Meet The Professor

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

Kevin Kalinsky, MD, MS
Associate Professor
Department of Hematology and Medical Oncology
Emory University School of Medicine
Director, Glenn Family Breast Center
Director, Breast Medical Oncology
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Commercial Support

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

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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, 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, 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 and Verastem Inc.

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

Dr Kalinsky — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Cyclacel Pharmaceuticals Inc, Eisai Inc, Immunomedics Inc, Lilly, Merck, Novartis, Pfizer Inc, Seagen Inc
Speakers Bureau	Genentech, a member of the Roche Group, Immunomedics Inc

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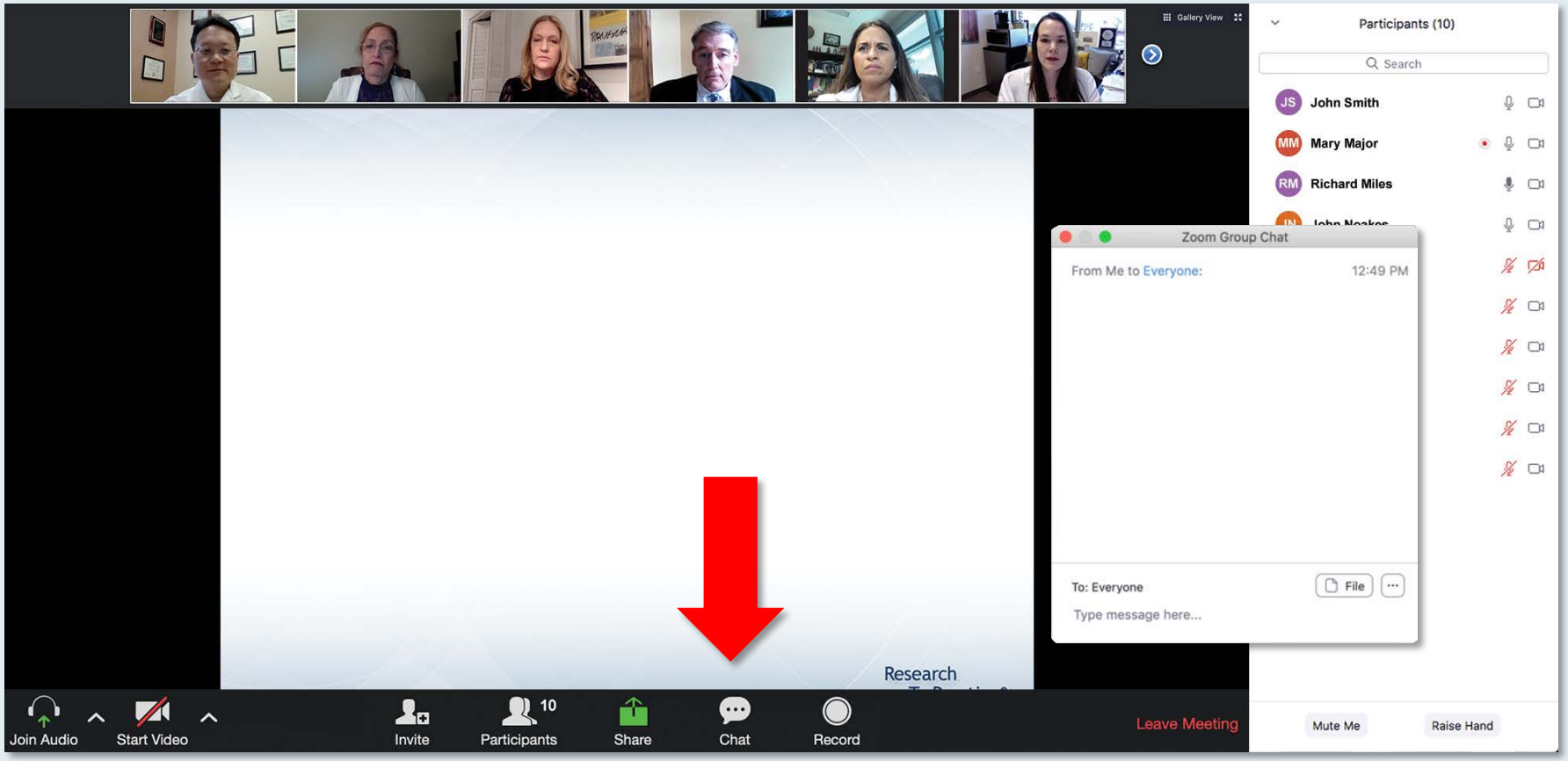

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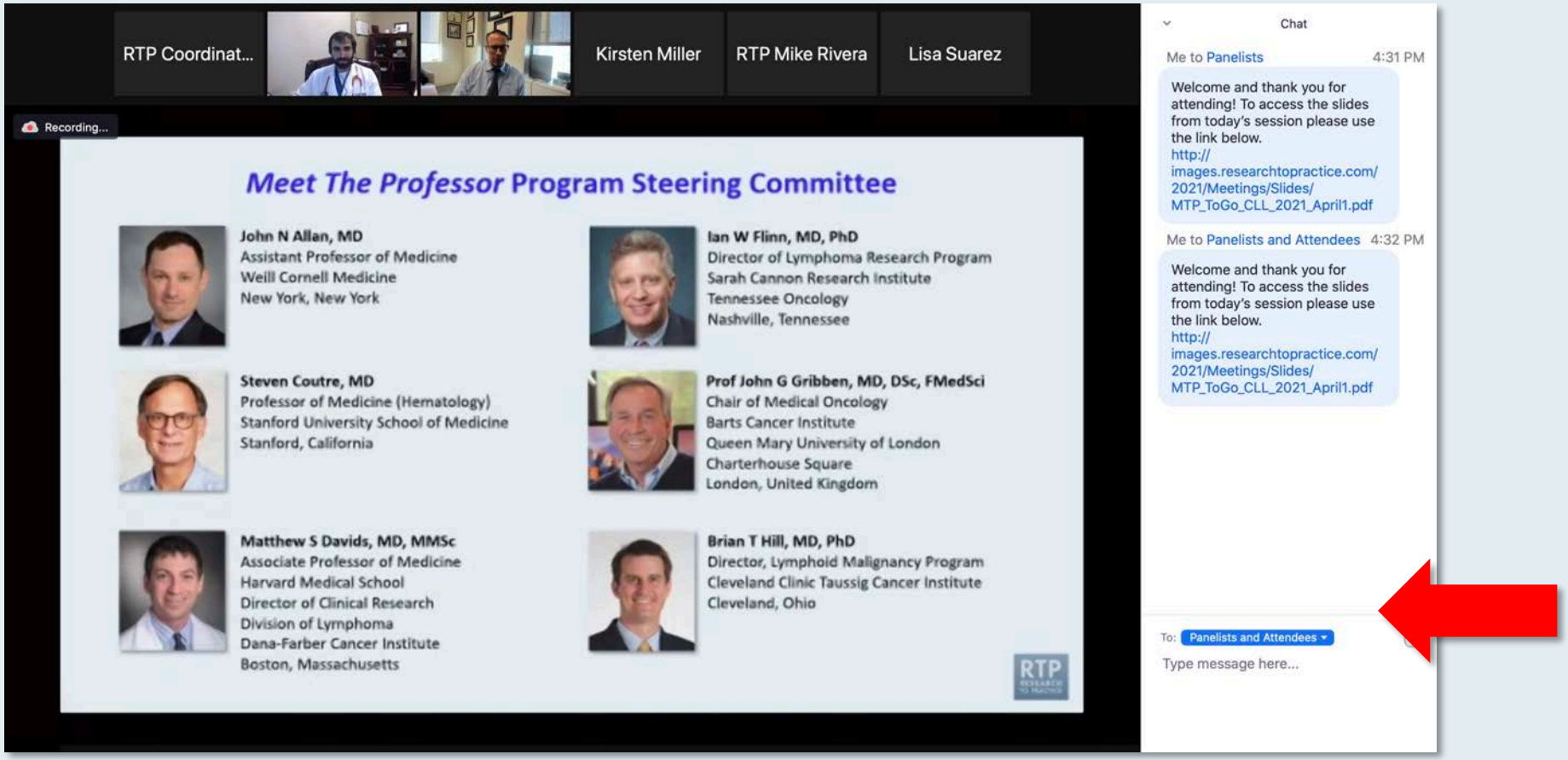

Drag the white line above the submission box up to create more space for your message.

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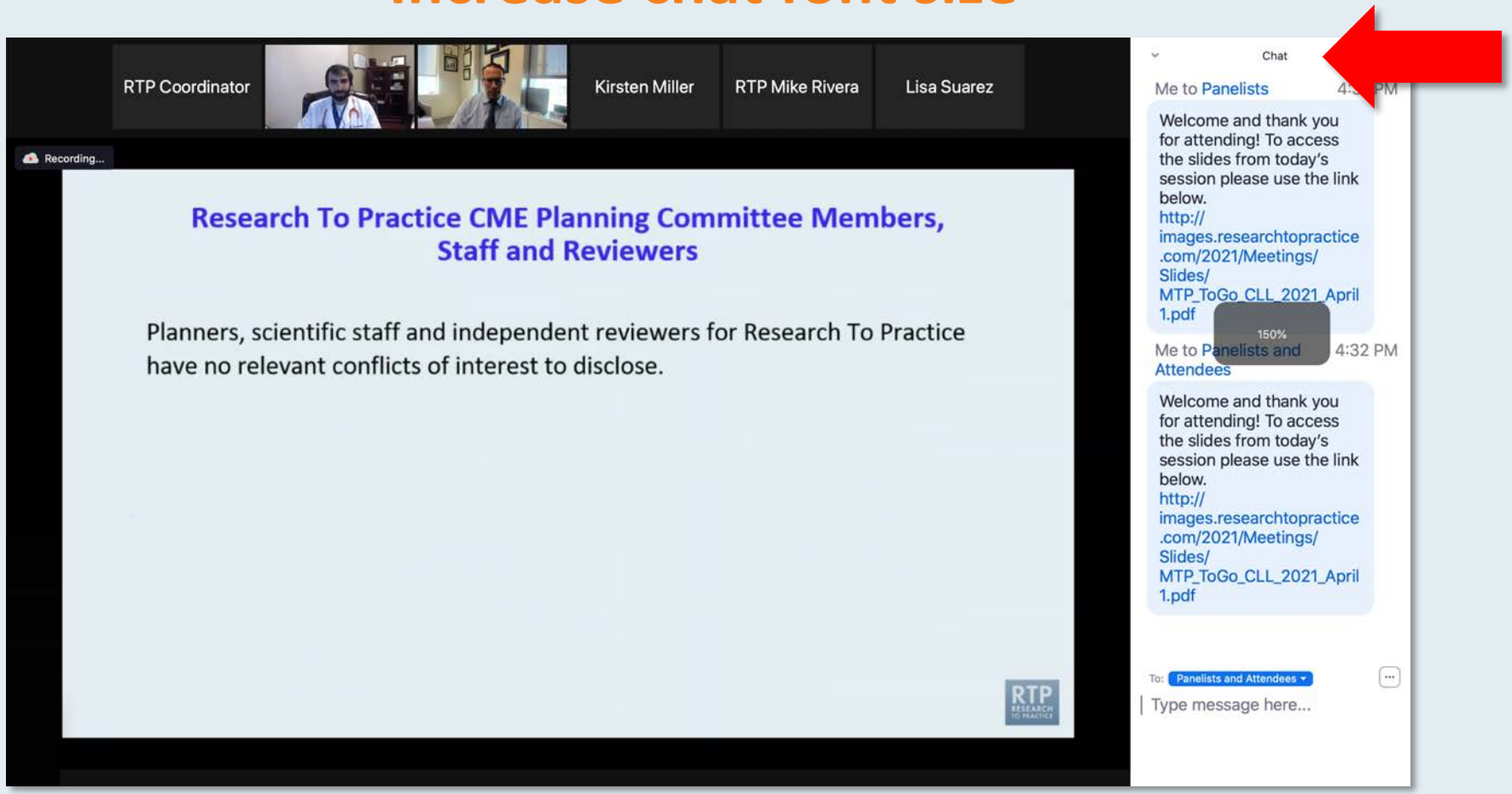

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of HER2-Low Breast Cancer

DR IAN KROP

DANA-FARBER CANCER INSTITUTE

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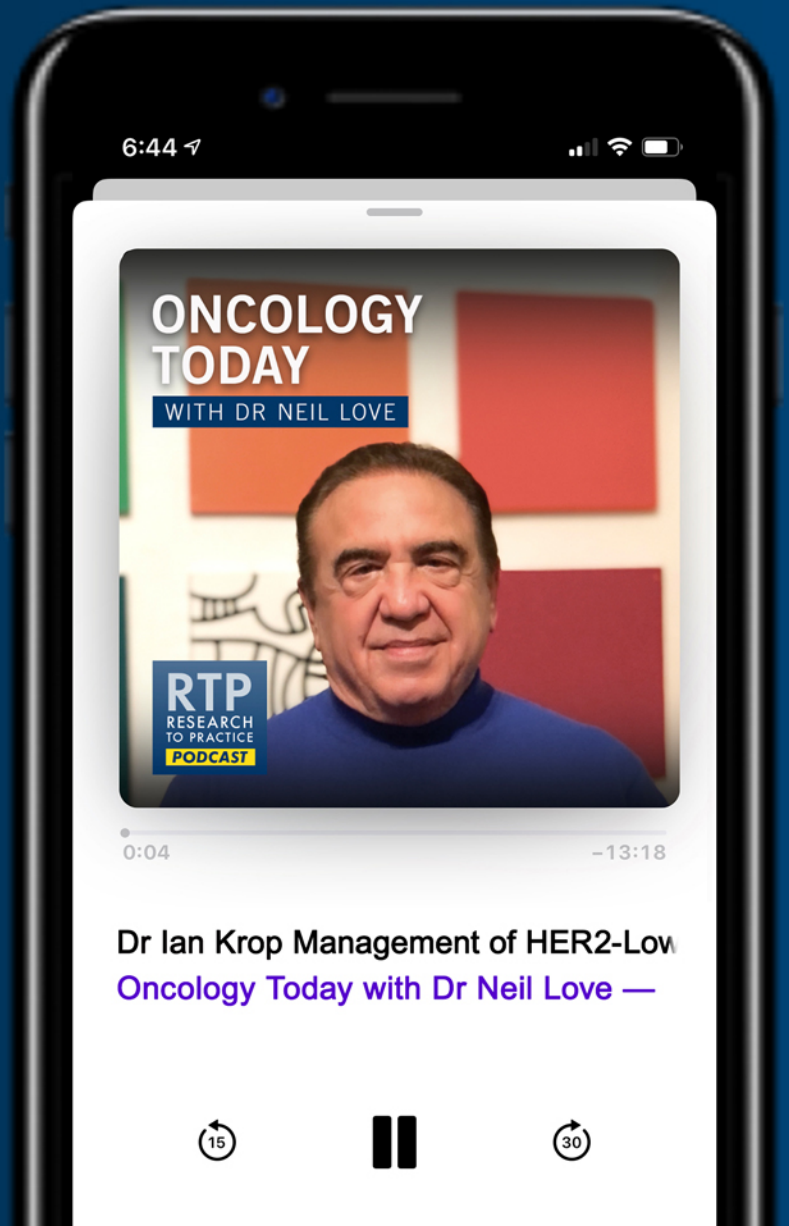
Spotify

Listen on Google Podcasts



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Current and Future Role of Immunotherapy in the Management of Lung Cancer

Thursday, November 18, 2021
5:00 PM – 6:00 PM ET

Faculty

Stephen V Liu, MD

Moderator

Neil Love, MD

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Meet The Professor

Management of BRAF-Mutant Melanoma

Monday, November 29, 2021
5:00 PM – 6:00 PM ET

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Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

Tuesday, November 30, 2021
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Optimizing the Management of Acute Myeloid Leukemia

Wednesday, December 1, 2021
5:00 PM – 6:00 PM ET

Faculty

Andrew H Wei, MBBS, PhD

Moderator

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Thursday, December 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Hope S Rugo, MD

Moderator

Neil Love, MD

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TO PRACTICE

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

Tuesday, December 7, 2021
8:00 PM – 9:45 PM ET

Faculty

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

Moderator

Erika Hamilton, MD

RTP RESEARCH TO PRACTICE

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of HER2-Positive Breast Cancer

Wednesday, December 8, 2021
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Faculty

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Virginia F Borges, MD, MMSc
Sara Hurvitz, MD
Ian E Krop, MD, PhD

Moderator

Lisa Carey, MD

RTP RESEARCH TO PRACTICE

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

Thursday, December 9, 2021
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Faculty

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Melinda Telli, MD

Professor Peter Schmid, FRCP, MD, PhD

Moderator

Hope S Rugo, MD

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Friday, December 10, 2021
7:30 AM – 9:30 AM ET

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Anthony R Mato, MD, MSCE
John M Pagel, MD, PhD
Jennifer Woyach, MD

Moderator

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

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Loretta J Nastoupil, MD
Gilles Salles, MD, PhD

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Ann S LaCasce, MD, MMSc

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

Friday, December 10, 2021
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Irene M Ghobrial, MD
Morie A Gertz, MD, MACP
Peter Voorhees, MD

Moderator

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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

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Research Honoring Richard F Emslander, MD
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Co-Leader, VICC Breast Cancer Research Program
Oncology Section Head, Division of Hematology/Oncology
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Vanderbilt-Ingram Cancer Center
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Moderator
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Research To Practice
Miami, Florida

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Chair, Department of Medicine
Charles A Dewey Professor of Medicine
University of Rochester
Rochester, New York

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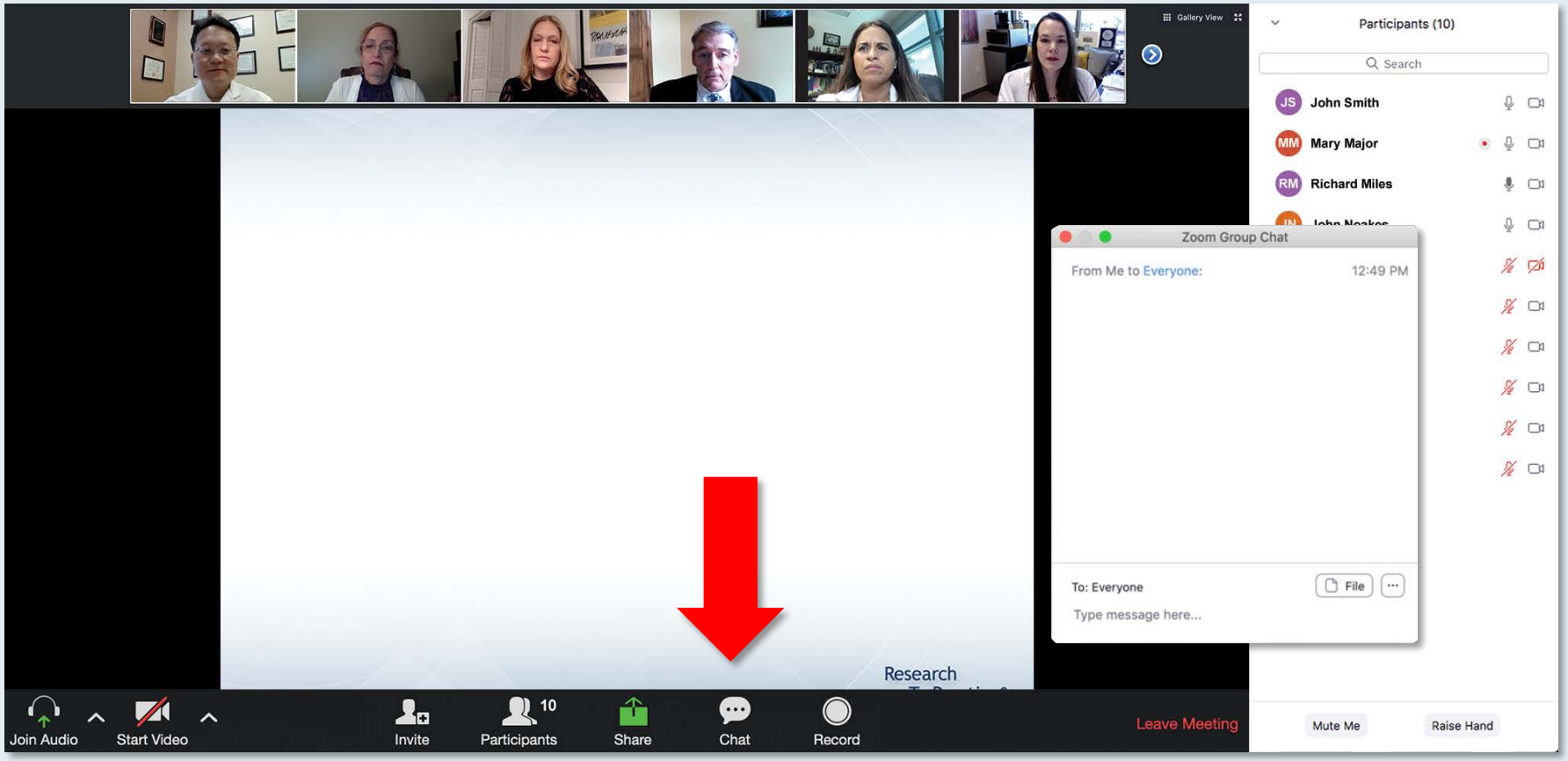

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Dhatri Kodali, MD
Texas Oncology
Houston, Texas

Ranju Gupta, MD
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania

Ann Partridge, MD, MPH
Dana-Farber Cancer Institute
Boston, Massachusetts

Arielle Heeke, MD
Levine Cancer Institute
Charlotte, North Carolina

Debra Patt, MD, PhD, MBA
Dell Medical School
The University of Texas at Austin
Austin, Texas

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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?

 Dr Goetz	Abemaciclib/ fulvestrant	 Dr Kalinsky	Palbociclib/fulvestrant
 Dr Jhaveri	Palbociclib/fulvestrant	 Dr Mayer	Abemaciclib/ fulvestrant
 Dr Kaklamani	Ribociclib/fulvestrant	 Dr O'Regan	Ribociclib/fulvestrant

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Meet The Professor with Dr Kalinsky

MODULE 1: Journal Club with Dr Kalinsky – Part 1

MODULE 2: Case Presentations

- Dr Partridge: A 65-year-old woman with ER-positive, PR-negative, HER2-negative metastatic breast cancer (mBC)
- Dr Heeke: A 30-year-old woman with ER/PR-positive, HER2-negative mBC with a PIK3CA mutation
- Dr Patt: A 46-year-old woman with ER/PR-positive, HER2-negative, node-positive localized breast cancer who had HER2-positive disease after neoadjuvant therapy
- Dr Kodali: A 60-year-old woman with ER-positive, HER2-negative, node-positive breast cancer
- Dr Gosain: A 77-year-old woman with Stage IIIC ER/PR-positive, HER2-negative breast cancer
- Dr Gupta: A 49-year-old woman with ER/PR-positive, HER2-negative mBC

MODULE 3: San Antonio Breast Cancer Symposium® 2021 Preview

MODULE 4: Beyond the Guidelines

MODULE 5: Journal Club with Dr Kalinsky – Part 2

MODULE 6: Appendix — Key Data Sets

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2021 ASCO ANNUAL MEETING

Education Session

WHY SURGERY IS NOT ALWAYS FIRST:

IDEAL INDICATIONS FOR PREOPERATIVE SYSTEMIC THERAPY

Kevin Kalinsky, MD, MS

Associate Professor of Medicine

Director, Glenn Family Breast Center

Winship Cancer Institute of Emory University

June 2021

RTP RESEARCH TO PRACTICE

ASCO 2021 Educational Book

BREAST CANCER

When the World Throws You a Curve Ball: Lessons Learned in Breast Cancer Management

Samilia Obeng-Gyasi, MD, MPH[1]; Charlotte E. Coles, PhD, MRCP, FRCR[2]; Jade Jones, MD[3]; Ruth Sacks, MD[3]; Sara Lightowlers, MB BChir, MRCP, FRCR[2,4]; Judith M. Bliss, MD[4]; A. Murray Brunt, MBBS, FRCP, FRCR[5]; Joanne S. Haviland, MSc, BSc[4]; Anna M. Kirby, MD, MB BChir, MRCP, FRCR[6]; and Kevin Kalinsky, MD, MS[3]

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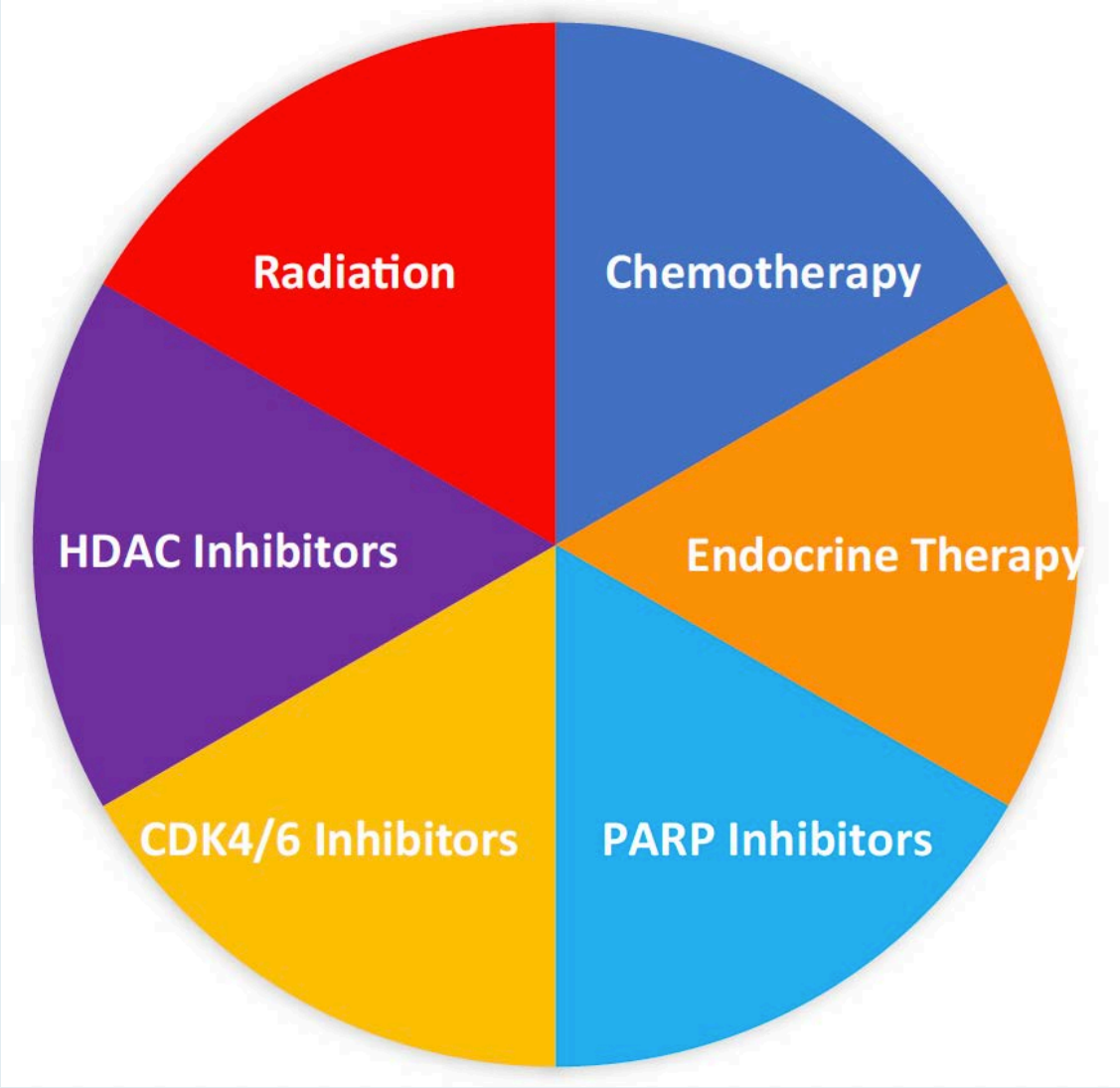
Breast Cancer Research and Treatment (2021) 189:1–13
https://doi.org/10.1007/s10549-021-06291-8

REVIEW

Clinical trial data and emerging immunotherapeutic strategies: hormone receptor-positive, HER2– negative breast cancer

Matthew R. Kearney[1] · Julia E. McGuinness[1] · Kevin Kalinsky[2]

Therapies Combined with Checkpoint Inhibition



Kearney MR et al. *Breast Cancer Res Treat* 2021;189(1):1-13.

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editorials

On the Road to Precision: Understanding the Biology Driving Genomic Assays

Kevin Kalinsky, MD, MS[1]; Alexandra Thomas, MD[2]; and David W. Cescon, MD, PhD[3]

J Clin Oncol 2021;39(2):100-2

Editorial Commentary on: Buus R et al. Molecular Drivers of Onco*type* DX, Prosigna, EndoPredict, and the Breast Cancer Index: A TransATAC Study. *J Clin Oncol* 2021;39(2):126-35.

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2021 ASCO ANNUAL MEETING

Abstract 1005

TREATMENT-RELATED SIDE EFFECTS AND VIEWS ABOUT DOSAGE ASSESSMENT TO SUSTAIN QUALITY OF LIFE:

RESULTS OF AN ADVOCATE-LED SURVEY OF PATIENTS WITH METASTATIC BREAST CANCER (MBC)

Anne Loeser,* Jeffrey Peppercorn, Mark E. Burkard, Kevin Kalinsky, Hope Rugo, Aditya Bardia

* Founder, Patient-Centered Dosing Initiative

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Case Presentation – Dr Partridge: A 65-year-old woman with ER-positive, PR-negative, HER2-negative metastatic breast cancer (mBC)

Dr Ann Partridge

- 1988: ER-positive, PR-negative, HER2-negative, BRCA1/2 wildtype s/p lumpectomy/ALND and adjuvant RT
- 2018: Metastases to liver, peritoneum
- 7/2018: Palbociclib/letrozole, with palbociclib dose reduced to 100 mg due to fatigue, cytopenias
- 5/2021: PD in peritoneum
- Clinical trial of oral SERD imlunestrant combined with everolimus

Case Presentation – Dr Heeke: A 30-year-old woman with ER/PR-positive, HER2-negative mBC with a PIK3CA mutation

Dr Arielle Heeke

- 9/2013: ER/PR-positive, HER2-positive IDC s/p neoadjuvant TCH, bilateral mastectomy and SLNB, with 3.1-cm residual IDC and lymphovascular invasion and 6 positive nodes → Radiation therapy
- Completed trastuzumab x 1 year, tamoxifen x 1 year stopped due to toxicity
- 6/2018: Presented to ER with progressively worsening pain
- Imaging: Widespread ER/PR-positive, HER2-negative bony metastases with a PIK3CA mutation → Goserelin/anastrozole/palbociclib
- 3/2020: PD in the liver → Goserelin/fulvestrant/abemaciclib
- 7/2020: PD in lung and liver → Paclitaxel/carboplatin
- 3/2021: Intracranial metastases → SRS → Alpelisib/fulvestrant, with Grade 4 hyperglycemia
  - SGLT2 inhibitor, metformin and alpelisib held then resumed at reduced dose

Question

- When do you introduce treatment with alpelisib? How do you manage alpelisib-associated hyperglycemia?

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Case Presentation – Dr Patt: A 46-year-old woman with ER/PR-positive, HER2-negative, node-positive localized breast cancer who had HER2-positive disease after neoadjuvant therapy

Dr Debra Patt

- Initially diagnosed with ER/PR-positive, HER2-negative IDC, Ki-67: 55%
- Neoadjuvant dose-dense AC-paclitaxel → Bilateral mastectomy
  - Pathology: 1.7-cm residual tumor, with 3 positive lymph nodes
  - Now, ER/PR-positive, HER2-positive

Questions

- How would you pivot her treatment now to reduce the risk from her HER2-positive disease?
- What is the likelihood of discordance between the ER/PR or HER2 after neoadjuvant chemotherapy?
- What risk reducing strategies would you recommend at this time — APHINITY or KATHERINE or other HER2-directed strategies?
- Would she benefit from neratinib in terms of risk reduction? If initiating neratinib, how would you optimize tolerability in terms of dose modification or administration of other drugs to mitigate toxicity?

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Case Presentation – Dr Kodali: A 60-year-old woman with ER-positive, HER2-negative, node-positive breast cancer

Dr Dhatri Kodali

- Diagnosed with ER-positive, HER2-negative, node-positive (x3) localized breast cancer
- Patient refused (neo)adjuvant chemotherapy but requested and received adjuvant abemaciclib

Questions

- Are there data for using adjuvant abemaciclib for a patient with high-risk ER-positive breast cancer who has not received chemotherapy?
- In the monarchE study they included high-risk patients, with 3 positive lymph nodes or those with high Ki-67 Grade 3 cancer. Would you consider adjuvant abemaciclib for younger patients with these high-risk features?

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Case Presentation – Dr Gosain: A 77-year-old woman with Stage IIIC ER/PR-positive, HER2-negative breast cancer

Dr Rahul Gosain

- 12/2019: Multifocal Stage IIIC, ER/PR-positive, HER2-negative left breast cancer
- Neoadjuvant TC x 4 → Lumpectomy, with residual disease → Mastectomy → RT
- Discussed CDK4/6-containing clinical trials, but pt declined → Adjuvant anastrozole

Questions

- Although she has received adjuvant anastrozole x 1 year, would you consider adding abemaciclib now that it has been approved? For what duration?
- With the approval of adjuvant abemaciclib, is adjuvant capecitabine in this setting still relevant?
- Would PARP inhibitors have a role here?
- PARP inhibitors can cause bone marrow suppression, which can be further exacerbated by future use of CDK4/6 inhibitors. Is that a concern?

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Case Presentation – Dr Gupta: A 49-year-old woman with ER/PR-positive, HER2-negative mBC

Dr Ranju Gupta

- 2013: DCIS s/p lumpectomy/RT + tamoxifen x 6 months → Bilateral mastectomy
  - Genetic testing: Negative
- 3/2016: Metastases in cervical and right paratracheal, mediastinal and axillary lymph nodes
  - ER (100%), PR (90%), HER2-negative
- Palbociclib/letrozole
- 5/2019: PD, with liver metastases (ER-positive, PR-negative, HER2-negative)
- NGS: ESR1 mutation → Abemaciclib/fulvestrant
- 7/2020: New liver metastases → Capecitabine
- 4/2021: New liver metastases
- 5/2021 FES PET: Liver metastases are non-FES avid, Hilar node is FES avid → Liposomal doxorubicin

Question

- Are you using the FES PET scan in your practice? And if yes, how and when? How do you interpret the findings?

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Kalinsky

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MODULE 3: San Antonio Breast Cancer Symposium® 2021 Preview

MODULE 4: Beyond the Guidelines

MODULE 5: Journal Club with Dr Kalinsky – Part 2

MODULE 6: Appendix — Key Data Sets

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San Antonio Breast Cancer Symposium 2021 Preview

Abstracts from Dr Kalinsky

- Bidard F-C et al. **SERENA-6: A Phase III study to assess the efficacy and safety of AZD9833 (camizestrant) compared with aromatase inhibitors when given in combination with palbociclib or abemaciclib in patients with HR+/HER2- metastatic breast cancer with detectable ESR1m who have not experienced disease progression on first-line therapy.** SABCS 2021;Abstract OT2-11-05.
- Brett JO et al. **Association between co-existing genomic alterations and abemaciclib benefit in patients with metastatic hormone receptor-positive breast cancer with ESR1 mutations following disease progression on prior endocrine therapy plus palbociclib or ribociclib.** SABCS 2021;Abstract PD2-03.
- Chien AJ et al. **I-SPY2 endocrine optimization protocol (EOP): A pilot neoadjuvant endocrine therapy study with amcenestrant as monotherapy or in combination with abemacicilib or letrozole in molecularly selected HR+/HER2- clinical stage 2/3 breast cancer.** SABCS 2021;Abstract OT1-10-02.

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San Antonio Breast Cancer Symposium 2021 Preview (Cont)

Abstracts from Dr Kalinsky (Continued)

- Kalinsky KM et al. **Distant-disease free interval in participants (pts) with 1-3 positive lymph nodes (LN), hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with Recurrence Score (RS) < or = 25 randomized to endocrine therapy (ET) +/- chemotherapy (CT): SWOG s1007 (RxPONDER).** SABCS 2021;Abstract GS2-07.

Other Oral Abstracts

- Krop I et al. **Datopotamab deruxtecan in advanced/metastatic HER2- breast cancer: Results from the phase 1 TROPION-PanTumor01 study.** SABCS 2021;Abstract GS1-05.
- Goodwin PJ et al. **CCTGMA.32, a phase III randomized double-blind placebo controlled adjuvant trial of metformin (MET) vs placebo (PLAC) in early breast cancer (BC): Results of the primary efficacy analysis (clinical trials.gov NCT01101438).** SABCS 2021;Abstract GS1-08.

San Antonio Breast Cancer Symposium 2021 Preview (Cont)

Other Oral Abstracts (Continued)

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

San Antonio Breast Cancer Symposium 2021 Preview (Cont)

Other Oral Abstracts (Continued)

- Braybrooke J et al. **Taxane with anthracycline versus taxane without anthracycline: An individual patient-level meta-analysis of 16,500 women with early-stage breast cancer in 13 randomised trials.** SABCS 2021;Abstract GS2-06.
- Kubler K et al. **Tamoxifen instigates uterine cancer development by activating PI3K signaling and supersedes PIK3CA driver mutations.** SABCS 2021;Abstract GS2-09.
- Bidard FC 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.

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MODULE 4: Beyond the Guidelines

MODULE 5: Journal Club with Dr Kalinsky – Part 2

MODULE 6: Appendix — Key Data Sets

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In general, when ordering a genomic assay for a 45-year-old premenopausal woman with ER-positive, HER2-negative breast cancer, which of the following, if any, are you most likely to utilize?

	Node-negative	Node-positive
 Dr Goetz	21-gene assay	21-gene assay
 Dr Jhaveri	RSClin	I would not order a genomic assay
 Dr Kaklamani	21-gene assay	I would not order a genomic assay
 Dr Kalinsky	21-gene assay	21-gene assay
 Dr Mayer	21-gene assay	21-gene assay
 Dr O'Regan	21-gene assay	21-gene assay

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In general, when ordering a genomic assay for a 65-year-old postmenopausal woman with ER-positive, HER2-negative breast cancer, which of the following, if any, are you most likely to utilize?

	Node-negative	Node-positive
 Dr Goetz	21-gene assay	21-gene assay
 Dr Jhaveri	RSClin	21-gene assay
 Dr Kaklamani	21-gene assay	21-gene assay
 Dr Kalinsky	21-gene assay	21-gene assay
 Dr Mayer	21-gene assay	21-gene assay
 Dr O'Regan	21-gene assay	21-gene assay

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For a 65-year-old woman s/p surgical excision of an ER-positive, HER2-negative, node-negative localized breast cancer, assume an Onco*type* DX® 21-gene assay was ordered prior to your seeing the patient.

Would your decision to use chemotherapy be influenced by the Onco*type* DX Recurrence Score® (RS)?

65-Year-Old Woman, Node-Negative

	0.6 cm	1.5 cm	3.0 cm
 Dr Goetz	No	>25	>25
 Dr Jhaveri	>25	>25	>25
 Dr Kaklamani	>25	>25	>25
 Dr Kalinsky	>25	>25	>25
 Dr Mayer	No	>25	>25
 Dr O'Regan	No	>30	>25

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For a 50-year-old premenopausal woman s/p surgical excision of an ER-positive, HER2-negative, node-negative localized breast cancer, assume an Onco*type* DX 21-gene assay was ordered prior to your seeing the patient.

Would your decision to use chemotherapy be influenced by the Onco*type* DX RS?

50-Year-Old Premenopausal Woman, Node-Negative

	0.6 cm	1.5 cm	3.0 cm
 Dr Goetz	>20	>20	Patient discussion
 Dr Jhaveri	>16	>16	>25
 Dr Kaklamani	>21	>21	>21
 Dr Kalinsky	>20	>20	Patient discussion
 Dr Mayer	>31	>25	>25
 Dr O'Regan	>25	>25	>20

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A 65-year-old woman s/p surgical excision of a 1.5-cm ER-positive, HER2-negative, node-positive localized breast cancer, assume an Onco*type* DX 21-gene assay was ordered prior to your seeing the patient.

Would your decision to use chemotherapy be influenced by the Onco*type* DX RS?

65-Year-Old Woman, Node-Positive

	Microscopic disease in 1 node	1 positive node	2 positive nodes
 Dr Goetz	>25	>25	>25
 Dr Jhaveri	>25	>25	>25
 Dr Kaklamani	>25	>25	>25
 Dr Kalinsky	>25	>25	>25
 Dr Mayer	>25	>25	>25
 Dr O'Regan	>25	>25	>25

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A 50-year-old premenopausal woman s/p surgical excision of a 1.5-cm ER-positive, HER2-negative, node-positive localized breast cancer, assume an Onco*type* DX 21-gene assay was ordered prior to your seeing the patient.

Would your decision to use chemotherapy be influenced by the Onco*type* DX RS?

50-Year-Old Premenopausal Woman, Node-Positive

	Microscopic disease in 1 node	1 positive node	2 positive nodes
 Dr Goetz	>25	>25	>25
 Dr Jhaveri	>16	No	No
 Dr Kaklamani	Patient discussion	No	No
 Dr Kalinsky	>10	>0	>0
 Dr Mayer	>20	>16	No
 Dr O'Regan	>25	>20	>20

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?

 Dr Goetz	Abemaciclib/ fulvestrant	 Dr Kalinsky	Palbociclib/fulvestrant
 Dr Jhaveri	Palbociclib/fulvestrant	 Dr Mayer	Abemaciclib/ fulvestrant
 Dr Kaklamani	Ribociclib/fulvestrant	 Dr O'Regan	Ribociclib/fulvestrant

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?

 Dr Goetz	Ribociclib/letrozole	 Dr Kalinsky	Palbociclib/letrozole
 Dr Jhaveri	Palbociclib/letrozole	 Dr Mayer	Abemaciclib/ exemestane
 Dr Kaklamani	Ribociclib/letrozole	 Dr O'Regan	Ribociclib/letrozole

IDC = infiltrating ductal carcinoma; AI = aromatase inhibitor

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?

 Dr Goetz	Ribociclib/letrozole	 Dr Kalinsky	Palbociclib/letrozole
 Dr Jhaveri	Palbociclib/letrozole	 Dr Mayer	Abemaciclib/letrozole
 Dr Kaklamani	Ribociclib/letrozole	 Dr O'Regan	Ribociclib/letrozole

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

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MODULE 3: San Antonio Breast Cancer Symposium® 2021 Preview

MODULE 4: Beyond the Guidelines

MODULE 5: Journal Club with Dr Kalinsky – Part 2

MODULE 6: Appendix — Key Data Sets

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Journal Club with Dr Kalinsky

- Pusztai L et al. **Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: Results from the adaptively randomized I-SPY2 trial.** *Cancer Cell* 2021; 39(7):989-98.e5.
- Wander SA et al. **Clinical outcomes with abemaciclib after prior CDK4/6 inhibitor progression in breast cancer: A multicenter experience.** *J Natl Compr Canc Netw* 2021;1-8.
- Griffiths JI et al. **Serial single-cell genomics reveals convergent subclonal evolution of resistance as early-stage breast cancer patients progress on endocrine plus CDK4/6 therapy.** *Nat Cancer* 2021;2(6):658-71.
- Hopson MB et al. **Phase II study of propranolol feasibility with neoadjuvant chemotherapy in patients with newly diagnosed breast cancer.** *Breast Cancer Res Treat* 2021;188(2):427-32.
- McGuinness JE et al. **Diffuse optical tomography breast imaging measurements are modifiable with pre-surgical targeted and endocrine therapies among women with early stage breast cancer**. *Breast Cancer Res Treat* 2021;189(1):297-304.

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TO PRACTICE

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MODULE 4: Beyond the Guidelines

MODULE 5: Journal Club with Dr Kalinsky – Part 2

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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.

First Results from a Phase III Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy (ET) +/- Chemotherapy (CT) in Patients (pts) with 1-3 Positive Nodes, Hormone Receptor-Positive (HR+) and HER2-Negative (HER2-) Breast Cancer (BC) with Recurrence Score (RS) ≤25: SWOG S1007 (RxPonder)

Kalinsky K et al.

SABCS 2020;Abstract GS3-00.

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

REGISTRATION

Recurrence Score 0-25

Recurrence Score >25

Off study
Chemotherapy followed by Endocrine therapy recommended

RANDOMIZATION

N = 5,000 pts

Arm 1:
Chemotherapy followed by endocrine therapy

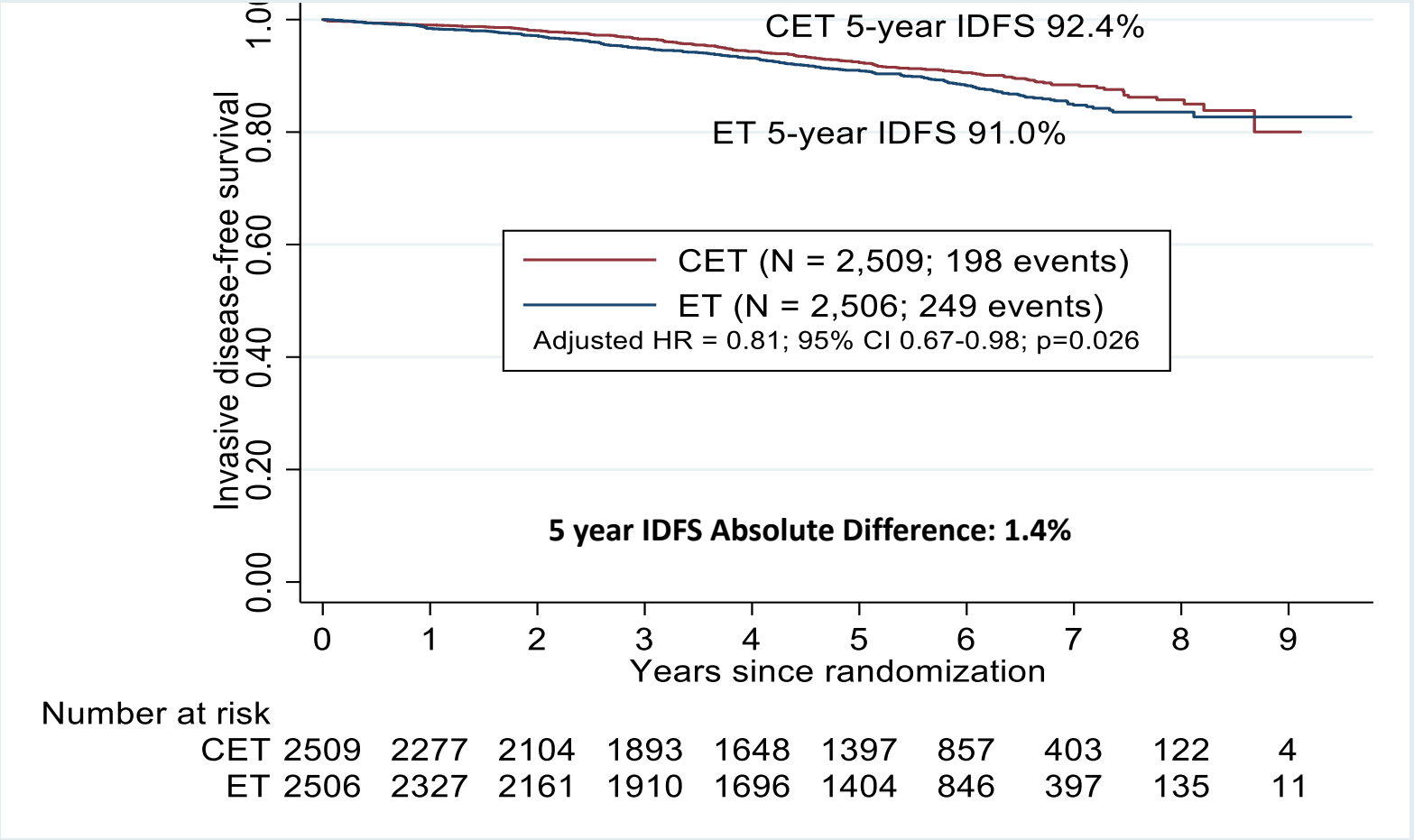
Arm 2:
Endocrine therapy alone

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

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

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

RxPONDER: Invasive Disease-Free Survival (IDFS) in Overall Population by Treatment Arm



CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

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

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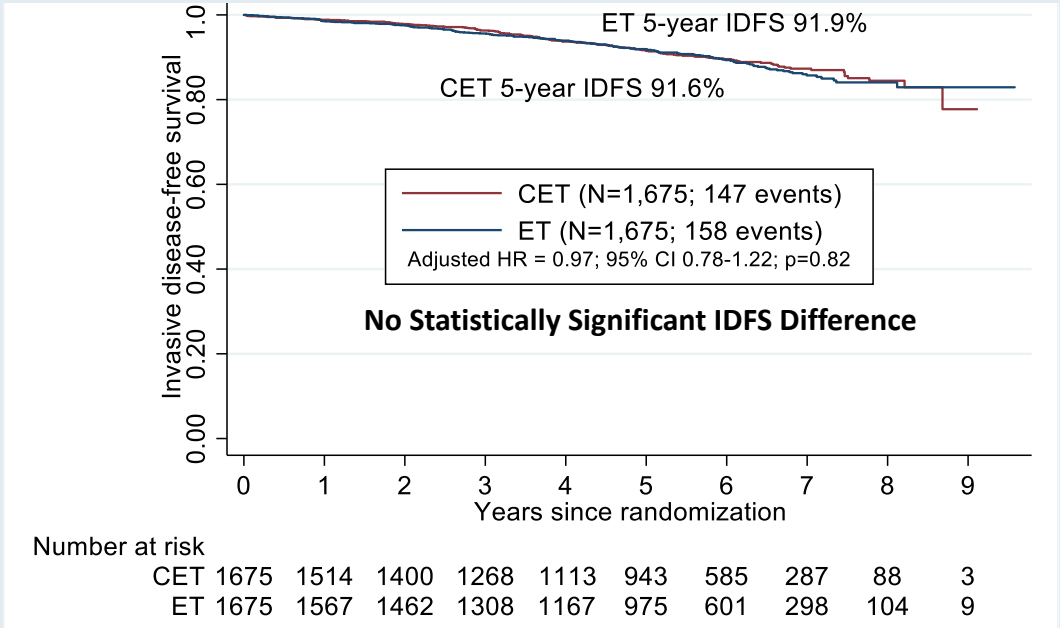
RxPONDER: IDFS Stratified by Menopausal Status

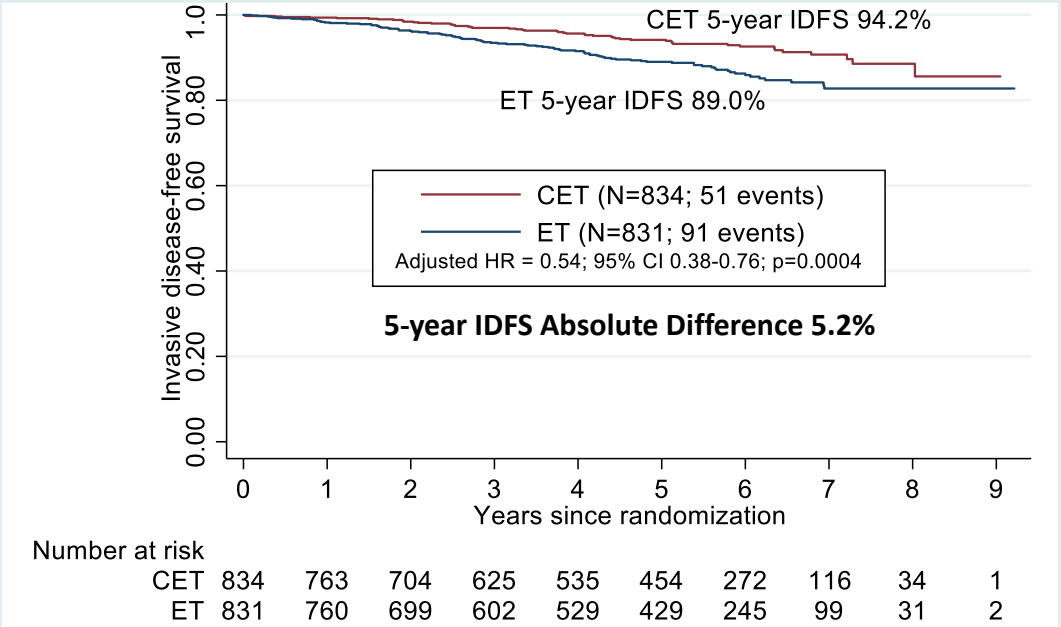
Postmenopausal



IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Premenopausal



IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

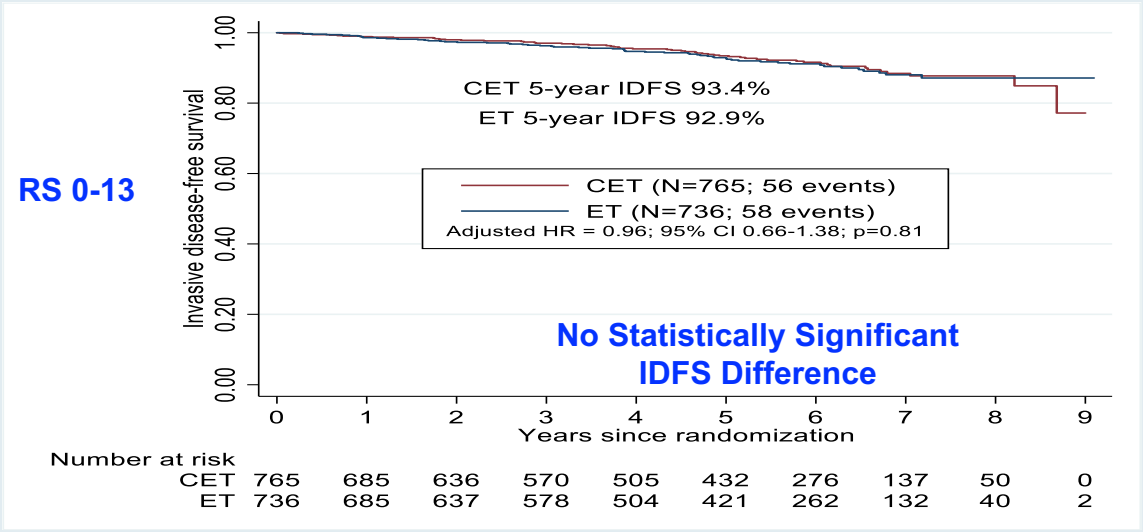
Kalinsky K et al. SABCS 2020;Abstract GS3-00.

RTP RESEARCH TO PRACTICE

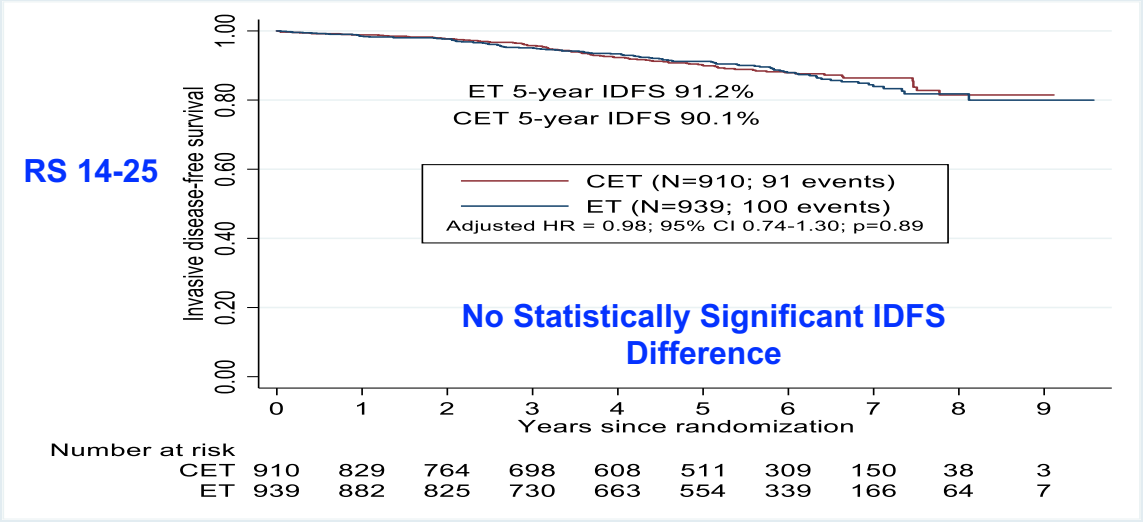
IDFS Stratified by Recurrence Score and Menopausal Status

Postmenopausal

RS 0-13

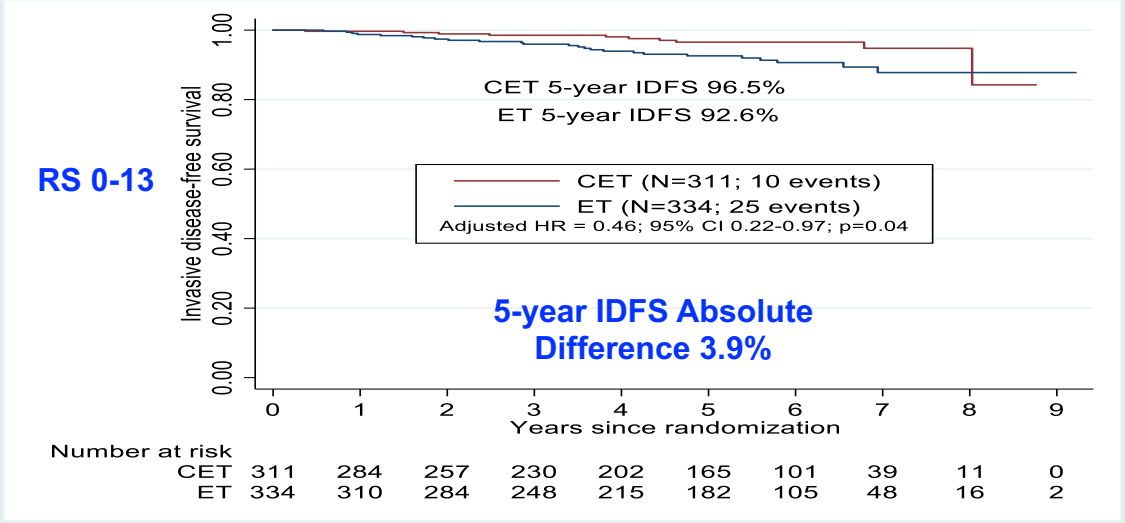


RS 14-25

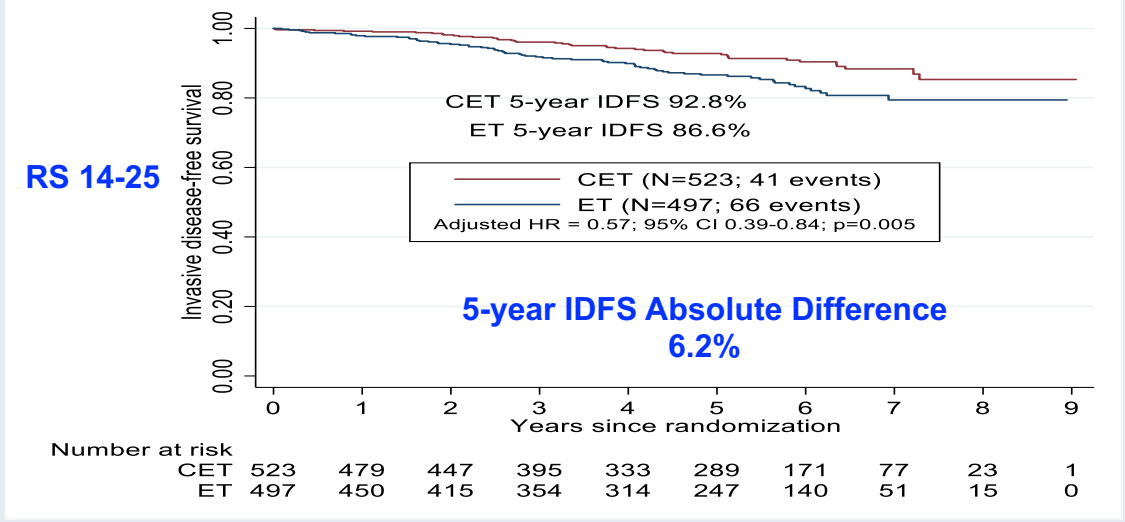


Premenopausal

RS 0-13



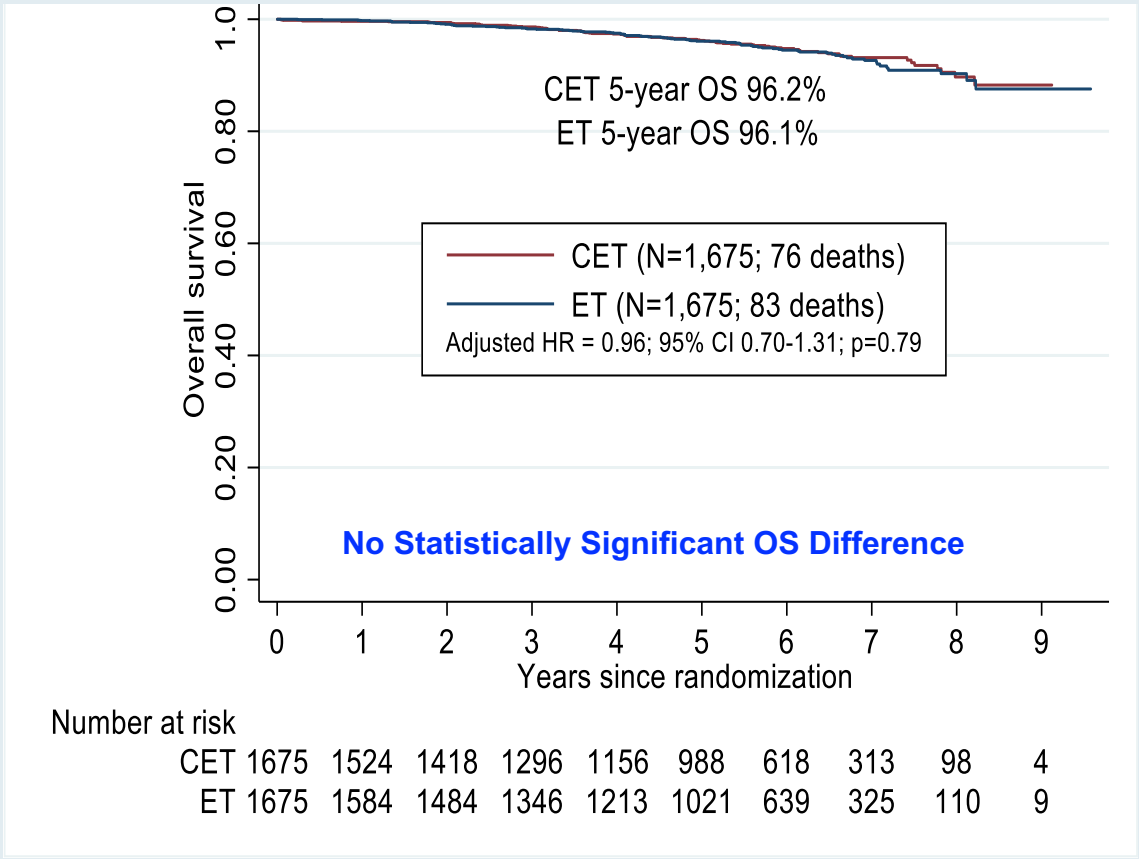
RS 14-25



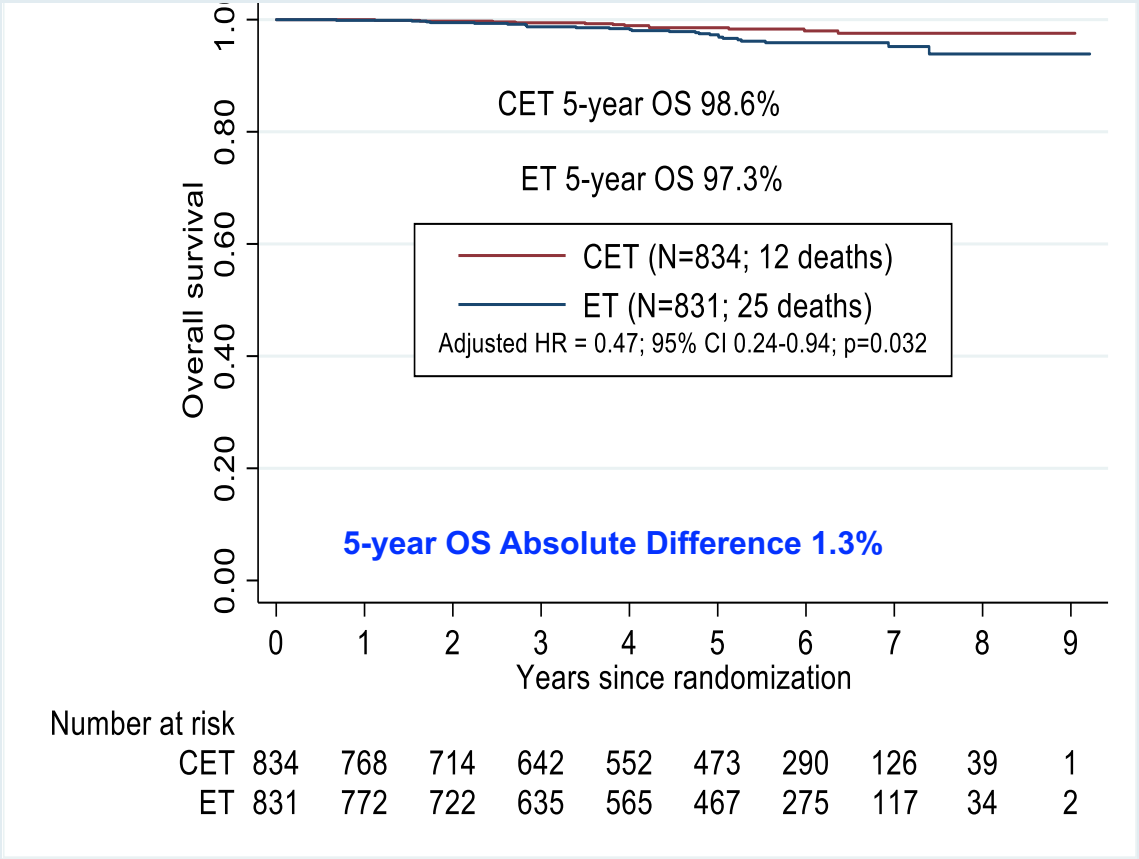
Kalinsky K et al. SABCS 2020;Abstract GS3-00.

Overall Survival by Menopausal Status

Postmenopausal



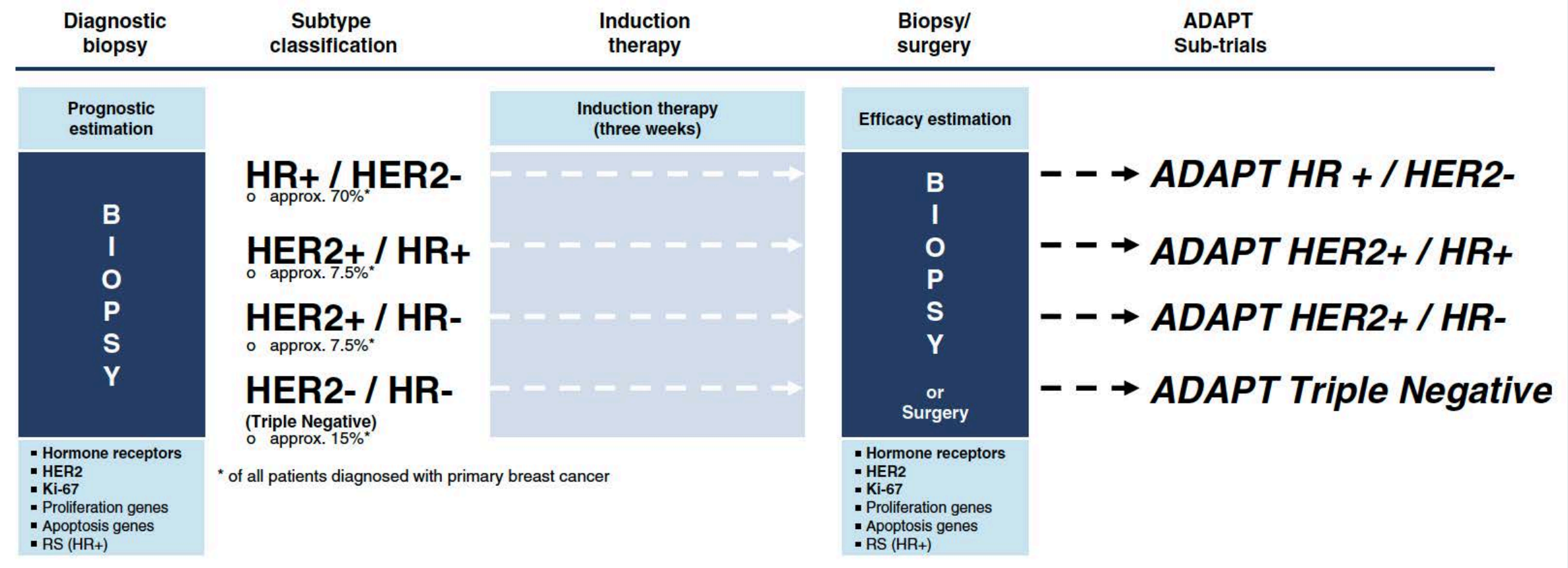
Premenopausal



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

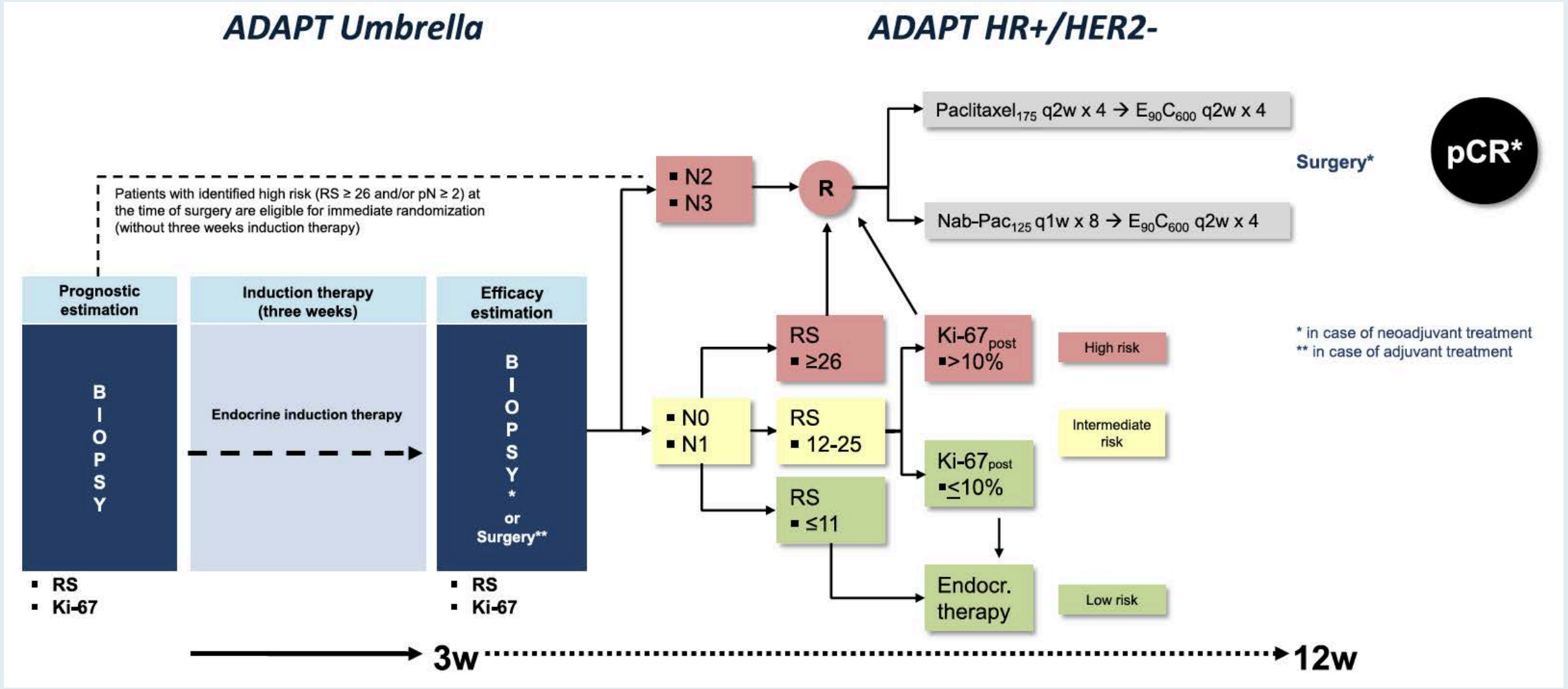
RTP RESEARCH TO PRACTICE

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

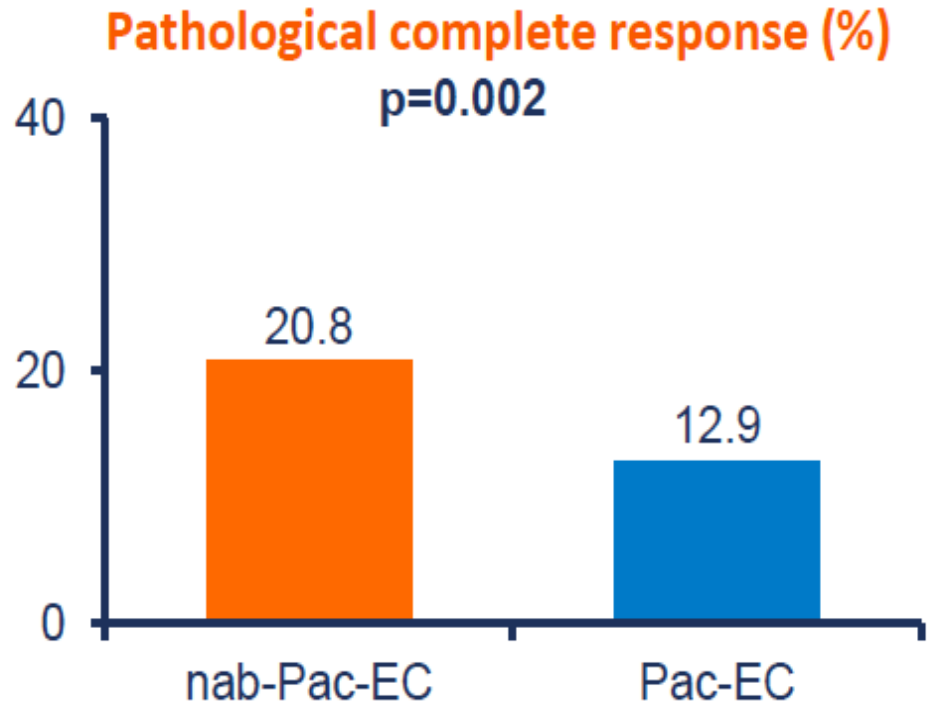


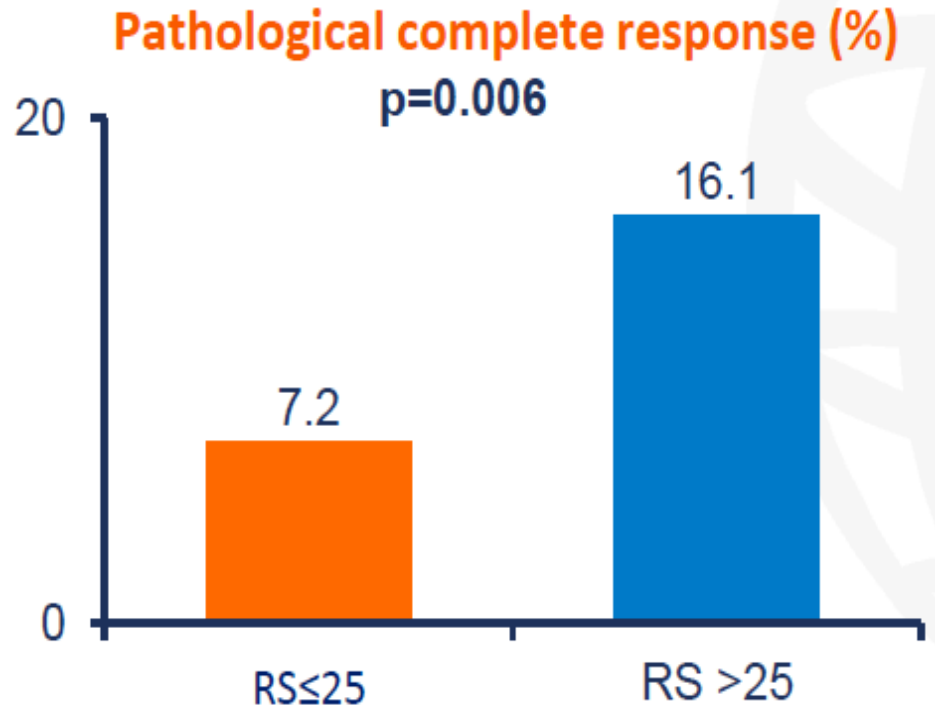
Hofmann et al. *Trials* 2013;14:261.

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.

RTP RESEARCH TO PRACTICE

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%

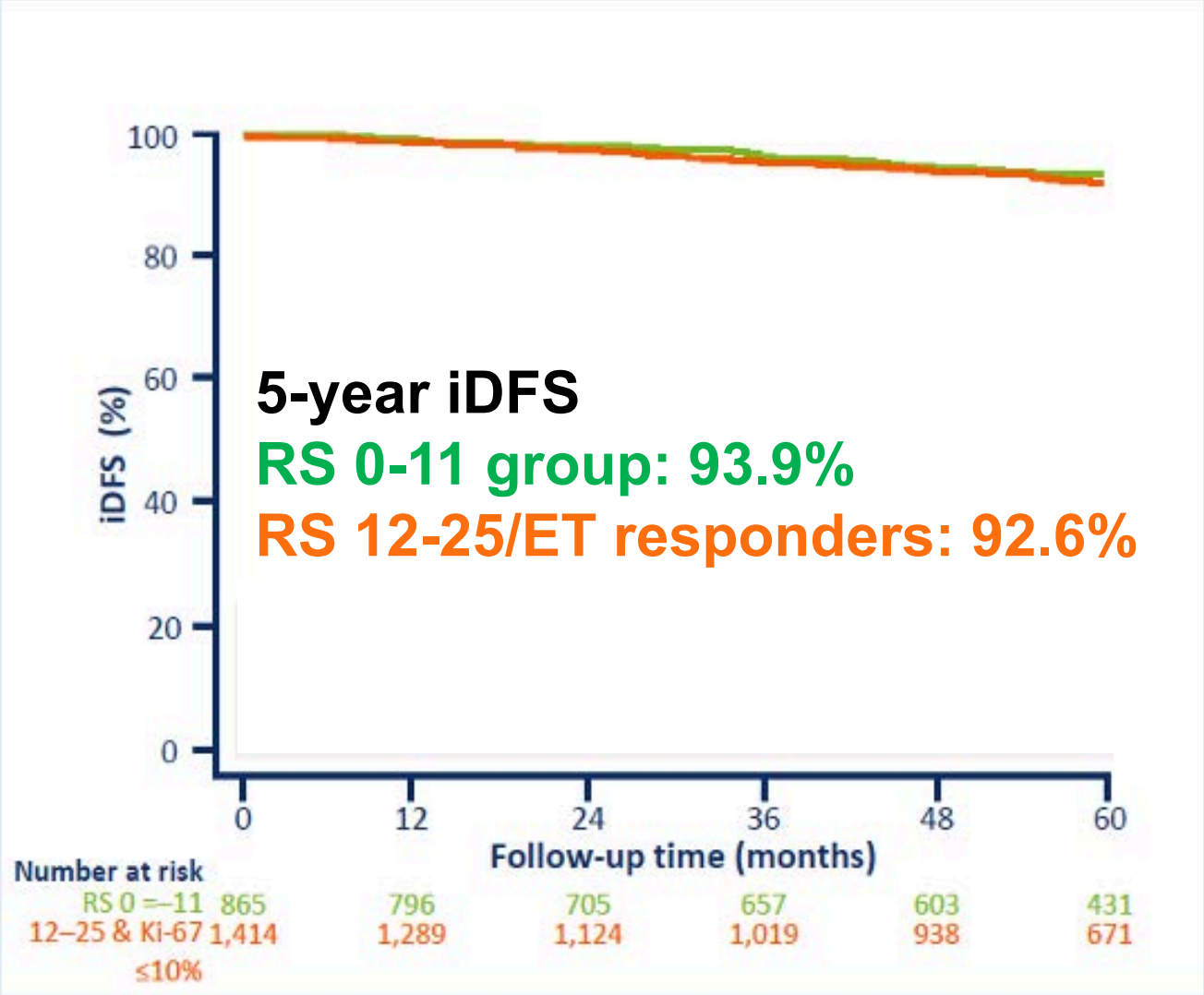
↓

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

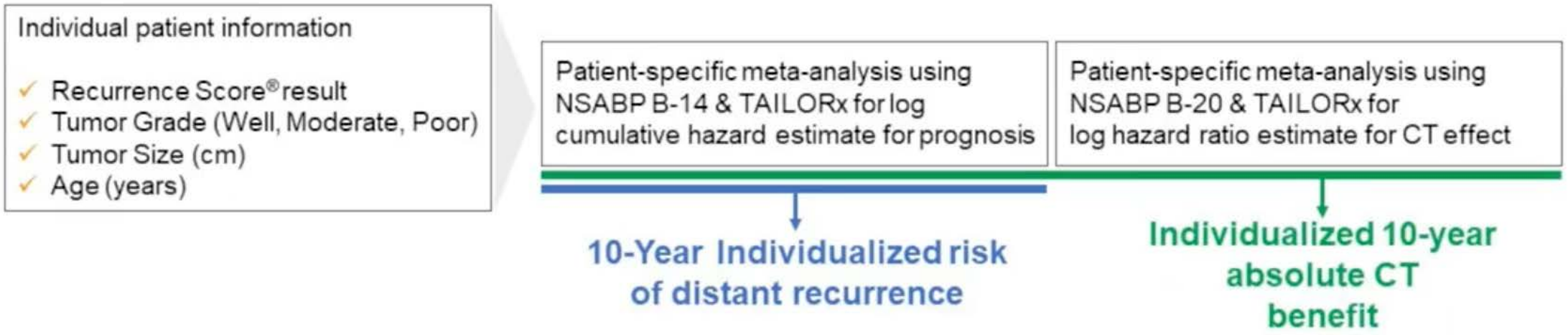
Development and Validation of a Tool Integrating the 21-Gene Recurrence Score and Clinical-Pathological Features to Individualize Prognosis and Prediction of Chemotherapy Benefit in Early Breast Cancer

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



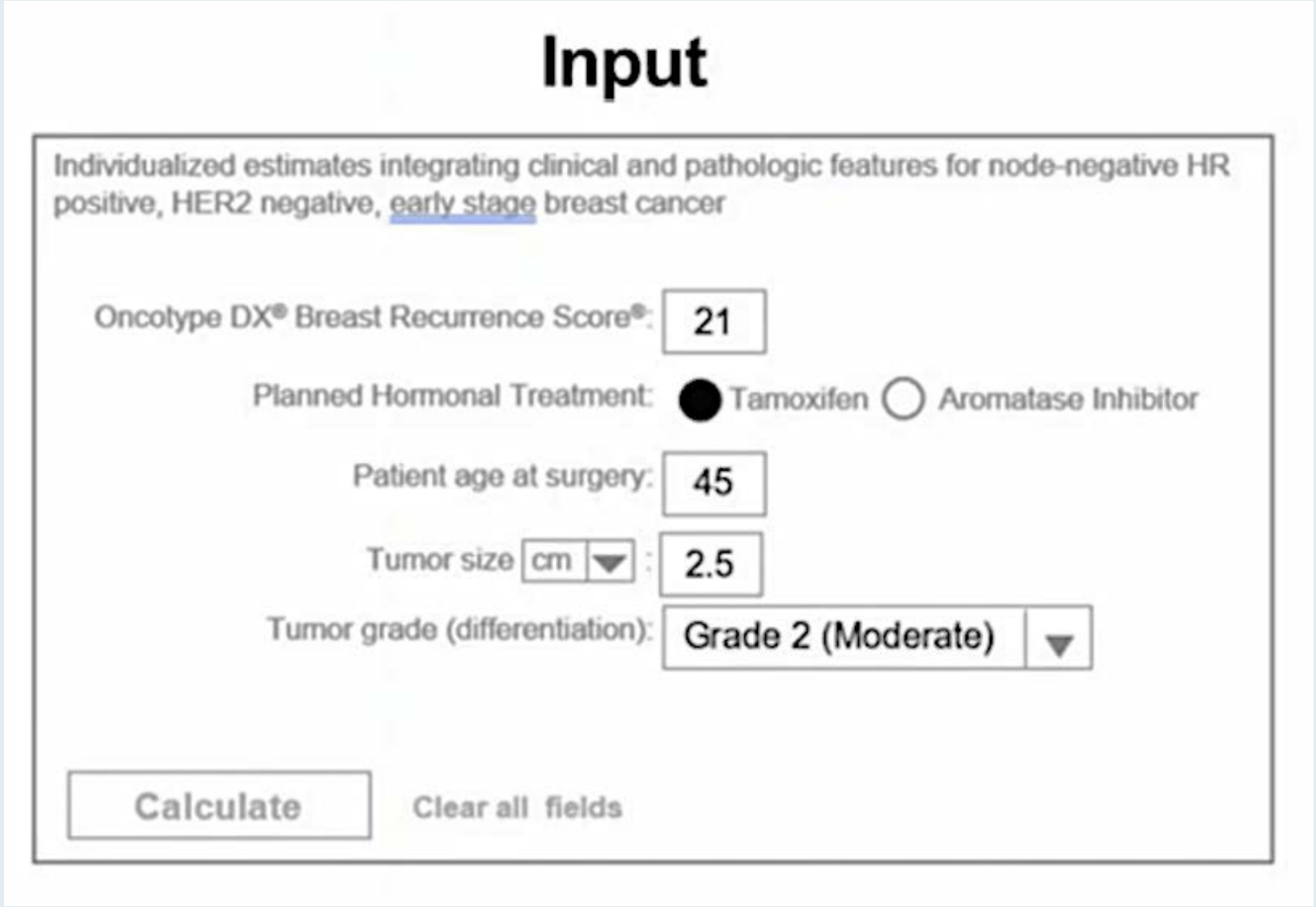
- **Meta-analysis** using NSABP B-14, TAILORx, and NSABP B-20 for individualized prognosis and individualized prediction of chemotherapy benefit
- Prognosis meta-analysis uses baseline risk from TAILORx so RSClin tool risk estimates reflect **current medical practice**
- RSClin tool estimates for distance-recurrence 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 Eduational Tool – Individualized Patient Information



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

RTP RESEARCH TO PRACTICE

RSClin Eduational Tool – Individualized Patient Information

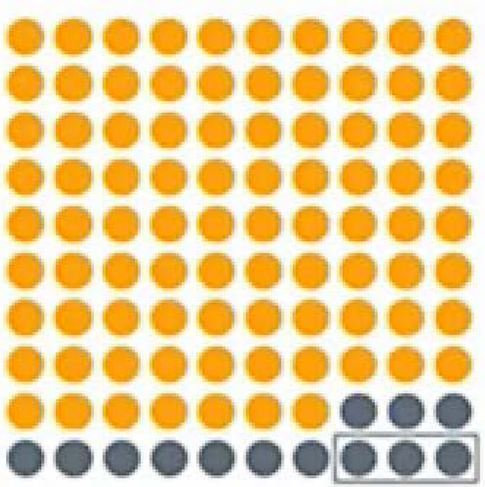
Output

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

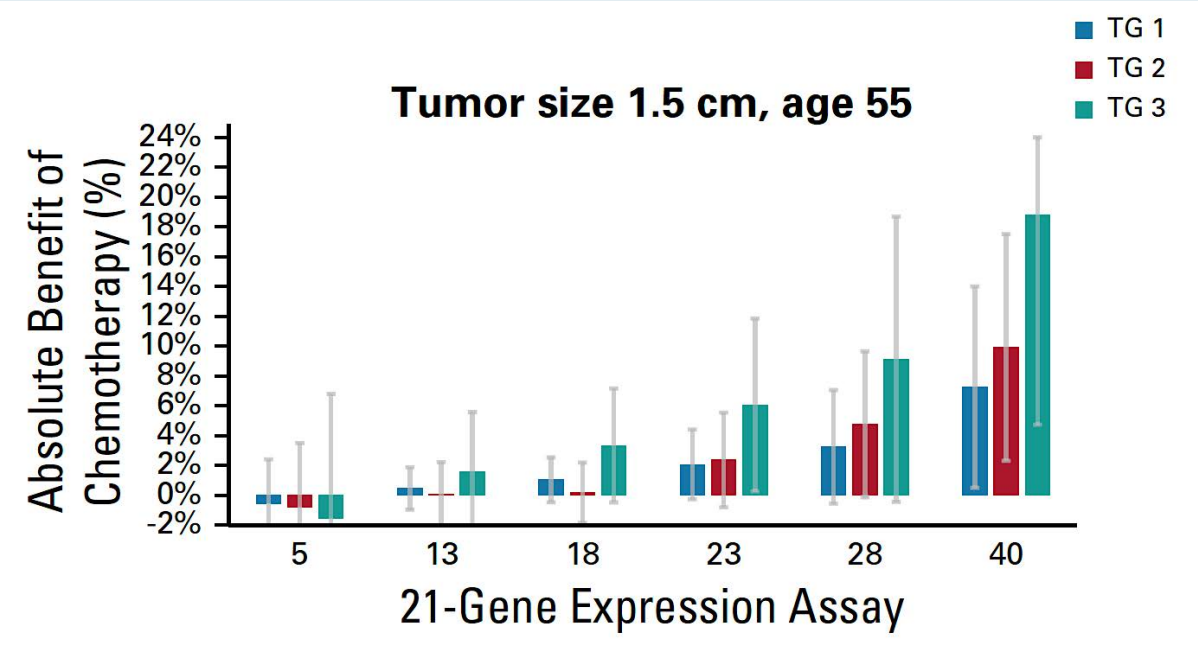
13% of patients expected to recur with Tamoxifen

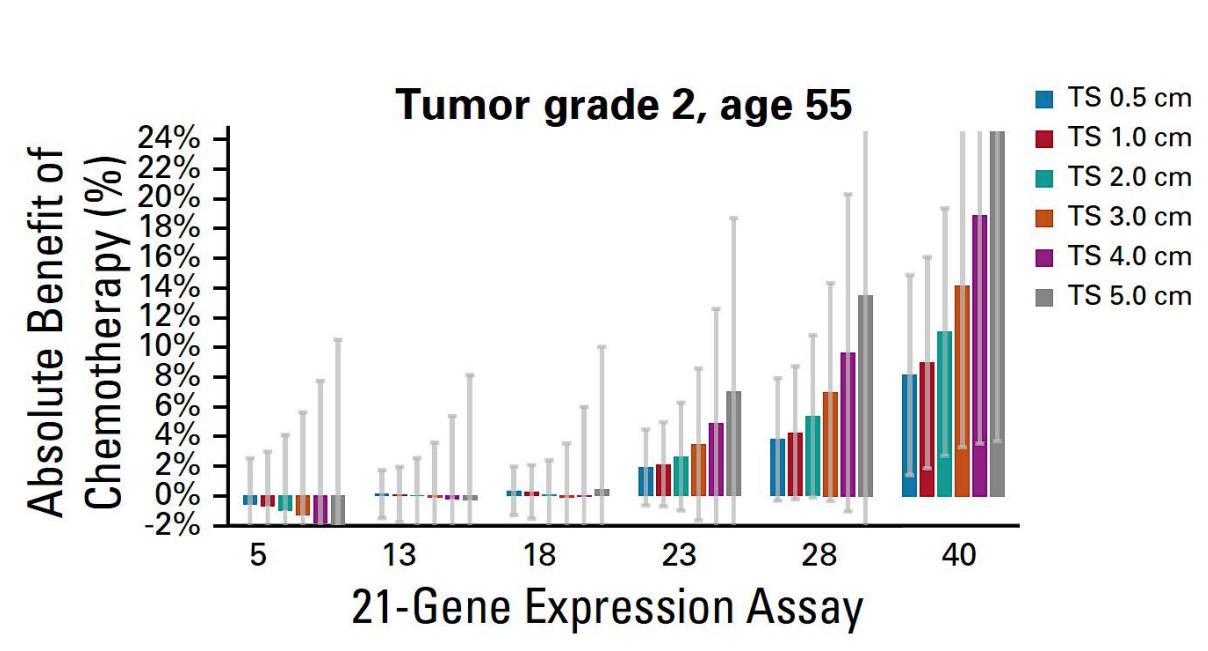
3% of patients expected to benefit from chemotherapy

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

RTP RESEARCH TO PRACTICE

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

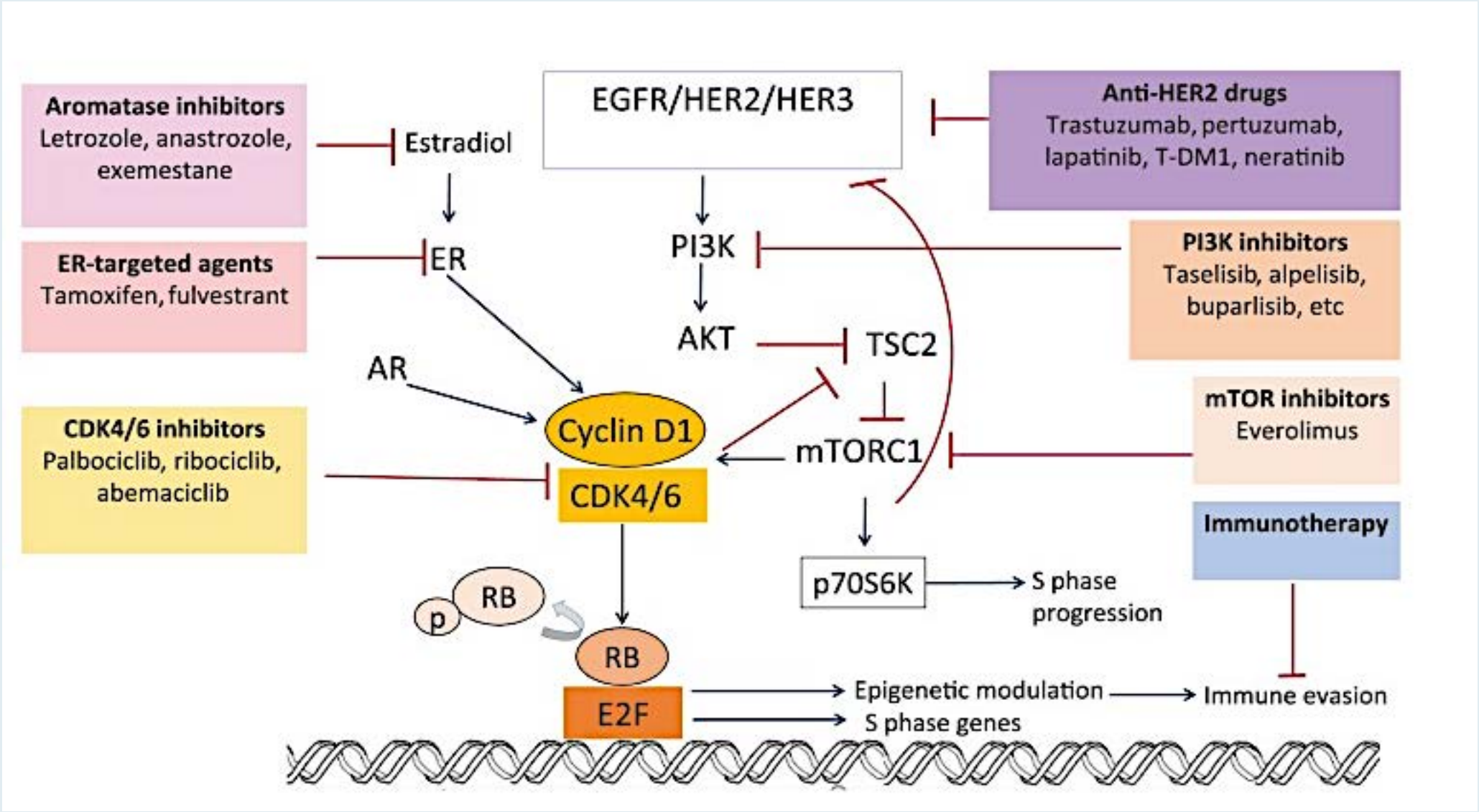
Sparano JA et al. *J Clin Oncol* 2021;39(6):557-64.

RTP RESEARCH TO PRACTICE

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

RTP
RESEARCH
TO PRACTICE

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.

Key Trials Exploring CDK4/6 Inhibitors in Localized Breast Cancer

	MonarchE	PALLAS	PENELOPE-B
Number of patients	5,637	5,760	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	23.7 months	42.8 months
iDFS	92.2% (Abemaciclib + ET) vs. 88.7% (ET alone) at 2 years Ki67 ≥20% group-91.6% vs. 87.1%	88.2% (Palbociclib + ET) vs. 88.5% (ET alone)	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%	–

Pooja Advani, *ASCO Daily News.* Feb. 25. 2021; https://dailynews.ascopubs.org/do/10.1200/ADN.21.200483/full/

RTP RESEARCH TO PRACTICE

Phase III Adjuvant Trials of CDK4/6 Inhibitor Therapy for HR-Positive, HER2-Negative Localized Breast Cancer, with Results

Trial name	Phase	N	Treatment arms	Primary endpoint
PENELOPE-B[1]	III	1,250	• Palbociclib + ET • Placebo + ET	IDFS: HR = 0.93 (p = 0.525)
PALLAS[2]	III	5,760	• Palbociclib + ET • ET alone	IDFS: HR = 0.93 (p = 0.51)
monarchE[3]	III	5,637	• Abemaciclib + ET • ET alone	IDFS: HR = 0.75 (p = 0.01)
EarLEE-1[4]	III	~2,000	• Ribociclib + ET • Placebo + ET	Pending release of results

[1]Loibl S et al. *J Clin Oncol* 2021;39(14):1518-30; [2]Mayer EL et al. *Lancet Oncol* 2021;22(2):212-22;
[3]Johnston SRD et al. *J Clin Oncol* 2020;38(34):3987-98; [4]Jiminez MM et al. *Ann of Oncol* 2017;28(5):V107.

RTP RESEARCH TO PRACTICE

FDA Approves Adjuvant Abemaciclib with Endocrine Therapy for Early Breast Cancer

Press Release: October 12, 2021

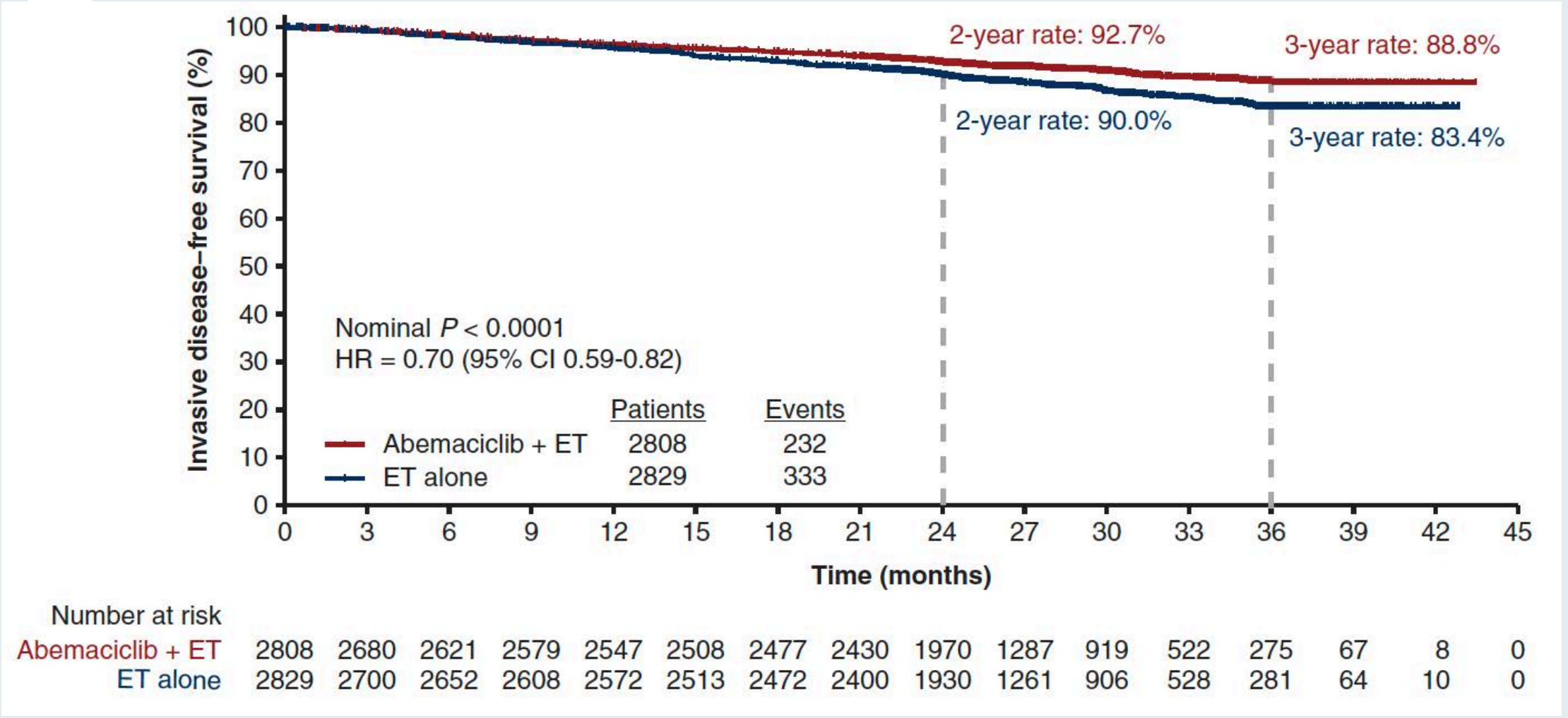
"The Food and Drug Administration approved abemaciclib with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of 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

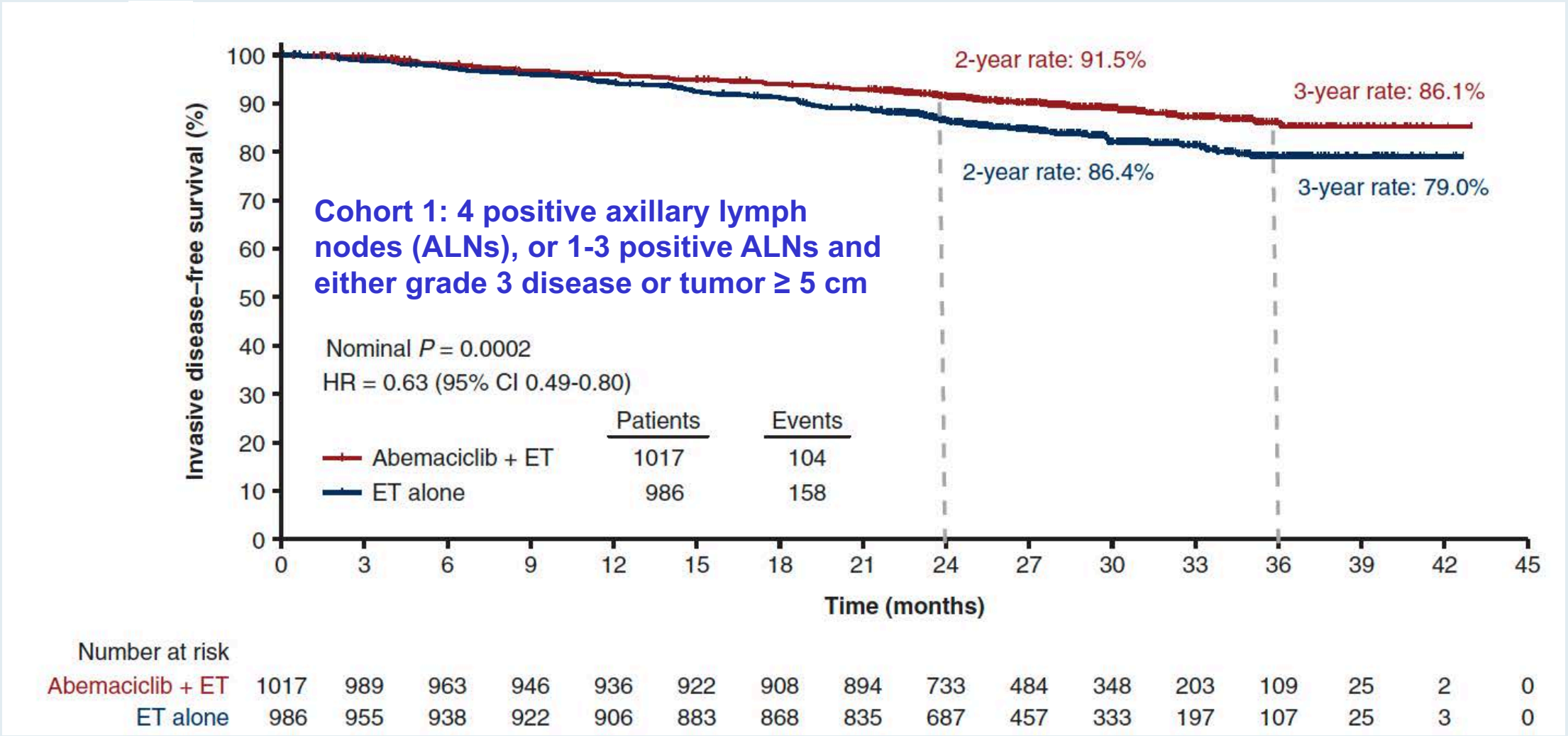
monarchE: Invasive Disease-Free Survival in the Intent-to-Treat (ITT) Population with Adjuvant Abemaciclib



Harbeck N et al. *Ann Oncol* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

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



Harbeck N et al. *Ann Oncol* 2021;[Online ahead of print].

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.

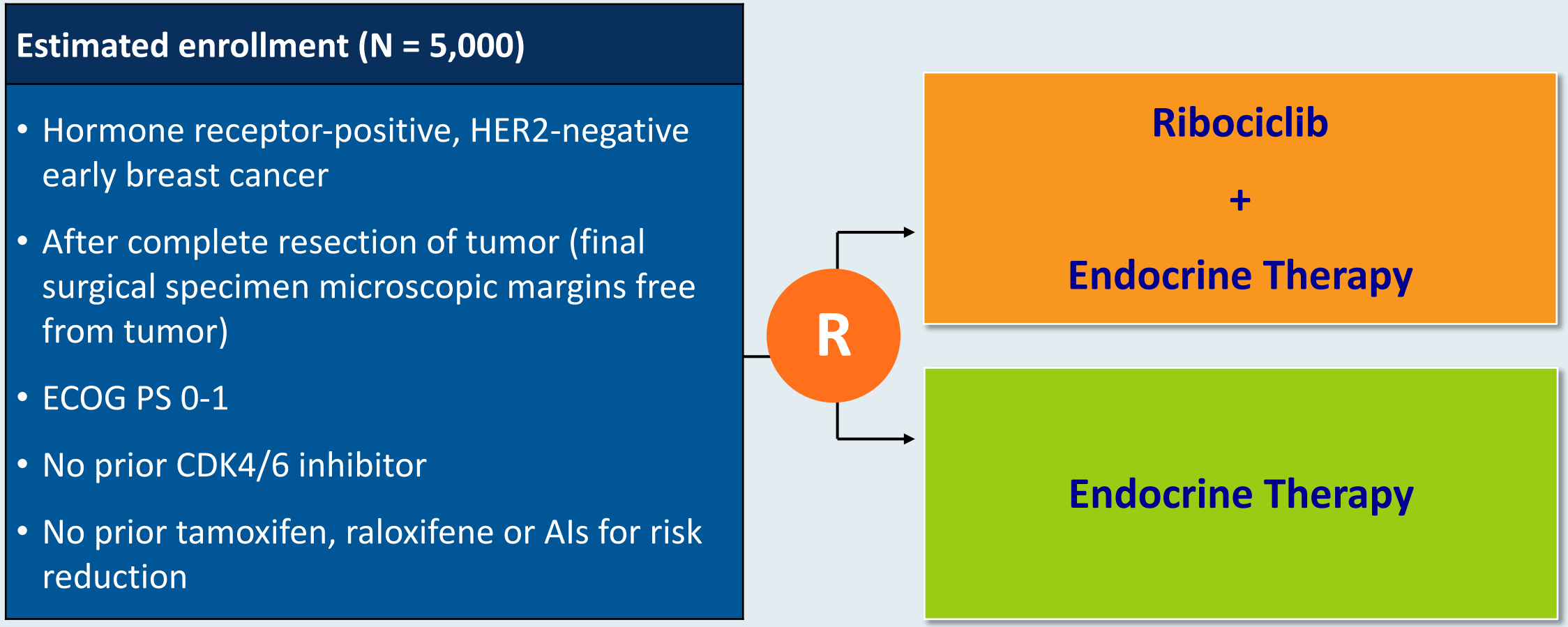
monarchE: Select Adverse Events

	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.

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;[Online ahead of print].

N Engl J Med 2021;384:2394-405

The NEW ENGLAND JOURNAL of MEDICINE

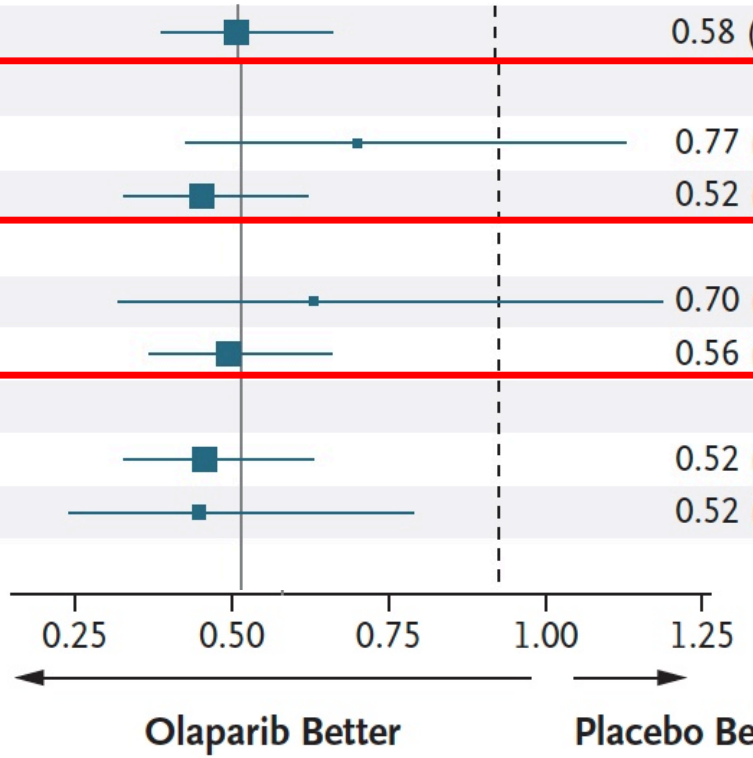
ORIGINAL ARTICLE

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*

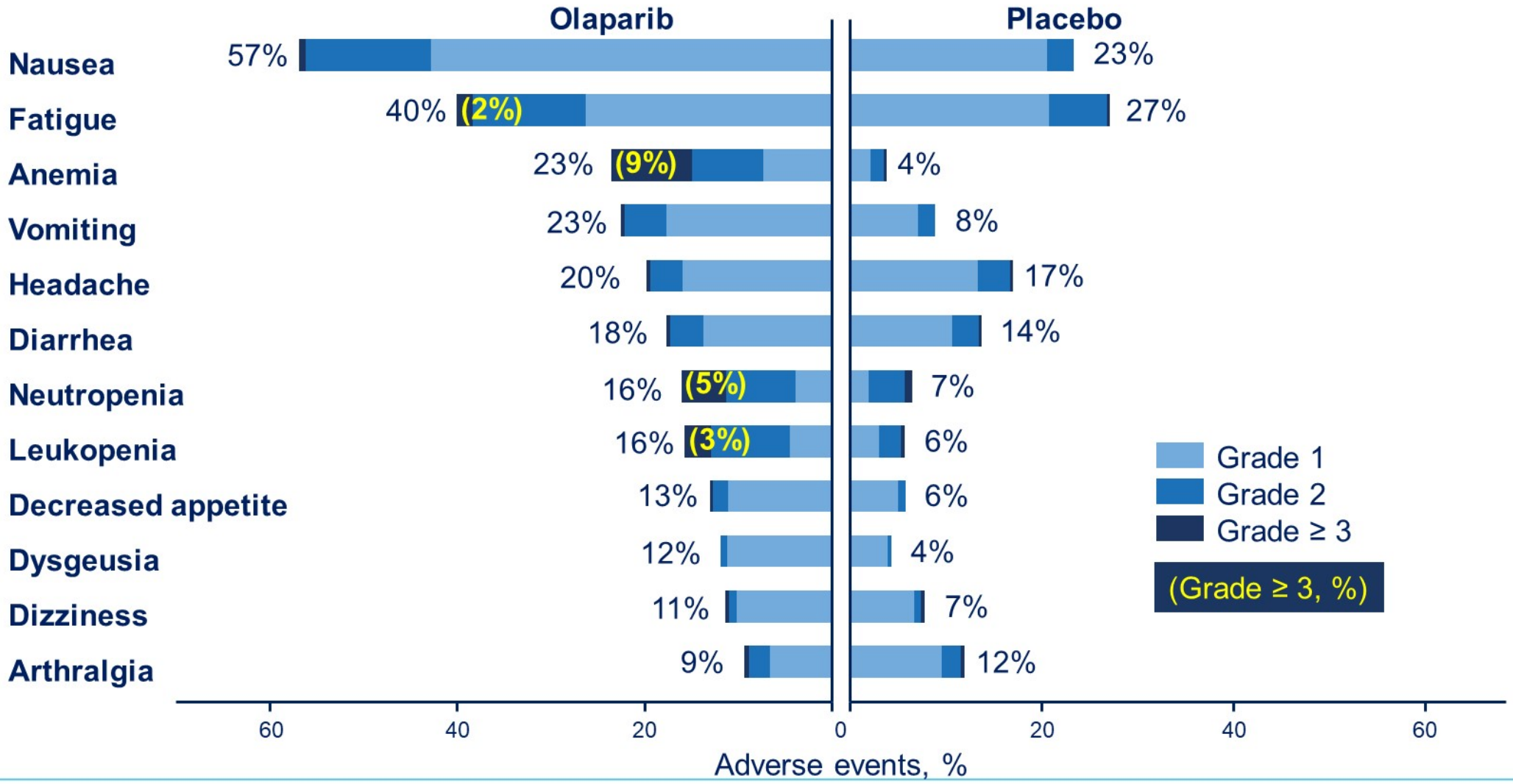
OlympiA: 3-Year Invasive DFS

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

Current Management of ER-Positive mBC

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.

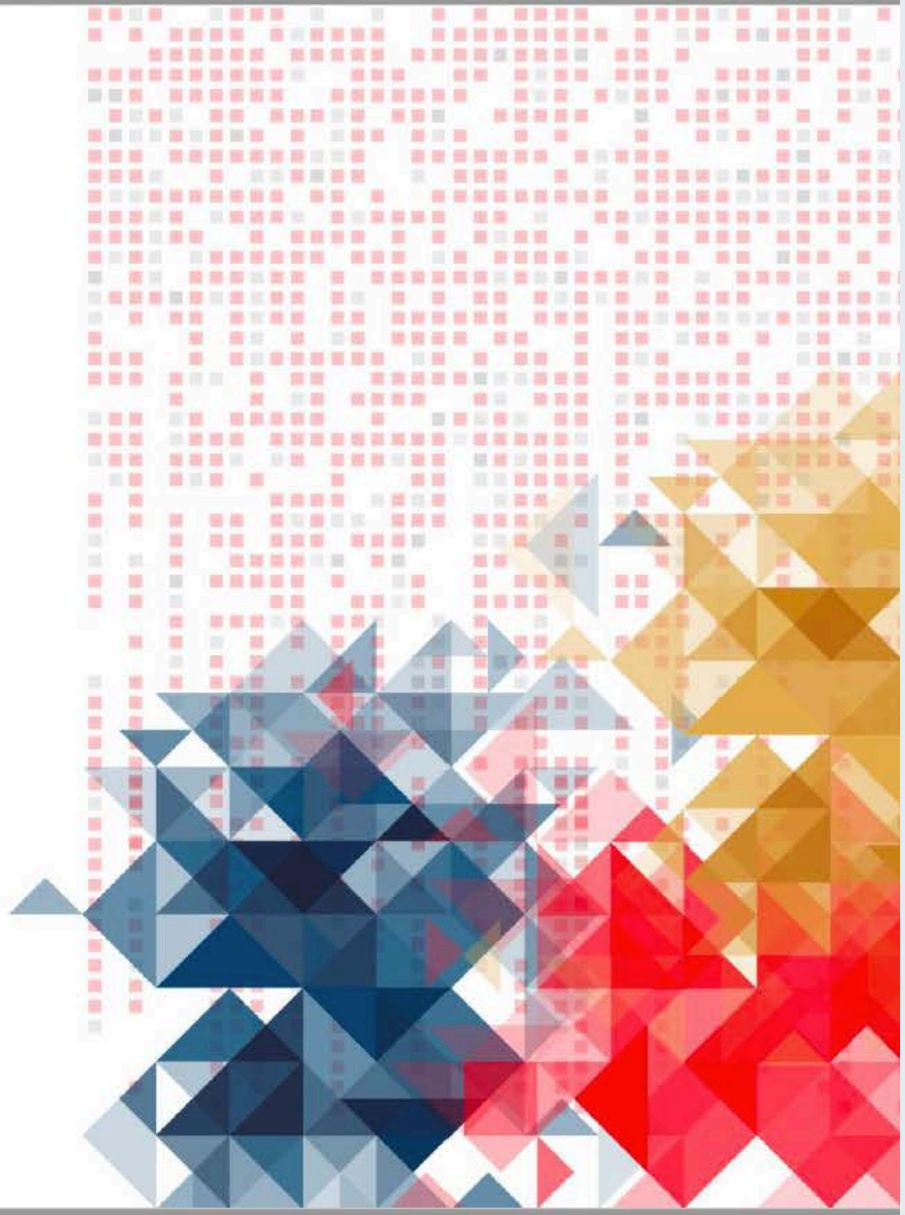
2021 ESMO congress

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

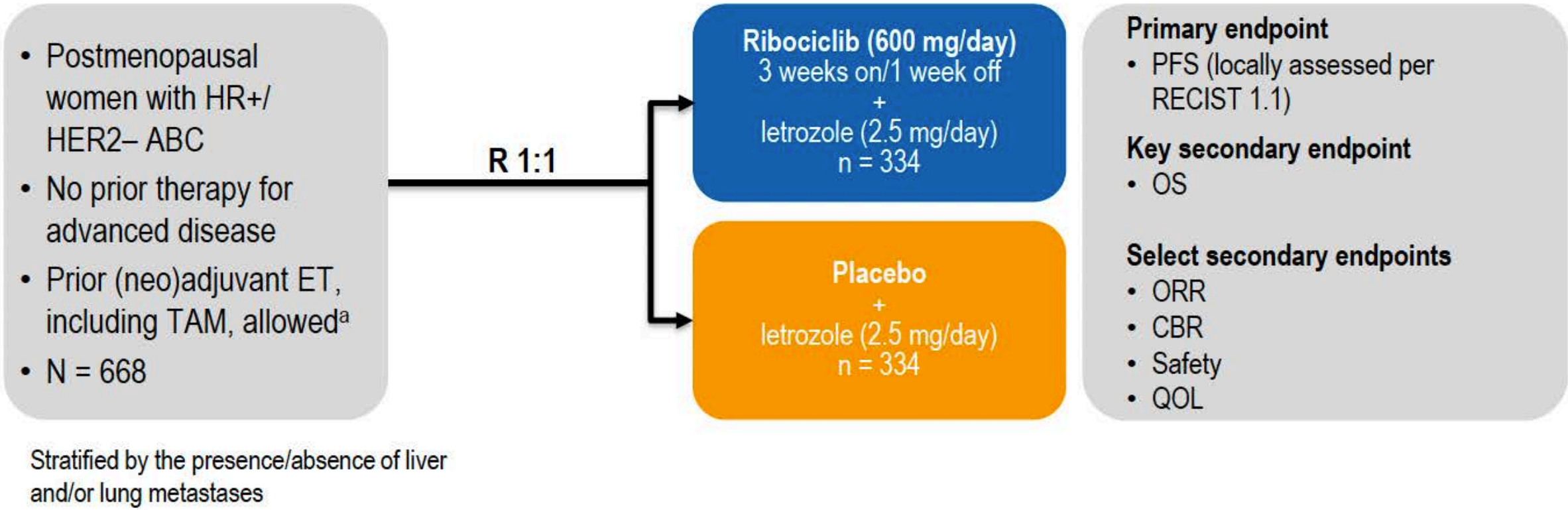
Gabriel N. Hortobagyi,[1] Salomon M. Stemmer,[2] Howard A. Burris,[3] Yoon Sim Yap,[4] Gabe Sonke,[5] Lowell Hart,[6] Mario Campone,[7] Katarina Petrakova,[8] Eric P. Winer,[9] Wolfgang Janni,[10] Pierfranco Conte,[11] David A. Cameron,[12] Fabrice André,[13] Carlos Arteaga,[14] Juan Pablo Zarate,[15]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

[1]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Institute of Oncology, Davidoff Center, Rabin Medical Center, Tel Aviv University, Tel Aviv, Israel; [3]Sarah Cannon Research Institute, Nashville, TN; [4]Department of Medical Oncology, National Cancer Centre Singapore, Singapore; [5]Medical Oncology, Netherlands Cancer Institute and BOOG Study Center, Amsterdam, the Netherlands; [6]Florida Cancer Specialists, Sarah Cannon Research Institute, Fort Myers, FL, USA; [7]Department of Medical Oncology, Institut de Cancérologie de l'Ouest/René Gauducheau, Saint-Herblain, France; [8]Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic; [9]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [10]Department of Gynecology, University of Ulm, Ulm, Germany; [11]Department of Surgery, Oncology and Gastroenterology, University of Padua and Division of Medical Oncology 2, Istituto Oncologico Veneto, IRCCS, Padua, Italy; [12]Edinburgh Cancer Research Centre, Institute of Genomics and Cancer, University of Edinburgh, Edinburgh, UK; [13]Department of Medical Oncology, Institut Gustave Roussy, Medical School, Université Paris Saclay, Villejuif, France; [14] UT Southwestern Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; [15]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [16]Novartis Pharma AG, Basel, Switzerland; [17]Baylor University Medical Center, Texas Oncology, US ONCOLOGY, Dallas, TX



RTP RESEARCH TO PRACTICE

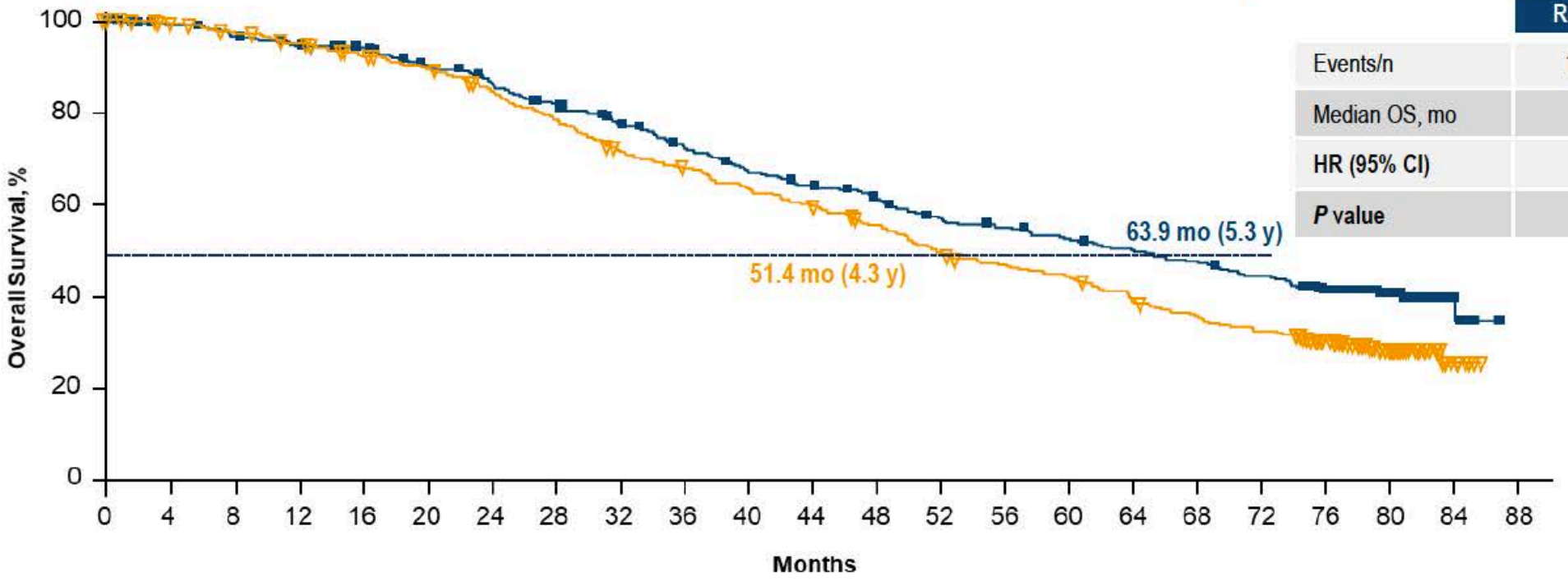
MONALEESA-2 Study Design



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



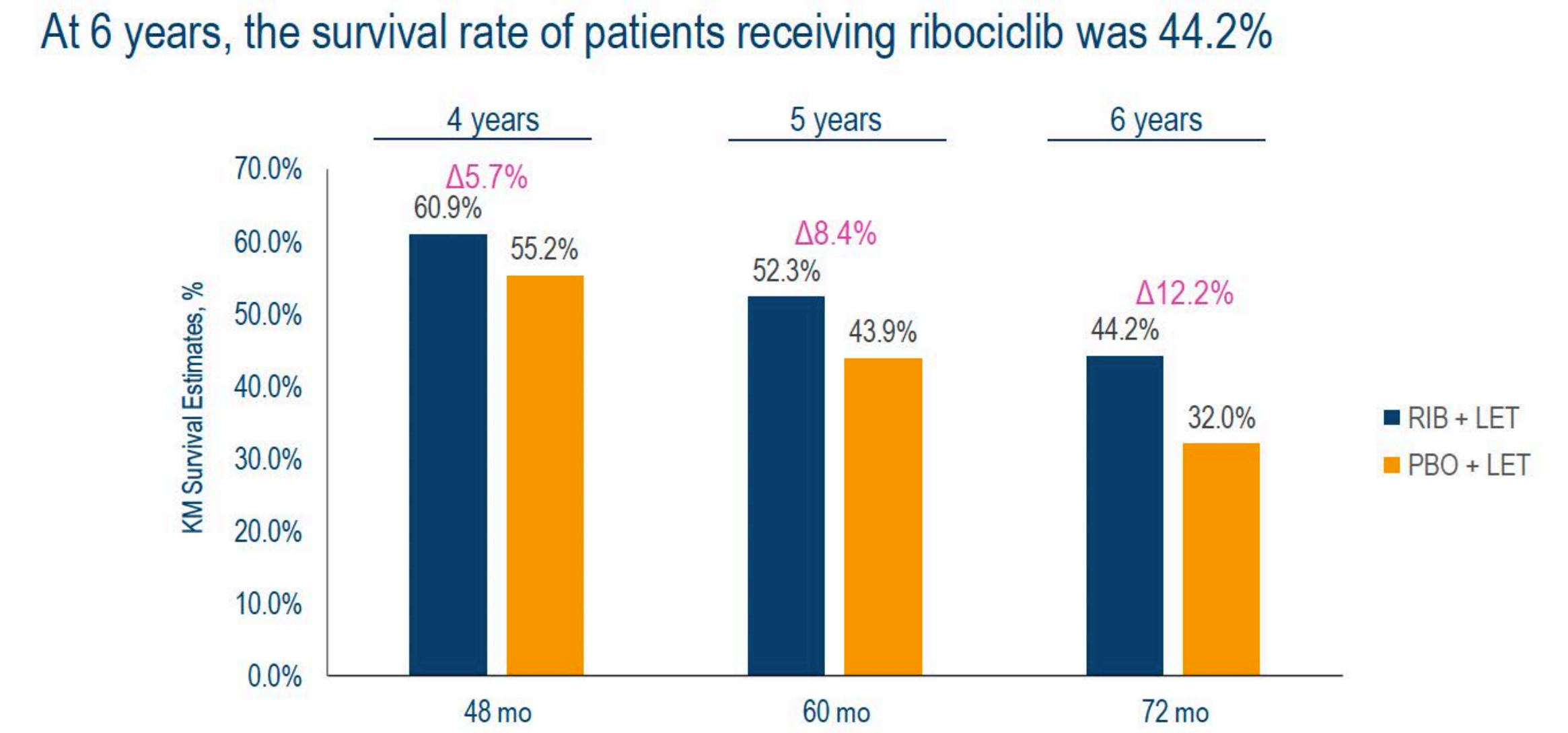
	RIB + LET	PBO + LET
Events/n	181/334	219/334
Median OS, mo	63.9	51.4
HR (95% CI)	0.76 (0.63-0.93)	
P value	.004	

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

Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

RTP RESEARCH TO PRACTICE

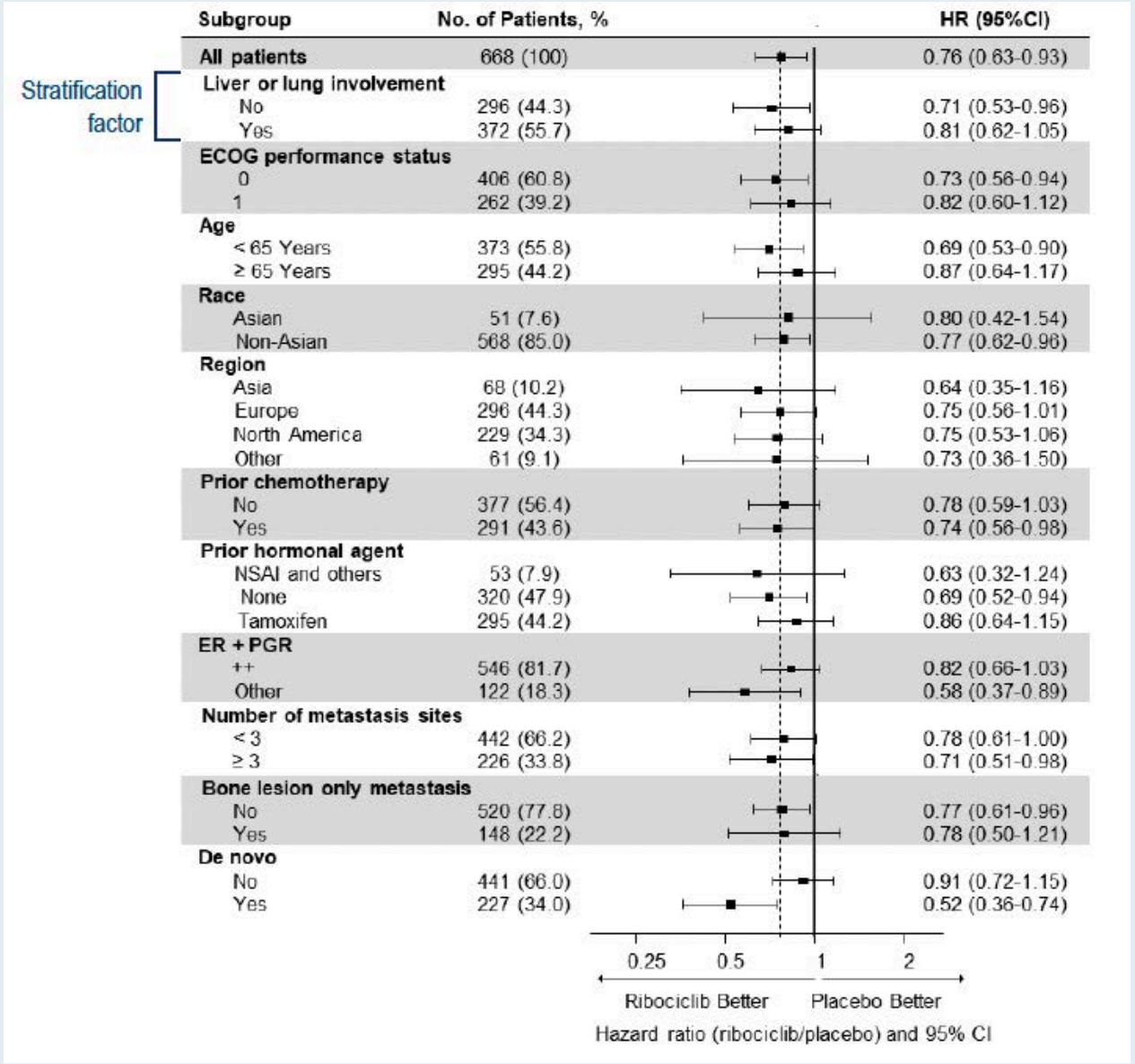
MONALEESA-2: The Overall Survival Benefit Increased Over Time



Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

RTP RESEARCH TO PRACTICE

MONALEESA-2: OS Benefit Across Key Subgroups



Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

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.

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

Press Release – September 19, 2021

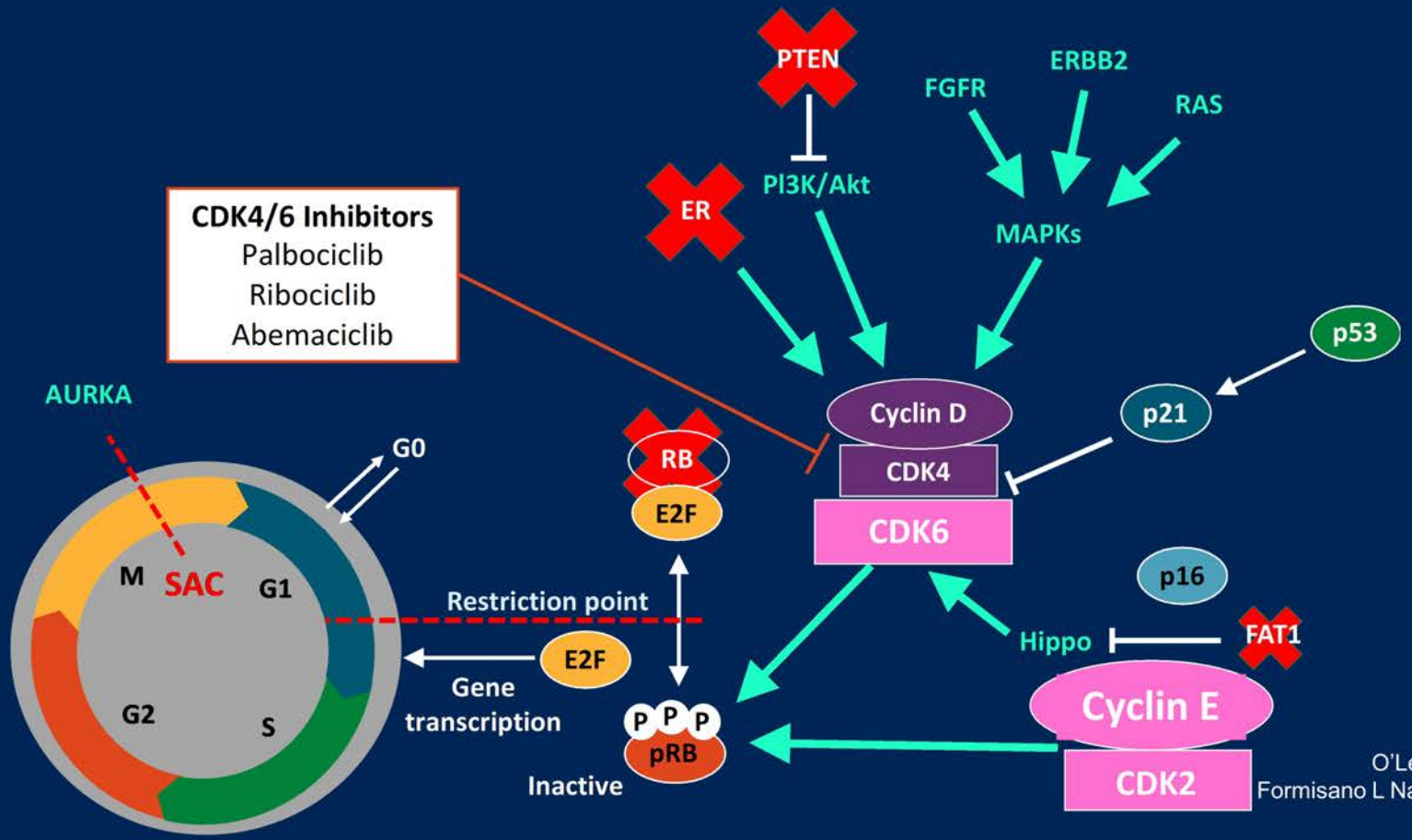
"HARMONIA, an international, randomized, Phase III, multicenter, open-label study of ribociclib versus palbociclib, both in combination with endocrine therapy, in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced or metastatic breast cancer 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

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

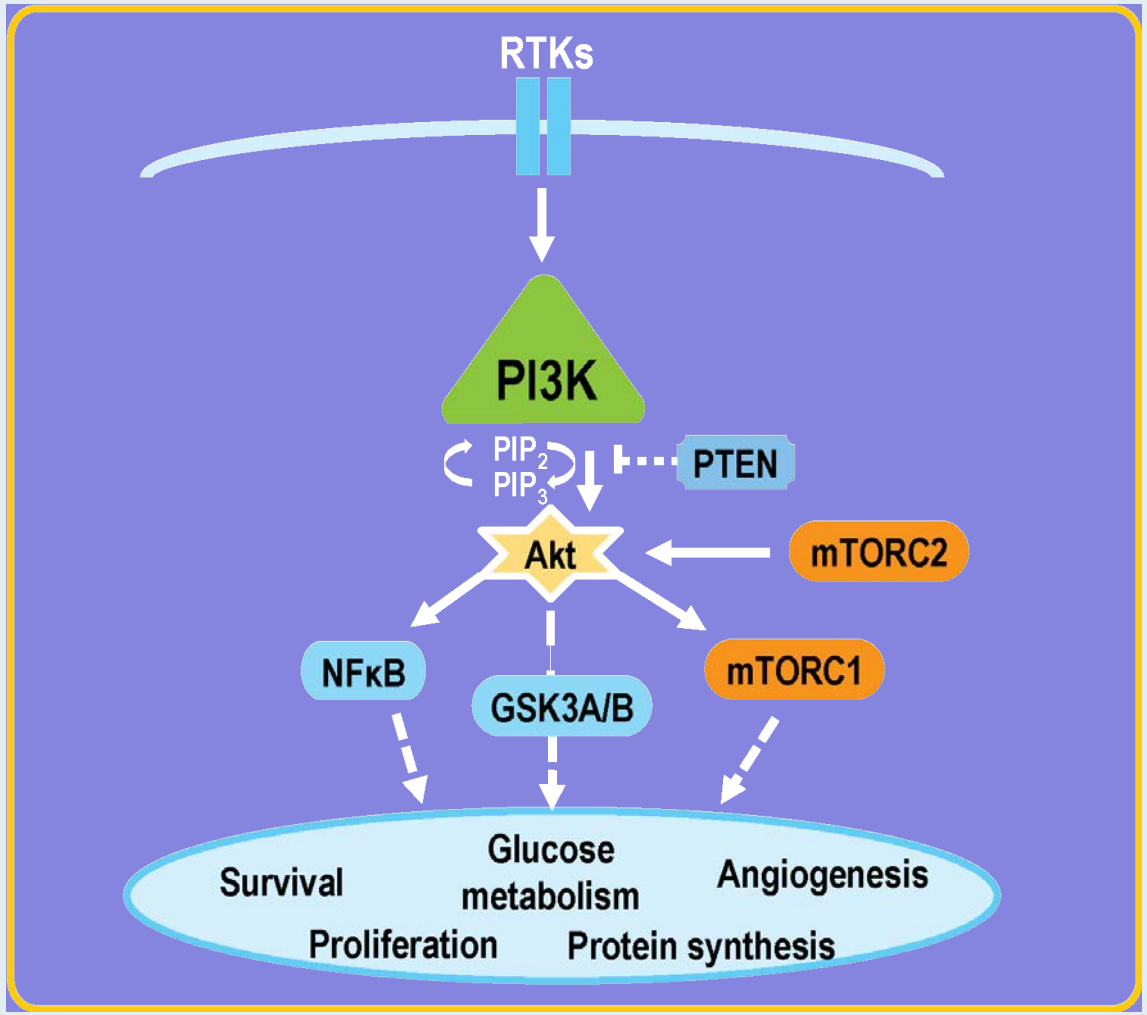
Ongoing Studies of CDK4/6 Inhibitor After Disease Progression on a CDK4/6 Inhibitor for mBC

- **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.

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]

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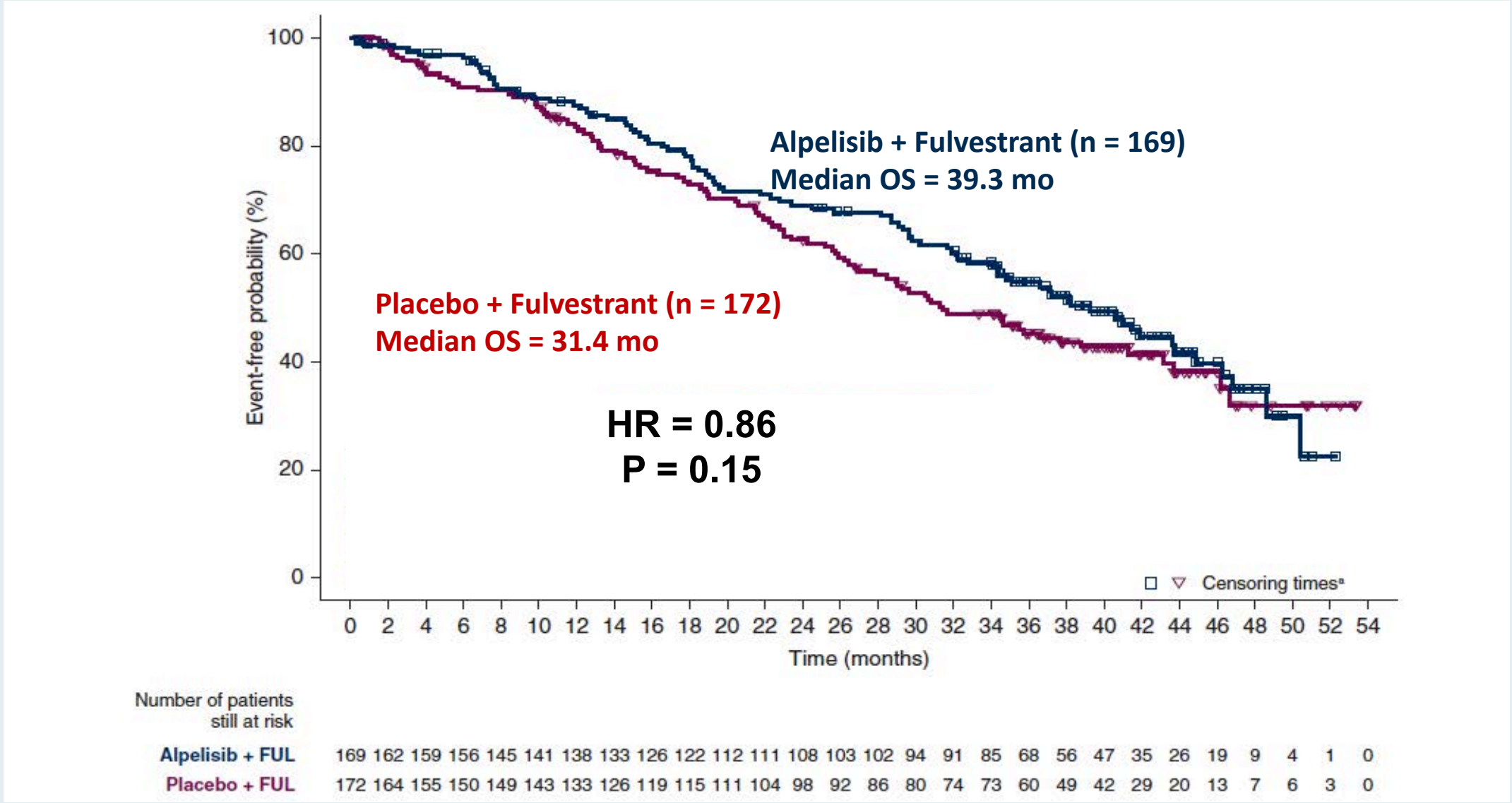
Available online 25 November 2020

***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

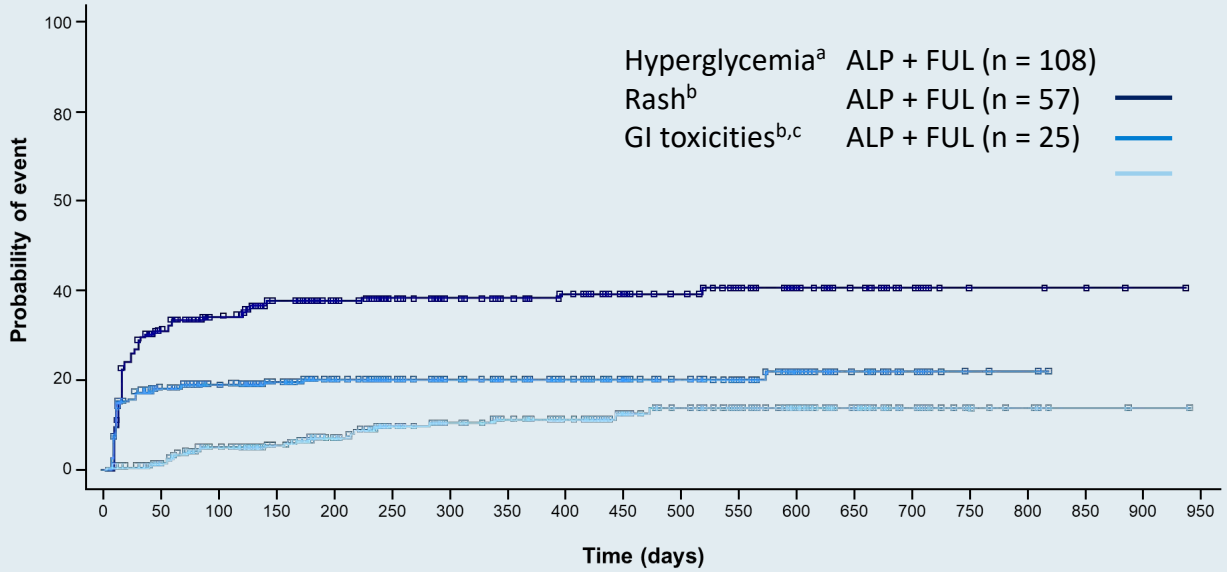
Adverse Event	Alpelisib–Fulvestrant Group (N = 284)			Placebo–Fulvestrant Group (N = 287)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	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)

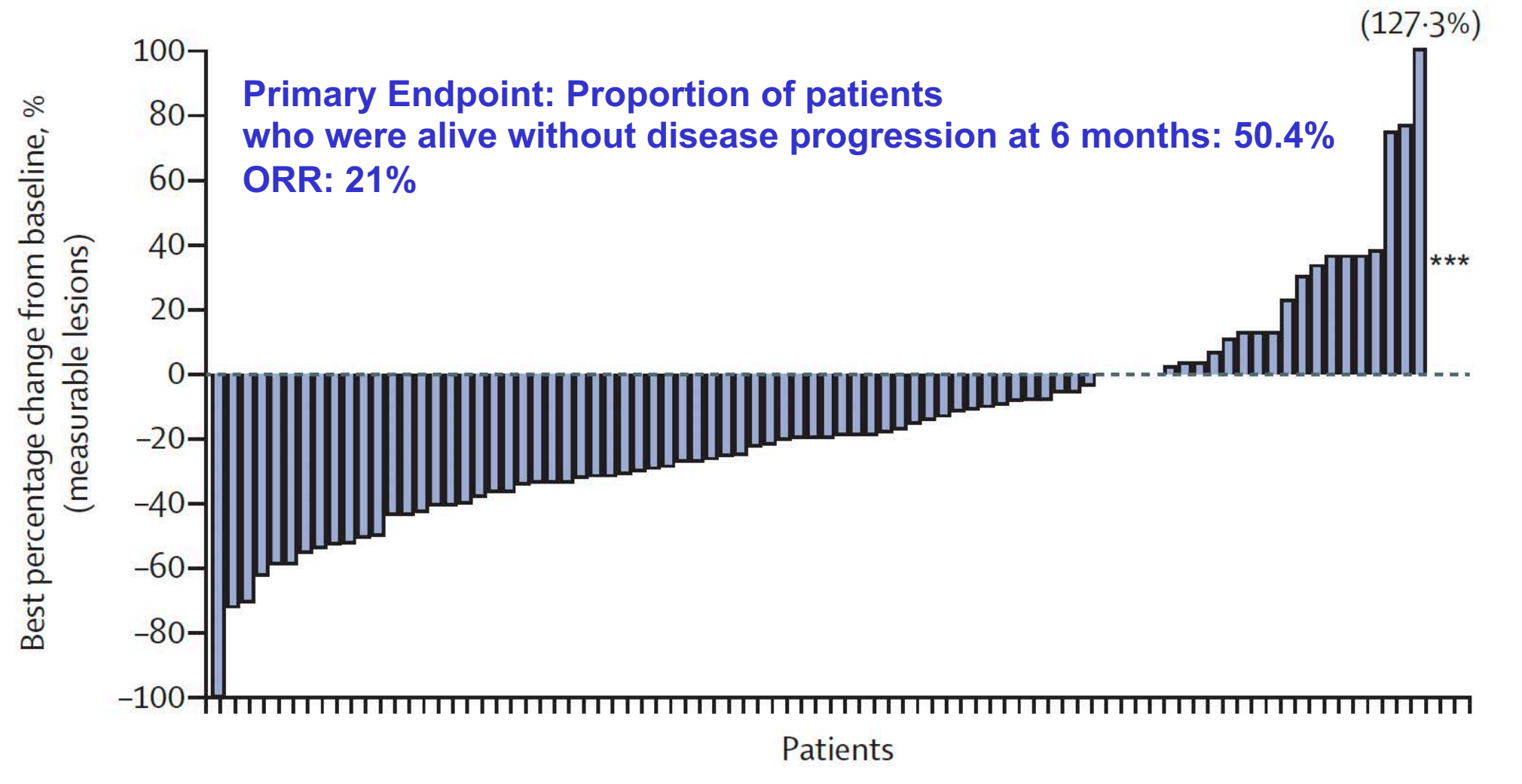
- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

[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.

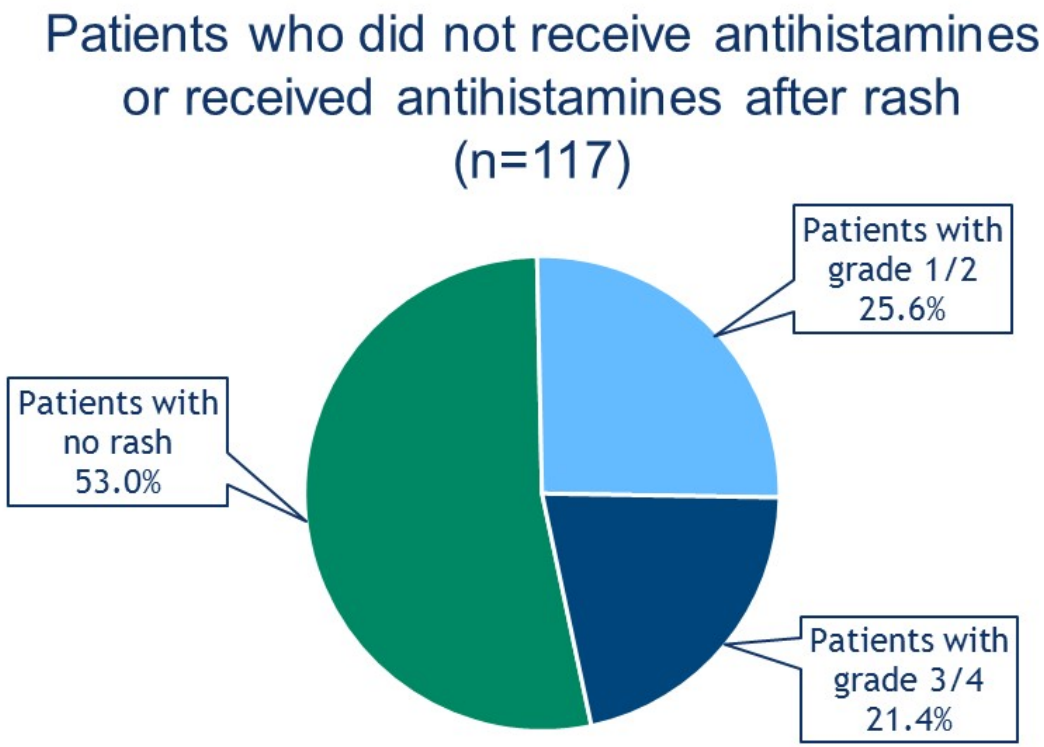
RTP RESEARCH TO PRACTICE

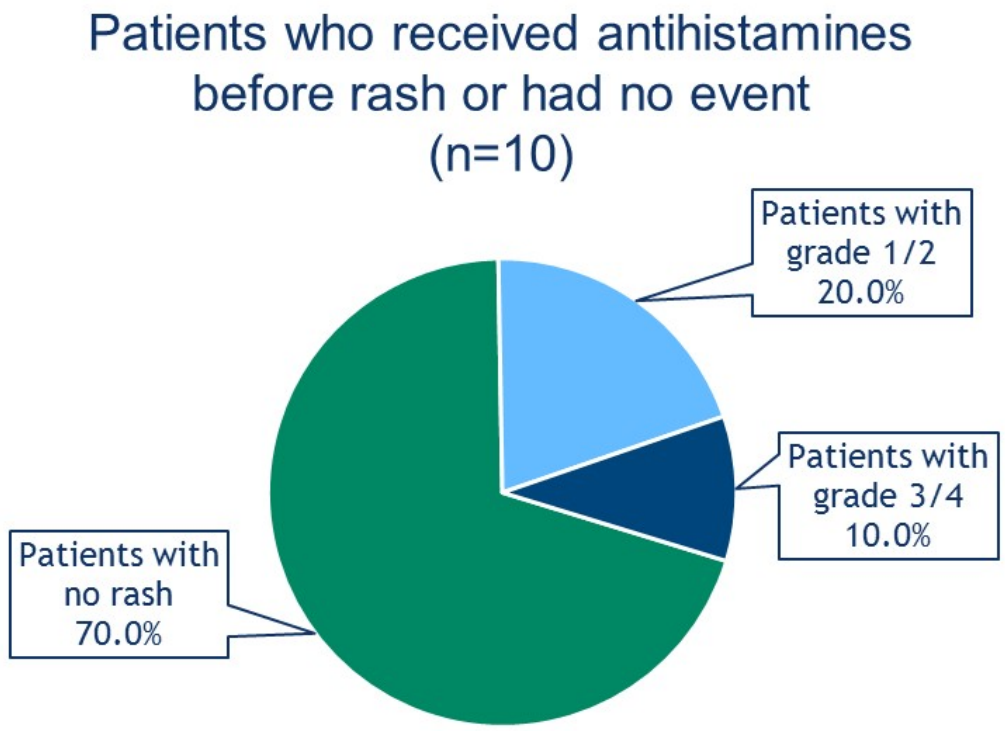
BYLieve Efficacy Outcomes



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

BYLieve: Incidence of Rash with and without Prophylactic Antihistamines





Rugo HS et al. ASCO 2020;Abstract 1006.

RTP RESEARCH TO PRACTICE

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

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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
Elacestrant (RAD-1901)	EMERALD (Phase III)	• Elacestrant • SoC	Prior CDK4/6 inhibitor tx + fulvestrant or AI	August 2022
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

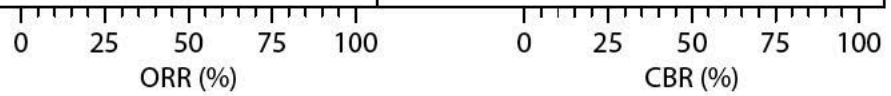
AMEERA-1: Subgroup Analyses of Phase 1/2 Study of Amcenestrant (SAR439859), an Oral Selective Estrogen Receptor (ER) Degrader (SERD), with Palbociclib in Postmenopausal Women with ER+/Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Advanced Breast Cancer (aBC)

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.

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

Meet The Professor

Current and Future Role of Immunotherapy in the Management of Lung Cancer

Thursday, November 18, 2021
5:00 PM – 6:00 PM ET

Faculty

Stephen V Liu, MD

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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