Meet The Professor

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

Ruth O'Regan, MD
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Rochester, New York

Commercial Support

This activity is supported by educational grants from Exact Sciences Inc, Novartis and Sanofi Genzyme.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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Dr O'Regan — Disclosures

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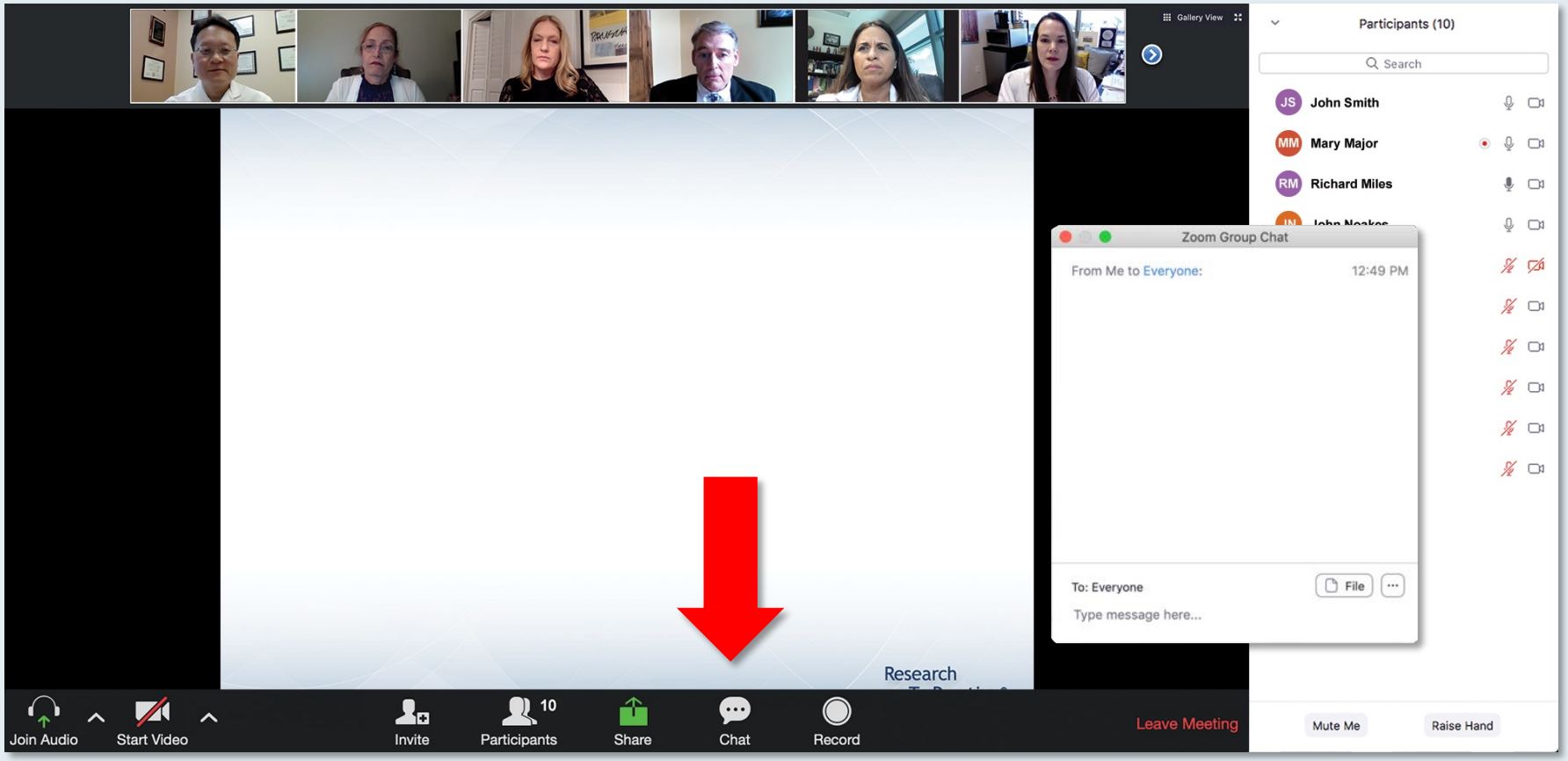

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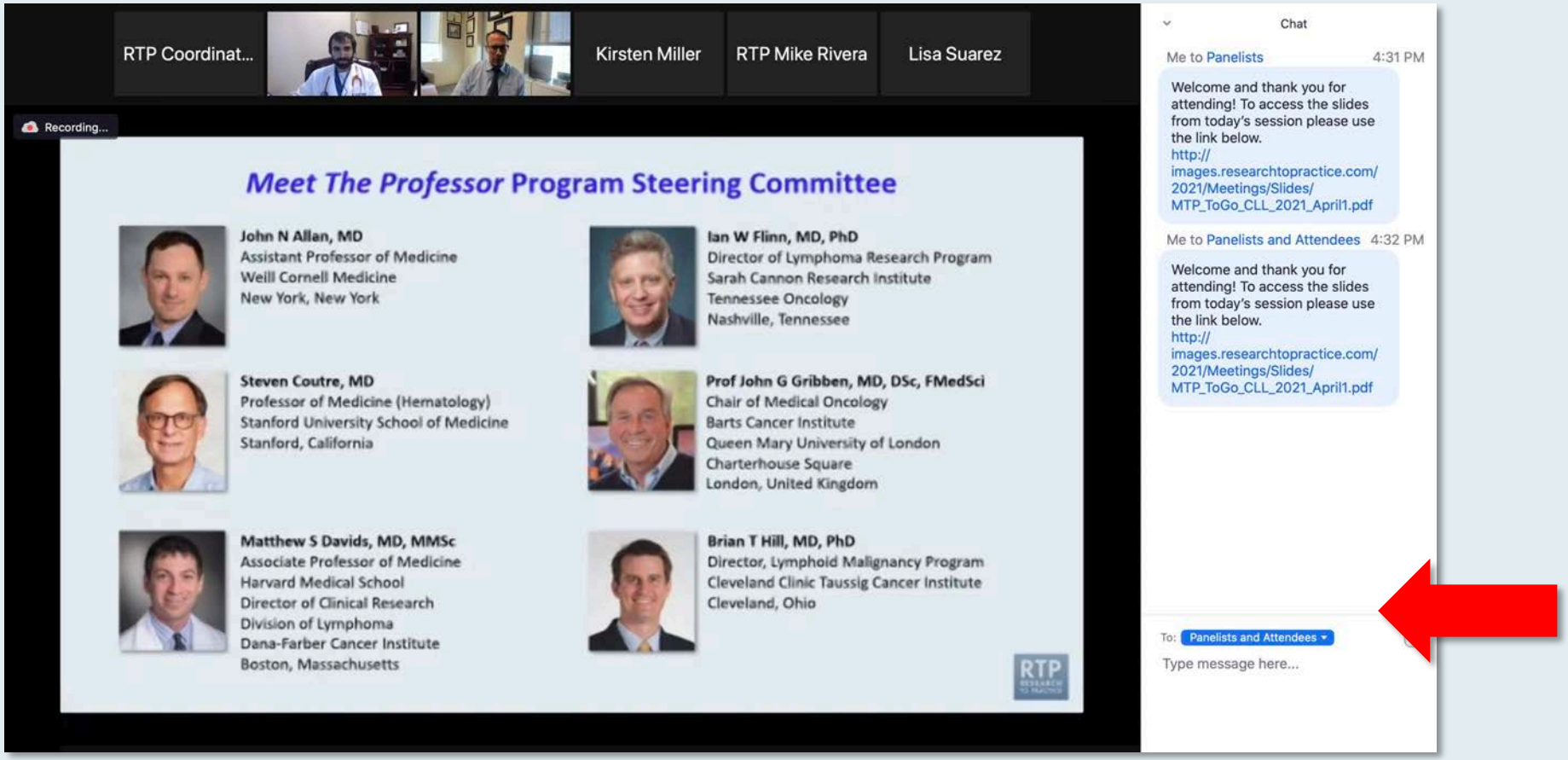

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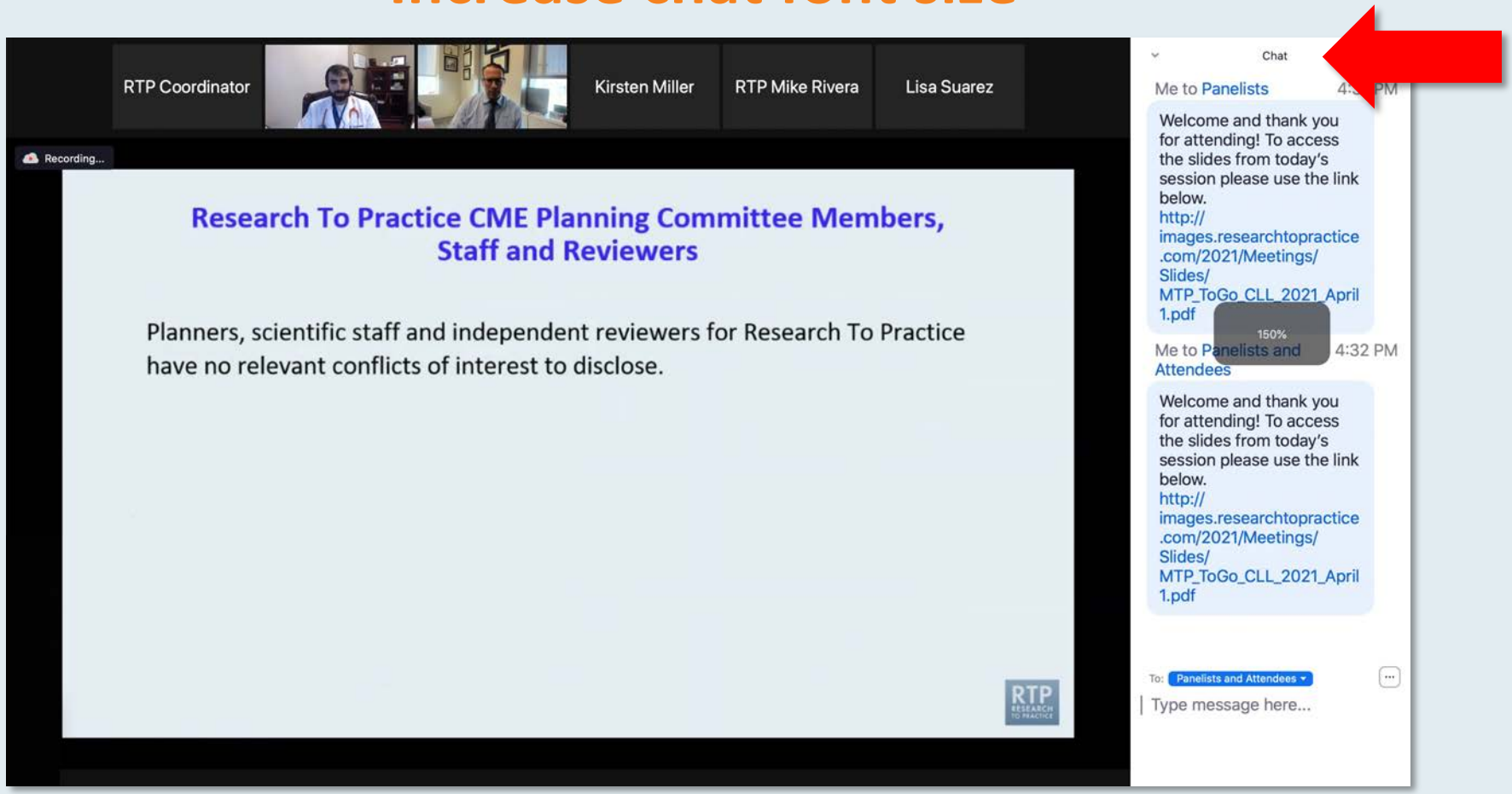

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of HER2-Low Breast Cancer

DR IAN KROP

DANA-FARBER CANCER INSTITUTE

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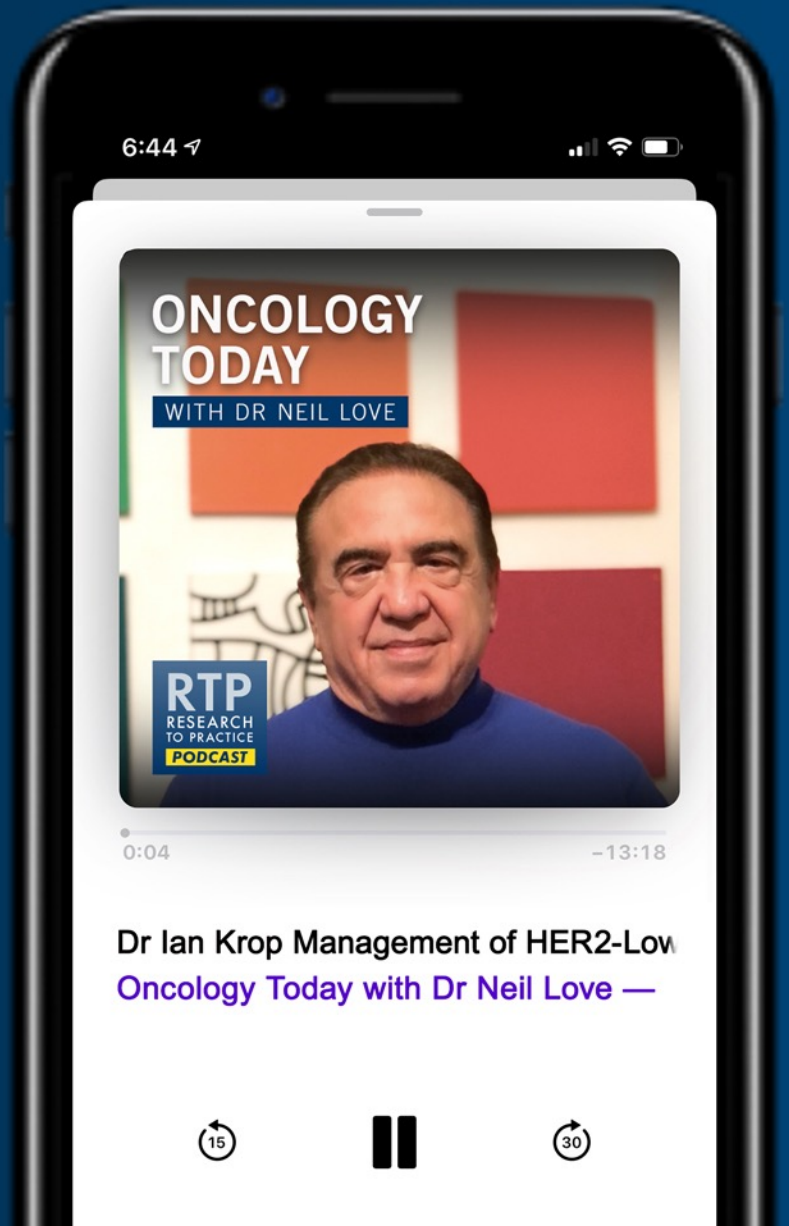

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Follicular Lymphoma

Tuesday, January 4, 2022
5:00 PM – 6:00 PM ET

Faculty

Laurie H Sehn, MD, MPH
Additional faculty to be announced.

Moderator

Neil Love, MD

RTP Year in Review 2022

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Breast Cancer

Thursday, January 6, 2022
5:00 PM – 6:00 PM ET

Faculty

Harold J Burstein, MD, PhD
Additional faculty to be announced.

Moderator

Neil Love, MD

RTP Year in Review 2022

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Colorectal Cancer (Part 1 of a 3-Part Series)

Wednesday, January 19, 2022
10:15 PM – 11:45 PM ET

Faculty

Cathy Eng, MD
Alan P Venook, MD
Additional faculty to be announced.

Moderator

To be announced.

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RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Gastroesophageal Cancers (Part 2 of a 3-Part Series)

Thursday, January 20, 2022
9:15 PM – 10:45 PM ET

Faculty

Yelena Y Janjigian, MD
Eric Van Cutsem, MD, PhD
Additional faculty to be announced.

Moderator

Samuel J Klempner, MD

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RESEARCH
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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hepatobiliary Cancers (Part 3 of a 3-Part Series)

Friday, January 21, 2022
9:15 PM – 10:45 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD
Robin K Kelley, MD

Moderator

Tanios Bekaii-Saab, MD

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RESEARCH TO PRACTICE

Promising Investigational Agents and Strategies for Patients with Metastatic Non-Small Cell Lung Cancer Who Experience Disease Progression on Immune Checkpoint Inhibitor Therapy

Wednesday, January 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Edward B Garon, MD, MS

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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Meet The Professor Program Participating Faculty

Matthew P Goetz, MD
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Research Honoring Richard F Emslander, MD
Professor of Oncology and Pharmacology
Director, Mayo Clinic Breast SPORE
Co-Leader, Women's Cancer Program
Mayo Clinic
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Professor of Medicine
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AB Alexander Distinguished Chair in Oncology
Associate Director for Clinical Research
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Associate Professor
Department of Hematology and Medical Oncology
Emory University School of Medicine
Director, Glenn Family Breast Center
Director, Breast Medical Oncology
Winship Cancer Institute of Emory University
Atlanta, Georgia

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Meet The Professor Program Participating Faculty

Ingrid A Mayer, MD, MSCI
Professor of Medicine
Ingram Professor of Cancer Research
Co-Leader, VICC Breast Cancer Research Program
Oncology Section Head, Division of Hematology/Oncology
Vanderbilt University Medical Center
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

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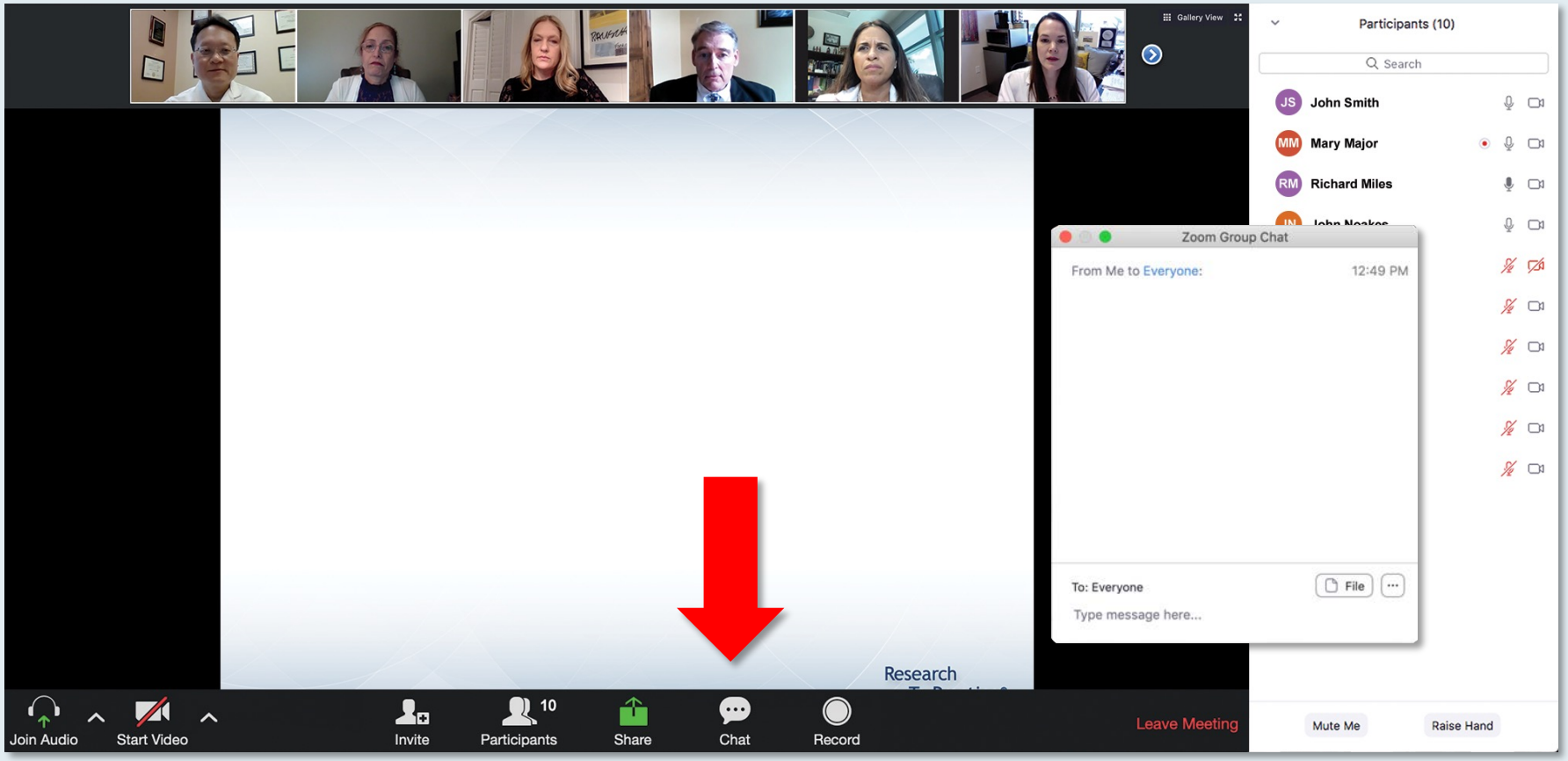

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Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky

Raman Sood, MD
Brooks
Memorial Hospital
Dunkirk, New York

Shaachi Gupta, MD, MPH
Florida Cancer Specialists and
Research Institute
Lake Worth, Florida

Andrea Stebel, MD
Newport Breast Care
Newport Beach, California

Arielle Heeke, MD
Levine Cancer Institute
Atrium Health
Charlotte, North Carolina

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

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Meet The Professor with Dr O'Regan

Module 1: Use of Genomic Assays for Localized ER-Positive Breast Cancer

- Dr Agrawal: A 48-year-old premenopausal woman with an ER/PR-positive, HER2-negative, node-negative IDC

Module 2: Selection of a First-Line CDK4/6 Inhibitor for ER-Positive Metastatic Breast Cancer (mBC)

- Dr Sood: A 46-year-old woman with ER/PR-positive, HER2-negative mBC

Module 3: Management of ER-Positive Oligometastatic Breast Cancer

- Dr Heeke: A 41-year-old woman with ER/PR-positive, HER2-negative oligometastatic BC

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- Dr Stebel: A 60-year-old woman with ER/PR-positive, HER2-negative mBC with a PIK3CA mutation

Module 5: CDK4/6 Inhibitors in the Adjuvant Setting

- Dr Gupta: A 51-year-old postmenopausal woman with Stage IIIB ER/PR-positive, HER2-negative, node-positive BC

Module 6: PARP Inhibitors for Localized ER-Positive Breast Cancer with a BRCA Mutation

- Dr Agrawal: A 38-year-old woman with ER/PR-positive, HER2-negative, node-positive IDC with a germline BRCA1 mutation

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Case Presentation – Dr Agrawal: A 48-year-old premenopausal woman with an ER/PR-positive, HER2-negative, node-negative IDC

Dr Laila Agrawal

- 12-mm, Grade 2, strongly ER/PR-positive, HER2-negative, node-positive x 2 IDC
- Lumpectomy and SLNB
- Ovarian suppression and letrozole
  - Vaginal dryness and dyspareunia

Questions

- Would you recommend chemotherapy or genomic testing?
- How do you discuss sexual concerns with your patients?
- Who in the clinic has the role to bring that up?
- Do you utilize questionnaires?
- Do you ask patients every visit?
- What resources are available at your institutions for women who have sexual health concerns after cancer diagnosis and treatment?

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N Engl J Med 2021;385:2336-47

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer

K. Kalinsky, W.E. Barlow, J.R. Gralow, F. Meric-Bernstam, K.S. Albain, D.F. Hayes, N.U. Lin, E.A. Perez, L.J. Goldstein, S.K.L. Chia, S. Dhesy-Thind, P. Rastogi, E. Alba, S. Delaloge, M. Martin, C.M. Kelly, M. Ruiz-Borrego, M. Gil-Gil, C.H. Arce-Salinas, E.G.C. Brain, E.-S. Lee, J.-Y. Pierga, B. Bermejo, M. Ramos-Vazquez, K.-H. Jung, J.-M. Ferrero, A.F. Schott, S. Shak, P. Sharma, D.L. Lew, J. Miao, D. Tripathy, L. Pusztai, and G.N. Hortobagyi

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

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

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

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

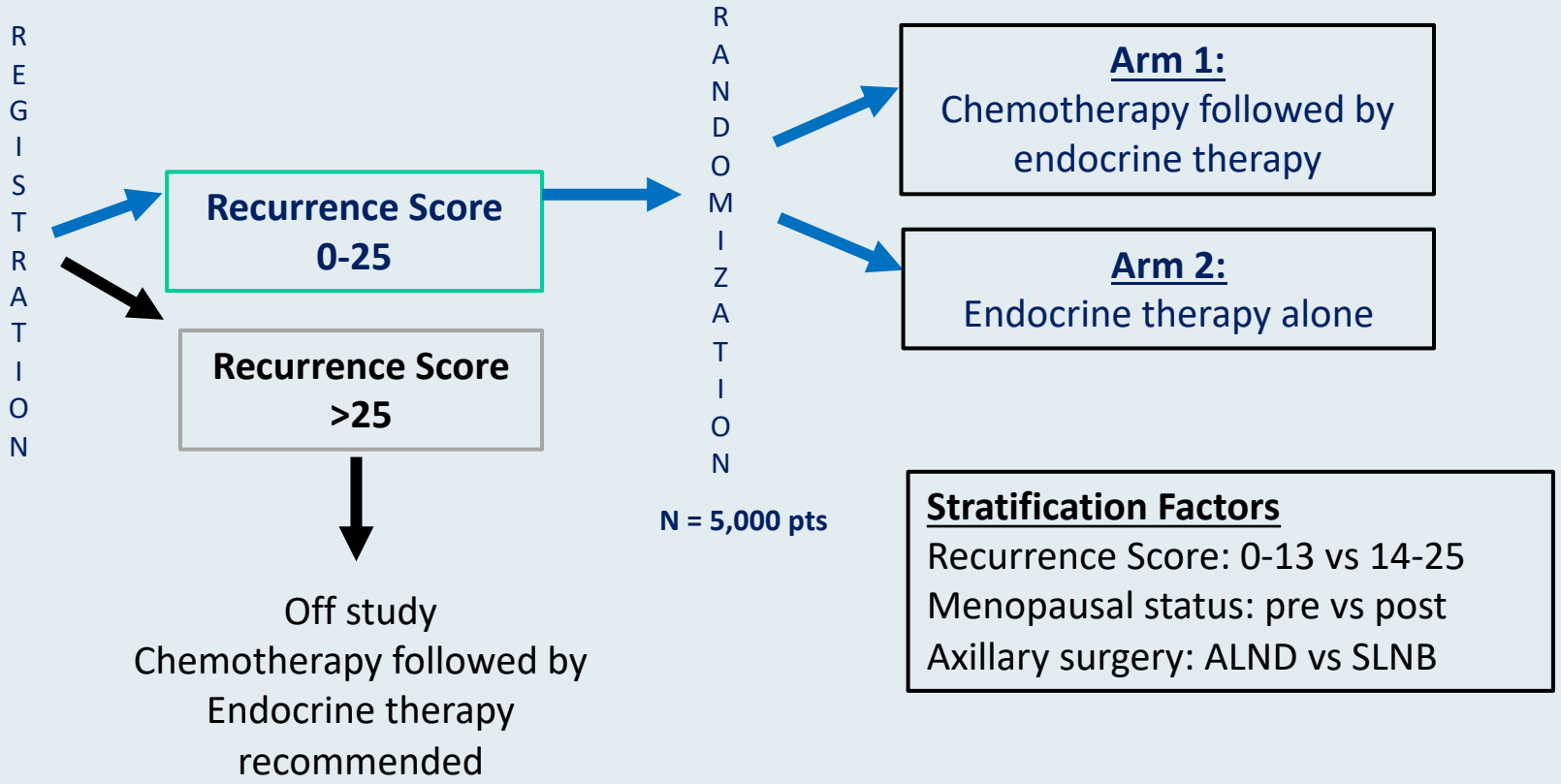
On Behalf of the RxPonder Investigators

SABCS® 2021;Abstract GS2-07.

RxPONDER Trial Schema

Key Entry Criteria

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



Stratification Factors

Recurrence Score: 0-13 vs 14-25
Menopausal status: pre vs post
Axillary surgery: ALND vs SLNB

* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.
† Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.
SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection

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

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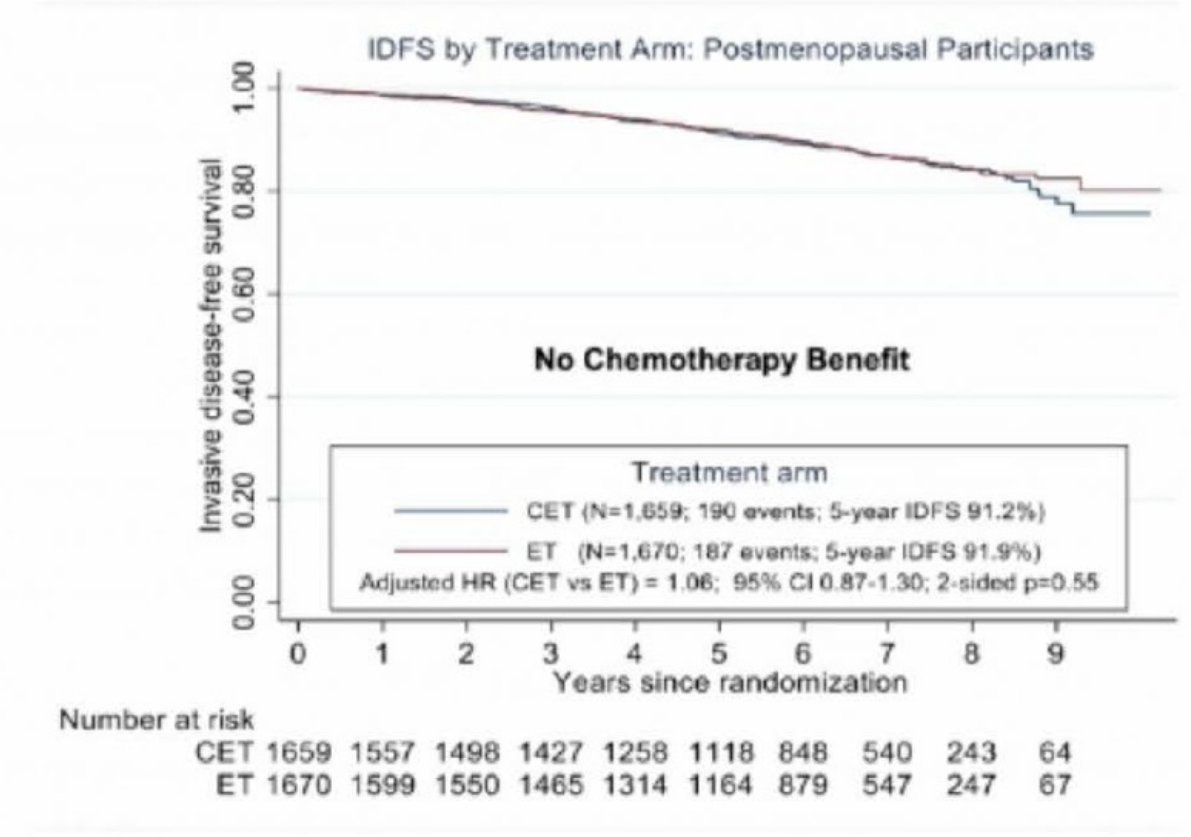
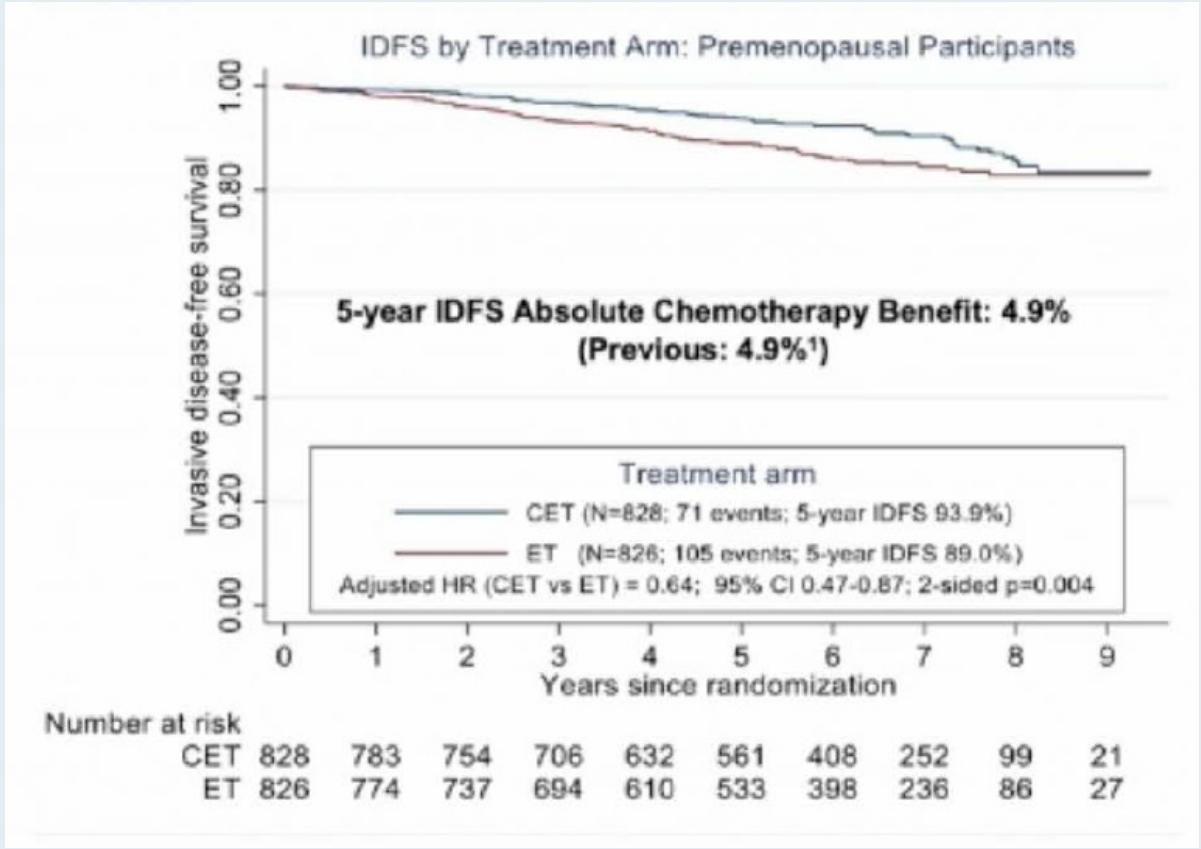
RxPONDER Updated Analysis: IDFS Stratified by Menopausal Status

Postmenopausal



Premenopausal



IDFS = invasive disease-free survival

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

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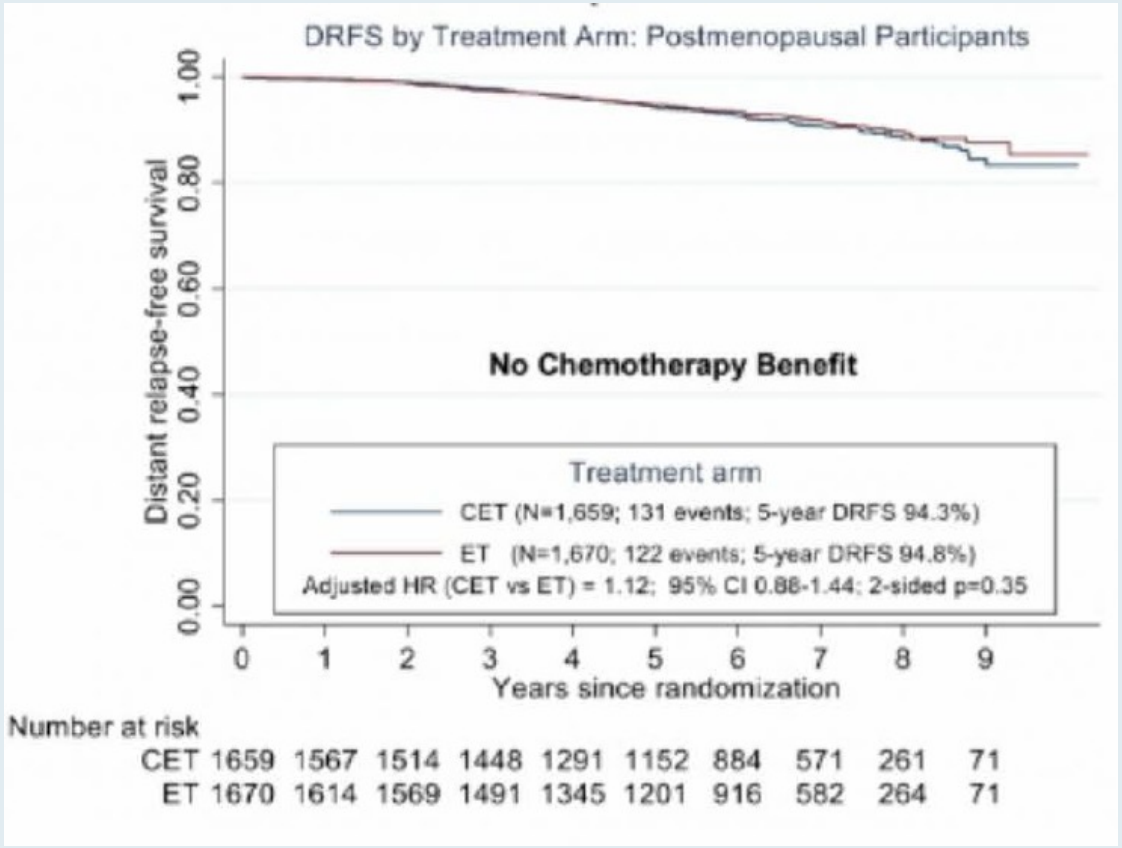
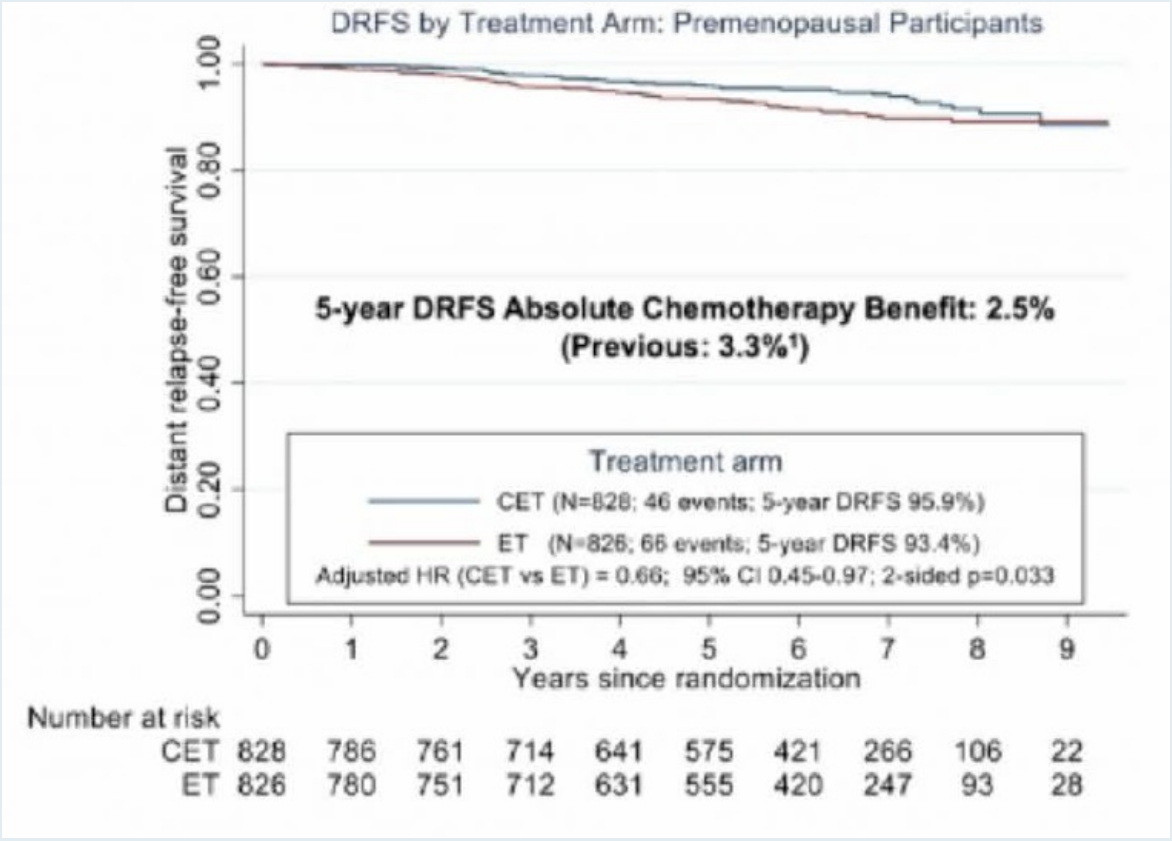
RxPONDER Updated Analysis: DRFS Stratified by Menopausal Status

Postmenopausal



Premenopausal

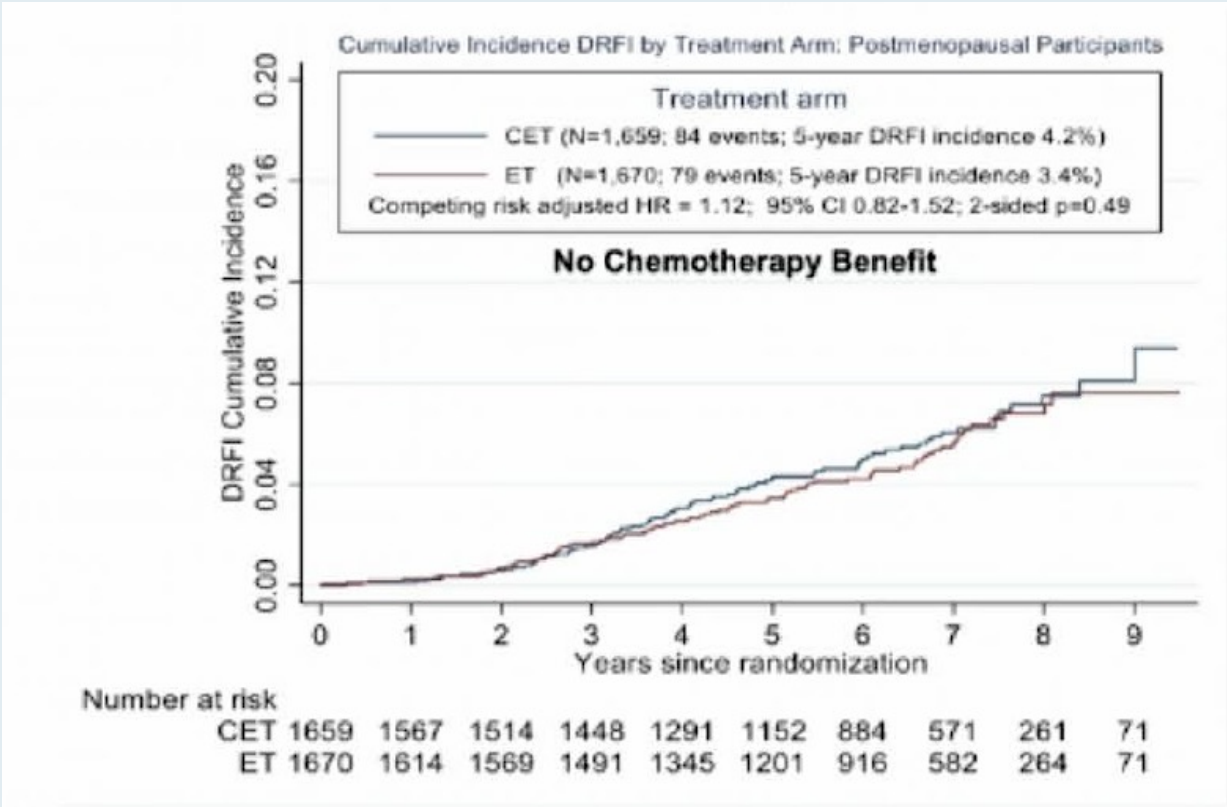


DRFS = distant recurrence-free survival

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

RxPONDER New Analysis: DRFI Stratified by Menopausal Status

Postmenopausal



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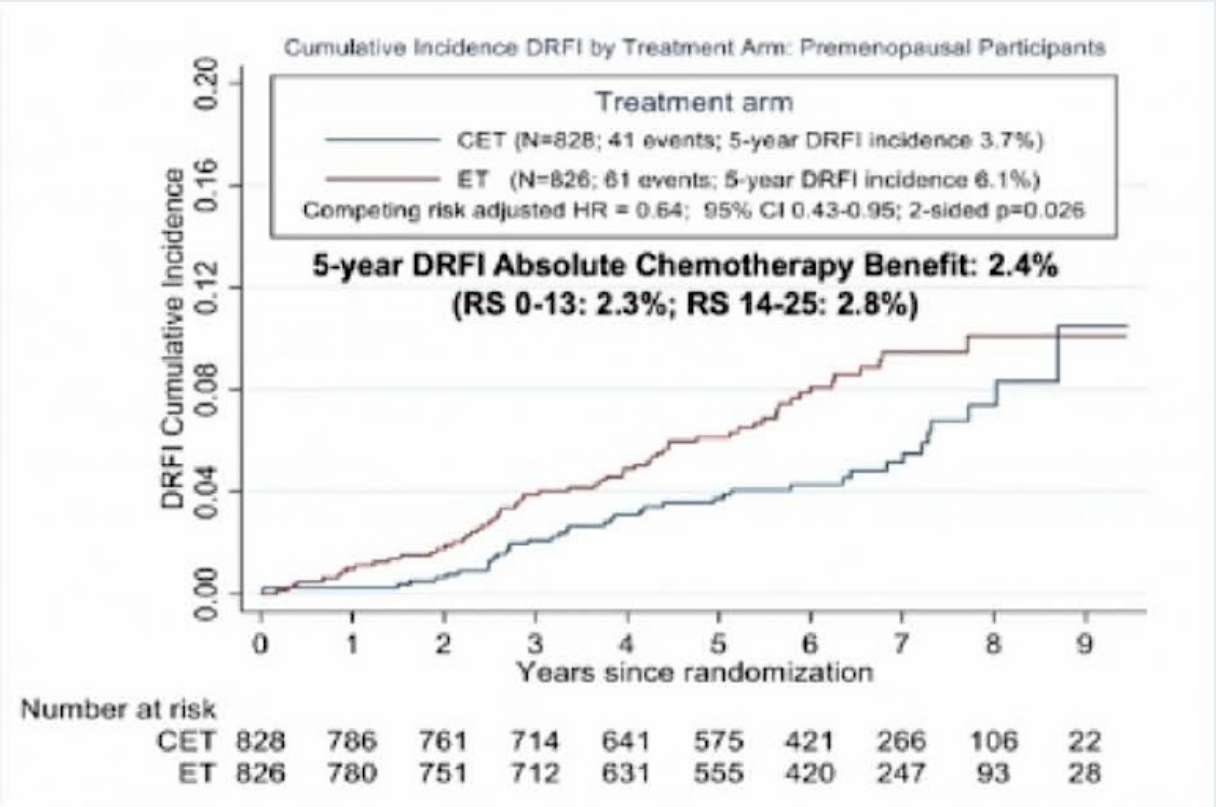

Time from randomization assignment to date of first invasive recurrence (distant) or death from breast cancer

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

DRFI = distant recurrence-free interval

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

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San Antonio Breast Cancer Symposium 2021

- Taylor C et al. **Using Onco*type* DX Breast Recurrence Score® (RS) assay to define the role of neoadjuvant endocrine therapy (NET) in early-stage hormone receptor positive (HR+) breast cancer (BC).** SABCS 2021;Abstract P2-15-02.
- Bradley R et al. **Aromatase inhibitors versus tamoxifen in pre-menopausal women with estrogen receptor positive early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7,030 women in four randomised trials.** SABCS 2021;Abstract GS2-04.
- Regan MM et al. **Randomized comparison of adjuvant aromatase inhibitor exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): Update of the combined TEXT and SOFT trials.** SABCS 2021;Abstract GS2-05.

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Case Presentation – Dr Sood: A 46-year-old woman with ER/PR-positive, HER2-negative metastatic breast cancer

Dr Raman Sood

- 1/2016: ER/PR-positive, HER2-negative, clinically node-positive left invasive lobular carcinoma
- PET: Multiple bone lesions, biopsy-proven metastatic disease
- Leuprolide/tamoxifen → Oophorectomy and switched to letrozole
- 5/2016: Palbociclib added after insurance-related delay
- 1/2017 PET: Complete remission and subsequent annual PET scans remain NED

Questions

- Would you still go back and remove the breast primary?
- In light of her response to letrozole/palbociclib, how long would you continue the combination therapy? Or would you continue them on single-agent letrozole or other hormonal agents?

San Antonio Breast Cancer Symposium 2021 (Continued)

- Carey L et al. **Correlative analysis of overall survival by intrinsic subtype across the MONALEESA-2, -3, and -7 studies of ribociclib + endocrine therapy in patients with HR+/HER2− advanced breast cancer.** SABCS 2021;Abstract GS2-00.
- O'Shaughnessy J et al. **Overall survival subgroup analysis by metastatic site from the phase 3 MONALEESA-2 study of first-line ribociclib + letrozole in postmenopausal patients with advanced HR+/HER2- breast cancer.** SABCS 2021;Abstract GS2-01.
- Bianchini G et al. **Circulating tumor DNA (ctDNA) dynamics in patients with hormone receptor positive (HR+)/HER2 negative (HER2-) advanced breast cancer (aBC) treated in first line with ribociclib (R) and letrozole (L) in the BioItaLEE trial.** SABCS 2021;Abstract GS3-07.
- Bidard F-C et al. **Fulvestrant-palbociclib vs continuing aromatase inhibitor-palbociclib upon detection of circulating ESR1 mutation in HR+ HER2- metastatic breast cancer patients: Results of PADA-1, a UCBG-GINECO randomized phase 3 trial.** SABCS 2021;Abstract GS3-05.

2021 ESMO congress

Abstract LBA17_PR

Overall Survival Results From the Phase III MONALEESA-2 Trial of Postmenopausal Patients With HR+/HER2− Advanced Breast Cancer Treated With Endocrine Therapy ± Ribociclib

Gabriel N. Hortobagyi,[1] Salomon M. Stemmer,[2] Howard A. Burris,[3] Yoon Sim Yap,[4] Gabe Sonke,[5] Lowell Hart,[6] Mario Campone,[7] Katarina Petrakova,[8] Eric P. Winer,[9] Wolfgang Janni,[10] Pierfranco Conte,[11] David A. Cameron,[12] Fabrice André,[13] Carlos Arteaga,[14] Juan Pablo Zarate,[15] Arunava Chakravartty,[15] Tetiana Taran,[16] Fabienne Le Gac,[16] Paolo Serra,[16] Joyce O'Shaughnessy[17]

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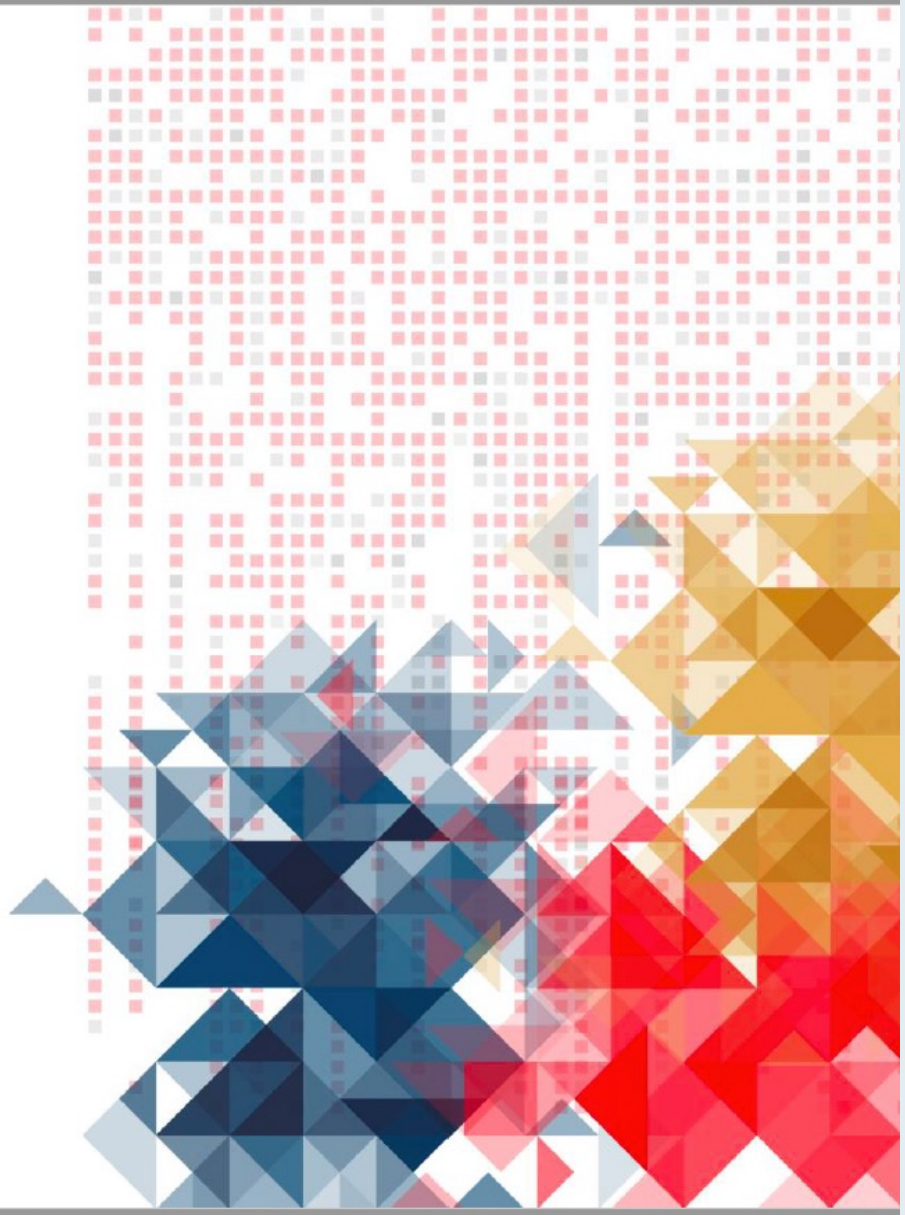

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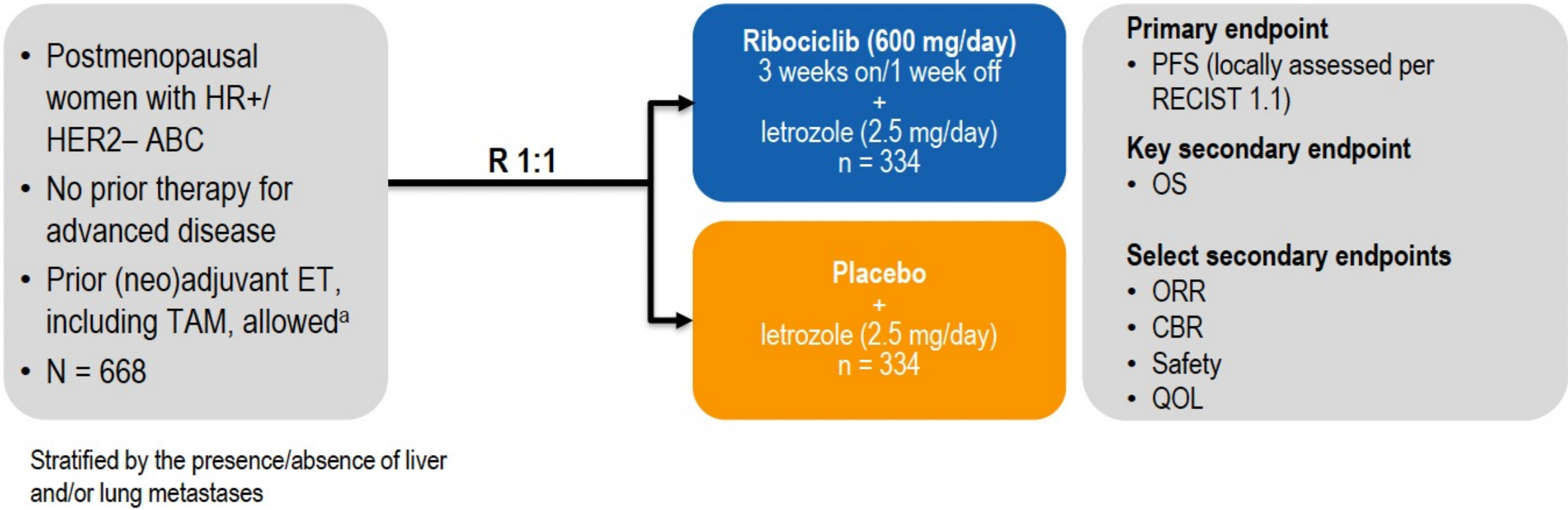
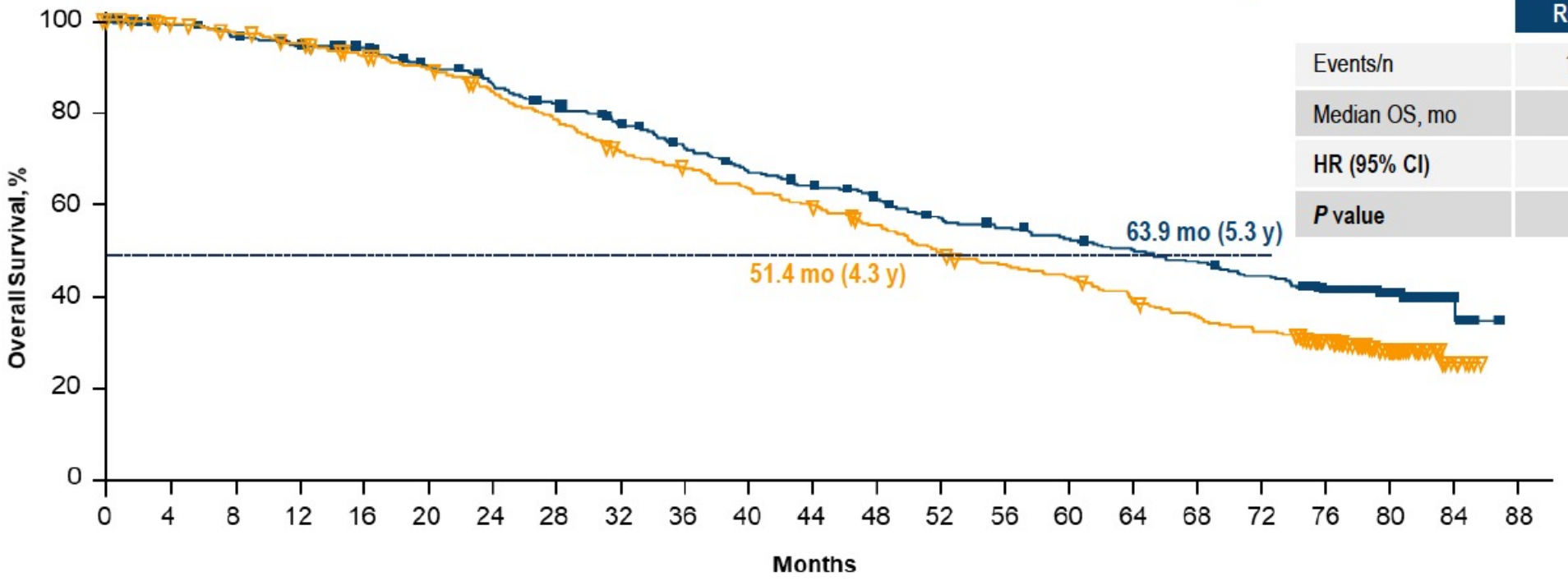
MONALEESA-2 Study Design



Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

MONALEESA-2: Overall Survival

Improvement in median OS was 12.5 months with ribociclib plus letrozole



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

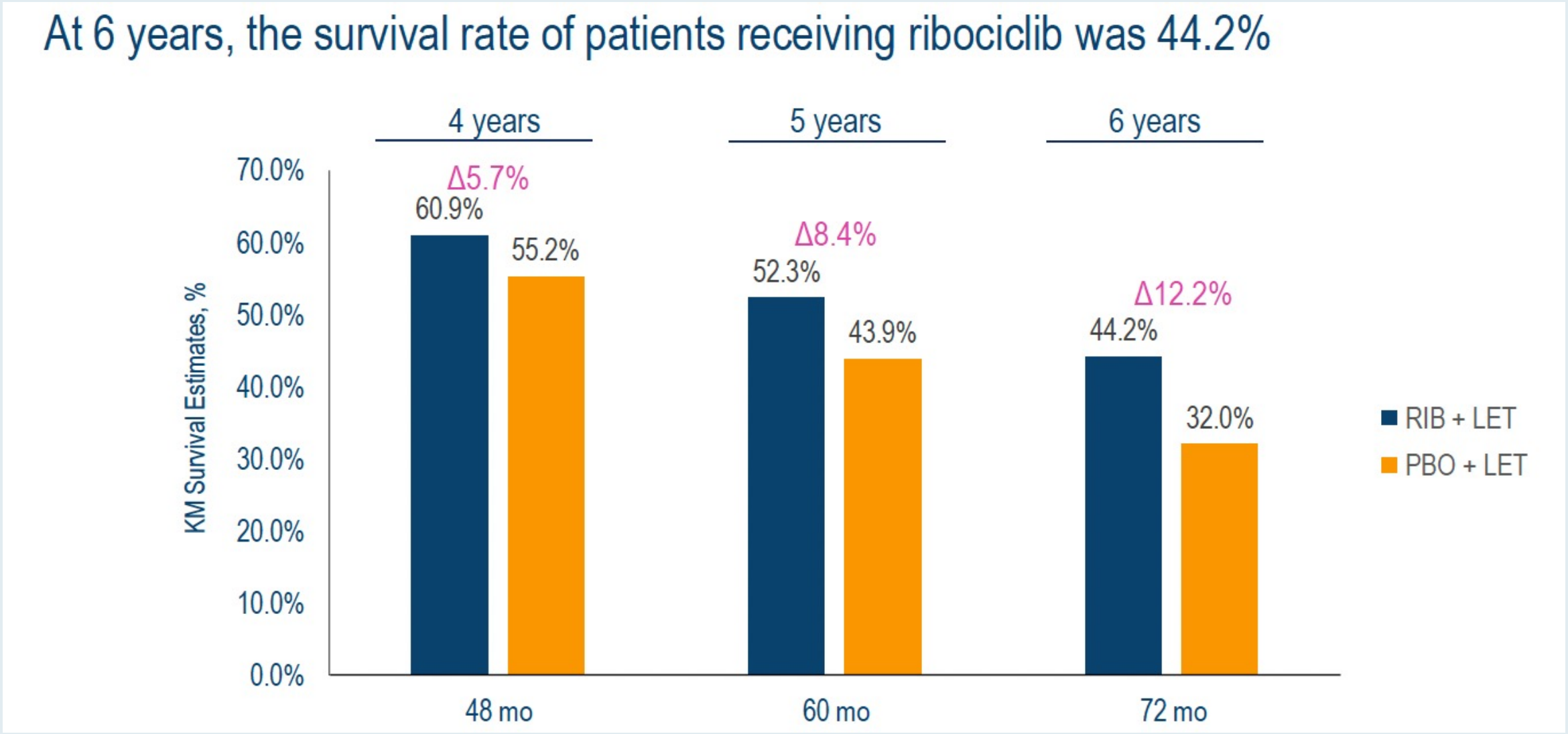
No. at risk

RIB + LET	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
PBO + LET	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

The P value of .004 crossed the prespecified boundary to claim superior efficacy

Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

MONALEESA-2: The Overall Survival Benefit Increased Over Time



Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

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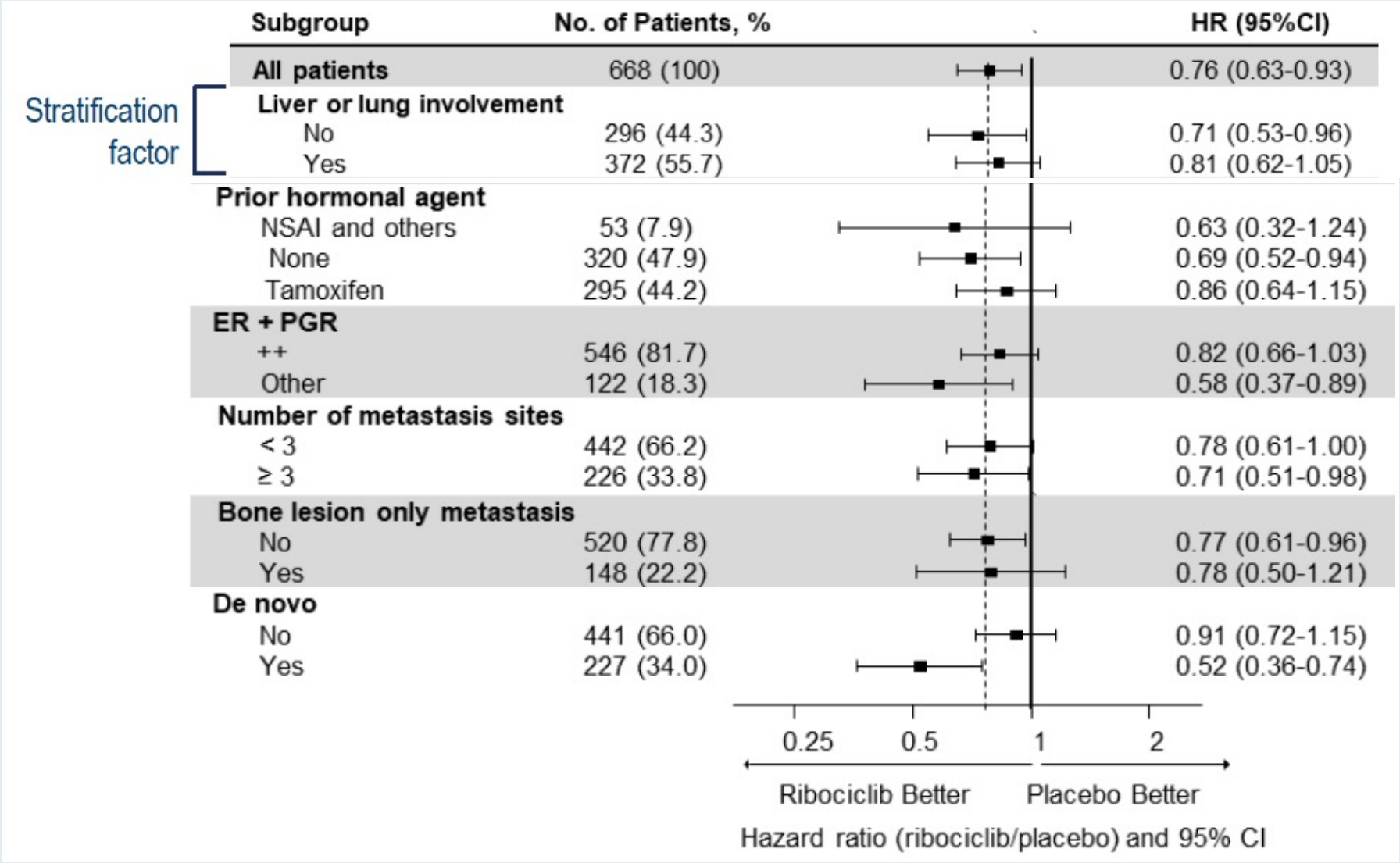
MONALEESA-2: OS Benefit Across Key Subgroups



Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

Randomized Trials of Endocrine Therapy with and without CDK4/6 Inhibition

Line	Trial	Schema	PFS HR compared to endocrine alone	OS HR compared to endocrine alone
First line	PALOMA-1	Letrozole ± palbociclib	0.49	0.897
	PALOMA-2	Letrozole ± palbociclib	0.58	NR
	MONALEESA-2	Letrozole ± ribociclib	0.56	0.76
	MONALEESA-3	Fulvestrant ± ribociclib	0.55	0.72
	MONALEESA-7 (premenopausal)	Goserelin + AI or tamoxifen ± ribociclib	0.55	0.71
	MONARCH 3	Letrozole or anastrozole, ± abemaciclib	0.54	NR
Second line	PALOMA-3	Fulvestrant ± palbociclib	0.46	0.75
	MONARCH 2	Fulvestrant ± abemaciclib	0.55	0.757

Finn RS et all. *Breast Cancer Res Treat* 2020; Finn RS et al. *NEJM* 2016; Hortobagyi GN et al. *Ann Oncol* 2019, ESMO 2021; Slamon DJ et al. *Ann Oncol* 2021; Im SA et al. *NEJM* 2019; Goetz MP et al. *JCO* 2017; Loibl S et al. *Oncologist* 2017; Sledge GW Jr et al. *JAMA Oncol* 2020.

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

RTP RESEARCH TO PRACTICE

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

IDC = infiltrating ductal carcinoma; AI = aromatase inhibitor

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

Meet The Professor with Dr O'Regan

Module 1: Use of Genomic Assays for Localized ER-Positive Breast Cancer

- Dr Agrawal: A 48-year-old premenopausal woman with an ER/PR-positive, HER2-negative, node-negative IDC

Module 2: Selection of a First-Line CDK4/6 Inhibitor for ER-Positive Metastatic Breast Cancer (mBC)

- Dr Sood: A 46-year-old woman with ER/PR-positive, HER2-negative mBC

Module 3: Management of ER-Positive Oligometastatic Breast Cancer

- Dr Heeke: A 41-year-old woman with ER/PR-positive, HER2-negative oligometastatic BC

Module 4: Treatment Options for ER-Positive mBC Progressing on a First-Line CDK4/6 Inhibitor

- Dr Stebel: A 60-year-old woman with ER/PR-positive, HER2-negative mBC with a PIK3CA mutation

Module 5: CDK4/6 Inhibitors in the Adjuvant Setting

- Dr Gupta: A 51-year-old postmenopausal woman with Stage IIIB ER/PR-positive, HER2-negative, node-positive BC

Module 6: PARP Inhibitors for Localized ER-Positive Breast Cancer with a BRCA Mutation

- Dr Agrawal: A 38-year-old woman with ER/PR-positive, HER2-negative, node-positive IDC with a germline BRCA1 mutation

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Case Presentation – Dr Heeke: A 41-year-old woman with ER/PR-positive, HER2-negative oligometastatic breast cancer

Dr Arielle Heeke

- 12/2020: Two right primary breast tumors, DCIS, and oligometastases to the right acetabulum
  - ER/PR-positive, HER2-negative
- Endocrine therapy x 3 months, with response
- "Neoadjuvant" ddAC → ddPaclitaxel

Questions

- How do you define oligometastatic disease? How do you select the patients that are appropriate for these intensive therapies?
- How do you balance the long-term consequences of chemo and estrogen deprivation, and estrogen deprivation's impacts on quality of life in the short-term but also cardiovascular and mental or neuronal health long-term?

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr O'Regan

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Case Presentation – Dr Stebel: A 60-year-old woman with ER/PR-positive, HER2-negative metastatic breast cancer with a PIK3CA mutation

Dr Andrea Stebel

- Treated elsewhere with ddAC → paclitaxel and anastrozole x 5 years for a Stage IIB ER-positive, HER2-negative IDC
- Two years after completion of adjuvant anastrozole: Cervical adenopathy – biopsy-proven metastatic disease
- Re-start anastrozole, but PD within 6 months
- Abemaciclib initiated but fulvestrant declined → Mild PD
- Testing on archived tissue reveals PIK3CA mutation
- Fulvestrant/alpelisib

Questions

- Would you have added fulvestrant to abemaciclib after the mild progression of her disease?
- Would you have switched her to fulvestrant/alpelisib?

RTP RESEARCH TO PRACTICE

Int J Mol Sci 2021 Nov 2;22(21):11878

International Journal of
Molecular Sciences

MDPI

Review

PI3Kinase Inhibition in Hormone Receptor-Positive Breast Cancer

Ajay Dhakal [1], Luna Acharya [2], Ruth O'Regan [3], Shipra Gandhi [4] and Carla Falkson [1,*]

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

EMERALD

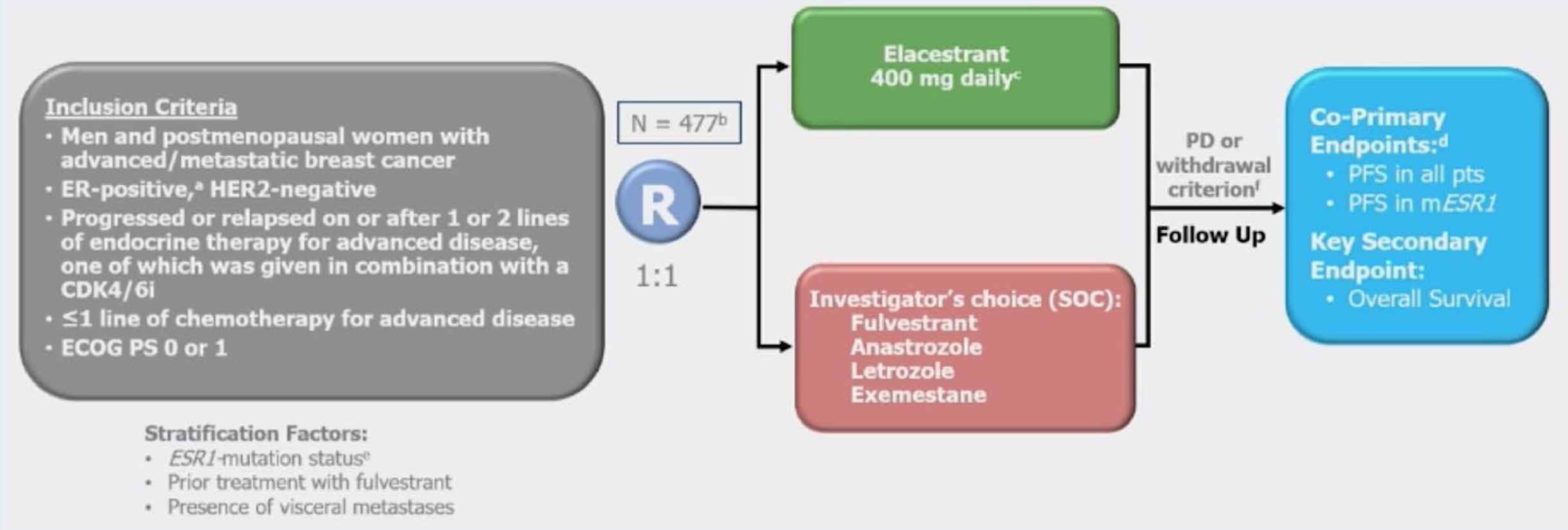
Elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC) following progression on prior endocrine and CDK4/6 inhibitor therapy: Results of EMERALD phase 3 trial

Bardia A,[1] Neven P,[2] Streich G,[3] Montero AJ,[4] Forget F,[5] Mouret-Reynier MA,[6] Sohn JH,[7] Vuylsteke P,[8] Harnden KK,[9] Khong H,[10] Kocsis J,[11] Dalenc F,[12] Kaklamani V,[13] Dillon P,[14] Babu S,[15] Waters S,[16] Deleu I,[17] Garcia-Saenz J,[18] Bria E,[19] Cazzaniga M,[20] Lu J,[21] Aftimos P,[22] Cortes J,[23] Liu S,[24] Laurent D,[25] Conlan MG,[26] Bidard FC[27]

SABCS 2021;Abstract GS2-02.

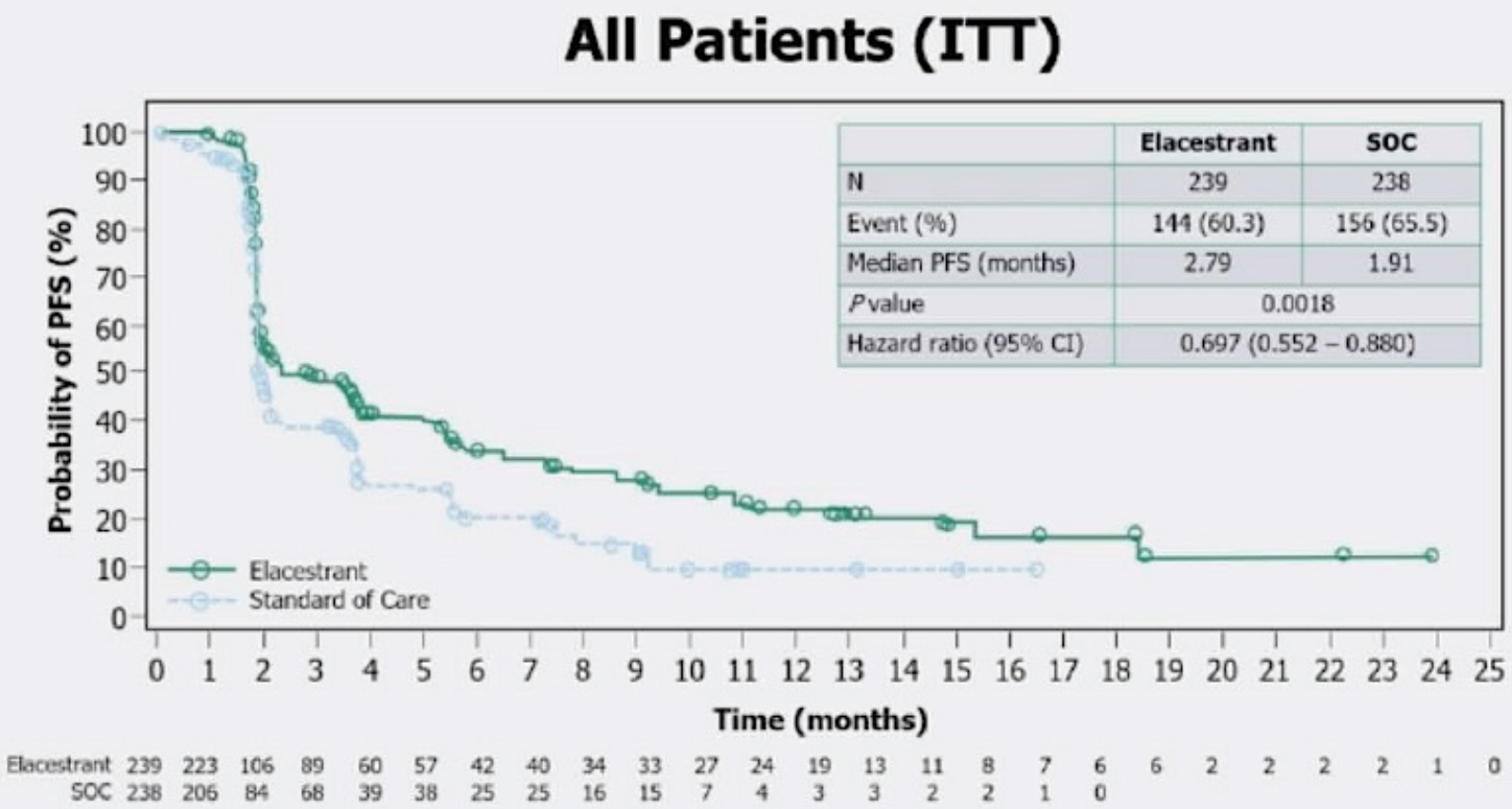
RTP RESEARCH TO PRACTICE

EMERALD Phase III Trial Design



Bardia A et al. SABCS 2021;Abstract GS2-02.

EMERALD: Progression-Free Survival by IRC



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

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

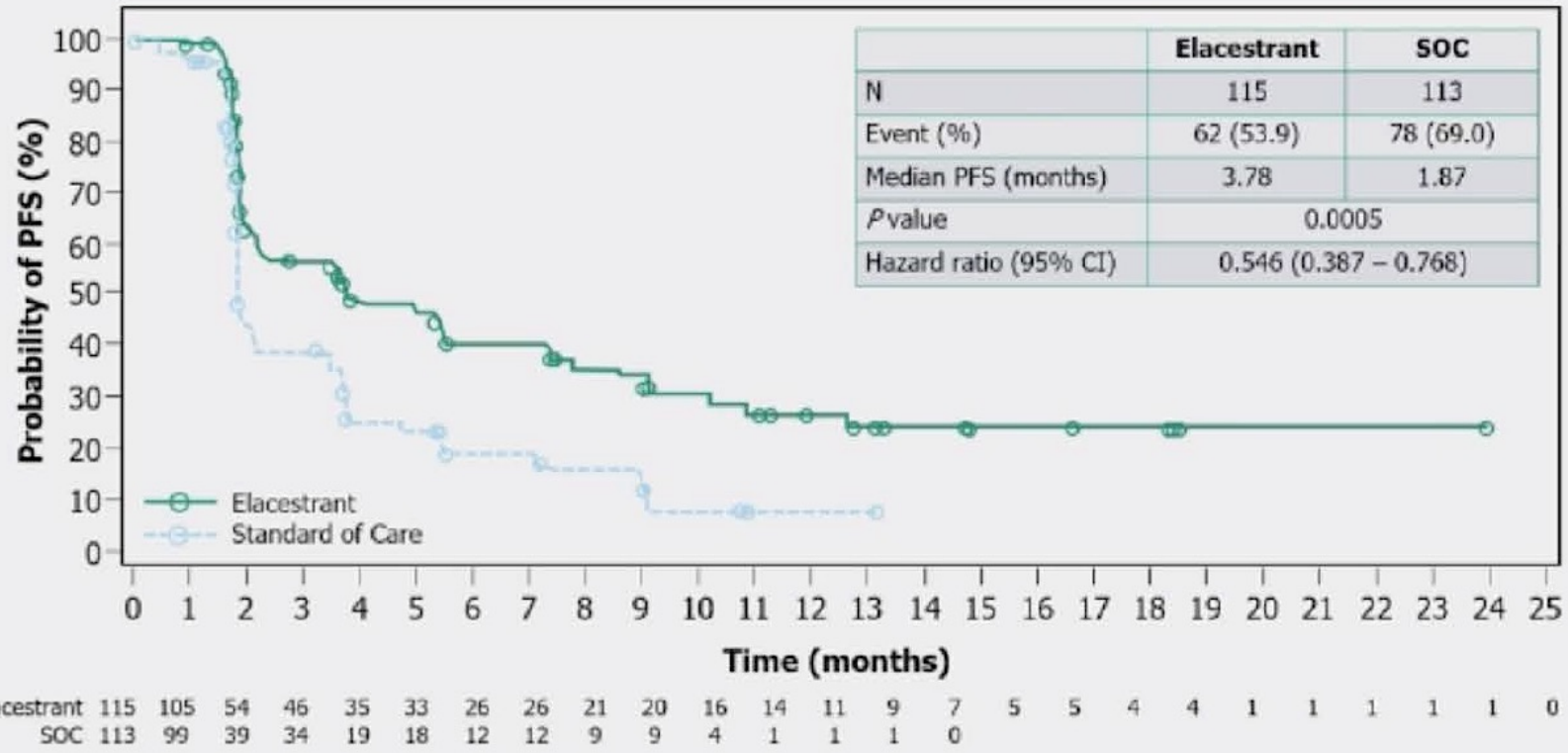
Elacestrant demonstrated a significant improvement versus SOC in all patients with ER+/HER2- advanced/metastatic breast cancer following CDK4/6i therapy

Bardia A et al. SABCS 2021;Abstract GS2-02.

RTP RESEARCH TO PRACTICE

EMERALD: Progression-Free Survival by IRC

Patients With Tumors Harboring *mESR1*



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

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

Elacestrant demonstrated a significant improvement versus SOC in patients with ER+/HER2- advanced/metastatic breast cancer and *mESR1* following CDK4/6i therapy

Bardia A et al. SABCS 2021;Abstract GS2-02.

RTP RESEARCH TO PRACTICE

EMERALD: Treatment-Emergent Adverse Events

	Elacestrant N = 237, n (%)		SOC					
			Total N = 229, n (%)		Fulvestrant N = 161, n (%)		AI N = 68, n (%)	
Preferred Term	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	-	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)	2 (0.8)	19 (8.3)	-	12 (7.5)	-	7 (10.3)	-
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	-	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	-	28 (17.4)	-	9 (13.2)	-
Diarrhea	33 (13.9)	-	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	-
Aspartate aminotransferase increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	-
Headache	29 (12.2)	4 (1.7)	26 (11.4)	-	18 (11.2)	-	8 (11.8)	-
Constipation	29 (12.2)	-	15 (6.6)	-	10 (6.2)	-	5 (7.4)	-
Hot flush	27 (11.4)	-	19 (8.3)	-	15 (9.3)	-	4 (5.9)	-
Dyspepsia	24 (10.1)	-	6 (2.6)	-	4 (2.5)	-	2 (2.9)	-
Alanine aminotransferase increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	-	6 (8.8)	1 (1.5)

Bardia A et al. SABCS 2021;Abstract GS2-02.

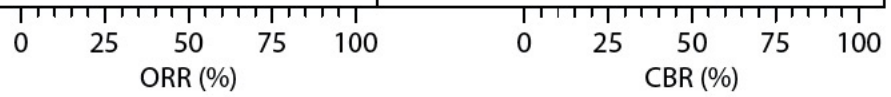
AMEERA-1: Subgroup Analyses of Phase 1/2 Study of Amcenestrant (SAR439859), an Oral Selective Estrogen Receptor (ER) Degrader (SERD), with Palbociclib in Postmenopausal Women with ER+/Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Advanced Breast Cancer (aBC)

Chandarlapathy S et al.

ESMO 2021;Abstract 264P.

AMEERA-1: Response and Clinical Benefit Rate with Amcenestrant and Palbociclib for Endocrine-Resistant ER-Positive, HER2-Negative mBC

	N	ORR[a] n (%)	CBR[b] n (%)
Response-evaluable patients	34	11 (32.4)	25 (73.5)
Immediate prior therapy			
(Neo)adjuvant	15	4 (26.7)	8 (53.3)
Advanced	19	7 (36.8)	17 (89.5)
Baseline *ESR1* mutation status			
Wild type	26	8 (30.8)	18 (69.2)
Mutant	8	3 (37.5)	7 (87.5)
Prior AI in the adjuvant setting			
No	14	5 (35.7)	11 (78.6)
Yes	20	6 (30.0)	14 (70.0)
Prior SERM in the adjuvant setting			
No	16	4 (25.0)	11 (68.8)
Yes	18	7 (38.9)	14 (77.8)



AI, aromatase inhibitors; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.
[a]Confirmed CR or PR; [b]CR, PR, or SD ≥ 24 weeks.
Gray shading represents the 90% CI of the response-evaluable population.

Select Ongoing Phase II/III Trials of Oral SERDs in Development for ER-Positive, HER2-Negative Advanced Breast Cancer

Drug	Trial name (phase)	Treatment arms	Setting	Estimated study completion date
Amcenestrant (SAR439859)	AMEERA-3 (Phase II)	• Amcenestrant • Endocrine monotherapy	Prior hormonal tx	July 2025
Amcenestrant (SAR439859)	AMEERA-5 (Phase III)	• Amcenestrant + Palbociclib • Letrozole + Palbociclib	Untreated ABC	May 2027
Camizestrant (AZD9833)	SERENA-4 (Phase III)	• Camizestrant + Palbociclib • Anastrozole + Palbociclib	Untreated ABC	February 2029
Giredestrant (GDC-9545)	acelERA (Phase II)	• Giredestrant • Endocrine monotherapy	Prior systemic and/or targeted tx	January 2024
Giredestrant (GDC-9545)	persevERA (Phase III)	• Giredestrant + Palbociclib • Letrozole + Palbociclib	Untreated ABC	March 2027

SERD: Selective ER degrader

www.clinicaltrials.gov. Accessed August 2021

RTP RESEARCH TO PRACTICE

A patient who presents with ER-positive, HER2-negative mBC with liver and bone metastases that is stable on palbociclib/letrozole is found on imaging to have asymptomatic disease progression. Genomic testing reveals a PIK3CA mutation. What would you recommend?

 Dr Goetz	Switch to alpelisib/fulvestrant	 Dr Kalinsky	Switch to alpelisib/fulvestrant
 Dr Jhaveri	Switch to alpelisib/fulvestrant	 Dr Mayer	Switch to alpelisib/fulvestrant
 Dr Kaklamani	Switch to alpelisib/fulvestrant	 Dr O'Regan	Switch to alpelisib/fulvestrant

RTP RESEARCH TO PRACTICE

A patient who presents with ER-positive, HER2-negative mBC with liver and bone metastases that is stable on palbociclib/letrozole is found on imaging to have asymptomatic disease progression. Genomic testing reveals no PIK3CA mutation. What would you recommend?

 Dr Goetz	Switch to everolimus/ET	 Dr Kalinsky	Switch to everolimus/ET
 Dr Jhaveri	Switch to everolimus/ET	 Dr Mayer	Switch to everolimus/ET
 Dr Kaklamani	Switch to everolimus/ET	 Dr O'Regan	Switch to everolimus/ET

RTP RESEARCH TO PRACTICE

A patient with ER-positive mBC experiences asymptomatic disease progression on palbociclib/letrozole. Genomic testing reveals a PIK3CA mutation. Her baseline fasting glucose is 130 mg/dL and hemoglobin A1c is 6.5%. Would you recommend alpelisib/fulvestrant for this patient?

 Dr Goetz	No	 Dr Kalinsky	Yes, with standard-dose alpelisib
 Dr Jhaveri	Yes, with reduced-dose alpelisib	 Dr Mayer	Yes, with standard-dose alpelisib
 Dr Kaklamani	Yes, with standard-dose alpelisib	 Dr O'Regan	Yes, with standard-dose alpelisib

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr O'Regan

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Case Presentation – Dr Gupta: A 51-year-old postmenopausal woman with Stage IIIB ER/PR-positive, HER2-negative, node-positive breast cancer

Dr Shaachi Gupta

- PMH: Hypertension, obesity
- 6/2021: 5.8-cm ER/PR-positive, HER2-negative, node-positive left breast papillary carcinoma and Ki67, 35%
- Neoadjuvant ddAC x 4 → Weekly paclitaxel
- 9/2021 repeat ultrasound: Slight increase in breast and lymph node
- 10/2021: Modified radical mastectomy and ALND
  - Residual invasive mucinous carcinoma and DCIS and 2 positive lymph nodes

Questions

- What has been your experience with adjuvant abemaciclib-associated toxicity?
- Besides the usual anti-diarrheal regimens, do you do anything else to manage the diarrhea?

RTP RESEARCH TO PRACTICE

Cancer 2021;127:3302-3309

Review Article

Adjuvant Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor–Positive Breast Cancer: One Monarch to Rule Them All?

Ajay Dhakal, MD[1,2]; Carla Falkson, MD[1,2]; and Ruth M. O'Regan, MD [1,2]

FDA Approves Adjuvant Abemaciclib with Endocrine Therapy for Early Breast Cancer

Press Release: October 12, 2021

"The Food and Drug Administration approved abemaciclib with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test. This is the first CDK 4/6 inhibitor approved for adjuvant treatment of breast cancer.

FDA also approved the Ki-67 IHC MIB-1 pharmDx assay as a companion diagnostic for selecting patients for this indication.

Efficacy was evaluated in monarchE (NCT03155997), a randomized (1:1), open-label, two-cohort multicenter trial that included adult women and men with HR-positive, HER2-negative, node-positive, resected, early breast cancer with clinical and pathological features consistent with a high risk of disease recurrence."

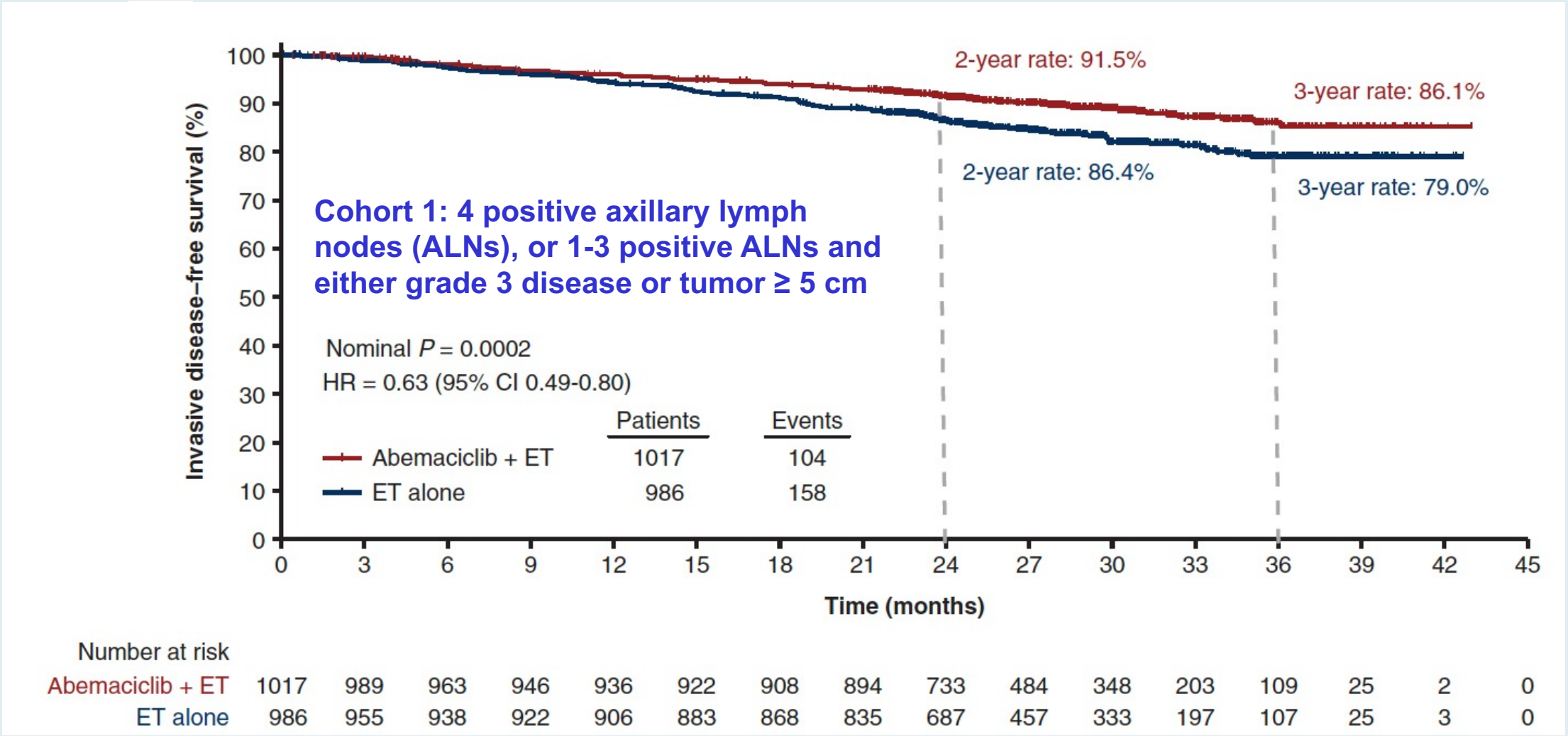
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abemaciclib-endocrine-therapy-early-breast-cancer

ASCO Rapid Recommendation Update for Abemaciclib for HR-Positive, HER2-Negative, Node-Positive Localized Breast Cancer

- Abemaciclib with endocrine therapy (ET — tamoxifen or an aromatase inhibitor) is FDA approved for adjuvant treatment of HR-positive, HER2-negative, node-positive localized breast cancer with high risk of recurrence **and a Ki-67 score ≥20%**.
- Based on analyses reported by Harbeck and colleagues, the panel recommends that abemaciclib for 2 years with ET for 5 years or longer may be offered to the broader intent-to-treat population of patients with resected HR-positive, HER2-negative, node-positive localized breast cancer at high risk of recurrence, defined as having >4 positive axillary lymph nodes **or** as having 1 to 3 positive axillary lymph nodes and 1 or more of the following features: histologic Grade III, tumor size >5 cm **or Ki-67 index >20%**.
- Despite similar hazard ratios in favor of abemaciclib regardless of Ki-67 status, relatively few low Ki-67 tumors were reported in monarchE. When discussing treatment options with patients, the potential benefits (improved IDFS) should be weighed against the potential harms (treatment toxicity, financial cost).

Harbeck N et al. *Ann Oncol* 2021;[Online ahead of print].
https://www.asco.org/practice-patients/guidelines/breast-cancer#/11081

monarchE: Invasive Disease-Free Survival in Cohort 1, Ki67-High Population with Adjuvant Abemaciclib



Harbeck N et al. *Ann Oncol* 2021 Dec; 32(12):1571-81.

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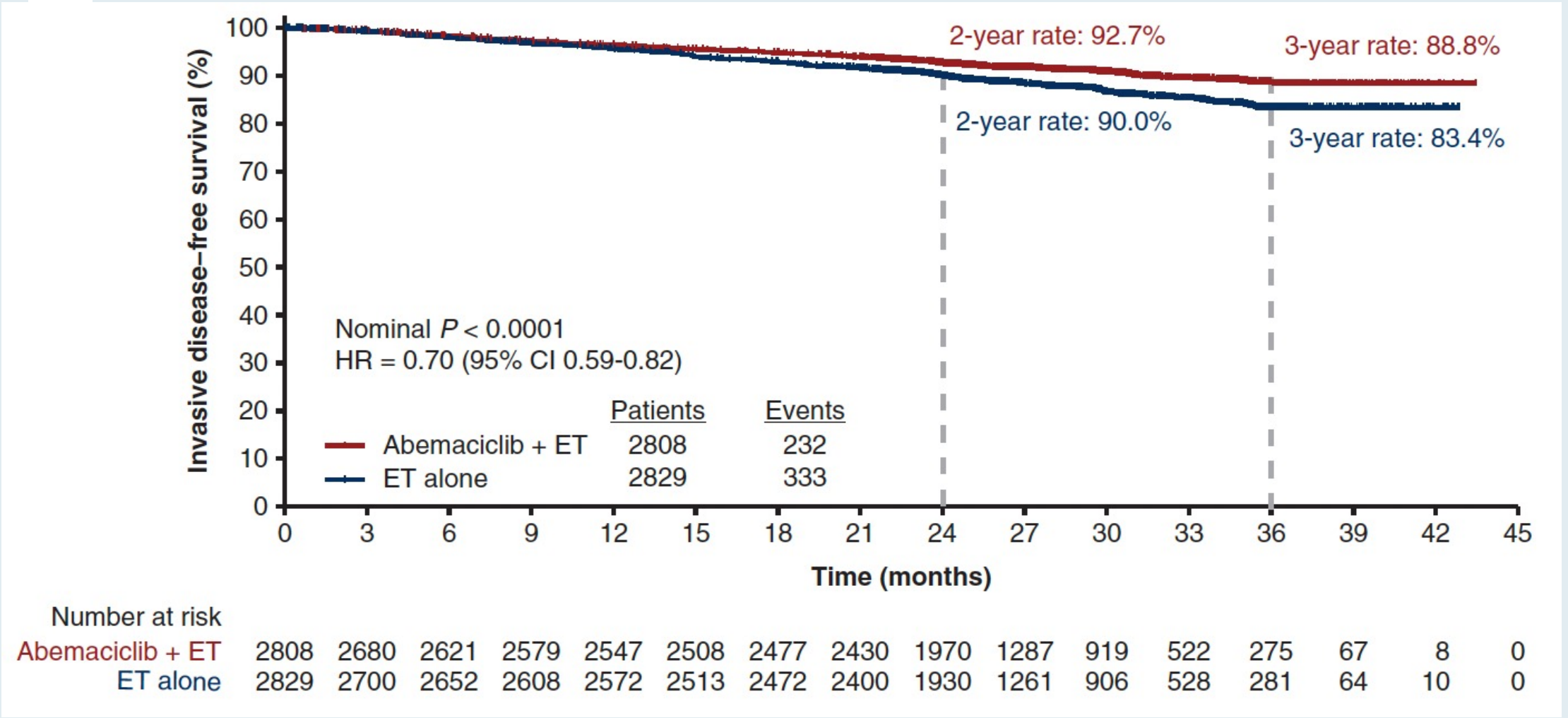
monarchE: Invasive Disease-Free Survival in the Intent-to-Treat (ITT) Population with Adjuvant Abemaciclib



Harbeck N et al. *Ann Oncol* 2021 Dec; 32(12):1571-81.

Case Presentation SABCS 2021 – Dr Sood: An 89-year-old woman with ER-positive, node-positive localized breast cancer being considered for adjuvant abemaciclib

Dr Raman Sood
Dunkirk, New York

- Underwent left breast mastectomy which revealed 4 out of 6 positive lymph nodes
- No evidence of metastatic disease
- Good performance status
- Ki-67 assay not performed
- Potential treatment: Adjuvant abemaciclib

Question

- Could the faculty justify the potential toxicity of this treatment approach in an elderly patient?

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

Tuesday, December 7, 2021
7:00 PM – 8:45 PM CT

Faculty
Aditya Bardia, MD, MPH **Joyce O'Shaughnessy, MD**
Kevin Kalinsky, MD, MS

Moderator
Erika Hamilton, MD

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Regulatory and reimbursement issues aside, would you generally recommend adjuvant abemaciclib to a patient with a T2 primary and 1 positive node?

1. No
2. Yes
3. Yes, if Ki-67 >20%

What would you estimate as the 5-year risk of recurrence for a patient with an ER-positive T2 primary tumor and 1 positive lymph node after receiving adjuvant chemotherapy with standard endocrine treatment (without an adjuvant CDK4/6 inhibitor)?

1. <5%
2. 5%-10%
3. 11%-20%
4. 21%-30%
5. 31%-40%
6. 41%-50%
7. >50%

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Approximately what proportion of your patients with ER-positive localized breast cancer would wish to receive adjuvant abemaciclib if the absolute reduction in 5-year risk of recurrence were 2% to 3%?

1. <5%
2. 5%-10%
3. 11%-30%
4. 31%-50%
5. 51%-70%
6. >70%

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Meet The Professor with Dr O'Regan

Module 1: Use of Genomic Assays for Localized ER-Positive Breast Cancer

- Dr Agrawal: A 48-year-old premenopausal woman with an ER/PR-positive, HER2-negative, node-negative IDC

Module 2: Selection of a First-Line CDK4/6 Inhibitor for ER-Positive Metastatic Breast Cancer (mBC)

- Dr Sood: A 46-year-old woman with ER/PR-positive, HER2-negative mBC

Module 3: Management of ER-Positive Oligometastatic Breast Cancer

- Dr Heeke: A 41-year-old woman with ER/PR-positive, HER2-negative oligometastatic BC

Module 4: Treatment Options for ER-Positive mBC Progressing on a First-Line CDK4/6 Inhibitor

- Dr Stebel: A 60-year-old woman with ER/PR-positive, HER2-negative mBC with a PIK3CA mutation

Module 5: CDK4/6 Inhibitors in the Adjuvant Setting

- Dr Gupta: A 51-year-old postmenopausal woman with Stage IIIB ER/PR-positive, HER2-negative, node-positive BC

Module 6: PARP Inhibitors for Localized ER-Positive Breast Cancer with a BRCA Mutation

- Dr Agrawal: A 38-year-old woman with ER/PR-positive, HER2-negative, node-positive IDC with a germline BRCA1 mutation

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Case Presentation – Dr Agrawal: A 38-year-old woman with ER/PR-positive, HER2-negative, node-positive IDC with a germline BRCA1 mutation

Dr Laila Agrawal

- T2 ER/PR-positive, HER2-negative localized IDC, BRCA1 mutation, Ki-67: 40%
- Neoadjuvant AC → paclitaxel, with CR
- Bilateral mastectomies and ALND, with 9-mm residual disease in the breast, 23/25 positive nodes
- Adjuvant RT, ovarian suppression plus aromatase inhibitor

Questions

- In patients with a BRCA1 mutation and ER/PR-positive disease, how do you decide between an adjuvant PARP inhibitor versus adjuvant abemaciclib?
- How do you counsel your patients on the risk of hematological cancer with a PARP inhibitor? How do you preempt or manage PARPi-associated toxicities?
- How do approach genetic testing? Are there particular panels that you find to be the most beneficial? Do breast cancer patients need to have extended panels or do the 8 or 9 gene high risk for breast seem sufficient to you? Do you ever utilize somatic panels or molecular panels up front in patients without metastatic disease?
- For patients who have a VUS in a BRCA1 or 2 gene, would you consider those patients candidates for a PARP inhibitor? What about patients who had a PALB2 mutation?

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J Clin Oncol 2021;[Online ahead of print].

ASCO rapid recommendations

Adjuvant PARP Inhibitors in Patients With High-Risk Early-Stage HER2-Negative Breast Cancer and Germline *BRCA* Mutations: ASCO Hereditary Breast Cancer Guideline Rapid Recommendation Update

Nadine M. Tung, MD[1]; Dana Zakalik, MD[2]; and Mark R. Somerfield, PhD[3]; for the Hereditary Breast Cancer Guideline Expert Panel

ASCO Rapid Recommendations Updates highlight revisions to select ASCO guideline recommendations as a response to the emergence of new and practice-changing data. The rapid updates are supported by an evidence review and follow the guideline development processes outlined in the ASCO Guideline Methodology Manual. The goal of these articles is to disseminate updated recommendations, in a timely manner, to better inform health practitioners and the public on the best available cancer care options.

ASCO 2021 Adjuvant PARPi Updated Recommendations

- **For patients with early-stage, HER2-negative breast cancer** with high risk of recurrence and germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants, 1 year of adjuvant olaparib should be offered after completion of (neo)adjuvant chemotherapy and local treatment, including radiation therapy.
- **For those who underwent surgery first**, 1 year of adjuvant olaparib should be offered for patients with triple-negative breast cancer and tumor size >2 cm or any involved axillary nodes.
- **For those with hormone receptor (HR)-positive disease**, 1 year of adjuvant olaparib should be offered to those with at least 4 involved axillary lymph nodes.
- For patients who received neoadjuvant chemotherapy, 1 year of adjuvant olaparib should be offered to patients with triple-negative breast cancer and any residual cancer; **for patients with HR-positive disease**, 1 year of adjuvant olaparib should be offered to patients with residual disease and a clinical stage, pathologic stage, estrogen receptor and tumor grade score ≥3.

Tung NM et al. *J Clin Oncol* 2021;39(26):2959-61.

N Engl J Med 2021;384:2394-405

The NEW ENGLAND JOURNAL of MEDICINE

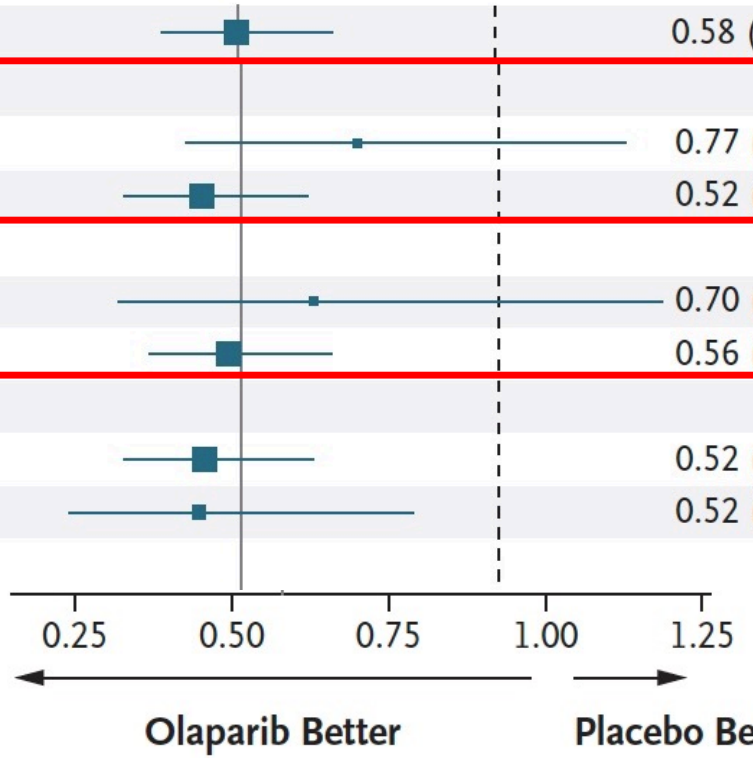
ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R.D. Gelber, E. de Azambuja, A. Fielding, J. Balmaña, S.M. Domchek, K.A. Gelmon, S.J. Hollingsworth, L.A. Korde, B. Linderholm, H. Bandos, E. Senkus, J.M. Suga, Z. Shao, A.W. Pippas, Z. Nowecki, T. Huzarski, P.A. Ganz, P.C. Lucas, N. Baker, S. Loibl, R. McConnell, M. Piccart, R. Schmutzler, G.G. Steger, J.P. Costantino, A. Arahmani, N. Wolmark, E. McFadden, V. Karantza, S.R. Lakhani, G. Yothers, C. Campbell, and C.E. Geyer, Jr., for the OlympiA Clinical Trial Steering Committee and Investigators*

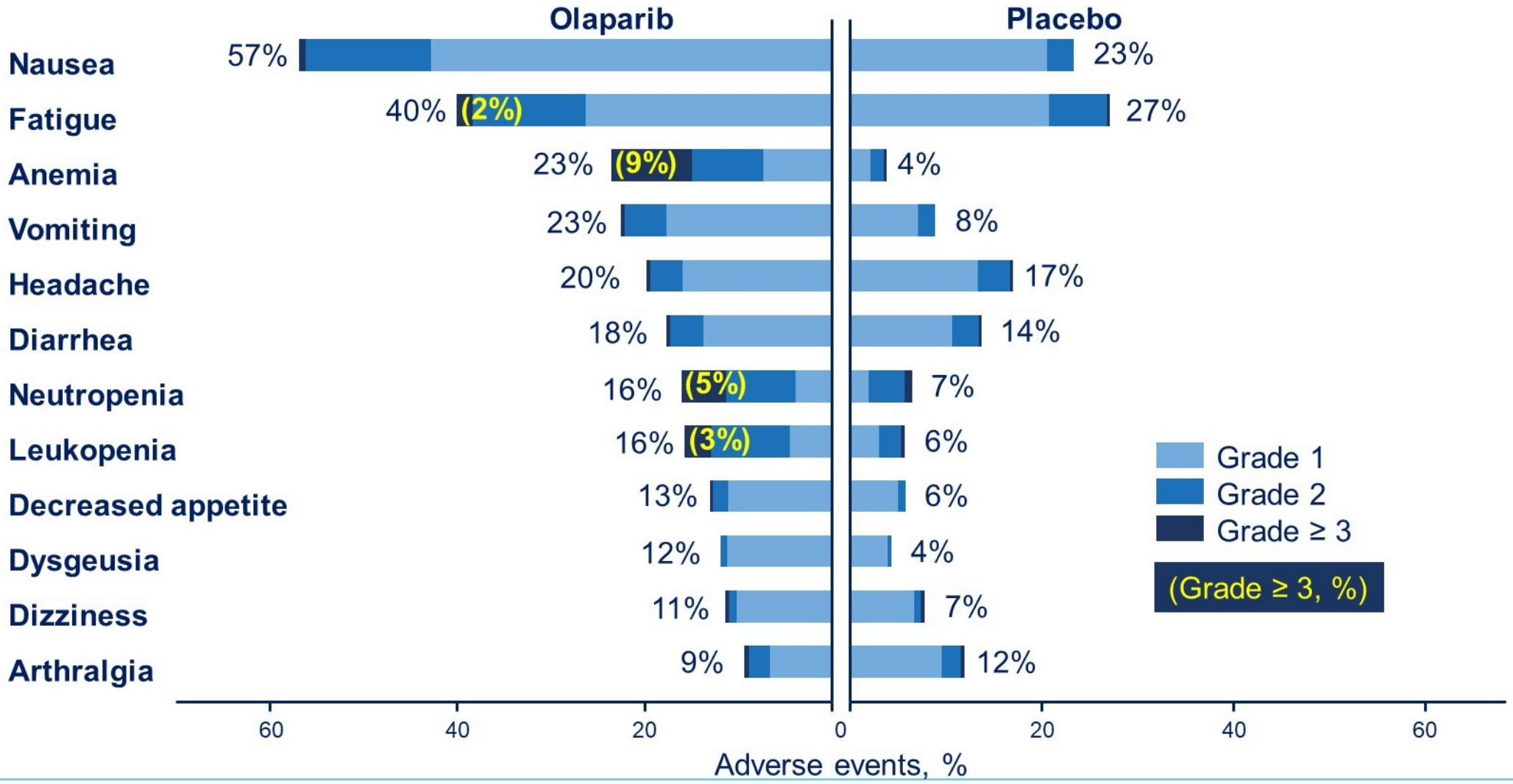
OlympiA: 3-Year Invasive DFS

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)
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



Tutt ANJ et al. *N Engl J Med* 2021;384:2394-405.

OlympiA: Adverse events of any grade ≥ 10%



Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Oral agents for ovarian suppression

Dr Laila Agrawal

- I think my patients would be very interested in an oral agent for ovarian suppression rather than coming into the clinic for monthly injections.
- They get a big ice pack to put on their abdomen to numb the pain from the injections.
- They get a large implant. In some cases it's painful, there can be bruising and it's disruptive to their lives to come in every single month during this treatment.
- One concern that I would have is the efficacy, especially for my patients that I'm treating with an aromatase inhibitor, because missing doses – escape from ovarian suppression – could be a major concern.
- Do you think these agents will be studied in breast cancer? And if so, how can we ensure that the study design will be applicable to my patients in the clinic in a real-world situation?

Email Case Submission – Dr Padmaja V Mallidi: A 59-year-old postmenopausal woman with bilateral IDCs of different histologies

- 11/2021 breast imaging: Abnormal findings in bilateral breasts
  - Right breast: Two masses 45 mm in greatest extent, ER/PR-positive, HER2-negative (cT2N0)
  - Left breast: One mass 27 mm in greatest extent, ER-positive, PR-negative, HER2-positive (cT2N0)
- No strong family history of cancer but referred for genetics

Questions

- What neoadjuvant regimen would you consider?
- Would you consider TCHP now or other trastuzumab-based regimens?

APPENDIX: Other Key Data Sets

Genomic Classifiers for Localized ER-Positive Breast Cancer

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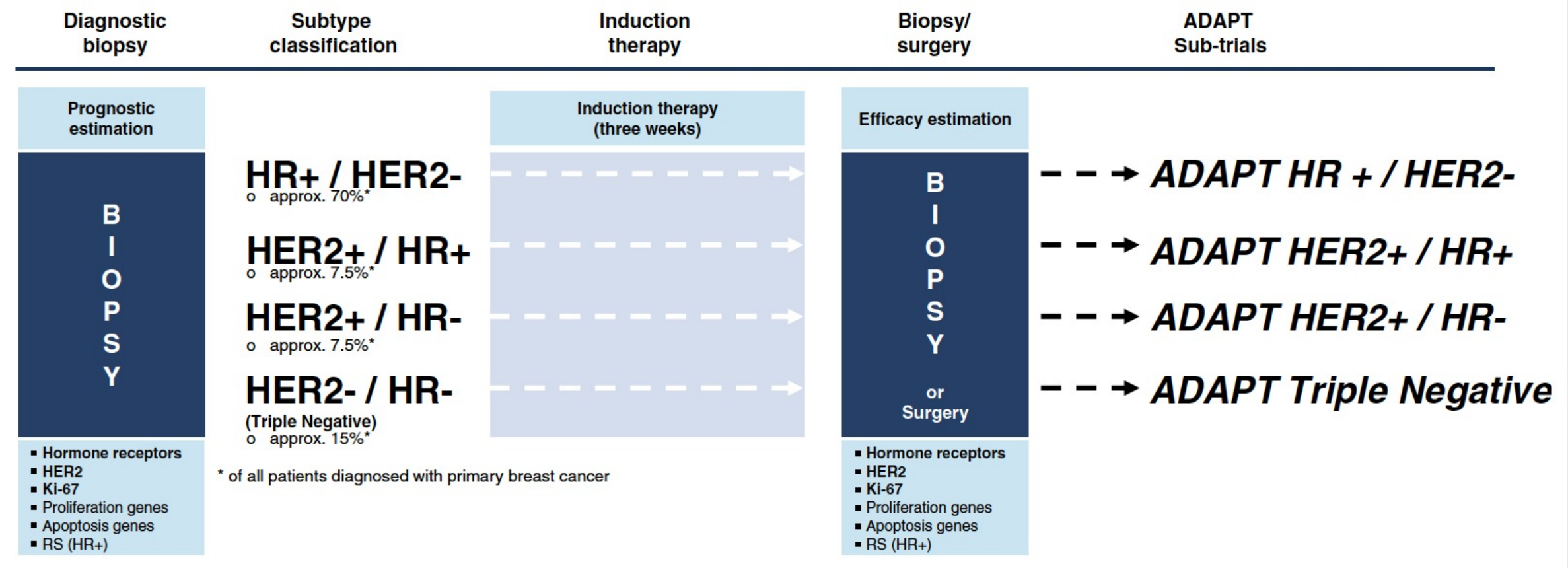
NCCN Guidelines: Gene Expression Assays for Consideration of Adjuvant Systemic Therapy

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus
21-gene (Oncotype Dx) (for pN0)	Yes	Yes	Preferred	1
21-gene (Oncotype Dx) for pN1 (1–3 positive nodes)[c]	Yes	Yes	Postmenopausal: Preferred	1
			Premenopausal: Other	2A
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A

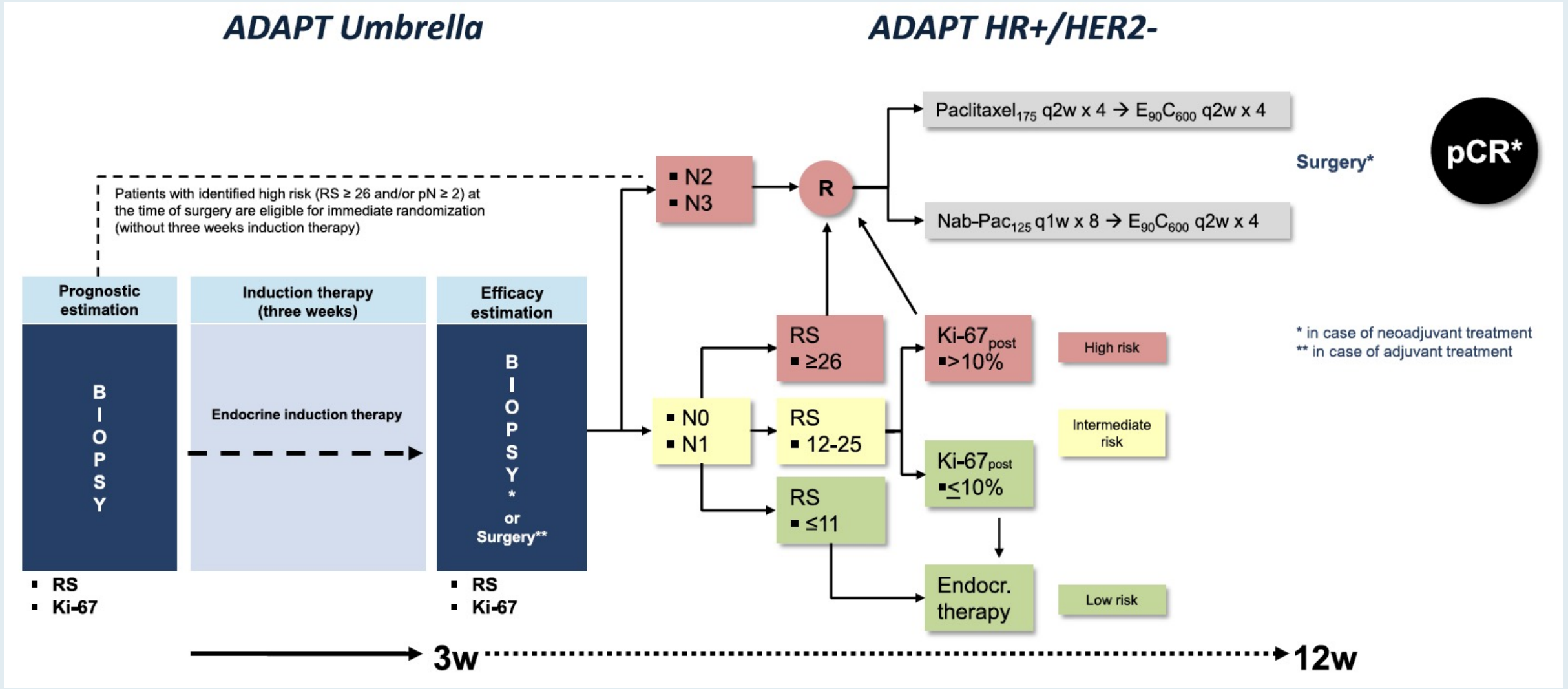
NCCN Guidelines. Breast Cancer. Version 6.2021. August 16, 2021.

Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial: ADAPT Umbrella Trial Design



Hofmann et al. *Trials* 2013;14:261.

ADAPT HR-Positive, HER2-Negative Trial Design

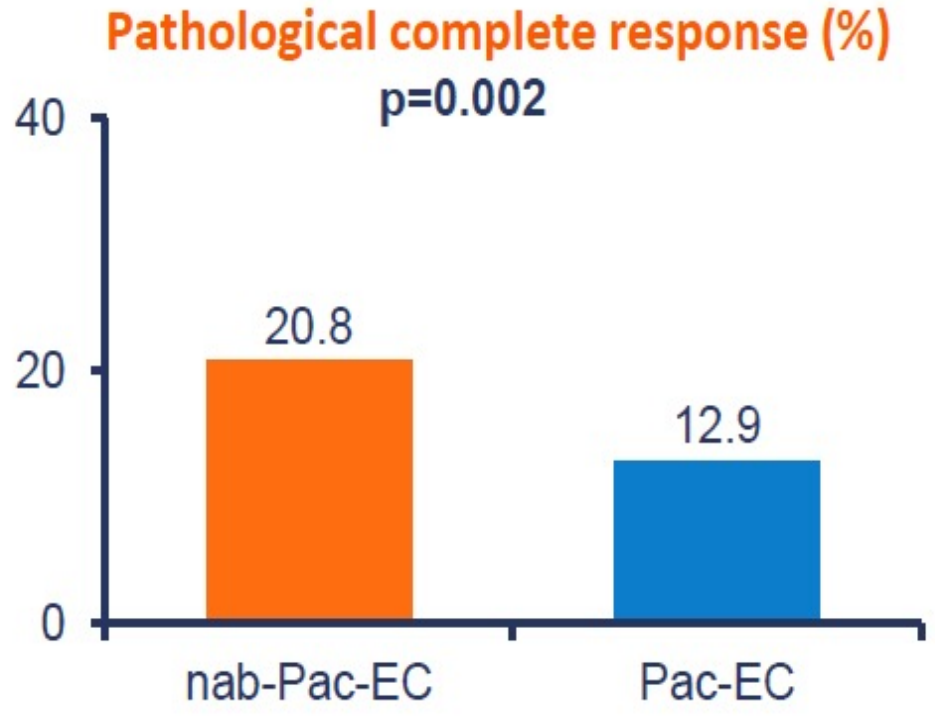


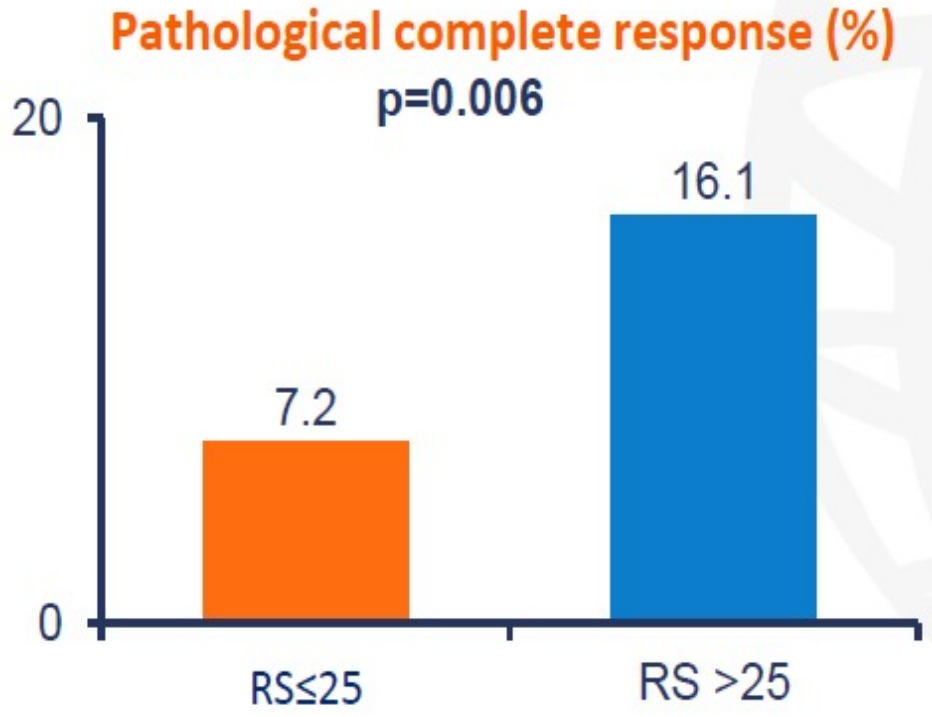
Hofmann et al. *Trials* 2013;14:261.

ADAPT HR-Positive, HER2-Negative Neoadjuvant Study: pCR Rates by Treatment Type and Recurrence Score (RS)

Eligible patients with high-risk early breast cancer (EBC)

- **cN0–1 with RS>25 *OR***
- **RS 12–25 and (centrally measured); post-endocrine Ki-67 >10% *OR***
- **cN2-3 status *OR***
- **G3 and Ki-67 >40%**





- RS could help select patients for neoadjuvant chemotherapy in high-risk HR-positive, HER2-negative EBC

Kuemmel S et al. SABCS 2020;Abstract GS4-03.

ADAPT HR-Positive, HER2-Negative (Part 1): Primary Endpoint – 5-Year Invasive Disease-Free Survival (iDFS)

Patients with HR+/HER2- localized breast cancer (LBC) AND clinically high-risk LBC (cT2-4) OR clinically node-positive OR G3 OR Ki-67 ≥15%

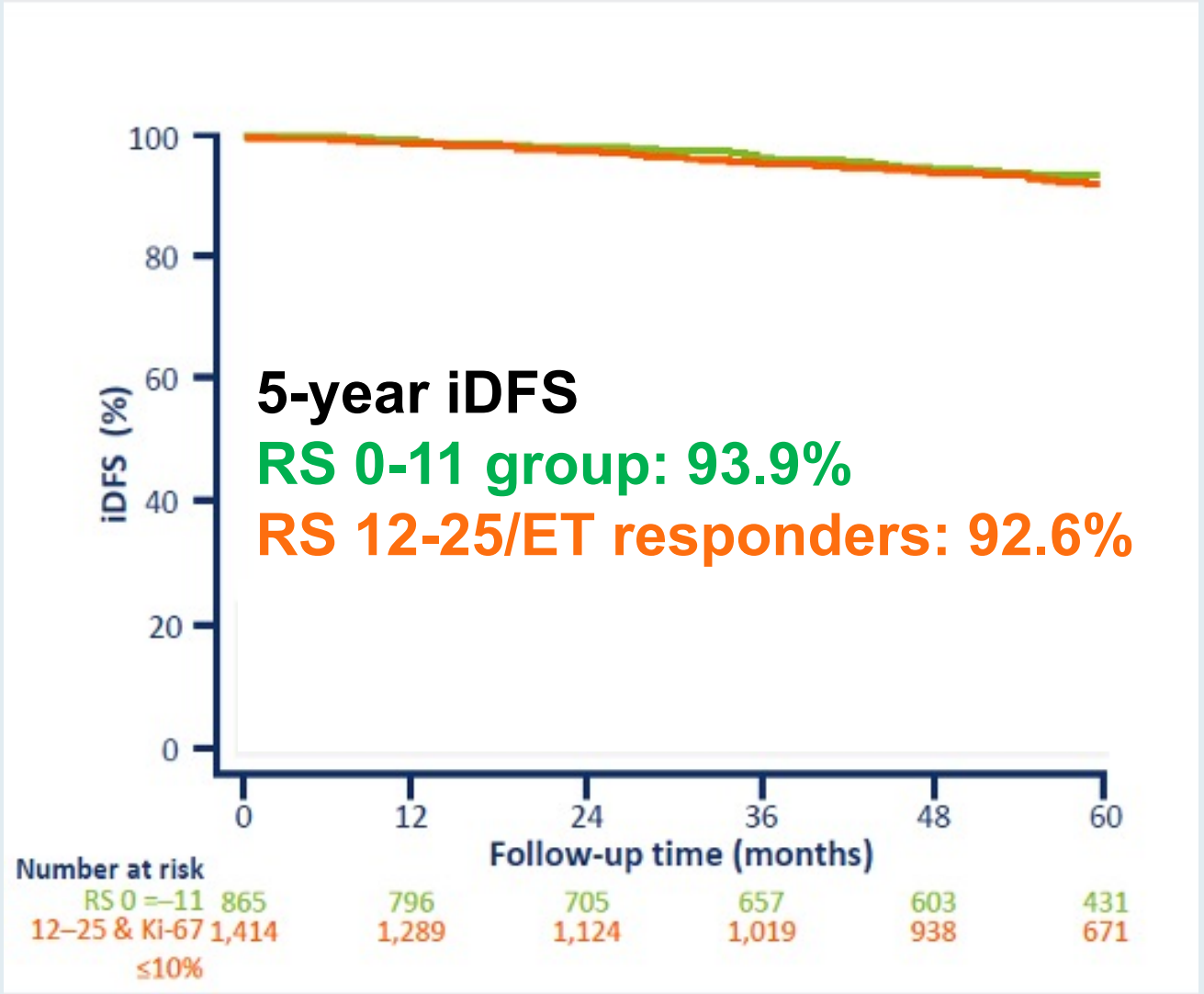
↓

All patients (N = 4,691) received 3 (+/-1) weeks of standard ET presurgery prior to Ki-67 assessment

↓

Part 1: Patients with RS 0-11 OR 12-25 and post-endocrine central Ki-67 ≤10% received ET alone (n = 2,356)

Part 2: Patients with RS >25 OR RS 12-25 with post-endocrine central Ki-67 >10% OR c/p N2-3 received chemotherapy (n = 2,335)



Harbeck N et al. SABCS 2020;Abstract GS4-04.

RTP RESEARCH TO PRACTICE

rapid communications

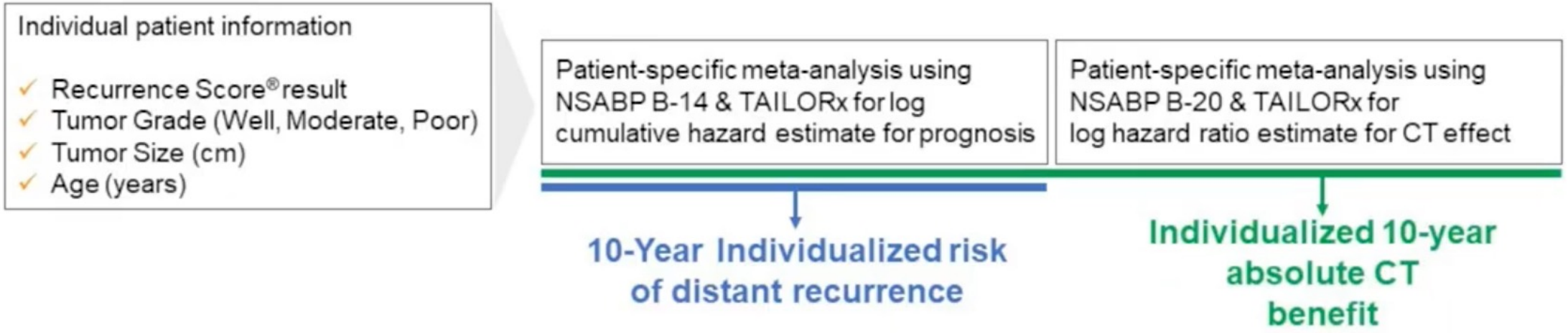
Development and Validation of a Tool Integrating the 21-Gene Recurrence Score and Clinical-Pathological Features to Individualize Prognosis and Prediction of Chemotherapy Benefit in Early Breast Cancer

Joseph A. Sparano, MD[1]; Michael R. Crager, PhD[2]; Gong Tang, PhD[3]; Robert J. Gray, PhD[4]; Salomon M. Stemmer, MD[5]; and Steven Shak, MD[2]

J Clin Oncol 2021;39(6):557-64

Methodology of the RSClin™ Education Tool

HR+, HER2-, Node-negative Patients



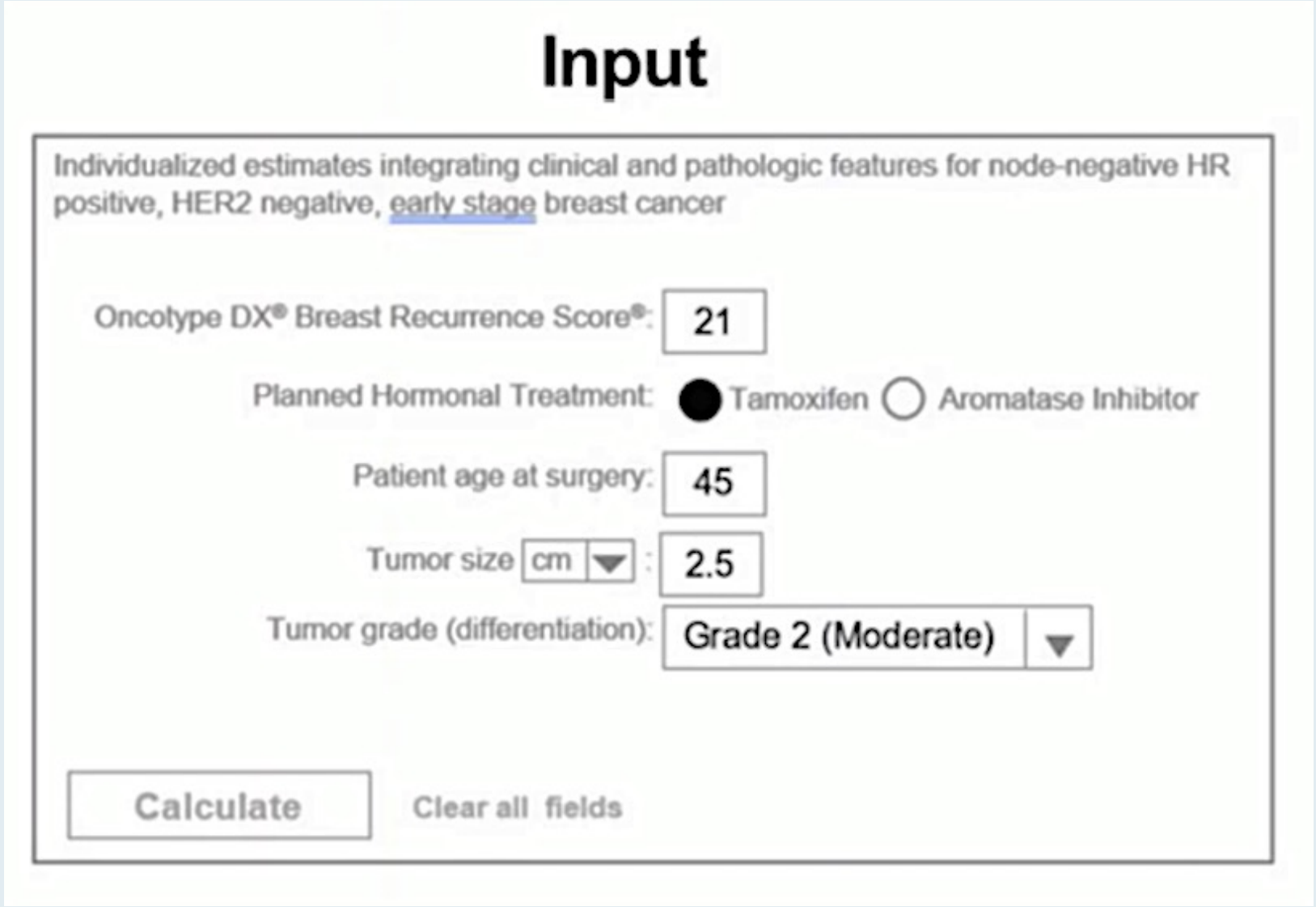
- **Meta-analysis** using NSABP B-14, TAILORx, and NSABP B-20 for individualized prognosis and individualized prediction of chemotherapy benefit
- Prognosis meta-analysis uses baseline risk from TAILORx so RSClin tool risk estimates reflect **current medical practice**
- RSClin tool estimates for distance-recurrence risk **externally validated** in Clalit study patients (Israel)

Sparano, et al. *J Clin Oncol*. 2020.

Sparano JA et al. *J Clin Oncol* 2021;39(6):557-64.

RTP RESEARCH TO PRACTICE

RSClin Educational Tool – Individualized Patient Information



www.oncotypeiq.com/en-US/announcements/SABCS

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RSClin Educational Tool – Individualized Patient Information

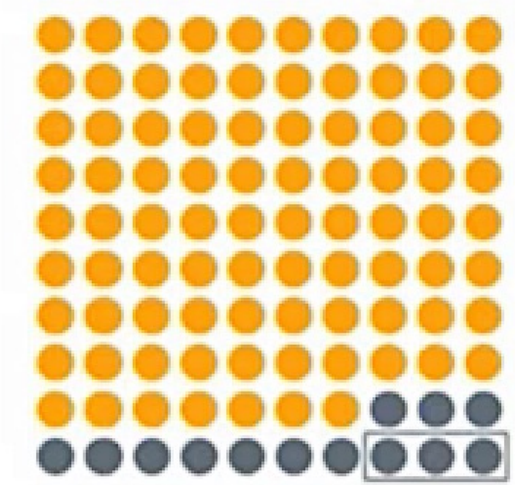
Output

Calculation Estimates

When patient specific characteristics are added to the Oncotype DX Breast Recurrence Score result, the following risk estimates provide additional information on your patient:

Individualized distant recurrence risk at 10 years **13%** (95% CI: 9% – 17%)

Individualized absolute chemotherapy benefit **3%** (95% CI: -1% – 7%)



87% of patients not expected to recur with Tamoxifen

13% of patients expected to recur with Tamoxifen

3% of patients expected to benefit from chemotherapy

www.oncotypeiq.com/en-US/announcements/SABCS

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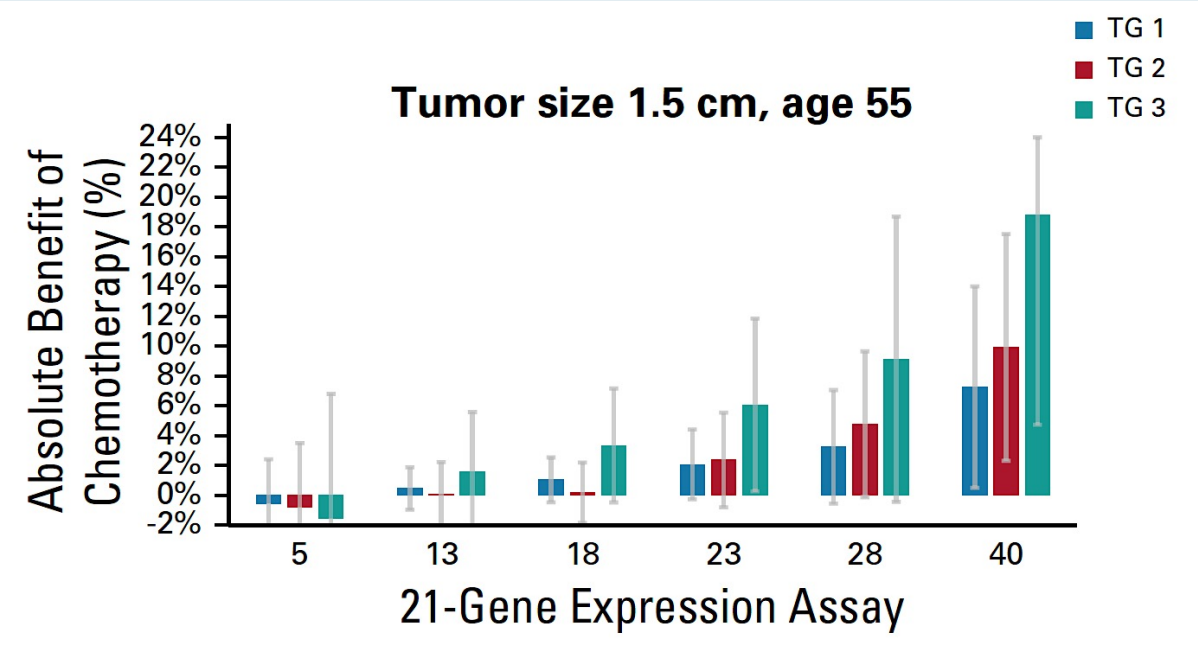
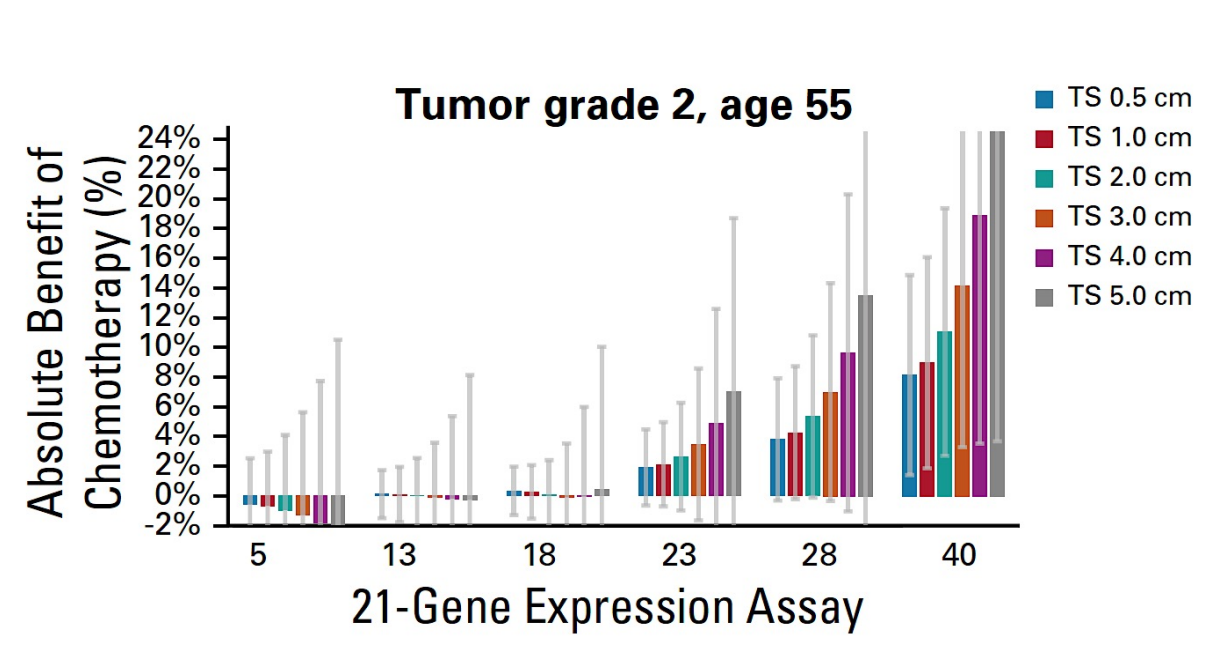
RSClin Tool Provides Individualized Estimates for Chemotherapy Benefit Based on RS, Age, Tumor Size and Tumor Grade for ER-Positive, HER2-Negative, Node-Negative Breast Cancer





The absolute chemotherapy benefit estimate ranges from 0% to 15% as the RS ranges from 11 to 50 using RSClin for a 55-year-old woman with a 1.5-cm intermediate-grade tumor

Sparano JA et al. *J Clin Oncol* 2021;39(6):557-64.

RTP RESEARCH TO PRACTICE

Evolving Clinical Decision-Making for ER-Positive Localized Breast Cancer

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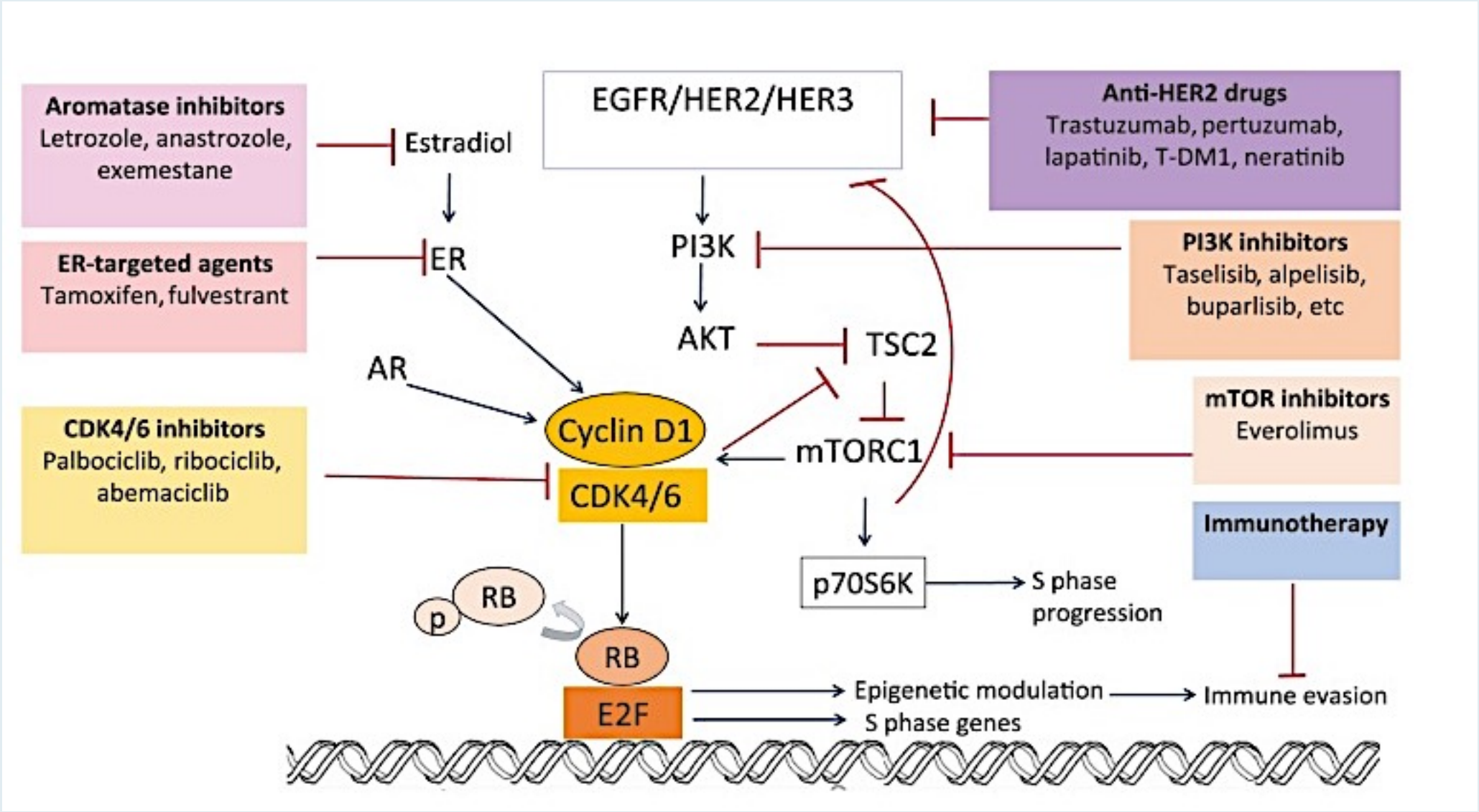
Rationale for the Evaluation of CDK4/6 Inhibitors in ER-Positive, HER2-Negative Breast Cancer



Pernas S et al. *Ther Adv Med Oncol* 2018;10:1758835918786451.

RTP RESEARCH TO PRACTICE

Abemaciclib Indications and Use

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA approved test. (1.1, 2.1, 14.1)
- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. (1.2)
- in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. (1.2)
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. (1.2)

Revised: 10/2021

Abemaciclib package insert, accessed October 22, 2021.

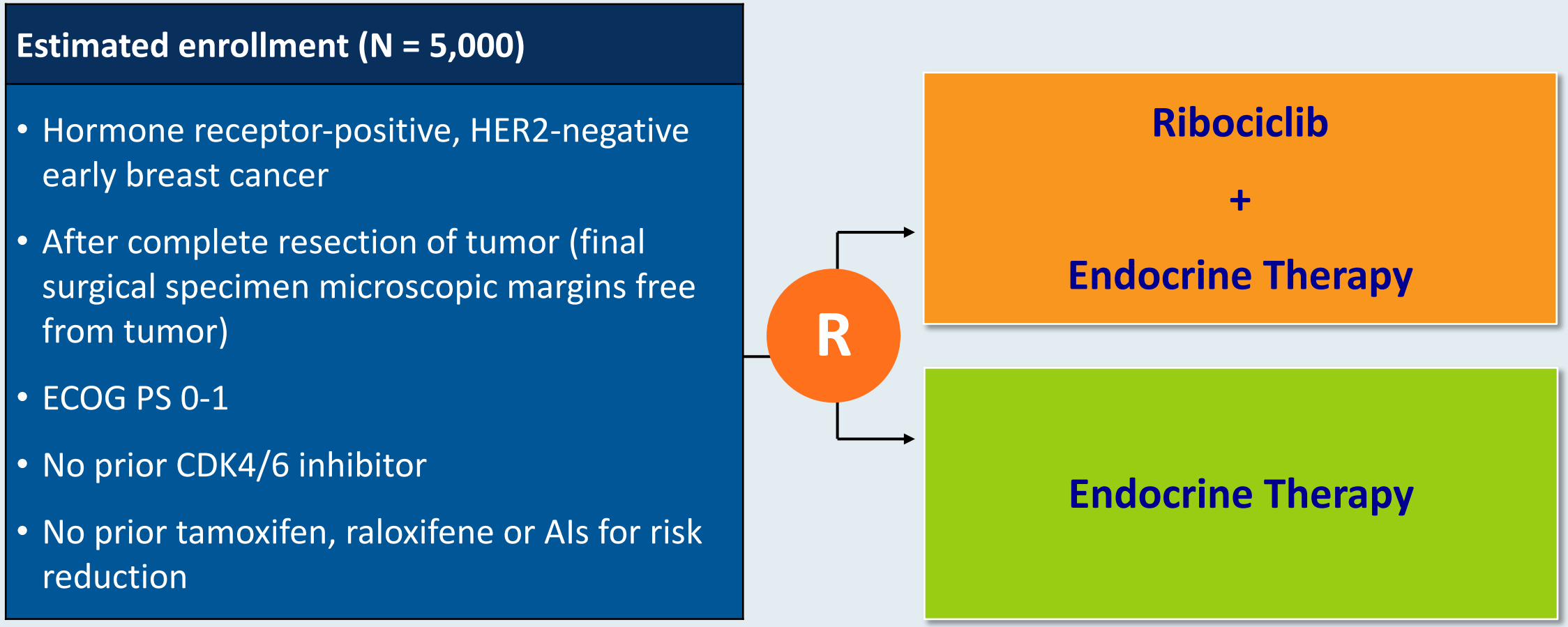
monarchE: Select Adverse Events

	Abemaciclib + ET (n = 2,791)			ET Alone (n = 2,800)		
≥ 10% in Either Arm	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any adverse event	2,731 (97.9)	1,200 (43.0)	70 (2.5)	2,410 (86.1)	335 (12.0)	19 (0.7)
Diarrhea	2,294 (82.2)	212 (7.6)	0	199 (7.1)	3 (0.1)	0
Neutropenia	1,246 (44.6)	501 (18.0)	18 (0.6)	141 (5.0)	16 (0.6)	3 (0.1)
Fatigue	1,073 (38.4)	78 (2.8)	0	433 (15.5)	4 (0.1)	0
Leukopenia	1,027 (36.8)	301 (10.8)	4 (0.1)	171 (6.1)	10 (0.4)	0
Abdominal pain	948 (34.0)	37 (1.3)	0	227 (8.1)	9 (0.3)	0
Nausea	779 (27.9)	13 (0.5)	0	223 (8.0)	1 (0.0)	0
Anemia	638 (22.9)	47 (1.7)	1 (0.0)	90 (3.2)	9 (0.3)	1 (0.0)
Arthralgia	571 (20.5)	6 (0.2)	0	876 (31.3)	18 (0.6)	0
Hot flush	393 (14.1)	3 (0.1)	0	587 (21.0)	8 (0.3)	0
Lymphopenia	372 (13.3)	140 (5.0)	2 (0.1)	94 (3.4)	13 (0.5)	0
Thrombocytopenia	341 (12.2)	25 (0.9)	6 (0.2)	40 (1.4)	1 (0.0)	2 (0.1)

- Abemaciclib dose adjustments due to AEs: 68.1% (56.9% dose omissions and 41.2% dose reductions)
- Abemaciclib discontinuation due to AEs: 16.6%
- Discontinuation of ET due to AEs in the control arm: 0.8%

Johnston SRD et al. *J Clin Oncol* 2020;38(34):3987-98.

NATALEE: Ongoing Adjuvant Phase III Trial Design



Primary endpoint: Invasive disease-free survival

Secondary endpoints include recurrence-free survival, overall survival and quality of life

www.clinicaltrials.gov. NCT03701334. Accessed August 2021.

Key Trials Exploring CDK4/6 Inhibitors in Localized Breast Cancer

	MonarchE	PALLAS	PENELOPE-B
Number of patients	5,637	5,761	1,250
Eligibility	≥ N2 or N1 with at least one of the following: grade 3, tumor size ≥ 5 cm, or Ki-67 ≥ 20%.	Anatomic stage II/III	Lack of pCR after NACT CPS-EG score ≥3 or ≥2 with ypN+
Study treatment	Abemaciclib-continuous (twice daily) Duration: 2 years	Palbociclib (once a day)-3 weeks on/1 week off Duration: 2 years	Palbociclib (once a day)-3 weeks on/1 week off Duration: 1 year
Timing of initiation of CDK4/6i in relation to ET	Within 12 weeks of beginning adjuvant ET	Within 6 months of beginning adjuvant ET	NA
Discontinuation rate	27.7%	42.0%	19.5%
Median follow-up time	19.1 months	31.0 months[1]	42.8 months
iDFS	92.2% (Abemaciclib + ET) vs. 88.7% (ET alone) at 2 years Ki67 ≥20% group-91.6% vs. 87.1%	84.2% (Palbociclib + ET) vs. 84.5% (ET alone)[1]	2 years: 88.3% (Palbociclib + ET) vs. 84% (ET alone) 3 years: 81.2% vs. 77.7% 4 years: 735 vs. 72.4%
DRFS	93.8% vs. 90.8%	89.3% vs. 90.7%	–

https://dailynews.ascopubs.org/do/10.1200/ADN.21.200483/full/; [1]Gnant M et al. SABCS 2021;Abstract GS1-07.

RTP RESEARCH TO PRACTICE

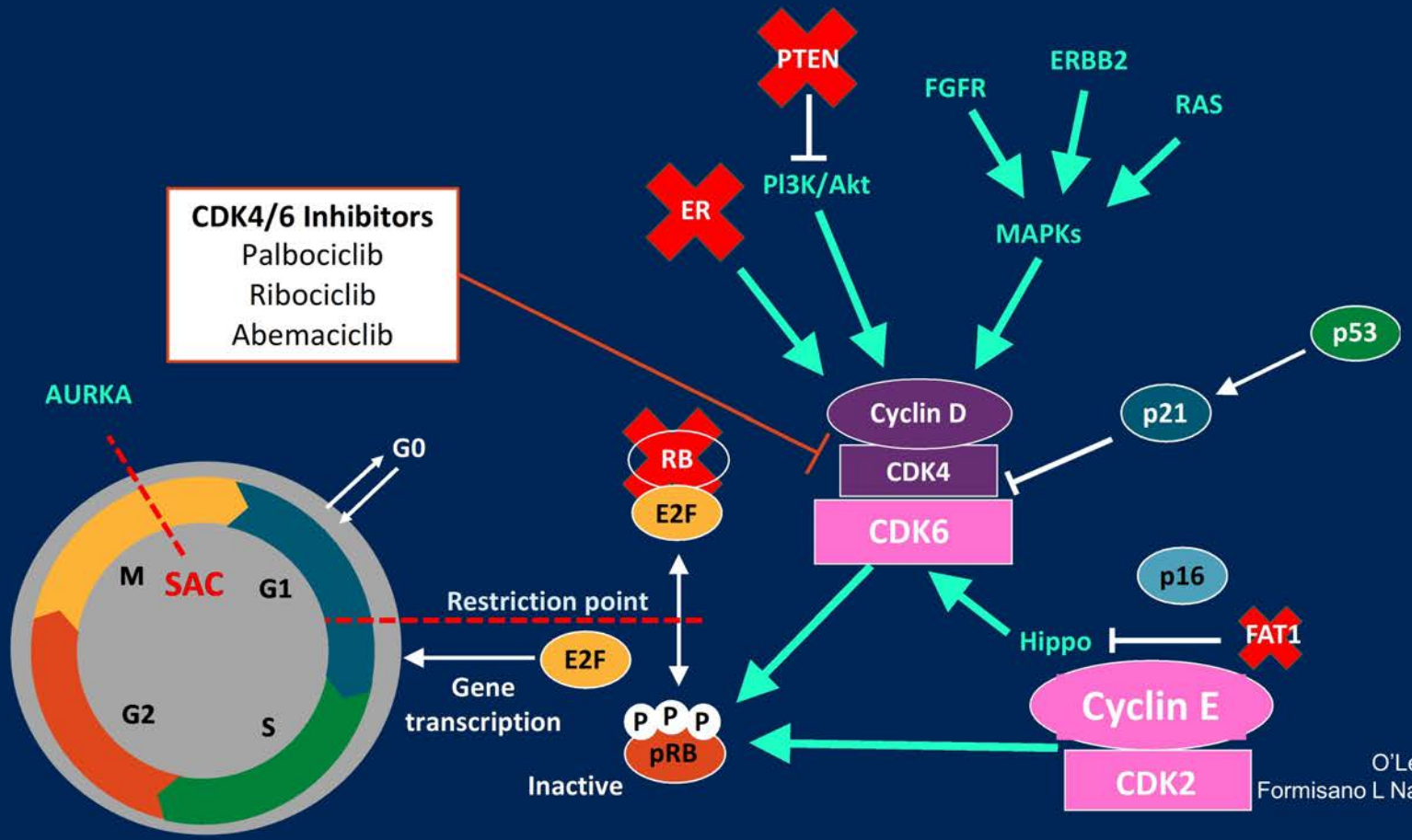
Current Management of ER-Positive mBC

Common Side Effects and Dosing of CDK4/6 Inhibitors

	Palbociclib		Abemaciclib		Ribociclib	
Dosing	125 mg qd 3 wk on, 1 wk off		200 mg BID continuously		600 mg qd 3 wk on, 1 wk off	
Common adverse events	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Neutropenia Thrombocytopenia	95% 76%	54% 19%	88% 42%	27% 2%	46% 37%	29% 10%
Diarrhea Nausea Vomiting	16% 23% 5%	0 0 0	90% 65% 35%	20% 5% 2%	22% 46% 25%	3% 2% 0

Barroso-Sousa R et al. *Breast Care* 2016;11:167-73.

Mechanisms of Resistance to CDK4/6 inhibitors



O'Leary B Cancer Discov 2018; 8:1390-1403
Formisano L Nature Communications 2019; 10: 1373-64
Razavi P ASCO 2019. Abstract 1009
Costa C Cancer Discov 2020;10:72–85
Wander SA Cancer Discov 2020;10:1174–93

Ongoing Studies of CDK4/6 Inhibitor After Disease Progression on a CDK4/6 Inhibitor for mBC

- **Phase II MAINTAIN trial of ribociclib with or without fulvestrant**
  - HR-positive mBC
  - Disease progression on an AI and CDK4/6 inhibitor

- **Phase II PALMIRA trial of palbociclib rechallenge with endocrine therapy**
  - HR-positive, HER2-negative advanced breast cancer
  - Disease progression on letrozole or fulvestrant with palbociclib after obtaining clinical benefit

www.clinicaltrials.gov. NCT02632045. Accessed October 2021; www.clinicaltrials.gov. NCT03809988. Accessed October 2021.

New Phase III HARMONIA Trial Will Compare Palbociclib to Ribociclib for HR-Positive, HER2-Negative Advanced Breast Cancer

Press Release – September 19, 2021

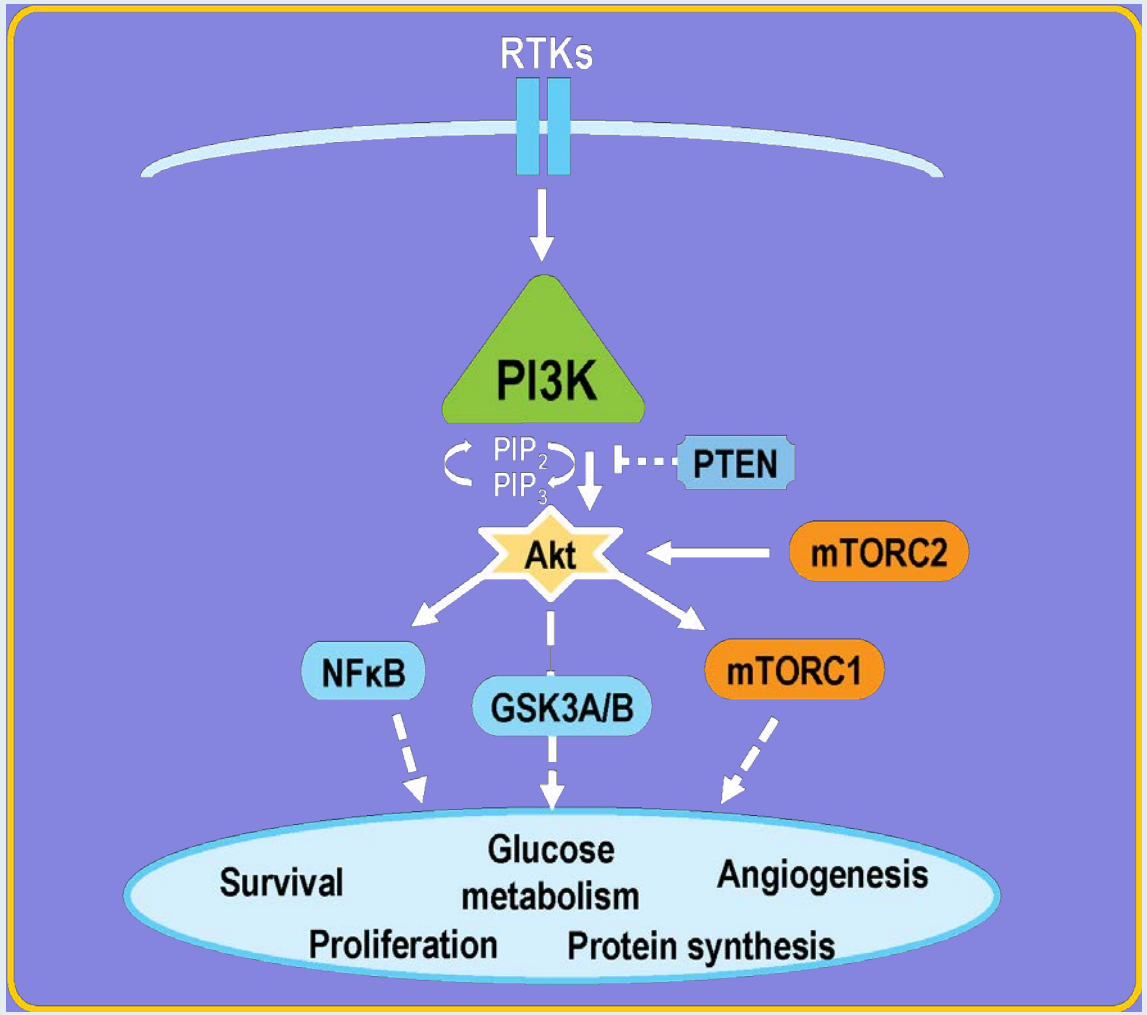
"HARMONIA, an international, randomized, Phase III, multicenter, open-label study of ribociclib versus palbociclib, both in combination with endocrine therapy, in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced or metastatic breast cancer with a HER2-enriched (HER2E) intrinsic subtype [has been announced]. HARMONIA is the first prospective Phase III trial to enroll patients selected by RNA-based molecular subtyping of their tumors and the first to directly compare two CDK4/6 inhibitors in patients with HR+/HER2- advanced breast cancer.

The primary endpoint of HARMONIA is progression free survival, and the study will evaluate if ribociblib positively alters tumor biology, enabling a better response to endocrine therapy compared to palbociclib.

HARMONIA enrollment is expected to begin in Q1 2022. Patients with the basal-like subtype may also enroll. This exploratory cohort of patients will be treated with a chemotherapy-based regimen as these tumors behave more like triple-negative breast cancer."

https://www.novartis.com/news/media-releases/novartis-announces-collaboration-harmonia-phase-iii-head-head-trial-evaluating-kisqali-vs-ibrance-patients-hrher2-advanced-breast-cancer

PI3K Inhibitors: Mechanism of Action



- PI3K is involved in the activation of Akt.
- Hyperactivation of the PI3K pathway is implicated in malignant transformation, cancer progression and endocrine therapy resistance.
- PIK3CA encodes the alpha isoform of the PI3K catalytic subunit.
- Around 40% of patients with HR+, HER- BC present with an activating PIK3CA tumor mutation.
- Alpelisib is a specific inhibitor of the PI3K alpha isoform.

André F et al. ESMO 2018;Abstract LBA3_PR.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Alpelisib plus fulvestrant for *PIK3CA*-mutated, hormone receptor-positive, human epidermal growth factor receptor-2—negative advanced breast cancer: final overall survival results from SOLAR-1

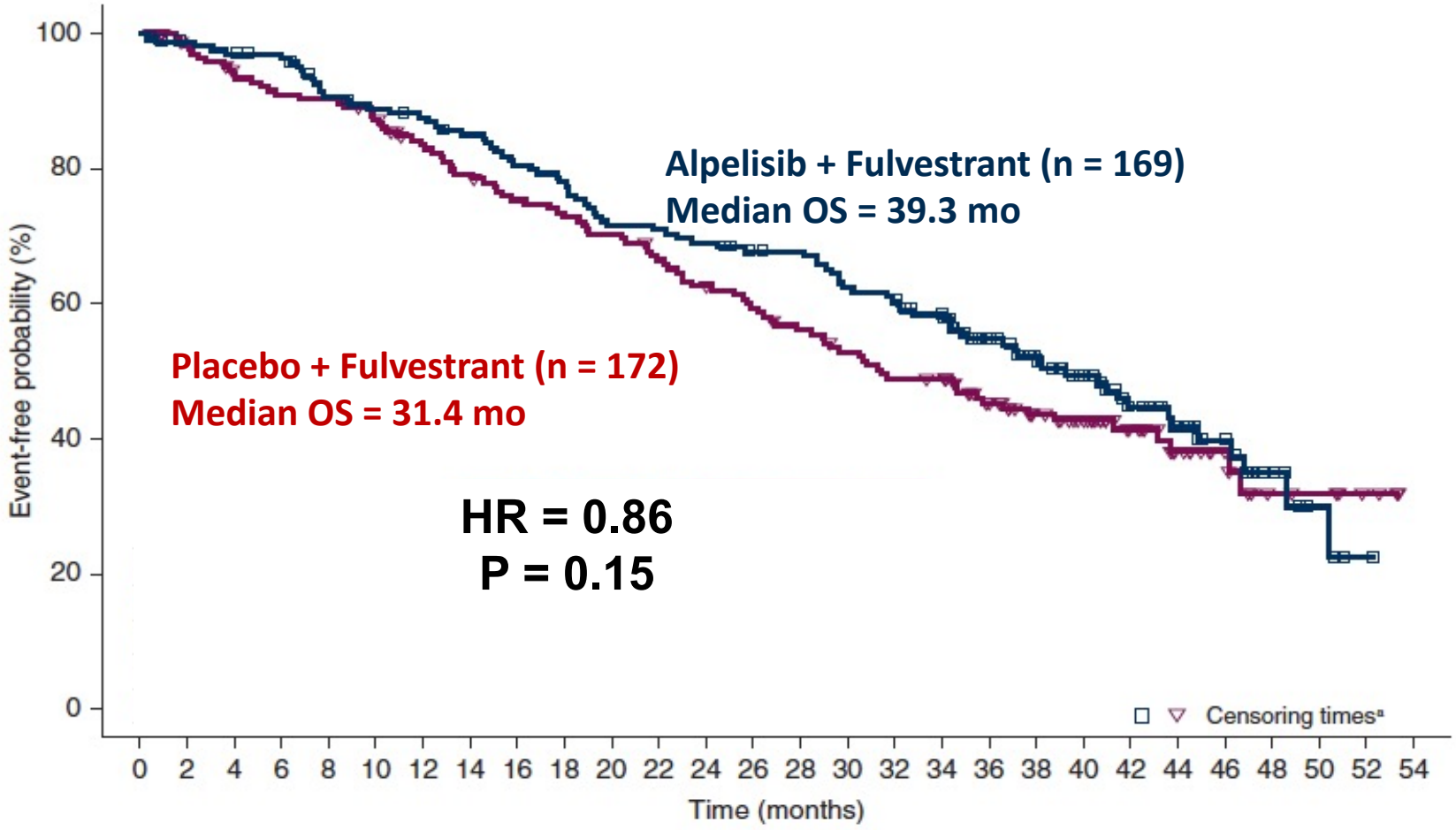
F. André[1*], E. M. Ciruelos[2], D. Juric[3], S. Loibl[4], M. Campone[5], I. A. Mayer[6], G. Rubovszky[7], T. Yamashita[8], B. Kaufman[9], Y.-S. Lu[10], K. Inoue[11], Z. Pápai[12], M. Takahashi[13], F. Ghaznawi[14], D. Mills[15], M. Kaper[14], M. Miller[14], P. F. Conte[16], H. Iwata[17] & H. S. Rugo[18]

[1]Department of Medical Oncology, Institut Gustave Roussy, Villejuif and Paris Saclay University, Orsay, France; [2]Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; [3]Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, USA; [4]Department of Medicine and Research, German Breast Group, GBG Forschungs GmbH, Neu-Isenburg, Germany; [5]Medical Oncology, Institut de Cancerologie de l'Ouest, Saint-Herblain, Nantes Cedex, France; [6]Hematology/Oncology, Vanderbilt University, Nashville, USA; [7]Department of Medical Oncology and Clinical Pharmacology, National Institute of Oncology, Budapest, Hungary; [8]Department of Breast and Endocrine Surgery, Kanagawa Cancer Center, Yokohama, Japan; [9]Medical Oncology, Tel Aviv University, Sheba Medical Centre, Tel Hashomer, Israel; [10]Medical Oncology, National Taiwan University Hospital, Taipei, Taiwan; [11]Breast Surgery, Saitama Cancer Center, Saitama, Japan; [12]Medical Oncology, Hungarian Defence Forces Medical Centre, Budapest, Hungary; [13]Breast Surgery, NHO Hokkaido Cancer Center, Sapporo, Japan; [14]Novartis Pharmaceuticals Corporation, East Hanover, USA; [15]Novartis Pharma AG, Basel, Switzerland; [16]Medical Oncology, Universita di Padova and Oncologia Medica 2, Istituto Oncologico Veneto IRCCS, Padua, Italy; [17]Breast Oncology, Aichi Cancer Center Hospital, Aichi, Japan; [18]Breast Department, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA

Available online 25 November 2020

***Ann Oncol* 2021;32(2):208-17.**

SOLAR-1: OS for Patients with Advanced Breast Cancer with a PIK3CA Mutation



André F et al. *Ann Oncol* 2021;32(2):208-17.

SOLAR-1: Select Adverse Events in Overall Patient Population

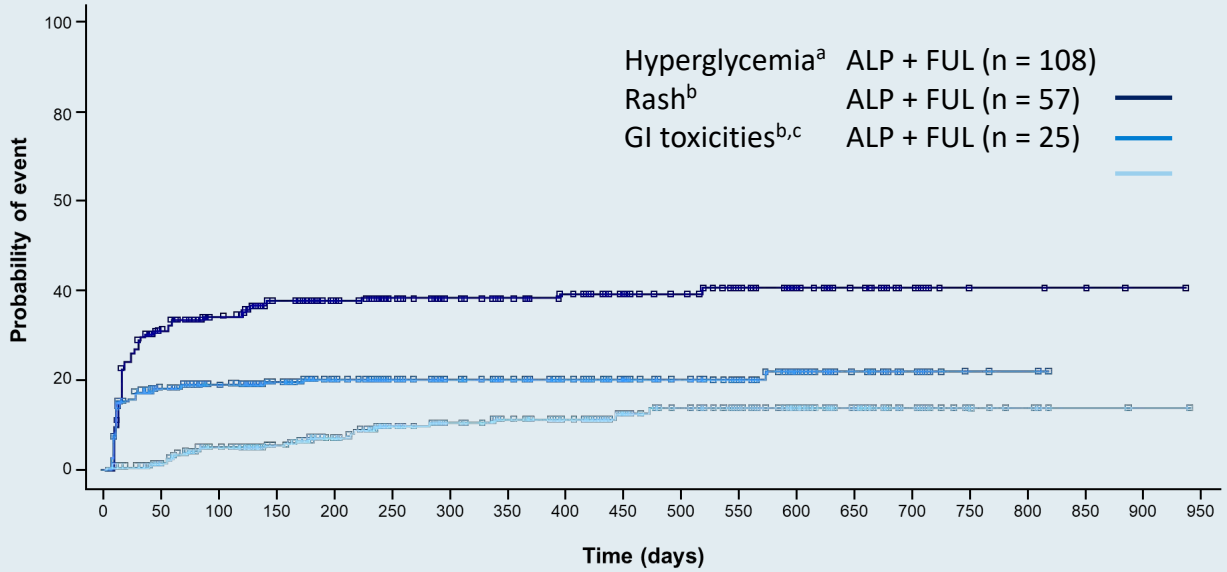
Adverse Event	Alpelisib–Fulvestrant Group (N = 284)			Placebo–Fulvestrant Group (N = 287)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0

André F et al. *N Engl J Med* 2019;380:1929-40.

Time Course of Adverse Events in SOLAR-1

- The most common grade ≥3 AEs in the ALP arm were hyperglycemia, rash, and diarrhea
- In the ALP arm, hyperglycemia and/or rash were typically experienced in the first few weeks of treatment with ALP + FUL, whereas GI toxicities could occur at any time during study therapy
- Median time to onset and median time to improvement by ≥1 grade are shown in the table below

Probability of First Occurrence of Grade 3 AESI Events



Time to Onset and Time to Improvement of AESIs

	Median time to onset, days	Median time to improvement by ≥1 grade, days
Hyperglycemia	15	6
Rash	13	11
Diarrhea	139	18

AE, adverse event; AESI, adverse event of special interest; ALP, alpelisib; FUL, fulvestrant; GI, gastrointestinal; PBO, placebo.

[a] Based on laboratory values rather than single preferred term.
[b] Based on grouped terms.
[c] Of the grade ≥ 3 gastrointestinal (GI) toxicities, 76% of them were grade ≥ 3 diarrhea.

Rugo HS et al. *Annals Onc* 2020.

Lancet Oncol 2021;22:489-98.

Alpelisib plus fulvestrant in *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study

Hope S Rugo, Florence Lerebours, Eva Ciruelos, Pamela Drullinsky, Manuel Ruiz-Borrego, Patrick Neven, Yeon Hee Park, Aleix Prat, Thomas Bachelot, Dejan Juric, Nicholas Turner, Nickolas Sophos, Juan Pablo Zarate, Christina Arce, Yu-Ming Shen, Stuart Turner, Hemanth Kanakamedala, Wei-Chun Hsu, Stephen Chia

BYLieve: A Phase II, Open-Label, 3-Cohort, Noncomparative Trial (NCT03056755)

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

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

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

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

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

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

Treatment crossover between cohorts is not permitted

Primary endpoint

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

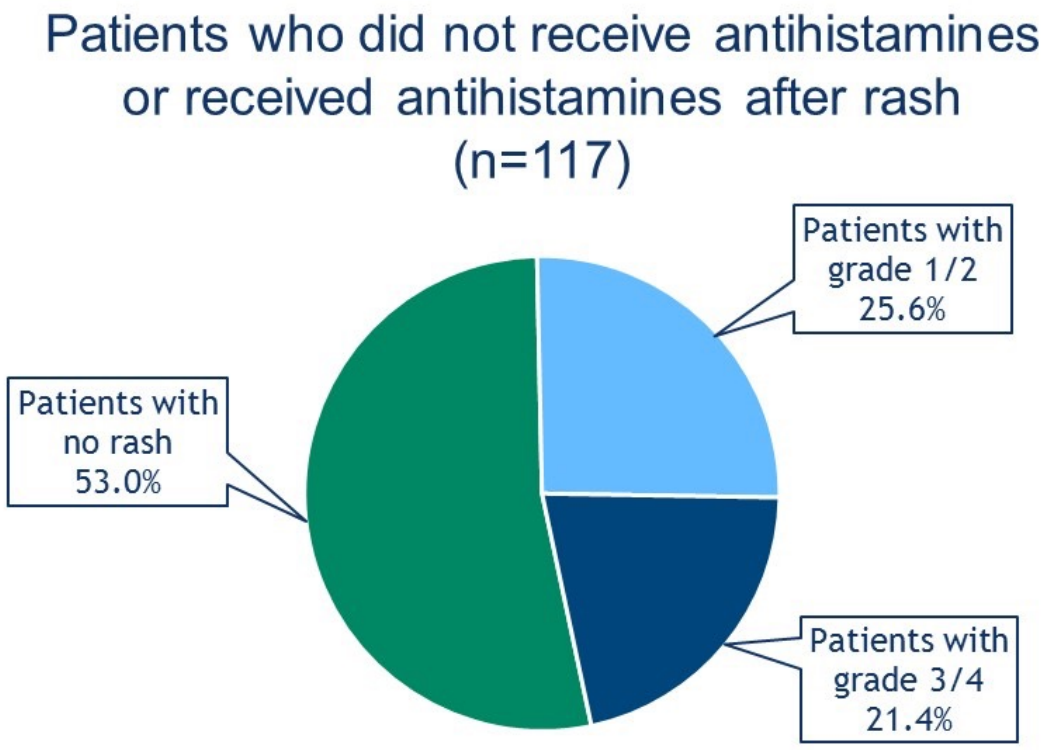
(assessed in each cohort)

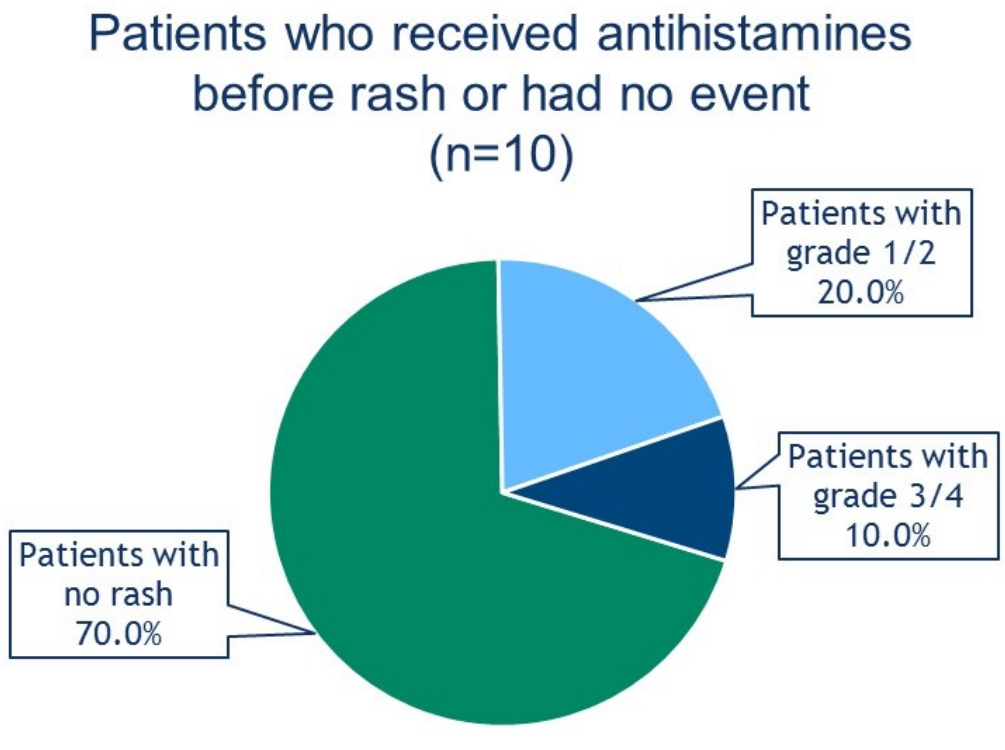
- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

[a]Men in the letrozole cohort and premenopausal women also received goserelin 3.6 mg SC every 28 days or leuprolide 7.5 mg IM every 28 days for adequate gonadal suppression. [b]Enrollment in each cohort continued until at least 112 patients with a centrally confirmed *PIK3CA* mutation was reached.
[c]IM on D1 and D15 of Cycle 1 and D1 for all other cycles thereafter. [d]Oral QD.

Cohort A: Rugo et al. *Lancet Oncol* 2021.

BYLieve: Incidence of Rash with and without Prophylactic Antihistamines

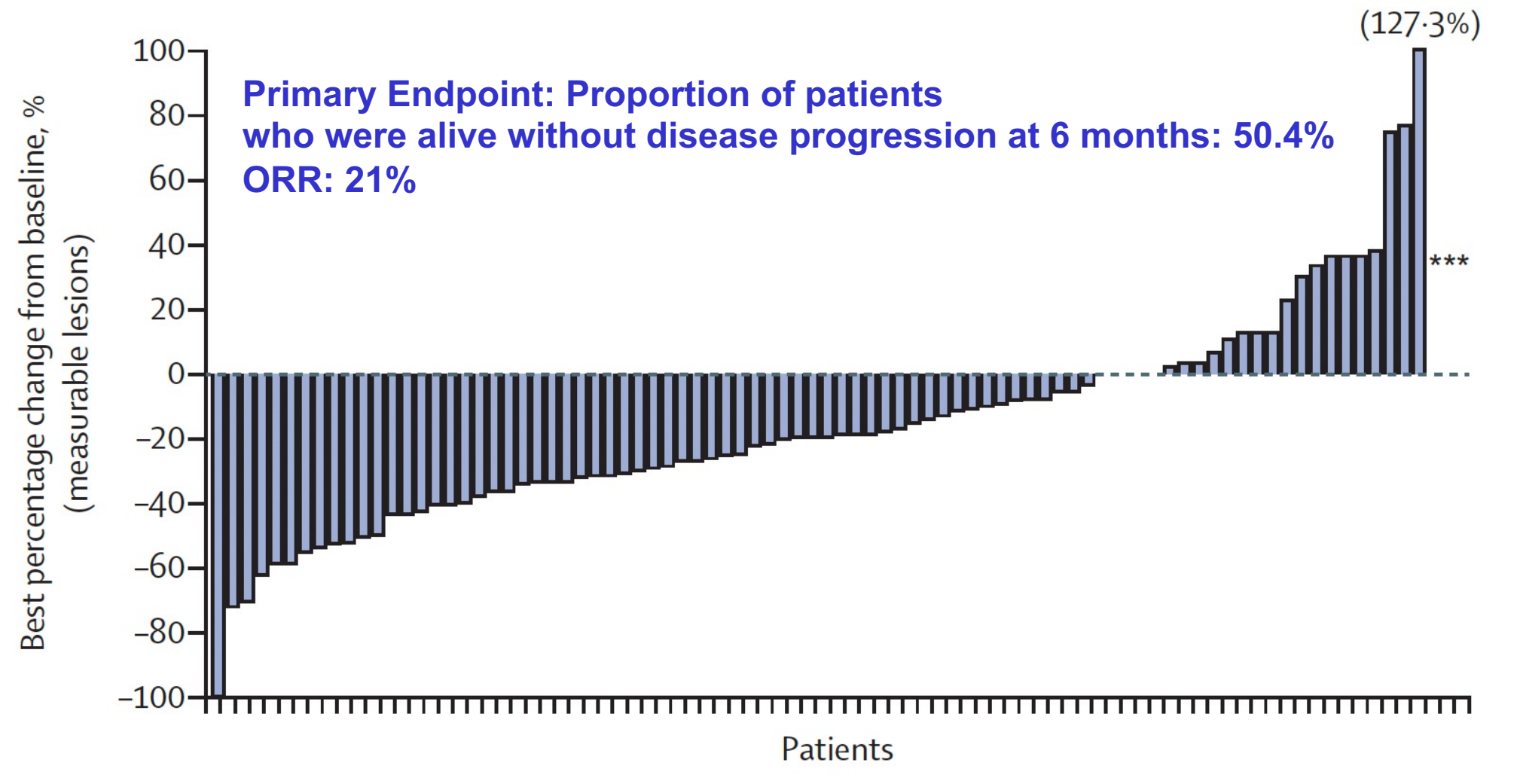




Rugo HS et al. ASCO 2020;Abstract 1006.

RTP RESEARCH TO PRACTICE

BYLieve Efficacy Outcomes



Rugo HS et al. *Lancet Oncol* 2021;22:489-98.

Efficacy of Everolimus for AI-Pretreated ER-Positive mBC

Study	Phase	Study arms	Population	Median PFS months	HR	*p*-value
PrE0102	II	Everolimus + fulvestrant Placebo + fulvestrant	Overall	10.3 vs 5.1	0.61	0.02
BOLERO-2	III	Everolimus + exemestane Placebo + exemestane	Overall *PIK3CA*mut tumor *PIK3CA*mut ctDNA	7.8 vs 3.2 6.7 vs 2.8 6.9 vs 2.7	0.45 0.51 0.37	<0.0001 Not reported Not reported

Kornblum et al. *J Clin Oncol* 2018;36:1556; Yardley et al. *Adv Ther* 2013;30:870; Hortobagyi et al. *J Clin Oncol* 2016;34:419; Moynahan et al. *Br J Cancer* 2017;116:726.

RTP RESEARCH TO PRACTICE

Future Management of ER-Positive mBC

RTP
RESEARCH
TO PRACTICE

Lancet Oncol 2020;21:345-57

Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial

Robert H Jones, Angela Casbard*, Margherita Carucci, Catrin Cox, Rachel Butler, Fouad Alchami, Tracie-Ann Madden, Catherine Bale, Pavel Bezecny, Johnathan Joffe, Sarah Moon, Chris Twelves, Ramachandran Venkitaraman, Simon Waters, Andrew Foxley, Sacha J Howell*

FAKTION: Capivasertib + Fulvestrant for AI-Resistant ER-Positive, HER2-Negative mBC

- Phase II study of capivasertib + fulvestrant vs placebo + fulvestrant (N = 140)
  - Relapse or progression on an AI
  - Capivasertib (AZD5363): selective, oral AKT inhibitor
- Capivasertib + fulvestrant improved PFS in endocrine-resistant mBC vs placebo + fulvestrant
  - Primary endpoint met
  - Trend toward improvement in OS
- Ongoing Phase III CAPitello291 Trial
- IPATunit150: ipatasertib +/- palbociclib and fulvestrant

Outcome	CAP + FULV (n = 69)	PBO + FULV (n = 71)
Median PFS, mo	10.3	4.8
	HR: 0.57 *P* = 0.0035	
Median OS, mo	26.0	20.0
	HR: 0.59 *P* = 0.071	

- Similar benefit was observed in patients with PI3K/AKT/PTEN-activated and nonactivated tumors
- 39% of patients in the capivasertib + fulvestrant arm required dose reductions, primarily due to diarrhea and rash, and 12% discontinued due to toxicity

Jones RH et al. *Lancet Oncol* 2020;21:345-57.

RTP RESEARCH TO PRACTICE

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Follicular Lymphoma

Tuesday, January 4, 2022
5:00 PM – 6:00 PM ET

Faculty

Laurie H Sehn, MD, MPH
Additional faculty to be announced.

Moderator

Neil Love, MD

RTP Year in Review 2022

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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