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

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Monday, June 6, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty

Javier Cortés, MD, PhD
Matthew P Goetz, MD
Erika Hamilton, MD
Ian E Krop, MD, PhD
Hope S Rugo, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Faculty

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

Matthew P Goetz, MD
Erivan K Haub Family Professor of Cancer Research
Honoring Richard F Emslander, MD
Professor of Oncology and Pharmacology
Director, Mayo Clinic Breast SPORE
Co-Leader, Women's Cancer Program
Chair, Breast Cancer Research Committee
Vice Chair, Academic and Community Research United (ACCRU)
Mayo Clinic
Rochester, Minnesota

Erika Hamilton, MD
Director, Breast and Gynecologic Research Program
Sarah Cannon Research Institute/Tennessee Oncology
Nashville, Tennessee

Ian E Krop, MD, PhD
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Director, Clinical Trials Office
Chief Clinical Research Officer
Yale Cancer Center
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Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
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Chief, Division of Breast Oncology
Associate Director, Susan F Smith Center for Women's Cancers
Senior Physician
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Clinicians in the Meeting Room

Networked iPads are available.

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

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

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Clinicians Attending via Zoom

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

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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.

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About the Enduring Program

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

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Friday June 3	**Acute Myeloid Leukemia and Myelodysplastic Syndromes** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Lung Cancer 6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)
Saturday June 4	**Prostate Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Gastrointestinal Cancers 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Sunday June 5	**Ovarian Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Monday June 6	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Breast Cancer 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Tuesday June 7	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

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Breast Cancer

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Hope S Rugo, MD
Sara M Tolaney, MD, MPH

Multiple Myeloma

Tuesday, June 7, 2022

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Ajai Chari, MD
Elizabeth O'Donnell, MD
Robert Z Orlowski, MD, PhD

Spencer H Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Philip L Brooks, MD
Northern Light Eastern Maine Medical Center and Lafayette Family Cancer Institute
Brewer, Maine

Shams Bufalino, MD
Advocate Aurora Health
Park Ridge, Illinois

Lionel A Kankeu Fonkoua, MD
Mayo Clinic
Rochester, Minnesota

Shaachi Gupta, MD, MPH
Florida Cancer Specialists
Lake Worth, Florida

Zanetta S Lamar, MD
Florida Cancer Specialists
Naples, Florida

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Vignesh Narayanan, MD
Colorado Permanente Medical Group (CPMG)
Lone Tree, Colorado

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Namrata I Peswani, MD
Harold C Simmons
Comprehensive Cancer Center
Richardson, Texas

Matthew R Strickland, MD
Massachusetts General Hospital
Cancer Center
Boston, Massachusetts

Erik Rupard, MD
The Reading Hospital
West Reading, Pennsylvania

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Exact Sciences, Gilead Sciences Inc, Lilly, Merck, Puma Biotechnology Inc, Sanofi Genzyme, and Seagen 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.

Dr Love — Disclosures

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Dr Cortés — Disclosures

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Contracted Research	AstraZeneca Pharmaceuticals LP, Baxalta GmbH, Bayer HealthCare Pharmaceuticals, Eisai Inc, F Hoffmann-La Roche Ltd, Guardant Health, Merck Sharp & Dohme LLC, Pfizer Inc, PIQUR Therapeutics, Puma Biotechnology Inc, Queen Mary University of London, Roche Laboratories Inc, Servier Affaires Medicales, Takeda Pharmaceuticals USA Inc
Honoraria	Celgene Corporation, Daiichi Sankyo Inc, Eisai Inc, Lilly, Merck Sharp & Dohme LLC, Novartis, Pfizer Inc, Roche Laboratories Inc, Samsung Bioepis
Patents	WO 2014/199294 A, US 2019/ 0338368 A1
Stock	MEDSIR, Nektar, Leuko Labs Inc (stock owned by relative)
Travel, Accommodation, Expenses	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Eisai Inc, Gilead Sciences Inc, Novartis, Pfizer Inc, Roche Laboratories Inc

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Dr Goetz — Disclosures

Consulting Agreements (Honoraria to Institution)	ARC Therapeutics, AstraZeneca Pharmaceuticals LP, bioTheranostics Inc, Biovica, Blueprint Medicines, Eagle Pharmaceuticals, Lilly, Novartis, Pfizer Inc, Sanofi Genzyme, Sermonix Pharmaceuticals
Contracted Research (To Institution)	Lilly, Pfizer Inc, Sermonix Pharmaceuticals

Dr Hamilton — Disclosures

Consulting Agreements (Paid to Institution)	Arcus Biosciences,Arvinas, AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, CytomX Therapeutics, Daiichi Sankyo Inc, Dantari, Deciphera Pharmaceuticals Inc, Eisai Inc, Genentech, a member of the Roche Group, Greenwich LifeSciences Inc, H3 Biomedicine, iTeos Therapeutics, Janssen Biotech Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mersana Therapeutics Inc, Novartis, Orum Therapeutics, Pfizer Inc, Puma Biotechnology Inc, Relay Therapeutics, Seagen Inc, Silverback Therapeutics
Contracted Research (Paid to Institution)	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, ADC Therapeutics, Akesobio Australia Pty Ltd, Amgen Inc, ArQule Inc, Arvinas, AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, Compugen, Curis Inc, CytomX Therapeutics, Daiichi Sankyo Inc, Dana-Farber Cancer Institute, Deciphera Pharmaceuticals Inc, eFFECTOR Therapeutics Inc, Ellipses Pharma, EMD Serono Inc, Fochon Pharmaceuticals Ltd, FUJIFILM Pharmaceuticals USA Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, H3 Biomedicine, Harpoon Therapeutics, Hutchison MediPharma, ImmunoGen Inc, Immunomedics Inc, Incyte Corporation, InventisBio, Jacobio Pharmaceuticals Group Co Ltd, Karyopharm Therapeutics, Leap Therapeutics Inc, Lilly, Lycera, MacroGenics Inc, Marker Therapeutics Inc, Merck, Mersana Therapeutics Inc, Merus BV, Molecular Templates, Myriad Genetic Laboratories Inc, Novartis, NuCana, Olema Oncology, OncoMed Pharmaceuticals Inc, Onconova Therapeutics Inc, ORIC Pharmaceuticals Inc, Orinove Inc, Pfizer Inc, PharmaMar, Pieris Pharmaceuticals Inc, Pionyr Immunotherapeutics, Plexxikon Inc, Puma Biotechnology Inc, Radius Health Inc, Regeneron Pharmaceuticals Inc, Repertoire Immune Medicines, Rgenix, Seagen Inc, Sermonix Pharmaceuticals, Shattuck Labs, Silverback Therapeutics, Stemcentrx, Sutro Biopharma, Syndax Pharmaceuticals Inc, Syros Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, Transcenta Holding Ltd, Treadwell Therapeutics, Verastem Inc, Vincerx Pharma, Zenith Epigenetics, Zymeworks Inc

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Dr Krop — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, MacroGenics Inc, Seagen Inc, Taiho Oncology Inc
Contracted Research (Clinical Trial Support Paid to Institution)	Genentech, a member of the Roche Group, MacroGenics Inc, Pfizer Inc

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Dr Rugo — Disclosures

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Contracted Research	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, Immunomedics Inc, Lilly, MacroGenics Inc, Merck, Novartis, OBI Pharma Inc, Odonate Therapeutics, Pfizer Inc, Seagen Inc, Sermonix Pharmaceuticals
Honoraria	Mylan, Puma Biotechnology Inc
Travel	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, MacroGenics Inc, Merck, Mylan, Novartis, Pfizer Inc

Dr Tolaney — Disclosures

Consulting Agreements	4D Pharma PLC, AstraZeneca Pharmaceuticals LP, Athenex, BeyondSpring Pharmaceuticals Inc, Bristol-Myers Squibb Company, Certara, Chugai Pharmaceutical Co Ltd, CytomX Therapeutics, Daiichi Sankyo Inc, Eisai Inc, Ellipses Pharma, Genentech, a member of the Roche Group, Gilead Sciences Inc, Infinity Pharmaceuticals Inc, Kyowa Kirin Co Ltd, Lilly, Merck, Mersana Therapeutics Inc, NanoString Technologies, Nektar, Novartis, Odonate Therapeutics, OncoPep, OncoSec Medical, OncXerna Therapeutics Inc, Pfizer Inc, Puma Biotechnology Inc, Samsung Bioepis, Sanofi Genzyme, Seagen Inc, Zentalis Pharmaceuticals, Zymeworks Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Cyclacel Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Merck, NanoString Technologies, Nektar, Novartis, Odonate Therapeutics, Pfizer Inc, Sanofi Genzyme, Seagen Inc

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Agenda

Module 1 – Optimizing the Management of ER-Positive Localized Breast Cancer — Dr Goetz

Module 2 – New and Novel Treatment Strategies for Localized Triple-Negative Breast Cancer (TNBC) — Dr Hamilton

Module 3 – Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Dr Krop

Module 4 – Evolving Clinical Decision-Making for Patients with HER2-Positive Metastatic Breast Cancer (mBC) — Dr Cortés

Module 5 – Selection and Sequencing of Therapy for ER-Positive, HER2-Negative mBC — Dr Rugo

Module 6 – Recent Advances in the Care of Patients with Metastatic TNBC (mTNBC) — Dr Tolaney

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Breast Cancer Survey Respondents

Virginia F Borges, MD, MMSc

Adam M Brufsky, MD, PhD

Harold J Burstein, MD, PhD

Javier Cortés, MD, PhD

Kevin R Fox, MD

Matthew P Goetz, MD

Erika Hamilton, MD

Sara A Hurvitz, MD

Komal Jhaveri, MD

Kevin Kalinsky, MD, MS

Ian E Krop, MD, PhD

Kathy D Miller, MD

Rita Nanda, MD

Ruth O'Regan, MD

Joyce O'Shaughnessy, MD

Hope S Rugo, MD

Sandra M Swain, MD

Melinda Telli, MD

Sara M Tolaney, MD, MPH

Andrew Tutt, PhD, MBChB

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MODULE 1: Optimizing the Management of ER-Positive Localized Breast Cancer

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ASCO special articles

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

Fabrice Andre, MD[1]; Nofisat Ismaila, MD, MSc[2]; Kimberly H. Allison, PhD[3]; William E. Barlow, PhD[4]; Deborah E. Collyar, BSc[5]; Senthil Damodaran, MD, PhD[6]; N. Lynn Henry, MD, PhD[7]; Komal Jhaveri, MD[8,9]; Kevin Kalinsky, MD, MS[10]; Nicole M. Kuderer, MD[11]; Anya Litvak, MD[12]; Erica L. Mayer, MD, MPH[13]; Lajos Pusztai, MD[14]; Rachel Raab, MD[15]; Antonio C. Wolff, MD[16]; and Vered Stearns, MD[16]

J Clin Oncol. 2022;40(16):1816-1837.

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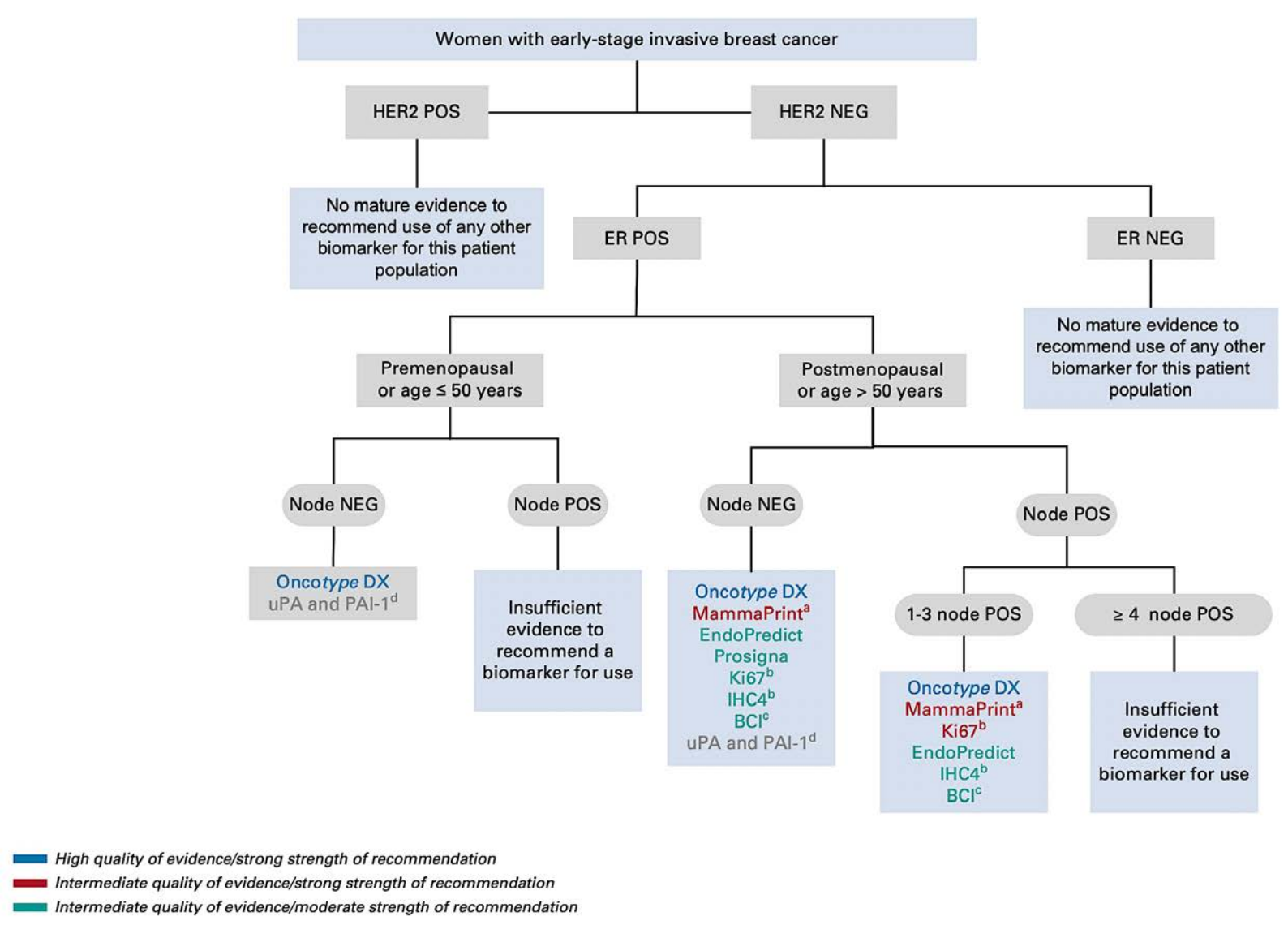
Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update



Andre et. al, *J Clin Oncol*. 2022;40(16):1816-1837.

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In general, when ordering a genomic assay for a woman with ER-positive, HER2-negative breast cancer, which, if any, are you most likely to use?

Clinical endpoint	45-year-old premenopausal		65-year-old postmenopausal	
	Node-positive	Node-negative	Node-positive	Node-negative
21-gene assay	13	16	17	15
70-gene signature	1	1	1	2
12-gene assay	1	0	1	0
RSClin	0	2	0	2
Other	1*	1†	1*	1†
I would not order a genomic assay	4	0	0	0

* Neoadjuvant: 70-gene signature; adjuvant: 21-gene assay; † 21-gene assay and calculate RSClin as needed

Survey of clinical investigators

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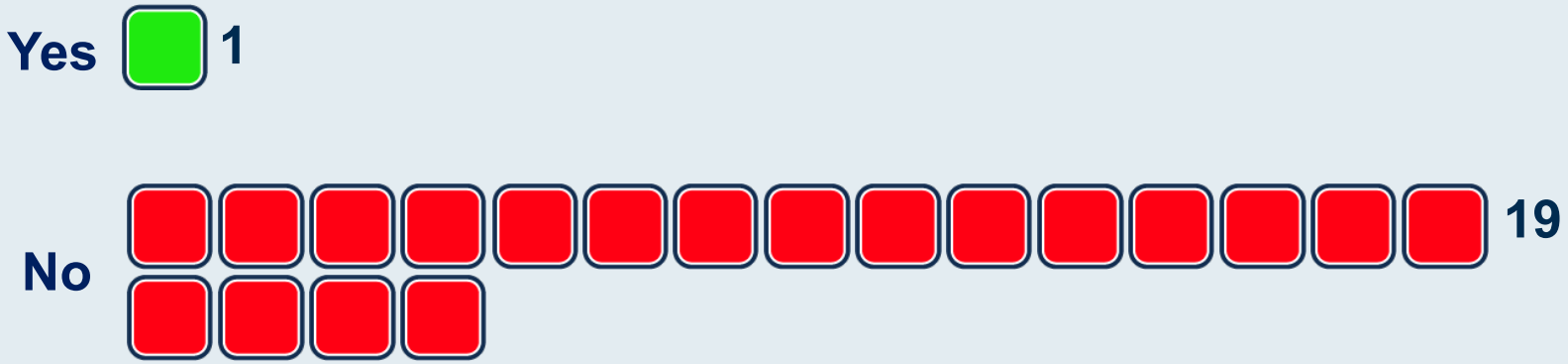
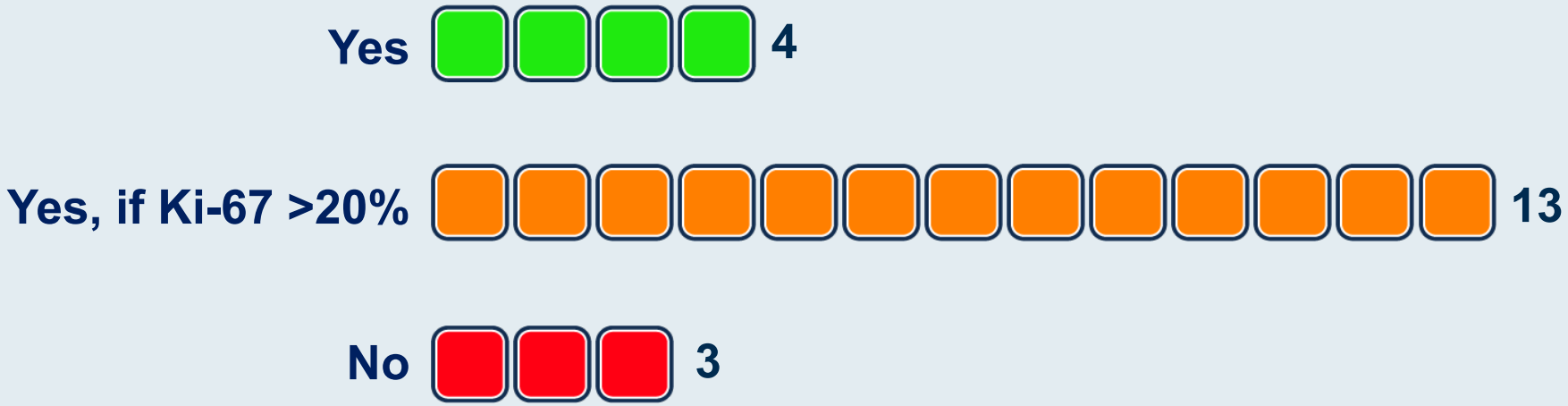
In general, would you recommend chemotherapy to a 65-year-old woman with a 2.3-cm node-negative infiltrating ductal carcinoma (IDC) with a 21-gene Recurrence Score of 24?



Survey of clinical investigators

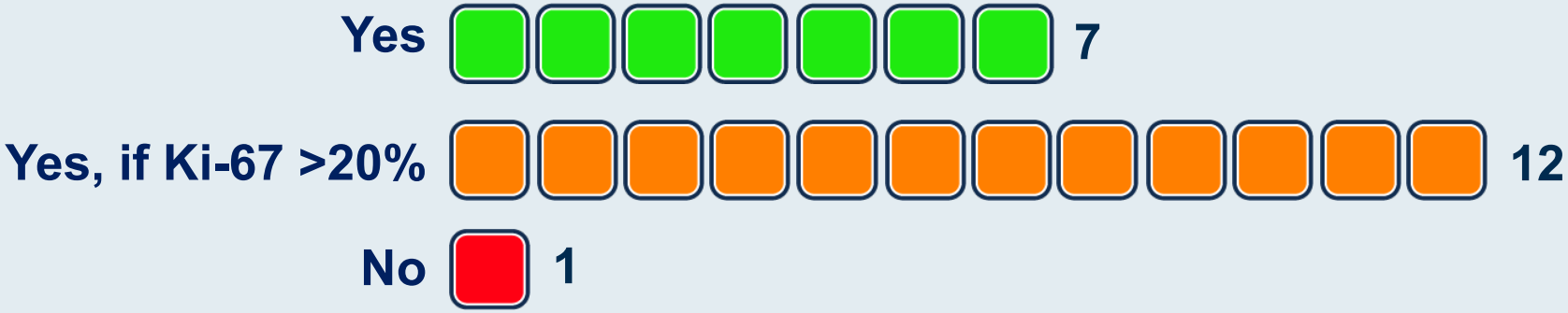
Assuming you were able to access abemaciclib for a patient with a T2 primary tumor and 1 positive node, would you recommend it?



Survey of clinical investigators

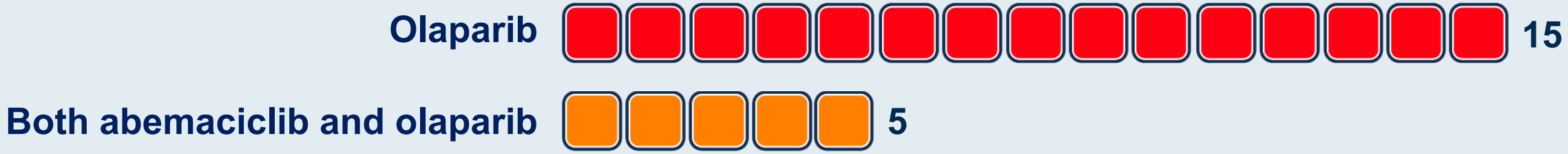
Assuming you were able to access it, would you generally recommend adjuvant abemaciclib to a 65-year-old woman with ER-positive, HER2-negative BRCA wild-type localized breast cancer and 4 positive nodes?

A 60-year-old woman with a 4-cm ER-positive, HER2-negative BRCA wild-type localized breast cancer receives neoadjuvant AC followed by paclitaxel and at surgery is found to have multifocal residual disease and 1 positive lymph node. Would you offer adjuvant abemaciclib as part of treatment?

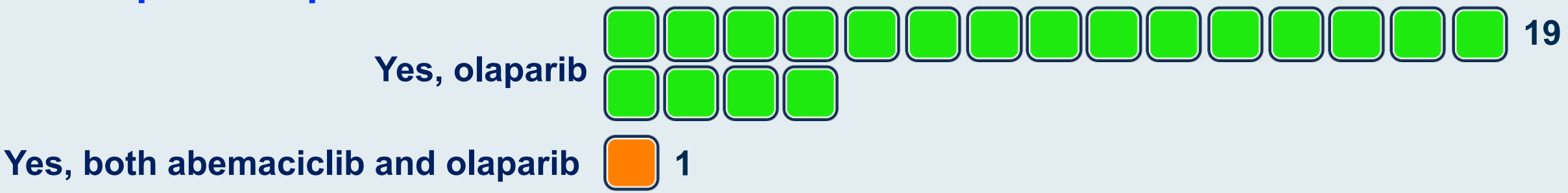


Survey of clinical investigators

A 65-year-old woman presents with ER-positive, HER2-negative localized breast cancer with a germline BRCA mutation and 4 positive nodes. Assuming you had access, which agents, if any, would you include as adjuvant treatment in addition to hormonal therapy?



A 60-year-old woman with a 4-cm ER-positive, HER2-negative localized breast cancer with a germline BRCA mutation receives neoadjuvant AC → paclitaxel and at surgery is found to have multifocal residual disease and 1 positive lymph node. Would you offer adjuvant abemaciclib and/or olaparib as part of treatment?



Survey of clinical investigators

Optimizing the Management of ER-Positive Early Breast Cancer (BC)

Matthew Goetz, M.D.
Erivan K. Haub Family Professor of Cancer Research
Honoring Richard F. Emslander, M.D.
Professor of Oncology and Pharmacology
Division of Medical Oncology, Department of Oncology
Mayo Clinic in Rochester, MN

Outline

- Treating patients with chemotherapy based upon a “static” genomic score
  - Phase III RxPONDER trial
  - MINDACT
- Treating patients based on an “adaptive” biomarker (Ki-67)
- Key efficacy and safety outcomes observed in the Phase III monarchE
- FDA approval of adjuvant abemaciclib with endocrine therapy and identification of appropriate patients for this strategy
- Other ongoing studies (NATALEE) evaluating CDK4/6 inhibitors for localized ER-positive breast cancer

RxPONDER Schema

Key Entry Criteria
- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

Arm 1:
Chemotherapy Followed by Endocrine Therapy

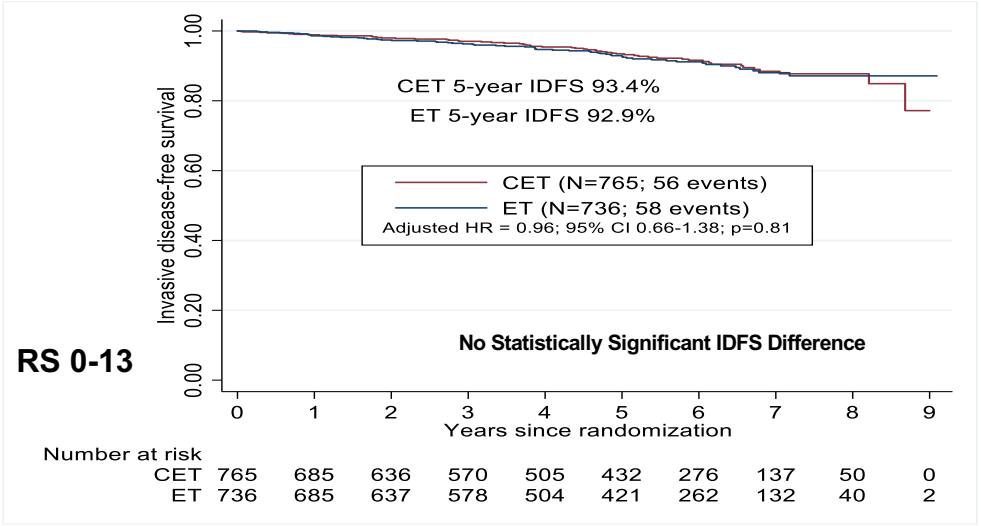
Arm 2:
Endocrine Therapy Alone

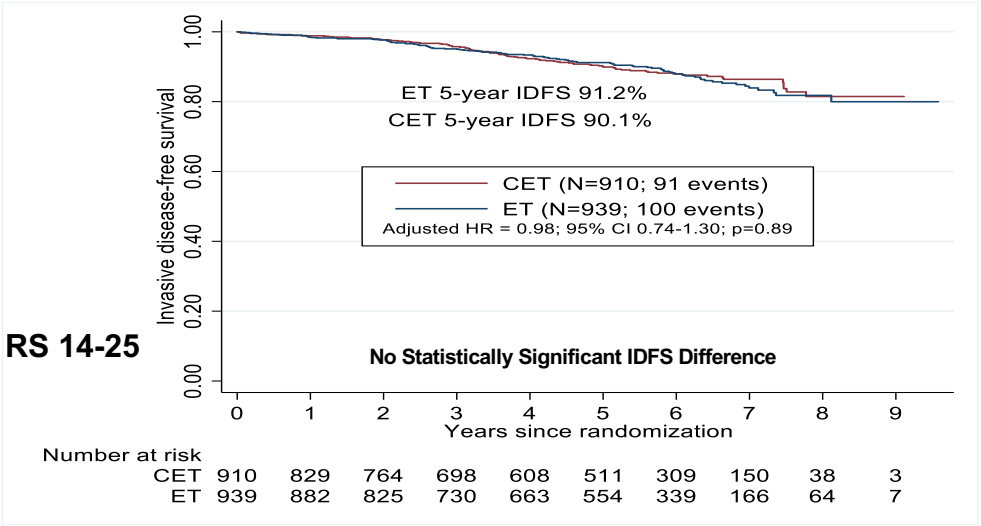
Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

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

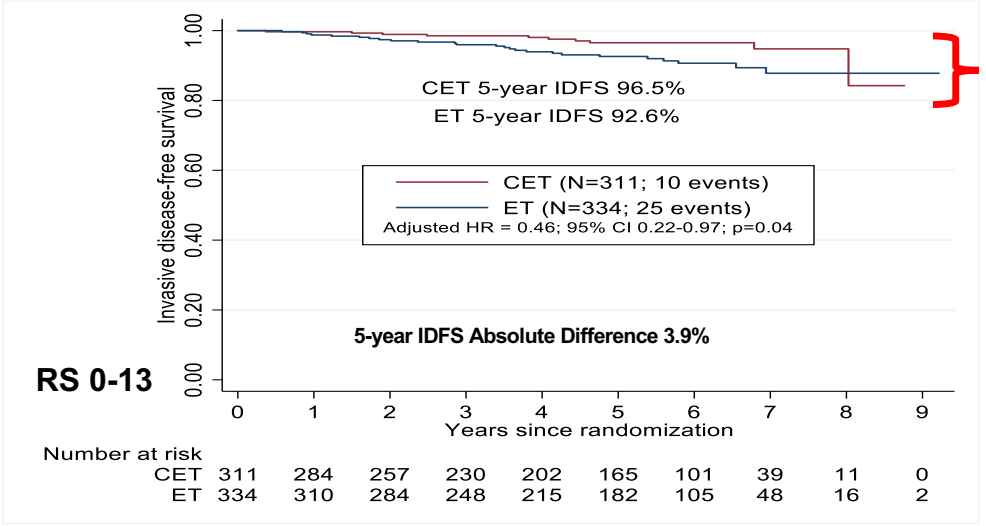
IDFS Stratified by Recurrence Score and Menopausal Status

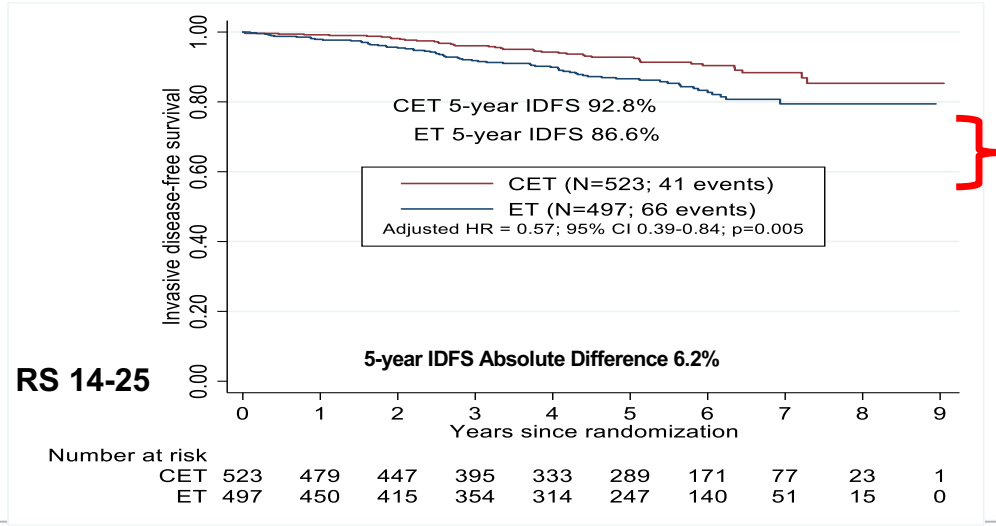
Postmenopausal





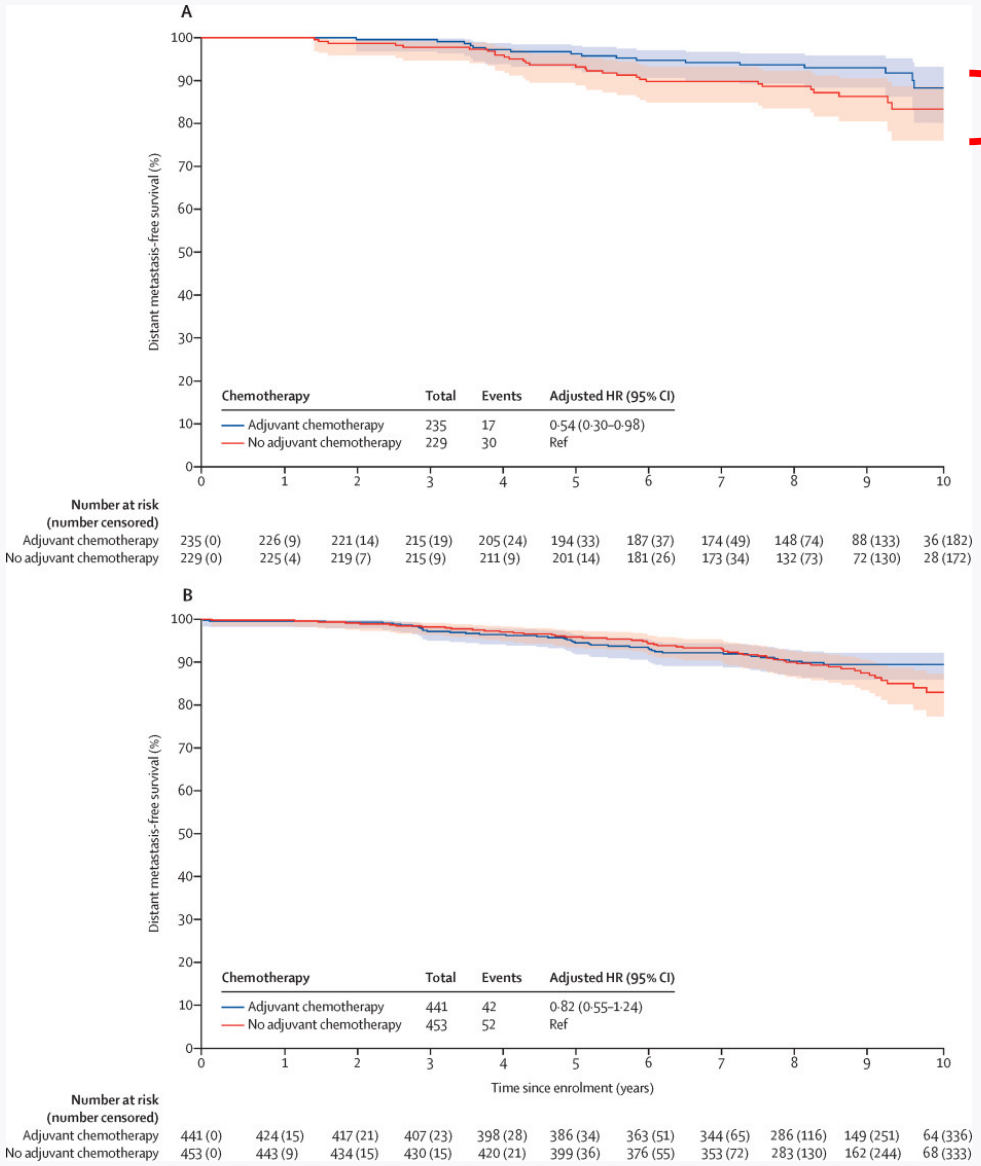
Premenopausal





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

Distant Metastasis-Free Survival in MINDACT according to Age: Clinical High-risk, Genomic Low-risk by Age

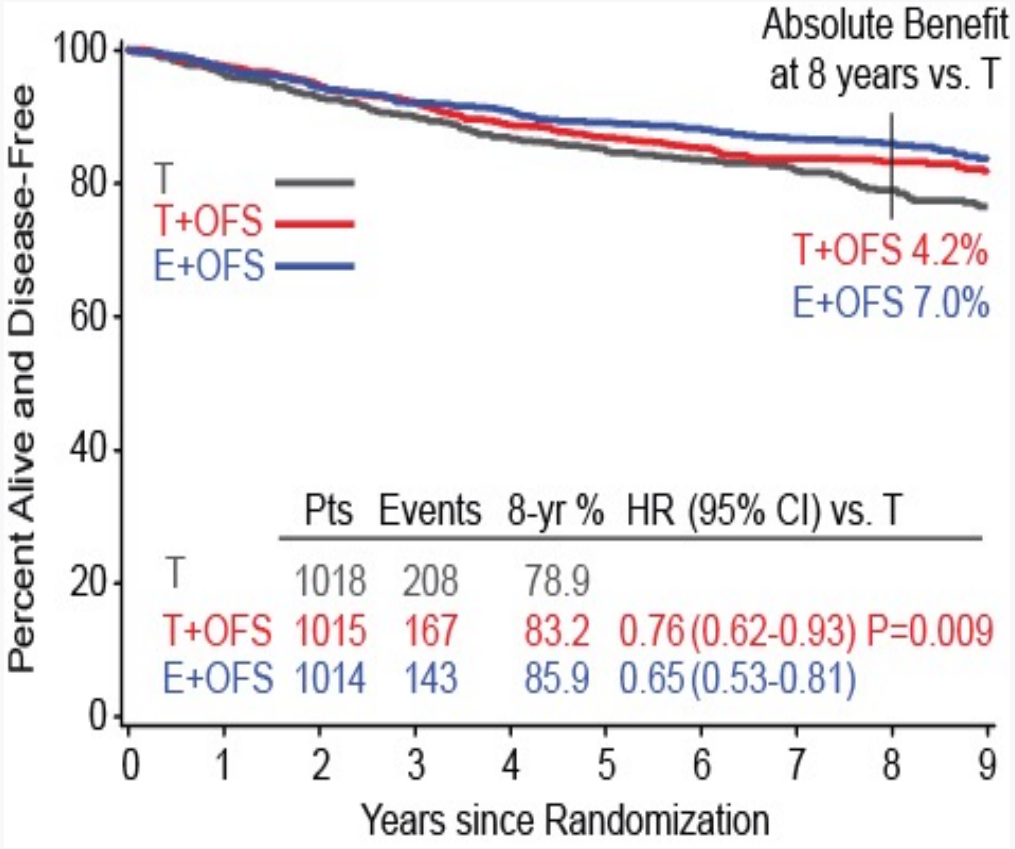


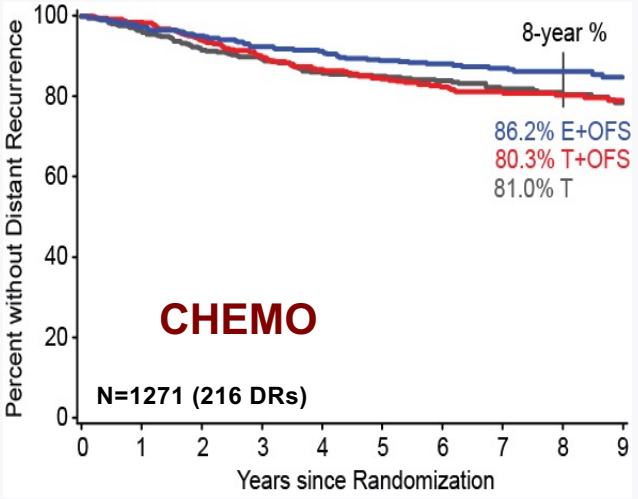
(A) Patients aged 50 years or younger

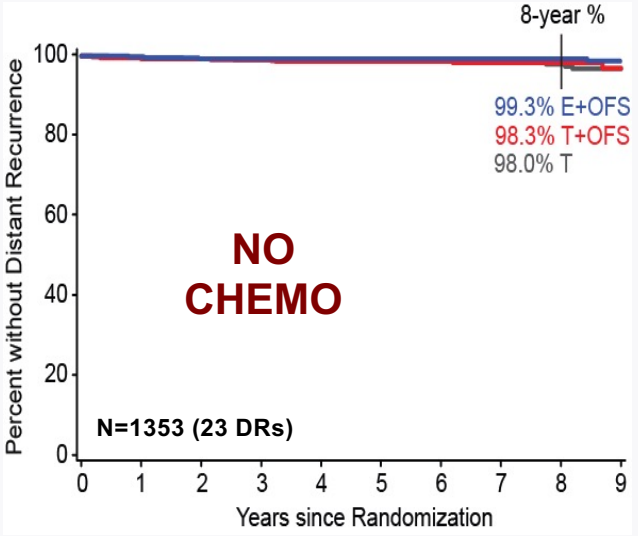
(B) patients aged older than 50 years.

Piccart Lancet Oncology 2021

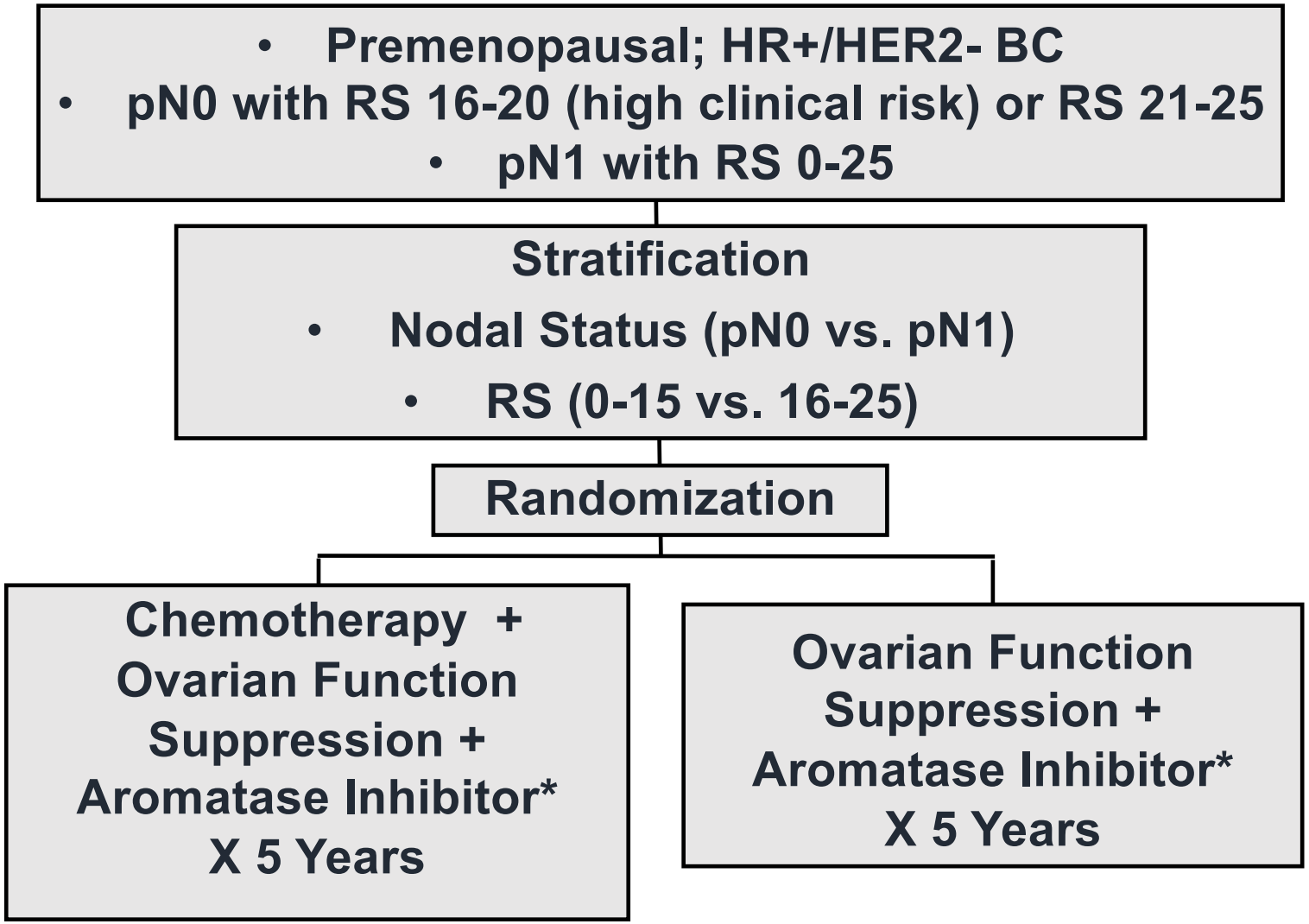
SOFT 8-Year Update: T+OFS Significantly Improves DFS vs. T-Alone; Exemestane Adds More Benefit





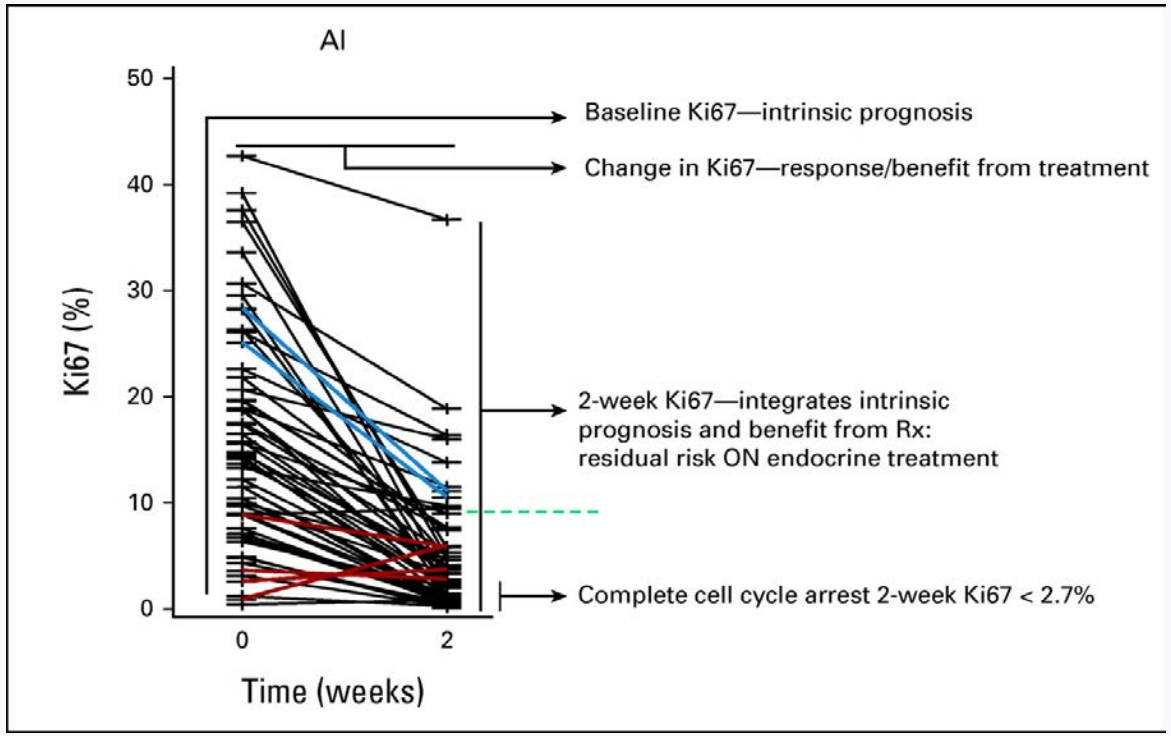


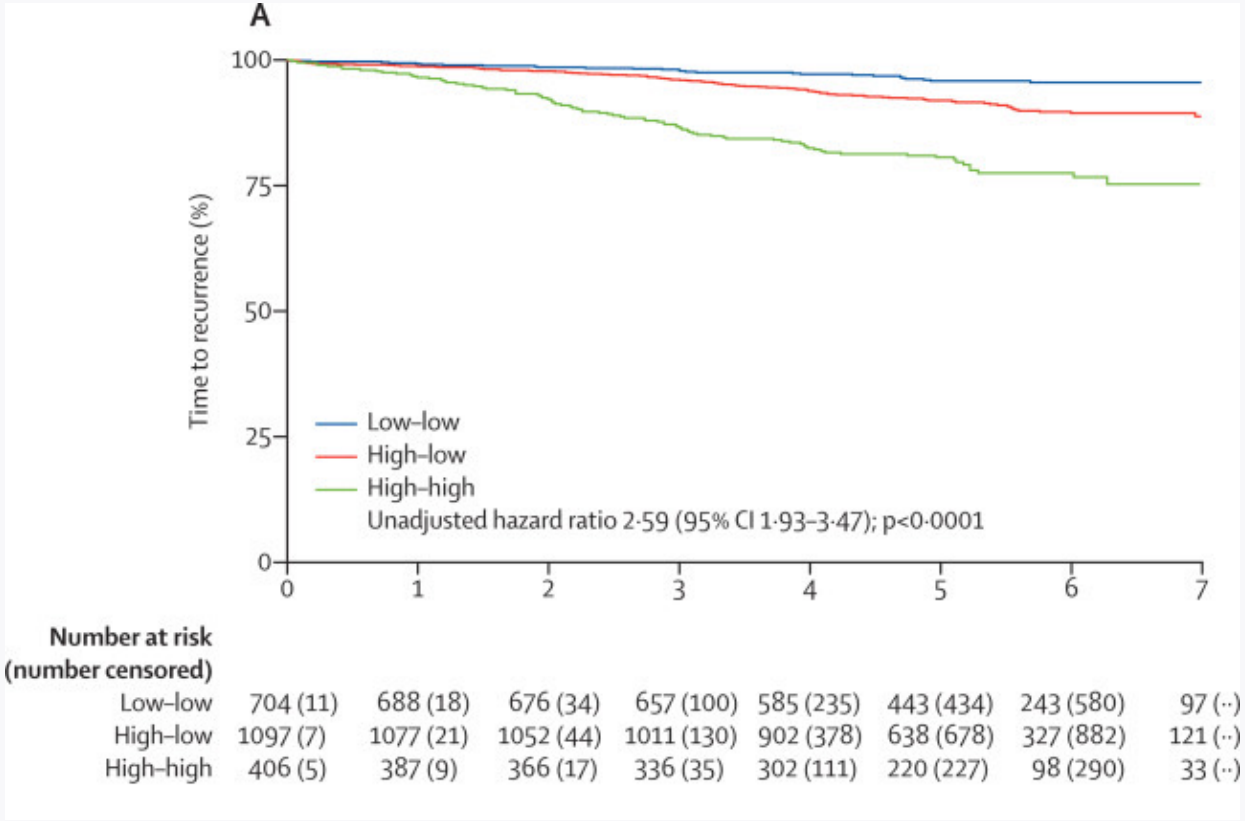
BR009: Schema (slide courtesy of Terry Mamounas)



* Tamoxifen can be used if AI is not tolerated

Endocrine Treatment Based on an "Adaptive" Biomarker (Ki-67): Findings from POETIC



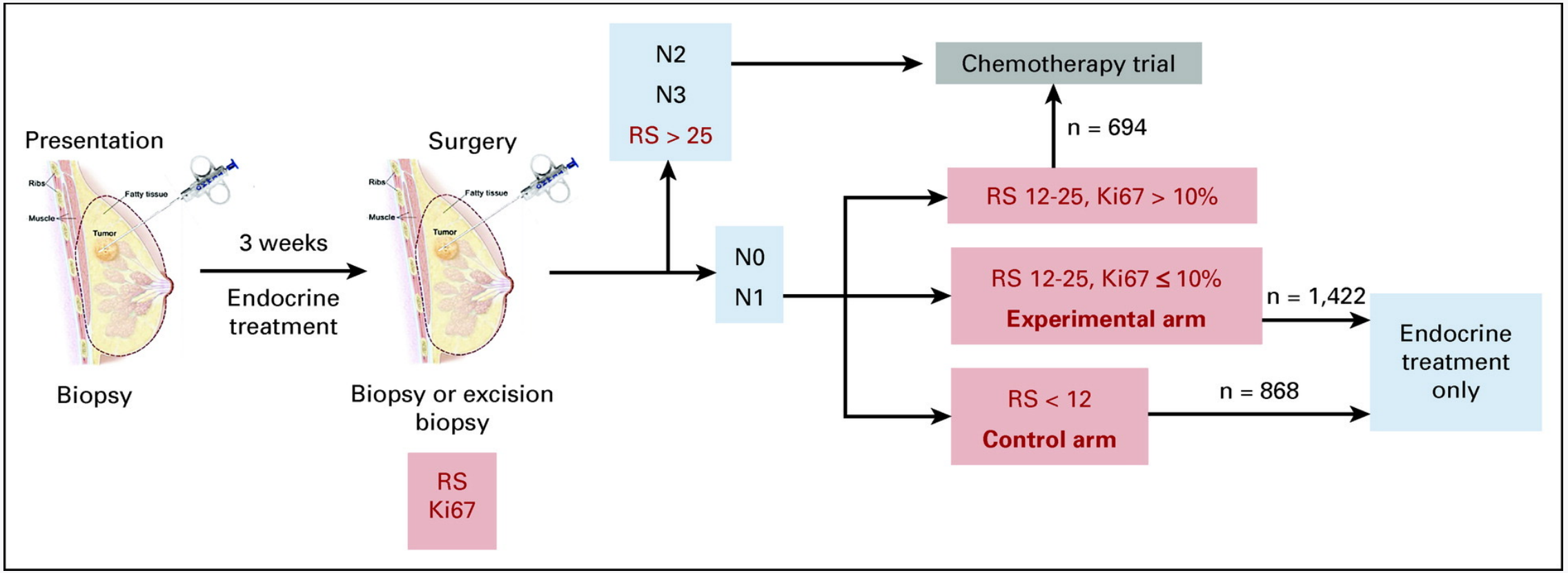


Number at risk (number censored)								
Low–low	704 (11)	688 (18)	676 (34)	657 (100)	585 (235)	443 (434)	243 (580)	97 (··)
High–low	1097 (7)	1077 (21)	1052 (44)	1011 (130)	902 (378)	638 (678)	327 (882)	121 (··)
High–high	406 (5)	387 (9)	366 (17)	336 (35)	302 (111)	220 (227)	98 (290)	33 (··)

Dowsett M J Clin Oncol 2022 and Smith et al. Lancet Oncol 2020

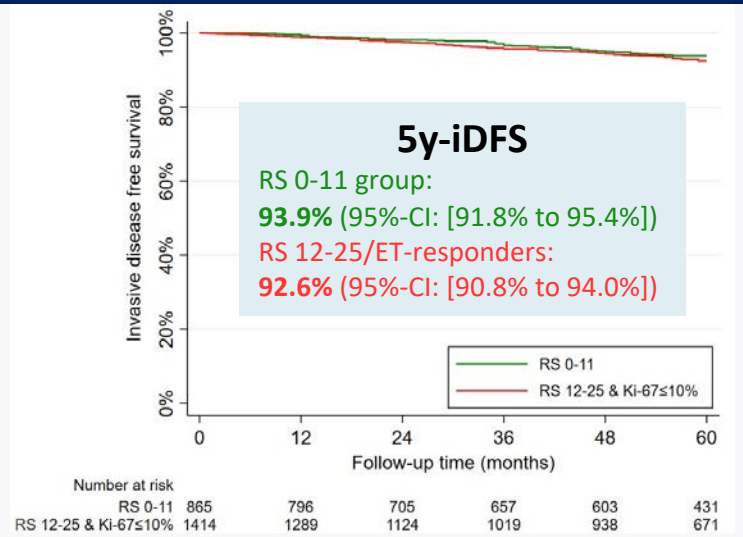
ADAPT

Integration of the 21 Gene RS and endocrine therapy response, defined as Ki67 ≤ 10% after 3 weeks' presurgical endocrine therapy (ET; $Ki67_{post}$≤ 10%).



Dowsett M J Clin Oncol 2022 and Nitz et al. J Clin Oncol 2022

ADAPT: 5-year IDFS



5y-iDFS

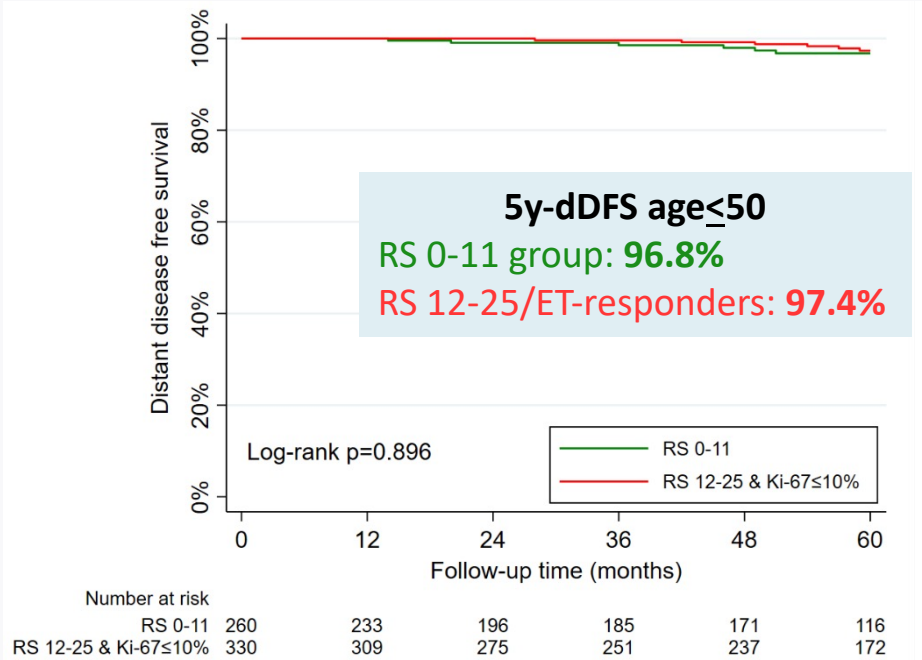
RS 0-11 group:
93.9% (95%-CI: [91.8% to 95.4%])
RS 12-25/ET-responders:
92.6% (95%-CI: [90.8% to 94.0%])

Trial Hypothesis: 5y-iDFS Noninferiority

95%-LCL of 5y-iDFS difference: -3.3%
(RS12-25/ET-responders vs. RS0-11)

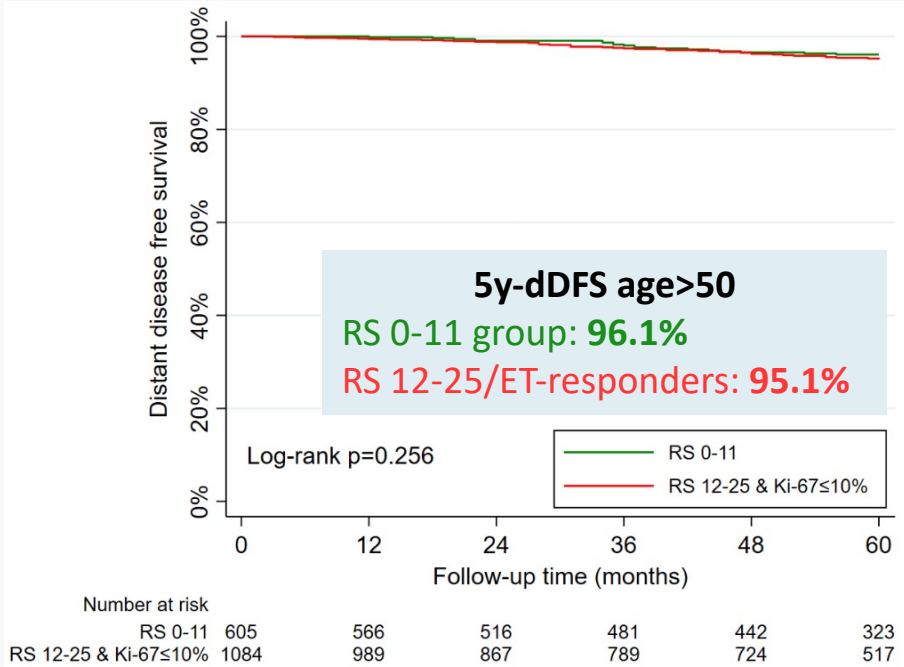
The one-sided lower 95% confidence limit of the observed 5y-iDFS difference (-1.3%) was -3.3%; thus, the pre-specified criterion to accept the primary NI-hypothesis was met (p=.05).

dDFS in age ≤50 years



5y-dDFS age≤50
RS 0-11 group: **96.8%**
RS 12-25/ET-responders: **97.4%**

dDFS in age >50 years



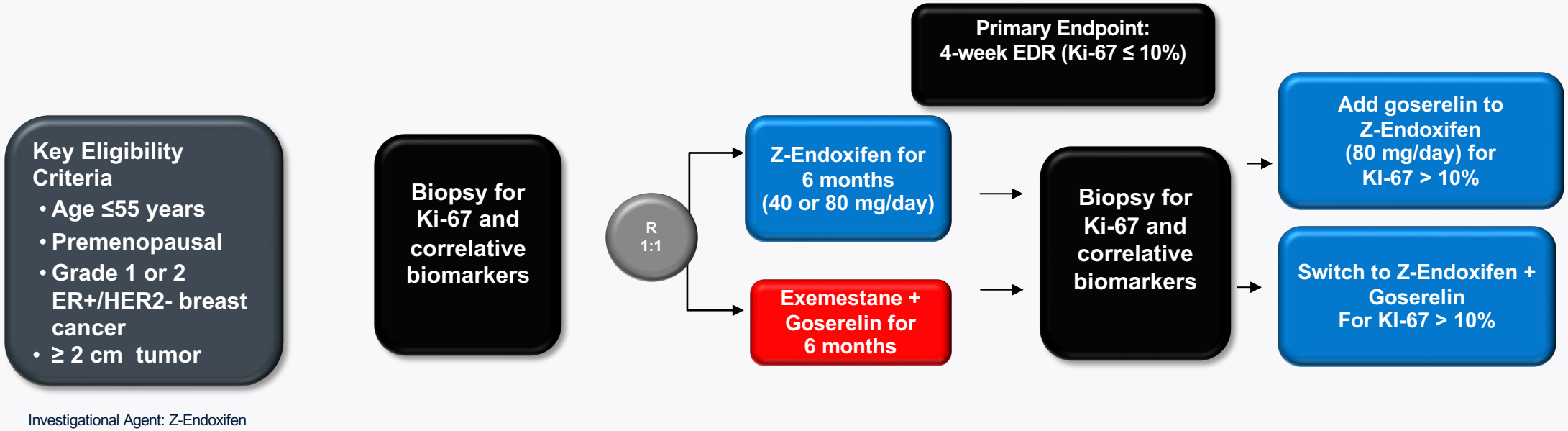
5y-dDFS age>50
RS 0-11 group: **96.1%**
RS 12-25/ET-responders: **95.1%**

Summary: Ki-67 and Neoadjuvant Endocrine Therapy

- **POETIC: Perioperative AI therapy in postmenopausal women: Elevated Ki-67 (>10%) after 2 weeks of AI therapy identifies patients with increased risk for breast cancer recurrence**
- **ADAPT: ET response (Ki-67 < 10%) more likely with AI than with tamoxifen (78% versus 41%; P < .001). (premenopausal patients: Tam steady state levels likely not achieved at 3 weeks).**
- **For those that achieve ET response, both premenopausal and postmenopausal patients had dDFS (>96%)**
- **Need for new therapeutic strategies for premenopausal women other than AI + OFS**

Smith et al. Lancet Oncology 2020
Ma et al. Clin Canc Res 2017
Nitz et al. J Clin Oncol 2022

A Randomized Phase 2 Non-inferiority Trial of (Z)-endoxifen and Exemestane + Goserelin in Premenopausal Women (EVANGELINE)



Investigational Agent: Z-Endoxifen

Statistics: The primary endpoint is the endocrine sensitive disease (ESD) rate after 4 weeks (defined as Ki67 ≤ 10%). The expected ESD rate with exemestane + goserelin in pre-menopausal women is 70%. The non-inferiority margin is defined to be less than 15%. With a sample size of 81 subjects per treatment arm, a non-inferiority test for the difference between two proportions with a type I error of 0.15 (one-sided) will have a power of 85% to detect a non-inferiority margin difference between these two proportions of 0.15, when the week 4 ESD rate is 0.70.

Atossa Therapeutics

Matthew Goetz, PI

MonarchE Study Design

HR+, HER2-, high risk early breast cancer

High risk defined as:

- ≥4 positive axillary lymph nodes (ALN) OR
- 1-3 ALN and at least 1 of the below:
  - Tumor size ≥5 cm
  - Histologic grade 3
  - Centrally tested Ki67 ≥20%

N = 5637[a]

R
1:1

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

Abemaciclib (150mg twice daily for up to 2 years[b])
+ Standard of Care Endocrine Therapy
(5 to 10 years as clinically indicated)

Standard of Care Endocrine Therapy[b]
(5 to 10 years as clinically indicated)

Endocrine therapy of physician's choice

Other criteria:
- Women or men
- Pre-/ postmenopausal
- With or without prior adjuvant/neoadjuvant chemotherapy
- No distant metastases

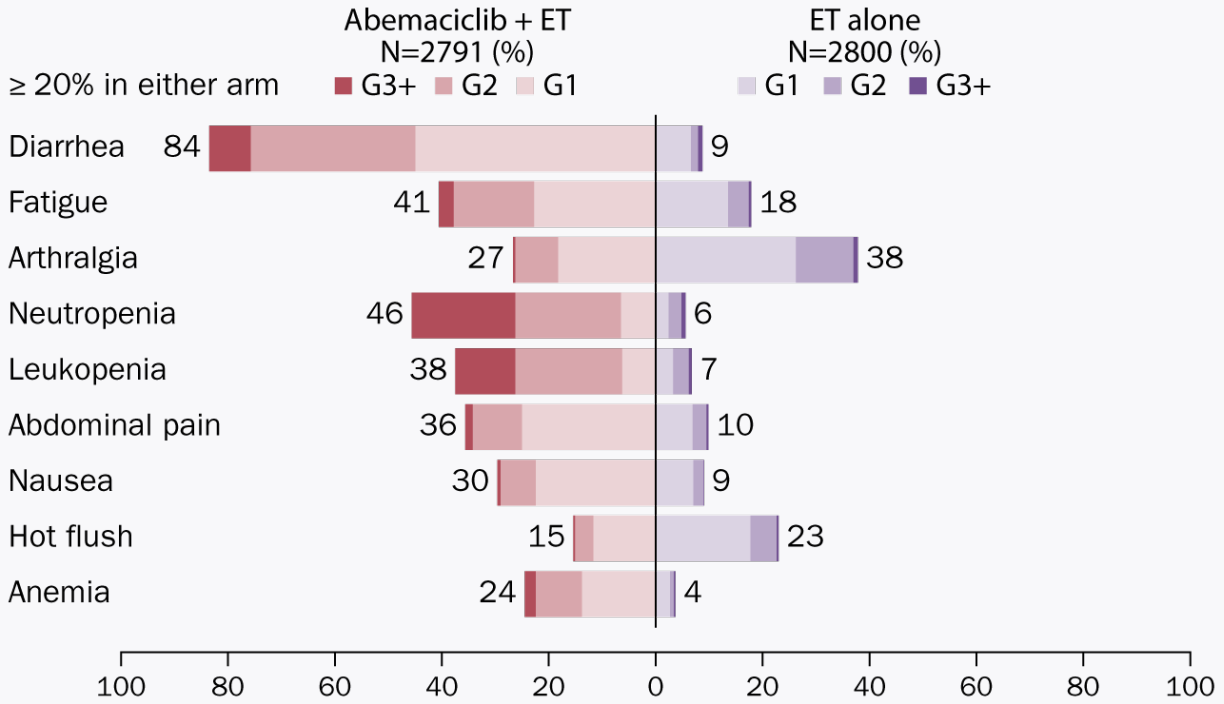
Primary Objective: Invasive disease-free survival (STEEP criteria)
Key Secondary Objectives: Distant relapse-free survival, Overall survival, Safety, Patient reported outcomes, and Pharmacokinetics

[a] Recruitment from July 2017 to August 2019; [b] Treatment period = first 2 years on study treatment after randomization

Johnston et al. J Clin Oncol 2020

MonarchE Safety Summary

AEs ≥20% in Both Treatment Arms[2]



Among the 2304 patients who experienced diarrhea[3]

- Median time to onset (any grade) was 8 days
- 20.5% had ≥1 dose reduction
- 22.9% had dose holds
- 5.0% of patients had their treatment discontinued

Other events of interest,[2] any grade	Abemaciclib + ET (n=2791)	ET alone (n=2800)
VTE, %	2.5	0.6
PE, %	1.0	0.1
ILD, %	3.2	1.3

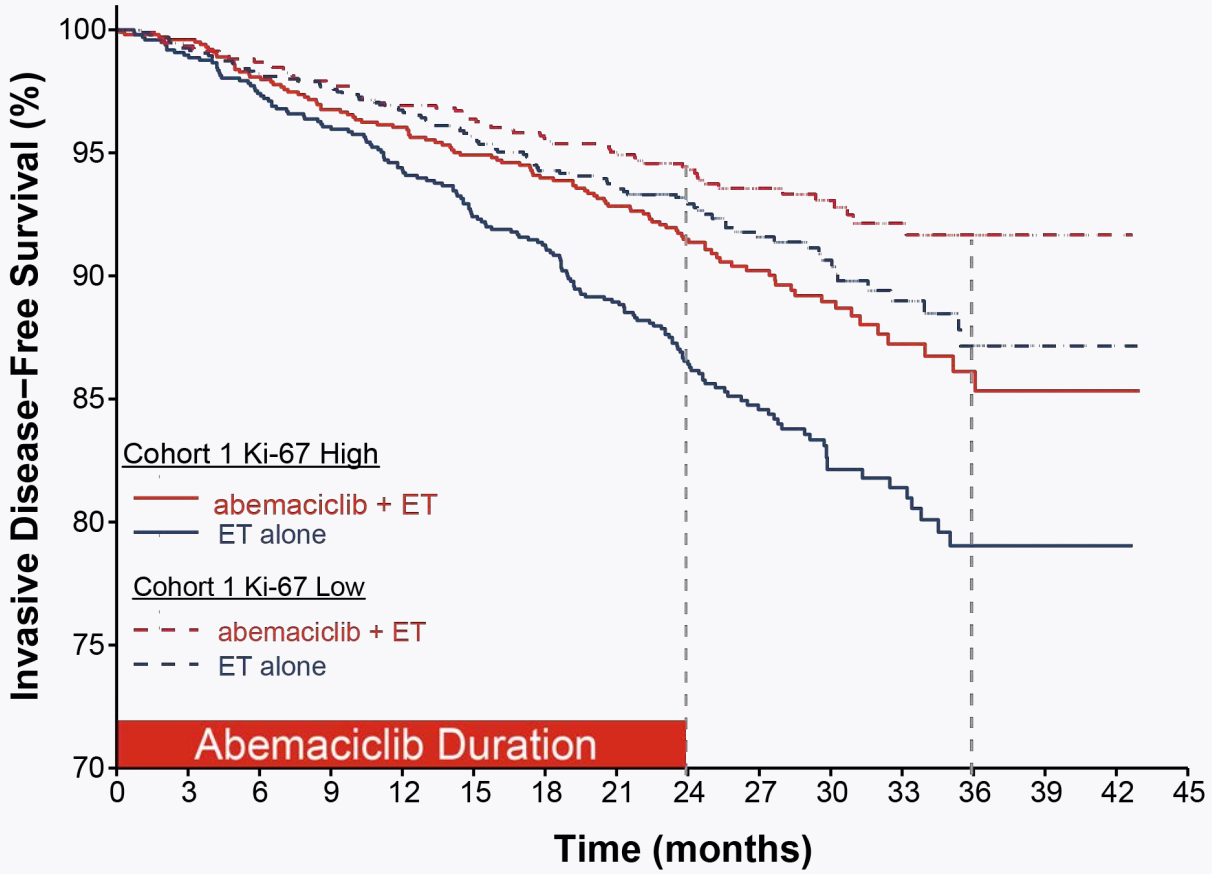
Safety data at additional follow-up are **consistent** with the known safety profile of abemaciclib[1]

Median duration of treatment: **24 months**

The safety population includes patients who received at least 1 dose of study treatment

1. Harbeck N, et al. *Ann Oncol.* 2021;S0923-7534(21):04494-X. 2. O'Shaughnessy J, et al. ESMO Virtual Plenary 2021. Abstract VP8-2021.
3. Tolaney S, et al. St. Gallen 2021. Abstract PO13.

Ki-67 as a Prognostic Marker in Cohort 1



	Abemaciclib + ET	ET Alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	986	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year Rates	91.7%	87.2%	

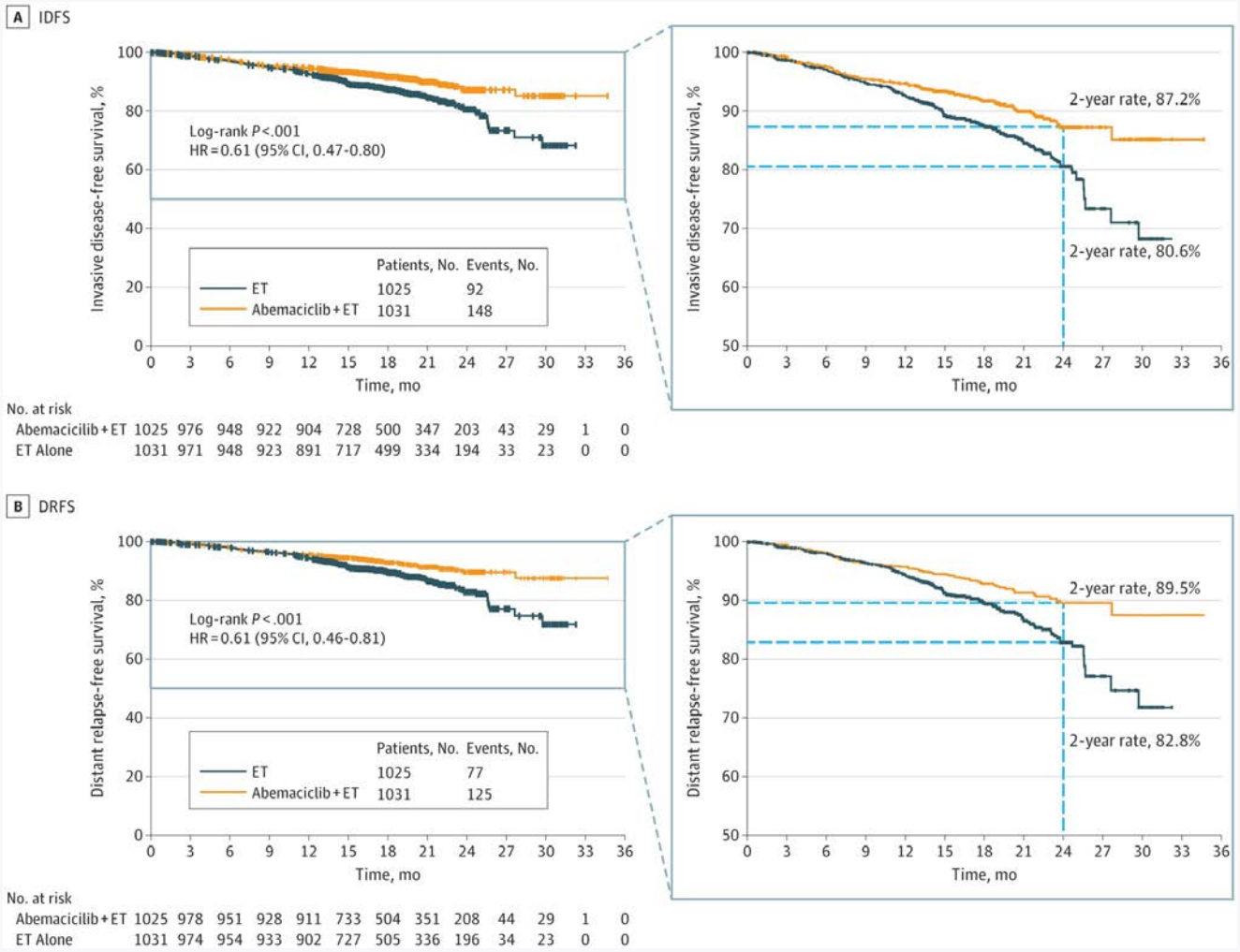
Ki-67 is prognostic

Ki-67 is not predictive of abemaciclib benefit

Ki-67 index was prognostic of worse outcome.
However, abemaciclib benefit was consistent regardless of Ki-67 index.

Harbeck et al. Ann Onco 2021 Dec;32(12):1571-1581

MonarchE: Patients who received neoadjuvant chemotherapy (NAC)

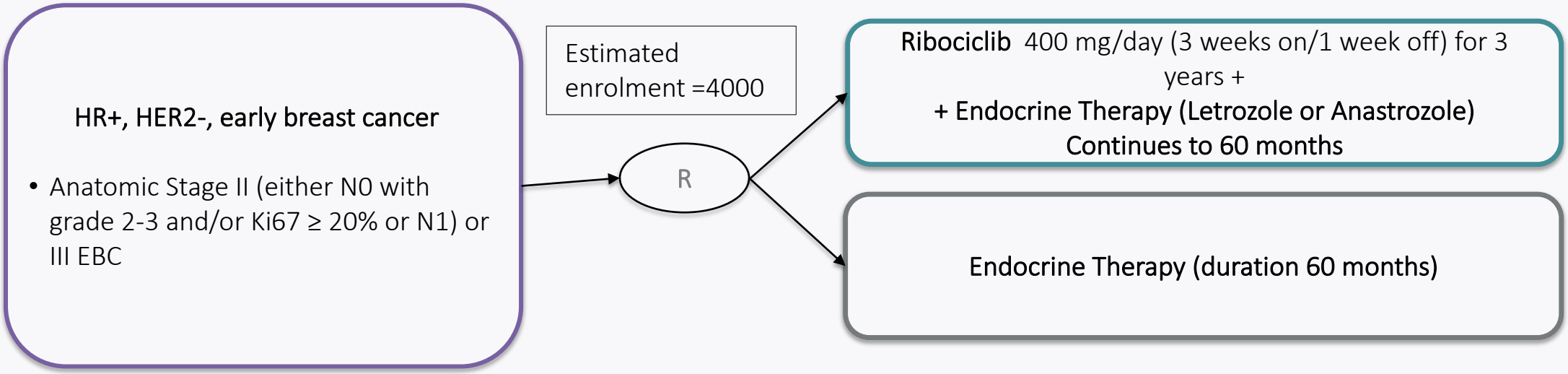


Two-year IDFS rates were 87.2% in the abemaciclib + ET arm and 80.6% in the ET arm – 6.6% difference

Two-year DRFS rates were 89.5% in the abemaciclib + ET arm and 82.8% in ET arm – 6.7% difference

Martin et al. JAMA Oncol 2022

Ongoing Adjuvant CDK 4/6 Inhibitor Trial: NATALEE



Other criteria:
- Women or men
- Pre*-/ postmenopausal
- With or without prior adjuvant/neoadjuvant chemotherapy
- No distant metastases

*Premenopausal and male patients will also receive goserelin 3.6 mg/28 d

Primary Objective: Invasive disease-free survival (STEEP criteria)
Key Secondary Objectives: recurrence-free survival, distant DFS, overall survival, patient-reported outcomes, and RIBO pharmacokinetics. Safety and tolerability will also be evaluated.

Slamon DJ, et al. J Clin Oncol 2019;37(15 suppl), Abstract TPS597.

Guidelines for Abemaciclib Use in Patients With EBC

FDA-Approved Indication[1]

Abemaciclib plus ET (tamoxifen or an AI) for the adjuvant treatment of adult patients with HR+ HER2-, node-positive EBC at a high risk of recurrence and a Ki-67 score of ≥20%

In monarchE, patients had to have tumor involvement in at least 1 ALN and either:

- ≥4 ALN, or
- 1-3 ALN and at least one of the following:
  - tumor grade 3
  - tumor size ≥ 50 mm
- Patients with available untreated breast tumor samples were tested retrospectively at central sites using the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay to establish if the Ki-67 score was ≥20%, specified in the protocol as “Ki-67 high”

ASCO Guidelines[2]

Abemaciclib for two years plus ET for ≥5 years may be offered to the broader ITT population of patients with resected, HR+ HER2-, node-positive, EBC at high risk of recurrence

High risk of recurrence is defined as having:

- >4 positive ALNs, or
- 1-3 ALNs, and one or more of the following
  - histologic grade 3 disease
  - tumor size >5 cm, or
  - Ki-67 index >20%

1. Verzenio. Package insert. Eli Lilly and Company; 2021. 2. American Society of Clinical Oncology. Accessed November 22, 2021. https://www.asco.org/practice-patients/guidelines/breast-cancer#/11081

Abstract VP1-2022

ESMO VIRTUAL PLENARY

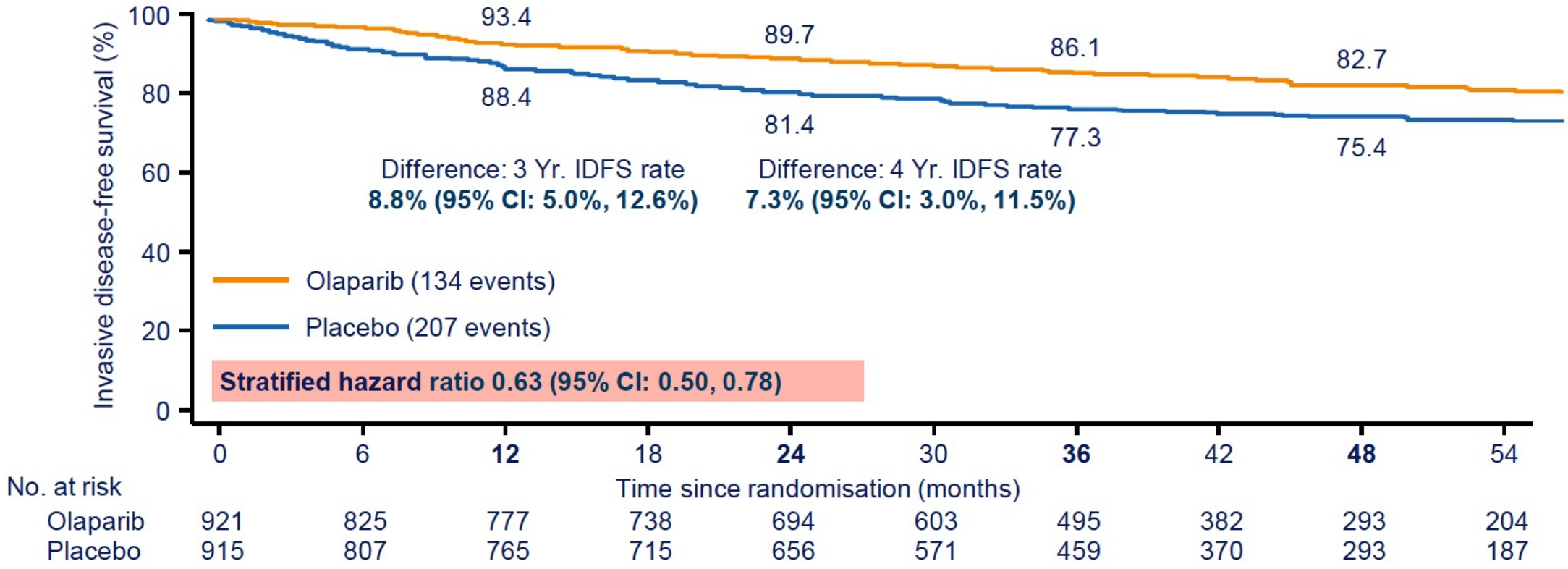
PRE-SPECIFIED EVENT DRIVEN ANALYSIS OF OVERALL SURVIVAL (OS) IN THE OLYMPIA PHASE III TRIAL OF ADJUVANT OLAPARIB (OL) IN GERMLINE *BRCA1/2* MUTATION (*gBRCAm*) ASSOCIATED BREAST CANCER

Andrew Nicholas James Tutt[1], Judy Garber[2], Richard D. Gelber[2], Kelly-Anne Phillips[3], Andrea Eisen[4], Oskar Thor Jóhannsson[5], Priya Rastogi[6], Karen Yongzhi Cui[7], Seock-Ah Im[8], Rinat Yerushalmi[9], Adam Matthew Brufsky[10], Maria Taboada[11], Giovanna Rossi[12], Greg Yothers[13], Christian Singer[14], Luis E. Fein[15], Niklas Loman[16], David Cameron[17], Christine Campbell[18], Charles Edward Geyer Jr[19]

[1]Breast Cancer Now Research Unit, Institute of Cancer Research, London, United Kingdom; [2]Dana Farber Cancer Institute, Boston, MA, USA; [3]Department of Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia; [4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Canada; [5]Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland; [6]Department of Oncology, NSABP Foundation, Pittsburgh, PA, USA; [7]Global Medicine Development, AstraZeneca US, Gaithersburg, MD, USA; [8]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; [9]Department of Oncology, Clalit Health Services, Petah Tikva, Israel; [10]Department of Hematology-Oncology, Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA; [11]AstraZeneca, Royston, United Kingdom; [12]Department of R&D, Breast International Group (BIG) – AISBL, Brussels, Belgium; [13]Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA, USA;

[14]Center for Breast Health, Medical University of Vienna, Vienna, Austria; [15]Department of Oncology, Instituto de Oncología de Rosario, Rosario, Santa Fe, Argentina; [16]Skane University Hospital, Lund, Sweden; [17]Department of Oncology, Edinburgh Cancer Centre, Edinburgh, United Kingdom; [18]Frontier Science Scotland, Kincraig, United Kingdom; [19]Department of Clinical Research, Houston Methodist Cancer Center, Houston, TX, USA

ANALYSIS OF IDFS (ITT) AT OS IA2

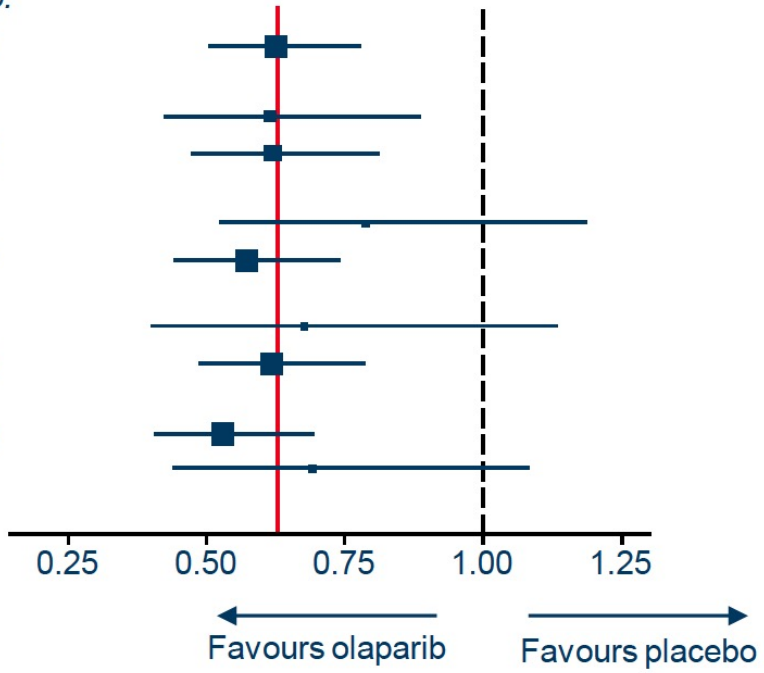


Andrew Nicholas James Tutt MB ChB PhD FMedSci

Tutt ANJ et al. ESMO Virtual Plenary 2022;Abstract VP1-2022.

SUBGROUP ANALYSIS IDFS

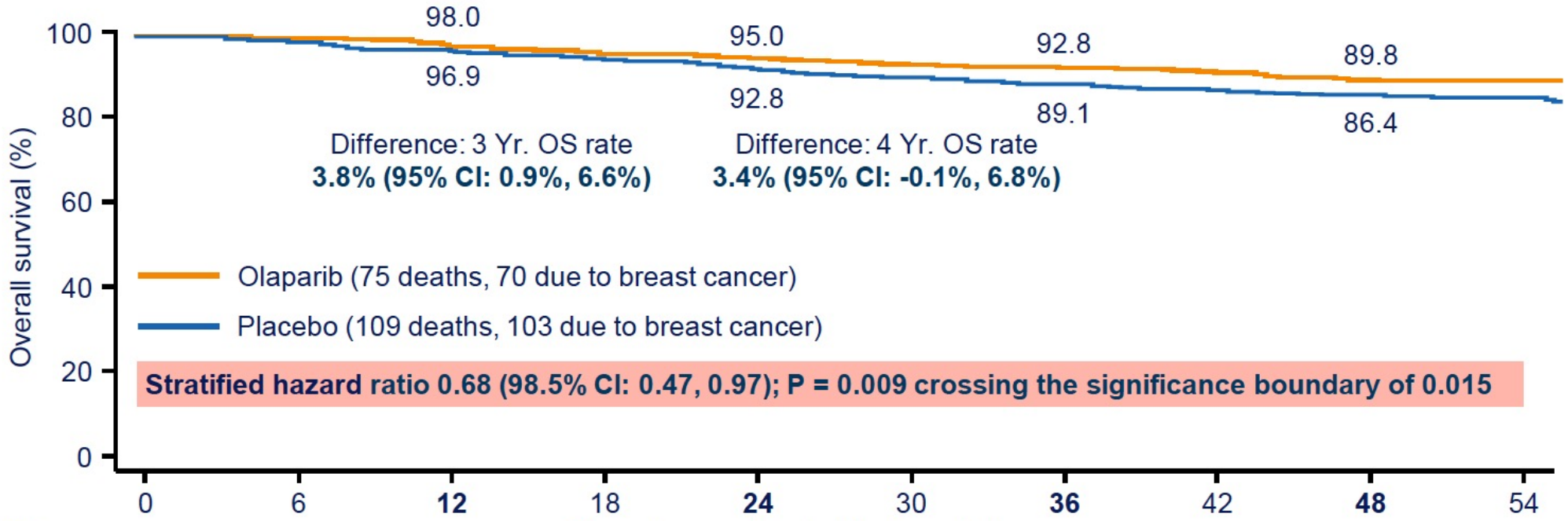
Subgroup	Olaparib	Placebo	HR (95% CI)	P value for heterogeneity
	No. of patients with an invasive disease event/total no.			
All patients	134 / 921	207 / 915	0.628 (0.504, 0.779)	NA
Prior chemo				0.977
Adjuvant	46 / 461	75 / 455	0.618 (0.425, 0.888)	
Neoadjuvant	88 / 460	132 / 460	0.622 (0.473, 0.813)	
Prior platinum				0.197
Yes	42 / 247	51 / 238	0.791 (0.523, 1.187)	
No	92 / 674	156 / 677	0.575 (0.443, 0.742)	
HR status				0.754
HR+/HER2-	25 / 168	34 / 157	0.680 (0.402, 1.134)	
TNBC	109 / 751	173 / 758	0.620 (0.487, 0.787)	
BRCA				0.615
BRCA1	83 / 579	149 / 588	0.533 (0.406, 0.695)	
BRCA2	34 / 235	44 / 216	0.693 (0.440, 1.082)	
BRCA1/2 both	0 / 2	0 / 3	NC	



All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

Tutt ANJ et al. ESMO Virtual Plenary 2022;Abstract VP1-2022.

SECOND OVERALL SURVIVAL INTERIM ANALYSIS - OS IA 2 (ITT)



No. at risk										
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

98.5% confidence intervals are shown for the hazard ratio because P < 0.015 is required for statistical significance

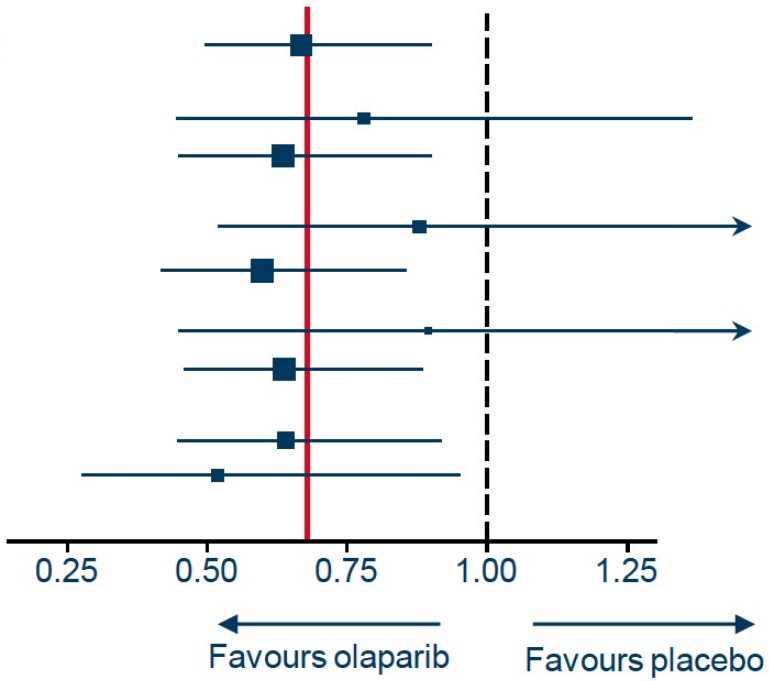
ESMO VIRTUAL PLENARY

Andrew Nicholas James Tutt MB ChB PhD FMedSci

Tutt ANJ et al. ESMO Virtual Plenary 2022;Abstract VP1-2022.

SUBGROUP ANALYSIS OF OS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	P value for heterogeneity
	No. of patients who died /total no.			
All patients	75 / 921	109 / 915	0.678 (0.503, 0.907)	NA
Prior chemo				0.543
Adjuvant	22 / 461	28 / 455	0.783 (0.444, 1.365)	
Neoadjuvant	53 / 460	81 / 460	0.638 (0.449, 0.900)	
Prior platinum				0.236
Yes	27 / 247	29 / 238	0.882 (0.520, 1.491)	
No	48 / 674	80 / 677	0.601 (0.417, 0.855)	
HR status				0.381
HR+/HER2-	16 / 168	17 / 157	0.897 (0.449, 1.784)	
TNBC	59 / 751	92 / 758	0.640 (0.459, 0.884)	
BRCA				0.845
BRCA1	49 / 579	75 / 588	0.643 (0.446, 0.918)	
BRCA2	16 / 235	28 / 216	0.521 (0.276, 0.951)	
BRCA1/2 both	0 / 2	0 / 3	NC	



All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

Andrew Nicholas James Tutt MB ChB PhD FMedSci

Tutt ANJ et al. ESMO Virtual Plenary 2022;Abstract VP1-2022.

MODULE 2: New and Novel Treatment Strategies for Localized Triple-Negative Breast Cancer (TNBC)

RTP
RESEARCH
TO PRACTICE

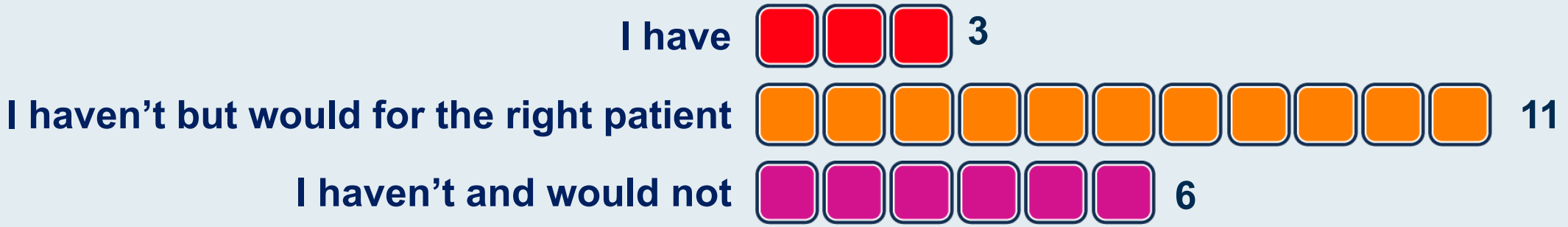
In general, what would you recommend as adjuvant therapy for a patient with a germline BRCA mutation and TNBC with a PD-L1 combined positive score (CPS) of 1 who had residual disease after neoadjuvant chemotherapy?

Does level of PD-L1 expression have any bearing on your response to the previous question?

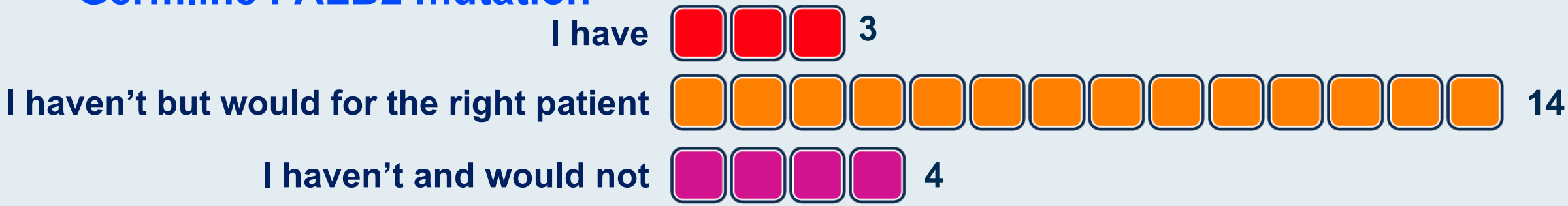
Yes = 3; no = 17

Regulatory and reimbursement issues aside, have you attempted or would you attempt to access olaparib as part of adjuvant therapy for a patient with TNBC who had residual disease after neoadjuvant chemotherapy and a…

Somatic BRCA mutation

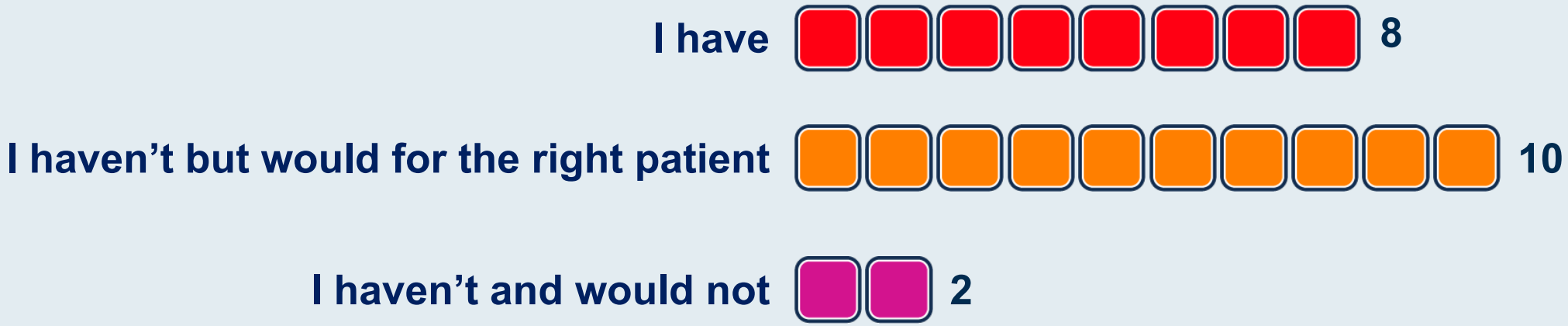


Germline PALB2 mutation



Survey of clinical investigators

Regulatory and reimbursement issues aside, have you combined or would you combine olaparib with adjuvant pembrolizumab for a patient with a germline BRCA mutation and PD-L1-positive TNBC who had residual disease after neoadjuvant chemotherapy/pembrolizumab?



Survey of clinical investigators

Do you generally administer adjuvant pembrolizumab to patients with localized breast cancer who receive neoadjuvant chemotherapy/pembrolizumab and are found at surgery to have a pathologic complete response?

Survey of clinical investigators

New and Novel Treatment Strategies for Localized Triple-Negative BC (TNBC)

Erika Hamilton, MD

Director, Breast & Gynecologic Cancer Research Program

Sarah Cannon Research Institute/ Tennessee Oncology

SARAH CANNON

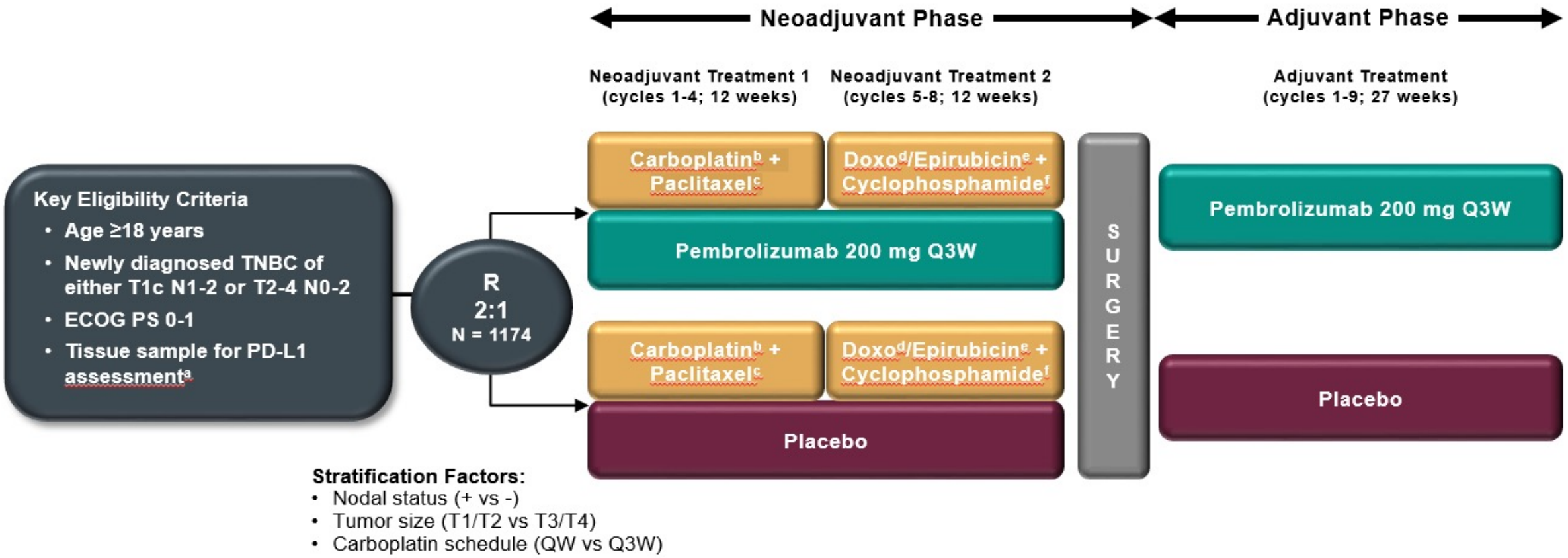
Agenda

- Immunotherapy for high risk early stage TNBC
  - KEYNOTE-522
- 27-gene IO score
- OlympiA – Adjuvant olaparib for gBRCA mutant
  - Key efficacy and safety data
- Novel agents
  - Sacituzumab govitecan (SASCIA)

Immunotherapy for high risk eTNBC

SARAH CANNON

KEYNOTE-522: Immunotherapy for early TNBC



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

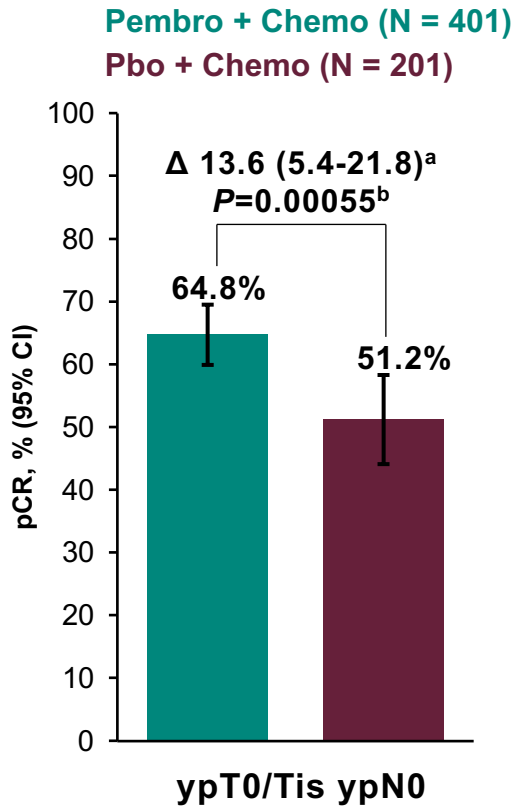
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

SARAH CANNON

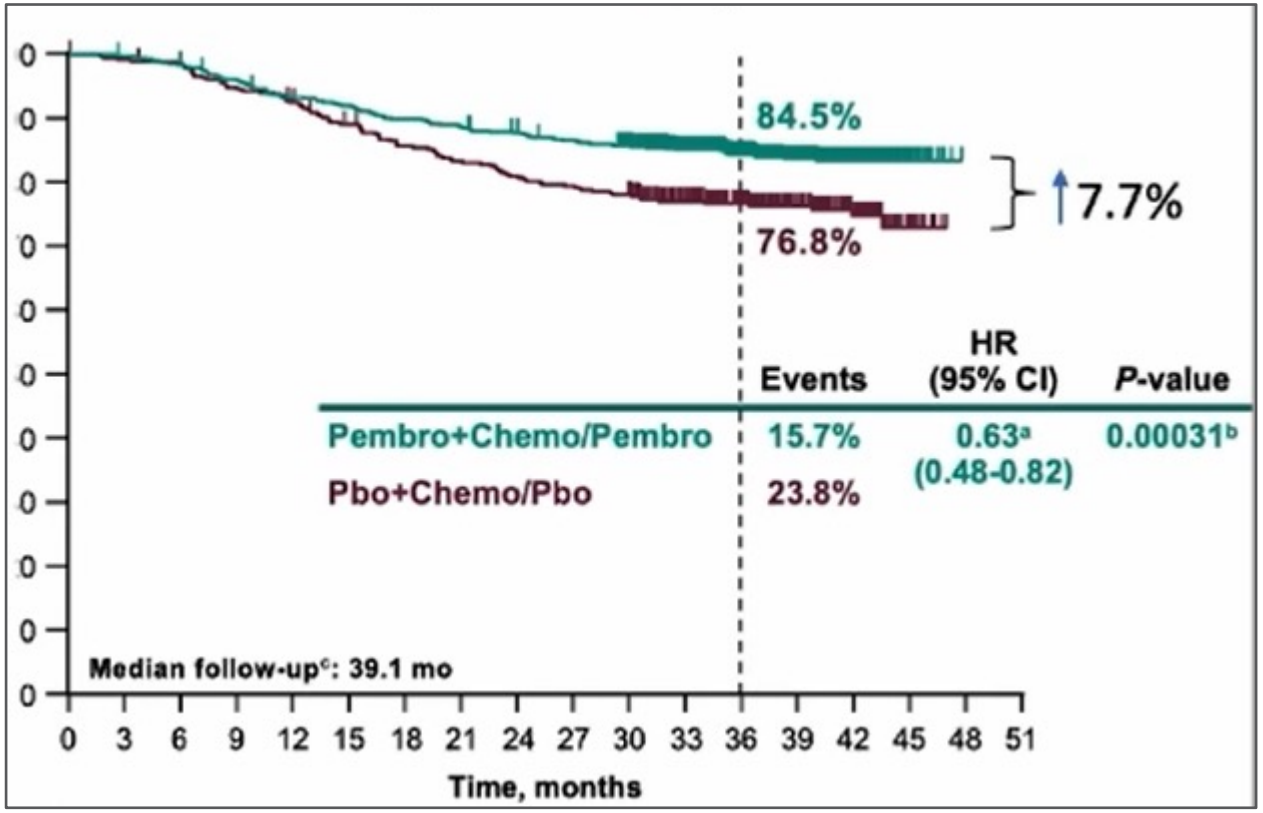
Schmid P et al. GS1-01, SABCS 2021

KEYNOTE-522: Efficacy data from interim analysis

Primary pCR Endpoint at IA1



EFS Analysis at IA4



1. pCR benefit with pembrolizumab consistent across all subgroups
2. Benefit in both N-/N+ patients
3. Similar benefit for patients with PD-L1- and PD-L1+ tumors

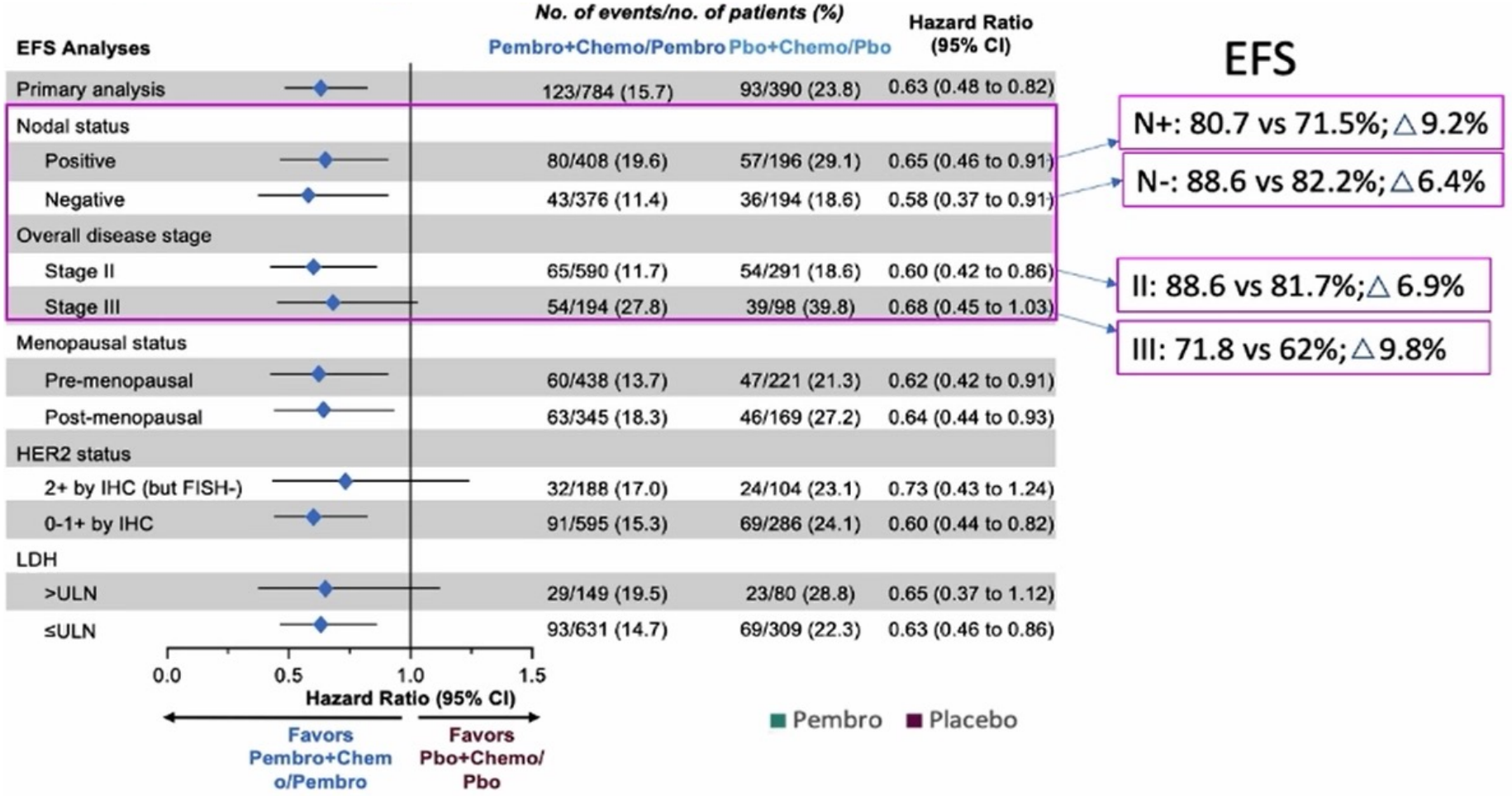
Significant improvement in EFS (7.7% absolute difference) with addition of pembro to chemo (neoadj) → adjuvant pembro

@ErikaHamilton9

SARAH CANNON

Schmid P et al. ESMO 2019 & 2021

KEYNOTE-522: Updated EFS based on nodal status and disease stage



- ✓ EFS benefit with pembrolizumab consistent in N +/- patients and irrespective of disease stage
- ✓ No new AE signals observed with adjuvant pembrolizumab based on this updated analysis

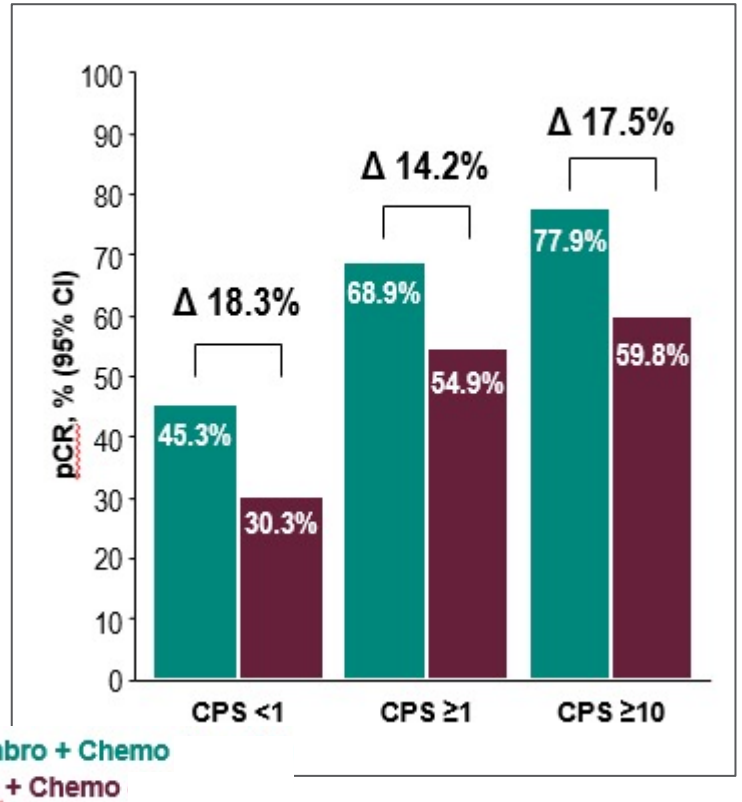
@ErikaHamilton9

SARAH CANNON

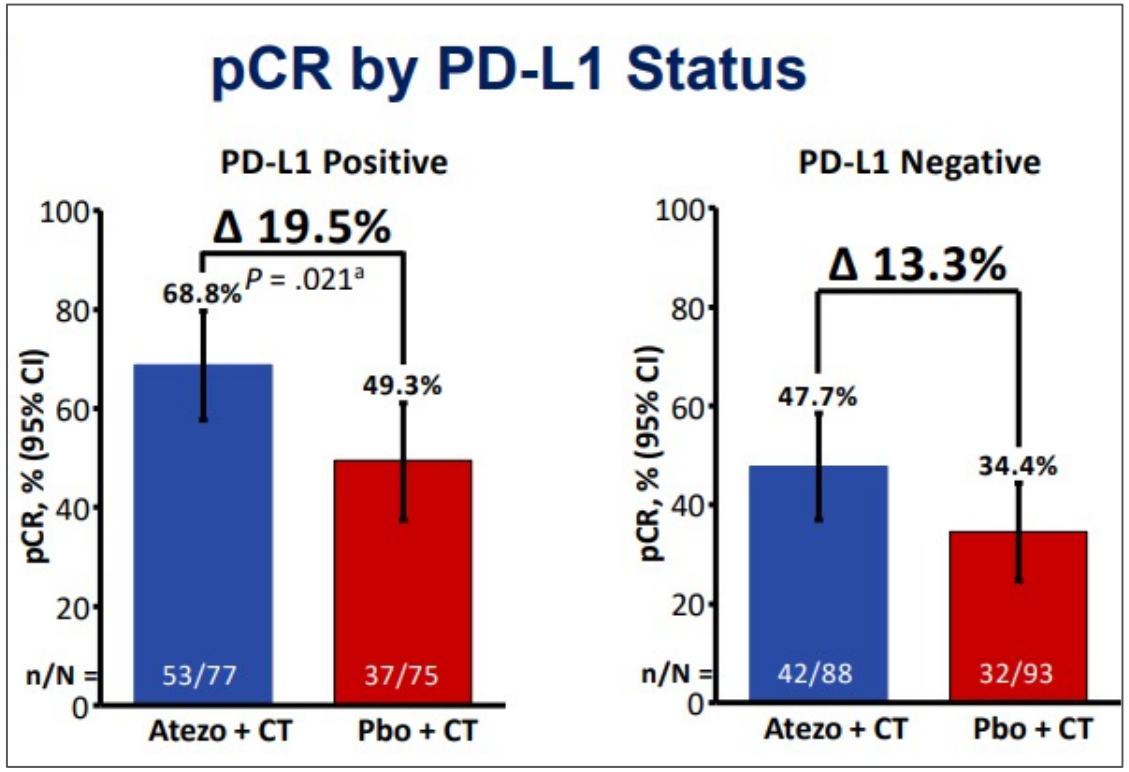
Schmid P et al. GS1-01, SABCS 2021

pCR rates based on PD-L1 expression with neoadjuvant IO

KEYNOTE-522
Pembrolizumab/placebo + chemo
eTNBC



IMpassion031
Atezolizumab/placebo + chemo
eTNBC



No difference in pCR rates based on PD-L1 status

Schmid P et al. ESMO 2021
Harbeck N et al. ESMO 2020

27-gene analysis to predict response to CPI

27-gene immuno-oncology (IO) signature

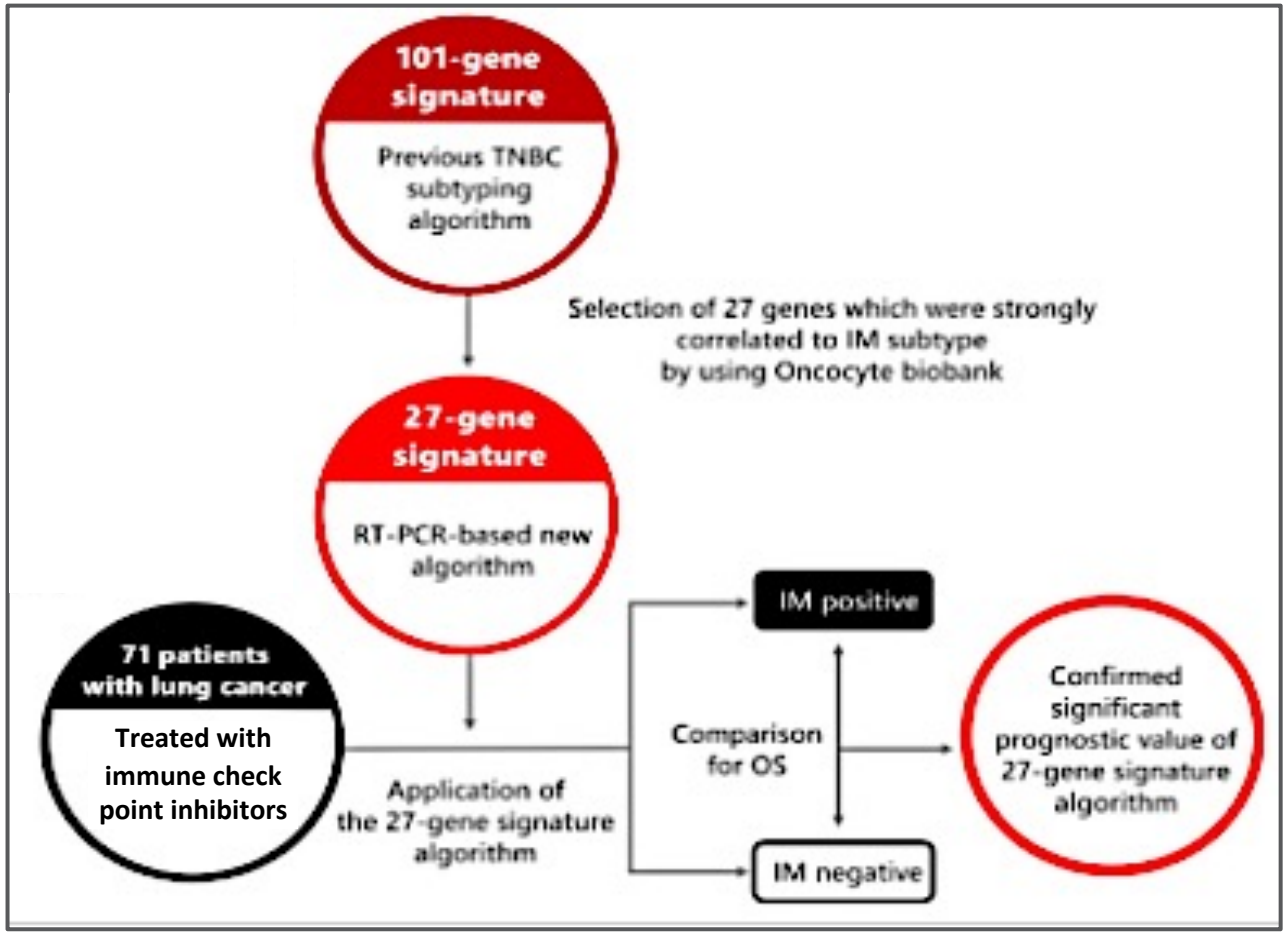
There is a need to identify a predictive biomarker for neoadjuvant immunotherapy!

A molecular subtyping method for TNBC was previously established using a 101-gene algorithm

The immunomodulatory (IM) subtype was narrowed to a 27-gene signature algorithm for clinical use and the assay can be performed

- by qPCR with a pre-established threshold
- using mRNA expression data obtained with RNA sequencing or microarrays

The 27-gene immuno-oncology (IO) signature predicted survival in lung cancer pts tx with checkpoint inhibitors



Iwase T et al. ASCO 2020

27-gene IO signature predicts pCR to IO+chemo in TNBC

- 55 patients with stage I-III primary TNBC
- Treated with neoadjuvant durvalumab + weekly paclitaxel → by dose-dense AC (NCT02489448)
- Tissue specimens were subjected to gene analysis to evaluate the performance of the 27-gene IO signature
- Clinical EP was odds ratio for pCR
- pCR: n=25 (45%); No pCR: n=30 (55%)

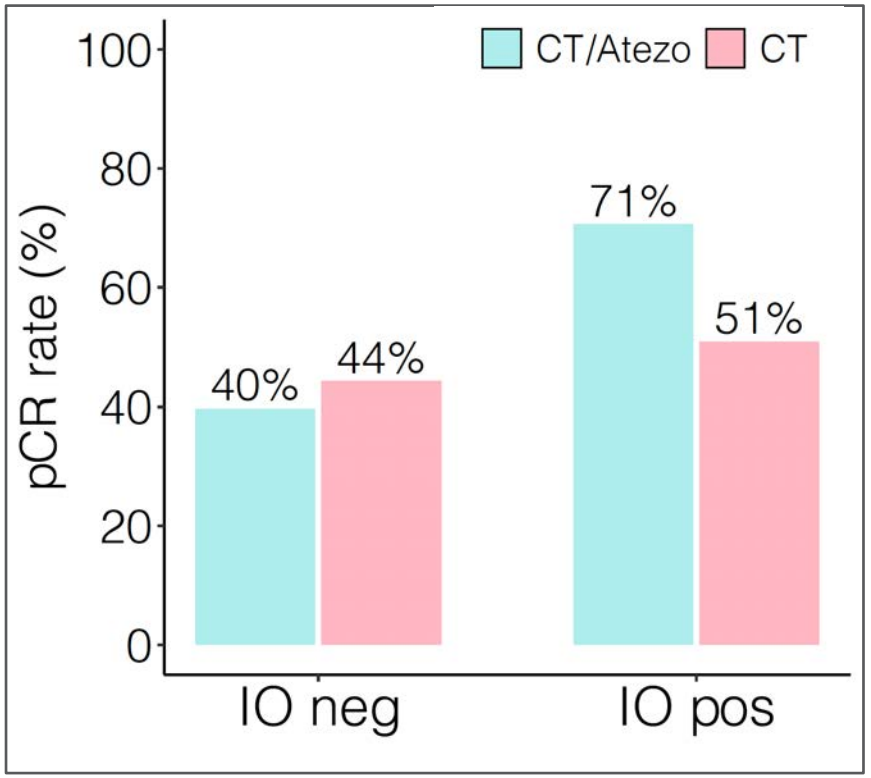
	Odds ratio	95% CI	p-value
27-gene signature test	4.125	1.36-13.47	< 0.015
PD-L1 expression	2.63	0.82-9.21	0.11

The 27-gene IO signature had superior accuracy for predicting pCR compared to PD-L1 exp by IHC

Iwase T et al. 2021

27-gene IO signature in NeoTRIPaPDL1 trial

- 258 patients with high risk (T1cN1; T2N1 or T3N0) primary TNBC
- Treated with neoadjuvant carbo+ nab-paclitaxel +/- atezolizumab
- Pre tx tissue specimens were subjected to RT-qPCR to evaluate association of pCR with the 27-gene IO signature (or IO score)



@ErikaHamilton9

Logistic regression analysis

	Odds ratio	95% CI	p-value
CT/Atezo	3.64	1.68-7.90	0.001
CT	1.31	0.64-2.67	0.46

Test of interaction p=0.029
(adjusted for PD-L1 and sTILs)

IO score is predictive of atezolizumab benefit over CT alone
(significant test of interaction after adjustment for PD-L1 and sTILs)

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Bianchini G. ESMO 2021

Adjuvant olaparib for gBRCA mutant BC

Early-stage TNBC

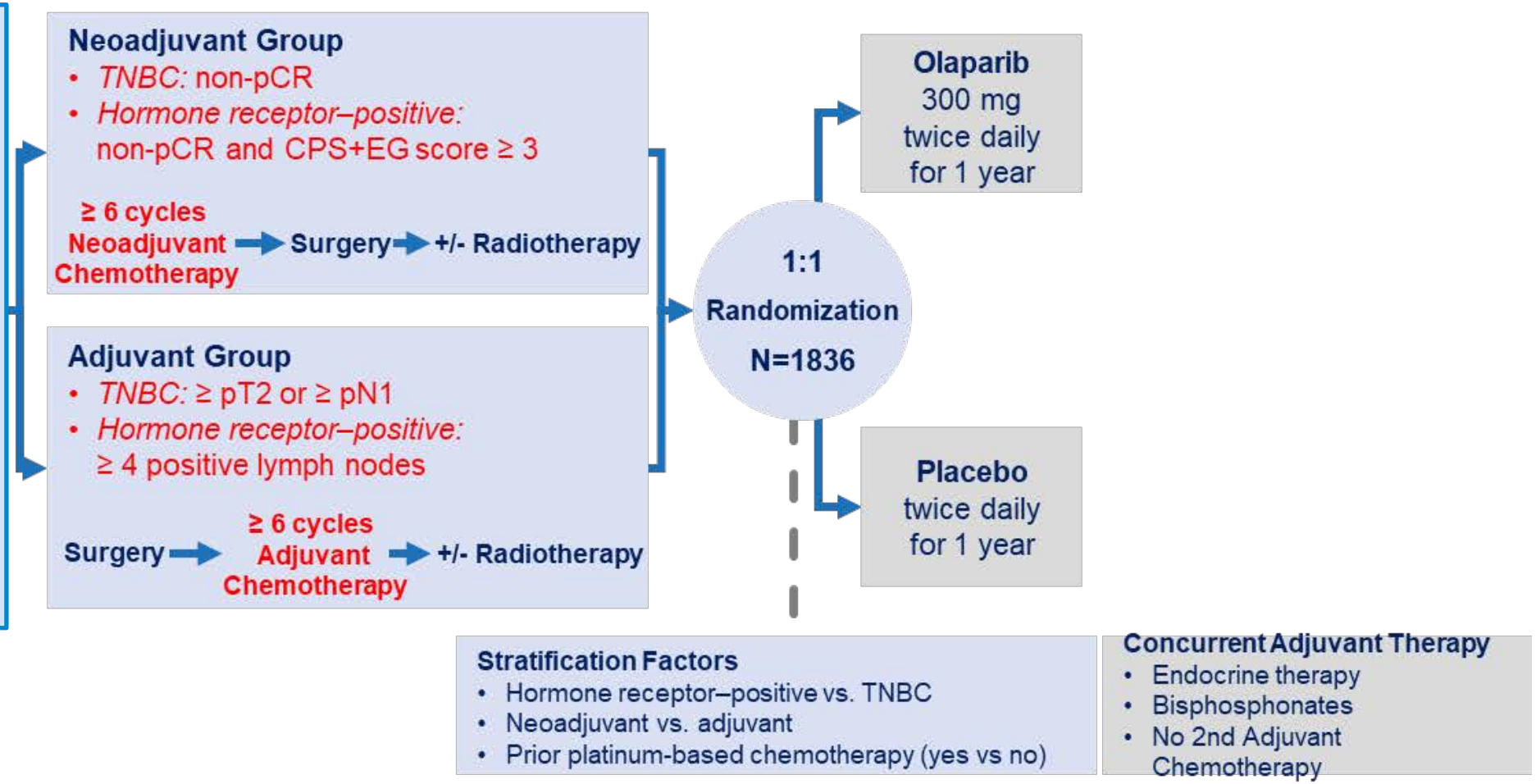
SARAH CANNON

OlympiA: Adjuvant olaparib in gBRCA BC

Germline BRCA 1/ 2 mutation

HER2-negative (HR+ or TNBC)

Stage II-III breast cancer or lack of pCR to NACT



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Tutt A et al. ASCO 2021

OlympiA: Select patient characteristics

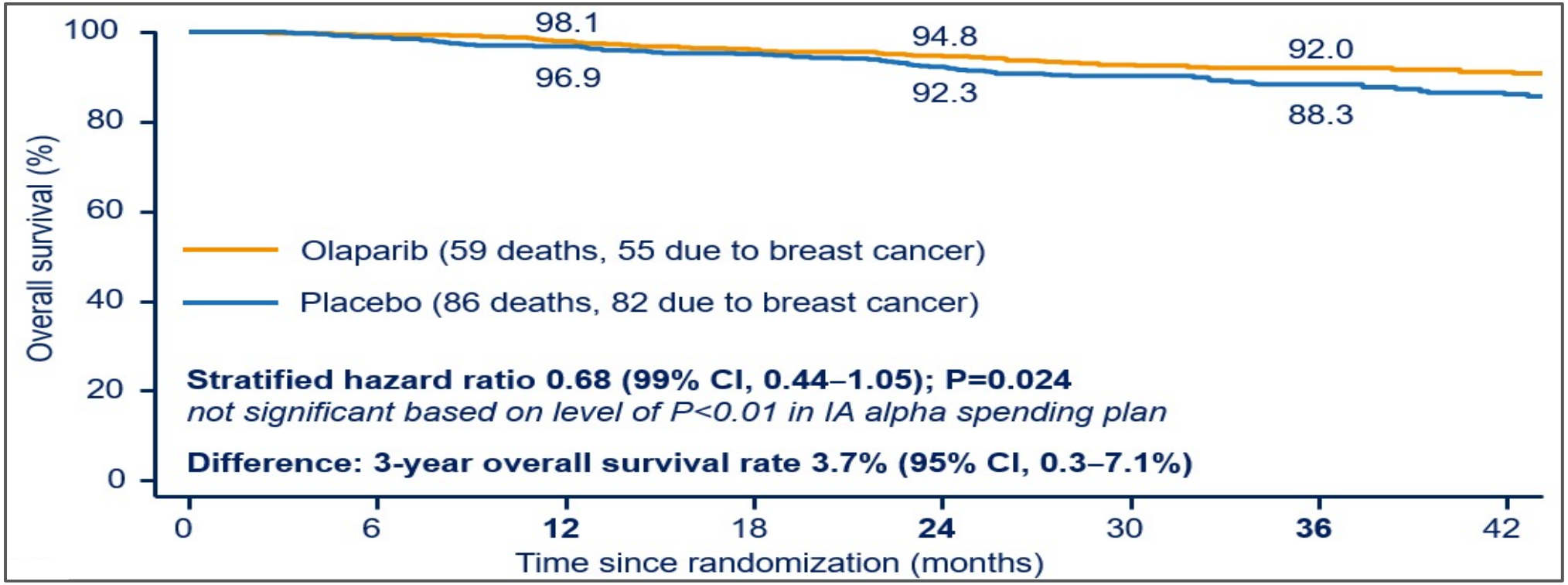
	Olaparib (N = 921)	Placebo (N = 915)
BRCA gene affected in germline		
BRCA1	657 (**71.3%**)	670 (**73.2%**)
BRCA2	261 (**28.3%**)	239 (**26.1%**)
BRCA1 and *BRCA2*	2 (0.2%)	5 (0.5%)
Hormone receptor status*		
Hormone receptor ≥ 1% / HER2-†	168 (**18.2%**)	157 (**17.2%**)
Triple-negative breast cancer‡	751 (**81.5%**)	758 (**82.8%**)
Prior chemotherapy		
Adjuvant (ACT)	461 (**50.1%**)	455 (**49.7%**)
Neoadjuvant (NACT)	460 (**49.9%**)	460 (**50.3%**)
Anthracycline and taxane regimen	871 (**94.6%**)	849 (**92.8%**)
Neo(adjuvant) platinum-based therapy	247 (**26.8%**)	239 (**26.1%**)
Concurrent endocrine therapy (HR–positive only)	146/168 (86.9%)	142/157 (90.4%)

*Defined by local test results
†Following a protocol amended in 2015, the first patient with hormone receptor–positive disease was enrolled in December 2015
‡Two patients are excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2–negative status

Tutt A et al. ASCO 2021

OlympiA: Overall survival at first data cutoff

2.5 years median follow up



Δ 3.7%

OS was not significant @ first IA (P=0.024)

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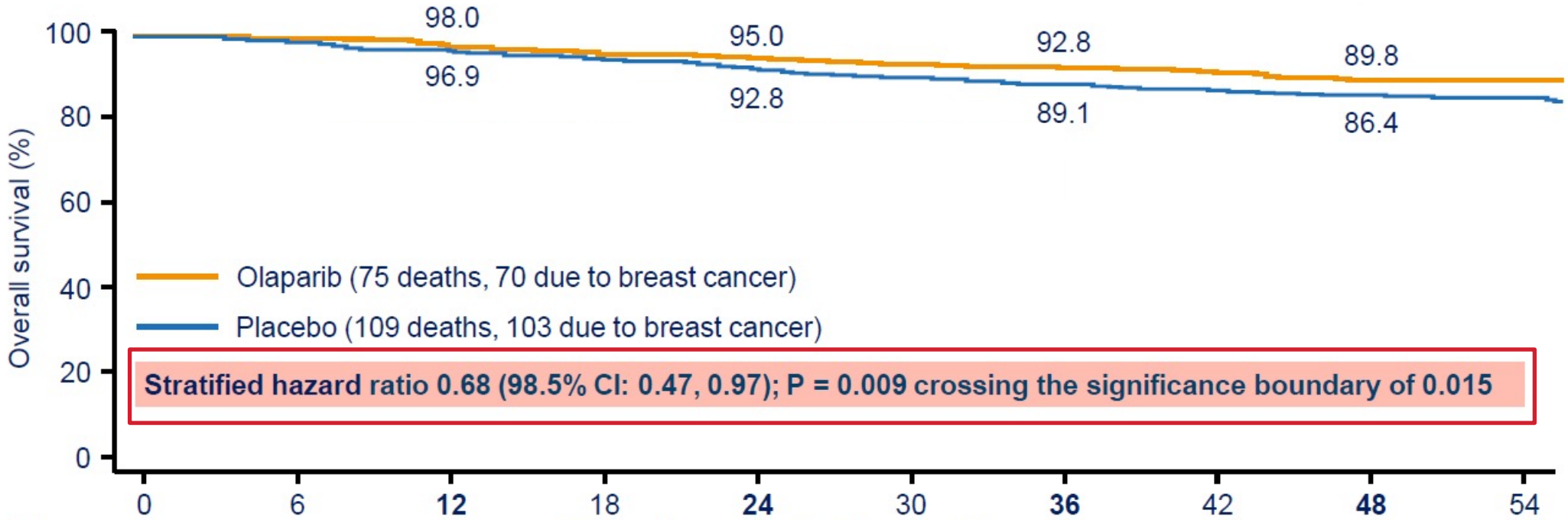
Tutt A et al. ASCO 2021

OlympiA: Overall survival at 2nd pre-planned IA

3.5 years median follow up



No. at risk										
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

98.5% confidence intervals are shown for the hazard ratio because P < 0.015 is required for statistical significance

Treatment effect was consistent across major subgroups including the BRCA1, BRCA2, HR+ and TNBC

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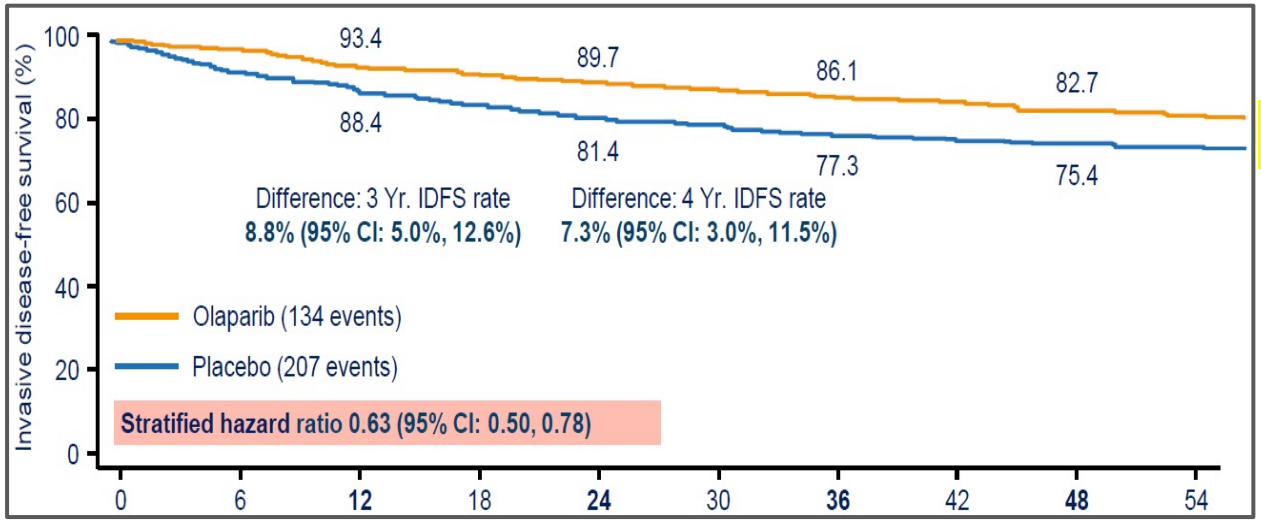
Tutt A et al ESMO Plenary 2022

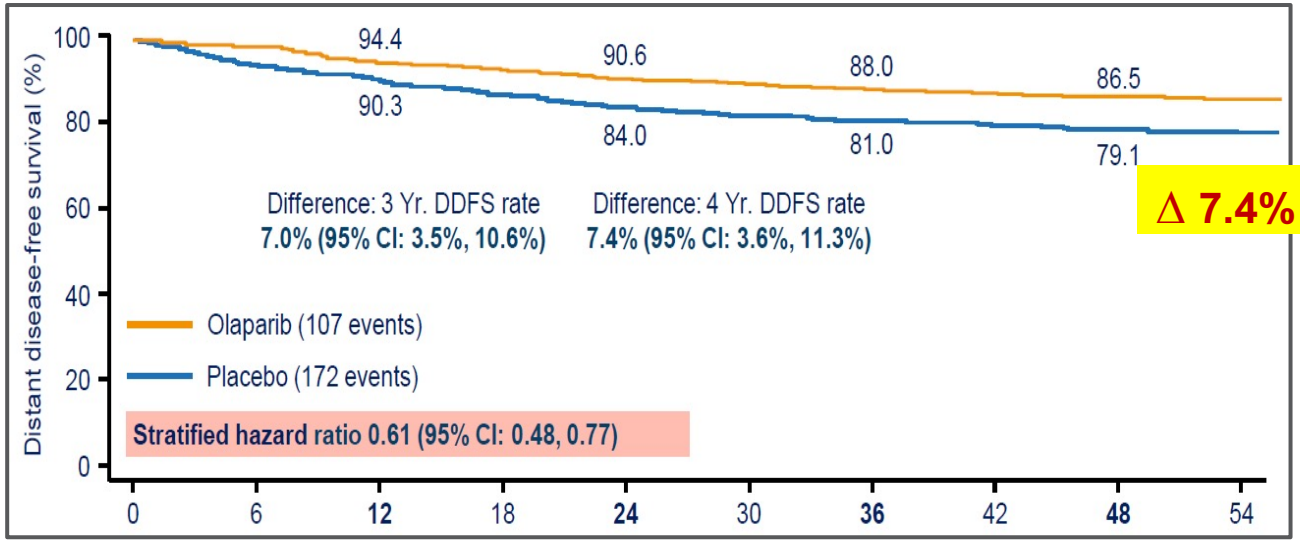
OlympiA: IDFS & DDFS at 2nd interim analysis

Primary Endpoint: IDFS



Δ 7.3%

Secondary Endpoint: DDFS



Δ 7.4%

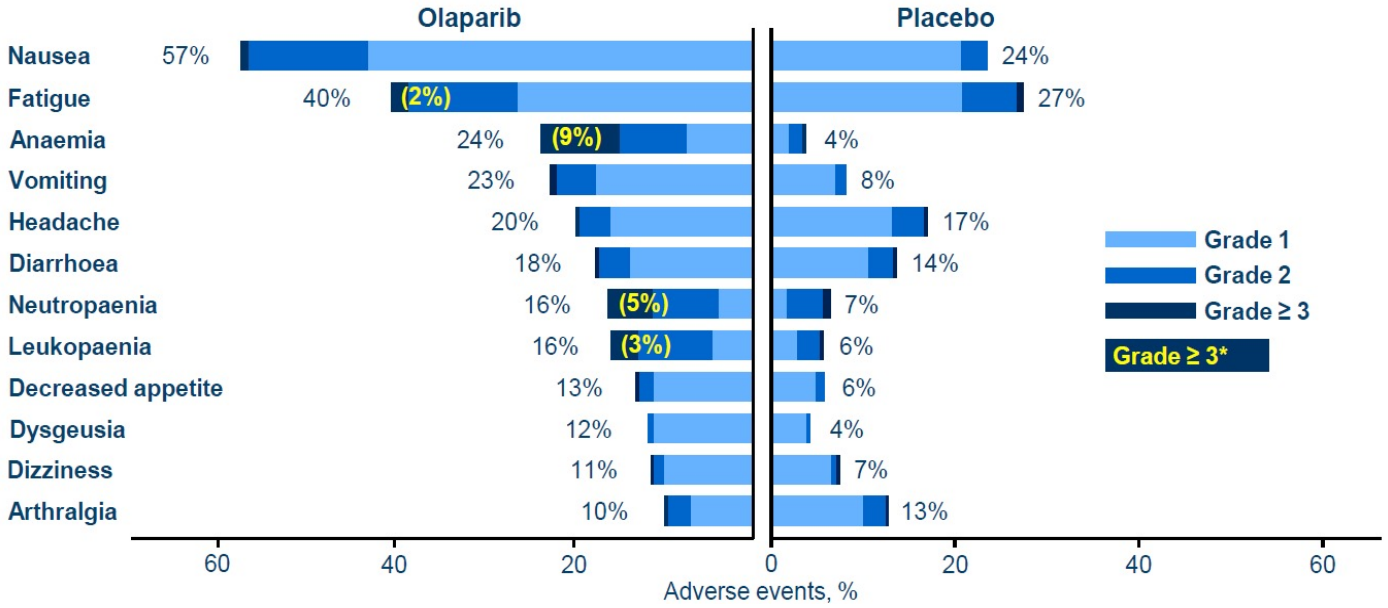
Early and persistent separation of the curves for IDFS & DDFS

No statistical evidence of heterogeneity among subgroups

Tutt A et al ESMO Plenary 2022

OlympiA: AE profile

AE of any grade in ≥10% of patients



No change in adverse event profile with longer follow up

Summary of adverse events

	Olaparib (N = 911)	Placebo (N = 904)
Any adverse event	**836 (91.8%)**	**758 (83.8%)**
Serious adverse event (SAE)	79 (8.7%)	**78 (8.6%)**
Adverse event of special interest*	**31 (3.4%)**	**51 (5.6%)**
MDS/AML	2 (0.2%)	3 (0.3%)
Pneumonitis	9 (1.0%)	**12 (1.3%)**
New primary malignancy	**21 (2.3%)**	**36 (4.0%)**
Grade ≥ 3 adverse event	**223 (24.5%)**	102 (11.3%)
Grade 4 adverse event	17 (1.9%)	4 (0.4%)
Adverse event leading to permanent discontinuation of treatment†	**98 (10.8%)**	**42 (4.6%)**
Adverse event leading to death‡	1 (0.1%)	2 (0.2%)

Tutt A et al ESMO Plenary 2022

What questions remain for early TNBC?

- What is the contribution of adjuvant pembrolizumab to EFS?
  - Could we omit the adjuvant pembro for those w/ pCR?
    - Impact of adjuvant pembrolizumab being evaluated in SWOG1418 (NCT2954874)

- How do we integrate KEYNOTE-522 into current adjuvant landscape?
  - With capecitabine (CREATE-X)?
  - With olaparib (OlympiA)?
    - We now have OS data with adjuvant olaparib

- Which TNBC pts can we “de-escalate” for?
  - Novel immune-gene signatures to select pts for neoadjuvant IO?

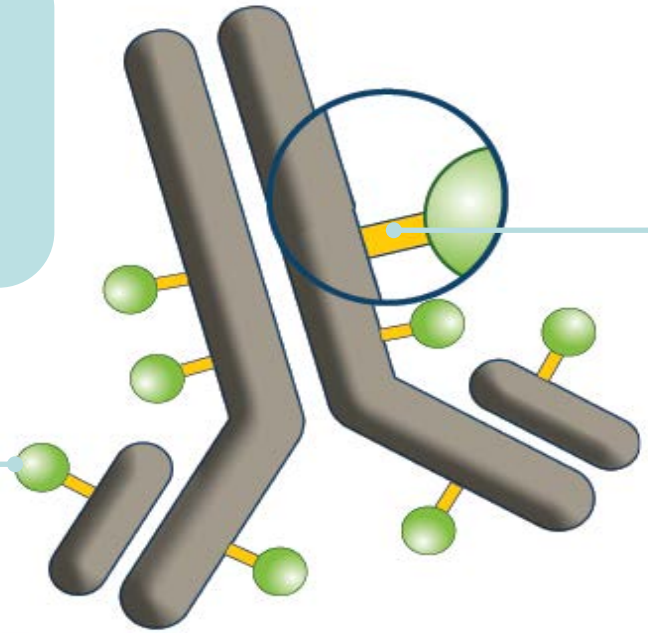
Novel agents

Early-stage TNBC

Sacituzumab govitecan

Humanized anti-Trop-2 antibody

- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC



Linker for SN-38

- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.5:1)

SN-38 payload

- SN-38 more potent than parent compound, irinotecan
- ADC delivers up to 136-fold more SN-38 than irinotecan *in vivo*

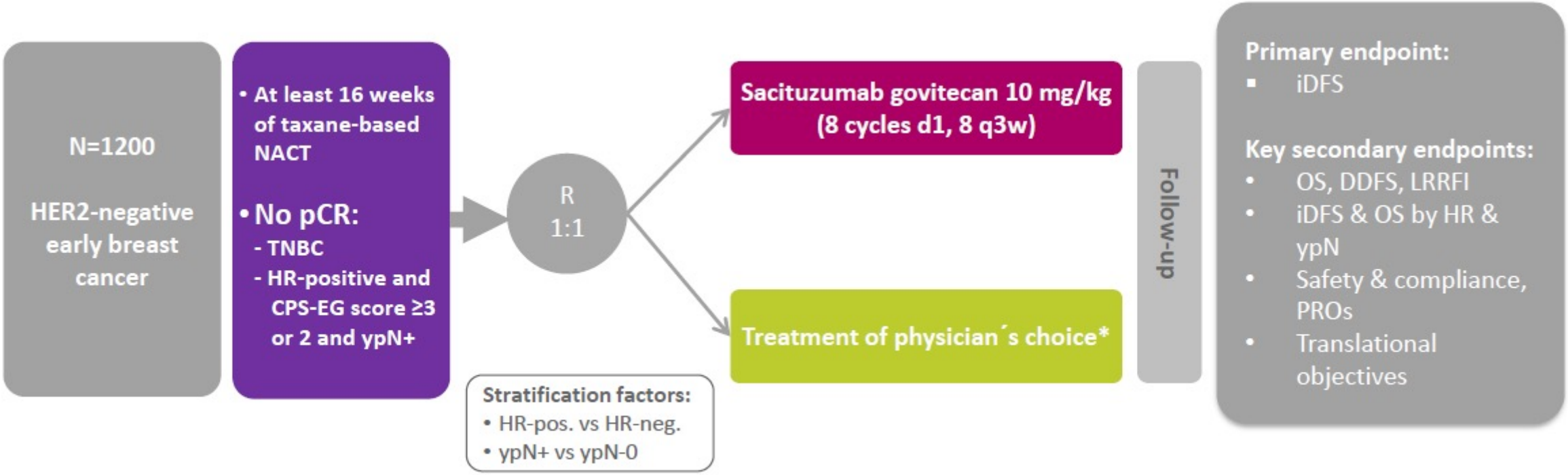
Phase 3 ASCENT trial

Significant improvement in mPFS with sacituzumab vs chemo (5.6 mo vs 1.7 mo, HR 0.41, P<0.001)

Significant improvement in mOS with sacituzumab vs chemo (12.1 mo vs 6.7 mo, HR 0.48, P<0.001)

Bardia A et al. NEJM 2021

SASCIA: Sacituzumab for residual disease after neoadjuvant chemo in eTNBC



* **Capecitabine** (Cape, 2000 mg/m^2/d, days 1-14, q21d for up to 8 cycles) or **platinum-based** chemotherapy (8 cycles) or **observation**.
Background therapy: in patients with HR-positive breast cancer, **endocrine-based therapy** will be administered according to local guidelines.

Prespecified **safety interim analysis (SIA)** conducted **after the first 50 randomized patients completed 4 cycles** of treatment (Cape, SG) **or three months of observation**.
IDMC recommended to continue study without any modifications

SARAH CANNON

Marme F et al. ESMO Breast 2022

Select ongoing trials

GLORIA : A Phase III, Randomized, Open-Label Study of the Anti-Globo H Vaccine Adagloxad Simolenin (OBI-822)/OBI-821 in the **Adjuvant** Treatment of Patients With High Risk, Early Stage Globo H-Positive Triple Negative Breast Cancer NCT03562637

T-Cell Immune Checkpoint Inhibition Plus Hypomethylation for Locally Advanced HER2-Negative Breast Cancer - A Phase II Neoadjuvant Window Trial of Pembrolizumab and Decitabine Followed by Standard Neoadjuvant Chemotherapy NCT02957968

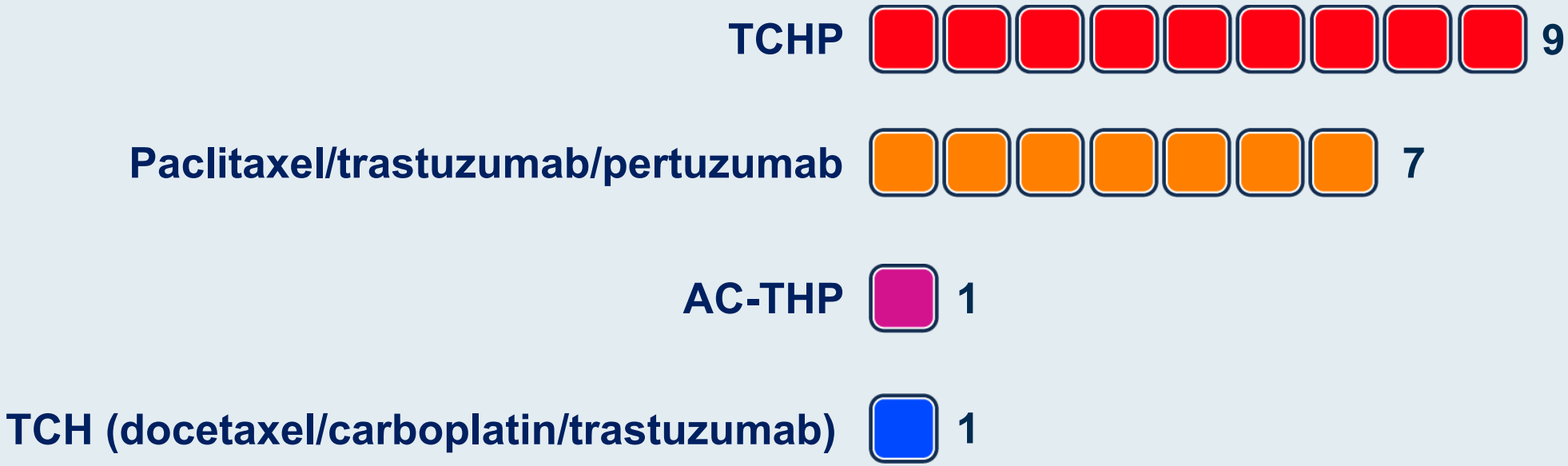
A Phase I Study of Rucaparib Administered Concurrently With Postoperative Radiotherapy in Patients With Triple Negative Breast Cancer With an Incomplete Pathologic Response Following Neo**adjuvant** Chemotherapy NCT03542175

PHOENIX DDR/Anti-PD-L1 Trial: A Pre-surgical Window of Opportunity and Post-surgical Adjuvant Biomarker Study of DNA Damage Response Inhibition and/or Anti-PD-L1 Immunotherapy in Patients With Neoadjuvant Chemotherapy Resistant Residual Triple Negative Breast Cancer NCT03740893

MODULE 3: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer

RTP
RESEARCH
TO PRACTICE

Which neoadjuvant systemic therapy, if any, would you generally recommend for a 65-year-old patient with a 2.5-cm ER-negative, HER2-positive, clinically node-negative IDC?



Survey of clinical investigators

A 65-year-old woman presents with a 3.4-cm ER-positive, HER2-positive IDC with biopsy-proven axillary nodes, receives neoadjuvant TCHP and at surgery is found to have 0.5 cm of residual tumor in the breast and no disease in the nodes. Regulatory and reimbursement issues aside, which adjuvant anti-HER2 therapy would you recommend?

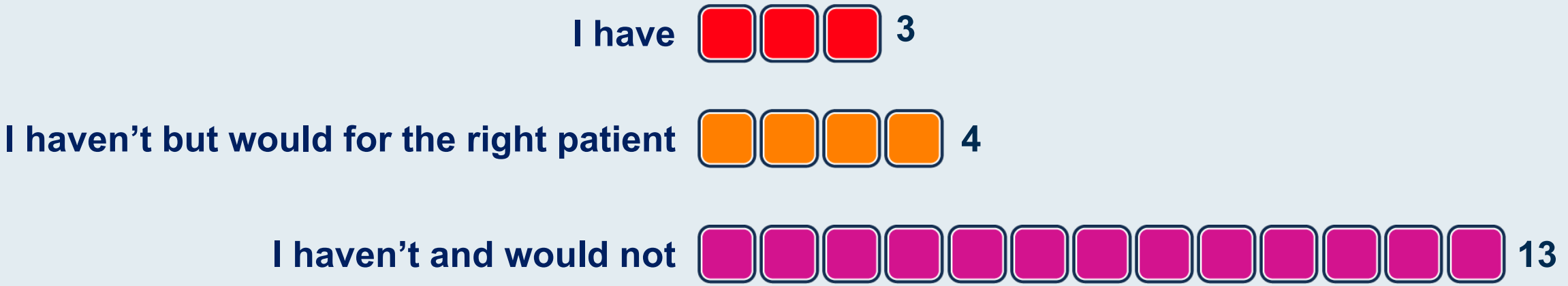
Survey of clinical investigators

In what situations do you generally administer postadjuvant neratinib to a patient with ER-positive, HER2-positive localized breast cancer?

- Residual disease in nodes or breast and initially node-positive or T3/T4
- Very high clinical risk
- Substantial residual disease (RCB II or greater), ER-positive, HER2-positive
- Very high residual burden and ER+ disease after optimal adjuvant and neoadjuvant therapy, along with endocrine therapy
- 4+ LN after neoadjuvant rx
- Very motivated patient with extensive nodal involvement
- Significant residual disease including positive nodes or patients with residual disease intolerant to T-DM1
- In those who have only had trastuzumab anti-HER2 therapy and met inclusion criteria for ExteNET trial or who have not tolerated trastuzumab/pertuzumab or T-DM1
- Pt with residual cancer after neoadjuvant TCHP, would give after T-DM-1

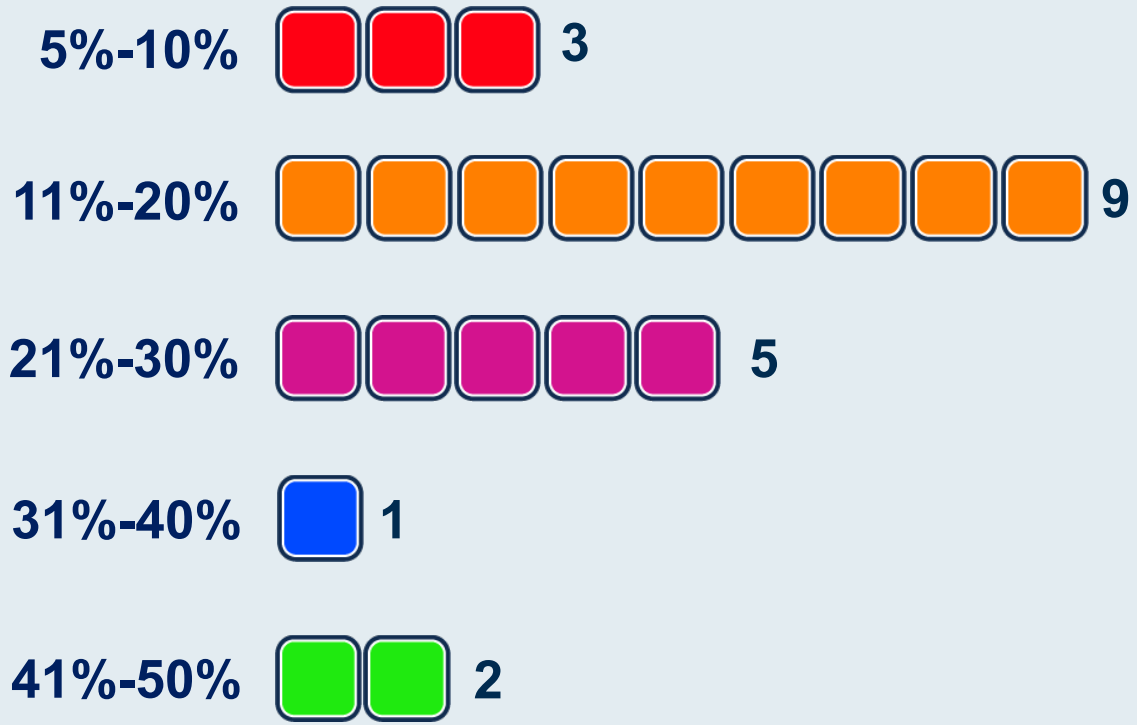
Survey of clinical investigators

Have you administered or would you administer postadjuvant neratinib to a patient with high-risk ER-negative, HER2-positive localized breast cancer?



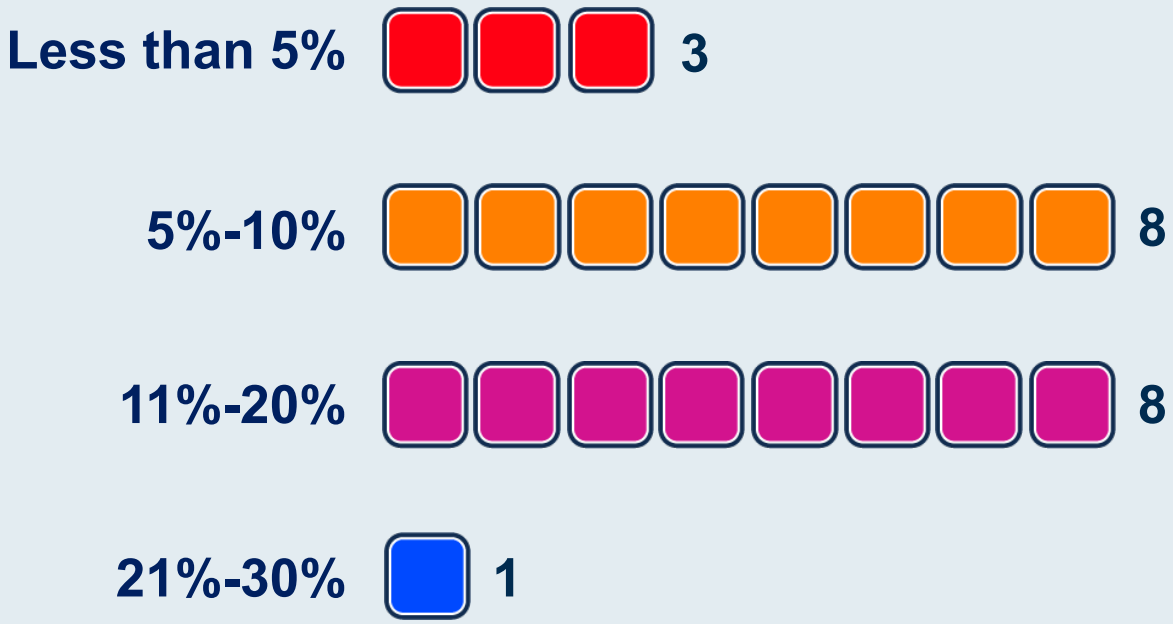
Survey of clinical investigators

A patient with ER-positive, HER2-positive localized breast cancer is about to start postadjuvant neratinib and asks you the likelihood that treatment will need to be withheld or discontinued due to toxicity before completing 1 year. Considering contemporary mitigation strategies, how would you respond?



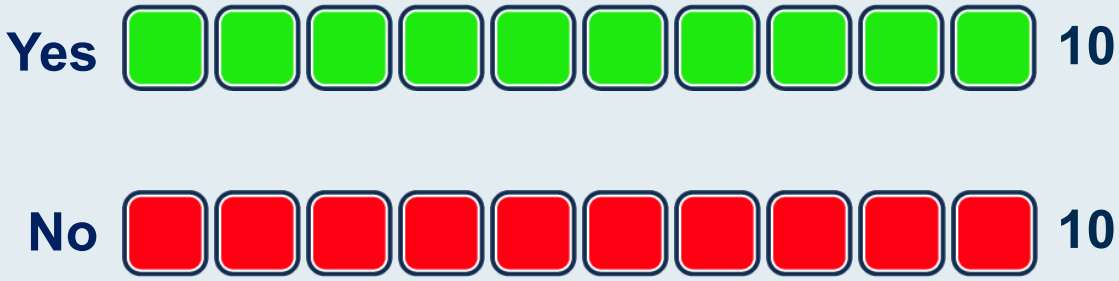
Survey of clinical investigators

In general, what proportion of patients in your practice who are receiving postneoadjuvant T-DM1 for HER2-positive localized breast cancer require treatment to be held due to toxicity?



Survey of clinical investigators

Assuming you were able to access postneoadjuvant trastuzumab deruxtecan for a younger patient with localized HER2-positive breast cancer who received neoadjuvant TCHP and was found to have significant residual disease at surgery, would you recommend it in this setting?



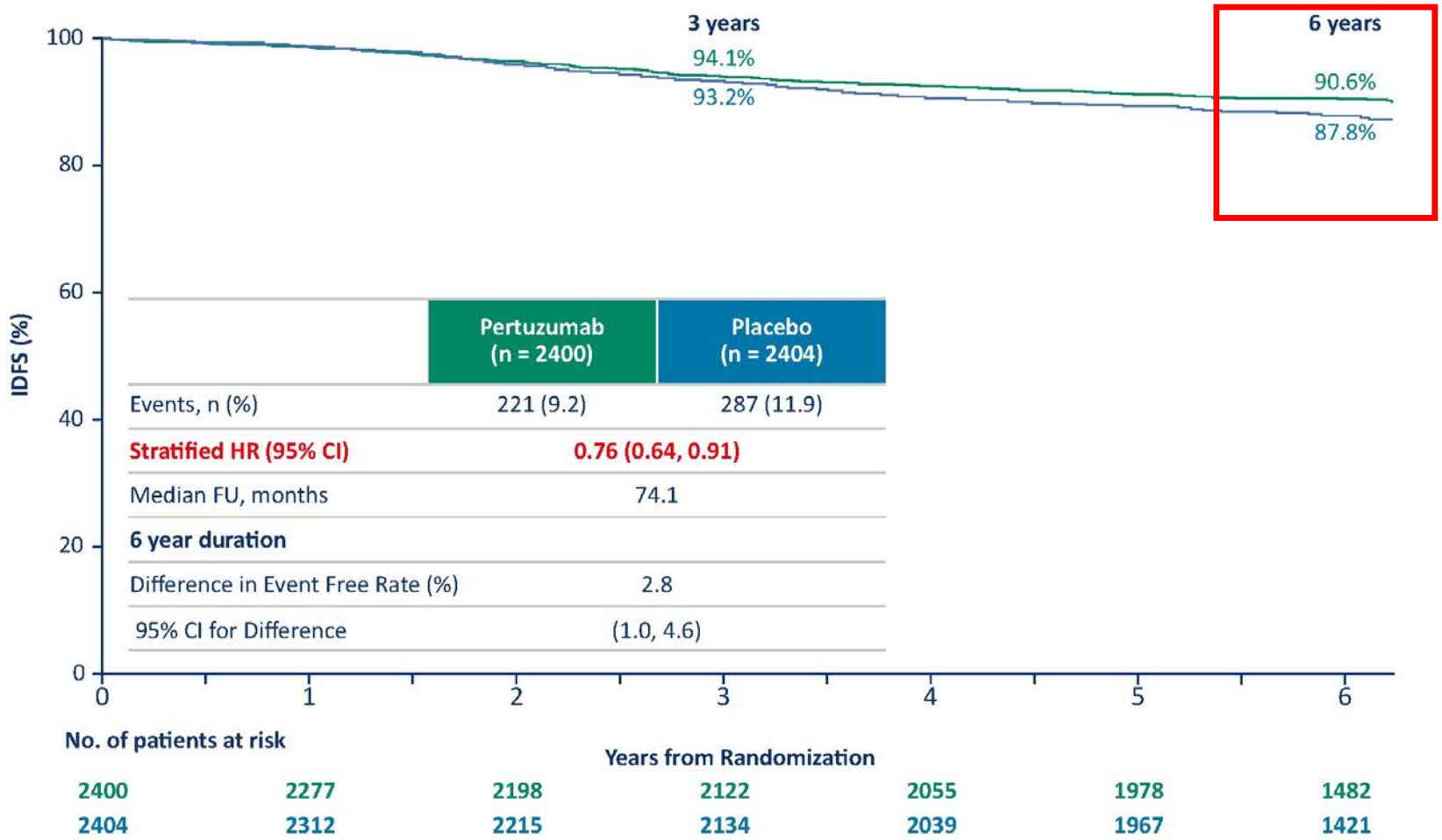
Survey of clinical investigators

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

Ian Krop MD PhD
Yale Cancer Center
June 2022

Patients with HER2+ early breast cancer now have generally favorable outcomes

Results from APHINITY study of chemotherapy/trastuzumab±pertuzumab



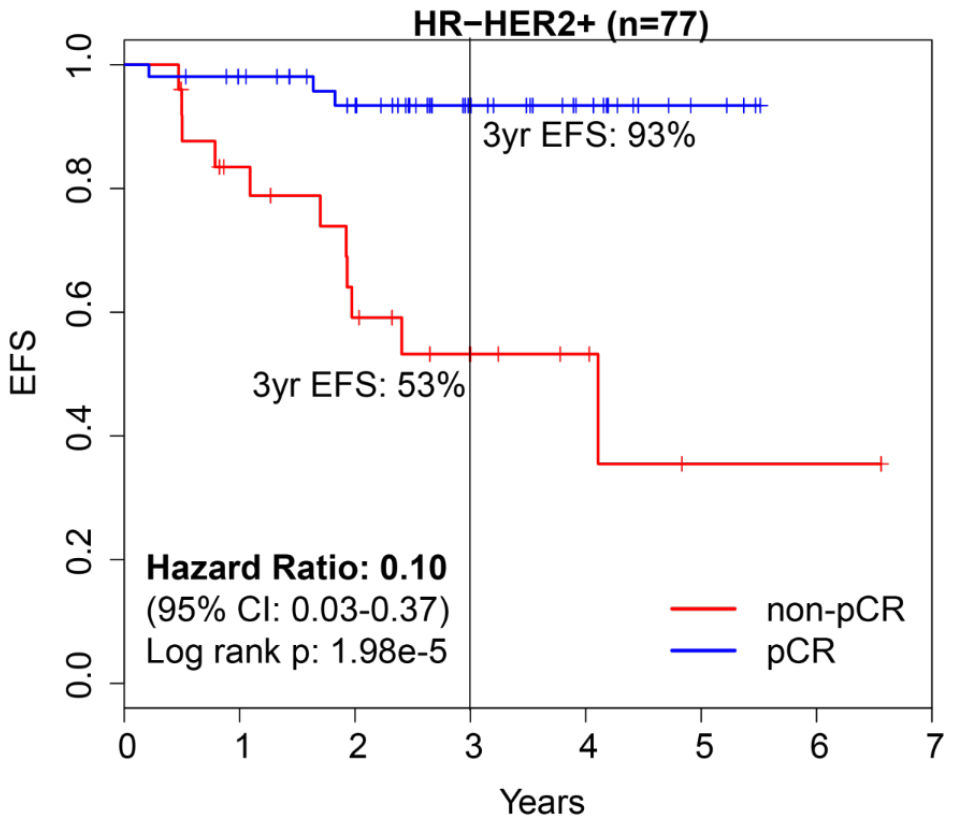
Piccart et al, SABCS 2019; Piccart et al, JCO 2021.

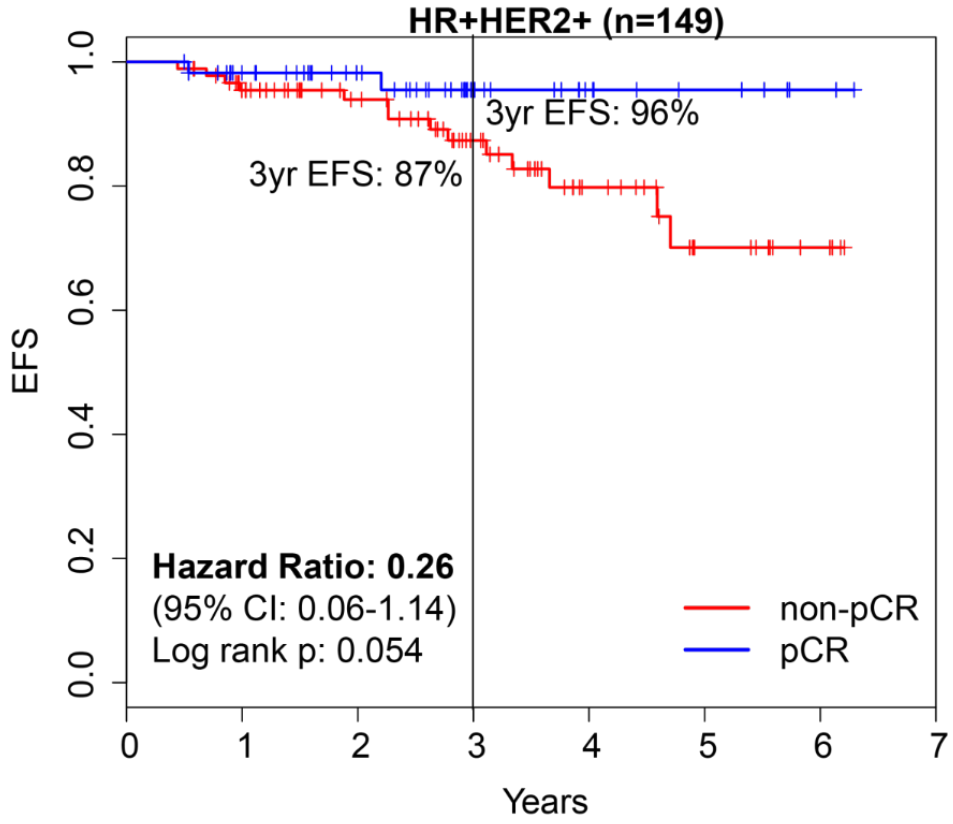
The era of personalized medicine in HER2+ EBC

- The favorable outcomes of HER2+ breast cancers provide opportunity to:
  - De-escalate therapy for lower risk patients to reduce the toxicities of treatment
  - Escalate therapy for minority of patients who are at risk for recurrence despite maximal current management
- To optimally tailor therapy requires effective risk stratification strategies

Achievement of pCR after neoadjuvant HER2-therapy is powerful prognostic marker

Influence of pCR on EFS in HER2+ Disease: I-SPY



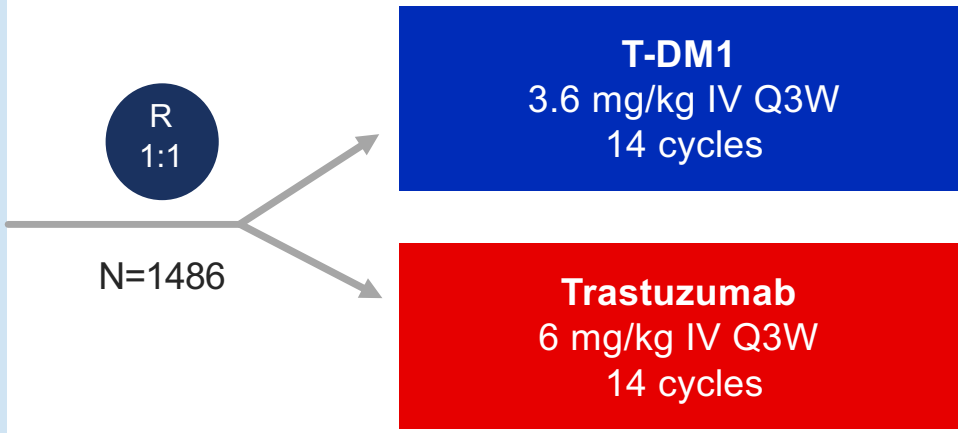


Difference between pCR vs. residual disease greater for ER- and ER+ consistent with meta-analysis from Cortazar et al, Lancet 2014

Yee et al, SABCS 2017; Yee et al, JAMA Oncol 2020

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



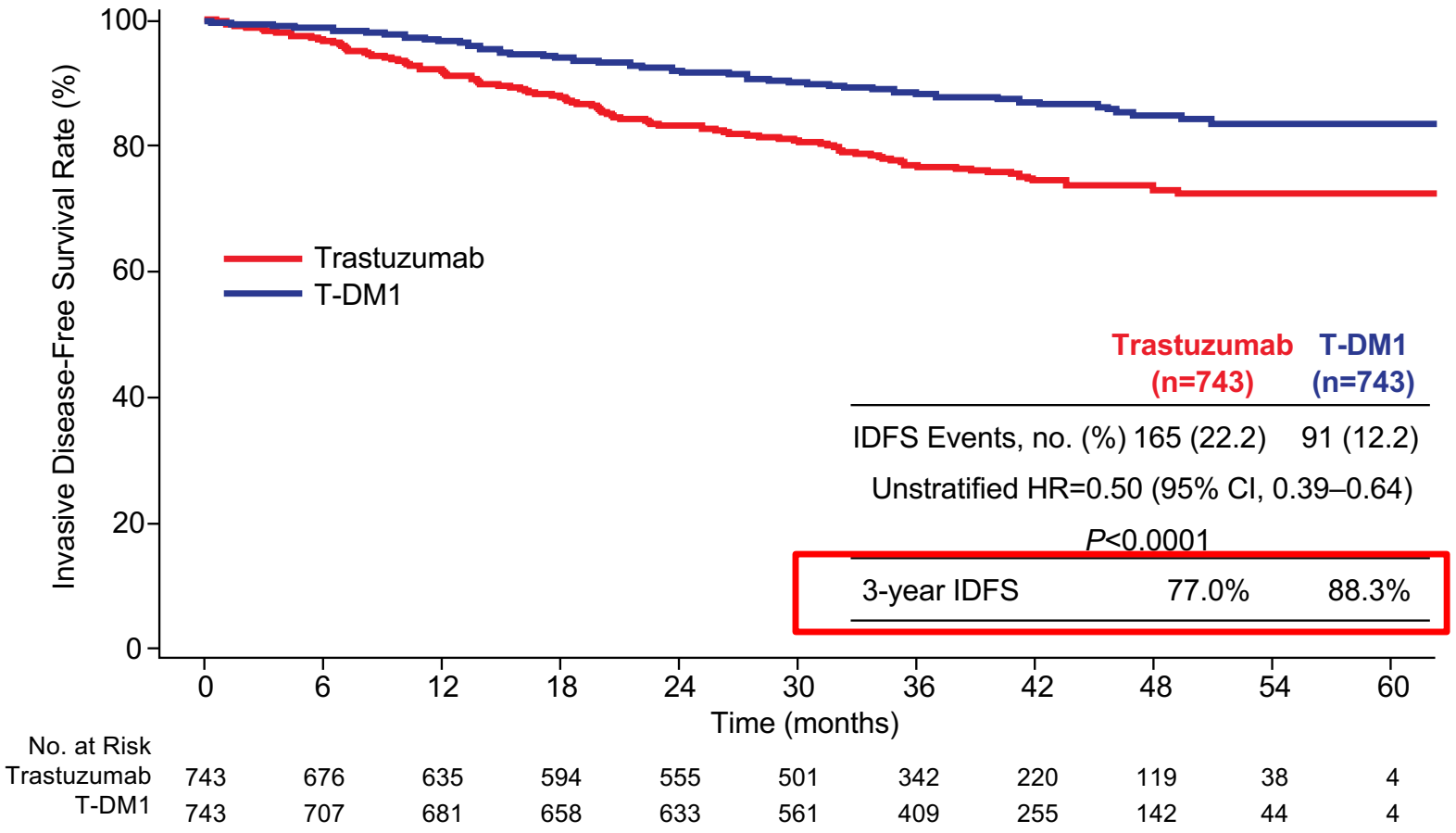
Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Geyer et al, SABCS 2018.

KATHERINE: Invasive Disease-Free Survival



Geyer et al, SABCS 2018; Von Minckwitz et al, N Engl J Med 2019.

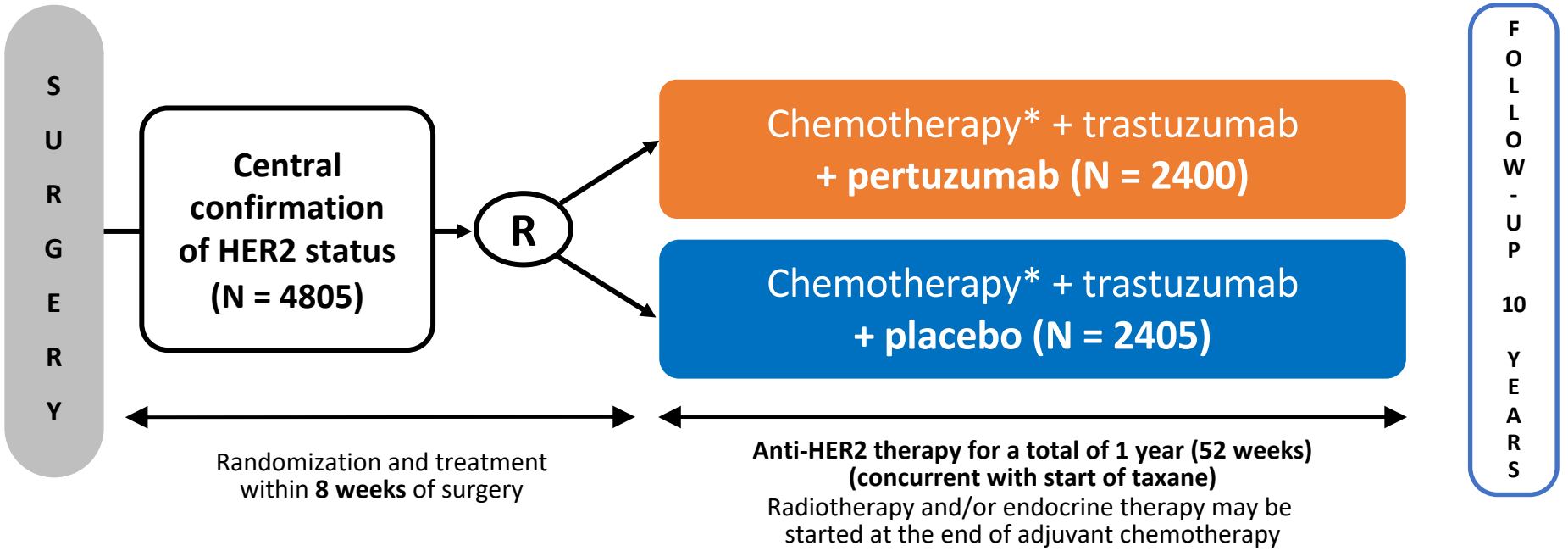
Implications of KATHERINE results

- 14 cycles of T-DM1 should be considered the standard of care for patients with residual disease after neoadjuvant HER2-directed therapy

- It is the SOC to treat most pts with moderate or high risk (Stage ≥2) HER2+ BC with neoadjuvant therapy in order to identify those pts with residual disease who may benefit from adjuvant T-DM1

- Should pertuzumab be included in the neoadjuvant regimen for all patients?

APHINITY: A Phase III adjuvant study investigating the benefit of pertuzumab when added to trastuzumab + chemotherapy



* Standard anthracycline or non-anthracycline (TCH) regimens were allowed: 3–4 x FEC (or FAC) → 3–4 x TH; 4 x AC (or EC) → 4 x TH; 6 x TCH

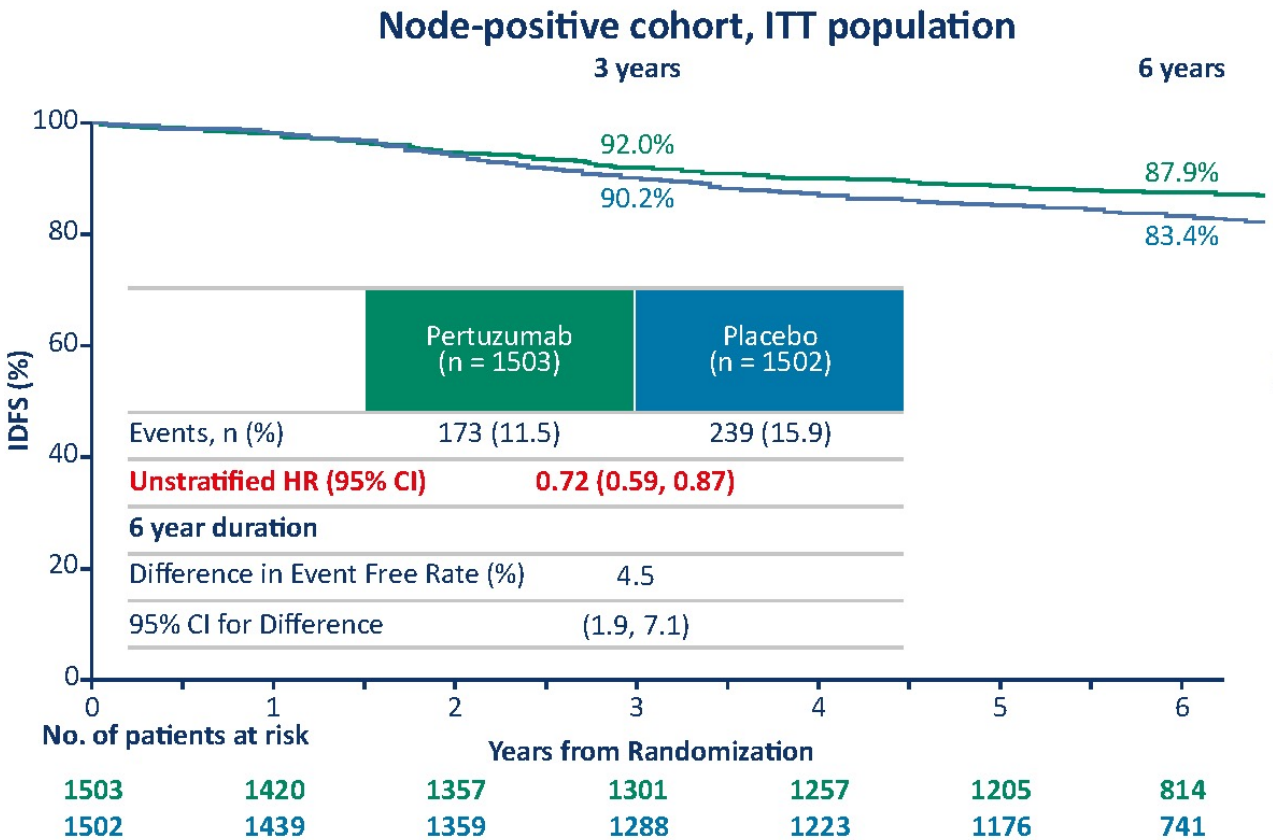
- **Primary endpoint:** IDFS (APHINITY definition differs from STEEP definition)
- **Secondary endpoints:** IDFS with 2nd primary non-breast primary cancers included, DFS, OS, RFI, DRFI, safety, and HRQoL
- **Stratification factors:** nodal status, HR status, chemotherapy regimen, geographic region, Protocol version (A vs. B)
- **Clinical cut off date (CCOD)** at the time of primary analysis was 19 Dec 2016, median follow up of 45.4 months

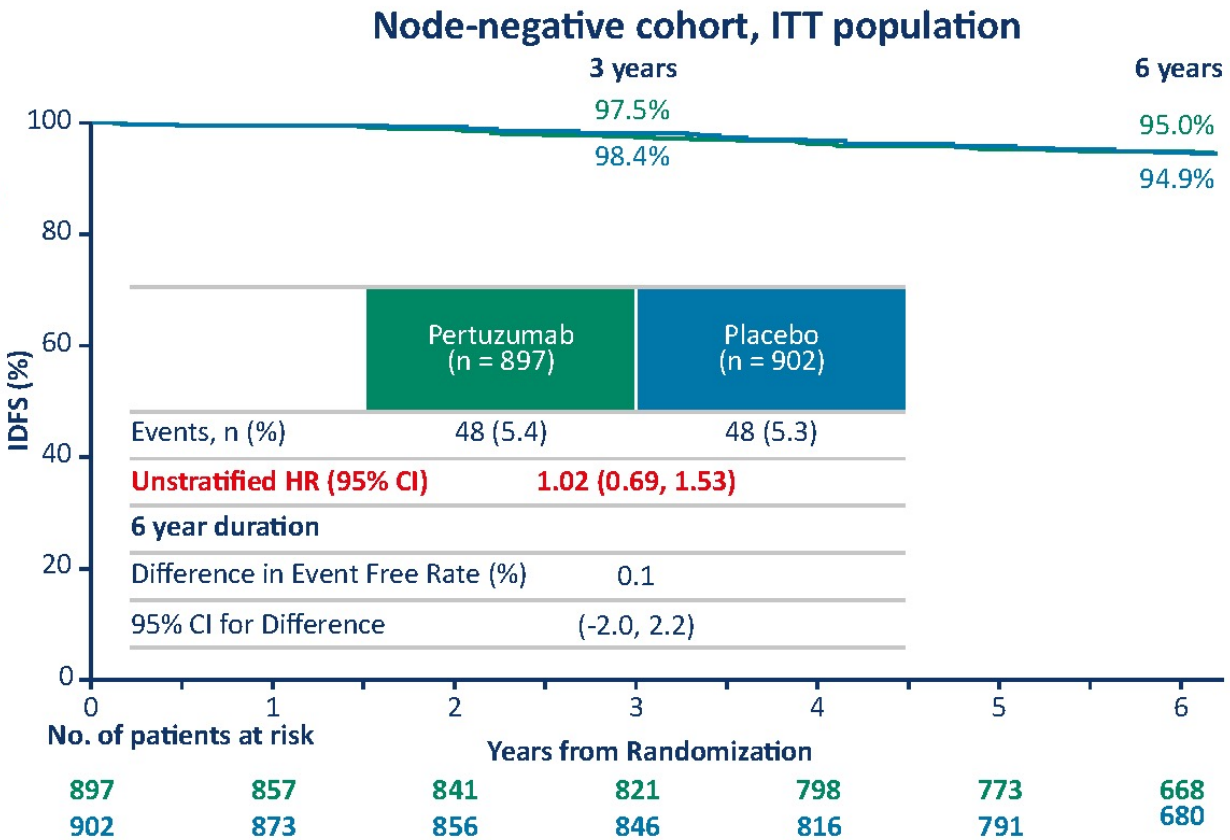
DFS, disease-free survival; DRFI, distant relapse-free interval; HR, hormone receptor; HRQoL, health-related quality of life; survival; OS, overall survival; RFI, relapse-free interval

Adapted from von Minckwitz et al. N Engl J Med 2017 IDFS, invasive disease-free www.clinicaltrials.gov/ct2/show/NCT01358877

Piccart et al, SABCS 2019

APHINITY Updated Analysis
Time to first IDFS event by treatment regimen and nodal status





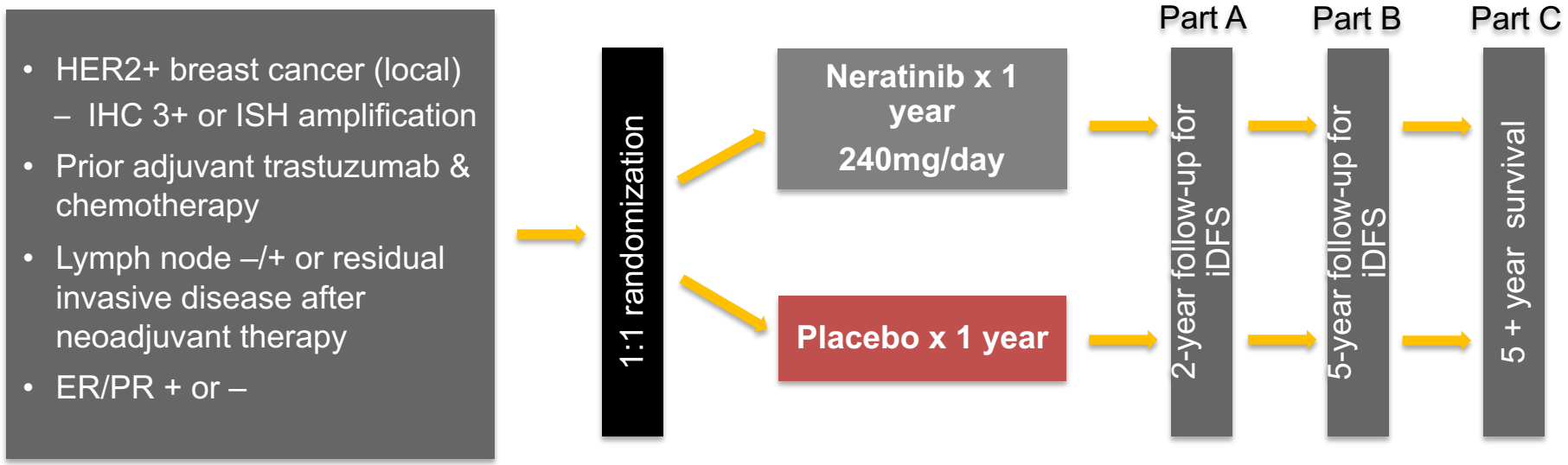
74.1 months median follow-up

Piccart et al, JCO 2021

What is optimal neoadjuvant therapy for high risk HER2+ EBC?

- Should pertuzumab be included in the neoadjuvant regimen for all patients?
  - YES, if clinically node positive
  - NO, if node negative?
    - In practice for T2 or larger clinically node negative cancers, would suggest using pertuzumab and if pCR (and no evidence of treatment effect in nodes) discontinue pertuzumab in adjuvant setting

ExteNET:Study design

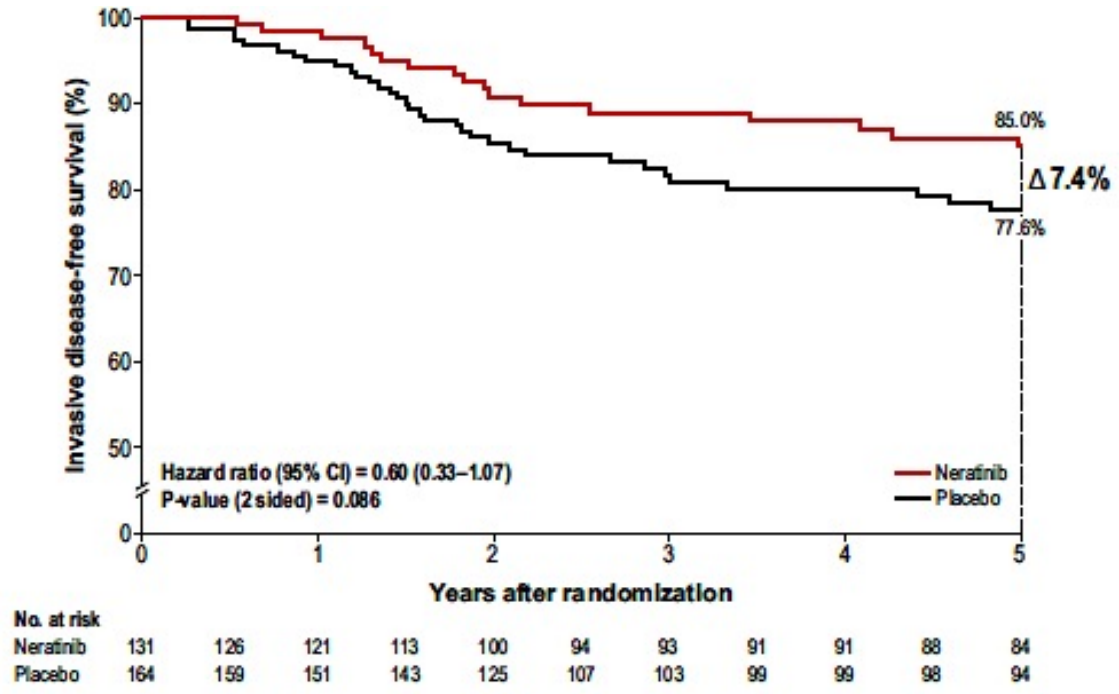


- Primary endpoint: invasive disease-free survival (iDFS)
- Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- Other analyses: biomarkers, health outcome assessment (FACT-B, EQ-5d)
- Stratified by: nodes 0, 1–3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

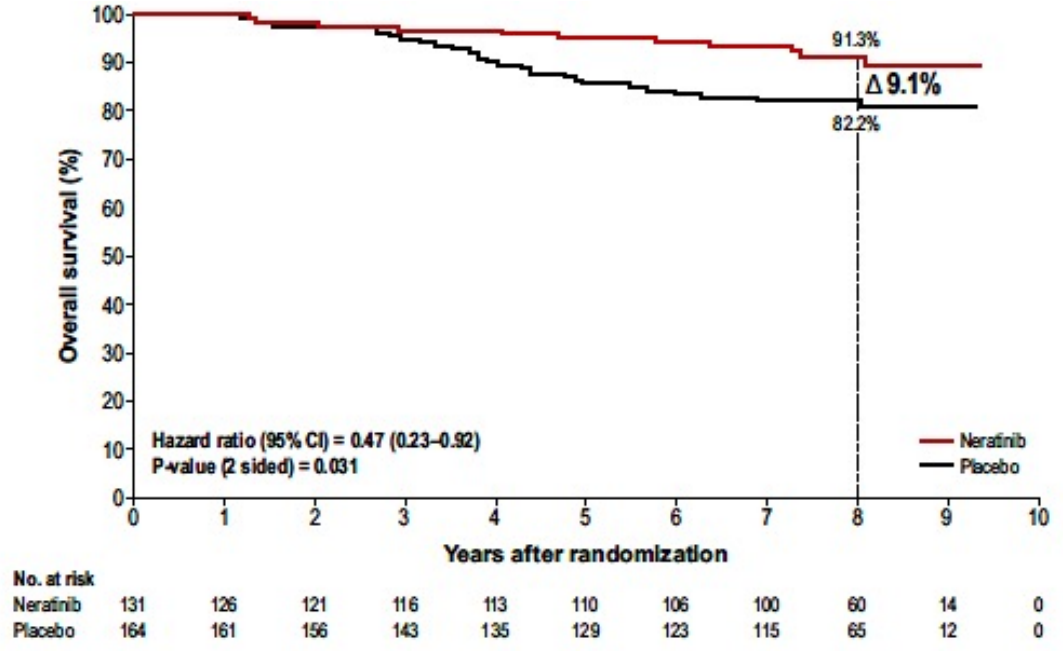
Chan et al, 2015 Breast Cancer Symposium.

ExteNET: Outcomes in HR+, ≤1 year from trastuzumab, and with residual disease after neoadjuvant therapy

iDFS at 5yrs



Overall Survival



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

ExteNET: Cumulative incidence of CNS disease as 1st site of recurrence

Population or Subgroup	CNS Events (No. Patients)		Cumulative Incidence of CNS Recurrences at 5 Years, % (95% CI)	
	Neratinib	Placebo	Neratinib	Placebo
$HR^+/\leq$ 1-year population	4 (670)	12 (664)	0.7 (0.2–1.7)	2.1 (1.1–3.5)
Nodal status				
Positive	4 (540)	10 (539)	0.8 (0.3-2.0)	2.2 (1.1-3.8)
Negative	0 (130)	2 (125)	0 (NE)	1.9 (0.4-6.0)
Prior trastuzumab regimen				
Concurrent	2 (411)	8 (415)	0.6 (0.1-1.9)	2.3 (1.1-4.3)
Sequential	2 (259)	4 (249)	0.9 (0.2-3.0)	1.8 (0.6-4.3)
Adjuvant or neoadjuvant therapy				
Adjuvant	3 (508)	6 (472)	0.7 (0.2-2.0)	1.5 (0.6-3.0)
Neoadjuvant	1 (162)	6 (192)	0.7 (0.1-3.3)	3.7 (1.5-7.4)
pCR status[a]				
No	1 (131)	5 (164)	0.8 (0.1-4.0)	3.6 (1.3-7.8)
Yes	0 (17)	1 (21)	0 (NE)	5.0 (0.3-21.2)

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

CONTROL study: dose escalation of neratinib minimizes Grade 3 diarrhea

Outcome	L (n=137)	BL (n=64)	CL (n=136)	CL-PRN (n=104)	DE1 (n=60)	DE2 (n=62)
Any grade diarrhea, n (%)	109 (80)	55 (86)	113 (83)	99 (95)	59 (98)	61 (98)
Grade 1	33 (24)	15 (23)	38 (28)	34 (33)	24 (40)	23 (37)
Grade 2	34 (25)	22 (34)	47 (35)	31 (30)	27 (45)	21 (34)
Grade 3	42 (31)	18 (28)	28 (21)	34 (33)	8 (13)	17 (27)
Grade 4	0	0	0	0	0	0
Median episodes of grade 3 diarrhea, n	1	1	1	1	2	1
Median time to first onset of grade 3 diarrhea, days	7.0	19.0	41.0	19.0	45.0	19.0
Median cumulative duration of grade 3 diarrhea per patient, days	3.0	3.0	3.5	2.0	2.5	2.0
Dose holds due to diarrhea, n (%)	20 (15)	12 (19)	22 (16)	15 (14)	7 (12)	8 (13)
Discontinuations due to diarrhea, n (%)	28 (20)	7 (11)	5 (4)	8 (8)	2 (3)	4 (6)
Hospitalizations due to diarrhea, n (%)	2 (2)	0	0	0	0	0

DE1:
120 mg x 7d
↓
160 mg x 7d
↓
240 mg qd

Chan A, et al. 2022 ESMO Breast: Abstract 73P

Who Should Receive Neratinib?

- Clear benefit (relative and absolute) in ER+HER2+ high risk patients
  - Must be balanced against significant toxicity risk
- No data giving neratinib after pertuzumab or T-DM1
  - All patients at sufficiently high risk to receive neratinib will have received pertuzumab and T-DM1
- So who should receive it?
  - Unclear, but my opinion is that it is reasonable option to consider in ER+ patients with multiple (ie 4+) positive nodes after neoadjuvant therapy

Utilizing neoadjuvant therapy to deescalate therapy

- Data are very clear that achieving pCR is associated with favorable outcome
  - Can we leverage the pCR endpoint to reduce the intensity of neoadjuvant therapy as well as escalate when appropriate?

COMPASS Trial Schema

Eligibility
HER2+ breast ca
Stage 2 or 3a
(T2-3, N0-2)
Newly diagnosed,
no prior therapy

Registration

Part 1 preop
THP x 4 (12 weeks)

pac weekly or doc q3w (T)
PLUS
trastuzumab (H) &
pertuzumab (P) q3w

Research Biopsy

Surgery

Part 1 pCR (~40-45%)
No further chemo

Part 2 RD (~55%)

SOC adjuvant therapy

Primary Objective: 3y RFS HER2+

Unanswered questions in HER2+ MBC

- Is there a role for next-generation HER2-therapies in early stage disease?

COMPASS HER2RD

Eligibility
HER2+ breast ca
Stage 2 or 3a
(T2-3, N0-2)
Newly diagnosed,
no prior therapy

Registration

Part 1 preop
THP x 4 (12 weeks)

pac weekly or doc q3w (T)
PLUS
trastuzumab (H) &
pertuzumab (P) q3w

Surgery

Part 1 pCR (~40-45%)
No further chemo
Complete HP

Part 2 RD (~55%)

SOC chemo as deemed necessary

Eligibility
HER2+ RD
Any ER-
ER+ if N+
~ 50% Part 1, 50%
outside enrollees

N=981

Registration

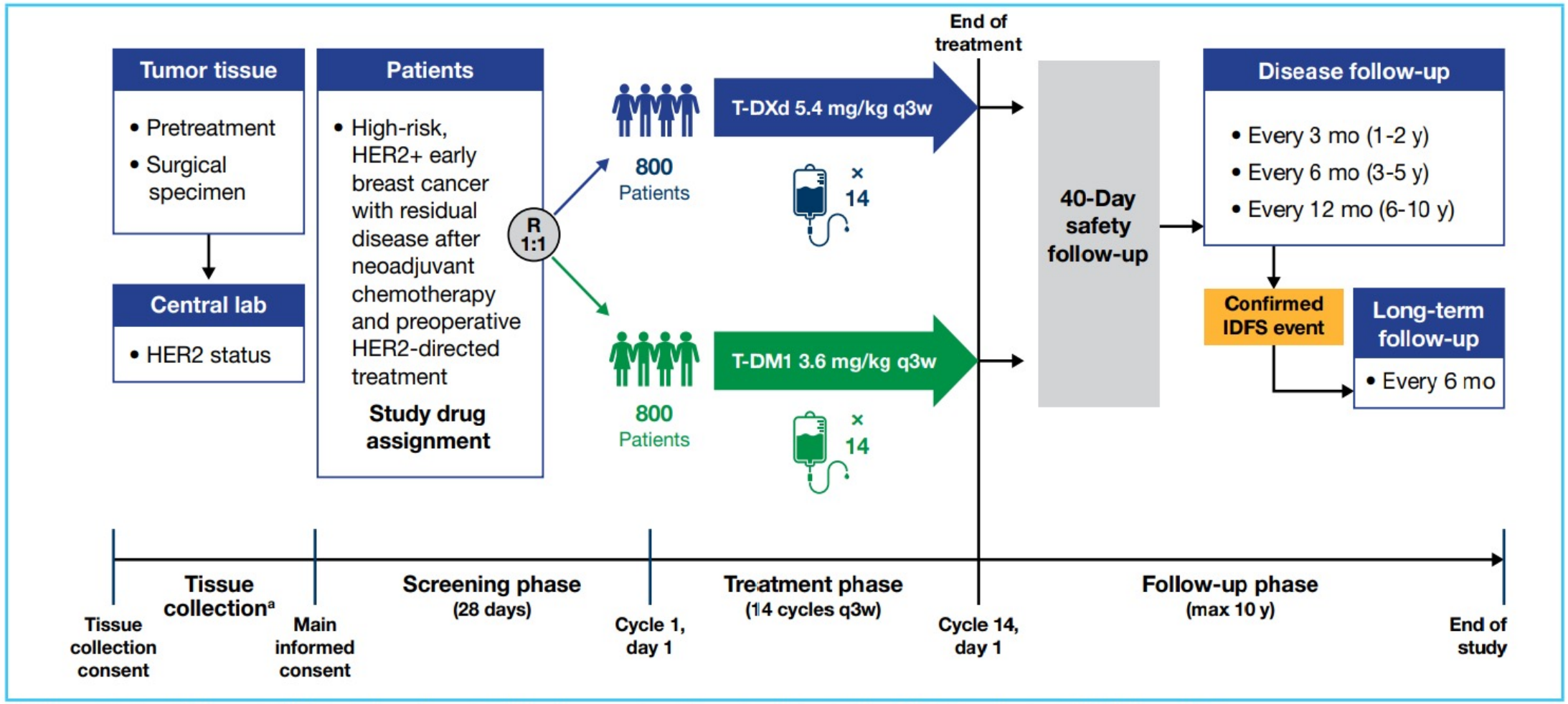
R

T-DM1 x 14 cycles

T-DM1 + tucatinib x14 cycles

Primary Objective: 3y IDFS

DESTINY-Breast05: A Multicenter, Open-Label, Randomized Phase 3 Trial Comparing the Efficacy and Safety of T-DXd vs T-DM1 in High-Risk Patients With HER2-Positive, Residual, Invasive Breast Cancer After Neoadjuvant Therapy (N≈1600)



HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; lab, laboratory; max, maximum; q3w, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a] Patients may move into the main screening phase before HER2 status results are available from the central laboratory.

Geyer et al. SABCS 2020 OT-03-01

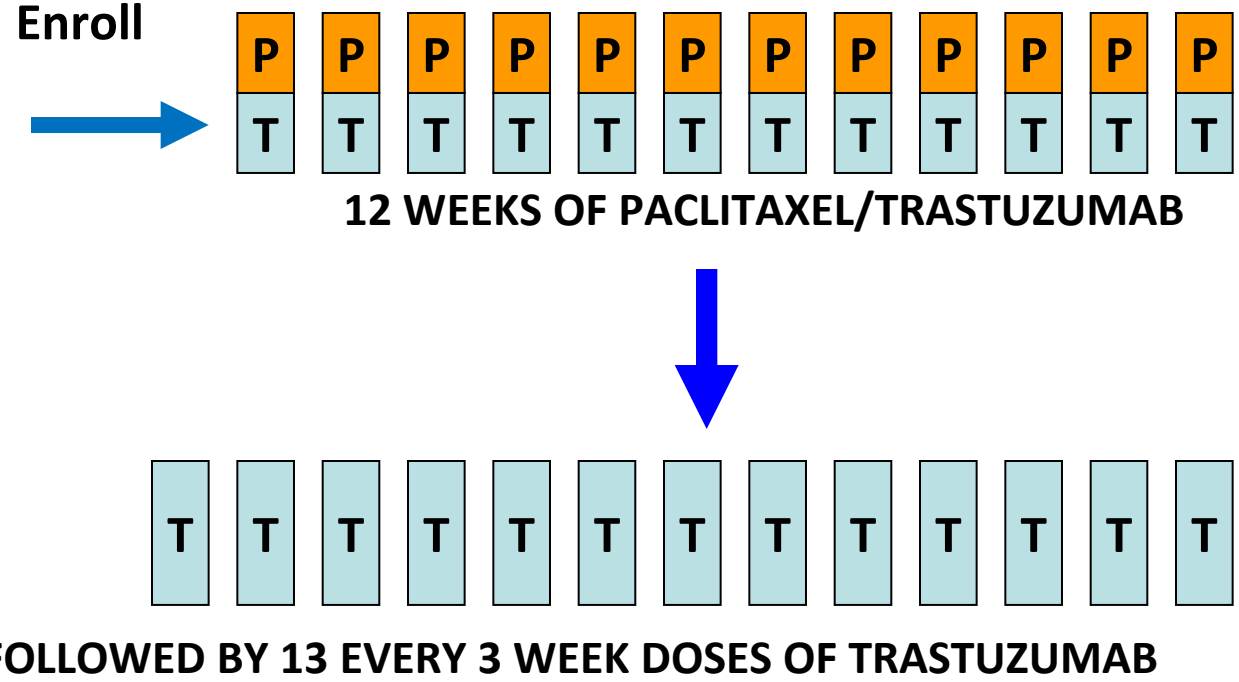
Optimizing treatment of small, node-negative HER2+ cancers

APT: DFCI-Led Single Arm, Multicenter, Low Risk Trial

HER2+
ER+ or ER-
Node Negative
< 3 cm
PS 0-1
Adequate organ fx

413 patients enrolled

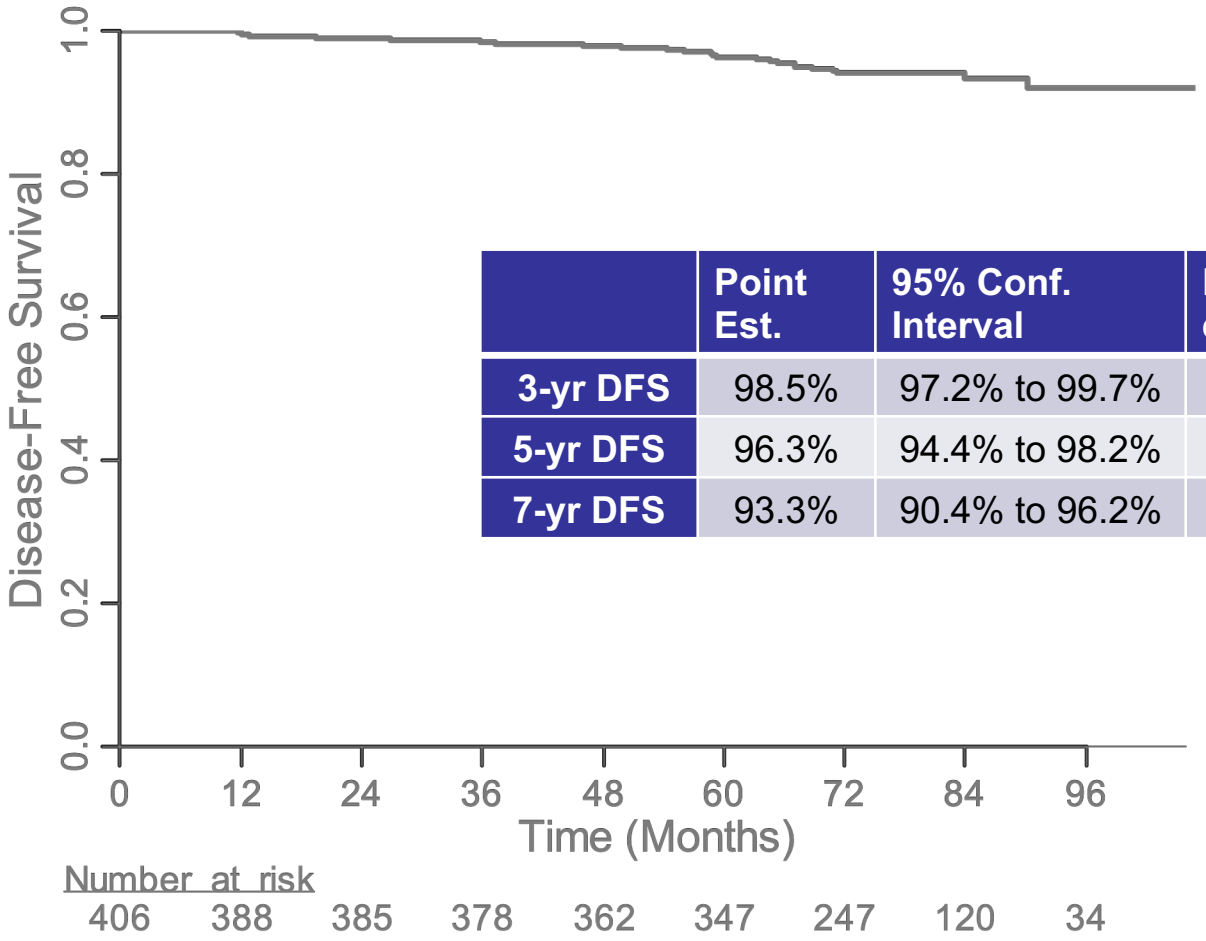
Enroll



Trial designed to determine if treatment with paclitaxel/trastuzumab is associated with a low (5%) rate of recurrence after 3 years

APT: Updated 7 year Disease Free Survival

Only 1% distant recurrence events



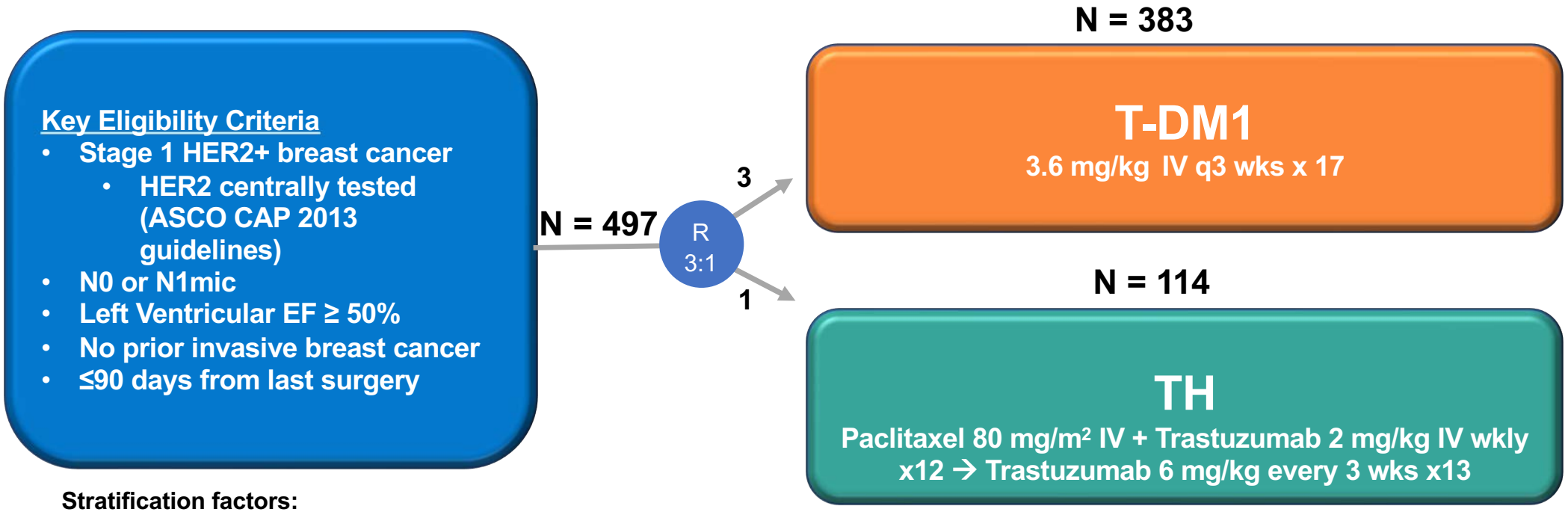
	Point Est.	95% Conf. Interval	No. of events
3-yr DFS	98.5%	97.2% to 99.7%	6
5-yr DFS	96.3%	94.4% to 98.2%	14
7-yr DFS	93.3%	90.4% to 96.2%	23

Tolaney et al, JCO 2019

Implications

- Paclitaxel and trastuzumab (TH) is associated with excellent outcomes and is a standard of care for patients with stage I HER2+ breast cancer
  - Not all patients require adjuvant trastuzumab-based chemotherapy (particularly T1aN0)

Study Design: ATEMPT Trial



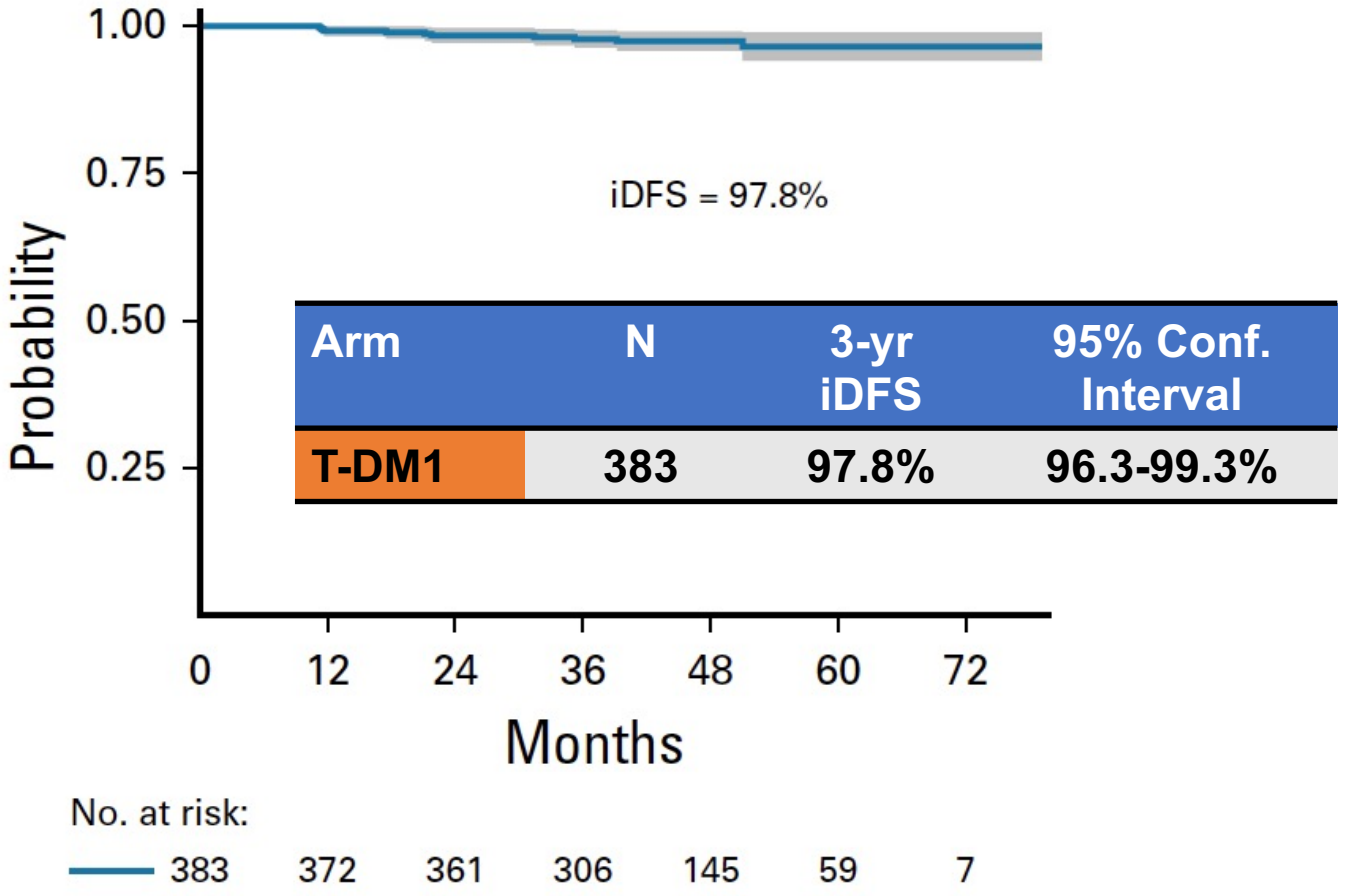
Stratification factors:

- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

*Radiation and endocrine therapy could be initiated after 12 weeks on study therapy

Tolaney et al, SABCS 2019

ATEMPT: Invasive Disease-Free Survival at 3 Years: T-DM1

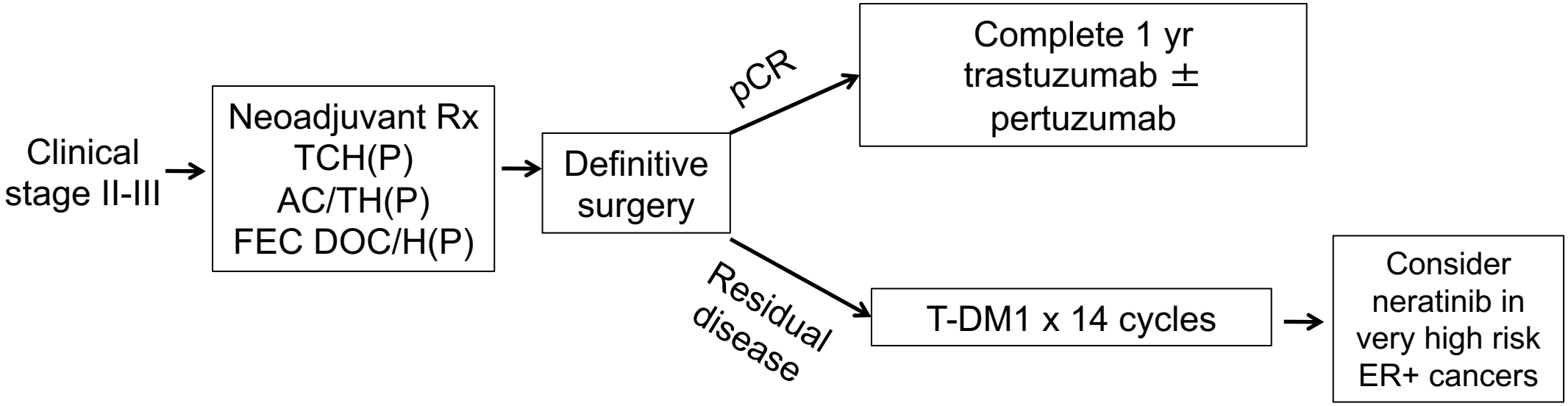


Arm	N	3-yr iDFS	95% Conf. Interval
T-DM1	383	97.8%	96.3-99.3%

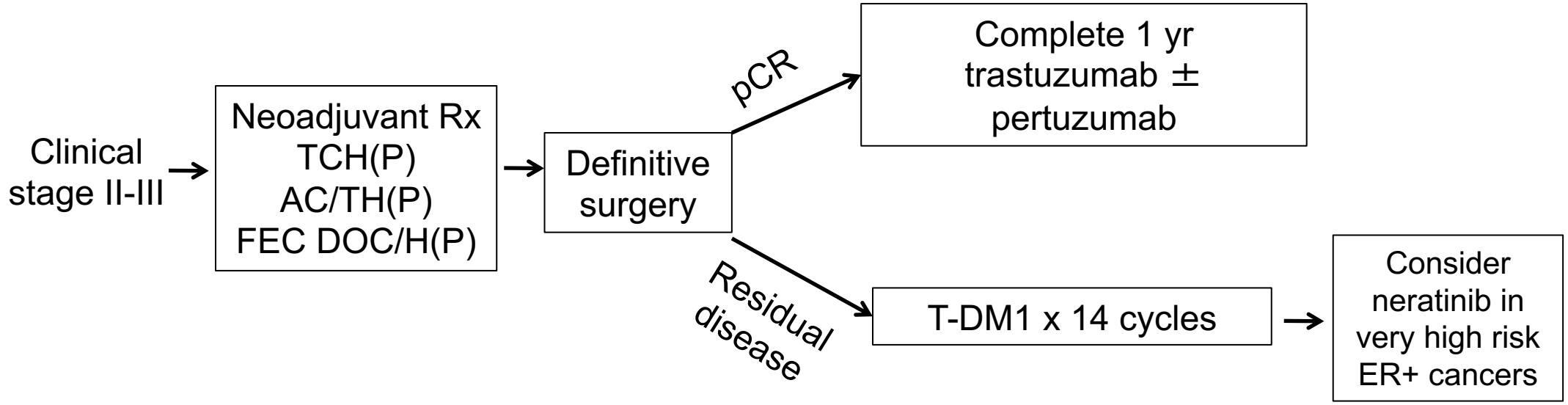
p<0.0001

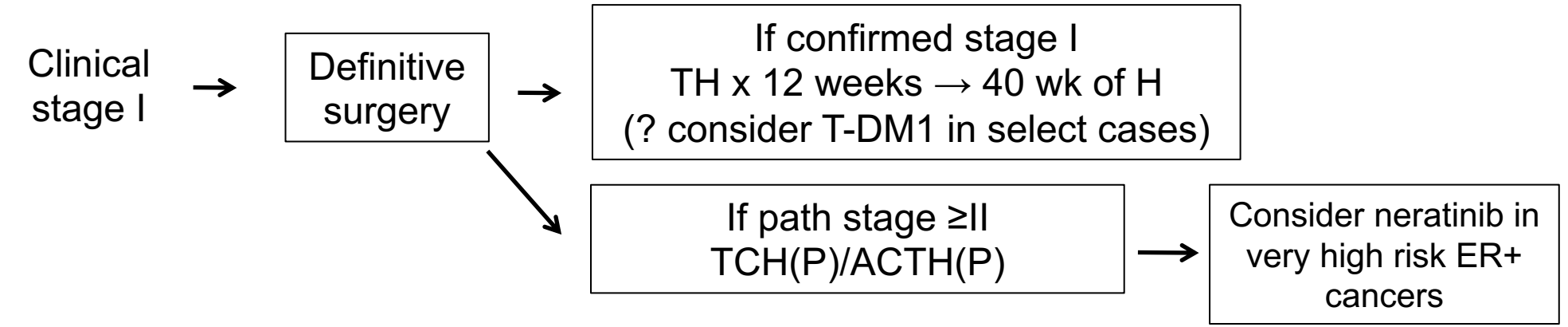
Tolaney et al, JCO 2021

Recommended Treatment Algorithm for Early-Stage HER2+ Breast Cancer



Recommended Treatment Algorithm for Early-Stage HER2+ Breast Cancer

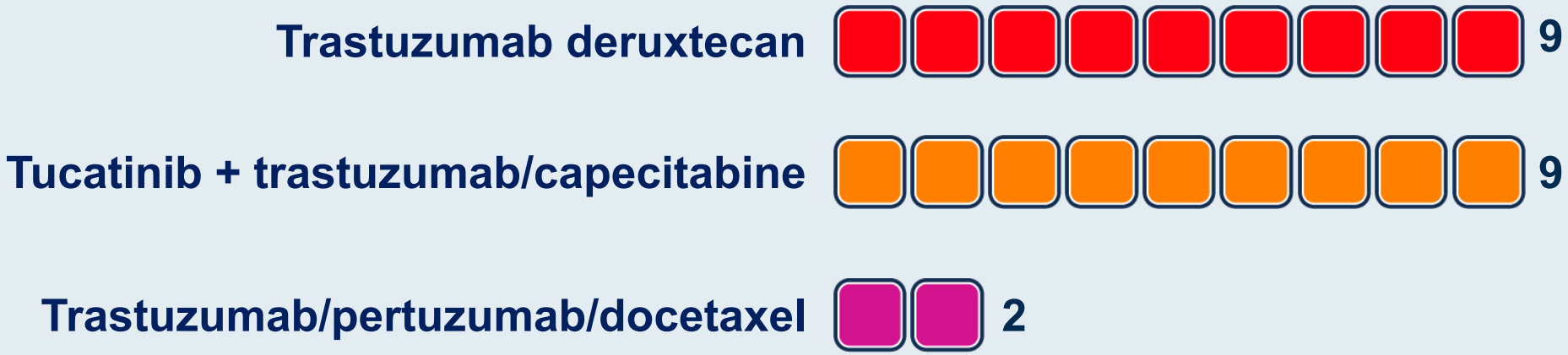




MODULE 4: Evolving Clinical Decision-Making for Patients with HER2-Positive Metastatic Breast Cancer (mBC)

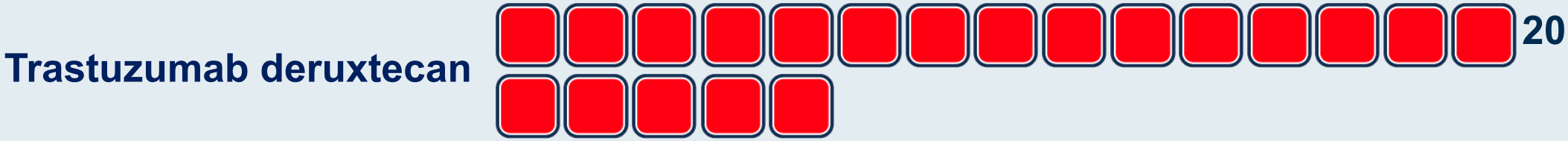
RTP
RESEARCH
TO PRACTICE

A 65-year-old woman with an ER-negative, HER2-positive IDC experiences asymptomatic recurrence in the liver and multiple brain metastases requiring whole-brain radiation therapy 12 months after completing neoadjuvant TCHP followed by adjuvant T-DM1. Regulatory and reimbursement issues aside, which systemic treatment would you recommend?



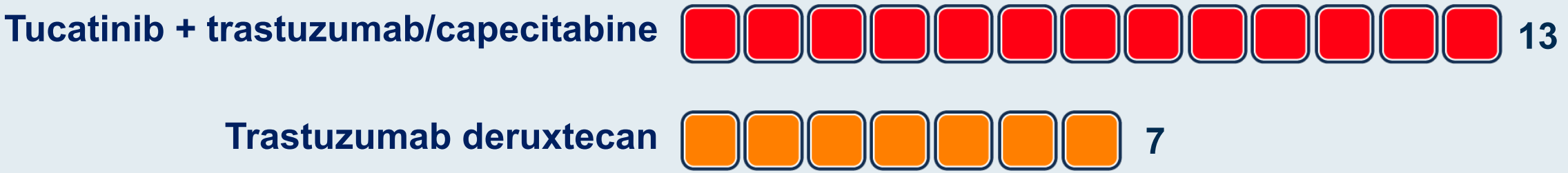
Survey of clinical investigators

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line docetaxel/trastuzumab/pertuzumab (THP) but after 1 year experiences asymptomatic disease progression with no evidence of CNS involvement. Regulatory and reimbursement issues aside, which systemic treatment would you recommend next?



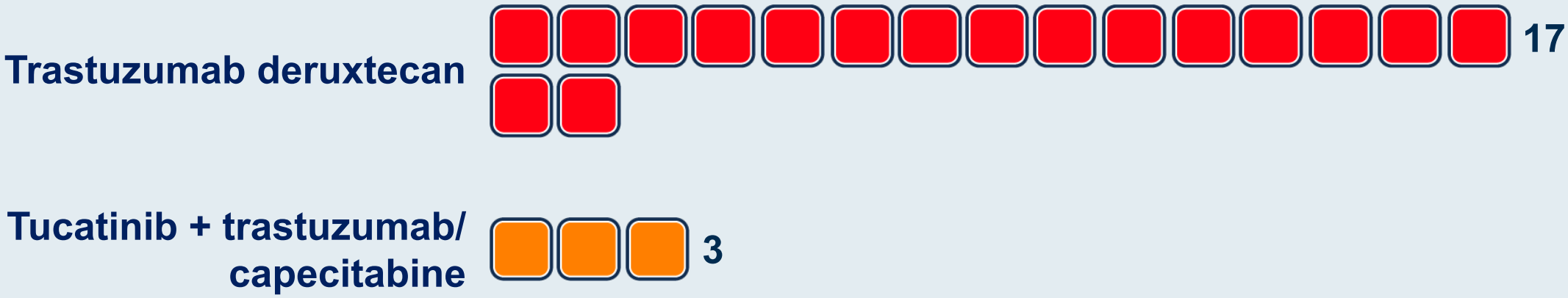
Survey of clinical investigators

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP but after 1 year experiences asymptomatic disease progression, including multiple brain metastases. Regulatory and reimbursement issues aside, which systemic treatment would you recommend next?



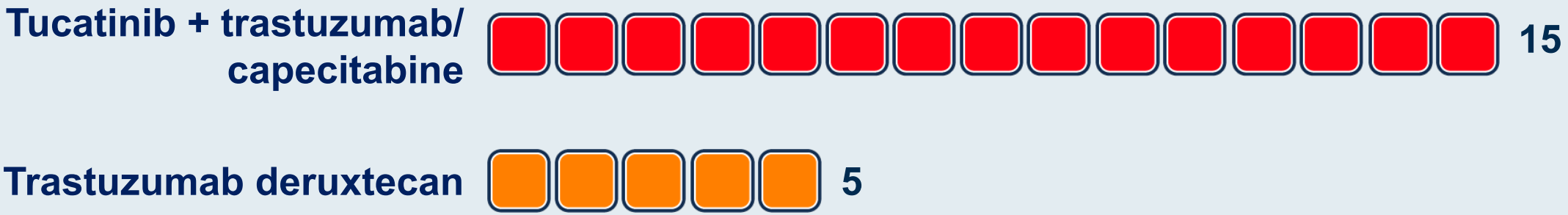
Survey of clinical investigators

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP followed by second-line T-DM1 on disease progression. She now presents with further asymptomatic progression but no evidence of CNS involvement. Regulatory and reimbursement issues aside, which systemic treatment would you recommend?



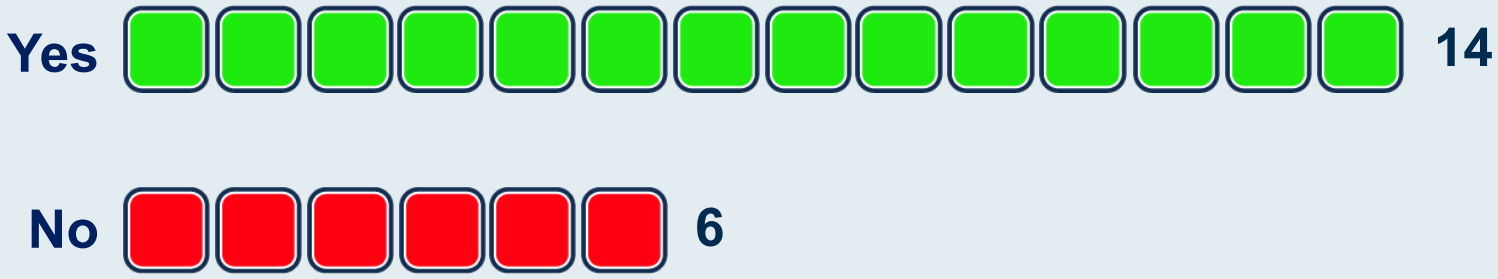
Survey of clinical investigators

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP followed by second-line T-DM1 on disease progression. She now presents with further asymptomatic progression with multiple brain metastases. Regulatory and reimbursement issues aside, which systemic treatment would you recommend?



Survey of clinical investigators

In general, for a patient with HER2-positive mBC and multiple asymptomatic bilateral brain metastases that would require whole-brain radiation who is about to receive tucatinib, trastuzumab and capecitabine as third-line therapy after TCHP and T-DM1, would you start systemic treatment and hold radiation therapy to the brain?



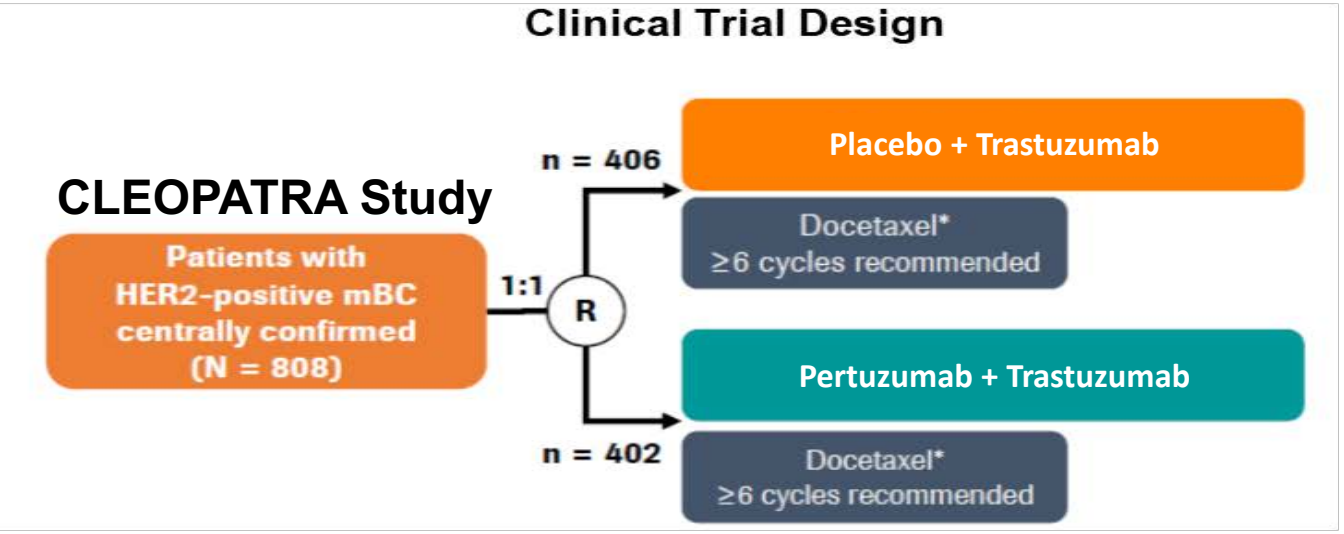
Survey of clinical investigators

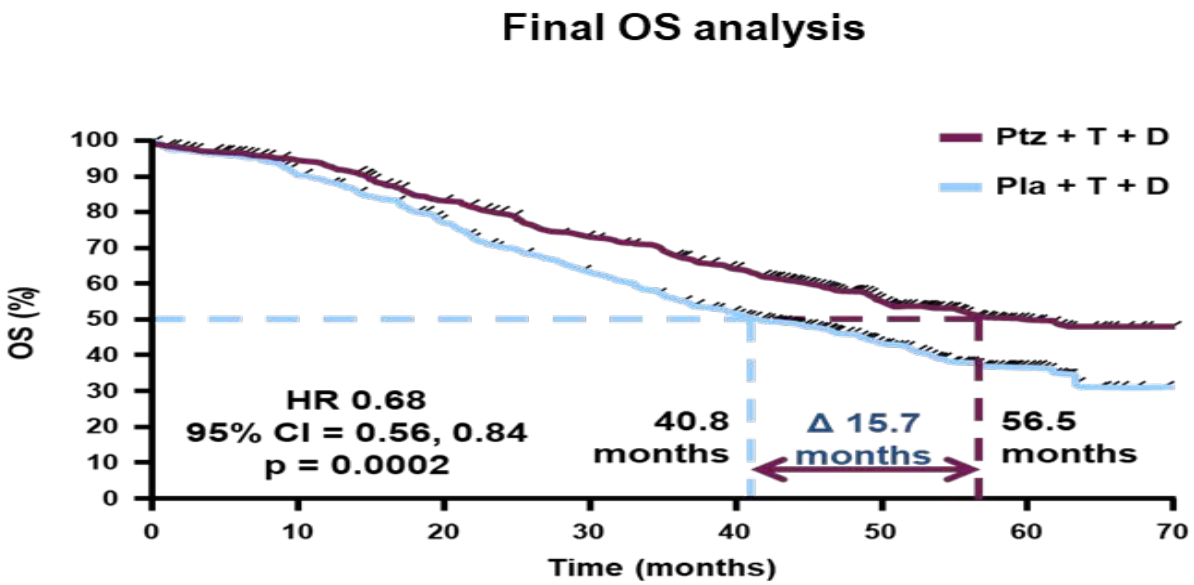
Evolving Clinical Decision-Making for Patients with HER2-Positive Metastatic BC (mBC)

Javier Cortes,
IBCC, International Breast Cancer Center, Quiron Group, Barcelona
Medica Scientia Innovation Research (MedSIR)
Barcelona, Spain & New Jersey, US

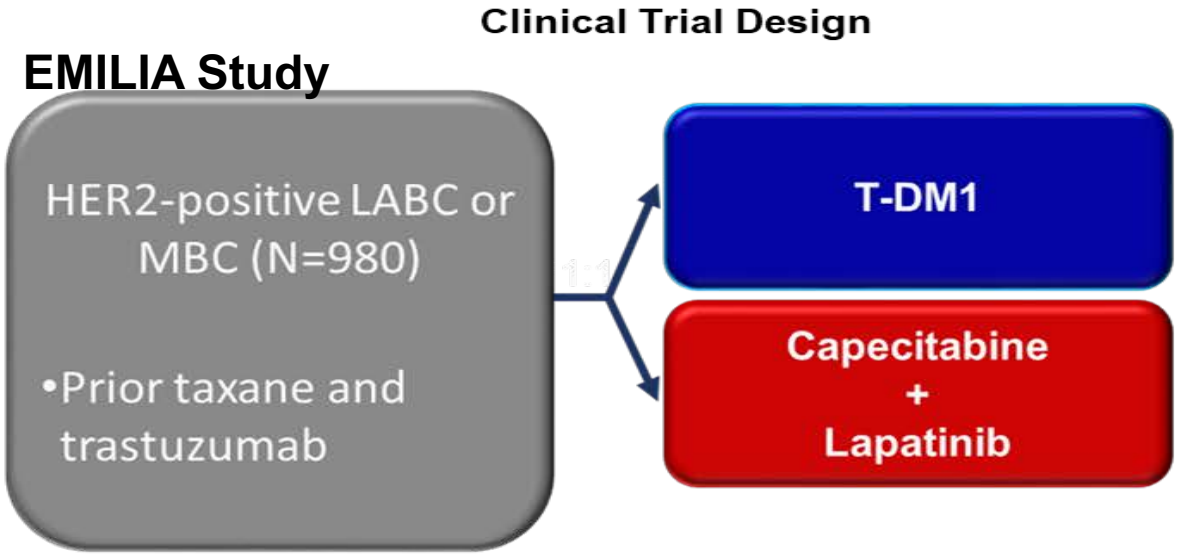
"UP TO 2022" FIRST- AND SECOND-LINE PREFERRED STRATEGIES

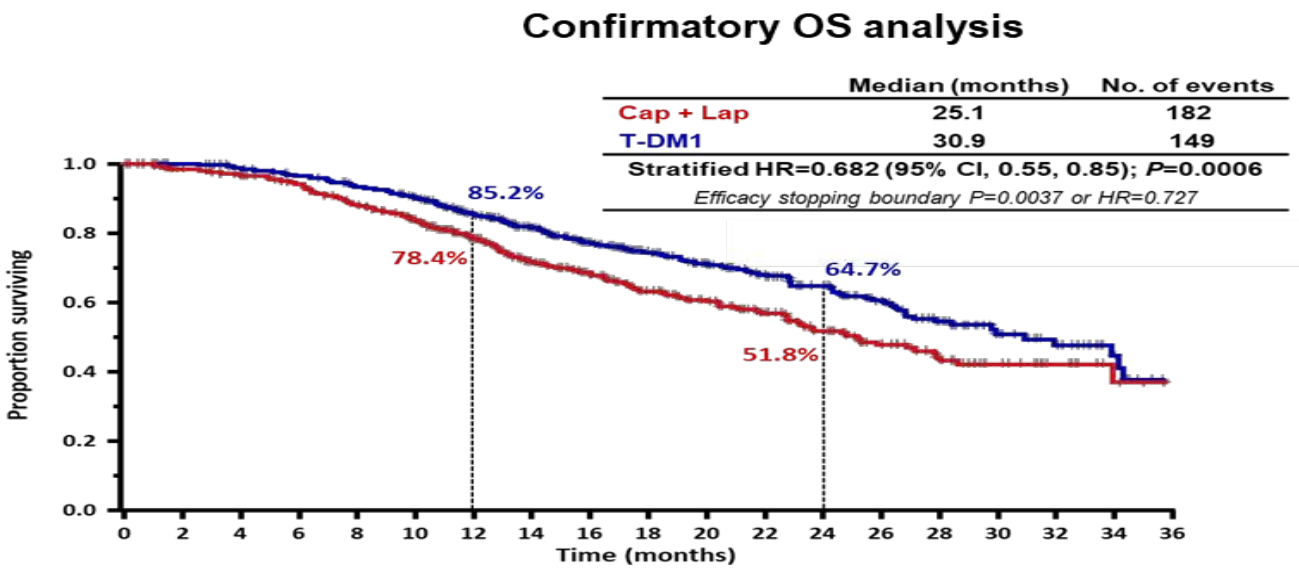
CLEOPATRA Study





EMILIA Study





Baselga J, et al. NEJM 2012; Swain S, et al. NEJM 2015; Verma S, et al. NEJM 2012

New TKIs

Clinical Trial Designs

HER2CLIMB[1]

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)

NALA Study[2]

HER2+ MBC (N=621)

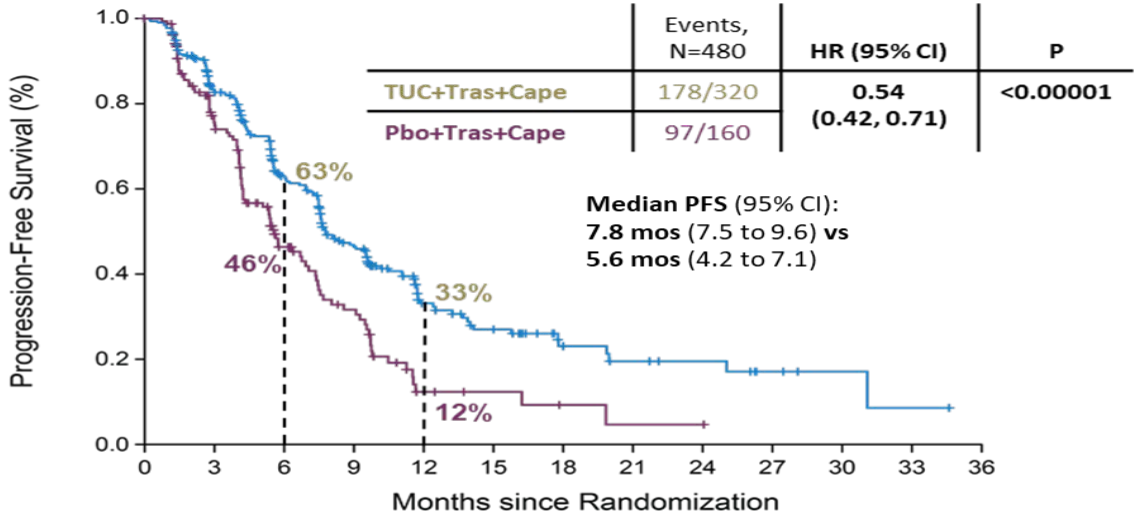
•Prior treatment with at least two HER2-directed regimens for metastatic breast cancer

1:1

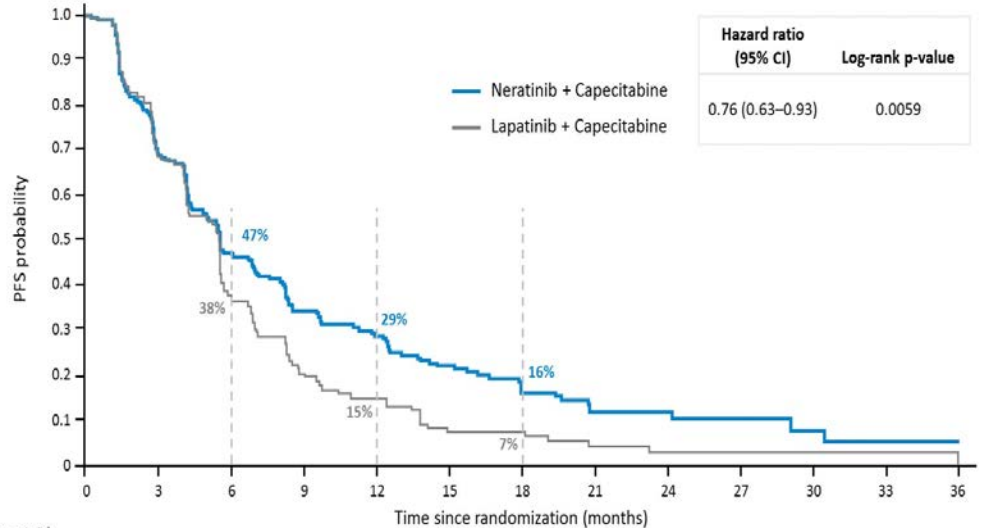
Capecitabine + Neratinib

Capecitabine + Lapatinib

Positive PFS data



	Events, N=480	HR (95% CI)	P
TUC+Tras+Cape	178/320	0.54 (0.42, 0.71)	<0.00001
Pbo+Tras+Cape	97/160		



Hazard ratio (95% CI)	Log-rank p-value
0.76 (0.63–0.93)	0.0059

1. Murthy R, et al. NEJM 2020; 2. Brufsky A, et al. ASCO 2019; 3. Laura C, et al. JCO 2020.

New TKIs

Clinical Trial Designs

HER2CLIMB[1]

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)

NALA Study[2]

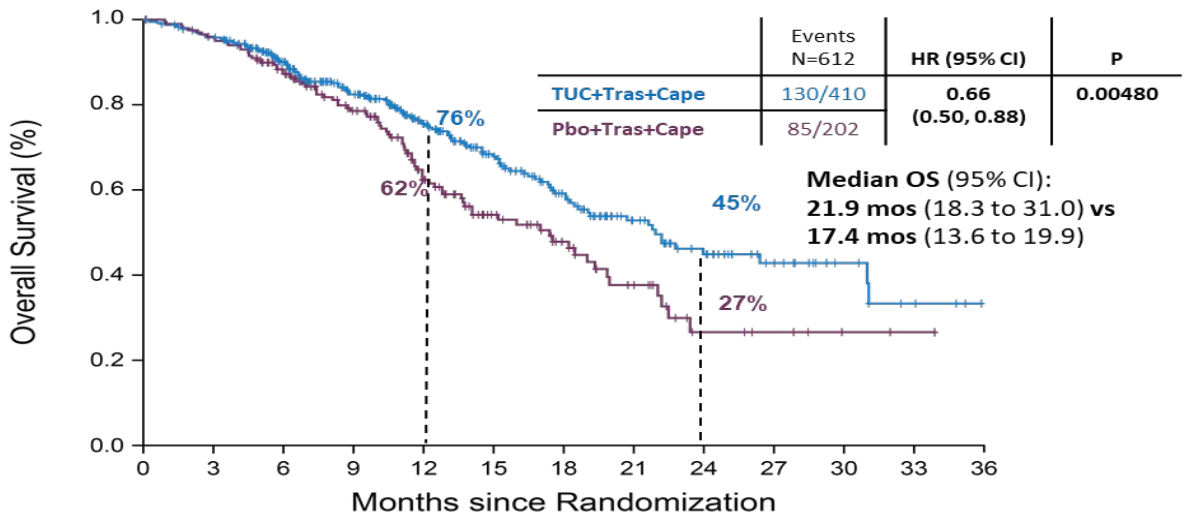
HER2+ MBC (N=621)

•Prior treatment with at least two HER2-directed regimens for metastatic breast cancer

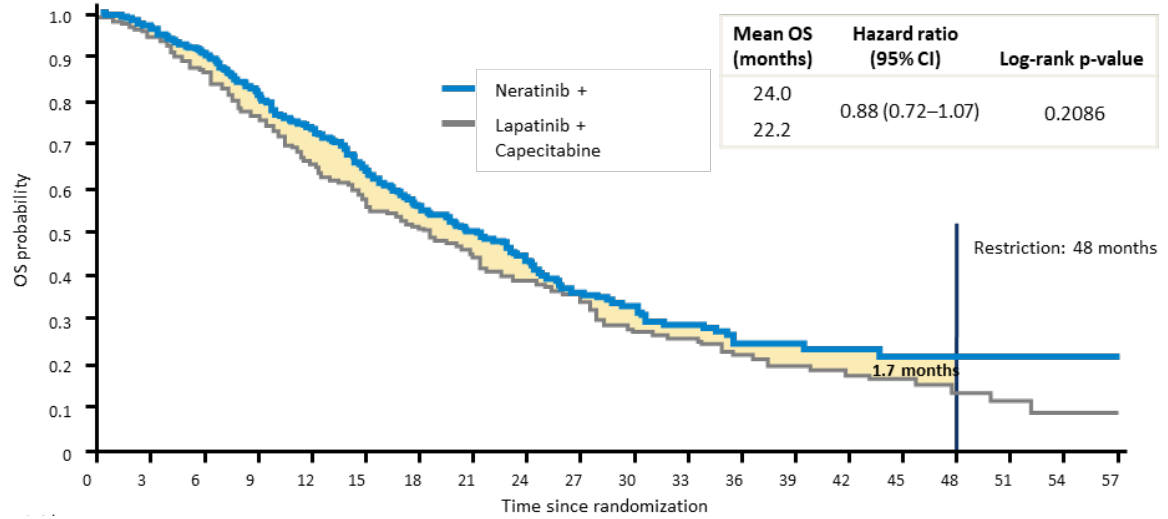
1:1

- **Capecitabine + Neratinib**
- **Capecitabine + Lapatinib**

OS data



	Events N=612	HR (95% CI)	P
TUC+Tras+Cape	130/410	0.66 (0.50, 0.88)	0.00480
Pbo+Tras+Cape	85/202		



Mean OS (months)	Hazard ratio (95% CI)	Log-rank p-value
24.0 22.2	0.88 (0.72–1.07)	0.2086

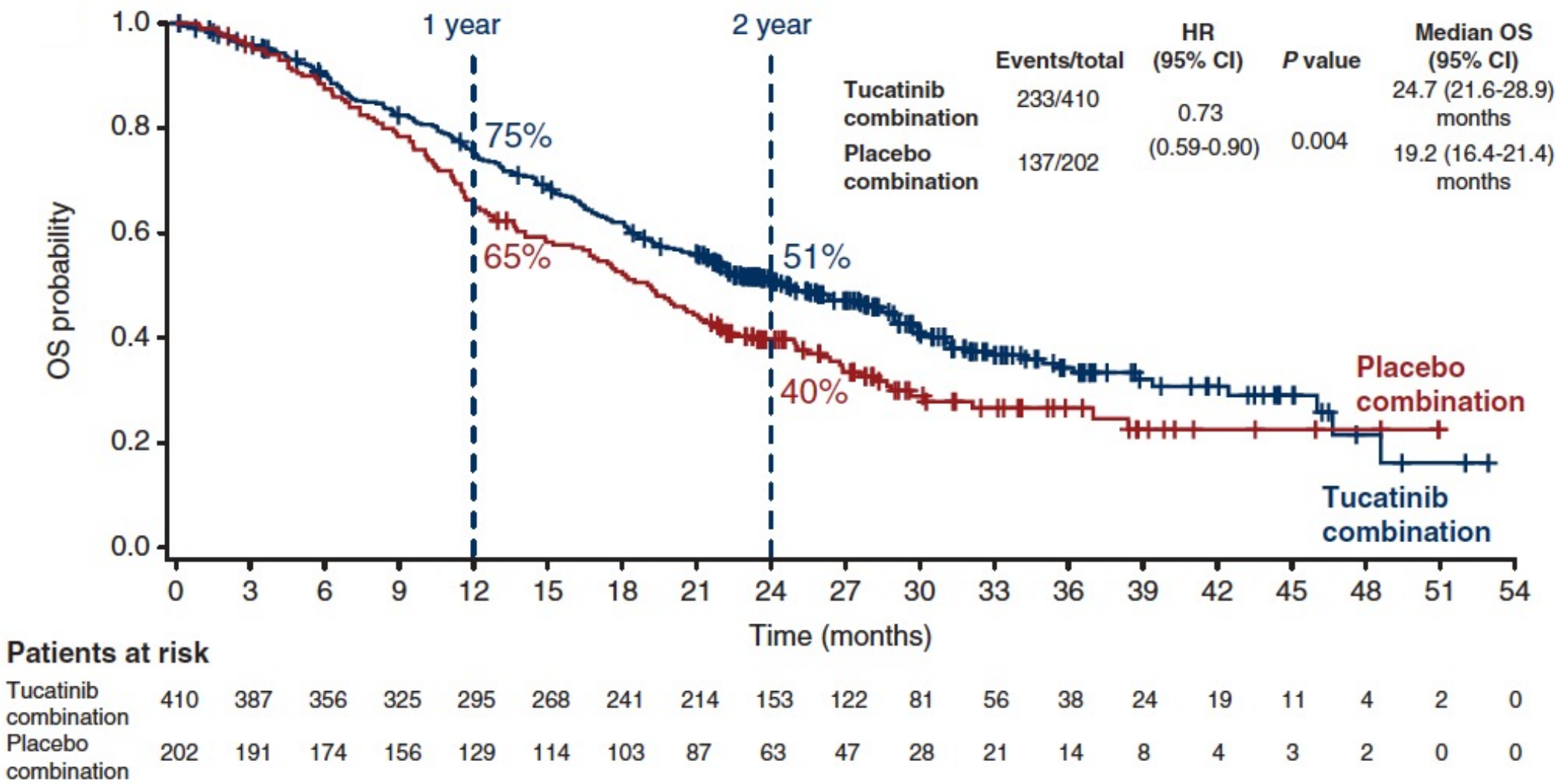
1. Murthy R, et al. NEJM 2020; 2. Brufsky A, et al. ASCO 2019; 3. Laura C, et al. JCO 2020.

Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis

G. Curigliano[1*], V. Mueller[2], V. Borges[3], E. Hamilton[4], S. Hurvitz[5], S. Loi[6], R. Murthy[7], A. Okines[8], E. Paplomata[9†], D. Cameron[10], L. A. Carey[11], K. Gelmon[12], G. N. Hortobagyi[7], I. Krop[13], S. Loibl[14], M. Pegram[15], D. Slamon[5], J. Ramos[16], W. Feng[16] & E. Winer[13]

Ann Oncol 2022;33(3):321-29.

HER2CLIMB: Final Overall Survival Analysis



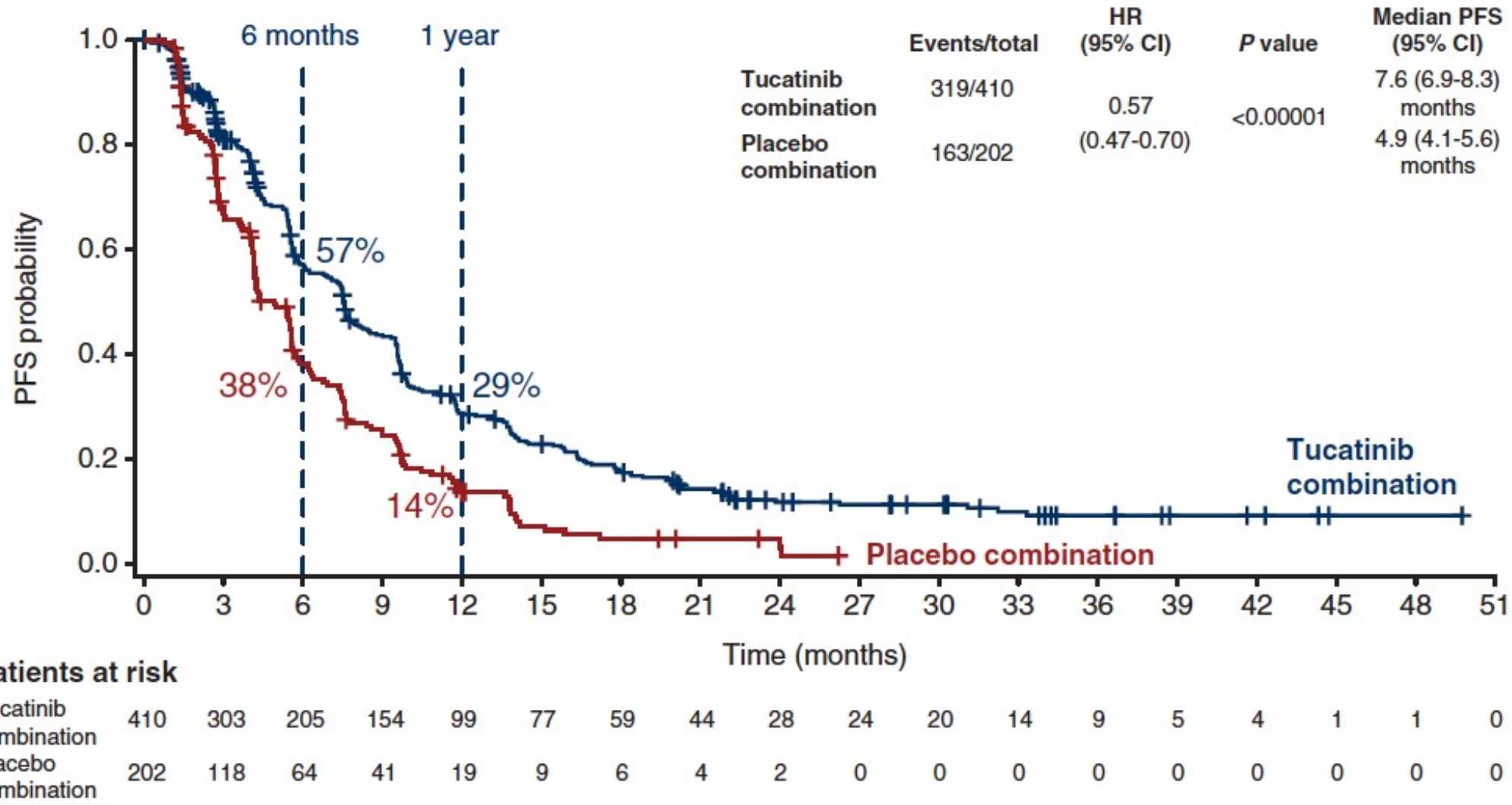
	Events/total	HR (95% CI)	*P* value	Median OS (95% CI)
Tucatinib combination	233/410	0.73 (0.59-0.90)	0.004	24.7 (21.6-28.9) months
Placebo combination	137/202			19.2 (16.4-21.4) months

Patients at risk

Tucatinib combination	410	387	356	325	295	268	241	214	153	122	81	56	38	24	19	11	4	2	0
Placebo combination	202	191	174	156	129	114	103	87	63	47	28	21	14	8	4	3	2	0	0

Curigliano G et al. *Ann Oncol* 2022;33(3):321-29.

HER2CLIMB: Progression-Free Survival (PFS)



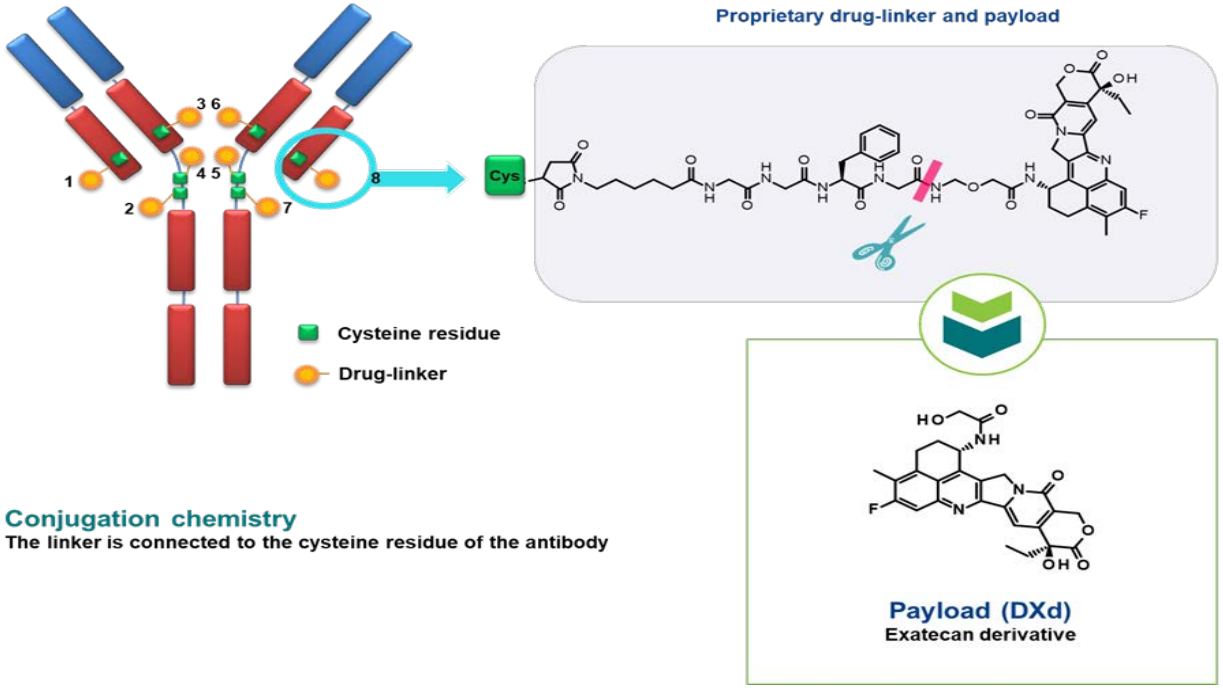
	Events/total	HR (95% CI)	*P* value	Median PFS (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<0.00001	7.6 (6.9-8.3) months
Placebo combination	163/202			4.9 (4.1-5.6) months

Patients at risk

Tucatinib combination	410	303	205	154	99	77	59	44	28	24	20	14	9	5	4	1	1	0
Placebo combination	202	118	64	41	19	9	6	4	2	0	0	0	0	0	0	0	0	0

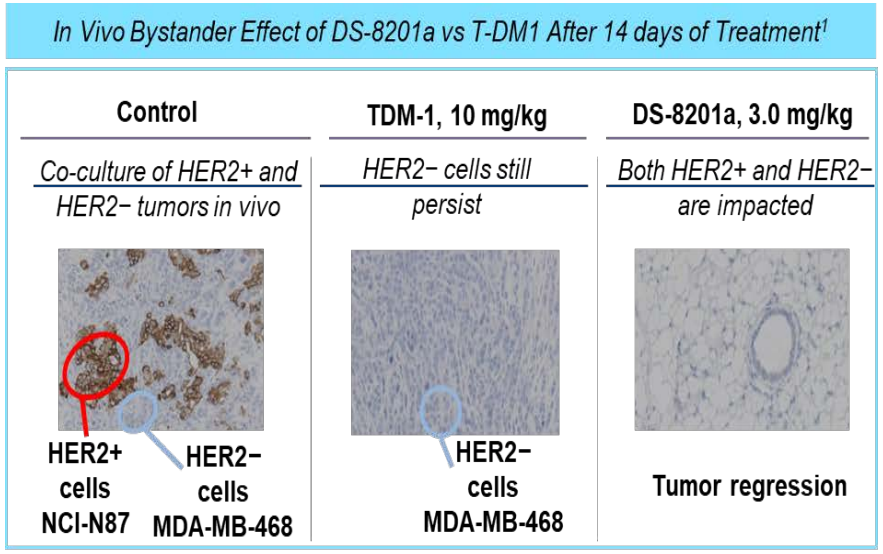
Curigliano G et al. *Ann Oncol* 2022;33(3):321-29.

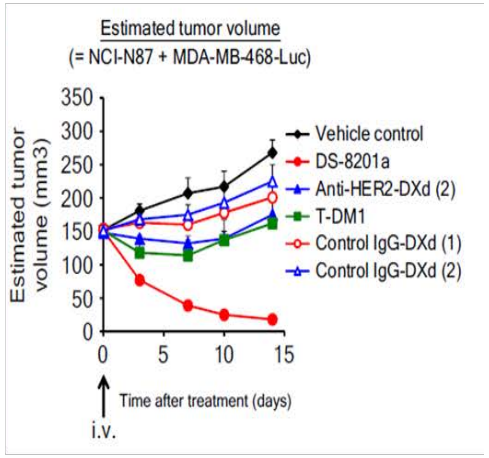
Trastuzumab-Deruxtecan

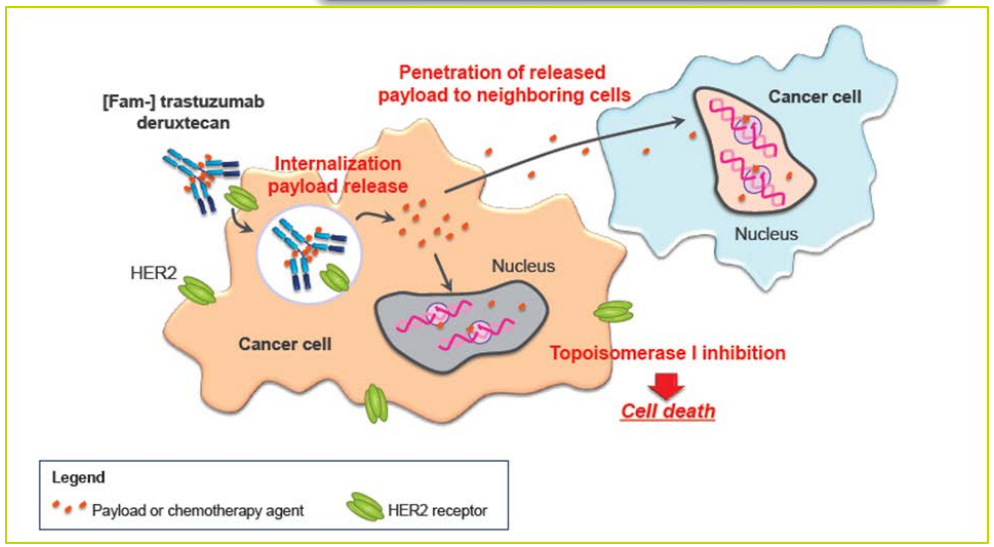


- *Payload with a different mechanism of action*
- *High potency of payload*
- *Payload with short systemic half-life*
- *Bystander effect*
- *Stable linker-payload*
- *Tumor-selective cleavable linker*
- *High drug-to-antibody ratio (~1:8)*

In Vivo Bystander Effect of DS-8201a vs T-DM1 After 14 days of Treatment[1]



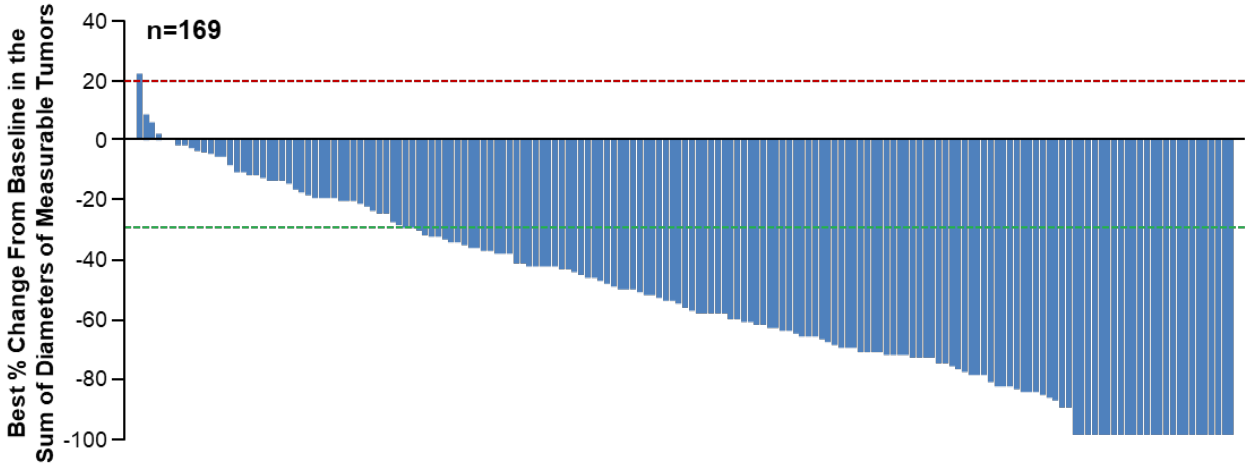




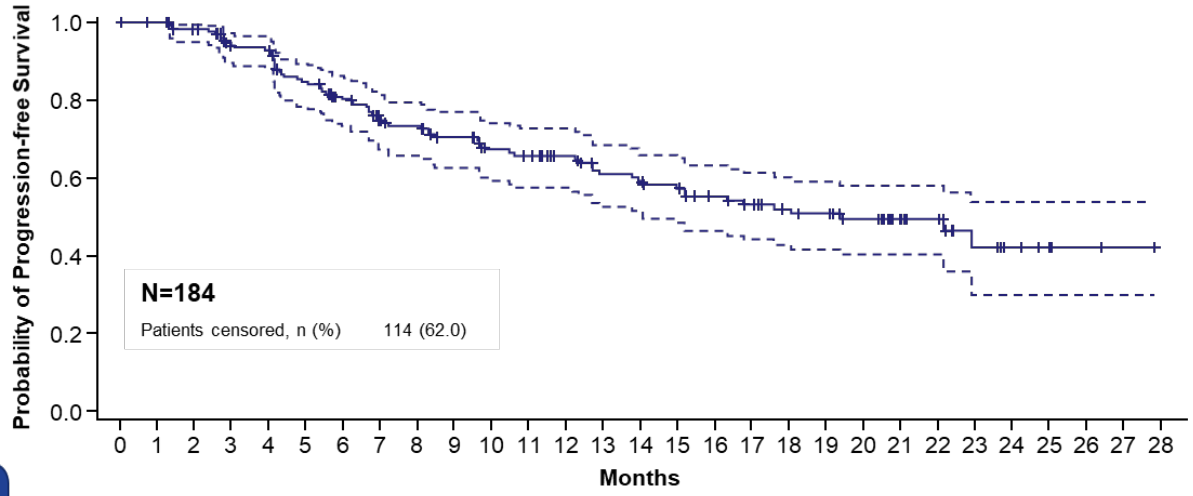
Iwata, et al. ASCO 2018; Ogitani, et al. Cancer Science 2016

Trastuzumab-Deruxtecan: DB01 Phase II study

ORR

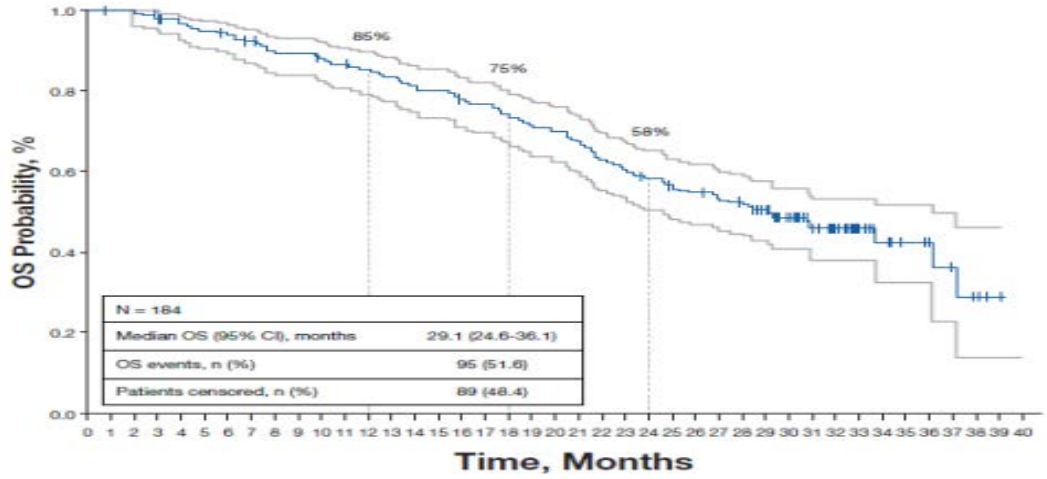


mPFS: 19.4 months



Intent-to-treat analysis	August 2019 DCO T-DXd 5.4 mg/kg (N=184)	June 2020 DCO T-DXd 5.4 mg/kg (N=184)	March 2021 DCO T-DXd 5.4 mg/kg (N=184)
Median duration of follow up (range), months	11.1 (0.7-19.9)	20.5 (0.7-31.4)	26.5 (0.7-39.1)
Patients remaining on treatment, n (%)	79 (42.9)	37 (20.1)	28 (15.2)
Confirmed ORR[a] by ICR, n (%) 95% CI	112 (60.9) 53.4-68.0	113[b] (61.4) 54.0-68.5	114 **(62.0)** 54.5-69.0
CR	11 (6.0)	12 (6.5)	13 (**7.1**)
PR	101 (54.9)	101 (54.9)	101 (54.9)
SD	67 (36.4)	66 (35.9)	65 (35.3)
PD	3 (1.6)	3 (1.6)	3 (1.6)
Not evaluable	2 (1.1)	2 (1.1)	2 (1.1)
Median DOR (95% CI), months	14.8 (13.8-16.9	20.8[b] (15.0-NE)	18.2 (15.0-NE)
Median time to response (95% CI), months	1.6 (1.4-2.7)	1.6 (1.4-2.7)	1.6 (1.4-2.7)
Median PFS (95% CI), months	16.4 (12.7-NE)	19.4 (14.1-NE)	**19.4** (14.1-25.0)
Median OS (95% CI), months	NE (NE-NE)	24.6 (23.1-NE)	**29.1** (24.6-36.1)

mOS: 29.1 months



Modi S, NEJM 2019; Modi S, et al. SABCS 2020; Saura C, et al. ESMO 2021

Adverse Events of Special Interest: Interstitial Lung Disease (DB01)

Interstitial Lung Disease, n (%)[a]	August 2019 DCO T-DXd 5.4 mg/kg (N=184)	June 2020 DCO T-DXd 5.4 mg/kg (N=184)	March 2021 DCO T-DXd 5.4 mg/kg (N=184)
Grade 1	5 (2.7)	6 (3.3)	7 (3.8)
Grade 2	15 (8.2)	16 (8.7)	16 (8.7)
Grade 3	1 (0.5)	1 (0.5)	1 (0.5)
Grade 4	0	0	0
Grade 5	4 (2.2)	5 (2.7)	5 (2.7)
Any grade/total	**25 (13.6)**	**28 (15.2)**	**29 (15.8)**

Median time from the first infusion of T-DXd to onset of ILD was 27.6 weeks (range, 6-76 weeks)

ILD, interstitial lung disease.

Modi S et al. SABCS 2020. Abstract PD3-06; Saura C, et al. ESMO 2021

Trastuzumab-Deruxtecan: DB03 Phase III study

Clinical Trial Design (Phase III- Destiny-Breast03)

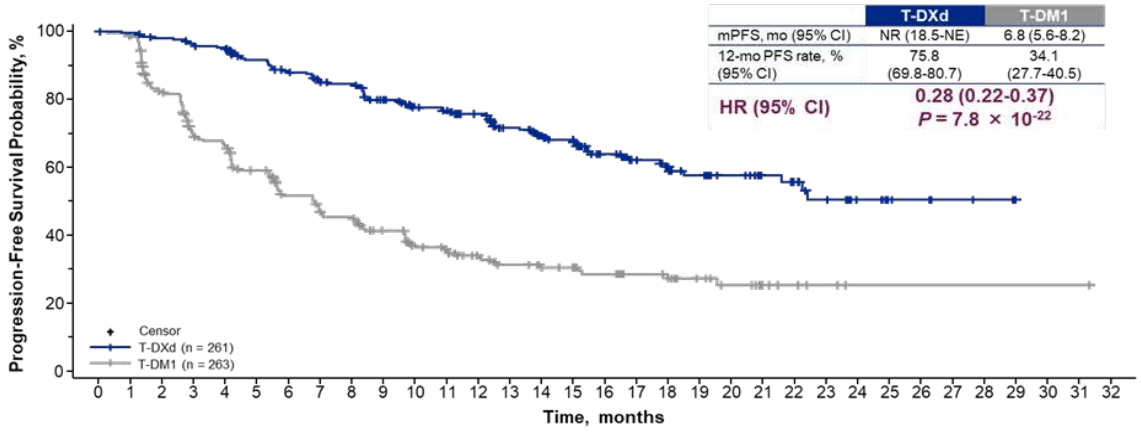
Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

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

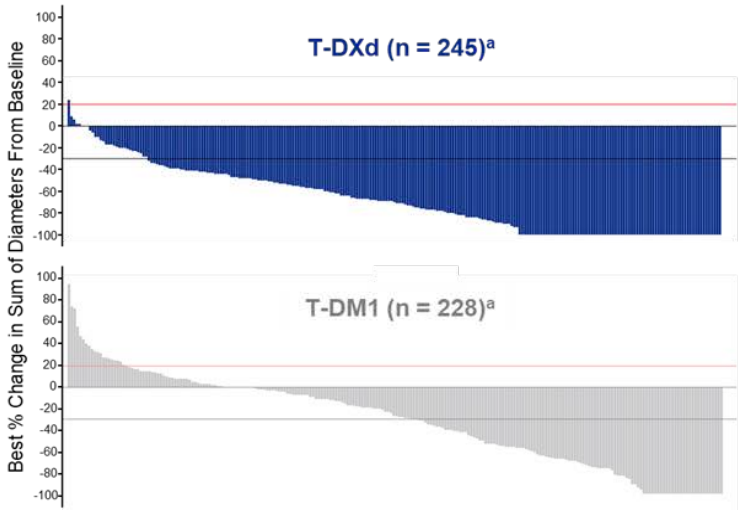
R 1:1

- T-DXd 5.4 mg/kg Q3W (n = 261)
- T-DM1 3.6 mg/kg Q3W (n = 263)

PFS

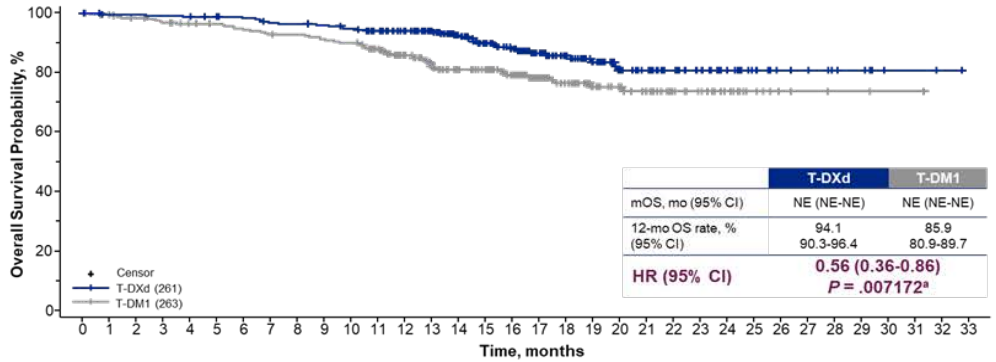


ORR



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b] [95% CI]	208 **(79.7)** [74.3-84.4]	90 **(34.2)** [28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

OS



Cortes J, et al. ESMO 2021; Cortes J, et al. NEJM 2022

Toxicity (DB03)

System Organ Class Preferred term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia[c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia[d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue[e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

Most drug-related TEAEs were gastrointestinal or hematological in nature

Cortes J, et al. ESMO 2021; Cortes J, et al. NEJM 2022

Adverse Events of Special Interest: Interstitial Lung Disease (DB03)

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

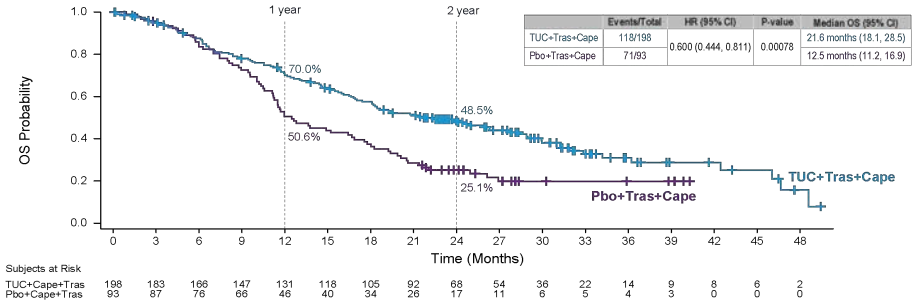
- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

Cortes J, et al. ESMO 2021; Cortes J, et al. NEJM 2022

HER2+ MBC patients with Brain Metastases
HER2CLIMB

	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	118/198	0.600 (0.444, 0.811)	0.00078	21.6 months (18.1, 28.5)
Pbo+Tras+Cape	71/93			12.5 months (11.2, 16.9)

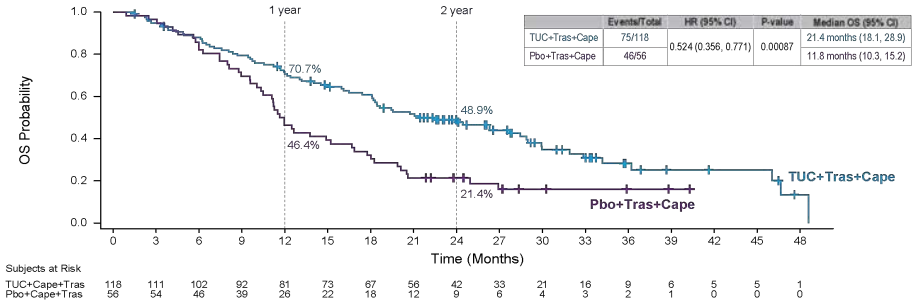
OS for All Patients with Brain Metastases



- OS benefit with tucatinib was improved with additional follow-up. Median OS was 9.1 months longer in the tucatinib arm compared with the control arm in all patients with brain metastases.
  - Previously reported, median OS was 6.1 months longer in tucatinib arm compared with control arm in all patients with brain metastases (18.1 vs 12.0 months)[4]

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

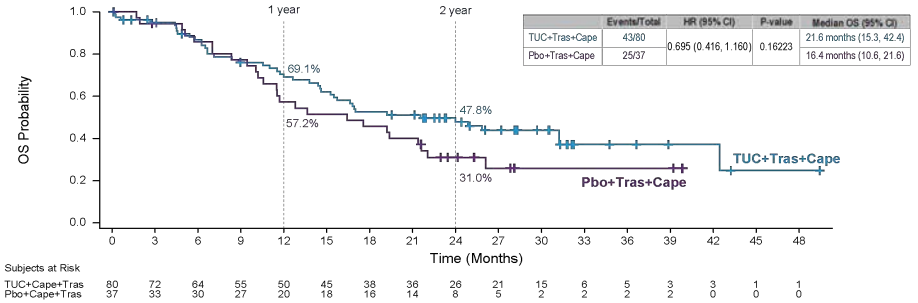
OS for Patients with Active Brain Metastases



- Median OS was 9.6 months longer in the tucatinib arm compared with the control arm in patients with active brain metastases.

	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	43/80	0.695 (0.416, 1.160)	0.16223	21.6 months (15.3, 42.4)
Pbo+Tras+Cape	25/37			16.4 months (10.6, 21.6)

OS for Patients with Treated Stable Brain Metastases

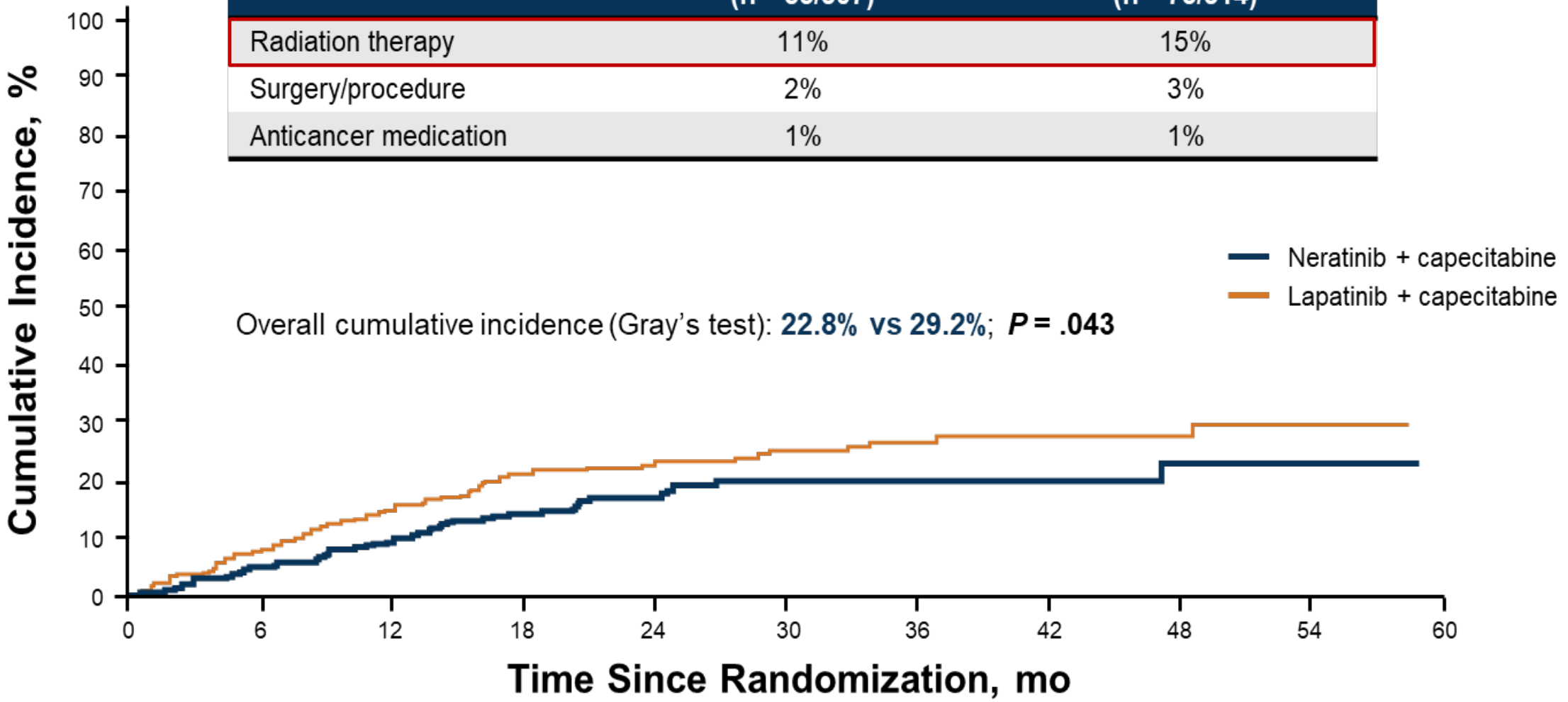


- Median OS was 5.2 months longer in the tucatinib arm compared with the control arm in patients with treated stable brain metastases.

Lin N, et al. SABCS 2021

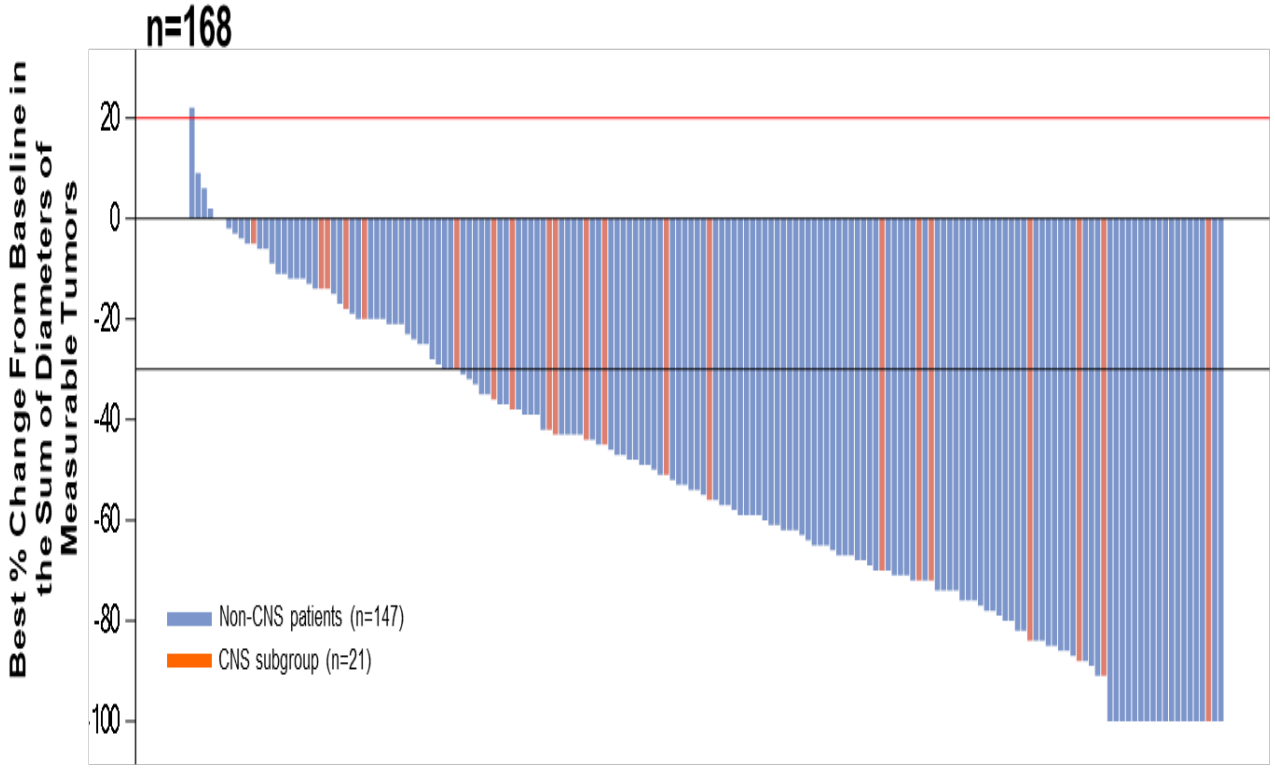
HER2+ MBC patients with Brain Metastases
NALA

Intervention	Neratinib + Capecitabine (n = 55/307)	Lapatinib + Capecitabine (n = 75/314)
Radiation therapy	11%	15%
Surgery/procedure	2%	3%
Anticancer medication	1%	1%

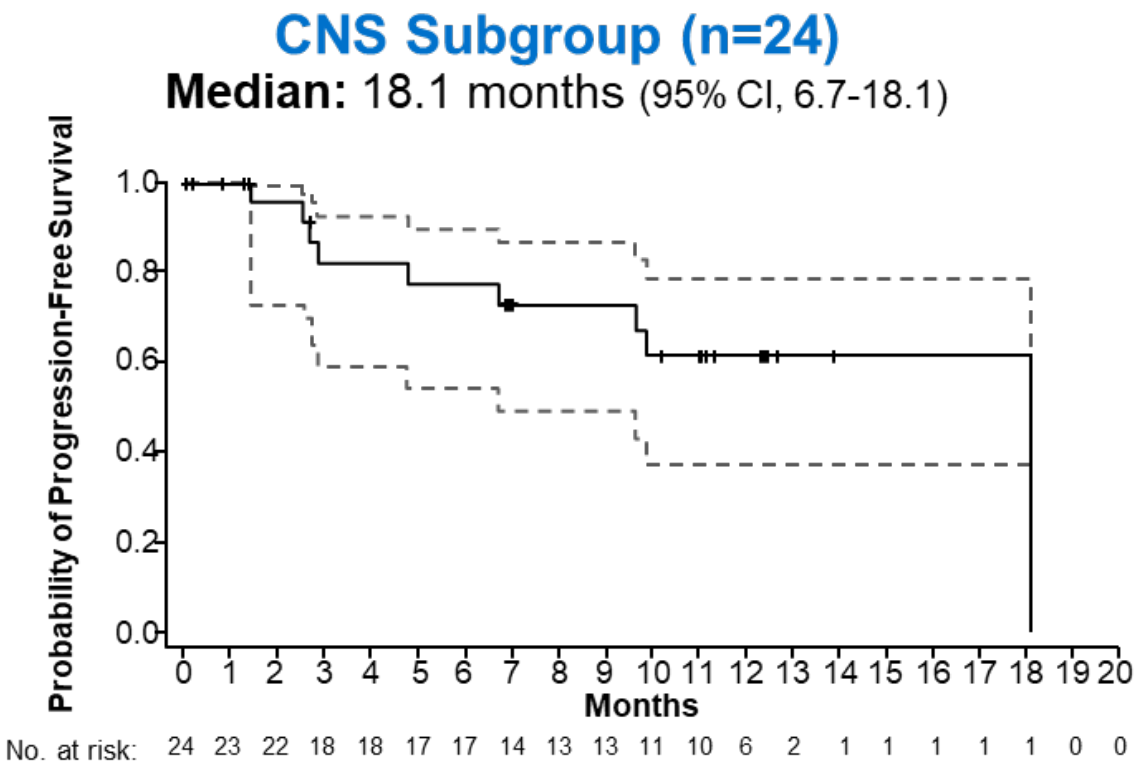


Saura C, et al. JCO 2020

HER2+ MBC patients with Brain Metastases
DB01



Includes patients who had both baseline and postbaseline target lesion assessments by ICR.
The line at 20% indicates PD; the line at −30% indicates PR.



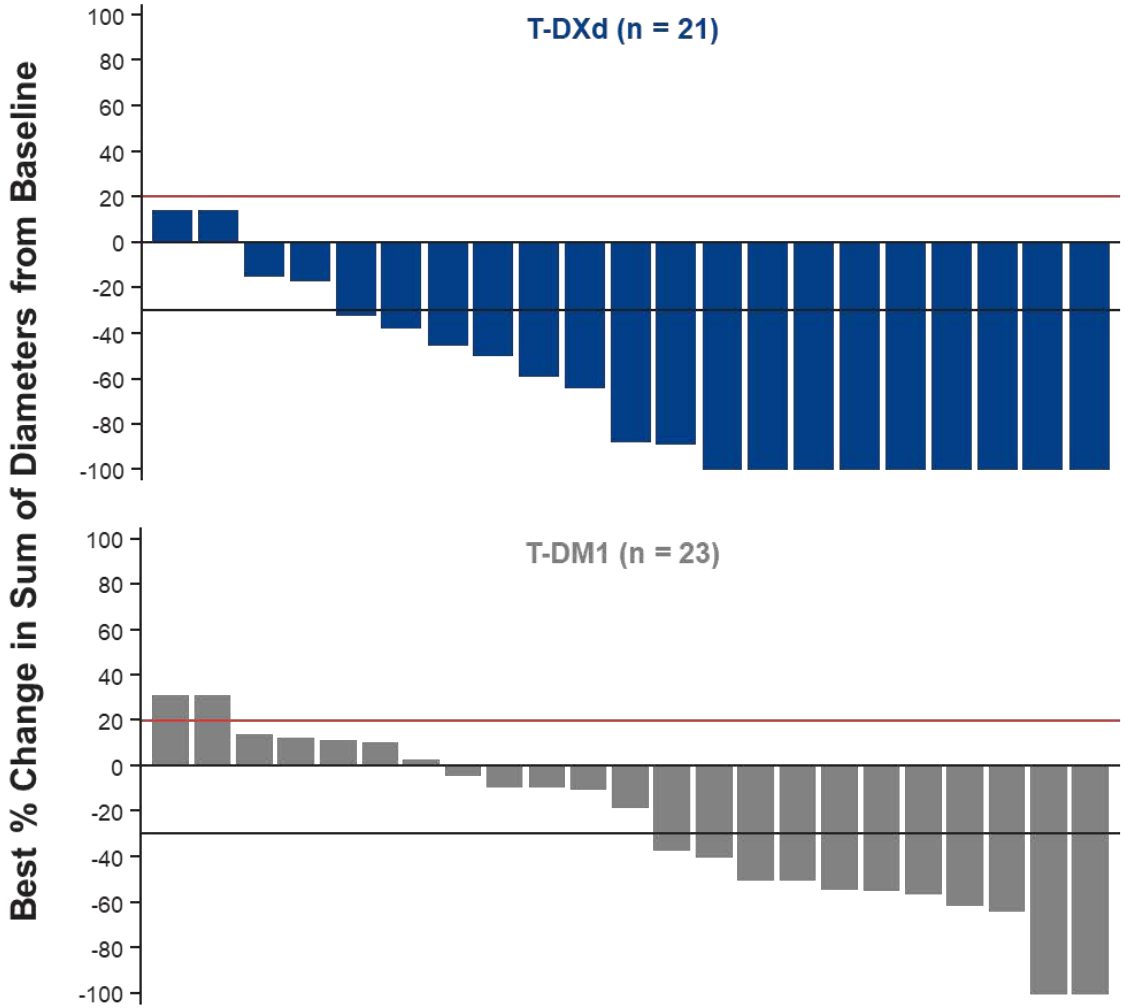
Median follow-up, 11.0 months (range, 0.7-19.6 months)

Patients who received T-DXd 5.4 mg/kg.

Jerusalem G, et al. ESMO Breast Cancer 2020.

HER2+ MBC patients with Brain Metastases
DB03

Intracranial Response per BICR using RECIST 1.1



	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

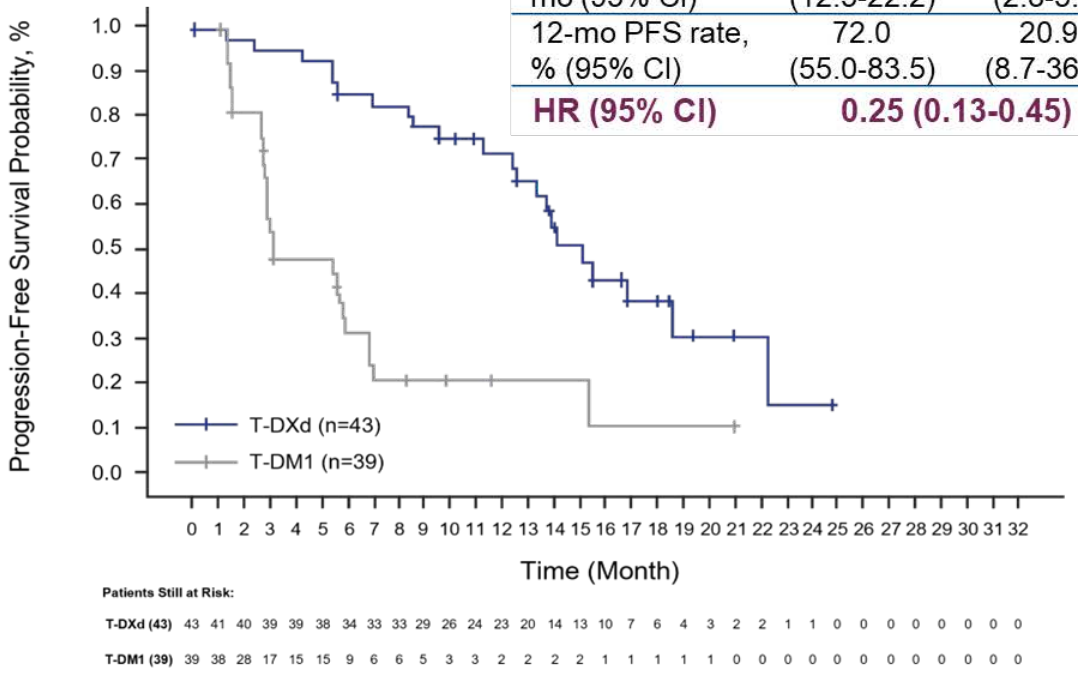
Hurvitz S, et al. SABCS 2021

HER2+ MBC patients with Brain Metastases
DB03

PFS KM Curves for Patients With and Without BM

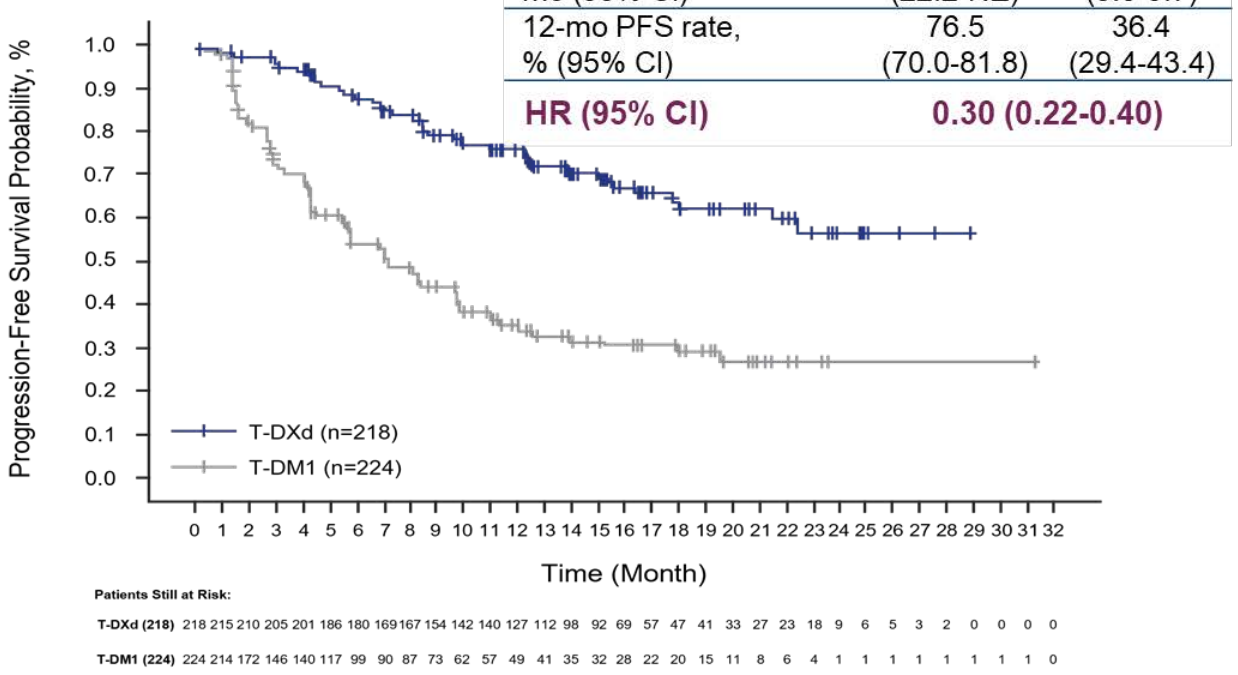
Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate, % (95% CI)	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	**0.25 (0.13-0.45)**	



No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate, % (95% CI)	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	**0.30 (0.22-0.40)**	



In patients with BM at baseline, PD was observed:

- In 48.8% (21/43) treated with T-DXd versus 69.2% (27/39) with T-DM1
- In the brain in 42.9% (9/21) treated with T-DXd versus 40.7% (11/27) with T-DM1

In patients without BM at baseline, PD was observed:

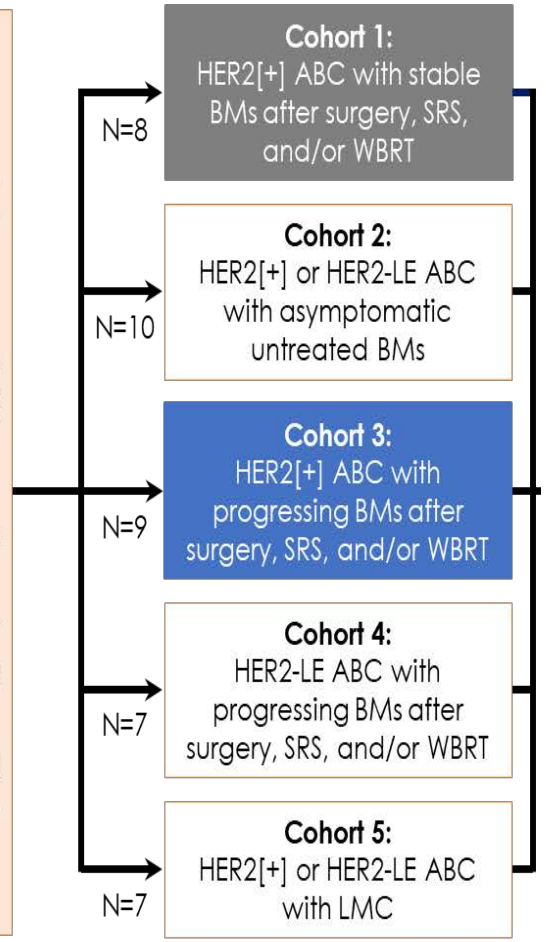
- In 28.9% (63/218) treated with T-DXd versus 57.1% (128/224) with T-DM1
- In the brain in 6.3% (4/63) treated with T-DXd versus 0.8% (1/128) with T-DM1

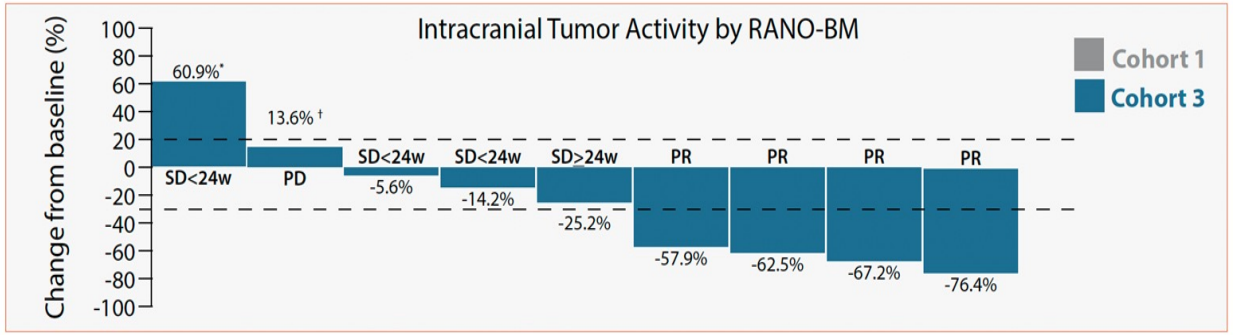
Hurvitz S, et al. SABCS 2021

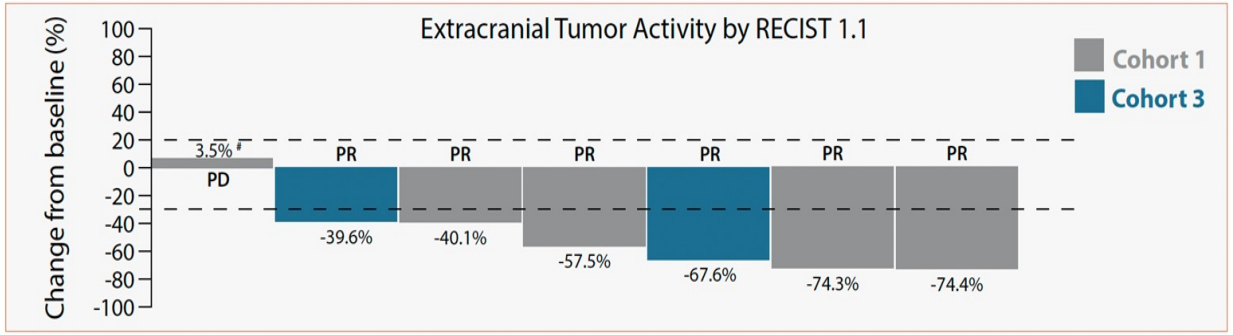
HER2+ MBC patients with Brain Metastases
DEBBRAH

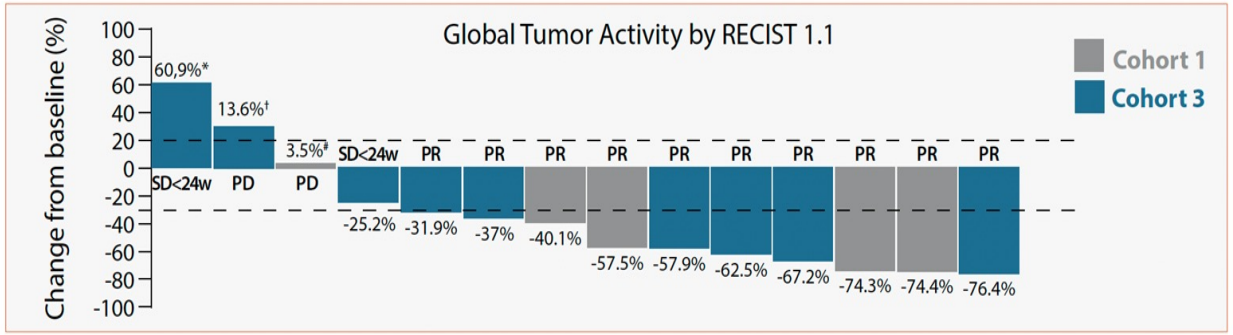
Key Eligibility Criteria

- Female or male pts aged ≥18 years
- HER2+ or HER-LE ABC with stable, progressing, or untreated BMs and/or LMC
- ECOG PS 0 or 1 (0–2 for **cohort 5**)
- Pts with HER2+ ABC: Prior treatment with a taxane and ≥1 line of anti-HER2 therapy in the metastatic setting
- Pts with HER2-LE ABC and:
  - HR-: ≥1 prior regimen of CT in the metastatic setting
  - HR+: 1 prior line of ET and ≥1 prior regimen of CT in the metastatic setting
- **Cohorts 2, 3, 4**: Measurable brain disease by on T1-weighted, gadolinium-enhanced MRI
- **Cohort 5**: LMC with CSF[+] cytology









Vaz M, et al. SABCS 2021; Perez-Garcia J, et al. Neuro-Oncology 2022

HER2+ MBC patients with Brain Metastases
TUXEDO-1

Inclusion/exclusion criteria

- Histologically confirmed HER2+ breast cancer
- Radiologically documented metastatic disease
- Newly diagnosed brain metastases or brain metastases progressing after prior local therapy
- Measurable disease (RANO-BM criteria)
- No indication for immediate local treatment
- No indication of leptomeningeal disease
- KPS >70%, ECOG <2
- Indication for systemic anti-HER2 treatment
- Prior exposure to trastuzumab and pertuzumab
- Prior exposure to T-DM1 allowed
- Life expectancy of at least 3 months
- Age >18 years
- LVEF ≥50%

→ Trastuzumab deruxtecan (5.4 mg/kg IV q3w) →

Follow up

Treatment until progression, unacceptable toxicity or withdrawal for any reason

↓

Further treatment according to local standard

Safety FU four weeks after EOT

Survival FU at 3, 9, 18 and 30 months

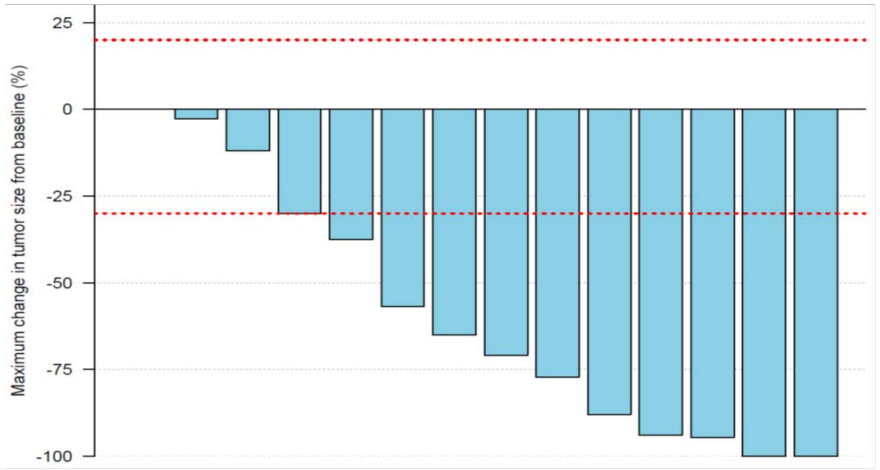
BM, brain metastasis; BW, body weight; CNS, central nervous system; D1, day 1; EOT, end of treatment; FU, follow up; IV, intravenous; KPS, Karnofsky performance; LVEF, left ventricular ejection fraction; q3w, once every 3 weeks; RANO, response assessment in neuro-oncology; T-DXd, trastuzumab deruxtecan.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

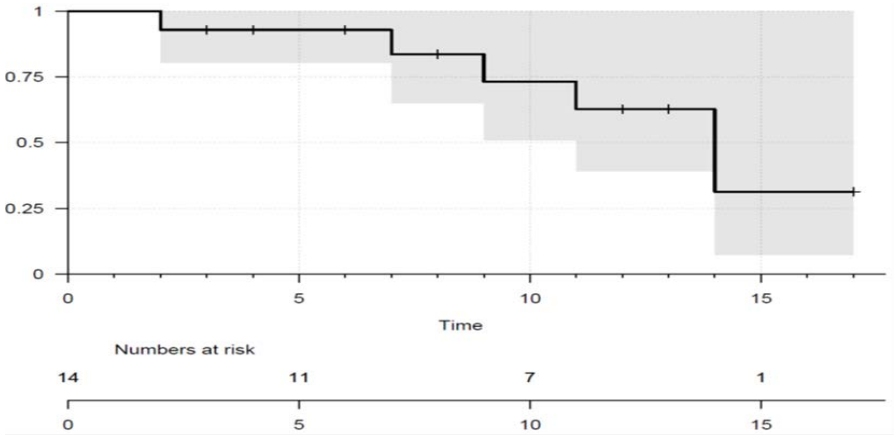
Primary Endpoint: ORR (CNS) by RANO-BM criteria

Secondary Endpoints:

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

Objective Response Rate (RANO-BM criteria)
ORR (intention-to-treat population; *n*=15): 73.3% (95% CI 48.1-89.1)



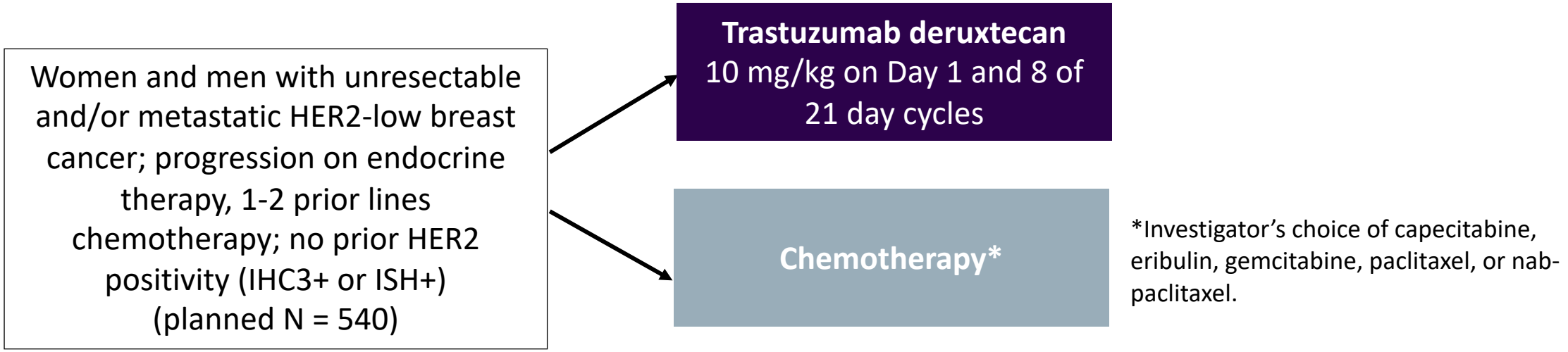


- PFS: 14 months (95% CI 11.0-n.r.)
- Median follow-up 11 months (range 3 – 17 months)

Bartsch R, et al. ESMO Breast 2022

DESTINY-Breast04: Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-low BC

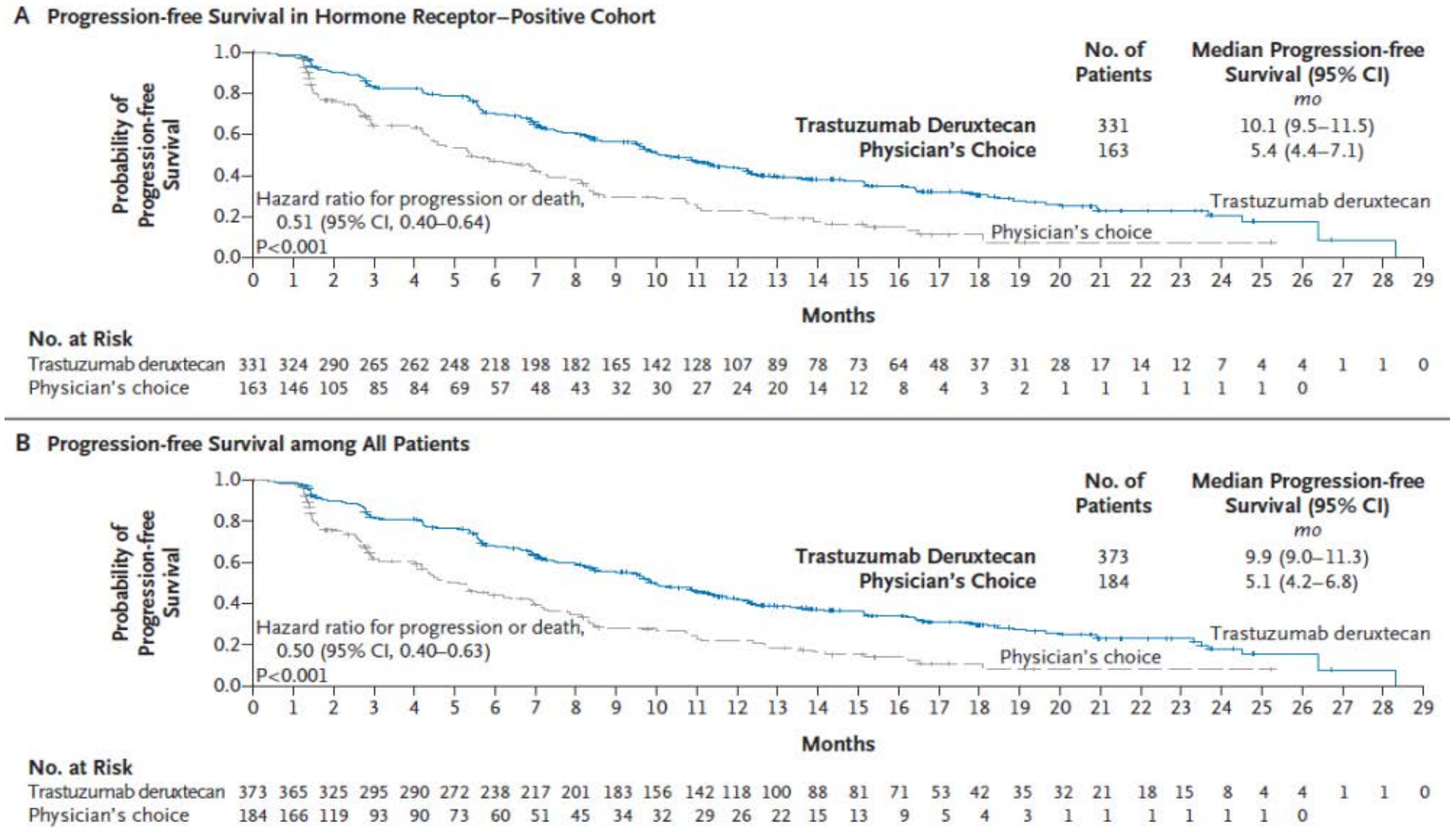
- International, randomized, open-label phase III study



- Primary endpoints: PFS per BICR in the HR+ population
- Secondary endpoints: PFS in the ITT, OS in the HR+ and ITT, DoR, ORR, PFS per investigator

Modi S, et al. ASCO 2022; Modi S, et al. NEJM 2022

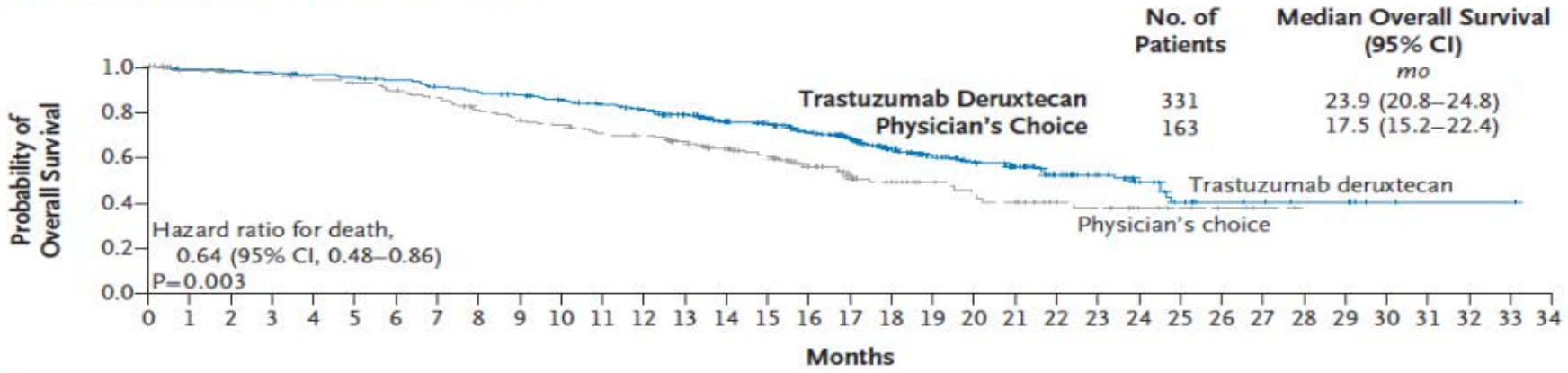
DESTINY-Breast04: Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-low BC



Modi S, et al. ASCO 2022; Modi S, et al. NEJM 2022

DESTINY-Breast04: Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-low BC

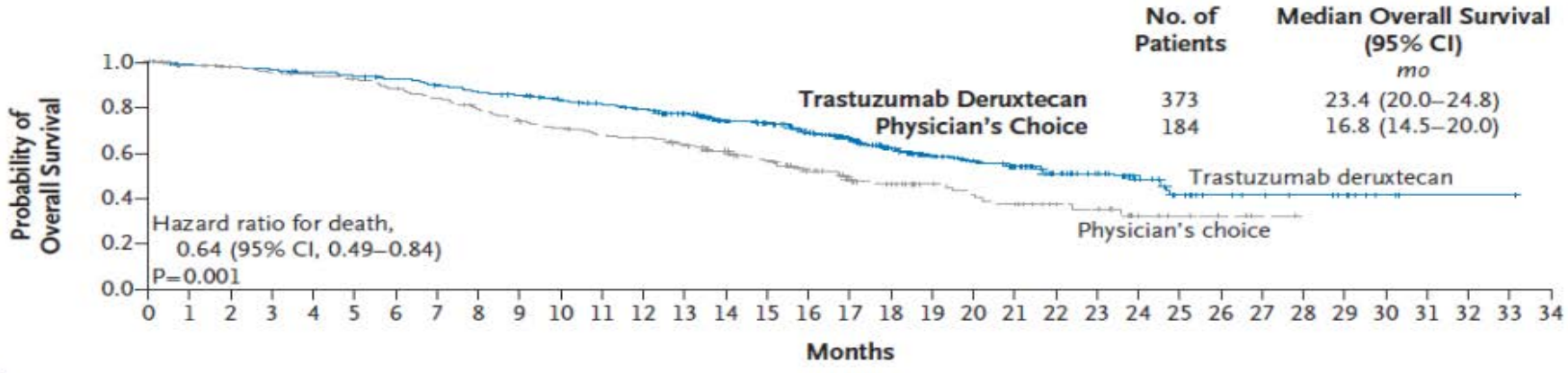
C Overall Survival in Hormone Receptor–Positive Cohort



No. at Risk

Trastuzumab deruxtecan	331	325	323	319	314	309	303	293	285	280	268	260	250	228	199	190	168	144	116	95	81	70	51	40	26	14	9	8	6	6	2	1	1	1	0
Physician's choice	163	151	145	143	139	135	130	124	115	109	104	98	96	89	80	71	56	45	37	29	25	23	16	14	7	5	3	1	0						

D Overall Survival among All Patients



No. at Risk

Trastuzumab deruxtecan	373	366	363	357	351	344	338	326	315	309	296	287	276	254	223	214	188	158	129	104	90	78	59	48	32	20	14	12	10	8	3	1	1	1	0
Physician's choice	184	171	165	161	157	153	146	138	128	120	114	108	105	97	88	77	61	50	42	32	28	25	18	16	7	5	3	1	0						

Modi S, et al. ASCO 2022; Modi S, et al. NEJM 2022

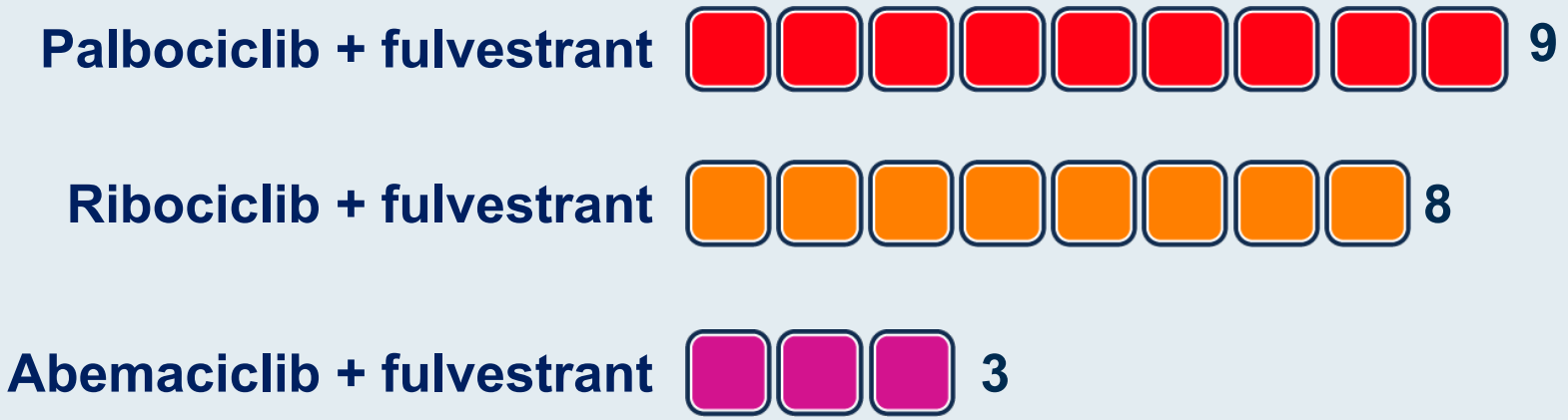
Ongoing studies to pay attention to in HER2+ MBC

HER2CLIMB-02	Randomized, Double-blind, Phase 3 Study of Tucatinib or Placebo in Combination With Ado-trastuzumab Emtansine (T-DM1) for Subjects With Unresectable Locally-advanced or Metastatic HER2+ Breast Cancer
HER2CLIMB-04	A Single Arm, Open Label Phase 2 Study of Tucatinib in Combination With Trastuzumab Deruxtecan in Subjects With Previously Treated Unresectable Locally-Advanced or Metastatic HER2+ Breast Cancer
HER2CLIMB-05	A Randomized, Double-blind, Phase 3 Study of Tucatinib or Placebo in Combination With Trastuzumab and Pertuzumab as Maintenance Therapy for Metastatic HER2+ Breast Cancer
Destiny Breast 07	A Phase 1b/2 Multicentre, Open-label, Modular, Dose-finding and Dose-expansion Study to Explore the Safety, Tolerability, and Anti-tumour Activity of Trastuzumab Deruxtecan (T-DXd) in Combination With Other Anti-cancer Agents in Patients With HER2-positive Metastatic Breast Cancer
Destiny Breast 09	Phase III Study of Trastuzumab Deruxtecan (T-DXd) With or Without Pertuzumab Versus Taxane, Trastuzumab and Pertuzumab in HER2-positive, First-line Metastatic Breast Cancer

MODULE 5: Selection and Sequencing of Therapy for ER-Positive, HER2-Negative mBC

RTP
RESEARCH
TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer has developed multiple minimally symptomatic bone metastases 2 years after starting adjuvant anastrozole. Which endocrine-based treatment would you most likely recommend?

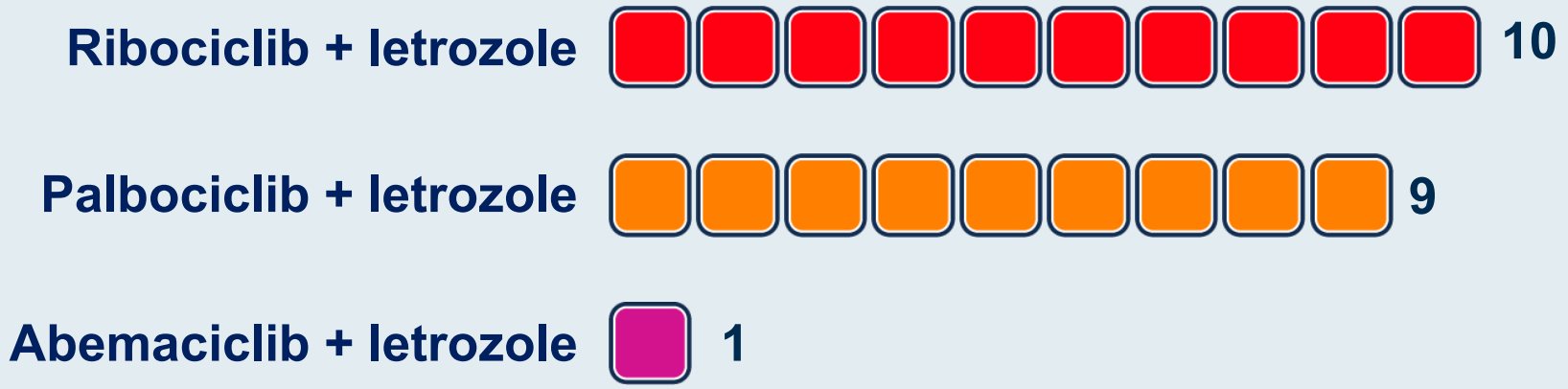


Survey of clinical investigators

A 65-year-old woman has completed 5 years of adjuvant anastrozole for an ER-positive, HER2-negative IDC but has now developed minimally symptomatic bone metastases 2 years after completing adjuvant anastrozole. Which endocrine-based treatment would you most likely recommend?

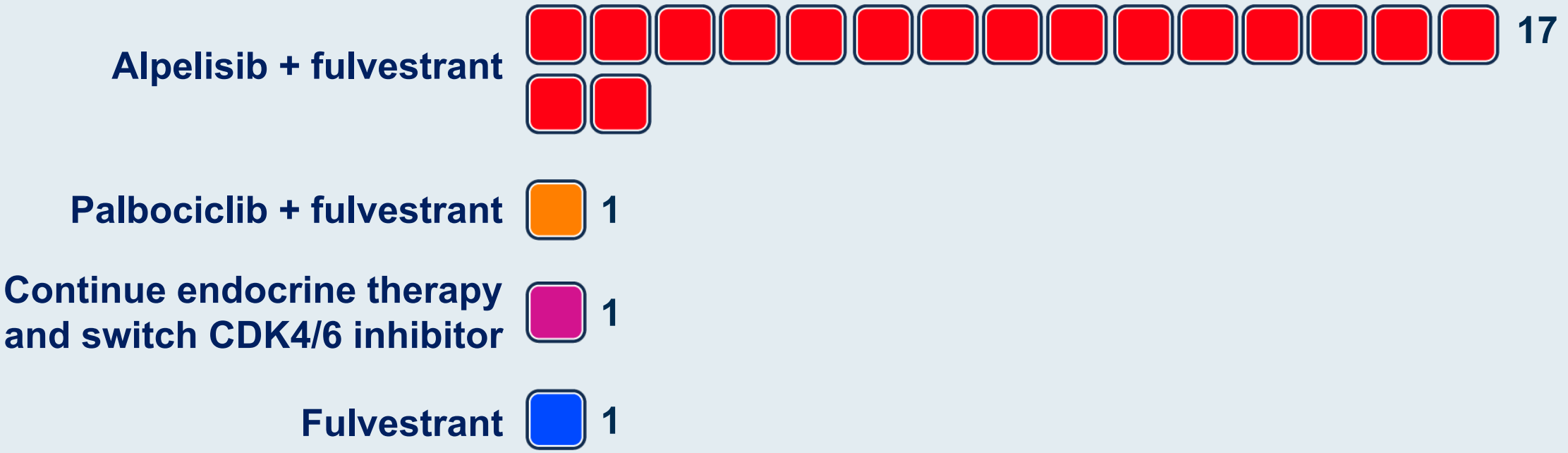
Survey of clinical investigators

A 65-year-old woman presents with de novo ER-positive, HER2-negative metastatic breast cancer (mBC) with asymptomatic bone metastases. Which endocrine-based treatment would you most likely recommend?



Survey of clinical investigators

In general, what would be your treatment approach for a 60-year-old woman with ER-positive, HER2-negative mBC who experiences asymptomatic disease progression on palbociclib/letrozole and is found to have a PIK3CA mutation?



Survey of clinical investigators

UCSF Helen Diller Family Comprehensive Cancer Center

Selection and Sequence of Therapy for ER Positive, HER2-Negative Metastatic Breast Cancer

Hope S. Rugo, MD

Professor of Medicine

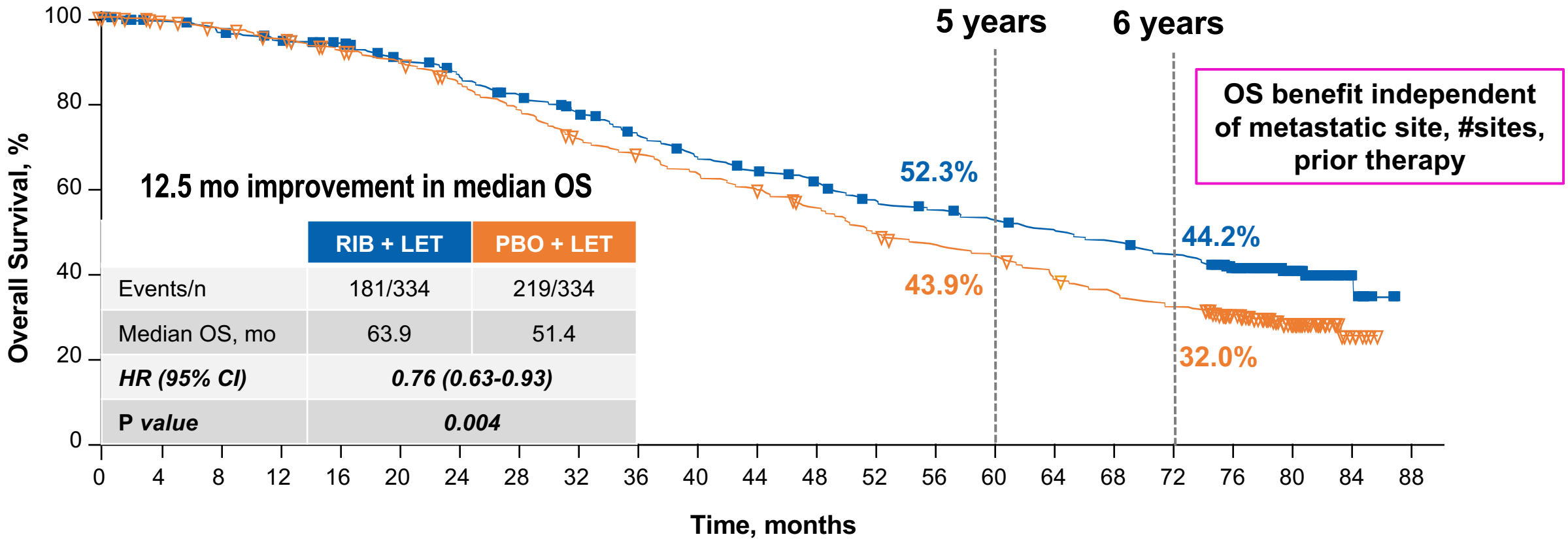
Director, Breast Oncology and Clinical Trials Education

University of California San Francisco Comprehensive Cancer Center

CDK4/6i: Phase III First-Line Studies in HR+ MBC

	Paloma-2 Finn et al, NEJM 2016; Rugo et al BCRT 2019, Finn et al, ASCO 2022	**Monaleesa-2** Hortobagyi et al, NEJM 2016; Ann Oncol 2018; Slamon JCO 2018, Hortobagyi et al, NEJM 2022	**Monaleesa-3** Slamon et al, NEJM 2020; Ann Onc 2022; Neven et al, ESMO BC 2022	**Monarch-3** Goetz et al,JCO 2017; Johnston et al, NPJ Breast 2019	**Monaleesa-7** Tripathy et al Lancet Oncol 2018; Im et al, NEJM 2019; Lu et al CCR 2022
Study design	**Letrozole/Pla vs Let/Palbociclib (1:2)**	**Letrozole/Pla vs Let/Ribociclib (1:1)**	**Fulvestrant/Pla vs Fulv/Ribociclib (2:1; 1st line subset)**	**Letrozole/Pla vs Let/Abemaciclib (1:2)**	**AI or TAM/Pla vs AI or Tam+OS/Ribociclib (1:1)**
Eligibility	**Postmenopausal First line**	**Postmenopausal First line**	**Postmenopausal First Line DFI>12 mo**	**Postmenopausal First line DFI>12 mo**	**Pre/perimenopausal One prior chemo allowed (14%)**
No. of pts	666 *No progression on AIs* ***DFI≤12 mo: 22%***	668 *No progression on AIs* ***DFI≤12 mo: 1-3%***	365 1st line/726 total *No progression on AIs* ***DFI≤12 mo: not allowed***	493 *No progression on Ais* ***DFI≤12 mo: not allowed***	672 **DFI≤12 mo 30% 60% no prior E rx**
PFS	**14.5 vs 27.6 mo** HR 0.56 (0.46-0.69) p<0.000001	**16.0 vs 25.3 mo** HR 0.556 (0.43-0.72); p=0.00000329	**19.2 vs 33.6 1st line** HR 0.55 (0.49-0.71) *(descriptive update)*	**14.8 vs 28.2 mo** HR 0.54 (0.418-0.698) P=0.00002	**13.0 vs 23.8 mo.** HR 0.55 (0.44-0.69) P<0.0001
OS	Median FU 90 mo **Med OS 51.2 v 55.9 mo HR 0.956 (0.777-1.777)** P=0.338 DFI>12 mo (41%) **Med OS 47.4 v 66.3 mo HR 0.728 (0.528-1.005)**	Median FU 80 mo **Med OS 51.4 v 63.9 mo HR 0.76 (0.63-0.93) P=0.004**	Median FU 70.8 mo. **Med OS 51.8 v 67.6 mo HR 0.67 (0.50-0.90)**	Not Reported	Median FU 53.5 mo **Median OS: 58.7 v 48mo HR 0.763 (0.608-0.956)**

Ribociclib Achieved Statistically Significant OS Benefit in the ML-2 ITT Population

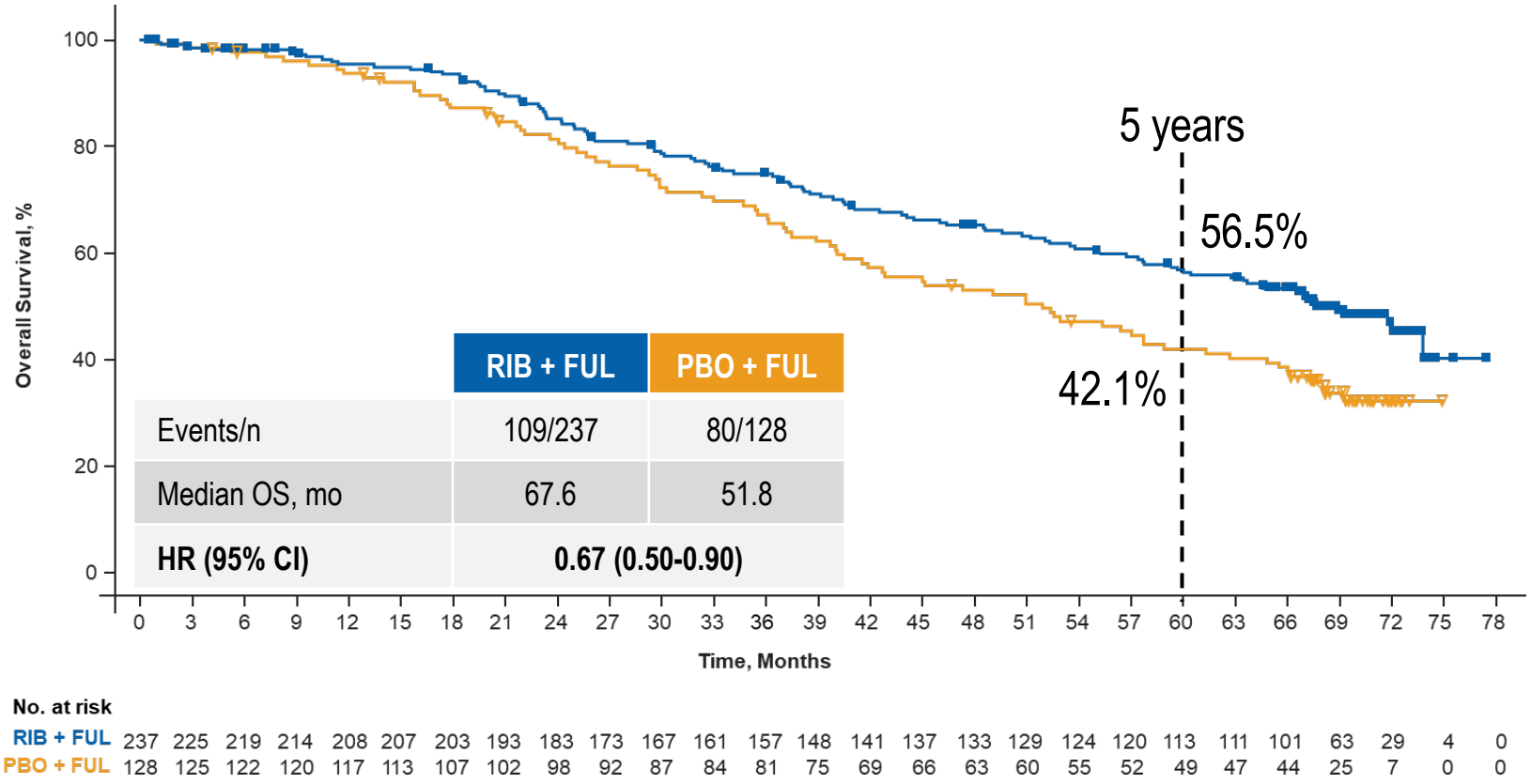


HR, hazard ratio; ITT, intention to treat; LET, letrozole; ML-2, MONALEESA-2; OS, overall survival; PBO, placebo; RIB, ribociclib.

Hortobagyi et al. NEJM 2022

ML-3: Median OS With First-Line Ribociclib Was 67.6 Months*

Ribociclib demonstrated a 15.8-month longer median OS and a relative reduction in the risk of death of 33% vs placebo



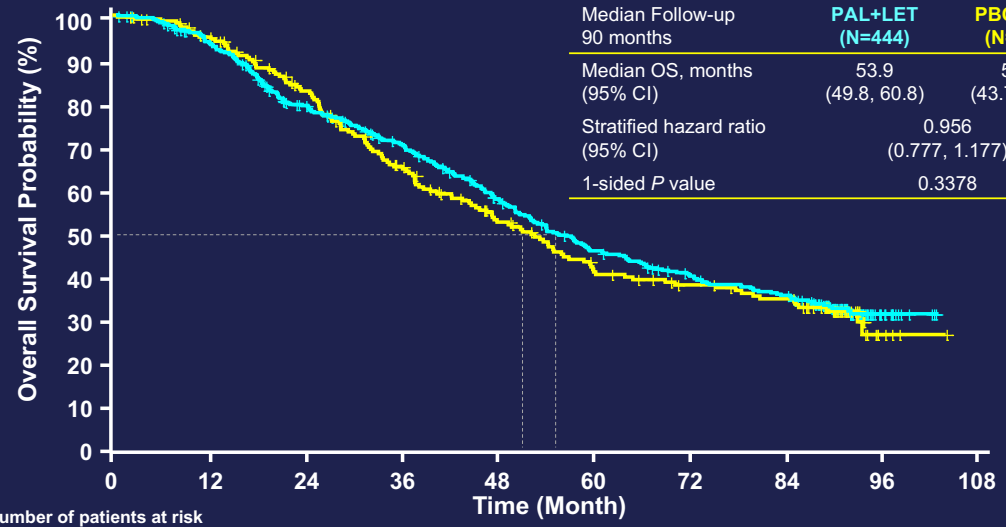
- ~50% of trial population was first-line (n=365)
- Median duration of follow-up from randomization to data cutoff was 70.8 months (minimum, 67.3 months)
- At 5 years, the survival rate of patients receiving ribociclib was 56.5%

FUL, fulvestrant; OS, overall survival; PBO, placebo; RIB, ribociclib.
Data cutoff, January 12, 2022.
* Patients continuing study treatment at the time of data cutoff (January 12, 2022): 16.5% with ribociclib + fulvestrant vs 8.6% with placebo + fulvestrant.

Neven et al, ESMO BC 2022

PALOMA-2 Overall Survival

Overall Survival – ITT

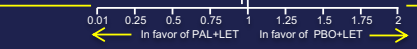


Median Follow-up 90 months	PAL+LET (N=444)	PBO+LET (N=222)
Median OS, months (95% CI)	53.9 (49.8, 60.8)	51.2 (43.7, 58.9)
Stratified hazard ratio (95% CI)	0.956 (0.777, 1.177)	
1-sided *P* value	0.3378	

ITT=intent-to-treat; LET=letrozole; OS=overall survival; PAL=palbociclib; PBO=placebo.

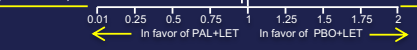
Overall Survival in Subgroups – ITT Population

Subgroup		n (%)	Hazard Ratio (95% CI)
All randomized patients		666 (100)	0.956 (0.777, 1.177)
Age	<65 y	404 (60.7)	1.007 (0.772, 1.314)
	≥65 y	262 (39.3)	0.871 (0.624, 1.216)
Region	North America	267 (40.1)	0.866 (0.630, 1.191)
	Europe	307 (46.1)	1.128 (0.826, 1.542)
	Asia/Pacific	92 (13.8)	0.744 (0.408, 1.358)
ECOG performance status	0	359 (53.9)	1.297 (0.933, 1.803)
	1/2	307 (46.1)	0.807 (0.611, 1.066)
Disease site	Visceral	324 (48.6)	0.916 (0.687, 1.221)
	Non-visceral	342 (51.4)	0.992 (0.734, 1.342)
Disease-free interval	De novo metastatic	248 (37.2)	1.193 (0.836, 1.701)
	≤12 months	146 (21.9)	1.021 (0.662, 1.577)
	>12 months	272 (40.8)	0.728 (0.528, 1.005)
Prior endocrine therapy	Yes	376 (56.5)	0.801 (0.612, 1.046)
	No	290 (43.5)	1.197 (0.858, 1.669)
Prior chemotherapy	Yes	322 (48.3)	0.869 (0.651, 1.159)
	No	344 (51.7)	1.046 (0.774, 1.414)
Bone-only disease	Yes	151 (22.7)	0.712 (0.462, 1.097)
	No	515 (77.3)	1.029 (0.811, 1.305)
Number of disease sites	1	204 (30.6)	0.879 (0.603, 1.283)
	2	169 (25.4)	0.938 (0.587, 1.500)
	≥3	293 (44.0)	1.045 (0.777, 1.404)



Overall Survival in Subgroups – ITT Population

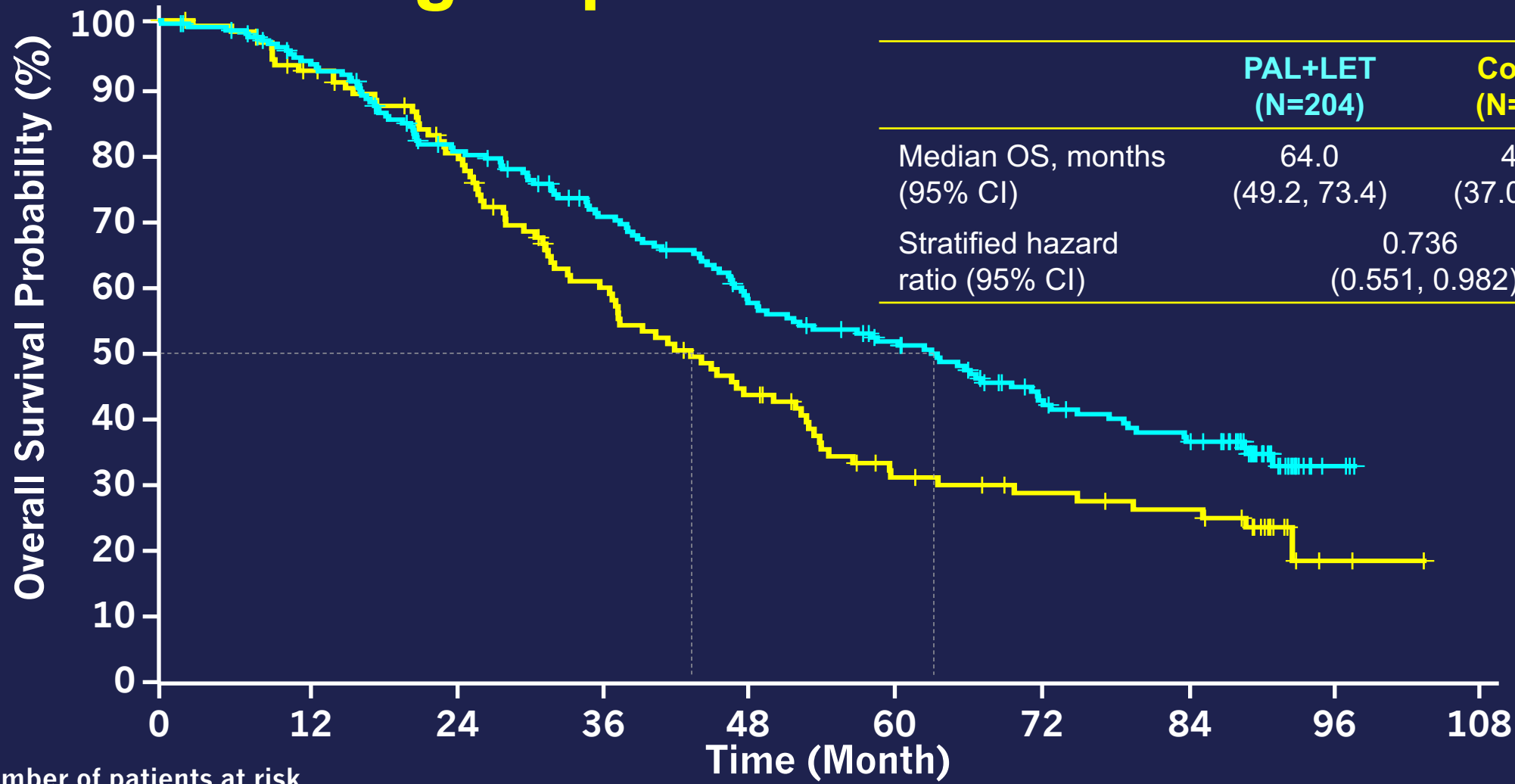
Subgroup		Median OS (95% CI)		Missing Survival Data (%)	
		PAL+LET	PBO+LET	PAL+LET	PBO+LET
All randomized patients		53.9 (49.8, 60.8)	51.2 (43.7, 58.9)	13	21
Age	<65 y	53.3 (47.0, 60.8)	54.4 (44.8, 60.2)	11	21
	≥65 y	58.6 (49.8, 66.7)	47.4 (36.2, 60.4)	17	21
Region	North America	53.8 (47.3, 61.3)	49.4 (37.0, 57.0)	16	23
	Europe	52.3 (46.0, 63.8)	53.8 (42.3, 78.7)	11	17
	Asia/Pacific	73.4 (47.3, NE)	55.1 (32.2, NE)	14	29
ECOG performance status	0	58.2 (52.1, 66.0)	85.9 (53.8, NE)	11	28
	1/2	47.3 (41.3, 60.8)	38.8 (32.2, 49.8)	16	16
Disease site	Visceral	48.1 (42.3, 53.8)	44.8 (32.2, 53.8)	13	23
	Non-visceral	60.8 (53.8, 72.3)	59.7 (47.4, 85.3)	14	20
Disease-free interval	De novo metastatic	54.6 (47.0, 69.1)	60.4 (49.8, 93.8)	10	24
	≤12 months	45.7 (36.1, 51.1)	37.7 (27.1, 56.4)	12	29
	>12 months	66.3 (52.1, 79.7)	47.4 (37.7, 57.0)	17	15
Prior endocrine therapy	Yes	53.3 (48.0, 62.9)	44.6 (34.3, 52.8)	16	18
	No	55.1 (47.3, 71.4)	60.4 (49.8, 93.8)	10	25
Prior chemotherapy	Yes	51.6 (45.6, 58.6)	44.6 (36.2, 54.4)	13	18
	No	58.4 (50.5, 71.7)	58.9 (47.7, 81.0)	14	24
Bone-only disease	Yes	63.5 (53.9, 79.7)	52.3 (42.3, 59.7)	16	15
	No	51.6 (46.9, 57.6)	49.8 (38.8, 60.4)	13	23
Number of disease sites	1	59.1 (53.8, 73.9)	54.4 (45.4, 70.3)	15	18
	2	60.8 (47.9, 87.2)	54.5 (33.5, NE)	15	37
	≥3	48.1 (41.3, 53.8)	45.8 (32.4, 57.0)	12	15



ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; LET=letrozole; NE=not estimable; PAL=palbociclib; PBO=placebo.

Finn et al, ASCO 2022

PALOMA-1 and PALOMA-2 Combined OS Analysis: Subgroup DFI >12 months



	PAL+LET (N=204)	Control (N=123)
Median OS, months (95% CI)	64.0 (49.2, 73.4)	44.6 (37.0, 53.2)
Stratified hazard ratio (95% CI)	0.736 (0.551, 0.982)	

Number of patients at risk

PAL+LET	204	185	154	130	106	88	68	57	3	0
Control	123	109	91	66	48	32	25	22	2	0

DFI=disease-free interval; LET=letrozole; OS=overall survival; PAL=palbociclib.

CDK 4/6i: Progression on Prior NSAI. Prior Therapy Matters!

	PALOMA 3 Turner et al, NEJM 2015, 2018; Cristofanilli Lancet Onc 2016; Rugo et al Oncologist 2021; Cristofanilli, CCR 2022	MONARCH 2 Sledge et al, JCO 2017 JAMA Oncol, 2020	MONALEESA 3 Slamon et al, JCO 2018 NEJM 2020, Ann Oncol 2021
Study design	**Fulv/pla vs fulv/ palbociclib**	**Fulv/pla vs fulv/ abemaciclib**	**Fulv/pla vs fulv/ ribociclib**
Patient #	**521**	**699**	**345 2nd line/726 total**
PFS **p value (HR)**	4.6 v 9.5 mo **HR 0.46 (0.36-0.59)** P<.0001	9.3 v 16.4 mo **HR 0.553 (0.606-0.945)** P<.001	ITT (1st+2nd line) 12.8 v 20.6 mo HR 0.59 (0.49-0.71) 2nd line: 9.1 v 14.6 **HR 0.571 (0.44-0.74)**
Time from randomization to chemotherapy	**8.8 vs 17.6 mo** **HR 0.583**	**22.1 vs 50.2 mo** **HR 0.625**	**ITT: 28.8 vs 48.1 mo** **HR 0.70**
Prior chemotherapy for metastatic disease	**31-36%**	**None**	**None**
Prior endocrine Rx	**Any number of lines**	**1**	**0 or 1**
OS	28 vs 34.9 mo **HR 0.791 (0.626-0.999)** **P=0.0246 (NS)** **No prior chemotherapy (66%)** 29.7 v 39.3 mo **HR 0.72 (0.55-0.94)** *Nominal p value 0.008*	37.3 vs 46.7 mo **HR 0.757 (0.606-0.945)** **P=0.01**	ITT (1st+2nd line) : 41.5 v 53.7 mo **HR 0.73 (0.59–0.90)** 2nd line 33.7 vs 39.7 mo, **HR 0.8 (0.59-1.04)**

Continuing CDK4/6i Post Progression: Primary Results of the MAINTAIN Trial

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

1:1

N=120

Arm 1
Ribociclib + Switch Endocrine Therapy*

Arm 2
Placebo + Switch Endocrine Therapy*

Primary Endpoint
- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints
- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and Blood Markers, including circulating tumor DNA

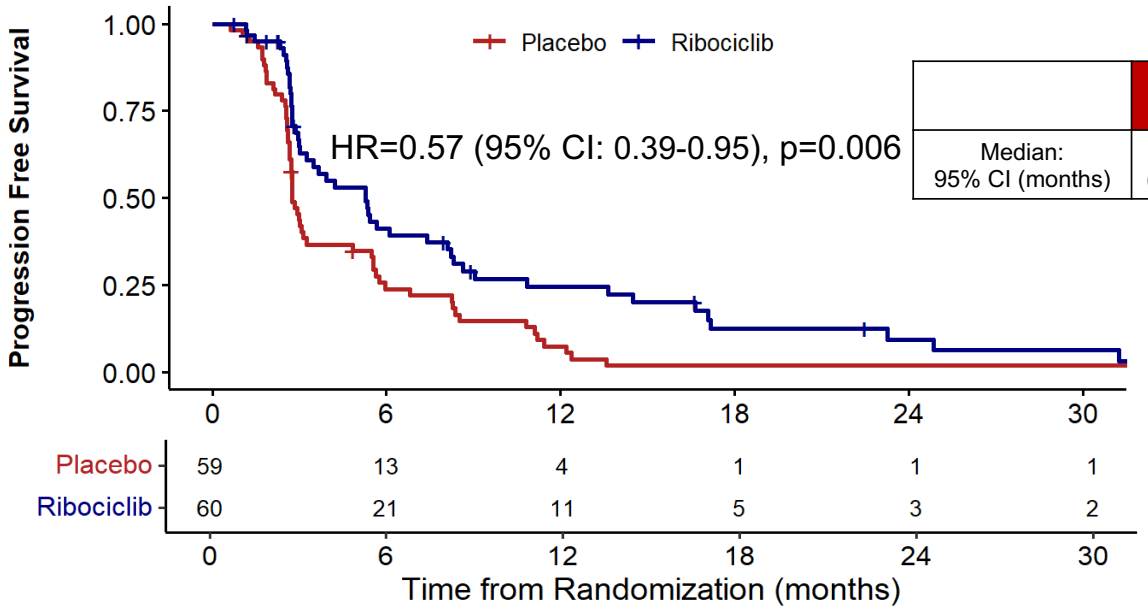
170 screened, 119 randomized
9 remain on rx, 1=placebo and 8=ribociclib
99 received fulvestrant
20 received exemestane

- Investigator initiated trial, 13 US sites
- Primary endpoint PFS, scans q 12 wks
- Median FU 18.2 mo
- 54 v 35% de novo MBC
- Visceral mets ~60%
- 12 v 7% chemo for MBC
- 10 v 2% intervening Rx post CDK4/6i
- 64 v 70% prior CDK4/6i>12 months

Kalinsky et al, ASCO 2022

Results

Primary Endpoint: Progression Free Survival (PFS)

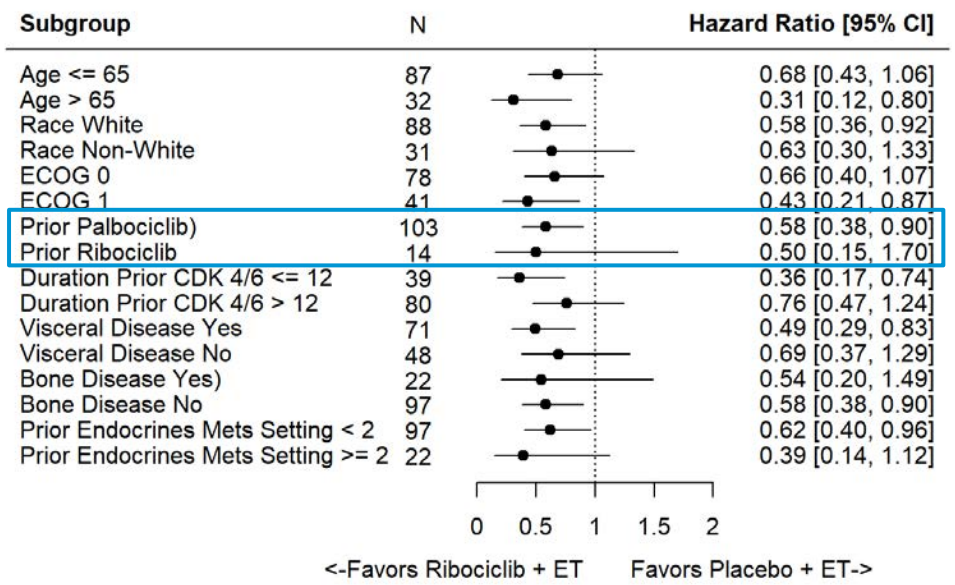


	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

Fulvestrant	Placebo (n=50)	Ribociclib (n=49)
Median (95% CI) (mos)	**2.76** (2.66-3.25)	**5.29** (2.96-8.12)

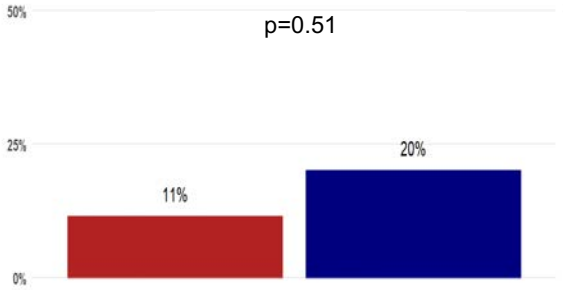
Exemestane	Placebo (n=9)	Ribociclib (n=11)
Median (95% CI) (mos)	**3.06** (1.84-5.95)	**5.36** (3.02-14.50)

Progression Free Survival by Subgroup



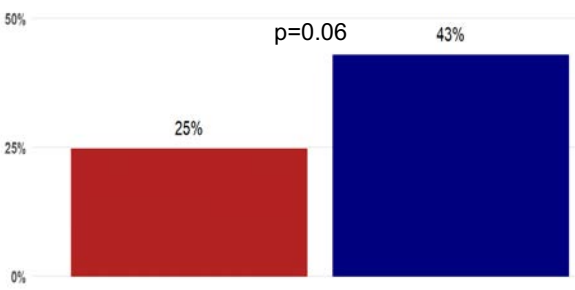
Overall Response and Clinical Benefit Rate

Overall Response Rate (n=70)



	Placebo + ET (n=35)	Ribociclib + ET (n=35)
CR	0 (0%)	2 (6%)
PR	4 (11%)	5 (14%)
Median DOR (IQR) (mos)	14.8 (6.7-21.3)	18.8 (11.4-50.2)

Clinical Benefit Rate (n=105)

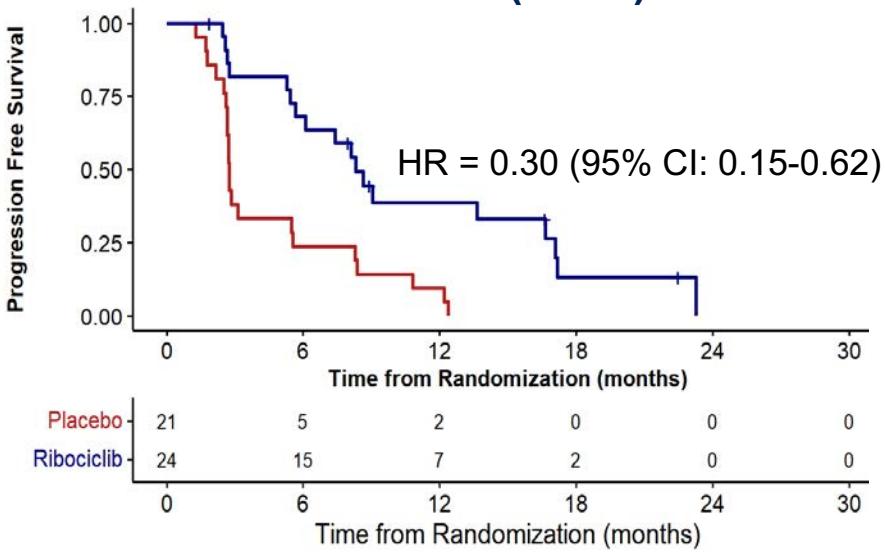


	Placebo + ET (n=57)	Ribociclib + ET (n=49)
CR, PR, or SD ≥ 24 weeks	14 (25%)	21 (43%)

IQR = Interquartile Range, CR = Complete response, PR = Partial Response, DOR = Duration of Response, SD = Stable Disease

Exploratory Analysis
PFS: Fulvestrant and *ESR1* Mutation Status

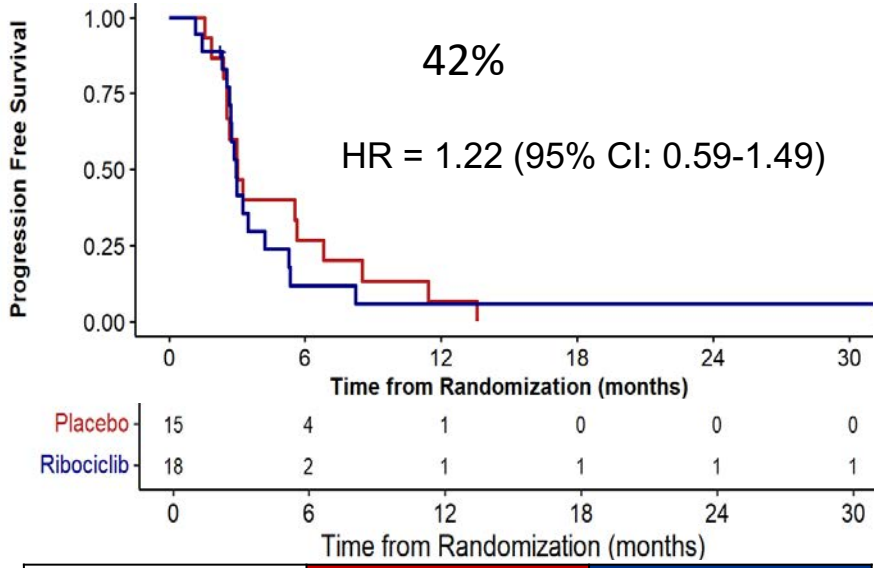
ESR1 WT (n=45)



	Placebo (n=21)	Ribociclib (n=24)
Median (95% CI) (mos)	**2.76** (2.66-5.49)	**8.32** (5.65-16.63)

0/24 pts (0%) had *CCND1* and/or *FGFR1* amplification on ribociclib arm

ESR1 Mutant (n=33)



	Placebo (n=15)	Ribociclib (n=18)
Median (95% CI) (mos)	**3.02** (2.53-5.62)	**2.96** (2.66-4.21)

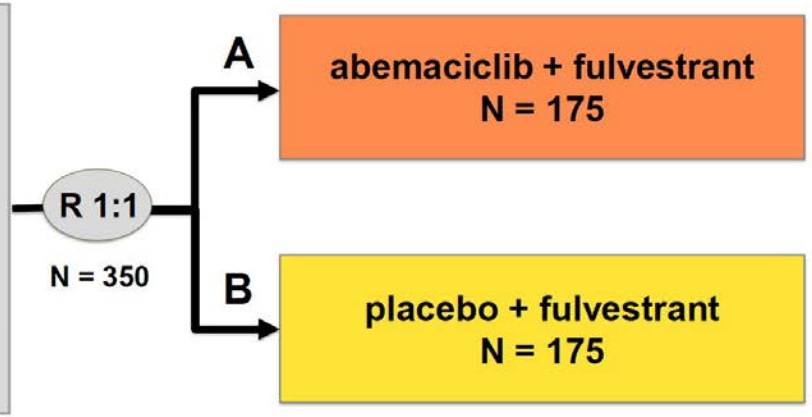
9/18 (50%) pts with *CCND1* and/or *FGFR1* amplification on ribociclib arm

Conclusions

- 1st prospective trial to show benefit from continuing/changing CDKi with progression
- PFS benefit was limited to ESR1 WT disease (significant co-mutations, exploratory)
- Validation needed
  - Ongoing postMONARCH study (Kalinsky PI)

Key Inclusion Criteria

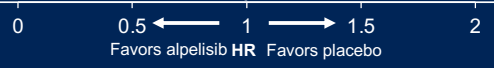
- HR+, HER2- MBC
- Men, or pre- and postmenopausal women
- Prior therapy:
  - Advanced setting: Disease progression on CDK4 & 6 inhibitor plus an aromatase inhibitor (AI) as initial therapy, **OR**
  - Adjuvant setting: Disease recurrence on or after CDK4 & 6 inhibitor plus ET



SOLAR-1 Biomarker Analysis

Alpelisib + FUL Is Effective Regardless of Gene Alteration Status

Gene	Placebo + FUL n/N	Placebo + FUL mPFS, mo	Alpelisib + FUL n/N	Alpelisib + FUL mPFS, mo	HR by Gene and Treatment	HR[a] (95% CI)
***TP53* WT**	**69/81**	**7.3**	**69/94**	**12.0**		**0.56 (0.39-0.80)**
TP53 Alt[b]	32/36	3.7	21/26	8.5		0.49 (0.28-0.87)
***ESR1* WT**	**90/105**	**5.5**	**78/107**	**11.0**		**0.51 (0.37-0.70)**
ESR1 Alt[b]	11/12	6.5	12/13	12.0		0.70 (0.29-1.67)
***CCND1* WT**	**75/84**	**5.7**	**67/89**	**11.2**		**0.47 (0.33-0.66)**
CCND1 Alt[b]	26/33	3.6	23/31	9.2		0.77 (0.43-1.37)
***MAP3K1* WT**	**90/104**	**5.5**	**81/107**	**10.9**		**0.54 (0.40-0.75)**
MAP3K1 Alt[b]	11/13	7.7	9/13	17.3		0.44 (0.17-1.10)
***ARID1A* WT**	**90/102**	**5.5**	**85/109**	**10.9**		**0.51 (0.37-0.70)**
ARID1A Alt[b]	11/15	12.4	5/11	22.1		0.50 (0.17-1.49)



[a]HR was calculated by adjusting additional biomarker variables TMB and PTEN Loss. [b]Data should be interpreted with caution due to the small sample size.
Alt, altered; *ARID1A*, AT-rich interaction domain 1A; *CCND1*, cyclin D1; *ESR1*, estrogen receptor 1; FUL, fulvestrant; HR, hazard ratio; *MAP3K1*, mitogen-activated protein kinase kinase 1; mPFS, median progression-free survival; *TP53*, tumor protein p53; WT, wild-type.

- Alpelisib had clinical benefit regardless of mutation status of selected genes, MAPK & PI3K pathway genes, or CDK4/6i resistance genes
  - More benefit with FGFR1/FGFR2 alterations, limited with MYC/RAD21
  - Longer mPFS with low TMB and alpelisib Rx
- The results in this analysis are hypothesis generating because of the small sample size

Juric et al, ASCO 2022

Update from FAKTION: Capivasertib + Fulvestrant for AI-Resistant ER+/HER2- Metastatic Breast Cancer

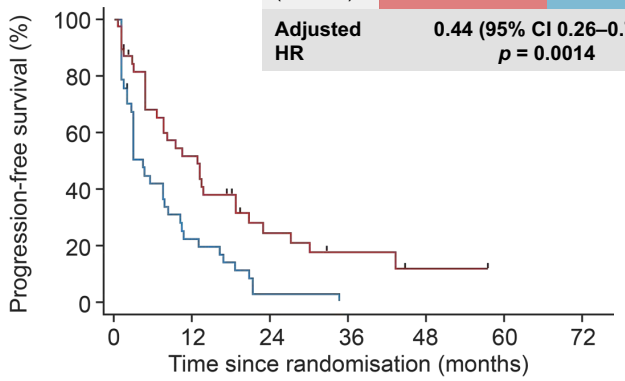
- Randomized phase II study of capivasertib + FULV vs placebo + FULV (N = 140)
  - Capivasertib: selective, oral AKT inhibitor
  - Improved PFS in all patients in the first analysis
  - No prior CDK4/6i
- NGS employed to further analyze the PIK3CA/MAPK pathway
  - Median FU 58.5 mo
- NGS identified 25% with mutations originally classified as non-altered
  - Overall, expanded testing with NGS detected PI3K/AKT/PTEN pathway alterations in 54% of participants (compared to 42% by the original testing methods)
- Primary toxicities: Diarrhea and rash
  - 39% of patients in the capivasertib + FULV arm required dose reductions, primarily due to diarrhea and rash, and 12% discontinued due to toxicity

Jones RH, et al. Lancet Oncol 2020.; ASCO 2022; Howell et al, Lancet Oncology 2022

- Capivasertib predominately benefited patients with alterations in the PIK3CA pathway
  - Median PFS 12.8 vs 4.6 months (HR 0.44; *p* = 0.0014)
  - Median OS 39.8 vs 20 months (HR 0.46; *p* = 0.005)
- The Phase III CAPItello-291 (NCT04305496) has completed accrual
  - Subset analysis planned

Pathway altered

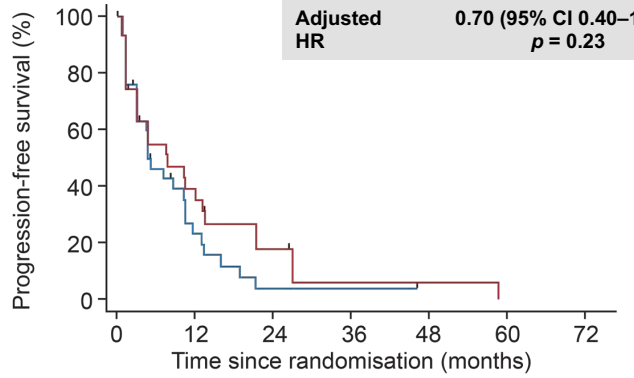
	Fulvestrant + capivasertib (n = 39)	Fulvestrant + placebo (n = 37)
Median PFS (95% CI)	12.8 months (6.6–18.8)	4.6 months (2.8–7.9)
Adjusted HR	0.44 (95% CI 0.26–0.72); *p* = 0.0014	



Number at risk							
Fulvestrant plus placebo	37	8	1	0	0	0	0
Fulvestrant plus capivasertib	39	19	7	3	1	0	0

Pathway non-altered

	Fulvestrant + capivasertib (n = 30)	Fulvestrant + placebo (n = 34)
Median PFS (95% CI)	7.7 months (3.1–13.2)	4.9 months (3.2–10.5)
Adjusted HR	0.70 (95% CI 0.40–1.25); *p* = 0.23	



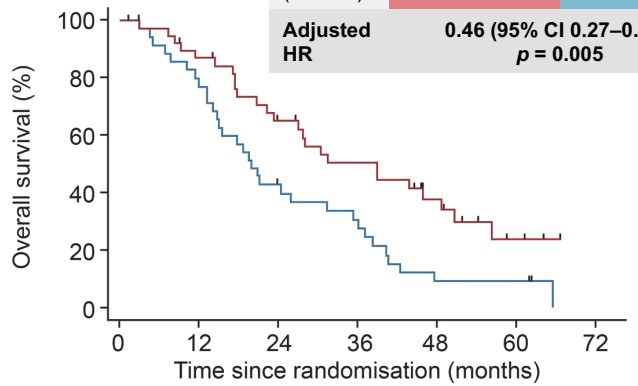
Number at risk							
Fulvestrant plus placebo	34	6	1	1	0	0	0
Fulvestrant plus capivasertib	30	10	4	1	1	0	0

CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

DCO Nov 2021

Pathway altered

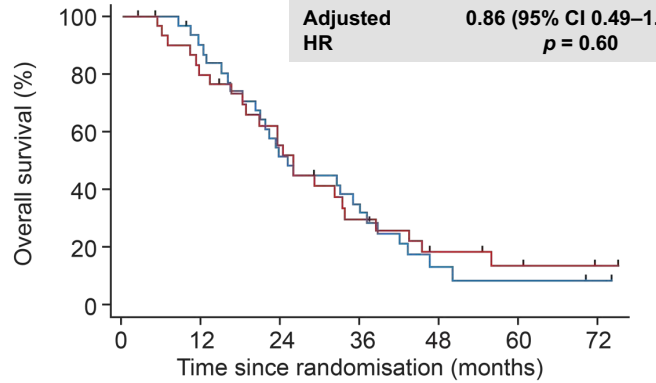
	Fulvestrant + capivasertib (n = 39)	Fulvestrant + placebo (n = 37)
Median OS (95% CI)	38.9 months (23.3–50.7)	20.0 months (14.8–31.4)
Adjusted HR	0.46 (95% CI 0.27–0.79); *p* = 0.005	



Number at risk							
Fulvestrant plus placebo	37	27	14	10	3	3	0
Fulvestrant plus capivasertib	39	33	23	17	10	3	0

Pathway non-altered

	Fulvestrant + capivasertib (n = 30)	Fulvestrant + placebo (n = 34)
Median OS (95% CI)	26.0 months (18.4–33.8)	25.2 months (20.3–36.2)
Adjusted HR	0.86 (95% CI 0.49–1.52); *p* = 0.60	



Number at risk							
Fulvestrant plus placebo	34	28	16	11	3	2	1
Fulvestrant plus capivasertib	30	24	16	8	5	3	1

CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

Next Steps: Phase III trials of AKT Inhibition in HR+ MBC

Capivasertib

- **CAPItello-291** (NCT04305496): Fulvestrant +/- Capi after AI
- **CAPItello-292** (NCT04862663): Fulvestrant/Palbociclib +/- Capi

Ipatasertib

- **FINER** (NCT04650581): Fulvestrant +/- Ipat after CDK4/6 inhibitor
- **IPATunity150** (NCT04060862): Fulvestrant/Palbociclib +/- Ipat

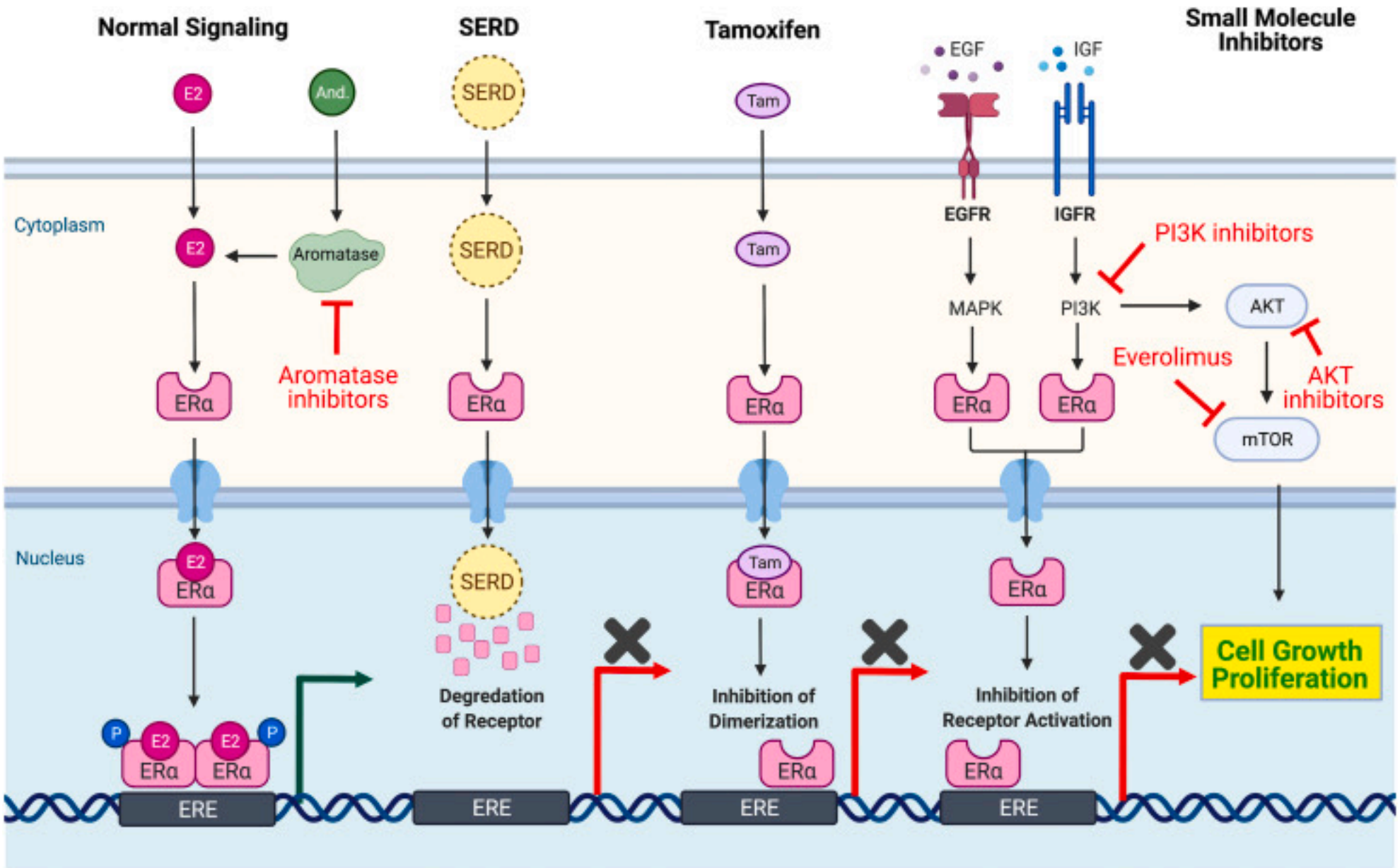
New PI3K inhibitors

- **Inavolisib:** phase II/III in patients with PIK3CA mutations; fulvestrant/Palbociclib +/- Inavolisib; phase Ib with giredestrant
  - Phase I/II trial, N=57. 68% hyperglycemia, 68% stomatitis (Bedard et al, ASCO 2022)
- **LOX783**: Brain-penetrant allosteric PI3Kα H1047R inhibitor; phase I

And more……

- SARM: selective androgen receptor modulator
  - Enobosarm: ORR 48%, CBR 80%, and median PFS 5.5 months in AR+++ (n=24); Phase III ARTEST trial in 3rd line metastatic setting
  - Fast track designation by FDA
- SERM: Lasofoxifene
  - Elaine 2: n=29 with abemaciclib: CBR 69% at 24 wks (ORR 50%), PFS 13 months
    - DVT 6.9% (n=2), one with risks (knee surgery etc)
  - Elaine 1: Phase II in ESR1 mut v fulvestrant
- Targeted therapy based on TMB and HER2 somatic mutations (lobular histology)
  - Pembrolizumab, nivolumab/ipilumumab in high TMB
  - Neratinib/fulvestrant/trastuzumab in HER2 mutation, very high rate of diarrhea

Palmieri ASCO 2021; Barroso-Sousa et al, SABCS 2021; Jhaveri et al, SABCS 2021; Damodaran et al, ASCO 2022



Elliott and Cescon, Breast 2022

Efficacy with Select Single Agent Oral SERDs in Phase 1 Trials

Key Advantages: Oral, highly potent, active against ESR1 mutation including Y537S

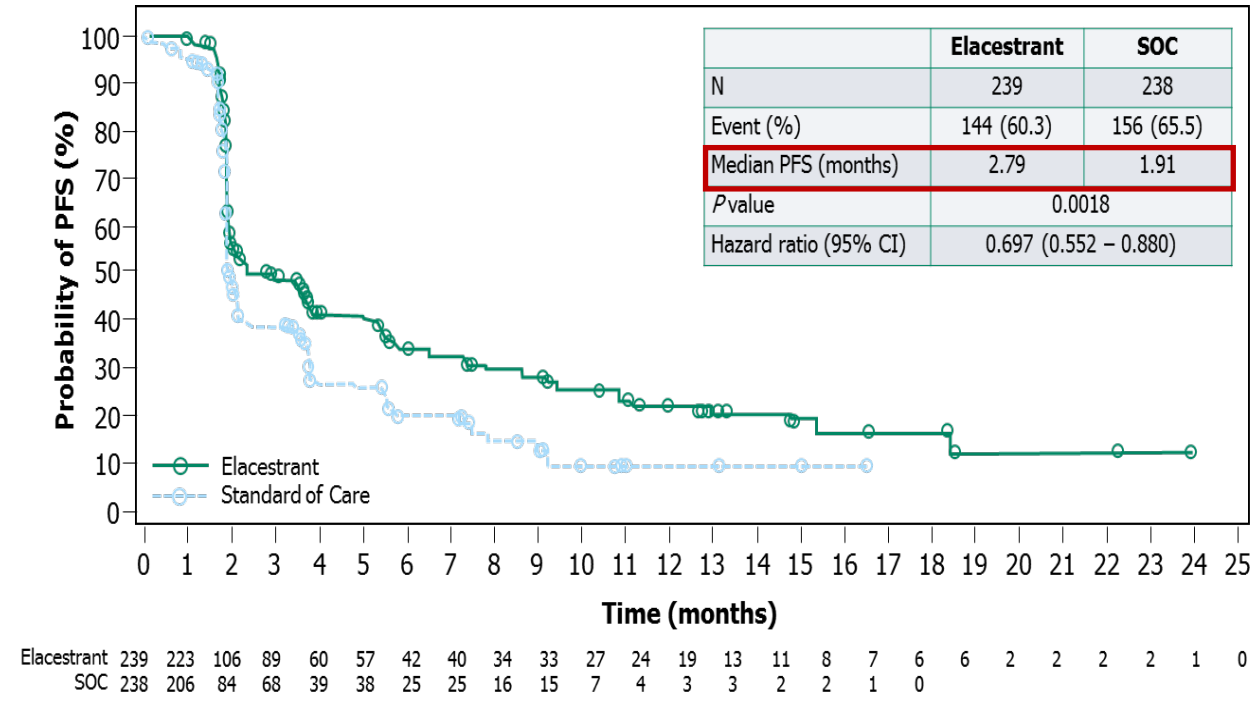
Oral SERD	N	Median Lines of Rx for MBC	Prior CDK 4/6i (%)	Prior Fulvestrant (%)	*ESR1* mutation at baseline (%)	RP2D	ORR (%)	CBR (%)	Median PFS (months)	Reference
LSZ-102#	77	4 (0-10)	58	60	41.7	450mg	1.4	9.1	1.8	Jhaveri CCR 2021
GDC-9545 (Giredestrant)	111	1 (0-3)	64	21	47	30mg	15	50	7.2	Jhaveri ASCO 2021
RAD1901 (Elacestrant)	50	3 (1-7)	52	52	50	400mg	19.4	42.6	4.5	Bardia JCO 2021
SAR439859 (Amcenestrant)	62	2 (1-8)	63	46.8	51	400mg	8.5	33.9	Not reported	Linden SABCS 2020
AZD9833 (Camizestrant)	98	3 (0-7)	69	58	43	75mg	10	35.3	5.4	Baird SABCS 2020
LY-3484356 (Imlunestrant)	72	2 (0-8)	90	39	49 (all cohorts)	400mg	12	55	6.5 mo (2nd line post CDKi)	Jhaveri et al ASCO 2022
G1T48 (Rintodestrant)	67	2 (0-9)	70	64	45	800mg	5	30	2.6-3.6	Aftimos SABCS 2020
D0502*	16	NA	Not reported	Not reported	NA	400mg	10	50	Not reported	Osborne SABCS 2020
Zn-C5	56##	2 (0-9)	70	46	41	50mg/25mg	5	38	3.8	Kalinsky SABCS 2021

#Further development discontinued; * 400mg dose; ## 41 with measurable disease

Courtesy of Jhaveri, modified

EMERALD Trial: Results in ITT Population

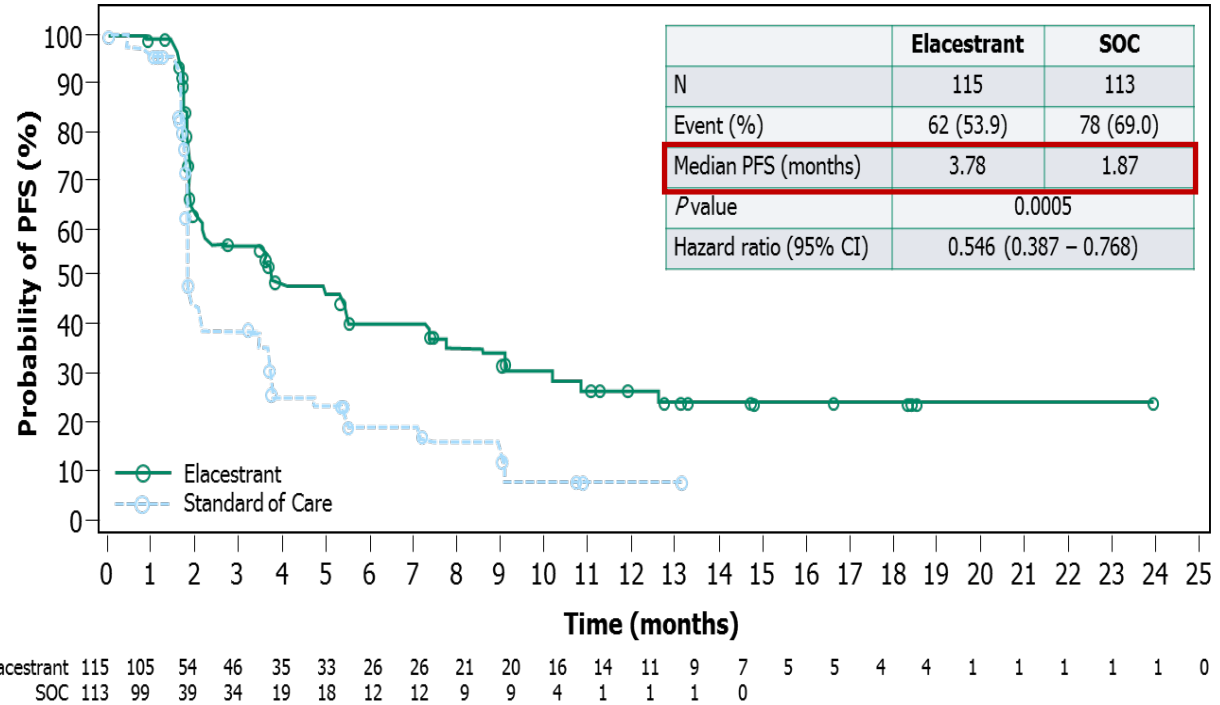
All Patients



	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

Elacestrant is associated with a 30% reduction in the risk of progression or death in all patients with ER+/HER2- mBC

Patients With Tumors Harboring *mESR1*



	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

Elacestrant is associated with a 45% reduction in the risk of progression or death in patients harboring *mESR1*

Bidard et al, JCO 2022

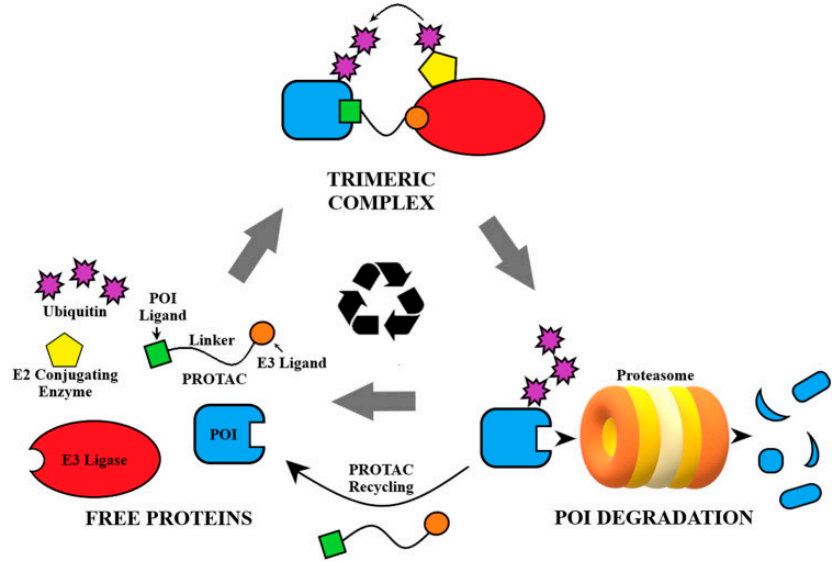
Randomized Trials in the Post-CDK4/6 Inhibitor Setting

	EMERALD (NCT03778931)	AMEERA-3 (NCT04059484)	aceERA (NCT04576455)	SERENA-2 (NCT04214288)	EMBER-3 (NCT04975348)
N	477	282	303	288	800
Patient Population	ER+/HER2- ABC	ER+/HER2- ABC (ET sensitivity required)	ER+/HER2- ABC Measurable disease	ER+/HER2- MBC	ER+/HER2- MBC
Number of Prior Therapies	1-2	0-2	0-2	0-2	1 (AI + CDK4/6i)
Prior Chemotherapy	20% had 1 line	Allowed (≤1) or CDK	Allowed (≤1)	Allowed (≤1)	Not allowed
Prior Fulvestrant	30%	Allowed	Allowed	Not allowed	Not allowed
Prior CDK 4/6i	100%	80%	Allowed	Allowed	Allowed
Treatment Arms	Elacestrant vs ET (AI or Fulvestrant)	Amcenestrant vs ET (AI, Tamoxifen or Fulvestrant)	Giredestrant vs ET (AI or Fulvestrant)	Camizestrant (various doses) vs Fulvestrant	Imlunestrant (N~370) vs ET (AI or Fulv) (N=280) vs Imlunestrant + Abemaciclib (N= 180)
Primary Endpoint	PFS in ITT and *ESR1* mutant	PFS	PFS	PFS	PFS
Results	**Positive IIT: 2.79 vs 1.891 HR 0.7 *ESR1*m: 3.78 vs 1.87HR 0.55**	**Did not meet primary EP**	**Did not meet primary EP**	Not yet reported	Not yet reported

Courtesy of Jhaveri

Newer ER Targeted Agents

- Multiple phase III trials are ongoing
- Newer agents
  - **PROTAC**: proteolysis targeting chimera, ARV-471
    - CBR 40% in phase I (n=47)
    - Phase 1/2 trial of ARV-471 alone or with Palbociclib ongoing (NCT04072952)
  - **CERCA**: serum ER covalent antagonist, H3B-6546 (n=94)
    - ORR 16%, CVR 40%, mPFS 3.8 mo but 7.3 mo with ESR1Y537S in phase I
    - Phase 1 trial of H3B6545 with Palbociclib is ongoing (NCT04288089)
  - **CERAN**: complete ER antagonist, OP-1250 (n=40)
    - ORR 18%, CBR 38%
    - Phase I trial OP-1250 + Palbociclib (NCT05266105)



Hamilton et al, SABCS 2021

Burke et al, Front Cell Dev Biol; 2022

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer

NCT03901339

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan 10 mg/kg IV days 1 and 8, every 21 days n=272

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

Endpoints

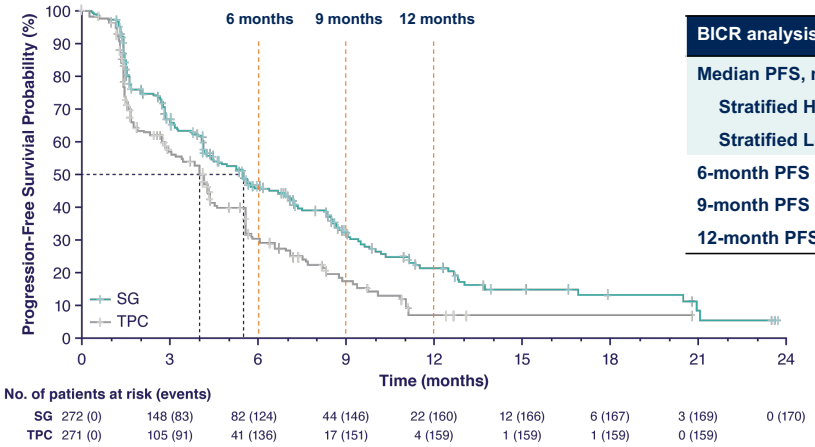
Primary
- PFS by BICR

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

Stratification:
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

Primary Endpoint: BICR-Assessed PFS per RECIST v1.1 in the ITT Population

SG demonstrated a statistically significant improvement in PFS vs TPC with a 34% reduction in the risk of disease progression/death; a higher proportion of patients were alive and progression-free at all landmark timepoints



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	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

- Heavily pre-treated HR+/HER2- MBC
  - 95% visceral mets
  - Median lines prior Rx for metastatic disease
    - ET: 3
    - Chemo: 3
- Safety
  - No new toxicity signals
  - Primary toxicity ≥gr3 is neutropenia and diarrhea
- QoI
  - Overall HRQoL benefit over TPC
  - Delayed deterioration in fatigue and global health status/QoL scales in EORTC QLQ-C30
- OS immature
- In light of DB04, a late line Rx option, and an option for HER20, HR+ MBC

Rugo et al, ASCO 2022

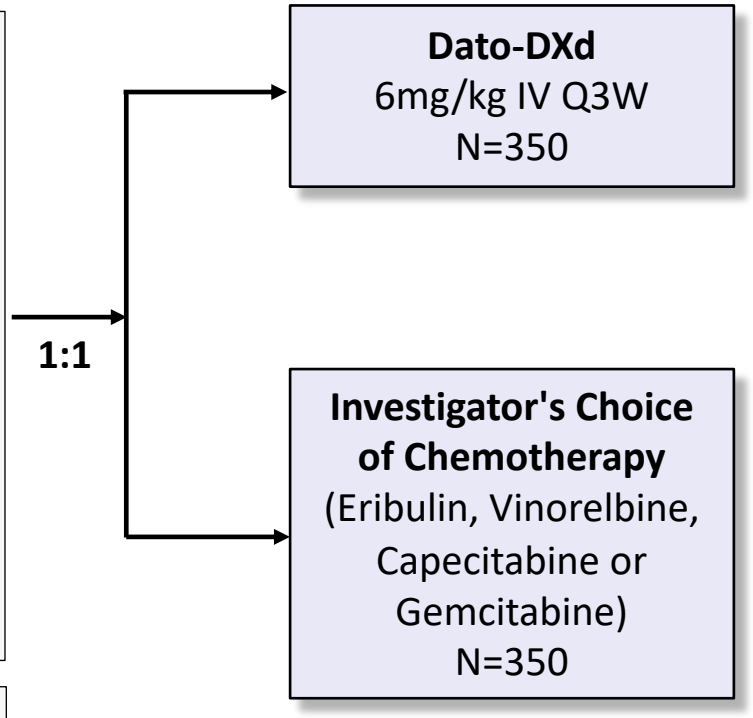
TROPION-Breast01

Key Eligibility Criteria

- HR-positive, HER2-negative inoperable/ metastatic breast cancer with disease progression following 1 or 2 lines of chemotherapy (& progressed on, or not suitable for, endocrine therapy)
- Targeted agents (i.e., inhibitors of mTOR, PD-1/PD-L1, CDK4/6, PARP) and endocrine therapies do not count as prior lines of chemotherapy
- At least 1 measurable lesion
- FFPE tumor sample
- Adequate organ function

Stratification factors:

- 1 vs. 2 previous lines of chemotherapy in the inoperable/metastatic setting
- Geographic location (US/Canada/EU vs rest of world)
- Previous CDK 4/6 inhibitor use



Dual primary endpoints
PFS (BICR), OS

Secondary endpoints
PFS (inv), ORR, DoR, DCR, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints
TROP2 IHC

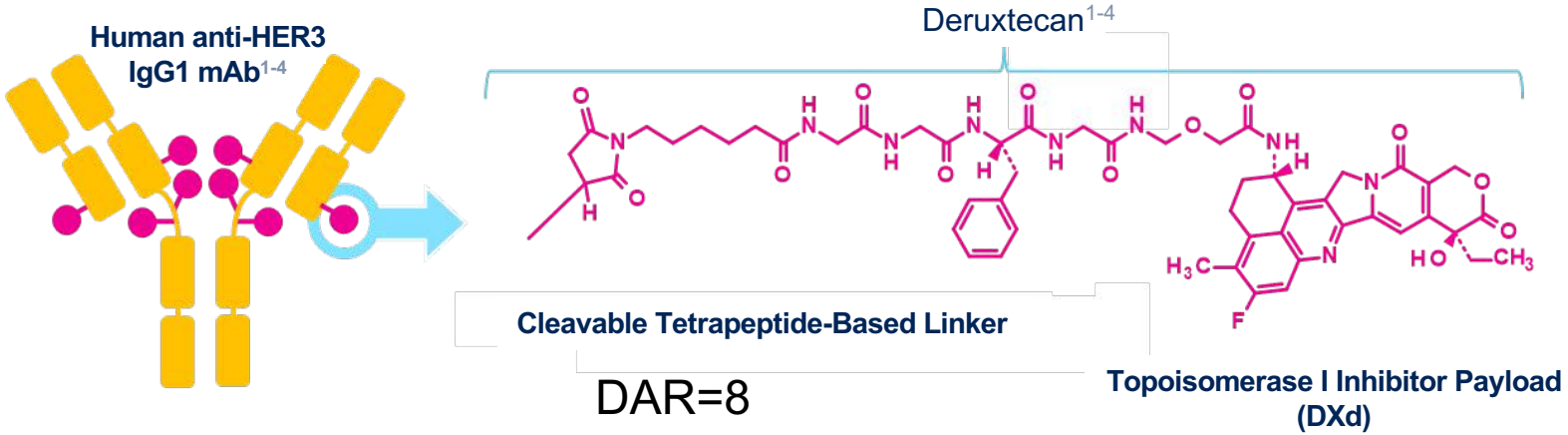
Statistical Considerations:

To strongly control the familywise type I error rate at the 5.0% level (2-sided), an alpha level of 1.0% will be allocated to the PFS dual primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses

Response assessment: Scan Q6W for 48 weeks, then Q9W until RECIST1.1 disease progression (as assessed by Investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional follow-up scan should be performed as per Imaging schedule.

Patritumab deruxtecan (U3-1402): HER3 ADC

113 patients with HR+/HER2- MBC



- Dose escalation/finding study
- HER3+ disease
- For HR+/HER2- cohort
  - ≥2 and ≤6 lines of prior chemotherapy; ≥2 for advanced disease
  - HER3 low and high
- Safety similar between 4.6 and 6.4 mg/kg IV q3wk
  - Most common toxicities: GI and heme
  - 10% discontinuation due to AEs
  - 27% grade 3 thrombocytopenia
  - 6.6% ILD; 1 death

Krop I, et al. ASCO 2022

Outcomes (BICR per RECIST 1.1)	HR+/HER2− (n=113) HER3-High and -Low
Confirmed ORR, % (95% CI[a])	30.1 (21.8-39.4)
Best overall response, %[b]	
PR	30.1
SD	50.4
PD	11.5
NE	8.0
DOR, median (95% CI), mo	7.2 (5.3-NE)
PFS, median (95% CI), mo	7.4 (4.7-8.4)
6-month PFS rate, % (95% CI)	53.5 (43.4-62.6)
OS, median (95% CI), mo	14.6 (11.3-19.5)

Summary

- We are learning more about the impact of treatment factors on OS with ET plus CDK4/6i including prior chemotherapy and disease-free interval
  - CDK4/6i should be employed as early as possible and before chemotherapy for MBC
    - P2: Surprising PFS but not OS benefit in DFI < 12 months as first line therapy
  - Sequencing of CDK4/6i still under investigation
    - Sonia trial (NCT03425838)
- Targeting the PI3Kinase pathway
  - New agents, broader definitions
- New approaches to hormone therapy
  - Broad range of SERDs/other agents
- Antibody drug conjugates
  - Changing the approach to chemotherapy for HR+/HER2 low disease
    - ADCs effectively deliver toxins to the cancer cell
      - Role of HER2 low, extent of prior treatment in decisions about sequential therapy
    - Still chemotherapy!

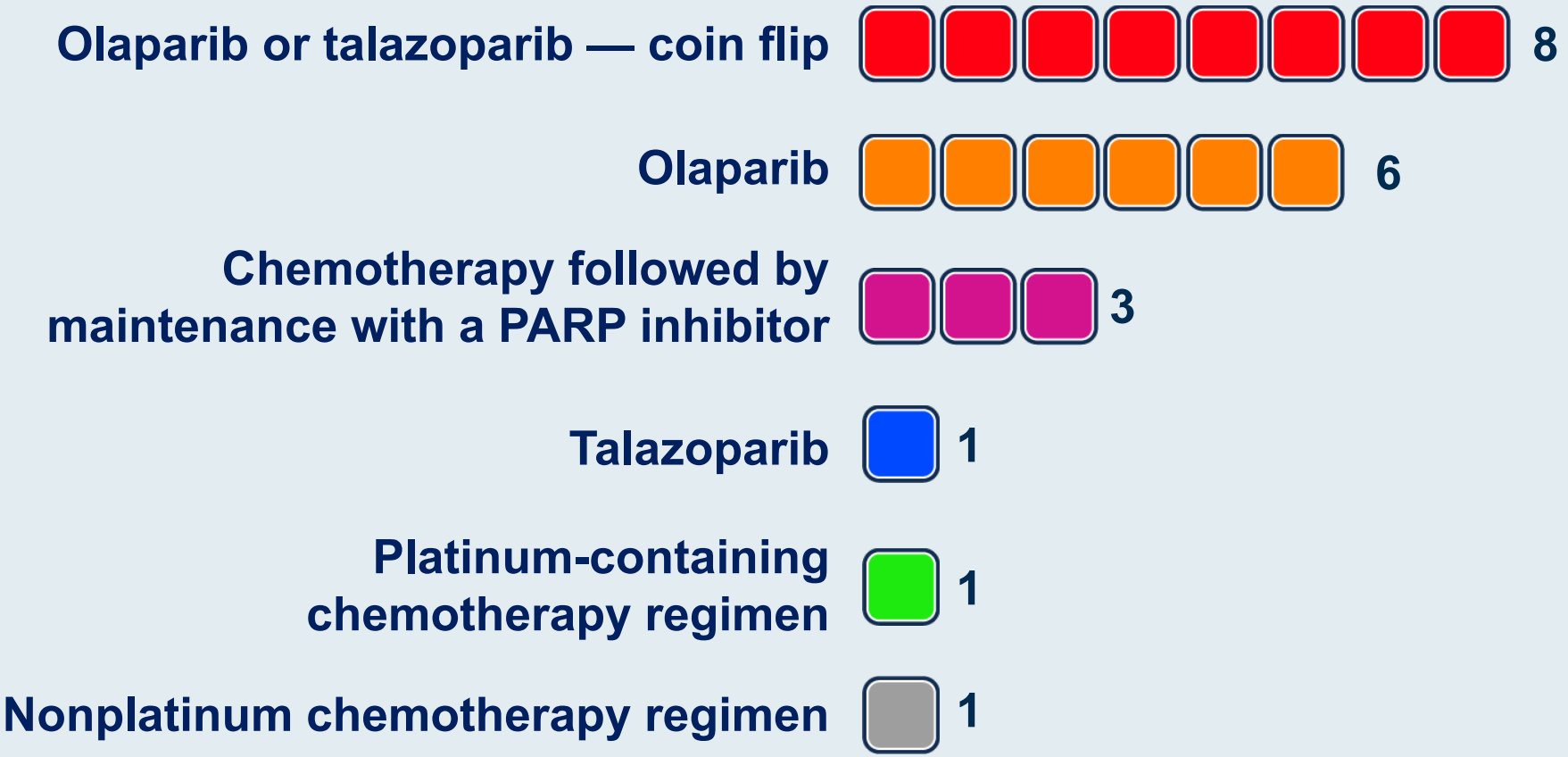
MODULE 6: Recent Advances in the Care of Patients with Metastatic TNBC

RTP
RESEARCH
TO PRACTICE

Have any of your patients been found to have MSI-high metastatic TNBC?

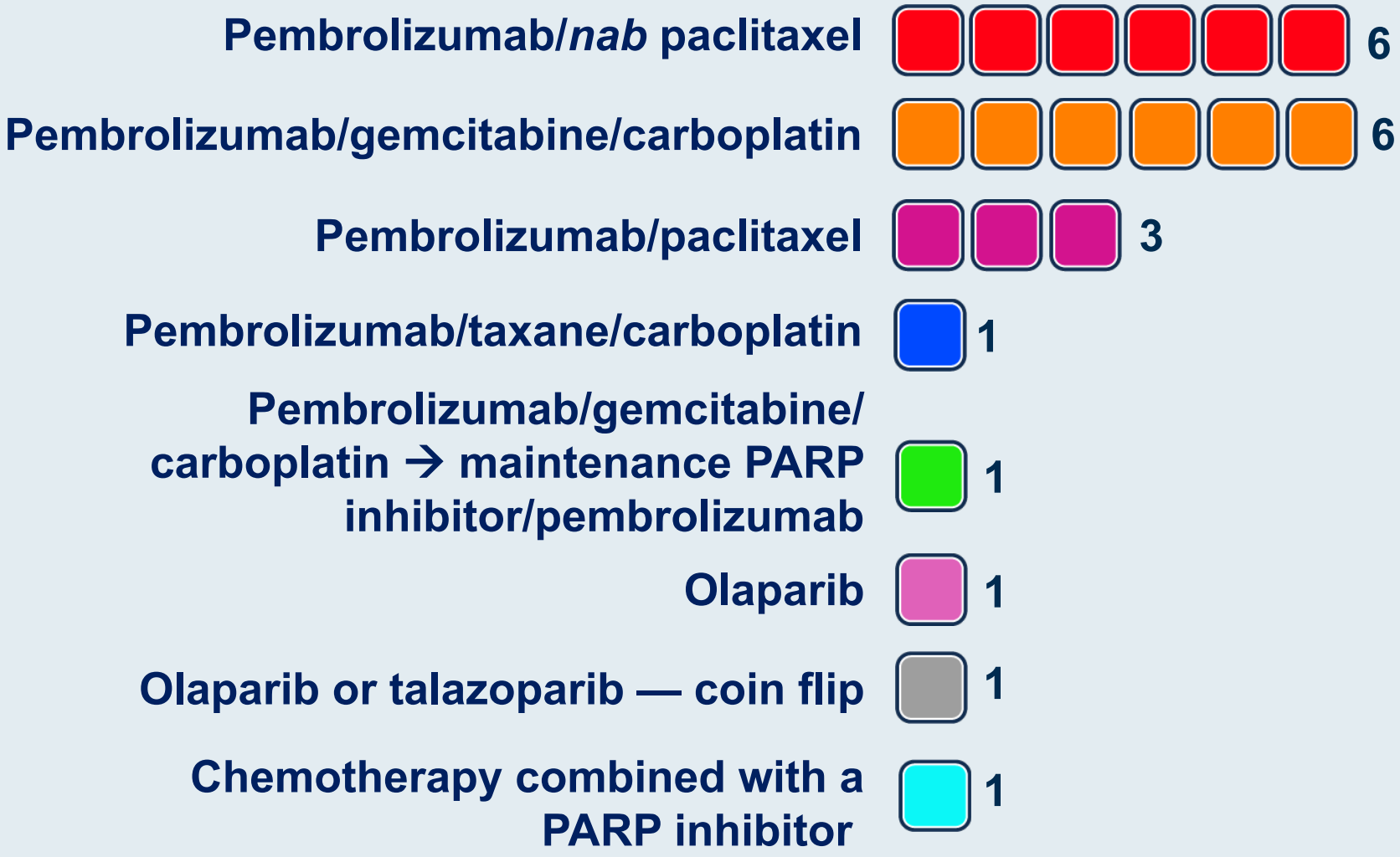
Survey of clinical investigators

What would be your preferred treatment approach for a 60-year-old patient with a BRCA germline mutation and de novo metastatic TNBC that is PD-L1-negative?



Survey of clinical investigators

What would be your preferred treatment approach for a 60-year-old patient with a BRCA germline mutation and de novo metastatic TNBC with a PD-L1 CPS of 10?

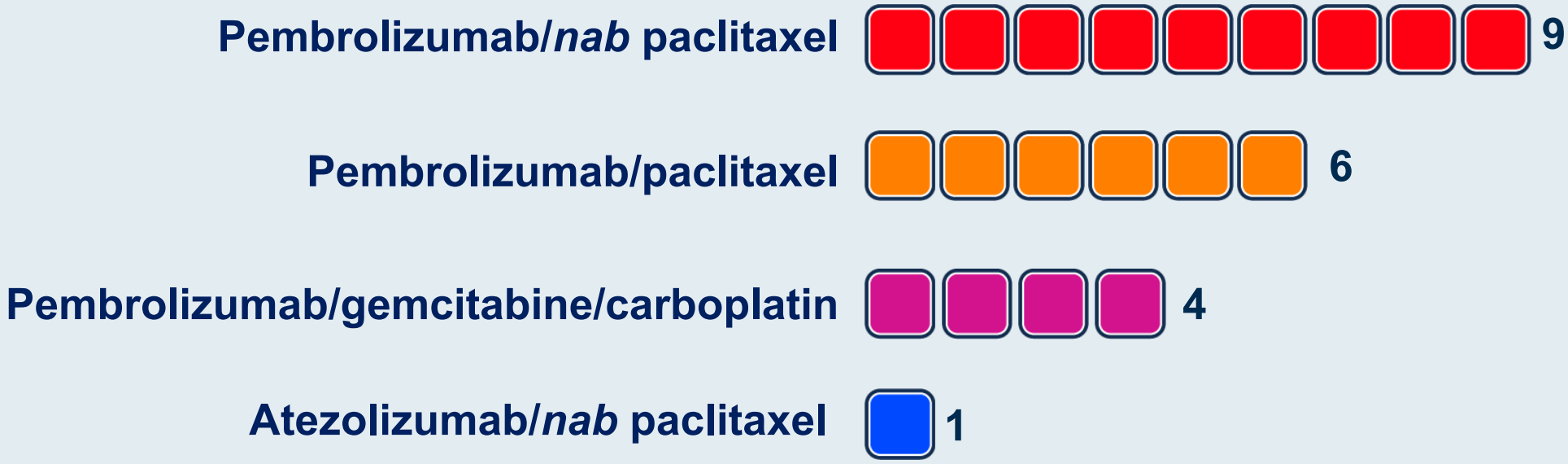


Survey of clinical investigators

What would be your preferred treatment approach for a 60-year-old patient with BRCA wild-type de novo metastatic TNBC with a PD-L1 CPS of >10?

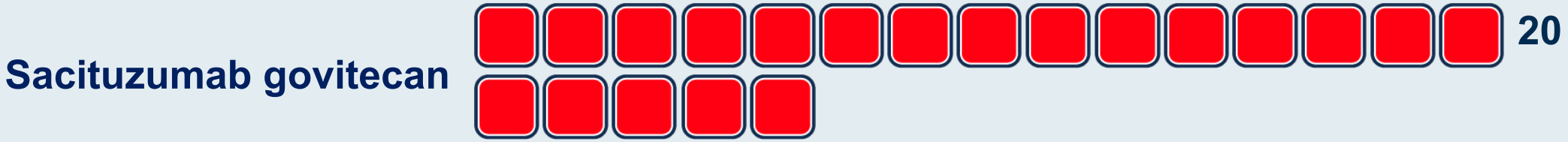
Survey of clinical investigators

A 60-year-old woman with BRCA wild-type TNBC and PD-L1 CPS >10 receives neoadjuvant carboplatin/paclitaxel/pembrolizumab → AC/pembrolizumab and attains a pathologic complete response. Three years after completion of adjuvant pembrolizumab, she develops metastatic TNBC (BRCA wild type, PD-L1 CPS >10). Which first-line treatment would you generally recommend?



Survey of clinical investigators

What treatment would you recommend next for a 60-year-old woman who received neoadjuvant AC-T for TNBC, developed mBC (BRCA wild type, PD-L1-positive) and experienced disease progression after 7 months of first-line pembrolizumab/paclitaxel?



Survey of clinical investigators

Recent Advances in the Care of Patients with Metastatic TNBC (mTNBC)

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HARVARD
MEDICAL SCHOOL

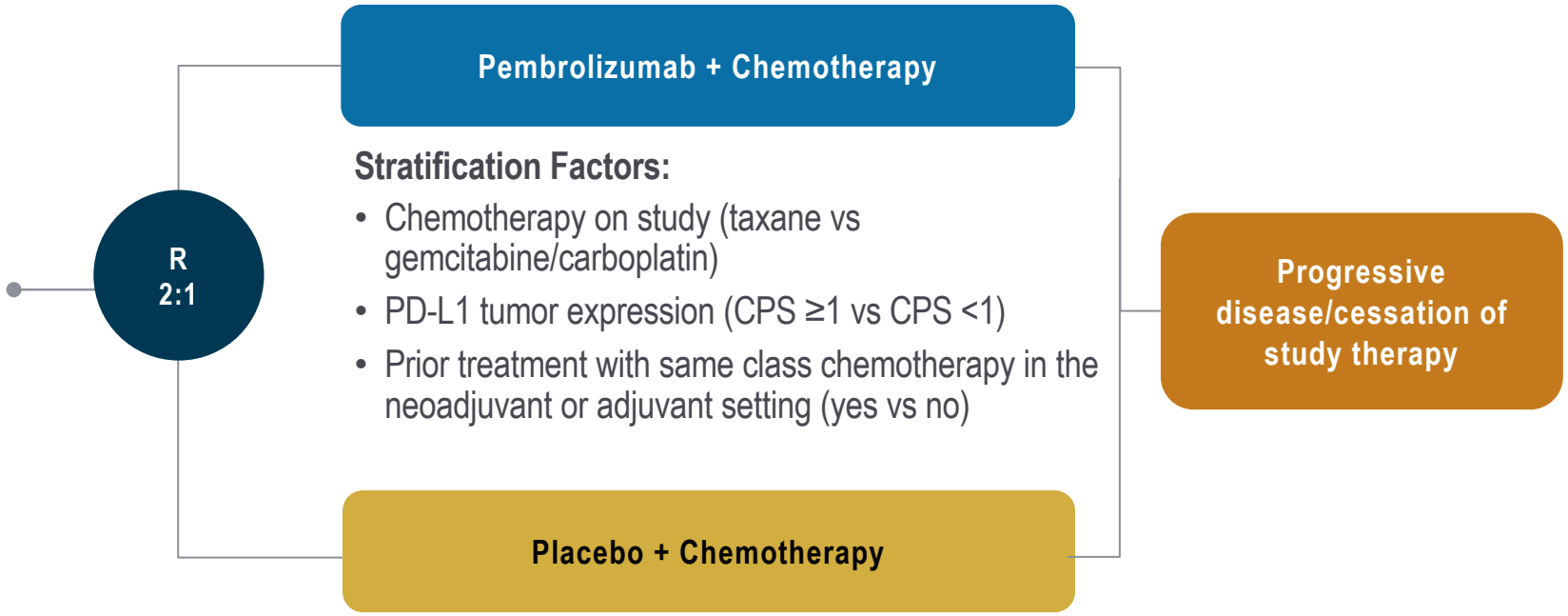
Dana-Farber
Cancer Institute

KEYNOTE-355: Study Design

Pembrolizumab + chemotherapy for advanced, metastatic TNBC

Patient Eligibility Criteria:

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

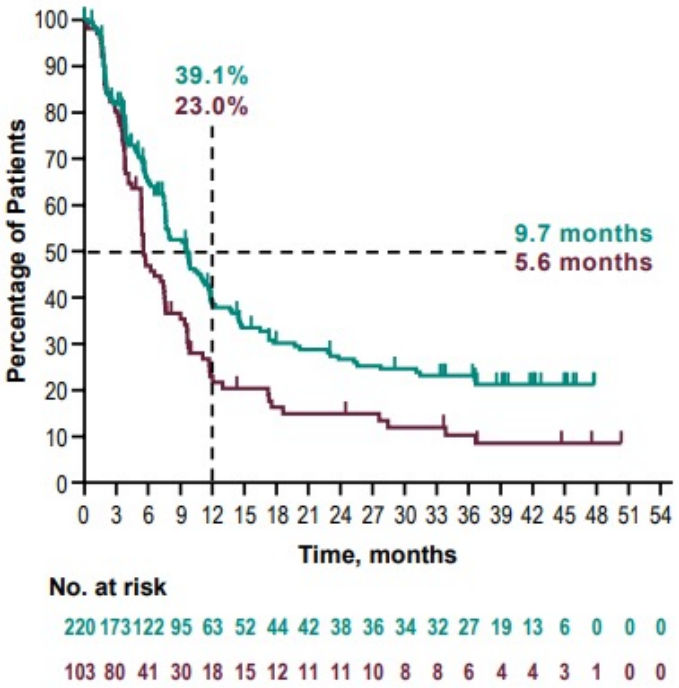


Cortes J, et al. Lancet. 2020;396:1817-1828.

KEYNOTE-355: PFS Analysis

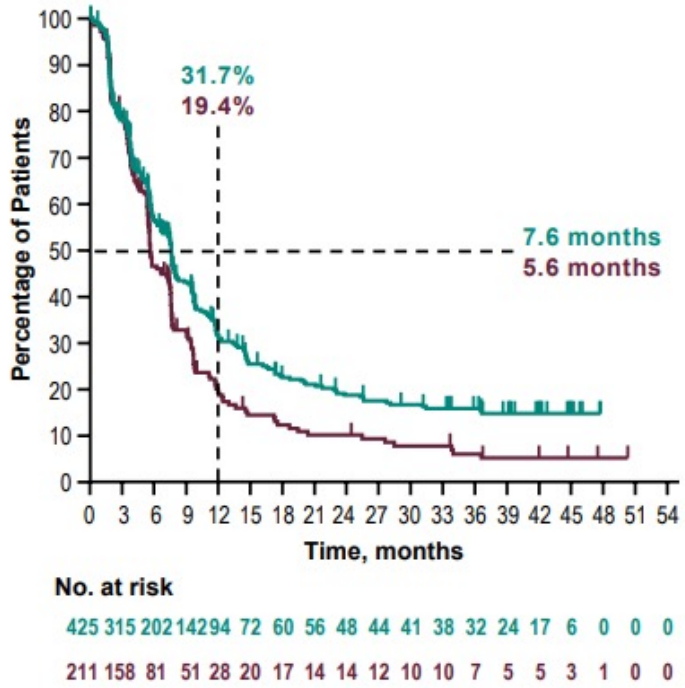
PD-L1 CPS ≥10

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



PD-L1 CPS ≥1

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



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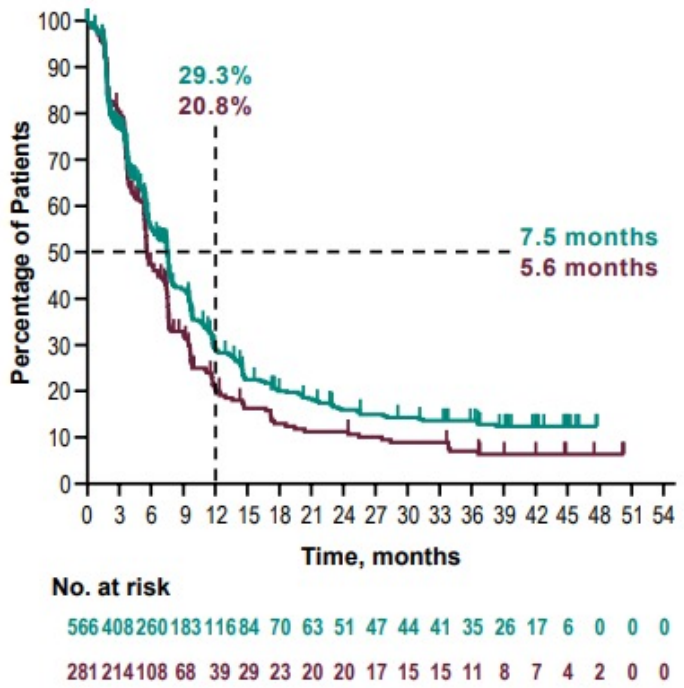
	n/N	Events	HR (95% CI)
Pembro + Chemo	406/566	71.7%	0.
Placebo + Chemo	217/281	77.2%	(0.70

Pembro + Chemo

Placebo + Chemo



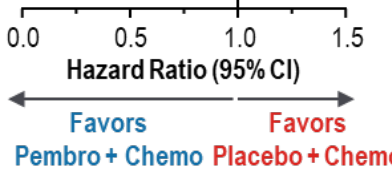
- Data cutoff: June 15, 2021

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

KEYNOTE-355: PFS Subgroup Analysis by On-Study Chemotherapy

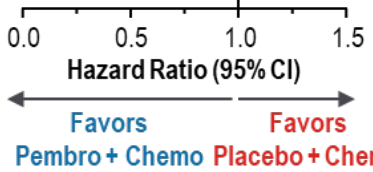
PD-L1 CPS ≥10

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	323	9.7	5.6	0.65 (0.49 to 0.86)
On-study chemotherapy				
Nab-Paclitaxel	99	9.9	5.5	0.57 (0.34 to 0.95)
Paclitaxel	44	9.6	3.6	0.33 (0.14 to 0.76)
Gemcitabine-Carboplatin	180	8.0	7.2	0.77 (0.53 to 1.11)



PD-L1 CPS ≥1

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	636	7.6	5.6	0.74 (0.61 to 0.90)
On-study chemotherapy				
Nab-Paclitaxel	204	6.3	5.3	0.66 (0.47 to 0.92)
Paclitaxel	84	9.4	3.8	0.46 (0.26 to 0.82)
Gemcitabine-Carboplatin	348	7.5	7.5	0.86 (0.66 to 1.11)



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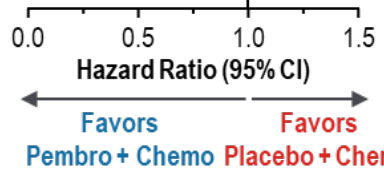
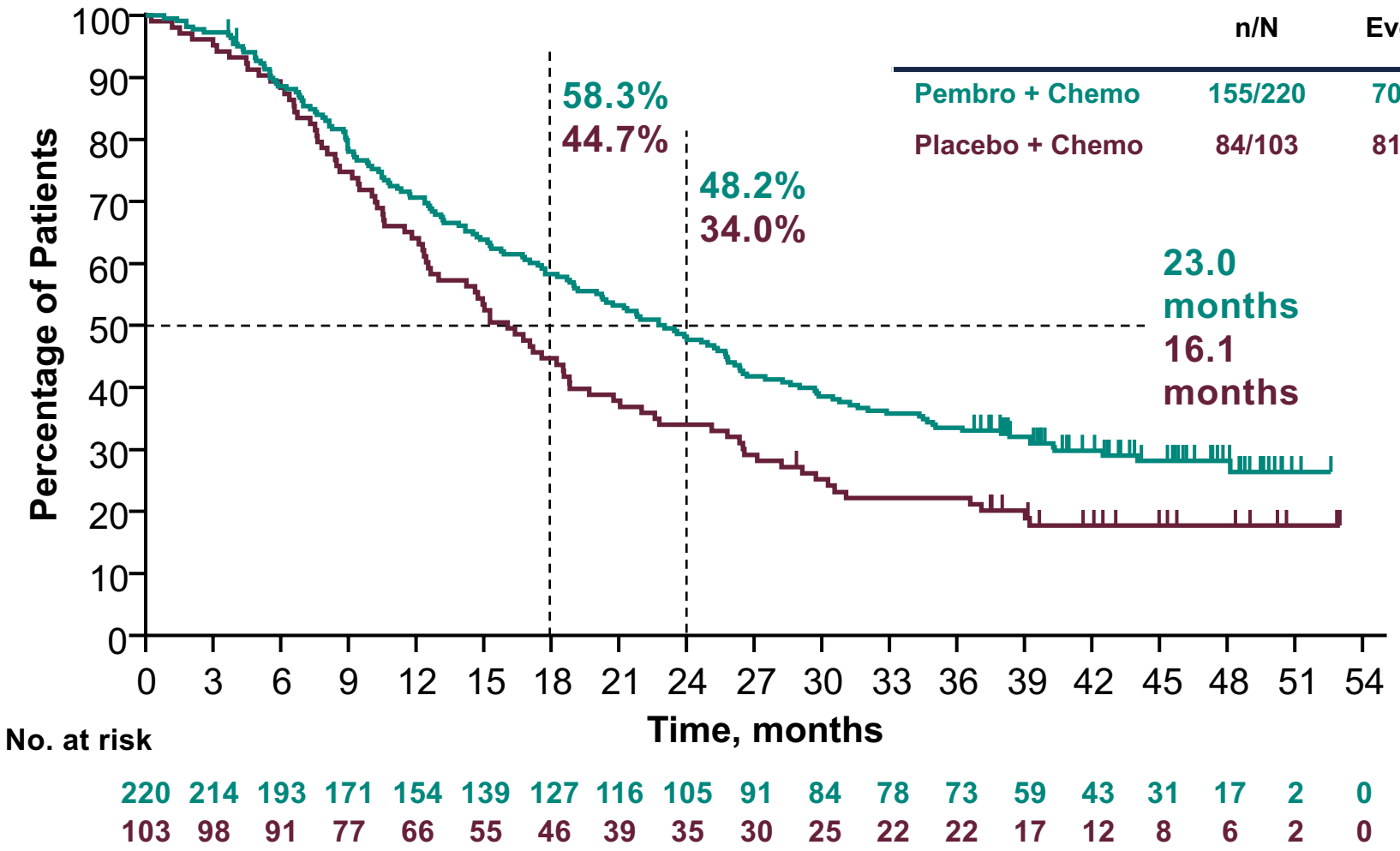
Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	847	7.5	5.6	0.82 (0.69 to 0.97)
On-study chemotherapy				
Nab-Paclitaxel	268	7.5	5.4	0.69 (0.51 to 0.93)
Paclitaxel	114	8.0	3.8	0.57 (0.35 to 0.93)
Gemcitabine-Carboplatin	465	7.4	7.4	0.93 (0.74 to 1.16)



Data cutoff December 11, 2019

- Rugo H et al, SABCS 2020. GS3-01.

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



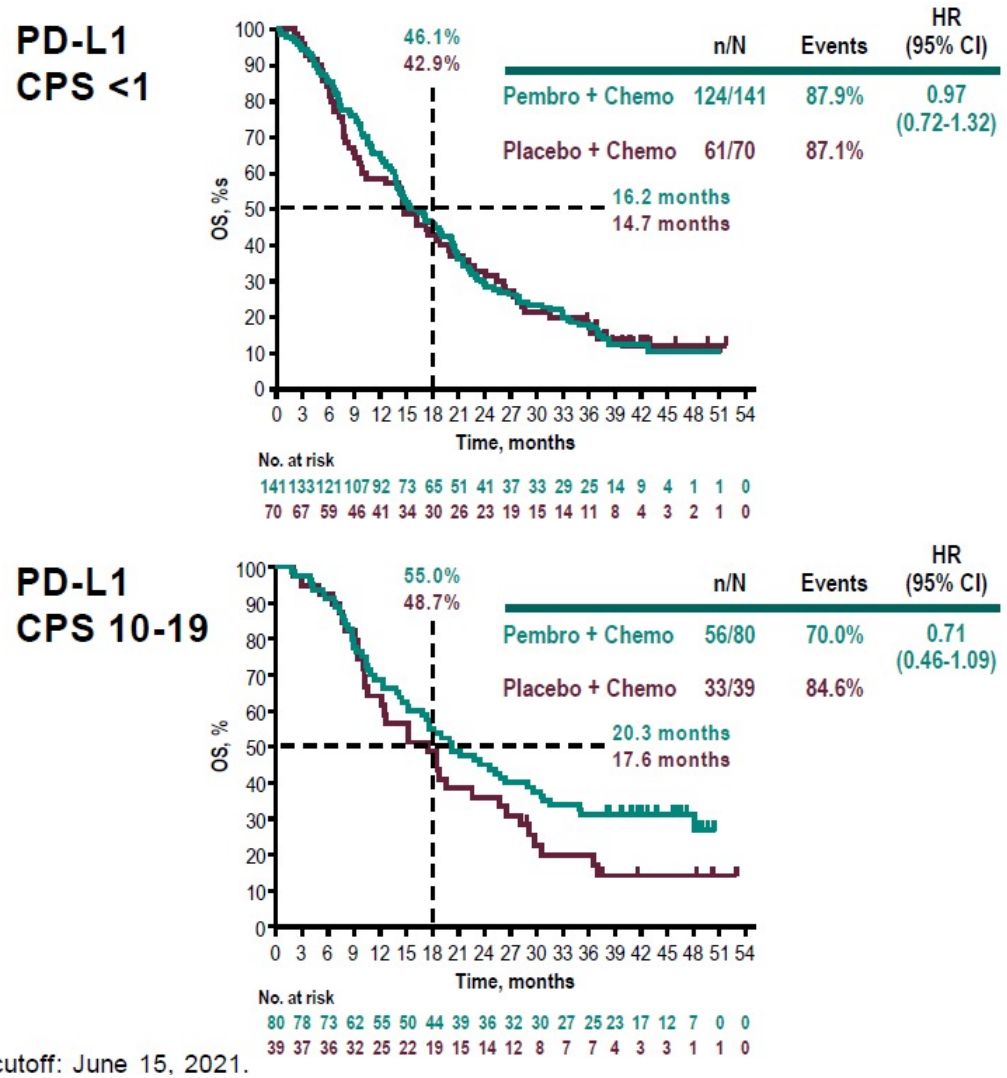
	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093*
Placebo + Chemo	84/103	81.6%		

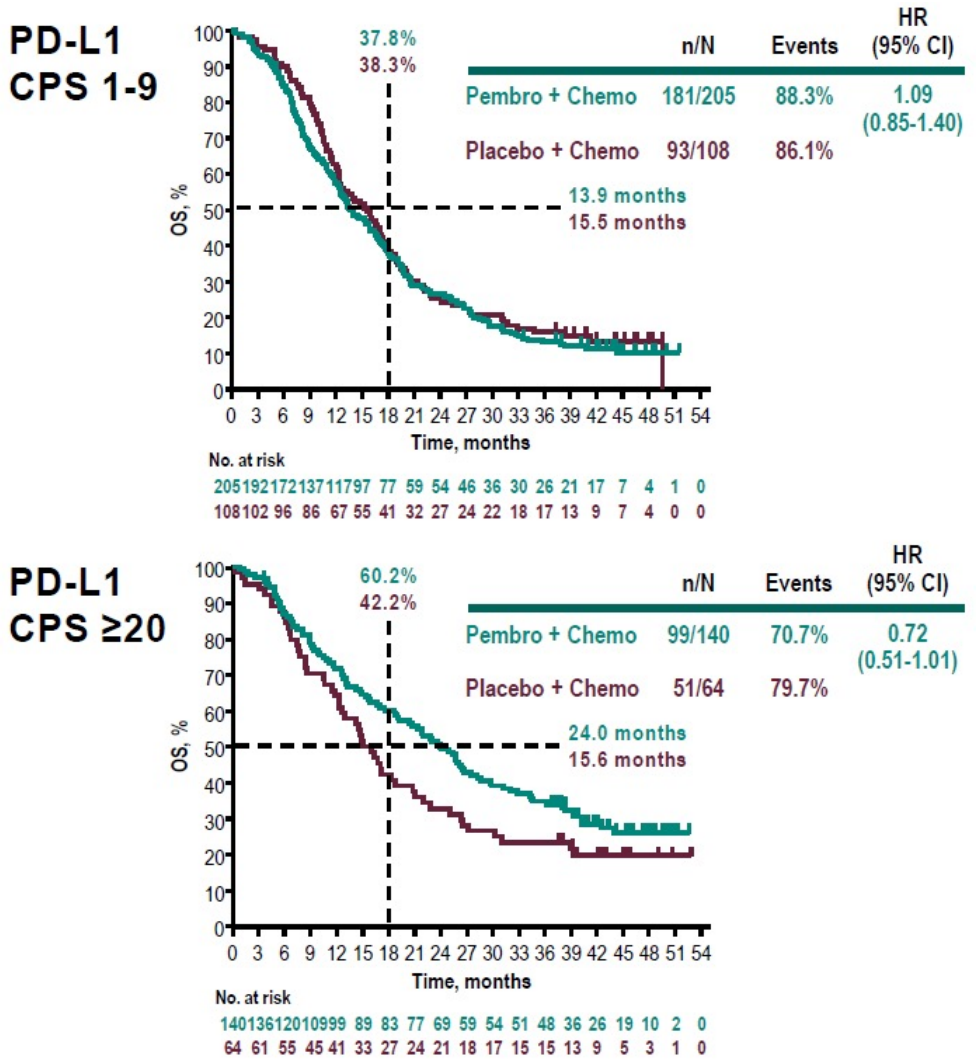
*Prespecified P value boundary of 0.0113 met.

Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

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

KEYNOTE-355: Overall Survival in Additional PD-L1 CPS Subgroups





Data cutoff: June 15, 2021.

- Cortes J, et al. SABCS 2021. Abstract GS1-03.

Targeting DNA repair

Efficacy of PARP Inhibitors in Patients with gBRCA Mutations and MBC

	OlympiAD Olaparib vs. TPC	**EMBRACA** Talazoparib vs. TPC	**BROCADE3** Carbo/paclitaxel + veliparib or placebo
PFS	**5.6 mos** vs. 2.9 mos **HR = 0.43** 95% CI (0.29, 0.63)	**5.8 mos** vs. 2.9 mos **HR= 0.60** 95% CI (0.41, 0.87)	**14.5 mos** vs. 12.6 mo **HR=0.705** 95% CI (0.56-0.88)
ORR	**51.8%** vs. 5.4% (n=83) (n=37) *Investigator assessment*	**61.8%** vs. 12.5% (n=102) (n=48) *Investigator assessment*	Thrombocytopenia: 40% vs 28% *Investigator assessment*

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

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

TBCRC 048: OLAPARIB EXPANDED
Benefit in gPALB2 + sBRCA

PALB2 N=13	s*BRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr **Somatic: 0/2 – both SD*** (limited assessments)	**8/16 PR (50%)**	**0/13 germline** **0/4 somatic**

New cohorts are beginning for g*PALB2* and s*BRCA1/2* breast cancer

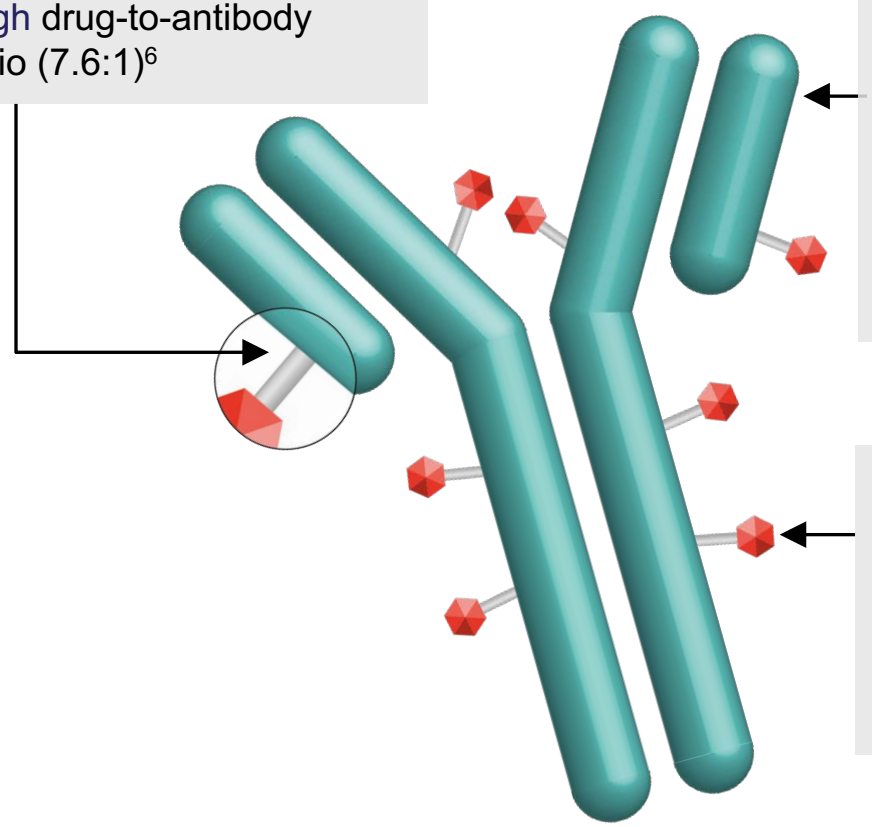
Tung N et al, ASCO 2020
Tung N et al, JCO 2020

Antibody Drug Conjugates

Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[7]

Linker for SN-38
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)[6]



Humanized anti–Trop-2 antibody
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

SN-38 payload
- SN-38 more potent than parent compound, irinotecan

ADC, antibody−drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

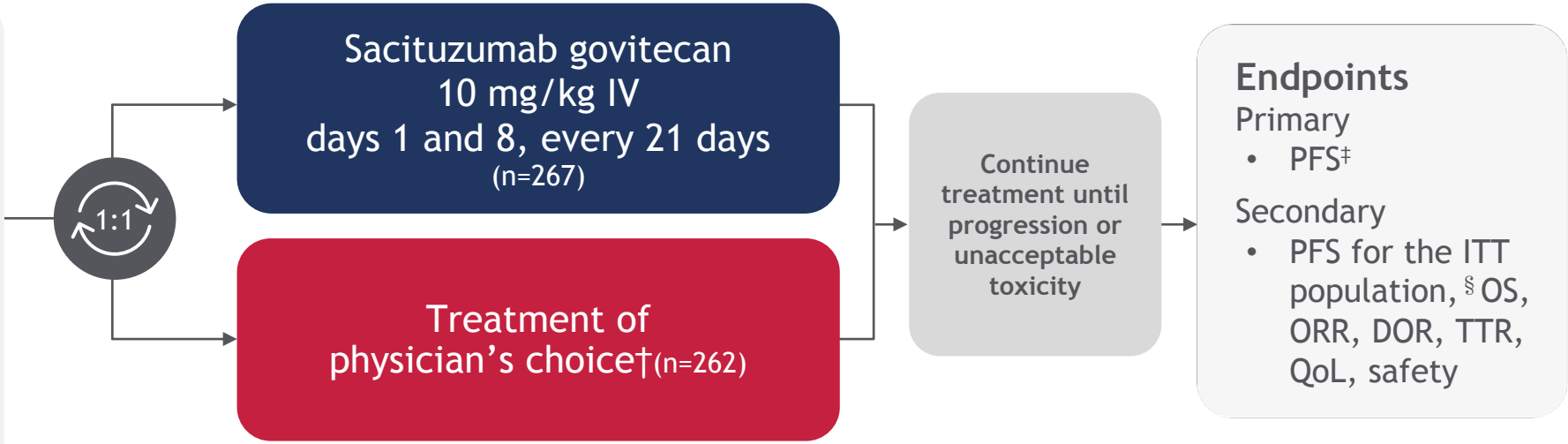
1. Vidula N et al. *J Clin Oncol.* 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One.* 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther.* 2020 Aug;20(8):871-885. 4. Nagayama A et al. *Ther Adv Med Oncol.* 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem.* 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget.* 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

ASCENT: A phase 3 confirmatory study of sacituzumab govitecan in 2L and later mTNBC[1-3]*

Metastatic TNBC

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

(N=529)



Stratification factors

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

NCT02574455

*ASCENT was an international, Phase 3, multicentre, open-label, randomised trial of patients with unresectable locally advanced or metastatic TNBC (N=529). †Treatment of physician's choice: eribulin, vinorelbine, gemcitabine, or capecitabine; ‡PFS measured by an independent centralised and blinded group of radiology experts who assessed tumour response using RECIST 1.1 criteria in patients without brain metastasis; §The full population or intention-to-treat population includes all randomised patients (with and without brain metastases).
DOR, duration of response; IV, intravenous; ITT, intention-to-treat; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours; TNBC, triple-negative breast cancer; TTR, time to response; QoL, quality of life.

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

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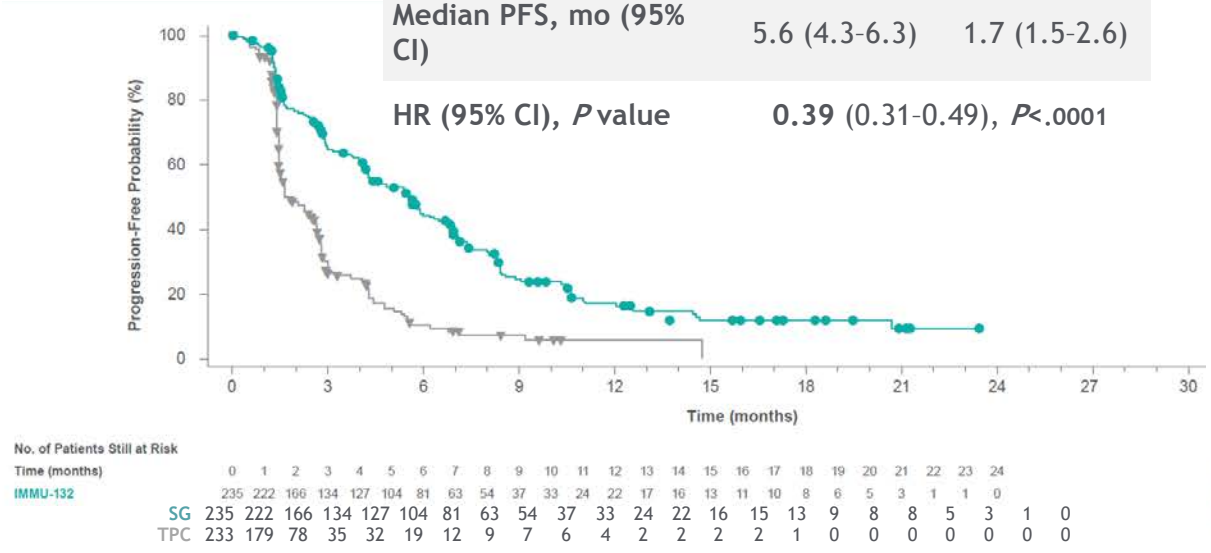
ASCENT: Statistically significant and clinically meaningful improvement in PFS and OS

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

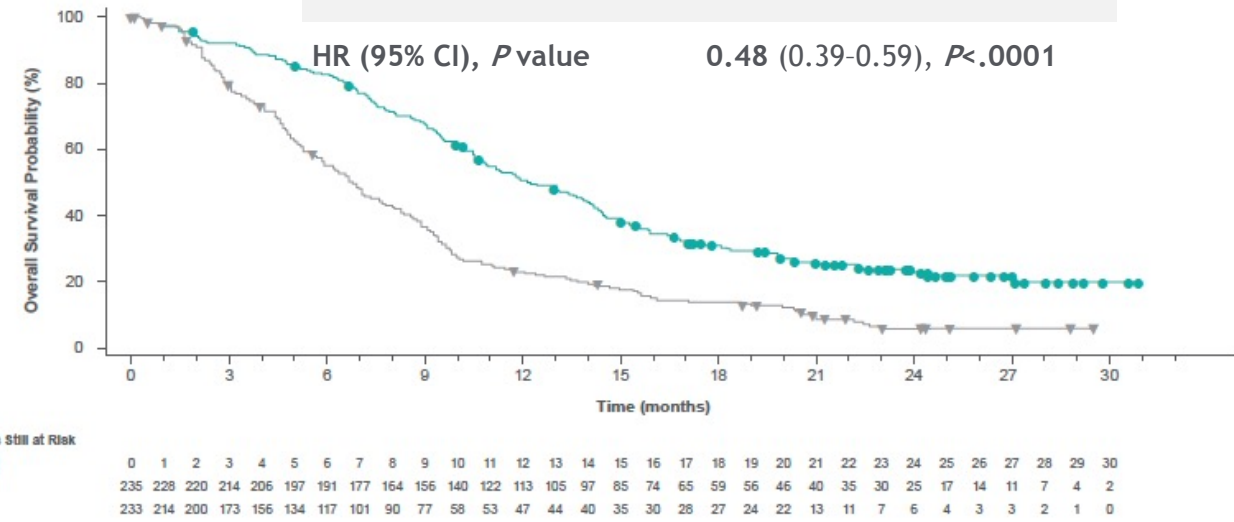
Progression-free survival (BICR Analysis)

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



Overall survival

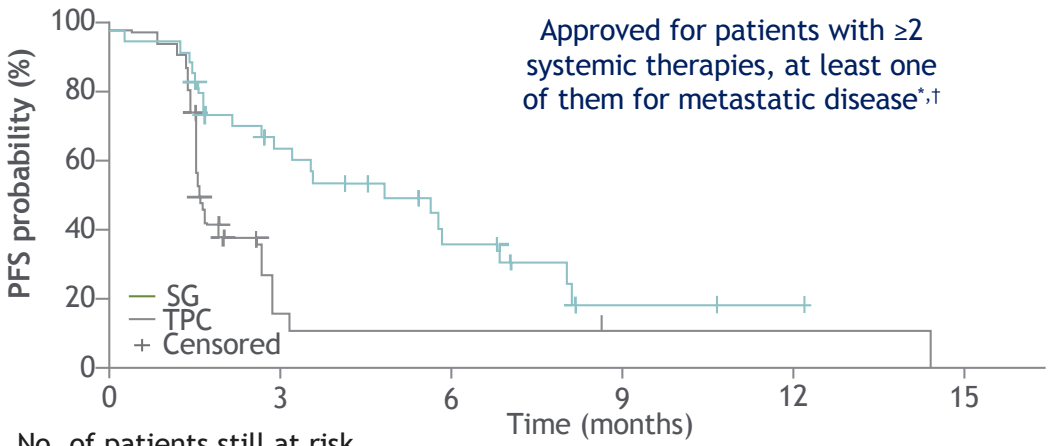
	SG (n=235)	TPC (n=233)
No. of events	173	199
Median OS, mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	**0.48** (0.39-0.59), ***P*<.0001**	



Bardia A et al, ASCO 2022

ASCENT: In patients with 2L mTNBC, PFS and OS improvement was consistent with the overall study population

Progression-free survival

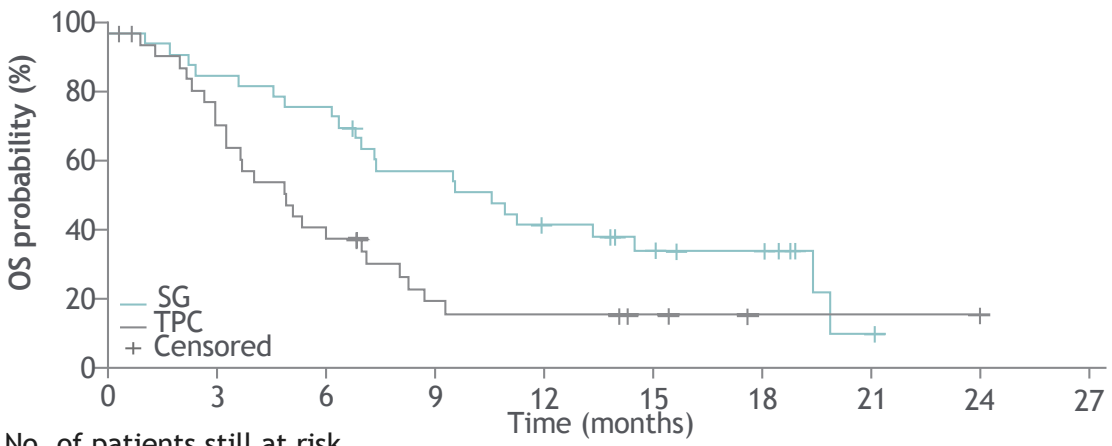


Approved for patients with ≥2 systemic therapies, at least one of them for metastatic disease*,†

No. of patients still at risk

SG	33	32	23	19	16	12	8	6	5	2	2	1	1	1	0	0
TCP	32	28	8	3	2	2	2	2	2	1	1	1	1	1	1	0

Overall survival



No. of patients still at risk

SG	33	32	31	29	28	26	26	21	19	19	17	15	13	13	11	9	7	7	7	4	2	1	0	0	0	0
TCP	32	29	27	22	17	14	12	10	8	6	5	5	5	5	5	3	2	2	1	1	1	1	1	1	1	0

BICR Analysis	SG (n=33)	TPC (n=32)
No. of events	21	23
Median PFS - mo (95%) CI	5.7 (2.6-8.1)	1.5 (1.4-2.6)
HR (95% CI)	0.41 (0.22-0.76)	

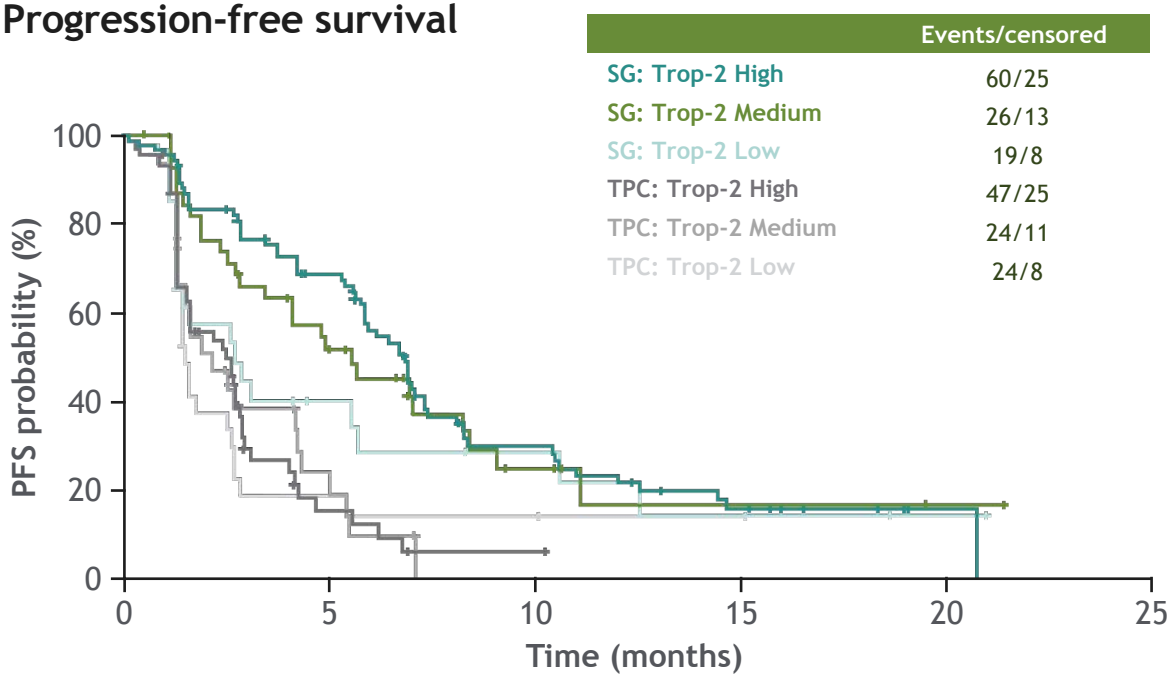
BICR Analysis	SG (n=33)	TPC (n=32)
No. of events	22	24
Median OS—mo. (95% CI)	10.9 (6.9-19.5)	4.9 (3.1-7.1)
HR (95% CI)	**0.51** (0.28-0.91)	

*TRODELVY (sacituzumab govitecan) Summary of Product Characteristics. Gilead Sciences Ireland UC. https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf. †TRODELVY (sacituzumab govitecan) Summary of Product Characteristics. Germany: https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_de.pdf

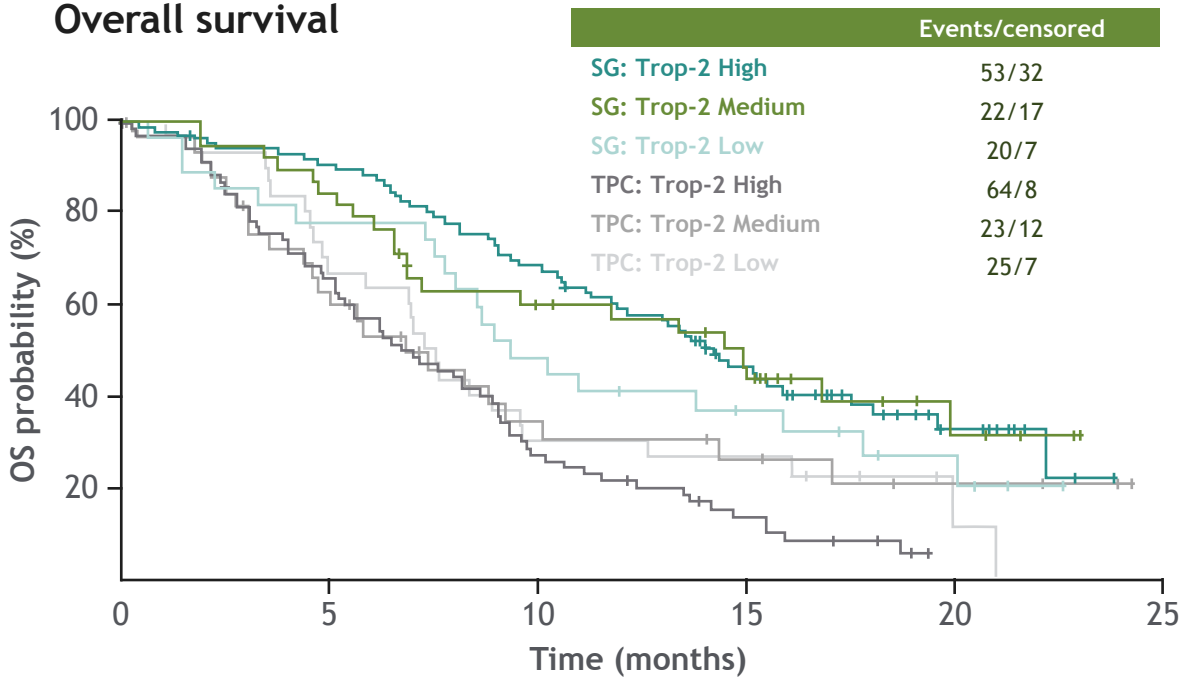
Assessed by independent central review in the brain-metastasis-negative population who recurred ≤12 months after (neo)adjuvant chemotherapy and received one line of therapy in the metastatic setting prior to study enrolment. BICR, blind independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice. 1. Carey LA, et al. Poster ASCO [Virtual meeting] 2021. (Poster 1080)

Clinical benefit with SG vs TPC is irrespective of level of Trop-2 expression, in previously treated mTNBC

Progression-free survival



Overall survival



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

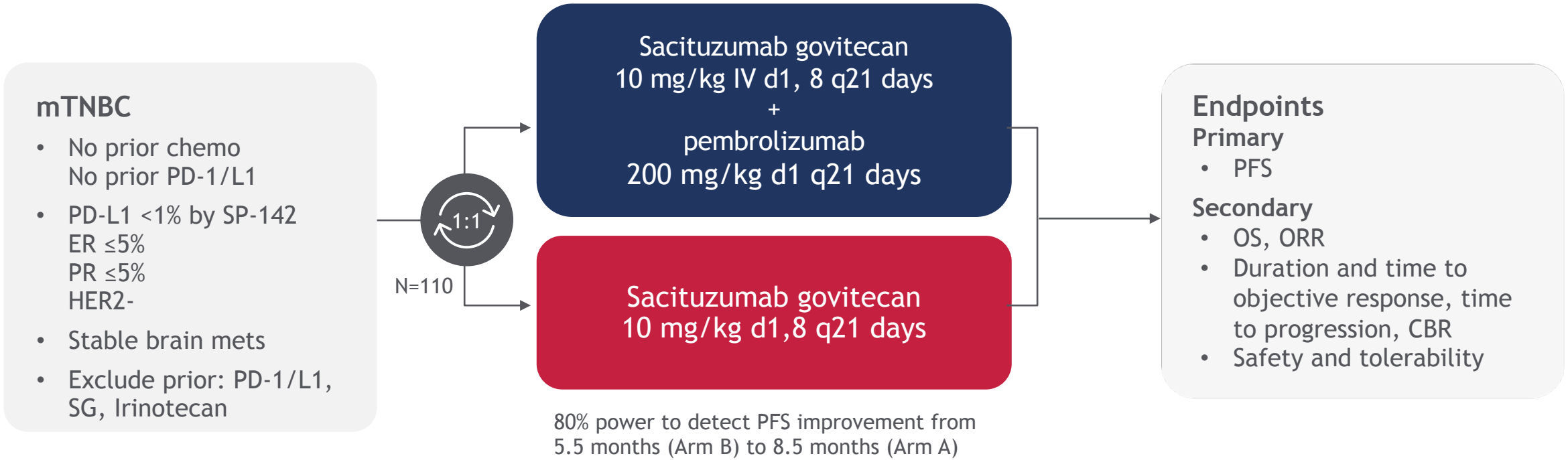
Assessed in brain-metastases-negative population. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
H-score, histochemical score; NE, not estimable; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.
1. Hurvitz SA, et al. Oral presentation. SABCS [Virtual meeting] 2020. (Abstract GS3-06).

Sacituzumab Govitecan (SG) versus Treatment of Physician's Choice (TPC) in Patients (pts) with Previously Treated, Metastatic Triple-Negative Breast Cancer (mTNBC): Final Results from the Phase 3 ASCENT Study

Aditya Bardia et al.

ASCO 2022;Abstract 1071.

SACI-IO TNBC: Sacituzumab govitecan +/– pembrolizumab in 1L PD-L1– mTNBC[1,2]



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

Dana-Farber Cancer Institute

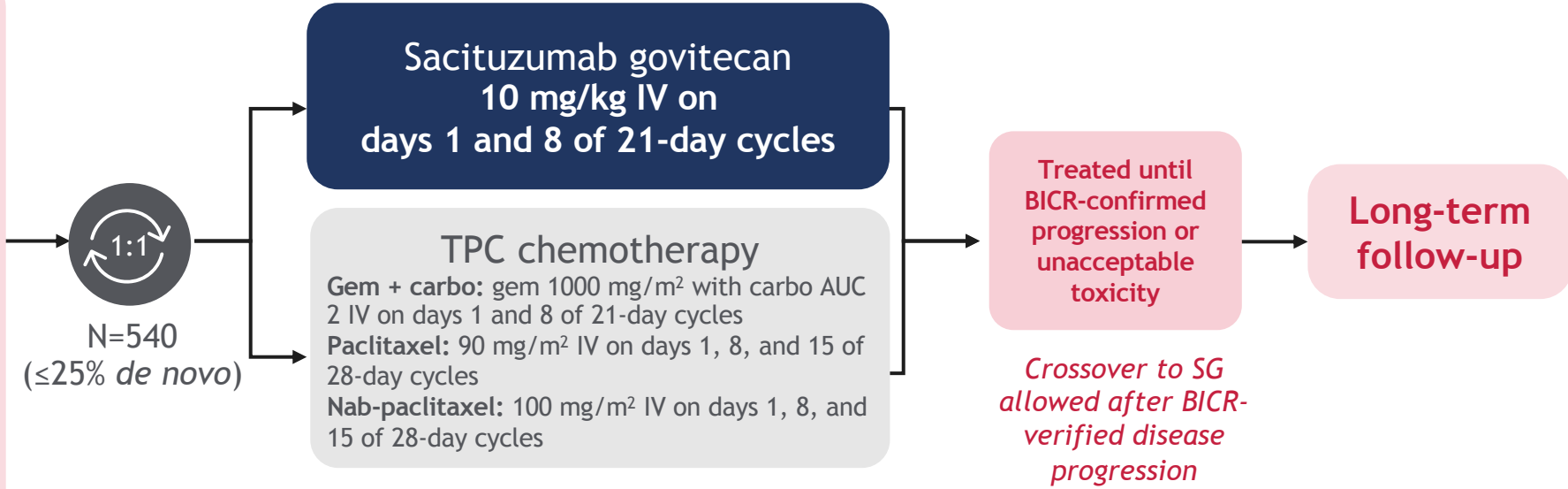
CBR, clinical benefit rate; ER, oestrogen receptor; HER2, human epidermal growth factor receptor; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PR, progesterone receptor; q21, 21 days cycle; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer.

1. Garrido-Castro, et al. Presentation. ASCO 2021. Abstract 1106; 2. ClinicalTrials.gov website. Available at: https://clinicaltrials.gov/ct2/show/NCT04468061 Accessed March 2022.

ASCENT 03: Sacituzumab govitecan vs TPC (Gem + carbo, paclitaxel, Nab-paclitaxel) in 1L PD-L1– mTNBC

1L mTNBC PD-L1–

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



Stratification Factors:

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

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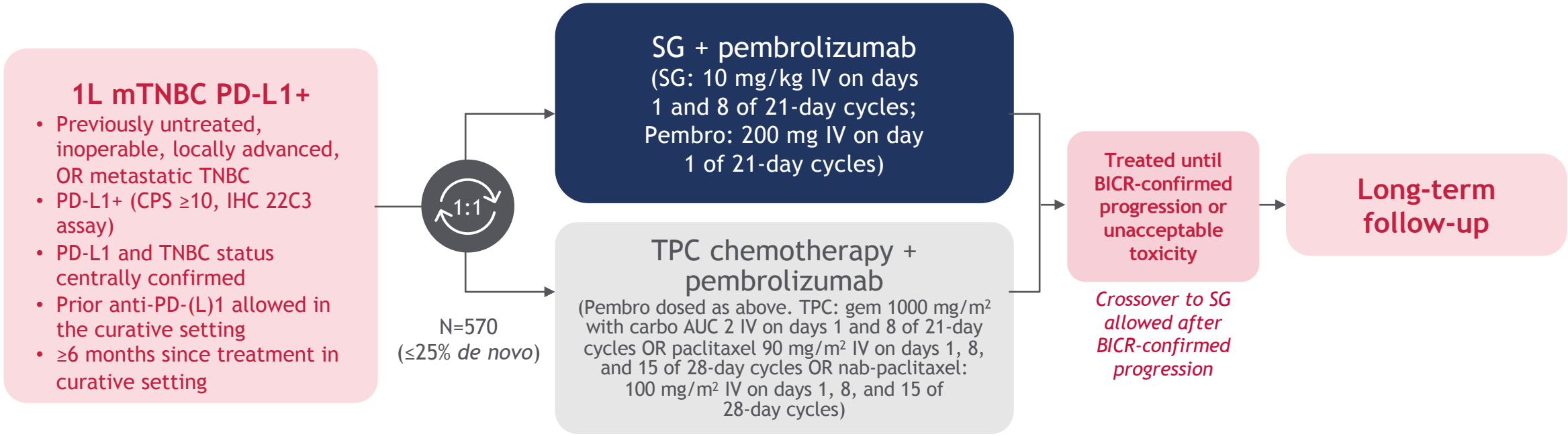
BICR, blinded independent central review; CPS, combined positive score; IHC, immunohistochemistry; mTNBC, metastatic triple negative breast cancer; PD-L1, programmed death ligand 1; R, randomized; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

1. EU Clinical trial register: EudraCT: 2021-005743-79. https://www.clinicaltrialsregister.eu/ctr-search/search/ Accessed April 2022.

ASCENT 04: Sacituzumab govitecan + pembrolizumab vs TPC + pembrolizumab in 1L PD-L1+ mTNBC



Stratification factors:

- *De novo* vs recurrent disease within 6–12 months of treatment in the curative setting vs recurrent disease >12 months after treatment in the curative setting
- Geographic region (US/Canada vs rest of world)
- Prior exposure to anti-PD-(L)1 therapy

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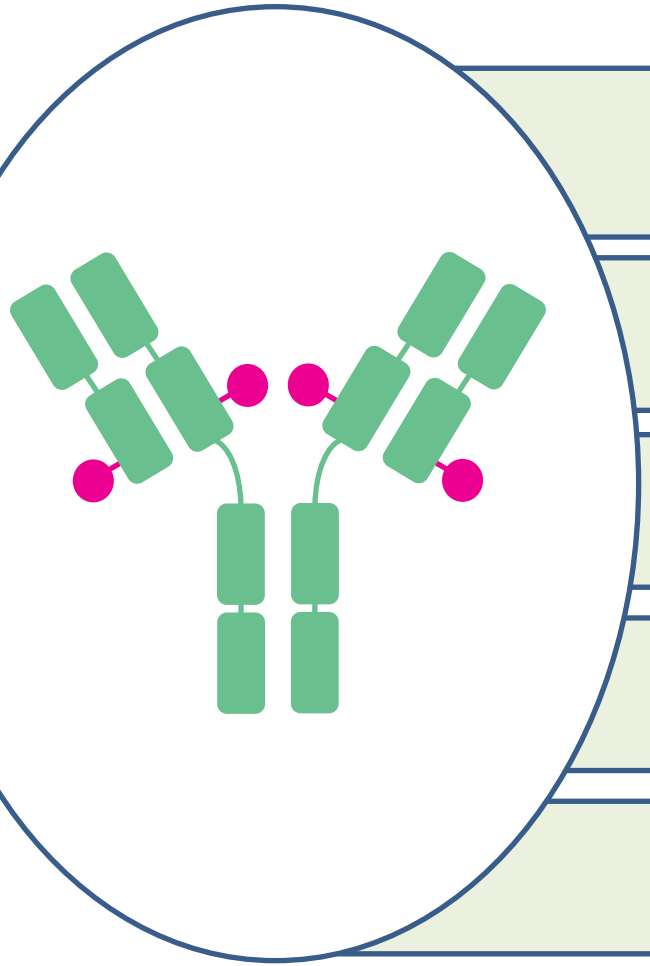
1L, first-line; AUC, area under the curve; BICR, blinded independent central review; Carbo, carboplatin; CPS, combined positive score; CI, confidence interval; Gem, gemcitabine; HR, hazard ratio; IHC, immunohistochemistry; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; PD-1, programmed cell death protein **1**; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

1. EU Clinical trial register: EudraCT: 2021-005742-14. https://www.clinicaltrialsregister.eu/ctr-search/search/ Accessed April 2022.

Datopotamab Deruxtecan (Dato-DXd): TROP2 ADC IN DEVELOPMENT

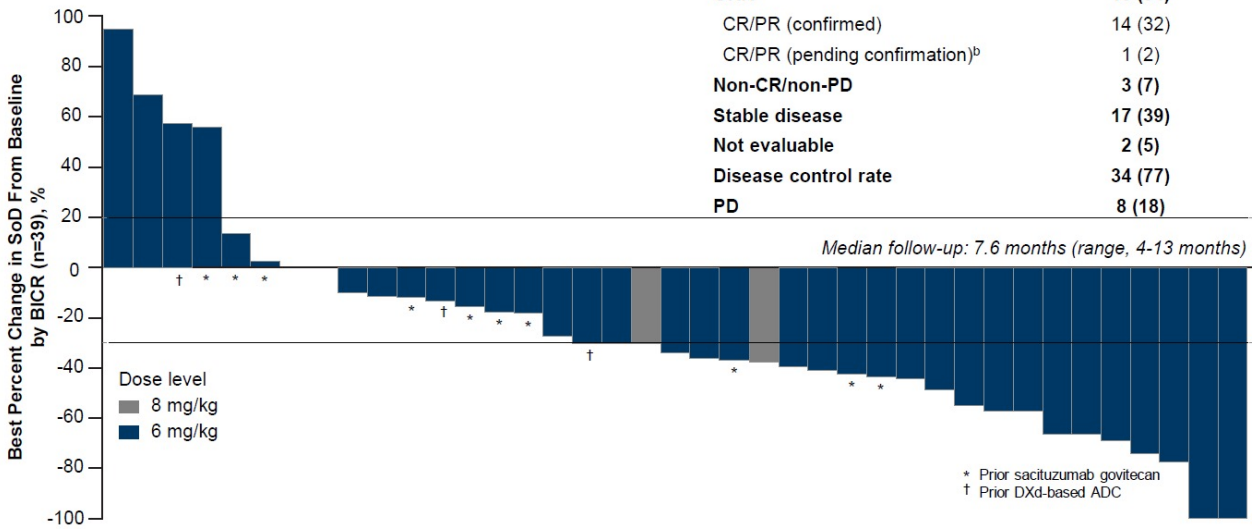


- Circulating free payload is negligible due to high stability of the linker, thereby limiting systemic exposure or nontargeted delivery of the payload[1]
- High-potency membrane-permeable payload (DXd) that requires TROP2-mediated internalization for release[2]
- DS-1062 has a DAR of 4 for optimized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

TROPION-PanTumor01: Dato-DXd in mTNBC

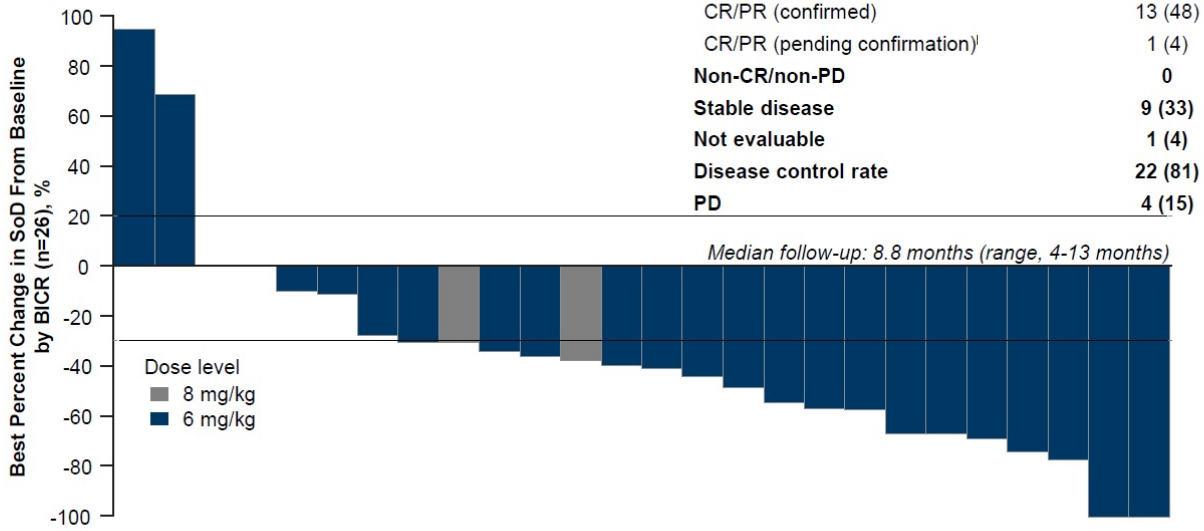
All patients with TNBC

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



Patients with TNBC without prior Topo I inhibitor-based ADC

Patients, n (%)	SG/DXd Naïve Patients (n=27)
ORR	**14 (52)**
CR/PR (confirmed)	13 (48)
CR/PR (pending confirmation)[l]	1 (4)
Non-CR/non-PD	**0**
Stable disease	**9 (33)**
Not evaluable	**1 (4)**
Disease control rate	**22 (81)**
PD	**4 (15)**



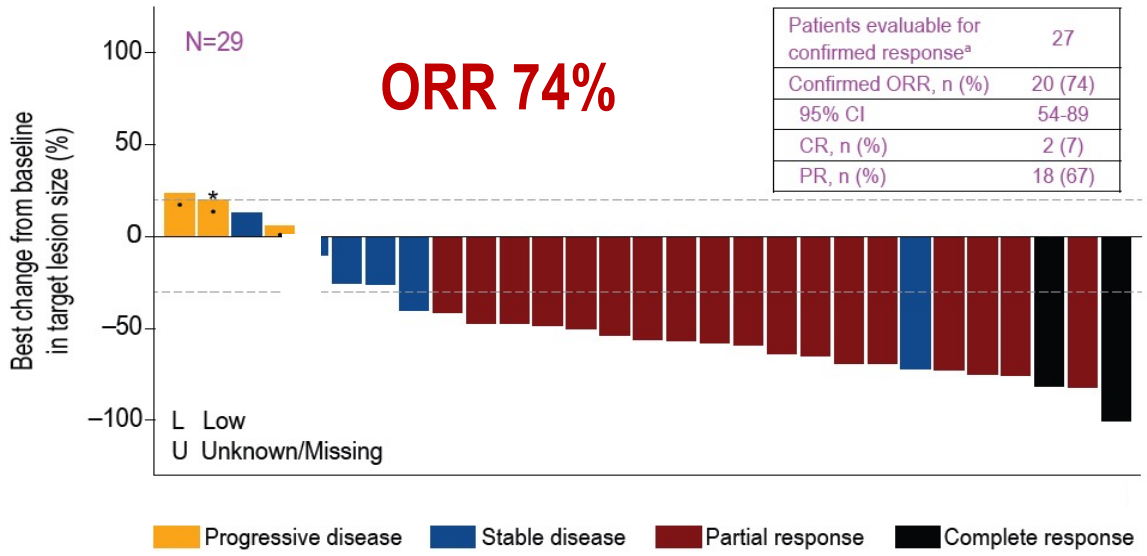
Krop I, et al. SABCS 2021. Abstract GS1-05.

BEGONIA Trial: Dato-DXd + Durvalumab

- No DLTs
- 28% G3 TRAEs; no G4/5 TRAEs
- 14% Dato-DXd dose reduction (all stomatitis)
- 7% treatment discontinuation
- Diarrhea 14%, all Grade 1
- No ILD/pneumonitis or neutropenic events

Preferred term, n (%) AEs all causes	Dato-DXd + D N=29			
	All Grades, ≥15% of patients	Grade 1	Grade 2	Grade ≥3
Stomatitis	20 (69)	8 (28)	8 (28)	4 (14)
Alopecia	19 (66)	13 (45)	6 (21)	0
Nausea	19 (66)	13 (45)	6 (21)	0
Constipation	11 (38)	8 (28)	3 (10)	0
Fatigue	11 (38)	9 (31)	2 (6.9)	0
Rash	9 (31)	8 (28)	1 (3)	0
Vomiting	5 (17)	3 (10)	2 (6.9)	0

Dato-DXd 6 mg/kg + D 1120 mg
69% visceral metastasis, 66% prior CT for EBC



Schmid P et al, ESMO Breast 2022

TROPION-Breast02 Study Schema

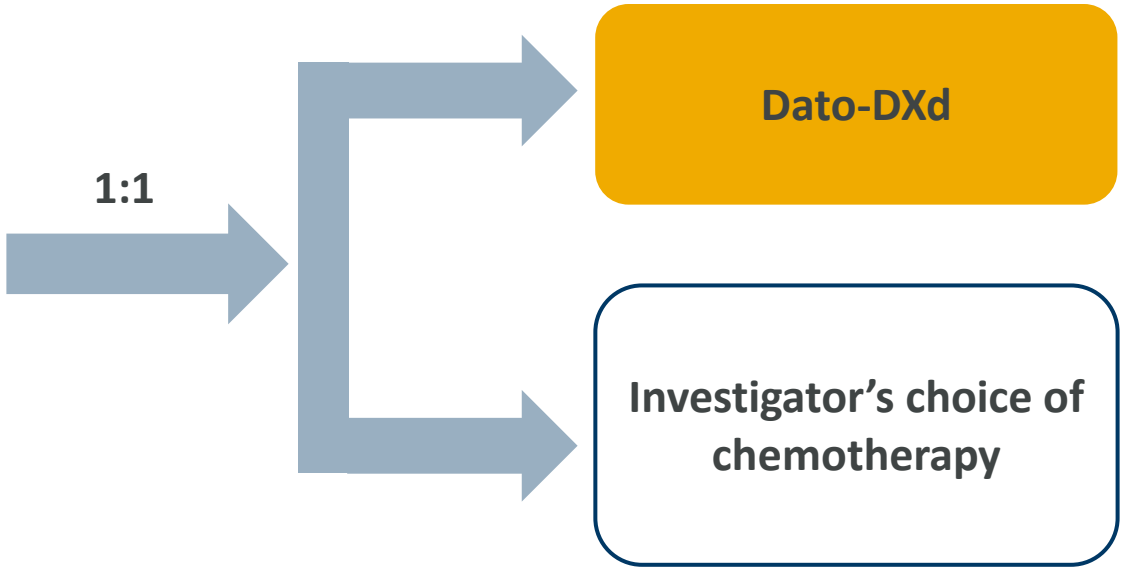
Full trial information to be posted to ClinicalTrials.gov

Key eligibility criteria:

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1 / PD-L1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:

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



Dual primary endpoint:
PFS (BICR) and OS

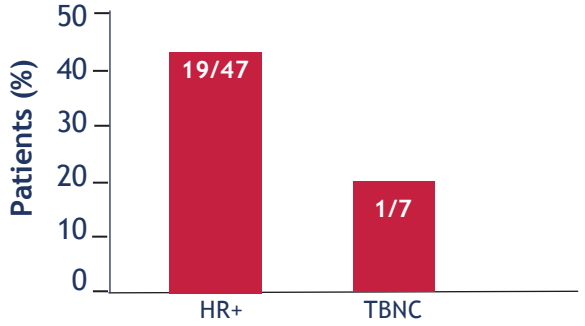
Secondary endpoints:
PFS (inv), ORR, DoR, safety

HER2-directed ADCs for HER2-low breast cancer

Potential treatment option for approximately 35% of patients[1]

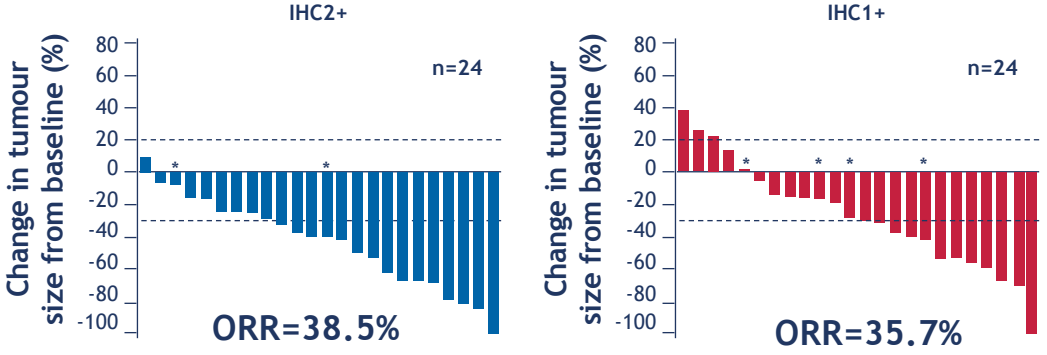
Trastuzumab deruxtecan[2]

Greater activity in HR+ HER2-low compared to TNBC HER2-low



Press release announcing positive results for DB-04

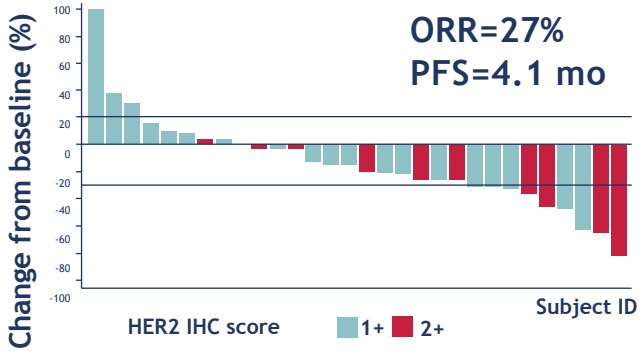
Similar benefit for HER2 2+ and 1+



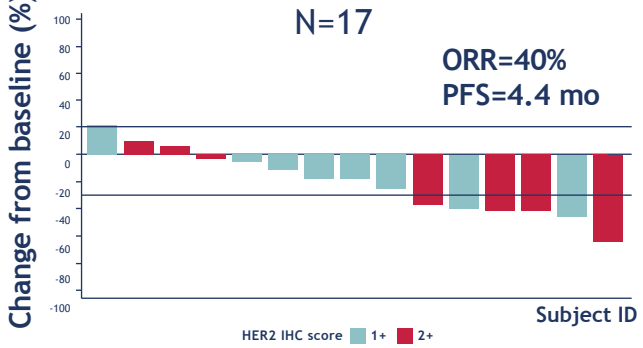
mPFS= 11.1 mo

Trastuzumab duocarmazine[3]

HR+ HER2-low
N=32

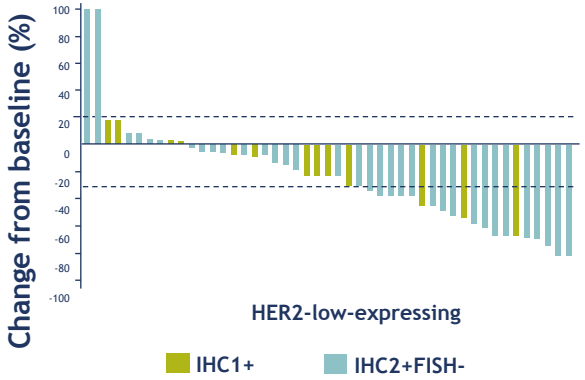


HR− HER2-low
N=17



RC48[4]

HER2 low
N=48



ORR=39.6%
PFS=5.7 mo

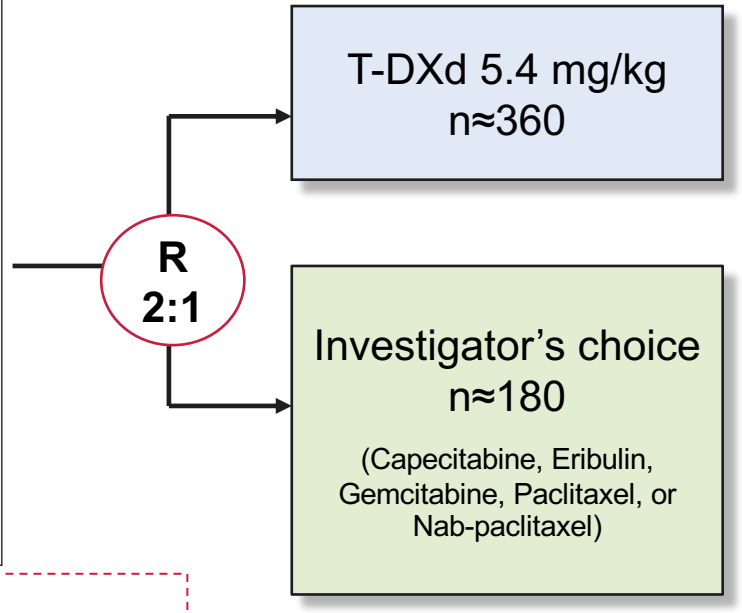
ADC, antibody-drug conjugate; FISH, fluorescence in-situ hybridisation; IHC, immunohistochemistry; ORR, objective reaction rate; PFS, progression-free survival.

1. Schettini F, et al. *npj Breast Cancer*. 2021;7:1; 2. Modi S, et al. *J Clin Oncol*. 2020;30:1887–1896; 3. Saura C, et al. Poster. ASCO 2018. Abstract 1014; 4. Wang J, et al. Poster. ASCO 2021. Abstract 1022.

DESTINY-Breast04: T-DXd vs Investigator's Choice in metastatic HER2-low breast cancer

Key Eligibility Criteria

- HER2-low (IHC 1+ or IHC 2+/ISH-)
- Unresectable or metastatic breast cancer
- Previously treated with 1 or 2 lines of chemotherapy in the metastatic setting
- If HR-positive, must have received prior endocrine therapy, no restriction on prior targeted therapy



Stratification factors:
- **HER2 IHC status assessed by central lab**: HER2 IHC 1+ vs HER2 IHC 2+/ISH-
- **Number of prior lines of chemotherapy**: 1 vs. 2
- **HR/CDK status**: HR-positive with prior CDK4/6 inhibitor treatment (min. 240) vs. HR-positive without prior CDK4/6 inhibitor treatment (max. 240) vs. HR-negative (max. 60)

Primary endpoint
- PFS (BICR) in HR+

Key Secondary endpoints
- PFS (BICR) HR+ & HR-
- OS in HR+
- OS in OS in HR+ & HR-

Secondary endpoints
- PFS (INV) in HR+
- ORR in HR+
- DoR (BICR) in HR+

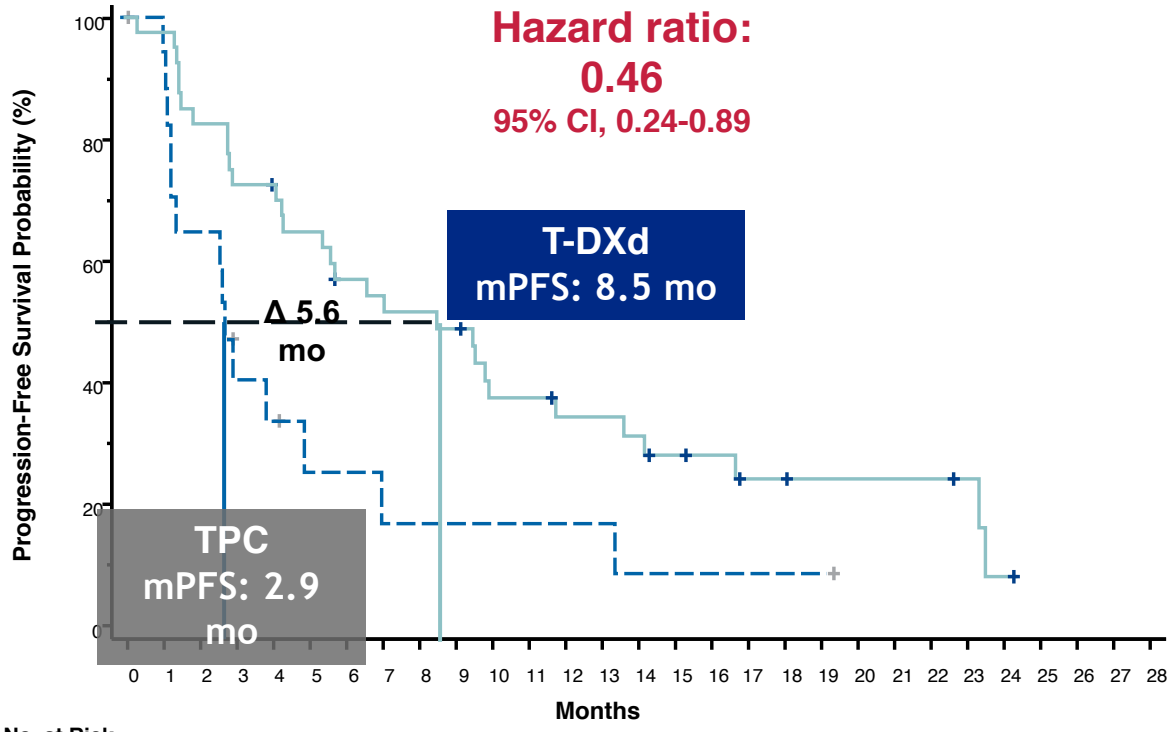
Significant improvement in PFS and OS in ITT and HR+ pts, with consistent results in TNBC

BICR=blinded independent central review; CDK=cyclin-dependent kinase; DoR=duration of response; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IHC=immunohistochemistry; INV=investigator assessment; ISH=in situ hybridization; max.=maximum; min.=minimum; ORR=objective response rate; OS=overall survival; PFS=progression free survival; T-DXd=trastuzumab deruxtecan

Modi S et al, ASCO 2022

PFS and OS in HR− (Exploratory Endpoints)

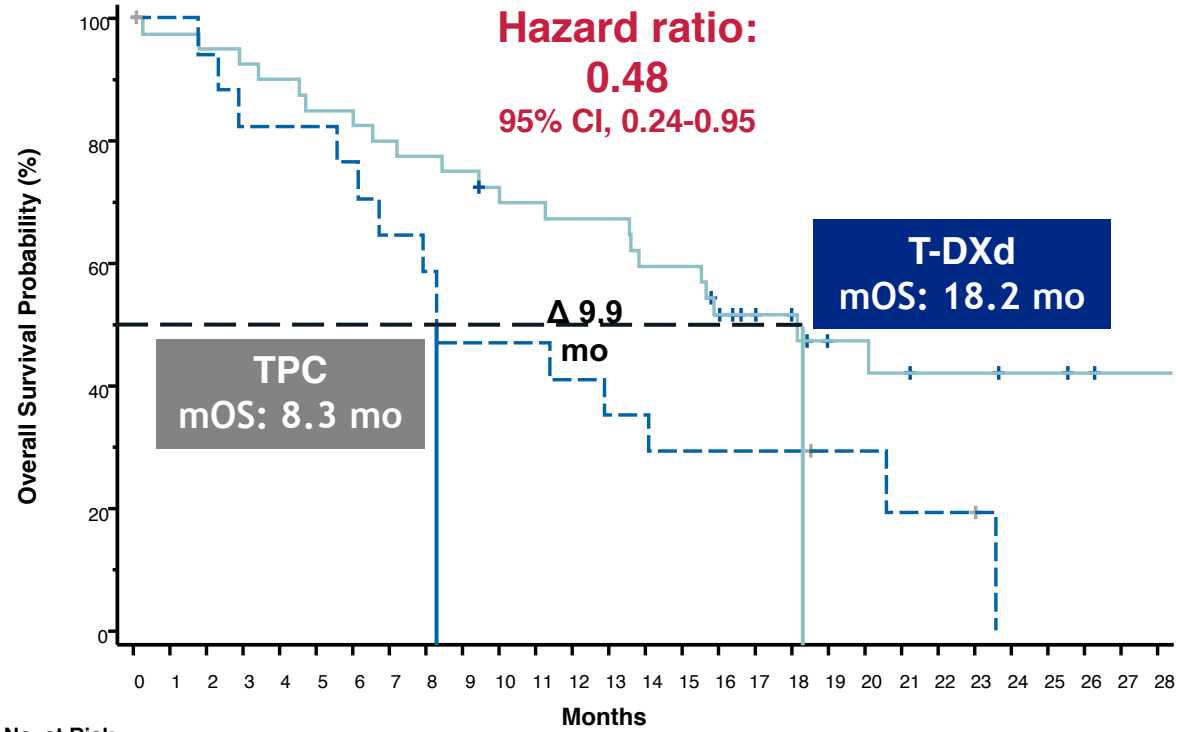
PFS



No. at Risk

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

OS



No. at Risk

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

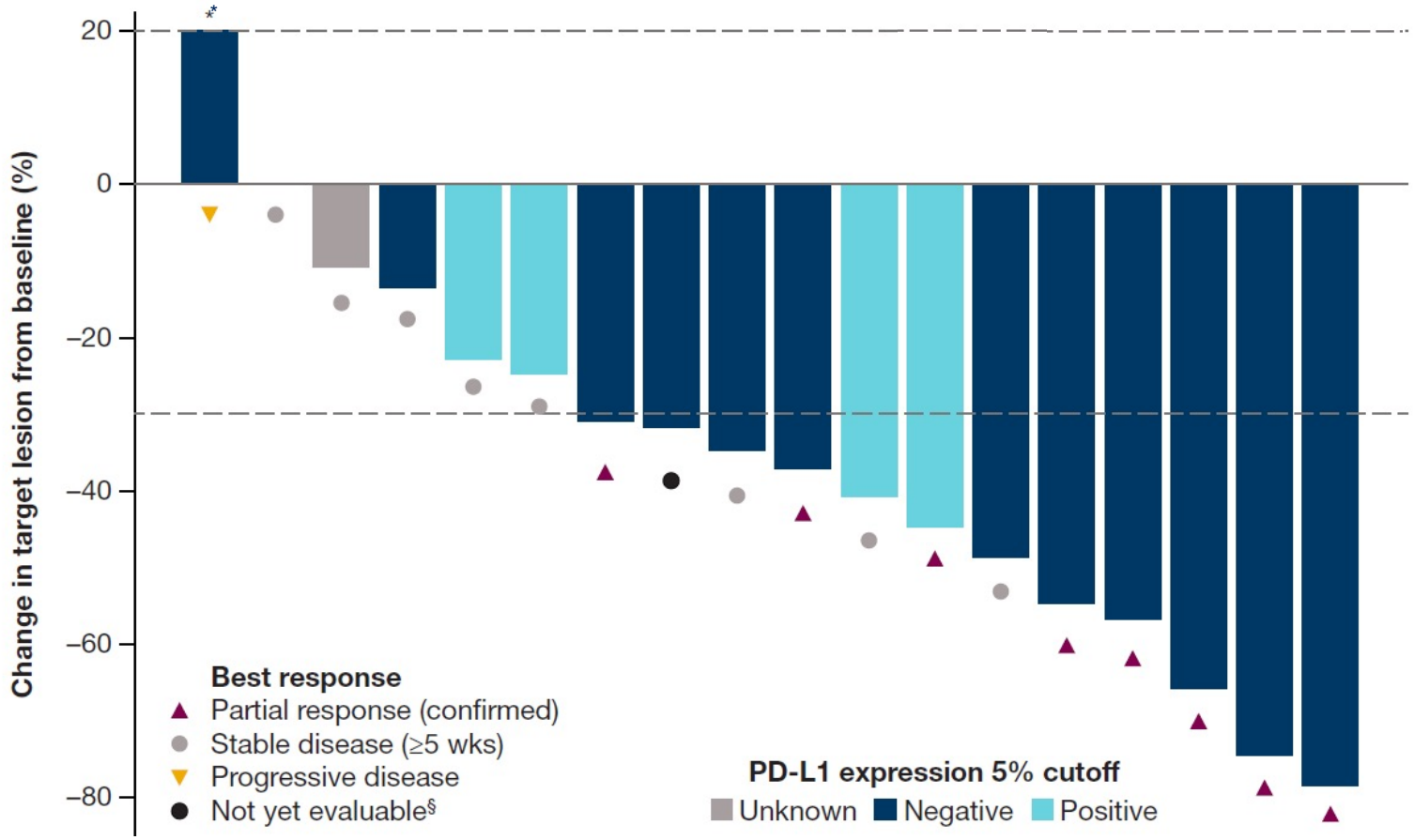
HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based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

Modi S et al, ASCO 2022

TDxd+ Durvalumab: Efficacy

- Responses were observed in both PD-L1–positive (confirmed ORR 1/1 [100%]) and PD-L1–negative (confirmed ORR 7/10 [70.0%]) groups

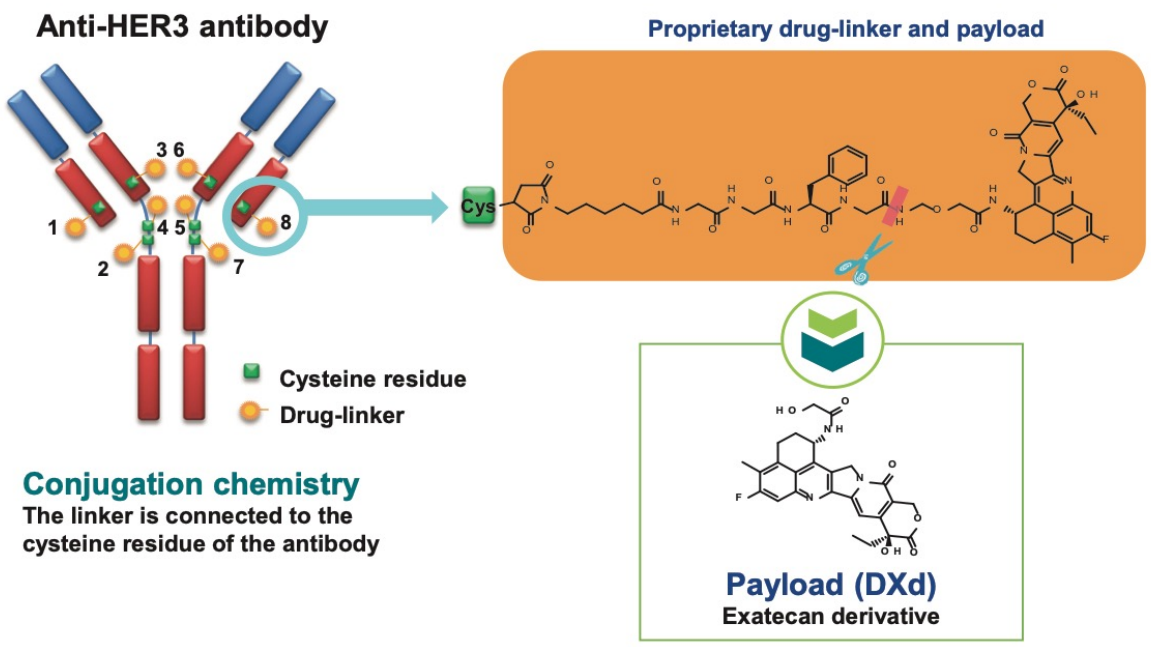
Parameter	D+T-DXd
Patients who completed at least 1 on-treatment assessment, n	18
Response evaluable analysis set, n‡	12
Confirmed ORR, n (%)‡ 95% CI Complete response, n Partial response, n	8/12 (66.7) 41.0, 86.7 0 8
Stable disease, n	8
Progressive disease, n	1

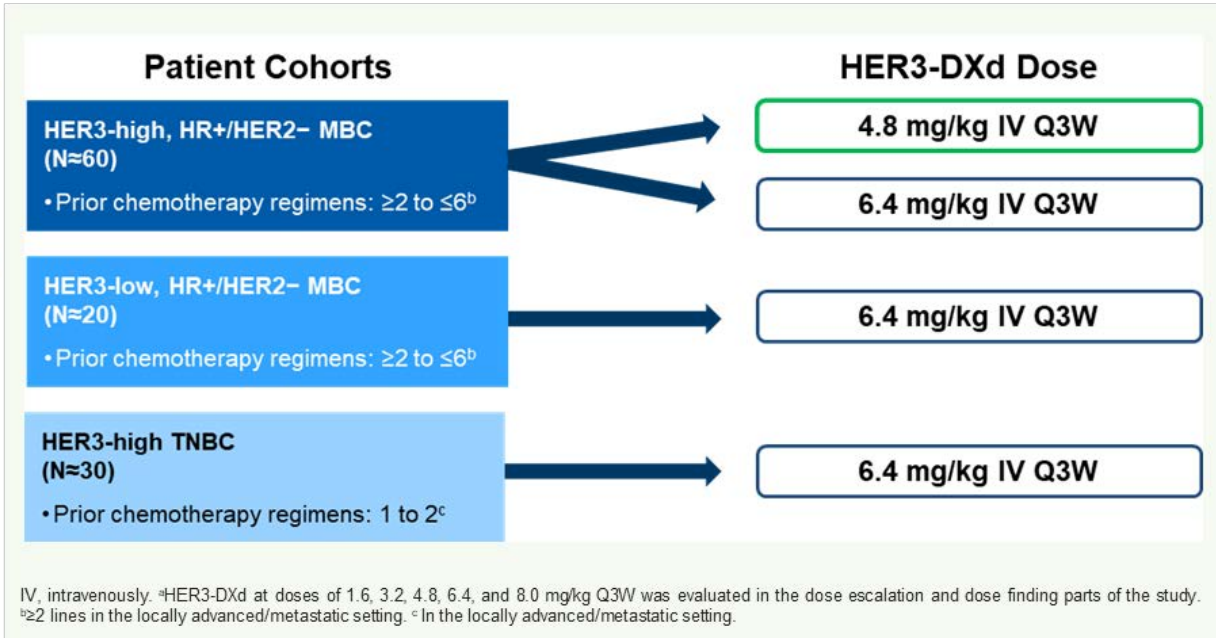


Will there be a role for TDxd+ Durvalumab in 1L HER2low TNBC?
And will activity be greater than TDxd alone even in PD-L1- negative patients?

Schmid P et al, ASCO 2021

Patritumab Deruxtecan: Her3 ADC

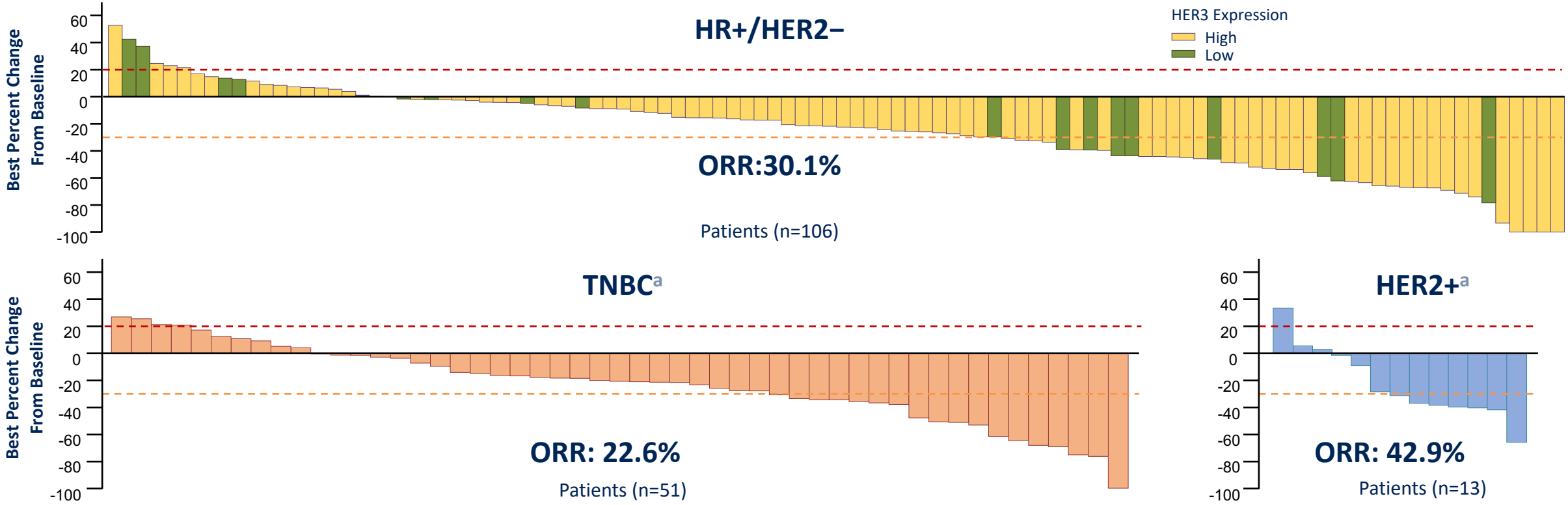




Krop I et al ASCO 2022

Change in Tumor Size From Baseline

Patritumab Deruxtecan
U31402-A-J101

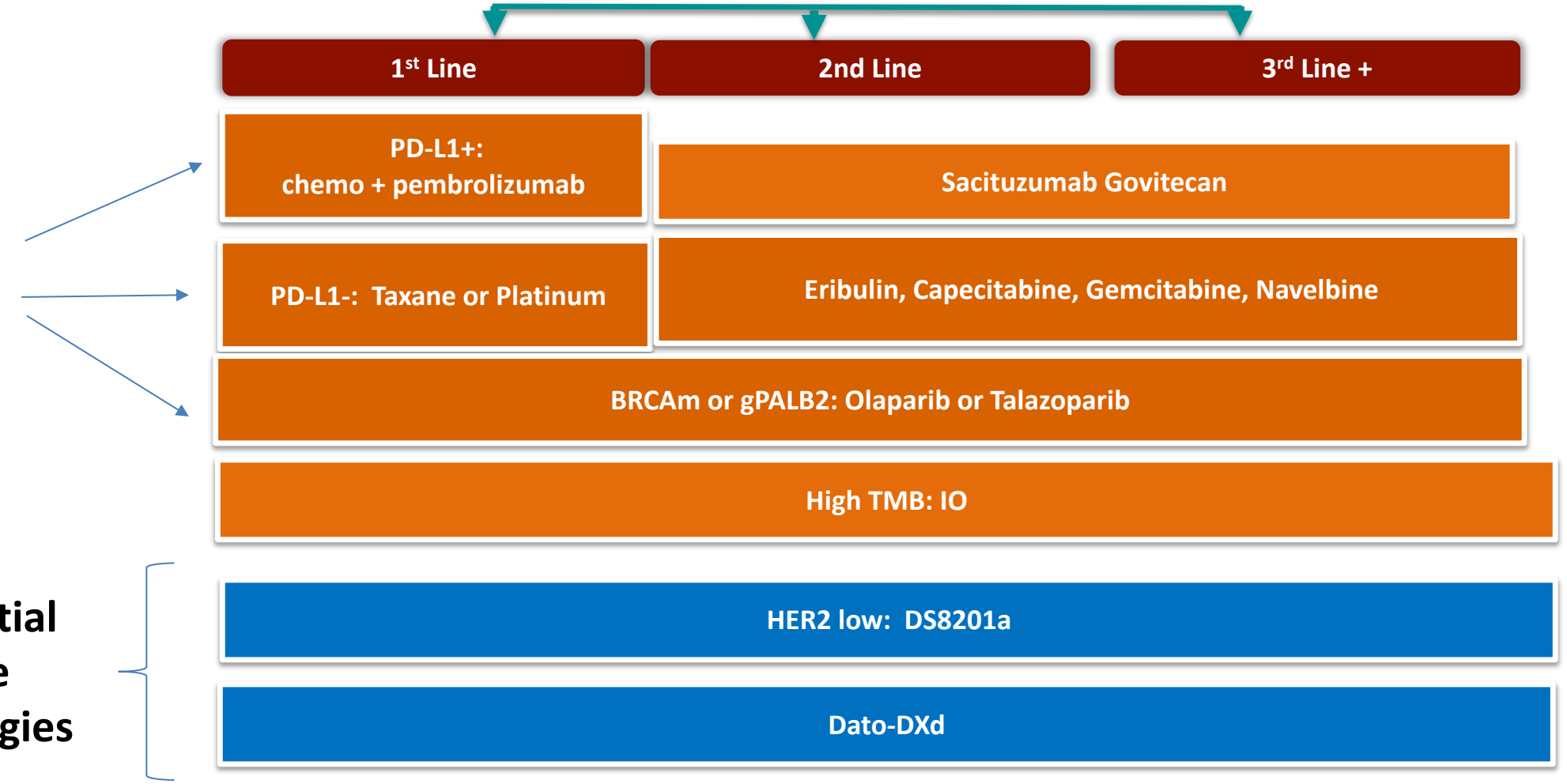


HER3-DXd induced a clinically meaningful decrease in tumor size by BICR in most patients across BC subtypes.[b]

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

Krop I et al ASCO 2022

Approach to Therapy for Metastatic TNBC+ disease: Move to Personalization



Breakfast with the Investigators: Multiple Myeloma

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Tuesday, June 7, 2022

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Ajai Chari, MD

Elizabeth O'Donnell, MD

Robert Z Orlowski, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME links will be posted in the chat (Zoom participants only) and emailed to all participants within 24 hours of the program.

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