Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

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Welcome FCS Members!

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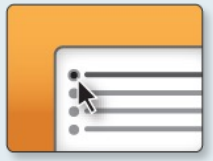
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the premeeting survey.

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

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

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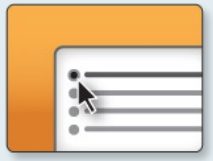
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the premeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME/ACPE/NCPD Credit: A credit link will be provided in the chat room at the conclusion of the program.

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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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Practical Perspectives: Experts Review Actual Cases of Patients with Endometrial Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, October 15, 2025
5:00 PM – 6:00 PM ET

Faculty

Kathleen N Moore, MD, MS
Matthew A Powell, MD

Moderator

Neil Love, MD

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TO PRACTICE

Practical Perspectives: Experts Review Actual Cases of Patients with HER2-Positive Gastrointestinal Cancers

A CME/MOC-Accredited Live Webinar

Tuesday, October 21, 2025
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Cancer Q&A: Understanding the Role and Reality of CAR (Chimeric Antigen Receptor) T-Cell Therapy for Non-Hodgkin Lymphoma

A Webinar Series for Clinicians and Patients,
*Developed in Partnership with Cancer*Care®

Patients	Clinicians
Wednesday, October 22, 2025	**Wednesday, November 12, 2025**
6:00 PM – 7:00 PM ET	**5:00 PM – 6:00 PM ET**

Faculty

Jeremy S Abramson, MD, MMSc
Loretta J Nastoupil, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Exploring Current Patterns of Care in the Community: Optimizing the Use of Oral Selective Estrogen Receptor Degraders for HR-Positive Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, October 29, 2025

5:00 PM – 6:00 PM ET

Faculty

Rinath M Jeselsohn, MD

Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

What Clinicians Want to Know: First-Line and Maintenance Therapy for Patients with Extensive-Stage Small Cell Lung Cancer

A CME/MOC-Accredited Live Webinar

Tuesday, November 11, 2025
5:00 PM – 6:00 PM ET

Faculty

Luis Paz-Ares, MD, PhD
Misty Dawn Shields, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Cancer Conference Update: 2025 ESMO Annual Meeting — Breast Cancer Highlights

CME/MOC-Accredited Live Webinar

Thursday, November 13, 2025
5:00 PM – 6:00 PM ET

Faculty

Professor Giuseppe Curigliano, MD, PhD
Priyanka Sharma, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Exciting CME Events You Do Not Want to Miss

A Friday Satellite Symposium Series Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

Acute Myeloid Leukemia
7:30 AM – 9:30 AM ET

Myelofibrosis and Systemic Mastocytosis
3:15 PM – 5:15 PM ET

Chronic Lymphocytic Leukemia
11:30 AM – 1:30 PM ET

Follicular Lymphoma and Diffuse Large B-Cell Lymphoma
7:00 PM – 9:00 PM ET

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss the Optimal Management of Breast Cancer

A 3-Part CME Satellite Symposium Series

Antibody-Drug Conjugates for Metastatic Breast Cancer

Tuesday, December 9, 2025

7:00 PM – 8:30 PM CT

HER2-Positive Breast Cancer

Wednesday, December 10, 2025

7:00 PM – 9:00 PM CT

Endocrine-Based Therapy

Thursday, December 11, 2025

7:00 PM – 9:00 PM CT

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Optimizing Treatment for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

A CME/MOC-Accredited Interactive Grand Rounds Series

October 2025 to March 2026

Steering Committee

Catherine C Coombs, MD
Matthew S Davids, MD, MMSc
Bita Fakhri, MD, MPH
Nicole Lamanna, MD
Jeff Sharman, MD
Jennifer Woyach, MD

Host a 1-hour session at your institution:
Email Meetings@ResearchToPractice.com
or call (800) 233-6153

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

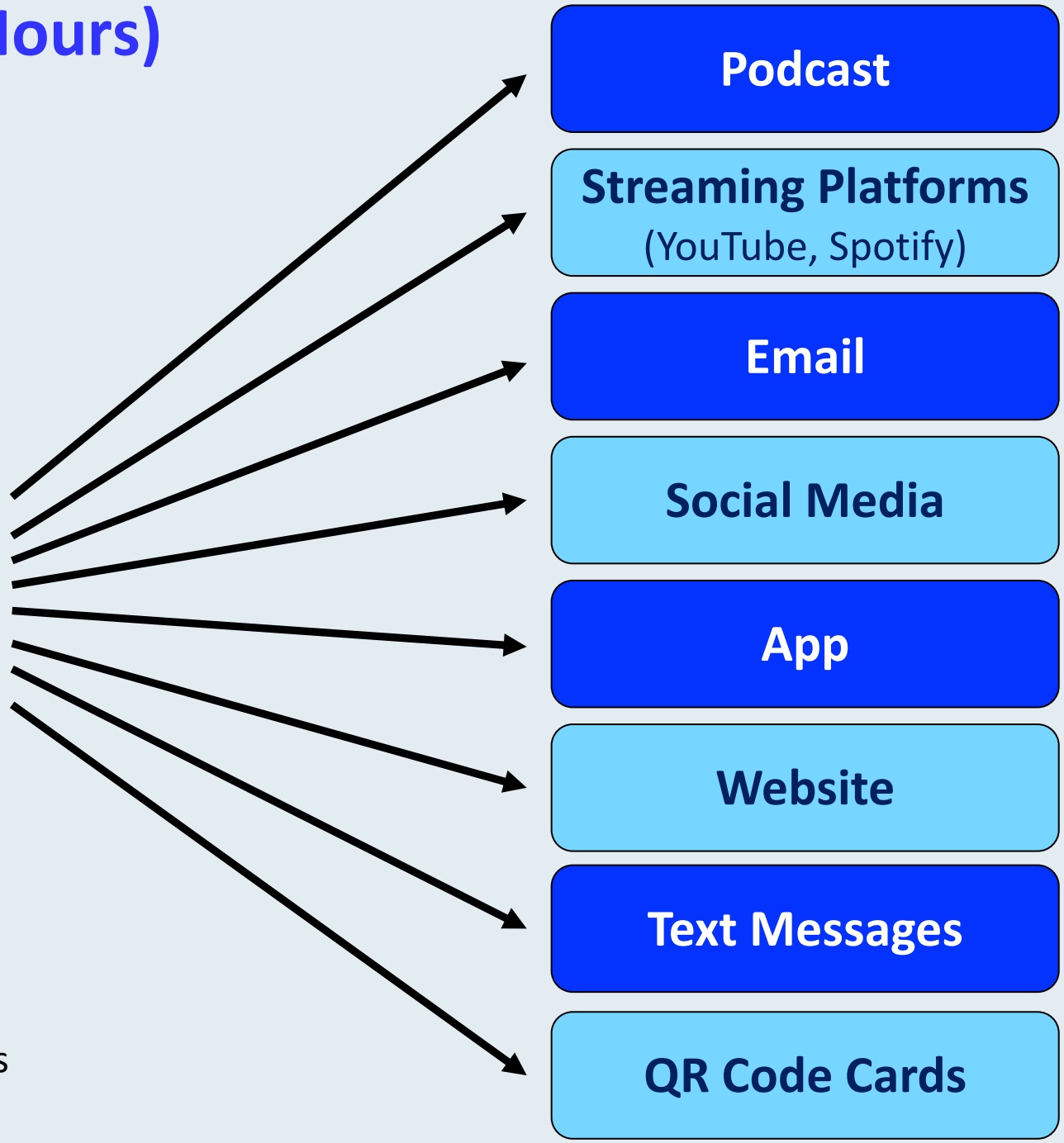
The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

RTP Content Production (Hours)
9/1/24 — 8/31/25

	Year	Month
Total	281	24 (12-31)
Final*	199	16 (9-31)
Recordings	93	8 (0-15)
Webinars	41	4 (0-6)
Cases	62	5 (2-6)
Meetings	94	8 (0-18)

*Presentations = 50 hours; Discussions = 150 hours



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RTP Playlist with Neil Love, MD

BREAST CANCER

Dr Hope Rugo: Interview (28 min)

SMALL CELL LUNG CANCER

Drs Stephen Liu and Charles Rudin: Cases (58 min)

GASTROESOPHAGEAL CANCER

Drs Geoffrey Ku and Zev Wainberg: Cases (61 min)

PROSTATE CANCER

Drs Emmanuel Antonarakis and Karim Fizazi: Year in Review (60 min)

ENDOMETRIAL AND OVARIAN CANCER

Dr Shannon Westin: Interview (52 min)

NEUROENDOCRINE TUMORS

Drs Simron Singh and Jonathan Strosberg: Meeting (50 min)

NON-HODGKIN LYMPHOMA

Drs Jeremy Abramson, Joshua Brody, Christopher Flowers, Ann LaCasce and Tycel Phillips: Meeting, cases (59 min)

CHRONIC LYMPHOCYTIC LEUKEMIA

Drs Jennifer Brown and Paolo Ghia: Year in Review (59 min)

ACUTE MYELOID LEUKEMIA

Dr Jorge Cortes: Interview (43 min)

MULTIPLE MYELOMA

Drs Natalie Callander and Sagar Lonial: Patient videos (59 min)

IMMUNE THROMBOCYTOPENIA

Drs Hanny Al-Samkari, James Bussel and Nichola Cooper: Think Tank (117 min)

OCULAR TOXICITES IN ONCOLOGY

Dr Neel Pasricha: Interview (54 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

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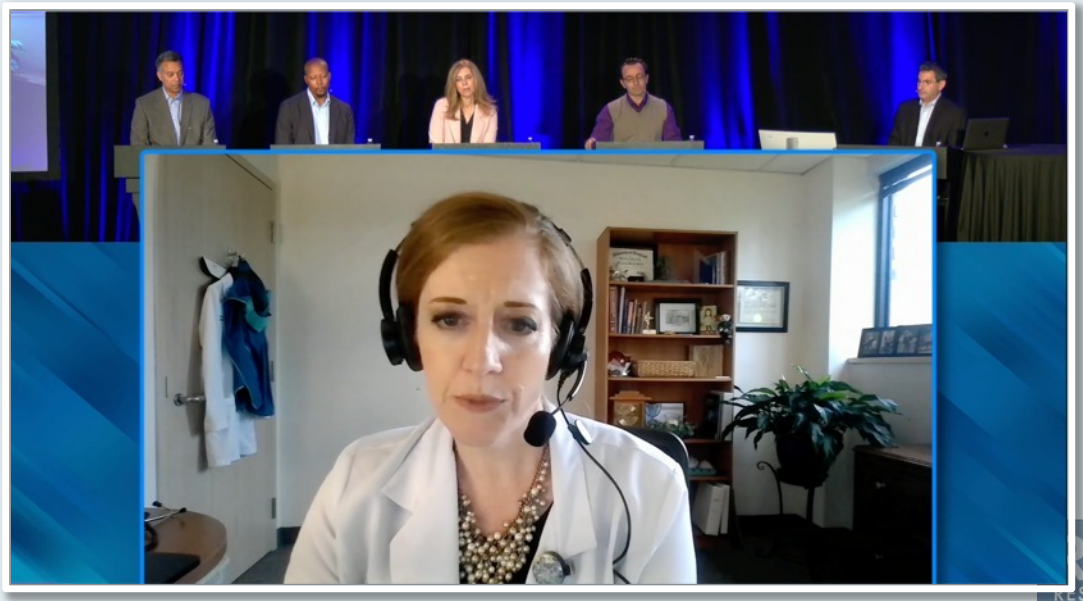

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RTP Playlist with Neil Love, MD

Webinar for patients and families on relapsed multiple myeloma with Drs Natalie Callander and Sagar Lonial.

Relapsed Multiple Myeloma: Where We Were, Where We Are (4 min)

Common Questions from the Beginning (5 min)

Choosing Treatment Options (4 min)

Clinical Research Trials (6 min)

Neuropathy (5 min)

Chimeric Antigen Receptor (CAR) T-Cell Therapy (6 min)

Bispecific Antibodies (8 min)

Antibody-Drug Conjugates: Belantamab Mafadotin (8 min)

Interacting with the Oncology Team (5 min)

Other Questions (4 min)

Recording of Entire Webinar (62 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

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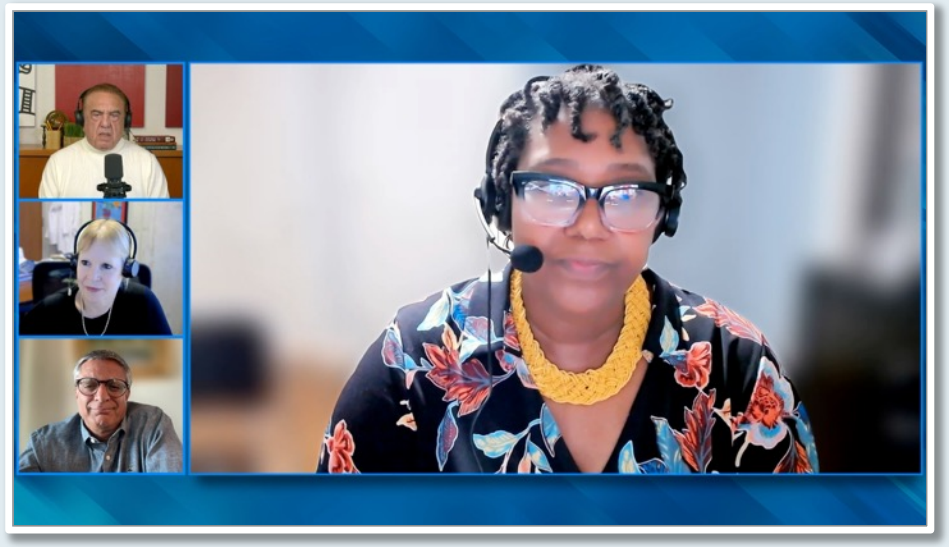

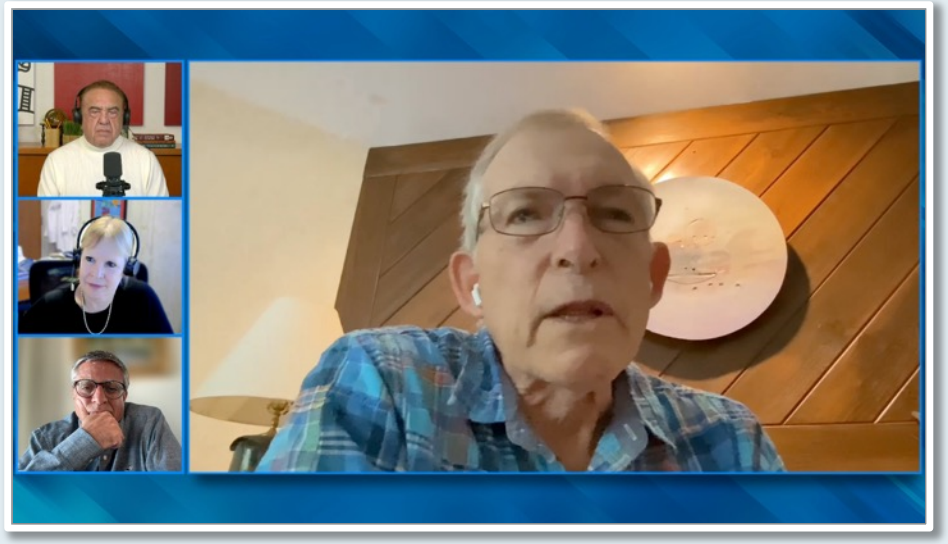

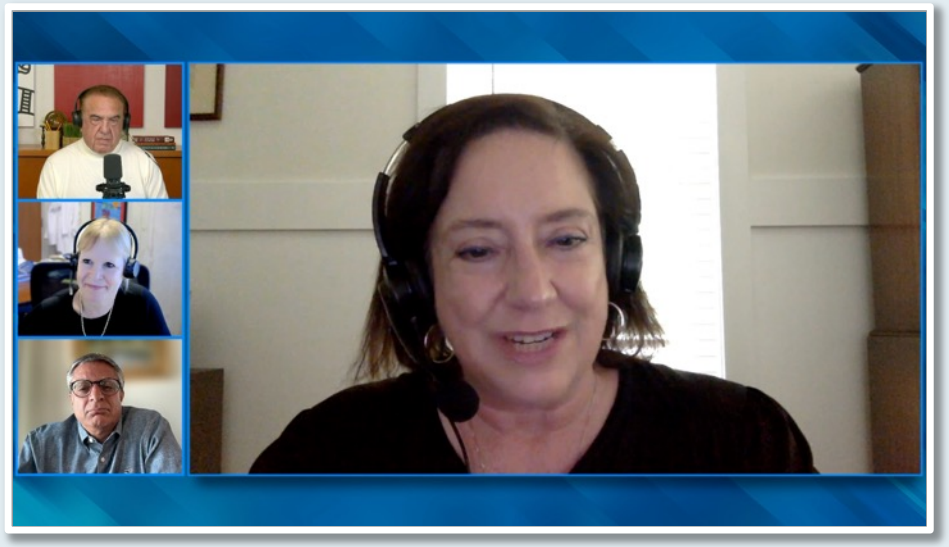

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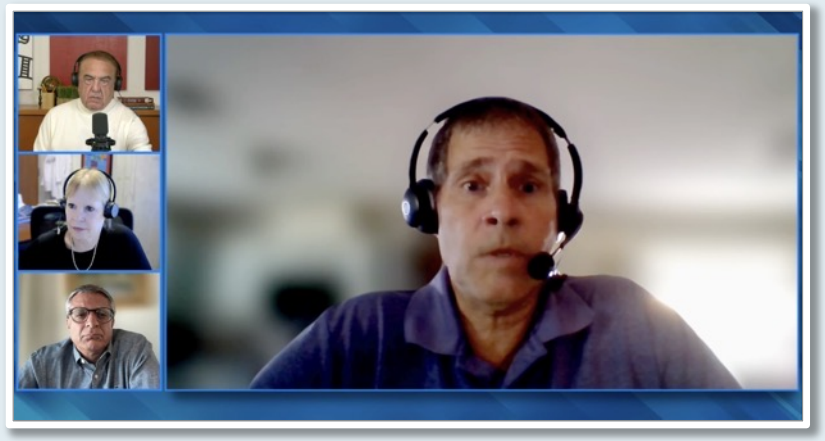

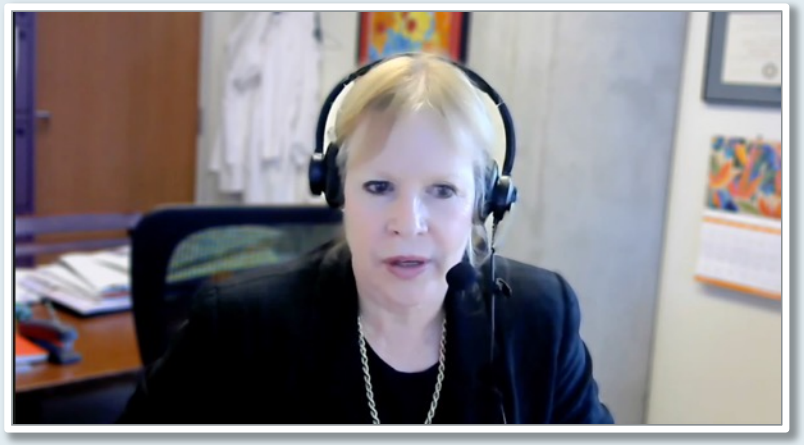

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Survey of Attendees and Other Community-Based General Medical Oncologists

September 30 – October 8, 2025

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Agenda

Module 1 — Breast Cancer: *Drs Burstein, Goetz, McArthur and Nanda*

Module 2 — Prostate Cancer: *Drs Antonarakis and M Smith*

Module 3 — Colorectal Cancer: *Drs Lieu and Strickler*

Module 4 — Diffuse Large B-Cell Lymphoma and Follicular Lymphoma: *Drs Lunning and S Smith*

Agenda

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Module 3 — Colorectal Cancer: *Drs Lieu and Strickler*

Module 4 — Diffuse Large B-Cell Lymphoma and Follicular Lymphoma: *Drs Lunning and S Smith*

Breast Cancer

Harold J Burstein, MD, PhD
Director of Academic Partnerships
Institute Physician
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Heather McArthur, MD, MPH, FASCO
Professor, Department of Internal Medicine
Clinical Director, Breast Cancer Program
Komen Distinguished Chair in Clinical Breast Cancer Research
UT Southwestern Medical Center
Dallas, Texas

Matthew P Goetz, MD
Erivan K Haub Family Professor of Cancer Research
Honoring Richard F Emslander, MD
Professor of Oncology and Pharmacology
Department of Oncology
Mayo Clinic
Rochester, Minnesota

Rita Nanda, MD
Director, Breast Oncology
Associate Professor of Medicine
Section of Hematology/Oncology
The University of Chicago
Chicago, Illinois

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MAYO CLINIC

Localized Hormone Receptor (HR)-Positive Breast Cancer (BC); Initial Therapy for Metastatic Disease

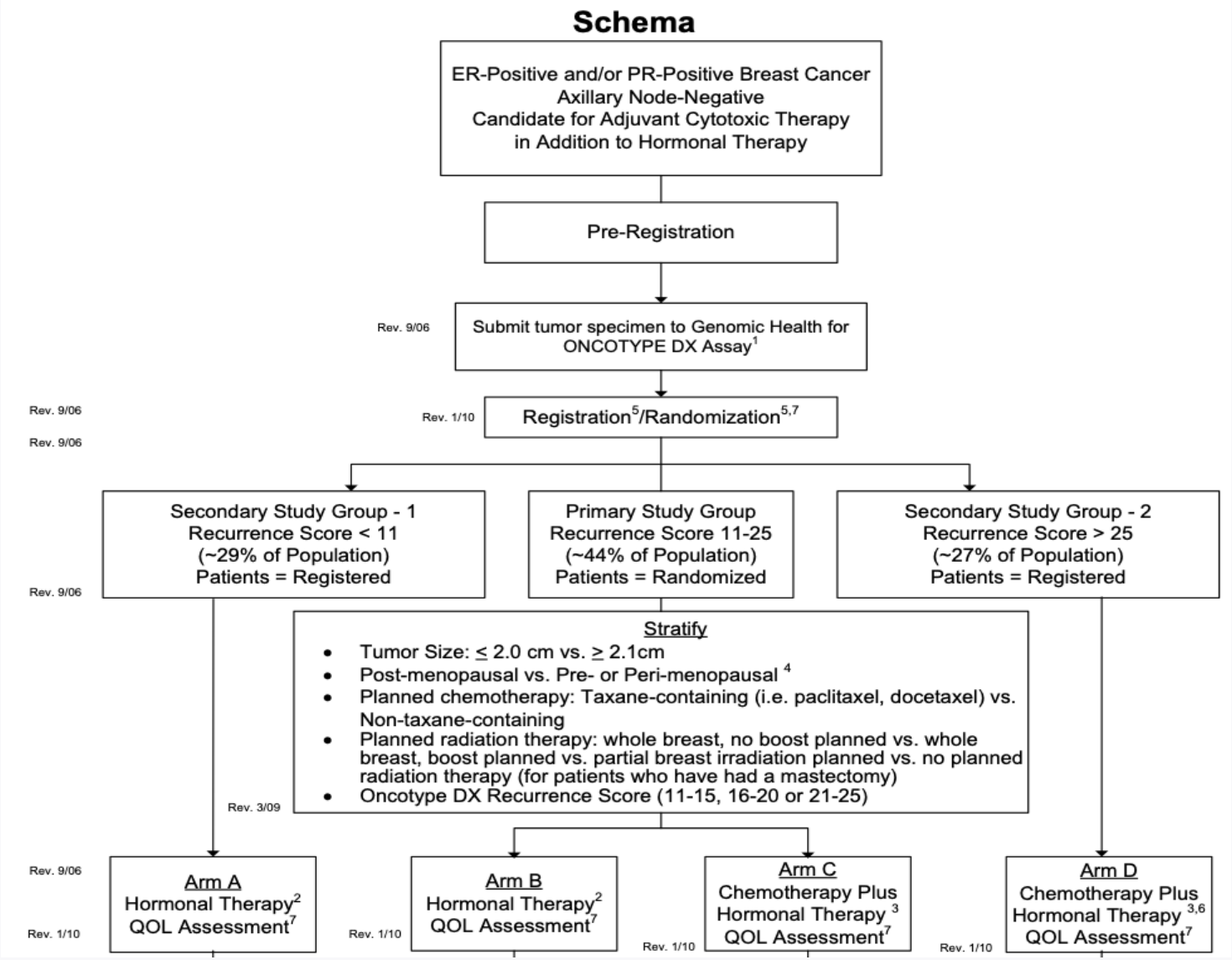
FCS 2025 Symposium

Matthew P. Goetz, M.D.
Erivan K. Haub Family Professor of Cancer Research
Honoring Richard F. Emslander, M.D.
Mayo Clinic
Rochester, MN USA

Outline

- Key studies informing the use of the 21-gene Recurrence Score (RS) to guide treatment decision-making for patients with HR-positive, HER2-negative BC
- Extended follow-up with the addition of abemaciclib and ribociclib, respectively, to standard adjuvant endocrine therapy for patients with localized HR-positive, HER2- negative BC
- Long-term follow-up from key clinical trials of approved CDK4/6 inhibitors in patients with HR-positive, HER2-negative metastatic BC
- Published data from the Phase III SERENA-6 trial of early therapeutic switching from an aromatase inhibitor to camizestrant after detection of an emergent ESR1 mutation during first-line therapy for HR-positive, HER2-negative mBC

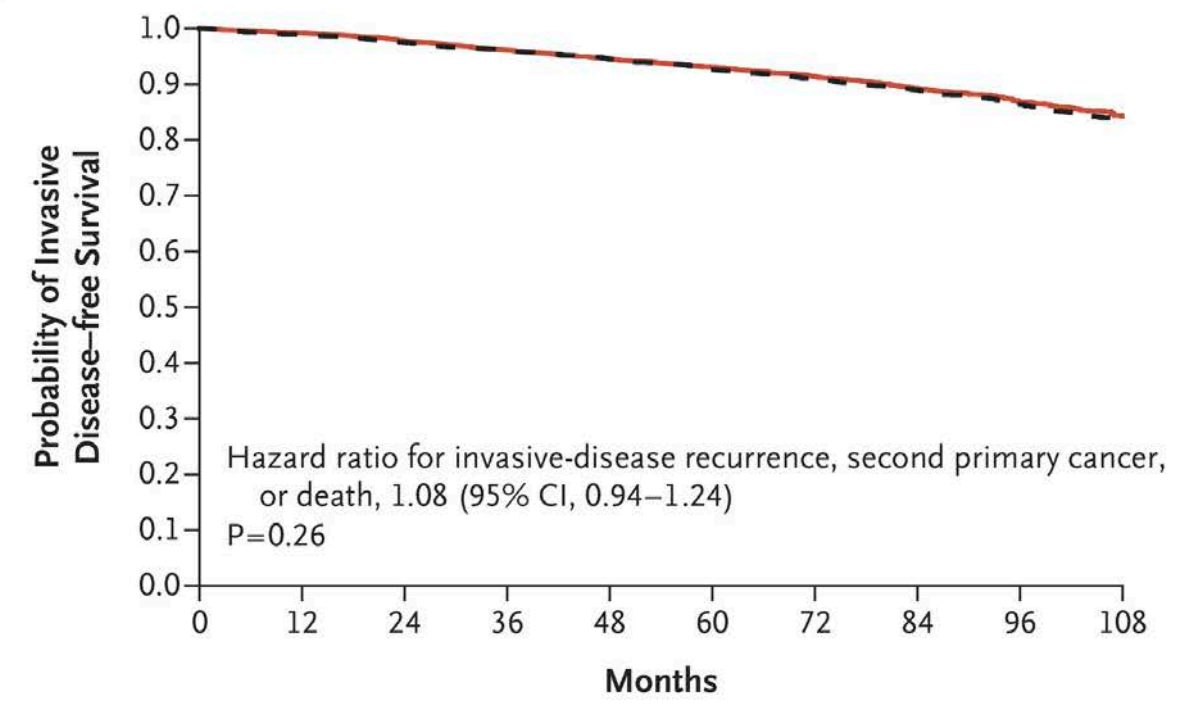
PACCT-1: Prospective Validation of 21-Gene Recurrence Score (RS)



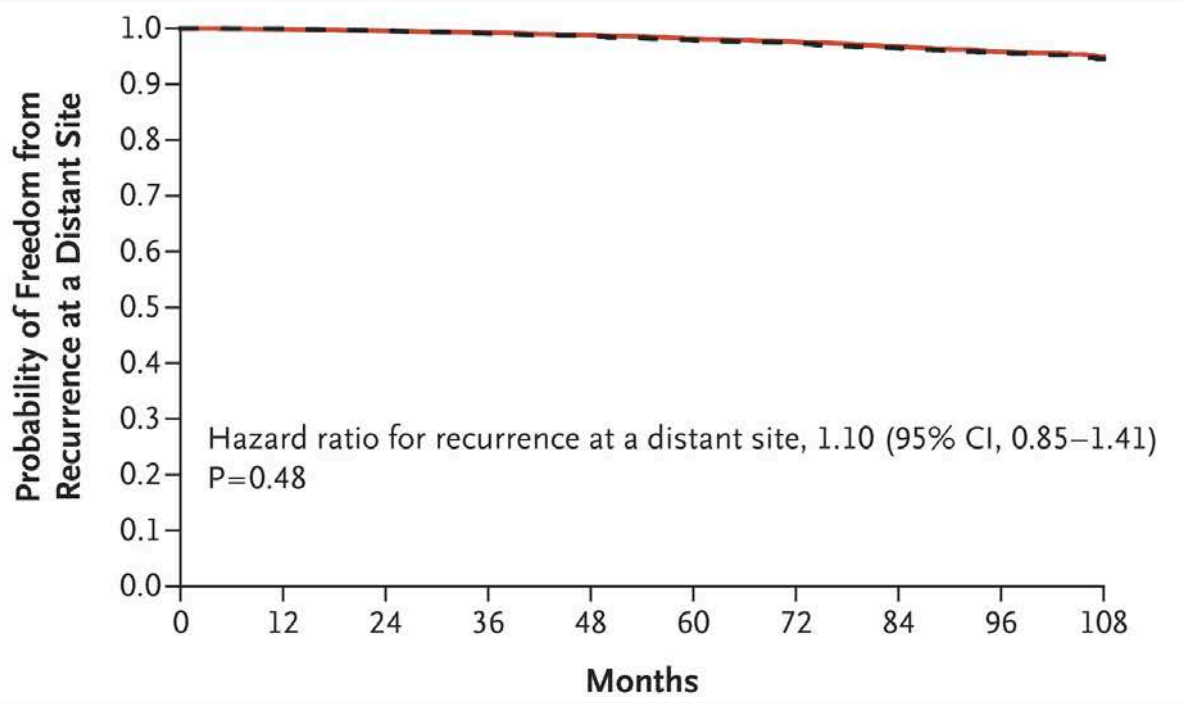
https://clinicaltrials.gov/study/NCT00310180.

PACCT-1: Clinical Outcomes (RS 11 to 25)

Invasive Disease-Free Survival

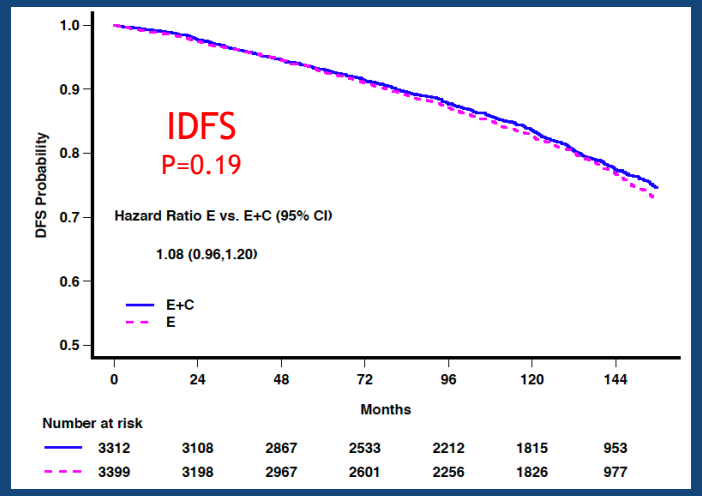


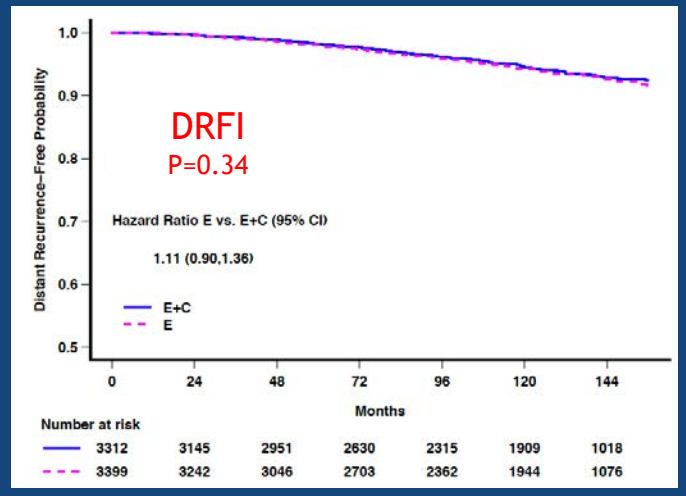
Freedom from Recurrence at a Distant Site

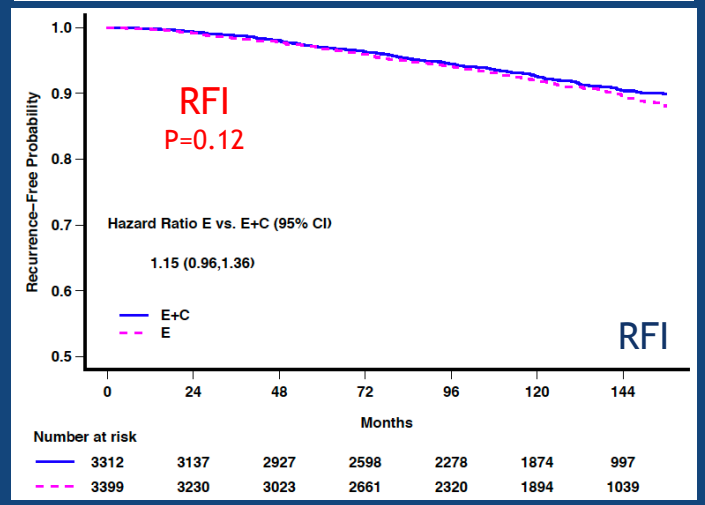


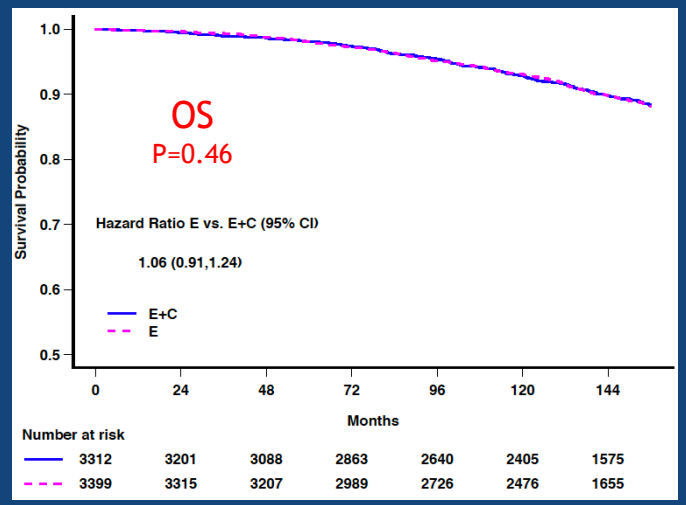
Sparano JA et al. *N Engl J Med*. 2018;379:111-121.

TAILORx: Updated Analysis - Kaplan-Meier Curves in RS 11-25 Arms (ITT population)







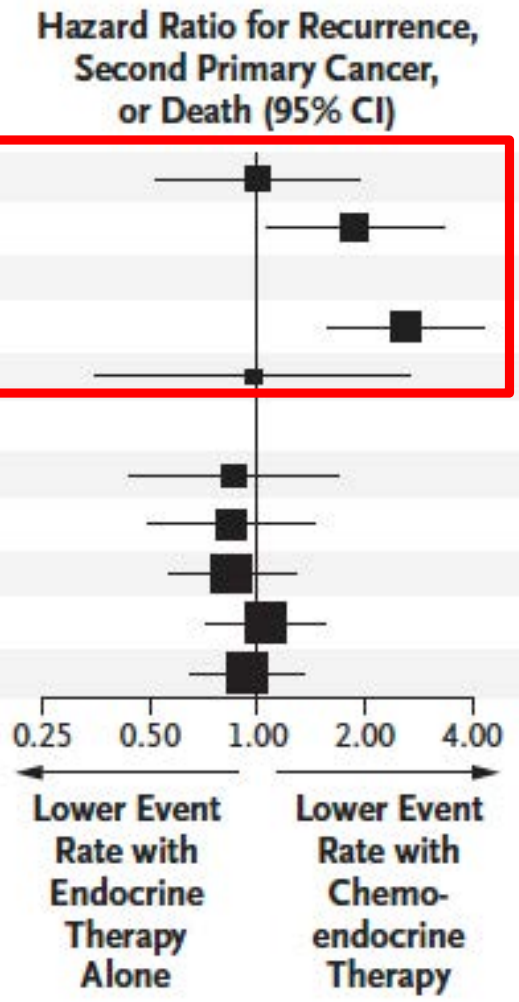


Primary trial conclusions unchanged: ET non-inferior to CET (N=6711)	
Event	Hazard Ratio: Arm B vs. C (95% CI)
IDFS	Primary analysis: 1.08 (0.94, 1.24, p=0.26)
	Updated analysis: 1.08 (0.96, 1.20)
DRFI	Primary analysis: 1.10 (0.85,1.41, p=0.48)
	Updated analysis: 1.11 (0.90, 1.36)
RFI	Primary analysis: 1.11 (0.90, 1.37, p=0.33)
	Updated analysis: 1.15 (0.96, 1.36)
OS	Primary analysis: 0.99 (0.79, 1.22, p=0.89)
	Updated analysis: 1.06 (0.91, 1.24)

Sparano JA et al. SABCS 2022;Abstract GS01-05

TAILORx: Effect of Age, RS, and Clinical Risk on Chemotherapy Benefit

Subgroup	No. of Patients	No. of Events
≤40 Yr of age	203	35
41–45 Yr of age	441	51
46–50 Yr of age		
Before menopause	630	69
After menopause	141	15
51–55 Yr of age		
Before menopause	287	34
After menopause	472	54
56–60 Yr of age	826	94
61–65 Yr of age	710	109
>65 Yr of age	628	117



3-way treatment interaction (IDFS)

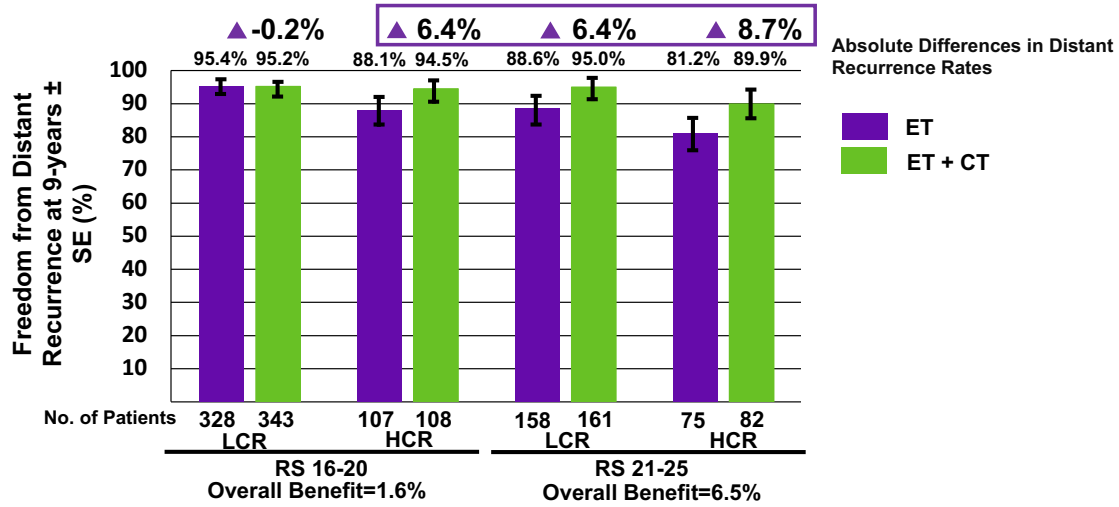
- Chemo-Age-RS (p=0.004)
- Chemo-Menopause-RS (p=0.02)

	Age < 50 Years: Estimated Absolute Chemo Benefit in 9-Year Distant Recurrence Rate
RS 16-20 (N=886)	Δ +1.6% (±SE 1.9%)
RS 21-25 (N=476)	Δ +6.5% (+SE 3.7%)

Sparano et al. N Engl J Med 2019; 380:2395-2405 (PMID: 31157962)

Development and validation of the RSClin educational tool integrating the 21-gene RS and clinicopathologic features

Clinical Risk Adds Insight into Chemotherapy Benefit in Women ≤50 Years With RS Results 16-20 and 21-25

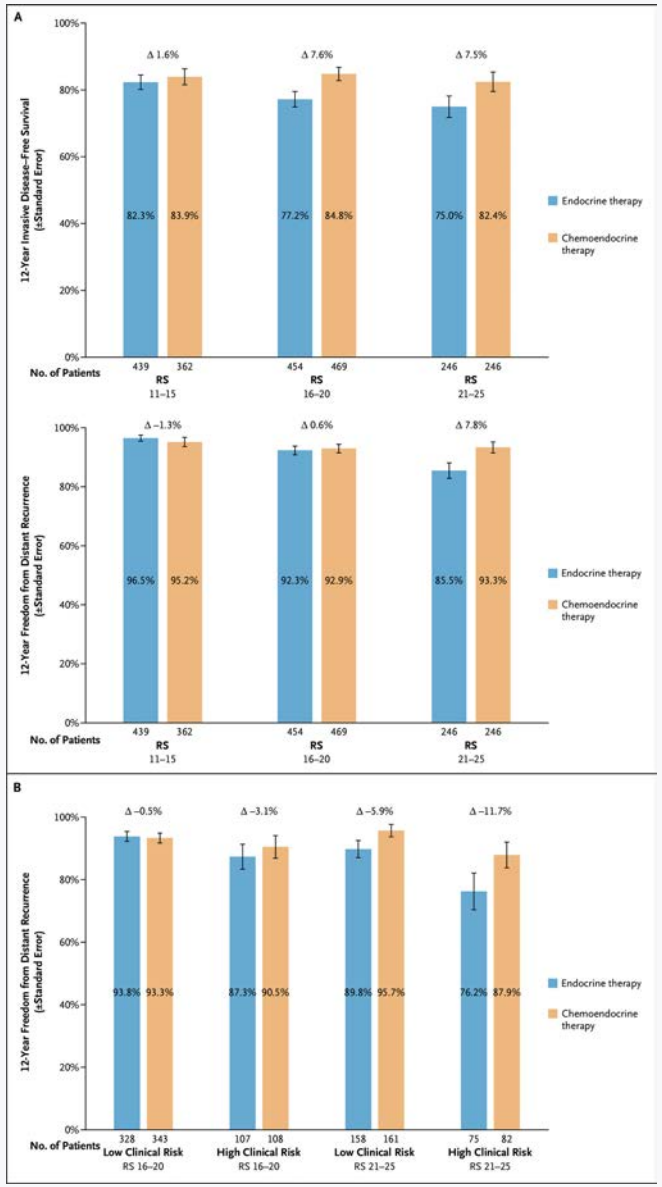


No CT benefit observed in women ≤50 years with RS result 16-20 & low clinical risk

LCR: Low clinical risk
HCR: High clinical risk
RS: Recurrence Score® results
ET: Endocrine therapy
CT: Chemotherapy
ET + CT: Chemo-endocrine therapy

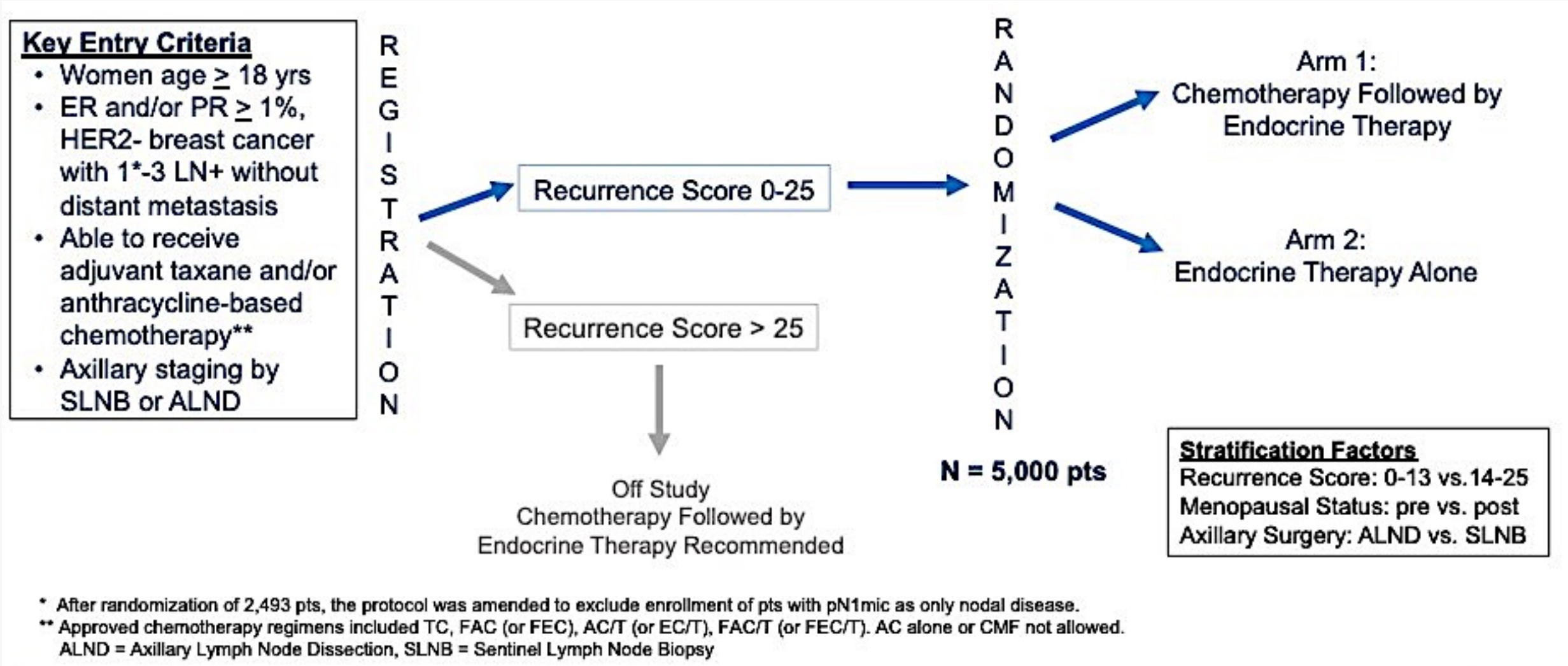
11

Sparano JA, et al. *N Engl J Med*. 2019;380(25):2395-2405.



Sparano JA et al. NEJM Evid. 2024 Aug;3(8):EVIDoa2300267.

RxPONDER: Study Design



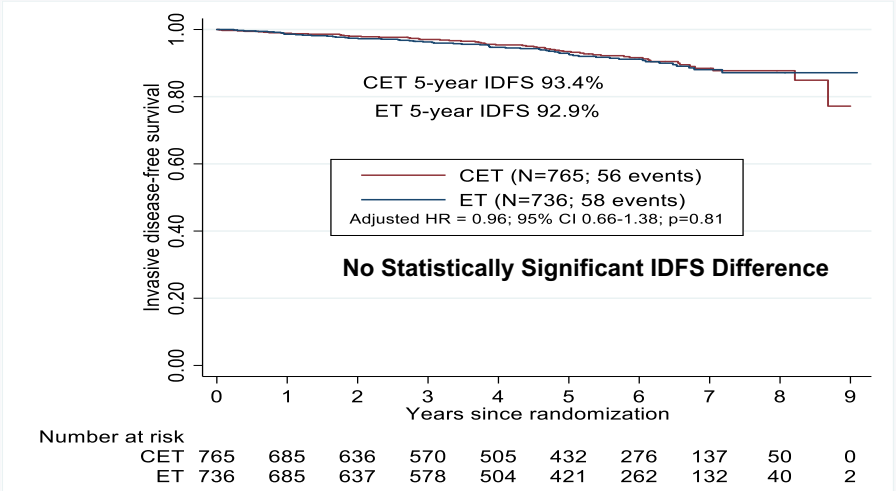
* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.
** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.
ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

Kalinsky K et al. SABCS 2020;Abstract GS3-00

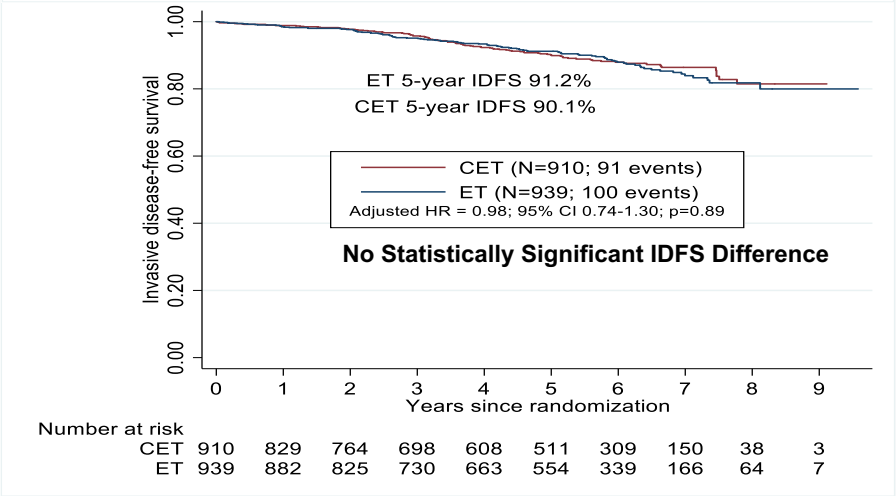
IDFS Stratified by Recurrence Score and Menopausal Status

Postmenopausal

RS 0-13

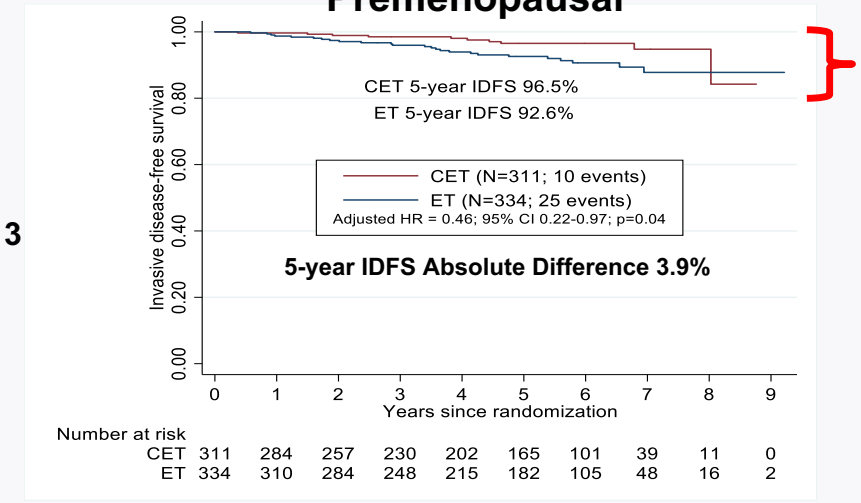


RS 14-25

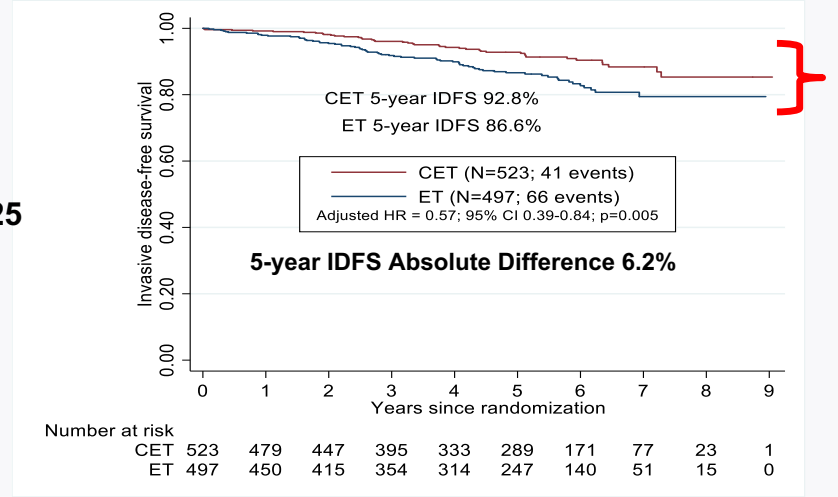


Premenopausal

RS 0-13



RS 14-25



Premenopausal patients:
84% and 75% received tamoxifen monotherapy in the chemo-endocrine and endocrine alone arms

Kalinsky K et al. SABCS 2020;Abstract GS3-00

Summary

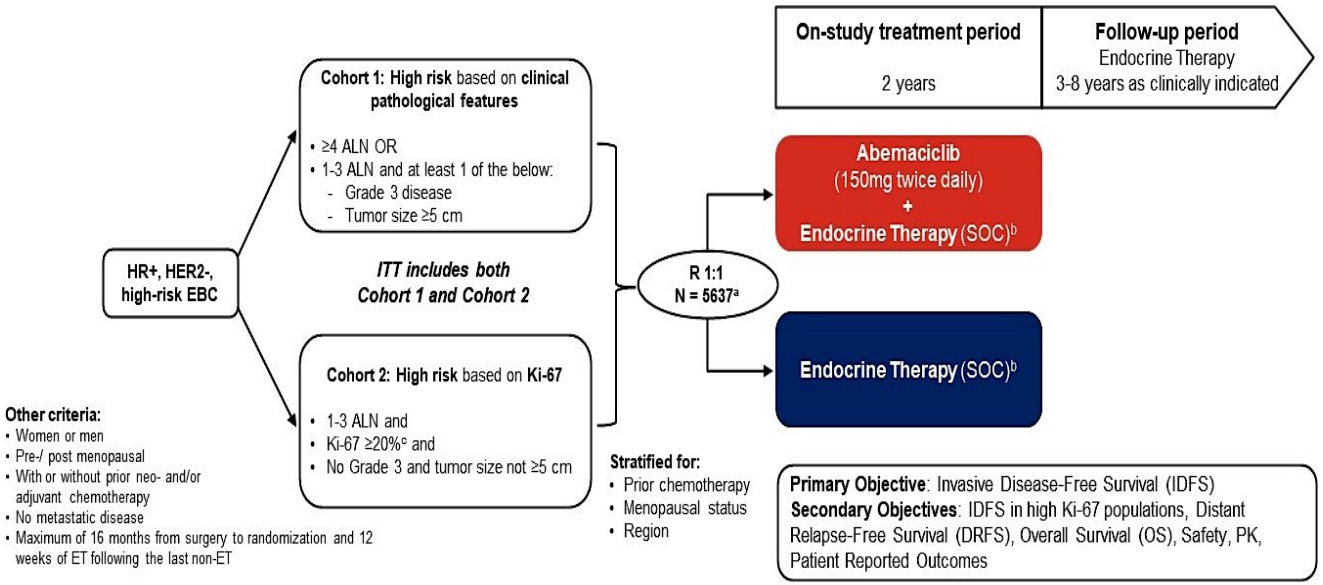
- In RxPONDER, the addition of chemotherapy to endocrine therapy did not significantly improve IDFS
  - Similar to TAILORx, an effect of age and menopausal status continues to be seen:
    - No benefit in postmenopausal women
    - In age <50, clear benefit of chemotherapy regardless of RS
    - Similar findings in MINDACT
- In TAILORx, RxPonder, and MINDACT, the predominant adjuvant hormonal therapy for premenopausal patients was tamoxifen (without OFS)
- NRG 009 will answer whether the addition of chemotherapy to optimal endocrine therapy (AI + OFS) significantly improves outcomes in premenopausal women with ER+/HER2- breast cancer

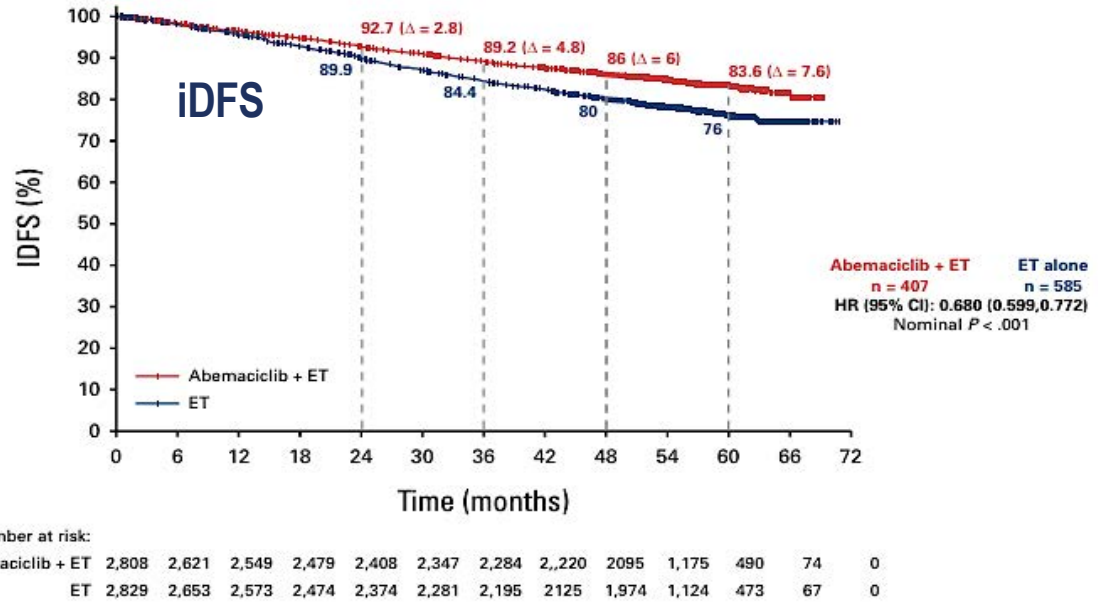
Adjuvant CDK4/6i Trials

Trial Name	N	CDK4/6i	Duration of CDKi	Eligibility	IDFS HR
Penelope-B	1250	Palbociclib	1 y	• Residual disease after 16 wk of neoadjuvant CT • CPS-EG score ≥3 or 2 with ypN+	HR = 0.93 (95% CI: 0.74-1.17) *P* = .53
PALLAS	5761	Palbociclib	2 y	• Stage II-III	HR = 0.96 (95% CI: 0.81-1.14) *P* = .65
monarchE	5637	Abemaciclib	2 y	• >4 ALN or • 1-3 ALN and at least 1 below: – T >5 cm – G3 – Ki-67 >20%	**HR = 0.680** **(95% CI: 0.599-0.772)** Nominal *P* < .001
NATALEE	5101	Ribociclib	3 y	• Stage II (either N0 with grade 2-3 and/or Ki67 ≥20% or N1) or III	HR = 0.749 (95% CI: 0.628-0.892) *P* = .0012

Loibl S et al. *J Clin Oncol*. 2021;39:1518-1530. Gnant M et al. *J Clin Oncol*. 2022;40:282-293.
Rastogi P et al. *J Clin Oncol.* 2024 Mar 20;42(9):987-993. Hortobagyi GN et al. *Ann Oncol*. 2025 Feb;36(2):149-157.

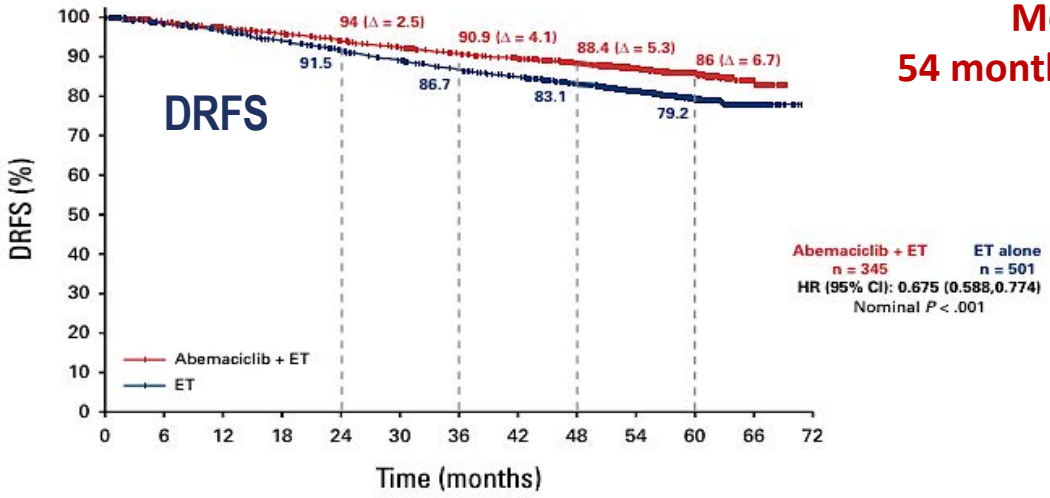
MonarchE





Number at risk:

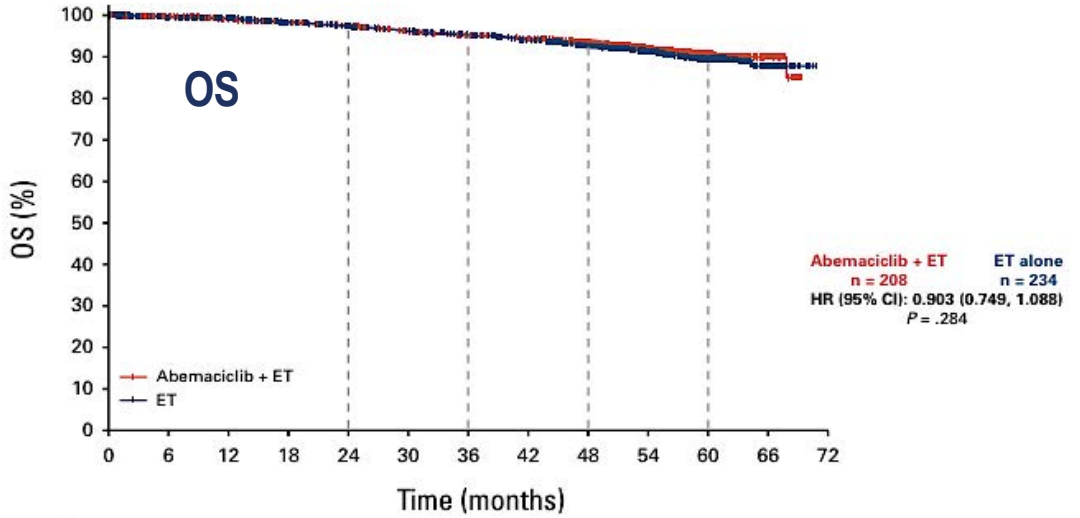
Abemaciclib + ET	2,808	2,621	2,549	2,479	2,408	2,347	2,284	2,,220	2095	1,175	490	74	0
ET	2,829	2,653	2,573	2,474	2,374	2,281	2,195	2125	1,974	1,124	473	67	0



Number at risk:

Abemaciclib + ET	2,808	2,630	2,567	2,500	2,434	2,375	2,313	2,258	2,141	1,202	500	75	0
ET	2,829	2,660	2,590	2,499	2,410	2,327	2,243	2,176	2,032	1,161	488	72	0

Median FU
54 months (IQR, 49-59).

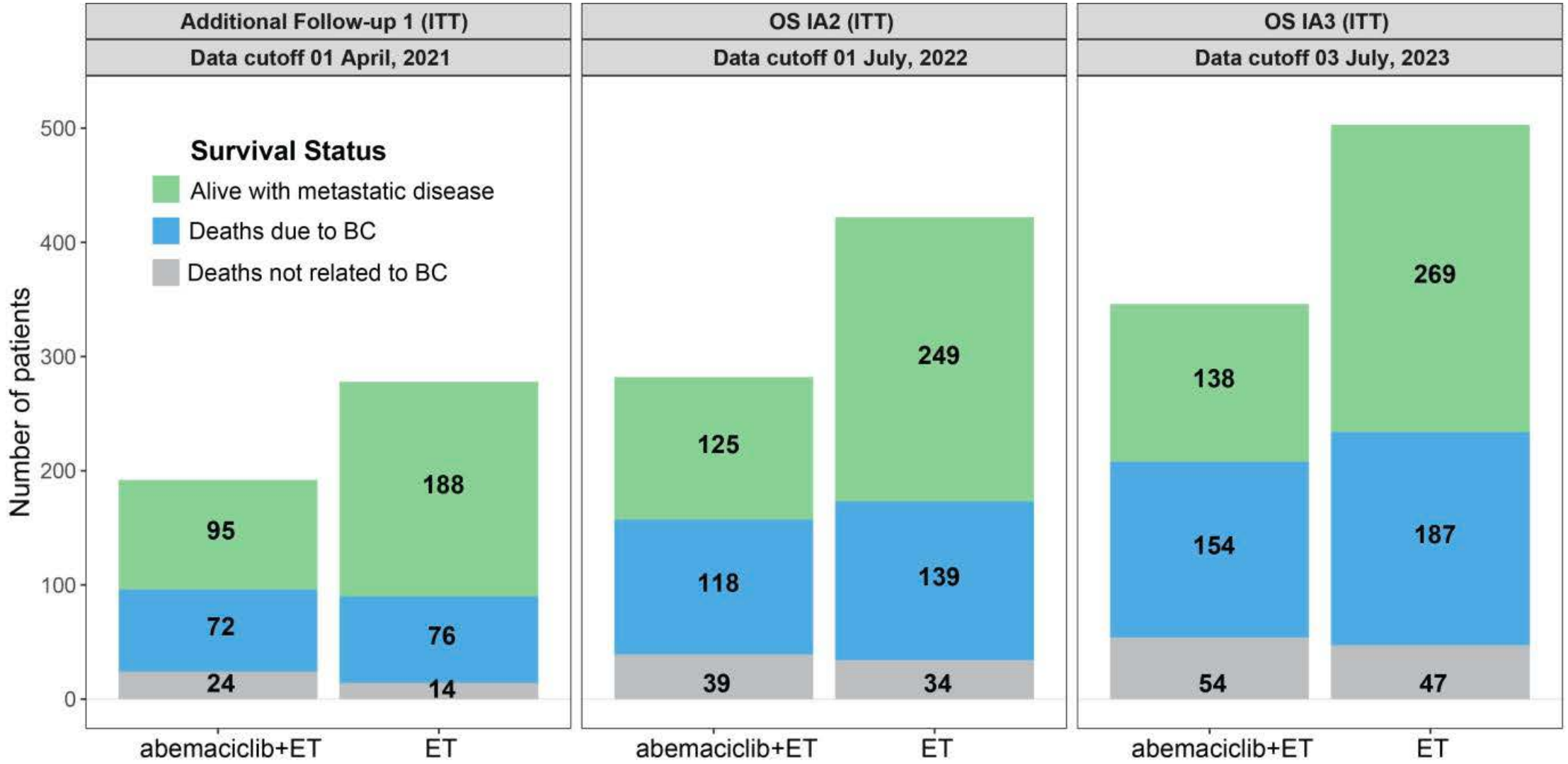


Number at risk:

Abemaciclib + ET	2,808	2,666	2,614	2,566	2,518	2,455	2,407	2,373	2,260	1,271	528	80	0
ET	2,829	2,705	2,664	2,599	2,545	2,496	2,440	2,382	2,243	1,279	538	77	0

Rastogi et al J Clin Oncol 2024: 42: 987-993

monarchE: Interim OS Analysis



Harbeck N. ESMO 2023;Abstract LBA17.

Abemaciclib increases overall survival in HR+, HER2-, high-risk early breast cancer with two years of therapy

Press Release: August 27, 2025

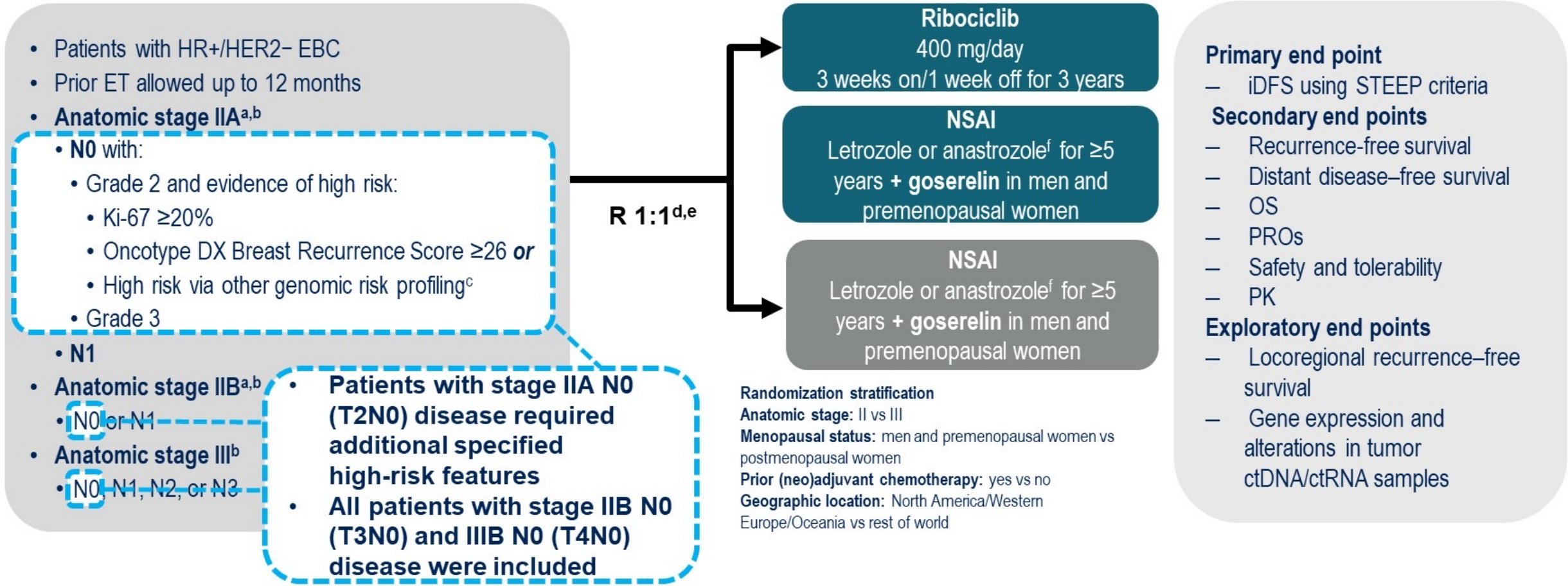
“[The manufacturer] today announced positive topline results from the primary overall survival (OS) analysis of the Phase 3 monarchE trial. Treatment with two years of abemaciclib plus endocrine therapy (ET) demonstrated a statistically significant and clinically meaningful improvement in OS compared to ET alone in patients with hormone receptor positive (HR+), HER2-, node-positive, high-risk early breast cancer.

The seven-year landmark analysis also demonstrated sustained benefit in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS), reinforcing the consistency and durability of treatment effect across endpoints.

Detailed results will be presented at a future medical meeting, submitted for publication in a peer-reviewed journal and discussed with regulatory bodies.”

https://investor.lilly.com/news-releases/news-release-details/lillys-verzenior-abemaciclib-increases-overall-survival-hr-her2

Phase III NATALEE: Study Design



[a] Enrollment of patients with stage II disease was capped at 40%. [b] N0 was determined either clinically and confirmed surgically as needed. [c] Genomic high risk is defined as at least one of the following: Oncotype Dx Breast Recurrence Score ≥26, PAM50 score of "High Risk," MammaPrint score of "High Risk," EndoPredict EPclin Risk score of "High Risk". [d] 5101 patients were randomized from January 10, 2019, to April 20, 2021. [e] Open-label design. [f] Per investigator choice.
ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N0, no nodal involvement/ node-negative; ITT, intention to treat; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥10 axillary lymph nodes or collarbone lymph nodes; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PROs, patient reported outcomes; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in adjuvant breast cancer trials.
1. Slamon D, et al. ASCO 2023. Oral; abstract LBA500. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract TPS597.

Yardley DA et al. ASCO 2024;Abstract 512

NATALEE STUDY: iDFS, DDFS & OS outcomes with RIB+NSAI after planned 3-year treatment

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **Anatomical stage IIA**[a]
- **Anatomical stage IIB**[a]
- **Anatomical stage III**

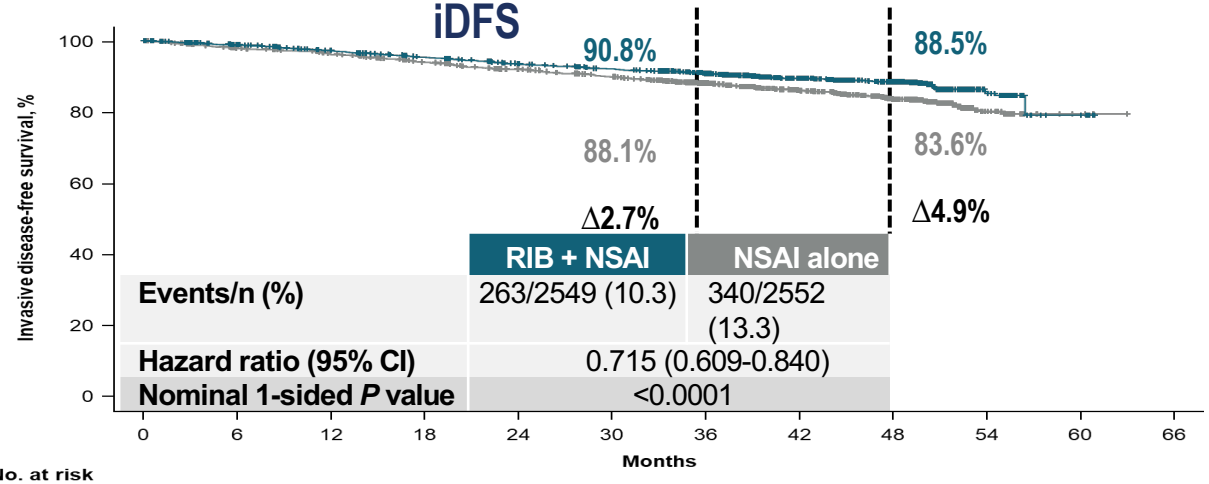
N = 5101[b]

R 1:1[c]

Ribociclib
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

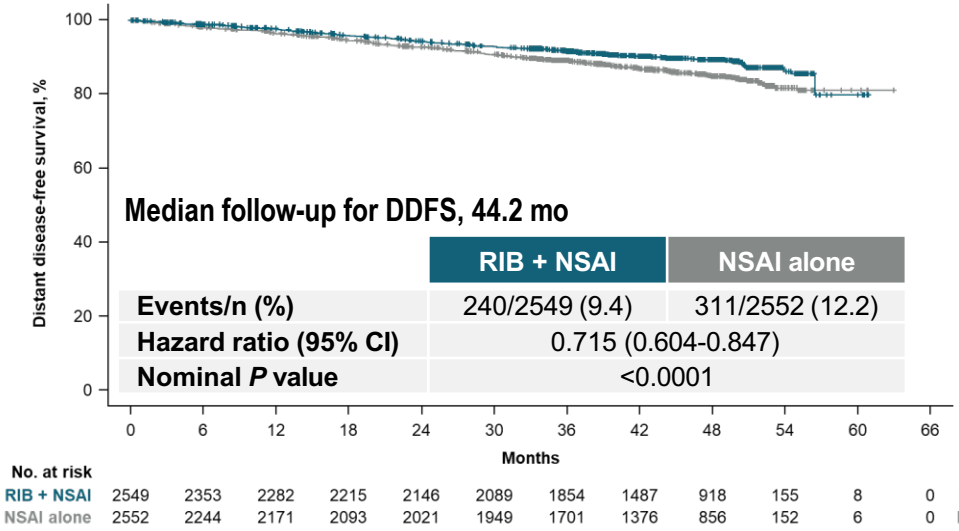
iDFS



	RIB + NSAI	NSAI alone
Events/n (%)	263/2549 (10.3)	340/2552 (13.3)
Hazard ratio (95% CI)	0.715 (0.609-0.840)	
Nominal 1-sided *P* value	<0.0001	

No. at risk												
RIB + NSAI	2549	2351	2275	2207	2133	2078	1843	1480	914	155	8	0
NSAI alone	2552	2240	2168	2082	2006	1935	1687	1366	848	150	6	0

DDFS

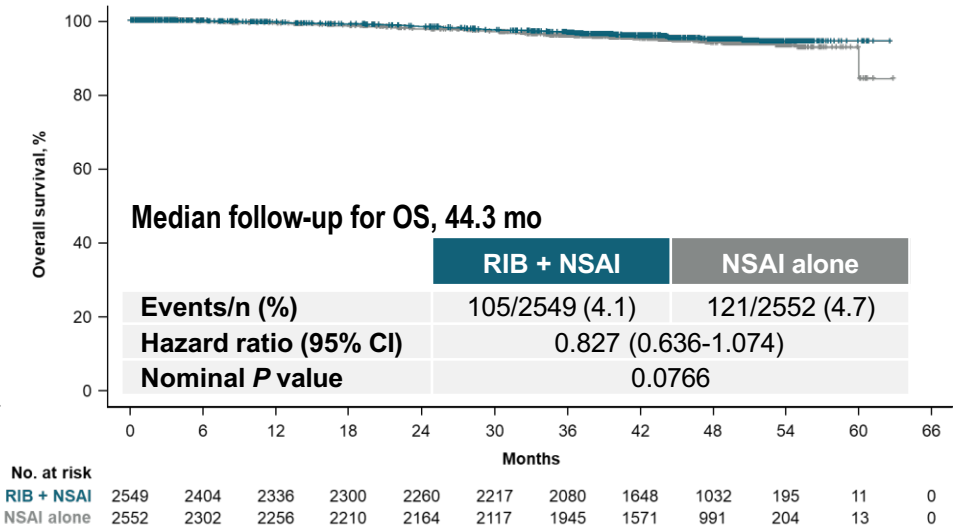


Median follow-up for DDFS, 44.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	240/2549 (9.4)	311/2552 (12.2)
Hazard ratio (95% CI)	0.715 (0.604-0.847)	
Nominal *P* value	<0.0001	

No. at risk												
RIB + NSAI	2549	2353	2282	2215	2146	2089	1854	1487	918	155	8	0
NSAI alone	2552	2244	2171	2093	2021	1949	1701	1376	856	152	6	0

OS



Median follow-up for OS, 44.3 mo

	RIB + NSAI	NSAI alone
Events/n (%)	105/2549 (4.1)	121/2552 (4.7)
Hazard ratio (95% CI)	0.827 (0.636-1.074)	
Nominal *P* value	0.0766	

No. at risk												
RIB + NSAI	2549	2404	2336	2300	2260	2217	2080	1648	1032	195	11	0
NSAI alone	2552	2302	2256	2210	2164	2117	1945	1571	991	204	13	0

Peter A. Fasching ESMO 2024;Abstract LBA13

Manufacturer to showcase transformative data in advanced prostate and early breast cancer at ESMO 2025

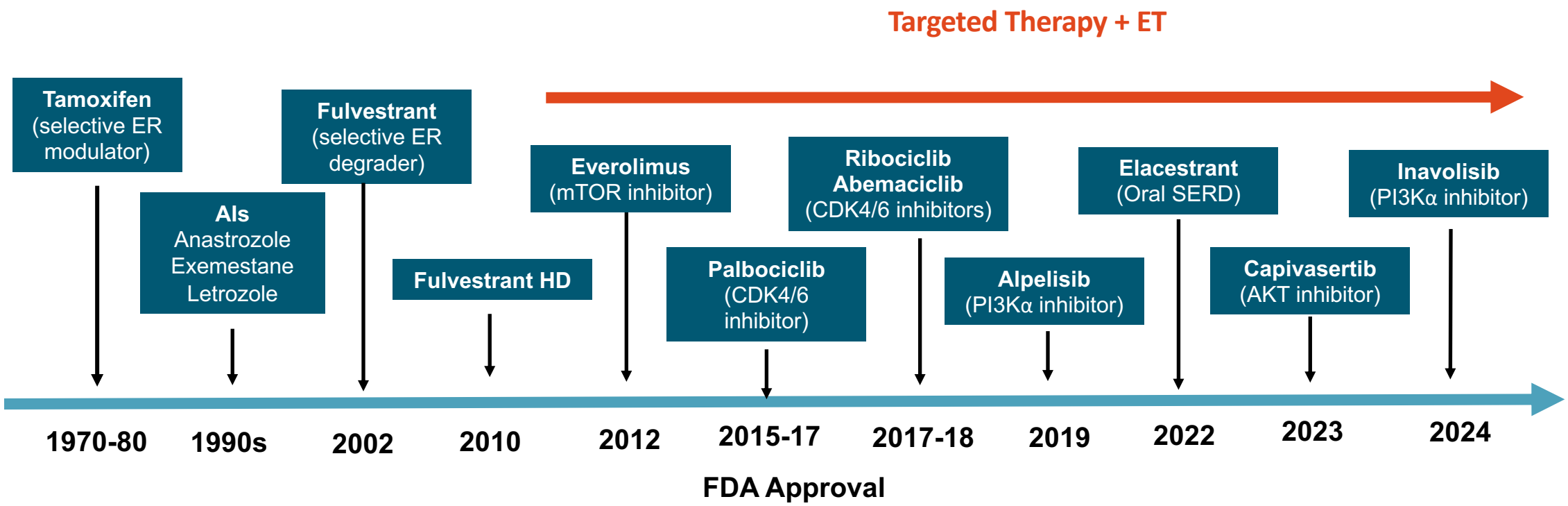
Sep 26, 2025

- *Key data from PSMAddition has been selected for a Presidential session; data to showcase the efficacy and safety of ^{177}Lu plus standard of care (SoC) versus SoC alone in PSMA + mHSPC*

- *NATALEE five-year analysis of ribociclib to provide further long-term insights into risk of recurrence reduction in a broad EBC patient population*

https://www.novartis.com/news/media-releases/novartis-showcase-transformative-data-advanced-prostate-and-early-breast-cancer-esmo-2025

Evolving Hormonal Treatment Landscape of HR+ Advanced MBC



First-Line Metastatic Trials with CDK4/6 Inhibitors

Trial	N	CDK4/6i	Endocrine Therapy	Phase	Median PFS, mo	Median OS, mo
PALOMA-1	165	**Palbociclib (P)**	Letrozole (L)	2	**10.2 (L)** vs **20.2 (L+P)** HR = 0.49 *P* = .0004	**34.5 (L)** vs **37.5 (P+L)** HR = 0.897 *P* =.28
PALOMA-2	666	**Palbociclib (P)**	Letrozole (L)	3	**14.5 (L)** vs **24.8 (L+P)** HR = 0.58 *P* < .001	**51.2 (L)** vs **53.9 (P+L)** HR = 0.96 *P* = .34
MONARCH 3	493	**Abemaciclib (A)**	NSAI	3	**14.8 (A)** vs **28.2 (ET+A)** HR = 0.54 *P* = .000002	**53.7 (AI)** vs **66.8 (AI + A)** HR = 0.804; 95% CI, 0.637-1.015 *P* = .067
MONALEESA-2	668	**Ribociclib (R)**	Letrozole (L)	3	**16.0 (L)** vs **25.3 (L+R)** HR = 0.568	**51.4 (L)** Vs **63.9 (R+L)** HR = 0.76; 95% CI, 0.63-0.93 *P* = .008
MONALEESA-7	672	**Ribociclib (R)**	ET (Tam or AI) + OFS	3	**13.0** (**ET**) vs **23.8** (**R+ET**) HR = 0.55 *P* < .0001	**48.0 (ET) vs 58.7 (ET+Rib)** HR: 0.76; 95% CI, 0.61–0.96

Finn. *Lancet Oncol.* 2014. Slamon J. *Clin Oncol.* 2024. Goetz. *Ann Oncol*. 2024. Hortobagyi. *N Engl J Med*. 2022. Lu. *Clin Canc Res.* 2022.
Finn RS et al. ASCO 2017;Abstract 1001

Summary of updated CDK 4/6i data

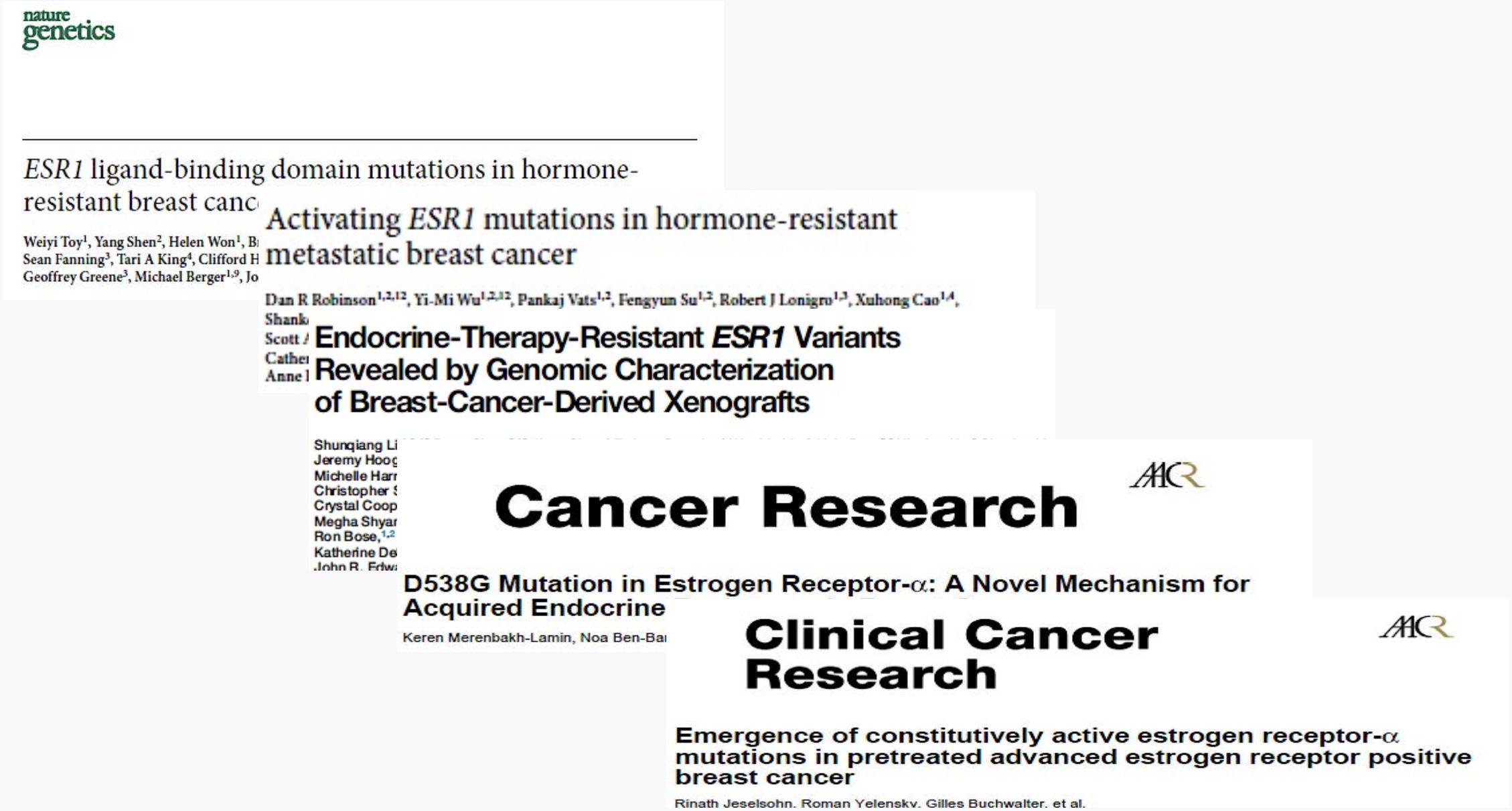
In the adjuvant setting, the addition of abemaciclib and ribociclib to standard of care ET improves DFS

OS data to be presented at ESMO (abemaciclib)

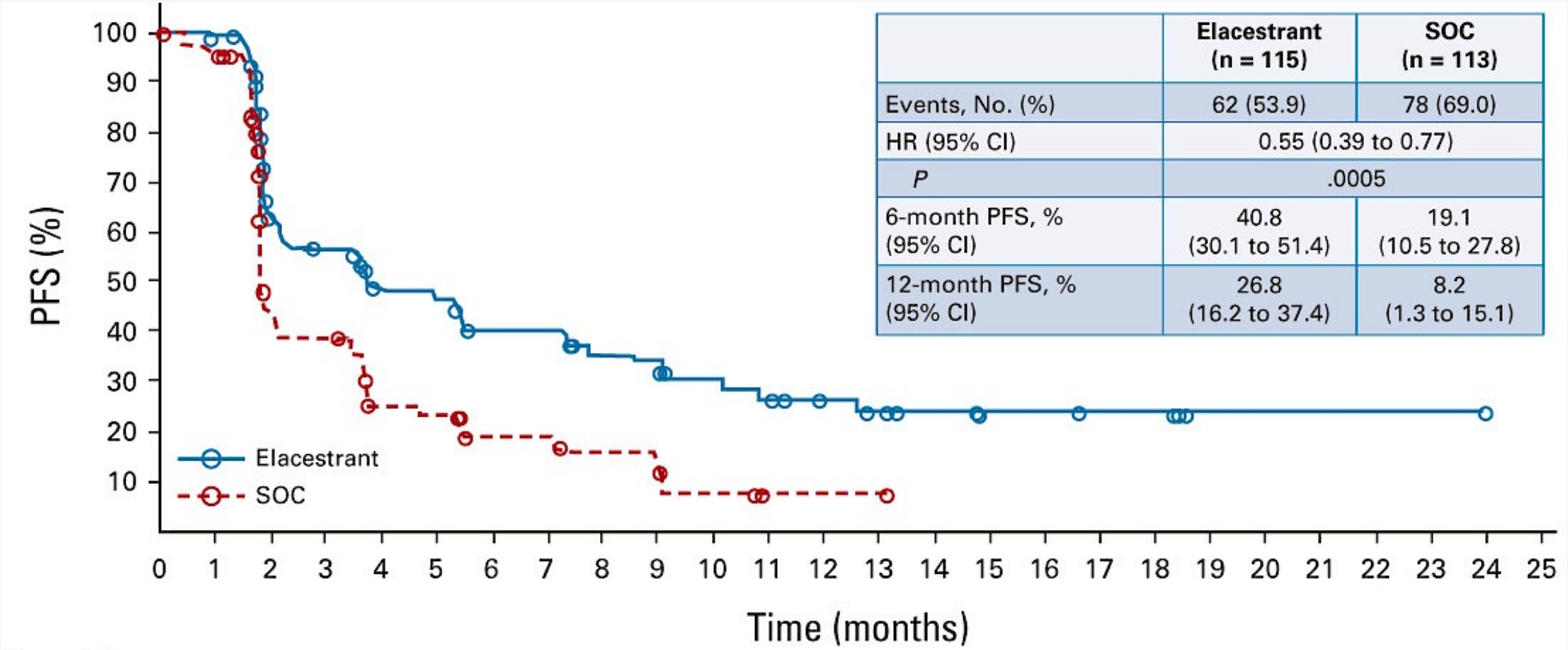
In the metastatic setting, CDK 4/6 inhibitors (ribociclib and abemaciclib) in combination with ET improve survival in the first- and second-line settings.

No head-to-head trials comparing palbociclib, ribociclib and abemaciclib

ESR1 Mutations: Therapeutic Implications



Phase III EMERALD: Elacestrant vs SOC in ESR1m Tumors



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

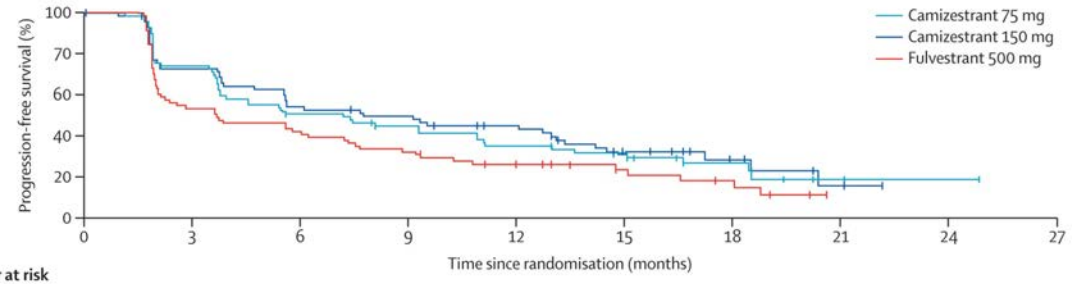
Based on these data, the FDA approved elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer (January 7, 2023)

Bidard FC et al. J Clin Oncol. 2022 Oct 1;40(28):3246-3256.

Camizestrant versus Fulvestrant in Post-menopausal Women with Estrogen receptor-positive, HER2-negative Advanced Breast Cancer (SERENA-2)

All Patients

	Camizestrant 75 mg (n=74)	Camizestrant 150 mg (n=73)	Fulvestrant 500 mg (n=73)
Patients with events (%)	50 (68%)	48 (66%)	57 (78%)
Median progression-free survival (90% CI), months	7·2 (3·7–10·9)	7·7 (5·5–12·9)	3·7 (2·0–6·0)
HR (90% CI)*	0·59 (0·42–0·82)	0·64 (0·46–0·89)	..
Stratified log-rank p value*	0·017	0·0090	..
6-month progression-free survival rate (90% CI)	50·3% (40·0–59·7)	53·6% (43·3–62·9)	40·0% (30·4–49·4)
12-month progression-free survival rate (90% CI)	34·3% (24·9–44·0)	44·5% (34·4–54·1)	25·3% (17·1–34·2)
Median follow-up (IQR), months	16·6 (12·9–19·4)	16·3 (12·9–18·3)	14·7 (12·7–20·1)

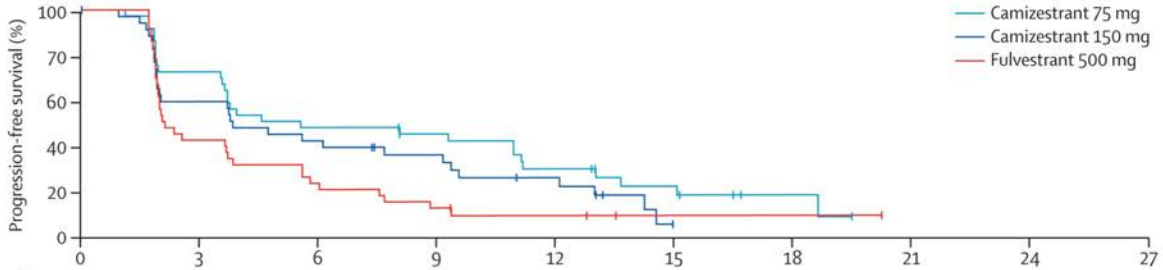


Number at risk (number censored)										
Camizestrant 75 mg	74 (0)	50 (6)	33 (7)	27 (9)	21 (9)	14 (13)	7 (19)	2 (22)	1 (23)	0 (24)
Camizestrant 150 mg	73 (0)	50 (4)	37 (4)	32 (6)	25 (10)	13 (15)	6 (21)	2 (23)	0 (25)	..
Fulvestrant 500 mg	73 (0)	37 (3)	28 (3)	22 (3)	14 (7)	8 (12)	5 (13)	0 (16)	..	..

Previous CDK 4/6 Inhibitors

A Previous CDK4/6 inhibitor

	Camizestrant 75 mg (n=38)	Camizestrant 150 mg (n=37)	Fulvestrant 500 mg (n=37)
Patients with events (%)	29 (76%)	29 (78%)	33 (89%)
Median progression-free survival (90% CI), months	5·5 (3·7–10·9)	3·8 (2·0–7·6)	2·1 (1·9–3·7)
HR (90% CI)*	0·49 (0·31–0·75)	0·68 (0·44–1·04)	..



Number at risk (number censored)										
Camizestrant 75 mg	38 (0)	27 (1)	18 (1)	15 (3)	10 (3)	5 (5)	2 (8)	0 (9)	..	..
Camizestrant 150 mg	37 (0)	21 (2)	15 (2)	11 (4)	7 (5)	0 (8)	..	..	..	..
Fulvestrant 500 mg	37 (0)	16 (0)	8 (0)	5 (0)	3 (1)	1 (3)	1 (3)	0 (4)	..	..

Oliveira et al. Lancet Oncology 2025

(Secondary) Prevention

“…, prevention is so much better than healing because it saves the labour of being sick.”

Thomas Adams
ca. 1618

Quoted in Muir CS. Cancer Res 1990;50:6441-8.

2025 ASCO ANNUAL MEETING

SERENA-6

Camizestrant + CDK4/6 inhibitor for the treatment of emergent *ESR1* mutations during first-line endocrine-based therapy and ahead of disease progression in patients with HR+/HER2– advanced breast cancer: Phase 3, double-blind ctDNA-guided SERENA-6 trial

Nicholas Turner*
Royal Marsden Hospital, London, UK

Additional authors:
Erica Mayer, Yeon Hee Park, Wolfgang Janni, Cynthia Ma, Massimo Cristofanilli, Giampaolo Bianchini, Kevin Kalinsky, Hiroji Iwata, Stephen Chia, Peter A. Fasching, Adam Brufsky, Zbigniew Nowecki, Javier Pascual, Lionel Moreau, Shin-Cheh Chen, Sasha McClain, Steven Fox, Cynthia Huang Bartlett, François-Clément Bidard*

*Contributed equally

SERENA-6 study design

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

→ R 1:1
N=315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

Stratification factors

- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

Continuing AI (anastrozole/letrozole) + CDK4/6i + placebo for camizestrant

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

Primary endpoint

PFS by investigator assessment (RECIST v1.1)

Secondary endpoints

- PFS2**
- OS**
- Safety
- Patient-reported outcomes

*Pre- or perimenopausal women, and men received a luteinizing hormone–releasing hormone agonist per clinical guidelines. **Key secondary endpoint.
OS, overall survival; PFS2, second progression-free survival; qd, once daily dose; R, randomized; RECIST, response evaluation criteria in solid tumors.

Baseline characteristics

SERENA-6

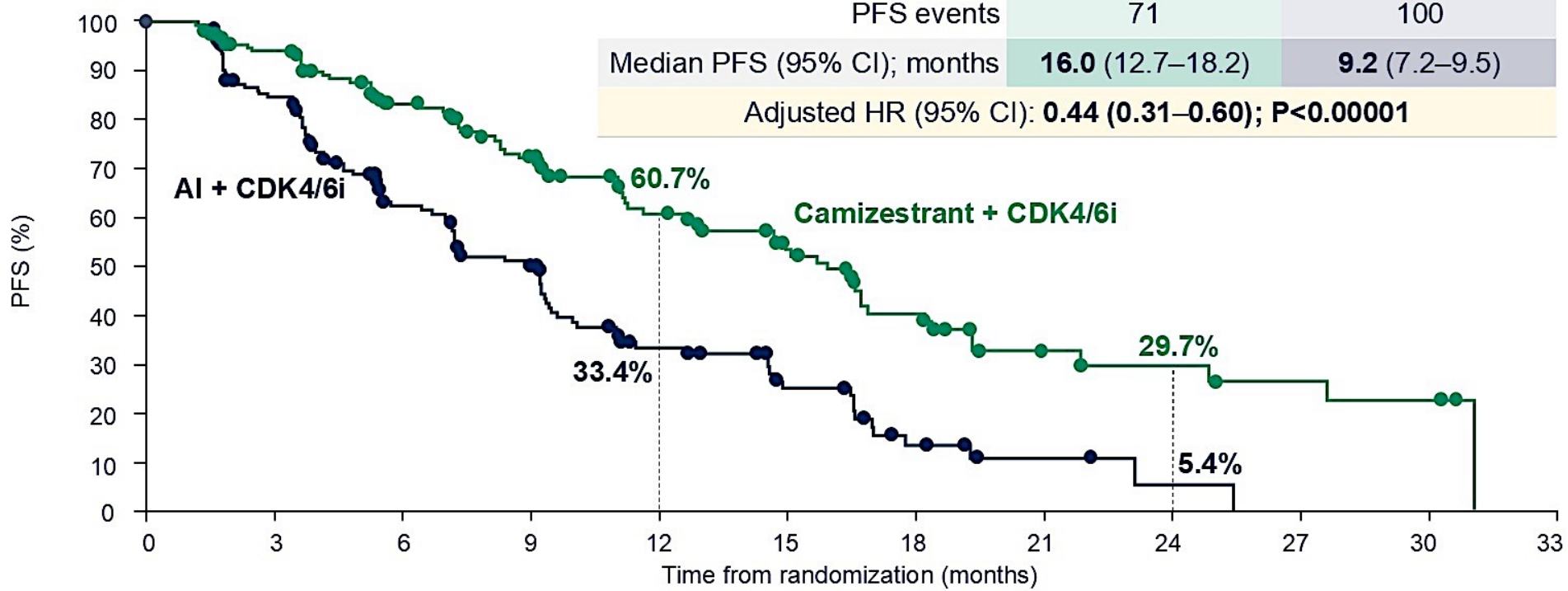
Characteristic		Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Median age (range) — years		61.0 (29–81)	60.5 (35–89)
Female — n (%)		157 (100)	155 (98)
Race — n (%)	White	97 (62)	102 (65)
	Asian/other	39 (25) / 21 (13)	34 (22) / 22 (14)
Postmenopausal status — n (%)		123 (78)	127 (80)
ECOG performance-status score — n (%)*	0/1	107 (68) / 48 (31)	98 (62) / 56 (35)
Visceral metastases — n (%)†		66 (42)	71 (45)
Time of *ESR1*m detection — n (%)†	At first test	84 (54)	84 (53)
	At a subsequent test‖	73 (47)	74 (47)
	Median (range) – months	22 (4–95)	22 (6–96)
Time from initiation of AI + CDK4/6i to randomization — n (%)†	≥18 months	97 (62)	100 (63)
	<18 months	60 (38)	58 (37)
	Median (range) – months	23 (7–96)	23 (6–96)
CDK4/6i continued at randomization — n (%)†	Palbociclib	119 (76)	119 (75)
	Ribociclib	24 (15)	23 (15)
	Abemaciclib	14 (9)	16 (10)
Most common *ESR1*m at baseline — n (%)‡	D538G	70 (45)	82 (52)
	Y537S	61 (39)	60 (38)
	Y537N	29 (19)	25 (16)

*Data was missing for 2 patients in the camizestrant + CDK4/6i arm and 3 patients in the AI + CDK4/6i. One patient in the AI+CDK4/6i group had a score of 2, which was a protocol deviation. †Stratification factors. ‖Subsequent tests were performed every 2-3 months after the initial test. ‡Three most prevalent *ESR1*m detected of the 11 qualifying mutations. Patients may have had more than one *ESR1*m. ECOG, Eastern Cooperative Oncology Group.

Primary endpoint: Investigator-assessed PFS

SERENA-6

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS events	71	100
Median PFS (95% CI); months	**16.0** (12.7–18.2)	**9.2** (7.2–9.5)
Adjusted HR (95% CI): **0.44 (0.31–0.60); P<0.00001**		



Number of patients at risk

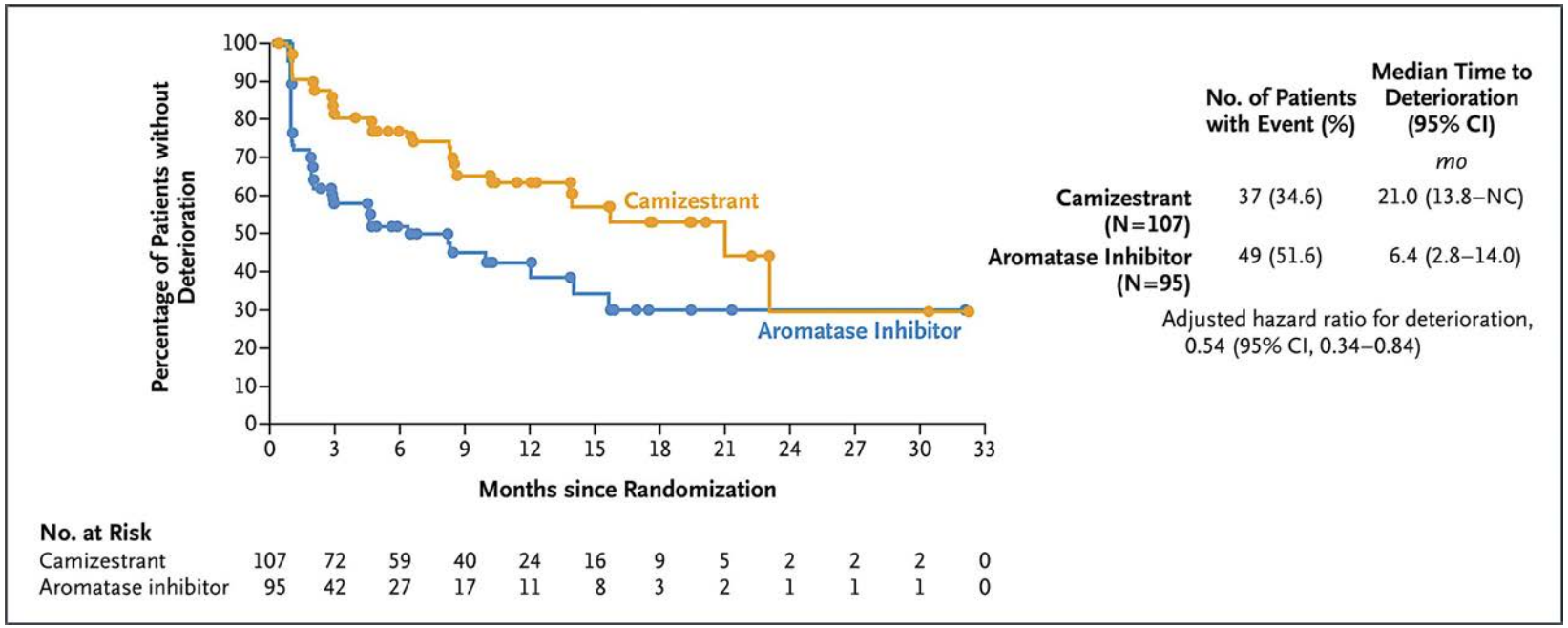
Camizestrant + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

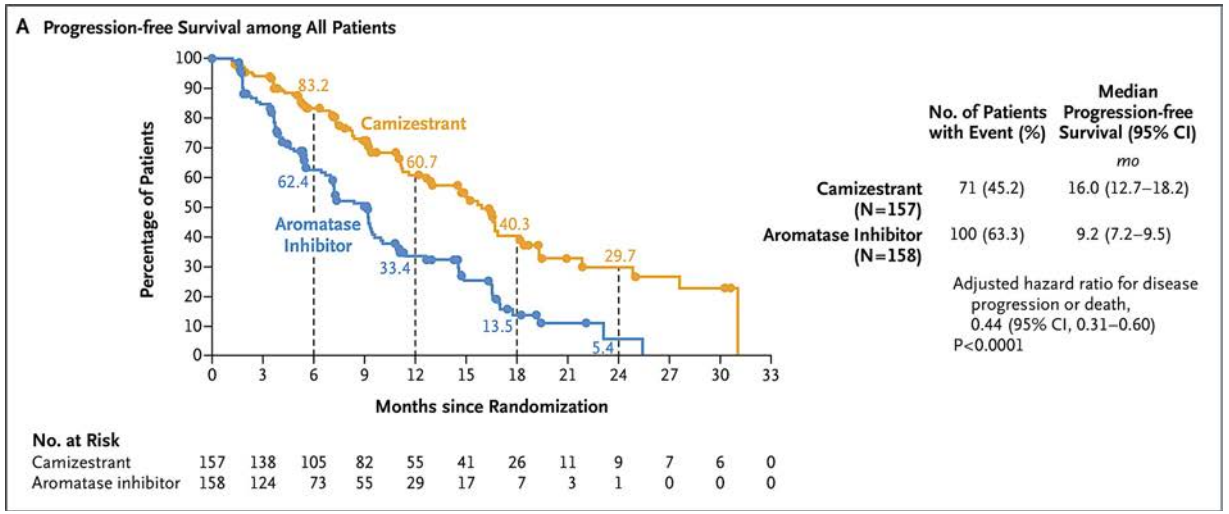
P-value crossed the threshold for significance (P=0.0001). PFS was defined per RECIST v1.1. HR was estimated using the Cox proportional hazard model adjusted for stratification factors.
CI, confidence interval; HR, hazard ratio.

Concerns regarding SERENA-6 Design

- The study design is testing:
  - new treatment strategy (ie molecular vs anatomical progression) and
  - a novel drug (Camizestrant)
  - both only being in the experimental arm
    - There is no crossover to determine which strategy results in better overall survival
- Question: Is there evidence that treating patients early (at the time of MRD relapse) prevents *symptomatic* progression of disease?

Time until Deterioration in Global Health Status and Quality of Life versus PFS: Disconnect between PFS and QOL Deterioration





Bidard et al. NEJM 2025

Summary

- *ESR1* mutations are a common mechanism of acquired resistance in the setting of aromatase inhibitors (+/- CDK4/6i)
- Oral SERDS: Limited antitumor activity in the post-CDK4/6i setting
  - Greater antitumor activity in patients with *ESR1* mutations and prior endocrine sensitivity
- SERENA-6: Value of switching from an AI to oral SERDS in the 1st line treatment of ER+ MBC with molecular progression (without radiographic progression)
  - Overall Survival: Unclear given the lack of crossover of the control treatment to camizestrant
  - Quality of Life: Need more information

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

monarchE: Primary Overall Survival (OS) Results of Adjuvant Abemaciclib + Endocrine Therapy (ET) for HR+, HER2-, High-Risk Early Breast Cancer (EBC)

Johnston SR et al.

ESMO 2025;Abstract LBA13.

PROFFERED PAPER | SUNDAY, OCTOBER 19 | 14:50 CEST

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists

- **Onco*type* DX or MammaPrint — how do you choose which one to use? Do you ever order both?**
- **Is there data with Onco*type* DX to support treatment de-escalation such as dropping the anthracycline or reducing to 4 cycles of TC?**
- **Do you use Onco*type* DX in the neoadjuvant setting? Would you use it for a tumor less than 0.5 cm? What about an isolated local recurrence?**

Questions from General Medical Oncologists

- **Case: Initial treatment for ILC >5 cm and >3 LNs on MRI? Mastectomy/ALD or neoadjuvant chemo or check Onco*type* or MammaPrint/BluePrint and then decide on neoadjuvant endocrine therapy vs chemo?**

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists

- **Do you use CDK4/6 inhibitors in the neoadjuvant setting?**
- **Can CDK4/6i be used to downstage HR-positive cancers for surgery if patients are nonresponsive to chemotherapy?**

Questions from General Medical Oncologists

- **How would you approach first-line therapy for a patient with HR-positive, HER2-negative mBC in visceral crisis: CDK4/6i with endocrine therapy or chemotherapy or chemoendocrine therapy?**

Questions from General Medical Oncologists

- **What is your preferred adjuvant CDK4/6i for a node-positive patient?**
- **When using ribociclib in the adjuvant setting, are you generally continuing for 3 years?**
- **When using adjuvant CDK4/6i, are you always following the indication, ie, would you use abema in a node-negative patient?**

Questions from General Medical Oncologists

- **Is there a current role for ctDNA in breast cancer?**

AT THE FOREFRONT
UChicago Medicine

Relapsed/Refractory Hormone Receptor-Positive Metastatic Breast Cancer

Rita Nanda, M.D.

Research To Practice CME Symposium
Orlando, Florida
October 11, 2025

2L Therapy post PD

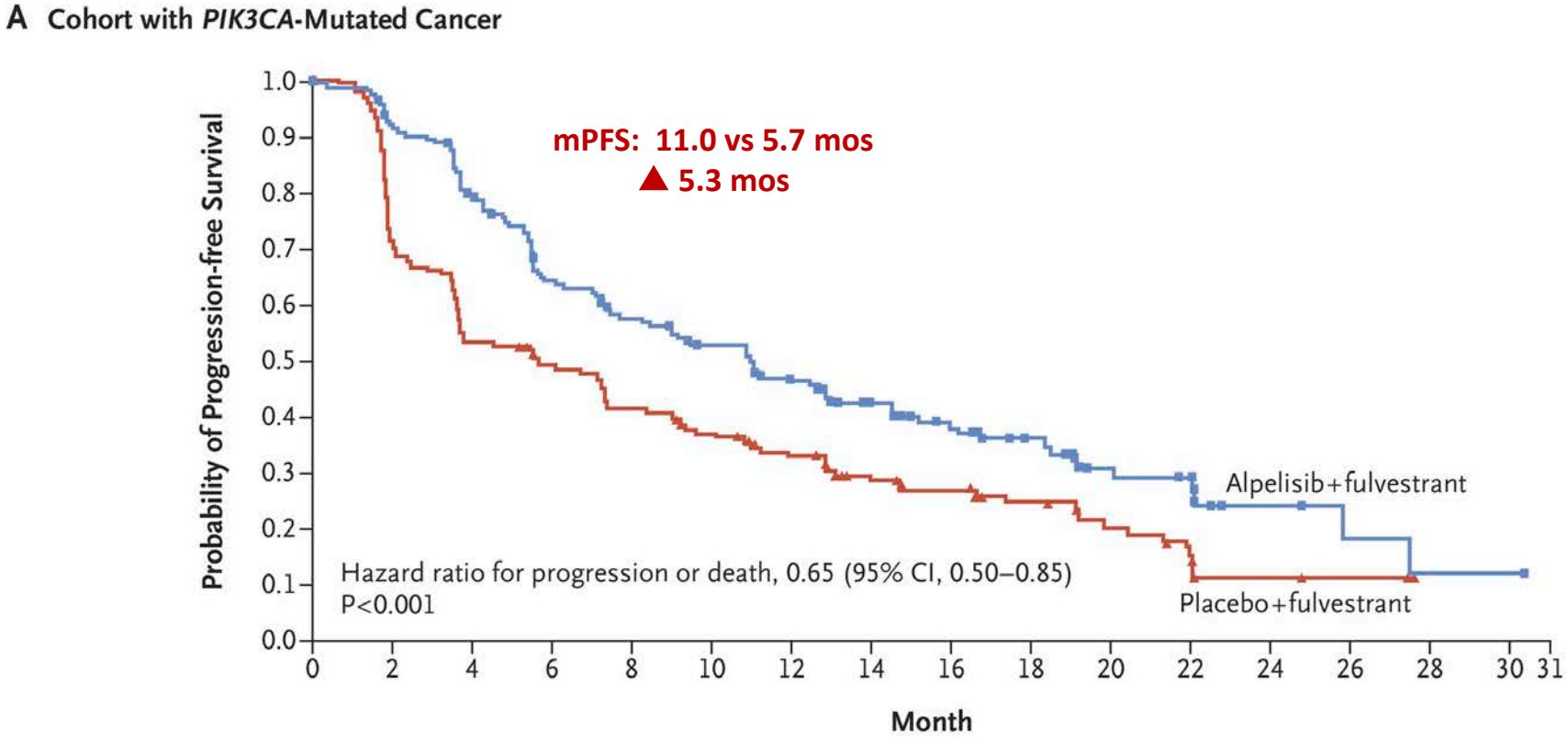
Molecularly Driven Recommendations

Targeted Therapies in 2L+ Setting

Agents targeting *PI3K* and *AKT* pathway

SOLAR-1 Trial - *PIK3CA*-mutated HR+/HER2- mBC
Phase 3 RCT of Fulvestrant + Alpelisib/Placebo in unselected

***PIK3CA* mutations occur in about 40% of HR+/HER2- breast cancers**
Alpelisib is α-selective PI3Ki



Key characteristics:
- HgbA1c < 6.4% allowed
- Lung or liver mets 50%
- 1st line 52%; 2nd line 46%
- Prior CDK4/6i 6%

Key toxicities with alpelisib:
- Hyperglycemia (G3/4 36%)
- Rash (G3/4 10%)
- Diarrhea (G3/4 7%)

BYLieve P2 Trial (all had PD post CDK4/6i): Similar Activity

André F et al. *N Engl J Med*. 2019;380(20):1929-1940.
Ciruelos. SABCS 2020. Abstr PD2-06.
Rugo et al. ASCO 2020 and SABCS 2020

CAPItello-291: P3 RCT Fulvestrant + Capivasertib/Placebo

Key Eligibility: **(N=708)**

- ER+/HER2- ABC (postmeno women)
- Recurrence on or < 12 mos from end of AI
- ≤ 2 lines prior ET for ABC
- ≤ 1 line of chemo for ABC
- Prior CDK4/6i allowed (≥ 51% required)
- No prior SERD or PI3K/AKT/mTORi
- HgbA1c < 8.0%

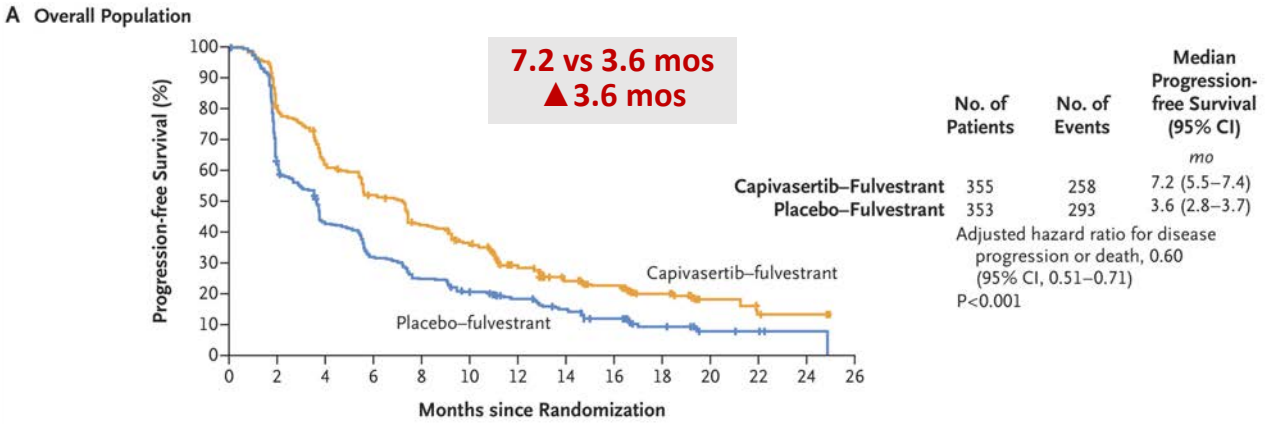
R → Fulvestrant + Capivasertib

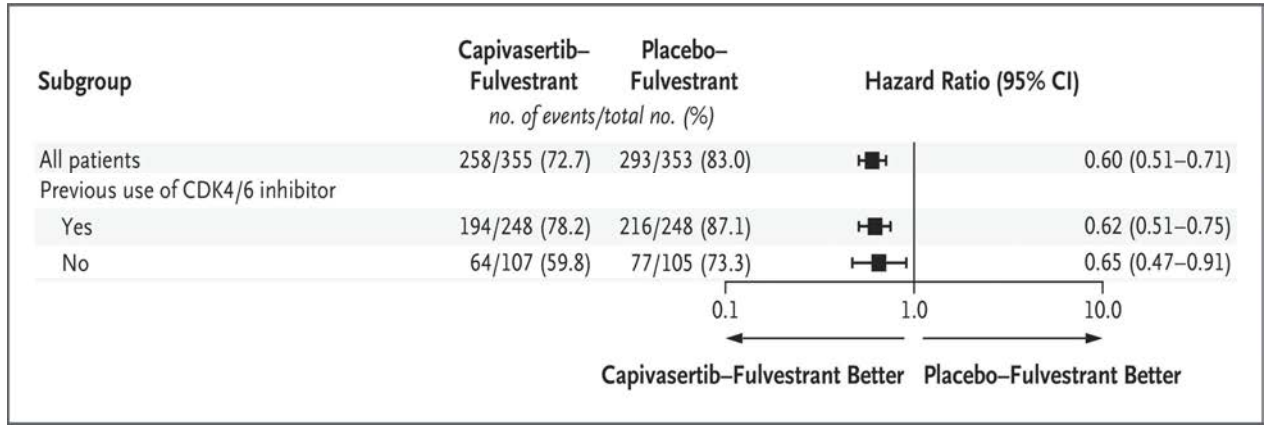
R → Fulvestrant + Placebo

Key Characteristics:

- Prior CDK4/6i: 69%
- Prior ET for ABC: 89%
- Prior chemo for ABC: 18%
- *AKT* pathway alterations: ~41%
- HgbA1c < 8% allowed

Overall population

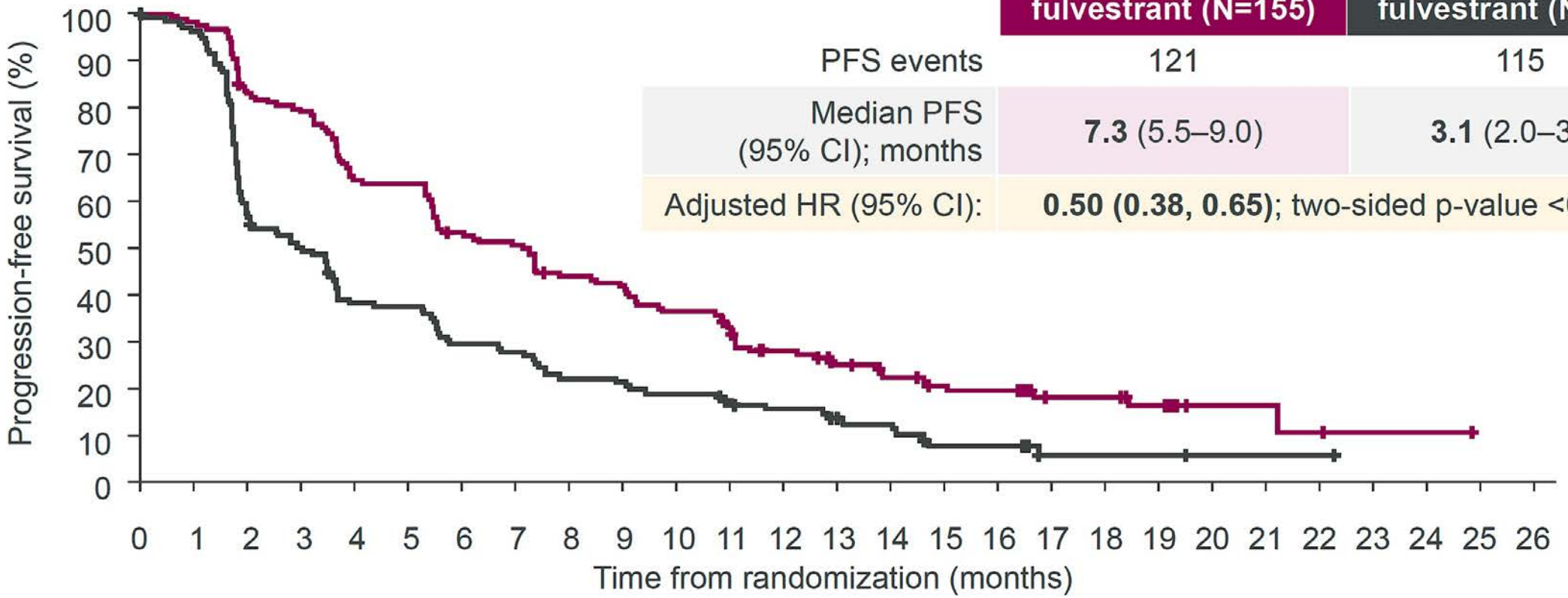




Similar benefit seen in those with alterations in *PIK3CA*, *AKT1*, or *PTEN*

Oliveira M et al. SABCS 2022; GS3-04; Turner et al NEJM 2023;388:2058

CAPItello-291: Progression-Free Survival (PFS) in the AKT Pathway-Altered Population



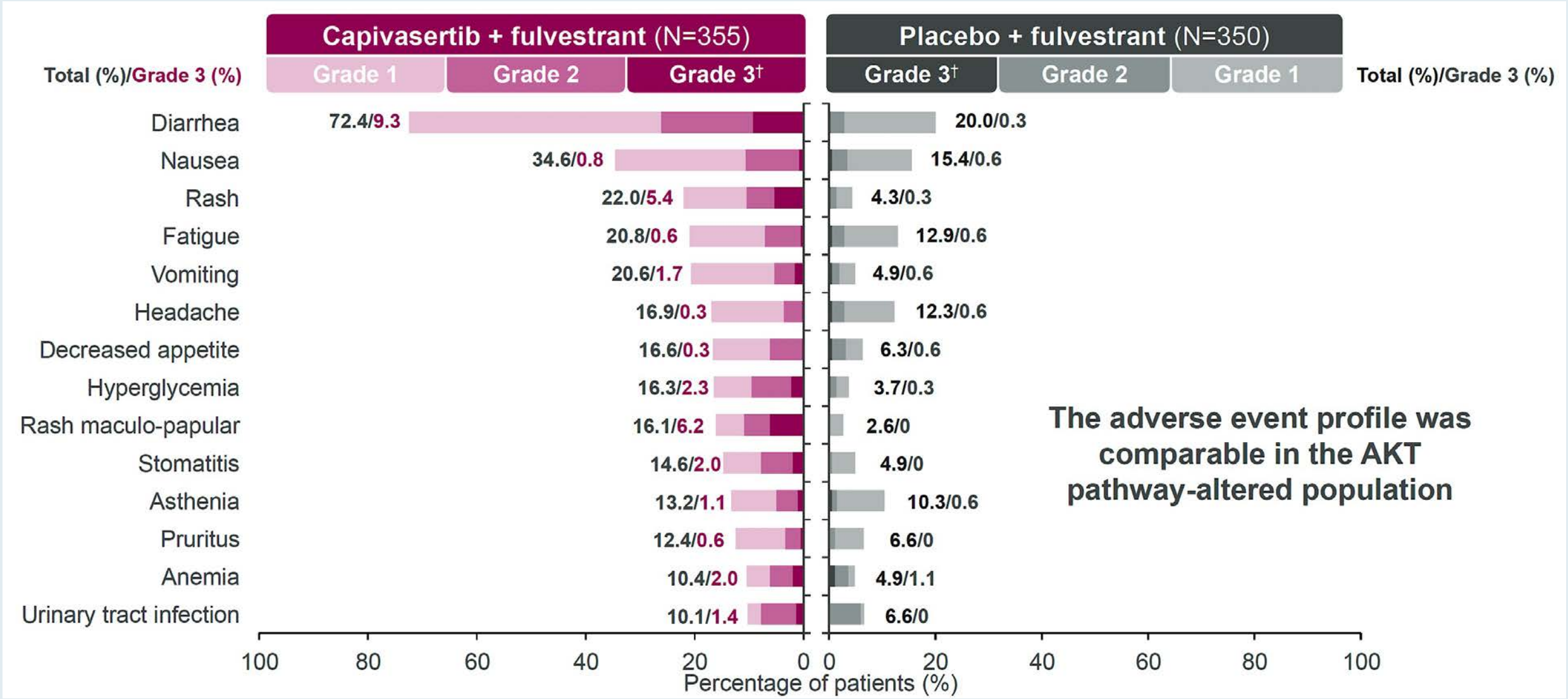
	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	

Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

Turner N et al. San Antonio Breast Cancer Symposium 2022;Abstract GS3-04.

CAPItello-291: Safety Profile



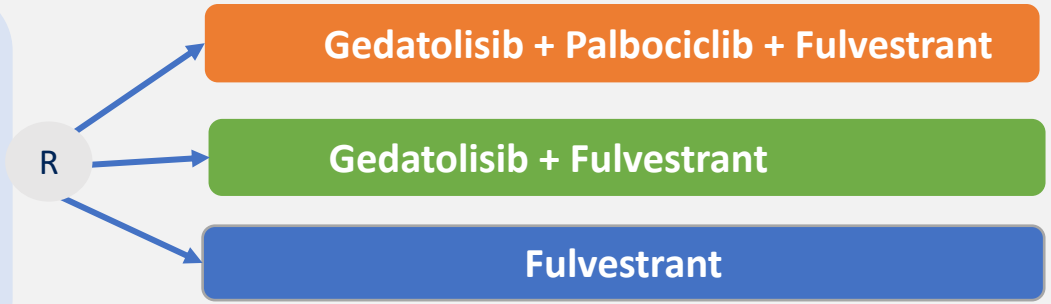
Turner N et al. San Antonio Breast Cancer Symposium 2022;Abstract GS3-04.

VIKTORIA-1: P3 RCT Gedatolisib pan-PI3K and mTORC1/2i

PRESS RELEASE

Key Eligibility:

- ER+/HER2- ABC
- Confirmed PIK3CA mutation status
- ≤ 2 lines prior ET for ABC
- No chemo for ABC
- Prior CDK4/6i + AI
- No prior *AKT*, *PI3K*, *mTORi*



Two cohorts *PIK3CAwt* (n=351) and *PIK3CAm* (n=350)

- Gedatolisib triplet:
  - mPFS (BICR) 9.3 mo triplet vs 2.0 mo fulv alone (HR, 0.24; 95% CI, 0.17–0.35; *P* <.0001).
- Gedatolisib doublet:
  - mPFS (BICR) 7.4 mo doublet vs 2.0 mo fulv alone (HR, 0.33; 95% CI, 0.24–0.48; *P* <.0001).

Targeted Therapies in 2L+ Setting

Agents targeting *ESR1*

EMERALD Open Label P3RCT – Elacestrant vs SOC ET

- Postmeno women and men with ER+/HER2- ABC or mBC
- ≤1 lines prior chemo for mBC
- 1 to 2 lines of ET
- Documented PD on CDK4/6 inhibitor
- Measurable disease or bone-only disease eligible

Strat factors
- *ESR1* status (by ctDNA)
- Prior fulvestrant
- Visceral disease

N = 466

R

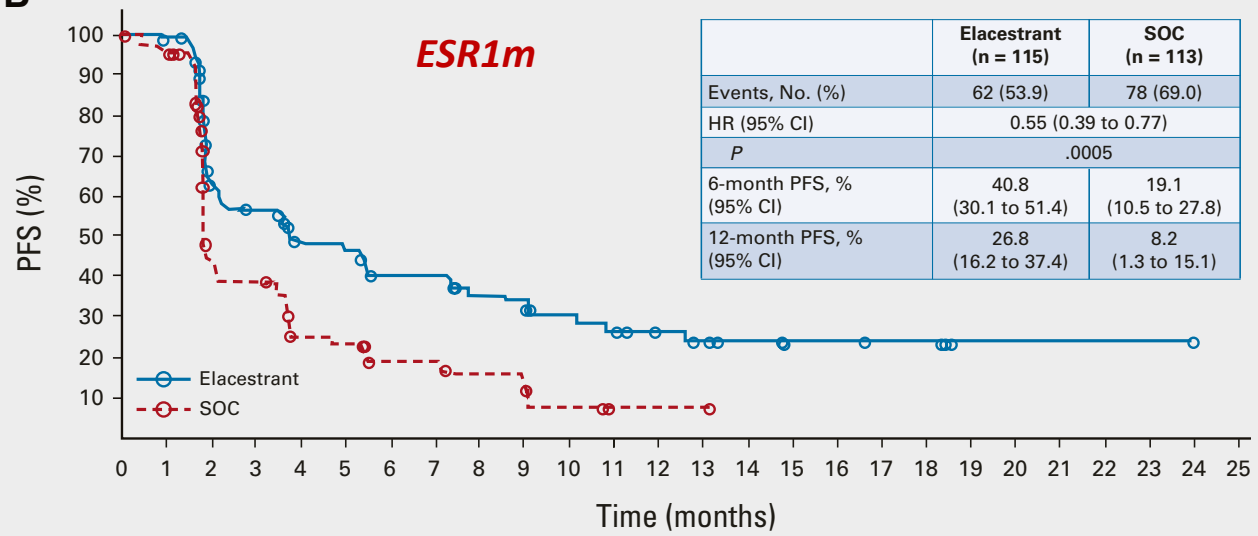
Elacestrant 400 mg PO QD

Endocrine therapy*

Key Characteristics:
- Visceral mets: ~70%
- Prior CDK4/6i: 100%
- Prior ET: 2 lines ~46%
- Prior chemo: 1 line 20%

* SOC ET: 69% received fulvestrant

B



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

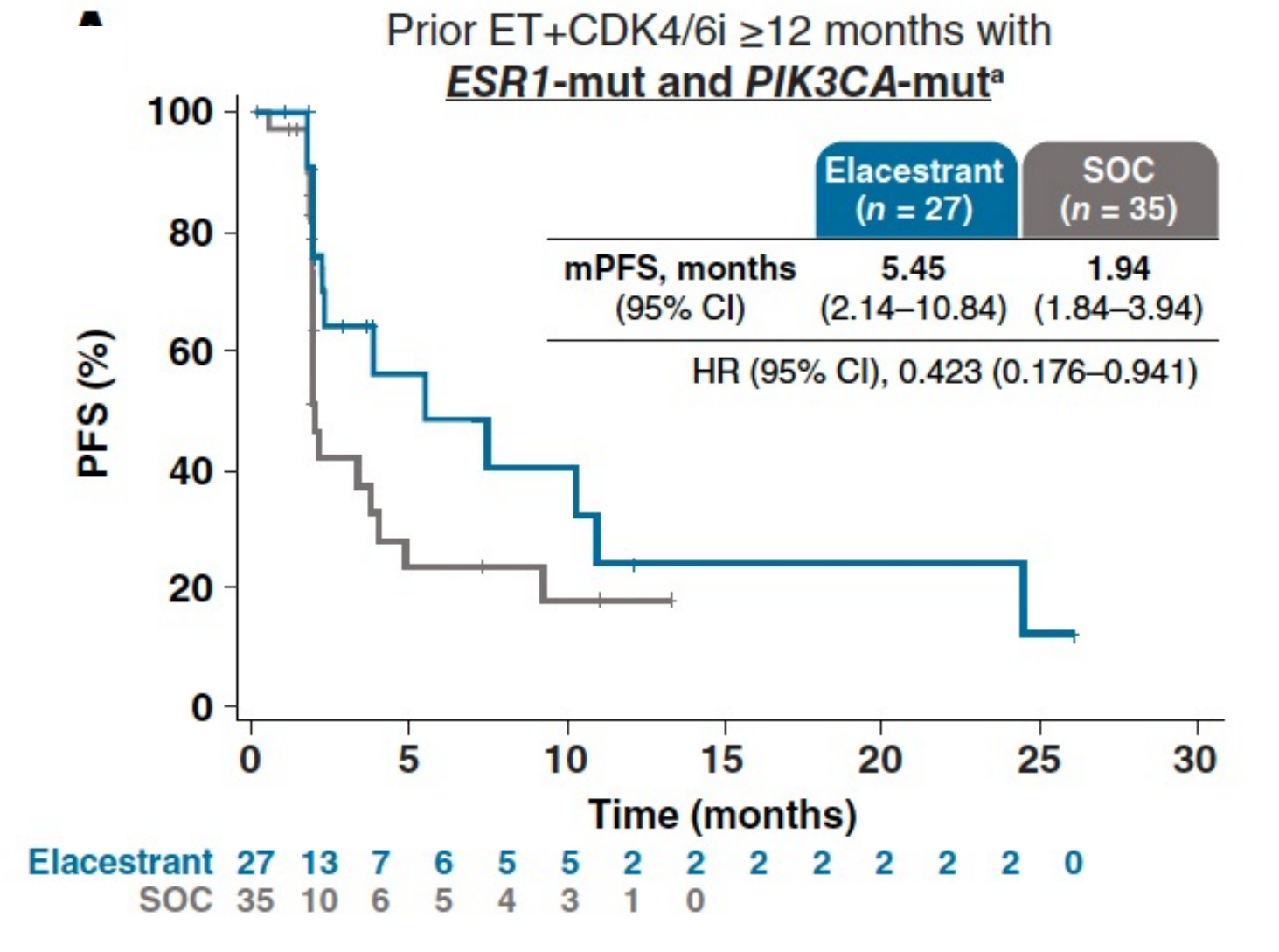
mPFS 3.78 vs 1.87 mos

HR 0.50 (95% CI 0.34-0.74), p=0.0005

Clinically significant benefit if ET sensitive disease, based on PFS duration on prior CDK4/6i:
- **≥ 6 mos: mPFS 4.1 vs 1.9 mos** (HR 0.52,.36-.74)
- **≥ 12 mos: mPFS 8.6 vs 1.9 mos** (HR 0.41,.26-.63)
- **≥ 18 mos: mPFS 8.6 vs 2.1 mos** (HR 0.47,.27-.79)

Bidard FC et al JCO 2022

Elacestrant for Patients with PIK3CA-Mutated Disease



ET = endocrine therapy; SOC = standard of care

Bardia A et al. *Clin Cancer Res* 2024 October 1;30(19):4299-309.

Elacestrant After ≥12 Months of ET and CDK4/6 Inhibition

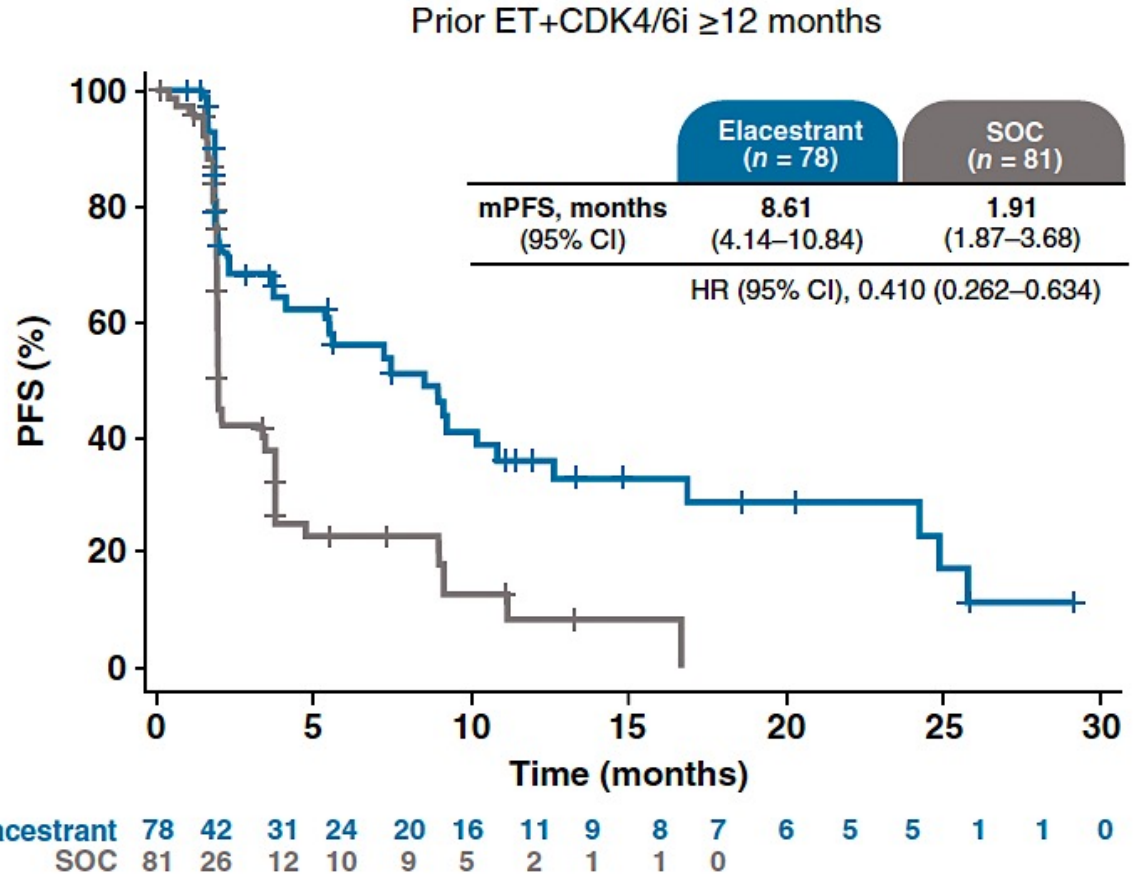


Figure 1.

PFS in patients who received prior ET+CDK4/6i ≥12 months in the metastatic setting. Kaplan–Meier estimates of PFS in patients with *ESR1*-mutated tumors and prior ET+CDK4/6i ≥12 months in the metastatic setting ($n = 159$).

mPFS = median progression-free survival

Bardia A et al. *Clin Cancer Res* 2024 October 1;30(19):4299-309.

RTP RESEARCH TO PRACTICE

EMBER-3 Trial: Open Label P3RCT

ER+, HER2- ABC

Men and Pre-[a]/Post-menopausal women

Prior therapy:

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification Factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]

R 1:1:1[b] N=874

- **A**: Imlunestrant 400 mg QD
- **B**: SOC ET[d,e] Fulvestrant or Exemestane
- **C[b]**: Imlunestrant 400 mg QD + abemaciclib[e]

Primary Endpoints

Investigator-assessed PFS for[f]:

- A vs B in patients with *ESR1*m[g]
- A vs B in all patients
- C vs A in all[h] patients

Key Secondary Endpoints

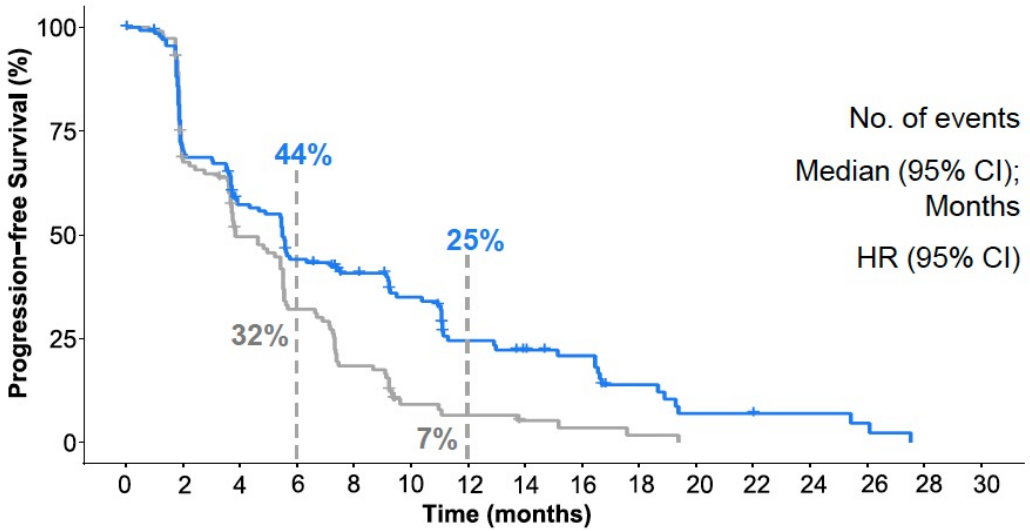
- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

- PFS and OS for C vs B in all[h] patients

Key Characteristics

- SOC ET: 88% Fulvestrant; 10% Exemestane
- ~35% *ESR1m*
- 40% *PI3K* pathway alterations
- ~60% prior CDK4/6i



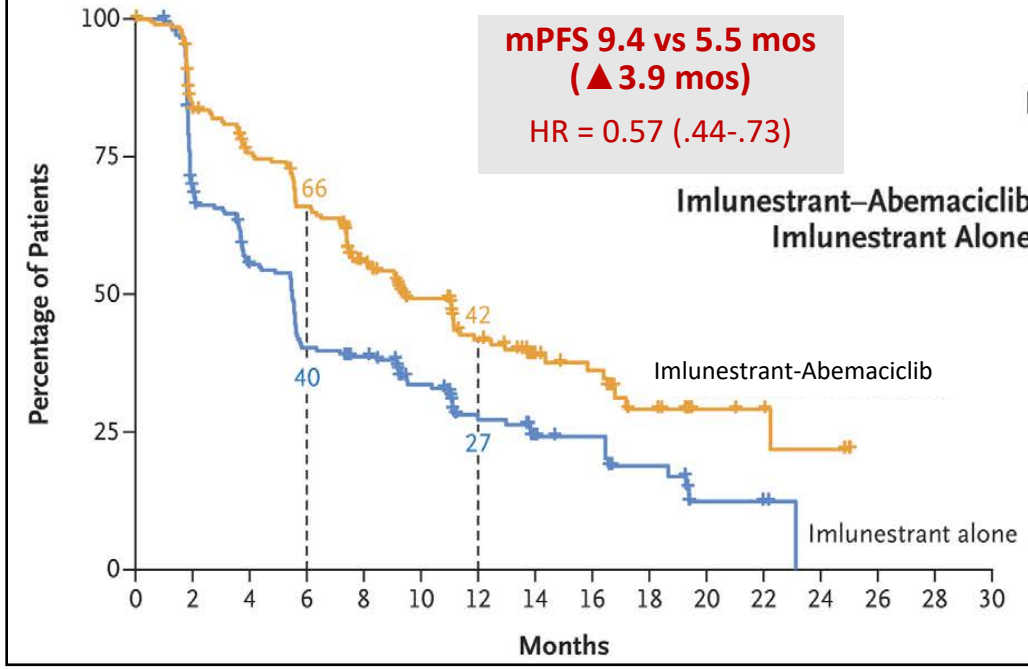
	Imlunestrant n=138	SOC ET n=118
No. of events	109	102
Median (95% CI); Months	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.46-0.82)[a]** *p*-value<0.001	

FDA Approval for *ESR1m* 9/25/25

Jhaveri K, et al. *NEJM* 2025;392:12.

EMBER-3 Study
Imlunestrant + Abema vs Imlunestrant Alone

PFS Imlu + Abema vs Imlu Alone: Overall population



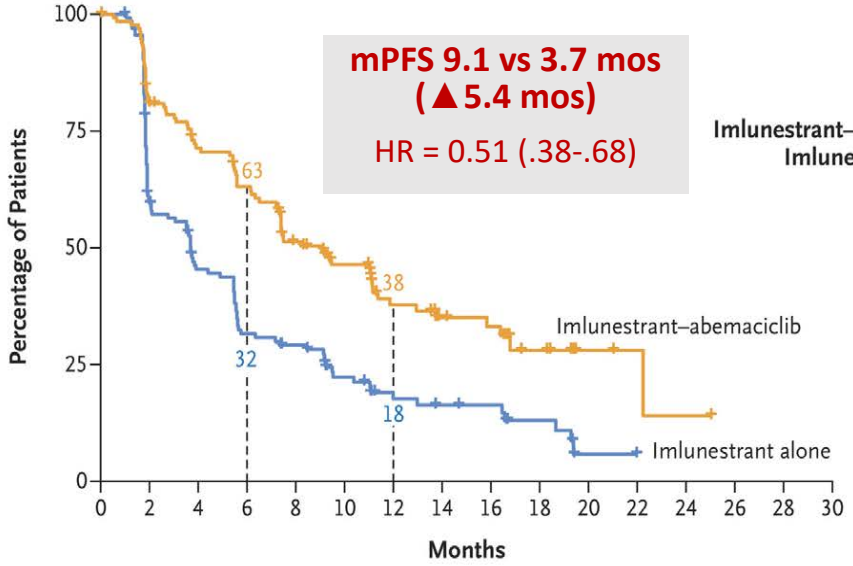
mPFS 9.4 vs 5.5 mos (▲3.9 mos)

HR = 0.57 (.44-.73)

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	213	114	9.4 (7.5–11.9)
Imlunestrant Alone	213	149	5.5 (3.8–5.6)

Hazard ratio for disease progression or death, 0.57 (95% CI, 0.44–0.73)
P<0.001

PFS Imlu + Abema vs Imlu Alone: Prior CDK4/6i



mPFS 9.1 vs 3.7 mos (▲5.4 mos)

HR = 0.51 (.38-.68)

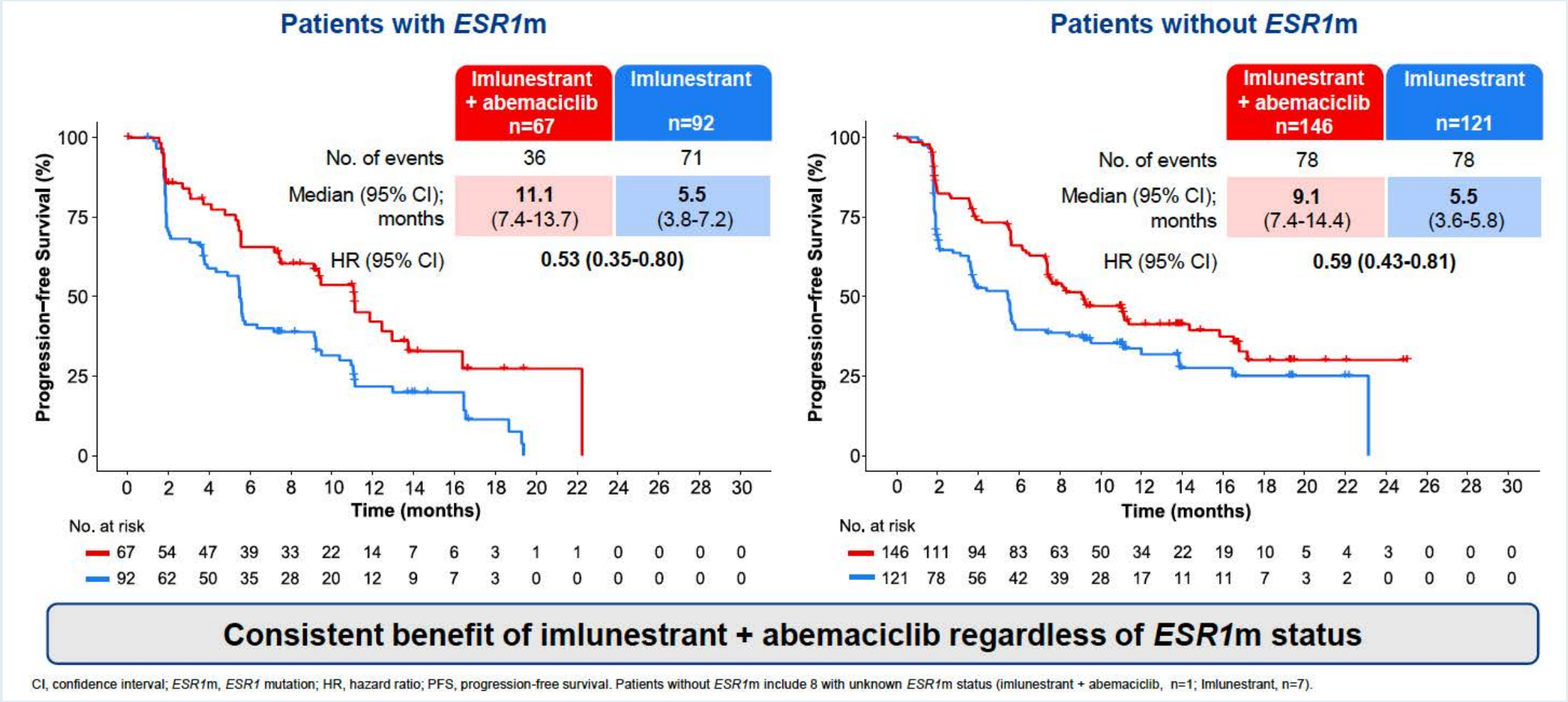
	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	139	79	9.1 (7.2–11.2)
Imlunestrant Alone	140	109	3.7 (2.1–5.5)

Hazard ratio for disease progression or death, 0.51 (95% CI, 0.38–0.68)

Benefit of Imlunestrant + Abema regardless of ESR1m status, PI3Km, and prior CDK4/6i use

Jhaveri K, et al. *NEJM* 2025;392:12.

EMBER-3: PFS with Imlunestrant and Abemaciclib by ESR1m Status

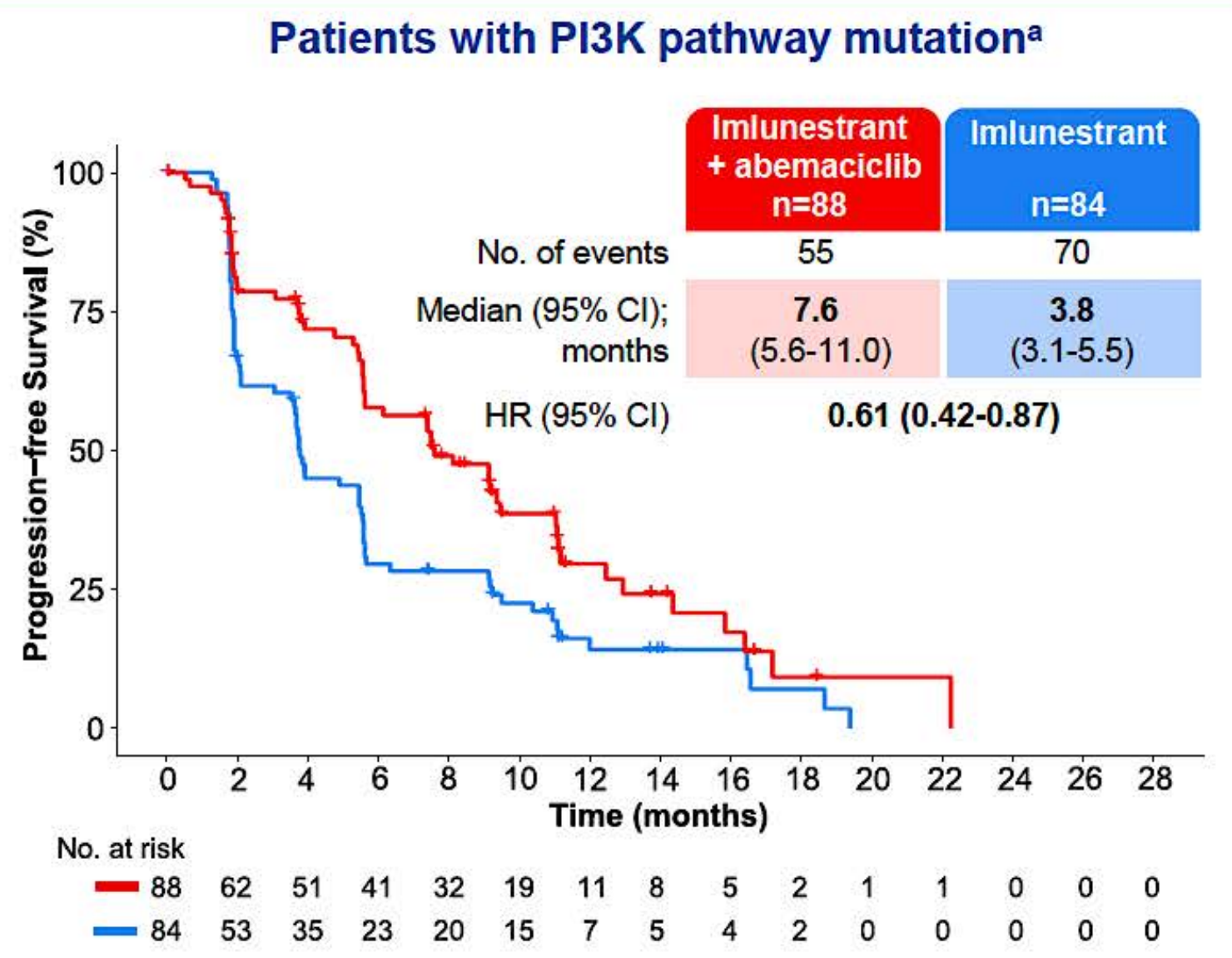


Consistent benefit of imlunestrant + abemaciclib regardless of *ESR1*m status

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; PFS, progression-free survival. Patients without *ESR1*m include 8 with unknown *ESR1*m status (imlunestrant + abemaciclib, n=1; Imlunestrant, n=7).

Jhaveri KL et al. San Antonio Breast Cancer Symposium 2024;Abstract GS1-01.

Imlunestrant and Abemaciclib for PIK3CA-Mutated Disease



Jhaveri KL et al. San Antonio Breast Cancer Symposium 2024;Abstract GS1-01.

FDA Approves Imlunestrant for Adults with ER-Positive, HER2-Negative, ESR1-Mutated Advanced or Metastatic Breast Cancer

Press Release: September 25, 2025

"The FDA has approved imlunestrant, an oral estrogen receptor antagonist, for the treatment of adults with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–), *ESR1*-mutated advanced or metastatic breast cancer (MBC) whose disease progressed after at least one line of endocrine therapy (ET).

In the Phase 3 EMBER-3 trial, imlunestrant reduced the risk of progression or death by 38% versus ET. Among patients with *ESR1*-mutated MBC, imlunestrant significantly improved progression-free survival (PFS) versus fulvestrant or exemestane, with a median PFS of 5.5 months vs 3.8 months (HR = 0.62 [95% CI: 0.46-0.82]); *p*-value = 0.0008."

https://investor.lilly.com/news-releases/news-release-details/us-fda-approves-inluriyo-imlunestrant-adults-er-her2-esr1

RTP RESEARCH TO PRACTICE

VERITAC-2: Open Label P3RCT

Key Eligibility Criteria

- Age ≥18 years old
- ER+/HER2- advanced or metastatic breast cancer
- Prior therapy:
  - 1 line of CDK4/6i + ET
  - ≤1 additional ET
  - Most recent ET for ≥6 months
  - No prior SERD (eg, fulvestrant, elacestrant)
  - No prior chemotherapy for advanced or metastatic disease
- Radiological progression during or after the last line of therapy

Randomization (1:1)

28-day Treatment Cycles

Vepdegestrant (n=313)
200 mg orally (once daily)

Fulvestrant (n=311)
500 mg IM
(days 1 and 15 of cycle 1; day 1 of subsequent cycles)

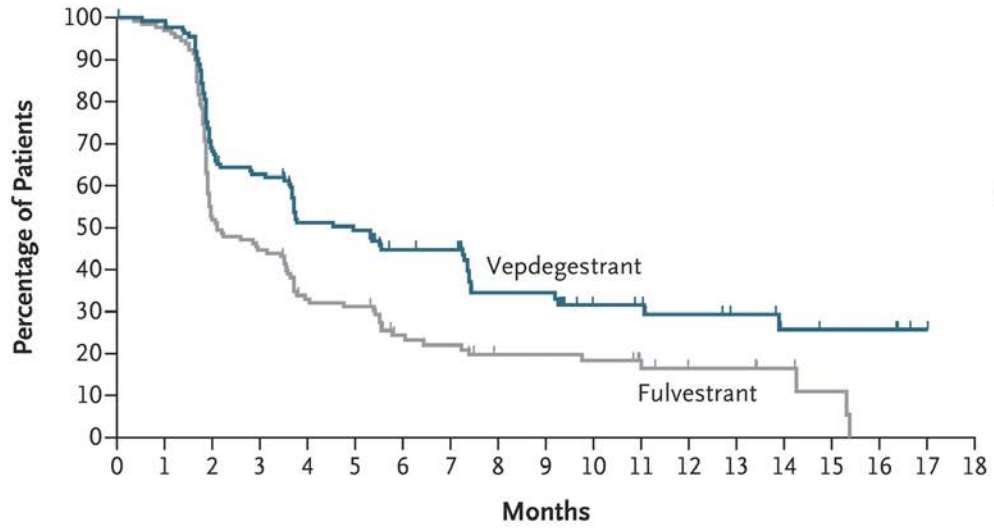
Stratification Factors:
- *ESR1* mutation[a] (yes vs no)
- Visceral disease (yes vs no)

Primary Endpoint:
- PFS by BICR in
  - *ESR1*m population
  - All patients

Secondary Endpoints:
- OS (key secondary)
- CBR and ORR by BICR
- AEs

Key Characteristics
- Visceral mets ~63%
- ~43% *ESR1m*
- 100% prior CDK4/6i
- ~ 80% 1 prior/~20% 2 prior LOT

Progression-free Survival among Patients with *ESR1* Mutations



	No. of Events (%)	Median Progression-free Survival
		mo
Vepdegestrant (N=136)	82 (60.3)	5.0 (3.7–7.4)
Fulvestrant (N=134)	103 (76.9)	2.1 (1.9–3.5)

Hazard ratio for disease progression or death, 0.58 (95% CI, 0.43–0.78)
P<0.001

mPFS 5.0 vs 2.1 mos (▲2.9 mos)

HR = 0.58 (0.43-0.78); p<0.001

Campone M, et al. *NEJM* 2025;393:556-68.

Antibody-Drug Conjugates

DESTINY Breast-04: P3 RCT T-DXd vs TPC in HER2-low mBC after 1-2 prior L Chemo for mBC

Key Eligibility:
- HER2- mBC
- 1-2L prior chemo for mBC

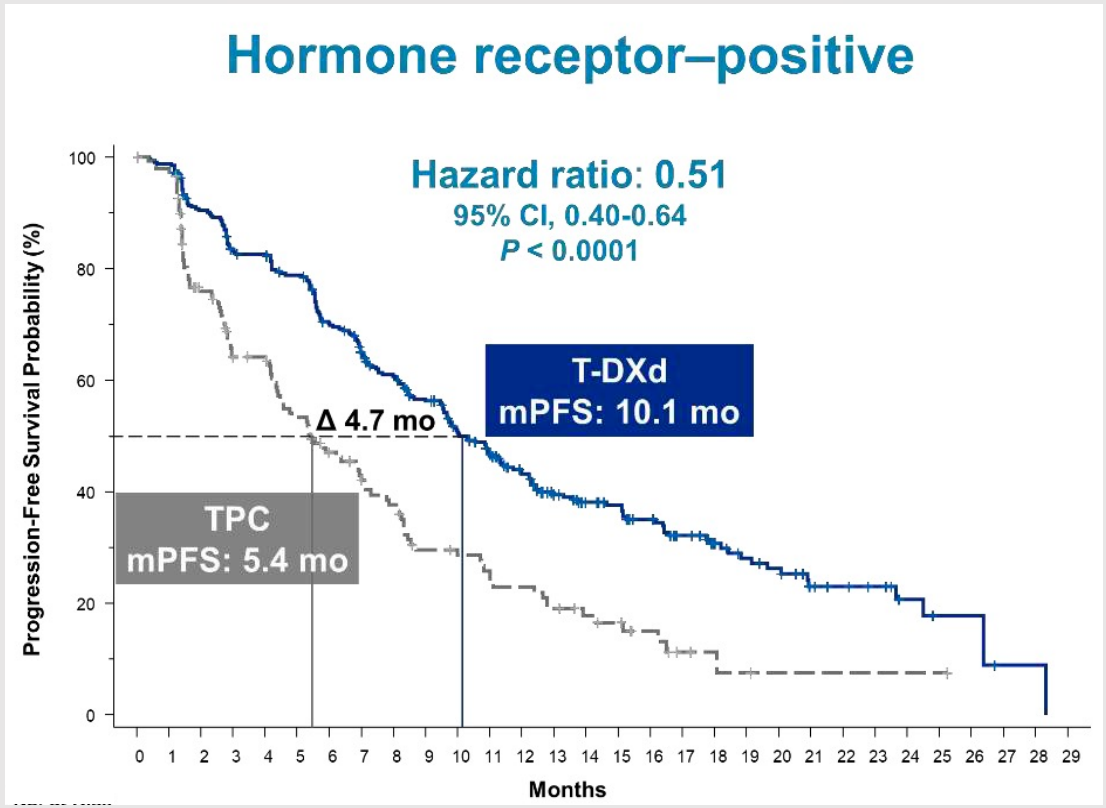
T-DXd

TPC

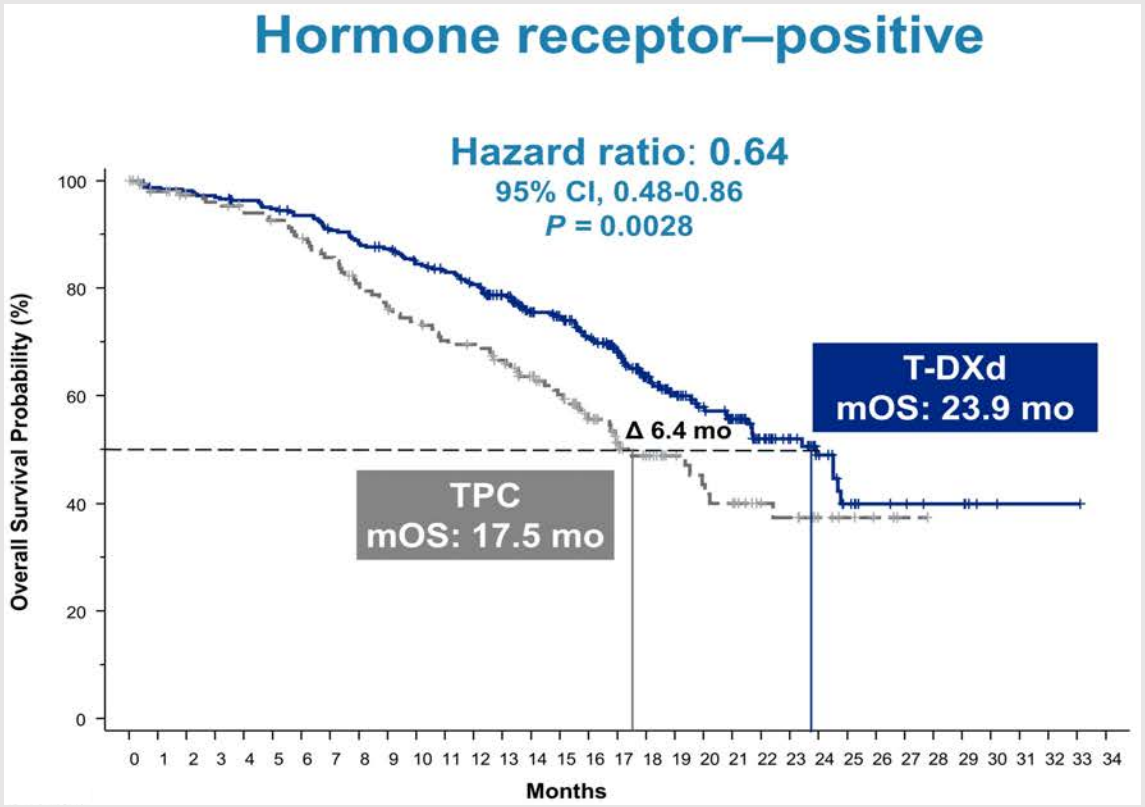
N=540 (HR+ 480)

TPC: cape, eribulin, gem, paclitaxel, or *nab* pac

PROGRESSION FREE SURVIVAL



OVERALL SURVIVAL



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

DESTINY Breast-06: P3 RCT T-DXd vs TPC in HER2-low/ultralow mBC in Chemo-naïve

Key Eligibility:
- HR+/HER2 lo/ultralo* mBC
- Chemo naïve for mBC
- > 2L ET for mBC or 1L ET if endo-resistant

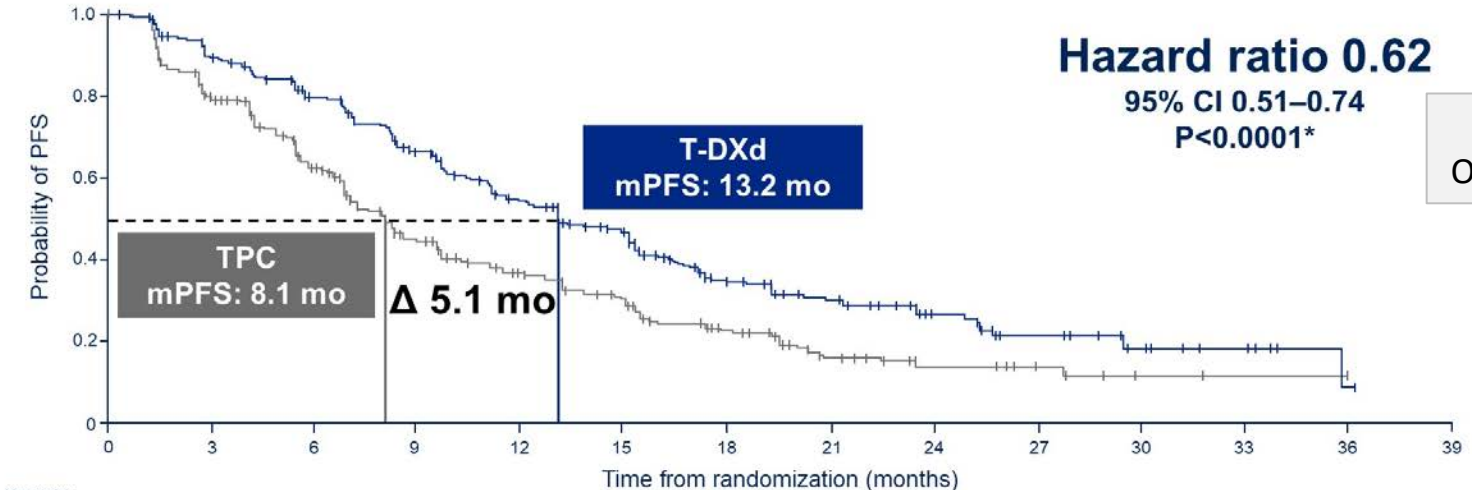
N=866

T-DXd

TPC

TPC: cape, paclitaxel, or *nab* pac

PFS (BICR) in HER2-low: primary endpoint



Similar PFS benefit seen in HER2 ultralow
OS data immature – 12 mos OS in HER2-low 87.6% vs 81.7% (NS)

Key Characteristics:
- HER2-low 82%
- De novo mBC ~31%
- Visceral ~85%
- 1º ET resistance ~31%

*HER2 low: IHC 1+, 2+ (ISH neg); HER2 ultralow: IHC 0 with any membrane staining

Curigliano et al. ASCO 2024;Absract LBA1000. Bardia et al. *NEJM* 2024;2110-22

DESTINY Breast-06: P3 RCT T-DXd vs TPC in HER2-low/ultralow mBC in Chemo-naïve

Key Eligibility:
- HR+/HER2 lo/ultralo* mBC
- Chemo naïve for mBC
- > 2L ET for mBC or 1L ET if endo-resistant

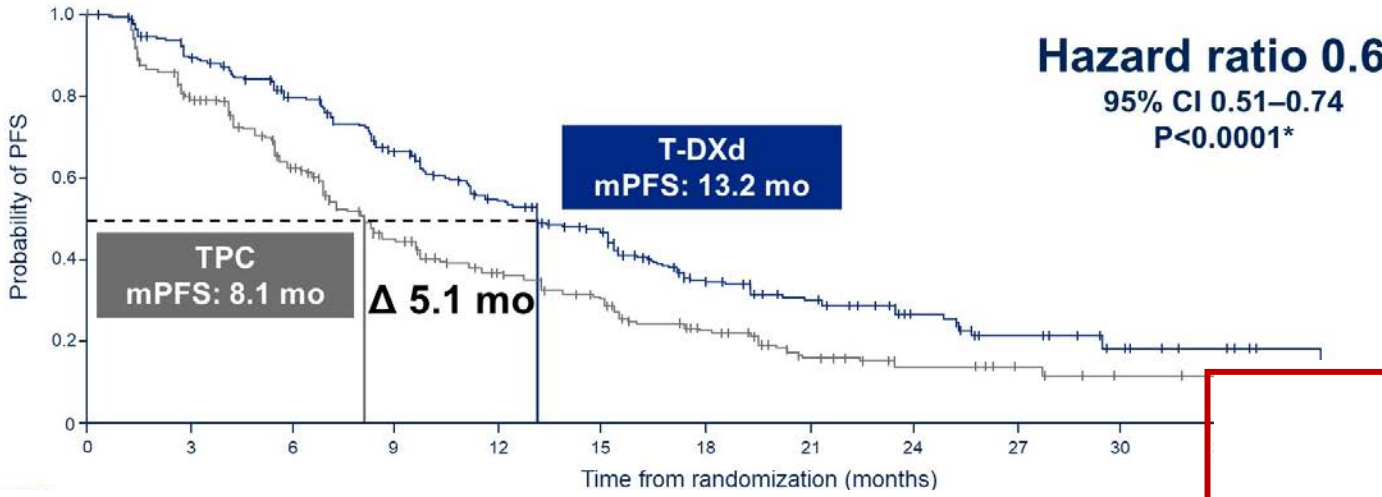
N=866

T-DXd

TPC

TPC: cape, paclitaxel, or *nab* pac

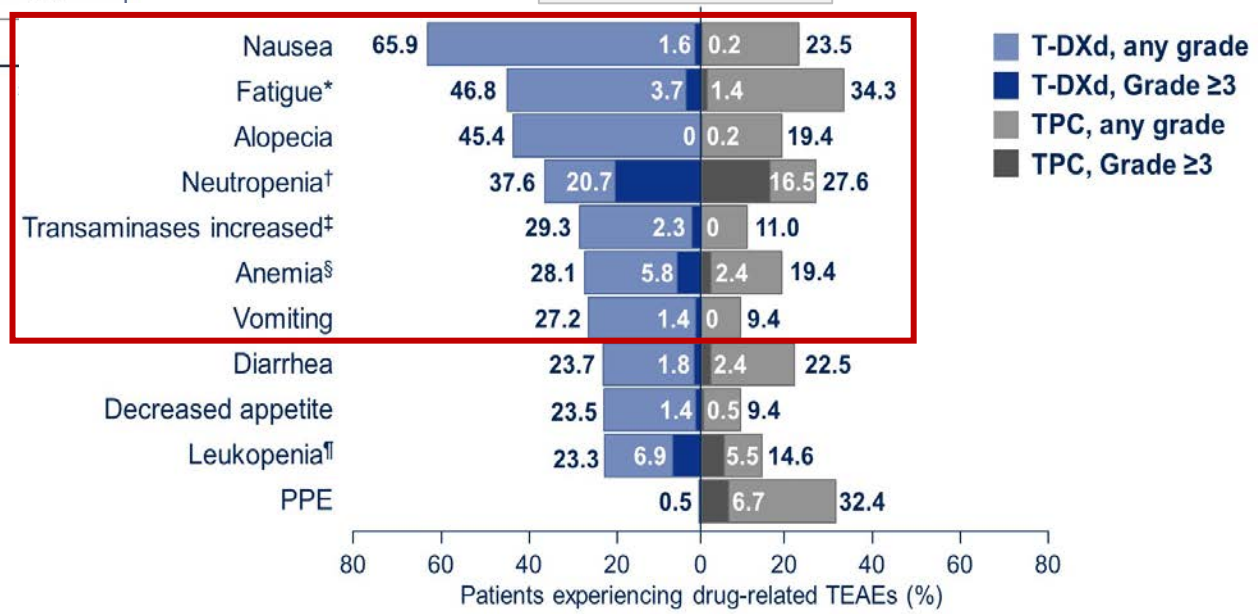
PFS (BICR) in HER2-low: primary endpoint



Hazard ratio 0.62
95% CI 0.51–0.74
P<0.0001*

Similar PFS benefit seen in HER2 ultralow
OS data immature – 12 mos OS in HER2-low 87.6% vs 81.7% (NS)

ILD all grade 11.3%
G3/4: 0.7% (n=3)
G5: 0.7% (n=3)



Key Characteristics:
- HER2-low 82%
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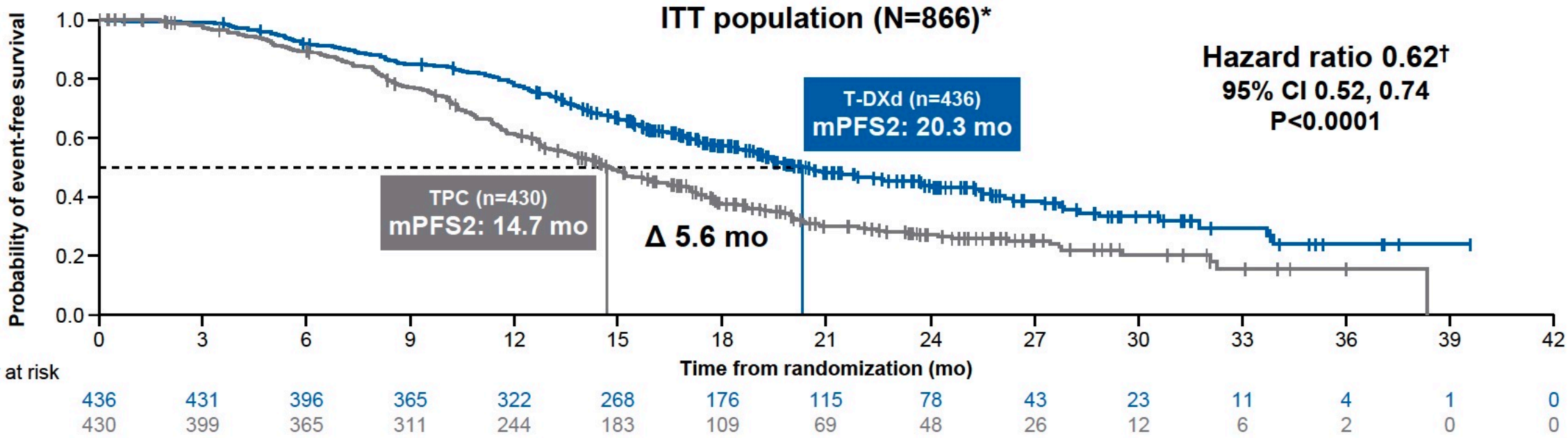
- Visceral ~85%
- 1º ET resistance ~31%

*HER2 low: IHC 1+, 2+ (ISH neg); HER2 ultralow: IHC 0 with any membrane staining

Curigliano et al. ASCO 2024;Absract LBA1000. Bardia et al. *NEJM* 2024;2110-22

PFS2 in the overall ITT population and time-to-progression subgroups



	<6-mo 1L TTP		6–12-mo 1L TTP		>12-mo 1L TTP	
	T-DXd (n=65)	TPC (n=59)	T-DXd (n=60)	TPC (n=52)	T-DXd (n=168)	TPC (n=166)
mPFS2, mo (95% CI)	18.9 (14.4, 24.0)	15.2 (10.9, 17.5)	17.1 (13.9, 31.8)	13.7 (10.3, 17.1)	20.0 (18.6, 25.3)	14.3 (12.6, 15.9)
PFS2 hazard ratio (95% CI)	0.73 (0.46, 1.14)†		0.59 (0.37, 0.94)†		0.57 (0.43, 0.75)†	

Delay in PFS2‡ was clinically meaningful in favor of T-DXd in the ITT population and TTP subgroups

*Of patients who received immediate post-discontinuation therapy (n=608), regimens included chemotherapy (66.7%), endocrine-based therapy (26.0%), ADC (7.8%), and targeted therapy alone (2.5%); †the hazard ratio and its CI was estimated from an unstratified Cox proportional hazards model; ‡PFS2 was defined by investigators according to local standard clinical practice as time from randomization to second progression (earliest progression event following first subsequent therapy) or death
ADC, antibody-drug conjugate; CI, confidence interval; ET, endocrine therapy; ITT, intent-to-treat; mo, months; (m)PFS2, (median) second progression-free survival / time from randomization to second progression or death;
T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

TROPICS-02: P3 RCT Sacituzumab Govitecan vs TPC in HR+/HER2- mBC

Key Eligibility:
- HER2- mBC
- **2-4L prior chemo for mBC**

N=543

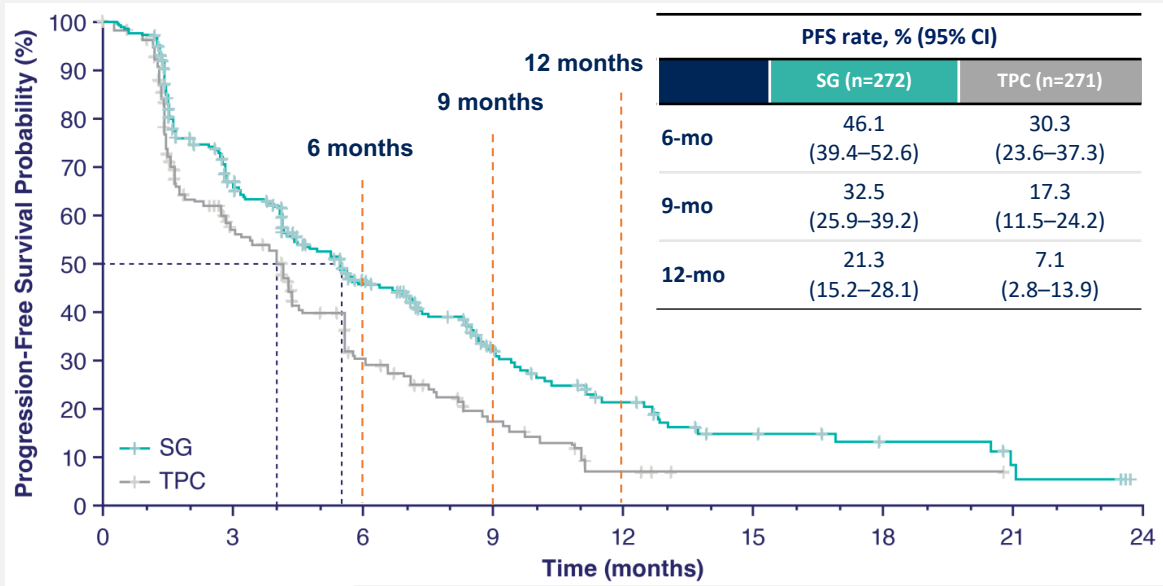
→ Sacituzumab Govitecan

→ TPC

PFS[1] Median F/U: 10.2 mos

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

▲1.5 mos



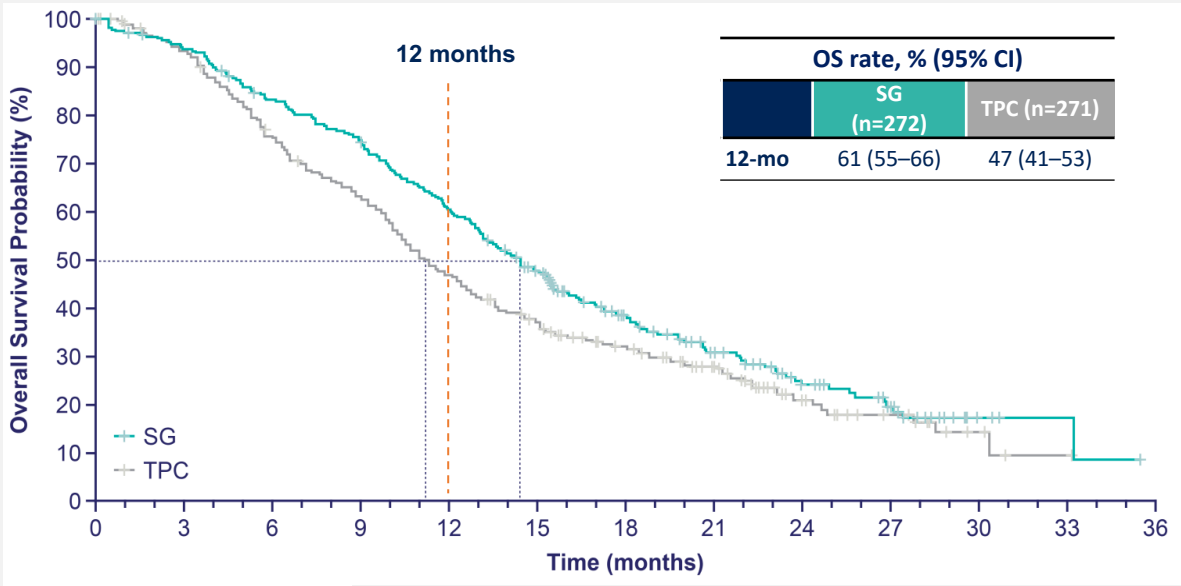
PFS rate, % (95% CI)

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

OS[2] Median F/U: 12.5 mos

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

▲3.2 mos



OS rate, % (95% CI)

	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376; 2. Rugo H, et al. ESMO 2022. Oral LBA76.

Phase III TROPiCS-02: Safety Summary

TEAEs,[a] n (%)		SG (n = 268)		TPC (n = 249)	
		Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Hematologic	Neutropenia[b]	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia[c]	98 (37)	20 (7)	69 (28)	8 (3)
	Thrombocytopenia[d]	17 (6)	1 (<1)	41 (16)	9 (4)
Gastrointestinal	Diarrhea	166 (62)	27 (10)	57 (23)	3 (1)
	Nausea	157 (59)	3 (1)	87 (35)	7 (3)
	Constipation	93 (35)	1 (<1)	61 (24)	0
	Vomiting	64 (24)	3 (1)	39 (16)	4 (2)
	Abdominal pain	53 (20)	10 (4)	34 (14)	2 (1)
Other	Alopecia	128 (48)	0	46 (18)	0
	Fatigue	105 (39)	16 (6)	82 (33)	9 (4)
	Asthenia	62 (23)	6 (2)	50 (20)	5 (2)
	Decreased appetite	57 (21)	4 (1)	52 (21)	2 (1)
	Dyspnea	49 (18)	5 (2)	39 (16)	11 (4)
	Headache	44 (16)	1 (<1)	36 (14)	2 (1)
	Pyrexia	39 (15)	2 (1)	45 (18)	0
	AST increased	33 (12)	4 (1)	44 (18)	8 (3)

The most common grade ≥ 3 TEAEs were neutropenia (52%), diarrhea (10%), and anemia (7%) in the SG group, and neutropenia (39%), thrombocytopenia (4%), fatigue (4%), and dyspnea (4%) in the TPC group

TEAEs = treatment-emergent adverse events; SG = sacituzumab govitecan, TPC = treatment of physician's choice

Tolaney S et al. ASCO 2023;Abstract 1003.

TROPION-Breast01: P3 RCT Dato-DXd vs Chemo in HR+/HER2– MBC

Key Eligibility Criteria

- HR+/HER2– MBC (HER2 IHC 0/1+/2+; ISH–)
- Progressed on and not suitable for ET
- **1-2 prior lines** of Chemo in inoperable/metastatic setting
- ECOG PS 0-1

N=732

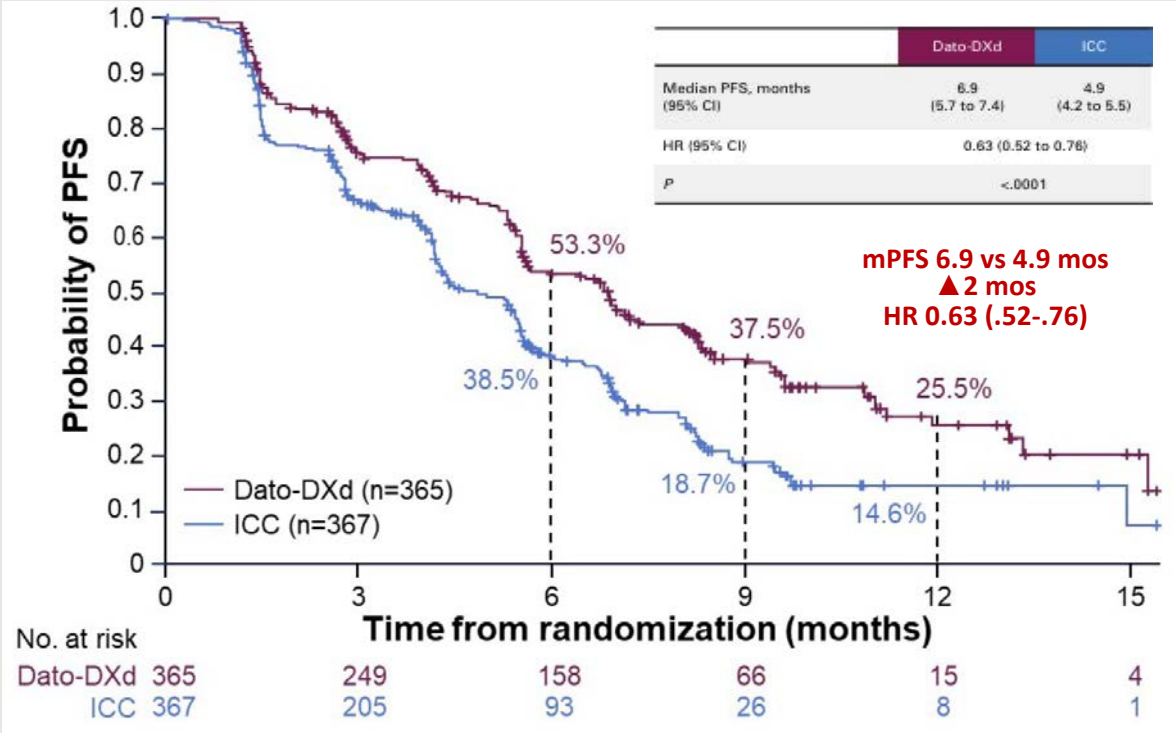
RANDOMIZED

1:1

Dato-DXd
6 mg/kg IV day 1 q3w
n=365

ICC[a]
Eribulin D1, 8 q3w; vinorelbine D1, 8 q3w;
gemcitabine D1, 8 q3w; capecitabine D1-14 q3w
n=367

Dual primary endpoints: PFS by BICR per RECIST v1.1, OS
Secondary endpoints: ORR, PFS by investigator, TFST, safety, PROs

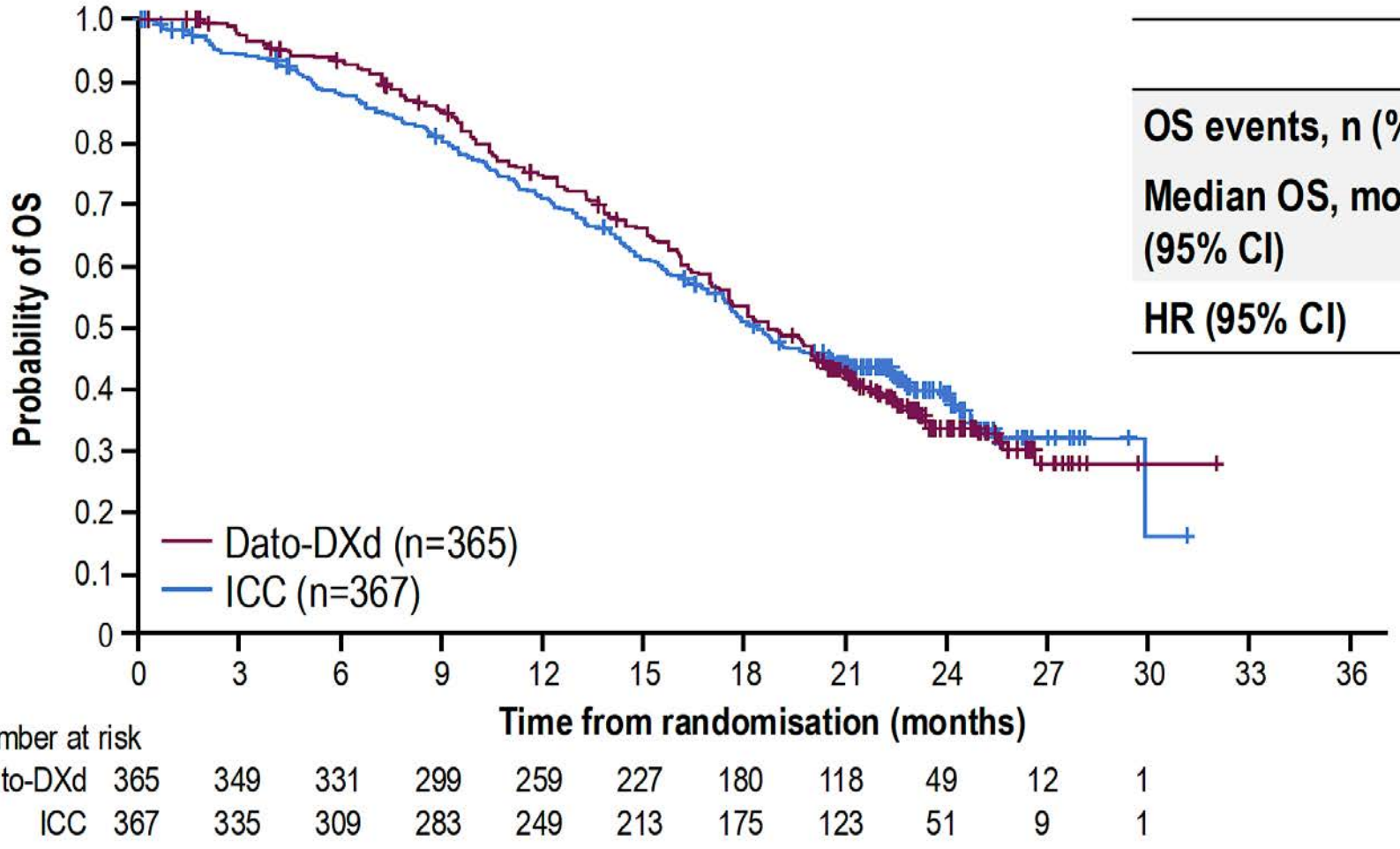


- Similar findings in those with prior CDK4/6i ≤ 12 mos vs > 12 mos
- Any grade stomatitis seen in 50% on Dato-DXd (6% G3) – 0.3% D/C rate due to stomatitis

[a] Investigator's choice of Chemo (ICC): eribulin, 1.4 mg/kg IV on D1, 8, q3w; vinorelbine, 25 mg/m^2 IV on D1, 8, q3w; gemcitabine 1000 mg/m^2 IV on D1, 8, q3w; capecitabine 1000 or 1250 mg/m^2 (dose per standard institutional practice BID D1-14, q3w.

Pernas S, et al. ASCO 2024. Abstract 1006
Bardia A et al. JCO 2024;43:285-96.

Phase III TROPION-Breast01: Overall Survival (OS)



	Dato-DXd	ICC
OS events, n (%)	223 (61)	213 (58)
Median OS, months (95% CI)	18.6 (17.3–20.1)	18.3 (17.3–20.5)
HR (95% CI)	**1.01 (0.83–1.22)**	

- Maturity: 59.6%
- Median follow-up: 22.8 months
- Protocol prespecified OS sensitivity analysis based on the stratification factors according to the eCRF*: **HR 0.99 (95% CI: 0.82–1.20)**

Dato-DXd = datopotamab deruxtecan; ICC = investigator's choice of chemotherapy

Pistilli B et al. ESMO Virtual Plenary 2025;Abstract VP1-2025.

Phase III TROPION-Breast01: Safety Profile

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

TRAEs = treatment-related adverse events; ILD = interstitial lung disease

Bardia A et al. ESMO 2023;Abstract LBA11.

FDA Approves Datopotamab Deruxtecan-dlnk for Unresectable or Metastatic HR-Positive, HER2-Negative Breast Cancer

Press Release: January 17, 2025

"On January 17, 2025, the Food and Drug Administration approved datopotamab deruxtecan-dlnk, a Trop-2-directed antibody and topoisomerase inhibitor conjugate, for adult patients with unresectable or metastatic, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC1+ or IHC2+/ISH-) breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease.

Efficacy was evaluated in TROPION-Breast01 (NCT05104866), a multicenter, open-label, randomized trial. Patients must have experienced disease progression, been deemed unsuitable for further endocrine therapy, and have received one or two lines of prior chemotherapy for unresectable or metastatic disease. Patients were excluded for a history of ILD/pneumonitis requiring steroids, ongoing ILD/pneumonitis, clinically active brain metastases, or clinically significant corneal disease. Patients also were excluded for ECOG performance status >1."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-datopotamab-deruxtecan-dlnk-unresectable-or-metastatic-hr-positive-her2-negative-breast

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 2.5 years followed by disease progression with multiple minimally symptomatic bone metastases

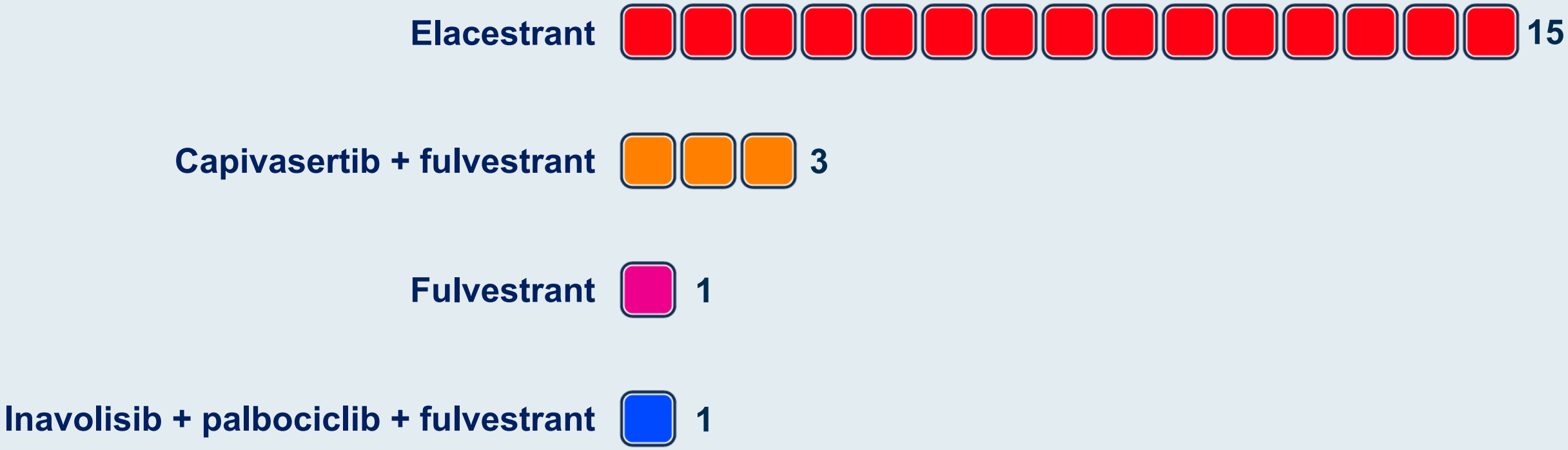
ESR1 mutation **PIK3CA mutation**

Survey of 20 US-based clinical investigators.

RTP RESEARCH TO PRACTICE

An 80-year-old woman (PS 1) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 2.5 years followed by disease progression with multiple minimally symptomatic bone metastases

ESR1 mutation **PIK3CA mutation**

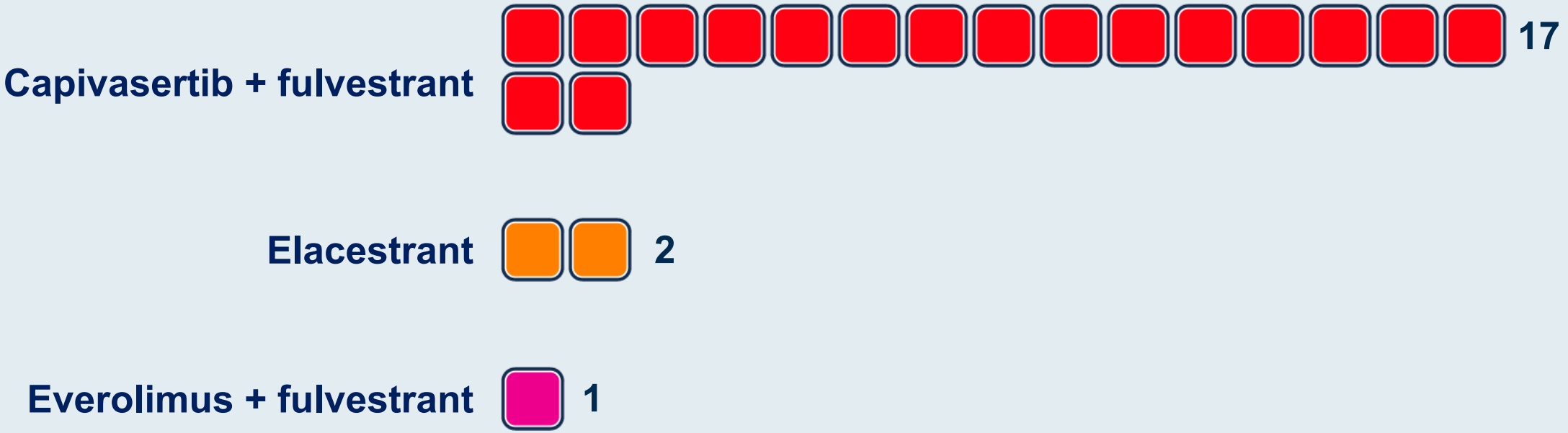


Survey of 20 US-based clinical investigators.

RTP RESEARCH TO PRACTICE

A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 10 months followed by disease progression with multiple minimally symptomatic bone metastases

ESR1 mutation **PIK3CA mutation**



Survey of 20 US-based clinical investigators.

RTP RESEARCH TO PRACTICE

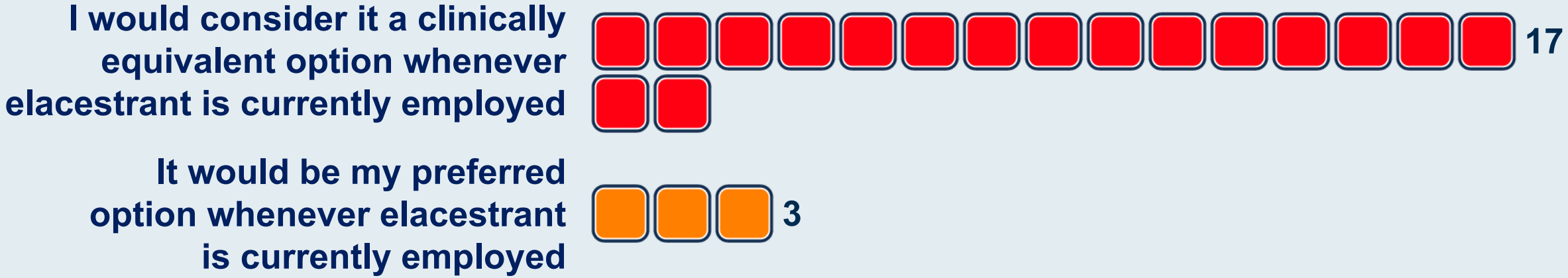
A 65-year-old woman (PS 0) with ER-positive, HER2-negative (IHC 0/null) de novo mBC receives ribociclib + letrozole for 2.5 years followed by disease progression with multiple symptomatic visceral metastases and normal LFTs

ESR1 mutation **PIK3CA mutation**

Survey of 20 US-based clinical investigators.

RTP RESEARCH TO PRACTICE

If imlunestrant were available, in which situations, if any, would you use this agent as monotherapy?



Regulatory and reimbursement issues aside, are there situations in which you would employ the combination of imlunestrant/abemaciclib for ER-positive, HER2-negative mBC?

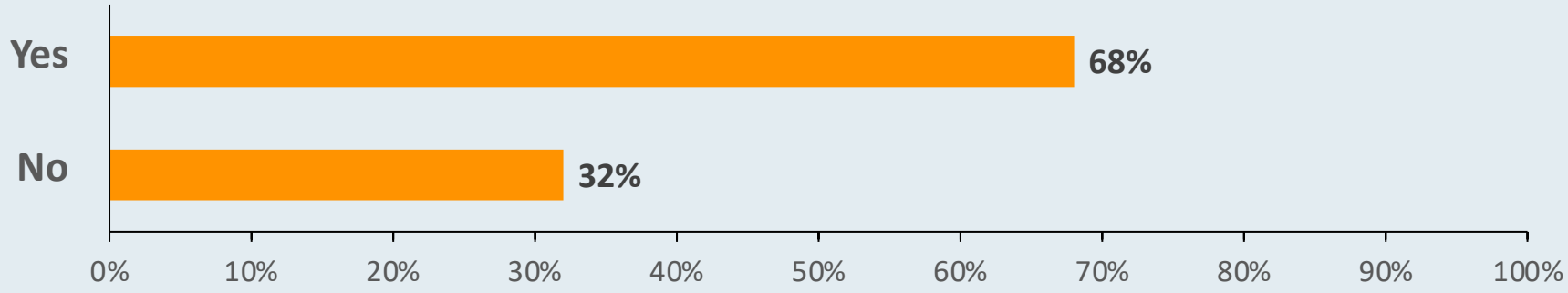
Survey of 20 US-based clinical investigators.

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, do you believe that the results from the SERENA-6 study justify the routine use of serial ctDNA monitoring for early detection of ESR1 mutations in patients with ER-positive, HER2-negative mBC receiving first-line therapy?

Clinical Investigators

General Medical Oncologists



Survey of 20 US-based clinical investigators and 50 general medical oncologists

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists

- **What would you recommend as second-line treatment for a patient with both ESR1 and PIK3CA mutations?**

Questions from General Medical Oncologists

- **Where does the combination of imlunestrant and abemaciclib fit in?**

Questions from General Medical Oncologists

- What is the current role of alpelisib?
- Would you use the inavolisib triplet for de novo mBC?
- What do you typically recommend as second-line treatment after progression on the first-line inavolisib triplet? Is rebiopsy necessary?

Questions from General Medical Oncologists

- **Case: 62-year-old woman with HR-positive, HER2-negative mBC whose disease progressed after 2 years on an AI + CDK4/6 inhibitor therapy. Bone and nodal mets, minimal symptoms. ESR1 and PIK3CA mutations. She has no diabetes but does have mild hepatic steatosis. HBA1C 6.8**

Questions from General Medical Oncologists

- **Can we sequence TROP2 ADC after TROP2 ADC?**
- **How do you choose between TROP2 ADC and HER2 ADC in patients eligible for both? Does biomarker profile really matter?**
- **Which do you typically use — sacituzumab govitecan or Dato-DXd?**

Questions from General Medical Oncologists

- How would you compare the toxicities and quality of life with sacituzumab govitecan versus Dato-DXd?
- How big of a concern are the ocular side effects of Dato-DXd? What about mucositis? How do you attempt to prevent and manage these toxicities?

Questions from General Medical Oncologists

- Are there situations in which it's safe to rechallenge with T-DXd after pneumonitis?
- How do you manage CDK4/6 inhibitor-associated ILD?
- Can T-DXd be used for a patient with decompensated heart failure — EF 35%?
- Should T-DXd be administered to patients with HR-negative, HER2-ultralow disease?

Management of HER2-Positive Breast Cancer

Harold J Burstein, MD, PhD
Director of Academic Partnerships
Institute Physician
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

pCR rates (%) with THP or TCHP

		THP	TCHP
HELEN-006	overall	66	58
	ER neg	86	70
	ER pos	53	48
neoCARHP	overall	64	66
	ER neg	78	78
	ER pos	56	59
EA1181	overall	44	
	ER neg	64	
	ER pos	33	

Key questions:

- Good enough?
- 18 wks or 12 wks?
- Heterogeneous tumors / HER2 2+ esp ER negative
- Will better adjuvant salvage make this yet-less relevant?

Chen XC et al. Lancet Oncol. 2025 Jan;26(1):27-36.
Gao HF et al. ASCO 2025;Abstract LBA500
Tung NM et al. ASCO 2025;Abstract 501

Destiny Breast 11

- Preoperative therapy for HER2+ early-stage breast cancer

- Arm A. T-DXd
- Arm B. T-DXd → THP
- Arm C. dd AC → THP

- Primary endpoint: pCR

T-DXd followed by THP before surgery showed statistically significant and clinically meaningful improvement in pathologic complete response in patients with high-risk HER2-positive early-stage breast cancer in DESTINY-Breast11 Phase III trial

PUBLISHED
7 May 2025

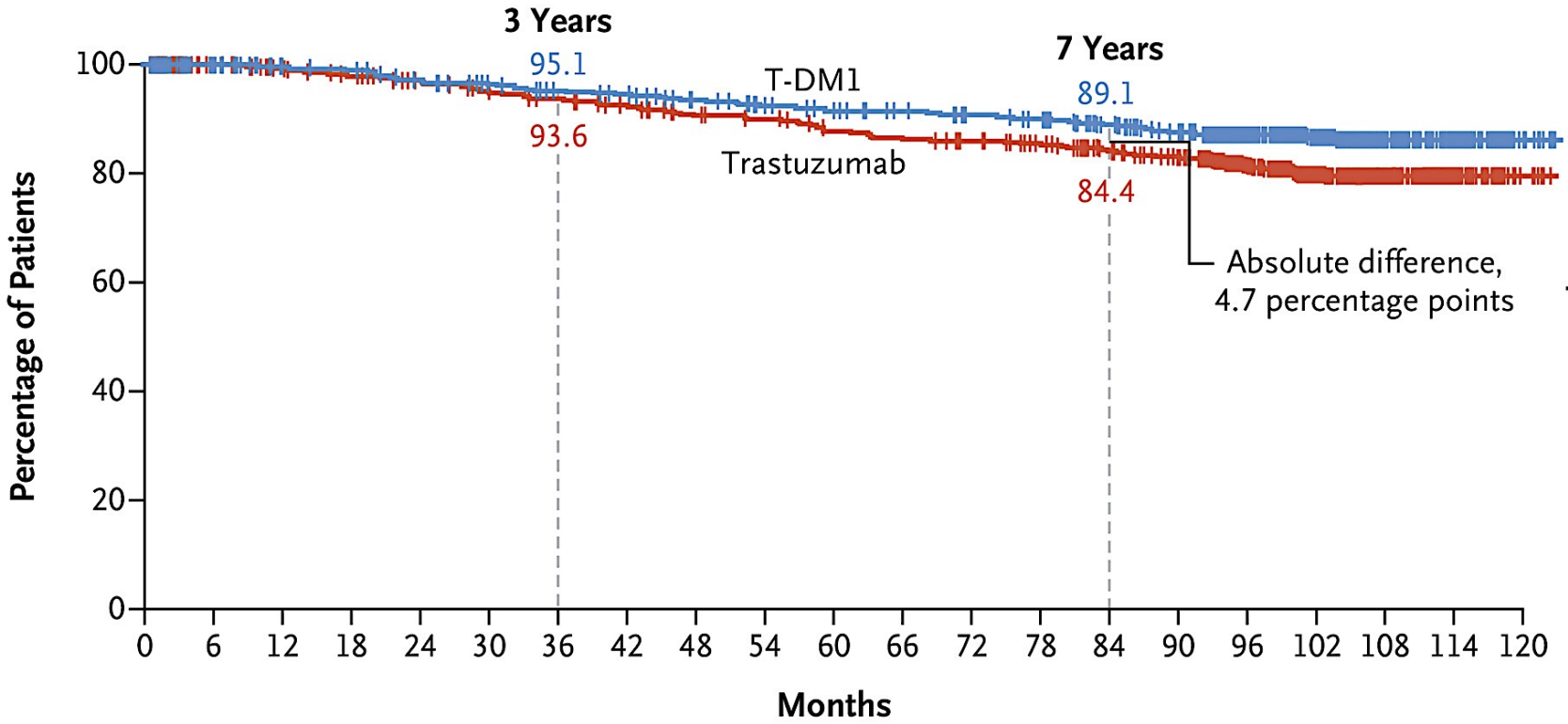
Destiny Breast 11

- Preoperative therapy for HER2+ early-stage breast cancer

- Arm A. T-DXd ✗
- Arm B. T-DXd → THP ✓
- Arm C. dd AC → THP

- Primary endpoint: pCR

KATHERINE Trial.



	Events *no. (%)*
T-DM1 (N=743)	89 (12.0)
Trastuzumab (N=743)	126 (17.0)

Unstratified hazard ratio for death, 0.66 (95% CI, 0.51–0.87); P=0.003
Boundary for statistical significance, hazard ratio <0.739 or P<0.0263

No. at Risk

T-DM1	743	719	702	695	675	662	649	642	626	614	604	597	585	576	554	530	394	312	158	93	14
Trastuzumab	743	696	677	661	643	625	616	600	586	576	558	549	543	532	511	490	374	280	146	72	9

Geyer C, et al. **N Engl J Med 2025;392:249-257**

Destiny Breast 05

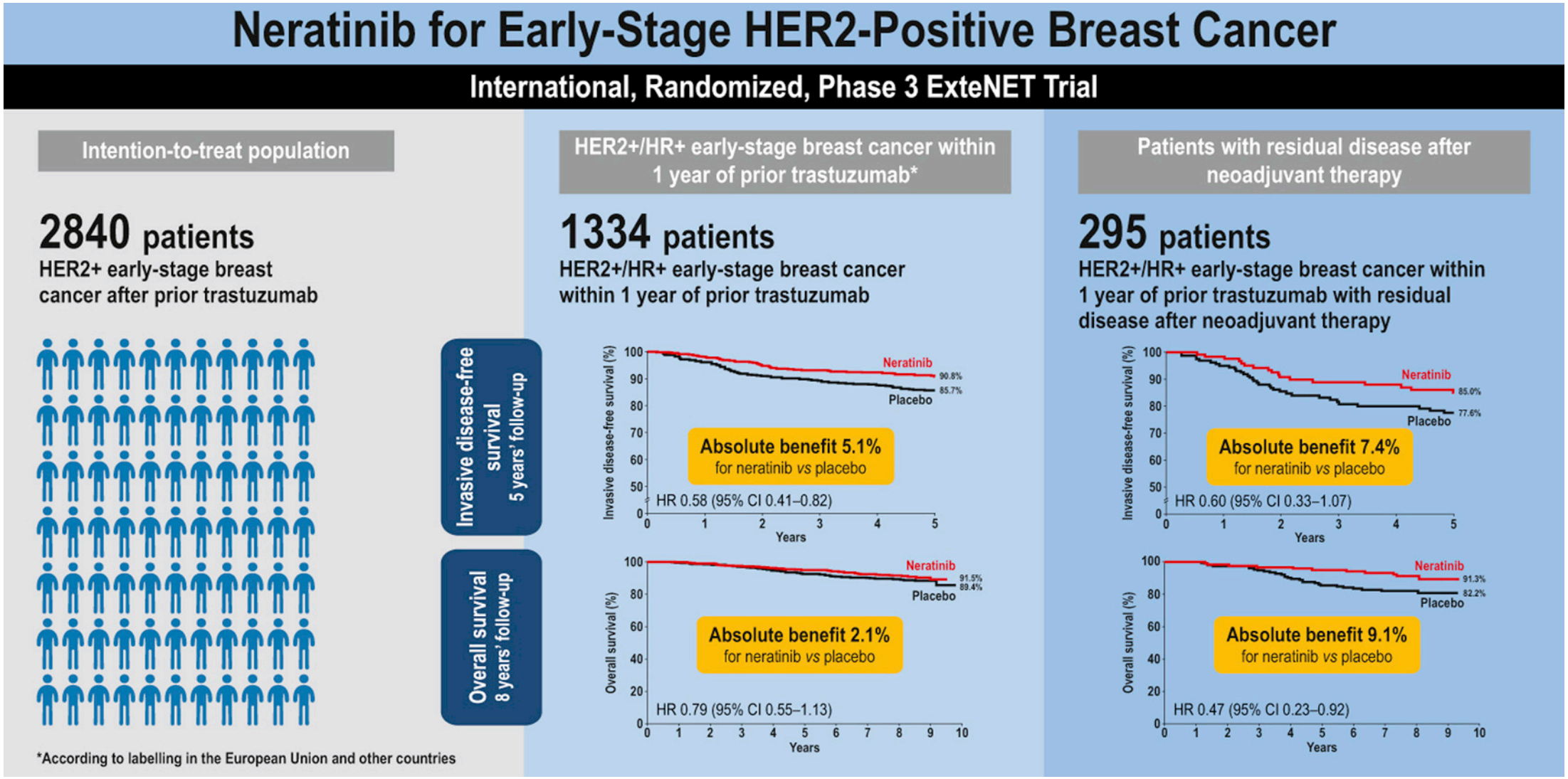
- Patients with residual HER2+ breast cancer in LN after neoadjuvant chemotherapy
- Arm A. T-DXd
- Arm B. TDM1

- Primary endpoint: iDFS

Sep 29, 2025 2:30 AM Eastern Daylight Time

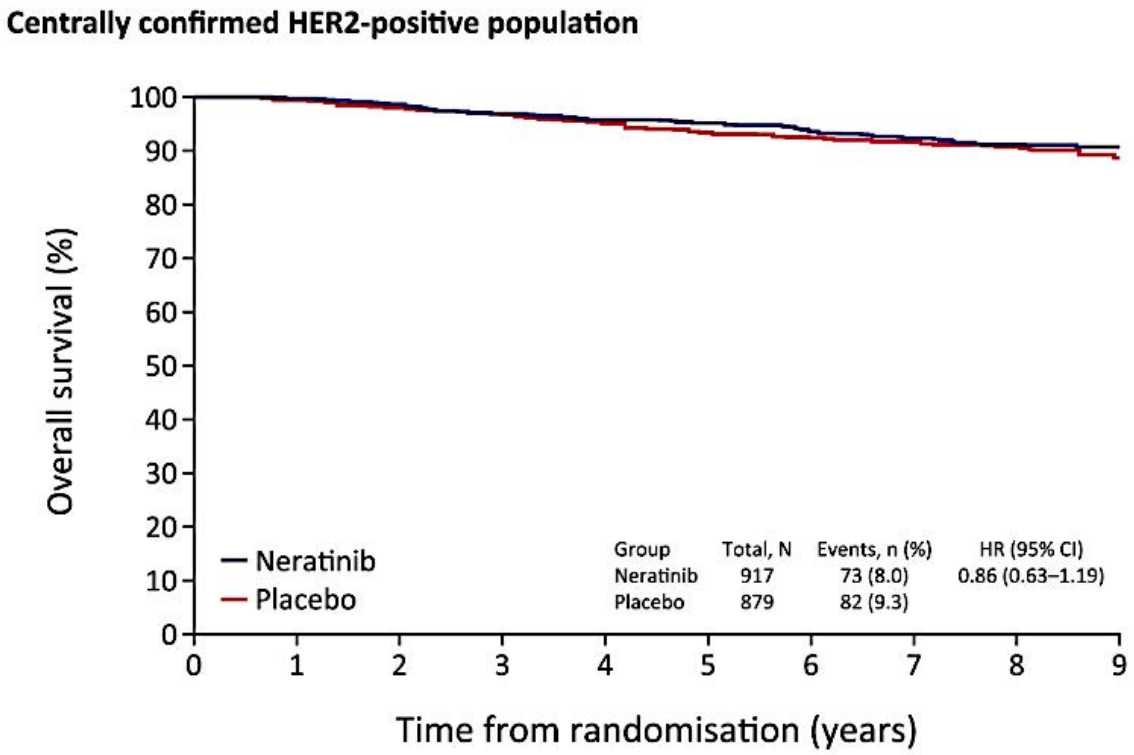
T-DXd Demonstrated Highly Statistically Significant and Clinically Meaningful Improvement in Invasive Disease-Free Survival Versus T-DM1 in DESTINY-Breast05 Phase 3 Trial in Patients with High-Risk Early Breast Cancer Following Neoadjuvant Therapy

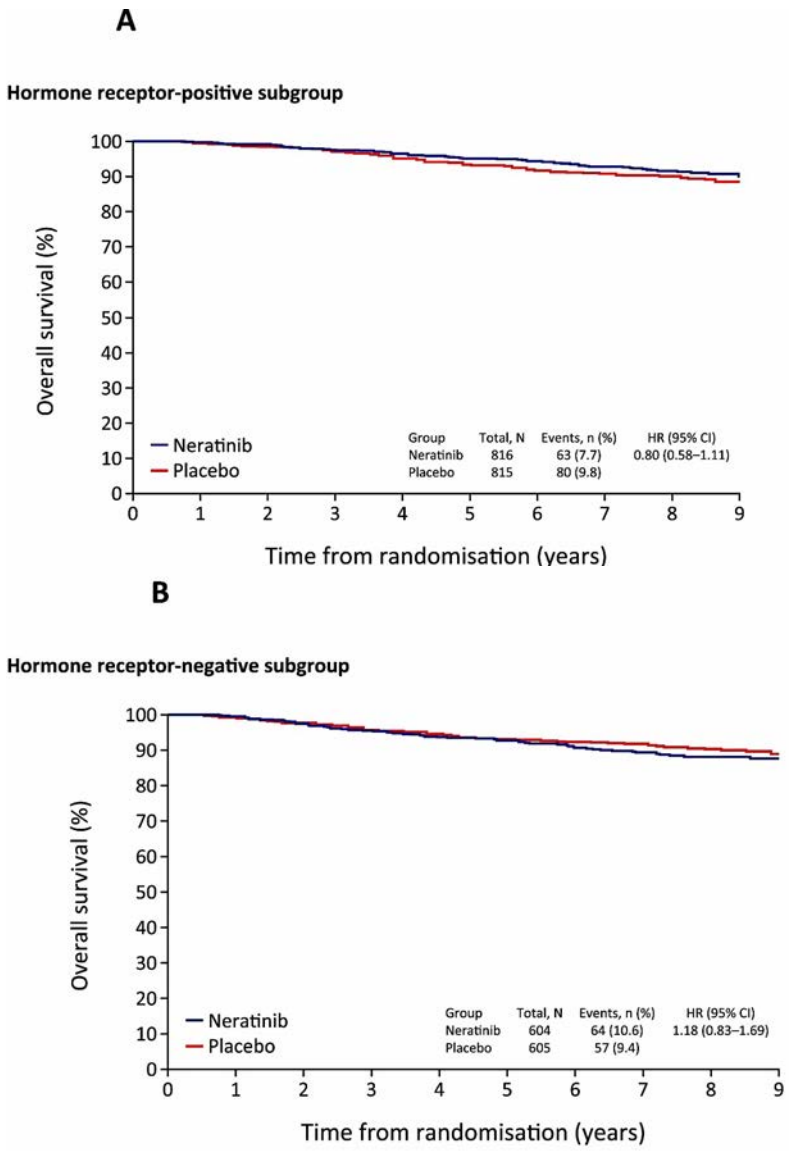
ExteNet: Neratinib after Trastuzumab-based adjuvant therapy



Chan A et al. Clin Breast Cancer. 2021 Feb;21(1):80-91.e7.

ExteNet: Neratinib after Trastuzumab-based adjuvant therapy





Holmes FA, et al. Euro J Cancer 2023;184, 48-59

DESTINY-Breast09 study design

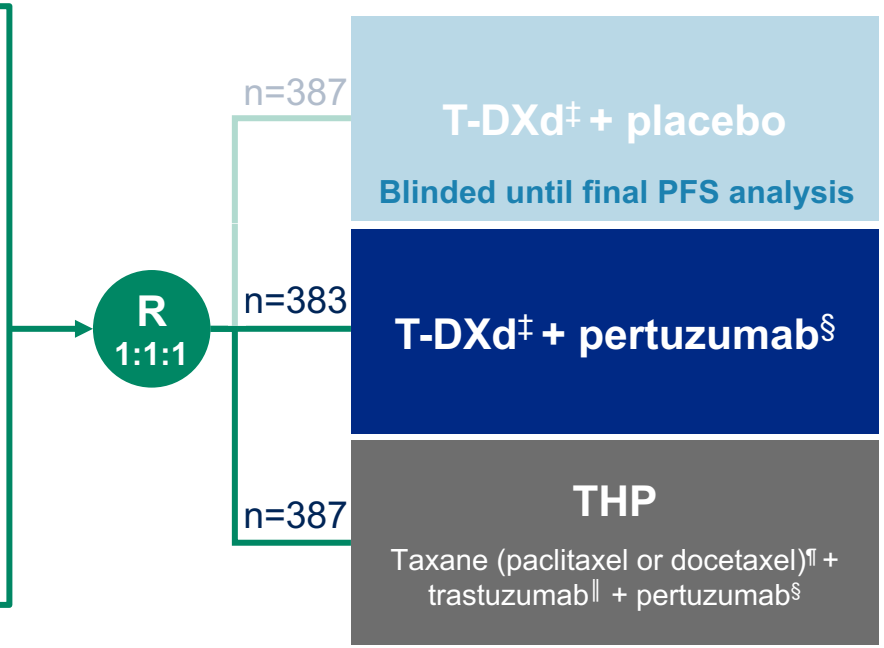
A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)

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)



Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

Secondary

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

At this planned interim analysis (DCO Feb 26, 2025), results are reported for the T-DXd + P and THP arms

*Open label for THP arm. Double blinded for pertuzumab in experimental arms; †HER2-targeted therapy or chemotherapy; ‡5.4 mg/kg Q3W; §840 mg loading dose, then 420 mg Q3W; ¶paclitaxel 80 mg/m² QW or 175 mg/m² Q3W, or docetaxel 75 mg/m² Q3W for a minimum of six cycles or until intolerable toxicity; ‖8 mg/kg loading dose, then 6 mg/kg Q3W

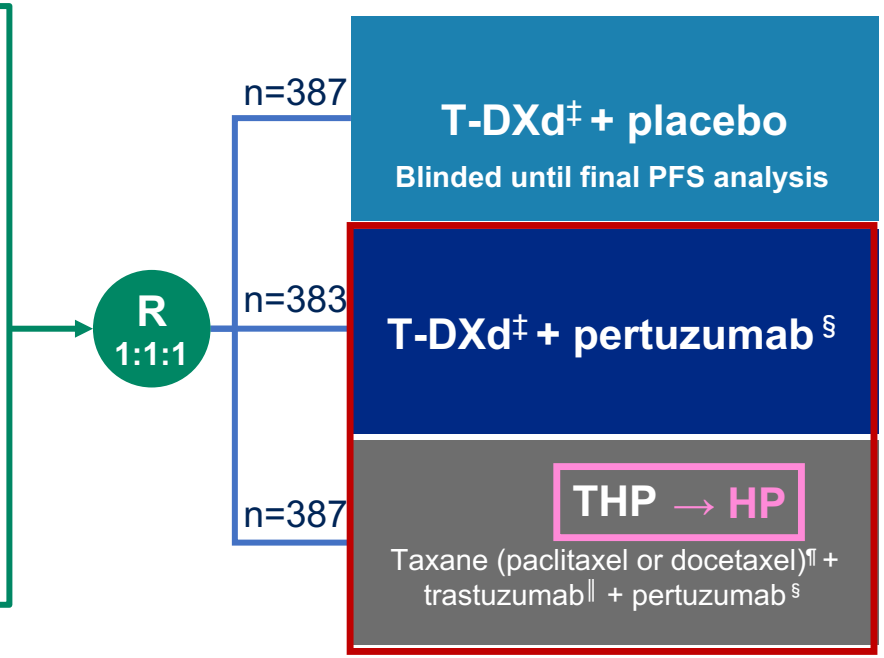
a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; DCO, data cutoff; DFI, disease-free interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR+/−, hormone receptor–positive/–negative; INV, investigator; mBC, metastatic breast cancer; mets, metastases; mo, months; ORR, objective response rate; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PFS2, second progression-free survival; *PIK3CA*m, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; Q3W, every 3 weeks; QW, once every week; R, randomization; T-DXd, trastuzumab deruxtecan

NCT04784715. Updated. May 6, 2025. Available from: https://clinicaltrials.gov/study/NCT04784715 (Accessed May 29, 2025)

DESTINY-Breast09 – 1L 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†**



Endpoints

Primary

- PFS (BICR)

Key secondary

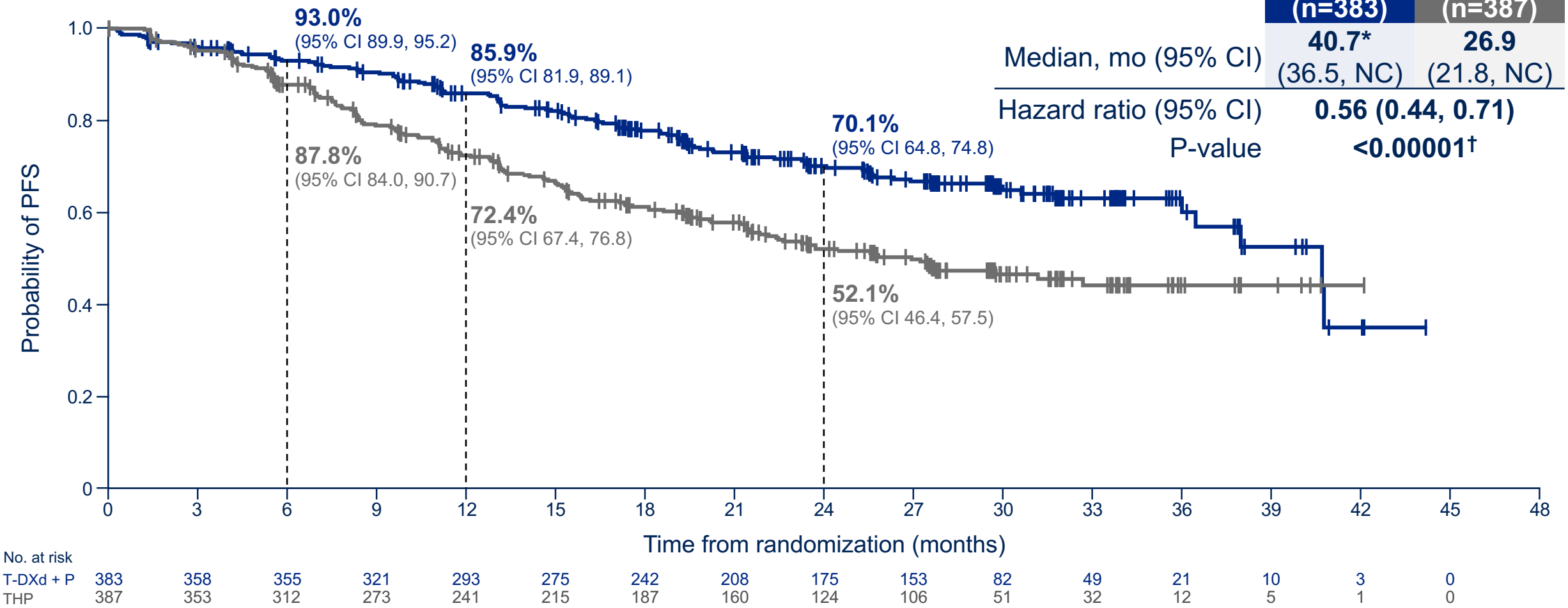
- OS

Secondary

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

- **Key participant characteristics**:
  - 51% de novo mBC; 54% HR+; ~82% IHC 3+
  - Of those initially diagnosed with ESB: ~ 80-85% received (neo)adjuvant chemo; **~ 58% trastuzumab**; **~15% pertuzumab**; **2% T-DM1**
  - Concurrent use of **ET in HR+**: **13.5% in T-DXd + P arm**; **38.3% in THP arm**

PFS (BICR): primary endpoint



	T-DXd + P (n=383)	THP (n=387)
Median, mo (95% CI)	40.7* (36.5, NC)	26.9 (21.8, NC)
Hazard ratio (95% CI)	0.56 (0.44, 0.71)	
P-value	<0.00001†	

No. at risk

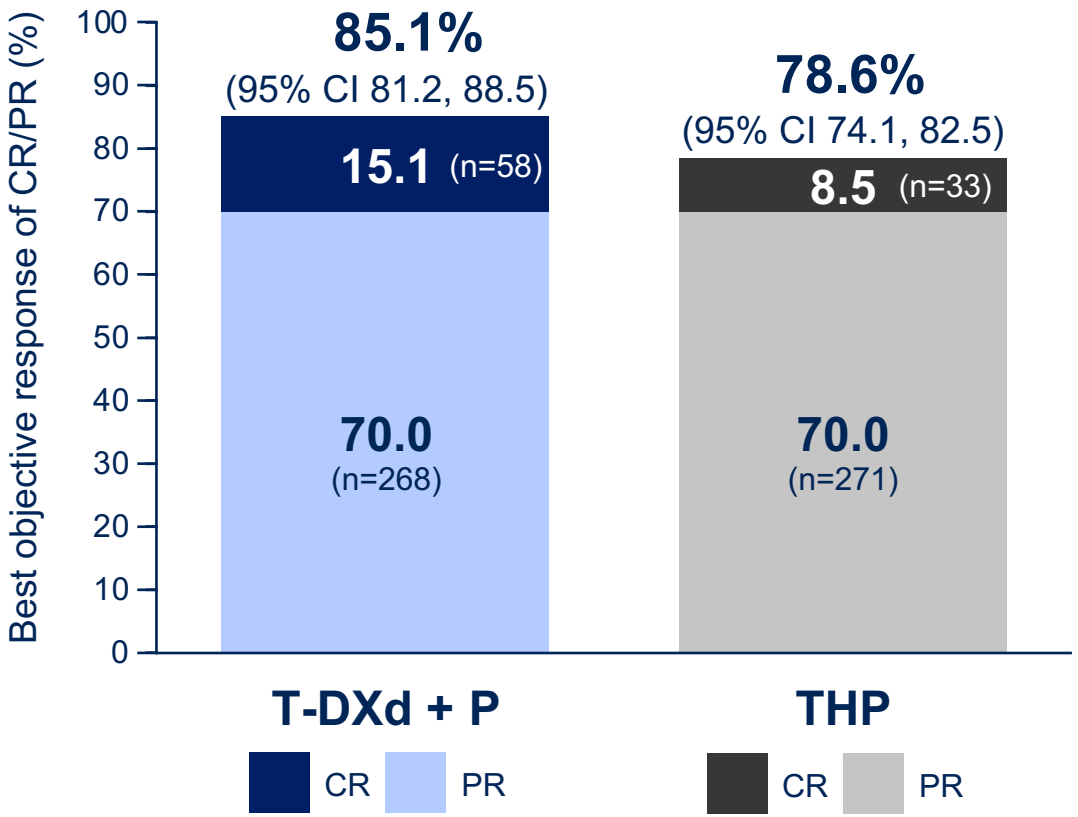
T-DXd + P	383	358	355	321	293	275	242	208	175	153	82	49	21	10	3	0
THP	387	353	312	273	241	215	187	160	124	106	51	32	12	5	1	0

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

*Median PFS estimate for T-DXd + P is likely to change at updated analysis; †stratified log-rank test. A P-value of <0.00043 was required for interim analysis superiority
BICR, blinded independent central review; CI, confidence interval; mo, months; (m)PFS, (median) progression-free survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

ORR and DOR (BICR)

Confirmed ORR*

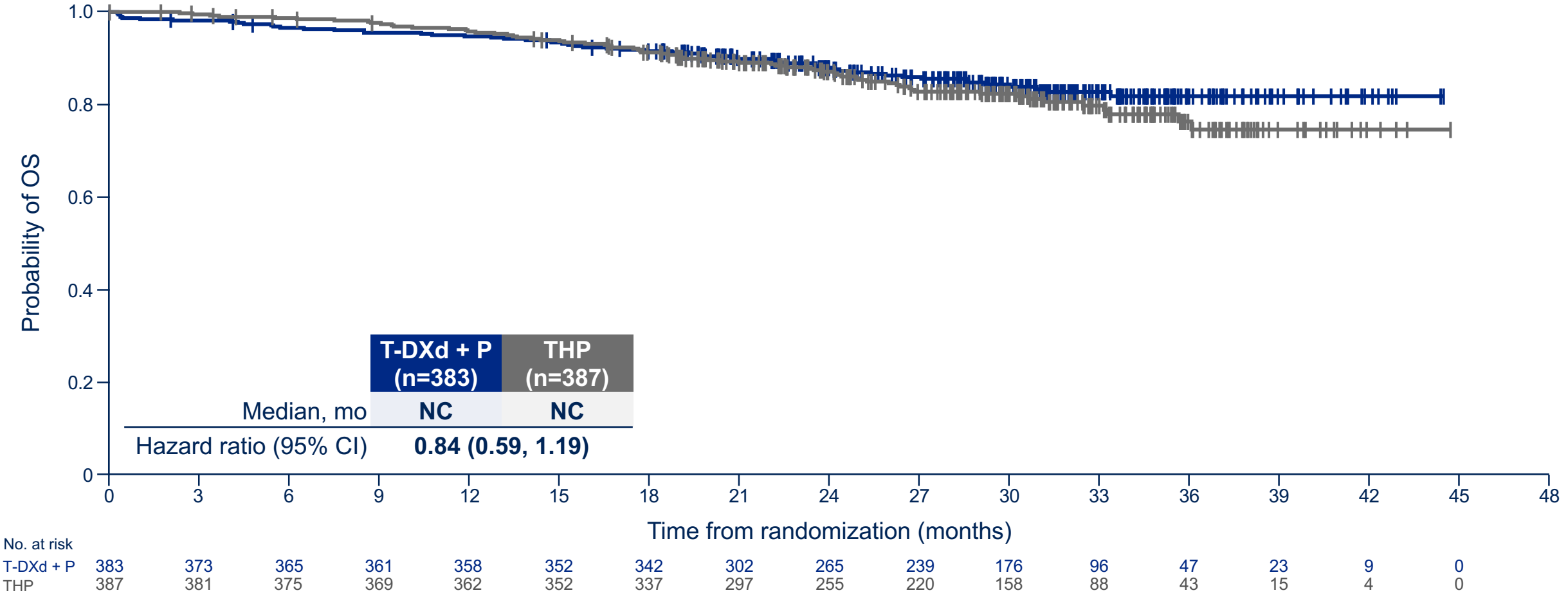


	T-DXd + P (n=383)	THP (n=387)
Median DOR, mo (95% CI)	39.2 (35.1, NC)	26.4 (22.3, NC)
Remaining in response at 24 mo (%)	73.3	54.9
Stable disease, n (%)	38 (9.9)	56 (14.5)

Response rates were greater with T-DXd + P vs THP and were durable

*Based on RECIST v1.1; response required confirmation after 4 weeks
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; mo, months; NC, not calculable; ORR, objective response rate; P, pertuzumab; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

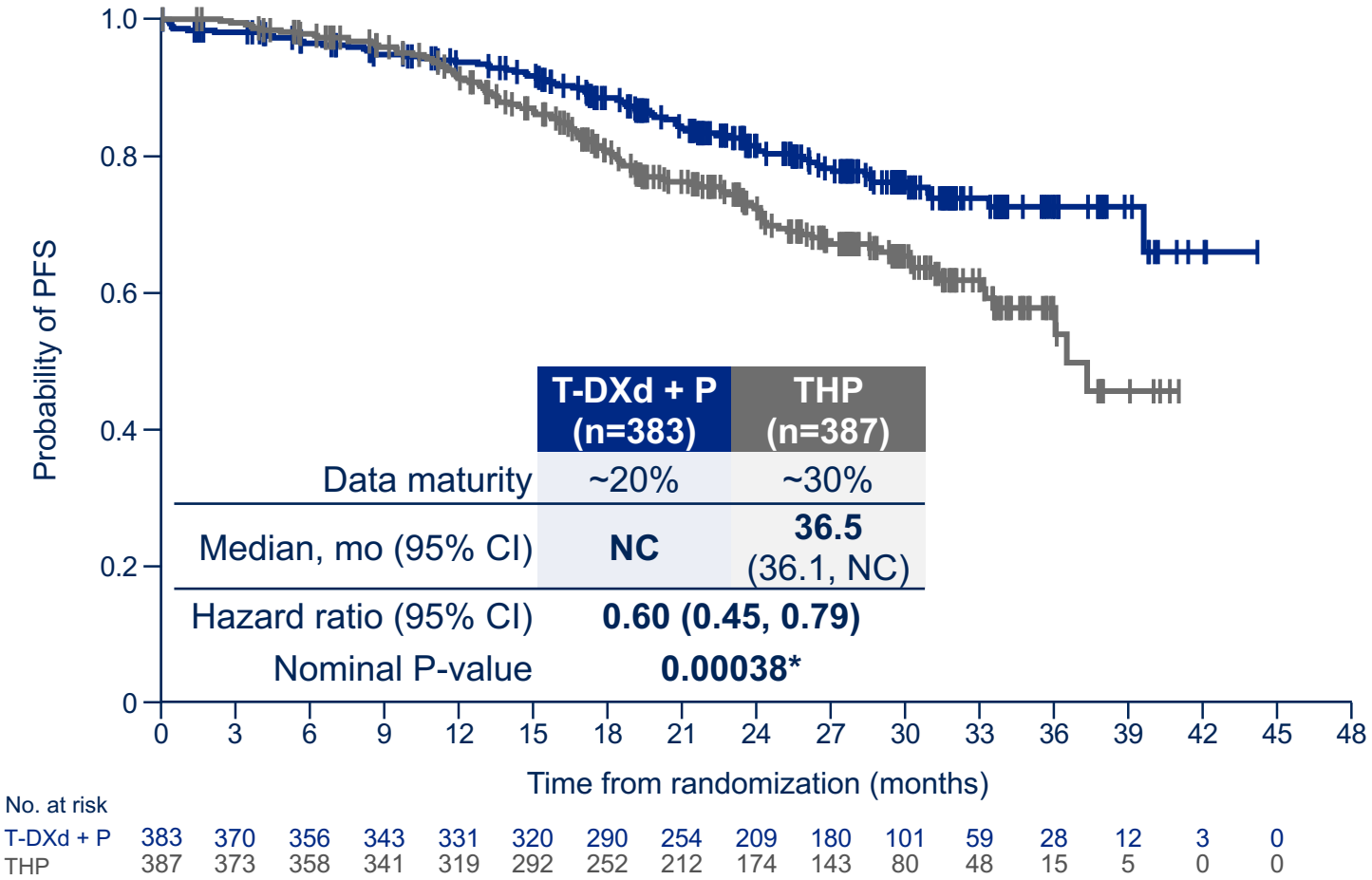
Overall survival (~16% maturity)



Early OS data suggest a positive trend favoring T-DXd + P over THP

CI, confidence interval; OS, overall survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

PFS2 (investigator assessment) and post-trial treatments



	T-DXd + P (n=383)	THP (n=387)
Data maturity	~20%	~30%
Median, mo (95% CI)	**NC**	**36.5** (36.1, NC)
Hazard ratio (95% CI)	**0.60 (0.45, 0.79)**	
Nominal P-value	**0.00038***	

	T-DXd + P (n=383)	THP (n=387)
Received post-discontinuation therapy in second line, n (%)†	124 (32.4)	181 (46.8)
Targeted therapy, n (%)†	111 (29.0)	166 (42.9)
T-DXd	6 (1.6)	39 (10.1)
T-DM1	7 (1.8)	47 (12.1)
Trastuzumab-containing regimen‡	78 (20.4)	51 (13.2)
Pertuzumab-containing regimen‡	53 (13.8)	34 (8.8)
Chemotherapy, n (%)†	68 (17.8)	57 (14.7)
Docetaxel	24 (6.3)	8 (2.1)
Paclitaxel	18 (4.7)	4 (1.0)
Capecitabine	24 (6.3)	35 (9.0)
Endocrine therapy, n (%)†	19 (5.0)	13 (3.4)

Clinically meaningful improvement in PFS2 with T-DXd + P vs THP

PFS2 was defined by investigators according to local standard clinical practice as the time from randomization to second progression (earliest progression event following first subsequent therapy) or death
*Stratified log-rank test; †percentages are based on the overall population. Therapies listed are not exhaustive. Patients may have received more than one type of therapy; ‡patients may have received trastuzumab and pertuzumab concurrently
CI, confidence interval; NC, not calculable; P, pertuzumab; PFS2, second progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Adverse events of special interest

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)

Left ventricular dysfunction†

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	4 (1.0)	30 (7.9)	7 (1.8)	1 (0.3)	0	42 (11.0)
THP (n=382)	1 (0.3)	19 (5.0)	7 (1.8)	0	0	27 (7.1)

Safety analysis set
*Adjudicated drug-related ILD/pneumonitis (grouped term) includes: chronic obstructive pulmonary disease, interstitial lung disease, organizing pneumonia, pneumonia, and pneumonitis, †left ventricular dysfunction (grouped term) includes: potential heart failure, cardiac failure, cardiac failure chronic, ejection fraction decreased, left ventricular dysfunction, and right ventricular failure
ILD, interstitial lung disease; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Incidence Increases by Line of Therapy

Using longitudinal US Flatiron Health de-identified database, 16063 MBC pts. 1955 with BM by index date

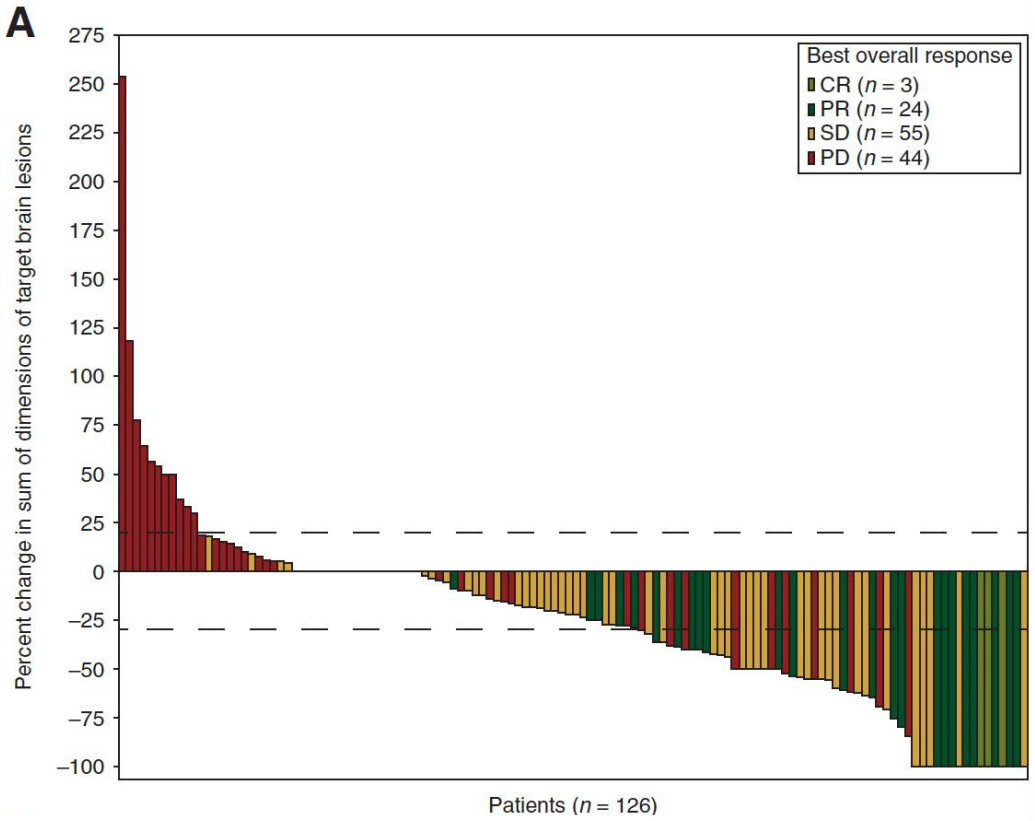
Line of therapy	HR+, HER2-positive	HR–, HER2-positive	HR+, HER2– [HR+, HER2-low]	TNBC [HR–, HER2-low]
Prevalence of BM, %				
1	193 (6.3)	101 (11.2)	134 (2.5) [199 (2.8)]	109 (10.3) [88 (12.1)]
2	341 (17.6)	149 (31.2)	150 (4.4) [275 (5.8)]	97 (17.6) [73 (17.3)]
3	265 (21.5)	102 (36.3)	125 (6.7) [231 (7.4)]	63 (22.0) [50 (20.8)]
4	199 (26.1)	59 (37.1)	104 (7.2) [189 (9.4)]	38 (24.7) [36 (27.9)]
5+	120 (26.5)	38 (36.9)	78 (8.5)	23 (32.4)

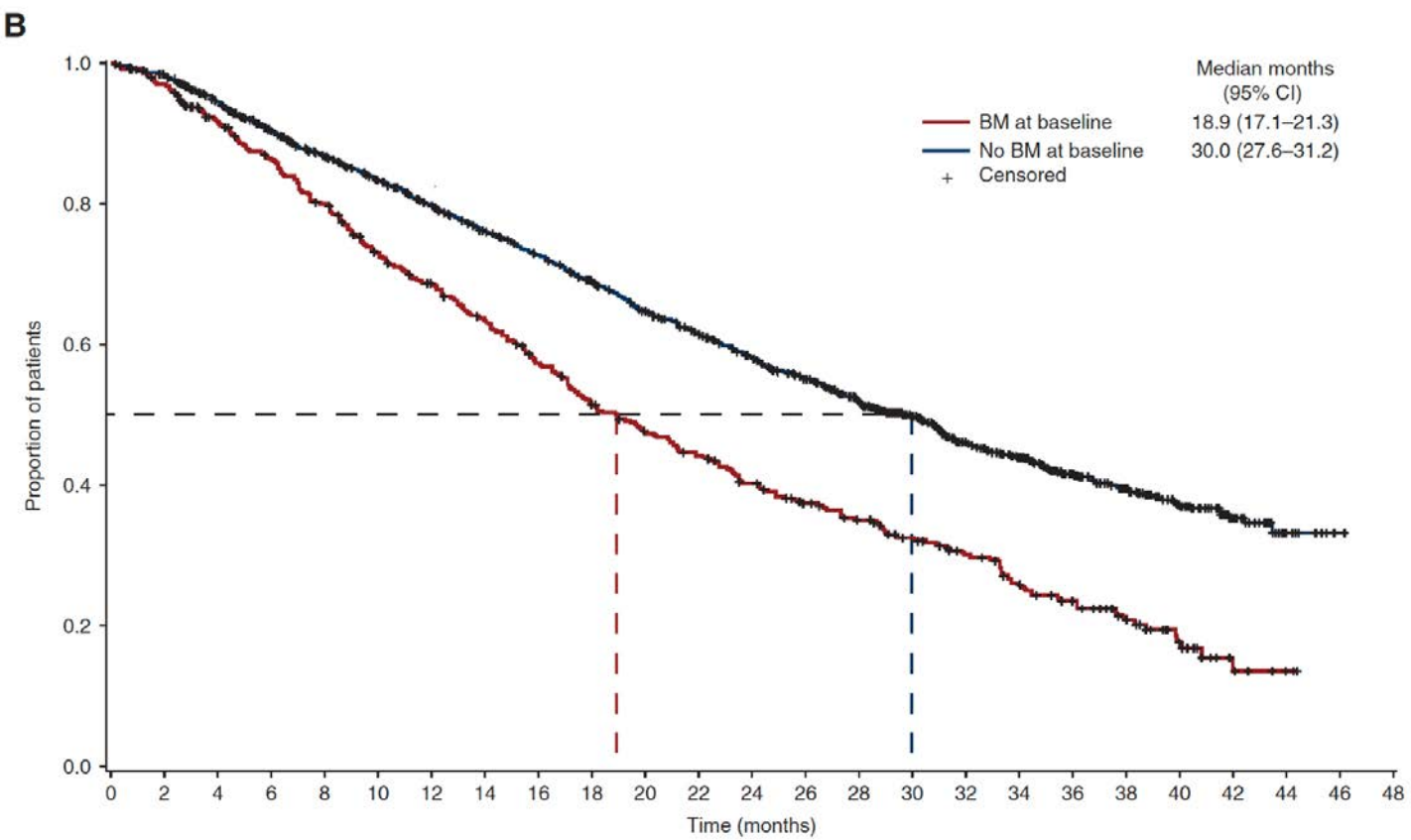
Generally, Incidence Increases Over Time; early event in ER-, HER2+

Sammons SL et al. SABCS 2023;Abstract PS11-01

T-DM1: First ADC to show HER2+ Brain Metastases Activity, KAMILLA

Phase IIIB, 2002 pts treated T-DM1, 398 had baseline BM, 126 patients with measurable BM.



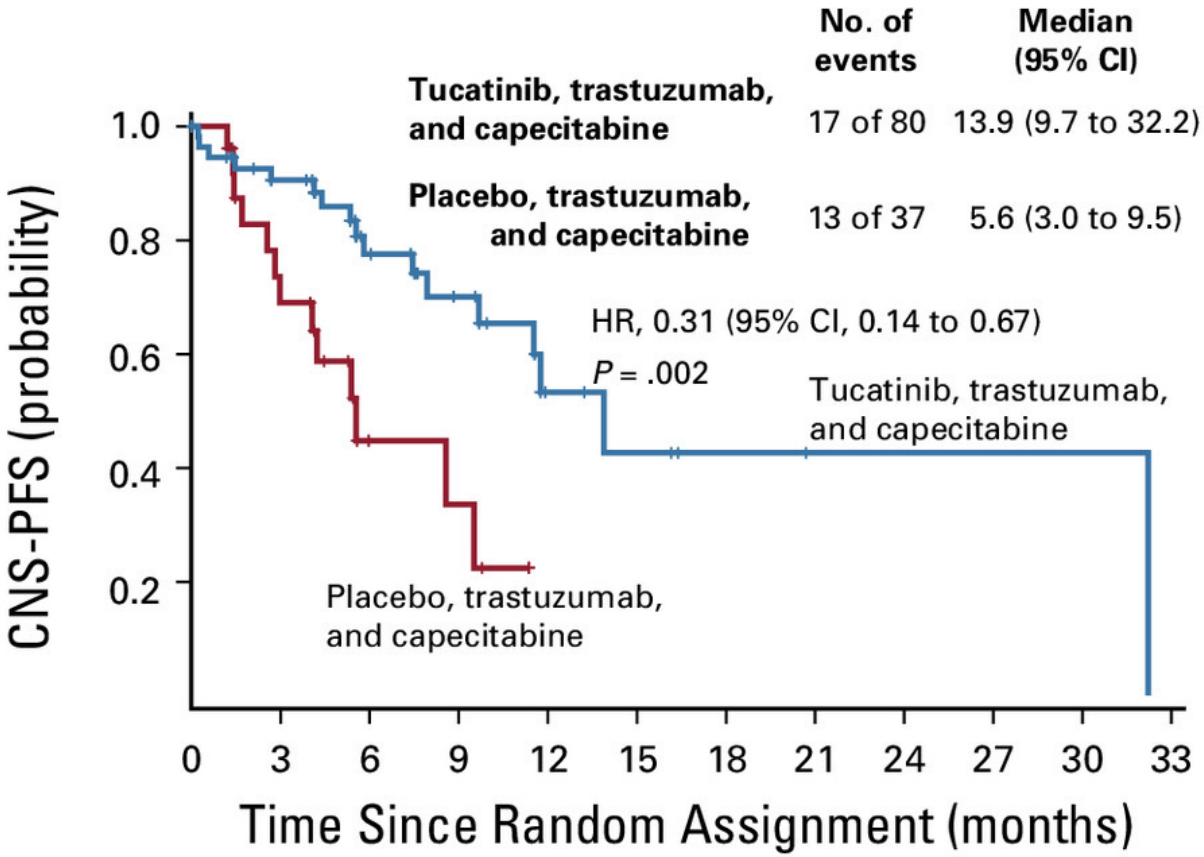


Intracranial ORR: 21%
mPFS 5.5m
mOS 19m

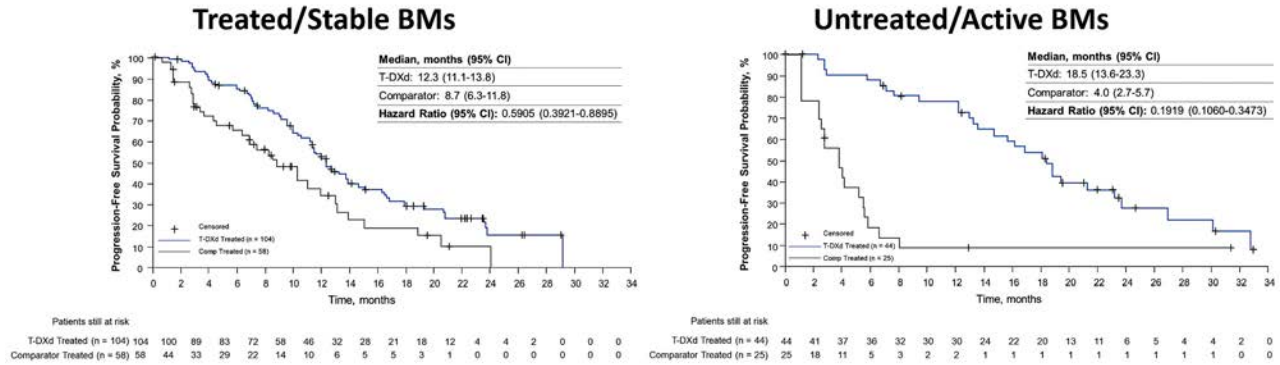
} Pts with baseline brain mets

Montemurro F et al. Ann Oncol. 2020 Oct;31(10):1350-1358.

Tucatinib and T-DXd prolongs CNS-PFS in HER2+ Stable and Active BMs



DESTINY-Breast01, -02, and -03



- **T-DXd demonstrated a trend towards prolonged CNS-PFS over comparator, with a noticeably greater advantage for patients with untreated/active BMs**

BICR, blinded independent central review; BM, brain metastasis; CNS, central-nervous system; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.
CNS-PFS was defined by BICR as only radiological progression.

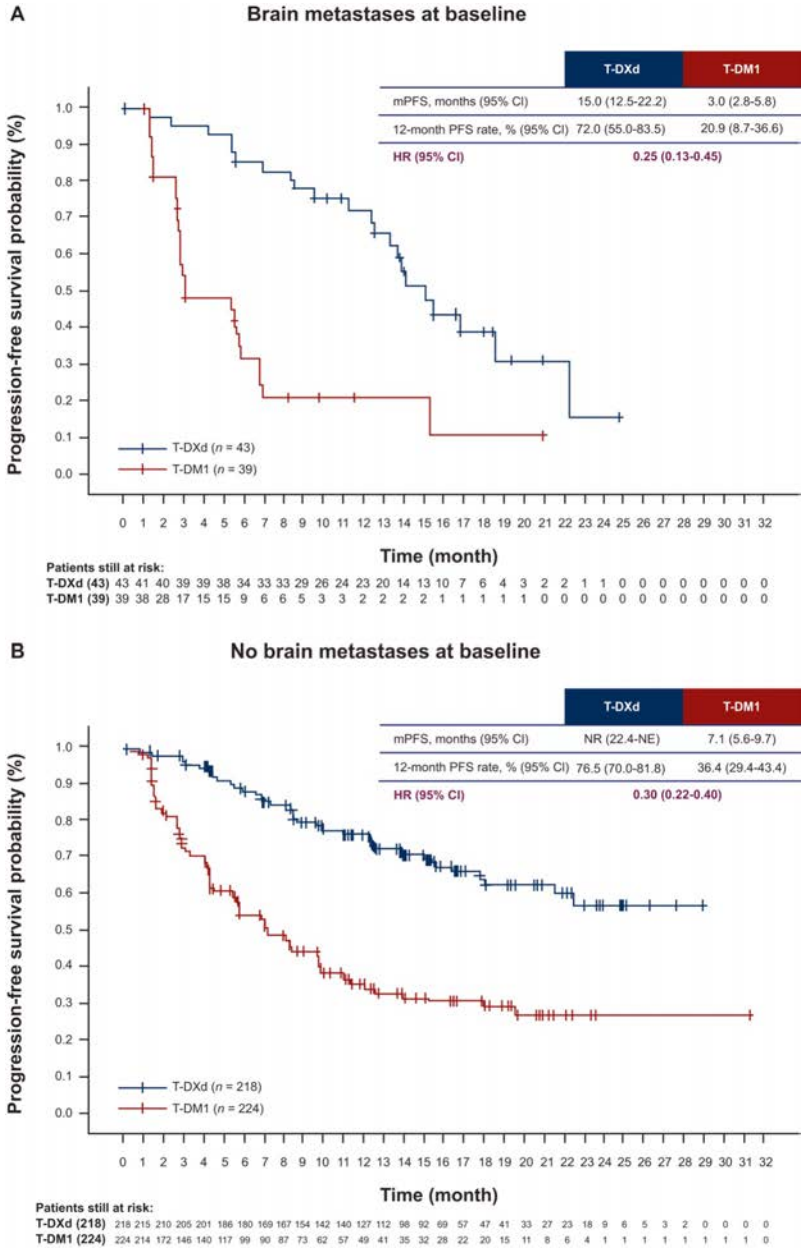
MADRID 2023 ESMO congress

Sara A. Hurvitz, MD

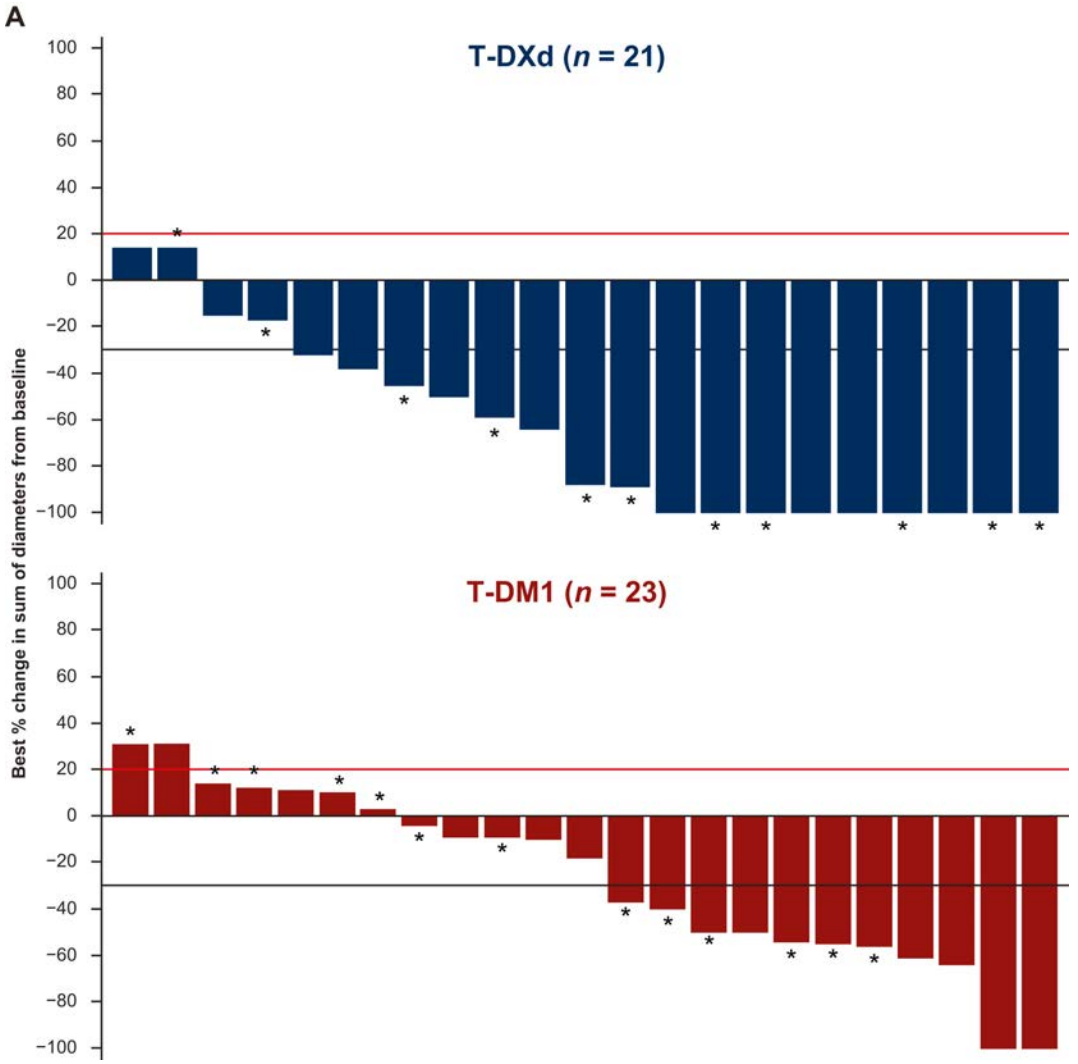
CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment

Lin NU et al. J Clin Oncol. 2020 Aug 10;38(23):2610-2619.
Hurvitz SA et al. ESMO 2023;Abstract 377O

DB-03: T-DXd > T-DM1 Stable and Active BrMs



iORR 65.7% with T-DXd versus 34.3% with T-DM1

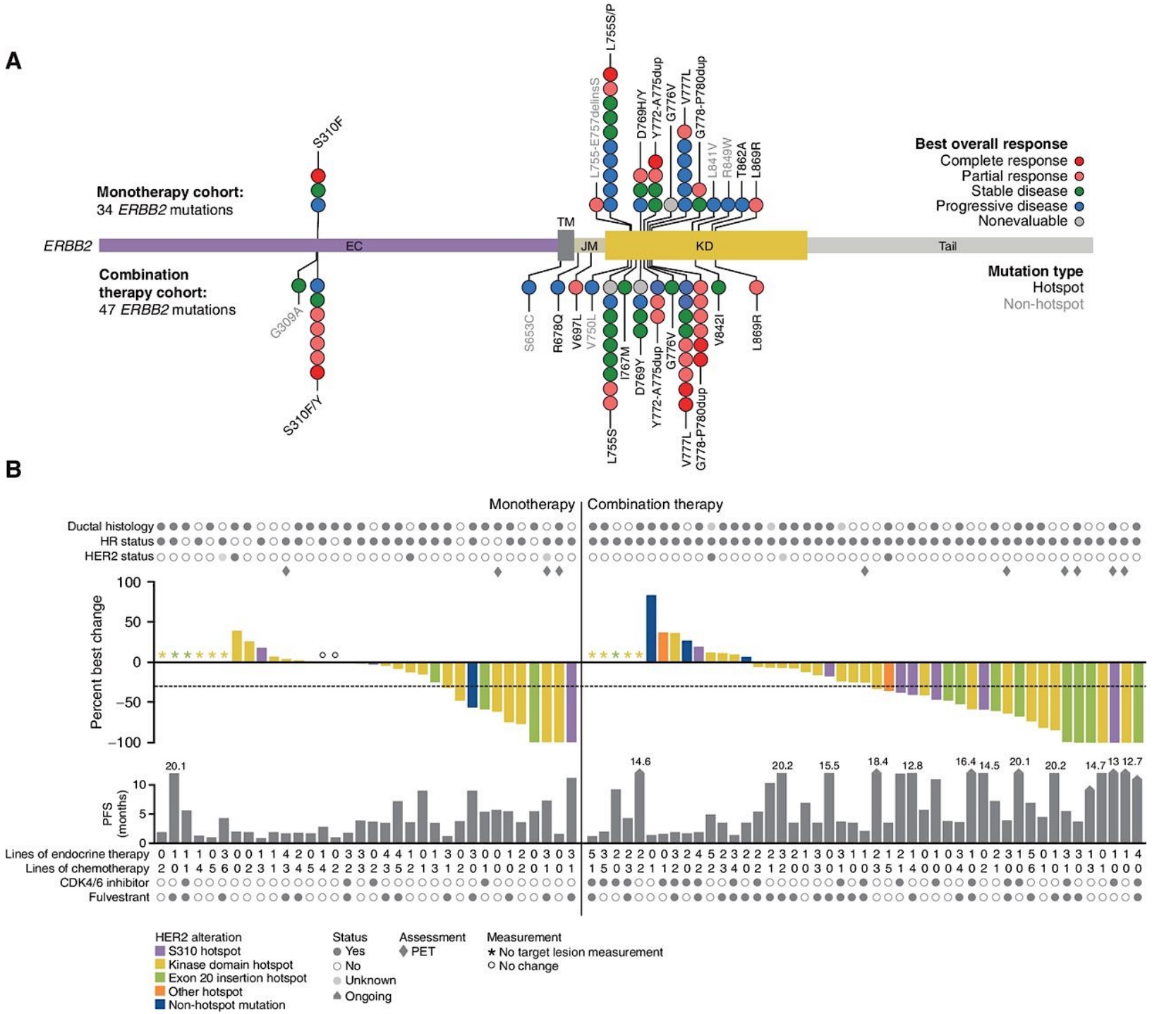


Hurvitz SA et al. ESMO Open. 2024 May;9(5):102924.

HER2 Mutations in Breast Cancer

- Prevalence: 2% overall; 3 to 5% of ER positive MBC; 5-8% of mILC

From: **Efficacy and Determinants of Response to HER Kinase Inhibition in HER2-Mutant Metastatic Breast Cancer**



Smyth LM et al. Cancer Discov. 2020 Feb;10(2):198-213.

HER2 Mutations in Breast Cancer

- Prevalence: 2% overall; 3 to 5% of ER positive MBC; 5-8% of mILC
- Treatment outcomes with TKIs

Table 2. Treatment efficacy

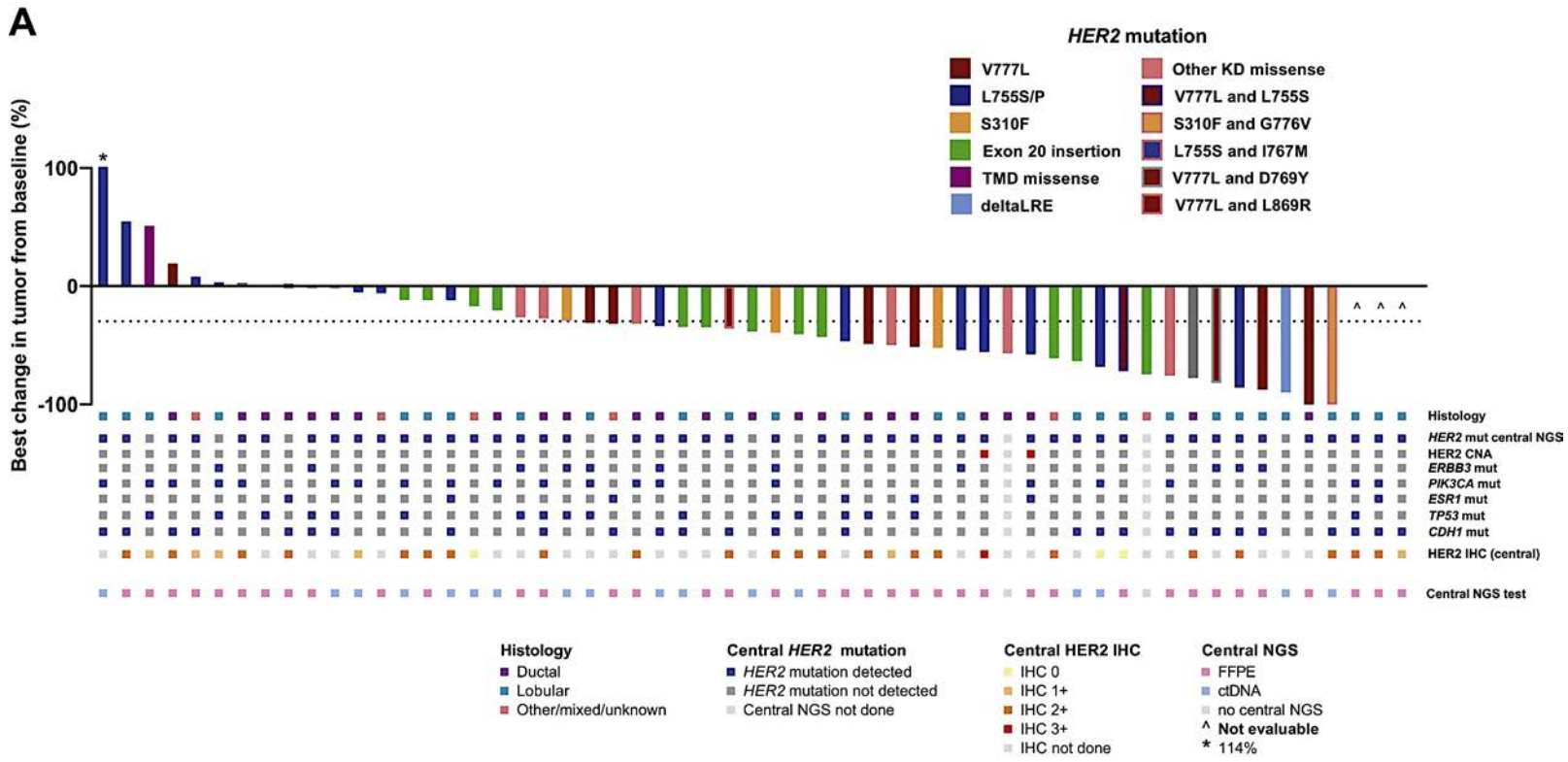
	Neratinib monotherapy		
Response	**ER$^+$**	**ER$^-$**	**Neratinib + fulvestrant**
All patients (intent to treat)[a]	(*n* = 23)	(*n* = 11)	(*n* = 47)
Confirmed overall objective response,[b] *n* (%)	4 (17.4)	4 (36.4)	14 (29.8)
Complete response	2 (8.7)	1 (9.1)	4 (8.5)
Partial response	2 (8.7)	3 (27.3)	10 (21.3)
Overall objective response rate (95% CI)	17.4 (5.0–38.8)	36.4 (10.9–69.2)	29.8 (17.3–44.9)
CBR,[c] % (95% CI)	30.4 (13.2–52.9)	36.4 (10.9–69.2)	46.8 (32.1–61.9)
Time to event (months), median (95% CI)			
PFS	3.6 (1.8–4.3)	2.0 (1–5.5)	5.4 (3.7–9.2)

Smyth LM et al. Cancer Discov. 2020 Feb;10(2):198-213.

HER2 Mutations in Breast Cancer

- Prevalence: 2% overall; 3 to 5% of ER positive MBC; 5-8% of mILC
- Treatment outcomes with TKIs

Neratinib + fulvestrant + trastuzumab
N = 57
ORR = 39%
Median PFS = 8.3 m

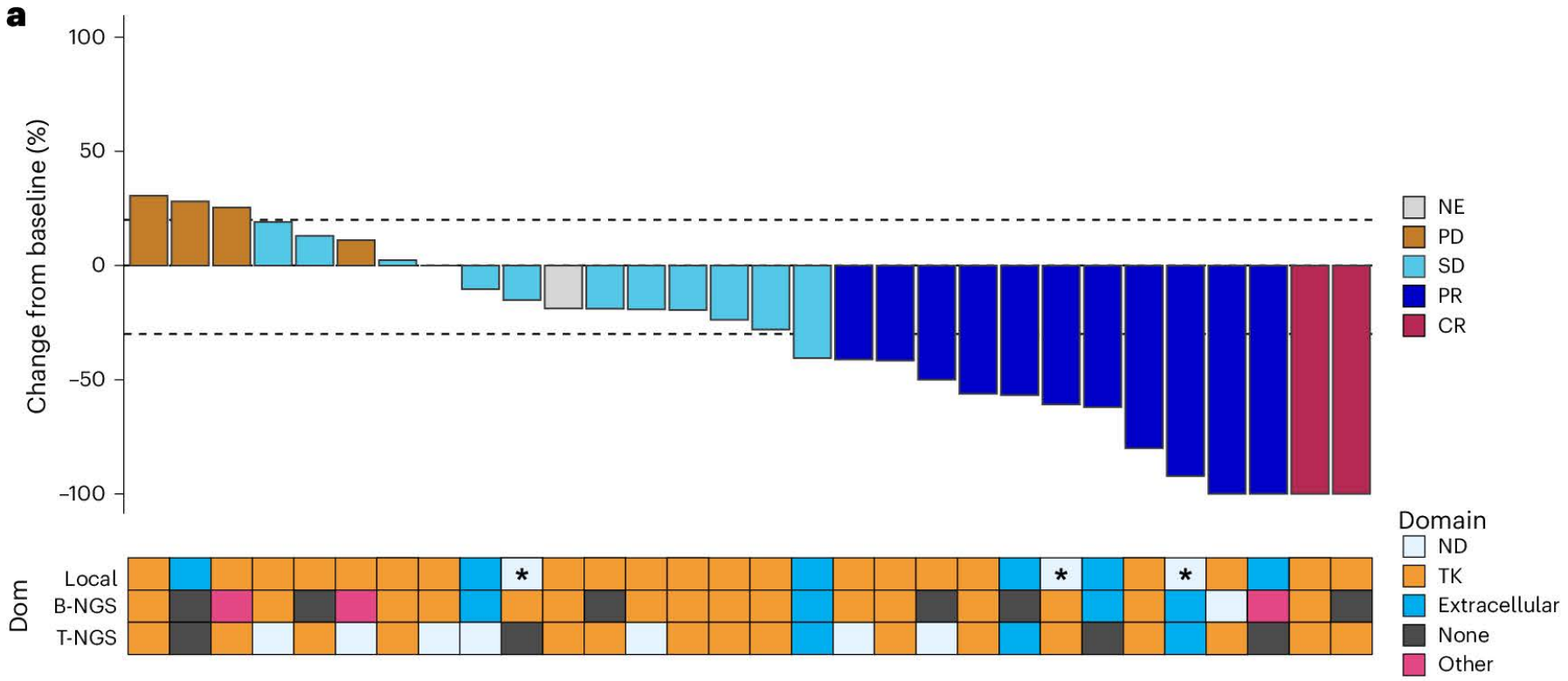


SUMMIT Trial
Jhaveri K, et al. Ann Oncol 2023

HER2 Mutations in Breast Cancer

- Prevalence: 2% overall; 3 to 5% of ER positive MBC; 5-8% of mILC
- Treatment outcomes with TKIs

Tucatinib + trastuzumab in HER2 mutated breast cancer
N = 31
ORR = 42%

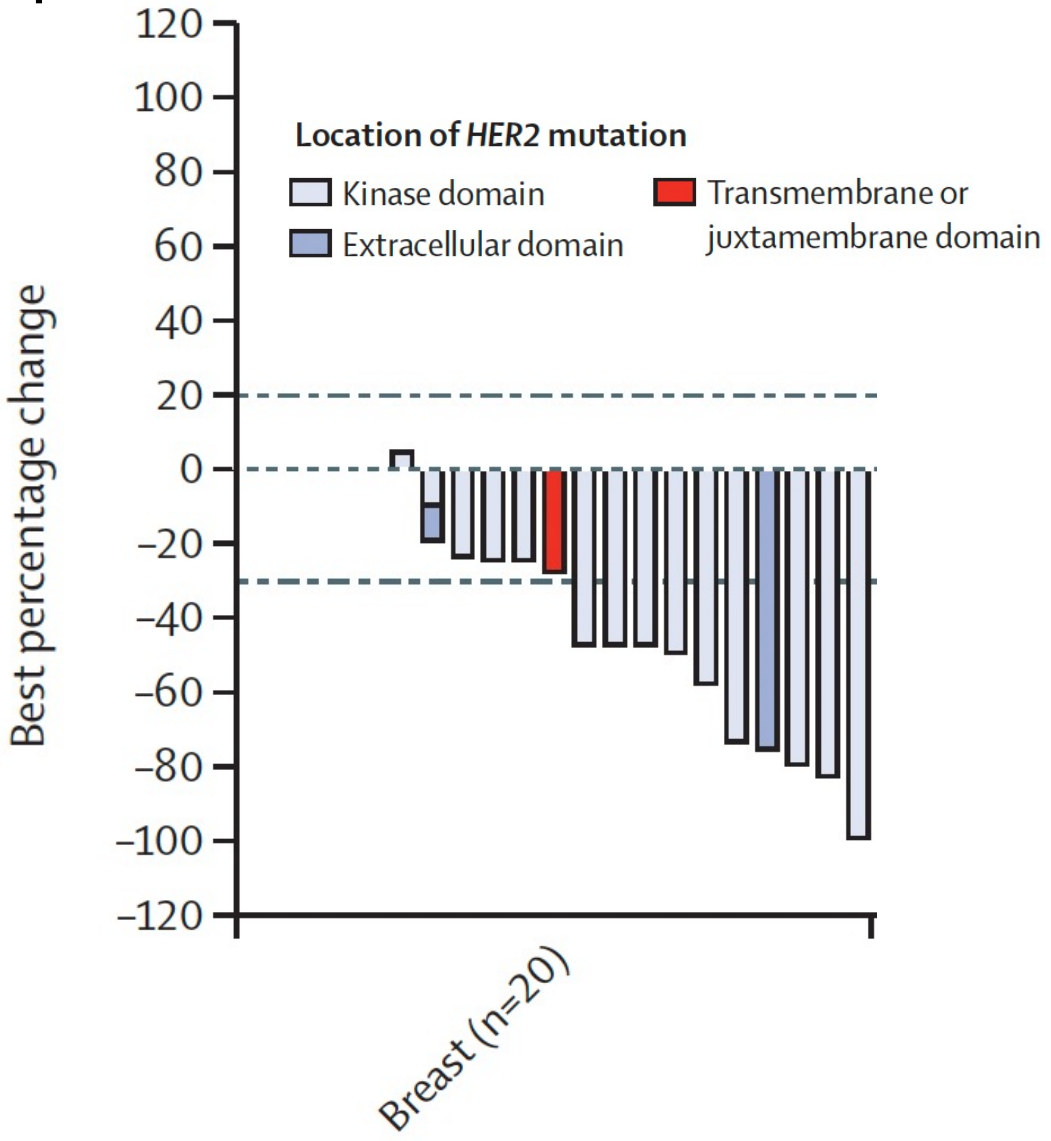


Okines AFC et al. Nat Med 2025

HER2 Mutations in Breast Cancer

- Prevalence: 2% overall; 3 to 5% of ER positive MBC: 5-8% of mILC
- Treatment outcomes with T-DXd

Breast cancer cohort
N = 20
ORR = 50%



DESTINYPanTumor01
Li BT, et al. Lancet Oncol 2024

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

DESTINY-Breast11: Neoadjuvant Trastuzumab Deruxtecan Alone (T-DXd) or Followed by Paclitaxel + Trastuzumab + Pertuzumab (T-DXd-THP) vs SOC for High-Risk HER2+ Early Breast Cancer (eBC)

Harbeck NA et al.

ESMO 2025;Abstract 291O.

PRESIDENTIAL SYMPOSIUM I | SATURDAY, OCTOBER 18 | 16:30 CEST

Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients (pts) with High-Risk Human Epidermal Growth Factor Receptor 2–Positive (HER2+) Primary Breast Cancer (BC) with Residual Invasive Disease After Neoadjuvant Therapy (tx): Interim Analysis of DESTINY-Breast05

Geyer CE et al.

ESMO 2025;Abstract LBA1.

PRESIDENTIAL SYMPOSIUM I | SATURDAY, OCTOBER 18 | 16:52 CEST

Questions from General Medical Oncologists

- **What is your current approach to first-line treatment for HER2-positive mBC?**
- **For patients with HER2-positive mBC receiving first-line T-DXd/pertuzumab, how should we approach:**
  - **Duration of T-DXd?**
  - **HER2 maintenance?**
  - **Maintenance therapy for HR-positive patients? CDKi?**

Questions from General Medical Oncologists

- **Neoadjuvant versus postadjuvant T-DXd — which is better?**
- **Should we be attempting to access T-DXd for our patients who undergo neoadjuvant therapy and are found to have residual disease at surgery?**

Questions from General Medical Oncologists

- What is the current role of neratinib in the postadjuvant setting? How may the earlier use of T-DXd impact your enthusiasm for this approach?
- Which subset of patients benefit the most from postadjuvant neratinib?
- How do people approach dosing with this agent?

Questions from General Medical Oncologists

- **Which is better for CNS disease — tucatinib/trastuzumab/capecitabine or T-DXd?**
- **How do you sequence HER2-targeted agents for patients with brain metastases?**

Questions from General Medical Oncologists

- **What is your clinical approach for patients with HER2-mutated mBC in the absence of HER2 amplification?**
- **Is either T-DXd or neratinib effective in HER2-mutant mBC?**

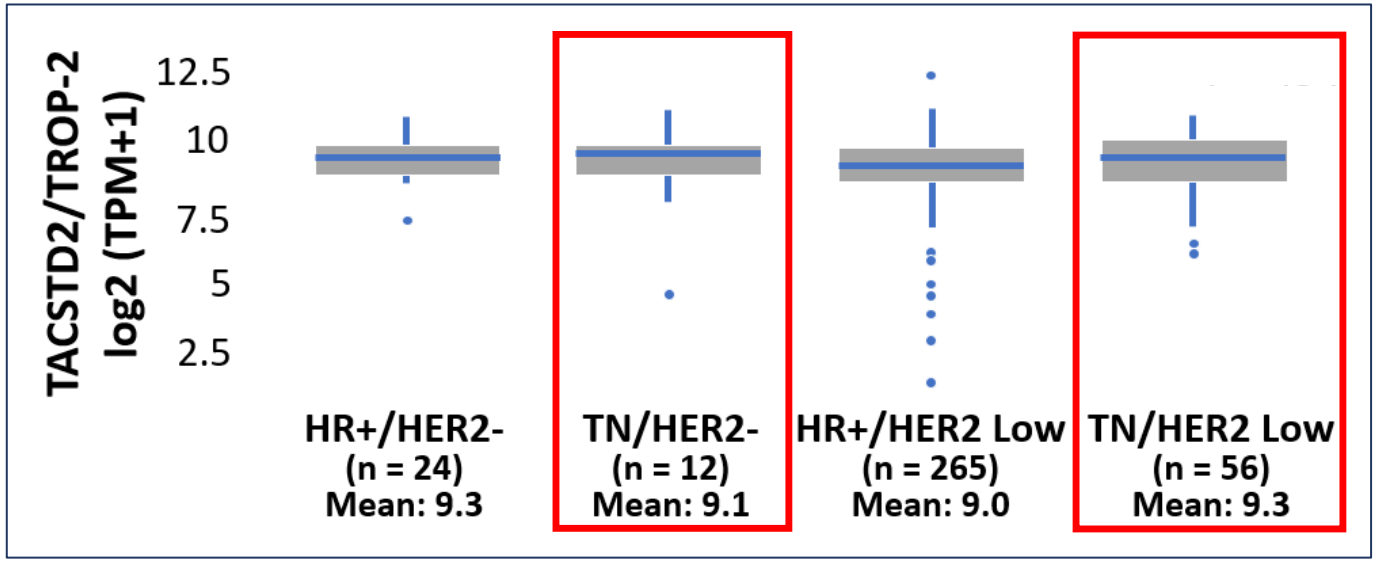
UT Southwestern
Medical Center

ADC Treatment Approaches for TNBC

Heather McArthur, MD, MPH, FASCO
Professor, Department of Internal Medicine
Director, Breast Cancer
Komen Distinguished Chair in Clinical Breast Cancer Research
UT Southwestern, Dallas, TX
Heather.McArthur@utsouthwestern.edu
@hmcarthur

TROP-2 as a Therapeutic Target

- Targeting broadly expressed markers allows for the selective delivery of potent agents
- TROP-2 is a pan-epithelial cancer antigen
  - Overexpressed in all breast cancer subtypes
  - Less expression on normal tissues
  - Excellent target for ADC
  - Marker of poor prognosis: larger tumor size, higher risk of recurrence
  - High TROP-2 levels: aggressive tumor, resistance to chemotherapy



Medford AJ et al. 2023 AACR. Abstract 960. Yao L et al. *Front Oncol*. 2023;13:1292211. Sakach E et al. *Cancers (Basel)*. 2022;14(23):5936.

TROP2-directed ADCs

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

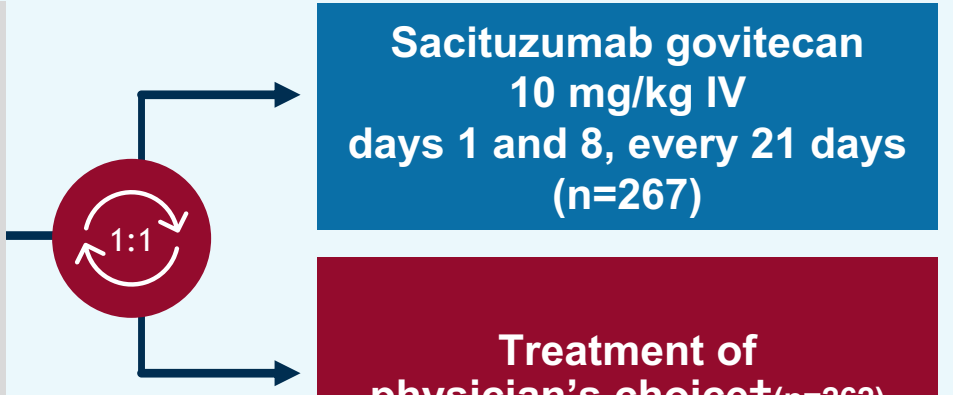
Sands J et al. ASCO 2018; Okajima D et al. ASCO 2018; Bardia A et al. ESMO Breast Cancer 2021; Cheng Y et al. Front Oncol 2022.

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

Metastatic TNBC

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

(N=529)



Stratification Factors

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

Continue treatment until progression or unacceptable toxicity

Endpoints

Primary

- PFS‡

Secondary

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

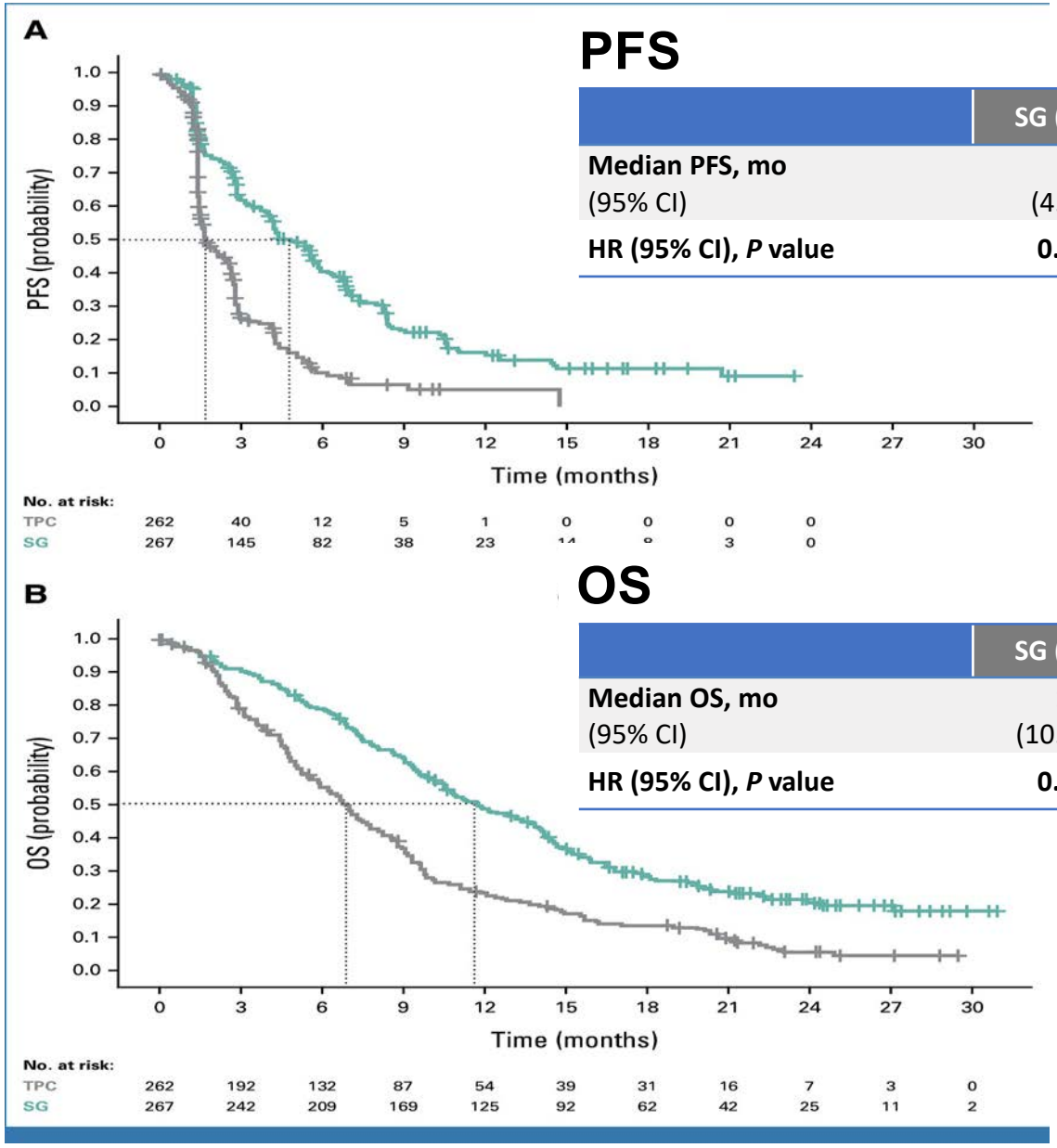
NCT02574455

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

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

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

ASCENT: PFS and OS in the ITT Population



PFS

	SG (n=267)	TPC (n=262)
Median PFS, mo (95% CI)	**4.8** (4.1-5.8)	**1.7** (1.5-2.5)
HR (95% CI), *P* value	**0.43** (0.33-0.51), ***P*<.0001**	

OS

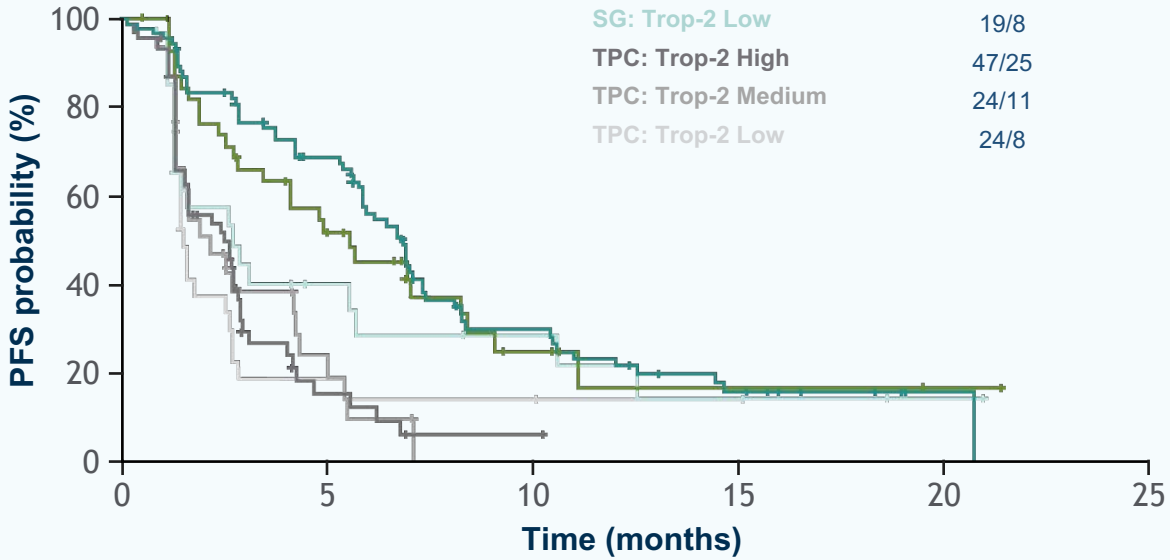
	SG (n=267)	TPC (n=262)
Median OS, mo (95% CI)	**11.8** (10.5-13.8)	**6.9** (5.9-7.7)
HR (95% CI), *P* value	**0.51** (0.42-0.62), ***P*<.0001**	

HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

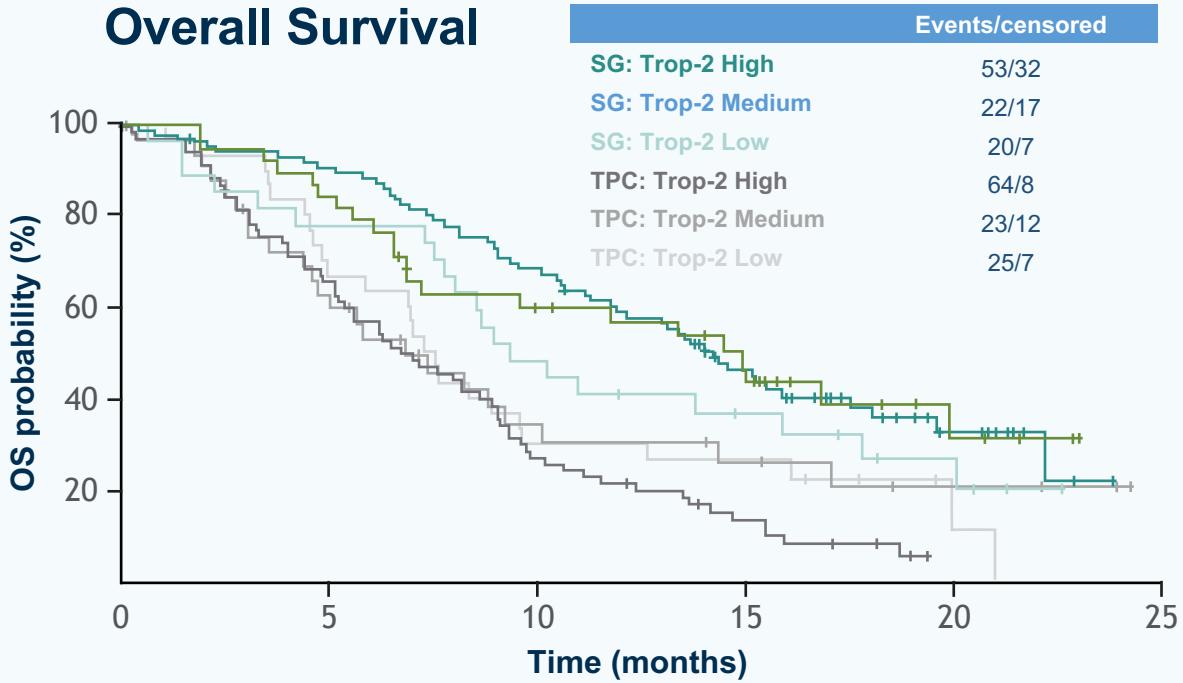
Bardia A et al. *N Engl J Med*. 2021;384(16):1529-1541.
Bardia A et al. *J Clin Oncol.* 2024:42(15):1738-1744.

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

Progression-free Survival



Overall Survival



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

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

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

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

1L mTNBC PD-L1–

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

N=540
(≤25% *de novo*)

Stratification Factors:

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

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

TPC Chemotherapy

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

Crossover to SG allowed after BICR-verified disease progression

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

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

1L mTNBC PD-L1–

centrally confirmed

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

Sacituzumab govitecan

28-day cycles
- **Nab-paclitaxel:** 100 mg/m2 IV on days 1, 8, and 15 of 28-day cycles

over to
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May 23, 2025: The study met its primary endpoint, demonstrating a highly statistically significant and clinically meaningful improvement in PFS compared to chemo in patients with 1st line mTNBC who are not candidates for PD-1/PD-L1 inhibitors

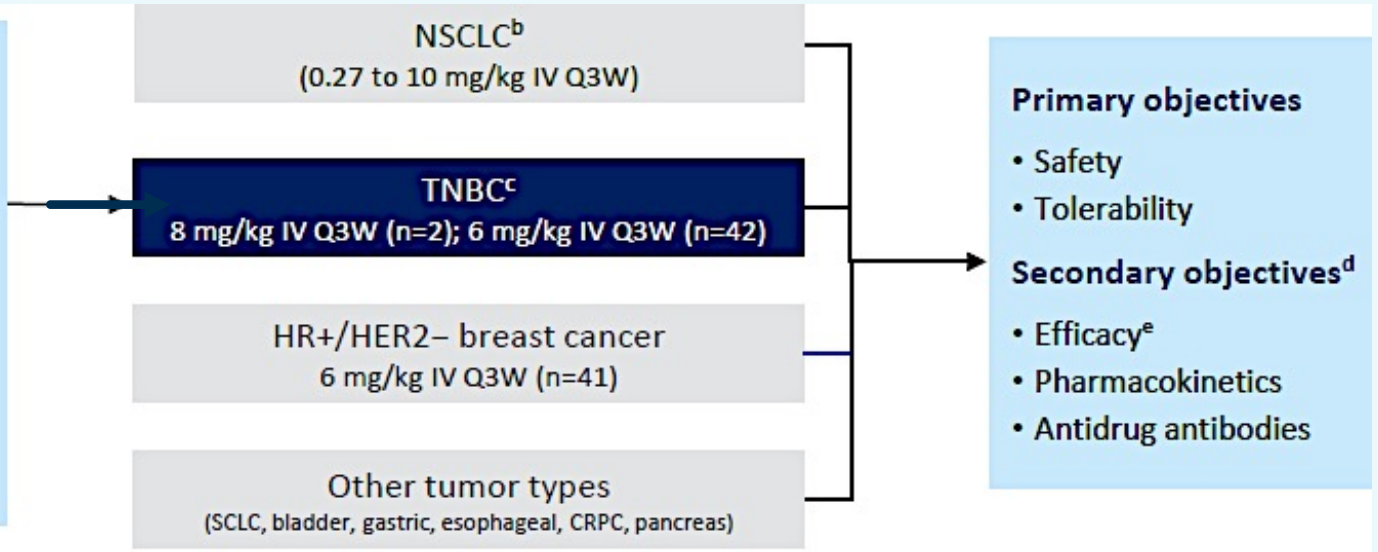
ESMO 2025: LBA20 - Primary Results From ASCENT-03 (Cortes et al):

A Randomized Phase 3 Study of Sacituzumab Govitecan (SG) vs Chemotherapy (Chemo) in Patients (pts) With Previously Untreated Advanced Triple-Negative Breast Cancer (TNBC) Who Are Unable to Receive PD-(L)1 Inhibitors (PD-[L]1i)

Dato-DXd in Advanced TNBC
TROPION-PanTumor01 Study

Study Design

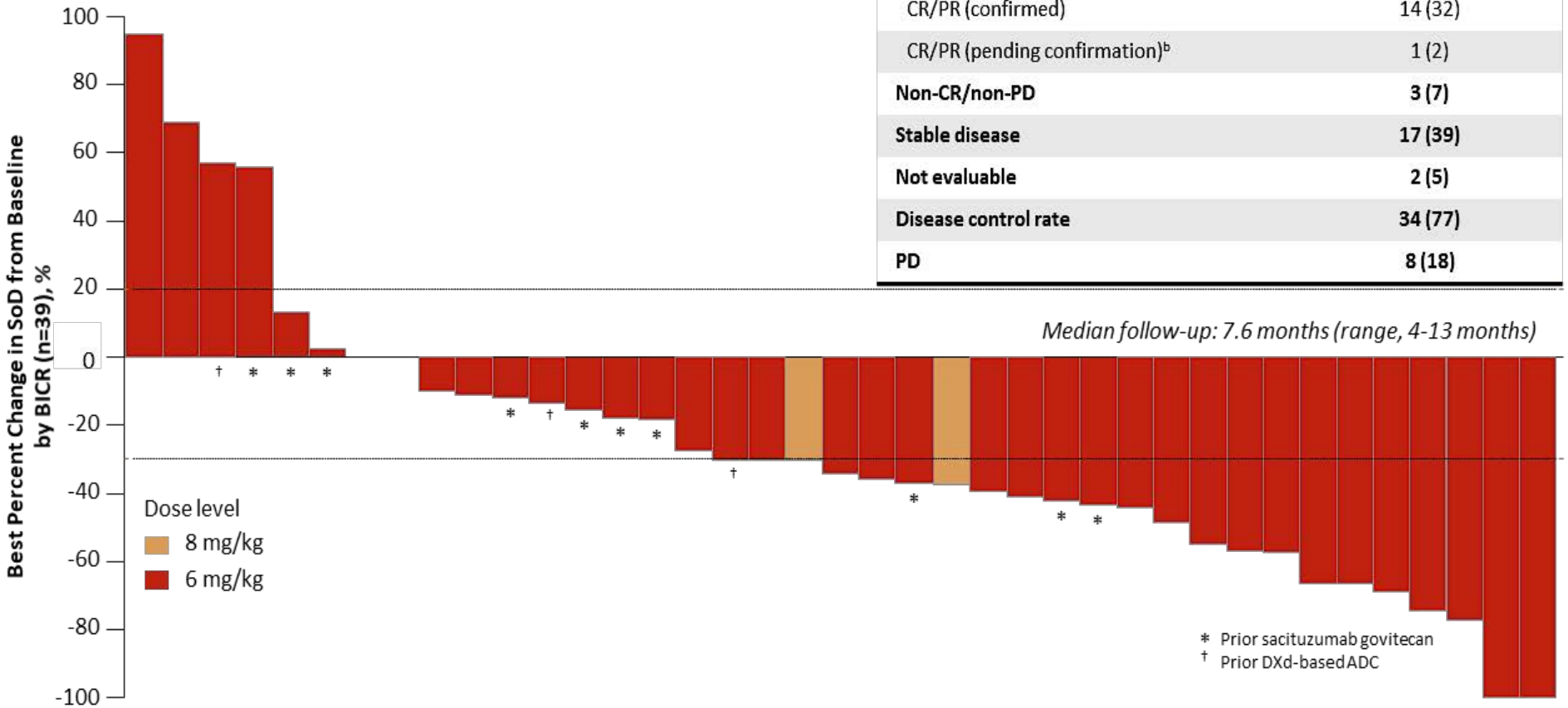
- Advanced/unresectable or metastatic HR–/HER2– (IHC 0/1+ or IHC2+/ISH-) breast cancer
- Relapsed or progressed after local standard treatments
- Unselected for TROP2 expression[a]
- Age ≥18 years (US) or ≥20 years (Japan)
- ECOG PS 0-1
- Measurable disease per RECIST 1.1
- Stable, treated brain metastases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



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

TROPION PanTumor-01: Responses observed with Dato-DXd after other ADC exposure

Patients, n (%)[a]	All Patients, (n=44)
ORR	**15 (34)**
CR/PR (confirmed)	14 (32)
CR/PR (pending confirmation)[b]	1 (2)
Non-CR/non-PD	**3 (7)**
Stable disease	**17 (39)**
Not evaluable	**2 (5)**
Disease control rate	**34 (77)**
PD	**8 (18)**



Responses seen with Dato-DXd (Trop-2 targeting ADC) **after**

- Sacituzumab govitecan (same antigen/different payload)
- T-DXd (different antigen/same payload)

Krop et al, SABCS 2021

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

TROPION-Breast02[1]

Key Eligibility Criteria:

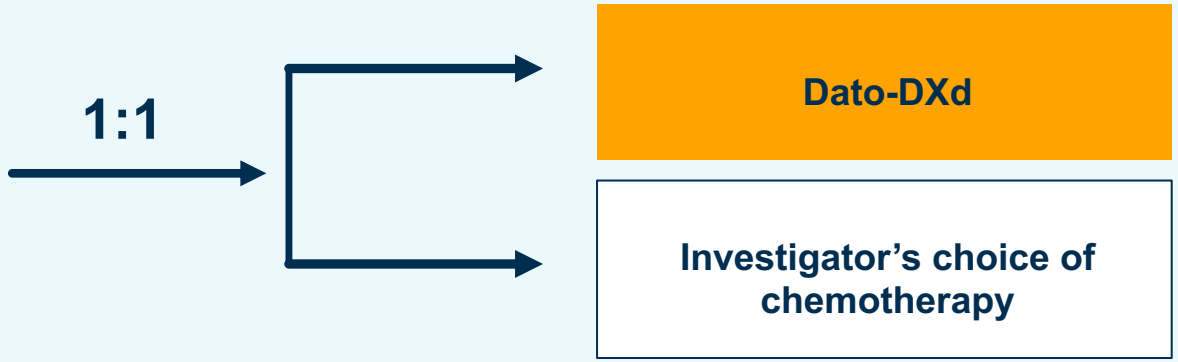
- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1/PDL1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification Factors:

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

Dual Primary Endpoint:
PFS (BICR) and OS

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



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

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

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

TROPION-Breast02[1]

Key Eligibility Criteria:

- Locally recurrent inoperable or metastatic TNBC
- ECOG PS 0 or 1

Stratification Factors:

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

Dual Primary Endpoint:
PFS (BICR) and OS

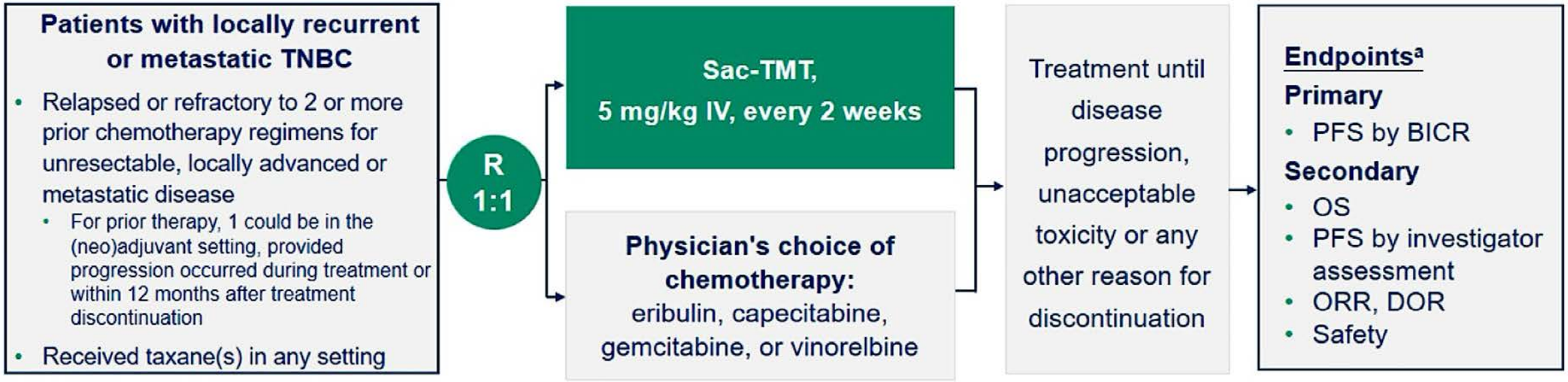
Secondary Endpoints:
PFS (inv), ORR, DoR, Safety

Oct 6, 2025: Positive high-level results from the TROPION-Breast02 Phase III trial showed datopotamab deruxtecan demonstrated a statistically significant and clinically meaningful improvement for the dual primary endpoints of OS and PFS compared to TPC as 1st-line treatment for patients with locally recurrent inoperable or mTNBC for whom IO was not an option

chemotherapy

ESMO 2025: LBA21 - Primary Results From TROPION-Breast02 (Dent et al):
First-Line (1L) Datopotamab Deruxtecan (Dato-DXd) vs Chemotherapy in Patients with Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer (mTNBC) for Whom Immunotherapy Was Not an Option: Primary Results from the Randomised, Phase 3 TROPION-Breast02 Trial

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



Stratification factors

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

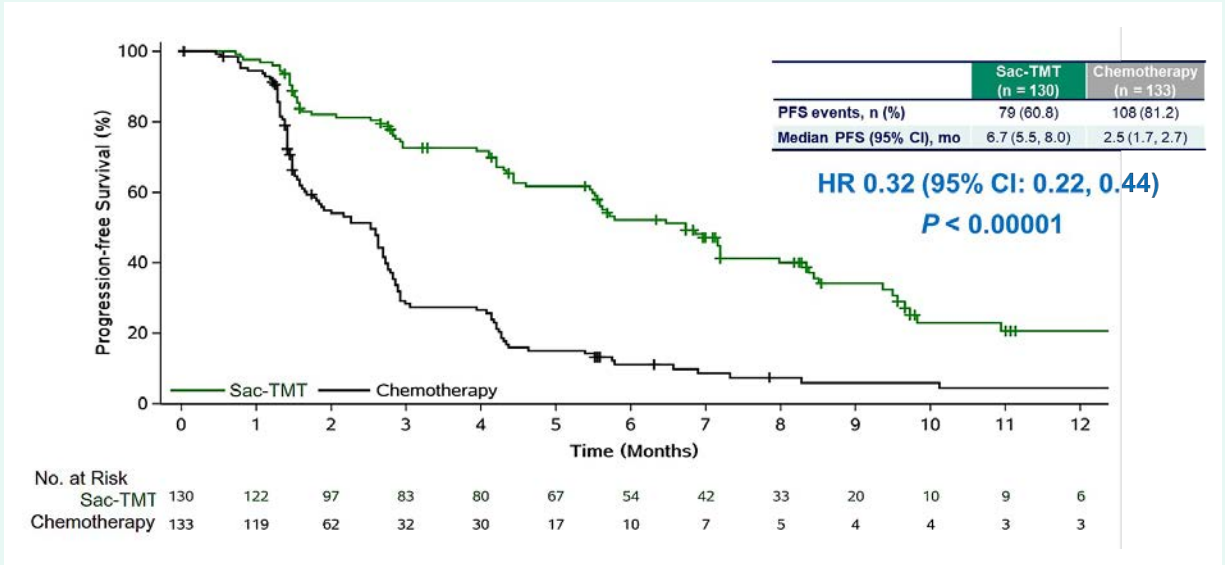
Tumor assessment

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

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

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

PFS

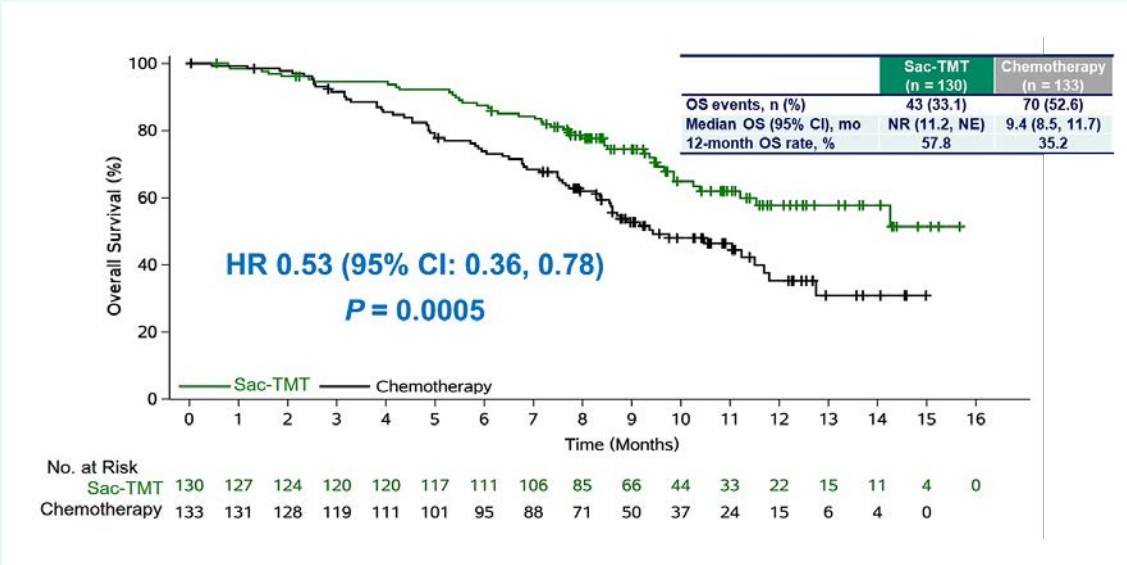


	Sac-TMT (n = 130)	Chemotherapy (n = 133)
PFS events, n (%)	79 (60.8)	108 (81.2)
Median PFS (95% CI), mo	6.7 (5.5, 8.0)	2.5 (1.7, 2.7)

HR 0.32 (95% CI: 0.22, 0.44)

P < 0.00001

OS



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

HR 0.53 (95% CI: 0.36, 0.78)

P = 0.0005

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

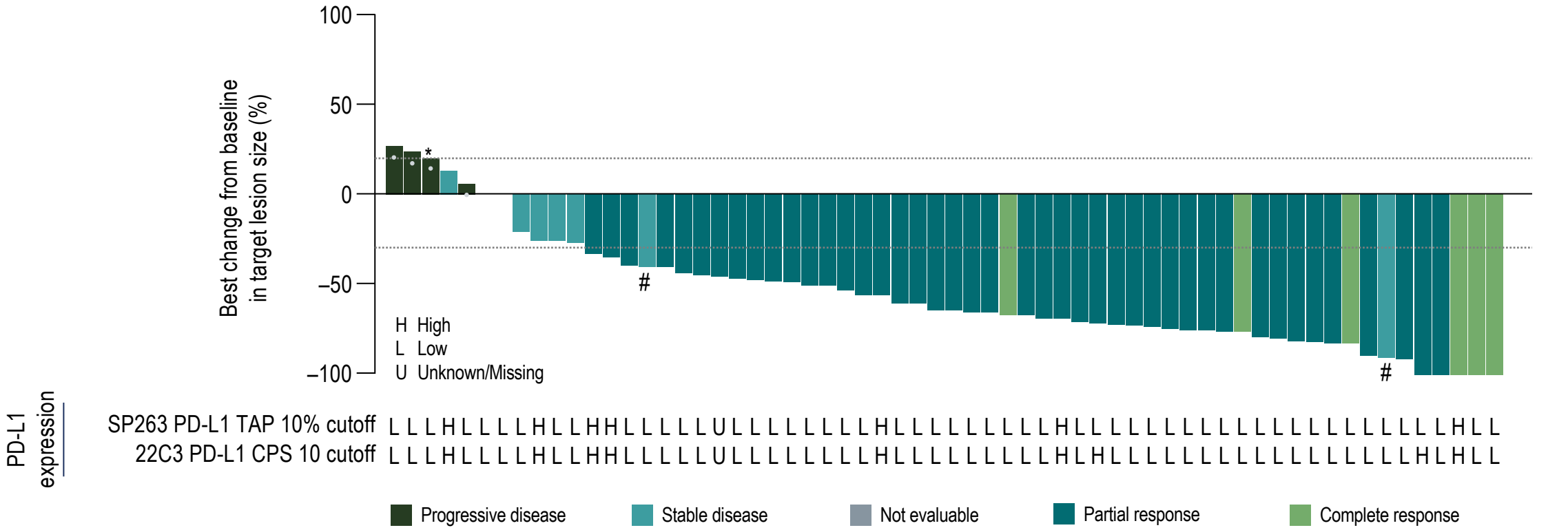
Will ADC + IO Become the New 1L SOC for mTNBC?

BEGONIA Arm 7: Dato-DXd + Durvalumab

1st Line 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



Schmid et al. ESMO 2023

TROPION-Breast05

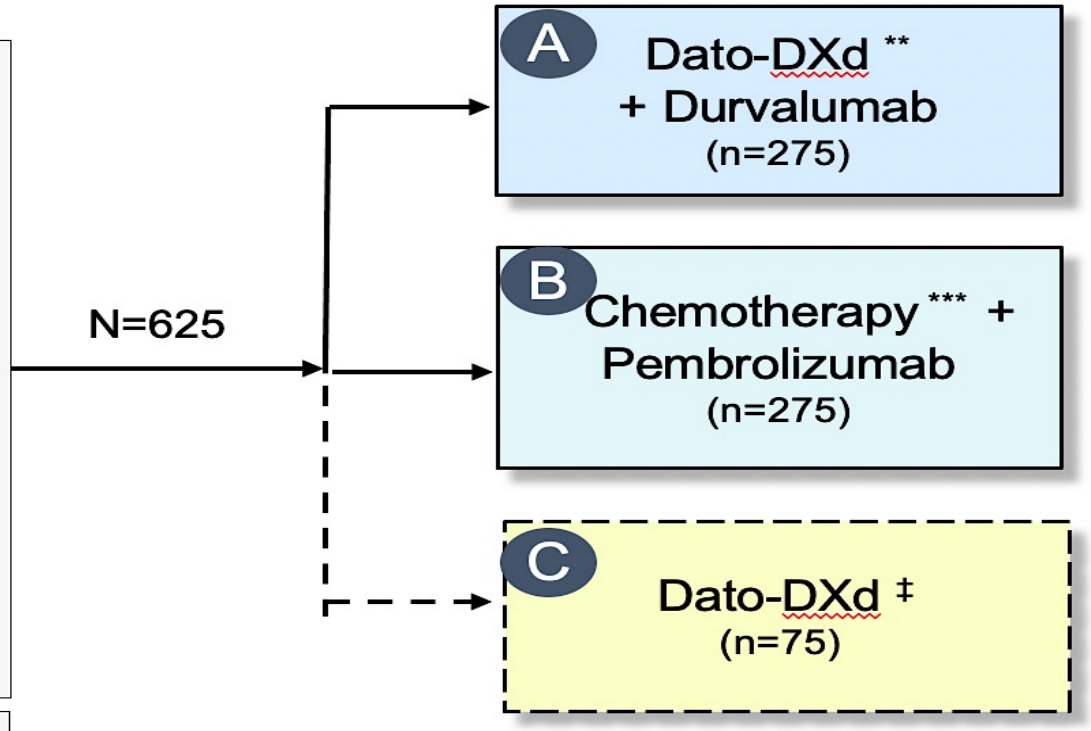
Dato-DXd +/- durva vs TPC + pembro in 1L PD-L1+ mTNBC

Key Eligibility Criteria

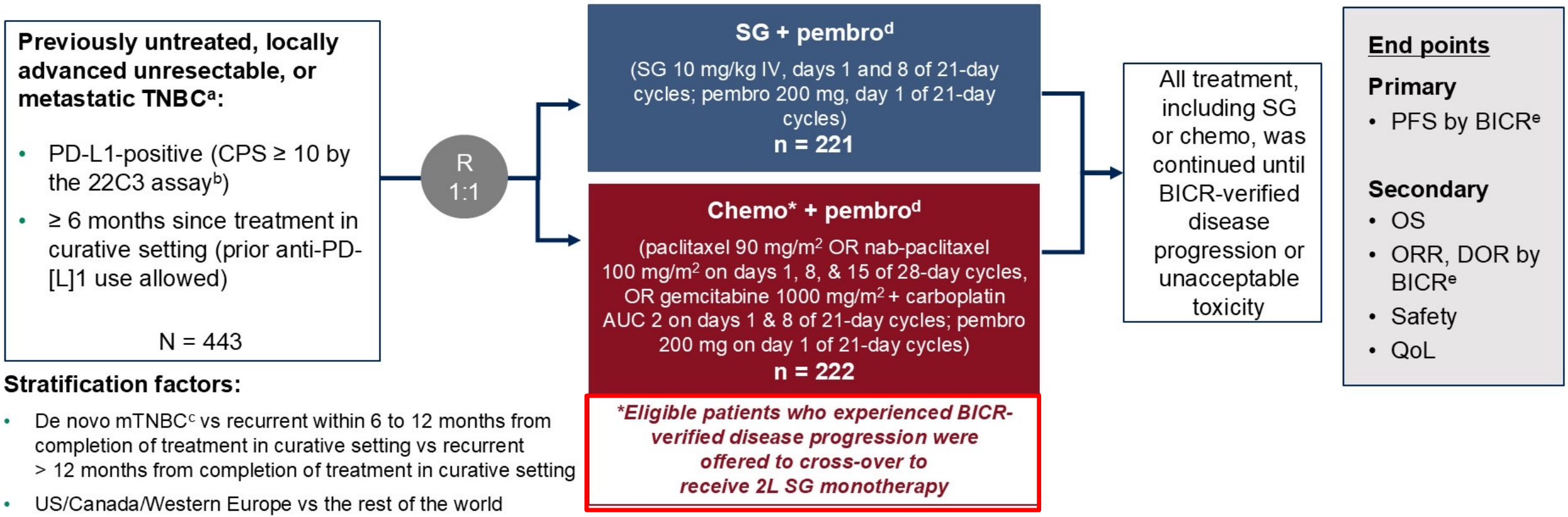
- Previously untreated metastatic or locally advanced inoperable TNBC (ER<1%, PR<1%, HER2neg)
- Measurable disease as defined by RECIST v1.1
- Adequate ECOG, hematologic and end-organ function
- PD-L1+ (CPS ≥ 10 IHC 22C3) by central testing
- No active brain metastases
- DFI≥ 6 mo since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed

Stratification factors:

- De novo, prior DFI 6 to ≤ 12 mo†, prior DFI >12 mo
- Geographic region (US/Canada/Europe vs Dato-DXd monotherapy arm enrolling countries vs ROW)
- Prior PD-1/PD-L1 treatment for early stage TNBC



ASCENT-04/KEYNOTE-D19 Study Design



Stratification factors:

- De novo mTNBC[c] vs recurrent within 6 to 12 months from completion of treatment in curative setting vs recurrent > 12 months from completion of treatment in curative setting
- US/Canada/Western Europe vs the rest of the world
- Prior exposure to anti-PD-(L)1 (yes vs no)

Tolaney et al. ASCO 2025

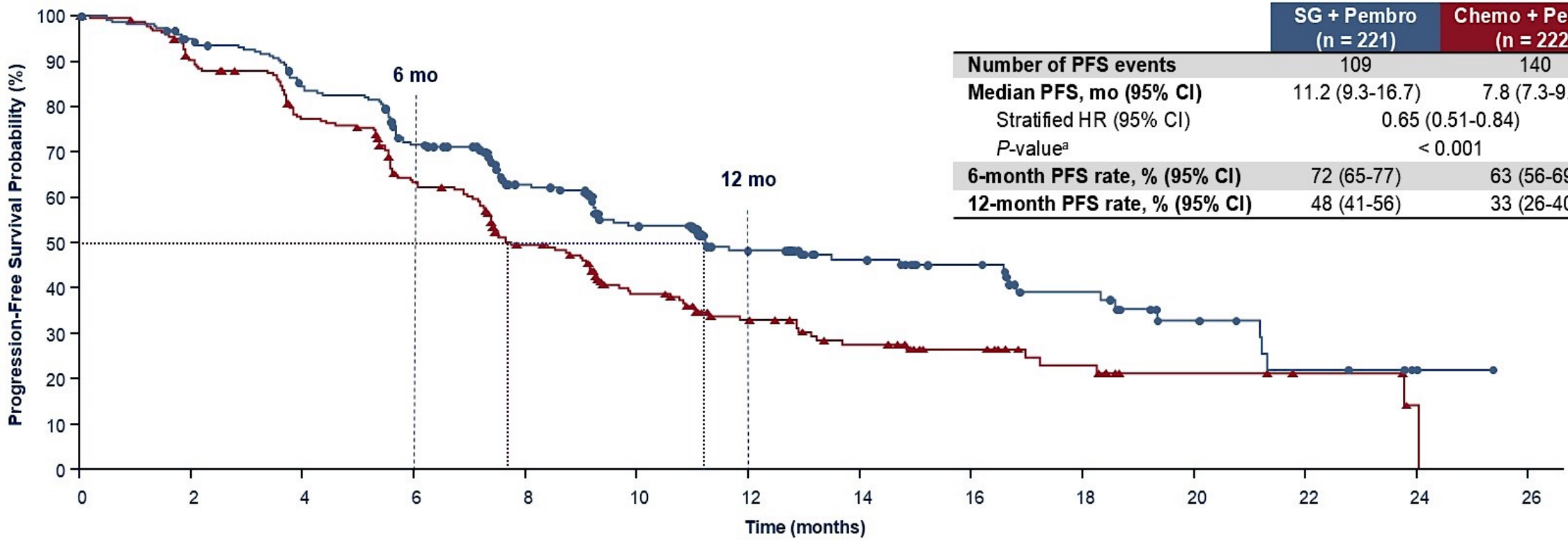
Demographics and Baseline Characteristics

ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Female sex, n (%)	221 (100)	222 (100)
Median age, (range) yr	54 (23-88)	55 (27-82)
≥ 65 yr, n (%)	58 (26)	57 (26)
Race or ethnic group,[a] n (%)		
White	139 (63)	118 (53)
Asian	43 (19)	63 (28)
Black	13 (6)	11 (5)
Other/not specified	26 (12)	30 (14)
Geographic region, n (%)		
US/Canada/Western Europe	85 (38)	85 (38)
Rest of the world[b]	136 (62)	137 (62)
ECOG PS at baseline,[c] n (%)		
0	156 (71)	154 (69)
1	65 (29)	67 (30)
Curative treatment-free interval, n (%)		
De novo	75 (34)	75 (34)
Recurrent within 6-12 mo	40 (18)	40 (18)
Recurrent > 12 mo	106 (48)	107 (48)

ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
PD-L1 CPS ≥ 10,[d] n (%)	221 (100)	222 (100)
Metastatic sites, n (%)		
Lymph node	159 (72)	154 (69)
Lung	111 (50)	95 (43)
Bone	61 (28)	45 (20)
Liver	55 (25)	57 (26)
Brain	8 (4)	6 (3)
Other[e]	81 (37)	71 (32)
Chemo selected prior to randomization,[f] n (%)		
Taxane	116 (52)	114 (51)
Gemcitabine/carboplatin	105 (48)	108 (49)
Prior anti-PD-(L)1 therapy,[g] n (%)	9 (4)	11 (5)

Tolaney et al. ASCO 2025

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)

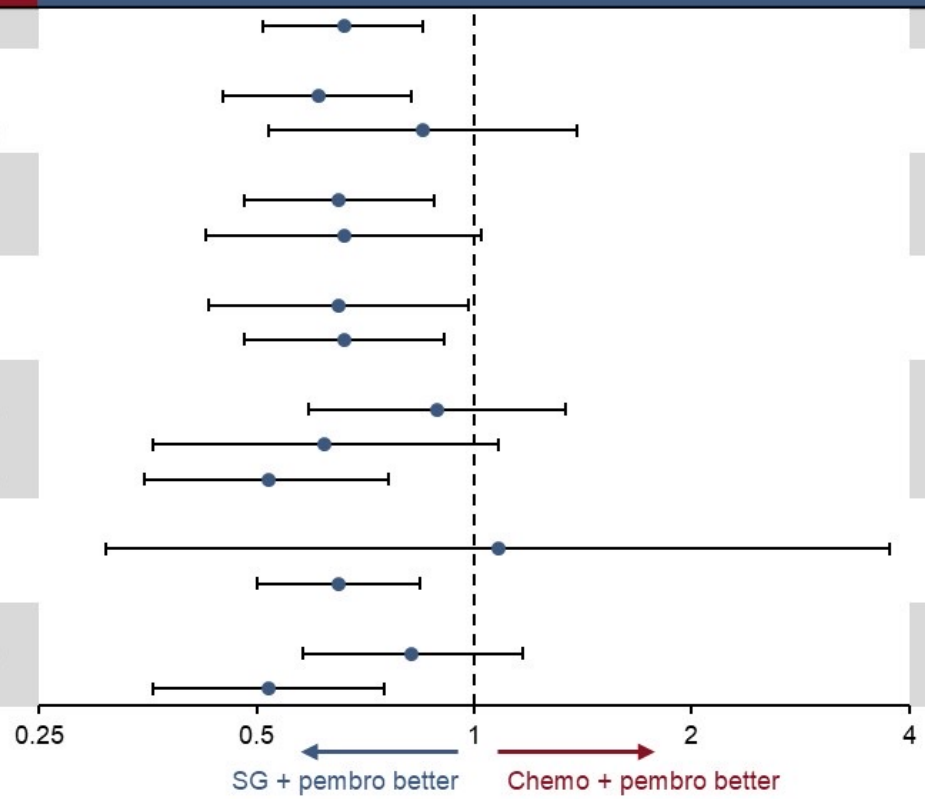
SG + Pembro	221 (0)	202 (11)	174 (33)	142 (59)	105 (75)	78 (89)	58 (96)	42 (98)	34 (99)	22 (103)	11 (106)	6 (109)	2 (109)	0 (109)
Chemo + Pembro	222 (0)	191 (21)	159 (48)	123 (76)	88 (102)	59 (120)	40 (128)	29 (134)	21 (135)	13 (137)	7 (138)	4 (138)	1 (139)	0 (140)

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

Tolaney et al. ASCO 2025

Subgroup Analysis of Progression-Free Survival by BICR

	SG + Pembro		Chemo + Pembro		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	n	Median PFS, mo (95% CI)	n	Median PFS, mo (95% CI)		
ITT population	221	**11.2** (9.3-16.7)	222	**7.8** (7.3-9.3)		0.66 (0.51-0.85)
Age group						
< 65 yr	163	**11.3** (9.3-16.8)	165	**7.5** (7.0-9.2)		0.61 (0.45-0.82)
≥ 65 yr	58	**11.1** (7.5-NR)	57	**9.3** (7.3-13.2)		0.85 (0.52-1.39)
ECOG PS						
0	156	**12.9** (9.3-16.8)	154	**8.7** (7.3-9.9)		0.65 (0.48-0.88)
≥ 1	65	**9.2** (7.5-18.3)	67	**7.5** (5.6-9.3)		0.66 (0.43-1.03)
Geographic region						
US/Canada/Western Europe	85	**11.7** (7.5-19.4)	85	**7.4** (5.7-9.9)		0.65 (0.43-0.98)
Rest of the world	136	**11.2** (9.3-16.7)	137	**8.4** (7.4-9.3)		0.66 (0.48-0.91)
Curative treatment-free interval						
De novo	75	**8.1** (7.3-18.6)	75	**7.7** (6.1-11.9)		0.89 (0.59-1.34)
Recurrent 6-12 mo	40	**9.9** (5.7-16.8)	40	**7.2** (4.4-9.1)		0.62 (0.36-1.08)
Recurrent > 12 mo	106	**16.6** (11.0-NR)	107	**8.7** (7.3-10.8)		0.52 (0.35-0.76)
Prior (neo)adjuvant anti-PD-(L)1 therapy						
Yes	9	**7.5** (0.9-NR)	11	**6.6** (2.1-NR)		1.08 (0.31-3.75)
No	212	**11.7** (9.3-16.8)	211	**7.8** (7.4-9.3)		0.65 (0.50-0.84)
Chemo selected prior to randomization						
Taxane	116	**11.1** (8.6-16.7)	114	**9.2** (7.2-12.9)		0.82 (0.58-1.17)
Gemcitabine/Carboplatin	105	**11.3** (9.2-21.2)	108	**7.4** (6.9-9.0)		0.52 (0.36-0.75)

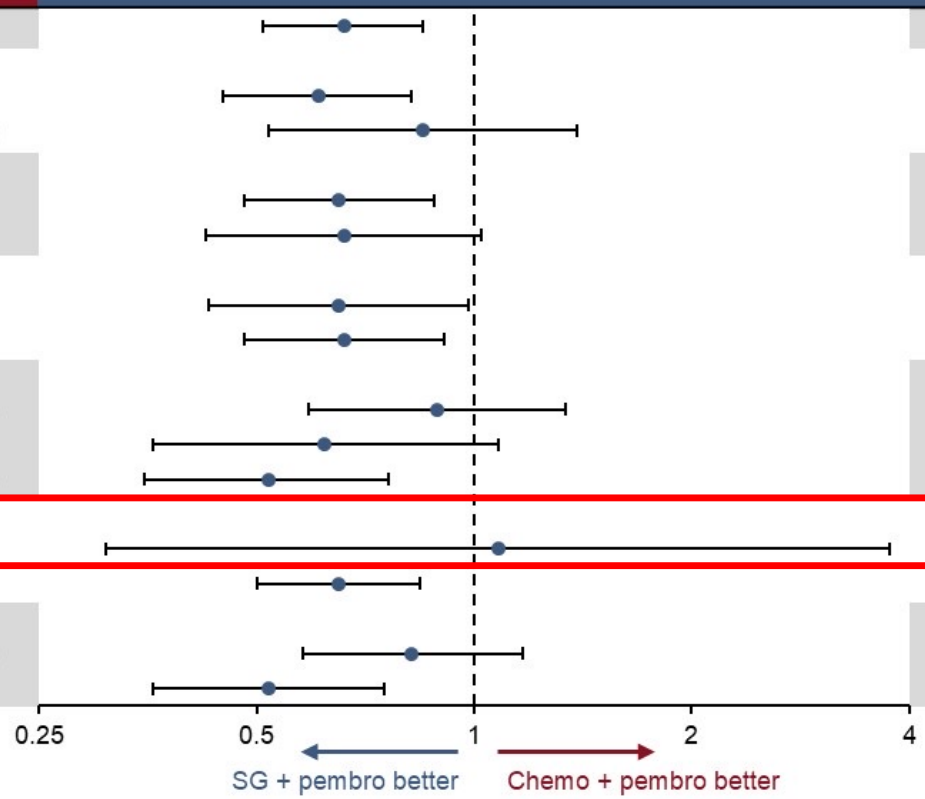


PFS benefit was observed for SG + pembro vs chemo + pembro across prespecified subgroups

Tolaney et al. ASCO 2025

Subgroup Analysis of Progression-Free Survival by BICR

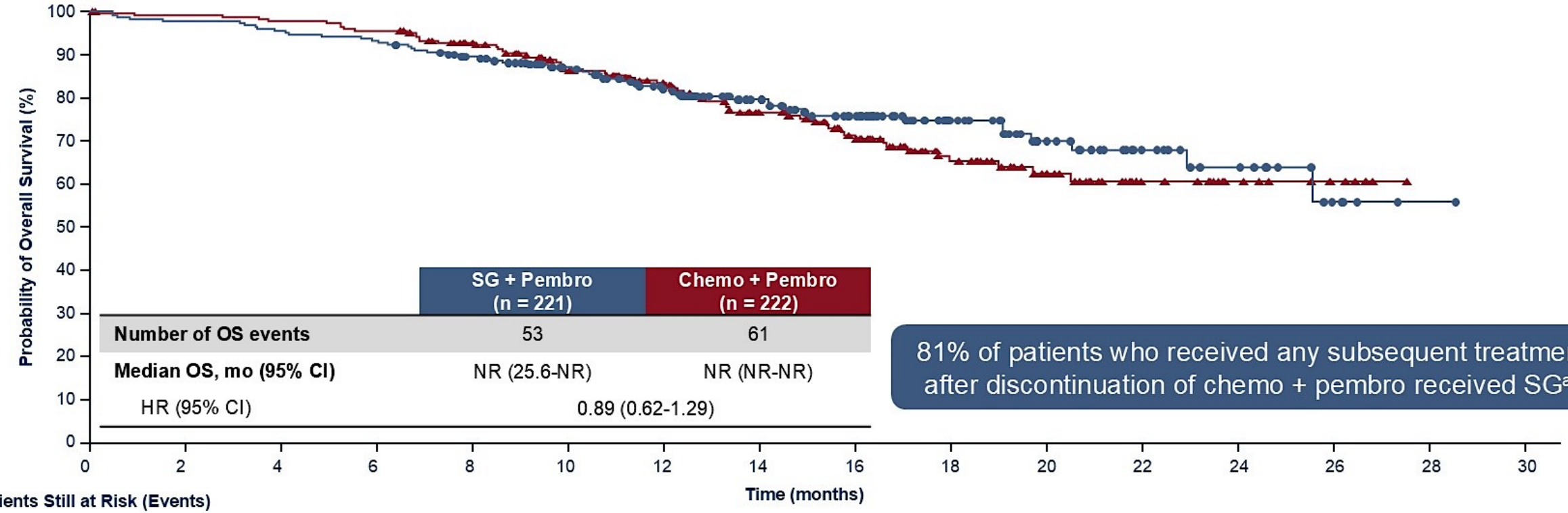
	SG + Pembro		Chemo + Pembro		Unstratified HR (95% CI)
	n	Median PFS, mo (95% CI)	n	Median PFS, mo (95% CI)	
ITT population	221	**11.2** (9.3-16.7)	222	**7.8** (7.3-9.3)	0.66 (0.51-0.85)
Age group					
< 65 yr	163	**11.3** (9.3-16.8)	165	**7.5** (7.0-9.2)	0.61 (0.45-0.82)
≥ 65 yr	58	**11.1** (7.5-NR)	57	**9.3** (7.3-13.2)	0.85 (0.52-1.39)
ECOG PS					
0	156	**12.9** (9.3-16.8)	154	**8.7** (7.3-9.9)	0.65 (0.48-0.88)
≥ 1	65	**9.2** (7.5-18.3)	67	**7.5** (5.6-9.3)	0.66 (0.43-1.03)
Geographic region					
US/Canada/Western Europe	85	**11.7** (7.5-19.4)	85	**7.4** (5.7-9.9)	0.65 (0.43-0.98)
Rest of the world	136	**11.2** (9.3-16.7)	137	**8.4** (7.4-9.3)	0.66 (0.48-0.91)
Curative treatment-free interval					
De novo	75	**8.1** (7.3-18.6)	75	**7.7** (6.1-11.9)	0.89 (0.59-1.34)
Recurrent 6-12 mo	40	**9.9** (5.7-16.8)	40	**7.2** (4.4-9.1)	0.62 (0.36-1.08)
Recurrent > 12 mo	106	**16.6** (11.0-NR)	107	**8.7** (7.3-10.8)	0.52 (0.35-0.76)
Prior (neo)adjuvant anti-PD-(L)1 therapy					
Yes	9	**7.5** (0.9-NR)	11	**6.6** (2.1-NR)	1.08 (0.31-3.75)
No	212	**11.7** (9.3-16.8)	211	**7.8** (7.4-9.3)	0.65 (0.50-0.84)
Chemo selected prior to randomization					
Taxane	116	**11.1** (8.6-16.7)	114	**9.2** (7.2-12.9)	0.82 (0.58-1.17)
Gemcitabine/Carboplatin	105	**11.3** (9.2-21.2)	108	**7.4** (6.9-9.0)	0.52 (0.36-0.75)



PFS benefit was observed for SG + pembro vs chemo + pembro across prespecified subgroups

Tolaney et al. ASCO 2025

Descriptive Overall Survival at Primary Analysis



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of OS events	53	61
Median OS, mo (95% CI)	NR (25.6-NR)	NR (NR-NR)
HR (95% CI)	0.89 (0.62-1.29)	

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

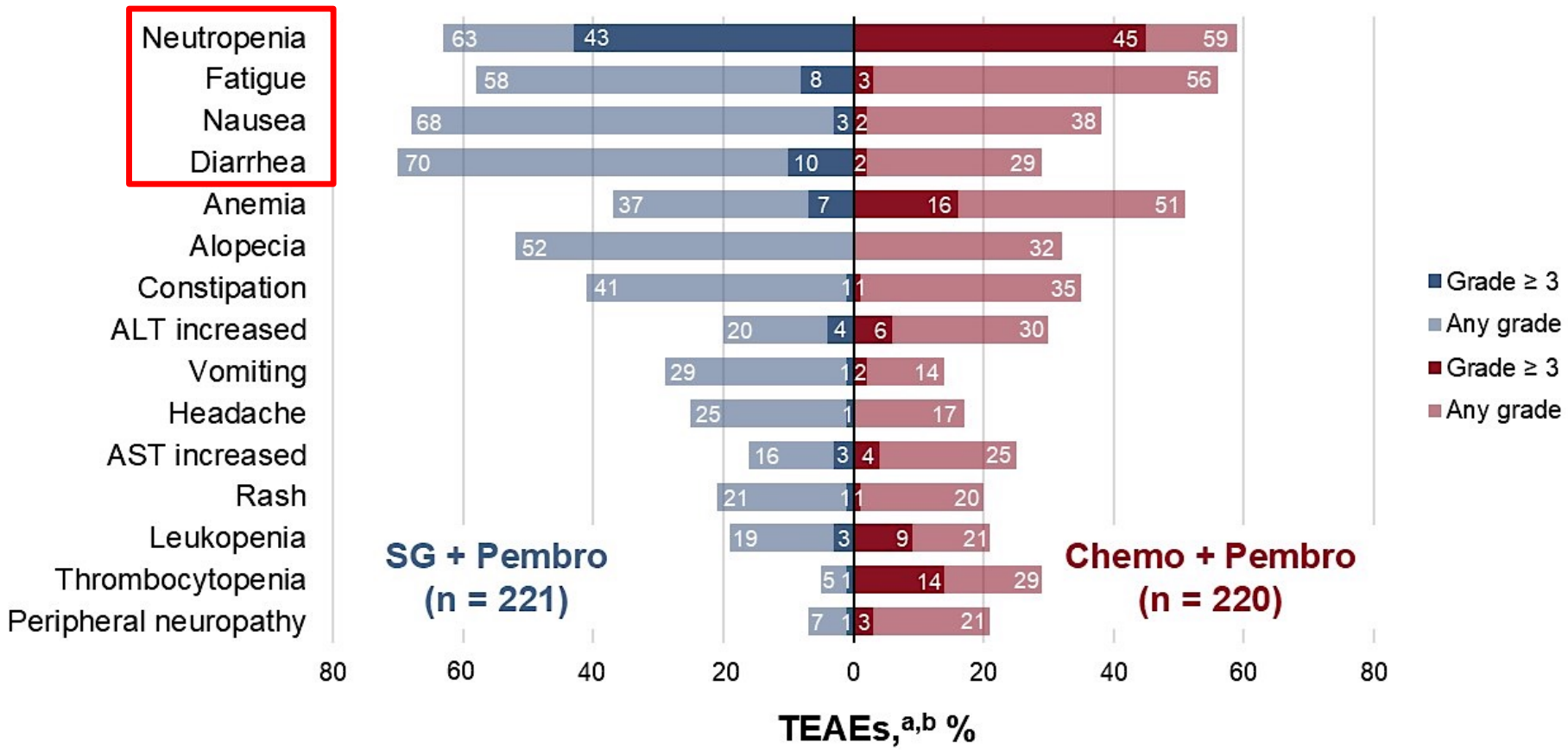
No. of Patients Still at Risk (Events)

SG + Pembro	221 (0)	216 (5)	211 (10)	206 (15)	190 (23)	162 (28)	138 (37)	111 (41)	88 (46)	55 (47)	36 (50)	21 (51)	14 (52)	5 (53)	1 (53)	0 (53)
Chemo + Pembro	222 (0)	218 (2)	215 (5)	210 (10)	193 (16)	166 (29)	142 (34)	111 (45)	87 (53)	56 (58)	38 (60)	19 (61)	11 (61)	6 (61)	0 (61)	

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

Tolaney et al. ASCO 2025

Most Common Adverse Events (≥20% in any group)



The AEs observed are consistent with the known profiles of both SG and pembro

Tolaney et al. ASCO 2025

Adverse Events of Special Interest

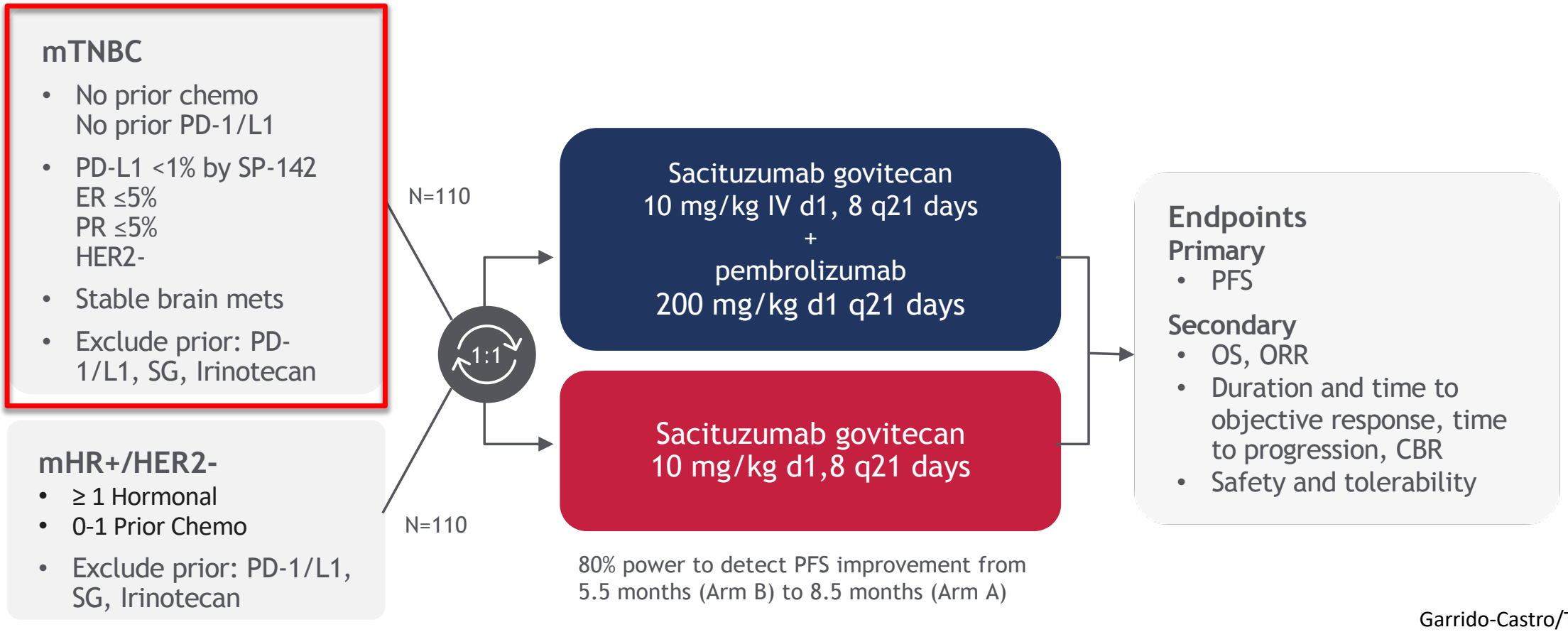
	AESI,[a] n (%)	SG + Pembro (n = 221)		Chemo + Pembro (n = 220)	
		Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
SG AESIs	Neutropenia[b]	143 (65)	104 (47)	132 (60)	100 (45)
	Hypersensitivity[b]	43 (19)	4 (2)	51 (23)	5 (2)
	Serious infections secondary to neutropenia[b]	6 (3)	5 (2)	3 (1)	3 (1)
	Diarrhea (Grade 3 or higher)	N/A	22 (10)	N/A	5 (2)
Pembro AESIs	Overall	30 (14)	9 (4)	56 (26)	16 (7)
	Infusion reactions (not immune-mediated)[a]	11 (5)	3 (1)	19 (9)	5 (2)
	Pneumonitis[b]	5 (2)	3 (1)	10 (5)	2 (1)
	Colitis[b]	4 (2)	1 (< 1)	1 (< 1)	1 (< 1)
	Hypothyroidism[b]	4 (2)	0	19 (9)	0
	Hypophysitis[b]	2 (1)	0	2 (1)	0
	Hyperthyroidism[b]	2 (1)	0	5 (2)	0
	Severe skin reactions,[b] including Stevens-Johnson syndrome and toxic epidermal necrolysis	2 (1)	2 (1)	2 (1)	2 (1)
	Hepatitis[b]	1 (< 1)	0	2 (1)	2 (1)
	Adrenal insufficiency[b]	1 (< 1)	0	2 (1)	1 (< 1)
	Pancreatitis[b]	0	0	2 (1)	2 (1)

AESIs were consistent with the known safety profiles of each agent; no new safety concerns were observed and no increased rates of AESIs were observed when combining SG with pembro

Tolaney et al. ASCO 2025

Sacituzumab: Ongoing Trials for Late Stage

SACI-IO TNBC and HR+: Sacituzumab govitecan +/– pembrolizumab in 1L PD-L1– mTNBC and HR+



80% power to detect PFS improvement from 5.5 months (Arm B) to 8.5 months (Arm A)

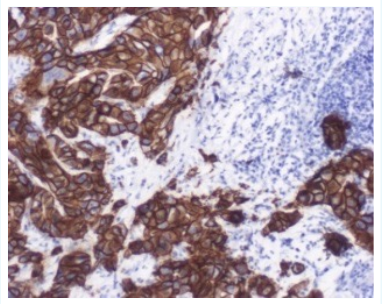
Garrido-Castro/Tolaney

NCT04468061

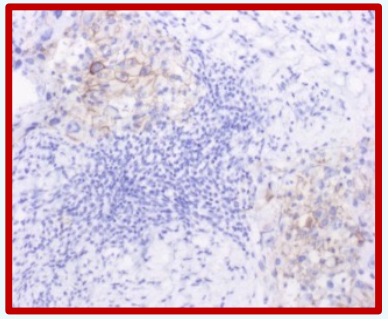
Prevalence of HER2-low by HR status

HER2 IHC Examples

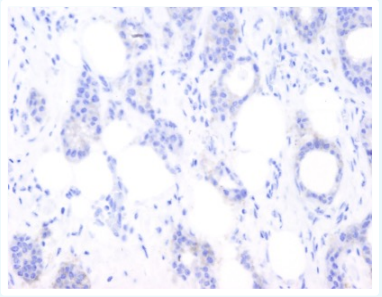
HER2+



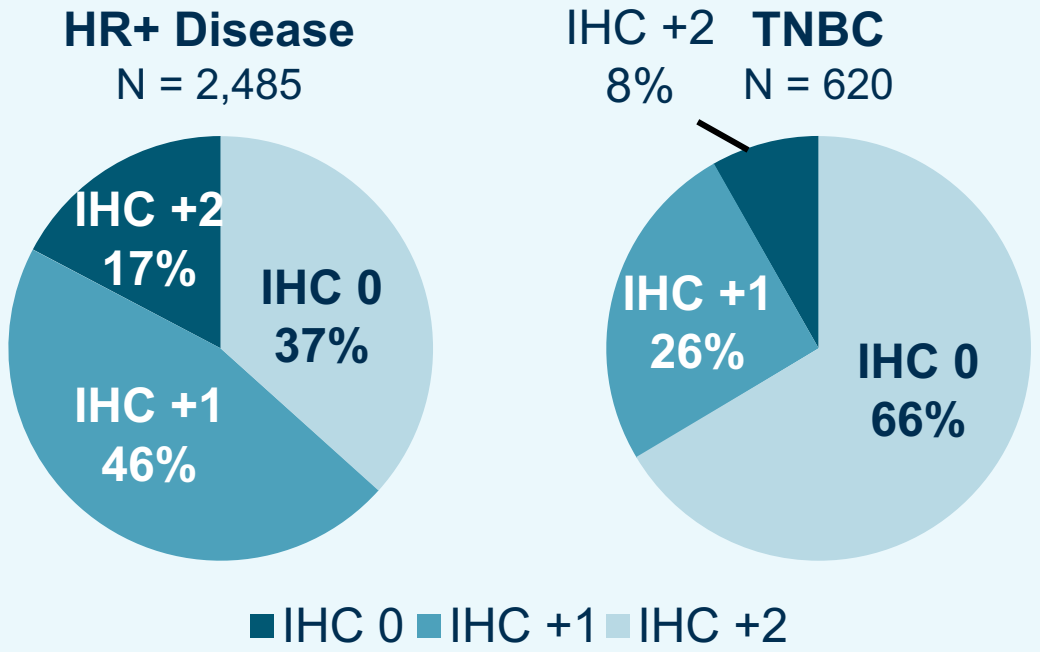
HER2-low



HER2-



HER2-negative

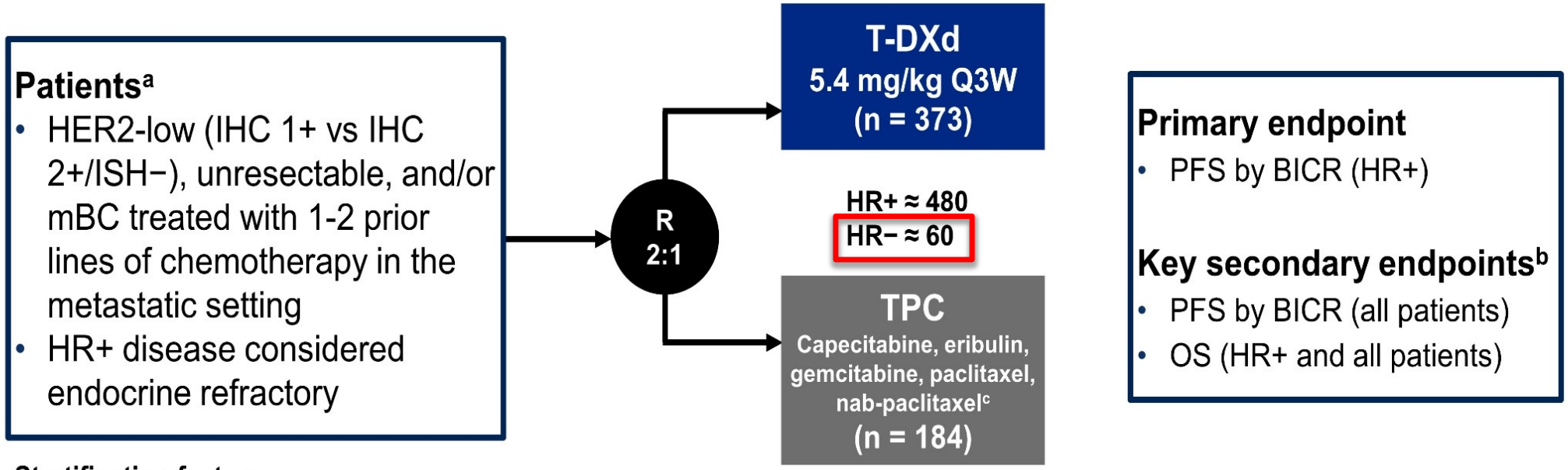


34% to **63%** of breast cancer patients considered HER2-negative under current guidelines express low levels of HER2

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

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

An open-label, multicenter study (NCT03734029)



Stratification factors

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

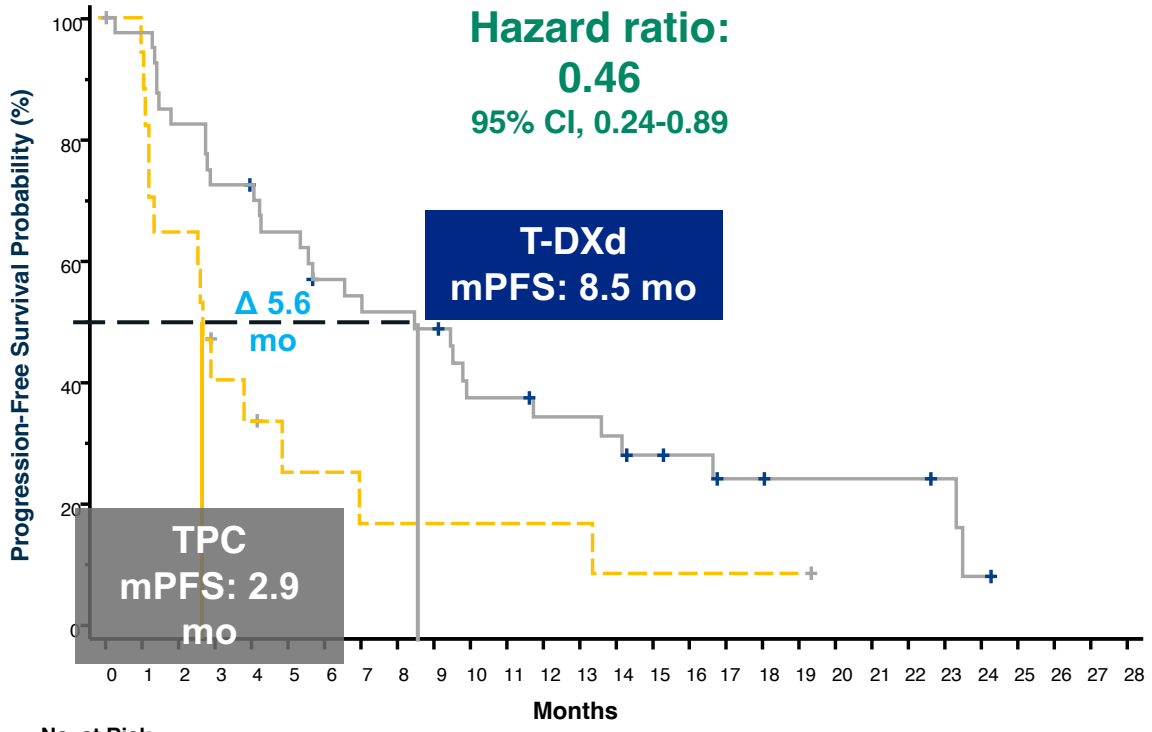
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization;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

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

Modi S, et al. *N Engl J Med*. 2022 Jul 7;387(1):9-20.

PFS and OS in HR− (Exploratory Endpoints)

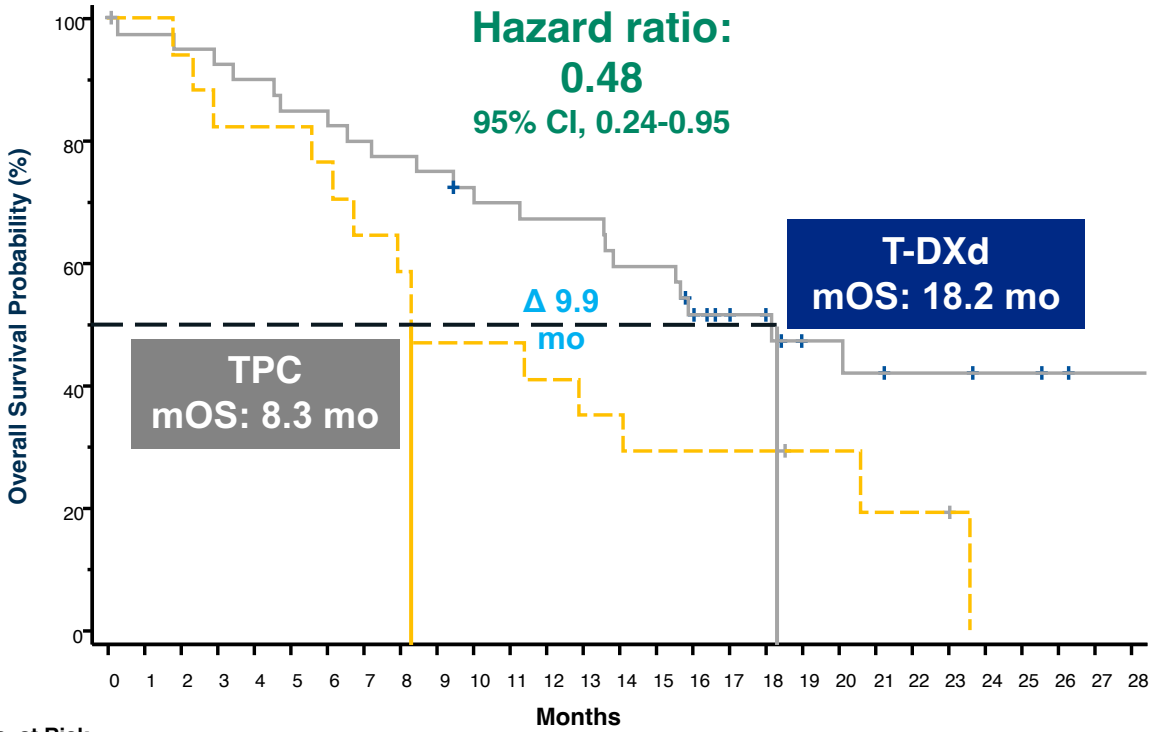
PFS



No. at Risk

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

OS



No. at Risk

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

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

Modi et al. ASCO 2022

HER2 Ultralow?: DESTINY-Breast15

Patient Population

All Patients:

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

HR+ (Early Progressors) = Cohort 3

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

HR–

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

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

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

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

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

Primary Endpoint: TTNT

Key Secondary: rwPFS

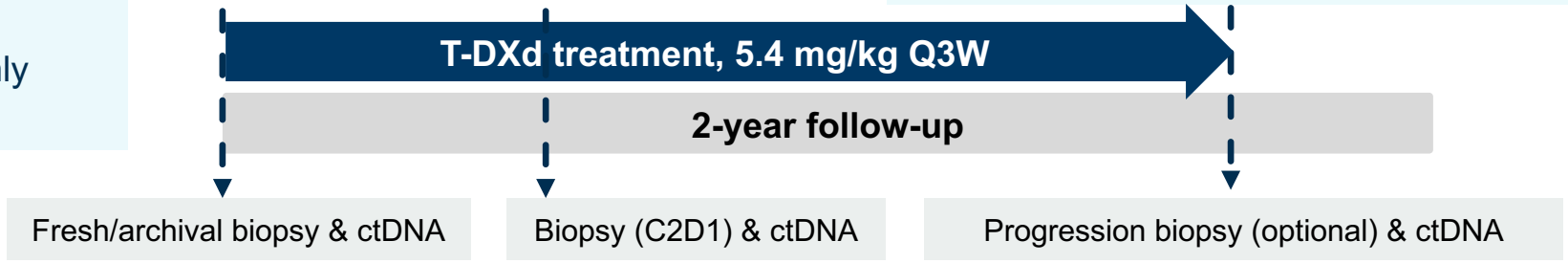
Secondary Endpoints:

- TTD
- QoL/PROs
- Tolerability
- ORR

Exploratory Endpoints: pathology/ translational research plan

Descriptive stats of primary endpoint for FAS in subgroups:

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



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

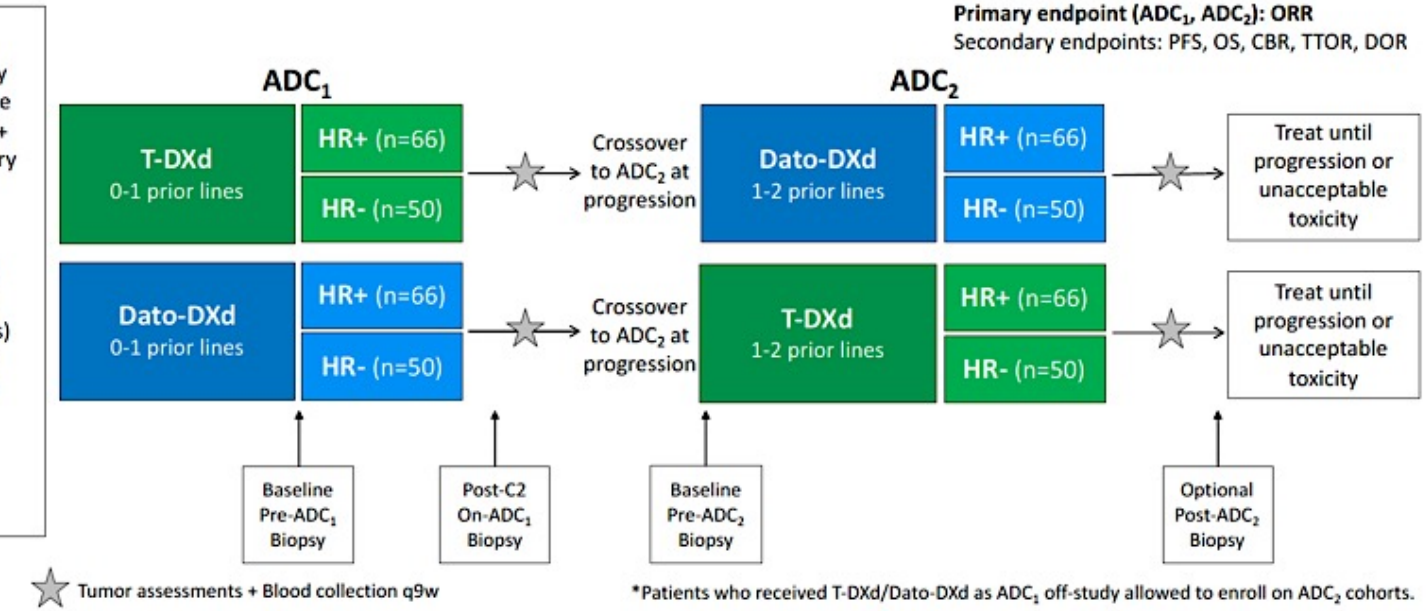
(NCT05950945)

TBCRC 064: Treatment of ADC-Refractory Breast Cancer with Dato-DXd or T-DXd (TRADE DXd). PI: Ana Garrido-Castro

Eligibility:

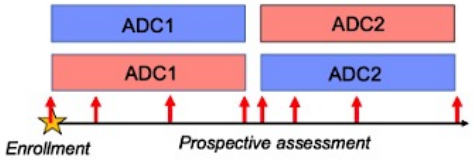
- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low BC: IHC 1+ or 2+/ISH- (any sample: primary or met)
- Measurable disease
- Prior endocrine therapy and CDK4/6 inhibitor for HR+ MBC
- Prior topo-I inhibitor allowed only in neo-/adjuvant setting(s) and if ≥12m elapsed since last dose to metastatic recurrence

*Randomization 1:1 to T-DXd or Dato-DXd as ADC_1 for allocation purposes.

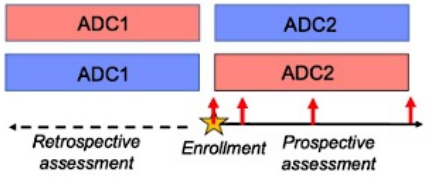


TBCRC-067 ENCORE: Multicenter Prospective Registry of Sequential ADCs in HER2- mBC PI: Laura Huppert

Cohorts 1 & 2: Enrollment Prior to ADC1



Cohorts 3 & 4: Enrollment Prior to ADC2



↑= Study Blood Draw (20ml)

- **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

Primary Endpoints:

- Real-world progression free survival of ADC1 (rwPFS1)
- Real-world progression free survival of ADC2 (rwPFS2)

Secondary Endpoints (for each ADC):

- Overall response rate (ORR), duration of response (DOR), best overall response (BOR), disease control rate (DCR)
- Real-world overall survival (rwOS)
- Safety

Exploratory Endpoints:

- Translational correlates of ADC response/resistance (see below)

A Randomized, Open-label, Phase 3 Study of Adjuvant Sacituzumab Govitecan + Pembrolizumab Versus Treatment of Physician's Choice in Patients With TNBC Who Have Residual Disease After Neoadjuvant Therapy and Surgery (ASCENT-05 / OptimICE-RD)

ascent-05

Study Design[1,2]

Trial registration number: NCT05633654

Residual invasive TNBC in breast or positive node(s) after neoadjuvant therapy and surgery

- History of cT1, cN1–2 or cT2–4, cN0–2 disease
- Received at least 6 cycles of neoadjuvant anthracycline- and/or taxane-based chemotherapy with or without an anti–PD-(L)1 agent
- TNBC diagnosis: ER and PR <10%, HER2-negative per ASCO/CAP
- Known gBRCA mutants excluded

N=1514

1:1 randomization

Sacituzumab Govitecan + Pembrolizumab x 8 cycles
SG: 10 mg/kg IV on d 1 and 8 of 21-d cycles
Pembro: 200 mg IV on d 1 of 21-d cycles

Treatment of Physician's Choice x 8 cycles

Pembro: 200 mg IV on d 1 of 21-d cycles
or
Pembro + capecitabine: pembro 200 mg IV on d 1 plus capecitabine 1000 mg/m² PO BID on d 1–14 of 21-d cycles

Long-term follow up

Primary
- iDFS

Secondary
- OS
- dDFS
- Safety
- QoL

Exploratory Biomarkers

Stratification Factors:
- Prior anti–PD-(L)1 therapy (yes vs no)
- Prior anthracycline-based therapy (yes vs no)
- Pathologic nodal status at the time of surgery (ypN0 vs ypN+)
- Geographic region (US vs East Asia vs RoW)

PI: Sara Tolaney

Study Diagram

A Phase 3, Randomized, Open-label, Study to Compare the Efficacy and Safety of Adjuvant MK-2870 in Combination with Pembrolizumab (MK-3475) Versus Treatment of Physician's Choice in Participants With Triple Negative Breast Cancer (TNBC) Who Received Neoadjuvant Therapy and Did Not Achieve a Pathological Complete Response (pCR) At Surgery

- **Centrally confirmed TNBC (ER<1%, PR<1%, HER2-)**
- **Non-pCR after at least 5 cycles of pembrolizumab and chemotherapy, including 1 cycle of anthracycline-based neoadjuvant therapy**
- **Randomization within 12 weeks of definitive surgery**
- **Adjuvant RT if indicated, completed before randomization**

Arm 1

Pembrolizumab 400 mg q6w x 5 doses
+
sac-TMT 4 mg/kg q2w x 12 doses

Arm 2

Treatment of Physician's Choice (TPC)
Pembrolizumab 400 mg q6w x 5 doses
or
Pembrolizumab 400 mg q6w x 5 doses and capecitabine 1000 mg/m2 to 1250 mg/m2 BID on Days 1-14 and Days 22-35 every 42 days x 4 (2 weeks on, 1 week off)

Stratification factors

1. Residual tumor and lymph node status:
   a. [Tumor < 1 cm (ypT1mi – T1b), ypN0] (capped at ~15%)
   vs
   b. [Tumor ≥ 1 cm (ypT1c+), ypN0] or [No tumor or tumor < 1 cm (ypT0 – T1b), ypN1]
   vs
   c. [Tumor ≥1 cm (ypT1c+), ypN1] or [No tumor or any tumor size (ypT0+), ypN2+]
2. TROP2 expression per IHC (low vs medium vs high).
3. Intention to use capecitabine (yes [capped at ~60%] vs no)

PI: Heather McArthur
NCT06393374

TROPION-Breast03
Study of Dato-DXd With or Without Durvalumab Versus ICT Without Pathological CR Following Neoadjuvant Therapy[1,2]

A Phase 3, Open-Label, Randomized Study of Dato-DXd With or Without Durvalumab Versus ICT in Patients With Stage I-III TNBC Who Have Residual Invasive Disease in the Breast and/or Axillary Lymph Nodes at Surgical Resection Following Neoadjuvant Systemic Therapy

Study Design

Patients with Stage I-III TNBC without pathological CR (N≈1075)

- Histologically confirmed invasive TNBC (ER <1%, PR <1%, HER2 negative)3,4,a
- Completed at least 6 cycles of neoadjuvant therapy containing an anthracycline and/or a taxane with or without carboplatin, with or without pembrolizumab
- Residual invasive disease after neoadjuvant therapy
- No evidence of locoregional or distant relapse
- Radiotherapy delivered before the start of study treatment
- No adjuvant systemic therapy
- ECOG PS 0–1
- Adequate bone marrow reserve and organ function
- No known germline BRCA1 or BRCA2 mutation

Randomization (2:1:2)[2]

- **Dato-DXd** 6 mg/kg IV Q3W × 8 cycles + **Durvalumab** 1120 mg IV Q3W × 9 cycles
- **Dato-DXd** 6 mg/kg IV Q3W × 8 cycles
- **Investigator's Choice of Therapy**[c] (capecitabine, pembrolizumab, or capecitabine + pembrolizumab)

Stratification Factors[2]:

- Prior neoadjuvant pembrolizumab (yes vs no); cap no at 40%
- Residual disease (<1 cm vs ≥1 cm)[d]; cap <1 cm at 20%
- Prior neoadjuvant platinum CT (yes vs no)

Primary Endpoint

- **Dato-DXd + durvalumab vs ICT:** iDFS

Secondary Endpoints

- **Dato-DXd + durvalumab vs ICT:** DDFS, OS
- **Dato-DXd vs ICT:** iDFS, DDFS, OS
- **Dato-DXd + durvalumab vs Dato-DXd:** iDFS, DDFS
- PROs, PK, immunogenicity, safety

Locations: North America, South America, Asia, Europe
ClinicalTrials.gov Identifier: NCT05629585

PI: Aditya Bardia

If ADCs are more effective in the NEOADJUVANT setting will the post K522 question be relevant?

TB04 Study Design: Ph3 Dato-DXd + Durva in Neoadjuvant/Adjuvant TNBC

TROPION-Breast04

Key Eligibility Criteria

- Histologically confirmed Stage II or III unilateral or bilateral primary invasive breast cancer.
- TNBC (ER and PR < 1%) or hormone receptor-low breast cancer (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%), and HER2-negative.
- No evidence of distant disease.
- No prior surgery, radiation, or systemic anticancer therapy.
- ECOG PS 0 or 1.
- Adequate hematologic and organ function.

1:1

Experimental Arm

Dato-DXd + durvalumab
Q3W x 8 (24 weeks)

→ Durvalumab x 9 cycles +/- chemotherapy [a, b, c]

Control Arm

Pembrolizumab + carboplatin + paclitaxel
Q3W x 4 (12 weeks)

→ Pembrolizumab + doxorubicin or epirubicin + cyclophosphamide
Q3W x 4 (12 weeks)

→ Pembrolizumab x 9 cycles +/- chemotherapy [a, c, d]

Dual primary endpoints:
pCR and EFS

Secondary endpoints:
OS, DDFS, safety and tolerability, PROs, PK, immunogenicity

Exploratory endpoints include but are not limited to:
TROP2, PD-L1

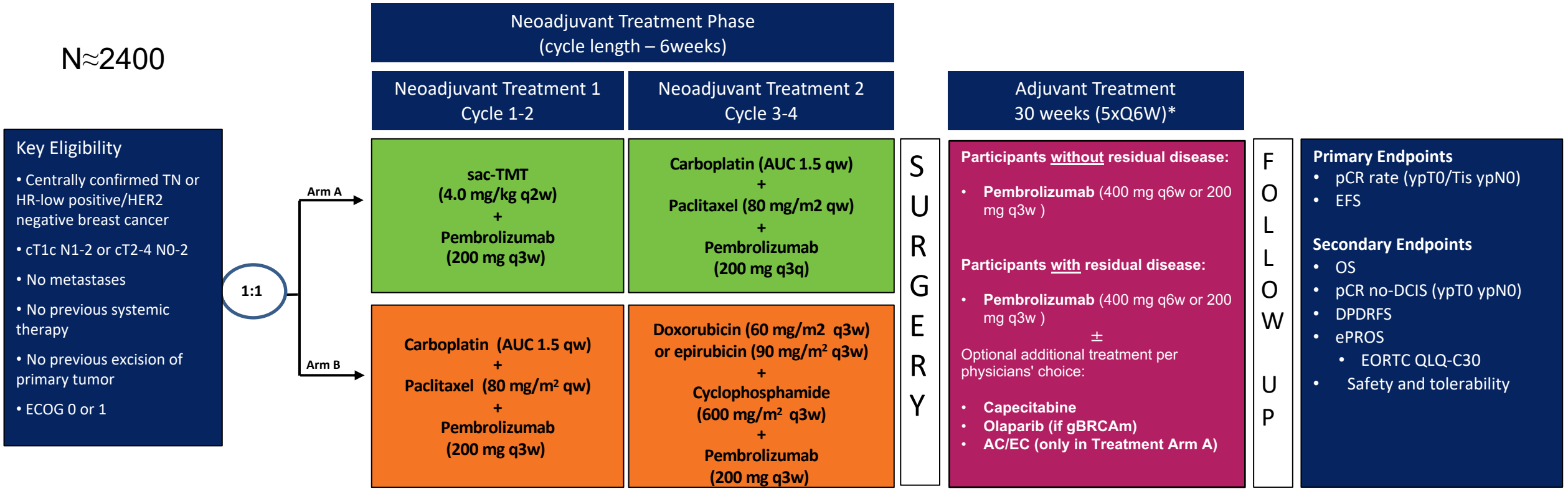
Stratification factors:

- Lymph node status (positive versus negative)
- Tumour stage (cT1 to cT2 versus cT3 to cT4
- Hormone receptor status (hormone receptor-negative [ER and PR < 1%] versus hormone receptor-low (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%])
- Geographic region (US/Canada/Europe/Australia versus Rest of World).

a. Endocrine therapy is permitted for participants with hormone receptor-low tumours. No adjuvant CDK4/6 inhibitor (eg, abemaciclib, ribociclib).
b. Adjuvant chemotherapy may be given in combination with durvalumab for participants with residual disease. Chemotherapy options at discretion of investigator, either: doxorubicin/epirubicin + cyclophosphamide, followed by paclitaxel + carboplatin; doxorubicin/epirubicin + cyclophosphamide followed by paclitaxel; carboplatin + paclitaxel; capecitabine.
c. Olaparib may be administered to participants who are g*BRCA*-positive with residual disease.
d. Adjuvant capecitabine may be given in combination with pembrolizumab for participants with residual disease, at the discretion of investigator.

PI: Heather McArthur
NCT06112379

TroFuse-032 Study Design



Adjuvant radiotherapy is permitted after surgery concurrently with pembrolizumab.
XRT must be completed before optional additional TPC (if used).

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Primary Results from ASCENT-03: A Randomized Phase 3 Study of Sacituzumab Govitecan (SG) vs Chemotherapy (Chemo) in Patients (pts) with Previously Untreated Advanced Triple-Negative Breast Cancer (TNBC) Who Are Unable to Receive PD-(L)1 Inhibitors (PD-[L]1i)

Cortés JC et al.

ESMO 2025;Abstract LBA20.

PROFFERED PAPER | SUNDAY, OCTOBER 19 | 9:15 CEST

First-Line (1L) Datopotamab Deruxtecan (Dato-DXd) vs Chemotherapy in Patients with Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer (mTNBC) for Whom Immunotherapy Was Not an Option: Primary Results from the Randomised, Phase 3 TROPION-Breast02 Trial

Dent RA et al.

ESMO 2025;Abstract LBA21.

PROFFERED PAPER | SUNDAY, OCTOBER 19 | 9:25 CEST

Questions from General Medical Oncologists

- **Is sacituzumab in combination with pembrolizumab the new standard of care first-line treatment for PD-L1-positive mTNBC?**
- **If a patient received pembrolizumab in the early TNBC setting, would you use it in combination with sacituzumab if they progress?**
- **Is a TROP2-directed ADC now standard of care first-line treatment for patients with mTNBC not eligible for I/O? How will you select between sacituzumab and Dato-DXd for these patients?**

Questions from General Medical Oncologists

- **How do you manage the toxicities (diarrhea, neutropenia) associated with sacituzumab/pembrolizumab? Do you generally use prophylactic growth factors?**

Questions from General Medical Oncologists

- **To which patients with localized TNBC and a BRCA mutation do you give olaparib and pembrolizumab?**

Questions from General Medical Oncologists

- **What's your approach to prevention and management of anemia associated with olaparib? How about GI side effects? Is there an update on the incidence of AML/MDS with PARPi?**

Questions from General Medical Oncologists

- **Are there any data on using PARP inhibitors in combination with any of the available antibody-drug conjugates?**
- **Is there evidence of intracranial efficacy with either sacituzumab or Dato-DXd in patients with brain metastases?**

Questions from General Medical Oncologists

- **Case: 60F treated with KN-522 for Stage IIIC TNBC with pCR. Approximately 1 year into follow-up she developed neuro symptoms and underwent surgical debulking and XRT for a 3-cm brain lesion. No other evidence of disease. HER2 1+ — what would you recommend as systemic management?**

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