What I Tell My Patients:
New Treatments and Clinical Trial Options

An NCPD Hybrid Symposium Series
Held During the 47th Annual ONS Congress

Breast Cancer

Friday, April 29, 2022
6:00 PM – 8:00 PM PT

Faculty

Jamie Carroll, APRN, MSN, CNP
Sara A Hurvitz, MD
Kelly Leonard, MSN, FNP-BC
Hope S Rugo, MD

Moderator

Neil Love, MD

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Faculty

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

Sara A Hurvitz, MD
Professor of Medicine
Director, Breast Cancer Clinical Trials Program
Division of Hematology-Oncology
David Geffen School of Medicine at UCLA
Medical Director, Clinical Research Unit
Jonsson Comprehensive Cancer Center
Santa Monica, California

Kelly Leonard, MSN, FNP-BC
Family Nurse Practitioner
Dana-Farber Cancer Institute
Boston, Massachusetts

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

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Ms Carroll — Disclosures

Advisory Committee	Sanofi Genzyme

Dr Hurvitz — Disclosures

Contracted Research Paid to Institution	Ambrx, Amgen Inc, Arvinas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, CytomX Therapeutics, Daiichi Sankyo Inc, Dignitana AB, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Immunomedics Inc, Lilly, MacroGenics Inc, Novartis, OBI Pharma Inc, Orinove Inc, Pfizer Inc, Phoenix Molecular Designs, Pieris Pharmaceuticals Inc, Puma Biotechnology Inc, Radius Health Inc, Sanofi Genzyme, Seagen Inc, Zymeworks Inc
Preclinical Work (Grant Paid to UCLA)	Ambrx, Samumed
National/International PI	Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Novartis, Seagen Inc
Steering Committee	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Lilly, Novartis, Sanofi Genzyme, Seagen Inc
Travel Expenses	Lilly (2019)
Uncompensated Consulting/Advisory Boards	4D Pharma PLC, Ambrx, Amgen Inc, Artios Pharma, Arvinas, bioTheranostics Inc, Daiichi Sankyo Inc, Dantari, Genentech, a member of the Roche Group, Immunomedics Inc, Lilly, MacroGenics Inc, NKMAX CO Ltd, Novartis, Pieris Pharmaceuticals Inc, Pyxis Oncology, Seagen Inc

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Ms Leonard — Disclosures

No relevant conflicts of interest to disclose

Dr Rugo — Disclosures

Consulting Agreement	Samsung Bioepis (limited consulting)
Contracted Research	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, Immunomedics Inc, Lilly, MacroGenics Inc, Merck, Novartis, OBI Pharma Inc, Odonate Therapeutics, Pfizer Inc, Seagen Inc, Sermonix Pharmaceuticals
Honoraria	Mylan, Puma Biotechnology Inc
Travel	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, MacroGenics Inc, Merck, Mylan, Novartis, Pfizer Inc

Commercial Support

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Research To Practice CME Planning Committee Members, Staff and Reviewers

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

Clinicians in the Meeting Room

Networked iPads are available.

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

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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

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

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

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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"
14th Annual RTP-ONS NCPD Symposium Series
ONS Congress, Anaheim, California — April 27 - May 1, 2022

Thursday April 28	**Prostate Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Ovarian Cancer 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)
	Non–Small Cell Lung Cancer 6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)
	Hepatobiliary Cancers 8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)
Friday April 29	**Small Cell Lung Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Chronic Lymphocytic Leukemia 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)
	Breast Cancer 6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)
	Acute Myeloid Leukemia and Myelodysplastic Syndromes 8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)
Saturday April 30	**Cervical and Endometrial Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Bladder Cancer 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

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What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

An NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Small Cell Lung Cancer

Friday, April 29, 2022

6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty

Marianne J Davies, DNP, MSN, RN, APRN
Matthew Gubens, MD, MS
Lowell L Hart, MD
Chaely J Medley, MSN, AGNP

Breast Cancer

Friday, April 29, 2022

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Jamie Carroll, APRN, MSN, CNP
Sara A Hurvitz, MD
Kelly Leonard, MSN, FNP-BC
Hope S Rugo, MD

Chronic Lymphocytic Leukemia

Friday, April 29, 2022

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Lesley Camille Ballance, MSN, FNP-BC
Amy Goodrich, CRNP
Lowell L Hart, MD
Anthony R Mato, MD, MSCE

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Friday, April 29, 2022

8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)

Faculty

Ilene Galinsky, NP
Eunice S Wang, MD

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

An NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Cervical and Endometrial Cancer

Saturday, April 30, 2022
6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty
Paula J Anastasia, MN, RN, AOCN
Robert L Coleman, MD
David M O'Malley, MD
Jaclyn Shaver, MS, APRN, CNP, WHNP

Bladder Cancer

Saturday, April 30, 2022
12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty
Monica Averia, MSN, AOCNP, NP-C
Shilpa Gupta, MD
Brenda Martone, MSN, NP-BC, AOCNP
Sumanta Kumar Pal, MD

Join Us After ONS for Our Series Continuation

What I Tell My Patients —
A 2-Part NCPD Webinar Series

Hodgkin and Non-Hodgkin Lymphomas

Date and time to be announced

Gastroesophageal Cancers

Wednesday, May 18, 2022

5:00 PM – 6:00 PM ET

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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?

If you could “replay your life” would you still choose to practice medical oncology?

1. Yes
2. Yes, but I would have preferred to work in a nonclinical oncology role
3. No

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Faculty

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Mayo Clinic
Rochester, Minnesota

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Agenda

Module 1 – Localized ER-positive breast cancer; role of CDK inhibitors

Module 2 – ER-positive metastatic breast cancer

Module 3 – Localized HER2-positive breast cancer

Module 4 – Metastatic HER2-positive breast cancer

Module 5 – Localized triple-negative breast cancer (TNBC); role of immunotherapy

Module 6 – Metastatic TNBC

Agenda

Module 1 – Localized ER-positive breast cancer; role of CDK inhibitors

Module 2 – ER-positive metastatic breast cancer

Module 3 – Localized HER2-positive breast cancer

Module 4 – Metastatic HER2-positive breast cancer

Module 5 – Localized triple-negative breast cancer (TNBC); role of immunotherapy

Module 6 – Metastatic TNBC

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SELF-ASSESSMENT QUIZ

Which of the following toxicities is more common with palbociclib and ribociclib than with abemaciclib?

1. Gastrointestinal toxicity
2. Neutropenia
3. Anemia
4. Peripheral neuropathy
5. I don’t know

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SELF-ASSESSMENT QUIZ

Which of the following toxicities is more common with abemaciclib than with palbociclib and ribociclib?

1. Gastrointestinal toxicity
2. Neutropenia
3. Anemia
4. Peripheral neuropathy
5. I don’t know

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SELF-ASSESSMENT QUIZ

Which CDK4/6 inhibitor requires that an electrocardiogram be conducted prior to the initiation of treatment?

1. Palbociclib
2. Ribociclib
3. Abemaciclib
4. I don’t know

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SELF-ASSESSMENT QUIZ

What effect was observed in the Phase III trial of adjuvant abemaciclib?

1. Fewer recurrences
2. Fewer deaths
3. Both

FDA Approves Adjuvant Abemaciclib with Endocrine Therapy for Localized Breast Cancer

Press Release – October 12, 2021

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

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

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

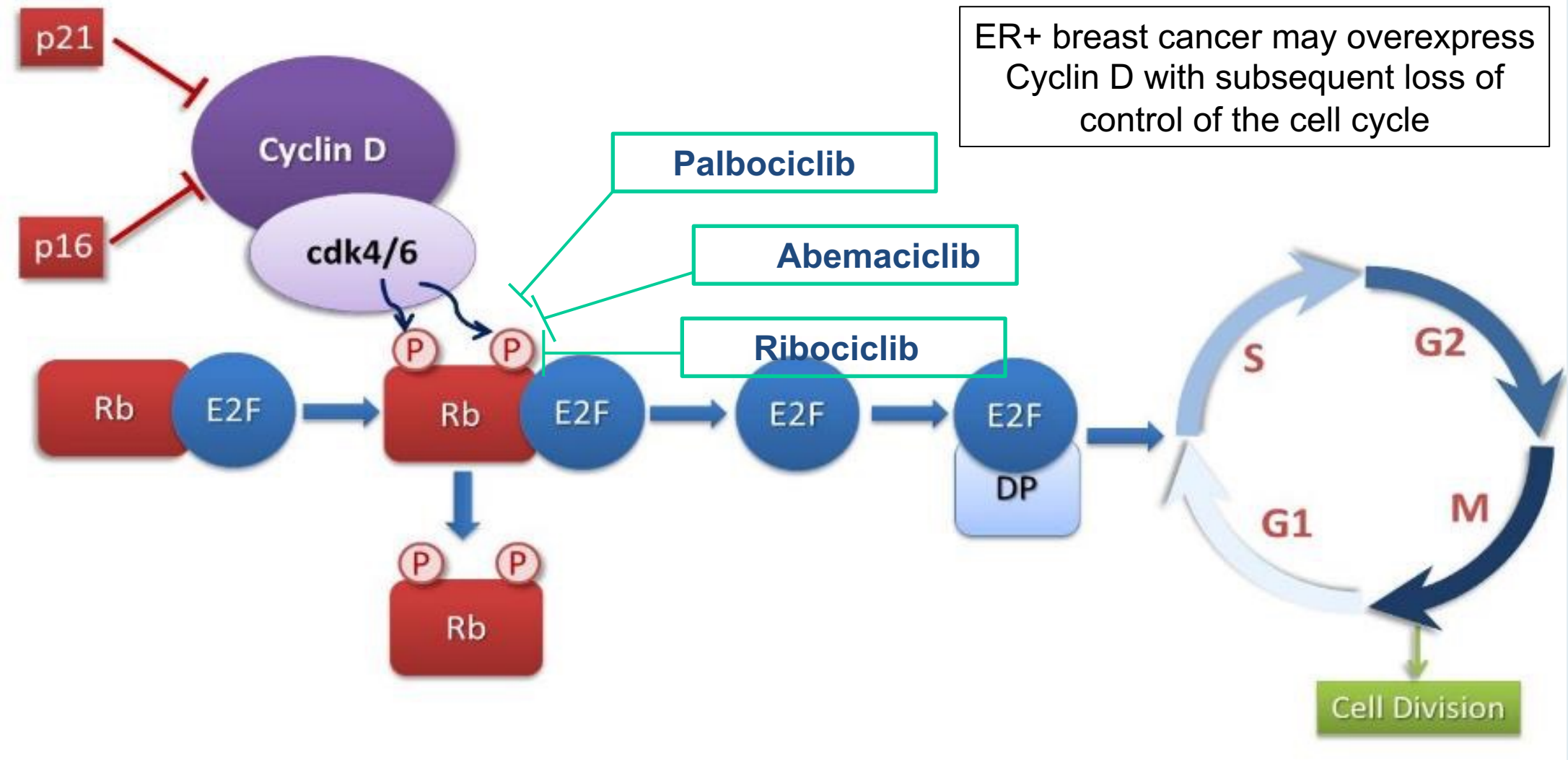
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abemaciclib-endocrine-therapy-early-breast-cancer

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

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

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

CDK4/6 Regulates Cell Cycle Progression



Adapted from Finn et al, 2016.

Key Trials Exploring CDK4/6 Inhibitors for Localized Breast Cancer

	MonarchE	PALLAS	PENELOPE-B
Number of patients	5,637	5,761	1,250
Eligibility	≥ N2 or N1 with at least one of the following: Grade 3, tumor size ≥ 5 cm, or Ki-67 ≥ 20%.	Anatomic stage II/III	Lack of pCR after NACT CPS-EG score ≥3 or ≥2 with ypN+
Study treatment	Abemaciclib-continuous (twice daily) Duration: 2 years	Palbociclib (once a day)-3 weeks on/1 week off Duration: 2 years	Palbociclib (once a day)-3 weeks on/1 week off Duration: 1 year
Timing of initiation of CDK4/6i in relation to ET	Within 12 weeks of beginning adjuvant ET	Within 6 months of beginning adjuvant ET	NA
Discontinuation rate	27.7%	42.0%	19.5%
Median follow-up time	19.1 months	31.0 months[1]	42.8 months
iDFS	92.2% (Abemaciclib + ET) vs. 88.7% (ET alone) at 2 years Ki67 ≥20% group-91.6% vs. 87.1%	84.2%(Palbociclib + ET) vs. 84.5%(ET alone)[1]	2 years: 88.3% (Palbociclib + ET) vs. 84% (ET alone) 3 years: 81.2% vs. 77.7% 4 years: 73.5% vs. 72.4%
DRFS	93.8% vs. 90.8%	89.3% vs. 90.7%	–

ET = endocrine therapy; iDFS = invasive disease-free survival; DRFS = distant relapse-free survival

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

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Ann Oncol 2021 Dec;32(12):1571-81.

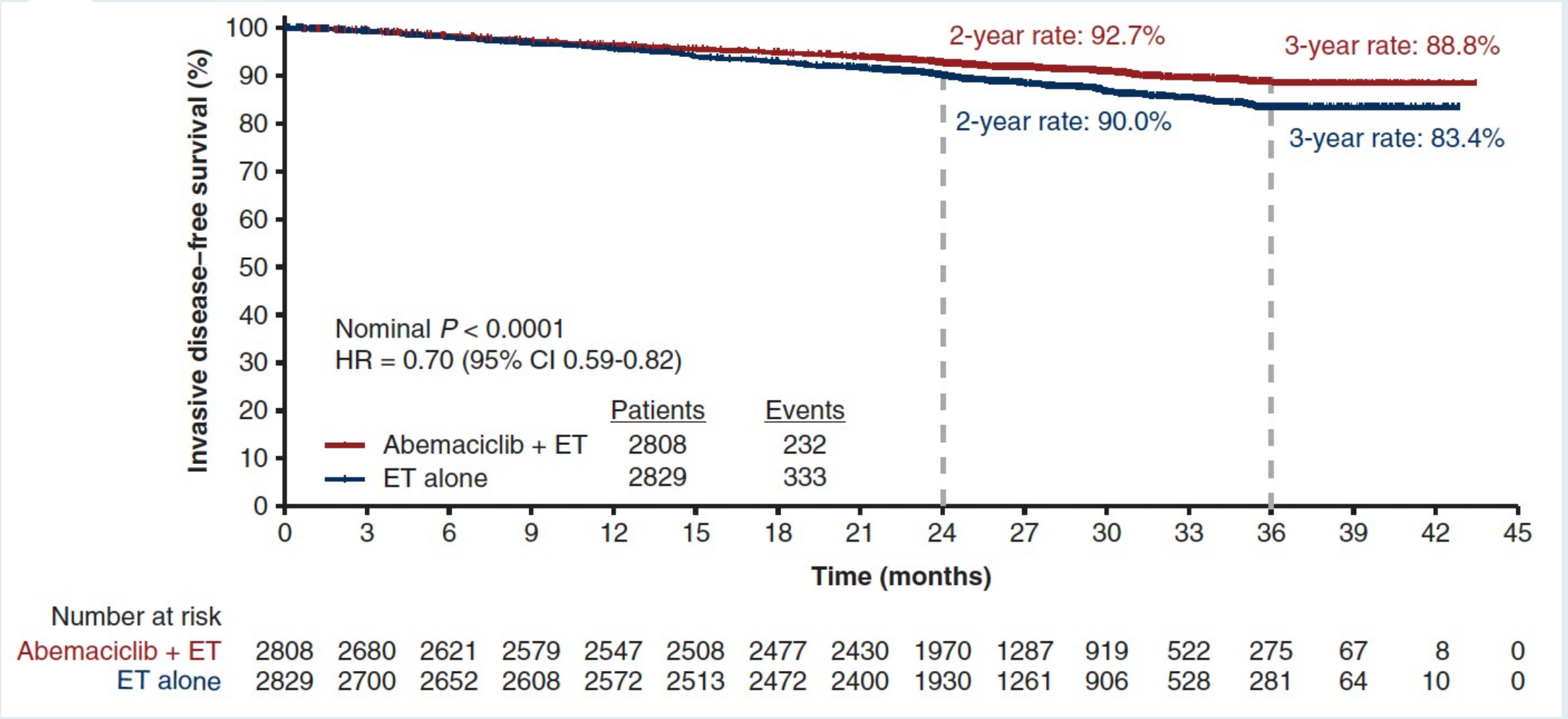
ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study

N. Harbeck[1*†], P. Rastogi[2†], M. Martin[3], S. M. Tolaney[4], Z. M. Shao[5], P. A. Fasching[6], C. S. Huang[7], G. G. Jaliffe[8], A. Tryakin[9], M. P. Goetz[10], H. S. Rugo[11], E. Senkus[12], L. Testa[13], M. Andersson[14], K. Tamura[15], L. Del Mastro[16,17], G. G. Steger[18], H. Kreipe[19], R. Hegg[20], J. Sohn[21], V. Guarneri[22,23], J. Cortés[24,25], E. Hamilton[26], V. André[27], R. Wei[27], S. Barriga[27], S. Sherwood[27], T. Forrester[27], M. Munoz[27], A. Shahir[27], B. San Antonio[27], S. C. Nabinger[27], M. Toi[28], S. R. D. Johnston[29‡] & J. O'Shaughnessy[30‡], On behalf of the monarchE Committee Members

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



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

monarchE: Select Adverse Events (AEs)

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

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

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

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GOOD SCIENCE
BETTER MEDICINE
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Ann Oncol 2022;[Online ahead of print]

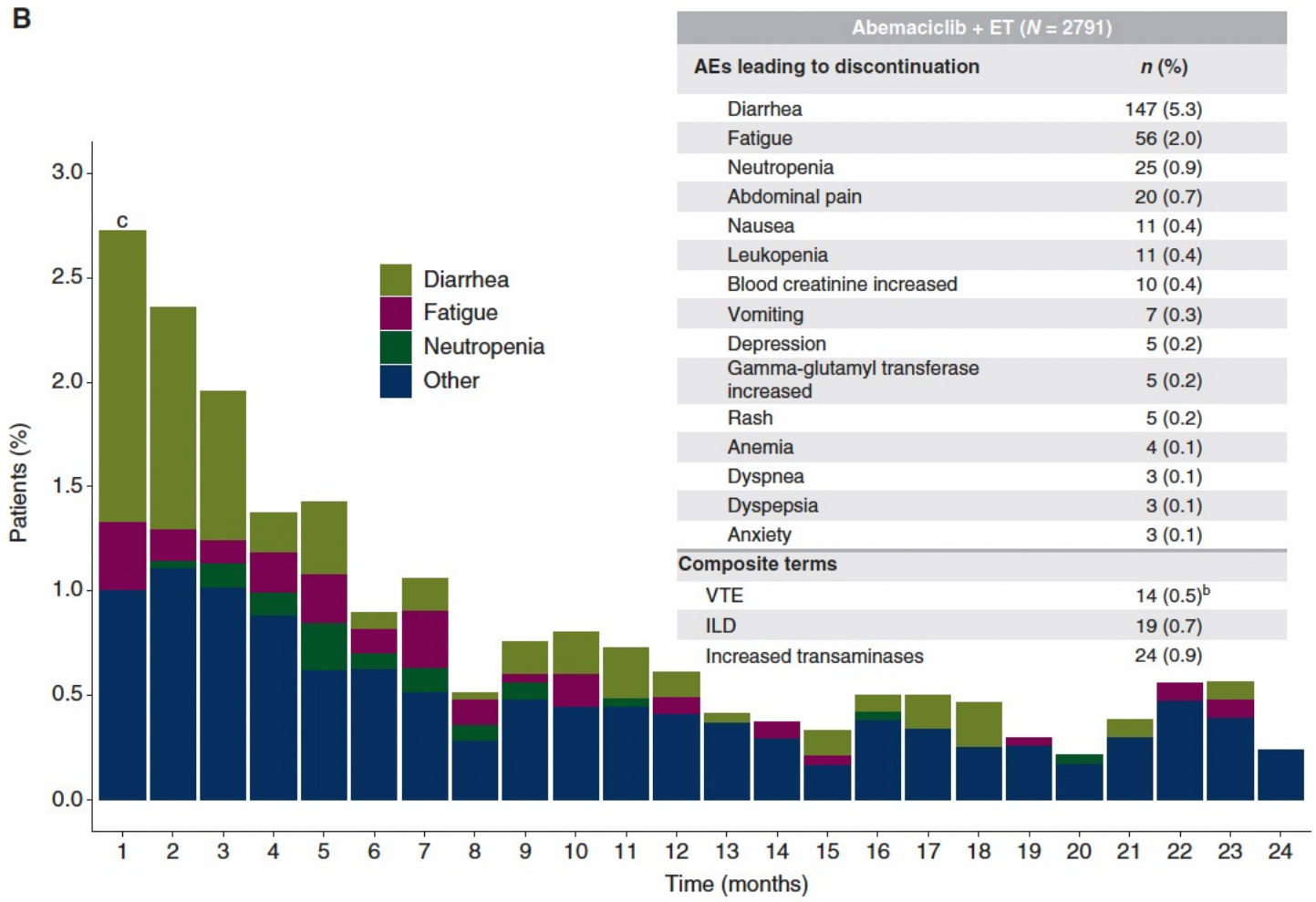
ANNALS OF ONCOLOGY
driving innovation in oncology

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[†]

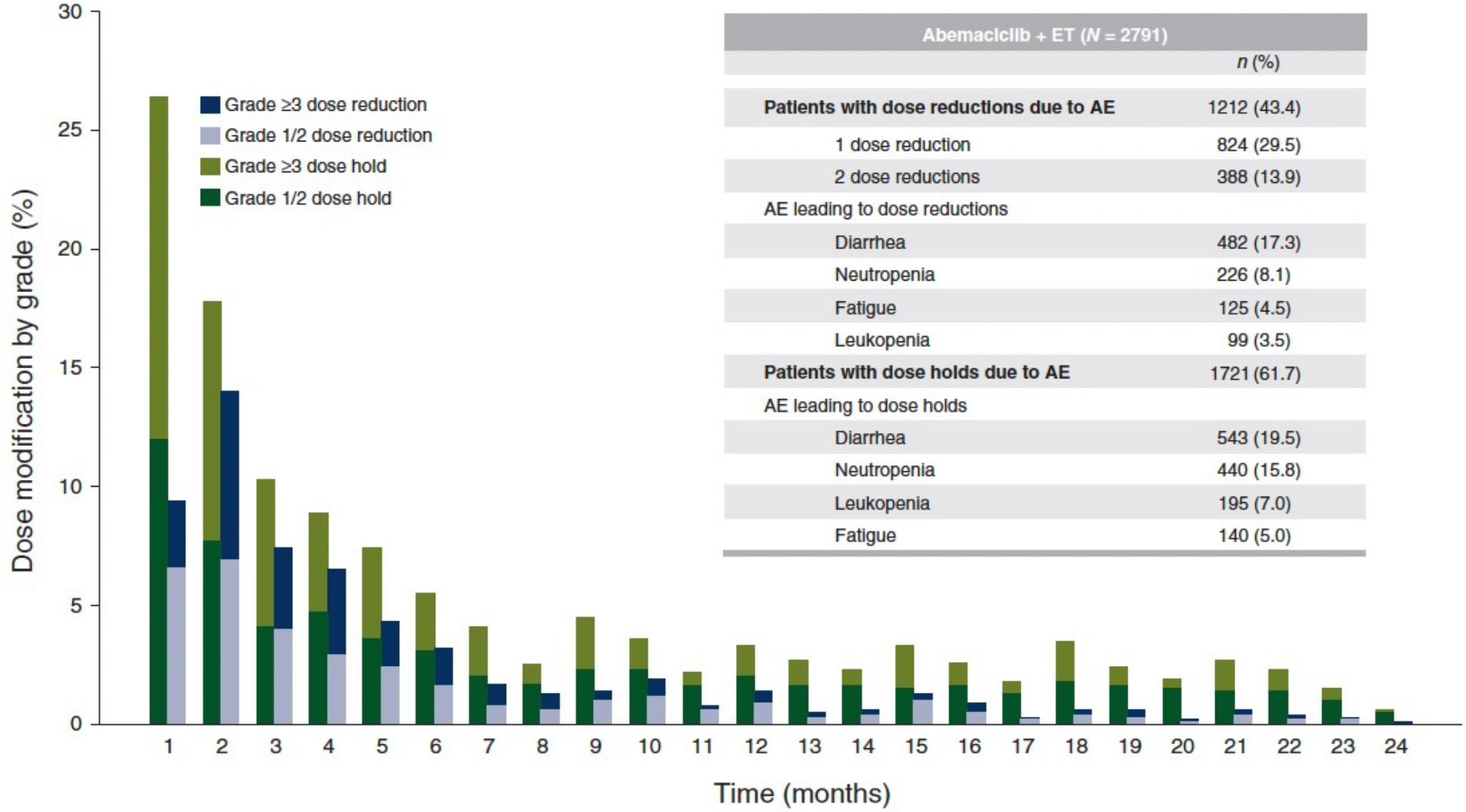
monarchE: Discontinuations in the Abemaciclib Arm Due to Adverse Events



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].

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Questions — Sara A Hurvitz, MD

Patients with high-risk localized ER-positive, HER2-negative breast cancer

- **How do you explain to a patient how endocrine treatment, including CDK4/6 inhibitors, works and the potential benefits of adding abemaciclib to adjuvant hormonal therapy?**

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Commentary — Sara A Hurvitz, MD

Important general points made to all patients with early breast cancer

- **Early stage breast cancer is curable but it is impossible to know who is cured.**
- **Sometimes recurrences can happen years after an initial diagnosis.**
- **Microscopic cancer cells can escape the breast months - years before the cancer is found in the breast. These cells may be too small to see on imaging.**
- **Medicine given at the time of diagnosis of an early stage cancer can treat those hiding cancer cells, reducing the chance that cancer will return.**

Commentary — Sara A Hurvitz, MD

- **A recurrence outside the breast (eg, liver, lung) is not curable; treatments are aimed at preventing a “distant” or “metastatic” recurrence**
- **Science is advancing such that we are beginning to be able to “see under the hood,” detect what is wrong in the “engine,” and in some cases have tools to fix the problem**
- **This requires us to identify which type of breast cancer a patient has so that the most effective treatment can be recommended**

Commentary — Sara A Hurvitz, MD

Patients with high-risk localized ER-positive, HER2-negative breast cancer

- **33 yo woman ER+ HER2- IDC, high grade, LN+, neoadjuvant AC-T, residual disease in breast (1 cm) and lymph nodes (3/12) seen in follow up.**
- **Hormone receptor positive tumors are fueled by estrogen (lock and key analogy); therapies that interfere with that relationship reduce cancer growth and have been shown to improve long term survival**
  - **Stress endocrine therapy is potentially more important than any other treatment received**

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Commentary — Sara A Hurvitz, MD

- **HR+ cancers seem to also benefit from a newer class of oral drugs called CDK4/6 inhibitors, that block the cancer cell from dividing (or, creating new cancer cells)**
  - **One of these drugs (abemaciclib) has been shown to reduce the risk of cancer returning for patients with higher risk features (for example, lymph node involvement)**
  - **A person who takes this drug has approximately a 30% reduction in the risk that their cancer will return in the next 3 years compared to a patient who does not (88% of pts cancer free with the drug at 3 years, 83% cancer free without)**

Questions — Jamie Carroll, APRN, MSN, CNP

Patients with high-risk localized ER-positive, HER2-negative breast cancer

- **What are some of the key issues you discuss with patients who are receiving adjuvant abemaciclib, including side effects associated with ovarian suppression, aromatase inhibitors and abemaciclib?**
- **What are some of the psychosocial issues that arise in this situation?**

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Commentary — Jamie Carroll, APRN, MSN, CNP

Patients with high-risk localized ER-positive,HER2-negative breast cancer

- **Key issues that I discuss with patients are the menopausal side effects from OFS (ovarian function suppression) and aromatase inhibitors. I try to layer things so patients can get used to one drug before adding another. The younger the patient is, the more challenging the menopausal side effects can be.**
- **I try to highlight the changes to sexual function because I feel that often is a topic not discussed in detail. We talk through vaginal dryness, dyspareunia, the use of vaginal lubricants and moisturizers and how each works for them. Many women also have a reduction in libido and don't share.**
- **With abemaciclib, we discuss the need for frequent lab monitoring as well as the risk of diarrhea.**

Commentary — Jamie Carroll, APRN, MSN, CNP

- **As I see my patients frequently in clinic, I am able to pick up on nuances between spouse and patient. One patient had different body language and she later shared that she and her husband were experiencing marital discord with her lack of desire. She still loved him but didn't feel that he was supportive of her through her vaginal dryness and lack of libido.**
- **Psychosocial issues are also noted above. The biggest concern is how these side effects affect a marriage. Often times, we only think about side effects of chemotherapy and the requirement of spouse to do more as the woman is more fatigued. I find that husbands can get caregiver fatigue and relationships can be challenged during the endocrine therapy portion of care.**

Agenda

Module 1 – Localized ER-positive breast cancer; role of CDK inhibitors

Module 2 – ER-positive metastatic breast cancer

Module 3 – Localized HER2-positive breast cancer

Module 4 – Metastatic HER2-positive breast cancer

Module 5 – Localized triple-negative breast cancer (TNBC); role of immunotherapy

Module 6 – Metastatic TNBC

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SELF-ASSESSMENT QUIZ

CDK4/6 inhibitors have been shown to improve time to progression but not overall survival.

1. Agree
2. Disagree
3. I don’t know

SELF-ASSESSMENT QUIZ

The PI3 kinase inhibitor alpelisib is used for patients with metastatic ER-positive, HER2-negative breast cancer with a…

1. EGFR somatic mutation
2. PIK3CA somatic mutation
3. IDH somatic mutation
4. All of the above
5. I don’t know

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

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

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

Common Side Effects and Dosing of CDK4/6 Inhibitors

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

Barroso-Sousa R et al. *Breast Care* 2016;11(3):167-73.

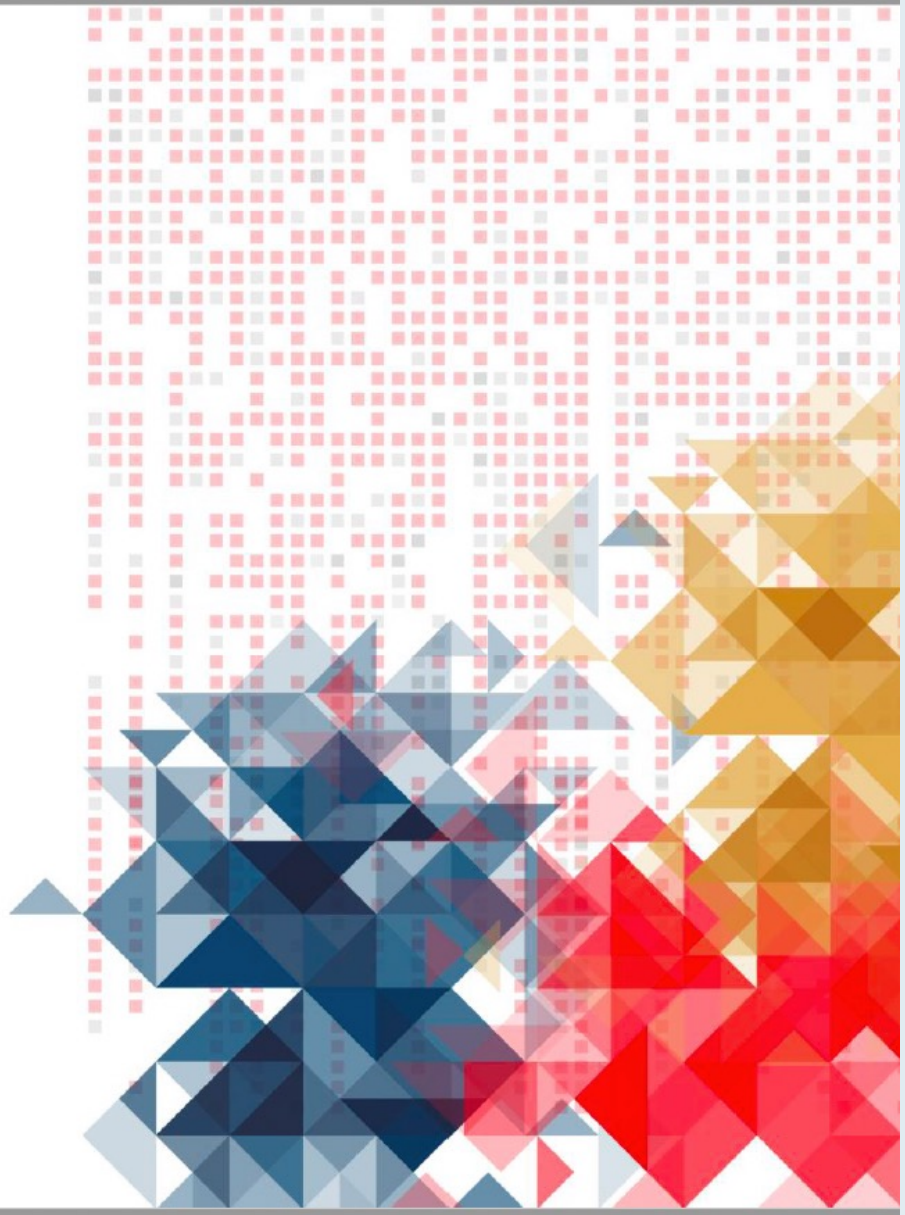
2021 ESMO congress

Abstract LBA17_PR

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

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

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



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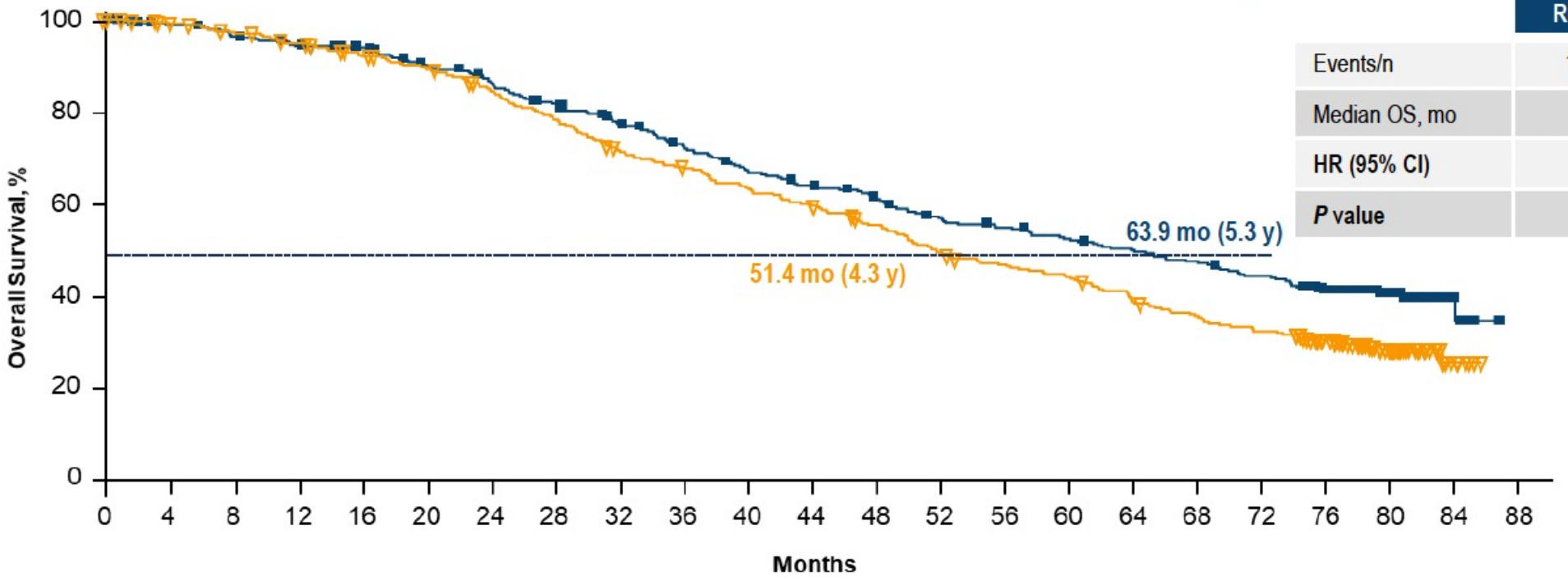
MONALEESA-2: Overall Survival (OS)

Improvement in median OS was 12.5 months with ribociclib plus letrozole



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

No. at risk

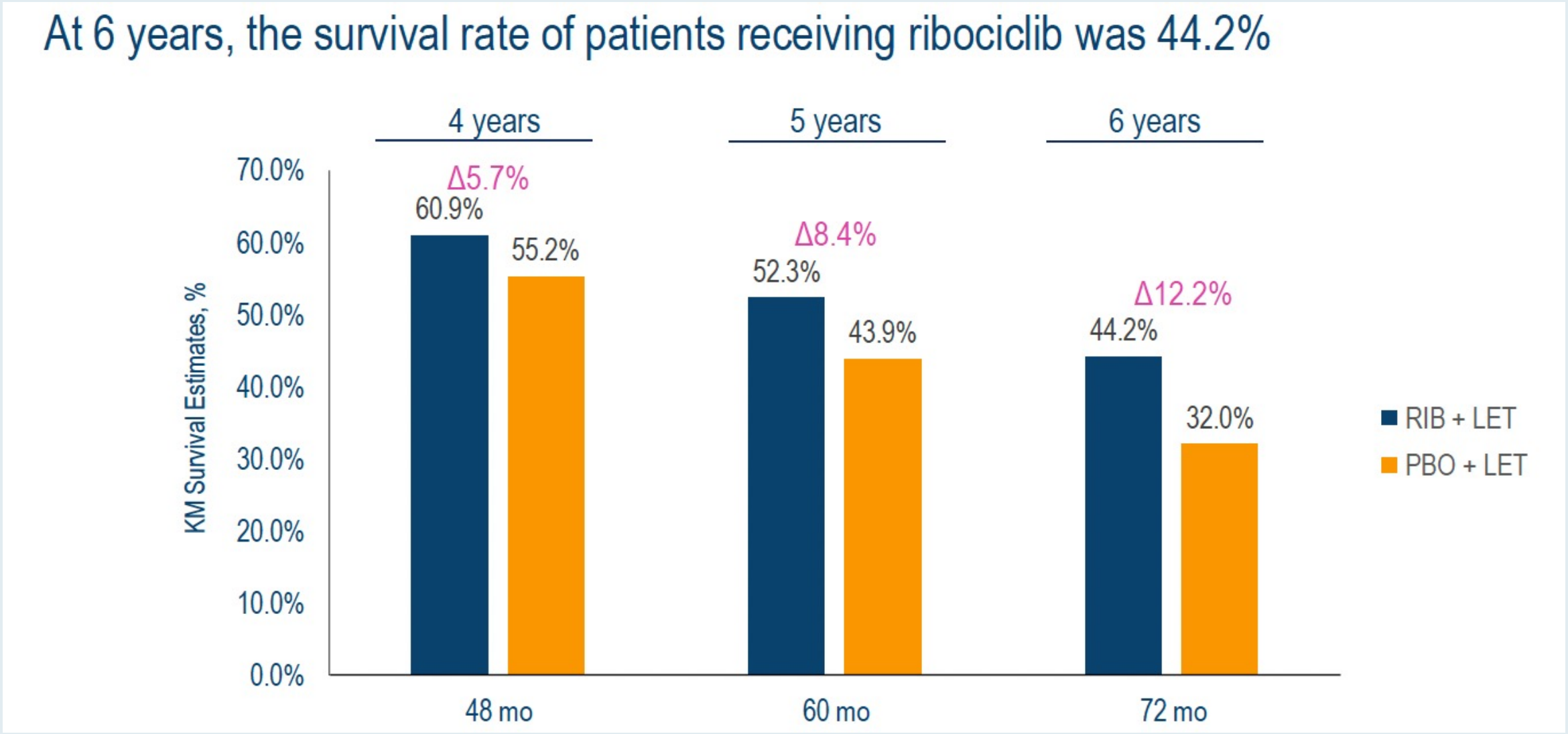
RIB + LET	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
PBO + LET	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

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

Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

RTP RESEARCH TO PRACTICE

MONALEESA-2: Overall Survival Benefit Increased Over Time



Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

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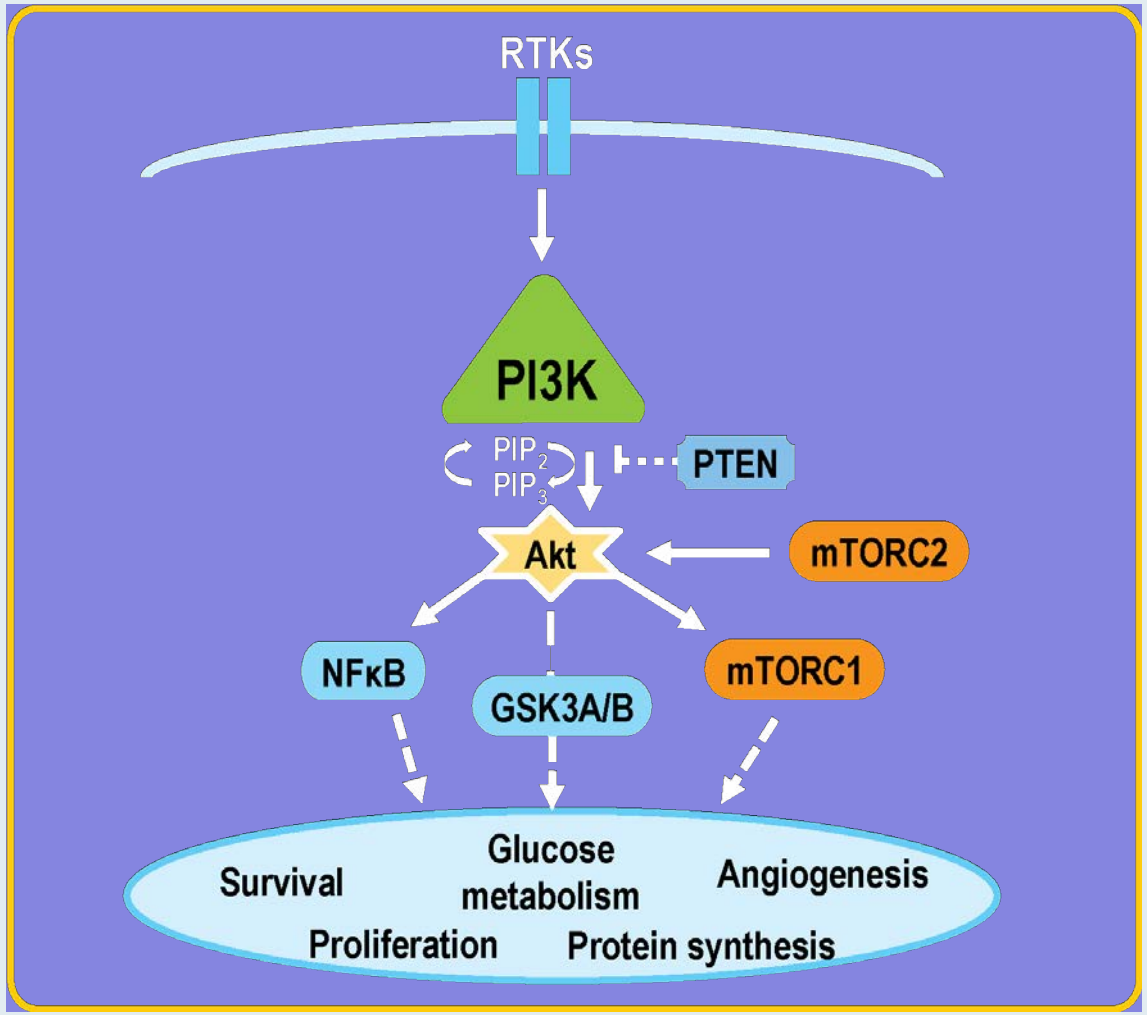
PI3K Inhibitors: Mechanism of Action



- PI3K is involved in the activation of Akt.
- Hyperactivation of the PI3K pathway is implicated in malignant transformation, cancer progression and endocrine therapy resistance.
- PIK3CA encodes the alpha isoform of the PI3K catalytic subunit.
- Around 40% of patients with HR-positive, HER2-negative breast cancer present with an activating PIK3CA tumor mutation.
- Alpelisib is a specific inhibitor of the PI3K alpha isoform.

André F et al. ESMO 2018;Abstract LBA3_PR.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

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

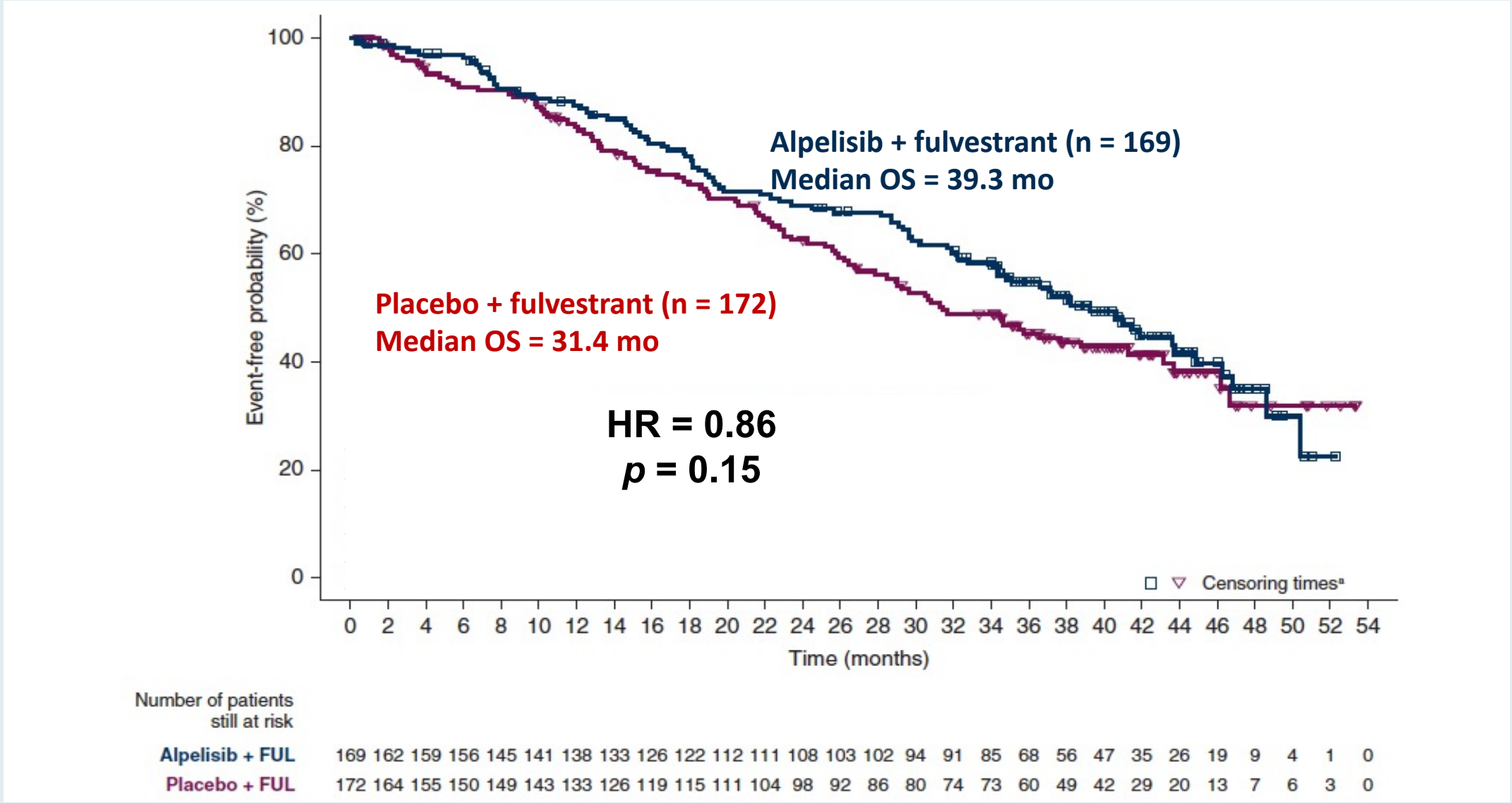
F. André[1*], E. M. Ciruelos[2], D. Juric[3], S. Loibl[4], M. Campone[5], I. A. Mayer[6], G. Rubovszky[7], T. Yamashita[8], B. Kaufman[9], Y.-S. Lu[10], K. Inoue[11], Z. Pápai[12], M. Takahashi[13], F. Ghaznawi[14], D. Mills[15], M. Kaper[14], M. Miller[14], P. F. Conte[16], H. Iwata[17] & H. S. Rugo[18]

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

Available online 25 November 2020

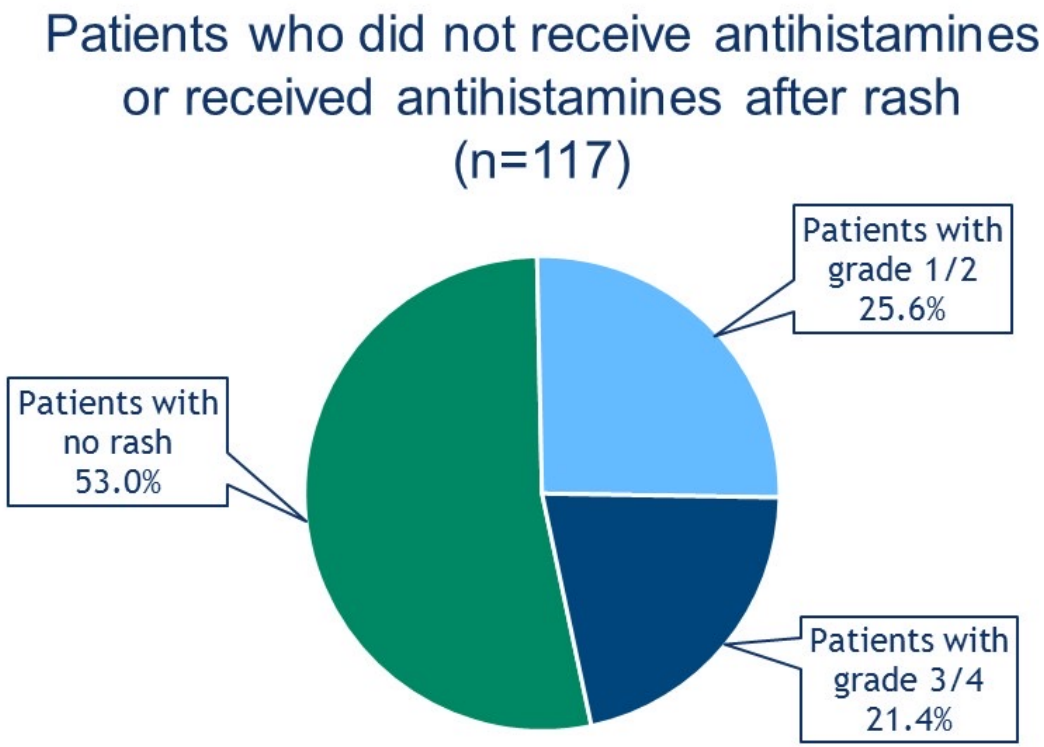
***Ann Oncol* 2021;32(2):208-17.**

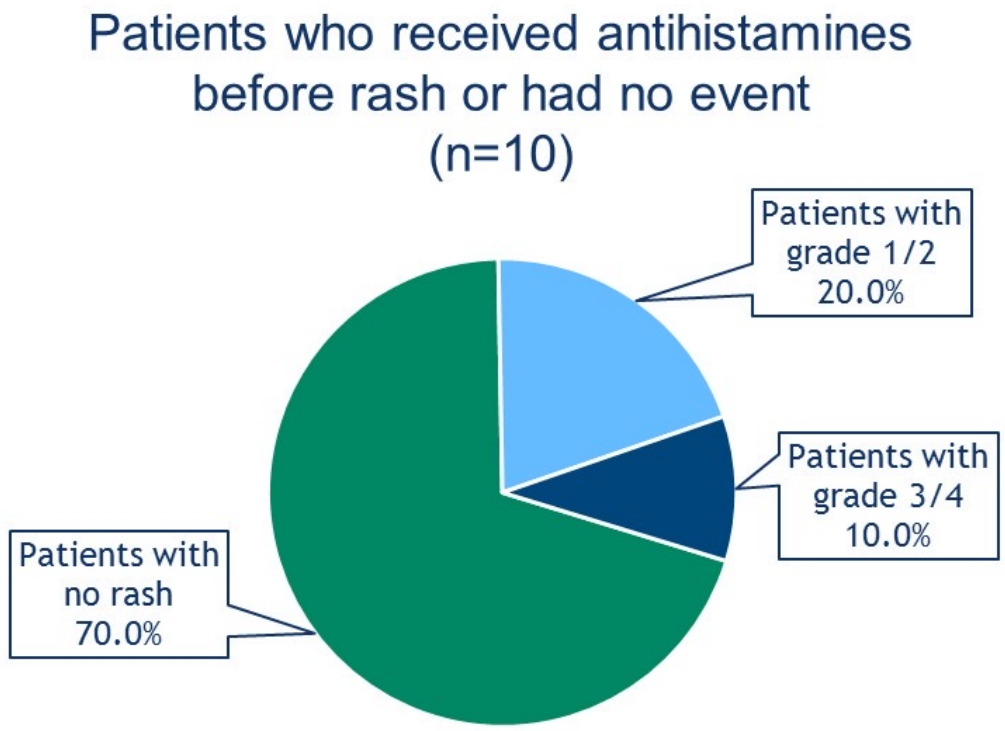
SOLAR-1: Overall Survival (OS) for Patients with Advanced Breast Cancer with a PIK3CA Mutation



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

BYLieve: Incidence of Rash with and without Prophylactic Antihistamines





Rugo HS et al. ASCO 2020;Abstract 1006.

Questions — Hope S Rugo, MD

A patient with ER-positive metastatic breast cancer

- **In what clinical situations are CDK4/6 inhibitors used for metastatic ER-positive breast cancer?**
- **How do you select which CDK4/6 inhibitor to use, and how do you explain the potential benefits and goals of treatment to a patient?**

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TO PRACTICE

Commentary — Hope S Rugo, MD

A patient with ER-positive metastatic breast cancer

- **In what clinical situations are CDK4/6 inhibitors used for metastatic ER-positive breast cancer?**
  - **CDK4/6i added to endocrine therapy have significantly improved both PFS, and in specific trials, OS. I give them first-line with either an AI or fulvestrant if the patient was on an AI at time of recurrence.**
    - **One interesting question is use of CDK4/6i after progression**
- **How do you select which CDK4/6 inhibitor to use, and how do you explain the potential benefits and goals of treatment to a patient?**
  - **I use the combination of efficacy data balanced with toxicity and try to tailor this to the individual patient. For medicare patients, patient assistance is important.**
  - **I discuss the response and durability of response, control of symptoms as well as how we manage side effects and what is required by the patient in terms of monitoring.**

RTP RESEARCH TO PRACTICE

Commentary — Hope S Rugo, MD

- **Please cite brief instructive examples of actual clinical experiences with patients in your practice.**
  - **38 yo with MBC**
    - **Age 27: bilateral mastectomy for grade 3 ER/PR+ 3 cm node neg IDC; Ki67 32%**
    - **Rx: TC x 4 followed by tamoxifen x 5 years, ending 2016**
    - **9/20: left leg pain; found to have a large lytic lesion in left femur with cortical breakthrough and a large hilar node; nail placed with cement**
    - **10/20 started goserelin/ribociclib/letrozole followed by BSO**
      - **Dose reduced to 400 mg ribo due to rash**

Commentary — Hope S Rugo, MD

- **Patient 2**
  - **Age 41: 3 cm HR+ DCIS rx with surgery, declined RT, took one year of tamoxifen**
  - **Age 48: lump and pain in breast, biopsy + HR+ IDC. Genetic testing declined. Staging: mediastinal adenopathy, sternal lesion, lung nodule. Bx sternum: HR+ IDC**
  - **Rx: goserelin, letrozole and palbociclib**
- **Patient 3**
  - **Age 34: left breast T2N0 Grade 3 IDC, right breast DCIS; Rxd with TC x 4 then tamoxifen x 3 years**
  - **Age 38: abdominal pressure, found to have widespread mets to nodes, lung, liver and bone. Liver Bx+ HR MBC, PIK3CA mutation, FGFR1 amplification**
  - **Rx: goserelin, letrozole and abemaciclib, dose reduced to 250 mg due to diarrhea, then increased back to 300 mg**
  - **PD in liver after ~18 months**

Questions — Kelly Leonard, MSN, FNP-BC

A patient with ER-positive metastatic breast cancer

- **What are some of the key issues you discuss with patients who are about to start a CDK4/6 inhibitor in combination with endocrine therapy for metastatic breast cancer?**
- **How do you assess and optimize adherence to oral therapies?**
- **What are some of the psychosocial issues that arise in this situation?**

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Commentary — Kelly Leonard, MSN, FNP-BC

A patient with ER-positive metastatic breast cancer

- **Side effects and symptom management for CDK4/6 inhibitors: low blood counts (specifically neutropenia with Palbociclib), fatigue, GI upset (ie, diarrhea and mild nausea), oral sores, fatigue, hair thinning.**
- **We will check CBC and CMP every 2 weeks for the first 2 months of therapy on CDK4/6 inhibitors, then monthly thereafter (neutropenia is particularly common with Palbociclib).**
- **Abemaciclib → potential side effect = pneumonitis. We review signs and symptoms to look out for, ie, shortness of breath and cough. If patients are experiencing these symptoms, we will have them hold the drug and obtain CT chest, and potentially pulmonary function testing.**

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Commentary — Kelly Leonard, MSN, FNP-BC

- **Ribociclib → potential for prolonged QTcF. Obtain an EKG prior to starting treatment, then repeat EKG on day 14 of cycle 1, and then at the beginning of cycle 2 (then as needed).**
- **Nurse navigators/pharmacy team make an initial call to the patient just before they are about to start treatment to review the schedule and potential side effects.**
- **We typically will check in with patients 2 weeks after they begin therapy at the time of their first lab check to make sure that they are tolerating the medication well, and then we will see them on a monthly basis.**

Commentary — Kelly Leonard, MSN, FNP-BC

- **61 y/o female with metastatic breast cancer (originally had a T3N ER+/PR-/HER2- breast cancer), she was non-compliant with her letrozole in the adjuvant setting prior to her metastatic diagnosis this year. She started to notice GI symptoms in mid-2021 (poor appetite, nausea, and 60-pound weight loss). She did finally see her PCP and had a colonoscopy, and she was found to have a met at the splenic flexure. She was started on Palbociclib and was instructed to resume her Letrozole. She only started the Palbociclib and did not start her Letrozole until we saw her in clinic 1 month later. She has been tolerating this regimen very well thus far, aside from some fatigue, but she is still able to work full time as an aide in a rehab facility.**

Commentary — Kelly Leonard, MSN, FNP-BC

- **She lives about an hour and a half from our clinic, and transportation has been an issue for her since she lives by herself and does not have her own vehicle. She takes public transportation to get to work. She does continue to work full time. We connected her with our social work department, and she was provided with transportation to and from clinic once a month for her visits. We also have our nurse navigator check in with her every 2 weeks over the phone to ensure she is doing okay with her medications and is taking them as prescribed (particularly since she was initially confused about starting both Letrozole and Palbociclib together).**

Agenda

Module 1 – Localized ER-positive breast cancer; role of CDK inhibitors

Module 2 – ER-positive metastatic breast cancer

Module 3 – Localized HER2-positive breast cancer

Module 4 – Metastatic HER2-positive breast cancer

Module 5 – Localized triple-negative breast cancer (TNBC); role of immunotherapy

Module 6 – Metastatic TNBC

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SELF-ASSESSMENT QUIZ

A 60-year-old woman presents with a palpable 2.5-cm breast mass that on biopsy is diagnosed as an ER-negative, HER2-positive infiltrating ductal carcinoma (IDC). Biopsy of a small axillary lymph node is positive. In general, the most common next step in this situation is…

1. Surgery to remove the primary tumor and axillary dissection followed by systemic therapy
2. Neoadjuvant systemic therapy followed by surgery
3. Either a or b
4. Neither a nor b
5. I don’t know

RTP RESEARCH TO PRACTICE

SELF-ASSESSMENT QUIZ

A patient with a HER2-positive IDC responds to neoadjuvant chemotherapy and trastuzumab/pertuzumab, but at surgery residual disease is detected. In general, the most common next treatment is…

1. Trastuzumab
2. Trastuzumab/pertuzumab
3. T-DM1
4. Observation
5. I don’t know

RTP RESEARCH TO PRACTICE

SELF-ASSESSMENT QUIZ

Patients who receive postadjuvant neratinib after chemotherapy/anti-HER2 therapy for HER2-positive localized breast cancer have a significant reduction in the risk of recurrence if the tumor is…

1. ER-positive
2. ER-negative
3. Both a and b
4. Neither a nor b
5. I don’t know

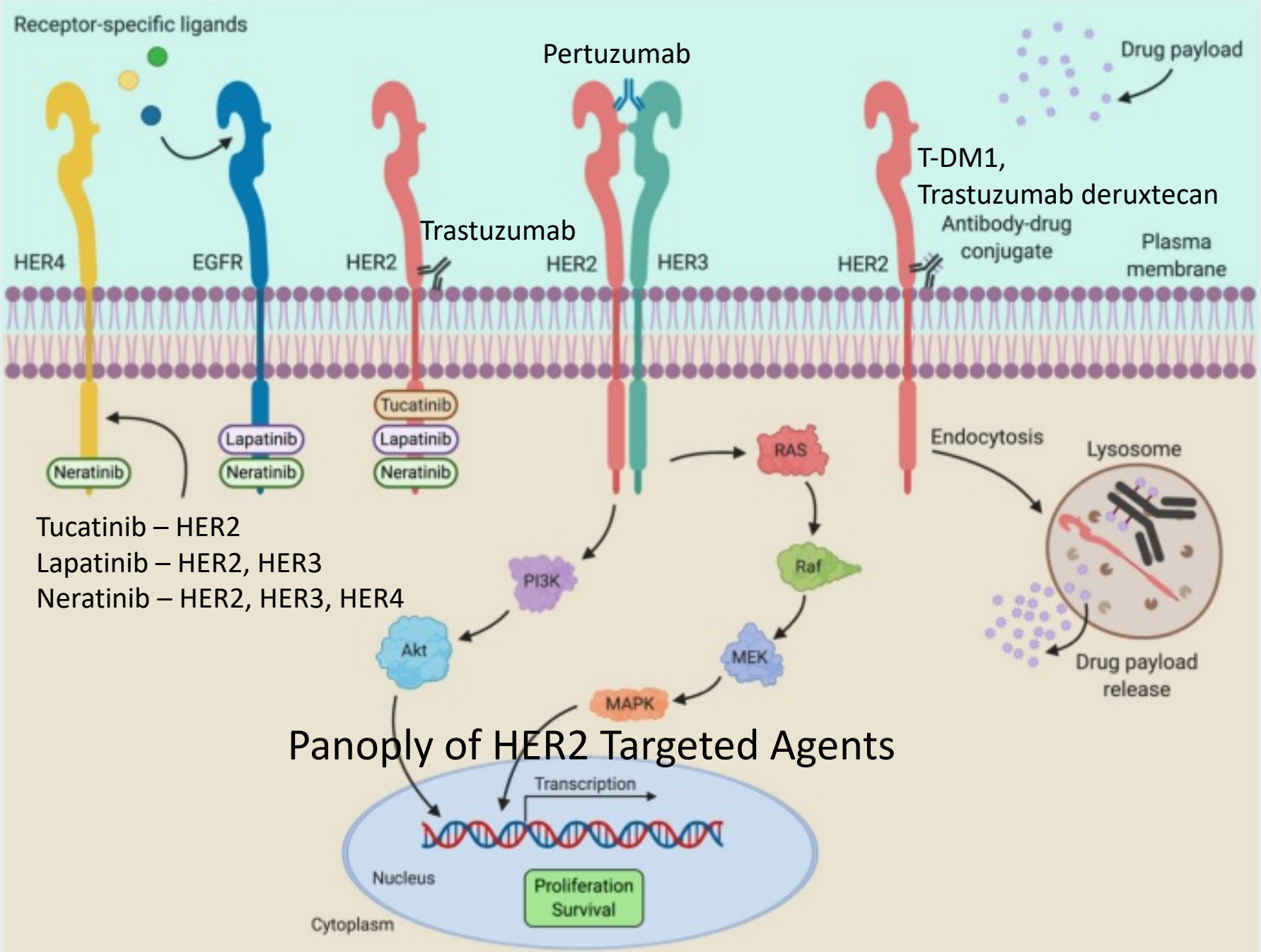
RTP RESEARCH TO PRACTICE

SELF-ASSESSMENT QUIZ

The most common side effect/toxicity of neratinib is…

1. Hand-foot syndrome
2. Diarrhea
3. Cytopenias
4. I don’t know

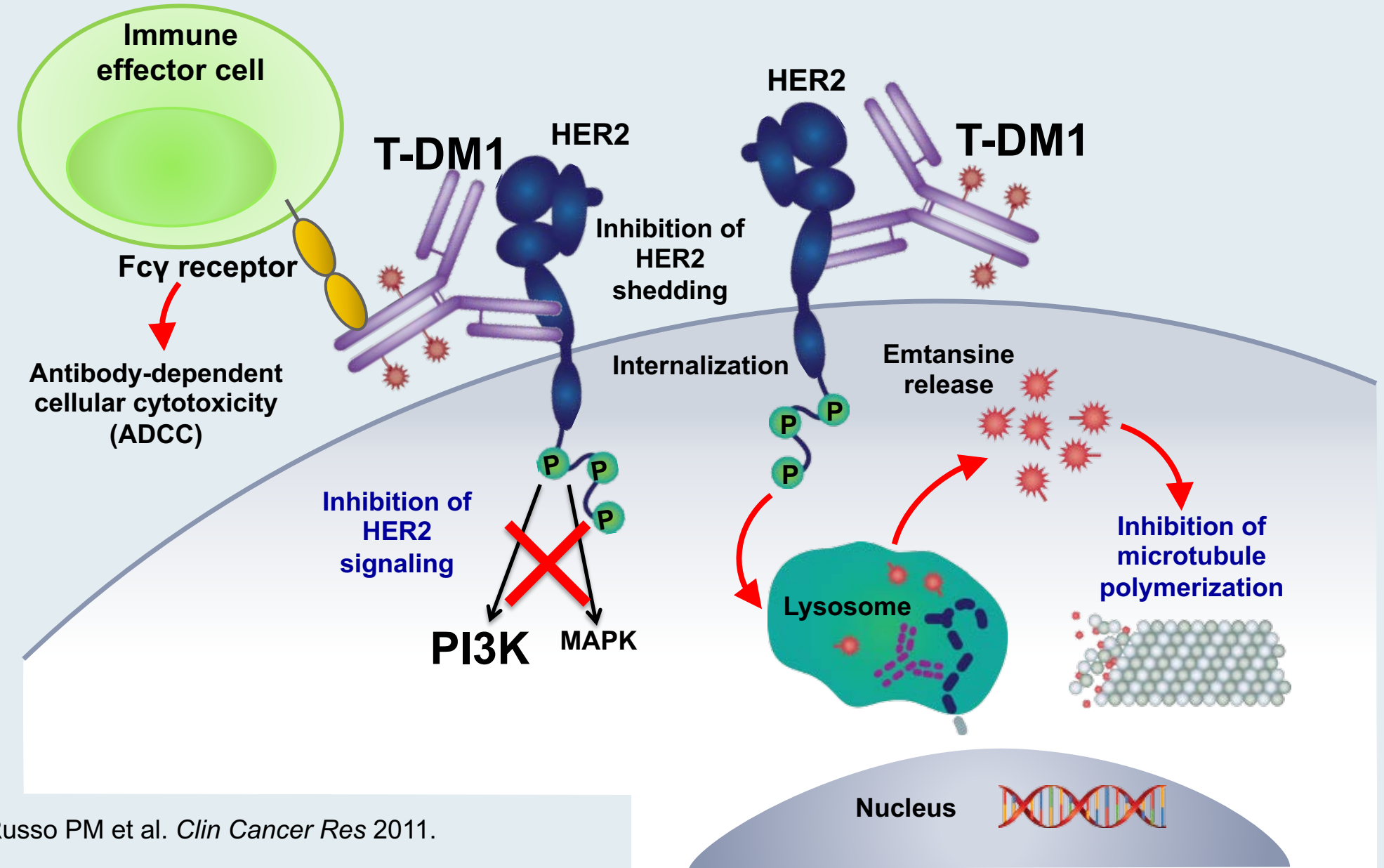
Panoply of HER2 Targeted Agents



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

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

Trastuzumab Emtansine (T-DM1): Mechanisms of Action



Adapted from LoRusso PM et al. *Clin Cancer Res* 2011.

FDA-Approved Agents for Localized HER2-Positive Breast Cancer

Agent	Setting	Pivotal trial(s)	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 plus trastuzumab plus pertuzumab vs placebo	2017
Neratinib	Extended adjuvant treatment of 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-H = doxorubicin, cyclophosphamide, and trastuzumab; AC-T = doxorubicin, cyclophosphamide and paclitaxel; AC-T-H = doxorubicin, cyclophosphamide, paclitaxel and trastuzumab; H = trastuzumab; PD = pertuzumab and docetaxel; PT = trastuzumab and pertuzumab; PTD = pertuzumab, trastuzumab and docetaxel; TC = docetaxel and cyclophosphamide; TC-H = docetaxel, cyclophosphamide and trastuzumab; TD = trastuzumab and docetaxel; THP = docetaxel, trastuzumab and pertuzumab

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

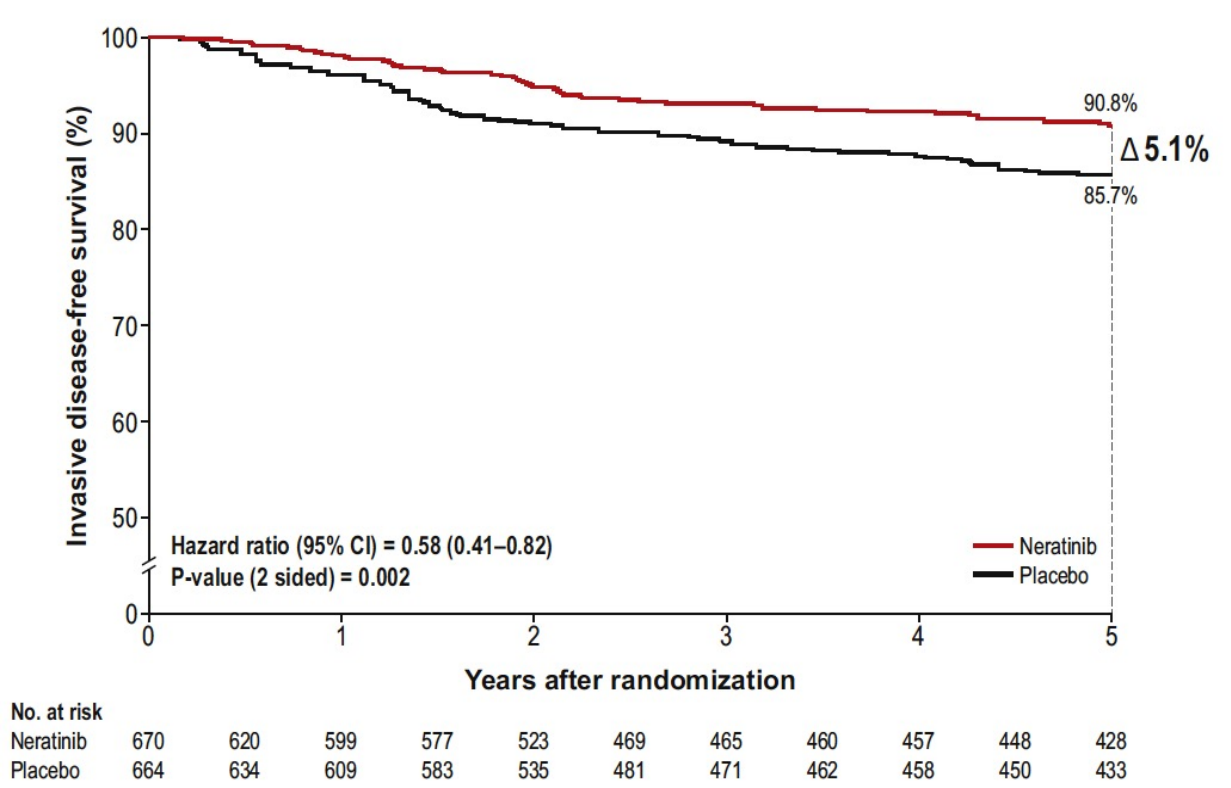
Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial

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

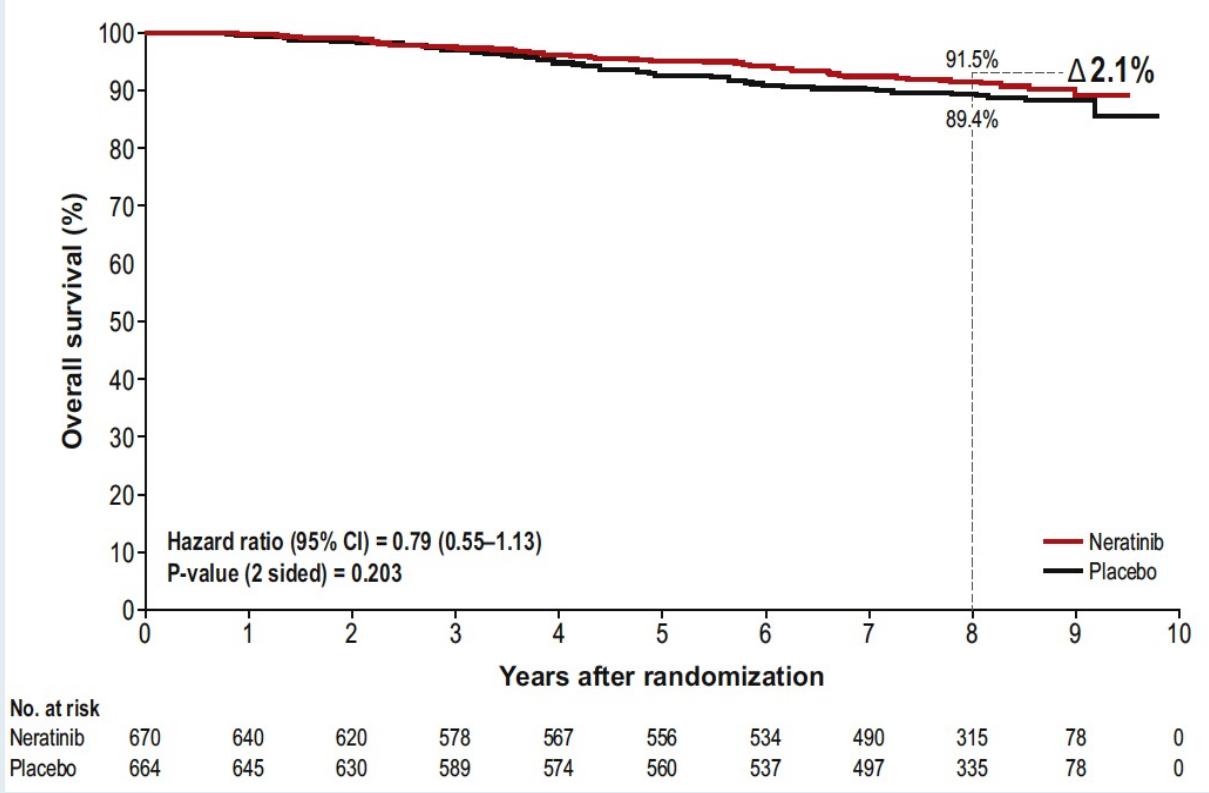
***Clin Breast Cancer* 2021;21(1):80-91.**

ExteNET: Final Analysis of Neratinib for HER2-Positive Localized Breast Cancer

Invasive disease-free survival at 5 years*



Overall survival at 8 years*



* HR-positive/≤ 1-year population

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

RTP RESEARCH TO PRACTICE

ExteNET: Cumulative Incidence of CNS Recurrences

Population or subgroup	Events, n		Cumulative incidence of CNS recurrences	
	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) Neoadjuvant (n = 354)	 3 1	 6 6	 0.7% 0.7%	 1.5% 3.7%
pCR status (n = 354) No (n = 295) Yes (n = 38)	 1 0	 5 1	 0.8% 0	 3.6% 5.0%

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

ExteNET: Adverse Events

Summary of AEs

	Neratinib (n = 662)	Placebo (n = 657)
Any TEAE	649 (98)	567 (86)
Grade 3 or 4 TEAE	327 (49)	76 (12)
Fatal TEAE	1 (<1)	0 (0)
Serious TEAE	45 (7)	36 (6)
Treatment-related TEAE	630 (95)	360 (55)
Serious treatment-related TEAE	19 (3)	5 (<1)
TEAE leading to		
Treatment discontinuation	178 (27)	30 (5)
Study withdrawal	11 (2)	2 (<1)
Dose reduction	203 (31)	13 (2)
Hospitalization	41 (6)	35 (5)
Dose interruption	280 (42)	75 (11)

Frequent Treatment-Emergent AEs (TEAEs)

	Neratinib (n = 662)		Placebo (n = 657)	
	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Diarrhea	365 (55)	261 (39)	213 (32)	7 (1)
Nausea	280 (42)	9 (1)	135 (21)	2 (<1)
Fatigue	177 (27)	13 (2)	129 (20)	2 (<1)
Vomiting	150 (23)	24 (4)	41 (6)	2 (<1)
Abdominal pain	145 (22)	11 (2)	58 (9)	1 (<1)
Headache	119 (18)	6 (<1)	125 (19)	1 (<1)
Upper abdominal pain	90 (14)	6 (<1)	35 (5)	3 (<1)
Rash	90 (14)	3 (<1)	40 (6)	0 (0)
Decreased appetite	79 (12)	1 (<1)	13 (2)	0 (0)
Muscle spasms	81 (12)	0 (0)	21 (3)	1 (<1)

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

RTP RESEARCH TO PRACTICE

CONTROL Trial: Strategies to Improve Neratinib Tolerability

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

- Neratinib poorly tolerated in ExteNET
  - 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.

Treatment-Emergent Diarrhea in the ExteNET and CONTROL Studies

Outcome	ExteNET (*n* = 1408)	L (*n* = 137)	BL (*n* = 64)	CL (*n* = 136)	CL-PRN (*n* = 104)	DE (*n* = 60)
Treatment-emergent diarrhea incidence, *n* (%)						
No diarrhea	65 (5)	28 (20)	9 (14)	23 (17)	5 (5)	1 (2)
Grade 1	323 (23)	33 (24)	16 (25)	38 (28)	34 (33)	25 (42)
Grade 2	458 (33)	34 (25)	21 (33)	47 (35)	32 (31)	25 (42)
Grade 3	561 (40)	42 (31)	18 (28)	28 (21)	33 (32)	9 (15)
Grade 4	1 (<1)	0	0	0	0	0
Action taken, *n* (%)						
Dose hold	477 (34)	20 (15)	12 (19)	22 (16)	15 (14)	7 (12)
Dose reduction	372 (26)	10 (7)	3 (5)	10 (7)	12 (12)	2 (3)
Discontinuation	237 (17)	28 (20)	5 (8)	5 (4)	8 (8)	2 (3)
Hospitalization	20 (1)	2 (1)	0	0	0	0

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

FDA Approves Dose-Escalation Label Update for Neratinib in HER2-Positive Breast Cancer

Press Release – July 1, 2021

"The FDA has approved a labeling supplement to the US prescribing information for neratinib that includes the dose-escalated use of the agent in patients with HER2-positive breast cancer, as examined in the phase 2 CONTROL trial… In the multicenter, open-label, multicohort CONTROL trial, investigators examined neratinib, administered at a daily dose of 240 mg for up to 1 year, in patients with early-stage, HER2-positive breast cancer who had received loperamide prophylaxis and additional anti-diarrheal treatment, as needed. Neratinib dose escalation with loperamide, if needed, was also evaluated. Patients in this cohort were administered neratinib at a daily dose of 120 mg for week 1, followed by a daily dose of 160 mg for week 2, and a 240-mg daily dose for week 3 and thereafter for the duration of treatment.

Results from the trial indicated that dose escalation in the extended adjuvant setting, paired with loperamide prophylaxis and additional anti-diarrheal treatment, resulted in *more than a 60% reduction in the percentage of patients who experienced grade 3 diarrhea* compared with what had been observed in the phase 3 ExteNET trial (NCT00878709), where no dose escalation or antidiarrheal prophylaxis was required. These rates were 13% vs 40% in the CONTROL and ExteNET trials, respectively.

Moreover, compared with ExteNET, this approach *reduced the median cumulative days of grade 3 diarrhea by 50% (5 days vs 2.5 days) and reduced discontinuation rates by approximately 80% (17% vs 3%)."*

www.onclive.com/view/fda-approves-dose-escalation-label-update-for-neratinib-in-her2-breast-cancer

RTP RESEARCH TO PRACTICE

Questions — Sara A Hurvitz, MD

Patients with localized HER2-positive breast cancer

- **How do you approach patients with localized HER2-positive breast cancer in terms of neoadjuvant, adjuvant and postadjuvant treatment?**
- **How do you explain the goals of neoadjuvant treatment to patients?**

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TO PRACTICE

Commentary — Sara A Hurvitz, MD

Patients with localized HER2-positive breast cancer

- **What I tell patients: Giving therapy prior to surgery:**
  - **Allows us to see whether the tumor is responding to the therapy selected**
    - **If it is not appropriately shrinking, we have the opportunity to change therapy.**
    - **We do not have the ability to know if therapy is working if we give it after surgery**
  - **Allows us to gauge one's risk of recurrence**
    - **Patients who have no cancer remaining in the breast/lymph nodes ("pCR") at the time of surgery have a low chance of recurrence**
    - **Approximately 60% of patients will have pCR after treatment**
  - **Allows us to improve poor prognosis if there is cancer remaining at surgery**
    - **This new therapy (T-DM1) has been shown to reduce the chance of cancer returning**

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TO PRACTICE

Commentary — Sara A Hurvitz, MD

- **For >T1c, I give TCHP x 6 → surgery →**
  - **If surgery shows**
    - **pCR: complete a year of H (+P if was node positive)**
    - **residual disease: T-DM1 x 14 cycles**
  - **If HR+, endocrine therapy is given for >5 years**

Questions — Jamie Carroll, APRN, MSN, CNP

Patients with localized HER2-positive breast cancer

- **How do you prepare a patient to receive neoadjuvant docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP)?**
- **How do you prepare a patient to receive postadjuvant neratinib?**
- **What are some of the psychosocial issues that arise in this situation?**

Commentary — Jamie Carroll, APRN, MSN, CNP

Patients with localized HER2-positive breast cancer

- **I'm a very visual person so I try to graph out on a time line when patients will be getting treatment. As HER2-positive breast cancer treatment is very long, patients can get easily lost at initial consult in the length of treatment as well as the adjuvant recommendation. Repetition is key. At each visit, we discuss our goal — pCR — as well as the recommendation for either Trastuzumab or T-DM1 after surgery.**
- **I break down the medications and ensure they know the difference between chemotherapy and HER2-targeting therapy. At a high level, I discuss side effects as well as the options to complement treatment such as scalp cooling, port, cryotherapy. Breast cancer patients are very well read and do their research.**
- **I let them know what to expect each day that they come for treatment. Labs, office visit and then the length of their chemo session. This helps set expectations.**

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Commentary — Jamie Carroll, APRN, MSN, CNP

- **Neratinib gets a bad rap. After ExteNET, we were using anti-diarrheals but only to manage the diarrhea. Now I think we've learned to dose escalate, and patients do better with the escalation strategy following CONTROL protocol.**
- **I have patients who start full dose and have immense toxicity. Along with my clinical pharmacist, we've developed hourly anti-diarrheal regimens for them.**
- **The biggest psychosocial issue is the fact that a HER2-positive breast cancer patient is on treatment for a long time. I had one patient tell me she was ready to be a wife and mom again. I think we can sometimes forget how this affects every part of their lives.**
- **Although we do better with managing side effects from neratinib, patients generally have more side effects than with trastuzumab, so it can be challenging when they've been feeling well, to recommend treatment with increased side effects.**

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Agenda

Module 1 – Localized ER-positive breast cancer; role of CDK inhibitors

Module 2 – ER-positive metastatic breast cancer

Module 3 – Localized HER2-positive breast cancer

Module 4 – Metastatic HER2-positive breast cancer

Module 5 – Localized triple-negative breast cancer (TNBC); role of immunotherapy

Module 6 – Metastatic TNBC

SELF-ASSESSMENT QUIZ

Trastuzumab deruxtecan carries a black box warning for…

1. QT interval prolongation
2. Interstitial lung disease
3. Cardiovascular events
4. I don’t know

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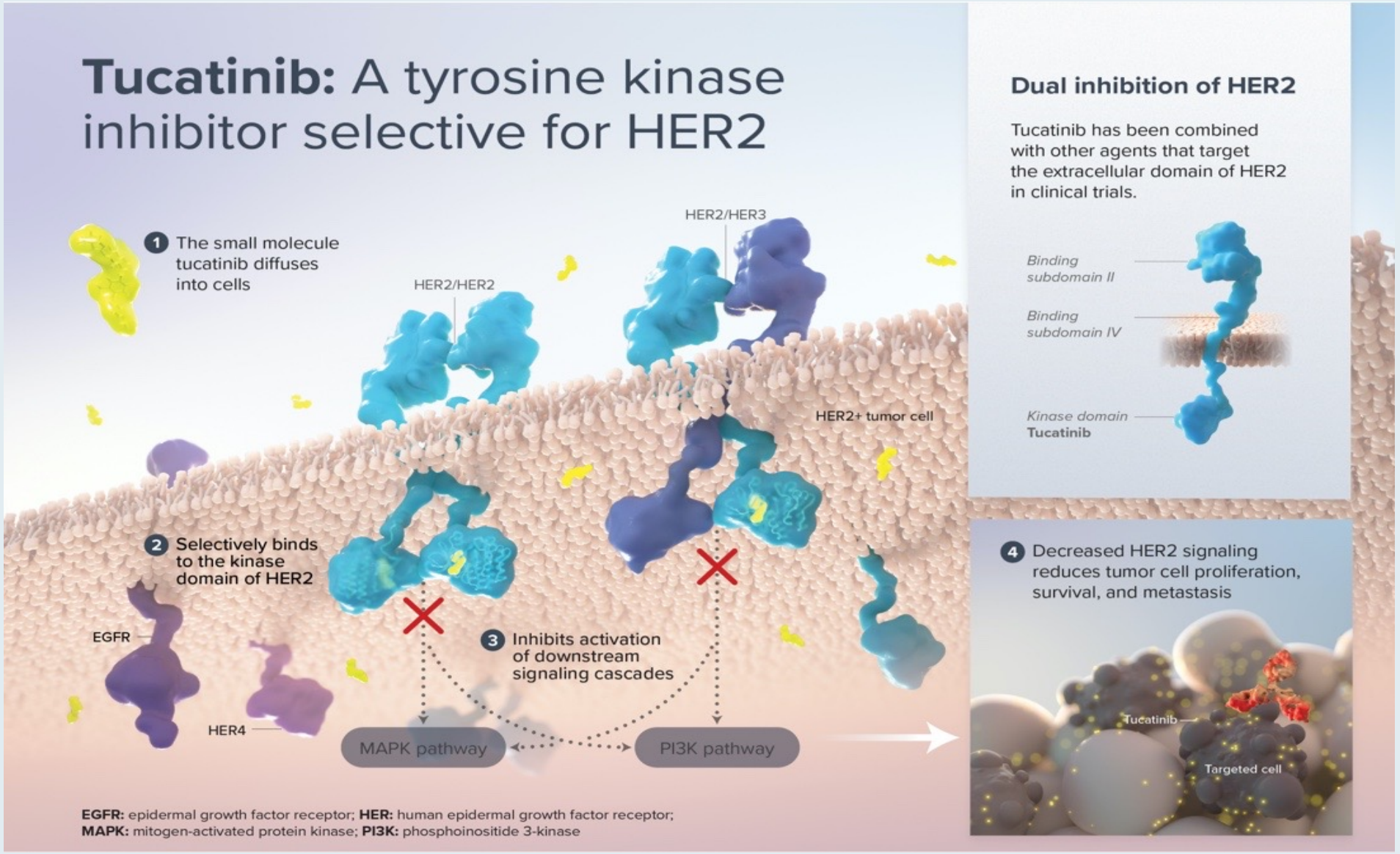
TO PRACTICE

Tucatinib Mechanism of Action



www.seagen.com/science/pipeline/tucatinib

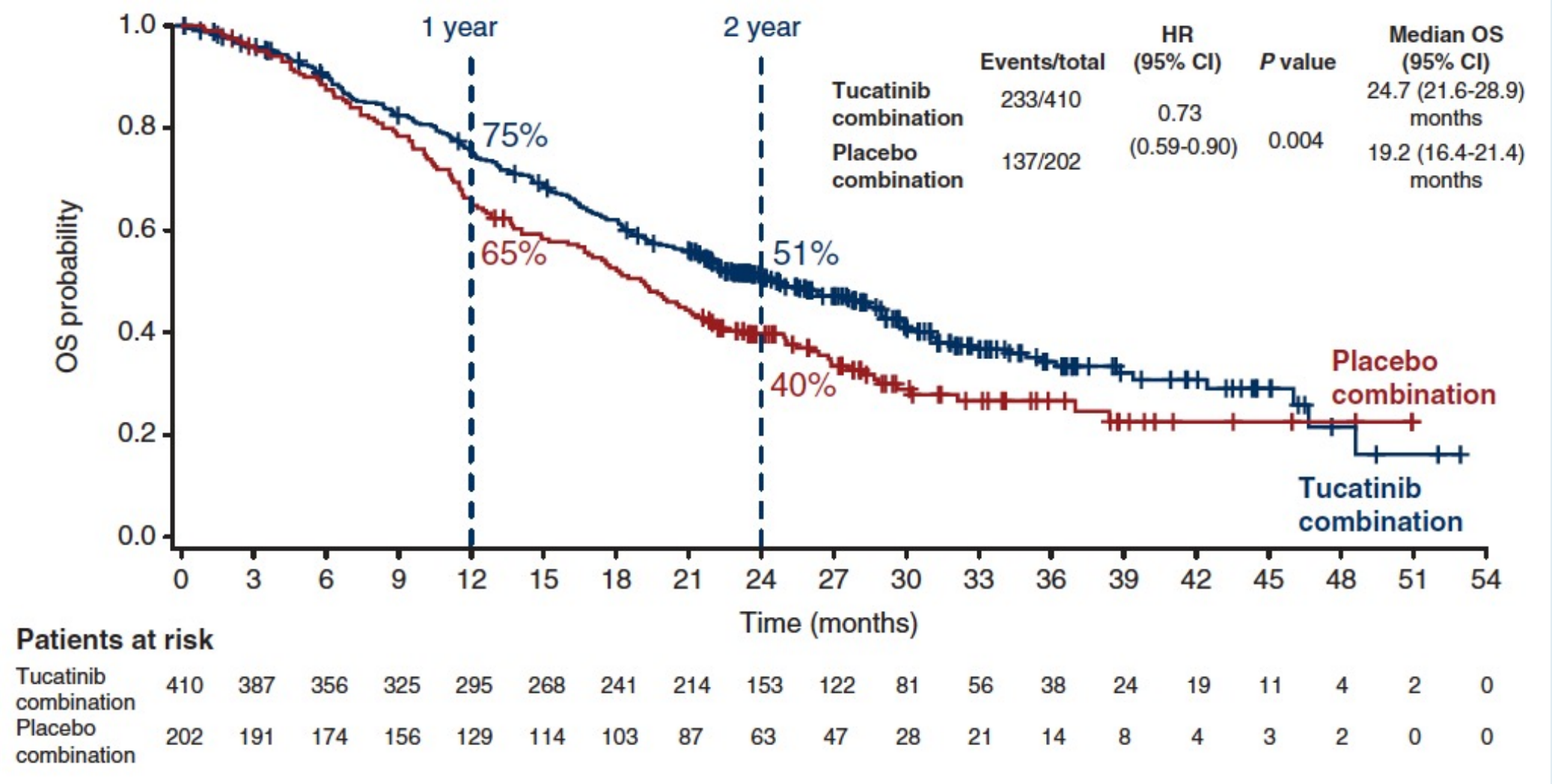
RTP RESEARCH TO PRACTICE

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]

Ann Oncol 2022;33(3):321-29.

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

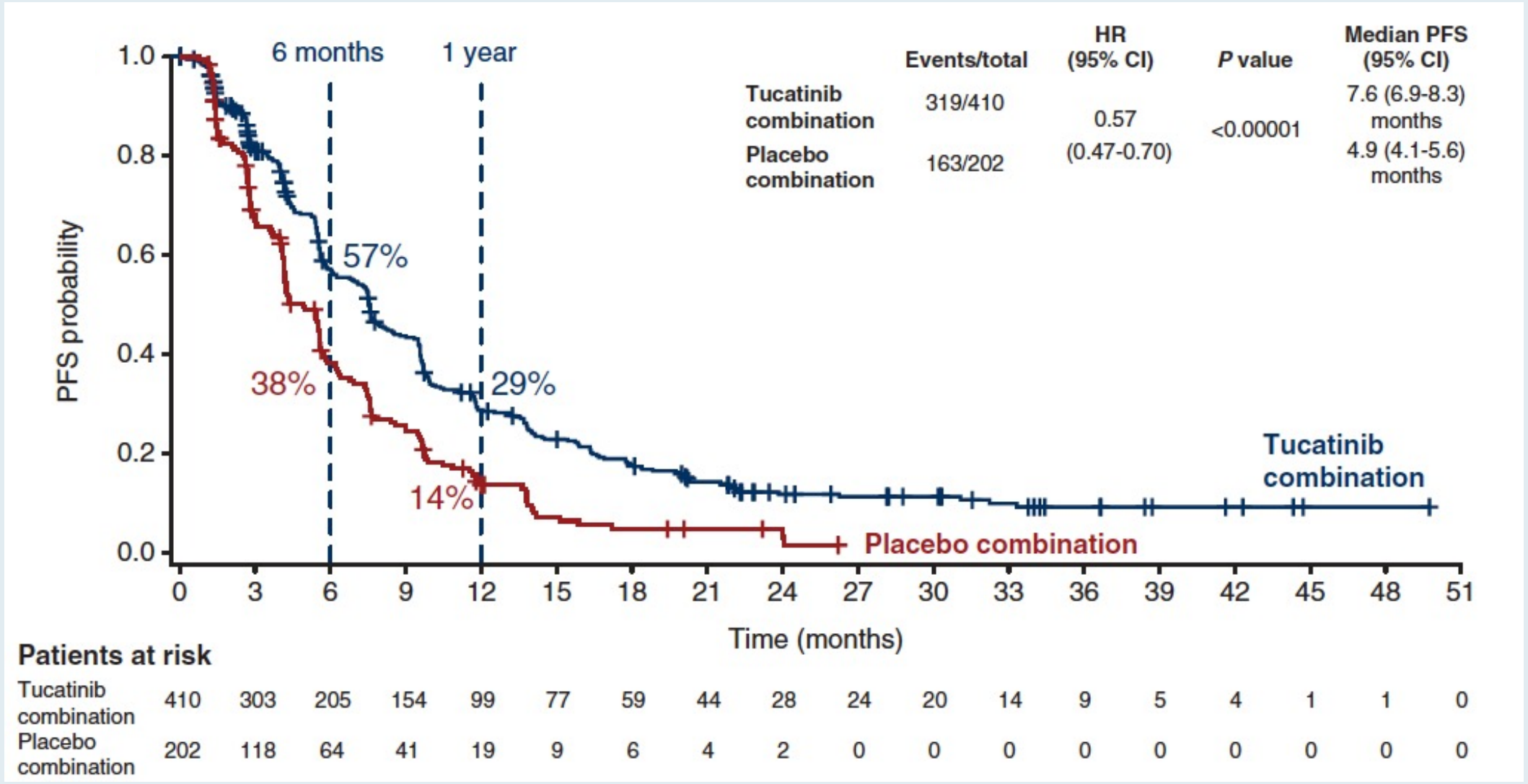
Patients at risk

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):321-29.

RTP RESEARCH TO PRACTICE

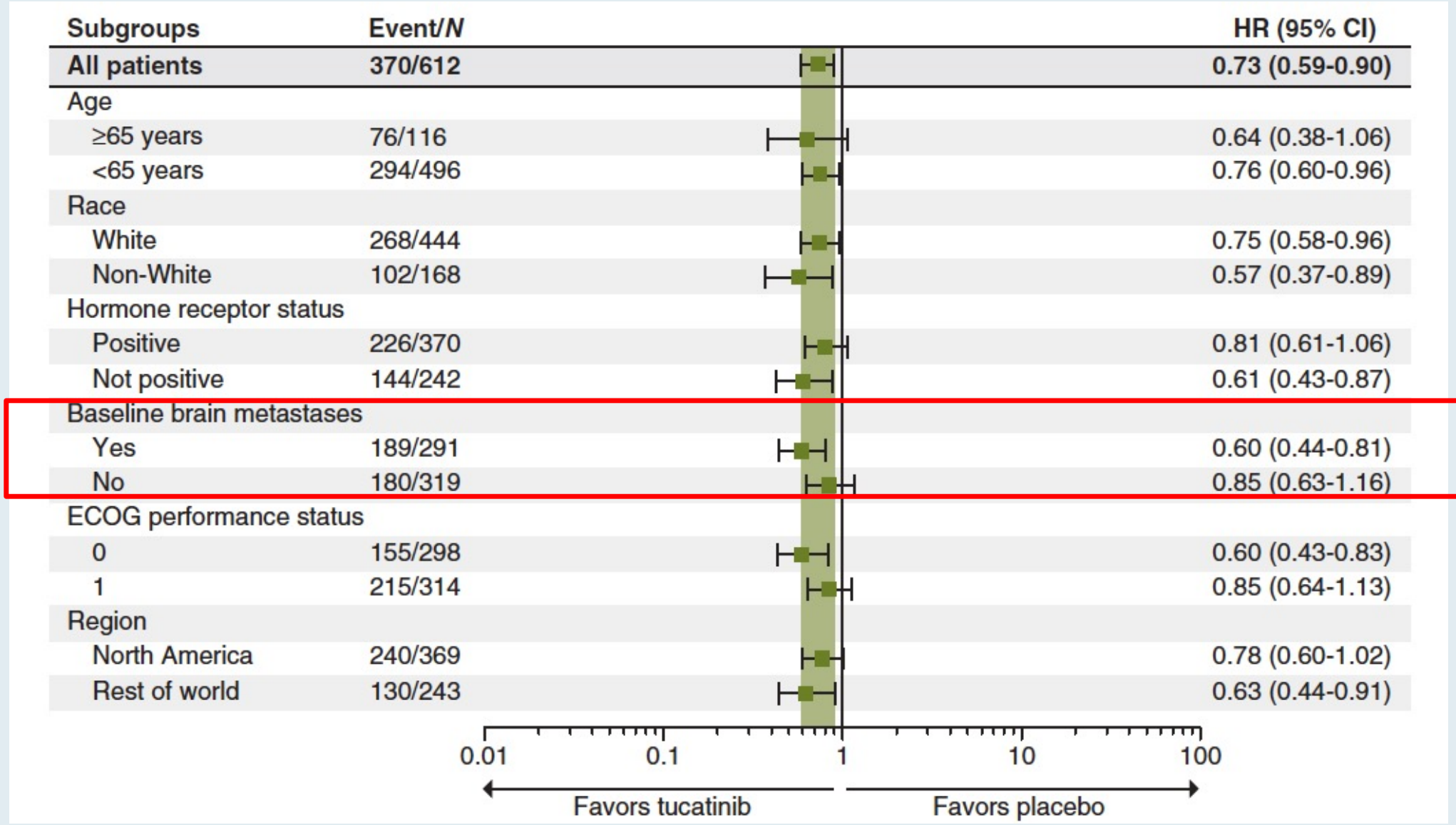
HER2CLIMB: Progression-Free Survival (PFS)



	Events/total	HR (95% CI)	*P* value	Median PFS (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<0.00001	7.6 (6.9-8.3) months
Placebo combination	163/202			4.9 (4.1-5.6) months

Curigliano G et al. *Ann Oncol* 2022;33(3):321-29.

HER2CLIMB: Overall Survival for Patients with Baseline Brain Metastases



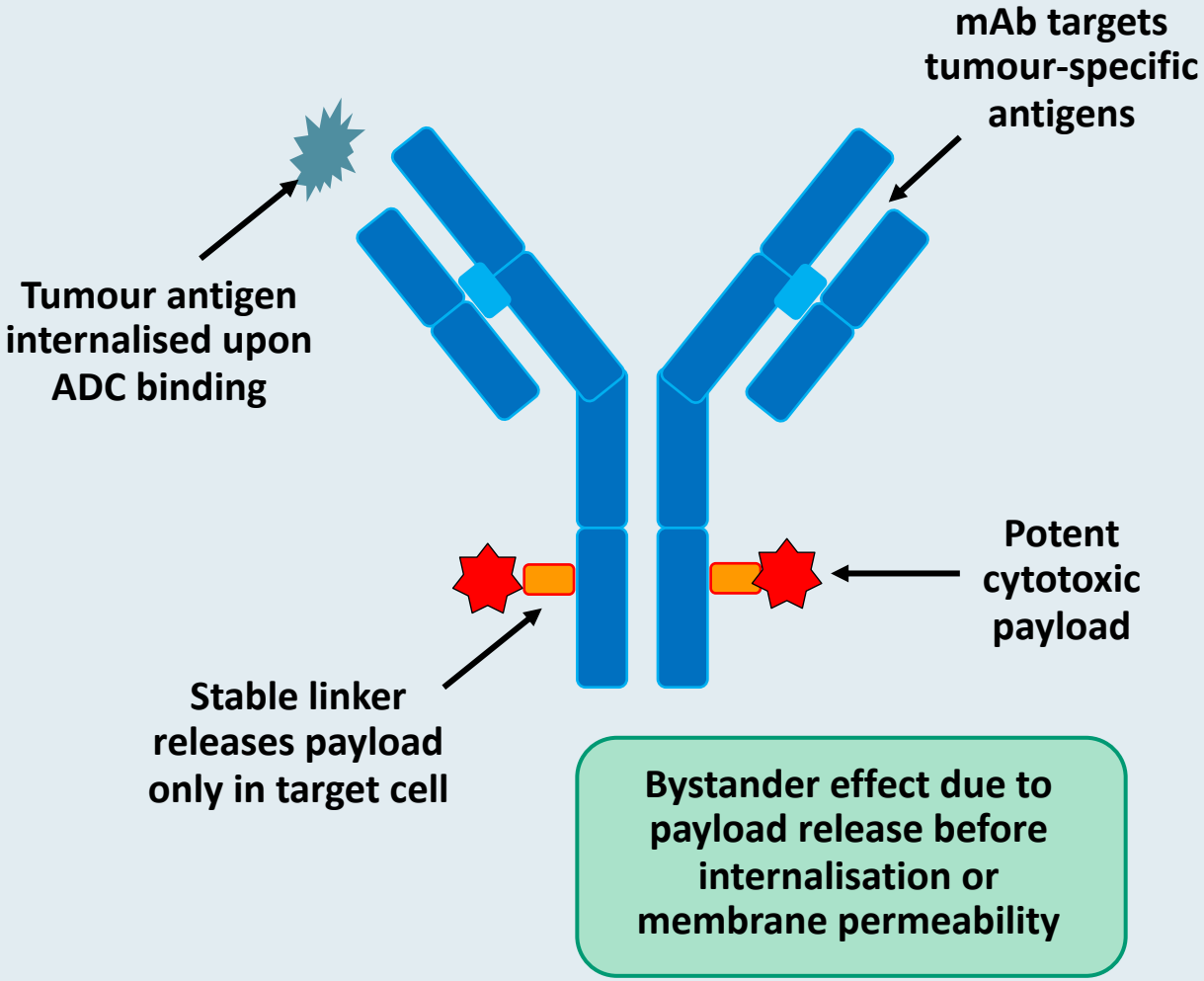
Curigliano G et al. *Ann Oncol* 2022;33(3):321-29.

HER2CLIMB: Safety Outcomes

Select adverse events	Tucatinib (n = 404)		Placebo (n = 197)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	99.3%	55.2%	97.0%	48.7%
Diarrhea	80.9%	12.9%	53.3%	8.6%
PPE syndrome	63.4%	13.1%	52.8%	9.1%
Nausea	58.4%	3.7%	43.7%	3.0%
Fatigue	45.0%	4.7%	43.1%	4.1%
Vomiting	35.9%	3.0%	25.4%	3.6%
Stomatitis	25.5%	2.5%	14.2%	0.5%
Increased AST	21.3%	4.5%	11.2%	0.5%
Increased ALT	20.0%	5.4%	6.6%	0.5%

Murthy RK et al. SABCS 2019;Abstract GS1-01; Murthy RK et al. *N Engl J Med* 2020;382(7):597-609.

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.

The NEW ENGLAND JOURNAL of MEDICINE

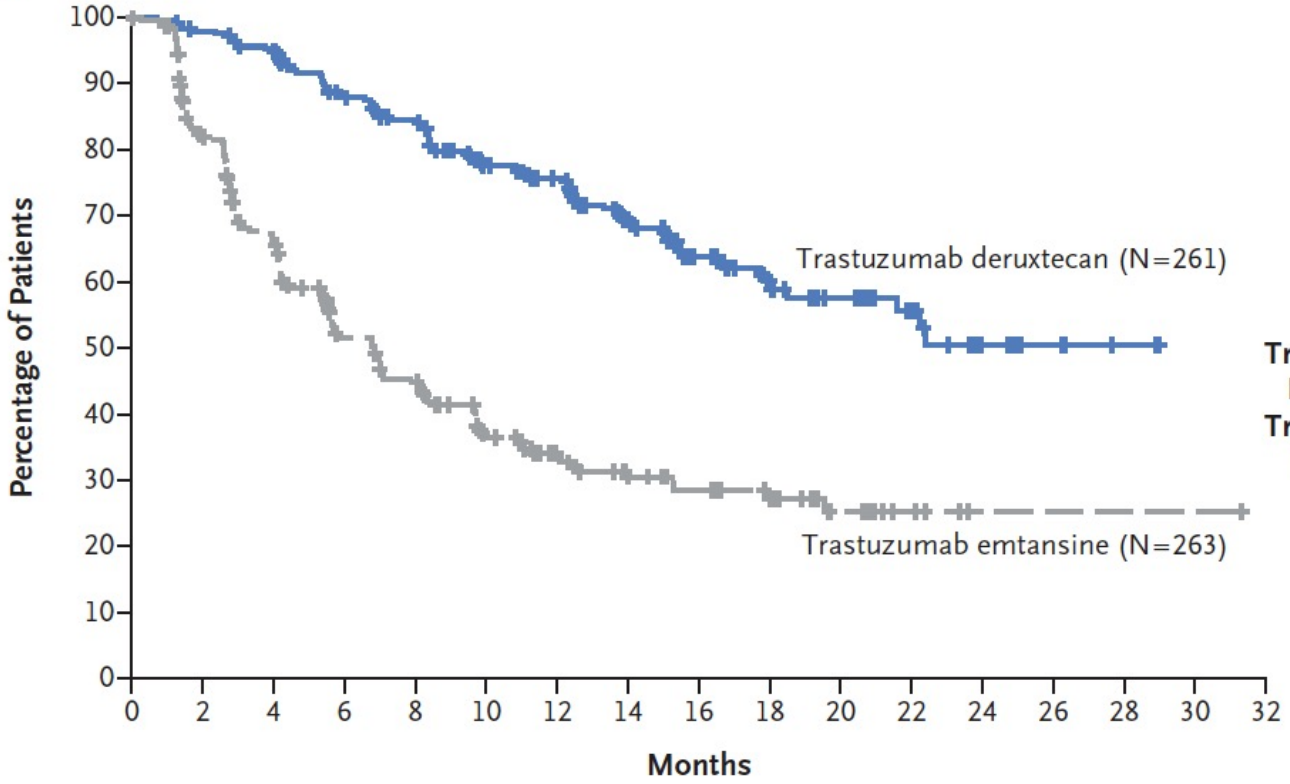
N Engl J Med 2022;386(12):1143-54.

ORIGINAL ARTICLE

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

DESTINY-Breast03: Progression-Free Survival



No. at Risk																
Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2	
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	1	0

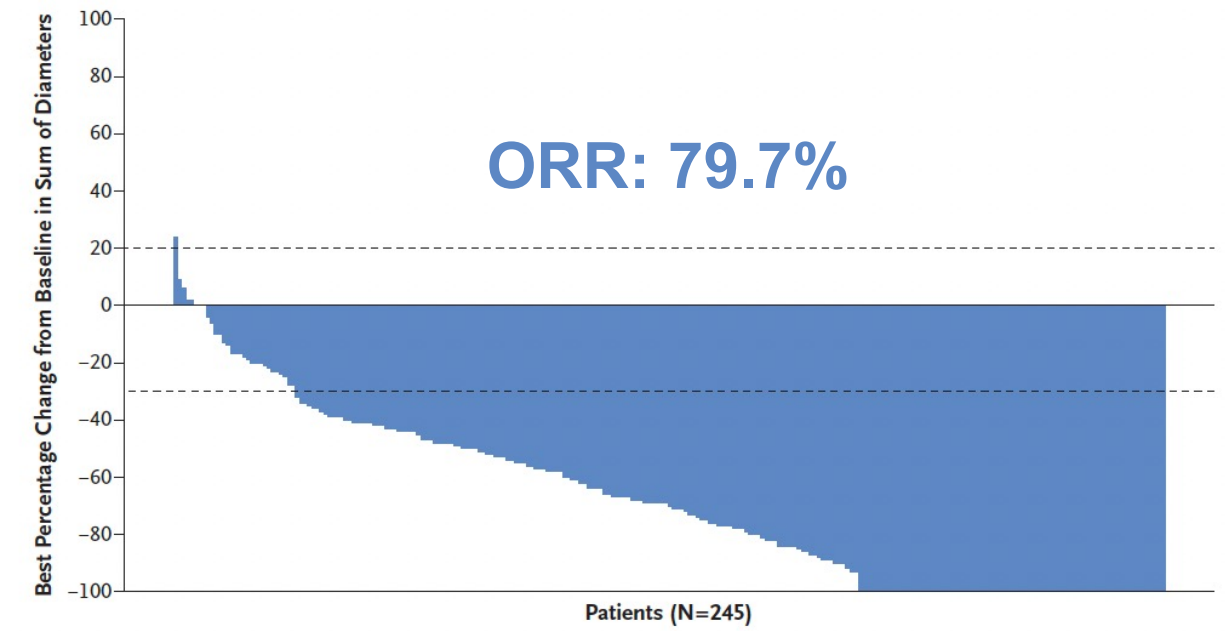
	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

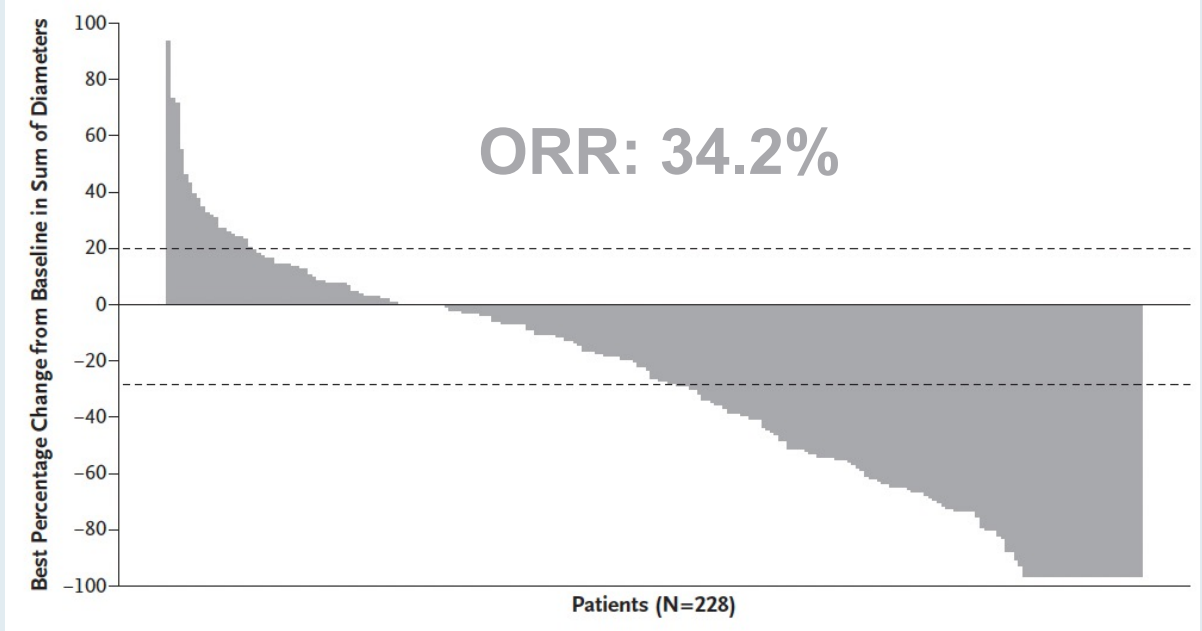
Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

DESTINY-Breast03: Antitumor Activity

Trastuzumab deruxtecan



Trastuzumab emtansine



ORR = overall response rate

Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

RTP RESEARCH TO PRACTICE

DESTINY-Breast03: Most Common Drug-Related Adverse Events and Adjudicated Drug-Related Interstitial Lung Disease or Pneumonitis

Event	Trastuzumab Deruxtecan (N=257)		Trastuzumab Emtansine (N=261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Most common drug-related adverse events				
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia‖	93 (36.2)	1 (0.4)	6 (2.3)	0
Adjudicated drug-related interstitial lung disease or pneumonitis**	27 (10.5)	2 (0.8)	5 (1.9)	0

Cortes J et al. *N Engl J Med* 2022;386(12):1143-54.

RTP RESEARCH TO PRACTICE

Questions — Hope S Rugo, MD

Patients with metastatic HER2-positive breast cancer

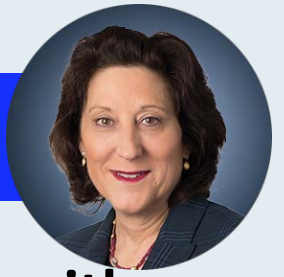
- **How do you select second-line treatment for patients with HER2-positive metastatic disease?**
- **How does the presence of brain metastases affect your approach?**

Commentary — Hope S Rugo, MD

Patients with metastatic HER2-positive breast cancer

- **How do you select second-line treatment for patients with HER2-positive metastatic disease?**
  - **I focus on disease control and durability of response balanced with toxicity and convenience, as well as response to first-line treatment.**
  - **In general, I would select trastuzumab deruxtecan given the dramatic results from DB04.**
- **How does the presence of brain metastases affect your approach?**
  - **It depends on the extent of brain lesions. For a single brain lesion without systemic progression, I would continue maintenance trastuzumab and pertuzumab. For more extensive disease I would recommend tucatinib, capecitabine and trastuzumab.**

Commentary — Hope S Rugo, MD



- **Age 40: diagnosed with de novo HR+/HER2+ MBC to bone and liver; treated with paclitaxel, trastuzumab and pertuzumab x 6 months followed by trastuzumab and pertuzumab with anastrozole**
  - **3 years later she presented with headaches, brain MRI showed 3 brain lesions, treated with SRS**
  - **2 years later one lesion increased in size, treated with SRS**
    - **Treatment changed to tucatinib, capecitabine and continued trastuzumab**
- **32 yo woman with BRCA2 mutation presented with de novo metastatic disease to liver at 8 months of pregnancy. HR-, HER2+**
  - **Treated with THP followed by HP (had breast surgery and SBRT to liver lesion) with PD after 15 months in lung**
  - **Treated with T-DM1 x 14 months with PD in lung**
  - **Treated with T-DXd on Destiny Breast01 starting 8/18**
    - **At 4 years she had a tiny increase in her lung nodule treated with SBRT**

RTP RESEARCH TO PRACTICE

Questions — Kelly Leonard, MSN, FNP-BC

Patients with metastatic HER2-positive breast cancer

- **How do you prepare a patient to receive the HER2CLIMB regimen?**
- **How do you prepare a patient to receive trastuzumab deruxtecan?**
- **What are some of the psychosocial issues that arise in these situations?**

Commentary — Kelly Leonard, MSN, FNP-BC

Patients with metastatic HER2-positive breast cancer

- **Agents used in HER2CLIMB regimen → trastuzumab, capecitabine, and tucatinib. Trastuzumab is administered IV every 3 weeks, capecitabine is taken orally twice daily for 14 days on, then 7 days off each cycle, then tucatinib is taken orally twice daily for 21 days on, then 7 days off.**
- **Trastuzumab → generally well tolerated. Obtain echo prior to starting, then every 3 months or so thereafter, given risk of cardiotoxicity.**
- **Capecitabine → palmar plantar erythema (ie, redness, peeling, and discomfort), encourage liberal moisturization; GI upset (ie, loose stool, oral sores), lower blood counts, fatigue.**

Commentary — Kelly Leonard, MSN, FNP-BC

- **Tucatinib → diarrhea, nausea, oral sores, and hepatotoxicity (LFTs and bili are monitored with labs). Can take loperamide as needed for diarrhea; sometimes will prescribe diphenoxylate/atropine if no relief with loperamide.**
- **Potential side effects of T-DXd → low blood counts (ie, neutropenia), cardiotoxicity (ie, reduced left ventricular ejection fraction), GI upset (nausea, diarrhea, oral sores), pneumonitis.**
- **Obtain echocardiogram prior to starting T-DXd and approx every 3 months.**
- **Review signs and symptoms of pneumonitis → shortness of breath, cough.**

Commentary — Kelly Leonard, MSN, FNP-BC

- **48 y/o female with metastatic breast cancer (to lung and liver), who received her first cycle of T-DXd on 4/1. At baseline, she has dyspnea on exertion due to her disease. Ten days after she received her first T-DXd treatment, she noticed increasing dyspnea on exertion and intermittent cough. Was sent to local ED and had CT chest, findings consistent with pneumonitis. Started on prednisone. D/c'ing T-DXd and switching to Eribulin. This was an interesting case, because typically we do not see pneumonitis present so soon after the first dose (usually we see this several weeks to several months into treatment).**

Commentary — Kelly Leonard, MSN, FNP-BC

- **This woman has been very anxious during her course of treatment. She was just diagnosed with metastatic disease approx 1 year ago, and this was soon after she had completed treatment in the adjuvant setting. So understandably, it has been a difficult year. She is married and has a teenager who is in high school. She does not work. She has a strong support system at home, but she does come alone to all of her appointments since she comes from out of state, as her husband needs to be home with their son.**

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RESEARCH
TO PRACTICE

Agenda

Module 1 – Localized ER-positive breast cancer; role of CDK inhibitors

Module 2 – ER-positive metastatic breast cancer

Module 3 – Localized HER2-positive breast cancer

Module 4 – Metastatic HER2-positive breast cancer

Module 5 – Localized triple-negative breast cancer (TNBC); role of immunotherapy

Module 6 – Metastatic TNBC

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SELF-ASSESSMENT QUIZ

Currently the most common approach for a patient with localized TNBC is…

1. Neoadjuvant chemotherapy
2. Neoadjuvant chemotherapy + immune checkpoint inhibitor
3. I don’t know

SELF-ASSESSMENT QUIZ

Prior to making a decision about adjuvant treatment for TNBC with 1 positive node…

1. Patients with a family history of breast cancer should have germline testing
2. All patients should have germline testing
3. I don’t know

N Engl J Med 2022;386(6):556-67

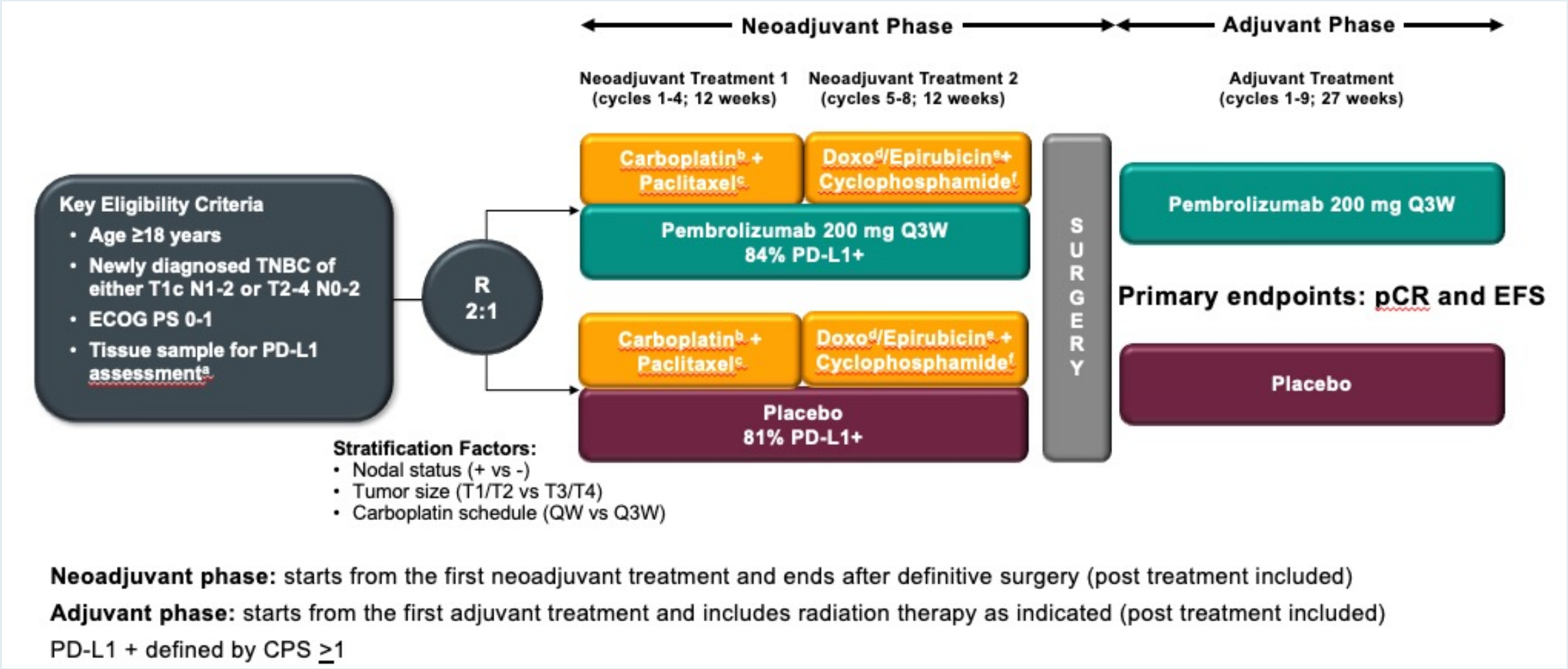
The NEW ENGLAND JOURNAL of MEDICINE

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



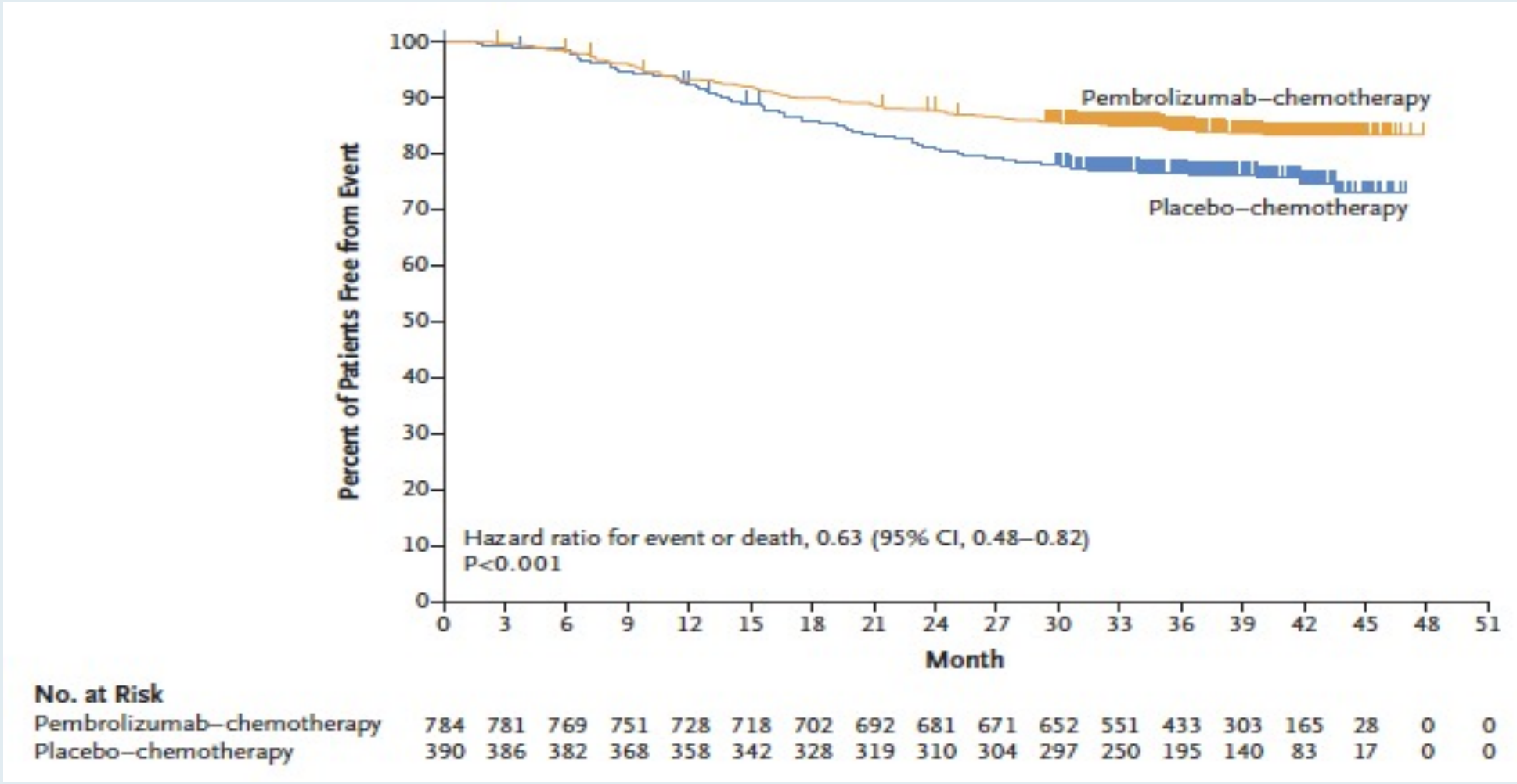
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

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

PD-L1 + defined by CPS ≥1

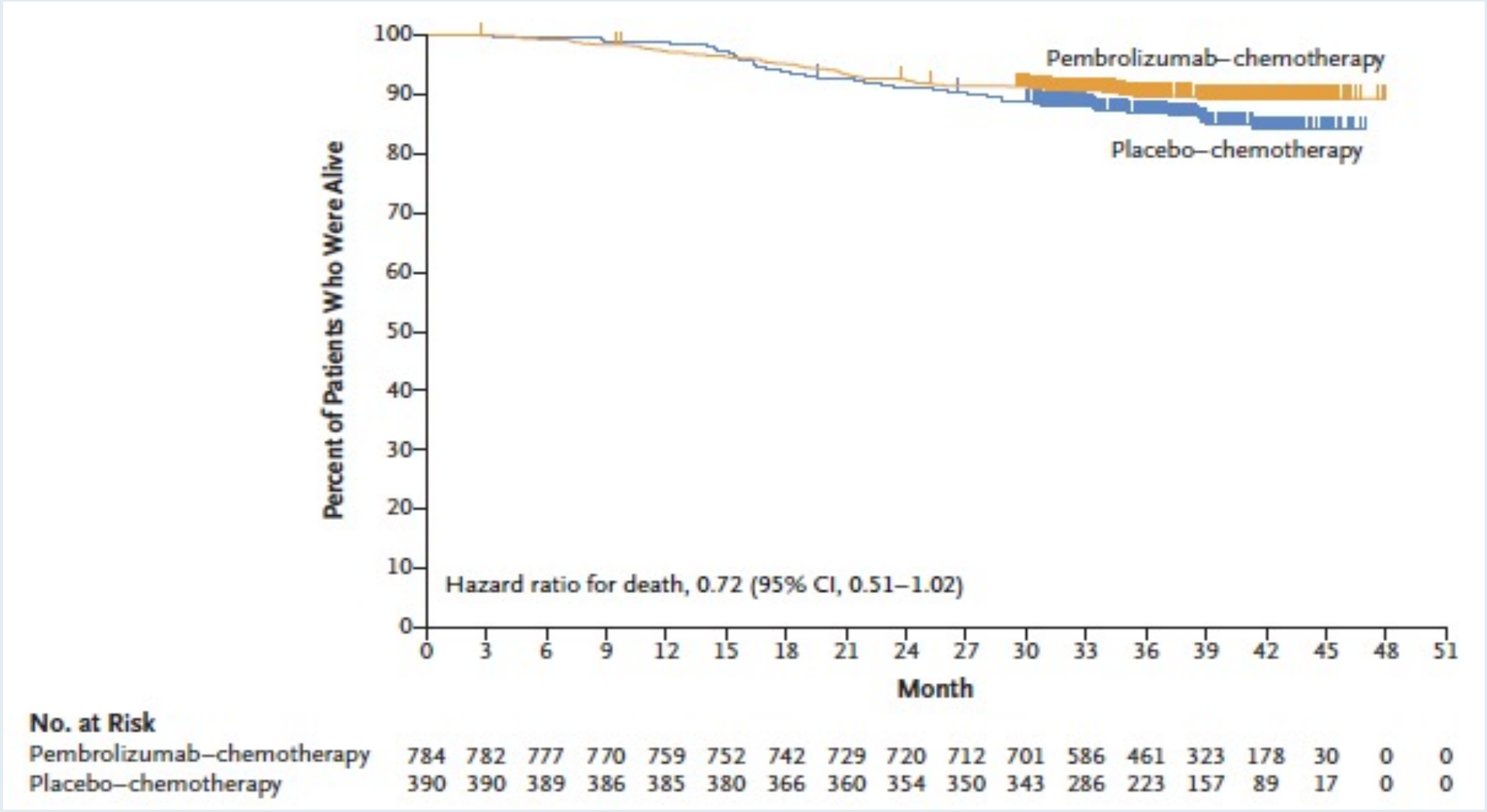
Schmid P et al. *N Engl J Med* 2020;382:810-821.

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-522: Overall Survival According to Treatment Group (ITT Population)



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

Symptoms of Immunotherapy Toxicity

Hypophysitis
(fatigue)

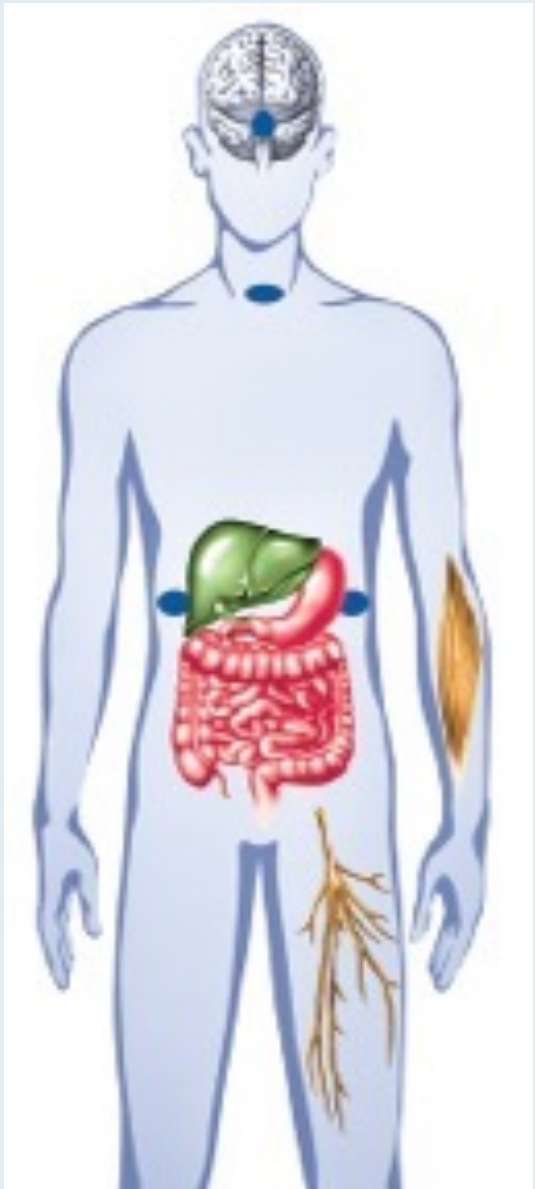
Thyroiditis
(over/underactive thyroid)

Adrenal Insufficiency
(fatigue)

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

Colitis
(diarrhea, abd pain)

Dermatitis
(skin rash, itch, blistering)



Pneumonitis
(dyspnea, cough)

Myocarditis
(chest pain, dyspnea)

Hepatitis
(abn LFTs, jaundice)

Pancreatitis
(abd pain)

Neurotoxicities
(MG, encephalitis)

Arthritis
(joint pain)

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TO PRACTICE

FDA Approves Olaparib as Adjuvant Treatment for Patients with HER2-Negative High-Risk Localized Breast Cancer and Germline BRCA Mutations Who Have Received Neoadjuvant of 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 2022

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]

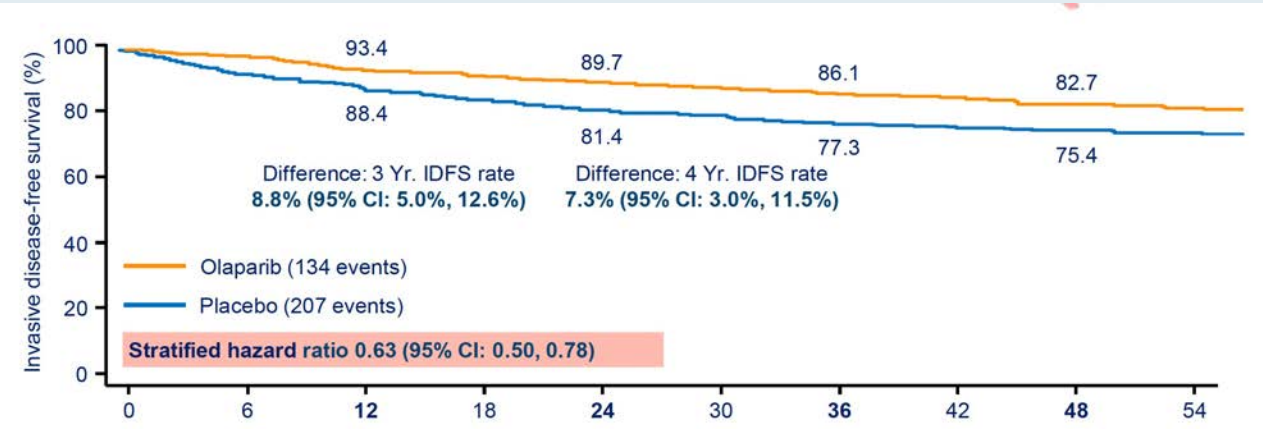
[1]Breast Cancer Now Research Unit, Institute of Cancer Research, London, United Kingdom; [2]Dana Farber Cancer Institute, Boston, MA, USA; [3]Department of Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia; [4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Canada; [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

ESMO

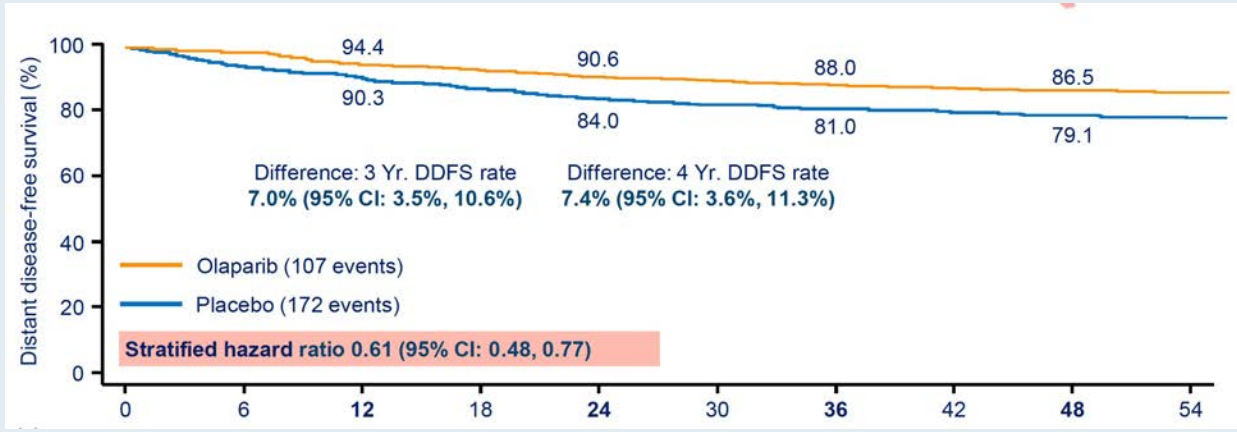
RTP RESEARCH TO PRACTICE

OlympiA: Invasive and Distant Disease-Free Survival (DFS)

Invasive DFS (IDFS)



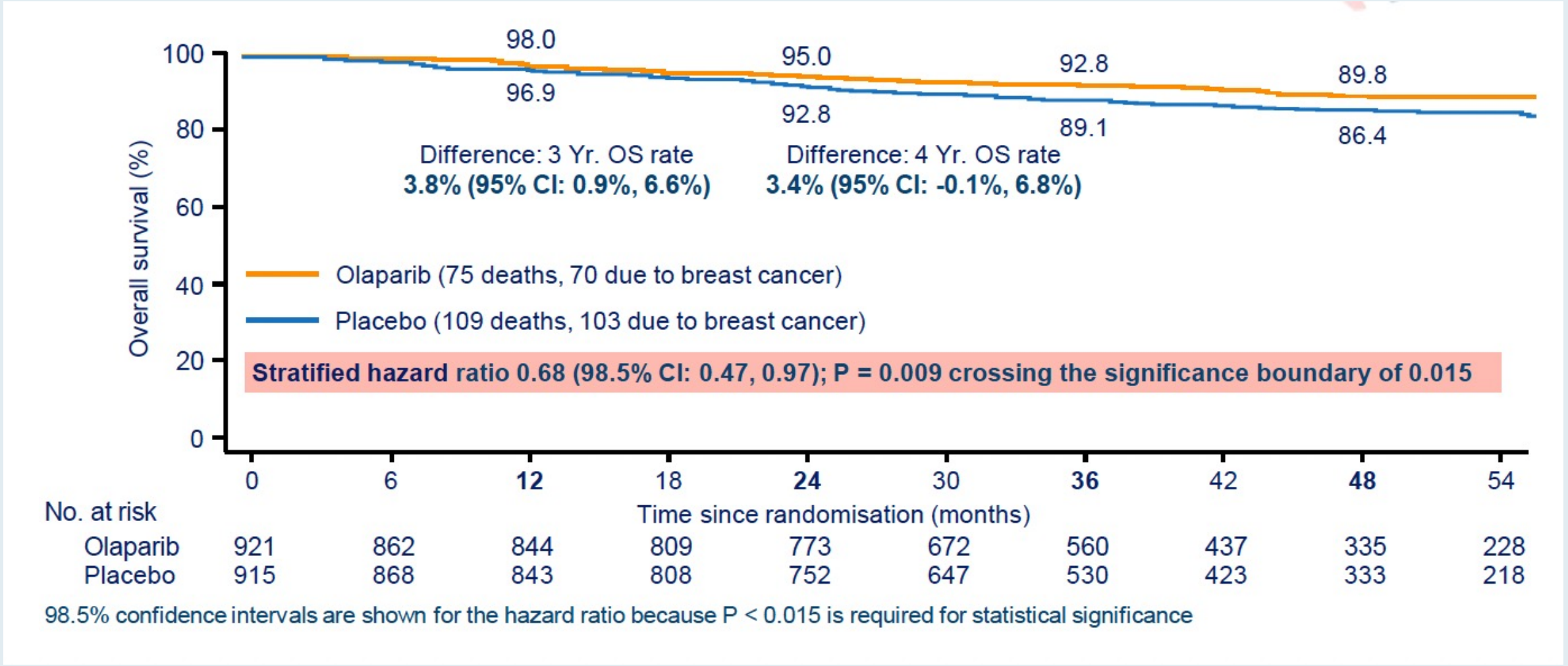
Distant DFS (DDFS)



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

RTP RESEARCH TO PRACTICE

OlympiA: Overall Survival



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

Questions — Sara A Hurvitz, MD

Patients with localized triple-negative breast cancer (TNBC); role of immunotherapy

- **How do you approach the patient with localized TNBC in terms of neoadjuvant versus adjuvant treatment and the use of immunotherapy?**

Commentary — Sara A Hurvitz, MD

Patients with localized triple-negative breast cancer (TNBC); role of immunotherapy

- ***43 yo woman 2.3 cm triple negative, high grade, 1 lymph node suspicious, biopsy positive. Treated with neoadjuvant tax/carbo/pembro → AC/pembro → surgery. Adjuvant treatment based on pathologic response?***
- **Triple negative breast cancer has traditionally been treated with chemotherapy alone.**
- **Giving therapy prior to surgery:**
  - **Allows us to see whether the tumor is responding to the therapy selected**
    - **If it is not appropriately shrinking, we have the opportunity to change therapy.**
    - **We do not have the ability to know if therapy is working if we give it after surgery**
    - **Those patients with no cancer left at surgery have a low chance of cancer returning**

RTP RESEARCH TO PRACTICE

Commentary — Sara A Hurvitz, MD

- **Recently, pembrolizumab, which works by improving the immune system's response against breast cancer, has been shown to increase the chance that cancer will be gone by the time of surgery (pCR) and reduces the chance of cancer coming back several years after surgery.**
- **My approach:**
  - **If a patient has stage II TNBC, I use the above pembrolizumab-based regimen in the neoadjuvant setting**
  - **For stage I TNBC, I prefer a non-anthracycline, taxane/platinum approach either prior to or after surgery**

Questions — Jamie Carroll, APRN, MSN, CNP

Patients with localized triple-negative breast cancer (TNBC); role of immunotherapy

- **How do you prepare a patient to receive an anti-PD-1/PD-L1 antibody as part of their treatment?**
- **What are some of the key complications associated with immunotherapy that you monitor for?**
- **What are some of the psychosocial issues that arise in this situation?**

Commentary — Jamie Carroll, APRN, MSN, CNP

Patients with localized triple-negative breast cancer (TNBC); role of immunotherapy

- **I describe to patients that immunotherapy (KEYNOTE-522) helps increase the rate of pCR but any time we add medications to their regimen, we have the risk of increased side effects.**
- **Immunotherapy is the case of the "itis." I describe it as ramping up their immune system to fight the cancer. At times, the immune system "ramps up" too much and we see inflammation. This can occur basically in any body organ but more commonly occurs as: dermatitis, pneumonitis. Unfortunately, I had a patient develop hypophysitis and now is on long term steroids. I think it's important to highlight that some side effects are permanent.**
- **I also highlight if diarrhea presents then they cannot take loperamide and must call us.**

Commentary — Jamie Carroll, APRN, MSN, CNP

- **I have a patient who is 35 yo and received neoadjuvant PD-L1 treatment in combination with chemotherapy. She developed hypophysitis and hypothyroidism. She presented with fatigue during chemotherapy. It can be difficult to tease out side effects as we all know chemotherapy causes fatigue as well. Cortisol was undetectable and she now follows in Endocrinology.**
- **It can be challenging when someone wants to put breast cancer behind them if the treatments we gave now have life long toxicities. It can be a constant reminder of their cancer journey.**

Agenda

Module 1 – Localized ER-positive breast cancer; role of CDK inhibitors

Module 2 – ER-positive metastatic breast cancer

Module 3 – Localized HER2-positive breast cancer

Module 4 – Metastatic HER2-positive breast cancer

Module 5 – Localized triple-negative breast cancer (TNBC); role of immunotherapy

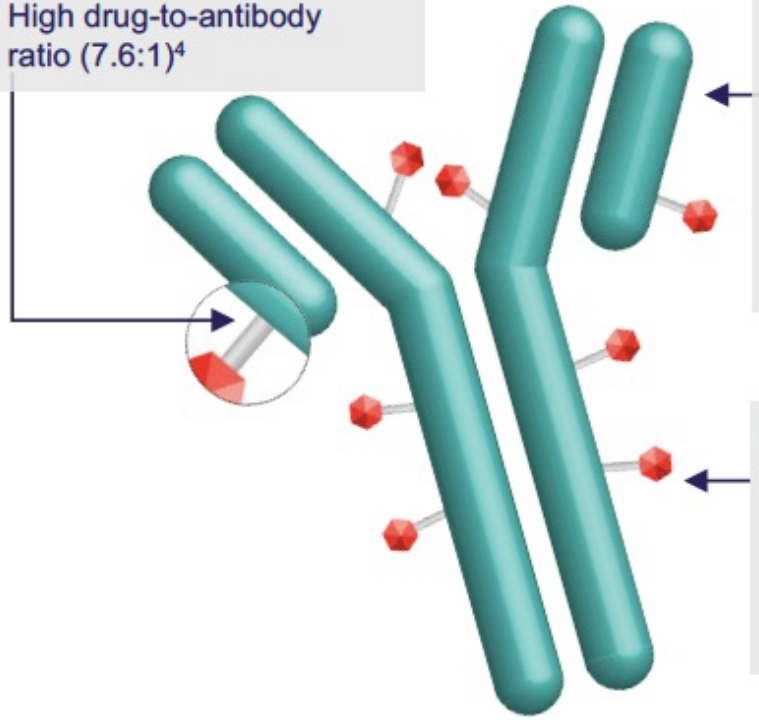
Module 6 – Metastatic TNBC

RTP RESEARCH TO PRACTICE

Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

- SG is distinct from other ADCs[1-4]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody
  - Hydrolysis of the linker also releases SN-38 extracellularly in the tumor microenvironment (bystander effect)
- Granted FDA accelerated approval for mTNBC[5]
- Landmark ASCENT study demonstrated a significant survival improvement of SG over chemotherapy, with a tolerable safety profile in pretreated mTNBC[6]
  - Median PFS of 5.6 vs 1.7 months (HR 0.41, *P*<0.0001)
  - Median OS of 12.1 vs 6.7 months (HR 0.48, *P*<0.0001)

Linker for SN-38
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)[4]



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

SN-38 payload
- SN-38 more potent than parent compound, irinotecan

ADC, antibody-drug conjugate; FDA, US Food and Drug Administration; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Goldenberg DM, et al. *Expert Opin Biol Ther.* 2020;20:871-885. 2. Nagayama A, et al. *Ther Adv Med Oncol.* 2020;12:1758835920915980. 3. Cardillo TM, et al. *Bioconjugate Chem.* 2015;26:919-931. 4. Goldenberg DM, et al. *Oncotarget.* 2015;6:22496-224512. 5. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020. 6. Bardia A, et al. ESMO 2020. Abstract LBA17.

Hurvitz SA et al. SABCS 2020;Abstract GS3-06.

N Engl J Med 2021;384(16):1529-41.

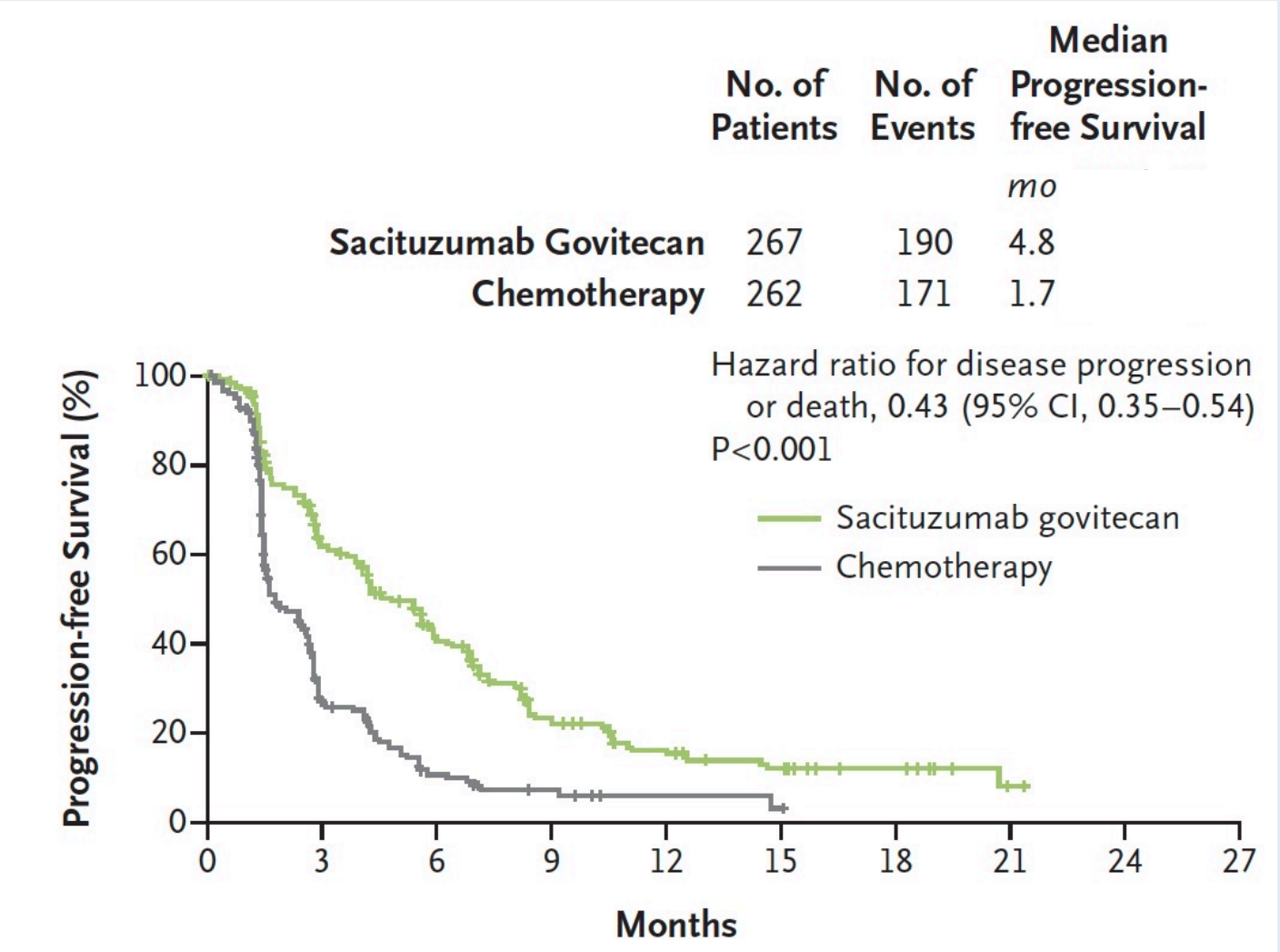
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, R. Weaver, T. Traina, F. Dalenc, P. Aftimos, F. Lynce, S. Diab, J. Cortés, J. O'Shaughnessy, V. Diéras, C. Ferrario, P. Schmid, L.A. Carey, L. Gianni, M.J. Piccart, S. Loibl, D.M. Goldenberg, Q. Hong, M.S. Olivo, L.M. Itri, and H.S. Rugo, for the ASCENT Clinical Trial Investigators*

ASCENT: Progression-Free Survival (Overall Population)



Bardia A et al. *N Engl J Med* 2021;384(16):1529-41.

RTP RESEARCH TO PRACTICE

Questions — Hope S Rugo, MD

Patients with metastatic TNBC

- **How do you determine which second-line treatment to use for patients with metastatic TNBC?**
- **What is an antibody-drug conjugate and specifically what is sacituzumab govitecan?**
- **In what situations do you use sacituzumab govitecan and what do you say to patients about potential benefits?**

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TO PRACTICE

Commentary — Hope S Rugo, MD

Patients with metastatic TNBC

- **How do you determine which second-line treatment to use for patients with metastatic TNBC?**
  - **This depends on response to first-line treatment to some degree, but I would choose the agent with the best impact on PFS and OS, balancing with toxicity**
- **What is an antibody-drug conjugate and specifically what is sacituzumab govitecan?**
  - **Antibodies to proteins highly expressed on tumor cells, linked to potent toxins**
  - **Sacituzumab govitecan is a Trop 2 antibody linked to the active metabolite of irinotecan, SN-38**
- **In what situations do you use sacituzumab govitecan and what do you say to patients about potential benefits?**
  - **As early as possible in patients with mTNBC. I discuss the Phase III ASCENT trial which showed improved PFS and OS compared to TPC, and I review the toxicity carefully.**

RTP RESEARCH TO PRACTICE

Commentary — Hope S Rugo, MD

- **33 yo presented with right breast swelling**
  - **Diagnosed with T3N1 TNBC**
  - **Rx: neoadjuvant chemotherapy with paclitaxel/carbo then DD AC with tumor growth in skin and SC node, surgery not possible. Treated then with gem/carbo/pembro (PD-L1 with SP142 4%) then pembro due to pancytopenia, followed by RT/capecitabine, then with PD in lung, node**
  - **Rx: sacituzumab with 6 month response**
- **55 yo presented with right breast mass, found to have N+ TNBC.**
  - **Treated with neoadjuvant AC/T with residual disease at surgery followed by RT, capecitabine, then pembrolizumab x 1 year on S1418**
  - **Presented with brain mets at end of pembro, with multiple lung nodules, treated with SRS to brain lesions**
  - **Treated with sacituzumab x 6 months**

RTP RESEARCH TO PRACTICE

Questions — Kelly Leonard, MSN, FNP-BC

Patients with metastatic TNBC

- **What do you say to patients who are about to receive sacituzumab govitecan?**
- **What are some of the psychosocial issues that arise in this situation?**

RTP
RESEARCH
TO PRACTICE

Commentary — Kelly Leonard, MSN, FNP-BC

Patients with metastatic TNBC

- **Potential side effects of Sacituzumab → fatigue, diarrhea, nausea, vomiting, alopecia, low blood counts (and associated complications, including febrile neutropenia), allergic reaction**
- **53 y/o female with triple negative metastatic breast cancer (to bones and lungs). One week after receiving cycle 1 day 8 sacituzumab, she developed fever of 101.3 and was found to be neutropenic with ANC of 300. She was admitted for febrile neutropenia (no source of infection identified) and was discharged home 3 days later once counts recovered. She then received Filgrastim on days 2, 3, 4 and Pegfilgrastim on day 8 of each subsequent cycle.**

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RESEARCH
TO PRACTICE

Commentary — Kelly Leonard, MSN, FNP-BC

- **This woman is single and lives alone. She does not have any children, but she has a very supportive brother who she is close with. She works for a real estate company, and she has needed to reduce her hours. Her employer has been supportive, and she has been able to work remotely some days.**

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TO PRACTICE

Appendix of Recent Data Sets

Common Side Effects and Dosing of CDK4/6 Inhibitors

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

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

RTP RESEARCH TO PRACTICE

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

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

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

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

RTP RESEARCH TO PRACTICE

SOLAR-1: Select Adverse Events in Overall Patient Population

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

André F et al. *N Engl J Med* 2019;380(20):1929-40.

Lancet Oncol 2021;22(4):489-98.

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

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

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

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib with endocrine therapy (ET: fulvestrant or letrozole) for HR-positive, HER2-negative advanced breast cancer (ABC) with a PIK3CA mutation

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

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

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

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

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

Treatment crossover between cohorts is not permitted

Primary endpoint

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

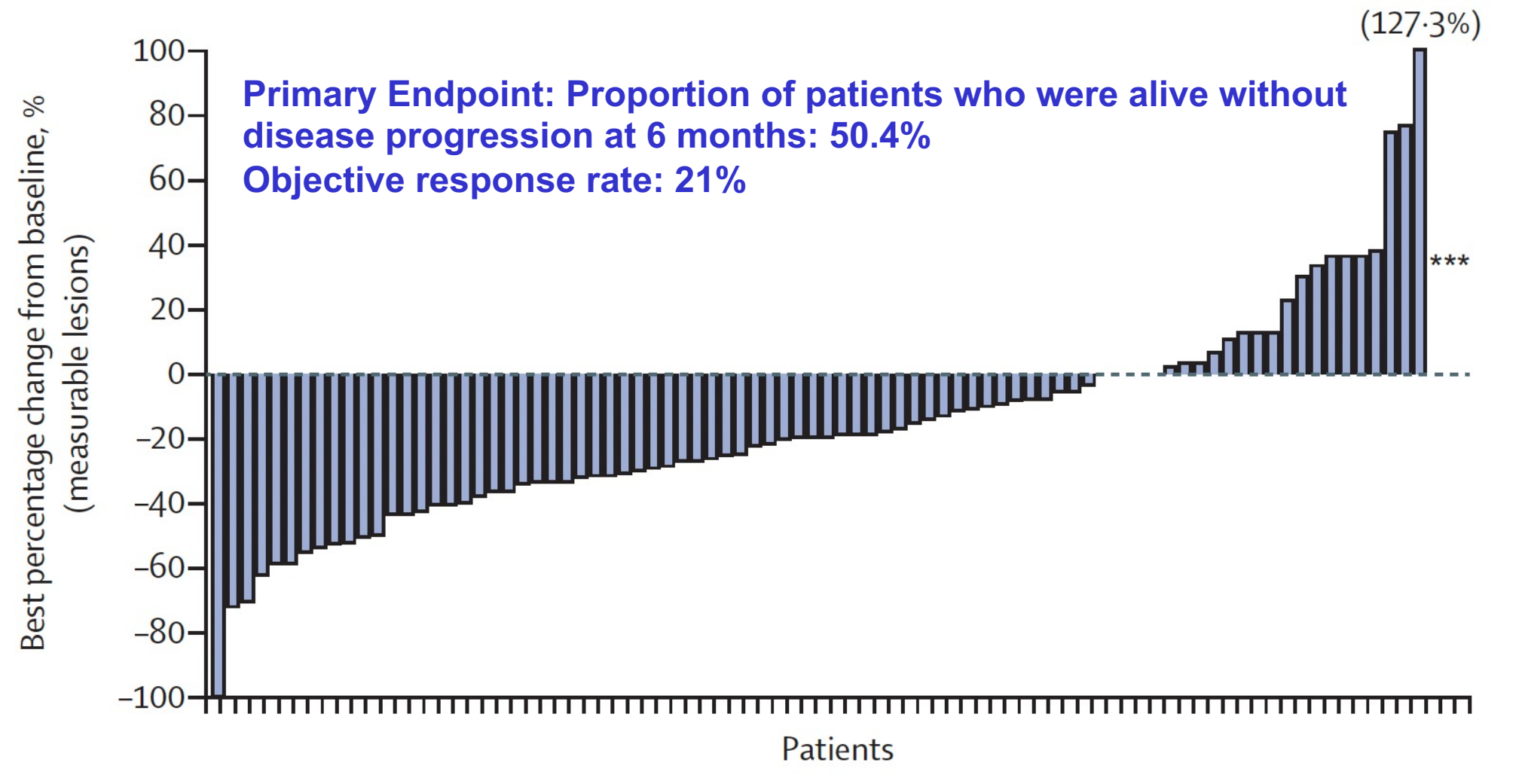
(assessed in each cohort)

- Progression-free survival (PFS)
- PFS2
- Objective response rate, clinical benefit rate, duration of response
- Overall survival
- Safety

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

Cohort A: Rugo HS et al. *Lancet Oncol* 2021;22(4): 489-98.

BYLieve Efficacy Outcomes



Rugo HS et al. *Lancet Oncol* 2021;22(4):489-98.

N Engl J Med 2022;386(12):1143-54.

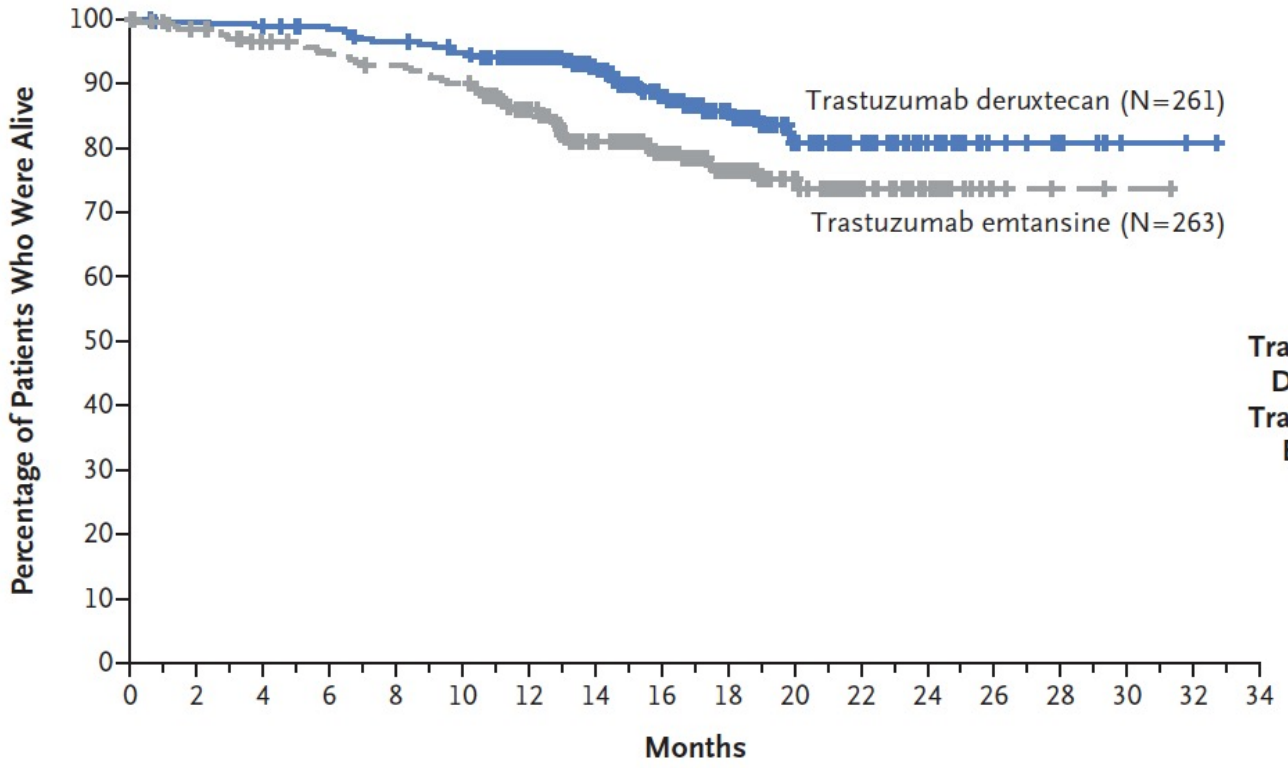
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

DESTINY-Breast03: First Interim Analysis of Overall Survival



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55 (95% CI, 0.36–0.86)
P=0.007

No. at Risk

Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

Cortes J et al. *N Engl J Med 2022;*386(12):1143-54.

N Engl J Med 2021;384(16):1529-41.

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ORIGINAL ARTICLE

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

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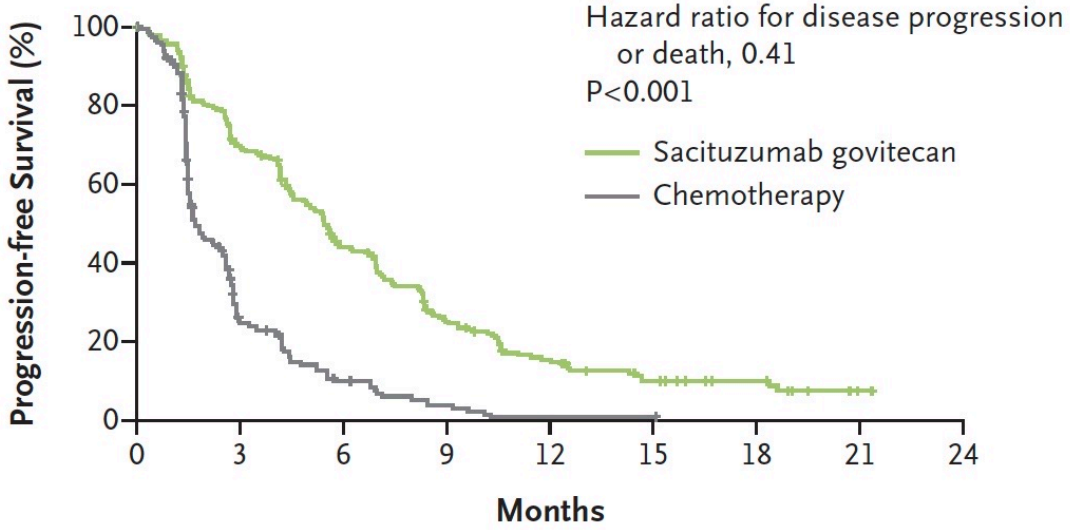
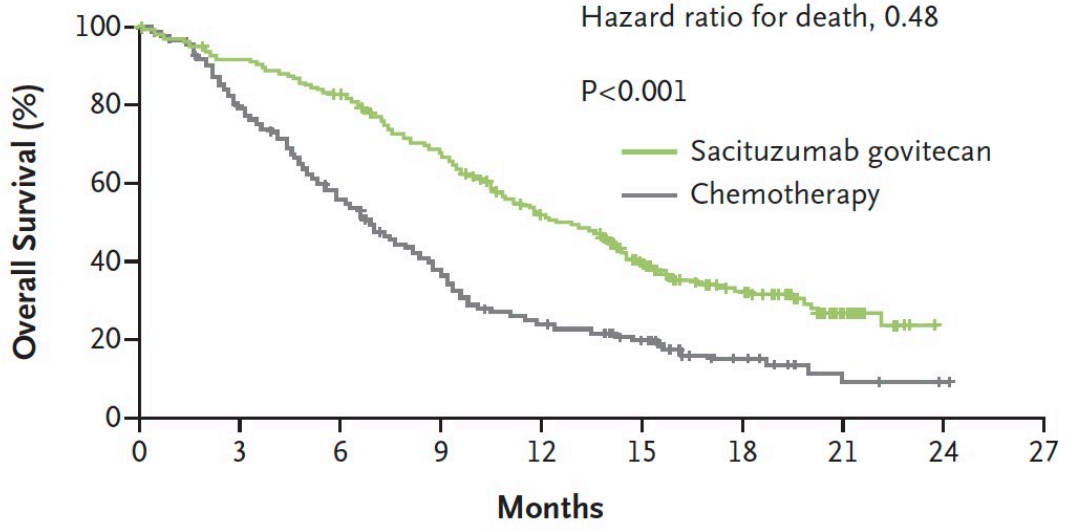
ASCENT: Progression-Free Survival and Overall Survival Among Patients without Brain Metastases

	No. of Patients	No. of Events	Median Progression-free Survival
			mo
Sacituzumab Govitecan	235	166	5.6
Chemotherapy	233	150	1.7



	No. of Patients	No. of Events	Median Overall Survival
			mo
Sacituzumab Govitecan	235	155	12.1
Chemotherapy	233	185	6.7



Bardia A et al. *N Engl J Med* 2021;384(16):1529-41.

RTP RESEARCH TO PRACTICE

ASCENT: Selected Adverse Events

Adverse event	Patients (N = 108)		
	Any grade	Grade 3	Grade 4
Gastrointestinal disorders			
Nausea	67%	6%	0
Diarrhea	62%	8%	0
Vomiting	49%	6%	0
Blood and lymphatic system disorders			
Neutropenia	64%	26%	16%
Anemia	50%	11%	0
Abnormal values			
Decrease white blood cell counts	21%	8%	3%

Bardia A et al. *N Engl J Med* 2021;384(16):1529-41.

Abstract VP1-2022

ESMO VIRTUAL PLENARY 2022

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]

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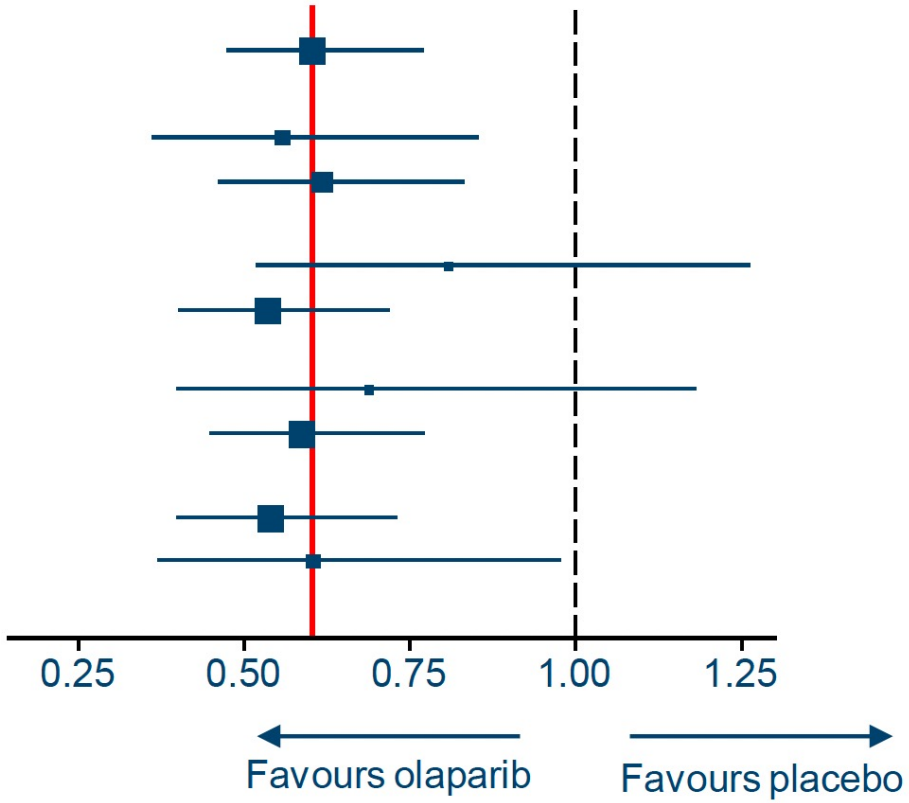
OlympiA: Subgroup Analysis of DDFS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for distant disease-free survival (95%CI)
	No. of patients with a distant disease event/total no.		
All patients	107 / 921	172 / 915	0.607 (0.476, 0.771)
Prior chemo			
Adjuvant	33 / 461	59 / 455	0.562 (0.363, 0.855)
Neoadjuvant	74 / 460	113 / 460	0.623 (0.463, 0.832)
Prior platinum			
Yes	36 / 247	43 / 238	0.812 (0.519, 1.263)
No	71 / 674	129 / 677	0.540 (0.403, 0.719)
HR status			
HR+/HER2-	23 / 168	31 / 157	0.692 (0.399, 1.182)
TNBC	84 / 751	141 / 758	0.591 (0.450, 0.772)
BRCA			
BRCA1	66 / 579	118 / 588	0.544 (0.400, 0.732)
BRCA2	28 / 235	41 / 216	0.609 (0.373, 0.979)
BRCA1/2 both	0 / 2	0 / 3	NC



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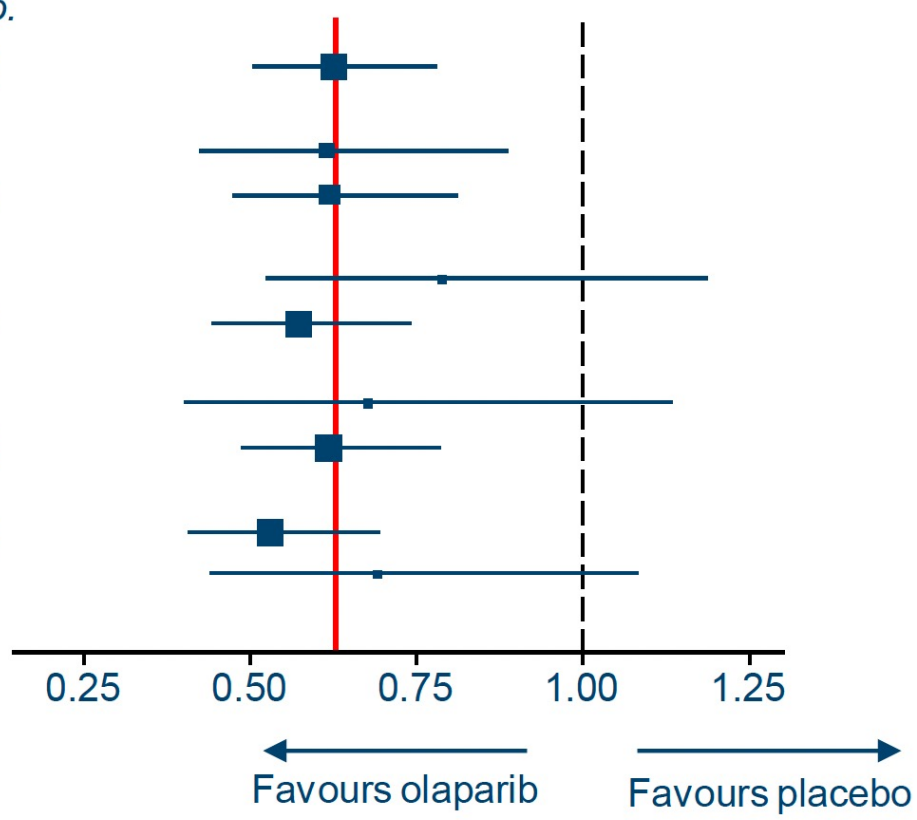
OlympiA: Subgroup Analysis of IDFS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for invasive disease-free survival (95% CI)
	No. of patients with an invasive disease event/total no.		
All patients	134 / 921	207 / 915	0.628 (0.504, 0.779)
Prior chemo			
Adjuvant	46 / 461	75 / 455	0.618 (0.425, 0.888)
Neoadjuvant	88 / 460	132 / 460	0.622 (0.473, 0.813)
Prior platinum			
Yes	42 / 247	51 / 238	0.791 (0.523, 1.187)
No	92 / 674	156 / 677	0.575 (0.443, 0.742)
HR status			
HR+/HER2-	25 / 168	34 / 157	0.680 (0.402, 1.134)
TNBC	109 / 751	173 / 758	0.620 (0.487, 0.787)
BRCA			
BRCA1	83 / 579	149 / 588	0.533 (0.406, 0.695)
BRCA2	34 / 235	44 / 216	0.693 (0.440, 1.082)
BRCA1/2 both	0 / 2	0 / 3	NC



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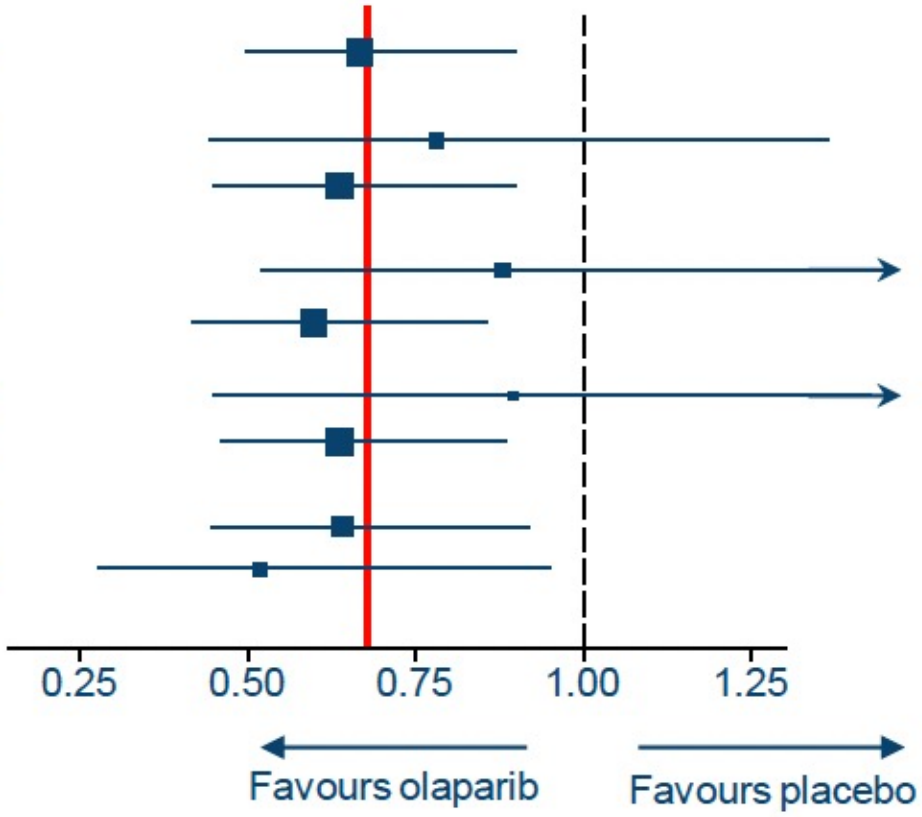
OlympiA: Subgroup Analysis of Overall Survival

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)
	No. of patients who died /total no.		
All patients	75 / 921	109 / 915	0.678 (0.503, 0.907)
Prior chemo			
Adjuvant	22 / 461	28 / 455	0.783 (0.444, 1.365)
Neoadjuvant	53 / 460	81 / 460	0.638 (0.449, 0.900)
Prior platinum			
Yes	27 / 247	29 / 238	0.882 (0.520, 1.491)
No	48 / 674	80 / 677	0.601 (0.417, 0.855)
HR status			
HR+/HER2-	16 / 168	17 / 157	0.897 (0.449, 1.784)
TNBC	59 / 751	92 / 758	0.640 (0.459, 0.884)
BRCA			
BRCA1	49 / 579	75 / 588	0.643 (0.446, 0.918)
BRCA2	16 / 235	28 / 216	0.521 (0.276, 0.951)
BRCA1/2 both	0 / 2	0 / 3	NC



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What I Tell My Patients:
New Treatments and Clinical Trial Options

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