What I Tell My Patients:
Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Fifteenth Annual RTP Symposium Series Held During the Annual ONS Congress

Breast Cancer

Wednesday, April 26, 2023
6:00 PM – 8:00 PM

Faculty

Jamie Carroll, APRN, MSN, CNP
Virginia Kaklamani, MD, DSc
Joyce O'Shaughnessy, MD
Ronald Stein, JD, MSN, NP-C, AOCNP

Moderator

Neil Love, MD

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Faculty

Jamie Carroll, APRN, MSN, CNP
Mayo Clinic
Rochester, Minnesota

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

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

Ronald Stein, JD, MSN, NP-C, AOCNP
Clinical Instructor of Medicine
USC Norris Comprehensive Cancer Center
Los Angeles, California

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Ms Carroll — Disclosures

Advisory Committee	Lilly, Pfizer Inc, Sanofi, Sermonix Pharmaceuticals

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Dr Kaklamani — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Puma Biotechnology Inc, TerSera Therapeutics LLC
Contracted Research	Eisai Inc
Data and Safety Monitoring Board/Committee	Bristol-Myers Squibb Company
Speakers Bureau	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Exact Sciences Corporation, Genentech, a member of the Roche Group, Gilead Sciences Inc, Novartis, Pfizer Inc, Seagen Inc

Dr O'Shaughnessy — Disclosures

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

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Mr Stein — Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Exact Sciences Corporation, Lilly, Merck, Puma Biotechnology Inc, Seagen Inc, and TerSera Therapeutics LLC.

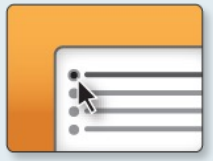
Research To Practice NCPD Planning Committee Members, Staff and Reviewers

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

Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

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

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

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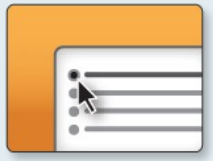
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

Get NCPD Credit: An NCPD credit link will be provided in the chat room at the conclusion of the program.

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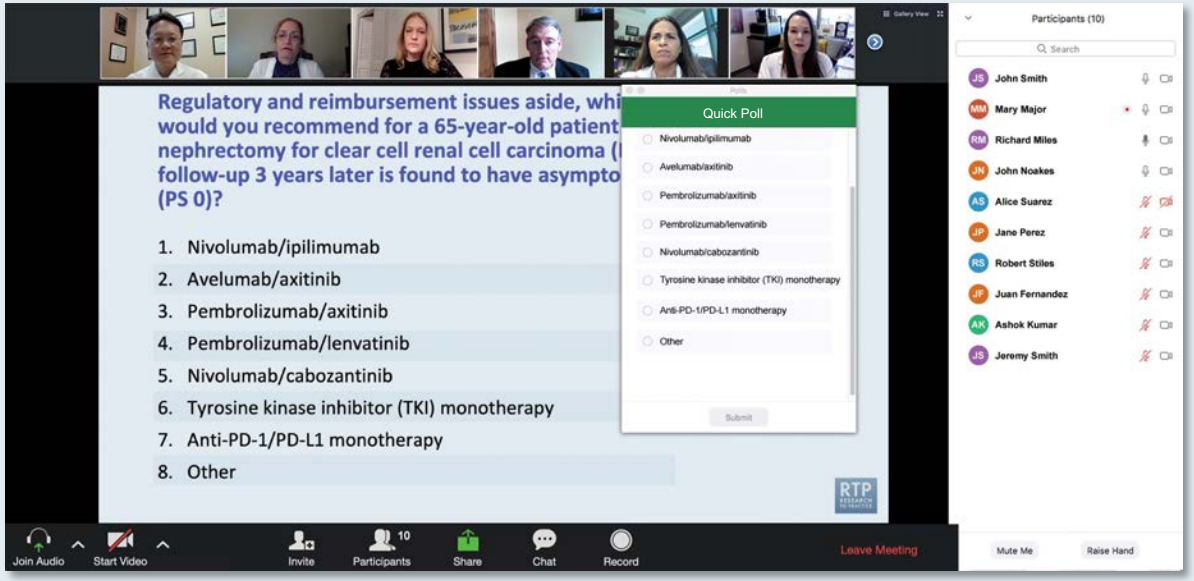
Clinicians, Please Complete the Pre- and Postmeeting Surveys



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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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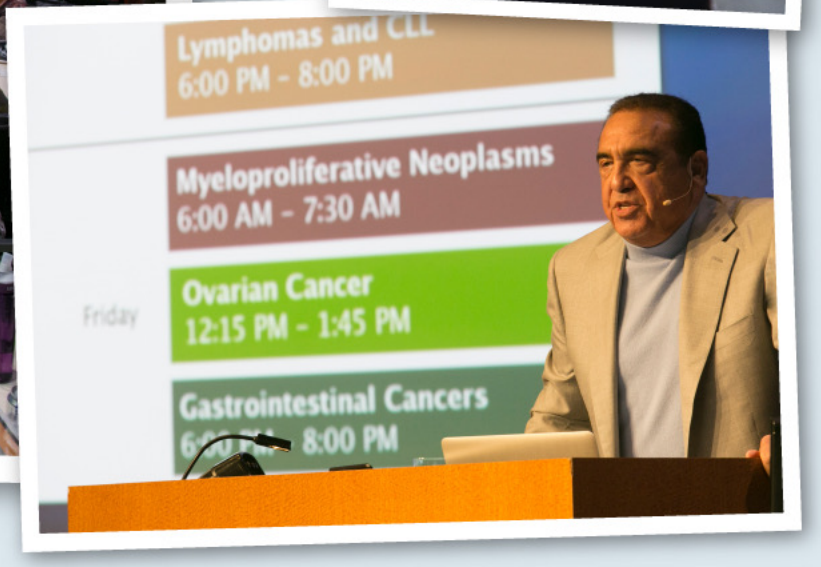
What I Tell My Patients

2009-2023

85 Symposia 355 Faculty



“What I Tell My Patients”
Fifteenth Annual RTP-ONS NCPD Symposium Series
ONS Congress, San Antonio, Texas — April 26 to 29, 2023

Wednesday April 26	**Cervical and Endometrial Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Breast Cancer 6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)
Thursday April 27	**Diffuse Large B-Cell Lymphoma** 6:00 AM – 7:30 AM CT (7:00 AM – 8:30 AM ET)
	Chronic Lymphocytic Leukemia 12:15 PM – 1:45 PM CT (1:15 PM – 2:45 PM ET)
	HER2-Targeted Antibody-Drug Conjugates 6:00 PM – 7:30 PM CT (7:00 PM – 8:30 PM ET)
Friday April 28	**Hepatobiliary Cancers** 6:00 AM – 7:30 AM CT (7:00 AM – 8:30 AM ET)
	Ovarian Cancer 12:15 PM – 1:45 PM CT (1:15 PM – 2:45 PM ET)
	Lung Cancer 6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)
Saturday April 29	**Acute Myeloid Leukemia, Myelodysplastic Syndromes and Myelofibrosis** 6:00 AM – 7:30 AM CT (7:00 AM – 8:30 AM ET)
	Prostate Cancer 12:15 PM – 1:45 PM CT (1:15 PM – 2:45 PM ET)

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Cervical and Endometrial Cancer Faculty

Paula J Anastasia, MN, RN, AOCN
GYN Oncology Patient-Nurse Educator
Los Angeles, California

Jennifer Filipi, MSN, NP
Department of Gynecologic Oncology
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

Michael J Birrer, MD, PhD
Vice Chancellor, UAMS
Director, Winthrop P Rockefeller Cancer Institute
Director, Cancer Service Line
Professor of Biochemistry and Molecular Biology
Director's Endowed Chair for the Winthrop
P Rockefeller Cancer Institute
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Brian M Slomovitz, MD
Professor, OB-GYN, Florida International University
Director, Gynecologic Oncology
Co-Chair, Cancer Research Committee
Mount Sinai Medical Center
Miami, Florida

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Breast Cancer Faculty

Jamie Carroll, APRN, MSN, CNP
Mayo Clinic
Rochester, Minnesota

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

Virginia Kaklamani, MD, DSc
Professor of Medicine
Ruth McLean Bowman Bowers Chair in Breast Cancer Research and Treatment
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San Antonio, Texas

Ronald Stein, JD, MSN, NP-C, AOCNP
Clinical Instructor of Medicine
USC Norris Comprehensive Cancer Center
Los Angeles, California

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Diffuse Large B-Cell Lymphoma Faculty

Christopher R Flowers, MD, MS
Chair, Professor
Department of Lymphoma/Myeloma
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Robin Klebig, APRN, CNP, AOCNP
Hematology Outpatient APP Supervisor
Assistant Professor of Medicine
Nurse Practitioner, Lymphoma Group
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Amy Goodrich, CRNP
Nurse Practitioner
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Johns Hopkins Medicine
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Matthew Lunning, DO
Associate Professor
Medical Director, Cellular Therapy
Assistant Vice Chair of Research, Department of Medicine
Assistant Vice Chancellor for Clinical Research
Fred and Pamela Buffett Cancer Center
University of Nebraska Medical Center
Omaha, Nebraska

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Chronic Lymphocytic Leukemia Faculty

John N Allan, MD
Associate Professor of Clinical Medicine
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New York, New York

Corinne Hoffman, MS, APRN-CNP, AOCNP
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The James Comprehensive Cancer Center
The Ohio State University Wexner Medical Center
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Adam S Kittai, MD
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The Ohio State University
The OSUCCC – James
Columbus, Ohio

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HER2-Targeted Antibody-Drug Conjugates Faculty

Lyudmila A Bazhenova, MD
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Lung Cancer Unit Leader
Director, Hematology and Oncology Fellowship Training Program
UC San Diego Moores Cancer Center
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Thoracic Cancer Center
Massachusetts General Hospital
Boston, Massachusetts

Virginia Kaklamani, MD, DSc
Professor of Medicine
Ruth McLean Bowman Bowers Chair in Breast Cancer Research and Treatment
AB Alexander Distinguished Chair in Oncology
Leader, Breast Oncology Program
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San Antonio, Texas

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MD Anderson Cancer Center
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Zev Wainberg, MD, MSc
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Los Angeles, California

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Hepatobiliary Cancers Faculty

Ahmed Omar Kaseb, MD, CMQ
John E and Dorothy J Harris Professor in
Gastrointestinal Cancer Research
Member, National Hepatobiliary Task Force, NCI, USA
Tenured Professor and Director, Hepatocellular
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Director, MD Anderson HCC SPORE
Editor-in-Chief, Journal of Hepatocellular Carcinoma
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UCLA Health
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Amanda K Wagner, APRN-CNP, AOCNP
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The Ohio State University
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Ovarian Cancer Faculty

Courtney Arn, CNP
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Richard T Penson, MD, MRCP
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Jaclyn Shaver, MS, APRN, CNP, WHNP
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OU Health
Oklahoma City, Oklahoma

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Lung Cancer Faculty

Stephen V Liu, MD
Associate Professor of Medicine
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Nurse Practitioner
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Chief Academic Office
Professor, Thoracic/Head and Neck Medical Oncology
Director, Mesothelioma Program
The University of Texas
MD Anderson Cancer Center
Houston, Texas

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Acute Myeloid Leukemia, Myelodysplastic Syndromes and Myelofibrosis Faculty

Ilene Galinsky, NP
Senior Adult Leukemia Program Research
Nurse Practitioner
Dana-Farber Cancer Institute
Boston, Massachusetts

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Clinical Director of Leukemia Services
Associate Chief of Clinical Affairs
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Executive Director
Mays Cancer Center at UT Health San Antonio
MD Anderson Cancer Center
Mays Family Foundation Distinguished
University Presidential Chair
Professor of Medicine
San Antonio, Texas

Sara M Tinsley-Vance, PhD, APRN, AOCN
Nurse Practitioner and Researcher
Malignant Hematology
Moffitt Cancer Center
Tampa, Florida

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Prostate Cancer Faculty

Neeraj Agarwal, MD, FASCO
Professor of Medicine
Senior Director for Clinical Research Innovation
Huntsman Cancer Institute Presidential Endowed Chair of Cancer Research
Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
Huntsman Cancer Institute, University of Utah (NCI-CCC)
Salt Lake City, Utah

Susan K Roethke, MSN, CRNP, AOCNP, ANP-BC
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Fox Chase Cancer Center
Philadelphia, Pennsylvania

Kathy D Burns, RN, MSN, AGACNP-BC, OCN
Genitourinary Medical Oncology
City of Hope Comprehensive Cancer Center
Duarte, California

Sandy Srinivas, MD
Professor of Oncology
Clinical Research Leader, GU Oncology
Stanford University
Stanford, California

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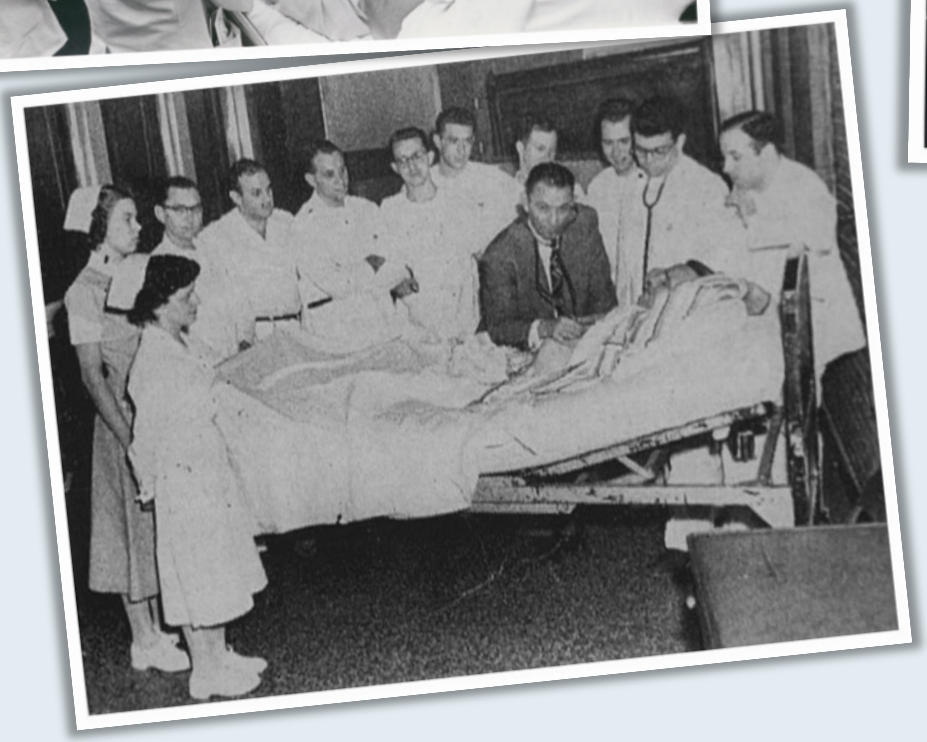

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The Core Oncology Triad
Developing an Individualized Oncology Strategy

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What I Tell My Patients

2023 ONS Congress

San Antonio, Texas

Symposia Themes

- New agents and therapies; ongoing trials related to specific clinical scenarios
- Patient education: Preparing to receive new therapies
- The bond that heals
- THANKS! (Great job)

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How was it different to take care of this patient versus another patient in the same oncologic setting?

What unique biopsychosocial factors (eg, attitude, comorbidities, social support) were considered in the overall management of this case?

ONS 2023 Playlist

ONS Cervical and Endometrial Cancer
Almost Cut My Hair — **Crosby, Stills, Nash & Young**
Still the Same — **Bob Seger & The Silver Bullet Band**
Beautiful Day — **U2**
Victim of Love — **Eagles**
ONS Breast Cancer
Jane — **Jefferson Starship**
Gimme Shelter — **The Rolling Stones**
Rock and Roll Music — **The Beatles**
Everybody I Love You — **Crosby, Stills, Nash & Young**
ONS Diffuse Large B-Cell Lymphoma
Suite: Judy Blue Eyes — **Crosby, Stills, Nash & Young**
Straight On — **Heart**
Clocks — **Coldplay**
Boom, Like That — **Mark Knopfler**

https://www.researchtopractice.com/ONS2023/Playlist

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ONS 2023 Playlist

ONS Chronic Lymphocytic Leukemia
A Message — **Coldplay**
Sit Yourself Down — **Stephen Stills**
Jammin' Me — **Tom Petty and The Heartbreakers**
Carry On — **Crosby, Stills, Nash & Young**
ONS HER2-Targeted Antibody-Drug Conjugates
Good Vibrations — **The Beach Boys**
Simple Man — **Bad Company**
Yellow — **Coldplay**
The Walker — **Fitz and The Tantrums**
ONS Hepatobiliary Cancers
One — **Creed**
Like Water — **Bad Company**
Bitter Sweet Symphony — **The Verve**
Live for the Music — **Bad Company**

https://www.researchtopractice.com/ONS2023/Playlist

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ONS 2023 Playlist

ONS Ovarian Cancer
Blue on Black — **Kenny Wayne Shepherd Band**
Come as You Are — **Nirvana**
Feel Like a Number — **Bob Seger & The Silver Bullet Band**
To Live and Die in L.A. — **Wang Chung**
ONS Lung Cancer
Girl on the Moon — **Foreigner**
Small Town Trap — **Eve 6**
City of Blinding Lights — **U2**
Brass in Pocket — **The Pretenders**
ONS Acute Myeloid Leukemia, Myelodysplastic Syndromes and Myelofibrosis
Little Queen — **Heart**
She's Long Gone — **The Black Keys**
I Won’t Back Down — **Tom Petty**
Magic — **The Cars**

https://www.researchtopractice.com/ONS2023/Playlist

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ONS 2023 Playlist

ONS Prostate Cancer
Burnin’ Sky — **Bad Company**
Heartbroken, in Disrepair — **Dan Auerbach**
In My Place — **Coldplay**
Learn to Fly — **Foo Fighters**

https://www.researchtopractice.com/ONS2023/Playlist

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Moderator

Neil Love, MD

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Clinical Instructor of Medicine
USC Norris Comprehensive Cancer Center
Los Angeles, California

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Agenda

Module 1: ER-Positive, HER2-Negative Localized Breast Cancer — PART 1

Module 2: ER-Positive, HER2-Negative Localized Breast Cancer — PART 2

Module 3: ER-Positive Metastatic Breast Cancer

Module 4: Localized HER2-Positive Breast Cancer

Module 5: HER2-Positive and HER2-Low Metastatic Breast Cancer — PART 1

Module 6: HER2-Positive and HER2-Low Metastatic Breast Cancer — PART 2

Module 7: PARP Inhibitors

Module 8: Immune Checkpoint Inhibitors

Agenda

Module 1: ER-Positive, HER2-Negative Localized Breast Cancer — PART 1

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Module 6: HER2-Positive and HER2-Low Metastatic Breast Cancer — PART 2

Module 7: PARP Inhibitors

Module 8: Immune Checkpoint Inhibitors

Jamie Carroll, APRN, MSN, CNP

40-year-old premenopausal woman with a 6-cm node-negative, ER-positive, HER2-negative localized IDC and an Onco*type* DX® Recurrence Score® of 29

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Dr Kaklamani
San Antonio, Texas

Clinical Research Background

Dr O'Shaughnessy
Dallas, Texas

- **Current role of the 21-gene Recurrence Score (node-positive); other genomic assays**
- **Adjuvant ovarian suppression/ablation**
- **LHRH agonist for fertility and ovarian function preservation**
- **Adjuvant CDK4/6 inhibitors**

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Agenda

Module 1: ER-Positive, HER2-Negative Localized Breast Cancer — PART 1

Module 2: ER-Positive, HER2-Negative Localized Breast Cancer — PART 2

Module 3: ER-Positive Metastatic Breast Cancer

Module 4: Localized HER2-Positive Breast Cancer

Module 5: HER2-Positive and HER2-Low Metastatic Breast Cancer — PART 1

Module 6: HER2-Positive and HER2-Low Metastatic Breast Cancer — PART 2

Module 7: PARP Inhibitors

Module 8: Immune Checkpoint Inhibitors

Ronald Stein, JD, MSN, NP-C, AOCNP

47-year-old woman with a node-positive, ER-positive, HER2-negative localized IDC who received adjuvant abemaciclib

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Dr Kaklamani
San Antonio, Texas

Clinical Research Background

Dr O'Shaughnessy
Dallas, Texas

- **Current role of the 21-gene Recurrence Score (node-positive); other genomic assays**
- **Adjuvant ovarian suppression/ablation**
- **LHRH for fertility and ovarian function preservation**
- **Adjuvant CDK4/6 inhibitors**

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Genomic Assays

Available assays

- Onco*type* DX
- MammaPrint
- Prosigna
- PAM50
- Breast Cancer Index

Key issues

- Benefit of adding chemotherapy to endocrine therapy for premenopausal and postmenopausal patients

Ovarian Function Suppression

Available agents

- Goserelin (FDA-approved)
- Leuprolide
- Triptorelin

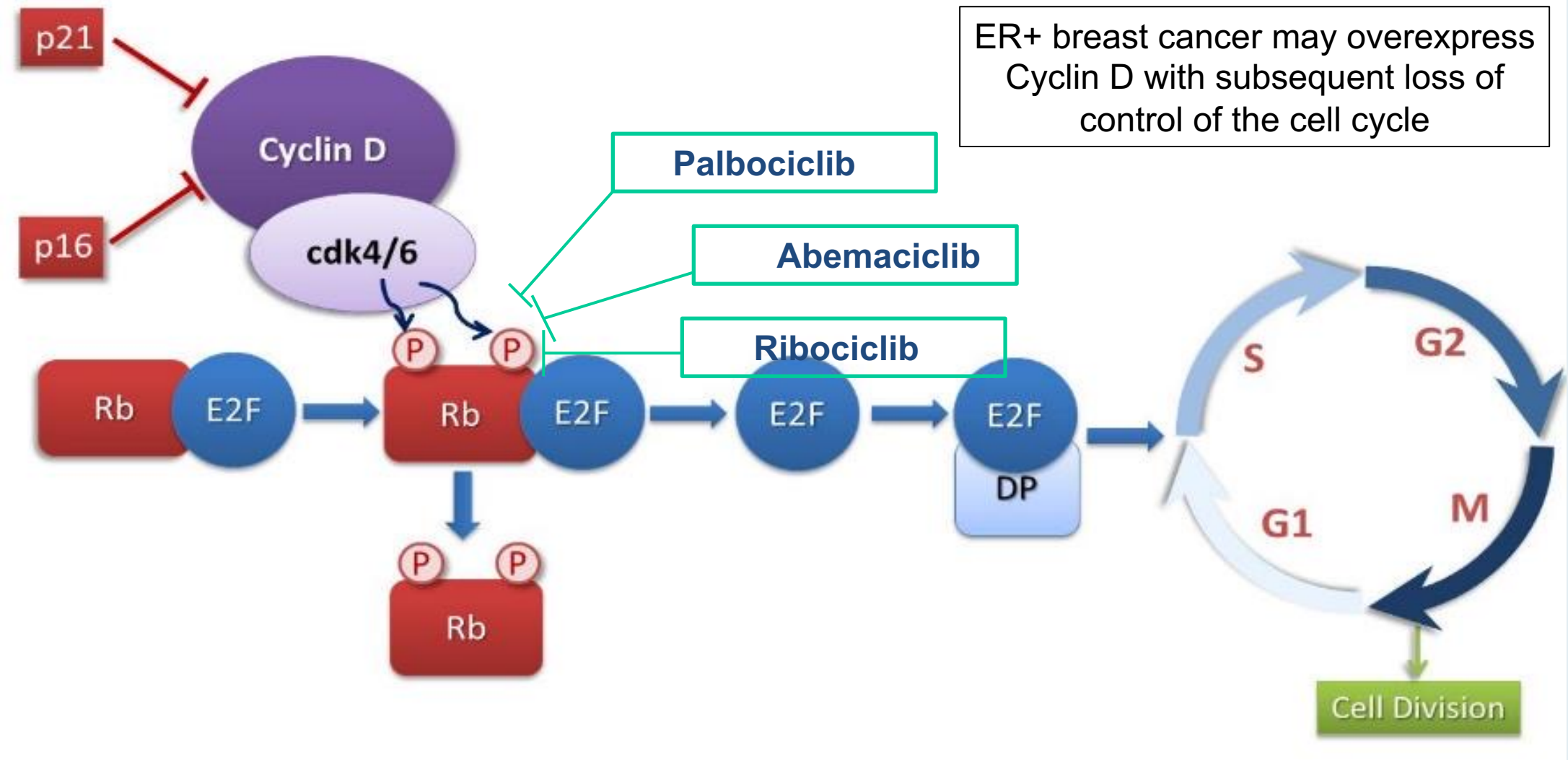
Mechanism of action

- Prevents the ovaries from producing estrogen

Key Issues

- Adjuvant treatment for pre- and perimenopausal women
- Timing of initiation (At least one week prior to chemotherapy)
- Duration of therapy

CDK4/6 Regulates Cell Cycle Progression



Adapted from Finn et al, 2016.

CDK4/6 Inhibitors

Agent	Current indications and usage in ER-positive, HER2-negative BC
Palbociclib	• With an AI as initial endocrine-based therapy for metastatic disease • With fulvestrant after disease progression on ET for metastatic disease
Ribociclib	• With an AI as initial endocrine-based therapy for metastatic disease • With fulvestrant as initial endocrine-based therapy or after disease progression on ET for postmenopausal women or men with metastatic disease
Abemaciclib	• **With ET as adjuvant treatment for node-positive, early breast cancer at high risk of recurrence** • As monotherapy for metastatic disease with progression following ET and chemotherapy in the metastatic setting • With fulvestrant after disease progression on ET for metastatic disease • With an AI as initial endocrine-based therapy for metastatic disease

FDA Expands Early Breast Cancer Indication for Abemaciclib with Endocrine Therapy

Press Release – March 3, 2023

"The Food and Drug Administration (FDA) approved abemaciclib 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.

Patients defined as high risk included those having either ≥4 pALN (pathologic axillary lymph nodes) or 1-3 pALN and either tumor grade 3 or a tumor size ≥50 mm.

Abemaciclib was previously approved for the above high-risk population with the additional requirement of having a Ki-67 score ≥20%. Today's approval removes the Ki-67 testing requirement."

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

San Antonio Breast Cancer Symposium®, December 6-10, 2022

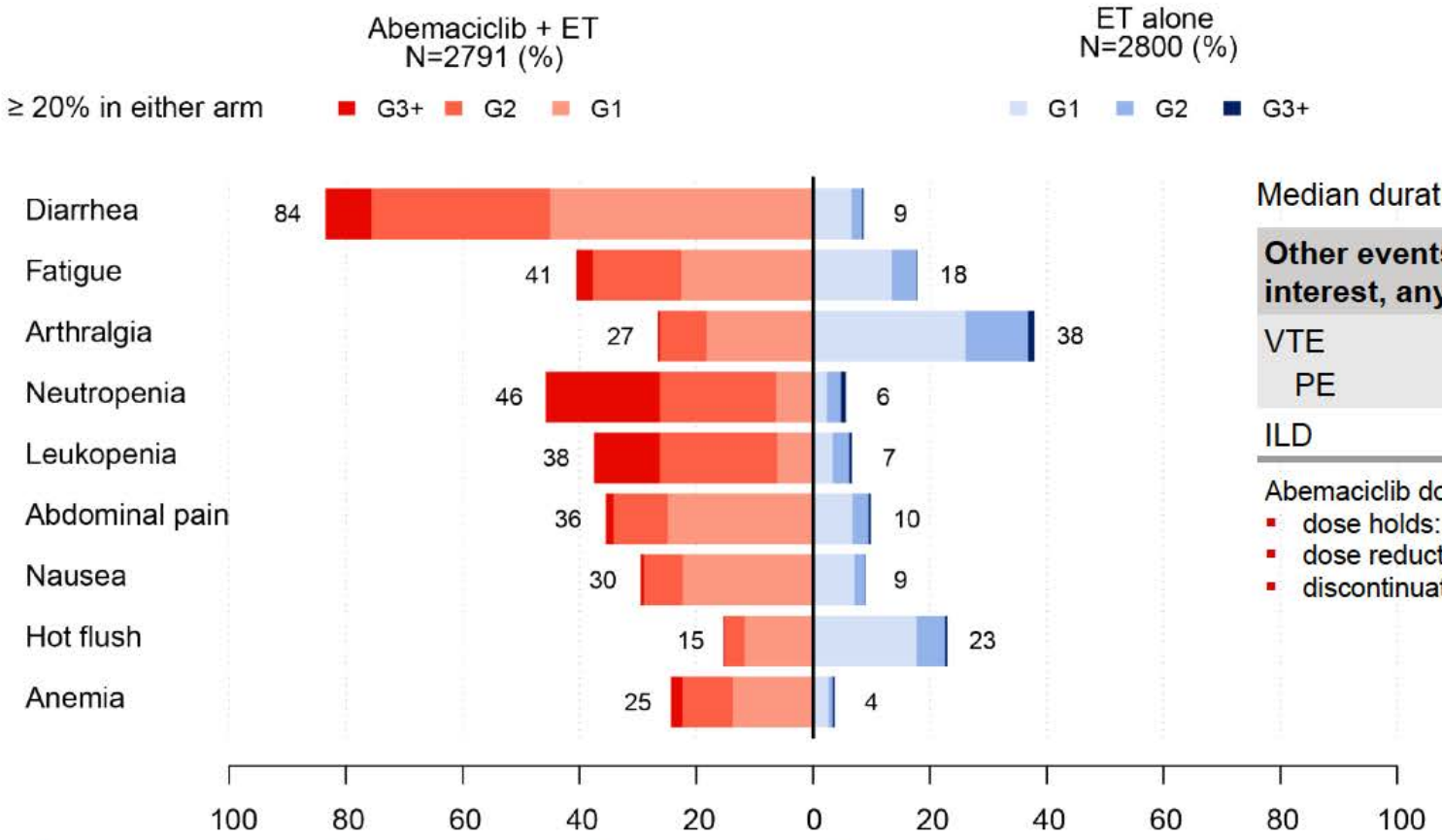
Abstract GS1-09

Abemaciclib plus endocrine therapy for HR+, HER2-, node-positive, high-risk early breast cancer: results from a pre-planned monarchE overall survival interim analysis, including 4-year efficacy outcomes

Stephen R.D. Johnston[1], Masakazu Toi, Joyce O'Shaughnessy, Priya Rastogi, Mario Campone, Patrick Neven, Chiun-Sheng Huang, Jens Huober, Georgina Garnica Jaliffe, Irfan Cicin, Sara M. Tolaney, Matthew P. Goetz, Hope S. Rugo, Elzbieta Senkus, Laura Testa, Lucia Del Mastro, Chikako Shimizu, Ran Wei, Ashwin Shahir, Maria Munoz, Belen San Antonio, Valérie André, Nadia Harbeck, Miguel Martin

[1]Royal Marsden NHS Foundation Trust, London, United Kingdom

monarchE: Safety



Median duration of abemaciclib: 23.7 months.

Other events of interest, any grade	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.7
PE	1.0	0.1
ILD	3.3	1.3

Abemaciclib dose adjustments due to AEs
- dose holds: 61.7%
- dose reductions: 43.6%
- discontinuations 18.5% [8.9% after dose reduction]

All patients who received at least one dose of study treatment were included in the safety population

The safety profile of abemaciclib is considered manageable and acceptable for this high-risk population

VTE = venous thromboembolic events; PE = pulmonary embolism; ILD = interstitial lung disease

Johnston SRD et al. SABCS 2022;Abstract GS1-09.

Ribociclib Phase III NATALEE Trial Meets Primary Endpoint at Interim Analysis Demonstrating Clinically Meaningful Benefit in Broad Population of Patients with Early Breast Cancer

Press Release: March 27, 2023

"• *NATALEE is the first and only positive Phase III study of a CDK4/6 inhibitor demonstrating consistent benefit in a broad population of patients with Stage II and III HR+/HER2- early breast cancer (EBC) at risk of recurrence, including those with no nodal involvement*

• *Approximately 30% to 60% of people with HR+/HER2- Stage II and III EBC treated with ET only remain at risk of breast cancer recurrence*

Positive topline results [were announced] from an interim analysis of NATALEE, a Phase III trial evaluating ribociclib plus endocrine therapy (ET) in a broad population of patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early breast cancer (EBC) at risk of recurrence. The Independent Data Monitoring Committee recommended stopping the trial early as the primary endpoint of invasive disease-free survival (iDFS) has been met. Ribociclib plus ET significantly reduced the risk of disease recurrence, compared to standard adjuvant ET alone, with consistent benefit in patients with stage II and stage III EBC regardless of nodal involvement."

https://www.novartis.com/news/media-releases/novartis-kisqali-phase-iii-natalee-trial-meets-primary-endpoint-interim-analysis-demonstrating-clinically-meaningful-benefit-broad-population-patients-early-breast-cancer

RTP RESEARCH TO PRACTICE

Agenda

Module 1: ER-Positive, HER2-Negative Localized Breast Cancer — PART 1

Module 2: ER-Positive, HER2-Negative Localized Breast Cancer — PART 2

Module 3: ER-Positive Metastatic Breast Cancer

Module 4: Localized HER2-Positive Breast Cancer

Module 5: HER2-Positive and HER2-Low Metastatic Breast Cancer — PART 1

Module 6: HER2-Positive and HER2-Low Metastatic Breast Cancer — PART 2

Module 7: PARP Inhibitors

Module 8: Immune Checkpoint Inhibitors

Jamie Carroll, APRN, MSN, CNP

67-year-old woman with ER-positive, HER2-negative metastatic breast cancer with an ESR1 mutation who received elacestrant

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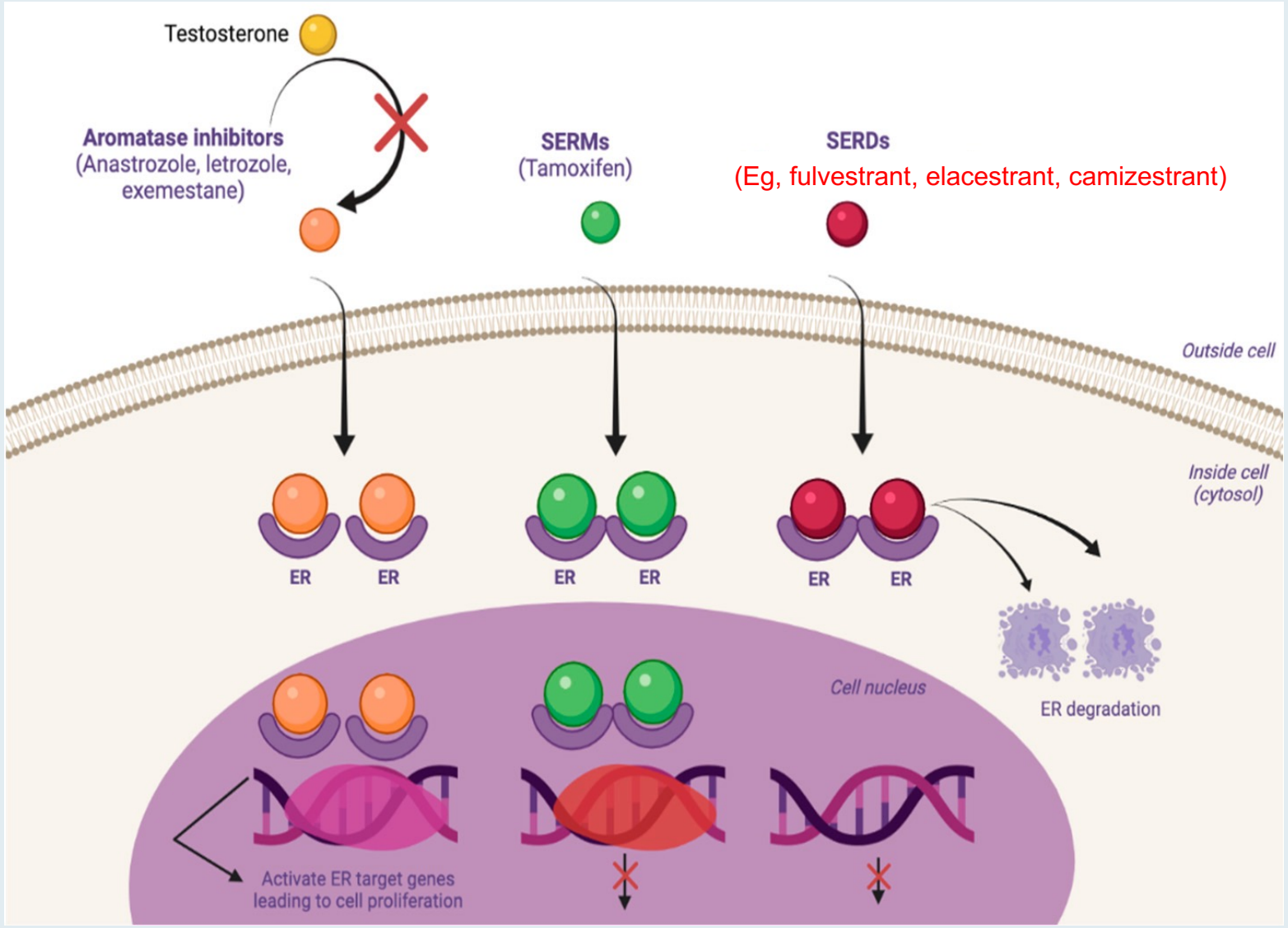
Dr Kaklamani
San Antonio, Texas

Clinical Research Background

Dr O'Shaughnessy
Dallas, Texas

- **Choice of first-line CDK4/6 inhibitor**
- **Approved and investigational oral SERDs**
- **ESR1 mutations**
- **Capivasertib**

Mechanism of Action of Different Endocrine Therapies



Hernando C et al. *Int J Mol Sci* 2021;22:7812.

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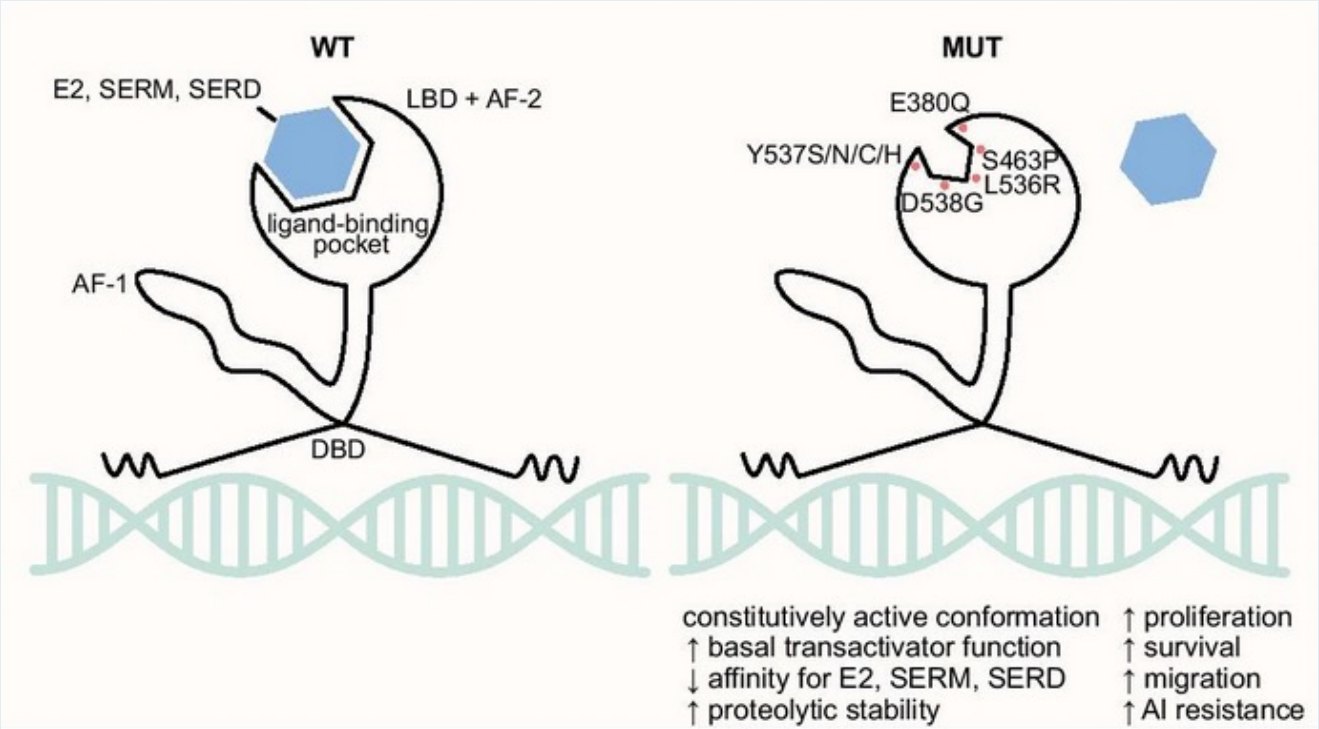
ESR1 Mutations and Resistance to Endocrine Therapies

- Mutations in the ligand binding domain (LBD) of the ESR1 gene were shown to be present in ~18% of endocrine-resistant hormone receptor-positive breast cancer cases.



- ESR1 LBD mutations result in estrogen-independent activation of estrogen receptors and lead to resistance to AIs.

Brett JO et al. *Breast Cancer Res* 2021;23(1):85; Schiavon G et al. *Sci Transl Med* 2015;7(313):313ra182; Droste A and Schmidt M. *J Cancer Metastasis Treat* 2023;9:2.

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Elacestrant

Mechanism of action

- **Oral SERD (selective estrogen receptor degrader)**

Indication

- **For postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression after at least 1 line of endocrine therapy**

Recommended dose

- **One 345 mg tablet po qd, with food**

Elacestrant package insert, 1/2023.

Camizestrant

Mechanism of action

- **Oral SERD**

Indication

- **Investigational**

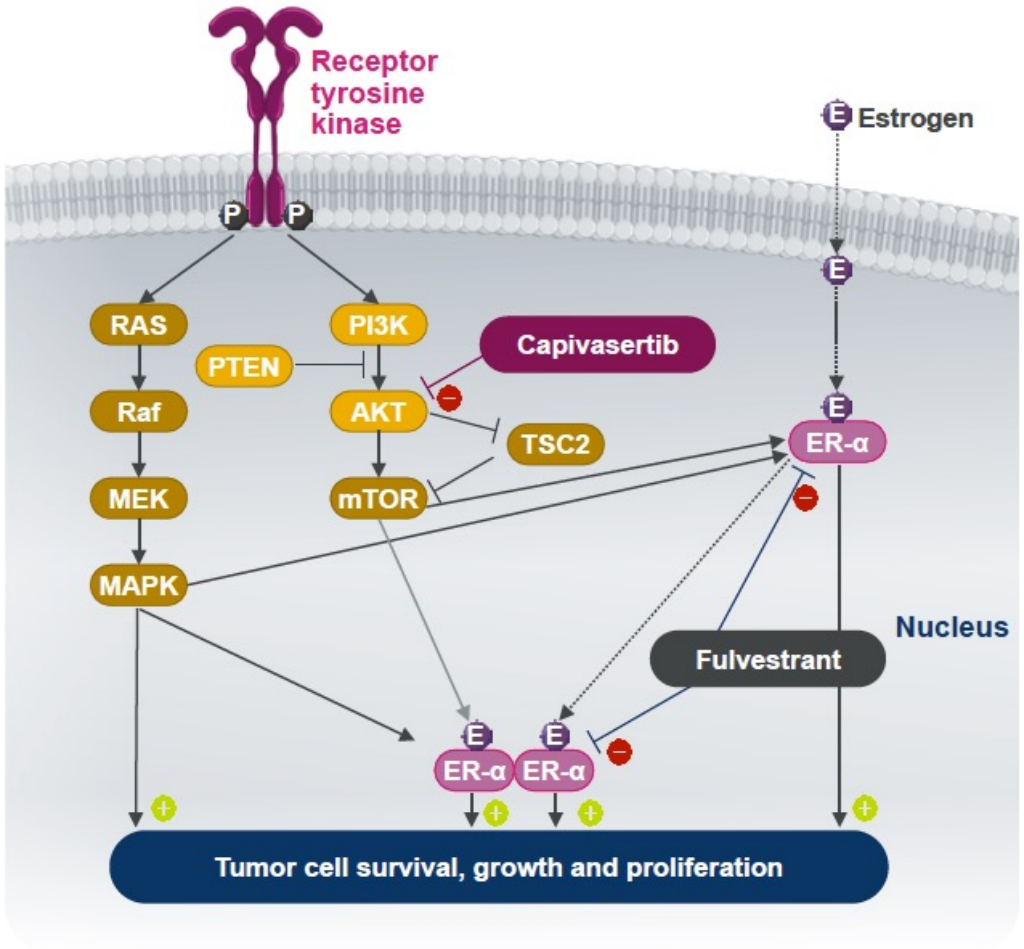
Key clinical trial

- **Phase II SERENA-2 trial evaluating camizestrant in postmenopausal women with locally advanced or metastatic ER-positive, HER2-negative breast cancer previously treated with endocrine therapy**

Oliveira M et al. SABCS 2022;Abstract GS3-02.

Capivasertib Mechanism of Action

- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*, but may also occur in cancers without those genetic alterations.[1,2] AKT signalling is also implicated in the development of resistance to endocrine therapy[2]
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)



Turner NC et al. SABCS 2022;Abstract GS3-04.

Capivasertib

Mechanism of action

- AKT inhibitor

Indication

- Investigational

Pivotal clinical data

- Phase III CAPItello-291 trial evaluating capivasertib with fulvestrant for locally advanced or metastatic hormone receptor-positive, HER2-negative breast cancer after recurrence or disease progression on or after treatment with an aromatase inhibitor

Turner NC et al. SABCS 2022;Abstract GS3-04.

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Module 7: PARP Inhibitors

Module 8: Immune Checkpoint Inhibitors

Jamie Carroll, APRN, MSN, CNP

26-year-old premenopausal woman with a HER2-positive localized IDC who received postadjuvant neratinib

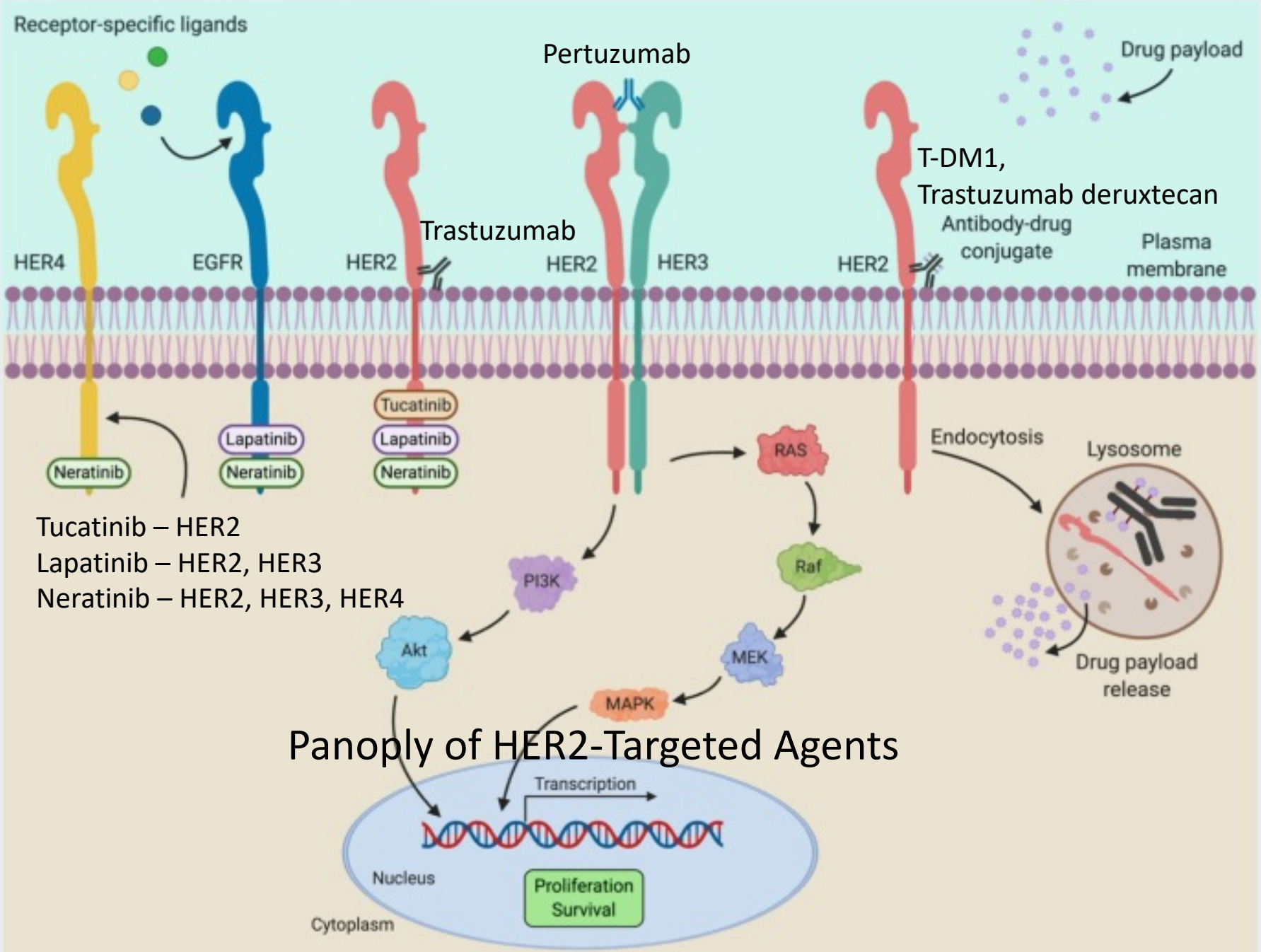
Dr Kaklamani
San Antonio, Texas

Clinical Research Background

Dr O'Shaughnessy
Dallas, Texas

- **Postadjuvant neratinib**
  - **Role of ER status in patient selection**
  - **Prevention and management of diarrhea**

Panoply of HER2-Targeted Agents



Tucatinib – HER2
Lapatinib – HER2, HER3
Neratinib – HER2, HER3, HER4

Tesch ME, Gelmon KA. Drugs 2020;80:1811-30.

CONTROL Trial: Strategies to Improve Neratinib Tolerability

Background: Neratinib is approved for extended-adjuvant therapy in HER2-positive breast cancer

- Neratinib was poorly tolerated in the ExteNET trial:
  - Discontinuation rate 17%
  - Grade 3 diarrhea 40%

Objective: Improve GI tolerability of neratinib

Methods: **Sequential single-arm interventions for patients who receive adjuvant therapy**

- Cohort 1 (L): Loperamide (n = 137)
- Cohort 2 (BL): Budesonide + loperamide (n = 64)
- Cohort 3 (CL or CL-PRN): Colestipol + loperamide (n = 136) or colestipol + as-needed loperamide (n = 104)
- Cohort 4 (DE): Neratinib dose escalation; ongoing (n = 60)

Barcenas CH et al. *Ann Oncol* 2020;31(9):1223-30.

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Module 7: PARP Inhibitors

Module 8: Immune Checkpoint Inhibitors

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Ronald Stein, JD, MSN, NP-C, AOCNP

49-year-old woman with recurrent HER2-positive metastatic breast cancer who received T-DXd

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Dr Kaklamani
San Antonio, Texas

Clinical Research Background

Dr O'Shaughnessy
Dallas, Texas

- **Sequencing of therapies for HER2-positive breast cancer**
  - **Tucatinib**
  - **Trastuzumab deruxtecan (T-DXd)**
- **Management of HER2-positive brain metastases**

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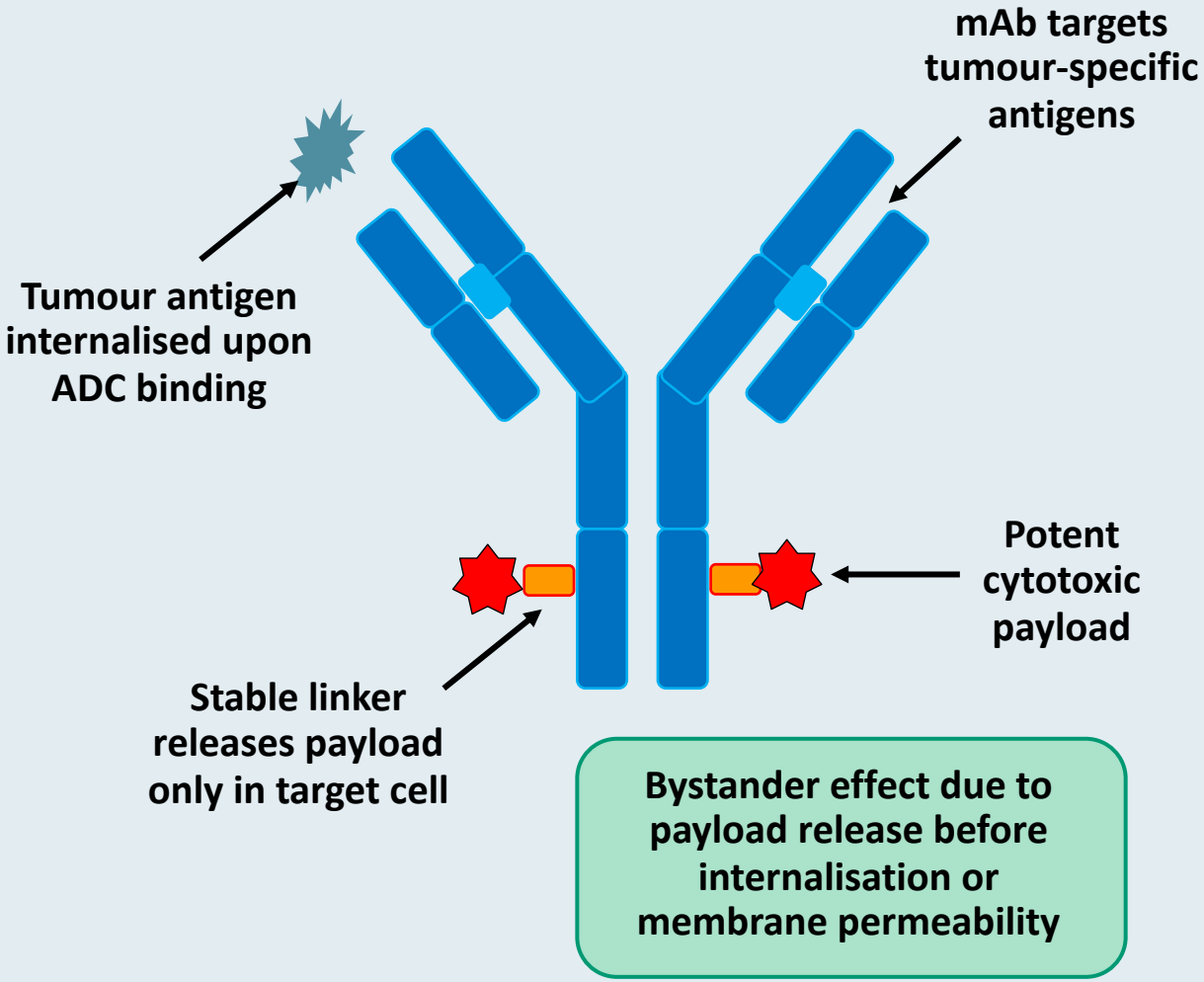
HER2-Targeting Antibody-Drug Conjugates (ADCs)



ADC Attributes	T-DM1	T-DXd
Payload MoA	Antimicrotubule	Topoisomerase I inhibitor
Drug-to-antibody ratio	~3.5:1	~8:1
Tumor-selective cleavable linker?	No	Yes
Evidence of bystander antitumor effect?	No	Yes

Schmid P et al. SABCS 2021.

Trastuzumab Deruxtecan

Mechanism of action

- **Antibody-drug conjugate directed against HER2**

Indication

- **For patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting or in the (neo)adjuvant setting and have experienced disease recurrence during or within 6 months of completing therapy**
- **For patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy**

Recommended dose

- **5.4 mg/kg IV infusion q3wk until disease progression or unacceptable toxicity**

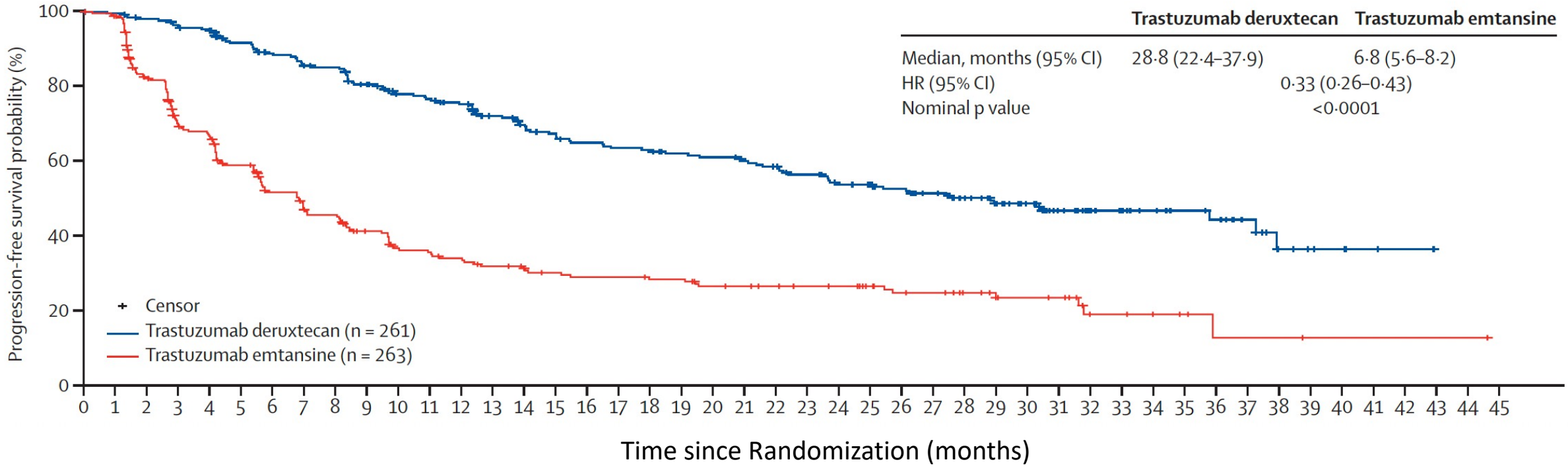
Trastuzumab deruxtecan package insert, 11/2022.

Lancet 2023 January 14;401:105-17.

Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial

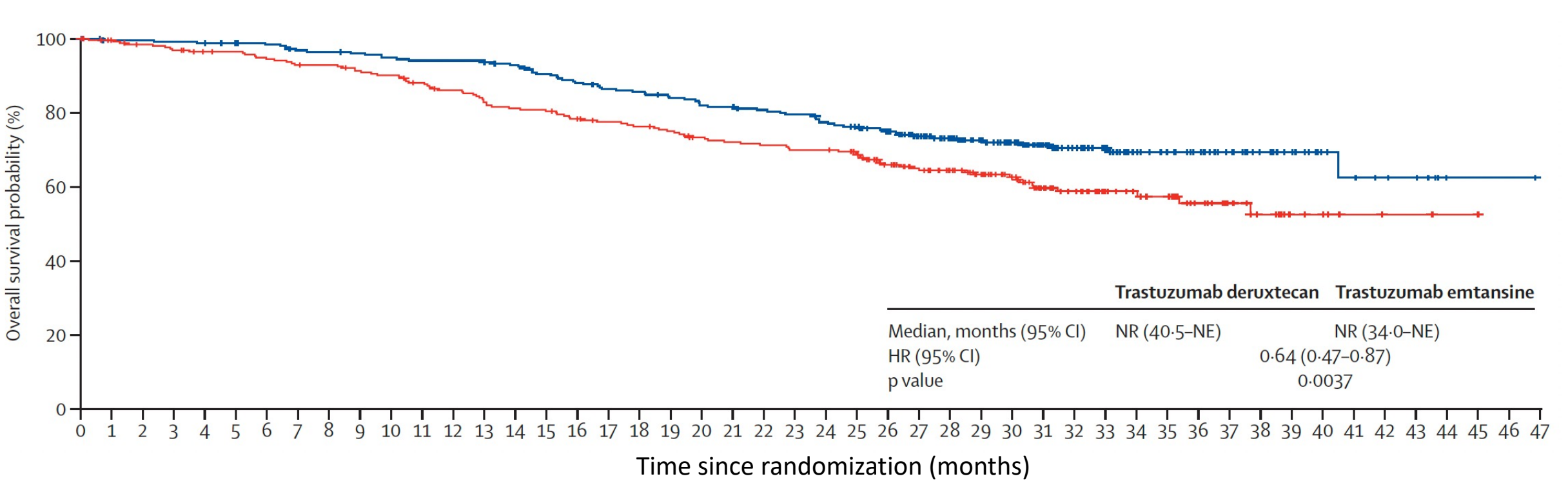
Sara A Hurvitz, Roberto Hegg, Wei-Pang Chung, Seock-Ah Im, William Jacot, Vinod Ganju, Joanne Wing Yan Chiu, Binghe Xu, Erika Hamilton, Srinivasan Madhusudan, Hiroji Iwata, Sevilay Altintas, Jan-Willem Henning, Giuseppe Curigliano, José Manuel Perez-Garcia, Sung-Bae Kim, Vanessa Petry, Chiun-Sheng Huang, Wei Li, Jean-Sebastien Frenel, Silvia Antolin, Winnie Yeo, Giampaolo Bianchini, Sherene Loi, Junji Tsurutani, Anton Egorov, Yali Liu, Jillian Cathcart, Shahid Ashfaque, Javier Cortés

DESTINY-Breast03: Progression-Free Survival



Hurvitz SA et al. *Lancet* 2023;401:105-17.

DESTINY-Breast03: Overall Survival



Hurvitz SA et al. *Lancet* 2023;401:105-17.

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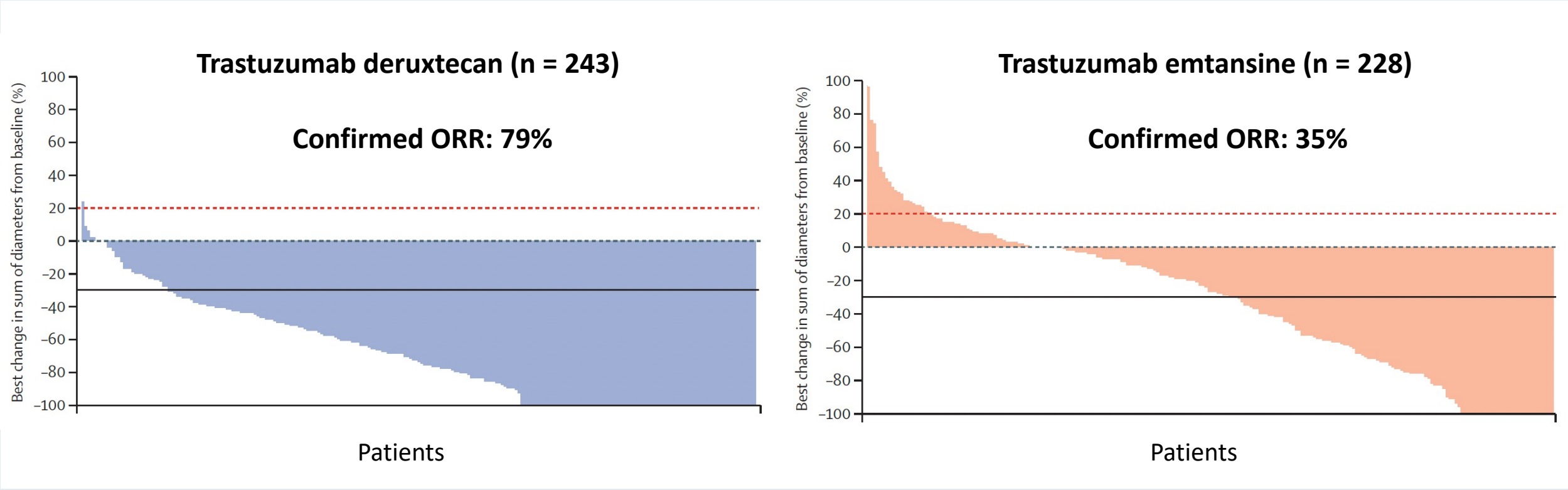
DESTINY-Breast03: Antitumor Activity



Hurvitz SA et al. *Lancet* 2023;401:105-17.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

N Engl J Med. 2022;387(1):9-20.

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Module 7: PARP Inhibitors

Module 8: Immune Checkpoint Inhibitors

Jamie Carroll, APRN, MSN, CNP

57-year-old woman with HER2-positive breast cancer and brain metastases who received tucatinib/trastuzumab/capecitabine

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Dr Kaklamani
San Antonio, Texas

Clinical Research Background

Dr O'Shaughnessy
Dallas, Texas

- **Sequencing of therapies for HER2-positive breast cancer**
  - **Tucatinib**
  - **Trastuzumab deruxtecan (T-DXd)**
- **Management of HER2-positive brain metastases**

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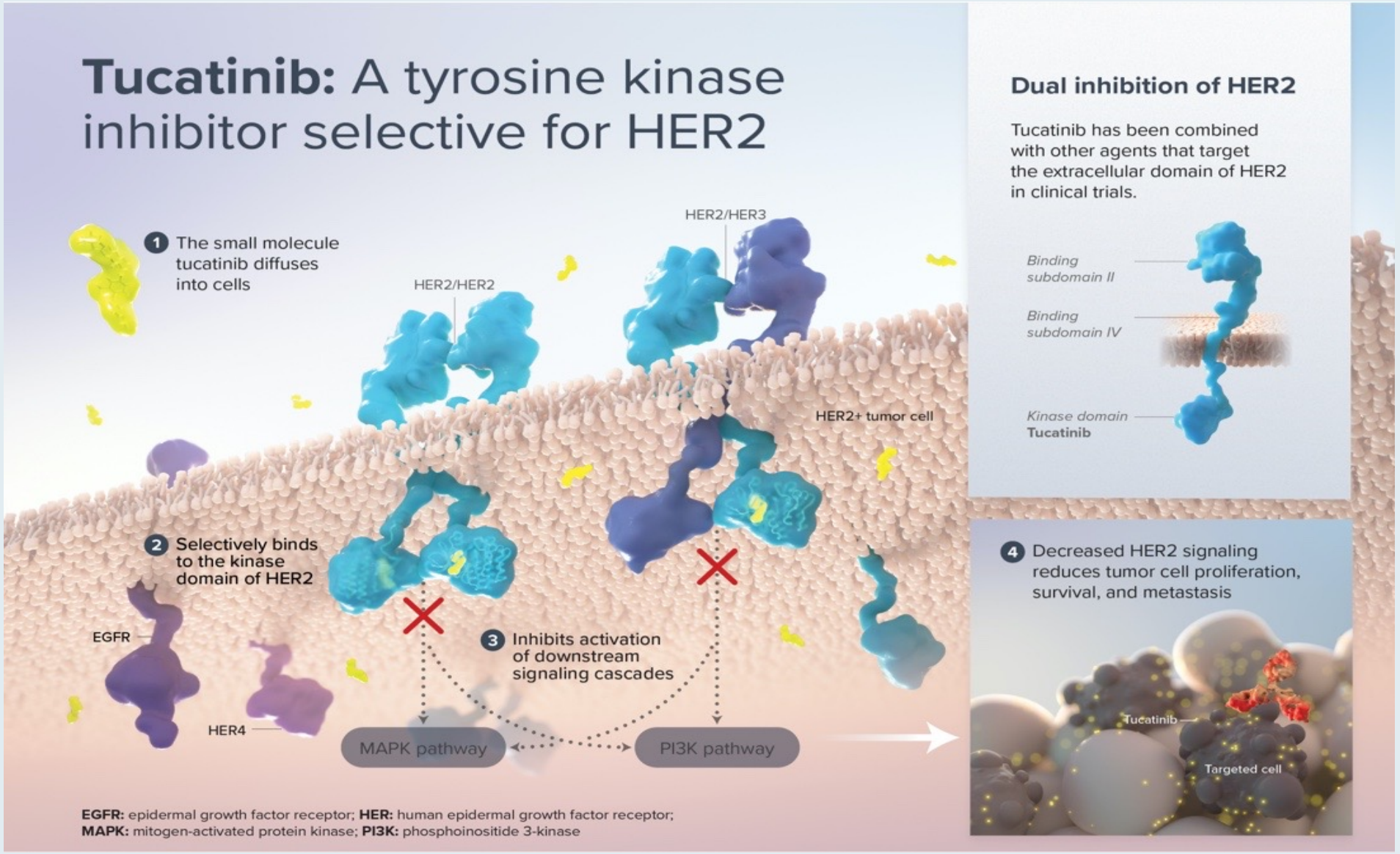
Tucatinib Mechanism of Action



Catenacci DV et al. ESMO 2021;Abstract 1434TiP.

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Tucatinib

Mechanism of action

- **HER2 tyrosine kinase inhibitor**

Indication

- **In combination with trastuzumab and capecitabine for patients with advanced unresectable or metastatic HER2-positive breast cancer who have received 1 or more prior anti-HER2-based regimens in the metastatic setting**

Recommended dose

- **300 mg po BID with or without food**

Tucatinib package insert, 1/2023.

Agenda

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Module 8: Immune Checkpoint Inhibitors

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Ronald Stein, JD, MSN, NP-C, AOCNP

49-year-old woman with a germline BRCA1 mutation and localized TNBC who received adjuvant olaparib

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Dr Kaklamani
San Antonio, Texas

Clinical Research Background

Dr O'Shaughnessy
Dallas, Texas

- **Spectrum of somatic and germline mutations**
- **Clinical use of PARP inhibitors in the adjuvant and metastatic settings**
- **Tolerability/toxicity of PARP inhibitors**

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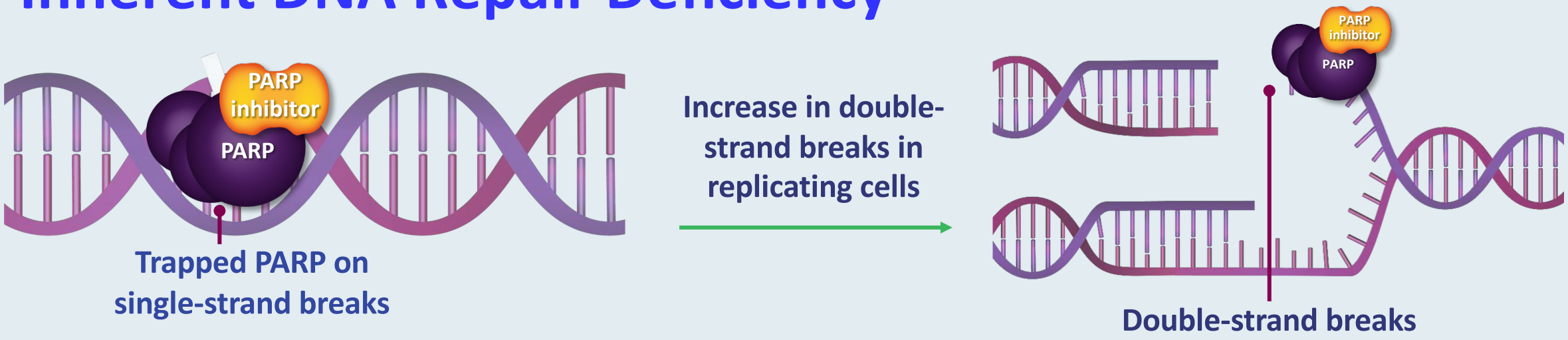
PARPi Exploits the Baseline Vulnerability of Cells with Inherent DNA Repair Deficiency



O'Connor MJ. *Mol Cell*. 2015.

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PARP Inhibitors

Olaparib

- **Indications:**
  - **Adjuvant treatment for patients with gBRCAm, HER2-negative high-risk localized breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy; administered for 1 year**
  - **Treatment for patients with gBRCAm, HER2-negative mBC who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with HR-positive breast cancer should have been treated with prior endocrine therapy or be considered inappropriate for endocrine therapy**

Talazoparib

- **Indication:**
  - **Treatment for patients with gBRCAm HER2-negative locally advanced or metastatic breast cancer**

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Ronald Stein, JD, MSN, NP-C, AOCNP

42-year-old woman with localized TNBC who received neoadjuvant chemotherapy/pembrolizumab followed by adjuvant pembrolizumab

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Dr Kaklamani
San Antonio, Texas

Clinical Research Background

Dr O'Shaughnessy
Dallas, Texas

- **KEYNOTE-522**
- **KEYNOTE-355: Relevance of PD-L1 expression**
- **Immune-mediated toxicities associated with immunotherapy**

Pembrolizumab

Mechanism of action

- PD-1 inhibitor

Indication

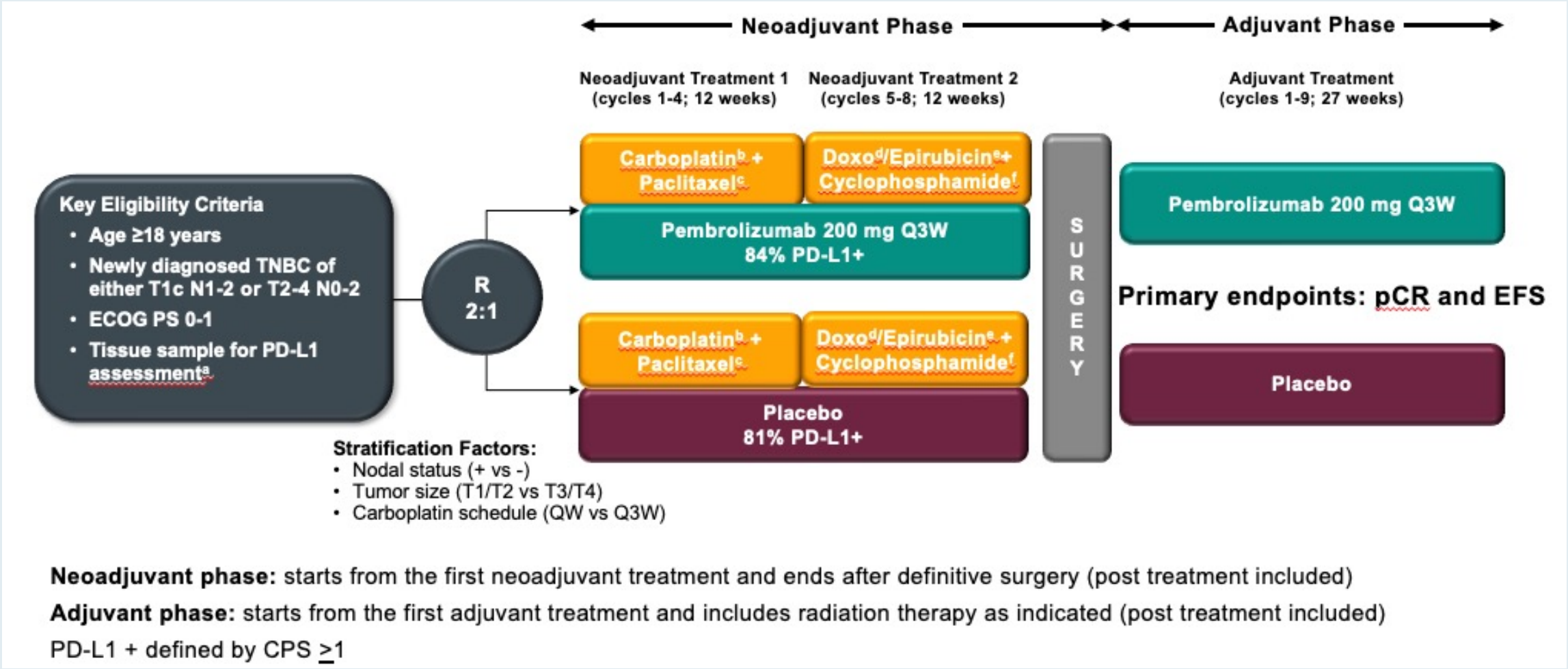
- In combination with chemotherapy as neoadjuvant treatment and continued as single agent after surgery for high-risk early-stage TNBC
- In combination with chemotherapy for patients with advanced/metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10)

Recommended dose

- 200 mg every 3 weeks or 400 mg every 6 weeks

Pembrolizumab package insert, 4/2023.

KEYNOTE-522: Phase III Trial Schema



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

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

PD-L1 + defined by CPS ≥1

Schmid P et al. *N Engl J Med* 2020;382:810-21.

APPENDIX

ER-Positive, HER2-Negative Localized Breast Cancer

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San Antonio Breast Cancer Symposium – December 6-10, 2022

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

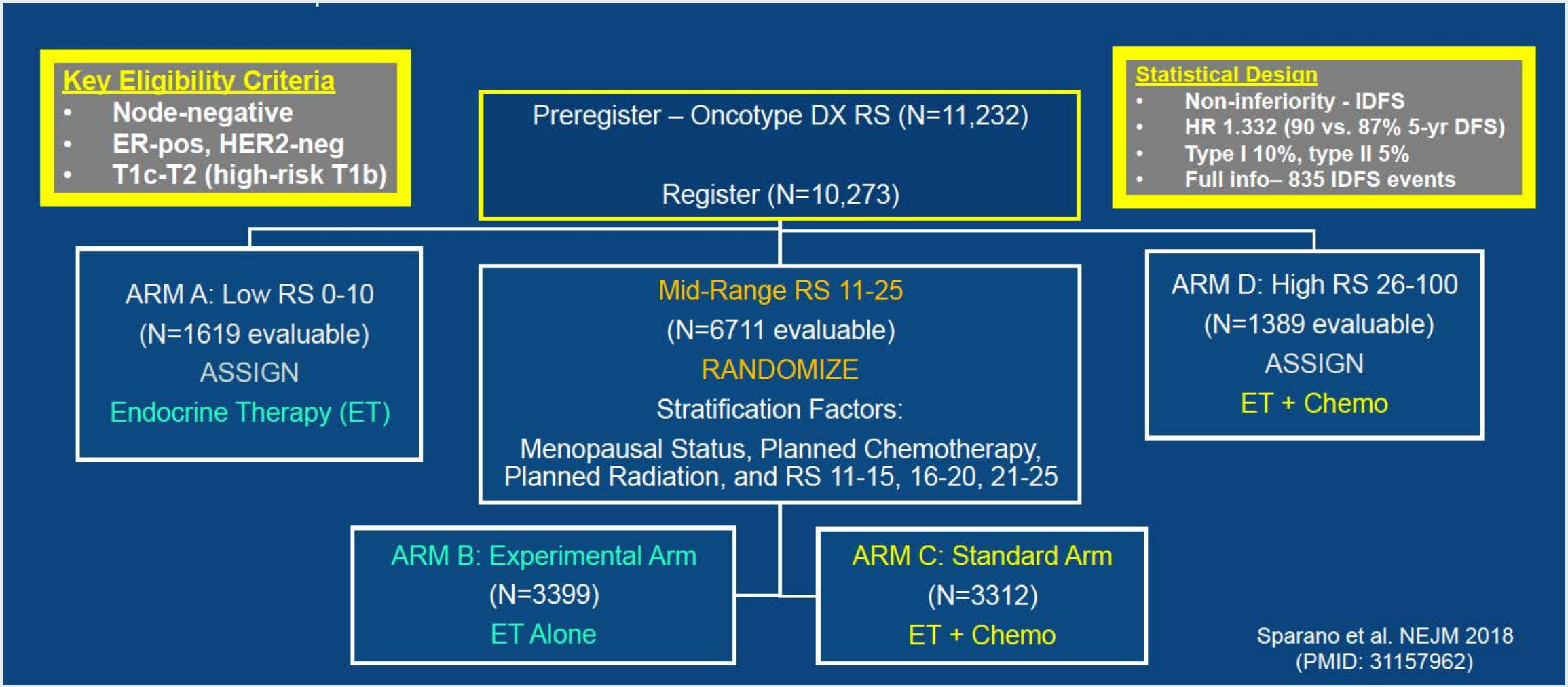
Abstract GS1-05

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

on behalf of the TAILORx Investigators

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

TAILORx Study Design: Treatment Assignment and Randomization



RS = Recurrence Score

Sparano JA et al. SABCS 2022;Abstract GS1-05.

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TAILORx Updated Analysis: Conclusions

- **Longer median followup and more events in randomized group**
  - Median 11.0 vs. 7.5 years
  - IDFS (1295 vs. 836) and DRFI (375 vs. 250) events
- **Main study findings unchanged for RS 11-25 arms (primary objective)**
  - ET non-inferior to CET for IDFS (primary endpoint) and DRFI (secondary endpoint)
  - RFI and OS also similar between treatment arms (exploratory endpoints)
- **Other exploratory key study findings also similar to original analysis**
  - Chemotherapy benefit for women ≤ 50 with RS 21-25
  - Some chemotherapy benefit for women ≤ 50 with RS 16-20 and high clinical risk
- **New findings of updated analyses (exploratory)**
  - Late recurrences > 5 years exceed early recurrence
  - Racial disparities for black women associated with early but not late recurrence

Sparano JA et al. SABCS 2022;Abstract GS1-05.

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

Abstract GS2-07

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

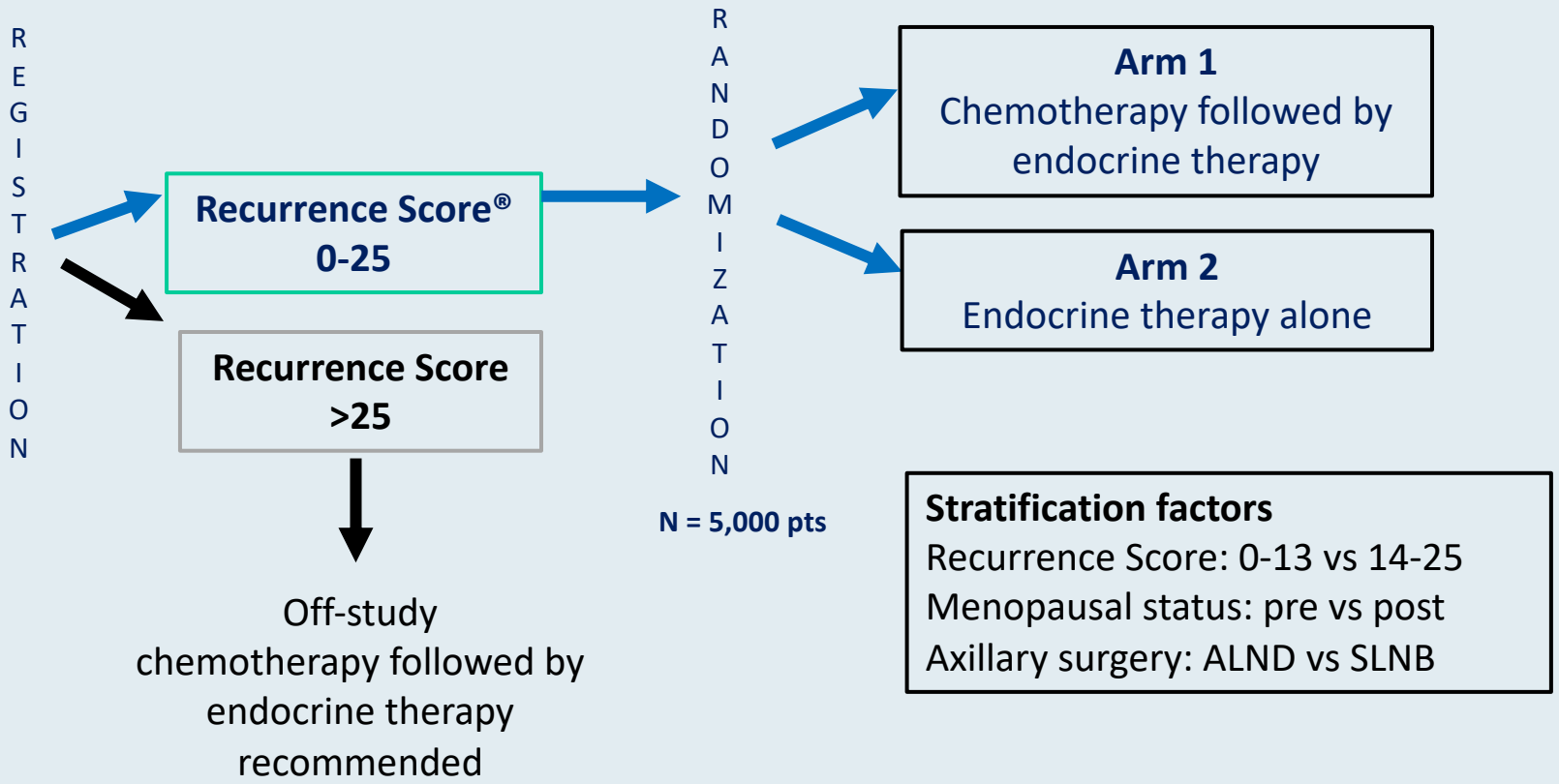
Kevin Kalinsky, William E Barlow, Julie R Gralow, Funda Meric-Bernstam, Kathy S Albain, Daniel F Hayes, Nancy U Lin, Edith A Perez, Lori J Goldstein, Stephen K Chia, Sukhbinder Dhesy-Thind, Priya Rastogi, Emilio Alba, Suzette Delaloge, Miguel Martin, Catherine M Kelly, Manuel Ruiz-Borrego, Miguel Gil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

RxPONDER Trial Schema

Key Entry Criteria

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



LN = lymph nodes; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection

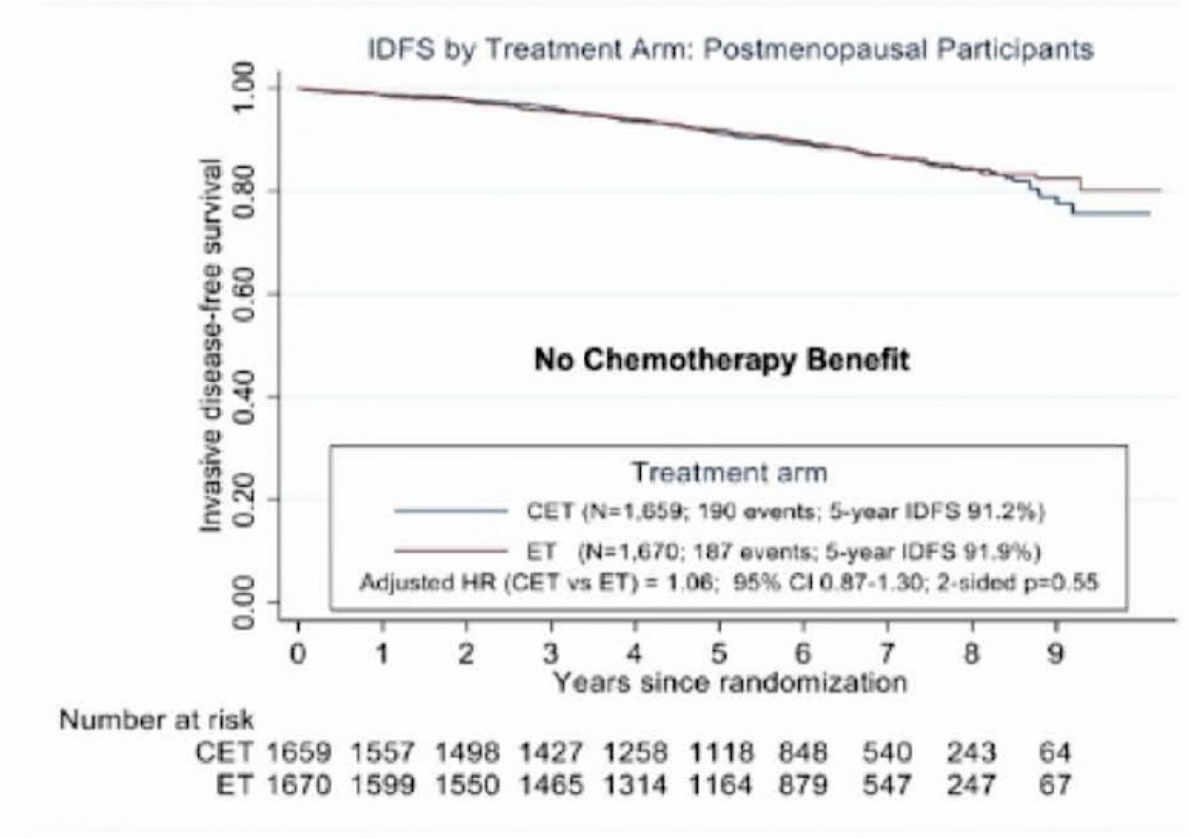
* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.

† Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.

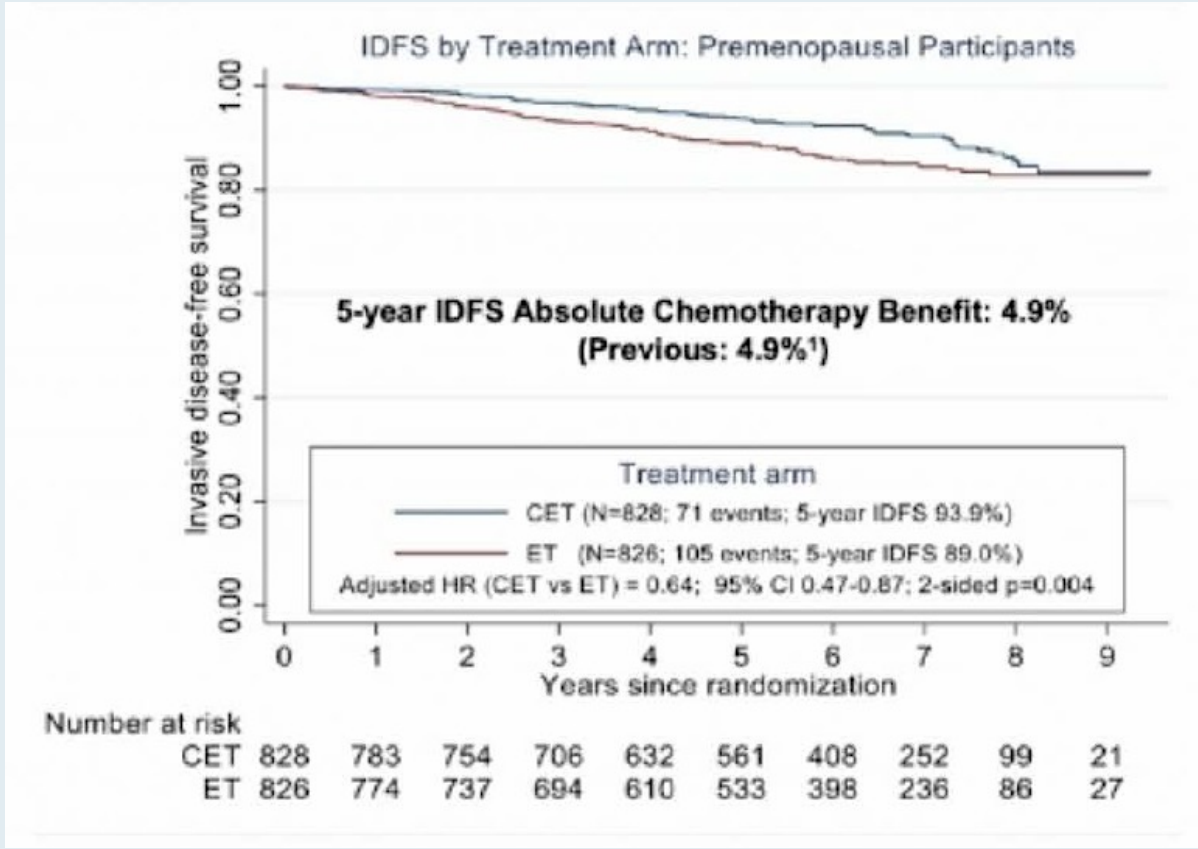
Kalinsky K et al. SABCS 2020;Abstract GS3-00.

RxPONDER Updated Analysis: IDFS Stratified by Menopausal Status

Postmenopausal



Premenopausal



IDFS = invasive disease-free survival; CET = chemotherapy followed by endocrine therapy; ET = endocrine therapy

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

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J Clin Oncol 2022;40(16):1816-37.

ASCO special articles

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

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

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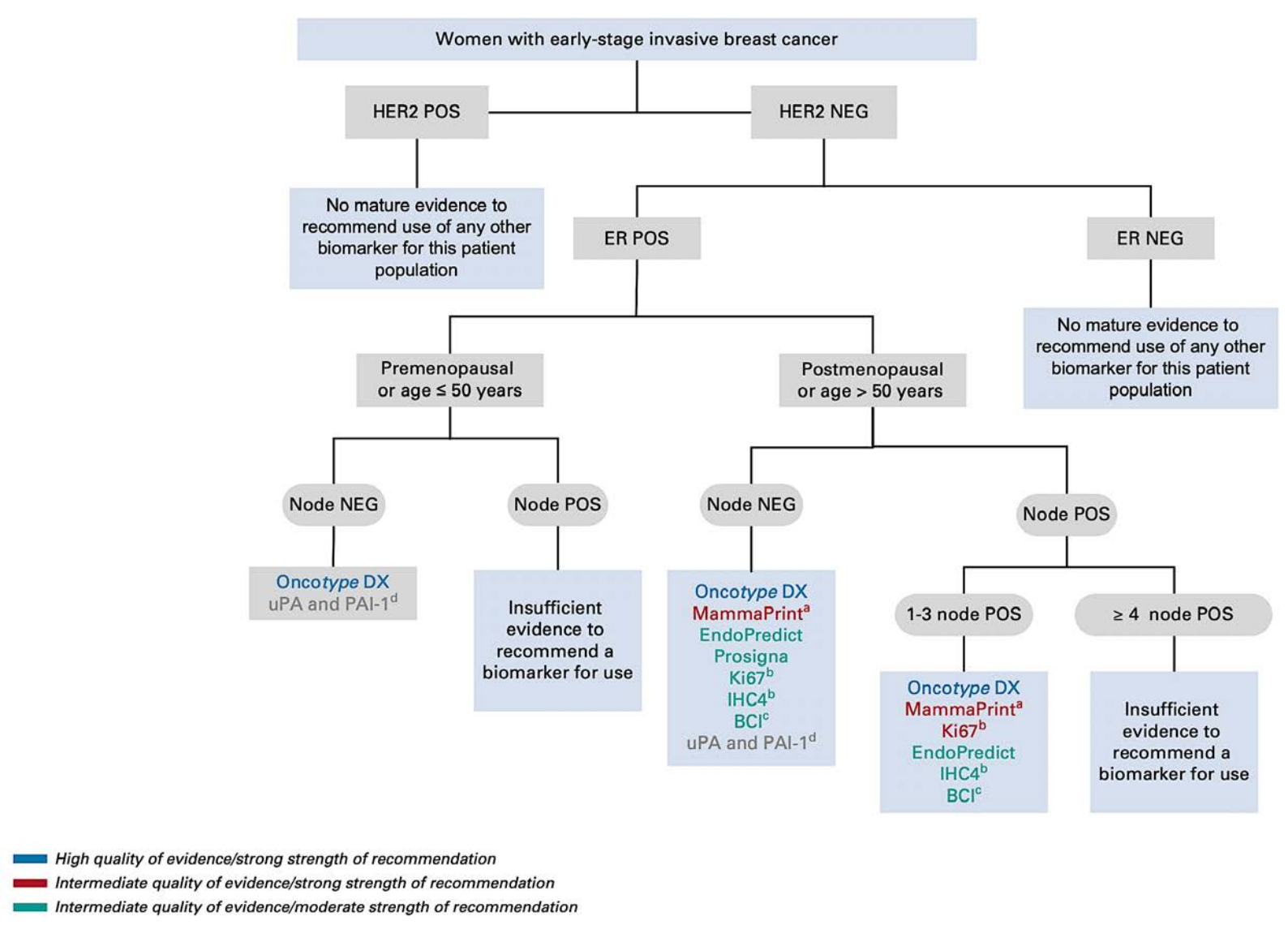
Biomarkers for Adjuvant Endocrine Therapy and Chemotherapy in Localized Breast Cancer: ASCO Guideline Update



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

RTP RESEARCH TO PRACTICE

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 (Onco*type* DX®) (for pN0)	Yes	Yes	Preferred	1
21-gene (Onco*type* 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

National Comprehensive Cancer Network (NCCN®). NCCN clinical practice guidelines in oncology. Breast cancer — Version 4.2022. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 2022.

RTP RESEARCH TO PRACTICE

FDA Expands Early Breast Cancer Indication for Abemaciclib with Endocrine Therapy

Press Release – March 3, 2023

"The Food and Drug Administration (FDA) approved abemaciclib 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.

Patients defined as high risk included those having either ≥4 pALN (pathologic axillary lymph nodes) or 1-3 pALN and either tumor grade 3 or a tumor size ≥50 mm.

Abemaciclib was previously approved for the above high-risk population with the additional requirement of having a Ki-67 score ≥20%. Today's approval removes the Ki-67 testing requirement."

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

San Antonio Breast Cancer Symposium®, December 6-10, 2022

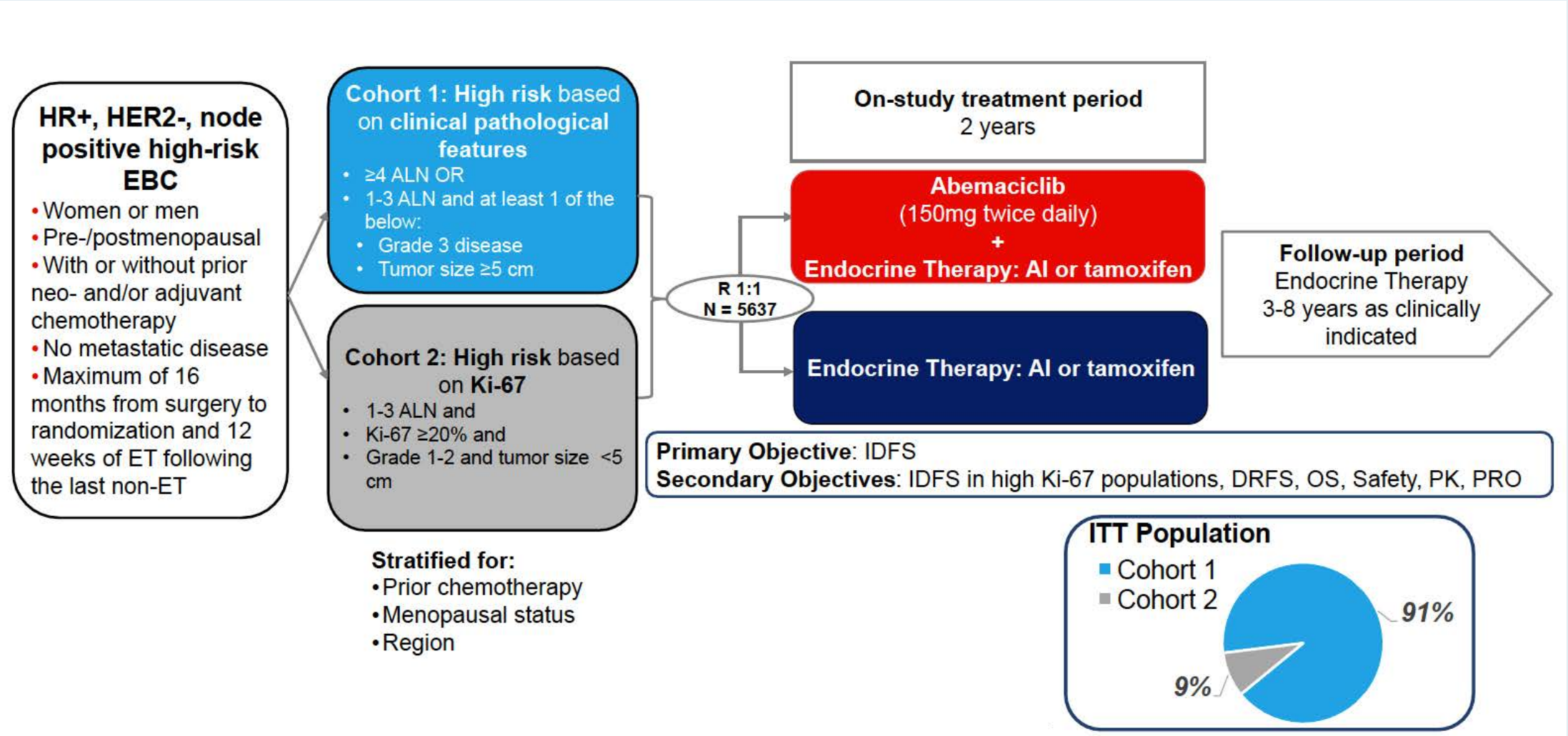
Abstract GS1-09

Abemaciclib plus endocrine therapy for HR+, HER2-, node-positive, high-risk early breast cancer: results from a pre-planned monarchE overall survival interim analysis, including 4-year efficacy outcomes

Stephen R.D. Johnston[1], Masakazu Toi, Joyce O'Shaughnessy, Priya Rastogi, Mario Campone, Patrick Neven, Chiun-Sheng Huang, Jens Huober, Georgina Garnica Jaliffe, Irfan Cicin, Sara M. Tolaney, Matthew P. Goetz, Hope S. Rugo, Elzbieta Senkus, Laura Testa, Lucia Del Mastro, Chikako Shimizu, Ran Wei, Ashwin Shahir, Maria Munoz, Belen San Antonio, Valérie André, Nadia Harbeck, Miguel Martin

[1]Royal Marsden NHS Foundation Trust, London, United Kingdom

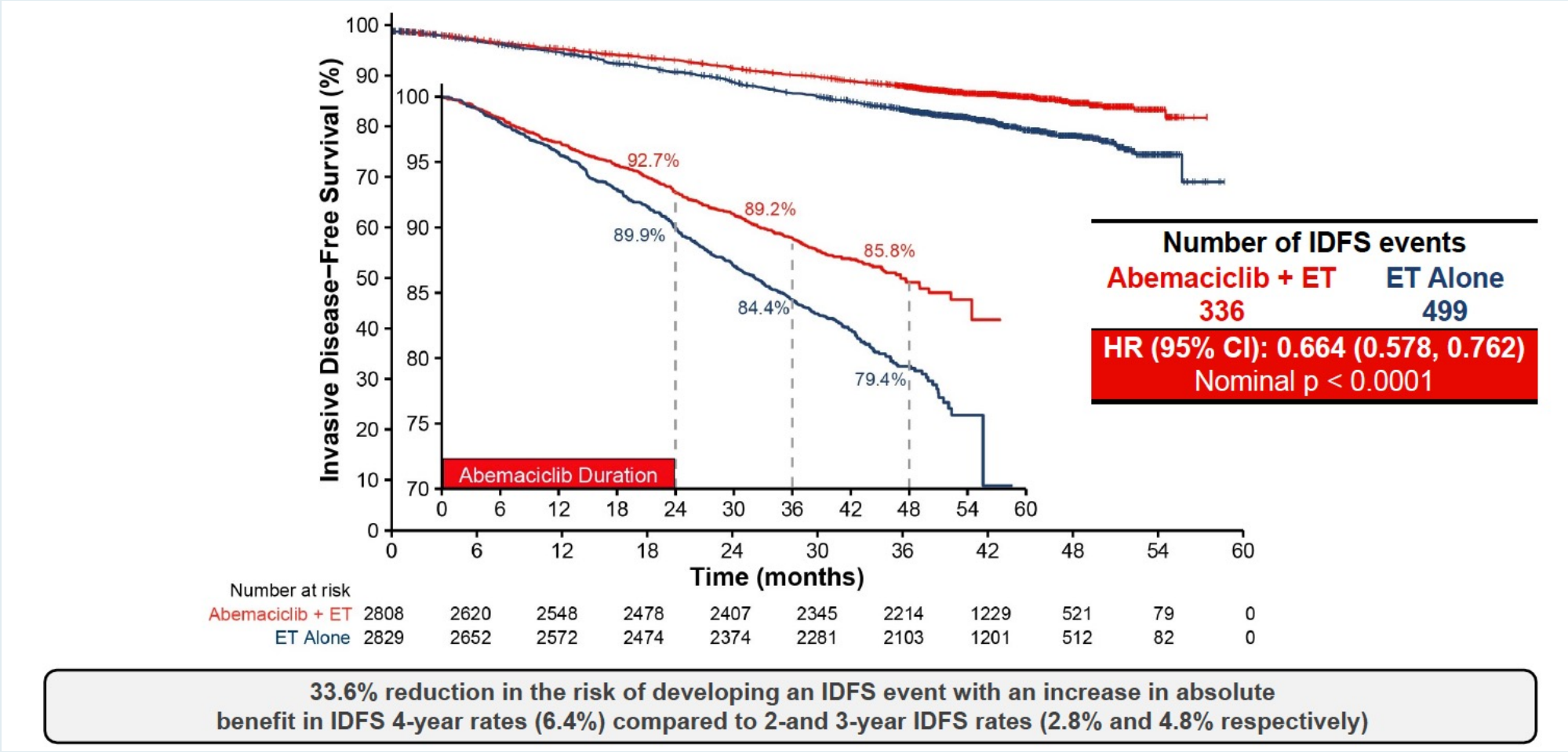
monarchE Phase III Study Design



EBC = early breast cancer; ET = endocrine therapy; IDFS = invasive disease-free survival; DRFS = distant relapse-free survival; OS = overall survival; PK = pharmacokinetics; PRO = patient-reported outcomes

Johnston SRD et al. SABCS 2022;Abstract GS1-09.

monarchE: IDFS (ITT Population)

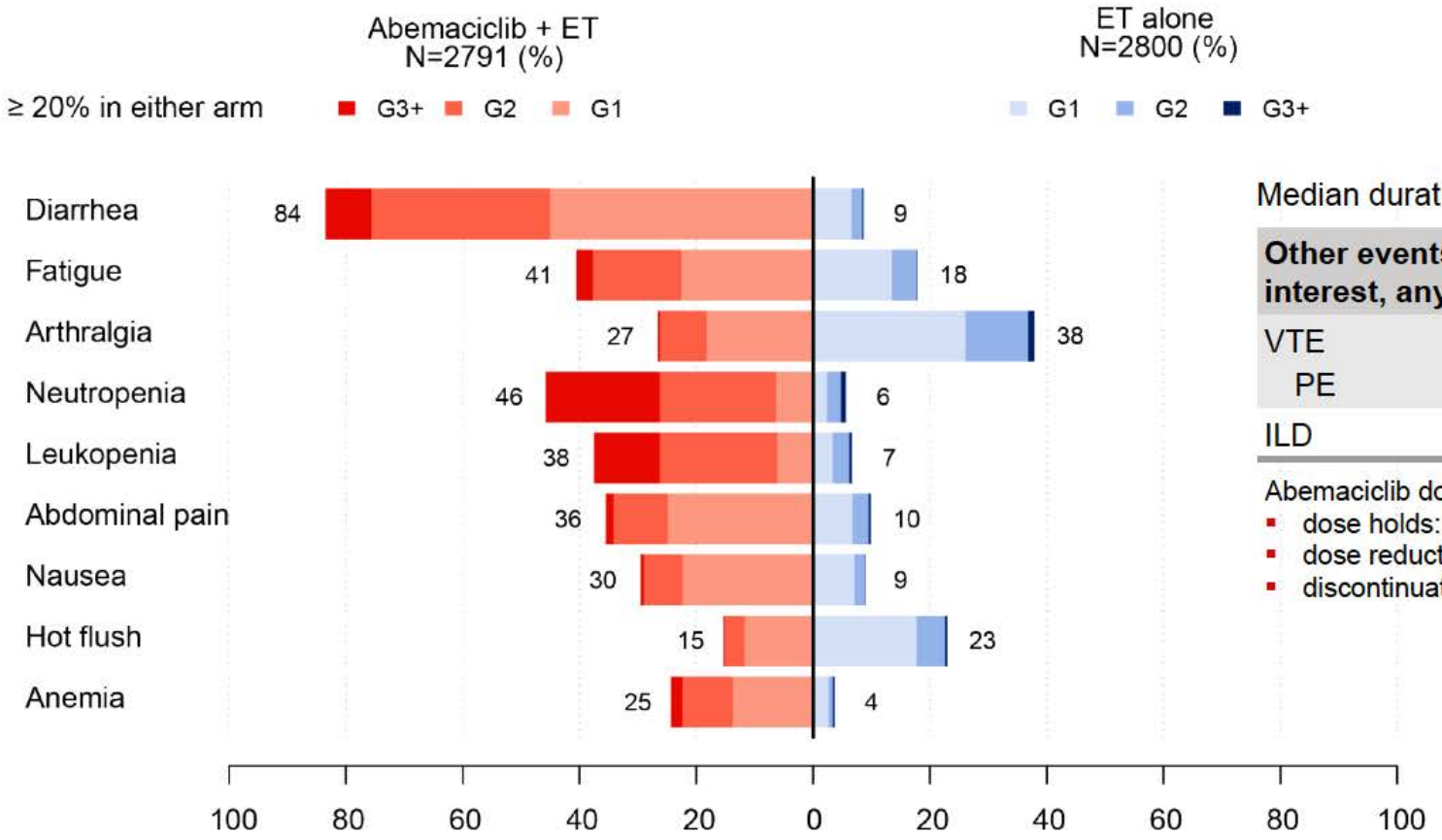


- Abemaciclib treatment benefit deepened over time
- Ki-67 is prognostic, but not predictive of abemaciclib benefit

Johnston SRD et al. SABCS 2022;Abstract GS1-09.

RTP RESEARCH TO PRACTICE

monarchE: Safety



Median duration of abemaciclib: 23.7 months.

Other events of interest, any grade	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.7
PE	1.0	0.1
ILD	3.3	1.3

Abemaciclib dose adjustments due to AEs
- dose holds: 61.7%
- dose reductions: 43.6%
- discontinuations 18.5% [8.9% after dose reduction]

All patients who received at least one dose of study treatment were included in the safety population

The safety profile of abemaciclib is considered manageable and acceptable for this high-risk population

VTE = venous thromboembolic events; PE = pulmonary embolism; ILD = interstitial lung disease

Johnston SRD et al. SABCS 2022;Abstract GS1-09.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

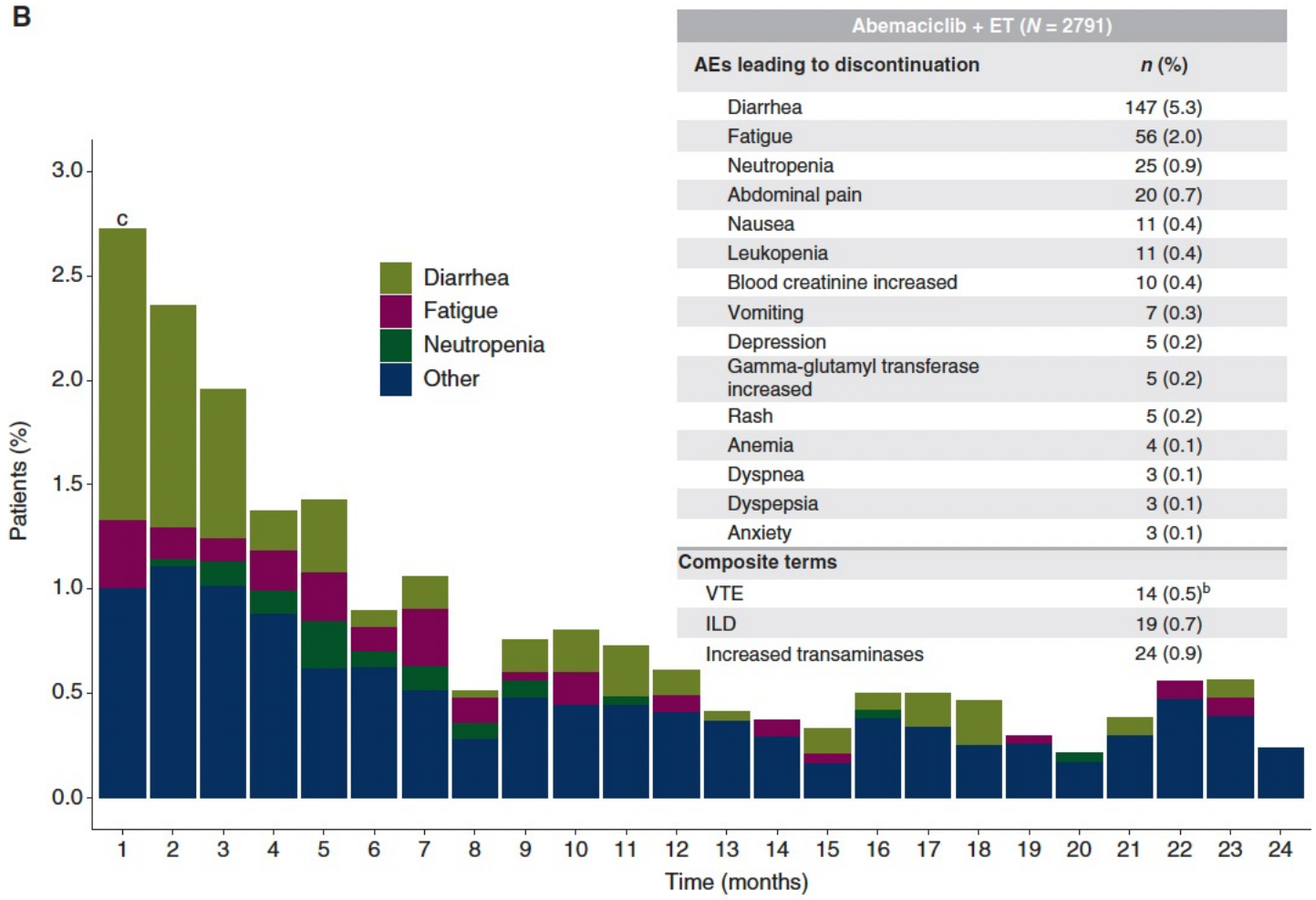
2022;[Online ahead of print]

ORIGINAL ARTICLE

Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study

H. S. Rugo[1*], J. O'Shaughnessy[2], F. Boyle[3,4], M. Toi[5], R. Broom[6], I. Blancas[7,8], M. Gumus[9], T. Yamashita[10], Y.-H. Im[11], P. Rastogi[12], F. Zagouri[13], C. Song[14], M. Campone[15], B. San Antonio[16], A. Shahir[16], M. Hulstijn[16], J. Brown[16], A. Zimmermann[16], R. Wei[16], S. R. D. Johnston[17], M. Reinisch[18] & S. M. Tolaney[19], on behalf of the monarchE Committee Members[†]

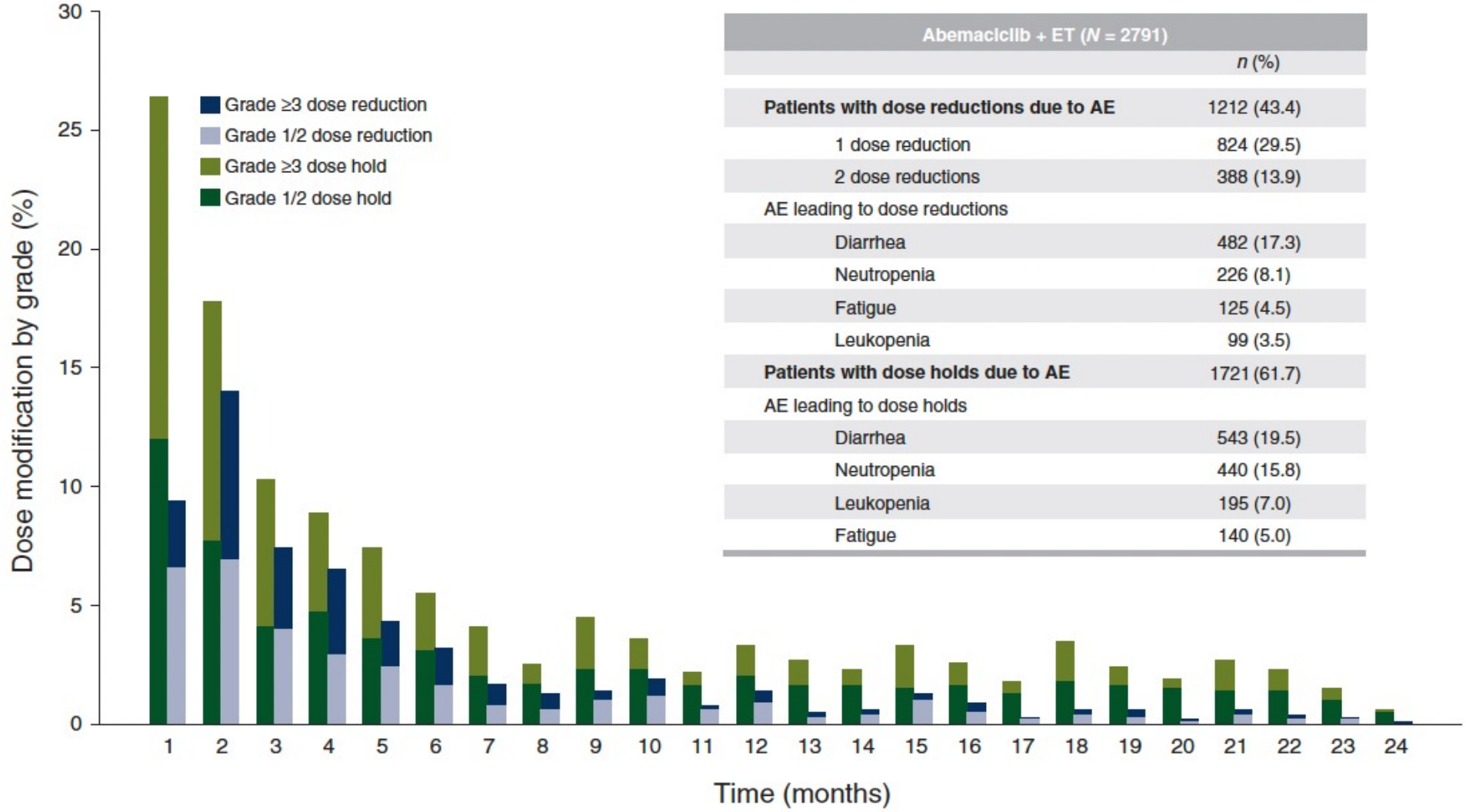
monarchE: Discontinuations Due to Adverse Events (AEs) on the Abemaciclib Arm



Abemaciclib + ET (*N* = 2791)	
AEs leading to discontinuation	***n*** **(%)**
Diarrhea	147 (5.3)
Fatigue	56 (2.0)
Neutropenia	25 (0.9)
Abdominal pain	20 (0.7)
Nausea	11 (0.4)
Leukopenia	11 (0.4)
Blood creatinine increased	10 (0.4)
Vomiting	7 (0.3)
Depression	5 (0.2)
Gamma-glutamyl transferase increased	5 (0.2)
Rash	5 (0.2)
Anemia	4 (0.1)
Dyspnea	3 (0.1)
Dyspepsia	3 (0.1)
Anxiety	3 (0.1)
Composite terms	
VTE	14 (0.5)[b]
ILD	19 (0.7)
Increased transaminases	24 (0.9)

Rugo HS et al. *Ann Oncol* 2022;[Online ahead of print].

monarchE: Abemaciclib Dose Modifications



Abemaciclib + ET (*N* = 2791)	*n* (%)
Patients with dose reductions due to AE	1212 (43.4)
1 dose reduction	824 (29.5)
2 dose reductions	388 (13.9)
AE leading to dose reductions	
Diarrhea	482 (17.3)
Neutropenia	226 (8.1)
Fatigue	125 (4.5)
Leukopenia	99 (3.5)
Patients with dose holds due to AE	1721 (61.7)
AE leading to dose holds	
Diarrhea	543 (19.5)
Neutropenia	440 (15.8)
Leukopenia	195 (7.0)
Fatigue	140 (5.0)

Rugo HS et al. *Ann Oncol* 2022;[Online ahead of print].

OXFORD

JNCI J Natl Cancer Inst (2019) 111(2): djy185

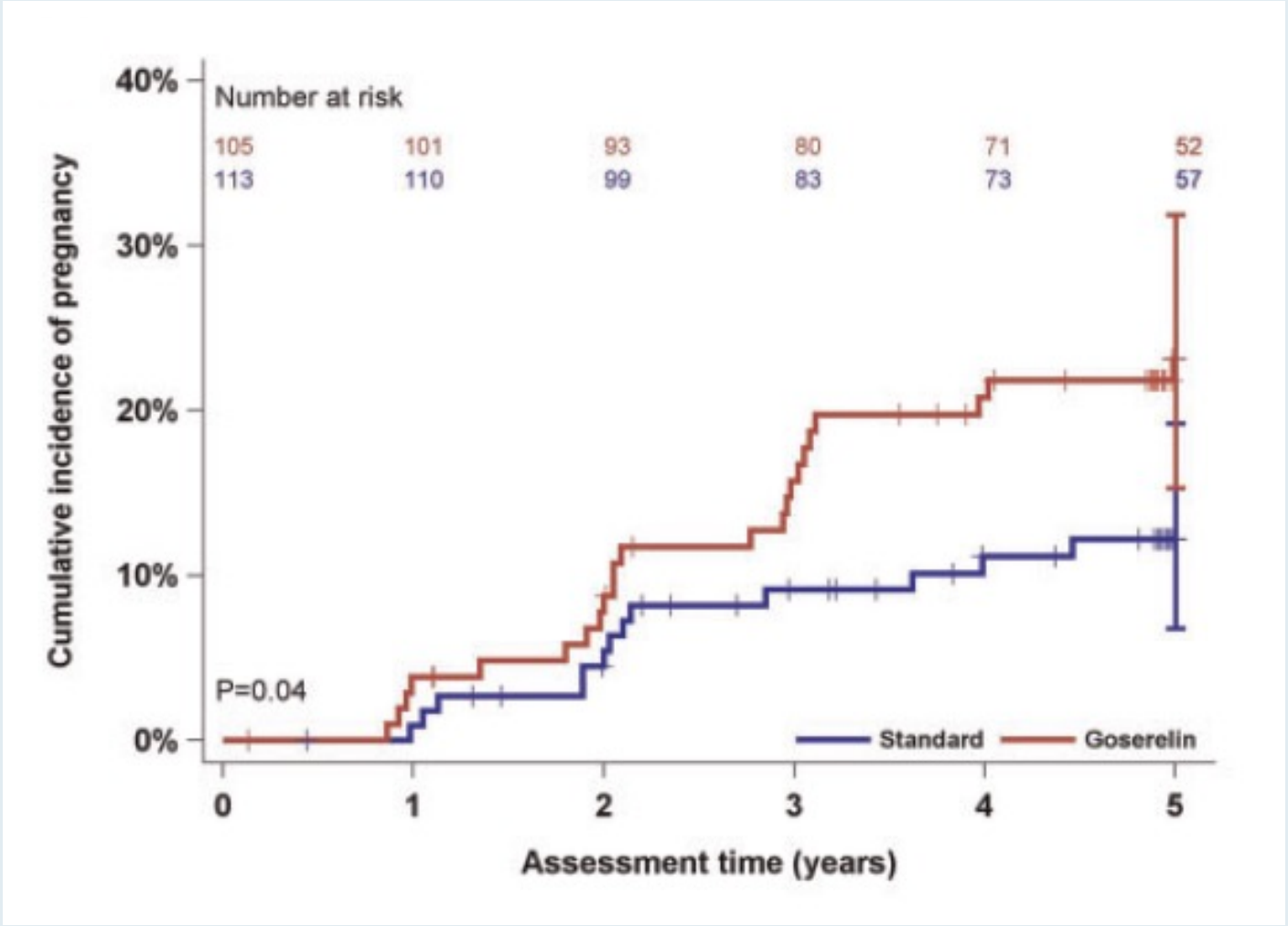
doi: 10.1093/jnci/djy185
First published online October 27, 2018
Brief Communication

BRIEF COMMUNICATION

Final Analysis of the Prevention of Early Menopause Study (POEMS)/SWOG Intergroup S0230

Halle C. F. Moore, Joseph M. Unger, Kelly-Anne Phillips, Frances Boyle, Erika Hitre, Anna Moseley, David J. Porter, Prudence A. Francis, Lori J. Goldstein, Henry L. Gomez, Carlos S. Vallejos, Ann H. Partridge, Shaker R. Dakhil, Agustin A. Garcia, Julie R. Gralow, Janine M. Lombard, John F. Forbes, Silvana Martino, William E. Barlow, Carol J. Fabian, Lori M. Minasian, Frank L. Meyskens Jr, Richard D. Gelber, Gabriel N. Hortobagyi, Kathy S. Albain

POEMS Final Analysis: Incidence of Pregnancy with Goserelin and Chemotherapy versus Standard Chemotherapy Alone for Premenopausal Women with Stage I to IIIA ER/PR-Negative Breast Cancer



Moore HCF et al. *J Natl Cancer Inst* 2019;111(2):210-13.

RTP RESEARCH TO PRACTICE

VOLUME 36 · NUMBER 19 · JULY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

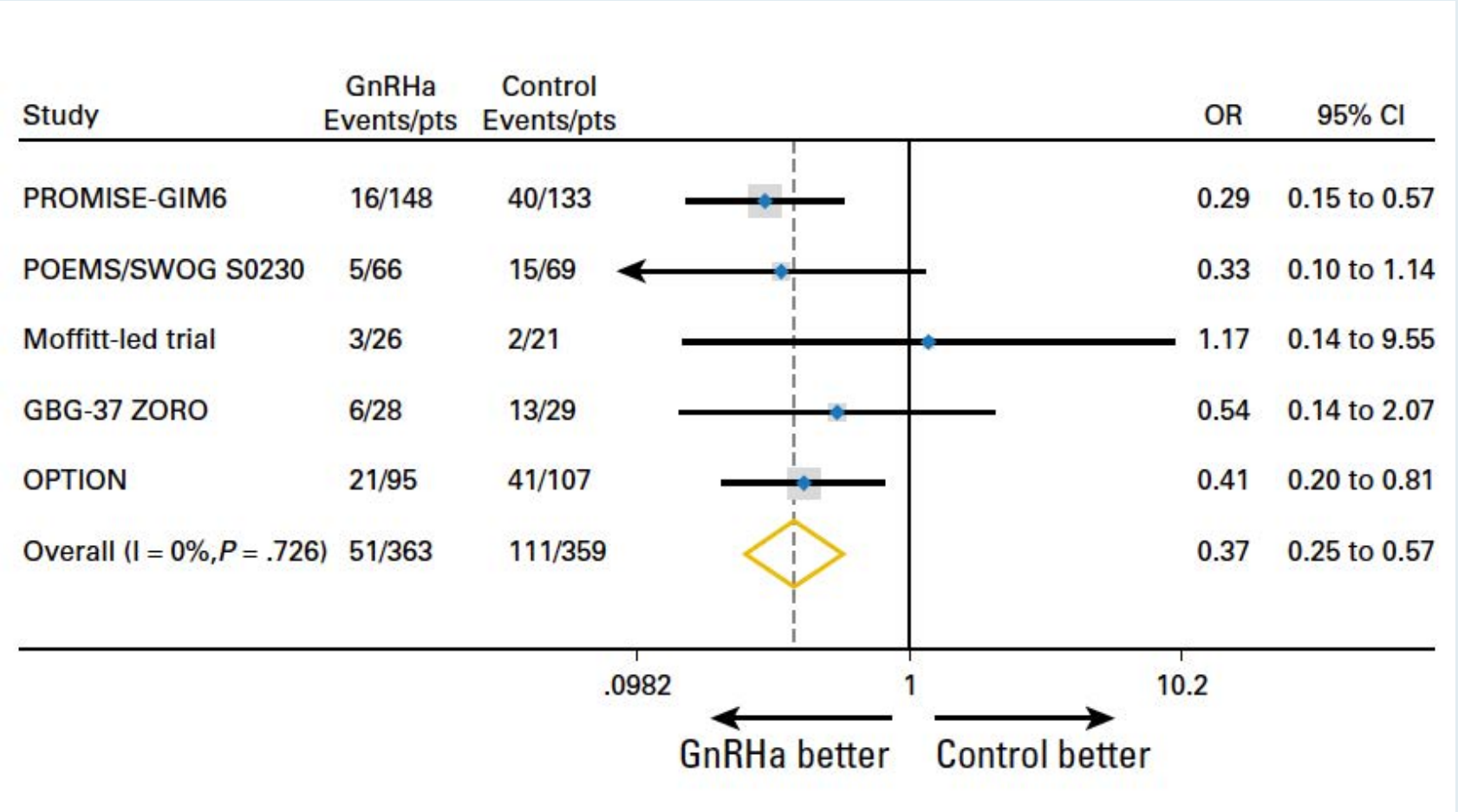
REVIEW ARTICLE

Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient–Level Data

Matteo Lambertini, Halle C.F. Moore, Robert C.F. Leonard, Sibylle Loibl, Pamela Munster, Marco Bruzzone, Luca Boni, Joseph M. Unger, Richard A. Anderson, Keyur Mehta, Susan Minton, Francesca Poggio, Kathy S. Albain, Douglas J.A. Adamson, Bernd Gerber, Amy Cripps, Gianfilippo Bertelli, Sabine Seiler, Marcello Ceppi, Ann H. Partridge, and Lucia Del Mastro

Meta-analysis of Gonadotropin-Releasing Hormone Analogues During Chemotherapy for Localized Breast Cancer: Premature Ovarian Insufficiency by Trial

- 873 randomized patients from 5 major trials were included in the meta-analysis



Lambertini M et al. *J Clin Oncol* 2018;36(19):1981-90.

ER-Positive Metastatic Breast Cancer

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San Antonio Breast Cancer Symposium®, December 6-10, 2022

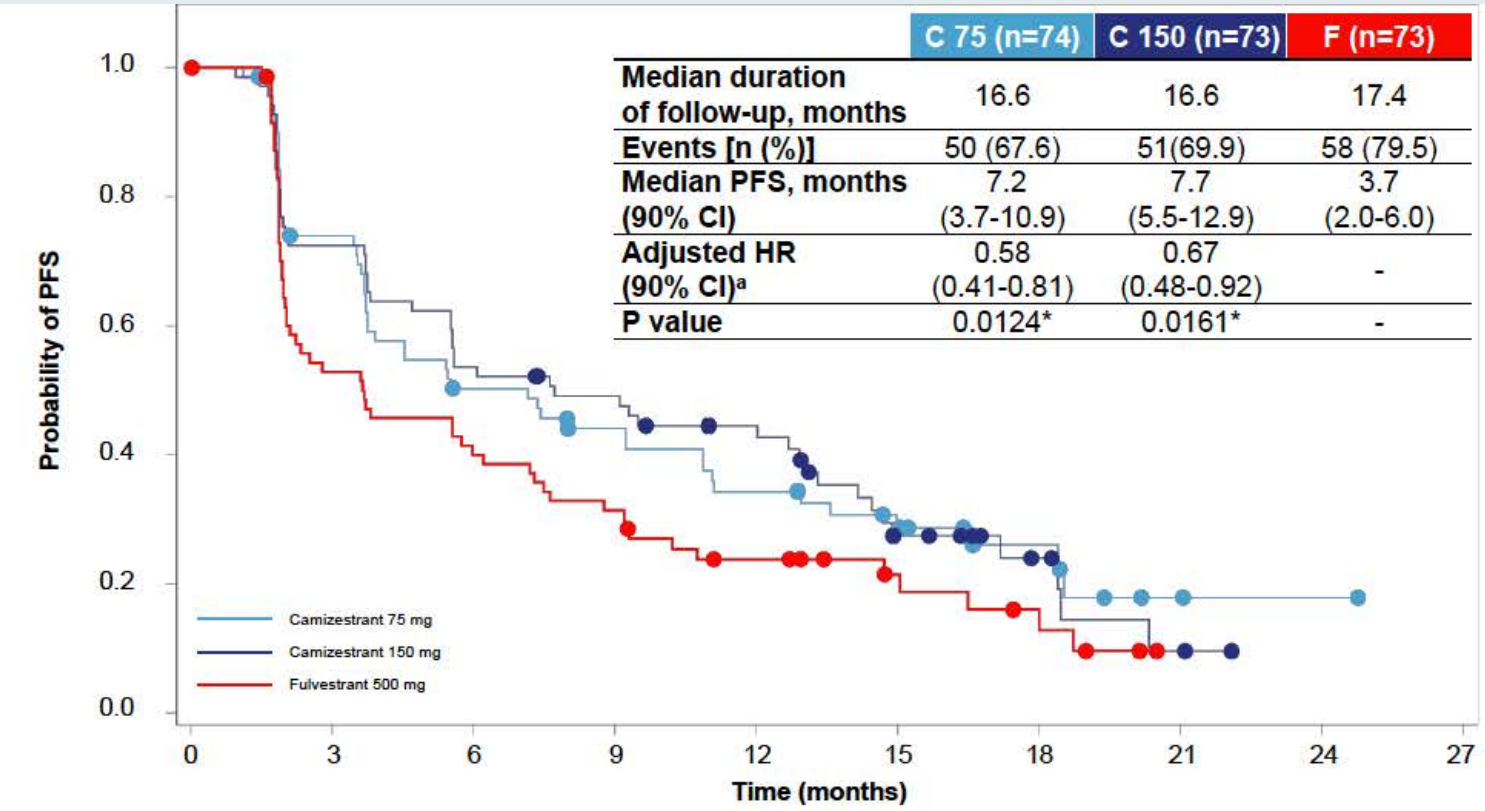
Abstract GS3-02

Camizestrant, a next-generation oral SERD *vs* fulvestrant in post-menopausal women with advanced ER-positive HER2-negative breast cancer: Results of the randomized, multi-dose Phase 2 SERENA-2 trial

Mafalda Oliveira, MD, PhD[1], Denys Pominchuk, PhD[2], Zbigniew Nowecki MD[3], Erika Hamilton, MD[4], Yaroslav Kulyaba, MD[5], Timur Andabekov, PhD[6], Yevhen Hotko, MD[7], Tamar Melkadze, MD[8], Gia Nemsadze, MD, PhD[9], Patrick Neven, MD[10], Yuriy Semegen, MD[11], Vladimir Vladimirov, MD[12], Claudio Zamagni, MD[13], Hannelore Denys, MD, PhD[14], Frédéric Forget, MD[15], Zsolt Horvath, MD, PhD[16], Alfiya Nesterova, MD, PhD[17], Maxine Bennett, PhD[18], Bistra Kirova, MBChB, MSc[19], Teresa Klinowska, PhD[20], Justin P O Lindemann, MBChB, MB[18], Delphine Lissa, PharmD, PhD[18], Alastair Mathewson, PhD[18], Christopher J Morrow, PhD[18], Zuzana Traugottova, MD[21], Ruaan van Zyl, PhD[22], Ekaterine Arkania, MD[23]

[1]Medical Oncology Department, Vall d'Hebron University Hospital and Breast Cancer Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [2]Medical Center Verum, Kyiv, Ukraine; [3]The Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [5]Makiivka City Hospital of Donetsk Region, Makiivka, Ukraine; [6]AV Medical Group, St Petersburg, Russian Federation; [7]Central City Hospital, Uzhgorod National University, Uzhgorod, Ukraine; [8]Oncology and Hematology Department, Academician Fridon Todua Medical Center – Research Institute of Clinical Medicine Tbilisi, Georgia; [9]The Institute of Clinical Oncology, Tbilisi, Georgia; [10]Multidisciplinary Breast Center, University Hospitals Leuven – Campus Gasthuisberg, Leuven, Belgium; [11]Bukovynsky Clinical Oncology Center, Chernivtsi, Ukraine; [12]Pyatigorsky Oncology Dispensary, Pyatigorsk, Russia; [13]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [14]Department of Medical Oncology, Ghent University Hospital, Belgium; [15]Centre Hospitalier de l'Ardenne-Site de Libramont, Libramont-Chevigny, Belgium; [16]Center of Oncoradiology, Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary; [17]Republican Clinical Oncology Dispensary of the Ministry of Health of the Republic of Tatarstan, Russian Federation; [18]Research and Early Development, Oncology R&D, AstraZeneca, Cambridge, UK; [19]Oncology Patient Safety, Oncology R&D, AstraZeneca, Cambridge, UK; [20]Late Development, Oncology R&D, AstraZeneca, Cambridge, UK; [21]Parexel International, Prague, Czech Republic; [22]Parexel International, Bloemfontein, South Africa; [23]Helsicore Israeli Georgian Medical Research Clinic, Tbilisi, Georgia.

SERENA-2 Primary Endpoint: Progression-Free Survival (PFS) by Investigator Assessment



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

C 75	74	50	33	27	21	14	7	2	1	0
C 150	73	50	37	32	25	12	6	2	0	
F	73	37	28	22	14	8	5	0		

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

CDK4/6i: CDK4/6 inhibitor; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

In the overall population, camizestrant produces a statistically significant and clinically meaningful improvement in PFS for both 75 and 150 mg camizestrant doses over fulvestrant

Oliveira M et al. SABCS 2022;Abstract GS3-02.

RTP RESEARCH TO PRACTICE

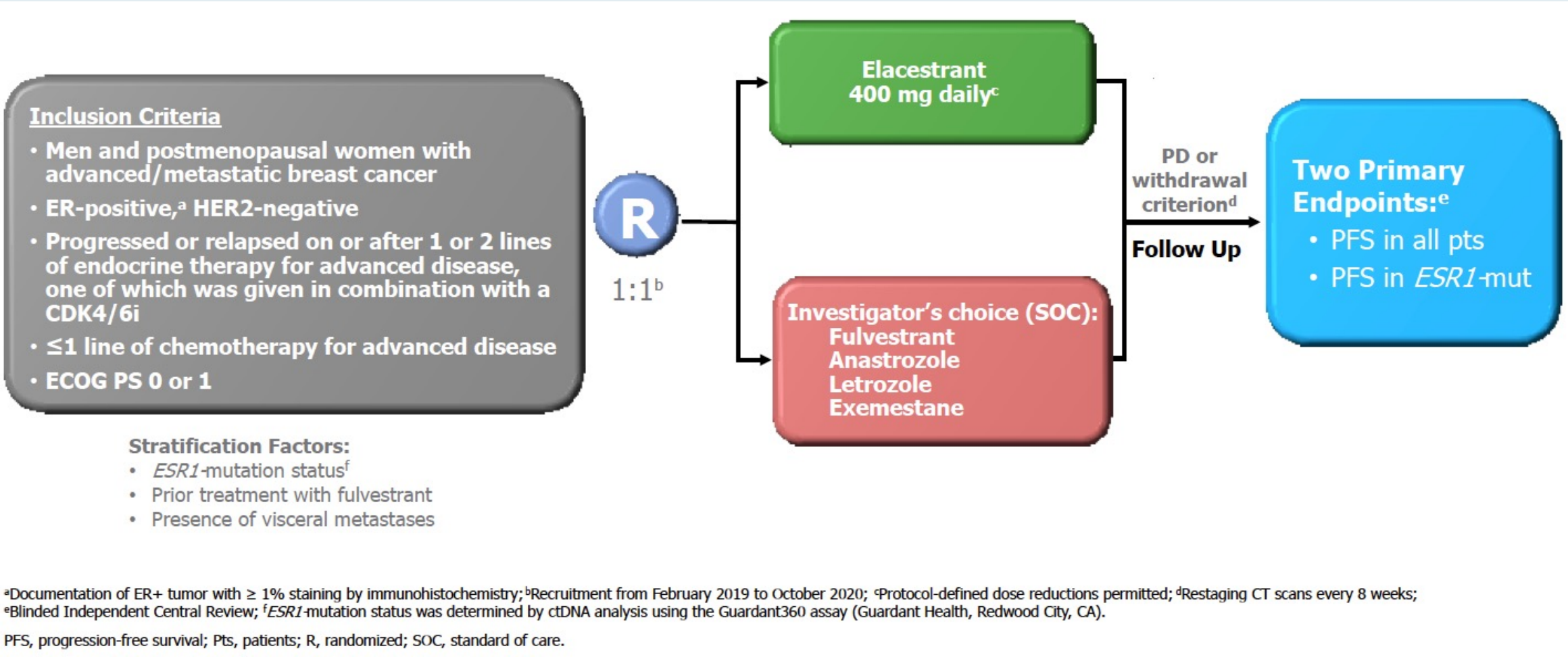
EMERALD: PFS Analyses by CDK4/6 Inhibitor Duration

Duration of CDK4/6i	<6 months		6-12 months		12-18 months		≥18 months	
All patients	**Elacestrant (n = 29)**	**SOC ET (n = 29)**	**Elacestrant (n = 52)**	**SOC ET (n = 46)**	**Elacestrant (n = 52)**	**SOC ET (n = 40)**	**Elacestrant (n = 98)**	**SOC ET (n = 119)**
Median PFS	3.6 mo	1.9 mo	1.9 mo	1.9 mo	3.5 mo	1.8 mo	5.5 mo	3.3 mo
Patients with ESR1 mutations	**Elacestrant (n = 9)**	**SOC ET (n = 8)**	**Elacestrant (n = 25)**	**SOC ET (n = 21)**	**Elacestrant (n = 23)**	**SOC ET (n = 25)**	**Elacestrant (n = 55)**	**SOC ET (n = 56)**
Median PFS	1.9 mo	1.9 mo	1.9 mo	1.8 mo	5.5 mo	1.8 mo	8.6 mo	2.1 mo

SOC ET = standard endocrine therapy

Bardia A et al. SABCS 2022;Abstract GS3-01.

EMERALD Phase III Trial Design



[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

Bardia A et al. SABCS 2022;Abstract GS3-01.

EMERALD: Safety Summary

- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.

Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

Bardia A et al. SABCS 2022;Abstract GS3-01.

RTP RESEARCH TO PRACTICE

Select Ongoing Phase III Trials of Oral SERDs in Development for HR-Positive Advanced Breast Cancer (ABC)

Trial	N	Randomization	Setting	Est primary completion
SERENA-4	1,342	• Camizestrant + palbociclib • Anastrozole + palbociclib	Untreated ABC	August 2026
persevERA	978	• Giredestrant + palbociclib • Letrozole + palbociclib	Untreated ABC	April 2024
SERENA-6	302	• Camizestrant + (palbociclib or abemaciclib) • (Anastrozole or letrozole) + (palbociclib or abemaciclib)	Detectable ESR1 mutation w/o PD during first-line AI + CDK4/6i	September 2023
EMBER-3	860	• Imlunestrant • Imlunestrant + abemaciclib • Investigator's choice of ET	ABC previously treated with ET + CDK4/6i	April 2024
evERA	320	• Giredestrant + everolimus • Exemestane + everolimus	ABC previously treated with ET + CDK4/6i	July 2024
heredERA	812	• Giredestrant + pertuzumab/trastuzumab/hyaluronidase-zzxf • Pertuzumab/trastuzumab/hyaluronidase-zzxf	Untreated ER+, HER2+ ABC after first-line pertuzumab/trastuzumab/ hyaluronidase-zzxf + taxane	August 2026

SERD = selective ER degrader

www.clinicaltrials.gov. Accessed November 2022.

RTP RESEARCH TO PRACTICE

Capivasertib and Fulvestrant for Patients with Aromatase Inhibitor-Resistant Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results from the Phase III CAPItello-291 Trial

Turner NC et al.

SABCS 2022;Abstract GS3-04.

CAPItello-291 Phase III Study Design

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Capivasertib	400 mg twice daily, 4 days on, 3 days off	43.7% altered
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks	
Placebo	Twice daily, 4 days on, 3 days off	37% altered
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks	

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

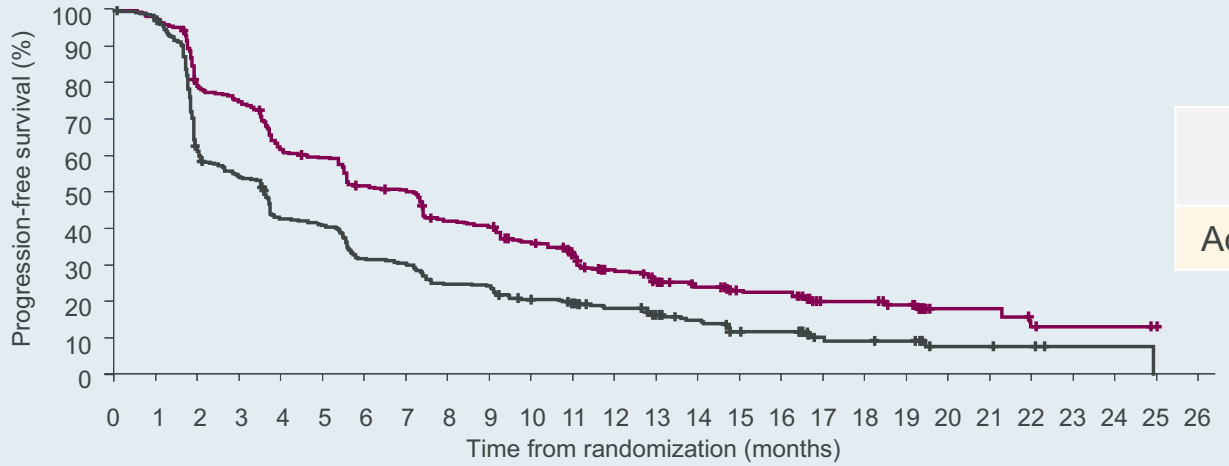
Summary of Demographics

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

Turner NC et al. SABCS 2022;Abstract GS3-04.

CAPItello-291 Dual-Primary Endpoint: Investigator-Assessed PFS in the Overall Population

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



Number of patients at risk

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

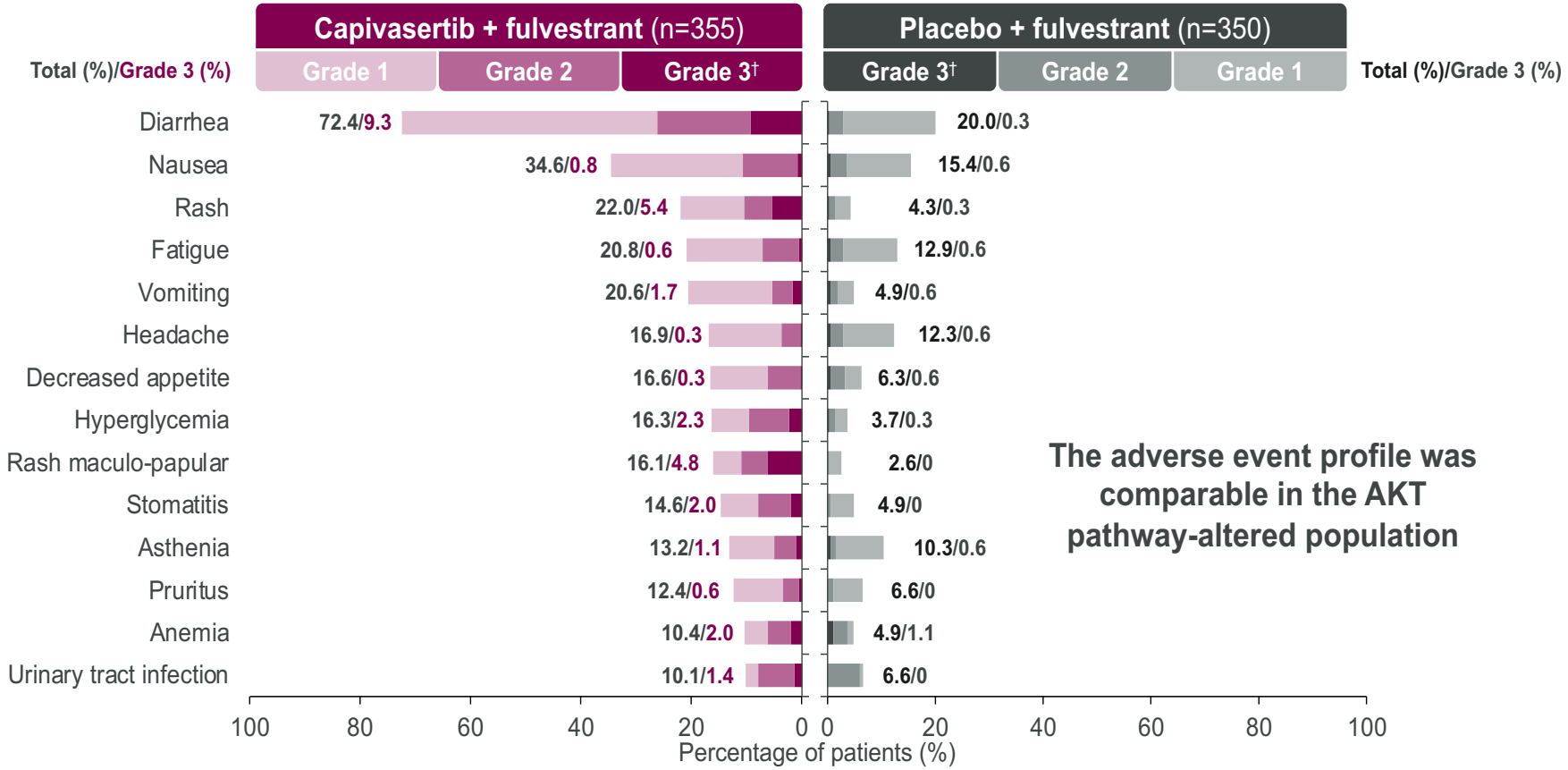
	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	

Turner NC et al. SABCS 2022;Abstract GS3-04.

RTP RESEARCH TO PRACTICE

CAPItello-291: Safety

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



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

Turner NC et al. SABCS 2022;Abstract GS3-04.

HER2-Positive Localized Breast Cancer

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FDA-Approved Agents for Localized HER2-Positive Breast Cancer

Agent	Setting	Pivotal trials	Regimens	Year approved
Trastuzumab	Adjuvant, HER2-positive localized breast cancer (LBC), first line	NSABP B-31 N9831 BCIRG 006 HERA	AC-T-placebo vs AC-T-H AC-T vs AC-H vs AC-T-H ACT vs ACT-H vs TC-H Observation vs trastuzumab	2006
Pertuzumab	Neoadjuvant, HER2-positive LBC	NEOSPHERE	TD vs PTD vs PT vs PD	2013
Pertuzumab	Adjuvant, HER2-positive LBC	APHINITY	Chemotherapy + trastuzumab + pertuzumab vs placebo	2017
Neratinib	Extended adjuvant, HER2-positive LBC	ExteNET	Placebo vs neratinib	2017
T-DM1	Adjuvant, HER2-positive LBC with residual disease after neoadjuvant taxane and trastuzumab-based treatment	KATHERINE	Trastuzumab vs T-DM1	2019

AC-T = doxorubicin, cyclophosphamide and paclitaxel; AC-T-H = doxorubicin, cyclophosphamide, paclitaxel and trastuzumab; AC-H = doxorubicin, cyclophosphamide, and trastuzumab; TC-H = docetaxel, cyclophosphamide and trastuzumab; TD = trastuzumab and docetaxel; PTD = pertuzumab, trastuzumab and docetaxel; PT = trastuzumab and pertuzumab; PD = pertuzumab and docetaxel

Choong GM et al. *CA Cancer J Clin* 2020;70(5):355-74.

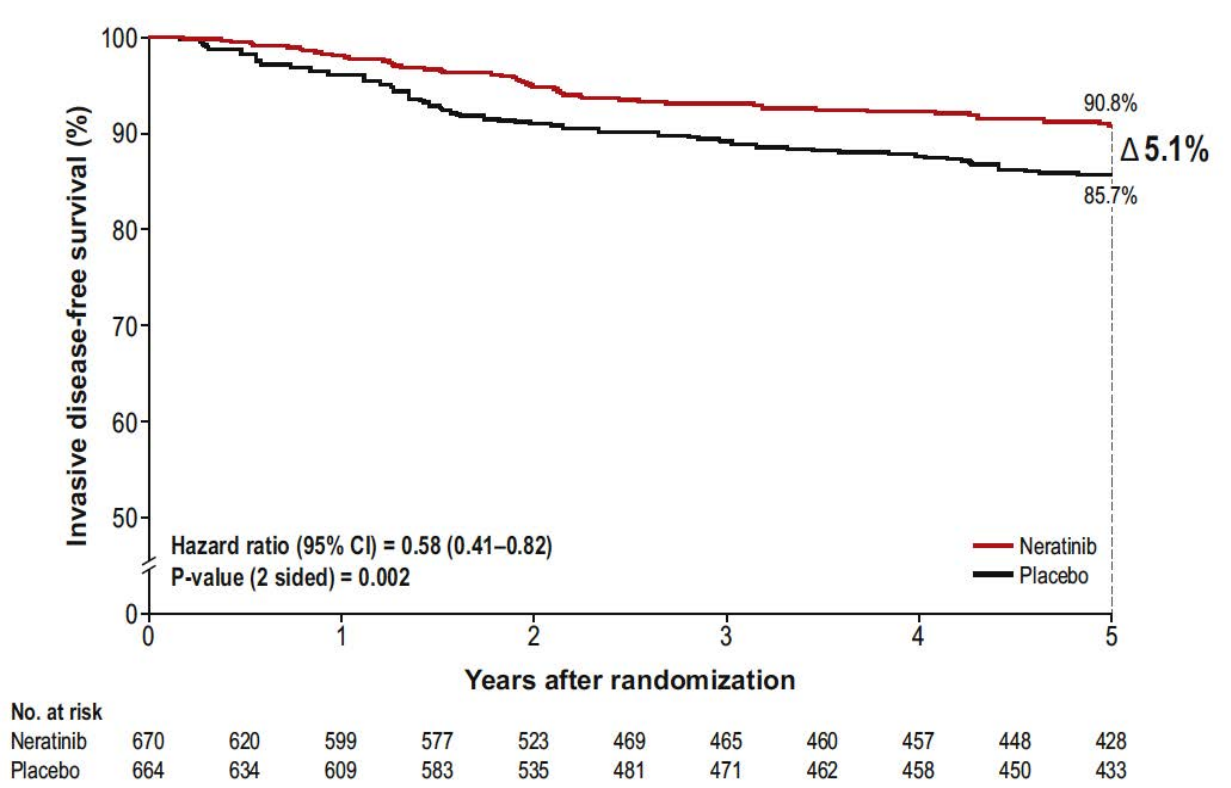
Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial

Arlene Chan,[1] Beverly Moy,[2] Janine Mansi,[3] Bent Ejlertsen,[4] Frankie Ann Holmes,[5] Stephen Chia,[6] Hiroji Iwata,[7] Michael Gnant,[8] Sibylle Loibl,[9] Carlos H. Barrios,[10] Isil Somali,[11] Snezhana Smichkoska,[12] Noelia Martinez,[13] Mirta Garcia Alonso,[14] John S. Link,[15] Ingrid A. Mayer,[16] Søren Cold,[17] Serafin Morales Murillo,[18] Francis Senecal,[19] Kenichi Inoue,[20] Manuel Ruiz-Borrego,[21] Rina Hui,[22] Neelima Denduluri,[23] Debra Patt,[24] Hope S. Rugo,[25] Stephen R.D. Johnston,[26] Richard Bryce,[27] Bo Zhang,[27] Feng Xu,[27] Alvin Wong,[27] Miguel Martin,[28] for the ExteNET Study Group

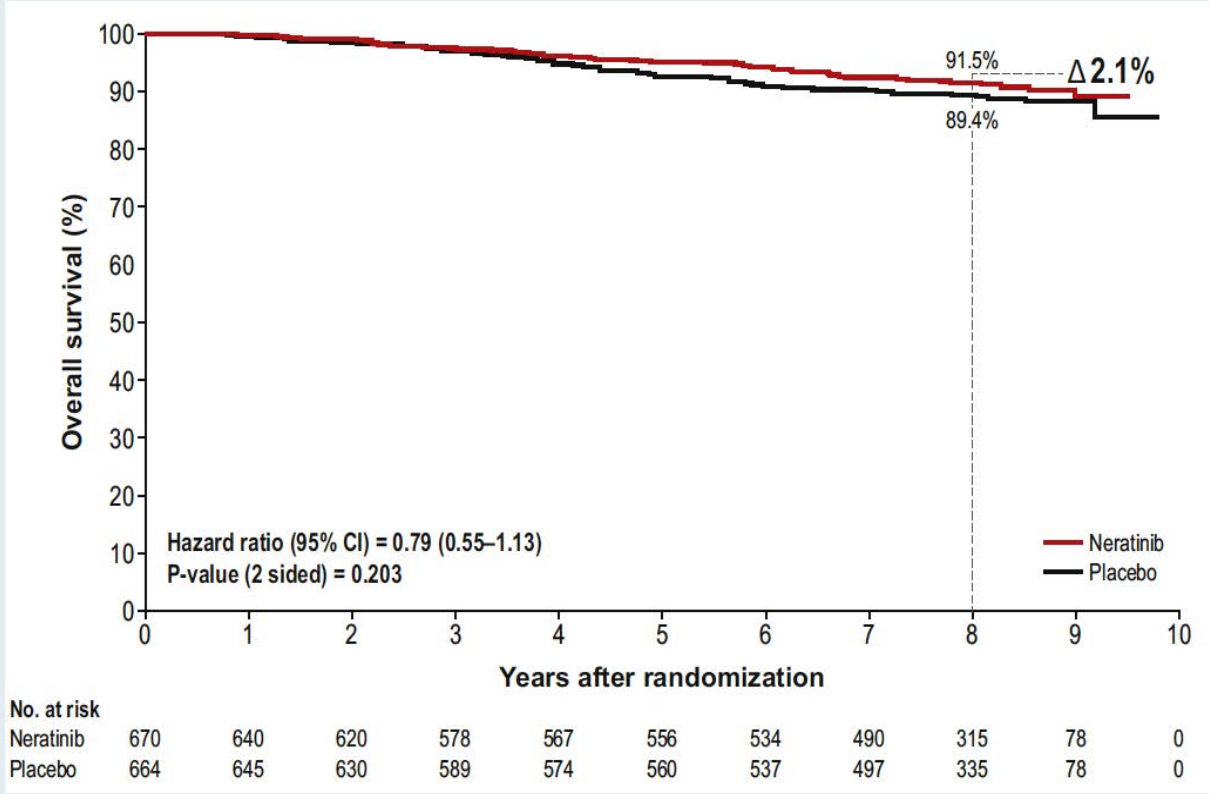
***Clin Breast Cancer* 2021;21(1):80-91.**

ExteNET: Final Analysis with Neratinib for HER2-Positive Localized Breast Cancer (HR+/≤ 1-Year Population)

Invasive disease-free survival at 5 years



Overall survival at 8 years



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

RTP RESEARCH TO PRACTICE

ExteNET: Cumulative Incidence of CNS Recurrence

Population or subgroup	Events, n		Cumulative incidence of CNS recurrence	
	Neratinib	Placebo	Neratinib	Placebo
Intention-to-treat population (n = 2,840)	16	23	1.3%	1.8%
HR-positive/≤1-year population (EU indication) (n = 1,334)	4	12	0.7%	2.1%
Adjuvant or neoadjuvant therapy (n = 1,334)				
Adjuvant (n = 980)	3	6	0.7%	1.5%
Neoadjuvant (n = 354)	1	6	0.7%	3.7%
pCR status (n = 354)				
No (n = 295)	1	5	0.8%	3.6%
Yes (n = 38)	0	1	0	5.0%

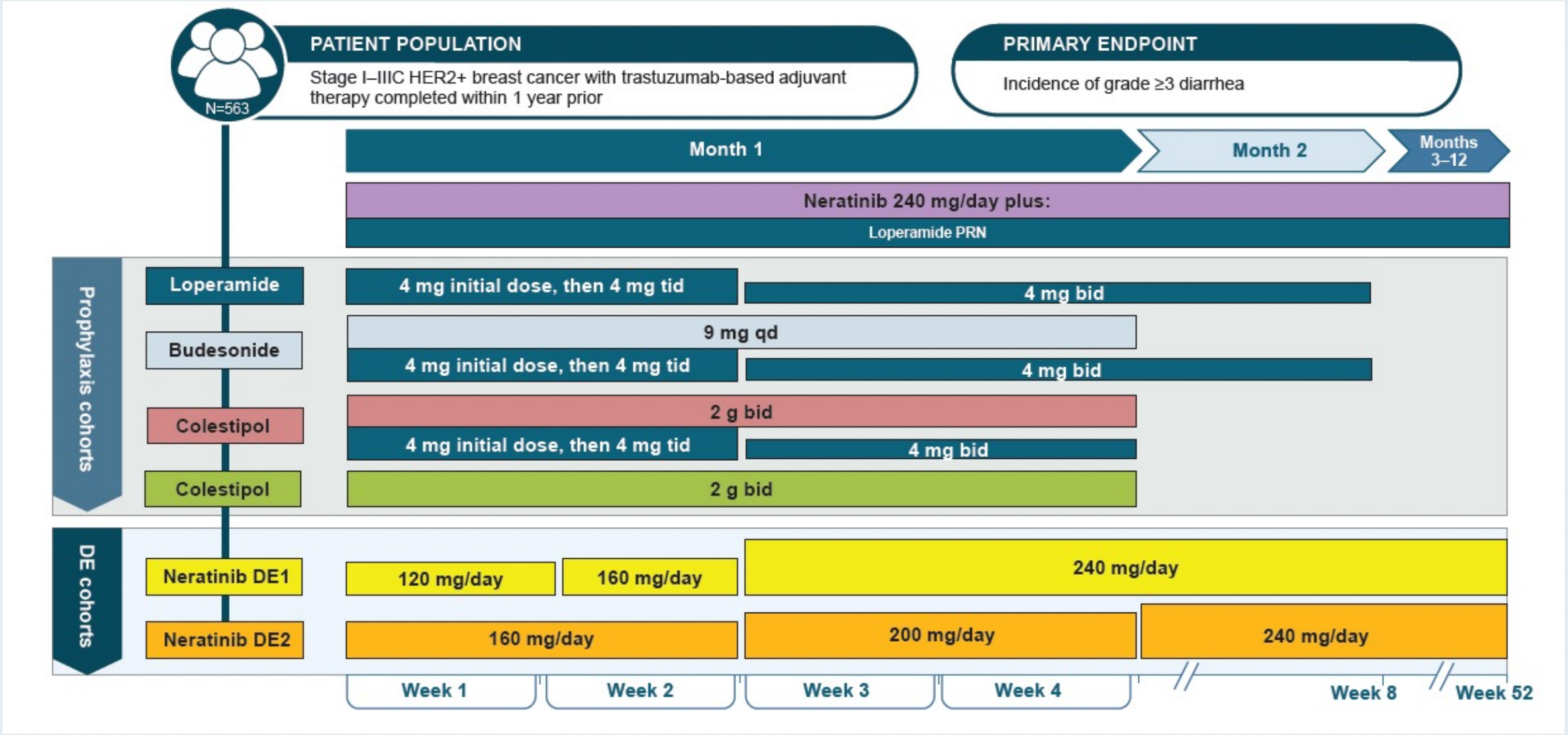
Chan A et al. *Clin Breast Cancer* 2021;21(1):80-91; Holmes FA et al. San Antonio Breast Cancer Symposium 2020;Abstract PD3-03.

Effect of Diarrheal Prophylaxis or Dose Escalation on Neratinib-Associated Diarrhea and Tolerability in Patients with HER2+ Early-Stage Breast Cancer: Final Findings from the CONTROL Trial

Chan A et al.

ESMO Breast 2022;Abstract 73P.

CONTROL Trial Cohorts: Study Schema



Chan A et al. ESMO Breast 2022;Abstract P73.

CONTROL: Diarrhea Profile

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

Chan A et al. ESMO Breast 2022;Abstract P73.

CONTROL: Conclusions

- These final findings from the CONTROL study show improved tolerability of neratinib with all diarrhea prophylaxis and DE schedules. These results demonstrate that neratinib is well tolerated as extended-adjuvant treatment for patients with HER2-positive breast cancer after 1 year of trastuzumab.
- Adoption of neratinib DE with loperamide PRN during the first 2 weeks of treatment (DE1 cohort) was associated with a lower rate of Grade 3 diarrhea compared to the CONTROL prophylaxis strategies, the DE2 strategy and the neratinib arm in the ExteNET trial.
- The DE1 cohort also had the lowest rate of diarrhea-related discontinuations (3%) and dose holds (12%) compared to the other strategies investigated in the CONTROL trial and the neratinib arm in the ExteNET trial.
- These findings suggest that several modalities, most notably neratinib DE1 with loperamide PRN, allow patients to stay on treatment longer and receive the full benefit of neratinib therapy.
- The US package label for neratinib now includes both the mandatory loperamide prophylaxis regimen and the DE1 strategy from CONTROL as diarrhea-mitigation strategies.

Chan A et al. ESMO Breast 2022;Abstract P73.

HER2-Positive or HER2-Low Metastatic Breast Cancer

RTP
RESEARCH
TO PRACTICE

FDA Grants Regular Approval to Fam-Trastuzumab Deruxtecan-nxki for Breast Cancer

Press Release – May 4, 2022

"The Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy.

In December 2019, fam-trastuzumab deruxtecan-nxki received accelerated approval for adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. The following trial was the confirmatory trial for the accelerated approval.

Efficacy was based on DESTINY-Breast03 (NCT03529110), a multicenter, open-label, randomized trial that enrolled 524 patients with HER2-positive, unresectable, and/or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-fam-trastuzumab-deruxtecan-nxki-breast-cancer

RTP RESEARCH TO PRACTICE

Trastuzumab Deruxtecan Granted FDA Approval for HER2-Low Breast Cancer

Press Release – August 5, 2022

"Today, the US Food and Drug Administration approved fam-trastuzumab-deruxtecan-nxki, an IV infusion for the treatment of patients with unresectable (unable to be removed) or metastatic (spread to other parts of the body) HER2-low breast cancer. This is the first approved therapy targeted to patients with the HER2-low breast cancer subtype, which is a newly defined subset of HER2-negative breast cancer.

Patients with HER2-low breast cancer are eligible for fam-trastuzumab-deruxtecan-nxki if they have received a prior chemotherapy in the metastatic setting, or their cancer returned during, or within 6 months of completing, adjuvant chemotherapy.

This approval is based on DESTINY-Breast04, a randomized, multicenter, open label clinical trial that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer."

https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-her2-low-breast-cancer

RTP RESEARCH TO PRACTICE

ASCO rapid recommendations

Chemotherapy and Targeted Therapy for Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That Is Either Endocrine-Pretreated or Hormone Receptor–Negative: ASCO Guideline Rapid Recommendation Update

Beverly Moy, MD, MPH[1]; R. Bryan Rumble, MSc[2]; and Lisa A. Carey, MD, ScM[3]; for the Chemotherapy and Targeted Therapy for HER2-Negative Metastatic Breast Cancer that is Either Endocrine-Pretreated or Hormone Receptor–Negative Expert Panel

Updated Recommendation

Patients with HER2 IHC 1+ or 2+ and ISH-negative metastatic breast cancer who have received at least one prior chemotherapy for metastatic disease, and if hormone receptor–positive are refractory to endocrine therapy, should be offered treatment with trastuzumab deruxtecan

J Clin Oncol 2022 August 4;[Online ahead of print].

RTP RESEARCH TO PRACTICE

2022 ASCO ANNUAL MEETING **Abstract LBA3** DESTINY-Breast04

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

Shanu Modi Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, NY, USA

June 5, 2022

Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

On behalf of the DESTINY-Breast04 investigators

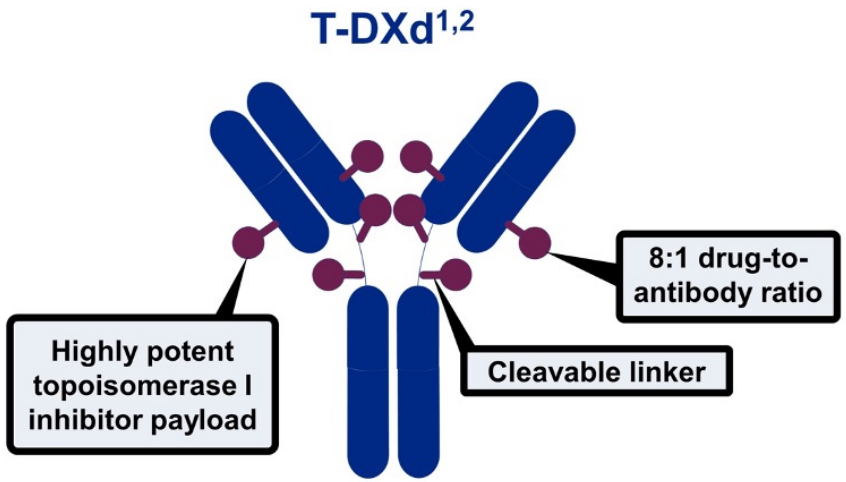
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

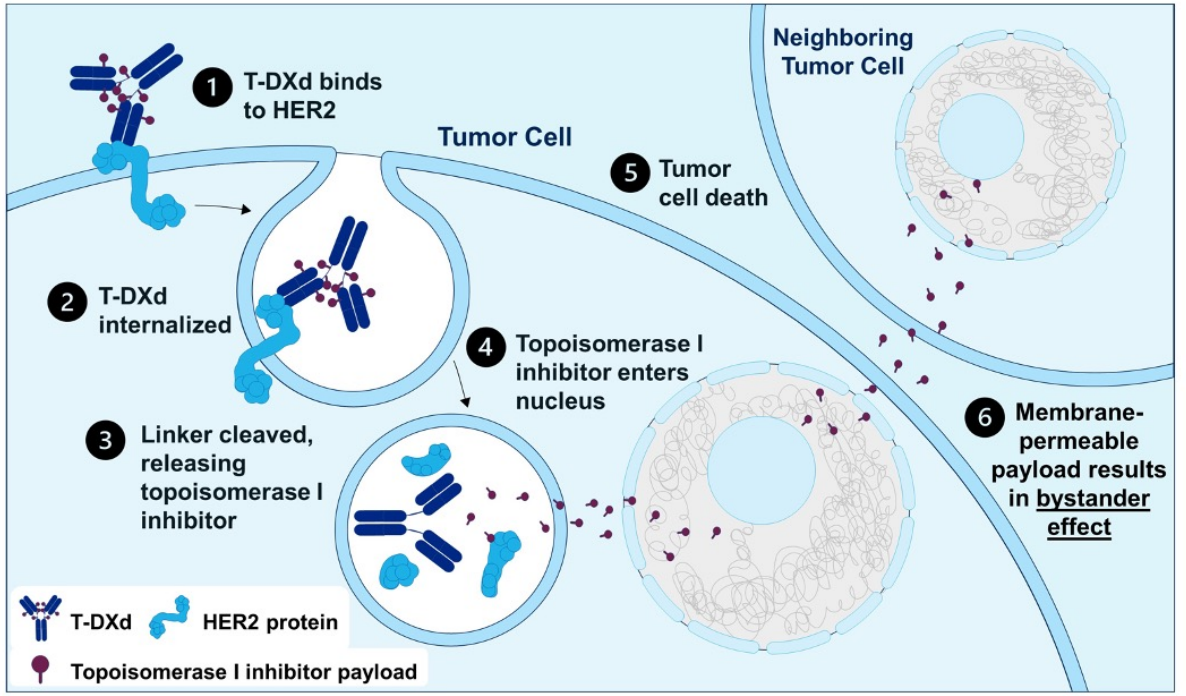
Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

T-DXd Mechanism of Action, Bystander Effect and Rationale for Targeting HER2-Low Breast Cancer



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



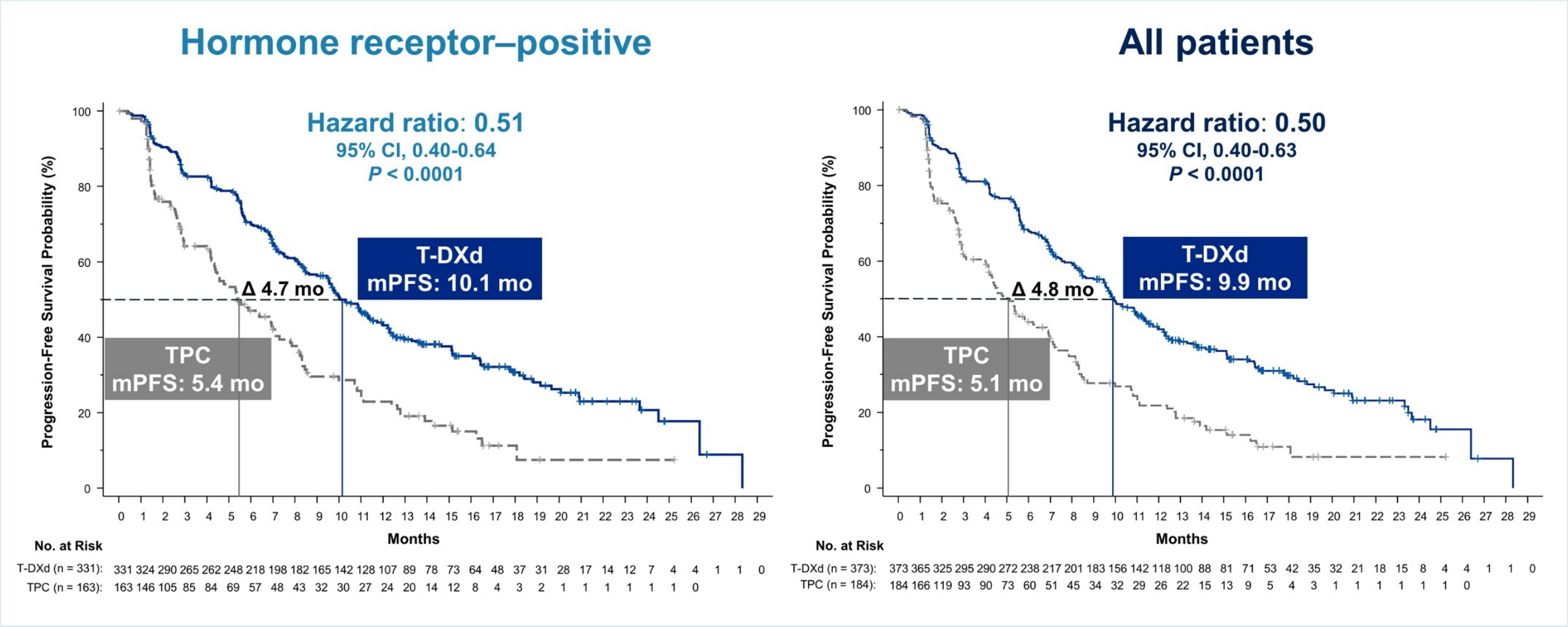
Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

ORR = objective response rate

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022 July 7;387(1):9-20.

DESTINY-Breast04: PFS for HR-Positive (Primary Endpoint) and All Patients



mPFS = median progression-free survival

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022 July 7;387(1):9-20.

RTP RESEARCH TO PRACTICE

Ann Oncol 2022 March;33(3):321-9.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

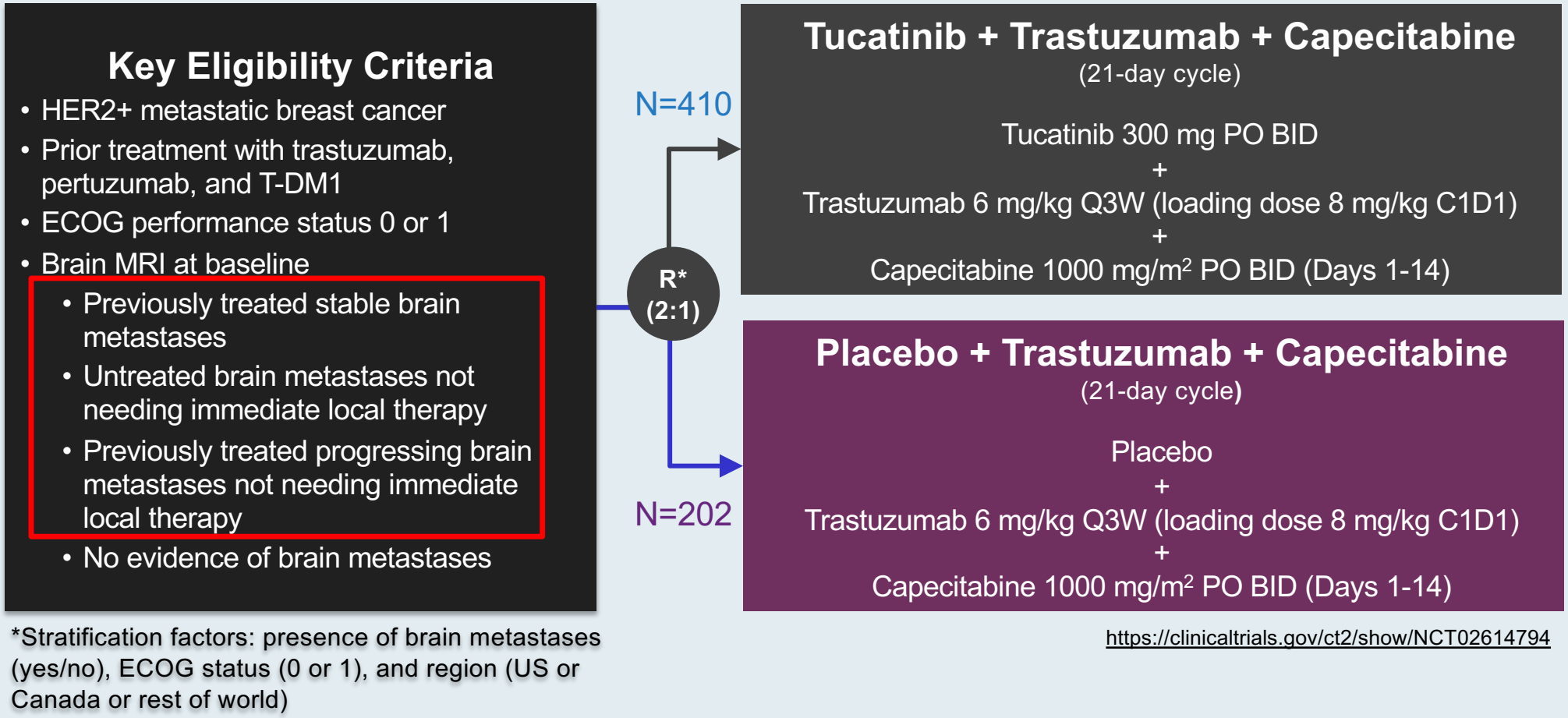
ORIGINAL ARTICLE

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

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

RTP RESEARCH TO PRACTICE

HER2CLIMB Trial Design

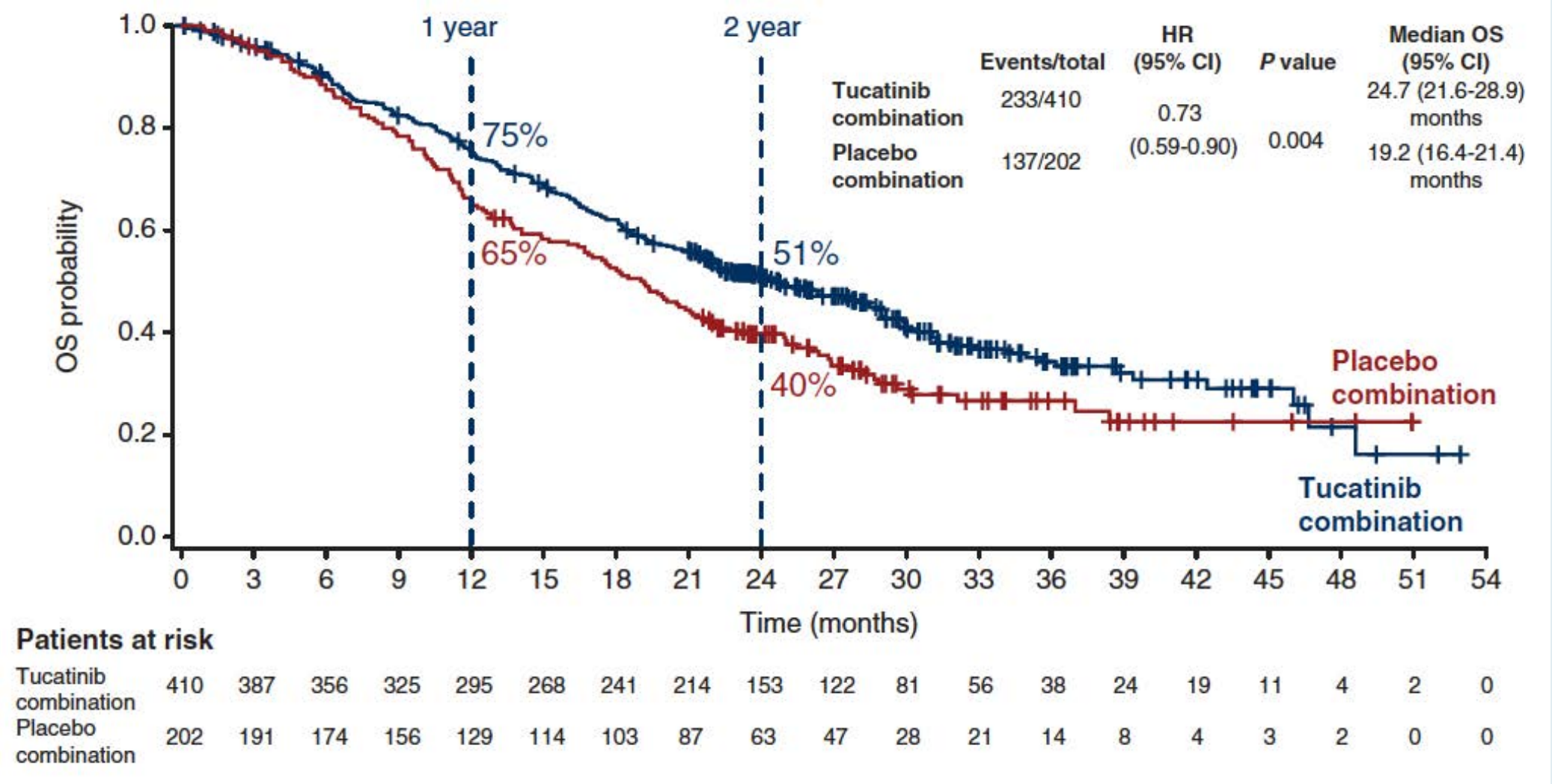


*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

https://clinicaltrials.gov/ct2/show/NCT02614794

Murthy RK et al. SABCS 2019;Abstract GS1-01.

HER2CLIMB: Final Overall Survival (OS) Analysis



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

Patients at risk

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

Curigliano G et al. *Ann Oncol* 2022;33(3):321-9.

RTP RESEARCH TO PRACTICE

HER2CLIMB: Adverse Events

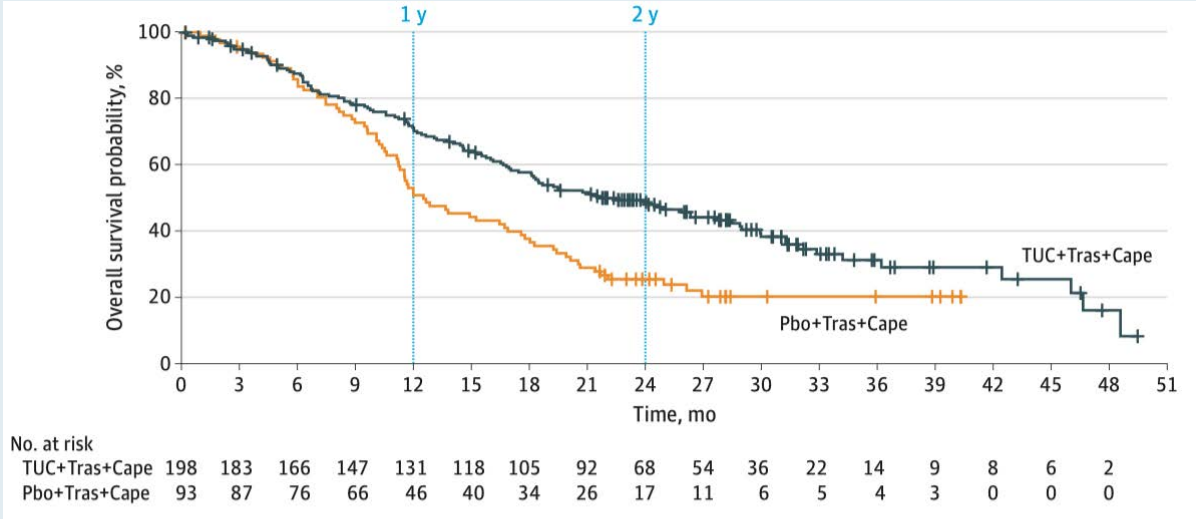
Adverse event	Tucatinib combination (*N* = 404) *n* (%)		Placebo combination (*N* = 197) *n* (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	401 (99.3)	245 (60.6)	191 (97.0)	101 (51.3)
Diarrhea	331 (81.9)	53 (13.1)	106 (53.8)	17 (8.6)
Palmar-plantar erythrodysesthesia syndrome	264 (65.3)	57 (14.1)	105 (53.3)	18 (9.1)
Nausea	243 (60.1)	16 (4.0)	88 (44.7)	7 (3.6)
Fatigue	193 (47.8)	22 (5.4)	87 (44.2)	8 (4.1)
Vomiting	152 (37.6)	13 (3.2)	51 (25.9)	8 (4.1)
Decreased appetite	105 (26.0)	3 (0.7)	41 (20.8)	0
Stomatitis	105 (26.0)	10 (2.5)	28 (14.2)	1 (0.5)
Headache	96 (23.8)	3 (0.7)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	89 (22.0)	19 (4.7)	22 (11.2)	1 (0.5)
Anemia	88 (21.8)	17 (4.2)	24 (12.2)	5 (2.5)
Alanine aminotransferase increased	85 (21.0)	23 (5.7)	13 (6.6)	1 (0.5)
Blood bilirubin increased	81 (20.0)	4 (1.0)	21 (10.7)	5 (2.5)

Curigliano G et al. *Ann Oncol* 2022 March;33(3):321-9.

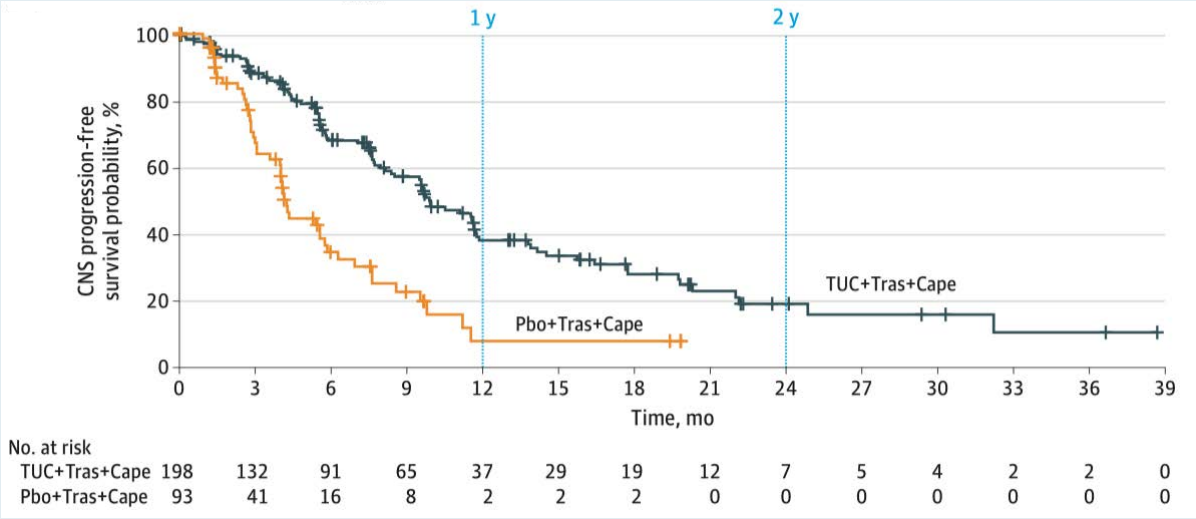
RTP RESEARCH TO PRACTICE

HER2CLIMB: Overall Survival and Intracranial Progression-Free Survival for Patients with Brain Metastases

OS



IPFS



Lin NU et al. *JAMA Oncol* 2023;9(2):197-205.

RTP RESEARCH TO PRACTICE

ARTICLES
https://doi.org/10.1038/s41591-022-01935-8
nature medicine

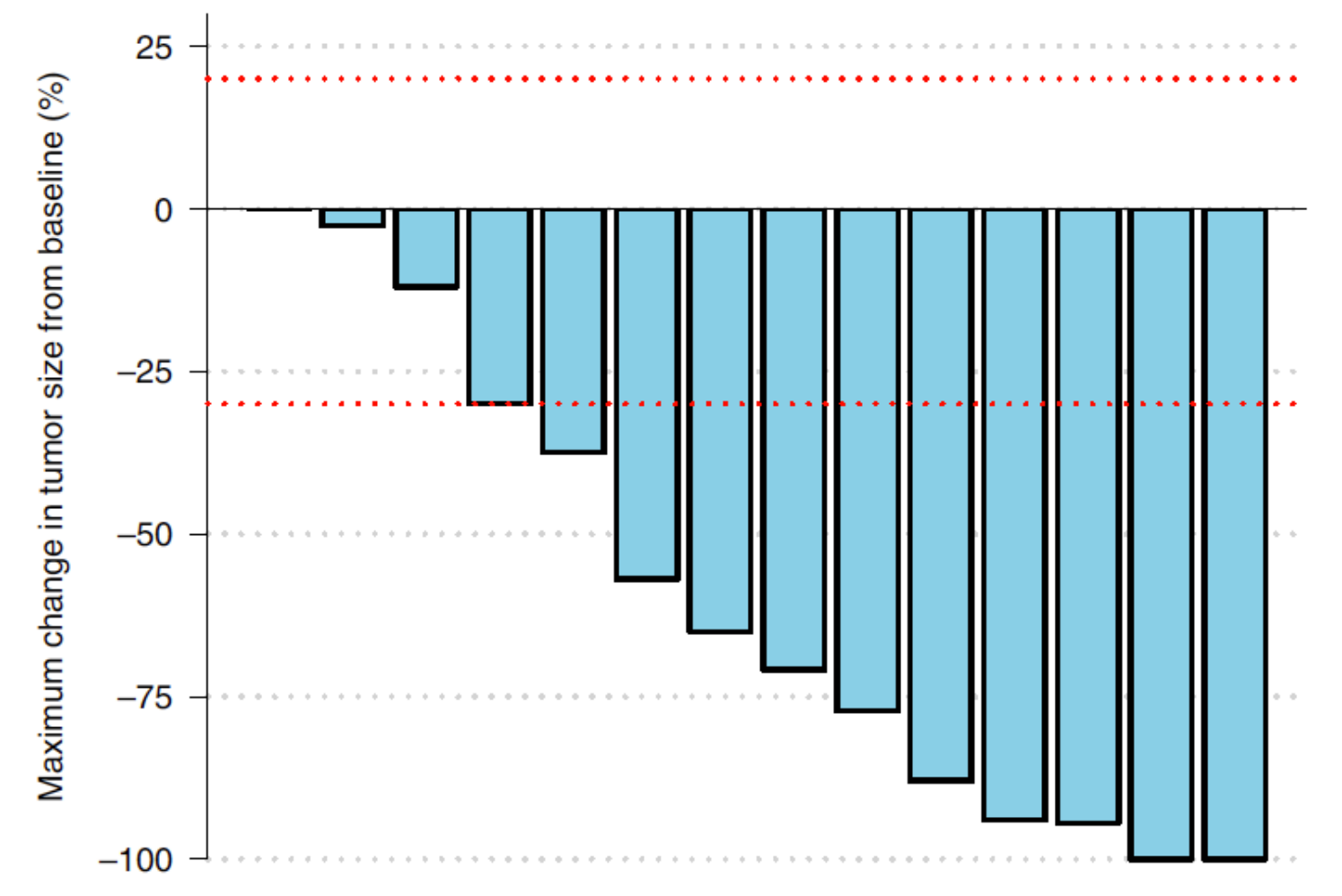
OPEN

Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial

Rupert Bartsch[1], Anna Sophie Berghoff[1], Julia Furtner[2], Maximilian Marhold[1], Elisabeth Sophie Bergen[1], Sophie Roider-Schur[3], Angelika Martina Starzer[1], Heidrun Forstner[1], Beate Rottenmanner[1], Karin Dieckmann[4], Zsuzsanna Bago-Horvath[5], Helmuth Haslacher[6], Georg Widhalm[7], Aysegül Ilhan-Mutlu[1], Christoph Minichsdorfer[1], Thorsten Fuereder[1], Thomas Szekeres[6], Leopold Oehler[3], Birgit Gruenberger[8], Christian F. Singer[9], Ansgar Weltermann[10], Rainer Puhr[1] and Matthias Preusser[1] ✉

2022;28;1840-7.

TUXEDO-1: Response with Trastuzumab Deruxtecan by RANO-BM Criteria



RANO-BM = Response assessment in neuro-oncology brain metastases

Bartsch R et al. *Nature Med* 2022;28;1840-7.

RTP RESEARCH TO PRACTICE

PARP Inhibitors

FDA Approves Olaparib as Adjuvant Treatment for HER2-Negative High-Risk Localized Breast Cancer with a Germline BRCA Mutation Previously Treated with Neoadjuvant or Adjuvant Chemotherapy

Press Release – March 11, 2022

"Olaparib has been approved by the US Food and Drug Administration (FDA) for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), human epidermal growth factor receptor 2 (HER2)-negative high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Patients will be selected for therapy based on an FDA-approved companion diagnostic for olaparib.

The approval was based on results from the Phase 3 OlympiA trial, including data for the trial's primary endpoint of invasive disease-free survival (IDFS), which were presented during the 2021 American Society of Clinical Oncology Annual Meeting and published in *The New England Journal of Medicine,* as well as overall survival (OS) data from a more recent interim analysis."

https://finance.yahoo.com/news/fda-approves-lynparza-olaparib-adjuvant-005100263.html

RTP RESEARCH TO PRACTICE

Abstract VP1-2022

ESMO VIRTUAL PLENARY

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

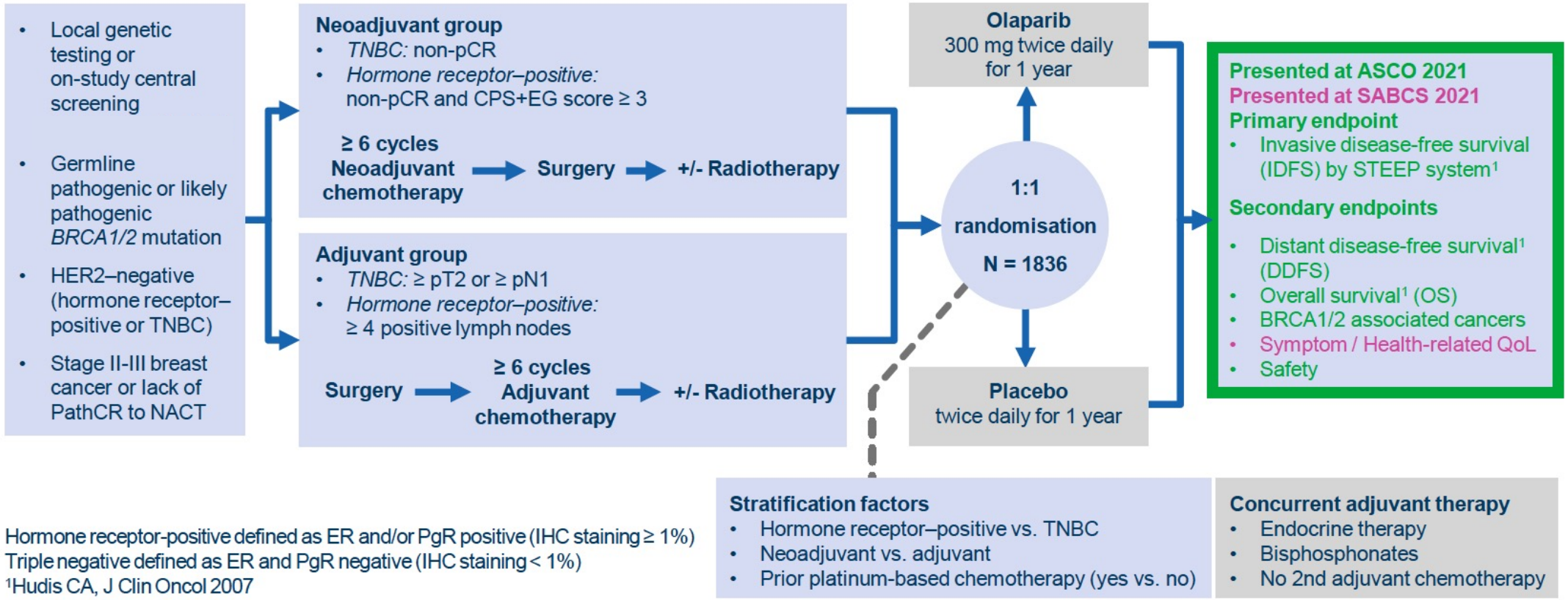
Andrew Nicholas James Tutt[1], Judy Garber[2], Richard D. Gelber[2], Kelly-Anne Phillips[3], Andrea Eisen[4], Oskar Thor Jóhannsson[5], Priya Rastogi[6], Karen Yongzhi Cui[7], Seock-Ah Im[8], Rinat Yerushalmi[9], Adam Matthew Brufsky[10], Maria Taboada[11], Giovanna Rossi[12], Greg Yothers[13], Christian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

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

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

RTP RESEARCH TO PRACTICE

OLYMPIA: TRIAL SCHEMA

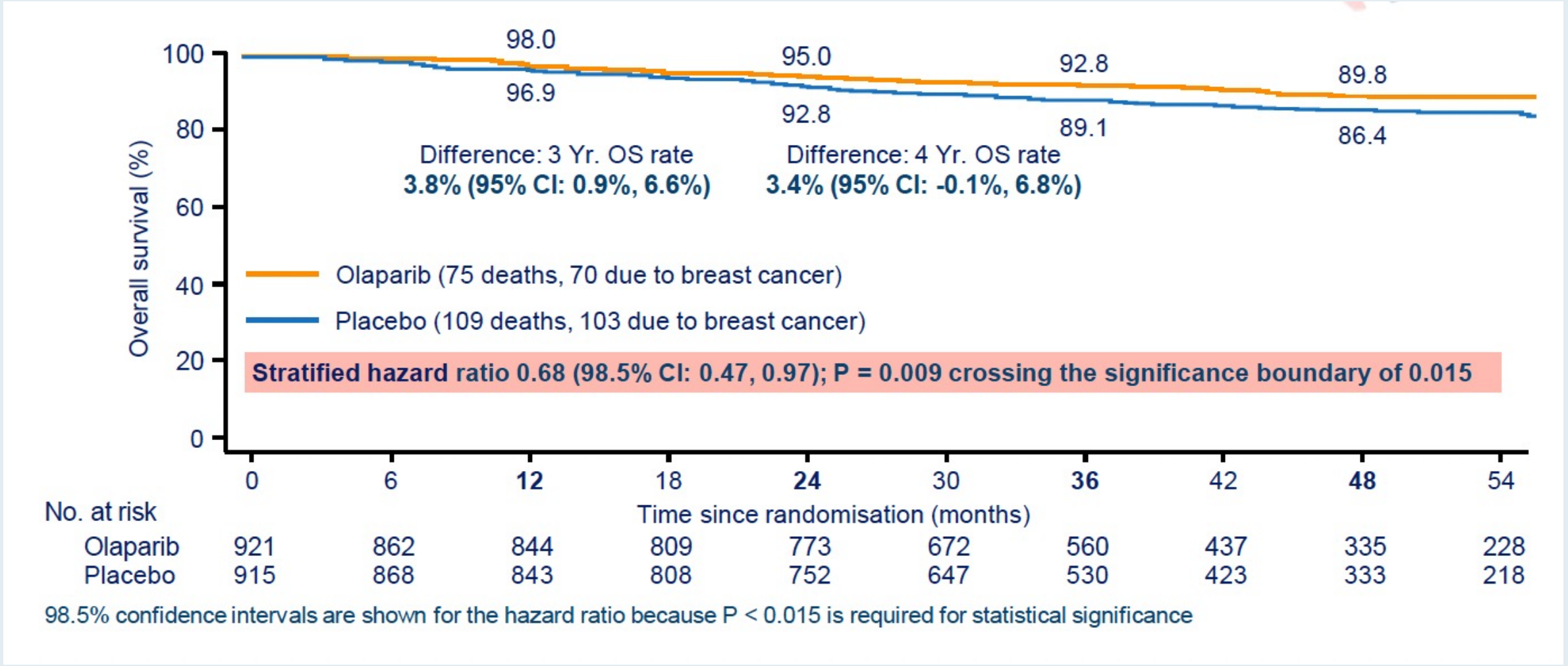


Hormone receptor-positive defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Andrew Nicholas James Tutt MB ChB PhD FMedSci

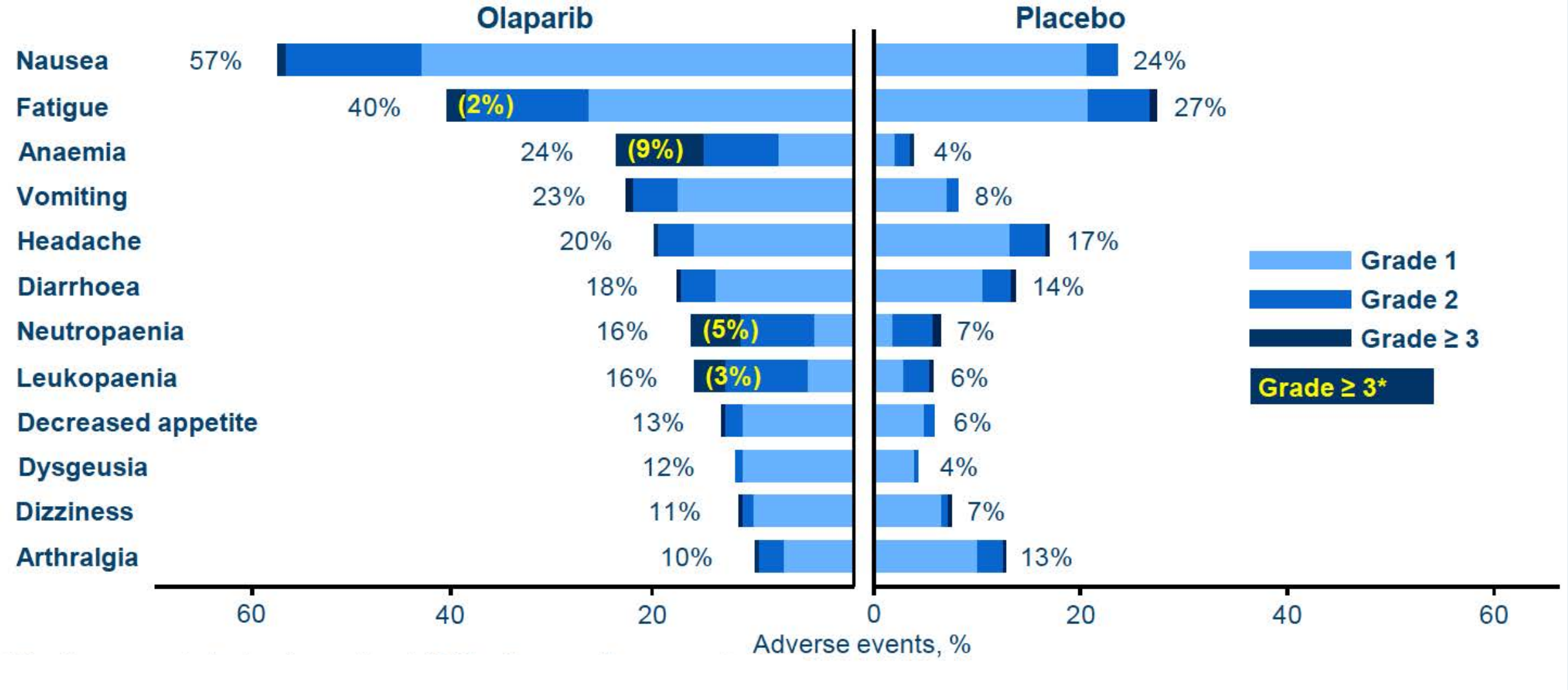
Tutt ANJ et al. ESMO Virtual Plenary 2022;Abstract VP1-2022.

OlympiA: Overall Survival



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

OlympiA: Adverse Events of Any Grade in ≥10% of Patients



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

Pivotal Phase III Trials Supporting the FDA Approvals of Olaparib and Talazoparib for Metastatic Breast Cancer with a Germline BRCA Mutation

Trial	Eligibility	Randomization	Primary endpoint
OlympiAD[1] (n = 302)	• HER2-negative metastatic BC – ER-positive and/or PR-positive or TNBC • Deleterious or suspected deleterious gBRCA mutation • Prior anthracycline and taxane • ≤2 prior chemotherapy lines in metastatic setting	• Olaparib • Physician's choice – Capecitabine – Eribulin – Vinorelbine	• PFS by blinded independent central review
EMBRACA[2] (n = 431)	• HER2-negative locally advanced or metastatic BC • Germline BRCA1 or BRCA2 mutation • ≤3 prior cytotoxic chemotherapy regimens • Prior treatment with a taxane and/or anthracycline unless medically contraindicated	• Talazoparib • Physician's choice – Capecitabine – Eribulin – Gemcitabine – Vinorelbine	• PFS by blinded independent central review

[1] Robson M et al. *N Engl J Med* 2017;377(6):523-33. [2] Litton JK et al. SABCS 2017;Abstract GS6-07; www.clinicaltrials.gov. Accessed August 2019.

OlympiAD and EMBRACA: Efficacy Summary

	OlympiAD[1-3]	EMBRACA[4-6]
HR (PFS)	0.58	0.54
HR (PFS) ER/PR-positive	0.82	0.47
HR (PFS) TNBC	0.43	0.60
HR (OS)	0.84	0.76
ORR	59.9% (vs 28.8% TPC)	67.6% (vs 27.2% TPC)

TPC = treatment of physician's choice

Cross-trial comparisons are challenging in terms of determining the relative efficacy and tolerability of treatments

[1] Robson M et al. *N Engl J Med* 2017;377(6):523-33. [2] Robson M et al. *Ann Oncol* 2019;30(4):558-66. [3] Robson M et al. San Antonio Breast Cancer Symposium 2019;Abstract PD4-03. [4] Litton JK et al. *N Engl J Med* 2018;379(8):753-63. [5] Litton JK et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07. [6] Rugo HS et al. ASCO 2018;Abstract 1069.

OlympiAD and EMBRACA: Adverse Event (AE) and Quality of Life Summary

	OlympiAD [1,2]	EMBRACA[3,4]
Serious AEs Grade ≥3	36.6% (vs 50.5% TPC)	25.5% (v. 25.4% TPC)
Anemia Grade ≥3	16.1%	39.2%
Neutropenia Grade ≥3	9.3%	20.9%
Thrombocytopenia Grade ≥3	2.4%	14.7%
MDS/AML	0	0
Nausea (any grade)	58.0%	48.6%
Alopecia (any grade)	3.4%	25.2%
Dose modification/reduction due to AE	25.4% (vs 30.8% TPC)	66% (vs 60% TPC)
Treatment discontinuation due to AE	4.9% (vs 7.7% TPC)	5.9% (vs 8.7% TPC)

Cross-trial comparisons are challenging in terms of determining the relative efficacy and tolerability of treatments

[1] Robson M et al. *N Engl J Med* 2017;377(6):523-33. [2] Robson M et al. *Ann Oncol* 2019;30(4):558-66. [3] Litton JK et al. *N Engl J Med* 2018;379(8):753-63. [4] Litton JK et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07.

Immunotherapy

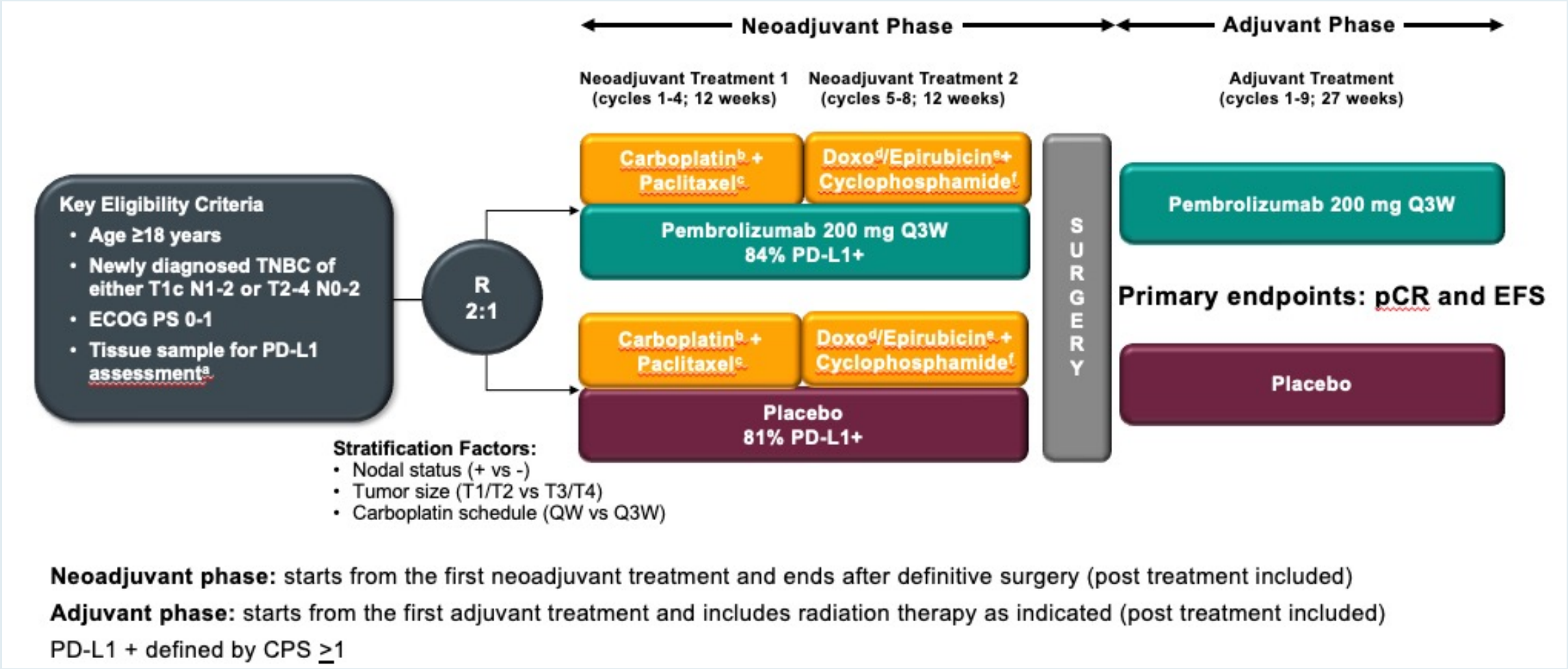
The NEW ENGLAND JOURNAL of MEDICINE
2022;386(6):556-67

ORIGINAL ARTICLE

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, R. Dent, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, M. Untch, P.A. Fasching, F. Cardoso, J. Andersen, D. Patt, M. Danso, M. Ferreira, M.-A. Mouret-Reynier, S.-A. Im, J.-H. Ahn, M. Gion, S. Baron-Hay, J.-F. Boileau, Y. Ding, K. Tryfonidis, G. Aktan, V. Karantza, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

KEYNOTE-522: Phase III Trial Schema



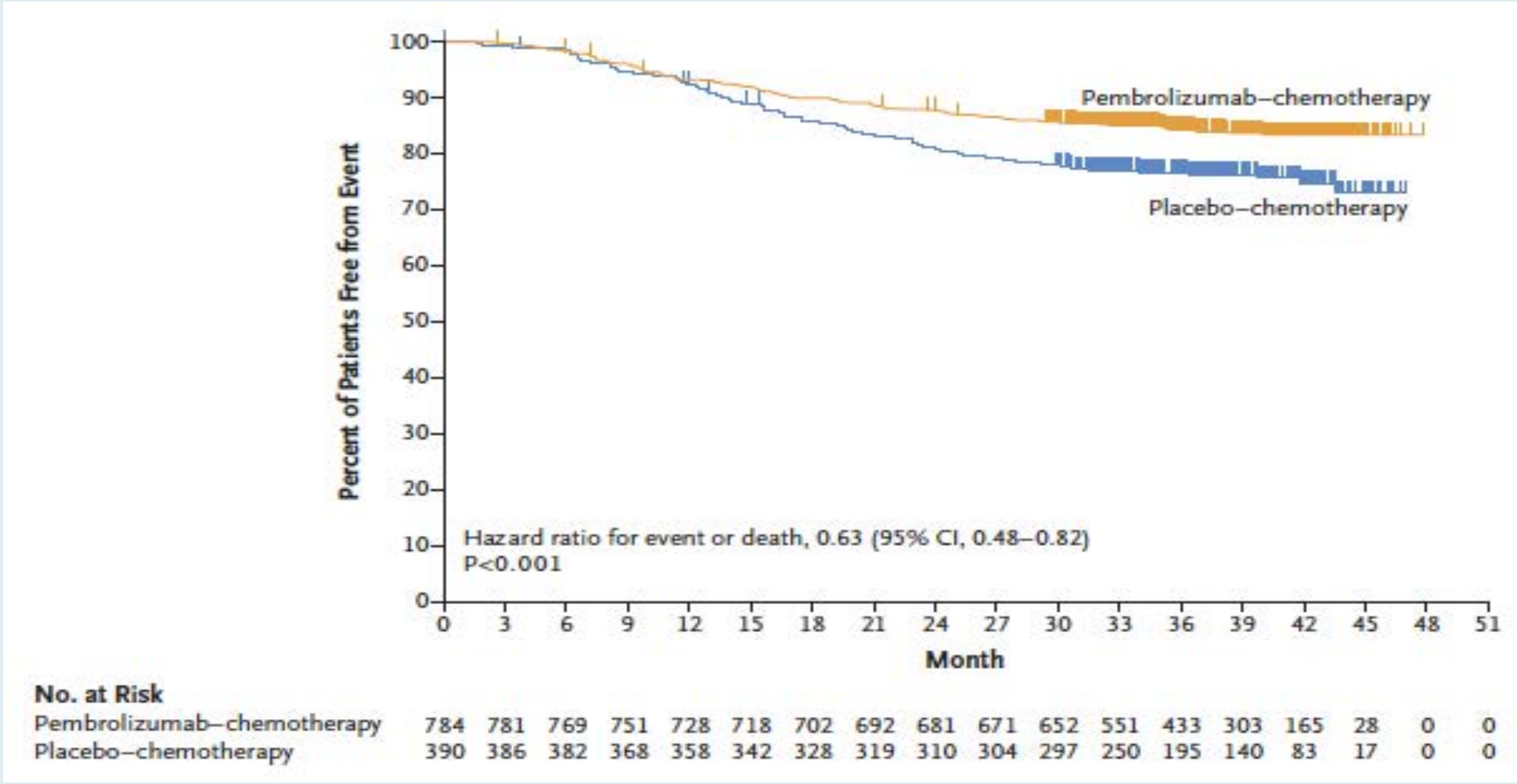
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

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

PD-L1 + defined by CPS ≥1

Schmid P et al. *N Engl J Med* 2020;382:810-21.

KEYNOTE-522: Event-Free Survival According to Treatment Group (ITT Population)



Schmid P et al. *N Engl J Med* 2022;386(6):556-67.

KEYNOTE-355: Adverse Events

Event	Pembrolizumab–Chemotherapy (N=562)		Placebo–Chemotherapy (N=281)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any adverse event	554 (98.6)	438 (77.9)	276 (98.2)	207 (73.7)
Adverse events that were attributed to the trial regimen†	541 (96.3)	383 (68.1)	267 (95.0)	188 (66.9)
Anemia	276 (49.1)	93 (16.5)	129 (45.9)	41 (14.6)
Neutropenia	231 (41.1)	167 (29.7)	107 (38.1)	84 (29.9)
Nausea	221 (39.3)	9 (1.6)	116 (41.3)	4 (1.4)
Alopecia	186 (33.1)	5 (0.9)	94 (33.5)	3 (1.1)
Fatigue	161 (28.6)	16 (2.8)	84 (29.9)	7 (2.5)
Neutrophil count decreased	126 (22.4)	98 (17.4)	74 (26.3)	57 (20.3)
Alanine aminotransferase increased	115 (20.5)	34 (6.0)	46 (16.4)	13 (4.6)
Immune-mediated adverse events‡	149 (26.5)	30 (5.3)	18 (6.4)	0
Hypothyroidism	89 (15.8)	2 (0.4)	9 (3.2)	0
Hyperthyroidism	24 (4.3)	1 (0.2)	3 (1.1)	0
Pneumonitis	14 (2.5)	6 (1.1)	0	0
Colitis	10 (1.8)	2 (0.4)	4 (1.4)	0
Severe skin reactions	10 (1.8)	10 (1.8)§	1 (0.4)	0

Cortes J et al. *N Engl J Med* 2022;387(3):217-26.

RTP RESEARCH TO PRACTICE

Symptoms of Immunotherapy Toxicity

Hypophysitis
(fatigue)

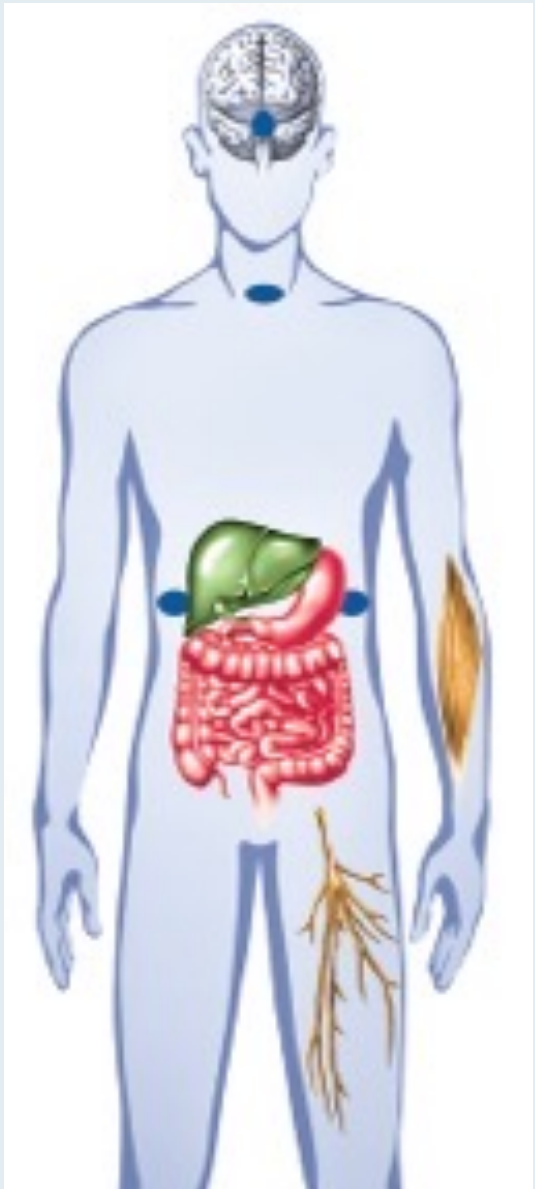
Thyroiditis
(over/underactive thyroid)

Adrenal Insufficiency
(fatigue)

Diabetes Mellitus
(type I, II, fatigue, DKA)

Colitis
(diarrhea, abd pain)

Dermatitis
(rash, itch, blistering)



Pneumonitis
(dyspnea, cough)

Myocarditis
(chest pain, dyspnea)

Hepatitis
(abn LFTs, jaundice)

Pancreatitis
(abd pain)

Neurotoxicities
(MG, encephalitis)

Arthritis
(joint pain)

RTP
RESEARCH
TO PRACTICE

What I Tell My Patients:
Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Fifteenth Annual RTP Symposium Series Held During the Annual ONS Congress

Breast Cancer

Wednesday, April 26, 2023
6:00 PM – 8:00 PM

Faculty

Jamie Carroll, APRN, MSN, CNP
Virginia Kaklamani, MD, DSc
Joyce O'Shaughnessy, MD
Ronald Stein, JD, MSN, NP-C, AOCNP

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

What I Tell My Patients:
Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Fifteenth Annual RTP Symposium Series Held During the Annual ONS Congress

Diffuse Large B-Cell Lymphoma

Thursday, April 27, 2023
6:00 AM – 7:30 AM

Faculty

Christopher R Flowers, MD, MS
Amy Goodrich, CRNP
Robin Klebig, APRN, CNP, AOCNP
Matthew Lunning, DO

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us! Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

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Virtual attendees: The NCPD credit link is posted in the chat room.

NCPD/ONCC credit information will be emailed to each participant within 1 to 2 business days.

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