Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Clinical Care of Patients with Metastatic Breast Cancer

Monday, June 2, 2025
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Harold J Burstein, MD, PhD
Javier Cortés, MD, PhD
Rebecca A Dent, MD, MSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

Moderator

Hope S Rugo, MD

RTP RESEARCH TO PRACTICE

Faculty

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

Javier Cortés, MD, PhD
Head, IBCC International Breast Cancer Center
Barcelona, Spain

Rebecca A Dent, MD, MSc
Senior Consultant
National Cancer Centre Singapore
Singapore

Kevin Kalinsky, MD, MS
Professor of Medicine
Director, Division of Medical Oncology
Director, Glenn Family Breast Center
Winship Cancer Institute at Emory University
Atlanta, Georgia

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

Moderator
Hope S Rugo, MD
Director, Women's Cancers Program
Division Chief, Breast Medical Oncology
Professor, Department of Medical Oncology
and Therapeutics Research
City of Hope Comprehensive Cancer Center
Duarte, California
Professor Emeritus, UCSF

RTP
RESEARCH
TO PRACTICE

Contributing Faculty

Sara A Hurvitz, MD, FACP
Professor
Senior Vice President
Clinical Research Division
Fred Hutchinson Cancer Center
Head, Division of Hematology/Oncology
UW Medicine
Seattle, Washington

Komal Jhaveri, MD, FACP
Patricia and James Cayne Chair for Junior Faculty
Associate Attending Physician
Breast Medicine Service and Early Drug Development Service
Section Head, Endocrine Therapy Research Program
Clinical Director, Early Drug Development Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
Associate Professor of Medicine
Weill Cornell College of Medicine
New York, New York

Dr Burstein — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Dr Cortés — Disclosures
Faculty

Consulting and Advisor	AbbVie Inc, AstraZeneca Pharmaceuticals LP, AvenCell Europe GmbH, Bioasis Technologies Inc, Biocon, BioInvent, BioNTech SE, Bliss Biopharmaceutical (Hangzhou) Co Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Circle Pharma, Daiichi Sankyo Inc, Delcath Systems Inc, Ellipses Pharma, ExpreS2ion Biotechnologies, Gilead Sciences Inc, Hexagon Bio, HiberCell, Jazz Pharmaceuticals Inc, Leuko Labs Inc, Lilly, Menarini Group, MSD, pharmaand GmbH, QED Therapeutics, Reveal Genomics, Roche Laboratories Inc, Seagen Inc, Zymeworks Inc
Contracted Research Funding to Institution	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Eisai Inc, F Hoffmann-La Roche Ltd, Guardant Health, IQVIA, MSD, Pfizer Inc, PIQUR Therapeutics, Queen Mary University of London, Roche Laboratories Inc, Servier Affaires Medicales, Takeda Pharmaceuticals USA Inc
Honoraria	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Eisai Inc, Gilead Sciences Inc, Lilly, MSD, Novartis, Pfizer Inc, Roche Laboratories Inc, Stemline Therapeutics Inc, Zuellig Pharma
Patents	WO 2014/199294 A, US 2019/0338368 A1
Stock Options/Stock — Public Companies	Leuko Labs Inc
Travel, Accommodation, Expenses	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Eisai Inc, Gilead Sciences Inc, MSD, Novartis, Pfizer Inc, Roche Laboratories Inc, Stemline Therapeutics Inc
Nonrelevant Financial Relationships	MAJ3 Capital

Prof Dent — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Dr Kalinsky — Disclosures
Faculty

Advisory Committees	AstraZeneca Pharmaceuticals LP, Biotheranostics Inc, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Menarini Silicon Biosystems, Merck, Mersana Therapeutics Inc, Myovant Sciences, Novartis, Pfizer Inc, ProteinQure, Puma Biotechnology Inc, Regor Therapeutics, Relay Therapeutics, Seagen Inc

RTP RESEARCH TO PRACTICE

Dr O'Shaughnessy — Disclosures
Faculty

Advisory Committees and Consulting Agreements	Aadi Bioscience, Agendia Inc, Amgen Inc, Aptitude Health, AstraZeneca Pharmaceuticals LP, BioNTech SE, Bristol Myers Squibb, Daiichi Sankyo Inc, Duality Biologics, Eisai Inc, Ellipses Pharma, Exact Sciences Corporation, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Guardant Health, HiberCell, Jazz Pharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Pfizer Inc, Pierre Fabre, Puma Biotechnology Inc, RayzeBio Inc, Roche Laboratories Inc, Sanofi, Seagen Inc, Stemline Therapeutics Inc, Summit Therapeutics, Tempus, TerSera Therapeutics LLC

RTP
RESEARCH
TO PRACTICE

Dr Rugo — Disclosures
Moderator

Advisory Committees	Bristol Myers Squibb, Chugai Pharmaceutical Co Ltd, Napo Pharmaceuticals Inc, Sanofi, Viatris
Contracted Research (Institutional Research Support)	Ambrx, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Merck, Novartis, OBI Pharma Inc, Pfizer Inc, Stemline Therapeutics Inc

Dr Hurvitz — Disclosures
Survey Participant

Contracted Research	Ambrx, Amgen Inc, Arvinas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Celcuity, CytomX Therapeutics, Daiichi Sankyo Inc, Dantari, Dignitana AB, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Greenwich LifeSciences Inc, GSK, Lilly, MacroGenics Inc, Novartis, OBI Pharma Inc, Orinove Inc, Orum Therapeutics, Pfizer Inc, Phoenix Molecular Designs, Pieris Pharmaceuticals Inc, Puma Biotechnology Inc, Radius Health Inc, Samumed, Sanofi, Seagen Inc, Stemline Therapeutics Inc, Zymeworks Inc

RTP
RESEARCH
TO PRACTICE

Dr Jhaveri — Disclosures
Survey Participant

Consultant/Advisory Board Roles	AstraZeneca Pharmaceuticals LP, Bicycle Therapeutics, Blueprint Medicines, Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Menarini Group, Novartis, Olema Oncology, Pfizer Inc, RayzeBio Inc, Scorpion Therapeutics, Stemline Therapeutics Inc, Zymeworks Inc
Research Funding (Support to Institution)	AstraZeneca Pharmaceuticals LP, Blueprint Medicines, Eisai Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Pfizer Inc, Puma Biotechnology Inc, RayzeBio Inc, Scorpion Therapeutics, Zymeworks Inc
Travel and Accommodations	AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Pfizer Inc

RTP
RESEARCH TO PRACTICE

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: Aadi Bioscience, AbbVie Inc, ADC Therapeutics, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Black Diamond Therapeutics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Clovis Oncology, Coherus BioSciences, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, Exact Sciences Corporation, Exelixis Inc, Genentech, a member of the Roche Group, Genmab US Inc, Geron Corporation, Gilead Sciences Inc, GSK, Hologic Inc, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Jazz Pharmaceuticals Inc, Johnson & Johnson, Karyopharm Therapeutics, Kite, A Gilead Company, Kura Oncology, Legend Biotech, Lilly, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Nuvalent, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Rigel Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, and Tesaro, A GSK Company.

RTP
RESEARCH
TO PRACTICE

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Puma Biotechnology Inc, and Stemline Therapeutics Inc.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

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.

RTP
RESEARCH TO PRACTICE

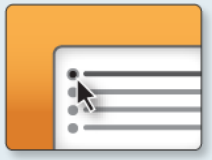
Friday May 30	**Immunotherapy and Antibody–Drug Conjugates in Lung Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Colorectal Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	EGFR Mutation–Positive Non–Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday May 31	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Non–Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 1	**Chronic Lymphocytic Leukemia (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	HER2–Positive Gastrointestinal Cancers 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 2	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Multiple Myeloma (Webinar) 6:00 PM – 7:00 PM CT (7:00 PM – 8:00 PM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 3	**Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

RTP
RESEARCH TO PRACTICE

Clinicians in the Meeting Room

Networked iPads are available.

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



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

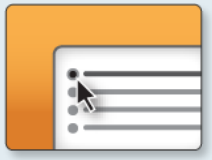
Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

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

RTP RESEARCH TO PRACTICE

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 pre- and postmeeting surveys.

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

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

RTP
RESEARCH TO PRACTICE

About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Clinical Care of Patients with Metastatic Breast Cancer

Monday, June 2, 2025
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Harold J Burstein, MD, PhD
Javier Cortés, MD, PhD
Rebecca A Dent, MD, MSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

Moderator

Hope S Rugo, MD

RTP RESEARCH TO PRACTICE

Agenda

MODULE 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Cortés

MODULE 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Kalinsky

MODULE 3: Available Therapies for Patients with HR-Positive, HER2-Negative Disease Progressing on CDK4/6 Inhibition — Dr Burstein

MODULE 4: Current and Potential Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Dr O'Shaughnessy

MODULE 5: Current and Future Strategies for Patients with Endocrine-Refractory HR-Positive mBC — Dr Rugo

MODULE 6: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Prof Dent

RTP RESEARCH TO PRACTICE

Agenda

MODULE 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Cortés

MODULE 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Kalinsky

MODULE 3: Available Therapies for Patients with HR-Positive, HER2-Negative Disease Progressing on CDK4/6 Inhibition — Dr Burstein

MODULE 4: Current and Potential Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Dr O'Shaughnessy

MODULE 5: Current and Future Strategies for Patients with Endocrine-Refractory HR-Positive mBC — Dr Rugo

MODULE 6: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Prof Dent

RTP RESEARCH TO PRACTICE

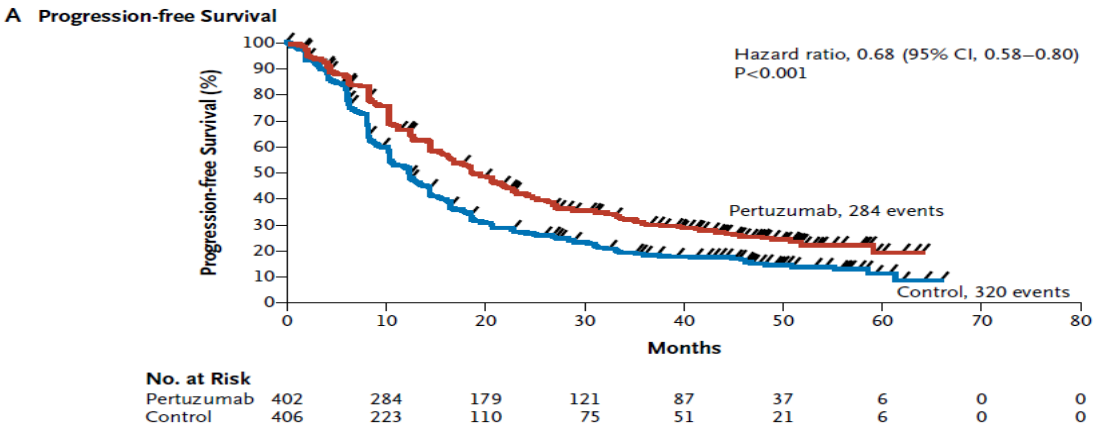
OPTIMIZING THE MANAGEMENT OF HER2-POSITIVE METASTATIC BREAST CANCER (MBC)

Javier Cortés MD PhD

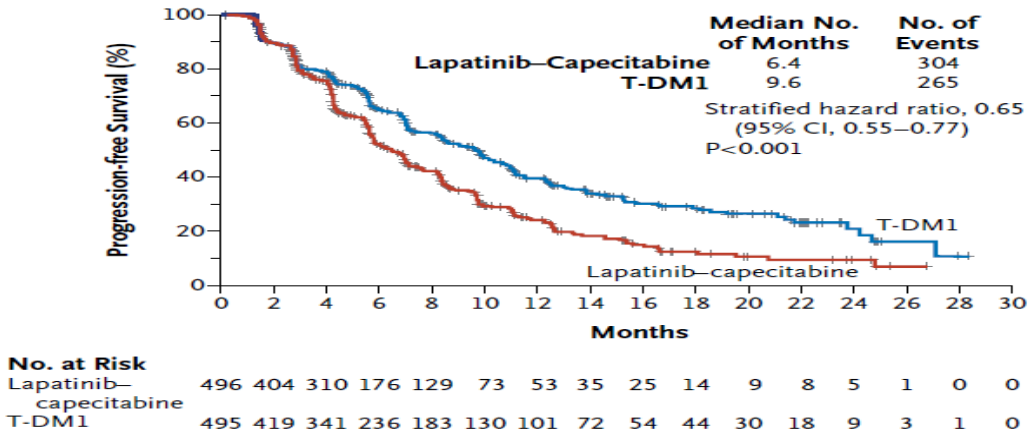
- International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Barcelona, Spain
- IOB Madrid, Hospital Beata Maria Ana, Madrid Spain
- Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain
- Medica Scientia Innovation Research (MEDSIR) - Oncoclínicas&Co, Jersey City (New Jersey, USA), Sao Paulo (Brazil).

Largest improvements in HER2 MBC

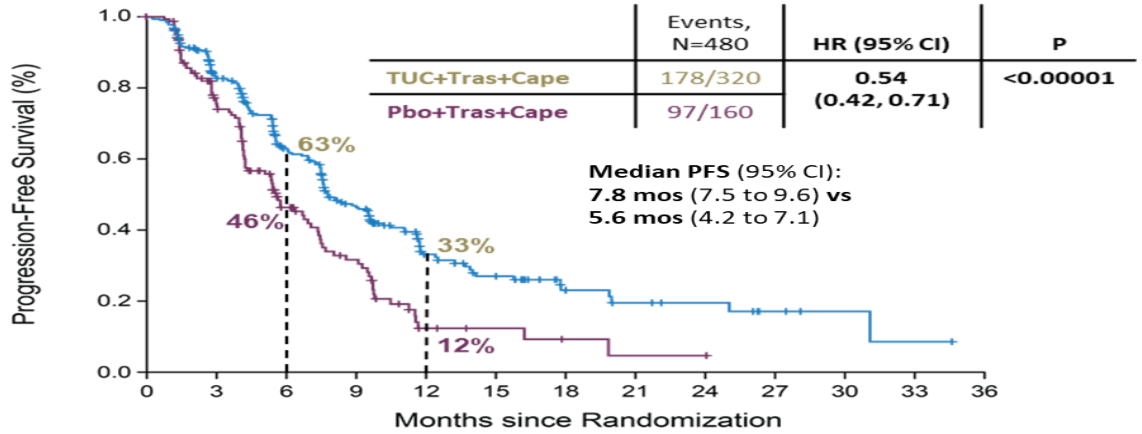
CLEOPATRA: + Pertuzumab



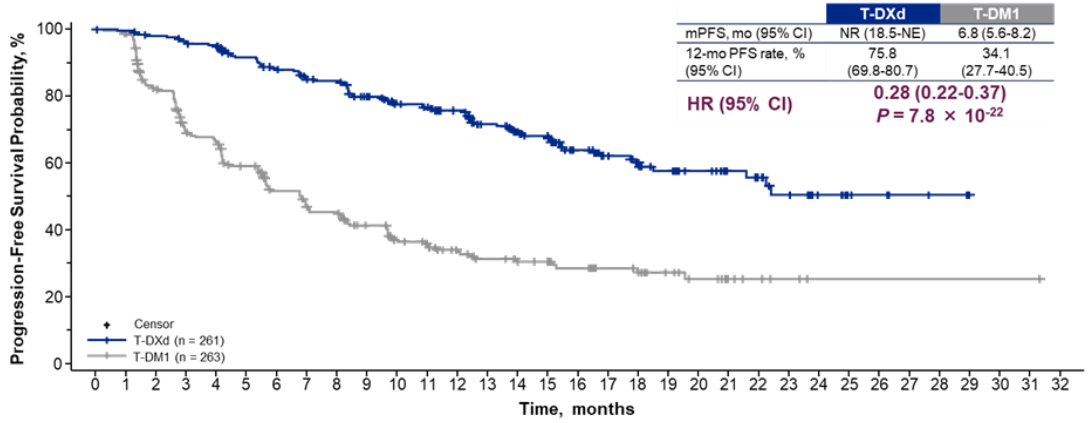
EMILIA: T-DM1



HER2CLIMB: + Tucatinib



Destiny-Breast03: T-DXd



Baselga J, et al . NEJM 2012; Verma S, et al. NEJM 2012; Murthy R, et al. NEJM 2020; Cortes J, et al. NEJM 2022

Can we optimize the Cleopatra strategy?

Can we optimize the Cleopatra strategy?
AFT-38 PATINA Study Design

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

Key eligibility criteria
- Completion of induction chemotherapy and no evidence of disease progression (i.e., CR, PR, or SD)

N=518

R 1:1

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

Trastuzumab ± pertuzumab + endocrine therapy

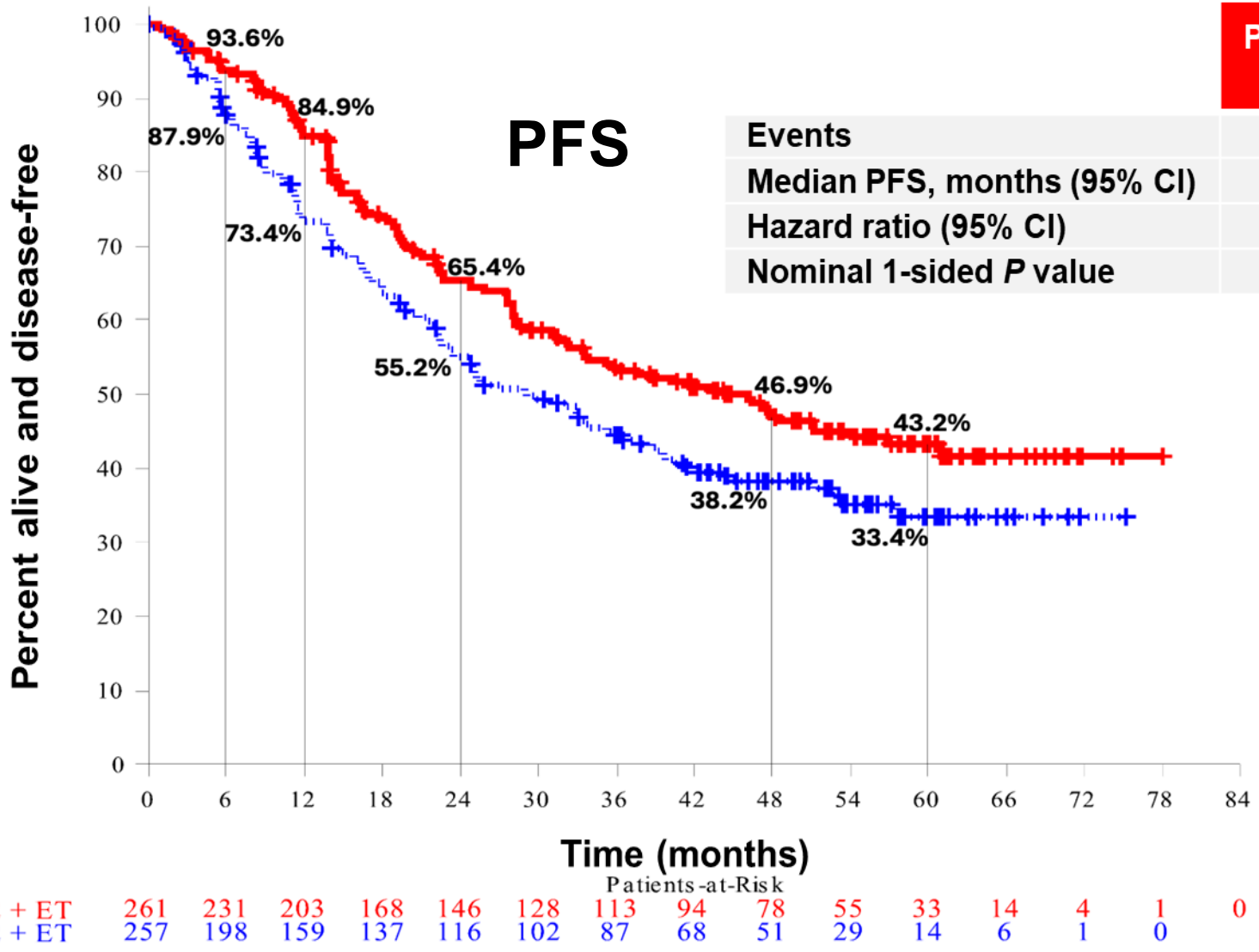
Until PD or toxicity

SURVIVAL FOLLOW-UP

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

Metzger O, et al. SABCS 2024

PATINA Study: Baseline Characteristics and outcomes

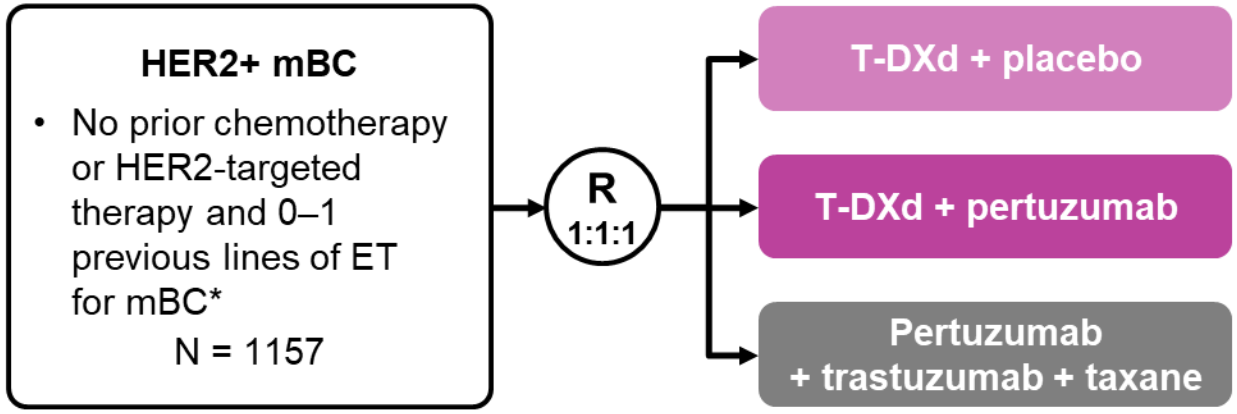


	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

Metzger O, et al. SABCS 2024

DESTINY-Breast09 is expected to change the SoC in 1L HER2+ mBC

DESTINY-Breast09: Phase III study of 1L T-DXd ± pertuzumab[1]



Primary endpoint
- PFS (BICR)

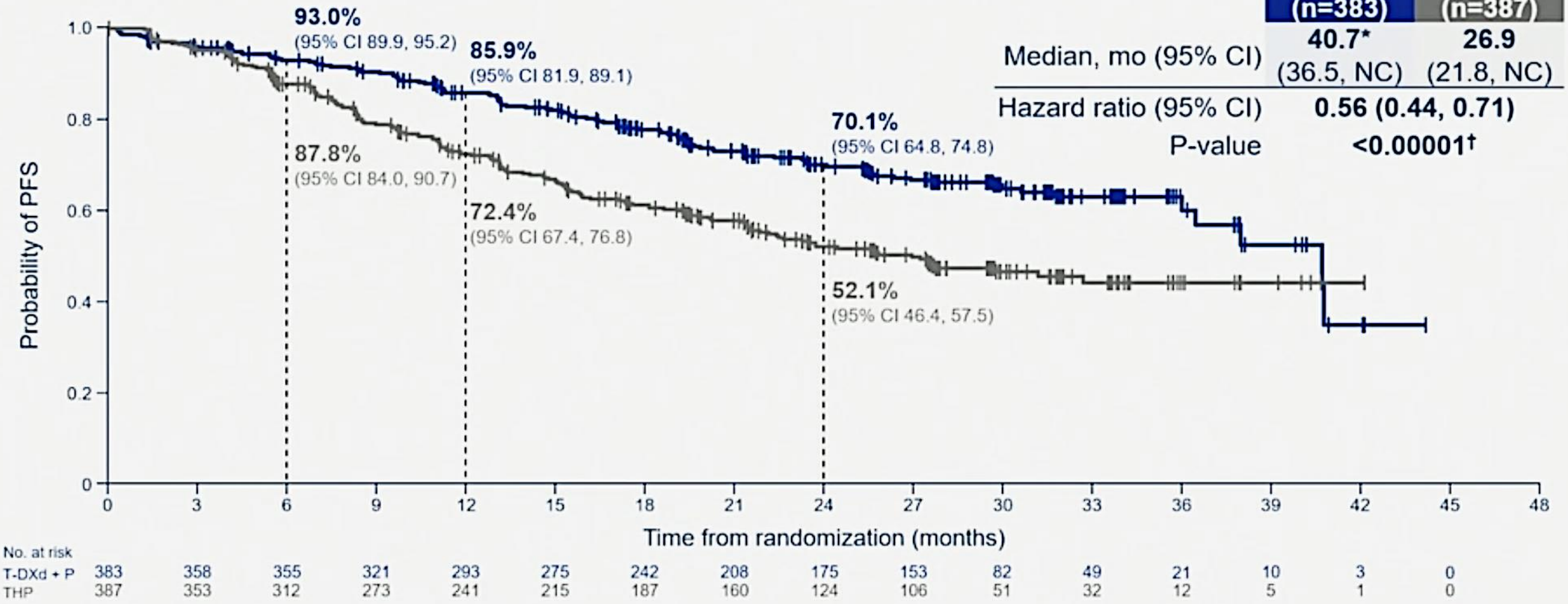
Press release[2]

T-DXd plus pertuzumab demonstrated highly statistically significant and clinically meaningful improvement in progression-free survival vs. THP as 1st-line therapy for patients with HER2-positive metastatic breast cancer

- **The PFS improvement with T-DXd + pertuzumab highlights the importance of maintaining dual HER2-targeted therapy with pertuzumab**
- **The T-DXd monotherapy arm remains blinded to patients and investigators and will continue to the final PFS analysis[2]**

Tolaney S, et al. ASCO 2025

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†	

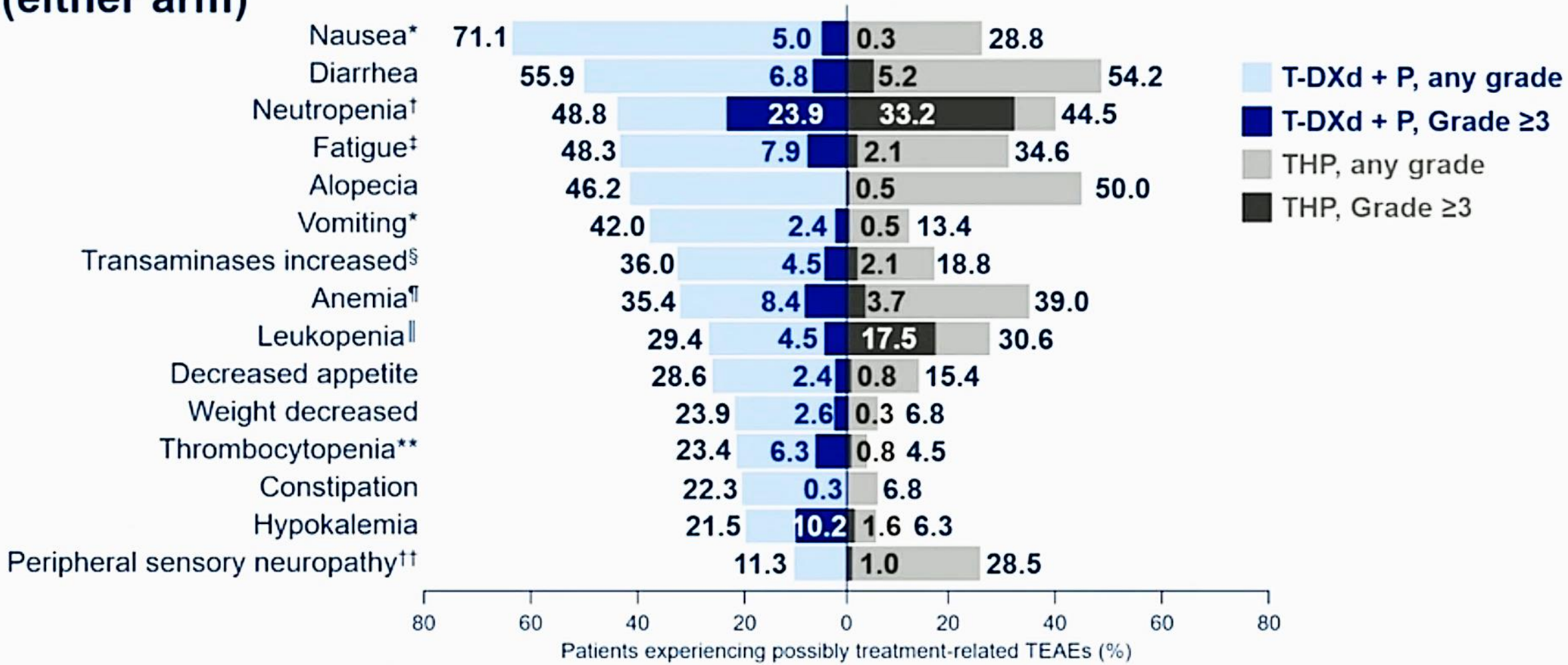
No. at risk

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

Possibly treatment-related (investigator assessed) TEAEs in ≥20% of patients (either arm)



*Antiemetic prophylaxis was recommended but not mandated by protocol. †neutropenia (grouped term) includes: neutropenia and neutrophil count decreased. ‡fatigue (grouped term) includes: fatigue, asthenia, malaise, and lethargy. §transaminases increased (grouped term) includes: transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increase. ¶anemia (grouped term) includes: anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased. ‖leukopenia (grouped term) includes: leukopenia and white blood cell count decreased. **thrombocytopenia (grouped term) includes: platelet count decreased and thrombocytopenia. ††peripheral sensory neuropathy (grouped term) includes: neuropathy peripheral, peripheral sensory neuropathy, and polyneuropathy
P, pertuzumab; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; 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)

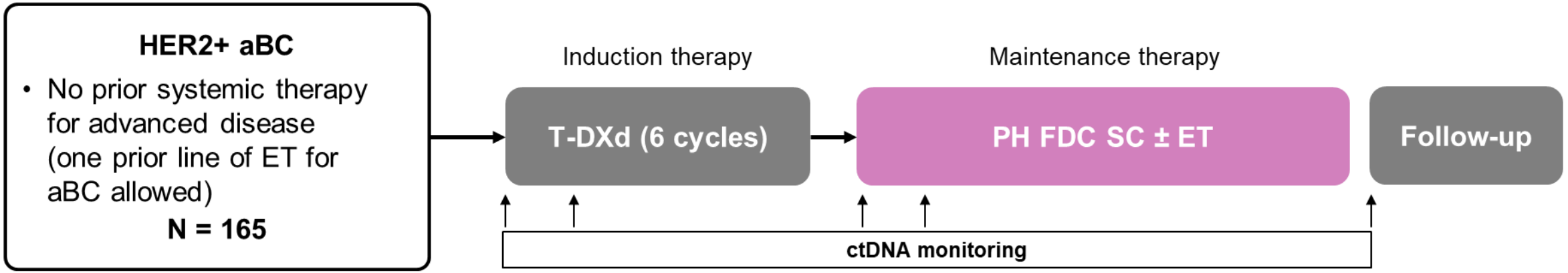
Left ventricular dysfunction†

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

DEMETHER will inform the feasibility of a T-DXd induction–PH FDC SC maintenance approach in patients with HER2+ aBC

DEMETHER: Phase II study of 1L T-DXd induction followed by maintenance PH FDC SC[1,2]



Primary endpoints
- 1-year PFS, 3-year OS

DEMETHER results will complement DESTINY-Breast09, aiming to build on CLEOPATRA in terms of cytotoxic induction therapy duration while taking into consideration the time to best response with T-DXd, to help optimise efficacy, tolerability and QoL for patients treated in the 1L setting

PI, J Cortes

Brain Metastases Are Common in Patients With advanced Solid tumors

Almost **50%** of **HER2+** mBC

median OS: 11 – 25 mo

>40% of **mNSCLC**

median OS without targeted agents: 4 – 12 mo

25 - 45% of **mTNBC**

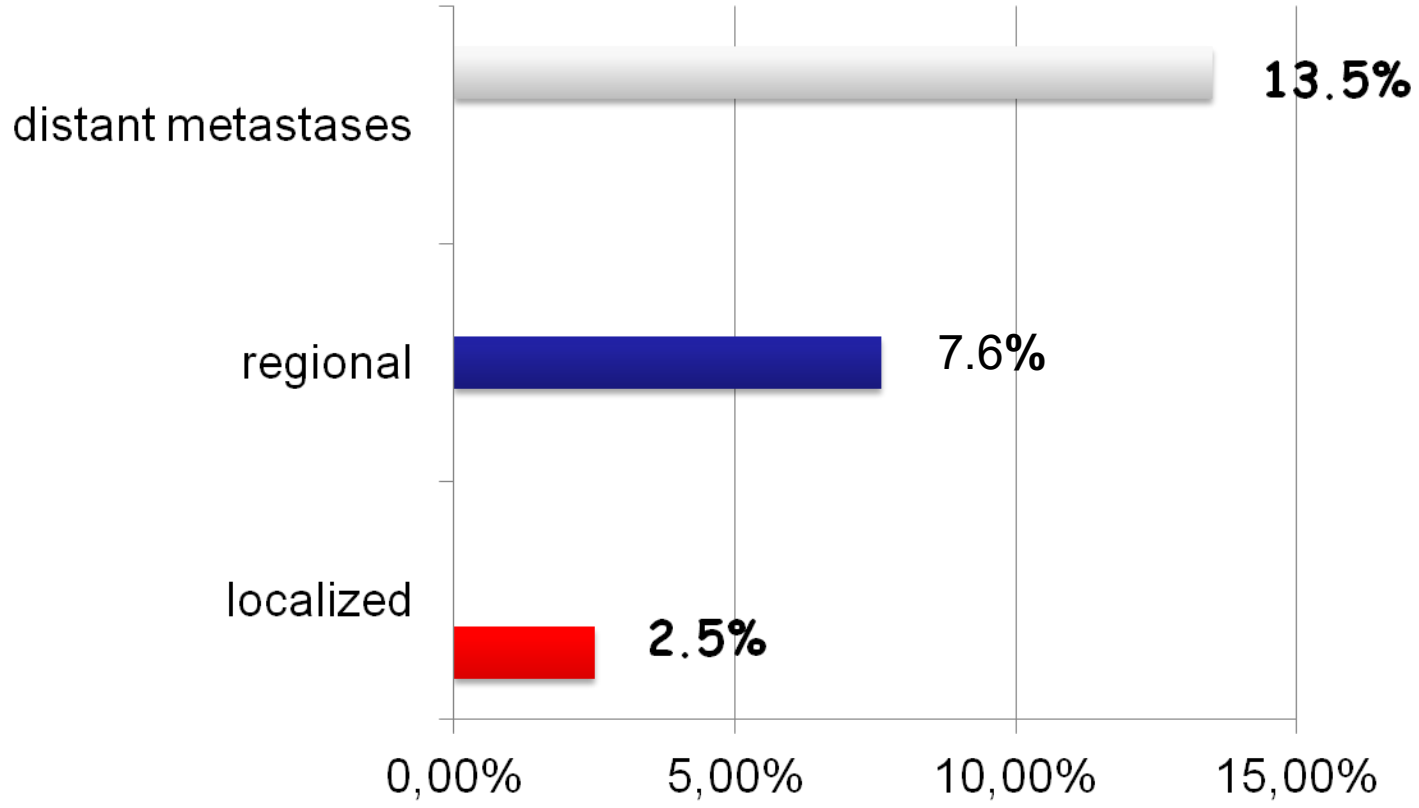
median OS: 4 to 9 mo

40 - 60% of stage IV **Melanoma**

median OS wo ICIs: 3 – 6 mo

1. Olson EM, et al. *Breast*. 2013;22(4):525-531; 2. Altaha R, et al. *Cancer*. 2005;103(3):442-443;
2. Martin M, et al. Rep Pract Oncol Radiother. 2022; 27(3): 527–544

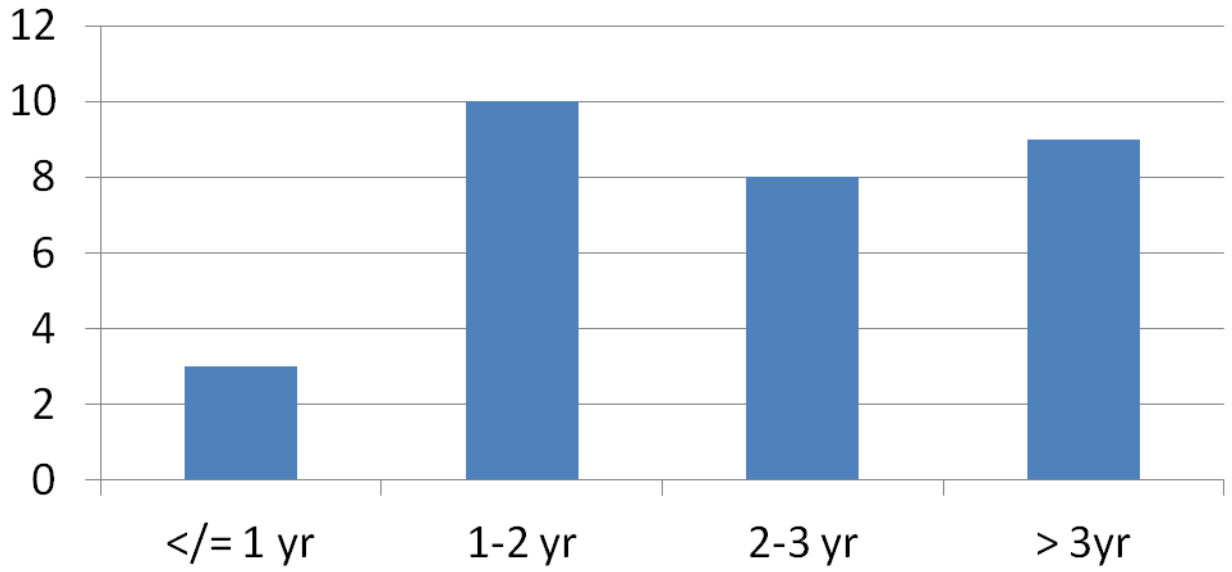
Risk of brain metastases by stage of disease (Breast cancer)



Branholtz-sloan, et al. JCO 2004

Risk of HER2+ CNS Metastases continues over time

Of N=64 patients alive >/= 3 years from MBC diagnosis, the number of patients who developed new brain metastases in each time interval:



Olson et al, Breast 2013

Tucatinib: HER2CLIMB

Key Eligibility Criteria

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

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
Treatment (21-day cycle)

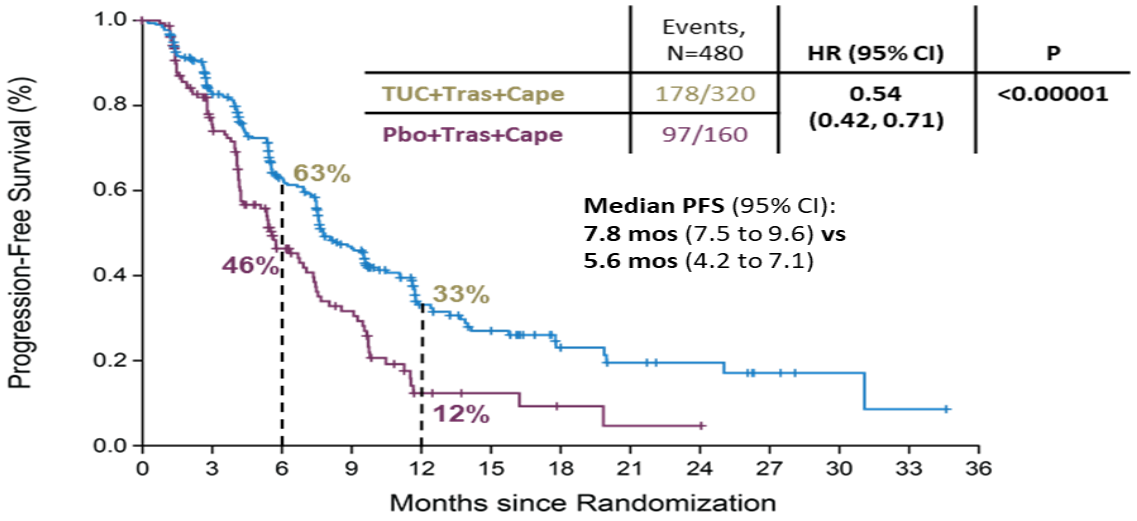
Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

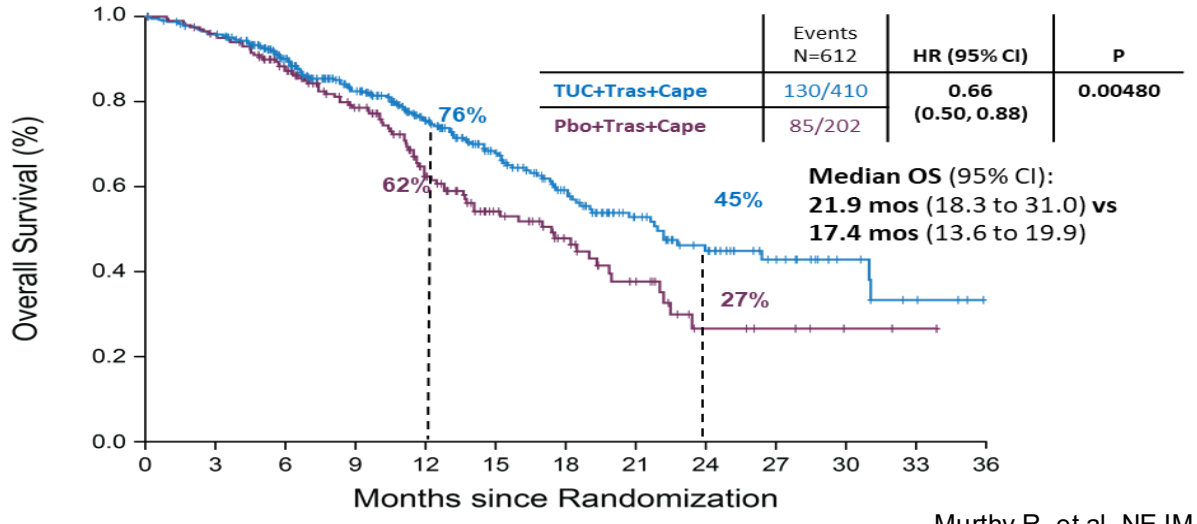
Placebo + Trastuzumab + Capecitabine
Treatment (21-day cycle)

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

PFS data



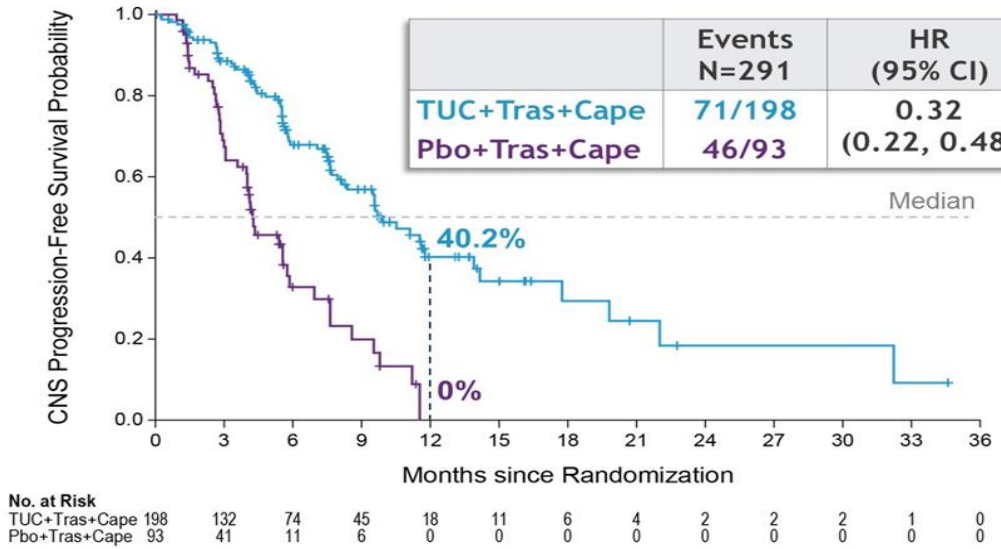
OS data



Murthy R, et al. NEJM 2020

Tucatinib: HER2CLIMB; CNS-PFS (1) and OS (2) in pts with BM

1)

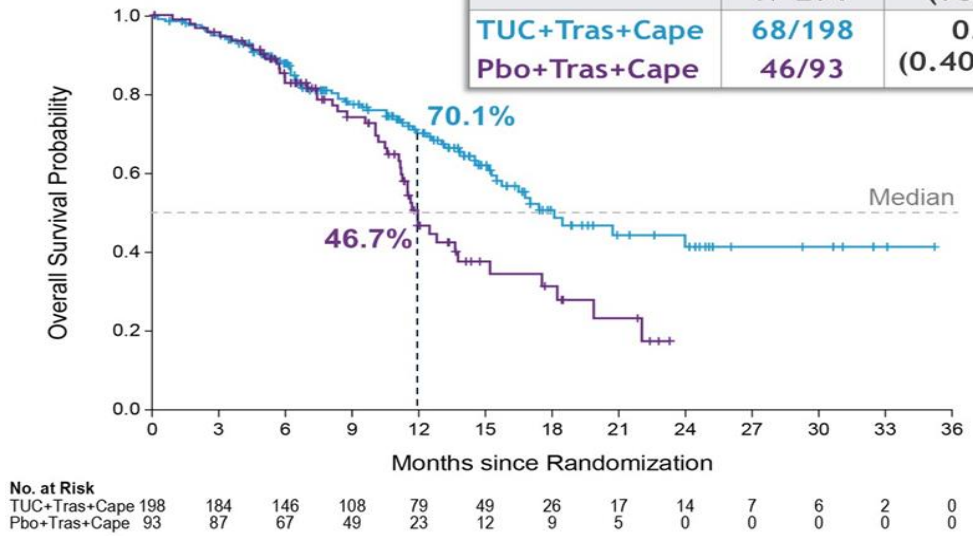


	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	71/198	0.32 (0.22, 0.48)	<0.00001
Pbo+Tras+Cape	46/93		

Risk of CNS progression or death was reduced by 68% in patients with brain metastases

One-year CNS-PFS (95% CI):	
TUC+Tras+Cape 40.2% (29.5, 50.6)	Pbo+Tras+Cape 0%
Median CNS-PFS (95% CI):	
9.9 months (8.0, 13.9)	4.2 months (3.6, 5.7)

2)



	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		

Risk of death was reduced by 42% in patients with brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape 70.1% (62.1, 76.7)	Pbo+Tras+Cape 46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

Lin N, et al. ASCO 2020

T-DXd: DB12

Patient population
- Aged ≥18 years
- Pathologically documented HER2+ advanced or metastatic BC with or without baseline brain metastases
- Received ≤2 prior lines of therapy in the metastatic setting (tucatinib naïve)
- Disease progression on prior HER2-directed regimens
- ECOG PS 0 or 1
- No known or suspected leptomeningeal metastases

Baseline brain metastases (N=263)*
- Stable BMs (previously treated)
- Active BMs (untreated or previously treated / progressing [not requiring immediate local therapy])

T-DXd 5.4 mg/kg IV Q3W†

Primary endpoint:
- PFS

Additional endpoints included:
- CNS PFS
- OS
- ORR
- CNS ORR
- Safety and tolerability

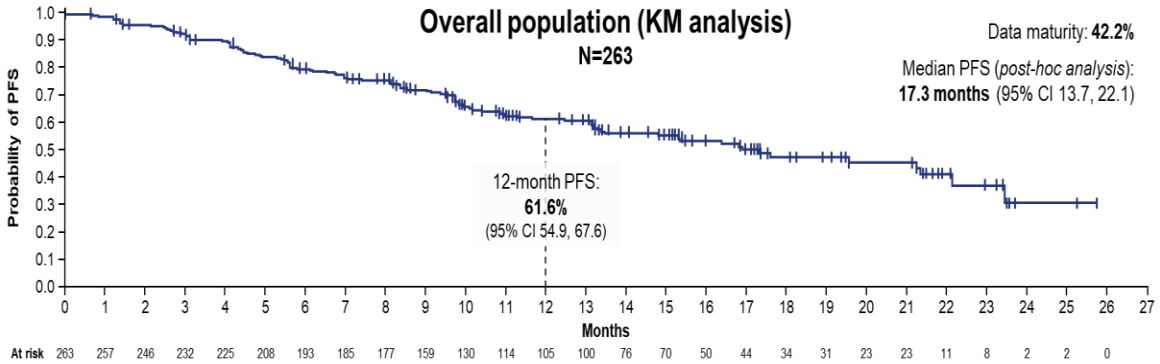
No baseline brain metastases (N=241)

T-DXd 5.4 mg/kg IV Q3W†

Primary endpoint:
- ORR

Additional endpoints included:
- OS
- Safety and tolerability

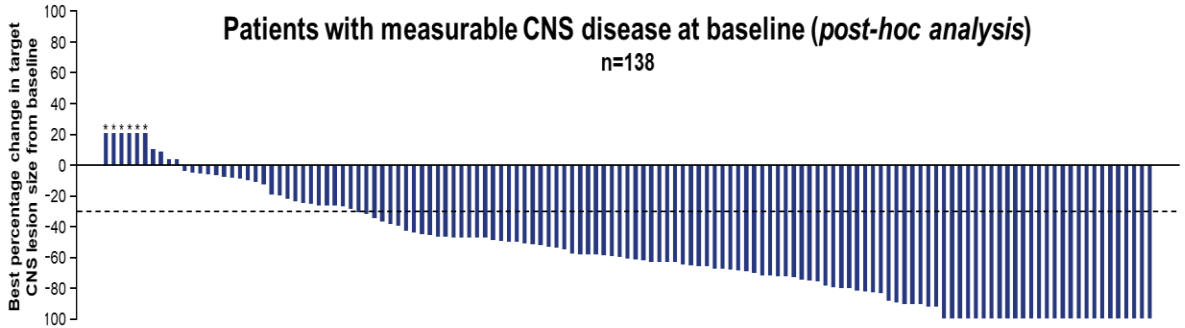
Baseline BMs: CNS PFS



	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	Active BM subgroups: Untreated (n=39) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=67) *Post-hoc analysis*
Overall no. events	111	64	47	20	27
12-month PFS, % (95% CI)	**61.6 (54.9, 67.6)**	62.9 (54.0, 70.5)	59.6 (49.0, 68.7)	47.0 (29.6, 62.7)	66.7 (53.4, 76.9)

T-DXd showed consistent 12-month PFS in patients with stable and active BMs

Baseline BMs: CNS ORR



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

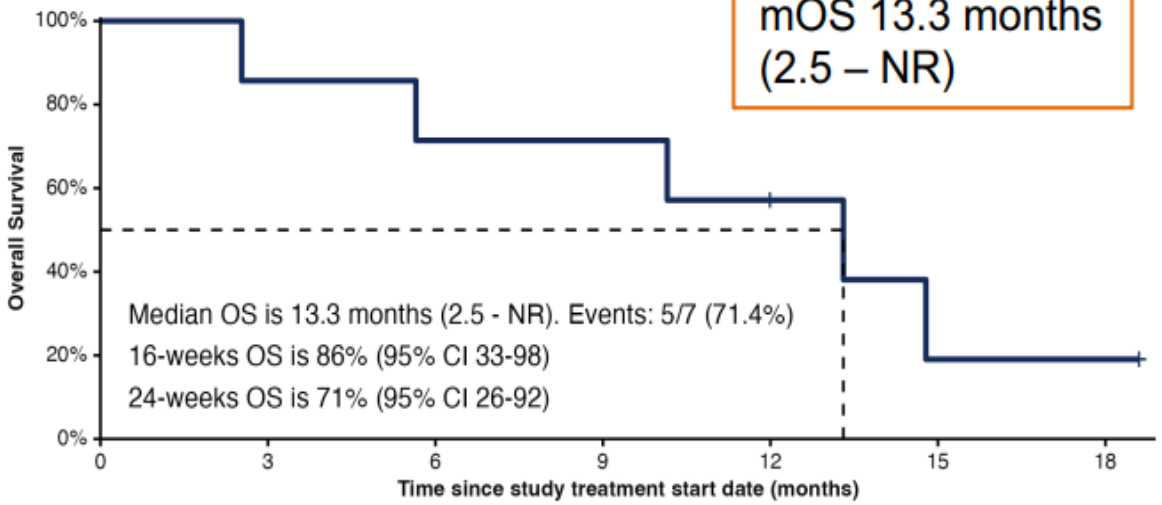
T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

Lin N, et al. ESMO 2024

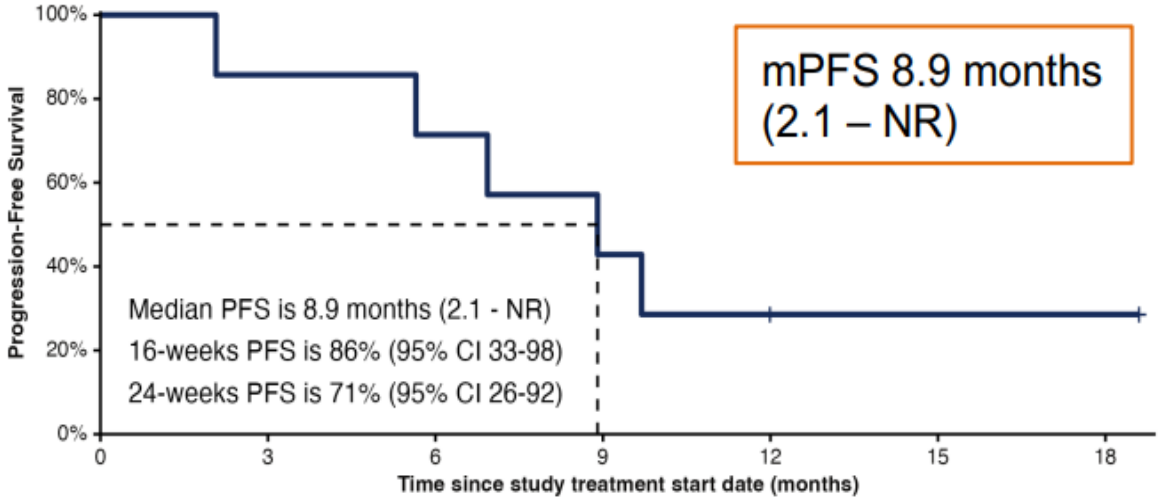
T-DXd in pathological confirmed LMC: DEBBRAH study

HER2 status: Positive 3 (42.9%) Low 4 (57.1%)

Overall survival



PFS according to RANO-BM and RECIST v1.1

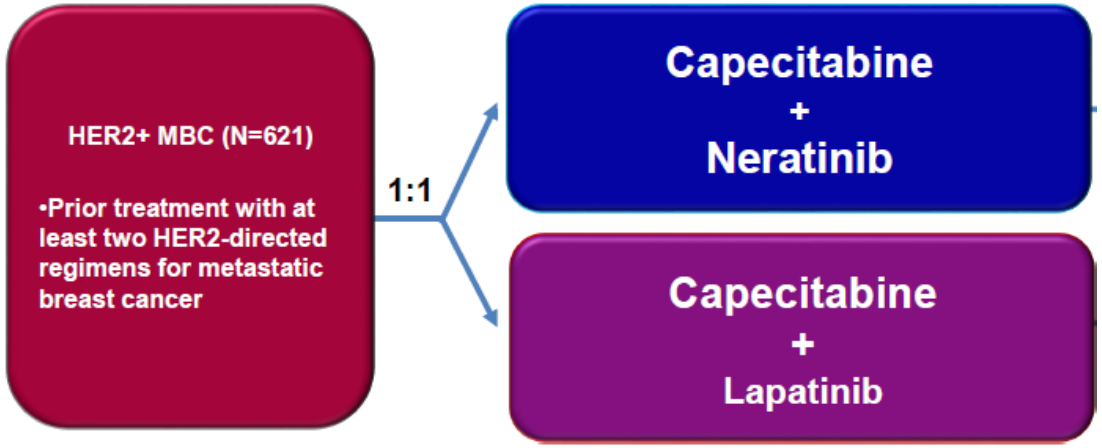


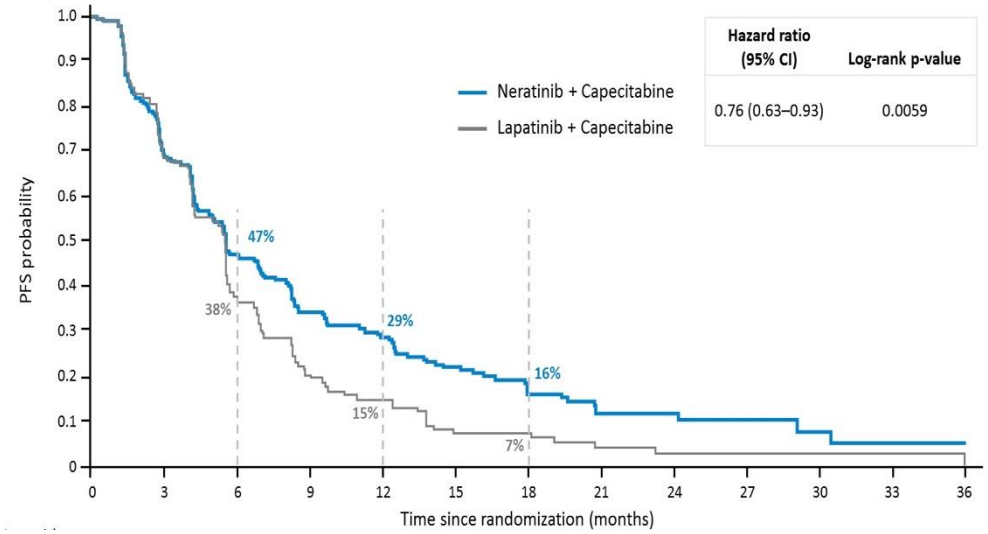
	Intracranial	Extracranial	All lesions
Best Overall Response	n = 7	n = 7	n = 7
CR	1 (14.3%)	0 (0%)	0 (0%)
SD ≥ 24w	1 (14.3%)	2 (28.6%)	2 (28.6%)
SD < 24w	0 (0%)	0 (0%)	0 (0%)
Non-CR/Non-PD ≥ 24w	2 (28.6%)	3 (42.9%)	3 (42.9%)
Non-CR/Non-PD < 24w	1 (14.3%)	0 (0%)	1 (14.3%)
PD	0 (0%)	1 (14.3%)	1 (14.3%)
NE	2 (28.6%)	1 (14.3%)	0 (0%)
Objective Response Rate (ORR)	n = 5	n = 6	n = 7
Yes	1 (20%)	0 (0%)	0 (0%)
No	4 (80%)	6 (100%)	7 (100%)
Clinical Benefit Rate (CBR)	n = 5	n = 6	n = 7
Yes	4 (80%)	5 (83.3%)	5 (71.4%)
No	1 (20%)	1 (16.7%)	2 (28.6%)

Vaz M, et al. SABCS 2023; Vaz M, et al. Med 2025

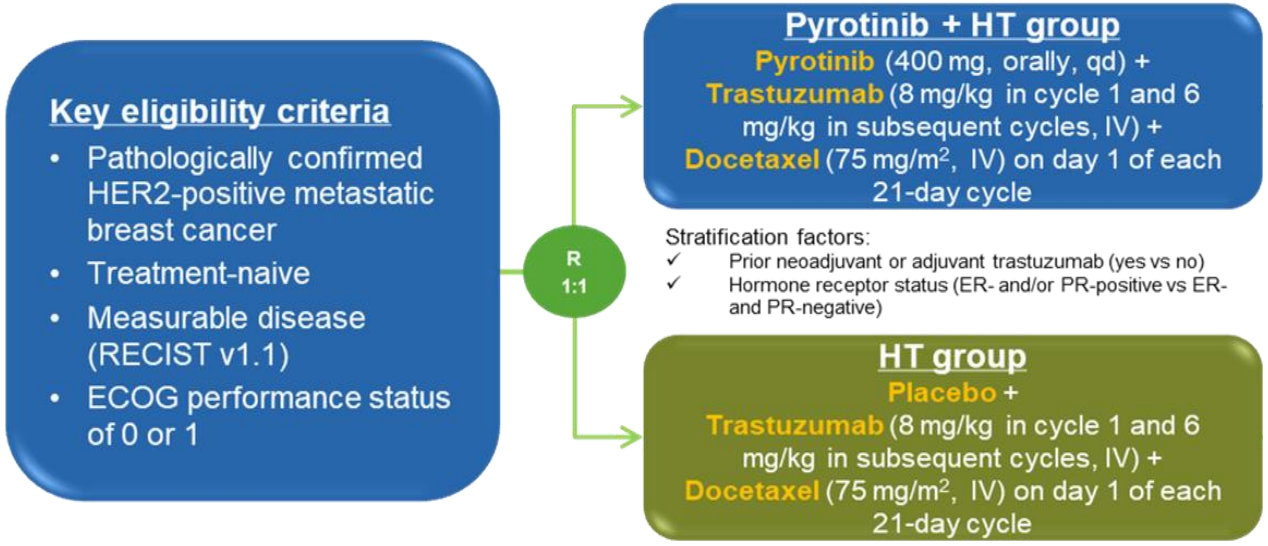
“New” antiHER2+ drugs with positive data in Phase III Trials

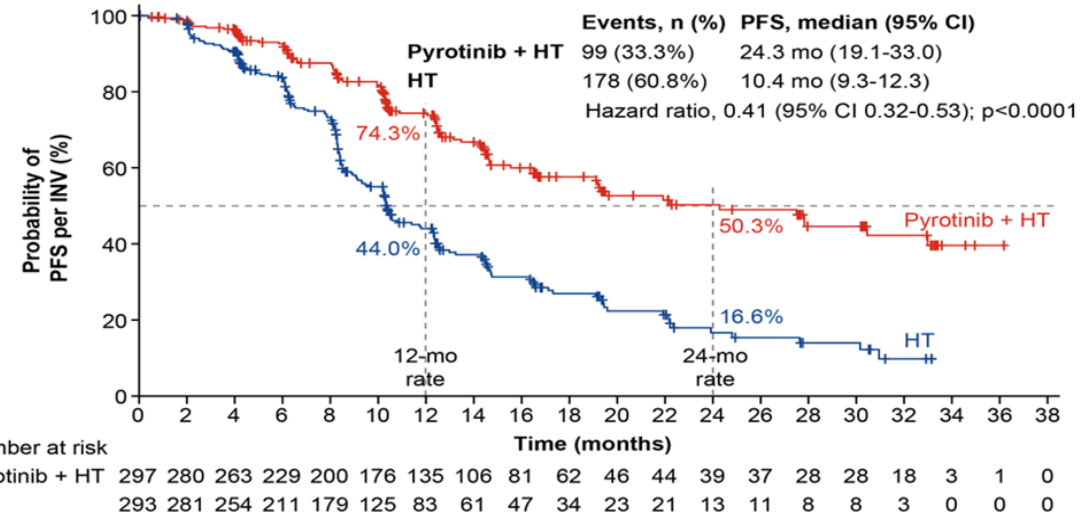
NALA Study[1]





Phila Study[2]



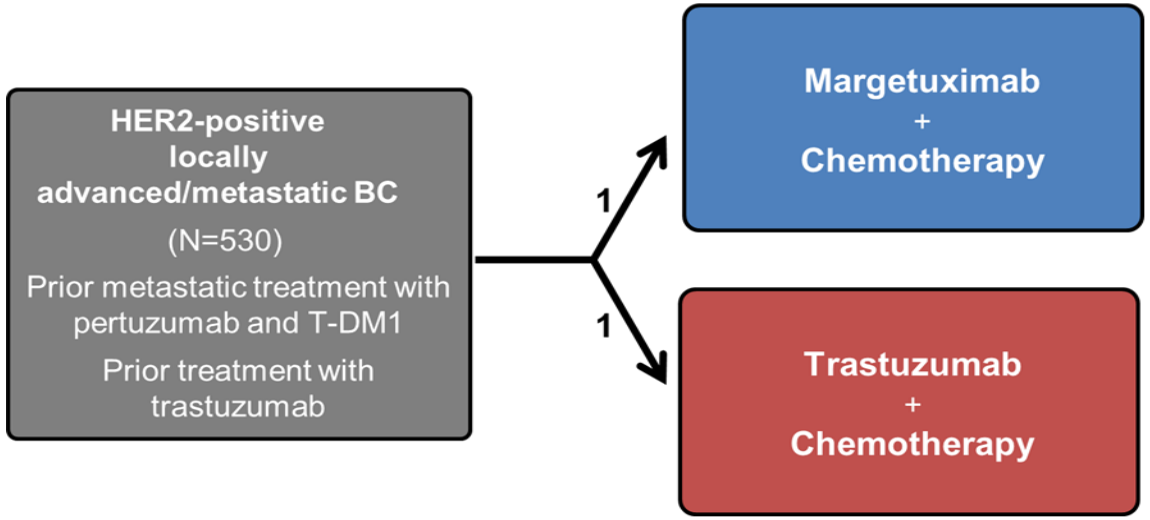


1. Brufsky A, et al. ASCO 2019; 2. Binghe Xu, et al. ESMO 2022

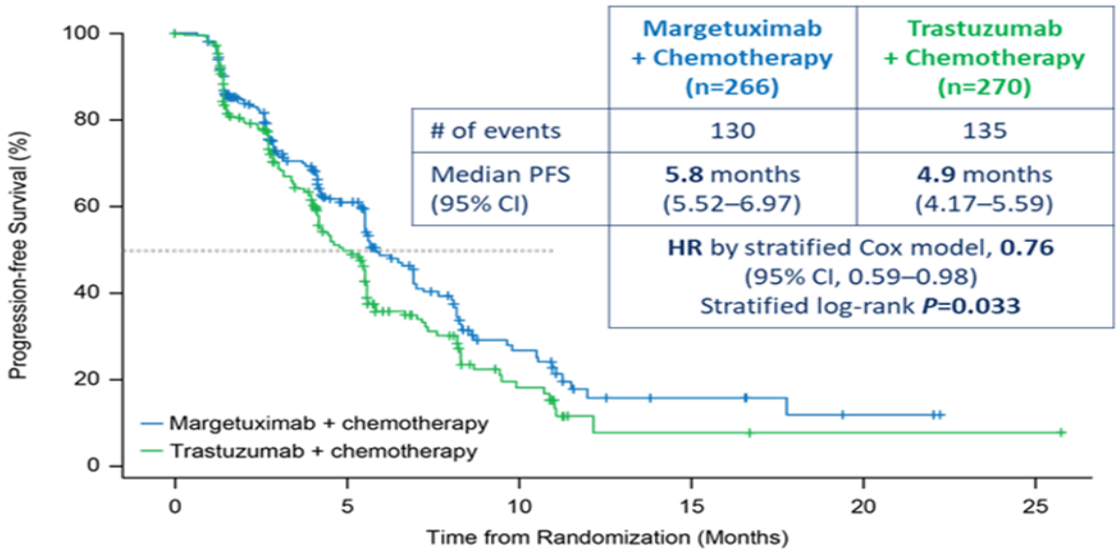
“New” antiHER2+ drugs with positive data in Phase III Trials

SOPHIA Study1

Clinical Trial Design



PFS (Central Blinded)

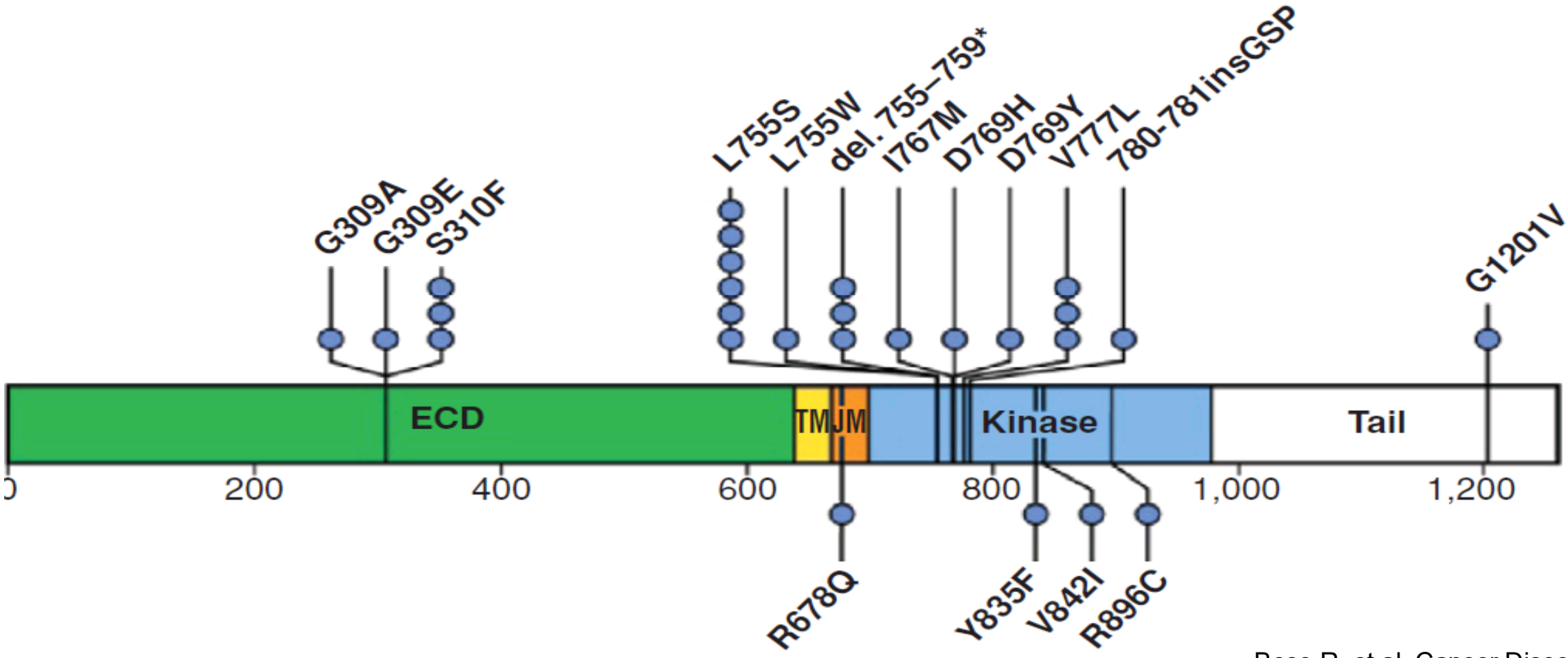


- **Trastuzumab-Duocarmazine** (TULIP) show PFS benefit over antiHER2 therapy; but OS not achieved
- **Disitamab vedotin** (RC48-C006) show PFS Benefit over lapatinib and capecitabine; OS immature
- **ARX-788** (ACE-Breast 02) show PFS Benefit over lapatinib and capecitabine; but OS not achieved

1. Rugo H, et al. ASCO 2019

HER2 mutations

– *HER2* amplification is an increase in the number of copies of *HER2* without an increase in other genes
– Activation *ERBB2* mutations are somatic point mutations in *ERBB2* that activate the pathway



Bose R, et al. Cancer Discov. 2013

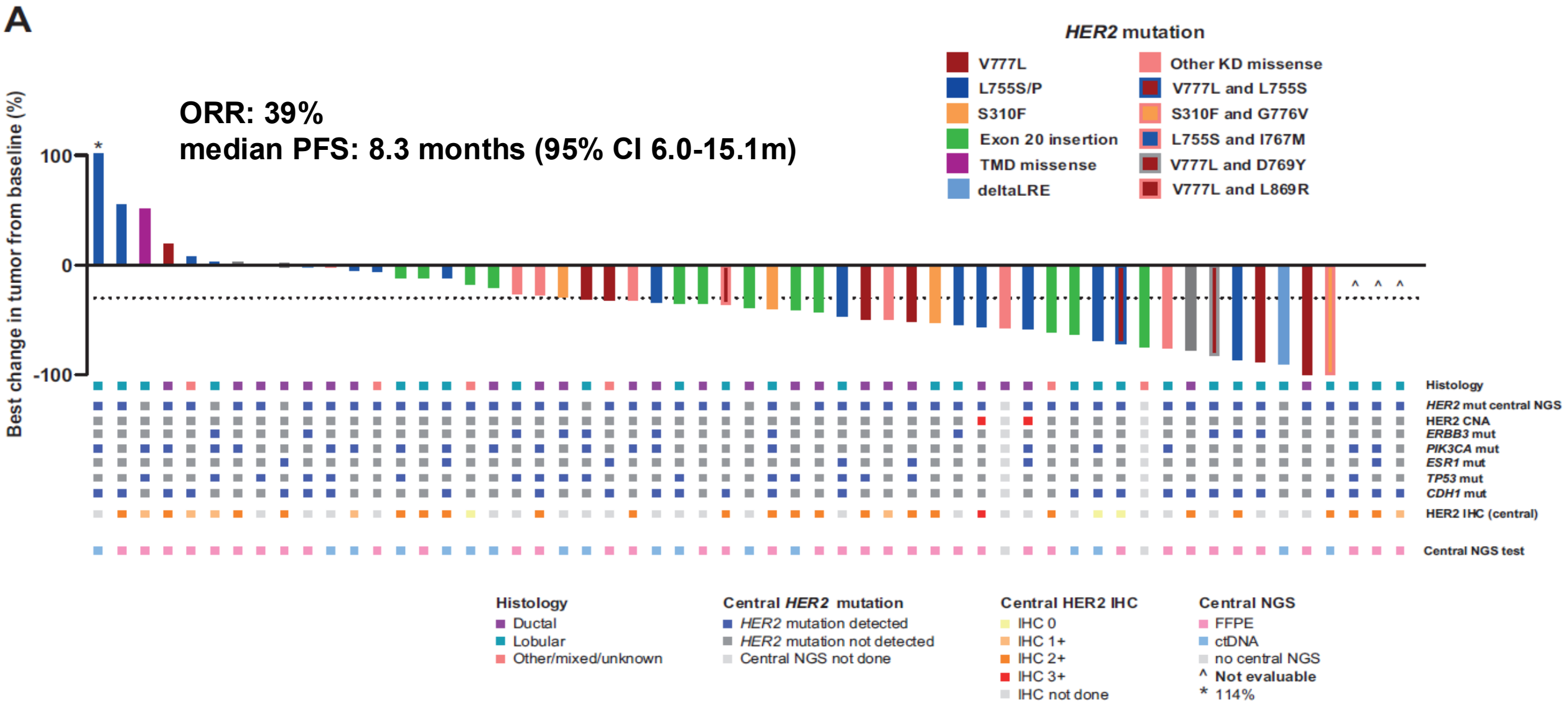
HER2 mutation: SUMMIT trial

- Open-label, multinational, multihistology, phase 2, signal-seeking study of neratinib as monotherapy or in combination in patients with tumors harboring *HER2* mutations
- Neratinib dosage: 240 mg oral daily as monotherapy or in combination until disease progression or toxicity
- Loperamide prophylaxis for cycle 1
- Fulvestrant 500 mg intramuscular on days 1 and 15 of first cycle and on day 1 of subsequent cycles
  - *HER2*-mutant breast cancer monotherapy: patients with HR-negative breast cancer, including TNBC
  - *HER2*-mutant breast cancer combination therapy: neratinib plus fulvestrant for patients with HR-positive breast cancer

Efficacy	Neratinib Monotherapy (n = 24)	Neratinib + Fulvestrant (n = 12)
Objective response rate at 8 weeks, n	8	5
CR	2	2
PR	6	3
Objective response rate (95% CI)	33.3 (15.6, 35.3)	41.7 (15.2, 72.3)
Clinical benefit, n	10.0	7.0
CBR (95% CI)	41.7 (21.1, 63.4)	58.3 (27.7, 84.8)
Median PFS, months (95% CI)	3.5 (1.9, 4.3)	3.7 (2.1, 6.7)

Hyman DM, et al. Nature 2019

HER2 mutation in HR+ MBC: SUMMIT trial
Neratinib + Fulvestrant + trastuzumab (n=57 pts)



Jhaveri K, et al. Ann Oncol 2023

2025 – HER2+ MBC

- **T-DXd** may become the SOC for patients with HER2-positive MBC in the first-line setting. However...
  - ✓ DEMETHER trial: It is reasonable to consider T-DXd as induction therapy for a fixed number of cycles.
  - ✓ Maintenance therapy: Ongoing clinical trials will help define the optimal strategy.
- **Brain metastases** are common in HER2-positive MBC. New drugs have shown activity, and current clinical guidelines may need to be revised.
- **Several agents** were explored prior to the introduction of T-DXd, and their role in patients pretreated with T-DXd remains unclear.
- **HER2 mutations** are rare, but new TKIs appear to be active in this setting.

If the ASCO 2025 presentation of the Phase III DESTINY-Breast09 trial of trastuzumab deruxtecan with pertuzumab versus docetaxel/trastuzumab/pertuzumab (THP) as first-line therapy for HER2-positive mBC confirms the positive press release, how will it affect your initial management of ER/PR-negative, HER2-positive mBC?

 Dr Burstein	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Cortés	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Prof Dent	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Kalinsky	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr O'Shaughnessy	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Rugo	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Hurvitz	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Jhaveri	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP

RTP RESEARCH TO PRACTICE

If the ASCO 2025 presentation of the Phase III DESTINY-Breast09 trial of trastuzumab deruxtecan with pertuzumab versus THP as first-line therapy for HER2-positive mBC confirms the positive press release, how will it affect your initial management of ER/PR-positive, HER2-positive mBC?

 Dr Burstein	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Cortés	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Prof Dent	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Kalinsky	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr O'Shaughnessy	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Rugo	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Hurvitz	I will likely prioritize trastuzumab deruxtecan/pertuzumab over THP
 Dr Jhaveri	I will likely prioritize THP over trastuzumab deruxtecan/pertuzumab

RTP RESEARCH TO PRACTICE

If trastuzumab deruxtecan/pertuzumab receives regulatory approval in the first-line setting, how will you approach maintenance therapy for patients with ER/PR-negative, HER2-positive disease for whom you employ this regimen?

	Maintenance therapy	Duration
 Dr Burstein	Trastuzumab + pertuzumab	Indefinitely
 Dr Cortés	Trastuzumab + pertuzumab (subQ)	Until progression or unacceptable toxicity
 Prof Dent	Trastuzumab + pertuzumab	Indefinitely
 Dr Kalinsky	Trastuzumab + pertuzumab	—
 Dr O'Shaughnessy	Trastuzumab + pertuzumab	Until progression
 Dr Rugo	Trastuzumab + pertuzumab	5 to 10 years if no PD
 Dr Hurvitz	Trastuzumab + pertuzumab	Until progression
 Dr Jhaveri	Trastuzumab + pertuzumab	Until progression

subQ = subcutaneous; PD = progressive disease

If trastuzumab deruxtecan/pertuzumab receives regulatory approval in the first-line setting, how will you approach maintenance therapy for patients with ER/PR-positive, HER2-positive disease for whom you employ this regimen?

 Dr Burstein	Trastuzumab + pertuzumab + ET +/- CDK4/6i
 Dr Cortés	Trastuzumab + pertuzumab + ET (consider palbociclib)
 Prof Dent	Trastuzumab + pertuzumab + ET +/- palbociclib
 Dr Kalinsky	Trastuzumab + pertuzumab + ET (consider palbociclib)
 Dr O'Shaughnessy	Trastuzumab + pertuzumab + ET + palbociclib
 Dr Rugo	Trastuzumab + pertuzumab + AI + palbociclib
 Dr Hurvitz	Trastuzumab + pertuzumab + ET + palbociclib
 Dr Jhaveri	Trastuzumab + pertuzumab + ET

ET = endocrine therapy; CDK4/6i = CDK4/6 inhibitor; AI = aromatase inhibitor

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER/PR-negative, HER2-positive mBC receives first-line THP but then develops extensive systemic disease progression and multiple brain metastases. Regulatory and reimbursement issues aside, which systemic treatment would you recommend as second-line therapy?

	Asymptomatic	Symptomatic
 Dr Burstein	Trastuzumab deruxtecan	Trastuzumab deruxtecan
 Dr Cortés	Trastuzumab deruxtecan	Trastuzumab deruxtecan
 Prof Dent	Trastuzumab deruxtecan	Trastuzumab deruxtecan
 Dr Kalinsky	Trastuzumab deruxtecan	Trastuzumab deruxtecan
 Dr O'Shaughnessy	Trastuzumab deruxtecan	Trastuzumab deruxtecan
 Dr Rugo	Trastuzumab deruxtecan	Trastuzumab deruxtecan
 Dr Hurvitz	Trastuzumab deruxtecan	Trastuzumab deruxtecan
 Dr Jhaveri	Trastuzumab deruxtecan	Trastuzumab deruxtecan

Do you currently test for HER2 mutations in patients with mBC? Outside of a clinical trial, would you administer neratinib-based therapy to a patient with progressive HER2-mutant mBC?

	HER2 mutation testing	HR-positive	HR-negative
 Dr Burstein	Yes, in select patients	Yes	Yes
 Dr Cortés	Yes, in select patients	Yes	Yes
 Prof Dent	Yes, in all patients	Yes	Yes
 Dr Kalinsky	Yes, in all patients	Yes	Yes
 Dr O'Shaughnessy	Yes, in all patients	Yes	Yes
 Dr Rugo	Yes, in all patients	Yes	Yes
 Dr Hurvitz	Yes, in all patients	Yes	Yes
 Dr Jhaveri	Yes, in all patients	Yes	Yes

A 65-year-old woman with HR-positive, HER2-mutant breast cancer has developed multiple metastases 9 months after starting adjuvant ribociclib with anastrozole. ESR1, PIK3CA, AKT1 and PTEN are negative. Regulatory and reimbursement issues aside, which treatment would you most likely recommend for this patient?

 Dr Burstein	Abemaciclib + fulvestrant
 Dr Cortés	Trastuzumab deruxtecan
 Prof Dent	Tucatinib/trastuzumab combo or trastuzumab deruxtecan
 Dr Kalinsky	Neratinib + trastuzumab + fulvestrant; T-DXd if patient is really symptomatic
 Dr O'Shaughnessy	Trastuzumab deruxtecan
 Dr Rugo	Neratinib + trastuzumab + fulvestrant
 Dr Hurvitz	Neratinib + trastuzumab + fulvestrant
 Dr Jhaveri	Neratinib + trastuzumab + fulvestrant

Agenda

MODULE 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Cortés

MODULE 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Kalinsky

MODULE 3: Available Therapies for Patients with HR-Positive, HER2-Negative Disease Progressing on CDK4/6 Inhibition — Dr Burstein

MODULE 4: Current and Potential Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Dr O'Shaughnessy

MODULE 5: Current and Future Strategies for Patients with Endocrine-Refractory HR-Positive mBC — Dr Rugo

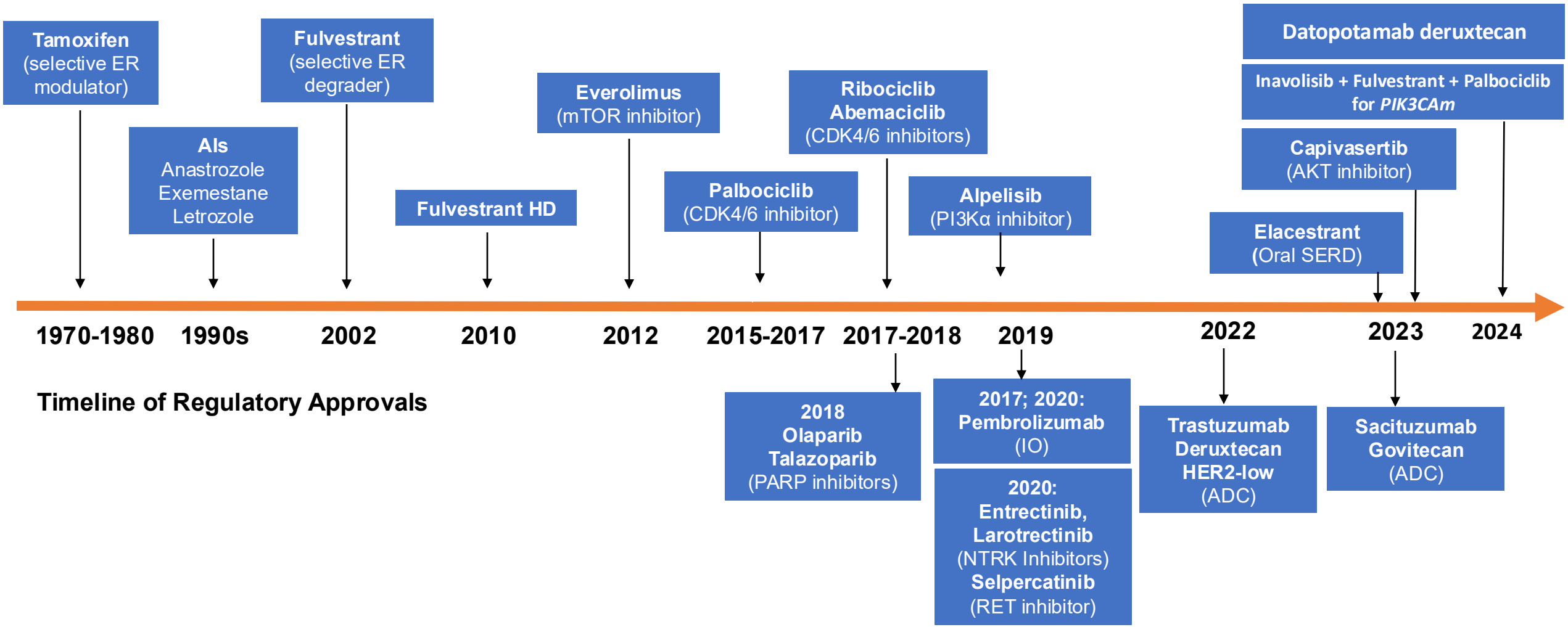
MODULE 6: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Prof Dent

RTP RESEARCH TO PRACTICE

Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC

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

Treatment Landscape of HR+ Advanced MBC



AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ER, estrogen receptor; ET, endocrine therapy; HD, high dose; HR, hormone receptor; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PI3Kα, phosphoinositide 3-kinase α.

Brufsky AM. Cancer Treat Rev. 2017;59:22-32; Lim E, et al. Oncology. 2012;26:688-694; Croxtall JD, et al. Drugs. 2011;71:363-380; Carlson RW, et al. J Clin Oncol. 2010;28:3917-3921; NCCN. Breast cancer (v4.2023). 2023. Accessed June 1, 2024. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; Bardia et al ESMO 2023; Curigliano et al ASCO 2024

Results for Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2[1]	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	No
MONALEESA-2[2]	Ribociclib	1st Line/AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7[3a]	Ribociclib	1st Line/AI or Tam	Pre/Peri	0.55	Yes	0.70	Yes
MONARCH-3[4]	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.75	No (@IA2)
PALOMA-3[5]	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2[6]	Abemaciclib	2nd Line/Fulv	Pre/Post	0.55	Yes	0.78	Yes
MONALEESA-3[7]	Ribociclib	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	0.72	Yes

a. Missing survival data (ie, pts who withdrew consent or were lost to follow-up) and were censored (assumed to be alive) at time of analysis: 13% in palbo+AI arm vs 21% in control arm.
b. 27% of patients in control arm went on to receive a CDK4/6i (24% received palbociclib).
c. PFS/OS data reported for approved AI subset.

AI indicates aromatase inhibitor; Fulv, fulvestrant; IA2, interim analysis 2; NR, not reported; Rx, therapy.

1. PALOMA-2: Finn R, et al. *N Engl J Med*. 2016;375:1925-1936; Rugo H, et al. *Breast Cancer Res Treat*. 2019;174:719-729. Finn R, et al. ASCO 2022. LBA1003. **2.** MONALEESA-2: Hortobagyi G, et al. *N Engl J Med*. 2016;375:1738-1748; Hortobagyi G, et al. *Ann Oncol*. 2018;29:1541-1547; Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR. **3.** MONALEESA-7: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915; Im S-A, et al. *New Engl J Med*. 2019;381:307-316. **4.** MONARCH-3: Goetz M, et al. *J Clin Oncol*. 2017;35:3638-3646; Johnson S, et al. NPJ *Breast Cancer. 2019;5:5.* Goetz MP, et al. ESMO 2022. Abstract LBA 15. **5.** PALOMA-3: Turner NC, et al. *New Engl J Med*. 2015;373:209-219; Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439; Turner NC, et al. *New Engl J Med*. 2015;373:1672-1673. **6.** MONARCH-2: Sledge G, et al. *J Clin Oncol*. 2017;35:2875-2884; Sledge G, et al. *JAMA Oncol*. 2020;6:116-124**. 7.** MONALEESA-3: Slamon D, et al. *J Clin Oncol*. 2018;36:2465-2472; Slamon D, et al. *New Engl J Med*. 2020;382:514-524.

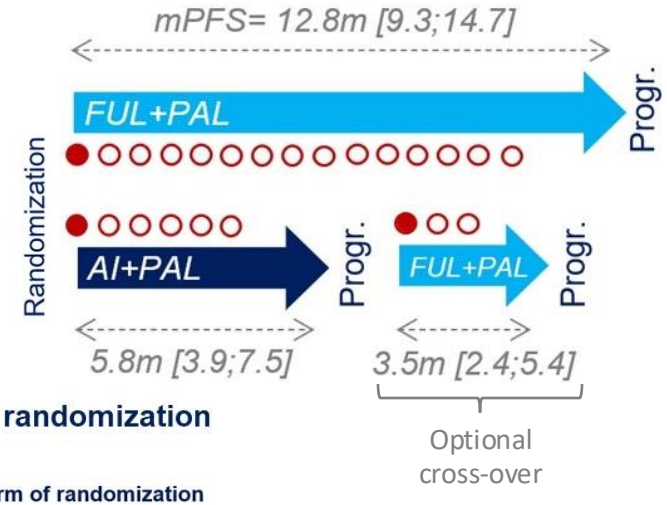
Prevalence of *ESR1* Mutations in Untreated vs Treated ER+/HER2- mBC

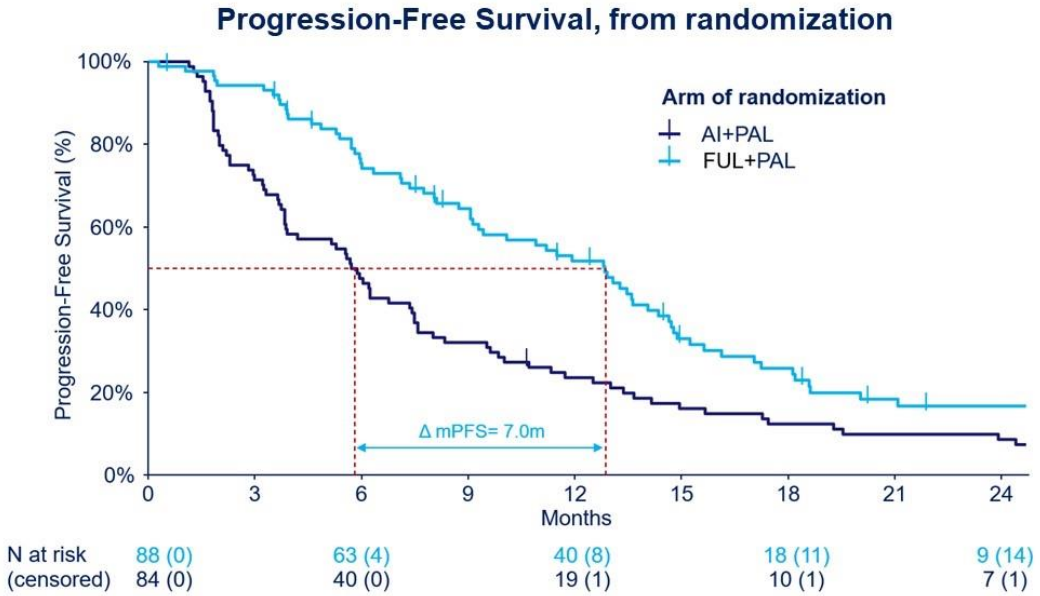
Treatment Setting	*ESR1* Mutation Prevalence[1-5]
At Initiation of First-Line ET	~5%
Second-Line	~33%
Third-Line	Up to 40%

1. Jeselsohn R et al. *Clin Cancer Res* 2014;20:1757-1767; **2.** Jeselsohn R et al. *Cancer Cell* 2018;33:173-186; **3.** Allouchery V et al. *Breast Cancer Res* 2018;20:40;
4. Schiavon G et al. Sci Transl Med 2015;7(313):313ra182; **5.** Brett JO et al. *Breast Cancer Res* 2021;23(1):85.

Phase III PADA-1:
Observed Benefit from Starting SERDs Earlier in *ESR1*m

- *AI-sensitive ER+ HER2- mBC*
- *No prior treatment for mBC*
- *Evaluable disease*





FUL+PAL mPFS: 12.8 months, 95%CI [9.3;14.7]

AI+PAL mPFS: 5.8 months, 95%CI [3.9;7.5]

PFS HR= 0.54 [0.38;0.75]

Optional cross-over (N=49 patients)

mPFS: 3.5 months, 95%CI [2.4;5.4]

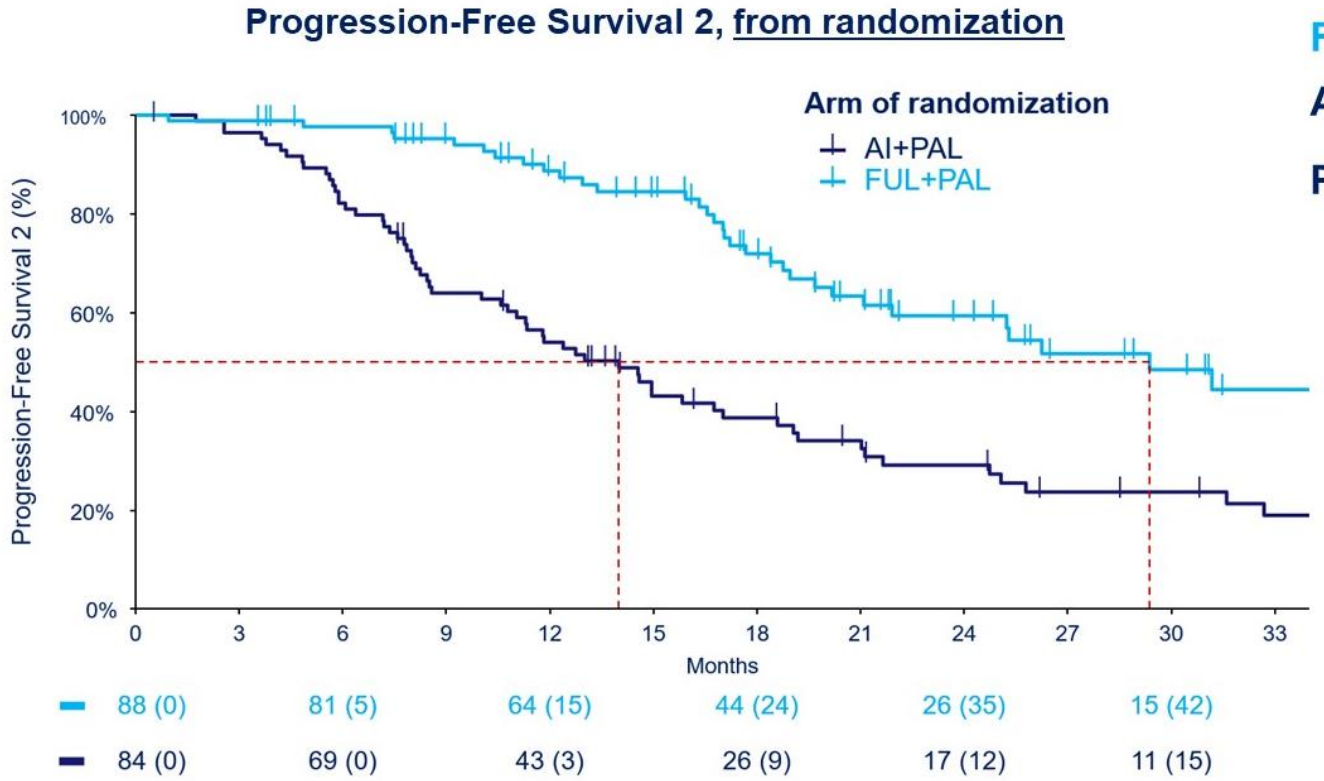
2021 analysis [2]
N=134 events
11.9 months
5.7 months
0.61
3.5 months

[2] Bidard *et al.*, Lancet Oncol 2022

Cabel L et al. ASCO 2023;Abstract 1002

Phase III PADA-1: Secondary Endpoint
PFS2

Data cut-off: June 21, 2022 N= 93 PFS2 events (54% maturity)



FUL+PAL mPFS2: 29.4 months, 95%CI [21.9;NR]

AI+PAL mPFS2: 14.0 months, 95%CI [11.0;18.6]

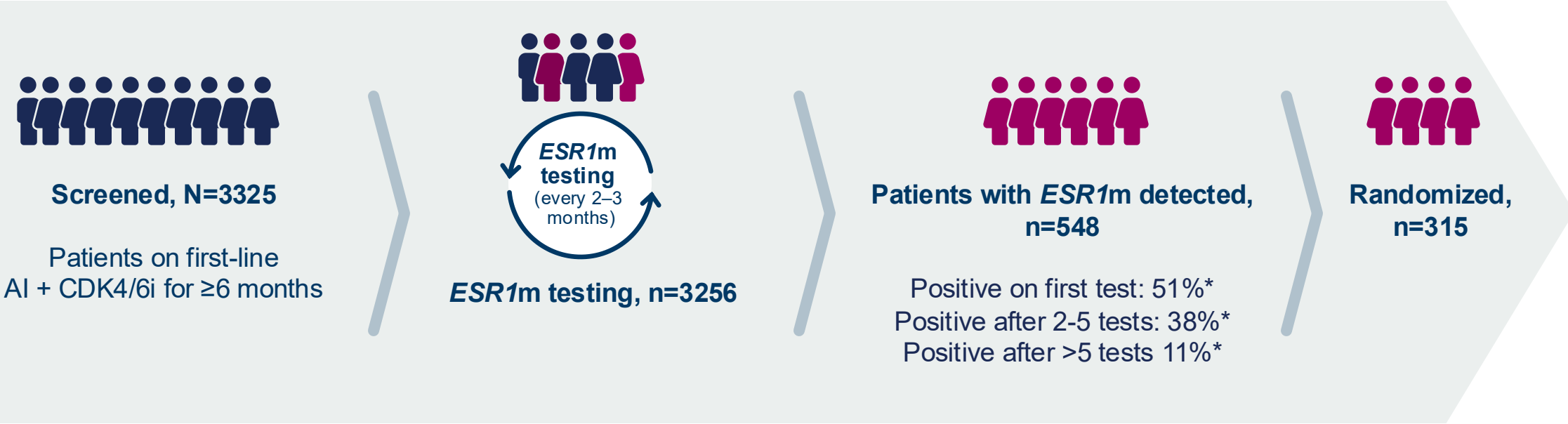
PFS2 HR= 0.37 [0.24;0.56]

Data cut-off: June 21, 2022; PFS2: time to 2nd progression or death in both arms

Cabel L et al. ASCO 2023;Abstract 1002

*ESR1*m surveillance during first-line AI+CDK4/6i

SERENA-6



Patients tested for *ESR1*m in ctDNA with Guardant360 CDx every 2–3 months at time of routine staging scans

Patients ongoing in surveillance when screening closed, n=1949

Discontinued (n=233) due to:

- Screen failure (n=200)
  - Concurrent disease progression (n=53)
  - Patient not meeting other eligibility criteria (n=48)
  - Reason not provided (n=99)
- Withdrew consent, lost to follow-up or unknown (n=33)

A crude estimate of the proportion of patients with emergent *ESR1*m during the study period is 42%, calculated from the 548 patients with a positive test/(the number of patients tested for *ESR1*m [n=3256] minus the number of patients that were still ongoing in surveillance when screening closed [n=1949]).

Number of tests to obtain a positive *ESR1*m test result based on n=521 patients who met all the eligibility criteria for the *ESR1m* surveillance step. Patients were screened for inclusion into the study from 264 sites in 23 countries.

Of the 3325 patients screened for inclusion, ctDNA from patient blood samples were tested for *ESR1*m using Guardant360CDx (Guardant Health, Redwood City, CA, US).

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

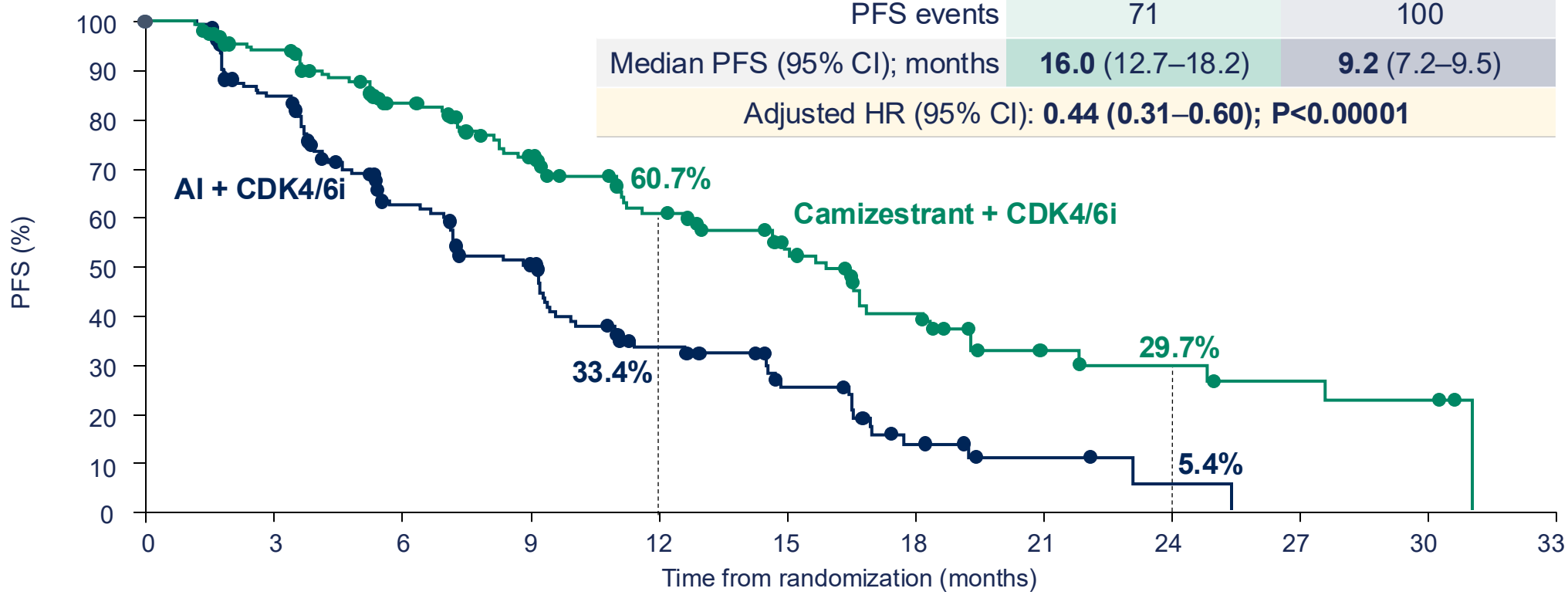
Characteristic		Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Median age (range) — years		61.0 (29–81)	60.5 (35–89)
Female — n (%)		157 (100)	155 (98)
Race — n (%)	White	97 (62)	102 (65)
	Asian/other	39 (25) / 21 (13)	34 (22) / 22 (14)
Postmenopausal status — n (%)		123 (78)	127 (80)
ECOG performance-status 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**		



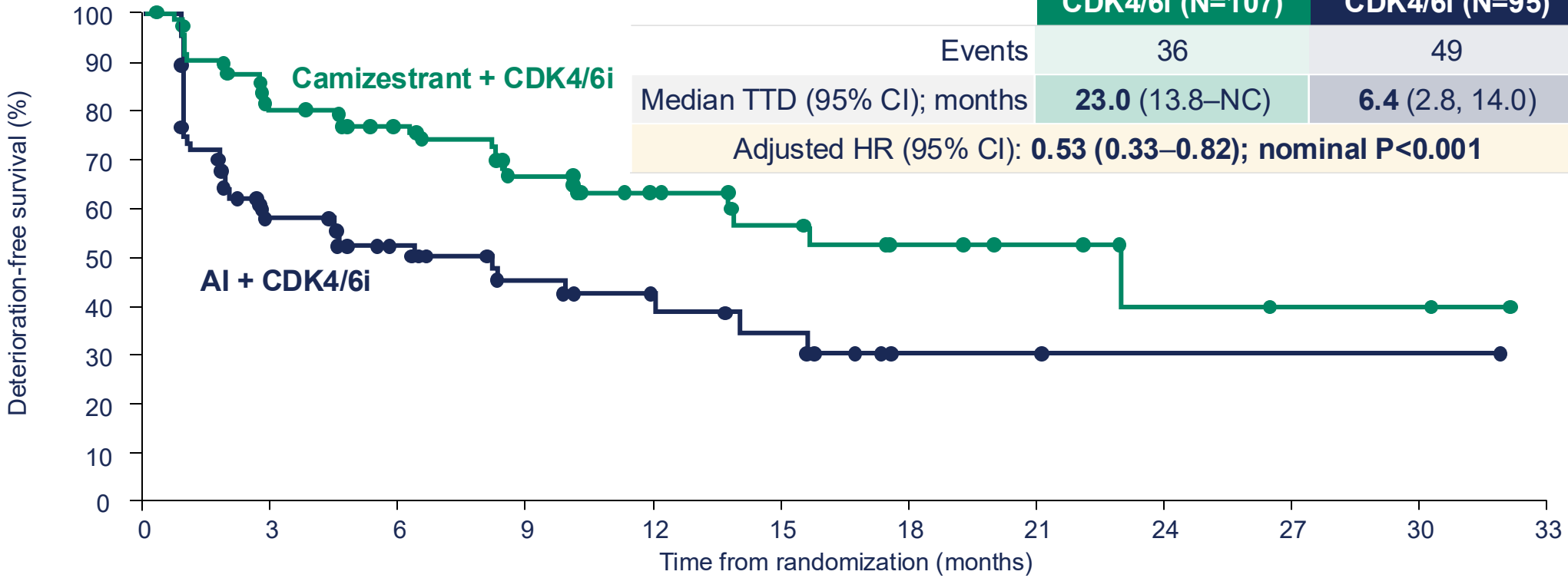
Number of patients at risk

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.

Time to deterioration in global health status/quality of life

EORTC QLQ-C30



	Camizestrant + CDK4/6i (N=107)	AI + CDK4/6i (N=95)
Events	36	49
Median TTD (95% CI); months	**23.0** (13.8–NC)	**6.4** (2.8, 14.0)
Adjusted HR (95% CI): **0.53 (0.33–0.82); nominal P<0.001**		

Number of patients at risk

Camizestrant + CDK4/6i	107	72	59	40	24	16	9	6	3	2	2	0
AI + CDK4/6i	95	42	26	16	11	8	2	2	1	1	1	0

- Camizestrant + CDK4/6i also delayed the time to deterioration in pain compared with AI + CDK4/6i

Assessments were conducted at baseline, weeks 4, 8 and 12 and then every 8 weeks until PFS2. Analysis conducted in patients with a baseline score and at least one post-baseline assessment. TTD in global health status/quality of life, an exploratory endpoint, was defined as the time from randomization to first deterioration that was confirmed at a subsequent timepoint measured using the European Organization for Research and Treatment of Cancer 30-item quality-of-life questionnaire (**EORTC QLQ-30**). Deterioration was defined as a decrease from baseline ≥16.6. HR was estimated using the Cox proportional hazard model stratified by time of *ESR1*m detection (one test vs more than one test), and time from initiation of AI + CDK4/6i to randomization (<18 months vs. ≥18 months). NC, not calculable; TTD, time-to-deterioration.

Second progression-free survival (PFS2)

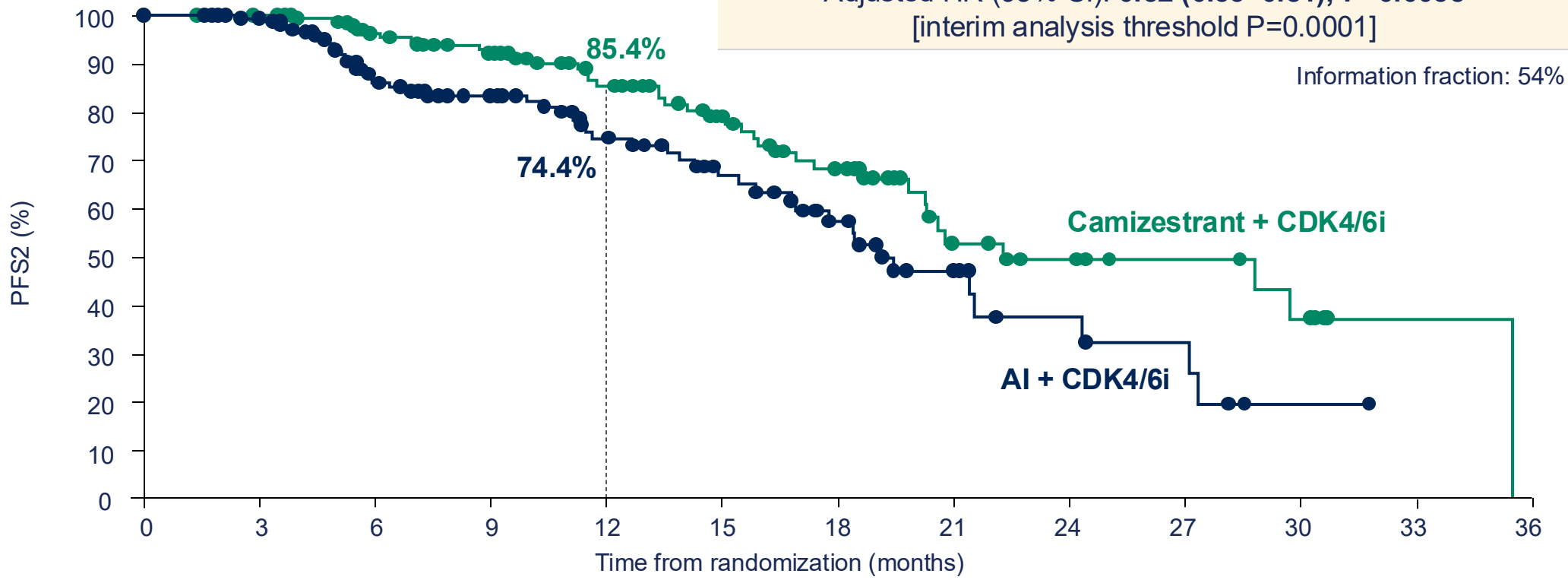
Key secondary endpoint

SERENA-6

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS2 events	38	47

Adjusted HR (95% CI): **0.52 (0.33–0.81); P=0.0038**
[interim analysis threshold P=0.0001]

Information fraction: 54%

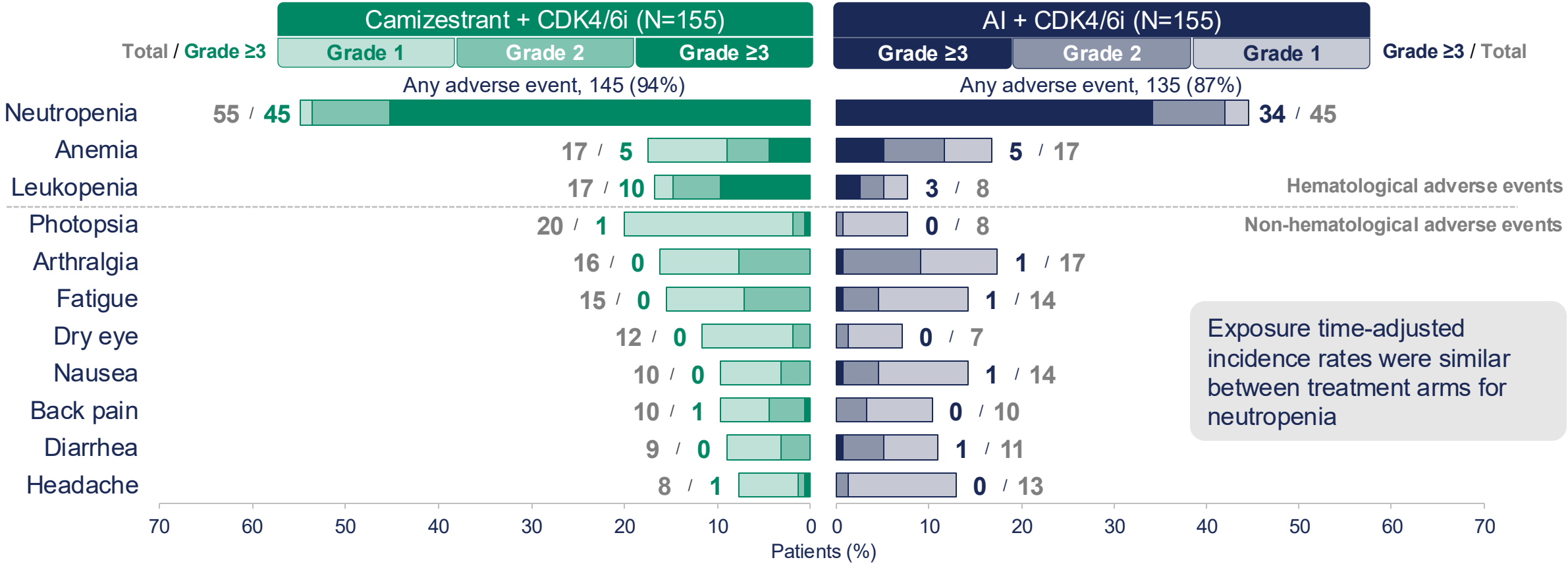


Number of patients at risk

Camizestrant + CDK4/6i	157	146	120	103	74	55	39	17	12	9	6	1	0
AI + CDK4/6i	158	144	98	78	55	38	25	12	7	5	1	0	0

HR was estimated using the Cox proportional hazard model adjusted for stratification factors. Final PFS2 analysis will occur at 158 PFS2 events.

Adverse events (≥10% of patients)

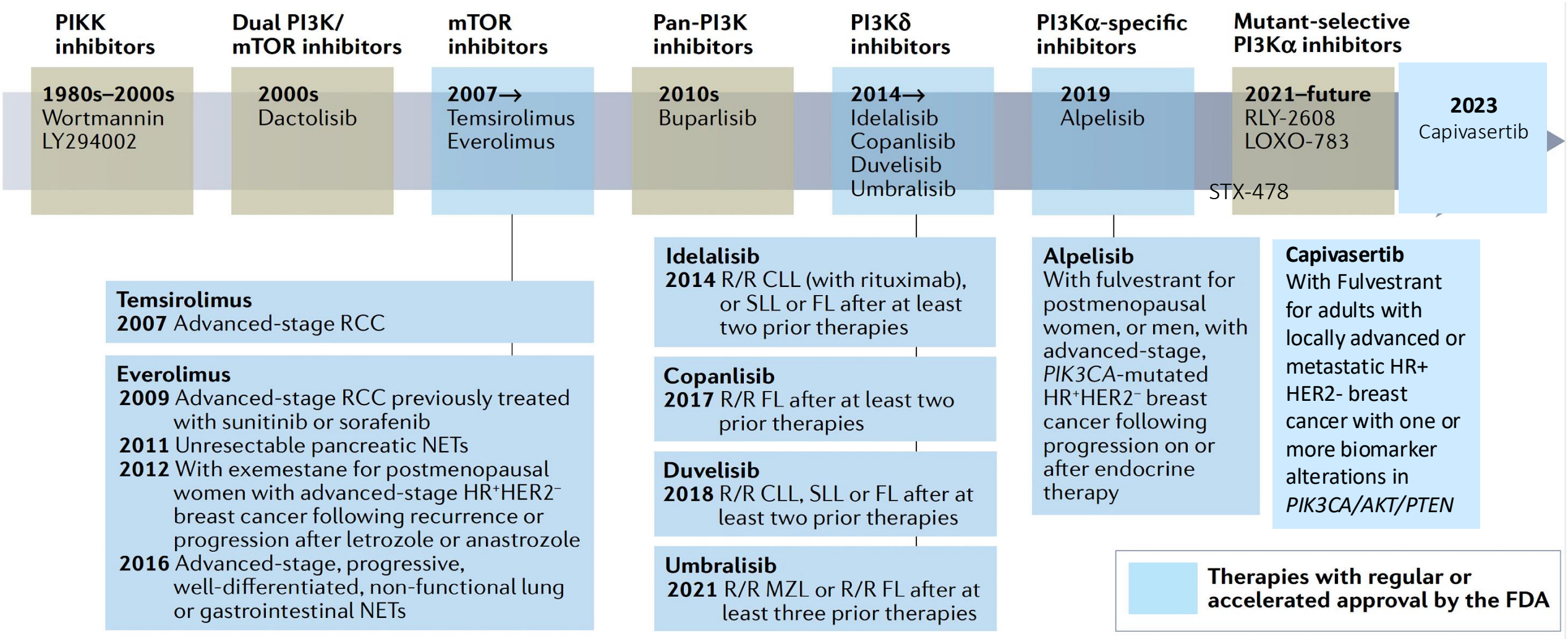


Exposure time-adjusted incidence rates were similar between treatment arms for neutropenia

Photopsia (brief flashes of light in the peripheral vision) did not impact daily activities: If experienced, visual effects had no/minimal impact on daily activities, were typically ≤1 minute, ≤3 days/week, and reversible. There were no structural changes in the eye and no changes in visual acuity

Neutropenia is reported as a group term that includes neutropenia and decreased neutrophil count; anemia is reported as a group term that includes anemia and hemoglobin decreased; leukopenia is reported as a group term that includes leukopenia and white blood cell count decrease. Bradycardia and sinus bradycardia were reported in the camizestrant + CDK4/6i arm only, in 8 patients (5.2%) and 4 patients (2.6%), respectively. No (sinus) bradycardia AEs were grade ≥3, and none of these events required treatment discontinuation. Impact of visual effects was measured using the Visual Symptom Assessment Questionnaire.

Drugging the PI3K Pathway Through the Decades



CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MZL, marginal zone lymphoma; NET, neuroendocrine tumor; R/R, relapse/refractory; RCC, renal cell carcinoma; SLL, small lymphocytic lymphoma.

Adapted from Vasan N, et al. Nat Rev Clin Oncol. 2022;19:471-485

INAVO120: A Phase III, randomized, double-blind, placebo-controlled study[1,2]

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2– aBC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **No prior therapy for aBC**
- **Fasting glucose <126 mg/dL and HbA_{1c} <6.0%**

Enrollment period: January 2020 to September 2023

N = 325

R 1:1

Inavolisib (9 mg PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)†

Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)†

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral disease (yes vs. no)
- Endocrine resistance (primary vs. secondary)‡
- Region (North America/Western Europe vs. Asia vs. Other)

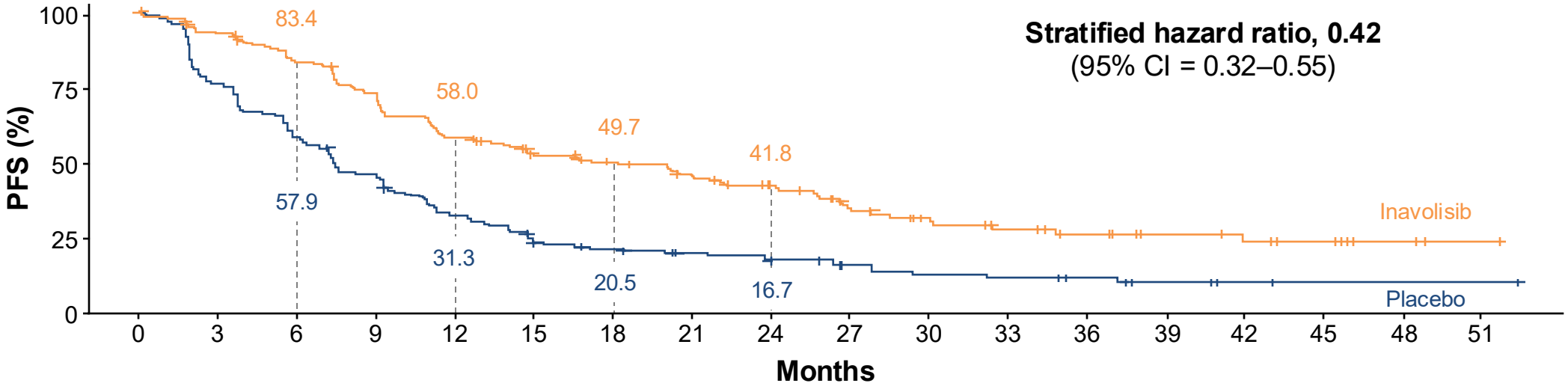
- Primary endpoint: Investigator-assessed PFS
- Secondary endpoints included: OS; investigator-assessed ORR, BOR, CBR, and DoR; PROs

ClinicalTrials.gov number, NCT04191499.
Adapted from Jhaveri KJ, *et al*. SABCS 2023 (Abstract GS03-13). * Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine, Inc.). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu); † Pre-menopausal women received ovarian suppression; ‡ Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[3]
Primary: Relapse while on the first 2 years of adjuvant ET; secondary: Relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.
aBC, advanced breast cancer; BOR, best overall response; C, cycle; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; D, day; DoR, duration of response; ET, endocrine therapy; HbA_{1c}, glycated hemoglobin; HER2–, HER2-negative; HR+, hormone receptor-positive; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, by mouth; PRO, patient-reported outcome; Q4W, every 4 weeks; QD, daily; R, randomization.
1. Turner NC, *et al. N Engl J Med* 2024; **391:**1584–1596; 2. Jhaveri KJ, *et al*. SABCS 2023 (Abstract GS03-13); 3. Cardoso F, *et al. Ann Oncol* 2018; **29:**1634–1657.

INAVO120 updated PFS

	Events, n (%)	Median, months (95% CI)
Inavolisib (n = 161)	103 (64.0)	17.2 (11.6–22.2)
Placebo (n = 164)	141 (86.0)	7.3 (5.9–9.2)

Stratified hazard ratio, 0.42
(95% CI = 0.32–0.55)



Median follow-up:
34.2 months

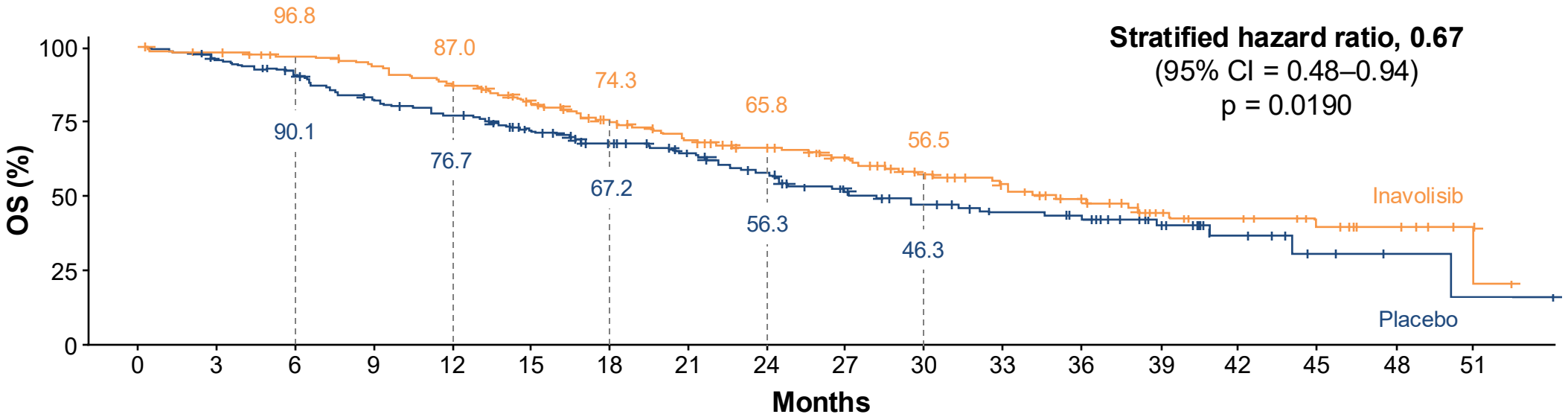
No. at risk																		
Inavolisib	161	146	129	112	89	73	65	57	46	32	25	19	15	11	10	7	3	1
Placebo	164	125	95	74	50	34	30	24	21	14	11	10	8	4	2	1	1	1

The improvement in PFS was maintained during longer follow-up

Data cutoff: November 15, 2024.
CI, confidence interval; PFS, progression-free survival.

INAVO120 key secondary endpoint: OS

	Deaths, n (%)	Median, months (95% CI)
Inavolisib (n = 161)	72 (44.7)	34.0 (28.4–44.8)
Placebo (n = 164)	82 (50.0)	27.0 (22.8–38.7)



Median follow-up: **34.2 months**

No. at risk

Inavolisib	161	155	149	142	131	114	99	88	78	67	54	43	34	22	19	13	7	1
Placebo	164	155	142	127	119	104	90	77	63	48	42	36	32	18	10	4	2	1

Improvement in median OS: 7 months. The prespecified boundary for statistical significance (p < 0.0469) was crossed

Data cutoff: November 15, 2024.
CI, confidence interval; OS, overall survival.

INAVO120 key post-progression therapies

	Inavolisib		Placebo	
Patients, n (%)	**Second line**	**Third line or greater**	**Second line**	**Third line or greater**
Discontinued treatment	111/161 (68.9)		144/164 (87.8)	
No subsequent therapy – death	17/161 (10.6)		22/164 (13.4)	
Received subsequent therapy*	83/111 (74.8)	48/111 (43.2)	109/144 (75.7)†	56/144 (38.9)
Chemotherapy (any)	46/83 (55.4)	41/48 (85.4)	79/109 (72.5)	49/56 (87.5)
Capecitabine	26/83 (31.3)	14/48 (29.2)	37/109 (33.9)	24/56 (42.9)
Paclitaxel	12/83 (14.5)	17/48 (35.4)	20/109 (18.3)	16/56 (28.6)
Eribulin	1/83 (1.2)	11/48 (22.9)	6/109 (5.5)	17/56 (30.4)
Antibody–drug conjugate (any)	1/83 (1.2)	8/48 (16.7)	1/109 (0.9)	20/56 (35.7)
Trastuzumab deruxtecan	0	6/48 (12.5)	1/109 (0.9)	16/56 (28.6)
Sacituzumab govitecan	0	2/48 (4.2)	0	8/56 (14.3)
PI3K inhibitor (any)	5/83 (6.0)	2/48 (4.2)	11/109 (10.1)	3/56 (5.4)
Alpelisib	5/83 (6.0)	2/48 (4.2)	9/109 (8.3)	2/56 (3.6)
mTOR kinase inhibitor (everolimus)	8/83 (9.6)	4/48 (8.3)	10/109 (9.2)	9/56 (16.1)
CDK4/6 inhibitor (any)	8/83 (9.6)	3/48 (6.2)	5/109 (4.6)	3/56 (5.4)
Ribociclib	1/83 (1.2)	1/48 (2.1)	5/109 (4.6)	0
Abemaciclib	2/83 (2.4)	2/48 (4.2)	0	2/56 (3.6)
Other (any)	6/83 (7.2)	0	3/109 (2.8)	5/56 (8.9)

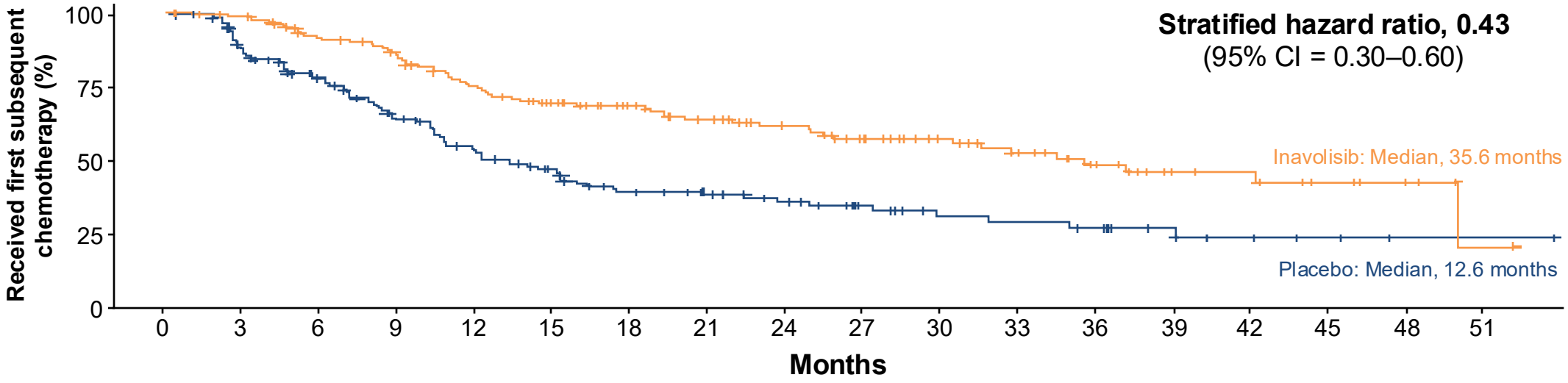
Following treatment discontinuation, fewer patients in the inavolisib group than in the placebo group received chemotherapy in the second line, antibody–drug conjugates in the third line or later, or a PI3K inhibitor in the second line or later

Data cutoff: November 15, 2024.* Twenty-eight of 111 patients (20.7%) did not receive subsequent therapy in the inavolisib arm due to PD (12 patients), death/censored (7), AEs (2), loss to follow-up (1), non-compliance with study drug (1), physician decision (1), symptomatic deterioration (1), or withdrawal by subject (3). Eleven patients in the inavolisib group had not received subsequent treatment but were documented being alive as of the clinical cutoff date. Thirty-four of 144 patients (23.6%) did not receive subsequent therapy in the placebo group due to PD (24 patients), death/censored (4), withdrawal by subject (3), symptomatic deterioration (2), or AEs (1). Twelve patients in the placebo arm had not received subsequent treatment but were documented being alive as of the clinical cutoff date; † One-hundred-and-ten patients in this group received post-progression therapies but one patient was excluded as they were listed as “not applicable” in the database.
AE, adverse event; CDK4/6, cyclin-dependent kinase 4/6; mTOR, mammalian target of rapamycin; PD, progressive disease; PI3K, phosphatidylinositol 3-kinase.

INAVO120 time to first subsequent chemotherapy

	Events n, (%)	Median, months (95% CI)
Inavolisib (n = 161)	64 (39.8)	35.6 (25.4–NR)
Placebo (n = 164)	94 (57.3)	12.6 (10.4–16.1)

Stratified hazard ratio, 0.43
(95% CI = 0.30–0.60)



Median follow-up:
34.2 months

No. at risk																		
Inavolisib	161	153	136	122	104	89	77	67	57	47	39	31	23	14	13	9	5	1
Placebo	164	134	111	89	68	58	45	40	31	22	16	15	13	9	5	3	1	1

Median time to first subsequent chemotherapy was substantially delayed by almost 2 years (23 months)

Data cutoff: November 15, 2024.
CI, confidence interval; NR, not reached.

INAVO120 overview of AEs

Patients, n (%) with at least one:	Inavolisib (n = 161)	Placebo (n = 163)
Any-grade AE	161 (100)	163 (100)
Grade 3–4 AE	146 (90.7)	138 (84.7)
Grade 5 AE*	6 (3.7)	2 (1.2)
Serious AE	44 (27.3)	22 (13.5)
AE leading to discontinuation of treatment		
Inavolisib/placebo	11 (6.8)	1 (0.6)
Palbociclib	10 (6.2)	0
Fulvestrant	6 (3.7)	0
AE leading to dose reduction of treatment		
Inavolisib/placebo	24 (14.9)	6 (3.7)
Palbociclib	65 (40.4)	56 (34.4)

There was a low discontinuation rate due to AEs

Data cutoff: November 15, 2024. AE severity was graded per National Cancer Institute Common Terminology Criteria for AEs v5.0. * None of the grade 5 AEs were reported as related to study treatment by investigators.
The grade 5 AEs reported were cerebral hemorrhage, cerebrovascular accident, gastrointestinal hemorrhage, acute coronary syndrome, death, and COVID-19 in the inavolisib group, and COVID-19 pneumonia, and cardiac arrest in the placebo group.[1]
AE, adverse event. 1. Turner NC, *et al. N Engl J Med* 2024; **391:**1584–1596.

INAVO120 selected AEs*

	Inavolisib (n = 161)		Placebo (n = 163)	
Patients, n (%)	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
Neutropenia	147 (91.3)	133 (82.6)	148 (90.8)	131 (80.4)
Thrombocytopenia	80 (49.7)	22 (13.7)	75 (46.0)	8 (4.9)
Stomatitis or mucosal inflammation	89 (55.3)	9 (5.6)	47 (28.8)	0
Anemia	64 (39.8)	11 (6.8)	62 (38.0)	3 (1.8)
Hyperglycemia	102 (63.4)	11 (6.8)	22 (13.5)	0
Diarrhea†	84 (52.2)	6 (3.7)	26 (16.0)	0
Nausea	47 (29.2)	0	32 (19.6)	0
Rash	43 (26.7)	0	32 (19.6)	1 (0.6)
Ocular toxicities‡	47 (29.2)	1 (0.6)	26 (16.0)	0
Aspartate transaminase/ alanine transaminase increase	34 (21.1)	7 (4.3)	37 (22.7)	4 (2.5)
Vomiting	26 (16.1)	2 (1.2)	10 (6.1)	2 (1.2)
Lymphopenia	6 (3.7)	1 (0.6)	15 (9.2)	3 (1.8)
Pneumonitis§	5 (3.1)	1 (0.6)	2 (1.2)	0

Longer exposure to inavolisib did not lead to a new safety signal, nor changes in the safety profile

Data cutoff: November 15, 2024. AEs in bold are key risks. * Grouped by medical concept; † Grade 2 (which is impactful on quality of life) in 29 patients (18.0%) in the inavolisib group and in seven patients (4.3%) in the placebo group; All were grades 1 or 2. with the exception of one Grade 3 cataract unrelated to inavolisib treatment
‡ The most common ocular toxicities observed were dry eye in 14 patients in the inavolisib group (8.7%) and seven patients in the placebo group (4.3%), and blurred vision in eight (5.0%) and two patients (1.2%), respectively.
§ Two patients each (1.2%) at grades 1 and 2. AE, adverse event.

Toxicity Summary : Everolimus, Capivasertib, Alpelisib, Inavolisib

	Alpelisib (PI3Ki)		Inavolisib (PI3Ki)		Capivasertib (AKTi)		Everolimus (mTORi)	
Toxicity	**All grades**	**Grade 3+**	**All Grades**	**Grade 3+**	**All grades**	**Grade 3+**	**All grades**	**Grade 3+**
Diarrhea %	57.7	6.7	48.1	3.7	72.4	9.3	30	2
Rash %	35.6	9.9	25.3	0	38	12.1	36	1
Hyperglycemia %	63.7	36.6	58.6	5.6	16.9	2	13	4
Stomatitis %	24.6	2.5	51.2	5.6	14.6	2	56	8
Discontinuation rate	**25%**		**6.8%**		**13%**		**19%**	

Rugo et al Ann Oncology 2020; Rugo et al ASCO 2023; Baselga et al NEJM 2012; Jhaveri et al SABCS 2023

A 65-year-old woman presents with de novo ER-positive, HER2-negative (IHC 0) mBC with asymptomatic bone metastases. Regulatory and reimbursement issues aside, which endocrine-based treatment would you most likely recommend if biomarker evaluation revealed a PIK3CA mutation?

 Dr Burstein	Palbociclib + AI
 Dr Cortés	Palbociclib + AI
 Prof Dent	Ribociclib + AI
 Dr Kalinsky	Ribociclib + AI
 Dr O'Shaughnessy	Ribociclib + AI
 Dr Rugo	Ribociclib + AI
 Dr Hurvitz	Ribociclib + AI
 Dr Jhaveri	Ribociclib + AI

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0) breast cancer has developed multiple metastases 2 years after completing 5 years of adjuvant anastrozole. Regulatory and reimbursement issues aside, which endocrine-based treatment would you most likely recommend for this patient if biomarker evaluation results were as follows?

	ESR1-, PIK3CA-, AKT/PTEN-	ESR1-, PIK3CA+, AKT/PTEN-
 Dr Burstein	Palbociclib + fulvestrant	Capivasertib + ET or IPF
 Dr Cortés	Palbociclib + AI	Palbociclib + AI
 Prof Dent	Ribociclib + AI	Ribociclib + AI
 Dr Kalinsky	Ribociclib + AI	Ribociclib + AI
 Dr O'Shaughnessy	Abemaciclib + fulvestrant	IPF
 Dr Rugo	Ribociclib + AI	Ribociclib + AI
 Dr Hurvitz	Ribociclib + fulvestrant or ribociclib + AI	Ribociclib + fulvestrant
 Dr Jhaveri	Ribociclib + AI	Ribociclib + AI

ET = endocrine therapy; IPF = inavolisib, palbociclib and fulvestrant

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0) breast cancer has developed multiple metastases 2 years after starting adjuvant anastrozole. Regulatory and reimbursement issues aside, which endocrine-based treatment would you most likely recommend for this patient if biomarker evaluation results were as follows?

	ESR1-, PIK3CA+, AKT/PTEN-	ESR1-, PIK3CA-, AKT/PTEN+	ESR1+, PIK3CA+, AKT/PTEN-
 Dr Burstein	Capivasertib + ET or IPF	Capivasertib + ET	Imlunestrant + abemaciclib
 Dr Cortés	IPF	Abemaciclib + fulvestrant	IPF
 Prof Dent	IPF	Capivasertib + fulvestrant	IPF
 Dr Kalinsky	IPF	Ribociclib + fulvestrant	IPF
 Dr O'Shaughnessy	IPF	Abemaciclib + fulvestrant	Imlunestrant + abemaciclib
 Dr Rugo	IPF	Capivasertib + fulvestrant	IPF
 Dr Hurvitz	IPF	Ribociclib + fulvestrant	IPF
 Dr Jhaveri	IPF	Ribociclib + fulvestrant	Imlunestrant + abemaciclib

IPF = inavolisib, palbociclib and fulvestrant

Regulatory and reimbursement issues aside, do you believe the emerging results from the Phase III SERENA-6 study justify the routine use of circulating tumor DNA (ctDNA) monitoring for early detection of ESR1 mutations?
If so, how often would you conduct ctDNA analysis?

	Use of ctDNA	Frequency of ctDNA analysis
 Dr Burstein	Yes	—
 Dr Cortés	I'm not sure	N/A
 Prof Dent	Yes	Every 3 months
 Dr Kalinsky	Yes	Every 3 months
 Dr O'Shaughnessy	Yes	Every 3 months
 Dr Rugo	I'm not sure	Every 3 to 4 months
 Dr Hurvitz	No	N/A
 Dr Jhaveri	No	N/A

Regulatory and reimbursement issues aside, do you believe the emerging results from the Phase III SERENA-6 study justify an early change in treatment from an AI to an oral selective estrogen receptor degrader for patients with ER-positive, HER2-negative mBC in whom an ESR1 mutation is identified during first-line therapy?

 Dr Burstein	No
 Dr Cortés	I'm not sure
 Prof Dent	I'm not sure - likely
 Dr Kalinsky	Awaiting maturity of PFS2 data
 Dr O'Shaughnessy	Yes
 Dr Rugo	I'm not sure
 Dr Hurvitz	No
 Dr Jhaveri	Not yet - awaiting PFS2 and OS data

RTP RESEARCH TO PRACTICE

Agenda

MODULE 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Cortés

MODULE 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Kalinsky

MODULE 3: Available Therapies for Patients with HR-Positive, HER2-Negative Disease Progressing on CDK4/6 Inhibition — Dr Burstein

MODULE 4: Current and Potential Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Dr O'Shaughnessy

MODULE 5: Current and Future Strategies for Patients with Endocrine-Refractory HR-Positive mBC — Dr Rugo

MODULE 6: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Prof Dent

RTP RESEARCH TO PRACTICE

Targeted Treatments for advanced, ER+ breast cancer

Harold J. Burstein, MD, PhD

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

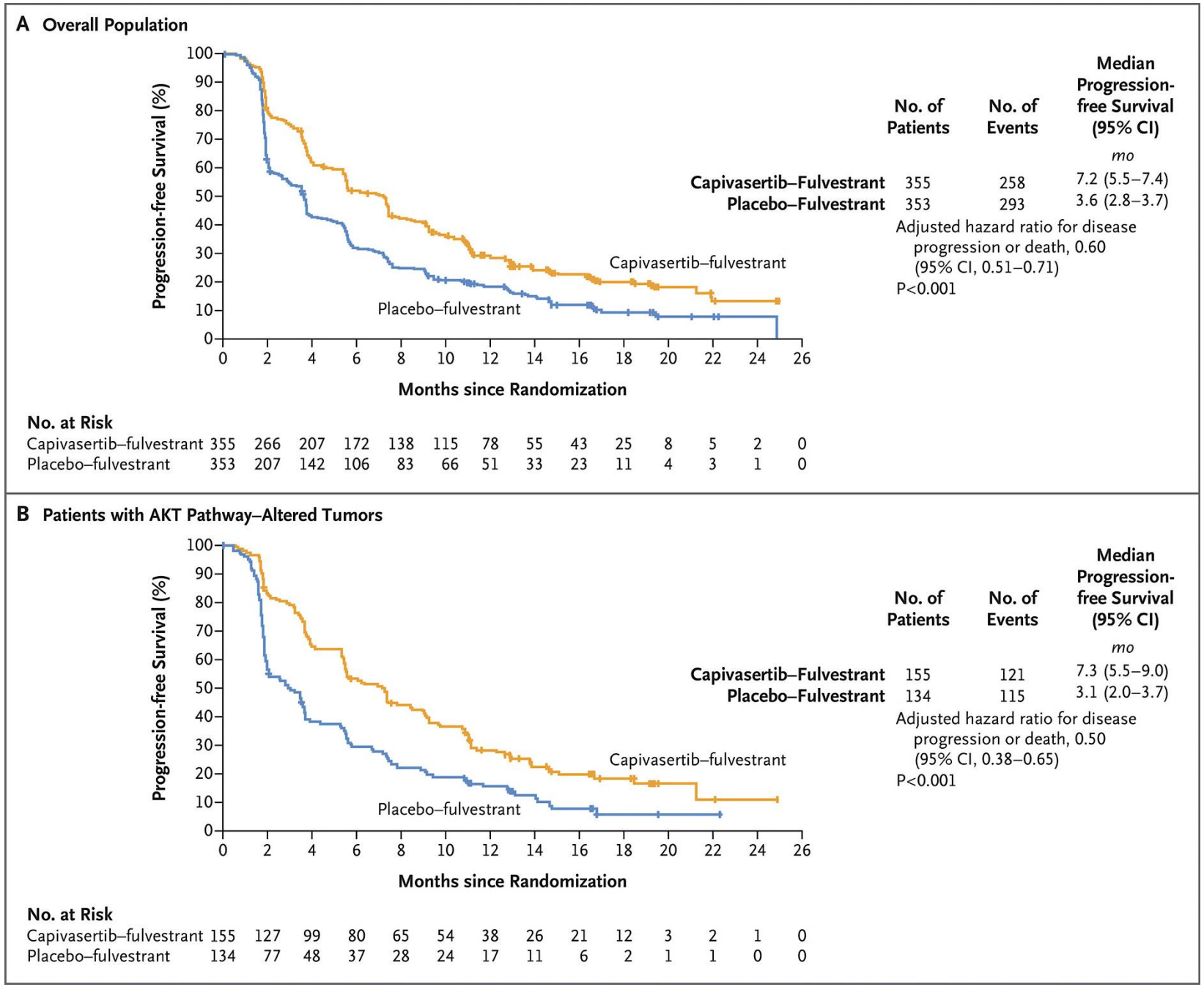
Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

CAPItello-291



N Engl J Med 2023;388:2058-2070

Phase III CAPItello-291: Safety

Table 2. Most Frequent Adverse Events in the Overall Population (Safety Population).*

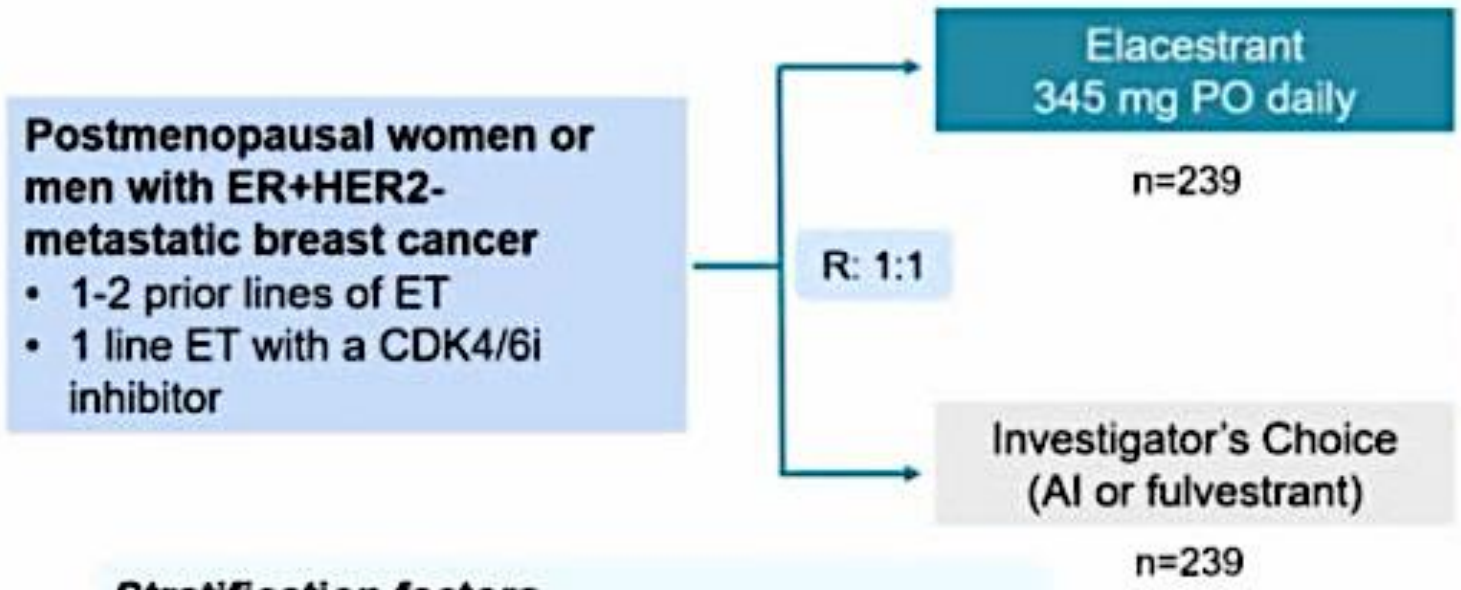
Event	Capivasertib–Fulvestrant (N=355)					Placebo–Fulvestrant (N=350)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	343 (96.6)	52 (14.6)	139 (39.2)	139 (39.2)	9 (2.5)	288 (82.3)	115 (32.9)	118 (33.7)	44 (12.6)	10 (2.9)
Diarrhea	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	70 (20.0)	60 (17.1)	9 (2.6)	1 (0.3)	0
Rash†	135 (38.0)	57 (16.1)	35 (9.9)	43 (12.1)	0	25 (7.1)	19 (5.4)	5 (1.4)	1 (0.3)	0
Nausea	123 (34.6)	85 (23.9)	35 (9.9)	3 (0.8)	0	54 (15.4)	42 (12.0)	10 (2.9)	2 (0.6)	0
Fatigue	74 (20.8)	49 (13.8)	23 (6.5)	2 (0.6)	0	45 (12.9)	35 (10.0)	8 (2.3)	2 (0.6)	0
Vomiting	73 (20.6)	54 (15.2)	13 (3.7)	6 (1.7)	0	17 (4.9)	10 (2.9)	5 (1.4)	2 (0.6)	0
Headache	60 (16.9)	47 (13.2)	12 (3.4)	1 (0.3)	0	43 (12.3)	33 (9.4)	8 (2.3)	2 (0.6)	0
Decreased appetite	59 (16.6)	37 (10.4)	21 (5.9)	1 (0.3)	0	22 (6.3)	11 (3.1)	9 (2.6)	2 (0.6)	0
Hyperglycemia	58 (16.3)	24 (6.8)	26 (7.3)	7 (2.0)	1 (0.3)	13 (3.7)	8 (2.3)	4 (1.1)	1 (0.3)	0
Stomatitis	52 (14.6)	24 (6.8)	21 (5.9)	7 (2.0)	0	17 (4.9)	15 (4.3)	2 (0.6)	0	0
Asthenia	47 (13.2)	29 (8.2)	14 (3.9)	4 (1.1)	0	36 (10.3)	31 (8.9)	3 (0.9)	2 (0.6)	0
Pruritus	44 (12.4)	32 (9.0)	10 (2.8)	2 (0.6)	0	23 (6.6)	19 (5.4)	4 (1.1)	0	0
Anemia	37 (10.4)	15 (4.2)	15 (4.2)	7 (2.0)	0	17 (4.9)	4 (1.1)	9 (2.6)	4 (1.1)	0
Urinary tract infection	36 (10.1)	8 (2.3)	23 (6.5)	5 (1.4)	0	23 (6.6)	2 (0.6)	21 (6.0)	0	0

* The safety population included all the patients who received at least one dose of capivasertib, fulvestrant, or placebo. The listed events were reported as a single term (or for rash, as a group term) in at least 10% of the patients for any grade in the capivasertib–fulvestrant group. Adverse events are reported regardless of the relationship to capivasertib, fulvestrant, or placebo.

† The group term of rash includes the preferred terms of rash, rash macular, maculopapular rash, rash papular, and rash pruritic.

Turner et al. *N Engl J Med* 2023;388:2058-70

EMERALD (Study RAD1901-308)



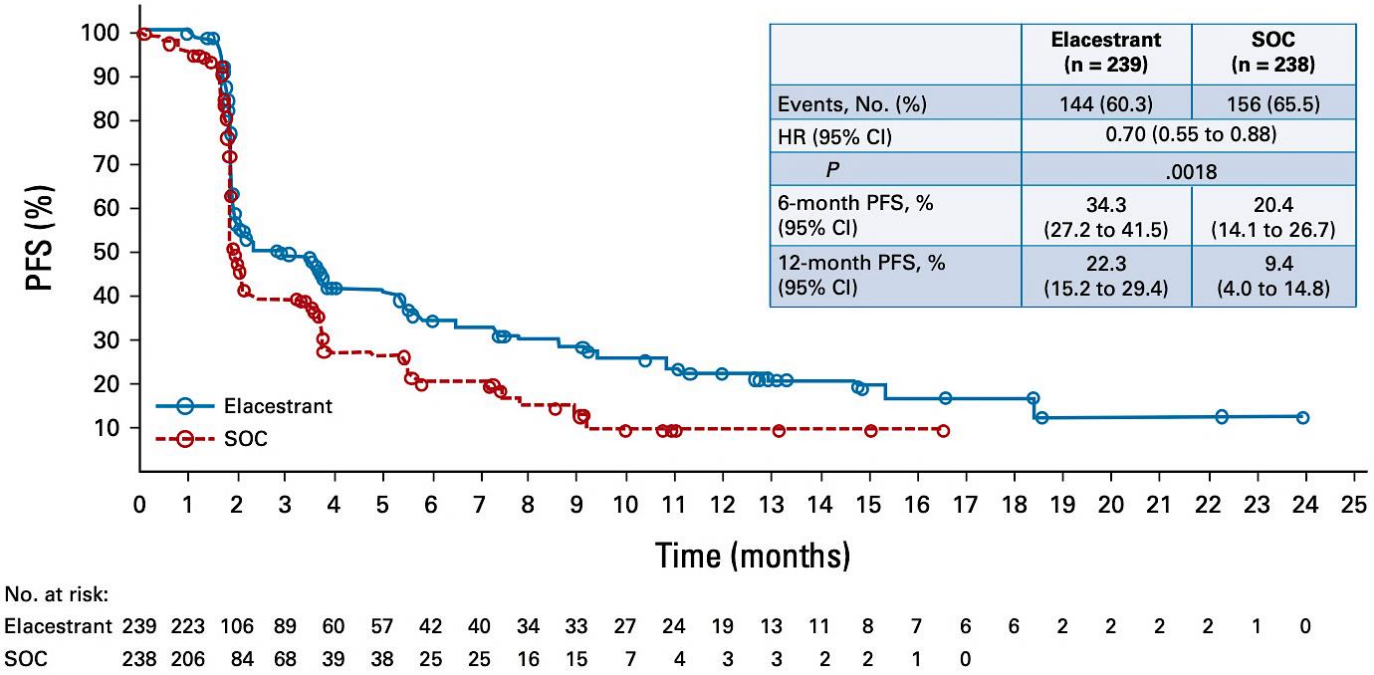
Primary endpoint
- PFS per BICR in *ESR1*-mut and ITT

Secondary endpoint
- OS in *ESR1*-mut and ITT

Stratification factors
- *ESR1* mutation(s) (detected or not detected)
- Prior treatment with fulvestrant (yes or no)
- Visceral metastases (yes or no)

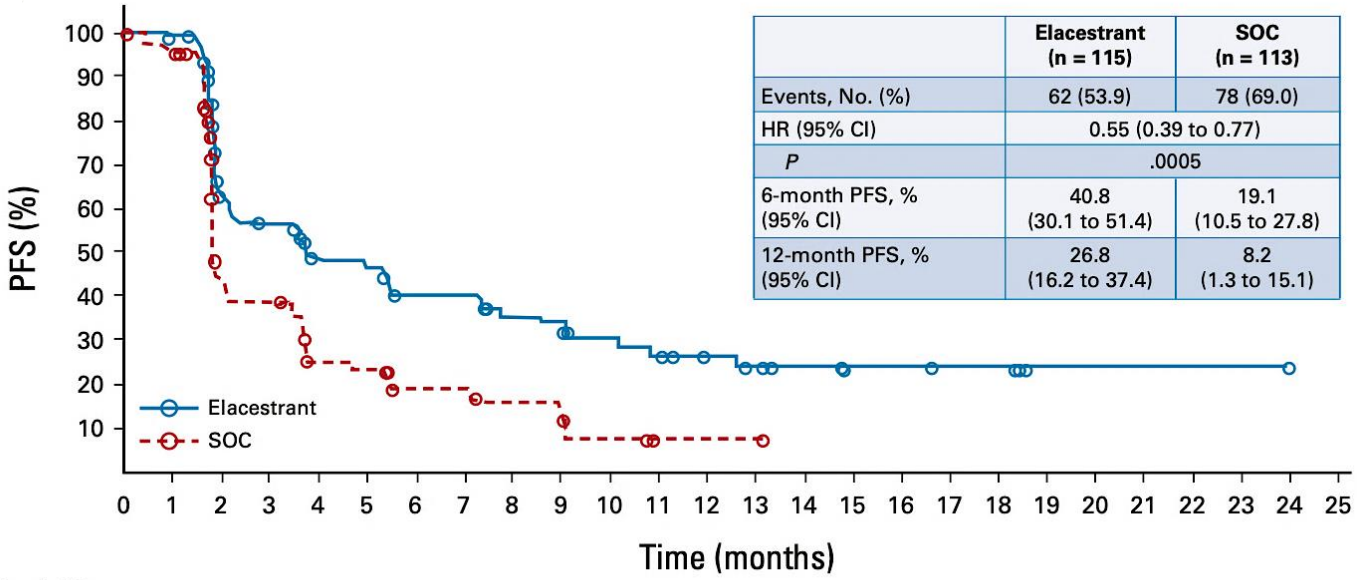
EMERALD: Efficacy Results

PFS in all patients



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

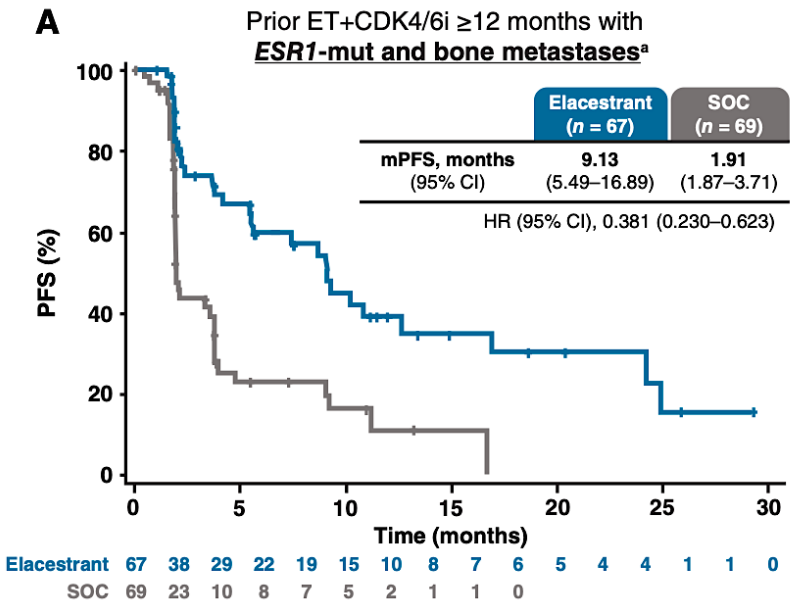
PFS in ESR1m patients

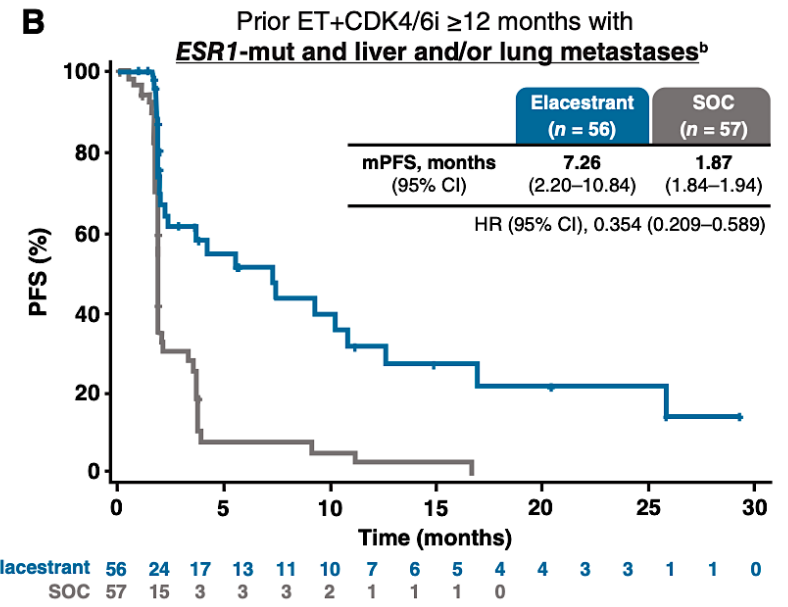


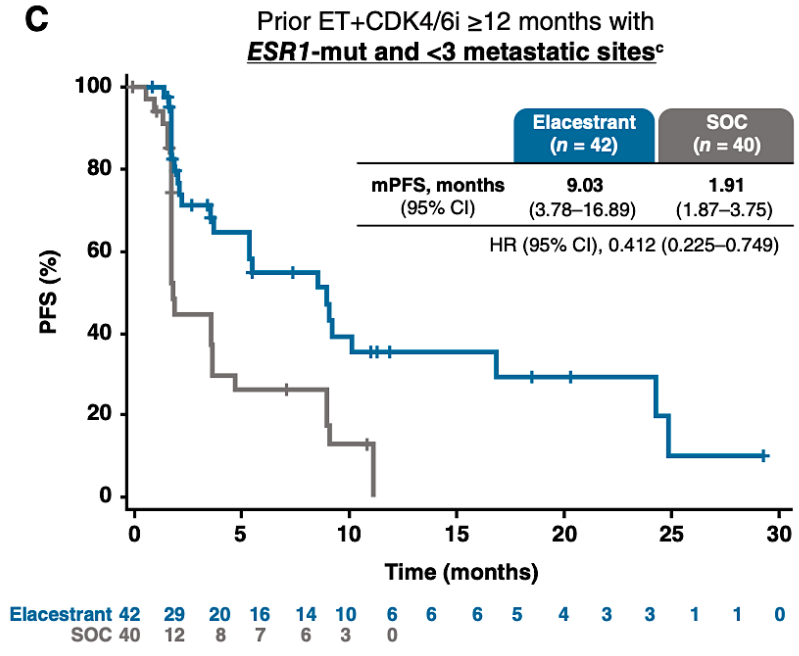
	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

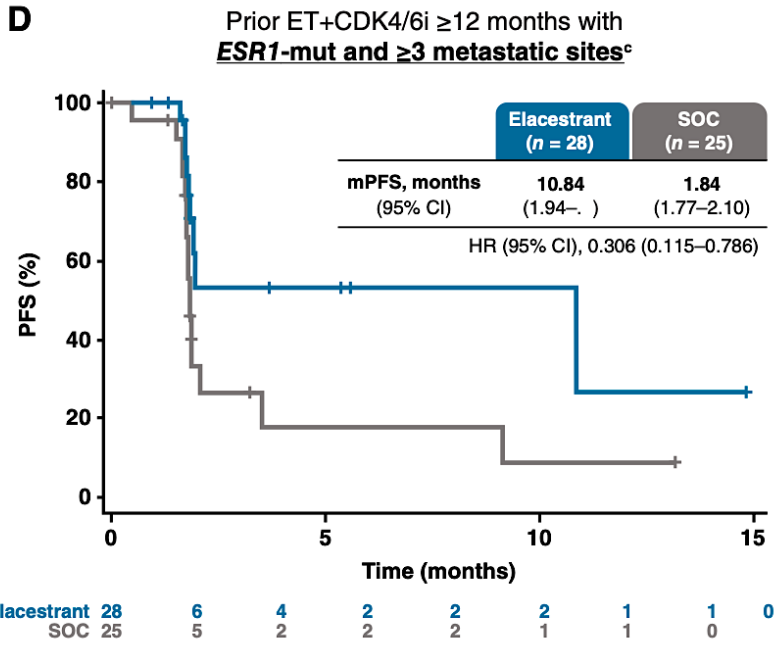
Bidard FC et al. *J Clin Oncol* 2022;40(28):3246-3256.

EMERALD: Subgroup Analyses









Bardia A et al. *Clin Cancer Res* 2024;30(19):4299-4309.

EMERALD: Safety Profile

AEs[c] Occurring in ≥ 10% of Patients in Any Arm	Elacestrant		Total	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)[d]	6 (2.5)	43 (18.8)	2 (0.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)
Vomiting	45 (19.0)[e]	2 (0.8)	19 (8.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0
Diarrhea	33 (13.9)	0	23 (10.0)	2 (0.9)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0
Constipation	29 (12.2)	0	15 (6.6)	0
Hot flush	27 (11.4)	0	19 (8.3)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)

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

EMBER-3 Study Design

ER+, HER2- ABC

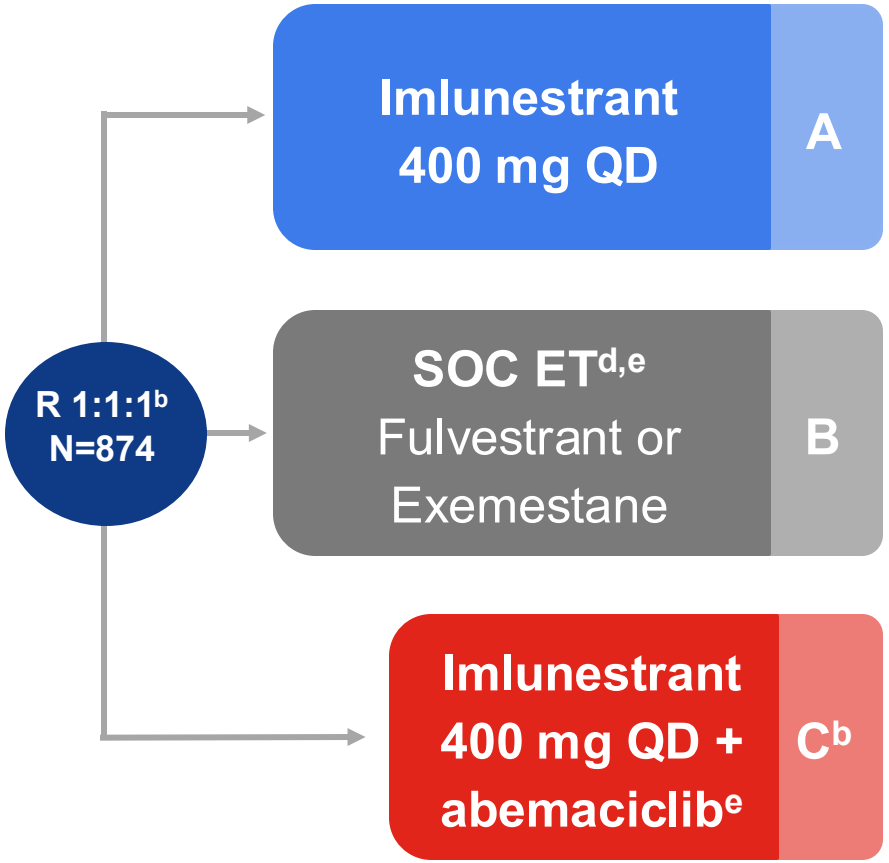
Men and Pre-[a]/Post-menopausal women

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]



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

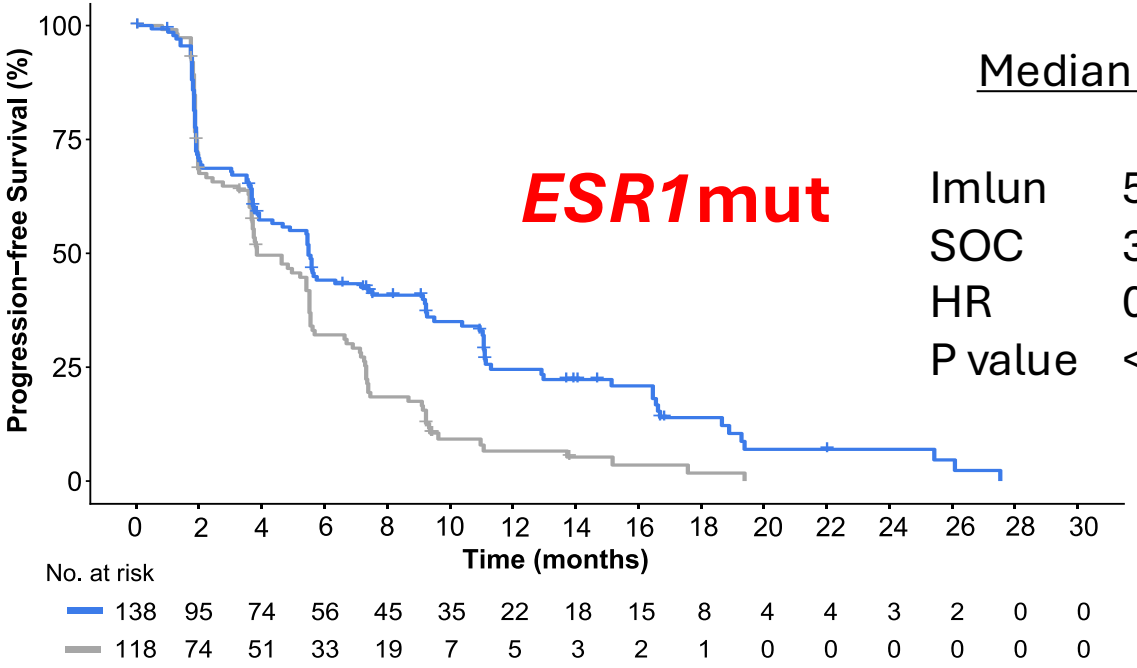
Exploratory Endpoints

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

ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 to November 2023 across 195 sites in 22 countries. [a] A GnRH agonist was required in men and premenopausal women; [b] Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c] East Asia vs United States/European Union vs others; [d] Investigator's choice; [e] Labeled dose; [f] Scans every 8 weeks for the first 12 months, then every 12 weeks; [g] *ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h] Analysis conducted in all concurrently randomized patients.

EMBER-3:
Outcomes by tumor ESR1 status

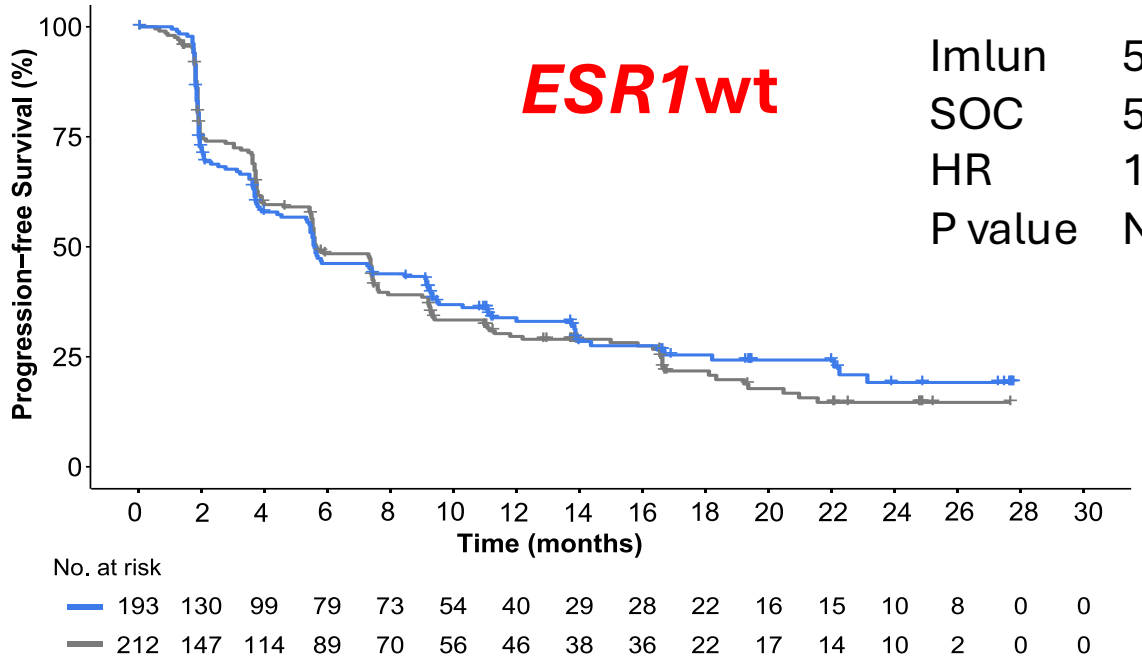
Imlunestrant vs SOC



***ESR1*mut**

Median PFS

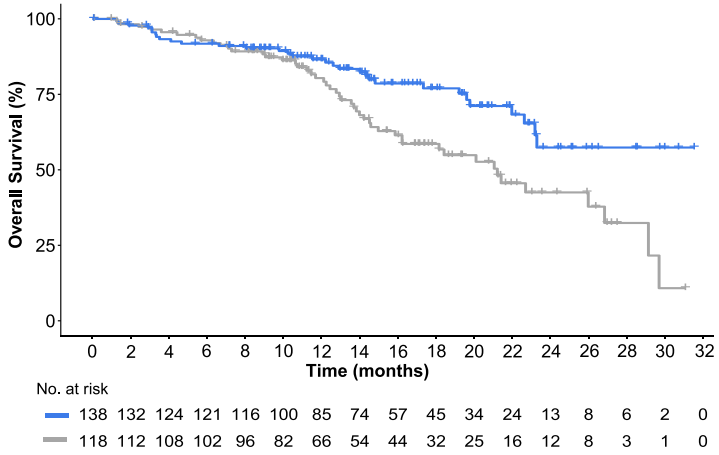
Imlun	5.5 m
SOC	3.8 m
HR	0.62
P value	< 0.001



***ESR1*wt**

Imlun	5.6 m
SOC	5.7 m
HR	1.0
P value	NS

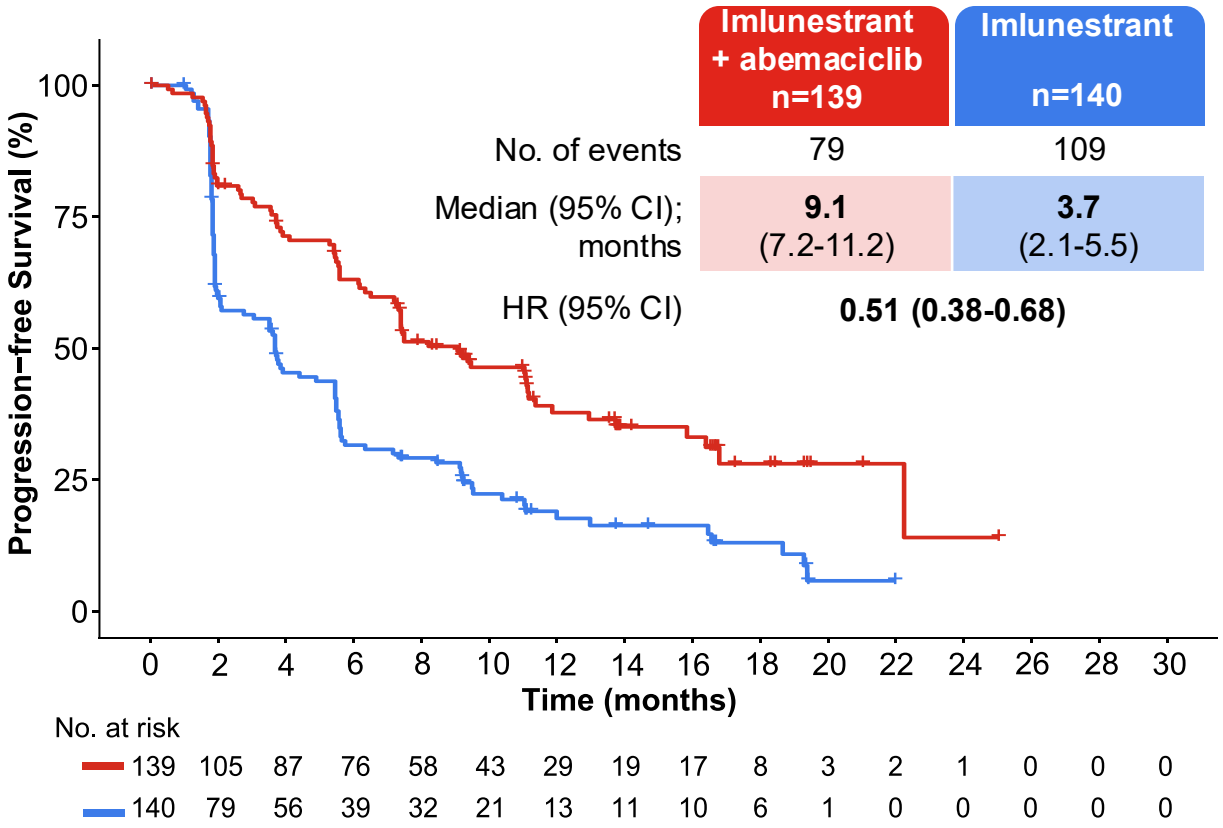
Overall Survival in ESR1mut



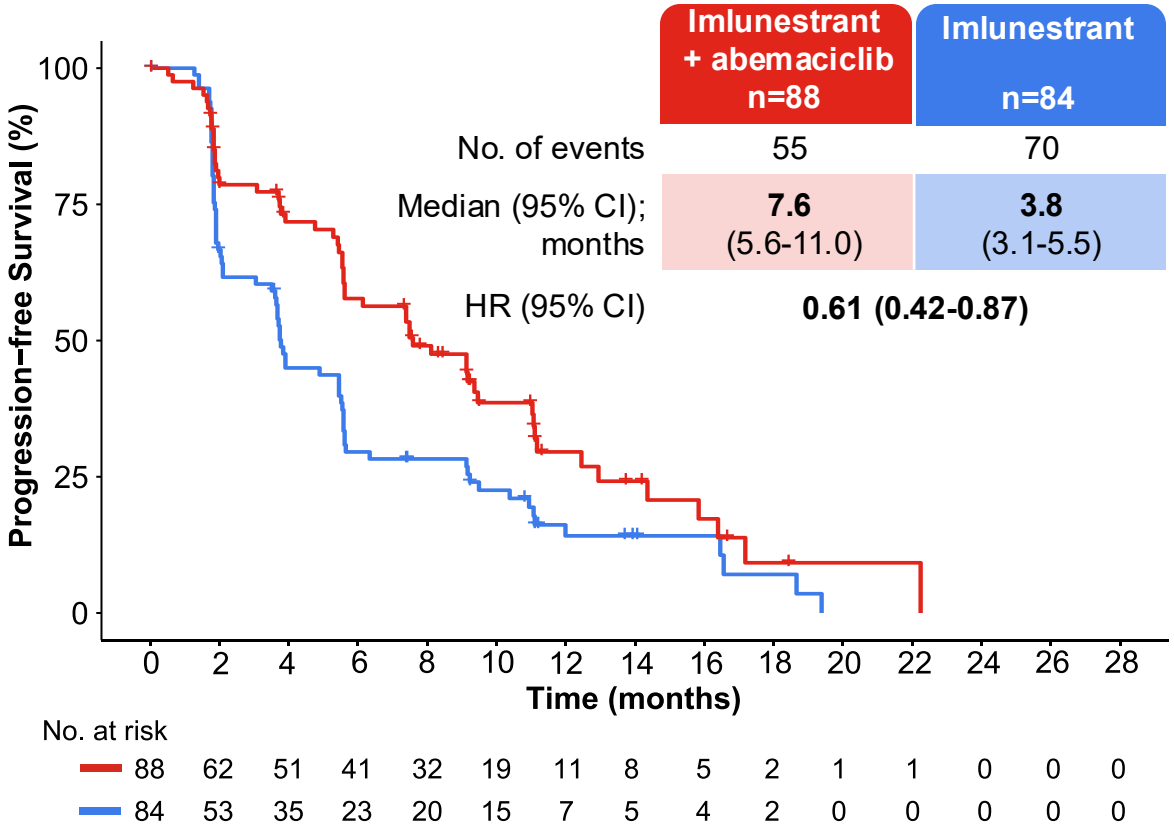
N Engl J Med 2025;392:1189-1202

Subgroup Analysis: Imlunestrant + Abemaciclib vs Imlunestrant Investigator-assessed PFS in Key Clinical Subgroups

Patients with prior CDK4/6i treatment

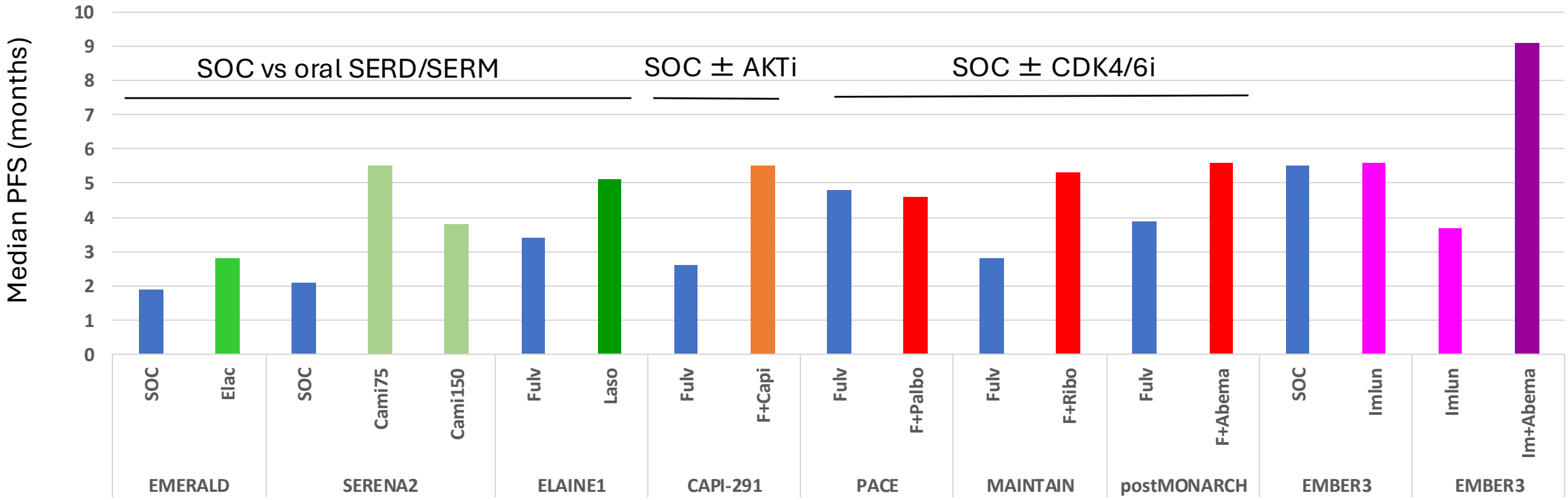


Patients with PI3K pathway mutation[a]



Jhaveri K et al. SABCS 2024

Median Progression Free Survival in Recent Randomized Trials of Endocrine Therapy: *Outcomes among patients with prior CDK4/6 inhibitor treatment**



*there are a lot of problems with cross study comparisons, especially in unplanned subset analyses:
extent/types of prior therapy, variable tumor genomics/biomarker profile,
SOC options, sample size, exposure vs resistance, investigator vs BICR, etc.

** Denotes subset of larger study cohort

VERITAC-2: Global Phase 3 Trial of Vepdegestrant

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

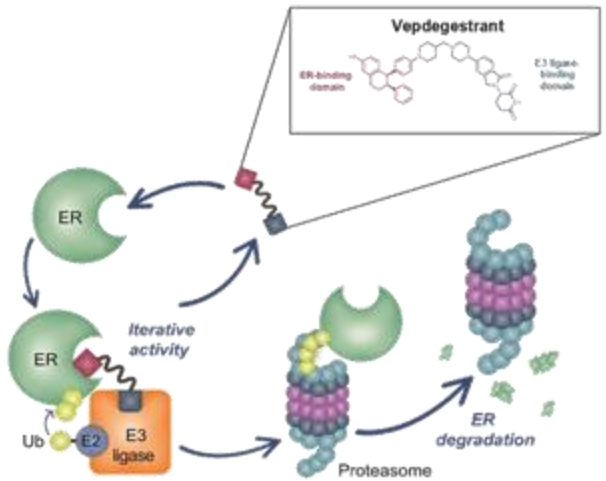
Vepdegestrant (n=313)
200 mg orally (once daily)

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



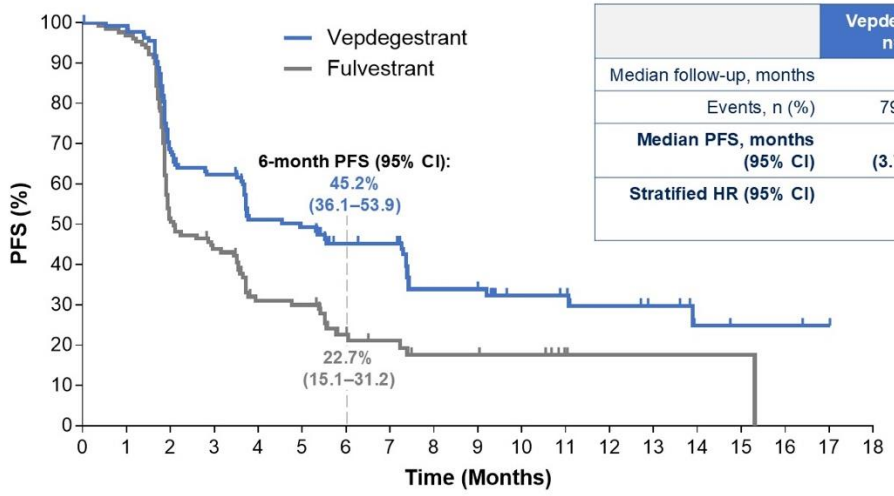
Vepdegestrant has a unique MOA that directly harnesses the ubiquitin-proteasome system to degrade ER[8]

Data cutoff date: Jan 31, 2025
Clinicaltrials.gov: NCT05654623

[a]*ESR1*m status was assessed in ctDNA by Foundation Medicine, except in China, where Origmed testing was used.
AE=adverse event; BICR=blinded independent central review; CBR=clinical benefit rate; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; *ESR1*m=estrogen receptor 1 gene mutation; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; IM=intramuscularly; ORR=objective response rate; OS=overall survival; PFS=progression-free survival, SERD=selective estrogen receptor degrader.

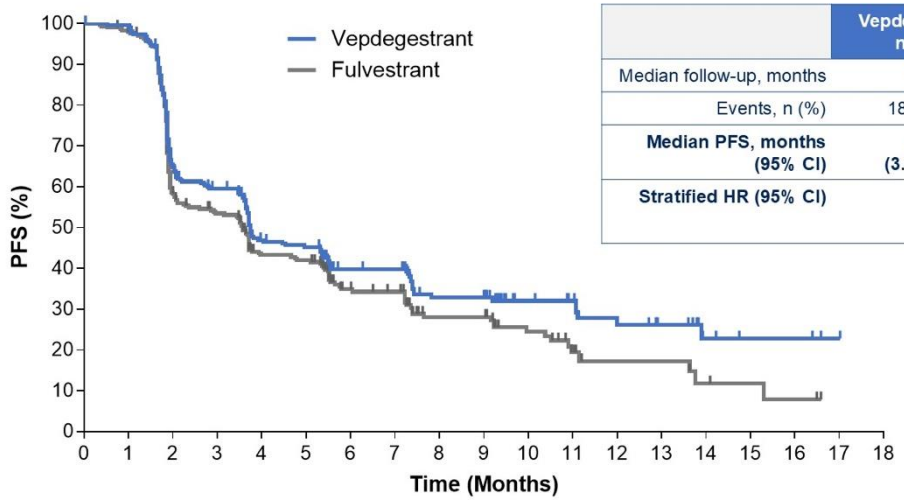
Phase III VERITAC-2: Key Endpoints

PFS by BICR in Patients With *ESR1*m

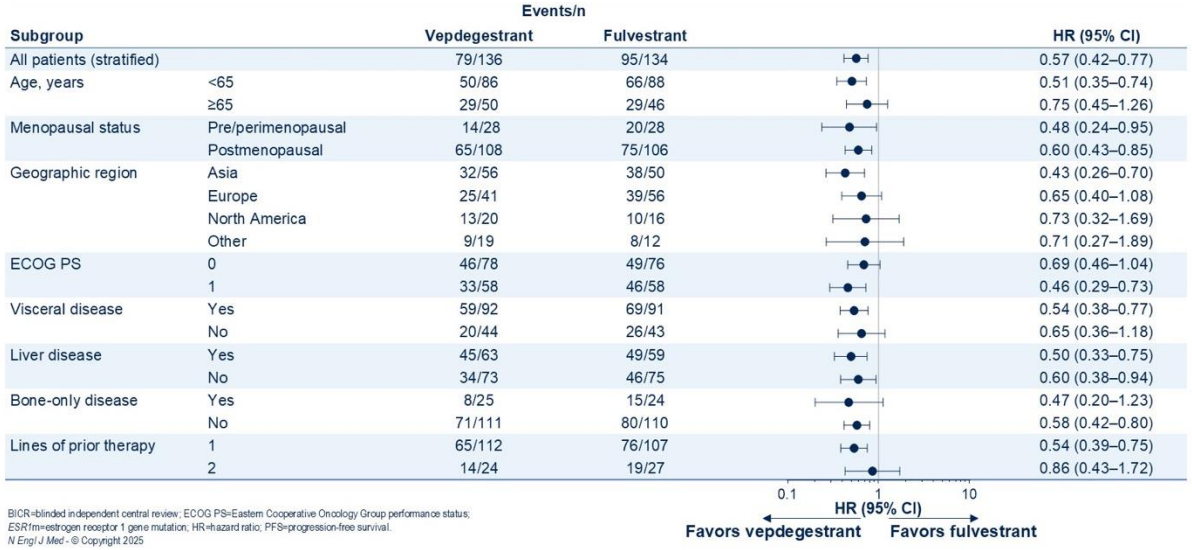


	Vepdegestrant n=136	Fulvestrant n=134
Median follow-up, months	7.4	6.0
Events, n (%)	79 (58)	95 (71)
Median PFS, months (95% CI)	**5.0 (3.7–7.4)**	**2.1 (1.9–3.5)**
Stratified HR (95% CI)	**0.57 (0.42–0.77)**	
	2-sided *P*<0.001	

PFS by BICR in All Patients



	Vepdegestrant n=313	Fulvestrant n=311
Median follow-up, months	7.4	7.2
Events, n (%)	186 (59)	198 (64)
Median PFS, months (95% CI)	**3.7 (3.6–5.3)**	**3.6 (2.2–3.8)**
Stratified HR (95% CI)	**0.83 (0.68–1.02)**	
	2-sided *P*=0.07	



Subgroup		Events/n Vepdegestrant	Fulvestrant	HR (95% CI)
All patients (stratified)		79/136	95/134	0.57 (0.42–0.77)
Age, years	<65	50/86	66/88	0.51 (0.35–0.74)
	≥65	29/50	29/46	0.75 (0.45–1.26)
Menopausal status	Pre/perimenopausal	14/28	20/28	0.48 (0.24–0.95)
	Postmenopausal	65/108	75/106	0.60 (0.43–0.85)
Geographic region	Asia	32/56	38/50	0.43 (0.26–0.70)
	Europe	25/41	39/56	0.65 (0.40–1.08)
	North America	13/20	10/16	0.73 (0.32–1.69)
	Other	9/19	8/12	0.71 (0.27–1.89)
ECOG PS	0	46/78	49/76	0.69 (0.46–1.04)
	1	33/58	46/58	0.46 (0.29–0.73)
Visceral disease	Yes	59/92	69/91	0.54 (0.38–0.77)
	No	20/44	26/43	0.65 (0.36–1.18)
Liver disease	Yes	45/63	49/59	0.50 (0.33–0.75)
	No	34/73	46/75	0.60 (0.38–0.94)
Bone-only disease	Yes	8/25	15/24	0.47 (0.20–1.23)
	No	71/111	80/110	0.58 (0.42–0.80)
Lines of prior therapy	1	65/112	76/107	0.54 (0.39–0.75)
	2	14/24	19/27	0.86 (0.43–1.72)

BICR=blinded independent central review; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*m=estrogen receptor 1 gene mutation; HR=hazard ratio; PFS=progression-free survival.

Interim OS data were immature at data cutoff

Hamilton E et al. ASCO 2025;Abstract LBA1000.

Phase III VERITAC-2: Safety (All Treated Patients)

Overview

TEAEs, %	Vepdegestrant (n=312)	Fulvestrant (n=307)
Any grade	87	81
Grade ≥3	23	18
Serious	10	9
Leading to treatment discontinuation	3	1
Leading to dose reduction	2	NA
TRAEs, %		
Any grade	57	40
Grade ≥3	8	3

QT prolongation

- TEAEs: vepdegestrant,10%; fulvestrant, 1%
- A QT interval sub-study (n=88) confirmed a mild increase (11.1 ms) from baseline in mean QTcF, with upper 90% CI (13.7 ms) <20 ms,[f] **indicating no large QT-prolonging effect**

TEAEs in >10% of Patients in Either Group

TEAE, %	Vepdegestrant (n = 312)		Fulvestrant (n = 307)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Fatigue[a]	27	1	16	1
ALT increased[b]	14	1	10	1
AST increased[b]	14	1	10	3
Nausea	13	0	9	1
Anemia[b, c]	12	2	8	3
Neutropenia[d]	12	2[e]	5	1[e]
Back pain	11	1	7	<1
Arthralgia	11	1	11	0
Decreased appetite	11	<1	5	0

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GI=gastrointestinal; QTcF=corrected QT interval using Fridericia's method; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.
[a]Includes fatigue and asthenia. [b]No between-group differences were observed for ALT/AST increases or anemia based on laboratory values. [c]Includes anemia, hemoglobin decreased, and iron deficiency anemia. [d]Includes neutropenia and neutrophil count decreased. No events led to dose reductions or treatment discontinuation in either treatment group. There were no events of febrile neutropenia in the vepdegestrant group and 1 event of grade 2 febrile neutropenia in the fulvestrant group. [e]1 patient with grade 4 event. [f]Based on a concentration-QTc population modeling analysis.

Deaths occurred in 43 patients with ESR1m and 80 patients overall, representing 22% and 20% of targeted events, respectively

Hamilton E et al. ASCO 2025;Abstract LBA1000.

A 65-year-old woman presents with de novo ER-positive, HER2-negative (IHC 0) mBC, receives ribociclib with anastrozole and initially responds but then experiences disease progression 2 years later. Regulatory and reimbursement issues aside, which treatment would you most likely recommend for this patient if biomarker evaluation results were as follows?

	ESR1-, PIK3CA-, AKT/PTEN-	ESR1-, PIK3CA+, AKT/PTEN-	ESR1-, PIK3CA-, AKT/PTEN+
 Dr Burstein	Abemaciclib + fulvestrant	Capivasertib + fulvestrant	Capivasertib + fulvestrant
 Dr Cortés	Exemestane/everolimus	Capivasertib + fulvestrant	Capivasertib + fulvestrant
 Prof Dent	Abemaciclib + fulvestrant	Capivasertib + fulvestrant	Capivasertib + fulvestrant
 Dr Kalinsky	Exemestane/everolimus	Capivasertib + fulvestrant	Capivasertib + fulvestrant
 Dr O'Shaughnessy	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant
 Dr Rugo	Exemestane/everolimus	Capivasertib + fulvestrant	Capivasertib + fulvestrant
 Dr Hurvitz	Everolimus/fulvestrant	Capivasertib + fulvestrant	Capivasertib + fulvestrant
 Dr Jhaveri	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant	Capivasertib + fulvestrant or abemaciclib + imlunestrant

A 65-year-old woman presents with de novo ER-positive, HER2-negative (IHC 0) mBC, receives ribociclib with anastrozole and initially responds but then experiences disease progression 2 years later. Regulatory and reimbursement issues aside, which treatment would you most likely recommend for this patient if biomarker evaluation results were as follows?

	ESR1+, PIK3CA-, AKT/PTEN-	ESR1+, PIK3CA+, AKT/PTEN-	ESR1+, PIK3CA-, AKT/PTEN+
 Dr Burstein	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant	Capivasertib + fulvestrant
 Dr Cortés	Elacestrant	Elacestrant	Elacestrant
 Prof Dent	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant
 Dr Kalinsky	Abemaciclib + imlunestrant	Capivasertib + fulvestrant	Capivasertib + fulvestrant
 Dr O'Shaughnessy	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant
 Dr Rugo	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant	Capivasertib + fulvestrant
 Dr Hurvitz	Elacestrant	Elacestrant	Elacestrant
 Dr Jhaveri	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant	Capivasertib + fulvestrant or abemaciclib + imlunestrant

An 80-year-old woman presents with de novo ER-positive, HER2-negative (IHC 0) mBC, receives ribociclib with anastrozole and initially responds but then experiences disease progression 2 years later. Biomarker evaluation reveals ESR1 and PIK3CA mutations but is negative for AKT1/PTEN alterations. Regulatory and reimbursement issues aside, what would be your most likely next treatment?

 Dr Burstein	Imlunestrant
 Dr Cortés	Elacestrant
 Prof Dent	Abemaciclib + fulvestrant
 Dr Kalinsky	Elacestrant
 Dr O'Shaughnessy	Abemaciclib + imlunestrant
 Dr Rugo	Elacestrant
 Dr Hurvitz	Elacestrant
 Dr Jhaveri	Abemaciclib + imlunestrant

RTP RESEARCH TO PRACTICE

Based on published research data and your own clinical experience, indirectly, how would you compare the global efficacy of elacestrant to that of imlunestrant when administered as monotherapy for endocrine therapy-pretreated, ER-positive, HER2-negative mBC with an ESR1 mutation?

 Dr Burstein	I'm not sure
 Dr Cortés	Efficacy is about the same
 Prof Dent	I'm not sure
 Dr Kalinsky	Efficacy is about the same
 Dr O'Shaughnessy	Imlunestrant is more efficacious
 Dr Rugo	Efficacy is about the same
 Dr Hurvitz	Efficacy is about the same
 Dr Jhaveri	Efficacy is about the same

RTP RESEARCH TO PRACTICE

Agenda

MODULE 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Cortés

MODULE 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Kalinsky

MODULE 3: Available Therapies for Patients with HR-Positive, HER2-Negative Disease Progressing on CDK4/6 Inhibition — Dr Burstein

MODULE 4: Current and Potential Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Dr O'Shaughnessy

MODULE 5: Current and Future Strategies for Patients with Endocrine-Refractory HR-Positive mBC — Dr Rugo

MODULE 6: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Prof Dent

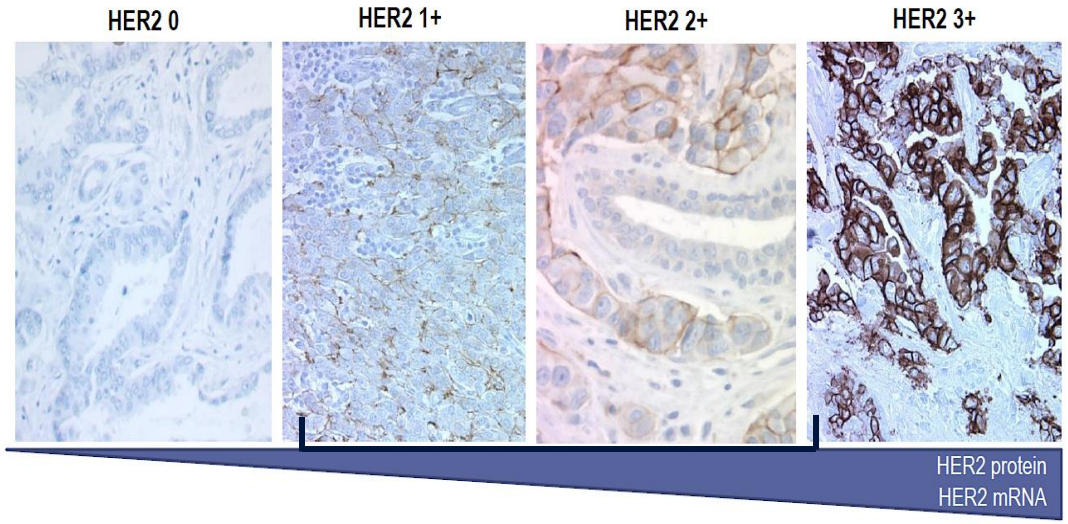
RTP RESEARCH TO PRACTICE

Current and Potential Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease

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

Trastuzumab Deruxtecan active in HER2-low MBC

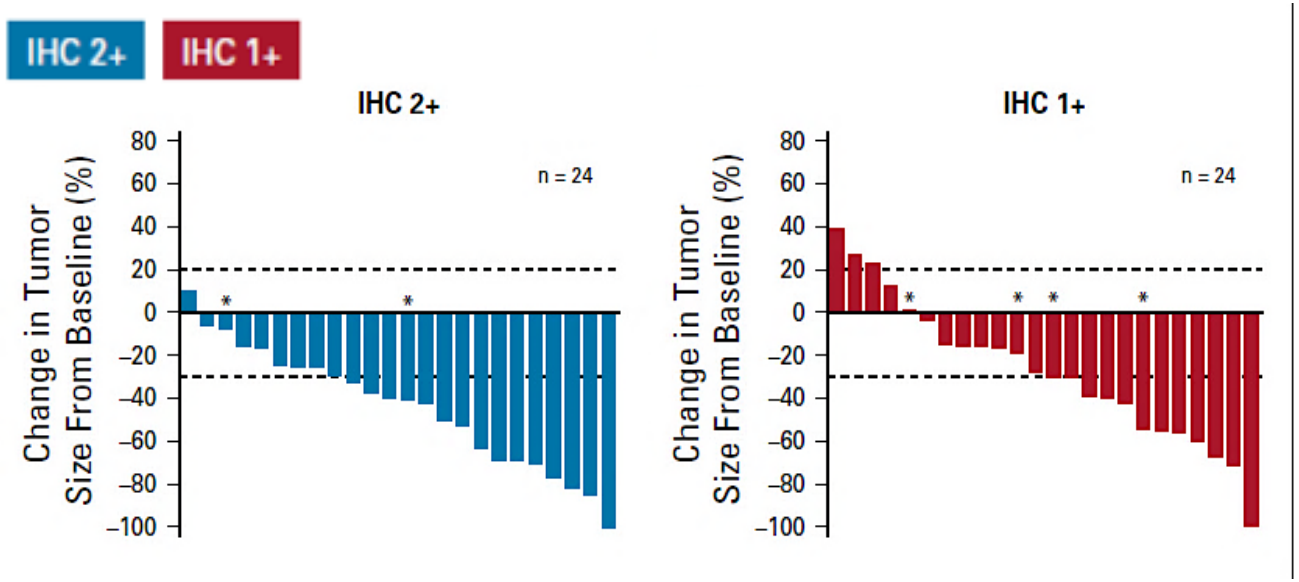
HER2: Continuum of expression in breast cancer



HER2-low
HER2 IHC 2+/ISH- OR IHC 1+/ISH – or untested

Of ~6100 breast cancer cases by IHC
~ 75% of cases of HR+ BC were considered HER2-low
~ 49% of cases of TNBC were considered HER2-low

T-DXd: Best percent change in tumor size in HER2-low MBC



Confirmed ORR: 37%
Confirmed DCR: 87%
Median DoR: 10.4 months
Median PFS: 11.1 months

- T-DXD demonstrated significant anti-tumor activity in HER2 IHC 2+ and 1+ tumors

Penault-Llorca F. ESMO E-learning module
Modi S et al. JCO 2020

Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-Low BC (DB-04)

Clinical trial design (phase 3 – DESTINY-Breast04)

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

R 2:1

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

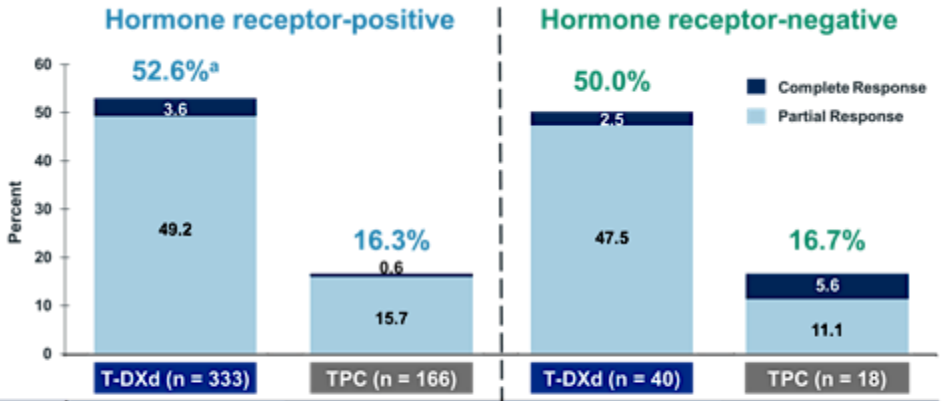
HR+ ≈ 480
HR− ≈ 60

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

Primary endpoint
- PFS by BICR (HR+)

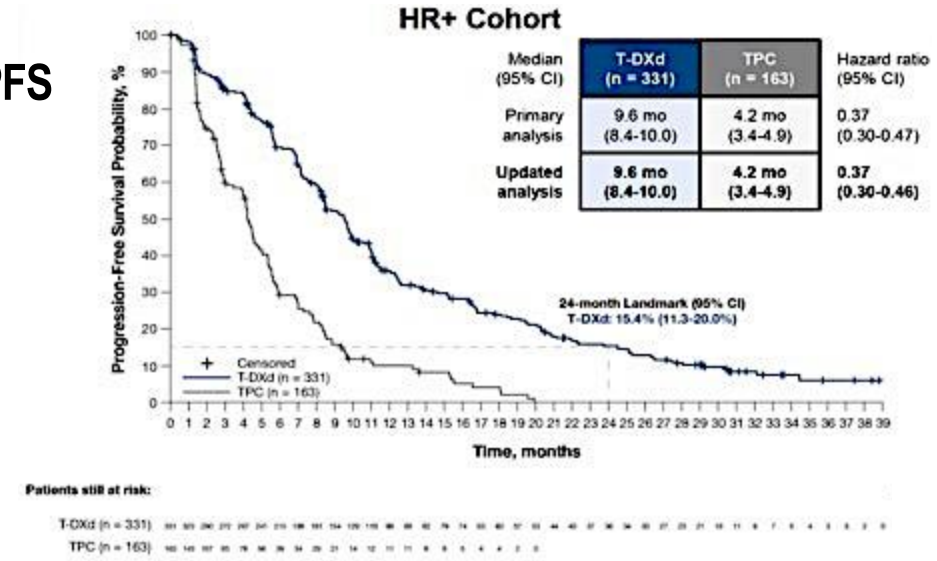
Key secondary endpoints[d]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

ORR

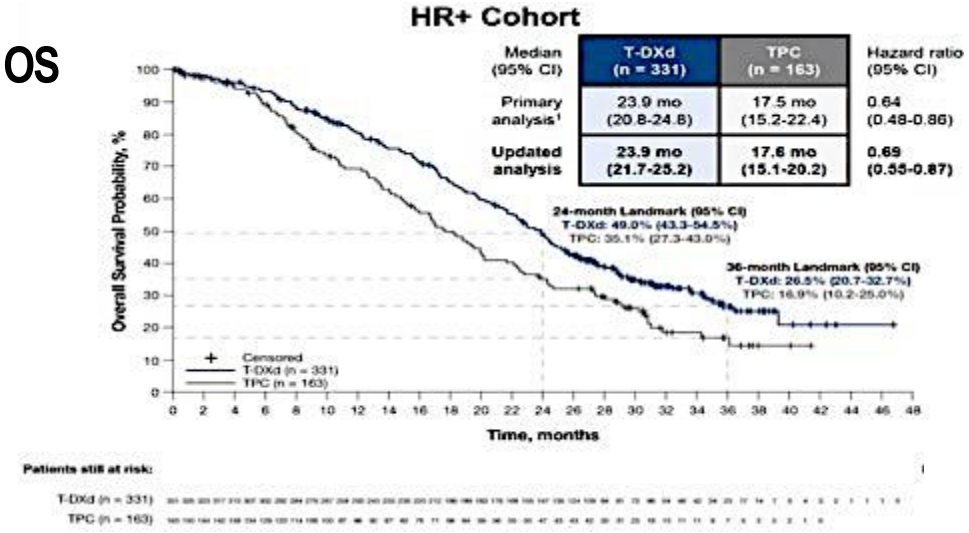


	Hormone receptor-positive		Hormone receptor-negative	
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive Disease, %	7.8	21.1	12.5	33.3
Not Evaluable, %	4.2	12.7	7.5	5.6
Clinical Benefit Rate[b], %	71.2	34.3	62.5	27.8
Duration of Response, months	10.7	6.8	8.6	4.9

PFS



OS

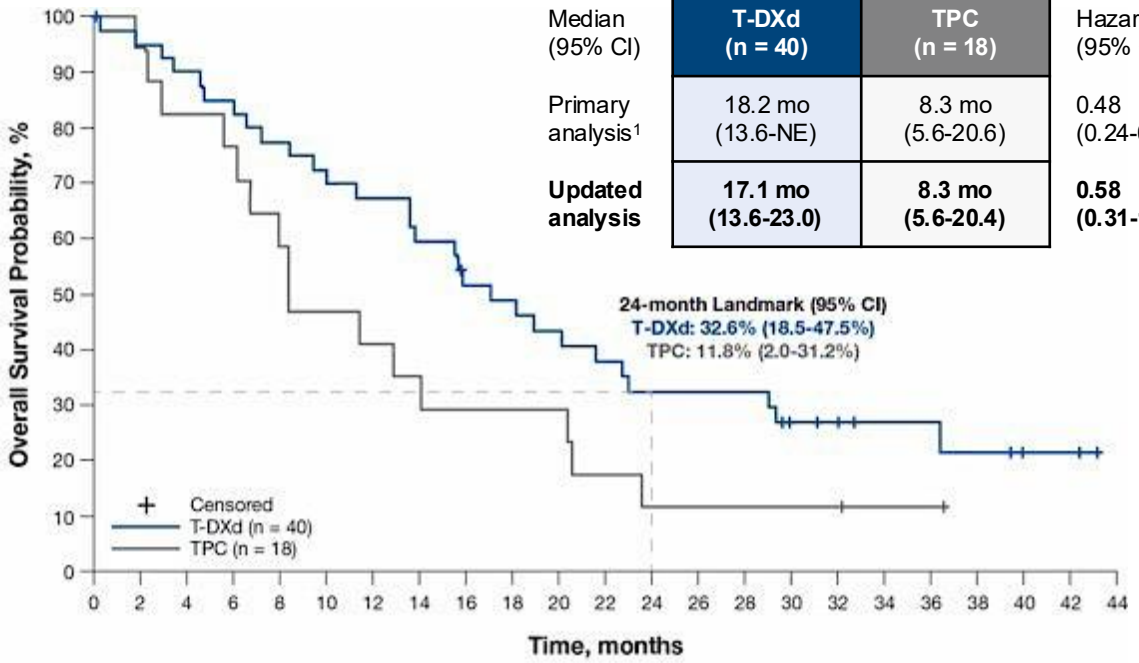


Modi S et al. *N Engl J Med*. 2022;387(1):9-20. Modi S et al. 2023 ESMO Congress. Abstract 376O.

DESTINY-Breast04: Efficacy in the HR− Cohort (exploratory analyses)

Overall Survival

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**



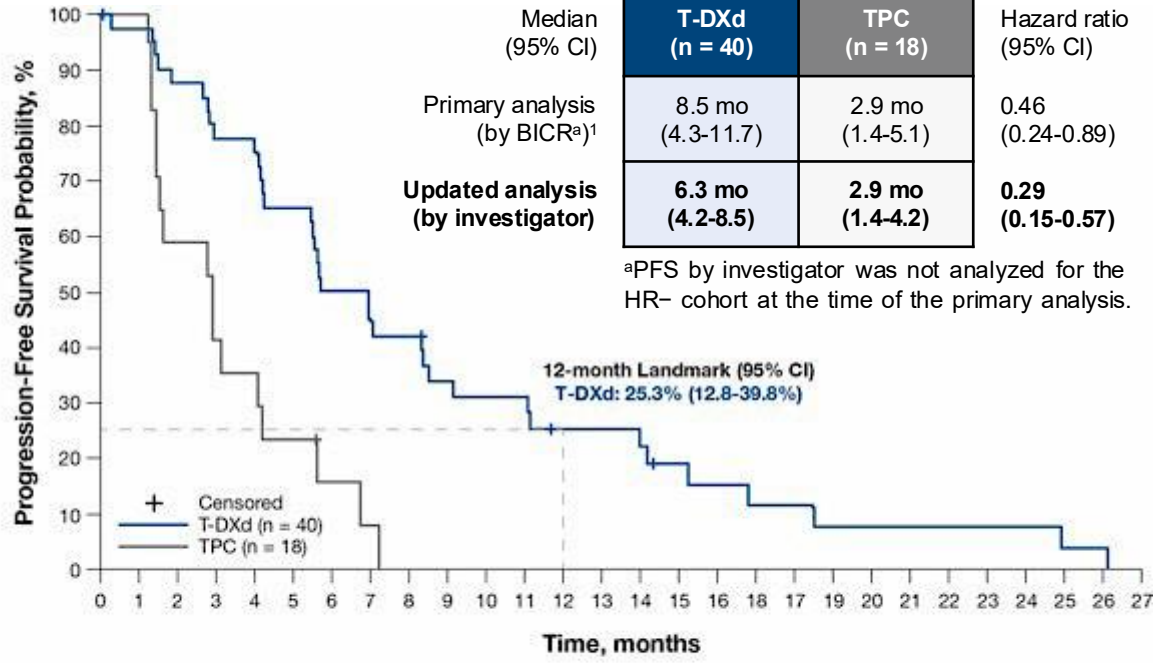
Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

Progression-Free Survival (by Investigator)

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.



Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

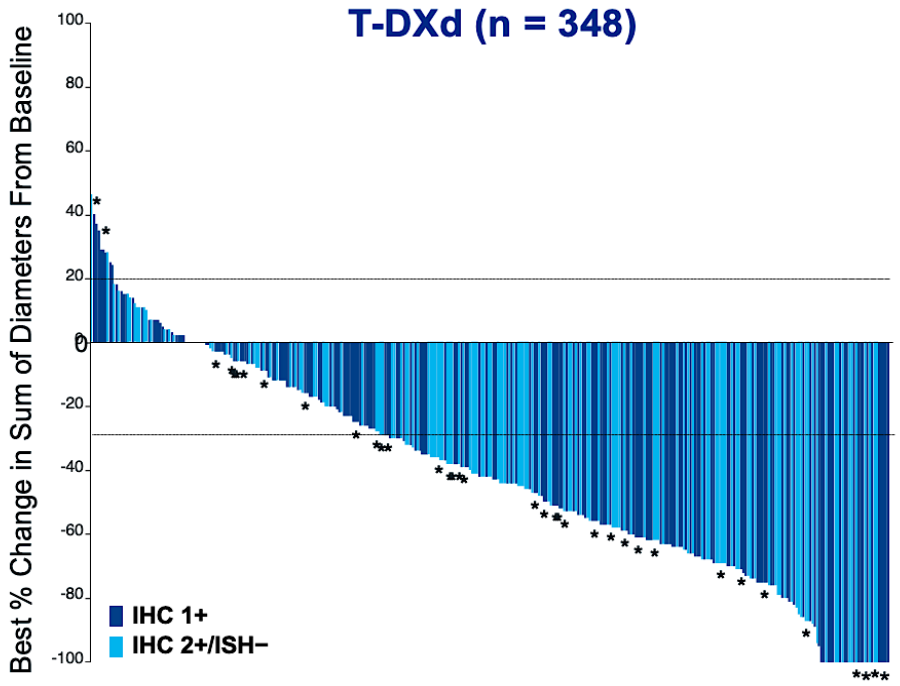
- Median FU now 32 months vs 18.4 at primary analysis
- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

BICR, blinded independent central review; HR, hormone receptor; mo, month; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi S et al. *N Engl J Med*. 2022;387(1):9-20. Modi S. 2023 ESMO Congress. Abstract 376O.

Is HER2 IHC score predictive of T-DXd activity?

In DESTINY-Breast04, **no difference** in activity b/w HER2 IHC 1+ and 2+/ISH-

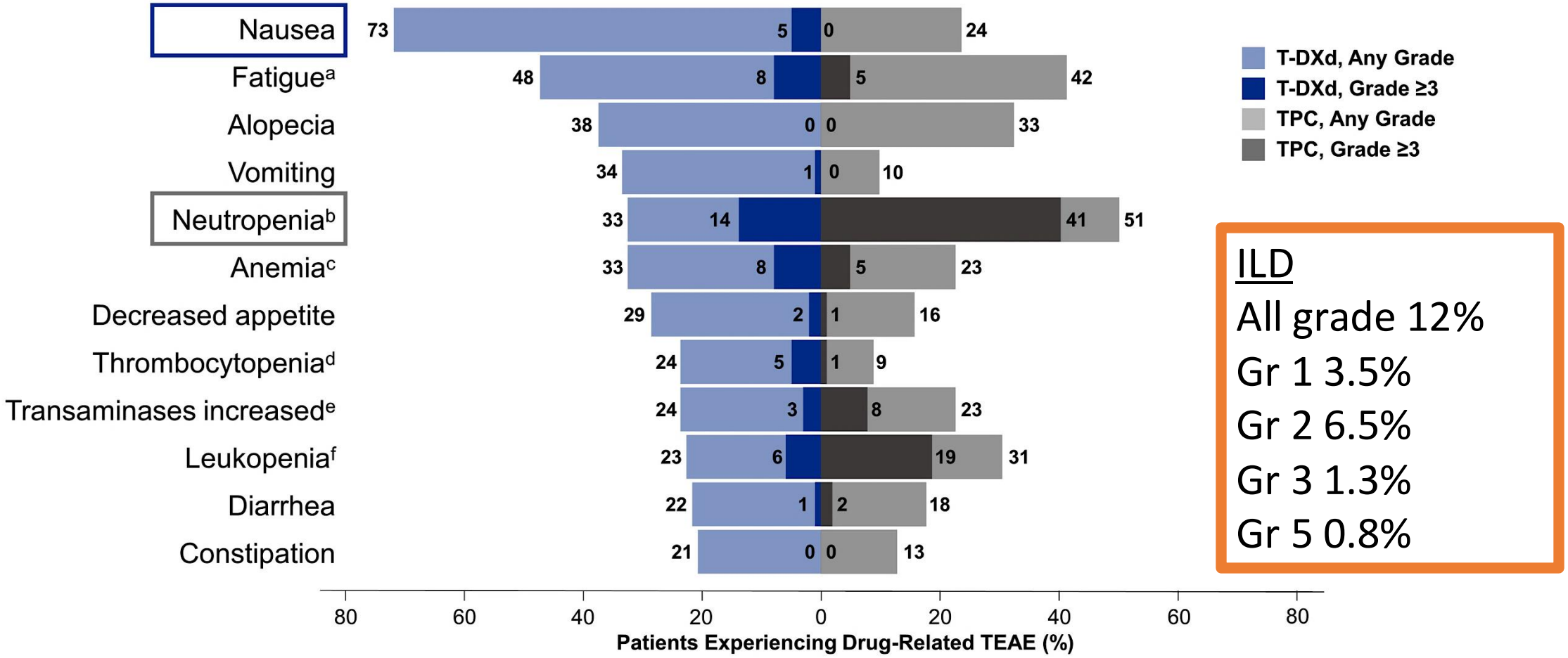


Subgroup Analysis: PFS in HR+

	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)

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

Drug-Related TEAEs in ≥20% of Patients



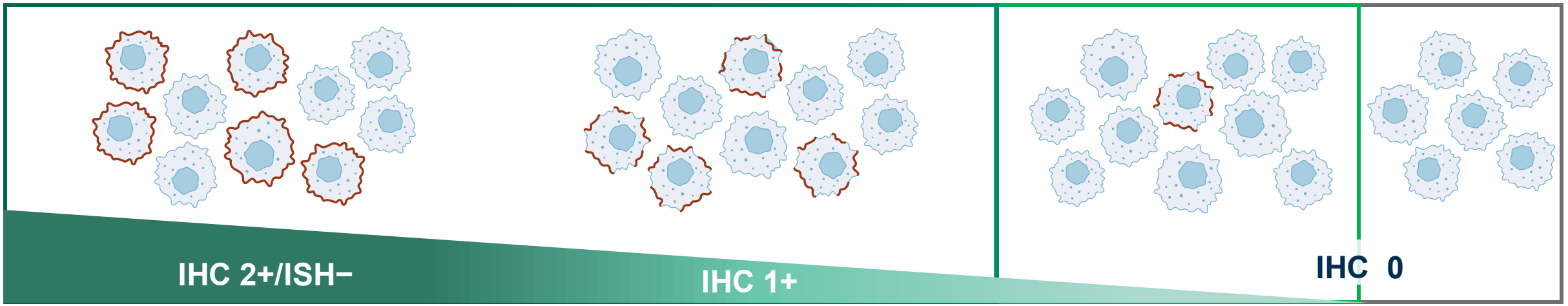
ILD
All grade 12%
Gr 1 3.5%
Gr 2 6.5%
Gr 3 1.3%
Gr 5 0.8%

T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

What About HER2-ultralow in mTNBC?

HER2-low
~60–65%[2,3]

HER2-ultralow
~20–25%[2–4]



IHC 2+/ISH−	IHC 1+	IHC 0	
Weak-to-moderate complete membrane staining in >10% tumor cells	Faint, incomplete membrane staining in >10% tumor cells	Faint, incomplete membrane staining in ≤10% tumor cells	Absent / no observable membrane staining

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

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

DESTINY-Breast06: A Phase 3, Randomized, Multicenter, Open-Label Study (NCT04494425)

PATIENT POPULATION

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

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

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

R 1:1

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

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

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

Other secondary

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

At DCO, 119 patients (14.0%) remained on treatment: 89 (20.5%) T-DXd and 30 (7.2%) TPC
Median duration of follow up: 18.2 mo (ITT)

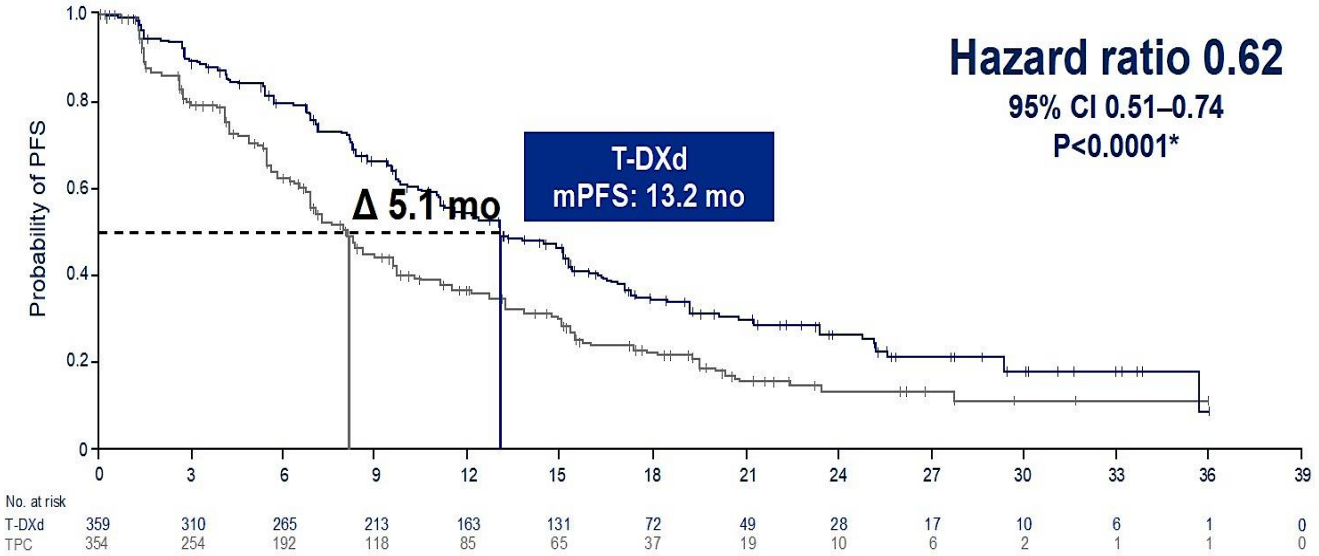
TPC	n (%)
Capecitabine	257 (59.8)
Nab-paclitaxel	105 (24.4)
Paclitaxel	68 (15.8)

Patient population

- ~30% primary endocrine resistance
- ~30% de novo metastatic disease
- 3% bone only disease
- ~66% liver metastases
- HER2 ultra-low similar to HER2 low population
- Median 2 prior lines of ET
- 89% prior CDKi (9%<6 mo), ~30% other targeted agents
- ~54% chemotherapy for early-stage disease

Curigliano G et al. ASCO 2024. LBA1000. Bardia A et al. *N Engl J Med*. 2024;391(22):2110-2122.

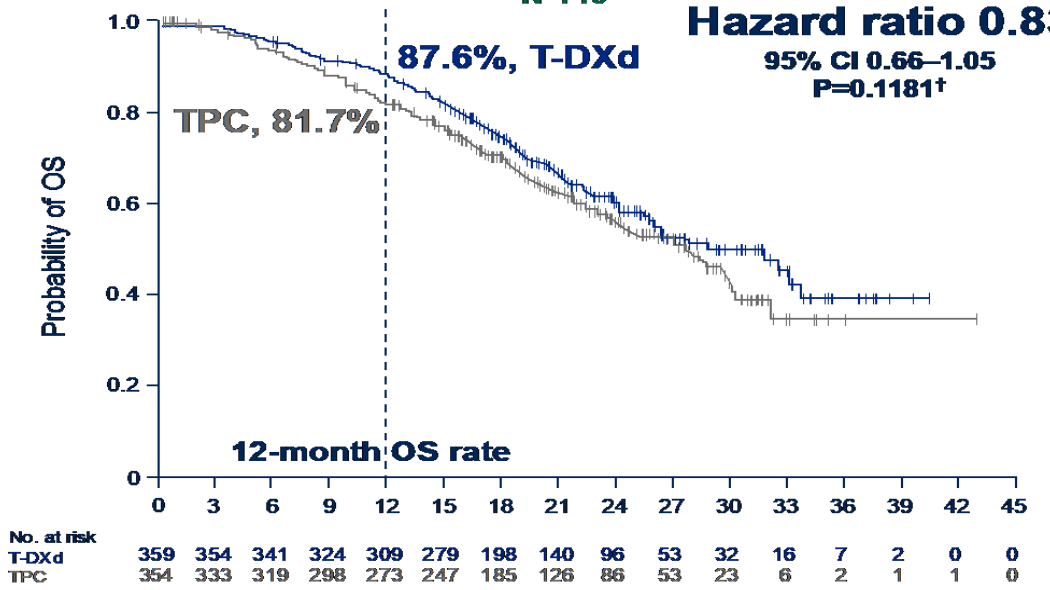
PFS (BICR) in HER2-low: primary endpoint



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

HER2-low*

N=713



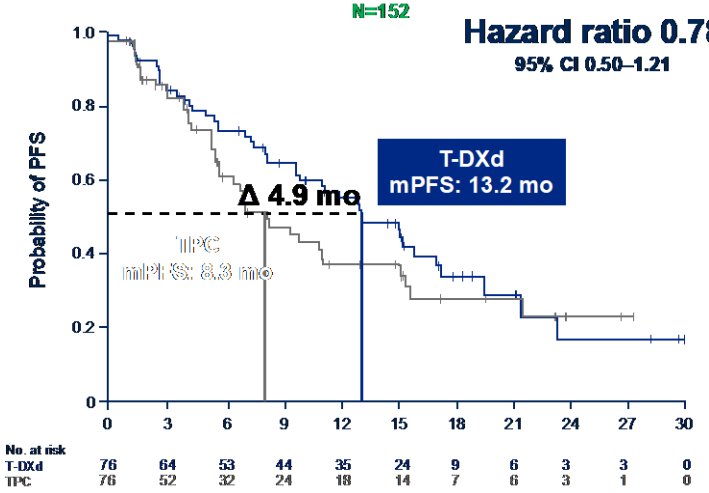
20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

PFS and OS in HER2-ultralow

Prespecified exploratory analyses

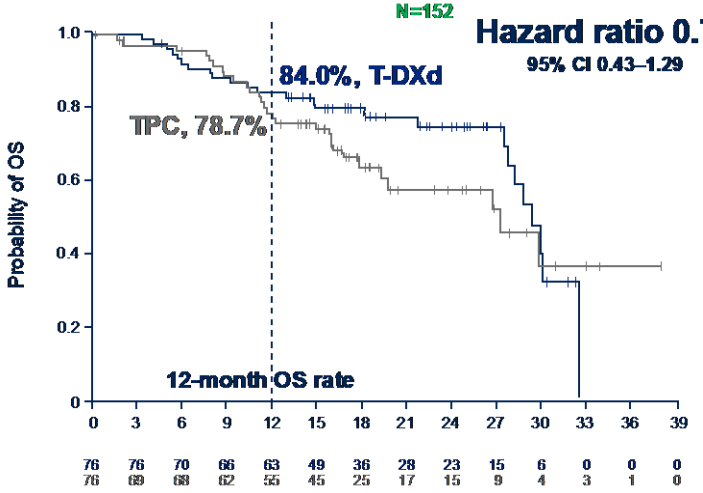
PFS (BICR)

N=152



OS*

N=152

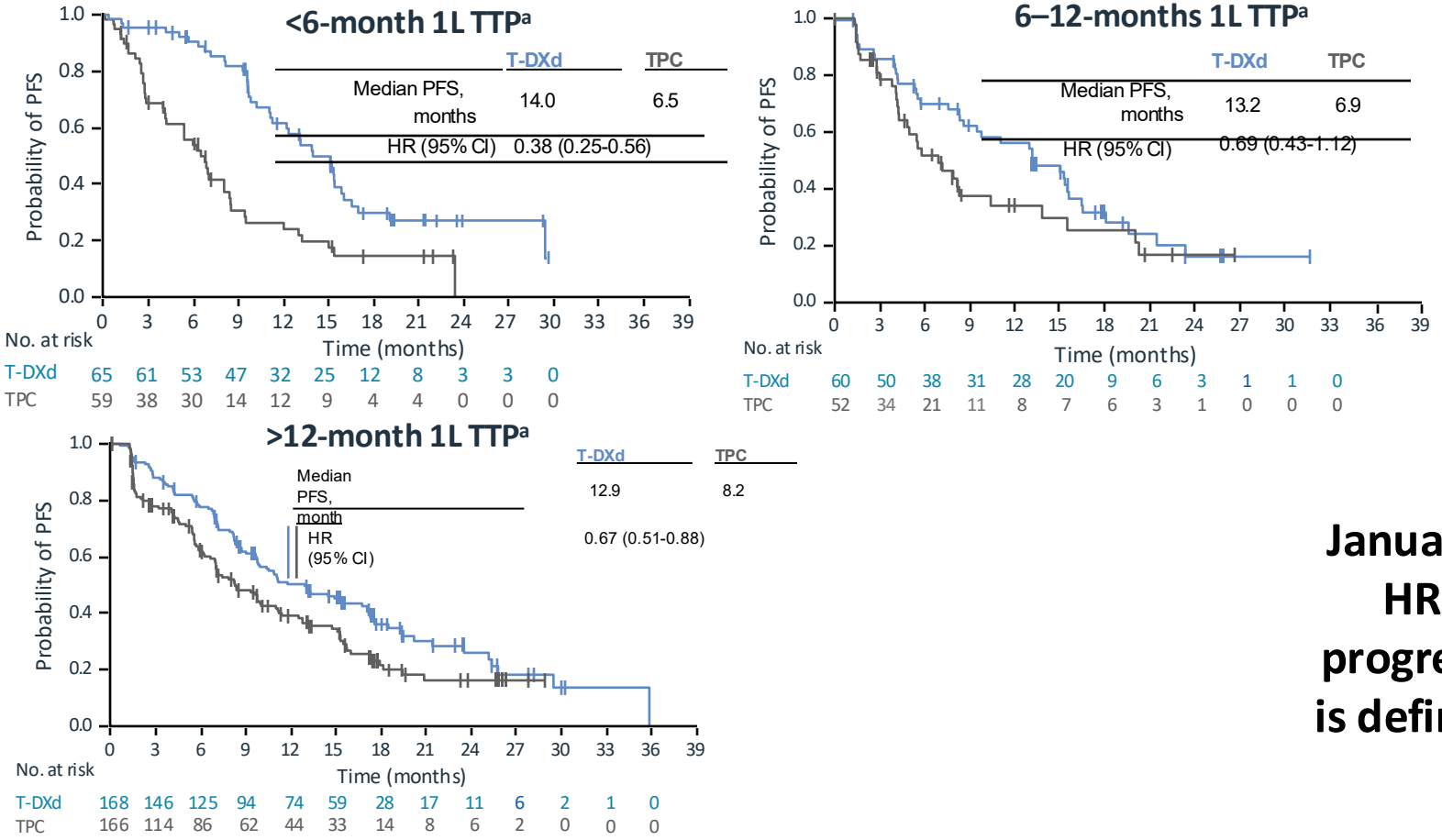


PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

Curigliano G et al. ASCO 2024. LBA1000.
Bardia A et al. *N Engl J Med*. 2024;391(22):2110-2122.

DESTINY-Breast06 (phase 3): T-DXd Efficacy by Time to Progression on 1L ET + CDK4/6 inhibitor

PFS by time to progression on 1L ET + CDK4/6i and ET resistance



January 27, 2025 FDA approved T-DXd for HR+ HER2-low or ultralow MBC that progressed on ET for MBC. HER2-ultralow is defined as IHC 0 with membrane staining by PATHWAY 4B5 Ab assay

[a]TTP analysis included patients with PD on prior 1L ET + CDK4/6i (65.8% of the ITT population).
[b]Primary endocrine resistance defined as relapse in the first 2 years of adjuvant ET, or PD <6 mo of 1L ET for mBC; secondary (acquired) endocrine resistance defined as relapse after the first 2 years on adjuvant ET, or relapse within 12 mo of completing adjuvant ET, or PD >6 mo after initiating ET for mBC.

Bardia A et al. SABCS 2024. Abstract LB1-04.

College of American Pathologists Updated HER2 Testing

Allison K, Krismurti U. CAP Biomarker Testing of Specimens from Patients with Carcinoma of the Breast Version 1.6.0.0, March 2025

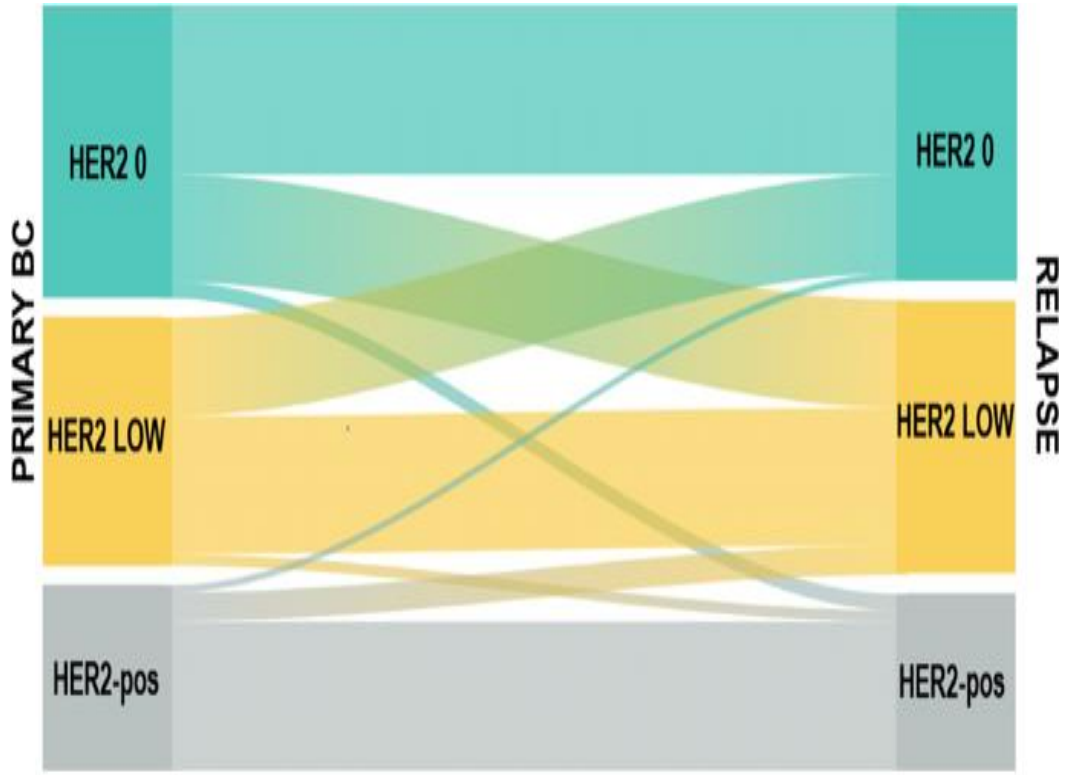
Table 4. Reporting Results of HER2 Testing by Immunohistochemistry (IHC)

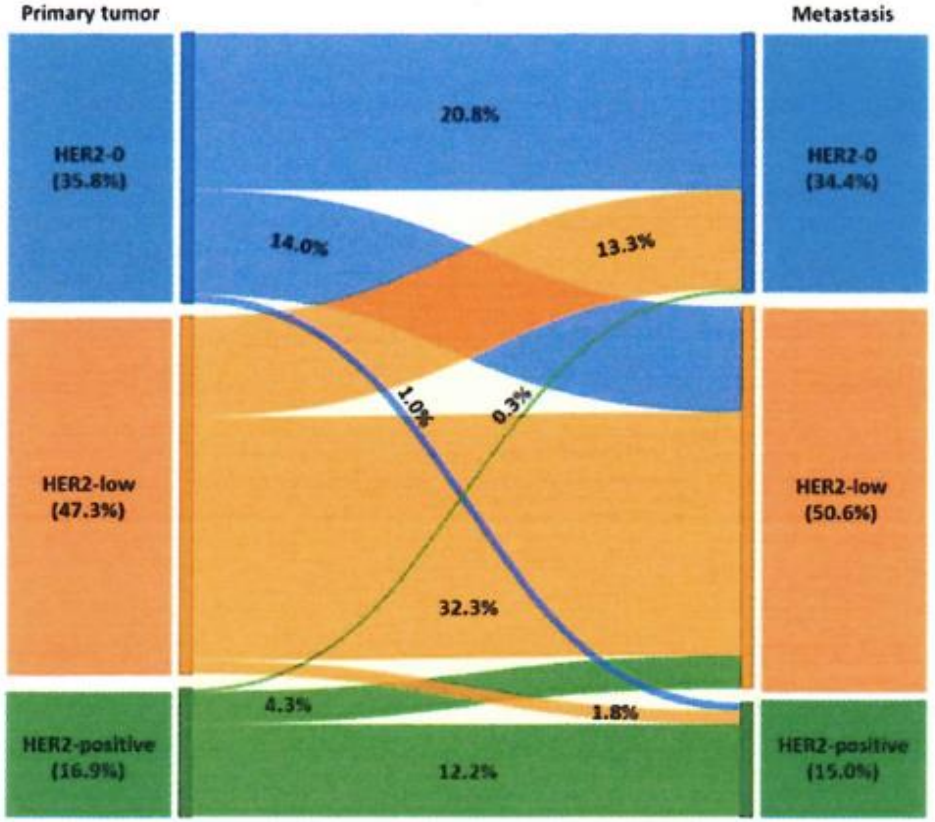
Result Category	Criteria
Negative (Score 0 or 0+)#	No staining observed (0/absent membrane staining) *or* **Membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of tumor cells (0+/with membrane staining)**
Negative (Score 1+)#	Incomplete membrane staining that is faint/barely perceptible and within >10% of tumor cells
Equivocal (Score 2+)#†	Weak to moderate complete membrane staining in >10% of tumor cells *or* Complete membrane staining that is intense but within ≤10% of tumor cells*
Positive (Score 3+)	Complete membrane staining that is intense and >10% of tumor cells*

* Readily appreciated using a low-power objective and observed within a homogeneous and contiguous population of invasive tumor cells.

HER2-Low expression is dynamic in breast cancer

- **HER2 status can change between early and relapsed setting**
  - IHC 0 on the primary often converts to HER2-low upon recurrence





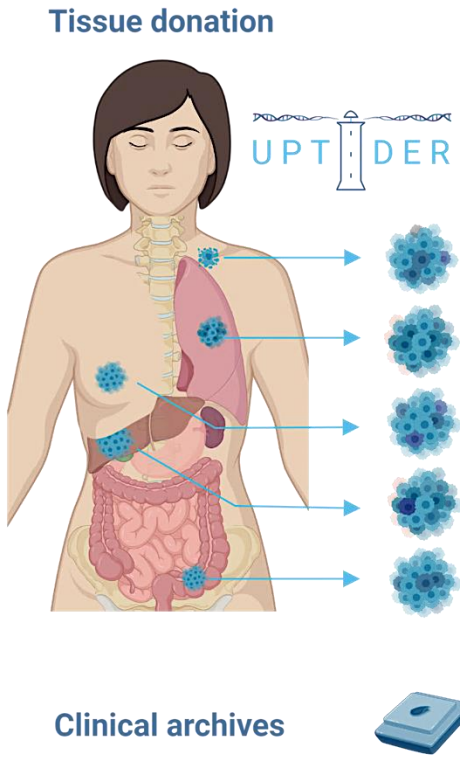
- **Liquid biopsy: HER2- CTCs can spontaneously convert into HER2-expressing CTCs and vice versa**

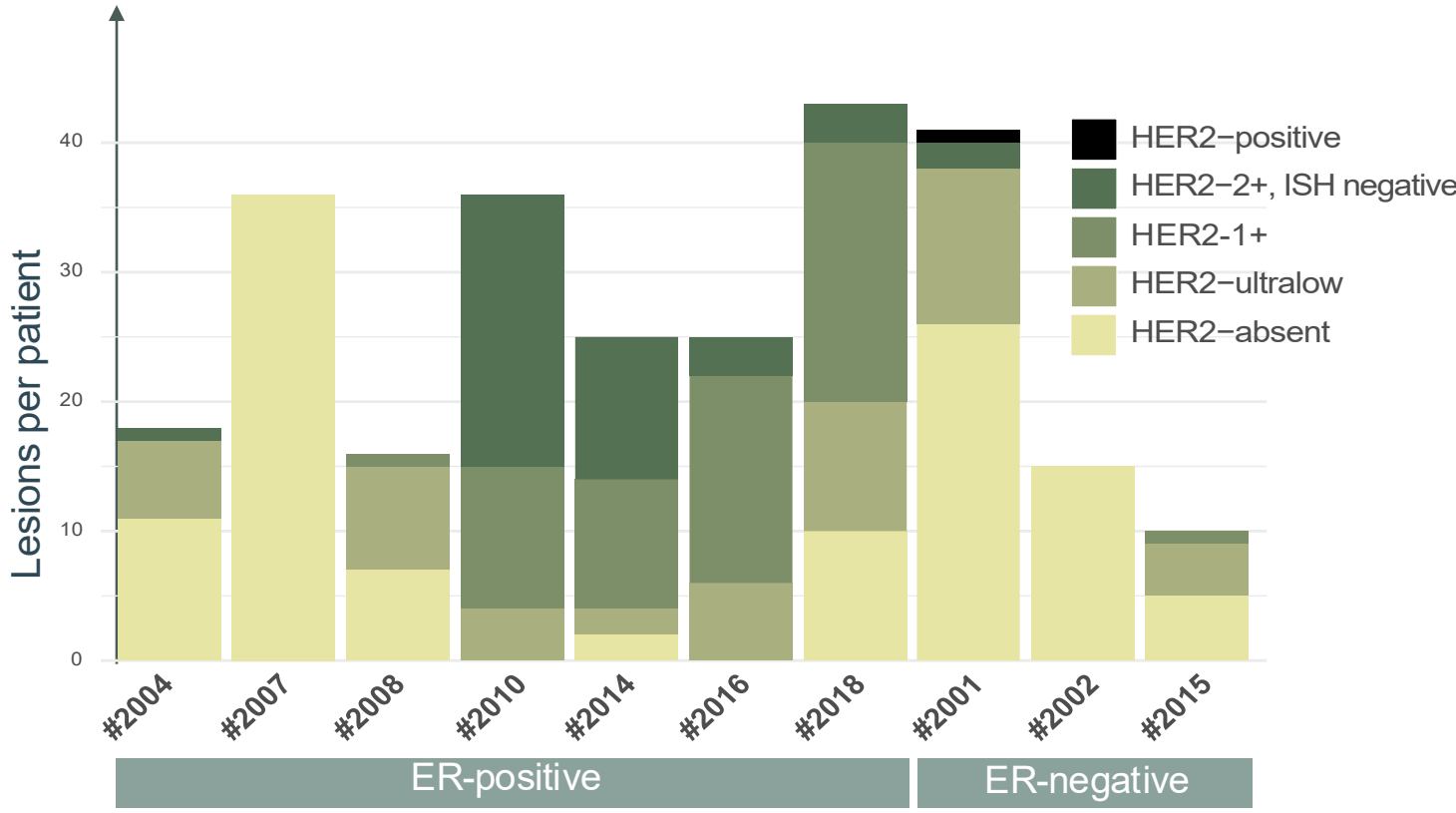
Tarantino P, et al *Eur J Cancer*. 2022;163:35–43; Miglietta F, et al. *NPJ Breast Cancer*. 2021;7(1):137; Bergeron A. et al. Presented at USCAP 2022; Bardia et al Nature 2016.

HER2-Low Expression is Heterogeneous within Metastases

An autopsy study has also demonstrated a significant spatial heterogeneity for HER2-low expression, with 8/10 of the patients studied having concomitant HER2-low, HER2-ultralow and HER2-0 lesions

10 patients with *HER2*-non-amplified metastatic breast cancer





Geukens T, et al. *Eur J Cancer* 2023; 188:152-160.

Dana-Farber Cancer Institute
BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

DESTINY-Breast15 Study Design: Unanswered Questions

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 Early Progressors (n = 50)

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

Primary Endpoint: TTNT

Key Secondary: rwPFS

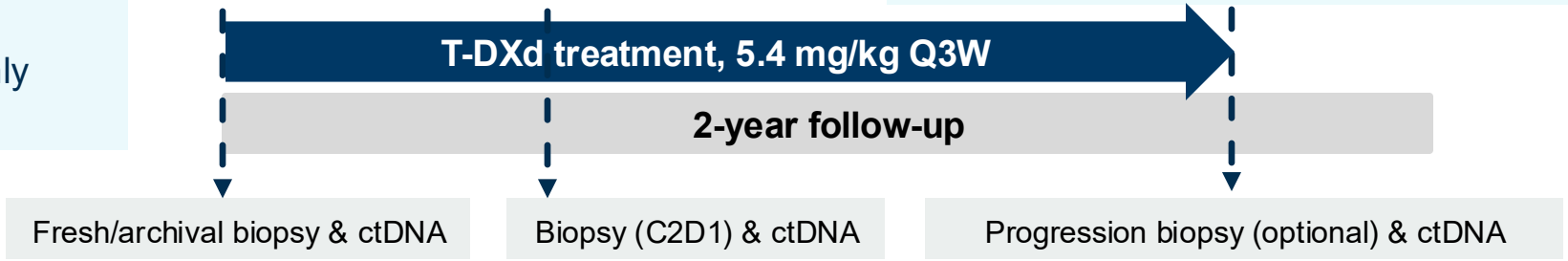
Secondary Endpoints:

- 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.

Strategies to enhance efficacy: DESTINY Breast 08 (DB-08) for HER2 low MBC

Part 1: Dose Finding

Patient population

- HR+ or HR−, HER2-low (IHC 1+ or IHC 2+/ISH−) metastatic breast cancer
  - HR+ patients: ≥1 prior line of ET and ≥1 prior line of CTX for metastatic disease
  - HR− patients: ≥1 prior line of CTX for metastatic disease

Centrally assigned

- Module 1: T-DXd + capecitabine (HR+ or HR−)
- Module 2: T-DXd + durvalumab + paclitaxel (HR+ or HR-)
- Module 3: T-DXd + capivasertib (HR+ or HR)
- Module 4: T-DXd + anastrozole (HR+) patients
- Module 5: T-DXd + fulvestrant (HR+) patients only)

CTX, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan.

Part 2: Dose Expansion Based on RP2D From Part 1

Patient population

- **Module 1** (HR+ or HR−)
  - HR+: only 1 prior line of ET but no prior CTX for mBC
  - HR−: only 1 prior line of CTX for mBC
- **Module 2** (HR−): no prior CTX for mBC[a]
- **Module 3** (HR−): only 1 prior line of CTX for mBC
- **Modules 4 and 5** (HR+): only 1 prior line of ET but no prior CTX for mBC

Allocation to open modules (dependent on available RP2D)

A

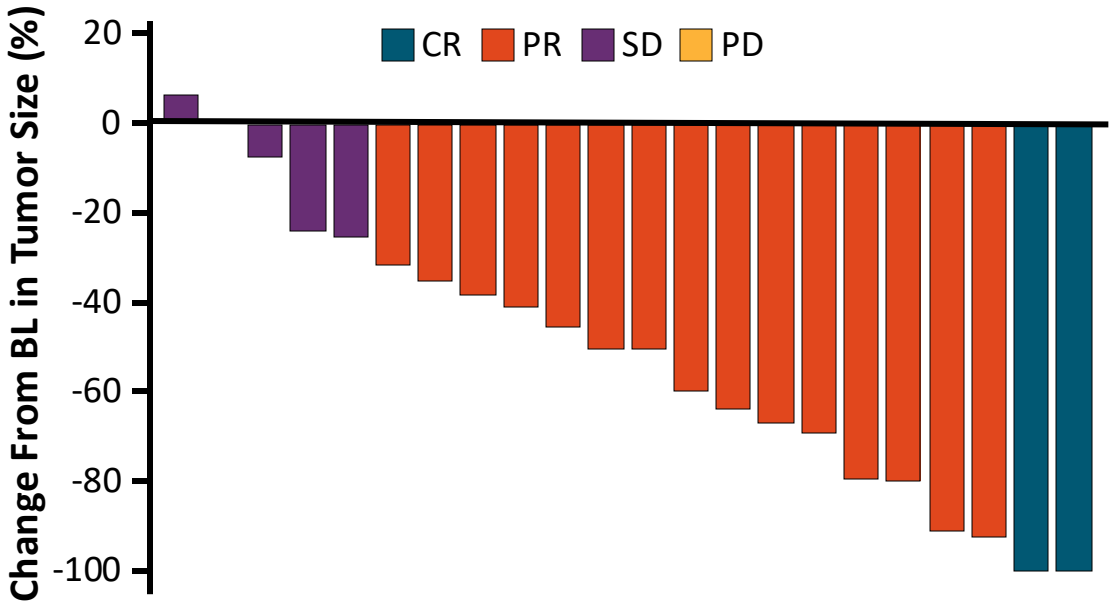
- Module 1: T-DXd + capecitabine (HR+ or HR−)
- Module 2: T-DXd + durvalumab + paclitaxel (HR−)
- Module 3: T-DXd + capivasertib (HR−)
- Module 4: T-DXd + anastrozole (HR+)
- Module 5: T-DXd + fulvestrant (HR+)

[a] Patients who have received CTX in the neoadjuvant or adjuvant setting are eligible, as long as they have had a disease-free interval of >12 months.
[b] Molecularly defined subgroup of special interest, PD-L1(+).
[c] Molecularly defined subgroup of special interest, AKT/PTEN/PIK3CA altered

Clinicaltrials.gov Identifier: NCT04556773

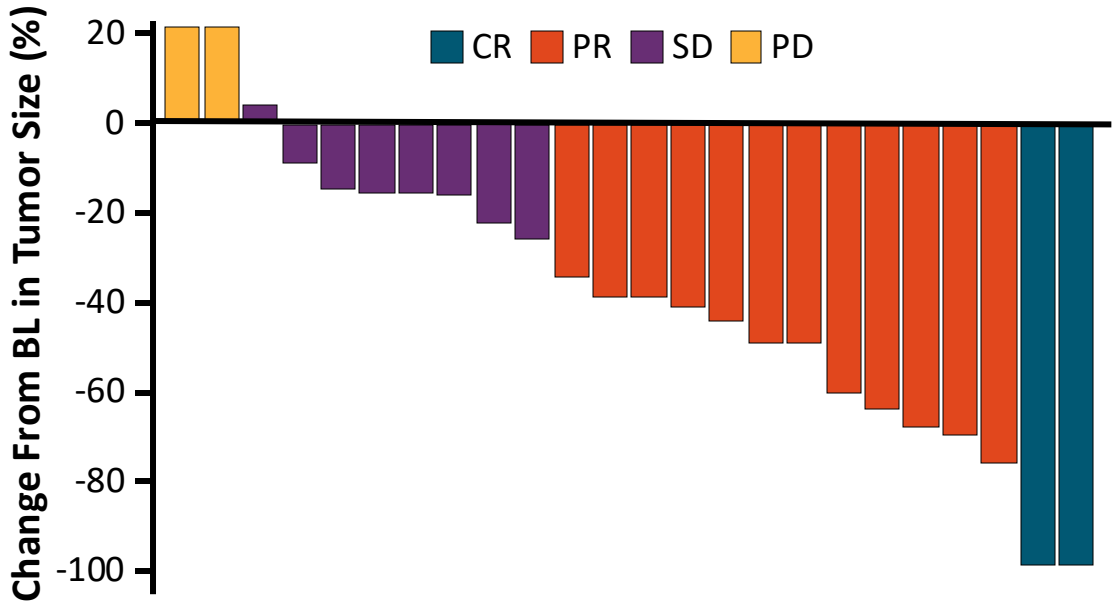
TRIO-US B-12 TALENT: Phase II neoadjuvant trial
T-Dxd +/- anastrozole for HER2-low, HR+ early stage BC

Arm A: T-DXd (n = 25*)



Response, n (%)	Arm A: T-DXd (n = 25)
ORR	17 (68)
▪ CR	2 (8)
▪ PR	15 (60)

Arm B: T-DXd + Anastrozole (n = 24†)

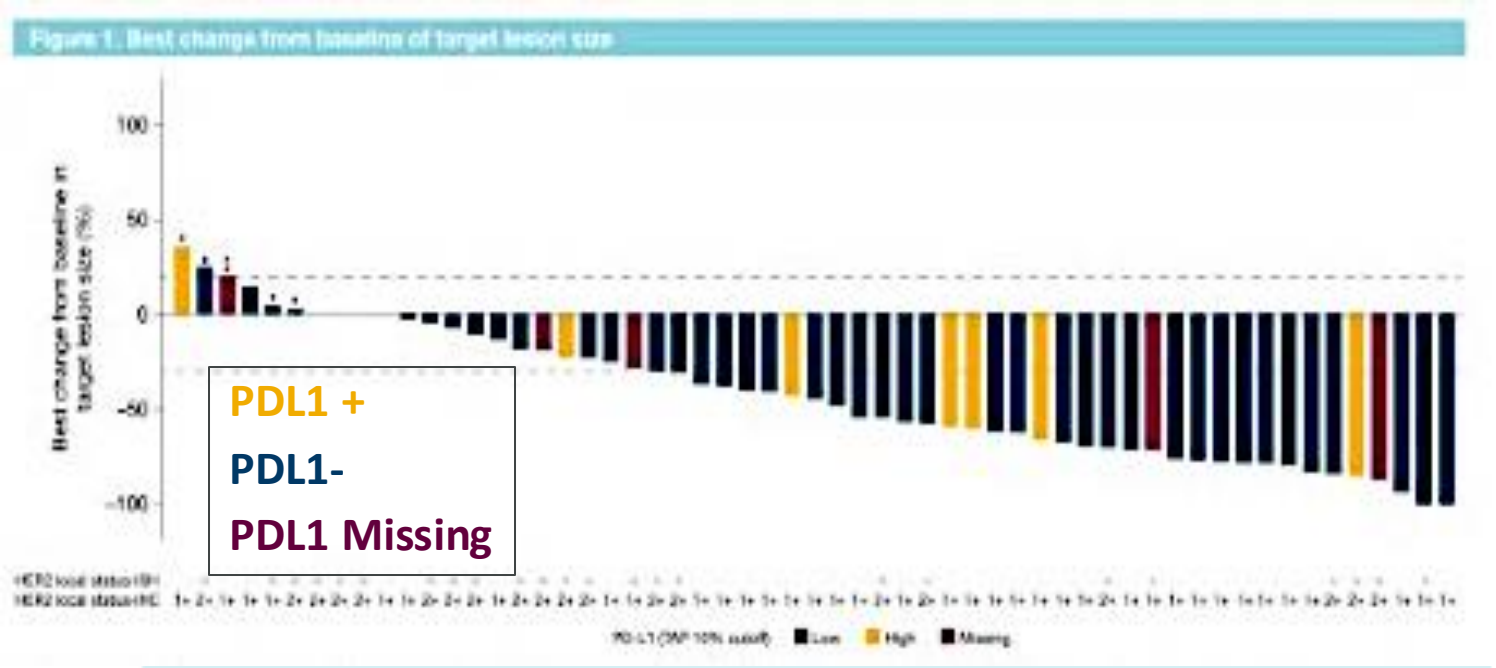


Response, n (%)	Arm B: T-DXd + Anastrozole (n = 24)
ORR	14 (58)
▪ CR	2 (8)
▪ PR	12 (50)

*n = 4 still on tx; n = 3 discontinued prematurely but still had imaging and included in ORR analysis per protocol. †n = 5 still on tx.

Is HER2 IHC score predictive of T-DXd activity in 1L mTNBC?

In BEGONIA (T-DXd + durvalumab for HER2-low TNBC), **no difference** in activity b/w HER2 IHC 1+ and 2+/ISH-



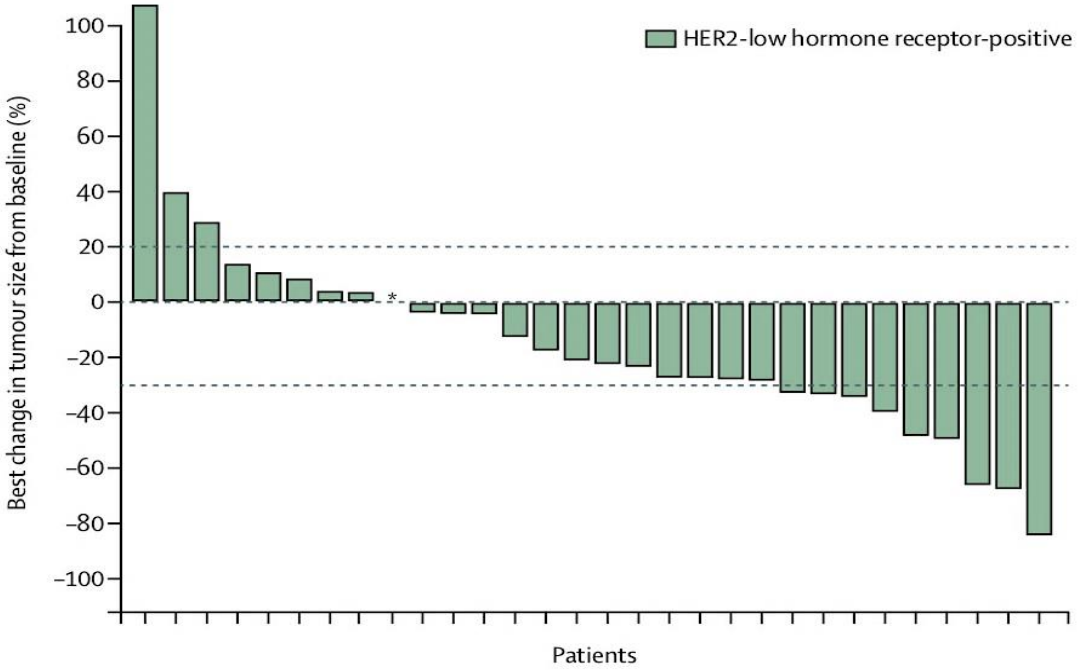
HER2 status, local testing	IHC 1+ n=37	IHC 2+/ISH− n=21
Confirmed ORR, n (%)	25 (67.6)	8 (38.1)
95% CI	50.2–82.0	18.1–61.6
Unconfirmed ORR, n (%)	26 (70.3)	9 (42.9)
95% CI	53.0–84.1	21.8–66.0

Schmid P, et al. SABCS 2022. PD11-08.

Other Novel ADCs for HER2-Low MBC

Trastuzumab duocarmazine (SYD985)

Trastuzumab mAB, Cleavable linker, Duocarmycin (vc-*seco*-DUBA)
DAR: 2.4 to 2.8



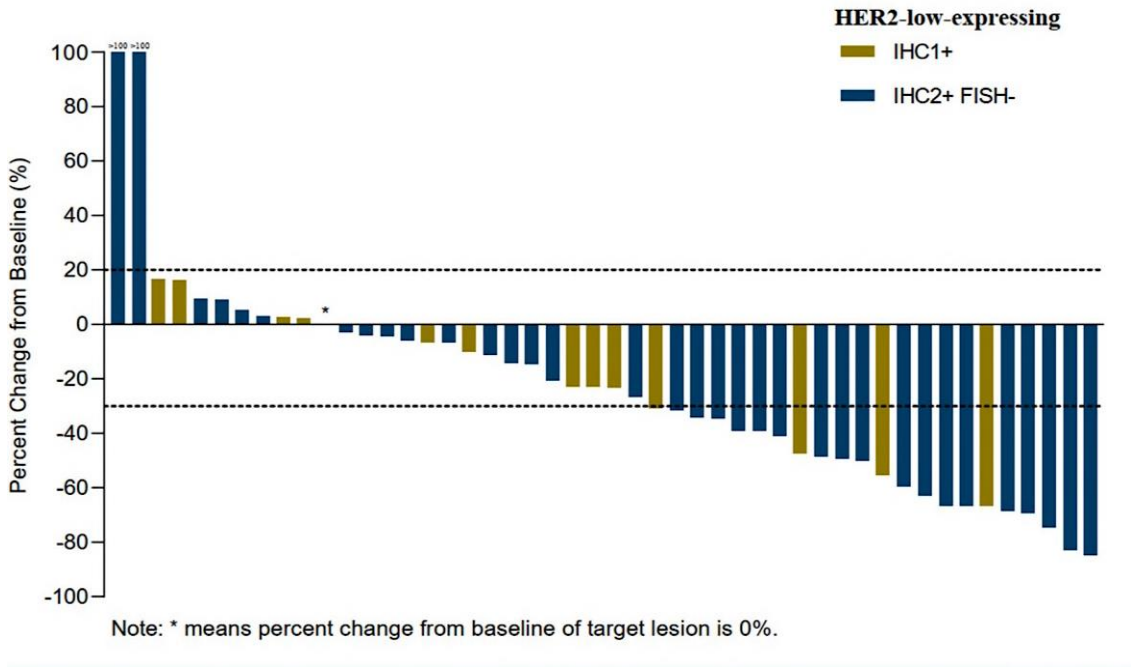
49 HER2-low MBC patients: ORR 32%, mPFS 4 mo

-HR+ (32/49): ORR 28%

- TNBC (17/49): ORR 40%

Disitamab Vedotin (RC48-ADC)

humanized anti-HER2 mAB, cleavable linker, Monomethyl auristatin E (MMAE): DAR ~ 4



48 HER2-low MBC patients: ORR 40%, mPFS 5.7 mo

HER2 2+: ORR 42.9%

HER2 1+: 30.8%

Banerji U et al. Lanc Onc 2019; Wang J et al. ASCO 2021

Ongoing Trials with SYD985 and Disitamab

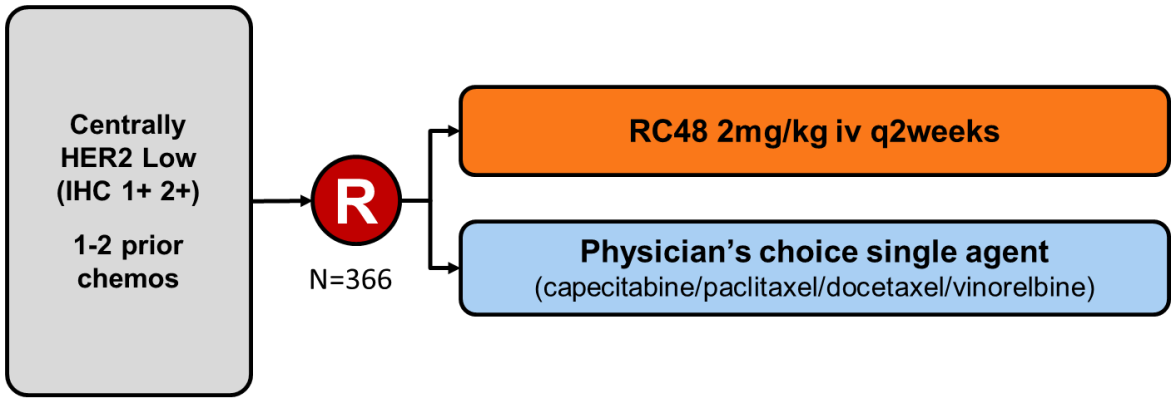
- Phase 1 Trial: SYD985 + Paclitaxel for HER2-Low MBC (NCT04602117)

SYD985 1.2 mg/kg q3wk x 6 + Paclitaxel weekly

- Phase 1 Trial: SYD985 + Niraparib in solid tumors (NCT04235101)
- I-SPY Trial: Neoadjuvant SYD985 for HER2-Low Early-Stage BC

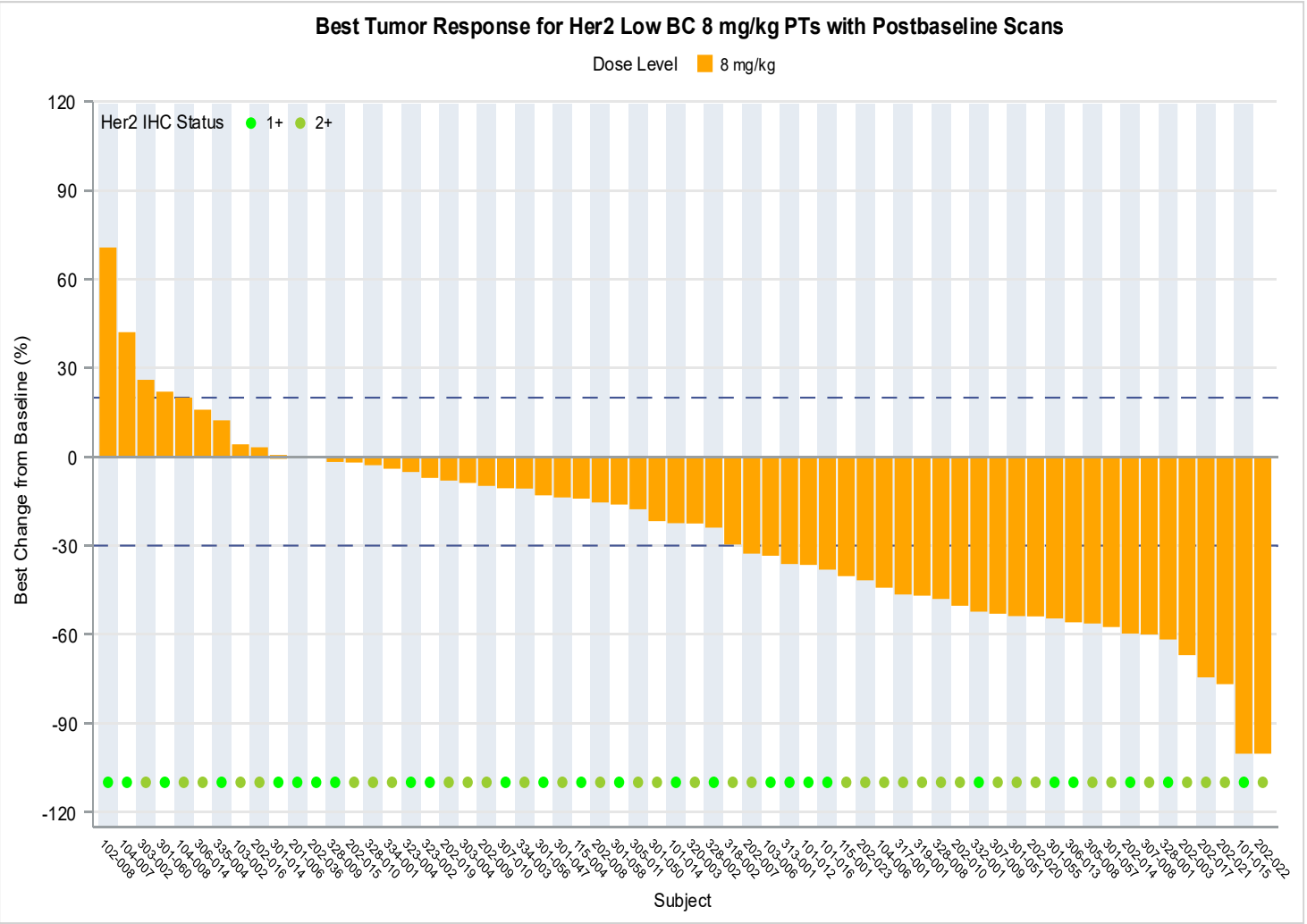
SYD985 1.2 mg/kg q3wk x4 → AC q2-3week x 4 → Sx

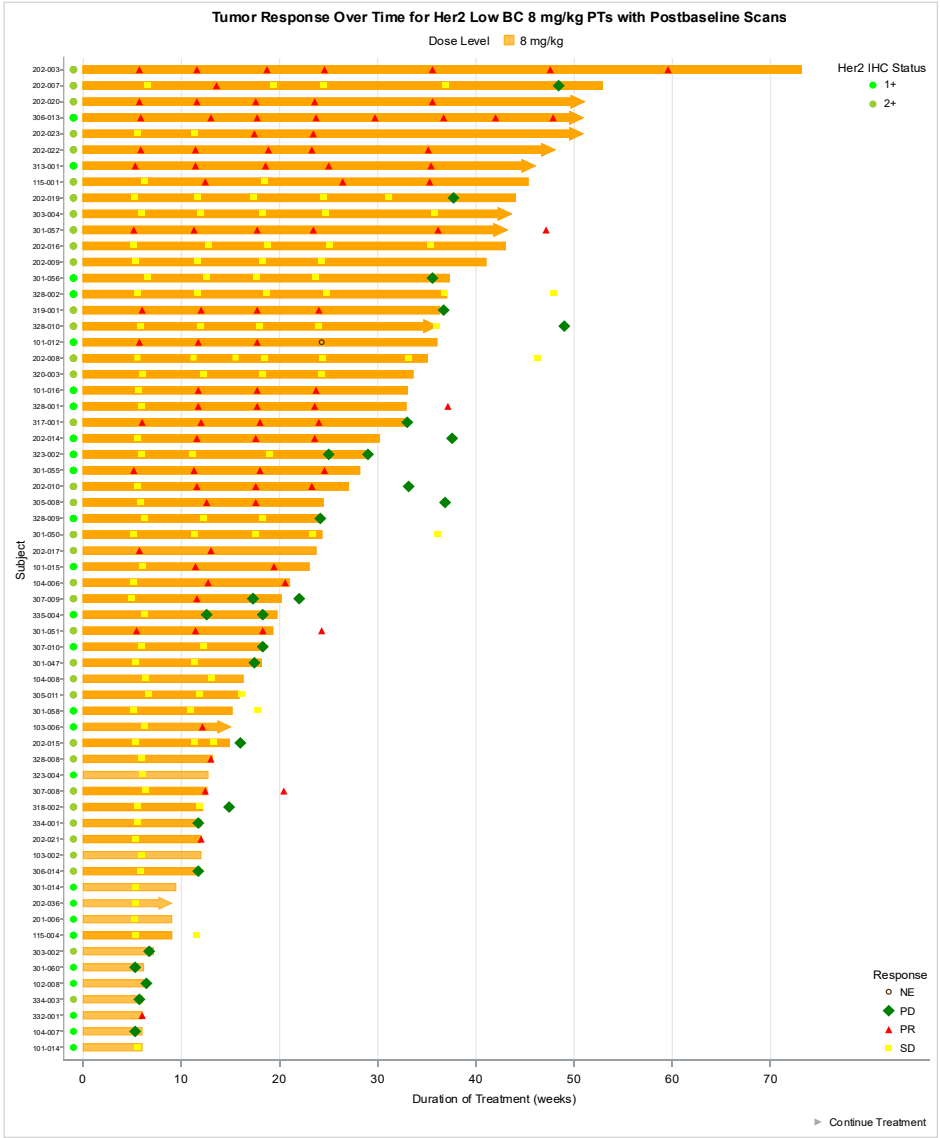
Randomized Phase 3 Study: Disitamab vs TPC HER2-Low MBC (NCT04400695)



Primary Endpoint = PFS

DB-1303 HER2-directed ADC with novel topo1 inhibitor payload with bystander effect
Best Tumor Response, Duration of Response in HER2 Low MBC



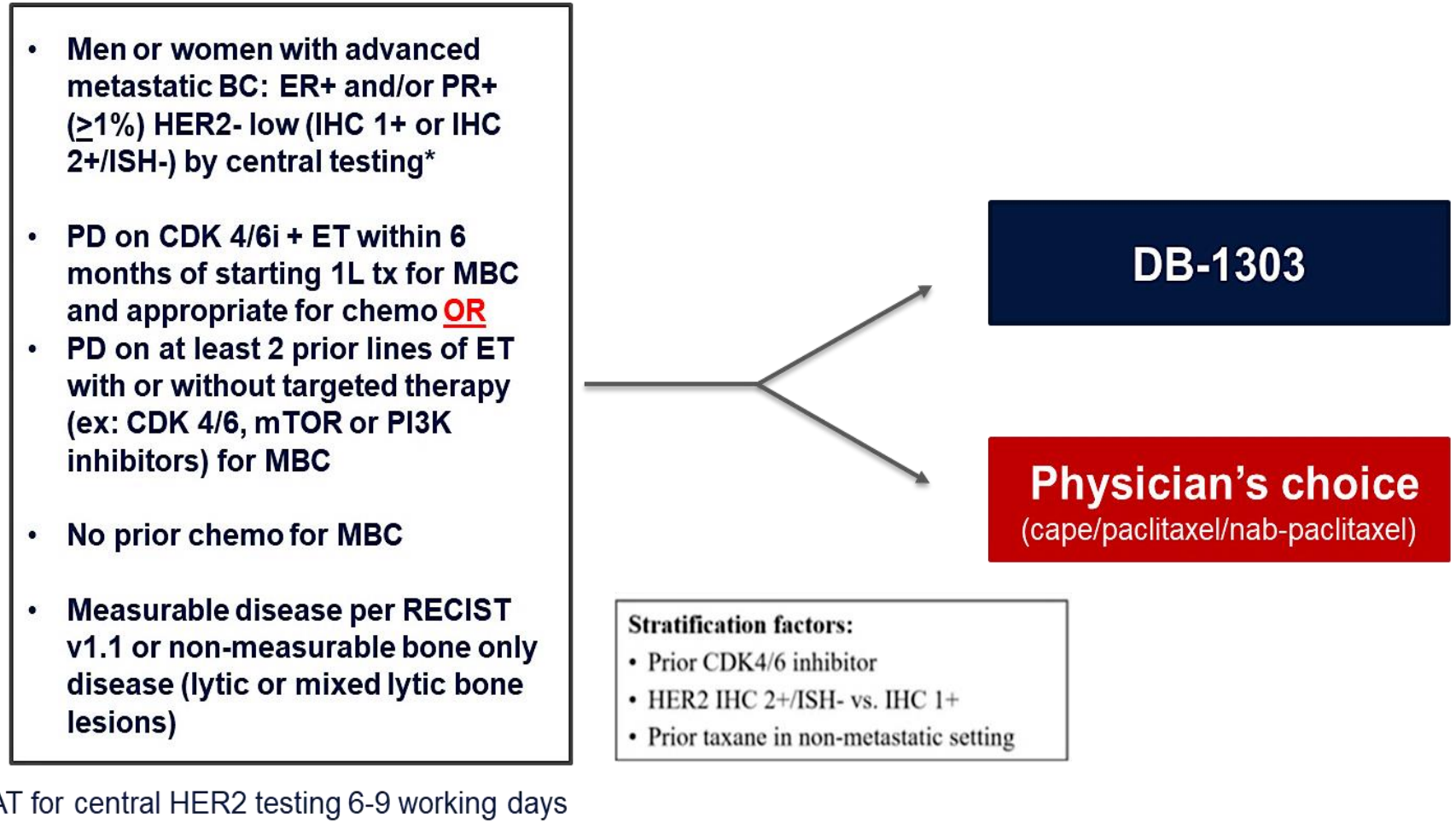


EAS: Efficacy Analysis Set includes all subjects enrolled and who received at least one dose of DB-1303/BNT323, have baseline efficacy assessment, and have either at least one post-baseline efficacy assessment or discontinued study treatment.

data cutoff: : 07Apr 2024

BRE 421 | 23189 (DYNASTY-Breast02): Trial for HR+/HER2low MBC after progression on ET

DB-1303 is a HER2-targeted ADC with a topoisomerase I inhibitor payload



*TAT for central HER2 testing 6-9 working days

O'Shaughnessy et al. ESMO 2024;Abstract 436TiP.

Summary: Targeting HER2 Low & Ultralow Breast Cancer

- HER2 low/ultralow expression is dynamic, changes with therapy, and is heterogeneously expressed in metastases
- New CAP guidance on reporting HER2 low/ultralow
- T-DXd is more effective than single agent chemotherapy in 1L (HR+) and 2L (HR+/TN) in HER2 low/ultralow (1L) and HER2 low (2L) disease
- Toxicity is manageable with chest CT surveillance for ILD
- Several new HER2-targeted ADCs show early promise in treating HER2 low MBC, with anti-tubulin and alkylator payloads
- Are TROP2- and HER2-directed ADCs with topo1 inhibitors non-cross-resistant or does payload and/or Mab need to change?

A 65-year-old woman presents with de novo ER-positive mBC, receives ribociclib with anastrozole and initially responds but then experiences disease progression 6 months later. Biomarker evaluation is negative for ESR1 mutations and PIK3CA/AKT1/PTEN alterations. Regulatory and reimbursement issues aside, what would be your most likely next treatment?

	HER2 low (IHC 1+)	HER2 ultralow (IHC 0 with membrane staining)
 Dr Burstein	Abemaciclib + fulvestrant	Abemaciclib + fulvestrant
 Dr Cortés	Trastuzumab deruxtecan	Capecitabine
 Prof Dent	Trastuzumab deruxtecan	Depends on disease burden
 Dr Kalinsky	Everolimus + fulvestrant	Everolimus + fulvestrant
 Dr O'Shaughnessy	Abemaciclib + imlunestrant	Abemaciclib + imlunestrant
 Dr Rugo	Everolimus + fulvestrant	Everolimus + fulvestrant
 Dr Hurvitz	Everolimus + fulvestrant	Everolimus + fulvestrant
 Dr Jhaveri	Trastuzumab deruxtecan	Trastuzumab deruxtecan

A 65-year-old woman presents with de novo ER/PR-negative, HER2-low (IHC 1+), PD-L1-positive, BRCA-negative mBC, receives pembrolizumab/chemotherapy and initially responds but then experiences disease progression 6 months later. Regulatory and reimbursement issues aside, what would be your most likely next treatment?

 Dr Burstein	Sacituzumab govitecan
 Dr Cortés	Sacituzumab govitecan
 Prof Dent	Sacituzumab govitecan
 Dr Kalinsky	Sacituzumab govitecan
 Dr O'Shaughnessy	Sacituzumab govitecan
 Dr Rugo	Sacituzumab govitecan
 Dr Hurvitz	Trastuzumab deruxtecan
 Dr Jhaveri	Sacituzumab govitecan

RTP RESEARCH TO PRACTICE

Outside of a clinical trial setting, have you administered or would you administer trastuzumab deruxtecan to a patient with mBC as described?

	ER negative, HER2 ultralow	HR positive, HER2 IHC 0	HER2 IHC 0, HER2 mutation
 Dr Burstein	I have	I have	I have
 Dr Cortés	I have not but would for the right patient	I have not but would for the right patient	I have not but would for the right patient
 Prof Dent	I have	I have not but would for the right patient	I have
 Dr Kalinsky	I have	I have	I have
 Dr O'Shaughnessy	I have not but would for the right patient	I have not but would for the right patient	I have
 Dr Rugo	I have not but would for the right patient	I have not and would not	I have
 Dr Hurvitz	I have not but would for the right patient	I have not but would for the right patient	I have not but would for the right patient
 Dr Jhaveri	I have not and would not	I have not and would not	I have

Do you use chest imaging to monitor a patient receiving trastuzumab deruxtecan who otherwise does not require chest imaging?
How often would you order imaging if the patient remained asymptomatic?

	Use chest imaging	Frequency of chest imaging
 Dr Burstein	No	N/A
 Dr Cortés	Yes	Every 3 months
 Prof Dent	Yes	Every 6 to 9 weeks in first year
 Dr Kalinsky	Yes	Every 9 weeks
 Dr O'Shaughnessy	Yes	Every 9 weeks
 Dr Rugo	Yes	Every 9 to 12 weeks
 Dr Hurvitz	Yes	Every 8 to 12 weeks
 Dr Jhaveri	Yes	Every 6 to 9 weeks

Do you evaluate pulmonary function, either clinically or by specific tests? For a patient who develops Grade 1 interstitial lung disease (ILD) while receiving trastuzumab deruxtecan, how do you approach retreatment?

	Evaluate pulmonary function	Treatment of Grade 1 ILD
 Dr Burstein	No	Hold T-DXd until resolution
 Dr Cortés	No	Hold T-DXd, treat with steroids, consider restart
 Prof Dent	Yes, occasionally	Hold T-DXd, treat with steroids, consider restart
 Dr Kalinsky	No	Hold T-DXd until resolution
 Dr O'Shaughnessy	No	Hold T-DXd, treat with steroids, restart T-DXd at a reduced dose
 Dr Rugo	No	Hold T-DXd, treat with steroids, consider restart
 Dr Hurvitz	No	Hold T-DXd until resolution
 Dr Jhaveri	Yes	Hold T-DXd, treat with steroids, consider restart

T-DXd = trastuzumab deruxtecan

Agenda

MODULE 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Cortés

MODULE 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Kalinsky

MODULE 3: Available Therapies for Patients with HR-Positive, HER2-Negative Disease Progressing on CDK4/6 Inhibition — Dr Burstein

MODULE 4: Current and Potential Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Dr O'Shaughnessy

MODULE 5: Current and Future Strategies for Patients with Endocrine-Refractory HR-Positive mBC — Dr Rugo

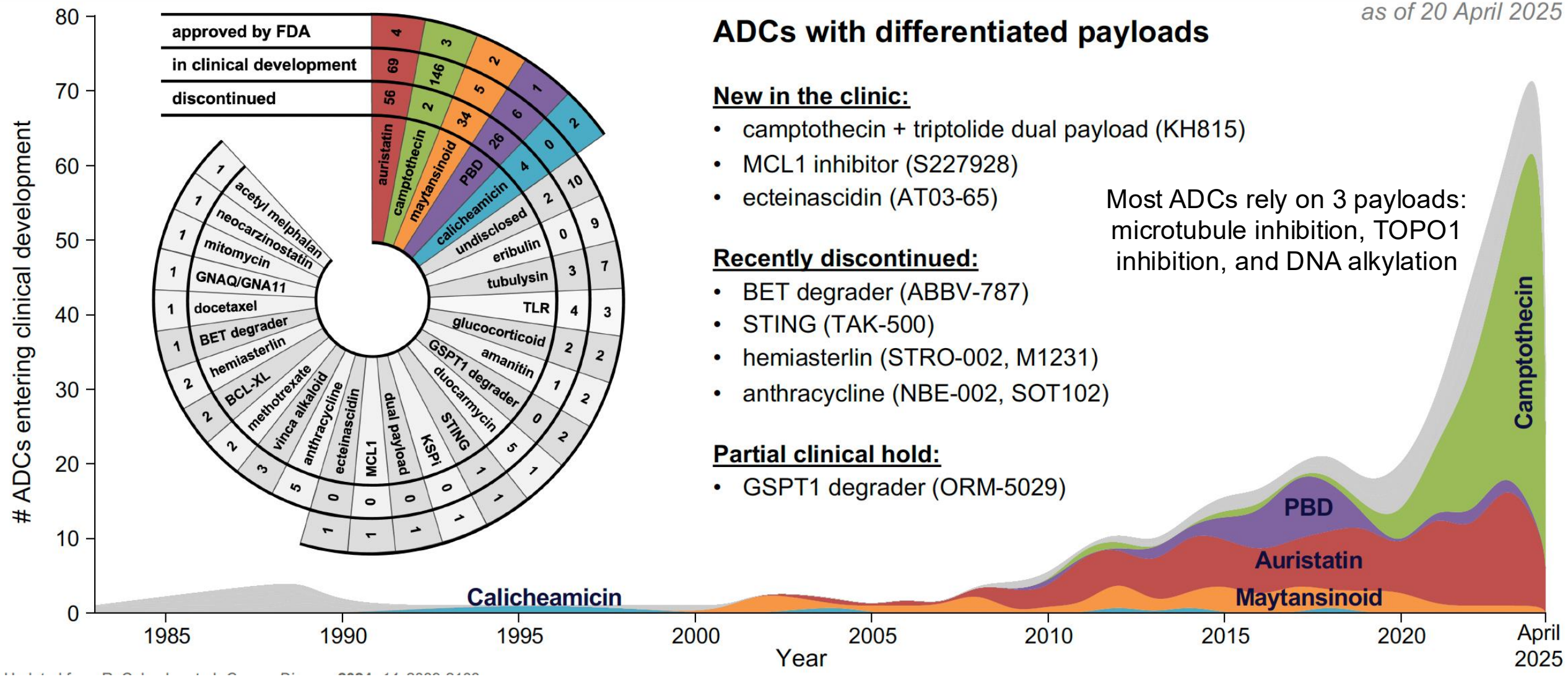
MODULE 6: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Prof Dent

RTP RESEARCH TO PRACTICE

ADCs: Current and Future Strategies for Patients with Endocrine-Refractory HR+ mBC (excluding T-DXd)

Hope S. Rugo, MD
Director, Women's Cancers Program
Division Chief, Breast Medical Oncology
Professor, Department of Medical Oncology & Therapeutics Research
City of Hope Comprehensive Cancer Center
Professor Emeritus, UCSF

Trends in ADC Development Over 4 Decades

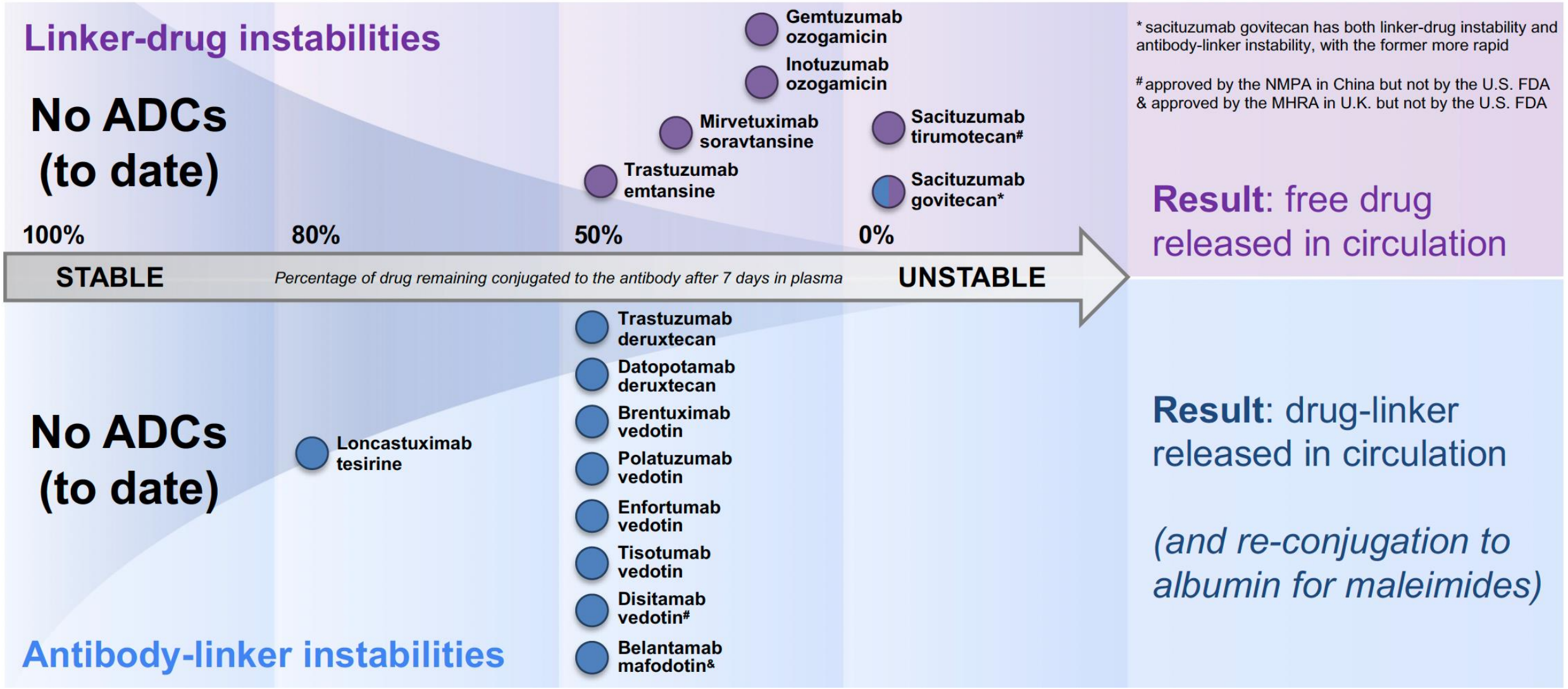


R. Colombo, AACR 2025 and Columbo et al, Cancer Discovery 2024

ADCs Approved for HR+/HER2- mBC as of 5.2025

	Sacituzumab govitecan (SG)	**Datopotamab deruxtecan*** (Dato-Dxd)	**Trastuzumab deruxtecan** (T-DXd)
Approval	HR+/HER2- mBC after at least one line of chemotherapy	HR+/HER2- mBC after at least one line of chemotherapy	Endocrine resistant, HER2 low/ultra-low HR+/HER2- mBC
Antibody	hRS7 Humanized IgG1 mAb	MAAP-9001a Humanized IgG1 mAb	hRS7 Humanized IgG1 mAb
Payload	SN38 (DNA Topo I inhibitor)	DXd (DNA Topo I inhibitor)	DXd (DNA Topo I inhibitor)
Linker cleavage	Enzymatic and pH-dependent	Enzymatic	Enzymatic
Bystander effect	Yes	Yes	Yes
DAR	7.6	4	~8
Half-life	11-14h	~5 days	~5-6 days
Dosing	D1, D8 of Q3W schedule	Q3W	Q3W

All Approved ADCs have Linker Instabilities



R. Colombo, AACR 2025 and adapted from Columbo et al, Cancer Discovery 2024

TROPiCS-02: Phase III Study of Sacituzumab Govitecan in Locally Recurrent Inoperable or Metastatic HR+/HER2– BC

Metastatic or locally recurrent inoperable HR+/HER2– breast cancer that progressed after:*

- **≥1 endocrine therapy** and **CDK4/6 inhibitor**, and **taxanes** in any setting
- **Two to four lines** of **chemotherapy** for metastatic disease
- Measurable disease by RECIST 1.1

R
1:1

N=543

Sacituzumab govitecan (SG) 10 mg/kg IV
Days 1 and 8, every 21-day cycle
(n=272)

Treatment of physician's choice (TPC)
(capecitabine, vinorelbine, gemcitabine or eribulin)
(n=271)

Treatment was continued until progression or unacceptable toxicity

Endpoints

Primary
- PFS by BICR

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

STRATIFICATION

- Visceral metastases (yes vs. no)
- Endocrine therapy in metastatic setting ≥6 months (yes vs. no)
- Prior lines of chemotherapy for metastatic disease (2 vs. 3/4)

<u>Demographics</u>

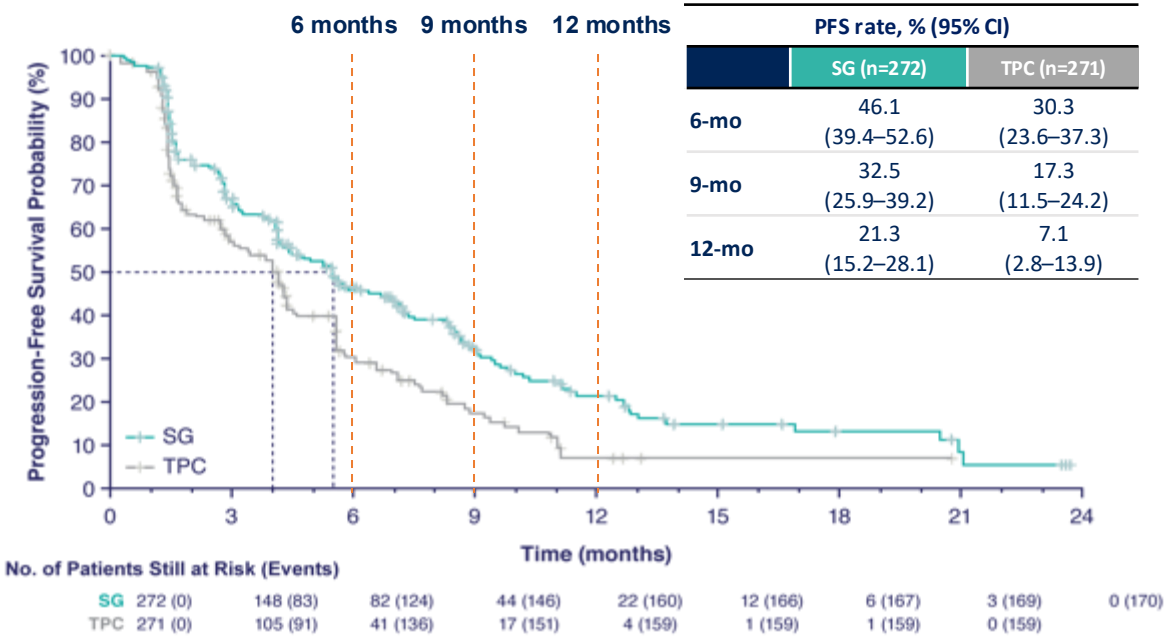
- Median lines of chemotherapy for MBC: 3
- 39% CDK4/6i >12 months
- 95% visceral metastases, 85% liver metastases

*Disease histology based on the ASCO/CAP criteria; †Single-agent standard-of-care treatment of physician's choice was specified prior to randomisation by the investigator.
ASCO, American Society of Clinical Oncology; BC, breast cancer; BICR, blinded independent central review; CAP, College of American Pathologists; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4/6; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IV, intravenous; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcome; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; SG, sacituzumab govitecan.
Adapted from: Rugo HS, et al. *J Clin Oncol*. 2022;40:3365–3376.

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

PFS[1]

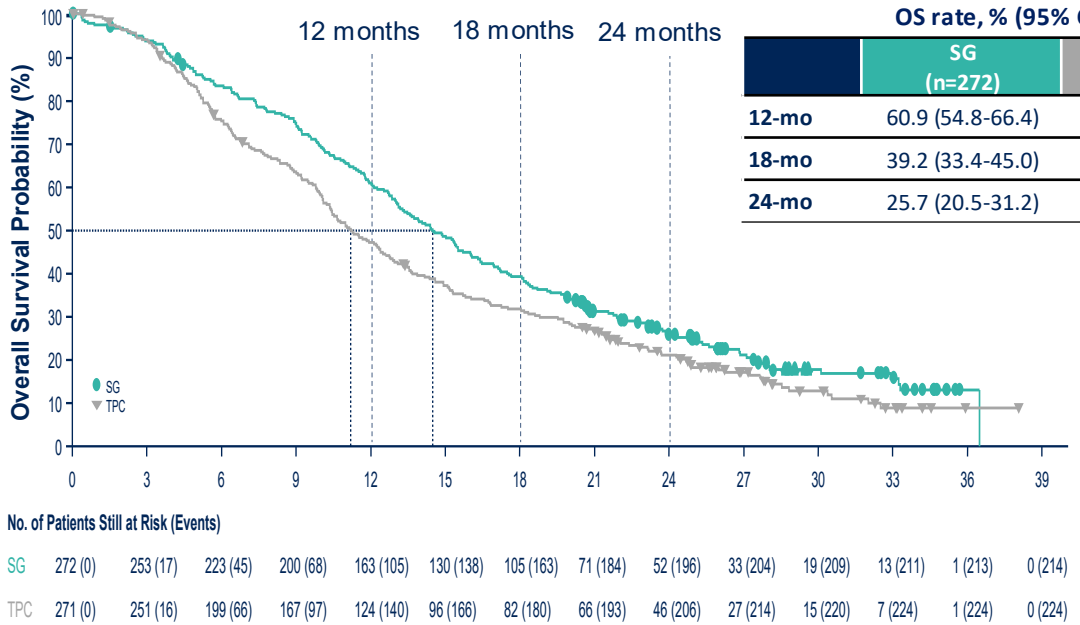
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

OS[2,3]

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



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

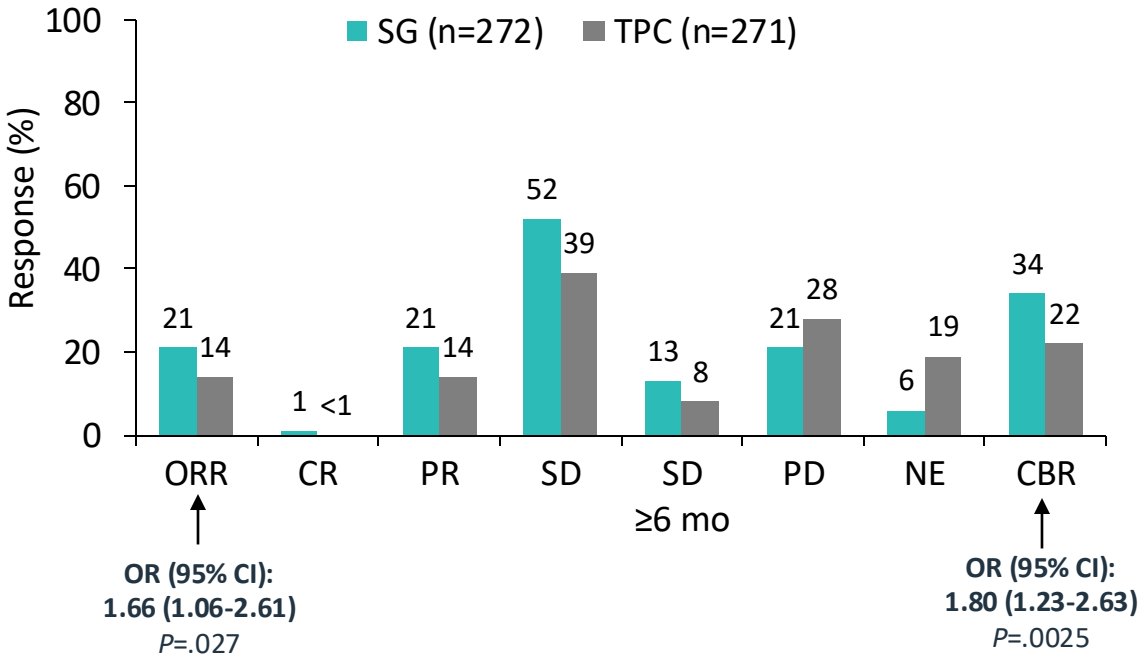
SG demonstrated a statistically significant improvement in PFS and OS vs TPC

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol. 2022.* doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76. 3. Tolaney et al, ASCO Abstract 1003; Rugo et al, Lancet 2023

No new toxicity signals compared to ASCENT

TROPiCS-02: Responses and Safety Summary

Tumor response



Median DoR, months (95% CI): 8.1 (6.7-8.9) vs **5.6** (3.8-7.9)

Safety summary

n (%)		SG (n=268)		TPC (n=249)	
AE Grade ≥3		199 (74)		149 (60)	
AEs → discontinuation		17 (6)		11 (4)	
AEs → dose delay		178 (66)		109 (44)	
AEs → dose reductions		91 (34)		82 (33)	
SAEs		74 (28)		48 (19)	
AEs → death[a]		6 (2)		0	
		Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic	Neutropenia	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia	98 (37)	20 (7)	69 (28)	8 (3)
	Thrombocytopenia	17 (6)	1 (<1)	41 (16)	9 (4)
GI	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)

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

Rugo HS et al. *J Clin Oncol*. 2022;40(29):3365-3376. Rugo HS et al. 2022 ESMO Congress. Abstract 1553O. Rugo HS et al. 2022 SABCS. Abstract GS1-11. Tolaney et al. 2023 ASCO Annual Meeting. Abstract 1003. Rugo HS et al. *Lancet*. 2023;402(10411):1423-1433.

ASCENT and TROPiCS-02: Safety Outcomes by UGT1A1 Status

UTG1A1

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

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

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

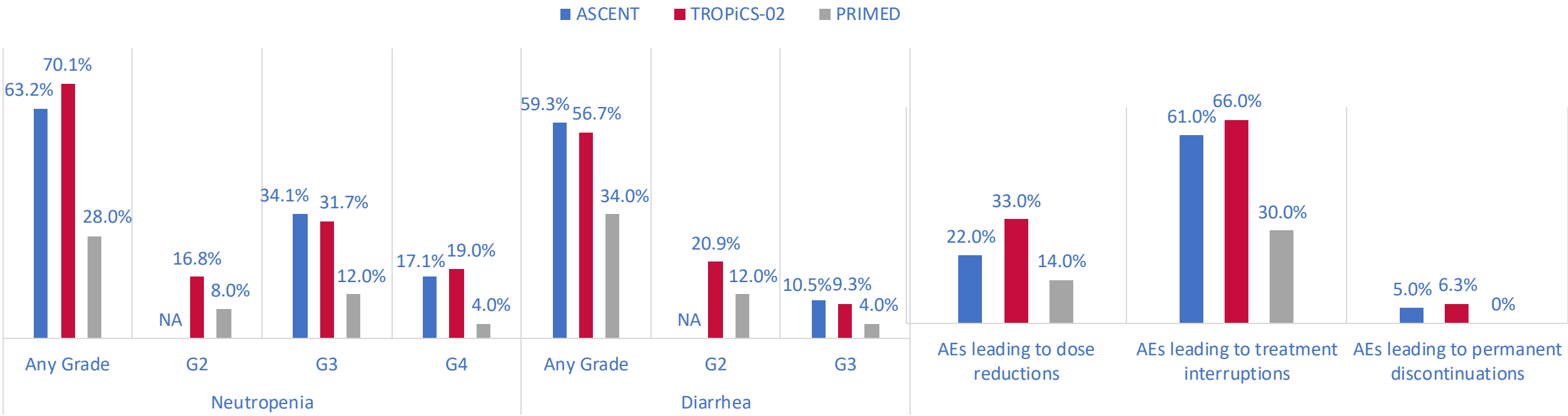
	ASCENT			TROPiCS-02		
Grade ≥3 TEAEs By UTG1A1 Status (%)	*1/*1 (wt)	*1/*28	*28/*28	*1/*1 (wt)	*1/*28	*28/*28
Neutropenia	53	47	59	45	57	64
Diarrhea	10	9	15	6	13	24
Anemia	4	6	15	6	8	8
Febrile neutropenia	3	5	18	6	7	4
Growth factor for neutropenia (initiated on/after first dose) overall 54%						
		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

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

Nelson, RS, et al. *Cancers.* 2021;13:1566.
Rugo, HS, et al. *npj Breast Cancer.* 2022;8:98.
Marmé, F, et al. *Annals of Oncol.* 2023;8(1suppl_4):101223-101223.
Rugo et al, Lancet 2023

Rates of Neutropenia and Diarrhea in ASCENT, TROPiCS-02, and PRIMED

AEs Leading to Dose Reductions, Rx Interruptions, and Permanent D/C in ASCENT, TROPiCS-02, and PRIMED



50 patients; loperamide 4 mg day 2,3,4 then 9, 10, 11; G-CSF SC day 3, 4 and 10, 11

G, grade; NA, not available.

Pérez-García JM, et al. Presented at 2024 ASCO Annual Meeting. Abstract 1101.

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

Key eligibility

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

R 1:1

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

TPC[b]
(n=367)

Continue until PD, unacceptable toxicity / other discontinuation criteria

Dual primary endpoints:

- PFS by BICR
- OS

Key secondary endpoints:

- ORR
- PFS (investigator assessed)
- Safety

Stratification factors

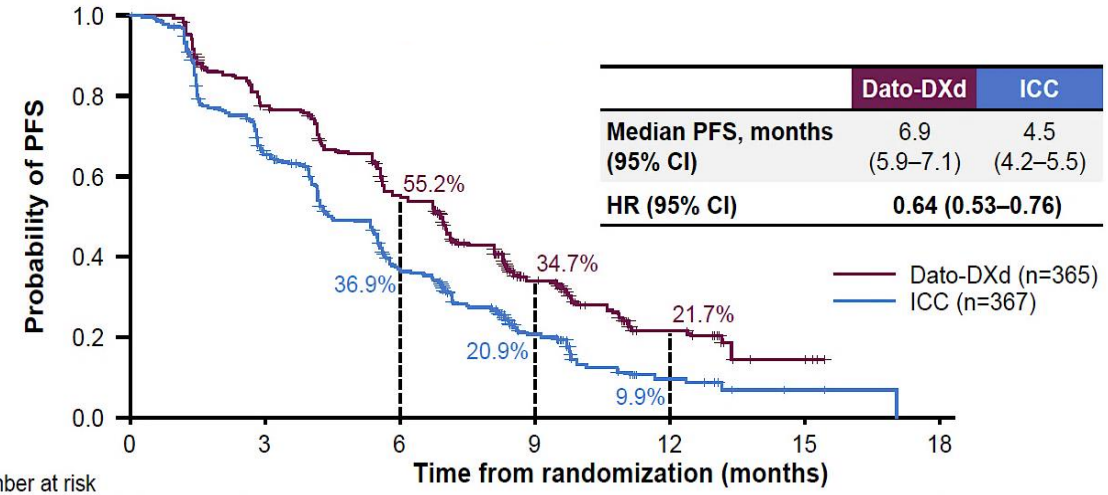
- Lines of chemo in unresectable/ metastatic setting (1 vs 2)
- Geographical location (US/Canada/ Europe vs ROW)
- Previous CDK4/6 inhibitor (yes vs no)

- At data cutoff (July 17, 2023), patients remaining on treatment:
  - Data-DXd, n=93
  - TPC, n=39
- Median FU: 10.8 months (now 22.8 mos)
- Median age 55, 1-2% AA/Black
- 82% prior CDK 4/6i
- Median one line of prior therapy (62%)

aIHC 0/1+/2+; ISH−; bInvestigator's choice of chemotherapy; cBy BICR per RECIST v1.1.
Dato-DXd, datopotamab deruxtecan; TPC, treatment of physician's choice.
Bardia A, et al. SABCS 2023. Abstract GS02-01; Bardia A, et al. J Clin Oncol 2025;43:285–96;

TROPION-Breast01: PFS and Time to Subsequent Therapy

PFS by investigator assessment

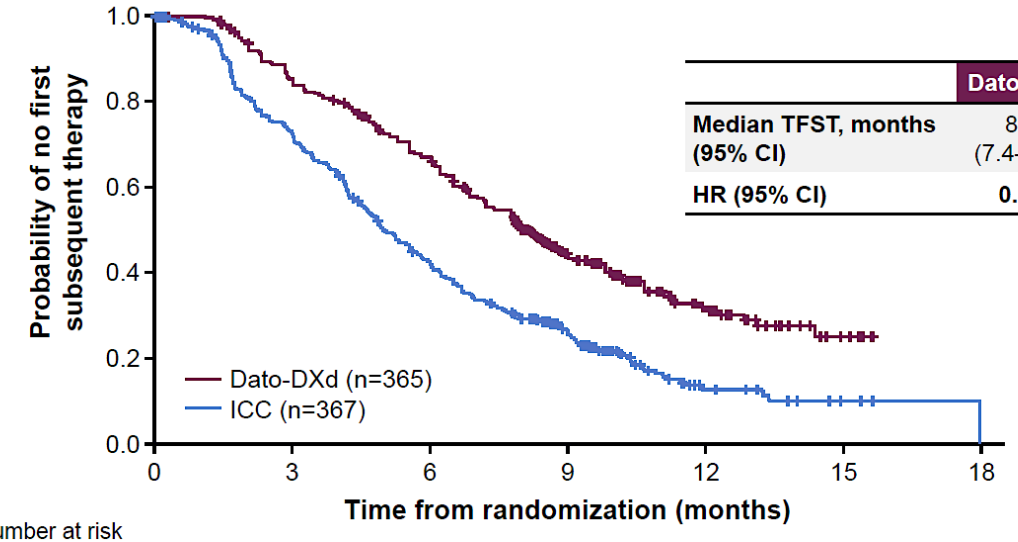


	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	0.64 (0.53–0.76)	

Number at risk

Dato-DXd	365	272	185	74	19	4	0
ICC	367	216	110	43	11	2	0

Time to subsequent therapy



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

Number at risk

Dato-DXd	365	304	231	110	36	7	0
ICC	367	256	147	65	13	4	0

PFS by BICR (primary endpoint)

- Median 6.9 vs 4.9 months
- HR 0.63 (95% CI: 0.52, 0)

Prior duration of CDK4/6i, ≤12 months

	Dato-DXd (n=151)	ICC (n=136)
Median PFS (95% CI), months	6.9 (5.5, 8.1)	4.2 (4.0, 5.5)
HR (95% CI)	0.61 (0.45, 0.81)	

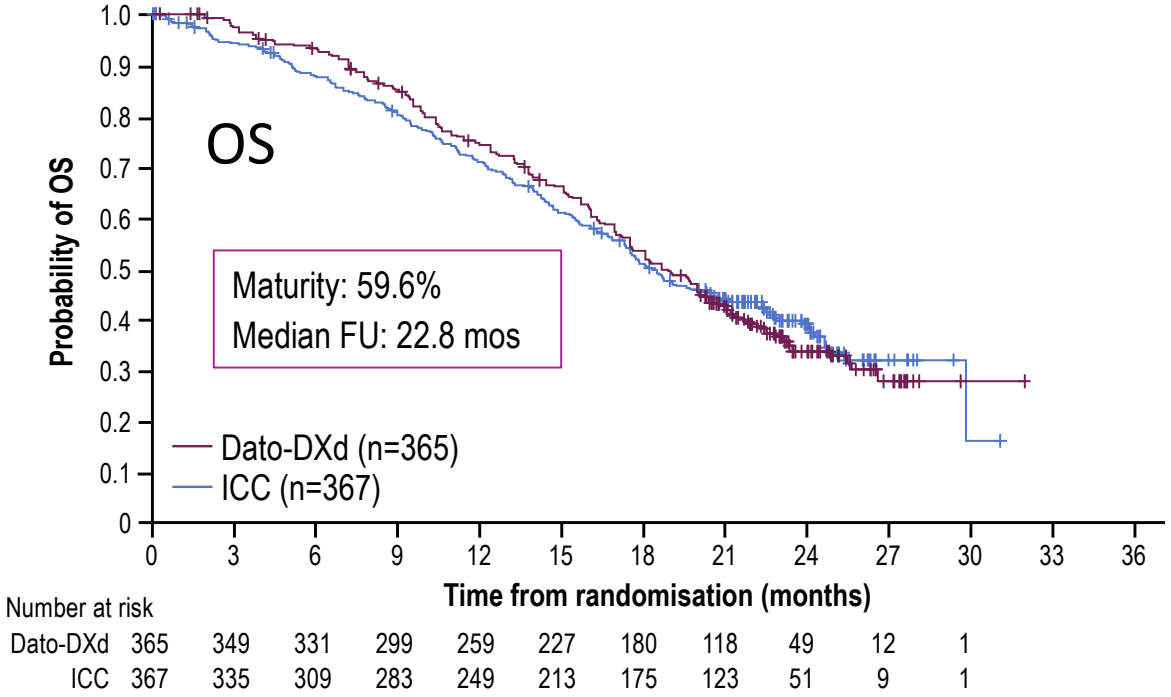
Prior duration of CDK4/6i, >12 months

	Dato-DXd (n=153)	ICC (n=164)
Median PFS (95% CI), months	7.1 (5.8, 8.5)	5.0 (4.1, 5.7)
HR (95% CI)	0.61 (0.45, 0.82)	

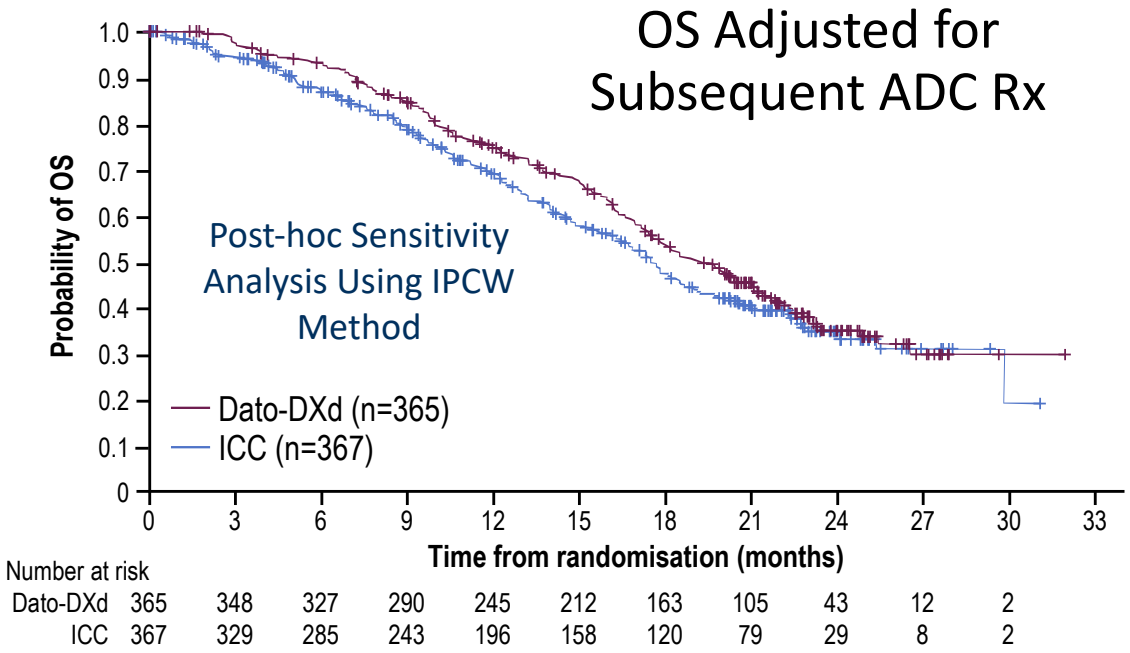
Bardia A, et al. SABCS 2023. Abstract GS02-01; Bardia A, et al. J Clin Oncol 2025;43:285–96;

Subsequent Anticancer Therapy and Overall Survival

- Use of ADCs as subsequent therapy after discontinuation of study treatment was imbalanced between Dato and ICC
- 74 vs 79% received subsequent therapy; 12 vs 24% received an ADC, most T-DXd



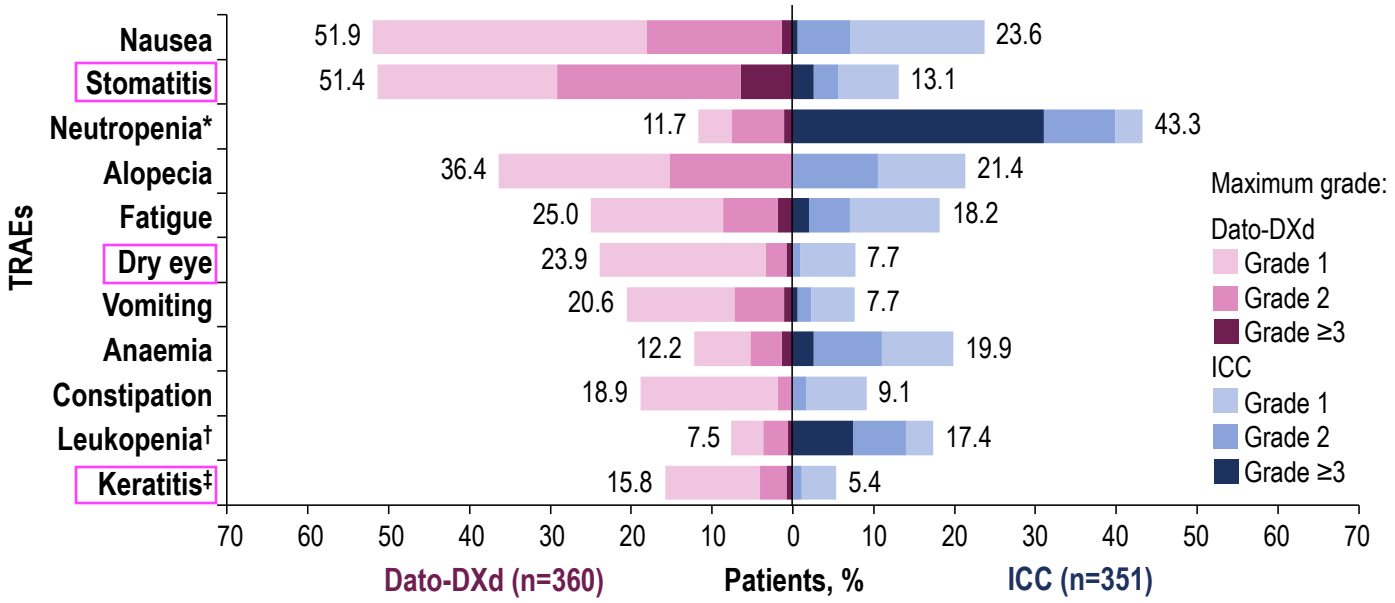
	Dato-DXd	ICC
OS events, n (%)	223 (61)	213 (58)
Median OS, months (95% CI)	18.6 (17.3–20.1)	18.3 (17.3–20.5)
HR (95% CI)	**1.01 (0.83–1.22)**	



	Dato-DXd	ICC
OS events, n (%)	195 (53)	177 (48)
Median OS, months	19.1	17.5
HR (95% CI)	0.86 (0.70–1.06)	

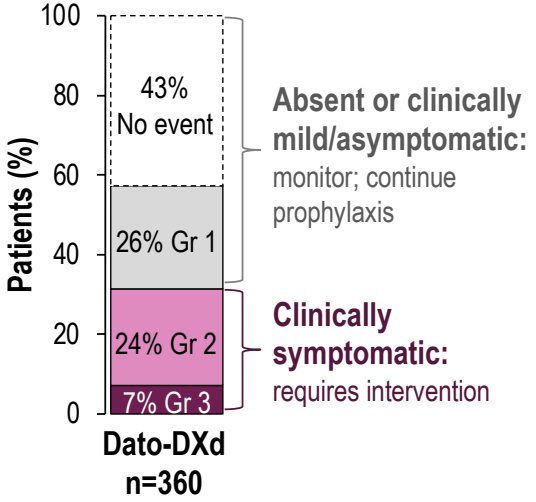
Data cutoff: 24 July 2024.

TRAEs Occurring in ≥10% of Patients and TRAEs of Special Interest

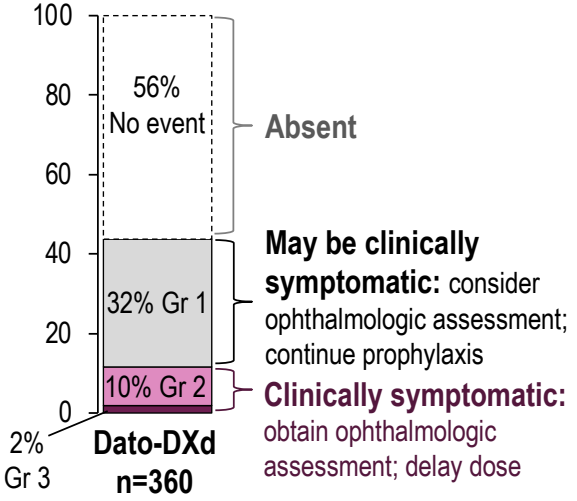


Data cutoff: 24 July 2024. Data are ordered according to frequency in either the Dato-DXd or ICC arms.
*Grouped term comprising neutropenia and neutrophil count decreased. †Grouped term comprising white blood cell count decreased and leukopenia. ‡Grouped term comprising keratitis, punctate keratitis, ulcerative keratitis.

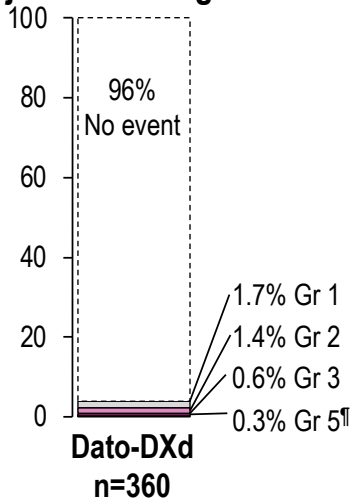
Oral mucositis/stomatitis*



Ocular surface events†



Adjudicated drug-related ILD‡



FDA approves datopotamab deruxtecan-dlnk for unresectable or metastatic, HR-positive, HER2-negative breast cancer

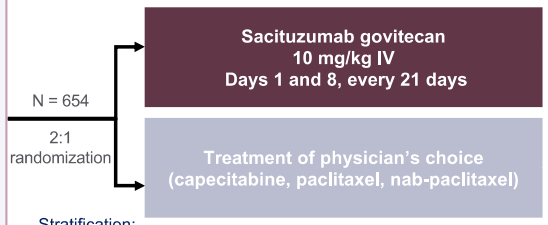
January 17, 2025, datopotamab deruxtecan-dlnk received US FDA approval for the treatment of adult patients with unresectable or metastatic, HR+/HER2- mBC *who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease*.

Steroid mouthwash and cold chips during infusion recommended to reduce stomatitis

Next Steps

Ascent-07:
First-line Chemotherapy in HR+

Key eligibility criteria:
- HR+/HER2* negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced mBC
- Progressed after 1 or more ET for mBC, or relapsed within 12 months of completing adjuvant ET or while receiving adjuvant ET
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Prior CDK 4/6i not required (no prior CDK 4/6i capped at 30%)



Primary Endpoint
- PFS by BICR

Key Secondary Endpoints
- OS
- ORR by BICR
- TTDD to Physical functioning

Secondary Endpoints
- PFS by investigator
- ORR by investigator
- DOR
- Safety

TroFuse-010: PD-L1-
Sacituzumab Tirumotecan in mHR+ BC

N=1200

Key inclusion criteria:
- Unresectable locally advanced or metastatic centrally-confirmed **HR+/HER2-** breast cancer
- Disease recurrence on/after **CDK4/6i** (in the early or metastatic setting)

Key exclusion criteria:
- Previously treated with **chemotherapy** in metastatic setting
- Disease **recurrence** within **6 months** after completion of adjuvant/neoadjuvant chemotherapy

Stratification Factors:
1) PD-L1 status (CPS<1 vs CPS 1-9 vs CPS≥10)
2) TROP2 expression (low+medium vs high)
3) Geographical Region (WE vs NA vs ROW)

R 3:3:2

- **Arm A: MK-2870**
- **Arm B: MK-2870 + Pembrolizumab**
- **Arm C: TPC***

***Treatment of Physician's Choice:**
Paclitaxel/ Nab-Paclitaxel/ Capecitabine/ Liposomal Doxorubicin

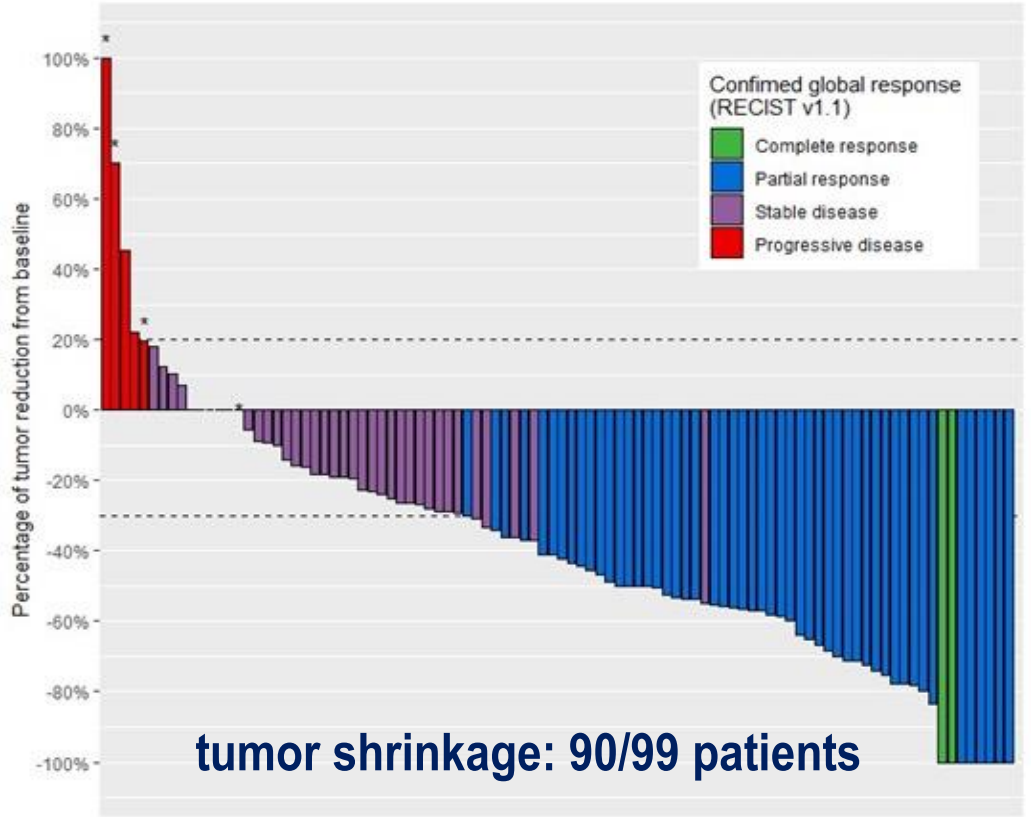
- Best sequencing in the metastatic setting?
- Optimal order of T-DXd (does order matter)?
- How effective are TROP2 ADCs after T-DXd?
- Should T-DXd always be given as first ADC for HER2 low/ultra-low?
- Change the target/change the payload?

- New agents under evaluation!

New Directions: Patritumab Deruxtecan

- Targets HER3, highly expressed across breast cancer subtypes; DAR 8
- ICARUS-BREAST01
  - Phase II study, HR+/HER2- mBC with one prior chemotherapy
  - Confirmed ORR 53.5%, 8.7 [8.1; 12.5]
    - No association of response with HER3 expression
  - PFS: 9.4 [8.1; 13.4]
- SOLTI VALENTINE
  - Neoadjuvant HER3-DXd +/-letrozole vs chemo (2:2:1); high risk HR+

	HER3-DXd N=50	HER3-DXd + LET N=48	Chemotherapy N=24	Overall N=122
pCR rate				
N	2	1	1	4
% (95%CI[a])	4.0% (0.5-13.7)	2.1% (0.1-11.1)	4.2% (0.1-21.1)	3.3% (0.9-8.2)
ORR				
N	35	39	17	91
% (95%CI[a])	70.0% (55.4-82.1)	81.3% (67.4-91.1)	70.8% (48.9-87.4)	74.6% (65.9-82.0)



TEAEs:

20% dose modifications

11% discontinuation

7% ILD, all grade 1

Toxicity

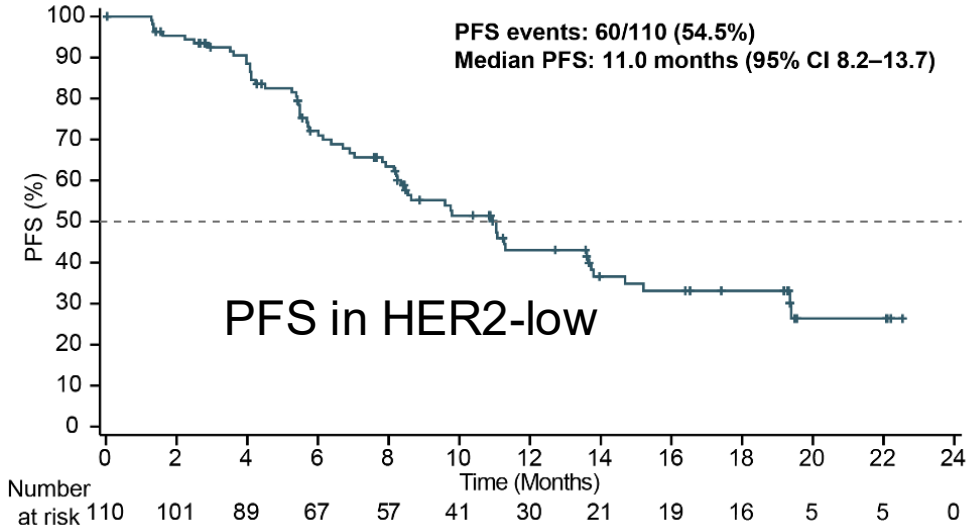
Nausea, fatigue, diarrhea (10% ≥gr 3),

12% >gr 3 neutropenia

Pistilli et al, ESMO 2024; Oliveira et al, SABCS 2024

Phase I Study of SHR-A1811, an anti-HER2 ADC

	HER2 +ve BC (N=136)	HER2-low BC (N=110)
BOR in EES		
CR	4 (3.0)	2 (1.9)
PR	102 (76.1)	65 (60.2)
SD	27 (20.1)	35 (32.4)
PD	1 (0.7)	6 (5.6)
ORR in EES	**79.1 (106/134, 71.2–85.6)**	**62.0 (67/108, 52.2–71.2)**
DoR, months	**23.6 (15.6–NE)**	**12.2 (7.3–NE)**
6-month rate	89.1	77.3
12-month rate	66.9	51.4
PFS, months	**20.0 (15.1–NE)**	**11.0 (8.2–13.7)**
6-month rate	87.4	72.1
12-month rate	65.6	43.1



TRAEs	Any grade	Grade 3–5
Any	**384 (98.2)**	**247 (63.2)**
Neutrophil count decreased	289 (73.9)	185 (47.3)
Anemia	276 (70.6)	101 (25.8)
White blood cell count decreased	253 (64.7)	125 (32.0)
Nausea	241 (61.6)	5 (1.3)
Platelet count decreased	173 (44.2)	62 (15.9)
Alopecia	157 (40.2)	0
Decreased appetite	154 (39.4)	6 (1.5)
Vomiting	154 (39.4)	3 (0.8)
Aspartate aminotransferase increased	143 (36.6)	2 (0.5)
Alanine aminotransferase increased	126 (32.2)	3 (0.8)
Hypoalbuminemia	108 (27.6)	1 (0.3)
Weight decreased	98 (25.1)	2 (0.5)

ILD in 10 patients (**2.6%**), predominantly grade 1–2
EES: Efficacy evaluable set
43% HER2 low had 3 or more lines of therapy

Yao et al, SABCS 2024

Novel ADCs for HR+/HER2- mBC: Phase I Data

- Emi-Le
  - B7-H4 directed Dolasynthen ADC with auristatin F-HPA payload, DAR 6
  - Fast track FDA designation
  - 37 pts with HR+ mBC
    - Median 7 lines prior Rx
    - 54% prior T-DXd or SG
  - Most common TRAEs
    - transient AST increase, reversible proteinuria, low-grade fatigue, nausea
  - Response correlated with B7-H4 expression and dose
    - Responses seen in TNBC but 3 patients with high B7-H4 had PD

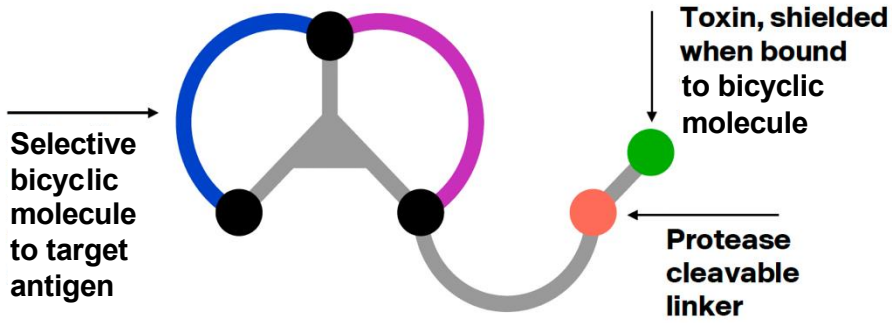
- Puxitatug samrotecan (P-Sam)
  - B7-H4 targeted TOP1i ADC with DAR 8
  - BLUESTAR: median 3 prior lines of chemotherapy
    - Toxicity: low grade nausea, fatigue, neutropenia
    - B7-H4 expressed in 68-80%
    - Confirmed ORR
      - 1.6mg/kg: ORR 40%, PFS 5.6 mo
      - 2.4 mg/kg: ORR 30%, PFS 8.1 mo

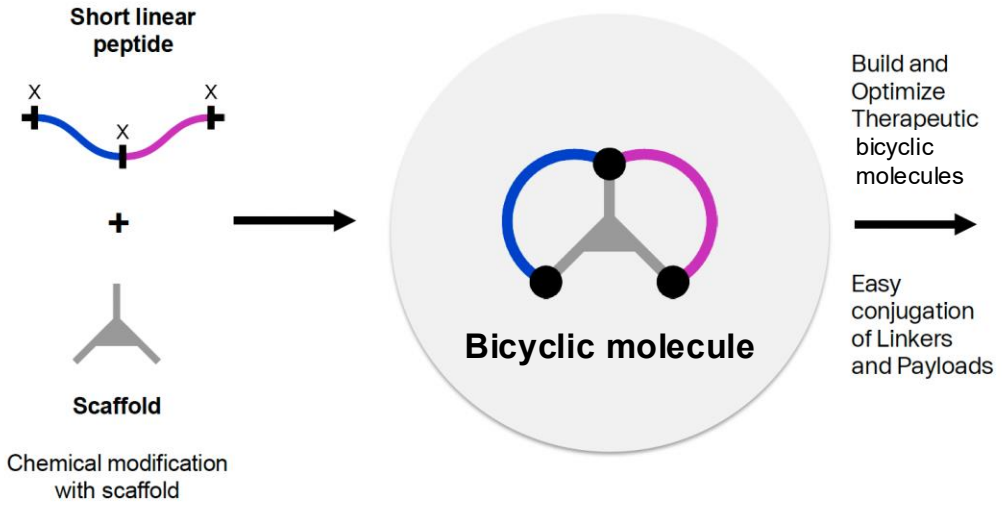
- Many others in phase I trials
  - IZA-BREN: EGFR/HER3 bispecific, TOP1i payload, data reported in mixed population

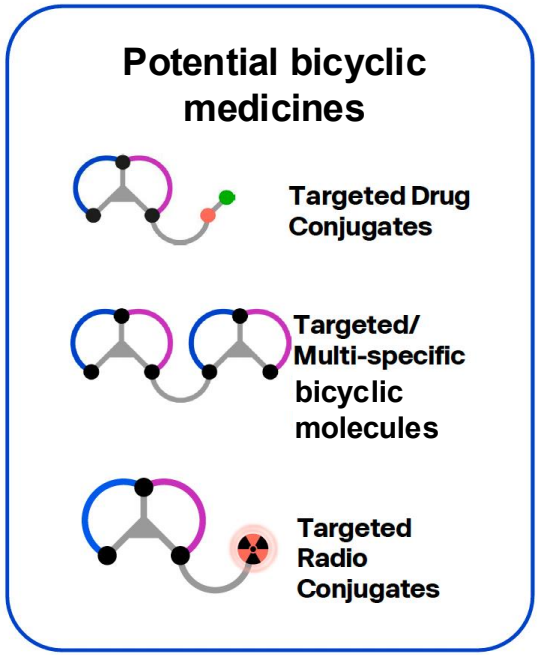
Baird et al, ESMO Breast 2025; Hamilton et al, ASCO 2025; Du et al, ESMO Breast 2025

New Types of Drug Conjugates

- Bicyclic peptide drug conjugates!
  - Short peptides chemically constrained with a central scaffold
- First-in-class: Zelenectide pevedotin
  - Nectin4 targeted, with MMAE payload
  - Amplified in ~20% HR+/HER2-





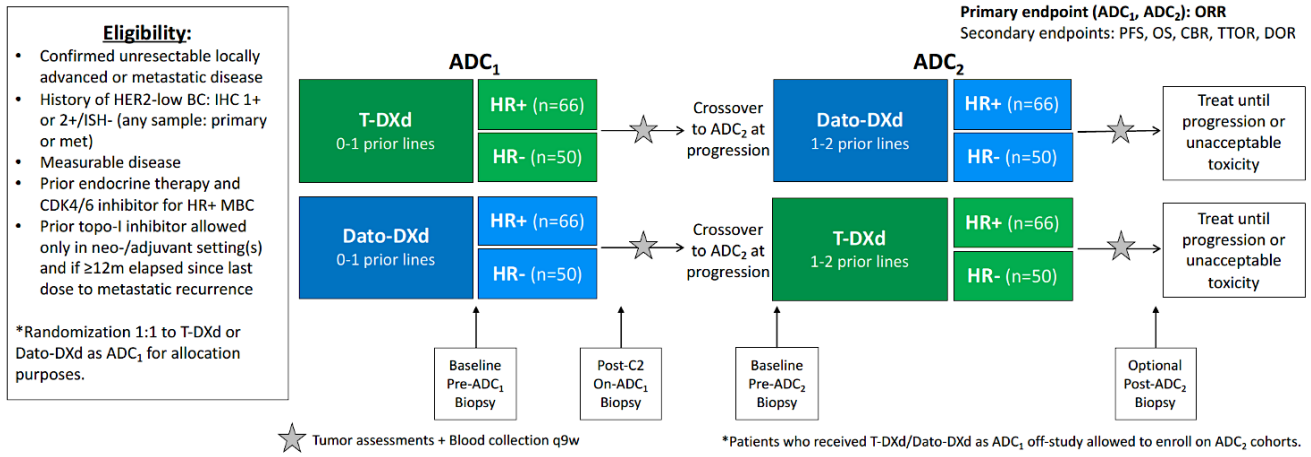


- Synthetic, highly constrained, tumor-targeting bicyclic peptides linked to cytotoxic payloads enable payload release in the tumor microenvironment
- Small, with molecular weight ~40 times less than some antibody-drug conjugates
- Rapidly distributed
- Short plasma half-lives that are believed to limit systemic exposure

Prospective Trials: Sequencing ADCs in HER2- MBC

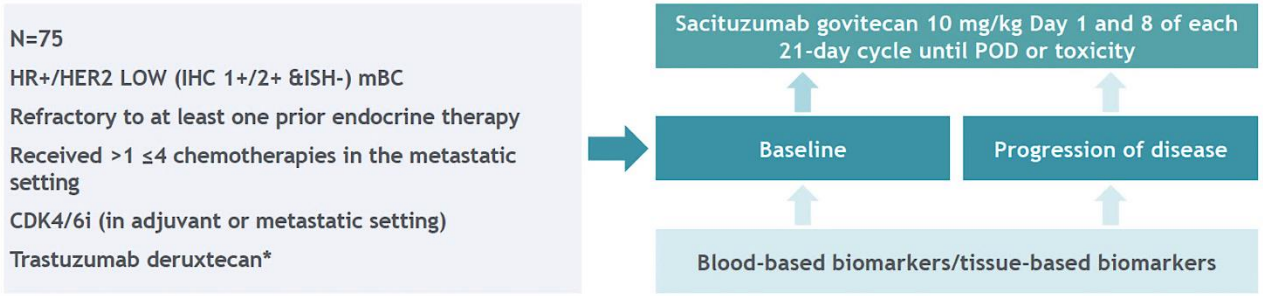
TBCRC 064 TRADE-DXd: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd: TRADE-DXd

NCT06533826; PI: Garrido-Castro



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

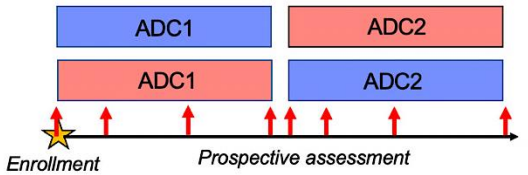
NCT06263543; PI: Mahtani



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

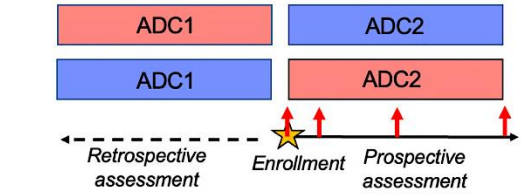
NCT06774027; PI: Huppert

Cohorts 1 & 2: Enrollment Prior to ADC1



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

Cohorts 3 & 4: Enrollment Prior to ADC2



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

= Study Blood Draw (20ml)

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

A 65-year-old woman presents with de novo ER-positive, HER2-negative (IHC 0) mBC, receives ribociclib with anastrozole and initially responds but then experiences disease progression 6 months later. Biomarker evaluation is negative for ESR1 mutations and PIK3CA/AKT1/PTEN alterations. She then receives capecitabine followed by further disease progression. Regulatory and reimbursement issues aside, what would be your most likely next treatment?

 Dr Burstein	Abemaciclib + fulvestrant
 Dr Cortés	Sacituzumab govitecan
 Prof Dent	Depends on disease burden; if burden is heavy may consider antibody-drug conjugate
 Dr Kalinsky	Datopotamab deruxtecan
 Dr O'Shaughnessy	Abemaciclib + imlunestrant
 Dr Rugo	Sacituzumab govitecan or datopotamab deruxtecan
 Dr Hurvitz	Datopotamab deruxtecan
 Dr Jhaveri	Sacituzumab govitecan or datopotamab deruxtecan

RTP RESEARCH TO PRACTICE

Based on published research data and your own clinical experience, indirectly, how would you compare the global efficacy and tolerability of datopotamab deruxtecan to that of sacituzumab govitecan for patients with HR-positive mBC?

	Efficacy	Tolerability
 Dr Burstein	I'm not sure	Sacituzumab govitecan is more tolerable
 Dr Cortés	Efficacy is about the same	Tolerability is about the same
 Prof Dent	Efficacy is about the same	Datopotamab deruxtecan is more tolerable
 Dr Kalinsky	Efficacy is about the same	Tolerability is about the same
 Dr O'Shaughnessy	Efficacy is about the same	Sacituzumab govitecan is more tolerable
 Dr Rugo	Efficacy is about the same	I'm not sure
 Dr Hurvitz	Efficacy is about the same	Datopotamab deruxtecan is more tolerable
 Dr Jhaveri	Efficacy is about the same	Efficacy is about the same

What is the primary toxicity patients experience with datopotamab deruxtecan that leads to withholding this regimen?

 Dr Burstein	Ocular; rash
 Dr Cortés	As reported in TROPION-Breast01
 Prof Dent	Mucositis
 Dr Kalinsky	Stomatitis
 Dr O'Shaughnessy	Stomatitis
 Dr Rugo	Stomatitis
 Dr Hurvitz	Stomatitis
 Dr Jhaveri	Stomatitis

Based on the published literature and/or your clinical experience, approximately what proportion of patients with HR-positive mBC receiving datopotamab deruxtecan experience mucositis? What preemptive strategies, if any, do you employ to prevent the development of mucositis associated with datopotamab deruxtecan?

	Chance of developing mucositis	Preemptive strategies
 Dr Burstein	10%	Steroid mouth rinse
 Dr Cortés	As reported in TROPION-Breast01	Steroid mouth rinse
 Prof Dent	40%	Ice chips/popsicles; steroid mouth rinse
 Dr Kalinsky	40%	Steroid mouth rinse
 Dr O'Shaughnessy	50%	Steroid mouth rinse; diet
 Dr Rugo	At least 30%	Steroid mouth rinse
 Dr Hurvitz	20%	Steroid mouth rinse
 Dr Jhaveri	50% - 60%	Steroid mouth rinse; ice chips; dental hygiene

Based on the published literature and/or your clinical experience, approximately what proportion of patients with HR-positive mBC receiving datopotamab deruxtecan experience ILD?
What is your approach to screening for ILD in patients with HR-positive mBC receiving datopotamab deruxtecan?

	Chance of developing ILD	Screening approach
 Dr Burstein	<5%	None
 Dr Cortés	As reported in TROPION-Breast01	None
 Prof Dent	Very few	Not approved
 Dr Kalinsky	~2%	Scans every 9 weeks
 Dr O'Shaughnessy	5%	None
 Dr Rugo	3% to 5%	Every 12 weeks, starting at 9 weeks
 Dr Hurvitz	<10%	Every 12 weeks
 Dr Jhaveri	1% - 2%	—

Agenda

MODULE 1: Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Cortés

MODULE 2: Individualized Selection of Up-Front Therapy for Patients with HR-Positive, HER2-Negative mBC — Dr Kalinsky

MODULE 3: Available Therapies for Patients with HR-Positive, HER2-Negative Disease Progressing on CDK4/6 Inhibition — Dr Burstein

MODULE 4: Current and Potential Future Role of HER2-Targeted Therapy for HER2-Low and HER2-Ultralow Disease — Dr O'Shaughnessy

MODULE 5: Current and Future Strategies for Patients with Endocrine-Refractory HR-Positive mBC — Dr Rugo

MODULE 6: Selection and Sequencing of Therapy for Patients with Metastatic Triple-Negative Breast Cancer — Prof Dent

National Cancer Centre Singapore
SingHealth

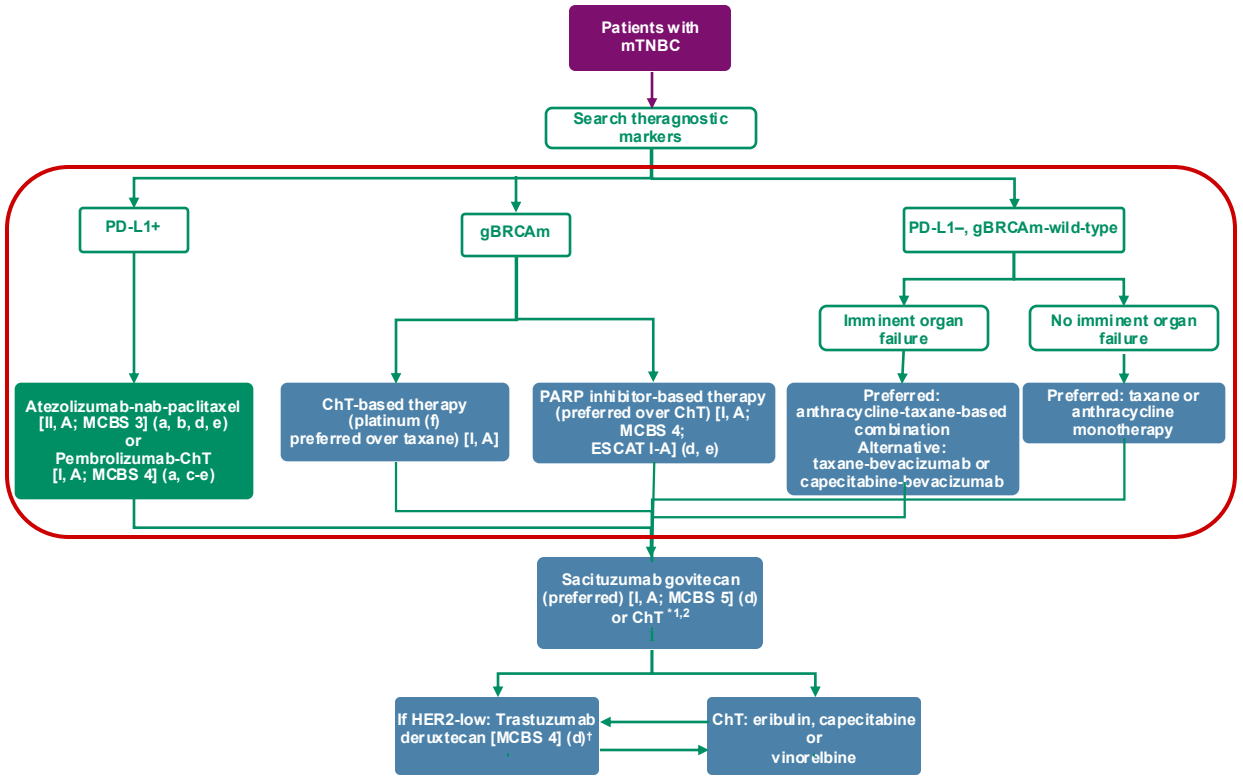
SingHealth DukeNUS ACADEMIC MEDICAL CENTRE
ONCOLOGY

Selection and Sequencing of Therapy for Patients with Metastatic TNBC (mTNBC)

Professor Rebecca Dent, MD FRCP (Canada)
Senior Consultant, Medical Oncology
National Cancer Centre Singapore, Duke-NUS Medical School

Current ESMO and National Comprehensive Cancer Network® (NCCN®) mTNBC treatment algorithm

Living ESMO Guidelines (May 2023)[1]



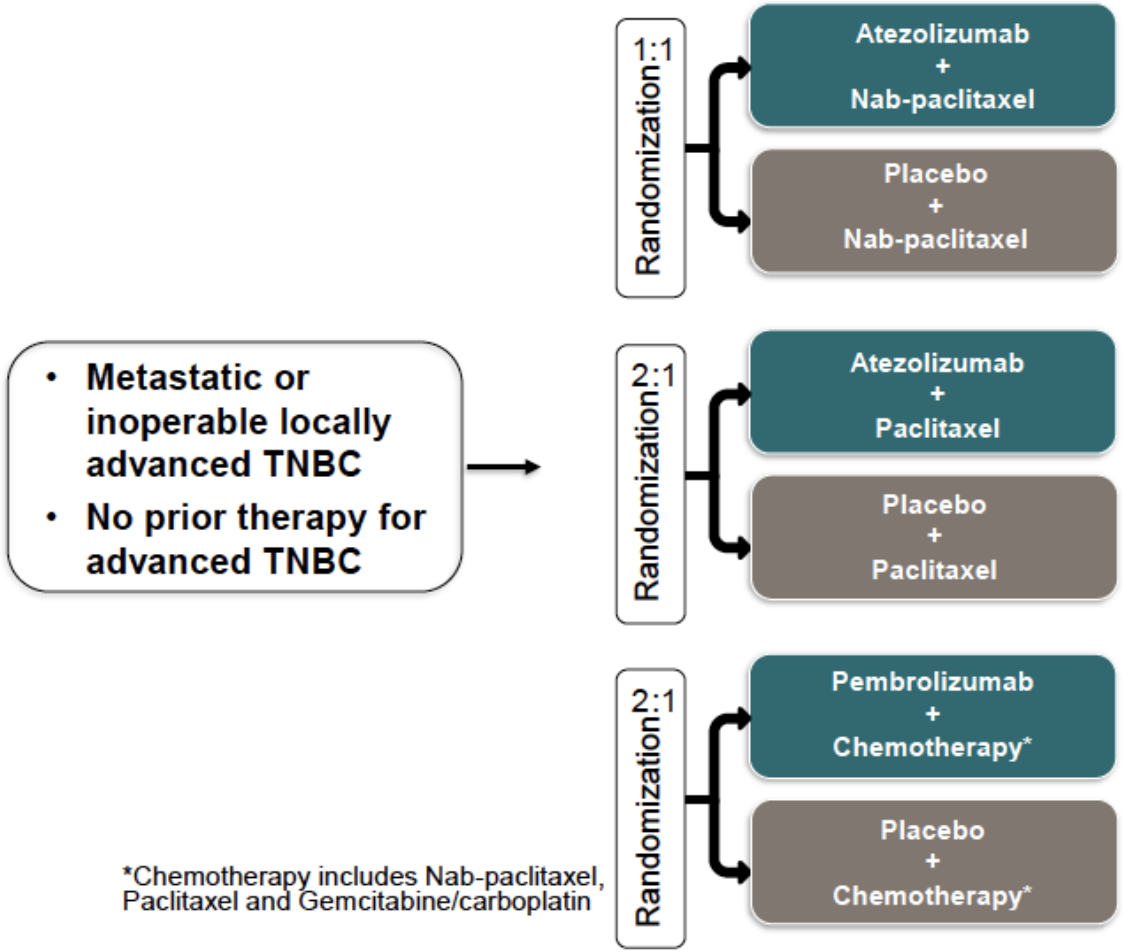
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Recommended Systemic Therapy Regimens For Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease[3]

HR-Negative and HER2-Negative (Triple-negative breast cancer; TNBC)

Setting	Subtype/Biomarkers	Regimen	
First line	PD-L1 CPS≥10 regardless of germline *BRCA1/2*mut status	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, or gemcitabine and carboplatin)[a]	NCCN Category 1, Preferred
	PD-L1 CPS<10 and no germline *BRCA1/2*mut	Systemic chemotherapy	
	PD-L1 CPS<10 and germline *BRCA1/2*mut	PARPi (olaparib, talazoparib) Platinum (cisplatin or carboplatin)	Category 1, Preferred
Second line	Germline *BRCA1/2*mut	PARPi (olaparib, talazoparib)	Category 1, Preferred
		Sacituzumab govitecan[b]	Category 1, Preferred
		Systemic chemotherapy or targeted agents	
	No germline *BRCA1/2*mut and HER2 IHC 0+, 1+ or 2+/ISH negative	**Fam-trastuzumab deruxtecan-nxki[c,d]**	Category 1, Preferred
Third line and beyond	Any	Systemic chemotherapy	
	Biomarker positive (i.e. MSI-H, NTRK, RET, TMB-H)	Targeted agent and emerging biomarker options	

Immunotherapy in TNBC

- Phase 3 trials assessing immune-checkpoint inhibitors in first-line setting (**TFI>6 months**)



IMpassion 130
N=902
TFI ≥12 months
VENTANA SP142 assay

Co-Primary endpoints:
PFS & OS
(ITT → Others)

Positive

IMpassion 131
N=943

Primary endpoint:
PFS
(PDL1+ 1% → Others)

Negative

Keynote 355
N=847
TFI ≥6 months
Dako 223C assay

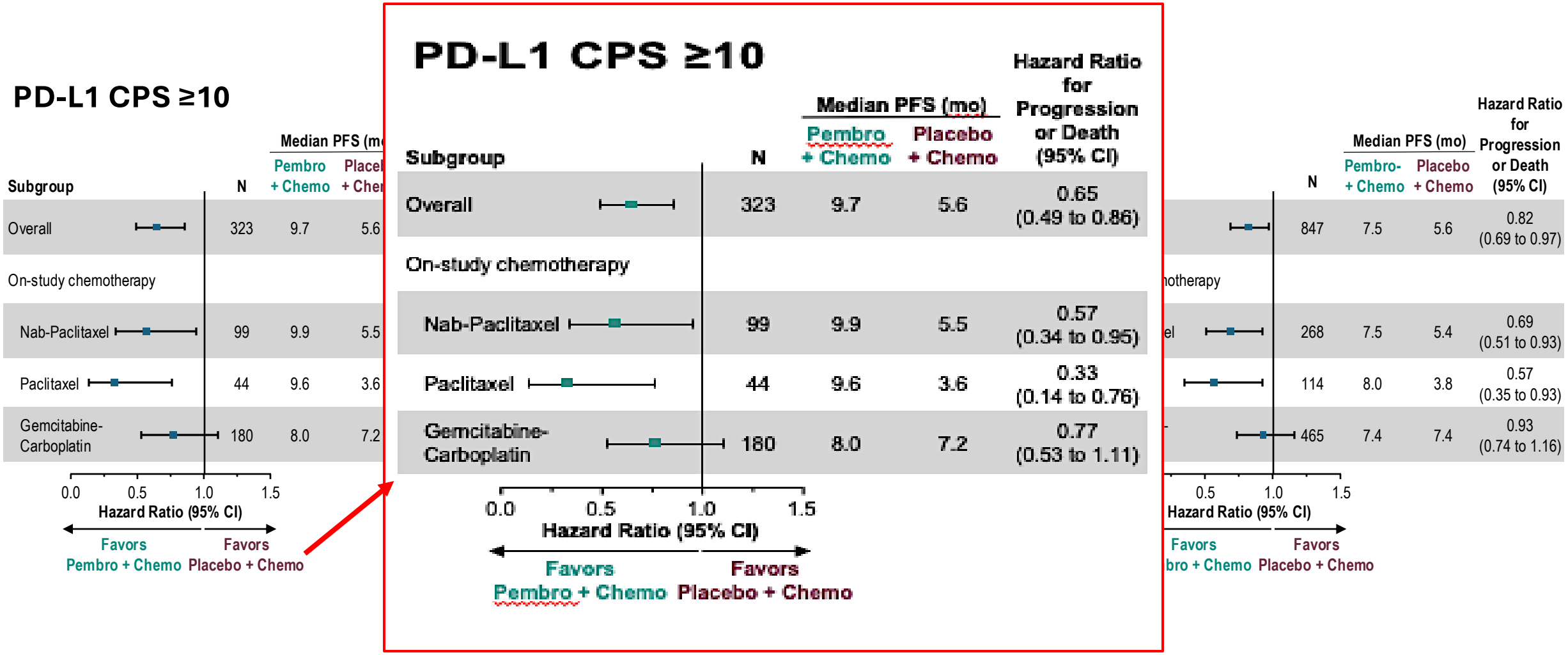
Co-Primary endpoints:
PFS & OS
(PDL1+ CPS≥10 → Others)

Positive

TORCHLIGHT: Toripalimab + nab-paclitaxel vs. nab-paclitaxel alone; Improvement PFS and OS

Positive

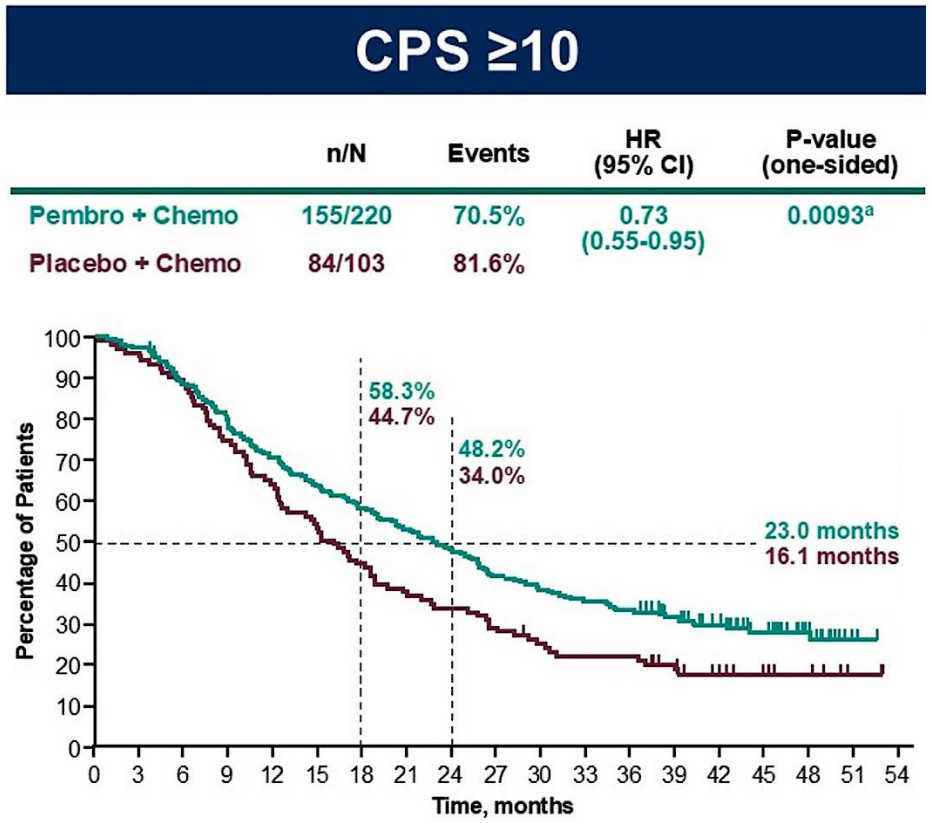
KEYNOTE 355 Progression-Free Survival in Subgroup by On-Study Chemotherapy

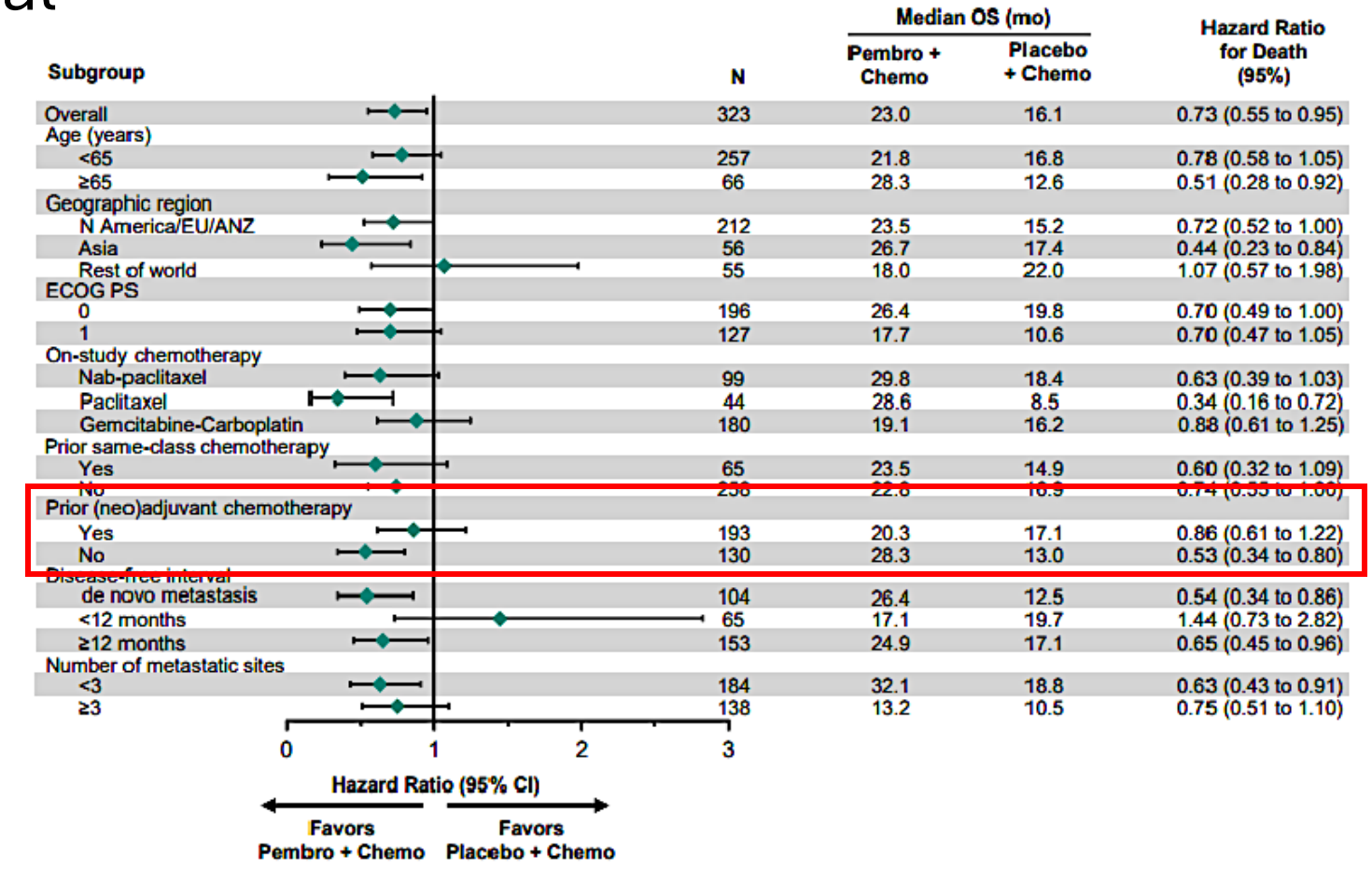


Rugo H SABCS 2020

Immunotherapy in mTNBC

- Keynote-355: Overall Survival





Which is the benefit of ICIs in early recurrent mTNBC?

Cortes, NEJM 2022

CAN Immunotherapy work in patients with mTNBC who experience early relapse?

IMpassion132

- Unresectable locally advanced/ metastatic TNBC
- Prior anthracycline and taxane for early TNBC
- Disease progression <12 months after last treatment with curative intent for early TNBC [a]
- No prior chemotherapy for advanced TNBC
- Known PD-L1 status (SP142)

R 1:1

Carboplatin/gemcitabine or capecitabine[b] + atezolizumab 1200 mg q3w

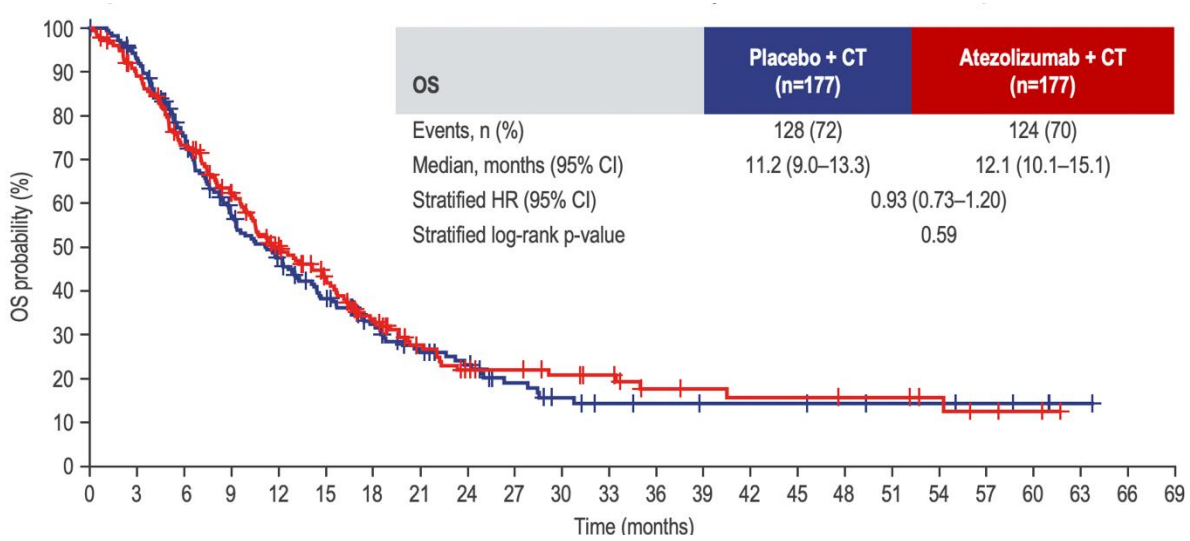
Carboplatin/gemcitabine or capecitabine[b] + placebo q3w

Treatment continued until disease progression or unacceptable toxicity

Stratification factors:
- Visceral (lung and/or liver) metastases
- CT backbone
- PD-L1 status (during all-comer enrolment)

Primary endpoint:
- OS (hierarchical testing: PD-L1+ TNBC[c] then, if positive, modified ITT population[d])

No improvement in OS in PD-L1+ TNBC



OS	Placebo + CT (n=177)	Atezolizumab + CT (n=177)
Events, n (%)	128 (72)	124 (70)
Median, months (95% CI)	11.2 (9.0–13.3)	12.1 (10.1–15.1)
Stratified HR (95% CI)	0.93 (0.73–1.20)	
Stratified log-rank p-value	0.59	

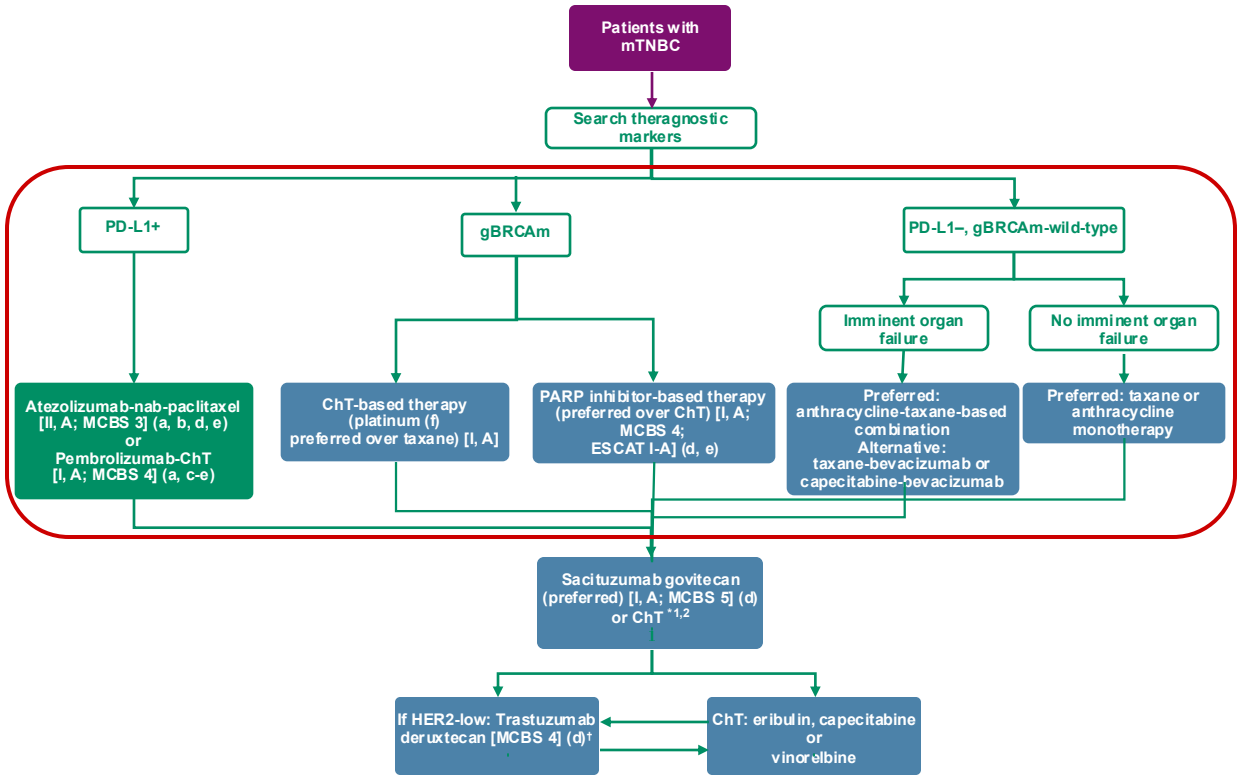
- 68% DFI<6mo
- 73% recv'd carbo/gem

Poor Outcomes:
PFS ~4 mo | OS ~12 mo

Dent R et al, Annals of Oncology 2024

Current ESMO and National Comprehensive Cancer Network® (NCCN®) mTNBC treatment algorithm

Living ESMO Guidelines (May 2023)[1]



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Recommended Systemic Therapy Regimens For Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease[3]

HR-Negative and HER2-Negative (Triple-negative breast cancer; TNBC)

Setting	Subtype/Biomarkers	Regimen	
First line	PD-L1 CPS≥10 regardless of germline *BRCA1/2*mut status	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, or gemcitabine and carboplatin)[a]	NCCN Category 1, Preferred
	PD-L1 CPS<10 and no germline *BRCA1/2*mut	Systemic chemotherapy	
	PD-L1 CPS<10 and germline *BRCA1/2*mut	PARPi (olaparib, talazoparib) Platinum (cisplatin or carboplatin)	Category 1, Preferred
Second line	Germline *BRCA1/2*mut	PARPi (olaparib, talazoparib)	Category 1, Preferred
		Sacituzumab govitecan[b]	Category 1, Preferred
		Systemic chemotherapy or targeted agents	
	No germline *BRCA1/2*mut and HER2 IHC 0+, 1+ or 2+/ISH negative	**Fam-trastuzumab deruxtecan-nxki[c,d]**	Category 1, Preferred
Third line and beyond	Any	Systemic chemotherapy	
	Biomarker positive (i.e. MSI-H, NTRK, RET, TMB-H)	Targeted agent and emerging biomarker options	

PARP inhibitors in metastatic TNBC

OLYMPIAD

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

R 2:1

Olaparib
300 mg tablets bd

Chemotherapy treatment of physician's choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

EMBRACA

Patients with locally advanced or metastatic HER2 negative BC and a germline BRCA1/2 mutation

Stratification factors
- Number of prior CT regimens (0 or ≥1)
- TNBC or HR+
- History of CNS mets or no CNS mets

R 2:1

Talazoparib
1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

Physicians choice of therapy (PCT): capecitabine, eribulin, gemcitabine or vinorelbine

Caveat:
Neither study has platinum as control arm

Robson, NEJM 2017; Litton, NEJM 2018

PARP Inhibition is standard of CARE FOR METASTATIC BREAST CANCER in patients with gBRCAm

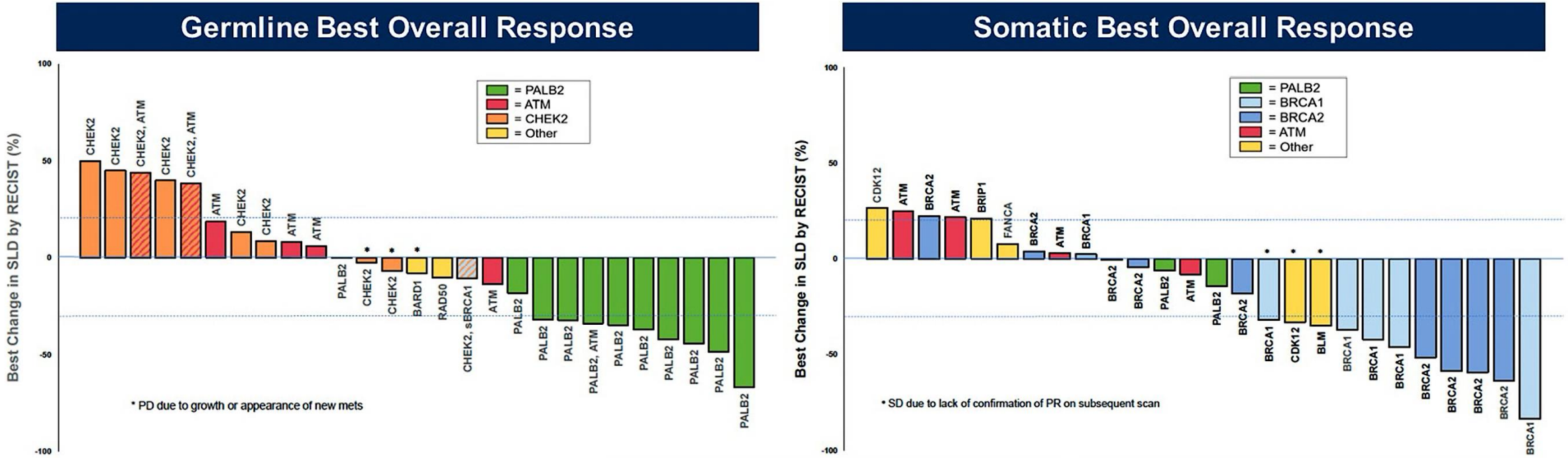
	Olaparib	Talazoparib
PFS	7 vs 4.2 (Δ 3 mos) (HR 0.58); p= 0.0009	8.3 vs 5.6 mos (Δ 3 mos) (HR 0.54); p< 0.0001
OS	HR 0.89 (NS)	HR 0.86 (NS)
ORR	59.9%	62.6%
mDOR	6.4 mos	5.4 mos

- Both trials showed benefit in terms of Quality of Life compared to chemotherapy

Robson M et al, NEJM 2017
Robson M et al, Eur J Cancer 2023
Litton J et al, NEJM 2018
Litton J et al, Ann Oncol 2020

PARP inhibitors in metastatic triple-negative breast cancer

- Beyond germline BRCA1 and BRCA2… Olaparib in **gPALB2 and sBRCA1/2**



PALB2 (N=13)	*BRCA1/2* (N=17)	*Only ATM or CHEK2* (N=17)
Germline: 9/11 PR (82%) Somatic: 0/2 (SD, limited assessments)	**Somatic: 8/16 PR (50%)**	Germline: 0/13 Somatic: 0/4

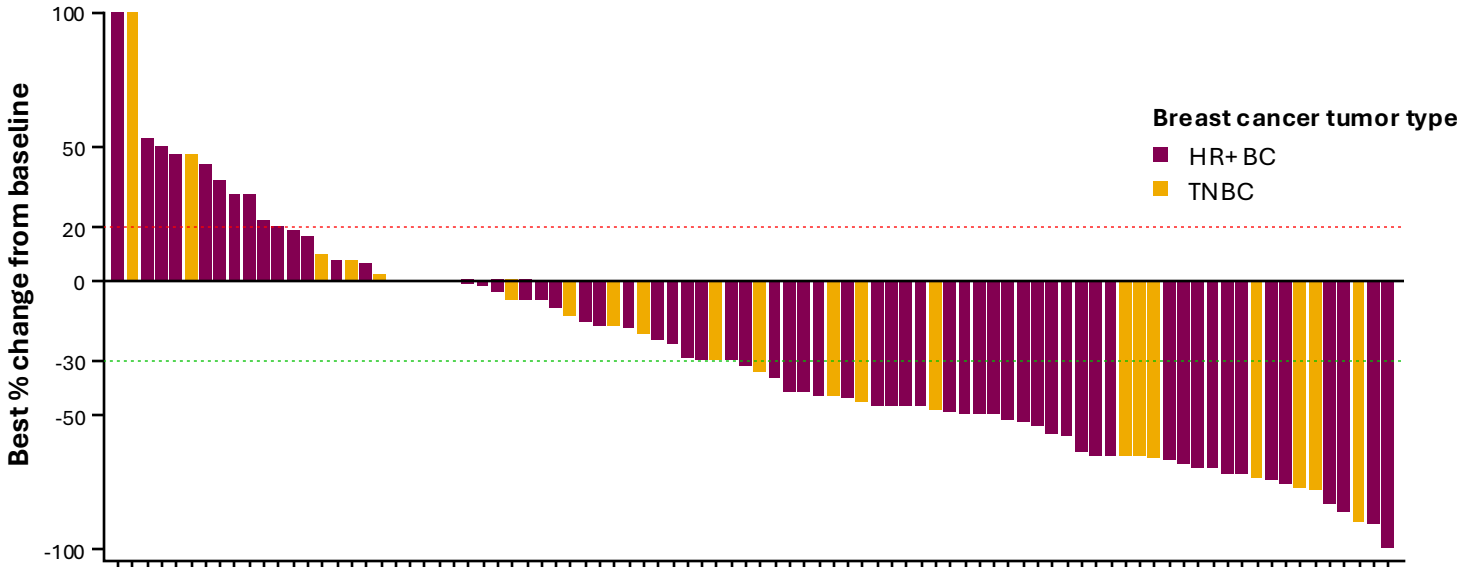
Tung, JCO 2020

PARP inhibitors in metastatic triple-negative breast cancer

- Next generation PARP1-selective inhibitors

- Saruparib is a first-in-class, potent new generation PARP inhibitor with high selectivity for PARP1.
- Wide therapeutic index, superior PK/PD properties and efficacy compared with approved PARP inhibitors
- Favorable safety profile and low rate of dose reduction compared with approved PARP inhibitors

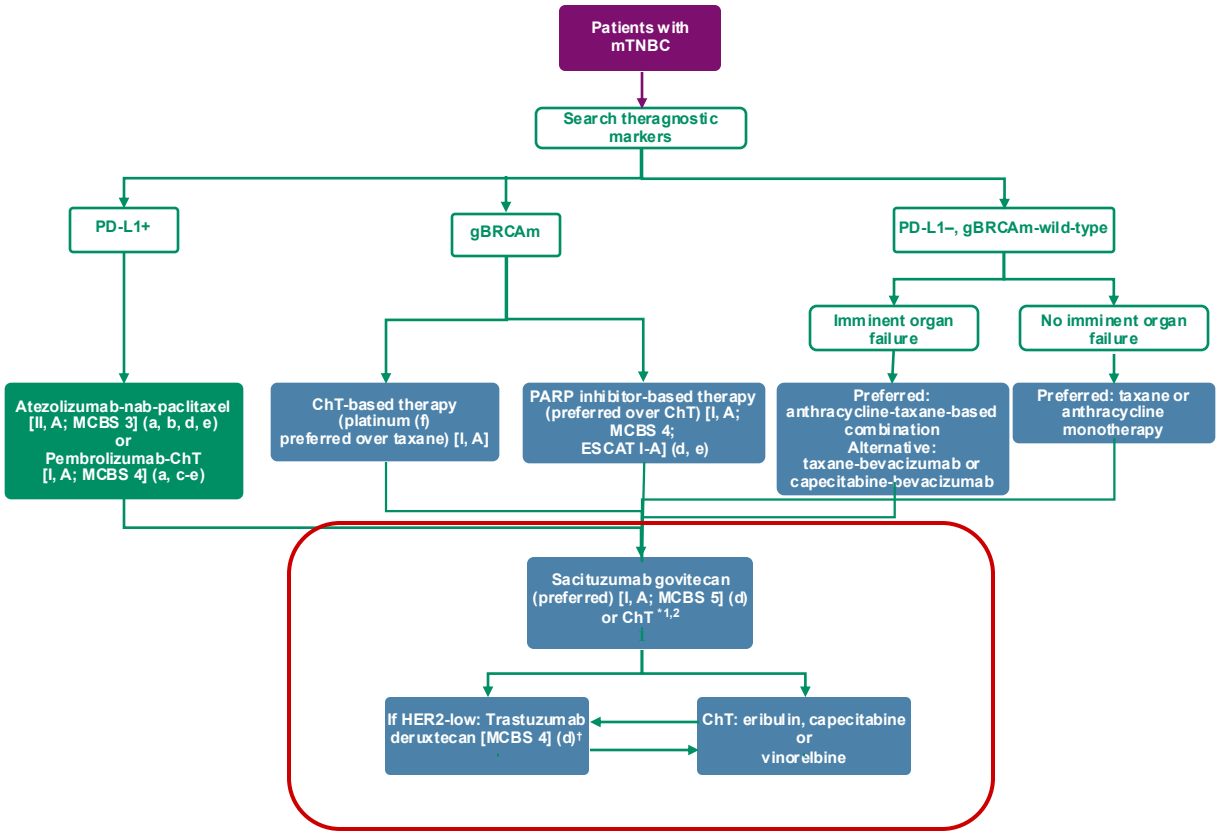
PETRA Trial with **Saruparib** (AZD5305)



Yap, AACR 2024

Current ESMO and National Comprehensive Cancer Network® (NCCN®) mTNBC treatment algorithm

Living ESMO Guidelines (May 2023)[1]



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Recommended Systemic Therapy Regimens For Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease[3]

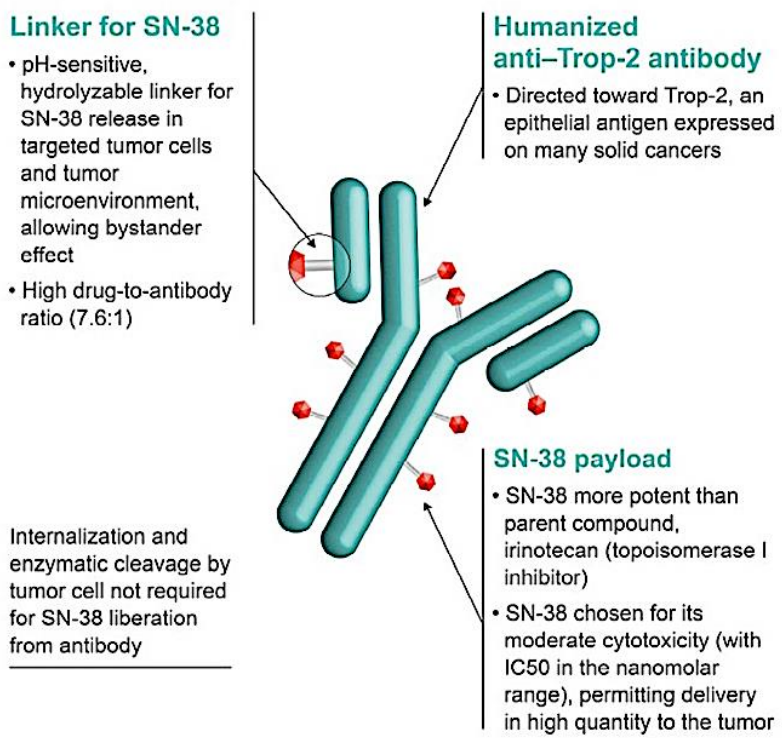
HR-Negative and HER2-Negative (Triple-negative breast cancer; TNBC)

Setting	Subtype/Biomarkers	Regimen	
First line	PD-L1 CPS≥10 regardless of germline *BRCA1/2*mut status	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, or gemcitabine and carboplatin)[a]	NCCN Category 1, Preferred
	PD-L1 CPS<10 and no germline *BRCA1/2*mut	Systemic chemotherapy	
	PD-L1 CPS<10 and germline *BRCA1/2*mut	PARPi (olaparib, talazoparib) Platinum (cisplatin or carboplatin)	Category 1, Preferred
Second line	Germline *BRCA1/2*mut	PARPi (olaparib, talazoparib)	Category 1, Preferred
		Sacituzumab govitecan[b]	Category 1, Preferred
		Systemic chemotherapy or targeted agents	
	No germline *BRCA1/2*mut and HER2 IHC 0+, 1+ or 2+/ISH negative	**Fam-trastuzumab deruxtecan-nxki[c,d]**	Category 1, Preferred
Third line and beyond	Any	Systemic chemotherapy	
	Biomarker positive (i.e. MSI-H, NTRK, RET, TMB-H)	Targeted agent and emerging biomarker options	

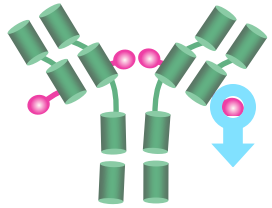
ADCs in metastatic triple-negative breast cancer

- Targeting Trop2 in mTNBC

Sacituzumab govitecan

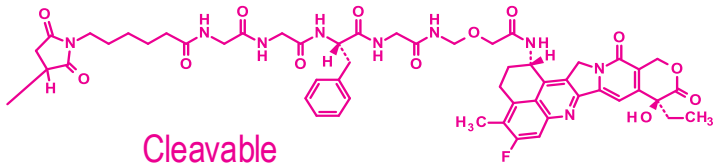


Datopotamab deruxtecan



- Payload mechanism of action: Topo-I inhibitor*
- High potency payload*
- Optimised drug to antibody ratio ≈4*†
- Payload with short systemic half-life*†
- Stable linker-payload*
- Tumour-selective cleavable linker*
- Bystander antitumour effect*

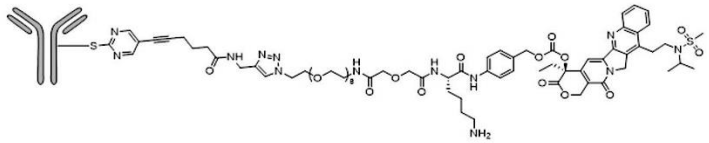
Deruxtecan



Cleavable tetrapeptide-based linker

Topo-I inhibitor payload (DXd)

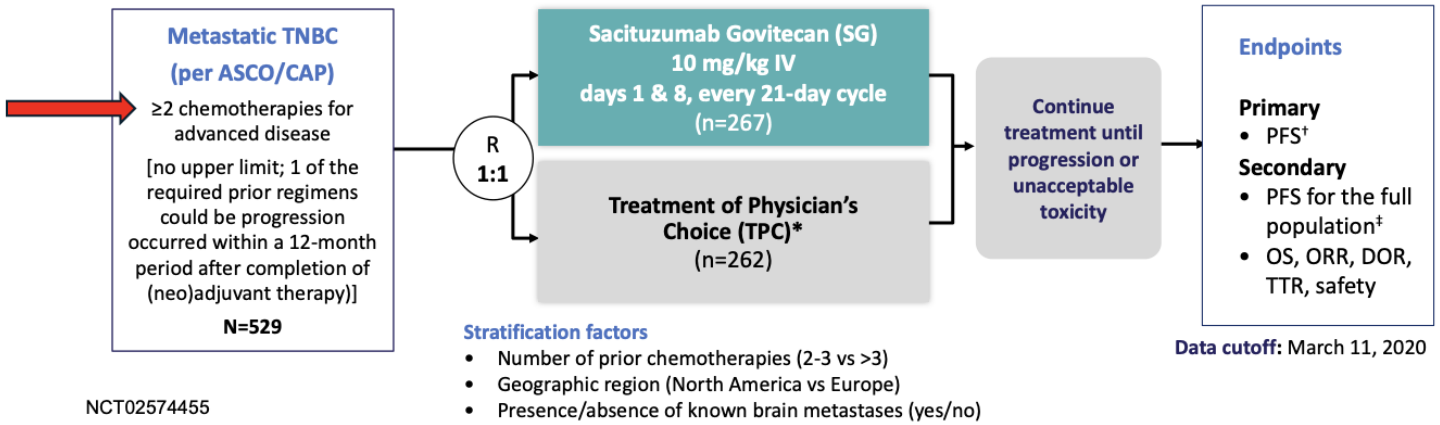
Sacituzumab tirumotecan (SKB264/MK-2870)



- anti-TROP2 ADC
- Sulfonyl pyrimidine-CL2A-carbonate linker
- **Payload**: belotecan-derivative topoisomerase I inhibitor
- **DAR**: 7.4

ADCs in metastatic triple-negative breast cancer

- Targeting Trop2 in mTNBC: ASCENT Trial – Study design

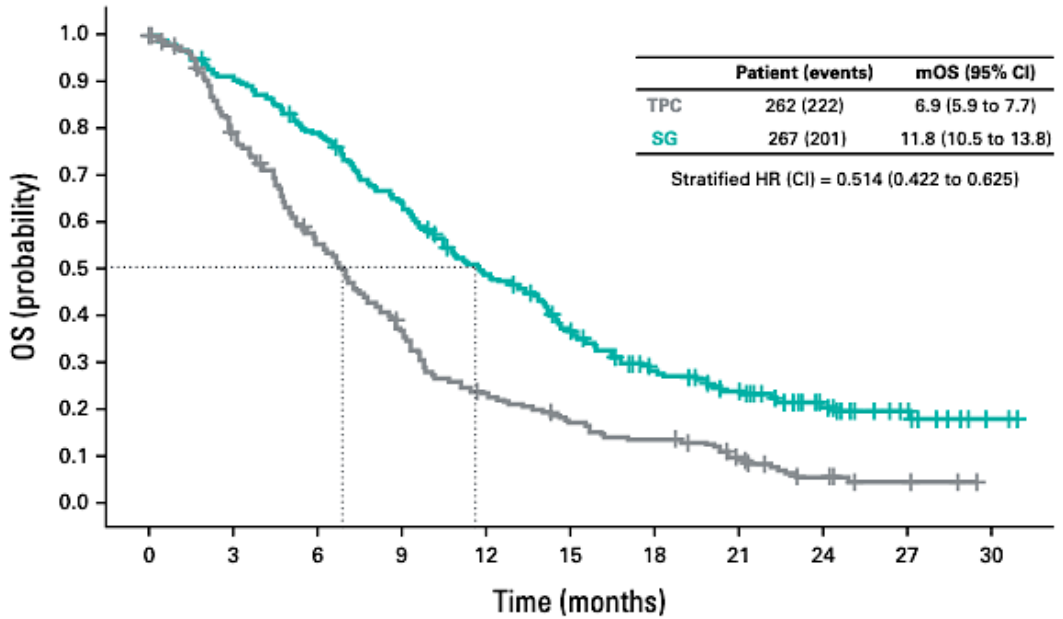


Demographics:
TPC: 53% eribulin, 20% vinorelbine, 15% gemcitabine, 13% capecitabine; 70% TN at initial diagnosis
Median prior regimens 4 (2-17); ~88% with visceral disease

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.

Sacituzumab Govitecan = SG

Overall Survival



Bardia, NEJM 2021
Bardia, JCO 2024

• Targeting Trop2 in mTNBC: OptiTROP-Breast01 Trial – Study design

A randomized, controlled, and open-label phase III study (NCT05347134)

Patients with locally recurrent or metastatic TNBC

- Relapsed or refractory to 2 or more prior chemotherapy regimens for unresectable, locally advanced or metastatic disease
  - For prior therapy, 1 could be in the (neo)adjuvant setting, provided progression occurred during treatment or within 12 months after treatment discontinuation
- Received taxane(s) in any setting

R 1:1

Sac-TMT, 5 mg/kg IV, days 1 &15 every 28-day cycle

Physician's choice of chemotherapy: eribulin, capecitabine, gemcitabine, or vinorelbine **every 21-day cycle**

Treatment until disease progression, unacceptable toxicity or any other reason for discontinuation

Endpoints[a]

Primary
- PFS by BICR

Secondary
- OS
- PFS by investigator assessment
- ORR, DOR
- Safety

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.

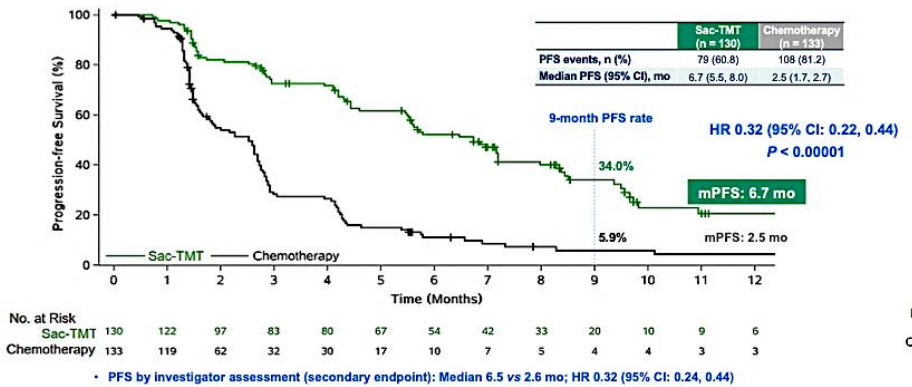
Choice of chemotherapy
- **Eribulin: 88 (66.2%)**
- Capecitabine: 4 (3.0%)
- Gemcitabine: 20 (15.0%)
- Vinorelbine: 21 (15.8%)

Patient population
- Median 3 vs 2 lines of prior chemotherapy
- 87% visceral mets
  - 35% liver

SAC-TMT

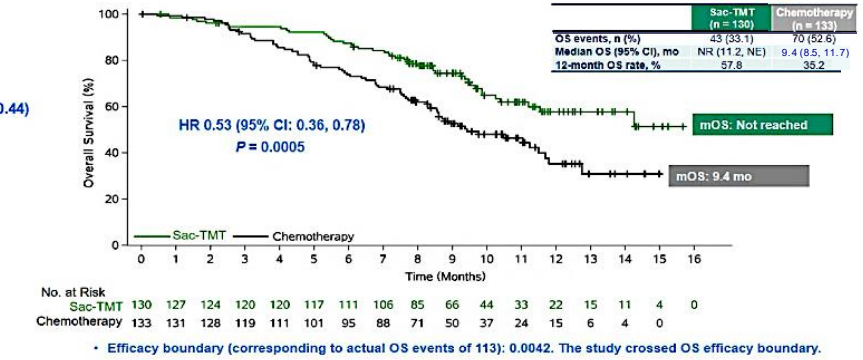
• Targeting Trop2 in mTNBC: OptiTROP-Breast01 Trial – Results

PFS by BICR



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

OS (interim)



• Efficacy boundary (corresponding to actual OS events of 113): 0.0042. The study crossed OS efficacy boundary.

Binghe Xu et al, ASCO 2024
Yin Y et al, Nat Med 2025

OptiTROP-Breast05 Study Design

Multicenter, open-label phase II study (NCT05445908)

Key eligibility criteria

- No prior systemic therapy for a/m TNBC
- PD-L1 positive or negative[a]
- DFI ≥6 months
- ECOG PS 0–1

→ **Sac-TMT (5 mg/kg Q2W)** →

Treatment until disease progression or unacceptable toxicity

Primary endpoint[b]

- ORR by investigator assessment

Secondary endpoints

- PFS, DOR, DCR, OS
- Safety

Tumor assessment

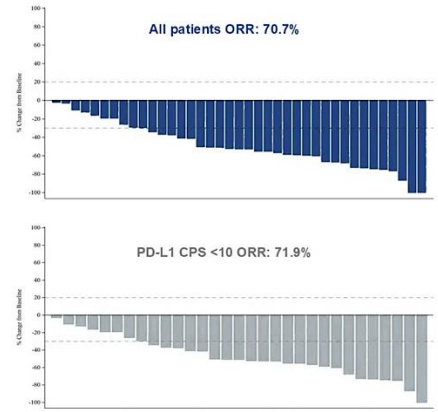
- Every 6 weeks for the first 18 months and every 12 weeks afterward.

[a]PD-L1 expression was assessed at a central lab with PD-L1 IHC 22C3 pharmDx.
[b]Tumor response was assessed using RECIST version 1.1.
DFI: disease-free interval; ECOG PS: Eastern Cooperative Oncology Group performance status; DCR: disease control rate; DOR: duration of response; RECIST: Response Evaluation Criteria in Solid Tumors.

Antitumor Responses

Antitumor Responses were observed regardless of PD-L1 expression.

	All patients (N = 41)	PD-L1 CPS <10[c] (N = 32)
ORR[a], n (%) (95% CI)	29 (**70.7**) (54.5, 83.9)	23 (**71.9**) (53.3, 86.3)
CR[b], n (%)	2 (4.9)	1 (3.1)
PR, n (%)	27 (65.9)	22 (68.8)
Confirmed PR, n (%)	24 (58.5)	19 (59.4)
SD, n (%)	9 (22.0)	7 (21.9)
DCR, n (%) (95% CI)	38 (**92.7**) (80.1, 98.5)	30 (**93.8**) (79.2, 99.2)

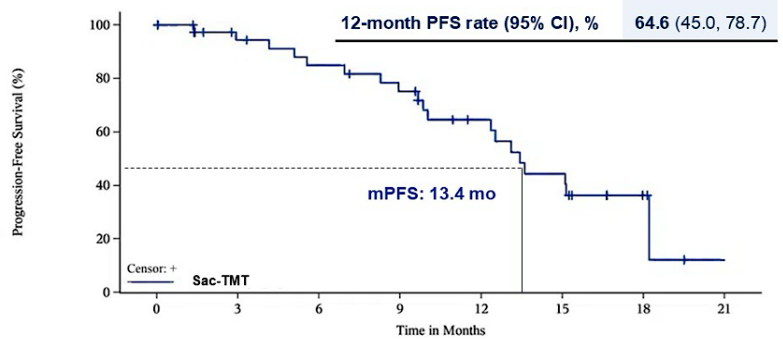


Data cutoff: Nov 18, 2024. **Median follow-up was 18.6 months.**
[a]Including confirmed PR/CR or response pending confirmation.
[b]All CRs were confirmed by investigators.
[c]PD-L1 expression was assessed at a central lab with PD-L1 IHC 22C3 pharmDx.
CR, complete response; PR, partial response; SD, stable disease.

Progression-Free Survival

PFS benefits were observed regardless of PD-L1 expression.

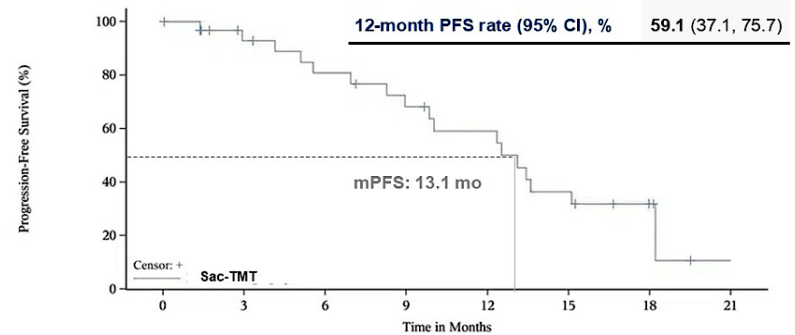
	All patients (N = 41)
PFS events, n (%)	20 (48.8)
Median PFS, months (95% CI)	**13.4** (9.9, 18.2)
12-month PFS rate (95% CI), %	**64.6** (45.0, 78.7)



Number of subjects at risk (Events)

Sac-TMT	41(0)	31(2)	27(5)	23(8)	16(11)	11(16)	4(18)	0(20)

	PD-L1 CPS <10 (N = 32)
PFS events, n (%)	18 (56.3)
Median PFS, months (95% CI)	**13.1** (8.9, 18.2)
12-month PFS rate (95% CI), %	**59.1** (37.1, 75.7)

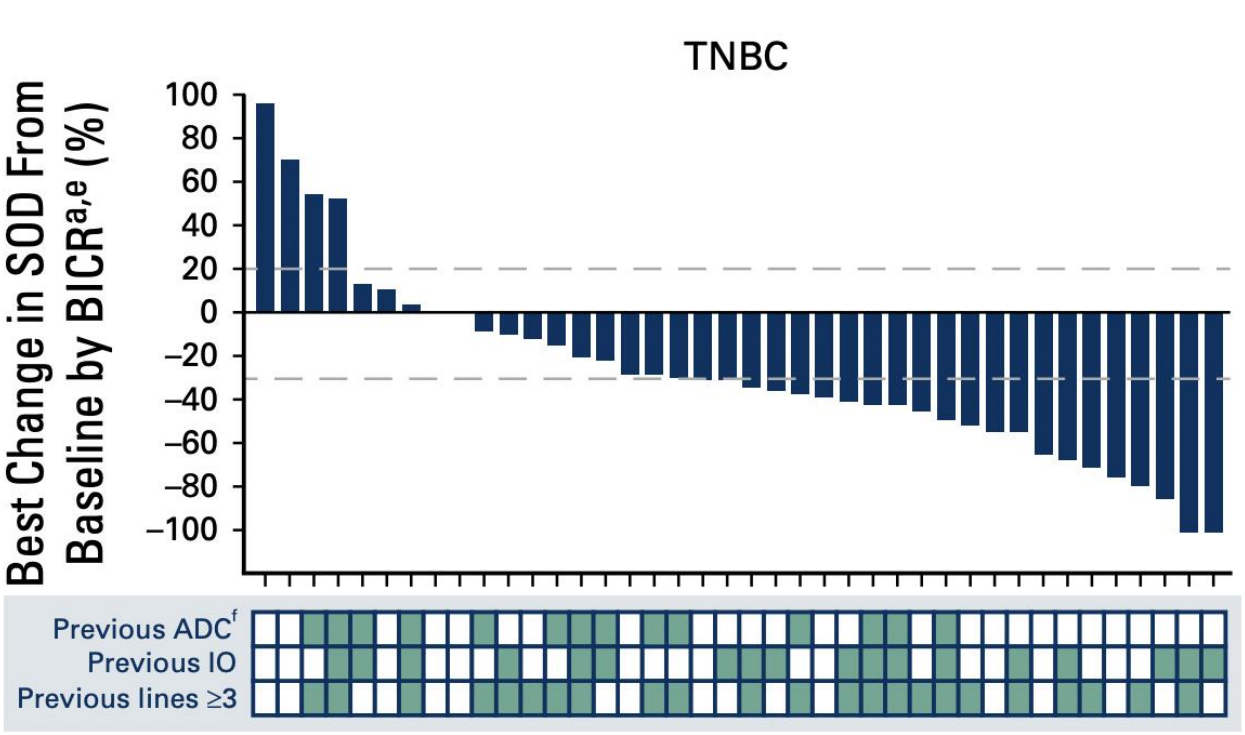


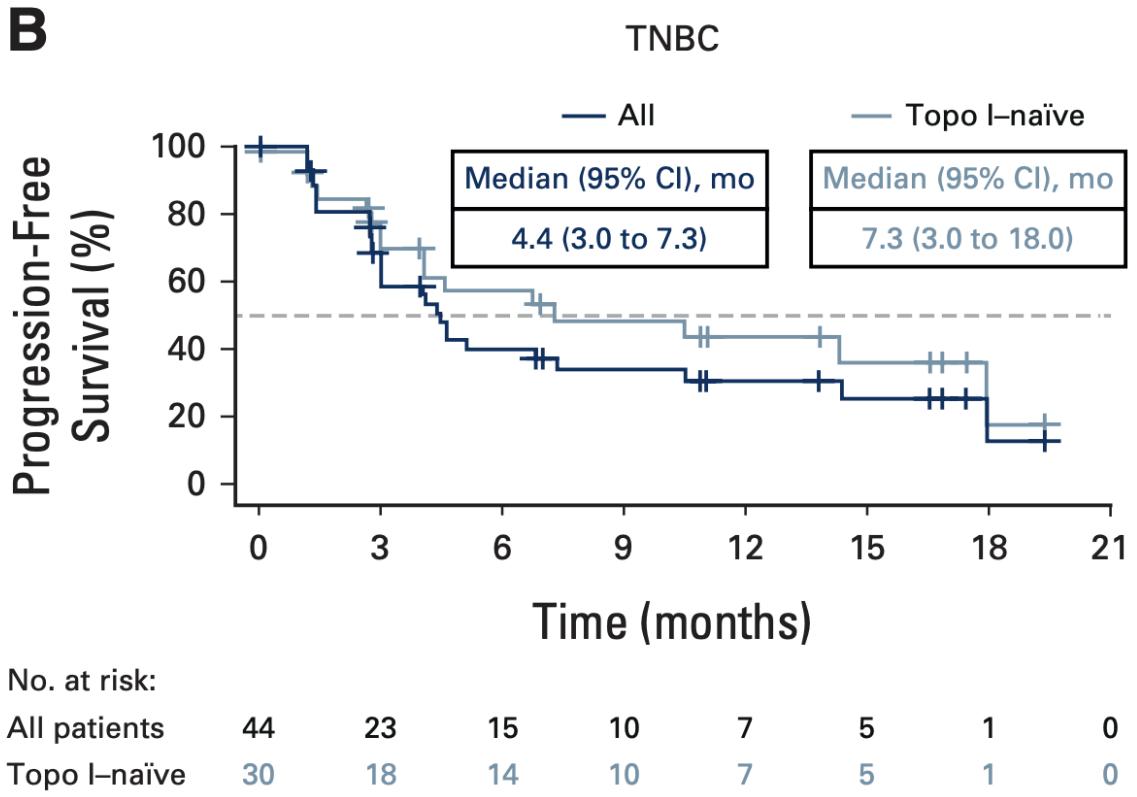
Number of subjects at risk (Events)

Sac-TMT	32(0)	24(2)	20(5)	16(8)	13(10)	8(15)	4(16)	0(18)

ADCs in metastatic triple-negative breast cancer

- Targeting Trop2 in mTNBC: Datopotamab deruxtecan in TROPION-PanTumor01 Study



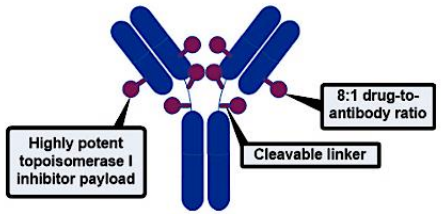


Bardia, JCO 2024

ADCs in metastatic triple-negative breast cancer

- Targeting HER2 in mTNBC: DESTINY-Breast04 – Study design

Trastuzumab deruxtecan (T-DXd)
HER2-directed ADC



Unresectable or metastatic **HER2-low** breast cancer (IHC 1+ or IHC 2+/ISH-) after a prior chemotherapy in the metastatic setting or disease recurrence during or within 6 months of completing adjuvant chemotherapy

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

R 2:1

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

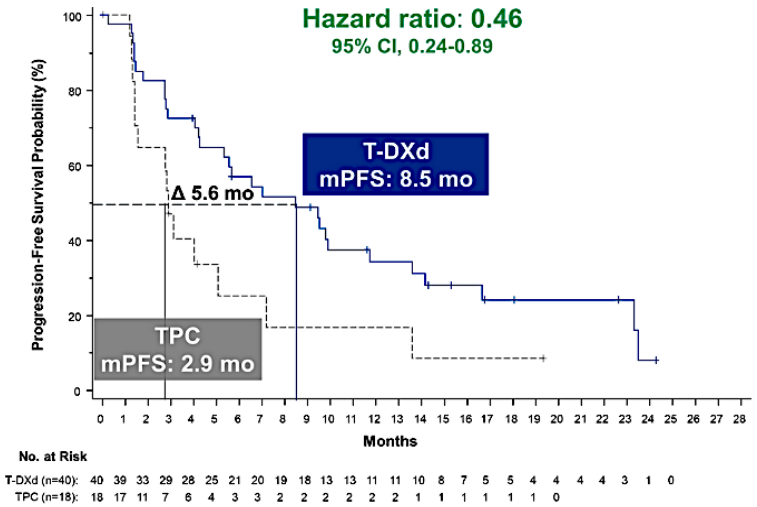
HR+ ≈ 480
HR− ≈ 60

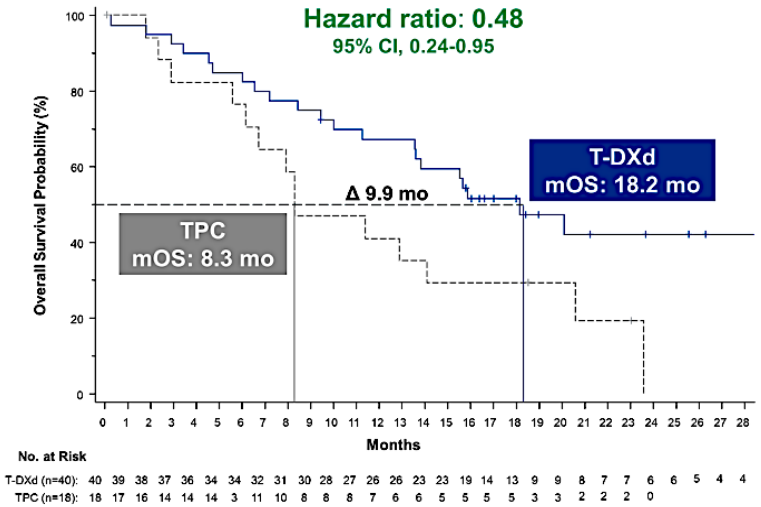
TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

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

Hormone receptor-negative





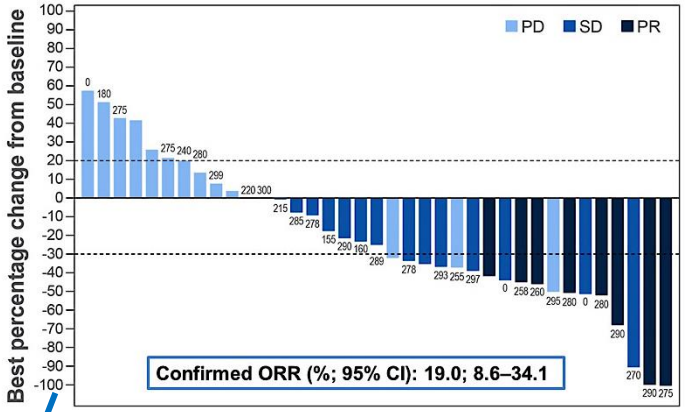
Modi, NEJM 2022; Modi ESMO 2023

ADCs in metastatic triple-negative breast cancer

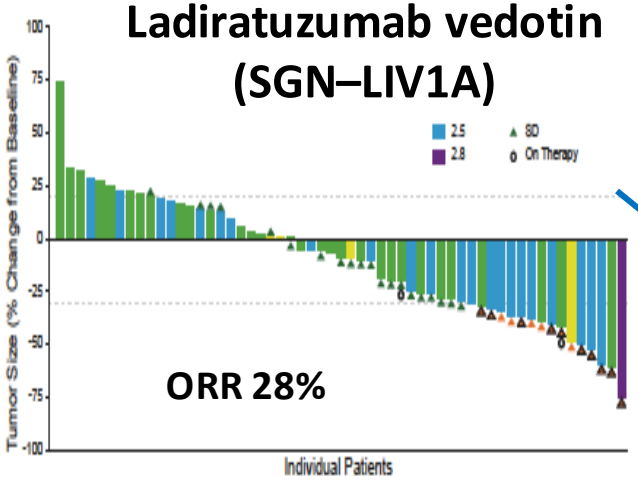
- Beyond Trop2 and HER2: emerging targets

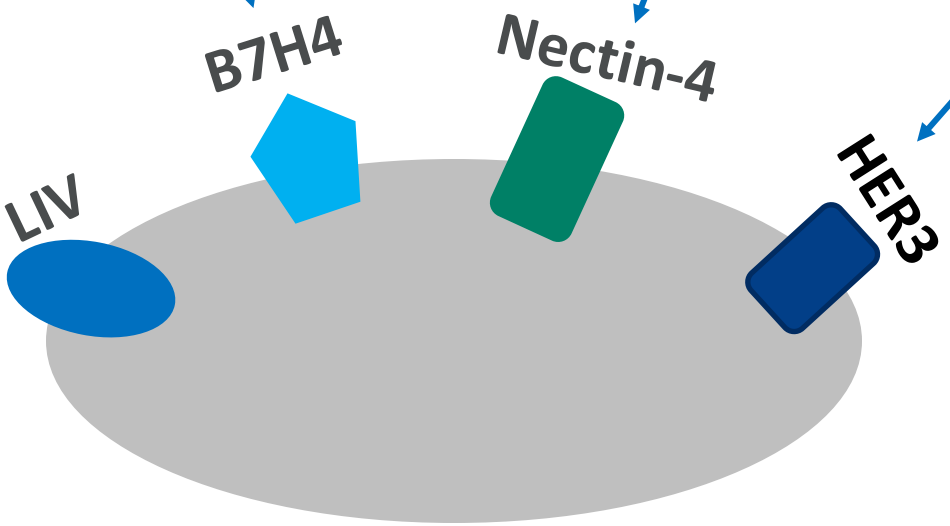
HS-20089

Enfortumab vedotin

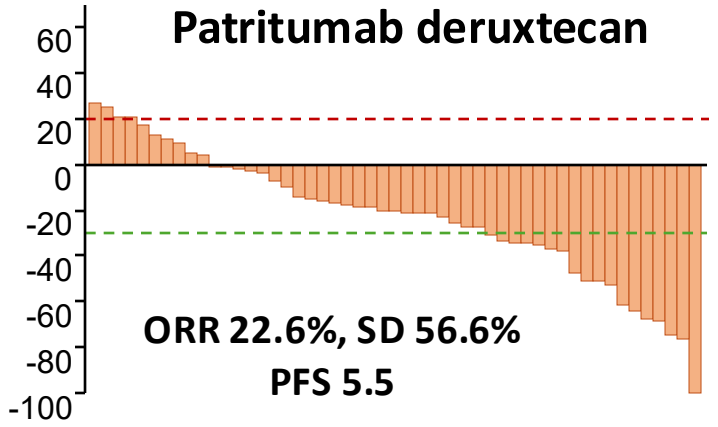


Ladiratuzumab vedotin (SGN–LIV1A)





Patritumab deruxtecan



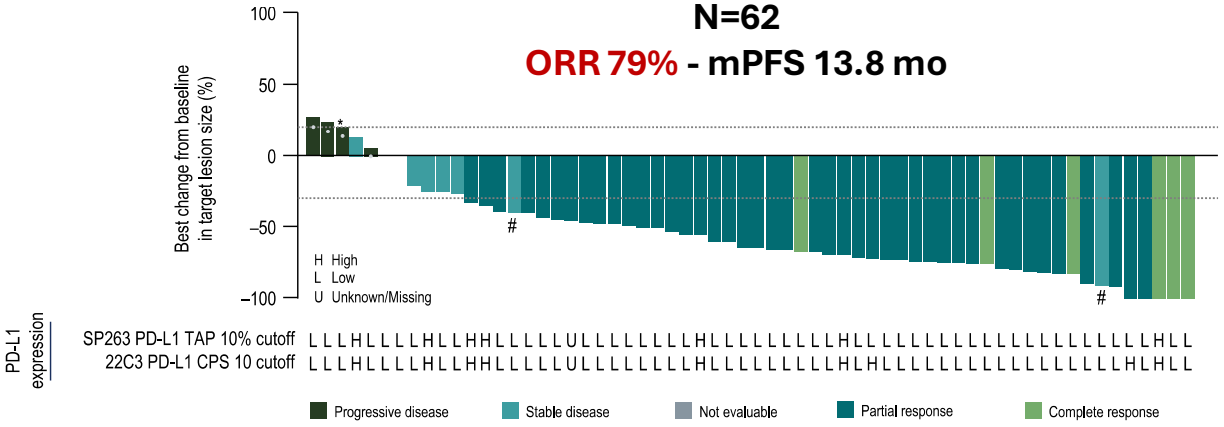
Adapted from Schmid

Krop ASCO 2022, Tsai ESMO 2021, Giordano ASCO 2024, Wu ESMO 2023

ADCs in metastatic triple-negative breast cancer

- Combining ADCs and immune-checkpoint inhibitors

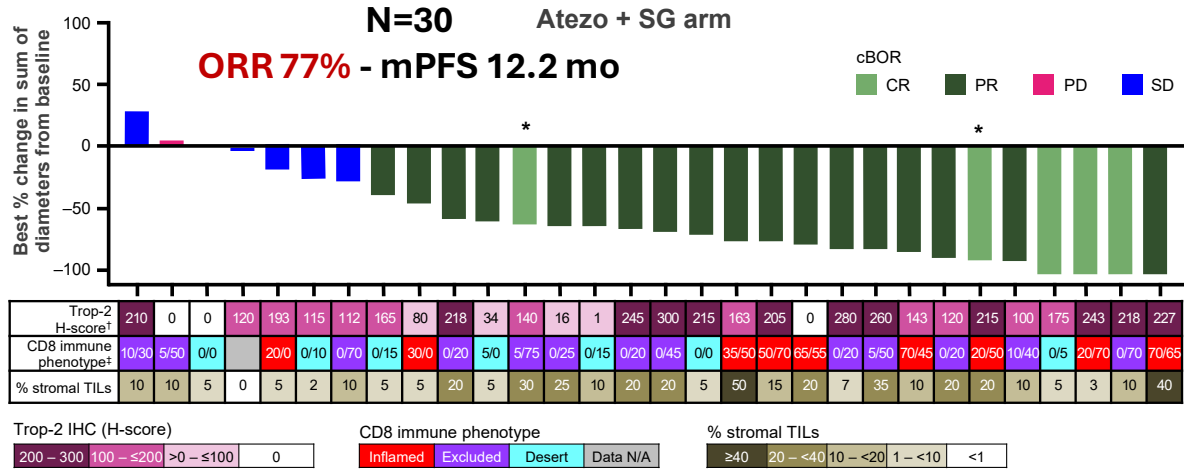
BEGONIA Trial
Dato-DXd + Durvalumab
in 1st line mTNBC



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

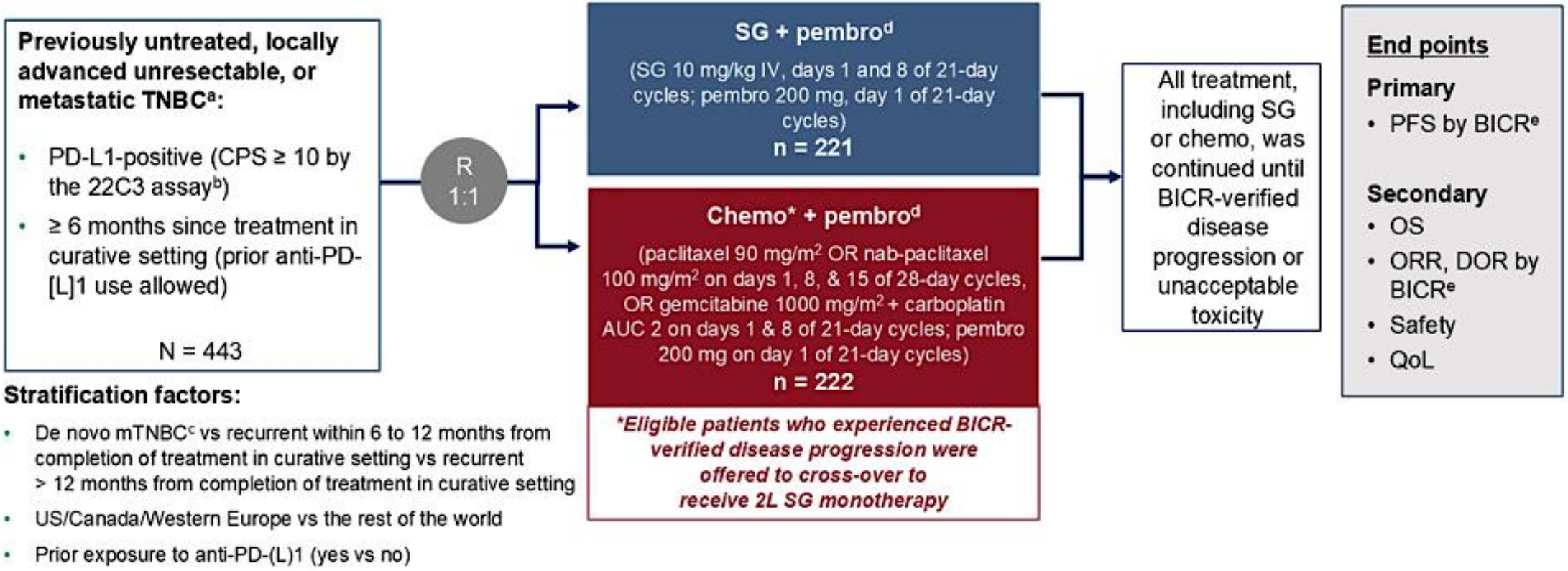
Schmid et al, ESMO 2023

Morpheus-PAN BC Trial
Sacituzumab Govitecan + Atezolizumab
in PD-L1+ 1st line mTNBC



Schmid et al, ESMO Breast 2024

ASCENT-04/KEYNOTE-D19: 1L sacituzumab govitecan + pembrolizumab vs chemotherapy + pembrolizumab for PD-L1+ advanced TNBC, primary results

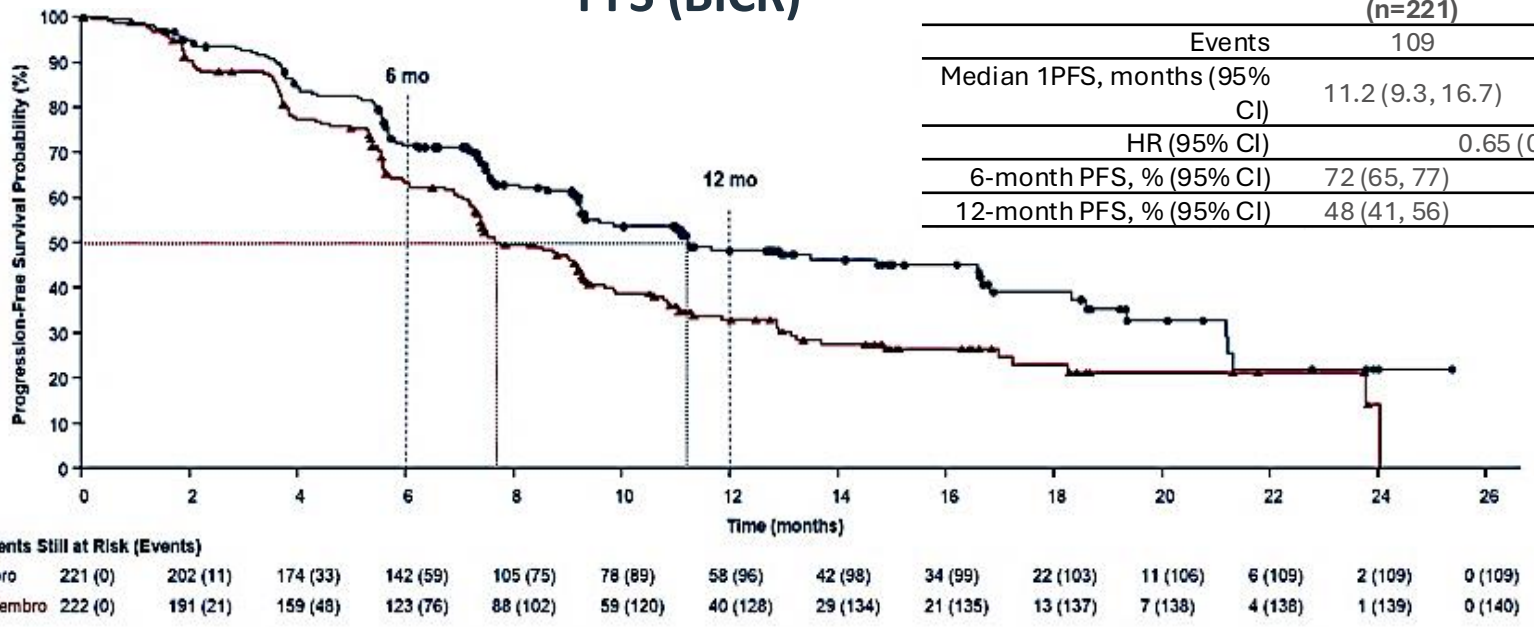


- Data cutoff date for primary PFS: March 3, 2025
- Median follow-up: 14 months (range 0.1–28.6 months)

Tolaney SM, et al. ASCO 2025. Abstract LBA109.

ASCENT-04/KEYNOTE-D19: Efficacy of 1L sacituzumab govitecan + pembrolizumab for PD-L1+ advanced TNBC

PFS (BICR)



	SG + pembrolizumab (n=221)	Chemo + Pembro (n=222)
Events	109	40
Median 1PFS, months (95% CI)	11.2 (9.3, 16.7)	7.8 (7.3, 9.3)
HR (95% CI)	0.65 (0.51, 84)	
6-month PFS, % (95% CI)	72 (65, 77)	63 (56, 69)
12-month PFS, % (95% CI)	48 (41, 56)	33 (26-10)

PFS by investigator assessment was consistent with BICR analysis

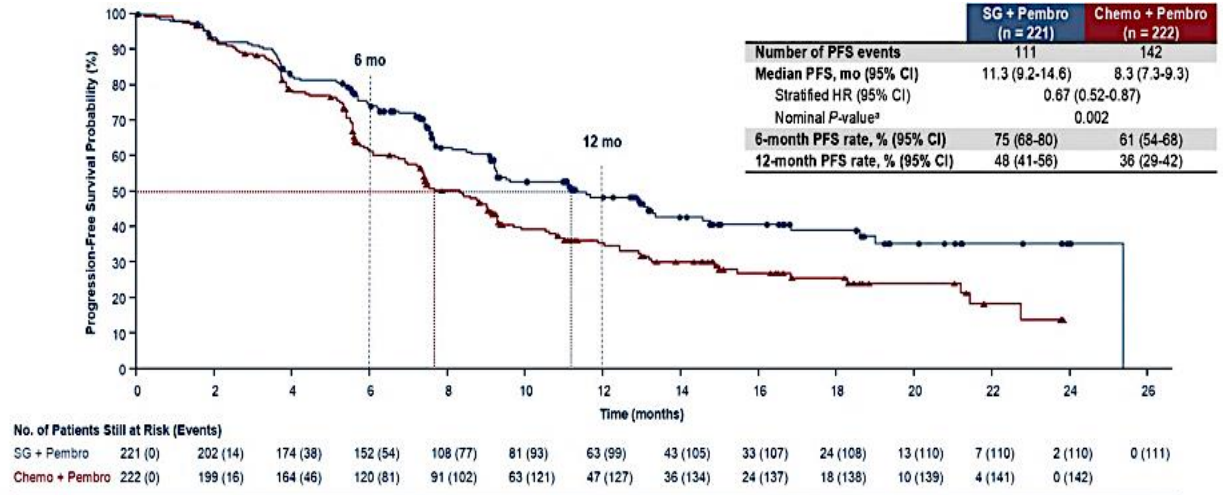
	SG + pembrolizumab (n=221)	Chemo + Pembro (n=222)
Events	111	142
Median 1PFS, months (95% CI)	11.3 (9.2, 14.6)	8.3 (7.3, 9.3)
HR (95% CI)	0.67 (0.52, 0.87); 0.002	
6-month PFS, % (95% CI)	75 (68, 80)	61 (54, 68)
12-month PFS, % (95% CI)	48 (41, 56)	38 (29, 42)

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

Tolaney SM, et al. ASCO 2025. Abstract LBA109.

ASCENT-04/KEYNOTE-D19: Efficacy of 1L sacituzumab govitecan + pembrolizumab for PD-L1+ advanced TNBC

PFS (Investigator assessed)



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	111	142
Median PFS, mo (95% CI)	11.3 (9.2-14.6)	8.3 (7.3-9.3)
Stratified HR (95% CI)	0.67 (0.52-0.87)	
Nominal *P*-value[a]	0.002	
6-month PFS rate, % (95% CI)	75 (68-80)	61 (54-68)
12-month PFS rate, % (95% CI)	48 (41-56)	36 (29-42)

PFS by investigator assessment was consistent with the BICR analysis, demonstrating PFS benefit with SG + pembro vs chemo + pembro

PFS subgroup analysis

	SG + Pembro n	SG + Pembro Median PFS, mo (95% CI)	Chemo + Pembro n	Chemo + Pembro Median PFS, mo (95% CI)	Unstratified HR (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 SM, et al. ASCO 2025. Abstract LBA109.

ASCENT-04/KEYNOTE-D19: Safety of 1L sacituzumab govitecan + pembrolizumab

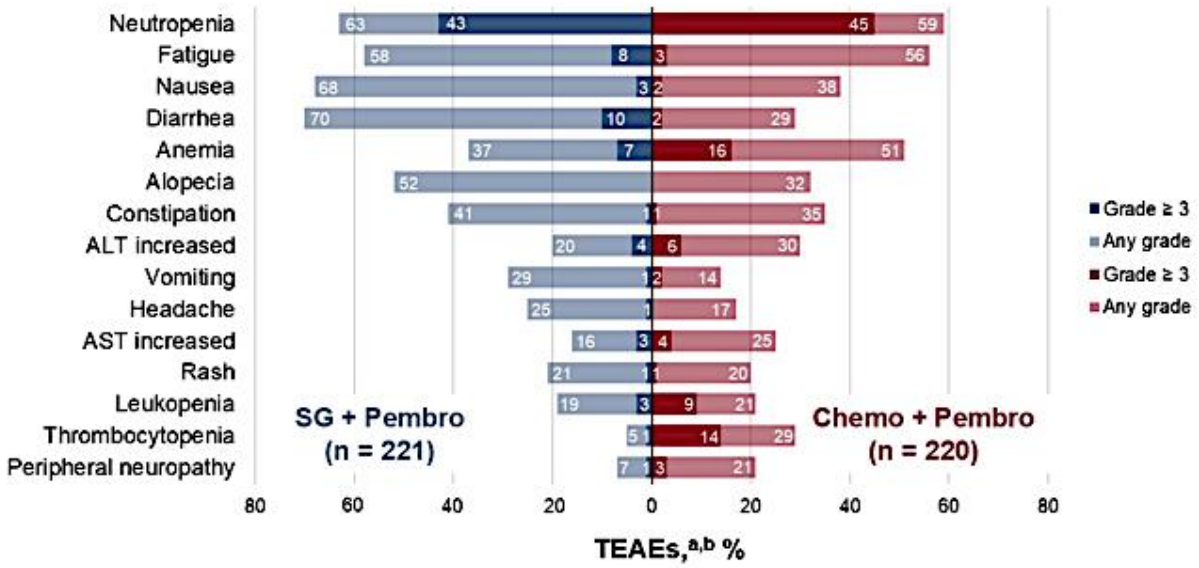
Exposure (ITT population)

Treatment component	SG + Pembro (n=221)		Chemo + Pembro (n=222)	
	SG	Pembro	Chemo	Pembro
All treated patients, n	221	221	220	220
Median duration of treatment, mo (range)	8.9 (0.0–27.1)	8.5 (0.0–26.8)	6.2 (0.0–26.3)	6.4 (0.0–25.6)

Safety

n (%)	SG + Pembro (n=221)	Chemo + Pembro (n=220)
Any TEAE Grade ≥ 3	220 (>99) 158 (71)	219 (>99) 154 (70)
Treatment-emergent SAE Treatment-related	84 (38) 61 (28)	68 (31) 42 (19)
TEAEs leading to treatment discontinuation	26 (12)	68 (31)
TEAEs leading to dose interruption	171 (77)	162 (74)
TEAEs leading to dose reduction	78 (35)	96 (44)
TEAEs leading to death Treatment-related	7 (3) 3 (1)	6 (3) 1 (<1)

Most common AEs (≥20% any group)



Tolaney SM, et al. ASCO 2025. Abstract LBA109.

Several Phase 3 clinical trials are evaluating the use of ADCs ± immunotherapy in 1L mTNBC

Target	Trial	Intervention	Control arm
TROP2	**PD-L1−negative or PD-L1/PD-1 inhibitor-ineligible population**		
	ASCENT-03[3]	**Sacituzumab govitecan**	**TPC** (gemcitabine/carboplatin, paclitaxel, or nab-paclitaxel)
	TROPION Breast-02[4]	**Datopotamab deruxtecan**	**ICC** (paclitaxel, nab-paclitaxel, carboplatin, capecitabine or eribulin mesylate)
	TroFuse-011[5]	**Sacituzumab tirumotecan† ± pembrolizumab**	**TPC** (gemcitabine and carboplatin, paclitaxel, or nab-paclitaxel)
	SKB264-III-11[6]	**Sacituzumab tirumotecan†**	**ICC** (paclitaxel, nab-paclitaxel, capecitabine, eribulin, or carboplatin)
	PD-L1+ population		
	ASCENT-04[7]	**Sacituzumab govitecan + pembrolizumab**	**TPC** (gemcitabine and carboplatin, paclitaxel, or nab-paclitaxel) + pembrolizumab
	TROPION Breast-05[8]	**Datopotamab deruxtecan ± durvalumab**	**ICC** (paclitaxel, nab-paclitaxel or gemcitabine + carboplatin) + pembrolizumab

ADCs (T-DXd and SG) are approved globally as monotherapy in previously treated mTNBC; SG, Dato-DXd and Sac-TMT are being evaluated in 1L mTNBC[2,5–9]

Take home messages

1. Immunotherapy and ADCs demonstrated to improve overall survival in patients with mTNBC
   Treatment positioning and novel combinations represent the new therapeutical challenge

2. Urgently need to understand the optimal ADC sequence: mechanisms of resistance to the antibody and to the payload should be characterized and validated for patient selection

3. Novel agents and biomarkers are emerging in mTNBC

4. In the future, **the lack of targets will no longer define this aggressive disease**

SingHealth DukeNUS ACADEMIC MEDICAL CENTRE

Regulatory and reimbursement issues aside, which treatment would you most likely recommend for a 65-year-old patient with de novo ER/PR-negative, HER2-negative (IHC 0), mBC with a germline BRCA mutation?

	PD-L1 positive	PD-L1 negative
 Dr Burstein	Pembrolizumab/paclitaxel	Paclitaxel
 Dr Cortés	Pembrolizumab/*nab* paclitaxel/carboplatin	Carboplatin/paclitaxel/bevacizumab
 Prof Dent	Pembrolizumab/paclitaxel	Olaparib
 Dr Kalinsky	Pembrolizumab + sacituzumab govitecan	Sacituzumab govitecan
 Dr O'Shaughnessy	Pembrolizumab/gemcitabine/carboplatin	Olaparib
 Dr Rugo	Pembrolizumab + sacituzumab govitecan	Olaparib
 Dr Hurvitz	Pembrolizumab + sacituzumab govitecan	Olaparib
 Dr Jhaveri	Pembrolizumab + sacituzumab govitecan	Olaparib

Regulatory and reimbursement issues aside, what would be your preferred next line of systemic therapy for a patient with ER/PR-negative, HER2-negative (IHC 0), PD-L1-positive mBC with a germline BRCA mutation who has experienced disease progression on first-line pembrolizumab/chemotherapy?

 Dr Burstein	Olaparib
 Dr Cortés	Olaparib
 Prof Dent	Olaparib
 Dr Kalinsky	Olaparib
 Dr O'Shaughnessy	Olaparib if first-line pembrolizumab/*nab* paclitaxel; sacituzumab govitecan if first-line pembrolizumab/carboplatin/gemcitabine
 Dr Rugo	Olaparib
 Dr Hurvitz	Olaparib
 Dr Jhaveri	Olaparib

RTP RESEARCH TO PRACTICE

For which specific DNA damage repair pathway abnormalities beyond germline BRCA1/2 would you attempt to access a PARP inhibitor for a patient with mBC?

 Dr Burstein	PALB2
 Dr Cortés	PALB2
 Prof Dent	PALB2 and somatic BRCA1/2
 Dr Kalinsky	Germline or somatic PALB2, somatic BRCA
 Dr O'Shaughnessy	gPALB2, gRAD51C or RAD51D
 Dr Rugo	PALB2
 Dr Hurvitz	PALB2
 Dr Jhaveri	PALB2

RTP RESEARCH TO PRACTICE

RTP Live from Chicago: Investigator Perspectives on Available Research Findings and Challenging Questions in the Management of Soft Tissue Sarcoma and Other Connective Tissue Disorders

A CME-Accredited Virtual Event Held in Conjunction with the 2025 ASCO® Annual Meeting

Tuesday, June 3, 2025

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Rashmi Chugh, MD

Mrinal Gounder, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code.
Online/Zoom attendees: The CME credit link is posted in the chat room.

RTP
RESEARCH TO PRACTICE