Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Localized HER2-Negative Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Wednesday, December 6, 2023

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Harold J Burstein, MD, PhD
Matthew P Goetz, MD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Lajos Pusztai, MD, DPhil, FASCO

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Harold J Burstein, MD, PhD
Institute Physician
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
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

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

Joyce O'Shaughnessy, MD
Celebrating Women Chair in
Breast Cancer Research
Baylor University Medical Center
Director, Breast Cancer Research Program
Texas Oncology
US Oncology
Dallas, Texas

Lajos Pusztai, MD, DPhil, FASCO
Professor of Medicine
Scientific Co-Director of the Center for Breast Cancer
Co-Leader, Genetics, Genomics
and Epigenetics Program
Yale Cancer Center
Yale School of Medicine
New Haven, Connecticut

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH
TO PRACTICE

Dr Burstein — Disclosures

No relevant conflicts of interest to disclose

RTP
RESEARCH
TO PRACTICE

Dr Goetz — Disclosures

Consulting Agreements (Fees to Institution)	ARC Therapeutics, AstraZeneca Pharmaceuticals LP, Biotheranostics Inc, Blueprint Medicines, Lilly, RNA Diagnostics, Sanofi, Seagen Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Atossa Therapeutics, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Pfizer Inc, Sermonix Pharmaceuticals
Data and Safety Monitoring Board/Committee	Seagen Inc
Moderator Service	Curio Science
Nonrelevant Financial Relationship	Clinical Education Alliance, Engage Health Media, JNCCN 360, Medscape, MJH Life Sciences, Total Health Conferencing

RTP RESEARCH TO PRACTICE

Dr Hurvitz — Disclosures

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

RTP
RESEARCH
TO PRACTICE

Dr O’Shaughnessy — Disclosures

Advisory Committee and Consulting Agreements	AbbVie Inc, Agendia Inc, Amgen Inc, Aptitude Health, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Carrick Therapeutics, Celgene Corporation, Daiichi Sankyo Inc, Eisai Inc, Fishawack Health, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genzyme Corporation, Gilead Sciences Inc, GSK, Incyte Corporation, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Ontada, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Pierre Fabre, Puma Biotechnology Inc, Roche Laboratories Inc, Samsung Bioepis, Sanofi, Seagen Inc, Stemline Therapeutics Inc, Synthon, Theralink, Veru
Nonrelevant Financial Relationship	prIME Oncology

RTP RESEARCH TO PRACTICE

Dr Pusztai — Disclosures

Advisory Committee and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Exact Sciences Corporation, Merck, Natera Inc, Pfizer Inc, Predicine
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Exact Sciences Corporation, Merck, Natera Inc, Pfizer Inc

RTP
RESEARCH
TO PRACTICE

Commercial Support

This symposium is sponsored by Research To Practice and supported by grants from AstraZeneca Pharmaceuticals LP, Exact Sciences Corporation, Lilly, Merck, Natera Inc, Novartis, and TerSera Therapeutics LLC. This is not an official program of the San Antonio Breast Cancer Symposium®.

Research To Practice CME Planning Committee Members, Staff and Reviewers

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

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

RTP
RESEARCH
TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of HER2-Low Breast Cancer

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

Thursday, December 7, 2023

7:15 PM – 8:45 PM CT (8:15 PM – 9:45 PM ET)

Faculty

Aditya Bardia, MD, MPH

Lisa A Carey, MD, ScM, FASCO

Shanu Modi, MD

Professor Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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

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

Friday, December 8, 2023

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

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

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

Multiple Myeloma
7:00 PM – 9:00 PM PT

Moderator
Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Follicular, Mantle Cell and Hodgkin Lymphoma (Part 1 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:30 AM – 10:00 AM PT (10:30 AM – 1:00 PM ET)

Faculty

Jeremy S Abramson, MD, MMSc
Stephen M Ansell, MD, PhD
Nancy L Bartlett, MD
Jonathon B Cohen, MD
Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Diffuse Large B-Cell Lymphoma (Part 2 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Michael Dickinson, MD
Grzegorz S Nowakowski, MD
Gilles Salles, MD, PhD
Laurie H Sehn, MD, MPH
Jason Westin, MD, MS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Chronic Lymphocytic Leukemia (Part 3 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Farrukh T Awan, MD
Matthew S Davids, MD, MMSc
Stephen J Schuster, MD
William G Wierda, MD, PhD
Jennifer Woyach, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Amrita Krishnan, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

JOIN US IN 2024 FOR THE RETURN OF

The Annual
National General Medical Oncology Summit

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

MARCH 22-24, 2024

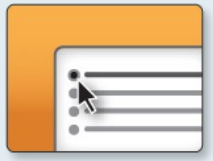
JW Marriott Miami Turnberry

To Learn More or to Register, Visit
www.ResearchToPractice.com/Meetings/GMO2024

Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the premeeting survey.

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

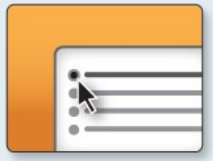
Complete Your Evaluation: Tap the CME/NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

RTP RESEARCH TO PRACTICE

Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the premeeting survey at the beginning of each module.

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

Get CME/NCPD Credit: CME and NCPD credit links will be provided in the chat room at the conclusion of the program. MOC and ONCC credit information will be emailed to attendees within the next 2-3 business days.

RTP
RESEARCH
TO PRACTICE

About the Enduring Program

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

RTP
RESEARCH
TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Localized HER2-Negative Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Wednesday, December 6, 2023

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Harold J Burstein, MD, PhD
Matthew P Goetz, MD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Lajos Pusztai, MD, DPhil, FASCO

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Role of Genomic Assays in Treatment Decision-Making for Localized ER-Positive, HER2-Negative Breast Cancer — Dr Goetz

Module 2: Integration of Ovarian Function Suppression into the Management of Breast Cancer in Premenopausal Patients — Dr Burstein

Module 3: Role of CDK4/6 Inhibitors and Other Novels Agents in Therapy for ER-Positive Localized Breast Cancer — Dr Hurvitz

Module 4: Optimizing the Use of Neoadjuvant and Adjuvant Therapy for Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 5: Emerging Role of Circulating Tumor DNA Evaluation in the Management of Breast Cancer — Dr Pusztai

RTP
RESEARCH
TO PRACTICE

Breast Cancer Survey Respondents

Aditya Bardia, MD, MPH
François-Clément Bidard, MD, PhD
Adam Brufsky, MD, PhD
Harold J Burstein, MD, PhD
Lisa A Carey, MD, ScM, FASCO
Matthew P Goetz, MD
Erika Hamilton, MD
Sara A Hurvitz, MD, FACP
Komal Jhaveri, MD, FACP
Virginia Kaklamani, MD, DSc
Jane Lowe Meisel, MD
Shanu Modi, MD
Joyce O'Shaughnessy, MD
Mark Pegram, MD
Lajos Pusztai, MD, DPhil, FASCO
Hope S Rugo, MD
Paolo Tarantino, MD
Prof Peter Schmid, FRCP, MD, PhD
Priyanka Sharma, MD
Eric P Winer, MD

RTP
RESEARCH
TO PRACTICE

Consulting Faculty

Adam M Brufsky, MD, PhD
Professor of Medicine
Co-Director, Comprehensive Breast Cancer Center
UPMC Hillman Cancer Center
Department of Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

Priyanka Sharma, MD
Frank B Tyler Professor in Cancer Research
Division of Medical Oncology
Department of Internal Medicine
The University of Kansas Cancer Center
Westwood, Kansas

Jane Lowe Meisel, MD
Associate Professor of Hematology and Medical Oncology
Associate Vice Chair of Faculty Development and Promotions
Winship Cancer Institute of Emory University
Atlanta, Georgia

Paolo Tarantino, MD
Medical Oncologist
Advanced Research Fellow
Dana-Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

Mark D Pegram, MD
Susy Yuan-Huey Hung Endowed Professor of Oncology
Director, Clinical and Translational Research Unit
Associate Director for Clinical Research
Stanford Comprehensive Cancer Institute
Stanford, California

Eric P Winer, MD
Alfred Gilman Professor of Medicine and Pharmacology
Director, Yale Cancer Center
President and Physician-in-Chief
Smilow Cancer Hospital
New Haven, Connecticut

RTP
RESEARCH TO PRACTICE

Analysis of Time to Recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) Trial According to Estrogen Receptor and Progesterone Receptor Status

Dowsett M, on behalf of the ATAC Trialists' Group.

SABCS 2003;Abstract 4.

GENERAL SESSION 1 | WEDNESDAY, DECEMBER 3 | 10:15 AM CT

Positive Phase III Results for Inavolisib Combination in People with Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer with a PIK3CA Mutation

Press Release – December 5, 2023

Positive results were announced from the Phase III INAVO120 study of the investigational therapy inavolisib in combination with palbociclib and fulvestrant as a potential first-line treatment option for people with PIK3CA-mutated, hormone receptor-positive, HER2-negative, endocrine-resistant, locally advanced or metastatic breast cancer.

"The study met its primary endpoint of progression-free survival (PFS), demonstrating a statistically significant and clinically meaningful improvement compared to palbociclib and fulvestrant alone. Overall survival data were immature at this time, but a clear positive trend has been observed. Follow-up will continue to the next analysis. [...]

The inavolisib combination was well tolerated and adverse events were consistent with the known safety profiles of the individual study treatments, with no new safety signals observed."

https://www.roche.com/media/releases/med-cor-2023-12-05

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Role of Genomic Assays in Treatment Decision-Making for Localized ER-Positive, HER2-Negative Breast Cancer — Dr Goetz

Module 2: Integration of Ovarian Function Suppression into the Management of Breast Cancer in Premenopausal Patients — Dr Burstein

Module 3: Role of CDK4/6 Inhibitors and Other Novels Agents in Therapy for ER-Positive Localized Breast Cancer — Dr Hurvitz

Module 4: Optimizing the Use of Neoadjuvant and Adjuvant Therapy for Triple-Negative Breast Cancer — Dr O'Shaughnessy

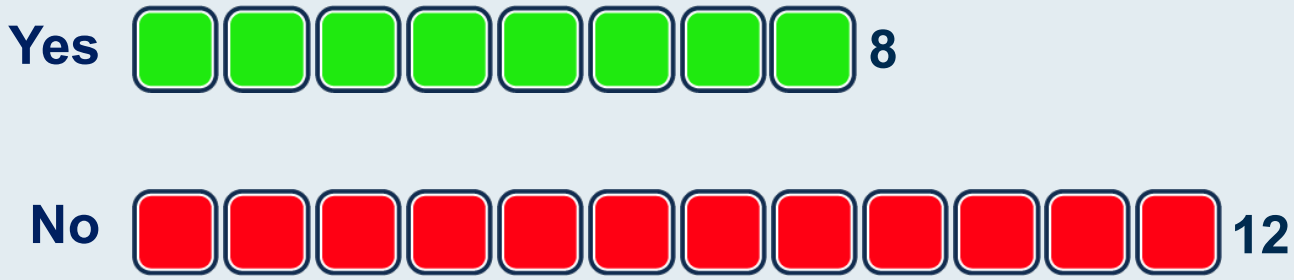
Module 5: Emerging Role of Circulating Tumor DNA Evaluation in the Management of Breast Cancer — Dr Pusztai

For a 65-year-old postmenopausal patient with ER-positive, HER2-negative, node-negative localized breast cancer, a 21-gene Recurrence Score of 20 and 1 positive node, would you recommend adjuvant chemotherapy?

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

For a 65-year-old postmenopausal patient with ER-positive, HER2-negative, node-negative localized breast cancer, a 21-gene Recurrence Score of 20 and 3 positive nodes, would you recommend adjuvant chemotherapy?

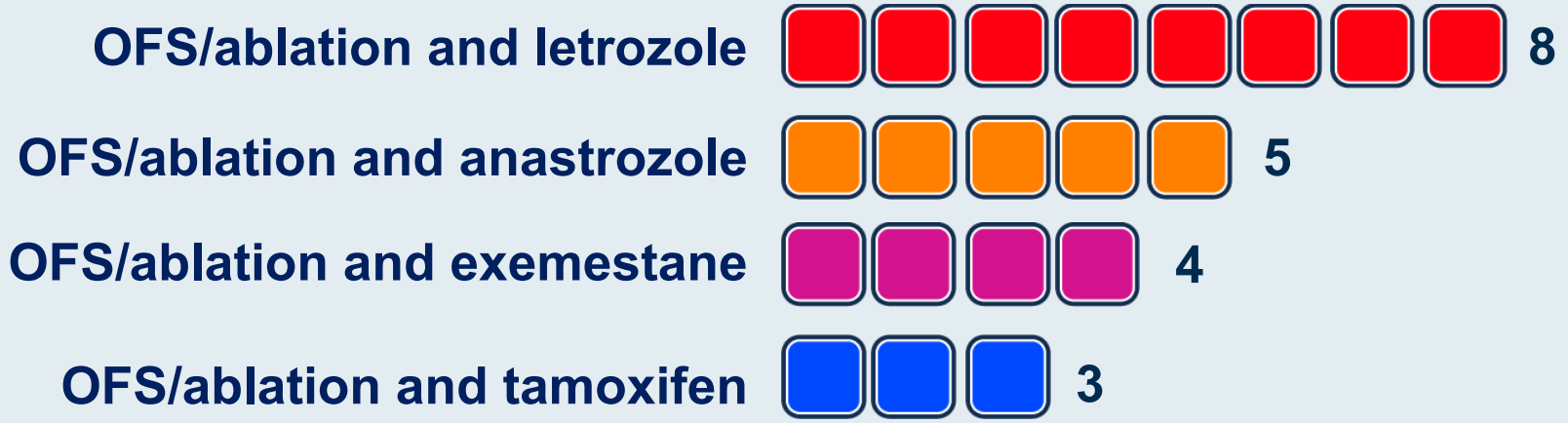


Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Which adjuvant endocrine treatment would you most likely recommend for a 40-year-old premenopausal patient with ER-positive, HER2-negative localized breast cancer, a 21-gene Recurrence Score of 8 and 1 positive node?

Would you recommend adjuvant chemotherapy?	
Yes, but I would offer OFS/ablation as an alternative	7
Yes	7
No	6

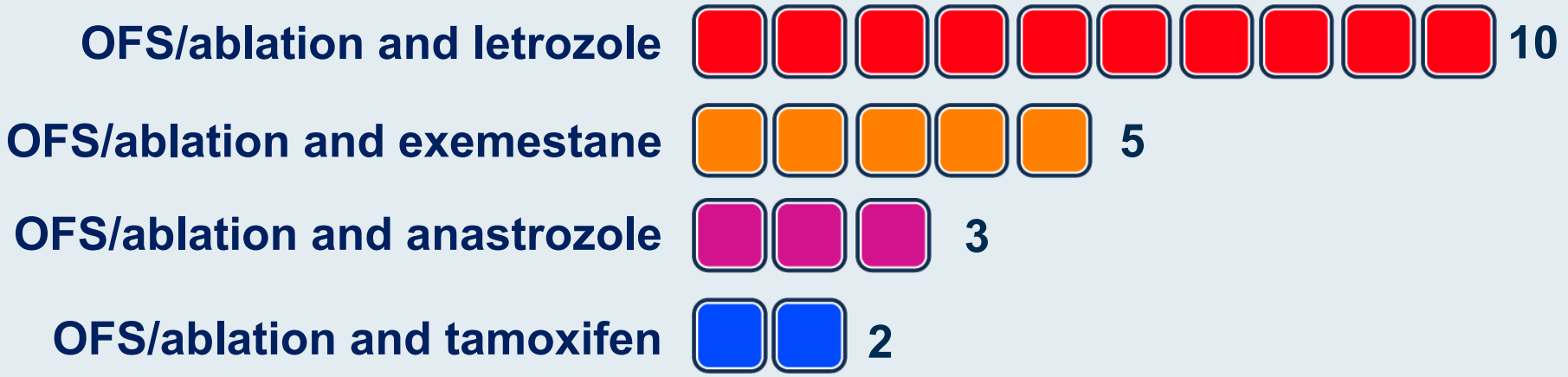


Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Which adjuvant endocrine treatment would you most likely recommend for a 40-year-old premenopausal patient with ER-positive, HER2-negative localized breast cancer, a 21-gene Recurrence Score of 20 and 1 positive node?

Would you recommend adjuvant chemotherapy?	
Yes	15
Yes, but I would offer OFS/ablation as an alternative	4
No	1



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Original Reports | Care Delivery

Identifying Patterns and Barriers in OncotypeDX Recurrence Score Testing in Older Patients With Early-Stage, Estrogen Receptor–Positive Breast Cancer: Implications for Guidance and Reimbursement

Dario Trapani, MD[1,2,3]; Qingchun Jin, MPH[4]; Caroline C. Block, MD[1,2,3]; Rachel A. Freedman, MD, MPH[1,2,3]; Nancy U. Lin, MD[1,2,3]; Paolo Tarantino, MD[1,2,3]; Elizabeth A. Mittendorf, MD, PhD[2,3,5]; Tari A. King, MD[2,3,5]; Susan C. Lester, MD, PhD[2,3,6]; Jane E. Brock, MD, PhD[2,3,6]; Nabihah Tayob, PhD[4]; Craig A. Bunnell, MD, MPH, MBA[1,2,3]; Sara M. Tolaney, MD, MPH[1,2,3]; and Harold J. Burstein, MD, PhD[1,2,3]

DOI https://doi.org/10.1200/OP.22.00731

JCO Oncol Pract 2023;19(8):560-70.

Use of genomic assays in the management of node-positive disease

Priyanka Sharma, MD

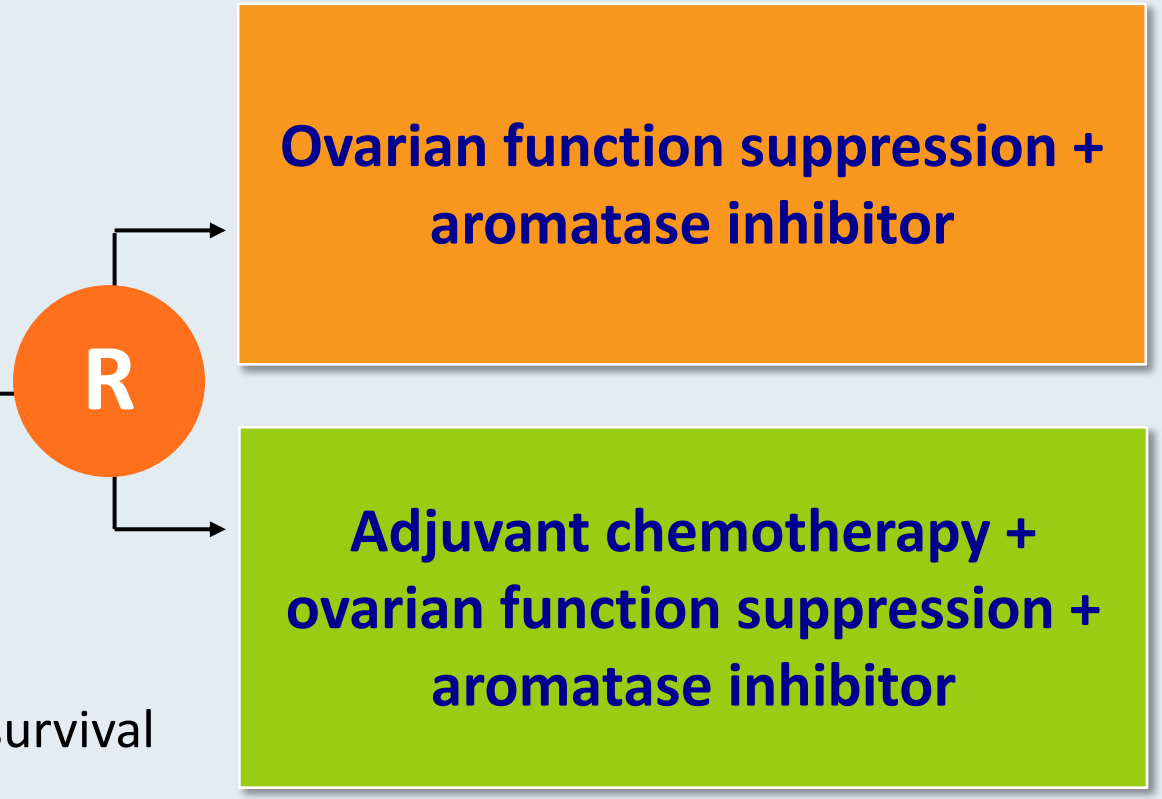
RTP
RESEARCH
TO PRACTICE

NRG-BR009 (OFSET): An Ongoing Phase III Trial Evaluating the Addition of Adjuvant Chemotherapy to Ovarian Function Suppression and ET for Premenopausal Patients with ER-Positive, HER2-Negative Breast Cancer and a Recurrence Score® (RS) of ≤25

Trial Identifier: NCT05879926

Estimated enrollment: N = 3,960

- Premenopausal
- HR-positive/HER2-negative
- pT1-3/N0-1/M0
- Oncotype DX® RS ≤25



Primary endpoint: Invasive breast cancer-free survival

ET = endocrine therapy

www.clinicaltrials.gov. Accessed December 2023; https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Breast_Trials.pdf

Selection of patients for adjuvant tamoxifen monotherapy versus ovarian suppression/ablation

Jane Lowe Meisel, MD

Paolo Tarantino, MD

Priyanka Sharma, MD

RTP
RESEARCH
TO PRACTICE

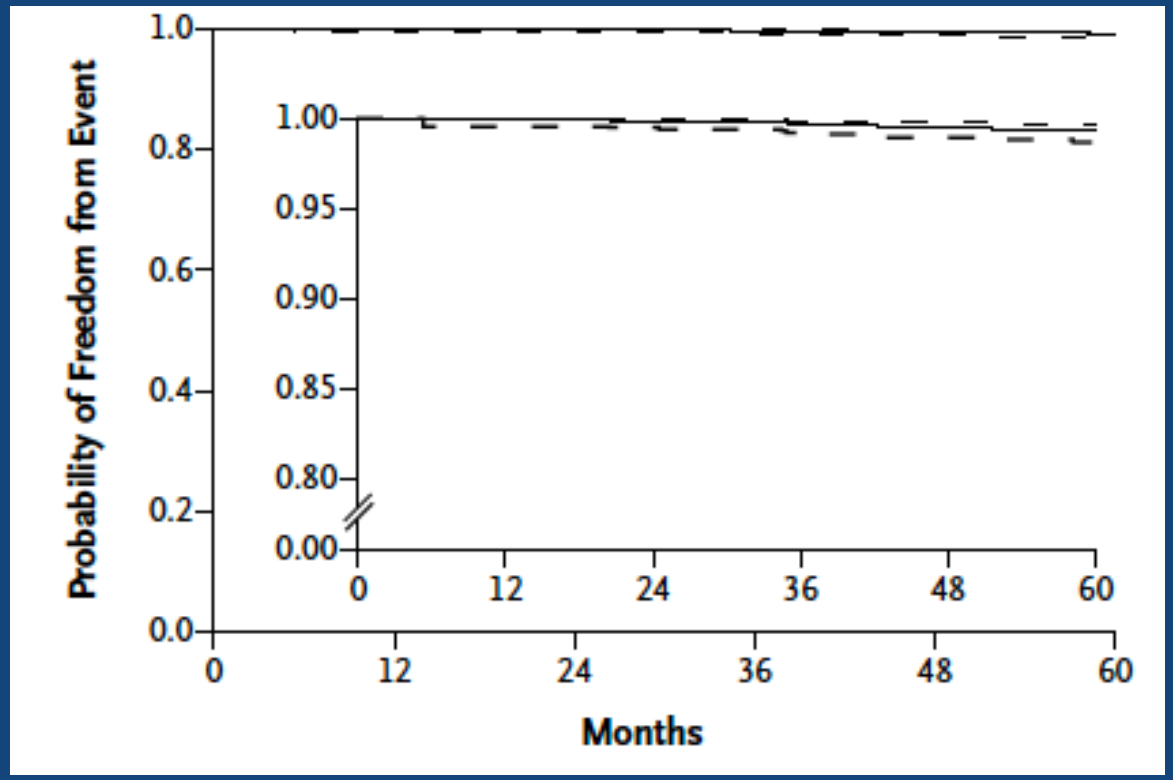
Role of Genomic Assays in Treatment Decision-Making for Localized ER-Positive, HER2-Negative Breast Cancer

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

- Long-term recurrence and survival data from the TAILORx assessing the 21-gene Recurrence Score® (RS) to guide adjuvant chemotherapy decisions for node-negative, ER-positive, HER2-negative early-stage BC and review of RSClin
- Review of Phase III RxPONDER trial data regarding the role of chemotherapy for patients with ER-positive, HER2-negative BC with 1 to 3 positive lymph nodes and a 21-gene RS of ≤25
- Other genomic assays in ER-positive early BC

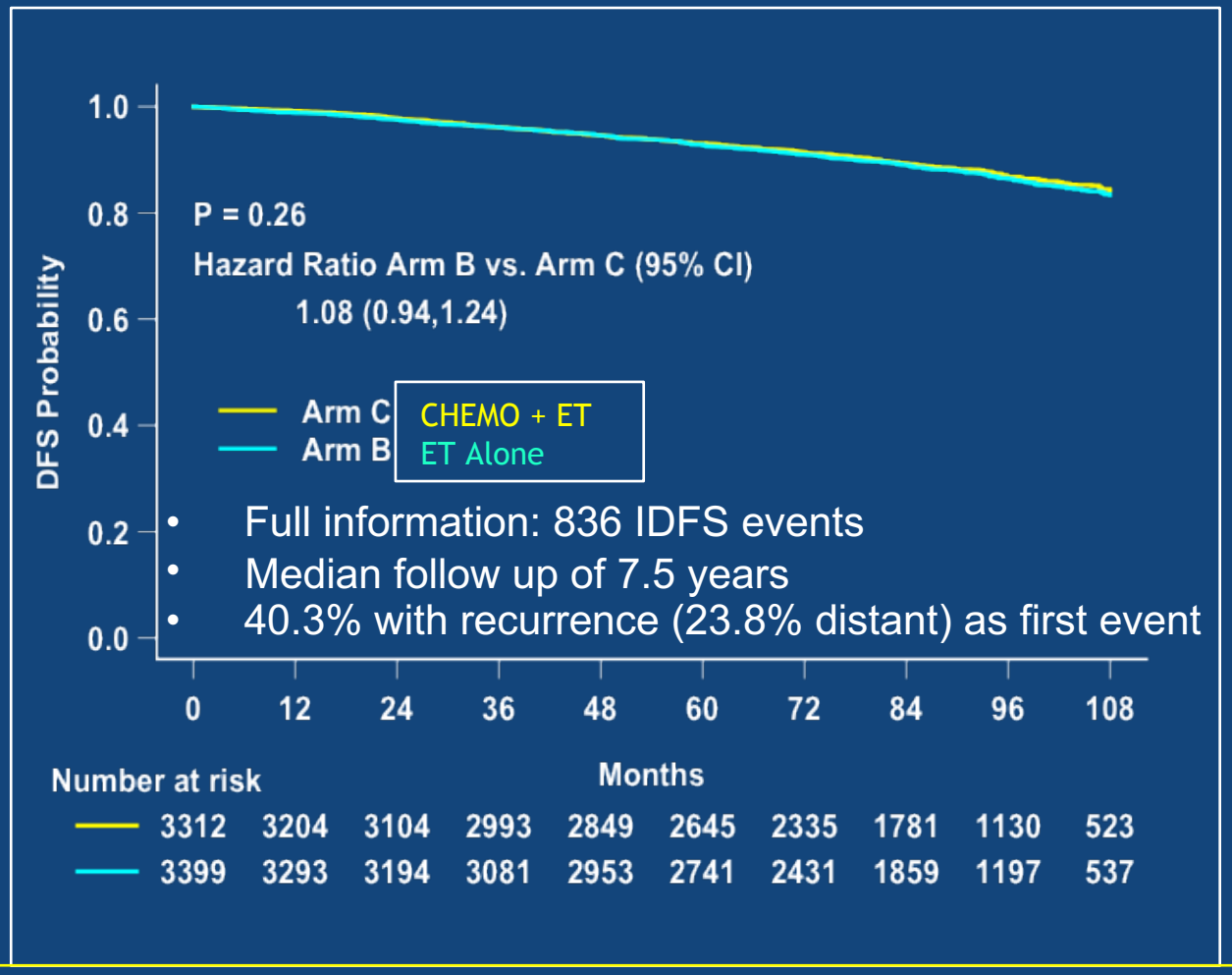
TAILORx: Summary of Key Results
Level 1A Evidence



Low RS 0-10 (16% study population)

DRFI Rate 99.3% at 5 years

(Sparano et al. NEJM 2015 [PMID: 2641234])



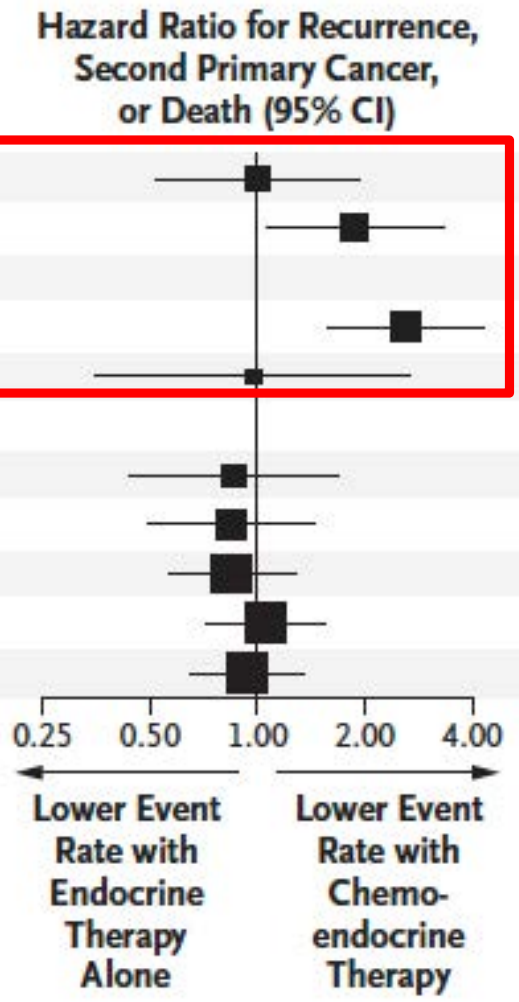
RS 11-25 (69% study population)

ET non-inferior to CET (HR 1.08, p=0.26)

(Sparano et al. NEJM 2018 [PMID: 29860917])

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

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



3-way treatment interaction (IDFS)

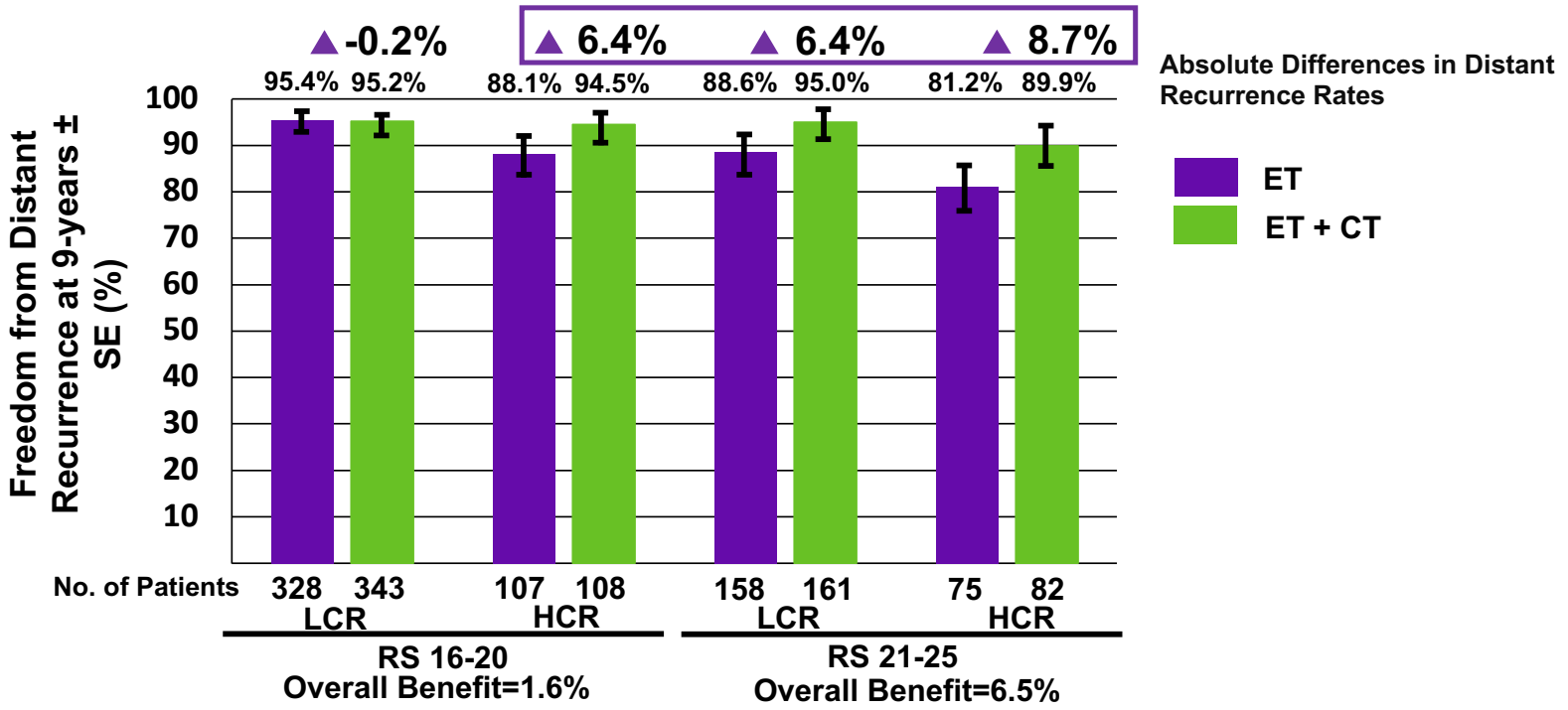
- Chemo-Age-RS (p=0.004)
- Chemo-Menopause-RS (p=0.02)

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

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

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

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

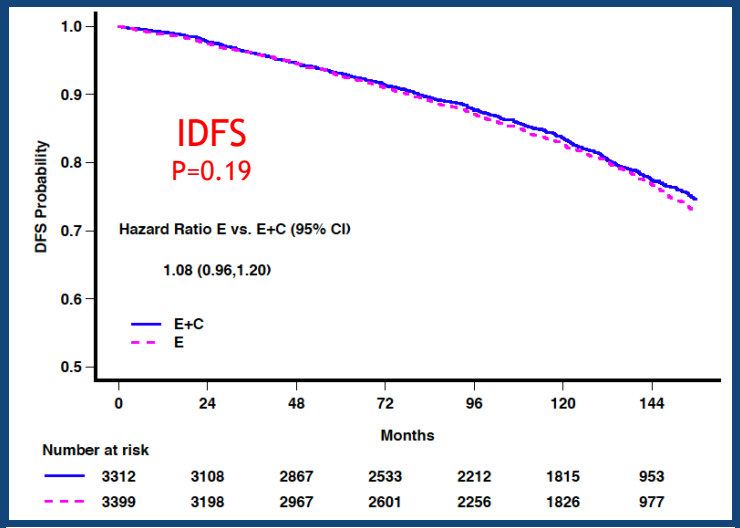


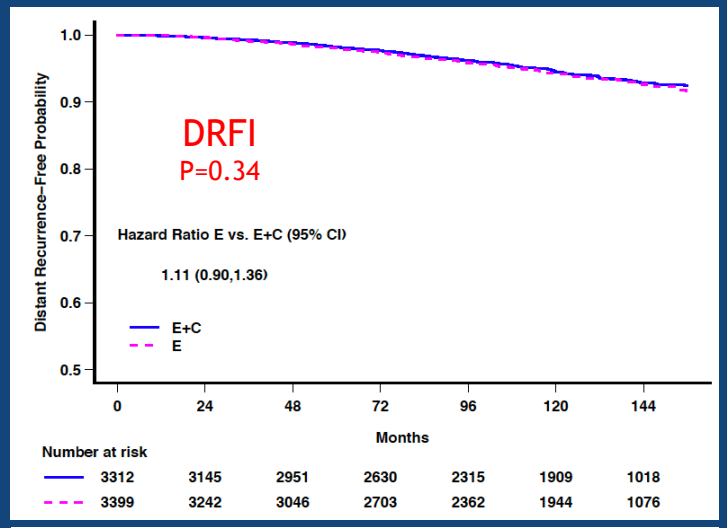
No CT benefit observed in women ≤50 years with RS result 16-20 & low clinical risk

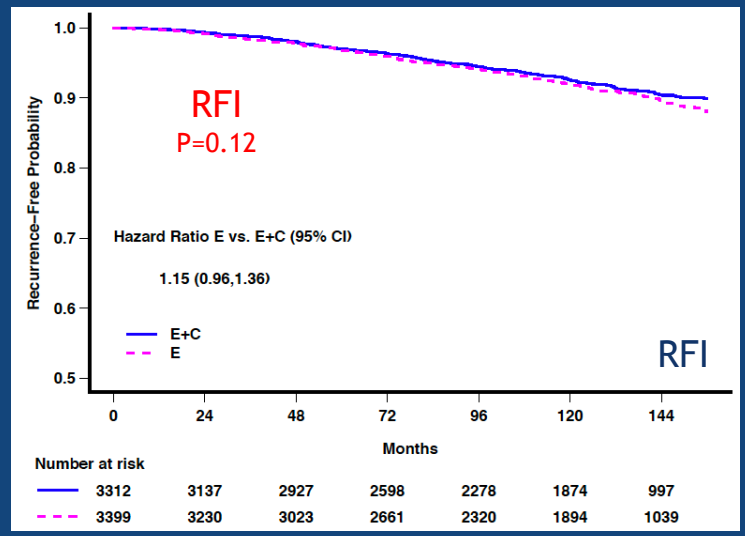
LCR: Low clinical risk
HCR: High clinical risk
RS: Recurrence Score® results
ET: Endocrine therapy
CT: Chemotherapy
ET + CT: Chemo-endocrine therapy

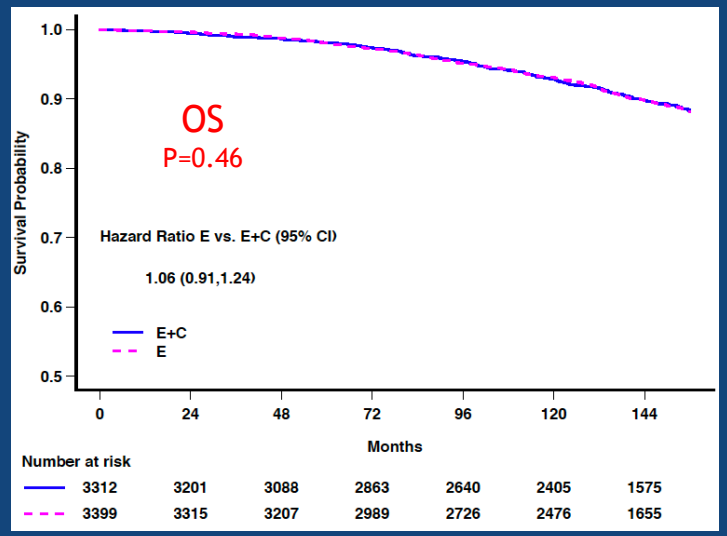
Sparano JA, et al. *N Engl J Med*. 2019;380(25):2395-2405.

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



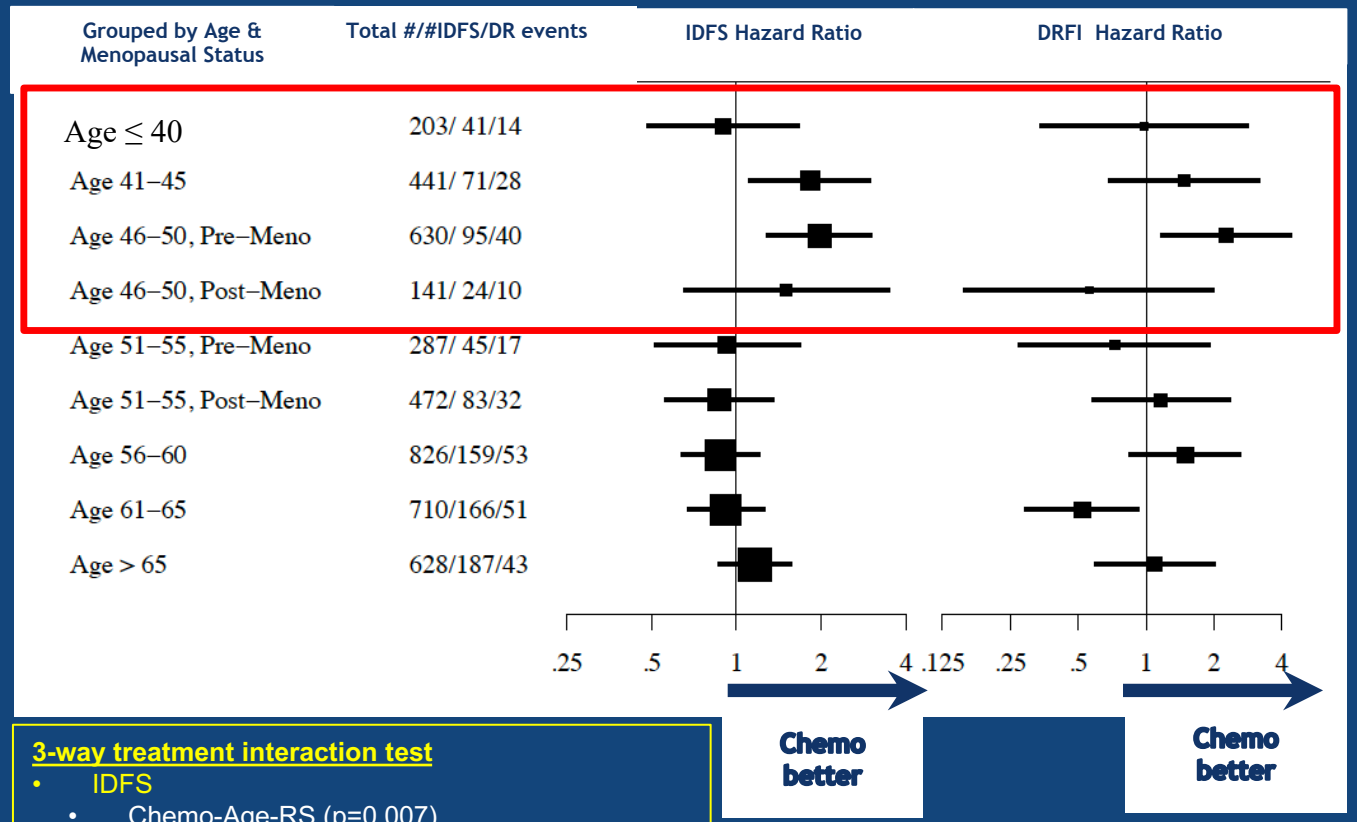






Primary trial conclusions unchanged: ET non-inferior to CET (N=6711)	
Event	Hazard Ratio: Arm B vs. C (95% CI)
IDFS	Primary analysis: 1.08 (0.94, 1.24, p=0.26)
	Updated analysis: 1.08 (0.96, 1.20)
DRFI	Primary analysis: 1.10 (0.85,1.41, p=0.48)
	Updated analysis: 1.11 (0.90, 1.36)
RFI	Primary analysis: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

Summary

- Long-term recurrence and survival data from TAILORx confirm that the addition of chemotherapy to endocrine therapy does not significantly improve IDFS, RFI, DRFI or OS in women with RS 11-25
  - Interaction between age and menopausal status:
    - No benefit in postmenopausal women
    - In age <50, small benefit in patients with RS 16-20 with larger benefit in patients with RS 21-25
    - Effects larger in age <50 with higher clinical risk

Outline

- Long-term recurrence and survival data from the TAILORx assessing the 21-gene Recurrence Score (RS) to guide adjuvant chemotherapy decisions for node-negative, ER-positive, HER2-negative early-stage BC and review of RSClin
- Review of Phase III RxPONDER trial data regarding the role of chemotherapy for patients with ER-positive, HER2-negative BC with 1 to 3 positive lymph nodes and a 21-gene RS of ≤25
- Other genomic assays in ER-positive early BC

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

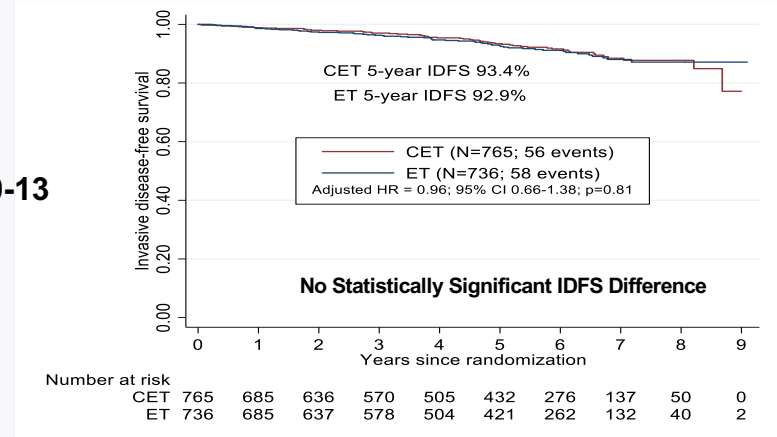
Kevin Kalinsky, William E Barlow, Julie R Gralow, Funda Meric-Bernstam, Kathy S Albain, Daniel F Hayes, Nancy U Lin, Edith A Perez, Lori J Goldstein, Stephen K Chia, Sukhbinder Dhesy-Thind, Priya Rastogi, Emilio Alba, Suzette Delaloge, Miguel Martin, Catherine M Kelly, Manuel Ruiz-Borrego, Miguel Gil 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

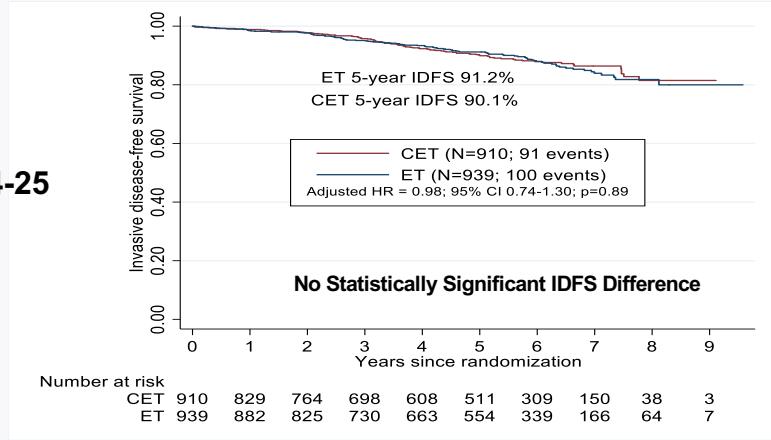
IDFS Stratified by Recurrence Score and Menopausal Status

Postmenopausal

RS 0-13

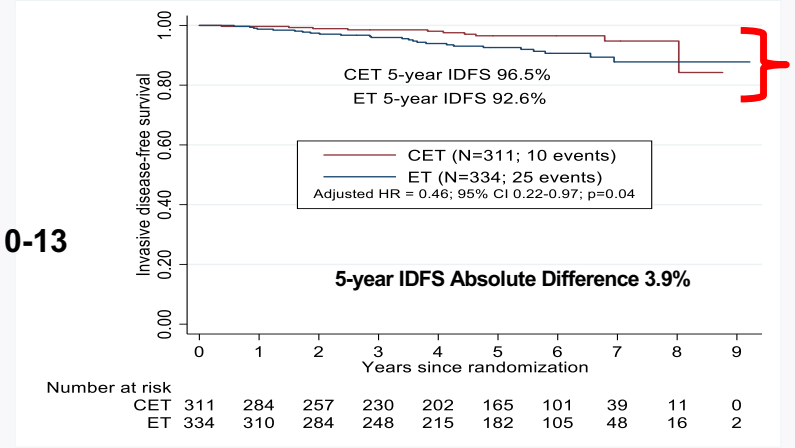


RS 14-25

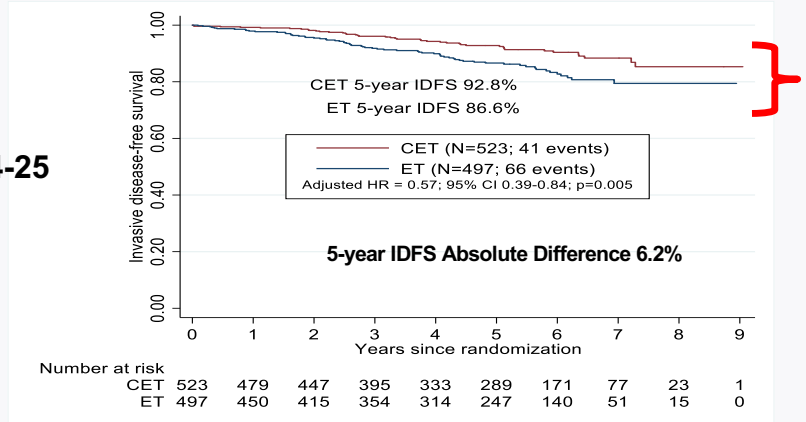


Premenopausal

RS 0-13



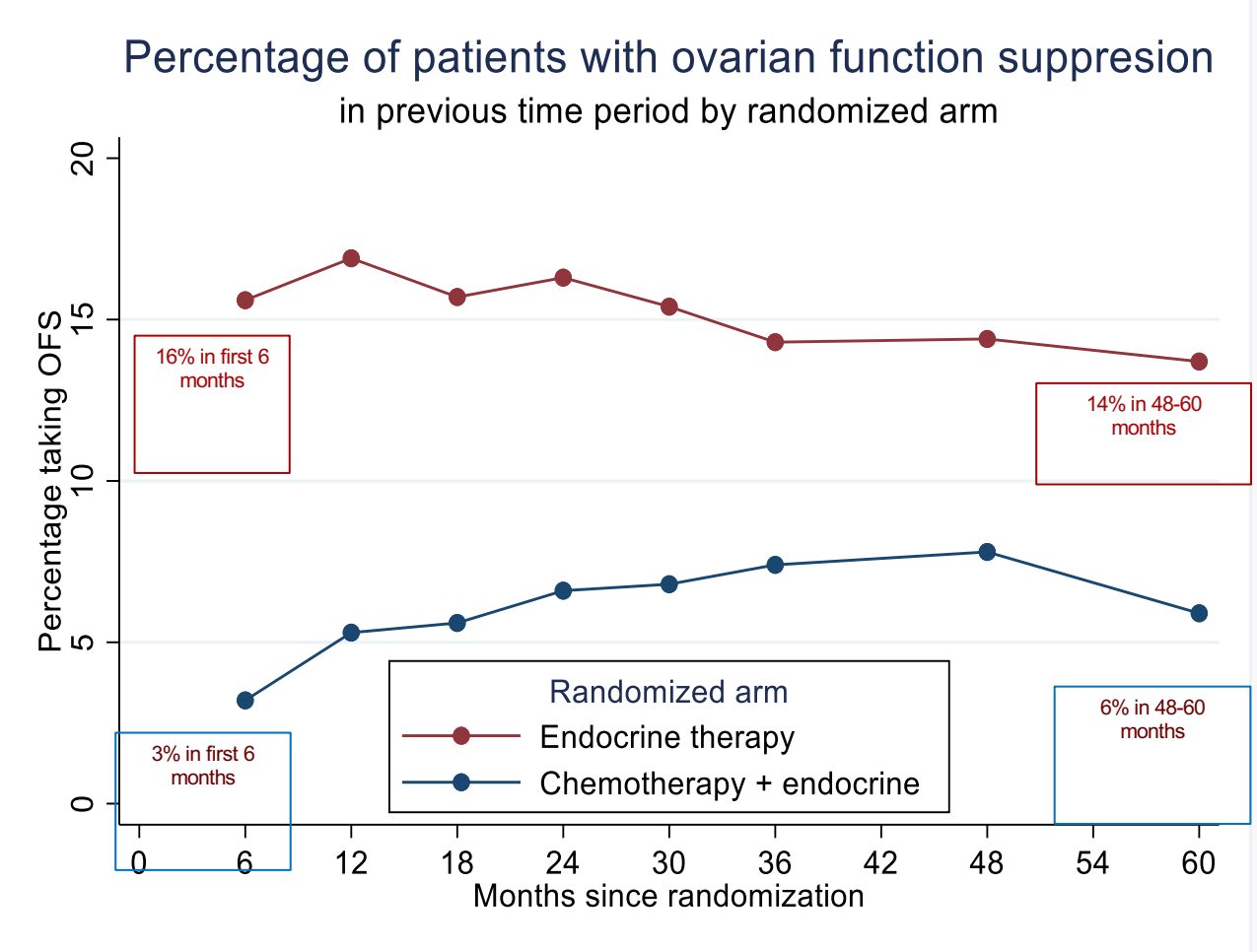
RS 14-25



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

Kalinsky et al SABCS 2021

OFS Rate in Premenopausal Pts in Tx Arms Over Time

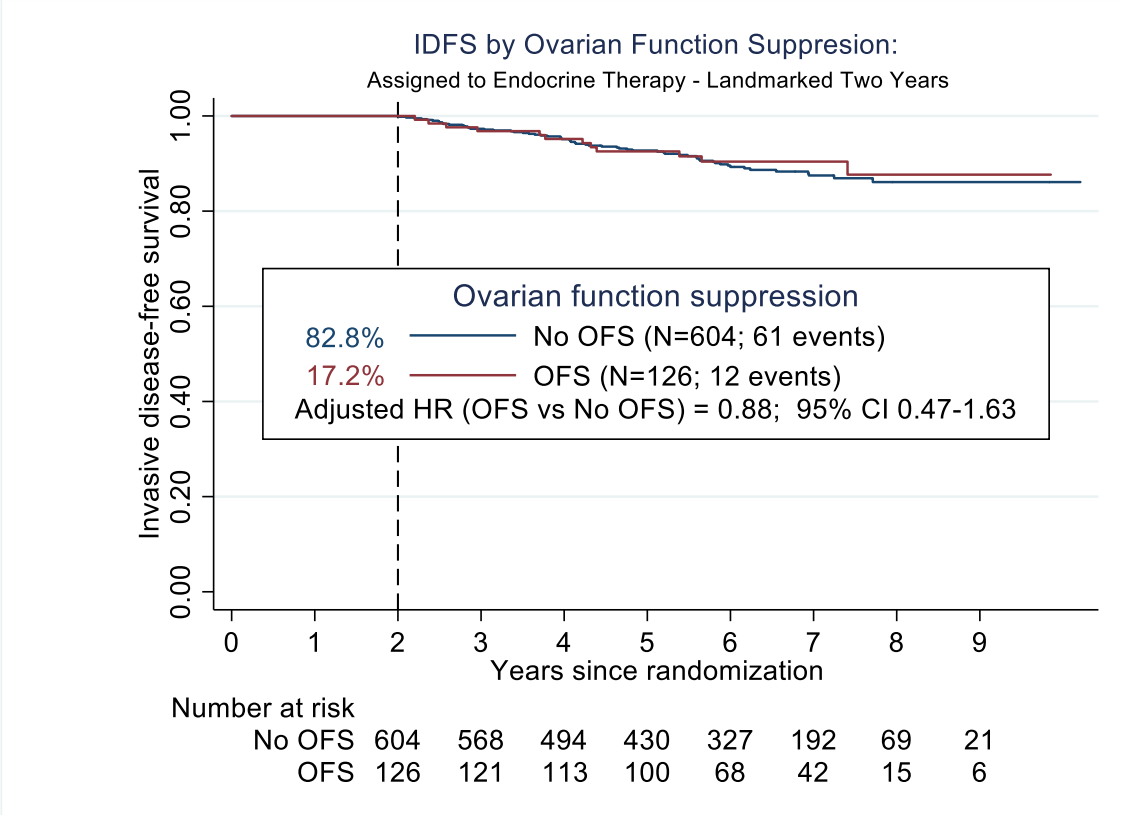


Though higher in endocrine therapy arm, OFS rate remains low and consistent in both arms

Site reported at fixed time points if premenopausal pts underwent OFS during previous time interval

Kalinsky et al SABCS 2021

Landmarked Two-Year IDFS by OFS or Not in Premenopausal Pts in Endocrine Tx Arm



OFS = medical suppression for at least two 6-month time intervals or b/l oophorectomy** in first 24 months

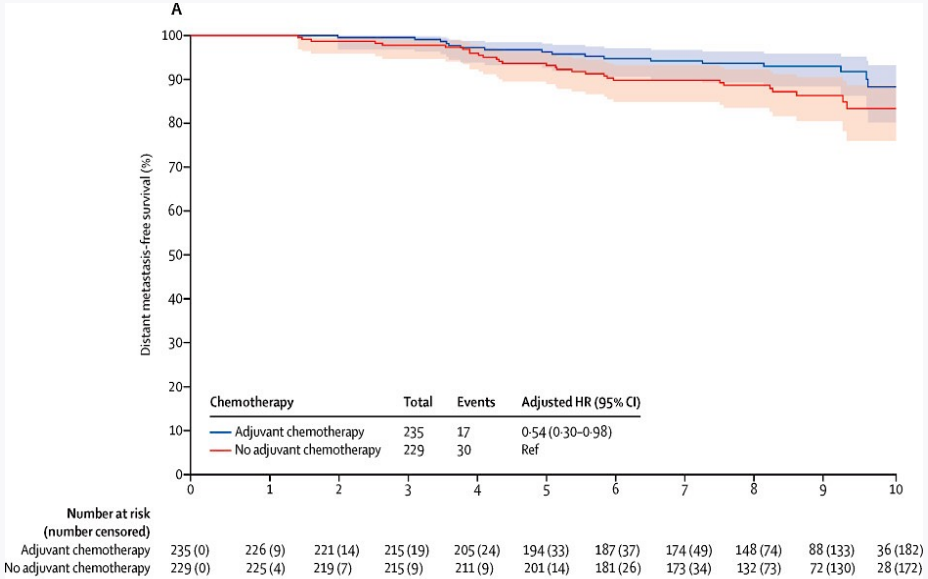
No IDFS difference in premenopausal women if OFS or not in first 24 months assigned to endocrine therapy

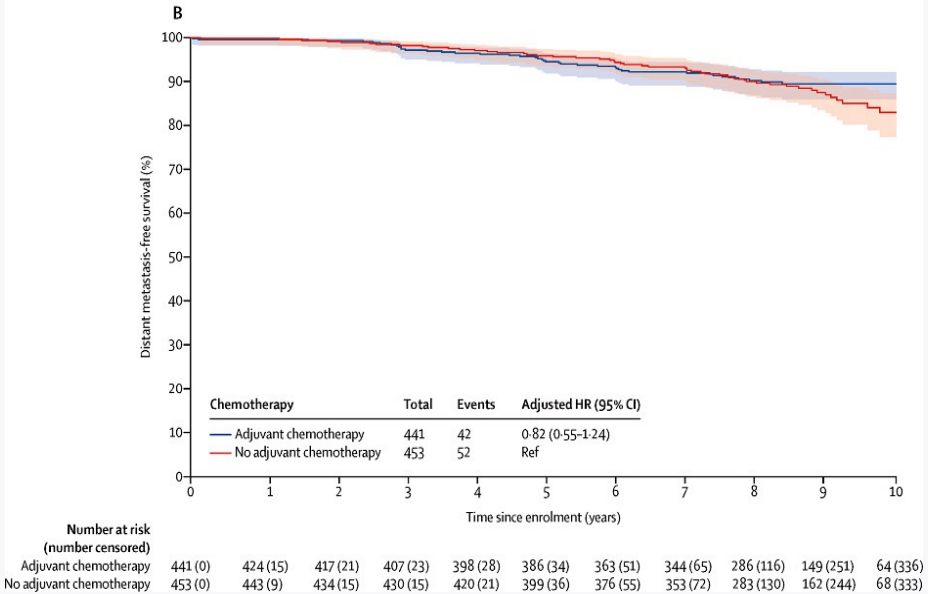
*Adjusted for RS

**4% in ET and 2% in CET s/p b/l oophorectomy in first 24 months

Kalinsky et al SABCS 2021

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





(A) Patients aged 50 years or younger
(B) Patients aged older than 50 years

Piccart Lancet Oncology 2021

Summary

- In RxPONDER, the addition of chemotherapy to endocrine therapy did not significantly improve IDFS
  - Similar to TAILORx, an effect of age and menopausal status continues to be seen:
    - No benefit in postmenopausal women
    - In age <50, clear benefit of chemotherapy regardless of RS
    - Similar findings in MINDACT
- In TAILORx, RxPONDER, and MINDACT, the predominant adjuvant hormonal therapy for premenopausal patients was tamoxifen (without OFS)
- NRG-BR009 will answer whether the addition of chemotherapy to optimal endocrine therapy (AI + OFS) significantly improves outcomes in premenopausal women with ER+/HER2- breast cancer

NRG-BR009 (PI, Terry Mamounas)

- Premenopausal; HR+/HER2- BC
- pN0 with RS 16-20 (high clinical risk) or RS 21-25
- pN1 with RS 0-25

Stratification

- Nodal Status (pN0 vs. pN1)
- RS (0-15 vs. 16-25)

Randomization

Chemotherapy + Ovarian Function Suppression + Aromatase Inhibitor* X 5 Years	Ovarian Function Suppression + Aromatase Inhibitor* X 5 Years

* Tamoxifen can be used if AI is not tolerated

Outline

- Long-term recurrence and survival data from the TAILORx assessing the 21-gene Recurrence Score (RS) to guide adjuvant chemotherapy decisions for node-negative, ER-positive, HER2-negative early-stage BC and review of RSClin
- Review of Phase III RxPONDER trial data regarding the role of chemotherapy for patients with ER-positive, HER2-negative BC with 1 to 3 positive lymph nodes and a 21-gene RS of ≤25
- Other genomic assays (MammaPrint®, Prosigna®) in ER-positive early BC

Evaluation of PAM50 intrinsic Subtypes in SOFT

2023 ASCO ANNUAL MEETING

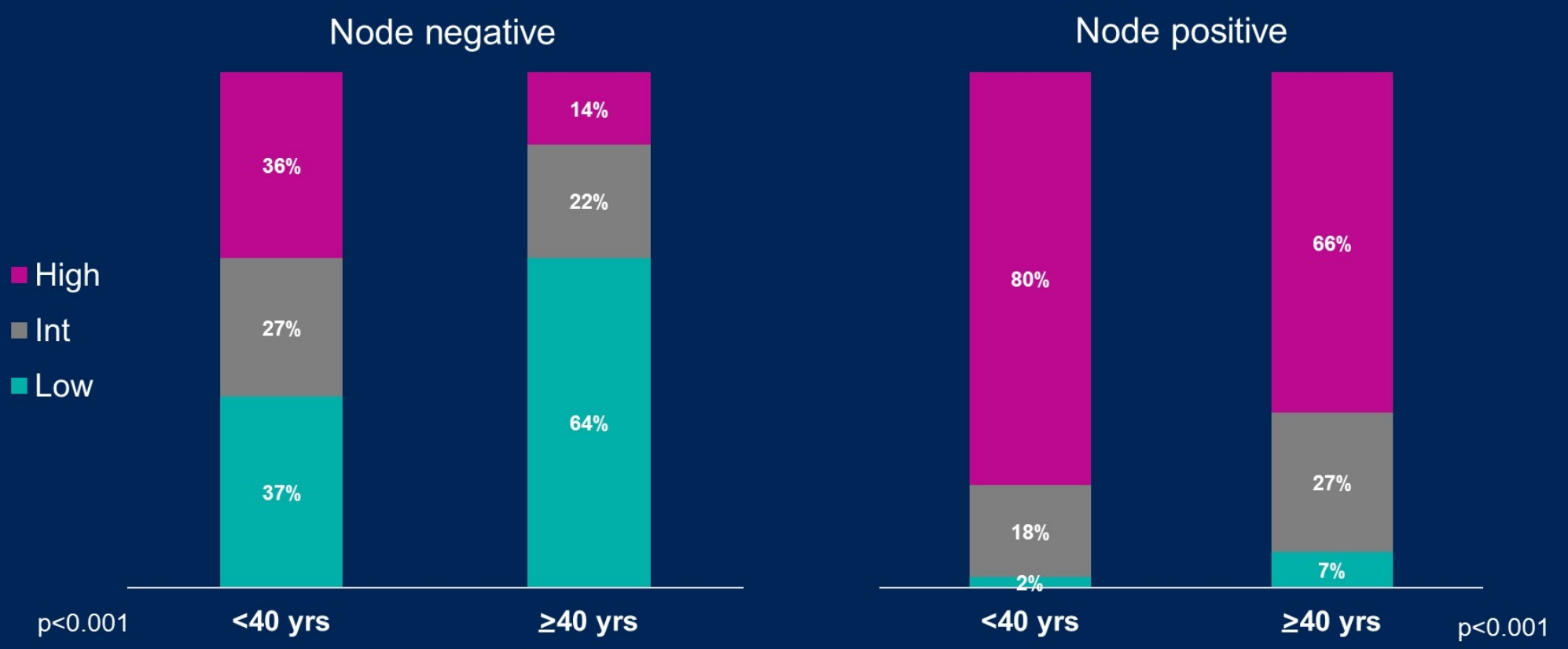
Evaluation of PAM50 intrinsic subtypes and ROR scores in HR+ HER2- breast cancers diagnosed in premenopausal women: a secondary analysis of the SOFT trial

Lauren C Brown[1,2], Stephen J Luen[1,2], Ramyar Molania[1,7], Franco Caramia[1], Peter Savas[1,2], Courtney Van Geelen[1], Nuria Chic[1], Gini F. Fleming[3], Rosita Kammler[4], Marco Colleoni[5], Giuseppe Viale[6], Terence P Speed[7,8], Meredith M Regan[9], Prudence A Francis[1], Sherene Loi[1,2]

1 Peter MacCallum Cancer Centre, Melbourne, Australia; 2 The Sir Peter MacCallum Department of Medical Oncology, University of Melbourne, Parkville, Australia; 3 Section of Hematology Oncology, The University of Chicago, Chicago, IL, USA; 4 International Breast Cancer Study Group, Coordinating Center, Central Pathology Office, Bern, Switzerland; 5 Division of Medical Senology, IEO, European Institute of Oncology IRCCS, Milan, Italy; 6 International Breast Cancer Study Group Central Pathology Office, IEO European Institute of Oncology IRCCS, University of Milan, Milan, Italy; 7 Bioinformatics Division, Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia; 8 School of Mathematics and Statistics, University of Melbourne, Victoria, Australia; 9 Division of Biostatistics, International Breast Cancer Study Group Statistical Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

PRESENTED BY: LAUREN C. BROWN, LAURENC.BROWN@PETERMAC.ORG

PAM50 High-Risk Subgroups More Common in Very Young Women



Score categories

Node negative: Low 0-40 Int. 41-60 High. 61-100

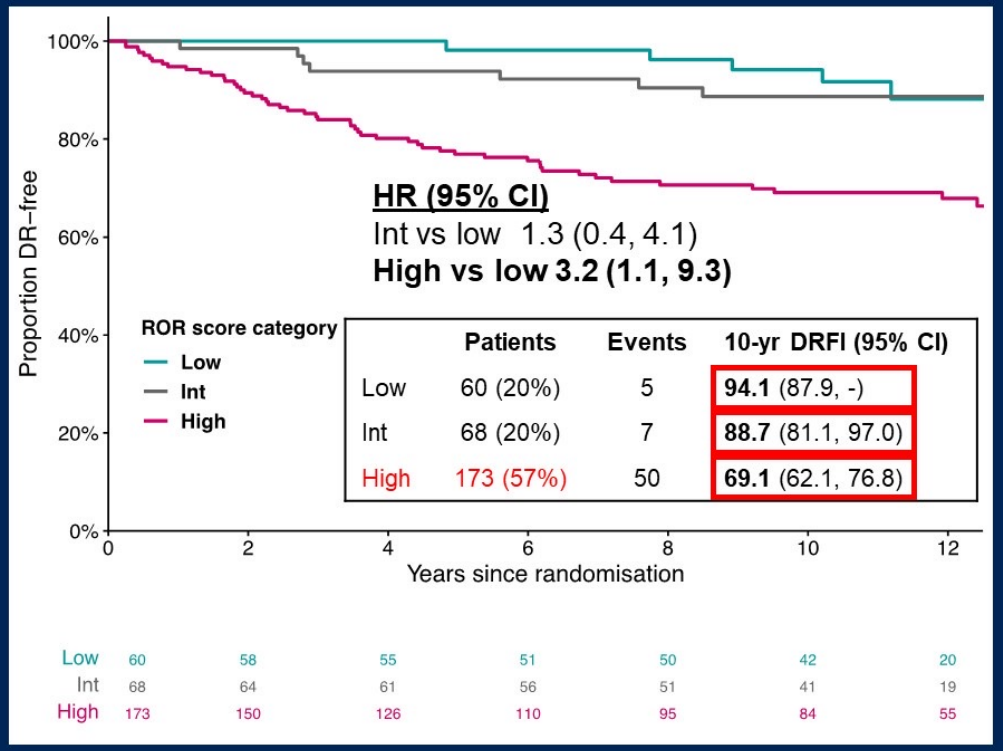
Node 1-3 positive: Low 0-15 Int. 16-40 High. 41-100; all N>4 were high risk

PRESENTED BY: LAUREN C. BROWN, LAURENC.BROWN@PETERMAC.ORG

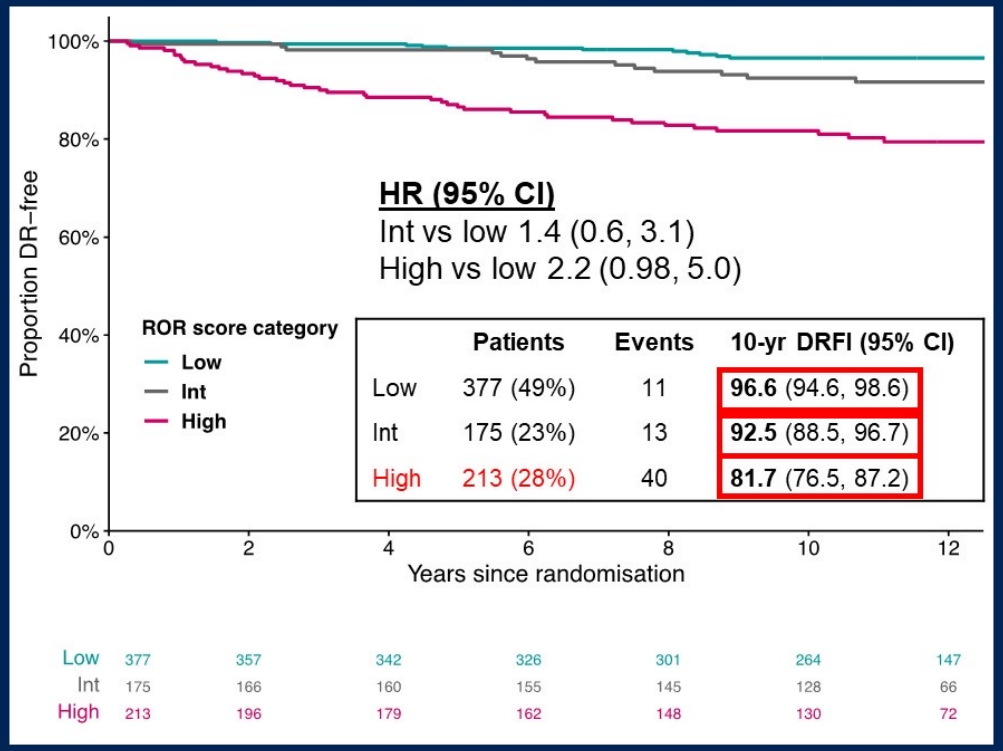
PAM50 ROR and Prognosis in Very Young vs Young Women

PAM50 ROR categories and prognosis: very young vs young

Very young, <40yrs n=301 (28%)



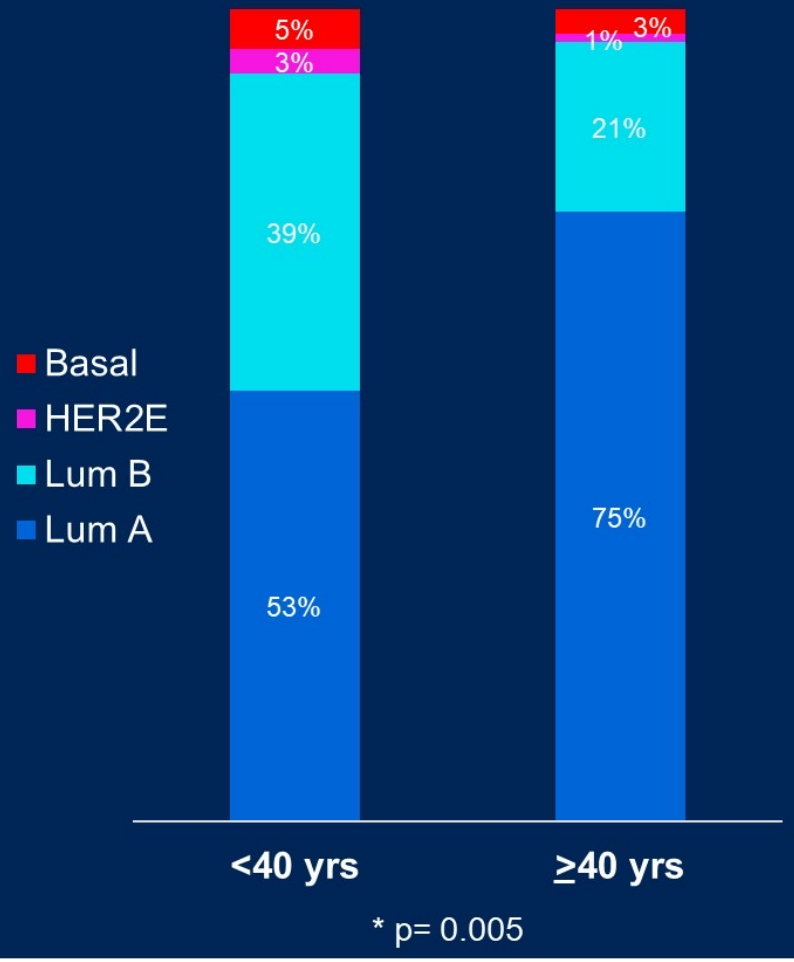
Young, ≥40yrs n=765 (72%)



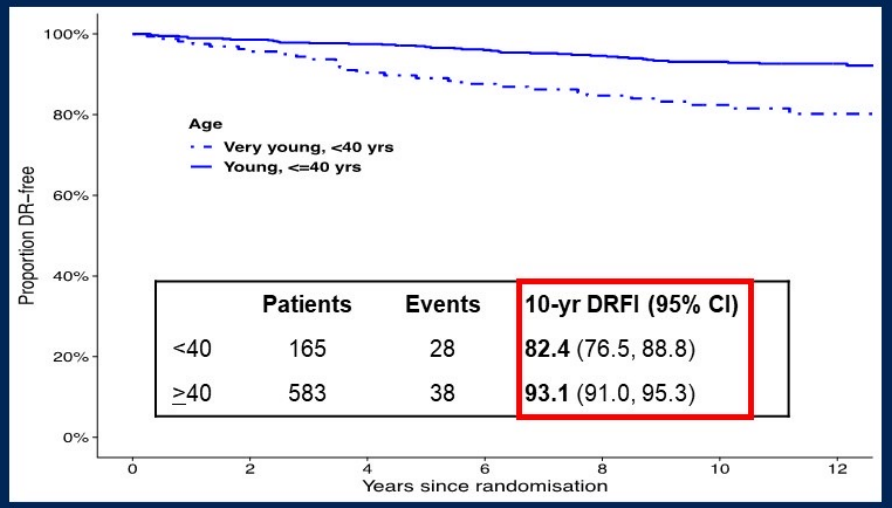
PRESENTED BY: LAUREN C. BROWN, LAURENC.BROWN@PETERMAC.ORG

PAM50 Intrinsic Subtypes and Prognosis

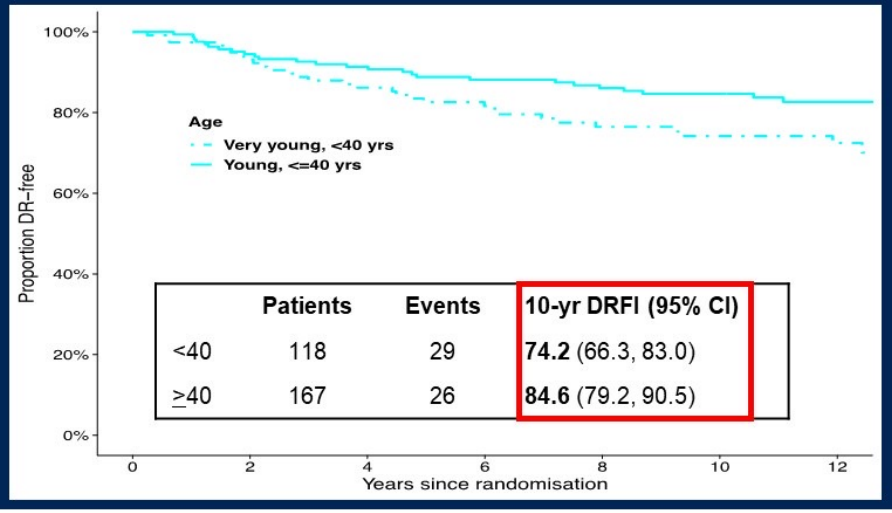
PAM50 Intrinsic subtype distribution and prognosis by age



Luminal A, <40yr vs ≥40yr



Luminal B, <40yr vs ≥40yr



PRESENTED BY: LAUREN C. BROWN, LAURENC.BROWN@PETERMAC.ORG

Summary

- SOFT PAM50 ROR scores demonstrate that a higher proportion of very young women (<40) have higher-risk tumors (luminal B, basal, and HER2 enriched)
- Higher frequency of homologous recombination deficiency (HRD) genomic features in patients <40 years of age compared with patients ≥40 years, with frequency increasing in patients <35 years of age at randomization[1]
- The totality of these data suggest that while optimal endocrine therapy (AI + OFS) is likely to improve outcomes in very young women (compared to tamoxifen alone), ER+/HER2- BC in very young women is a different disease and a subset may derive benefit from chemotherapy (NRG-BR009)

1. S.J. Luen et al. Annals of Oncology 2023

Agenda

Module 1: Role of Genomic Assays in Treatment Decision-Making for Localized ER-Positive, HER2-Negative Breast Cancer — Dr Goetz

Module 2: Integration of Ovarian Function Suppression into the Management of Breast Cancer in Premenopausal Patients — Dr Burstein

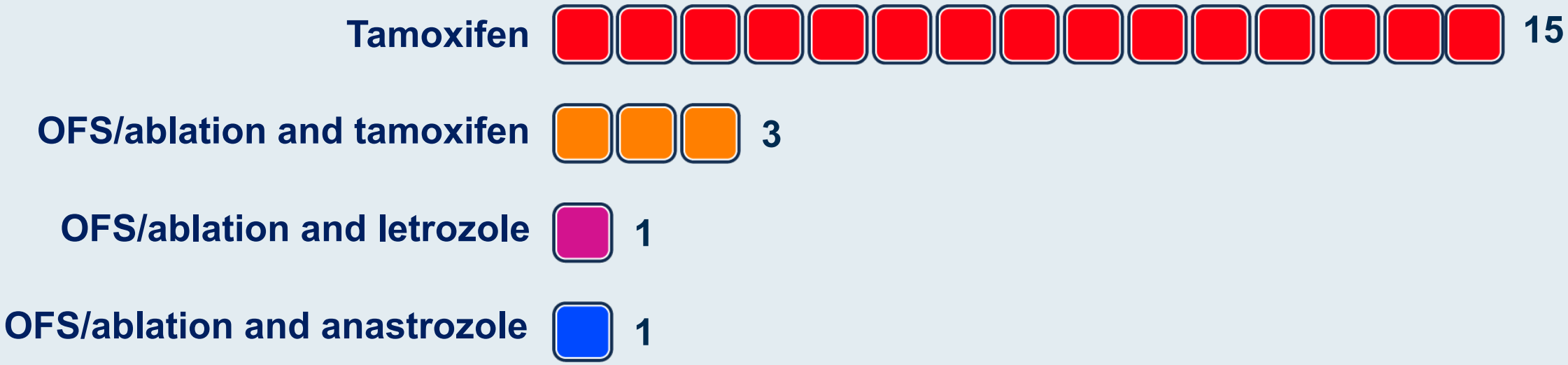
Module 3: Role of CDK4/6 Inhibitors and Other Novels Agents in Therapy for ER-Positive Localized Breast Cancer — Dr Hurvitz

Module 4: Optimizing the Use of Neoadjuvant and Adjuvant Therapy for Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 5: Emerging Role of Circulating Tumor DNA Evaluation in the Management of Breast Cancer — Dr Pusztai

Which adjuvant endocrine treatment would you most likely recommend for a 40-year-old premenopausal patient with ER-positive, HER2-negative, node-negative localized breast cancer and a 21-gene Recurrence Score® of 8?

Would you recommend adjuvant chemotherapy?	
No	20



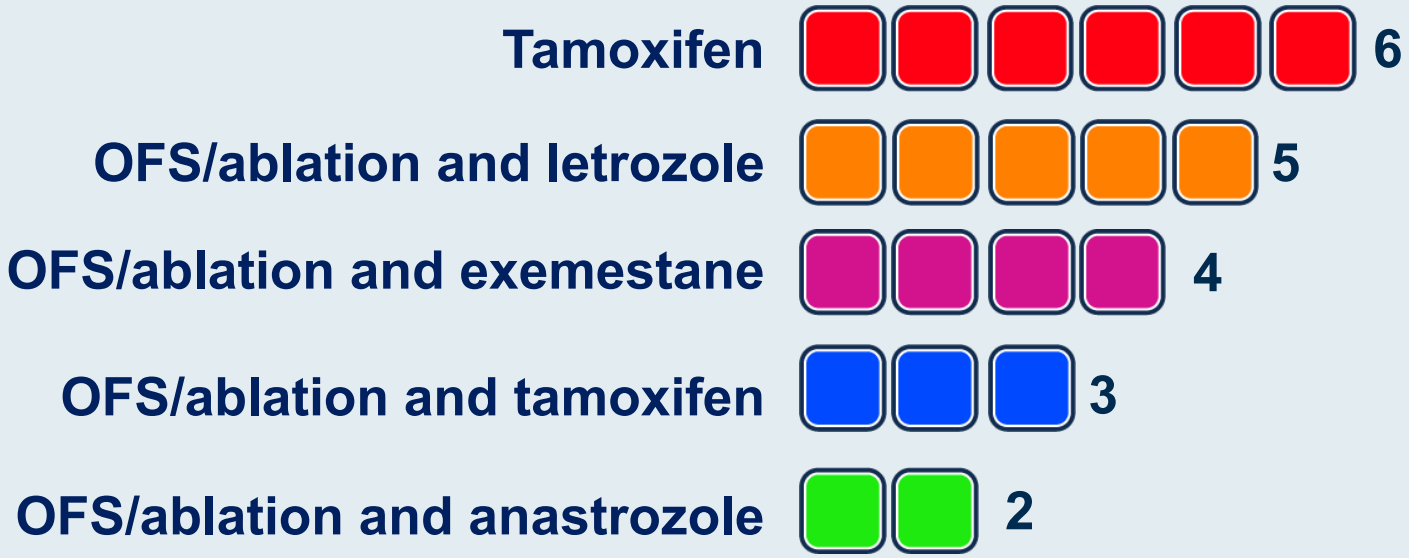
OFS = ovarian function suppression

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Which adjuvant endocrine treatment would you most likely recommend for a 40-year-old premenopausal patient with ER-positive, HER2-negative, node-negative localized breast cancer and a 21-gene Recurrence Score of 20?

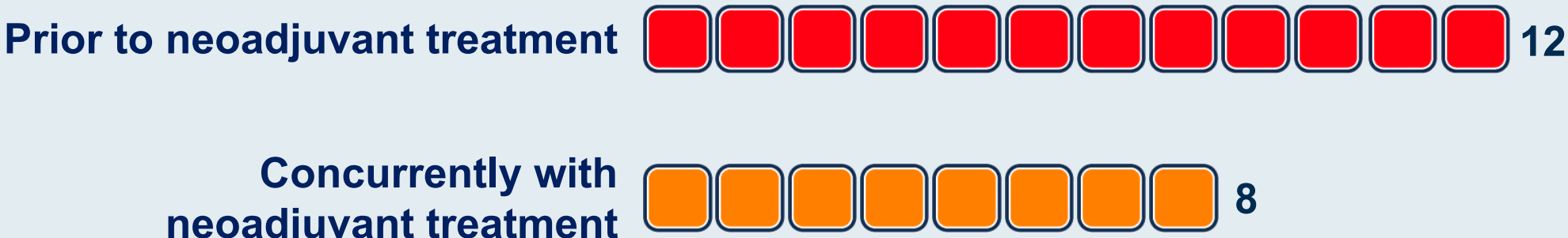
Would you recommend adjuvant chemotherapy?	
Yes, but I would offer OFS/ablation as an alternative	10
Yes	5
No	5



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

A 28-year-old premenopausal woman with a 2.8-cm, ER/PR-positive, HER2-negative infiltrating ductal carcinoma who is interested in preserving fertility is going to receive neoadjuvant chemotherapy/pembrolizumab. When, if at all, would you initiate a GnRHa?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Ovarian function suppression to minimize chemotherapy-induced ovarian damage

Jane Lowe Meisel, MD

RTP
RESEARCH
TO PRACTICE

Ovarian Function Suppression in Early Breast Cancer

Harold J. Burstein, MD, PhD

@drhburstein

hburstein@partners.org

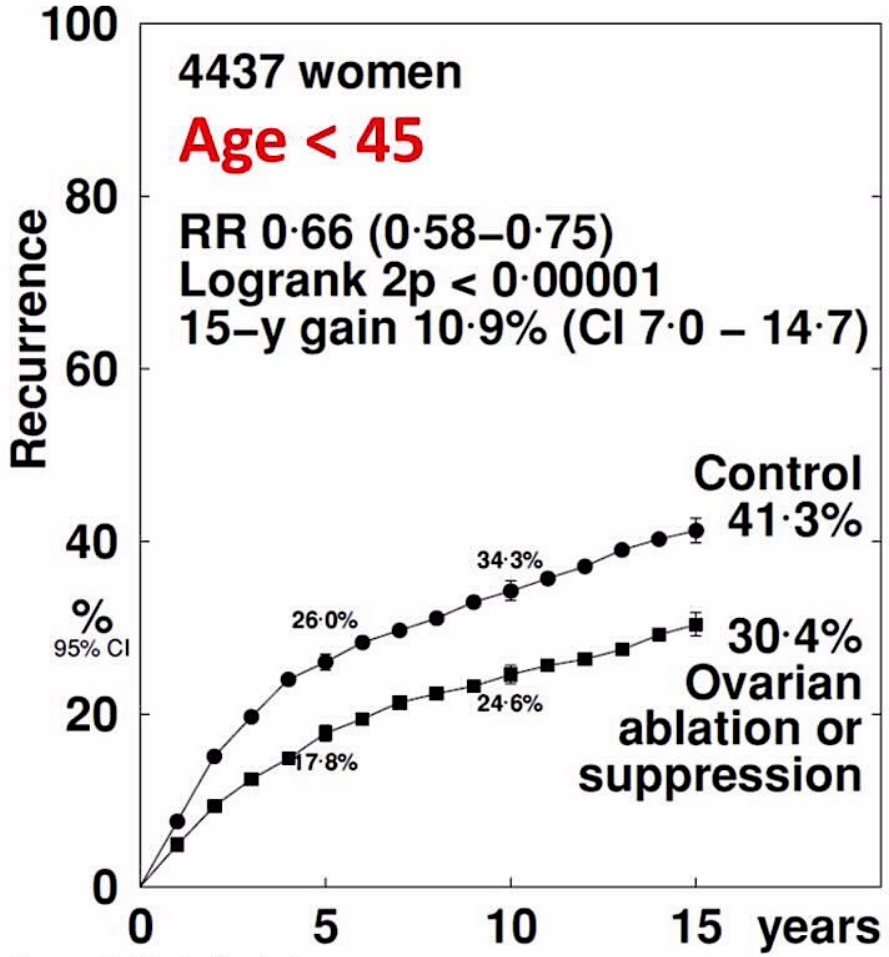
2023 ASCO ANNUAL MEETING

Effects of ovarian ablation or suppression on breast cancer recurrence and survival: patient-level meta-analysis of 14,999 pre-menopausal women in 25 randomized trials

Early Breast Cancer Trialists Collaborative Group (EBCTCG)

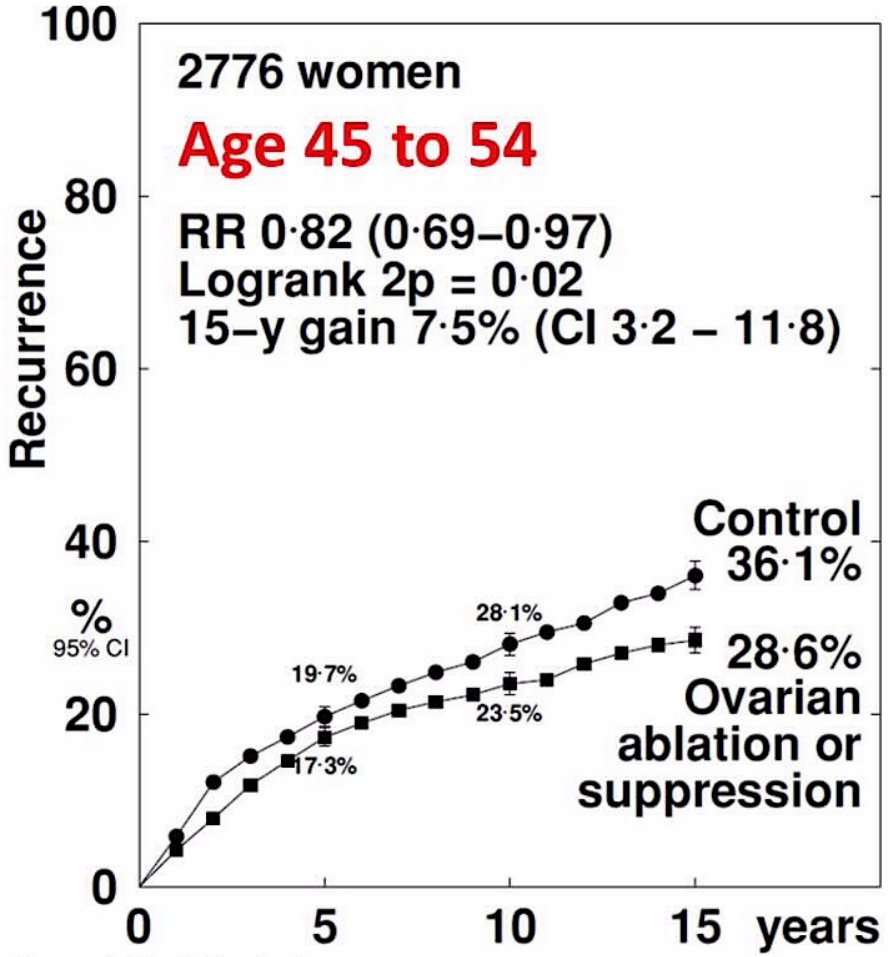
Writing Committee: Richard Gray, Rosie Bradley, Jeremy Braybrooke, Mike Clarke, Robert Hills, Richard Peto, Jonas Bergh, Sandra Swain, Rodrigo Arriagada, Judith Bliss, Allan Hackshaw, Hyun-Ah Kim, Woo Chul Noh, John Yarnold, Nancy Davidson, Prudence Francis, Meredith Regan

Ovarian ablation/suppression vs not: Recurrence (A) No chemotherapy or premenopausal after



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	4·52 (412 / 9119)	1·86 (100 / 5384)	1·50 (41 / 2736)	1·11 (32 / 2885)
Control	5·77 (498 / 8637)	2·35 (110 / 4678)	2·41 (53 / 2201)	1·40 (30 / 2137)
Rate ratio, from	0·64 CI 0·55 – 0·75	0·75 CI 0·55 – 1·02	0·64 CI 0·40 – 1·01	0·65 CI 0·32 – 1·31
(O–E) / V	–66·8 / 149·9	–11·4 / 39·8	–8·0 / 17·6	–3·4 / 7·7



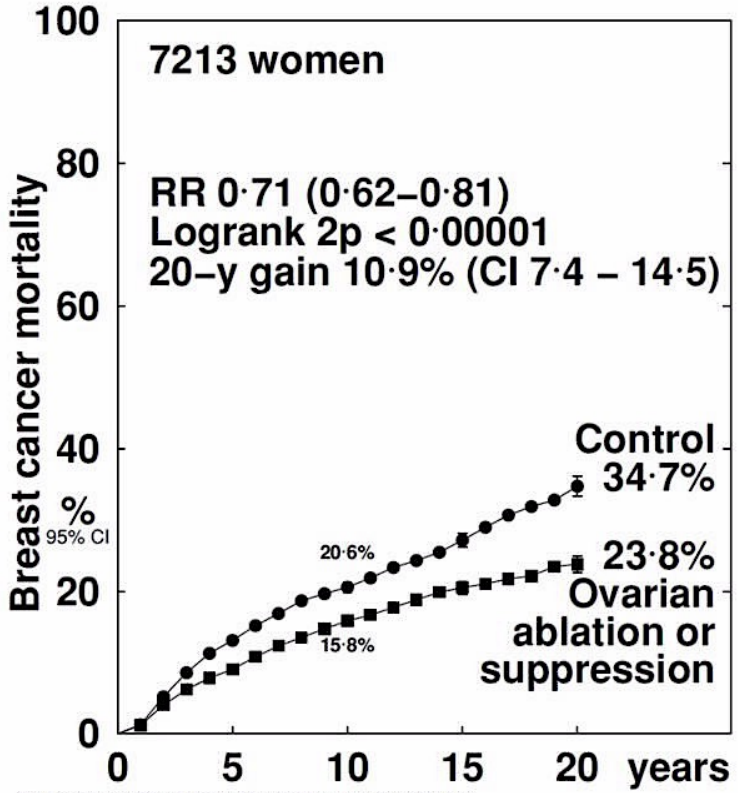
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	4·17 (255 / 6113)	1·72 (78 / 4548)	1·45 (37 / 2555)	1·52 (40 / 2635)
Control	4·17 (242 / 5807)	2·08 (88 / 4238)	2·27 (47 / 2072)	1·37 (24 / 1756)
Rate ratio, from	0·87 CI 0·69 – 1·08	0·71 CI 0·50 – 1·02	0·63 CI 0·38 – 1·05	1·25 CI 0·62 – 2·52
(O–E) / V	–11·0 / 76·4	–10·1 / 30·1	–6·9 / 15·1	1·7 / 7·7

Gray R et al. ASCO 2023;Abstract 503.

Ovarian ablation/suppression vs not: Mortality
(A) No chemotherapy or premenopausal after

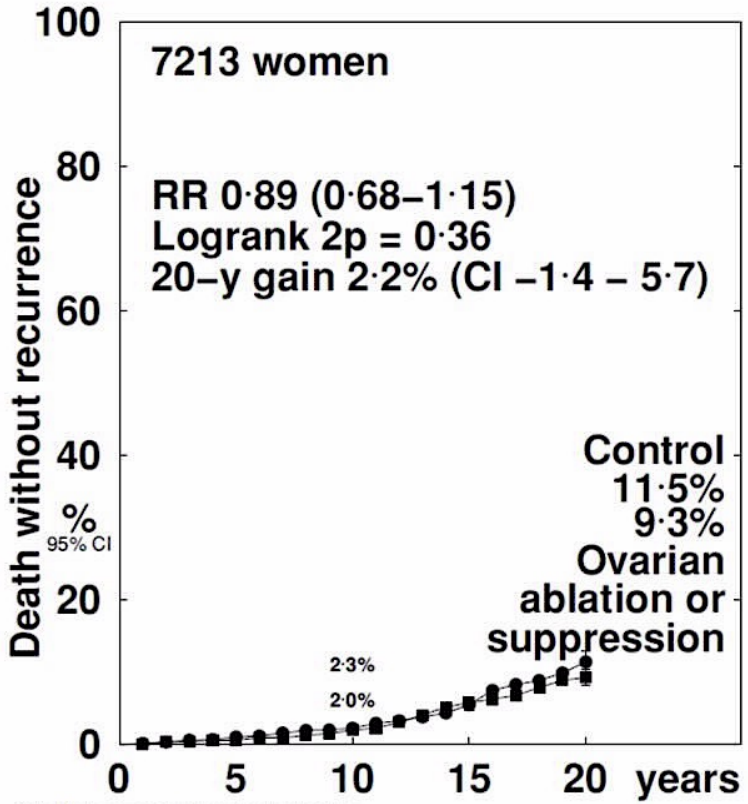
Breast cancer mortality



Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 9	Years 10 – 19	Year 20+
Abl./suppr.	2·01 ci 1·84 – 2·18	1·18 ci 0·95 – 1·41	1·30 ci 0·93 – 1·68
Control	2·19 ci 2·01 – 2·37	1·78 ci 1·47 – 2·09	1·47 ci 1·01 – 1·93
Rate ratio, from	0·74 ci 0·63 – 0·86	0·58 ci 0·42 – 0·81	0·82 ci 0·43 – 1·56
(O–E) / V	–51·7 / 169·2	–19·5 / 35·9	–1·9 / 9·4

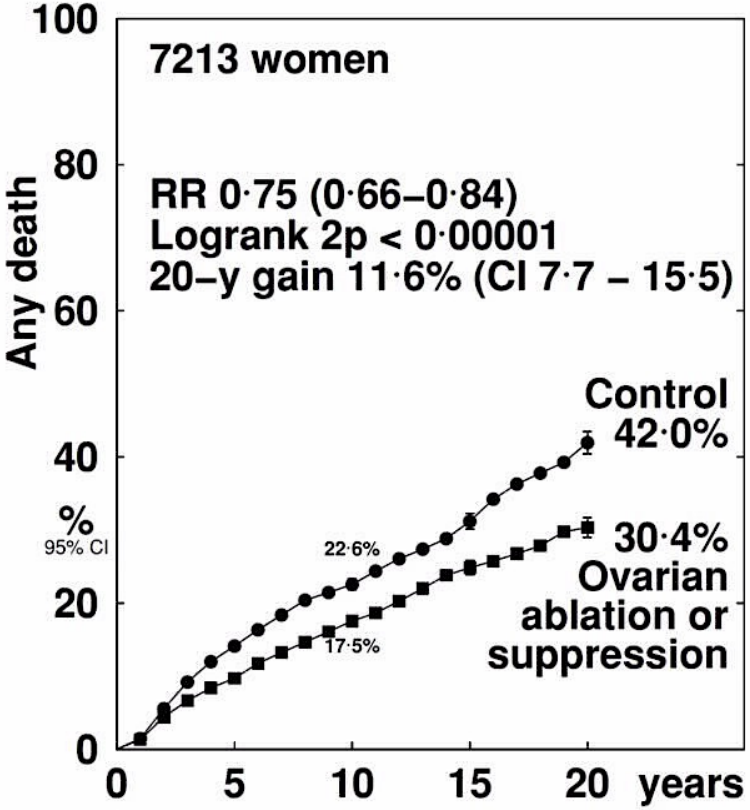
Death without recurrence



Death–without–recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 9	Years 10 – 19	Year 20+
Abl./suppr.	0·19 (49 / 25165)	0·73 (56 / 7648)	4·32 (146 / 3376)
Control	0·21 (50 / 23362)	0·86 (51 / 5905)	4·32 (106 / 2452)
Rate ratio, from	0·75 ci 0·46 – 1·22	0·89 ci 0·54 – 1·47	0·98 ci 0·67 – 1·44
(O–E) / V	–4·7 / 16·2	–1·8 / 15·4	–0·5 / 26·1

All cause mortality



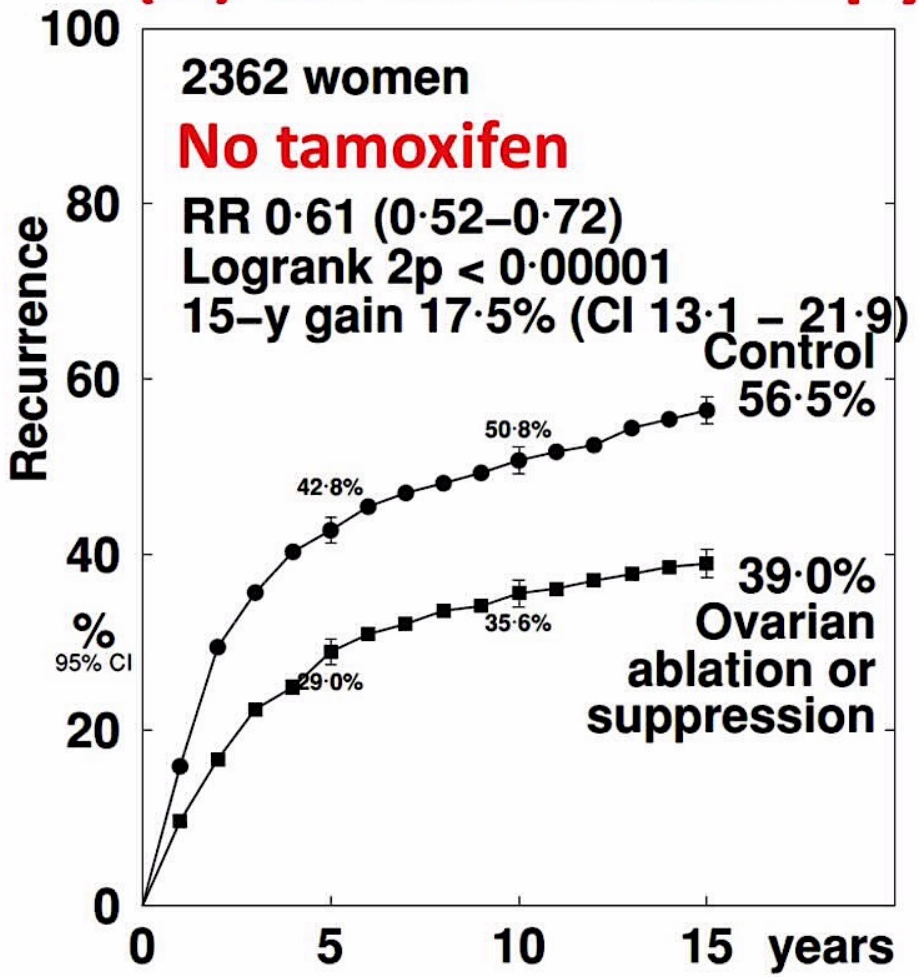
Death rates (% / year) and logrank analyses

Allocation	Years 0 – 9	Years 10 – 19	Year 20+
Abl./suppr.	2·22 (602 / 27161)	1·89 (160 / 8488)	5·40 (193 / 3573)
Control	2·43 (628 / 25843)	2·55 (178 / 6991)	5·52 (145 / 2625)
Rate ratio, from	0·74 ci 0·64 – 0·85	0·66 ci 0·50 – 0·87	0·93 ci 0·67 – 1·30
(O–E) / V	–56·4 / 185·5	–21·3 / 51·3	–2·4 / 35·5

Gray R et al. ASCO 2023;Abstract 503.

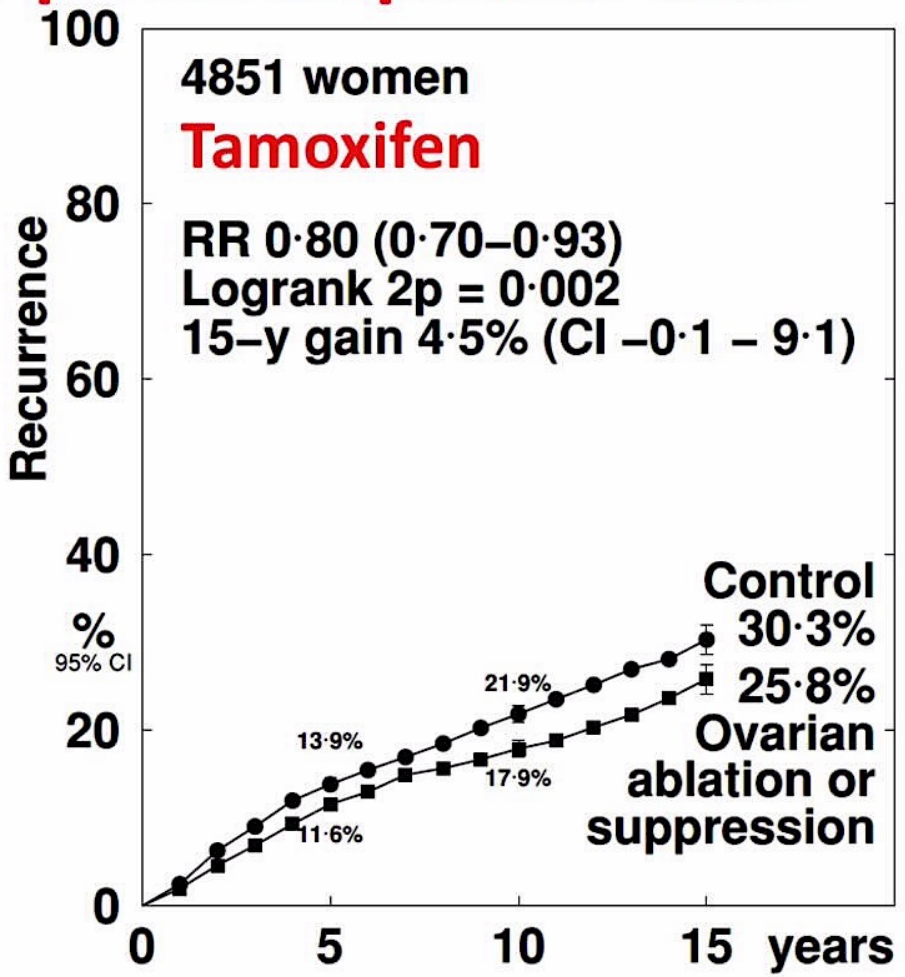
Ovarian ablation/suppress. vs not: Recurrence by tamoxifen use

(A) No chemotherapy or premenopausal after



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	8·37 (412 / 4921)	2·22 (82 / 3691)	1·26 (37 / 2945)	1·28 (69 / 5395)
Control	10·82 (427 / 3945)	2·90 (80 / 2757)	2·47 (52 / 2103)	1·37 (52 / 3785)
Rate ratio, from	0·60 CI 0·49 – 0·72	0·66 CI 0·43 – 0·99	0·47 CI 0·27 – 0·81	0·85 CI 0·51 – 1·42
(O–E) / V	–51·8 / 100·0	–9·6 / 22·8	–9·8 / 12·9	–2·4 / 14·3



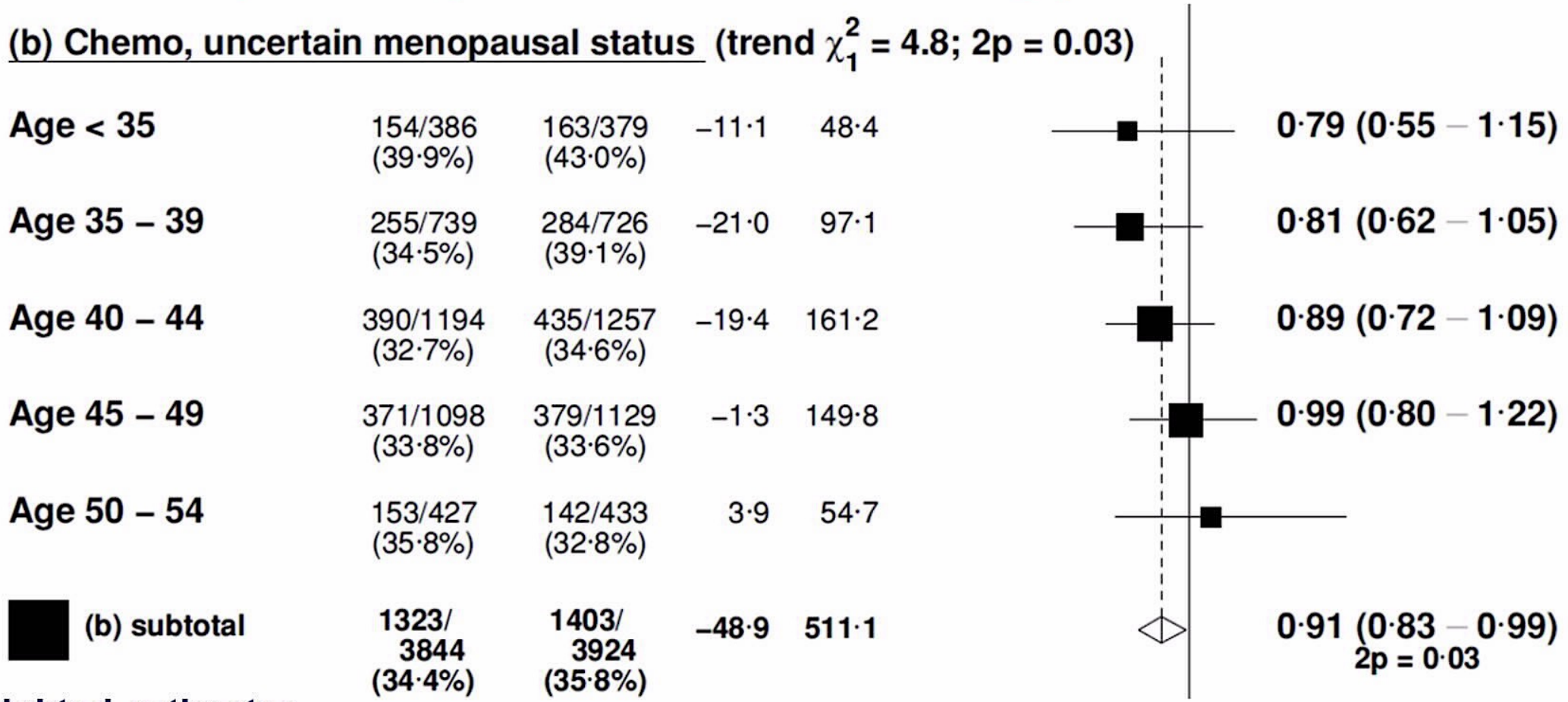
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Abl./suppr.	2·47 (255 / 10311)	1·54 (96 / 6242)	1·75 (41 / 2346)	2·40 (3 / 125)
Control	2·98 (313 / 10499)	1·92 (118 / 6159)	2·21 (48 / 2169)	1·85 (2 / 108)
Rate ratio, from	0·81 CI 0·68 – 0·97	0·78 CI 0·58 – 1·03	0·77 CI 0·50 – 1·20	1·94 CI 0·30 – 12·52
(O–E) / V	–26·1 / 126·3	–12·0 / 47·1	–5·0 / 19·7	0·7 / 1·1

Gray R et al. ASCO 2023;Abstract 503.

Ovarian ablation/suppress. vs not: Recurrence by age*

(B) Premenopausal prior to chemotherapy, uncertain after

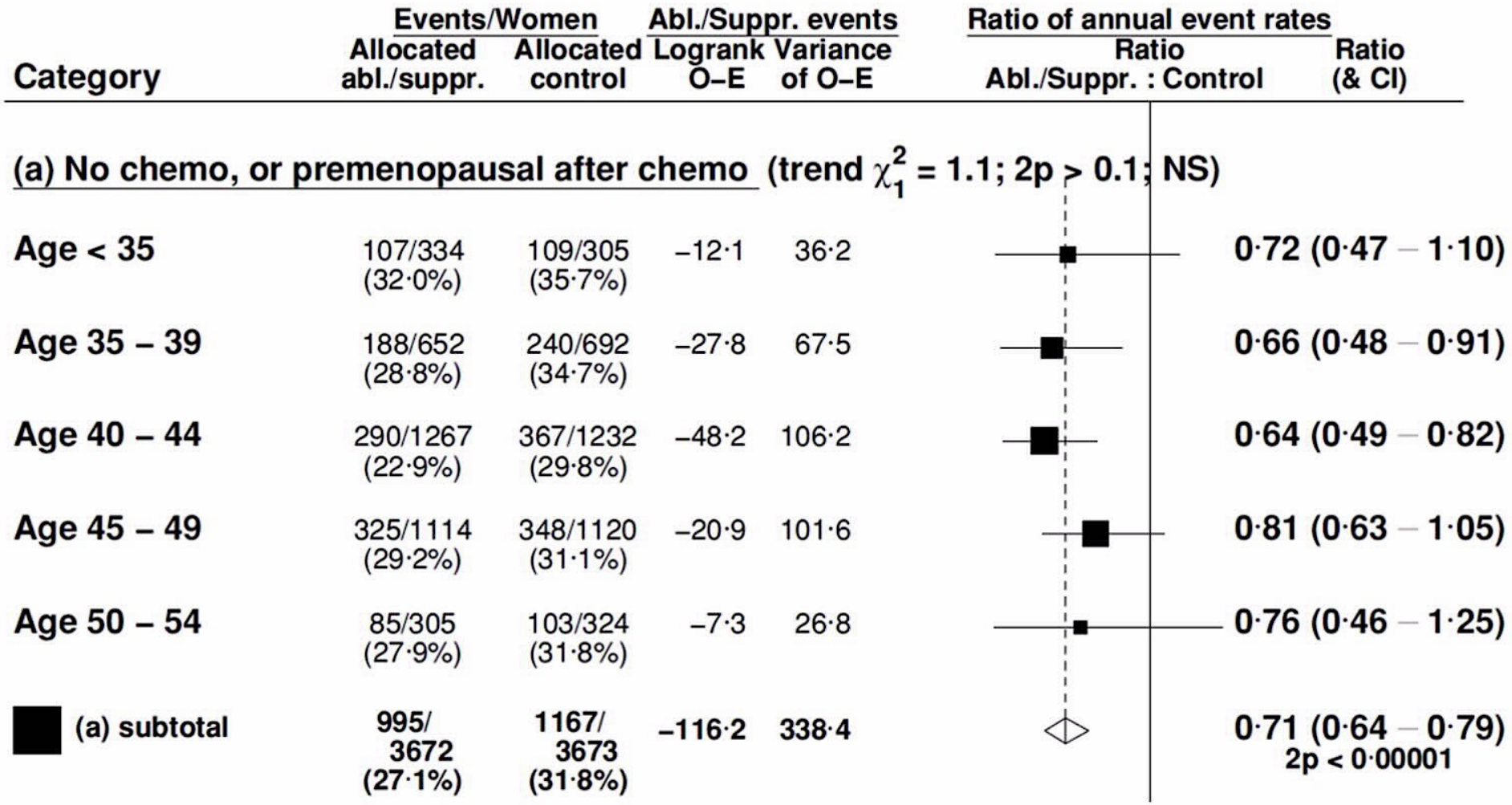


* ER-weighted estimates

Gray R et al. ASCO 2023;Abstract 503.

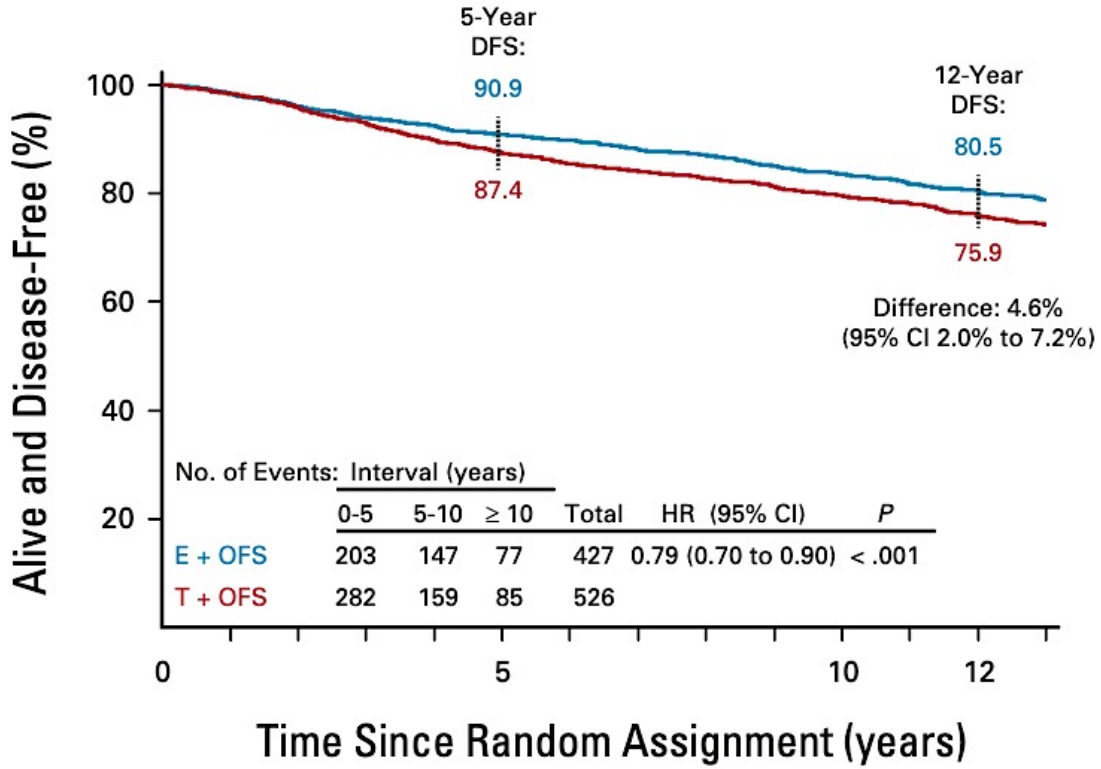
Ovarian ablation/suppression vs not: Recurrence by age

(A) No chemotherapy or premenopausal after chemotherapy



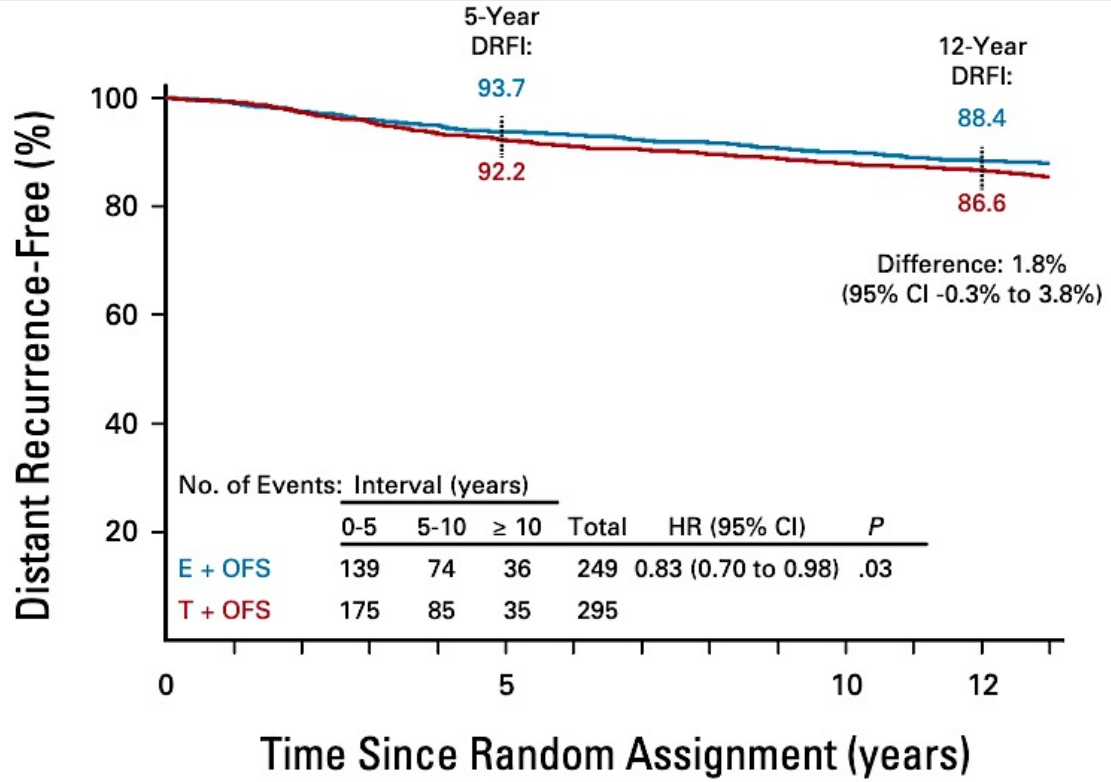
Gray R et al. ASCO 2023;Abstract 503.

SOFT/TEXT: DFS and DRFI Outcomes After a 13-Year Median Follow-Up



No. at risk (interval pyfu):

E + OFS	2,346	(10,626)	1,953	(8,701)	1,445	(4,139)
T + OFS	2,344	(10,572)	1,882	(8,414)	1,387	(3,999)
Interval HR (95% CI)		0.71 (0.59 to 0.85)		0.89 (0.71 to 1.11)		0.88 (0.65 to 1.20)



No. at risk (interval pyfu):

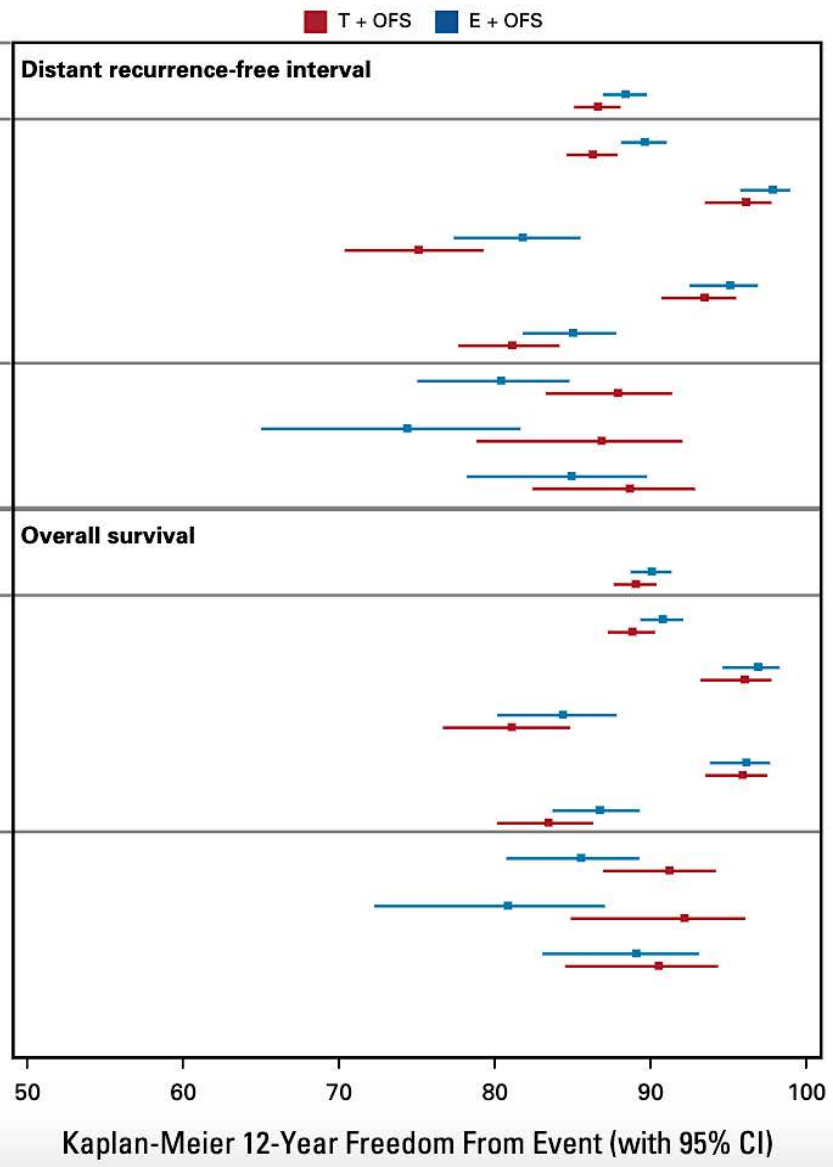
E + OFS	2,346	(10,755)	1,999	(9,025)	1,529	(4,461)
T + OFS	2,344	(10,780)	1,975	(8,976)	1,505	(4,430)
Interval HR (95% CI)		0.78 (0.63 to 0.98)		0.85 (0.62 to 1.16)		1.02 (0.64 to 1.63)

Pagani O et al. *J Clin Oncol* 2022;41(7):1376-82.

SOFT/TEXT: DRFI and OS Subgroup Analysis – 12-Year Outcomes

		No. of Events/ No. of Patients	T + OFS	E + OFS	Difference (95% CI)
Distant recurrence-free interval					
Overall		544/4,690	86.6	88.4	1.8 (-0.3 to 3.8)
HER2–		451/4,035	86.3	89.6	3.3 (1.2 to 5.5)
HER2–	SOFT no chemotherapy	25/892	96.1	97.9	1.7 (-0.8 to 4.2)
	SOFT prior chemotherapy	165/835	75.1	81.8	6.7 (0.7 to 12.7)
	TEXT no chemotherapy	52/991	93.5	95.1	1.6 (-1.5 to 4.8)
	TEXT chemotherapy	209/1,317	81.1	85.0	3.9 (-0.5 to 8.3)
HER2+		86/578	87.9	80.4	-7.5 (-13.8 to 1.2)
HER2+	SOFT	44/249	86.9	74.4	-12.5 (-23.0 to 2.0)
	TEXT	42/329	88.7	84.9	-3.7 (-11.4 to 3.9)
Overall survival					
Overall		473/4,690	89.1	90.1	1.0 (-0.9 to 2.9)
HER2–		398/4,035	88.8	90.8	2.0 (-0.1 to 4.0)
HER2–	SOFT no chemotherapy	29/892	96.1	96.9	0.9 (-1.9 to 3.7)
	SOFT prior chemotherapy	137/835	81.1	84.4	3.3 (-2.3 to 8.9)
	TEXT no chemotherapy	45/991	95.9	96.2	0.2 (-2.4 to 2.9)
	TEXT chemotherapy	187/1,317	83.5	86.8	3.3 (-0.9 to 7.4)
HER2+		66/578	91.2	85.6	-5.7 (-11.2 to 0.2)
HER2+	SOFT	32/249	92.2	80.9	-11.3 (-20.3 to 2.3)
	TEXT	34/329	90.5	89.1	-1.4 (-8.3 to 5.4)

HER2-unknown omitted (patients: 77; events: 7 DR, 8 OS)

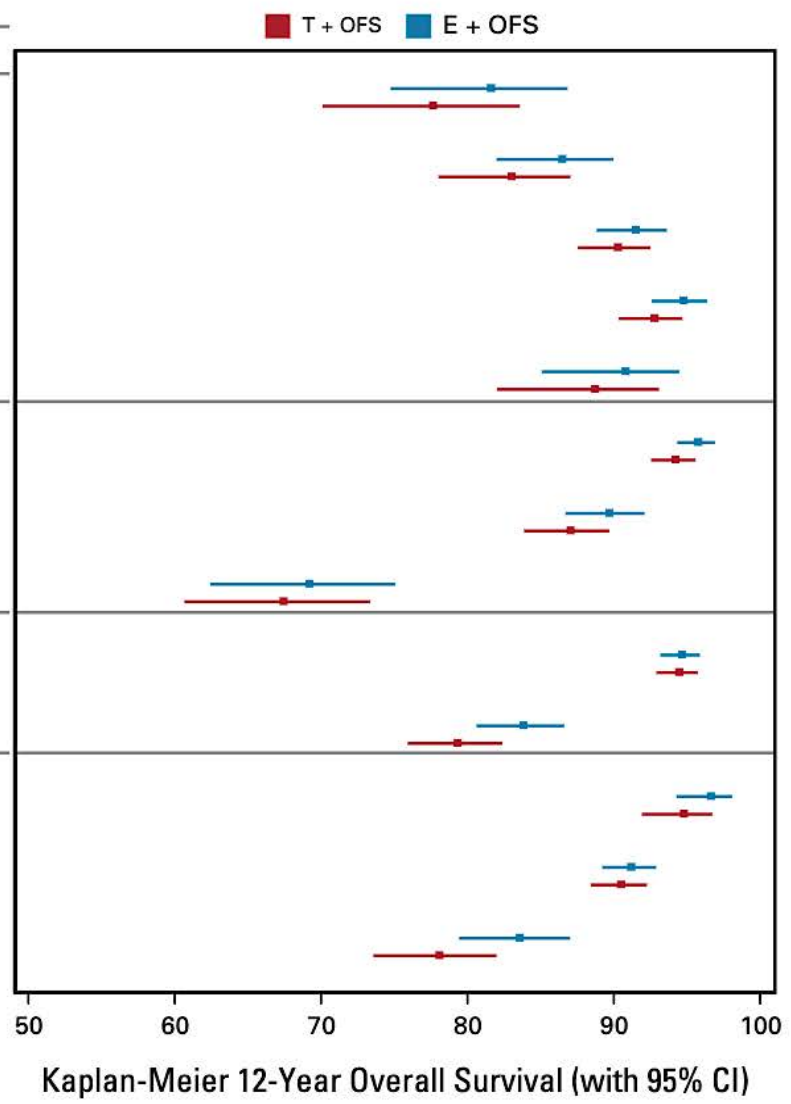


Pagani O et al. *J Clin Oncol* 2022;41(7):1376-82.

SOFT/TEXT: OS by Clinicopathologic Subgroups – 12-Year Outcomes

Subgroup		No. of Deaths/ No. of Patients	12-Year Overall Survival (%)		
			T + OFS	E + OFS	Difference
Age at random assignment (years)	< 35	67/350	77.6	81.6	4.0 (-5.0 to 12.9)
	35 – 39	98/653	83.0	86.5	3.5 (-2.5 to 9.4)
	40 – 44	114/1,303	90.3	91.5	1.2 (-2.2 to 4.6)
	45 – 49	87/1,352	92.8	94.8	2.0 (-0.8 to 4.8)
	50 +	32/377	88.7	90.8	2.1 (-5.0 to 9.1)
Positive LNs	pN0	117/2,365	94.2	95.8	1.5 (-0.4 to 3.5)
	pN+ 1-3	136/1,193	87.0	89.7	2.6 (-1.3 to 6.6)
	pN+ 4+	145/477	67.4	69.2	1.8 (-7.2 to 10.7)
Tumor size	≤ 2 cm	140/2,567	94.5	94.6	0.2 (-1.8 to 2.1)
	> 2 cm	245/1,409	79.3	83.8	4.5 (0.1 to 8.9)
Tumor grade	1	40/903	94.8	96.6	1.8 (-1.1 to 4.8)
	2	203/2,259	90.5	91.2	0.7 (-1.9 to 3.3)
	3	151/828	78.1	83.6	5.5 (-0.1 to 11.1)

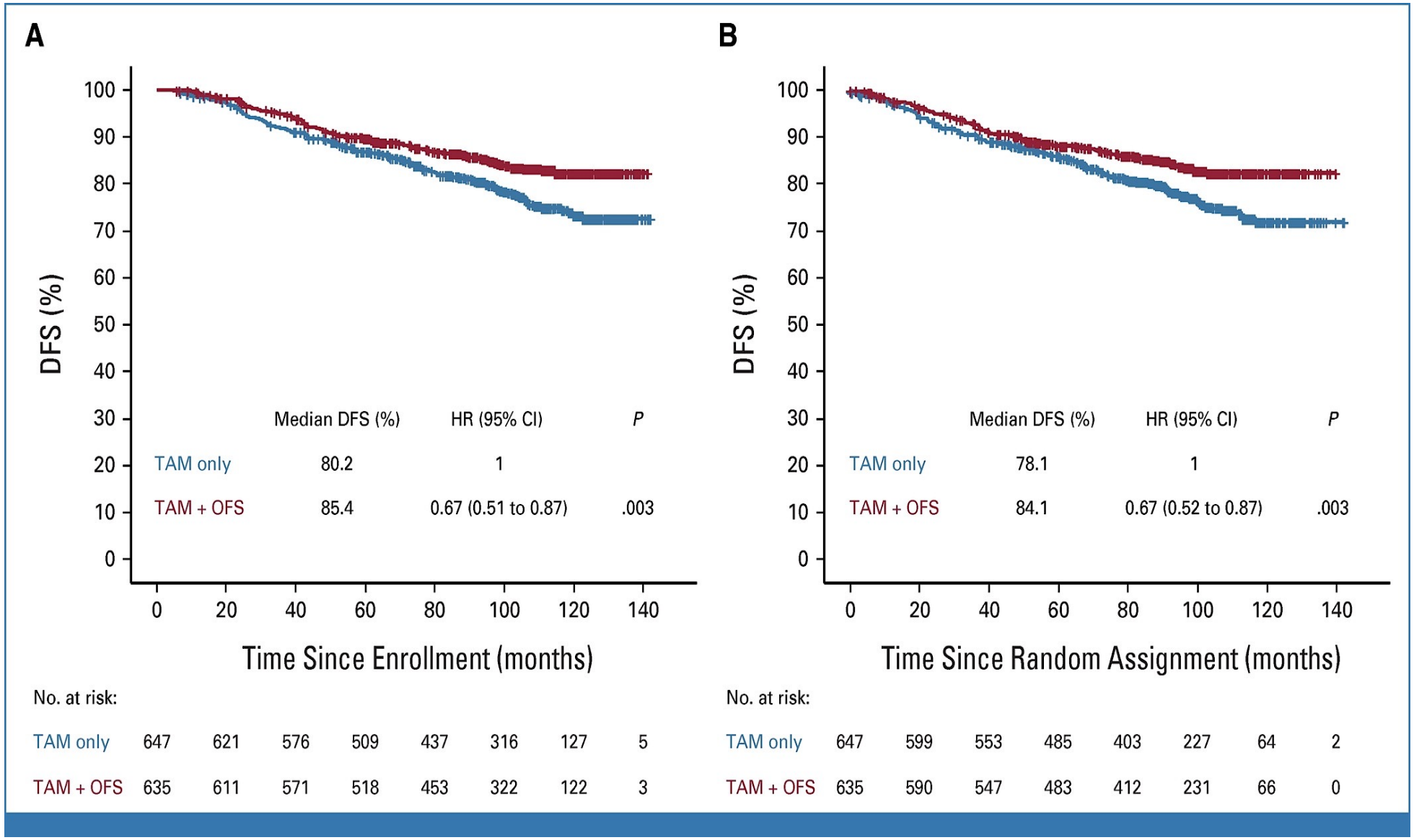
Omitted are 59 unknown T sizes and 45 unknown T grades



Pagani O et al. *J Clin Oncol* 2022;41(7):1376-82.

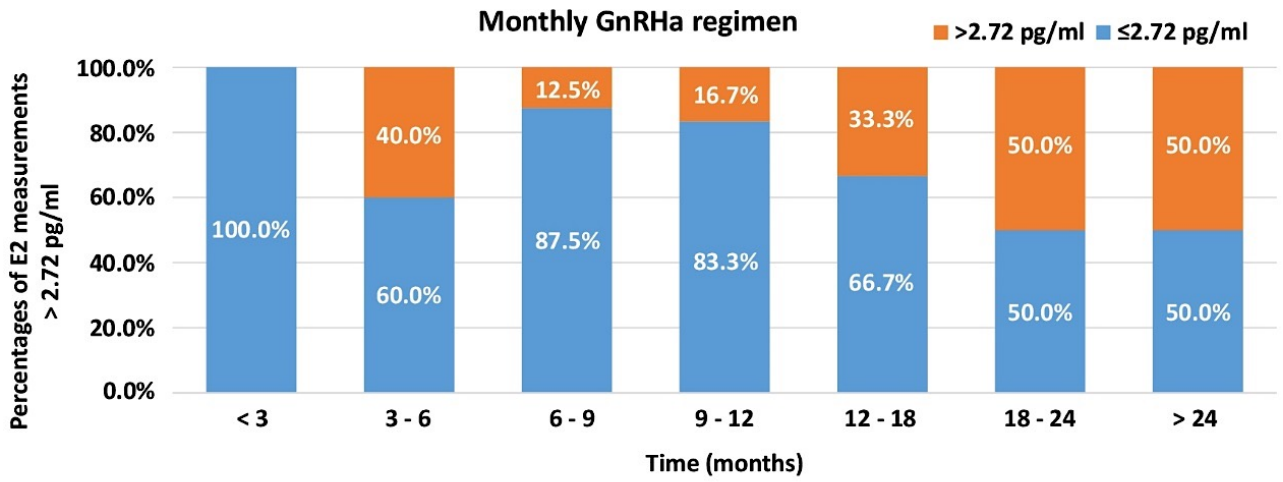
RTP RESEARCH TO PRACTICE

ASTRRA: tamoxifen vs OFS (2 years) + tamoxifen

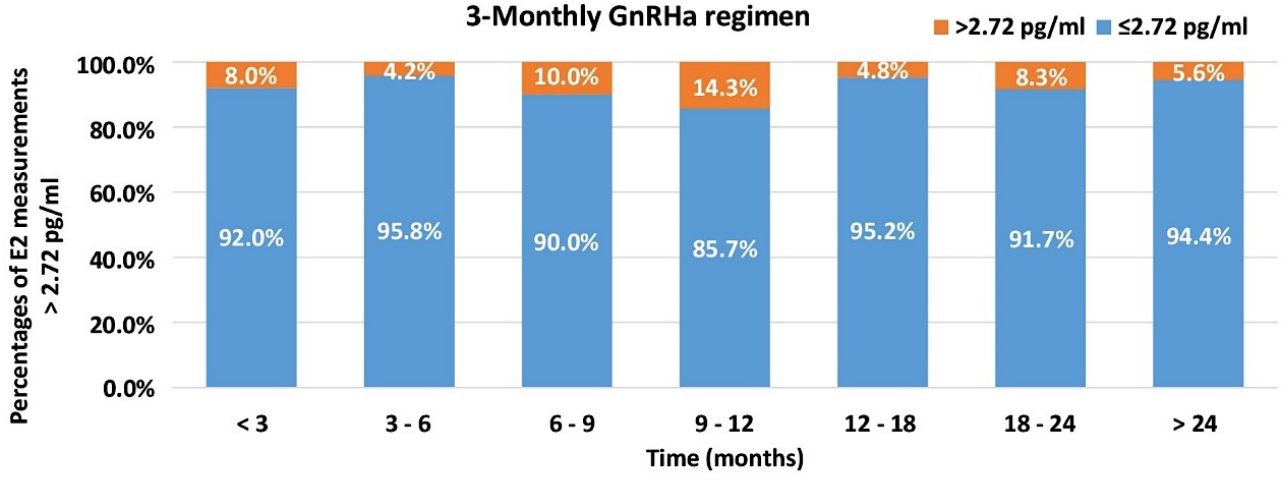


Soo Yeon Baek; Woo Chul Noh; Sei-Hyun Ahn; Hyun-Ah Kim; Jai Min Ryu; Seung Il Kim; Eun-Gyeong Lee; Seock-Ah Im; Yongsik Jung; Min Ho Park; Kyong Hwa Park; Su Hwan Kang; Joon Jeong; Eunhwa Park; Sung Yong Kim; Min Hyuk Lee; Lee Su Kim; Woosung Lim; Seonok Kim; Hee Jeong Kim; *Journal of Clinical Oncology* 2023 414864-4871.

Graphics. Percentages of E2 measurements > 2.72 pg/ml with monthly or 3-monthly GnRHa plus AI at each timepoint during OFS



>2.72 pg/ml	0	4	1	1	3	2	4
≤2.72 pg/ml	6	6	7	5	6	2	4
Total of measurements	6	10	8	6	9	4	8



>2.72 pg/ml	2	1	2	2	1	1	1
≤2.72 pg/ml	23	23	18	12	20	11	17
Total of measurements	25	24	20	14	21	12	18

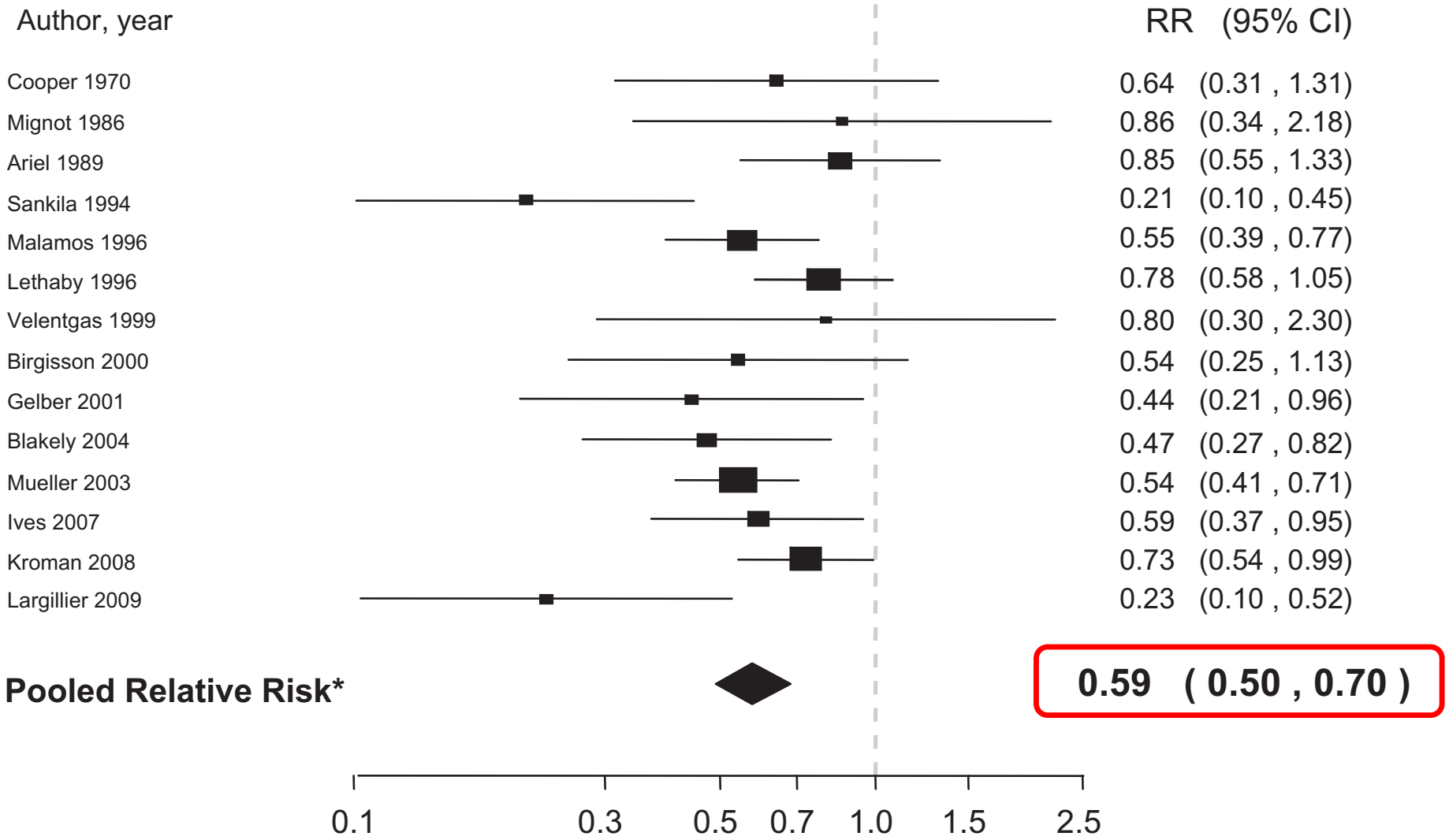
Blotta DA et al. ASCO 2023;Abstract 527.

Impact of Ovarian Suppression with GnRH agonists on Fertility Preservation During Chemotherapy

Study	N	Endpoint	Chemo	Chemo + GnRH
Del Mastro JAMA 2011	133	% 1-year amenorrheic	26%	9%
Lambertini JAMA 2015 PROMISE	281	% 5-year premenopausal fxn	64%	72%
Moore NEJM 2015 POEMS/SWOG-S0230	257	% 2-year ovarian failure	22%	8%

Is Pregnancy Safe after Breast Cancer?

Overall Survival

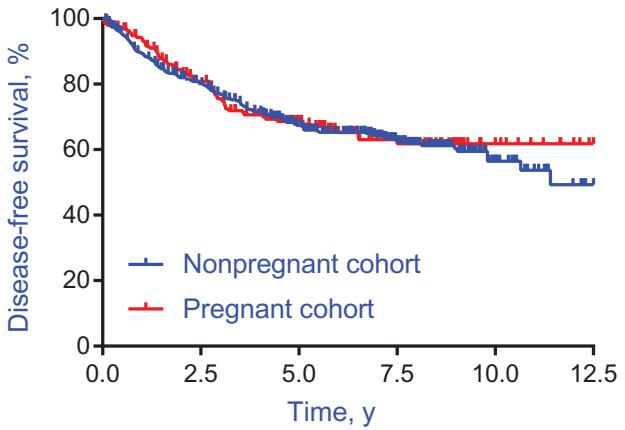


Azim, et al. Eur J Cancer 2011;47:74.

Pregnancy after Breast Cancer – Is It Safe for the Mother?

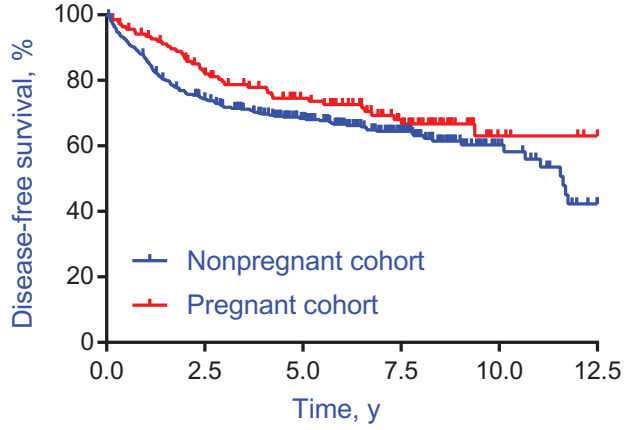
DFS

ER+



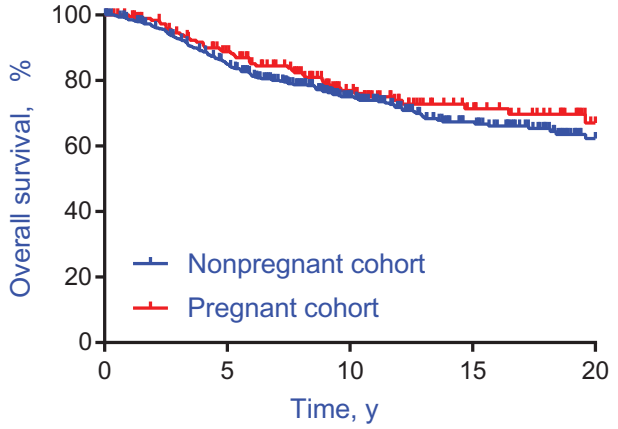
No. at risk						
Nonpregnant	492	346	233	134	32	5
Pregnant	194	138	88	50	17	4

ER-

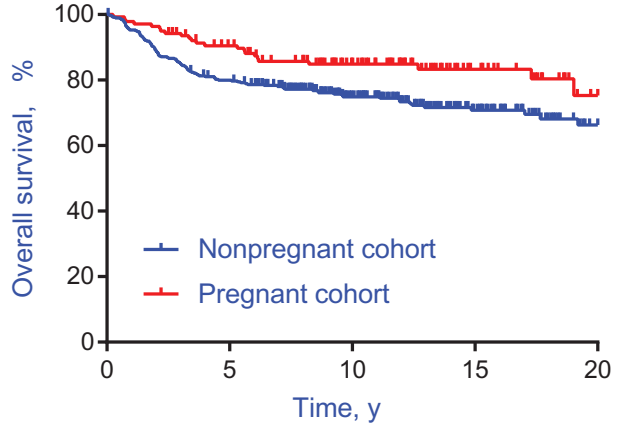


No. at risk						
Nonpregnant	382	264	200	112	30	11
Pregnant	139	105	81	52	12	8

OS



No. at risk						
Nonpregnant	492	381	213	114	48	
Pregnant	194	148	86	48	24	



No. at risk						
Nonpregnant	382	296	179	80	31	
Pregnant	139	117	77	35	13	

Lambertini M et al, J Natl Cancer Instit 2018;110:426-9

Is Pregnancy Safe Following ER-positive Disease? A Cohort Study

Pregnant cases

1. History of 1 BC
2. Became pregnant after BC diagnosis
3. No evidence of relapse before becoming pregnant
4. Known ER-status

Matched controls
3 controls/pregnant case

History of 1 BC matched according to

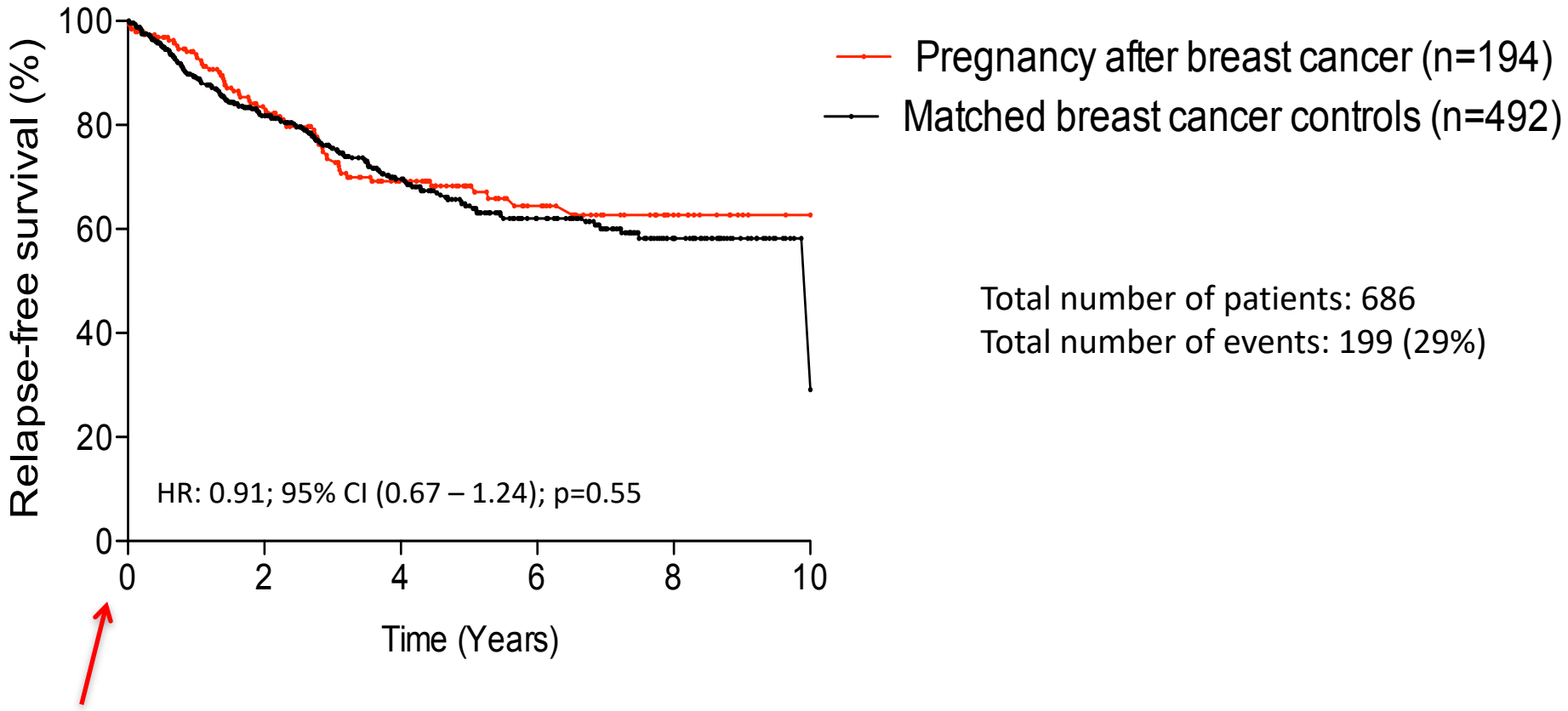
1. ER status (+ vs. -)
2. Nodal status (N0 vs. N+)
3. Adjuvant chemo, hormonal (Yes vs. No)
4. Age at diagnosis (< vs. > 35)
5. Year of diagnosis (± 5 years)

1,207 eligible patients

Azim H. et al; JCO 2012

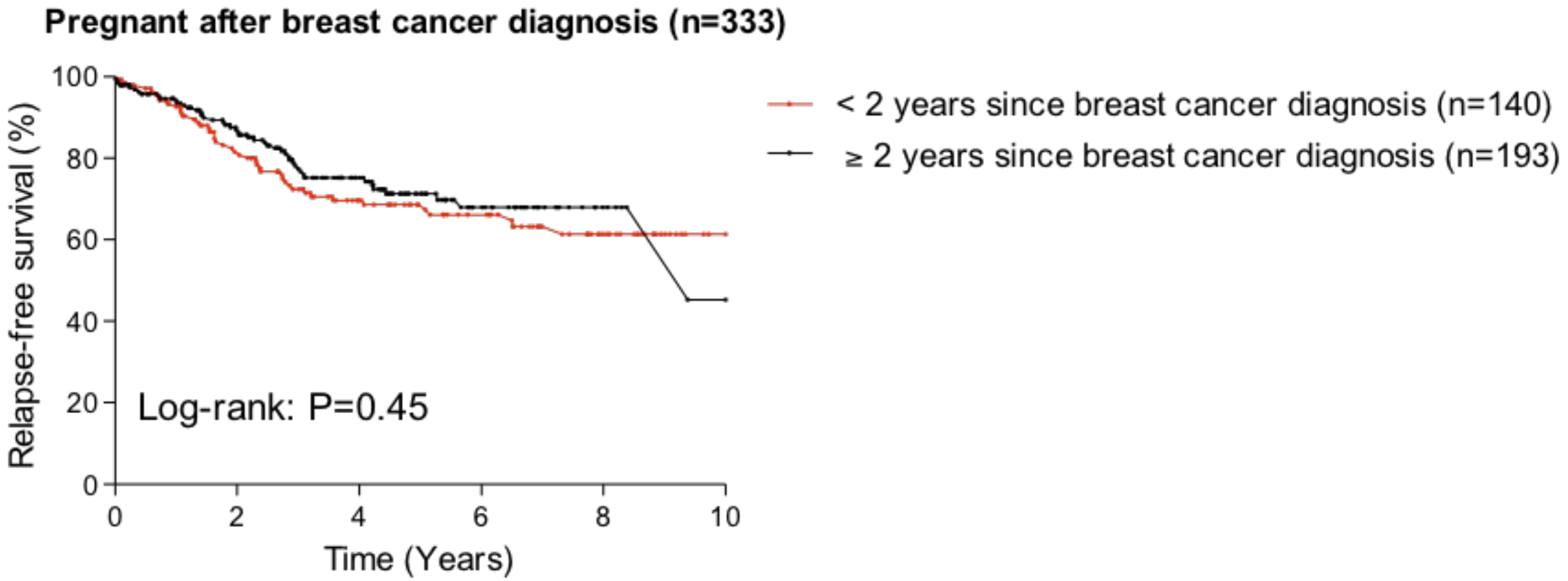
RFS of women who become pregnant following a diagnosis of ER+ breast cancer

Median follow-up from date of conception: 4.7 years (IQR: 3.1 – 6.9)



Azim H. et al; JCO 2012

No Adverse Effect of Early Pregnancy after ER+ Breast Cancer



Azim H. et al; JCO 2012

POSITIVE: Cumulative Incidence of Breast Cancer Events and Distant Recurrences.

Cohort:

Median age, 37 years

Median time since diagnosis, 29 months

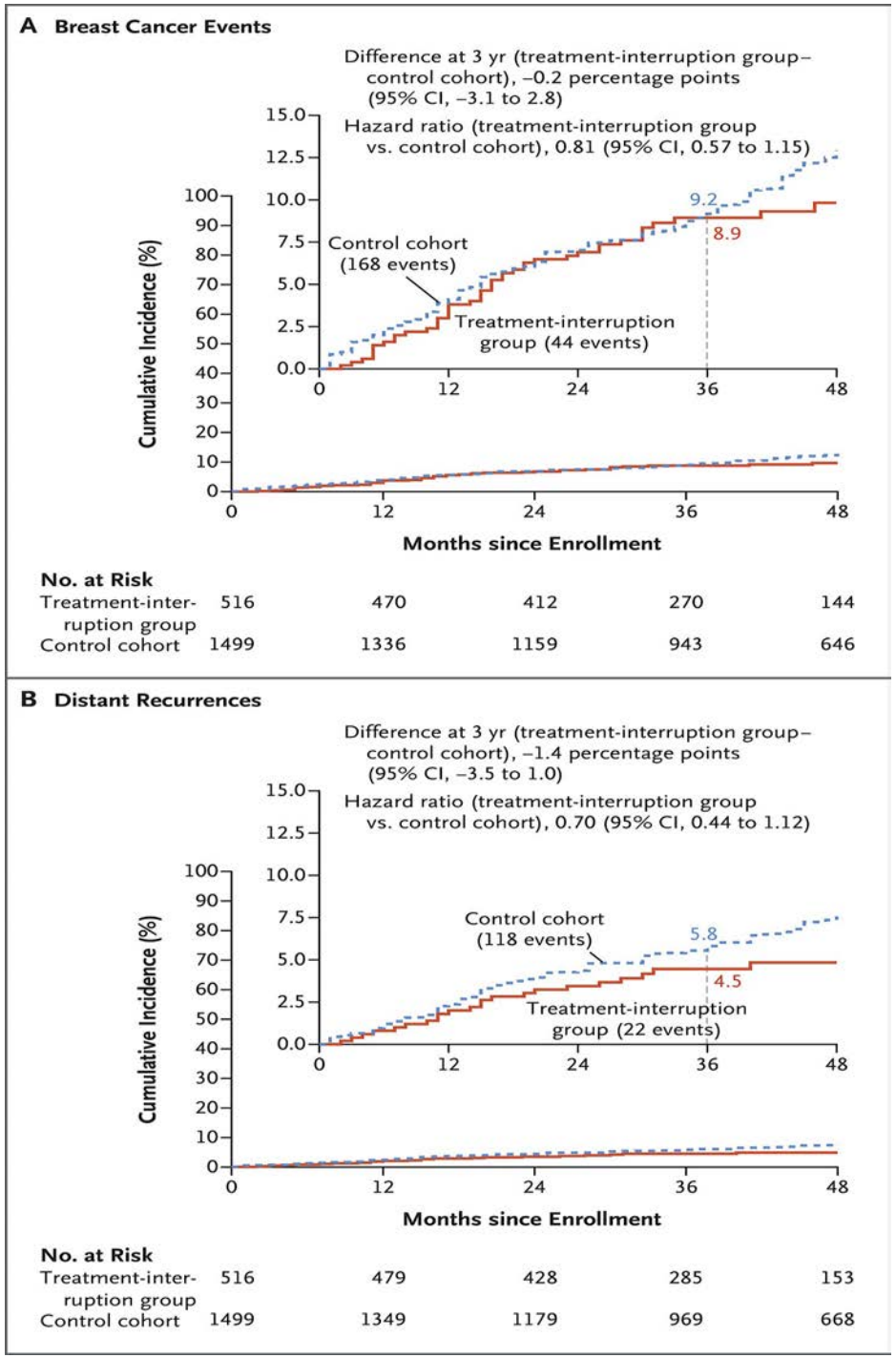
Node negative, 66%

Pregnancy rate, 74% of patients

Resumption of ET, 73%

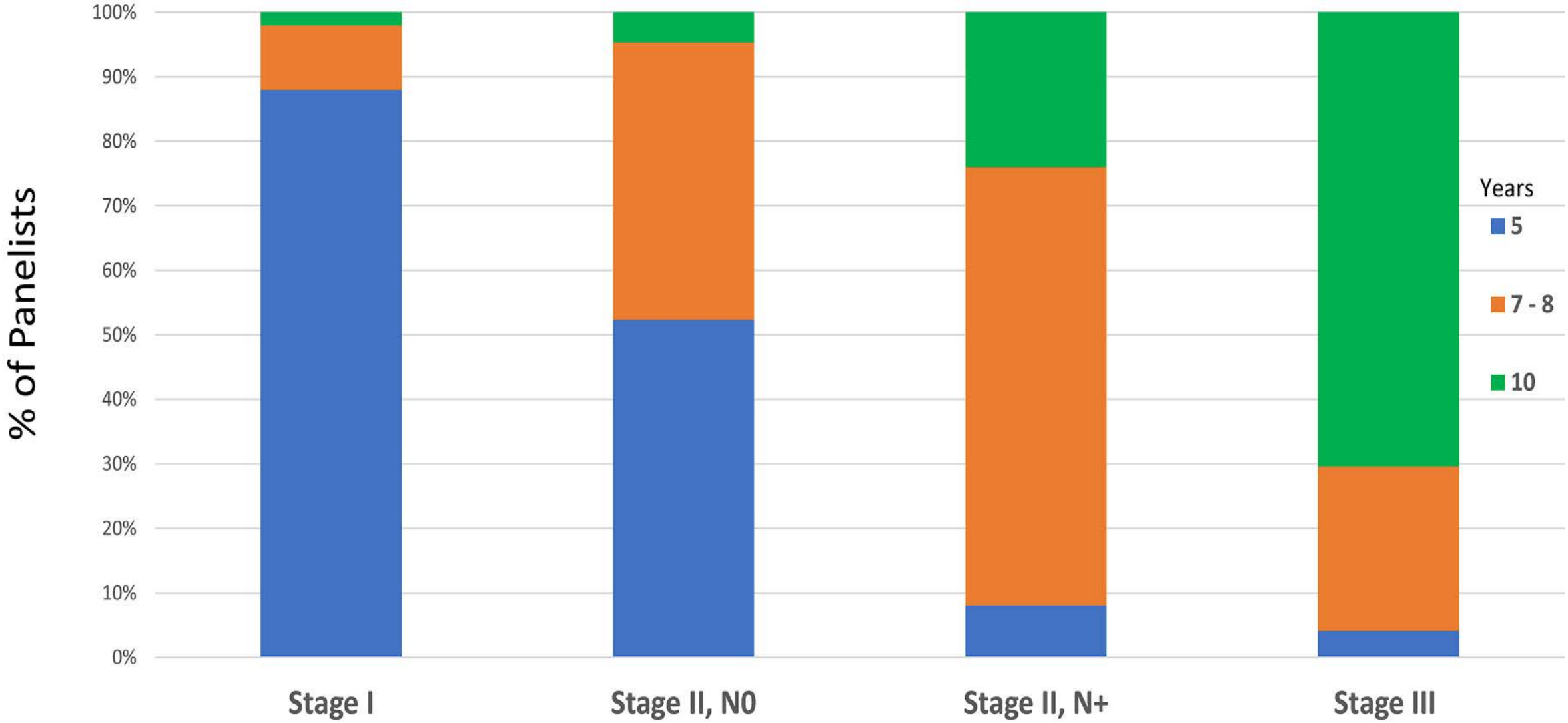
Three-year event rates

Overall, 9%



AH Partridge et al. N Engl J Med 2023;388:1645-1656.

Optimal Duration of ET: St Gallen Consensus Panel



Curigliano, Burstein, et al. Annals of Oncology DOI: (10.1016/j.annonc.2023.08.017)

Timing/duration of GnRH agonist

- Timing
  - If goal is ovarian protection, then start with chemotherapy
  - If goal is adjuvant ovarian suppression, then start at time of initiation of ET

- Duration
  - GnRH agonist duration linked to ET duration
  - Consider oophorectomy in women not interested in recovery of OF
  - Consider discontinuing GnRH when it is very unlikely to see recovery of OF

Agenda

Module 1: Role of Genomic Assays in Treatment Decision-Making for Localized ER-Positive, HER2-Negative Breast Cancer — Dr Goetz

Module 2: Integration of Ovarian Function Suppression into the Management of Breast Cancer in Premenopausal Patients — Dr Burstein

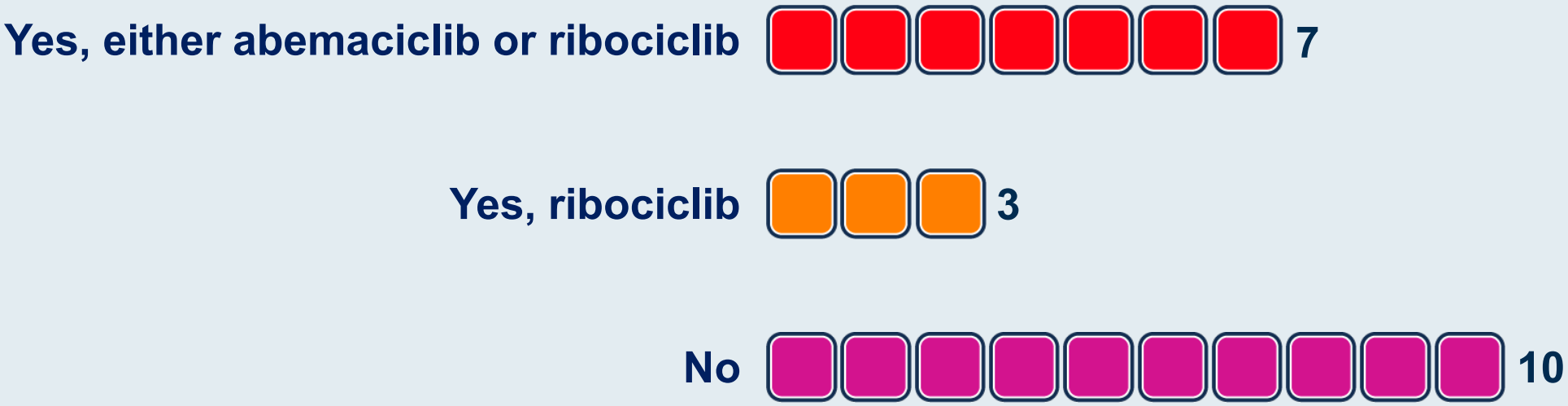
Module 3: Role of CDK4/6 Inhibitors and Other Novels Agents in Therapy for ER-Positive Localized Breast Cancer — Dr Hurvitz

Module 4: Optimizing the Use of Neoadjuvant and Adjuvant Therapy for Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 5: Emerging Role of Circulating Tumor DNA Evaluation in the Management of Breast Cancer — Dr Pusztai

RTP
RESEARCH
TO PRACTICE

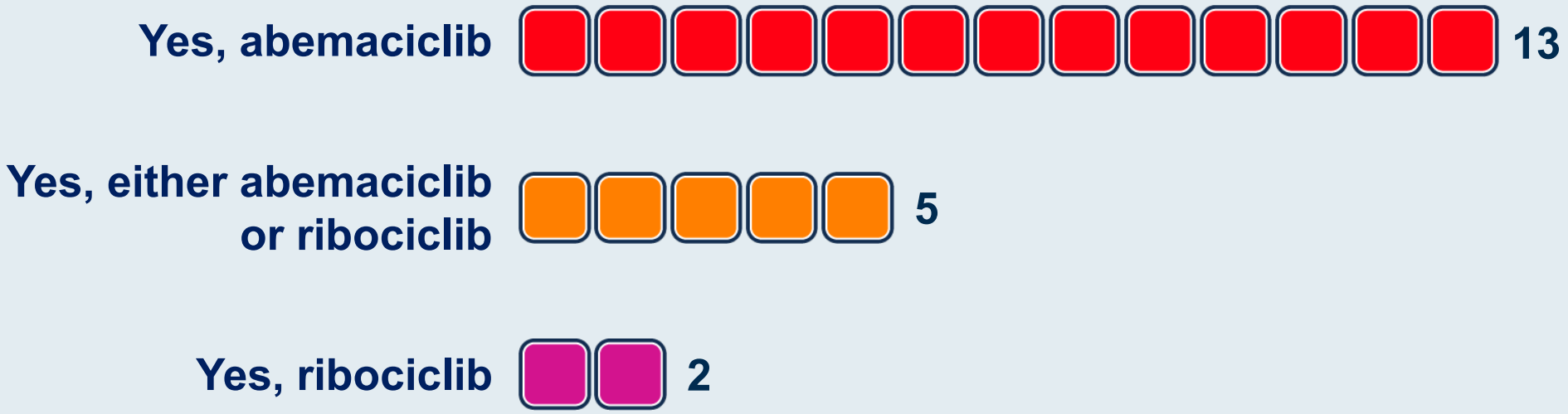
Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor to a woman with a Grade 2, 3-cm, ER-positive, HER2-negative localized breast cancer with 1 positive node?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

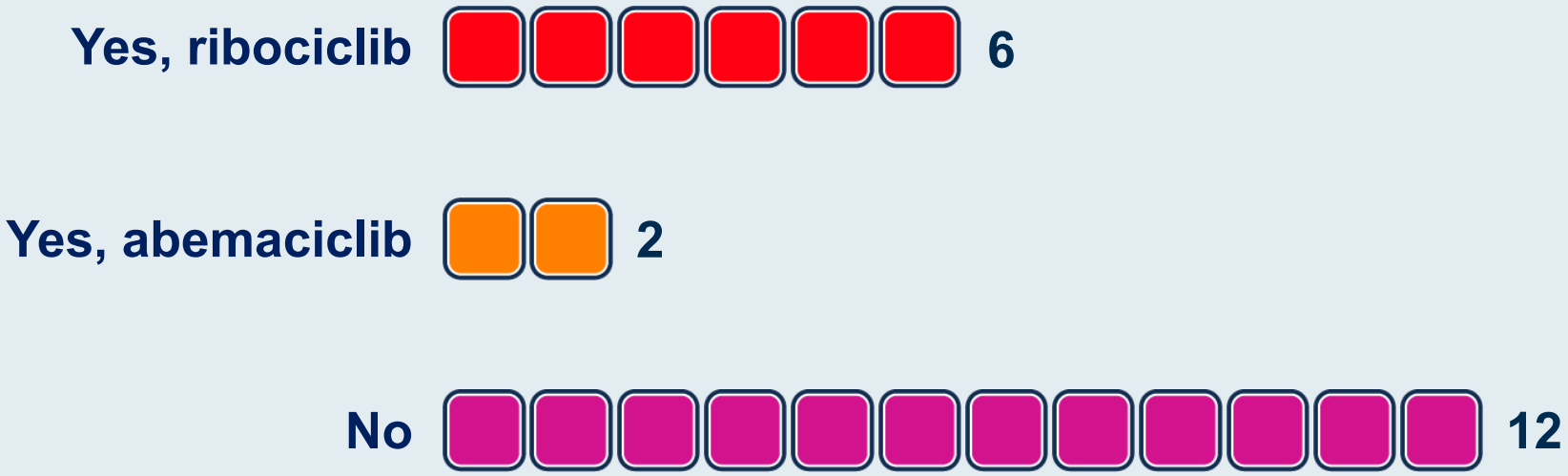
Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor to a woman with a Grade 3, 3-cm, ER-positive, HER2-negative localized BC with 1 positive node?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor to a woman with a Grade 2, 5.1-cm, ER-positive, HER2-negative, node-negative localized breast cancer?



Survey of 20 US-based clinical investigators November 2023

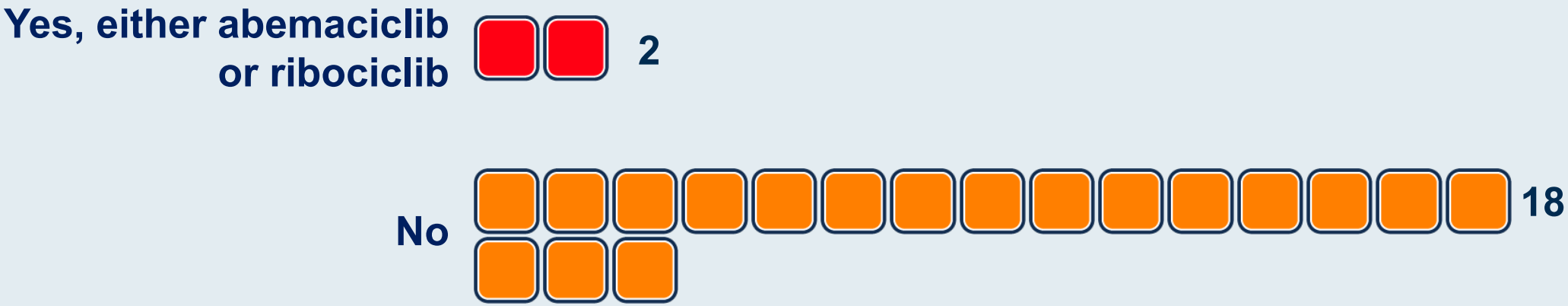
RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor to a woman with a Grade 2, 3-cm, ER-positive, HER2-negative, node-negative localized breast cancer?

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor to a woman with a Grade 2, 1.5-cm, ER-positive, HER2-negative, node-negative localized breast cancer?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

monarchE and NATALEE: Abemaciclib and ribociclib in the adjuvant setting

Mark D Pegram, MD

RTP
RESEARCH
TO PRACTICE

Integration of abemaciclib in the adjuvant setting; tolerability profiles of abemaciclib and ribociclib

Jane Lowe Meisel, MD

RTP
RESEARCH
TO PRACTICE

Use of adjuvant CDK4/6 inhibitors for patients at lower risk

Eric P Winer, MD

RTP
RESEARCH
TO PRACTICE

Role of CDK4/6 inhibitors and other novel agents in ER+ localized breast cancer

Sara A. Hurvitz, MD, FACP

Professor of Medicine
Head, Division of Hematology/Oncology,
University of Washington School of Medicine
Senior Vice President, Clinical Research Division,
Fred Hutchinson Cancer Center

Fred Hutch Cancer Center

UNIVERSITY of WASHINGTON

Neoadjuvant Studies Immune Therapy

Background:

Neoadjuvant systemic therapy leads to low rates (<10%) of pCR in ER+ disease!!

Higher grade ER+ breast cancers have higher responsiveness to chemo and maybe to immune therapy

CA209-7FL study design

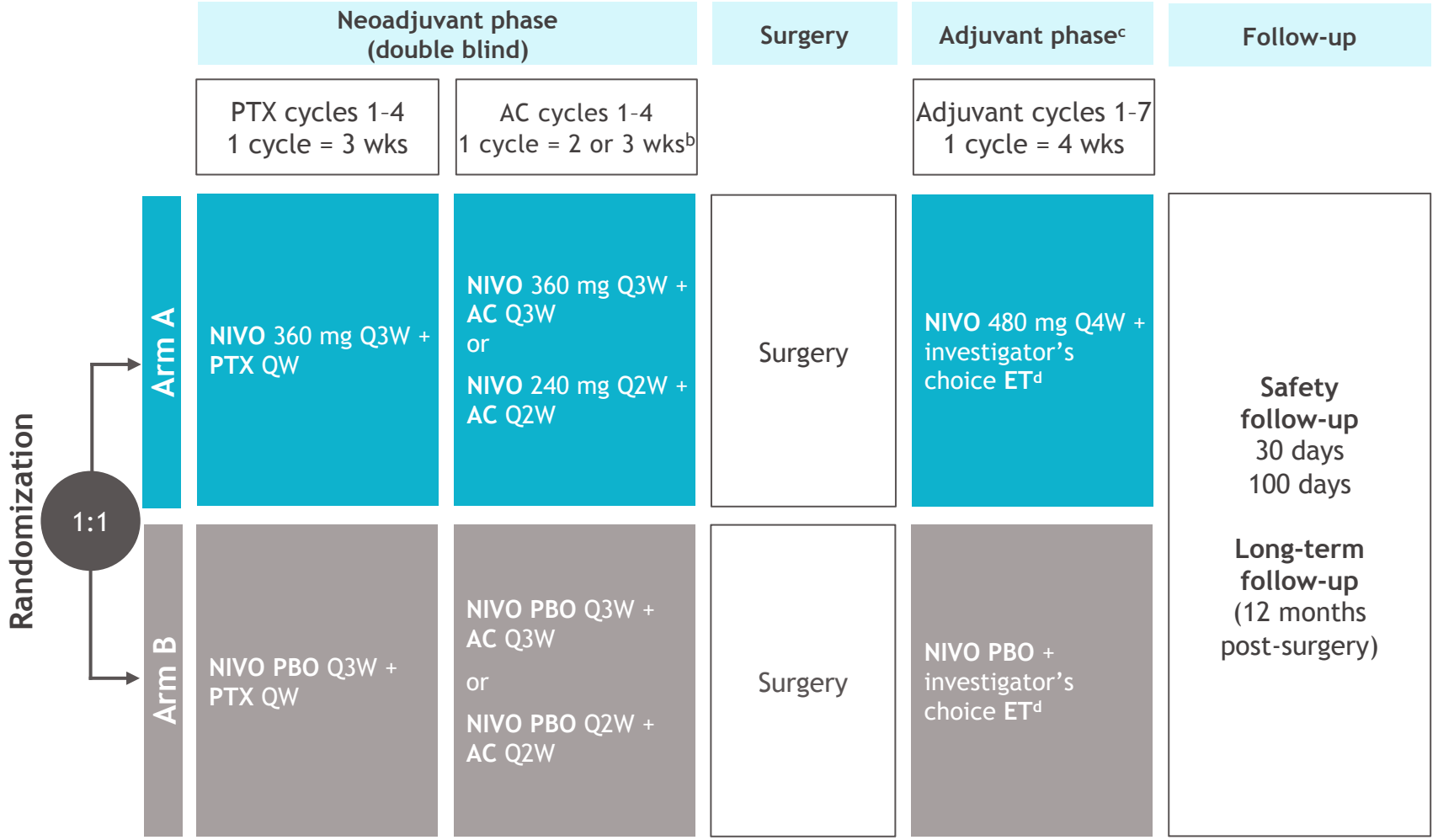
Screening

Key inclusion criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c-T2, cN1–cN2 or T3-T4**, cN0-cN2**
- **Grade 3 with ER ≥ 1% or grade 2 with ER 1-10%[a]**
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0–1

Stratification factors

- PD-L1 IC (≥ 1% or < 1%)
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)



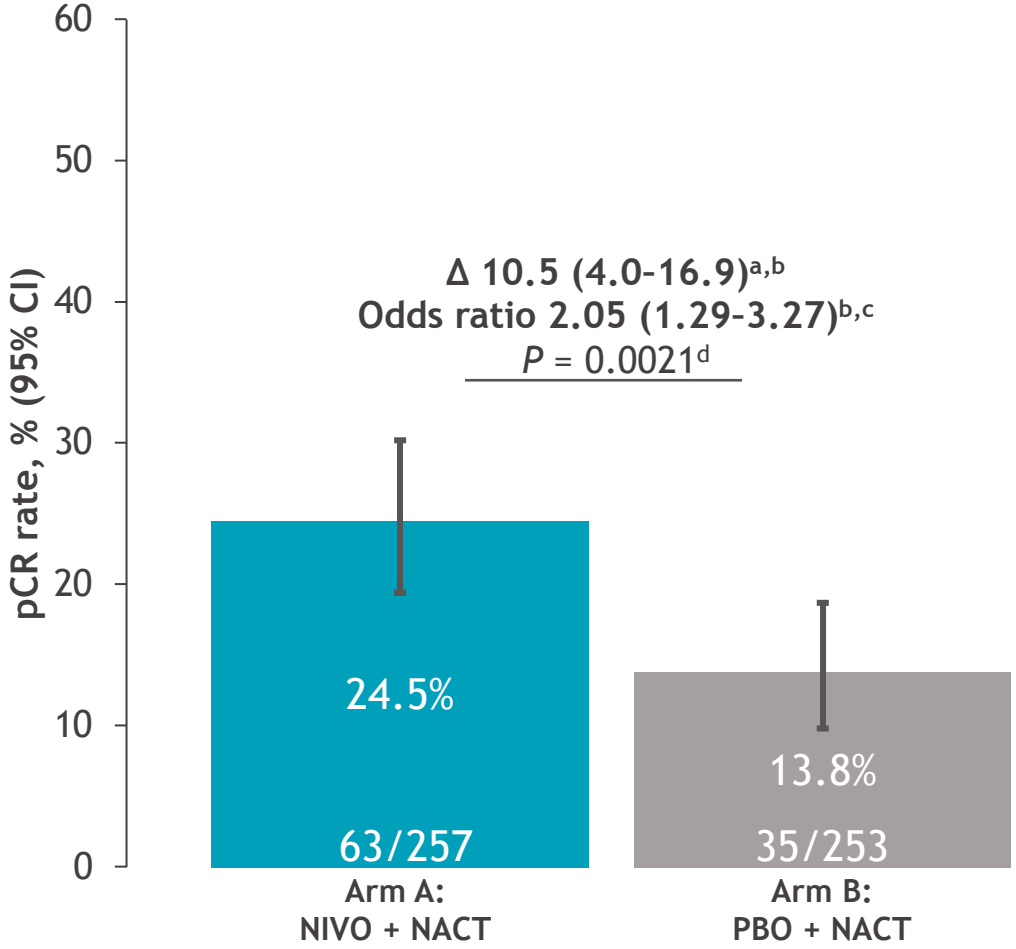
[a]Grade was determined locally by investigator. [b]Investigator's choice: anthracycline dosing frequency of Q2W or Q3W for AC cycles determined by the investigator. [c]After protocol amendment 3, the study was unblinded in the adjuvant phase. Participants in arm B will not receive NIVO PBO. [d]Available ET agents included tamoxifen, letrozole, anastrozole, and exemestane.

AC, anthracycline + cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; ER+, estrogen receptor-positive; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2-negative; IC, immune cell; N, lymph node involvement; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1; PTX, paclitaxel; QXW, every X weeks; T, size and extent of primary tumor; wk, week.

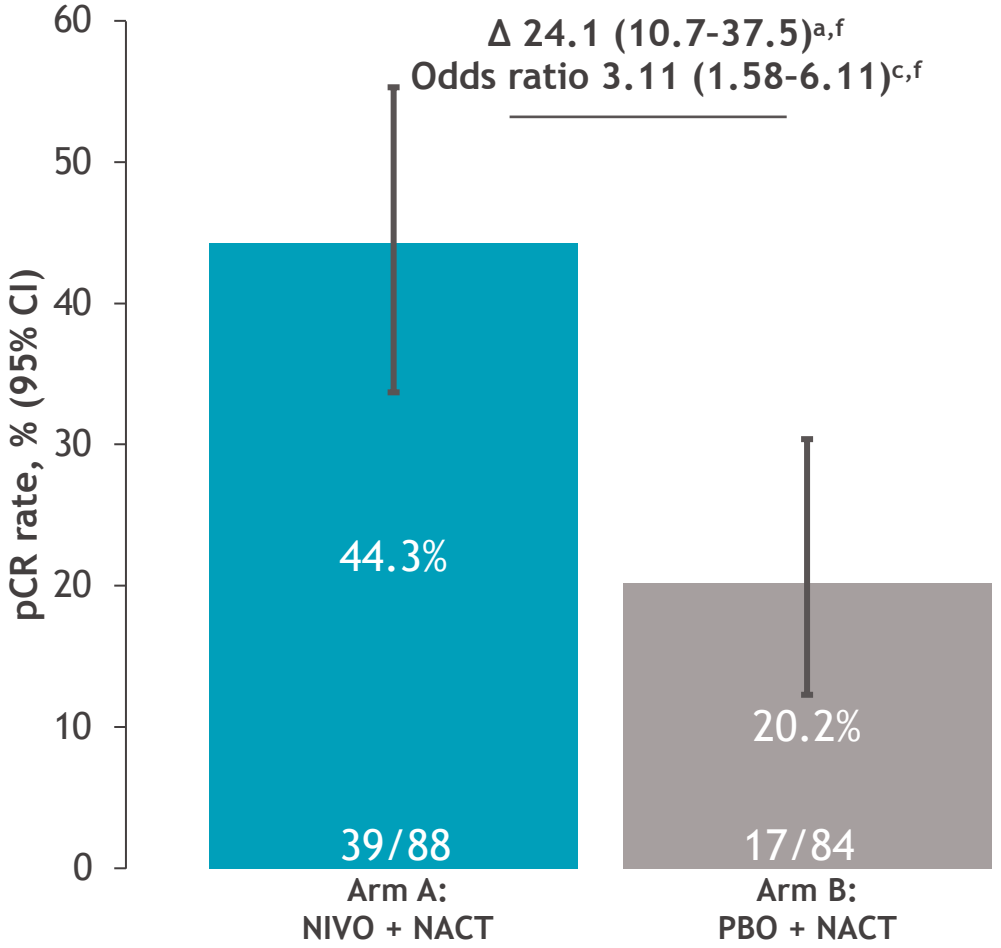
Loi S et al. ESMO 2023: LBA 20

pCR rate in mITT population and by PD-L1 IC ≥ 1%

mITT population (primary endpoint)



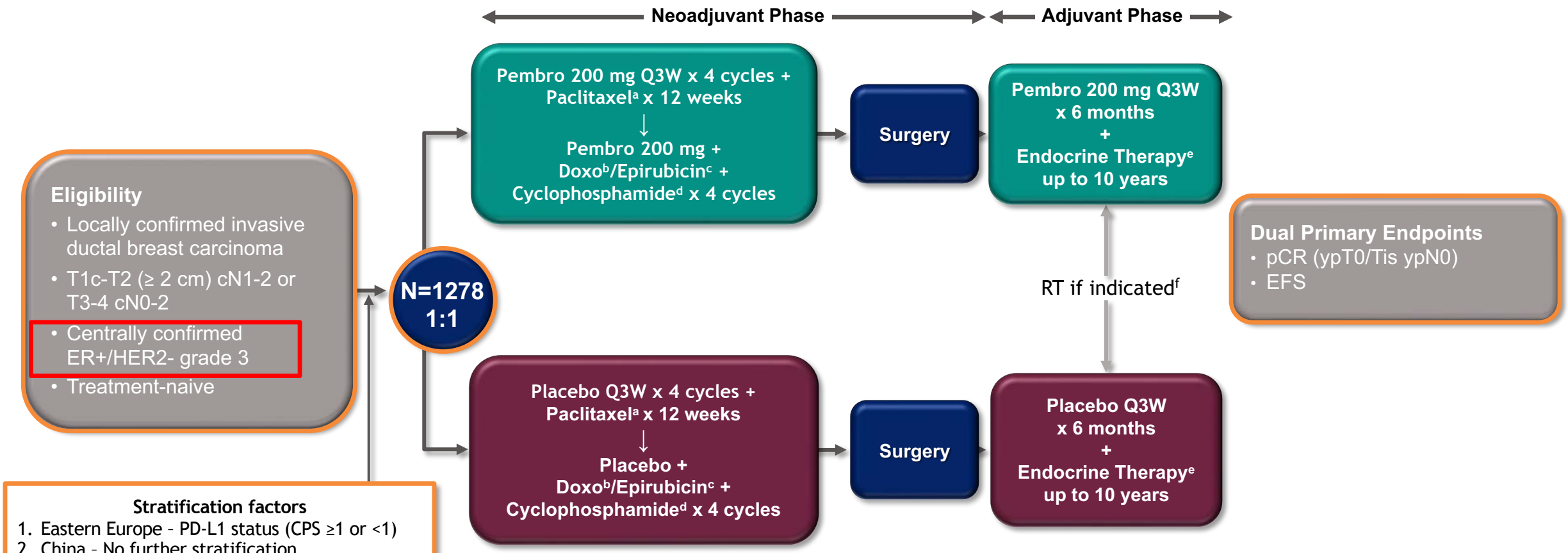
PD-L1 IC ≥ 1%[e] (secondary endpoint)



[a]Strata-adjusted difference in pCR (arm A−arm B) based on Cochran-Mantel-Haenszel method of weighting. [b]Stratified by PD-L1 by SP142 (< 1% vs ≥ 1%) and AC dose-frequency chemotherapy regimen (Q2W vs Q3W) per IRT. [c]Strata-adjusted odds ratio (arm A over arm B) using Mantel-Haenszel method. [d]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. [e]PD-L1 ICs and PD-L1-expressing tumor-infiltrating ICs as percentage of tumor area using the VENTANA SP142 assay. [f]Stratified by AC dose-frequency chemotherapy regimen.

AC, anthracycline + cyclophosphamide; CI, confidence interval; IC, immune cell; IRT, interactive response technology; mITT, modified intent-to-treat; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death ligand 1; QXW, every X weeks.

KEYNOTE-756 Study Design (NCT03725059)



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

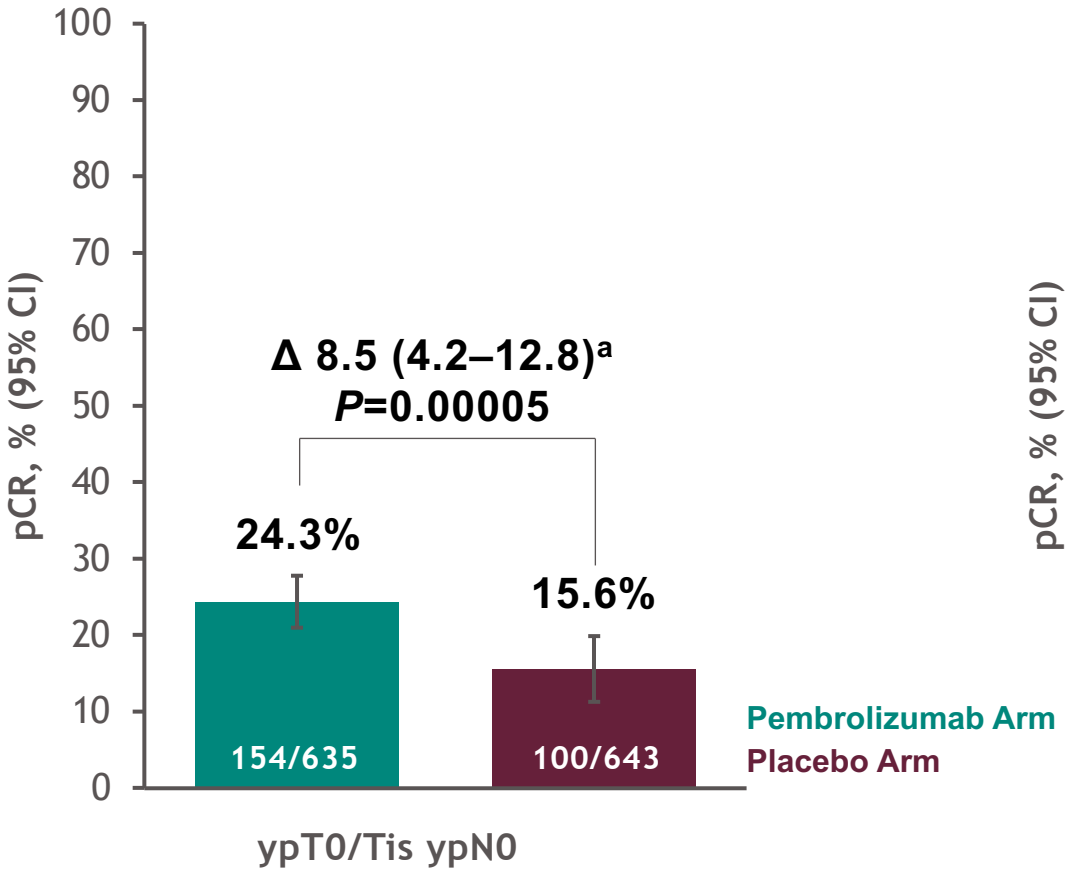
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Paclitaxel dose was 80 mg/m^2 QW. [b]Doxorubicin dose was 60 mg/m^2 Q3W. [c]Epirubicin dose was 100 mg/m^2 Q3W. [d]Cyclophosphamide dose was 600 mg/m^2 Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

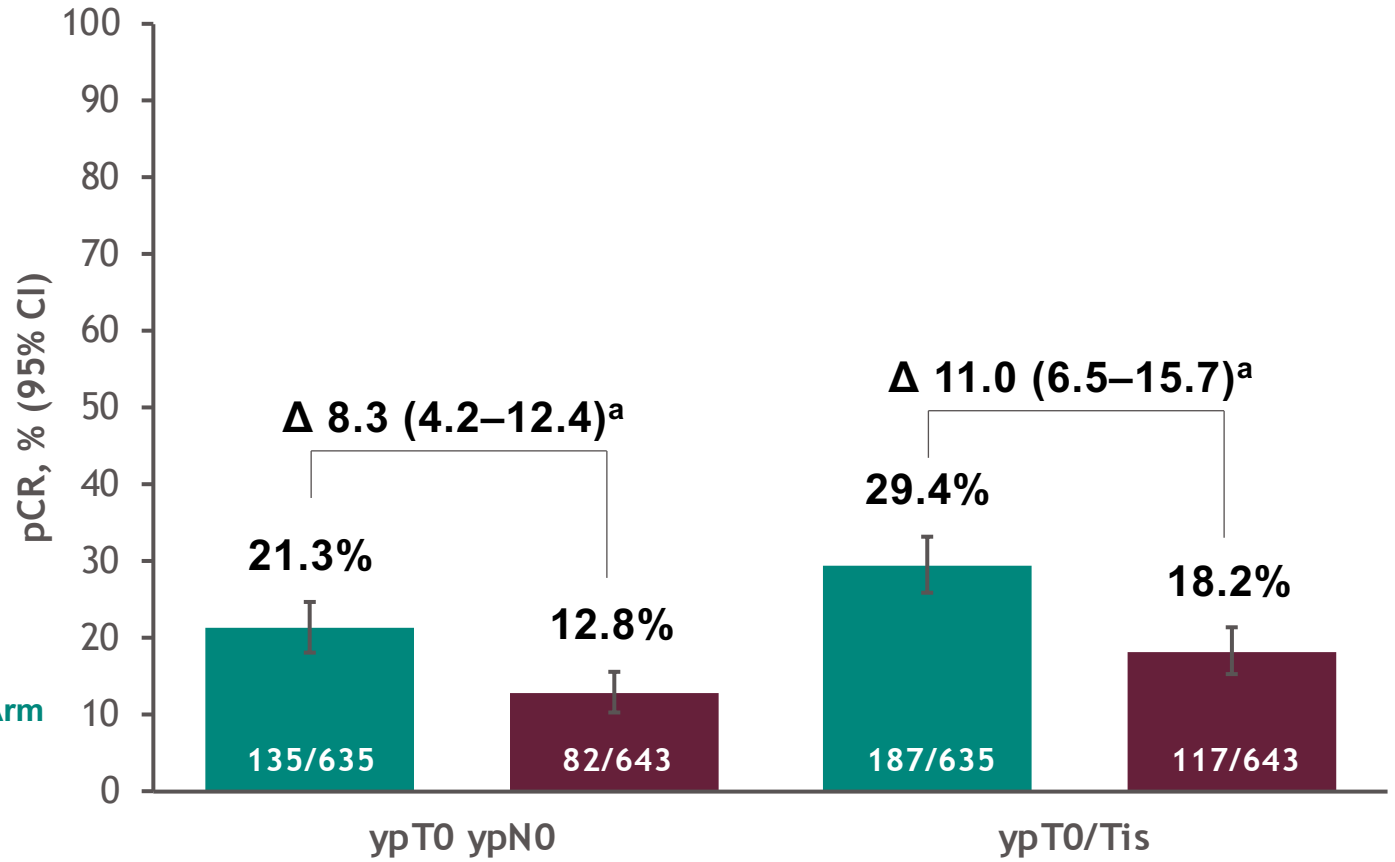
Cardoso F et al. ESMO 2023

Pathological Complete Response at IA1

Primary Endpoint



Secondary Endpoints: Other pCR Definitions



Cardoso F et al. ESMO 2023

[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by the analysis randomization stratification factors. Data cutoff date: May 25, 2023.

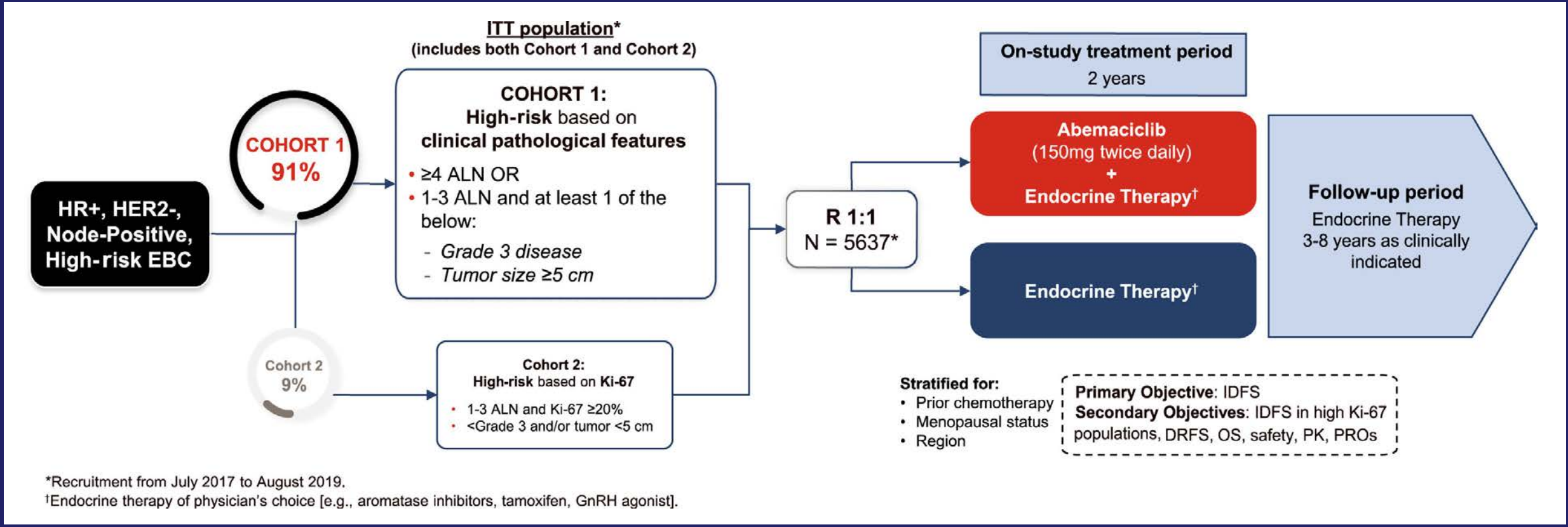
	CA209-7FL	Keynote-756
Checkpoint Inhibitor	Nivolumab	Pembrolizumab
N	**510**	**1278**
Grade 3	99%	100%
Node Positive	**80%**	**90%**
PD-L1+ by assay	**34% (SP142)**	**75% (223C CPS)**
pCR ITT chemo alone chemo + ICI	 13.8% 24.5% Δ 10.7%	 15.6% 24.3% Δ 8.7%
pCR PD-L1+ chemo alone chemo + ICI	 20.2% 44.3% Δ 24.1%	 19.6% 29.7% Δ 10.1%
pCR PD-L1 neg chemo alone chemo + ICI	 10.7% 14.2% Δ 3.5%	 2.6% 7.2% Δ 4.6%
Deaths	**2 (hepatitis, pneumonitis)**	**1 (myocardial infarction)**

Adjuvant CDK4/6 inhibitors

monarchE

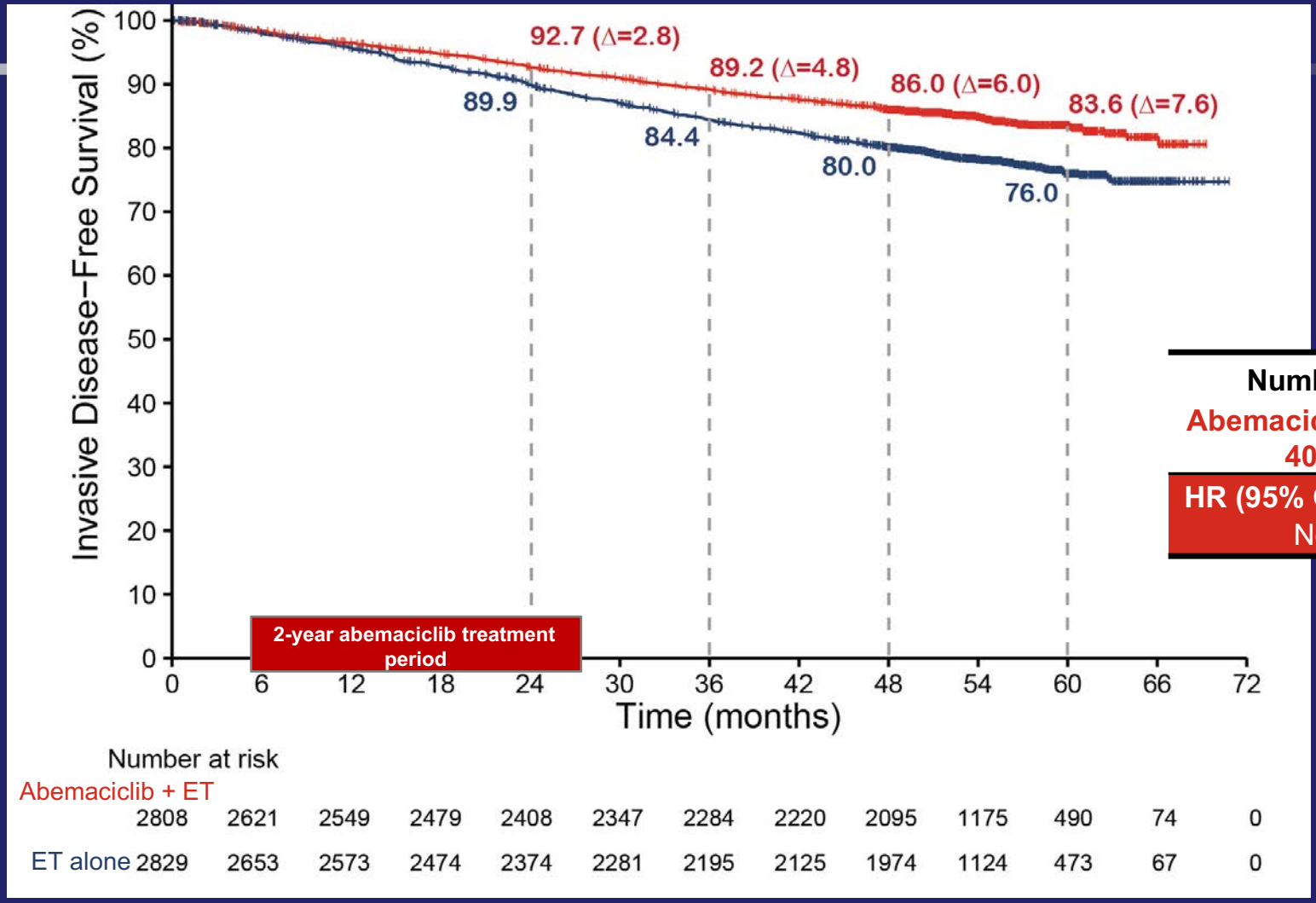
NATALEE

monarchE Study Design (NCT03155997): 5-year efficacy results



Median follow-up time is 4.5 years (54 months)
All patients are off abemaciclib
More than 80% of patients have been followed for at least 2 years since completing abemaciclib

Sustained IDFS Benefit in ITT



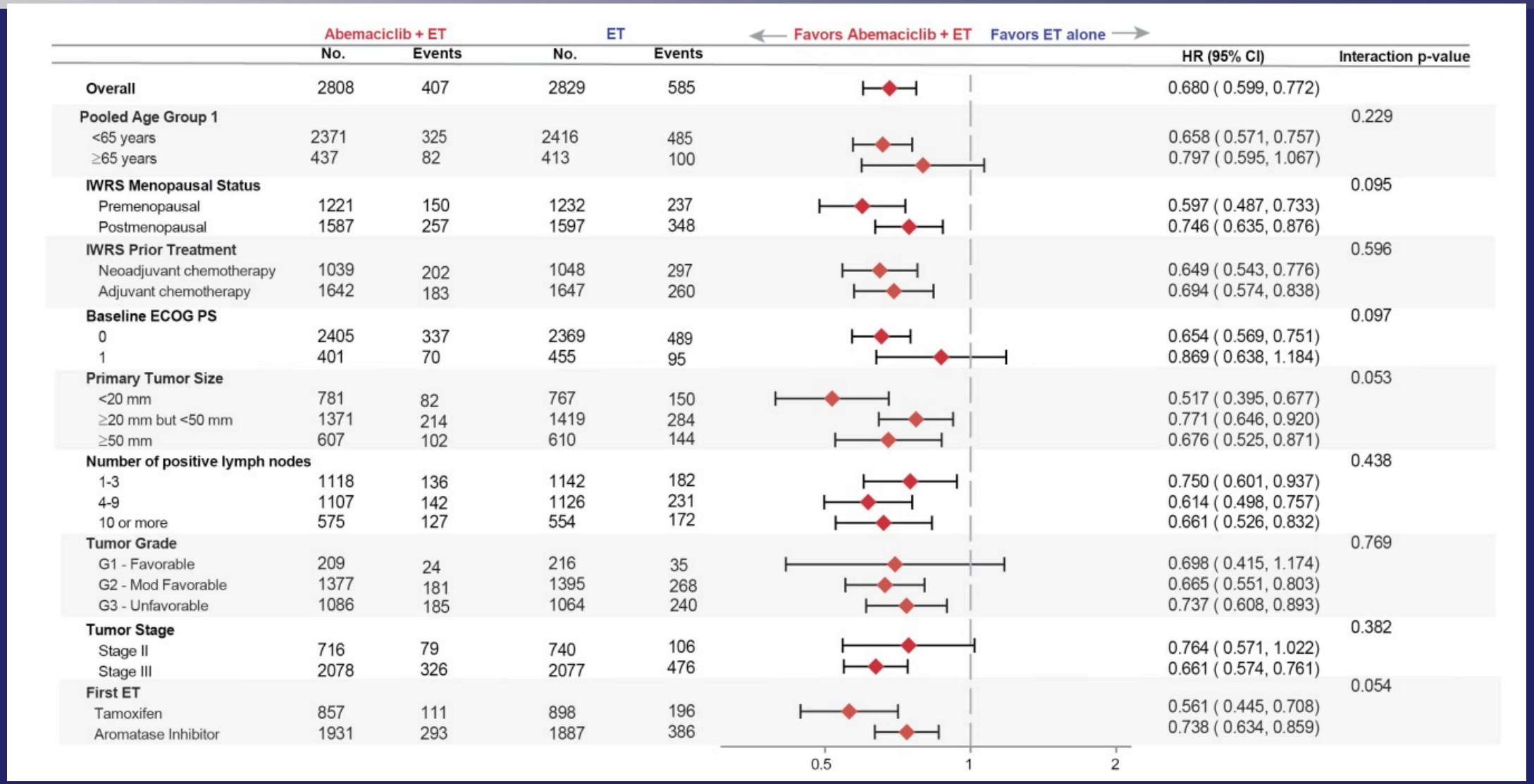
Number of IDFS events	
Abemaciclib + ET	ET Alone
407	585

HR (95% CI): 0.680 (0.599, 0.772)
Nominal p <0.001

32% reduction in the risk of developing an IDFS event.
The KM curves continue to separate and the absolute difference in IDFS rates between arms was 7.6% at 5 years

Nadia Harbeck, MD
ESMO, Madrid, Spain. 20 October 2023

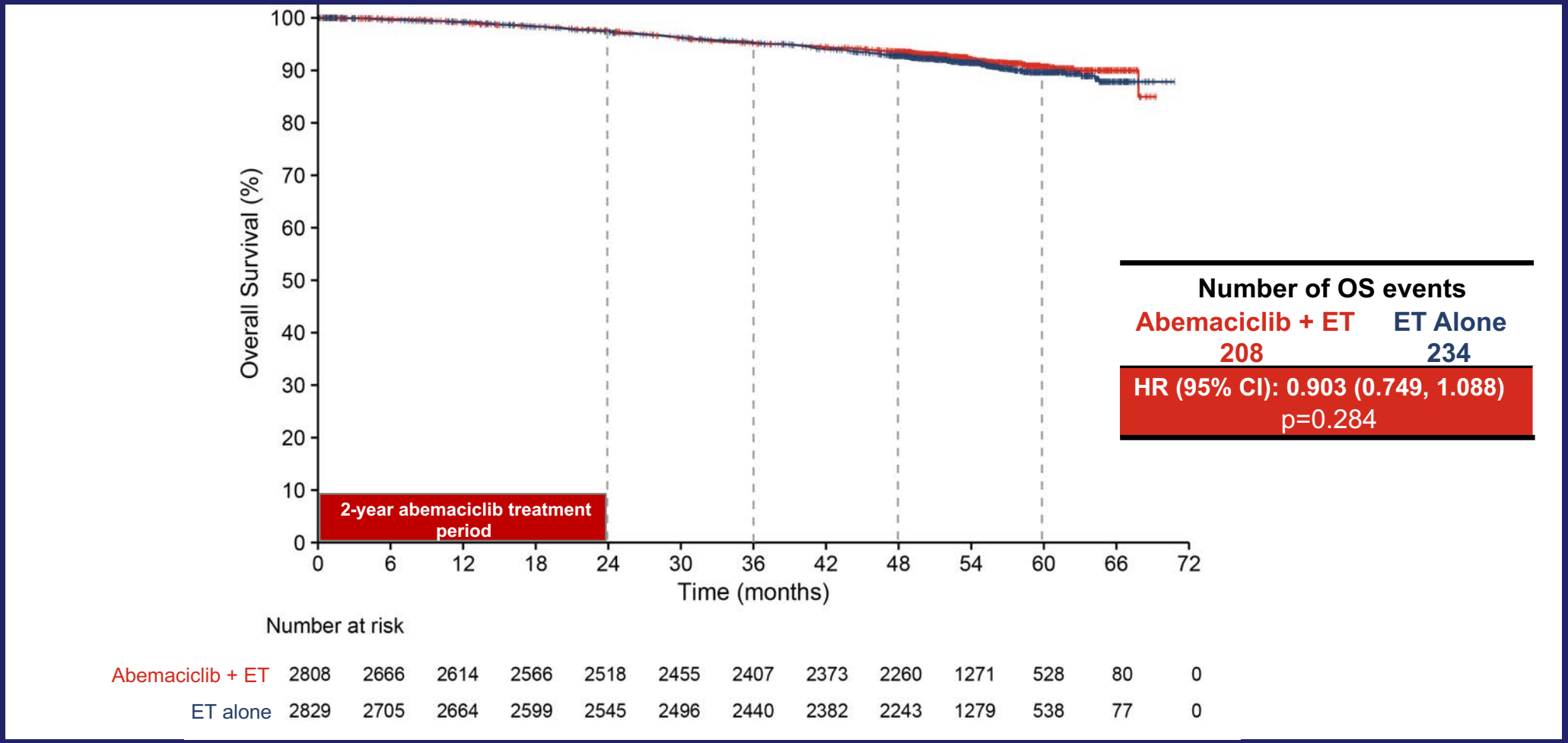
Consistent IDFS Benefit Observed in Selected Subgroups*



	Abemaciclib + ET No.	Abemaciclib + ET Events	ET No.	ET Events	HR (95% CI)	Interaction p-value
Overall	2808	407	2829	585	0.680 (0.599, 0.772)	
Pooled Age Group 1						0.229
<65 years	2371	325	2416	485	0.658 (0.571, 0.757)	
≥65 years	437	82	413	100	0.797 (0.595, 1.067)	
IWRS Menopausal Status						0.095
Premenopausal	1221	150	1232	237	0.597 (0.487, 0.733)	
Postmenopausal	1587	257	1597	348	0.746 (0.635, 0.876)	
IWRS Prior Treatment						0.596
Neoadjuvant chemotherapy	1039	202	1048	297	0.649 (0.543, 0.776)	
Adjuvant chemotherapy	1642	183	1647	260	0.694 (0.574, 0.838)	
Baseline ECOG PS						0.097
0	2405	337	2369	489	0.654 (0.569, 0.751)	
1	401	70	455	95	0.869 (0.638, 1.184)	
Primary Tumor Size						0.053
<20 mm	781	82	767	150	0.517 (0.395, 0.677)	
≥20 mm but <50 mm	1371	214	1419	284	0.771 (0.646, 0.920)	
≥50 mm	607	102	610	144	0.676 (0.525, 0.871)	
Number of positive lymph nodes						0.438
1-3	1118	136	1142	182	0.750 (0.601, 0.937)	
4-9	1107	142	1126	231	0.614 (0.498, 0.757)	
10 or more	575	127	554	172	0.661 (0.526, 0.832)	
Tumor Grade						0.769
G1 - Favorable	209	24	216	35	0.698 (0.415, 1.174)	
G2 - Mod Favorable	1377	181	1395	268	0.665 (0.551, 0.803)	
G3 - Unfavorable	1086	185	1064	240	0.737 (0.608, 0.893)	
Tumor Stage						0.382
Stage II	716	79	740	106	0.764 (0.571, 1.022)	
Stage III	2078	326	2077	476	0.661 (0.574, 0.761)	
First ET						0.054
Tamoxifen	857	111	898	196	0.561 (0.445, 0.708)	
Aromatase Inhibitor	1931	293	1887	386	0.738 (0.634, 0.859)	

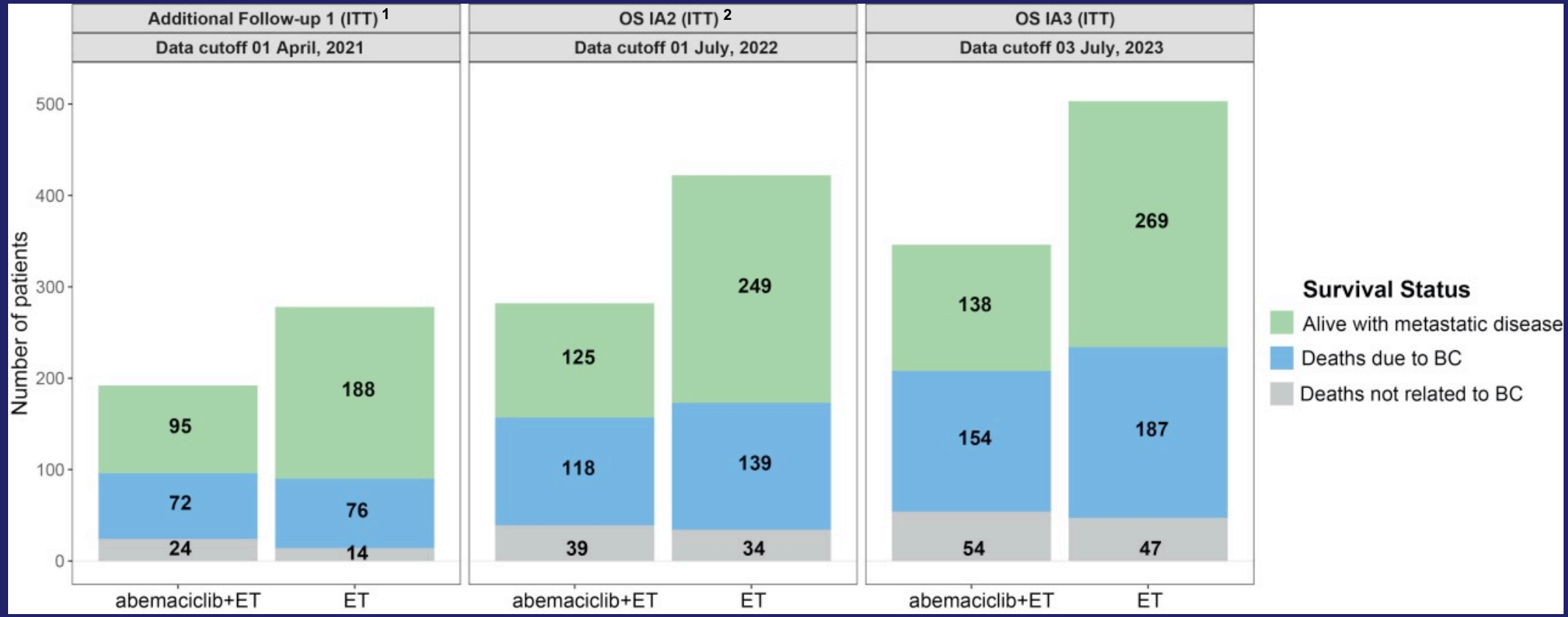
*Region of enrollment and Progesterone status data not shown

Fewer deaths in the Abemaciclib Arm in ITT



At OS IA3 statistical significance was not reached for OS

Fewer Patients with Metastatic Disease in the Abemaciclib Arm



The imbalance of incurable metastatic recurrence continues to be substantial at OS IA3

[1]Harbeck* N, Rastogi* P, et al. Ann Oncol. 2021;32(12):1571-1581 *co-first authors
[2]Johnston SRD, et al. Lancet Oncol. 2023;24:77-90

NATALEE study design

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

N=5101[b]

R 1:1[c]

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

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

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

Primary Endpoint
- iDFS using STEEP criteria

Secondary Endpoints
- Recurrence-free survival
- Distant disease-free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory Endpoints
- Loco-regional recurrence-free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Randomization stratification
Anatomic stage: II vs III
Menopausal status: Premenopausal women & men vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes/no
Geographic location: North America/Western Europe/Oceania vs Rest of world

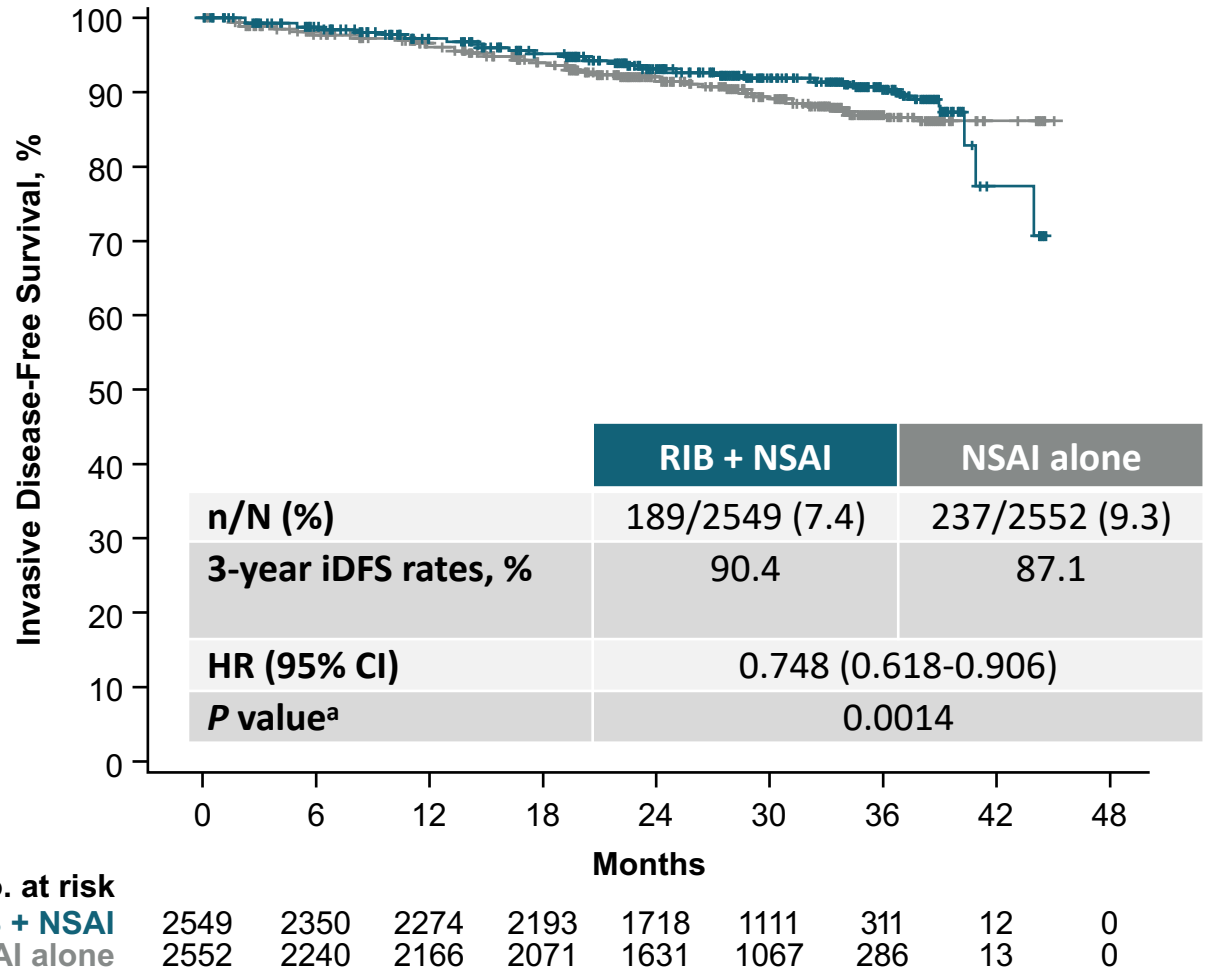
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HR+/HER2 −, hormone receptor-positive/ human epidermal growth factor receptor 2-negative; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. A trial to evaluate efficacy and safety of ribociclib with endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer (NATALEE). Accessed September, 2022. https://clinicaltrials.gov/ct2/show/NCT03701334. 2. Slamon DJ, et al. J Clin Oncol. 2019;37(suppl 15). Abstract TPS597.

Baseline characteristics

Parameter	RIB + NSAI n = 2549	NSAI alone n = 2552	All patients N = 5101
Age, median (min-max), years	52 (24-90)	52 (24-89)	52 (24-90)
Menopausal status, n (%)			
Premenopausal women and men[a]	1126 (44)	1132 (44)	2258 (44)
Postmenopausal women	1423 (56)	1420 (56)	2843 (56)
Anatomic stage[b,c], n (%)			
Stage IIA	479 (19)	521 (20)	1000 (20)
Stage IIB	532 (21)	513 (20)	1045 (20)
Stage III	1528 (60)	1512 (59)	3040 (60)
Nodal status at diagnosis, n (%)			
NX	272 (11)	264 (10)	536 (11)
N0	694 (27)	737 (29)	1431 (28)
N1	1050 (41)	1049 (41)	2099 (41)
N2/N3	483 (19)	467 (18)	950 (19)
Prior ET, n (%)[d]			
Yes	1824 (72)	1801 (71)	3625 (71)
Prior (neo)adjuvant CT, n (%)			
Yes	2249 (88)	2245 (88)	4494 (88)
ECOG PS, n (%)			
0	2106 (83)	2132 (84)	4238 (83)
1	440 (17)	418 (16)	858 (17)

[a] In the RIB+NSAI arm there were 11 men (0.4%) and in the NSAI alone arm there were 9 men (0.4%). [b] A total of 14 patients with Stage I disease were included: 9 pts (0.4%) in the RIB + ET arm and 5 pts (0.2%) in the ET alone arm. [c] Stage is derived using TNM from surgery for patients having not received (neo)adjuvant treatment, or as worst stage derived using TNM at diagnosis and TNM from surgery for patients having received (neo)adjuvant treatment. [d] Prior OFS was received by 670 pts (26.3%) in the RIB + NSAI arm and 620 pts (24.3%) in the NSAI alone arm.
CT, chemotherapy; ET, endocrine therapy; N0, no nodal involvement; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, 10 or more axillary lymph nodes or collarbone lymph nodes; NSAI, nonsteroidal aromatase inhibitor; NX, regional nodes were not assessed.

NATALEE iDFS



	RIB + NSAI	NSAI alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-year iDFS rates, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	0.0014	

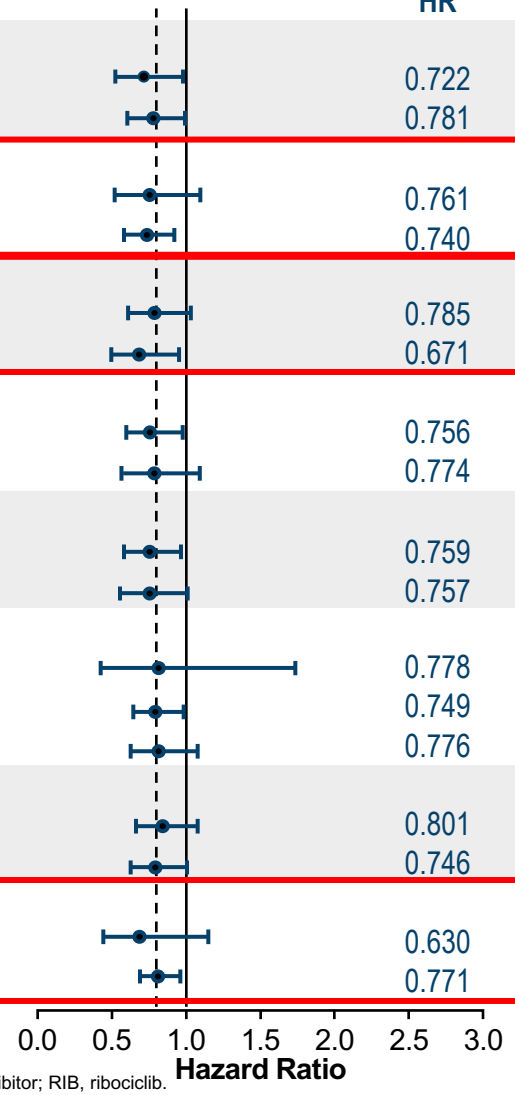
No. at risk									
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

[a] One-sided *P* value.
ET, endocrine therapy; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

- Median follow-up for iDFS is 27.7 mo for both arms
- Absolute iDFS benefit of RIB + NSAI at 3 years was 3.3%
- Risk of invasive disease was reduced by 25.2% with RIB + NSAI vs NSAI alone
- Based on the *P* value of 0.0014, the IDMC recommended to designate this as the final prespecified primary outcome analysis due to statistically significant and clinically meaningful efficacy; ongoing patients will remain on treatment and follow-up will continue as prespecified

iDFS benefit was consistent across pre-specified key subgroups

Subgroup	RIB + NSAI n = 2549	NSAI only n = 2552	HR	(95% CI)
Menopausal status				
Pre-menopausal women and men	71/1126	93/1132	0.722	(0.530, 0.983)
Post-menopausal women	118/1423	144/1420	0.781	(0.613, 0.997)
AJCC stage				
Stage II	49/1011	65/1034	0.761	(0.525, 1.103)
Stage III	140/1528	172/1512	0.740	(0.592, 0.925)
Prior CT				
Neoadjuvant	111/1085	132/1095	0.785	(0.610, 1.011)
Adjuvant	63/1223	89/1220	0.671	(0.486, 0.927)
Prior ET				
Yes	127/1824	157/1801	0.756	(0.598, 0.955)
No	62/725	80/751	0.774	(0.556, 1.079)
Region				
North America/Western Europe/Oceania	111/1563	139/1565	0.759	(0.591, 0.974)
Rest of world	78/986	98/987	0.757	(0.562, 1.019)
Histological grade at time of surgery				
Grade 1	9/213	12/217	0.778	(0.328, 1.846)
Grade 2	102/1460	125/1432	0.749	(0.577, 0.973)
Grade 3	61/684	78/702	0.776	(0.555, 1.085)
Ki67 status[a]				
Ki67 ≤20	76/1199	95/1236	0.801	(0.593, 1.083)
Ki67 >20	82/920	105/938	0.746	(0.559, 0.996)
Nodal status[b,c]				
N0	16/285	28/328	0.630	(0.341, 1.165)
N1-N3	173/2261	208/2219	0.771	(0.630, 0.944)



[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging. [c] Nodal status is from the worse stage derived per surgical specimen or at diagnosis

AJCC, American Joint Committee on Cancer; ET, endocrine therapy; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Summary: Two Positive Adjuvant CDK4/6i Trials, One Adjuvant CDK4/6i Approved

	NATALEE (ribociclib)	MONARCH-E (abemaciclib)
N	5101	5637
Length of CDK4/6i	3 years	2 years
Prior chemotherapy	88%	95%
Grade 3	27%	38%
Node negative	28%	0.2%
N1	41%	40%
≥N2	19%	60%
Discontinued IP prematurely	30%	28% at 19 mos f/u
Median follow up	27.7 mos	54 mos
3-year iDFS	90.4% vs. 87.1% △3.3%, HR 0.748, P=0.0014	89.2% vs 84.4% △4.8%
5-year IDFS	Not reached	83.6 vs. 76.0% △7.6%, HR 0.680, p<0.001

Select Trials of Neoadjuvant Ribociclib or Abemaciclib for ER-Positive, HER2-Negative Localized BC

Study	Phase	Setting	Treatment arms	Primary endpoint
MONALEESA-1 (Curigliano 2016)	II	Postmenopausal, Grade II/III, ≥1 cm breast lesion diameter	• Letrozole • Letrozole + ribociclib (400 or 600 mg/d)	CCCA Ribociclib 400 mg/d: 96% Ribociclib 600 mg/d: 92% Letrozole alone: 69%
neoMONARCH (Hurvitz 2020)	II	Postmenopausal, Stage I (tumor ≥1 cm), II, IIIA, or IIIB	• Anastrozole • Abemaciclib • Anastrozole + abemaciclib	CCCA Anastrozole: 14% Abemaciclib: 58% Anastrozole + abemaciclib: 68%
CORALLEEN (Prat 2020)	II	Postmenopausal, Stage I-IIIA, ≥2 cm breast lesion diameter	• Chemotherapy • Letrozole + ribociclib	ROR-Low Chemotherapy: 47% Letrozole + ribociclib: 48%
FELINE (Khan 2020)	II	Postmenopausal, >2 cm breast lesion diameter or node-positive	• Letrozole + placebo • Letrozole + ribociclib	Rate of PEPI score 0 Letrozole + placebo: 26% Letrozole + ribociclib: 25%

CCCA = complete cell cycle arrest; ROR = risk of relapse

Adjuvant PARP inhibitor

What about patients with HR+ high risk breast cancer AND a *BRCA1* or *BRCA2* mutation?

OlympiA: Trial schema

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → **Surgery** → **+/- Radiotherapy**

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → **≥ 6 cycles Adjuvant Chemotherapy** → **+/- Radiotherapy**

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

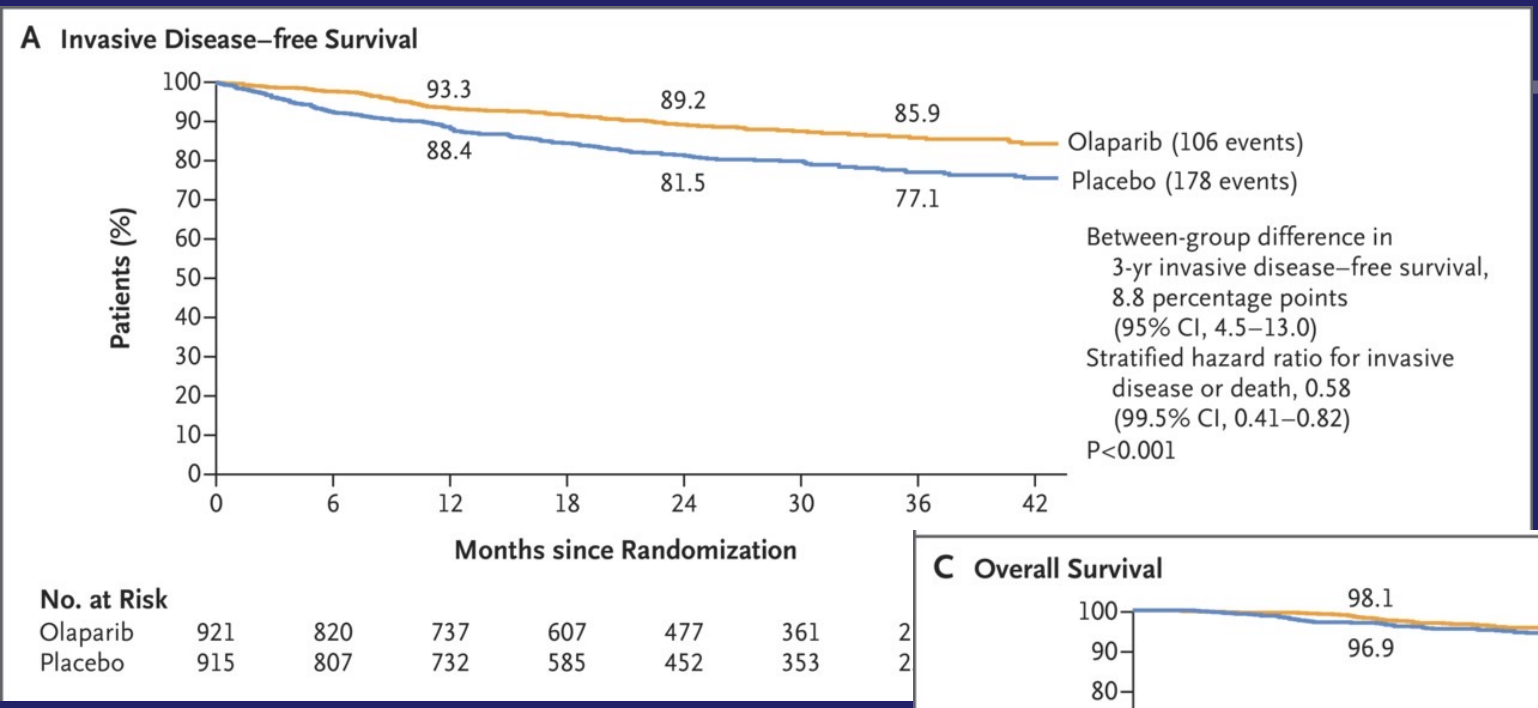
Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

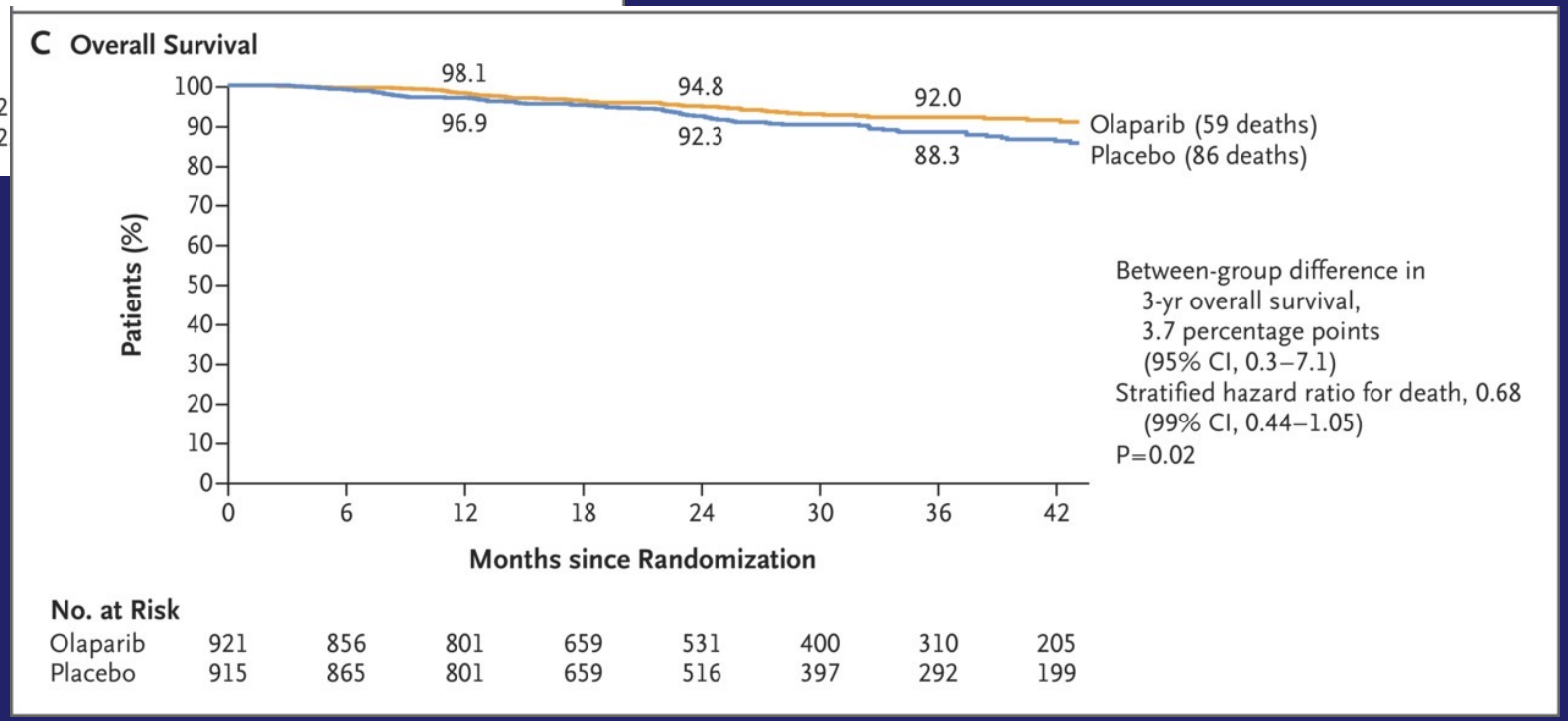
Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Hormone-receptor status — no. (%)‡		
Hormone-receptor positive and HER2 negative§	168 (18.2)	157 (17.2)
Triple-negative breast cancer¶	751 (81.5)	758 (82.8)

Tutt ANJ et al. N Engl J Med 2021;384:2394-2405

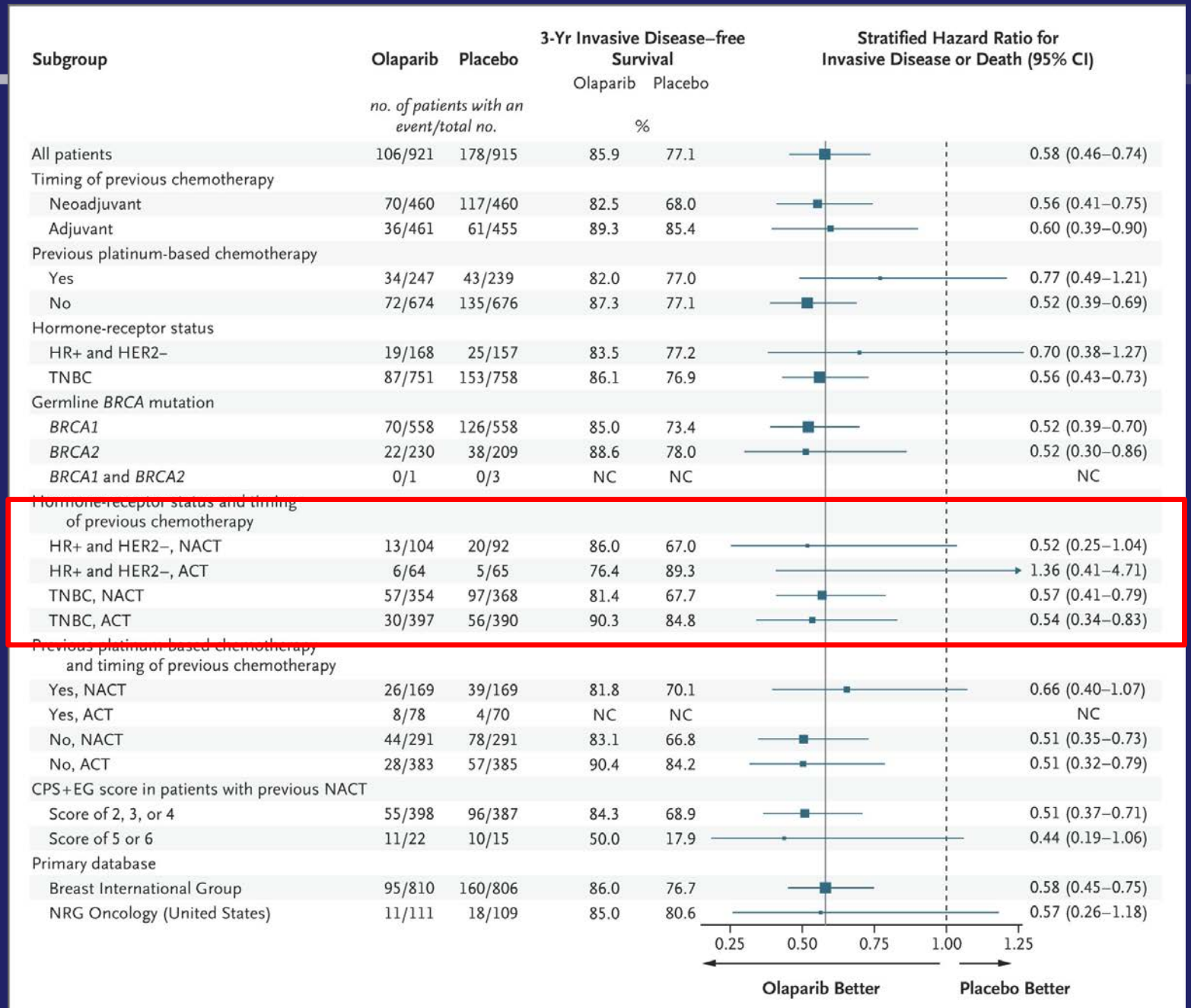
OlympiA: Adjuvant Olaparib for g*BRCA1/2m* BC





Tutt ANJ et al. N Engl J Med 2021;384:2394-2405

OlympiA: Adjuvant Olaparib for g*BRCA1/2m* BC



Subgroup	Olaparib	Placebo	3-Yr Invasive Disease–free Survival		Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
			Olaparib	Placebo	
	no. of patients with an event/total no.		%		
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Timing of previous chemotherapy					
Neoadjuvant	70/460	117/460	82.5	68.0	0.56 (0.41–0.75)
Adjuvant	36/461	61/455	89.3	85.4	0.60 (0.39–0.90)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC
Hormone-receptor status and timing of previous chemotherapy					
HR+ and HER2–, NACT	13/104	20/92	86.0	67.0	0.52 (0.25–1.04)
HR+ and HER2–, ACT	6/64	5/65	76.4	89.3	1.36 (0.41–4.71)
TNBC, NACT	57/354	97/368	81.4	67.7	0.57 (0.41–0.79)
TNBC, ACT	30/397	56/390	90.3	84.8	0.54 (0.34–0.83)
Previous platinum-based chemotherapy and timing of previous chemotherapy					
Yes, NACT	26/169	39/169	81.8	70.1	0.66 (0.40–1.07)
Yes, ACT	8/78	4/70	NC	NC	NC
No, NACT	44/291	78/291	83.1	66.8	0.51 (0.35–0.73)
No, ACT	28/383	57/385	90.4	84.2	0.51 (0.32–0.79)
CPS+EG score in patients with previous NACT					
Score of 2, 3, or 4	55/398	96/387	84.3	68.9	0.51 (0.37–0.71)
Score of 5 or 6	11/22	10/15	50.0	17.9	0.44 (0.19–1.06)
Primary database					
Breast International Group	95/810	160/806	86.0	76.7	0.58 (0.45–0.75)
NRG Oncology (United States)	11/111	18/109	85.0	80.6	0.57 (0.26–1.18)

Tutt ANJ et al. N Engl J Med 2021;384:2394-2405

Select Trials of Neoadjuvant Palbociclib for ER-Positive, HER2-Negative Localized BC

Study	Phase	Setting	Treatment arms	Primary endpoint
NeoPalAna (Ma 2017)	II	Any menopausal status, Stage II/III	• Anastrozole → palbociclib + anastrozole	CCCA (before vs after adding palbociclib): 26% vs 87%
NeoPal (Cottu 2018)	II	Any menopausal status, Stage II/III, node-positive not candidate for breast conserving surgery	• Chemotherapy • Letrozole + palbociclib	RCB 0-I rate: Chemotherapy: 16% Letrozole + palbociclib: 8%
PALLET (Johnston 2019)	II	Postmenopausal, ≥2 cm breast lesion diameter	• Letrozole • Letrozole → palbociclib + letrozole • Palbociclib → palbociclib + letrozole • Palbociclib + letrozole	<u>CCCA:</u> Letrozole: 47% Palbociclib + letrozole: 59% <u>Clinical response:</u> Letrozole: 50% Palbociclib + letrozole: 54%
PROMETEO-II (Pernas Simon 2023)	I	Any menopausal status, residual disease s/p anthracycline/taxane-based neoadjuvant chemo	• Palbociclib + letrozole prior to surgery (SUR)	CCCA: Prior to SUR: 4% At SUR: 59%

CCCA = complete cell cycle arrest; RCB = residual cancer burden

RTP RESEARCH TO PRACTICE

Conclusions

- High risk ER+ LN+ breast cancer available adjuvant options
  - ≥4 LN OR 1-3 LN and either grade 3 or T3: Abemaciclib
  - *BRCA* mutated, ≥4 LN or non-pCR and CPS EG ≥3 consider olaparib
  - For those who qualify for both, do not give abemaciclib and olaparib concurrently
  - Data regarding sequencing olaparib and abemaciclib is lacking
- Promising data for immune therapy + chemo!!
  - BUT….no EFS data. Toxicity (irreversible and/or life-threatening) must be considered. Not yet approved!

Agenda

Module 1: Role of Genomic Assays in Treatment Decision-Making for Localized ER-Positive, HER2-Negative Breast Cancer — Dr Goetz

Module 2: Integration of Ovarian Function Suppression into the Management of Breast Cancer in Premenopausal Patients — Dr Burstein

Module 3: Role of CDK4/6 Inhibitors and Other Novels Agents in Therapy for ER-Positive Localized Breast Cancer — Dr Hurvitz

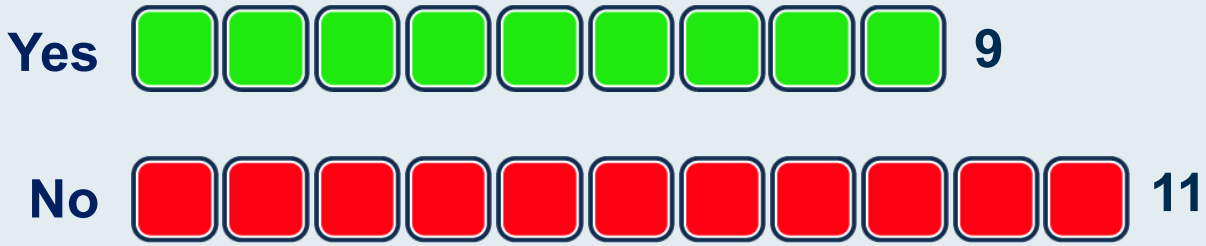
Module 4: Optimizing the Use of Neoadjuvant and Adjuvant Therapy for Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 5: Emerging Role of Circulating Tumor DNA Evaluation in the Management of Breast Cancer — Dr Pusztai

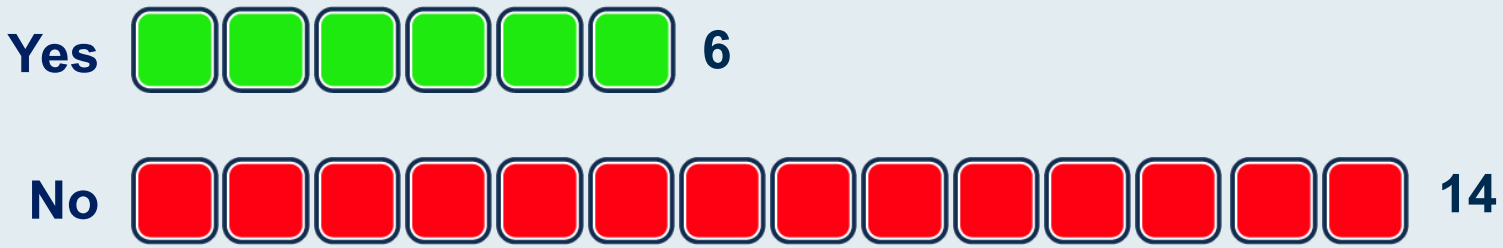
RTP
RESEARCH
TO PRACTICE

Based on your personal clinical experience and knowledge of available data, should olaparib be offered to patients with localized breast cancer and either a somatic or germline BRCA mutation in the following situations?

Any number of positive nodes



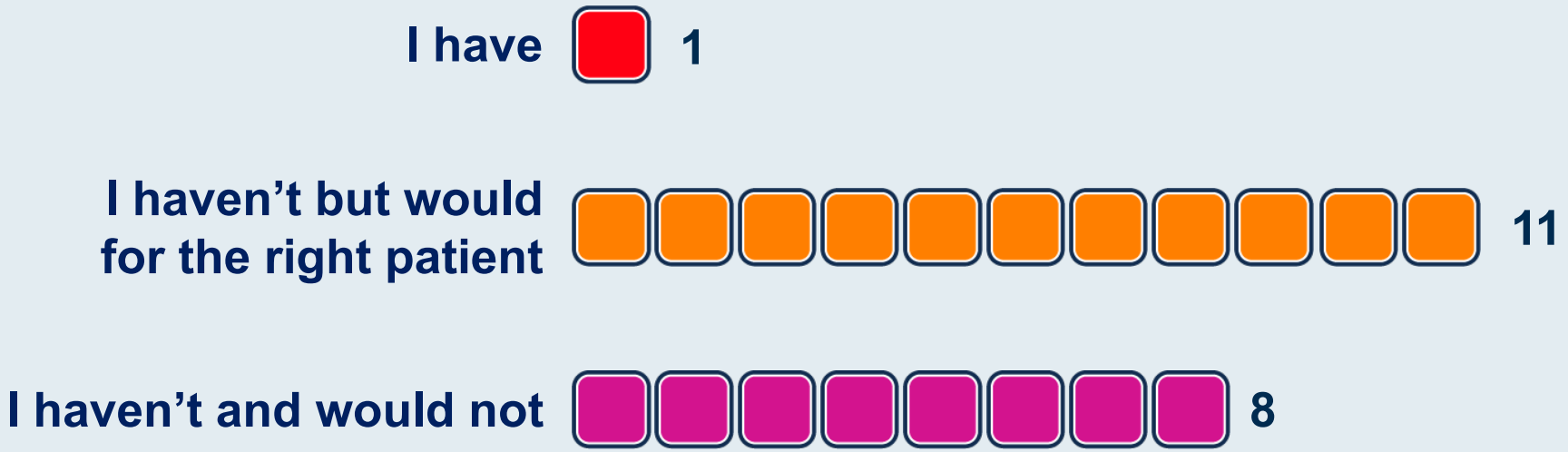
Select patients with node-negative tumors



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

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

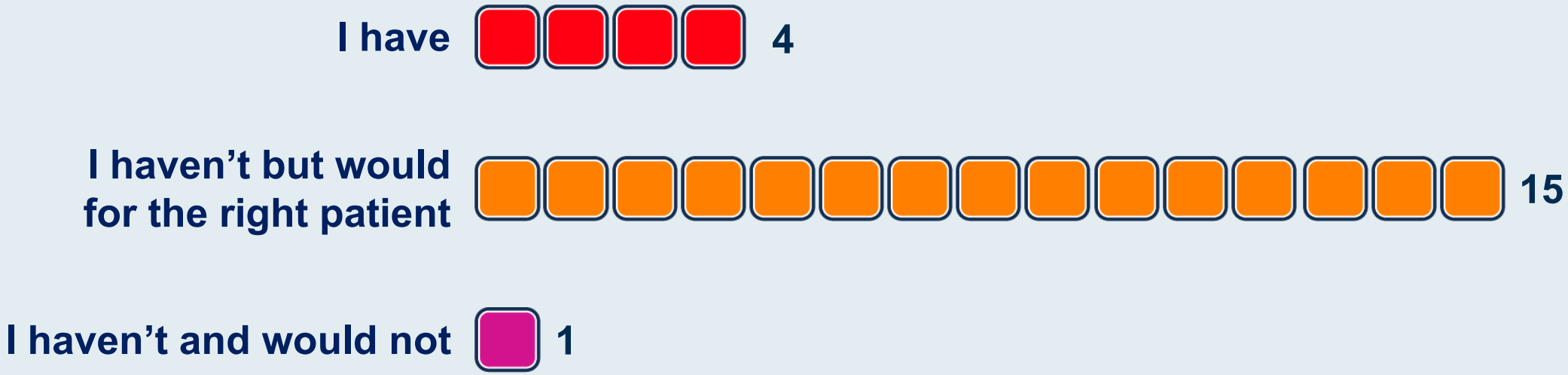


TNBC = triple-negative breast cancer

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

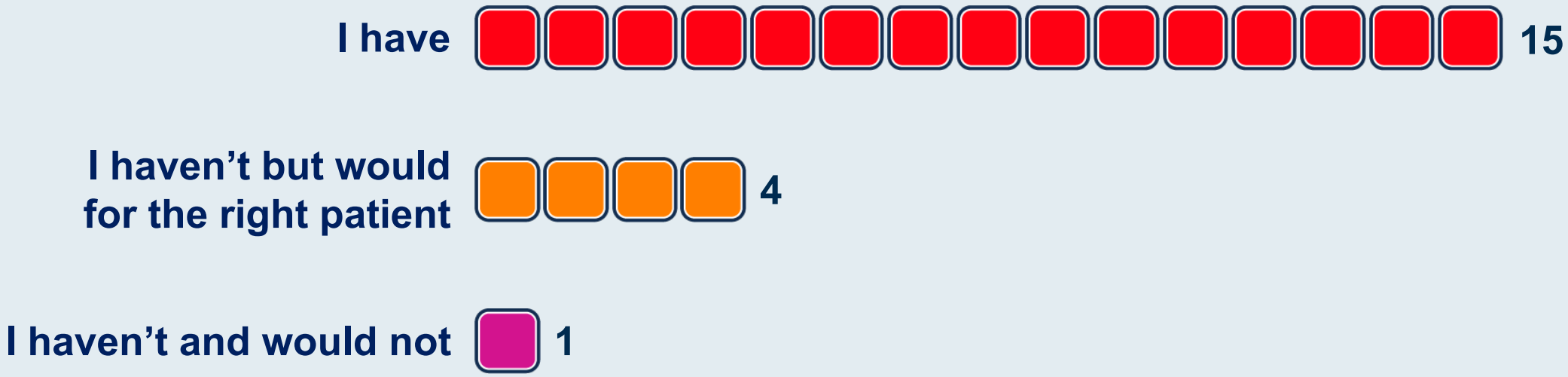
Regulatory and reimbursement issues aside, have you attempted or would you attempt to access olaparib as part of adjuvant therapy for a patient with a germline PALB2 mutation and TNBC who had residual disease after neoadjuvant chemotherapy?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

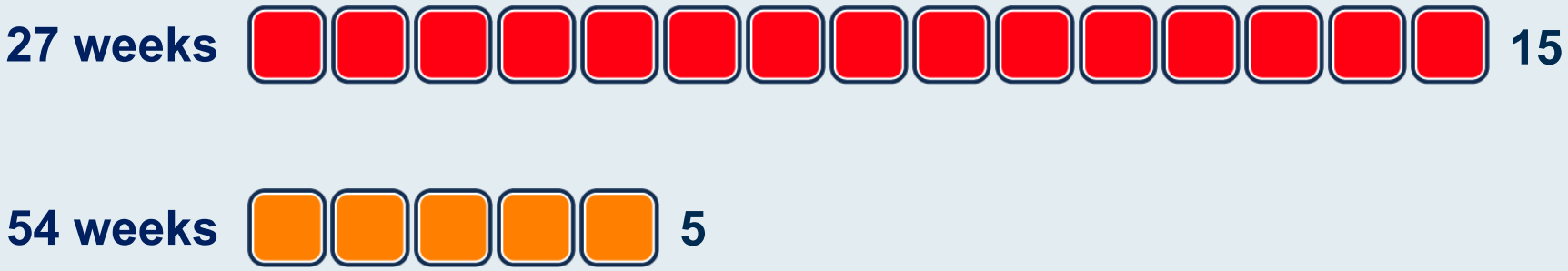
Regulatory and reimbursement issues aside, have you combined or would you combine olaparib with adjuvant pembrolizumab for a patient with a germline BRCA mutation and PD-L1-positive TNBC who had residual disease after neoadjuvant chemotherapy/ pembrolizumab?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

When administering neoadjuvant and adjuvant pembrolizumab, for how long do you generally administer the pembrolizumab in the adjuvant setting?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

KEYNOTE-522: Neoadjuvant pembrolizumab for localized triple-negative breast cancer; SCARLET: Phase III trial of shorter-course neoadjuvant pembrolizumab with chemotherapy

Paolo Tarantino, MD

Priyanka Sharma, MD

RTP
RESEARCH
TO PRACTICE

Adjuvant immunotherapy for localized triple-negative breast cancer: ALEXANDRA/IMpassion030 Phase III trial

Eric P Winer, MD

RTP
RESEARCH
TO PRACTICE

Genetic testing and role of PARP inhibitor/immunotherapy combinations for patients with triple-negative breast cancer; PARP inhibitor-associated toxicities

Adam M Brufsky, MD, PhD

RTP
RESEARCH
TO PRACTICE

Tolerability of the KEYNOTE-522 regimen; localized triple-negative breast cancer with BRCA mutations

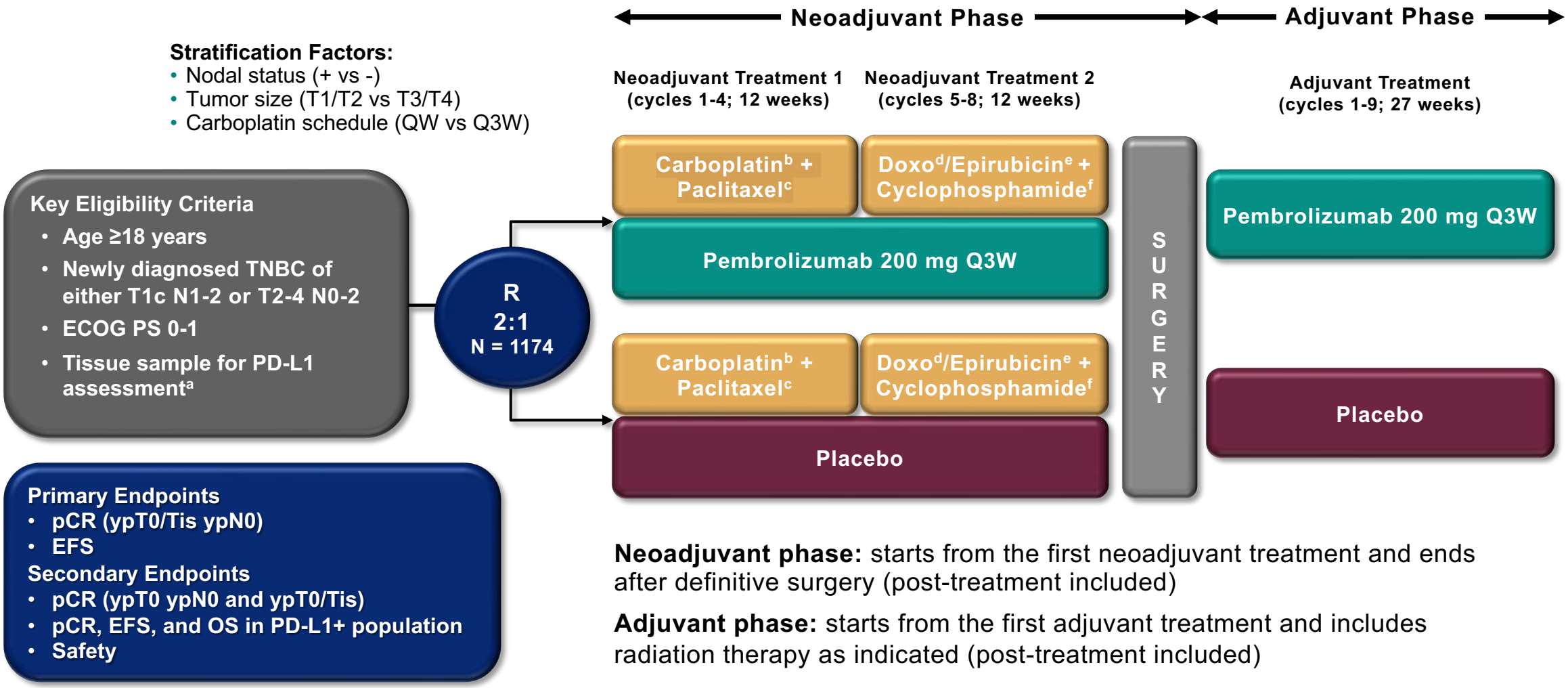
Jane Lowe Meisel, MD

RTP
RESEARCH
TO PRACTICE

Escalating and De-Escalating Therapy for Early-Stage Triple-Negative Breast Cancer

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

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



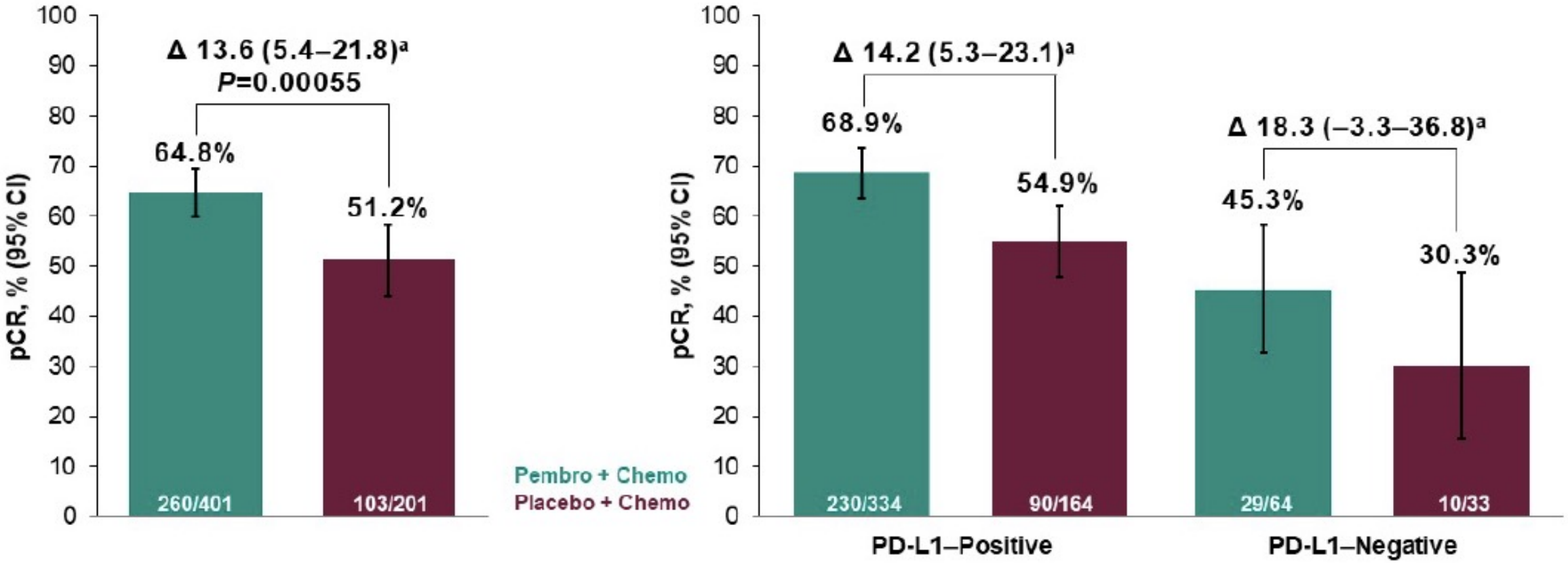
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

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

[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Schmid P et al. *NEJM* 2020;382:810-821

KEYNOTE-522: pCR endpoint

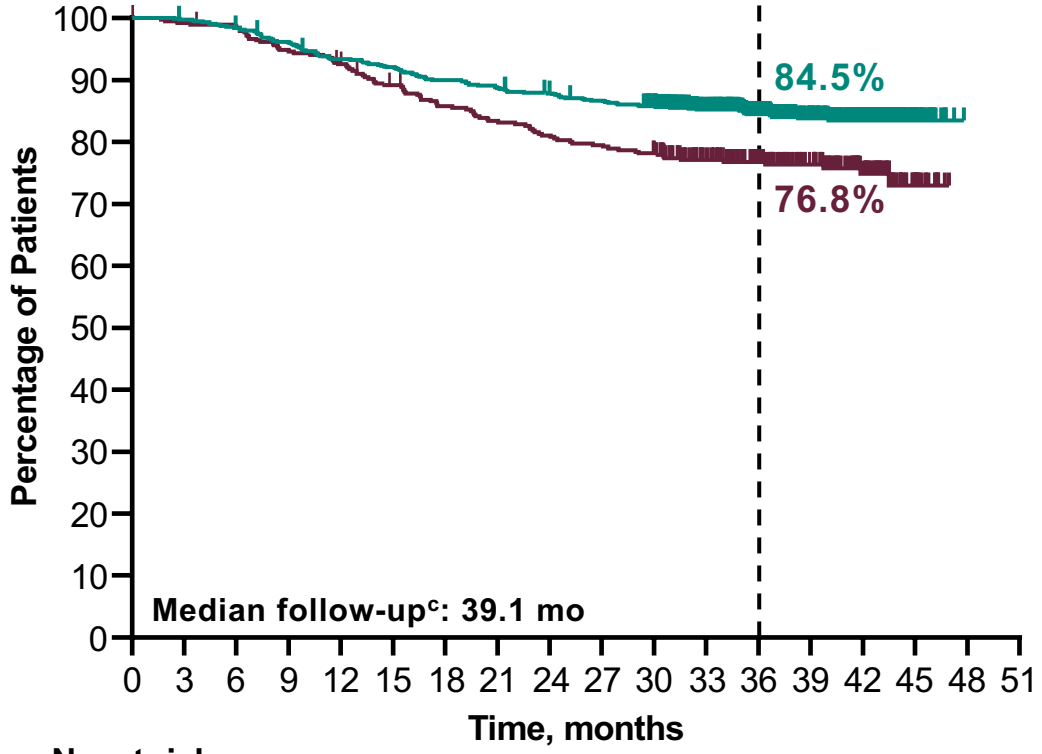


Schmid P et al. *ESMO* 2019; Abstract 1812

Schmid P et al. *NEJM* 2020;382:810-821

KEYNOTE-522: EFS

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

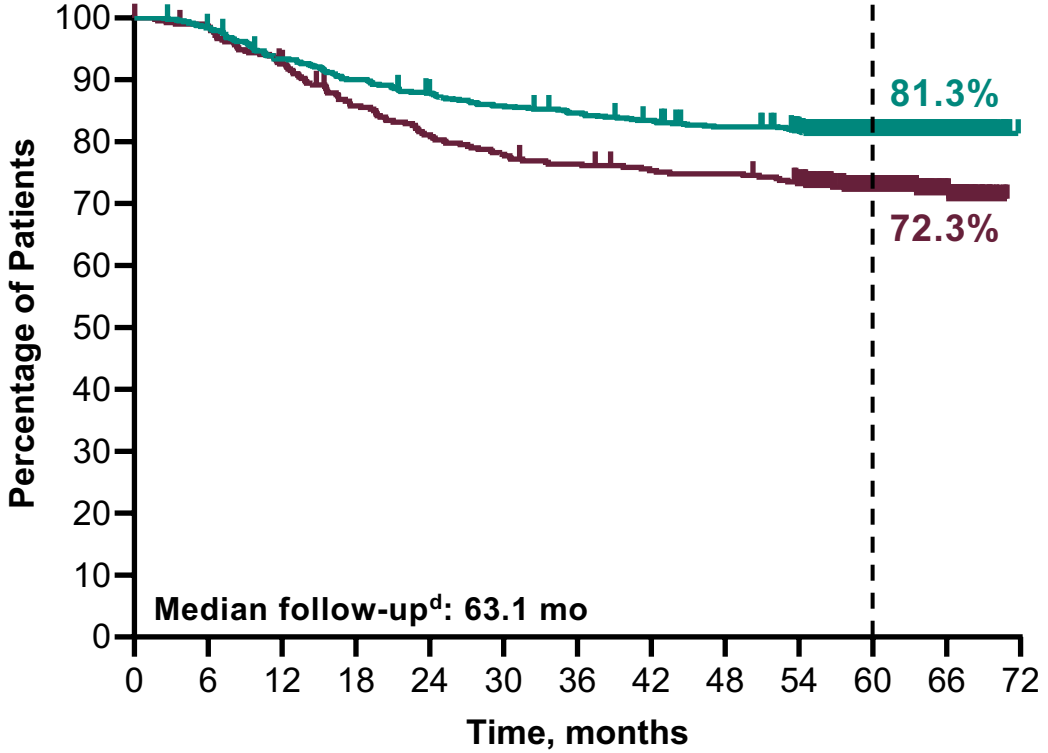


No. at risk

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

Schmid P et al. *NEJM* 2022;386:556-567

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



No. at risk

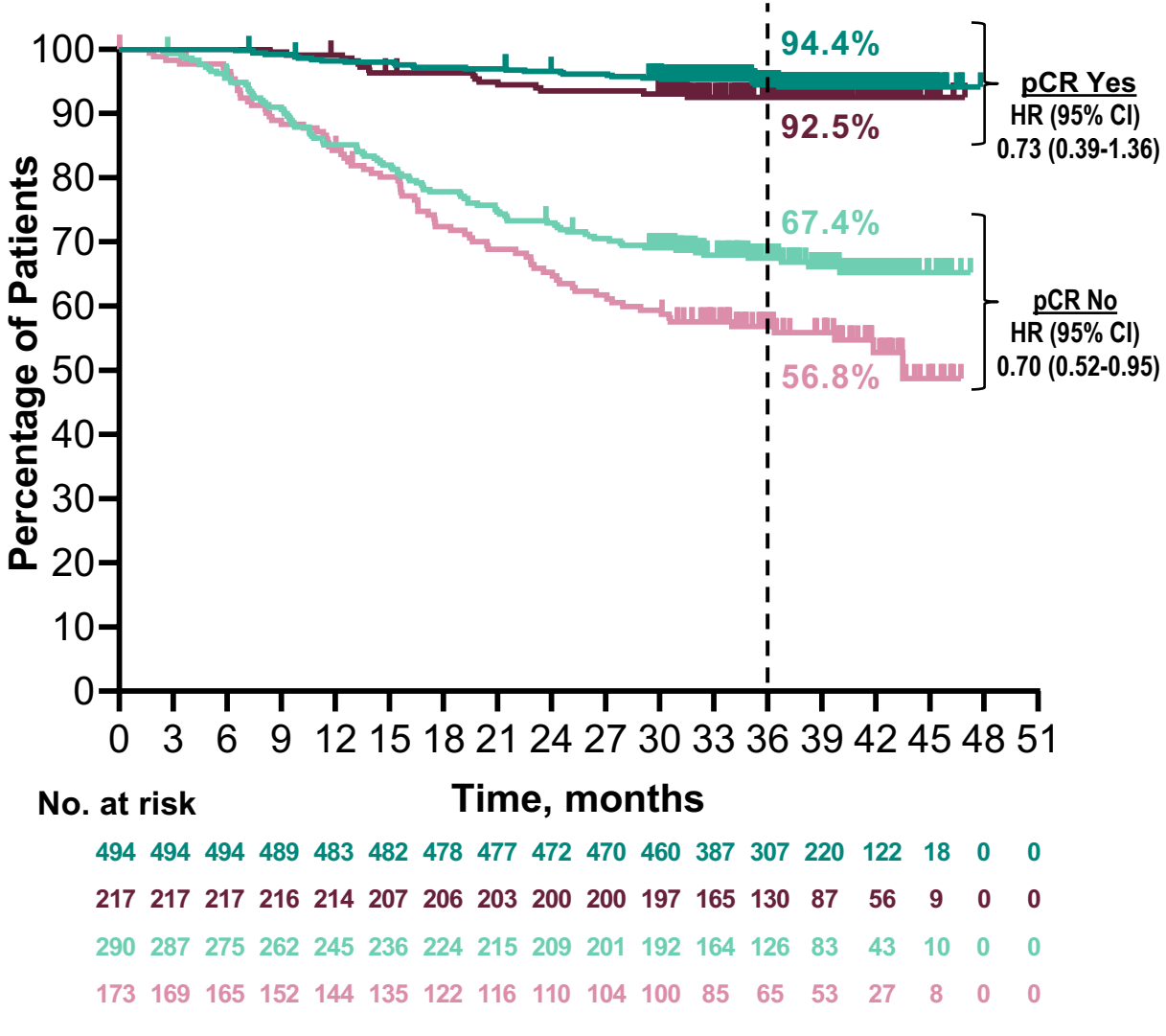
784	769	728	702	681	665	654	643	631	612	411	162	0
390	382	358	329	311	299	292	286	284	274	189	79	0

Schmid P et al. *ESMO* 2023; Abstract LBA18

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

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

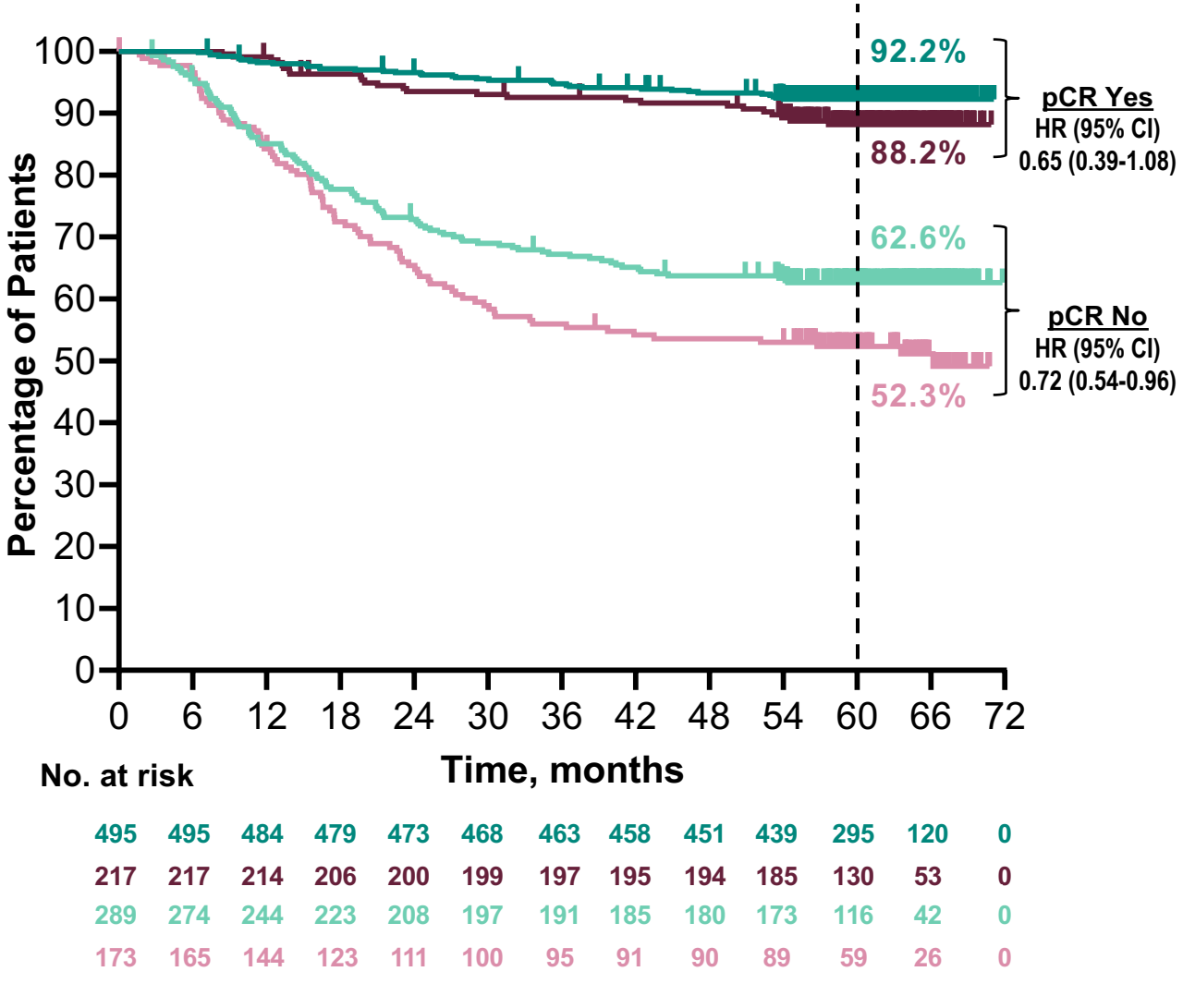
IA4



Data cutoff date: March 23, 2021.

Schmid P et al. *NEJM* 2022;386:556-567

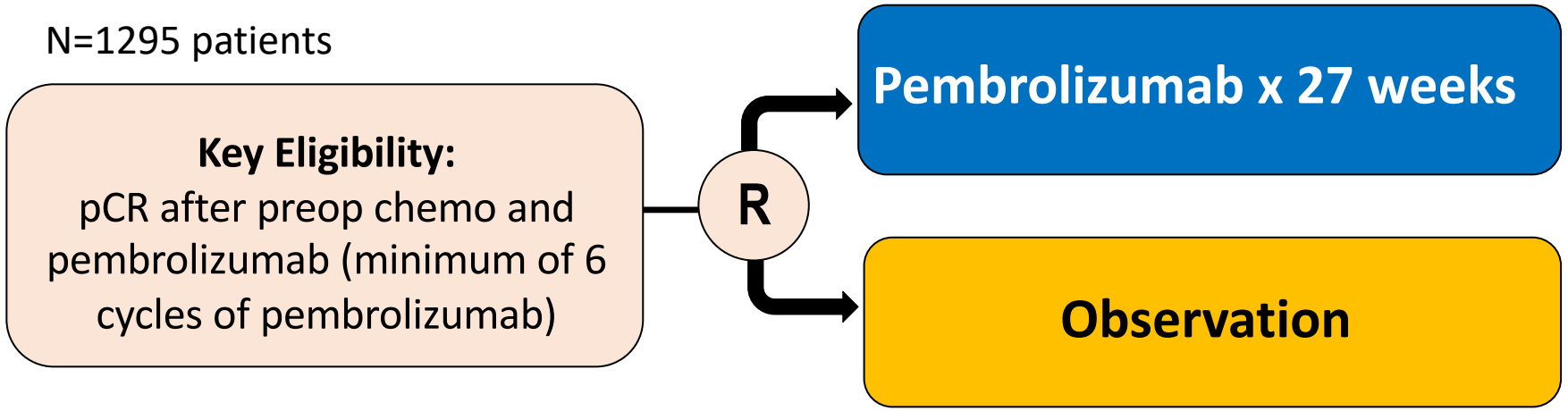
IA6



Data cutoff date: March 23, 2023.

Schmid P et al. *ESMO* 2023; Abstract LBA18

OptimICE-PCR: De-Escalation of Therapy in Early-Stage TNBC Patients Who Achieve pCR After Neoadj Chemo With Checkpoint Inhibitor Therapy



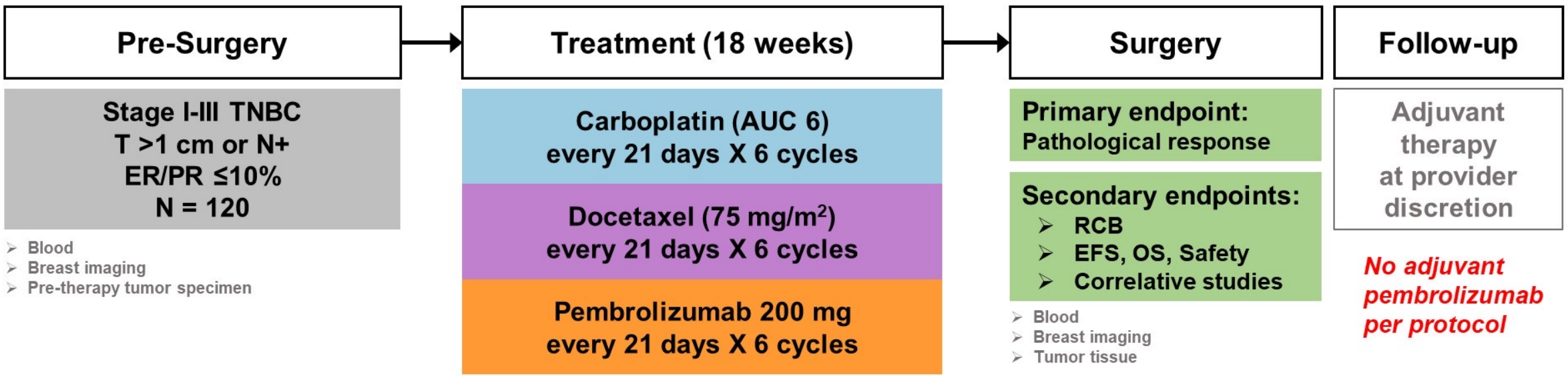
Primary outcome: Recurrence-Free Survival (RFS)
Secondary outcomes: toxicity, OS, locoregional recurrences, radiation AEs

PI: Sara Tolaney

Now accruing

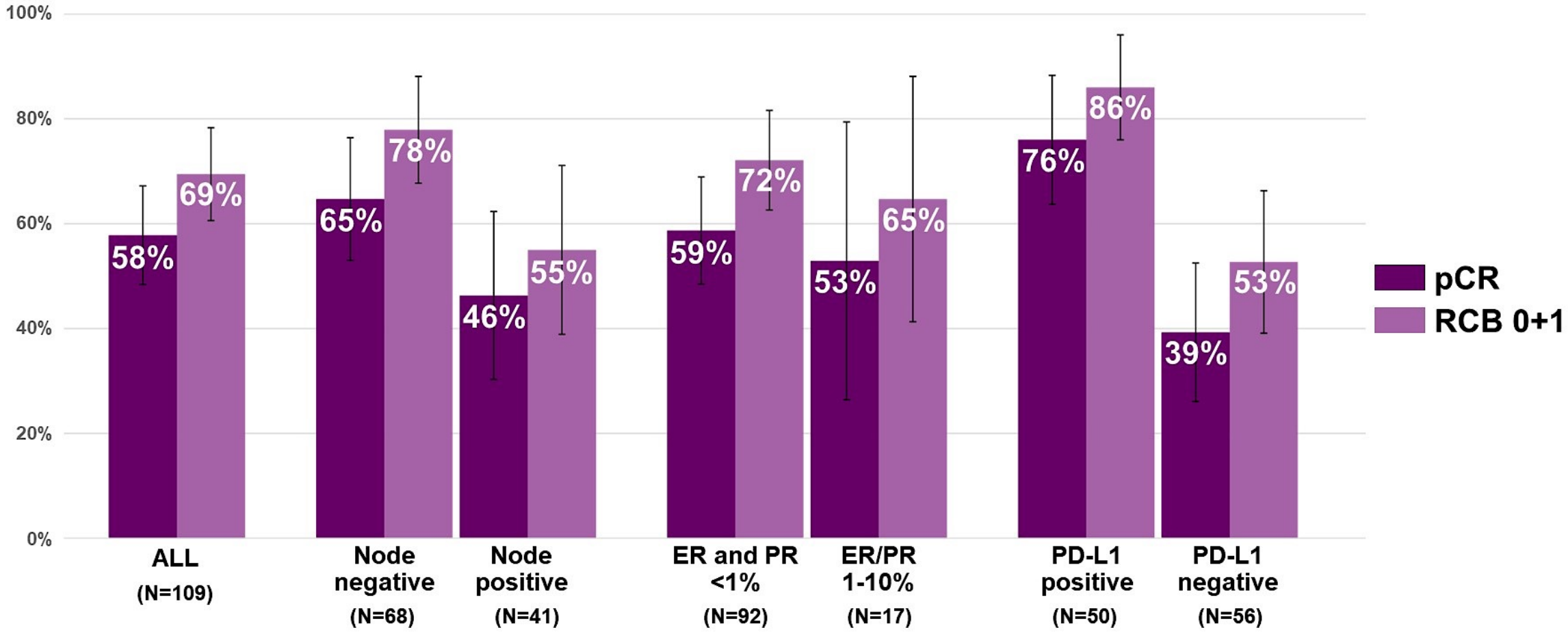
Clinicaltrials.gov: NCT05812807

Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)



Sharma P. ASCO 2022; Abstract 513

NeoPACT: pCR and RCB 0+1



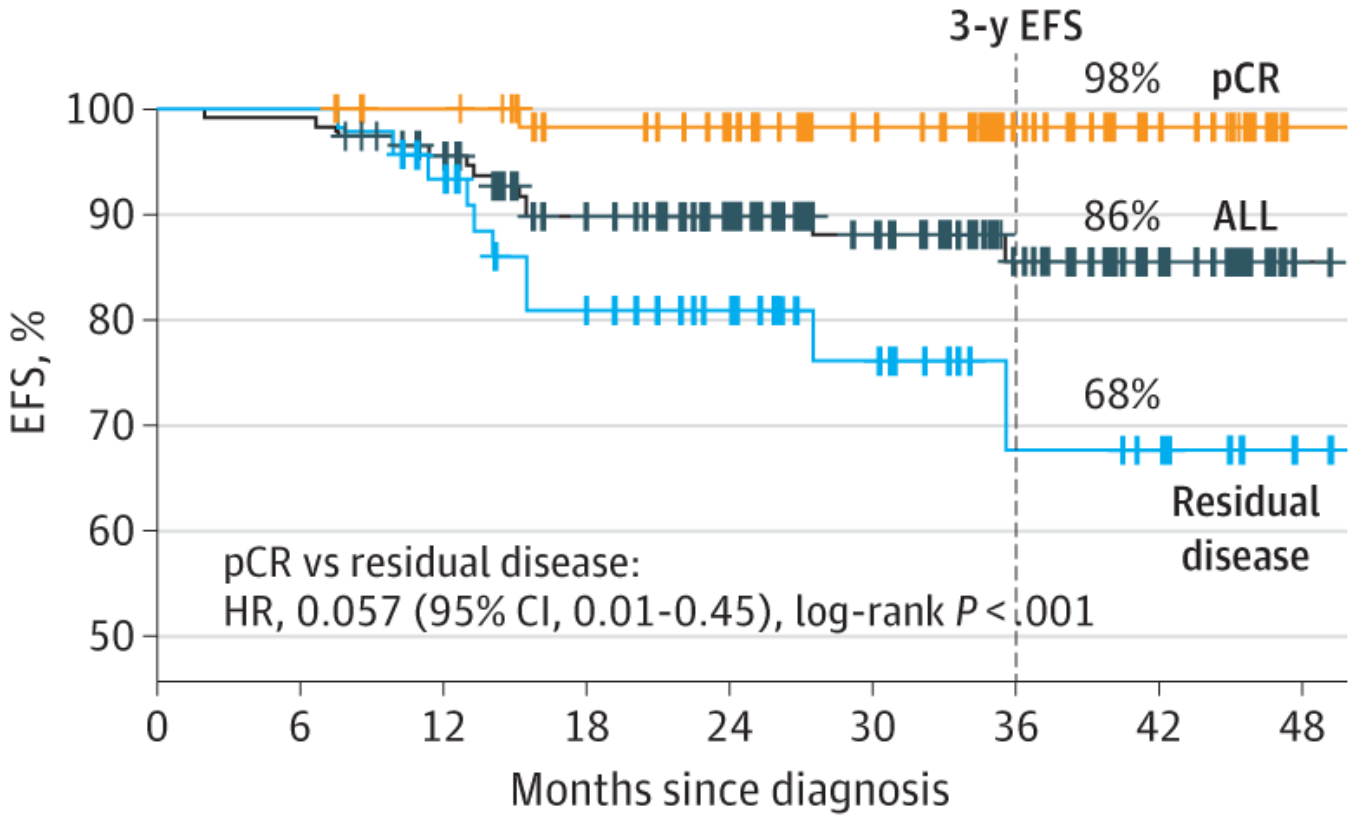
- No patients had disease progression during neoadjuvant treatment.
- Among patients with stage II-III disease and ER & PR IHC <1%, pCR and RCB 0+1 rates were 59% and 69%, respectively.
- pCR in TNM stage I, II, and III disease was 69%, 59%, and 43%, respectively.

Error bars represent 95% binomial confidence intervals

Sharma P. ASCO 2022; Abstract 513

NeoPACT: Event-Free Survival

Median follow-up:
27.4 months



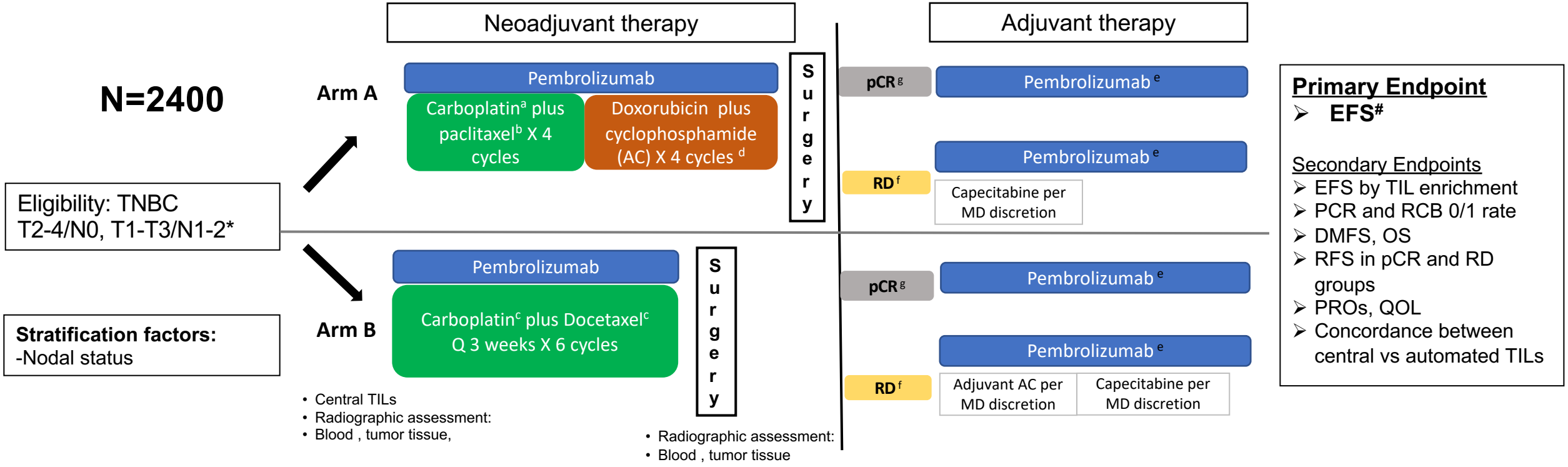
No. at risk									
ALL	115	114	103	87	71	53	32	17	1
pCR	64	64	62	55	46	37	24	11	0
Residual disease	47	47	40	31	25	16	8	6	1

Sharma P et al. *JAMA Oncol* 2023;[Online ahead of print].

S2212: Anthracycline free chemoimmunotherapy adapted to pCR (SCARLET)

Randomized non-inferiority trial

Hypothesis: In patients with early stage TNBC, carboplatin-taxane chemoimmunotherapy is non-inferior to taxane-platinum-anthracycline-based chemoimmunotherapy



*T4/N+ , any N3 and inflammatory breast cancer excluded

[a]Carboplatin QW or Q3W, [b] Paclitaxel QW.

[c] Carboplatin Q3W, Docetaxel Q3W

[d] AC every 2 or 3 weeks

[e] Total duration of neo plus adjuvant pembrolizumab = 51 weeks

[f] Adjuvant Olaparib per MD discretion in gBRCA+ allowed

[g] No Further Adjuvant chemotherapy.

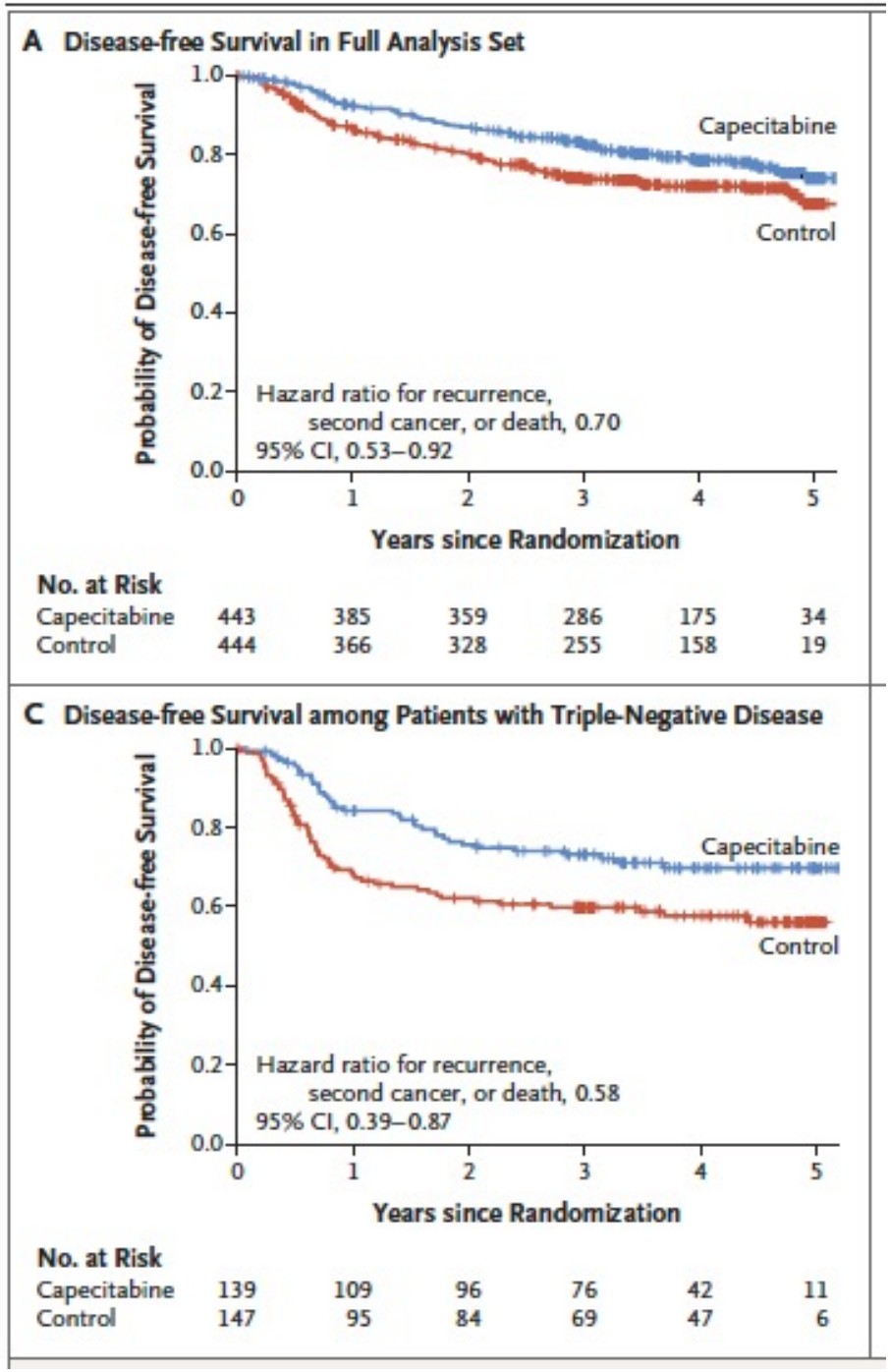
#adjusted for nodal status and TIL enrichment

Clinicaltrials.gov: NCT05929768

SWOG CANCER RESEARCH NETWORK

CREATE-X: Results

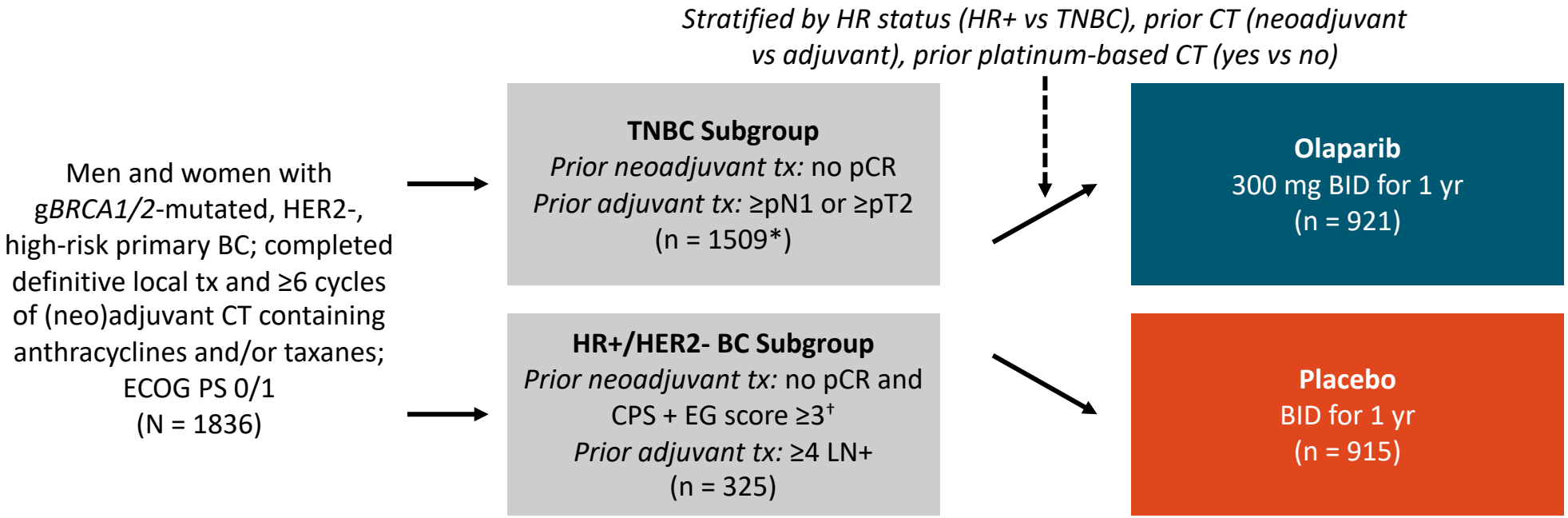
Hormone receptor status			0.21
Estrogen-receptor positive or progesterone-receptor positive	601	0.81 (0.55–1.17)	
Estrogen-receptor negative and progesterone-receptor negative	286	0.58 (0.39–0.87)	



Masuda et al. *NEJM* 2017;376:2147-2159

OlympiA: Study Design

- Prespecified interim analysis of international, randomized, double-blind phase III trial (data cutoff: Mar 27, 2020)



- **Primary endpoint:** iDFS
- **Secondary endpoints:** distant DFS, OS, safety

- Prespecified interim analysis of ITT population triggered when 165 invasive disease or death events occurred in first 900 patients enrolled (mature cohort); type I error rate controlled with superiority boundaries per hierarchical multiple-testing procedure

*Excluded n = 2 (both in olaparib arm) due to unconfirmed HER2- status.
†Staging system for BC-specific survival after neoadjuvant tx incorporating pretreatment clinical stage, ER status, nuclear grade, pathologic stage (range: 0-6).

Tutt A et al. *NEJM* 2021;384:2394-2405

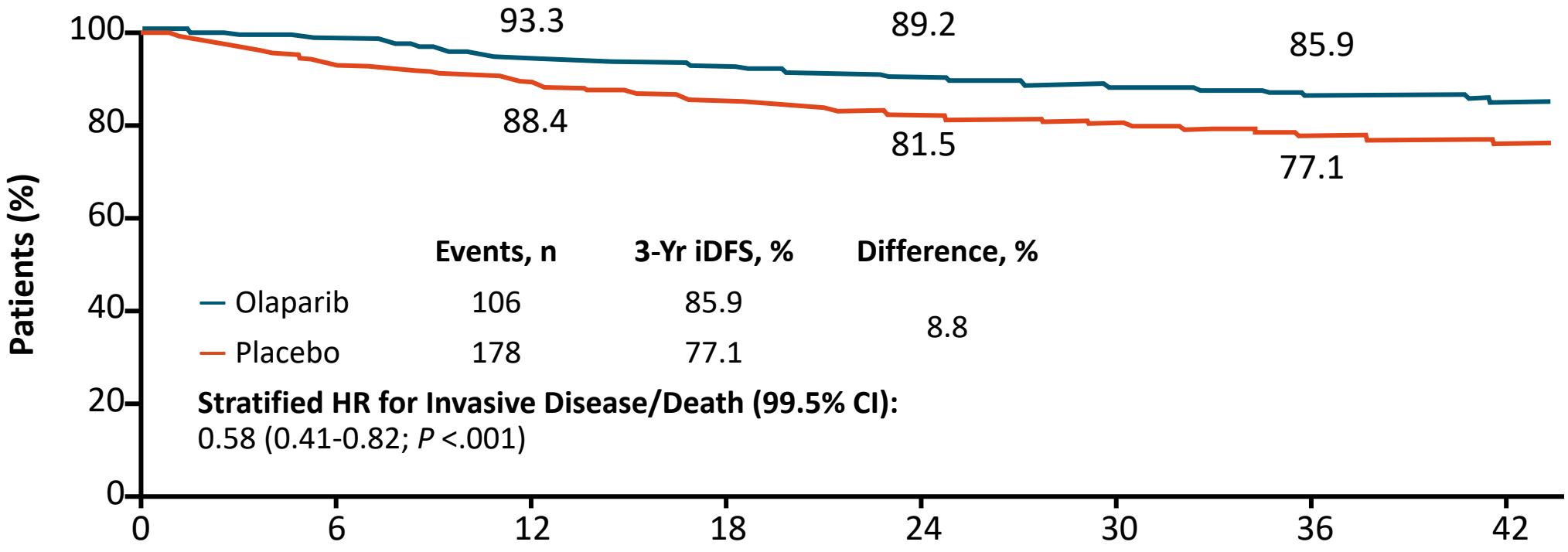
OlympiA: Baseline Patient Characteristics

Characteristic	Olaparib (n = 921)	Placebo (n = 915)
g*BRCA* mutation(s),* n (%)		
▪ *BRCA1*	657 (71.3)	670 (73.2)
▪ *BRCA2*	261 (28.3)	239 (26.1)
▪ *BRCA1* and *BRCA2*	2 (0.2)	5 (0.5)
Menopausal status (women only†), n (%)	n = 919	n = 911
▪ Premenopausal	572 (62.2)	553 (60.7)
▪ Postmenopausal	347 (37.8)	358 (39.3)
HR+/HER2-, n (%)	168 (18.2)	157 (17.2)
TNBC, n (%)	751 (81.5)	758 (82.8)
Concurrent ET (HR+ only), n/N (%)	146/168 (86.9)	142/157 (90.4)

*Data missing for n = 1 in each arm. †Trial enrolled 6 men (olaparib, n = 2; placebo, n = 4).

Tutt A et al. *NEJM* 2021;384:2394-2405

OlympiA: Invasive Disease-Free Survival (ITT)

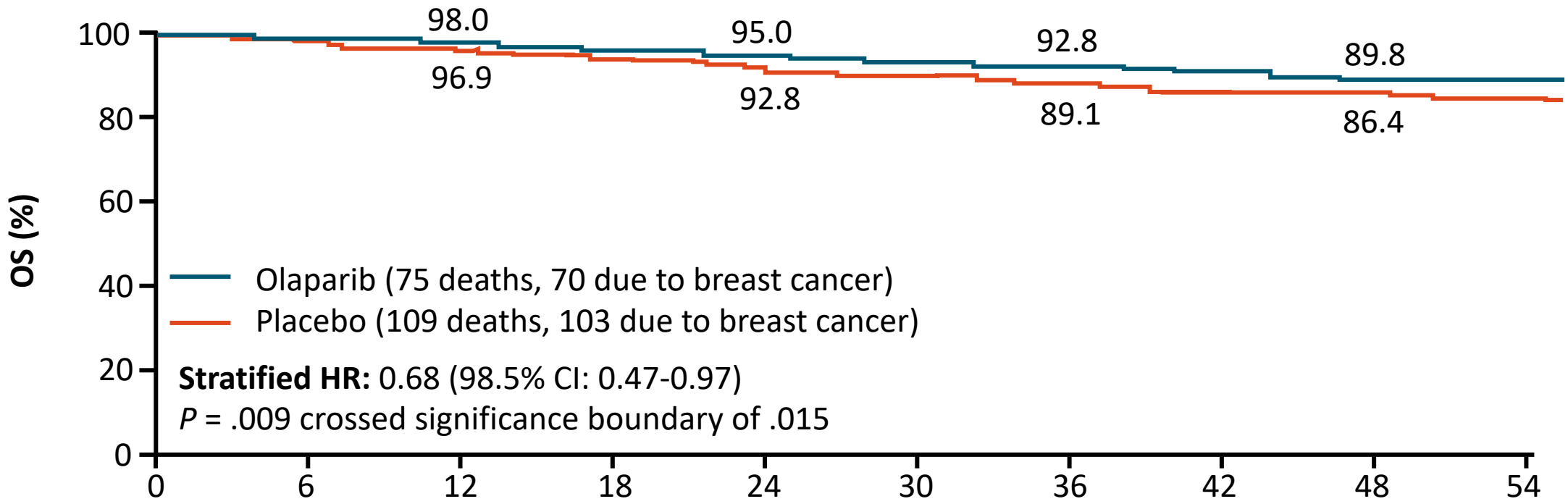


Patients at Risk, n

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

Tutt A et al. *NEJM* 2021;384:2394-2405

OlympiA: Overall Survival (Second Interim Analysis; Updated in 2022)



Patients at Risk, n									
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

Tutt A et al. *ESMO* 2022; Abstract VP1-2022 Geyer C et al. *Ann Oncol* 2022;33(12):1250-1268

OlympiA: AEs, Treatment Exposure, QoL

AE in ≥10% of Patients, n (%)	Olaparib (n = 911)		Placebo (n = 904)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Nausea	518 (56.9)	7 (0.8)	211 (23.3)	0
Fatigue	365 (40.1)	16 (1.8)	245 (27.1)	4 (0.4)
Anemia	214 (23.5)	79 (8.7)	35 (3.9)	3 (0.3)
Vomiting	206 (22.6)	6 (0.7)	74 (8.2)	0
Headache	180 (19.8)	2 (0.2)	152 (16.8)	1 (0.1)
Diarrhea	160 (17.6)	3 (0.3)	124 (13.7)	3 (0.3)
Decreased neutrophil count	146 (16.0)	44 (4.8)	59 (6.5)	7 (0.8)
Decreased WBC count	143 (15.7)	27 (3.0)	52 (5.8)	3 (0.3)
Decreased appetite	119 (13.1)	2 (0.2)	53 (5.9)	0
Dysgeusia	107 (11.7)	0	38 (4.2)	0
Dizziness	104 (11.4)	1 (0.1)	67 (7.4)	1 (0.1)
Arthralgia	84 (9.2)	2 (0.2)	107 (11.8)	2 (0.2)

- With olaparib, anemia was the most frequent AE at grade ≥3 in >1% patients
  - Transfusions: olaparib, 5.8%; placebo, 0.9%
- Median percentage of intended dose received: olaparib, 94.8%; placebo, 98.9%
- For the olaparib vs placebo arms:
  - Dose reductions: 25.0% vs 5.2%
  - Discontinuations due to AEs: 9.9% vs 4.2% (with olaparib, most commonly due to nausea, 2.0%; anemia, 1.8%; fatigue, 1.3%; decreased neutrophil count, 1.0%)

Tutt A et al. *NEJM* 2021;384:2394-2405

OlympiA: Safety

Safety Outcome, n (%)	Olaparib (n = 911)	Placebo (n = 904)
Any AE	835 (91.7)	753 (83.3)
Serious AE	79 (8.7)	76 (8.4)
AE of special interest	30 (3.3)	46 (5.1)
▪ MDS/AML	2 (0.2)	3 (0.3)
▪ Pneumonitis	9 (1.0)	11 (1.2)
▪ New primary malignancy	19 (2.1)	32 (3.5)
Grade ≥3 AE	221 (24.3)	102 (11.3)
Grade 4 AE	17 (1.9)	4 (0.4)
AE leading to permanent discontinuation	90 (9.9)	38 (4.2)

- AEs leading to death: olaparib, n = 1 (cardiac arrest); placebo, n = 2 (AML, ovarian cancer)

Tutt A et al. *NEJM* 2021;384:2394-2405

ASCENT-05/OptimICE-RD (AFT-65)

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

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

R 1:1

N=1514

Sacituzumab Govitecan + Pembrolizumab x 8 cycles

SG: 10 mg/kg IV on D1, D8 of 21-d cycles
Pembro: 200 mg IV on D1 of 21-d cycles

Treatment of Physician's Choice x 8 cycles
Pembro: 200 mg IV on D1 of 21-d cycles
or
Pembro + capecitabine: pembro 200 mg IV on D1 + capecitabine 1000 mg/m^2 PO BID on D1-14 of 21-d cycles

Long-term follow up

Key Study Endpoints

Primary
- iDFS (iBCFS per STEEP v2.0)

Secondary
- OS
- dDFS
- RFS
- Incidence of TEAEs and clinical laboratory abnormalities
- TTW of QoL based on FACT-B TOI scores

Exploratory Biomarkers
- Trop-2, PD-L1
- TIL, ctDNA

Exploratory QoLs
- FACT-B, PRO-CTCAE
- EQ-5D-5L, FCRI-SF

Clinicaltrials.gov: NCT05633654

Now accruing

ALLIANCE FOUNDATION TRIALS

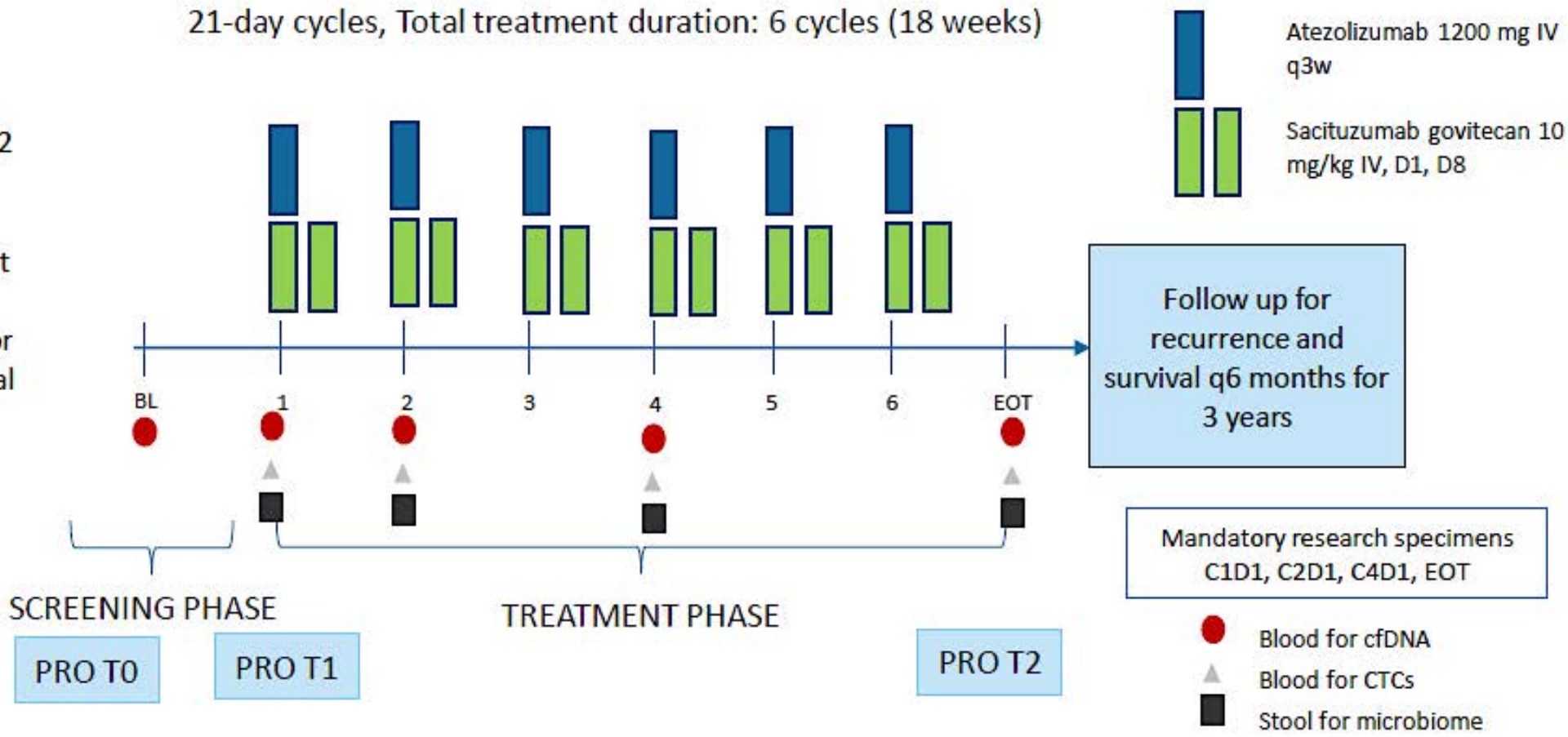
Tolaney S et al. *ASCO* 2023; Abstract TPS619

ASPRIA: A Single Arm Phase 2 Trial of Atezolizumab with Sacituzumab Govitecan to Prevent Recurrence in Triple Negative Breast Cancer

N=40

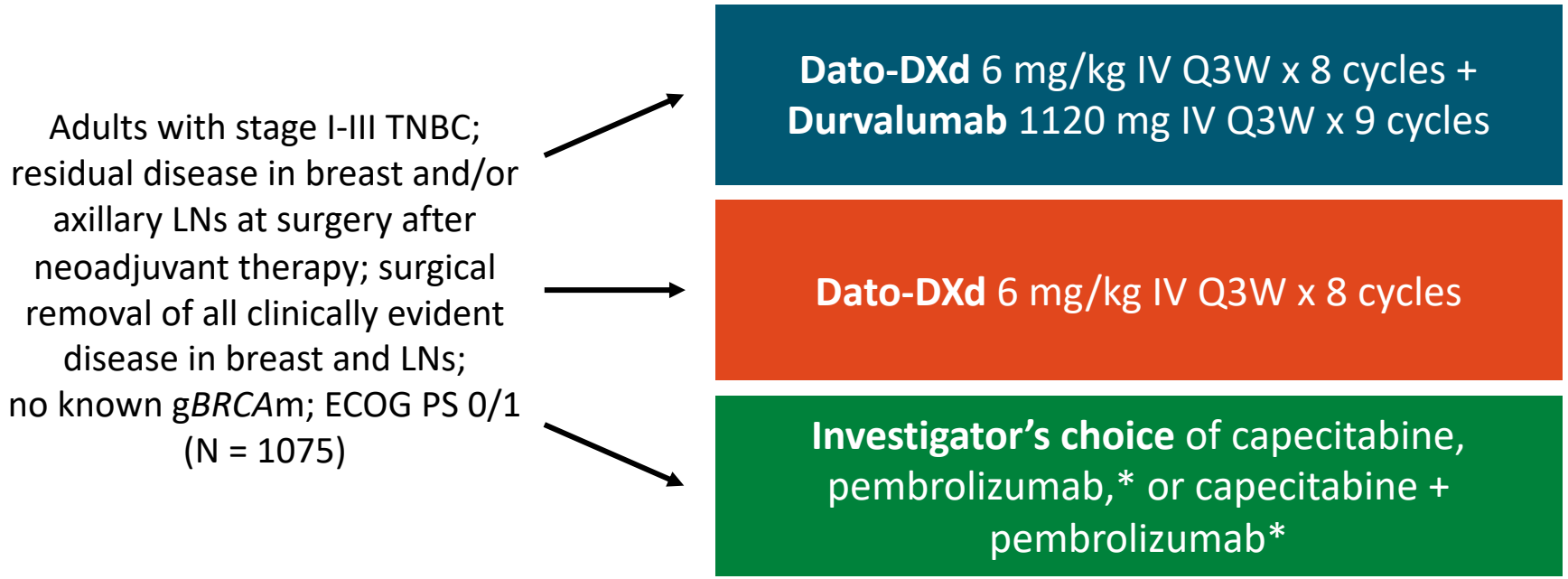
Eligibility

- TNBC residual disease within 12 months of last therapy (NACT, surgery, adjuvant therapy)
- Circulating tumor cfDNA (by central testing)



ClinicalTrials.gov: NCT04434040

Phase III TROPION-Breast03: Postneoadjuvant Dato-DXd ± Durva vs Investigator's Choice for Stage I-III TNBC



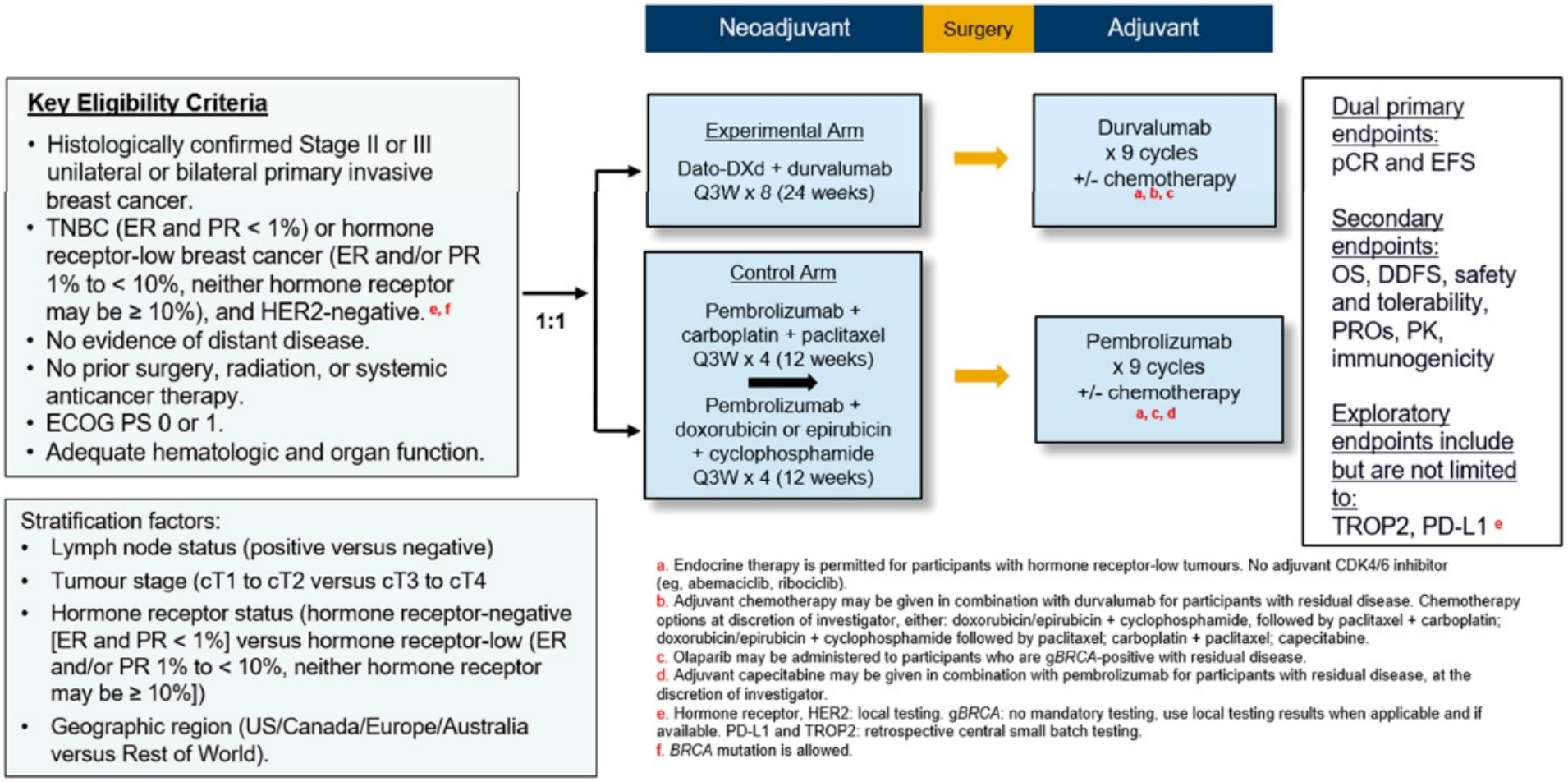
*Adjuvant pembrolizumab only for those treated with neoadjuvant pembrolizumab.

- **Primary endpoint:** iDFS for dato-DXd + durva vs investigator's choice
- **Secondary endpoints:** dDFS; OS; time to deterioration in physical functioning, GHS/QoL; fatigue; pharmacokinetics; immunogenicity; safety

ClinicalTrials.gov: NCT05629585

Phase 3, Open-Label, Randomized Study of Neoadjuvant Datopotamab Deruxtecan with Durvalumab +/- Chemotherapy followed by Adjuvant Durvalumab, Versus Neoadjuvant Pembrolizumab + Chemotherapy and Adjuvant Pembrolizumab, in Patients with Stage II-III Triple Negative Breast Cancer (TROPION-Breast04)

Figure 1 Study Design



a. Endocrine therapy is permitted for participants with hormone receptor-low tumours. No adjuvant CDK4/6 inhibitor (eg, abemaciclib, ribociclib).
b. Adjuvant chemotherapy may be given in combination with durvalumab for participants with residual disease. Chemotherapy options at discretion of investigator, either: doxorubicin/epirubicin + cyclophosphamide, followed by paclitaxel + carboplatin; doxorubicin/epirubicin + cyclophosphamide followed by paclitaxel; carboplatin + paclitaxel; capecitabine.
c. Olaparib may be administered to participants who are g*BRCA*-positive with residual disease.
d. Adjuvant capecitabine may be given in combination with pembrolizumab for participants with residual disease, at the discretion of investigator.
e. Hormone receptor, HER2: local testing. g*BRCA*: no mandatory testing, use local testing results when applicable and if available. PD-L1 and TROP2: retrospective central small batch testing.
f. *BRCA* mutation is allowed.

ClinicalTrials.gov: NCT06112379

Agenda

Module 1: Role of Genomic Assays in Treatment Decision-Making for Localized ER-Positive, HER2-Negative Breast Cancer — Dr Goetz

Module 2: Integration of Ovarian Function Suppression into the Management of Breast Cancer in Premenopausal Patients — Dr Burstein

Module 3: Role of CDK4/6 Inhibitors and Other Novels Agents in Therapy for ER-Positive Localized Breast Cancer — Dr Hurvitz

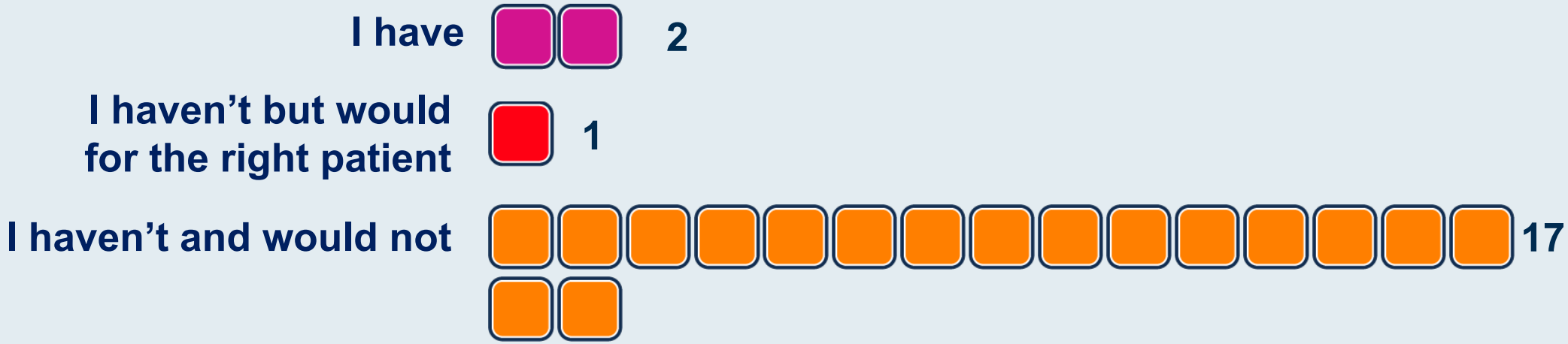
Module 4: Optimizing the Use of Neoadjuvant and Adjuvant Therapy for Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 5: Emerging Role of Circulating Tumor DNA (ctDNA) Evaluation in Breast Cancer — Dr Pusztai

RTP RESEARCH TO PRACTICE

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

Have you used or would you use a tumor-informed circulating tumor DNA (ctDNA) assay in this situation?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Have you used or would you use a tumor-informed ctDNA assay outside of a clinical trial in the care of patients with HER2-negative localized breast cancer?

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Please describe the last patient with HER2-negative localized breast cancer for whom you ordered a tumor-informed ctDNA assay:

Patient age	Prior treatment	ctDNA assay result	Comment
55 years	Neoadjuvant AC-T	Negative	No impact on treatment
42 years	AC-T then adjuvant abemaciclib	Negative	Equivocal findings on scans that weren't biopsy proven. Allowed us to move forward treating her curatively
52 years	Adjuvant AC-T then endocrine therapy for 10 years	Negative	The results reassured the patient
55 years	Adjuvant chemotherapy then endocrine therapy	Negative	An unusual case where we were trying to distinguish between a recurrence vs a new primary cancer
56 years	Adjuvant ddAC-T then anastrozole	Negative	Reassuring for 6 month f/u

AC-T = doxorubicin and cyclophosphamide followed by paclitaxel

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Potential utility of ctDNA assays in breast cancer

Eric P Winer, MD

Paolo Tarantino, MD

RTP
RESEARCH
TO PRACTICE

Potential advantages of ctDNA assessment for monitoring patients; DARE trial of ctDNA-guided second-line adjuvant therapy for patients with high residual-risk hormone receptor-positive, HER2-negative breast cancer

Mark D Pegram, MD

Jane Lowe Meisel, MD

RTP
RESEARCH
TO PRACTICE

Emerging Role of Circulating Tumor DNA (ctDNA) Evaluation in Breast Cancer

Lajos Pusztai, MD, DPhil

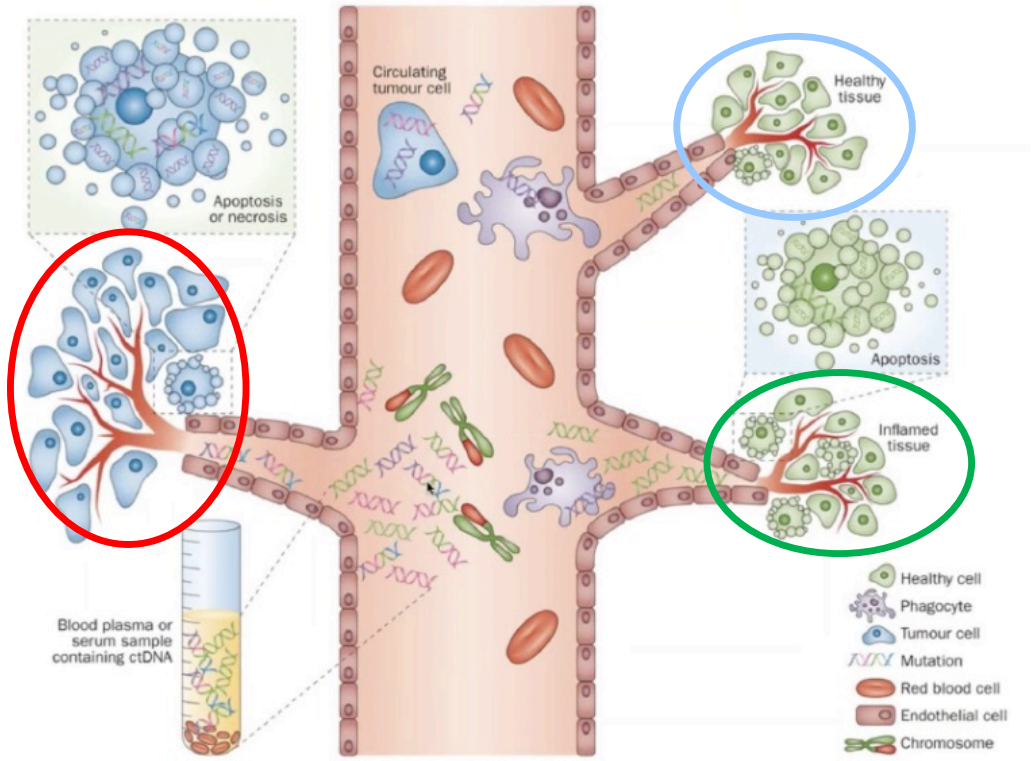
Agenda

Methods and optimal source material for detecting ctDNA, cfDNA, tumor fraction

- Rationale for ctDNA surveillance/monitoring during follow-up in early-stage BC
- ctDNA response during neoadjuvant therapy – molecular residual disease
- ctDNA testing to detect molecular relapse in patients with early-stage BC
- Active studies examining the clinical utility of ctDNA testing

Cell Free DNA (cfDNA), circulating tumor DNA (ctDNA), Tumor Fraction (TF) platforms and methods

Cell free DNA originates from healthy normal, inflamed normal, and cancer tissues



cfDNA = free DNA detectable in plasma

ctDNA = free DNA derived from cancer (tumor molecules/mL or mutant allele frequency)

TF = ctDNA proportion (percent) in total cfDNA (0% - >10%)

Methods*:

Tumor informed assays (personalized, tumor specific alterations)

Tumor agnostic assays (the usual cancer drivers)

* Sensitivity > 90% for mutations with > **0.5% allele frequency**, and **DNA input > 30 ng.**

Performances decrease when allele frequency < 0.1% or input DNA < 10 ng DNA.

Cell free DNA has a $T_{1/2}$ of ~30-120 minutes
Best captured from plasma using Streck tubes

Real-time monitoring of response
Detection of viable microscopic disease

Crowley E, et al. *Nat Rev Clin Oncol.* 2013;10(8):472-484.
Davidson BA, et al. *British J Cancer.* 2021 Sep 14;125(6):780-8.
Yu L, et al. *Plos One.* 2022 Apr 28;17(4):e0266889.

Rationale for ctDNA monitoring and early intervention in early-stage BC

Why drugs that eliminate micro-metastasis as adjuvant therapy do not cure clinically apparent metastatic disease

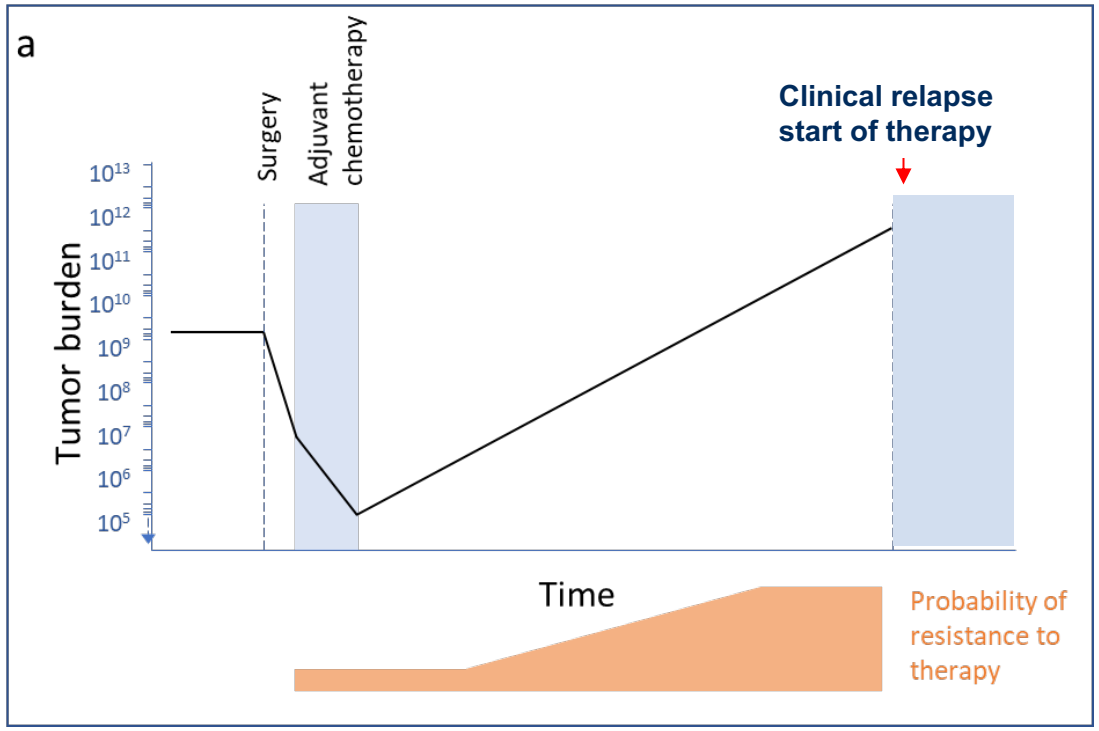
As tumor bulk increases, intratumor genomic heterogeneity increases. As intratumor heterogeneity increases, the chance of drug-resistant clones also increases[1]

[1]Schiavon G. et al. Analysis of ESR1 mutation in circulating tumour DNA demonstrates evolution during therapy for metastatic breast cancer. Sci Transl Med 7, 313ra182 (2015).

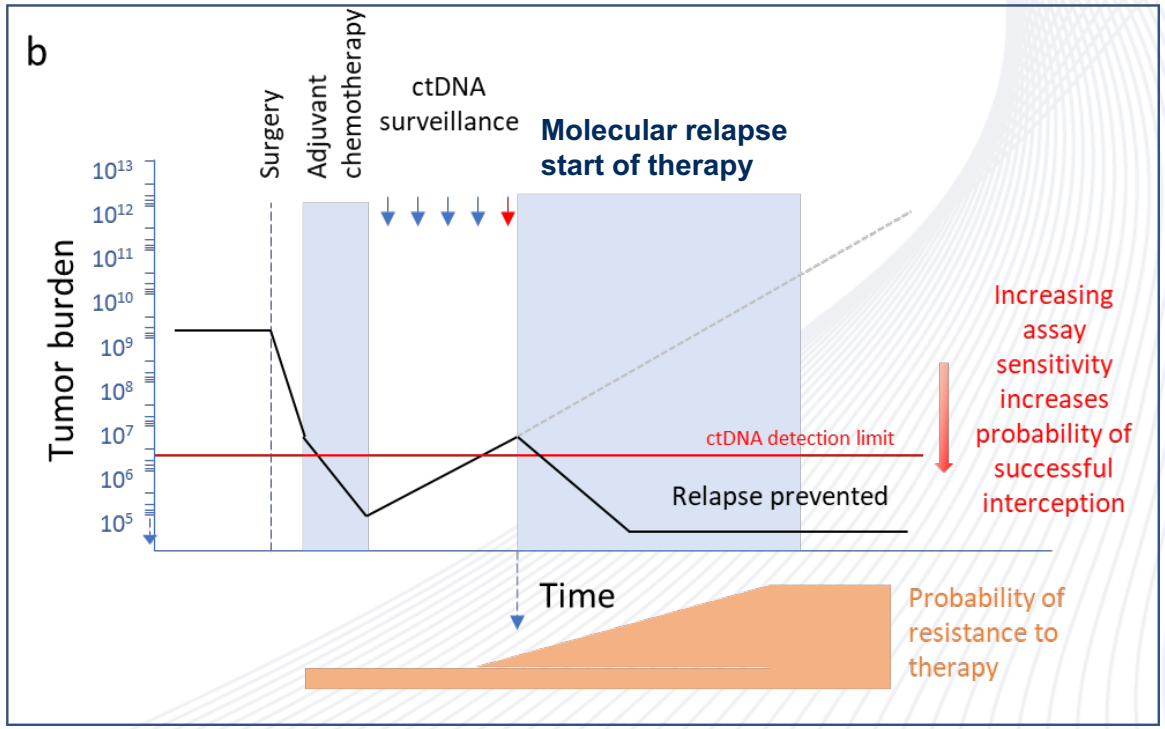
Hypothesis

At the time of molecular relapse, tumor bulk and tumor heterogeneity are still low, and therefore the chance of therapy working is higher

Current non-curative treatment paradigm

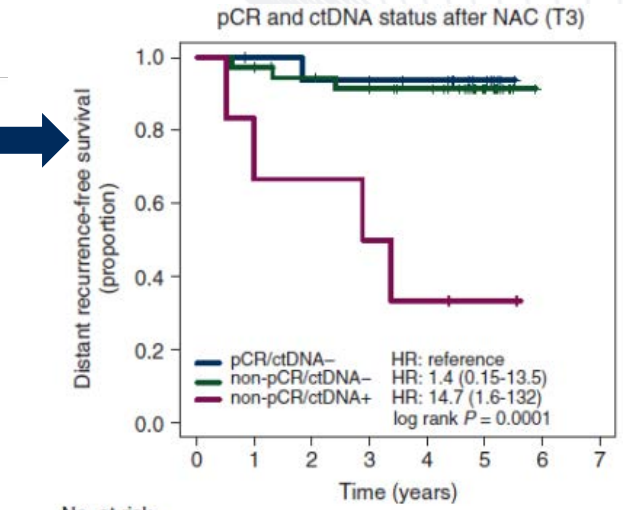


Future potentially curative treatment paradigm

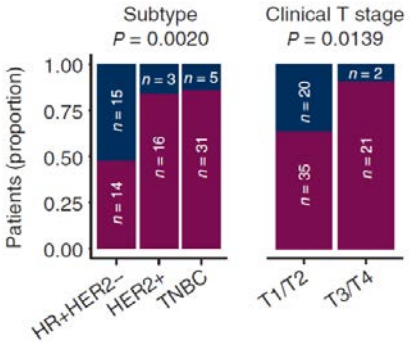


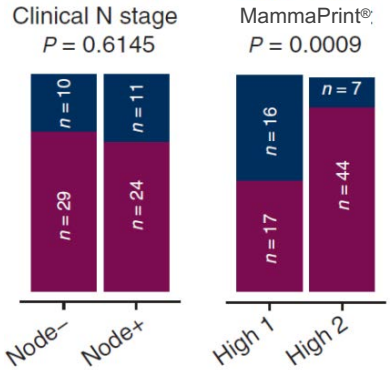
ctDNA changes as early predictors of response to preoperative therapy

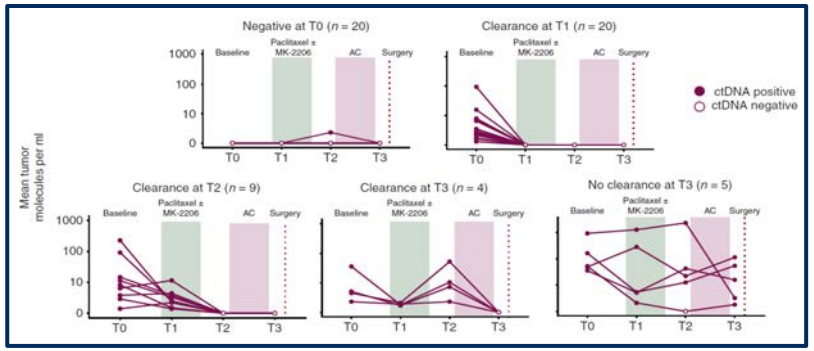
I-SPY2: ctDNA at 4 time points before, during and after neoadjuvant chemotherapy for stage II-III breast cancer



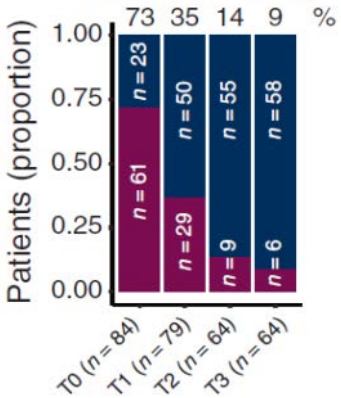
ctDNA positivity at baseline







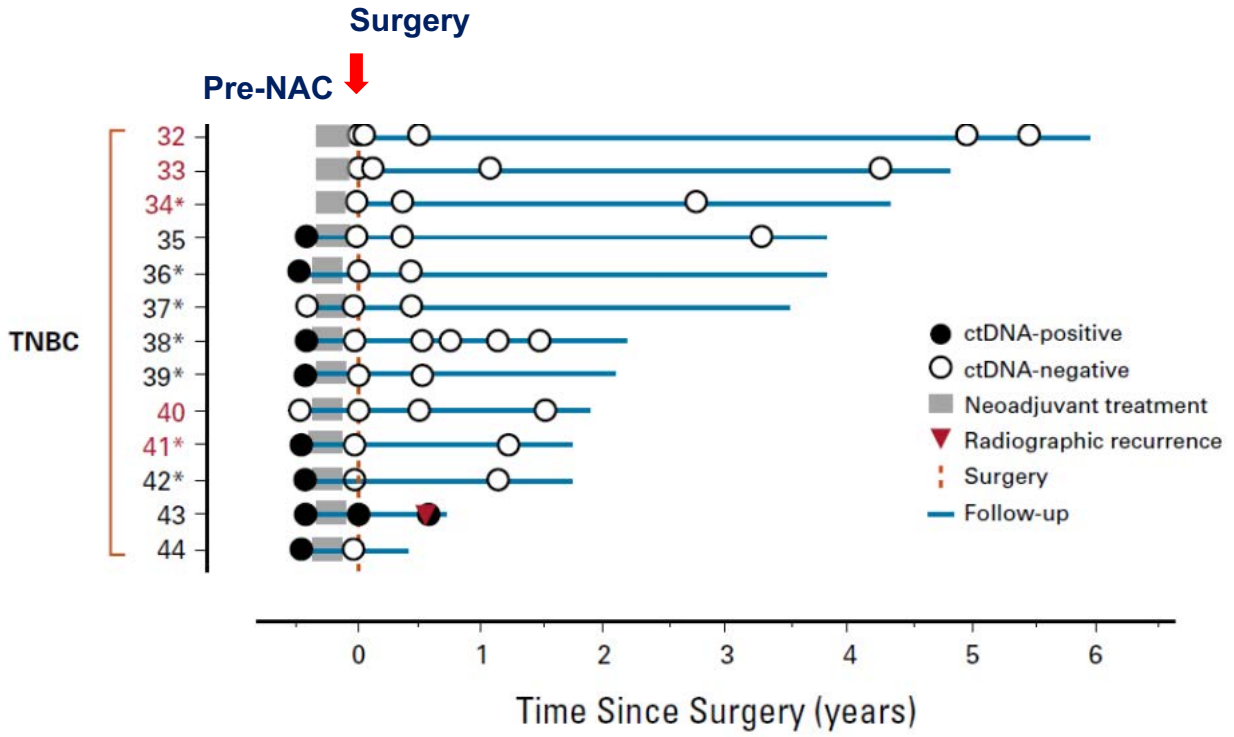
ctDNA positivity by time points

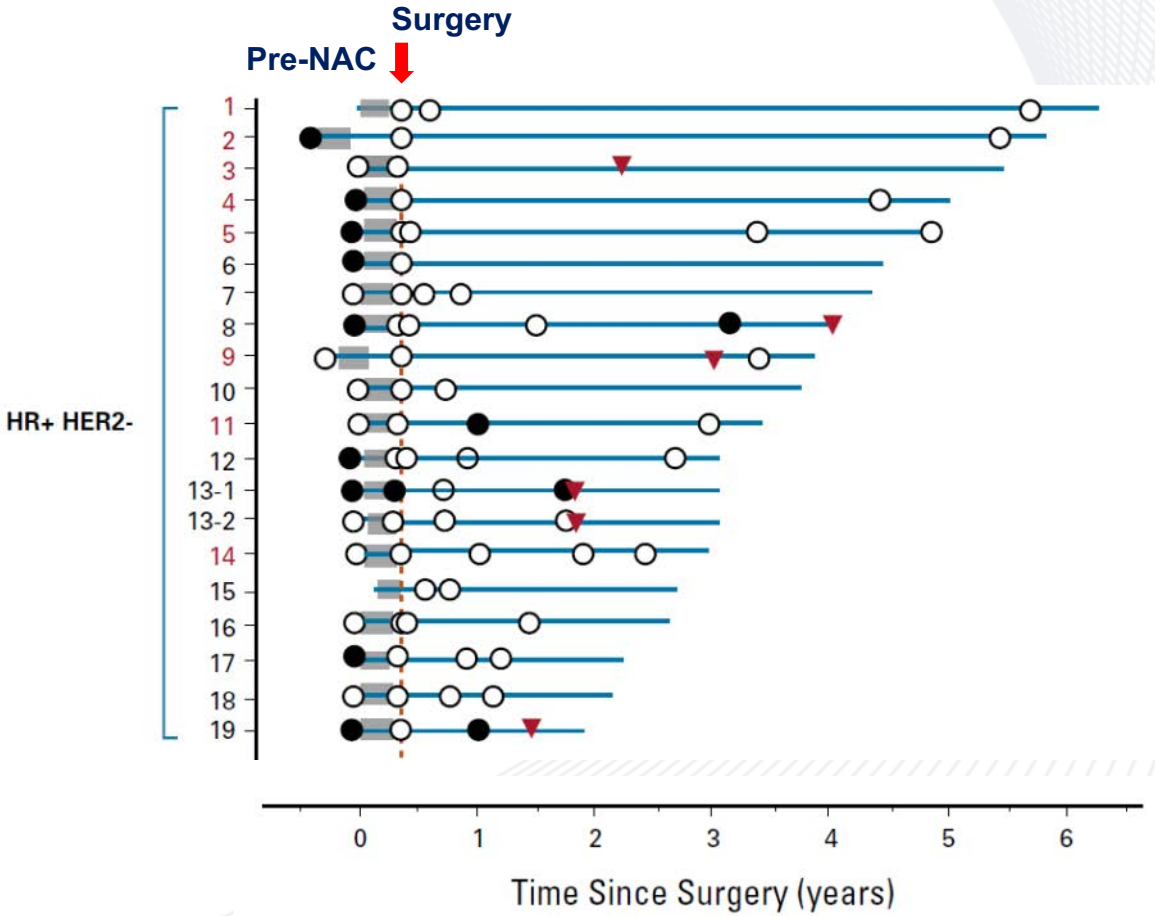


- All patients with pCR were ctDNA negative at surgery
- 85% of patients with no ctDNA clearance by week 3 had residual disease
- 15% of patients with RD had + ctDNA and had the worst prognosis
- ctDNA- RD had good prognosis

Magbanua MJ, et al. Annals of Oncol. 2021 Feb 1;32(2):229-39.

ctDNA changes after neoadjuvant chemotherapy (NAC) and during follow-up

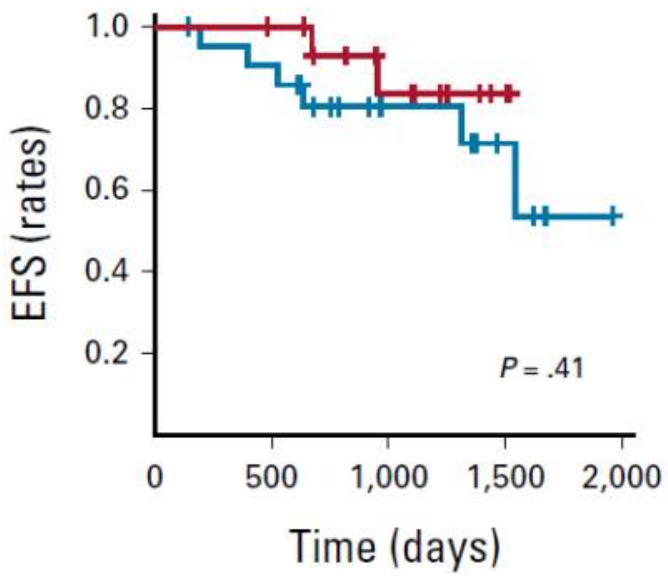




Cailleux F, et al. JCO Precision Onc. 2022 Sep;6:e2200148.

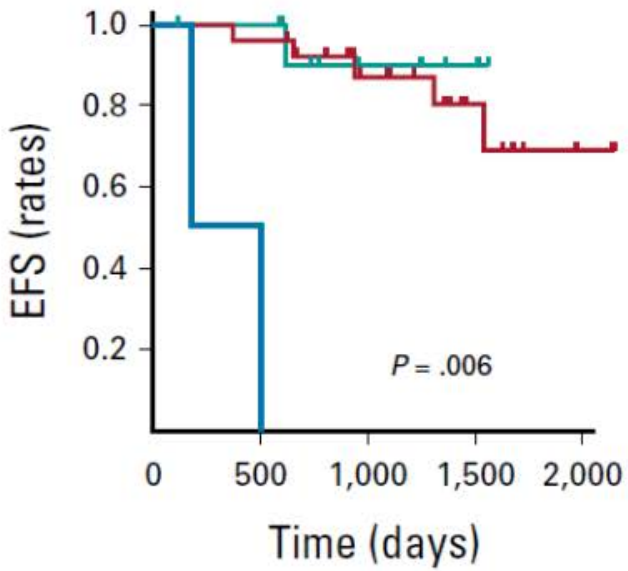
ctDNA changes as early predictors of event-free survival after neoadjuvant chemotherapy (NAC)

ctDNA status at baseline



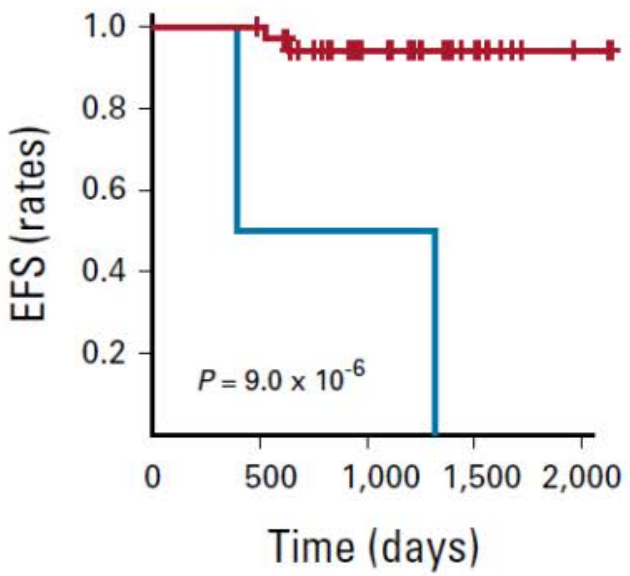
No. at risk:				
Detected	22	19	9	4
Not detected	16	15	9	2

ctDNA after NAC before surgery



No. at risk:					
pCR (all ctDNA-)	12	12	6	3	0
Detected	2	1	0	0	0
Not detected	27	25	16	7	2

ctDNA status during follow-up



No. at risk:					
Detected	2	1	1		
Not detected	36	35	20	9	2

All patients with pCR had negative cDNA before surgery
ctDNA negative residual disease had favorable outcome
ctDNA positivity during follow-up predicted recurrence

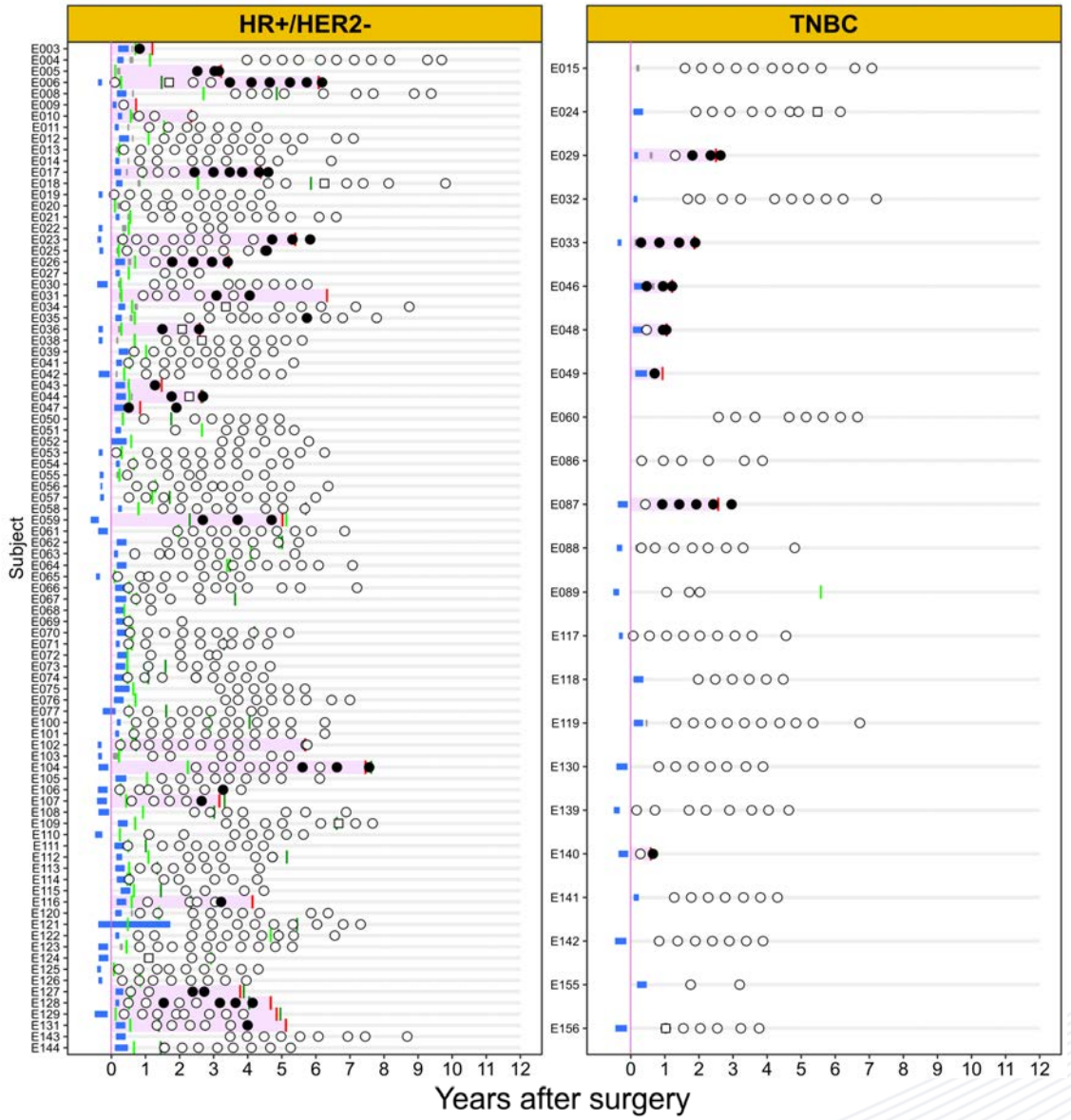
Cailleux F, et al. JCO Precision Onc. 2022 Sep;6:e2200148.

ctDNA surveillance to detect molecular relapse in early-stage BC

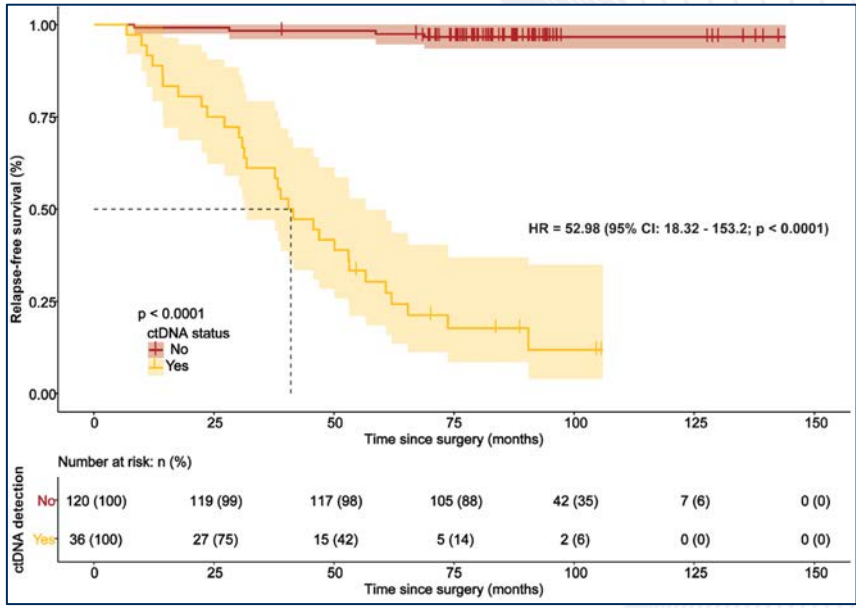
EBLIS study:
Serial plasma samples were tested for 156 patients with primary breast cancer.

Followed for up to 12 years with blood draws q6 months

ctDNA dynamics during follow up



Relapse-free survival



ctDNA was dectected ahead of clinical or radiological relapse in 30/34 patients; **sensitivity of 88%**

Shaw J et al. ASCO 2022; Abstract 562.

- Analytical validity ✓ It measures accurately what it suppose to measure
- Clinical validity ✓ It can predict a clinically relevant outcome
- Clinical utility ? Acting on the test result improve outcome

ctDNA positivity in the blood predicts clinical recurrence with 8-10 months of lead-time

February 2023
Centers for Medicare & Medicaid Services (CMS) approved coverage for the Signatera™ assay for recurrence monitoring in stage IIB-III breast cancer

Circulating Tumor DNA Analysis in Patients With Cancer

American Society of Clinical Oncology and College of American Pathologists Joint Review

Jason D. Merker, Geoffrey R. Oxnard, Carolyn Compton, Maximilian Diehn, Patricia Hurley, Alexander J. Lazar, Neal Lindeman, Christina M. Lockwood, Alex J. Rai, Richard L. Schilsky, Apostolia M. Tsimberidou, Patricia Vasalos, Brooke L. Billman, Thomas K. Oliver, Suanna S. Bruinooge, Daniel F. Hayes, Nicholas C. Turner

Arch Pathol Lab Med. 2018;142:1242–1253

results from ctDNA tests. There is no evidence of clinical utility and little evidence of clinical validity of ctDNA assays in early-stage cancer, treatment monitoring, or residual disease detection. There is no evidence of clinical validity or clinical utility to suggest that ctDNA assays are useful for cancer screening, outside of a clinical trial. Given the rapid pace of research, reevaluation of the literature will shortly be required, along with the development of tools and guidance for clinical practice.

https://www.natera.com/company/news/medicare-extends-coverage-of-nateras-signatera-mrd-test-to-breast-cancer/

Ongoing studies examining the clinical utility of ctDNA testing and treatment of molecular residual disease

Eligibility: ctDNA + Imaging -

TNBC

- ~~ZEST: Niraparib (NCT04915755), Signatera~~
- ASPRIA: Atezolizumab+Sacituzumab (NCT04434040) — **Single arm, phase II, post-NAC RD, USA**
- PERSEVERE: Various/matched (NCT04849364) — **Post-NAC RD, FM One mutation directed multi-arm Phase II, USA**

ER+

- DARE: Palbociclib (NCT04567420), Signatera — **Randomized phase II, USA**
- LEADER: Ribociclib (NCT03285412), Signatera — **Randomized phase II, USA**
- TRAK-ER: Fulv +Palbociclib (NCT04985266), Invitae PCMTM — **Randomized phase II, UK**
- TREAT: Elacestrant (NCT05512364) — **Randomized phase III, EORTC**

HER2+

- KAN-HER2 MRD: Neratinib+T-DM1 (NCT05388149), Inivata RaDaR — **Single arm, phase II post-NAC RD, CANADA**

ctDNA monitoring of ER+/HER2- high risk breast cancer during adjuvant endocrine therapy
Interim analysis of the DARE trial (NCT04567420)

Trial Schema

Eligibility: ER+, high risk for recurrence on adjuvant endocrine therapy

Signatera ctDNA surveillance q6 months

ctDNA- : Continue screening q6 months

ctDNA+ ⇒ staging with imaging

Learn ctDNA prevalence

No evidence of M1 disease

Learn imaging positivity rate at time of detecting + ctDNA

R 1:1

Learn if changing therapy improves metastases free survival

Arm A switch to Fulvestrant + palbociclib x 2yrs

Arm B continue adjuvant therapy

Assuming 80% event rate in the control arm by 2 years, and HR =0.5
N=100 patients randomized will provide 80% power with P ≤ 0.05

Updated Results

- 15 active sites
- 542 patients accrued between Feb 2021 – Oct 2022
- 474 patients with ctDNA testing (1120 assays)

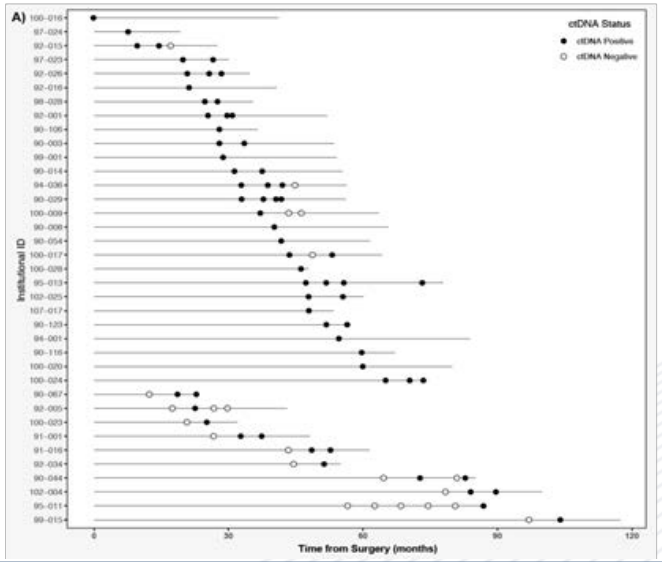
417 patients with ctDNA results

WES failure rate:
- 12% (57/474)
- 60% (57/95): insufficient tumor tissue

37 ctDNA+
median screening period
13.4 months/patient
(range: 3-32 months)

3.3% of Assays
8.9% of Patients

ctDNA detection during follow up (n=37)



- ctDNA surveillance of **stage II-III ER+/HER2- breast cancers with a median screening period of 13.4 months/patient** yielded 3.3% and 8.9% detection rates at assay and patient level, respectively.
- Serial screening increases detection rates; 27% of positive ctDNA tests occurred after an initial negative result.
- 71% of ctDNA+ patients had true molecular relapse without imaging-detectable metastatic disease.
- Randomization is open for any patients with ctDNA+ minimal residual disease, including those identified through routine commercial testing.

Important Caveats

Despite sound logic, it is possible to harm with serial molecular monitoring and early intervention

- The costs of liquid biopsies represent additional health care cost and out of pocket expense for patients.
- False positive results can lead to further testing, patient anxiety, and potential exposure to toxic and unnecessary therapies.
- Treating at an asymptomatic state can only lead to deterioration of quality of life, and possibly result in fewer treatment options later in the course of the disease.

For these reasons, currently the most appropriate use of liquid biopsies to detect molecular relapse is in the context of evidence generation (i.e registries, databases, prospective trials).

Conclusions

- Multiple studies showed high sensitivities and high positive predictive values for ctDNA to predict metastatic recurrence in patients with early-stage breast cancer (of all subtypes)
  - Tumor-informed assays are more sensitive and specific
  - Imaging positivity rate at first ctDNA detection is low (~25%) in ER+ disease but higher in TNBC (> 60%)
  - CMS provides coverage for the Signatera assay for recurrence monitoring in stage IIB-III breast cancers

- In neoadjuvant trials, week-3 ctDNA clearance predicts for pCR, and pCR is accompanied by ctDNA clearance
  - If early switching improves chance to achieve pCR; is currently being tested in I-SPY2.2 (NCT01042379)
  - ctDNA negative residual disease has better prognosis

- The most important unanswered question is if treatment of molecular relapse could delay or prevent subsequent clinical relapse
  - Currently accruing clinical trials in the USA that test clinical utility:
    - ER+: DARE https://clinicaltrials.gov/study/NCT04567420
    - ER+: LEADER https://clinicaltrials.gov/study/NCT03285412
    - TNBC RD: ASPIRA https://clinicaltrials.gov/study/NCT04434040
    - TNBC RD: PERSEVERE https://clinicaltrials.gov/search?term=NCT04849364

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Localized HER2-Negative Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Wednesday, December 6, 2023

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Harold J Burstein, MD, PhD
Matthew P Goetz, MD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Lajos Pusztai, MD, DPhil, FASCO

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of HER2-Low Breast Cancer

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

Thursday, December 7, 2023

7:15 PM – 8:45 PM CT (8:15 PM – 9:45 PM ET)

Faculty

Aditya Bardia, MD, MPH

Lisa A Carey, MD, ScM, FASCO

Shanu Modi, MD

Professor Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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

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

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. You may also use the iPads available in the meeting room to complete the course evaluation.

Online/Zoom attendees: The CME credit link is posted in the chat room.

RTP
RESEARCH
TO PRACTICE