Module 8: Triple-Negative Breast Cancer (TNBC)

Current and Future Role of TROP2-Directed Antibody-Drug Conjugates in Therapy for TNBC — Dr Brufsky

Established Treatment Paradigm for Localized and Metastatic TNBC — Dr Kalinsky

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Module 8: Triple-Negative Breast Cancer (TNBC)

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

Current and Emerging Evidence Supporting TROP2-Targeted ADCs in TNBC

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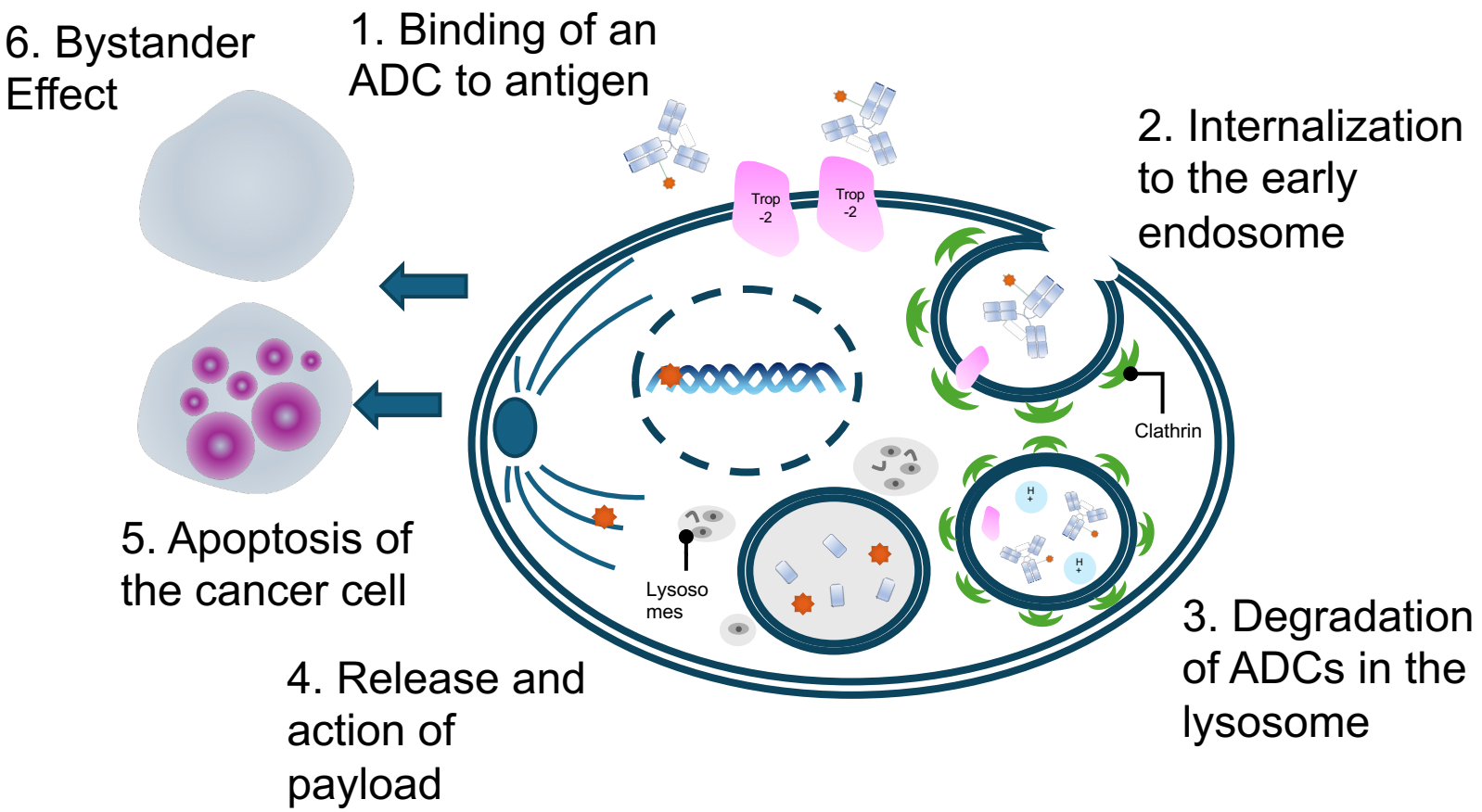
Disclosures

Consulting Agreements	Agendia Inc, AstraZeneca Pharmaceuticals LP, BriaCell, Celcuity, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Merck, Myriad Genetic Laboratories Inc, Novartis, Pfizer Inc, Puma Biotechnology Inc, Sanofi

ADCs: Selective Delivery of Toxic Payload

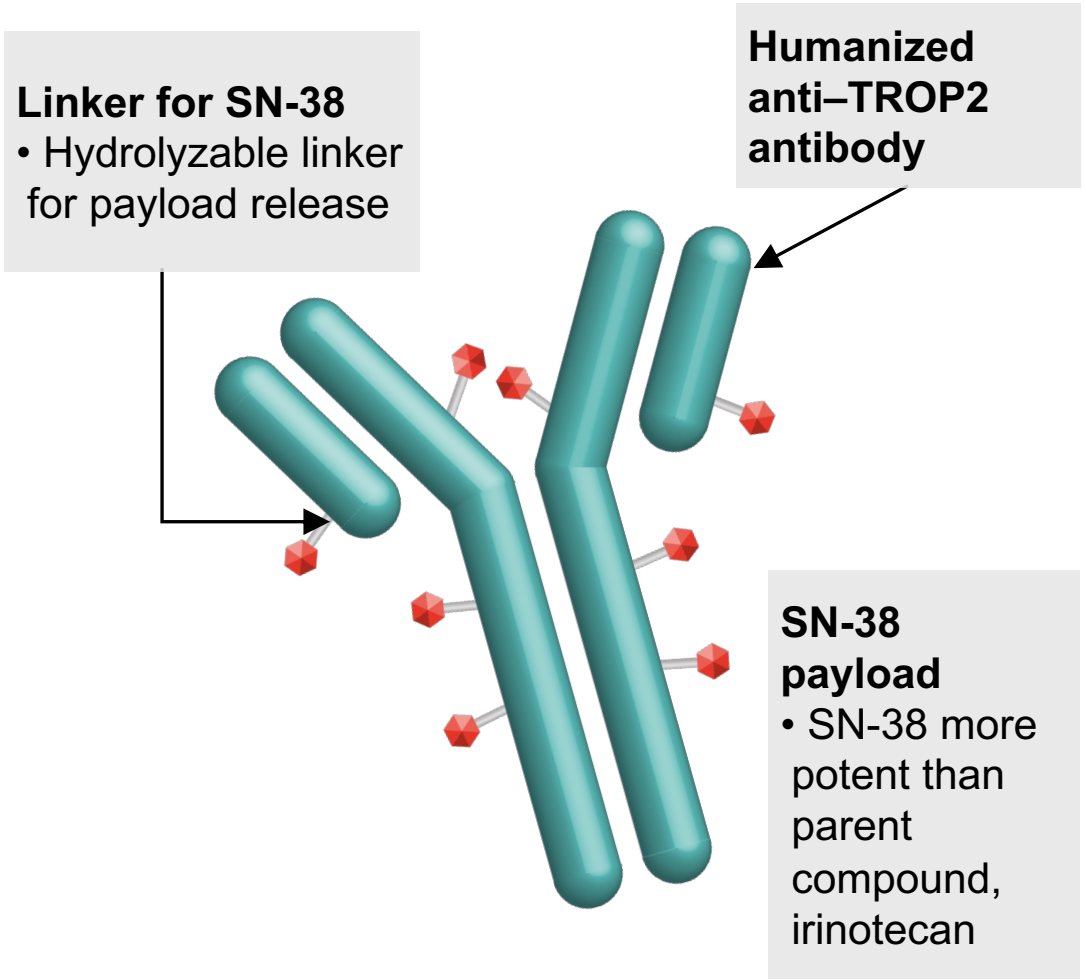


Nagayama A, et al. *Target Oncol.* 2017;12(6):719-739.

Sacituzumab Govitecan (SG): First-in-Class TROP2 ADC

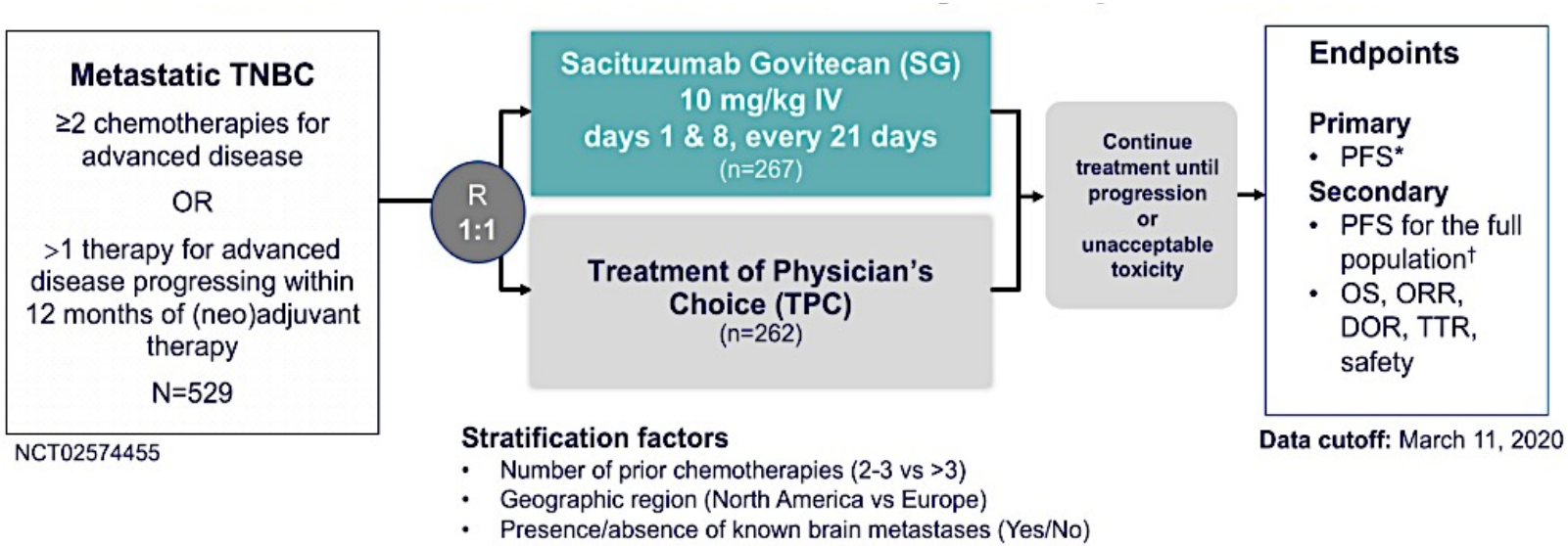
SG is distinct from other ADCs

- Antibody highly specific for Trop-2
- High drug-to-antibody ratio (7.6:1)
- Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
- Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect



Nagayama A, et al. *Ther Adv Med Oncol.* 2020;12:1758835920915980.
Cardillo TM, et al. *Bioconjugate Chem.* 2015;26(5):919-931.

ASCENT: SG vs Chemotherapy in Previously Treated mTNBC



- PFS and OS were significantly longer with sacituzumab govitecan than with single-agent chemotherapy
  - mPFS: 4.8 vs. 1.7 months (HR 0.41)
  - mOS: 11.8 vs. 6.9 months (HR 0.51)
- April 2021: FDA granted regular approval to sacituzumab govitecan for patients with unresectable locally advanced or mTNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease

Bardia A et al. *J Clin Oncol* 2024; 42(15):1738-44.

ASCENT-03: Study Design

Patients with previously untreated, locally advanced inoperable or metastatic TNBC[a]:

- Not candidates for PD-(L)1 inhibitors:
  - PD-L1 negative[b] tumors (CPS < 10)
  - PD-L1 positive[b] tumors (CPS ≥ 10) and previously treated with a PD-(L)1 inhibitor in curative setting
  - Ineligible for a PD-(L)1 inhibitor due to a comorbidity
- ≥ 6 months since treatment in curative setting
- Previously treated, stable CNS metastases were allowed

N = 558

R 1:1

Treatment was continued until BICR-verified progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
(days 1 and 8 of 21-day cycles)
n = 279

Chemotherapy
Paclitaxel 90 mg/m^2 OR nab-Paclitaxel 100 mg/m^2
(days 1, 8, and 15 of 28-day cycles) OR
Gemcitabine 1000 mg/m^2 + Carboplatin AUC2
(days 1 and 8 of 21-day cycles)
n = 279

Eligible patients were offered crossover to 2L SG, provided through the study, following BICR-verified disease progression

End points

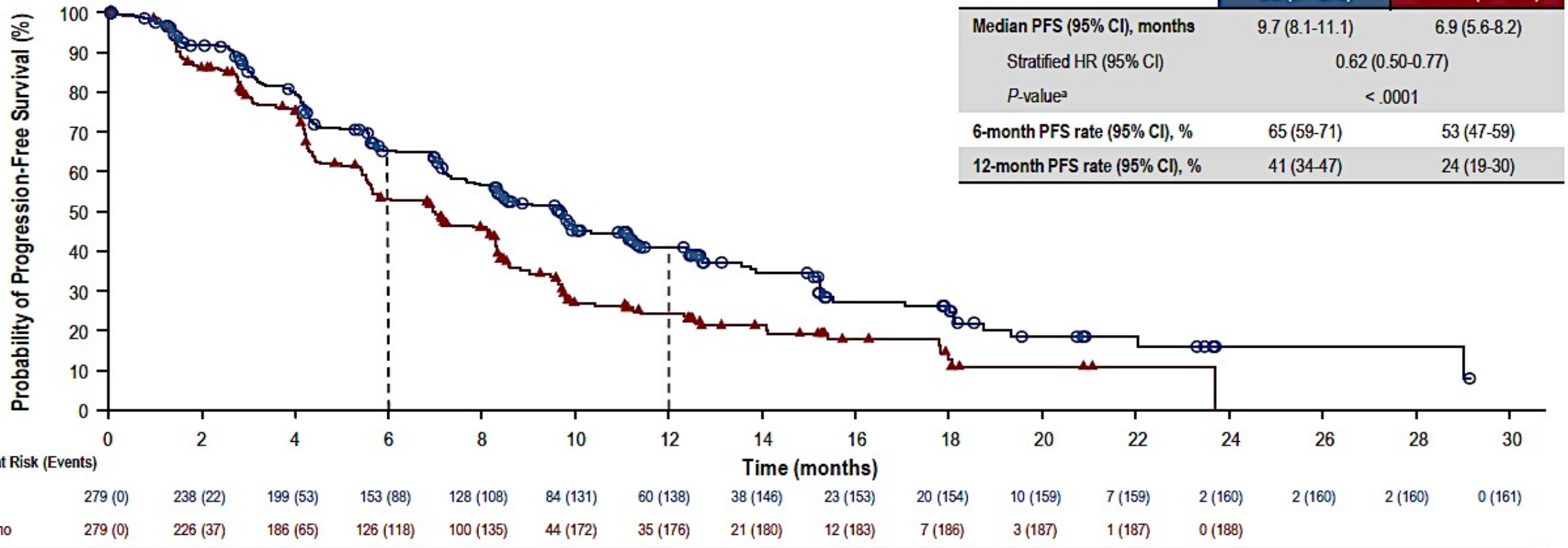
Primary
- PFS by BICR[d]

Secondary
- OS
- ORR, DOR, TTR by BICR[d]
- Safety
- QOL

Stratification factors:
- US/Canada/Western Europe vs rest of the world
- De novo mTNBC[c] vs recurrent within 6 to 12 months of treatment vs recurrent after > 12 months from treatment in curative setting

Cortes J, et al. ESMO 2025. Abstract LBA20.

ASCENT-03: Sacituzumab Govitecan vs Chemotherapy in Previously Untreated Metastatic TNBC – PFS

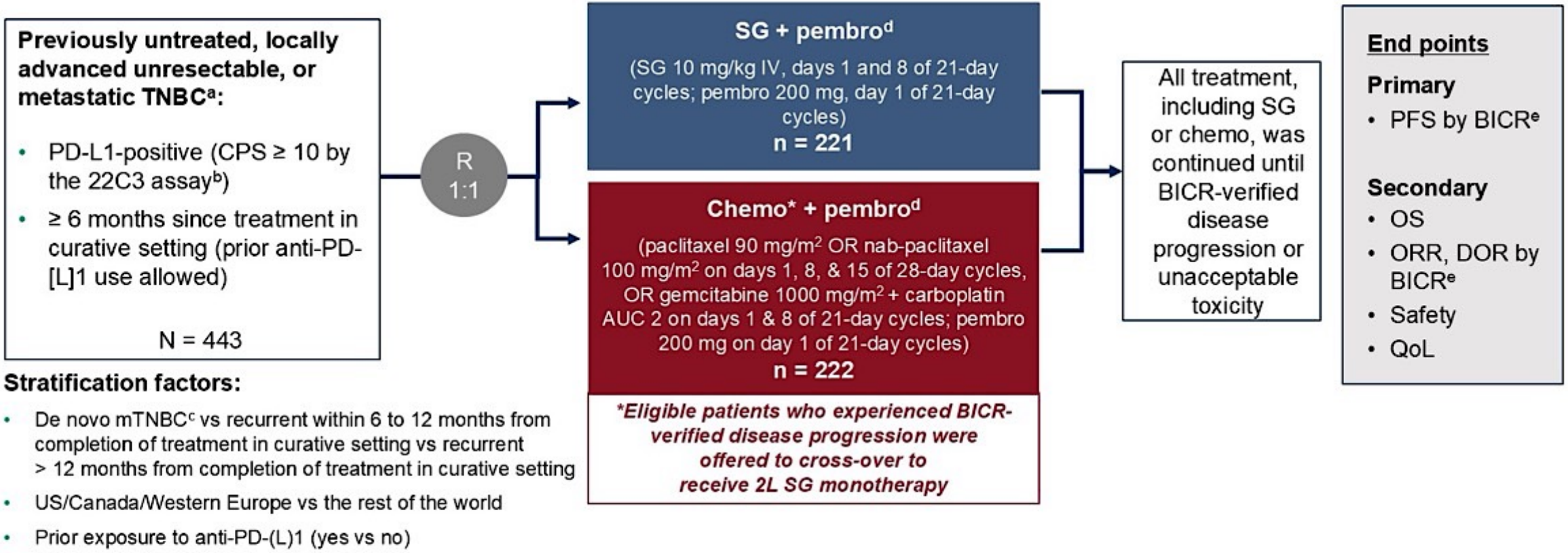


	SG (n = 279)	Chemo (n = 279)
Median PFS (95% CI), months	9.7 (8.1-11.1)	6.9 (5.6-8.2)
Stratified HR (95% CI)	0.62 (0.50-0.77)	
P-value[a]	< .0001	
6-month PFS rate (95% CI), %	65 (59-71)	53 (47-59)
12-month PFS rate (95% CI), %	41 (34-47)	24 (19-30)

SG demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo by BICR analysis, with a 38% reduction in risk of disease progression or death

Cortes J, et al. ESMO 2025. Abstract LBA20; Cortes J, et al. *N Engl J Med* 2025; 393(19):1912-25.

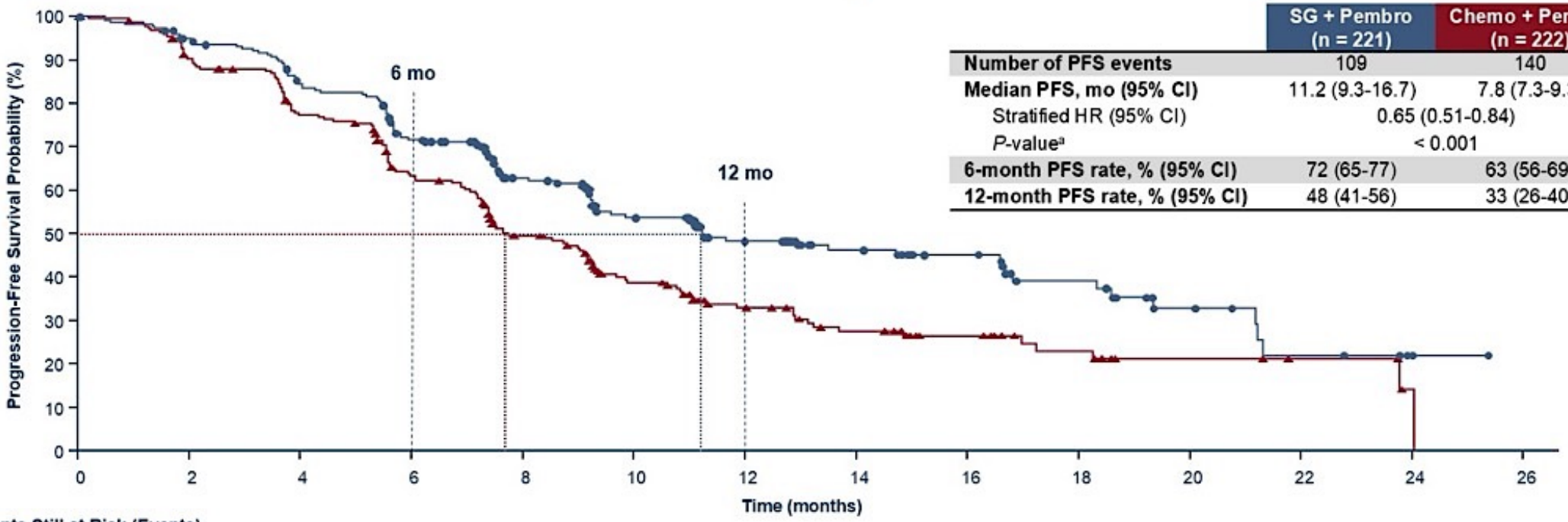
ASCENT-04: KEYNOTE-D19 Study Design



ClinicalTrials.gov identifier: NCT05382286.
[a]TNBC status determined according to standard American Society of Clinical Oncology-College of American Pathologists criteria. [b]Dako, Agilent Technologies. [c]Up to 35% de novo mTNBC. [d]Pembro was administered for a maximum of 35 cycles. [e]Per RECIST v1.1.

Tolaney SM et al. ASCO 2025;Abstract LBA109; Tolaney SM, et al; ASCENT-04/KEYNOTE-D19 Clinical Trial Investigators. *N Engl J Med.* 2026;394(4):354-366.

ASCENT-04: Progression-Free Survival by BICR



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	109	140
Median PFS, mo (95% CI)	11.2 (9.3-16.7)	7.8 (7.3-9.3)
Stratified HR (95% CI)	0.65 (0.51-0.84)	
P-value[a]	< 0.001	
6-month PFS rate, % (95% CI)	72 (65-77)	63 (56-69)
12-month PFS rate, % (95% CI)	48 (41-56)	33 (26-40)

No. of Patients Still at Risk (Events)

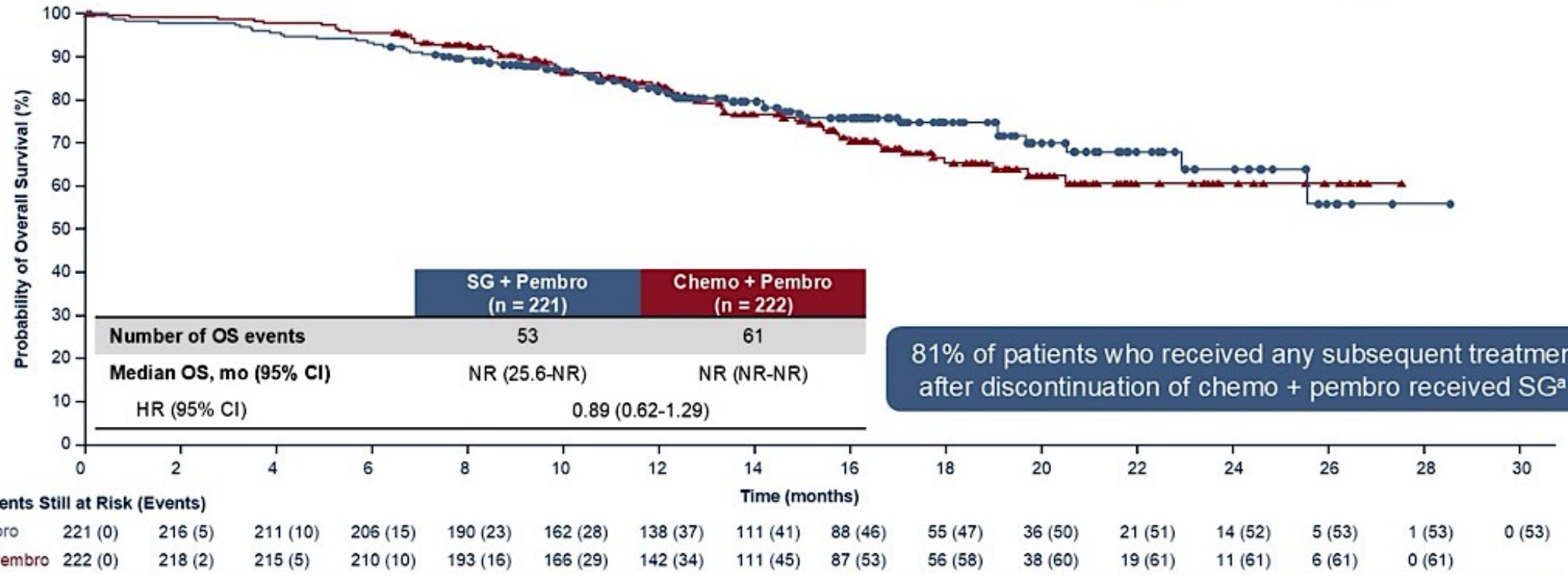
SG + Pembro	221 (0)	202 (11)	174 (33)	142 (59)	105 (75)	78 (89)	58 (96)	42 (98)	34 (99)	22 (103)	11 (106)	6 (109)	2 (109)	0 (109)
Chemo + Pembro	222 (0)	191 (21)	159 (48)	123 (76)	88 (102)	59 (120)	40 (128)	29 (134)	21 (135)	13 (137)	7 (138)	4 (138)	1 (139)	0 (140)

SG + pembro demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo + pembro by BICR analysis, with a 35% reduction in risk of disease progression or death

Data cutoff date: March 3, 2025.
[a]Two-sided *P*-value from stratified log-rank test.

Tolaney SM et al. ASCO 2025;Abstract LBA109; Tolaney SM, et al; ASCENT-04/KEYNOTE-D19 Clinical Trial Investigators. *N Engl J Med.* 2026;394(4):354-366.

ASCENT-04: Descriptive Overall Survival at Primary Analysis



81% of patients who received any subsequent treatment after discontinuation of chemo + pembro received SG[a]

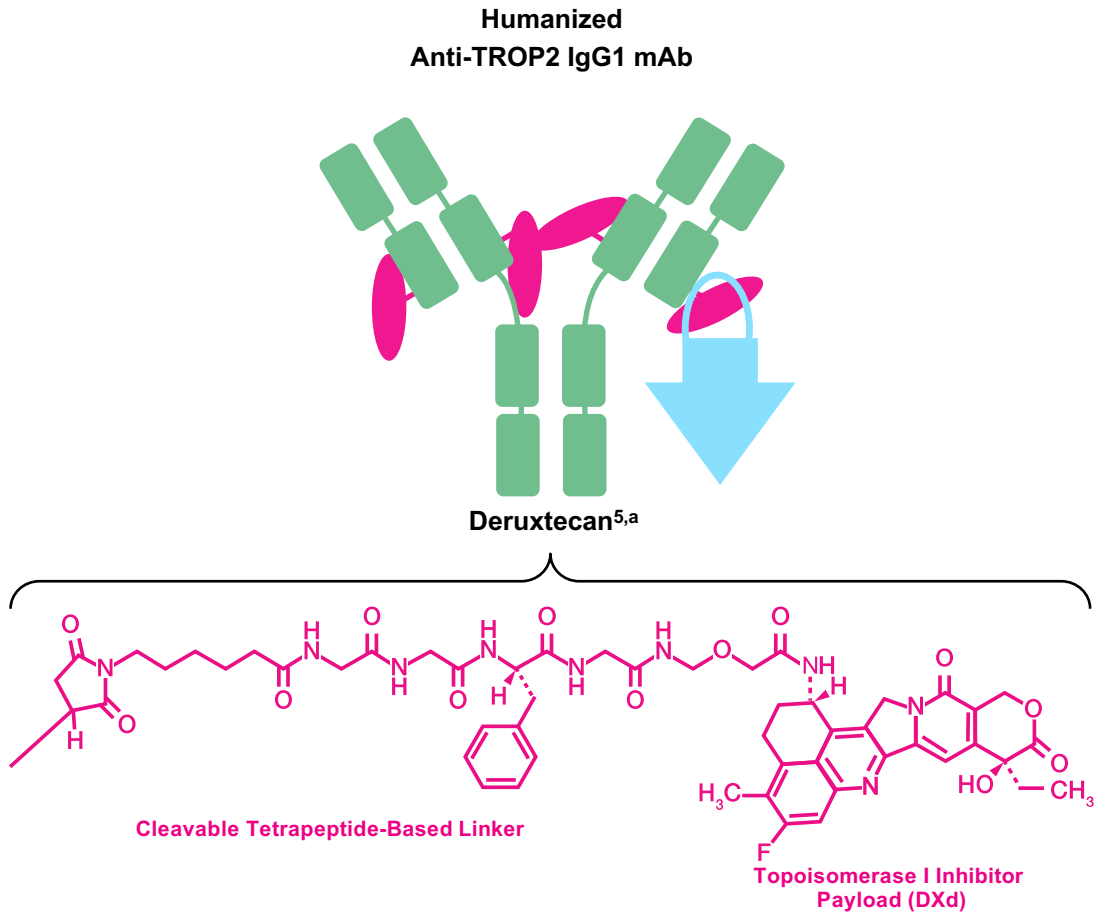
OS data were immature (maturity rate, 26%), however, a positive trend in improvement was observed for SG + pembro vs chemo + pembro

Data cutoff date: March 3, 2025. Median follow-up was 14.0 months (range, 0.1-28.6).
[a]Of the 96 patients who received SG monotherapy as subsequent anticancer therapy, 77 received it as part of the protocol-specified crossover after meeting all crossover eligibility criteria, including BICR-verification of disease progression; the remaining 19 patients received subsequent SG monotherapy as commercial supply.

Tolaney SM et al. ASCO 2025;Abstract LBA109; Tolaney SM, et al; ASCENT-04/KEYNOTE-D19 Clinical Trial Investigators. *N Engl J Med.* 2026;394(4):354-366.

Datopotamab Deruxtecan (Dato-DXd)

- Patients with relapsed/refractory advanced or metastatic TNBC have poor clinical outcomes[1]
- Dato-DXd is a differentiated TROP2-directed ADC designed with 3 components[2,3]:
  - A humanized anti-TROP2 IgG1 mAb
  - A topoisomerase I inhibitor payload (exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker
- Dato-DXd has demonstrated highly encouraging antitumor activity and manageable AEs in the NSCLC cohort[4]
  - 6 mg/kg has been selected as the dose for expansion into other advanced tumor types



[a]Actual drug positions may vary.

1. Bardia A, et al; ASCENT Clinical Trial Investigators. *N Engl J Med.* 2021;384(16):1529-1541. 2. Okajima D, et al. AACR-NCI-EORTC 2019. Abstract C026. 3. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 4. Spira A, et al. WCLC 2020. Abstract 3407. 5. Krop I, et al. SABCS 2019. Abstract GS1-03.

TROPION-Breast02: Study Design

Randomized, phase 3, open-label, global study (NCT05374512)

Key inclusion criteria:

- Patients with histologically or cytologically documented locally recurrent inoperable or metastatic TNBC*
- No prior chemotherapy or targeted systemic therapy in the locally recurrent inoperable or metastatic setting
- Immunotherapy not an option†
- ECOG PS 0 or 1
- No minimum DFI‡

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=323)

Investigator's choice of chemotherapy (ICC)#
Paclitaxel, nab-paclitaxel, capecitabine, eribulin mesylate/eribulin, carboplatin
(n=321)

Endpoints

Dual primary:

- OS
- PFS by BICR per RECIST v1.1

Secondary included:

- PFS (investigator-assessed)
- ORR, DoR
- Safety

Randomisation stratified by:

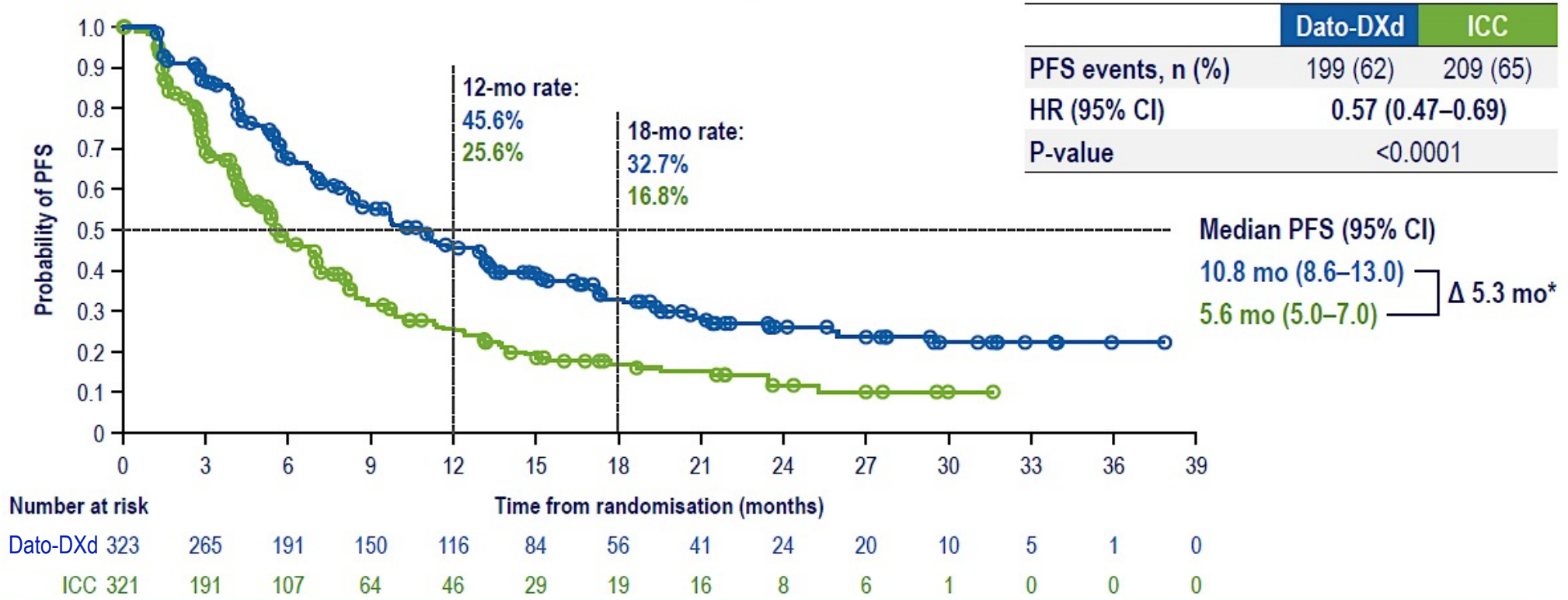
- Geographic region (US/Canada/Europe vs other geographic regions)
- PD-L1 status (high [CPS ≥10] vs low [CPS <10])§
- DFI history (*de novo* vs prior DFI 0–12 months vs prior DFI >12 months)¶

- Treatment continued until investigator-assessed RECIST v1.1 progressive disease, unacceptable toxicity, or another discontinuation criterion was met
- Following progression or discontinuation of study treatment, patients could receive subsequent therapies, including approved ADCs or chemotherapy, at the investigator's discretion‖

*According to ASCO/CAP criteria. †Including patients with PD-L1-low tumours, or patients with PD-L1-high tumours with (a) disease relapse after prior PD-(L)1 inhibitor therapy for early-stage breast cancer, (b) comorbidities precluding PD-(L)1 inhibitor therapy, or (c) no regulatory access to PD-(L)1 inhibitor therapy. ‡DFI defined as time between date of completion of treatment with curative intent and date of first documented local or distant disease recurrence. §Recruitment of patients with PD-L1-high tumours who would otherwise be eligible for pembrolizumab if regulatory access was available was capped at ~10% of randomised patients. ¶Recruitment of patients with DFI 0–12 months was capped at ~20% of randomised patients. #If no prior taxane, or prior taxane in the (neo)adjuvant setting and DFI >12 months: paclitaxel 80 mg/m^2 IV, D1, 8, 15, Q3W, or nab-paclitaxel 100 mg/m^2 IV, D1, 8, 15, Q4W; if prior taxane and DFI 0–12 months: capecitabine 1000 or 1250 mg/m^2 orally twice daily, D1–14, Q3W (dose determined by standard institutional practice), or eribulin mesylate 1.4 mg/m^2 / eribulin 1.23 mg/m^2 IV, Day 1, 8, Q3W, or carboplatin AUC6 IV, D1, Q3W. ‖In the Dato-DXd vs ICC arm, 65% vs 72% of patients received any subsequent therapy in any treatment line; 14% vs 30% received a subsequent ADC (sacituzumab govitecan, sacituzumab tirumotecan, trastuzumab deruxtecan).

Dent R, et al ESMO 2025. Abstract LBA21.

TROPION-Breast02: First-Line Dato-DXd in Locally Recurrent or Metastatic TNBC – PFS



	Dato-DXd	ICC
PFS events, n (%)	199 (62)	209 (65)
HR (95% CI)	0.57 (0.47–0.69)	
P-value	<0.0001	

Median PFS (95% CI)

10.8 mo (8.6–13.0)

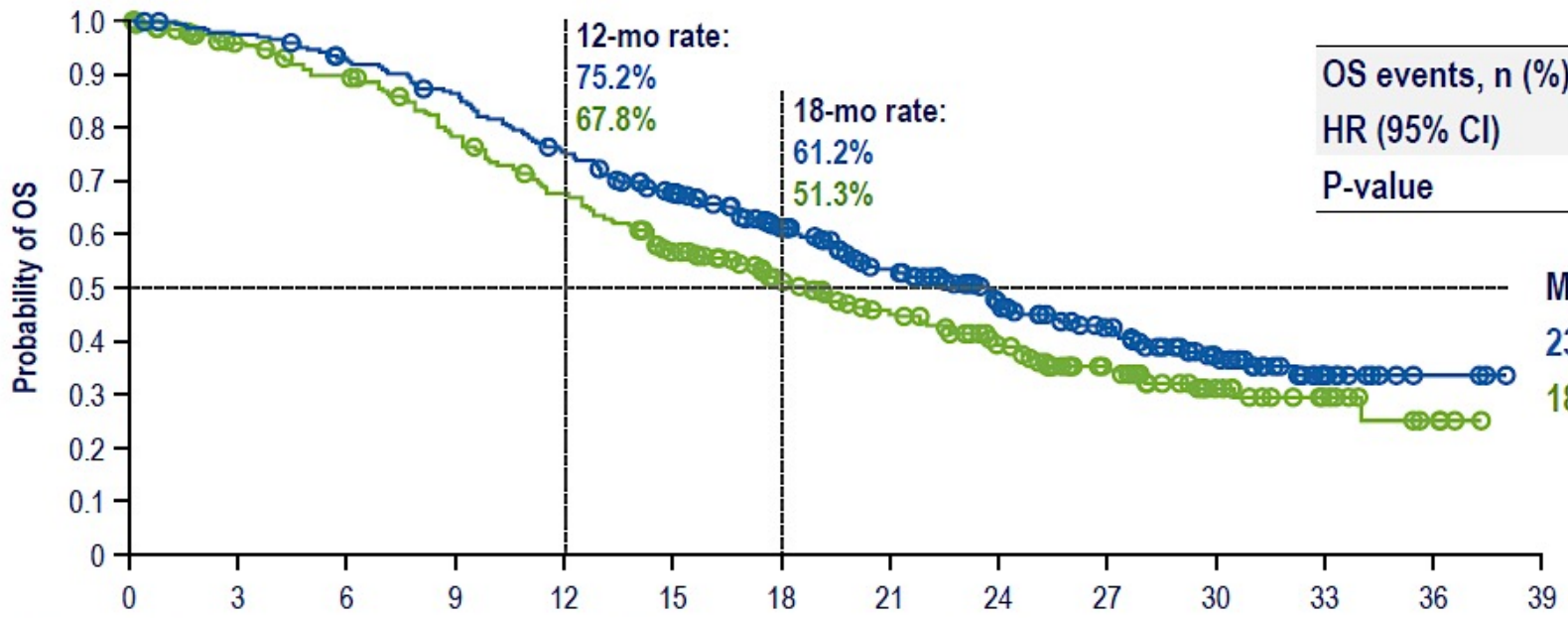
5.6 mo (5.0–7.0)

Δ 5.3 mo*

Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with ICC, reducing the risk of progression or death by 43%

Dent R, et al ESMO 2025. Abstract LBA21; Dent R et al. *Ann Oncol* 2026; Apr 3:S0923-7534(26)00130-4.

TROPION-Breast02: Overall Survival



	Dato-DXd	ICC
OS events, n (%)	168 (52)	181 (56)
HR (95% CI)	0.79 (0.64–0.98)	
P-value	0.0291	

Median OS (95% CI)

23.7 mo (19.8–25.6)

18.7 mo (16.0–21.8)

Δ 5.0 mo

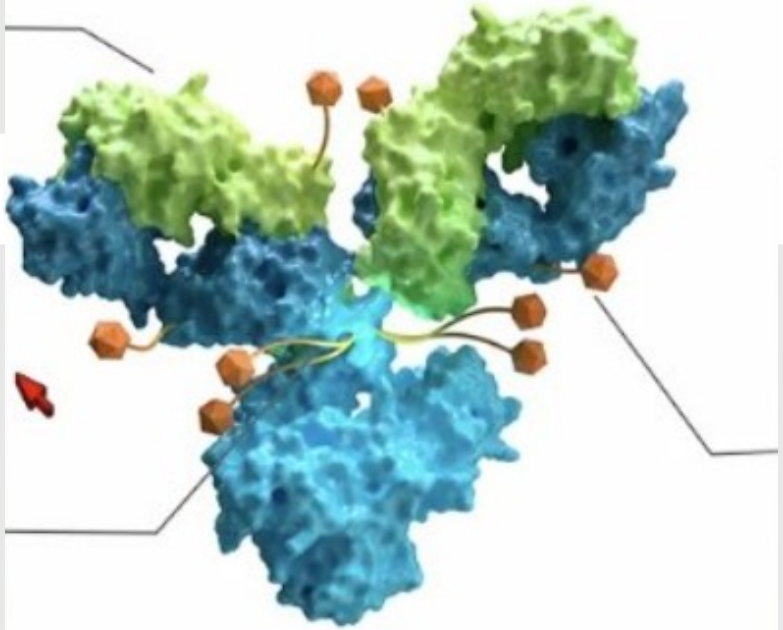
Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with ICC, reducing the risk of death by 21%

Dent R, et al ESMO 2025. Abstract LBA21; Dent R et al. *Ann Oncol* 2026; Apr 3:S0923-7534(26)00130-4.

Sacituzumab Tirumotecan (Sac-TMT)

- TROP2 ADC developed with a proprietary Kthiol (pyrimidine-thiol) linker conjugated to a novel topoisomerase I inhibitor at DAR 7.4

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

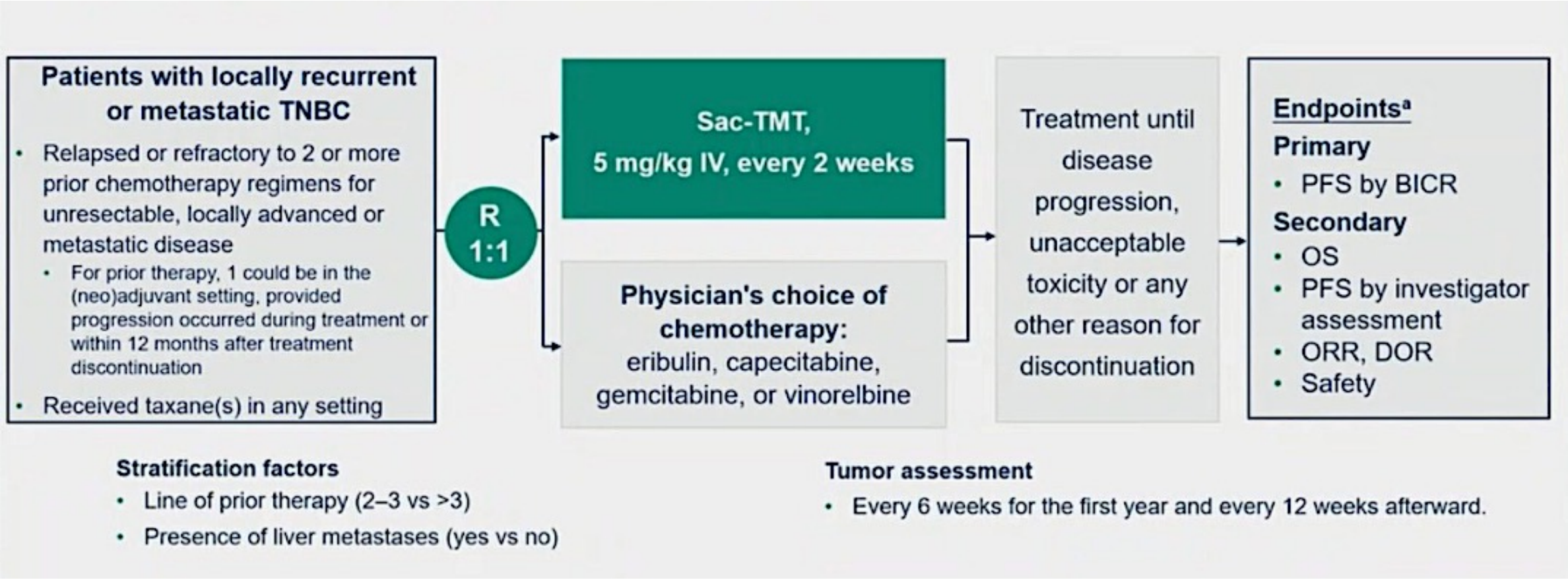


Linker
- **Kthiol conjugation:** irreversible coupling to improve stability of ADC
- **Payload release:** intracellular cleavage and extracellular hydrolysis in TME
- **Balanced stability:** balance between efficacy and safety to expand therapeutic window

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

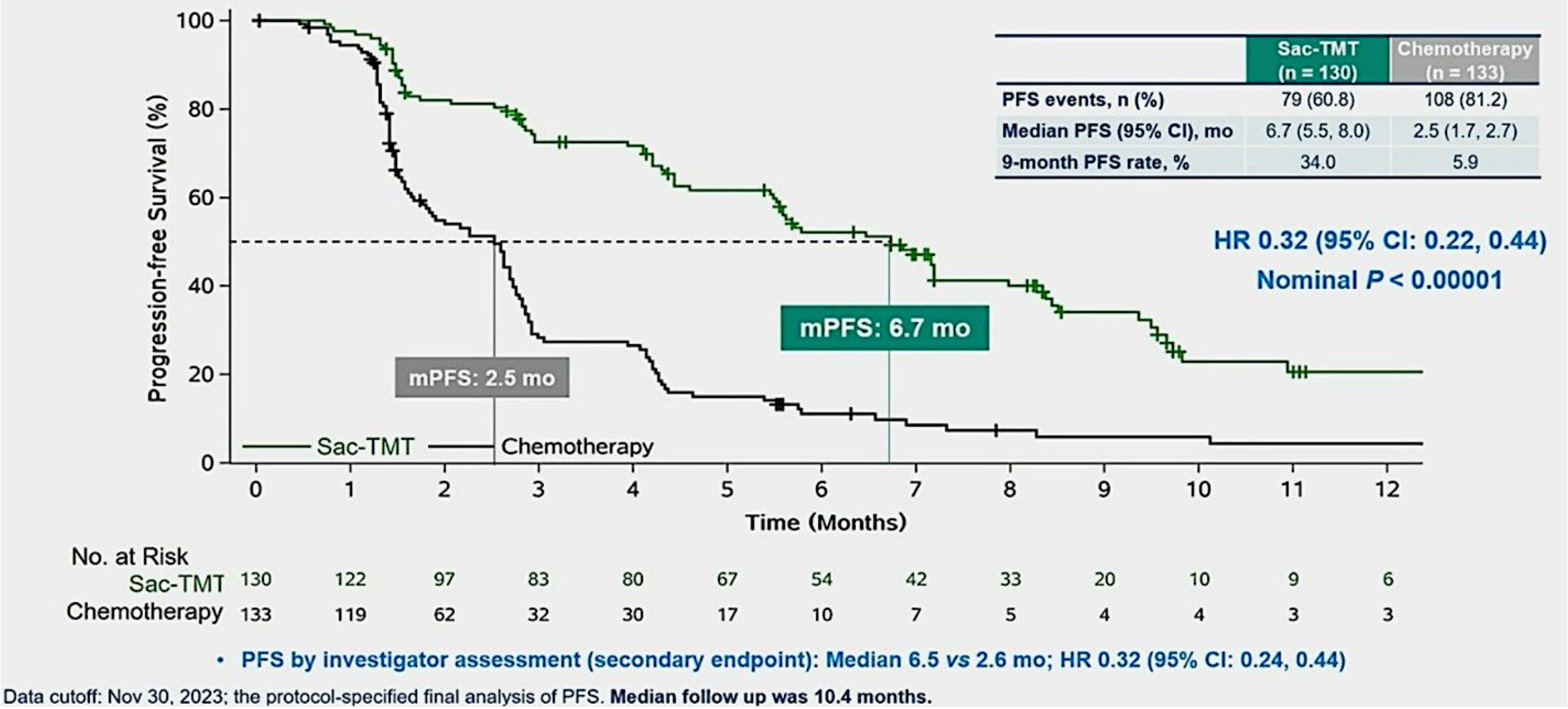
Fang W, et al. *J Clin Oncol.* 2024;42(16_suppl):8502.

OptiTROP-Breast01: Sac-TMT in Previously Treated Locally Recurrent or Metastatic TNBC



Xu B, et al. *J Clin Oncol.* 2024;42(16_suppl):104.

OptiTROP-Breast01: PFS by BICR (Final Analysis)



	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)
9-month PFS rate, %	34.0	5.9

- **PFS by investigator assessment (secondary endpoint): Median 6.5 *vs* 2.6 mo; HR 0.32 (95% CI: 0.24, 0.44)**

Data cutoff: Nov 30, 2023; the protocol-specified final analysis of PFS. **Median follow up was 10.4 months.**

Xu B, et al. *J Clin Oncol.* 2024;42(16_suppl):104.

Looking Ahead

TROPION-Breast05

Patient Population

- **PD-L1+ (CPS ≥10)** untreated, inoperable/locally advanced or metastatic TNBC
- **DFI ≥6 months since therapy in curative setting** (DFI 6–12 months capped at 20%)
- Prior PD-(L)1 use allowed in this setting
- History of ILD/pneumonitis and clinically significant corneal disease excluded

Study Design

R 1:1

N~625

- **Dato-DXd + durvalumab**
- **Dato-DXd monotherapy**
- **TPC chemo + pembrolizumab** *(gem + carbo; pac; nab-pac)*

Stratification Factors

- Geographic region
- Prior PD-(L)1
- *De novo* vs prior DFI 6–12 months vs prior DFI >12 months

Key Endpoints

- Primary: PFS by BICR
- Secondary: OS, PFS (per investigator), ORR, safety, PROs

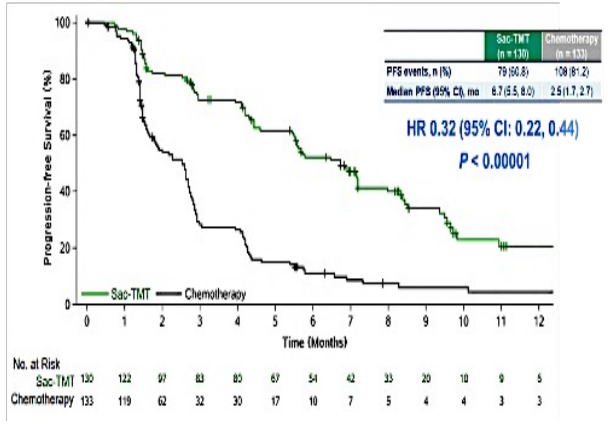
★ STILL ENROLLING

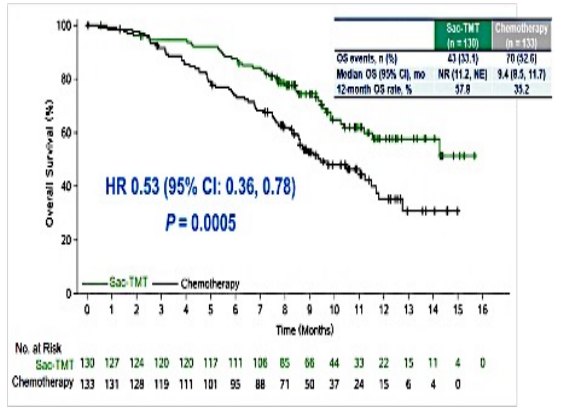
Sacituzumab Tirumotecan

(TROP2 ADC with Topo1 Payload)

- **OptiTROP-Breast 01** (Sac-TMT vs TPC (2L+) mTNBC) :
  - PFS 6.7 vs 2.5 mo (HR 0.32)
  - OS NR vs 9.4 mo (HR 0.53)

PFS | OS





- **OptiTROP-Breast05**, 1L mTNBC
  - All patients (n=41), mPFS=13.4 mos;
  - PD-L1 CPS > 10 (n=32), mPFS 13.1 mos

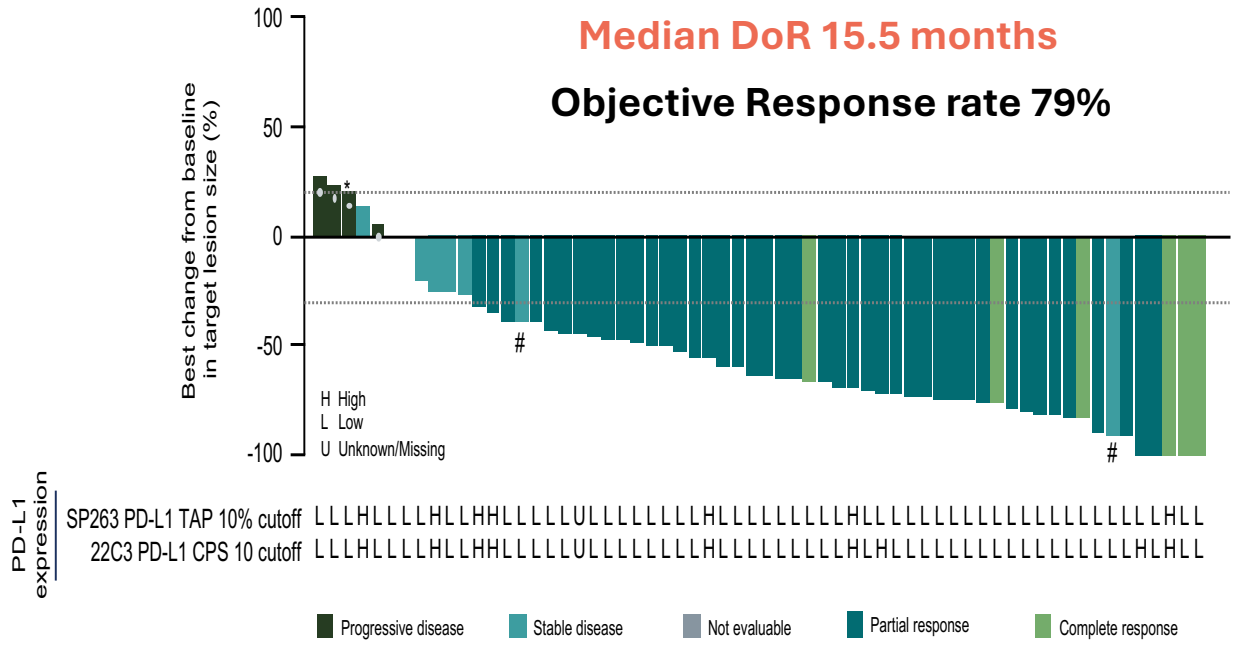
Xu B et al. ASCO 2024; Abstract 104; Yin Y et al. ASCO 2025;Abstract 1019.

Is There a Role for ICI in PDL1-Neg When Combined With ADC?

Dato-DXd plus durvalumab in 1st line mTNBC (87% PDL1-negative)

Median PFS 13.8 months
Median DoR 15.5 months

Objective Response rate 79%



Schmid P et al. ESMO 2023;Abstract 379MO.

DIAMOND (Ph 2): Dato-DXd +/- durvalumab in PD-L1- mTNBC

- Previously untreated, locally advanced inoperable or metastatic TNBC
- PD-L1- (CPS <10)
- No prior neoadj/adj IO within 6 mo

Stratification Factors:
De novo OR DFI≤12 mo OR DFI>12 mo

Dato-DXd

1:1

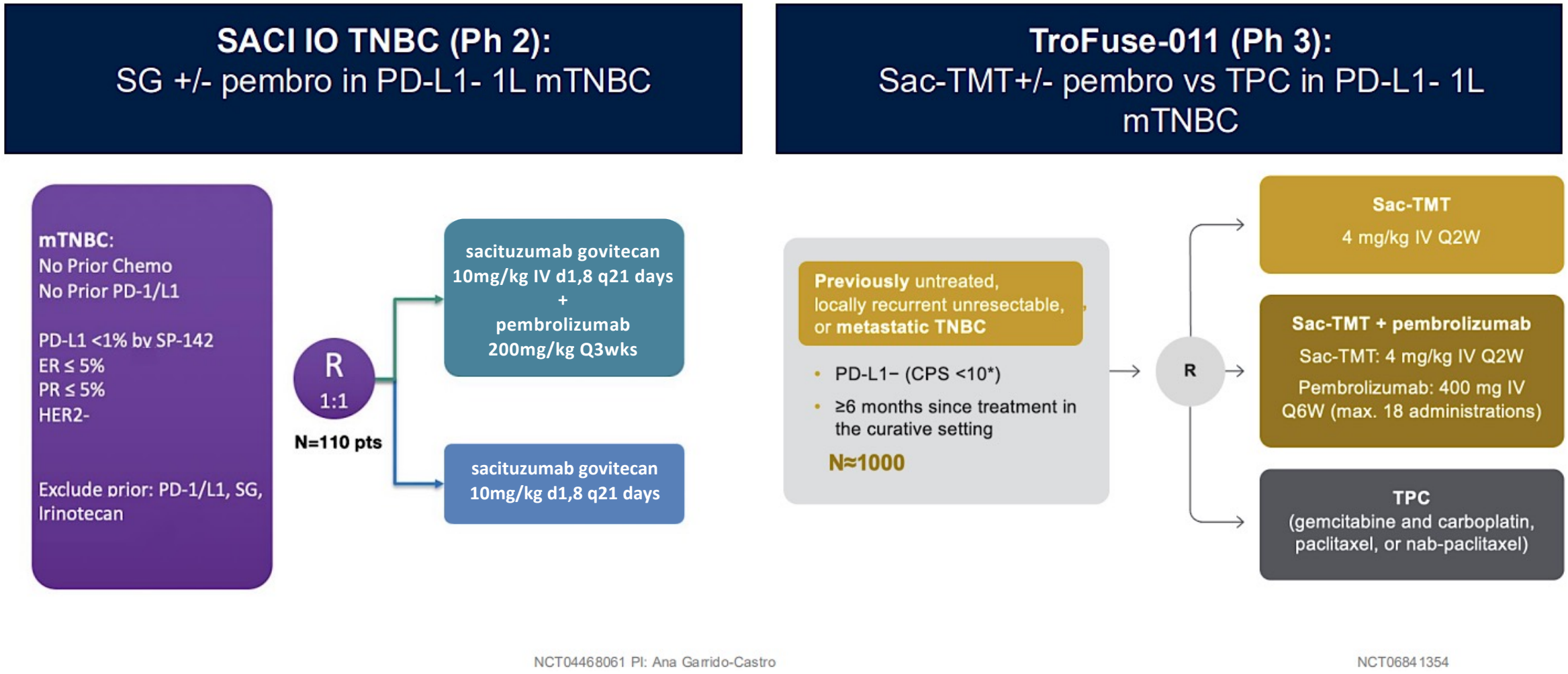
N=140

Dato-DXd + durvalumab

NCT06954480
PI:Peter Schmid

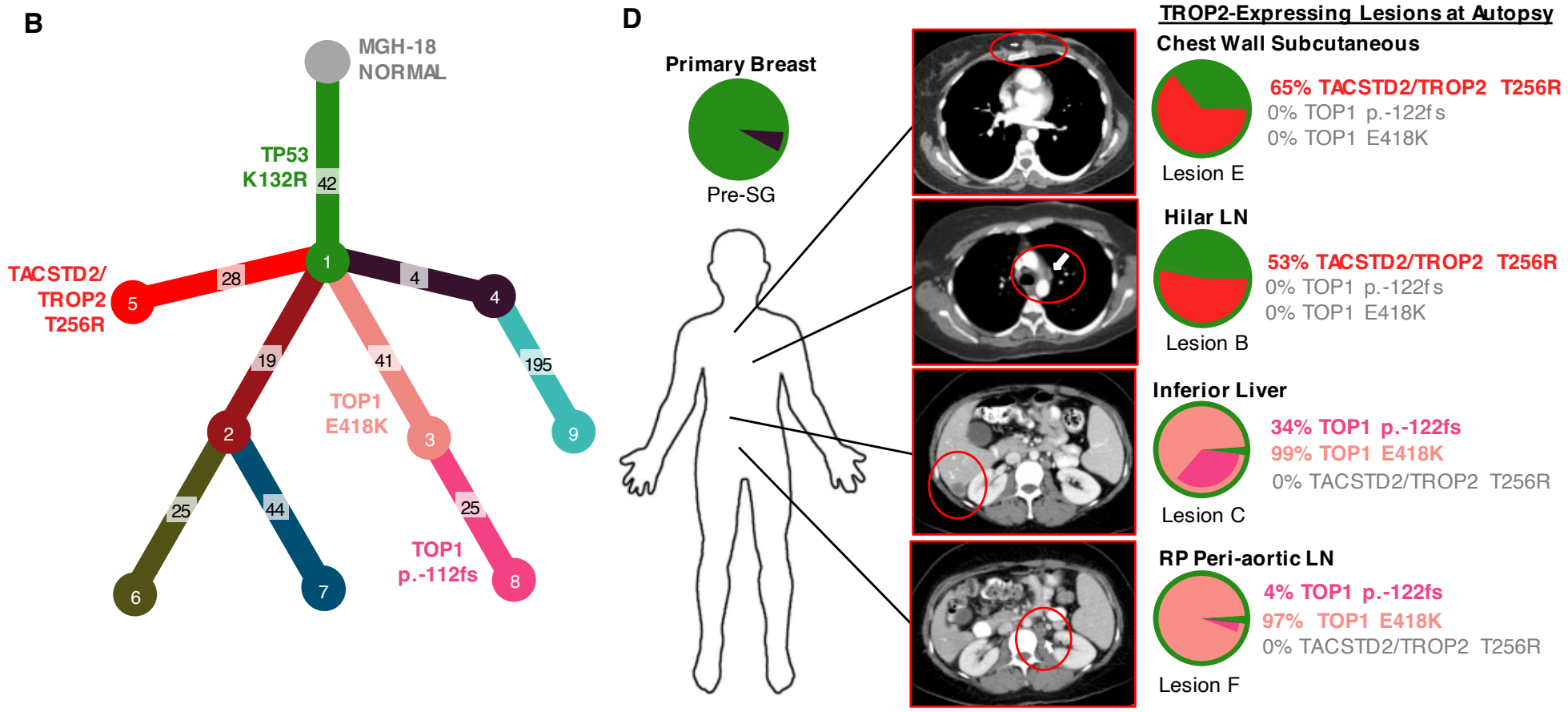
Schmid P et al. ESMO Virtual Plenary. Abstract VP1-2025.

Is There a Role for ICI in PDL1-Neg When Combined With ADC?



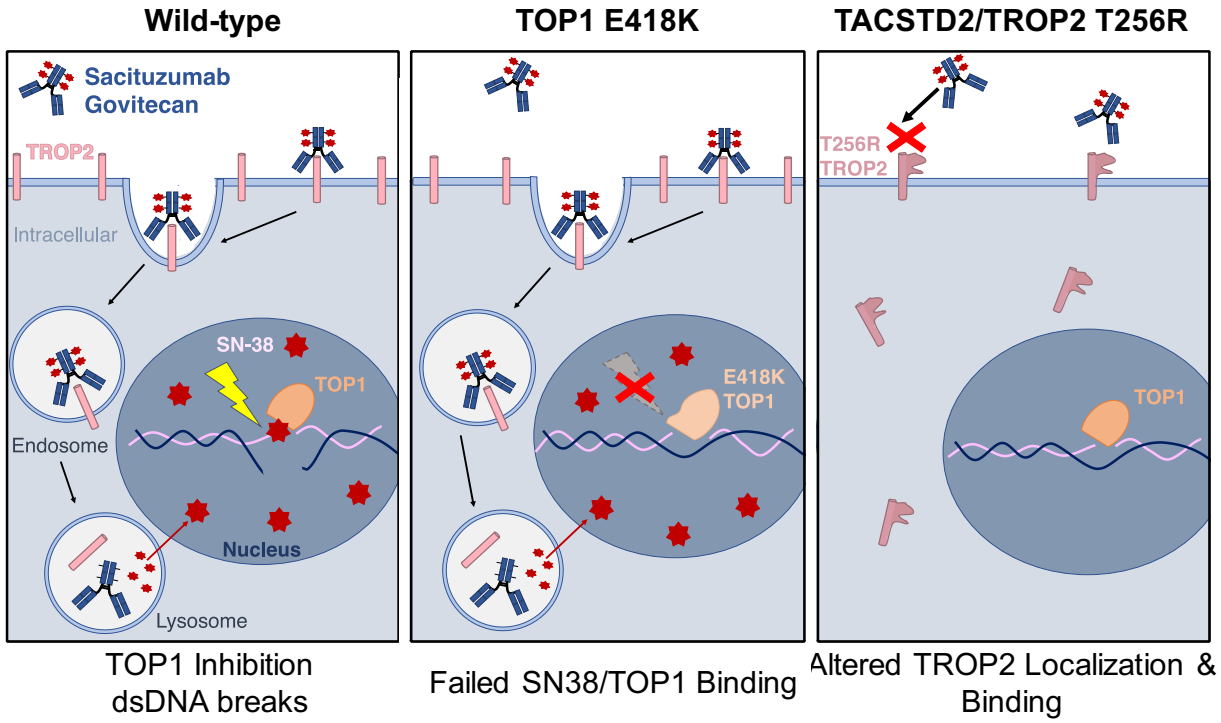
Courtesy of Adam Brufsky, MD, PhD

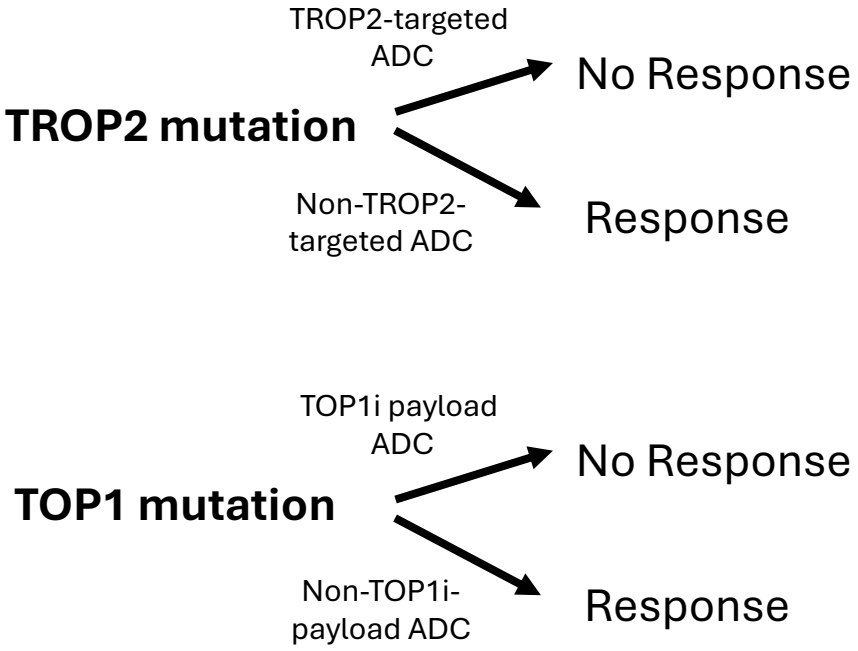
Mechanism Governing Resistance: Antibody vs Payload



TACSTD2, tumor associated calcium signal transducer 2; TOP1, topoisomerase I; TROP2, trophoblast cell-surface antigen 2.
Coates JT, et al. *Cancer Discov.* 2021;11(10):2436-2445.

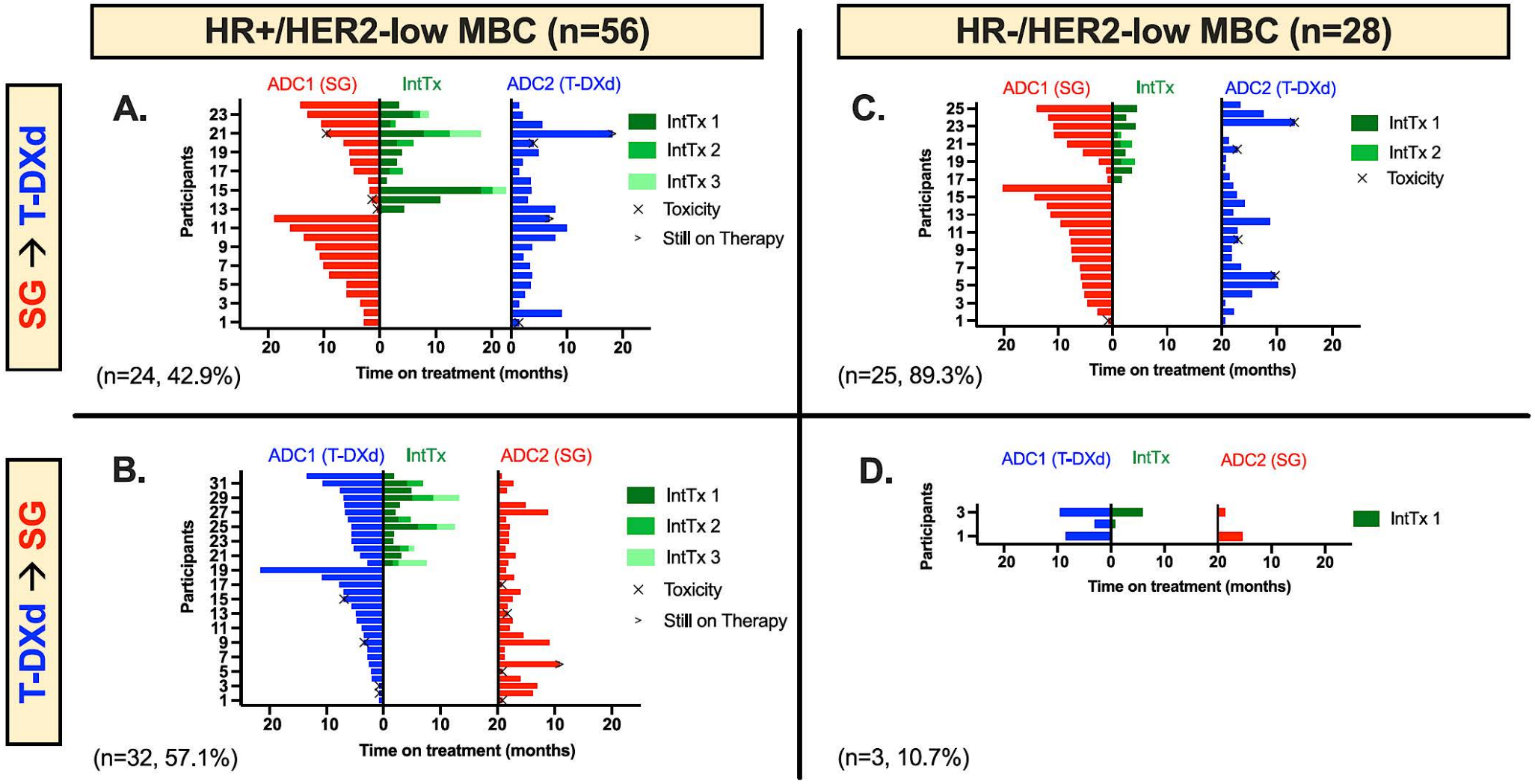
Implications of Resistance Mechanisms for ADC Sequencing





ADC, antibody-drug conjugate; *TACSTD2*, tumor associated calcium signal transducer 2; TOP1i, topoisomerase I inhibitor; TROP2, trophoblast cell-surface antigen 2.
Coates JT, et al. *Cancer Discov.* 2021;11(10):2436-2445.

Retrospective Data About Sequential Use of Topo1i ADCs

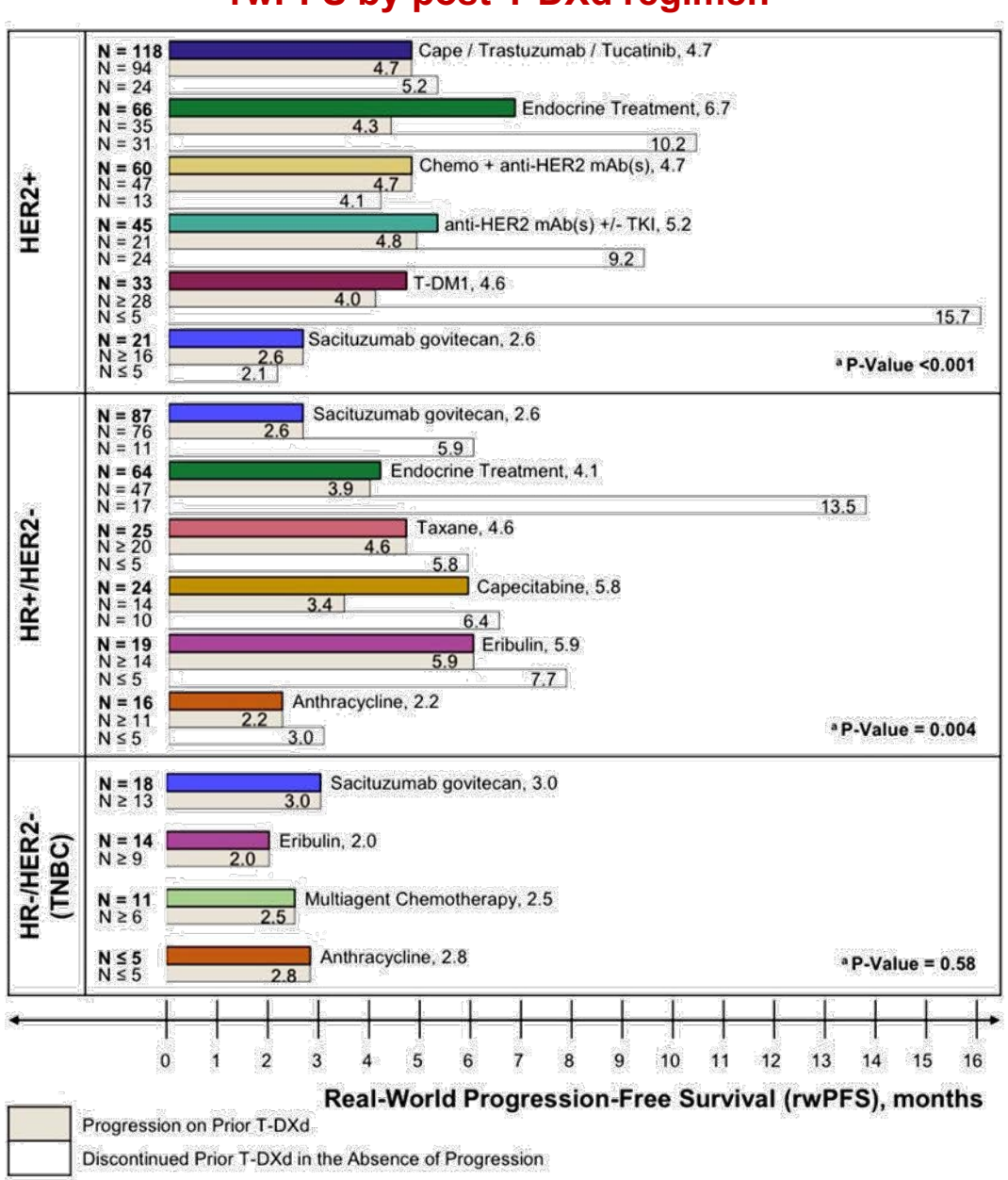


Huppert LA et al. *NPJ Breast Cancer.* 2025;11(1):34.

Retrospective Data About Sequential Use of Topo1i ADCs

- Using Flatiron registry data (n=**633**), evaluated real-world efficacy of **immediate subsequent therapy given after T-DXd**
- Short rwPFS (≤ 3mo) of SG post T-DXd suggests some degree of cross resistance among Topo1 ADCs

rwPFS by post-T-DXd regimen

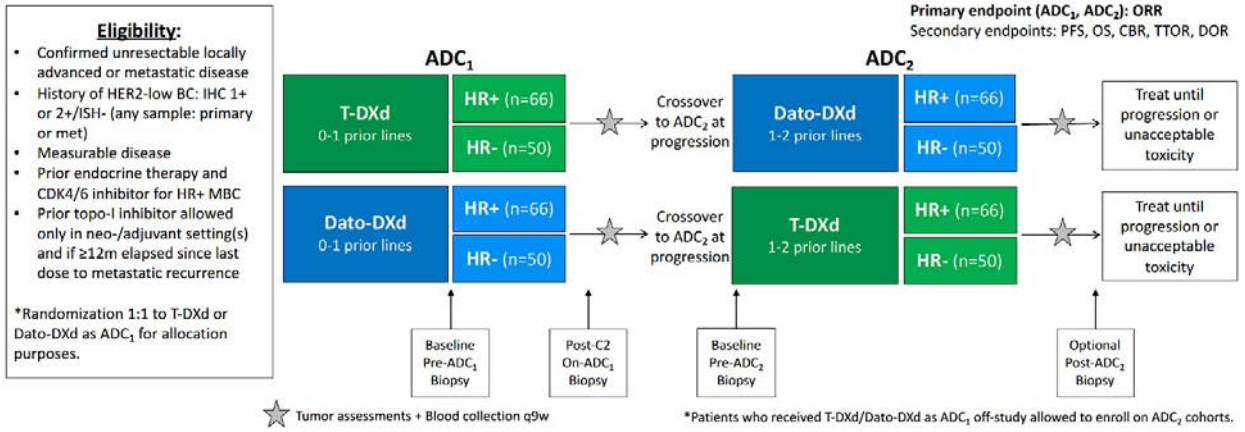


Tarantino P et al. *J Natl Cancer Inst.* 2025;117(11):2327-2335.

Prospective Trials of Sequential ADCs for HER2- MBC

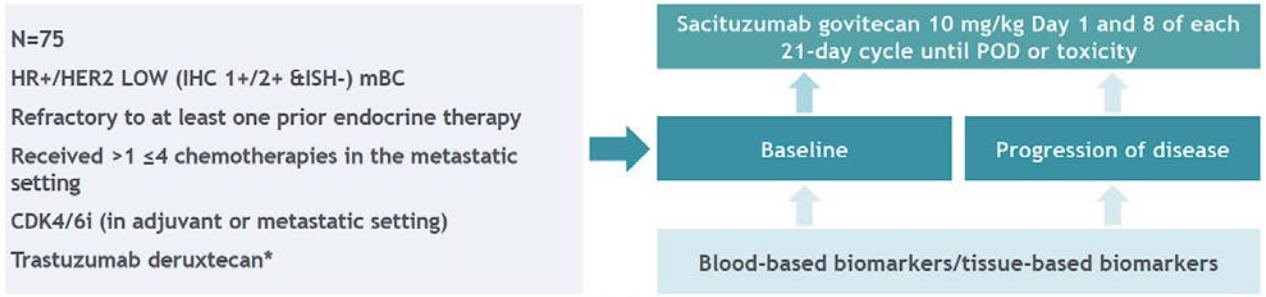
TBCRC 064 TRADE-DXd: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd: TRADE-DXd

NCT06533826; PI: Garrido-Castro



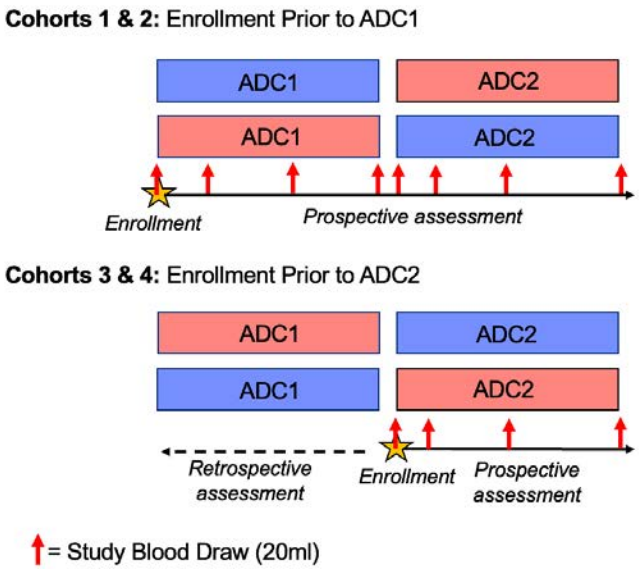
SERIES: Phase II, single-arm, multi-center, open-label study of SG post-progression on T-DXd

NCT06263543; PI: Mahtani



TBCRC 067 ENCORE: ProspectivE Registry of Sequential ANtibody Drug COnjugates in HER2 Negative Metastatic BREast Cancer

NCT06774027; PI: Huppert



- **Cohort 1:** HR+/HER2- MBC (~35 patients)
- **Cohort 2:** mTNBC (~25 patients)
- **Cohort 3:** HR+/HER2- MBC (~25 patients)
- **Cohort 4:** mTNBC (~15 patients)

For all cohorts:

- ADCs and imaging at least q12wk per SOC
- PRO data collection
- Research blood collection: Prior to C1D1, C2D1, C5D1, q4 cycles, end of treatment
- Archival tissue collection and research biopsy if SOC biopsy planned
- Intervening therapies between ADCs is allowed

Select Ongoing Phase III Trials of TROP2 ADCs as (Neo)Adjuvant Therapy for Localized TNBC

Neoadjuvant and adjuvant settings			
Trial identifier	**Est. N**	**Population**	**Regimen**
ADAPT-TN-III (NCT06081244)	348	Stage I or selected Stage II triple-negative or HR-low, HER2-negative breast cancer	Arm A: pembrolizumab + SG ± NACT → surgery → ± TPC; Arm B: SG ± NACT → surgery → ± TPC
ADAPT-TN-IV (NCT07178730)	765	Stage II-III triple-negative or HR-low, HER2-negative breast cancer	All: pembrolizumab + PCb + evaluation Cohort 1 (Stage II and cCR): → surgery → SoC; Cohort 2 (Stage III or non-cCR): → Arm A: pembrolizumab + SG → surgery → SoC; Arm B: pembrolizumab +AC/EC → surgery → SoC
TROPION-Breast04 (NCT06112379)	1,902	Stage II-III triple-negative or HR-low, HER2-negative breast cancer	Arm A: durvalumab + Dato-DXd → surgery → durvalumab ± chemotherapy ± olaparib; Arm B: KEYNOTE-522 regimen → surgery → pembrolizumab ± capecitabine ± olaparib

ADCs = antibody-drug conjugates; TNBC = triple-negative breast cancer; SG = sacituzumab govitecan; NACT = neoadjuvant chemotherapy; TPC = treatment of physician's choice; PCb = paclitaxel/carboplatin; cCR = complete clinical response; SoC = standard of care; AC= doxorubicin/cyclophosphamide; EC = epirubicin/cyclophosphamide

Xi G et al. *Front Immunol* 2026;17:1795426.

Select Ongoing Phase III Trials of TROP2 ADCs as (Neo)Adjuvant Therapy for Localized TNBC

Neoadjuvant and adjuvant settings			
Trial identifier	**Est. N**	**Population**	**Regimen**
TroFuse-032 (NCT06966700)	2,400	Localized (cT1cN1-2 or cT2-4N0-2) triple-negative or HR-low, HER2-negative breast cancer	Arm A: pembrolizumab + sac-TMT → pembrolizumab + wPCb → surgery → pembrolizumab ± capecitabine ± olaparib ± AC/EC; Arm B: KEYNOTE-522 regimen → surgery → pembrolizumab ± capecitabine ± olaparib
Adjuvant setting			
ASCENT-05 (NCT05633654)	1,514	Non-pCR triple-negative or HR-low, HER2-negative breast cancer after neoadjuvant therapy	Arm A: pembrolizumab + SG; Arm B: pembrolizumab ± capecitabine
TroFuse-012 (NCT06393374)	1,530	Non-pCR TNBC after neoadjuvant KEYNOTE-522 regimen	Arm A: pembrolizumab + sac-TMT; Arm B: pembrolizumab ± capecitabine

sac-TMT = sacituzumab tirumotecan; wPCb = weekly PCb; pCR = pathologic complete response

Xi G et al. *Front Immunol* 2026;17:1795426.

NCCN Guidelines: Recurrent Unresectable or Stage IV TNBC

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer)		
First-line	PD-L1 CPS ≥10 regardless of germline *BRCA1/2* PV status	Chemotherapy + pembrolizumab (category 1, preferred)
		Sacituzumab govitecan + pembrolizumab (category 1, preferred)
	PD-L1 CPS <10 and no germline *BRCA1/2* PV	Sacituzumab govitecan (category 1, preferred)
		Datopotamab deruxtecan (preferred)
		Systemic chemotherapy
	PD-L1 CPS <10 and germline *BRCA1/2* PV	PARP inhibitor (category 1, preferred)
		Platinum (category 1, preferred)
Second-line	Germline *BRCA1/2* PV	PARP inhibitor (category 1, preferred)
	Any	Sacituzumab govitecan (category 1, preferred)
		Systemic chemotherapy or targeted agents
	No germline *BRCA1/2* PV and HER2 IHC 1+ or 2+/ISH-negative	Trastuzumab deruxtecan (other recommended)

QUESTIONS?

Module 8: Triple-Negative Breast Cancer (TNBC)

Current and Future Role of TROP2-Directed Antibody-Drug Conjugates in Therapy for TNBC — Dr Brufsky

Established Treatment Paradigm for Localized and Metastatic TNBC — Dr Kalinsky

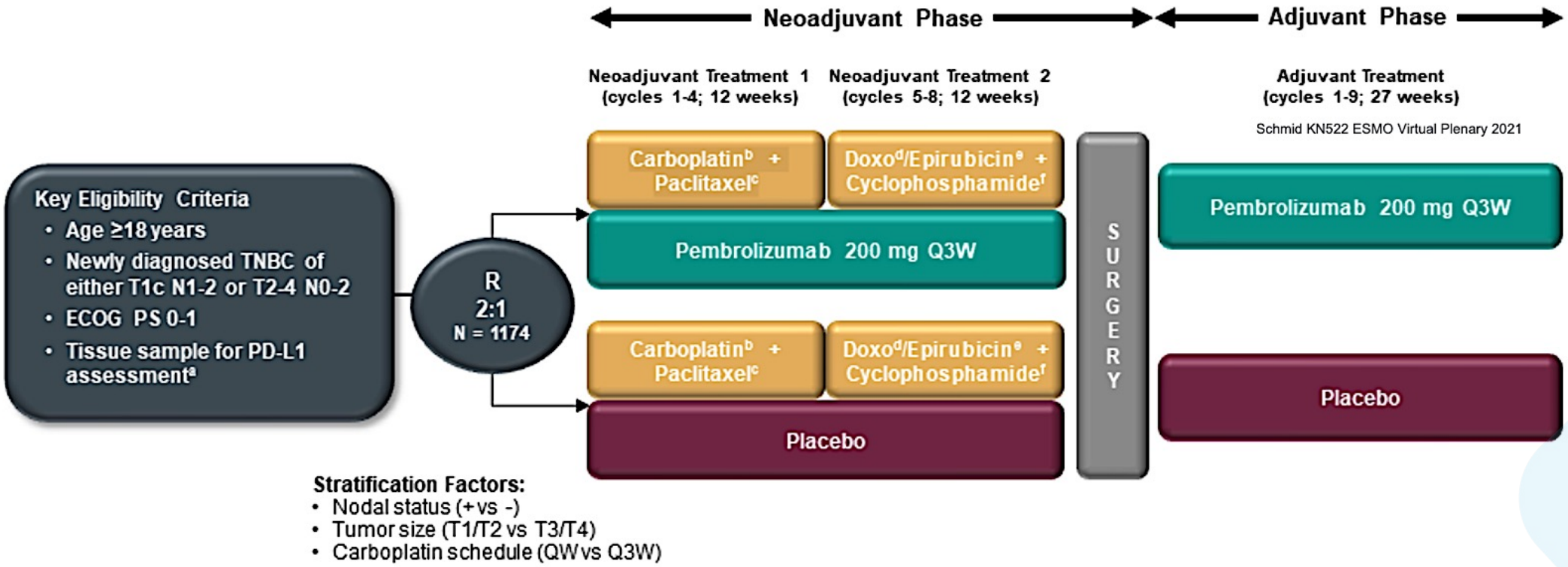
Established Treatment Paradigms for Localized and Metastatic TNBC

Kevin Kalinsky, MD, MS, FASCO
Professor of Medicine
Director, Division of Medical Oncology
Louisa and Rand Glenn Family Chair in Breast Cancer Research
Winship Cancer Institute of Emory University

Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bicycle Therapeutics, Biotheranostics Inc, A Hologic Company, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Jazz Pharmaceuticals Inc, Lilly, Menarini Silicon Biosystems, Merck, Mersana Therapeutics Inc, Myovant Sciences, Novartis, Pfizer Inc, ProteinQure, Puma Biotechnology Inc, RayzeBio, Regor Therapeutics, Relay Therapeutics, Seagen Inc
Nonrelevant Financial Relationships (Spouse)	Stock Options/Stock, Public Companies — Revolution Medicines Inc (prior employee of EQRx), ADC Therapeutics

KEYNOTE-522: Study Design (NCT03036488)



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

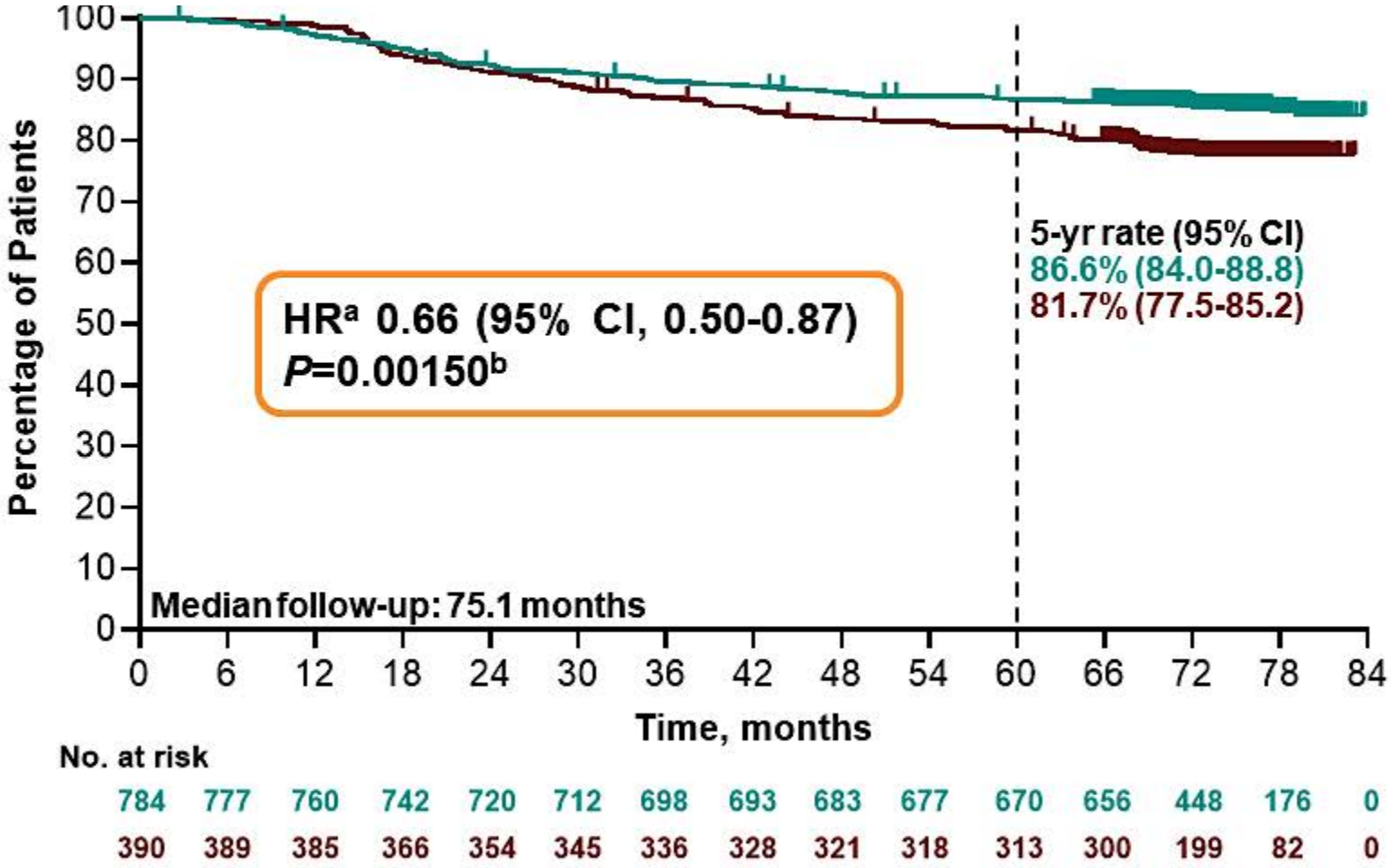
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer

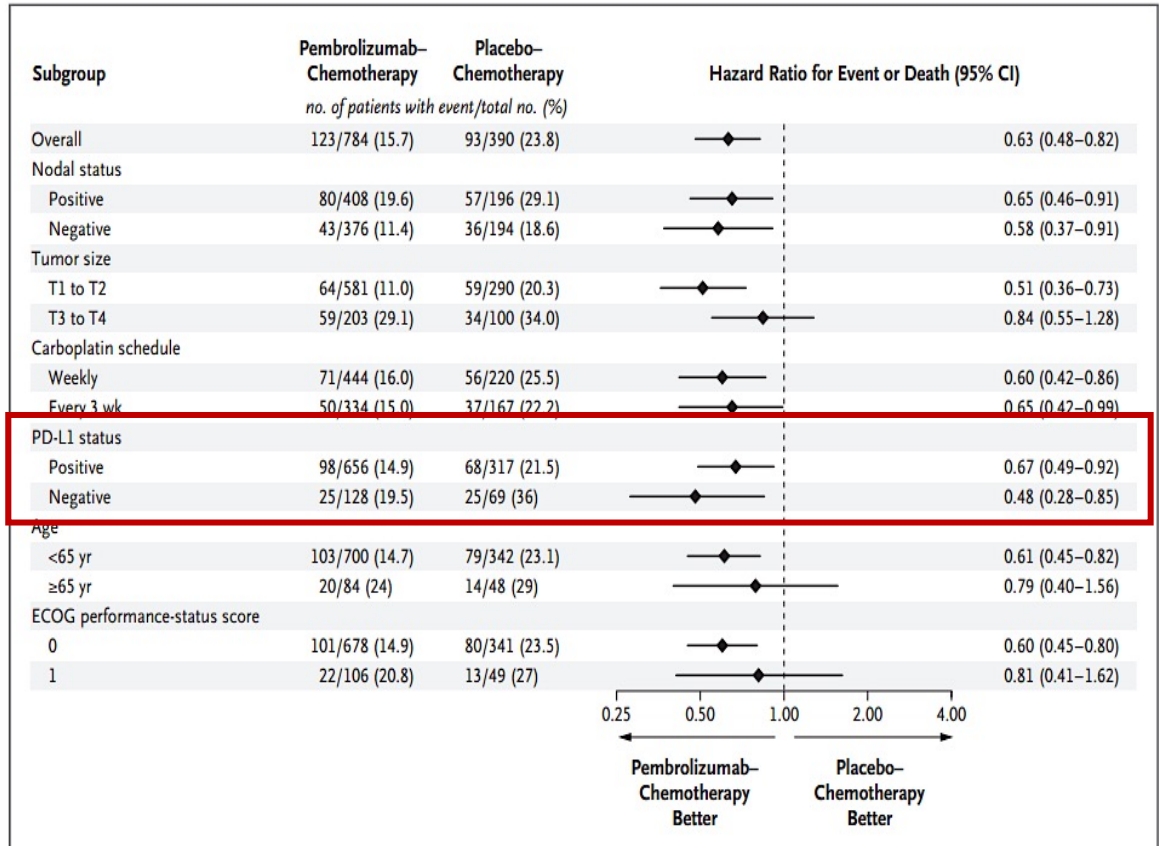


	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

[a]The unstratified piecewise HR was 0.87 (95% CI, 0.57-1.32) before the 2-year follow-up and 0.51 (95% CI, 0.35-0.75) afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis. Data cutoff date: March 22, 2024.

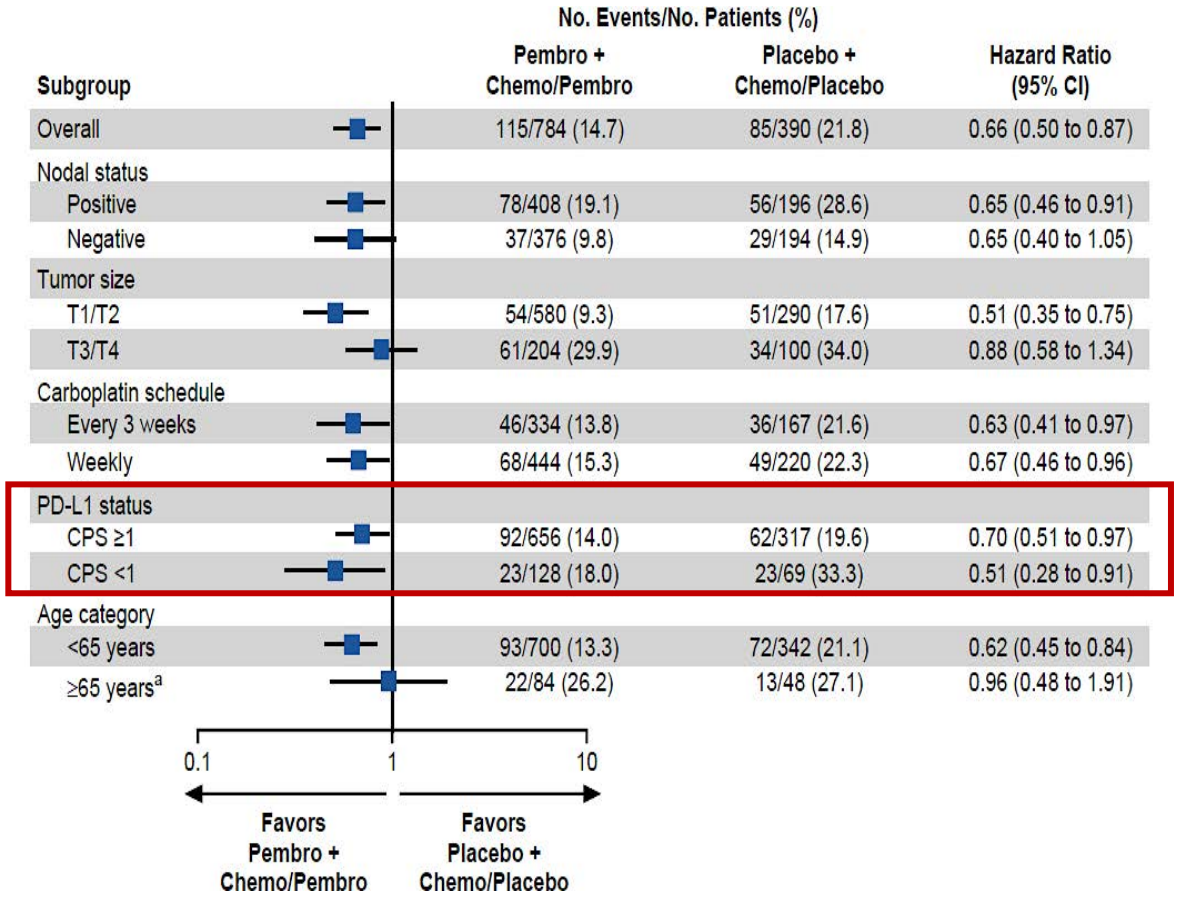
KEYNOTE-522

EFS



Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy
	no. of patients with event/total no. (%)	
Overall	123/784 (15.7)	93/390 (23.8)
Nodal status		
Positive	80/408 (19.6)	57/196 (29.1)
Negative	43/376 (11.4)	36/194 (18.6)
Tumor size		
T1 to T2	64/581 (11.0)	59/290 (20.3)
T3 to T4	59/203 (29.1)	34/100 (34.0)
Carboplatin schedule		
Weekly	71/444 (16.0)	56/220 (25.5)
Every 3 wk	50/334 (15.0)	37/167 (22.2)
PD-L1 status		
Positive	98/656 (14.9)	68/317 (21.5)
Negative	25/128 (19.5)	25/69 (36)
Age		
<65 yr	103/700 (14.7)	79/342 (23.1)
≥65 yr	20/84 (24)	14/48 (29)
ECOG performance-status score		
0	101/678 (14.9)	80/341 (23.5)
1	22/106 (20.8)	13/49 (27)

OS

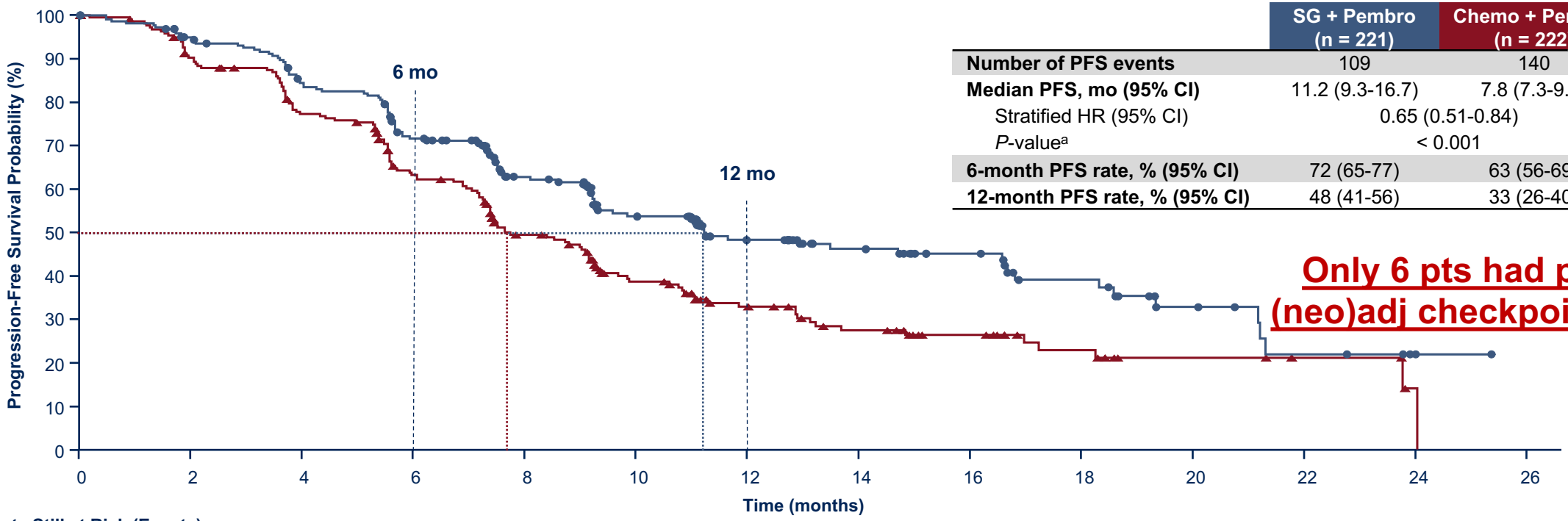


Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Placebo + Chemo/Placebo	Hazard Ratio (95% CI)
Overall	115/784 (14.7)	85/390 (21.8)	0.66 (0.50 to 0.87)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	0.65 (0.46 to 0.91)
Negative	37/376 (9.8)	29/194 (14.9)	0.65 (0.40 to 1.05)
Tumor size			
T1/T2	54/580 (9.3)	51/290 (17.6)	0.51 (0.35 to 0.75)
T3/T4	61/204 (29.9)	34/100 (34.0)	0.88 (0.58 to 1.34)
Carboplatin schedule			
Every 3 weeks	46/334 (13.8)	36/167 (21.6)	0.63 (0.41 to 0.97)
Weekly	68/444 (15.3)	49/220 (22.3)	0.67 (0.46 to 0.96)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	0.70 (0.51 to 0.97)
CPS <1	23/128 (18.0)	23/69 (33.3)	0.51 (0.28 to 0.91)
Age category			
<65 years	93/700 (13.3)	72/342 (21.1)	0.62 (0.45 to 0.84)
≥65 years[a]	22/84 (26.2)	13/48 (27.1)	0.96 (0.48 to 1.91)

Higher event rate in PD-L1 negative, benefit of pembrolizumab noted regardless of PD-L1 status (83% PD-L1+)

Schmid P et al. *N Engl J Med*. 2020;382(9):810-821. Schmid P et al. *N Engl J Med*. 2022;386(6):556-567; Schmid P et al. *N Engl J Med*. 2024;391:1981-91.

ASCENT-04: Progression-Free Survival by BICR



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	109	140
Median PFS, mo (95% CI)	11.2 (9.3-16.7)	7.8 (7.3-9.3)
Stratified HR (95% CI)	0.65 (0.51-0.84)	
P-value[a]	< 0.001	
6-month PFS rate, % (95% CI)	72 (65-77)	63 (56-69)
12-month PFS rate, % (95% CI)	48 (41-56)	33 (26-40)

Only 6 pts had prior (neo)adj checkpoint inh

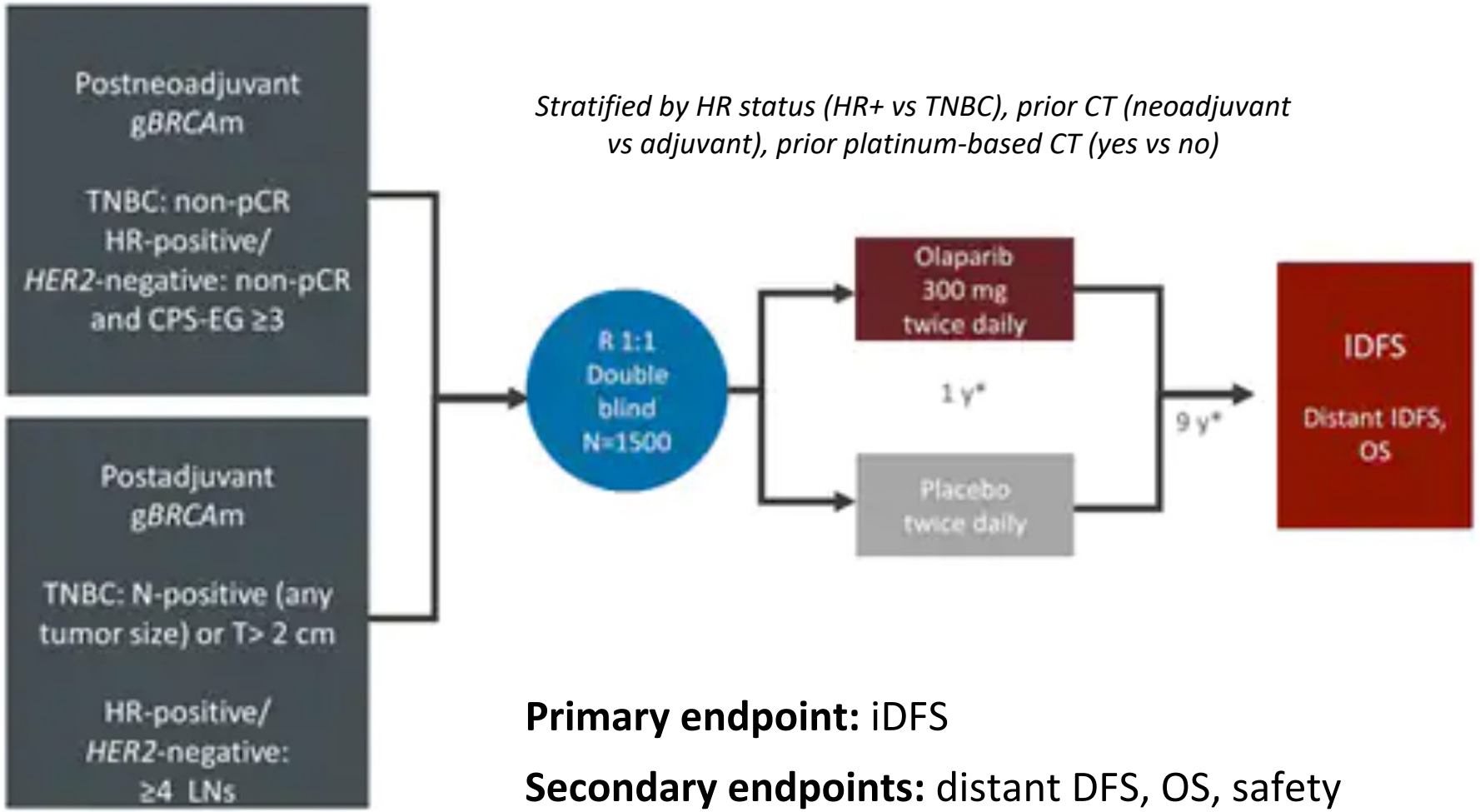
No. of Patients Still at Risk (Events)

SG + Pembro	221 (0)	202 (11)	174 (33)	142 (59)	105 (75)	78 (89)	58 (96)	42 (98)	34 (99)	22 (103)	11 (106)	6 (109)	2 (109)	0 (109)
Chemo + Pembro	222 (0)	191 (21)	159 (48)	123 (76)	88 (102)	59 (120)	40 (128)	29 (134)	21 (135)	13 (137)	7 (138)	4 (138)	1 (139)	0 (140)

SG + pembro demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo + pembro by BICR analysis, with a 35% reduction in risk of disease progression or death

Data cutoff date: March 3, 2025.
[a]Two-sided *P*-value from stratified log-rank test.
BICR, blinded independent central review; chemo, chemotherapy; HR, hazard ratio; PFS, progression-free survival; pembro, pembrolizumab; SG, sacituzumab govitecan.

OlympiA



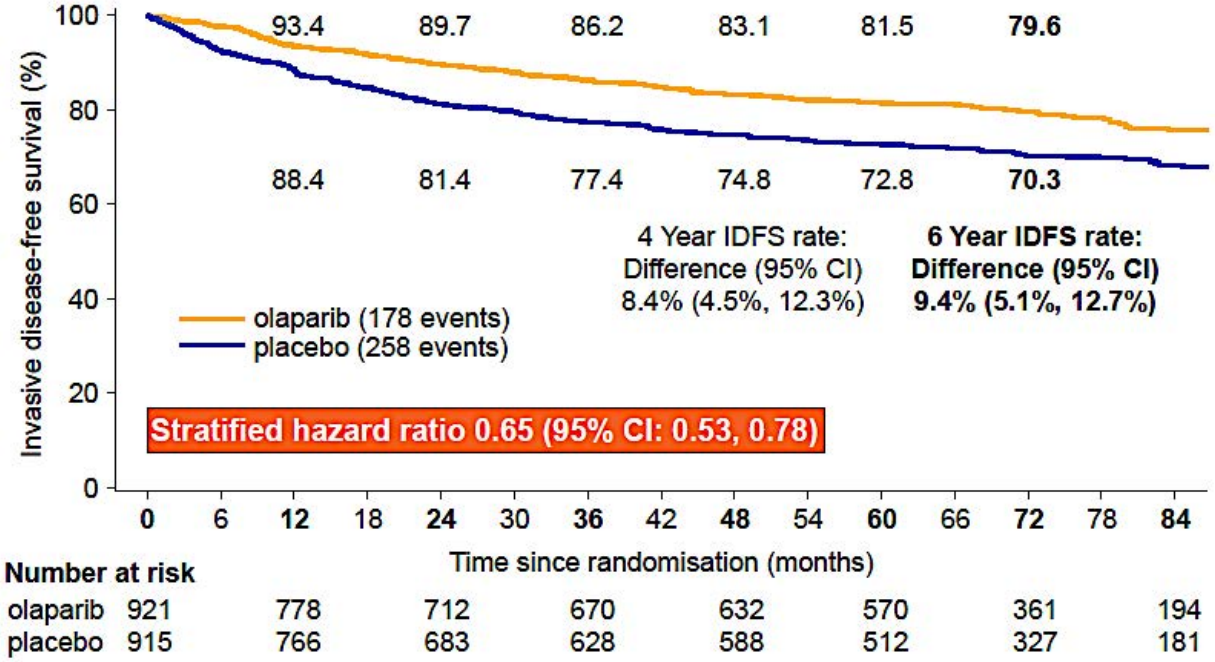
Stratified by HR status (HR+ vs TNBC), prior CT (neoadjuvant vs adjuvant), prior platinum-based CT (yes vs no)

Primary endpoint: iDFS

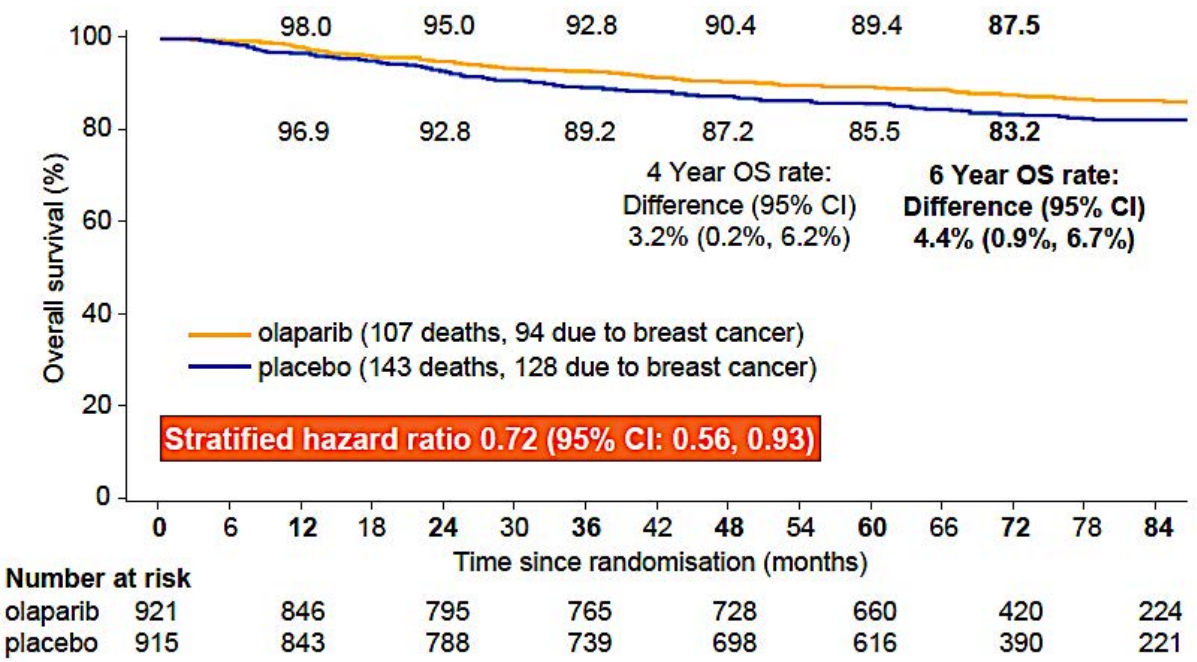
Secondary endpoints: distant DFS, OS, safety

OlympiA

IDFS



OS



Garber SABCS 2024

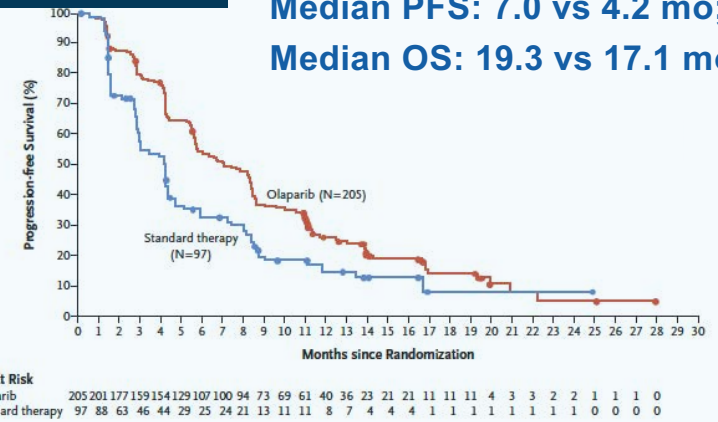
PARP Inhibition in gBRCA-Associated mBC

OlympiAD

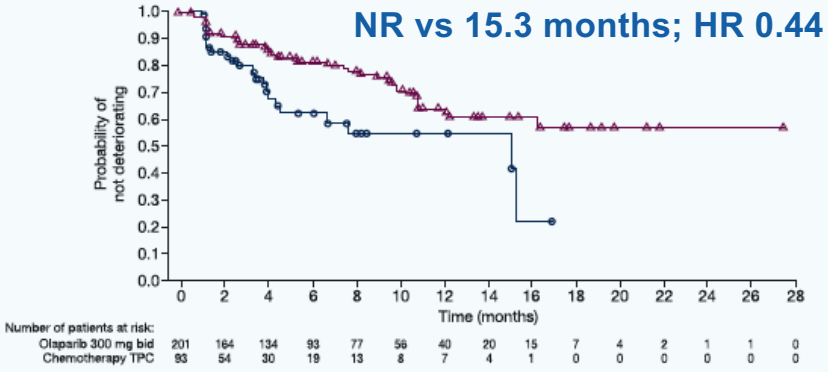
OLAPARIB vs Chemotherapy

Median PFS: 7.0 vs 4.2 mo; HR=0.58 (p<0.001)

Median OS: 19.3 vs 17.1 mo; HR=0.90 (p=0.51)



Median time to ≥10-point decrease in QLQ-C30: NR vs 15.3 months; HR 0.44 (95% CI, 0.25-0.77)

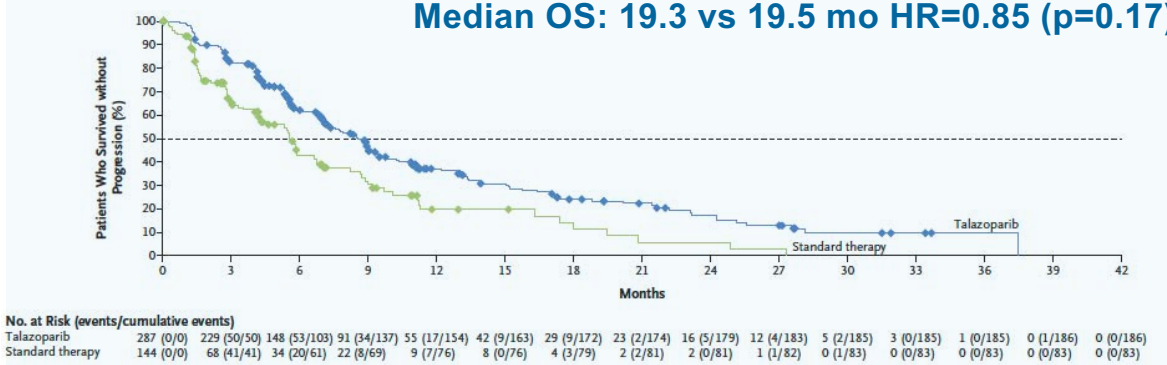


EMBRACA

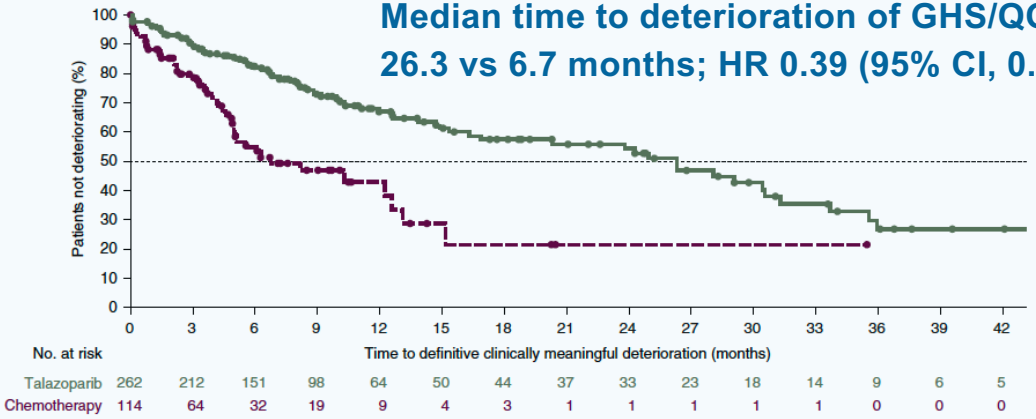
TALAZOPARIB vs Chemotherapy

Median PFS: 8.6 vs 5.6 mo; HR=0.54 (p<0.001)

Median OS: 19.3 vs 19.5 mo HR=0.85 (p=0.17)



Median time to deterioration of GHS/QOL: 26.3 vs 6.7 months; HR 0.39 (95% CI, 0.26-0.56)



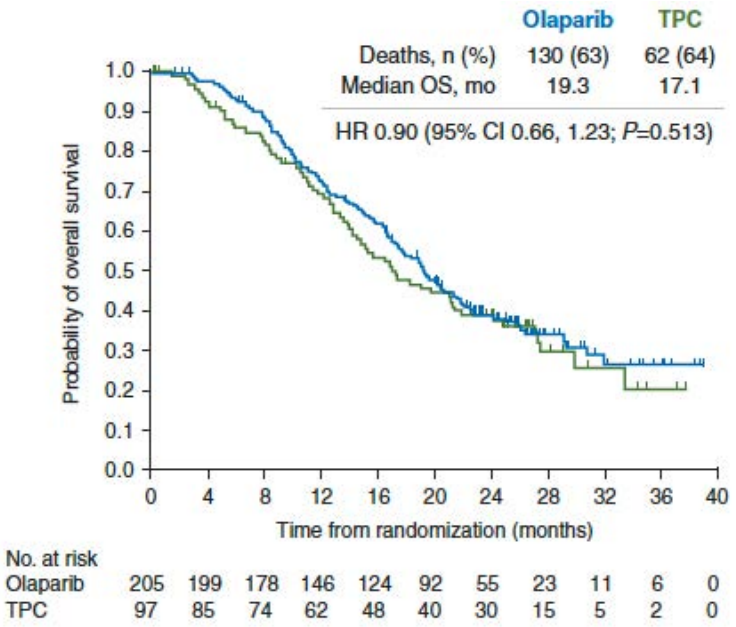
Robson M et al. N Engl J Med 2017;377(6):523-33; Robson M et al. Ann Oncol 2019;30(4):558-66; Litton J et al. N Engl J Med 2018;379:753-63: Robson M et al. Eur J Cancer 2019;120:20-30; Litton J et al. Ann Oncol 2020;31(11):1526-35.

Slide courtesy of Ana Garrido-Castro

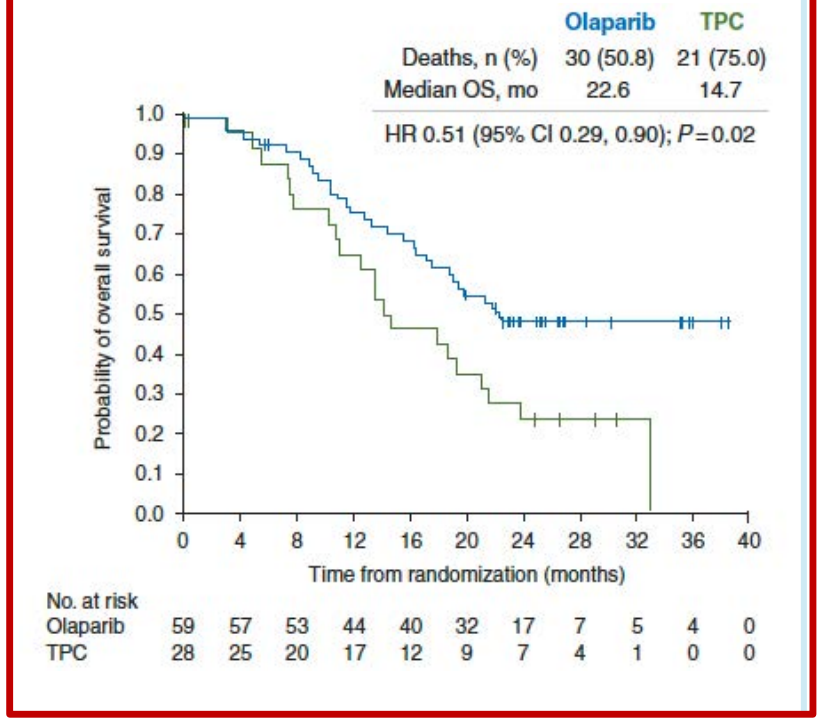
PARP Inhibition: OS Subgroup Analysis 1L vs 2/3L

OlympiAD

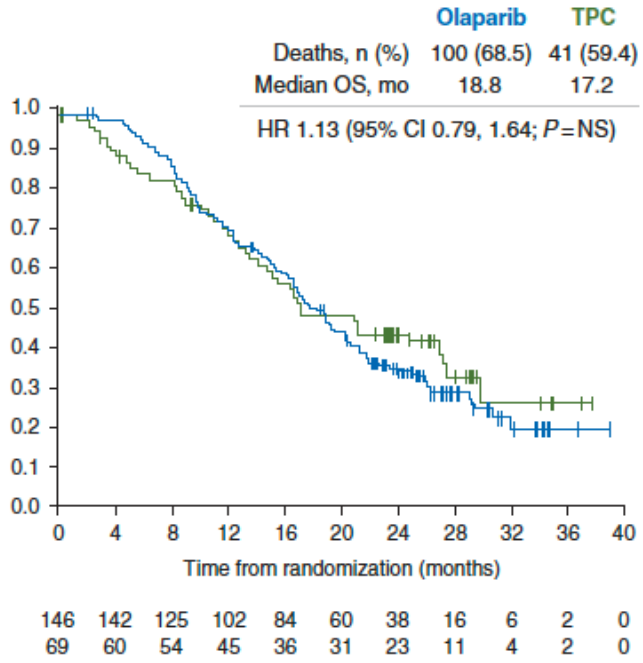
Overall



No prior chemotherapy for mBC (1L)



Prior chemotherapy (2/3L)

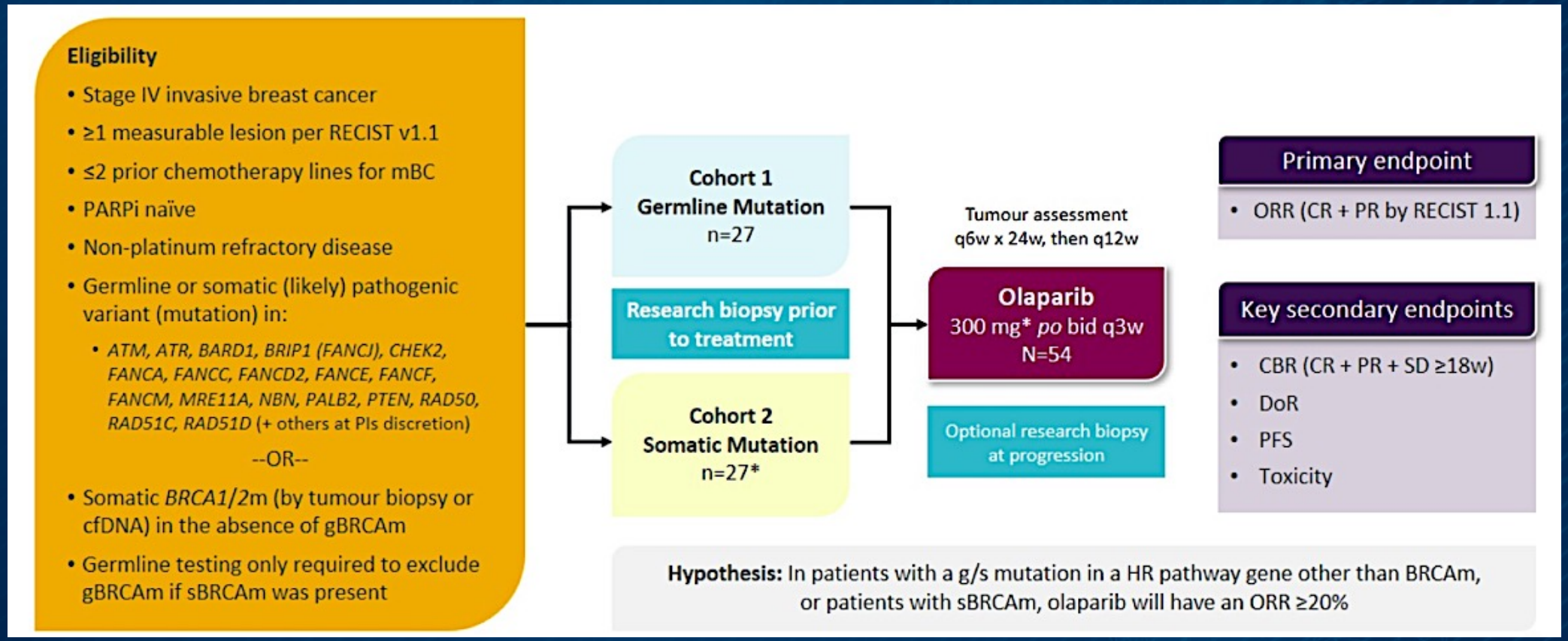


Robson M et al. Ann Oncol 2019;30(4):558-66.

- Given better QOL, PFS benefit possible OS benefit in the 1L setting, reasonable to consider PARPi as 1L therapy for patients with PD-L1 negative mTNBC (particularly if low burden of disease)
- For PDL1+, IO benefit not likely to be seen later line, so important to give IO first line

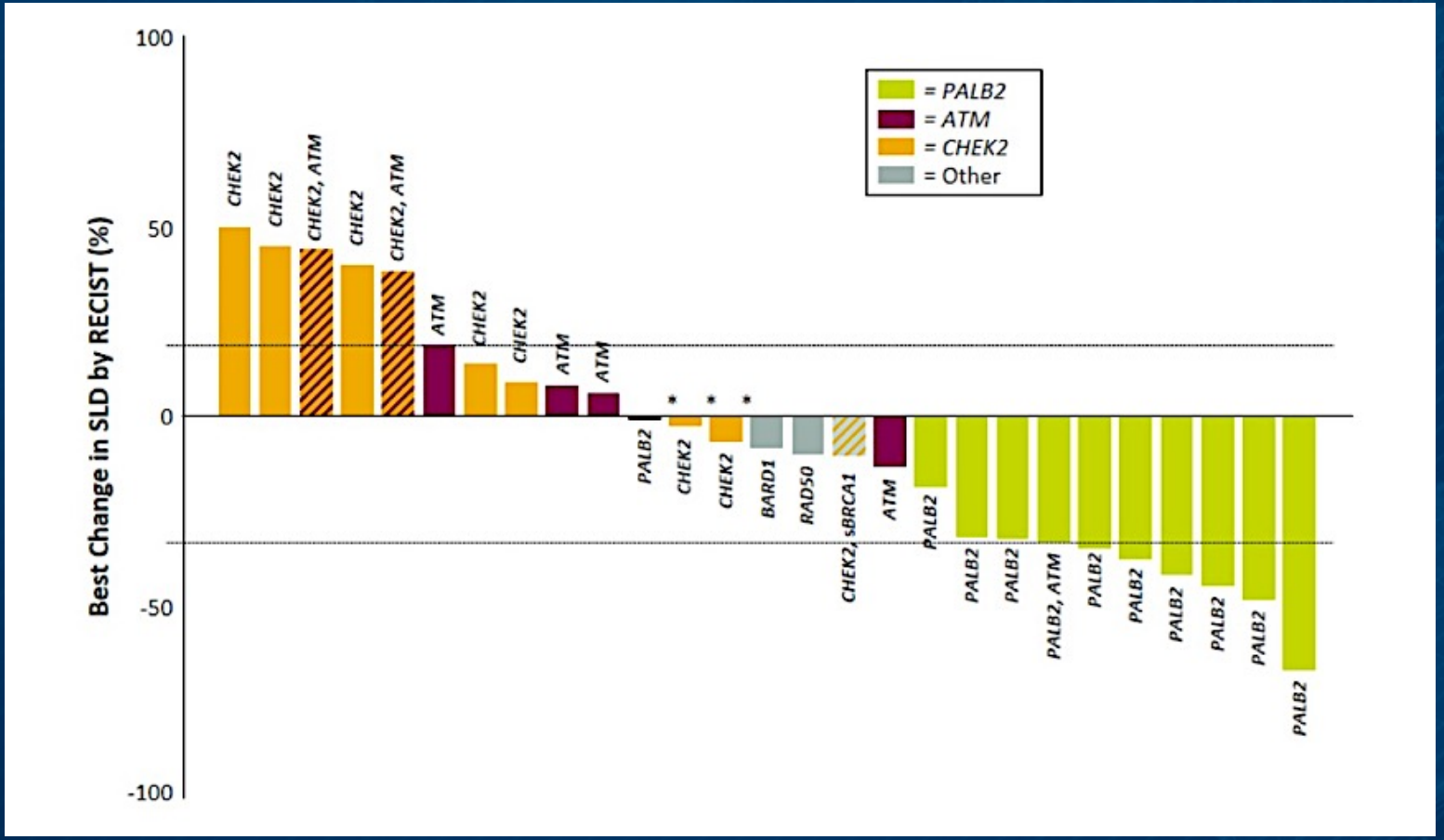
Slide courtesy of Ana Garrido-Castro

TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes



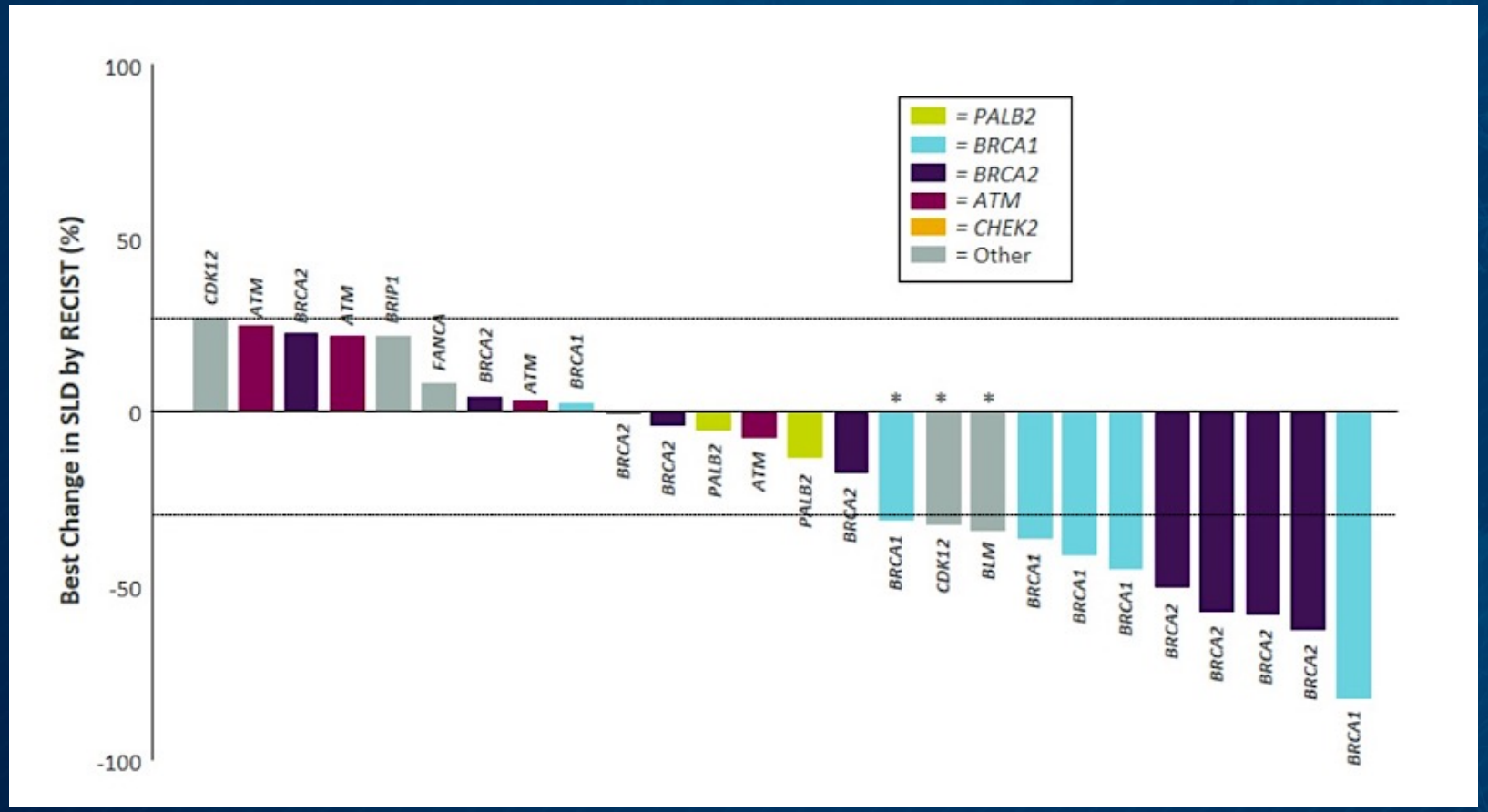
Tung et al. Presented at ASCO 2020

TBCRC 048: Responses in patients with g*PALB2* mutations in cohort 1



Tung et al. Presented at ASCO 2020

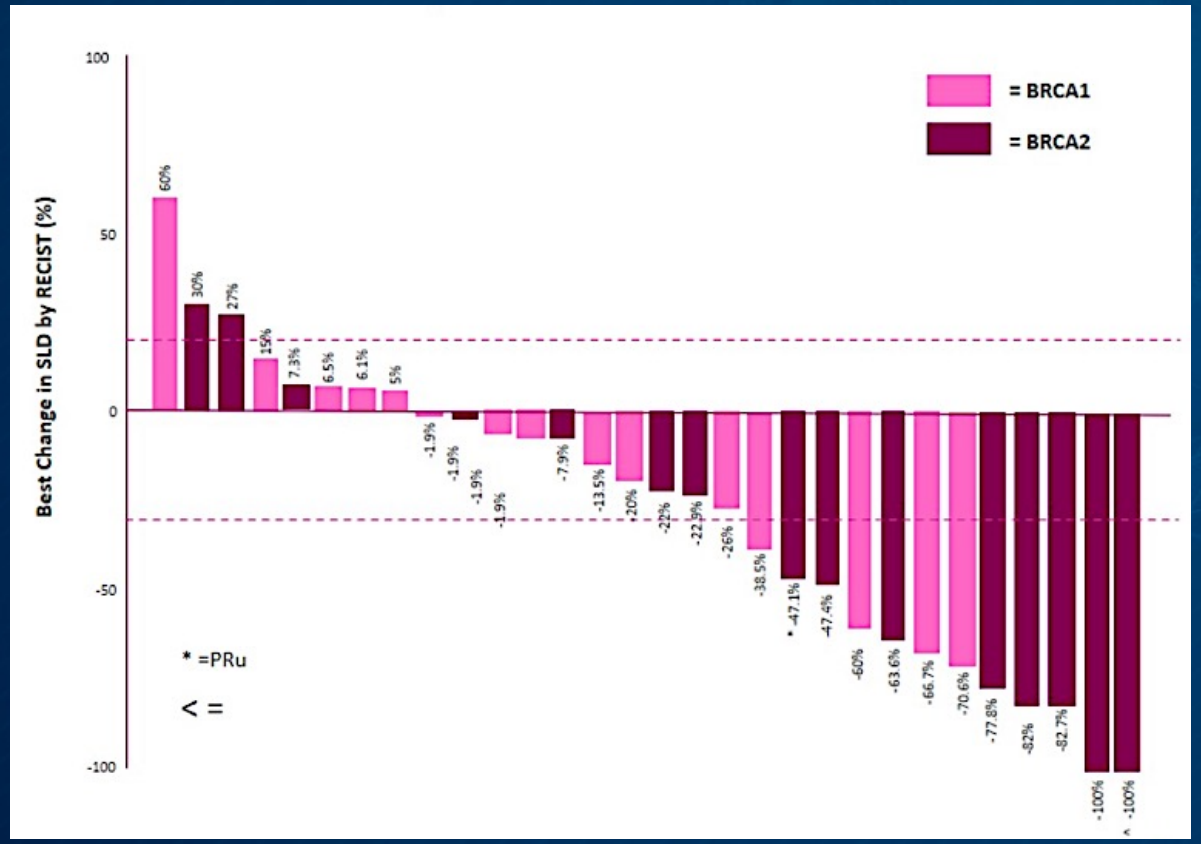
TBCRC 048: Responses primarily in patients with s*BRCA1*/2m in cohort 2



- sBRCA1/2m
  - ORR= 37% (11/30, 80% CI: 25%-50%)
  - CBR (18 wks)= 53% (16/30, 90% CI: 37%-69%)

Tung et al. Presented at ASCO 2020

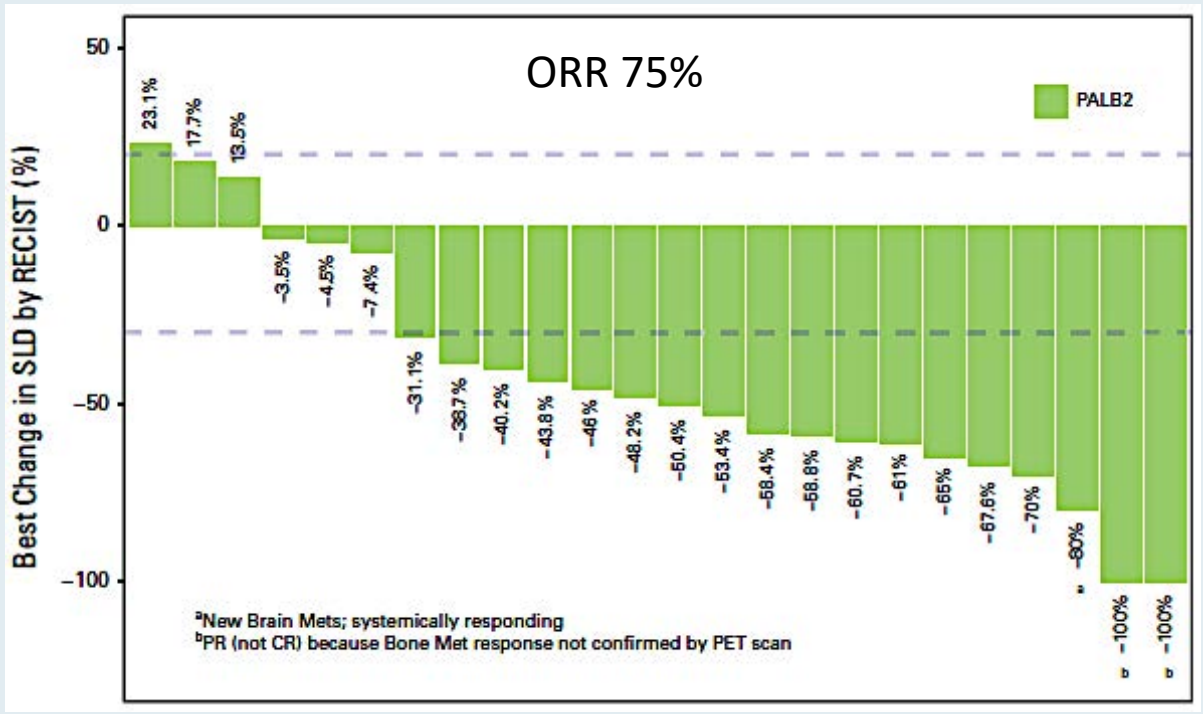
TBCRC 048: Meaningful responses seen in patients with s*BRCA1/2* mutations

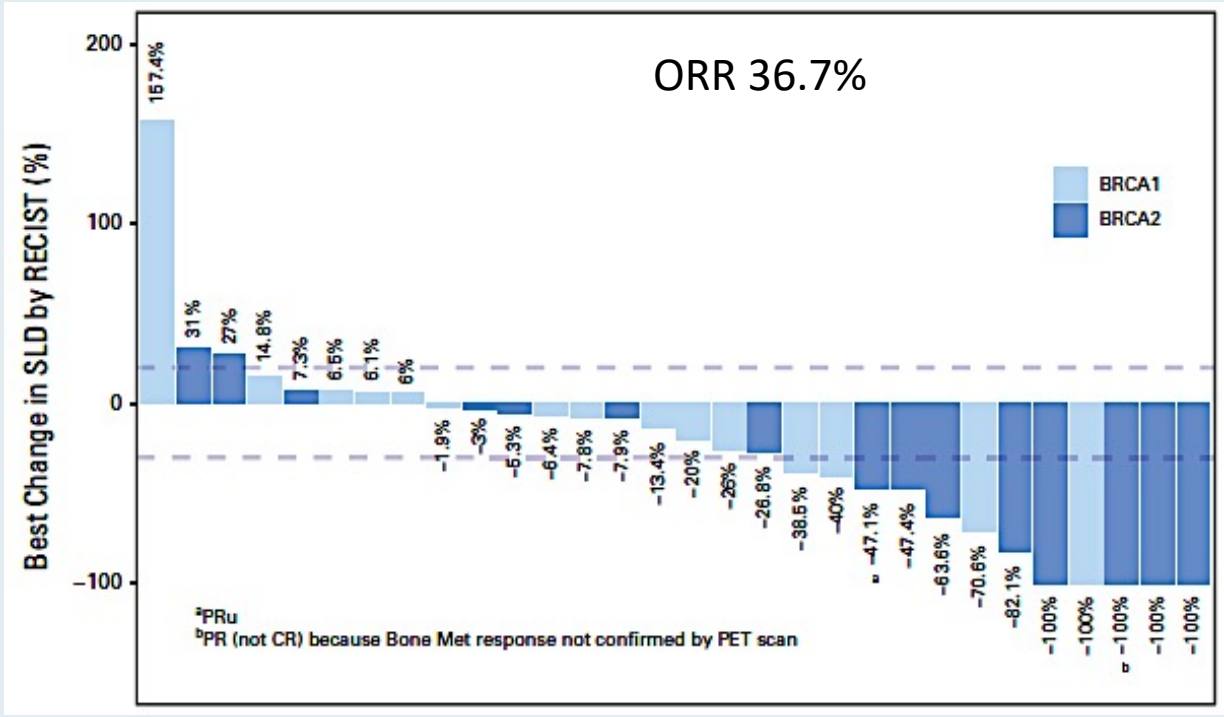


- ORR= 37% (11/30, 80% CI: 25%-50%)
- CBR (18 wks)= 53% (16/30, 90% CI: 37%-69%)

Tung et al. Presented at ASCO 2020

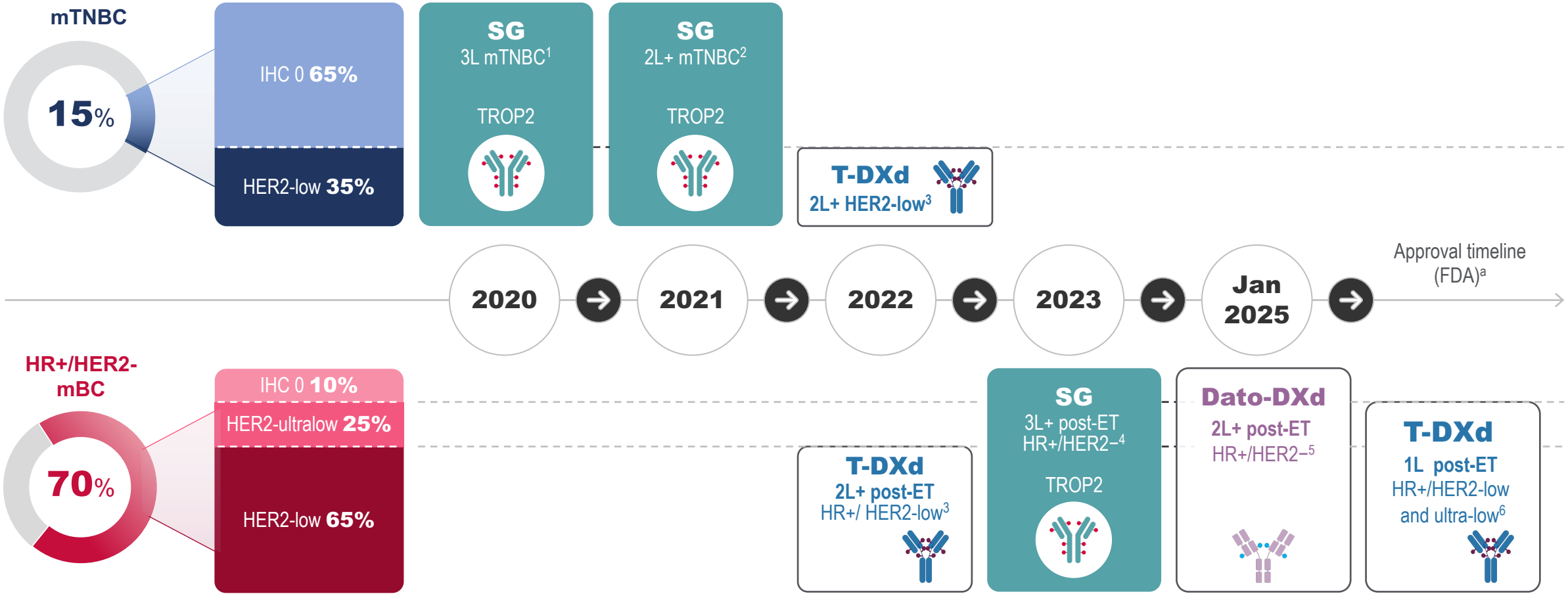
TBCRC 048: Olaparib Monotherapy in the Germline PALB2 Mutation and Somatic BRCA1/2 Mutation Expansion Cohorts





Tung NM et al. *J Clin Oncol* 2026;44:653-61.

ADCs have transformed the treatment landscape in HER2− mBCs, offering treatment options to patients with previously limited choices



See references in slide notes.

[a]Based on the FDA approvals. Please refer to local prescribing guidelines. ADC, antibody−drug conjugate; AML, acute myeloid leukaemia; ET, endocrine therapy; FDA, Food and Drug Administration; HER2+, HER2 positive; HER2-negative, HER2 negative; HR+, hormone receptor-positive; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

FDA Approved Drugs Database. Available on https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed: March 2025.

All drugs presented here are currently approved or have been recommended for approval by the EMA. Please refer to local prescribing guidelines. European Medicines Agency (EMA): Available on https://www.ema.europa.eu/en/medicines. Accessed: August 2025.

DESTINY-BREAST04: STUDY DESIGN

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)

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]

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

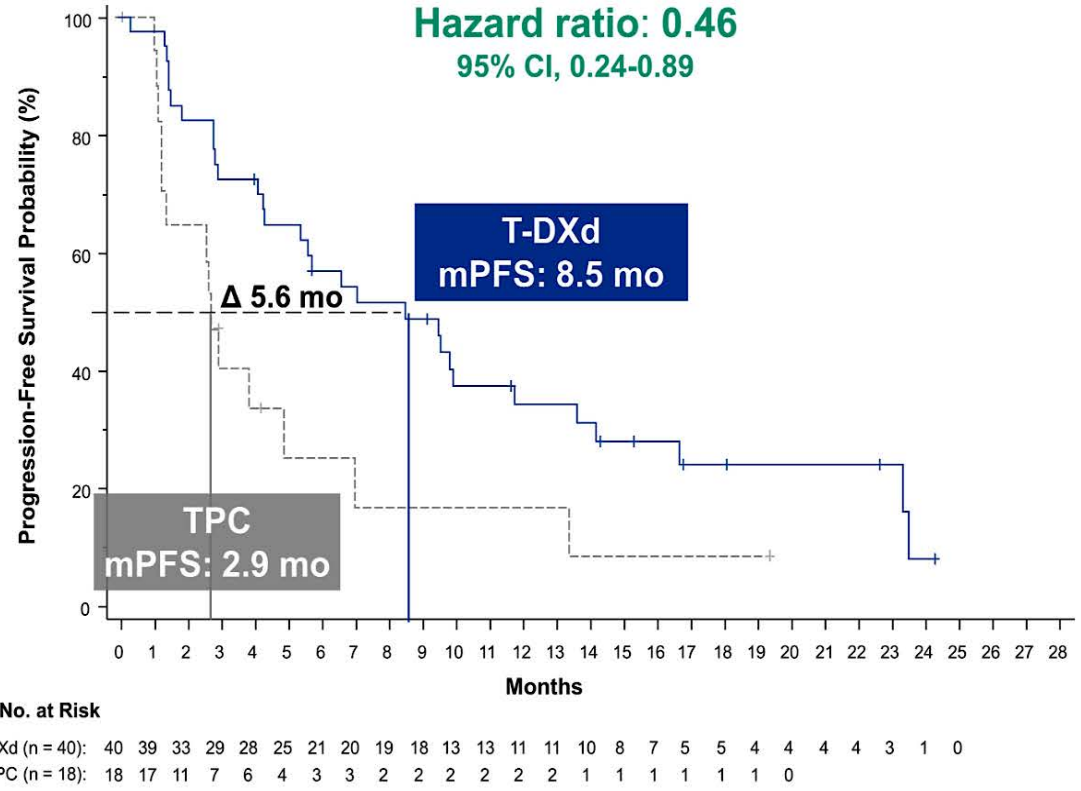
ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDKi, cyclin-dependent kinase 4/6 inhibitors; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only [IUO] assay system, at the time of study. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

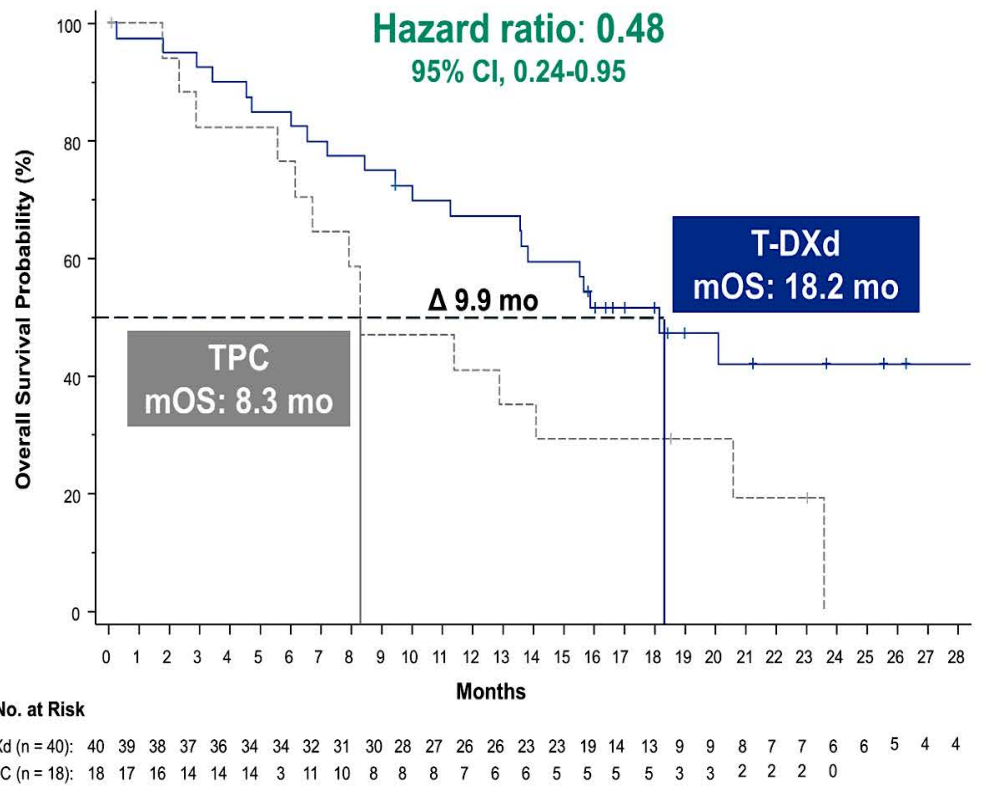
1. Modi S et al. *N Engl J Med*. 2022;387:9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

DESTINY-BREAST04: PFS AND OS IN HR- COHORT

Progression-Free Survival

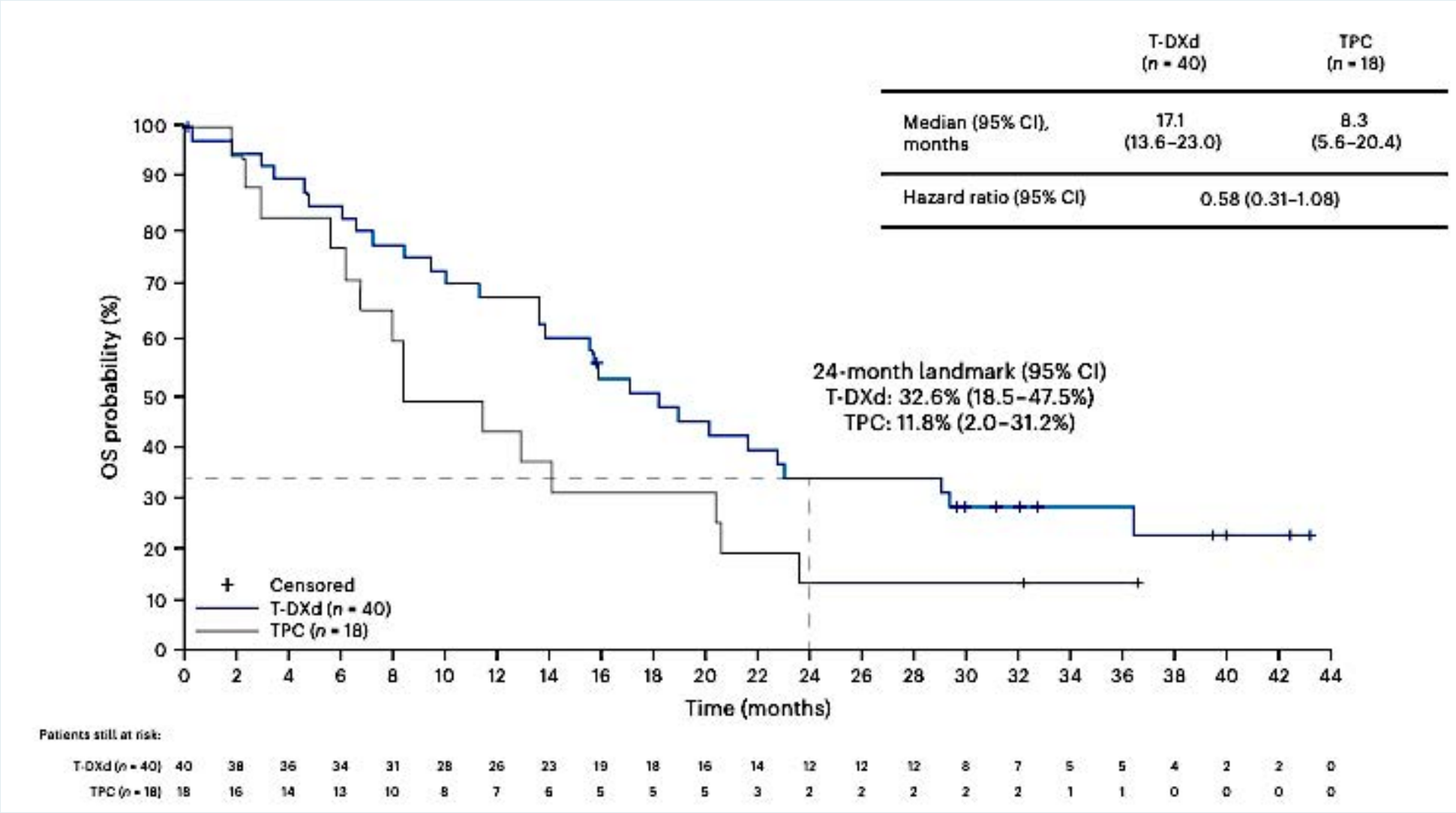


Overall Survival



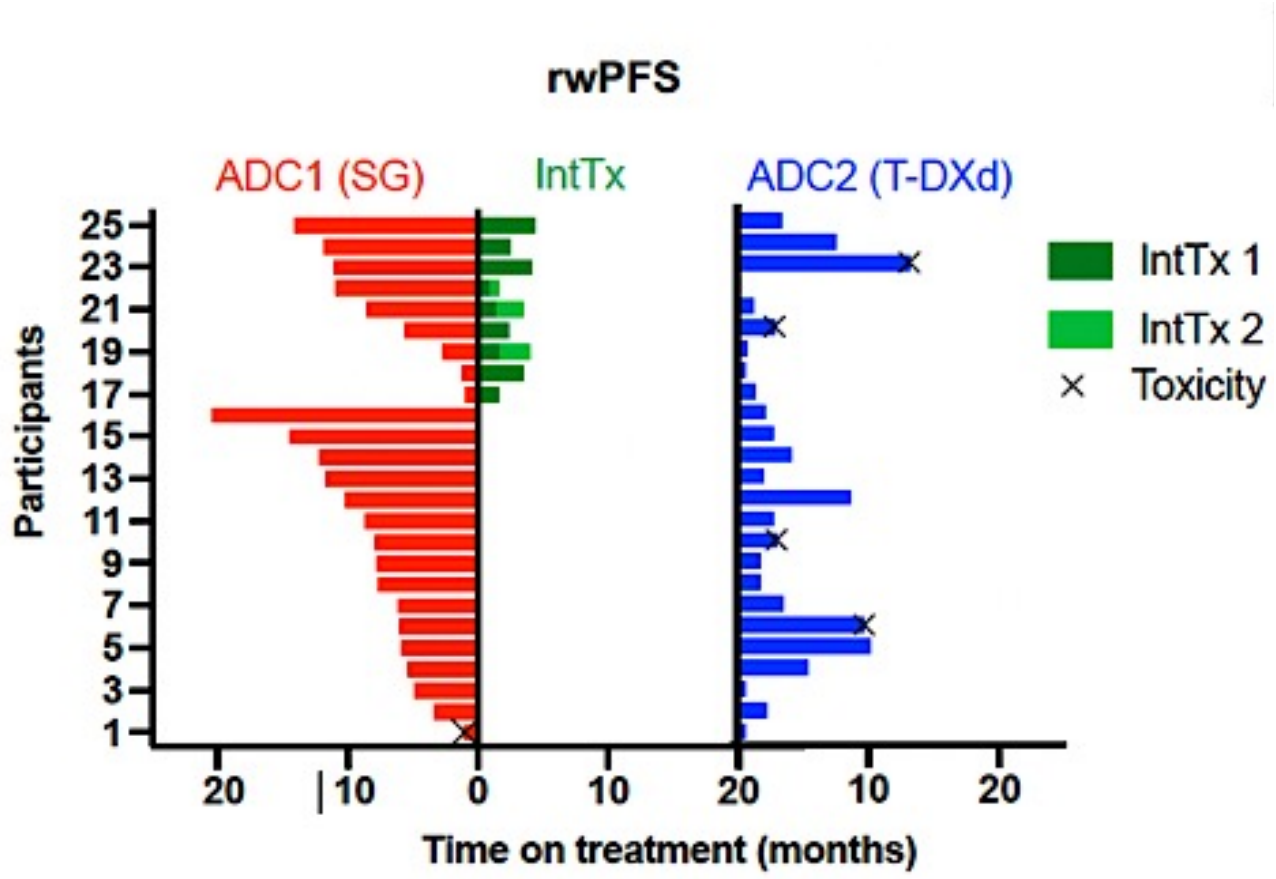
Modi S, et al.ASCO 2022. Abstract LBA3.

DESTINY-Breast04: Long-Term Survival in the HR-Negative Cohort



Modi S et al. *Nat Med* 2025;31(12):4205-13.

Sequential T-DXd Post Sacituzumab Govitecan in mTNBC



	ADC1 (SG)	ADC2 (T-DXd)
Median rwPFS from time of each ADC start, months	7.7	2.8
Median rwOS from time of each ADC start, months	16.2	6.5

On average, shorter PFS with ADC2

Huppert L et al, ASCO 2024

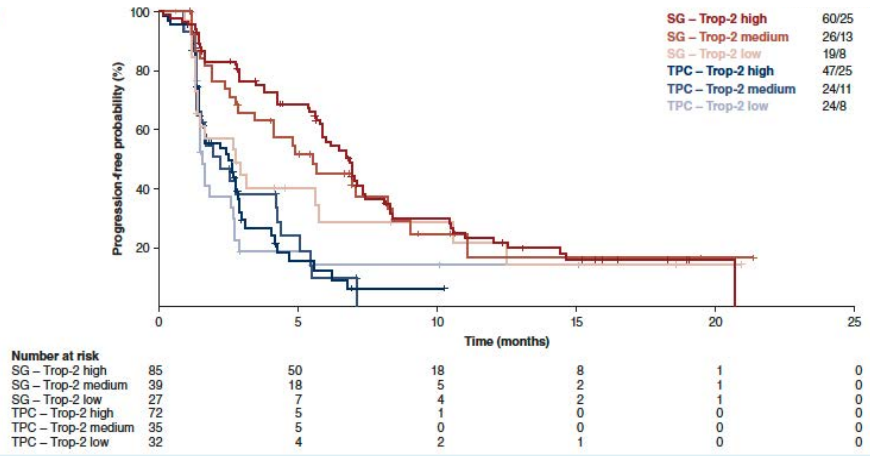
Does ADC Target Expression Matter?

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio Mays Cancer Center | AACR American Association for Cancer Research

ASCENT
TNBC
(n=290)

H-Score >200: 54%

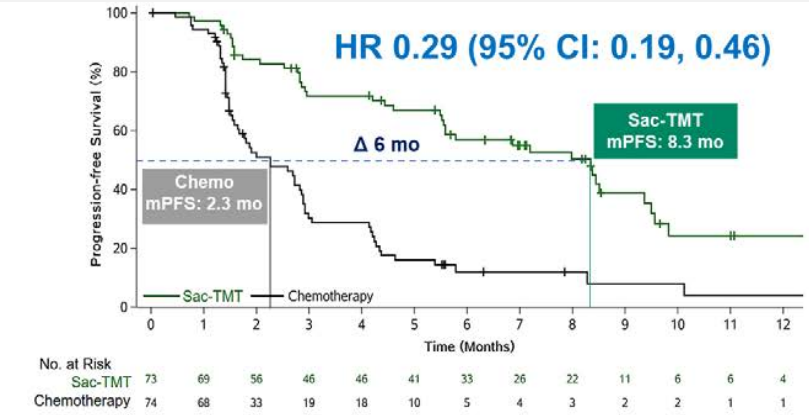


TROP2 (H-score)	SG N	SG PFS, mo (95% CI)	SG OS, mo (95% CI)	TPC N	TPC PFS, mo (95% CI)	TPC OS, mo (95% CI)
High (>200-300)	85	**6.9** (5.8-7.4)	**14.2** (11.3-17.5)	72	**2.5** (1.5-2.9)	**6.9** (5.3-8.9)
Medium (100-200)	39	**5.6** (2.9-8.2)	**14.9** (6.9-NE)	35	**2.2** (1.4-4.3)	**6.9** (4.6-10.1)
Low (0 to <100)	27	**2.7** (1.4-5.8)	**9.3** (7.5-17.8)	32	**1.6** (1.4-2.7)	**7.6** (5.0-9.6)

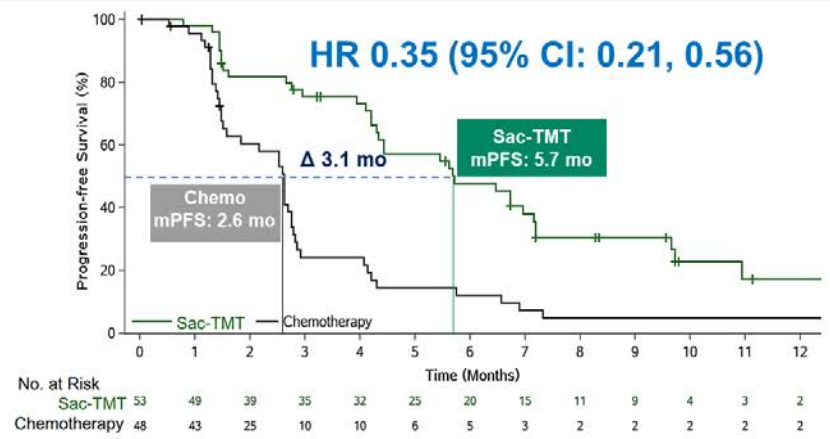
OptiTROP-Breast01
TNBC
(n=248)

H-Score >200: 59%

TROP2-High (H-score >200)



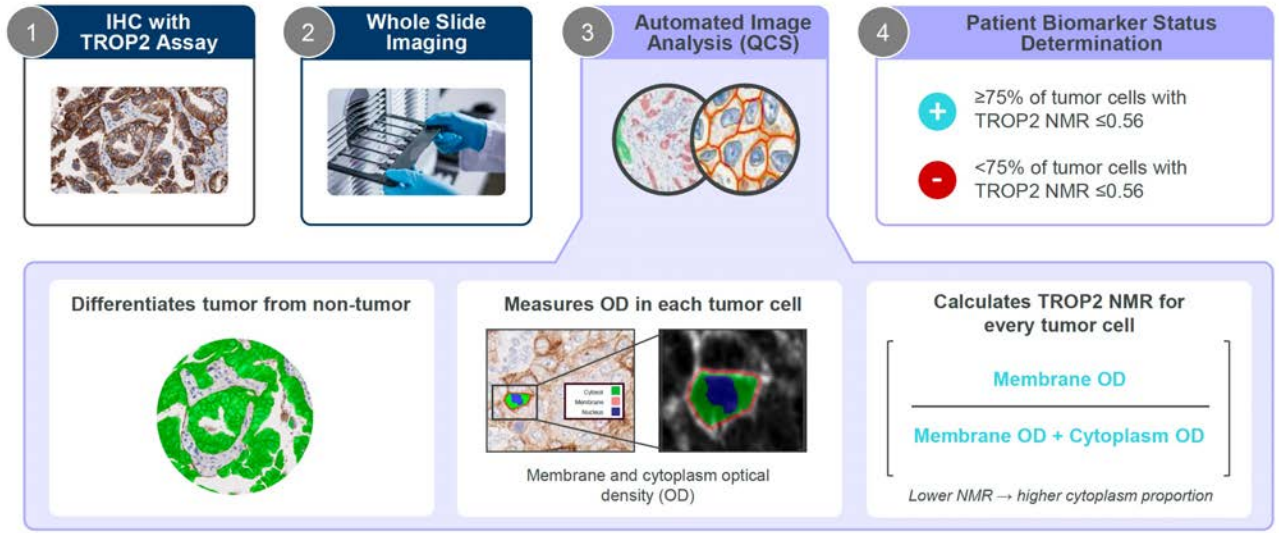
TROP2-Medium/Low (H-score ≤200)



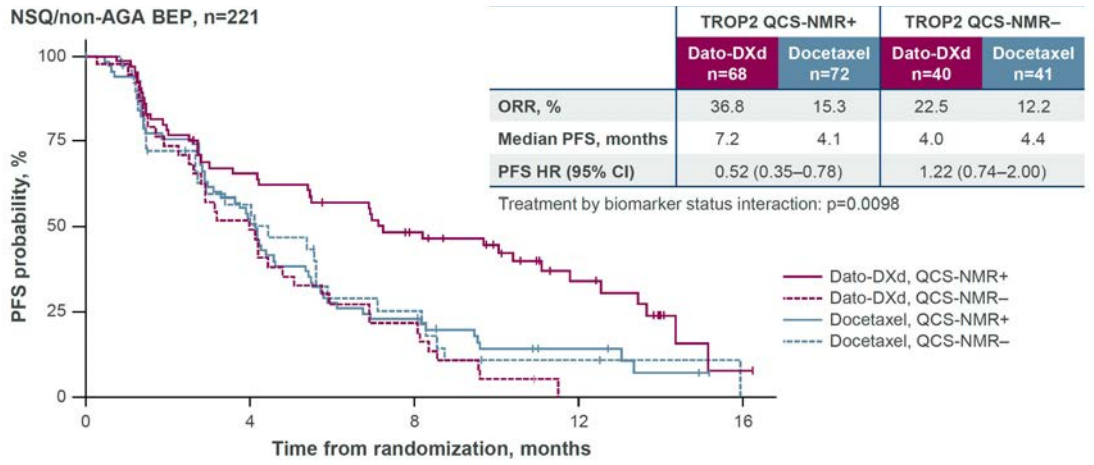
Bardia A et al. Ann Oncol 2021;32(9):1148-56; Xu B et al. ASCO 2024; Yin Y et al. Nat Med 2025;31(6):1969-75. Slide courtesy of Ana Garrido-Castro

Are we Measuring Target Expression Correctly?

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)



Efficacy of TROP2 QCS-NMR: Dato-DXd in Lung Cancer



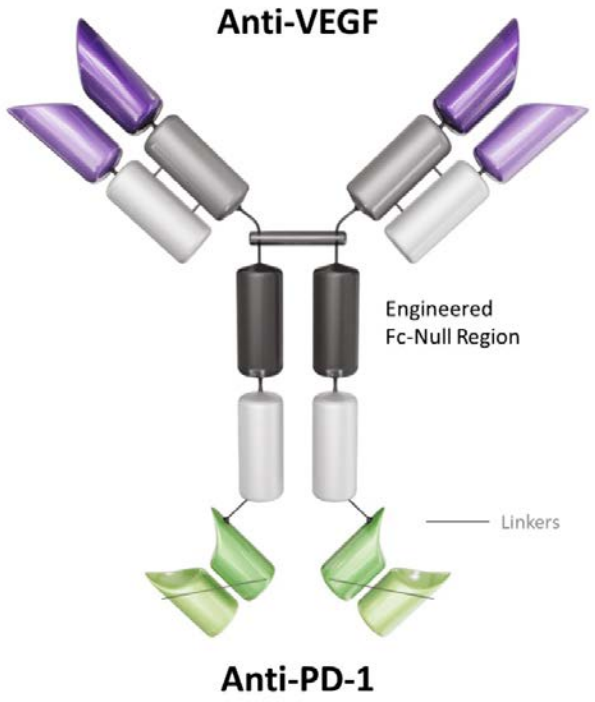
	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=68	Docetaxel n=72	Dato-DXd n=40	Docetaxel n=41
ORR, %	36.8	15.3	22.5	12.2
Median PFS, months	7.2	4.1	4.0	4.4
PFS HR (95% CI)	0.52 (0.35–0.78)		1.22 (0.74–2.00)	

Treatment by biomarker status interaction: p=0.0098

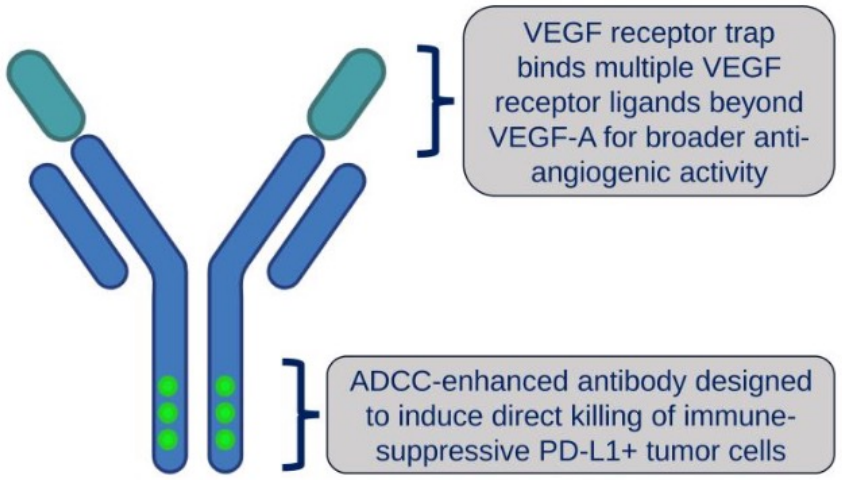
Need to better understand if quantitative target expression could help select patients more likely to benefit.

Courtesy of Puja Sapra. Garassino MC et al, World Lung 2024

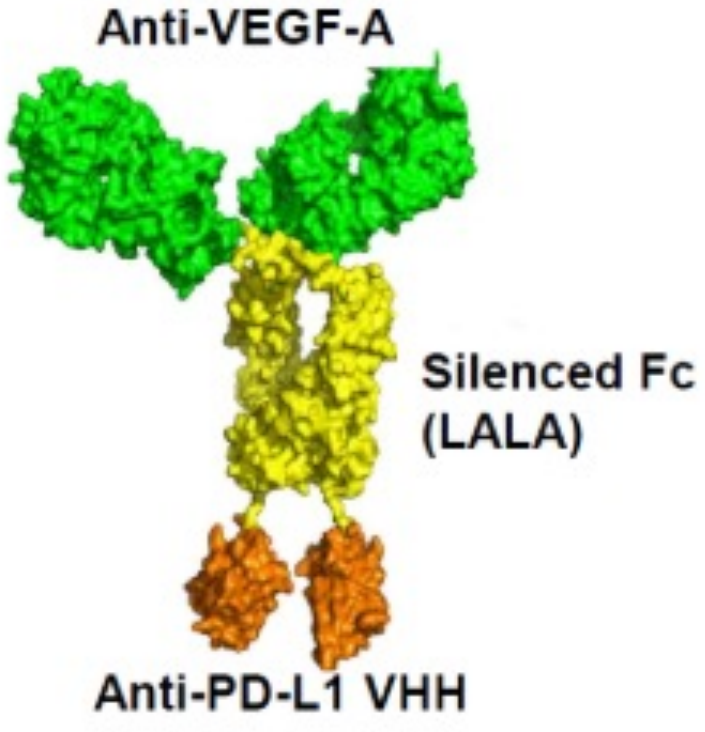
VEGF/PD1 or VEGF/PDL1 bispecific antibodies



Ivonescimab
(Summit Therapeutics)



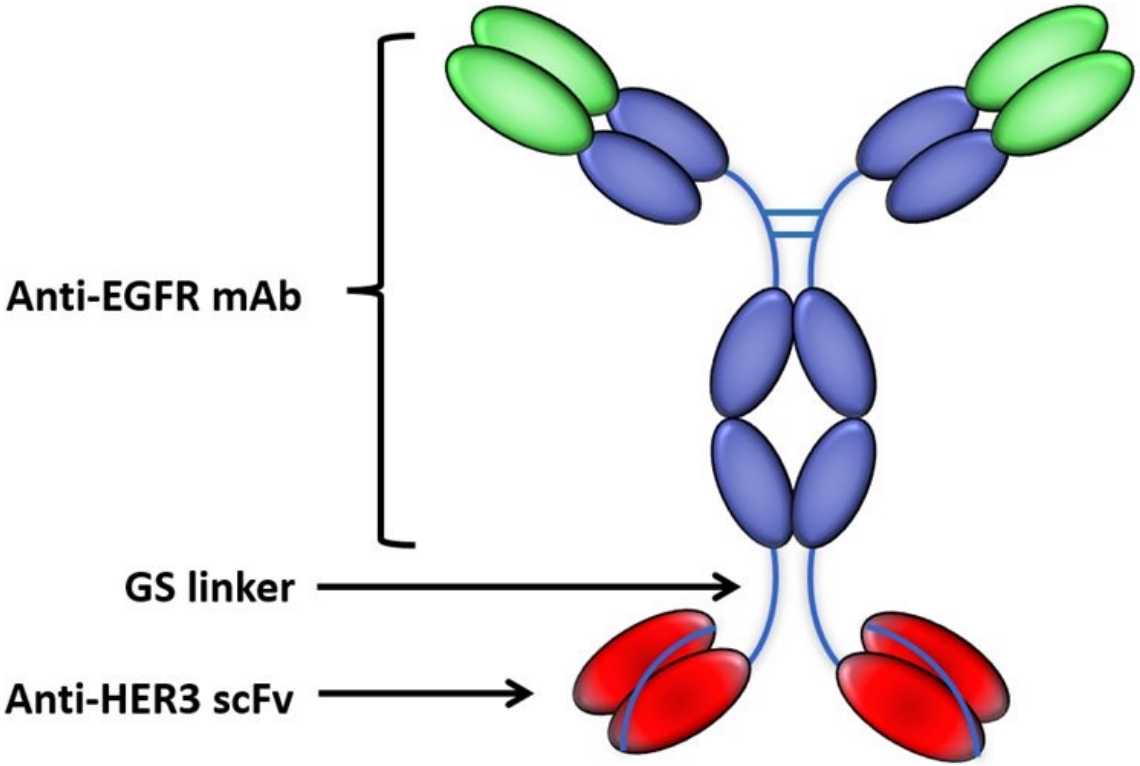
SYN-2510
(InstilBio)



BNT327
(BioNTech)

Izalontamab Brengitecan: EGFR x HER3 Bispecific ADC

Izalontamab brengitecan (Iza-bren)
anti-EGFR/anti-HER3 ADC

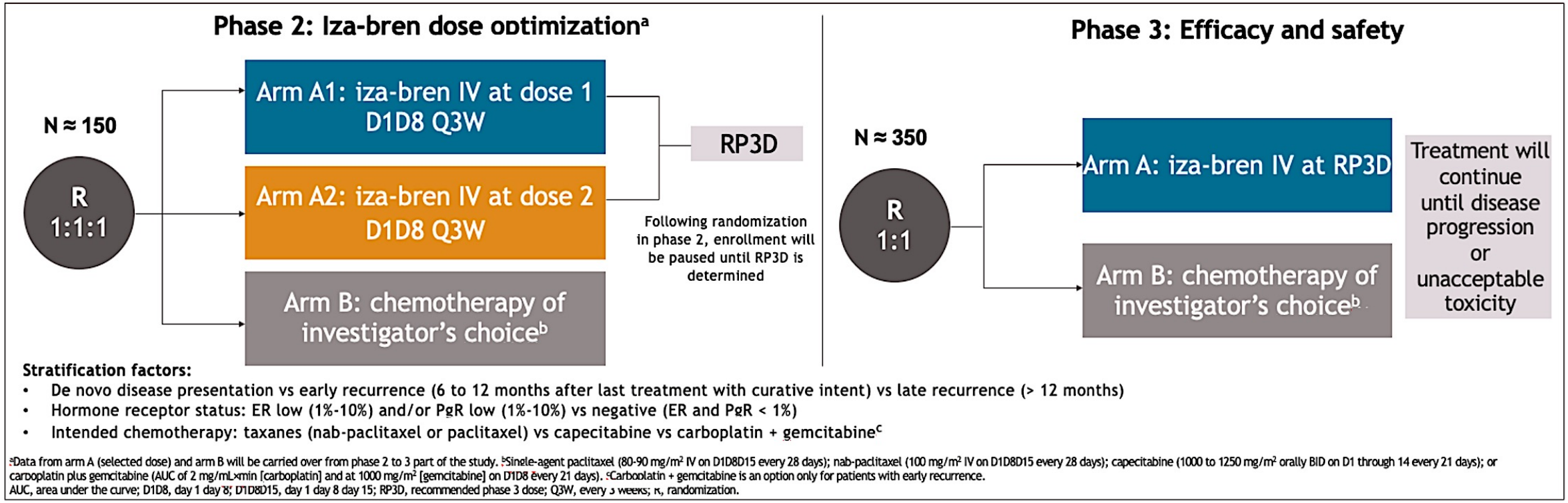


	Key features
Name(s)	• BL-B01D1 • BMS-986507 • Izalontamab brengitecan
Target	EGFR and HER3 • **EGFR component is identical to cetuximab** • EGFR is the dominant ADC MOA • HER3 affinity detuned (10x) relative to EGFR • Dual and single antigen binding
Payload	Novel camptothecin-derivative Topoisomerase I inhibitor agent (Ed-04)[a]
Linker	Cathepsin B cleavable linker
DAR	8
PK	Half-life: 1-2 days (ADC), 2-3 days (payload)
Other	• Structurally modified linker-payload vs DXd • High stability of link-payload in human serum • Slow-release effect of payload • Ability to block EGFR and HER3 signaling pathways • Potential for improved safety profile (ILD < 1%) • Most common AE: myelosuppression

BC type[1]	Median lines	cORR, 95% CI	mPFS (95% CI)
TNBC (n= 42)	3	38% (23.6-54.4)	5.7mo (4.3-NR)

A Phase 2/3 Trial of Iza-bren vs Standard-of-care Chemotherapy

In patients with previously untreated, locally advanced, recurrent inoperable, or metastatic triple-negative breast cancer or estrogen receptor-low, HER2-negative breast cancer ineligible for anti-PD-(L)1 and endocrine therapies (IZABRIGHT-Breast01)

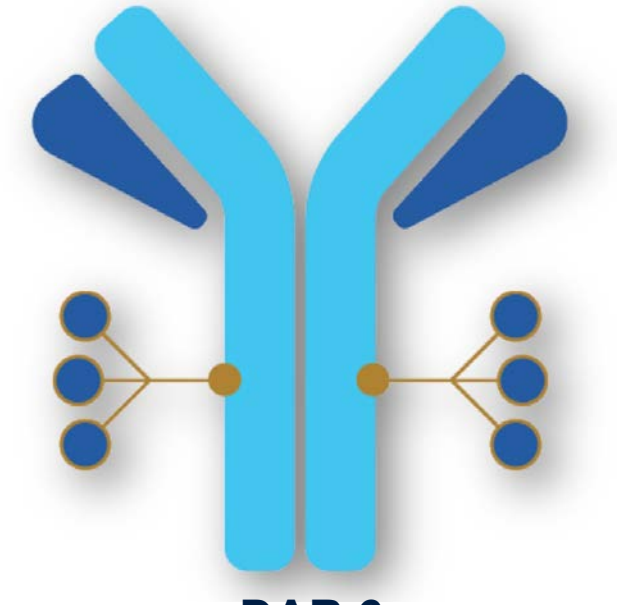


Loi S et al, TIPS poster, SABCS 2025

Emiltatug Ledadotin (Emi-Le): B7H4 ADC

Emi-Le(XMT-1660)

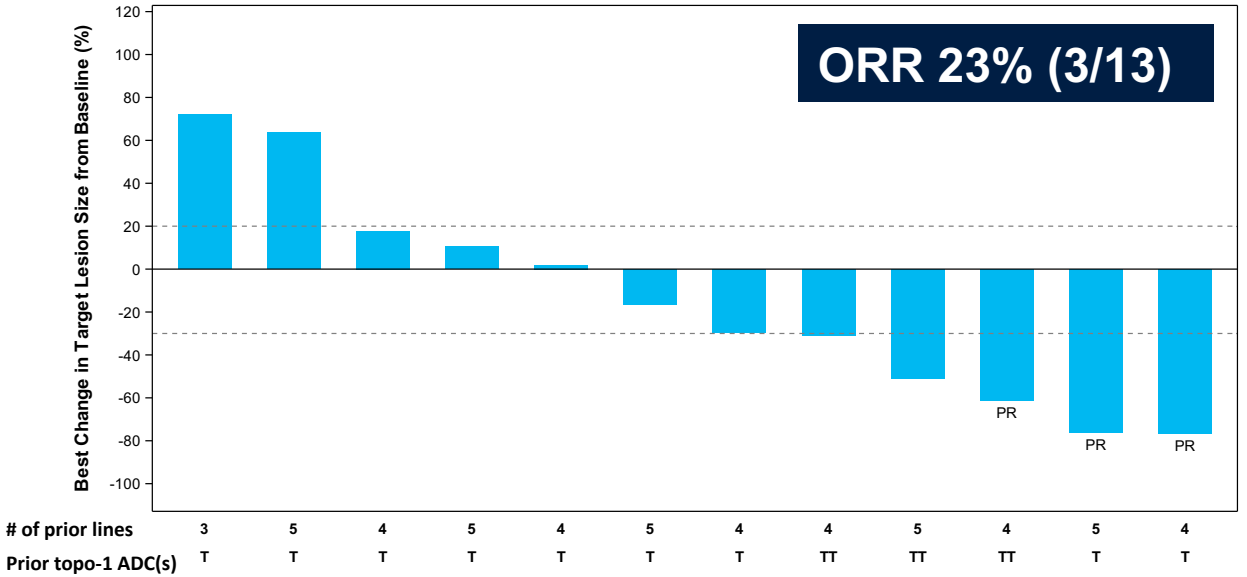
Anti-B7H4 (Dolasynthen Auristatin ADC)



DAR 6

Payload is a proprietary auristatin F-HPA microtubule inhibitor payload designed with controlled bystander effect (different from MMAE, MMAF and topo-1)

Clinical Activity in in B7H4 High Evaluable Patients with TNBC



38.9% B7H4 High

Hamilton E et al, ASCO 2025
Hamilton E et al, ESMO Breast 2025

QUESTIONS?

Module 9: HER2-Positive Breast Cancer

Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Dr Modi

Contemporary Management of HER2-Positive Metastatic Breast Cancer — Dr Hamilton

Faculty

Erika Hamilton, MD
Sarah Cannon Research Institute
Nashville, Tennessee

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

Shanu Modi, MD
Memorial Sloan Kettering Cancer Center
New York, New York

Co-Moderator
Susmitha Apuri, MD
Florida Cancer Specialists &
Research Institute
Inverness and Lecanto, Florida

Module 9: HER2-Positive Breast Cancer

Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Dr Modi

Contemporary Management of HER2-Positive Metastatic Breast Cancer — Dr Hamilton

Module 9: HER2-Positive Breast Cancer

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer (BC)

Shanu Modi, MD
Attending and Section Head, HER2 Breast Program
Memorial Sloan Kettering Cancer Center
New York, New York

Disclosures

Advisory Committees	ALX Oncology
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BioNTech SE, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, D3 Bio, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Jazz Pharmaceuticals Inc, Lilly, Nuvation Bio Inc, Pfizer Inc, Seagen Inc
Contracted Research	ALX Oncology, AstraZeneca Pharmaceuticals LP, Avacta Therapeutics, BioNTech SE, BriaCell, D3 Bio, Daiichi Sankyo Inc, Duality Biologics, Genentech, a member of the Roche Group, Nuvation Bio Inc, Pfizer Inc, Seagen Inc
Data and Safety Monitoring Boards/Committees	ALX Oncology

Recent Studies for High Risk HER2+ EBC

Neoadjuvant Trials:

- NeoCARHP
- CompassHER2
- DESTINY Breast-11

Adjuvant Trials:

- DESTINY Breast- 05
- ExteNET Update
- ELEANOR – Real World

EBC= early breast cancer

Personalizing Therapy for High Risk HER2+ Early Stage BC:

maximize outcomes and minimize toxicities

≥2cm or LN+ or LABC
ER+/ER-

↓

NEOADJUVANT TX:
AC-THP or TCHP

↓

SURGERY

↓

pCR → Trastuzumab +/- Pertuzumab → **5y DDFS ~95%**

Residual Disease → T-DM1 → **7y DRFS ~ 85%**

Neoadjuvant:

Pathological CR

De-escalating chemotherapy:

Eliminate polychemotherapy?

Any role for chemotherapy-free regimens?

De-escalate

Adjuvant:

Residual Disease

Escalation using Novel Agents:

Trastuzumab Deruxtecan

Tucatinib

Immune therapies

Escalate

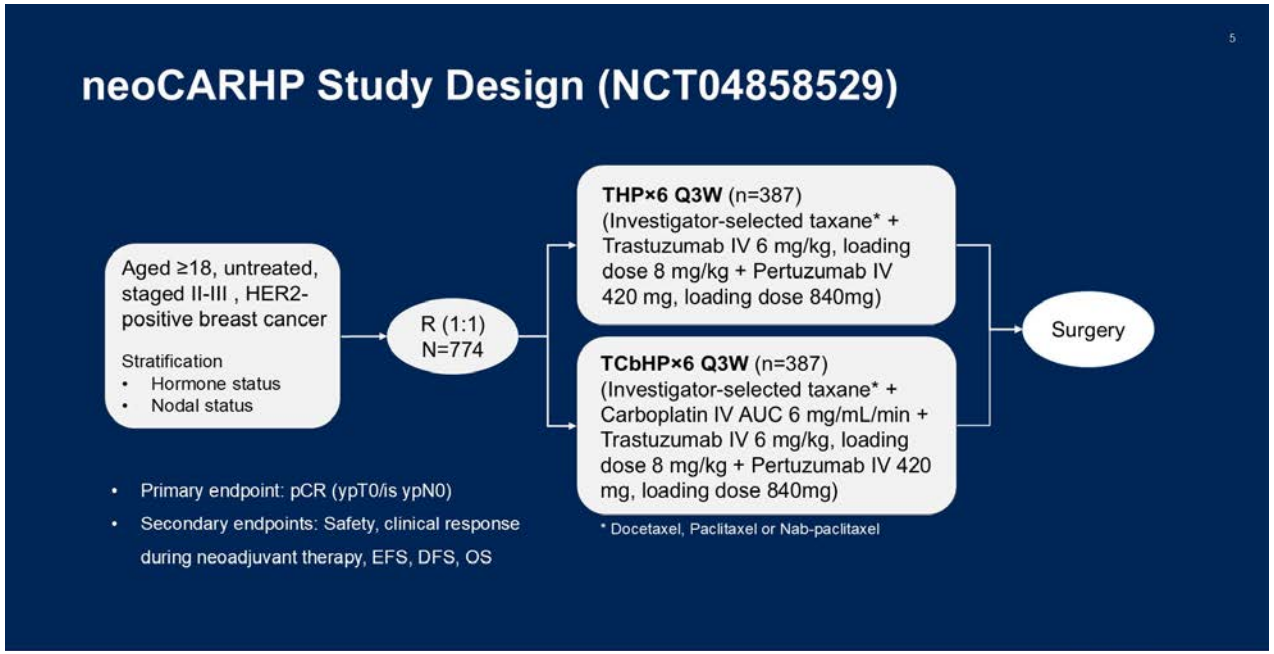
Takano T et al, Br Ca Res Treat 2024; Geyer C et al, NEJM 2025

Neoadjuvant De-Escalation Trials

neoCARHP: Phase 3 Randomized Trial of TCHP vs THP for HER2+ EBC

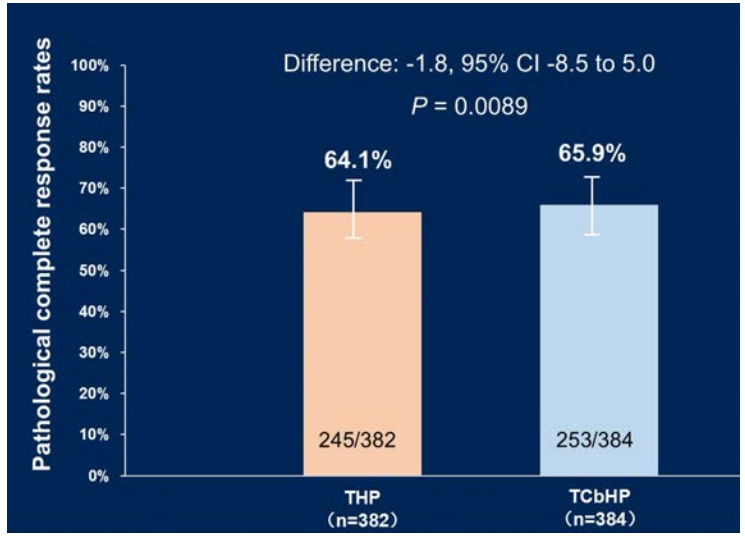
De-escalation: eliminating carboplatin

N=774



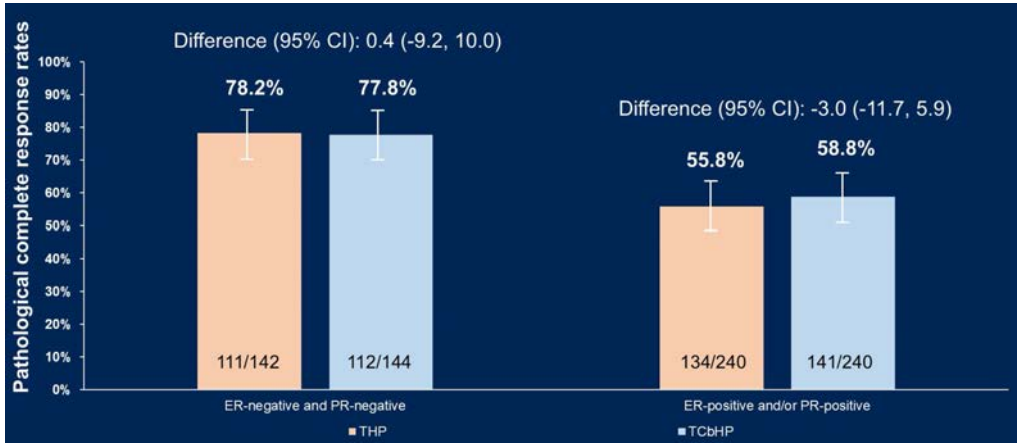
Stage 2: ~75%; Node Pos: 65%; HR+ : 60%

Primary Outcome: pCR



pCR in HR -

pCR in HR+

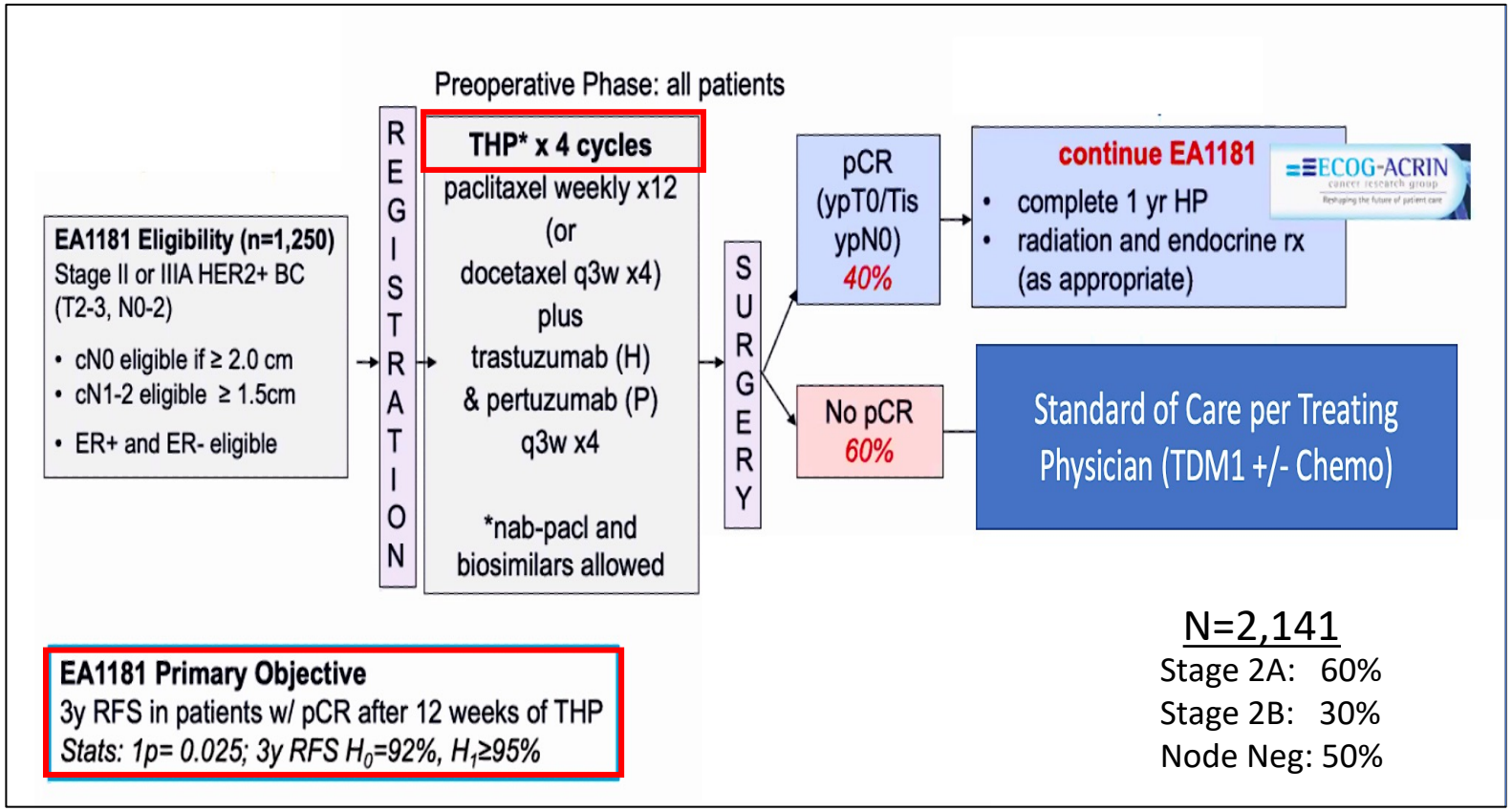


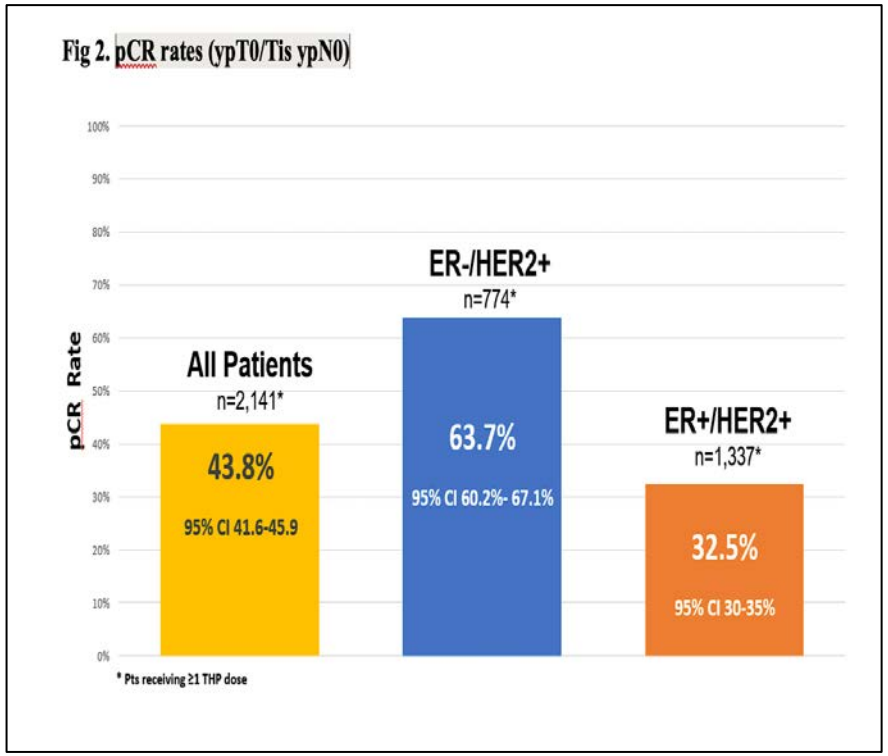
Awaiting EFS results

Gao, H-F, ASCO 2025

CompassHER2 Phase 2 Neoadjuvant Trial:

De-escalation: elimination of carboplatin and fewer cycles





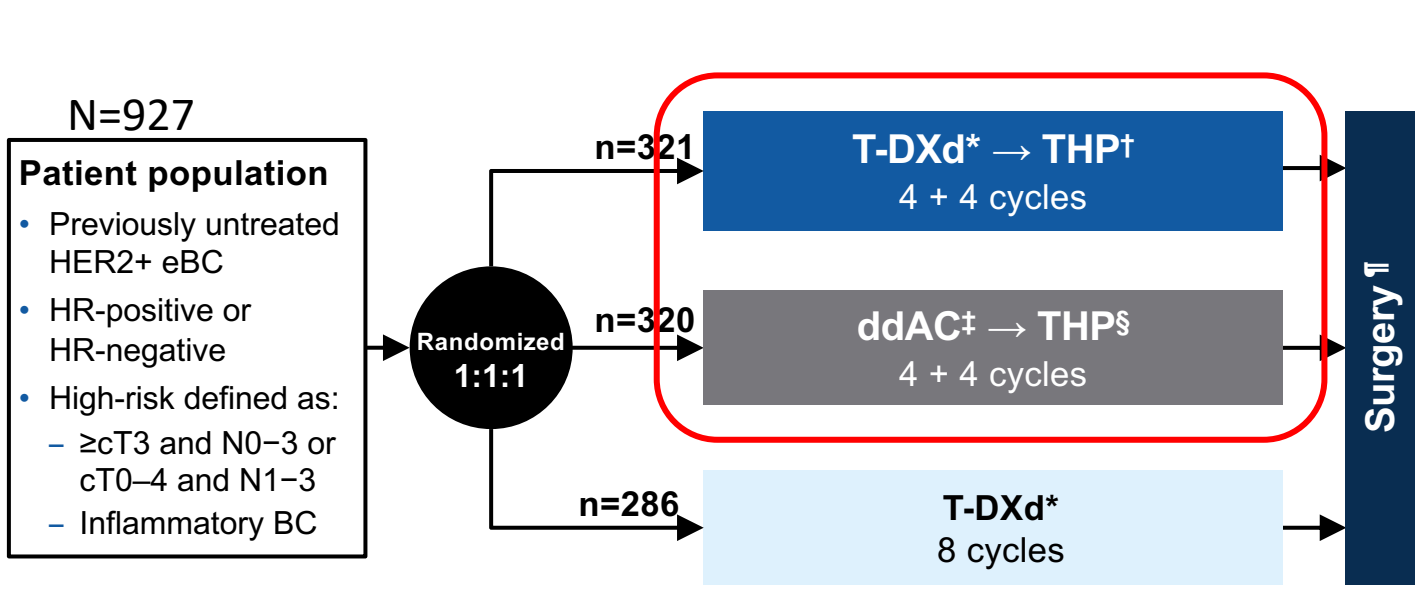
*Predictors of pCR: ER/PR-, HER2 3+

Awaiting EFS

Tung, N. ASCO 2025

DESTINY-Breast-11 RP3 Trial: Neoadjuvant T-Dxd for High Risk HER2+ BC

De-scalation with ADC Therapy



Recommended post-neoadjuvant treatment per study protocol‖

pCR: radiotherapy and concomitant trastuzumab ± pertuzumab for up to 1 year

No pCR: radiotherapy and T-DM1 for up to 14 cycles

HR-positive: endocrine therapy

Data cutoff: March 12, 2025

Primary endpoint

- pCR (ypT0/is ypN0) by blinded central review

Secondary endpoints

- pCR (ypT0 ypN0) by blinded central review
- EFS
- Safety
- Pharmacokinetics and immunogenicity
- Invasive disease-free survival
- Overall survival
- Health-related quality of life

Additional outcome measures

- Residual cancer burden (RCB)

The T-DXd alone arm closed on March 13 2024, following Independent Data Monitoring Committee recommendation

The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery

High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. *5.4 mg/kg Q3W; †paclitaxel (80 mg/m² QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m² Q2W) + cyclophosphamide (600 mg/m² Q2W); §paclitaxel (80 mg/m² QW) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ¶the recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment; ‖administered as part of the patient's SOC at the investigator's discretion. cT, clinical tumor stage; ER, estrogen receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization–positive; N, nodal stage; PR, progesterone receptor; QXW, every X weeks; T-DM1, trastuzumab emtansine; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0, absence of invasive and in-situ cancer in the breast and axillary nodes

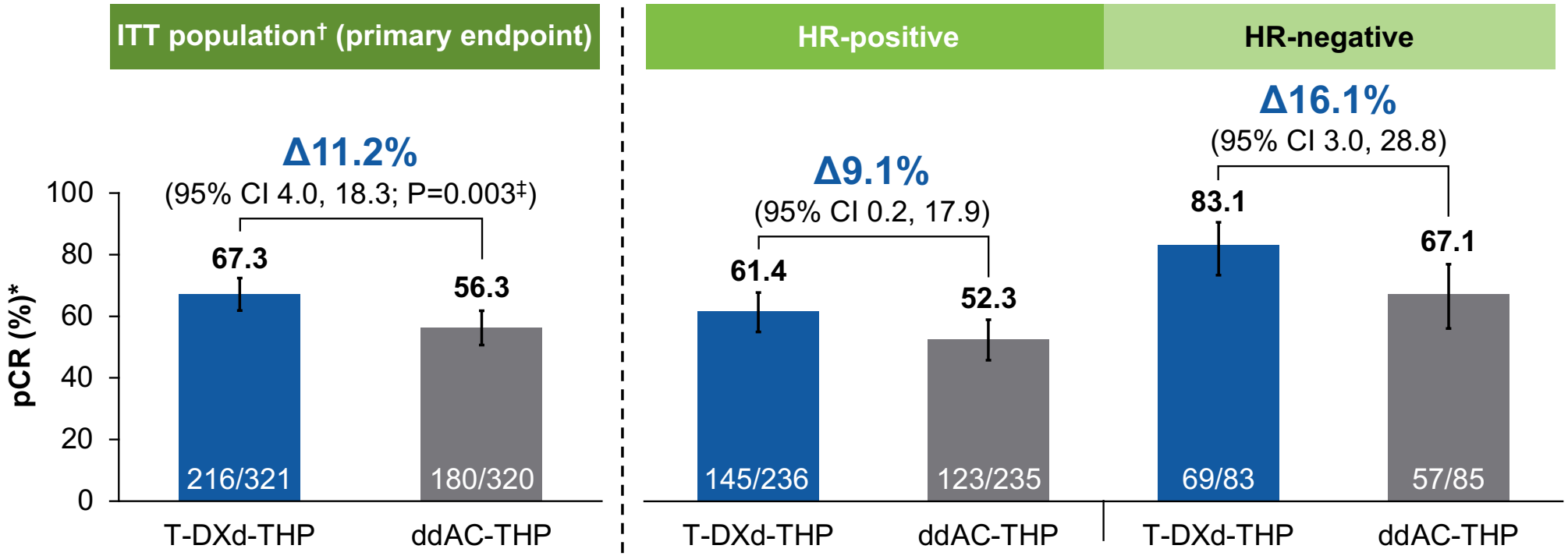
Harbeck, Modi et al, Ann Oncol 2026

DB-11: Patient demographics and key baseline characteristics

		T-DXd-THP (n=321)	ddAC-THP (n=320)	T-DXd (n=286)
Median (range) age, years		50 (25–82)	50 (23–79)	50 (23–79)
Female, n (%)		321 (100)	320 (100)	286 (100)
Geographical region, n (%)	Asia	152 (47.4)	152 (47.5)	124 (43.4)
	Western Europe	69 (21.5)	77 (24.1)	66 (23.1)
	North America	43 (13.4)	41 (12.8)	52 (18.2)
	Rest of world*	57 (17.8)	50 (15.6)	44 (15.4)
Race, n (%)†	Asian	160 (49.8)	157 (49.1)	127 (44.4)
	White	140 (43.6)	137 (42.8)	139 (48.6)
	Black or African American	5 (1.6)	7 (2.2)	7 (2.4)
	Other	12 (3.7)	10 (3.1)	8 (2.8)
Eastern Cooperative Oncology Group performance status score, n (%)	0	278 (86.6)	280 (87.5)	252 (88.1)
	1	43 (13.4)	40 (12.5)	34 (11.9)
HER2 status, n (%)‡	IHC 3+	280 (87.2)	283 (88.4)	254 (88.8)
	Other	40 (12.5)	36 (11.3)	32 (11.2)
HR status, n (%)§	Positive¶	236 (73.5)	235 (73.4)	205 (71.7)
Clinical tumor stage, n (%)	cT0–2	176 (54.8)	188 (58.8)	157 (54.9)
	cT3–4	145 (45.2)	132 (41.3)	129 (45.1)
Nodal status, n (%)‖	N0	26 (8.1)	35 (10.9)	20 (7.0)
	N+	287 (89.4)	281 (87.8)	254 (88.8)

*Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia; †not reported for four patients (1.2%), nine patients (2.8%) and five patients (1.7%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively; ‡centrally confirmed. Not categorized for one patient (0.3%) in the T-DXd-THP arm and missing for one patient (0.3%) in the ddAC-THP arm; §the proportion of patients with HR-negative disease was capped at 30% to reflect natural prevalence. Missing for two patients (0.6%) and one patient (0.3%) in the T-DXd-THP and T-DXd alone arms, respectively; ¶ER and/or
PR-positive per electronic case report form data; ‖unknown in eight patients (2.5%), four patients (1.3%), and 12 patients (4.2%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively

DB-11 Primary Endpoint : pCR (ypT0/is ypN0)



Neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP

Improvement was observed in both the HR-positive and HR-negative subgroups

For the ITT population, treatment effects were estimated by the difference in pCR with 95% CIs and P-values based on the stratified Miettinen and Nurminen's method, with strata weighting by sample size (ie Mantel–Haenszel weights)

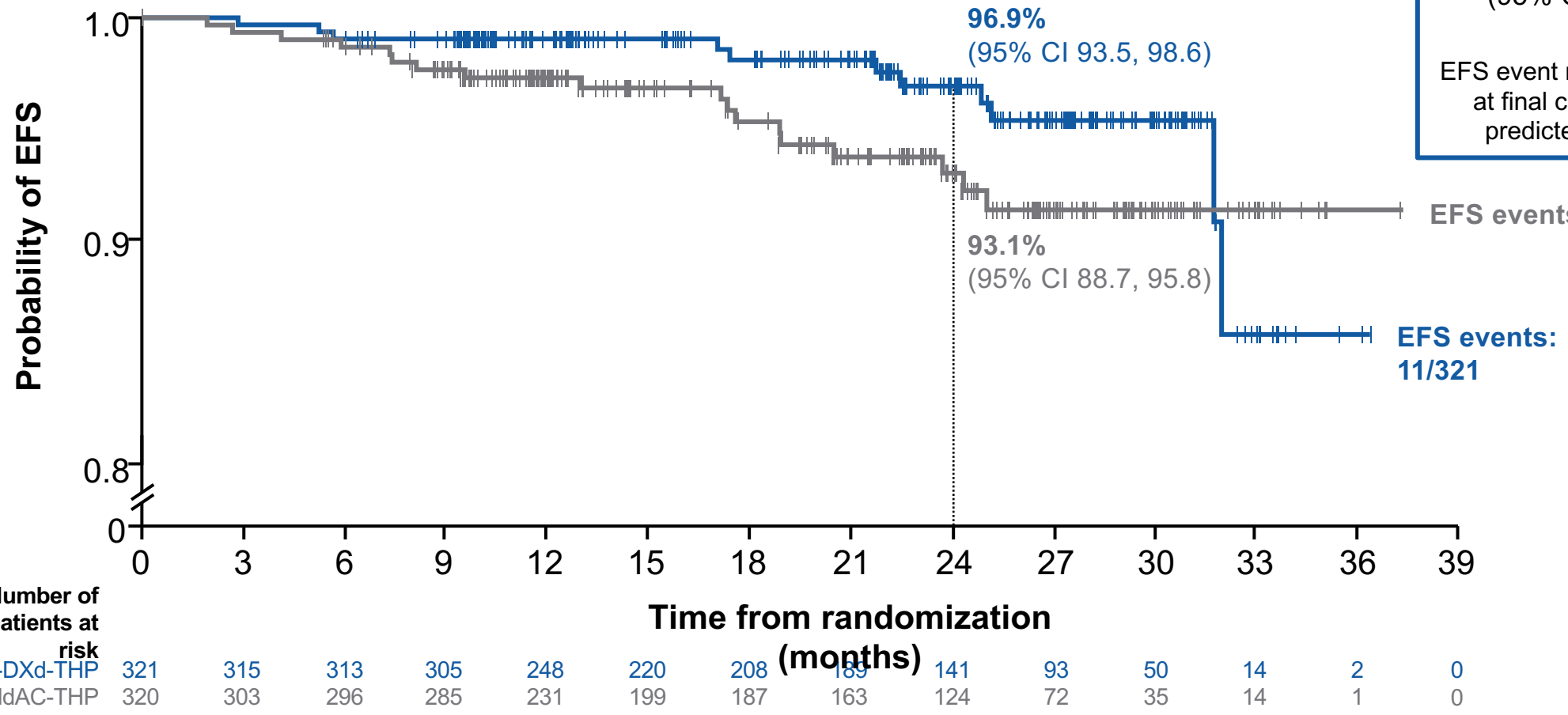
Patients with no valid records regarding pCR status for any reason were considered to be non-responders (including but not limited to withdrawal from the study, progression of disease or death before surgery, lack of surgical specimen, or defined as not evaluable by the central pathologist). Subgroup analyses were unstratified. *By blinded central review; †pCR responders were defined as patients who only received randomized study treatment (at least one dose) and had pCR; ‡two-sided P-value crossed the 0.03 prespecified boundary. ITT, intent-to-treat

Harbeck, Modi et al, Ann Oncol 2026

DB-11: EFS (interim)

Hazard ratio
0.56
(95% CI 0.26, 1.17)

2025),
EFS event maturity was 4.5%; at final cutoff, maturity is predicted to be ~10%*



Number of patients at risk														
T-DXd-THP	321	315	313	305	248	220	208	189	141	93	50	14	2	0
ddAC-THP	320	303	296	285	231	199	187	163	124	72	35	14	1	0

An early positive trend in EFS was observed, favoring T-DXd-THP vs ddAC-THP

The median duration of follow up was 24.3 months with T-DXd-THP and 23.6 months with ddAC-THP. *Predicted maturity assumes that the observed EFS hazard ratio continues after data cutoff (March 12, 2025)

Harbeck, Modi et al, Ann Oncol 2026

DB-11 Overall safety summary

n (%)	T-DXd-THP (n=320)*	ddAC-THP (n=312)*
Any AE	314 (98.1)	308 (98.7)
Grade ≥3	120 (37.5)	174 (55.8)
Any serious AE	34 (10.6)	63 (20.2)
AE leading to any dose reduction	58 (18.1)	60 (19.2)
AE leading to any drug interruption	121 (37.8)	170 (54.5)
AE leading to any treatment discontinuation	45 (14.1)	31 (9.9)
Any AE with outcome of death†	2 (0.6)	2 (0.6)
AE of special interest		
Drug-related adjudicated ILD/pneumonitis	14 (4.4)	16 (5.1)
Grade ≥3	2 (0.6)	6 (1.9)
Grade 5	1 (0.3)	1 (0.3)
Left ventricular dysfunction	4 (1.3)	19 (6.1)
Grade ≥3	1 (0.3)	6 (1.9)

T-DXd-THP is more effective and less toxic than SOC AC-THP and is poised to become a preferred neoadjuvant regimen for high risk HER2+ EBC

Harbeck, Modi et al, Ann Oncol 2026

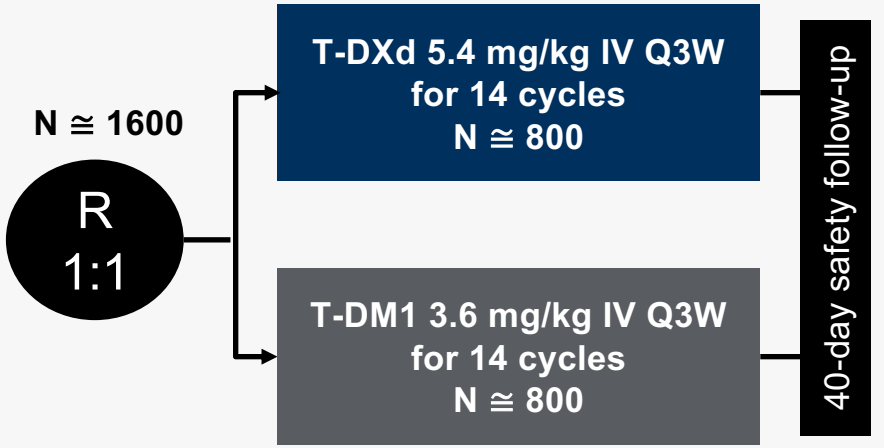
Escalation in Residual Disease/Adjuvant Trials

DESTINY B-05 (RP3): Adjuvant T-DXd in High Risk HER2+ BC with RD

Escalation with ADC therapy for high-risk residual disease

Key Eligibility Criteria

- **Residual invasive disease in the breast and/or axillary lymph nodes** after neoadjuvant chemotherapy with HER2-directed therapy (NAT)[a]
- **High-risk defined as presentation prior to NAT with:**
  - **Inoperable eBC (cT4,N0-3,M0 or cT1-3,N2-3,M0) OR**
  - **Operable eBC (cT1-3,N0-1,M0) with axillary node–positive disease (ypN1-3) after NAT**
- **Centrally confirmed HER2+** (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1



Primary endpoint

- IDFS

Key secondary endpoint

- DFS

Other secondary endpoints

- OS
- DRFI
- BMFI
- Safety

- Concomitant endocrine therapy was permitted
- Adjuvant XRT permitted (sequential or concurrent)
- Rigorous ILD monitoring with CT Chest scans

BMFI, brain metastasis–free interval; CT, computed tomography; eBC, early breast cancer; DCO, data cutoff; DFS, disease-free survival; DRFI, distant recurrence–free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; NAT, neoadjuvant therapy; OS, overall survival; Q3W, every 3 weeks; R, randomization; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]NAT is defined as ≥16 weeks' NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based chemotherapy.

Dr Charles E Geyer Jr, ESMO 2025; RD= residual disease

DB-05: Baseline demographics and clinical characteristics

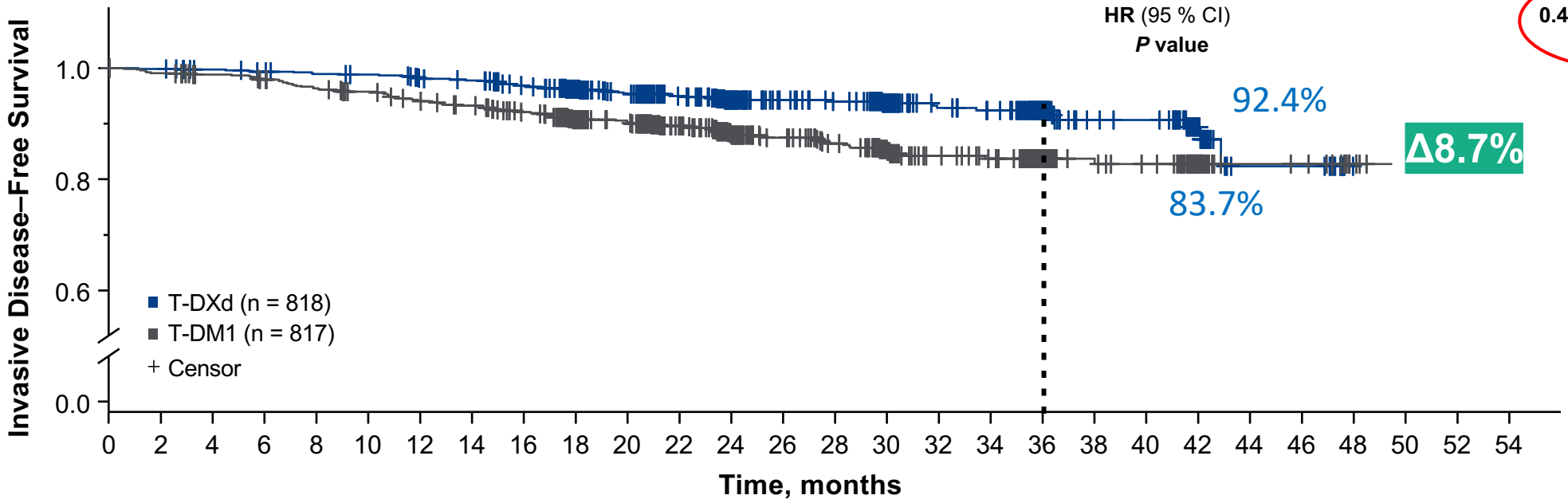
	T-DXd n = 818	T-DM1 n = 817
Age, median (range), years	50.3 (24-78)	50.6 (21-83)
<65	735 (89.9)	736 (90.1)
≥65	83 (10.1)	81 (9.9)
Female sex, n (%)	814 (99.5)	814 (99.6)
Race		
White	301 (36.8)	333 (40.8)
Black or African American	22 (2.7)	13 (1.6)
Asian	**399 (48.8)**	**386 (47.2)**
Other	96 (11.7)	85 (10.4)
Region, n (%)		
Asia	**392 (47.9)**	**380 (46.5)**
Europe	222 (27.1)	223 (27.3)
North America + Australia	57 (7.0)	72 (8.8)
Rest of world[a]	147 (18.0)	142 (17.4)
ECOG PS score, n (%)		
0	656 (80.2)	652 (79.8)
1	162 (19.8)	165 (20.2)
HER2 expression,[b] n (%)		
IHC 3+	**676 (82.6)**	**670 (82.0)**
IHC 2+ and ISH+	129 (15.8)	133 (16.3)
IHC 2+ and ISH−	2 (0.2)	0
IHC 1+ and ISH+	11 (1.3)	14 (1.7)
Hormone receptor status,[c] n (%)		
Positive	**581 (71.0)**	**583 (71.4)**
Negative	237 (29.0)	234 (28.6)

	T-DXd n = 818	T-DM1 n = 817
Operative status at disease presentation,[c] n (%)		
Operable (cT1-3, N0-1, M0)	387 (47.3)	393 (48.1)
Inoperable (cT4, N0-3, M0 or cT1-3, N2-3, M0)	**431 (52.7)**	**424 (51.9)**
Post-NAT pathologic nodal status,[c] n (%)		
Positive	**660 (80.7)**	**658 (80.5)**
Negative	158 (19.3)	159 (19.5)
Neoadjuvant HER2-targeted therapy, n (%)		
Trastuzumab alone	176 (21.5)	171 (20.9)
Trastuzumab + pertuzumab	**637 (77.9)**	**641 (78.5)**
Trastuzumab + other HER2-targeted therapy	3 (0.4)	3 (0.4)
Trastuzumab + pertuzumab + other HER2-targeted therapy	2 (0.2)	2 (0.2)
Neoadjuvant chemotherapy, n (%)		
Taxanes	818 (100)	817 (100)
Platinum compounds	386 (47.2)	392 (48.0)
Anthracycline	**423 (51.7)**	**399 (48.8)**
Radiotherapy treatment, n (%)		
Adjuvant radiotherapy	**764 (93.4)**	**759 (92.9)**
Concurrent	438 (53.5)	480 (58.8)
Sequential	326 (39.9)	279 (34.1)
No radiotherapy	54 (6.6)	58 (7.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NAT, neoadjuvant therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Included regions: Argentina, Brazil, Chile, Czech Republic, Israel, Mexico, Peru, Poland, Romania, Russian Federation. [b]Centrally confirmed. [c]As reported in electronic data capture.

DB-05 Primary endpoint: IDFS[a]

	T-DXd n = 818	T-DM1 n = 817
Patients with events, n (%)	**51** (6.2)	**102** (12.5)
3-year IDFS, % (95% CI)	**92.4** (89.7-94.4)	**83.7** (80.2-86.7)
HR (95 % CI)	**0.47** (0.34-0.66)	
***P* value**	**<0.0001[b]**	



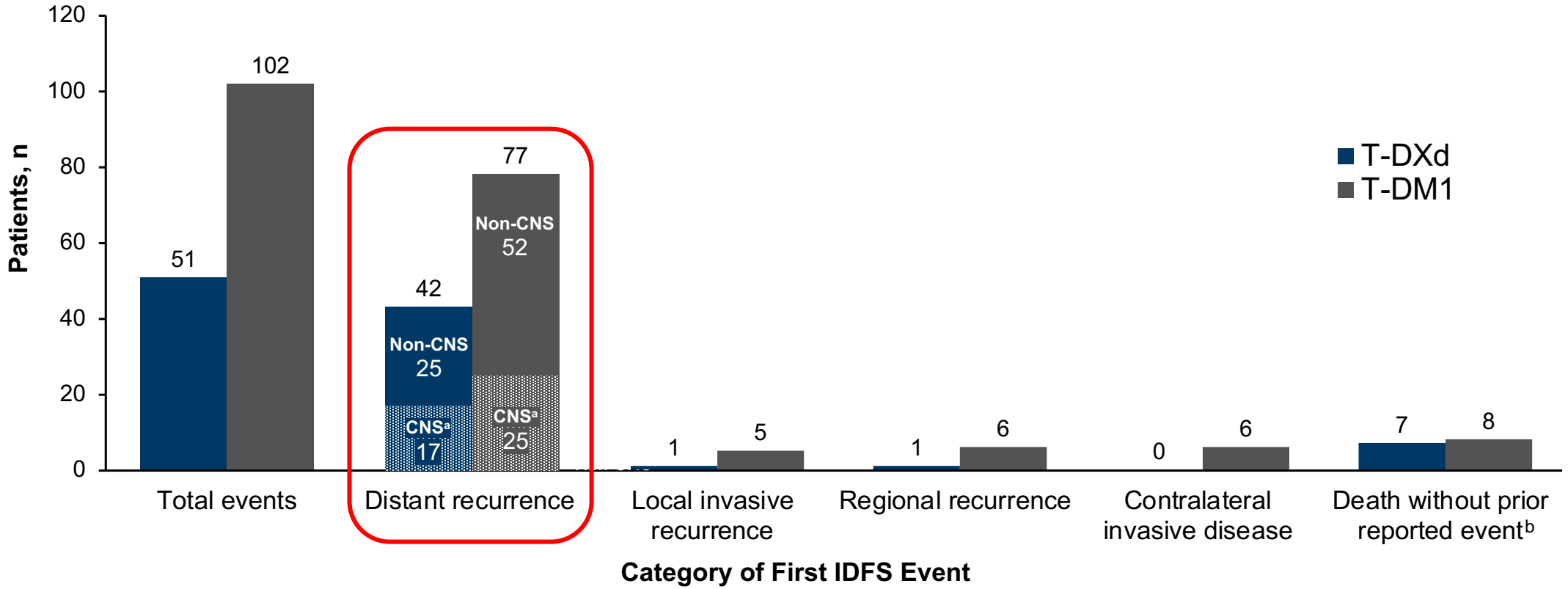
Number at Risk:

T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	337	233	186	177	120	84	79	38	14	13	4	1	1	0

53% reduction in the risk of invasive disease recurrence or death for T-DXd compared with T-DM1
Consistent benefit seen across subgroups

HR, hazard ratio; IDFS, invasive disease–free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Efficacy stopping boundary, *P* = 0.0183.
[a]IDFS is defined as the time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. [b]Two-sided *P* value from stratified log-rank test. Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

DB-05: First iDFS Events



Lower distant and locoregional recurrences were observed with T-DXd vs T-DM1, including CNS recurrences

OS data are immature and need longer followup

IDFS, invasive disease–free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Participants who experienced multiple types of IDFS events within 61 days of their first event are reported in the category according to the following hierarchy: distant recurrence CNS, distant recurrence non-CNS, local invasive recurrence, regional recurrence, contralateral breast cancer, and death without a previous event.

[a]CNS as sole site for distant recurrence or one of multiple distance recurrent sites [b]Causes of death in the T-DXd arm were 2 drug-related ILD, unrelated respiratory tract infection, acute respiratory failure (outside AE reporting period), acute respiratory distress syndrome (outside AE reporting period), and 2 disease progression, and in the T-DM1 arm were drug-related sepsis, unrelated ovarian cancer, unrelated aneurysm, unrelated pneumothorax, unrelated leiomyosarcoma, self-inflicted gun wound, and 2 disease progression.

Geyer CE, et al. Presented at ESMO 2025; 17–21 October. Berlin, Germany, Abstract LBA1.

DB-05: Adverse events of special interest:

ILD/pneumonitis and LV dysfunction

	Adjudicated Drug-related ILD					
n (%)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806)[a]	77 (9.6)	16 (2.0)	52 (6.5)	7 (0.9)	0	2 (0.2)
T-DM1 (n = 801)[a]	13 (1.6)	8 (1.0)	5 (0.6)	0	0	0

Adjuvant radiotherapy timing (sequential or concurrent) showed no differences in adjudicated drug-related ILD

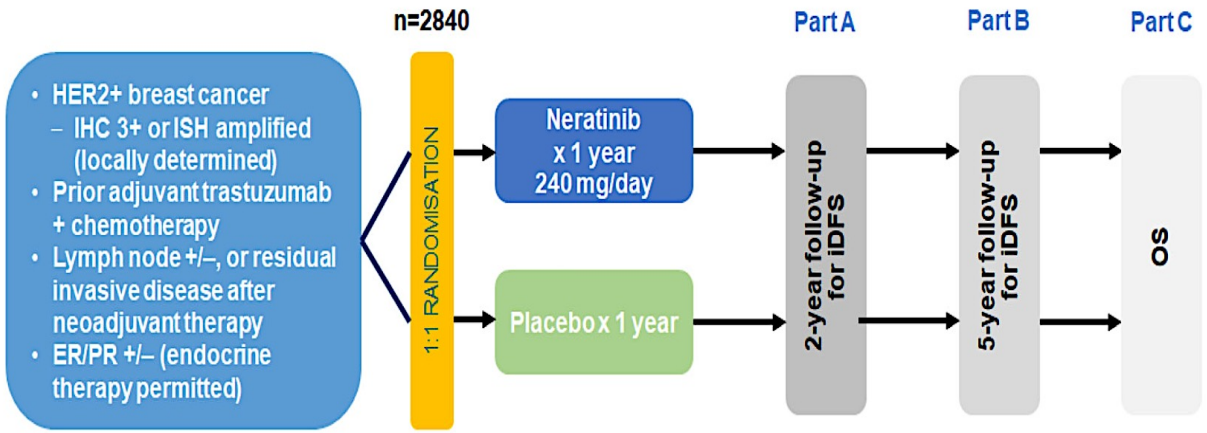
Similar distributions of any grade adjudicated drug-related ILD events were observed with sequential and concurrent radiotherapy in both treatment arms (T-DXd: 10.7% and 9.6.% vs T-DM1: 2.6% and 1.0%, respectively)

	LV dysfunction					
n (%)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806)[a]	23 (2.9)	1 (0.1)	20 (2.5)	2 (0.2)	0	0
T-DM1 (n = 801)[a]	14 (1.7)	0	11 (1.4)	3 (0.4)	0	0

NCCN has endorsed Adjuvant T-DXd for the high risk RD setting

Awaiting FDA Review

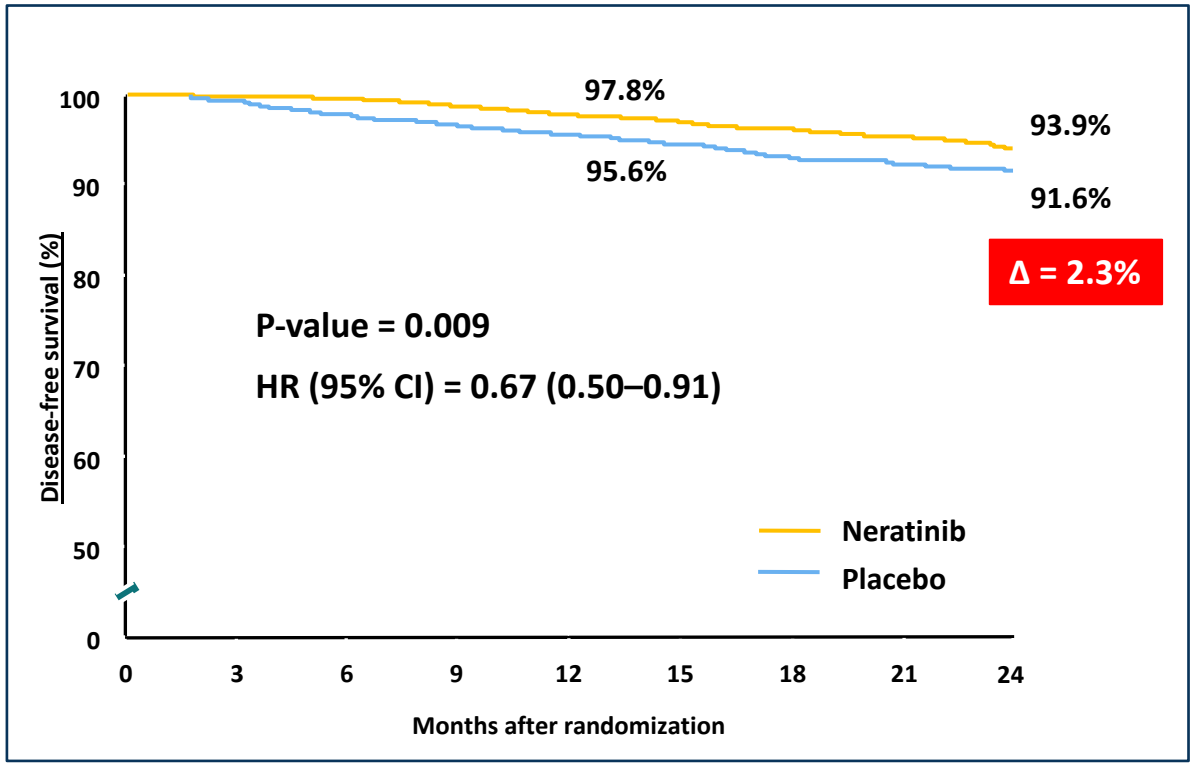
ExteNET Phase 3 Trial:
Neratinib as Extended Adjuvant Therapy for HER2+ BC



- Primary endpoint: iDFS
- Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, OS, safety
- Additional analysis: biomarkers, health outcome assessment (FACT-B, EQ-5D)
- Stratified by: nodes 0, 1–3 versus 4+, ER/PR status, concurrent versus sequential trastuzumab

Node Positive: 75%; ≥4 Nodes: 30%; HR+: 57%

Primary Endpoint: 2-year iDFS



- This benefit was maintained at 5 years
- No OS advantage in the final analysis
- 40% Grade 3 diarrhea

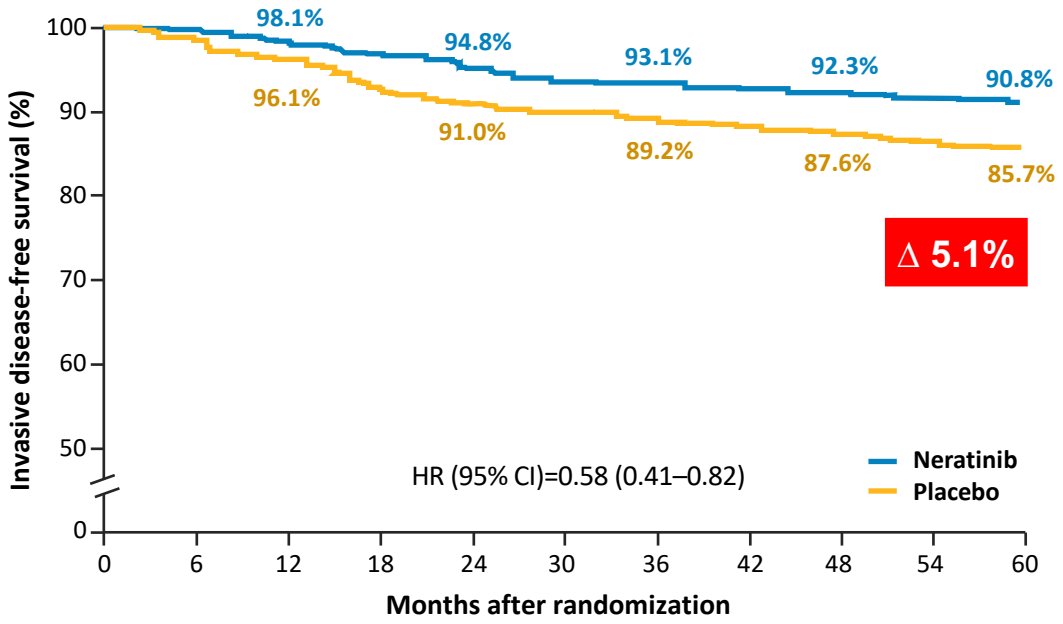
In 2017 the FDA approved adjuvant Neratinib post-trastuzumab

Martin et al, Lancet 2017; Chan et al, Clin Breast Can 2021; Holmes et al, Eur J Can 2023; Untch M et al. Oncol Ther. 2021;9:297-309; Chan et al. Lancet Oncol. 2016;17:367-377.

ExteNET: pts with HR+ and ≤1 Year from Trastuzumab (Descriptive Analyses)

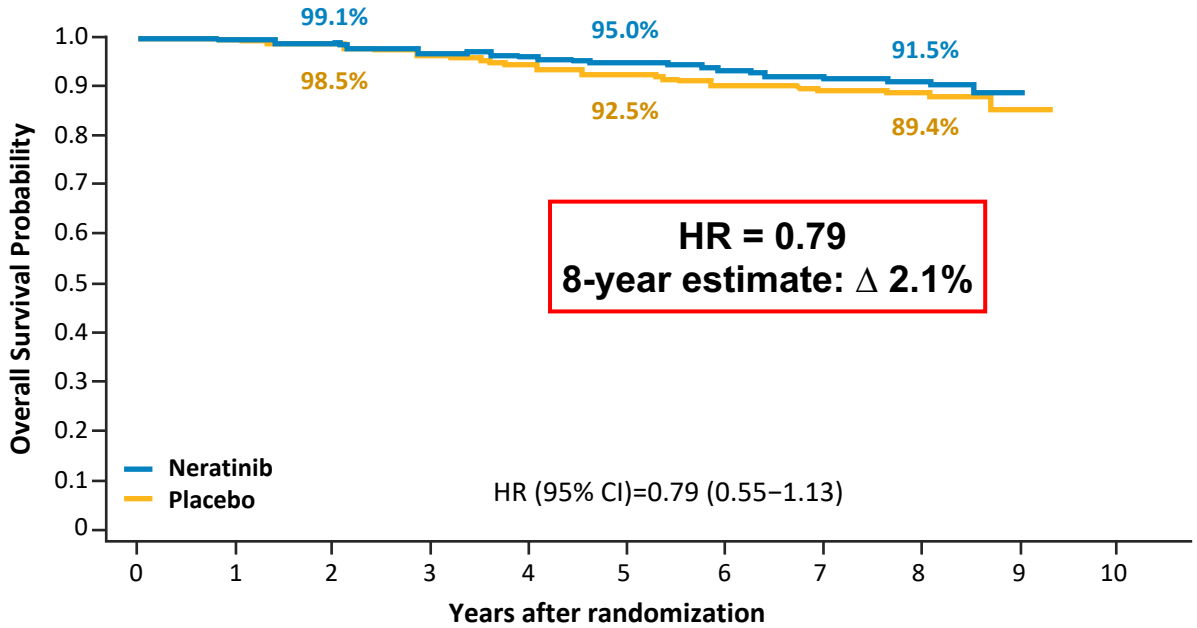
(n=1,334)

iDFS at 5 yrs



No. at risk HR+/≤1 year from trastuzumab											
Neratinib	670	620	599	577	523	469	465	460	457	448	428
Placebo	664	634	609	583	535	481	471	462	458	450	433

Overall Survival



No. at risk											
Neratinib	670	640	620	578	567	556	534	490	315	78	0
Placebo	664	645	630	589	574	560	537	497	335	78	0

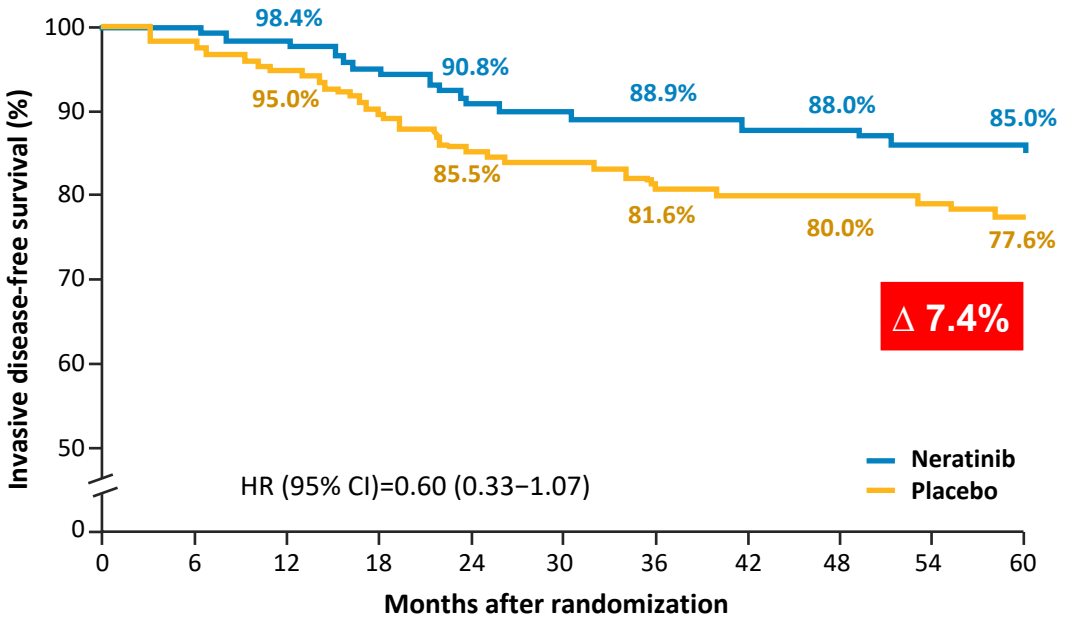
95% of the HR+ study population received concomitant endocrine therapy.

Chan, A. Clin Breast Cancer. 2021

exteNET Pts with Residual Disease, HR+, and ≤1 Year from Tras (Exploratory Analyses)

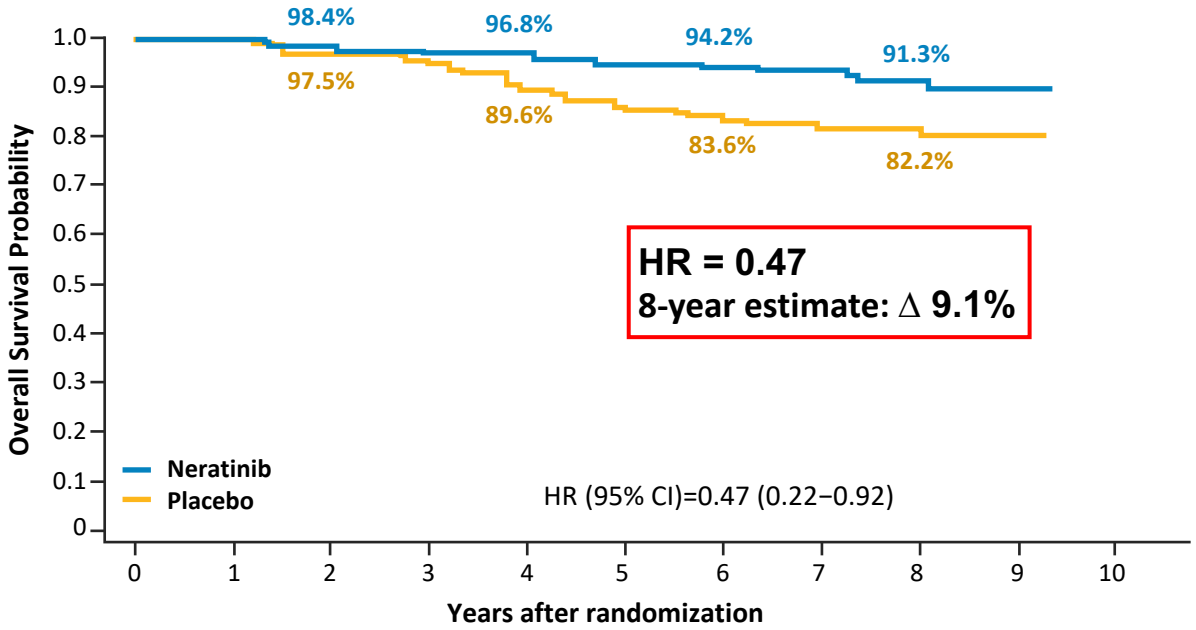
(n=295)

iDFS at 5 yrs



No. at risk											
Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

Overall Survival



No. at risk											
Neratinib	131	126	121	116	113	110	106	100	60	14	0
Placebo	164	161	156	143	135	129	123	115	65	12	0

Chan, A. Clin Breast Cancer. 2021.

exteNET exploratory analyses:
CNS recurrence in pts with HR+, ≤1 yr from Tras
(n=1,334)

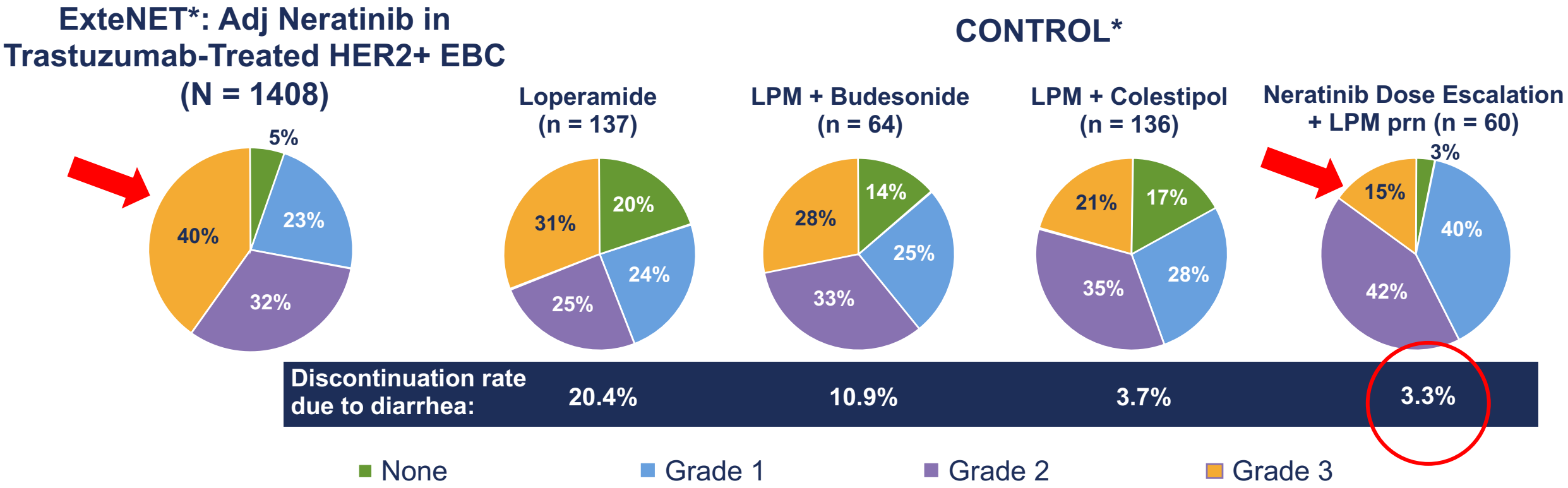
	Cumulative Incidence of CNS recurrences at 5 years, %	
	Neratinib, %	Placebo, %
All patients (*n*=1334)	0.7	2.1
Prior neoadjuvant therapy		
No (*n*=980)	0.7	1.5
Yes (*n*=354)	0.7	3.7

EMA 2018: approval for extended neratinib in pts with HR+ HER2+ within 1 yr of completing trastuzumab

Chan A, et al. Clin Br Can 2021

Control Trial: Dose Escalation Reduces Diarrhea with Neratinib

PREVENTIVE STRATEGIES REDUCED GRADE ≥ 3 DIARRHEA COMPARED TO EXTENET



Dose-escalation: 120 mg/day d1-7; 160 mg/day d8-14; then 240 mg/day….+ loperamide prn

Chan A, et al, SABCS 2019. Poster P5-14-03; Chan A, et al. Lancet Oncol. 2016;17:367-377; Hurvitz S, SABCS 2017. Abstract P3-14-01.

ELEANOR: Real-World Study Extended Neratinib in HR+/HER2+ Early Breast Cancer

N=285 patients; median follow-up 29.1m; European Countries

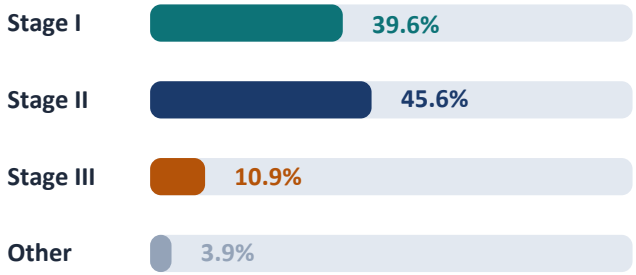
Patient Population

Inclusion Criteria

- HER2+/HR+ early breast cancer, Stage I–III
- Completed adjuvant trastuzumab-based therapy < 1 year ago
- Adult females | ECOG PS 0–2

Disease Characteristics

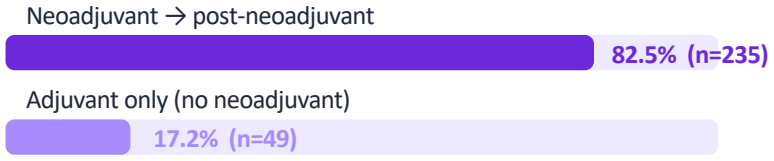
Clinical AJCC Stage at Diagnosis



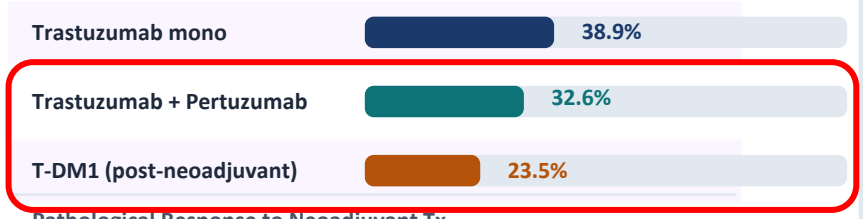
Node status cN0/N1mi 67.4% | **cN1 24.9%**

Prior Therapies Before Neratinib

Treatment Setting



Anti-HER2 Agent Received (MAS)



Pathological Response to Neoadjuvant Tx

Treatment: **Neratinib**

Duration:
12 months (median actual: 11.9 months)

Dosing:
Standard 240 mg/day | 44.3% started at reduced dose (<240 mg) with planned up-titration

Diarrhea prophylaxis:
86.4% of patients received prophylaxis

MAS = Main Analysis Set (n=285) | NST = no special type | ILC = invasive lobular carcinoma | T-DM1 = trastuzumab emtansine | pCR = pathological complete response

Lüftner et al., ESMO 2025

ELEANOR Study: Real-World Extended Neratinib in HR+/HER2+ Early Breast Cancer

Primary Endpoint: adherence ≥75% compliant days

96.8%

Adherence Rate

Patients with ≥75% compliant days

Primary endpoint met

20.6%

Grade ≥3 Diarrhea

vs. 39% in ExteNET (no prophylaxis era)

↓ 47% relative reduction

80.3%

Successfully Up-Titrated

Of patients who started low-dose (<240 mg/day) reached full dose

Dose escalation strategy

96.6%

24-Month DFS

Disease-free survival at 2 years

Consistent with ExteNET

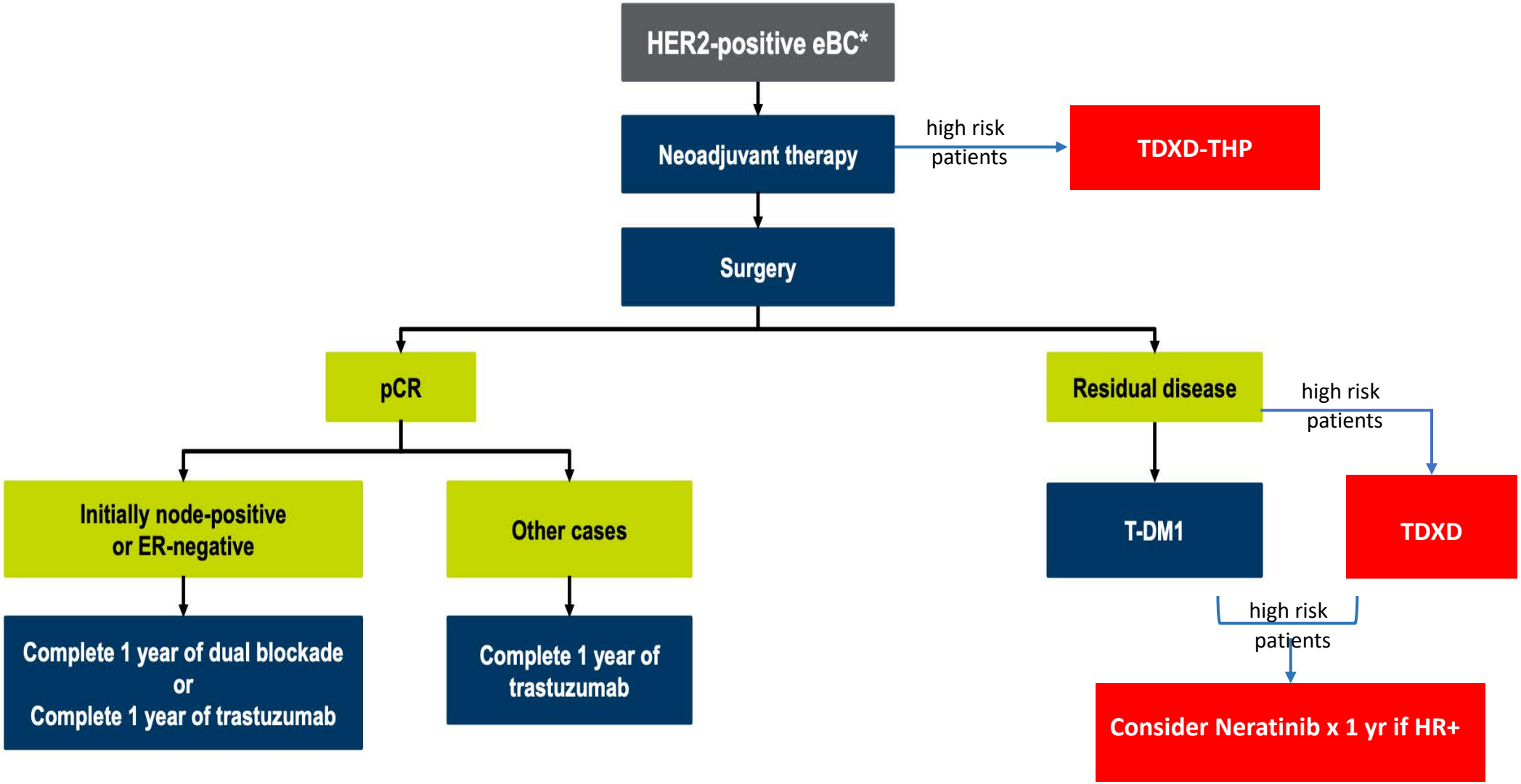
Successful real-world use of extended adjuvant neratinib after trastuzumab-based therapy (incl. T+P dual blockade and T-DM1) in HR+/HER2+ EBC. Mirrors the ExteNET EMA-label population

No data post T-DXD

DFS = disease-free survival | eBC = early breast cancer | HR+ = hormone receptor positive | T-DM1 = trastuzumab emtansine | MAS: n=285 | CS: n=279 | SAF: n=287

Lüftner et al., ESMO 2025

Future Approach To Stage II/III HER2+ EBC



QUESTIONS?

Module 9: HER2-Positive Breast Cancer

Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Dr Modi

Contemporary Management of HER2-Positive Metastatic Breast Cancer — Dr Hamilton

Contemporary Management of HER2-Positive Metastatic BC (mBC)

Erika Hamilton, MD

Chief Development Officer, Late Phase

Director, Breast Cancer Research Program

Sarah Cannon Research Institute

Nashville, TN, USA

SCRI Sarah Cannon Research Institute

April 25, 2026

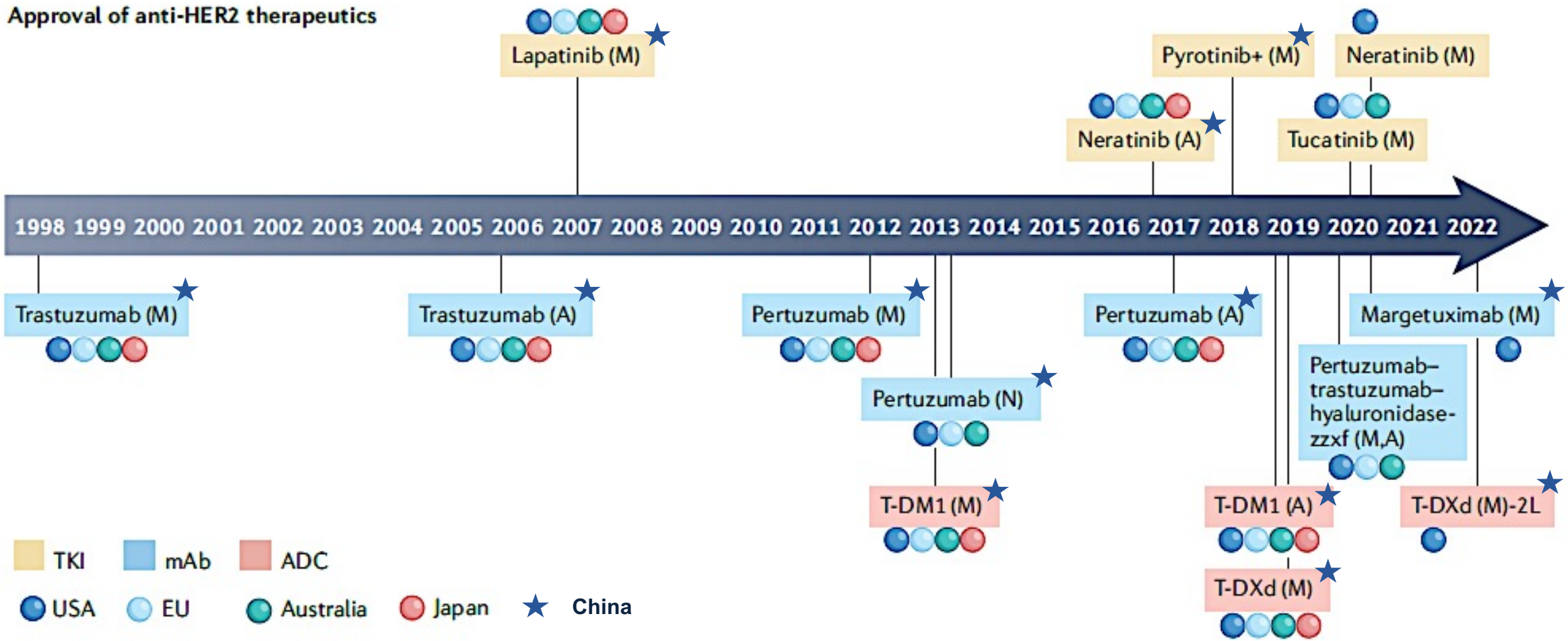
Disclosures

Consulting/Advisory Roles (All Payments to Institution)	Accutar Biotechnology Inc, Arvinas, AstraZeneca Pharmaceuticals LP, BeOne, Circle Pharma, Daiichi Sankyo Inc, Entos Pharmaceuticals, Genentech, a member of the Roche Group, Gilead Sciences Inc, Halda Therapeutics, Incyclix Bio, IQVIA, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Jefferies LLC, Johnson & Johnson, Lilly, Medical Pharma Services SRO, Mersana Therapeutics Inc, Novartis, Pfizer Inc, Pyxis Oncology, Samsung Bioepis, Shorla Oncology, Stemline Therapeutics Inc, Tempus, Zentalis Pharmaceuticals
Research Funding (All Payments to Institution)	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Accutar Biotechnology Inc, ADC Therapeutics, Akesobio Australia Pty Ltd, Amgen Inc, Aravive Inc, ARS Pharmaceuticals, Artios Pharma Limited, Arvinas, AstraZeneca Pharmaceuticals LP, AtlasMedx Inc, BeOne, Black Diamond Therapeutics Inc, Bliss Biopharmaceutical (Hangzhou) Co Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Compugen, Context Therapeutics, Cullinan Therapeutics, Curis Inc, CytomX Therapeutics, Daiichi Sankyo Inc, Dantari, Deciphera Pharmaceuticals Inc, Duality Biologics, eFFECTOR Therapeutics Inc, Eisai Inc, Ellipses Pharma, Elucida Oncology Inc, EMD Serono Inc, Fochon Pharmaceuticals, FUJIFILM Pharmaceuticals USA Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Harpoon Therapeutics, Hutchison MediPharma, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Inspirna, InventisBio, Jacobio Pharmaceuticals Group Co Ltd, Karyopharm Therapeutics, K-Group Beta, Kind Pharmaceuticals LLC, Leap Therapeutics Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Lycera, MacroGenics Inc, Marker Therapeutics Inc, Merck, Mereo BioPharma, Mersana Therapeutics Inc, Merus, Molecular Templates, Myriad Genetic Laboratories Inc, Novartis, NuCana, Olema Oncology, Oncothyreon, ORIC Pharmaceuticals, Orinove Inc, Orum Therapeutics, Pfizer Inc, pharmaand GmbH, PharmaMar, Pieris Pharmaceuticals Inc, Pionyr Immunotherapeutics, Plexxikon Inc, Prelude Therapeutics, ProFound Therapeutics, Radius Health Inc, Regeneron Pharmaceuticals Inc, Relay Therapeutics, Repertoire Immune Medicines, Seagen Inc, Sermonix Pharmaceuticals, Shattuck Labs, Stemline Therapeutics Inc, Sutro Biopharma, Syndax Pharmaceuticals, Syros Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, Tolmar, Transcenta, Treadwell Therapeutics, Verastem Inc, Zenith Epigenetics, Zymeworks Inc
Nonrelevant Financial Relationships	Dana-Farber Cancer Institute

Agenda

- FDA approved therapies for HER2+ breast cancer
- Recent trial data for HER2+ MBC
  - DESTINY-Breast09
  - HER2CLIMB-05
- Data from evidence-based treatment options
  - NALA
  - SOPHIA
- Treatment for HER2+ brain metastases
- Novel therapies under investigation for HER2+ MBC
- HER2 mutant MBC
- Current treatment algorithm for HER2+ MBC

FDA approved therapies for HER2+ breast cancer



A- adjuvant
M- metastatic
N- neoadjuvant

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Swain S et al. Nat Reviews Drug Discovery 2022

Historical treatment algorithm for HER2+ MBC

		Overall survival
1st line	Taxane + trastuzumab + pertuzumab	57.1 months
2nd line	Trastuzumab deruxtecan (T-DXd)	52.6 months
3rd line	Tucatinib + trastuzumab + capecitabine	24.7 months
4th line & later	Trastuzumab emtansine (T-DM1)	
	Capecitabine + neratinib	
	Margetuximab + chemo	
	Capecitabine + lapatinib	

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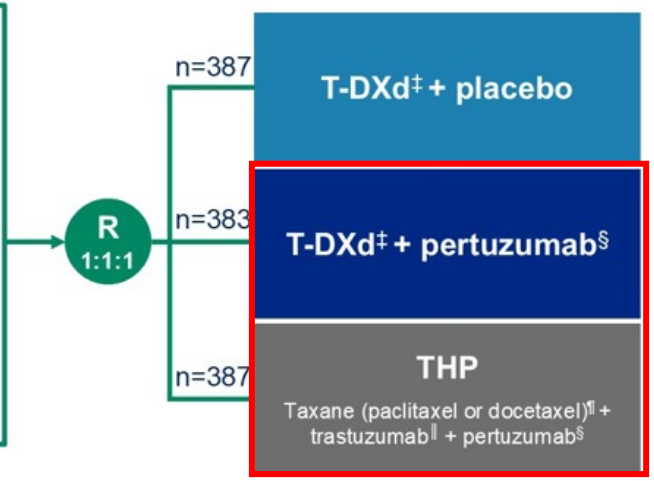
DESTINY-Breast09: 1L T-DXd + pertuzumab vs taxane/trastuzumab/pertuzumab for HER2+ MBC

Eligibility criteria

- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC†**

Stratification factors

- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)



- If T-DXd was discontinued due to AEs (except Grade >2 ILD), patients could switch to trastuzumab
- Concurrent use of ET (AI or tamoxifen) allowed for HR+ disease after 6 cycles of T-DXd or after stopping taxane in the THP arm

Primary Endpoint:

- PFS by BICR

Key Secondary Endpoint:

- OS (Overall Survival)

Key baseline characteristics

	T-DXd + P (n = 383)	THP (n = 387)
HER2 score by central test, n (%)		
IHC 3+	318 (83.0)	315 (81.4)
IHC <3 / ISH+	62 (16.2)	71 (18.3)
IHC NR / ISH+	3 (0.8)	1 (0.3)
HR status, n (%)		
Positive*	207 (54.0)	209 (54.0)
Negative	176 (46.0)	178 (46.0)
De-novo disease at diagnosis, n (%)	200 (52.2)	200 (51.7)
PIK3CA mutations detected, n (%)	116 (30.3)	121 (31.3)
Brain metastases, n (%)†	25 (6.5)	22 (5.7)
Visceral metastases, n (%)	281 (73.4)	268 (69.3)
Prior therapies (neo)adjuvant setting		
Prior chemotherapy	159 (41.5%)	152 (39.3%)
Prior targeted therapy	112 (29.2)	108 (27.9)

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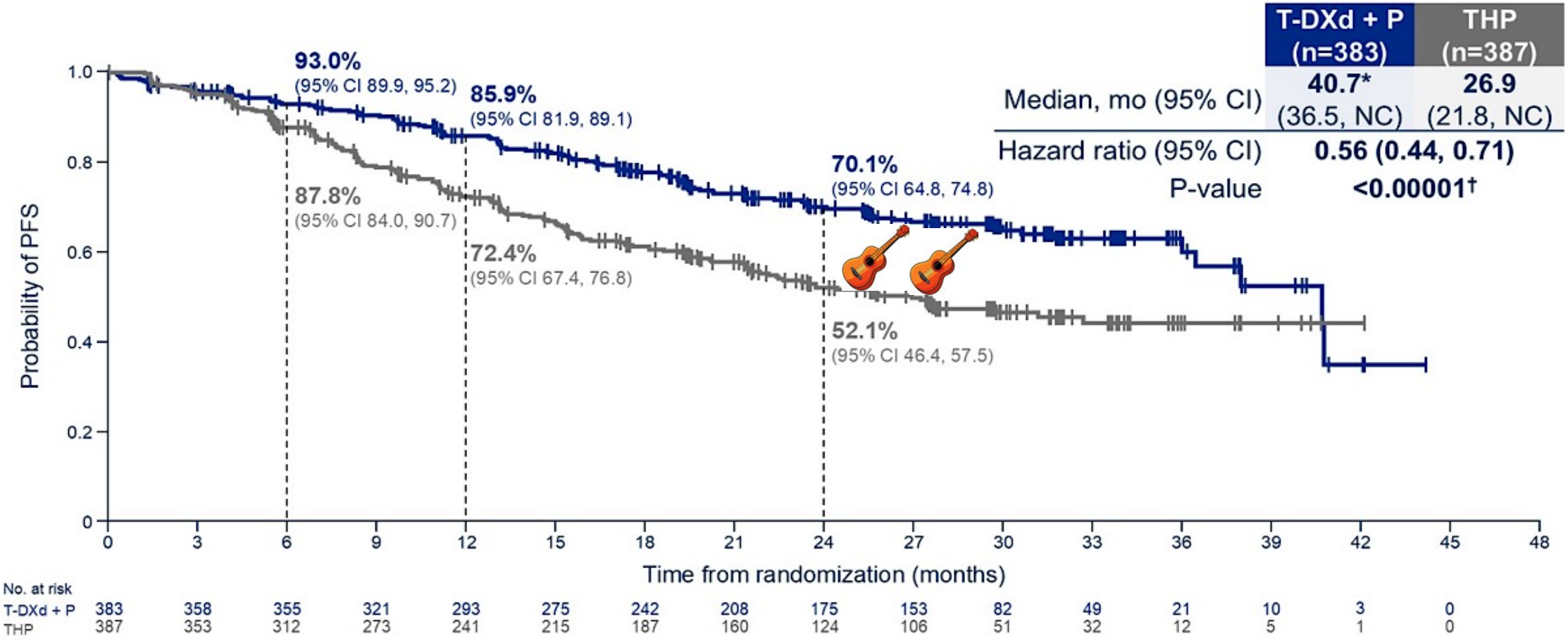
Tolaney SM et al. ASCO 2025

DESTINY-Breast09: PFS (BICR) Primary endpoint



Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

PFS Inv assessment: T-DXd + P 40.7 mo vs THP 20.7 mo (HR 0.49, p<0.00001)

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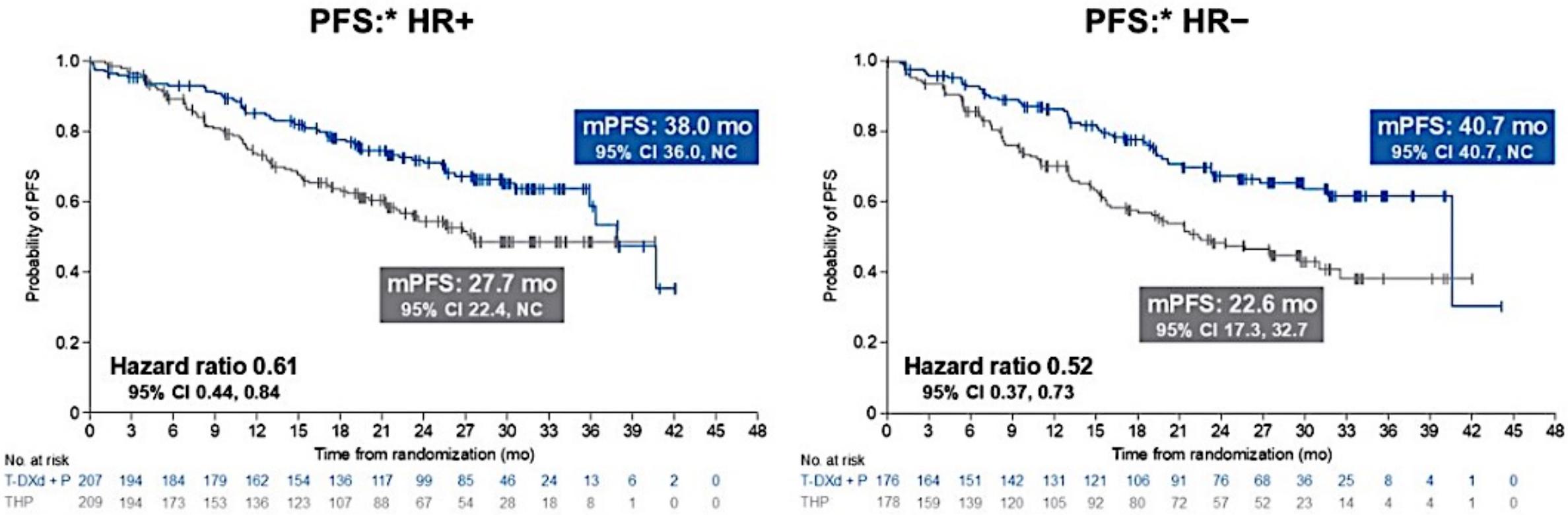
Tolaney S et al. ASCO 2025; Tolaney SM et al. N Engl J Med 2025.

DESTINY-Breast09: PFS by HR status

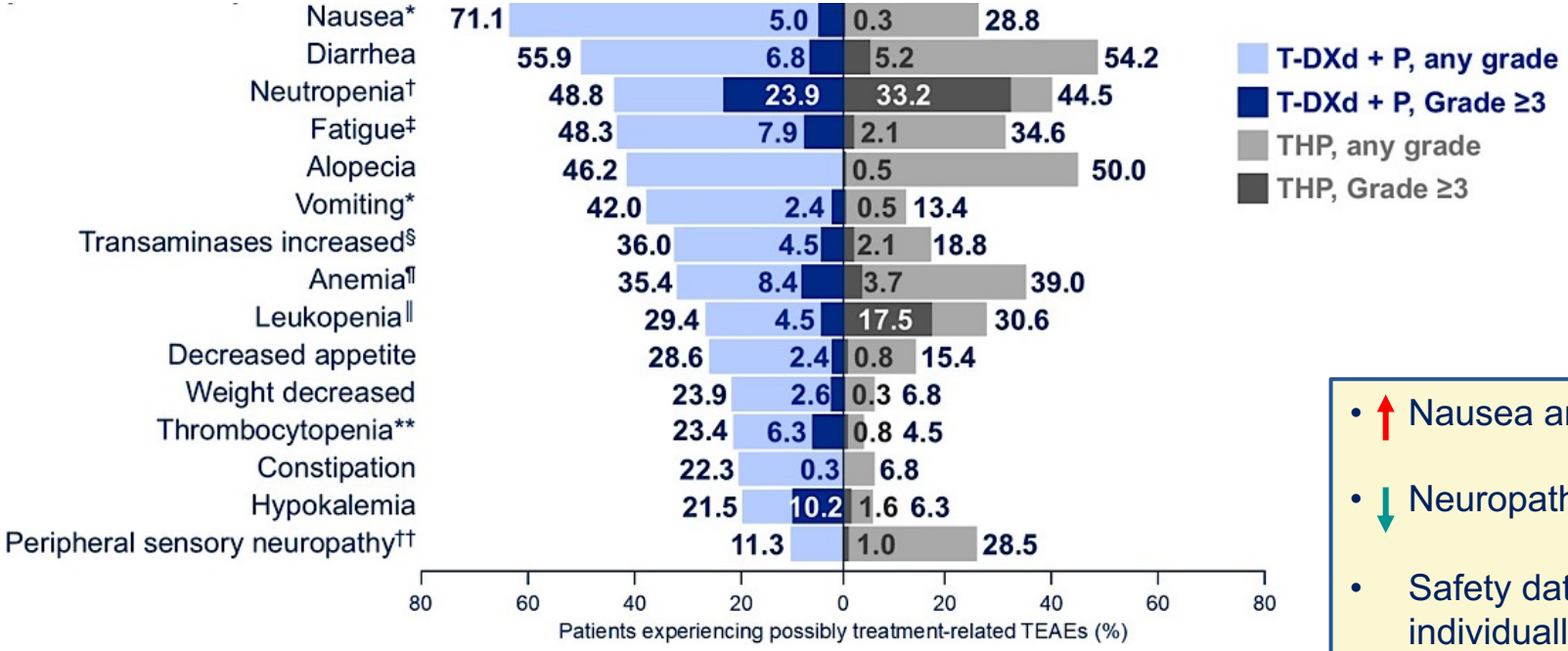


Patients with HR+ disease could receive concurrent ET after six cycles of T-DXd or discontinuation of taxane, which occurred in **13.5% (T-DXd + P)** versus 38.3% (THP) of patients

T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of HR status

DESTINY-Breast09: Safety

TEAEs in ≥20% of patients



- ↑ Nausea and ILD with T-DXd + P
- ↓ Neuropathy and G≥3 neutropenia with T-DXd + P
- Safety data consistent with known profiles of T-DXd and P individually

Adjudicated drug-related ILD/pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	17 (4.5)	27 (7.1)	0	0	2 (0.5)	46 (12.1)
THP (n=382)	2 (0.5)	2 (0.5)	0	0	0	4 (1.0)

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Tolaney S et al. ASCO 2025; Tolaney SM et al. N Engl J Med 2025.

Evolution of T-DXd in HER2+ MBC

Observed mPFS in months

*Comparisons are hypothesis-generating only as it is not possible to directly compare the studies due to differences in trial population and design; †capecitabine plus trastuzumab or lapatinib
1L, first line; 2L, second line; 3L, third line; a/mBC, advanced/metastatic breast cancer; CTx, chemotherapy; HER2+, human epidermal growth factor receptor 2–positive; mo, months; mPFS, median progression-free survival; P, pertuzumab; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; THP, taxane + trastuzumab + pertuzumab

1. Baselga J, et al. *N Engl J Med.* 2012;366:109–119; 2. Cottu P, et al. *Breast Cancer Res Treat.* 2024;209:419–430; 3. Hurvitz SA, et al. *Lancet.* 2023;401:105–117; 4. André F, et al. *Lancet.* 2023;401:1773–1785; 5. Modi S, et al. *N Engl J Med.* 2020;382:610–621

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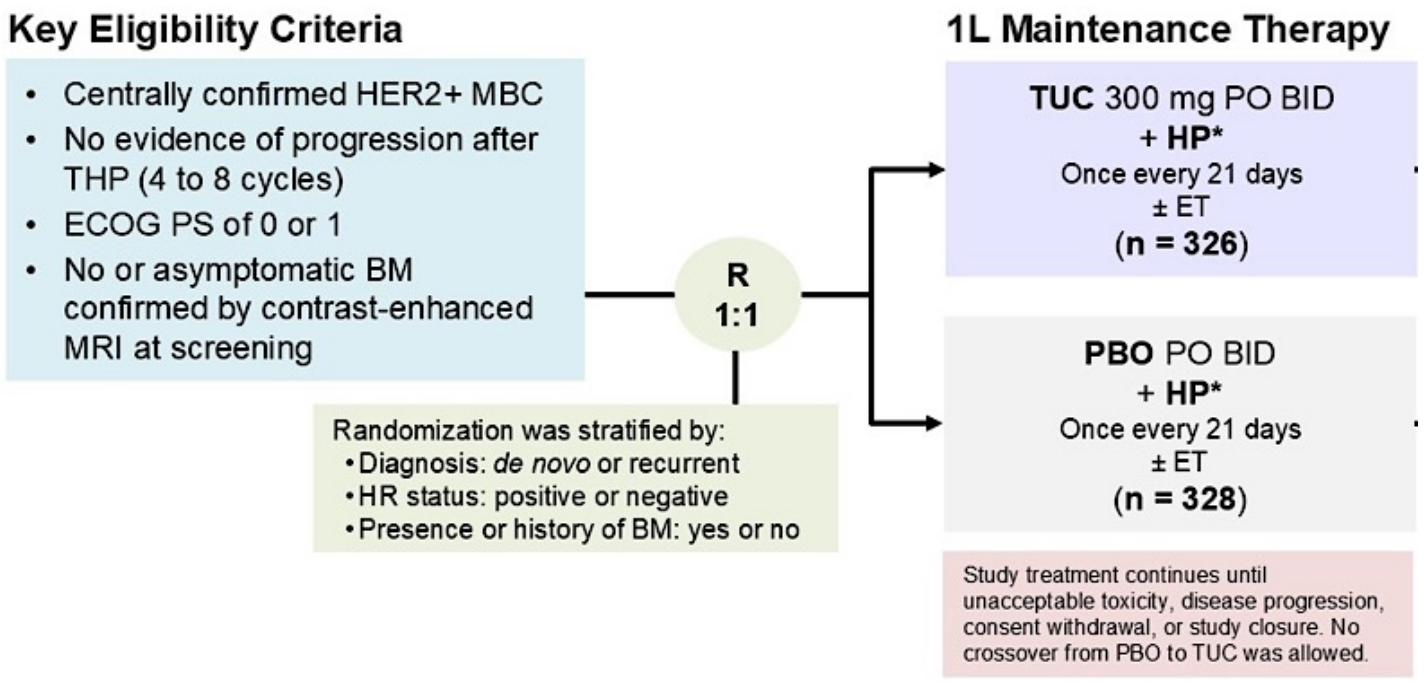
Slide credit: Tolaney S. ASCO 2025

HER2CLIMB-05: 1L maintenance therapy with tucatinib/placebo + HP for HER2+ MBC

Schema

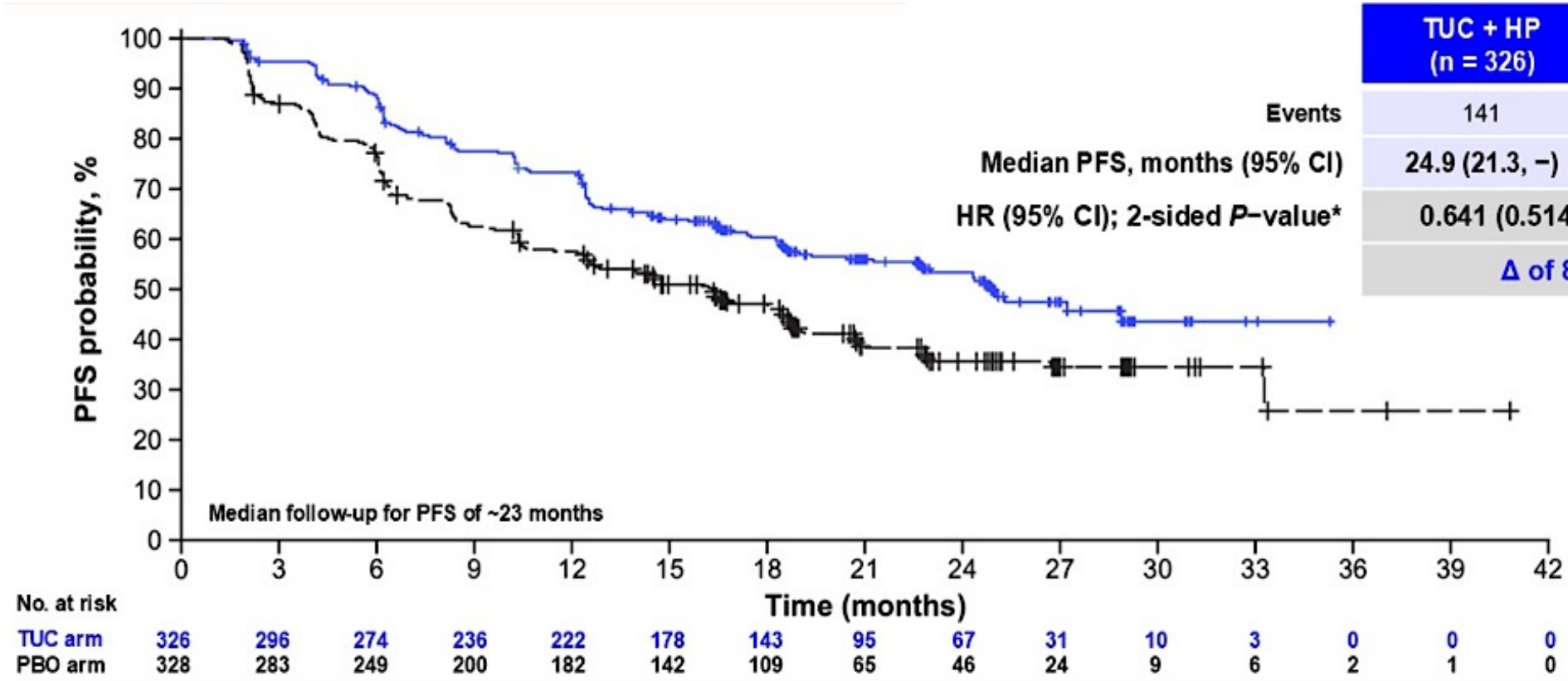


*HP: Herceptin/Perjeta

Patient Characteristics

Characteristics	TUC + HP (n = 326)	PBO + HP (n = 328)
HR status, n (%)		
Positive	168 (51.5)	176 (53.7)
Received ET	74 (44.0)	81 (46.0)
Negative	158 (48.5)	152 (46.3)
Presence or history of BM, n (%)	41 (12.6)	40 (12.2)
Visceral disease, n (%)	194 (59.5)	172 (52.4)
Disease status, n (%)		
De novo	227 (69.6)	226 (68.9)
Recurrent	99 (30.4)	102 (31.1)
Any prior (neo)adjuvant systemic therapy, n (%)	87 (26.7)	91 (27.7)
Prior trastuzumab*	60 (69.0)	67 (73.6)
Prior pertuzumab*	16 (18.4)	15 (16.5)
Induction HP cycles, median (range)	6 (4–10)	6 (4–11)
Induction T cycles, median (range)	6 (4–9)	6 (3–8)

HER2CLIMB-05: Primary EP- Investigator assessed PFS



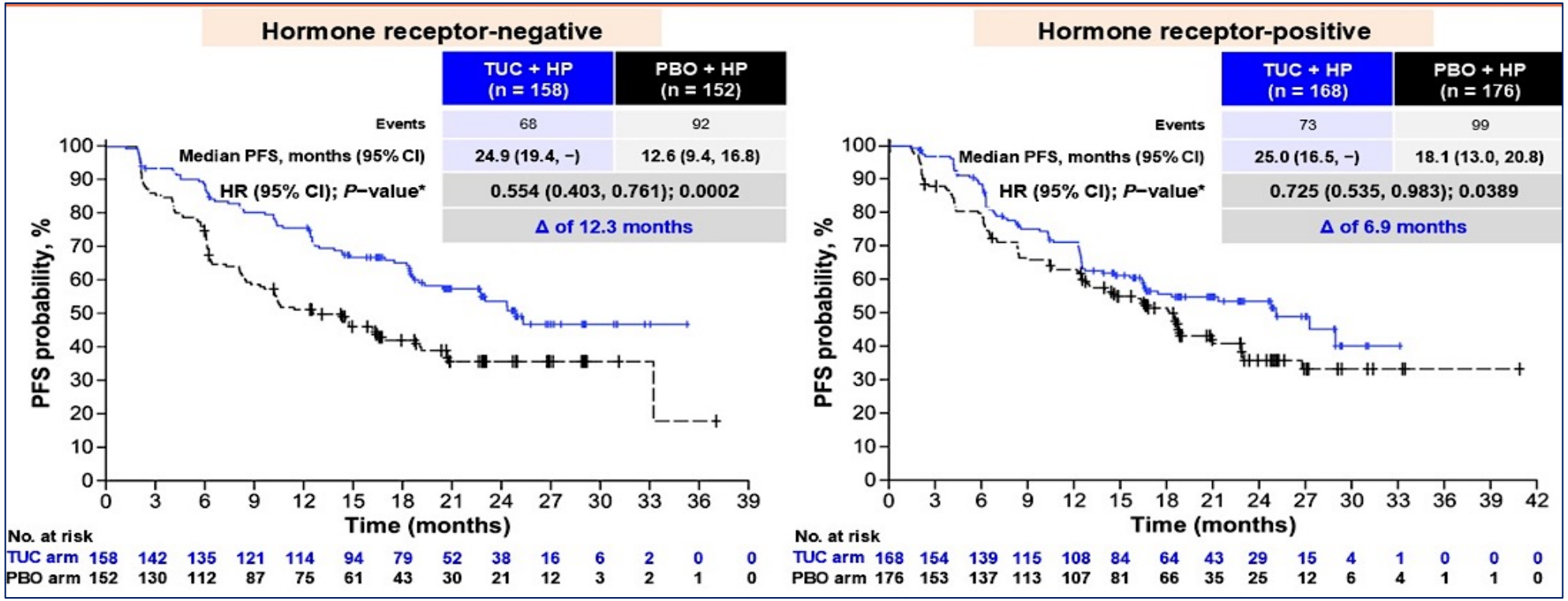
	TUC + HP (n = 326)	PBO + HP (n = 328)
Events	141	191
Median PFS, months (95% CI)	24.9 (21.3, –)	16.3 (12.6, 18.7)
HR (95% CI); 2-sided *P*–value*	0.641 (0.514, 0.799); < 0.0001	
	Δ of 8.6 months	

Addition of TUC to 1L maintenance therapy extended median PFS to over 2 years in patients with HER2+ MBC, an **8.6-month** improvement over HP, the standard-of-care.

Hamilton E et al. SABCS 2025; Dieras V et al. J Clin Oncol 2025.

HER2CLIMB-05: PFS by HR status

PFS by HR status



- PFS benefit was demonstrated regardless of HR status
- In patients with CNS mets at baseline, PFS doubled from 4.3 months → 8.5 months, HR .719 (0.406, 1.272)
- OS data are immature

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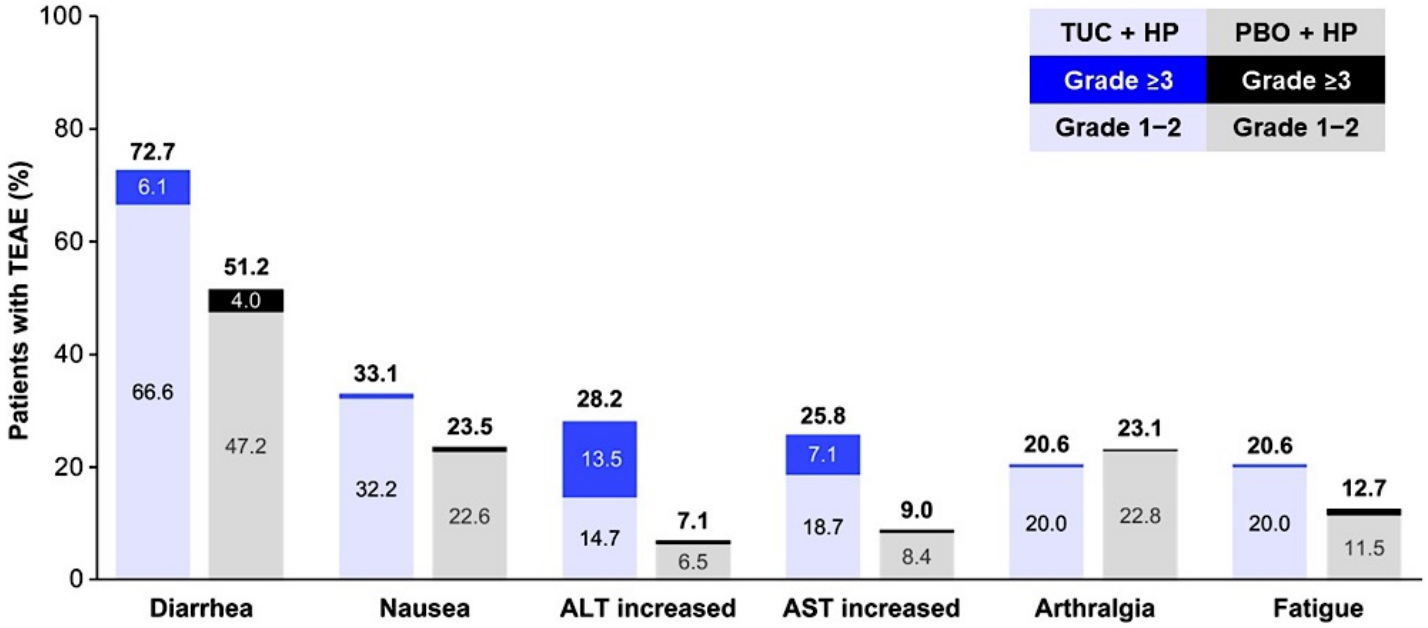
Hamilton E et al. SABCS 2025; Dieras V et al. J Clin Oncol 2025.

HER2CLIMB-05: Safety summary & TEAEs

n (%)	TUC + HP (n = 326)*	PBO + HP (n = 324)*
Duration of TUC/PBO treatment, months, median (range)	17.1 (0.4–36.5)	15.5 (0.5–41.3)
Patients with TEAE – Any	323 (99.1)	313 (96.6)
Grade ≥3	138 (42.3)	79 (24.4)
Serious TEAE	55 (16.9)	26 (8.0)
Leading to death	1 (0.3)	1 (0.3)
Discontinued from study treatment due to TEAE† – Any	45 (13.8)	15 (4.6)
TUC/PBO	44 (13.5)	7 (2.2)
H or P individually	2 (0.6)	5 (1.5)
H + P fixed dose combination	9 (2.8)	4 (1.2)
Most common TEAEs leading to TUC/PBO discontinuation		
Hepatic events††	25 (7.7)	0
Diarrhea	5 (1.5)	3 (0.9)
Dose modification due to TEAE – Any	182 (55.8)	112 (34.6)
TUC/PBO dose hold	161 (49.4)	82 (25.3)
TUC/PBO dose reduction	95 (29.1)	36 (11.1)

TEAE: treatment emergent adverse events

TEAEs in ≥20% of patients



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Hamilton E et al. SABCS 2025; Dieras V et al. J Clin Oncol 2025.

NALA: Neratinib + capecitabine for pretreated HER2+ MBC

Neratinib is an irreversible HER2 targeting tyrosine kinase inhibitor

Inclusion criteria

- Metastatic breast cancer (MBC)
- Centrally confirmed HER2+ disease
- ≥2 lines of HER2-directed therapy for MBC
- Asymptomatic and stable brain metastases permitted

R (1:1)

n=621

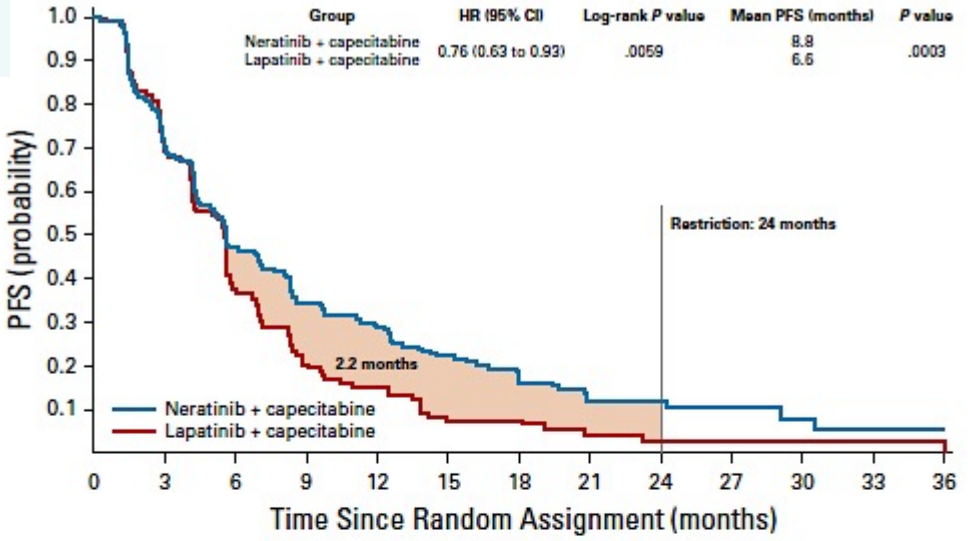
Neratinib 240 mg/d + Capecitabine 1500 mg/m² 14/21 d Loperamide (cycle 1)[a]

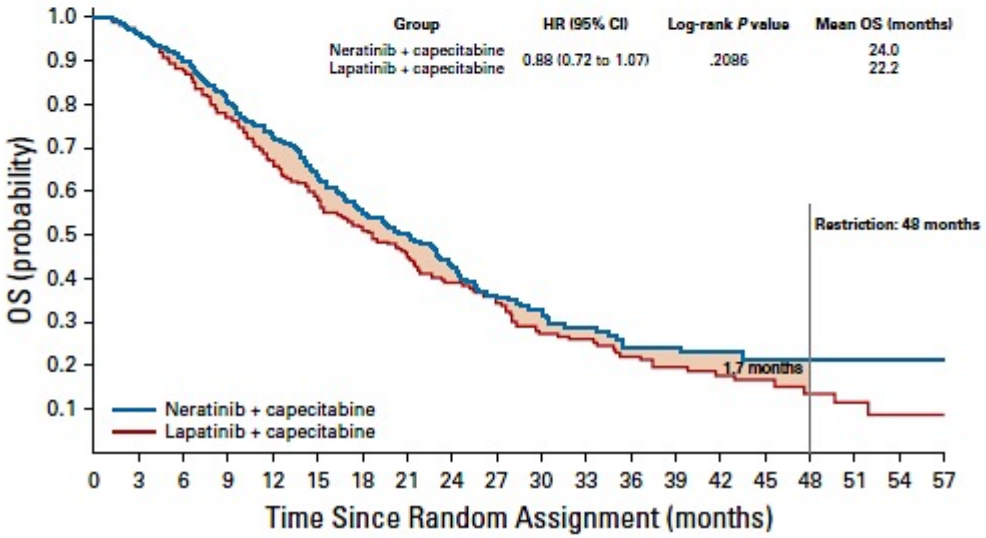
No endocrine therapy permitted

Lapatinib 1250 mg/d + Capecitabine 2000 mg/m² 14/21 d

- Significant improvement in mPFS with neratinib+cape vs lapatinib+cape
- Numerical improvement in OS with neratinib+cape

Co primary EPs: Centrally confirmed PFS & OS





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Saura C et al. JCO 2020

SOPHIA: Ph 3 trial of Margetuximab + chemotherapy for pretreated HER2+ MBC

Margetuximab is a Fc-engineered, HER2-targeted monoclonal antibody

HER2+ advanced breast cancer
- ≥2 prior anti-HER2 therapies, including pertuzumab
- 1-3 prior treatment lines in metastatic setting
- Prior brain metastasis ok if treated and stable

→ **Investigator's choice of chemotherapy** (capecitabine, eribulin, gemcitabine, or vinorelbine)

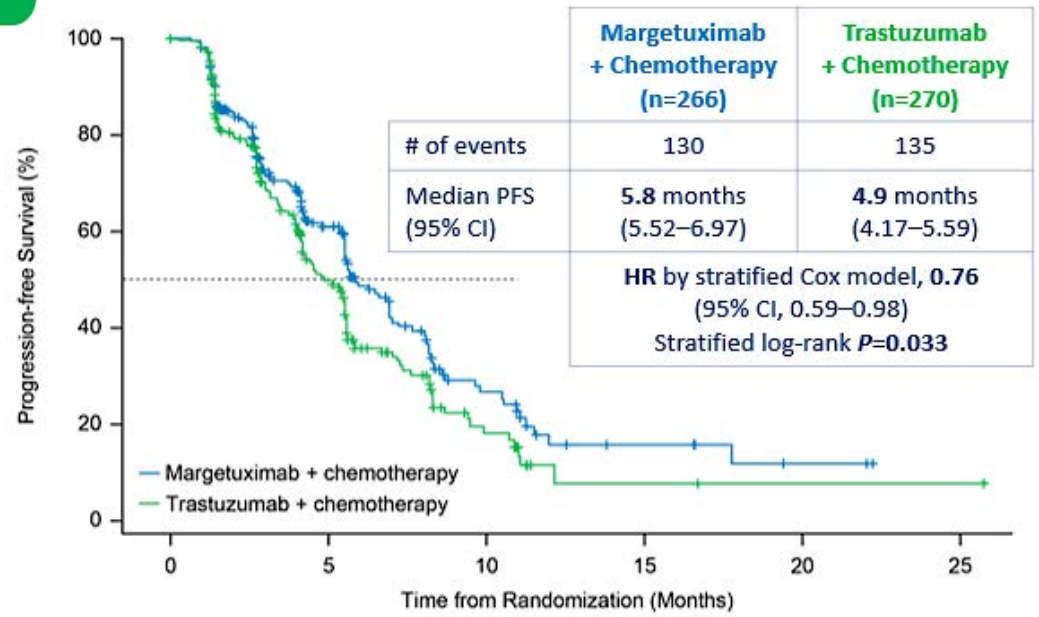
→ ***1:1 Randomization (N=536)***

→ **Arm 1**
Margetuximab (15 mg/kg Q3W) **+ chemotherapy**
in 3-week cycles

→ **Arm 2**
Trastuzumab (8 mg/kg loading → 6 mg/kg Q3W) **+ chemotherapy**
in 3-week cycles

Primary EP: PFS by CIBR

24% Risk Reduction of Disease Progression
Central Blinded Analysis (Primary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	130	135
Median PFS (95% CI)	**5.8** months (5.52–6.97)	**4.9** months (4.17–5.59)

HR by stratified Cox model, **0.76** (95% CI, 0.59–0.98)
Stratified log-rank ***P*=0.033**

Rugo HS et al. ASCO 2019

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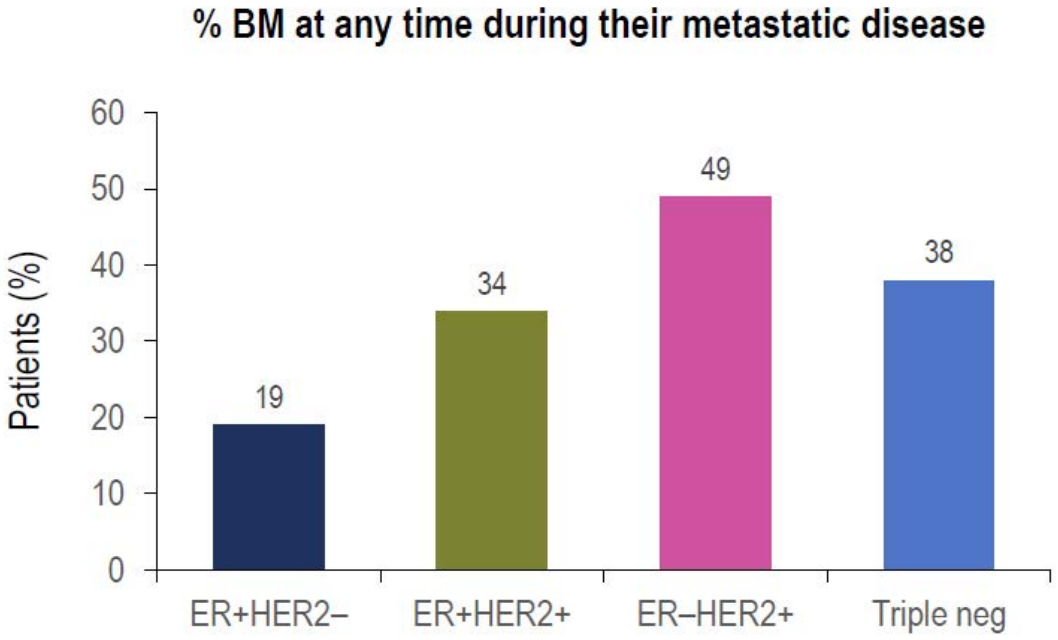
Breast cancer and Brain Metastases

- Breast cancer has 2nd highest incidence of brain metastasis among all cancers
- The brain is frequently the 1st site of relapse in HER2+ BC treated with trastuzumab, whether administered in the adjuvant or metastatic setting



NCI SEER registry
BCBM cohort (n=1268)

5-year percent survival analysis

	BCBM	All BC
HR+/HER2-	9.8 (6.9-13.3)	86.3 (86.2-86.5)
HR+/HER2+	21.9 (16.0-28.4)	85.6 (85.1-86.0)
HR-/HER2+	14.3 (8.5-21.5)	79.7 (79.0-80.4)
HR-/HER2-	**3.6 (1.6-6.9)**	**71.9 (71.4-72.4)**
All subtypes	11.3 (9.2-13.6)	84.3 (84.1-84.4)

BCBM= breast cancer brain mets

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Darlix A, *et al*. Br J Cancer 2019;121:991-1000;
Pasquier D, *et al*. Eur J Cancer 2020;125:22e30
Devanaboyina M. et al. ASCO 2021 Abstract 1031

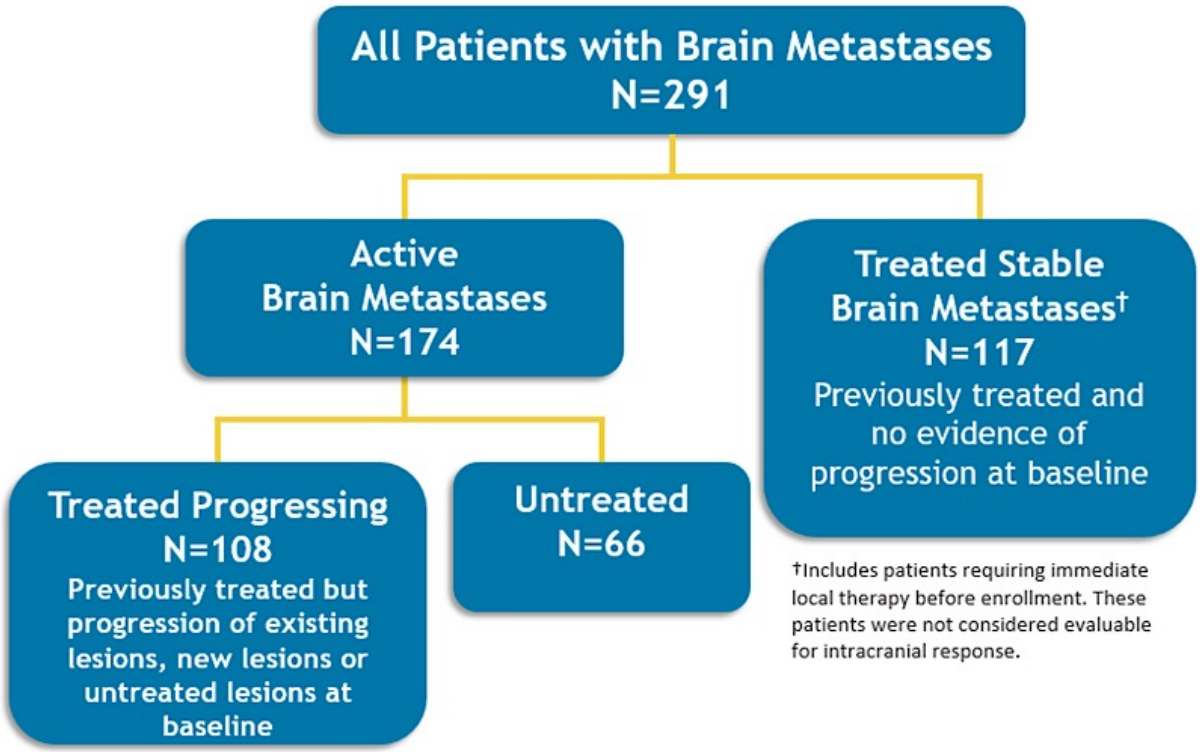
HER2CLIMB: 1st phase III trial to enroll patients with active brain mets

CNS penetrant TKIs (lapatinib, neratinib) had previously demonstrated activity in HER2+ MBC with brain mets
Tucatinib is HER2-specific TKI with the ability to cross the BBB

HER2CLIMB: Tucatinib/placebo with trastuzumab+cape for pretreated HER2+ MBC

CNS mets subset

- Brain MRI at baseline for all patients
- Brain MRI for brain metastases patients every 6 weeks in first 24 weeks, every 9 weeks thereafter
- Eligible brain metastases patients:
  - Not requiring immediate local therapy
  - Requiring local therapy during screening could be eligible after washout*

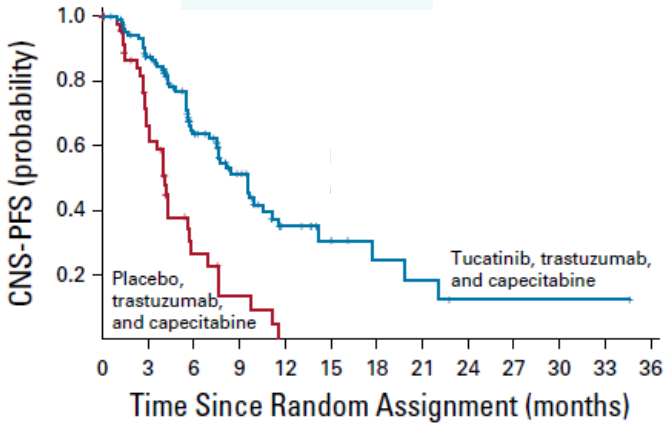


*These patients were included in the Treated Stable group for analysis.

HER2CLIMB: CNS data in patients with brain mets

A

CNS-PFS



No. at risk:

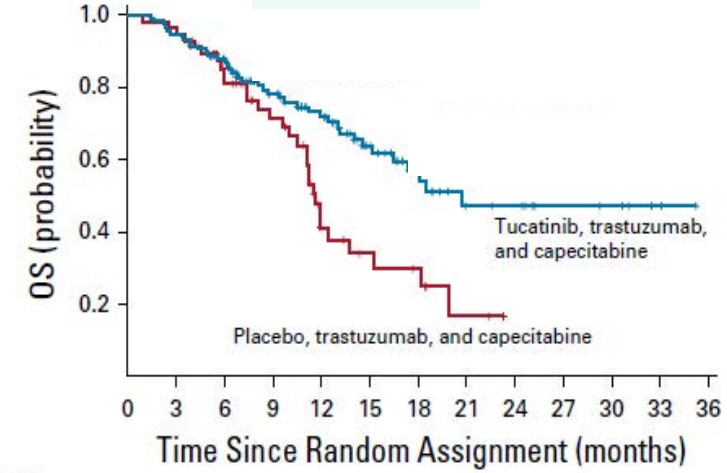
Tucatinib, trastuzumab, and capecitabine	118	89	49	29	12	7	4	3	1	1	1	1	0
Placebo, trastuzumab, and capecitabine	56	26	7	3	0	0	0	0	0	0	0	0	0

	Median PFS (months)
Tucatinib arm	9.5
Placebo arm	4.1
	HR 0.36 p <0.00001

Risk of progression or death in patients with active brain mets was reduced by 64%

B

CNS-OS



No. at risk:

Tucatinib, trastuzumab, and capecitabine	118	111	89	66	51	33	19	11	10	6	5	2	0
Placebo, trastuzumab, and capecitabine	56	54	39	29	12	8	6	2	0	0	0	0	0

	Median OS (months)
Tucatinib arm	20.7
Placebo arm	11.6
	HR 0.49 p 0.004

Risk of death in patients with active brain mets was reduced by 51%

In a separate analysis*, it was shown that the risk of developing new brain lesions or death was reduced by 48% in pts treated with tucatinib

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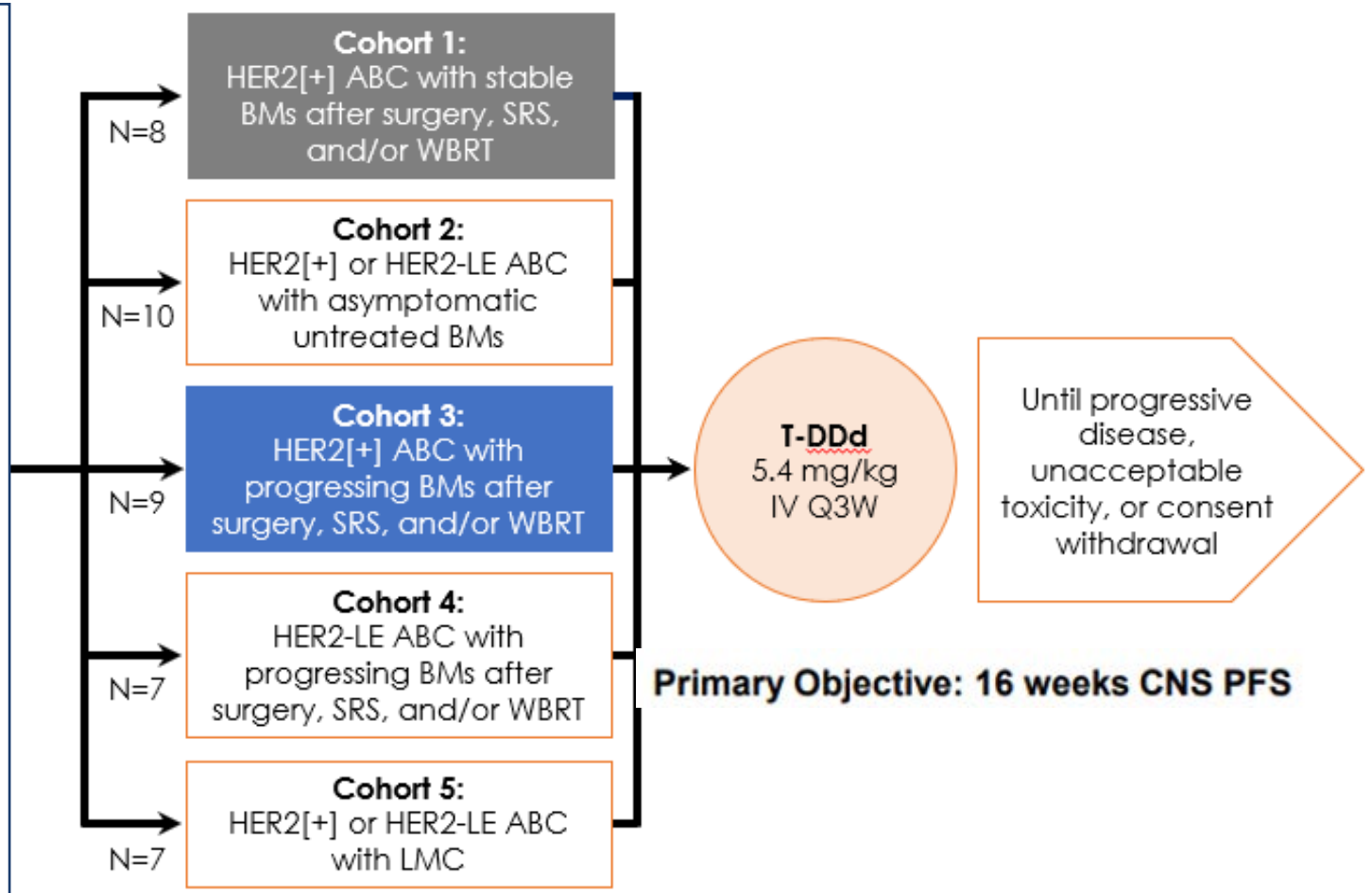
Lin NU et al. JCO 2020

*Bachelot T et al ESMO 2020

DEBBRAH: Ph 2 trial of T-DXd in pts with HER2+/ HER2-low MBC & history of brain mets

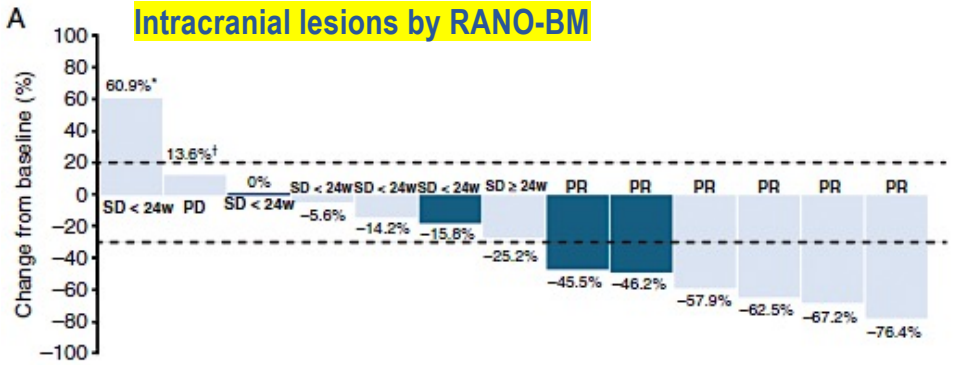
Cohorts 1 and 3 enrolled patients with **HER2+ MBC** and stable or progressing brain mets respectively

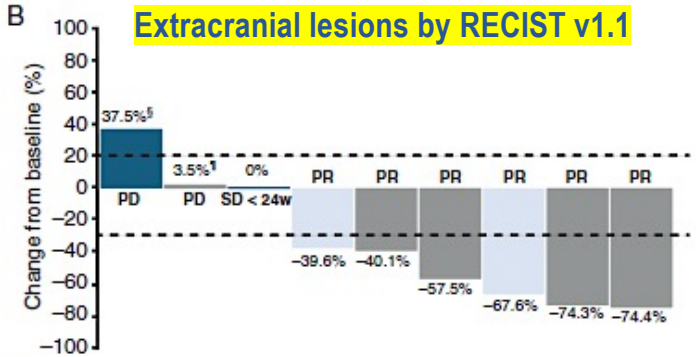
- HER2+ /HER2-low MBC with stable or active brain mets and/or leptomeningeal disease
- Pts with HER2+ MBC
  - Prior tx with a taxane and ≥1 prior line for MBC
- Pts with HER2-low MBC
  - ≥1 prior line of chemo for MBC
- Cohorts 2, 3, 4: Measurable brain lesions
- Cohort 5: LMC with CSF+ cytology

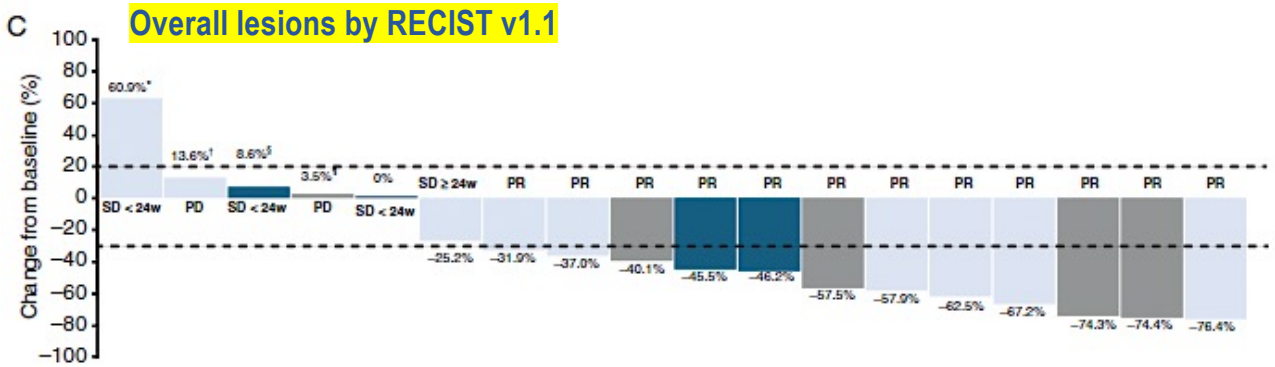


Vaz Batista M et al. SABCS 2021

DEBBRAH: Efficacy in patients with brain mets







		ORR	DCR
Cohort 1	HER2+ MBC stable BM	80%	80%
Cohort 2	HER2+/HER2-low untx BM	50%	100%
Cohort 3	HER2+ BM - PD after local tx	66.7%	89.9%

Progression free survival at 6 mo: 78.7%

Progression free survival at 9 mo: 61.4%

Encouraging intracranial & extracranial activity with T-DXd in pretreated HER2+ MBC with stable/active brain mets

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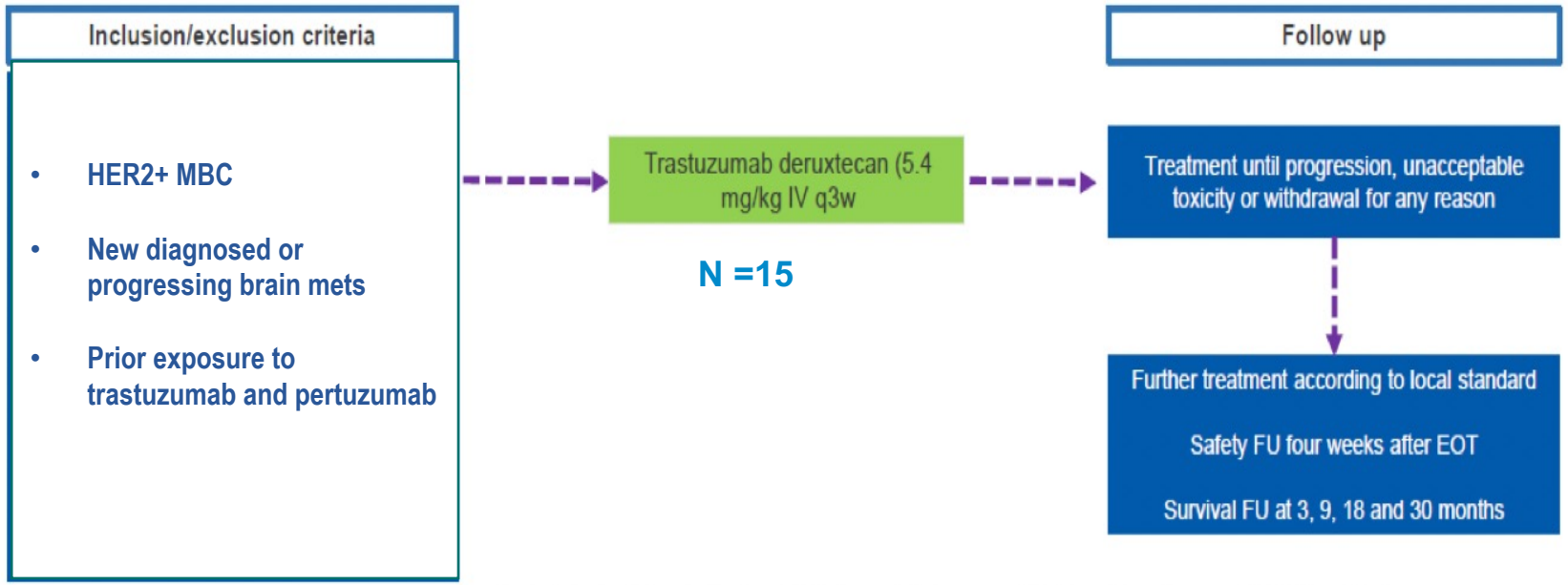
Perez-Garcia JM et al. Neuro-oncology 2023

TUXEDO-1: Prospective trial of T-DXd in pts with HER2+ MBC & active brain mets

Study schema



BM, brain metastasis; BW, body weight; CNS, central nervous system; D1, day 1; EOT, end of treatment; FU, follow up; IV, intravenous; KPS, Karnofsky performance; LVEF, left ventricular ejection fraction; q3w, once every 3 weeks; RANO, response assessment in neuro-oncology; T-DXd, trastuzumab deruxtecan.
EudraCT: 2020-000981-41.

Primary Endpoint: ORR (CNS) by RANO-BM criteria

Secondary Endpoints:

- Clinical Benefit Rate (CR+PR+SD ≥6 months)
- Extracranial Response rate
- PFS
- OS
- Safety
- Quality of Life

Patient population (n=15)

Visceral mets	80%
Progressive brain mets*	60%
Untreated brain mets	40%
Prior T-DM1	60%
Prior lapatinib	26.7%

* After local therapy

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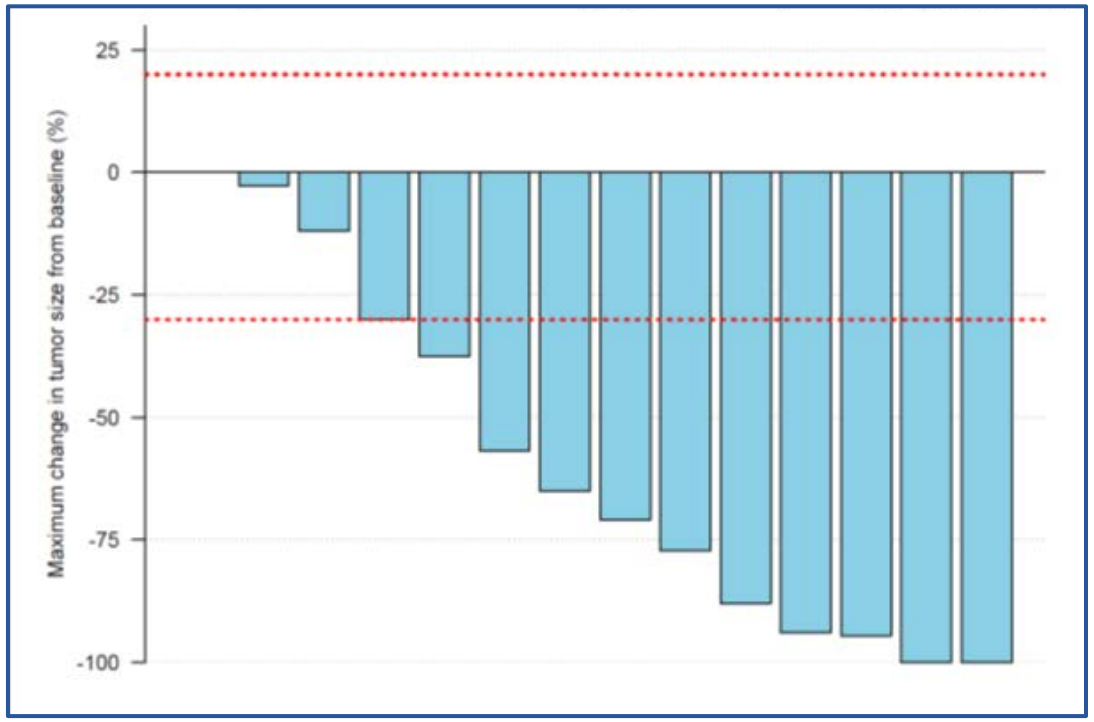
TUXEDO: Efficacy endpoints

ORR by RANO-BM criteria (Primary EP)



ORR (ITT population; *n*=15): 73.3% (95% CI 48.1-89.1)

Secondary Endpoints

Median follow-up: 11 months (range 3 – 17 months)

1. **PFS: 14 months (95% CI 11.0-n.r.)**

2. **CBR*: 86.7% (13/15) in ITT**
   CBR: 92.9% (13/14) in PP**

3. **Extracranial response rate:**
   Pts. with extracranial metastases at BL (*n*=13):
   PR 5/13 (27.8%)
   Pts with measurable extracranial disease at BL (*n*=8):
   PR 5/8 (62.5%)

4. **Median OS: Not reached**

- Study met primary EP
- No new safety signals reported (EF decrease G3 in 1 pt; ILD G2 in 1 pt)
- QoL maintained during treatment duration

* CR+PR+SD ≥6 months
** Per protocol population

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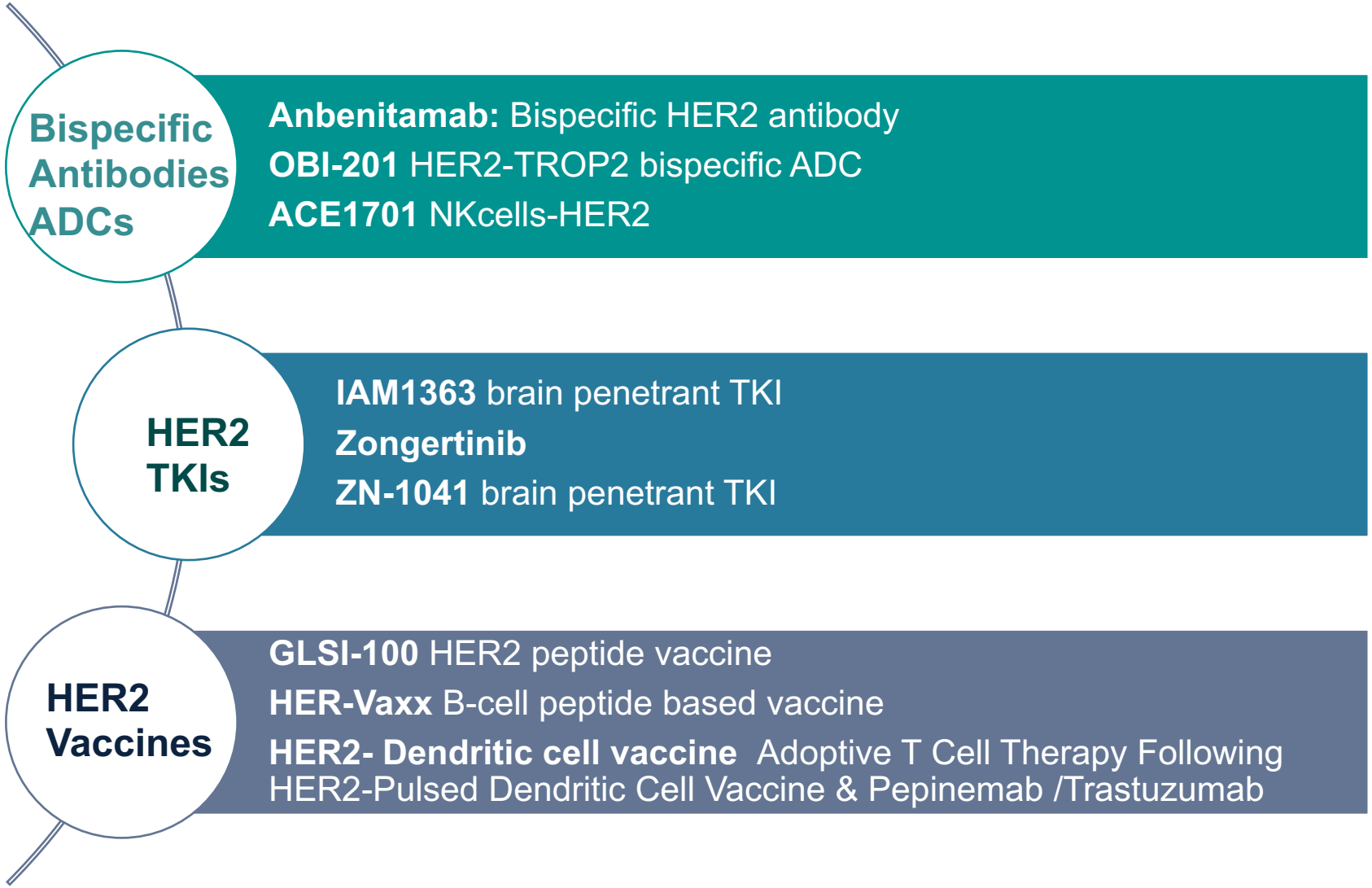
Bartsch R et al. ESMO Breast 2022

Select novel agents under consideration for HER2+ MBC



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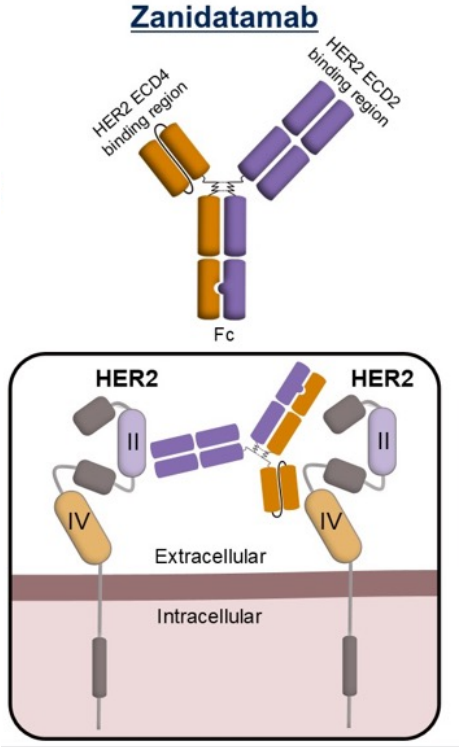
Zanidatamab - novel biparatropic antibody targeting HER2



Part 3 of a phase 1 trial
(NCT02892123)

Select eligibility criteria
- Unresectable, locally advanced or metastatic HER2-expressing[a] breast cancer
- ECOG PS ≤1
- Stable brain metastases allowed

Parallel single-arm cohorts (no randomisation)

HER2-positive mBC (IHC 3+ or IHC 2+/FISH+)
- Prior trastuzumab, pertuzumab, T-DM1
- 1-3 prior chemotherapy regimens

→ Zanidatamab + vinorelbine[b]
→ Zanidatamab + capecitabine[c]
→ Zanidatamab + paclitaxel[d]
→ Zanidatamab + capecitabine and tucatinib[e]

HER2-low mBC (IHC 1+ or IHC 2+/FISH-)
- 1-3 prior chemotherapy regimens

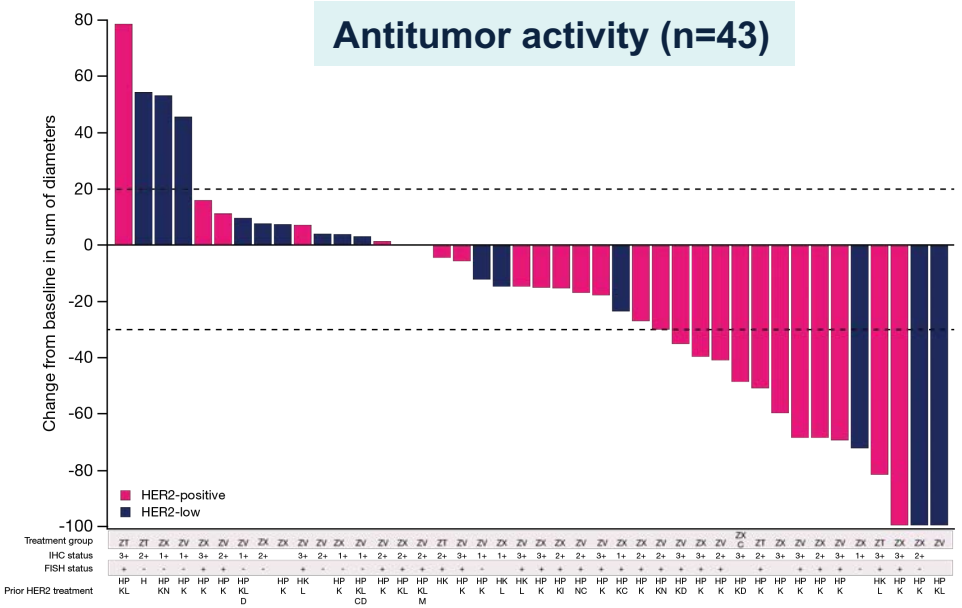
→ Zanidatamab + vinorelbine[b]
→ Zanidatamab + capecitabine[c]
→ Zanidatamab + paclitaxel[d]

Efficacy- HER2+ MBC
cORR: 43%
mDoR: > 1 year
PFS: 10.4 months

Safety (all pts):
G3/4 TEAE in 46%, no G5 events
G3 neutrophil count dec: 24%
G3 neutropenia: 9%
G3 diarrhea: 7%

- Zanidatamab is a dual HER2-targeted bispecific antibody that drives multiple antitumor MOAs, including[1]:
  - Facilitation of HER2 internalization and subsequent degradation
  - Reduction of HER2 on the cell surface
  - Inhibition of HER2 signaling pathways
  - Activation of immune-mediated effects (CDC, ADCC, and phagocytosis)

Antitumor activity (n=43)



- **EmpowHER-303 - Ongoing phase 3 trial of Zanidatamab/ trastuzumab + chemotherapy in T-DXd pretreated HER2+ MBC (NCT06435429)**

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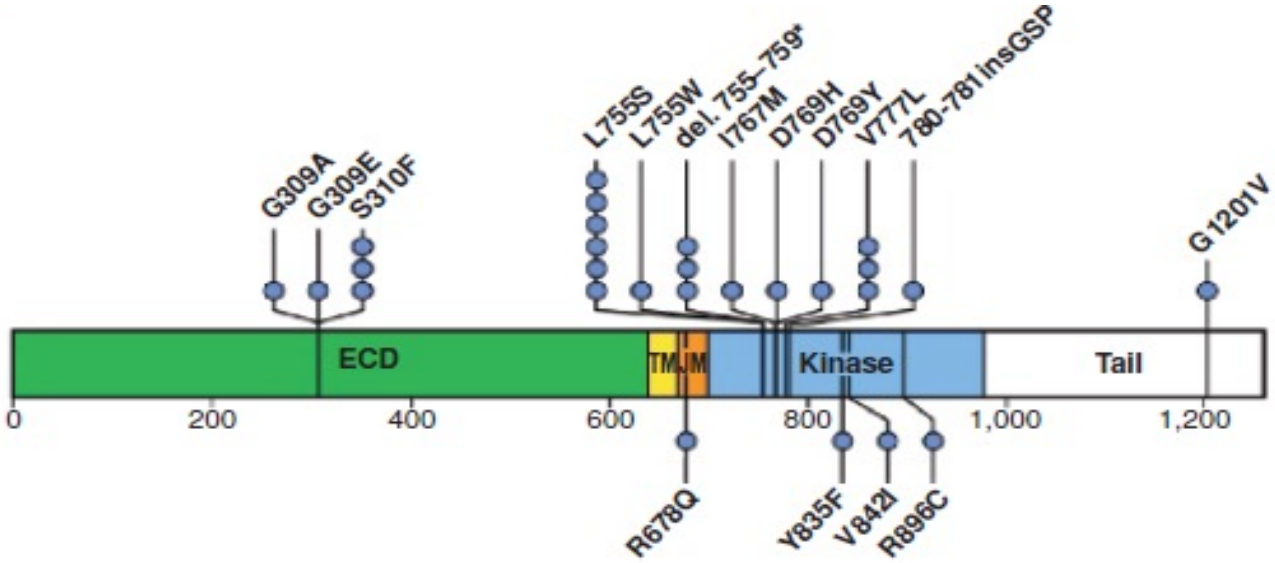
Hamilton E et al. ESMO BC 2025

Common HER2 somatic mutations in BC

HER2 overexpression/amplification: 15-20% of breast cancers

HER2 mutations : ~3-4% of HER2 non-amplified cancers



70% of mutations confined to kinase domain (mostly in exons 19 and 20)

20% of mutations found in the extracellular domain (ECD) (exon 8)

Kinase domain mutations are resistant to trastuzumab

- Increase kinase activity and activate downstream signaling pathways

- ~36 unique HER2-activating mutations have been identified and counting…
  - Some of these mutations are insensitive to 1st and 2nd generation TKIs, but can be targeted with the newer HER2-targeting agents

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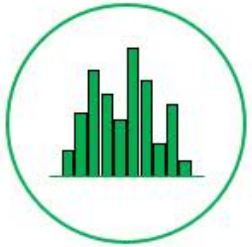
Connell. ESMO Open. 2017;2:e000279
Bose R et al. 2013
Cocco E et al. 2020

Characteristics of HER2-mutant breast cancer

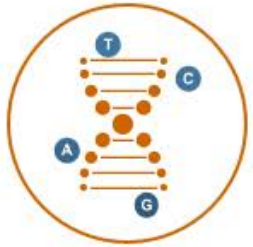


Incidence

- 2% Primary breast cancers
- 2–4% MBC
- 8% ER+ MBC with prior endocrine therapy
- Up to 15% in metastatic ILC

Histology

- Predominantly in hormone receptor-positive (luminal-A) and *HER2*-negative tumors
- Represented in all histology subtypes but enriched in lobular carcinoma



Genomics

- Occur across multiple domains of the protein (KD, ECD, TMD)
- Most common variants:
  - SNVs in KD
  - *Exon 20* insertions
  - S310F/Y in ECD
- Common co-mutations include *TP53*, *PIK3CA*, *ERBB3* and *CDH1*

Abbreviations: MBC, metastatic breast cancer; ILC, invasive lobular carcinoma; HER2mut, HER2 mutation; SNV, single nucleotide variant; KD, kinase domain; ECD, extracellular domain; TMD, transmembrane domain

1. Bose et al. Cancer Discovery 2013; 2. Razavi et al. Cancer Cell 2018; 3. Navar et al. Nat Genet 2019;51; 4. Croessmann et al. Clin Cancer Res 2019
5. Hyman et al. Nature 2018; 6. Smyth et al. Cancer Discov 2020; 7. Ma et al. Clin Cancer Res 2017; 8. Jhaveri et al. SABCS 2020

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Slide from Jhaveri K et al. SABCS 2021

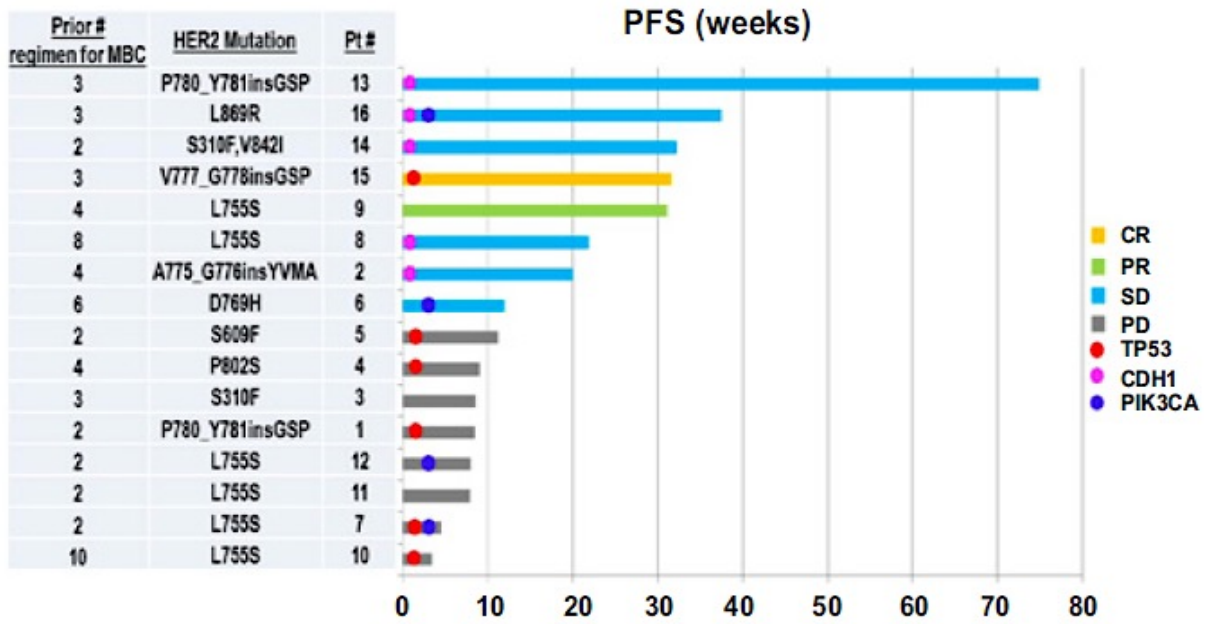
Activity of neratinib in HER2-mutant BC

MutHER - Single arm trial of neratinib in HER2 mutant (HER2 non-amplified) MBC

- Incidence of HER2 mutations – 2.4% (9/381 central testing); additional 13 pts (local testing)
- 21/22 cases were HR+
- 16 pts (median of 3 priors)
  - Responses: 1 CR, 1 PR
  - CBR: 31%
  - Median DoR: 24 weeks

Time to progression in pts with HER2 activating mutations

Prior # regimen for MBC	HER2 Mutation	Pt #
3	P780_Y781insGSP	13
3	L869R	16
2	S310F,V842I	14
3	V777_G778insGSP	15
4	L755S	9
8	L755S	8
4	A775_G776insYVMA	2
6	D769H	6
2	S609F	5
4	P802S	4
3	S310F	3
2	P780_Y781insGSP	1
2	L755S	12
2	L755S	11
2	L755S	7
10	L755S	10



- First report of neratinib activity in HER2-mutated, and HER2 non-amplified MBC

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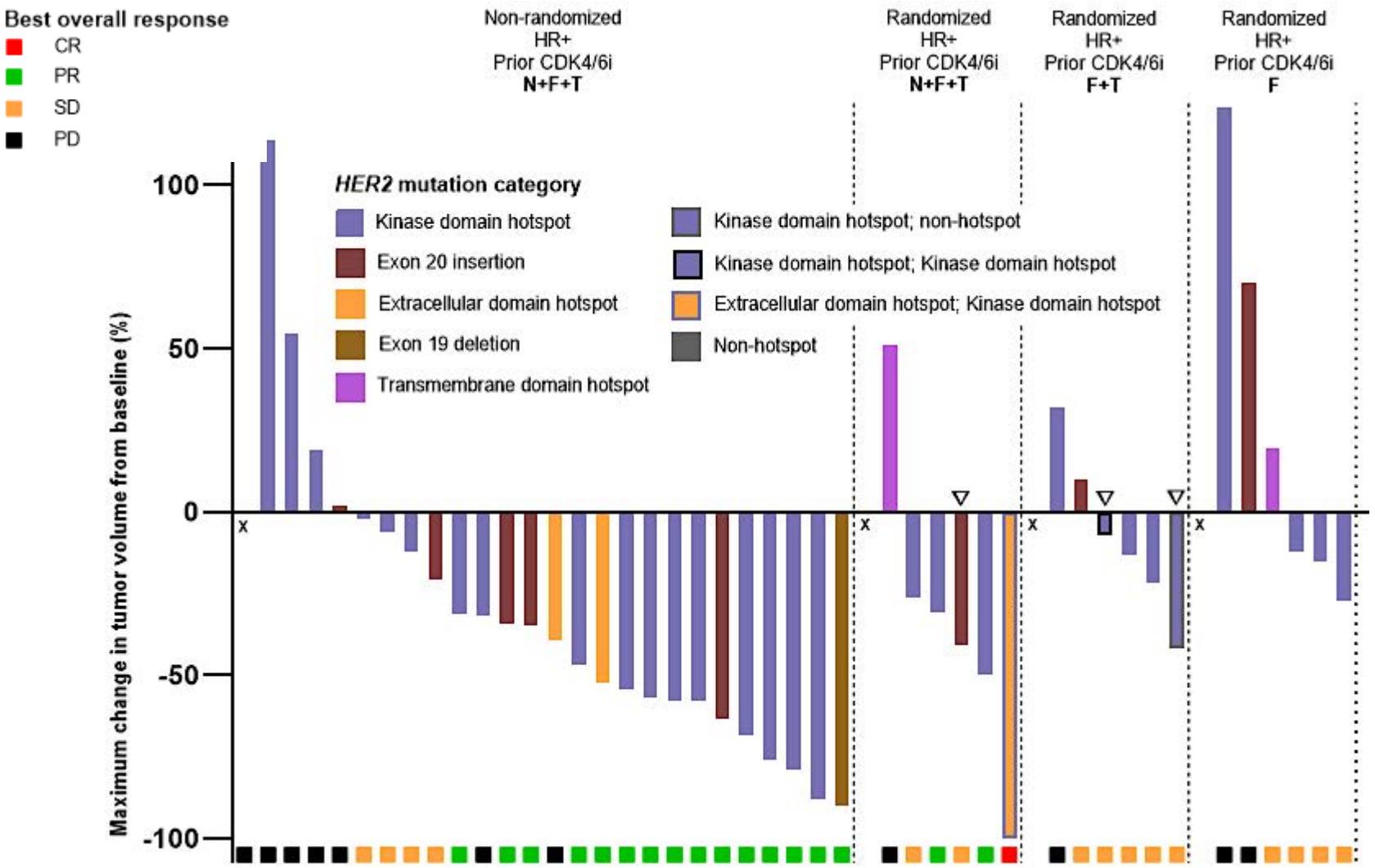
Ma C et al. Clin Cancer Res. 2017

SUMMIT: Change in tumor size (target lesions) in HR+ cohorts



N+F+T combination:

- ORR 42.4% (1 CR + 13 PRs)
- mPFS: 7.0 Months

- Study continues to enroll to the N+F+T arm

- N+F and F only arms closed on IDMC guidance

N= Neratinib
F= Fulvestrant
T= Trastuzumab

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Slide from Jhaveri K et al. SABCS 2021

Tucatinib + trastuzumab in HER2 mutant breast cancer

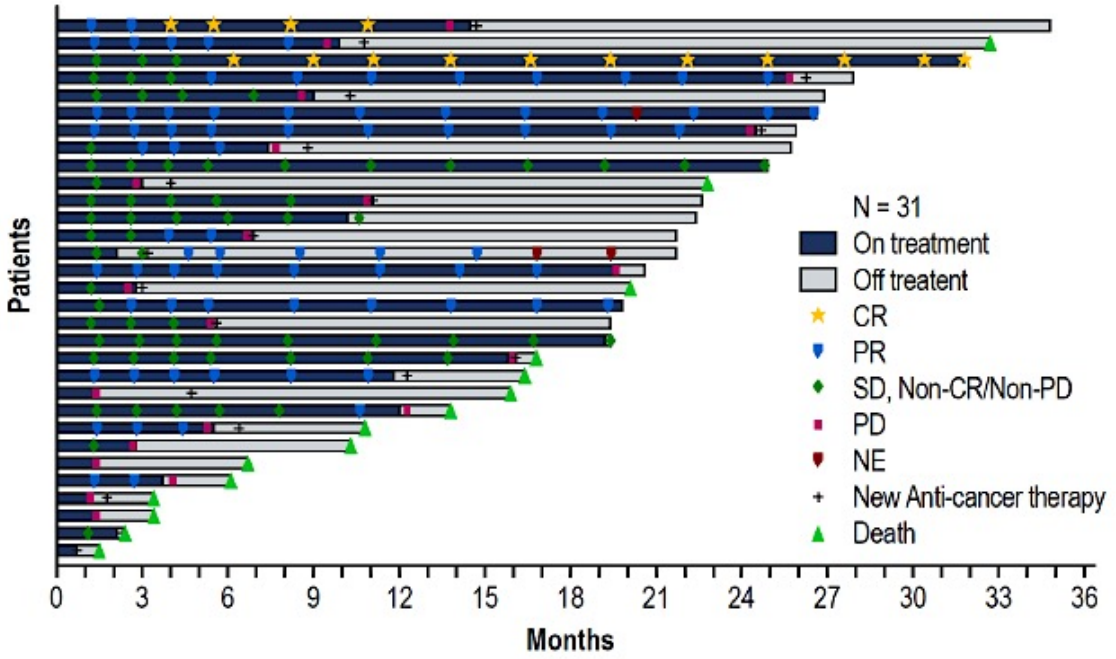
Final analysis of the **HER2 mutant MBC** cohort from a phase 2 basket trial of **tucatinib + trastuzumab** in HER2 altered solid tumors

- Key baseline characteristics (N=31)
  - 87% HR+ (all received fulvestrant)
  - 58% lobular histology
  - Median number of prior lines of treatment in the advanced/metastatic setting: 3

	Final analysis (n=31)
cORR[a], % (90% CI)	**41.9** (26.9–58.2)
Median DOR, mo (90% CI)	**18.2** (4.7–23.1)
DCR, % (90% CI)	**80.6** (65.3–91.2)
Median TTR, mo (range)	**1.4** (1.2–6.2)

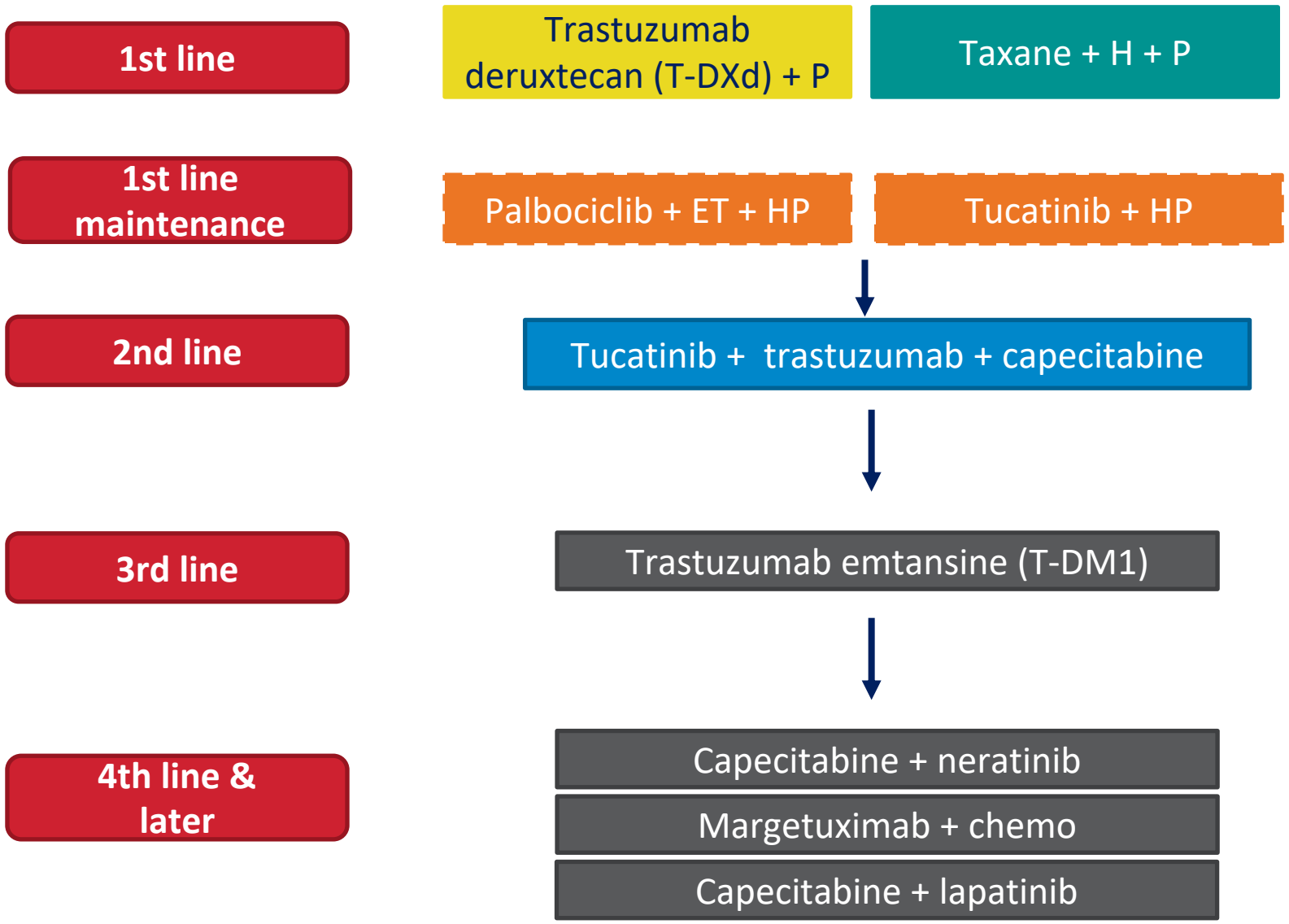
- Median follow-up: 24.9 months

Duration of treatment swimmer plot



- **Median PFS: 10.9 months; median OS: 32.7 months**
- **Study treatment was well tolerated, with a low rate of tucatinib discontinuation (6%) and no deaths due to TEAEs**

Current treatment algorithm for HER2+ MBC



Choice of treatment depends on

- **HR status**
- **Brain metastases**
- **PIK3CA mutations**
- **Patient comorbidities**

Clinical trials continue to remain an option!

HP: trastuzumab+ pertuzumab

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HER2 mutant MBC

- HER2-mutant MBC is clinically actionable and biologically distinct from HER2 amplification
- Neratinib-based regimens are active in HR+/HER2+ MBC and mTNBC*
- Tucatinib + trastuzumab shows the most compelling efficacy
- Enrollment in clinical trials evaluating novel therapies remains a good option for these patients

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*Jhaveri K et al. ASCO 2024

QUESTIONS?

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