nd line

Robson et al, NEJM 377:523. 2017 and Annals of Oncology 30:558. 2019

Agenda

Module 1: Optimizing the Care of Patients with HER2-Positive Metastatic Breast Cancer (mBC) – Dr Krop

Module 2: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer – Dr Tolaney

Module 3: Integrating Novel Agents and Approaches into the Management of Endocrine-Resistant Hormone Receptor-Positive mBC – Dr Kalinsky

Module 4: Tolerability Considerations with Approved and Investigational Antibody-Drug Conjugates – Dr O'Shaughnessy

Module 5: Other Important Care Considerations for Patients with mBC – Dr Hamilton

Integrating Novel Agents and Approaches into the Management of Endocrine-Resistant Hormone Receptor (HR)-Positive mBC

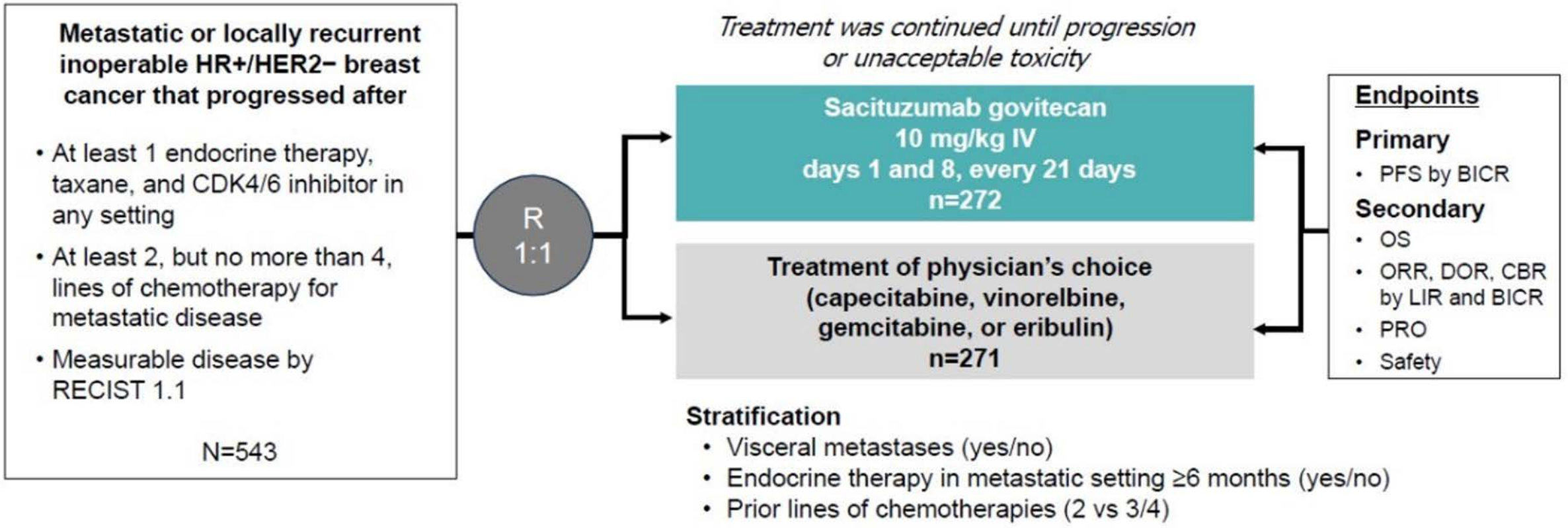
Kevin Kalinsky, MD, MS

Professor of Medicine

Director, Division of Medical Oncology

Louisa and Rand Glenn Family Chair in Breast Cancer Research

Sacituzumab Govitecan vs TPC in HR-Positive/HER2-Negative MBC: *TROPiCS-02*



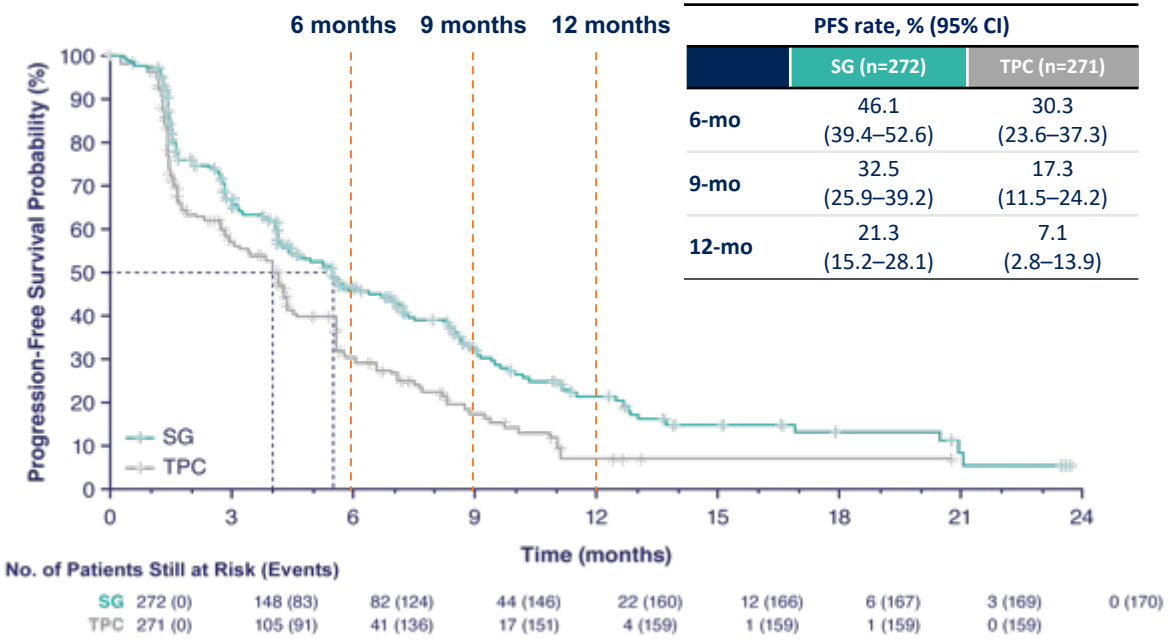
- BICR, blinded independent central review; LIR, local investigator review; IV, intravenous; PRO, patient-reported outcomes; RECIST, Response Evaluation Criteria in Solid Tumors.

Rugo HS, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS5-11.

TROPiCS-02 for HR+/HER2- Disease: PFS & OS in the ITT Population

PFS[1]

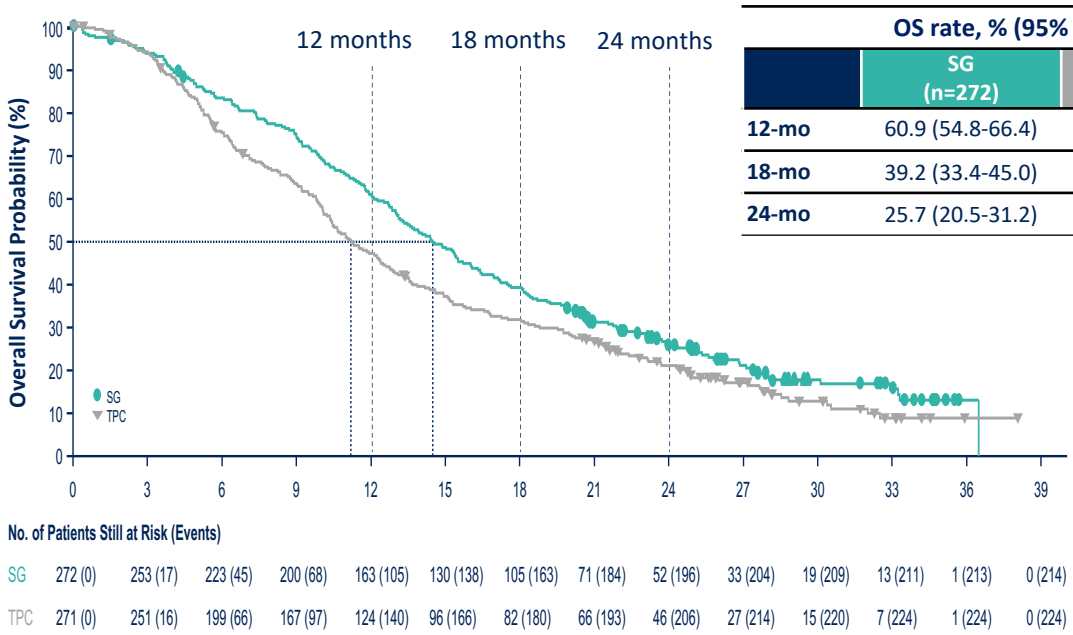
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



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)

OS[2,3]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.5 (13.0–16.0)	11.2 (10.2–12.6)
Stratified HR (95% CI)	**0.79** (0.65–0.95)	
Nominal *P* value	*P*=0.0133	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-mo	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-mo	25.7 (20.5-31.2)	21.1 (16.3-26.3)

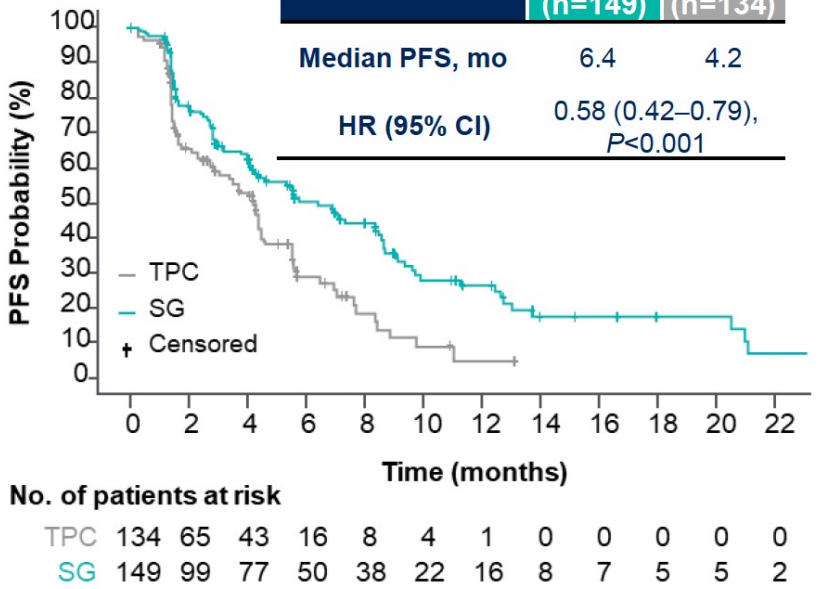
SG demonstrated a statistically significant improvement in PFS and OS vs TPC

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.

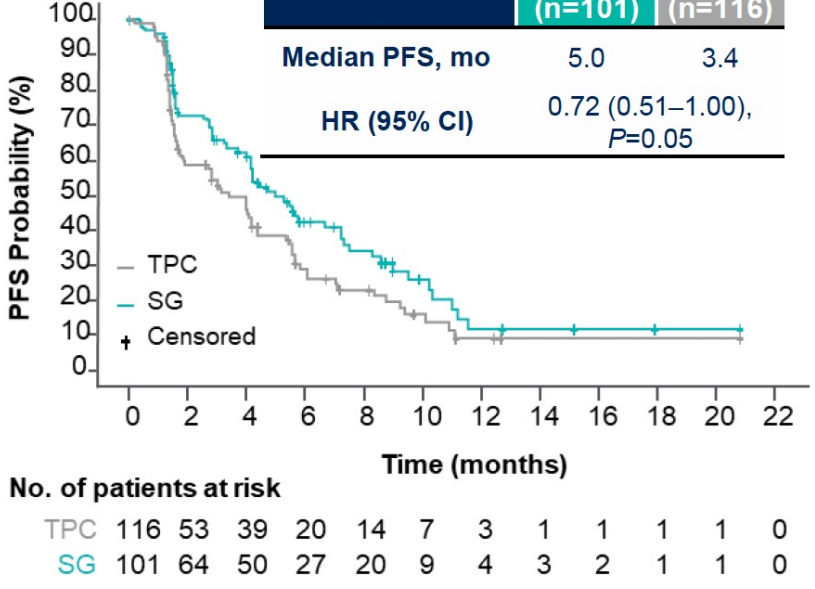
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. *J Clin Oncol. 2022*. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76. 3. Tolaney et al, ASCO Abstract 1003; Rugo et al, Lancet 2023

TROPiCS-02: Activity by HER2 IHC Score

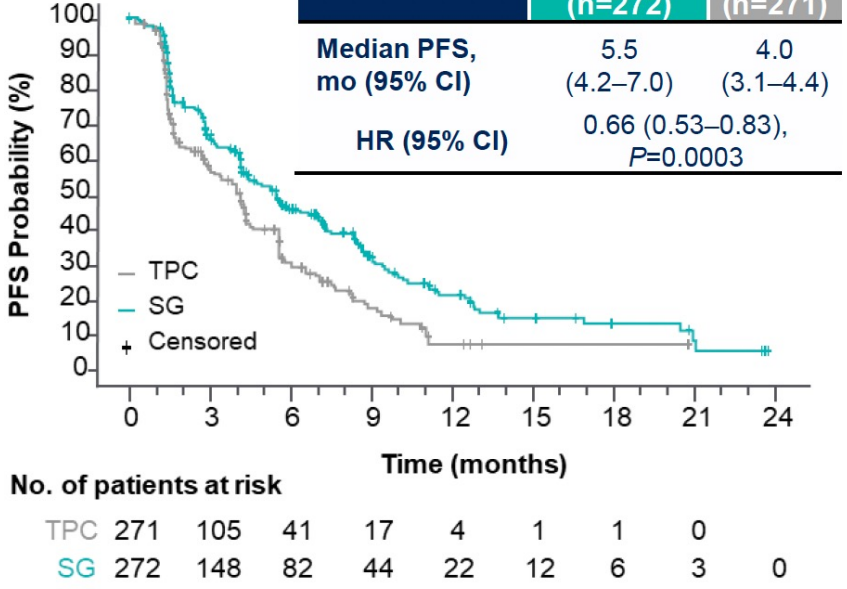
HER2-Low[a]



HER2 IHC0



ITT[1]



- Within the HER2-low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 (HR, 0.57) and 5.6 vs 4.0 (HR, 0.58) months, respectively
- The HR for median PFS in a sensitivity analysis of the HER2-low subgroup (excluding ISH-unverified) was similar (HR, 0.53)

- Schmid P, et al. Presented at: ESMO Congress 2022; September 9-13, 2022; Paris, France. Abstract 214MO.

TROPION-Breast01 (Phase 3): Datopotamab deruxtecan vs chemo for unresectable/inoperable or metastatic HR+, HER2− breast cancer

Key eligibility

- HR+/HER2−[a] breast cancer
- Previously treated with 1–2 lines of chemo (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0/1

R 1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

TPC[b]
(n=367)

Continue until PD, unacceptable toxicity / other discontinuation criteria

Dual primary endpoints[c]:

- PFS by BICR
- OS

Key secondary endpoint:

- ORR
- PFS (investigator assessed)
- Safety

Stratification factors

- Lines of chemo in unresectable/ metastatic setting (1 vs 2)
- Geographical location (US/Canada/ Europe vs ROW)
- Previous CDK4/6 inhibitor (yes vs no)

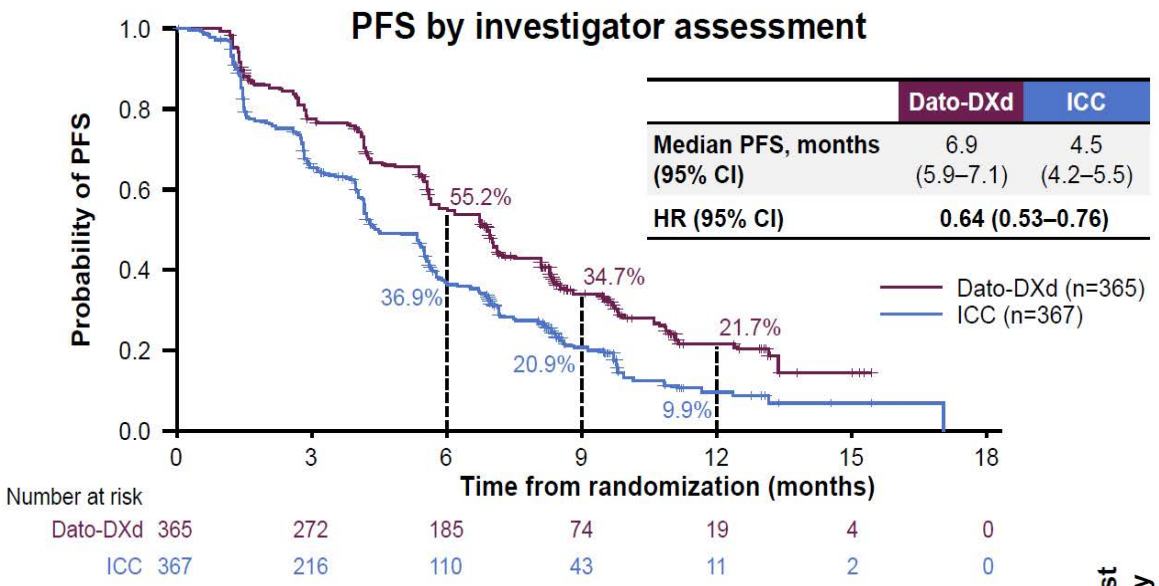
- At data cutoff (July 17, 2023), patients remaining on treatment:
  - Data-DXd, n=93
  - TPC, n=39
- Median follow-up: 10.8 months
- Median one line of prior therapy

aIHC 0/1+/2+; ISH−; bInvestigator's choice of chemotherapy; cBy BICR per RECIST v1.1.
Dato-DXd, datopotamab deruxtecan; TPC, treatment of physician's choice.

Bardia A, et al. SABCS 2023. Abstract GS02-01

TROPION-Breast01: PFS and time to subsequent therapy

PFS by investigator assessment

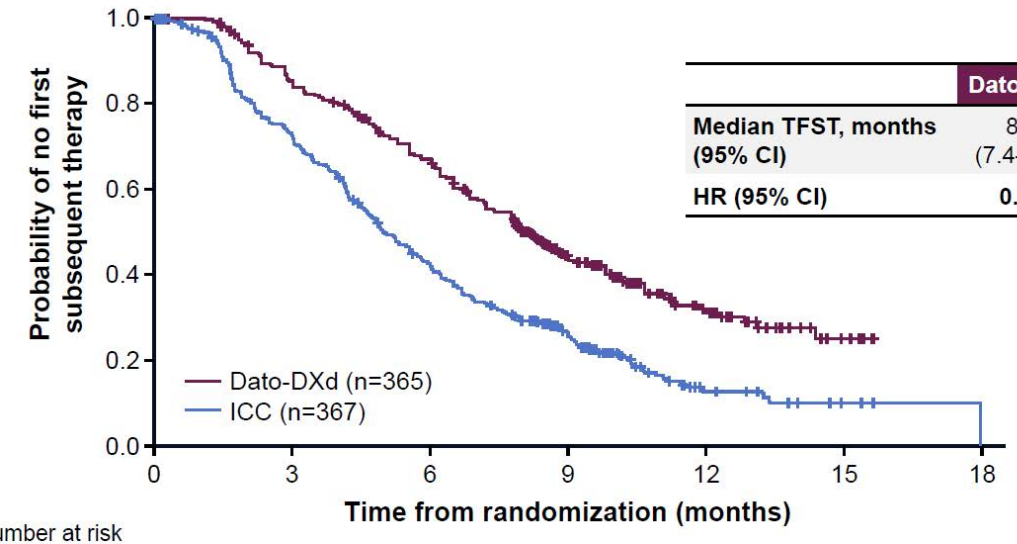


	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	0.64 (0.53–0.76)	

PFS by BICR (primary endpoint)

- Median 6.9 vs 4.9 months
- HR 0.63 (95% CI: 0.52, 0.76)

Time to subsequent therapy



	Dato-DXd	ICC
Median TFST, months (95% CI)	8.2 (7.4–8.9)	5.0 (4.6–5.7)
HR (95% CI)	0.53 (0.45–0.64)	

Bardia A, et al. SABCS 2023. Abstract GS02-01; Bardia A, Jhaveri K, Im SA, et al. *J Clin Oncol*. Published online September 12, 2024.

DESTINY-Breast04: Updated Survival Results of T-DXd in HER2-low Metastatic Breast Cancer

An open-label, multicenter study (NCT03734029)[1-3]

Patients[a]
- HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

N=557

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[d]
- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]
- **PFS by investigator**
- ORR by BICR and investigator
- DOR by BICR
- **Safety**
- Patient-reported outcomes (HR+)[e]

Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

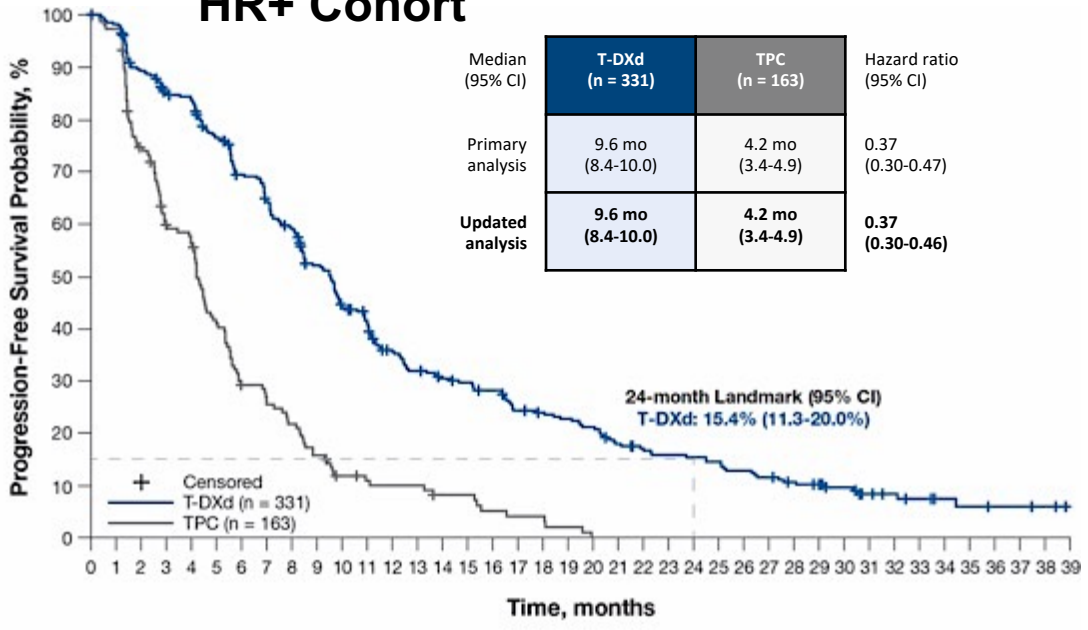
- At the primary analysis (data cutoff, January 11, 2022), median follow-up was 18.4 months
- The primary analysis of PFS was by BICR; this is comparing investigator assessment
- Patient population: Median one line of chemotherapy for MBC, 65-70% prior CDKi, 70% liver mets

Modi et al, NEJM 2022; ESMO 2023

DESTINY-Breast04: Updated Progression Free Survival (Investigator Assessed)

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**



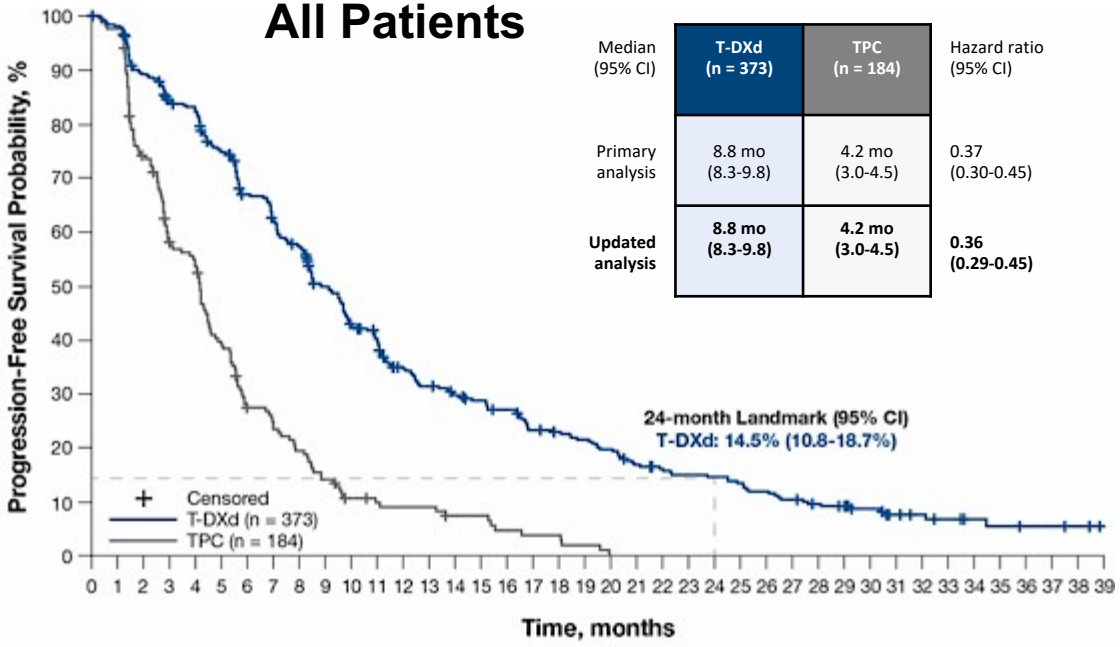
Patients still at risk:

T-DXd (n = 331) 331 323 290 272 247 241 215 198 181 154 129 119 98 88 82 79 74 63 60 57 53 44 40 37 36 34 30 27 23 21 16 11 9 7 5 4 3 3 2 0

TPC (n = 163) 163 143 107 83 78 56 39 34 29 21 14 12 11 11 8 8 5 4 4 2 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**



Patients still at risk:

T-DXd (n = 373) 373 364 327 304 297 267 234 216 198 166 140 130 107 97 90 85 79 67 64 60 55 46 42 39 38 35 31 27 23 21 16 11 9 7 5 4 3 3 2 0

TPC (n = 184) 184 163 121 92 85 61 41 35 29 21 14 12 11 11 8 8 5 4 4 2 0

Primary Analysis (BICR)

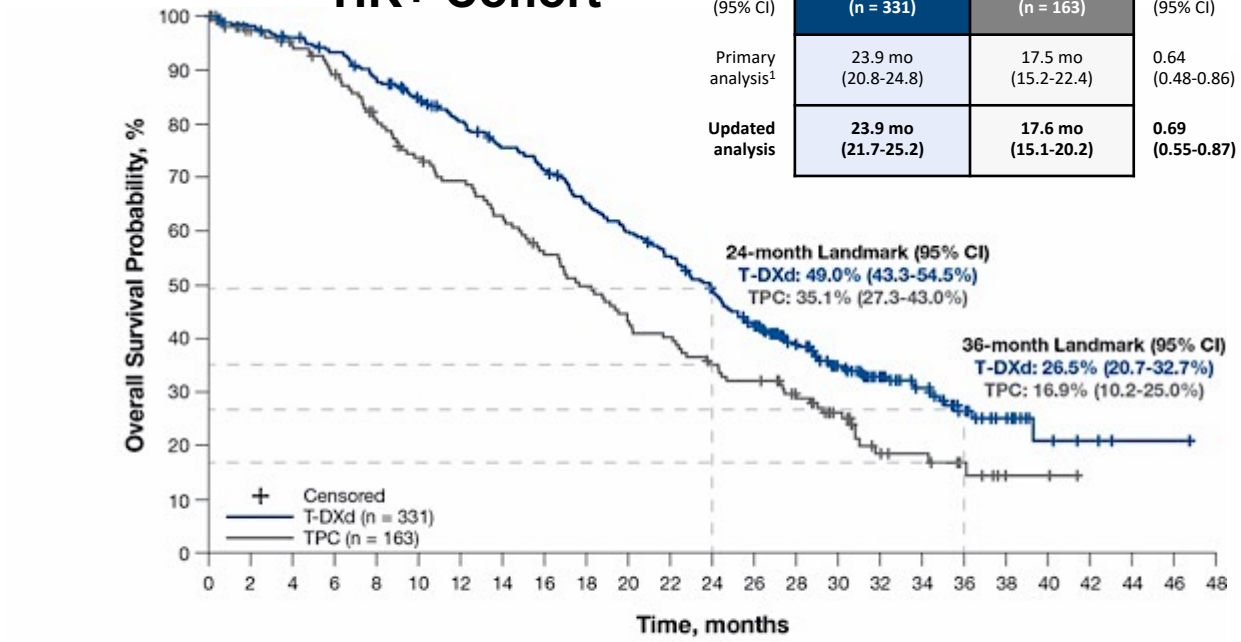
PFS	HR+		HR-		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=40)	TPC (n=18)	T-DXd (n=373)	TPC (n=184)
Median PFS, months	10.1	5.4	8.5	2.9	9.9	5.1
HR (95% CI); *P* value	0.51 (0.40-0.64); <0.0001		0.46 (0.24-0.89)		HR 0.50 (0.40-0.63); <0.0001	

Modi et al, NEJM 2022; ESMO 2023

DESTINY-Breast04: Updated Overall Survival

HR+ Cohort

	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Median (95% CI)			
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



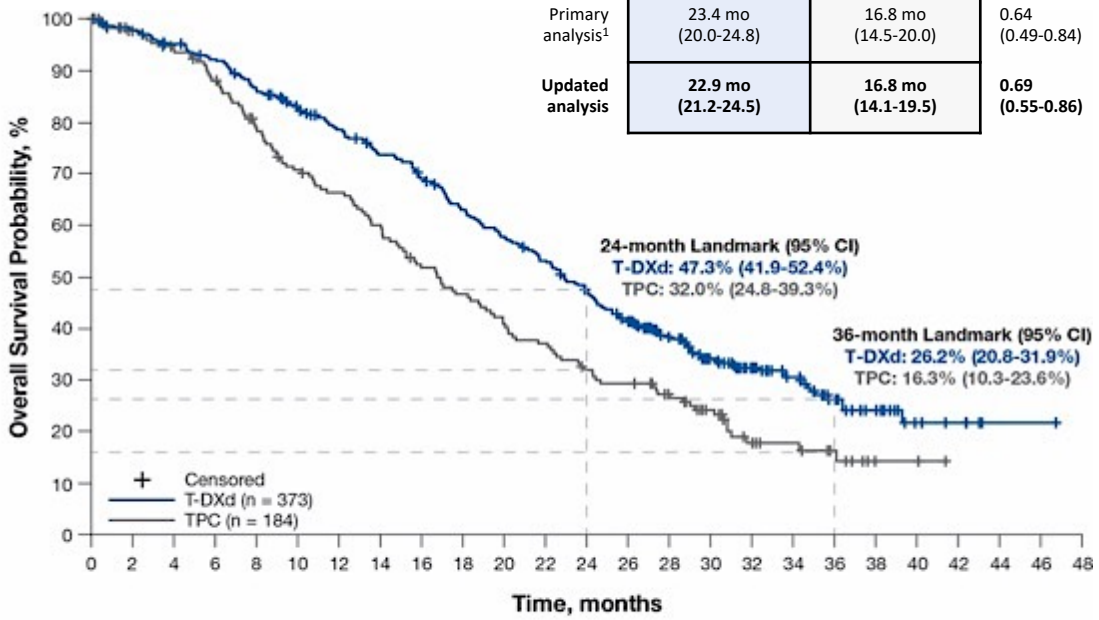
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Median (95% CI)			
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 309 295 286 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

Primary Analysis (BICR)

OS	HR+		HR-		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=40)	TPC (n=18)	T-DXd (n=373)	TPC (n=184)
Median OS, months	23.9	17.5	18.2	8.3	23.4	16.8
HR (95% CI); *P* value	HR 0.64 (0.48-0.86); 0.0028		0.48 (0.24-0.95)		HR 0.64 (0.49-0.84); 0.0010	

Modi et al, NEJM 2022; ESMO 2023

ADC in HR+ HER2- Advanced Breast Cancer

	DESTINY-Breast04*	TROPION-Breast01	TROPiCS-02
Rx	T-DXd vs TPC	Dato-DXd vs TPC	SG vs TPC
Antibody target	HER2	Trop2	Trop2
Chemo target	Topo1 (deruxtecan)	Topo1 (deruxtecan)	Topo1 (SN-38/irinotecan)
Prior chemo in ABC	1-2	1-2	2-4
mPFS	9.6 vs 4.2m (HR 0.37, 0.30-0.46)	6.9 vs 4.9m (HR 0.63, 0.52-0.76)	5.5 vs 4.0m (HR 0.66, 0.53-0.83)
mOS	23.9 vs 17.6m (HR 0.69, 0.55-0.87)	Not Significant**	14.5 vs 11.2m (HR 0.79, 0.65-0.95)
ORR	53% vs 16%	36% vs 23%	21% vs 14%
Toxicity of concern	ILD, cardiac, fatigue	ILD (less), stomatitis	GI, ANC

* Only allowed HER2-low

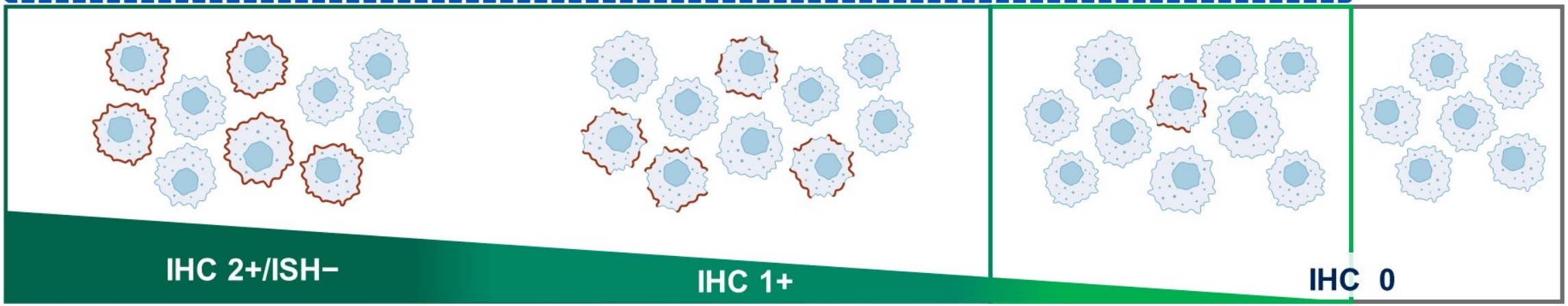
**High-level results from the TROPION-Breast01 Phase III trial of Dato-DXd compared to investigator's choice of chemotherapy did not achieve statistical significance in the final OS analysis in patients with inoperable or metastatic HR-positive, HER2-low or negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer previously treated with endocrine-based therapy and at least one systemic therapy.

https://www.astrazeneca.com/media-centre/press-releases/2024/datopotamab-deruxtecan-final-overall-survival-results-reported-in-patients-with-metastatic-hr-positive-her2-low-or-negative-breast-cancer-in-tropion-breast01-phase-iii-trial.html

Targeting 'low' and 'ultralow' HER2-expressing tumors in mBC

HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])

DESTINY-Breast06 patient population: ~85% of HR+, HER2− mBC



ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

1. Wolff AC, et al. *J Clin Oncol.* 2023;41:3867–3872; 2. Denkert C, et al. *Lancet Oncol.* 2021;22:1151–1161; 3. Chen Z, et al. *Breast Cancer Res Treat.* 2023;202:313–323; 4. Mehta S, et al. *J Clin Oncol.* 2024;42(Suppl. 16):Abstract e13156

Curigliano G et al. ASCO 2024;Abstract LBA1000.

Study design

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC

  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i

    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

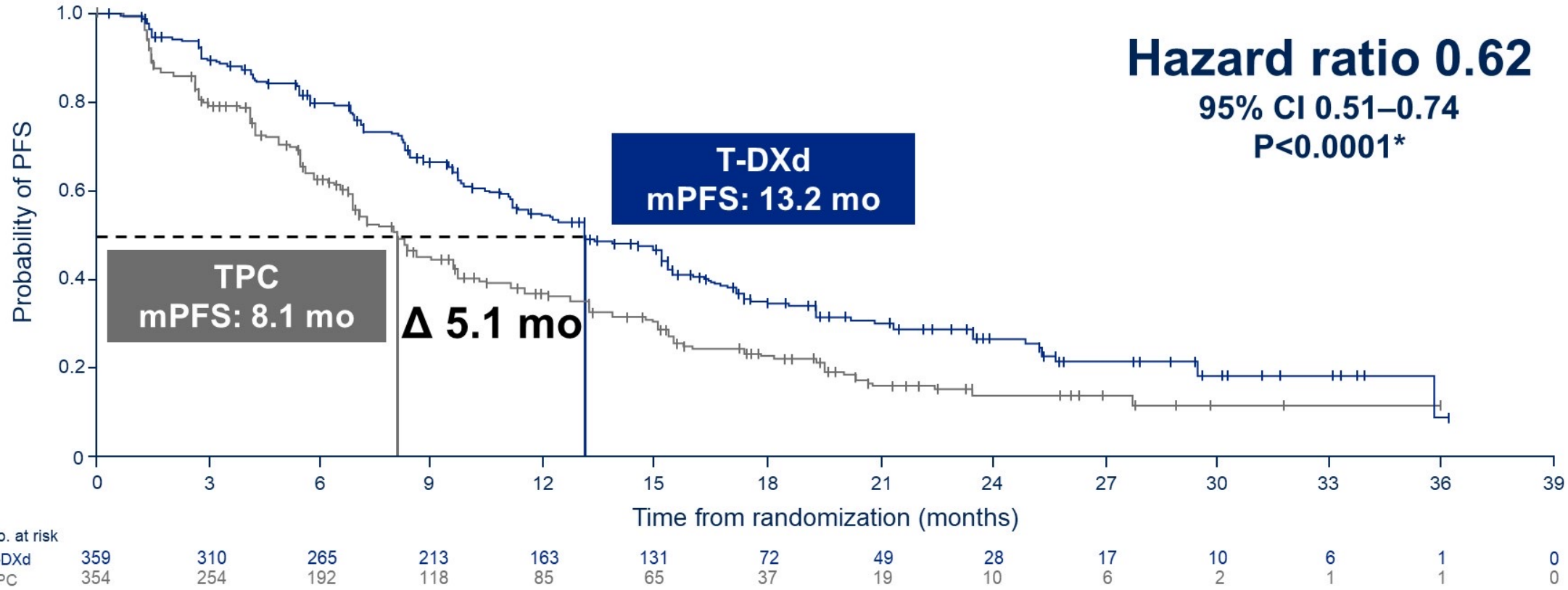
Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

*Study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+); †HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 as determined per central laboratory testing data); ‡to be presented separately
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice
NCT04494425. Updated. April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

Curigliano G et al. ASCO 2024;Abstract LBA1000.

PFS (BICR) in HER2-low: primary endpoint

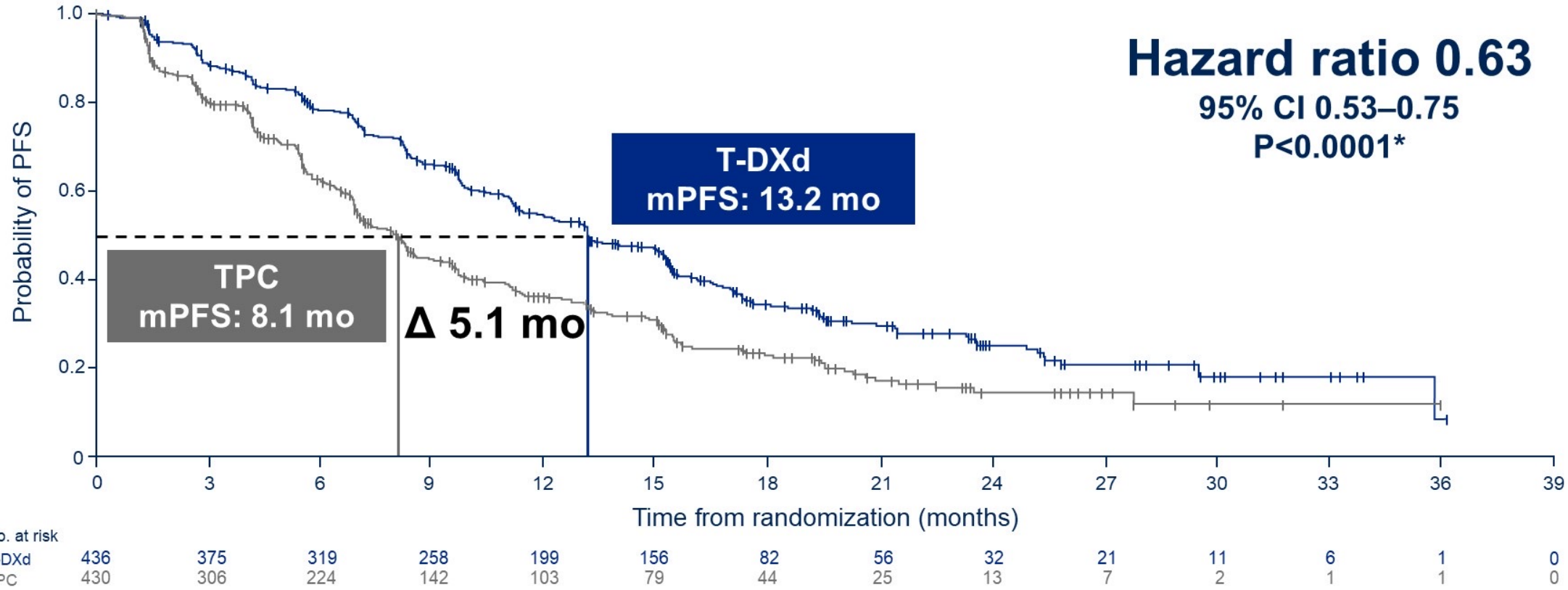


T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano G et al. ASCO 2024;Abstract LBA1000.

PFS (BICR) in ITT: key secondary endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in ITT

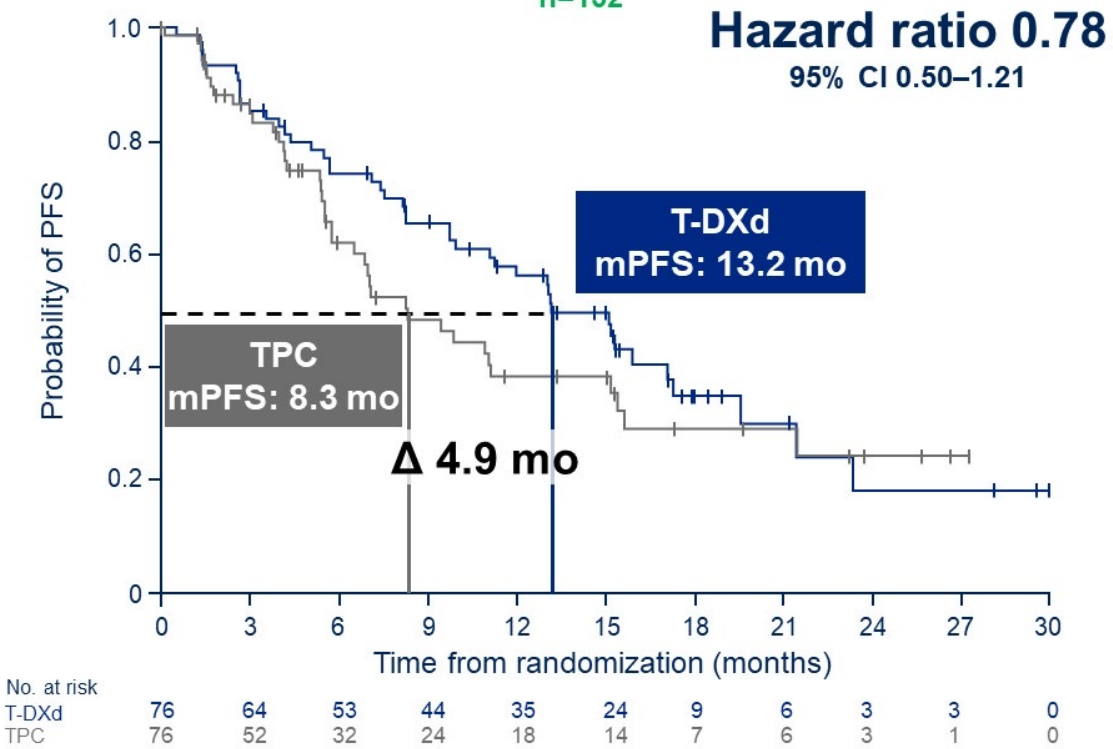
*P-value of <0.015 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; ITT, intent-to-treat; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano G et al. ASCO 2024;Abstract LBA1000.

PFS and OS in HER2-ultralow: prespecified exploratory analyses

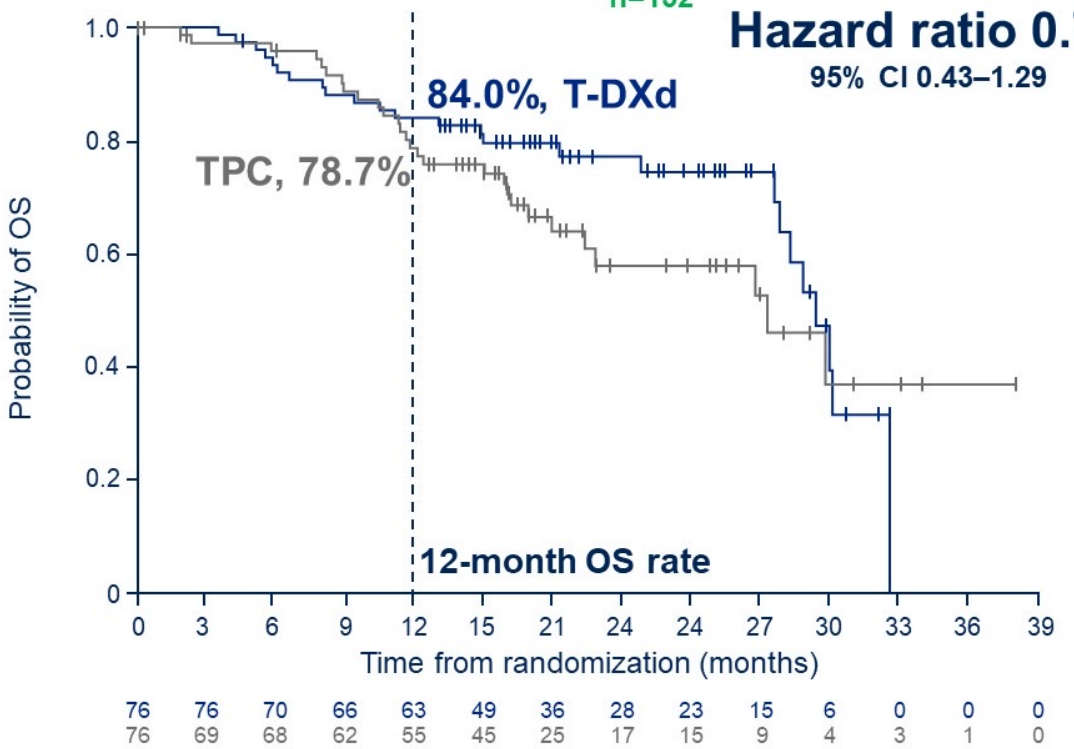
PFS (BICR)

n=152



OS*

n=152

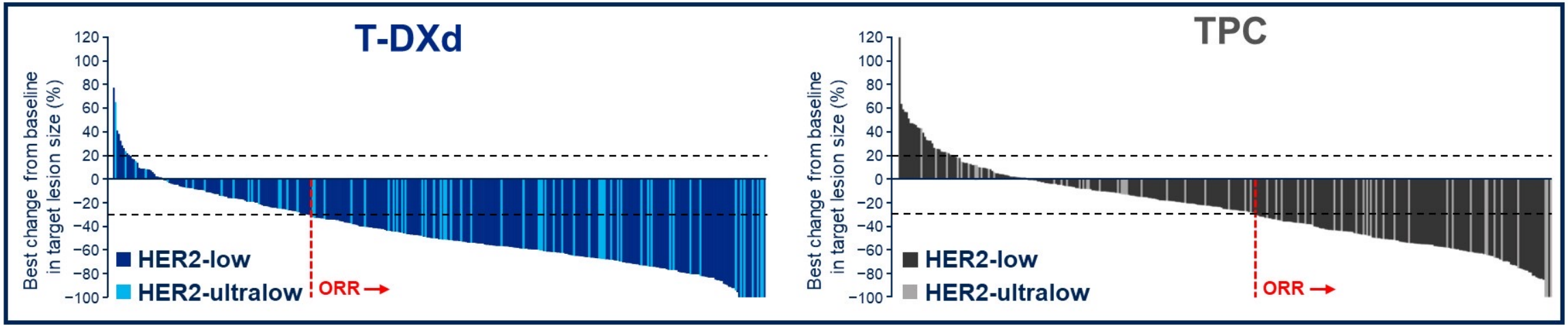


PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano G et al. ASCO 2024;Abstract LBA1000.

Antitumor activity



	HER2-low*		ITT		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Confirmed ORR, n (%)	**203 (56.5)**	**114 (32.2)**	**250 (57.3)**	**134 (31.2)**	**47 (61.8)**	**20 (26.3)**
Best overall response, n (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Median duration of response, mo	14.1	8.6	14.3	8.6	14.3	14.1

ORR based on RECIST v1.1; response required confirmation after 4 weeks
*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined by central laboratory testing data; †defined as complete response + partial response + stable disease at Week 24, by blinded independent central review
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRT, interactive response technology; ITT, intent-to-treat; mo, months; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

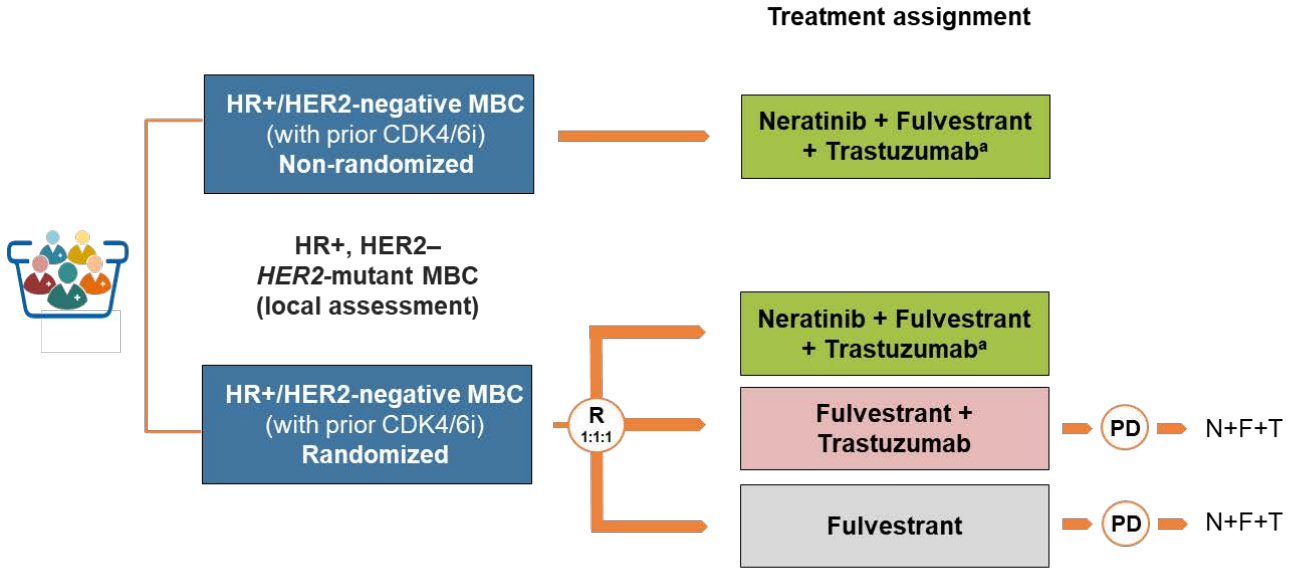
Curigliano G et al. ASCO 2024;Abstract LBA1000.

HER2 Mutation: Combinations needed for improved efficacy and durability

SUMMIT (NCT01953926): ER+ HER2- *ERBB2* mut Cohort

***HER2* mutation: 8% ER+ MBC**

15%: met ILC



[a]Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter

***HER2*-mutant MBC**

Primary endpoint

- Confirmed objective response rate (ORR; RECIST v1.1, centrally assessed)

Secondary endpoints

- Confirmed ORR (investigator-assessed)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety and PROs

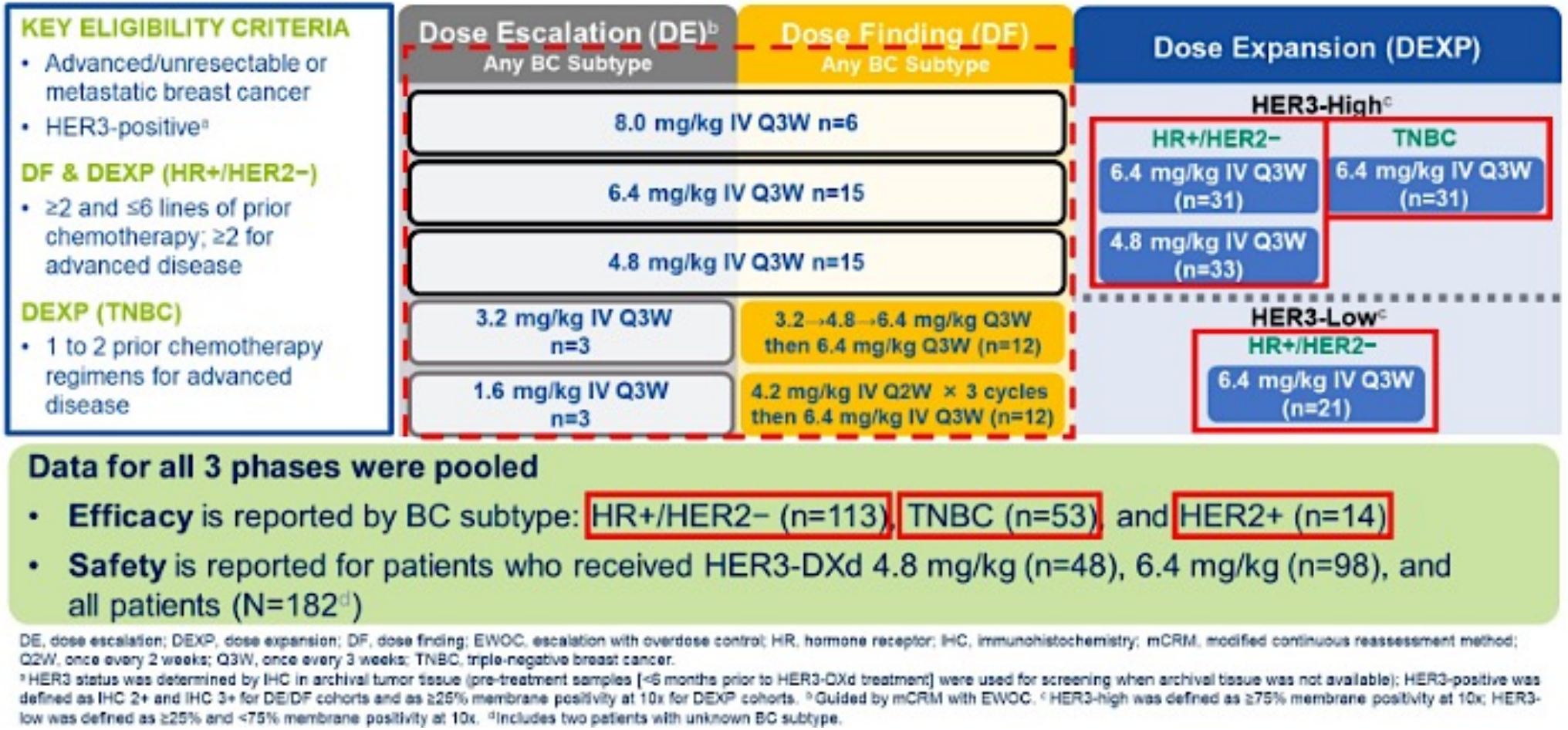
Treatment Regimen	ORR	PFS (months)	DOR (months)
Neratinib (n=23)	17%	3.6	6.5
Neratinib + Fulvestrant (n=47)	**30%**	**5.4**	**9.2**
Neratinib + Fulvestrant +Trastuzumab (n=57)	**39%**	**8.3**	**14.4**

NCCN endorsed (Category 2b)

Addition of T to N prolongs suppression of HER3 phosphorylation in HR+, HER2-negative, *HER2*-mutant breast cancer cell line model

Razavi et al Cancer cell 2018; Jhaveri et al SABCS 2021; Jhaveri et al ASCO 2022; Jhaveri Ann of Onc 2023

Phase 1/2 Trial in HER3-expressing MBC



Data for all 3 phases were pooled

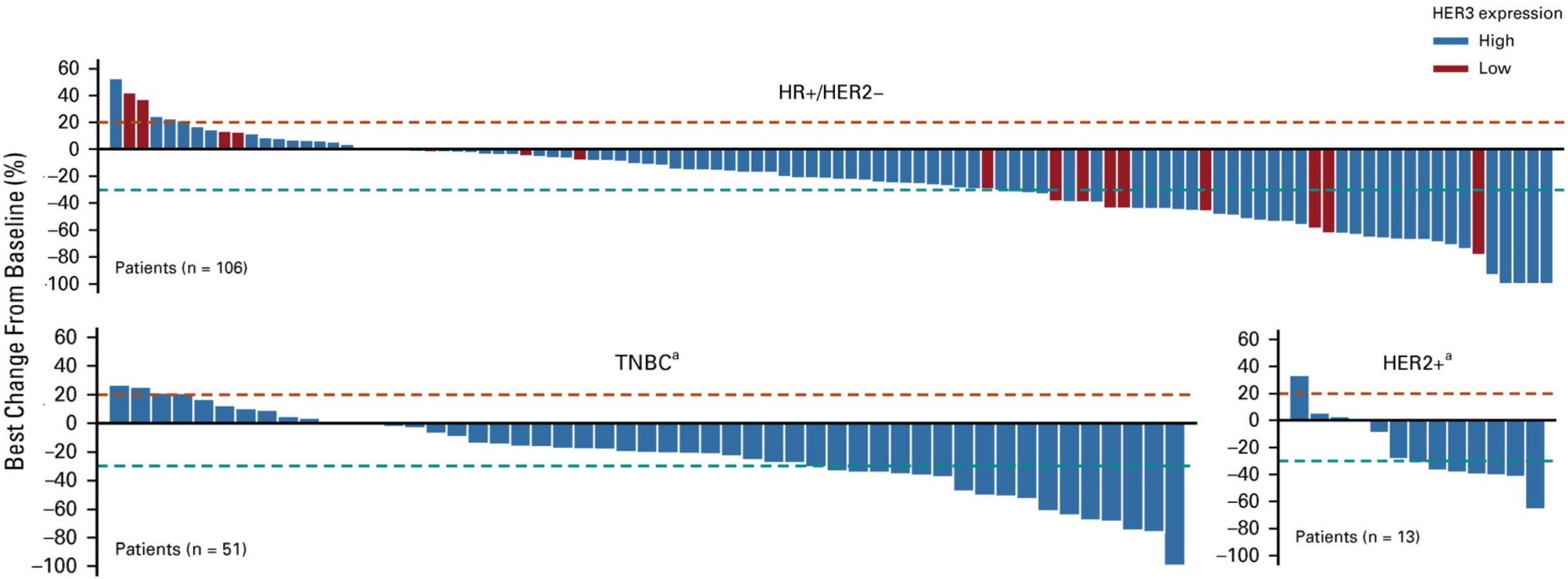
- **Efficacy** is reported by BC subtype: HR+/HER2− (n=113), TNBC (n=53) and HER2+ (n=14)
- **Safety** is reported for patients who received HER3-DXd 4.8 mg/kg (n=48), 6.4 mg/kg (n=98), and all patients (N=182[d])

DE, dose escalation; DEXP, dose expansion; DF, dose finding; EWOC, escalation with overdose control; HR, hormone receptor; IHC, immunohistochemistry; mCRM, modified continuous reassessment method; Q2W, once every 2 weeks; Q3W, once every 3 weeks; TNBC, triple-negative breast cancer.

[a] HER3 status was determined by IHC in archival tumor tissue (pre-treatment samples [<6 months prior to HER3-DXd treatment] were used for screening when archival tissue was not available); HER3-positive was defined as IHC 2+ and IHC 3+ for DE/DF cohorts and as ≥25% membrane positivity at 10x for DEXP cohorts. [b] Guided by mCRM with EWOC. [c] HER3-high was defined as ≥75% membrane positivity at 10x; HER3-low was defined as ≥25% and <75% membrane positivity at 10x. [d] Includes two patients with unknown BC subtype.

Krop I et al. ASCO 2022. Abstract 1002.

Patritumab Deruxtecan: Response



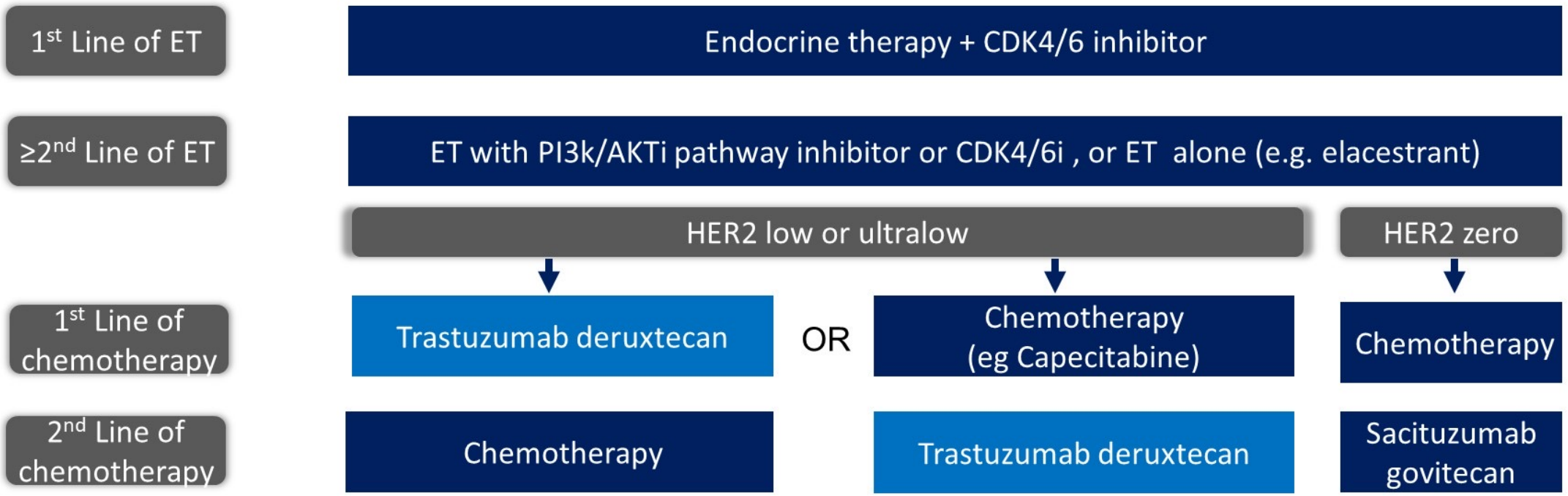
Krop IE et al. *J Clin Oncol* 2023;41(36):5550-5560.

Patritumab Deruxtecan: Efficacy Outcomes

Outcome (BICR per RECIST 1.1)	HR+/HER2− (n = 113) HER3-High[a] and HER3-Low	TNBC (n = 53) HER3-High[a]	HER2+ (n = 14) HER3-High[a]
Confirmed ORR (95% CI), %[b]	30.1 (21.8 to 39.4)	22.6 (12.3 to 36.2)	42.9 (17.7 to 71.1)
Best overall response, %[c]			
PR	30.1	22.6	42.9
SD	50.4	56.6	50.0
PD	11.5	17.0	7.1
NE	8.0	3.8	0
DCR (95% CI), %	80.5 (72.0 to 87.4)	79.2 (65.9 to 89.2)	92.9 (66.1 to 99.8)
CBR (95% CI), %	43.4 (34.1 to 53.0)	35.8 (23.1 to 50.2)	50.0 (23.0 to 77.0)
DOR, median (95% CI), months	7.2 (5.3 to NE)	5.9 (3.0 to 8.4)	8.3 (2.8 to 26.4)
PFS, median (95% CI), months	7.4 (4.7 to 8.4)	5.5 (3.9 to 6.8)	11.0 (4.4 to 16.4)
Six-month PFS rate (95% CI), %	53.5 (43.4 to 62.6)	38.2 (24.2 to 52.0)	51.6 (22.1 to 74.8)
OS, median (95% CI), months	14.6 (11.3 to 19.5)	14.6 (11.2 to 17.2)	19.5 (12.2 to NE)

Krop IE et al. *J Clin Oncol* 2023;41(36):5550-5560.

Approach to therapy for metastatic hormone receptor positive breast cancer



Faculty Case Presentations

Case Presentation – Dr Tolaney

59-year-old woman who had a prior stage 2 ER+ PR+ HER2 0 breast cancer 7 years ago and developed disease recurrence while on letrozole

- Presented with right arm pain and back pain, and imaging revealed bone metastases involving her spine and R humerus, pulmonary and liver metastases
- Biopsy of her liver demonstrated ER+ PR+ HER2 0 breast cancer
- Initiated therapy with fulvestrant + palbociclib
- Progressed 5 months later with increasing liver metastases, new bone metastases, and enlarged retroperitoneal adenopathy and evidence of mild lymphangitic disease in lungs; LFTs slightly elevated and some dyspnea on exertion
- NGS found no *ESR1* or *PI3K/AKT/PTEN* alterations
- A repeat liver biopsy was performed, ER+ PR+ HER2 ultralow
- Initiated therapy with T-DXd
- Improvement in LFTs and dyspnea within one cycle of therapy, and restaging at 6 weeks with improvement in disease

Case Presentation – Dr Kalinsky

2006: h/o stage III (T3N2aM0) ER+ PR+ Her2 – IDC of R breast treated with neoadjuvant chemo followed by R MRM 4/2006, then ovarian function with Leuprolide and Tamoxifen

Surg path – residual 3.5 cm tumor with LVI and metastatic disease to 8/11 R axillary LN. s/p postmastectomy XRT

Ovarian ablation + Leuprolide, treated with 5 yrs Tamoxifen until 2011

Case Presentation – Dr Kalinsky (Continued)

12/2014: Pt developed HA, dizziness, visual changes. MRI brain 12/10/2014 showed a 3.3 cm R cerebellar mass.

12/11/14: Suboccipital with mass excision. Path – met adenocarcinoma c/w mammary origin ER 98%, PR 99%, Her2 1+. SRS to cavity
Leuprolide + Anastrozole started 1/21/2015. Anastrozole alone continued after she underwent BSO in 11/2015.

9/2020: Progression of disease. Pt declined CDK4/6 initiation and opted for Exemestane alone

6/2021: Two new hepatic lesions on CT imaging, recommended discontinuation of Exemestane alone and initiation of Palbociclib + Letrozole

6/7/21-12/21: Palbociclib + Letrozole

Case Presentation – Dr Kalinsky (Continued)

1/5/22: Weekly paclitaxel due to rapid progression in liver. Disease progression

7/28/22: T-DXd initiated for HER2-low disease. Bilirubin 11. Climbed to 20. Then normal after 3 cycles

3/2023: CT CAP showed disease progression in the liver. Changed to carbo/gem and rapidly progressed and died from disease

Case Presentation – Dr Hamilton

- 62 yr old female who presents with back pain and imaging suggests lytic bone lesions.
- Biopsy reveals adenocarcinoma c/w breast primary, ER 85, PR 35, HER-2 2+ IHC, FISH nonamplified
- Staging reveals bone lesions and several 1 cm liver lesions
- Receives 1L palbociclib + letrozole
- Patient's disease responds to 1L treatment for 18 months and then progresses w/ new liver lesions
- Next gen sequencing reveals a HER2 mutation and a p53 mutation
- Patient was treated with neratinib + fulvestrant + trastuzumab on a clinical trial for 6 months and then experienced disease progression
- Patient discussion: Clinical trial with novel HER2 targeting agents or T-DXd

Agenda

Module 1: Optimizing the Care of Patients with HER2-Positive Metastatic Breast Cancer (mBC) – Dr Krop

Module 2: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer – Dr Tolaney

Module 3: Integrating Novel Agents and Approaches into the Management of Endocrine-Resistant Hormone Receptor-Positive mBC – Dr Kalinsky

Module 4: Tolerability Considerations with Approved and Investigational Antibody-Drug Conjugates – Dr O'Shaughnessy

Module 5: Other Important Care Considerations for Patients with mBC – Dr Hamilton

RTP RESEARCH TO PRACTICE

Tolerability Considerations with Approved and Investigational Antibody-Drug Conjugates (ADCs)

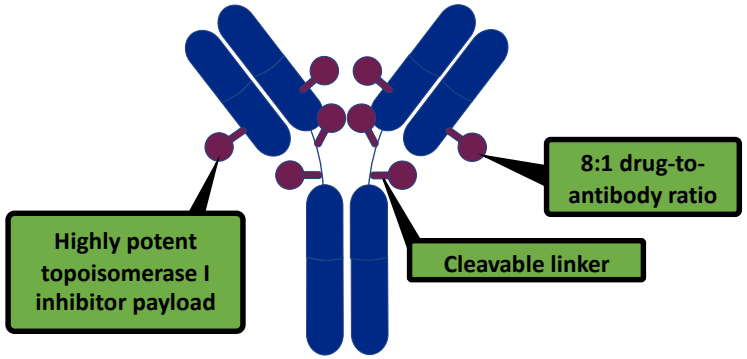
Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Texas Oncology
Sarah Cannon Research Institute
Dallas TX

Slide Credits, Hope Rugo, MD

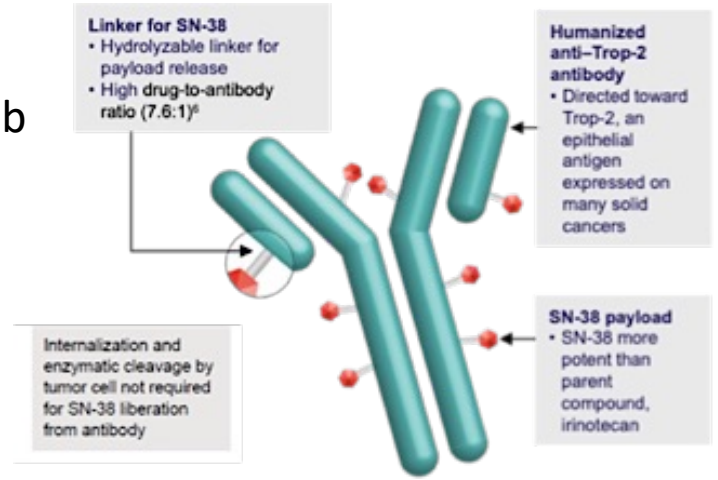
Safety of ADCs for Breast Cancer: Challenges

- Marked variations in adverse events despite
  - Similar payload MOA
  - Similar target of the toxin
- Toxicity not apparently related to drug to antibody ratio

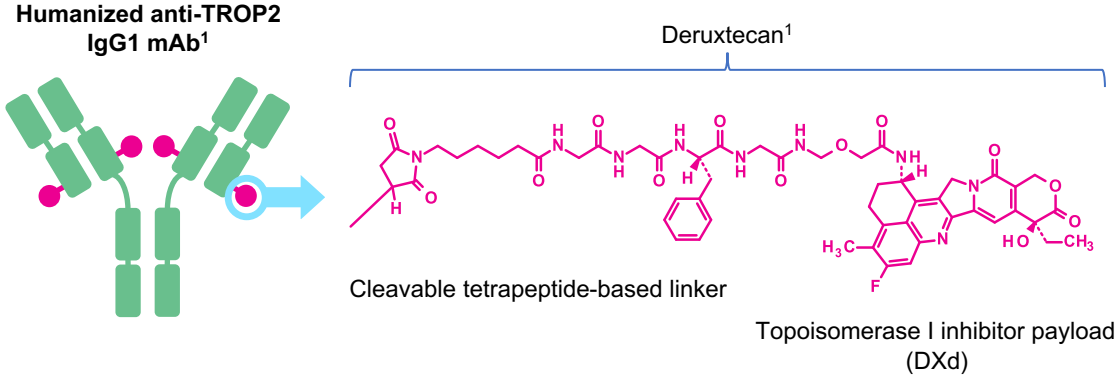
T-DXd



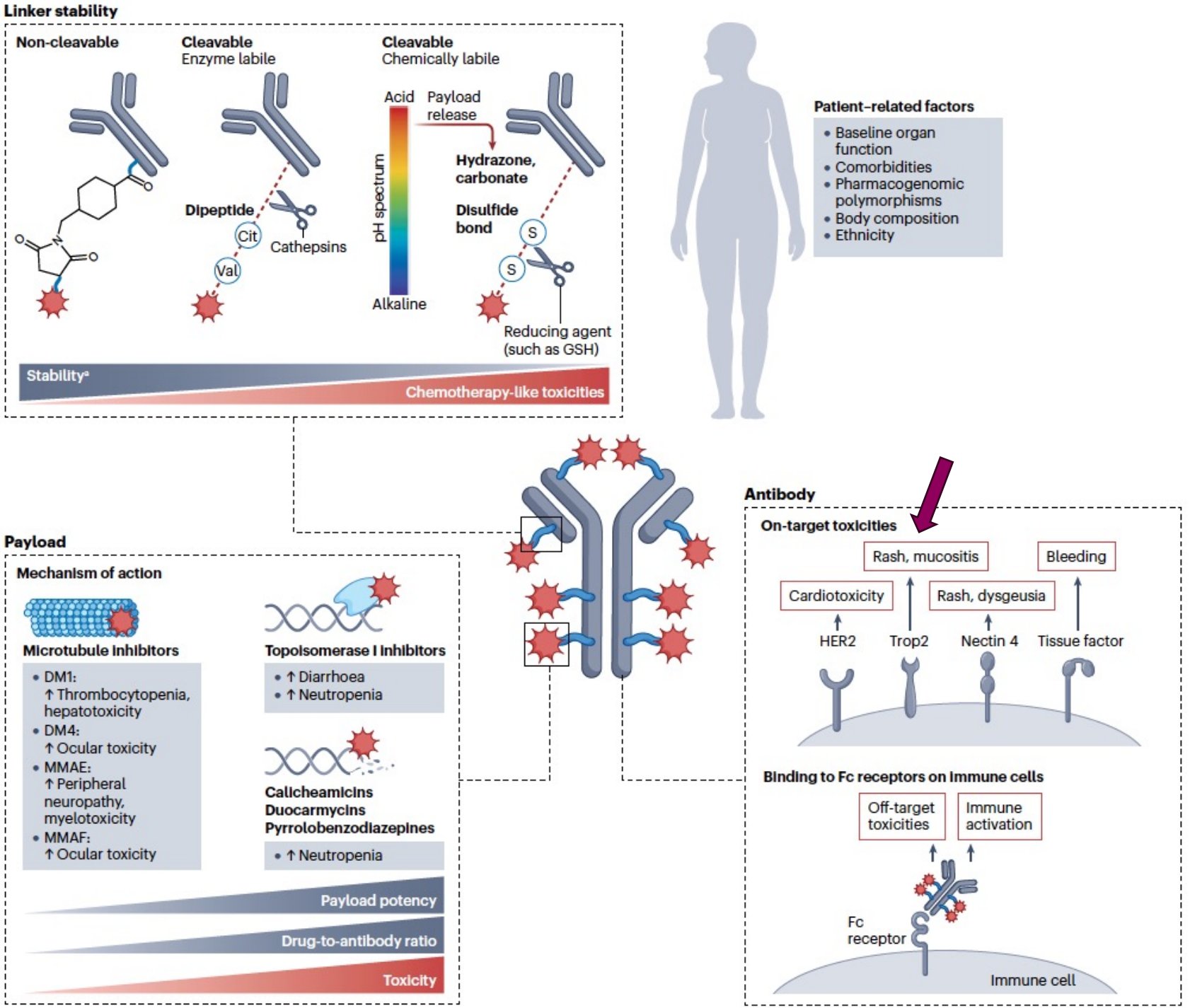
Sacituzumab govitecan



Datopotamab deruxtecan

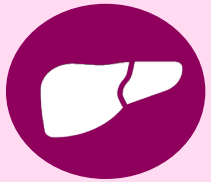


The molecular target impacts ‘On-Target’ toxicities – but the same target can confer different toxicities



Tarantino P, et al. *Nature Rev Clin Oncol.* 2023;20:558–576.

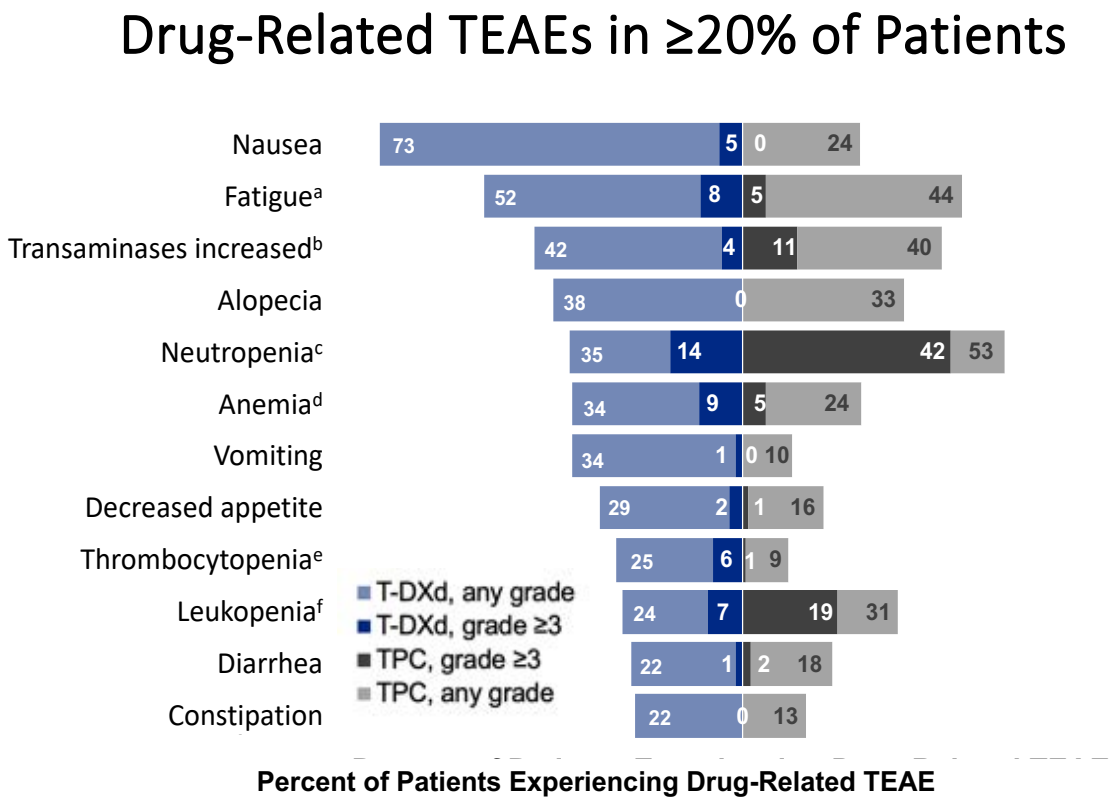
Each ADC has its own specific safety profile[1–4]

T-DM1	T-DXd	SG	Dato-DXd
 Thrombocytopenia	 Nausea and vomiting	 Neutropenia	 Nausea and vomiting
 Elevated liver enzymes	 ILD/pneumonitis	 Diarrhea	 Stomatitis
No alopecia	Moderate alopecia	Significant alopecia	Significant alopecia

ADC=antibody-drug conjugate; AE=adverse event; Dato-DXd=datopotamab deruxtecan; ILD=interstitial lung disease; SG=sacituzumab govitecan; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan.

1. Hurvitz SA, et al. Presented at SABCS 2022; December 6th–10th, 2022. San Antonio, TX, USA; abstract #GS2-02; 2. Modi S, et al. *N Engl J Med*. 2022;387(1):9–20; 3. Rugo H, et al. Presented at SABCS 2022; 6–10 December. San Antonio, TX. Abstract #GS1-11; 4. Meric-Bernstam F, et al. Presented at SABCS Annual Meeting 2022. 6–10 December. San Antonio, TX. Abstract #PD13-08.

Trastuzumab deruxtecan: DESTINY-Breast04



- Most common TEAEs associated with treatment discontinuation
  - T-DXd:10.2%, ILD/pneumonitis
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAEs associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue
  - TPC: 10.5% neutropenia
- Total on-treatment deaths
  - T-DXd: 3.8%; TPC: 4.7%
- Higher rates of drug discontinuation due to TEAEs and ILD in those >65 years

Modi S et al. N Engl J Med 2022;387:9-20
Modi S et al. ESMO 2023; Abstract 3760

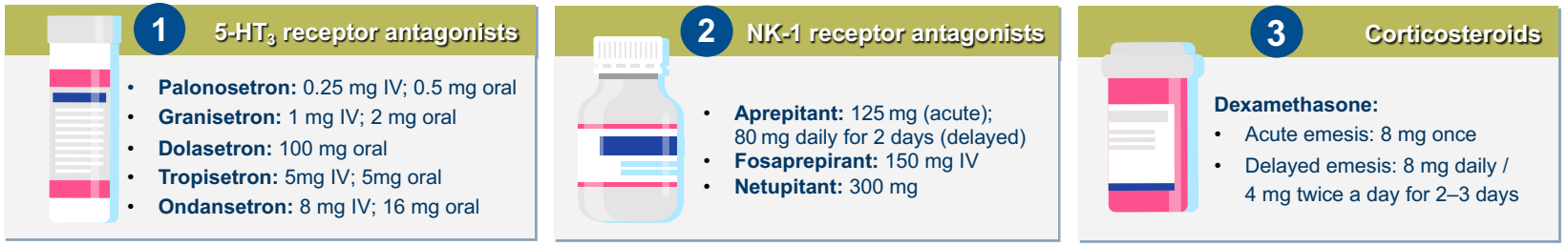
DESTINY-Breast04: Nausea and Vomiting

- 189/371 patients (50.9%) in the T-DXd arm and 64/172 patients (37.2%) in the TPC arm received antiemetic prophylaxis[a]
- Prophylaxis was not mandatory per study protocol, but was recommended

	Nausea		Vomiting	
n (%)	T-DXd n = 371	TPC n = 172	T-DXd n = 371	TPC n = 172
Dose reduction associated with N/V	17 (4.6)	4 (2.3)	3 (0.8)	1 (0.6)
Drug interruption associated with N/V	5 (1.3)	4 (2.3)	0	0
Drug discontinuation associated with N/V	1 (0.3)	0	1 (0.3)	0

Three Classes of Anti-Emetic Premedication is Recommended

This can be individualized to patient symptoms



N/V, nausea or vomiting; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]Prophylaxis included antiemetics and antinauseants, corticosteroids for systemic use, drugs for functional gastrointestinal disorders, or other.

Rugo et al. ESMO Breast 2023, Abstract 1850; NCCN 2023

Management of Breakthrough Nausea/Vomiting

- Breakthrough occurs in 30–50% of patients receiving a moderately emetogenic agent and guideline-directed prophylaxis
- Important interventions
  - Education prior to starting therapy
  - Provide standard rescue medications
    - Ondansetron
    - Lorazepam
    - Prochlorperazine
- **Olanzapine at bedtime d1-5 is remarkably effective at reducing nausea, and is also effective when extended for delayed nausea**
  - **Start at 2.5 mg* and increase as needed (1.25mg for some!)**

*Bajpai et al, SABCS 2023; Lancet Oncology 2024

DESTINY-Breast04: Adverse Events of Special Interest

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure, n (%)						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

- There were no new cases of ILD/pneumonitis since the primary analysis (data cutoff, January 11, 2022)[1]

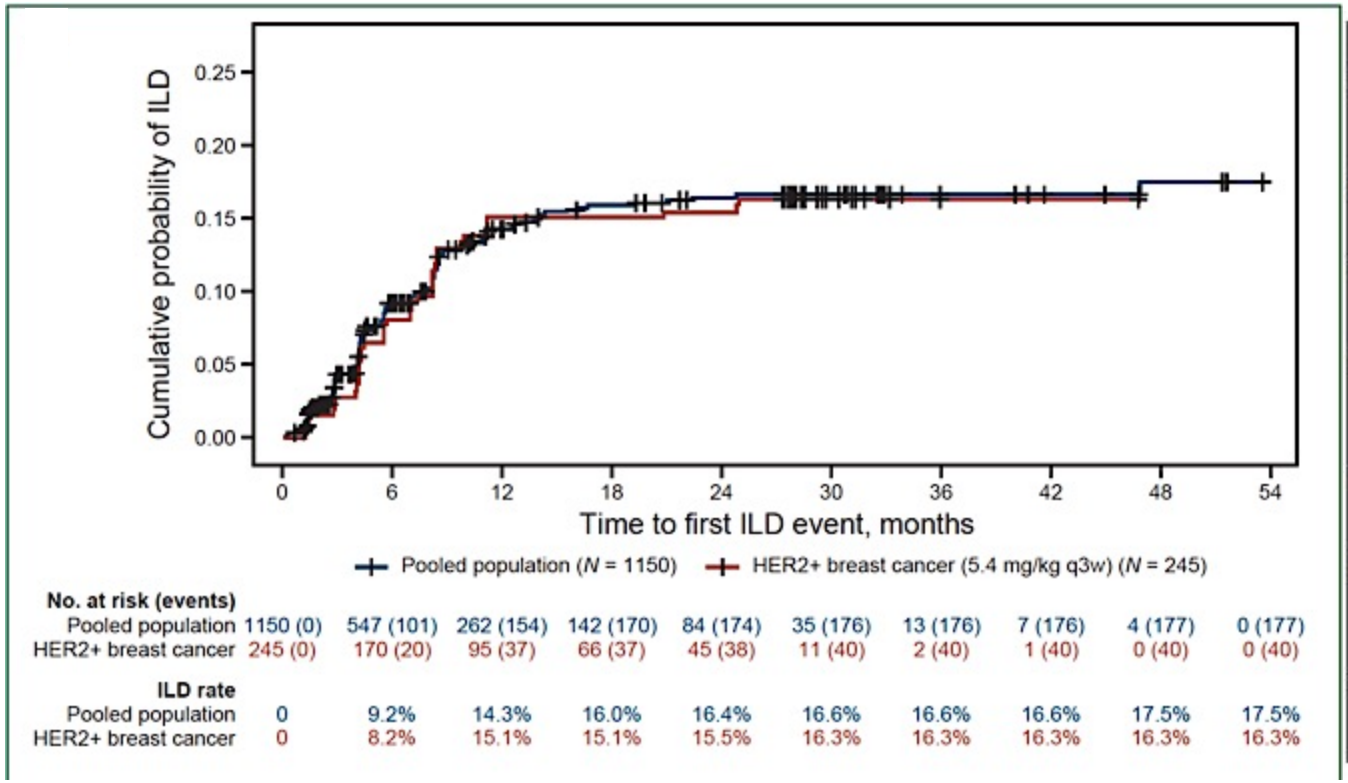
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

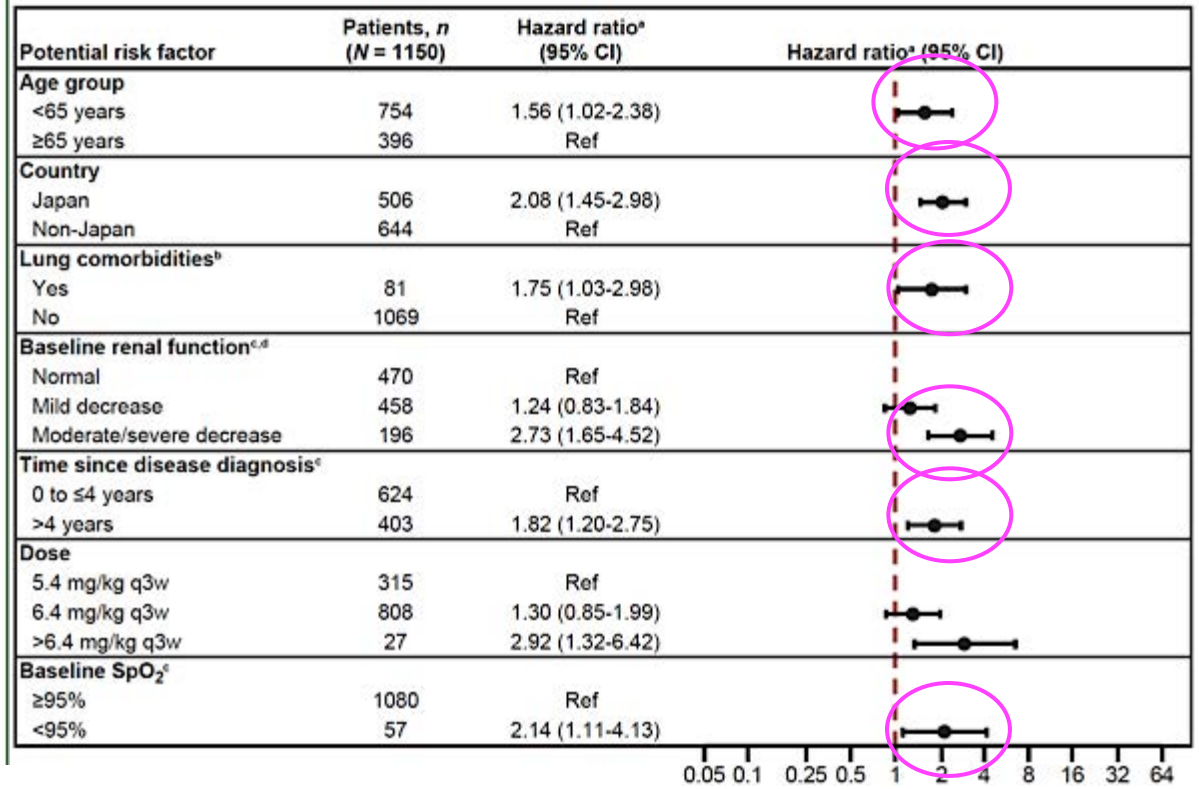
[a]At the primary analysis (data cutoff, January 11, 2022), grade 3 adjudicated drug-related ILD was reported in 5 patients (1.3%). At the current data cutoff, grade 3 adjudicated drug-related ILD is reported in 4 patients (1.1%) as 1 grade 3 ILD case worsened to grade 5 ILD. Consequently, there is an increase in the rate of grade 5 ILD (from 0.8% to 1.1%) without impact on the overall rate of adjudicated drug-related ILD. No ILD cases were pending adjudication at the updated data cutoff.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

Modi et al, ESMO 2023; Abstract 3760

Pooled Analysis of ILD/Pneumonitis in 9 Trastuzumab Deruxtecan Monotherapy Studies





- 1150 pts (44.3% breast cancer) with a median treatment duration 5.8 mo (0.7-56.3)
- Overall incidence: 15.4% (grade 5: 2.2%); grade 1-2: 77.4%
- 87% had their first event within 12 months of their first dose

Powell et al, ESMO Open 2022

It is recommended that patients treated with T-DXd should have HRCT scans at least every 12 weeks and every 6–9 weeks for those with respiratory symptoms[1]

Pre-T-DXd treatment

- Complete history and physical
- HRCT
- Baseline SpO_2
- Consider pulmonary consult for patients with significant lung comorbidities
- Provide patient education on risk and symptom identification

On T-DXd treatment

- **HRCT at least every 12 weeks, or every 6–9 weeks with baseline respiratory symptoms**
- Vital signs including SpO_2 and symptom assessment with treatment visits

If ILD suspected

T-DXd-related ILD/pneumonitis should be suspected when:
- Radiographic changes potentially consistent with ILD/pneumonitis are seen
- Patient experiences acute onset of new or worsening pulmonary signs/symptoms, such as dyspnoea, cough or fever

- Immediately hold T-DXd therapy and proceed with diagnostic workup

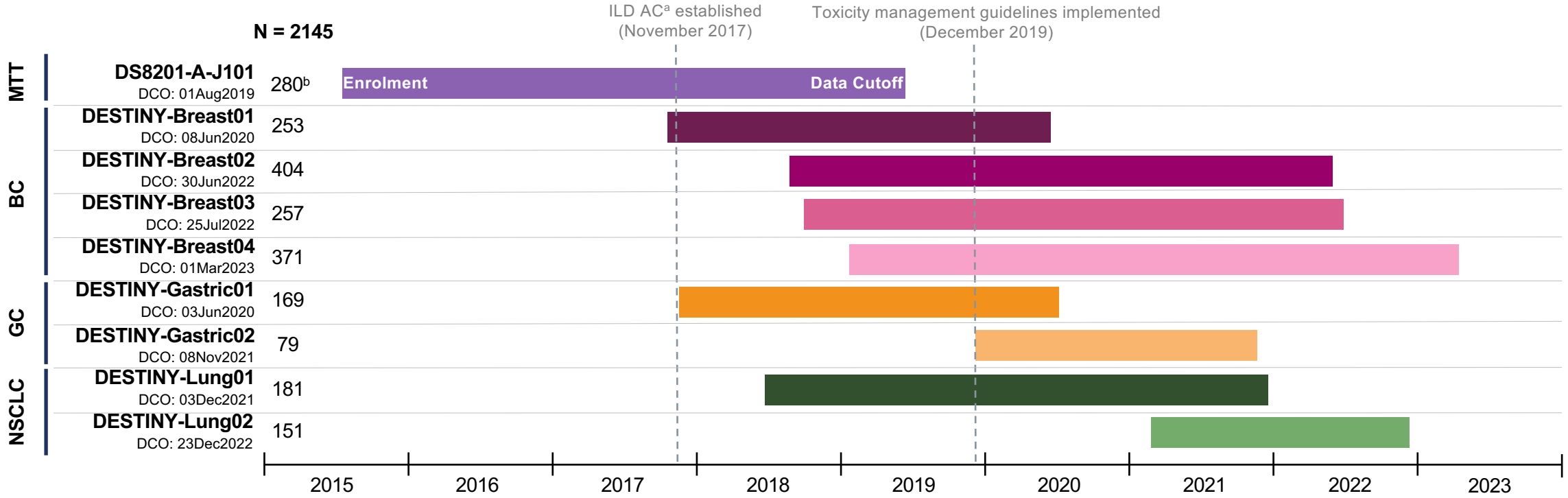
- Vitals and SpO_2, HRCT, blood tests
- If clinically indicated, consider PFTs, ABG, and bronchoscopy/BAL

Consider:
- Consultation of a pulmonologist
- Treatment with corticosteroids as clinically indicated

ABG=arterial blood gas; BAL=bronchoalveolar lavage; HRCT=high-resolution computerised tomography; ILD=interstitial lung disease; PFT=pulmonary function test; SpO2=peripheral oxygen saturation; T-DXd=trastuzumab deruxtecan.

1. Rugo HS, et al. *JCO Oncol Pract*. 2023;1–8.

POOLED ANALYSIS FOR GRADE 1 ILD RECHALLENGE



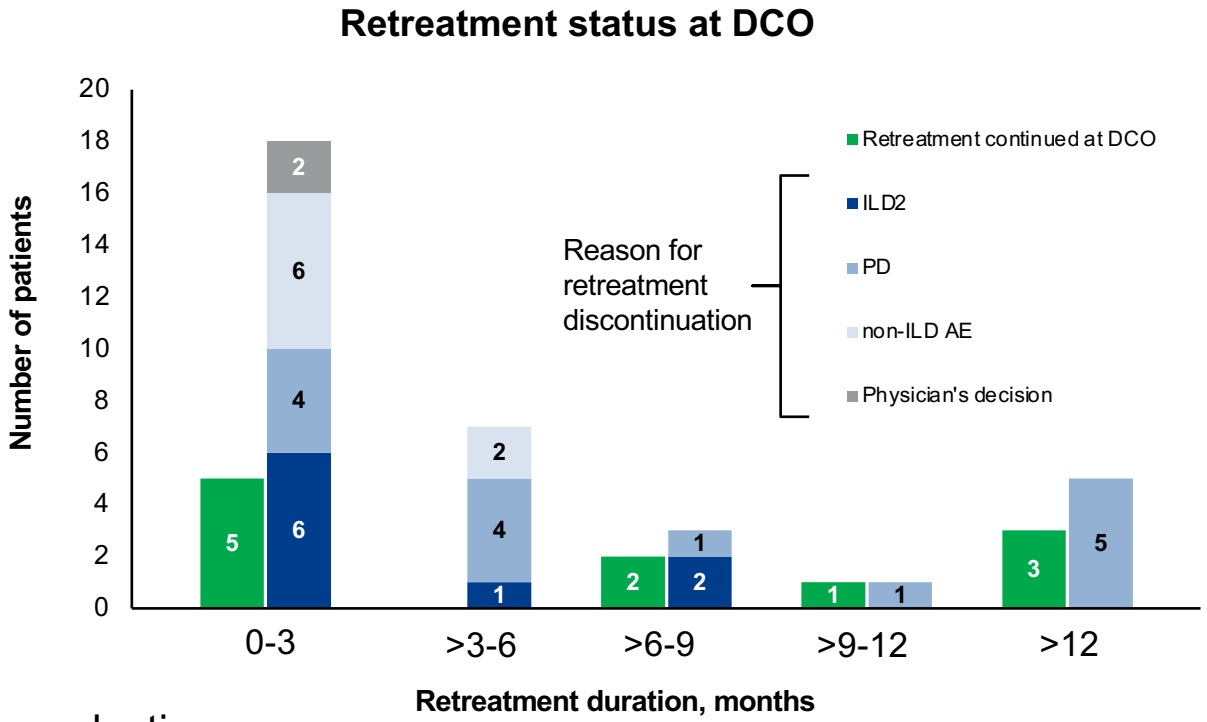
- Data were pooled from 9 clinical trials to identify patients with Gr 1 ILD as assessed by the investigators and confirmed by the adjudication committee (AC) who were retreated with T-DXd
  - All patients received at least 1 dose of T-DXd (5.4-8.0 mg/kg) monotherapy
- *T-DXd toxicity management guidelines recommend a dose reduction for retreatment if ILD takes longer than 28 days to resolve. At the time of study inclusions, guidelines recommended discontinuation of T-DXd if ILD had not resolved within 49 days from the last T-DXd dose[c]*

AC, adjudication committee; BC, breast cancer; DCO, data cutoff ; GC, gastric cancer; ILD, interstitial lung disease/pneumonitis; MTT, multiple tumor types; NSCLC, non–small cell lung cancer.
[a]Each AC session included an oncologist, a radiologist, and a pulmonologist. [b]Only patients who received at least 1 dose of T-DXd 5.4-8.0 mg/kg are included. The color bar for each study indicates the time from patient enrollment to data cut-off. [c]Guidelines have subsequently been updated to recommend discontinuation of T-DXd if ILD has not resolved within 126 days from the date of last drug dose.

Rugo et al, ESMO Breast 2024

T-DXd Retreatment Characteristics

	T-DXd retreatment (N = 45)
Dose level of T-DXd retreatment	
Same dose, n (%)	31 (68.9)
Reduced dose, n (%)	14 (31.1)
Median time to retreatment after ILD1 onset (range), days	28 (8-48)
Median retreatment cycles (range)	5.0 (1-37)
Patients with ILD2 (n = 15)	5.0 (2-23)
Patients without ILD2 (n = 30)	4.5 (1-37)
Median retreatment duration (range), days	85.0 (1-848)
Patients with ILD2 (n = 15)	85.0 (22-648)
Patients without ILD2 (n = 30)	82.5 (1-848)



- 68.9% (31/45) of patients were retreated without any dose reductions
- 24.4% (11/45) of patients were still receiving T-DXd retreatment at the DCOs of each respective study
- Progressive disease was the main reason for T-DXd retreatment discontinuation (33.3% [15/45] of patients)
  - 20.0% (9/45) of patients discontinued retreatment due to recurrent ILD (ILD2)
- **33.3% (15/45) of patients were retreated for >6 months and 17.8% (8/45) of patients were retreated for >12 months**

AE, adverse event; DCO, data cutoff; ILD, interstitial lung disease/pneumonitis; ILD1; first Gr 1 ILD event; ILD2, any-grade recurrent ILD event; PD, progressive disease; T-DXd, trastuzumab deruxtecan.

Rugo et al, ESMO Breast 2024

Sacituzumab govitecan: AEs in ASCENT and TROPiCS

		SG (n=258)			TPC (n=224)		
	TRAE	**All grade %**	**Grade 3, %**	**Grade 4, %**	**All grade, %**	**Grade 3, %**	**Grade 4, %**
Hematologic	**Neutropenia**	**63**	**34**	**17**	**43**	**20**	**13**
	Anemia	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia	16	9	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**	**59**	**10**	**0**	12	<1	0
	Nausea	**57**	**2**	**<1**	**26**	**<1**	**0**
	Vomiting	29	1	<1	10	<1	0
Other	**Fatigue**	**45**	**3**	**0**	**30**	**5**	**0**
	Alopecia	**46**	**0**	**0**	**16**	**0**	**0**

n (%)	SG (n=268)	TPC (n=249)
AE Grade ≥3	199 (74)	149 (60)
AEs → discontinuation	17 (6)	11 (4)
AEs → dose delay	178 (66)	109 (44)
AEs → dose reductions	91 (34)	82 (33)
SAEs	74 (28)	48 (19)
AEs → death[a]	6 (2)	0

[a]Of 6 AEs leading to death, 1 (septic shock due to neutropenic colitis) was considered treatment related by investigator

Bardia A, et al. N Engl J Med. 2021
Rugo et al, Lancet 2023

ASCENT and TROPiCS-02: Safety Outcomes by UGT1A1 Status

UGT1A1

- ✓ Variants affect enzymatic function, causing reduced metabolic capacity
- ✓ Over 50% of individuals may harbor an UTG1A1 polymorphism, dependent on genetic ancestry

	ASCENT		TROPiCS-02	
SG patients (n=250)	UTG1A1 Status n(%)	Dose Intensity (%)	UTG1A1 Status n(%)	Dose Intensity (%)
***1/*1 (wt)**	113 (44)	99.8	104 (38)	99
***1/*28**	96 (37)	99.5	119 (44)	98
***28/*28**	34 (13)	99.8	25 (9)	94

Grade ≥3 TEAEs Overall (%)	SG (n=268)
Neutropenia	52
Diarrhea	10
Anemia	8
Febrile neutropenia	6

	ASCENT			TROPiCS-02		
Grade ≥3 TEAEs By UTG1A1 Status (%)	*1/*1 (wt)	*1/*28	*28/*28	*1/*1 (wt)	*1/*28	*28/*28
Neutropenia	53	47	59	45	57	64
Diarrhea	10	9	15	6	13	24
Anemia	4	6	15	6	8	8
Febrile neutropenia	3	5	18	6	7	4
Growth factor for neutropenia (initiated on/after first dose) overall 54%						
				33	49	11

ASCENT: Treatment discontinuation due to TRAEs more common in *28 homozygous genotype

Nelson et al. *Cancers.* 2021;13:1566.
Rugo et al. *npj Breast Cancer.* 2022;8:98.
Marmé et al. *Annals of Oncol.* 2023;8(1suppl_4):101223-101223.
Rugo et al. Lancet. 2023 Oct 21;402(10411):1423-1433.

Datopotamab Deruxtecan in TROPION-Breast01: TRAEs in ≥15% of Patients and AESIs

System Organ Class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system				
Anaemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia*	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

- Most TRAEs were grade 1–2 and manageable

AESIs

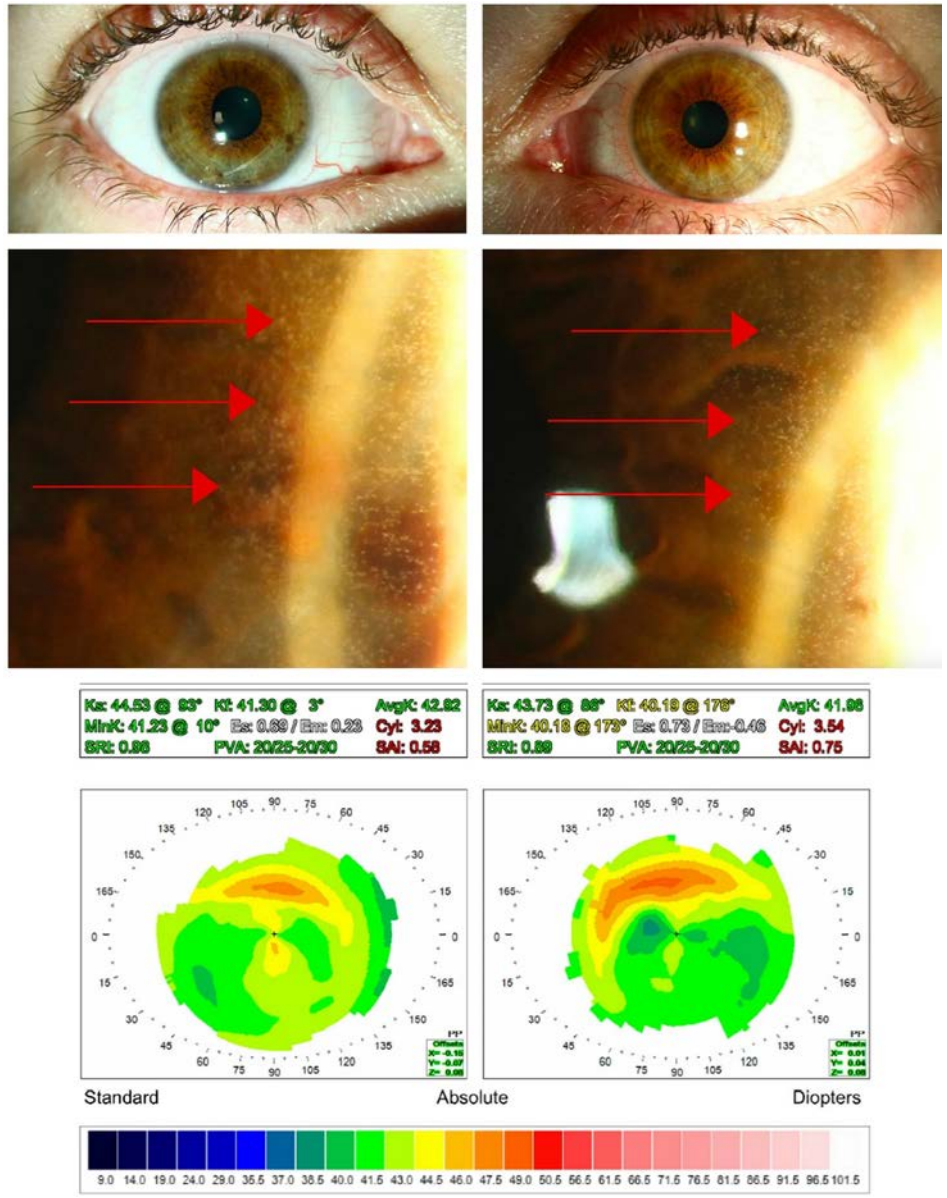
- Oral mucositis/stomatitis: led to treatment discontinuation in one patient in the Dato-DXd group
- Ocular events: most were dry eye; one patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related ILD: rate was low; mainly grade 1/2

Adjudicated drug-related ILD	Dato-DXd	ICC
All grades, n (%)	9 (3)	0
Grade ≥3, n (%)	2 (1)¶	0

Bardia et al, ESMO 2023; Abstract LBA11

ADC-Related Ocular Toxicities

- Most prevalent forms of ADC-related ocular surface AEs
  - Dry eye, keratitis/keratopathy, conjunctivitis, microcyst-like epithelial changes (MECs)
- **Microcyst-like epithelial changes (MECs):**
  - **Etiology**
    - Hyperreflective microcyst-like structures in the corneal epithelium's basal layer
    - Thought to be due to apoptotic cells engulfed within the layers of the corneal epithelium
  - **Symptoms**
    - Dry eye, blurred vision, tearing, and photophobia
  - **Prevention**
    - **Limited efficacy to date**
  - **Treatment**
    - Typically reversible with ADC dose delay, reduction, or discontinuation



Lindgren et. al. Curr Opthal Reports 2024

Adapted from Huppert

ADC-Related Ocular Toxicity

The Solution: ***Novel Preventative Therapies***

Drug Name	Mechanism
Vasoconstricting eye drops (given with ADC infusion)	Reduces drug uptake into the cornea during infusion
Cold compresses (during ADC infusion, similar to cold caps)	Reduces drug uptake into the cornea during infusion
Preservative-free artificial tears	Reduces eye dryness
Topical steroid eye drops	Slows down limbal stem cell regeneration, and in theory makes the cornea less susceptible to toxicity
Antihistamine eye drops	Inhibits non-specific micropinocytosis in the eye, thus blocking non-specific ADC uptake
Polylysine-grade-polyethylene glycol (PLL-g-PEG)	Inhibits drug uptake in human corneal epithelial cells in vitro

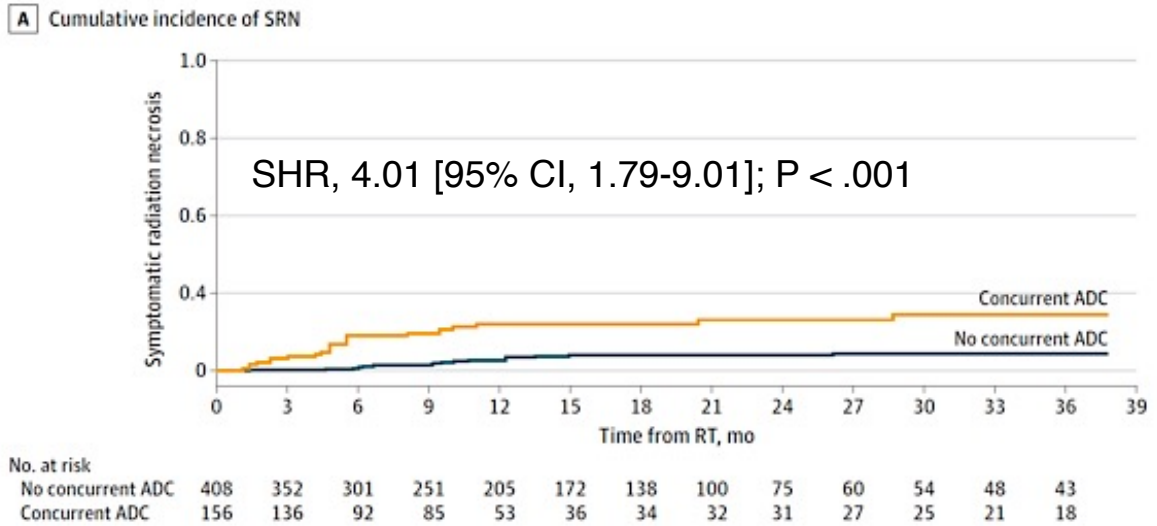
<u>Other:</u>

- Avoid the use of contact lenses during treatment
- Use caution when driving or operating machinery if visual symptoms arise

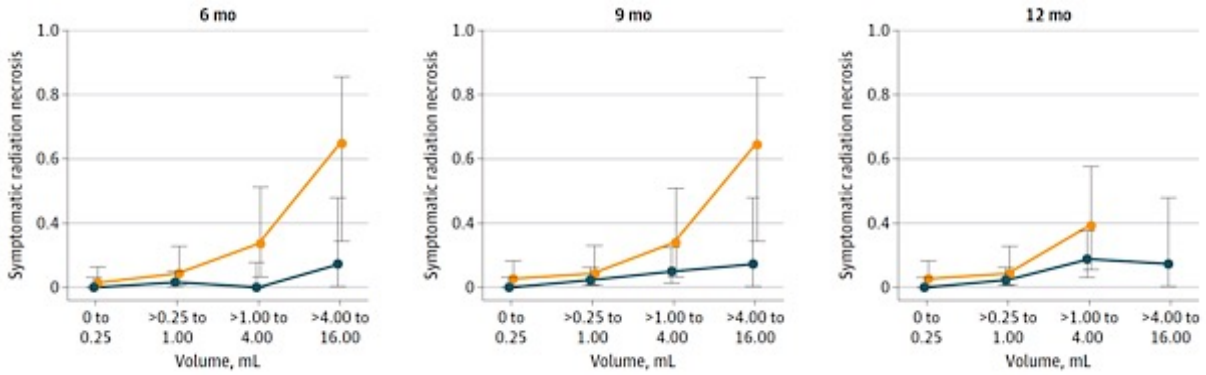
Courtesy of Pasricha and Huppert

Radiation Necrosis with Concurrent ADC and Stereotactic Brain Radiation?

Characteristic	Patient group[a]		All (N = 98)
	Concurrent ADC	No concurrent ADC	
Patients			
Age, median (range), y[b]	54 (27-77)	55 (34-77)	55 (27-77)
Sex			
Women	33/42 (78.6)	66/74 (89.2)	82/98 (83.7)
Men	9/42 (21.4)	8/74 (10.8)	16/98 (16.3)
Primary cancer diagnosis			
Breast	30/42 (71.4)	55/74 (74.3)	71/98 (72.4)
Non-small cell lung cancer, *ERBB2* variant	4/42 (9.5)	11/74 (14.9)	13/98 (13.3)
Esophageal and/or gastric cancer, *ERBB2* amplified	2/42 (4.8)	4/74 (5.4)	6/98 (6.1)
Salivary, *ERBB2* amplified	3/42 (7.1)	2/74 (2.7)	4/98 (4.1)
Other[c]	3/42 (7.1)	2/74 (2.7)	4/98 (4.1)
ADC received[d]			
Trastuzumab emtansine	21/42 (50.0)	43/74 (58.1)	52/98 (53.1)
Trastuzumab deruxtecan	14/42 (33.3)	42/74 (56.8)	50/98 (51.0)
Sacituzumab govitecan	7/42 (16.7)	23/74 (31.1)	26/98 (26.5)



MV analysis: SHR, 4.31 [95%CI, 1.95-9.50];P <.001



SHR: Subdistribution hazard ratios; MV: controlled for prior RT and volume

Lebow et al. JAMA Oncol. 2023 Oct 26;9(12):1729–1733.

Conclusions

- T-DM1, Sacituzumab, T-DXd and Datopotamab are highly effective, targeted ADCs that deliver a microtubule inhibitor or a topoisomerase 1 inhibitor to metastatic breast cancer
- ADCs with the same target and cytotoxic payload with same MOA can have different toxicities, eg, sacituzumab and datopotamab
- ADCs generally have less treatment-related toxicity than chemotherapy
- Proactive management of toxicities is critical in preventing treatment-limiting toxicities
- Dose reduction is generally effective in mitigating ADC-related toxicities
- All of these ADCs are being evaluated (or are established) in EBC where delivery of safe and effective doses is especially important

Faculty Case Presentations

Case Presentation – Dr Tolaney

69-year-old woman with de novo metastatic ER+ PR+ HER2 1+ breast cancer

- Presented 4-years ago with a left breast mass and enlarged LNs → biopsy c/w ER+ PR+ HER2 1+ IDC, grade 3, and FNA of LN positive
- CT scan revealed bone metastases and enlarged mediastinal and retroperitoneal nodes with L pleural effusion
- Thoracentesis revealed ER+ PR+ cells (HER2 not performed)
- Started letrozole + palbociclib → progressed after 25 months
- NGS with ESR1m and no *PI3K/PTEN/akt* mutations
- Started elacestrant, progressed on first restaging at 8 weeks
- Started fulvestrant + everolimus, progressed after 5 months
- Found to have enlarging dural metastases and brain imaging with a parenchymal lesion
- Entered a trial of Dato-DXd for brain metastases
- Initiated 3 drug anti-emetic prophylaxis and dexamethasone sw/sp prophylaxis 4x/day
- Required use of ondansetron as needed during weeks 2 and 3; rare mouth sores

Case Presentation – Dr Krop

- 52yo high school teacher presents with RUQ pain
  - CAP CT: Multiple liver lesions, largest 4 x 5 cm
- CT-guided biopsy: ER-PR-HER2 3+ adenoCA consistent with breast primary
- Started on paclitaxel/trastuzumab/pertuzumab
  - Initial PR, but progression after 14months
- Treatment changed to trastuzumab deruxtecan
  - After 9 weeks of therapy, restaging CAP CT: 50% reduction in size of liver lesions

Case Presentation – Dr Krop (Continued)

- 5 months after starting T-DXd
  - Routine CAP CT: continued partial response
  - New ground glass lung opacities bilateral lung bases
  - Pt denied dyspnea, cough, fever
  - O2 Saturation 97% on RA
  - COVID negative x2
  - PFTs WNL
- T-DXd held
- Pulmonary consultation
  - Dx: T-DXd pneumonitis (grade 1)
  - Rx: Prednisone 40mg orally qd x 21d
- 28d later repeat CT: resolution of ground glass opacities
  - Tapered prednisone over 4 weeks

Case Presentation – Dr Krop (Continued)

- Restarted T-DXd at 5.4mg/kg (original dose)
- 2 cycles later: Repeat CT
  - Continued partial response
  - Lungs clear
- Patient remained on treatment for 10 months, then had PD

Case Presentation – Dr Krop (Data Update)

- In analysis of 45 pts with resolved gr1 ILD who were retreated with T-DXd[1]
  - Duration of retreatment: 5 cycles
  - 18% received additional 12 mo of T-DXd
  - 1/3 had recurrent ILD, all grade 1/2

[1] Rugo et al, ESMO Breast 2024

Agenda

Module 1: Optimizing the Care of Patients with HER2-Positive Metastatic Breast Cancer (mBC) – Dr Krop

Module 2: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer – Dr Tolaney

Module 3: Integrating Novel Agents and Approaches into the Management of Endocrine-Resistant Hormone Receptor-Positive mBC – Dr Kalinsky

Module 4: Tolerability Considerations with Approved and Investigational Antibody-Drug Conjugates – Dr O'Shaughnessy

Module 5: Other Important Care Considerations for Patients with mBC – Dr Hamilton

Important care considerations for patients with Breast Cancer

Erika Hamilton, MD

December 12, 2024

SCRI Sarah Cannon Research Institute

Agenda

- Importance of Diversity, Equity and Inclusion (DEI) in clinical trials
- Value of early palliative care for patients with MBC
- Consideration of alternative therapeutic approaches

Why is DEI important in clinical trials?

- Participants in research should reflect the cultural diversity and milieu to be truly representative of the population they serve

- This includes diversity in race, ethnicity, gender, age as well geography, socioeconomic status etc.

- Lack of diversity can impact research negatively including
  - impeding our ability to generalize trial results
  - preventing advancements in clinical care due to limited participation
  - depriving some populations from the benefits of novel therapies

More importantly, lack of diversity, equity and inclusion in clinical trials is an ethical issue promoting health disparities and perpetuating a mistrust in the healthcare system

Guidance documents issued by FDA

- Calls for oncology trial specific diversity and inclusion

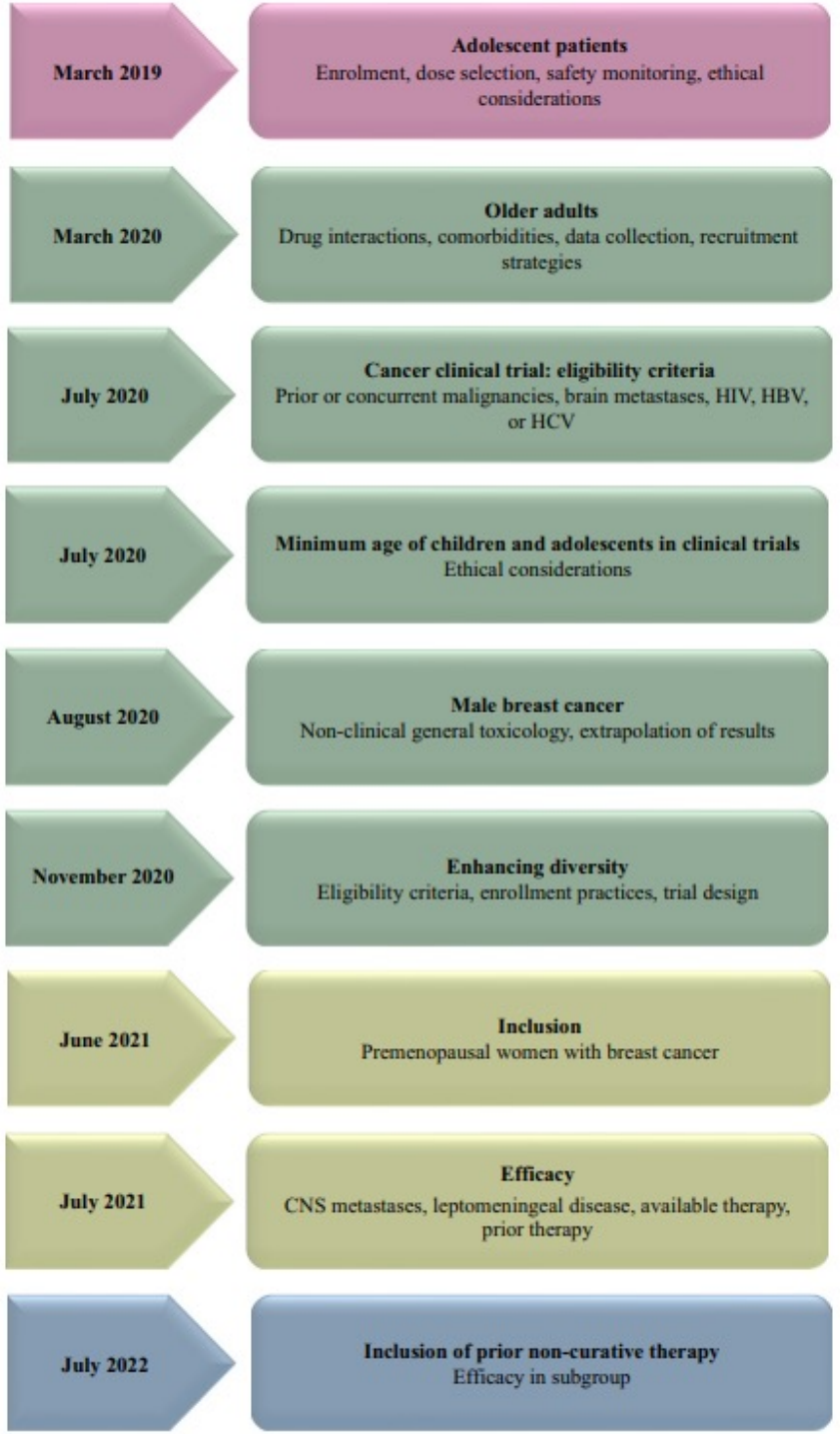


Figure from: Vidal L et al., ESMO Open 2024

What are barriers to diversity?

Social determinants of health

- Limited access to affordable, high-quality healthcare
- Exposure to environmental pollutants
- Quality of housing, infrastructure

Limited access to clinical trials

- Long distances to healthcare facility

Study design that excludes diverse populations

- Patients from rural areas – internet, travel time, accommodation near treatment center
- Patients more likely to have comorbidities

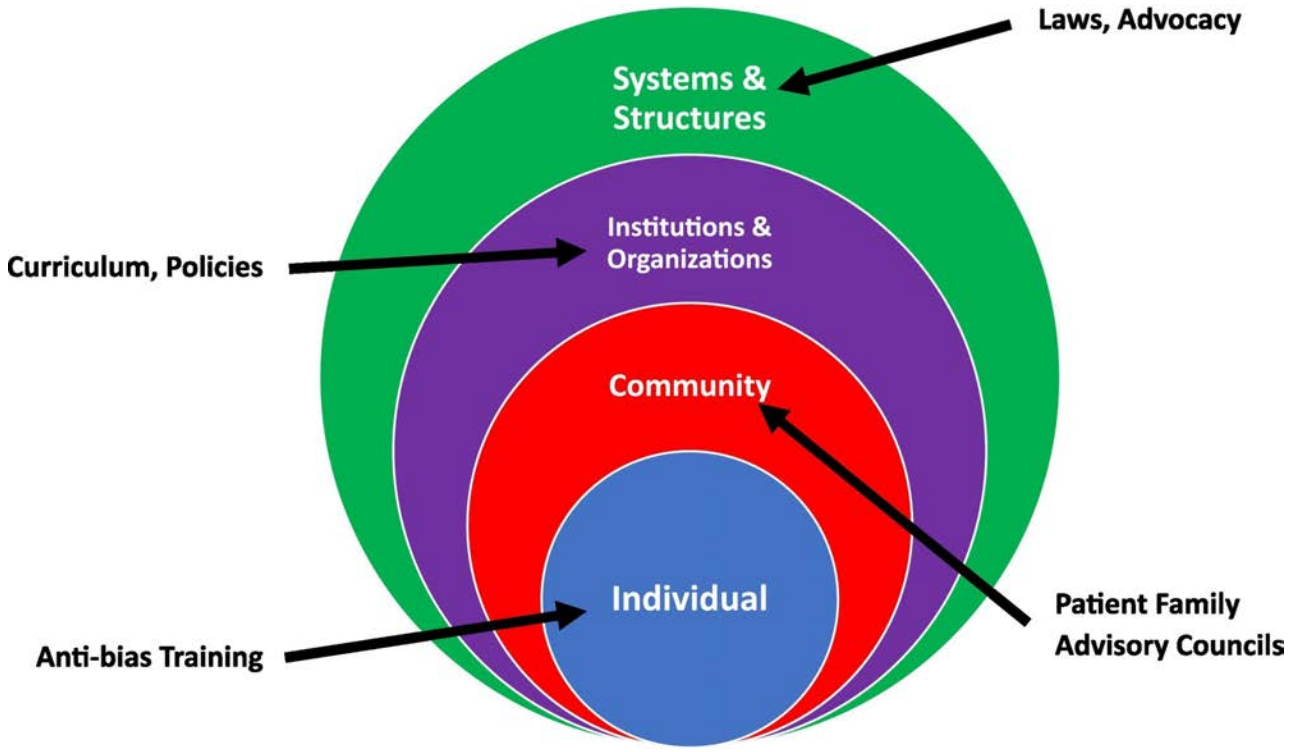


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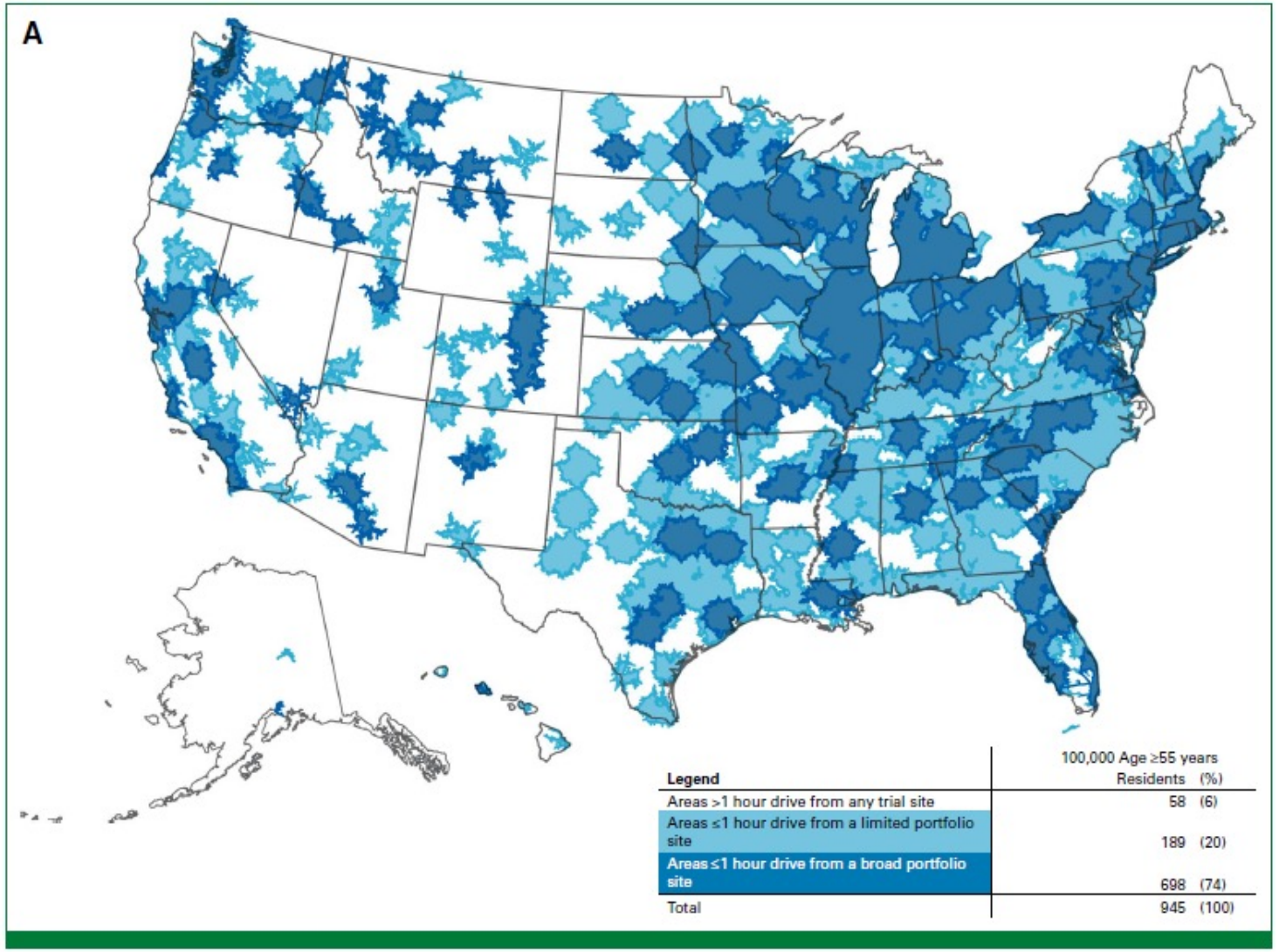
Figure from: Pothuri B et al., Gynecologic Oncology 2023

Geographic access to clinical trials



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Kirkwood MK et al., JCO Oncol Pract 2024

Strategies to improve diversity

Standardization of data collection for markers of diversity – cannot know what you don't document

Promote and support clinical trials in community practices – trials come to patients

Partner with social organizations to increase awareness of and encourage clinical trial participation

Increase staff diversity at clinics; continuous training to mitigate bias

Encourage clear communication of risk/benefit to patient

Barriers to inclusive participation in clinical trials and facilitators of diversity and inclusion

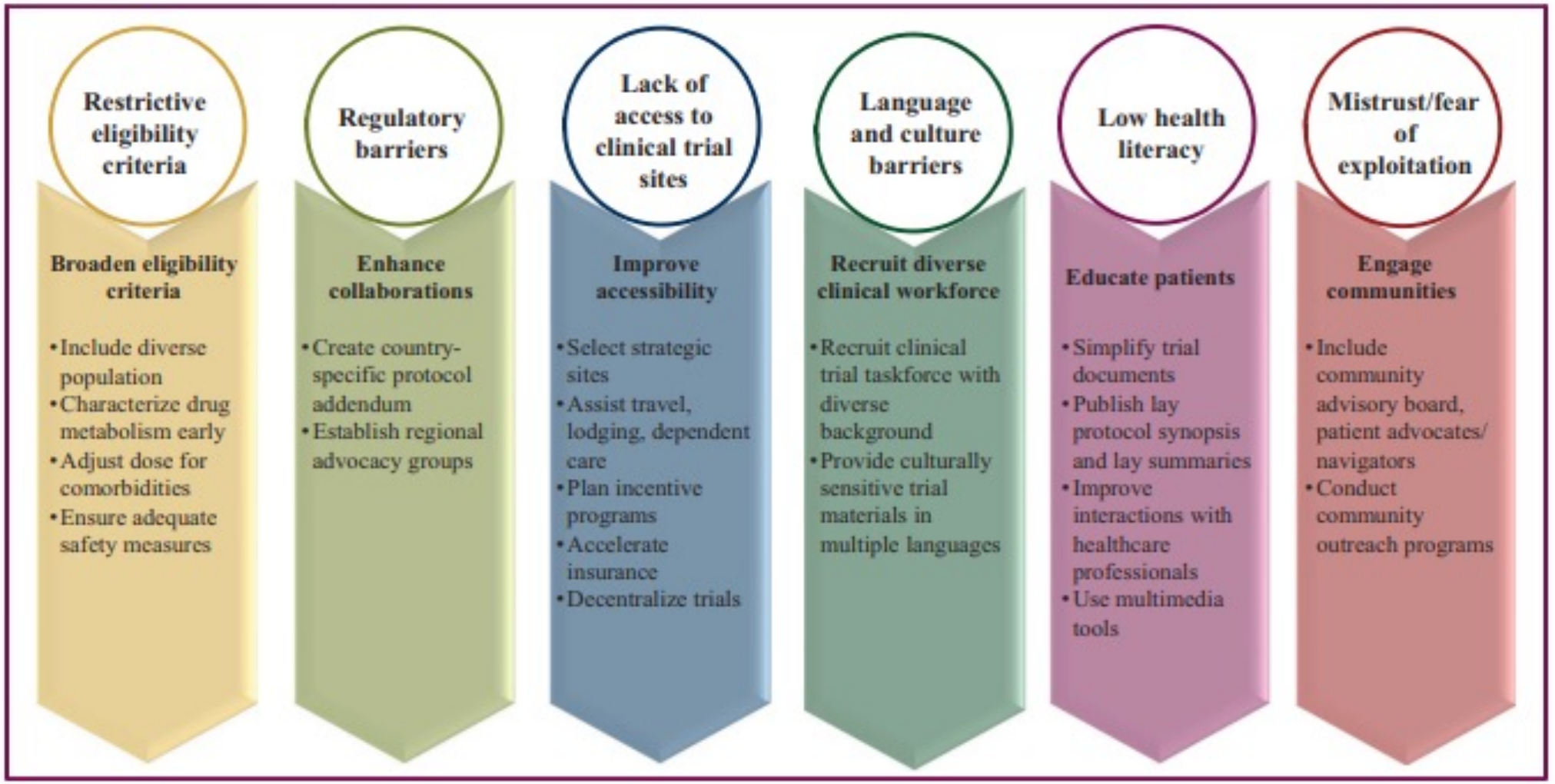

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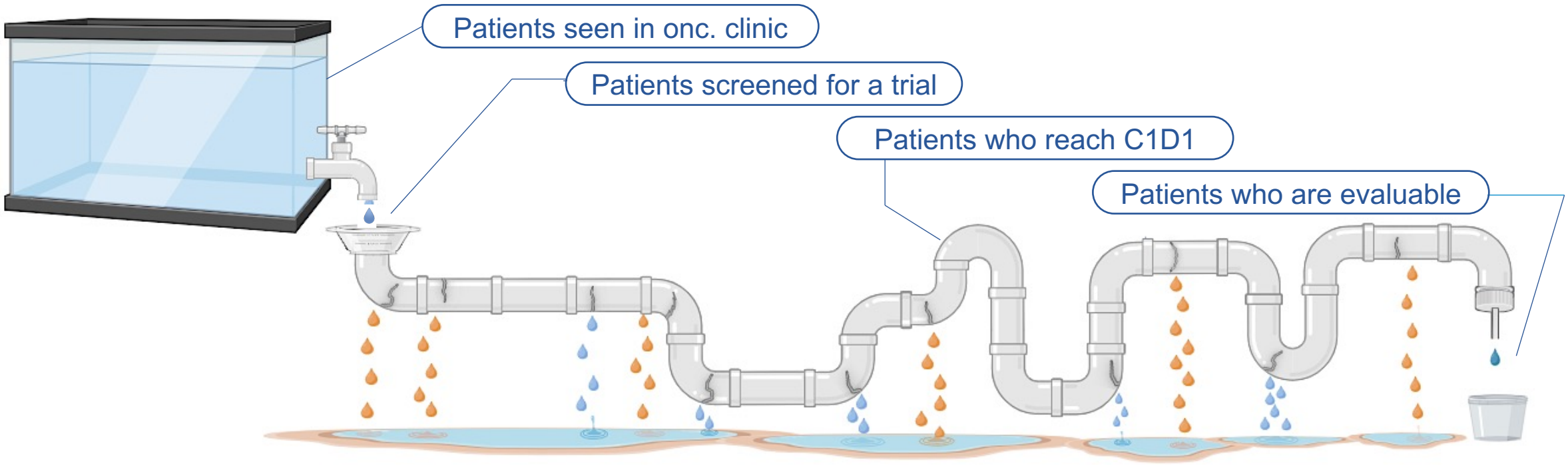
Figure from: Vidal L et al., ESMO Open 2024

Current State in Cancer Clinical Trials

The Leaking Pipeline of Patient Participation

STUDY DESIGN | PRE-ACTIVATION | RECRUITMENT | RETENTION | REPORTING POST-MARKETING



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Slide credit: Dr. Ishwariah Subbiah, SCRI

Breaking Down the Drivers of Non-Participation

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Slide credit: Dr. Ishwariah Subbiah, SCRI

How can we promote DEI in clinical trials?

Requires a **system-level overlay of support** at every step

Design of clinical trials

Practical eligibility criteria to promote inclusivity

Keeping patient burden in mind
- Avoiding multiple clinic visits
- Permitting local labs/scans

Providing necessary tools to participating sites to increase diversity
- Consents in multiple languages
- Travel reimbursements
- Copays for SOC drugs

There is no single solution!

Palliative care for patients with MBC

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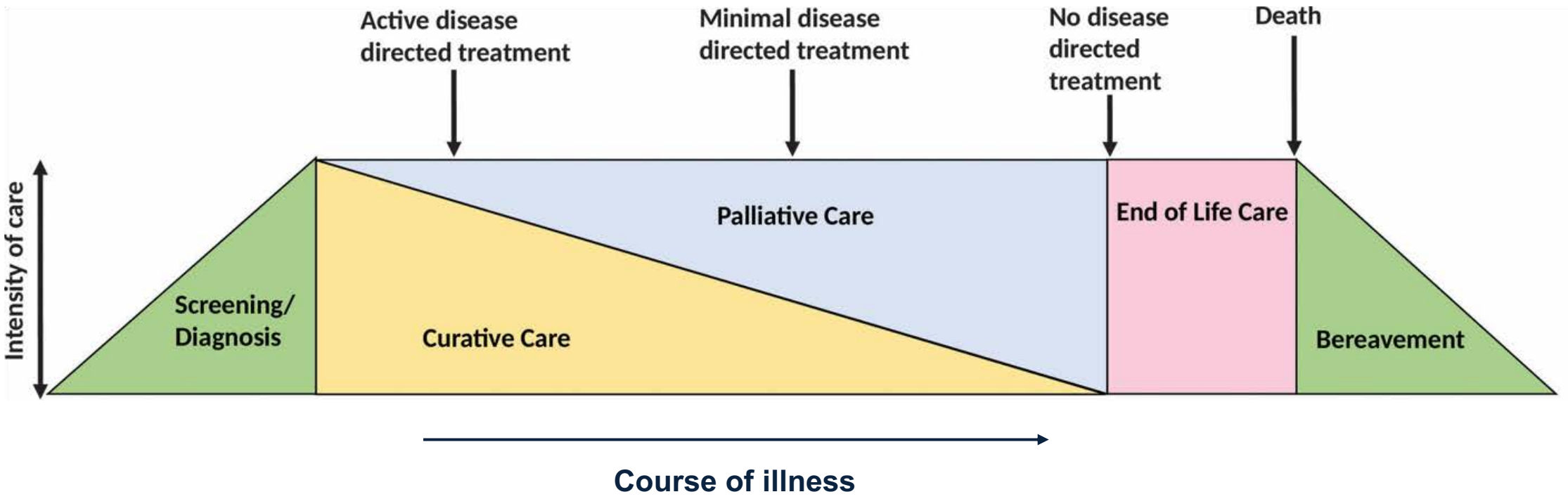
Phases of palliative care over disease journey

Misconception that palliative care is hospice care



All hospice care is palliative, but not all palliative care is hospice

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Figure credit: Masso et al., 2015; Myatra et al., 2014

Early randomized trials of palliative care

ENABLE II and III: Coordinated trials in which APN contacted patients and coordinated with palliative care and oncology specialists (Bakitas M et al. 2009, 2015)

Integrated studies in which patients were routinely referred to a specialist palliative care physician and/or an APN early in the illness trajectory (Temel J et al. 2010, Zimmerman C et al. 2014)

Both sets of trials resulted in positive outcomes – improvements in QoL that led to guideline and practice change

Palliative care is now more broadly defined as specialized, team-based care focused on alleviating the symptoms and stress of serious illness for patients and families, which is appropriate at any age and any stage of illness

ASCO 2016 guideline

All patients with advanced solid tumor cancers receive dedicated, interdisciplinary palliative care services **early** in the disease course, concurrent with active treatment in an integrated mode

APN: advanced practice nurse

Petrillo LA et al. ASCO Ed book 2024

How can early palliative care address needs of patients and caregivers?

Managing physical symptoms of cancer

Navigating shifts in risk/benefit ratio of symptom management ex: long term opioid therapy for chronic cancer-related pain

Managing side effects of treatment

Coordinating with the oncology team to recognize and address novel, late and long-term toxicity of therapies

Personalizing medical decision making and transitions

Supporting patient centered decision-making regarding therapies, treatment and hospitalization

Enhancing understanding of illness

Cultivating prognostic awareness in the setting of uncertain and highly variable outcomes including exceptional responses

Psychosocial support

Assist with coping with uncertainty and navigating change to identity, relationships, and function/ability to work

LA Petrillo et al. ASCO Ed book, 2024

Approaches to improve early palliative care implementation

- Educate patients and caregivers that palliative care is not necessarily end of life care
- Use symptom burden or other patient reported outcomes to trigger palliative care consultations
- Consider telehealth palliative care delivery or navigator led interventions
- Continue to provide palliative care training as part of medical training
- Raise awareness about the important role of palliative care services with the evolving oncologic treatment landscape

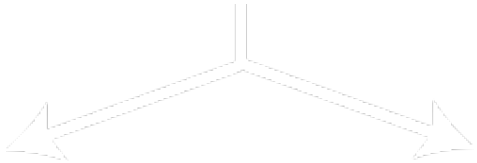
ASCO 2024 guideline updated to include early palliative care involvement for patients with heme malignancies and patients with solid tumors on phase 1 trials

Alternative therapies for MBC

What is Integrative Oncology?

Patient-centered, evidence-informed field of cancer care that utilizes

- mind and body practices
- natural products
- lifestyle modifications



alongside conventional cancer treatments

Aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum

Alternative therapies to address cancer related symptoms/ issues

Cancer fatigue

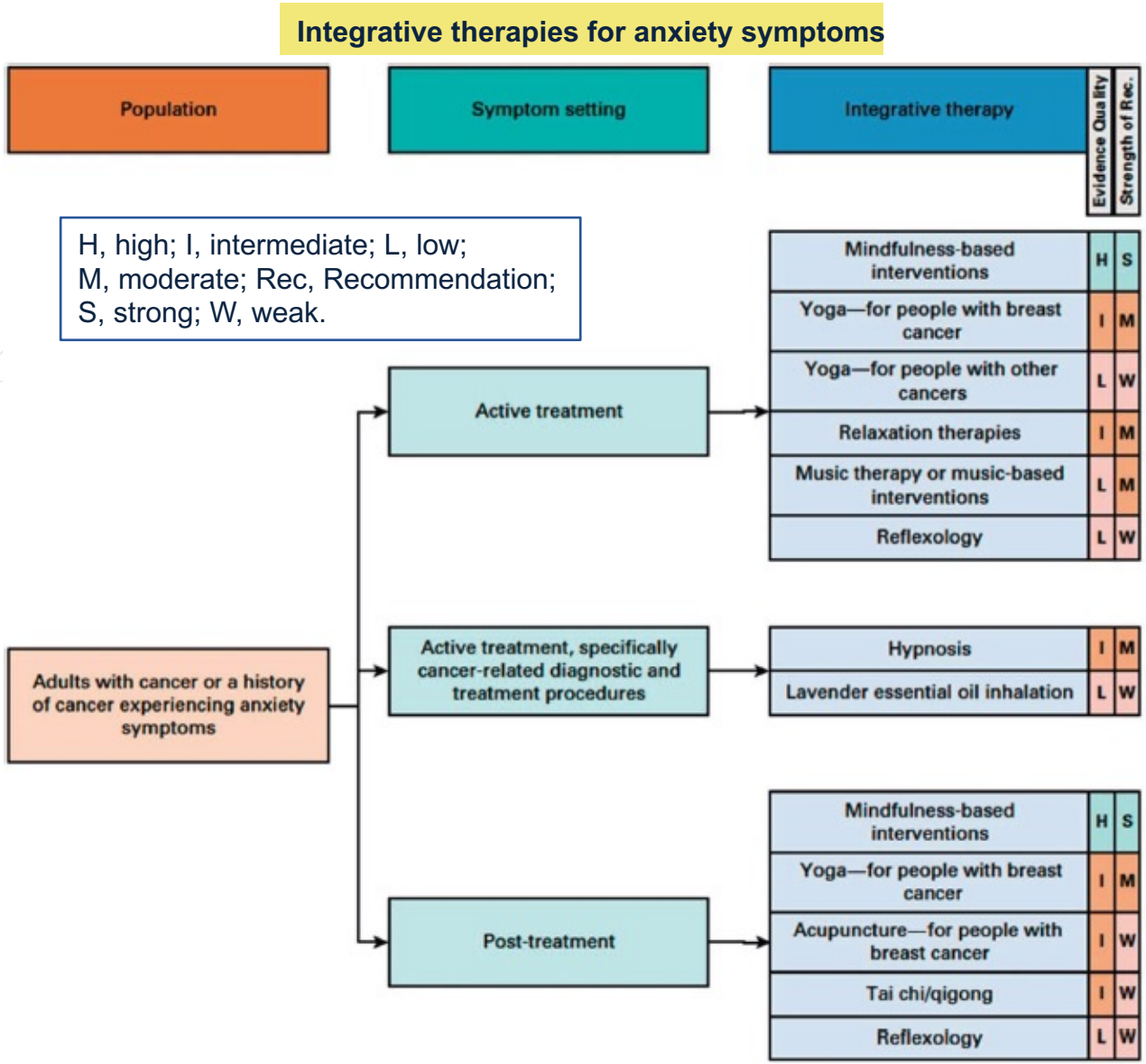
Mindful-based movement exercise therapies like tai chi and qigong, have demonstrated a robust impact on improving fatigue severity

Anxiety

Mindfulness-Based Interventions (MBI) like yoga, hypnosis, relaxation therapies, music therapy, reflexology, and lavender essential oils during active treatment may help

Depression

For patients undergoing active treatment, integrative therapies including MBIs, yoga, music therapy, relaxation, and reflexology are recommended



Gowin C et al. ASCO Ed book 2024

Acupuncture for Hot flashes

Hot flashes are a common side effect endocrine therapies, experienced by 51-81% of pts with BC

Reduce QoL and increase non-adherence to therapies

Three parallel randomized trials in US, China and S. Korea (n=158)

Pts with BC (stage 0-III), receiving ET

>14 hot flashes/ week

Patients were randomized 1:1 to

- Acupuncture arm: 2X/week for 10 weeks
- Control arm: Usual care for 10 weeks

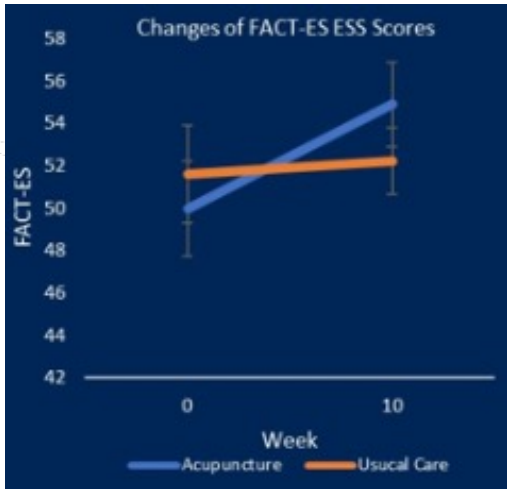
Primary EP: ESS of FACT-ES

Secondary EPs: FACT-B, Hot flash scores

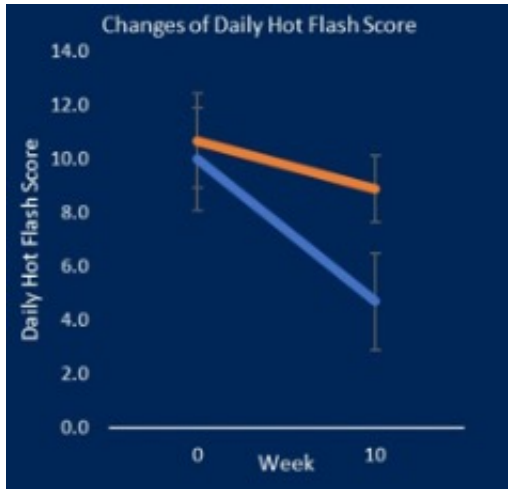
Pooled analysis of individual pt data from three countries

- Asian: 51%, White: 43%
- Age: 48 (25-73)
- Hot flashes/day: 6.2 vs 6.5

Changes of FACT ES ESS Scores



Changes of Daily Hot Flash Score



Acupuncture led to meaningful improvements in hot flashes, endocrine symptoms and QoL

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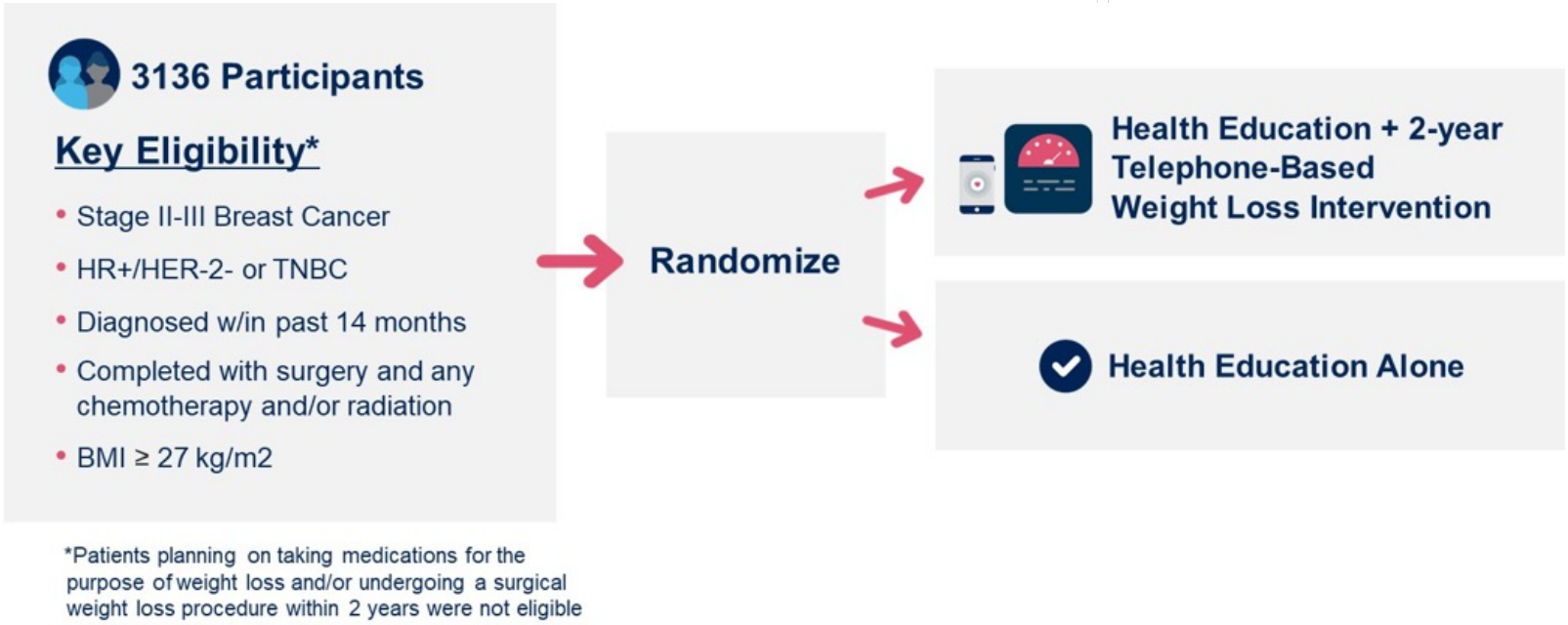
Lu W et al. ASCO 2022

Breast cancer weight loss (BWEL) trial

Higher BMI is linked to increased breast cancer mortality and increased risk of secondary cancers

BWEL trial evaluated the effect of telephone-based weight loss intervention (WLI) at 12 months on pts with EBC



*Patients planning on taking medications for the purpose of weight loss and/or undergoing a surgical weight loss procedure within 2 years were not eligible

Primary objective:
Assess impact of WLI on iDFS

Select secondary objectives:
Assess impact of WLI on
- Weight change
- OS, BC mortality, BC free survival
- PROs
- Adherence to ET

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Ligibel J et al. ASCO 2023

Breast cancer weight loss (BWEL) trial

Interventional arm
Health education + phone based WLI

- 42 calls over 2 years
- Each patient paired with a weight loss coach, based at Dana-Farber

- Weekly months 1-3
- Biweekly months 3-12
- Monthly months 13-24

+

Twice yearly webinars regarding diet and exercise

Twice yearly mailings of materials regarding healthy lifestyle

Quarterly study newsletter

Two year subscription to a health-related magazine

Control arm
Health education only

Twice yearly webinars regarding diet and exercise

Twice yearly mailings of materials regarding healthy lifestyle

Quarterly study newsletter

Two year subscription to a health-related magazine

Trial accrual: Aug 2016-Feb 2021
N=3160

Patient characteristics

Pre vs postmenopausal: 43% vs 57%

BMI <30kg/m^2 vs ≥30kg/m^2: 24% vs 76%

T3/T4: 20%

N1-N3: 81.5%

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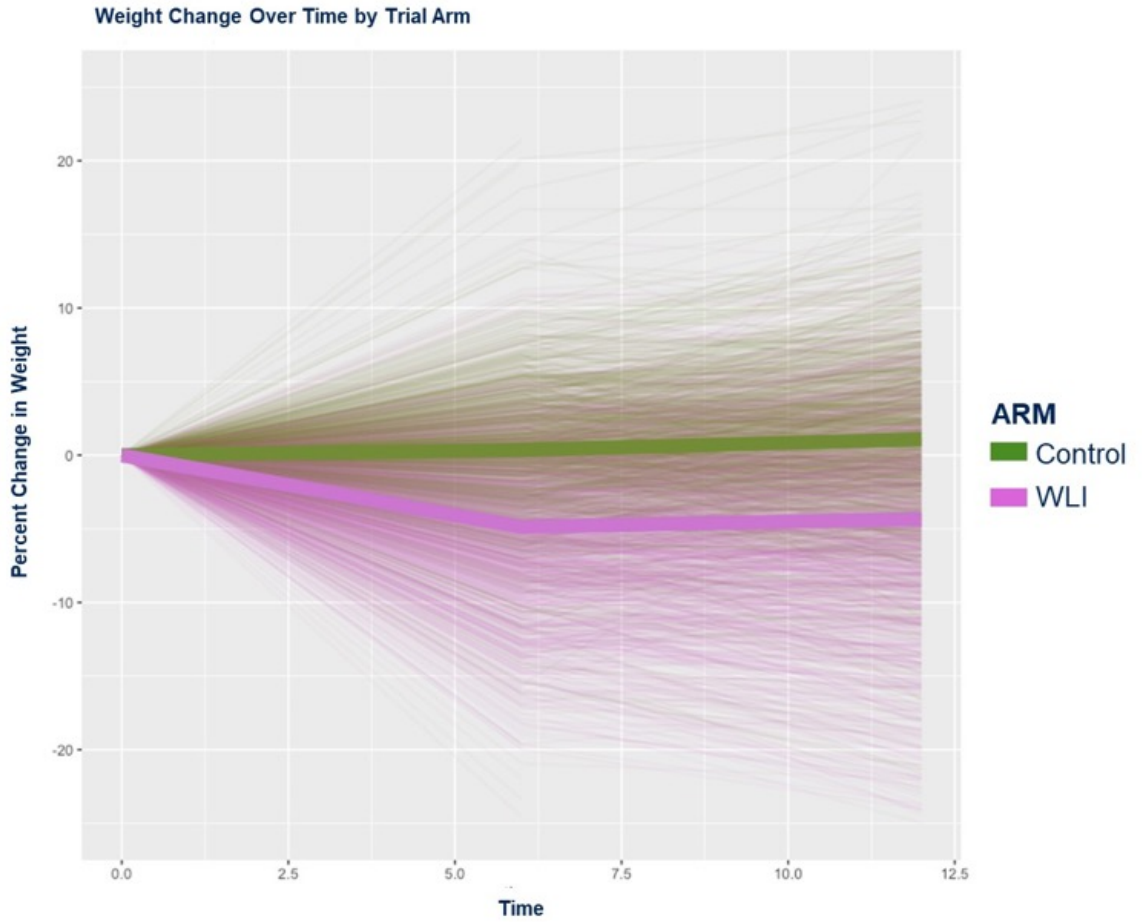
Ligibel J et al. ASCO 2023

BWEL Weight loss

	CONTROL (n=1173)	WLI (n=1222)	P VALUE
Absolute Weight Change at 6-months	+ 0.2 kg	- 4.4 kg	<0.0001
% Weight Change at 6-months	+ 0.3%	- 4.8%	<0.0001
Absolute Weight Change at 12-months	+ 0.7kg	- 4.4kg	<0.0001
% Weight Change at 12-months	+ 0.9%	- 4.8%	<0.0001



- ✓ A telephone and web-based weight-loss intervention led to significant and clinically meaningful weight loss in BC survivors who were overweight and obese
- ✓ Patients will continue to be followed to assess the impact on the primary outcomes- iDFS and other outcomes

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Ligibel J et al. ASCO 2023

Faculty Case Presentations

Case Presentation – Dr O'Shaughnessy

- 36 yo woman presented in 2006 with grade 3 left T2N1M1 UOQ TNBC and multiple small lung metastases (biopsy+ for TNBC) in third trimester of her first pregnancy. g*BRCA1/2* testing was negative. Primary TNBC showed *PIK3CA* mutation and AR++
- After delivery, she was treated on a clinical trial and was randomized to irinotecan/carboplatin + cetuximab and had CR in breast and in the pulmonary mets
- She continued on maintenance cetuximab per protocol and underwent left breast lumpectomy and SLN biopsy – pCR in both, followed by breast and locoregional radiation therapy. She was then post-menopausal
- 2 years later in 2008 she developed a solitary lung metastasis which was resected and showed cyclin E amplification
- She was treated on protocol with irinotecan/carboplatin + cetuximab followed by continued cetuximab (which she is still on 18 years later). Tumor-informed ctDNA testing negative
- Panel germline testing in 2019 reveal a *RAD51D* mutation and she opted to undergo BSO and bilateral mastectomy
- Her daughter is now a freshman in college

Case Presentation – Dr Kalinsky

1/5/2010: routine mammogram with 2cm spiculated mass in the right retroareolar region. u/s guided biopsy with moderately differentiated invasive ductal carcinoma, ER+, PR+, HER2-, 2+ on IHC, BRCA negative but has BRCA2 variant. s/p right modified radical mastectomy with reconstruction, 19 LN involved. Stage IIIC (T1cN3M0), nottingham 7. Enrolled in E5103 and received Doxorubicin/Cyclophosphamide x4 cycles followed by weekly paclitaxel from 8/5/2010-9/21/2010 plus Bevacizumab x18 cycles completed 5/2011.

She started Tamoxifen 11/5/2010, switched to Anastrozole 2/2013-9/2018.

PET-CT (8/30/18): Hypermetabolic lesion in the right hemipelvis (sacrum, ilium, acetabulum), pubic rami; hypermetabolic lesions in the left hemipelvis. Multiple hypermetabolic lesions in the osseous vertebral bodies and right posterior 11th rib.

Case Presentation – Dr Kalinsky (Continued)

R. iliac biopsy (9/14/18) metastatic mammary carcinoma; GATA3 and CK7 positive, ER 91-100%,

10/3/18: Fulvestrant and palbociclib 10/3/18. Palbo stopped due to low ANC

6/2/20: Abemaciclib 100 mg bid with continued fulvestrant

Guardant360 Aug 2021: ESR1 E380Q and Tp53 H179R.

5/12/22: Switched to everolimus 10mg and exemestane

Case Presentation – Dr Kalinsky (Continued)

Liver bx obtained 9/28/2022 showed metastatic breast carcinoma, consistent with known breast primary, biomarkers ER+7/8, PR+8/8, HER2 negative 0 by IHC. 9/26/2022 echo LVEF 64%.

She started treatment on phase 1 trial of fulvestrant, copanlisib and abemaciclib on 10/3/2022. Stopped after 7 cycles due to progression, with last dose of copanlisib on 4/10/2023 and abemaciclib on 4/24/2023.

5/2/23: She was then started on olaparib on 5/2/2023

2/24: progression of disease: switched to CDK4 trial. On for 6 months

8/24: progression of disease switched to capecitabine

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