What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of ER-Positive Breast Cancer

Part 2 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2022 San Antonio Breast Cancer Symposium®

Thursday, December 8, 2022
7:15 PM – 9:15 PM CT

Faculty

Aditya Bardia, MD, MPH
Matthew P Goetz, MD
Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Hope S Rugo, MD

Moderator

Neil Love, MD

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Faculty

Aditya Bardia, MD, MPH
Director, Breast Cancer Research Program
Associate Professor
Harvard Medical School
Attending Physician
Massachusetts General Hospital
Boston, Massachusetts

Matthew P Goetz, MD
Erivan K Haub Family Professor of Cancer Research
Honoring Richard F Emslander, MD
Professor of Oncology and Pharmacology
Enterprise Deputy Director, Translational Research
Director, Mayo Clinic Breast Cancer SPORE
Mayo Clinic
Rochester, Minnesota

Virginia Kaklamani, MD, DSc
Professor of Medicine
Ruth McLean Bowman Bowers Chair in Breast Cancer Research and Treatment
AB Alexander Distinguished Chair in Oncology
Associate Director for Clinical Research
Leader of the Breast Cancer Program
UT Health San Antonio
The University of Texas MD Anderson Cancer Center
San Antonio, Texas

Kevin Kalinsky, MD, MS
Associate Professor
Department of Hematology and Medical Oncology
Emory University School of Medicine
Director, Glenn Family Breast Center
Director, Breast Medical Oncology
Winship Cancer Institute of Emory University
Atlanta, Georgia

Hope S Rugo, MD
Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Moderator

Neil Love, MD
Research To Practice

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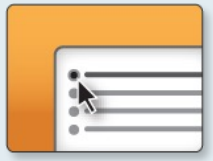
Clinicians in the Meeting Room

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 pre- and postmeeting surveys. 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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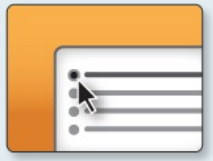
Clinicians Attending via Zoom

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 pre- and postmeeting surveys. 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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Addressing Current Questions and Controversies in the Management of Chronic Lymphocytic Leukemia — What Clinicians Want to Know

Part 1 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
11:30 AM – 1:30 PM CT (12:30 PM – 2:30 PM ET)

Faculty

Alexey V Danilov, MD, PhD
Matthew S Davids, MD, MMSc
Professor Dr Arnon P Kater, MD, PhD
Lindsey Roeker, MD
Philip A Thompson, MB, BS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Addressing Current Questions and Controversies in the Management of Hodgkin and Non-Hodgkin Lymphoma — What Clinicians Want to Know

Part 2 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
3:15 PM – 5:15 PM CT (4:15 PM – 6:15 PM ET)

Faculty

Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD
David G Maloney, MD, PhD
Loretta J Nastoupil, MD
Sonali M Smith, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Addressing Current Questions and Controversies in the Management of Multiple Myeloma — What Clinicians Want to Know

Part 3 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Jesús G Berdeja, MD
Rafael Fonseca, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD

Moderator

Neil Love, MD

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Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky

Jennifer L Dallas, MD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Susmitha Apuri, MD
Florida Cancer Specialists
Lutz, Florida

Kapisthalam (KS) Kumar, MD
Florida Cancer Specialists
Trinity, Florida

Alan B Astrow, MD
Weill Cornell Medicine
Brooklyn, New York

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Exact Sciences Corporation, Lilly, Novartis, Sanofi, and TerSera Therapeutics LLC.

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 Bardia — Disclosures

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Contracted Research	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Merck, Novartis, Pfizer Inc, Radius Health Inc, Sanofi

Dr Goetz — Disclosures

Advisory Committee	ARC Therapeutics, Biotheranostics Inc, Blueprint Medicines, Sanofi
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Biovica, Context Therapeutics, Eagle Pharmaceuticals, Lilly, Novartis, Pfizer Inc
Contracted Research	Lilly, Pfizer Inc, Sermonix Pharmaceuticals
Nonrelevant Financial Relationship (CME Presentation Fees)	Clinical Education Alliance, Medscape, MJH Life Sciences
Nonrelevant Financial Relationship (Panelist)	Total Health Conferencing

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Dr Kaklamani — Disclosures

Advisory Committee and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Athenex, Gilead Sciences Inc, Puma Biotechnology Inc
Contracted Research	Eisai Inc
Data and Safety Monitoring Board/Committee	Sanofi
Speakers Bureau	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Exact Sciences Corporation, Genentech, a member of the Roche Group, Gilead Sciences Inc, Novartis, Pfizer Inc, Seagen Inc

Dr Kalinsky — Disclosures

Advisory Committee	D Pharma PLC, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Gilead Sciences Inc, Lilly, Menarini Silicon Biosystems, Merck, Mersana Therapeutics Inc, Myovant Sciences, Novartis, OncoSec Medical, Pfizer Inc, Puma Biotechnology Inc, Seagen Inc, Takeda Phamraceuticals USA Inc
Contracted Research	Ascentage Pharma, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Lilly, Novartis
Data and Safety Monitoring Board/Committee	Merck

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Dr Rugo — Disclosures

Consultancy/Advisory Support	Blueprint Medicines, Napo Pharmaceuticals Inc, Puma Biotechnology Inc
Contracted Research	Ambrx, Astellas, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Lilly, Merck, Novartis, OBI Pharma Inc, Pfizer Inc, Pionyr Immunotherapeutics, Seagen Inc, Sermonix Pharmaceuticals, Taiho Oncology Inc, Veru Inc
Travel Support to Academic Meetings	AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Merck.

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Moderator

Neil Love, MD

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Agenda

Module 1: Current Role of Genomic Assays for Hormone Receptor (HR)-Positive Localized Breast Cancer — Dr Goetz

Module 2: Optimizing the Management of Localized ER-Positive Breast Cancer — Dr Kaklamani

Module 3: Selection and Sequencing of Therapy for Patients with ER-Positive Metastatic Breast Cancer (mBC) — Dr Kalinsky

Module 4: Recent Appreciation of HER2 Low as a Unique Subset of HR-Positive Breast Cancer — Dr Bardia

Module 5: Novel Strategies Under Investigation for Patients with HR-Positive mBC — Dr Rugo

Agenda

Module 1: Current Role of Genomic Assays for Hormone Receptor (HR)-Positive Localized Breast Cancer — Dr Goetz

▸ *Real World Cases and Questions*

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MODULE 1: Current Role of Genomic Assays for Hormone Receptor (HR)-Positive Localized Breast Cancer — Dr Goetz

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Case Presentation: 42-year-old premenopausal woman with 9-mm, Grade III, ER/PR-positive, HER2-negative, node-negative IDC – 21-gene RS: 22

Dr Alan Astrow (Brooklyn, New York)

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Case Presentation: 35-year-old premenopausal woman with 3.6-cm, ER/PR-positive, HER2-low (IHC 1+), sentinel node-positive (4/4) multifocal IDC, s/p bilateral mastectomies, adjuvant T → AC and OFS/AI — Ki67: 50%

Dr Laila Agrawal (Louisville, Kentucky)

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Current Role of Genomic Assays for Hormone Receptor (HR)-Positive Localized Breast Cancer

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

- Phase III RxPONDER trial evaluating the role of chemotherapy for patients with ER-positive, HER2-negative localized breast cancer with 1 to 3 positive lymph nodes and a 21-gene Recurrence Score (RS) of ≤25

- Updated findings, including 12-year event rates, from the Phase III TAILORx study

- 21-gene RS and neoadjuvant chemotherapy decision making

- Insight regarding poor correlation between the RS and chemotherapy response in premenopausal patients

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):1816-37.

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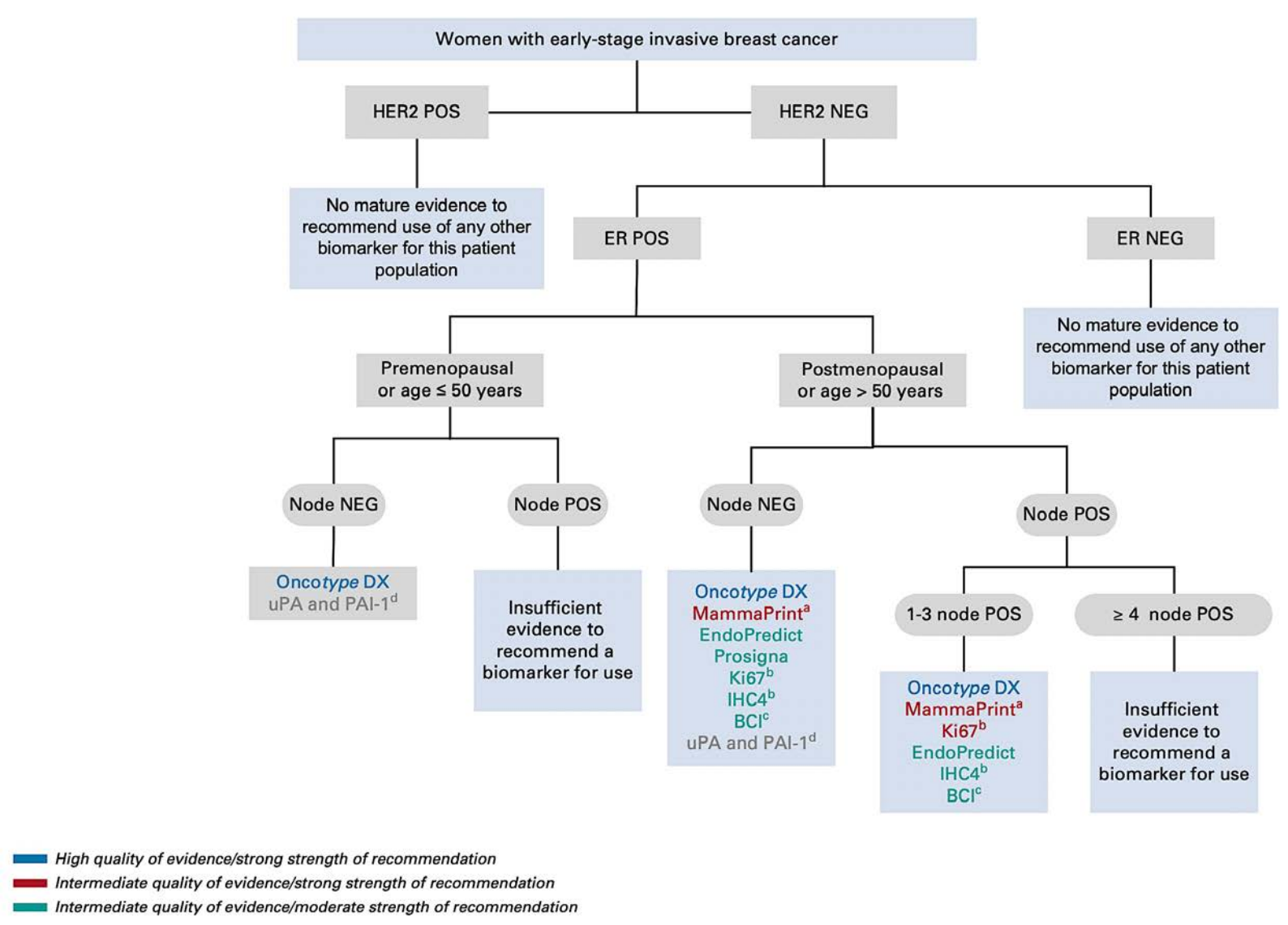
Biomarkers for Adjuvant Endocrine and Chemotherapy in Localized Breast Cancer: ASCO Guideline Update



Andre F et al. *J Clin Oncol* 2022;40(16):1816-37.

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San Antonio Breast Cancer Symposium®, December 7-10, 2021

RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer

Updated results from a phase 3 randomized clinical trial in participants (pts) with 1-3 positive lymph nodes, hormone receptor-positive (HR+) and HER2-negative breast cancer with recurrence score of 25 or less: SWOG S1007

Kevin Kalinsky, William E Barlow, Julie R Gralow, Funda Meric-Bernstam, Kathy S Albain, Daniel F Hayes, Nancy U Lin, Edith A Perez, Lori J Goldstein, Stephen K Chia, Sukhbinder Dhesy-Thind, Priya Rastogi, Emilio Alba, Suzette Delaloge, Miguel Martin, Catherine M Kelly, Manuel Ruiz-Borrego, Miguel Gil Gil, Claudia Arce-Salinas, Etienne G.C. Brain, Eun Sook Lee, Jean-Yves Pierga, Begoña Bermejo, Manuel Ramos-Vazquez, Kyung Hae Jung, Jean-Marc Ferrero, Anne F. Schott, Steven Shak, Priyanka Sharma, Danika L. Lew, Jieling Miao, Debasish Tripathy, Lajos Pusztai, Gabriel N. Hortobagyi

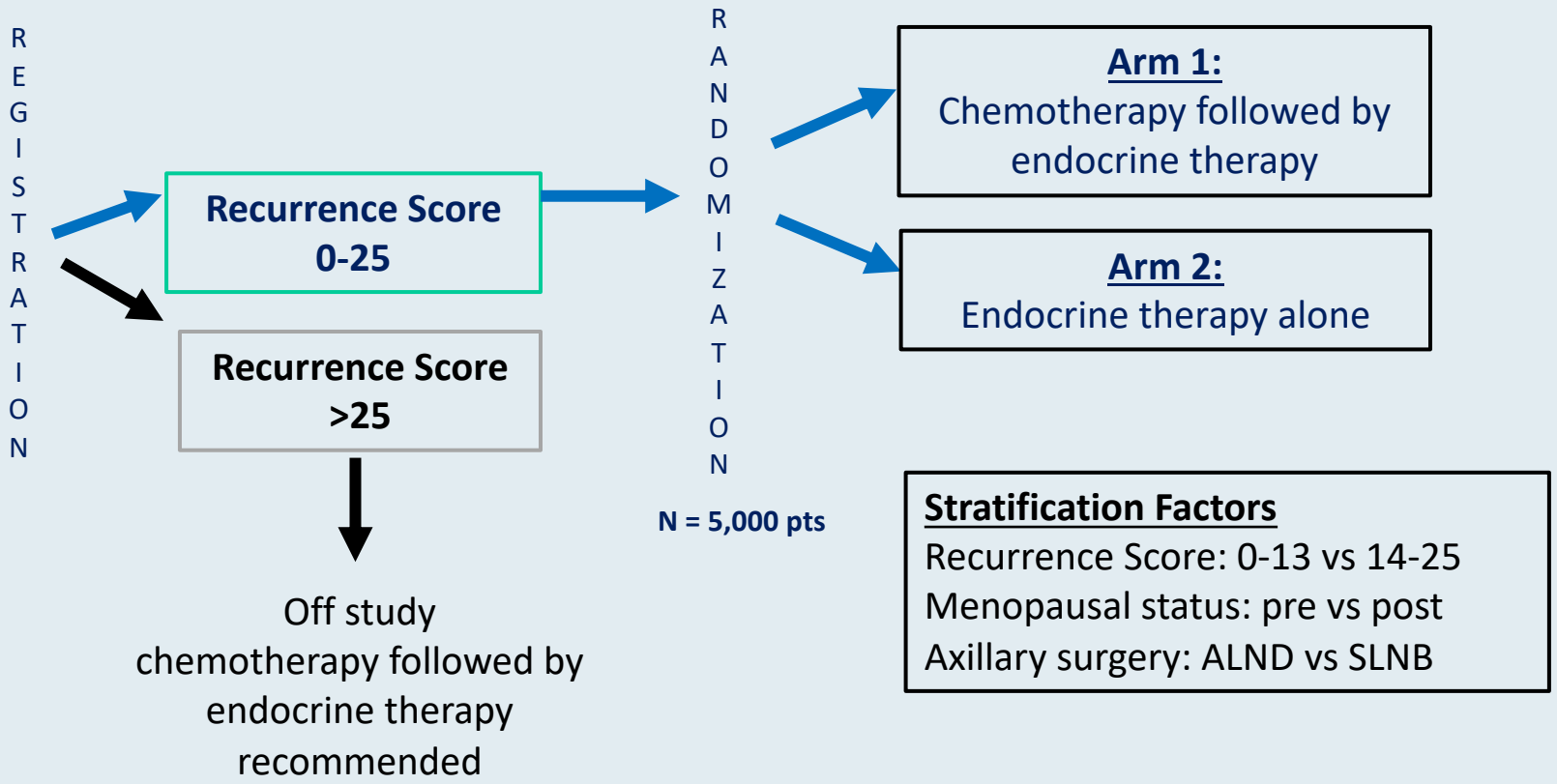
On Behalf of the RxPonder Investigators

SABCS 2021;Abstract GS2-07.

RxPONDER Trial Schema

Key Entry Criteria

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



* 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.

LN = lymph node; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; pts = patients

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

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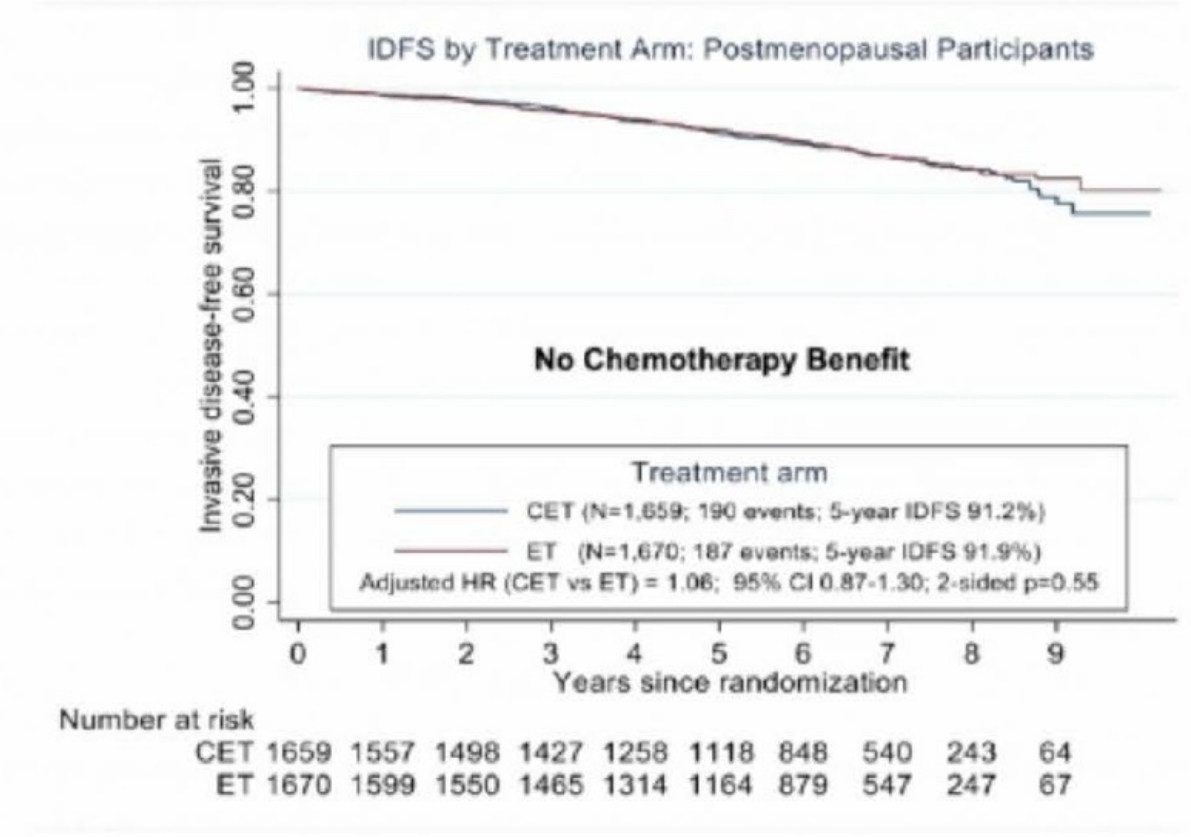
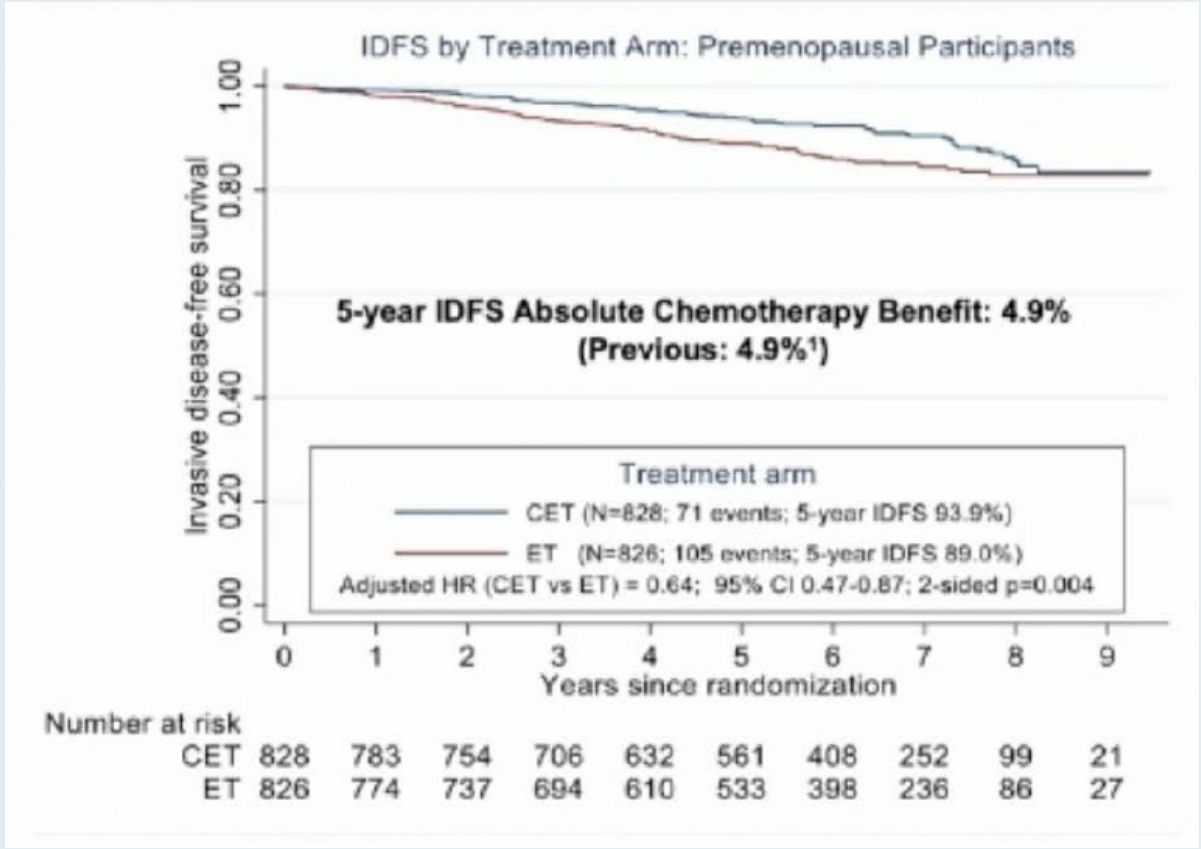
RxPONDER Updated Analysis: IDFS Stratified by Menopausal Status

Postmenopausal



Premenopausal



IDFS = invasive disease-free survival

Kalinsky K et al. SABCS 2021;Abstract GS2-07.

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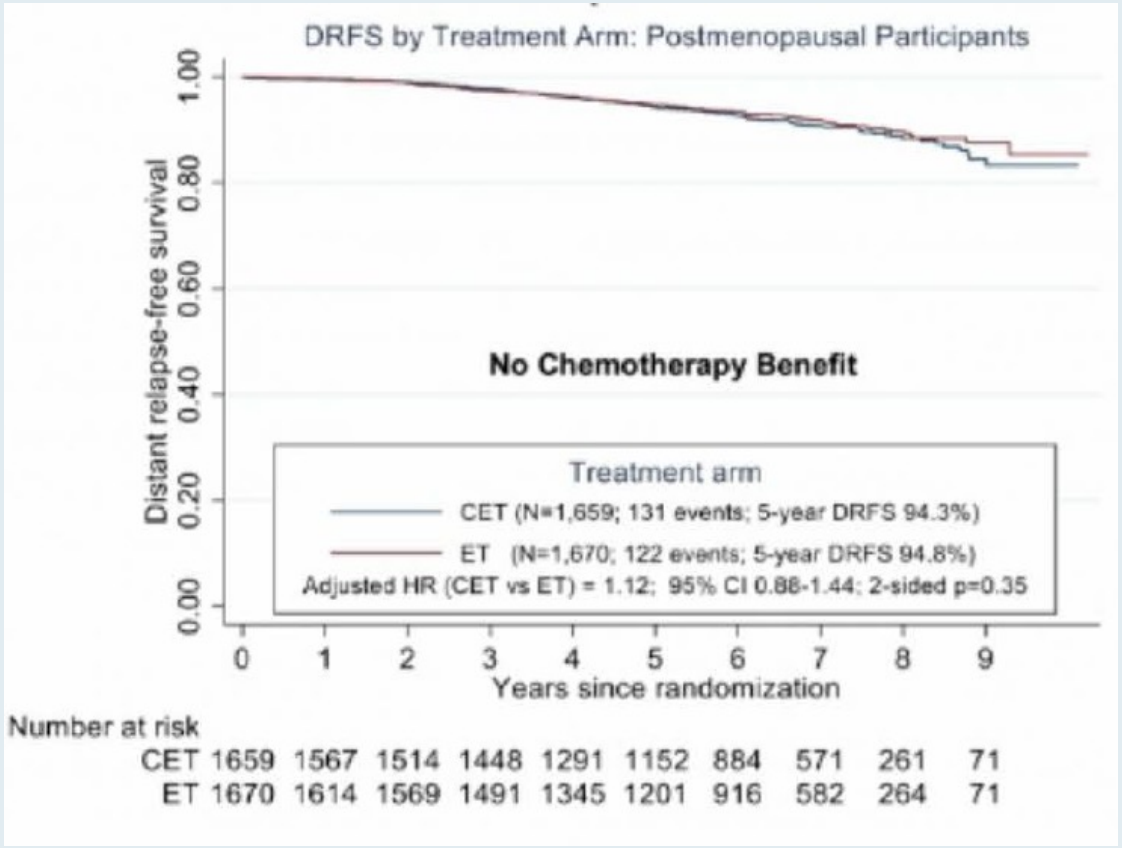
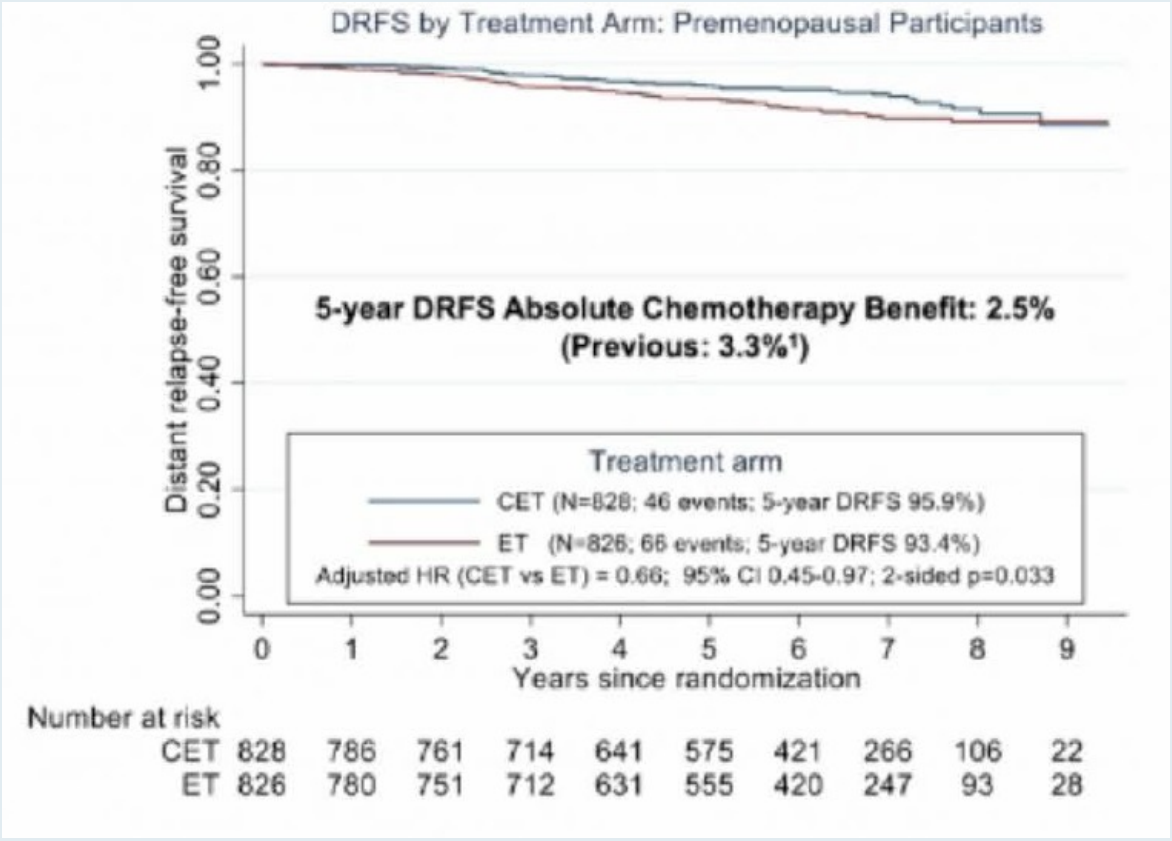
RxPONDER Updated Analysis: DRFS Stratified by Menopausal Status

Postmenopausal



Premenopausal

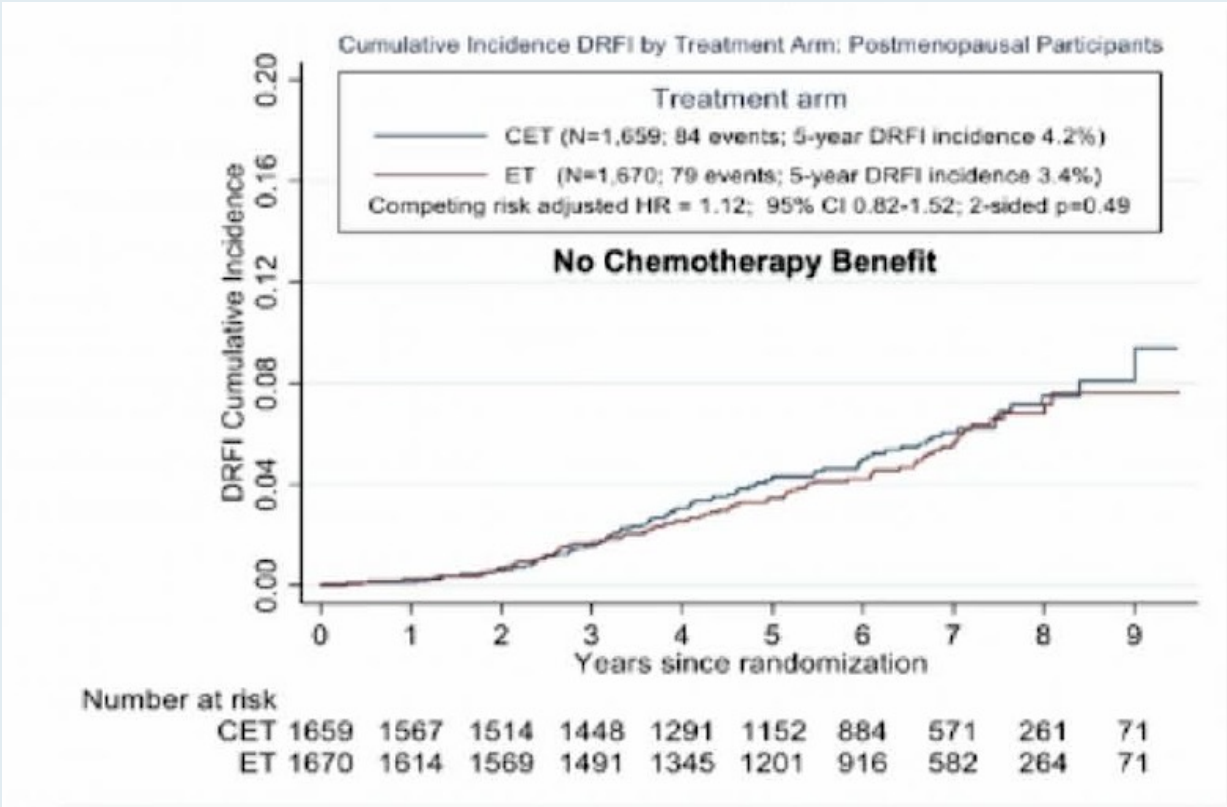


DRFS = distant recurrence-free survival

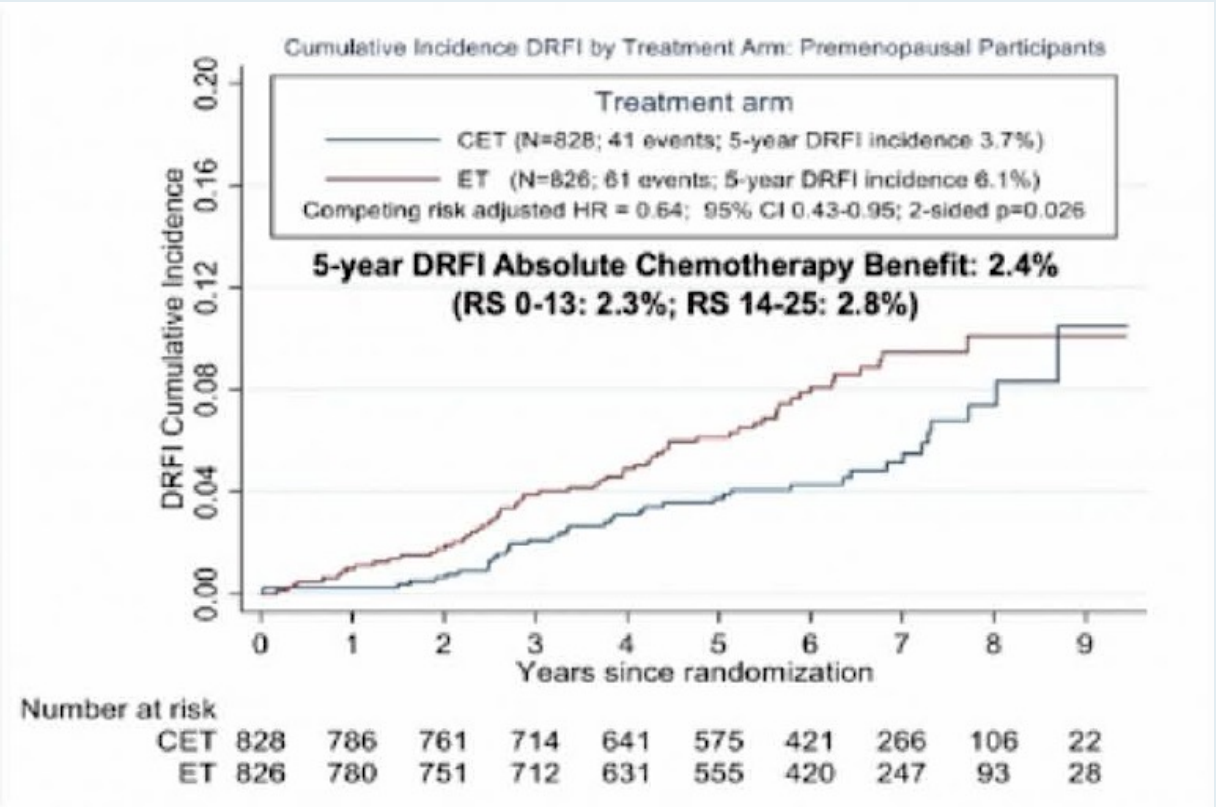
Kalinsky K et al. SABCS 2021;Abstract GS2-07.

RxPONDER New Analysis: DRFI Stratified by Menopausal Status

Postmenopausal



Premenopausal



Time from randomization assignment to date of first invasive recurrence (distant) or death from breast cancer

In multivariate analysis, higher RS (continuous) and larger tumor size remained independently prognostic in both treatment arms

DRFI = distant recurrence-free interval

Kalinsky K et al. SABCS 2021;Abstract GS2-07.

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Trial Assigning IndividuaLized Options for TReatment (TAILORx): An Update Including 12-Year Event Rates

Joseph A. Sparano, Robert J. Gray, Della F. Makower, Kathy S. Albain, Daniel F. Hayes, Charles E. Geyer, Elizabeth Claire Dees, Matthew P. Goetz, John A. Olson, Jr., Tracy G. Lively, Sunil Badve, Thomas J. Saphner, Timothy J. Whelan, Virginia Kaklamani, & George W. Sledge, Jr.

on behalf of the TAILORx Investigators

Funding: U.S. NIH/NCI U10CA180820, U10CA180794, UG1CA189859, UG1CA190140, UG1CA233160, UG1CA23337, UG1CA189869; U.S. Postal Service Breast Cancer Stamp Fund; Canadian Cancer Society Research Institute grants 015469, 021039; Breast Cancer Research Foundation, Komen Foundation.

TAILORx Study Design: Treatment Assignment & Randomization

Accrued Between April 2006 – October 2010

Key Eligibility Criteria
- **Node-negative**
- **ER-pos, HER2-neg**
- **T1c-T2 (high-risk T1b)**

Preregister – Oncotype DX RS (N=11,232)

Register (N=10,273)

Statistical Design
- **Non-inferiority - IDFS**
- **HR 1.332 (90 vs. 87% 5-yr DFS)**
- **Type I 10%, type II 5%**
- **Full info– 835 IDFS events**

ARM A: Low RS 0-10
(N=1619 evaluable)
ASSIGN
Endocrine Therapy (ET)

Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors:
Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

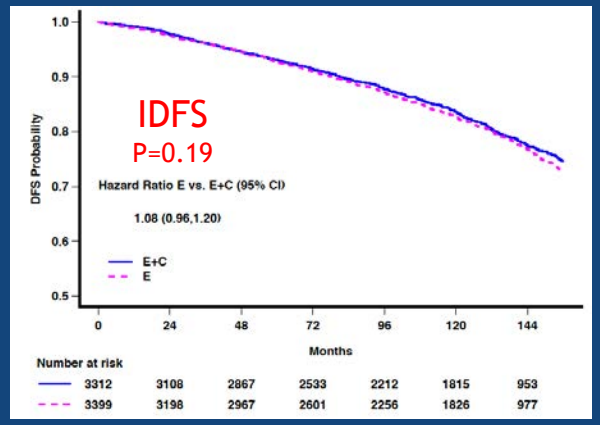
ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo

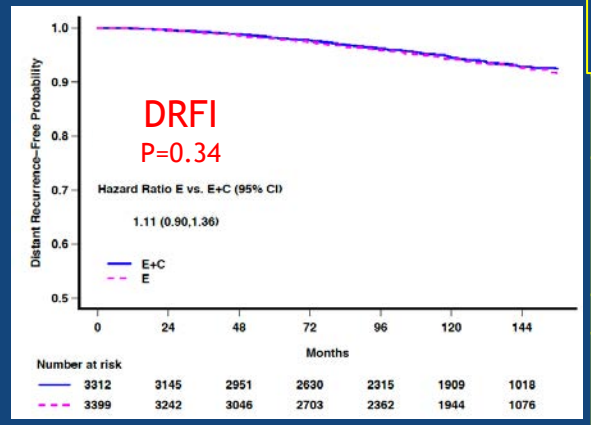
ARM B: Experimental Arm
(N=3399)
ET Alone

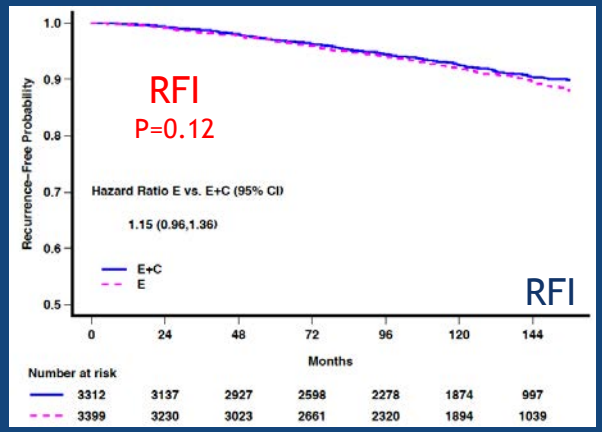
ARM C: Standard Arm
(N=3312)
ET + Chemo

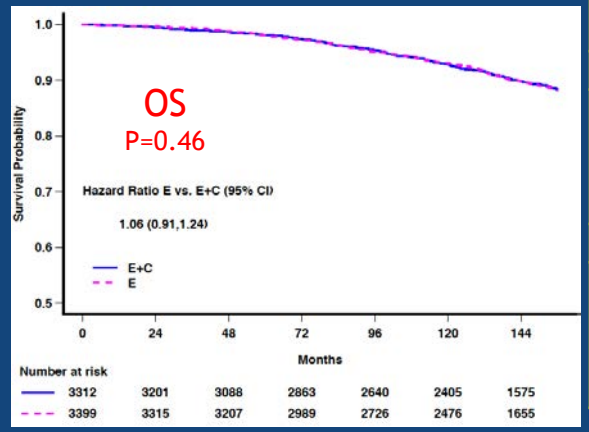
Sparano et al. NEJM 2018
(PMID: 31157962)

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





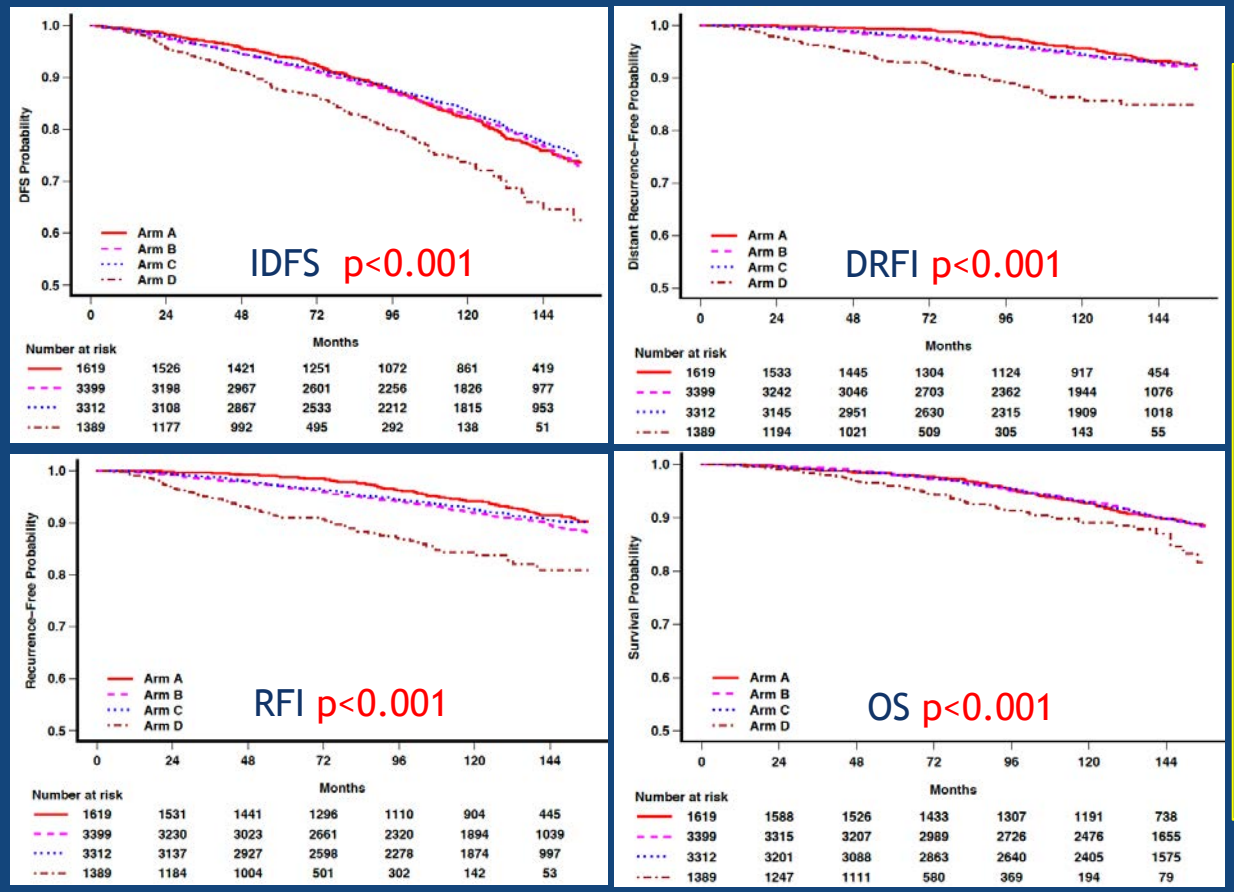




Primary trial conclusions unchanged:
ET non-inferior to CET (N=6711)

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

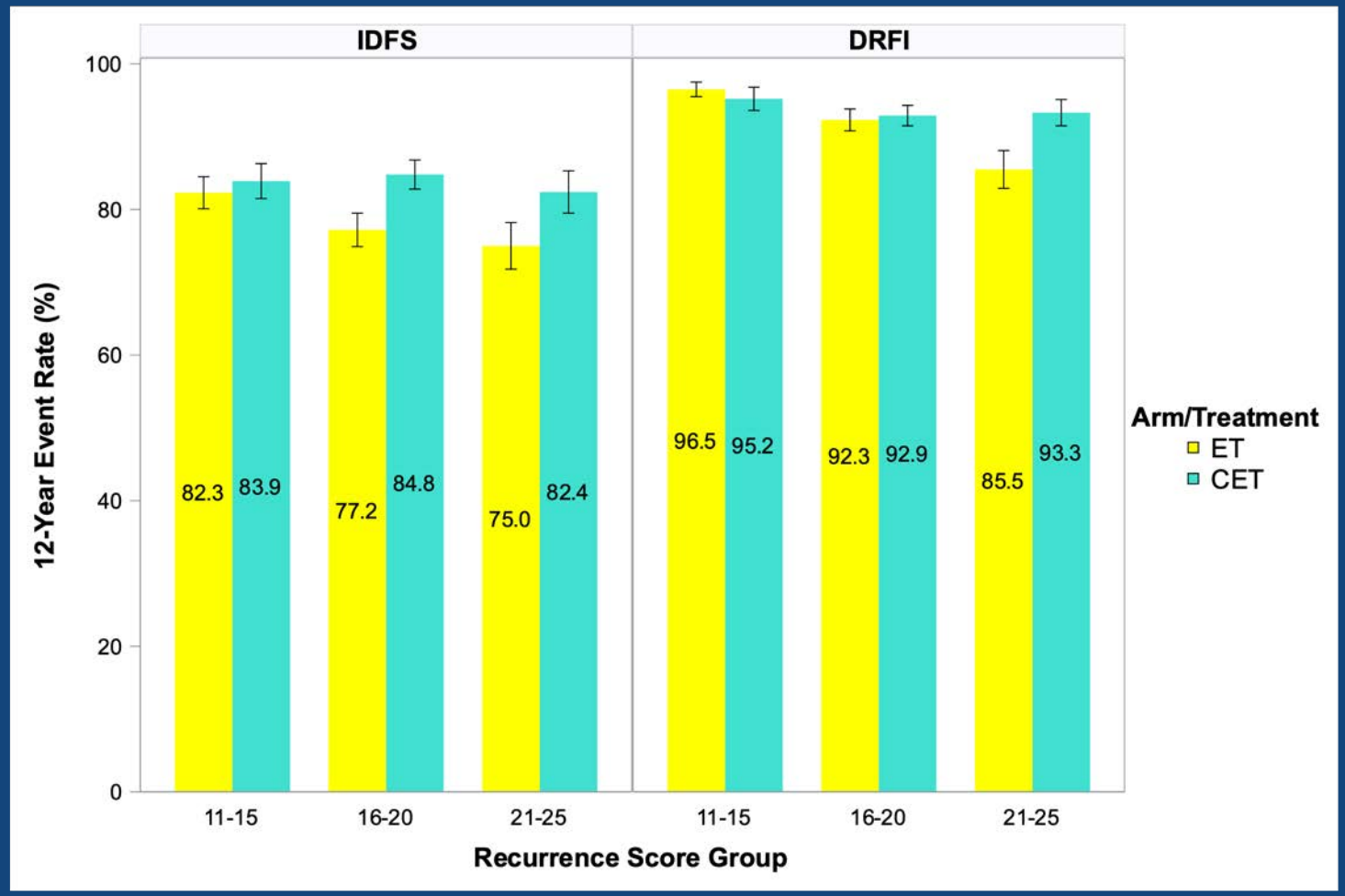
TAILORx: Updated Analysis- Kaplan-Meier Curves in All Arms (ITT population)



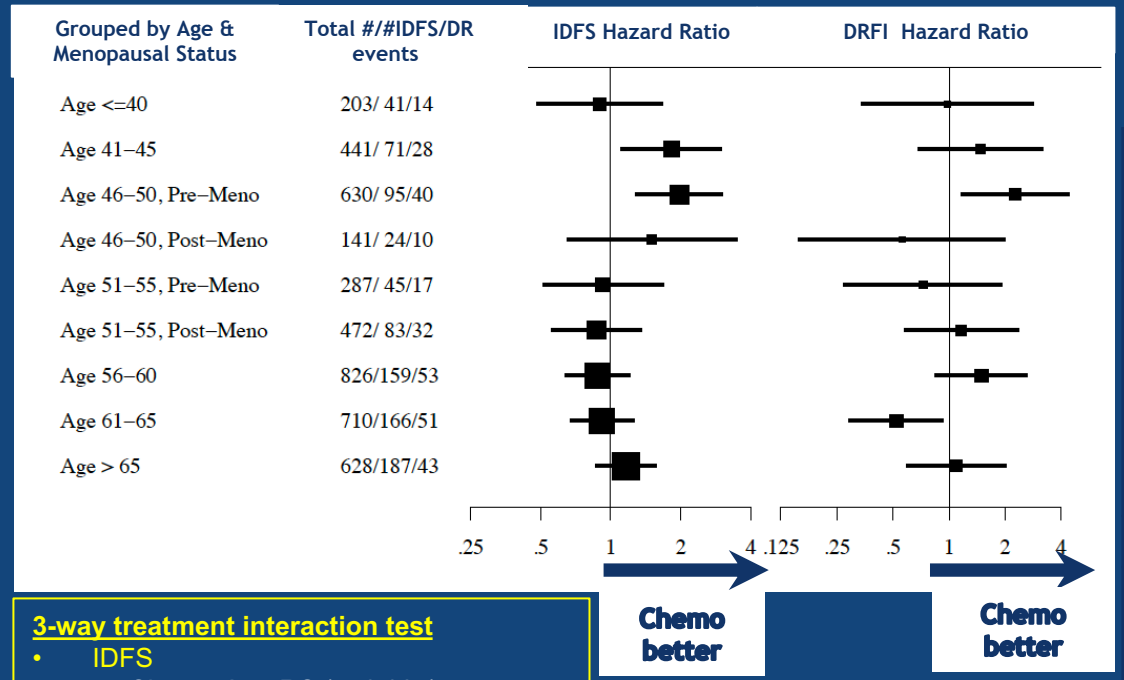
12-Year Event Rates (N=9719)

- **RS prognostic for all endpoints**
- **RS 0-10 (Arm A) – ET Alone**
  - DFRI rate: 93.2% (SE 0.8)
  - RFI rate: 91.4% (SE 0.9)
- **RS 11-25 (Arms B & C) – ET vs. CET**
  - < 1 % difference for all endpoints
    - IDFS: 76.8 vs. 77.4%
    - DRFI: 92.6 vs. 92.8%
    - RFI: 89.6 vs. 90.4%
    - OS: 89.8 vs. 89.8%
- **RS 26-100 (Arm D) – CET**
  - DFRI rate: 84.8% (SE 1.8)
  - RFI rate: 80.9 (SE 2.2)

TAILORx: Updated Analysis – Event Rates in RS 11-25 Arms and ≤ 50 Years (ITT Population)



TAILORx: Updated Analysis - Effect of Age, RS, and Clinical Risk on Chemotherapy Benefit (ITT Population)



3-way treatment interaction test

- IDFS
  - Chemo-Age-RS (p=0.007)
  - Chemo-Menopause-RS (p=0.06)
- DRFI
  - Chemo-Age-RS (p=0.43)
  - Chemo-Menopause-RS (p=0.26)

12-Year DRFI Rates in Age ≤ 50 Years & RS 16-25

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +0.4% (±SE 2.1%)	Low	671 (76%)	Δ -0.5% (±SE 2.2%)
		High	215 (24%)	Δ +3.1% (±SE 5.4%)
RS 21-25 (N=476)	Δ +7.8% (+SE 3.4%)	Low	319 (67%)	Δ +5.9% (±SE 3.4%)
		High	157 (33%)	Δ +11.7% (±SE 7.2%)

Conclusion

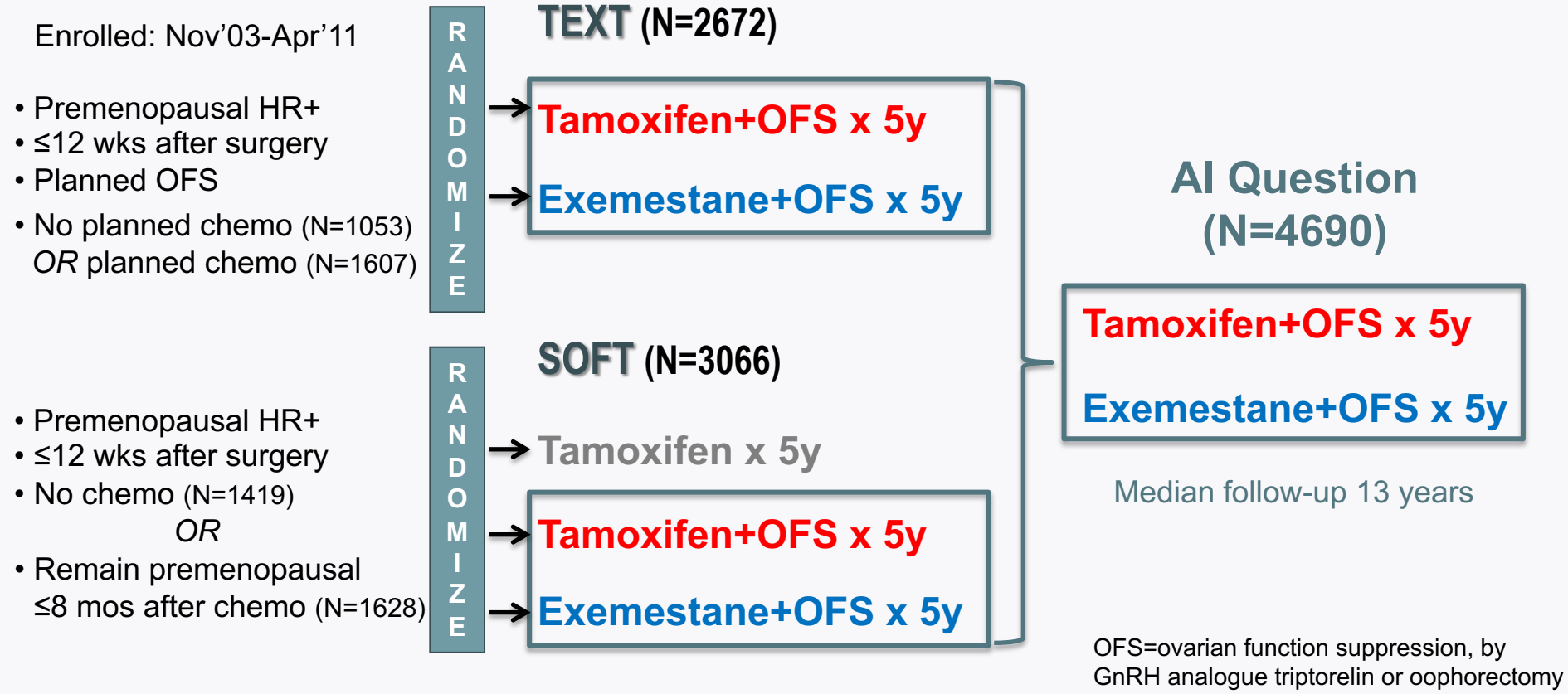
- Adjuvant chemotherapy provides no benefit in postmenopausal ER+/HER2- node negative patients (RS 11-25) and postmenopausal ER+/HER2-, 1-3 + LN (RS 0-25).

- Why did chemotherapy provide benefit in TailoRx and RxPonder premenopausal patients?
  - Endocrine Hypothesis:
    - Endocrine only arm: Inadequate endocrine therapy delivered (mostly tamoxifen and without OFS)
    - Chemotherapy treatment resulted in ovarian suppression not measured adequately
  - Cytotoxic hypothesis: chemotherapy eliminates micro-metastatic disease, independent of endocrine effects[1]

1.Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

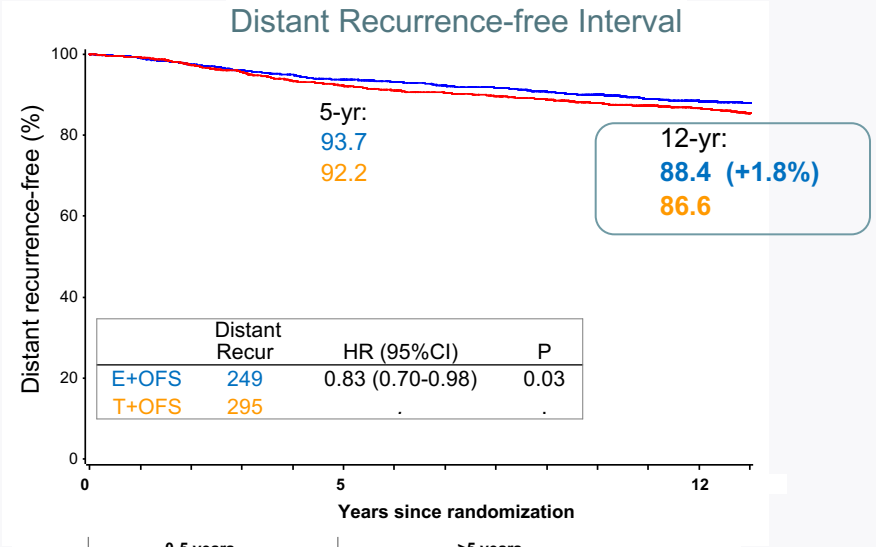
SOFT and TEXT

TEXT and SOFT Designs

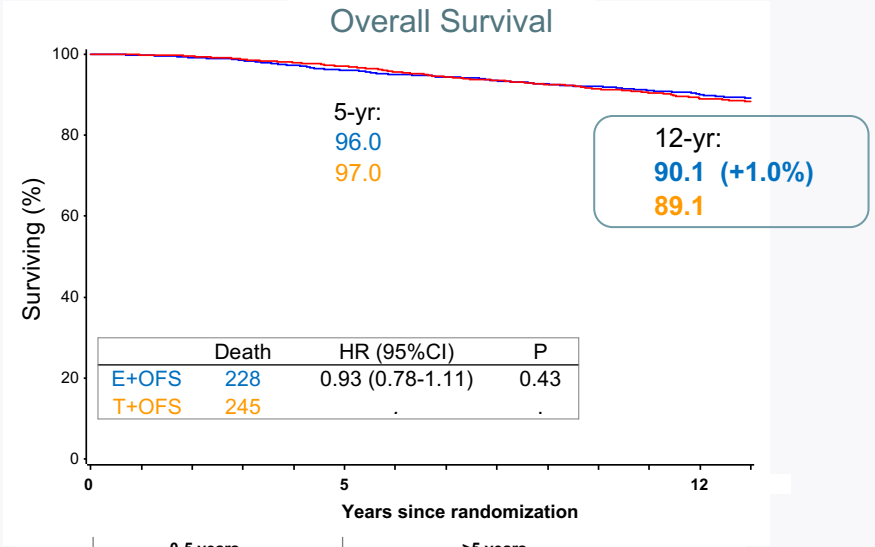


Pagani et al. NEJM 2014; Francis et al. NEJM 2014, Regan SABCS 2021

AI Question: SOFT+TEXT Overall Populations
13 years median follow-up



	0-5 years		>5 years	
	Recur	HR (95% CI)	Recur	HR (95% CI)
E+OFS:	139	0.78 (0.63-0.98)	110	0.90 (0.70-1.17)
T+OFS:	175	.	120	.
.	.	.	.	.
At risk:	4690 pts	21535 pyfu	3947 pts	26891 pyfu



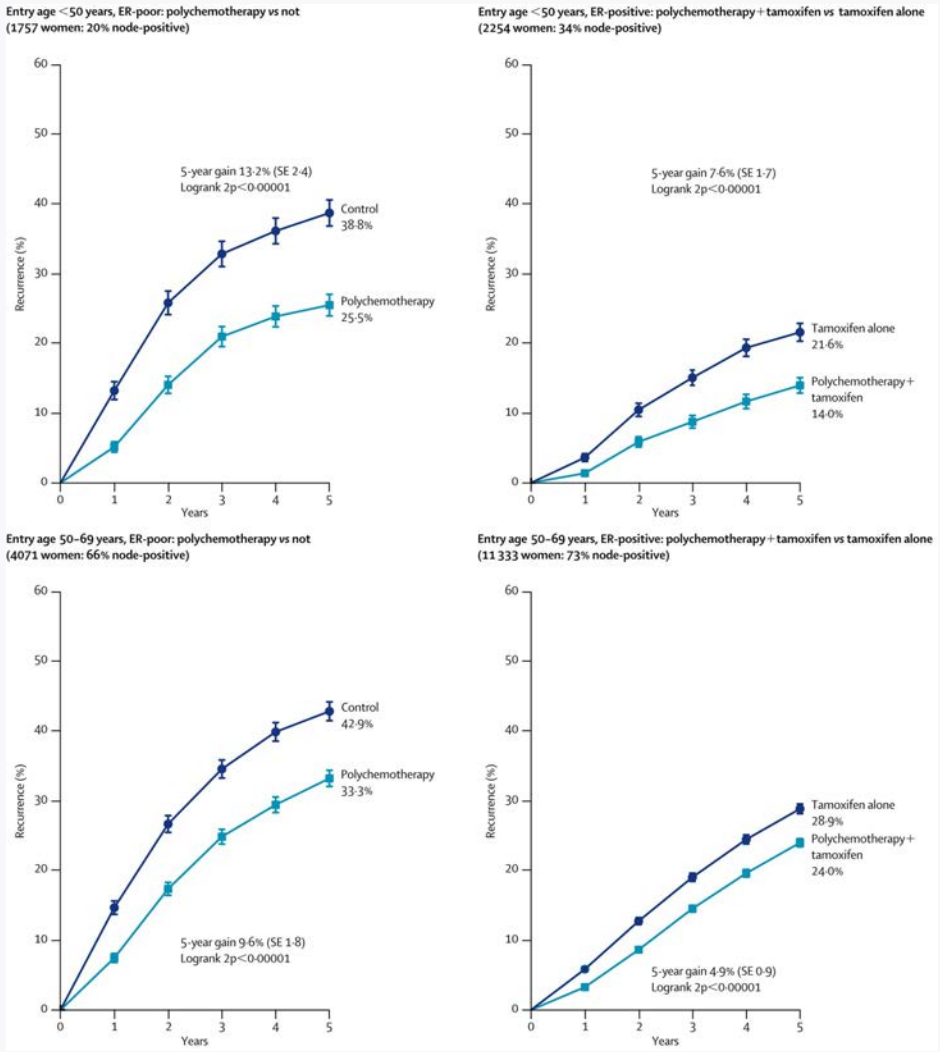
	0-5 years		>5 years	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)
E+OFS:	91	1.34 (0.98-1.84)	137	0.77 (0.62-0.97)
T+OFS:	68	.	177	.
.	.	.	.	.
At risk:	4690 pts	22467 pyfu	4283 pts	30294 pyfu

E+OFS vs T+OFS: absolute reduction in distant recurrence, 1.8% at 12 years
absolute reduction in death, 1.0% at 12 years

pyfu=person-years follow-up

Regan SABCS 2021 and J Clin Oncol (in press)

Polychemotherapy versus not, by entry age <50 or 50-69 years and ER status (Oxford Overview)

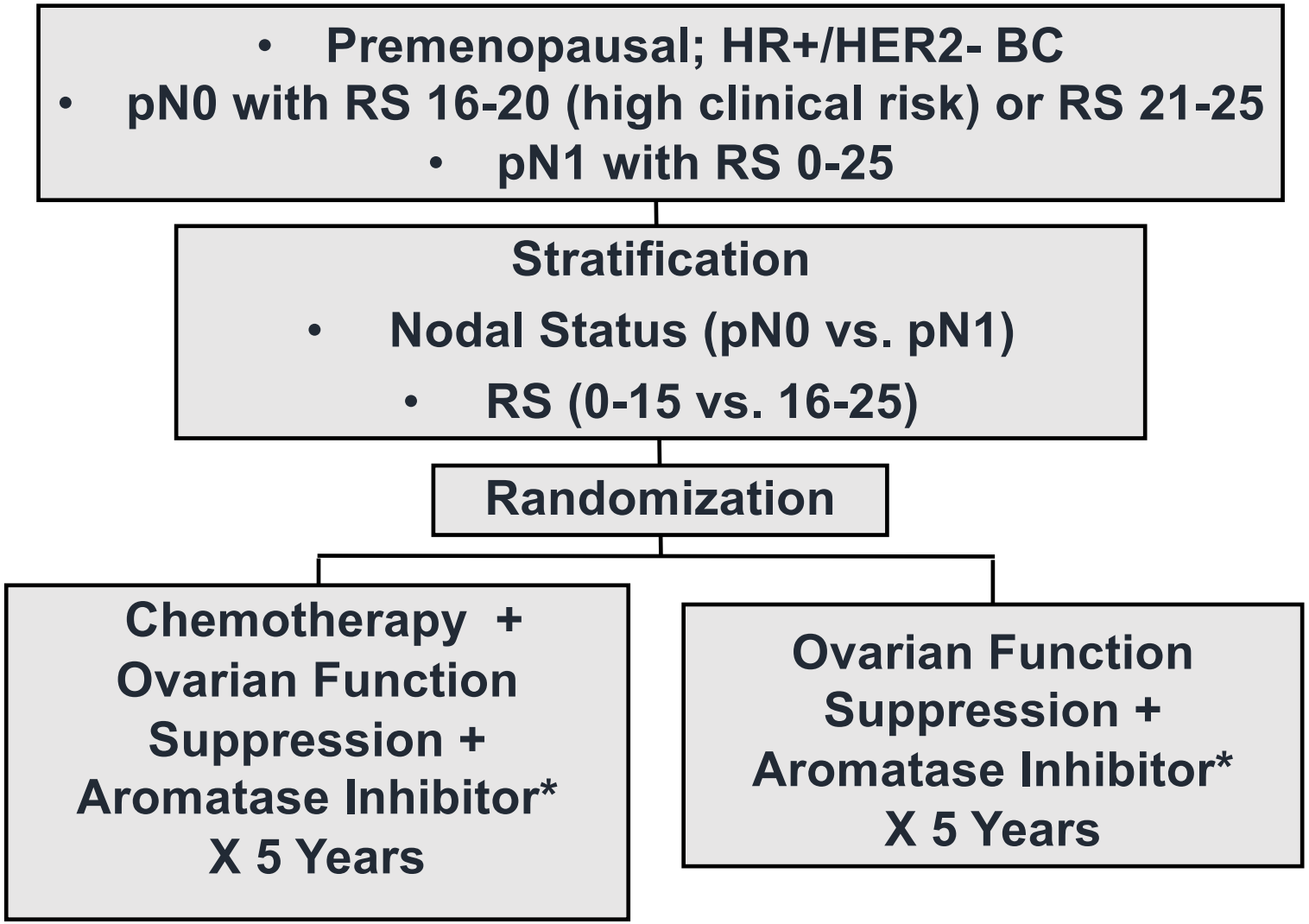


Age < 50: Enriched with tumors that harbor deficiencies in DNA repair?

Proportional risk reductions are a bit smaller, but clearly still evident

Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2005

BR009: Schema (slide courtesy of Terry Mamounas)



* Tamoxifen can be used if AI is not tolerated

Outline

- Phase III RxPONDER trial evaluating the role of chemotherapy for patients with ER-positive, HER2-negative localized breast cancer with 1 to 3 positive lymph nodes and a 21-gene Recurrence Score (RS) of ≤25

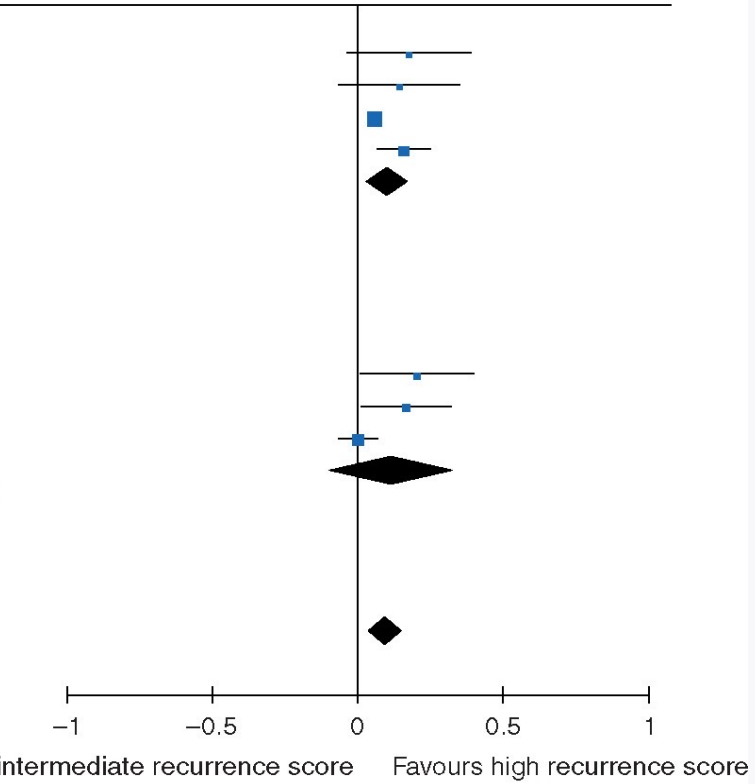
- Updated findings, including 12-year event rates, from the Phase III TAILORx study

- 21-gene RS and neoadjuvant chemotherapy decision making

- Insight regarding poor correlation between the RS and chemotherapy response in premenopausal patients

Meta-analysis: pCR rates in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy stratified based on 21-gene expression assay at diagnosis. Is pCR the best endpoint to determine chemotherapy benefit?

Reference	pCR: High recurrence score	pCR: Low–intermediate recurrence score	Weight(%)	Risk difference
High recurrence score >25				
Zelnak *et al.*[25]	3 of 17	0 of 11	5.9	0.18 (–0.04, 0.39)
Bear *et al.*[29]	2 of 14	0 of 14	6.2	0.14 (–0.07, 0.35)
Kantor *et al.*[26]	47 of 605	15 of 772	30.9	0.06 (0.03, 0.08)
Thekkekara *et al.*[23]	11 of 70	0 of 40	17.8	0.16 (0.07, 0.25)
Subtotal	63 of 706	15 of 837	60.9	0.11 (0.03, 0.18)
Heterogeneity: $\tau^2 = 0.00$ $\chi^2 = 5.75$, 3 d.f., $P = 0.12$; $I^2 = 48\%$				
Test for overall effect: $Z = 2.91$, $P = 0.004$				
High recurrence score >30				
Pivot *et al.*[27]	7 of 24	5 of 57	6.9	0.20 (0.01,0.40)
Yardley *et al.*[24]	4 of 24	0 of 36	9.7	0.17 (0.01, 0.32)
Soran *et al.*[28]	0 of 23	0 of 37	22.5	0.00 (–0.07, 0.07)
Subtotal	11 of 71	5 of 130	39.1	0.11 (–0.10, 0.33)
Heterogeneity: $\tau^2 = 0.03$ $\chi^2 = 14.66$, 2 d.f., $P = 0.001$; $I^2 = 86\%$				
Test for overall effect: $Z = 1.06$, $P = 0.29$				
Total	74 of 777	20 of 967	100.0	0.10 (0.04, 0.15)
Heterogeneity: $\tau^2 = 0.00$ $\chi^2 = 14.00$, 6 d.f., $P = 0.03$; $I^2 = 57\%$				
Test for overall effect: $Z = 3.24$, $P = 0.001$				
Test for subgroup differences: $\chi^2 = 0.01$, 1 d.f., $P = 0.94$; $I^2 = 0\%$				

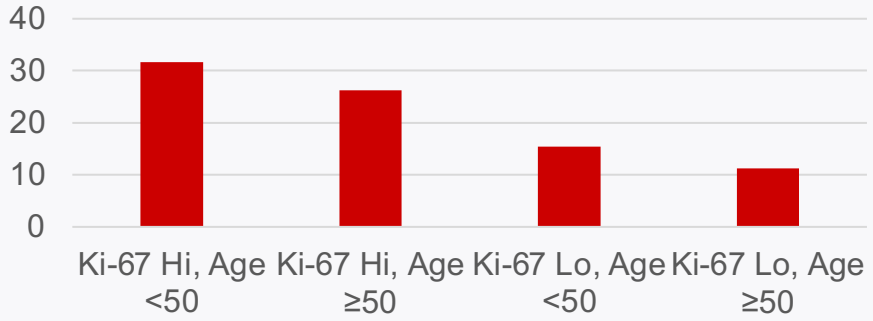


Boland et al. British Journal of Surgery, 2021

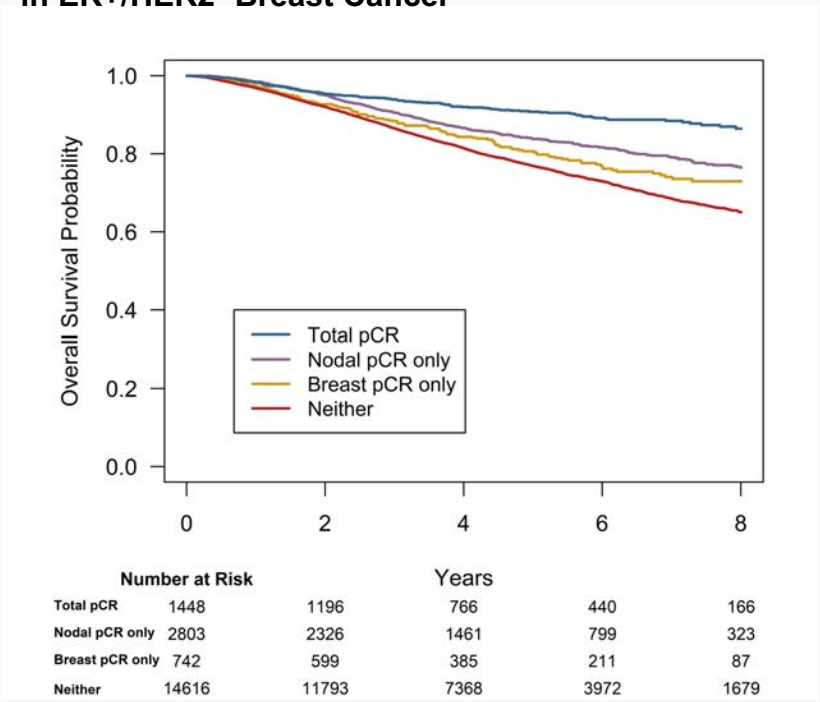
ER+/HER2- Breast Cancer Treated with Neoadjvuant Chemotherapy: Total pCR vs nodal pCR

NCDB: 2010-2018, 20,084 cN+ ER+/HER2- BC pts treated with NAC.

- 7.4% had total pCR
- **14.3% had nodal-only pCR**



Nodal pCR is highly prognostic for survival in ER+/HER2- Breast Cancer



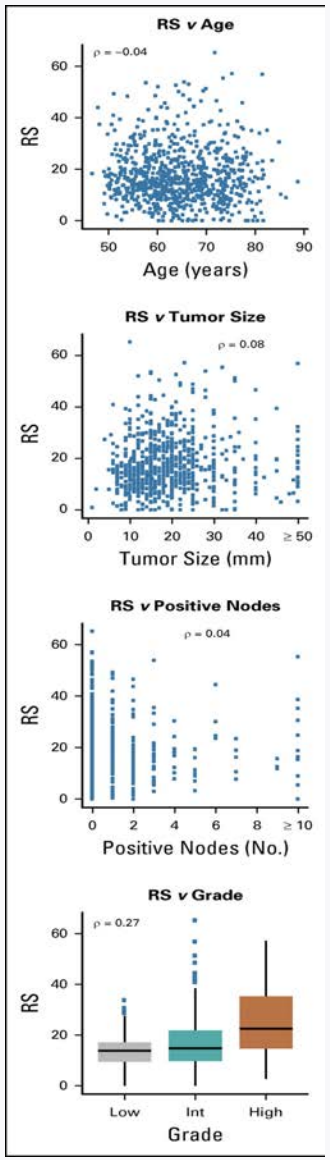
NCDB: Nodal pCR more likely in a) premenopausal pts and b) high Ki-67.

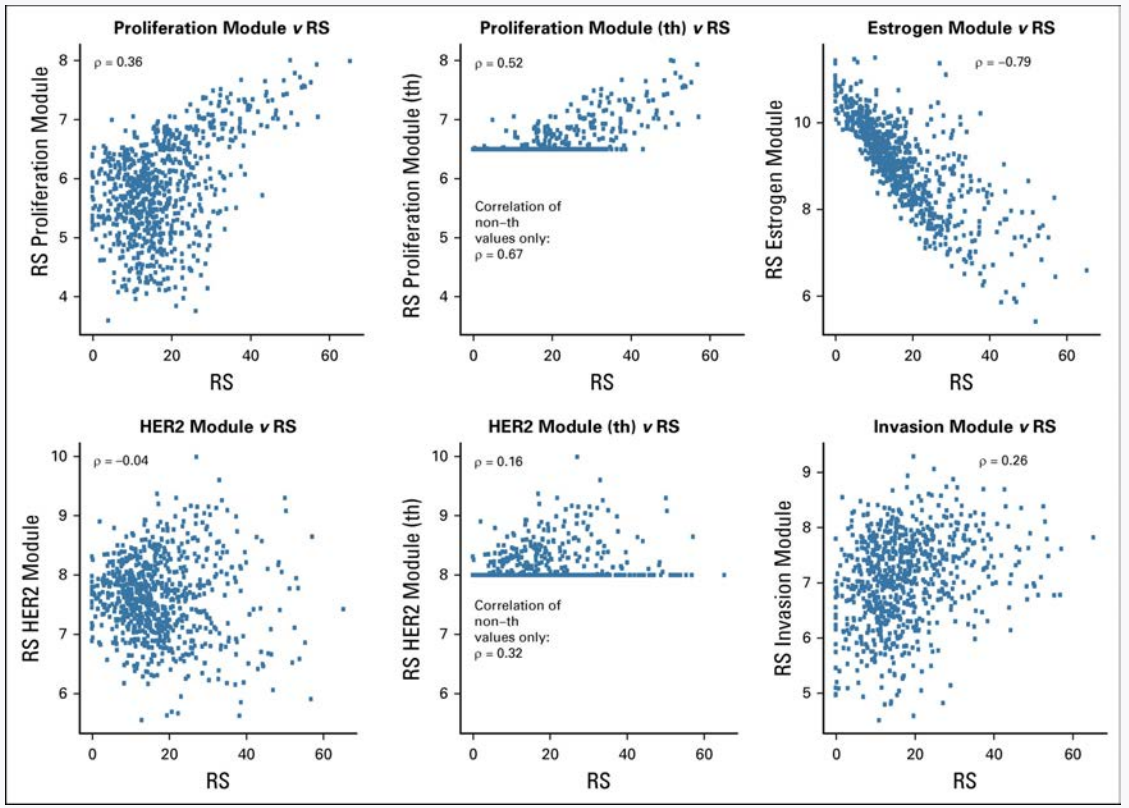
RxPONDER inclusion criteria (cT1-3, N1, Grade I or II, ER+/PR+/Her2-)

- Nodal pCR varied by age: 17.5% in age < 50 vs 13.6% in age ≥ 50, p<0.001
- Nodal pCR also varied by Ki-67: 16.8% in Ki-67 ≥ 20% vs 7.9% in Ki-67 < 20%, p<0.001

Moldovenau et al. SABCS 2022

Molecular Drivers of Oncotype DX, A TransATAC Study: The RS is mainly driven by the Estrogen Module





The estrogen module explained more than half of RS's variance (59.1%), while the proliferation module accounted for approximately a fifth of RS's information (19.4%)

Buus et al. J Clin Oncol 2021

Conclusion

- TAILORx and RxPONDER have provided prospective evidence for lack of adjuvant chemotherapy benefit in postmenopausal patients with RS <25
- In contrast, the RS may not be predictive of chemotherapy benefit in age <50 patients
  - NRG BR009 will provide the definitive answer to this question
- The RS is poorly correlated with the proliferation module but highly correlated with ER
- Additional clinical and pathological biomarkers may provide additional insight into those patients that derive benefit from chemotherapy.

1.Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

MODULE 2: Optimizing the Management of Localized ER-Positive Breast Cancer — Dr Kaklamani

RTP
RESEARCH
TO PRACTICE

Case Presentation: 40-year-old woman with 5.5-cm, ER/PR-positive, HER2-negative, node-positive (20/21) IDC, s/p bilateral mastectomies, BSO, adjuvant AC-T and initiation of letrozole/abemaciclib – Ki-67: 3%

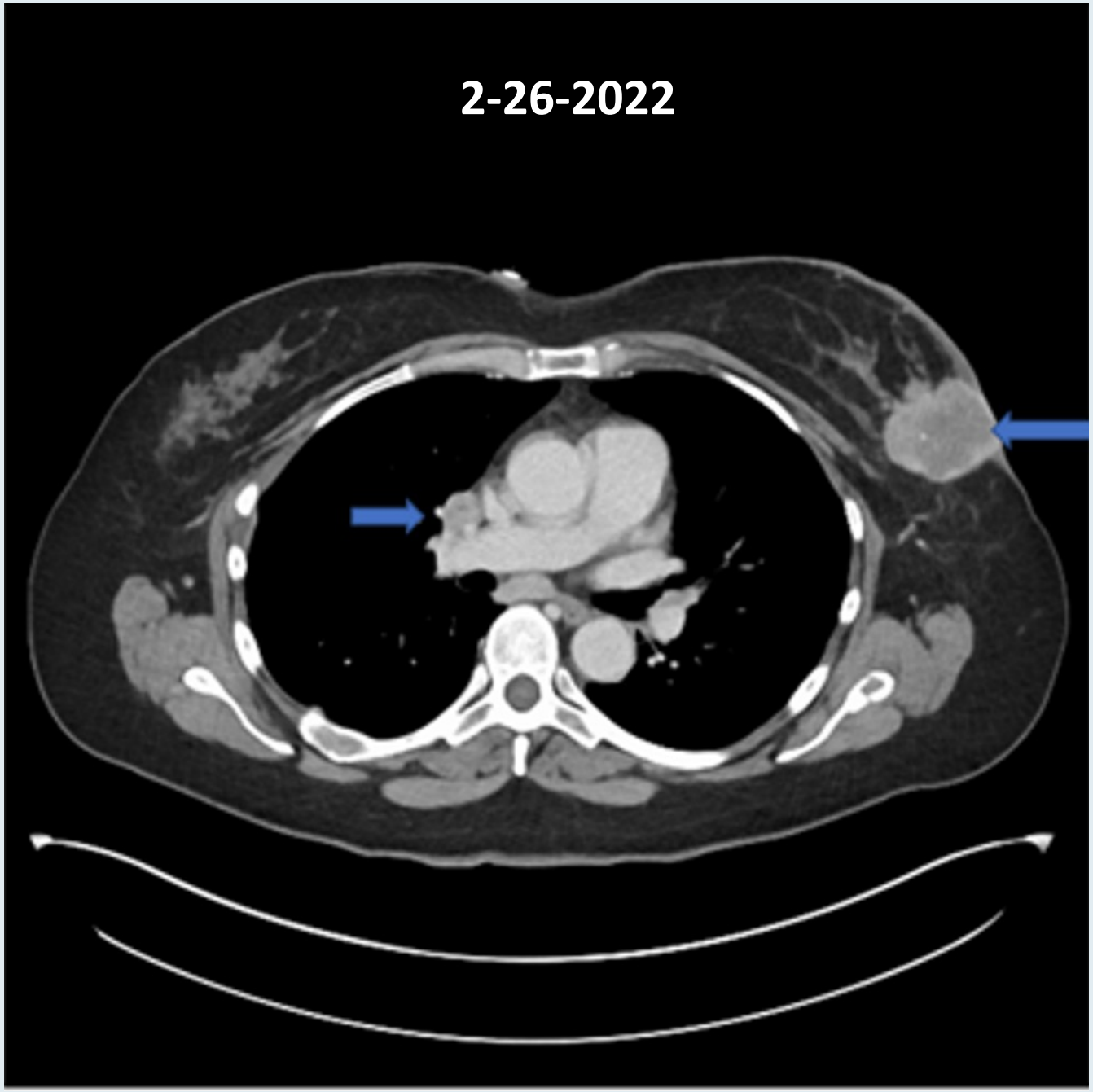
Dr Susmitha Apuri (Lutz, Florida)

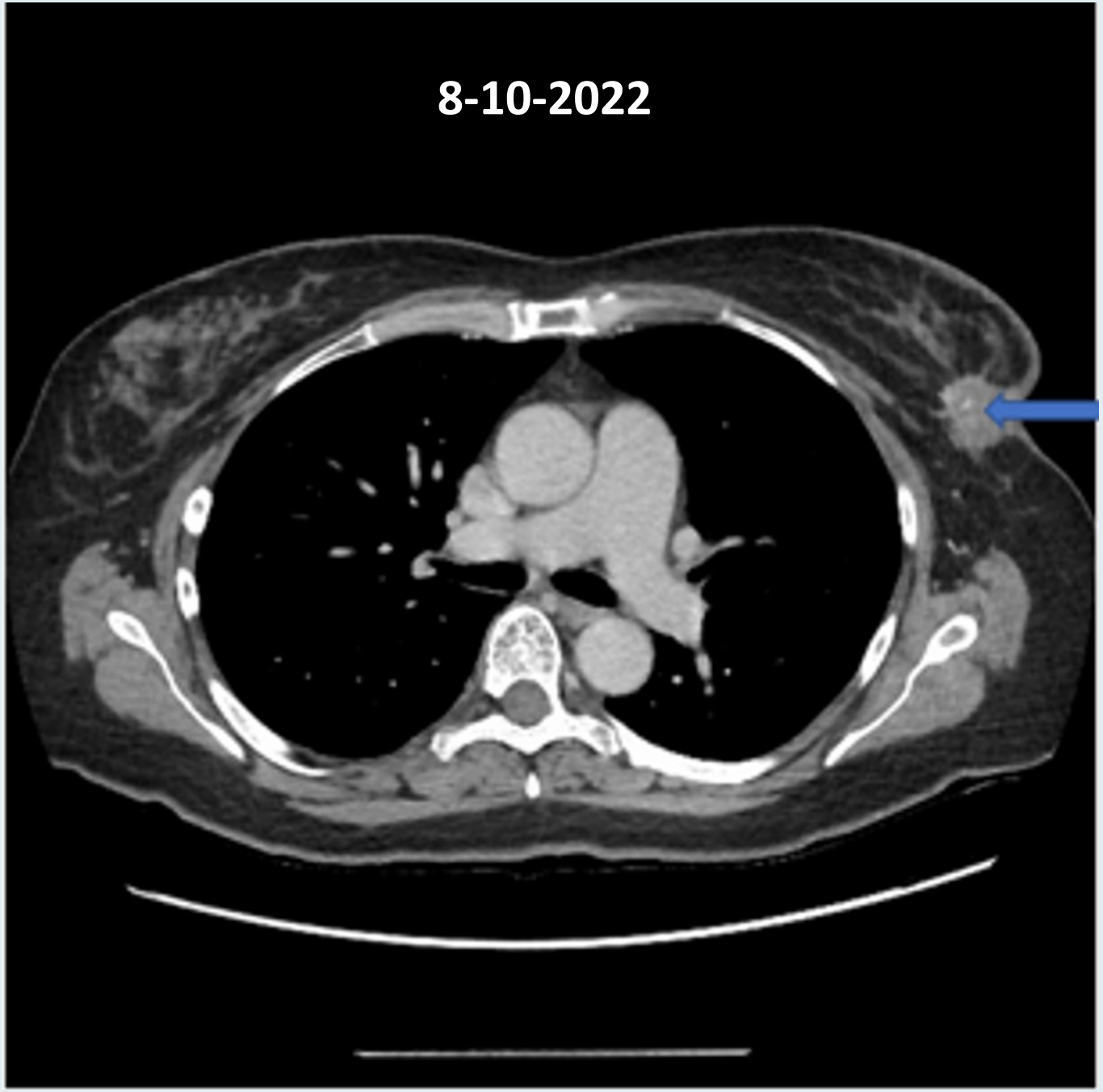
RTP RESEARCH TO PRACTICE

Case Presentation: 56-year-old woman with de novo ER-positive, PR-negative, HER2-negative ulcerated BC with pulmonary and extensive spinal metastases

Dr Jennifer Dallas (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE


2-26-2022


8-10-2022

Optimizing the Management of Localized ER-Positive Breast Cancer

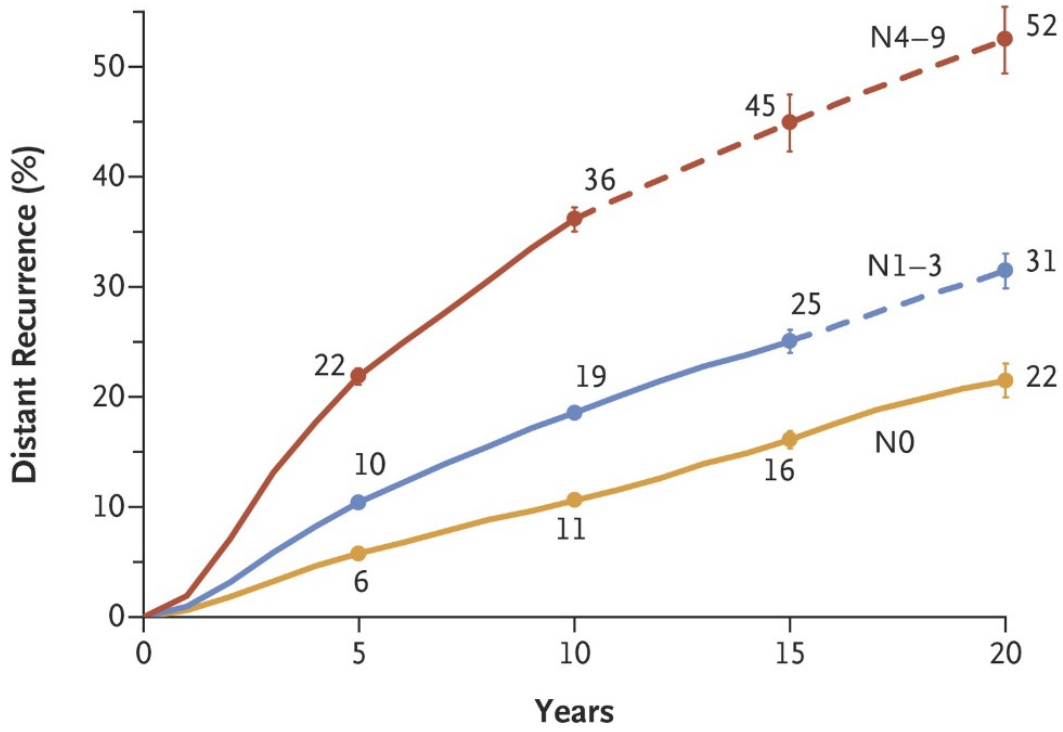
Virginia Kaklamani, MD DSc
Professor of Medicine
Leader, Breast Oncology Program

Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center

- Optimal duration of ET
- Role of OFS in preserving oncofertility and improving outcomes
- CDK4/6 inhibition in EBC
- PARPi in EBC

EBCTCG Meta-analysis of 62,923 women with ER+ BC

A Risk of Distant Recurrence



No. at Risk					
N4–9	12,333	8,116	2165	259	52
N1–3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

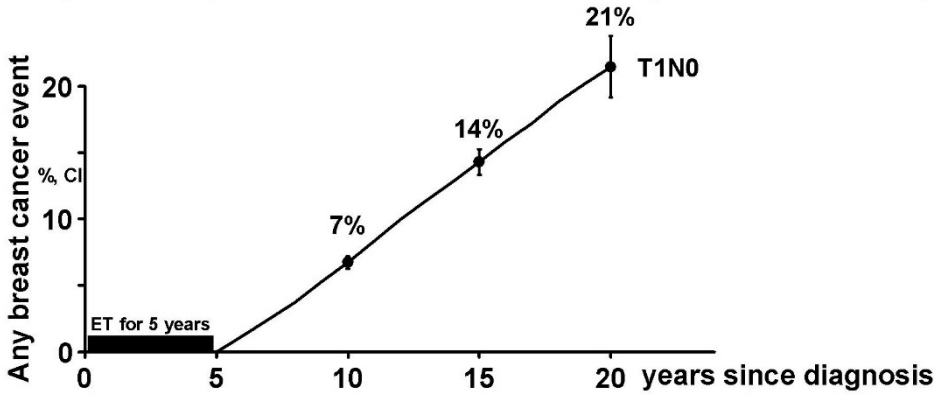
No. of Events — annual rate (%)				
N4–9	2568 (4.8)	969 (4.0)	121 (3.1)	13 (2.2)
N1–3	3126 (2.2)	1421 (1.9)	241 (1.7)	39 (1.8)
N0	1646 (1.2)	835 (1.1)	272 (1.3)	68 (1.4)

Factors associated with risk of late recurrence:

- LN status
- Tumor size
- Tumor grade
- PR and HER2 not predictive

Lowest-stage (T1N0) disease: Risk of ANY breast cancer event

21% risk, years 5-20 (14% DISTANT recurrence + 7% only local or contralateral)



Annual event rate (and no. of events), by 5-year time period

T1N0 (n=16K): **1.4%** (807) **1.7%** (309) **1.8%** (54)

Mays Cancer Center

UT Health San Antonio MD Anderson Cancer Center

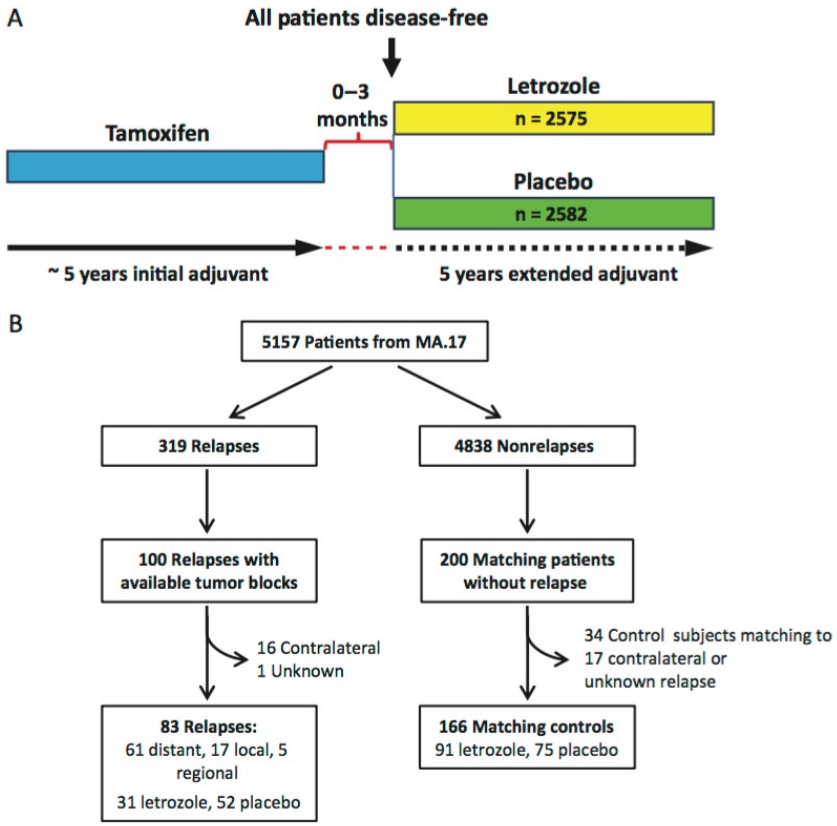
N Engl J Med 2017; 377:1836-1846

Clinical trials of Extended Endocrine Therapy

Trial	Therapy	n	Absolute Benefit in DFS
ATLAS	Tam x 5 yr	6846	3%*
aTTom	Tam x 5 yr	6953	3%*
MA.17	AI x 5 yr	5187	4.6%*
MA.17R	AI x 5 yr	1918	4%*
B14	Tam x 5 yr	1172	6%*
B33	AI x 5 yr	1598	2%
B42	AI x 5 yr	3966	3%
DATA	AI x 3 yr	1912	4%
IDEAL	AI x 2.5 yr	1824	3%
ABCSG-6a	AI x 3 yr	856	4.7%
ABCSG16	AI x 3 yr	3484	-0.8%
SOLE	AI cont vs intermittent	4884	1.7%

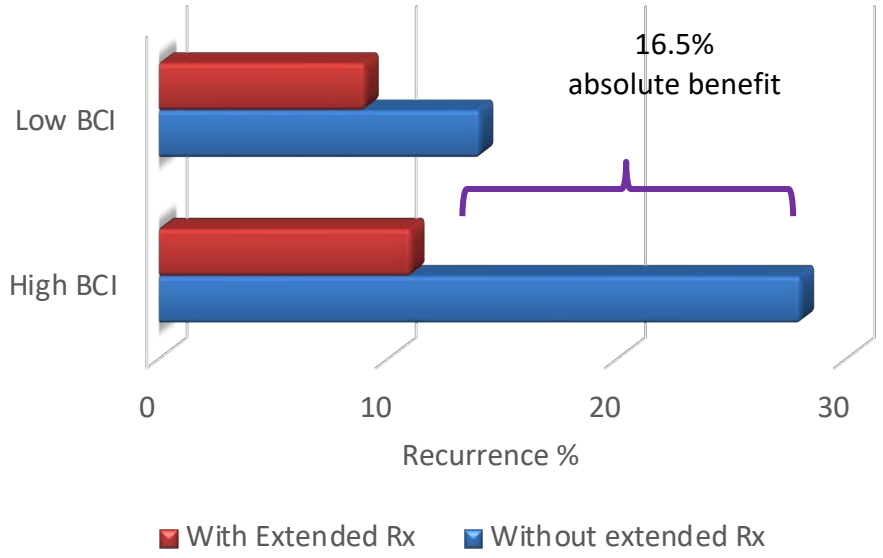
Prediction of Late Disease Recurrence and Extended Adjuvant Letrozole Benefit by the HOXB13/IL17BR Biomarker

Dennis C. Sgroi, Erin Carney, Elizabeth Zarrella, Lauren Steffel, Shemeica N. Binns, Dianne M. Finkelstein, Jackie Szymonifka, Atul K. Bhan, Lois E. Shepherd, Yi Zhang, Catherine A. Schnabel, Mark G. Erlander, James N. Ingle, Peggy Porter, Hyman B. Muss, Katherine I. Pritchard, Dongsheng Tu, David L. Rimm, Paul E. Goss



High H/I significantly associated with decreased recurrence in letrozole arm
OR=0.35, p=0.007

Interaction between H/I and letrozole, p=0.03



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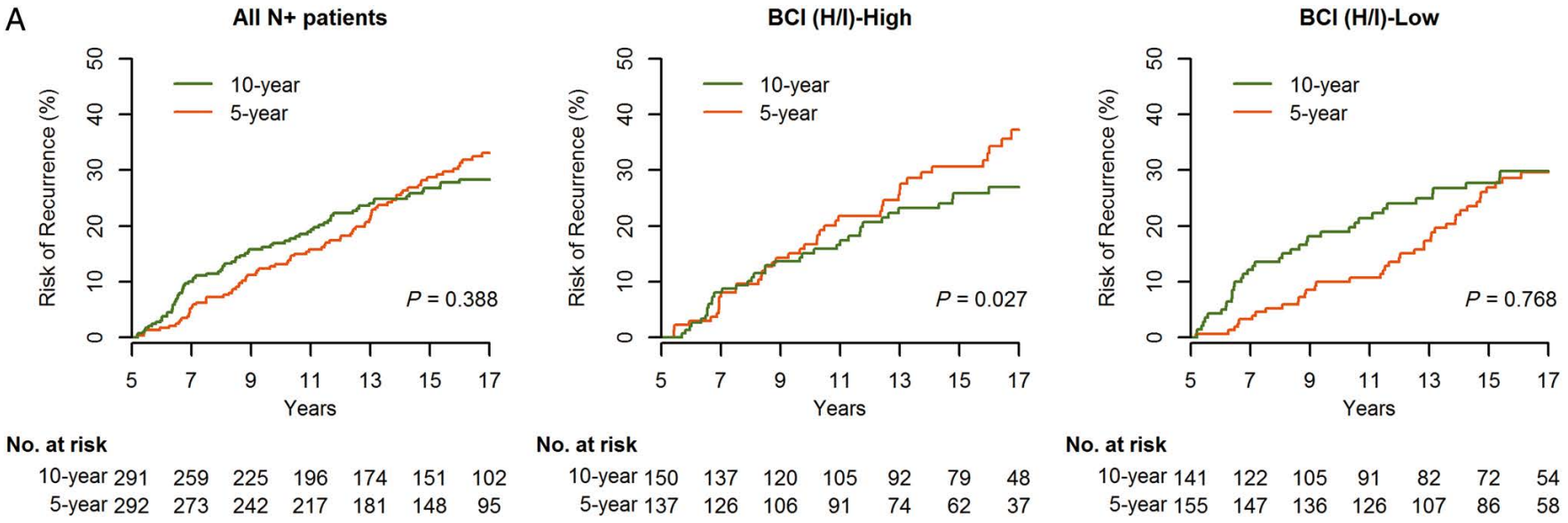
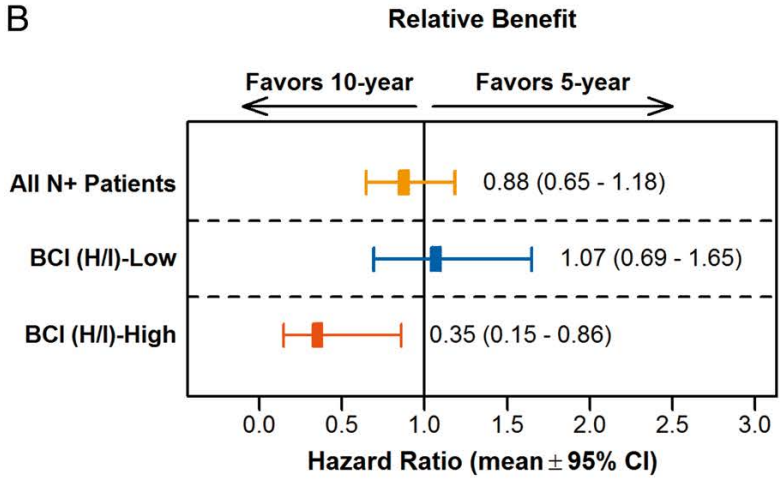
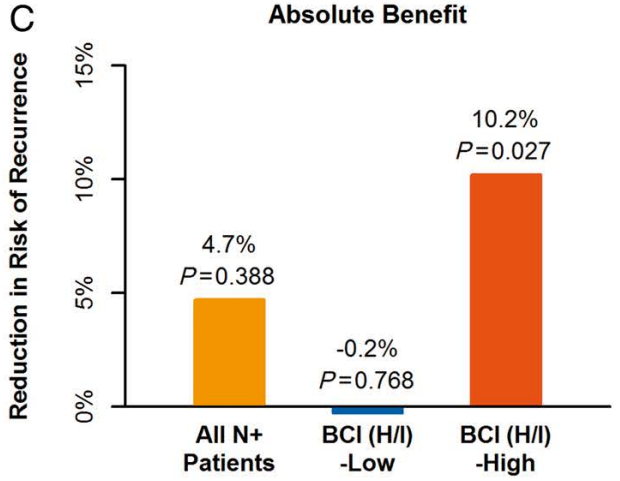
Lancet Oncol. 2013,14:1067-76.

aTTom: Predictive performance by BCI (H/I) groups based on RFI in HR+ N+ patients (n = 583).







51% of patients identified as low

Annals of Oncology, mdz289, https://doi.org/10.1093/annonc/mdz289

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MD Anderson Cancer Center

Factors Affecting Late Recurrence and Benefit from Extended Endocrine Therapy

- LN status
- Tumor Size
- Tumor Grade
- Prior Chemotherapy
- Switching from TAM to AI
- Genomic Assays

Tolerability

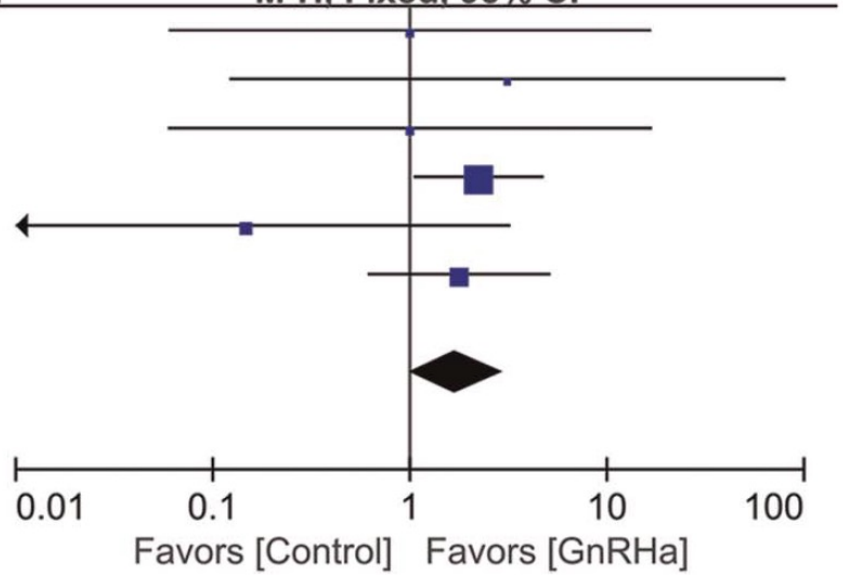
- Bone Fractures
- Osteoporosis
- Bone Pain
- Uterine ca
- VTEs

Forest Plot of the Rate of Spontaneous Pregnancy Achieved with GnRHa and Chemotherapy versus Chemotherapy Alone: All Patients

Study or Subgroup	GnRHa Events	GnRHa Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bernd Gerber et al.	1	30	1	30	5.0%	1.00 [0.06, 16.76]
Eman A. Elgindy et al.(A)	1	25	0	25	2.4%	3.12 [0.12, 80.39]
Eman A. Elgindy et al.(B)	1	25	1	25	5.0%	1.00 [0.06, 16.93]
Halle C. F. Moore et al.	22	105	12	113	47.2%	2.23 [1.04, 4.77]
Pamela N. Munster et al.	0	26	2	21	14.0%	0.15 [0.01, 3.24]
R. C. F. Leonard et al.	9	106	6	121	26.5%	1.78 [0.61, 5.17]
Total (95% CI)		**317**		**335**	**100.0%**	**1.72 [0.99, 2.99]**
Total events	34		22			

Heterogeneity: $Chi^2 = 3.29$, df = 5 (P = 0.65); $I^2 = 0\%$

Test for overall effect: Z = 1.92 (P = 0.06)



STAY TUNED FOR POSITIVE TRIAL

Li Z-Y et al. *Menopause* 2022;29(9):1093-100.

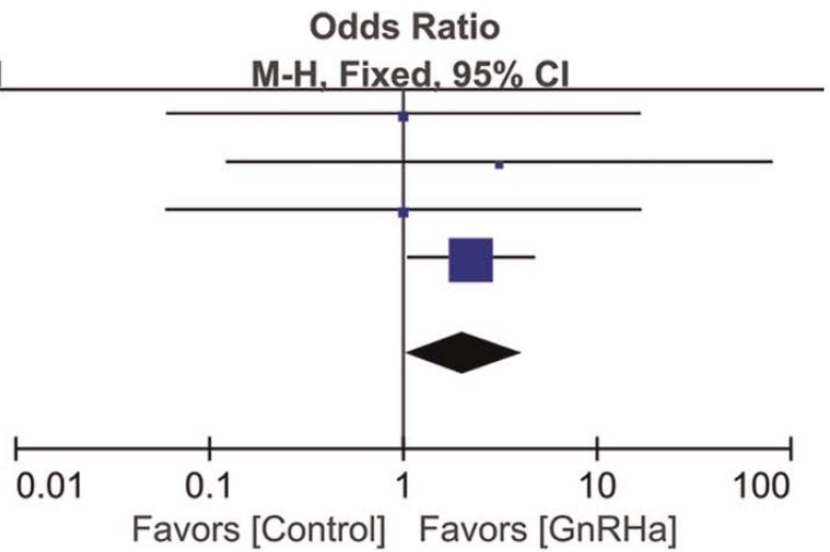
RTP RESEARCH TO PRACTICE

Forest Plot of the Rate of Spontaneous Pregnancy Achieved with GnRHa and Chemotherapy versus Chemotherapy Alone: HR-Negative Disease

	GnRHa		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bernd Gerber et al.	1	30	1	30	8.4%	1.00 [0.06, 16.76]
Eman A. Elgindy et al.(A)	1	25	0	25	4.1%	3.12 [0.12, 80.39]
Eman A. Elgindy et al.(B)	1	25	1	25	8.3%	1.00 [0.06, 16.93]
Halle C. F. Moore et al.	22	105	12	113	79.2%	2.23 [1.04, 4.77]
Total (95% CI)		**185**		**193**	**100.0%**	**2.06 [1.03, 4.11]**
Total events	25		14			

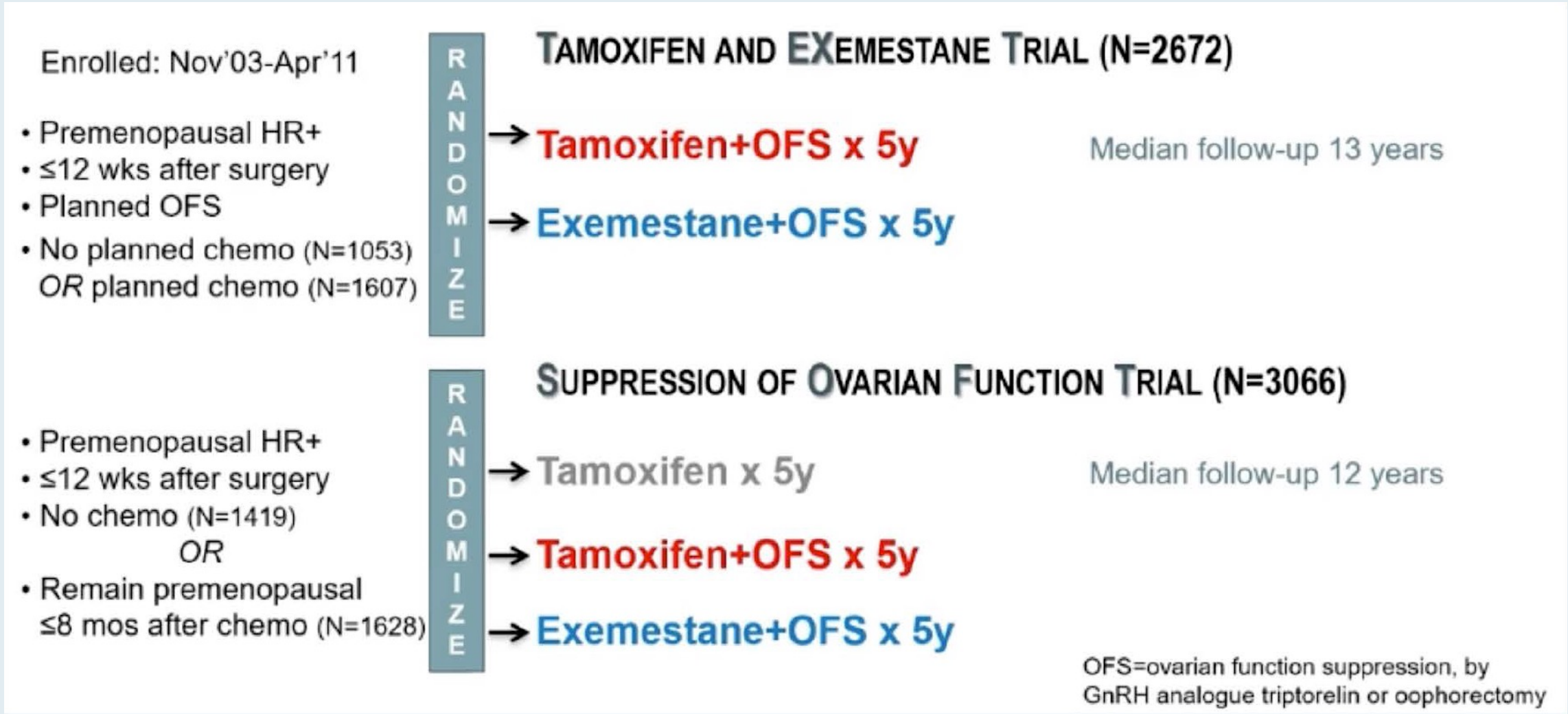
Heterogeneity: $Chi^2 = 0.61$, $df = 3$ ($P = 0.89$); $I^2 = 0\%$

Test for overall effect: $Z = 2.06$ ($P = 0.04$)



Li Z-Y et al. *Menopause* 2022;29(9):1093-100.

TEXT and SOFT Trial Designs

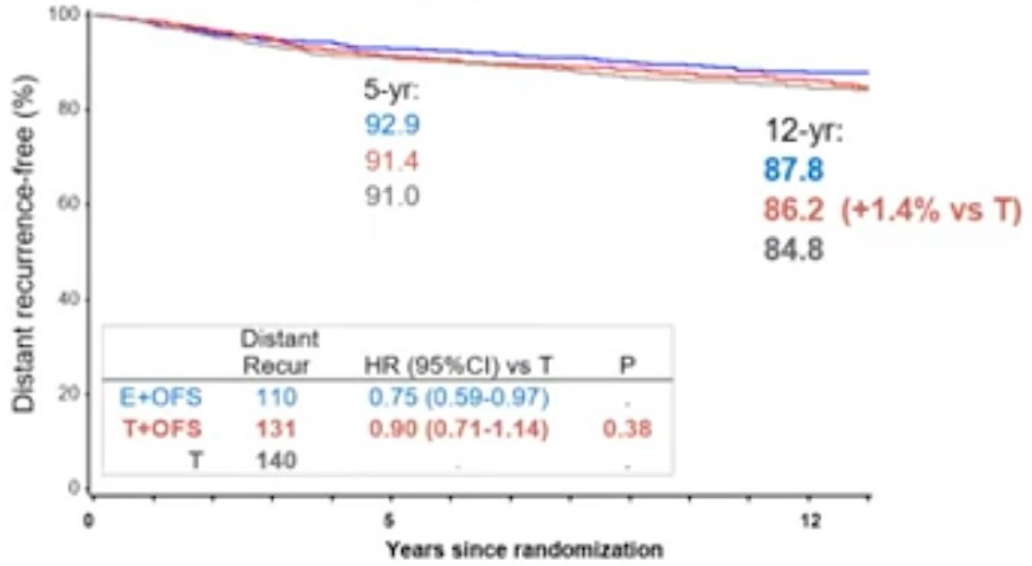


Regan MM et al. SABCS 2021;Abstract GS2-05.

OFS Question: SOFT Overall Population

35% LN+; 12 years median follow-up

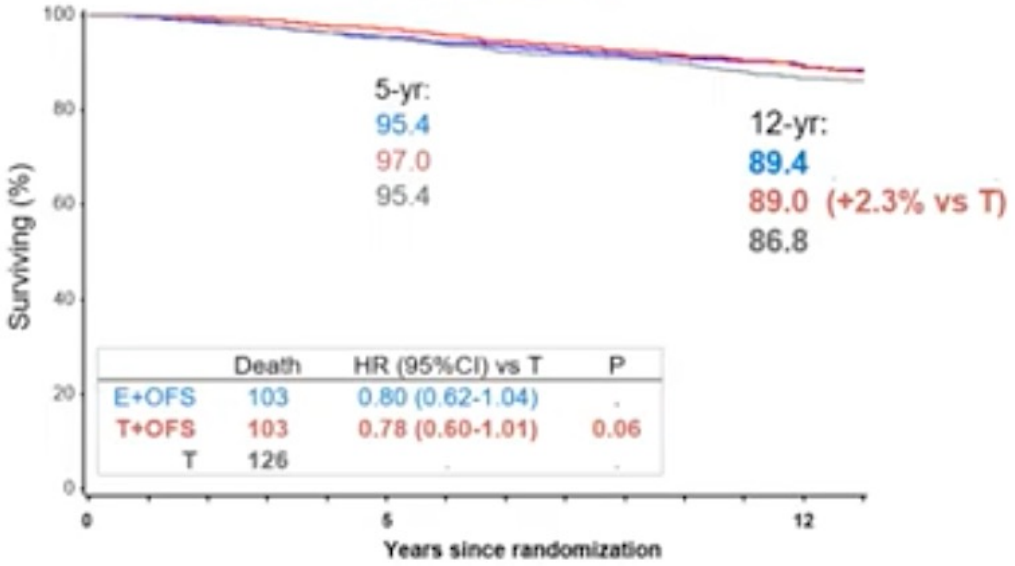
Distant Recurrence-free Interval



	Distant Recur	HR (95%CI) vs T	P
E+OFS	110	0.75 (0.59-0.97)	.
T+OFS	131	0.90 (0.71-1.14)	0.38
T	140	.	.

	0-5 years		>5 years	
	Recur	HR (95% CI) vs T	Recur	HR (95% CI) vs T
E+OFS:	68	0.76 (0.55-1.04)	42	0.74 (0.50-1.12)
T+OFS:	83	0.93 (0.69-1.25)	48	0.85 (0.58-1.26)
T:	87		53	
At risk:	**3047** pts	13787 pyfu	2521 pts	16343 pyfu

Overall Survival



	Death	HR (95%CI) vs T	P
E+OFS	103	0.80 (0.62-1.04)	.
T+OFS	103	0.78 (0.60-1.01)	0.06
T	126	.	.

	0-5 years		>5 years	
	Deaths	HR (95% CI) vs T	Deaths	HR (95% CI) vs T
E+OFS:	45	1.00 (0.66-1.51)	58	0.70 (0.50-0.98)
T+OFS:	29	0.63 (0.40-1.01)	74	0.86 (0.63-1.18)
T:	45		81	
At risk:	**3047** pts	14524 pyfu	2745 pts	18383 pyfu

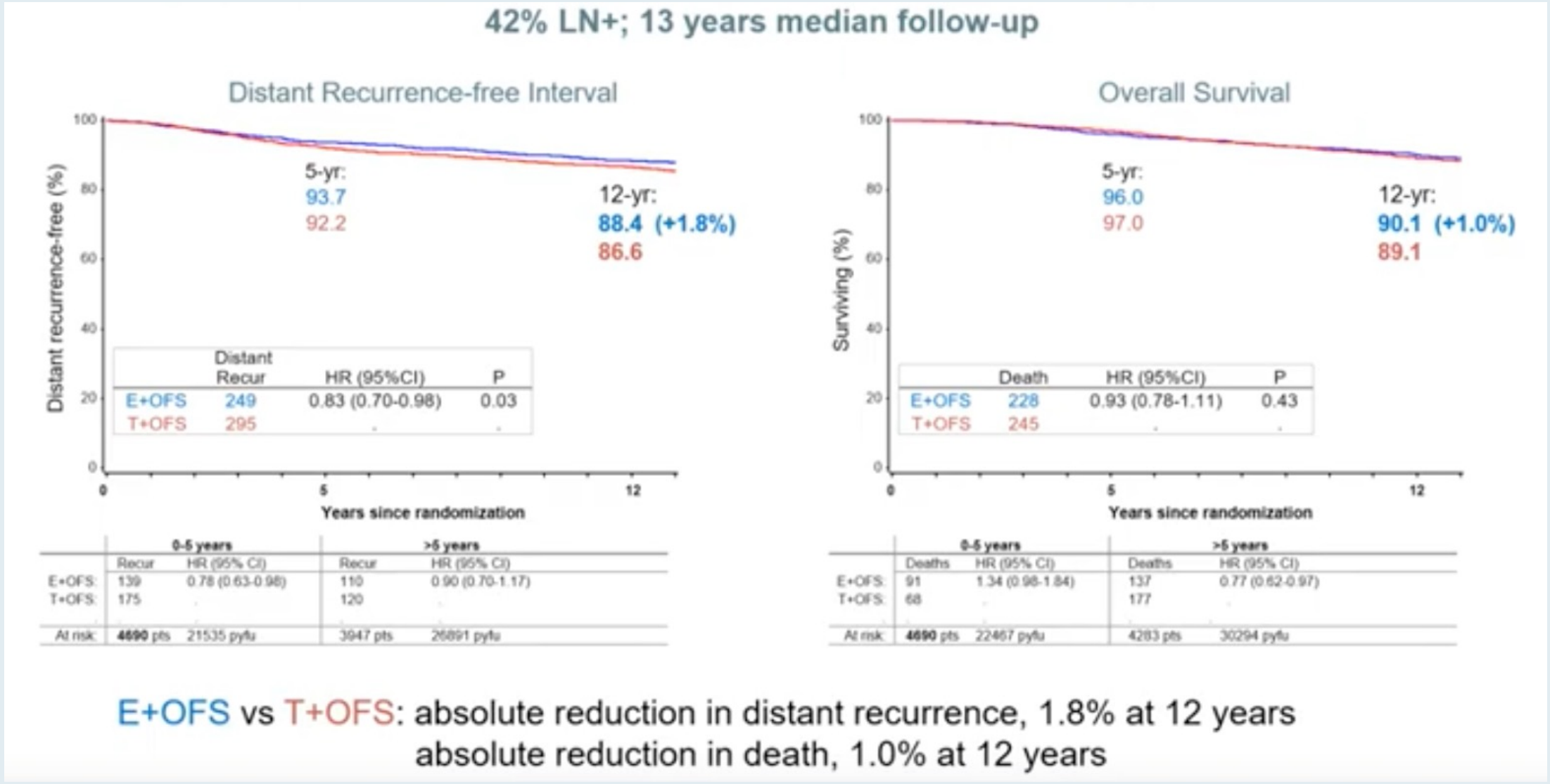
T+OFS vs T: absolute reductions in distant recurrence and death 1.4% and 2.3% at 12 years

E+OFS vs T: absolute reductions in distant recurrence and death 3.0% and 2.6% at 12 years

Regan MM et al. SABCS 2021;Abstract GS2-05.

RTP RESEARCH TO PRACTICE

AI Question: SOFT and TEXT Overall Populations



E+OFS vs T+OFS: absolute reduction in distant recurrence, 1.8% at 12 years
absolute reduction in death, 1.0% at 12 years

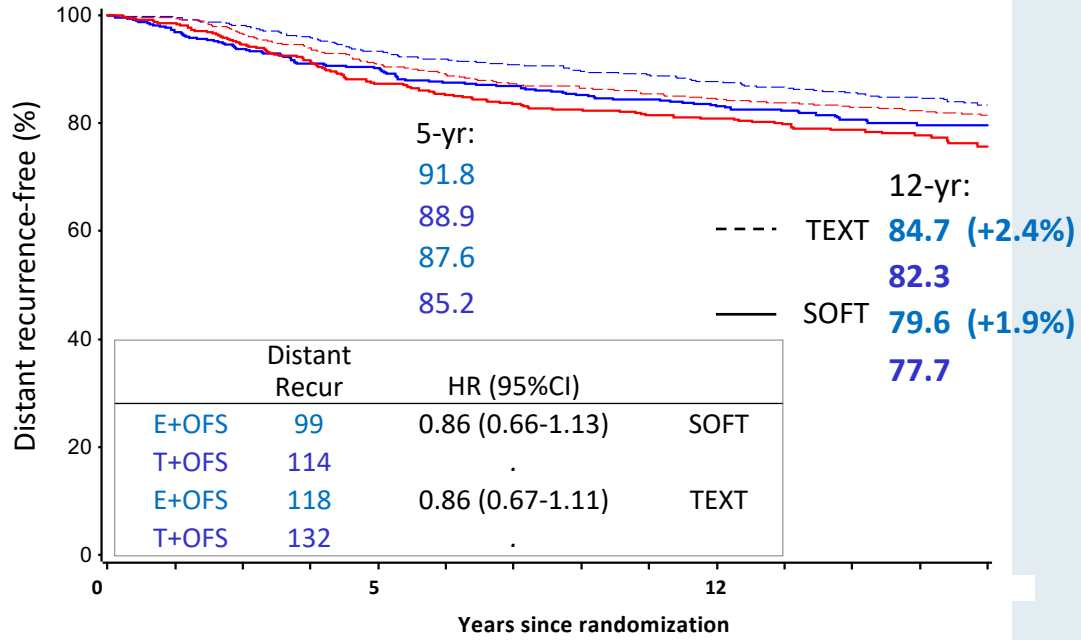
Regan MM et al. SABCS 2021;Abstract GS2-05.

RTP RESEARCH TO PRACTICE

SOFT+TEXT Chemotherapy Cohorts

57% & 66% LN+; 13 years median follow-up

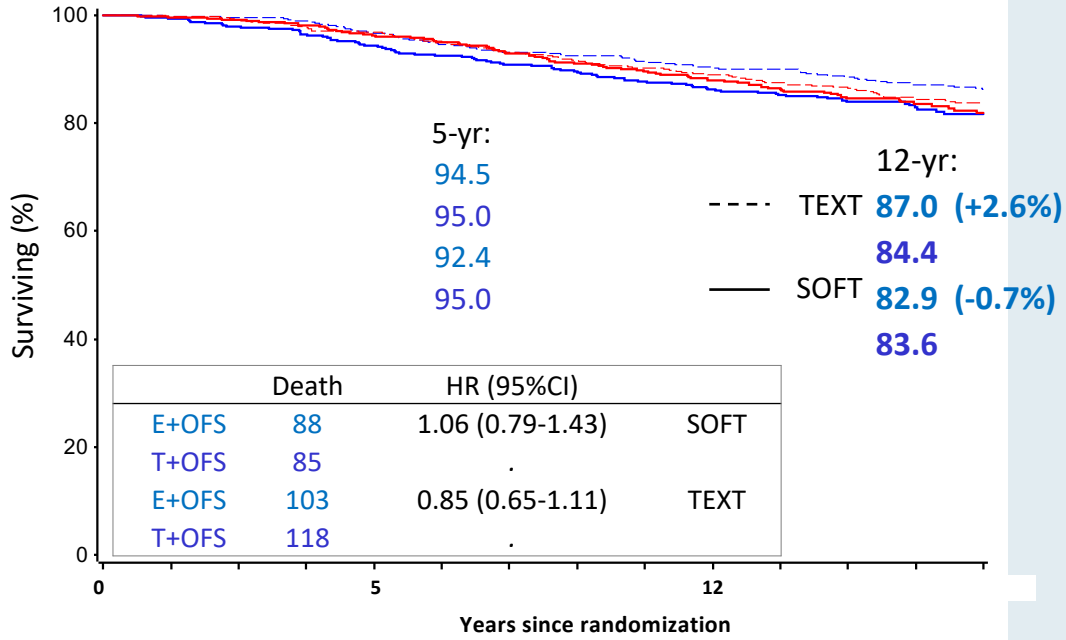
Distant Recurrence-free Interval



	Distant Recur	HR (95%CI)	
E+OFS	99	0.86 (0.66-1.13)	SOFT
T+OFS	114	.	
E+OFS	118	0.86 (0.67-1.11)	TEXT
T+OFS	132	.	

		0-5 years		>5 years	
		Recur	HR (95% CI)	Recur	HR (95% CI)
SOFT	E+OFS:	65	0.85 (0.61-1.19)	34	0.88 (0.56-1.41)
	T+OFS:	76	.	38	.
TEXT	E+OFS:	62	0.73 (0.52-1.01)	56	1.10 (0.75-1.61)
	T+OFS:	83	.	49	.
	At risk:	2694 pts	12086 pyfu	2166 pts	14702 pyfu

Overall Survival



	Death	HR (95%CI)	
E+OFS	88	1.06 (0.79-1.43)	SOFT
T+OFS	85	.	
E+OFS	103	0.85 (0.65-1.11)	TEXT
T+OFS	118	.	

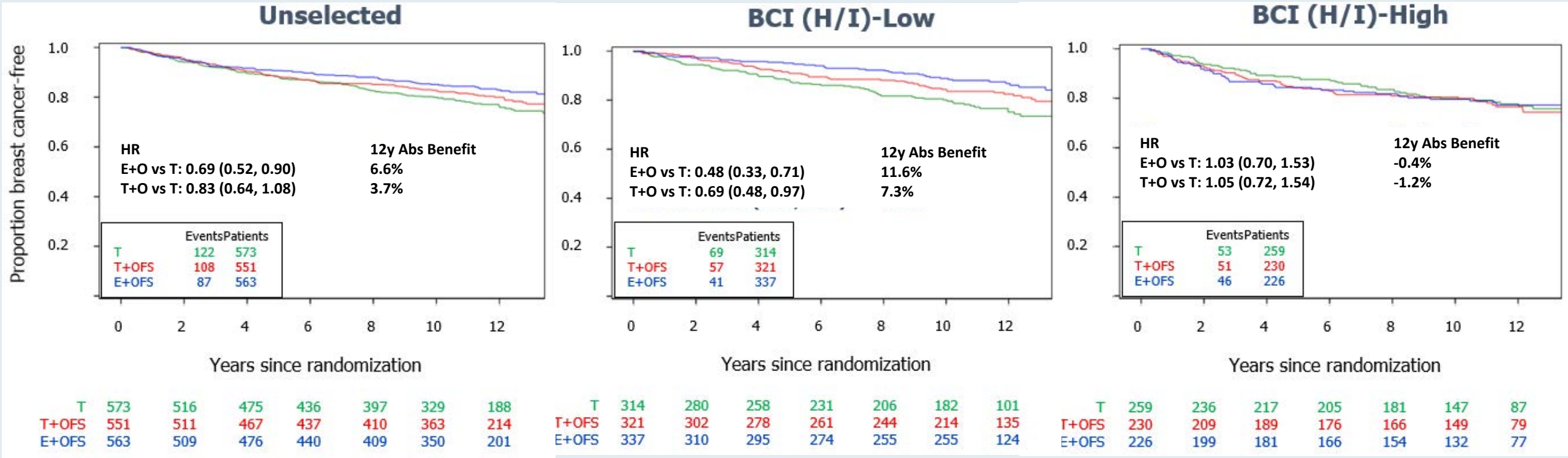
		0-5 years		>5 years	
		Deaths	HR (95% CI)	Deaths	HR (95% CI)
SOFT	E+OFS:	40	1.57 (0.96-2.57)	48	0.84 (0.57-1.22)
	T+OFS:	26	.	59	.
TEXT	E+OFS:	42	1.10 (0.71-1.70)	61	0.74 (0.53-1.03)
	T+OFS:	38	.	80	.
	At risk:	2694 pts	12774 pyfu	2395 pts	16928 pyfu

E+OFS vs T+OFS: reductions in distant recurrence 1.9% SOFT and 2.4% TEXT at 12 years
overall survival, -0.7% SOFT and +2.6% TEXT at 12 years

pyfu=person-years follow-up

RTP RESEARCH TO PRACTICE

BCI (H/I) Predictive Results for BCFI – Overall HR+ Cohort



- 58% of cancers were BCI (H/I)-Low and 42% were BCI (H/I)-High
- Significant treatment by biomarker interaction for EXE+OFS vs TAM (P<0.01 in adjusted analysis); less so for TAM+OFS vs TAM (P=0.16)

RTP RESEARCH TO PRACTICE

Guidelines for OFS

- ASCO:
  - Offer in women receiving chemotherapy
  - Offer to higher risk women: larger tumors, younger age, higher grade, pos LN
- St Gallen:
  - Offer in women who are less than 35yo, received chemotherapy, have 4+LN

monarchE Study Design (NCT03155997) (4y efficacy)

HR+, HER2-, node positive high-risk EBC

- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**

- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**

- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:

- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

On-study treatment period
2 years

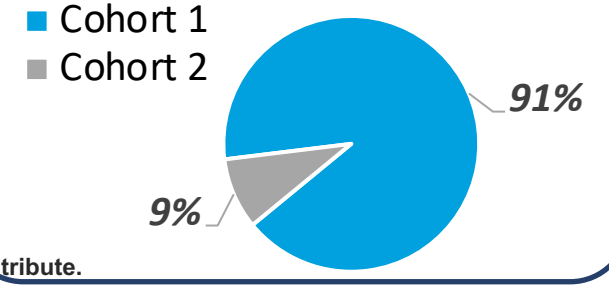
Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

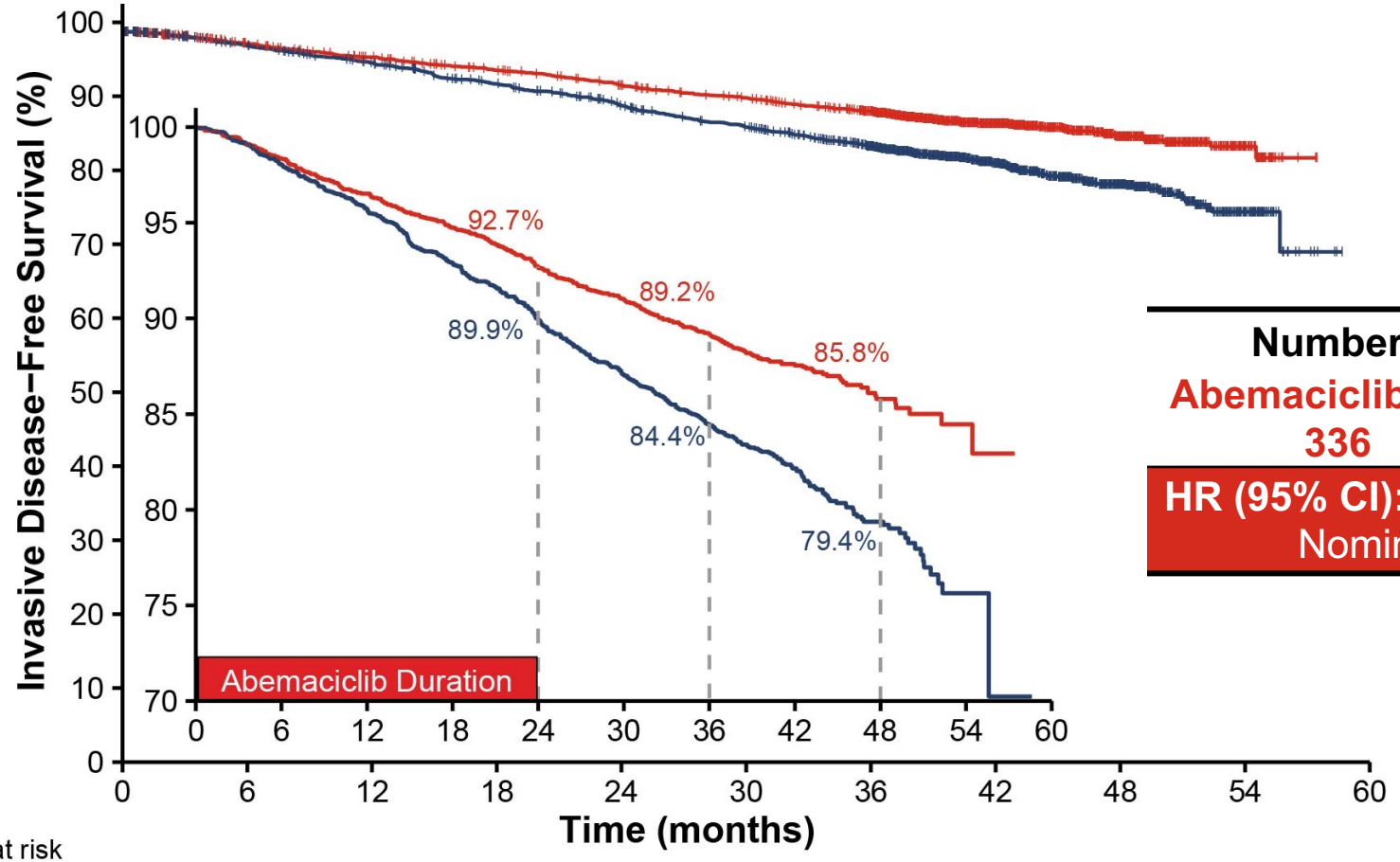
Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO

ITT Population



IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib



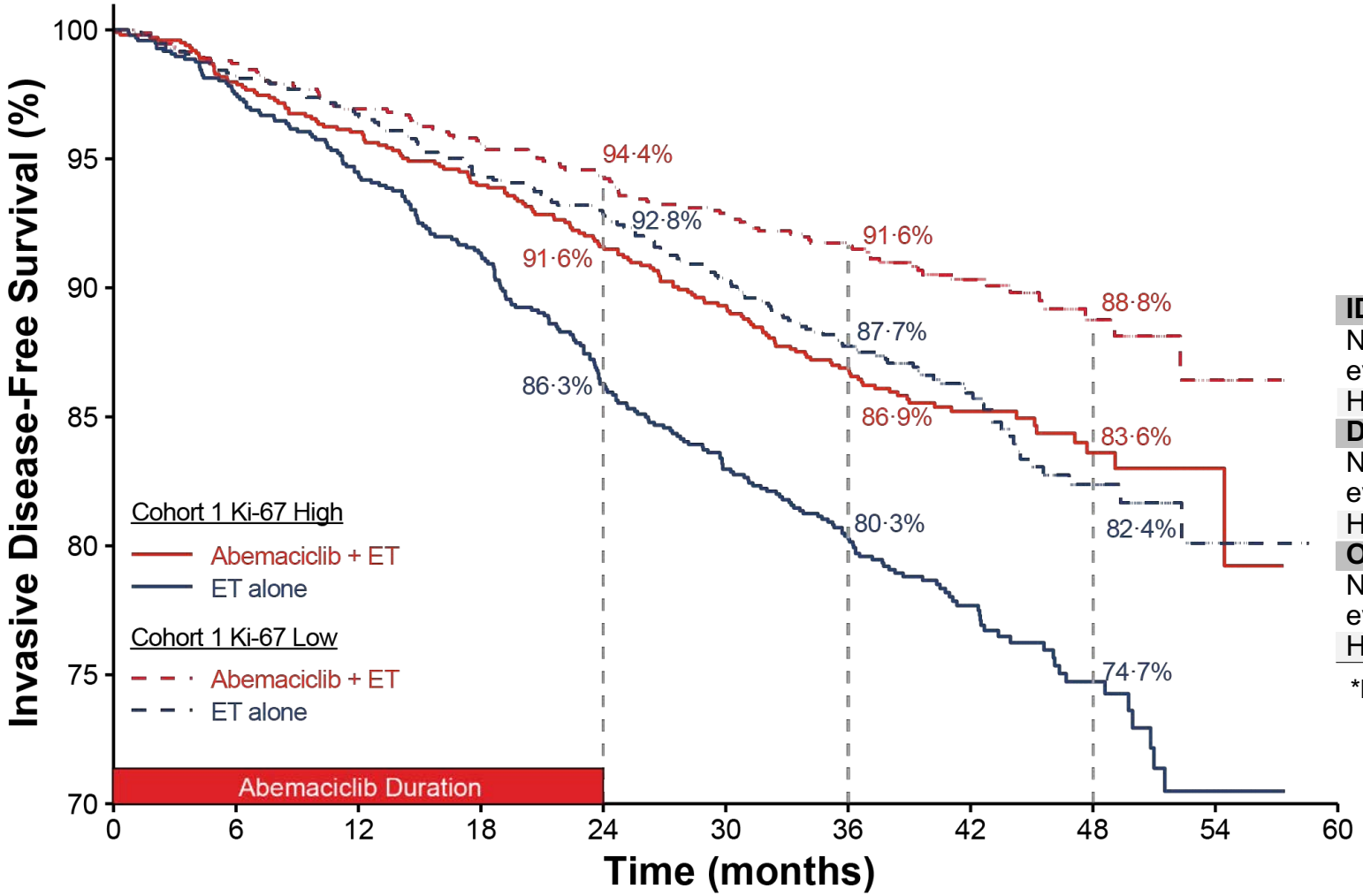
Number of IDFS events

Abemaciclib + ET	ET Alone
336	499

HR (95% CI): 0.664 (0.578, 0.762)
Nominal p < 0.0001

33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

Ki-67 is Prognostic, but Not Predictive of Abemaciclib Benefit



	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=1017	ET alone N=986	Abemaciclib + ET N=946	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of events, n	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

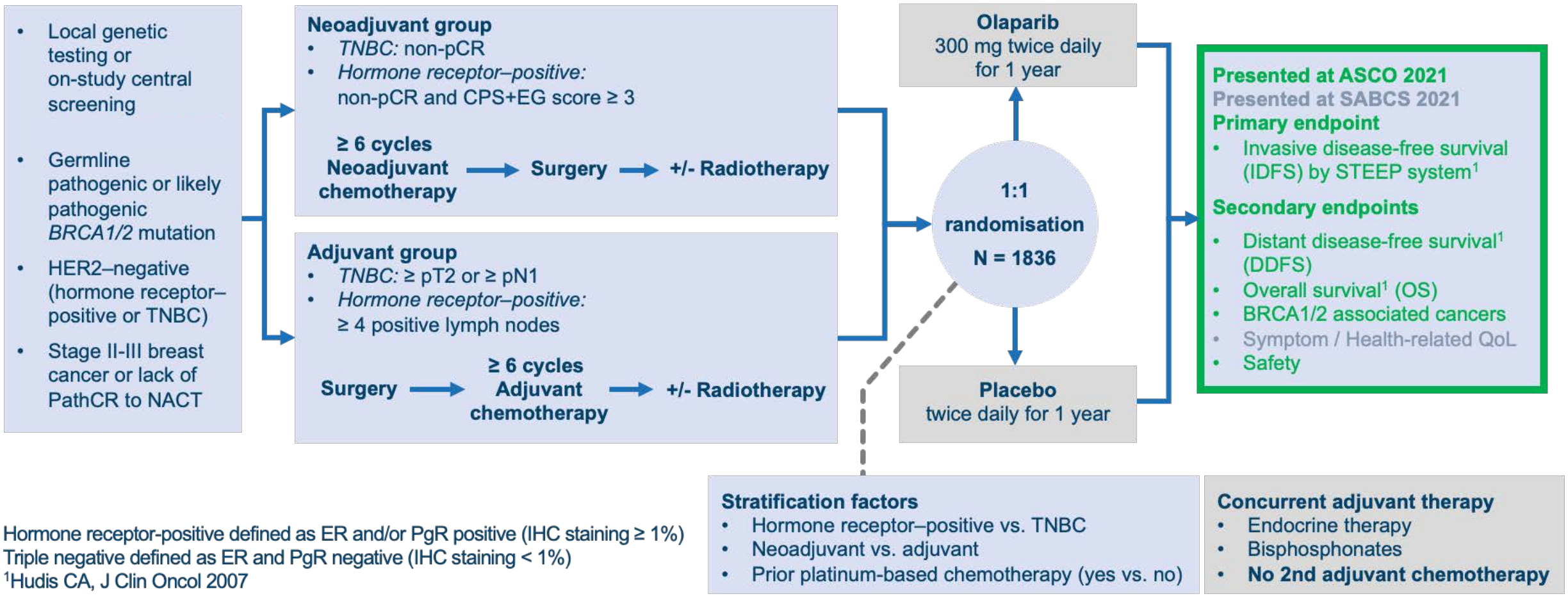
*Ki-67 value was missing in 1203 (23.5%) patients

Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index

Adjuvant CDK4/6i Reported Trials

	PALLAS	PENELOPE-B	MONARCH-E
N	5600	1250	5637
Length of CDK4/6i	2 year	1 year	2 year
Prior chemotherapy	82%	100%	95%
Tamoxifen use	32%	50%	30%
Grade 3	29%	47%	38%
Node negative	13%	Unknown	0.2%
N1	49%	Unknown	40%
≥N2	37%	50% (after NAC)	60%
Discontinued IP prematurely	42%	19.5%	28% (at 19 mos f/u)
Still on therapy	26%	0	10%
Median follow up	24 mos	42.8 mos	27.1 mos
2-year iDFS		88.3% vs 84% Δ4.3%	**92.7% vs 90.0%** **Δ2.7%**
3-year iDFS	88.2% vs. 88.5% Δ-0.3%	81.2% vs. 77.7% Δ3.5%	**88.8% vs 83.4%** **Δ5.4%, HR 0.696, P<0.0001**

OLYMPIA: TRIAL SCHEMA



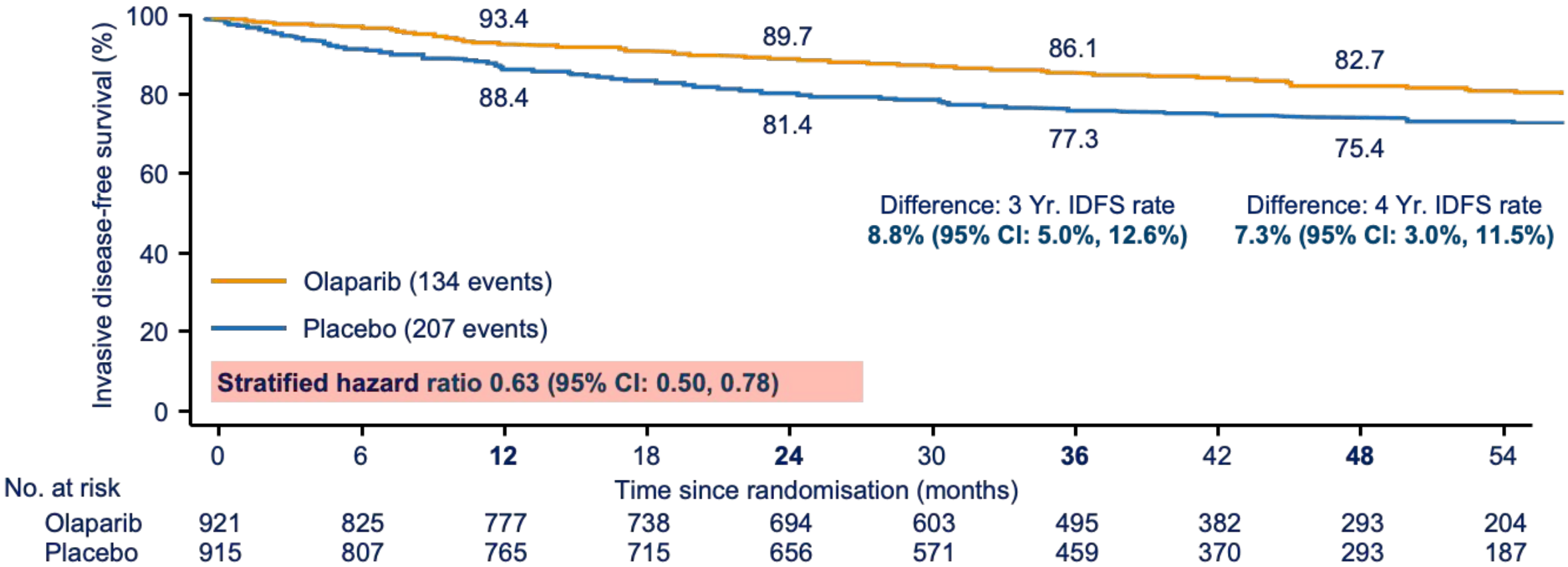
Hormone receptor-positive defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Comments on study population

- Very young (median 42-43, 25% > 50)
- 72.3% gBRCA1m
- 82.2% TNBC, no HER2+ (by design)
- 74.7% treated with mastectomy (46.5% bilateral)
- RRSO in ~60%

- CPS+EG score unfamiliar to many
  - http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=bcnt
  - Remember to use nuclear grade, not histologic or overall

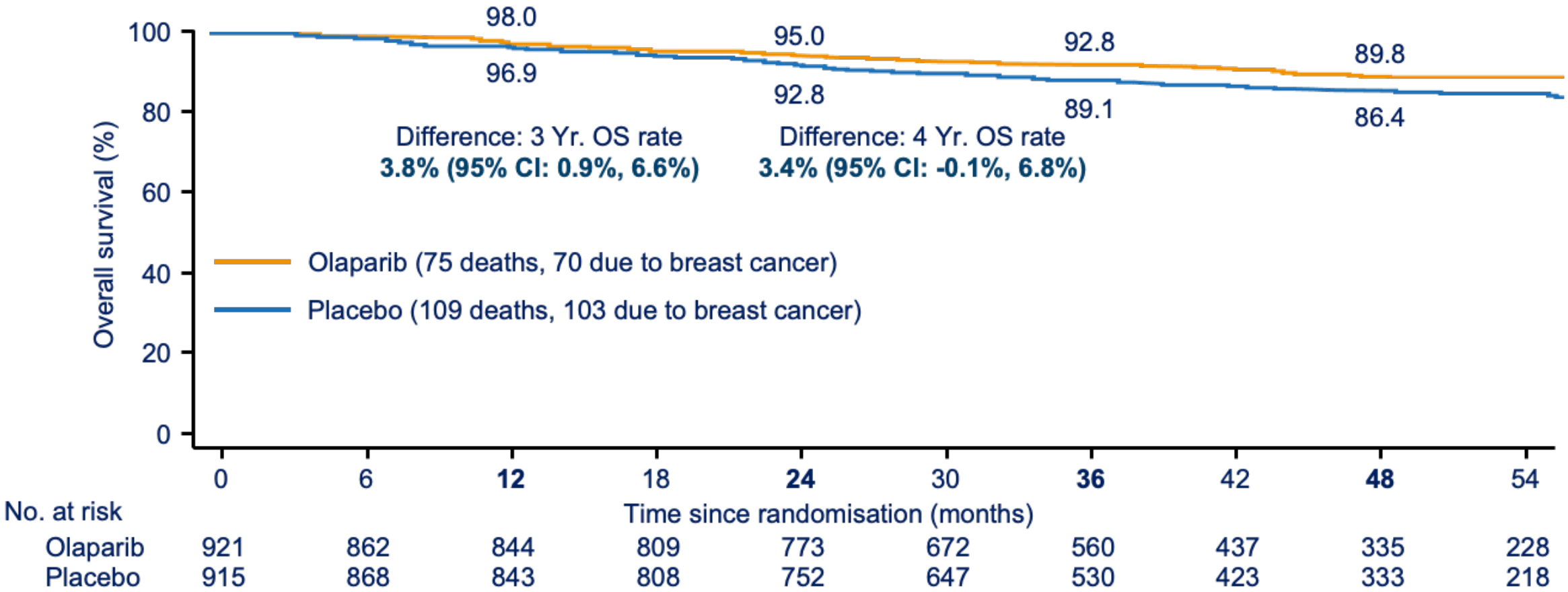
ANALYSIS OF IDFS (ITT) AT OS IA2



No. at risk									
Olaparib	921	825	777	738	694	603	495	382	293	204
Placebo	915	807	765	715	656	571	459	370	293	187

Tutt et al, ESMO Virtual Plenary March 2022

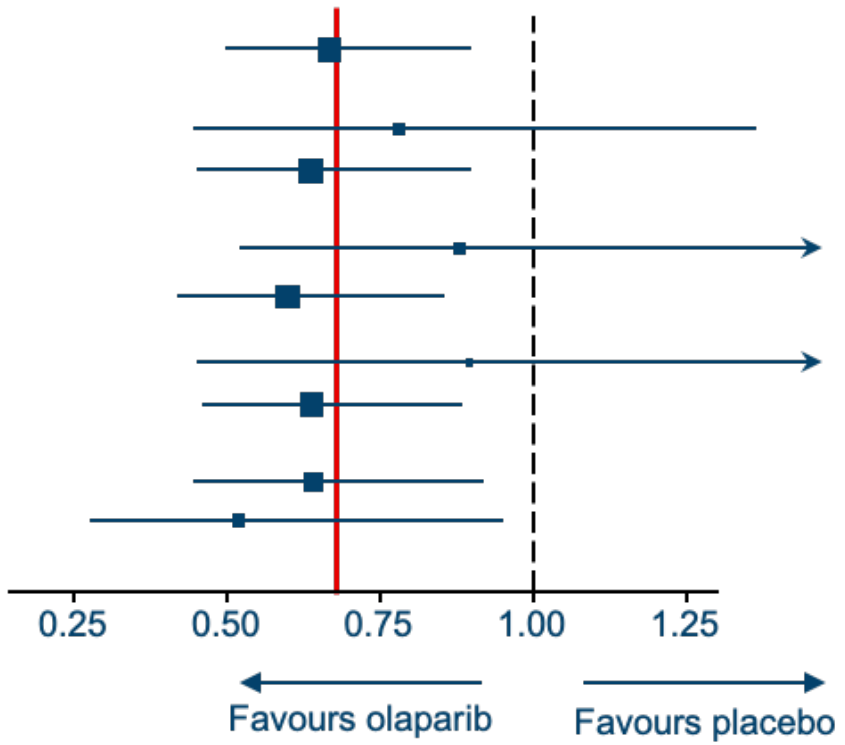
SECOND OVERALL SURVIVAL INTERIM ANALYSIS - OS IA 2 (ITT)



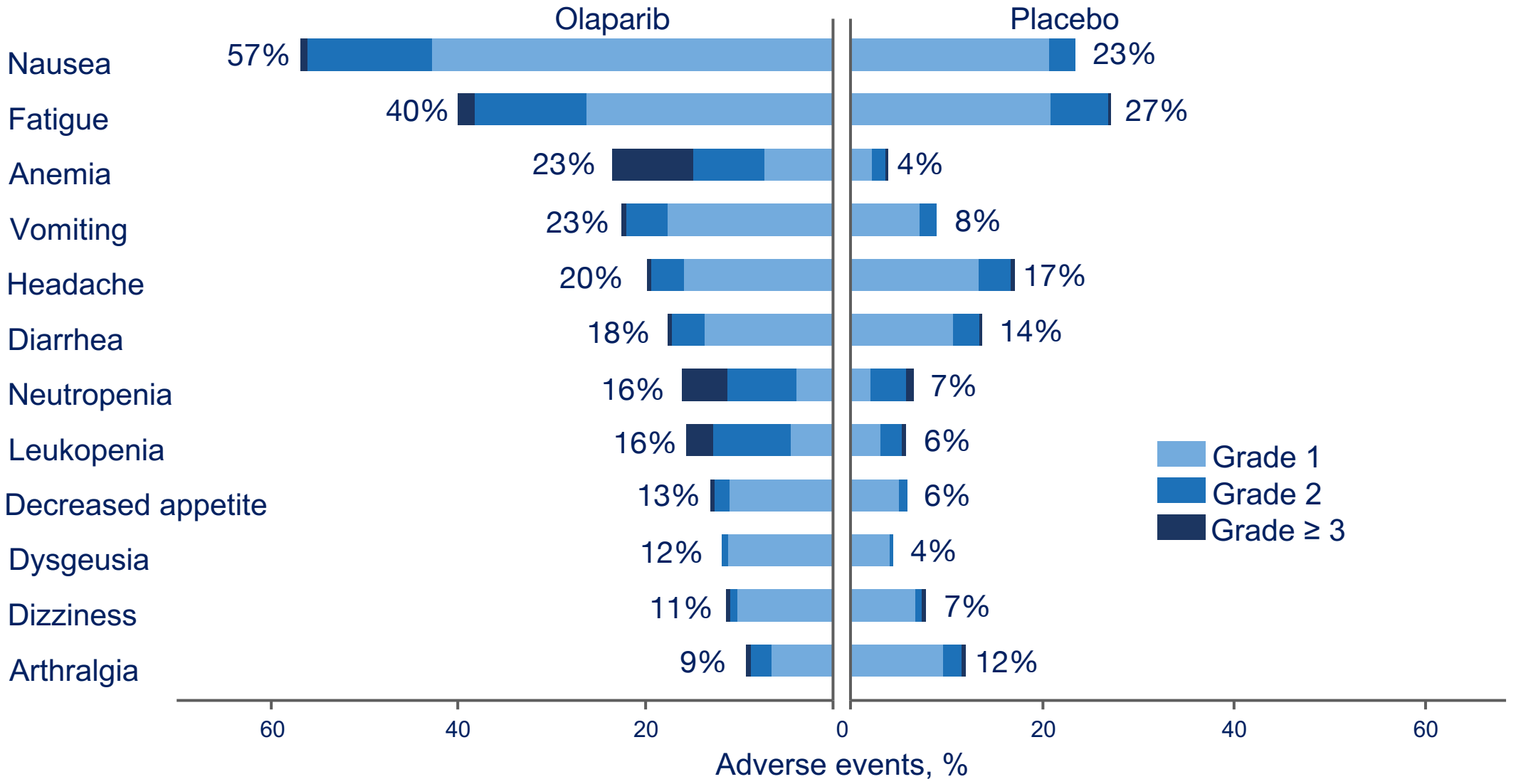
Tutt et al, ESMO Virtual Plenary March 2022

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


Olaparib
Placebo
Nausea
Fatigue
Anemia
Vomiting
Headache
Diarrhea
Neutropenia
Leukopenia
Decreased appetite
Dysgeusia
Dizziness
Arthralgia
57%
40%
23%
23%
20%
18%
16%
16%
13%
12%
11%
9%
23%
27%
4%
8%
17%
14%
7%
6%
6%
4%
7%
12%
Grade 1
Grade 2
Grade ≥ 3
60
40
20
0
20
40
60
Adverse events, %

Conclusions

- EET benefits few and adds to AEs
- OFS during chemo can preserve ovarian function
- OFS to high risk women. Can it replace chemo?
- CDK4/6i for high risk. Do we trust Ki67?
- PARPi for high risk. Do we perform CPS?

MODULE 3: Selection and Sequencing of Therapy for Patients with ER-Positive Metastatic Breast Cancer (mBC) — Dr Kalinsky

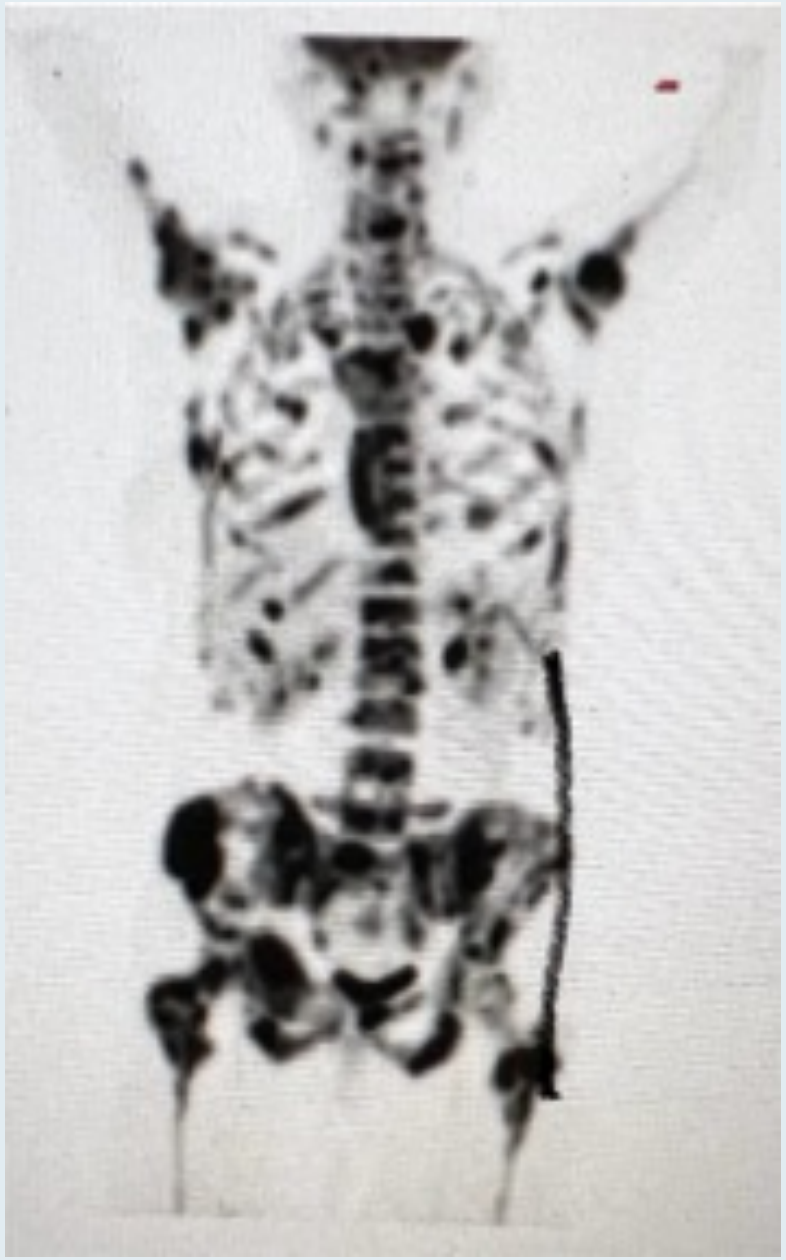
RTP
RESEARCH
TO PRACTICE

Case Presentation: 53-year-old woman with ER/PR-positive, HER2-low, PI3KCA-mutated mBC who experiences a dramatic response to rechallenge with fulvestrant and a CDK4/6i (abemaciclib); now with progression and cytopenias

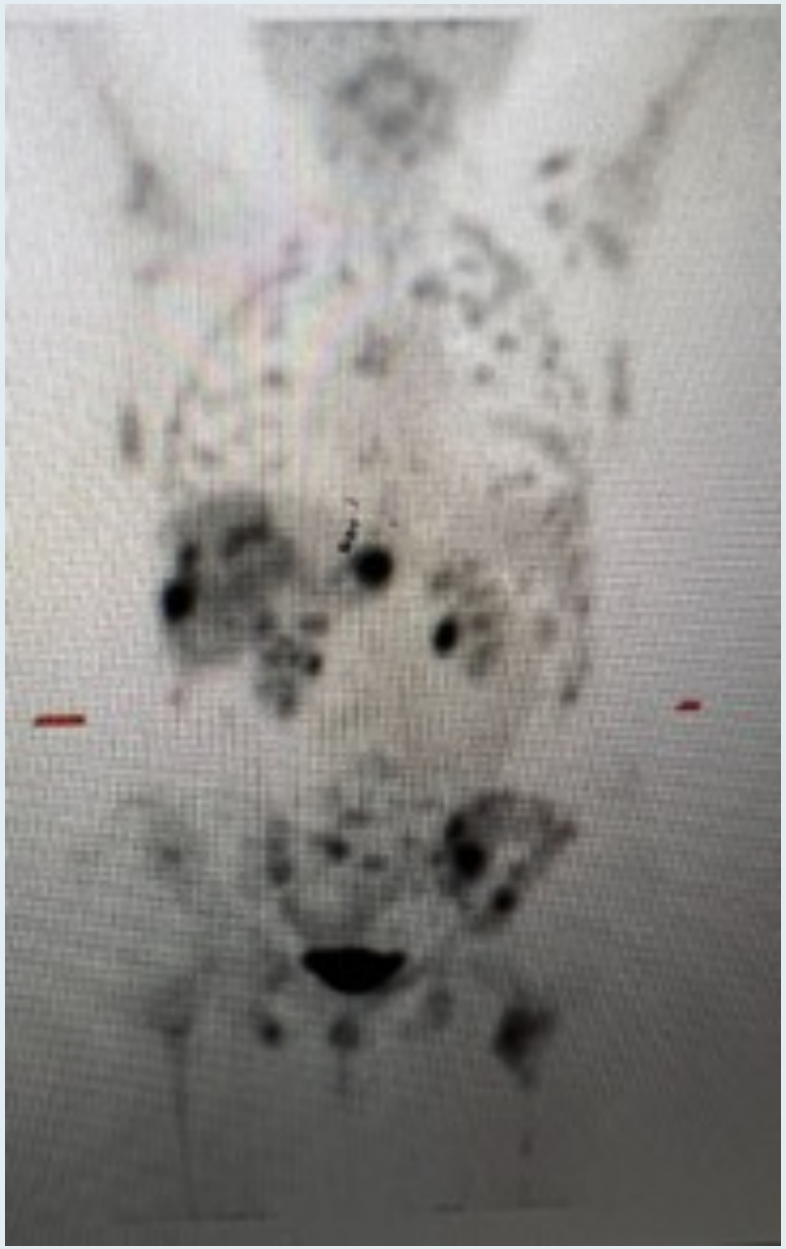
Dr KS Kumar (Trinity, Florida)

RTP RESEARCH TO PRACTICE

Before abemaciclib/fulvestrant



After abemaciclib/fulvestrant



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Selection and Sequencing of Therapy for Patients with ER-Positive Metastatic Breast Cancer

Kevin Kalinsky, MD, MS

Associate Professor of Medicine

Director, Glenn Family Breast Center

Director, Breast Medical Oncology

Louisa and Rand Glenn Family Chair in Breast Cancer Research

Results for Pivotal CDK 4/6 Inhibitor Trials

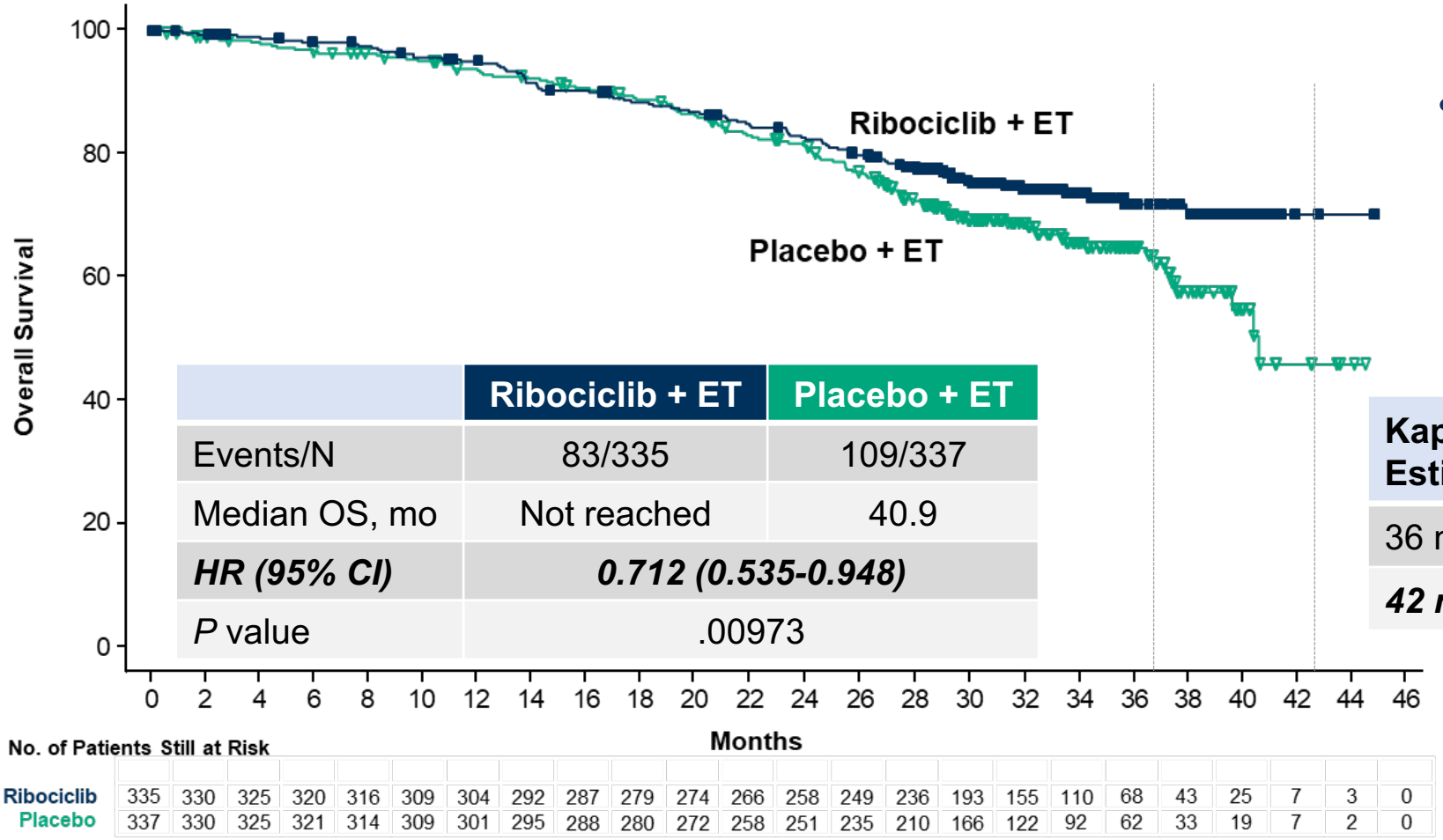
Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2[1]	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	No
MONALEESA-2[2]	Ribociclib	1st Line/AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7[3a]	Ribociclib	1st Line/AI or Tam	Pre/Peri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

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

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

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

MONALEESA-7: Overall Survival



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

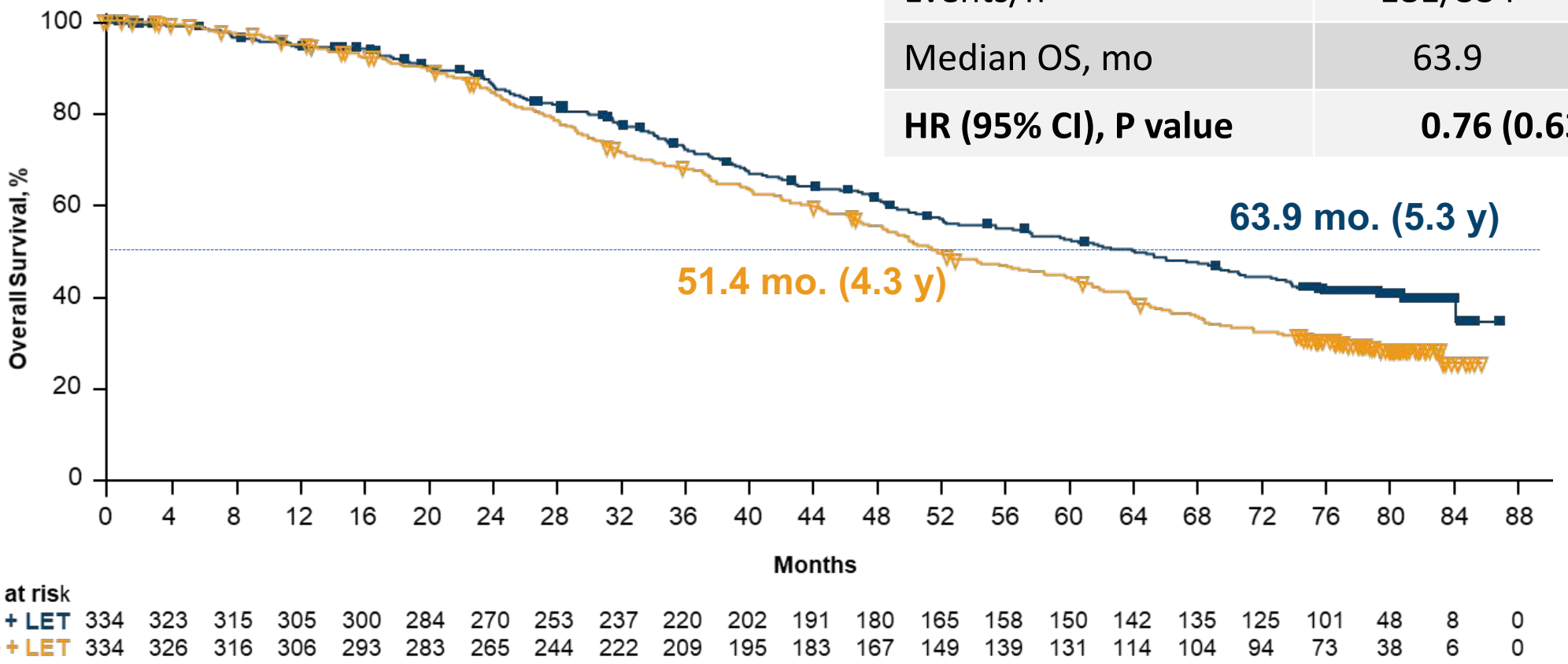
Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 mo	71.9%	64.9%
42 mo	***70.2%***	***46.0%***

Protocol-specified key secondary end point.
Im S-A, et al. *New Engl J Med*. 2019;381:307-316.

MONALEESA-2: Letrozole ± Ribociclib – Overall Survival

Final Analysis at 400 death events: Improvement in median OS of 12.5 mo

	RIB + LET	PBO + LET
Events/n	181/334	219/334
Median OS, mo	63.9	51.4
HR (95% CI), P value	**0.76 (0.63-0.93), .004**	



Key secondary end point.

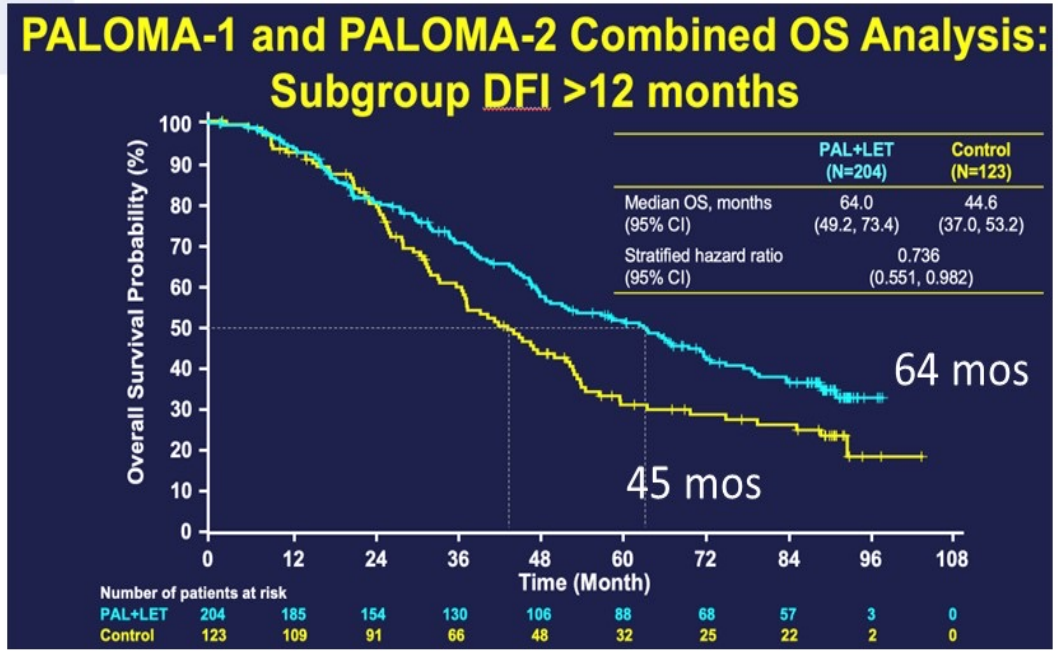
Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR.

Why are there OS differences between the studies?

Randomized P3 Trials	PALOMA-2 * Palbociclib	MONALEESA-2 Ribociclib	MONALEESA-7 Ribociclib	MONALEESA-3 Ribociclib 1L Cohort
De novo mBC	38%	34%	41%	20%
Disease-free interval				
DFI ≤ 12 mos	22%	1%	7%	0%
DFI > 12 mos	40%	NR	53%	80%
DFI > 24 mos	NR	60%	NR	NR

- DFI ≤ 12 mos in Paloma 1 ~ 35%
- Combined OS analysis with PALOMA-1 planned
- Analysis by DFI subgroup unplanned

No substantial differences in prior therapy, visceral disease, use of subsequent CDK46i in placebo arm, other variables

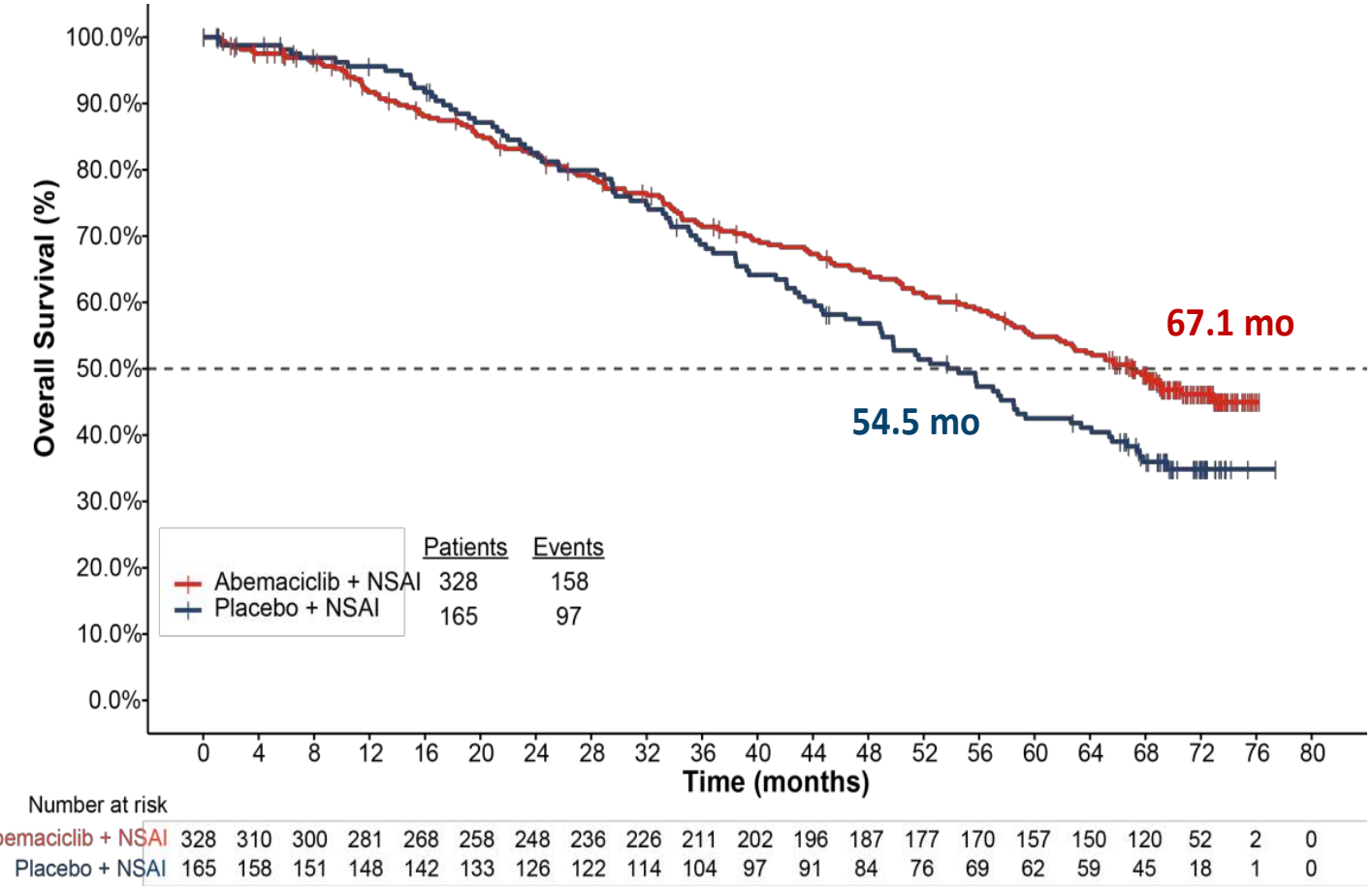


Limitations:
- Post hoc analyses
- Definition of "missing survival data"

- Paloma-2: Missing survival data and were censored at time of analysis: 13% in palbo+AI arm vs 21% in control arm. 27% of pts in control arm went on to receive a CDK4/6i (24% received palbo).

Finn et al NEJM 2016; Hortobagyi et al. NEJM 2016; Tripathy et al Lancet Oncol 2018; Slamon et al. NEJM 2020

MONARCH-3: NSAI ± Abemaciclib – Overall Survival



	abemaciclib + NSAI	placebo + NSAI
Median OS, (months)	67.1	54.5
HR (95% CI; *P* value)	0.754 (0.584-0.974) p-value 0.0301*	
Pre-planned OS IA2 Analysis Data cut: 02 Jul 2021		

*p-value did not reach threshold for statistical significance at this interim

31.5% of patients in the control arm and 10.1% in the abemaciclib arm received a subsequent CDK4 & 6 inhibitor

At this interim analysis, statistical significance was not reached but data are maturing favorably (HR 0.754, 95% CI: 0.584-0.974) and follow up continues. The observed difference in median OS was 12.6 months.

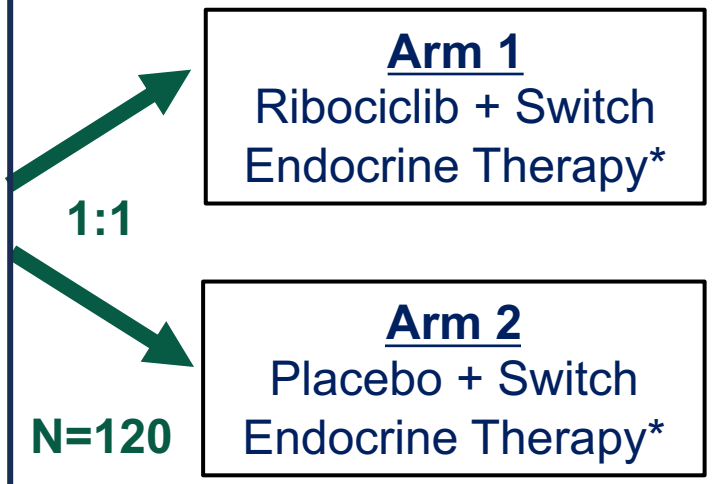
Key secondary end point.

Goetz M. et al. ESMO 2022. Abstract LBA15

Schema

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



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

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

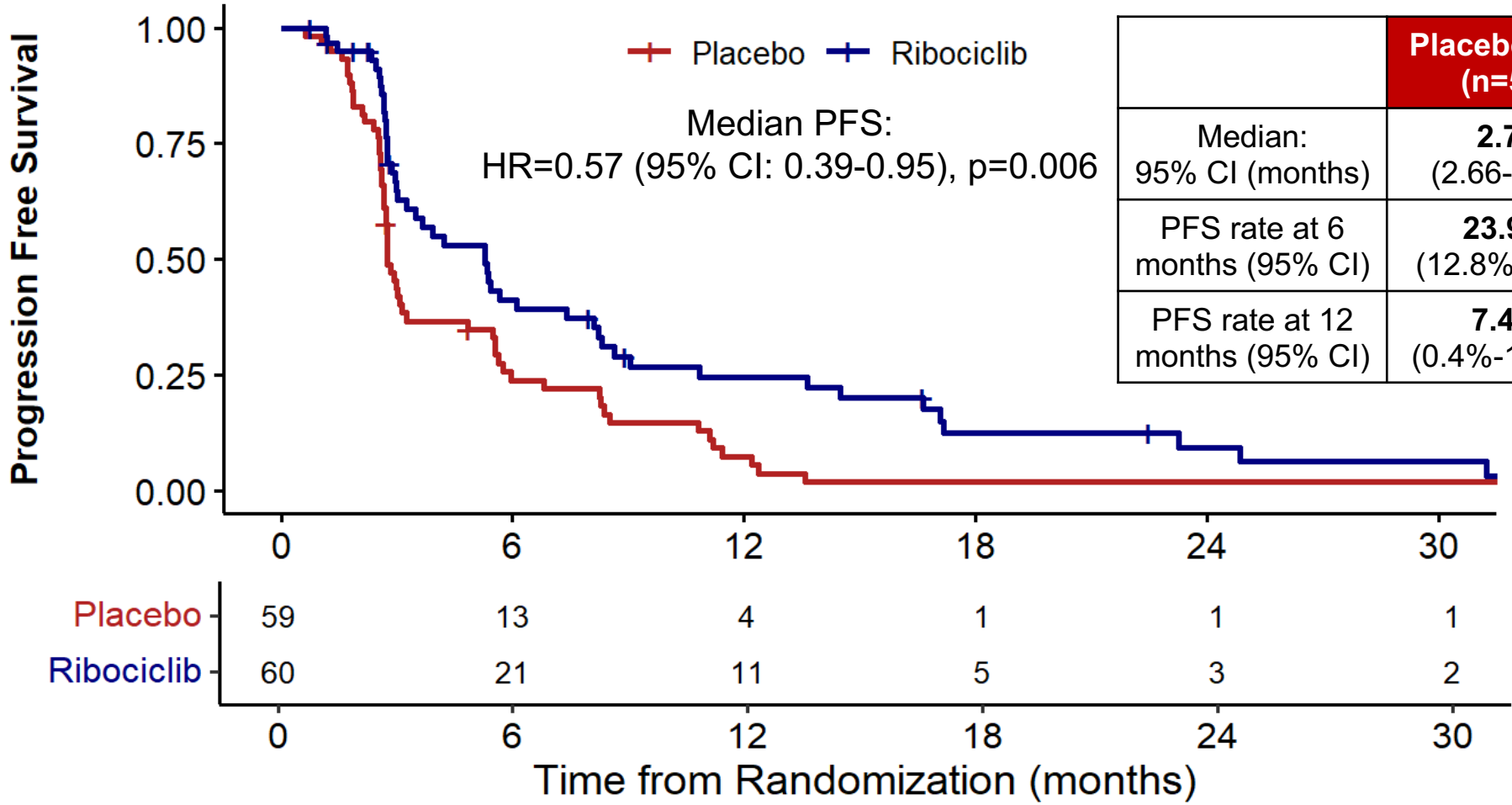
Patient Characteristics and Prior Treatment

	Placebo (n=59)	Ribociclib (n=60)
Female - no. (%)	58 (99%)	60 (100%)
Median age – years (IQR)	59 (52-65)	55 (48-67)
Race or ethnic group – no. (%)		
White	42 (71%)	46 (77%)
Black	8 (14%)	5 (8%)
Asian	2 (3%)	5 (8%)
Other or not specified	7 (12%)	4 (7%)
ECOG PS – no. (%)		
0	38 (64%)	40 (67%)
1	21 (36%)	20 (33%)
De Novo Metastasis at Dx - no. (%)* **	32 (54%)	21 (35%)
Visceral Metastasis – no. (%)	35 (59%)	36 (60%)
Bone-Only Disease – no. (%)	9 (15%)	13 (22%)
≥ 2 prior ET for MBC – no. (%)	11 (19%)	11 (18%)
Chemotherapy for MBC – no. (%)	7 (12%)	4 (7%)

	Placebo (n=59)	Ribociclib (n=60)
Prior CDK 4/6 inhibitor – no. (%)		
Palbociclib*	51 (86%)	52 (87%)
Ribociclib**	8 (14%)	6 (10%)
Abemaciclib	0 (0%)	2 (3%)
Median duration of prior CDK 4/6 inhibitor - months (IQR)	17 (11-23.5)	15.5 (12-21)
Prior CDK 4/6 inhibitor duration– no. (%)****		
≤ 12 months	21 (36%)	18 (30%)
> 12 months	38 (64%)	42 (70%)
Prior CDK 4/6 inhibitor in metastatic setting - no. (%)	59 (100%)	60 (100%)
Intervening treatment after progression on prior CDK 4/6 inhibitor - no. (%)	6 (10%)	1 (2%)

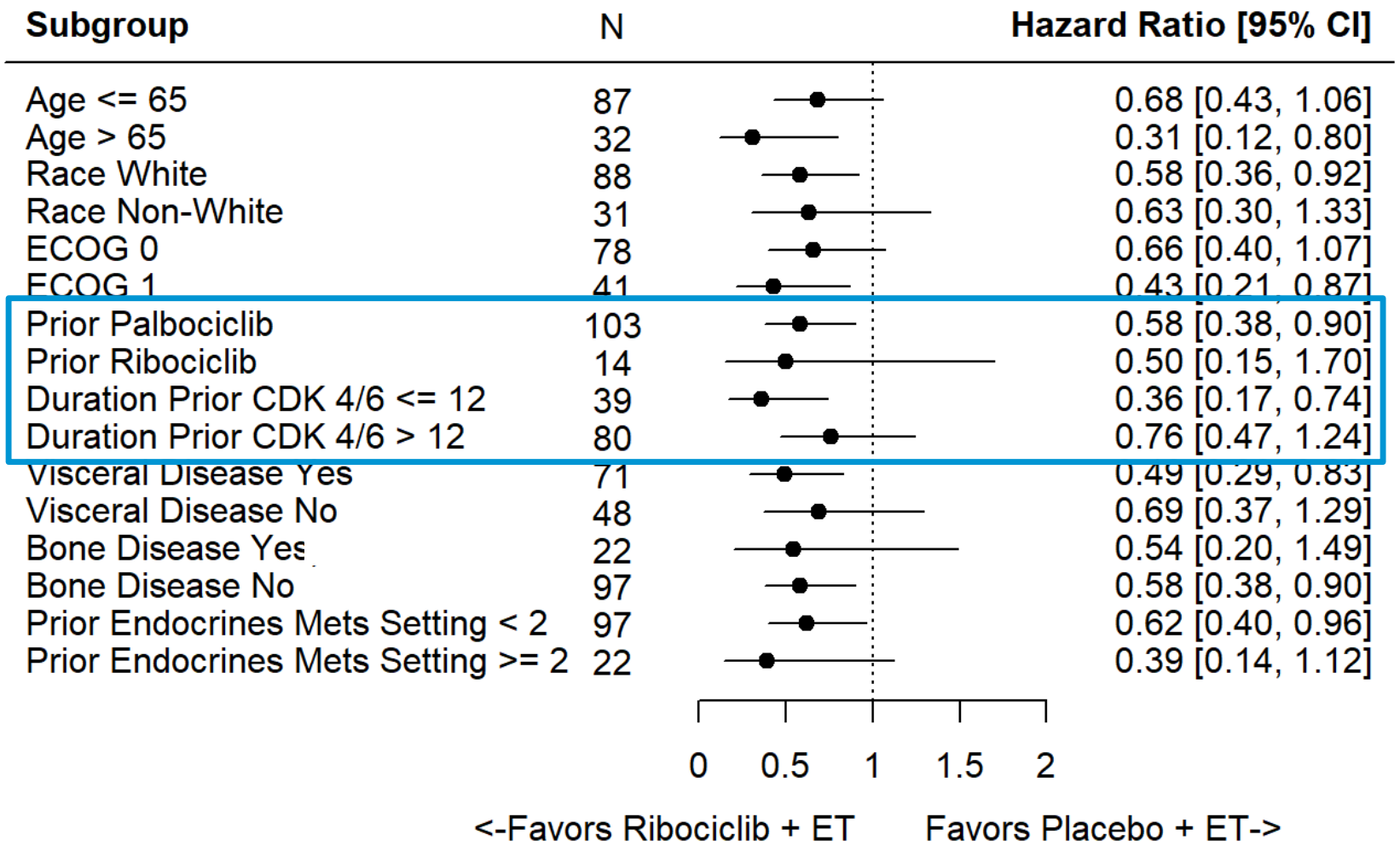
* Includes 1 pt who did not tolerate prior abemaciclib and 2 pts with insurance issues with ribociclib; ** Includes 1 pt who did not tolerate prior palbociclib;
p=0.035; * 10 pts (17%) in placebo arm and 7 pts (12%) in ribociclib arm on prior CDK4/6 inhibitor ≤ 6 months; IQR = interquartile range

Progression Free Survival

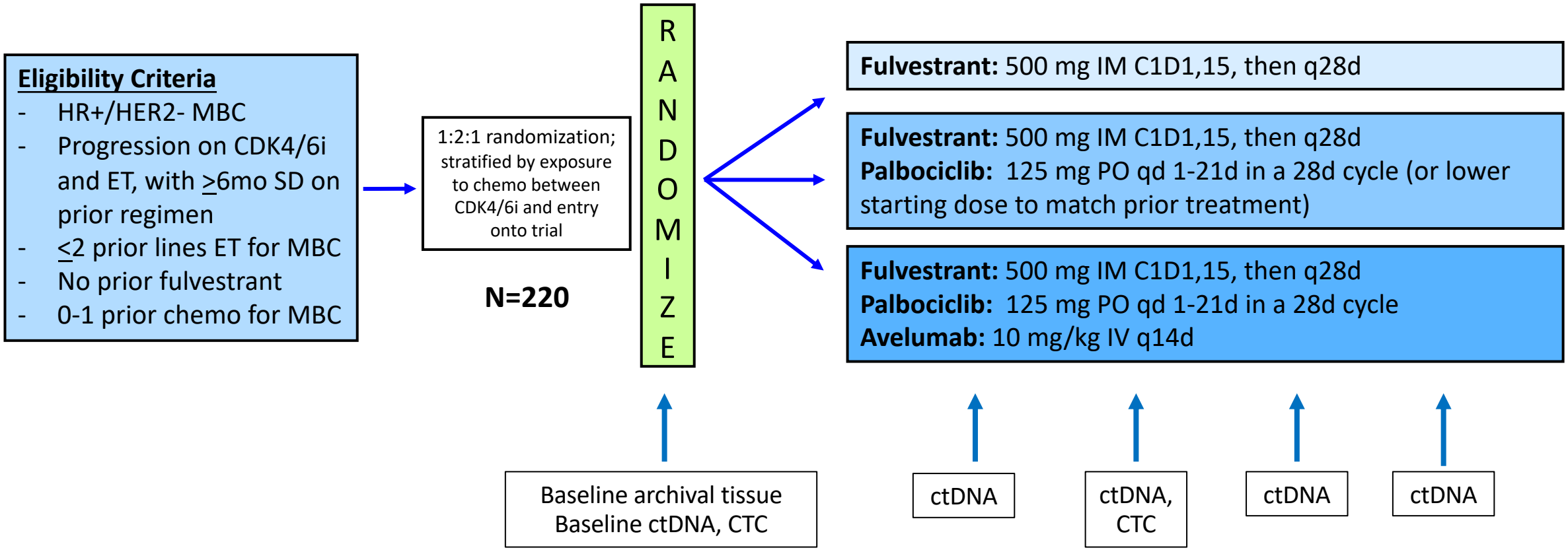


	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)
PFS rate at 6 months (95% CI)	**23.9%** (12.8%-35%)	**41.2%** (27.8%-54.6%)
PFS rate at 12 months (95% CI)	**7.4%** (0.4%-14.3%)	**24.6%** (12.5%-36.7%)

Progression Free Survival by Subgroup



PACE Trial: Schema



Primary objective: To compare PFS (RECIST-confirmed) for fulvestrant+palbociclib vs. fulvestrant alone

Secondary objectives: To compare PFS for fulvestrant+palbociclib+avelumab vs fulvestrant alone, response endpoints, safety, outcomes in predefined molecular subgroups including ESR1, PIK3CA, and Rb.

PACE Trial: Patient Demographics

	Fulvestrant (n=55)		Fulvestrant + Palbociclib (N=111)		Fulvestrant + Palbociclib + Avelumab (N=54)		Overall (n = 220)	
	N	%	N	%	N	%	N	%
Female	55	**100.0**	109	**98.2**	54	**100.0**	218	**99.0**
Age (median, range)	58 (36-77)		55 (28-77)		58 (25-83)		57 (25-83)	
Race								
White	47	**85.5**	88	**79.3**	44	**81.5**	179	**81.4**
Black	3	**5.5**	13	**11.7**	4	**7.4**	20	**9.1**
Asian	0	**0**	4	**3.6**	3	**5.6**	7	**3.2**
Other	5	**9.1**	6	**5.4**	3	**5.6**	14	**6.4**
Post-menopausal	47	**85.5**	87	**78.4**	44	**81.5**	178	**80.9**
De novo MBC	28	**50.9**	40	**36.0**	20	**37.0**	88	**40.0**
Visceral disease	29	**52.7**	70	**63.1**	33	**61.1**	132	**60.0**
Bone only disease	4	**7.3**	18	**16.2**	8	**14.8**	30	**13.6**
Measurable disease	37	**67.3**	73	**65.8**	39	**72.2**	149	**67.7**

Unknown values are omitted from the table.

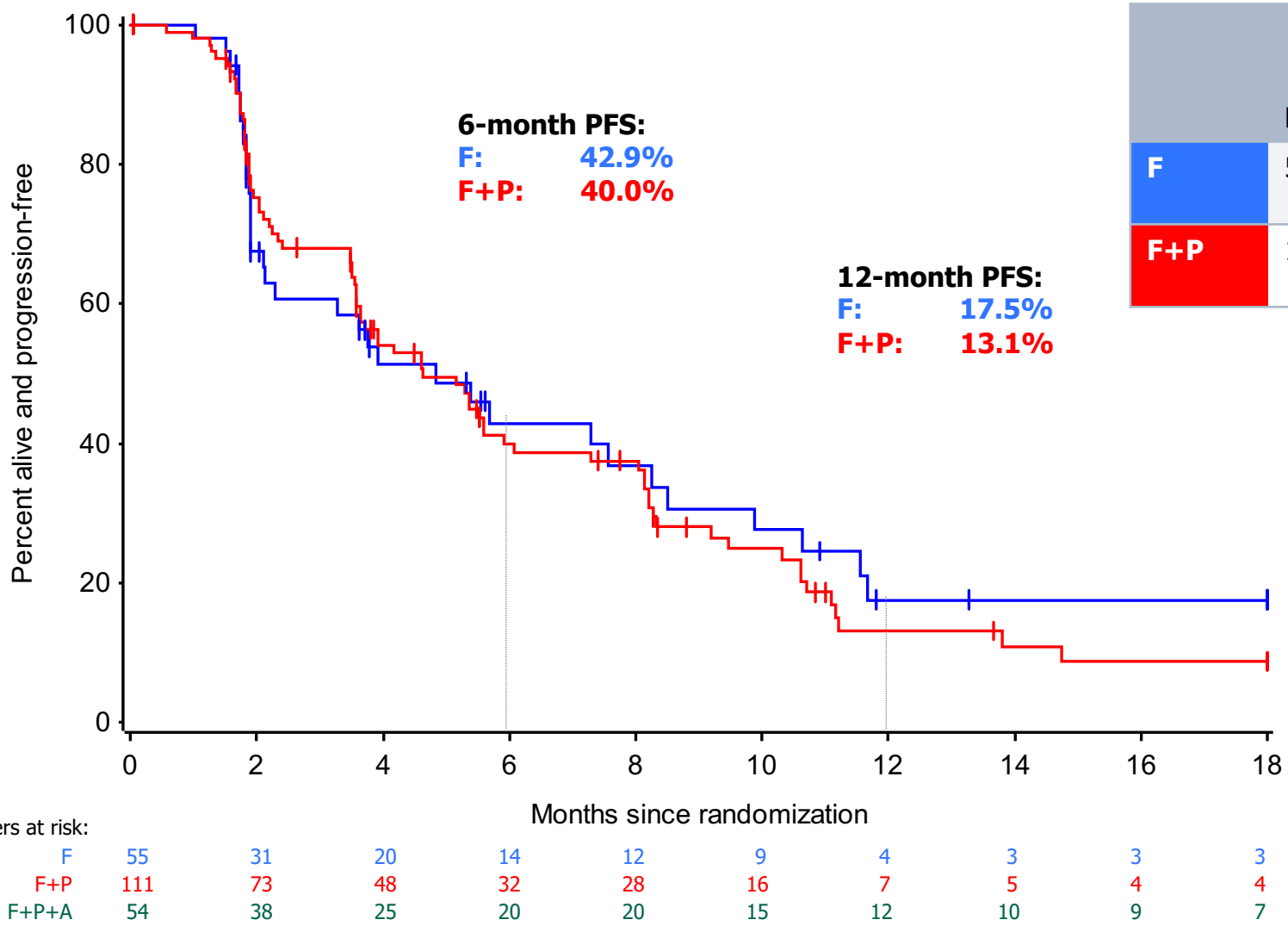
PACE: Prior Treatment Characteristics

	Fulvestrant (n=55)		Fulvestrant + Palbociclib (N=111)		Fulvestrant + Palbociclib + Avelumab (N=54)		Overall (n = 220)	
	N	%	N	%	N	%	N	%
Prior adjuvant endocrine exposure*								
Endocrine resistant	10	**18.2**	32	**28.8**	16	**29.6**	58	**26.4**
Endocrine sensitive	45	**81.8**	78	**70.3**	37	**68.5**	160	**72.7**
Prior CDK4/6i								
Palbociclib	52	**94.5**	102	**91.9**	46	**85.2**	200	**90.9**
Ribociclib	1	**1.8**	5	**4.5**	4	**7.4**	10	**4.5**
Abemaciclib	2	**3.6**	3	**2.7**	4	**7.4**	9	**4.1**
Duration of prior CDK4/6i + ET								
6-12 months	10	**18.2**	26	**23.4**	16	**29.6**	52	**23.6**
> 12 months	45	**81.8**	84	**75.7**	38	**70.4**	167	**75.9**
Prior chemotherapy for MBC	11	**20.0**	16	**14.4**	9	**16.7**	36	**16.4**
Line of MBC therapy initiated in PACE								
First Line	3	**5.5**	5	**4.5**	2	**3.7**	10	**4.5**
Second Line	42	**76.4**	83	**74.8**	44	**81.5**	169	**76.8**
> Second Line	10	**18.2**	21	**18.9**	7	**13.0**	38	**17.3**
Any systemic therapy between prior CDK4/6i and randomization	5	**9.1**	16	**14.4**	5	**9.3**	26	**11.8**

Unknown values are omitted from the table.

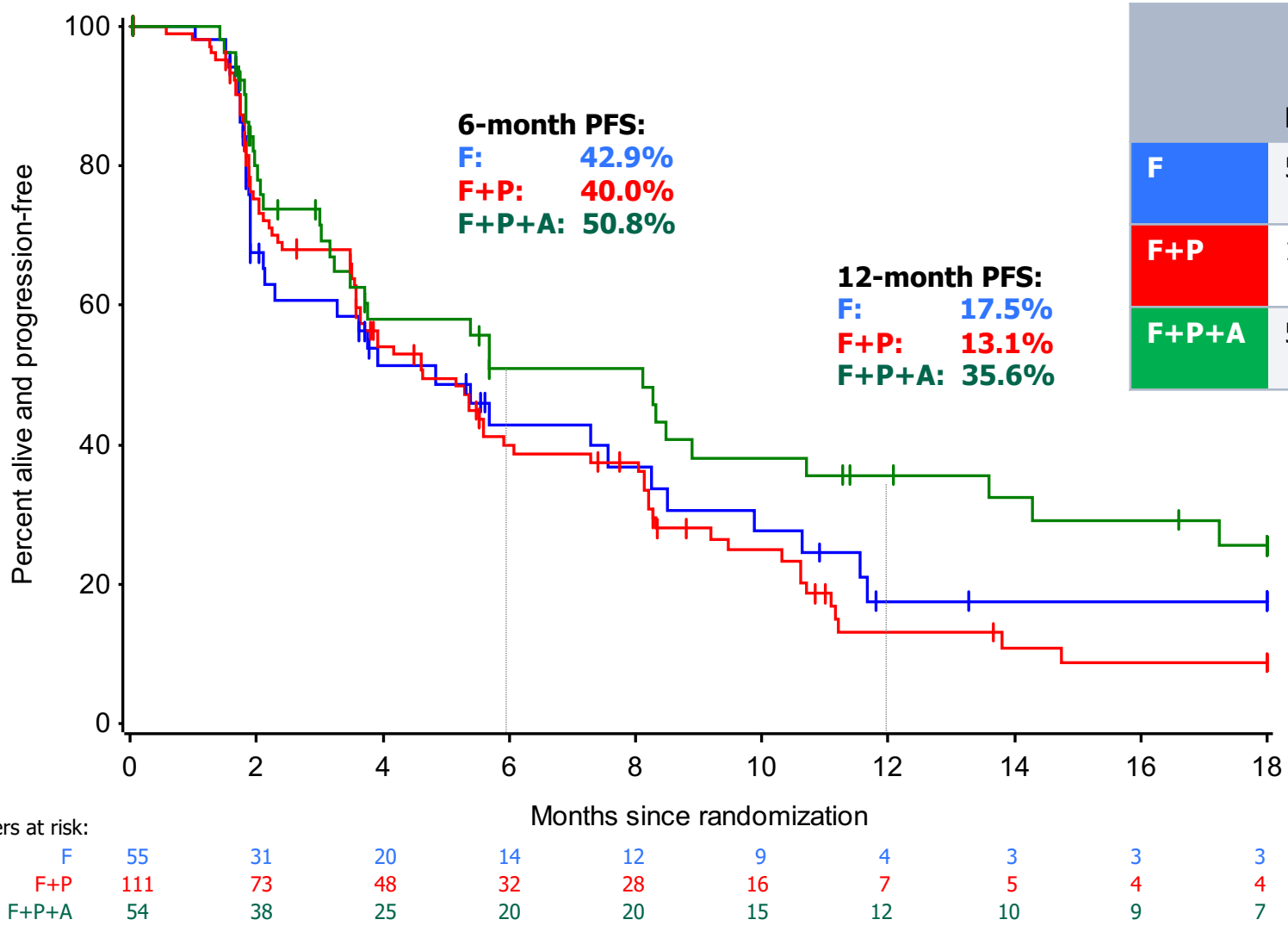
*Endocrine resistant: recur <1y of adj ET. Endocrine sensitive: *de novo* MBC, or no adj ET, or recur ≥1y after adj ET. Adapted from ESO-ESMO guidelines, Ann Oncol 2020

PACE: Progression Free Survival ITT



	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62

PACE: Progression Free Survival ITT



	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

BYLieve: A Phase 2, Open-Label, 3-Cohort, Noncomparative Trial

BYLieve
Alpelisib (BYL719) in patients with PIK3CA mutant, HR+, HER2- advanced breast cancer

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated HR+, HER2– ABC

Men or pre-/postmenopausal[a] women with HR+, HER2– ABC with a *PIK3CA* mutation

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

Patients who received CDKi + AI as immediate prior treatment (N=112)[b]
(Cohort A)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Patients who received CDKi + fulvestrant as immediate prior treatment (N=112)
(Cohort B)
Alpelisib 300 mg oral QD + letrozole 2.5 mg[d]

Patients who progressed on/after AI and received chemotherapy or ET as immediate prior treatment (N=112)
(Cohort C)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Treatment crossover between cohorts is not permitted

Primary endpoint

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort
- **Secondary endpoints include**

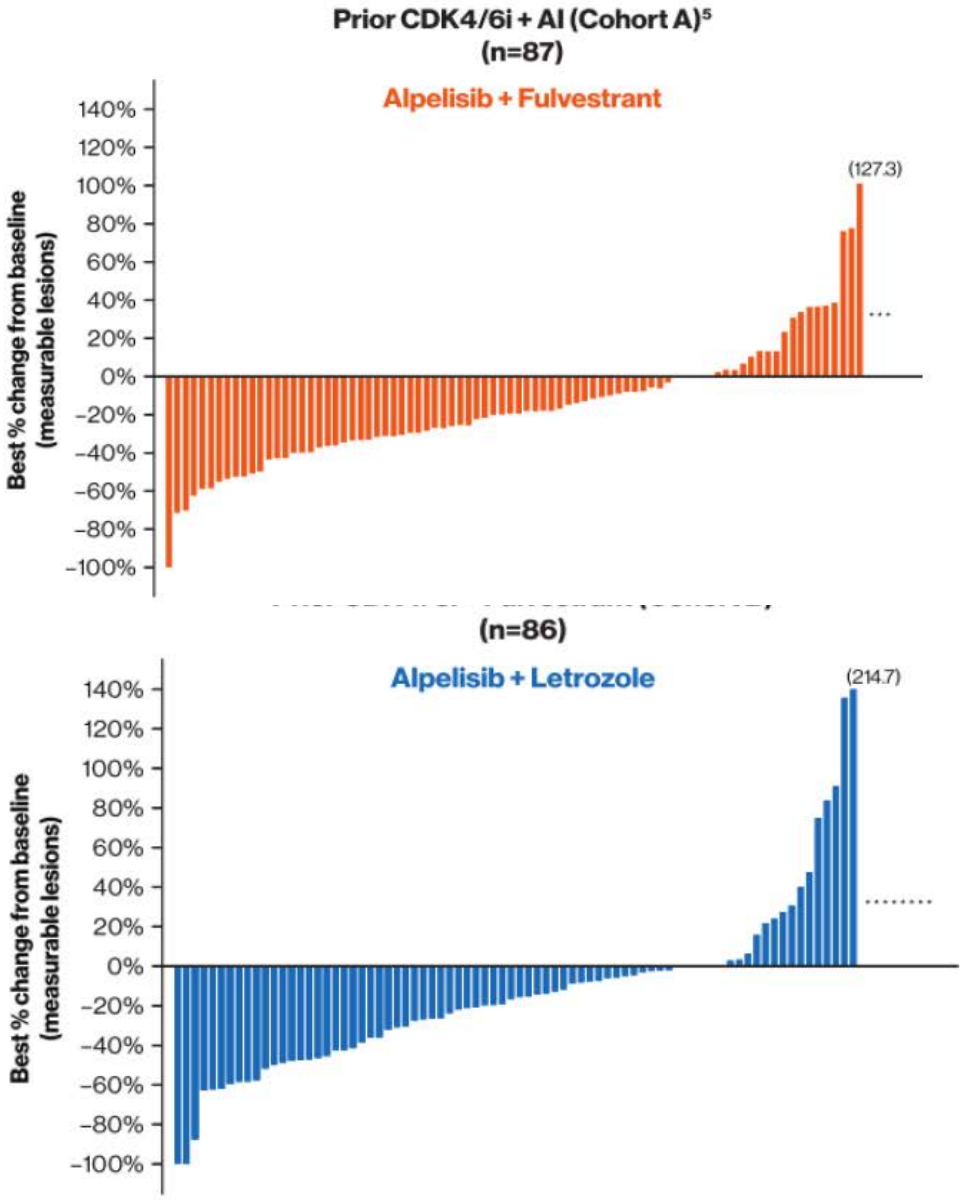
(assessed in each cohort)

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

- Rugo HS, et al. Lancet Oncol. 2021;22:489-498; Rugo HS, et al. ASCO 2020. Abstract 1006.

BYLieve Study of Alpelisib After CDK4/6i: Efficacy

Endpoint	BYLieve Trial[a,b]	
	Cohort A[a] Prior AI	Cohort B[b] Prior FULV
N	121	115
Alive, no PD @ 6 mo	50.4% met endpoint	46.1% met endpoint
Median PFS (mo)	7.3 mo	5.7 mo
ORR	21.0%	17.8%
CBR	42.0%	31.7%



a. Rugo HR, et al. ASCO 2020. Abstract 1040; b. Rugo HR, et al. SABCS 2020. Abstract PD2-07.

Summary of Selected Outcomes: BYLieve And SOLAR-1

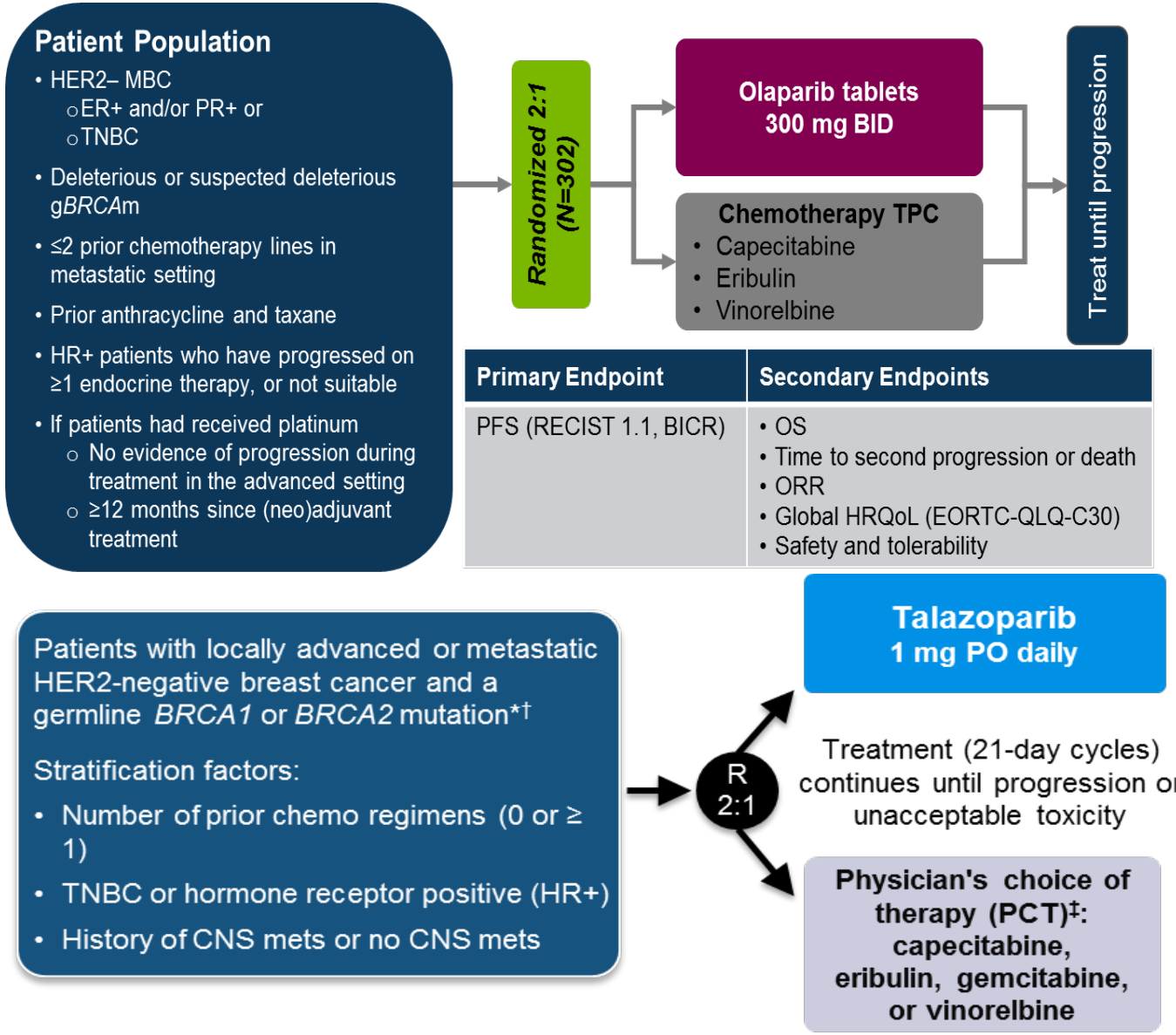
Endpoint	SOLAR-1 Trial Prior CDKi[a]		BYLieve Trial[b,c]	
	FULV + PBO	FULV + Alpelisib	Cohort A[b]	Cohort B[c]
N	11	9	121	115
Alive, no PD @ 6 mo	≈ 20%	44.4%	50.4%	46.1%
Median PFS (mo)	1.8 mo	5.5 mo	7.3 mo	5.7 mo
ORR	NR	NR	21.0%	17.8%
CBR	NR	NR	42.0%	31.7%

a. André F, et al. *N Engl J Med*. 2019;380:1929-1940; b. Rugo HR, et al. ASCO 2020. Abstract 1040; c. Rugo HR, et al. SABCS 2020. Abstract PD2-07.

PARP Inhibitors

- **OlympiAD**

- **EMBRACA**

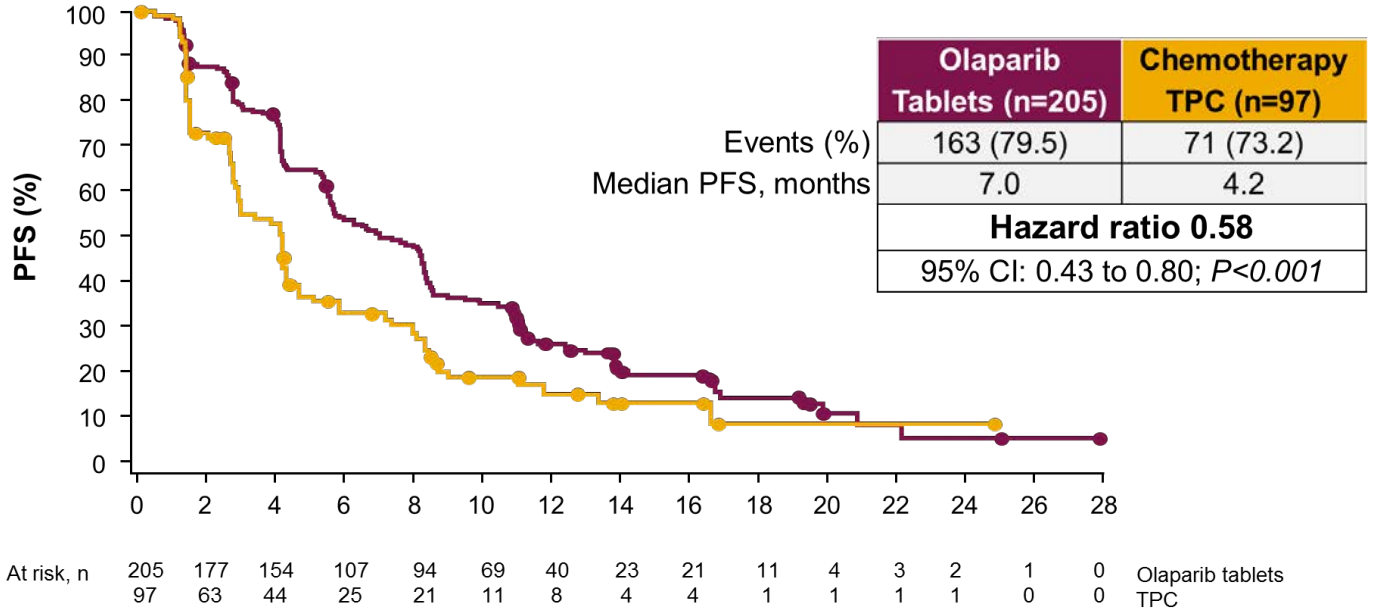


Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites

Litton JK, et al. N Engl J Med 2018;379:753-763. Robson M, et al. N Engl J Med 2017;377:523-533.

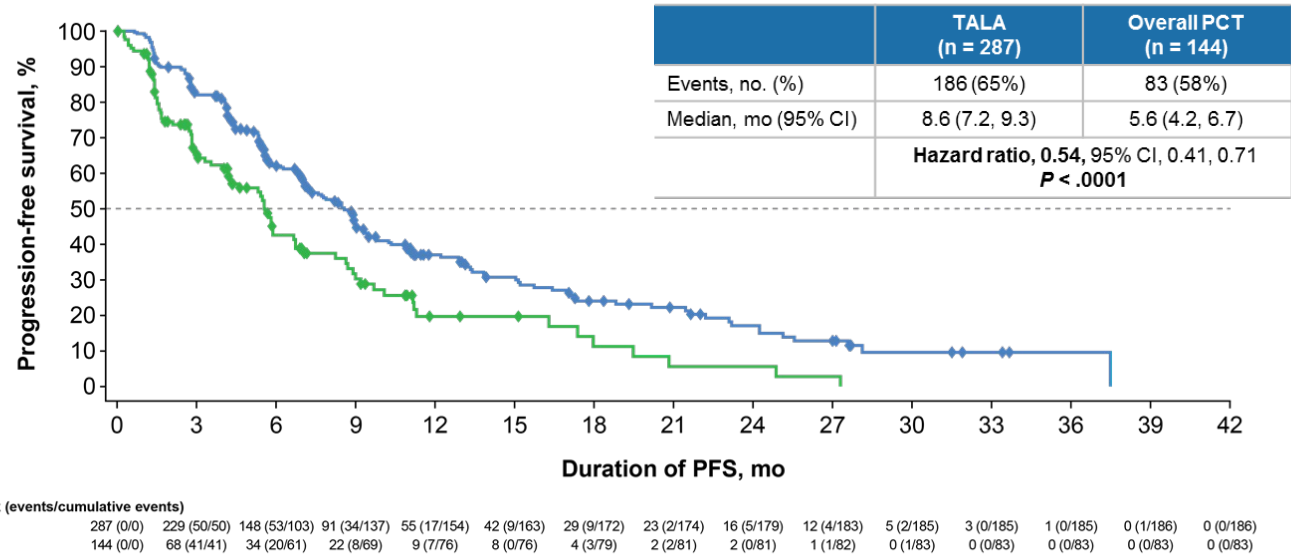
Progression-Free Survival

- **OlympiAD**



	Olaparib Tablets (n=205)	Chemotherapy TPC (n=97)
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
Hazard ratio 0.58		
95% CI: 0.43 to 0.80; *P<0.001*		

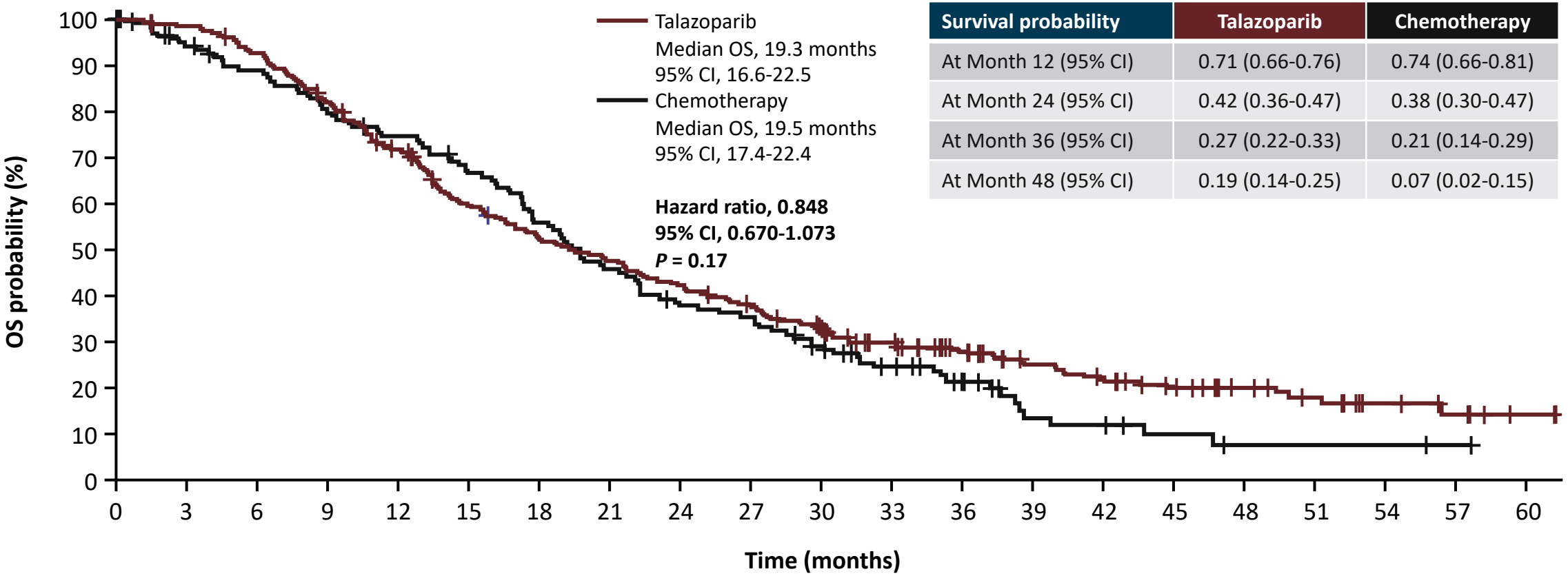
- **EMBRACA**



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

Litton JK, et al. N Engl J Med 2018;379:753-763. Robson M, et al. N Engl J Med 2017;377:523-533.

EMBRACA: Final OS



Survival probability	Talazoparib	Chemotherapy
At Month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
At Month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
At Month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
At Month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

Number of patients at risk

Talazoparib	287	280	264	232	199	163	143	128	113	101	85	68	54	41	35	27	20	15	9	6	2
Chemotherapy	144	125	116	105	96	86	71	58	48	44	34	25	18	8	7	4	2	2	2	1	0

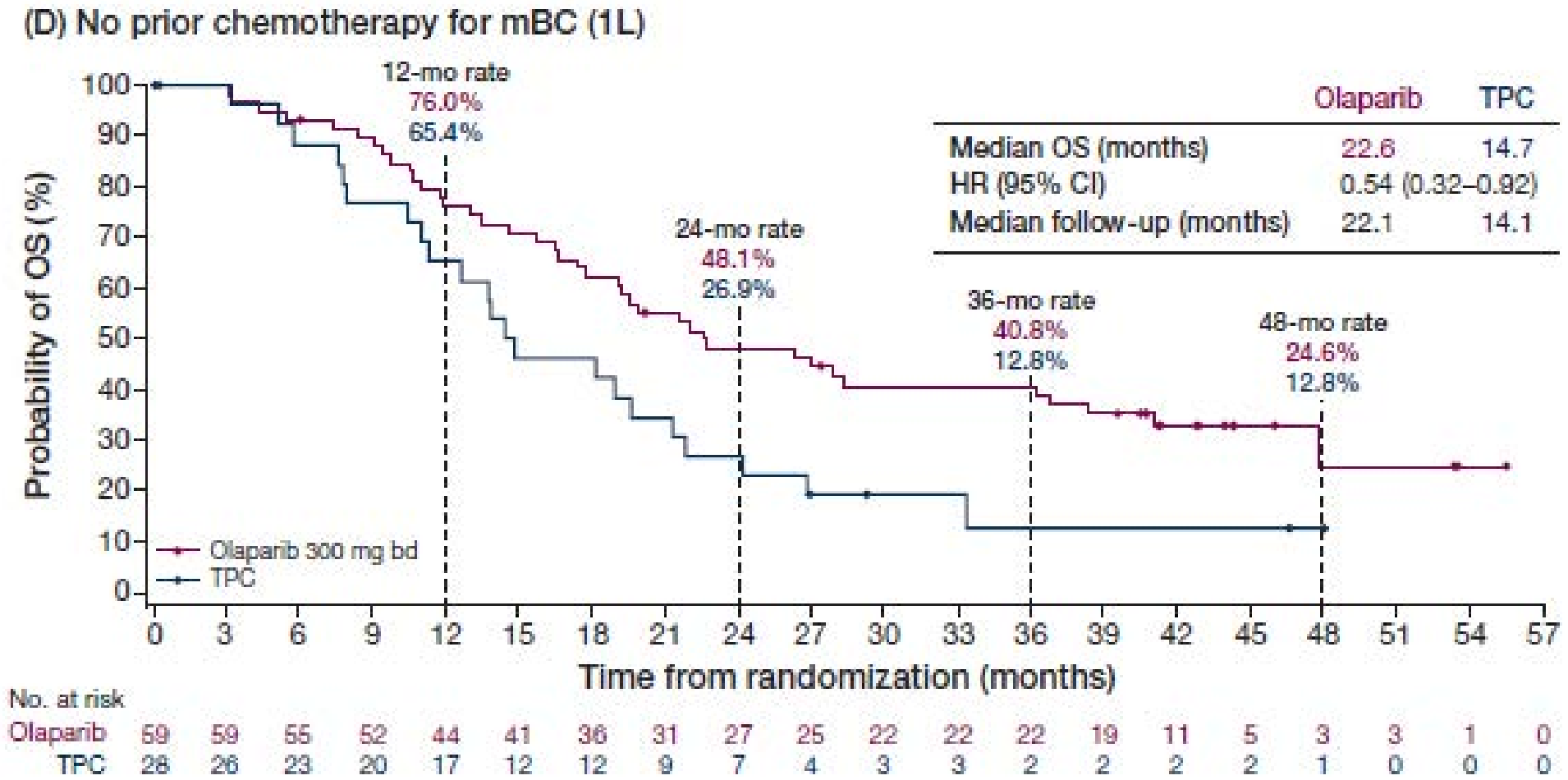
*ITT population

Litton JK, et al. AACR 2020. Abstract CT017.

OlympiAD: Extended OS Follow-Up

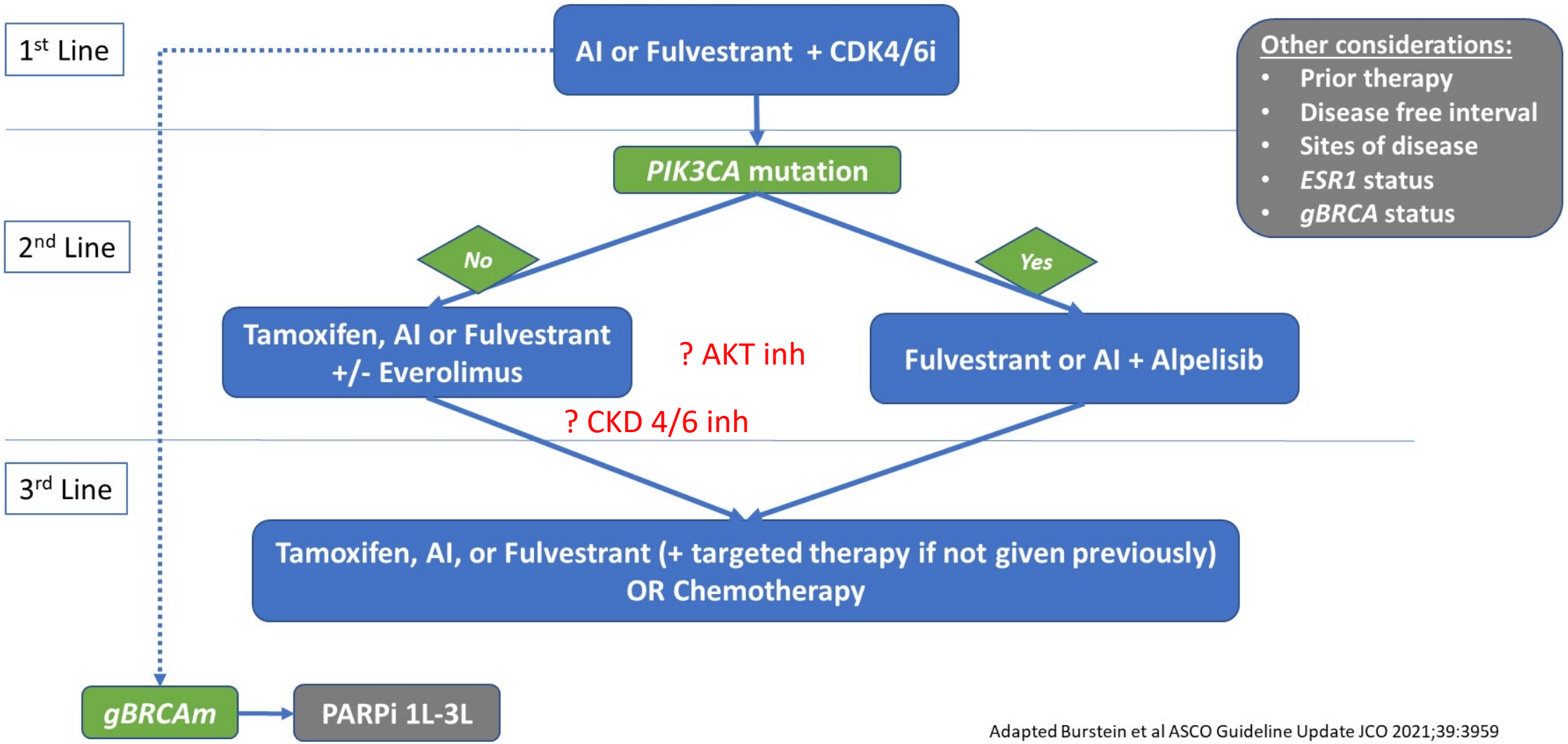
No statistically significant differences in survival curves in tissue receptor subtype

No new safety signal –No AML/MDS



Robson M, et al. SABCS 2019. PD4-03.

Current Approach: Treatment of HR+/HER2- mBC



Adapted Burstein et al ASCO Guideline Update JCO 2021;39:3959

Adopted from Claudine Isaacs

MODULE 4: Recent Appreciation of HER2 Low as a Unique Subset of HR-Positive Breast Cancer — Dr Bardia

RTP
RESEARCH
TO PRACTICE

Case Presentation: 39-year-old premenopausal woman with ER/PR-positive, HER2-low (IHC 1+) IDC, s/p adjuvant tamoxifen and OFS x 5 years, now with bone and liver metastases

Dr Laila Agrawal (Louisville, Kentucky)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 39-year-old premenopausal woman with ER/PR-positive, HER2-low (IHC 1+) IDC, s/p adjuvant tamoxifen and OFS x 5 years, now with bone and liver metastases (continued)

Dr Laila Agrawal (Louisville, Kentucky)

RTP RESEARCH TO PRACTICE

HER2 low Breast Cancer

Aditya Bardia, MD, MPH

Director, Breast Cancer Research,

Attending Physician, Mass General Hospital,

Associate Professor, Harvard Medical School

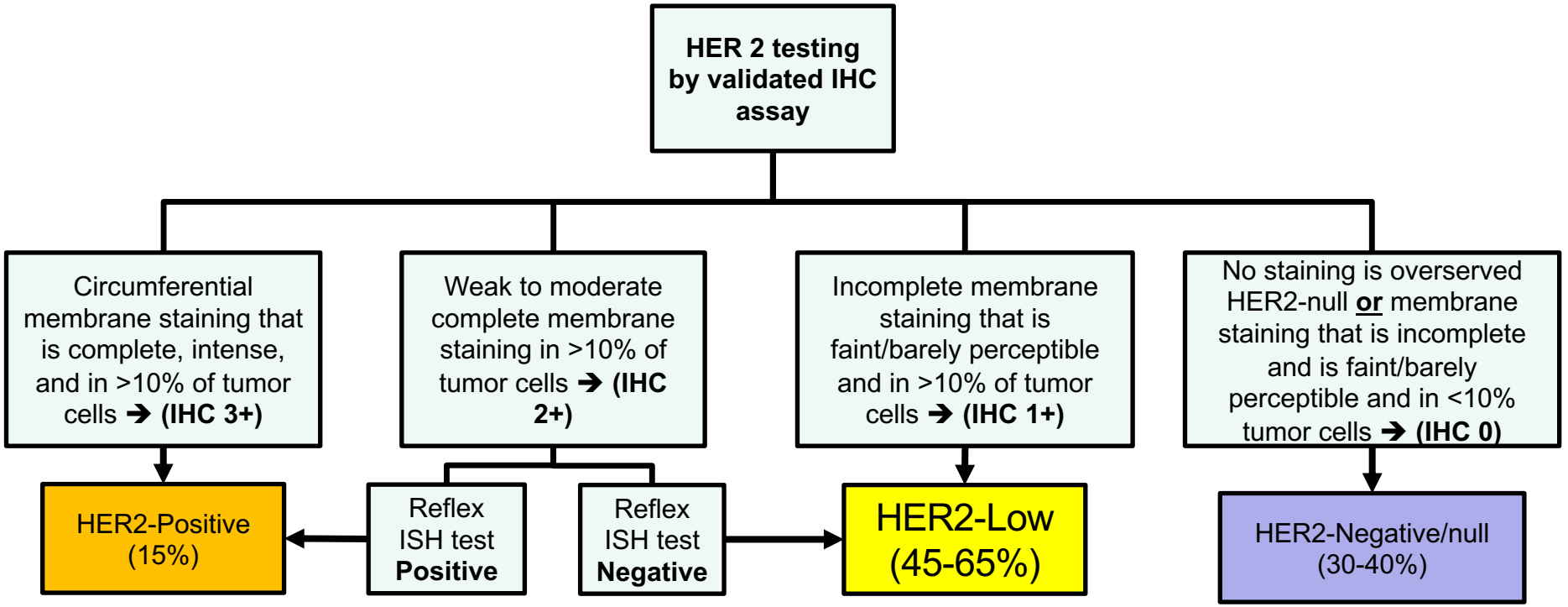
MASSACHUSETTS GENERAL HOSPITAL

CANCER CENTER

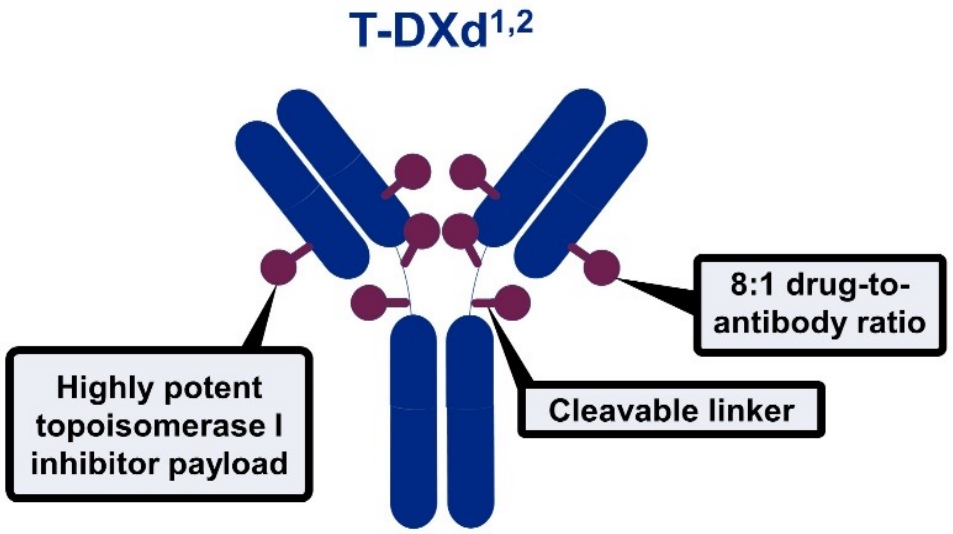
Objectives

- Understand rationale of ADCs for HER2 low breast cancer
- Gain knowledge related to HER2 ADC, trastuzumab deruxtecan, including efficacy and toxicity
- Review upcoming therapies for HER2 low breast cancer

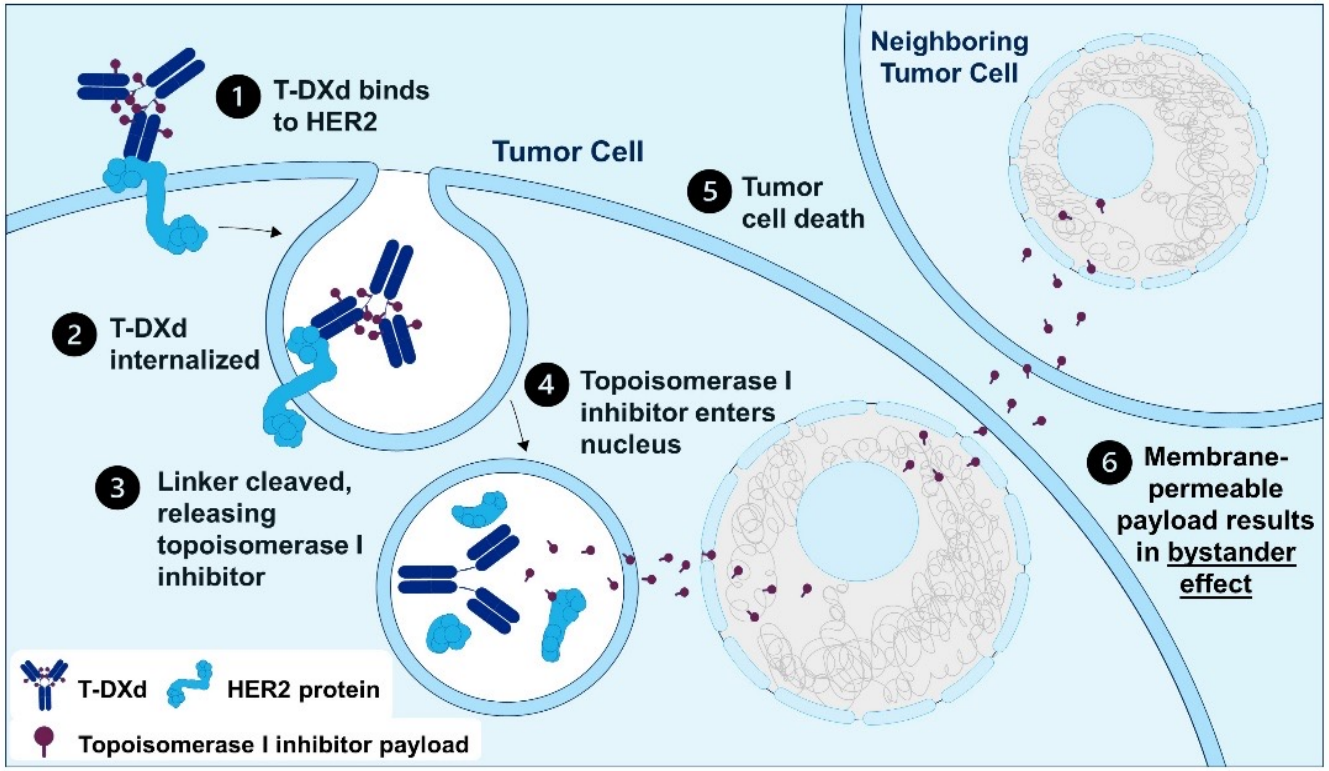
HER2-Low Breast Cancer: Current Definition



Trastuzumab Deruxtecan (T-DXd): Selective delivery of toxic payload



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]

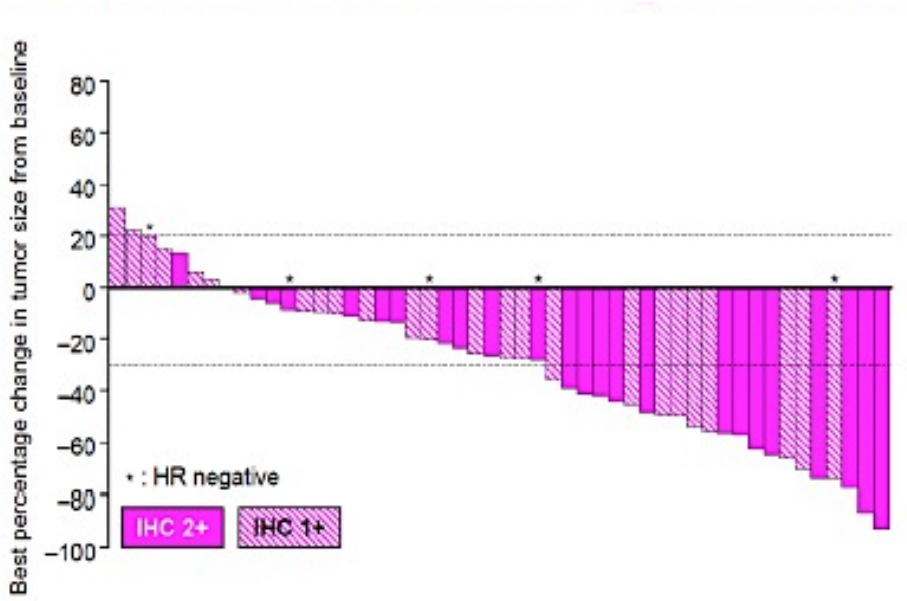


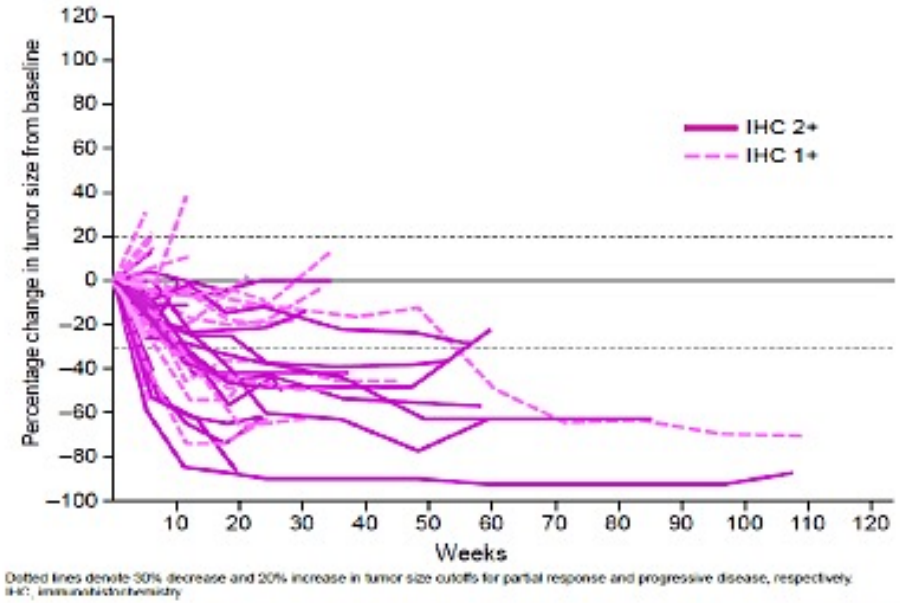
Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

Nagayama, A, et al. Target Oncol. 2017

Modi S, et al. ASCO 2022.

Trastuzumab Deruxtecan (T-DXd): HER2 Low Tumors





Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively.
IHC, immunohistochemistry.

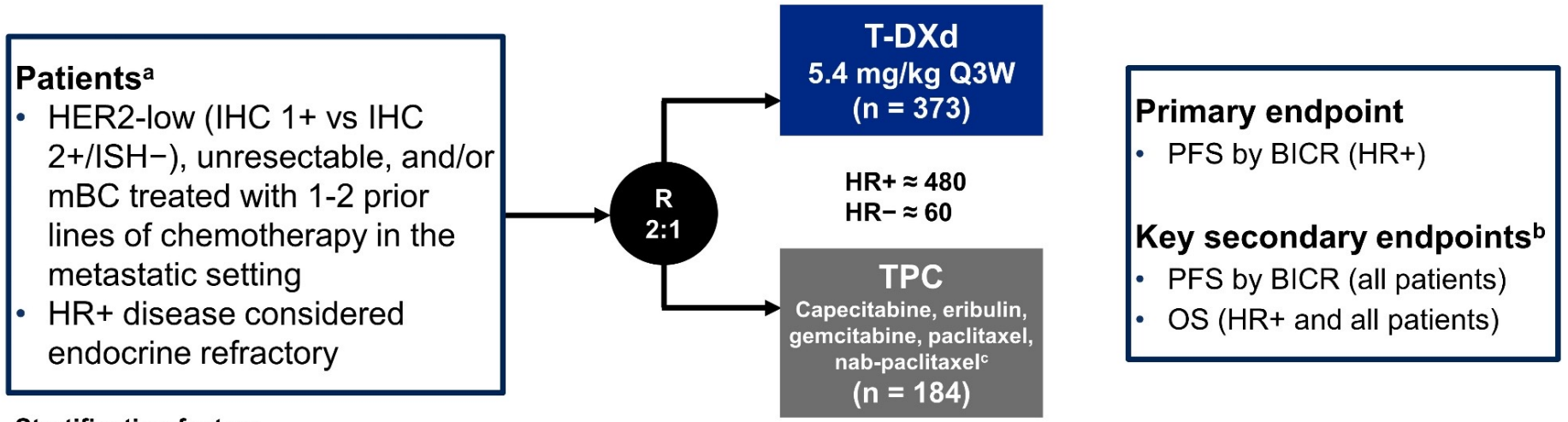
	Confirmed ORR	mDoR	mPFS
All (N = 51)	44.2% (N=43)	9.4m	7.6m
IHC 2+ (n = 24)	54.5% (N=22)	11.0m	13.6m
IHC 1+ (n = 27)	33.3% (N=21)	7.9m	5.7m
HR+ (n = 45)	47.4% (N=38)	11.0m	7.9m
Prior CDK4/6 inhibitor (n = 15)	33.3% (N=12)	NR	7.1m

Modi S et al. J Clin Oncol. 2020.

Trastuzumab Deruxtecan vs TPC: Study Design (DESTINY-B04)

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

An open-label, multicenter study (NCT03734029)



Stratification factors

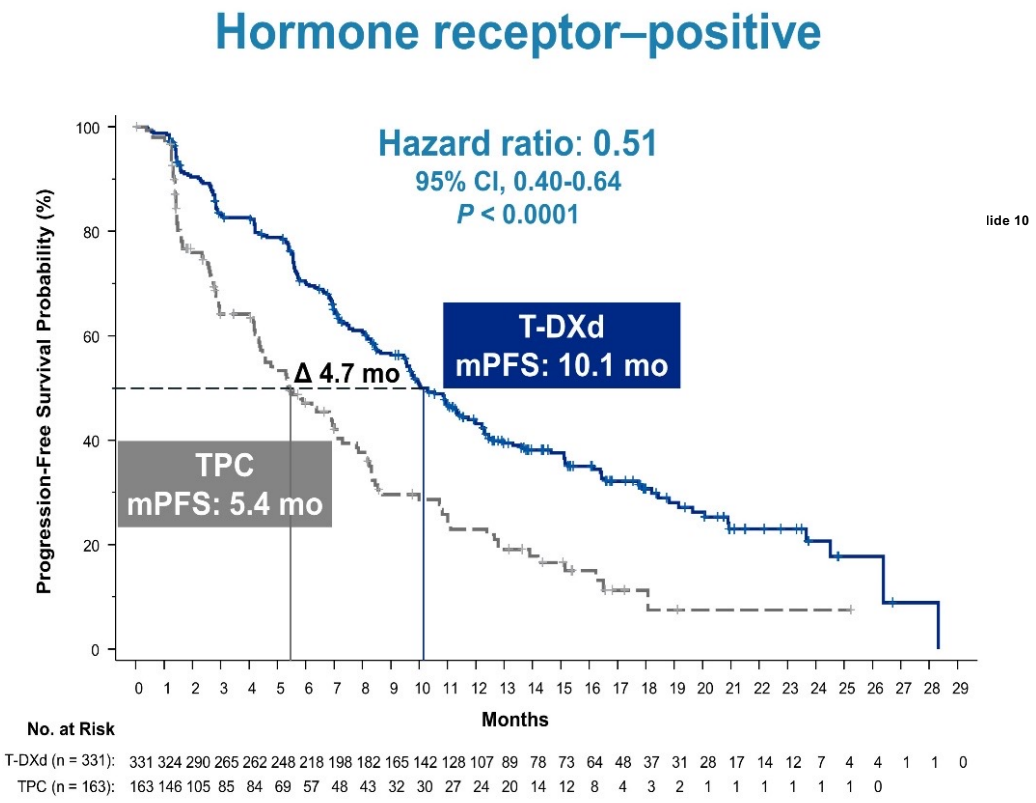
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

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

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

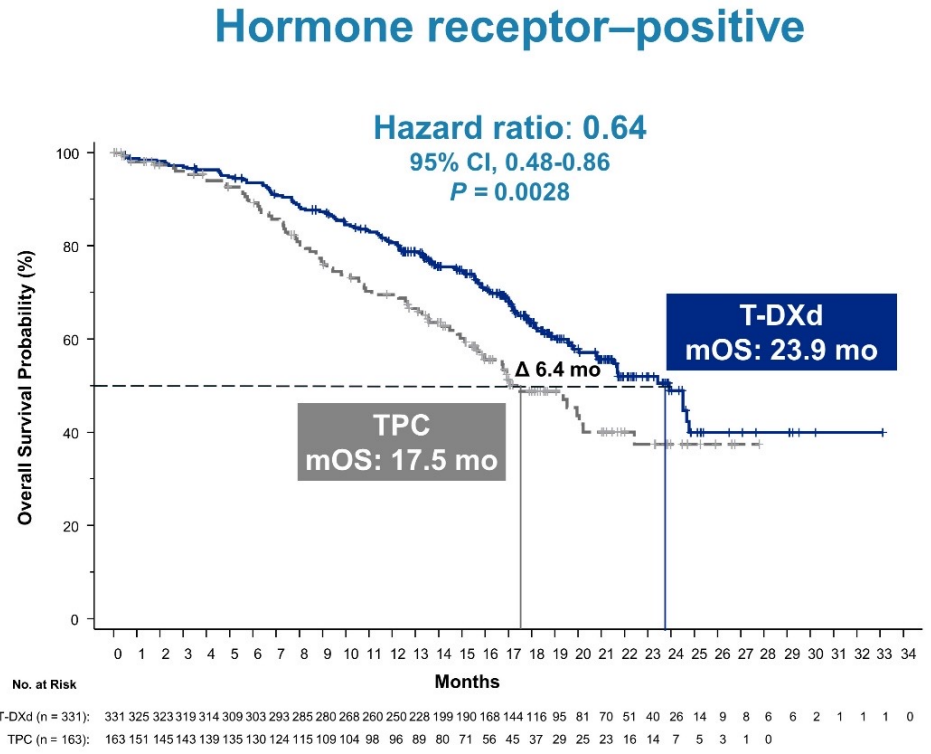
Trastuzumab Deruxtecan vs TPC: PFS (HR+/HER2 Low BC)

Progression-Free Survival



lide 10

Overall Survival

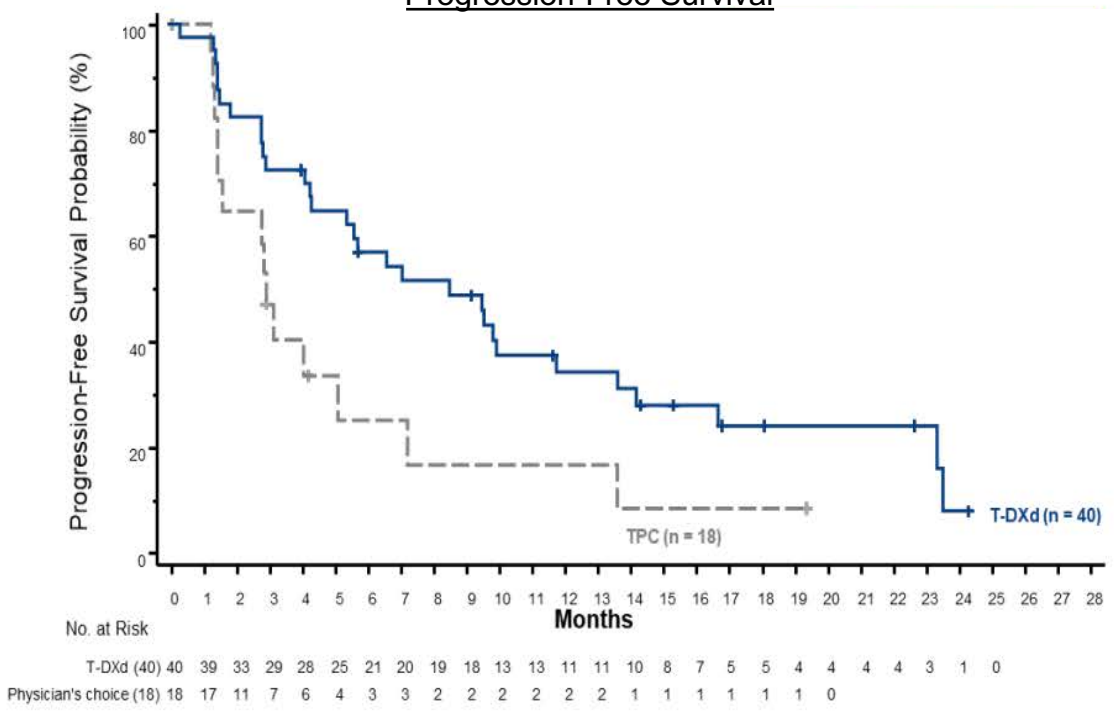


PFS by blinded independent central review.
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan;

Trastuzumab Deruxtecan: Efficacy in HER2-low mTNBC

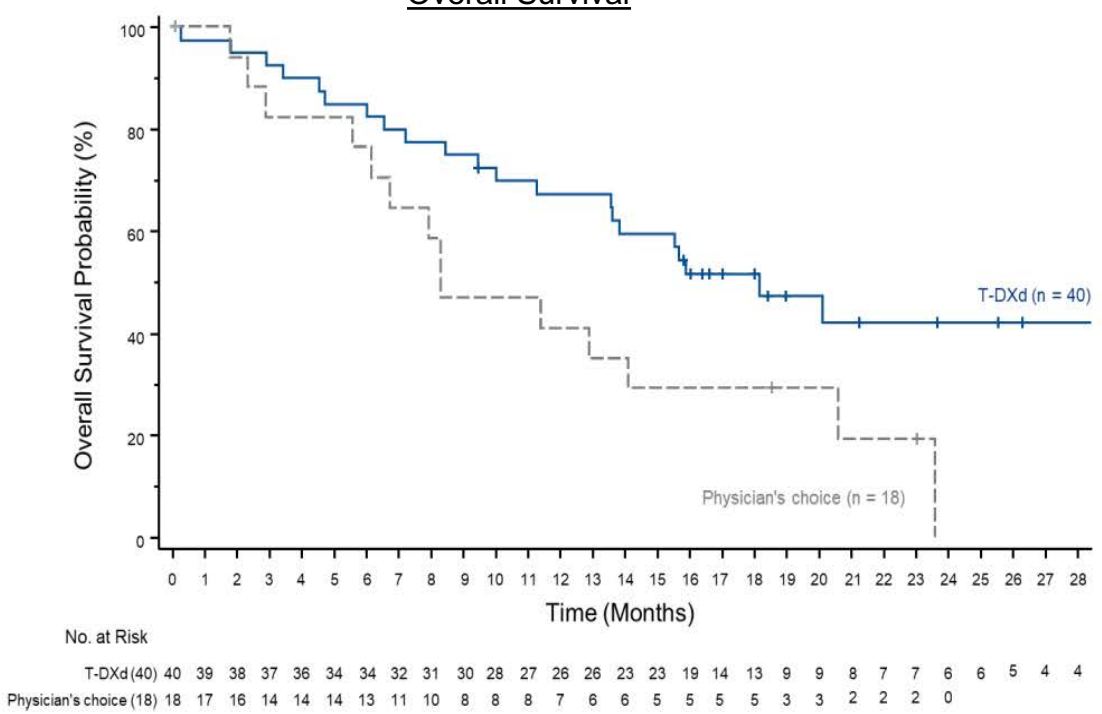
Exploratory Endpoint

Progression-Free Survival



	T-DXd (n=40)	TPC (n=18)
Median PFS (95% CI)	8.5 (4.3-11.7)	2.9 (1.4-5.1)
HR (95% CI), *P*-value	**0.46** (0.24-0.89)	

Overall Survival



	T-DXd (n=40)	TPC (n=18)
Median OS (95% CI)	18.2 (13.6-NE)	8.3 (5.6-20.6)
HR (95% CI), *P*-value	**0.48** (0.24-0.95)	

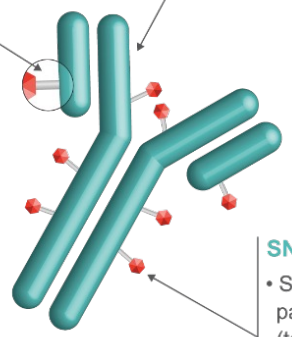
Modi S et al. *NEJM*. 2022.

What about activity of other ADCs for HER2 low MBC?

Trop2 ADC for HR+ MBC: Sacituzumab Govitecan

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

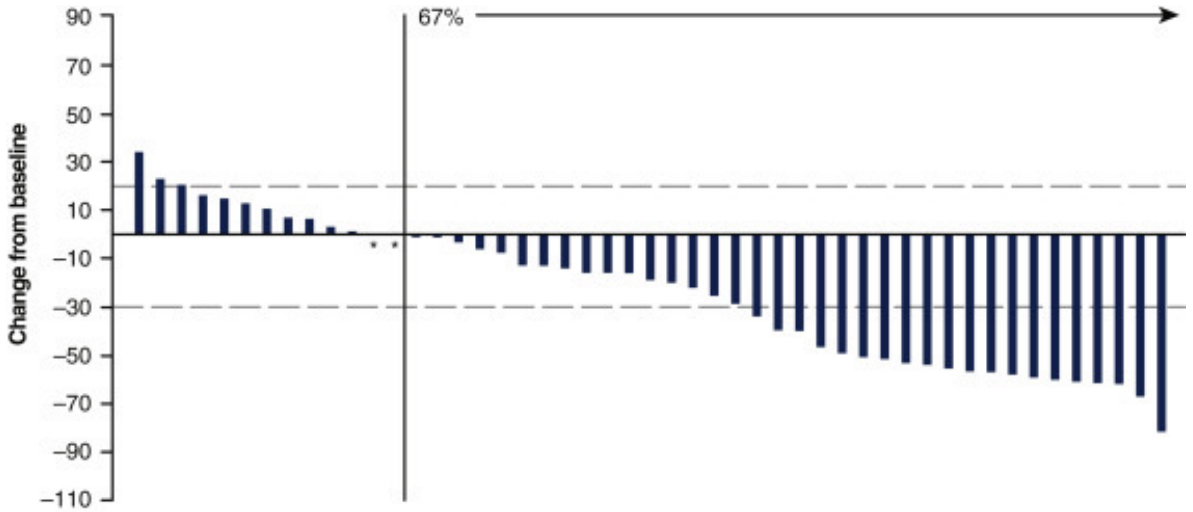
Linker for SN-38
- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)



SN-38 payload
- SN-38 more potent than parent compound, irinotecan (topoisomerase I inhibitor)
- SN-38 chosen for its moderate cytotoxicity (with IC50 in the nanomolar range), permitting delivery in high quantity to the tumor

Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody

Confirmed ORR = 31.5%



Phase I/II Basket Trial

≥3rd Line HR+/HER2- MBC N=54[a]

Other Advanced Epithelial Cancers

- Adults, ≥18 y
- Patients with metastatic epithelial cancers who progressed ≥1 standard therapeutic regimen for their disease
- ECOG performance status 0/1
- Measurable disease by CT/MRI

Sacituzumab govitecan 10 mg/kg IV

Days 1 and 8 every 21 days (restaging scans every 8 weeks)

Until progression or unacceptable toxicity

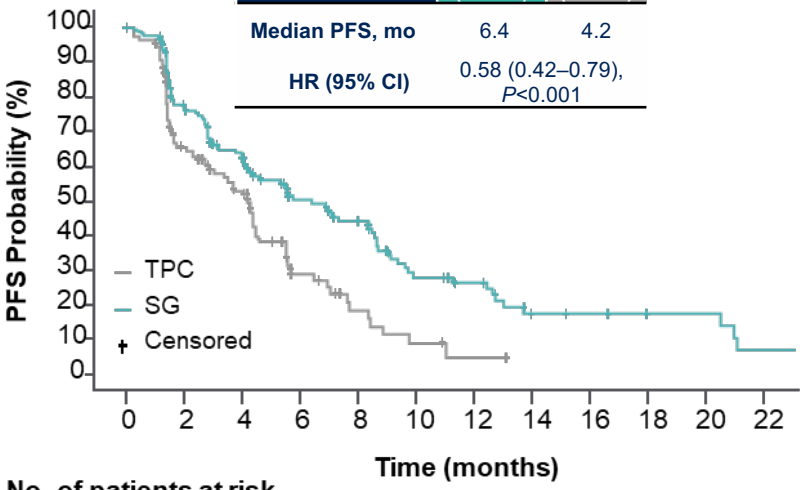
Endpoints:
- Response evaluation by investigators according to RECIST 1.1
- Duration of response
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety

Kalinsky K et al. Ann Oncol. 2020

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

HER2-Low[a]

	SG (n=149)	TPC (n=134)
Median PFS, mo	6.4	4.2
HR (95% CI)	0.58 (0.42–0.79), *P*<0.001	

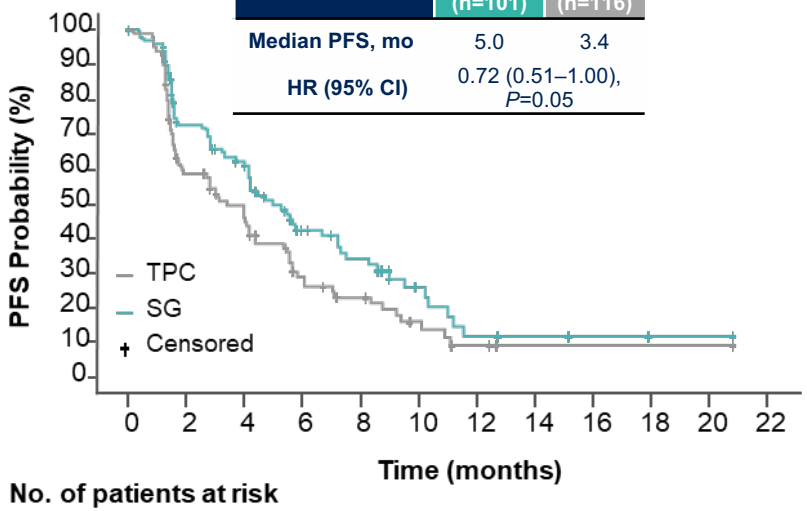


No. of patients at risk

TPC	134	65	43	16	8	4	1	0	0	0	0	0
SG	149	99	77	50	38	22	16	8	7	5	5	2

HER2 IHC0

	SG (n=101)	TPC (n=116)
Median PFS, mo	5.0	3.4
HR (95% CI)	0.72 (0.51–1.00), *P*=0.05	

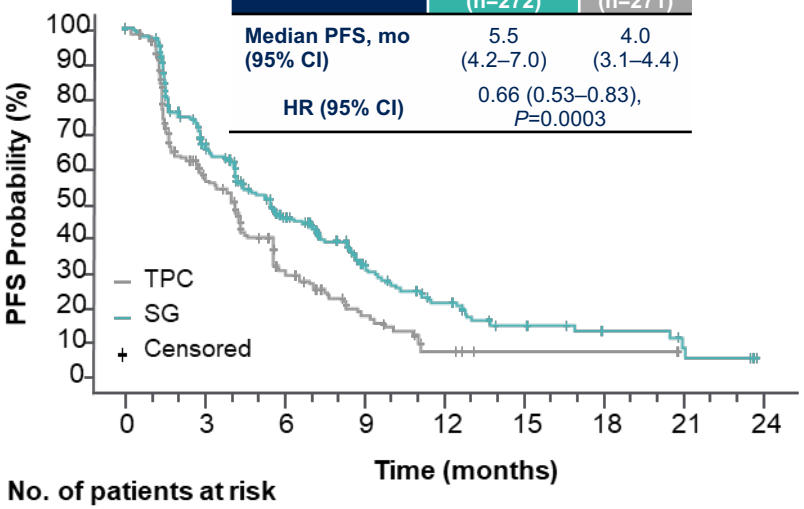


No. of patients at risk

TPC	116	53	39	20	14	7	3	1	1	1	1	0
SG	101	64	50	27	20	9	4	3	2	1	1	0

ITT[1]

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



No. of patients at risk

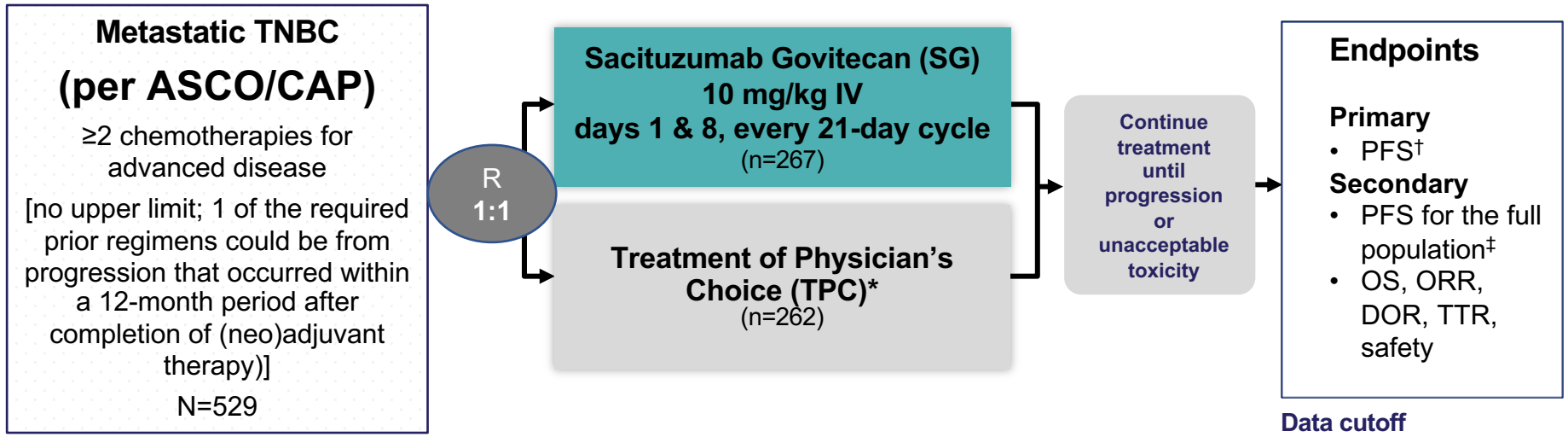
TPC	271	105	41	17	4	1	1	0	
SG	272	148	82	44	22	12	6	3	0

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

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

Presented by: Dr. Frederik Marmé

Phase III Study of Sacituzumab Govitecan vs TPC: ASCENT



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

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.

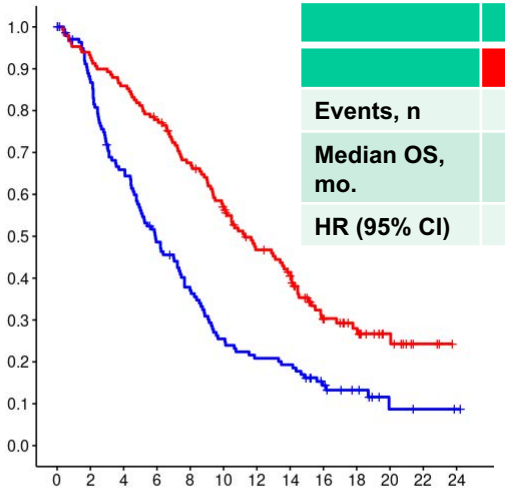
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Bardia A et al. *NEJM*. 2021

Sacituzumab Govitecan vs TPC: Efficacy in HER2 low mTNBC (ASCENT)

A

HER2 IHC0

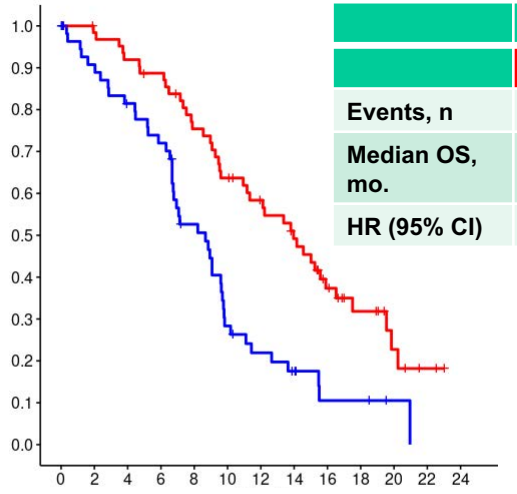


	HER2 IHC0	
	SG	TPC
Events, n	149	144
Median OS, mo.	11.3	5.9
HR (95% CI)	0.51 (0.39-0.66), *P*<0.001	

SG, HER2 IHC0	149	139	128	115	98	80	62	52	29	22	11	4	0
TPC, HER2 IHC0	144	118	88	64	48	33	27	25	15	9	3	2	1

B

HER-Low



	HER2-Low*	
	SG	TPC
Events, n	63	60
Median OS, mo.	14.0	8.7
HR (95% CI)	0.43 (0.28-0.67), *P*<0.001	

SG, HER2 IHC0	63	61	57	54	45	38	32	26	17	10	5	2	0
TPC, HER2 IHC0	60	49	43	38	26	14	10	7	3	3	1	0	0

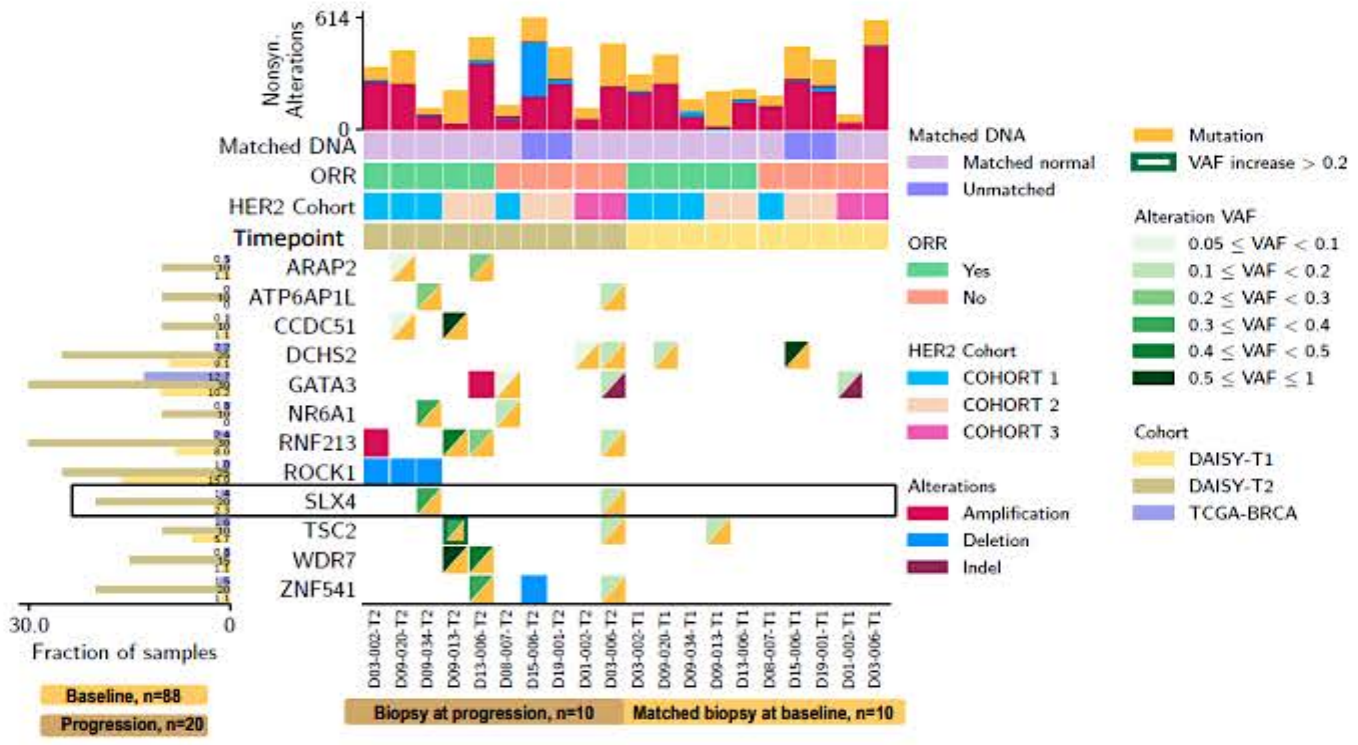
*HER2-Low defined as IHC1+ or ICH2+ and ISH-negative.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Hurvitz S et al. ESMO Breast. 2022

How to sequence the different ADCs?

Mechanism Governing Resistance: Trastuzumab Deruxtecan (DAISY)

- 20 frozen tumor biopsies at progression analyzed by WES
- 10 samples with matched biopsy at baseline

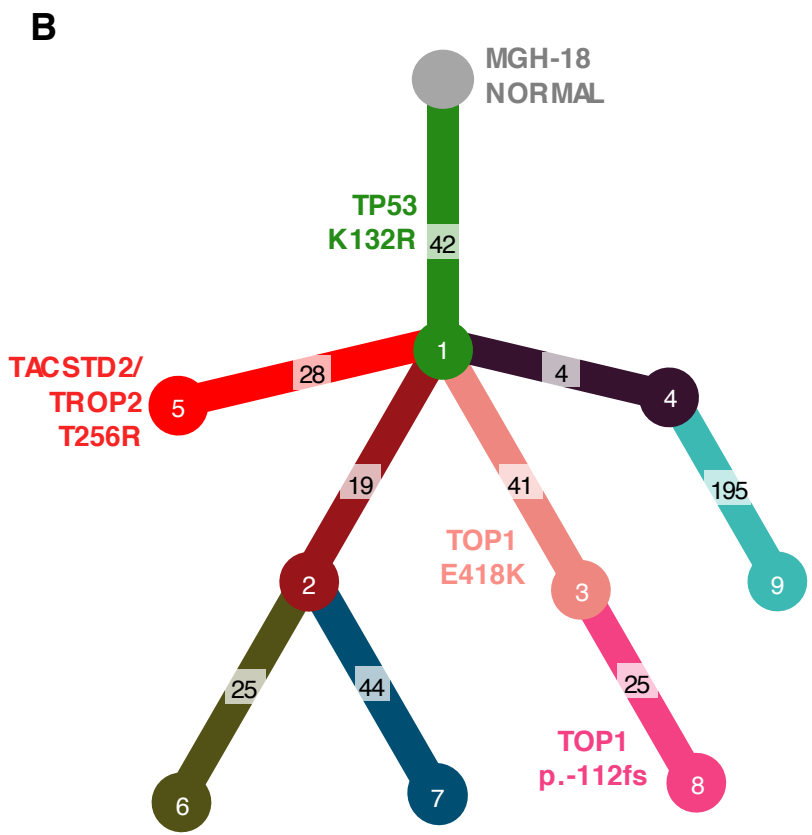


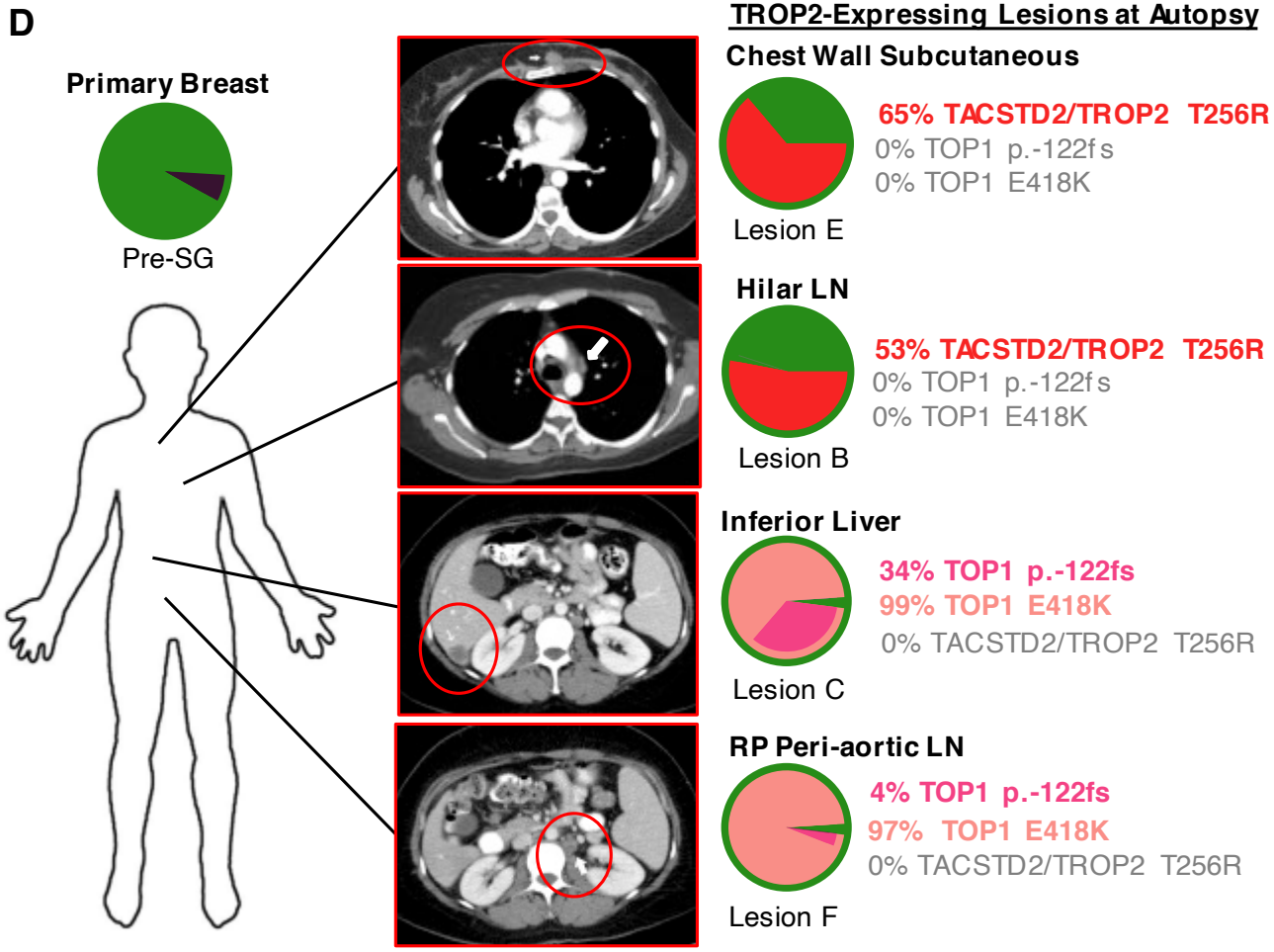
- *SLX4* encodes a DNA repair protein that regulates endonucleases, whose role in camptothecin resistance remains unclear
- 4/20 (20%) *SLX4* mutation biopsies at progression
- 2 *SLX4* mutations were not detectable in baseline samples
- 2 *SLX4* mutations there was no matched baseline sample

PARIS 2022 ESMO congress

M. F. Mosele, MD

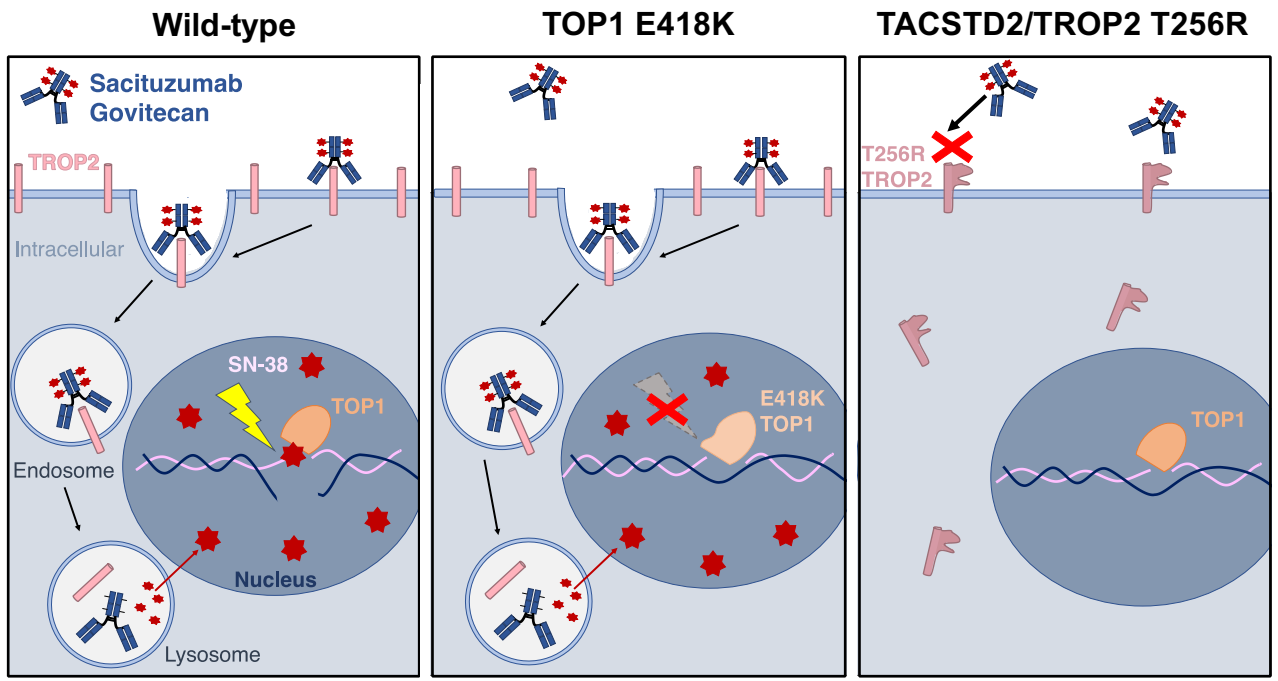
Mechanism Governing Resistance: Antibody vs Payload

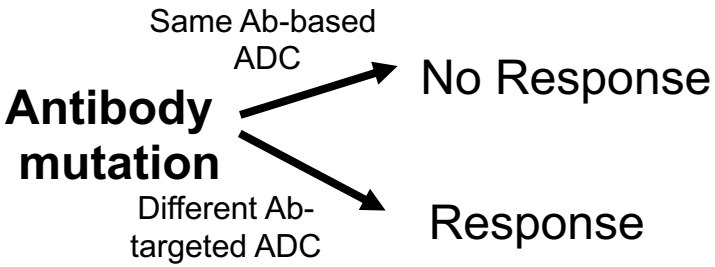


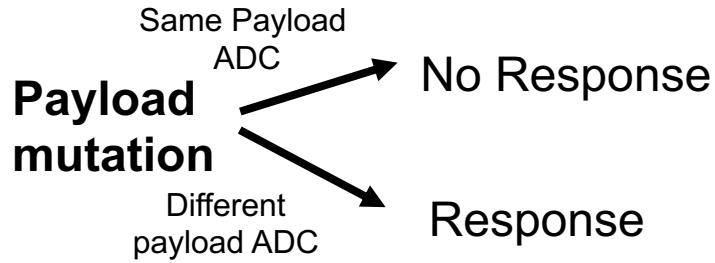


Coates, Sun et al Cancer Discovery 2021.

Implications of resistance mechanisms for ADC sequencing







Coates, Sun et al Cancer Discovery 2021.

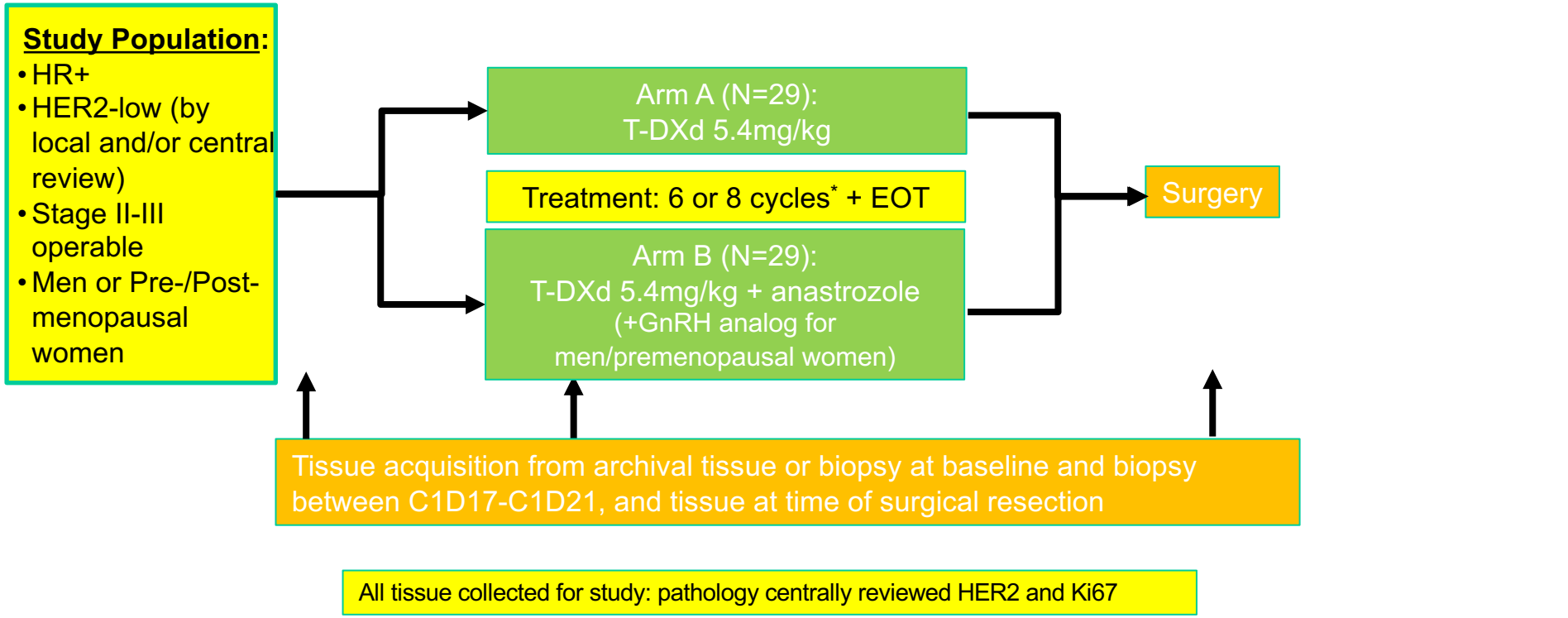
ADCs to target MBC: Multiple Agents in Development

Antibody Drug Conjugate	Target	Payload
Trastuzumab deruxtecan (DS-8201a)	HER2	Topo-1 inhibitor
Sacituzumab govitecan (IMMU-132)	Trop-2	Topo-1 inhibitor
Datopotamab deruxtecan (DS-1062)	Trop-2	Topo-1 inhibitor
Ladiratuzumab vedotin (SGN-LIV1a)	LIV-1	Microtubule inhibitor
Patritumab deruxtecan (U3-1402)	HER3	Topo-1 inhibitor
Trastuzumab duocarmazine	HER2	Alkylating agent
Disitamab vedotin	HER2	Microtubule inhibitor

Both target and payload important considerations for efficacy/toxicity profile and ADC sequencing

How about Early Breast Cancer?

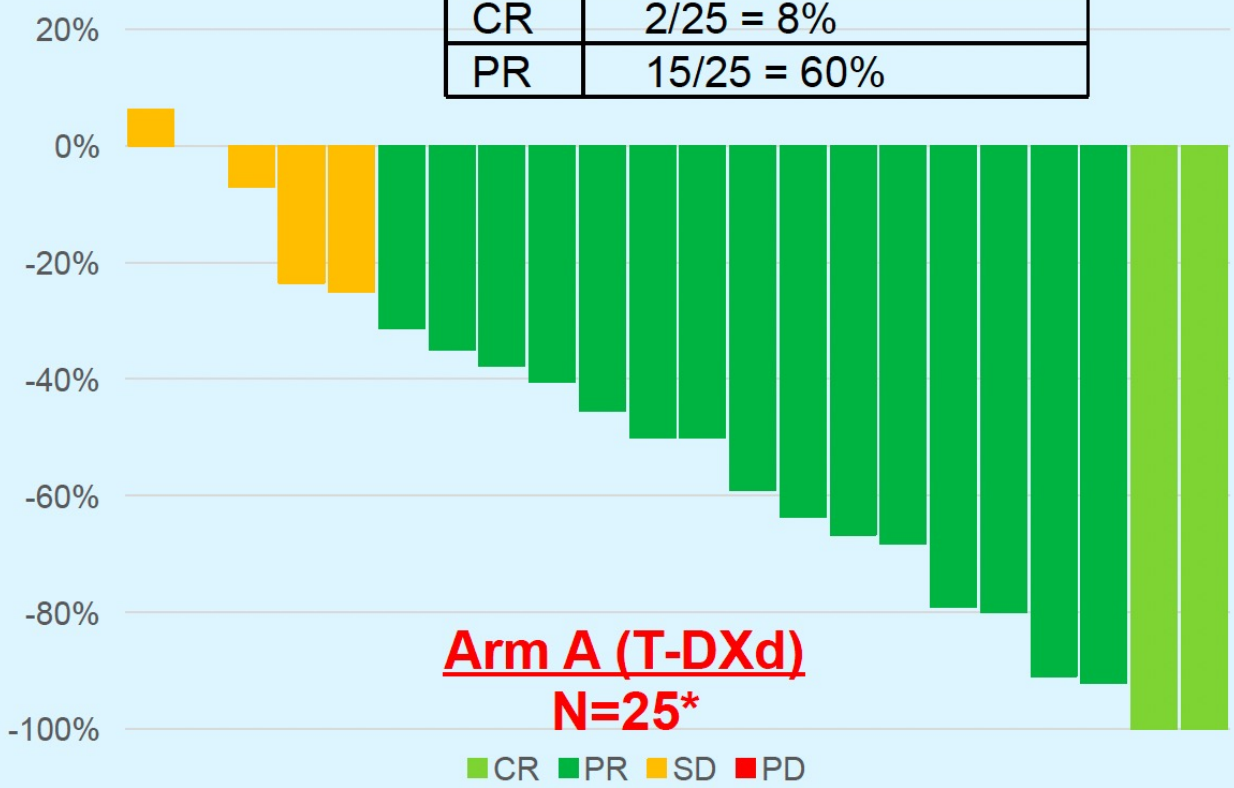
TRIO-US B-12 (TALENT): Study Design



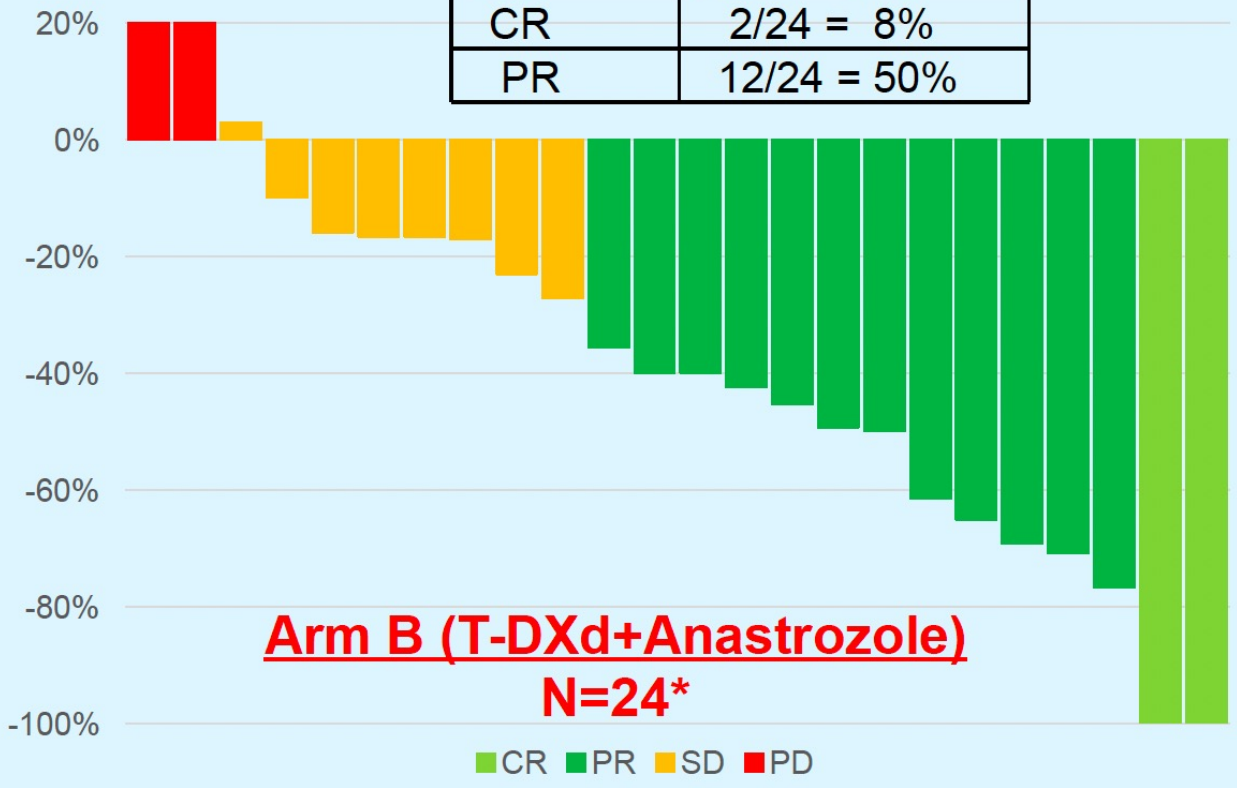
* Originally, 6 cycles of treatment were given but in 02/2022, an amendment increased the number of treatment cycles from 6 to 8 for newly enrolled participants, or those who had not yet had surgery. EOT 21-28 days after last dose of T-DXd.

Objective Response Rate with T-DXd (based on imaging)

Arm A	
ORR	17/25 = 68%
CR	2/25 = 8%
PR	15/25 = 60%



Arm B	
ORR	14/24 = 58%
CR	2/24 = 8%
PR	12/24 = 50%

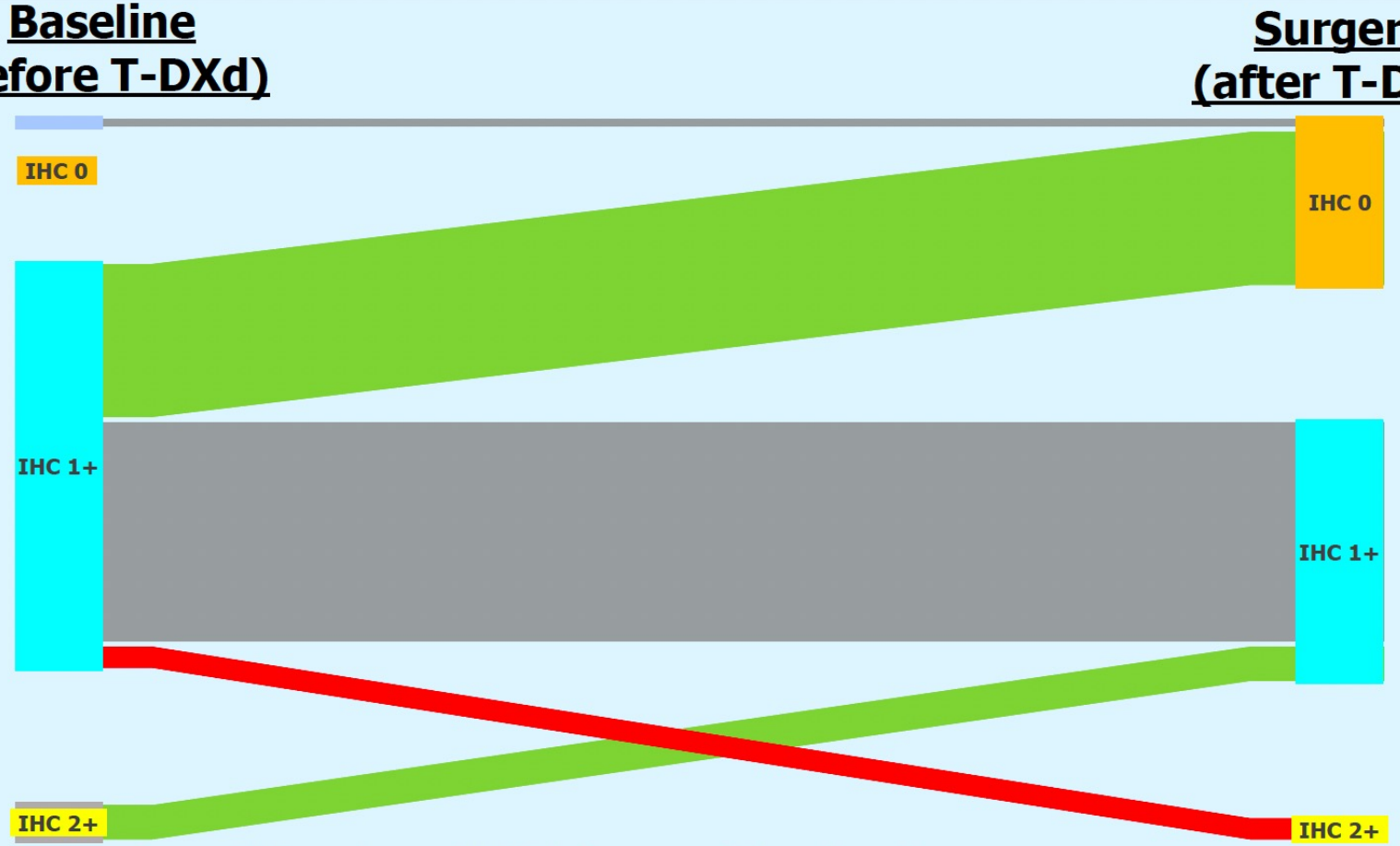


Waterfall plot with bars representing change in tumor size after treatment with T-DXd, compared to baseline, as per RECIST v1.1. Intention to treat population for ORR includes all who received at least 1 cycle of protocol therapy, data cutoff 11/25/2022.

- 4 patients still on treatment; 3 patients did have imaging (treatment discontinued prematurely), but included in intention to treat (ITT) denominator for ORR analysis per protocol

* 5 patients still on treatment

HER2 IHC Change from Baseline to Surgery with T-DXd (central review)



49% (17/35) had change in HER2 IHC after T-DXd treatment

Of those who had change, majority (88%) had decrease in HER2 IHC expression

Green: IHC staining of HER2 decreased from baseline to surgery
Gray: IHC staining of HER2 remained stable from baseline to surgery
Red: IHC staining of HER2 increased from baseline to surgery

Note: The observed change in IHC immunostaining may not accurately reflect changes in HER2 protein expression in carcinoma cells

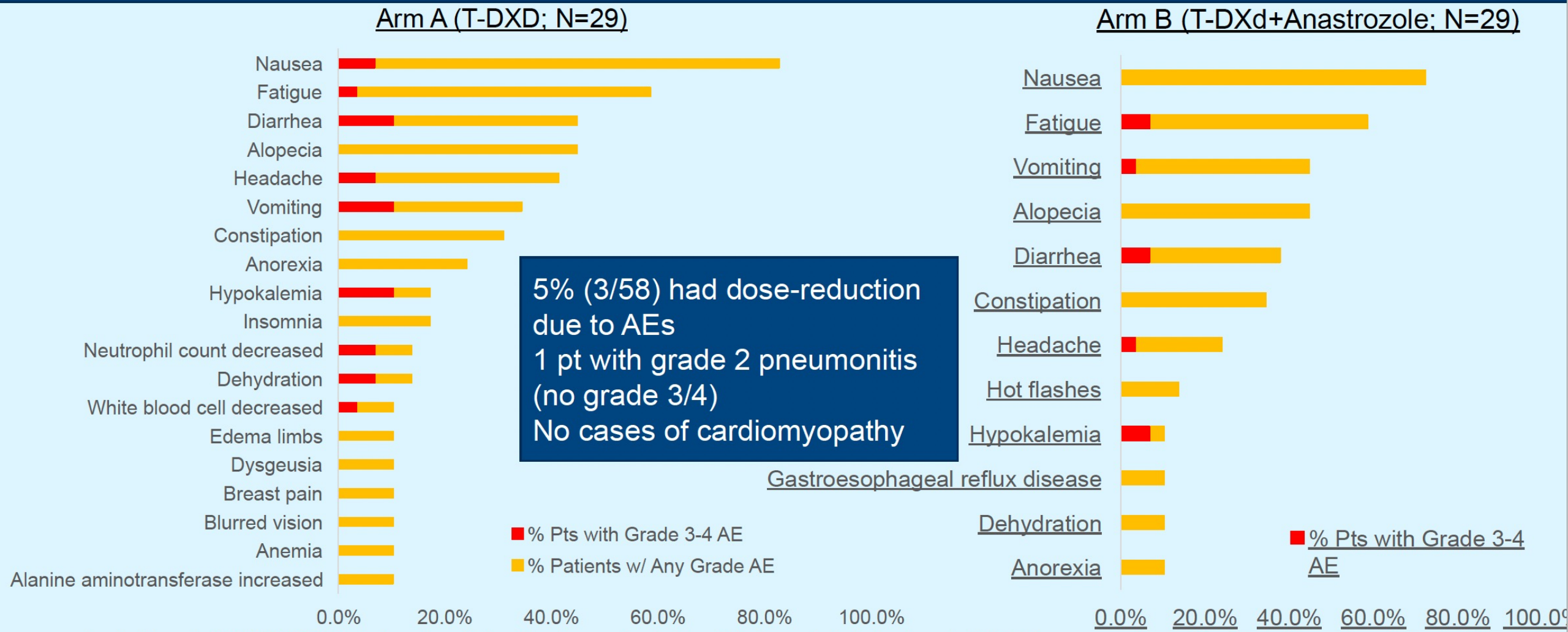
Residual Cancer Burden after T-DXd (by arm, cycles and stage)

Cycles	Stage at Baseline	Arm A (T-DXd) N=22*				Arm B (T-DXd+Anastrozole) N=20**			
		RCB-0	RCB-I	RCB-II	RCB-III	RCB-0	RCB-I	RCB-II	RCB-III
6 Cycles	Stage IIA	0	1 (5%)	2 (9%)	0	0	1 (5%)	6 (30%)	0
	Stage IIB	0	1 (5%)	4 (18%)	2 (9%)	0	0	3 (15%)	1 (5%)
	Stage IIIA	0	0	1 (5%)	2 (9%)	0	0	1 (5%)	1 (5%)
	Stage IIIB	0	0	1 (5%)	0	0	0	0	0
8 Cycles	Stage IIA	0	0	2 (9%)	0	0	1 (5%)	1 (5%)	0
	Stage IIB	0	0	1 (5%)	1 (5%)	0	0	2 (10%)	0
	Stage IIIA	1 (5%)	0	0	0	0	1 (5%)	0	0
	Stage IIIB	0	0	0	0	0	0	0	0

As of data cutoff 11/25/2022: surgical outcomes pending for 24% (7/29) patients being treated in Arm A and 31% (9/29) in Arm B.

- *4 pts discontinued early Arm A **3 pts discontinued early (included in denominator for intention to treat analysis) Arm B
- RCBi = Residual cancer burden index; RCB 0 = pCR; Histology or IHC Status did not appear to be associated with RCB response

Adverse Effects (T-DXd Related, ≥ 10%)



As of data cutoff 11/25/2022, includes all participants who received at least 1 dose of study treatment; AEs in 3 or more patients. 3 patients discontinued due to AEs.

1 death due to myocardial infarction after severe GI toxicity, possibly related.

Summary

- Trastuzumab deruxtecan has demonstrated impressive activity in HER2 low metastatic breast cancer, both HR+ and HR-, and approved in 2nd line (and plus) MBC setting.
- Sacituzumab govitecan approved for mTNBC, regardless of HER2 expression (not surprising). Activity also seen in HR+ metastatic breast cancer.
- There are multiple ADCs in development to target antigens overexpressed in MBC.
- Understanding mechanism of resistance, antibody vs payload, could help guide therapeutic sequencing of ADCs.
- Additional studies evaluating different ADCs targeting different antigens could redefine the current receptor-based classification of breast cancer.

MODULE 5: Novel Strategies Under Investigation for Patients with HR-Positive mBC — Dr Rugo

RTP
RESEARCH
TO PRACTICE

Case Presentation: 90-year-old woman with ER/PR-positive, HER2-low (IHC 1+) mBC and PD on multiple lines of endocrine and chemotherapy receives T-DXd

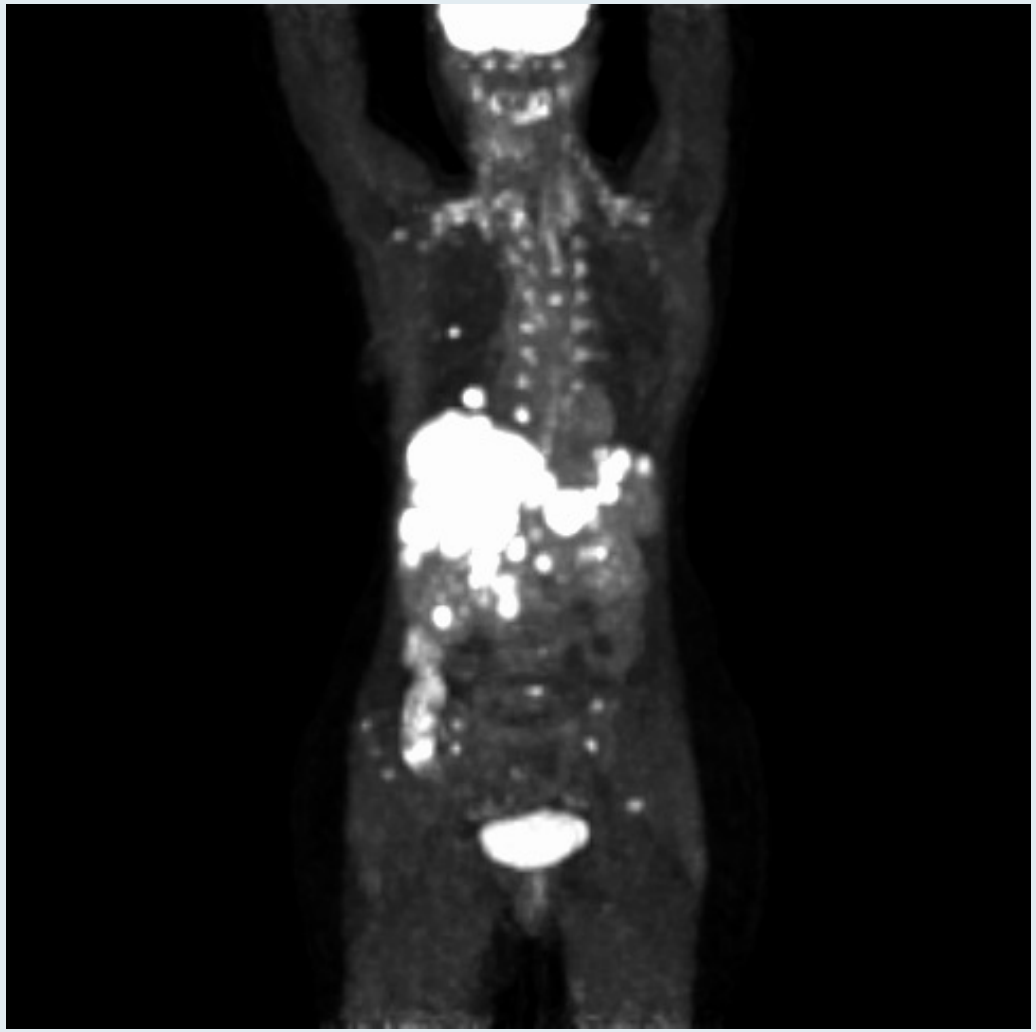
Dr Alan Astrow (Brooklyn, New York)

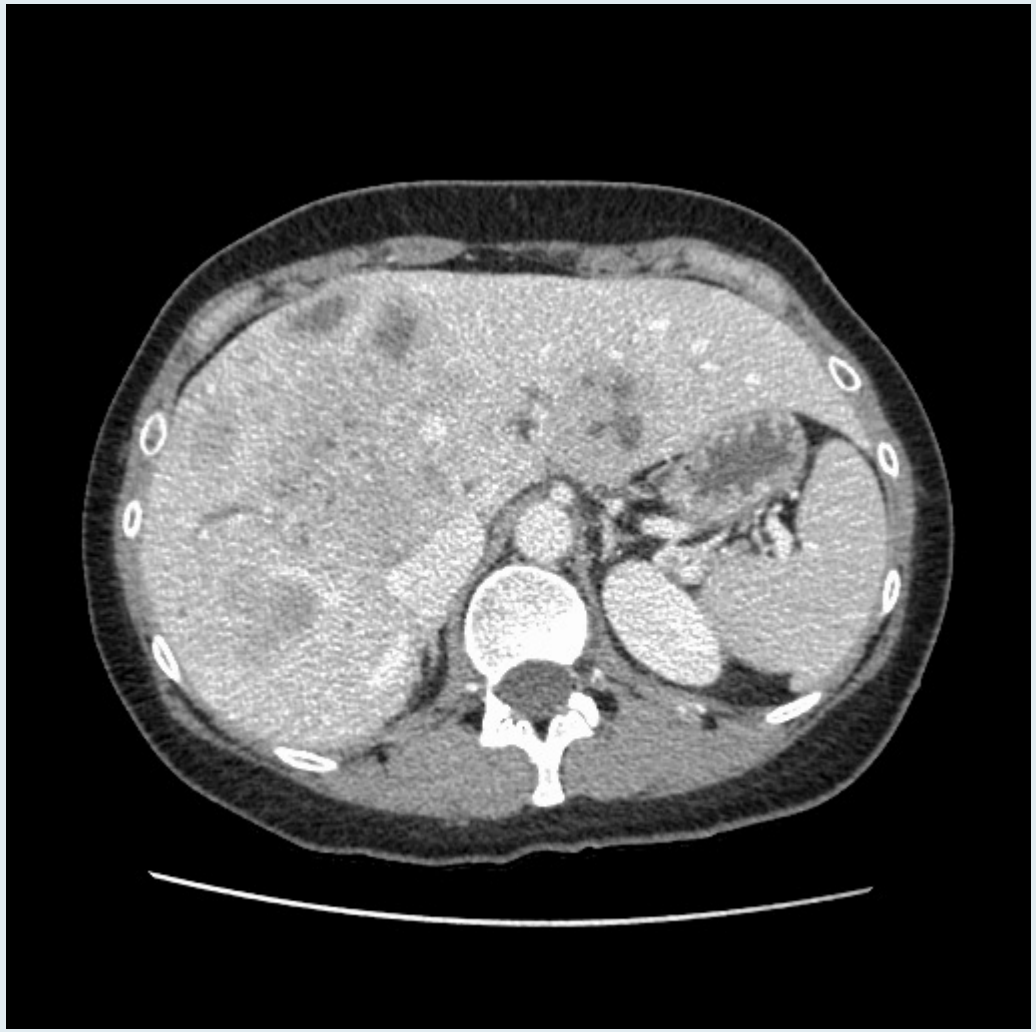
RTP
RESEARCH
TO PRACTICE

Case Presentation: 45-year-old woman with ER/PR-positive, HER2-low (IHC 2+) mBC, s/p fulvestrant/abemaciclib and now receiving exemestane/everolimus – ESR1 and PIK3CA mutations

Dr Jennifer Dallas (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE





UCSF Helen Diller Family Comprehensive Cancer Center

Novel Strategies Under Investigation for Patients with HR-Positive Metastatic Breast Cancer

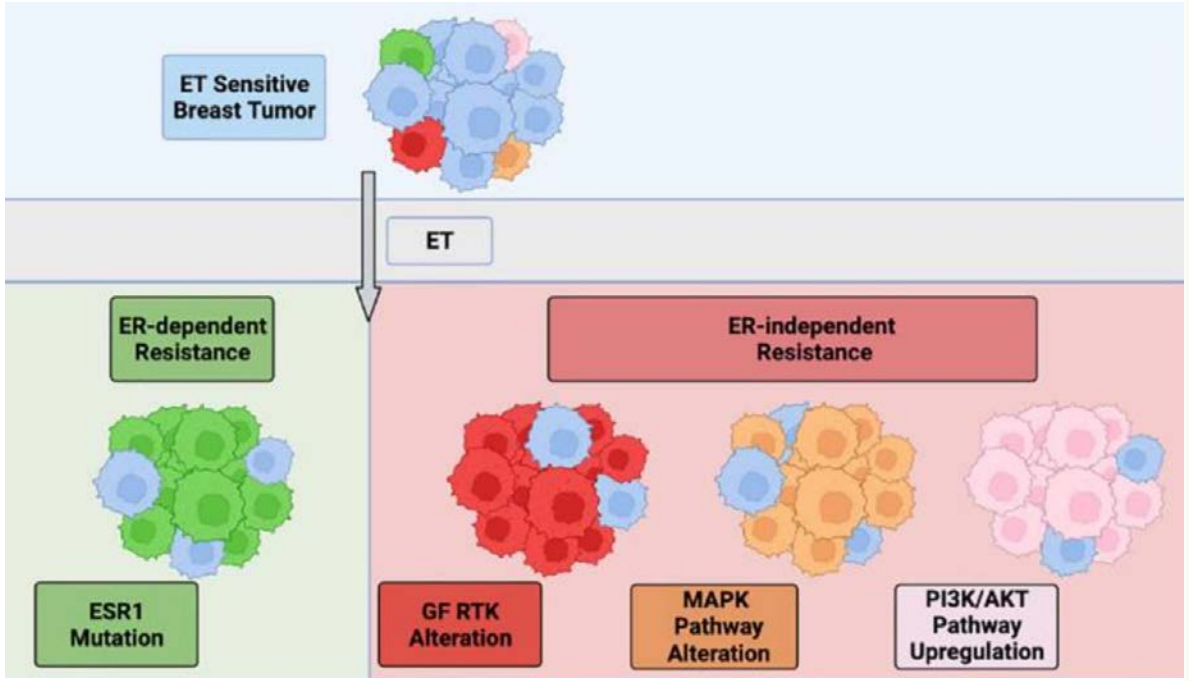
Hope S. Rugo, MD

Professor of Medicine

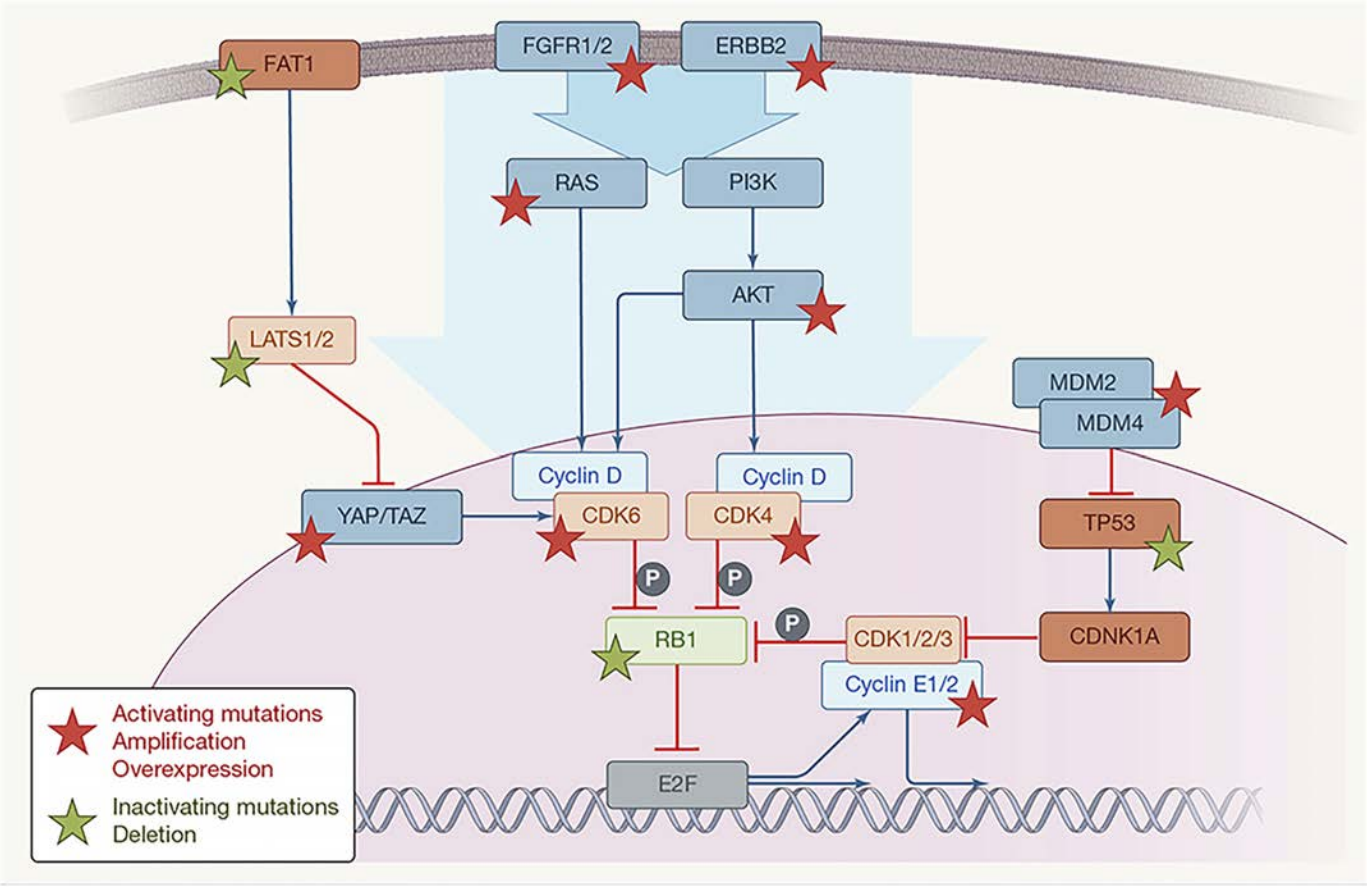
Director, Breast Oncology and Clinical Trials Education

University of California San Francisco Comprehensive Cancer Center

Resistance to ET + CDK4/6i: Now a High Unmet Need



ER dependent and independent mechanism of resistance



Major Mechanisms of Resistance to CDK4/6 Inhibitors

Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25
Álvarez-Fernández M, Malumbres M. *Cancer Cell*. 2020;37:514-529.

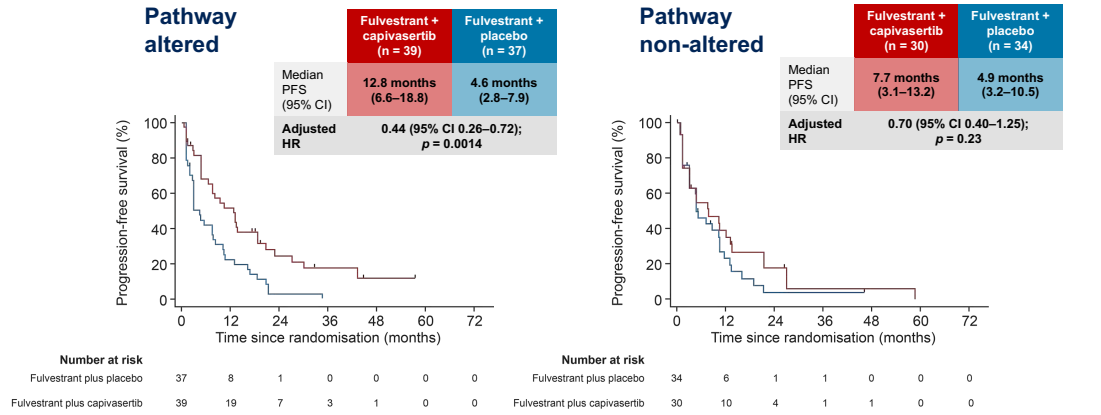
Inhibiting AKT

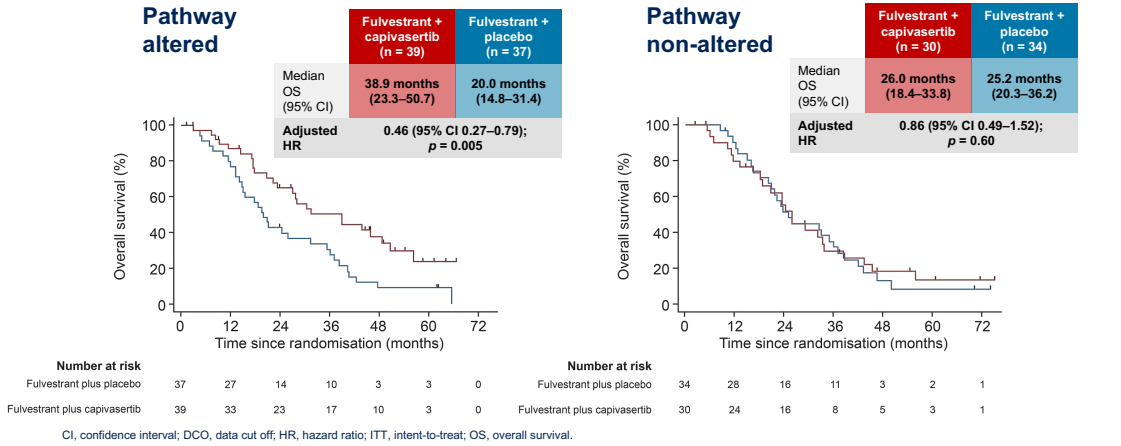
- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*
  - May also occur in cancers without these genetic alterations
  - AKT signalling implicated in development of ET resistance
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)

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

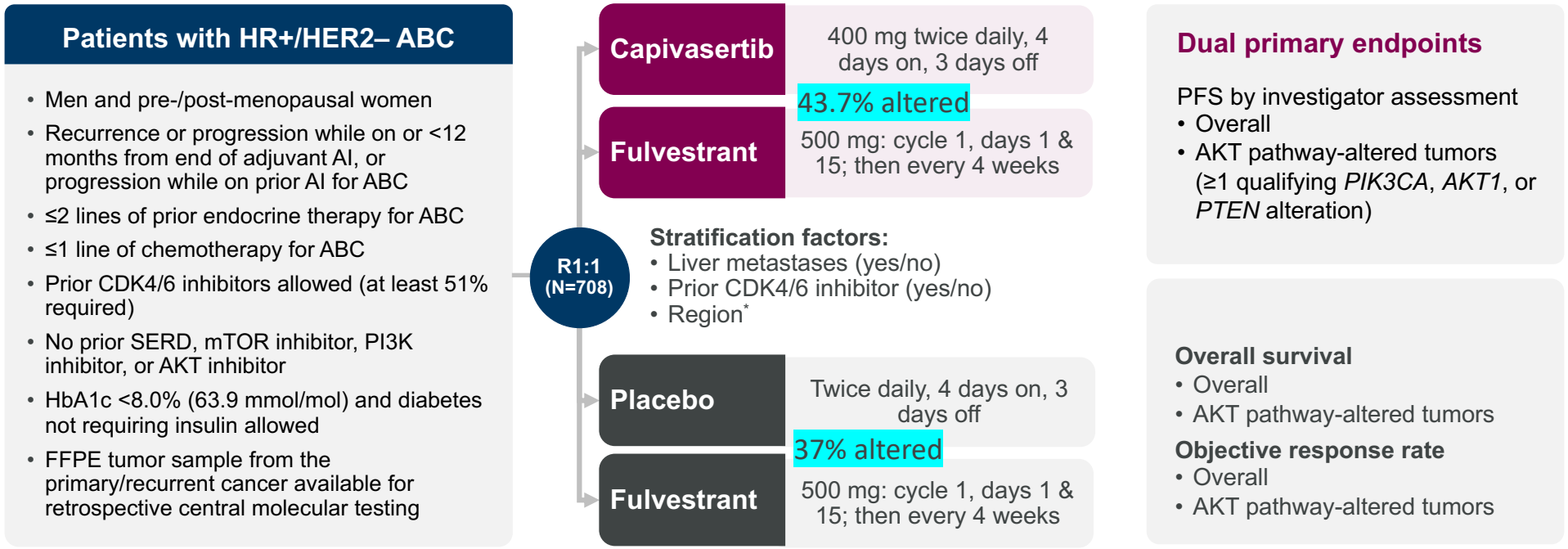
Phase II FAKTION Trial

- Adding Capi to Fulv in PM women with AI resistant HR+ MBC (no prior CDKi) improved PFS and OS, with most benefit in altered population





CAPItello-291: Phase III, randomized, double-blind, placebo-controlled study



Summary of Demographics

- Median age ~59
- Asian 26%, Black 1%
- Primary ET resistance ~38%
- Visceral mets ~68%
- One line of prior ET for MBC ~75%
- Prior CDK4/6i for MBC ~70%
- Chemotherapy for ABC ~18%

Turner et al, SABCS 2022

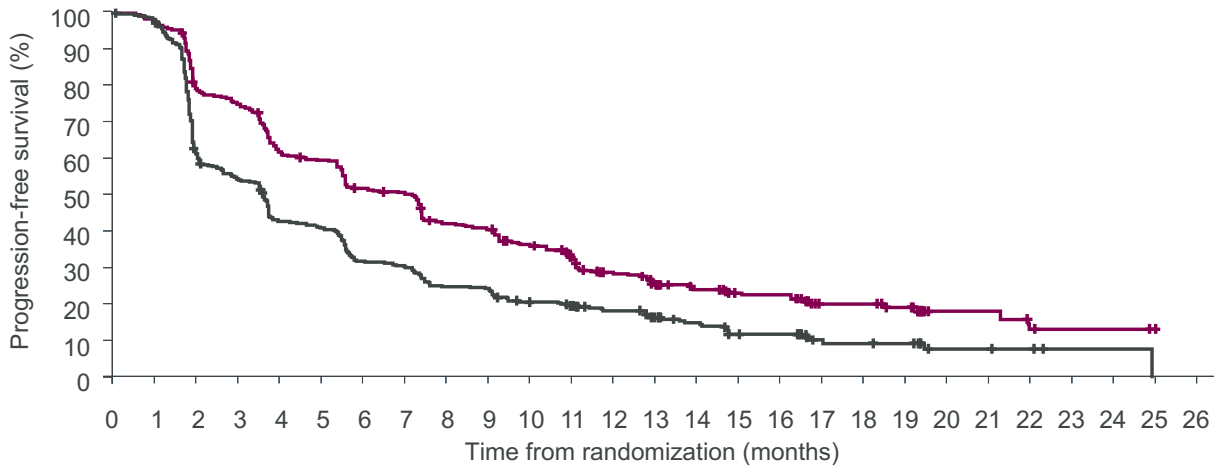
AKT Pathway Alterations

Alteration; n (%)			
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
	No sample available	10 (2.8)	4 (1.1)
	Preanalytical failure	39 (11.0)	34 (9.6)
	Post analytical failure	9 (2.5)	10 (2.8)

AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

Turner et al, SABCS 2022

Dual-primary endpoint: Investigator-assessed PFS in the overall population

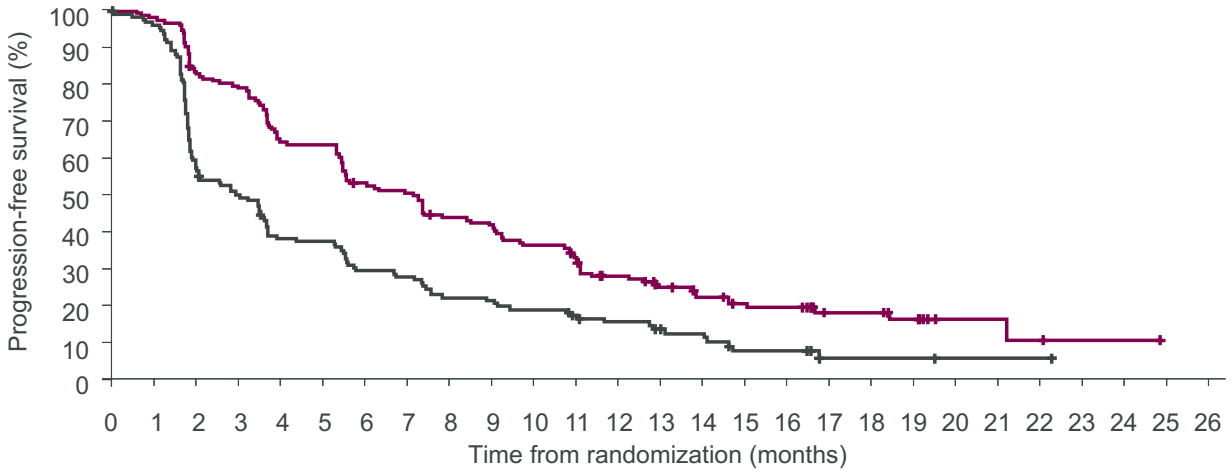


Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population



Number of patients at risk

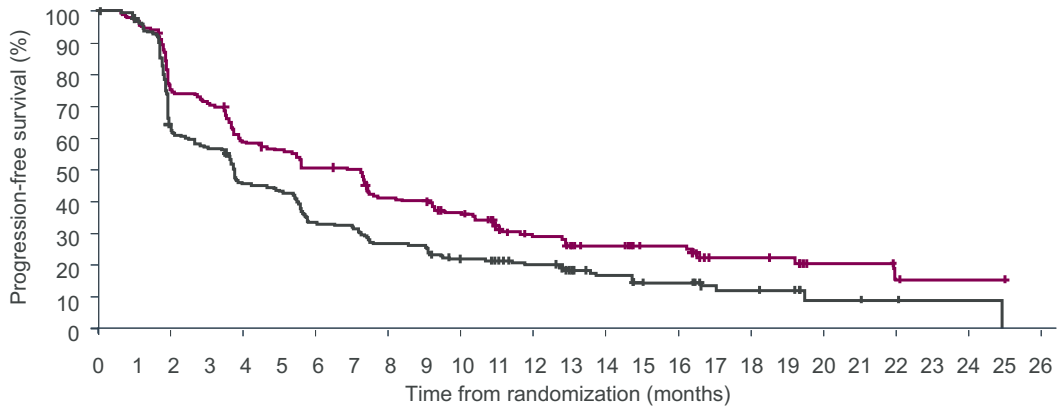
Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

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

Turner et al, SABCS 2022

Additional Analyses

Exploratory analysis: Investigator-assessed PFS in the non-altered population (including unknown†)



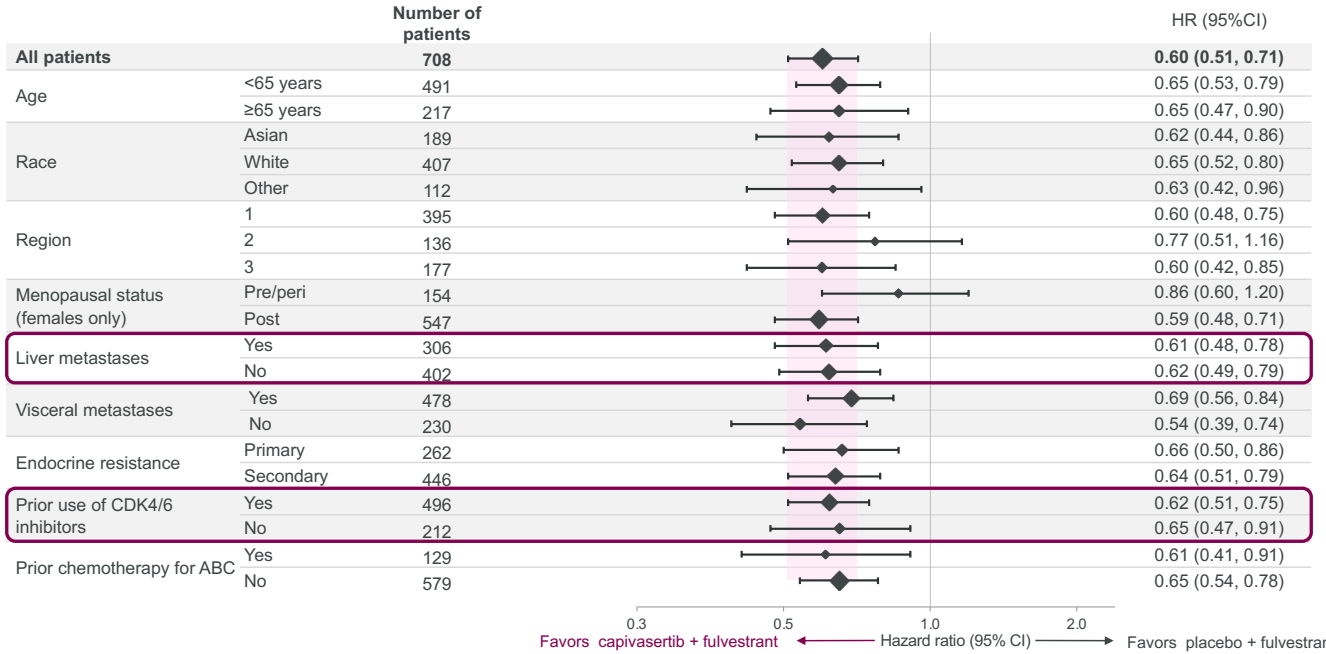
Number of patients at risk

Capivasertib + fulvestrant	200	180	139	131	108	102	92	90	73	71	61	49	40	33	29	22	22	13	13	12	5	5	3	1	1	1	0
Placebo + fulvestrant	219	205	130	118	94	89	69	65	55	54	42	39	34	27	22	18	17	10	9	8	3	3	2	1	1	0	0

	Capivasertib + fulvestrant (N=200)	Placebo + fulvestrant (N=219)
PFS events	137	178
Median PFS (95% CI); months	**7.2** (4.5–7.4)	**3.7** (3.0–5.0)
HR (95% CI):	**0.70 (0.56, 0.88)**	

Excluding unknowns (58 v 48): HR 0.79 (95% CI 0.61, 1.02)

Investigator-assessed PFS by subgroup: Overall population



Response per investigator assessment

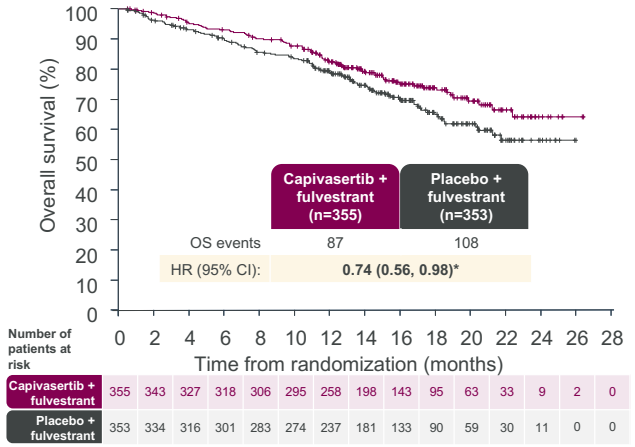
	Overall population		AKT pathway-altered population	
	Capivasertib + fulvestrant	Placebo + fulvestrant	Capivasertib + fulvestrant	Placebo + fulvestrant
Patients with measurable disease at baseline	310	320	132	124
Objective response rate; n (%)	71 (22.9)	39 (12.2)	38 (28.8)	12 (9.7)
Odds ratio (95% CI)*	2.19 (1.42, 3.36)		3.93 (1.93, 8.04)	

Turner et al, SABCS 2022

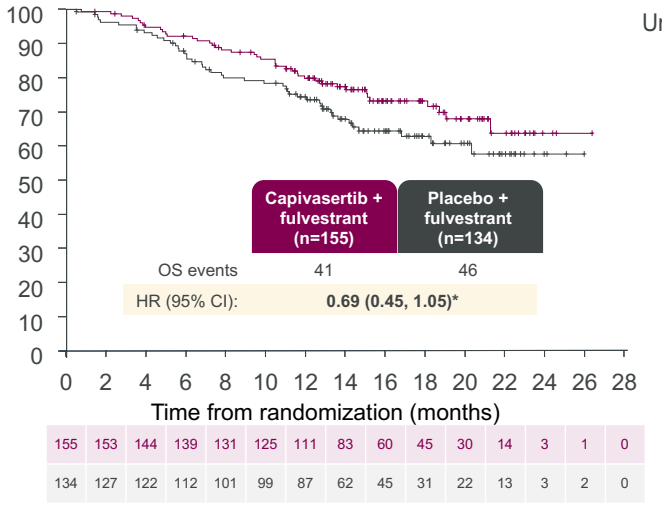
Overall Survival

- Overall survival immature at just 28% maturity
  - Less events in the Capi arm

Overall population

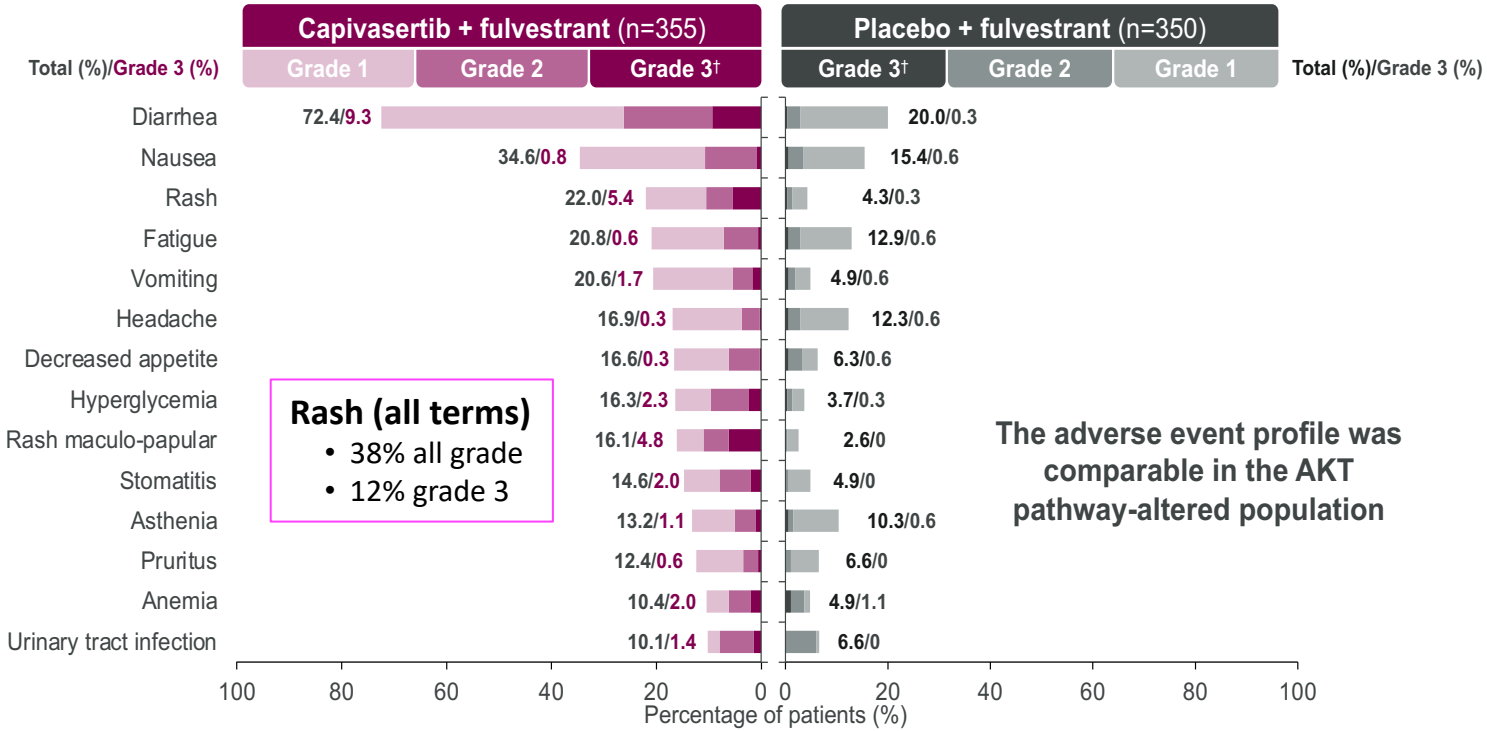


AKT pathway-altered population



Safety

Adverse events (>10% of patients) – overall population



Rash (all terms)
- 38% all grade
- 12% grade 3

The adverse event profile was comparable in the AKT pathway-altered population

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

AEs leading to:

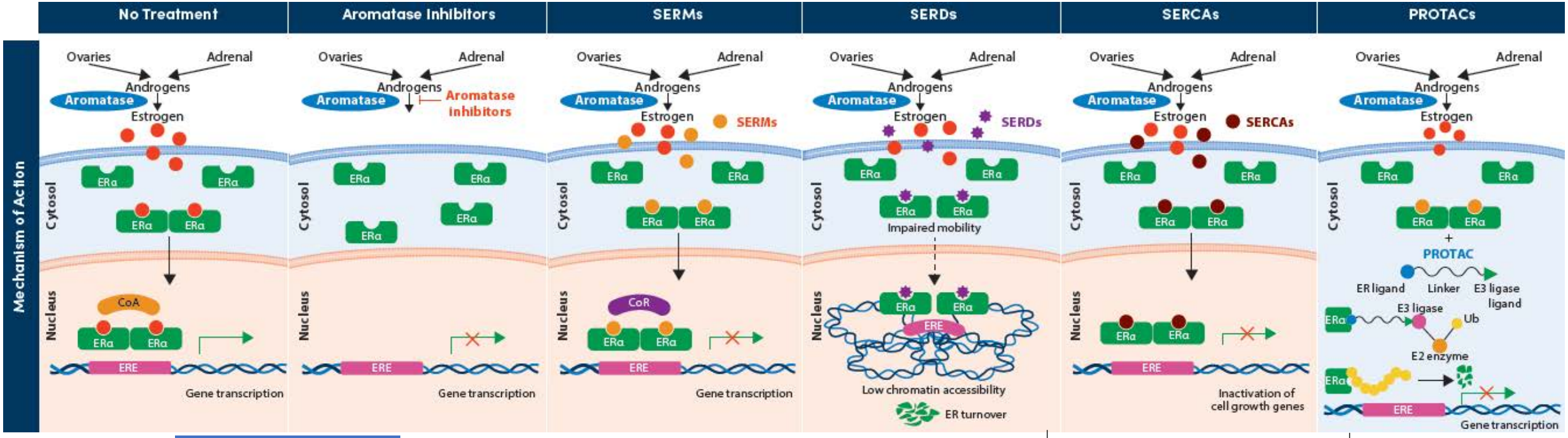
- Discontinuation capi/pla: 9.3 vs 0.6%
- Interruption capi/pla: 34.9 vs 10.3%
- Dose reduction capi/pla: 19.7 vs 1.7%

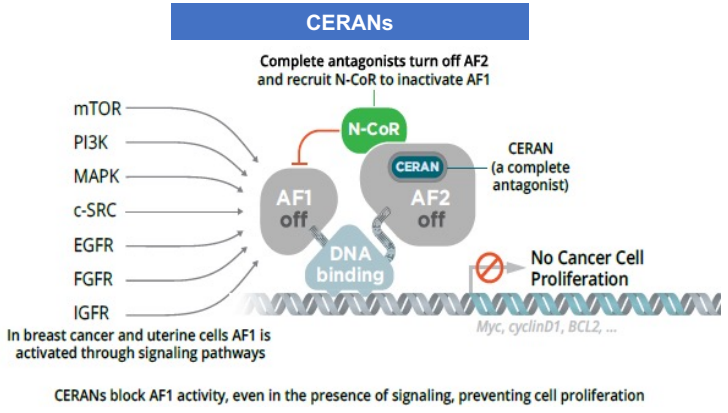
Turner et al, SABCS 2022

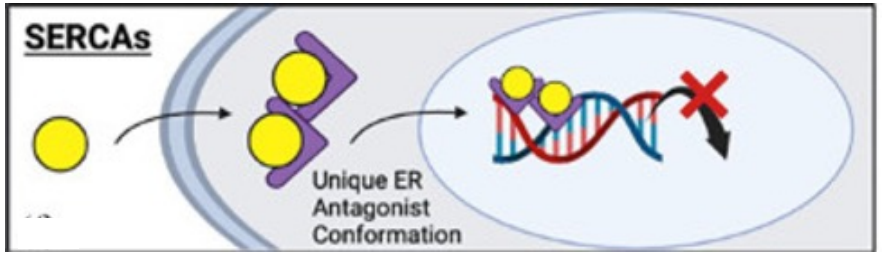
Conclusions and Next Steps

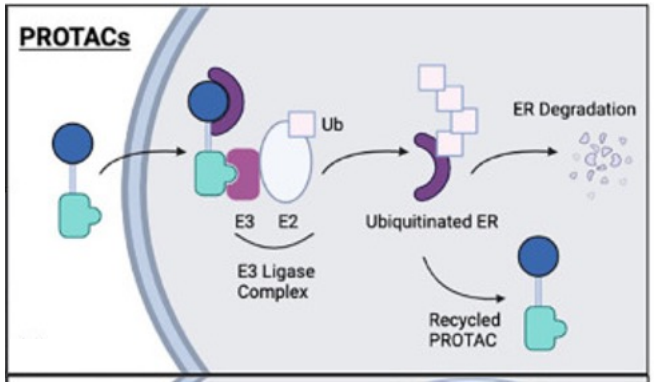
- Capivasertib/fulvestrant vs Pla/fulvestrant improved PFS in the overall population and in patients with tumor PIK3CA altered population; overall survival immature
- Efficacy in the subset of patients with non-altered tumors uncertain
  - Trial was not powered to look at this subgroup; small group with unknown mutation profile hard to take into account
- Benefit seen across subgroups including those with prior CDK4/6i and with visceral metastases
- Safety: GI toxicity, primarily lower grade resulted in modestly more discontinuations, dose holds and dose reductions of capivasertib
  - All/Grade 3 diarrhea 72/9%, rash 38/12%, hyperglycemia 16/2.3%, nausea 35/0.8%
- Data to be considered for regulatory approval
- Additional studies
  - **CAPItello-292** (NCT04862663): Fulvestrant/Palbociclib +/- Capi
  - Additional studies with ipatasertib with similar designs
  - New PIK3CA inhibitors: Inavolisib, LOX783 and more!

Mechanism of Action of New Endocrine Agents Targeting the ER Domain







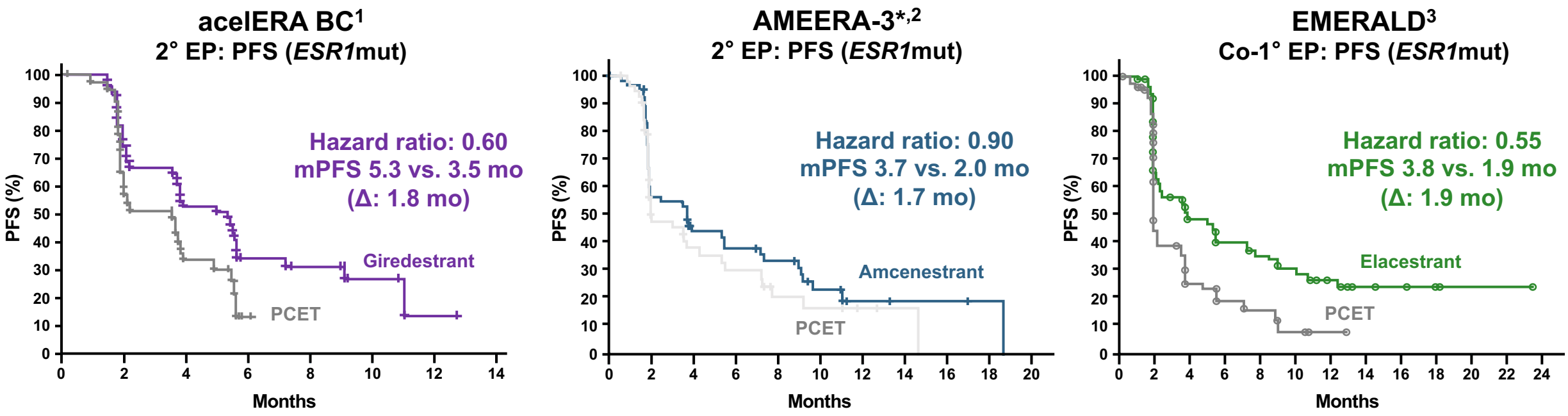


1. Hanker AB et al. *Cancer Cell.* 2020;37:496-513 2. Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25

Oral SERDS: Randomized Trials in the Post-CDK4/6 Inhibitor Setting

	EMERALD (NCT03778931)	AMEERA-3 (NCT04059484)	acelERA (NCT04576455)	SERENA-2 (NCT04214288)	EMBER-3 (NCT04975348)
N	477	282	303	288	830
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 1.87** **HR 0.55**	**Did not meet primary EP**	**Did not meet primary EP**	**Positive (SABCS 2022)** **3.7 vs 7.2 (75mg)** **HR 0.58** **3.7 vs 7.7(150mg)** **HR 0.67**	Not yet reported Modified from Jhaveri

A significant PFS benefit was seen in the *ESR1*-mutated population of EMERALD; a benefit trend was observed in acelERA BC and AMEERA-3



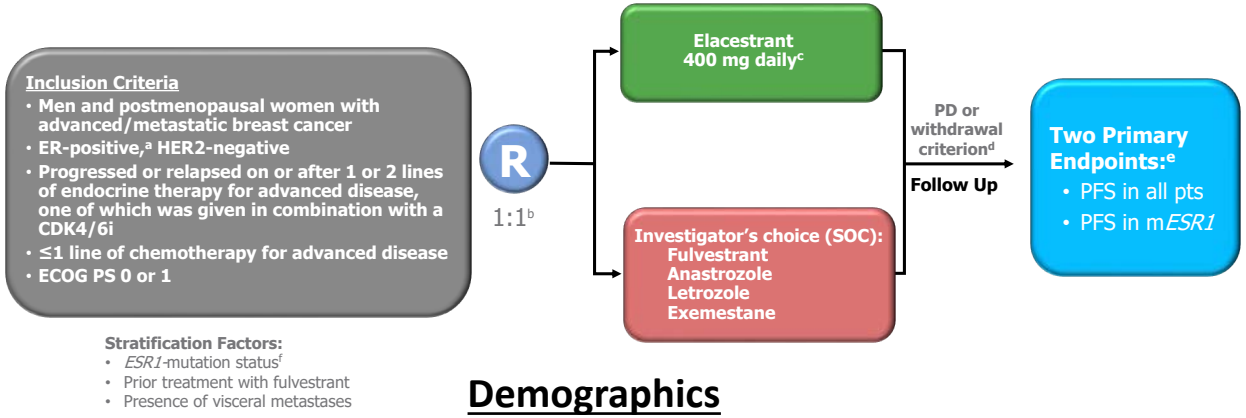
Giredestrant and elacestrant had comparable PFS hazard ratios vs. PCET in *ESR1*-mutated subpopulations; the HR for amcenestrant was notably higher

- It was announced in August 2022 that the amcenestrant clinical development programme will be discontinued.[4]

1° primary; 2°, secondary; BC, breast cancer; EP, endpoint; mo, months; mPFS, median progression-free survival; PCET, physician's choice of endocrine therapy; PFS, progression-free survival; SERD, selective oestrogen receptor degrader.

1. Martin M, *et al*. ESMO 2022 (Abstract 211MO; mini oral presentation); 2. Tolaney SM, *et al*. ESMO 2022 (Abstract 212MO; mini oral presentation); 3. Bidard F-C, *et al. J Clin Oncol* 2022; 4. https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668 (accessed August 2022).

EMERALD Phase 3 Trial: Elacestrant vs SOC ET



Demographics

- ~70% visceral mets
- ~40% 2 lines prior ET for MBC
- ~24% one line of chemotherapy
- 100% prior CDK4/6i

Conclusions

- Hazard ratios are relatively similar in pts who received >6 months prior CDK4/6i or longer
- Pts with endocrine sensitive disease had remarkable PFS with elacestrant alone
- Benefit was more marked in the ESR1 mutant population
- Next steps: combinations with targeted agents (ELEVATE)

Bardia, Bidard …… and **Kaklamani;** SABCS 2022

PFS by Duration of CDK4/6i: All Patients

Duration on CDK4/6i in the metastatic setting

	At least 6 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=202)	SOC (n=205)	Elacestrant (n=150)	SOC (n=160)	Elacestrant (n=98)	SOC (n=119)
Median PFS Months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 6 months (95% CI)	34.40 (26.70 - 42.10)	19.88 (12.99 - 26.76)	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)
PFS rate at 12 months (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months (95% CI)	16.24 (8.75 - 23.74)	3.21 (0.00 - 8.48)	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

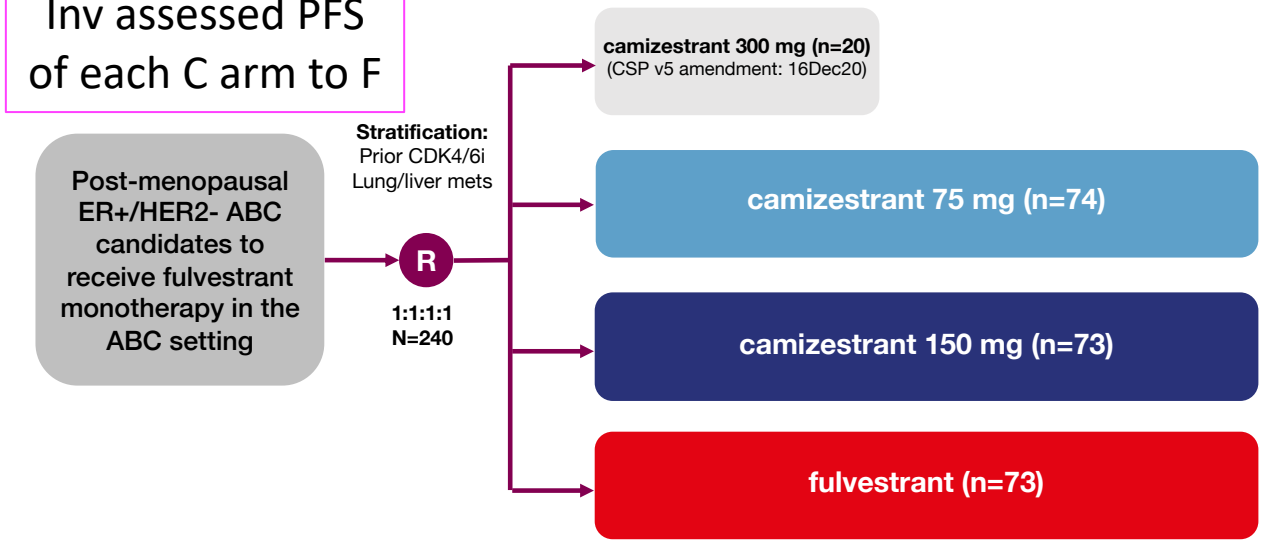
PFS by Duration of CDK4/6i: ESR1 mutant

Duration on CDK4/6i in the metastatic setting

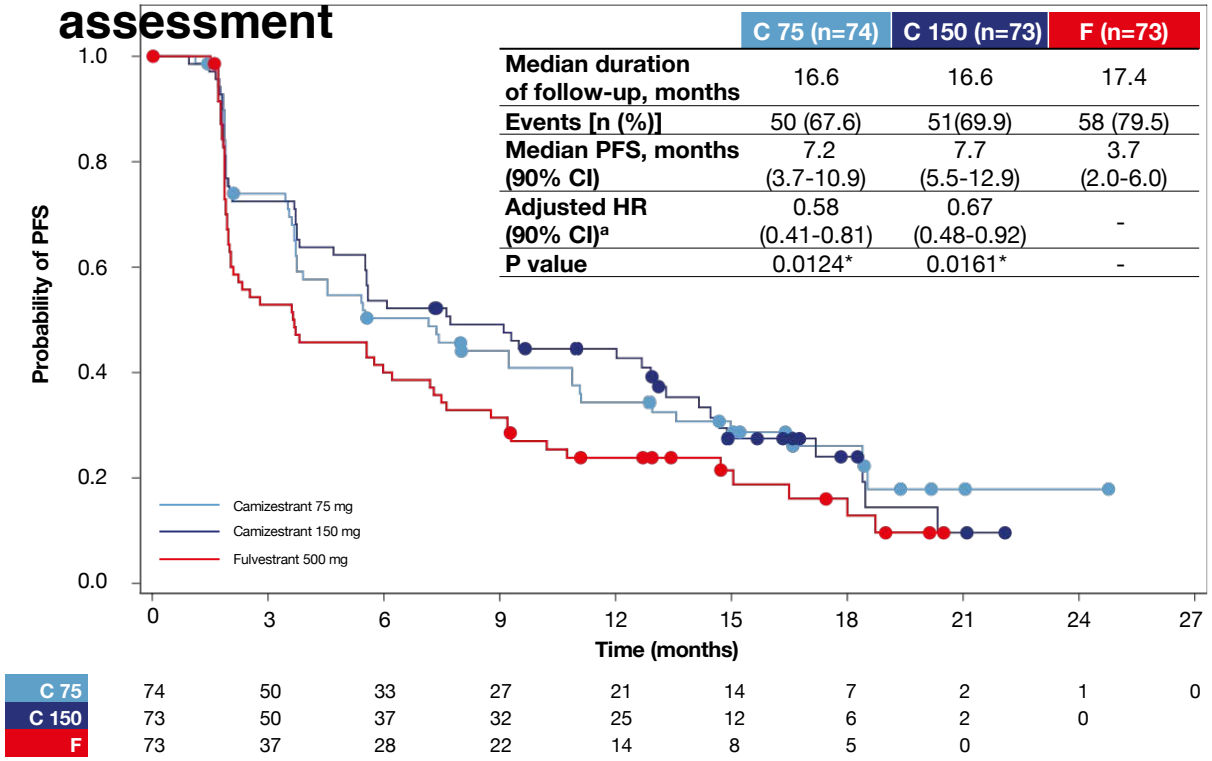
	At least 6 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=103)	SOC (n=102)	Elacestrant (n=78)	SOC (n=81)	Elacestrant (n=55)	SOC (n=56)
Median PFS Months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

SERENA-2 Phase 2 Trial: Camizestrant plus Fulvestrant

Primary endpt: Inv assessed PFS of each C arm to F



Primary endpoint: PFS by investigator assessment



	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

*Statistically significant; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

Demographics

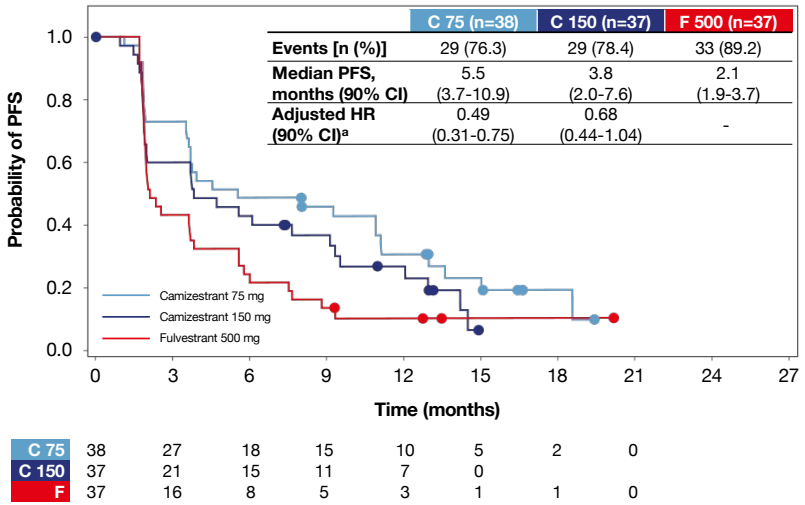
- 90-95% white
- Imbalance in liver (not visceral) mets: 31 v 41 vs 48%
- Imbalance in ESR1m: 30 v 36 v 48%
- 77% one line ET, 63% prior AI; 50% prior CDK4/6i
- Prior chemo for MBC: 22 v 12 v 26%

PFS by BICR: Significant discordance with inv PFS for 150 mg

	C 75 (n=74)	C 150 (n=73)	F (n=73)
Events [n (%)]	39 (52.7)	33 (45.2)	53 (72.6)
Median PFS, months (90% CI)	7.4 (4.5-10.9)	12.7 (9.3-18.4)	3.7 (2.0-3.8)
Adjusted HR (90% CI)[a]	0.56 (0.39-0.80)	0.47 (0.33-0.68)	-
P value	0.0079*	0.0004*	-

Oliveira et al, SABCS 2022

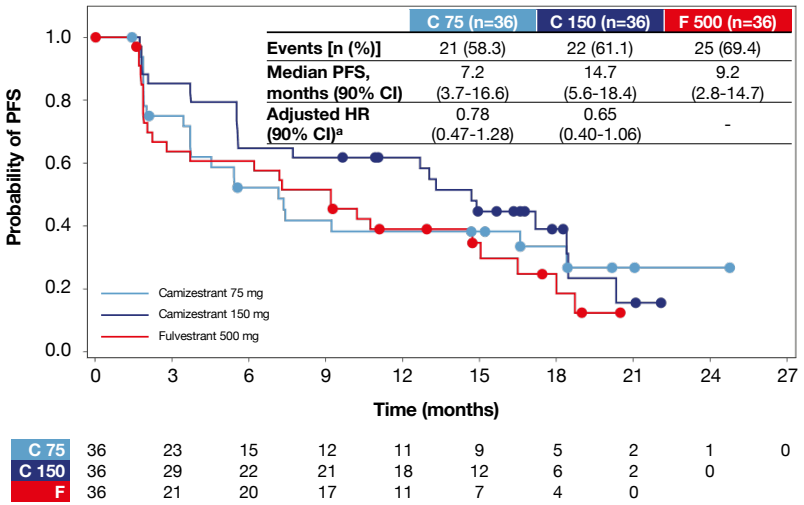
Prior CDK4/6i



	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-

C 75	38	27	18	15	10	5	2	0	
C 150	37	21	15	11	7	0			
F	37	16	8	5	3	1	1	0	

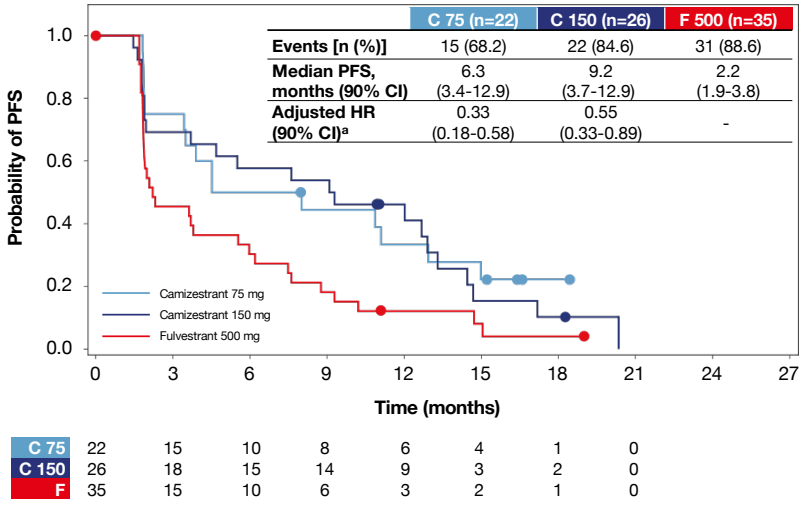
No prior CDK4/6i



	C 75 (n=36)	C 150 (n=36)	F 500 (n=36)
Events [n (%)]	21 (58.3)	22 (61.1)	25 (69.4)
Median PFS, months (90% CI)	7.2 (3.7-16.6)	14.7 (5.6-18.4)	9.2 (2.8-14.7)
Adjusted HR (90% CI)[a]	0.78 (0.47-1.28)	0.65 (0.40-1.06)	-

C 75	36	23	15	12	11	9	5	2	1	0
C 150	36	29	22	21	18	12	6	2	0	
F	36	21	20	17	11	7	4	0		

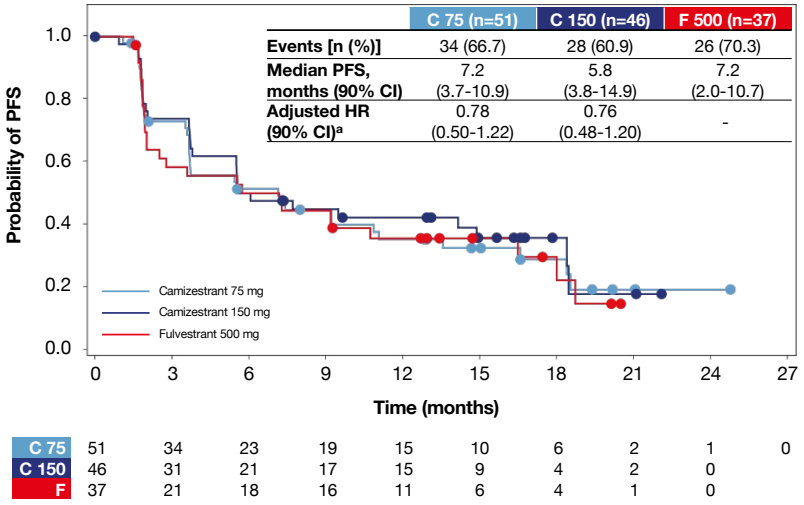
*ESR1*m detectable at baseline



	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

C 75	22	15	10	8	6	4	1	0
C 150	26	18	15	14	9	3	2	0
F	35	15	10	6	3	2	1	0

*ESR1*m not detectable at baseline



	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

Liver and/or lung mets

YES	C 75 (n=43)	C 150 (n=43)	F 500 (n=43)
Events [n (%)]	31 (72.1)	32 (74.4)	39 (90.7)
Median PFS, months (90% CI)	7.2 (3.6-11.1)	5.6 (3.7-9.1)	2.0 (1.9-3.6)
Adjusted HR (90% CI)[a]	0.43 (0.28-0.65)	0.55 (0.37-0.82)	-

NO	C 75 (n=31)	C 150 (n=30)	F 500 (n=30)
Events [n (%)]	19 (61.3)	19 (63.3)	19 (63.3)
Median PFS, months (90% CI)	5.5 (3.7-15.0)	14.5 (5.6-17.2)	9.2 (3.7-18.7)
Adjusted HR (90% CI)[a]	0.99 (0.57-1.69)	0.91 (0.53-1.56)	-

Biomarkers

- Camizestrant reduced ESR1 ctDNA to near zero by C2D1

Safety

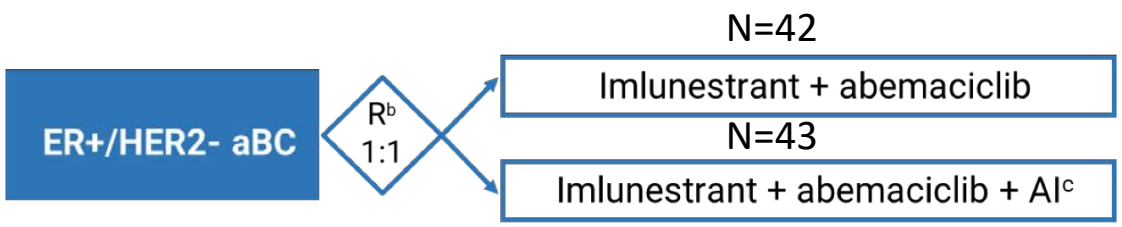
- Very low rate discontinuation
- Interruption TRAEs ~med 7 days: ~10%
- Very low rate of grade 3 AEs
- All grade AEs (low-high dose):
  - Photopsia: 12-25%
  - Sinus bradycardia: 5-26%
  - More fatigue, arthralgia, AST/ALT elevation at higher dose

Conclusion

- Met its primary endpoint
- No comment about dosing or imbalance in specific factors
  - Ph 3 trials ongoing
  - Dose: 75 mg

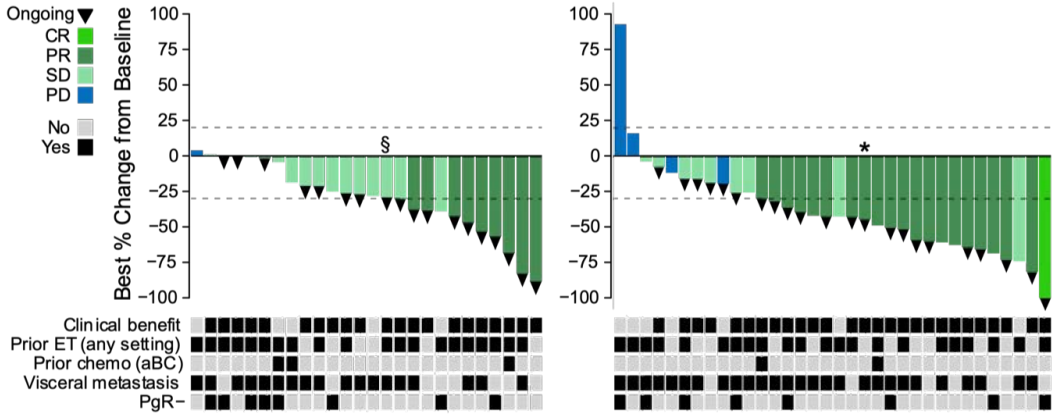
Oliveira et al, SABCS 2022

Imlunestrant: Phase Ia/b Trial



≤1 prior therapy for MBC, no prior CDK4/6i
ET sensitive disease (≥24 weeks on ET)

	Imlunestrant + abemaciclib N=42	Imlunestrant + abemaciclib + AI N=43	Total N=85
ORR, n/N (%)	9/28 (32)	20/34 (59)	29/62 (47)
Median TTR, months (min-max)	3.7 (1.6-10.9)	3.7 (1.7-7.1)	3.7 (1.6-10.9)
CBR, n/N (%)	30/42 (71)	34/43 (79)	64/85 (75)
12-month PFS, %	80	80	80



Demographics

- ESR1m: 7 v 10%
- Visceral mets: 50 v 65%
- De novo: 19 v 33%
- Measurable dse: 67 v 79%
- 70% Rxd in first line; 10% prior chemo
- Recurrence <12 mo adj Rx: 67 v 44%

RP2D Imlunestrant combined with abemaciclib

- 150 mg BID

Safety (all/gr3, averaged)

- Diarrhea: 92/10%
- Nausea: 59/0%
- Neutropenia: 41/14%

D/C for TRAE: 1%

Dose reduction for AE:

- Both: 6%
- Abema: 29%

- PFS: small number of events; 80% prog free at 12 mos
- ctDNA: ORR/PFS assoc with decline
- No PK drug interaction with abemaciclib
- Phase III trials ongoing in metastatic and adjuvant settings

Jhaveri et al, SABCS 2022

Additional Phase III SERD Trials for MBC: Examples

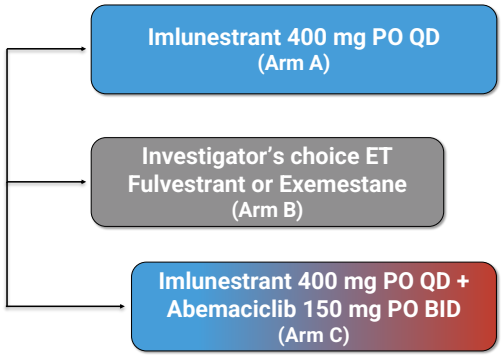
EMBER-3

1:1:1 Randomization
N = ~860

ER+, HER2-, Advanced Breast Cancer

- Relapsed on (neo) adjuvant/within 1 year of adjuvant AI, alone or in combination with a CDK4/6 inhibitor
  OR
- Progressed on 1L AI, alone or in combination with a CDK4/6 inhibitor
- Prior CDK4/6i treatment is expected if approved and reimbursed

Stratified for:
- Prior CDK4 & 6 inhibitor therapy
- Presence of visceral metastases
- Region

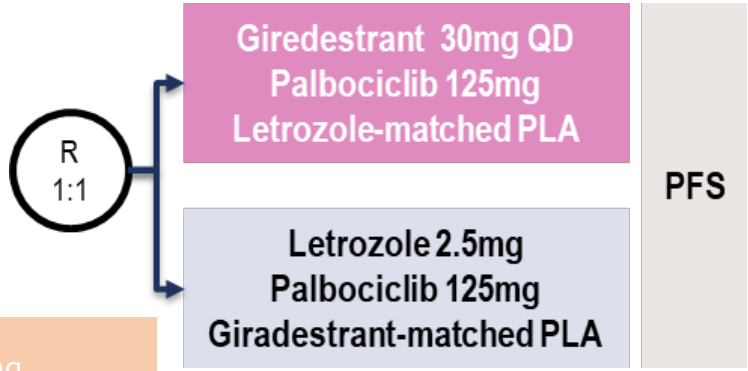


Primary Objective:
- Investigator-assessed PFS for A vs B
- Investigator-assessed PFS for A vs B in the *ESR1*-mutation detected population
- Investigator-assessed PFS for C vs A (gated, i.e. only tested if A vs B is stat sig)

Secondary Objectives:
- OS (gated), PFS by BICR, ORR, CBR, DoR, PRO's

persevERA

N=978
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

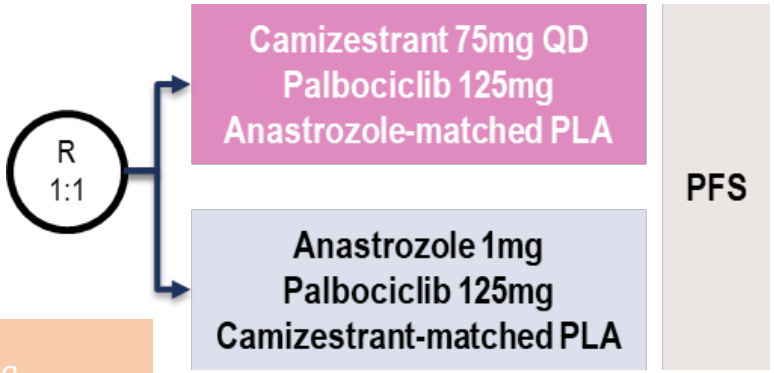


Recruiting

NCT04546009

SERENA-4

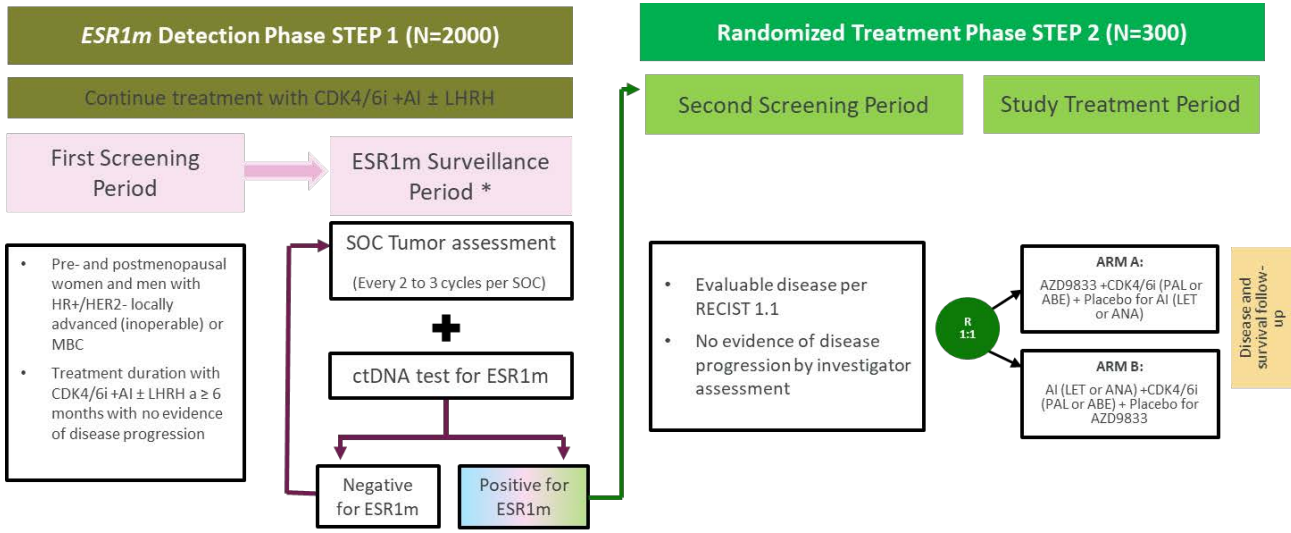
N=1342
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



Recruiting

NCT04711252

SERENA-6



ARV-471 (PROTAC ER Degrader): VERITAC Phase II Expansion Trial

- ARV-471 directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER then proteasomal degradation
- ≥1 ET for MBC, a CDK4/6i
  - 35 pts at 200mg/d; 36 pts at 500 mg/d
  - 58% ESR1 mutations; 79% prior fulvestrant, 45% liver mets
- Primary toxicities: fatigue, nausea, but ≤grade 2
- PFS

	All Patients	
	200 mg QD (n=35)	Total (N=71)
Events, n (%)	24 (68.6)	41 (57.7)
mPFS, mo (95% CI)	3.5 (1.8–7.8)	3.7 (1.9–8.3)

	Mutant *ESR1*	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)
Patients with mutant *ESR1*	(n=19)	(n=22)	(n=41)
CBR, % (95% CI)	47.4 (24.4–71.1)	54.5 (32.2–75.6)	51.2 (35.1–67.1)

Median ER degradation was 69% (range: 28%–95%)

Phase 3 VERITAC-2 Trial
- Fulvestrant vs ARV471 200 mg/d

Hurvitz, **Schott** et al, SABCS 2022

Newer ER Targeted Agents

- Other agents
  - **SERCA**: 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; Patel MR et al. SABCS 2021; Burke et al, Front Cell Dev Biol; 2022

And more……

- More oral SERDS in development
- 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

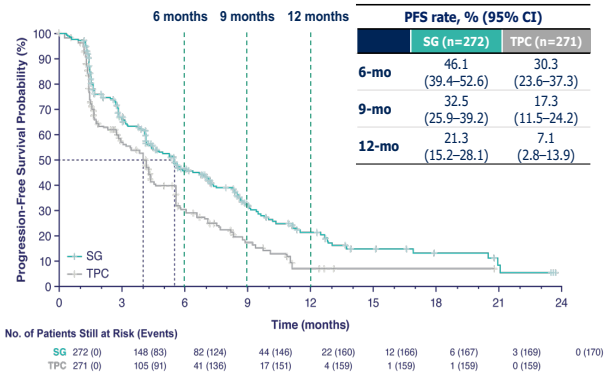
Palmieri ASCO 2021; Barroso-Sousa et al, SABCS 2021; Jhaveri et al, SABCS 2021; Damodaran et al, ASCO 2022

ADCs in HR+ MBC (not including HER2 low)

Phase III TROPiCS: Sacituzumab govitecan in HR+/HER2neg MBC

PFS[1]

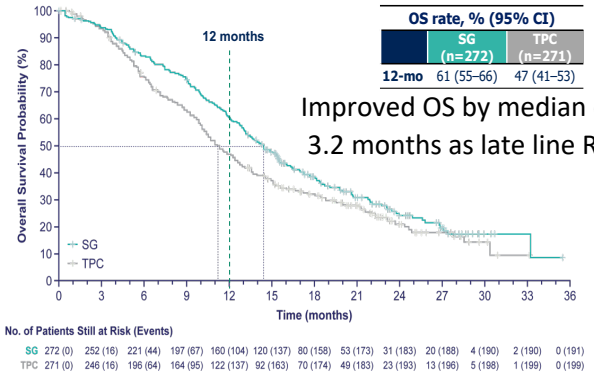
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



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

OS[2]

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



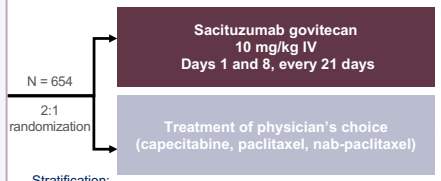
OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

Improved OS by median of 3.2 months as late line Rx

No Impact of TROP2 expression on efficacy

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

Ascent-07



Stratification:
- Duration of prior CDK 4/6i in metastatic setting (none/≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/EU vs. ROW)

Primary Endpoint
- PFS by BICR

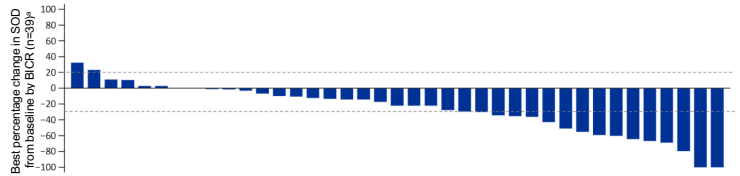
Key Secondary Endpoints
- OS
- ORR by BICR
- TTDD to Physical functioning

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

Rugo et al, JCO 2022, ESMO 2022, SABCS 2022

Phase 1 TROPION-PanTumor01: Datopotomab deruxtecan in HR+/HER2neg MBC

- N=40
- Median 2 prior chemo for MBC (1-6)
- Efficacy: ORR (all PR): 27%; CBR: 44%; med PFS 8.3 mo.
- Safety: stomatitis (Gr 3 10%); ILD Gr 2 and 3 (2 pts)



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

1:1

Dato-DXd
6mg/kg IV Q3W
N=350

Investigator's Choice of Chemotherapy
(Eribulin, Vinorelbine, Capecitabine or Gemcitabine)
N=350

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.

Targeting HER3: Patritumab deruxtecan; ORR 30%
Krop et al, ASCO 2022

Meric-Bernstam et al, SABCS 2022

Summary and Conclusions

- Exciting new data with novel approaches to the treatment of HR+ MBC
- Capivasertib
  - Improved PFS added to fulvestrant with better safety profile than existing PIK3CA inhibitors
  - Benefit in pathway non-altered population still unclear
  - Next step in combination with CDK4/6i, early stage?
- Oral SERDs
  - We are finally making progress!
  - Benefit clearer in ESR1m population
  - Multiple phase III trials in metastatic and early stage disease ongoing
- ADCs
  - Very encouraging efficacy in HR+/HER2 negative (and HER2 low disease)
  - Sequencing is the most important next question along with efficacy in earlier lines

Addressing Current Questions and Controversies in the Management of Chronic Lymphocytic Leukemia — What Clinicians Want to Know

Part 1 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
11:30 AM – 1:30 PM CT (12:30 PM – 2:30 PM ET)

Faculty

Alexey V Danilov, MD, PhD
Matthew S Davids, MD, MMSc
Professor Dr Arnon P Kater, MD, PhD
Lindsey Roeker, MD
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Neil Love, MD

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