Implications of Recent Data Sets for the Current and Future Management of Breast Cancer

Part 2 of a 3-Part Post-ESMO Congress 2023 CME/MOC-Accredited Live Webinar Series

Thursday, November 9, 2023
5:00 PM – 6:00 PM ET

Faculty

Aditya Bardia, MD, MPH
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Faculty

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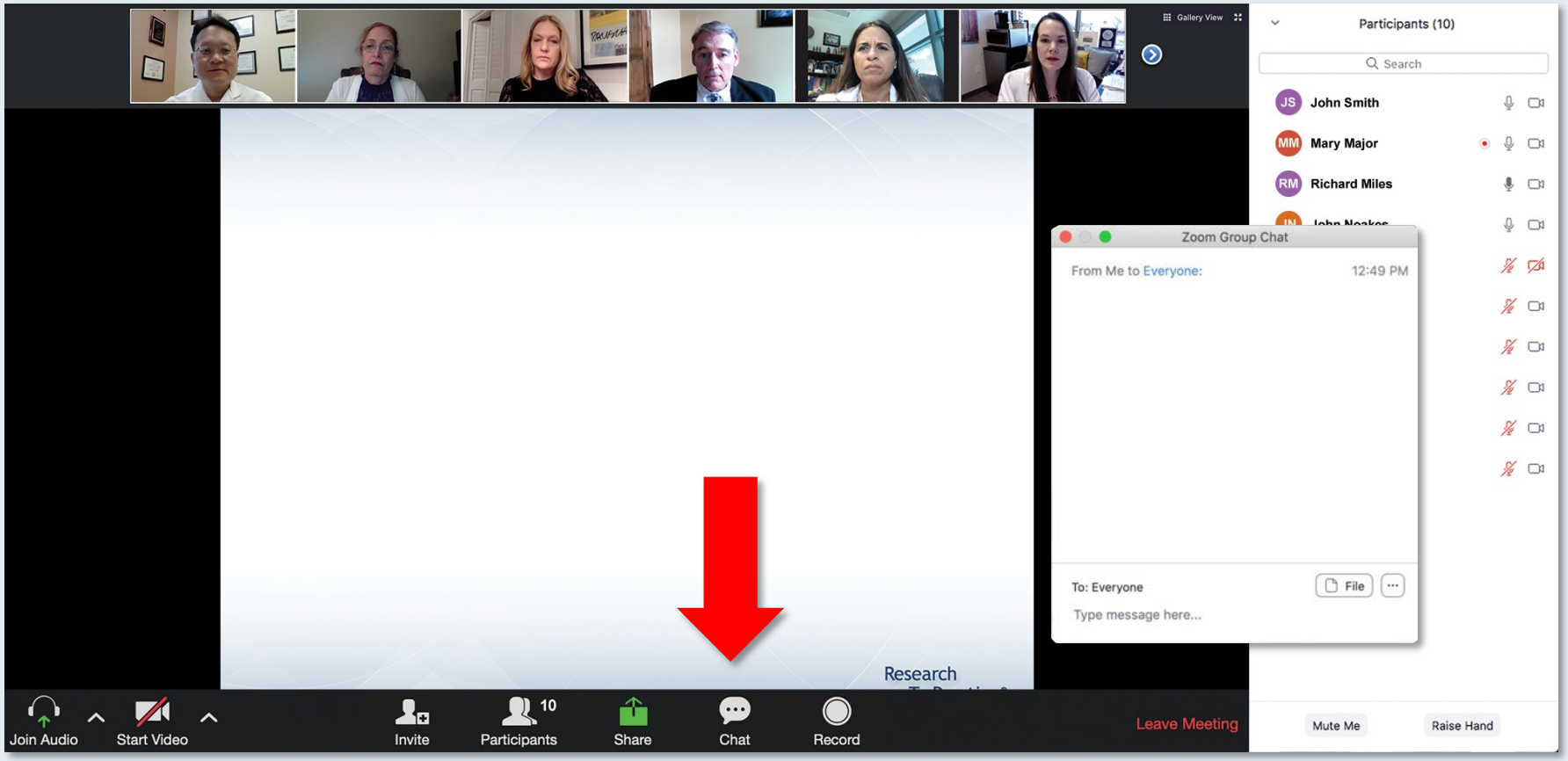

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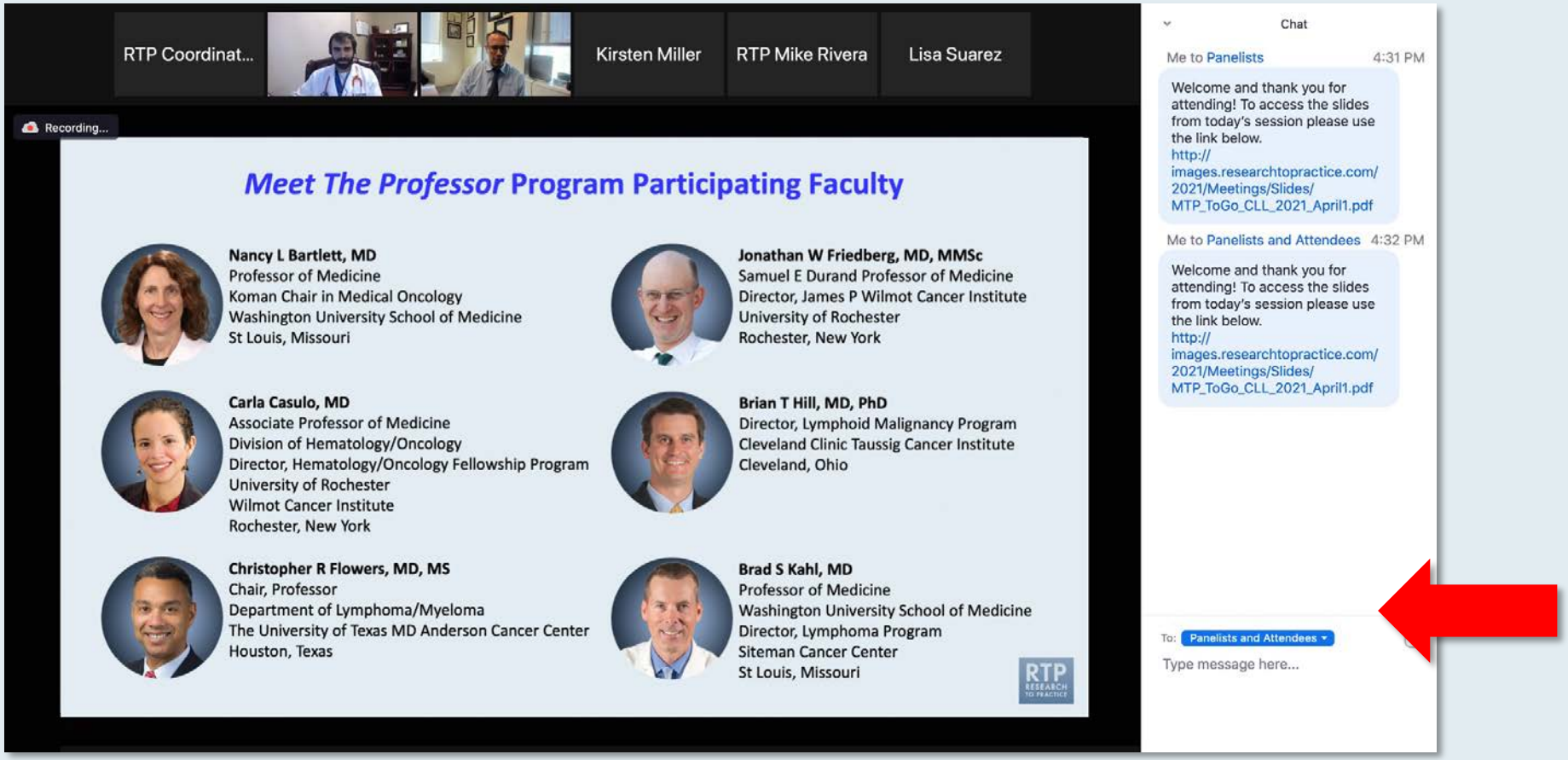

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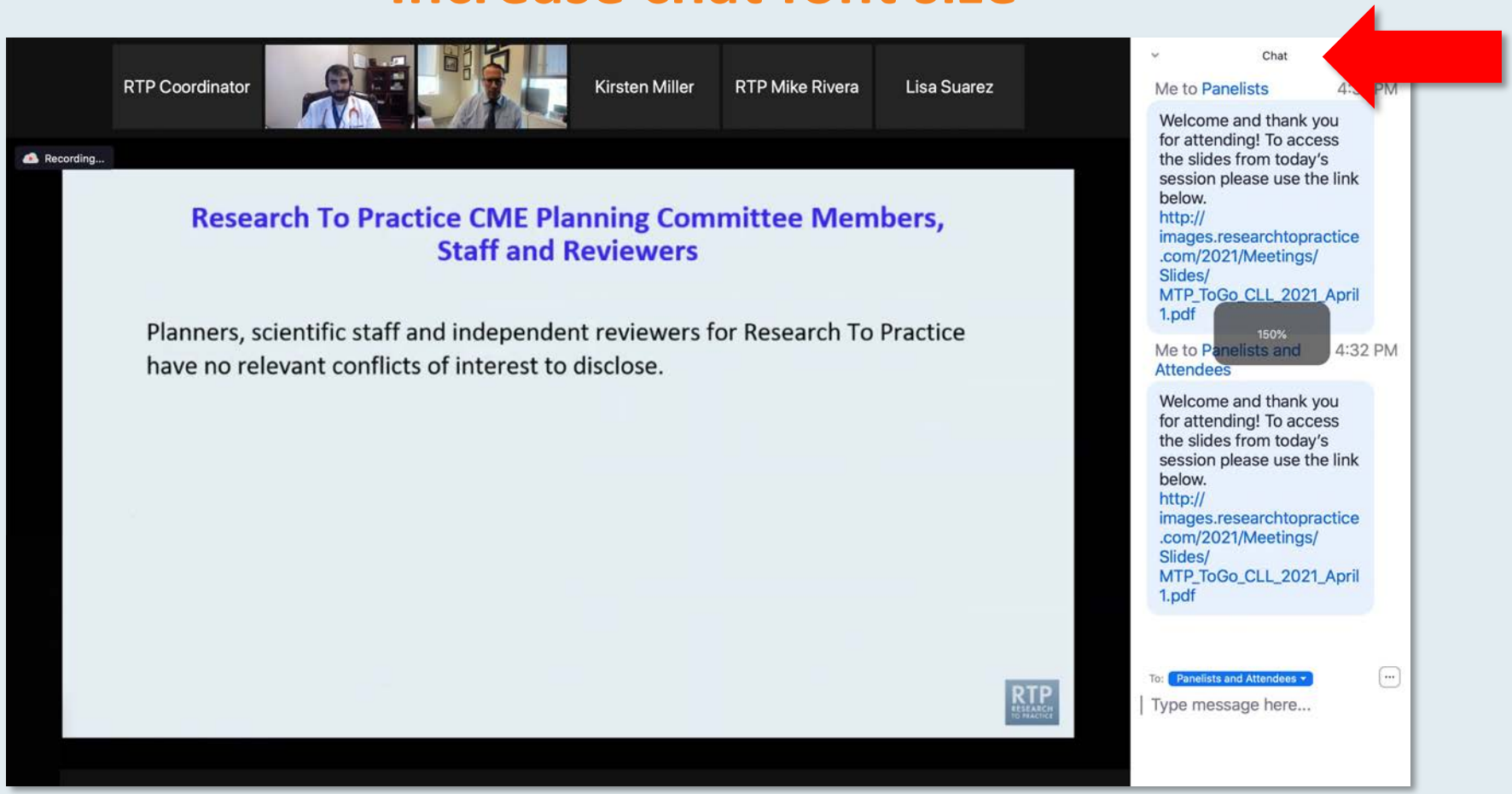

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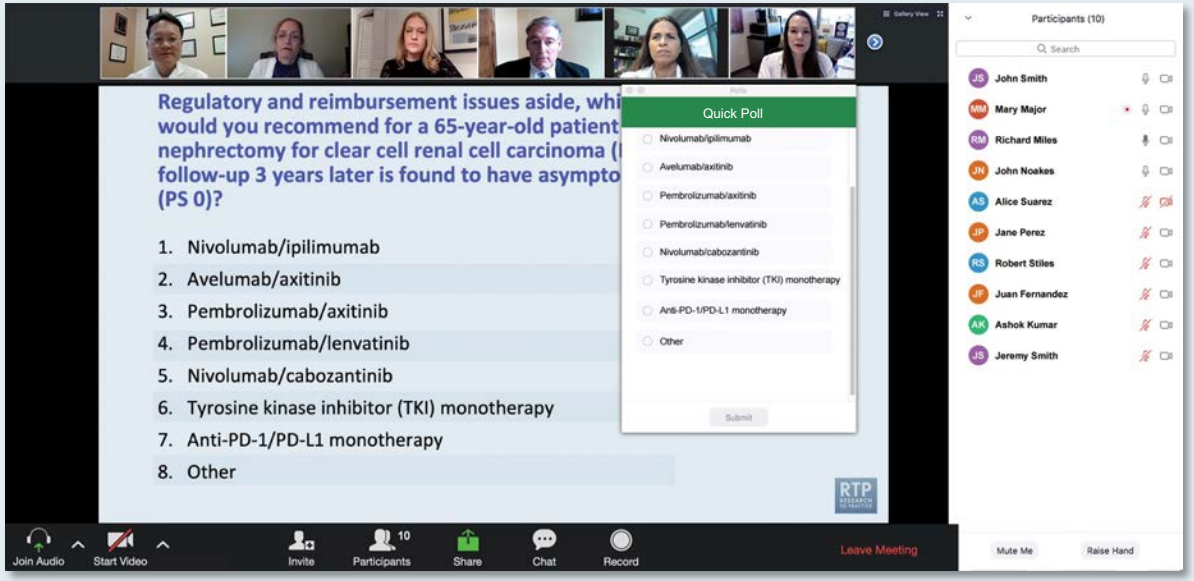

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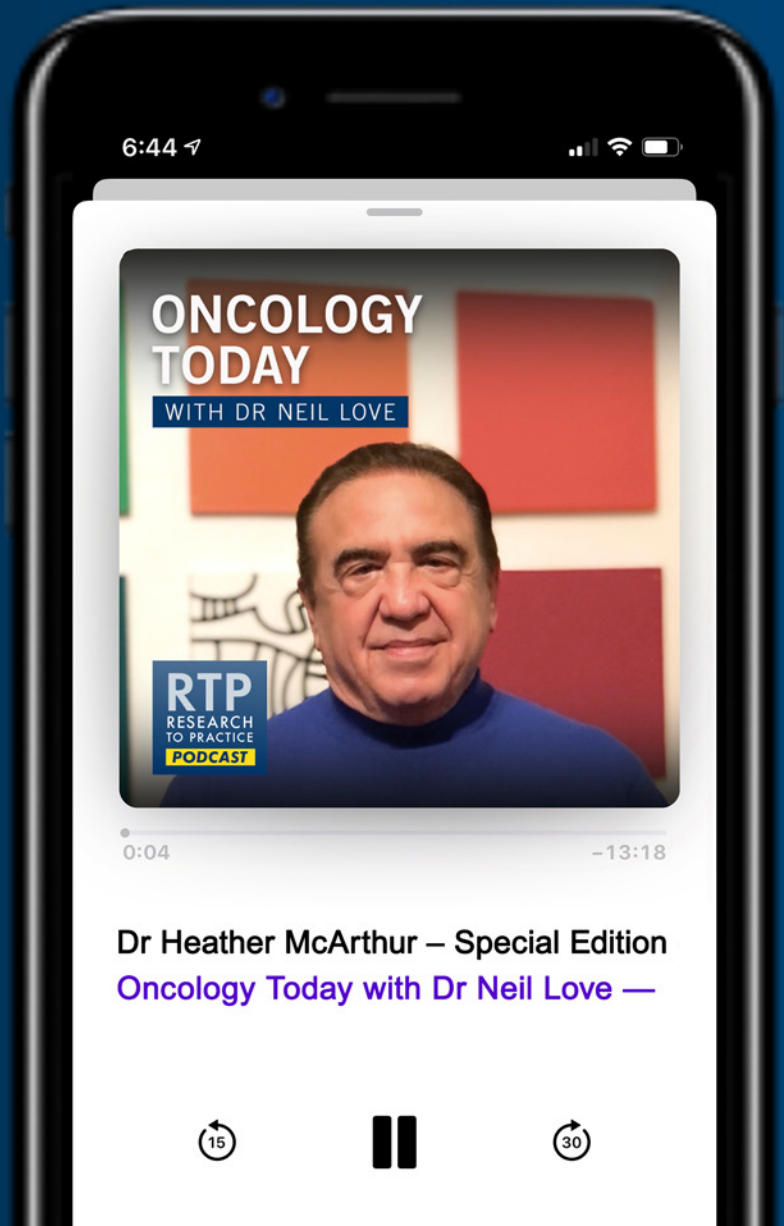

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Moderator

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Meet The Professor
Optimizing the Management of Gastroesophageal Cancers

Thursday, November 16, 2023
5:00 PM – 6:00 PM ET

Faculty

Samuel J Klempner, MD

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Neil Love, MD

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Inside the Issue: Targeted and Immunotherapeutic Approaches for Biliary Tract Cancers

A CME/MOC-Accredited Live Webinar

Wednesday, November 29, 2023
5:00 PM – 6:00 PM ET

Faculty

Lipika Goyal, MD, MPhil
Milind Javle, MD

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Breast Cancer

A 3-Part CME Satellite Symposium Series Held in Partnership with the 2023 San Antonio Breast Cancer Symposium®

ER-Positive Metastatic Breast Cancer

Tuesday, December 5, 2023

7:15 PM – 9:15 PM CT

Localized HER2-Negative Breast Cancer

Wednesday, December 6, 2023

7:15 PM – 9:15 PM CT

HER2-Low Breast Cancer

Thursday, December 7, 2023

7:15 PM – 8:45 PM CT

Moderator

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hematologic Cancers

A 4-Part CME Friday Satellite Symposium Series Preceding the 65th ASH Annual Meeting and Exposition

Friday, December 8, 2023

Follicular, Mantle Cell and Hodgkin Lymphoma
7:30 AM – 10:00 AM PT

Diffuse Large B-Cell Lymphoma
11:30 AM – 1:30 PM PT

Chronic Lymphocytic Leukemia
3:15 PM – 5:15 PM PT

Multiple Myeloma
7:00 PM – 9:00 PM PT

Moderator
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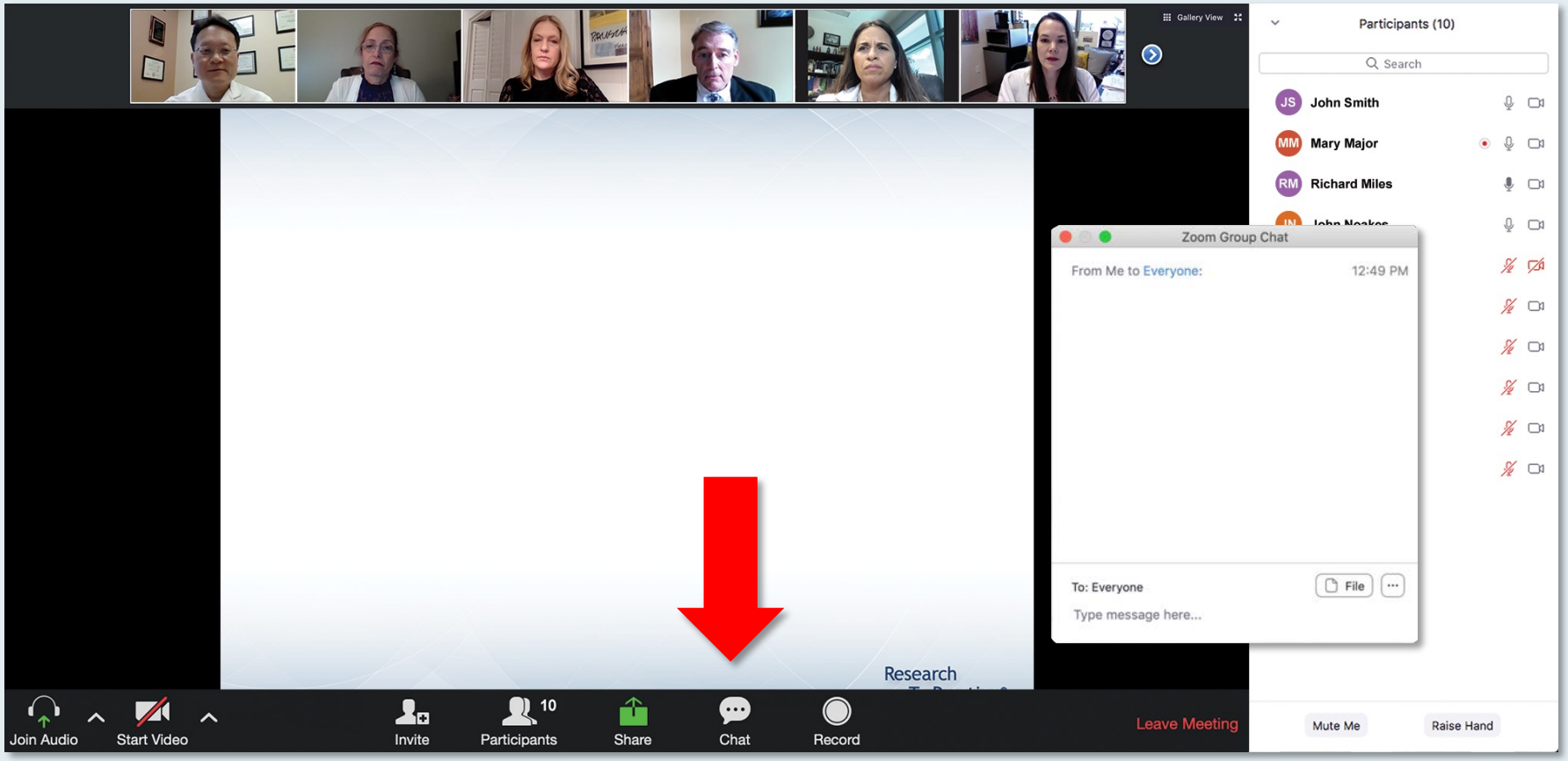

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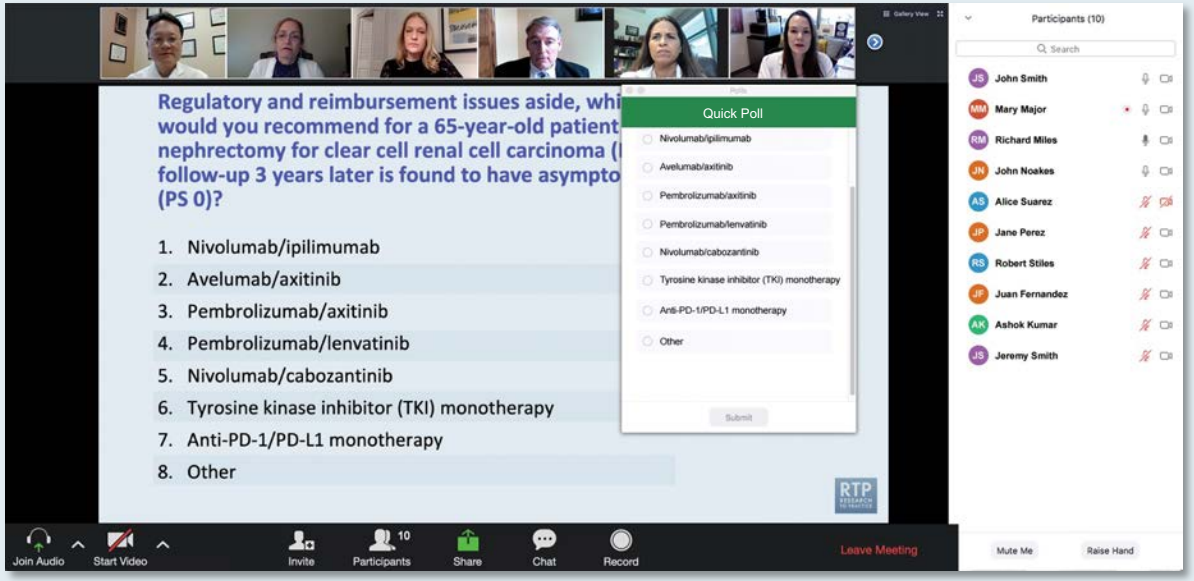

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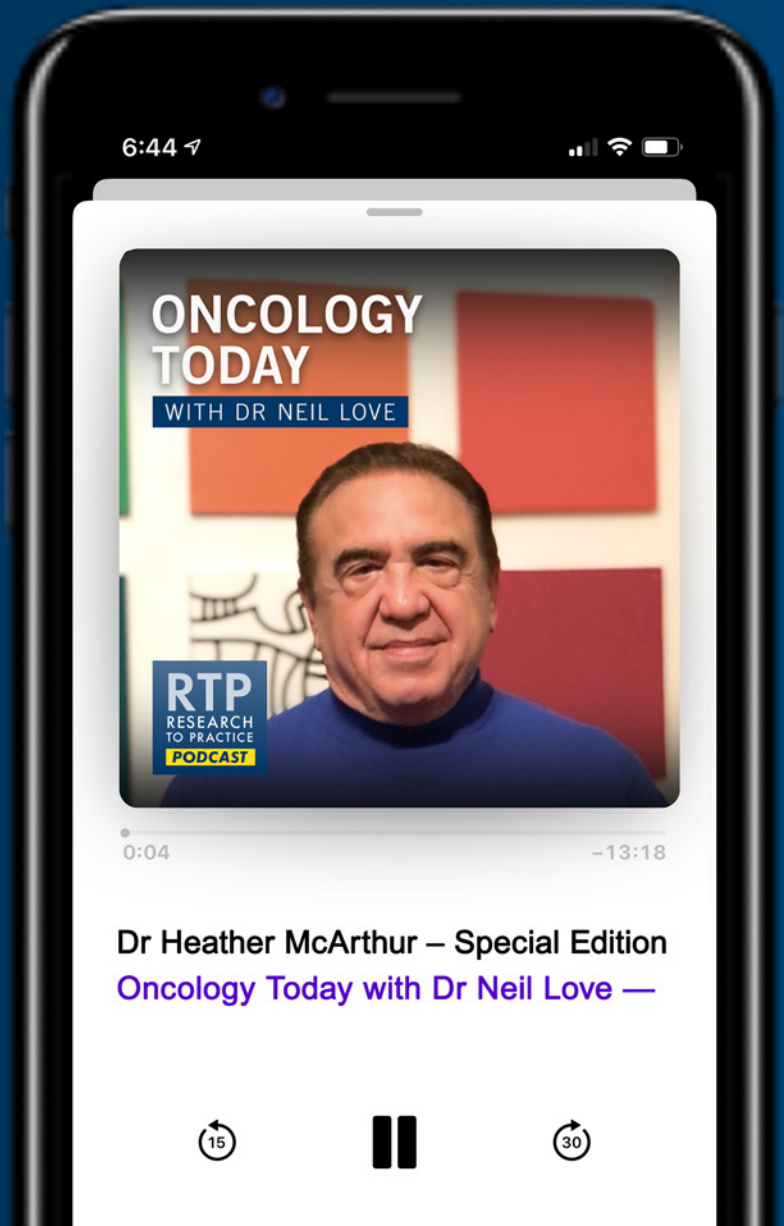

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Key Data Sets

Sara M Tolaney, MD, MPH

- Gluz O et al. Multiparametric prognostic score in early HR+/HER2- breast cancer: Impact of recurrence score, clinical-pathological factors, gene mutations and histology. ESMO 2023;Abstract LBA24.
- Sparano JA et al. Trial Assigning Individualized Options for Treatment (TAILORx): An update including 12-year event rates. SABCS 2022;Abstract GS1-05.
- Gray RG et al. Effects of ovarian ablation or suppression on breast cancer recurrence and survival: Patient-level meta-analysis of 14,993 pre-menopausal women in 25 randomized trials. ASCO 2023;Abstract 503.
- Harbeck N et al. Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer: Results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes. ESMO 2023;Abstract LBA17.
- Slamon DH et al. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: Primary results from the phase III NATALEE trial. ASCO 2023;Abstract LBA500.

Key Data Sets

Sara M Tolaney, MD, MPH (continued)

- Bardia A et al. Invasive disease-free survival (iDFS) across key subgroups from the phase III NATALEE study of ribociclib (RIB) + a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+/HER2- early breast cancer (EBC). ESMO 2023;Abstract LBA23.
- Cardoso F et al. KEYNOTE-756: Phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2- breast cancer. ESMO 2023;Abstract LBA21.
- Loi S et al. A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER+ HER2- primary breast cancer (BC). ESMO 2023;Abstract LBA20.

Key Data Sets

Sara M Tolaney, MD, MPH (continued)

- Schmid P et al. Pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: Updated EFS results from the phase III KEYNOTE-522 study. ESMO 2023;Abstract LBA18.
- Gianni L et al. Event-free survival (EFS) analysis of neoadjuvant taxane/carboplatin with or without atezolizumab followed by an adjuvant anthracycline regimen in high-risk triple negative breast cancer (TNBC): NeoTRIP Michelangelo randomized study. ESMO 2023;Abstract LBA19.
- Tutt A et al. Pre-specified event driven analysis of overall survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. ESMO Virtual Plenary 2022;Abstract VP1-2022.

Key Data Sets

Aditya Bardia, MD, MPH

- Hurvitz SA et al. A pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with brain metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03. ESMO 2023;Abstract 377O.
- Curigliano G et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): Final overall survival analysis. *Ann Oncol* 2022 March;33(3):321-9.
- Modi S et al. Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Updated survival results of the randomized, phase III DESTINY-Breast04 study. ESMO 2023;Abstract 376O.
- Li B et al. Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with solid tumors harboring specific HER2-activating mutations (HER2m): Primary results from the international phase II DESTINY-PanTumor01 (DPT-01) study. ESMO 2023;Abstract 654O.

Key Data Sets

Aditya Bardia, MD, MPH (continued)

- Tolaney SM et al. Final overall survival (OS) analysis from the phase 3 TROPiCS-02 study of sacituzumab govitecan (SG) in patients (pts) with hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (mBC). ASCO 2023;Abstract 1003.
- Cortés J et al. Efficacy and safety analyses by prior lines of chemotherapy from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2- metastatic breast cancer (mBC). ESMO 2023;Abstract 389P.
- Bardia A et al. Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer (BC): Primary results from the randomised phase III TROPION-Breast01 trial. ESMO 2023;Abstract LBA11.

Key Data Sets

Aditya Bardia, MD, MPH (continued)

- Schmid P et al. Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): Updated results from BEGONIA, a phase Ib/II study. ESMO 2023;Abstract 379MO.
- Hamilton EP et al. A phase 2 study of HER3-DXd in patients (pts) with metastatic breast cancer (MBC). ASCO 2023;Abstract 1004.
- Zhang J et al. First-in-human/phase I trial of HS-20089, a B7-H4 ADC, in patients with advanced solid tumors. ESMO 2023;Abstract 381O.

Agenda

INTRODUCTION: Pan-tumor approval of novel agents

MODULE 1: Treatment of ER-positive localized breast cancer (BC)

MODULE 2: Immunotherapy in localized BC

MODULE 3: PARP inhibition in BRCA-mutated localized BC

MODULE 4: Antibody-drug conjugates in metastatic disease (trastuzumab deruxtecan, sacituzumab govitecan, datopotamab deruxtecan, patritumab deruxtecan)

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Potential of Trastuzumab Deruxtecan as a Tissue-Agnostic Drug

"Over the last six years, the FDA has approved seven tissue agnostic drugs, and more are anticipated in the future. One promising candidate for a tissue agnostic classification is the antibody-drug conjugate trastuzumab deruxtecan (T-DXd). Currently, T-DXd is approved for the treatment of HER2-positive and HER2-low breast cancer, HER2-positive gastric or gastroesophageal junction adenocarcinoma, and non-small cell lung cancer with activating HER2 mutations. Ongoing clinical research is exploring the potential of T-DXd in various solid tumors that harbor specific HER2 molecular alterations, and encouraging results, including the interim data from the DESTINY-PanTumor02 trial, have been published, which suggest a tissue agnostic potential.

Published Phase I data as well as the interim results from the Phase II DESTINY-PanTumor02 trial indicate that patients with different HER2-positive advanced solid tumors may benefit from treatment with T-DXd. Based on the currently available data, it seems likely that T-DXd possesses pan-tumor activity. However, different clinical trials are ongoing, and it will be necessary to see the results from these trials before drawing a final conclusion. When discussing tissue agnostic potential, it is important to add that for most of the patients enrolled in the DESTINY-PanTumor02 and other trials, few treatment alternatives seem to exist, and T-DXd might be able to cover an unmet medical need."

Jorgesen JT. *Oncology* 2023 August 31;[Online ahead of print].

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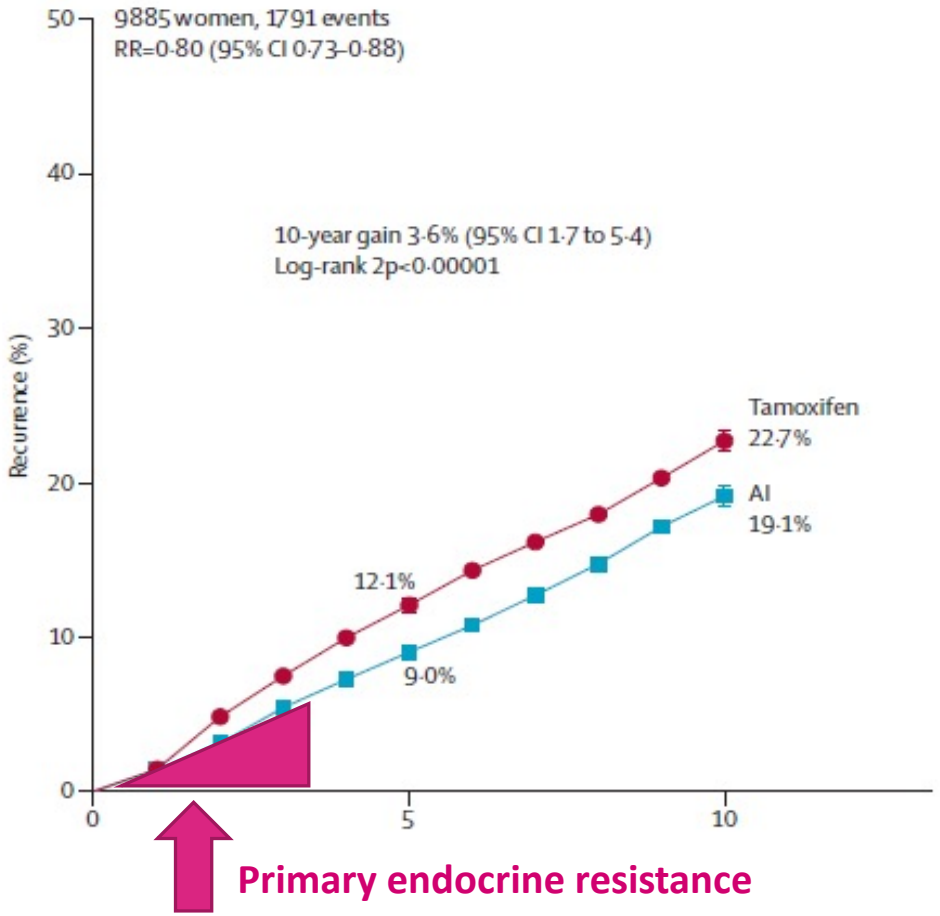
ADJUVANT ENDOCRINE THERAPY IN ER+ EBC

Endocrine therapy

- Tamoxifen, Aromatase inhibitors
- Ovarian suppression (LHRH analogues) in high-risk premenopausal women
- Extended adjuvant therapy (10 years vs. 5 years)

Unmet need

- Understanding who does / does not need adjuvant chemotherapy
- Identifying those with primary endocrine resistance HR-positive BC, and preventing or delaying recurrence with additional therapy



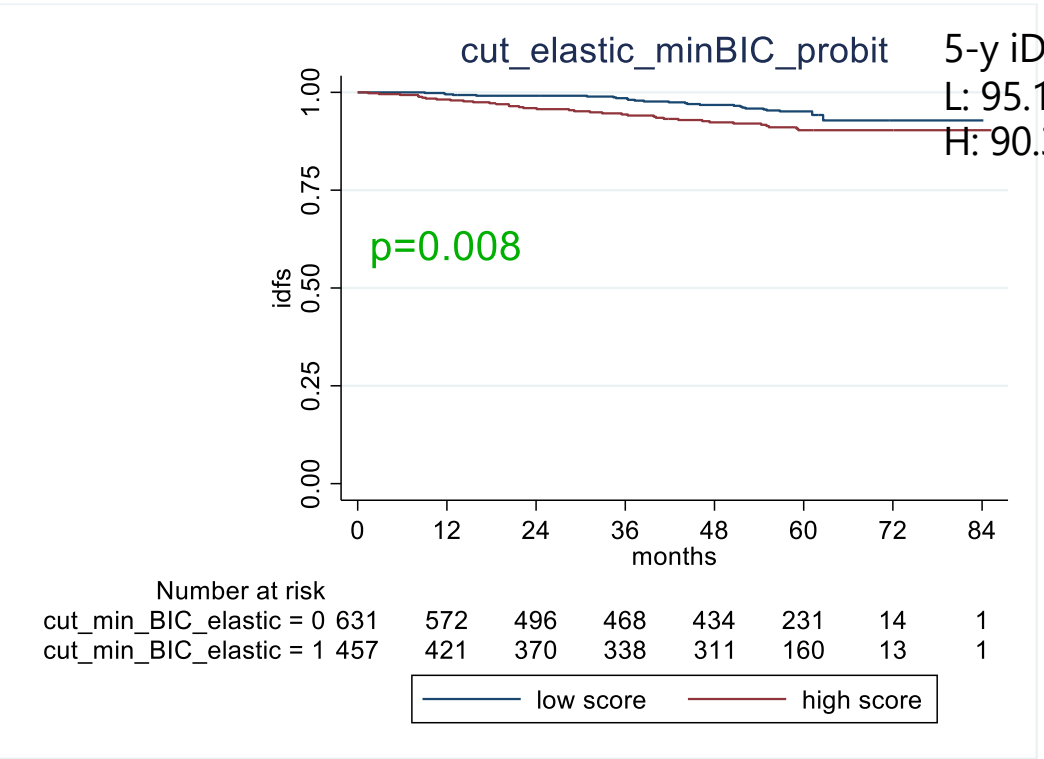
Cardoso F, et al. Ann Oncol. 2019;30:1194–1220.
Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015;386:1341–1352.

Stephen R D Johnston

Courtesy of Sara M Tolaney, MD, MPH

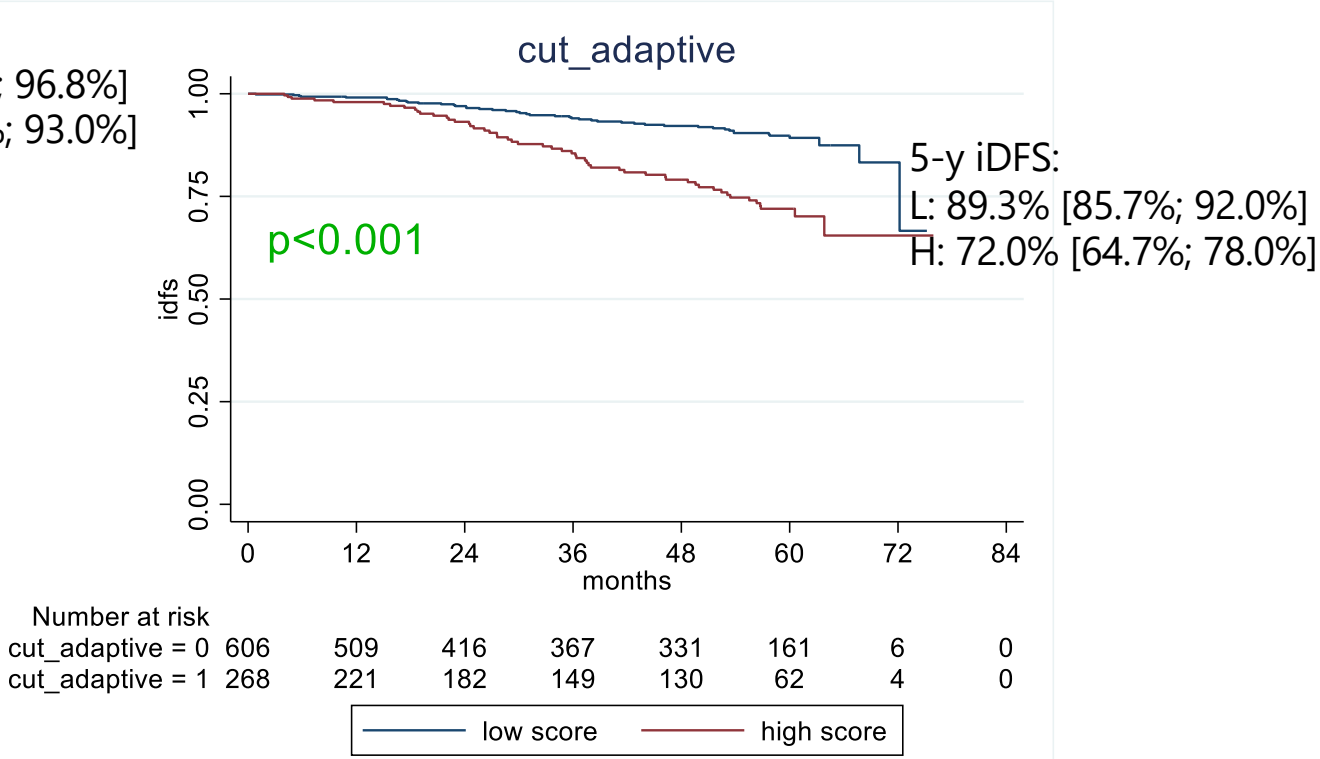
Prognostic score in validation cohorts

ET cohort



ET cohort prognostic score including tumor stage and PR expression (by IHC)

CT cohort



CT cohort prognostic score consisting of tumor and nodal stage, RS, ILC, PR expression (by IHC)
Sensitivity of 54% / specificity of 72%

Courtesy of Sara M Tolaney, MD, MPH

Gluz O et al, ESMO 2023

TAILORx Updated Analysis: Conclusions

- Longer median followup and more events in randomized group
  - Median 11.0 vs. 7.5 years
  - IDFS (1295 vs. 836) and DRFI (375 vs. 250) events
- Main study findings unchanged for RS 11-25 arms (primary objective)
  - ET non-inferior to CET for IDFS (primary endpoint) and DRFI (secondary endpoint)
  - RFI and OS also similar between treatment arms (exploratory endpoints)
- Other exploratory key study findings also similar to original analysis
  - Chemotherapy benefit for women ≤ 50 with RS 21-25
  - Some chemotherapy benefit for women ≤ 50 with RS 16-20 and high clinical risk
- New findings of updated analyses (exploratory)
  - Late recurrences > 5 years exceed early recurrence
  - Racial disparities for black women associated with early but not late recurrence

Sparano JA et al. SABCS 2022;Abstract GS1-05.

Case Presentation – Dr Tolaney: Recurrence Score

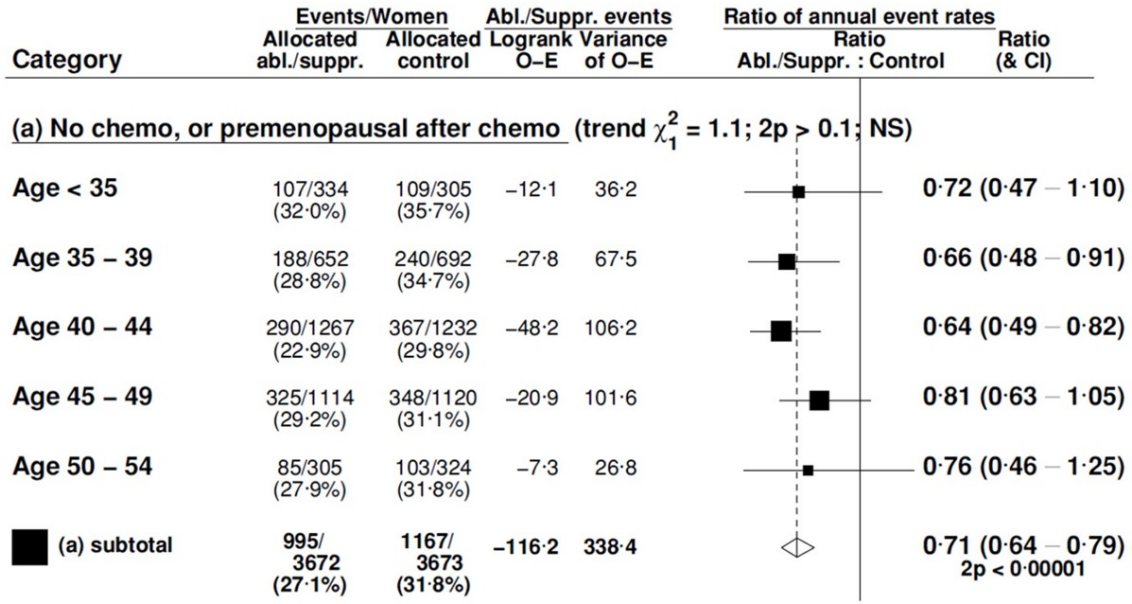
- 54 yo postmenopausal healthy woman with a mammographic abnormality is found to have a grade 3 IDC ER+, PR+ HER2 1+
- Undergoes lumpectomy and sentinel node biopsy
- 9mm grade 3 IDC ER+, PR+, HER2 1+, 0/1 SN

- Recurrence Score: 37

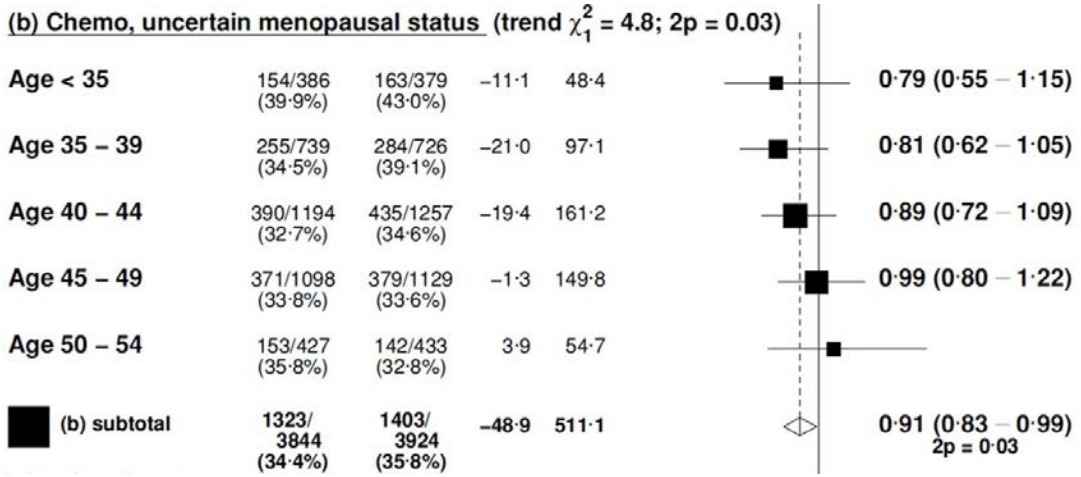
What about ovarian suppression?

Ovarian ablation/suppression vs not: Recurrence by age

(A) No chemotherapy or premenopausal after chemotherapy



(B) Premenopausal prior to chemotherapy, uncertain after[a]

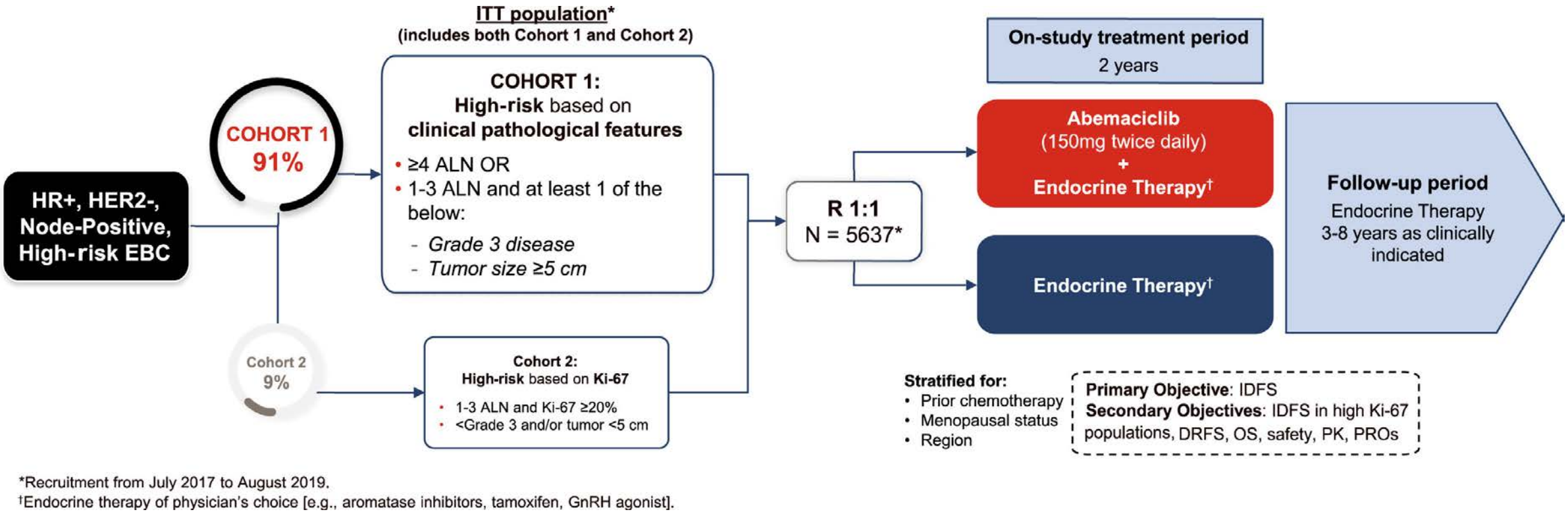


[a]ER-weighted estimates

Courtesy of Sara M Tolaney, MD, MPH

Gray R, et al. ASCO 2023. Abstract 503

monarchE: Study Design (NCT03155997)



*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

Courtesy of Sara M Tolaney, MD, MPH

Harbeck N et al, ESMO 2023

NATALEE study design

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 months
- **Anatomic stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomic stage IIB**[a]
  - N0 or N1
- **Anatomic stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 years

NSAI
Letrozole or anastrozole[d]
for ≥5 years
+ goserelin in men and
premenopausal women

NSAI
Letrozole or
anastrozole[d] for
≥5 years
+ goserelin in men and
premenopausal women

Primary end point
- iDFS using STEEP criteria

Secondary end points
- Recurrence-free survival
- Distant disease–free survival
- OS
- HRQoL
- Safety and tolerability
- PK

Exploratory end points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Randomization stratification
Anatomic stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQoL, health-related quality of life; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in adjuvant breast cancer trials.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from January 10, 2019, to April 20, 2021. [c] Open-label design. [d] Per investigator choice.
1. Slamon D, et al. ASCO 2023. Oral; abstract LBA500. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract TPS597.

Courtesy of Sara M Tolaney, MD, MPH

Bardia A et al, ESMO 2023

monarchE and NATALEE: Tolerability

≥ Grade 3 AE	monarchE		NATALEE	
	Abema	No Abema	Ribo	No Ribo
Neutropenia	19.7%	0.8%	43.8%	0.8%
Liver-Related AE*	1.8-2.6%	0.5-0.7%	8.3%	1.5%
QTC interval Prolongation	N/A	N/A	1.0%	0.5%
Diarrhea	7.8%	0.2%	0.6%	0.1%
Fatigue	2.9%	0.1%	0.7%	0.2%
VTE	1.3%	0.3%	0.6%	0.2%

Discontinued due to AE **Abemaciclib: 18.5%** **Ribociclib: 19%**

Different AEs

QOL tools did not capture early events (first QOL at 3 months)

Johnston S et al Lancet Oncology 2023; Johnston S et al SABCS 2023; Slamon D et al ASCO 2023
Rugo et al Annals of Oncology 2022; Fasching et al ESMO Virtual Plenary 2023

Courtesy of Sara M Tolaney, MD, MPH

Adjuvant CDK4/6 inhibition

- Adjuvant abemaciclib is standard of care for patients with high-risk ER+ breast cancer
- Will need to await longer follow-up data from NATALEE to understand benefits when patients have completed adjuvant ribociclib therapy
  - Could expand number of patients that benefit from therapy into intermediate risk patients
- Multiple remaining questions:
  - What is the optimal duration of therapy?
  - Is there an optimal CDK4/6 inhibitor?

Courtesy of Sara M Tolaney, MD, MPH

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INTRODUCTION: Pan-tumor approval of novel agents

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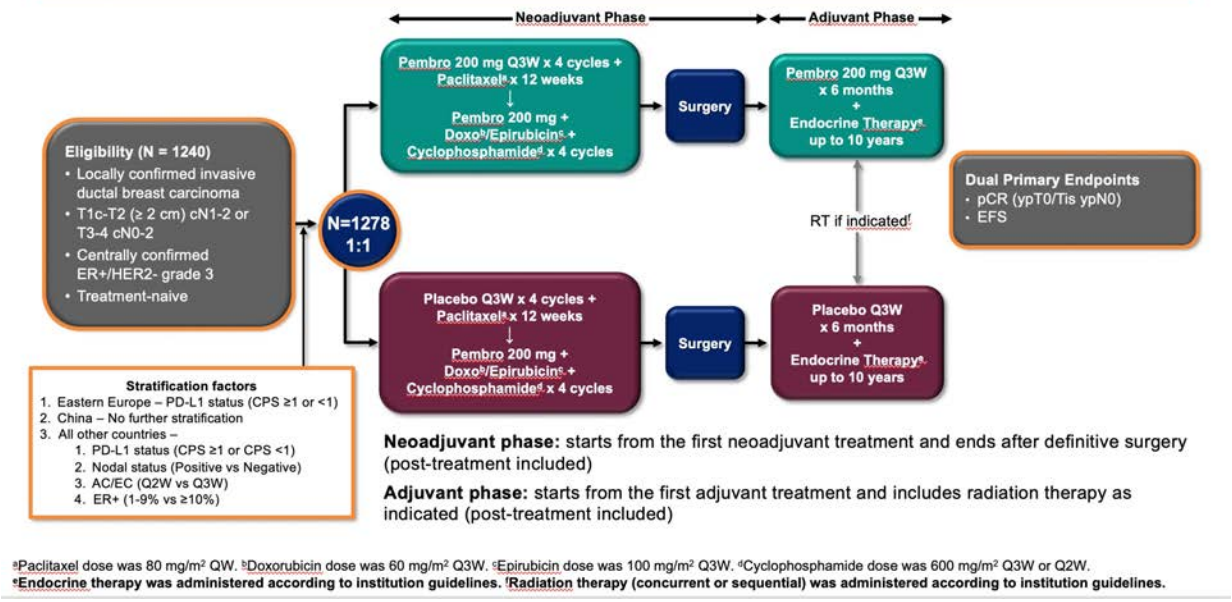
MODULE 2: Immunotherapy in localized BC

MODULE 3: PARP inhibition in BRCA-mutated localized BC

MODULE 4: Antibody-drug conjugates in metastatic disease (trastuzumab deruxtecan, sacituzumab govitecan, datopotamab deruxtecan, patritumab deruxtecan)

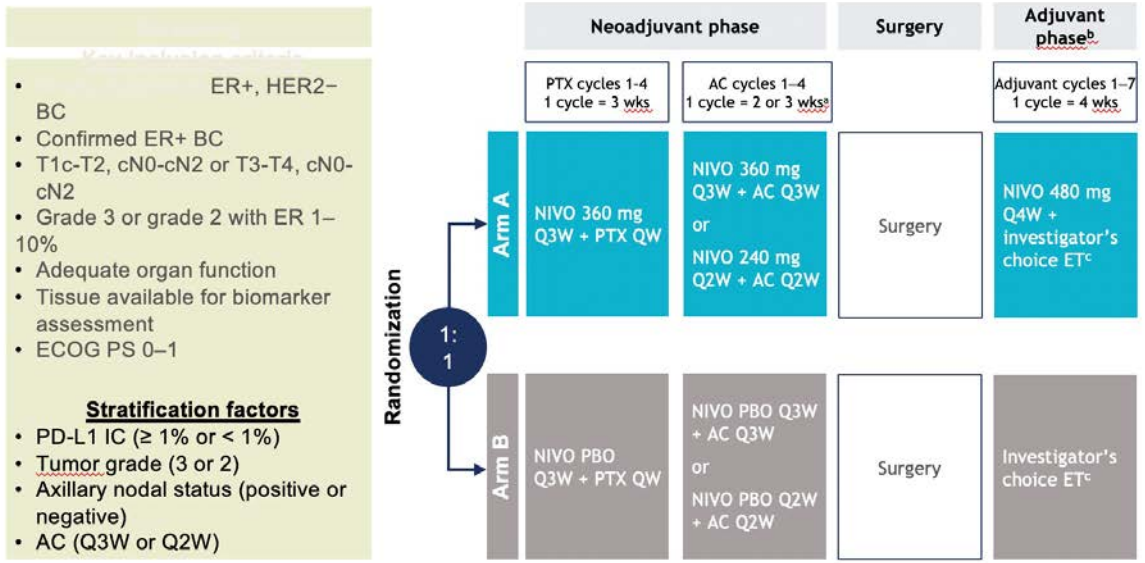
Preoperative Checkpoint Inhibition in ER+ Breast Cancer

KEYNOTE-756



Cardoso F et al, LBA21, ESMO 2023

CheckMate 7FL

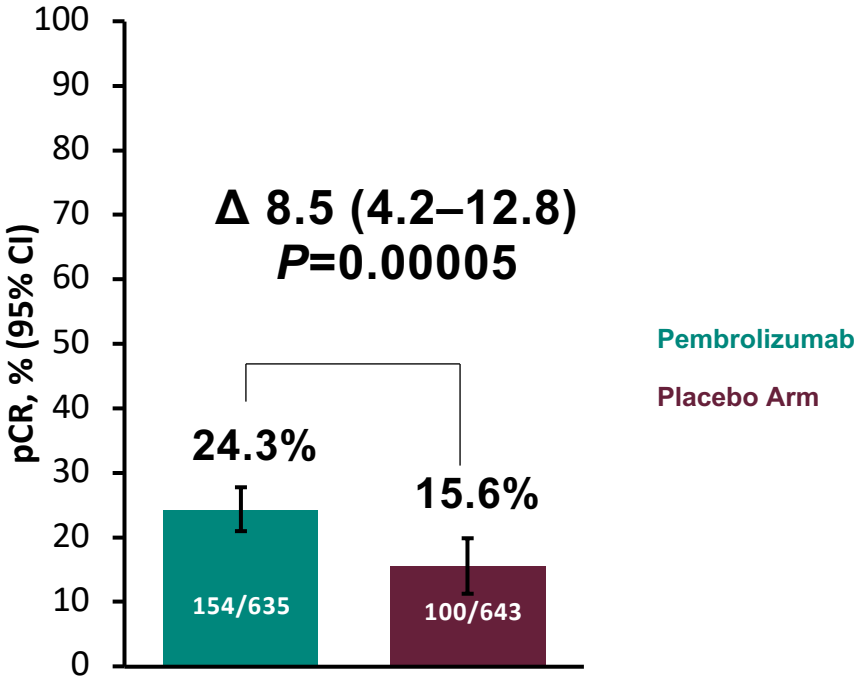


Loi S et al, LBA20, ESMO 2023

Courtesy of Sara M Tolaney, MD, MPH

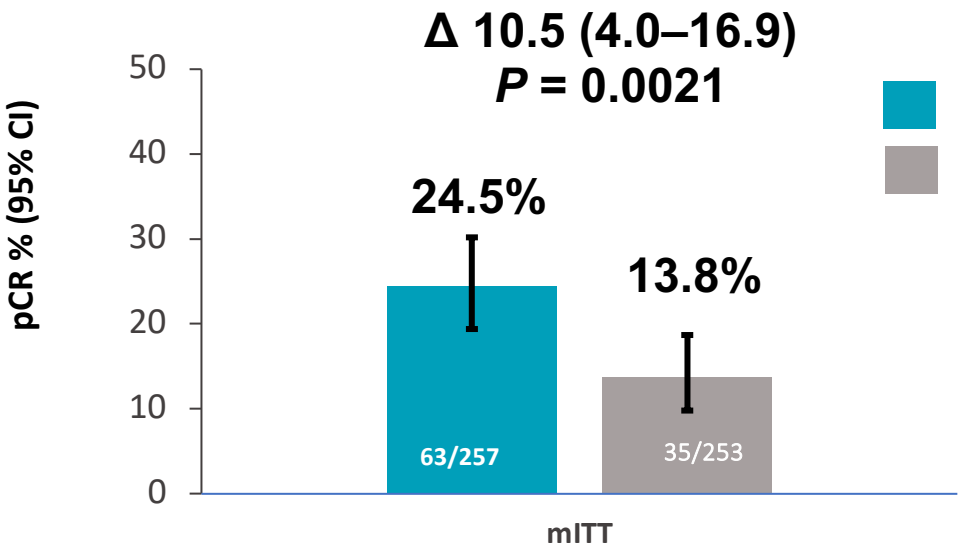
Preoperative Checkpoint Inhibition in ER+ Breast Cancer: pCR

KEYNOTE-756



Cardoso F et al, LBA21, ESMO 2023

CheckMate 7FL

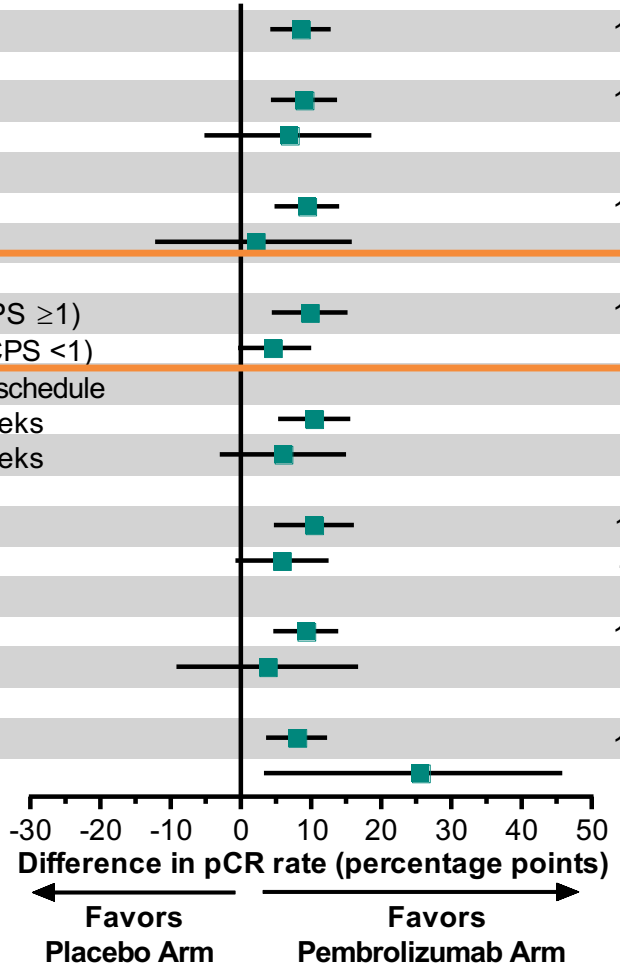


Loi S et al, LBA20, ESMO 2023

Courtesy of Sara M Tolaney, MD, MPH

KN-756: pCR (ypT0/Tis ypN0) in Subgroups & PD-L1 Status

Subgroup	No. with pCR/No. of Participants (%) Pembrolizumab Arm	Placebo Arm	pCR Rate Difference (95% CI)
Overall	154/635 (24.3)	100/643 (15.6)	8.5 (4.2 to 12.8)
Age category			
<65 years	135/546 (24.7)	89/567 (15.7)	9.0 (4.3 to 13.8)
≥65 years	19/89 (21.3)	11/76 (14.5)	6.9 (–5.2 to 18.6)
ECOG PS			
0	142/570 (24.9)	91/588 (15.5)	9.4 (4.8 to 14.1)
1	12/65 (18.5)	9/55 (16.4)	2.1 (–12.2 to 15.8)
PD-L1 status			
Positive (CPS ≥1)	143/482 (29.7)	96/489 (19.6)	9.8 (4.4 to 15.2)
Negative (CPS <1)	11/153 (7.2)	4/154 (2.6)	4.5 (–0.4 to 10.1)
Anthracycline schedule			
Every 3 weeks	97/415 (23.4)	55/425 (12.9)	10.4 (5.3 to 15.7)
Every 2 weeks	54/183 (29.5)	44/187 (23.5)	6.0 (–3.0 to 15.0)
Tumor size			
T1/T2	111/402 (27.6)	71/413 (17.2)	10.4 (4.7 to 16.1)
T3/T4	43/233 (18.5)	29/230 (12.6)	5.8 (–0.8 to 12.5)
Nodal status			
Positive	143/570 (25.1)	92/582 (15.8)	9.3 (4.6 to 13.9)
Negative	11/65 (16.9)	8/61 (13.1)	3.8 (–9.2 to 16.7)
ER positivity			
≥10%	135/601 (22.5)	87/600 (14.5)	8.0 (3.6 to 12.4)
<10%	19/34 (55.9)	13/43 (30.2)	25.6 (3.3 to 45.8)



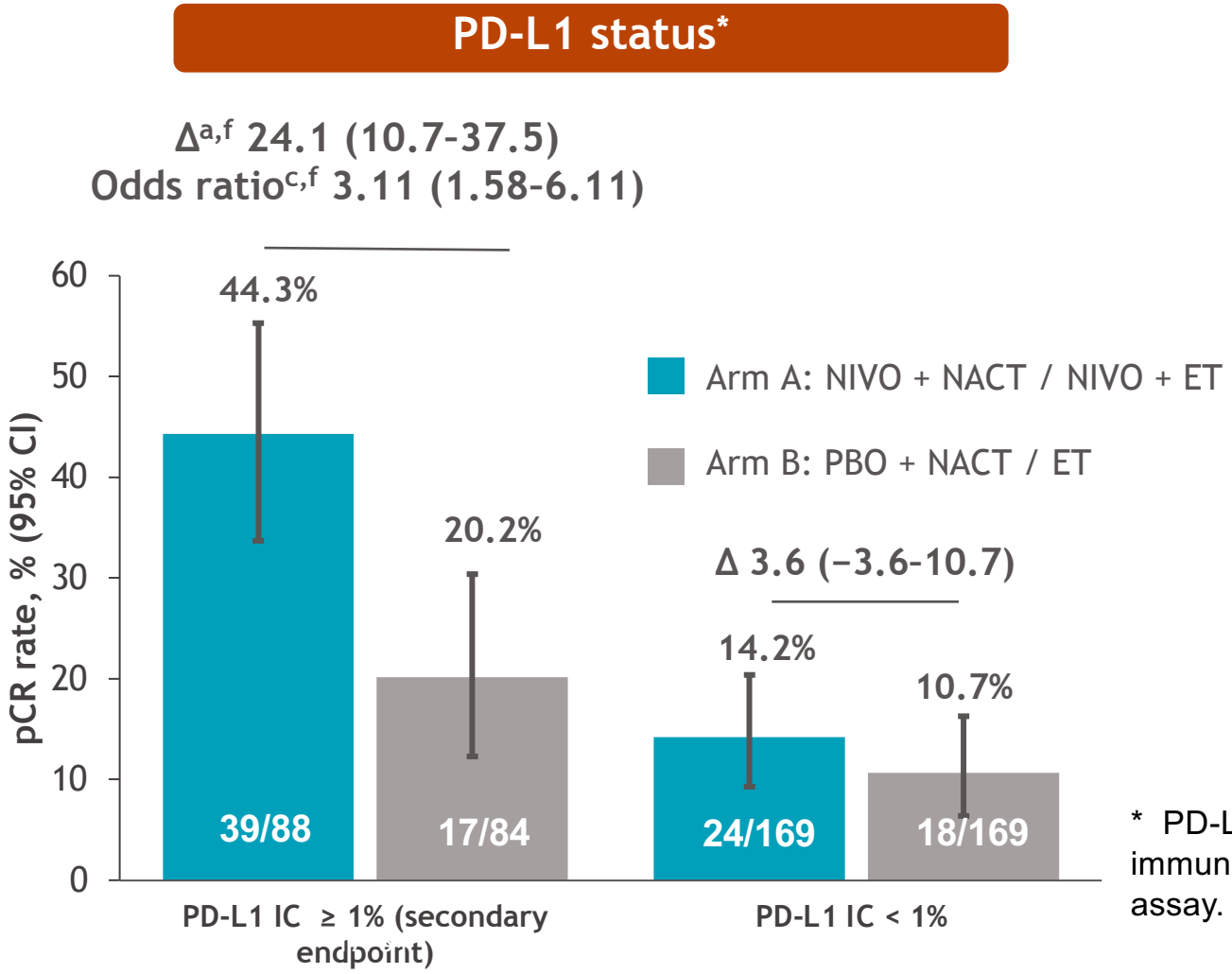
- **75% of ER+ Tumours PD-L1 Positive by 22C3 CPS assay (using CPS 1 cut-off)**
- **Benefit for Pembrolizumab seen regardless of PD-L1 status**
- **Larger difference in pCR rates in PD-L1 Positive vs Negative tumours (9.8% vs 4.5%, respectively)**
- **Benefits in ER-low (5% of study) similar to KN522**

* PD-L1 assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100).

Courtesy of Sara M Tolaney, MD, MPH

Cardoso F et al, LBA21, ESMO 2023

CM-7FL: pCR (ypT0/Tis, ypN0) rate by PD-L1 status *



- **34% of ER+ Tumors PD-L1 Positive by SP142 assay**
- **Benefit for Nivolumab much greater in PD-L1 positive tumours with difference in pCR for PD-L1 Positive vs Negative 24.8% vs 3.6%, respectively**
- **<5% of pts had ER-low tumors**

* PD-L1 immune cells and PD-L1–expressing tumor-infiltrating immune cells as percentage of tumor area using the VENTANA SP142 assay.

Courtesy of Sara M Tolaney, MD, MPH

Loi S et al, LBA20, ESMO 2023

Toxicity with Preoperative Checkpoint Inhibition

KEYNOTE-756

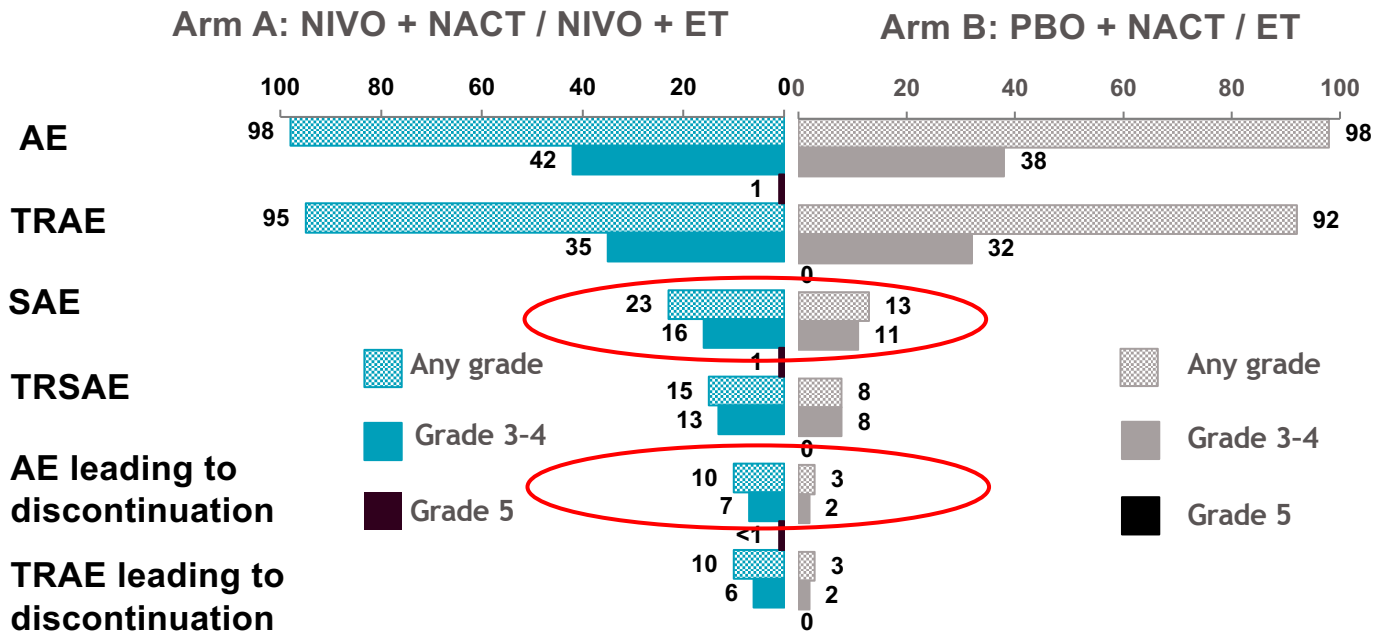
All Treatment-Related	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	98.4%	98.6%
Grade 3-5	52.5%	46.4%
Serious	18.5%	10.3%
Led to death	0.2%[a]	0
Led to discontinuation of any drug	19.1%	10.1%

1 death in PEMBRO arm due to acute myocardial infarct (QT related)

Cardoso F et al, LBA21, ESMO 2023

2.5% Adrenal Insuff, 1.9% hypophysitis
1.3% hepatitis, 2.8% pneumonitis

CheckMate 7FL



2 deaths in NIVO arm due to pneumonitis, hepatitis

Loi S et al, LBA20, ESMO 2023

5% adrenal Insuff, 2% hypophysitis
5% hepatitis, 3% pneumonitis

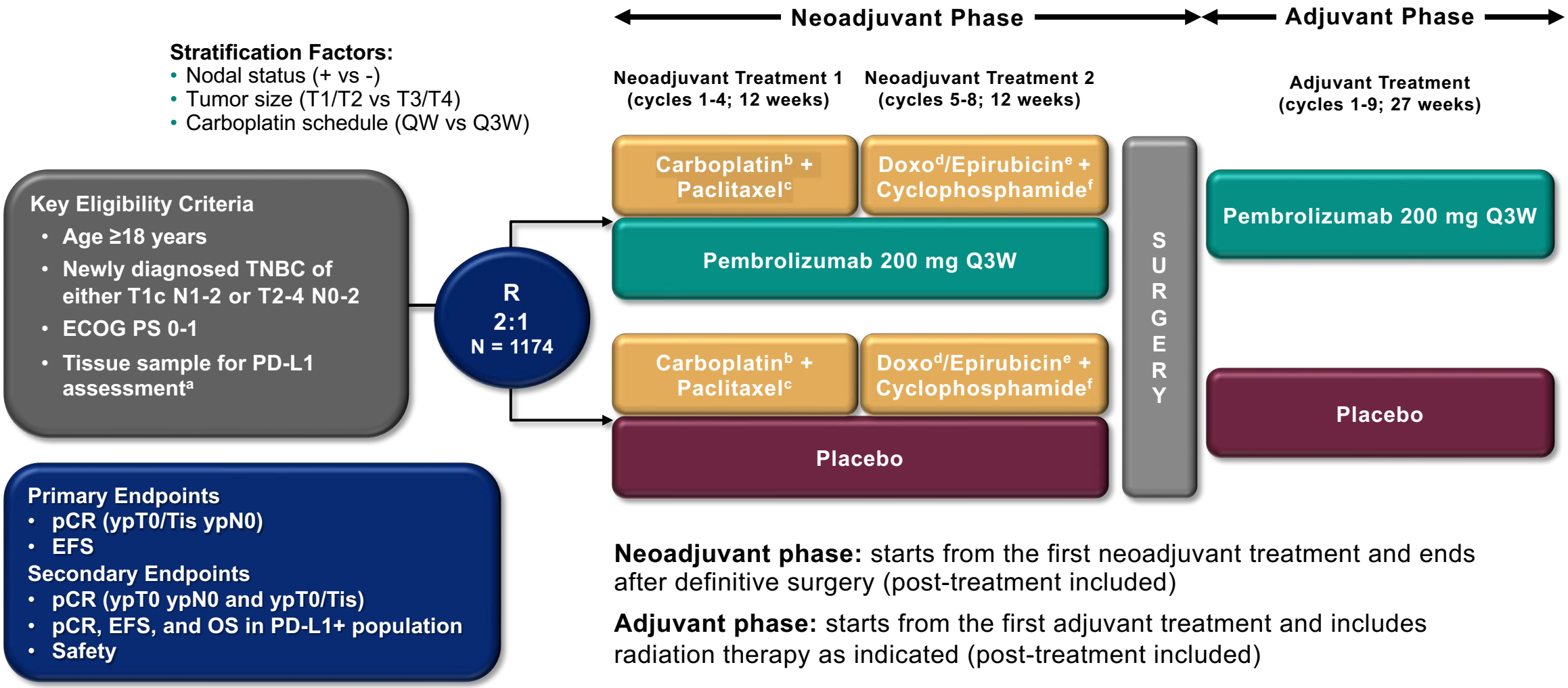
Courtesy of Sara M Tolaney, MD, MPH

Are we ready to start using checkpoint inhibition in the preoperative setting for stage 2/3 high grade ER+ breast cancer?

- Relationship between pCR and EFS is less clear in ER+ breast cancer→ patients receive additional adjuvant therapy that can influence EFS
  - CheckMate 7FL will not be powered for EFS given study was stopped early due to changing landscape with approval of adjuvant abemaciclib
- Critical to await EFS data to understand long term impact
  - Need to balance toxicity with benefits seen
  - Important to understand relationship between PD-L1 status and EFS
  - Further studies needed to understand safety of sequencing CDK4/6 inhibition post checkpoint inhibition given high rates of hepatitis/pneumonitis that have been seen with concurrent use in other studies
- *Limitation*: No use of adjuvant CDK4/6i given concerns of safety with concurrent CDK4/6i and checkpoint inhibition

Courtesy of Sara M Tolaney, MD, MPH

What about checkpoint inhibition in TNBC? KEYNOTE-522 5-year analysis



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

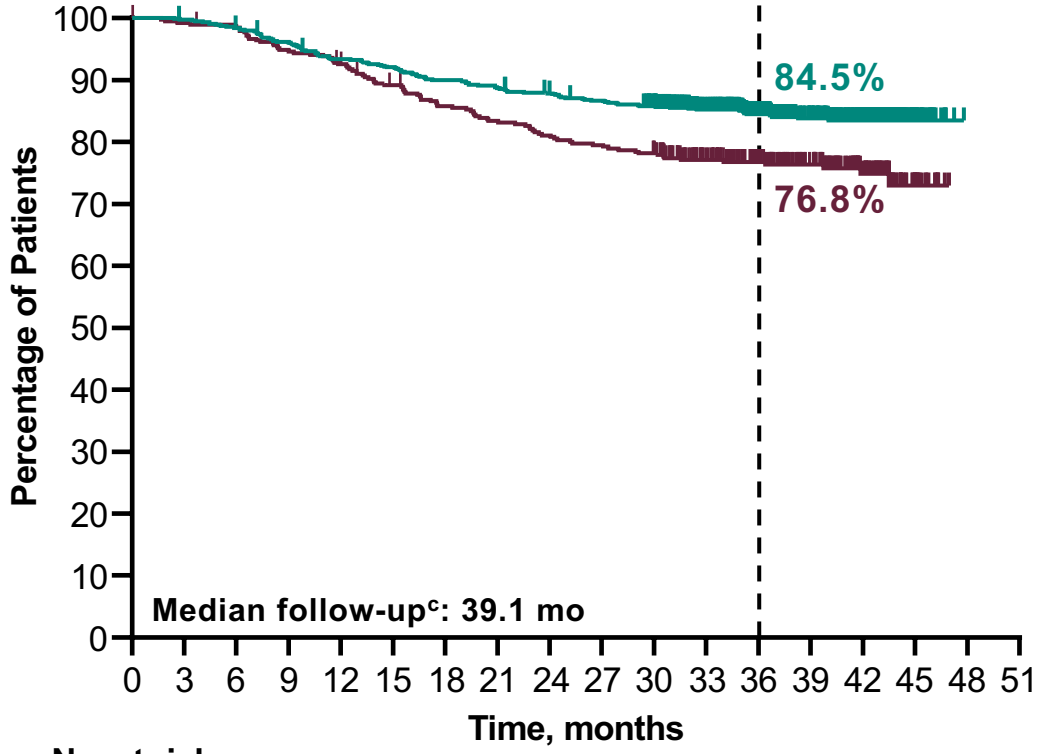
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[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/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Courtesy of Sara M Tolaney, MD, MPH

KEYNOTE-522: EFS

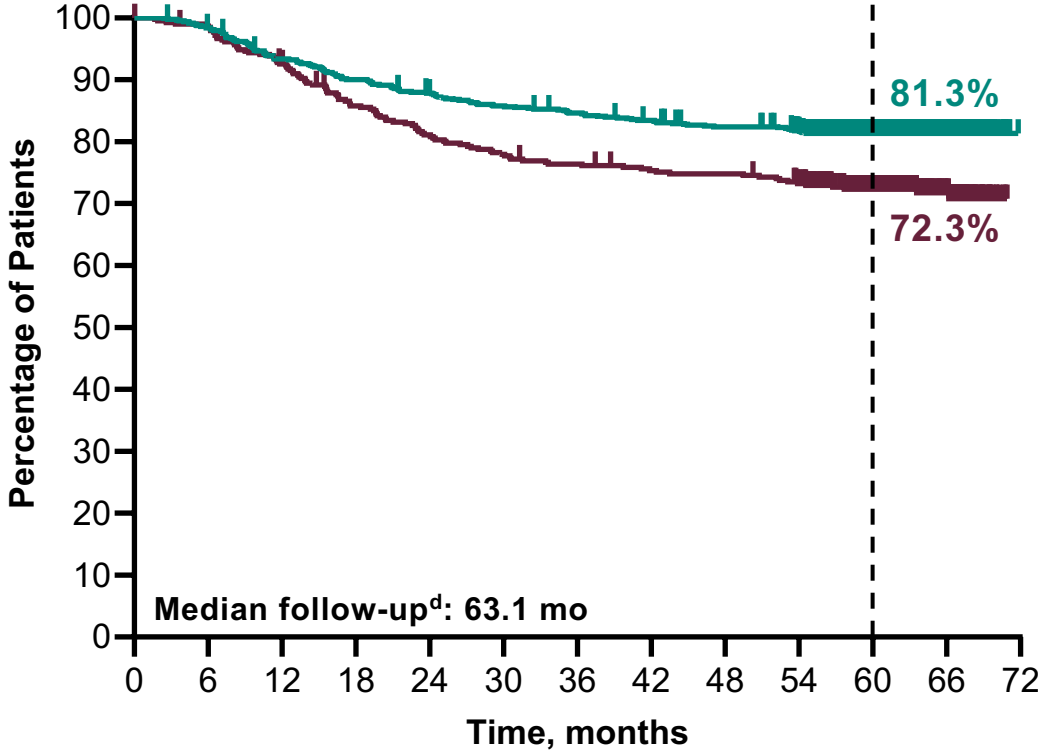
IA4	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Placebo + Chemo/Placebo	23.8%		



No. at risk

784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

IA6	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[a] (0.49-0.81)
Placebo + Chemo/Placebo	27.7%	



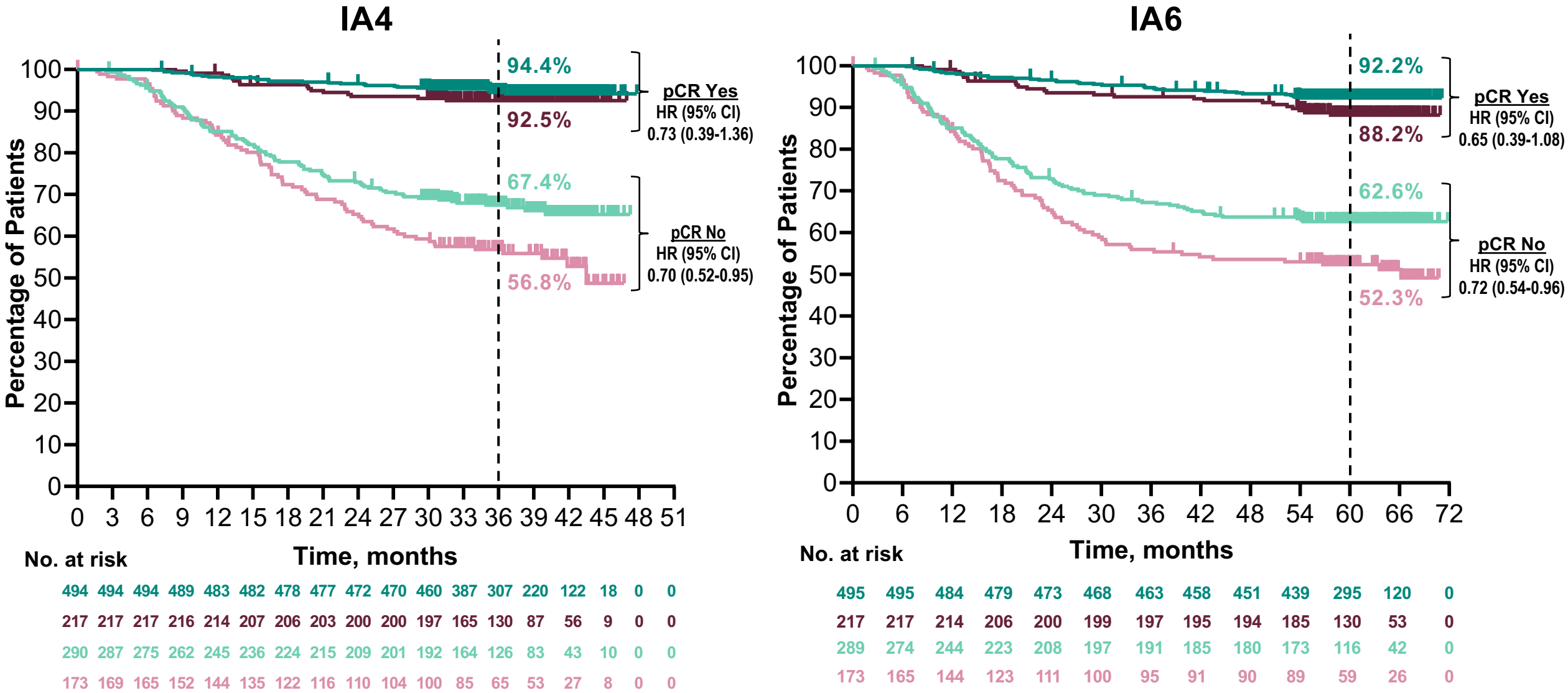
No. at risk

784	769	728	702	681	665	654	643	631	612	411	162	0
390	382	358	329	311	299	292	286	284	274	189	79	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 was crossed. [c]Defined as the time from randomization to the data cutoff date of March 23, 2021. [d]Defined as the time from randomization to the data cutoff date of March 23, 2023.

Courtesy of Sara M Tolaney, MD, MPH

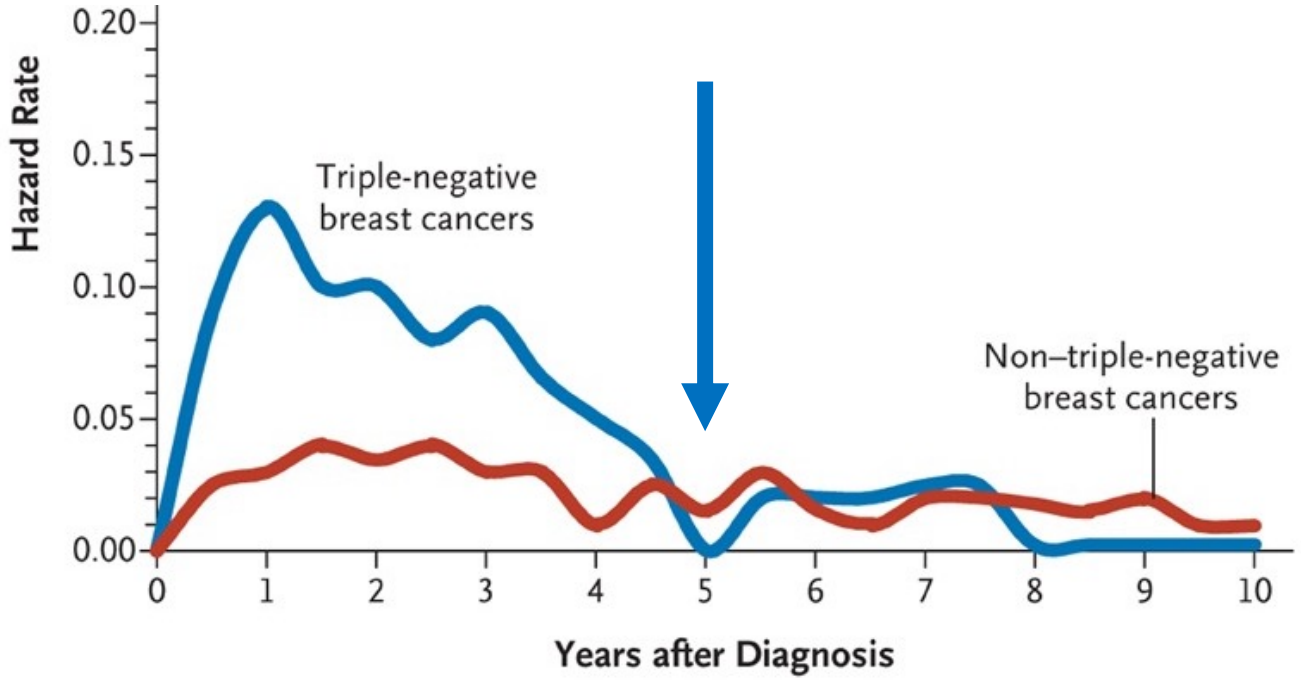
KEYNOTE-522: EFS by pCR (ypT0/Tis ypN0)



Courtesy of Sara M Tolaney, MD, MPH

pCRs are not all the same

Likely Increasing Cure Rates with Pembrolizumab



Trial	iDFS Median Follow-up
KEYNOTE-522	63.1 months

Courtesy of Sara M Tolaney, MD, MPH

Foulkes WD et al NEJM 2010; Schmid P et al ESMO 2023

NeoTRIP: Phase III open-label randomized trial

*HER-2 negative, ER and PgR negative early high-risk (T1cN1; T2N1; T3N0) or locally advanced unilateral breast cancer

R

**Carboplatin + *nab*-paclitaxel weekly for 2 wks every 3 for 8 cycles → S → AC/EC/FEC for 4 cycles

Carboplatin + *nab*-paclitaxel weekly for 2 wks every 3 for 8 cycles **+ Atezolizumab day 1 every 3 wks for 8 cycles → S → AC/EC/FEC for 4 cycles

FOLLOW UP

*ER, PgR, HER2 and PD-L1 (SP142; pos ≥ 1% IC) were centrally assessed before randomization

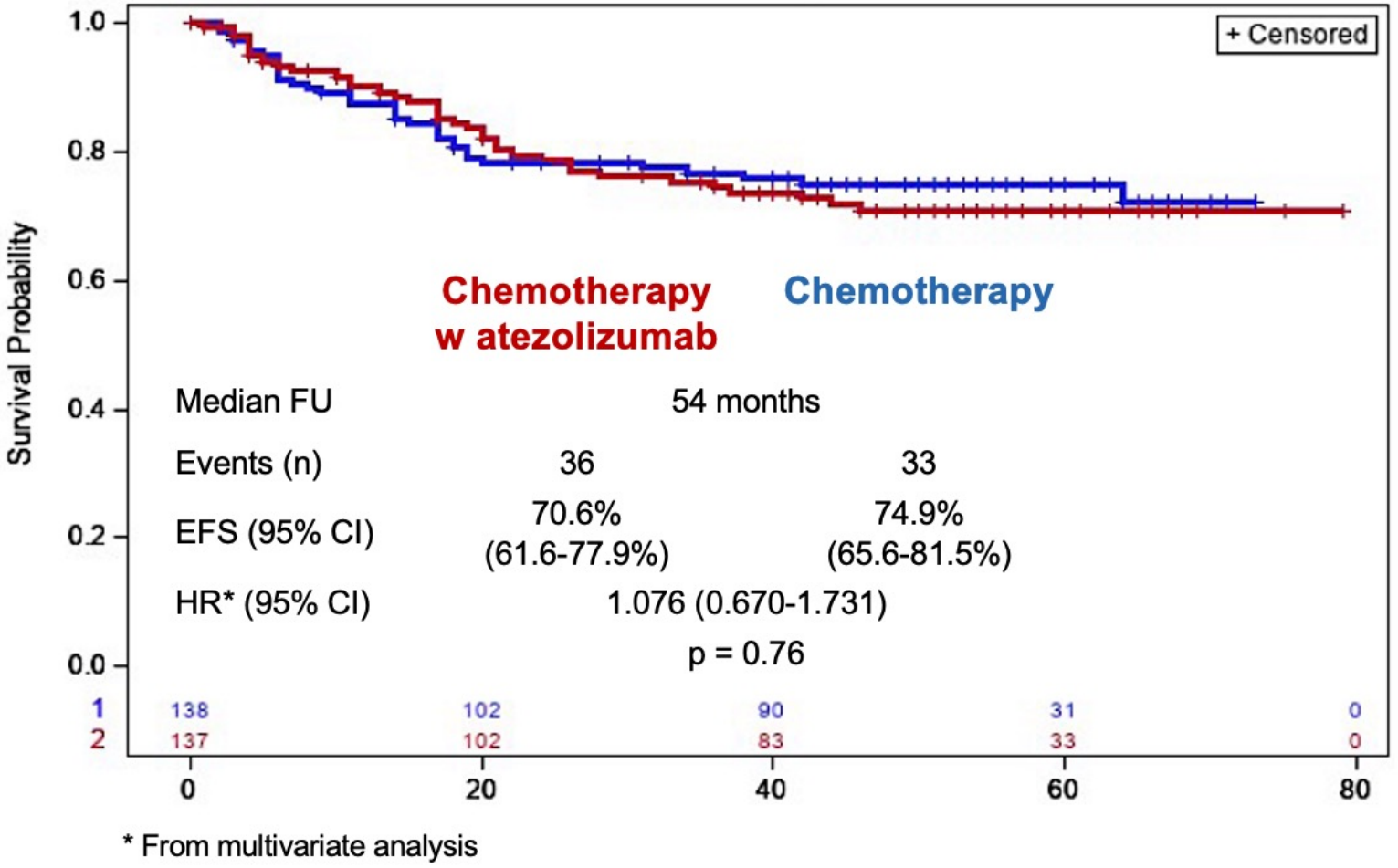
Tumour & Blood Banked for Correlative Studies

** carboplatin AUC 2 and nab-paclitaxel 125 mg/m^2 on d1,8 q 3 wks; atezolizumab 1200 mg d1 q3 wks

Courtesy of Sara M Tolaney, MD, MPH

Gianni et al, LBA 19, ESMO 2023

NeoTRIP 5-yr Event Free Survival



Why is there no benefit?

- Lack of anthracycline
- PD-L1i is less effective than PD-1i
- Imbalanced arms: higher TIL in the control arm
- Very high-risk tumors

Courtesy of Sara M Tolaney, MD, MPH

Gianni et al, LBA 19, ESMO 2023

Case Presentation – Dr Tolaney: Preoperative checkpoint inhibition for TNBC

- 44 yo premenopausal woman presented with a palpable breast mass
- Mammogram: 4x2x1.8 cm mass
- Breast MRI: 35 x 51x19 mm mass, prominent axillary LNs
- US axilla with prominent axillary node with cortical thickening
- Breast biopsy grade 3 iDC ER 0 PR 0 HER2 0
- FNA axillary node +
- Started preop carbo/paclitaxel/pembrolizumab
- 3 wks later--> ED with chest pain; Chest CT with no PE, but small pericardial effusion, ECHO confirmed this; negative troponin, cardiology felt c/w pericarditis and started on colchicine and ibuprofen
- Cardiac MRI done and repeat cardiac enzymes negative, symptoms resolved
- Followed EKG and troponins and restarted pembrolizumab
- Developed hypothyroidism
- Admitted after AC #2 for febrile neutropenia
- Went to surgery: 1cm residual disease, node-negative
- Received adjuvant capecitabine and pembrolizumab

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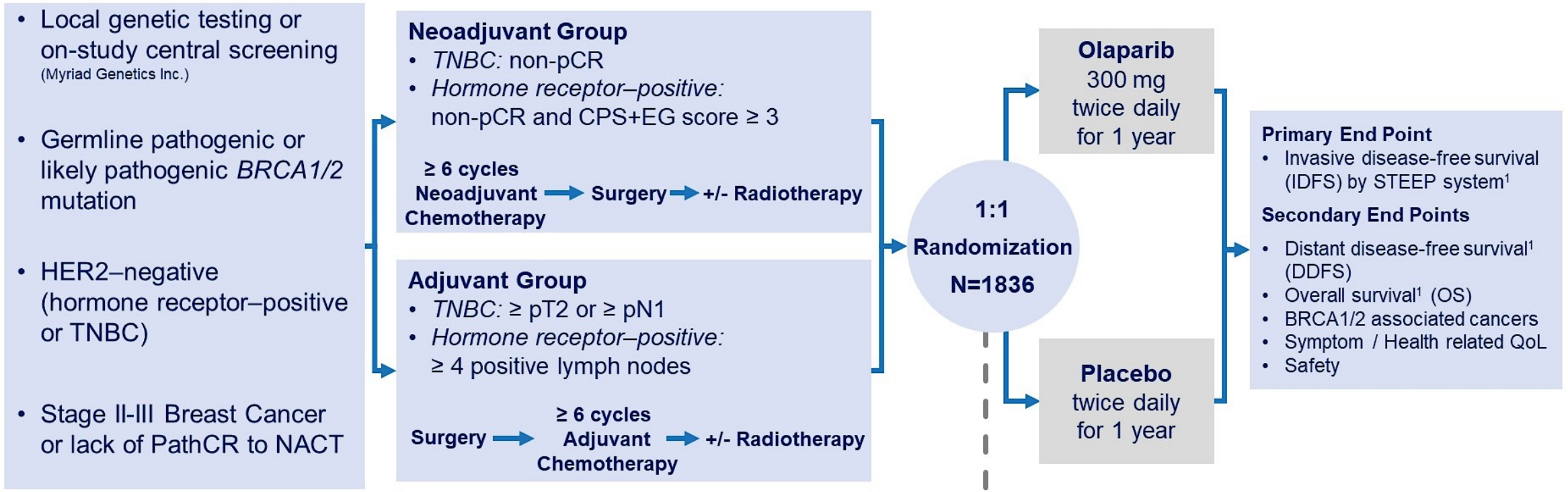
MODULE 3: PARP inhibition in BRCA-mutated localized BC

MODULE 4: Antibody-drug conjugates in metastatic disease (trastuzumab deruxtecan, sacituzumab govitecan, datopotamab deruxtecan, patritumab deruxtecan)

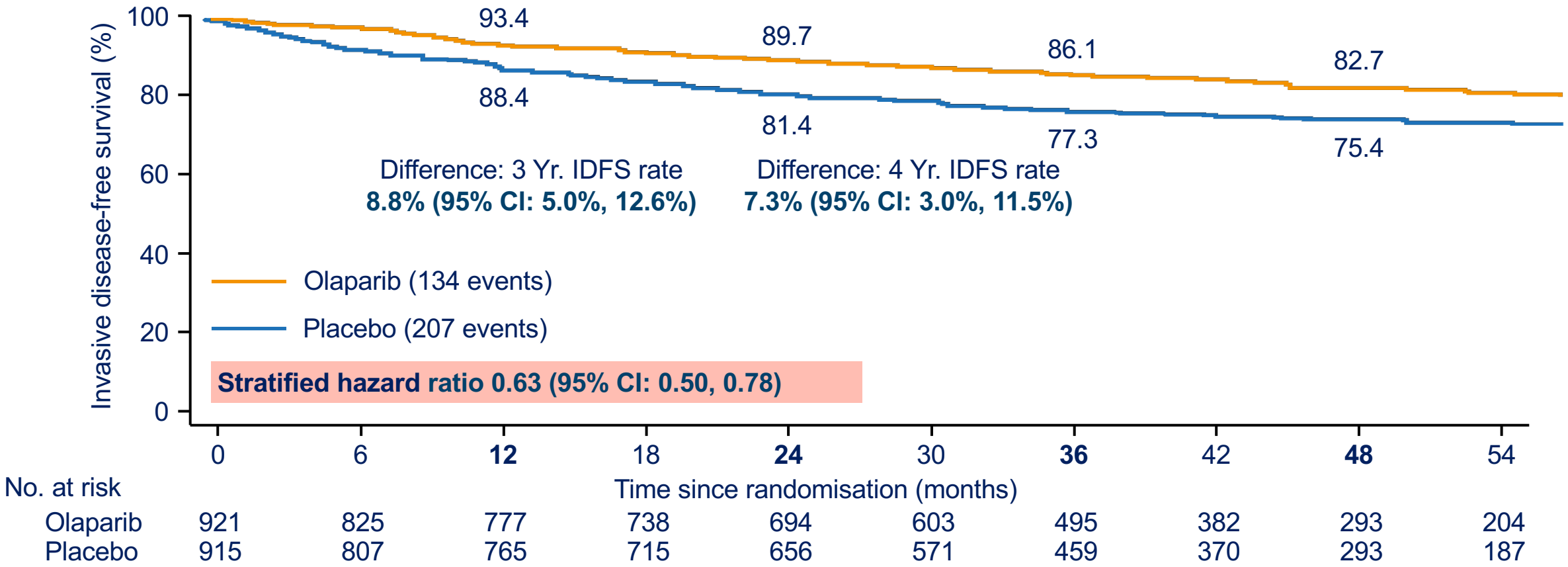
OlympiA: Study Design



Tutt A et al. ASCO 2021

Courtesy of Sara M Tolaney, MD, MPH

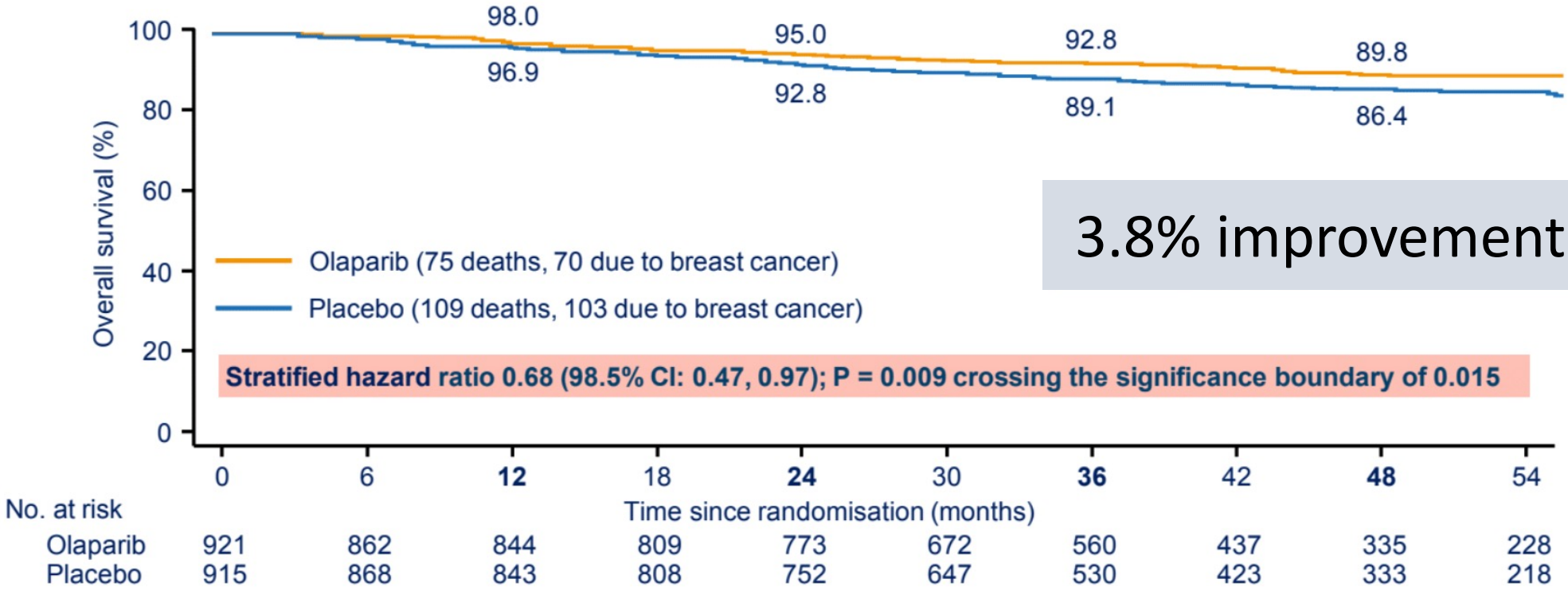
OlympiA: iDFS



Tutt A et al, ESMO Virtual Plenary 2022

Courtesy of Sara M Tolaney, MD, MPH

OlympiA: Overall Survival



3.8% improvement in OS at 36 mo

Courtesy of Sara M Tolaney, MD, MPH

Tutt A et al. ESMO Virtual Plenary 2022

Case Presentation – Dr Tolaney: Adjuvant olaparib

- 49 yo woman with known BRCA1 mutation had been undergoing MRI and mammogram screening
- Found to have a 1.8 cm TNBC with negative axillary US
- Rev’d preop ddACT
- 5mm residual disease
- Started olaparib 3 months ago
- Initial nausea resolved with ondansetron

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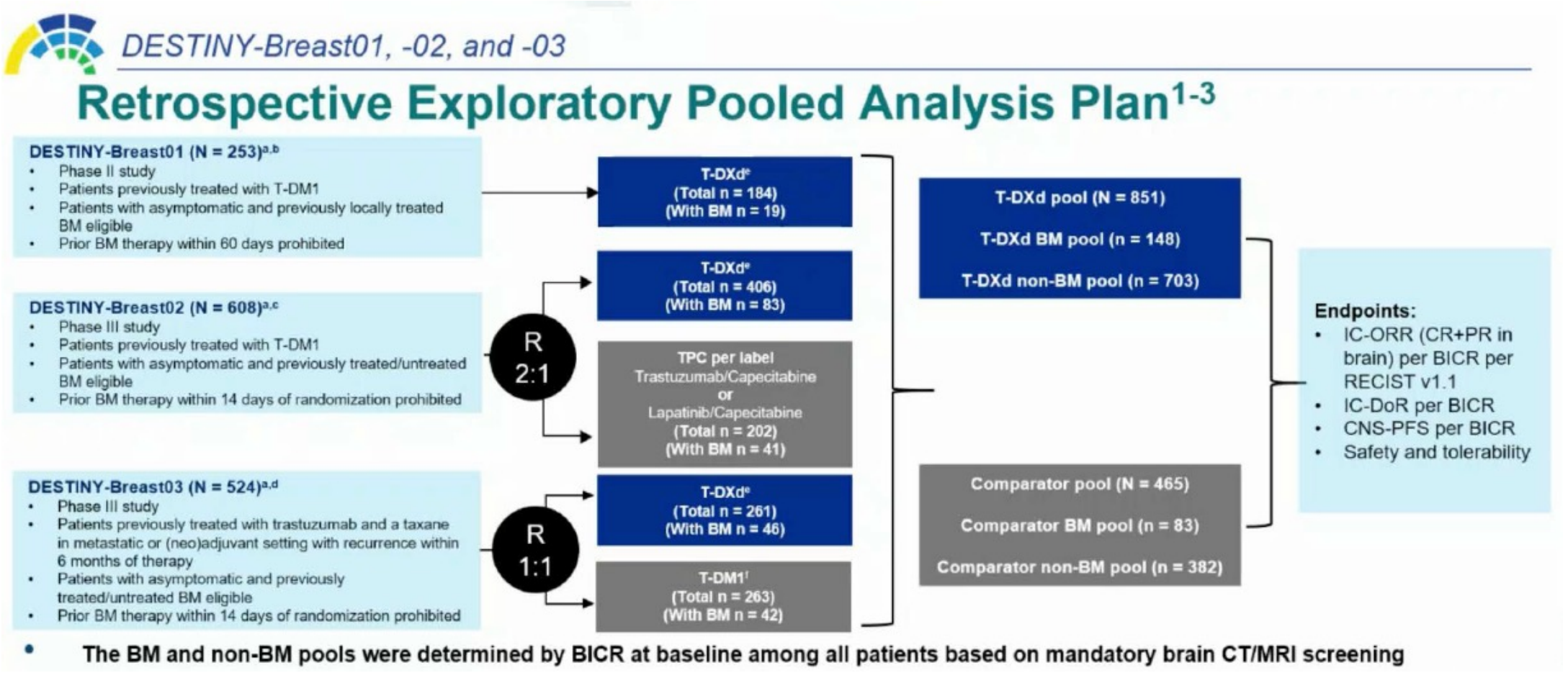
T-DXd in brain mets (pooled analysis)



Hurvitz SA et al. ESMO 2023;Abstract 377O.

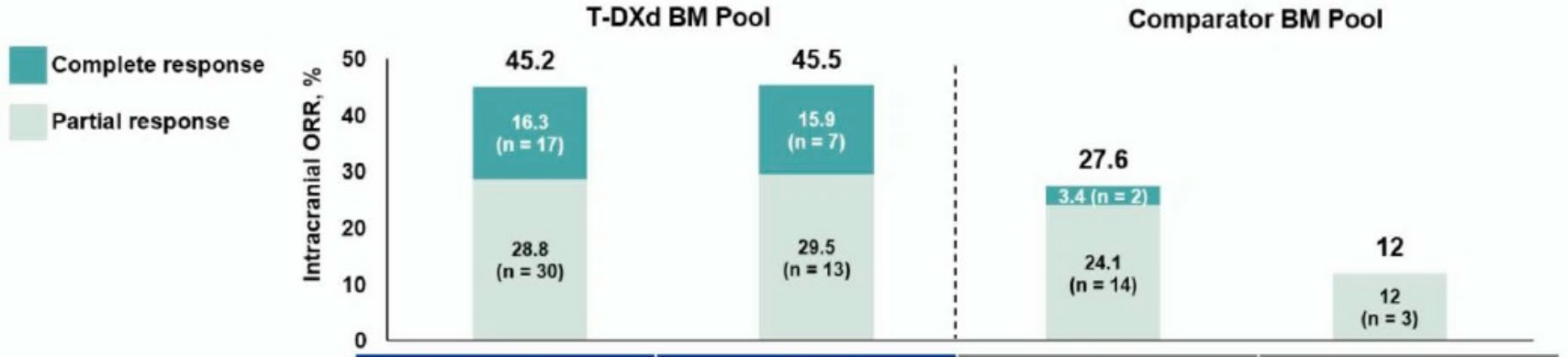
Courtesy of Aditya Bardia, MD, MPH

T-DXd in brain mets (pooled analysis)

DESTINY-Breast01, -02, and -03

Exploratory Best IC Response, ORR, and DoR per BICR

Intracranial ORR[a]



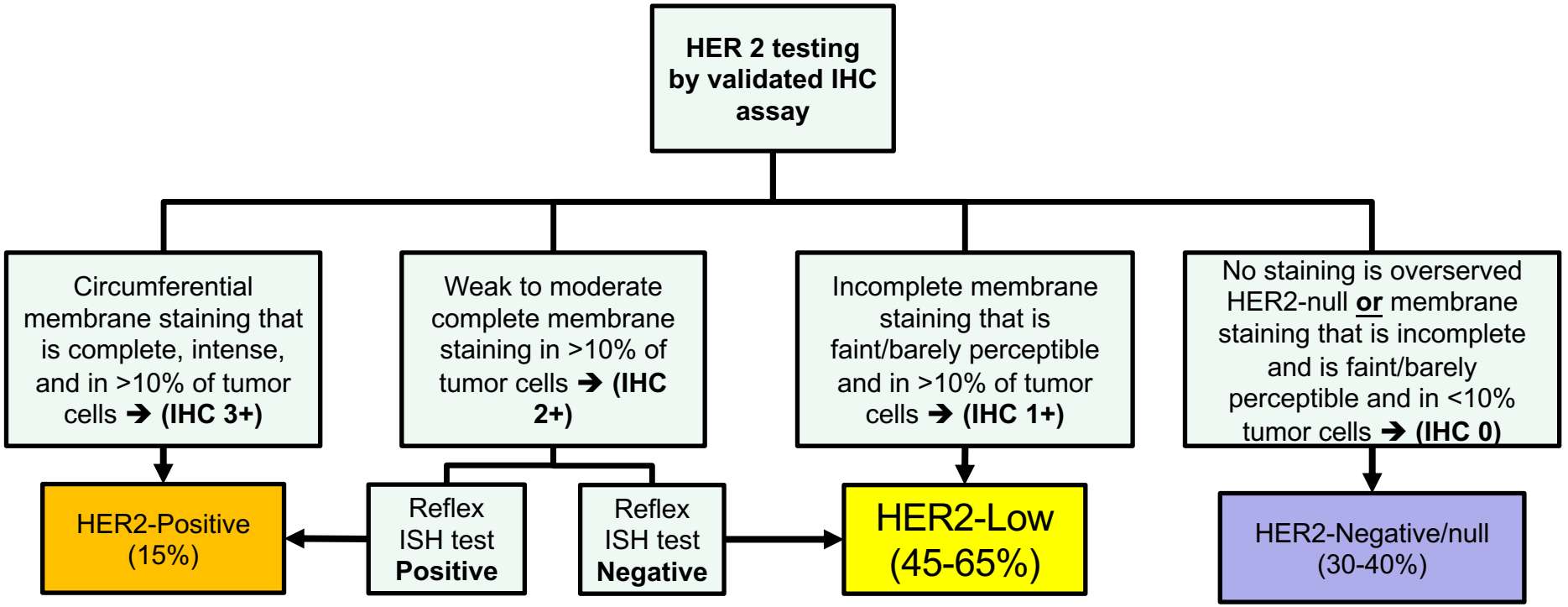
	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall IC response, n (%)				
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
Not evaluable/Missing	6 (5.8)	8 (18.2)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

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

Hurvitz SA et al. ESMO 2023;Abstract 377O.

Courtesy of Aditya Bardia, MD, MPH

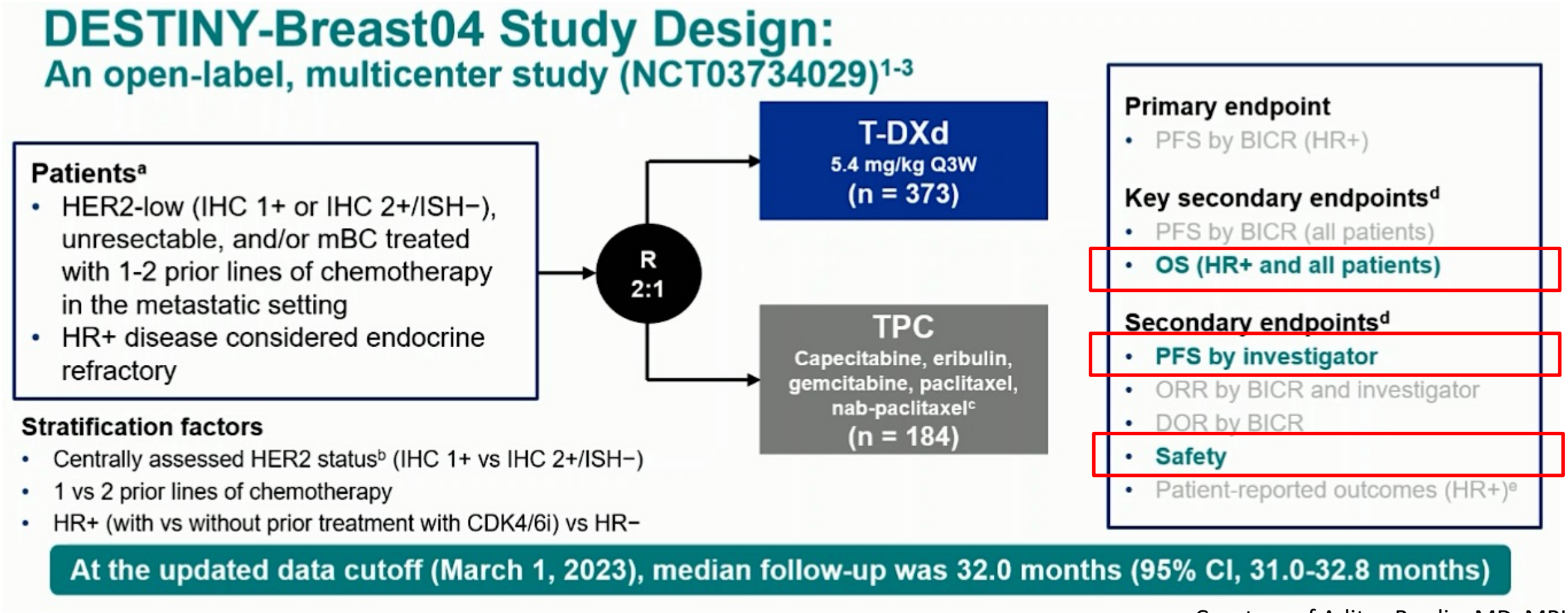
HER2-Low Breast Cancer: Current Definition



Courtesy of Aditya Bardia, MD, MPH

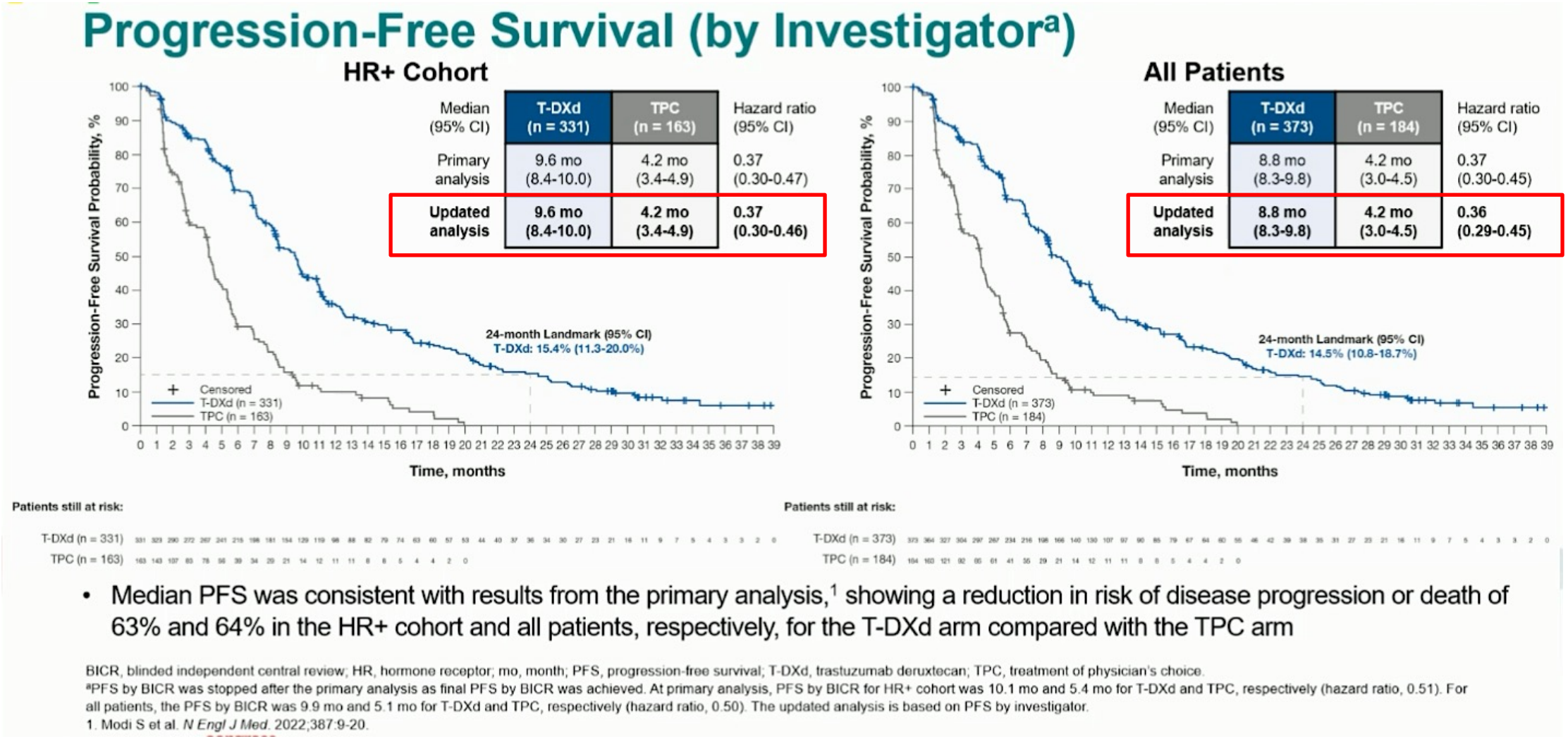
Phase 3 DESTINY-Breast04: Study Design

(T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Updated survival results



Courtesy of Aditya Bardia, MD, MPH

T-DXd in HER2 low (DESTINY-B04)



- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

BICR, blinded independent central review; HR, hormone receptor; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.

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

Modi S et al. ESMO 2023;Abstract 376O.

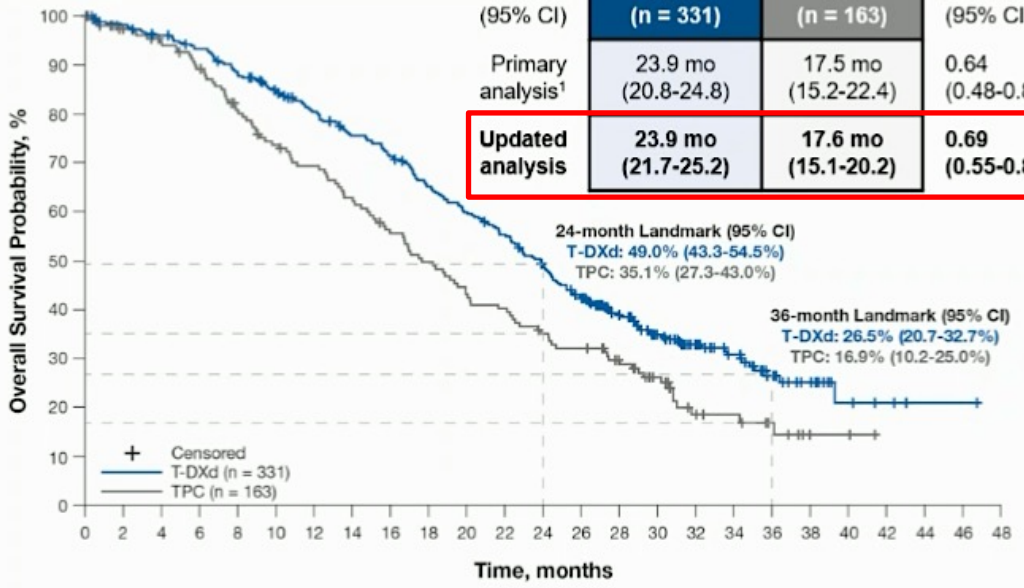
Courtesy of Aditya Bardia, MD, MPH

T-DXd in HER2 low (DESTINY-B04)

Overall Survival

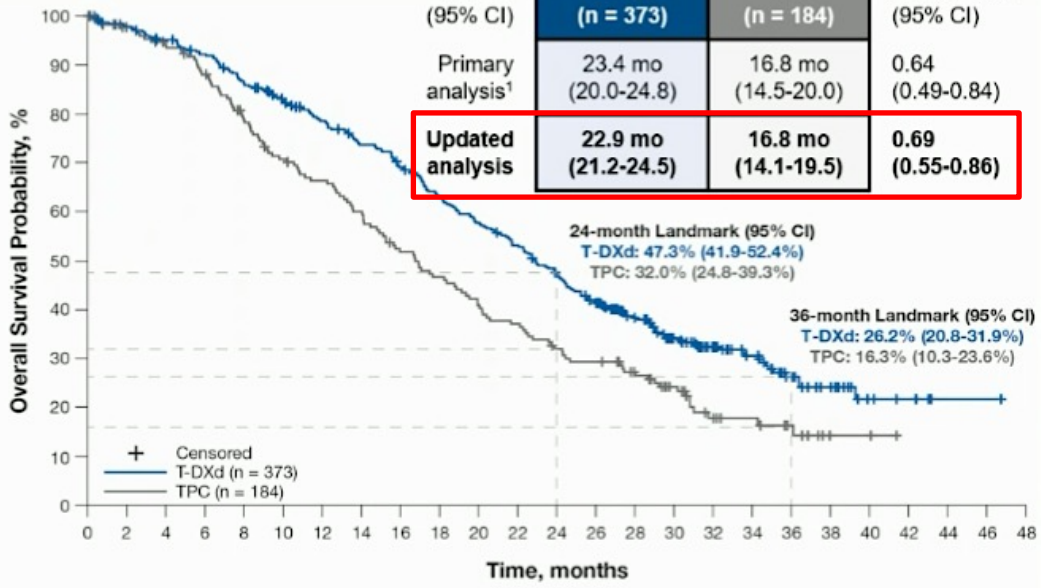
HR+ Cohort

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



All Patients

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



- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

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

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

Courtesy of Aditya Bardia, MD, MPH

T-DXd in HER2m (basket study)

DESTINY-PanTumor01

A Phase 2 study of T-DXd in patients with solid tumors harboring HER2m (NCT04639219)

Key eligibility criteria
- Patients with unresectable and/or metastatic solid tumors with locally determined prespecified HER2m
- Progression after prior treatment or with no satisfactory alternative treatment options
- Prior HER2-targeting therapy allowed

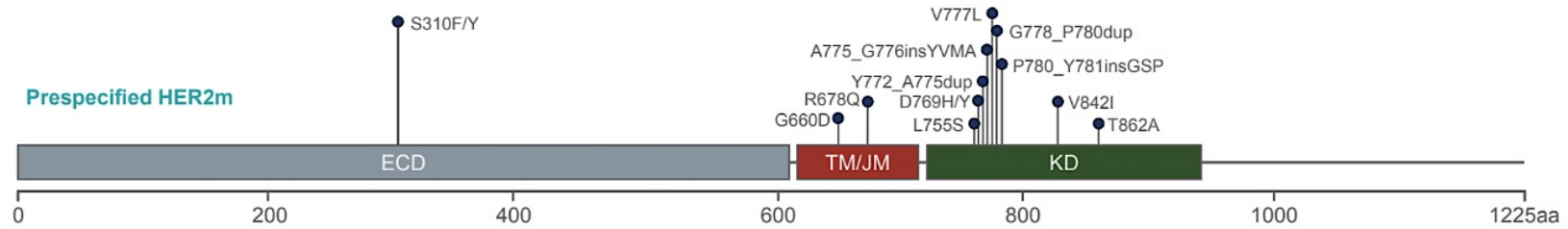
Key exclusion criteria
- HER2-positive (IHC 3+ or IHC 2+/ISH+) breast, gastric, or gastroesophageal junction cancer or HER2-mutant NSCLC
- History of non-infectious ILD/pneumonitis, current ILD, or suspected ILD that cannot be ruled out by imaging at screening

T-DXd
5.4 mg/kg
Q3W

Approx 100 participants
(max 20 per tumor type)

Primary endpoint
- Confirmed ORR (ICR)

Secondary endpoint
- DOR
- DCR
- Confirmed ORR (investigator assessed)
- PFS
- OS
- Safety and tolerability



DCR, disease control rate; DOR, duration of response; ECD, extracellular domain; HER2, human epidermal growth factor receptor 2; HER2m, activating HER2 mutations; ICR, independent central review; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; KD, kinase domain; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TM/JM, transmembrane/juxtamembrane domain

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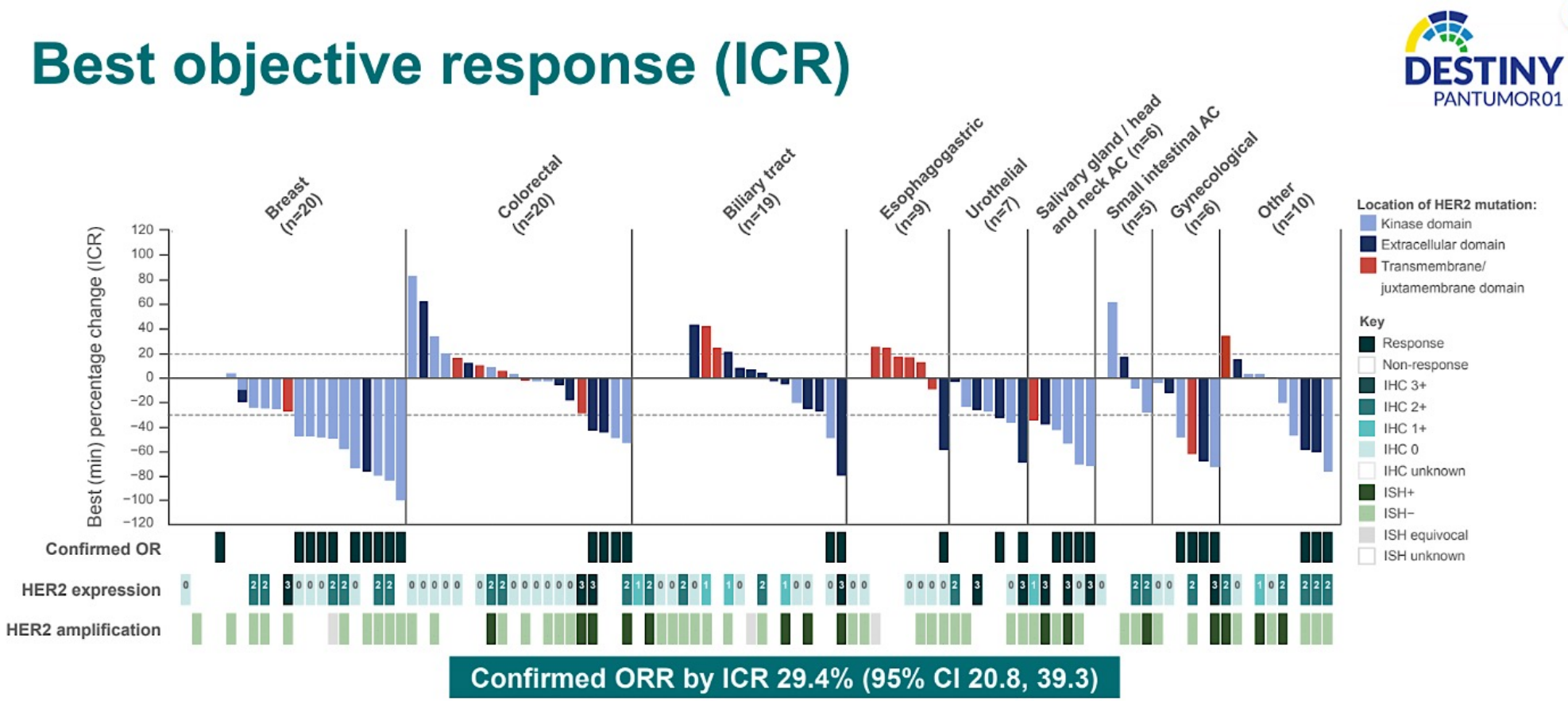
Courtesy of Aditya Bardia, MD, MPH

Patient disposition

Li B et al. ESMO 2023;Abstract 654O.

T-DXd in HER2m (basket study)

Best objective response (ICR)



Confirmed ORR by ICR 29.4% (95% CI 20.8, 39.3)

HER2 expression and amplification by central testing. Dashed reference lines at −30% and 20% indicate thresholds for partial response and progression, respectively. Confirmed OR as assessed by ICR according to all components of RECIST v1.1 (including best response in target lesion). Gynecological tumor types include cervical, endometrial, and ovarian. 'Other' tumor types includes esophageal, other neuroendocrine tumors, pancreatic, adenocarcinoma of unknown primary, extramammary Paget's disease, melanoma, and urachal. 3 patients had 2 distinct HER2 mutations

AC, adenocarcinoma; CI, confidence interval; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; min, minimum; OR, objective response; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors

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Bob T Li

Li B et al. ESMO 2023;Abstract 654O.

Courtesy of Aditya Bardia, MD, MPH

Case Presentation – Dr Bardia: 55F with HR+ MBC

55F with metastatic HR+ MBC (HER2 IHC = 1). Disease progression on various endocrine based therapy, and recently capecitabine and paclitaxel. PS = 1. No organ dysfunction. gBRCA = negative. PIK3CA and ESR1 WT. What therapy would you consider next?

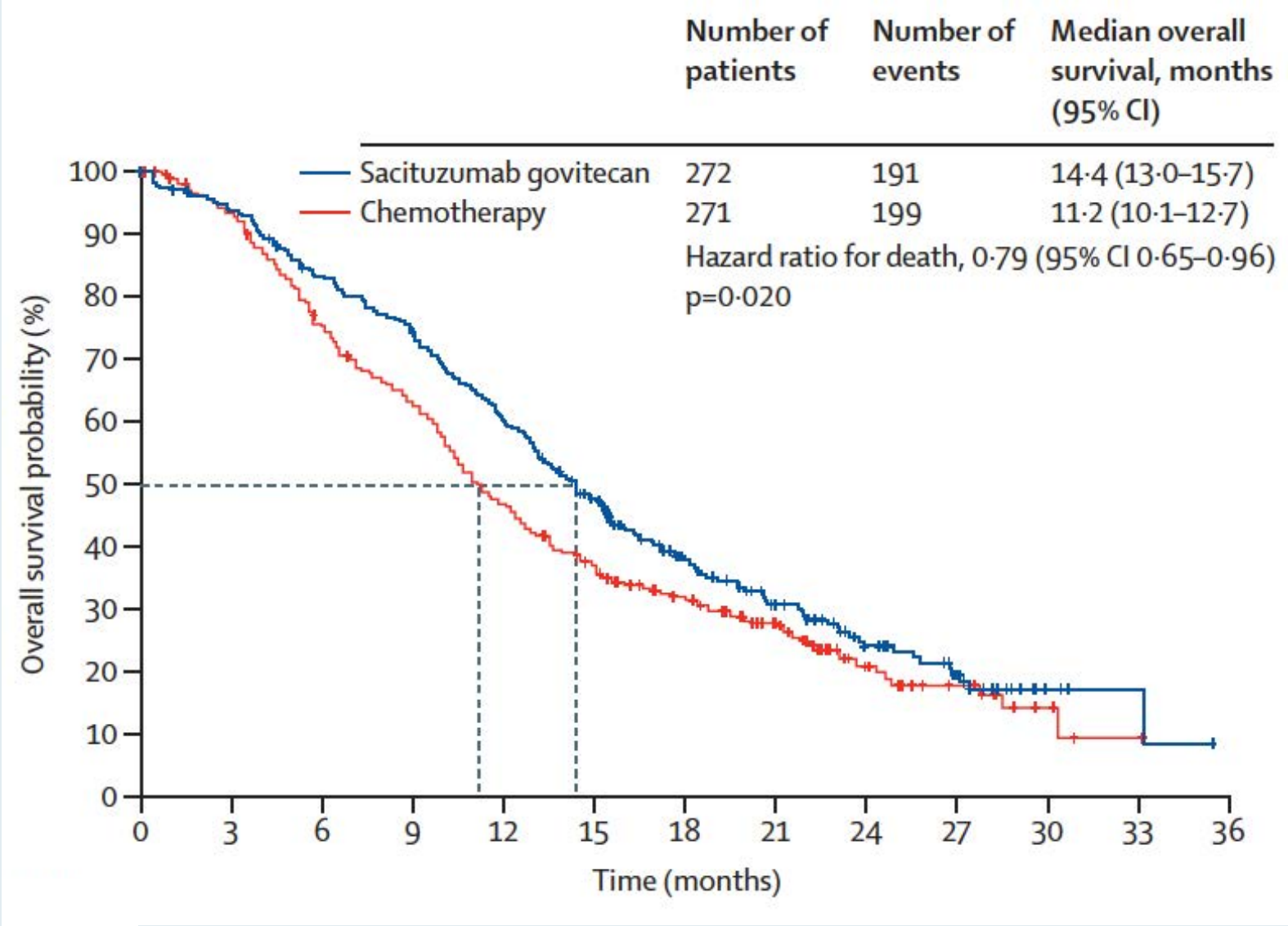
1. Eribulin
2. Vinorelbine
3. Sacituzumab Govitecan (SG)
4. Trastuzumab Deruxtecan (T-DXd)

Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial

Hope S Rugo, Aditya Bardia*, Frederik Marmé, Javier Cortés, Peter Schmid, Delphine Loirat, Olivier Trédan, Eva Ciruelos, Florence Dalenc, Patricia Gómez Pardo, Komal L Jhaveri, Rosemary Delaney, Theresa Valdez, Hao Wang, Monica Motwani, Oh Kyu Yoon, Wendy Verret, Sara M Tolaney*

***Lancet* 2023 October 21;402(10411):1423-33**

TROPiCS-02: Overall Survival in the Intention-to-Treat Population



Rugo HS et al. *Lancet* 2023 October 21;402(10411):1423-33.

Efficacy and Safety Analyses by Prior Lines of Chemotherapy from the Phase III TROPiCS-02 Study of Sacituzumab Govitecan (SG) vs Treatment of Physician's Choice (TPC) in Patients (pts) with HR+/HER2- Metastatic Breast Cancer (mBC)

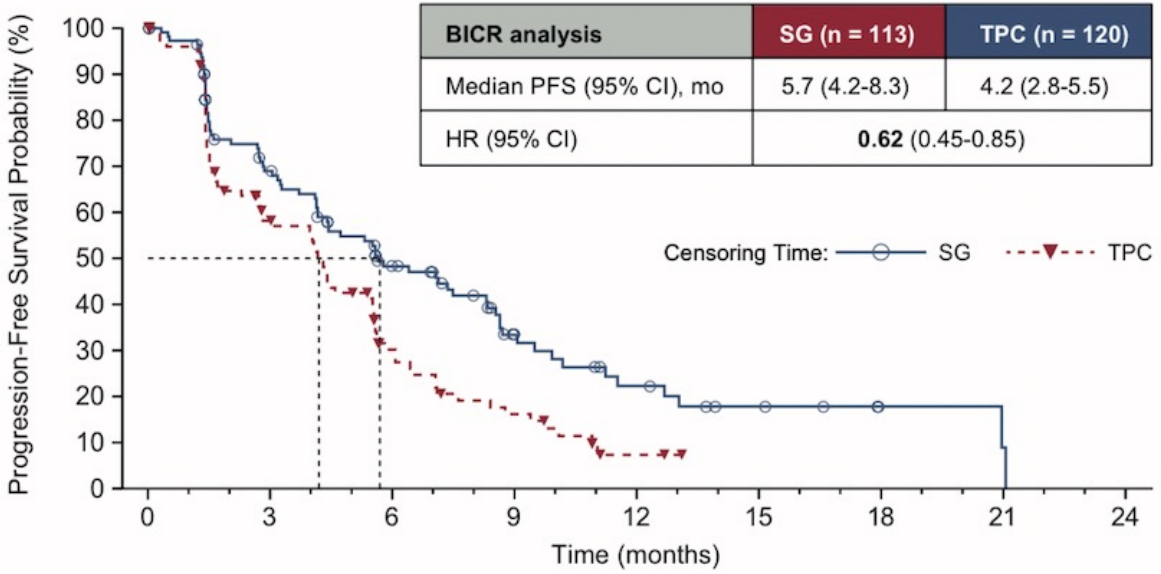
Cortés J et al.

ESMO 2023;Abstract 389P.

TROPiCS-02: PFS by Prior Lines of Chemotherapy (LoT)

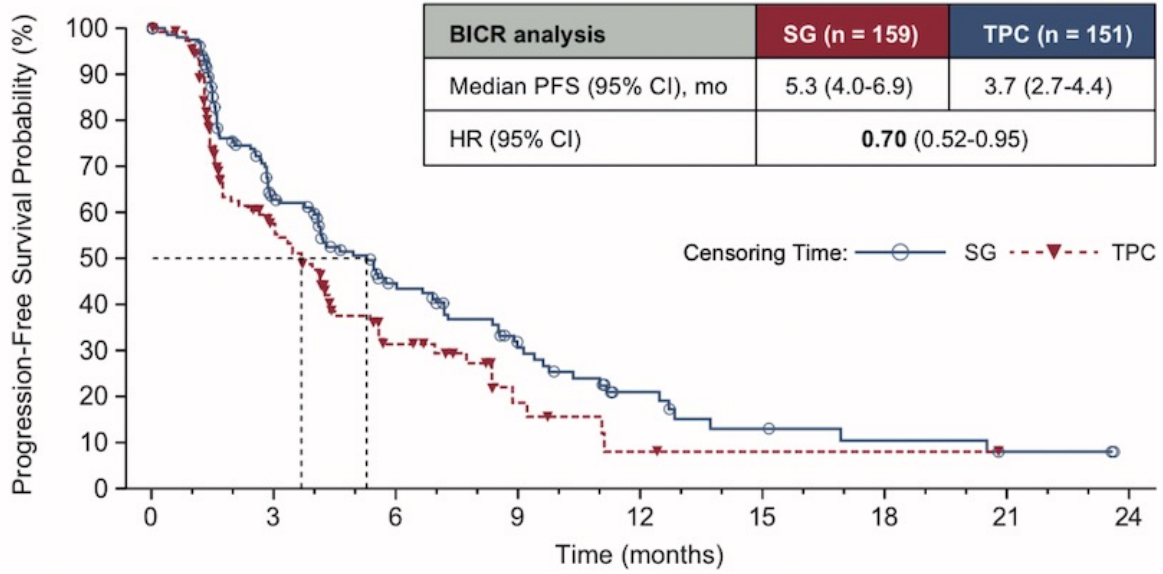
≤ 2 Prior LoT

BICR analysis	SG (n = 113)	TPC (n = 120)
Median PFS (95% CI), mo	5.7 (4.2-8.3)	4.2 (2.8-5.5)
HR (95% CI)	**0.62** (0.45-0.85)	



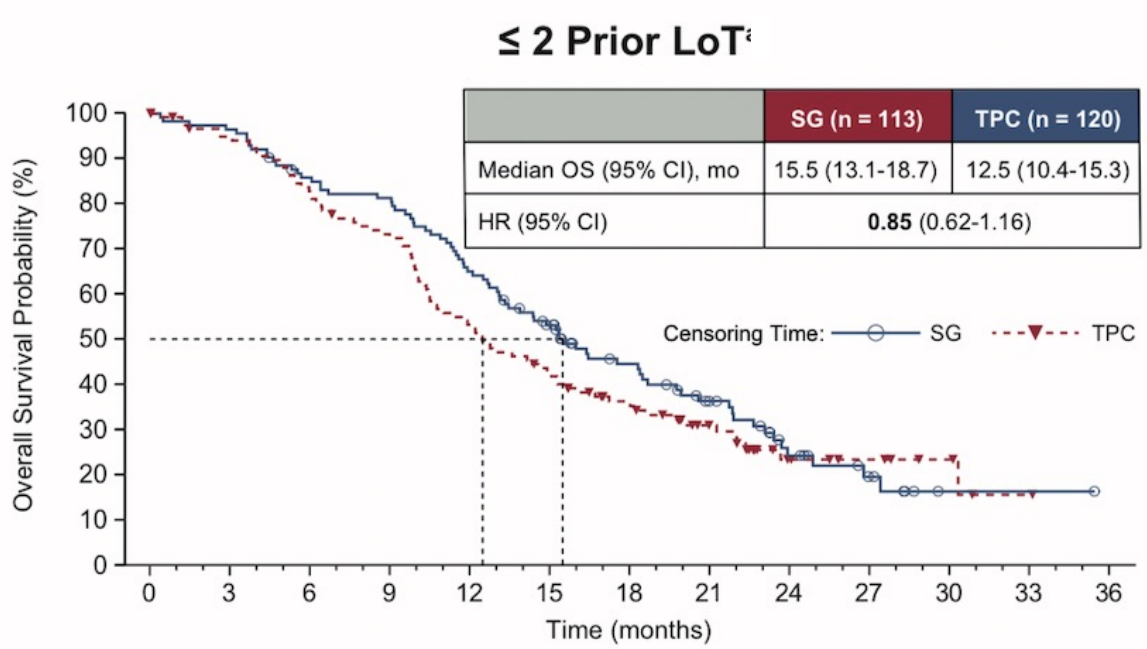
≥ 3 Prior LoT

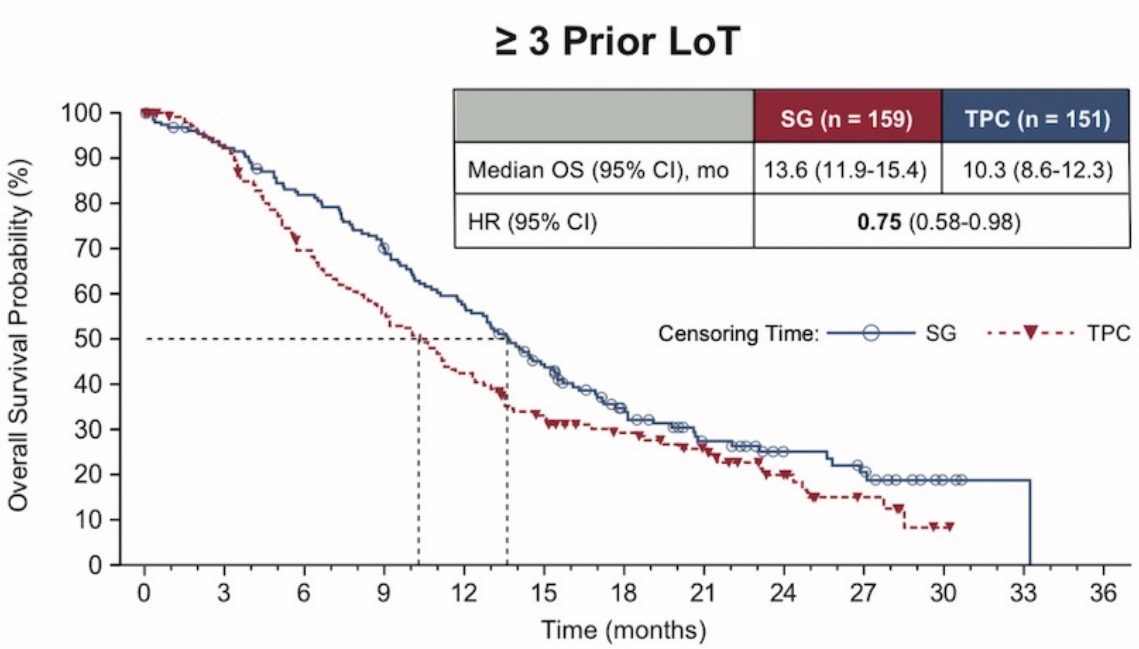
BICR analysis	SG (n = 159)	TPC (n = 151)
Median PFS (95% CI), mo	5.3 (4.0-6.9)	3.7 (2.7-4.4)
HR (95% CI)	**0.70** (0.52-0.95)	



Cortés J et al. ESMO 2023;Abstract 389P.

TROPiCS-02: OS by Prior Lines of Chemotherapy (LoT)

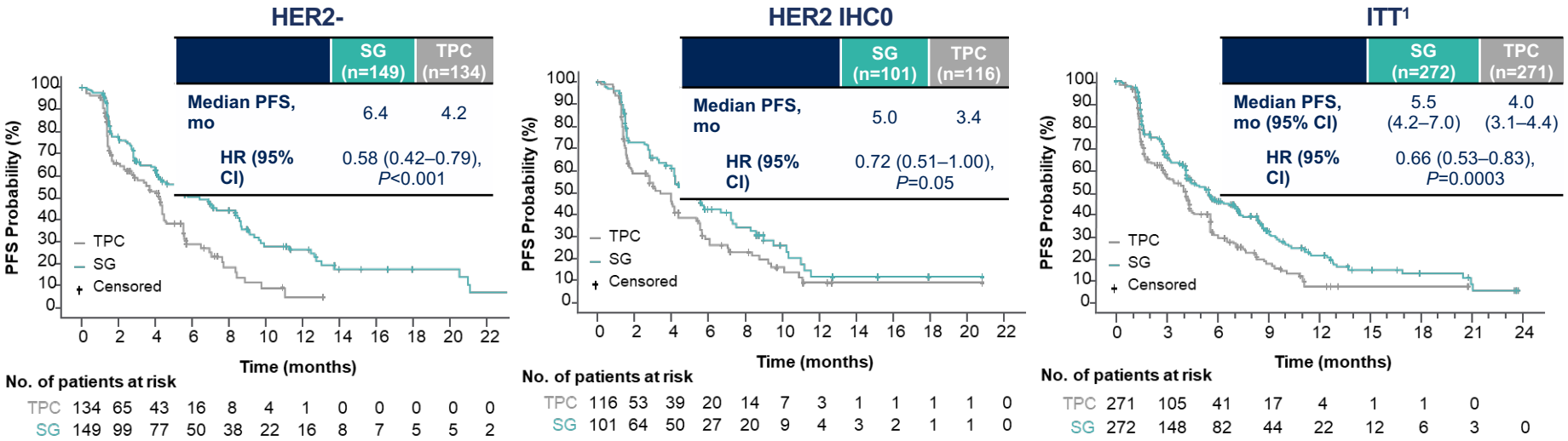




Cortés J et al. ESMO 2023;Abstract 389P.

RTP RESEARCH TO PRACTICE

Sacituzumab Govitecan vs TPC: Efficacy by HER2 status (TROPiCS-02)



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

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.
[b]39 patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-low, consistent with the trial eligibility criteria to enroll HER2-negative patients.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol.* 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print). Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.* 2022. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology.

Presented by: Dr. Frederik Marmé

Courtesy of Aditya Bardia, MD, MPH

Case Presentation – Dr Bardia: 65F with HR+ MBC

65F with metastatic HR+ MBC (HER2 IHC = 0). Disease progression on various endocrine based therapy, and recently capecitabine and paclitaxel. PS = 1. No organ dysfunction. gBRCA = negative. PIK3CA and ESR1 WT. What therapy would you consider next?

1. Eribulin
2. Vinorelbine
3. Sacituzumab Govitecan (SG)
4. Trastuzumab Deruxtecan (T-DXd)

Background: Dato-DXd

- **Dato-DXd** is a **TROP2-directed ADC**, that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells,[1] and has several unique properties*:
  - Optimised drug to antibody ratio ≈ 4
  - Stable linker-payload
  - Tumour-selective cleavable linker
  - Bystander antitumour effect
- Dato-DXd previously demonstrated **promising antitumour activity** and a **manageable safety profile** with a convenient Q3W schedule in pre-treated patients with **metastatic HR+/HER2– BC**[2]

Dato-DXd: Humanised anti-TROP2 IgG1 monoclonal antibody

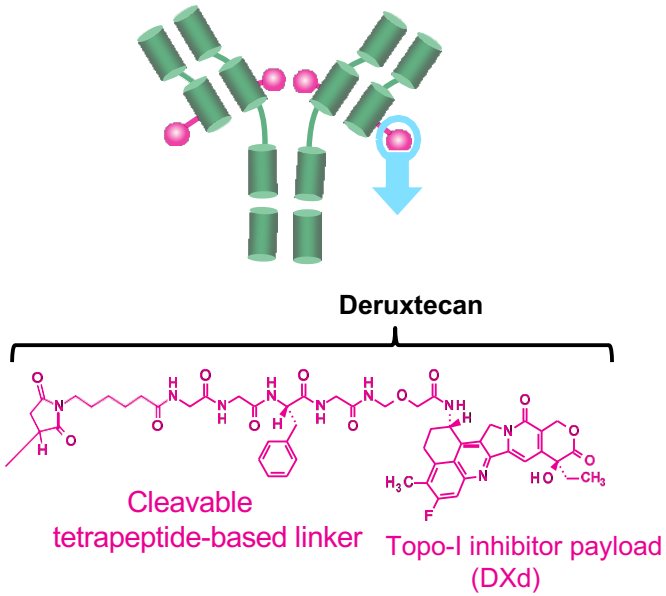


Image is for illustrative purposes only; actual drug positions may vary.

1. Okajima D, et al. *Mol Cancer Ther* 2021;20:2329–40;

2. Meric-Bernstam F, et al. Poster presentation at SABCS 2022: abstract PD13-08.

*The clinical relevance of these features is under investigation. Based on animal data.

Dato-DXd, datopotamab deruxtecan; IgG1, immunoglobulin G1; Q3W, every 3 weeks; Topo-I, topisomerase I.

Bardia A et al. ESMO 2023;Abstract LBA11.

Courtesy of Aditya Bardia, MD, MPH

Dato-DXd in HR+ MBC (TROPION-B01)

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

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

ICC
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Randomisation stratified by:

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

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

ICC: Investigator's choice of chemotherapy
Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W. BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy;

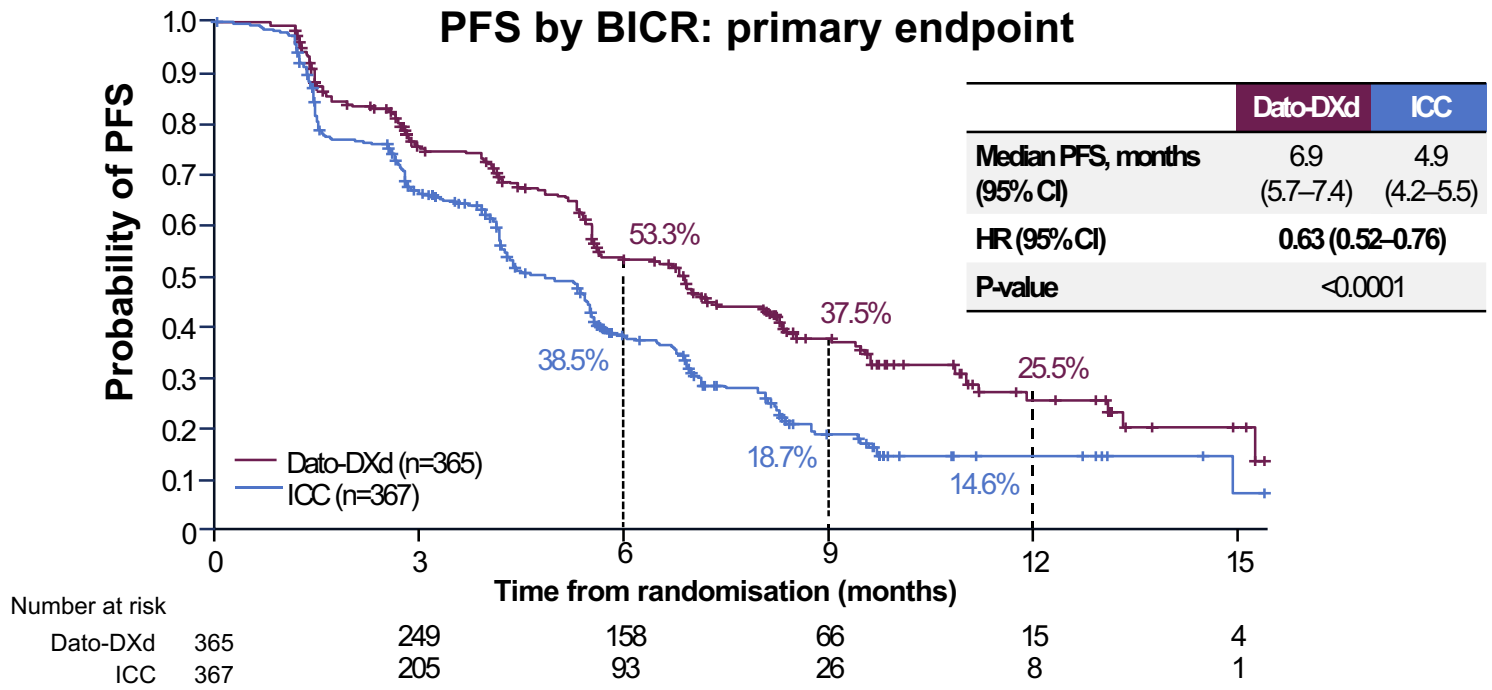
IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world.

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

Bardia A et al. ESMO 2023;Abstract LBA11.

Courtesy of Aditya Bardia, MD, MPH

Dato-DXd in HR+ MBC (TROPION-B01)



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

- **PFS by BICR was consistent across subgroups**

CI, confidence interval; HR, hazard ratio

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Bardia A et al. ESMO 2023;Abstract LBA11.

Courtesy of Aditya Bardia, MD, MPH

Dato-DXd in HR+ MBC (TROPION-B01)

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

- Most TRAEs were grade 1–2 and manageable

AESIs

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

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

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Bardia A et al. ESMO 2023;Abstract LBA11.

Courtesy of Aditya Bardia, MD, MPH

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Datopotamab Deruxtecan (Dato-DXd) + Durvalumab (D) as First-Line (1L) Treatment for Unresectable Locally Advanced/Metastatic Triple-Negative Breast Cancer (a/mTNBC)

Updated Results From BEGONIA, a Phase 1b/2 Study

Professor Peter Schmid, FRCP, MD, PhD

Barts Cancer Institute, Queen Mary University of London, London, UK

P. J. Wysocki,[1] C. X. Ma,[2] Y. H. Park,[3] R. Fernandes,[4] S. Lord,[5] R. D. Baird,[6] C. Prady,[7] K. H. Jung,[8] J. Asselah,[9] R. Huisden,[10] R. Stewart,[10] K. Heider,[10] P. Vukovic,[10] N. Denduluri,[11] Z. Nowecki[12]

[1]Jagiellonian University Medical College, Krakow, Poland; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [4]Schulich School of Medicine & Dentistry, Western University, London Health Sciences Centre, London, Ontario, Canada; [5]University of Oxford, Oxford, UK; [6]Cancer Research UK Cambridge Centre, Cambridge, UK; [7]Sherbrooke University, Centre intégré de cancérologie de la Montérégie, CISSS Montérégie Centre, Greenfield Park, Quebec, Canada; [8]Asan Medical Center - University of Ulsan, College of Medicine, Seoul, Korea; [9]McGill University Health Centre, Montreal, Québec, Canada; [10]AstraZeneca, Cambridge, UK; [11]AstraZeneca, Gaithersburg, MD, USA; [12]Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

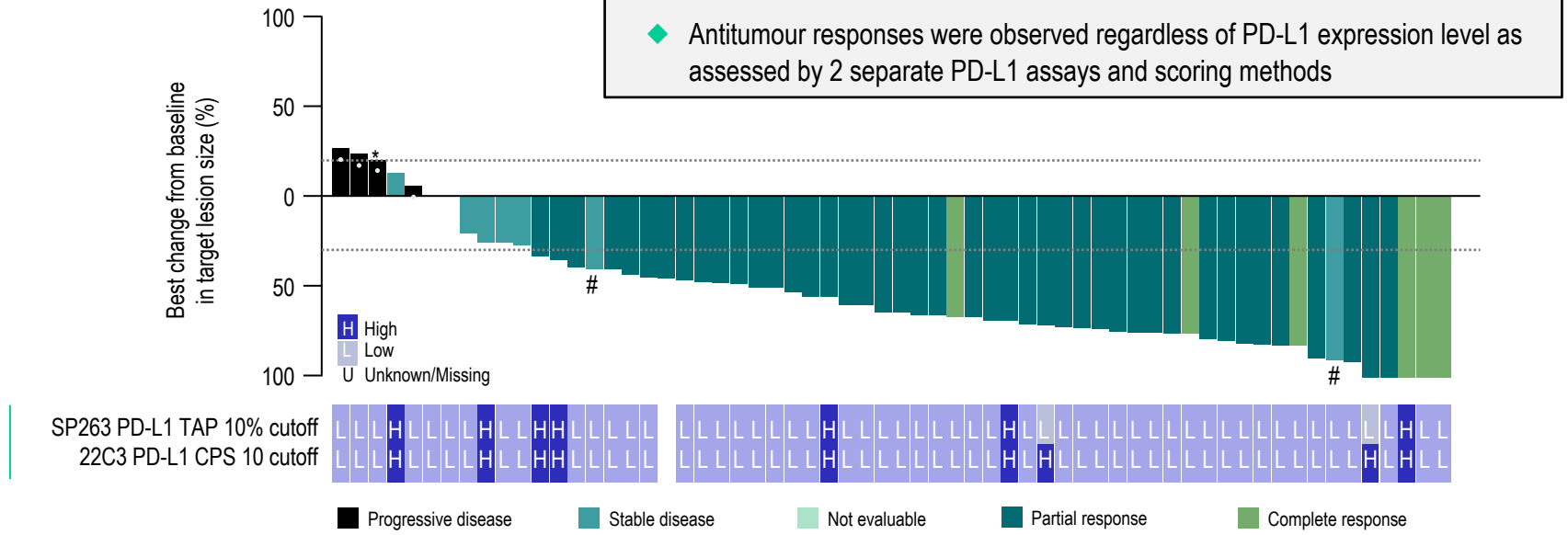
Courtesy of Aditya Bardia, MD, MPH

Dato-DXd and Durva (BEGONIA)

Antitumour Responses in 1L a/mTNBC

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%). PD-L1 expression was assessed by 1) immunohistochemistry using the VENTANA PD-L1 (SP263) Assay with expression defined as the percentage of the tumour area populated by tumour or immune cells with membranous staining (TAP), or 2) immunohistochemistry using the 22C3 antibody with expression defined as the number of PD-L1–staining tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100 (CPS). *If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with PD as best overall response. #Unconfirmed response.

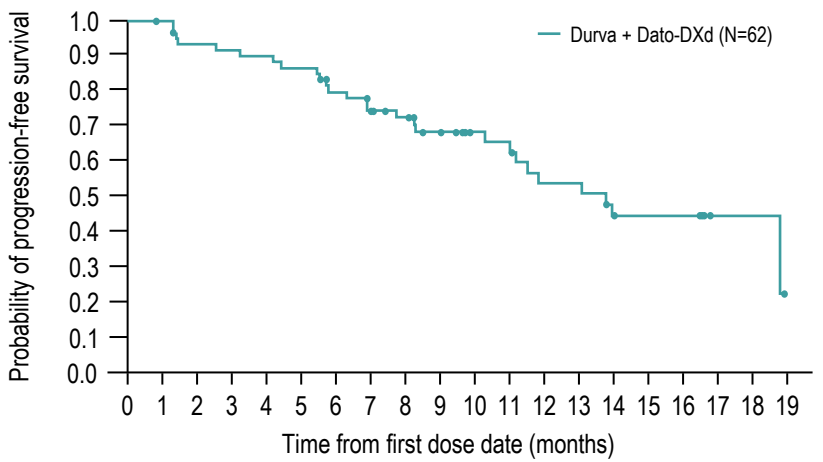
1L, first line; a/m TNBC, advanced/metastatic triple–negative breast cancer; CI, confidence interval; CPS, combined positive score; CR, complete response; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PR, partial response; TAP, tumour area positivity.

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

Courtesy of Aditya Bardia, MD, MPH

Dato-DXd and Durva (BEGONIA)

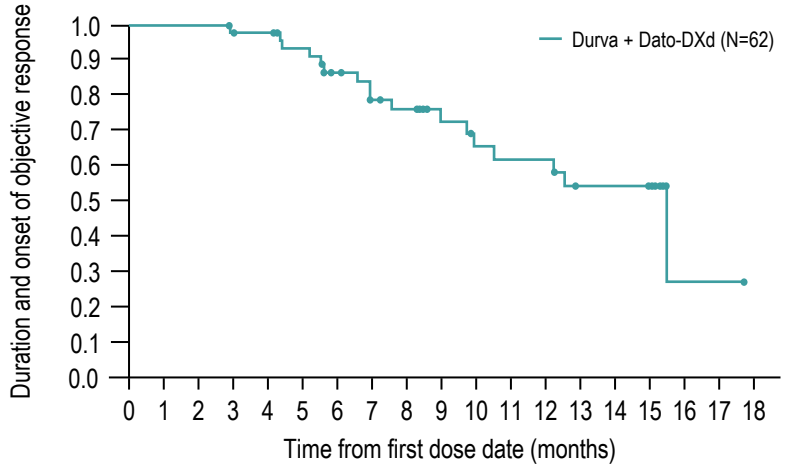
Median PFS was **13.8** months (95% CI, 11.0–NC)



Number of patients at risk

Durva + Dato-DXd	62	61	56	55	54	52	45	40	37	32	24	23	18	18	14	13	13	2	2	0

Median DoR was **15.5** months (95% CI, 9.92–NC)



Number of patients at risk

Durva + Dato-DXd	49	49	49	47	46	42	35	30	28	21	18	17	17	13	13	12	1	1	0

Kaplan-Meier analysis was performed. Circles indicate censored observations.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; PFS, progression-free survival.

Data cutoff: 02 Feb 2023

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

Courtesy of Aditya Bardia, MD, MPH

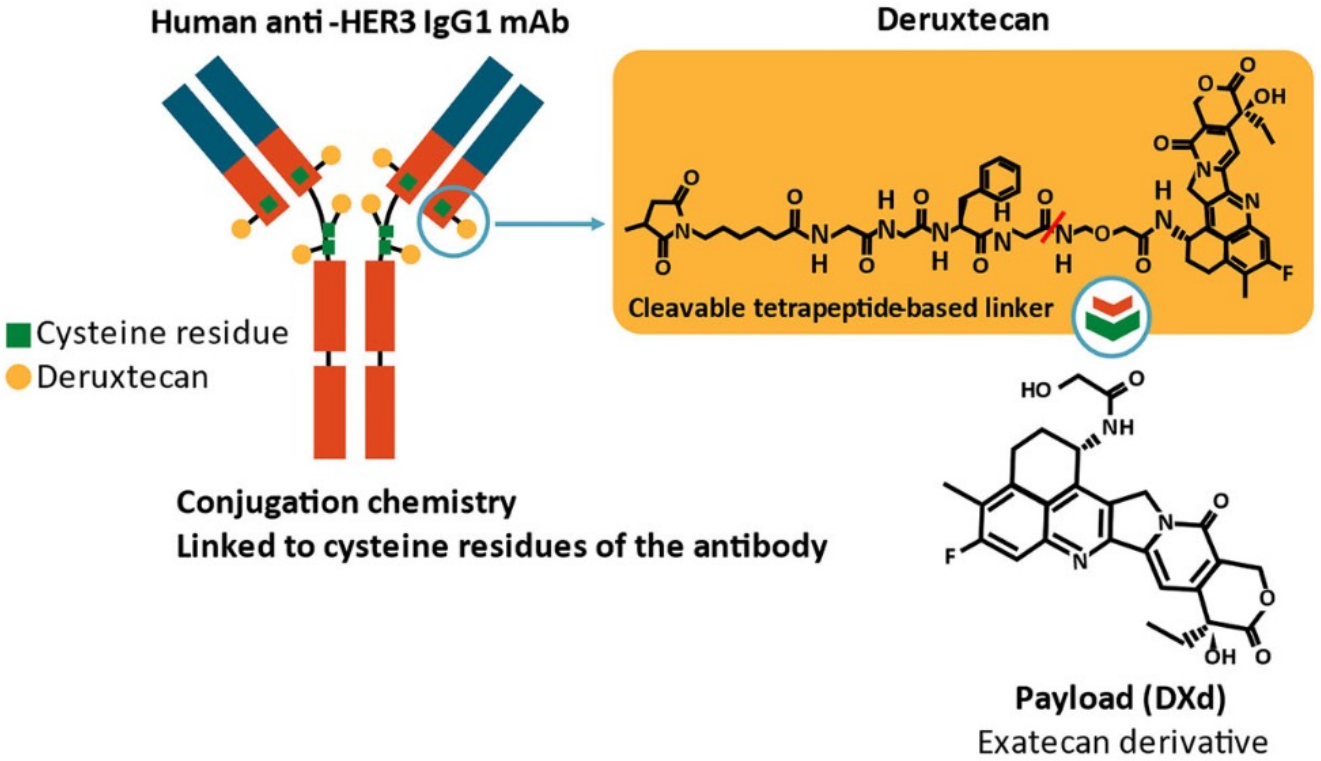
Case Presentation – Dr Bardia: 45F with HR+ MBC

45F with metastatic HR+ MBC (HER2 IHC = 1). Disease progression on various endocrine based therapy, and recently capecitabine. PS = 1. No organ dysfunction. gBRCA = negative. PIK3CA and ESR1 WT. Pt interested in treatment with minimal myelosuppression. Which of the following therapies would be your recommendation (including clinical trial)?

1. Eribulin
2. Datopotamab Deruxtecan (Dato-DXd)
3. Sacituzumab Govitecan (SG)
4. Trastuzumab Deruxtecan (T-DXd)

Patritumab-DXd (ADC targeting HER3)

Patritumab deruxtecan (U3-1402) is a novel ADC coupling an anti-HER3 mAb to DXd with a high DAR (8:1)



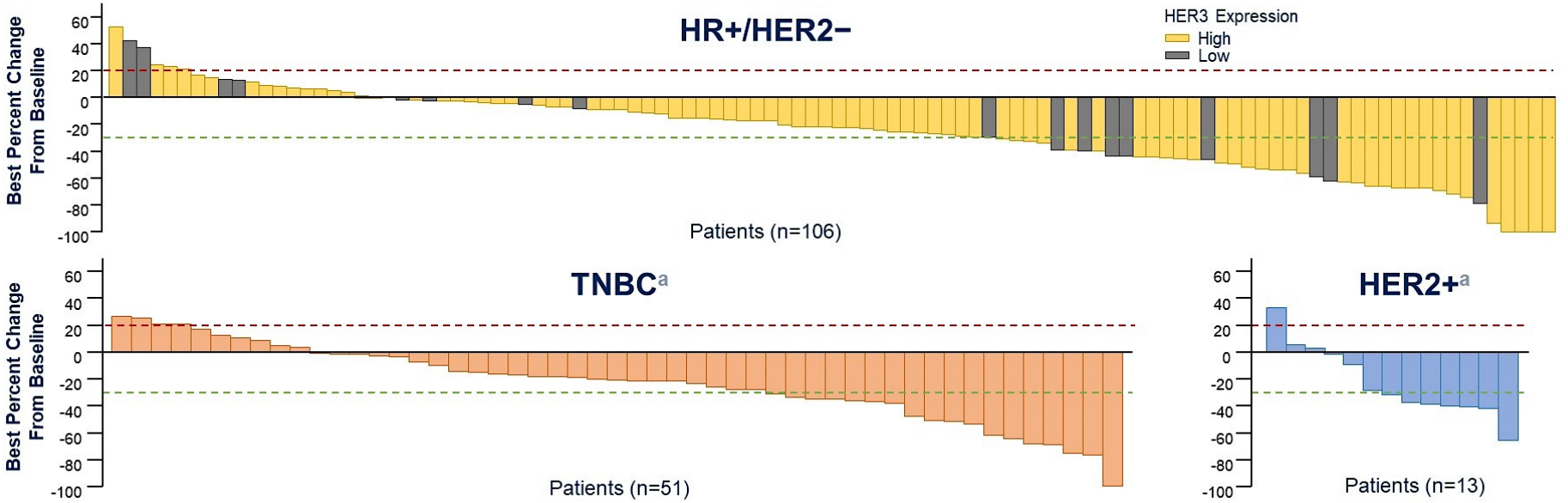
Krop IE et al. ASCO 2022;Abstract 1002.

Courtesy of Aditya Bardia, MD, MPH

Patritumab-DXd (ADC targeting HER3)

Change in Tumor Size From Baseline

Patritumab Deruxtecan
U31402-A-J101



HER3-DXd induced a clinically meaningful decrease in tumor size by BICR in most patients across BC subtypes.[b]

[a] Patients with TNBC and HER2+ were all HER3-high.
[b] Best percentage change from baseline in sum of diameters based on BICR for all target lesions identified is represented by patient. If any lesion measurement is missing at a post-baseline tumor assessment visit, that visit is not taken into consideration for best percent change from baseline in sum of diameters.

Krop IE et al. ASCO 2022;Abstract 1002.

Courtesy of Aditya Bardia, MD, MPH

Patritumab-DXd (ADC targeting HER3)

TEAEs in Patients Treated with 4.8 mg/kg and 6.4 mg/kg

Patritumab Deruxtecan
U31402-A-J101

- GI and hematologic toxicity were the most common TEAEs
- Rates of non-hematologic toxicity were similar at both doses and generally low grade
- Rates of grade ≥3 neutropenia, thrombocytopenia and leukopenia were numerically higher at 6.4 mg/kg vs 4.8 mg/kg
  - All events were managed by dose delay or reduction and were not associated with treatment discontinuation
  - No grade ≥3 TEAE of thrombocytopenia resulted in a grade ≥3 bleeding event

TEAEs (≥25% of all patients), %	4.8 mg/kg n=48		6.4 mg/kg n=98	
	All grade	Grade ≥3	All grade	Grade ≥3
TEAEs	**97.9**	**64.6**	**100**	**81.6**
Nausea	68.8	4.2	80.6	5.1
Platelet count decreased[a]	60.4	27.1	71.4	38.8
Neutrophil count decreased[a]	62.5	27.1	66.3	52.0
Decreased appetite	56.3	6.3	53.1	6.1
Vomiting	47.9	4.2	46.9	1.0
White blood cell count decreased[a]	45.8	10.4	45.9	23.5
Diarrhea	41.7	4.2	43.9	3.1
Anemia[a]	43.8	20.8	43.9	21.4
Aspartate aminotransferase increased	43.8	4.2	34.7	6.1
Stomatitis	25.0	0.0	34.7	1.0
Fatigue	31.3	0.0	33.7	3.1
Alanine aminotransferase increased	41.7	2.1	31.6	7.1
Constipation	22.9	0.0	29.6	0.0
Alopecia	20.8	NA	28.6	NA
Malaise	22.9	0.0	26.5	1.0

GI, gastrointestinal; NA, not applicable.
[a] Grouped terms: platelet count decreased (platelet count decreased, thrombocytopenia); neutrophil count decreased (neutrophil count decreased, neutropenia); white blood cell count decreased (leukopenia, white blood cell decreased); anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased).

Krop IE et al. ASCO 2022;Abstract 1002.

Courtesy of Aditya Bardia, MD, MPH

2023 ASCO ANNUAL MEETING

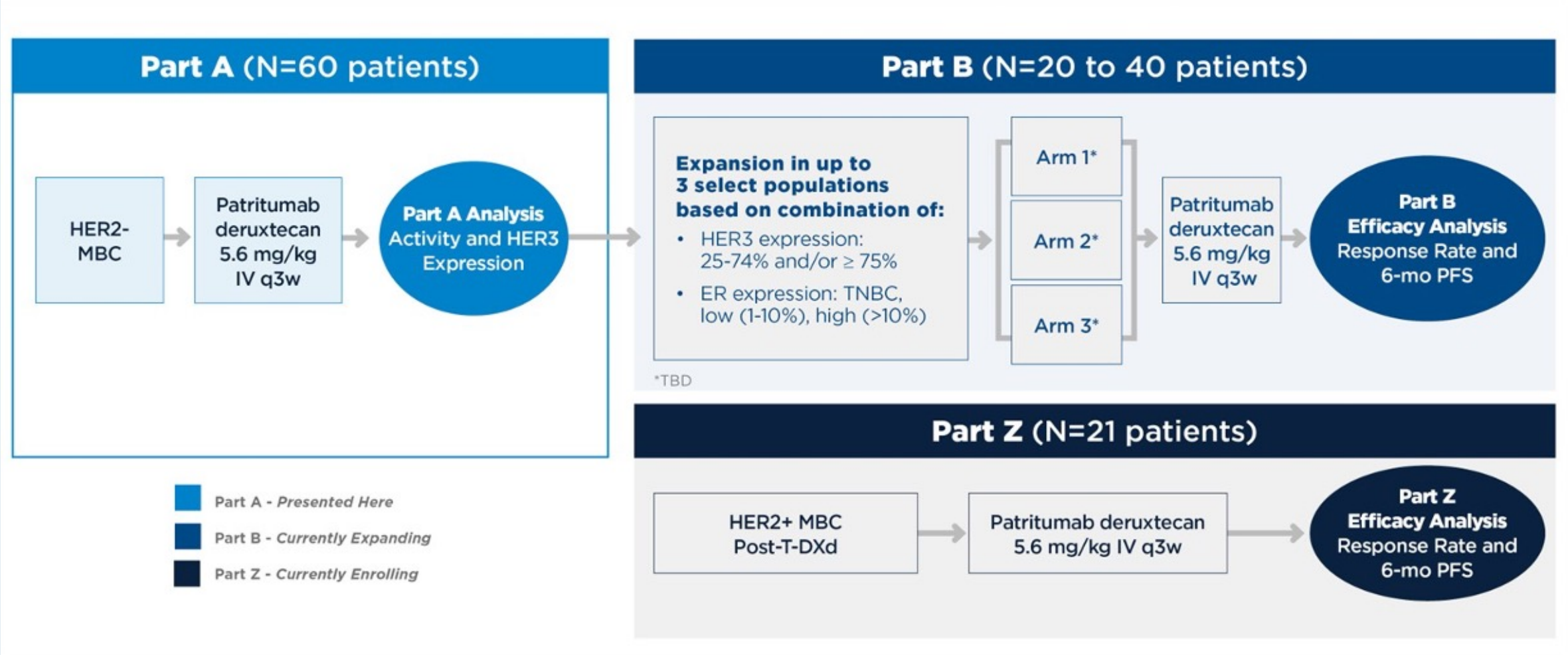
Abstract 1004

A Phase II Study of HER3-DXd in Patients with Metastatic Breast Cancer

Erika P. Hamilton, MD[1,2]; Ololade Dosunmu, MD, MPH[1]; Mythili Shastry, PhD[1]; Lindsey Finney, MS[1]; Dalila Sellami, MD[3]; David Sternberg, MD, PhD[3]; Vance Wright-Browne, MD[4]; Deborah Toppmeyer, MD[5]; William R. Gwin III, MD[6]; J. Thaddeus Beck, MD, FACP[7]; Jennifer Cultrera, MD[8]; Nusayba A. Bagegni, MD[9]; Katia Khoury, MD[10]; Arielle Heeke, MD[11]; Yuan Yuan, MD, PhD[12]

RTP RESEARCH TO PRACTICE

BRE 354: A Phase II Study of Patritumab Deruxtecan (HER3-DXd)



HER3 expression was not an enrollment criterion for Part A; HER3 expression was retrospectively assessed using immunohistochemistry.

Hamilton EP et al. ASCO 2023;Abstract 1004.

BRE 354: Response – Investigator Assessment

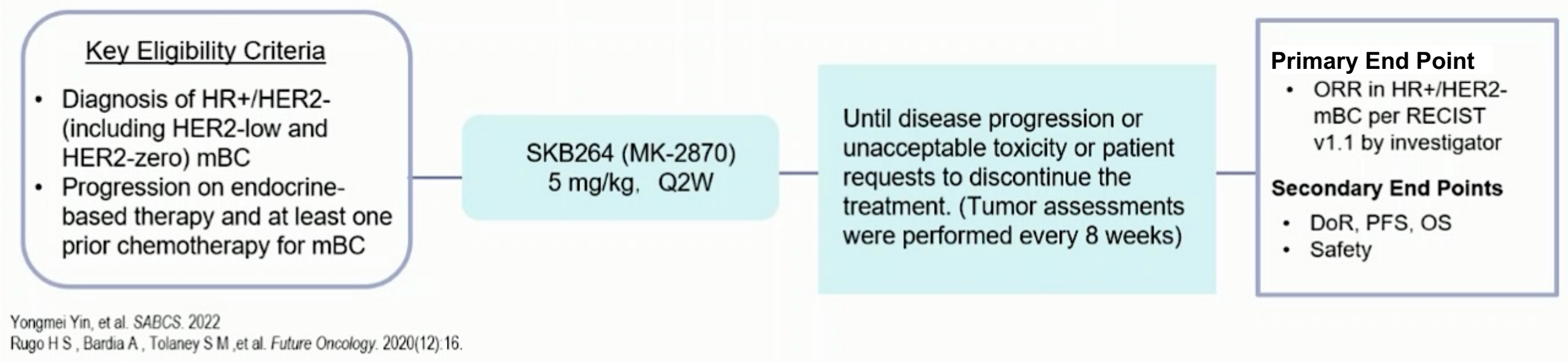
	Membrane HER3 ≥75% (N=30)	Membrane HER3 25%- 74% (N=13)	Membrane HER3 <25% (N=4)	Unknown Membrane HER3 Expression* (N=13)	Total (N=60) N (%)
Best Overall Response, n (%)					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
Stable disease (SD)	13 (43.3)	4 (30.8)	1 (25.0)	8 (61.5)	26 (43.3)
Progressive disease (PD)	5 (16.7)	1 (7.7)	1 (25.0)	0	7 (11.7)
Missing/no post baseline	2 (6.7)	2 (15.4)	0	2 (15.4)	6 (10.0)
ORR, n (%)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
95% CI	(17.3, 52.8)	(19.2, 74.9)	(6.8, 93.2)	(5.0, 53.8)	(23.1, 48.4)
CBR, n (%)**	**12 (40.0)**	**7 (53.8)**	**2 (50.0)**	**5 (38.5)**	**26 (43.3)**
95% CI	(22.7, 59.4)	(25.1, 80.8)	(6.8, 93.2)	(13.9, 68.4)	(30.6, 56.8)
DoR ≥6 months, n (%)†	4 (40.0)	2 (33.3)	2 (100)	2 (66.7)	10 (47.6)

Among patients with heavily pretreated BC, all-comer ORR was 35%, overall CBR was 43%, and DoR was at least 6 months in nearly half of all patients who responded.

Hamilton EP et al. ASCO 2023;Abstract 1004.

SKB264
(ADC targeting TROP2)

SKB264 (MK-2870) in previously treated (HR+)/ HER2-negative metastatic breast cancer (mBC): results from a phase I/II, single-arm, basket trial



Yongmei Yin, et al. *SABCS*. 2022
Rugo H S , Bardia A , Tolaney S M ,et al. *Future Oncology*. 2020(12):16.

Abstract **380MO**, presented by Yongmei Yin , at ESMO 2023, Madrid

Courtesy of Aditya Bardia, MD, MPH

SKB264
(ADC targeting TROP2)

	All patients (N=38)[a]
ORR, n (%)	**14 (36.8)**
Confirmed PR	12
DCR, n (%)	**34 (89.5)**
DoR	
Median (Range), mo	7.4 (4.2~14.9+)
6-mon DoR rate, % (95% CI)	80.0 (40.9, 94.6)
PFS	
Median (95% CI), mo	11.1 (5.4, 13.1)
6-mon PFS rate, % (95% CI)	61.2 (41.3, 76.1)
OS	
Median (95% CI), mo	NE (10.71, NE)
9-mon OS rate (95% CI), %	81.4 (57.1, 92.7)

a. of 41 patients were enrolled, 38 patients were evaluable for response assessment (defined as ≥1 on-study scan).

Abstract **380MO**, presented by Yongmei Yin , at ESMO 2023, Madrid

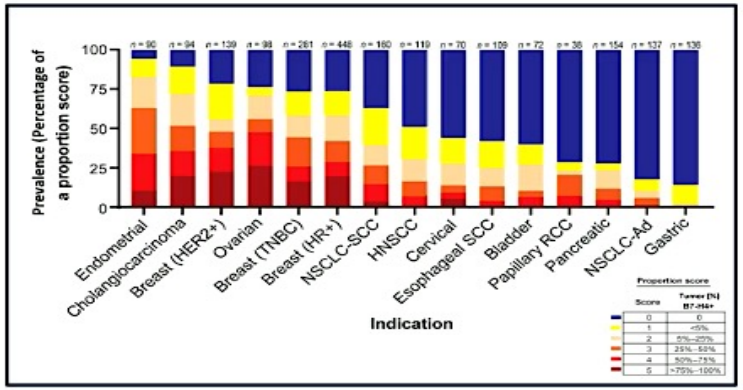
Courtesy of Aditya Bardia, MD, MPH

HS-20089
(ADC targeting B7-H4)

Background

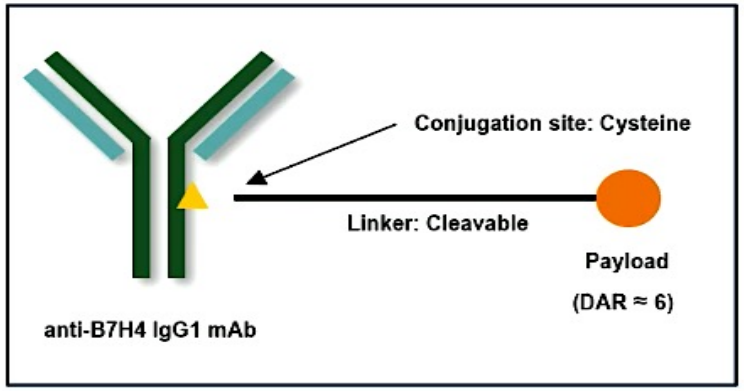
- B7 homolog 4 protein (B7-H4), a transmembrane glycoprotein in the B7 superfamily, is highly expressed in various types of solid tumors with low expression in normal tissues (Figure 1).
- HS-20089 is a novel B7-H4 targeted ADC, which conjugates a humanized anti-B7-H4 IgG1 monoclonal antibody with a small molecule toxin topoisomerase I inhibitor via a protease-cleavable linker (Figure 2).
- HS-20089 demonstrated a high affinity to human B7-H4 and potent anti-tumor activity in preclinical studies (Figure 3).

Figure 1. Expression of B7-H4 in Multiple Tumors*



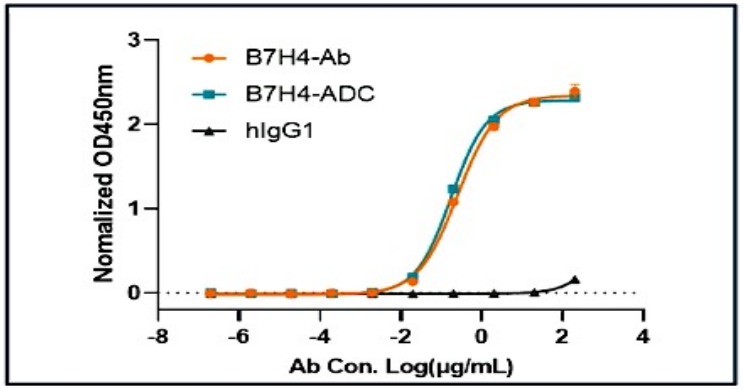
*Reference: Clin Cancer Res . 2022 Dec

Figure 2. Structure of HS-20089



DAR: Drug to antibody ratio.

Figure 3. Binding Activity to B7-H4 Human Protein



Method: ELISA.

MADRID 2023 ESMO congress

Zhang J et al. ESMO 2023;Abstract 381O.

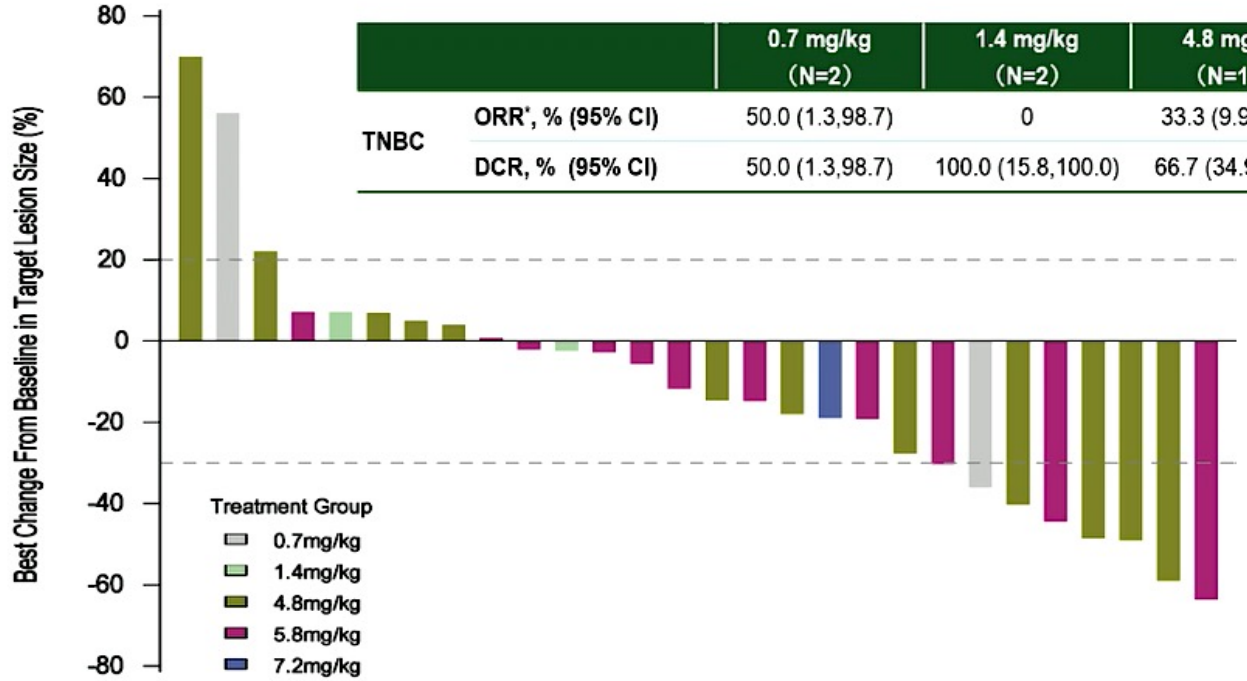
Courtesy of Aditya Bardia, MD, MPH

HS-20089
(ADC targeting B7-H4)

Efficacy - TNBC

- HS-20089 showed promising anti-tumor activity in triple-negative breast cancer (TNBC).
- At potential target therapeutic doses of 4.8 and 5.8 mg/kg, the ORR were 33.3% and 27.3%, respectively.

Figure 5. Best Percent Change of Target Lesions in TNBC



		0.7 mg/kg (N=2)	1.4 mg/kg (N=2)	4.8 mg/kg (N=12)	5.8 mg/kg (N=11)	7.2 mg/kg (N=1)	Total (N=28)
TNBC	ORR*, % (95% CI)	50.0 (1.3,98.7)	0	33.3 (9.9,65.1)	27.3# (6.0,61.0)	0	28.6 (13.2,48.7)
	DCR, % (95% CI)	50.0 (1.3,98.7)	100.0 (15.8,100.0)	66.7 (34.9,90.1)	81.8 (48.2,97.7)	100.0 (2.5,100.0)	75.0 (55.1,89.3)

*Assessed according to RECIST 1.1 by investigators.
#Including 1 confirmed PR and 2 PRs awaiting confirmation. Others were confirmed PRs.
ORR: Objective response rate.
DCR: Disease control rate.
PR: Partial response.

Clinical cutoff: August 17, 2023

MADRID 2023 ESMO congress

Zhang J et al. ESMO 2023;Abstract 381O.

Courtesy of Aditya Bardia, MD, MPH

Agenda

MODULE 4: Antibody-drug conjugates in metastatic disease (trastuzumab deruxtecan, sacituzumab govitecan, datopotamab deruxtecan, patritumab deruxtecan)

- ER-positive, HER2-negative disease
- ER-positive, HER2-low disease
- ER-negative, HER2-negative disease
- ER-negative, HER2-low disease

Implications of Recent Data Sets for the Current and Future Management of Lung Cancer

Part 3 of a 3-Part Post-ESMO Congress 2023 CME/MOC-Accredited Live Webinar Series

Tuesday, November 14, 2023
5:00 PM – 6:30 PM ET

Faculty

Luis Paz-Ares, MD, PhD
Zofia Piotrowska, MD, MHS
David R Spigel, MD

Moderator

Neil Love, MD

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Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

CME and MOC credit information will be emailed to each participant within 5 business days.

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