Video Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Breast Cancer

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Monday, June 5, 2023

7:00 PM – 9:30 PM CT

Faculty

Komal Jhaveri, MD
Kevin Kalinsky, MD, MS
Ian E Krop, MD, PhD
Joyce O'Shaughnessy, MD
Hope S Rugo, MD
Prof Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

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Faculty

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Winship Cancer Institute of Emory University
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Director, Clinical Trials Office
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New Haven, Connecticut

Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Director, Breast Cancer Research Program
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US Oncology
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Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Professor Peter Schmid, FRCP, MD, PhD
Lead, Centre of Experimental Cancer Medicine
Barts Cancer Institute
London, United Kingdom

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

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Contributing Investigators

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Director, Breast Cancer Clinical Trials Program
Division of Hematology-Oncology
David Geffen School of Medicine at UCLA
Los Angeles, California

Tiffany A Traina, MD, FASCO
Vice Chair, Department of Medicine
Section Head, Triple-Negative Breast Cancer Clinical Research Program
Associate Attending Physician
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Sara M Tolaney, MD, MPH
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Associate Director, Susan F Smith Center for Women's Cancers
Senior Physician
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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The consulting investigator interviews will be developed into a special program.

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

An email will be sent to all attendees when the activity is available.

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Dr Hurvitz — Disclosures

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

Dr Krop — Disclosures

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Dr O'Shaughnessy — Disclosures

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Travel Support to Academic Meetings	AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Merck

Prof Schmid — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Eisai Inc, Merck, Novartis, Pfizer Inc, Puma Biotechnology Inc, Roche Laboratories Inc
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Medivation Inc, a Pfizer Company, Novartis, OncoGenex Pharmaceuticals Inc, Roche Laboratories Inc

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Dr Tolaney — Disclosures

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Dr Traina — Disclosures

Consulting or Advisory Role	AstraZeneca Pharmaceuticals LP, Biotheranostics Inc, Daiichi Sankyo Inc, Exact Sciences Corporation, G1 Therapeutics Inc, GE Healthcare, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Hengrui Therapeutics Inc, Merck, Novartis, Pfizer Inc, Stemline Therapeutics Inc, TerSera Therapeutics LLC
Research Funding (to Institution)	Astellas, AstraZeneca Pharmaceuticals LP, Ayala Pharmaceuticals, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Pfizer Inc

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

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.

Friday June 2	**Gastroesophageal Cancers** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Non-Small Cell Lung Cancer 6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)
Saturday June 3	**Hepatobiliary Cancers** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 4	**Ovarian Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Lymphoma, Chronic Lymphocytic Leukemia and Multiple Myeloma 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Monday June 5	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Breast Cancer 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Tuesday June 6	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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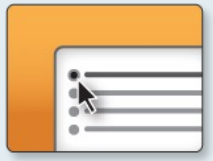
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the pre- and postmeeting surveys.

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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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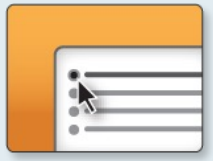
Clinicians Attending via Zoom

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



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

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

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PREMEETING SURVEY – Available Now

Clinicians in Attendance: If you have not already done so, please take a moment to complete the premeeting survey on the iPads for attendees in the room and on Zoom for those attending virtually. Your input on this survey will be integral to the program today.

A postmeeting survey will be posted toward the end of the session.

Thank you for your input.

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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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Video Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Breast Cancer

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Hope S Rugo, MD
Prof Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

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Agenda

Module 1: Long-Term Management of HER2-Positive Breast Cancer — Dr Krop

Module 2: Optimizing the Management of ER-Positive Localized Breast Cancer — Dr Kalinsky

Module 3: Considerations in the Care of Patients with ER-Positive mBC — Dr Jhaveri

Module 4: Novel and Emerging Strategies for ER-Positive mBC — Dr Rugo

Module 5: Evolving Clinical Decision-Making for Localized Triple-Negative Breast Cancer (TNBC) — Dr O'Shaughnessy

Module 6: Recent Advances in the Treatment of Metastatic TNBC (mTNBC) — Prof Schmid

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Agenda

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Management of CNS-only disease progression in patients with HER2-positive metastatic breast cancer

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

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A patient with ER-negative, HER2-positive mBC receives first-line THP followed by second-line trastuzumab deruxtecan, to which she experiences a partial response. She then presents with a single brain metastasis, which is removed, but no evidence of systemic disease progression. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 Dr Jhaveri	Continue trastuzumab deruxtecan
 Dr Kalinsky	Continue trastuzumab deruxtecan
 Dr Krop	Continue trastuzumab deruxtecan
 Dr O'Shaughnessy	Continue trastuzumab deruxtecan
 Dr Rugo	Continue trastuzumab deruxtecan
 Prof Schmid	Continue trastuzumab deruxtecan
 Dr Hurvitz	Continue trastuzumab deruxtecan
 Dr Tolaney	Continue trastuzumab deruxtecan
 Dr Traina	Continue trastuzumab deruxtecan

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Synergy between tucatinib and HER2-targeted antibody-drug conjugates

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

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Do you believe tucatinib has synergy with HER2-targeted antibody-drug conjugates through the upregulation of HER2?

 Dr Jhaveri	No	 Prof Schmid	I'm not sure
 Dr Kalinsky	Yes	 Dr Hurvitz	Yes, possibly
 Dr Krop	I'm not sure	 Dr Tolaney	Yes, at least preclinically
 Dr O'Shaughnessy	Yes	 Dr Traina	I'm not sure
 Dr Rugo	Yes		

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Management of trastuzumab deruxtecan-related adverse events

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

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Have you readministered or would you readminister trastuzumab deruxtecan to a patient who developed Grade 2 ILD?

 Dr Jhaveri	No	 Prof Schmid	Yes, if mild symptoms w/ limited degree of ILD
 Dr Kalinsky	No	 Dr Hurvitz	No
 Dr Krop	No	 Dr Tolaney	No
 Dr O'Shaughnessy	No	 Dr Traina	No
 Dr Rugo	No		

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What do you generally advise your patients who are about to begin treatment with trastuzumab deruxtecan regarding the potential for chemotherapy-like side effects (gastrointestinal toxicity, alopecia)?

 Dr Jhaveri	They are very likely to occur
 Dr Kalinsky	Likely to occur but with less severity than w/ traditional chemo
 Dr Krop	They are very likely to occur
 Dr O'Shaughnessy	Likely to occur but with less severity than w/ traditional chemo
 Dr Rugo	They are very likely to occur
 Prof Schmid	They are very likely to occur
 Dr Hurvitz	They are very likely to occur
 Dr Tolaney	They are very likely to occur
 Dr Traina	Likely to occur but with less severity than w/ traditional chemo

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Patient selection for and practical implementation of postadjuvant neratinib

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

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In what situations do you generally administer postadjuvant neratinib to patients with HER2-positive localized BC?

 Dr Jhaveri	Very high-risk ER+	 Prof Schmid	Practically never
 Dr Kalinsky	High-risk HR+, significant residual disease after neoadj. tx	 Dr Hurvitz	HR-positive, node-positive (high risk)
 Dr Krop	ER+ with multiple positive nodes	 Dr Tolaney	High-risk ER+ (residual node+ disease) after HER2-directed neoadj. tx with HP, then adj. T-DM1
 Dr O'Shaughnessy	HR+, node+ with residual disease s/p neoadj. TCHP	 Dr Traina	ER+, no pCR after neoadjuv. tx, high-risk LN+
 Dr Rugo	Very high-risk HR+, not eligible for CompassHER2 RD		

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When employing neratinib in the postadjuvant setting for localized HER2-positive BC, what initial dose do you typically use?

 Dr Jhaveri	120 mg
 Dr Kalinsky	120 mg
 Dr Krop	120 mg
 Dr O'Shaughnessy	160 mg
 Dr Rugo	120 mg
 Prof Schmid	N/A
 Dr Hurvitz	120 mg
 Dr Tolaney	120 mg
 Dr Traina	120 mg

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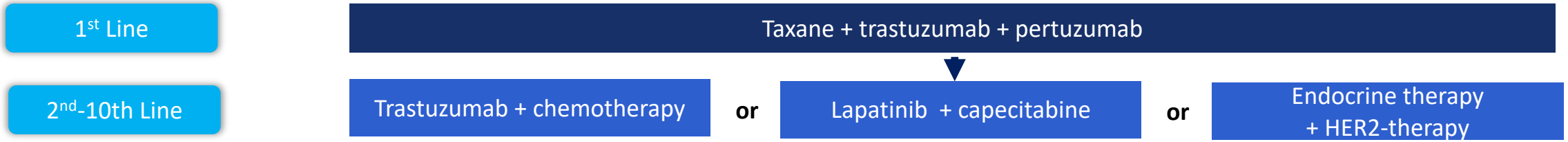
Long-Term Management of HER2-Positive Breast Cancer

Ian Krop MD PhD

June 2023

Treatment Paradigm for Metastatic HER2+ Breast Cancer (Circa 2013)



Efficacy of Chemotherapy + Trastuzumab or lapatinib is limited in ≥2rd line

Updated OS Analysis of DESTINY-Breast03

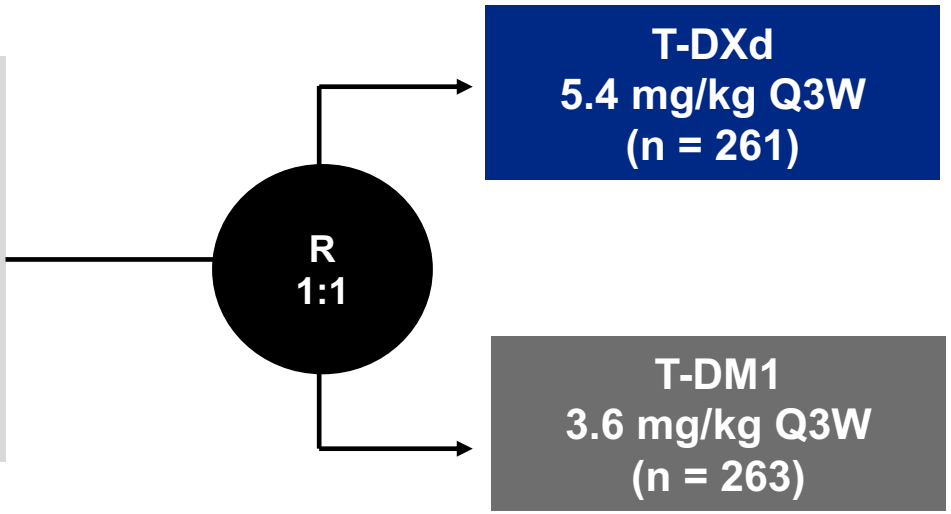
Randomized, open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy[b]

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS[c]

Secondary endpoints

- ORR (BICR and investigator)
- DoR (BICR)
- Safety

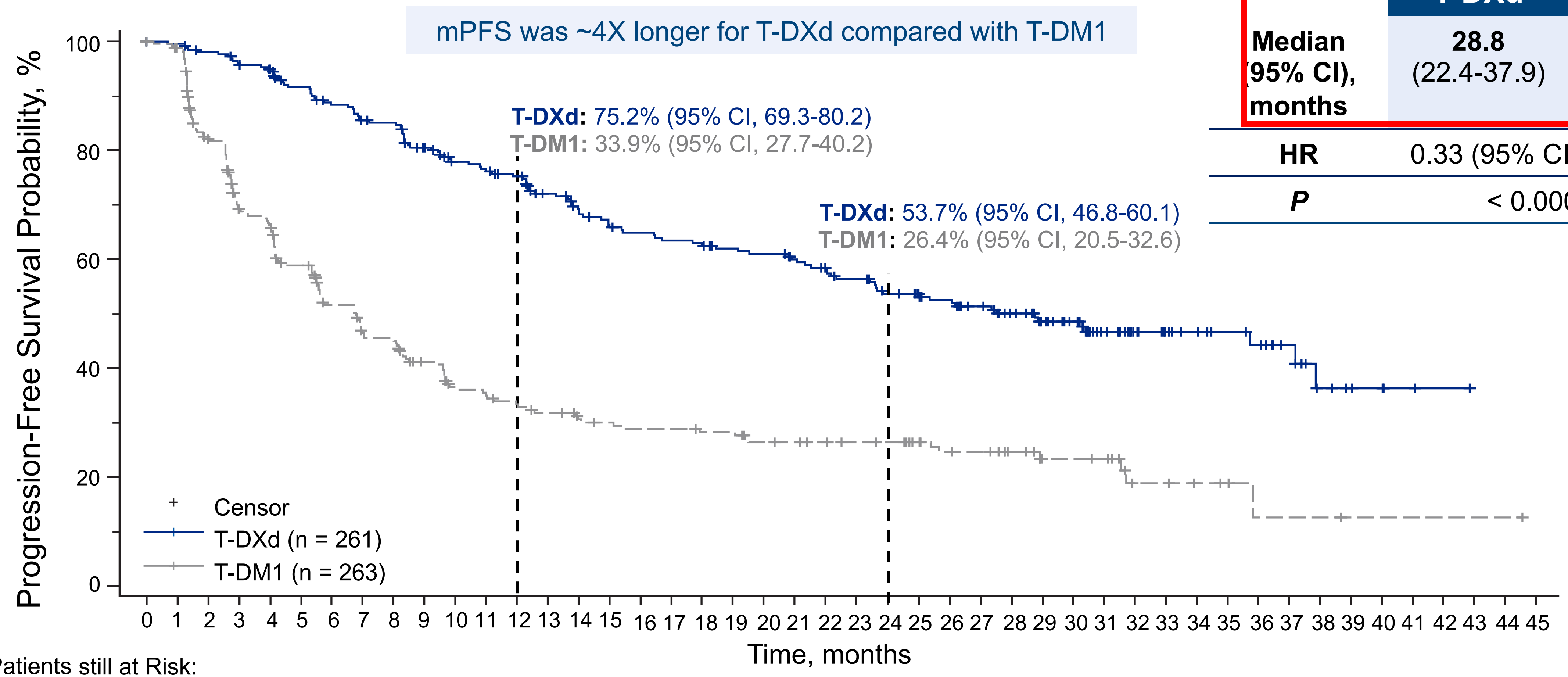
The prespecified OS interim analysis was planned with 153 events.[d] At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

BICR, blinded independent central review; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b]Progression during or within 6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]80% powered at 2-sided significance level of 5%. [d]Information fraction of 61%, with a *P* value boundary to reach statistical significance of 0.008. The *P* value was recalculated based on the actual OS events at the data cutoff.

Updated Primary Endpoint: PFS by BICR

	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	



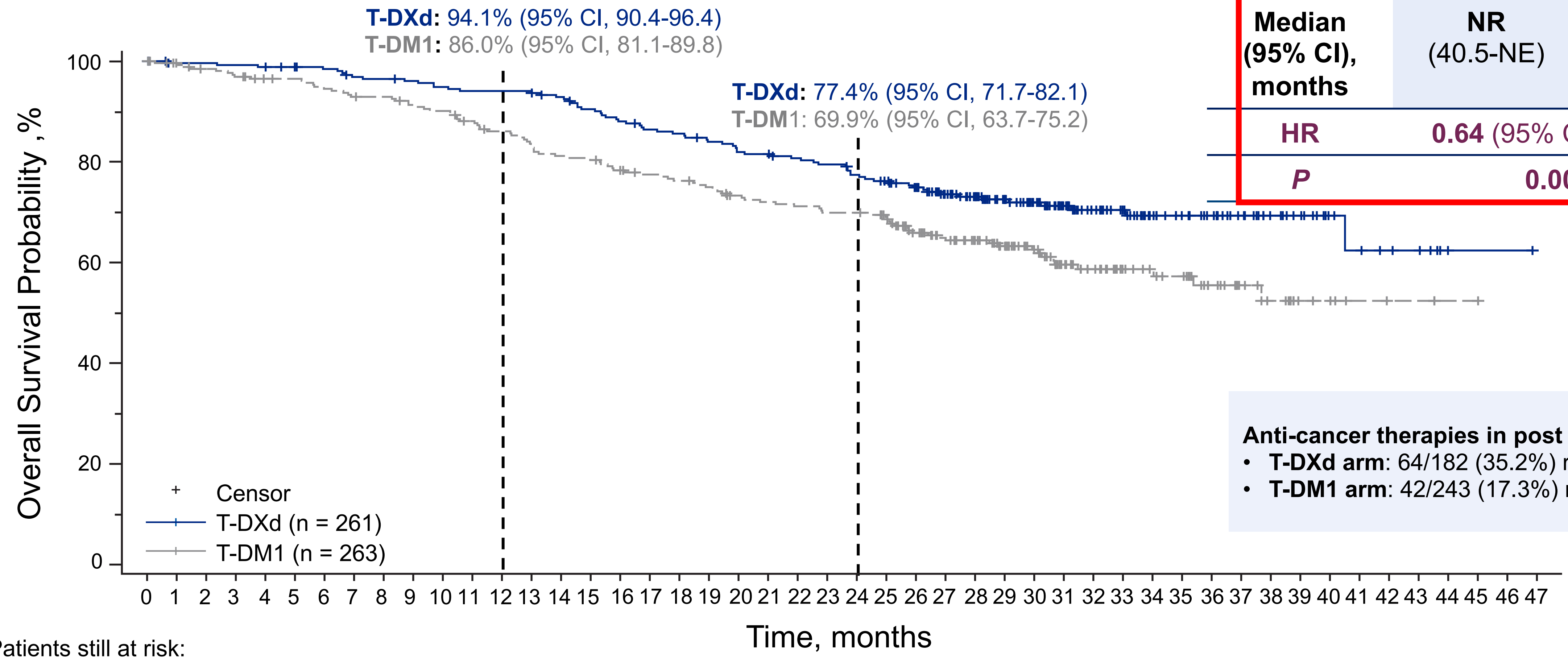
Patients still at Risk:

T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

Hurvitz Sa et al. SABCS 2022;Abstract GS2-02. Hurvitz SA et al. *Lancet* 2023;401:105-17.

Key Secondary Endpoint: Overall Survival

	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	



Patients still at risk:

T-DXd	261	256	256	255	254	251	249	244	243	241	238	236	236	236	231	224	218	213	211	206	201	200	196	193	187	182	173	156	142	124	109	91	73	64	51	44	38	30	22	18	11	9	7	6	1	1	1	0
T-DM1	263	257	252	248	243	242	237	233	232	227	224	217	211	203	199	197	191	186	183	179	172	169	167	164	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

Anti-cancer therapies in post trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Hurvitz Sa et al. SABCS 2022;Abstract GS2-02. Hurvitz SA et al. *Lancet* 2023;401:105-17.

Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd[1,2]
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis[3]
- There were no adjudicated drug-related grade 4 or 5 events

ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
1. Modi S et al. *N Engl J Med* 2020; 382(7): 610-21. 2. Powell CA et al. *ESMO Open* 2022; 7(4): 100554. 3. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]

- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

Protocol-prespecified statistical analysis plan

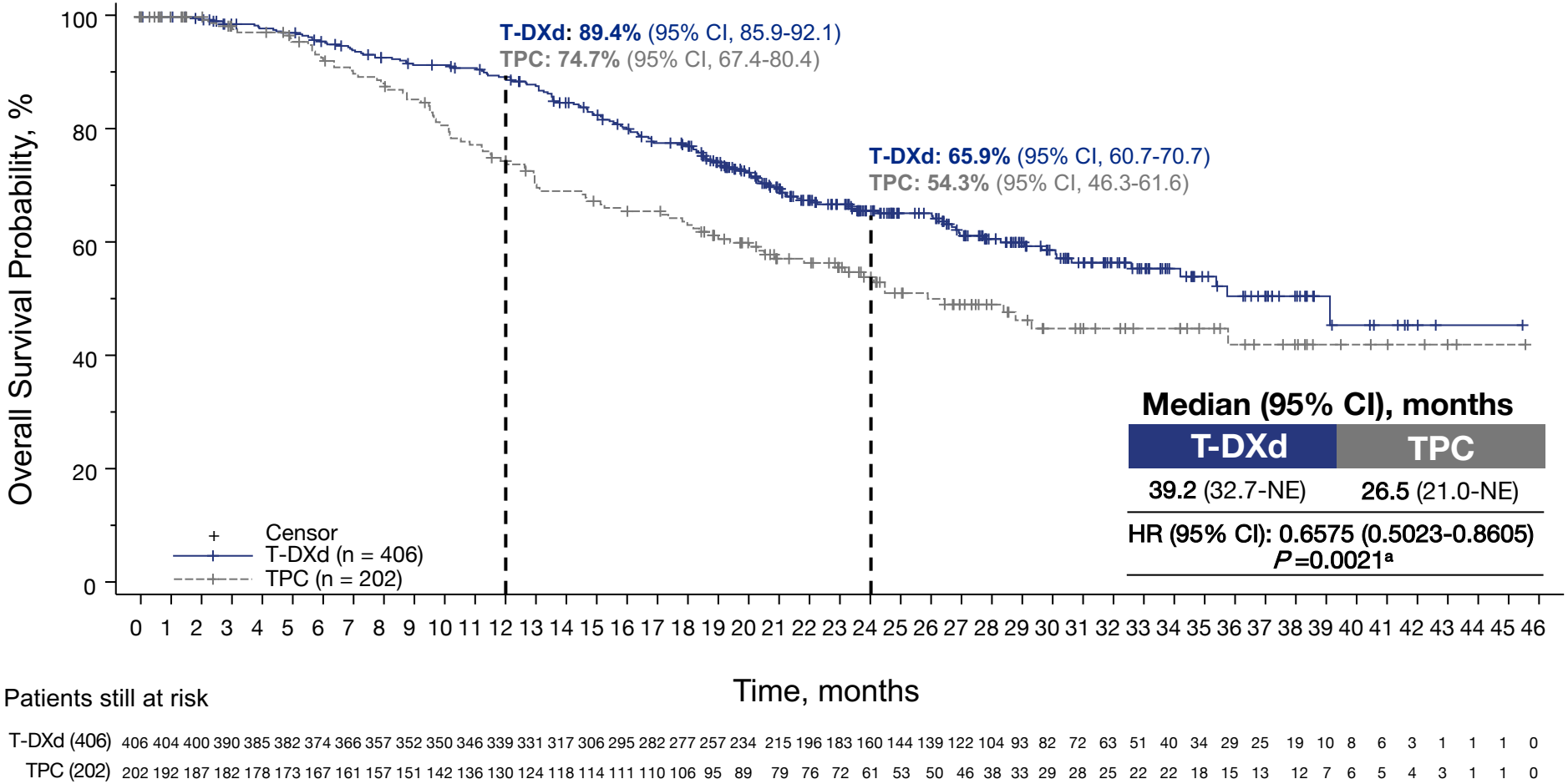
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

Krop I et al. SABCS 2022;Abstract GS2-01.

Key Secondary Endpoint: OS



In the TPC arm

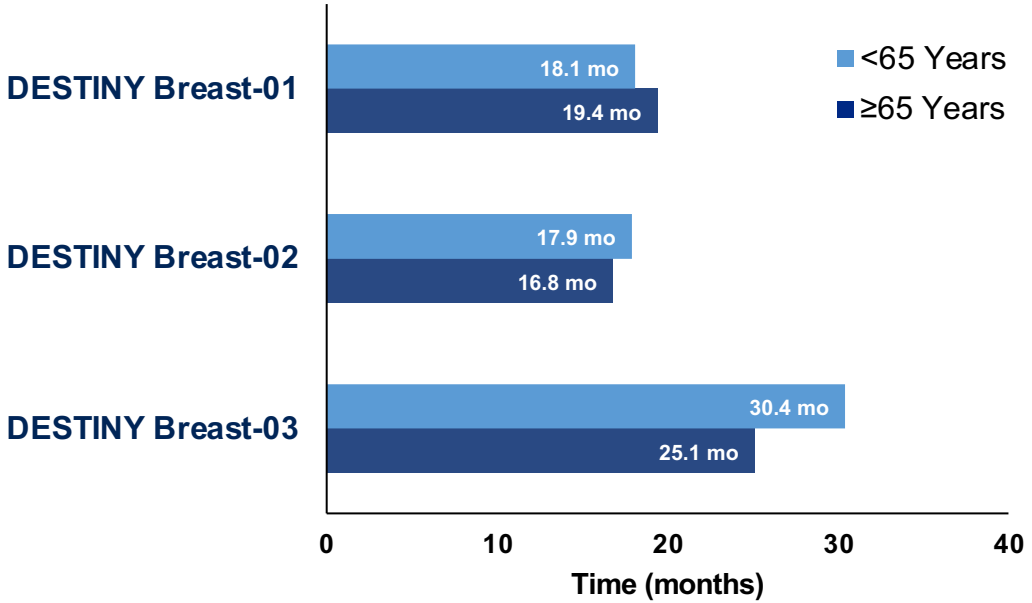
- **69.3% (140/202) of patients who discontinued therapy received a new systemic anticancer**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

[a]The boundary for statistical significance is 0.0040. HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Krop I et al. SABCS 2022;Abstract GS2-01. Andre F et al. *Lancet* 2023;401:1773-85.

Age Specific Efficacy of T-DXd

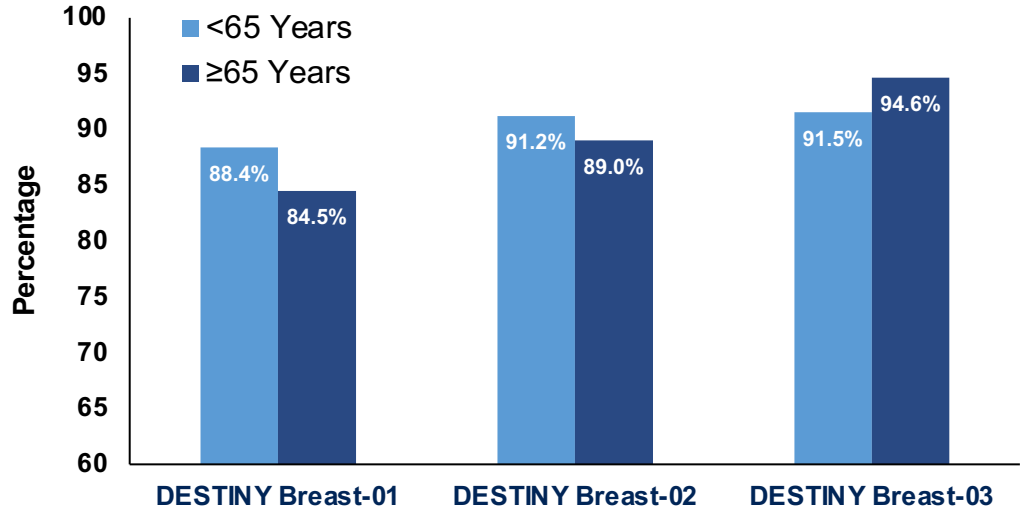
Median Progression Free Survival



Median Overall Survival

	DESTINY-Breast01		DESTINY-Breast02		DESTINY-Breast03	
	<65 (n = 140)	≥65 (n = 44)	<65 (n = 321)	≥65 (n = 85)	<65 (n = 212)	≥65 (n = 49)
mOS, months (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)

12-month Landmark Overall Survival



- Efficacy in patients aged <65 and ≥65 years treated with T-DXd was generally similar; however no formal comparison was made

Adapted from Krop et al, ASCO 2023

Age-specific safety and ILD rates for T-DXd

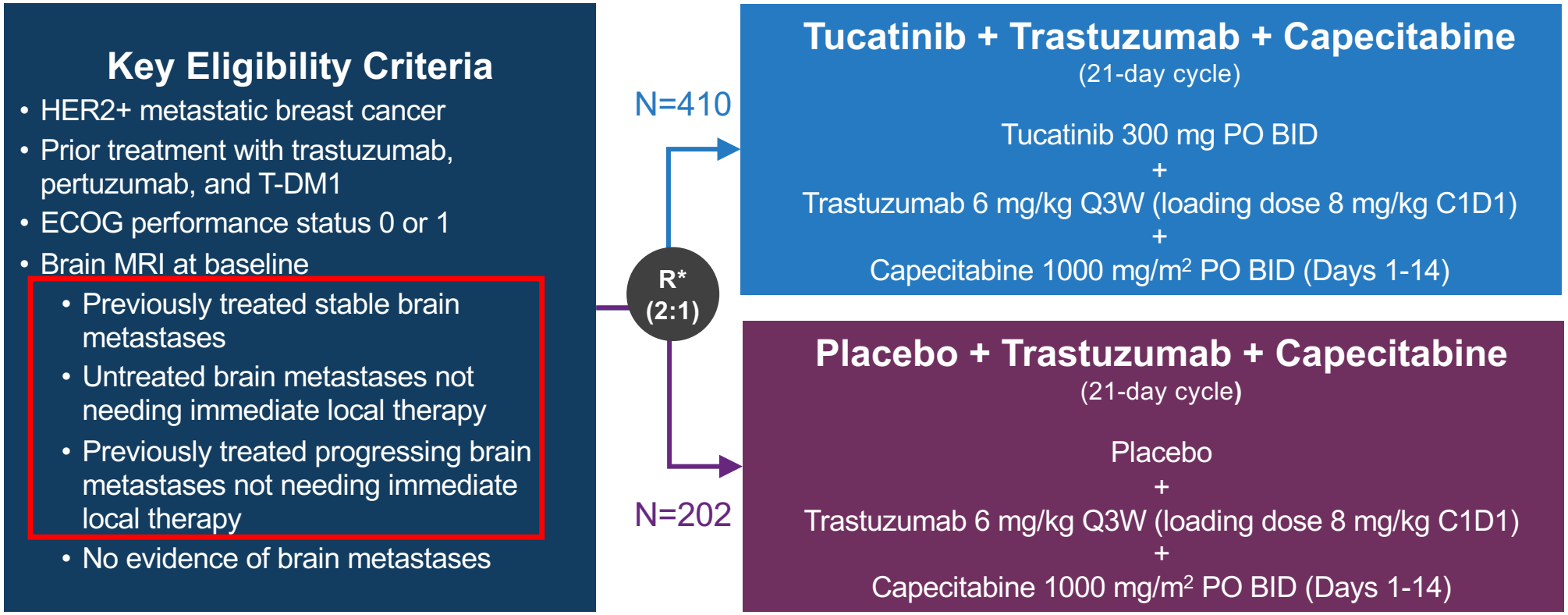
	T-DXd Pool		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)
Median treatment duration, mo (range)	**13.1 (0.7-44.0)**	**12.4 (0.7-45.1)**	**9.0 (0.7-35.6)**
TEAE, n (%)	**665 (99.6)**	**177 (100.0)**	**33 (100.0)**
Drug-related	653 (97.8)	176 (99.4)	33 (100.0)
TEAEs grade ≥3, n (%)	**358 (53.6)**	**116 (65.5)**	**17 (51.5)**
Drug-related	291 (43.6)	96 (54.2)	13 (39.4)
Serious TEAEs, n (%)	**162 (24.3)**	**57 (32.2)**	**10 (30.3)**
Drug-related	77 (11.5)	29 (16.4)	5 (15.2)
TEAEs associated with drug discontinuation, n (%)	**125 (18.7)**	**45 (25.4)**	**8 (24.2)**
Drug-related	100 (15.0)	42 (23.7)	8 (24.2)
TEAEs associated with dose reduction, n (%)	**163 (24.4)**	**51 (28.8)**	**10 (30.3)**
Drug-related	156 (23.4)	47 (26.6)	8 (24.2)
TEAEs associated with dose interruption, n (%)	**302 (45.2)**	**94 (53.1)**	**15 (45.5)**
Drug-related	226 (33.8)	74 (41.8)	11 (33.3)
TEAEs associated with death, n (%)	**17 (2.5)**	**10 (5.6)**	**0**
Drug-related	4 (0.6)	3 (1.7)	0

Rates of ILD

	T-DXd Pool		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)
Any grade, n (%)	**79 (11.8)**	**31 (17.5)**	**5 (15.2)**
1	21 (3.1)	7 (4.0)	0
2	48 (7.2)	20 (11.3)	5 (15.2)
3	4 (0.6)	3 (1.7)	0
4	0	0	0
5	6 (0.9)	1 (0.6)	0
≥3	10 (1.5)	4 (2.3)	0

Adapted from Krop et al, ASCO 2023

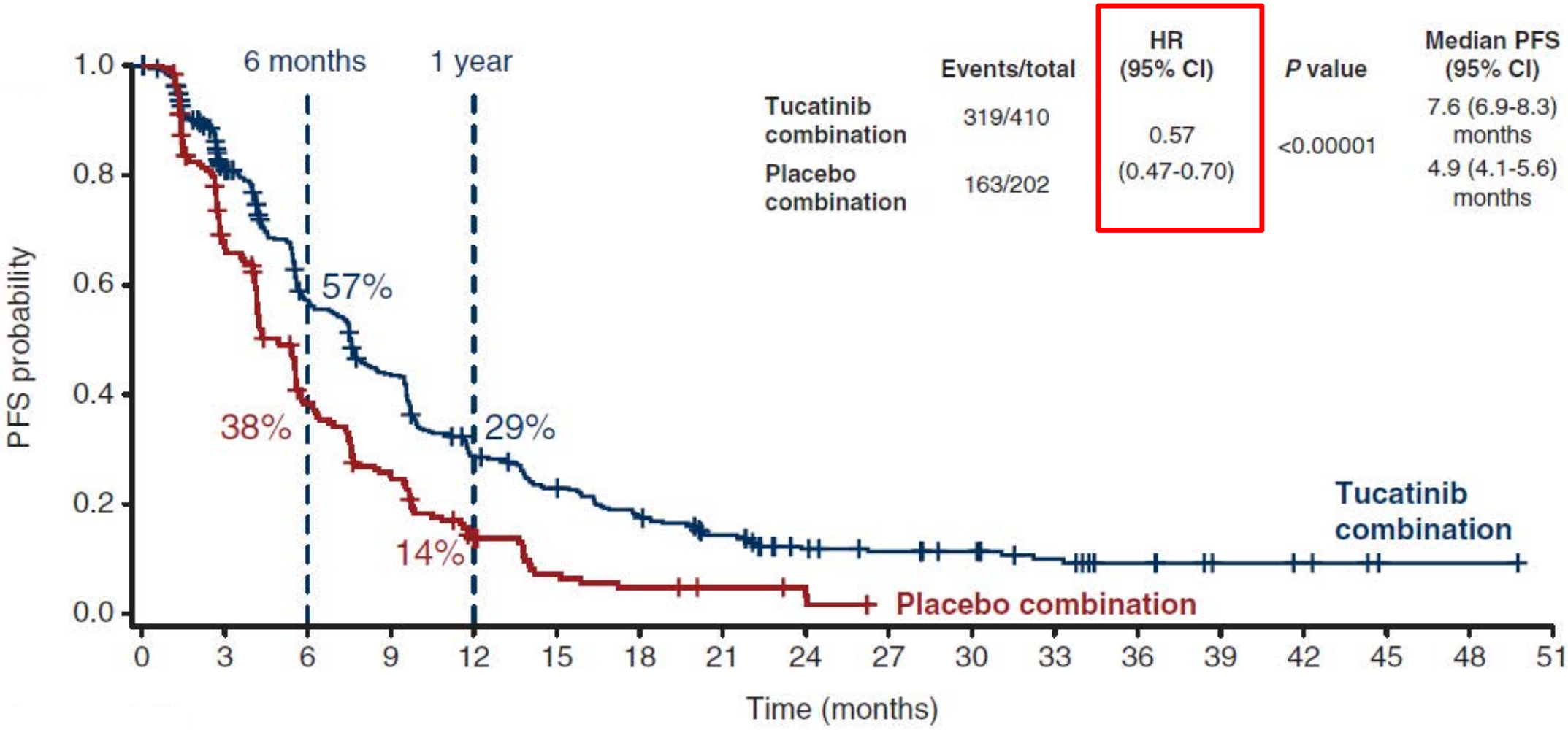
HER2CLIMB Trial Design



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

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

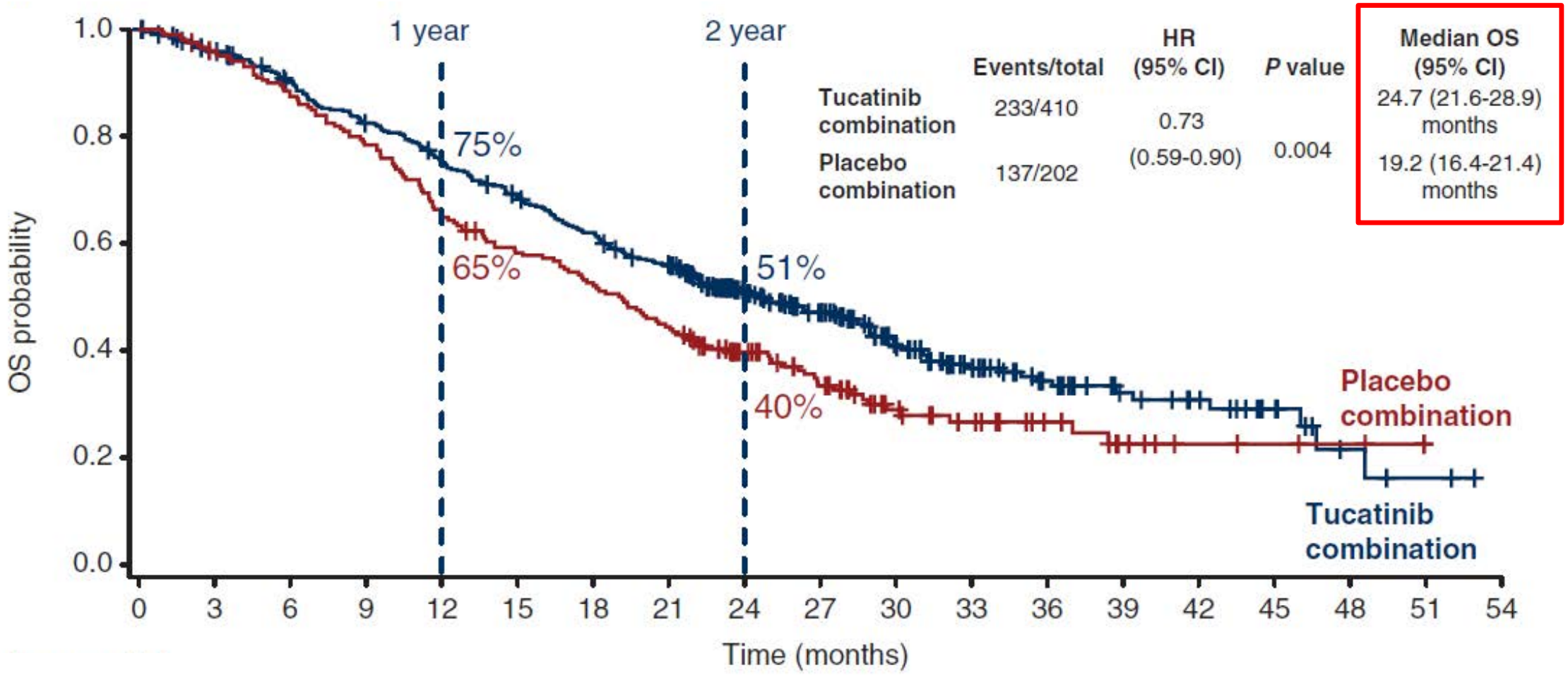
HER2CLIMB Updated PFS results



	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 et al, Annals Oncology 2022 33:321

HER2CLIMB Updated OS results



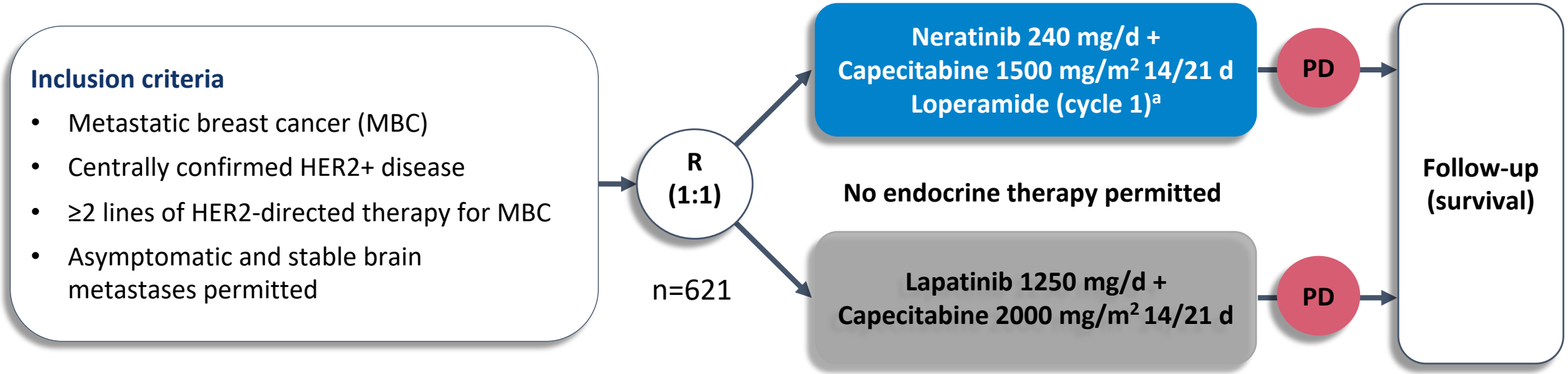
Curigliano et al, Annals Oncology 2022 33:321

HER2CLIMB: Adverse Events

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

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

NALA study design



Stratification variables

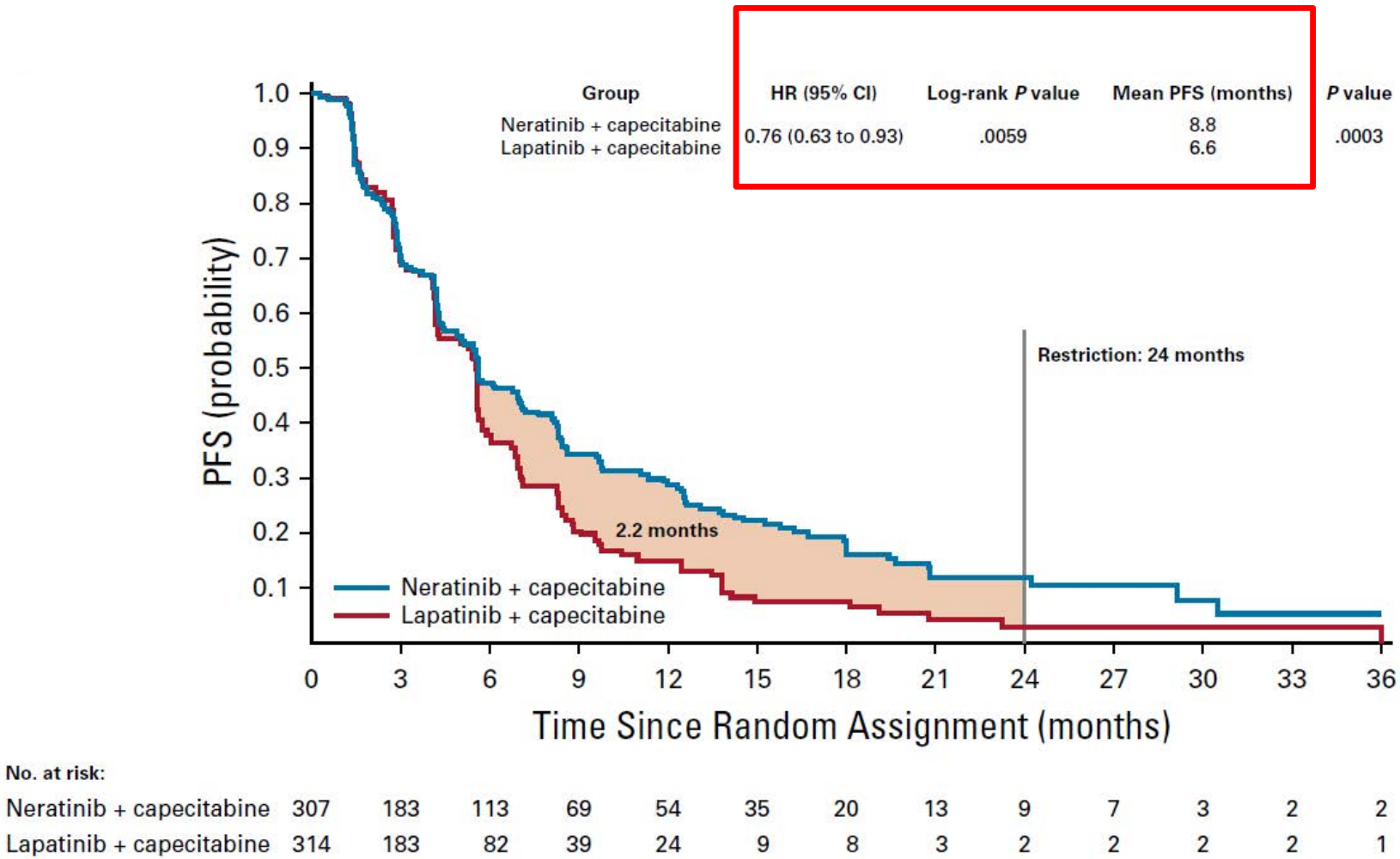
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

NALA Centrally Confirmed PFS

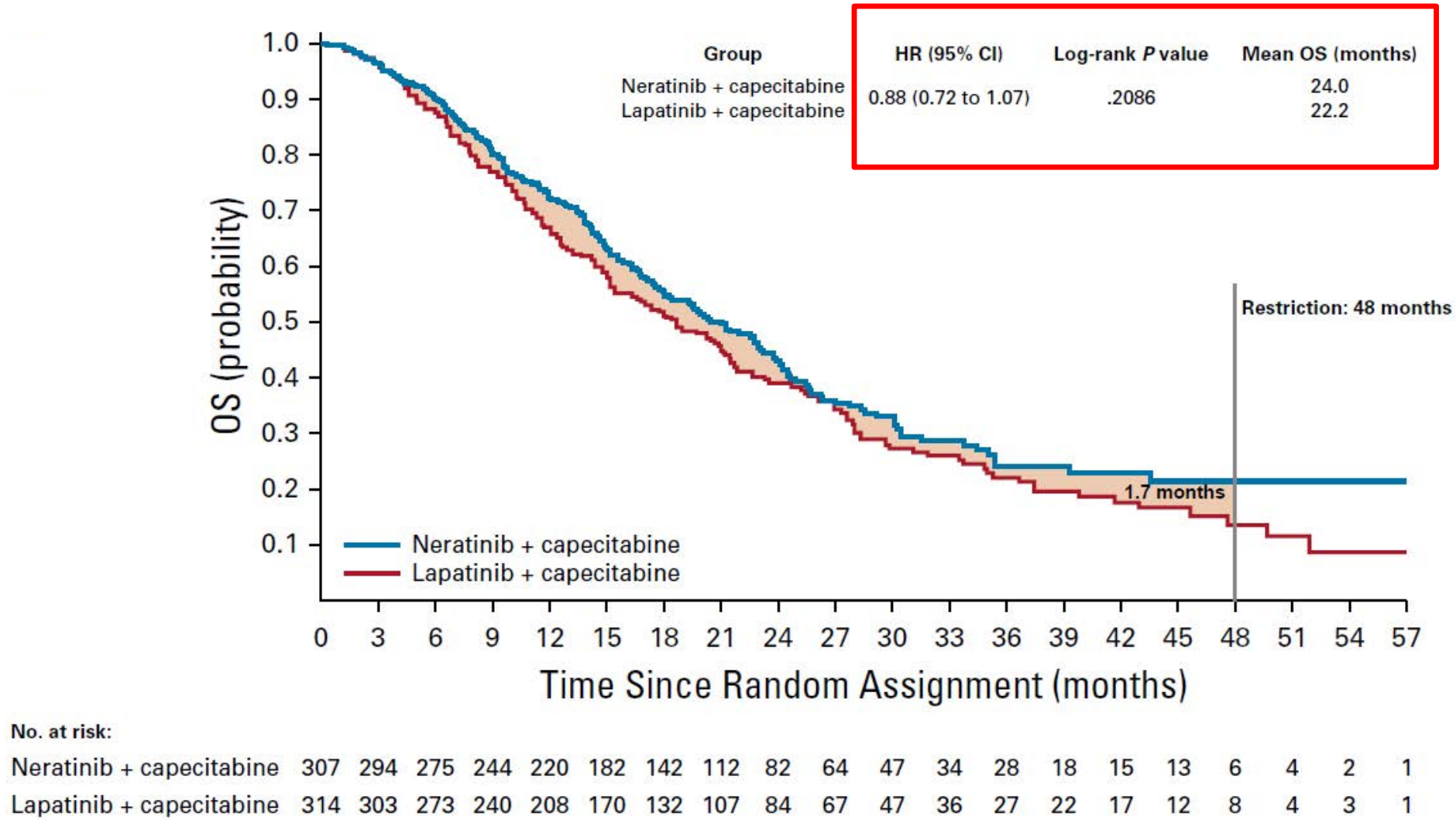


No. at risk:

Neratinib + capecitabine	307	183	113	69	54	35	20	13	9	7	3	2	2
Lapatinib + capecitabine	314	183	82	39	24	9	8	3	2	2	2	2	1

Saura et al, JCO 2020 38:3138

NALA Overall Survival Analysis



No. at risk:

Neratinib + capecitabine	307	294	275	244	220	182	142	112	82	64	47	34	28	18	15	13	6	4	2	1
Lapatinib + capecitabine	314	303	273	240	208	170	132	107	84	67	47	36	27	22	17	12	8	4	3	1

Saura et al, JCO 2020 38:3138

Most frequent grade 3/4 adverse events

	Neratinib + Capecitabine (n=303)		Lapatinib + Capecitabine (n=311)	
	All grade	Grade 3/4	All grade	Grade 3/4
Treatment-emergent AE, %	100	61	99	60
Diarrhea	83	24*	66	13*
Hand-foot syndrome	46	10	56	11
Hypokalemia	12	5	14	6
Nausea	53	4	42	3
Vomiting	46	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	35	3	22	2
Dehydration	6	2	6	2

Treatment discontinuation due to treatment-emergent AEs: N+C: 10.9%; L+C: 14.5%

*No Grade 4 diarrhea

CONTROL study: dose escalation of neratinib minimizes Grade 3 diarrhea

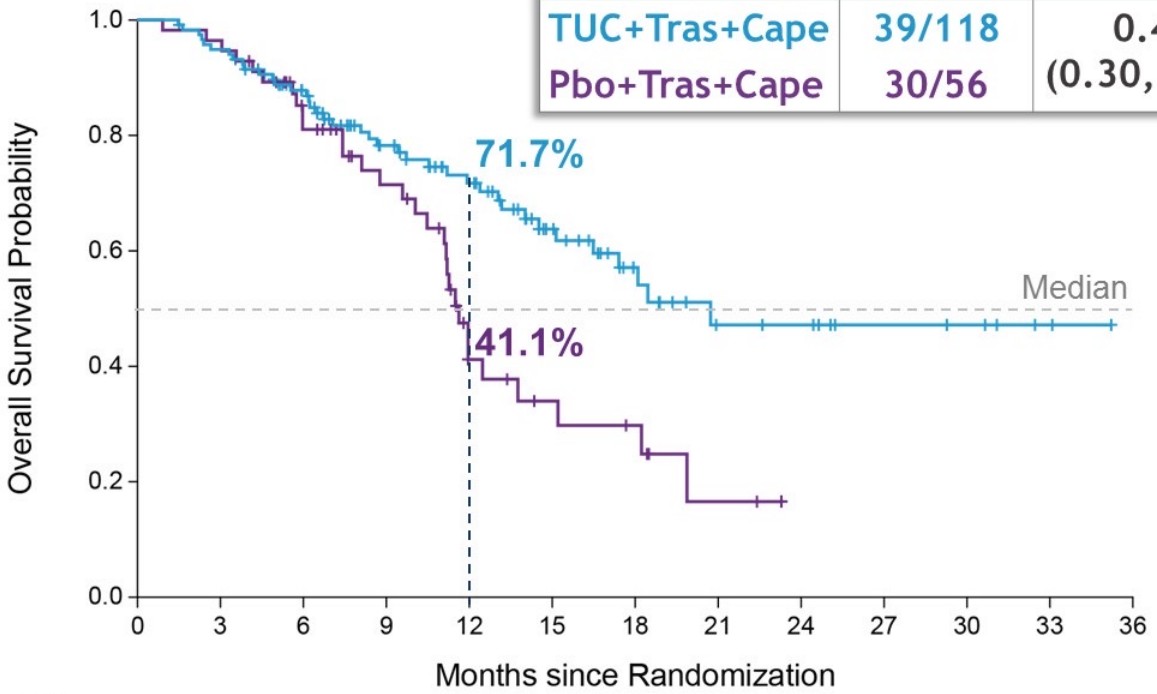
Outcome	L (n=137)	BL (n=64)	CL (n=136)	CL-PRN (n=104)	DE1 (n=60)	DE2 (n=62)
Any grade diarrhea, n (%)	109 (80)	55 (86)	113 (83)	99 (95)	59 (98)	61 (98)
Grade 1	33 (24)	15 (23)	38 (28)	34 (33)	24 (40)	23 (37)
Grade 2	34 (25)	22 (34)	47 (35)	31 (30)	27 (45)	21 (34)
Grade 3	42 (31)	18 (28)	28 (21)	34 (33)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

DE1:
120 mg x 7d
↓
160 mg x 7d
↓
240 mg qd

Chan A, et al. 2022 ESMO Breast: Abstract 73P

HER2CLIMB
OS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	39/118	0.49 (0.30, 0.80)	0.004
Pbo+Tras+Cape	30/56		



No. at Risk

TUC+Tras+Cape	118	111	89	66	51	33	19	11	10	6	5	2	0
Pbo+Tras+Cape	56	54	39	29	12	8	6	2	0	0	0	0	0

Risk of death was reduced by 51% in patients with active brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
71.7% (61.4, 79.7)	41.1% (25.5, 56.1)
Median OS (95% CI):	
20.7 months (15.1, NE)	11.6 months (10.5, 13.8)

NE: not estimable

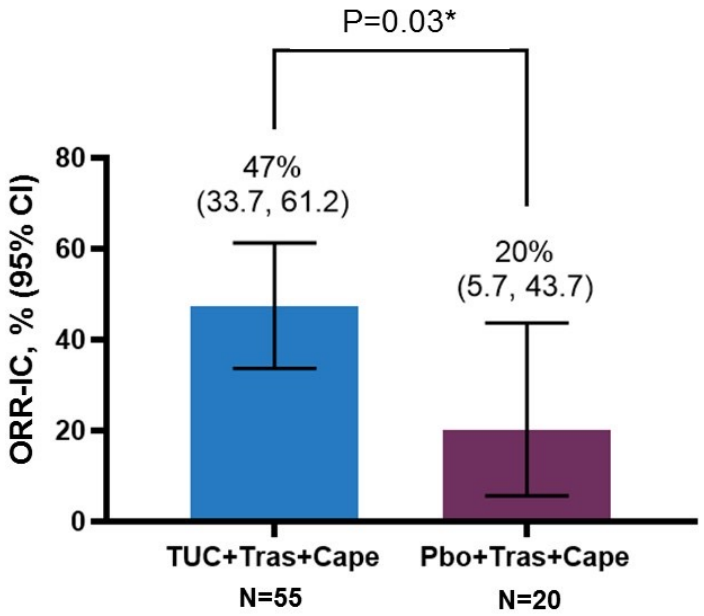
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

PRESENTED BY: Nancy Lin, nlin@partners.org

Presented By Nancy Lin

Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Confirmed Objective Response Rate (RECIST 1.1)



*Stratified Cochran-Mantel-Haenszel P value

	TUC+Tras+Cape (N=55)	Pbo+Tras+Cape (N=20)
Best Overall Intracranial Response[a], n (%)		
Complete Response (CR)	3 (5.5)	1 (5.0)
Partial Response (PR)	23 (41.8)	3 (15.0)
Stable Disease (SD)	24 (43.6)	16 (80.0)
Progressive Disease (PD)	2 (3.6)	0
Not Available[b]	3 (5.5)	0
Subjects with Objective Response of Confirmed CR or PR, n	26	4
Duration of Intracranial Response (DOR-IC)[e] (95% CI)[f], months	6.8 (5.5, 16.4)	3.0 (3.0, 10.3)

(a) Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).

PRESENTED BY: Nancy Lin, nlin@partners.org

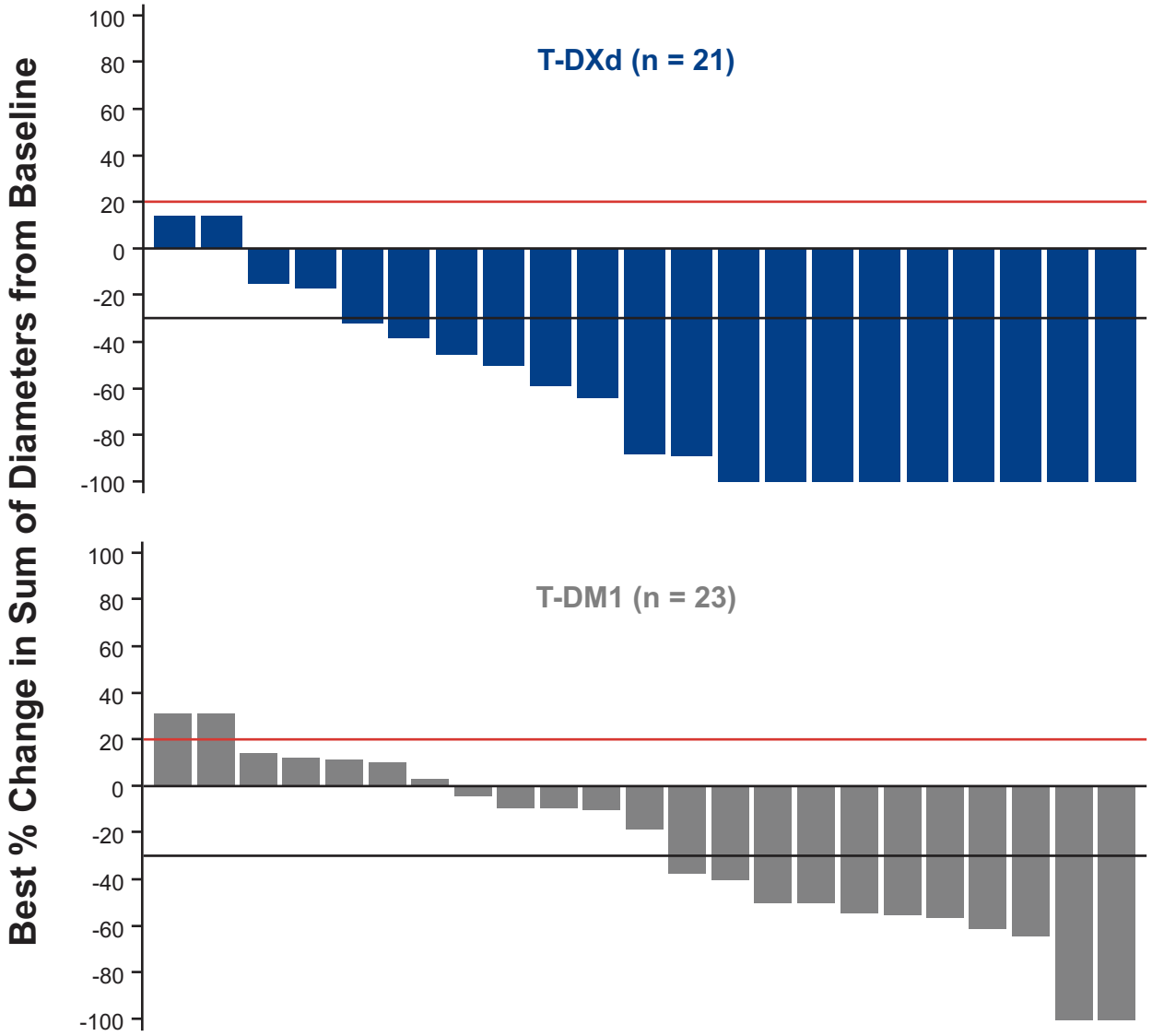
Presented By Nancy Lin at TBD

Neratinib and Capecitabine for CNS disease

- TBCRC 022: Phase 2 trial of patients with progressive HER2+ brain metastases treated with neratinib (240 mg po QD) and capecitabine (750 mg/m^2 BID 14d on/7d off)(N=49)
  - Efficacy in cohort without previous lapatinib (N=37):
    - 49% CNS objective response rate*
    - 5.5 mo median PFS
- NALA
  - Decreased time to intervention for CNS metastases (trial allowed patients with baseline asymptomatic and stable brain metastases)
    - Overall cumulative incidence: 22.8% vs 29.2%; **p=0.043**

Saura et al. JCO 2020;38:3138-49.
Freedman R et al. JCO 2019;37:1081

DB-03: Intracranial Response per BICR using RECIST 1.1



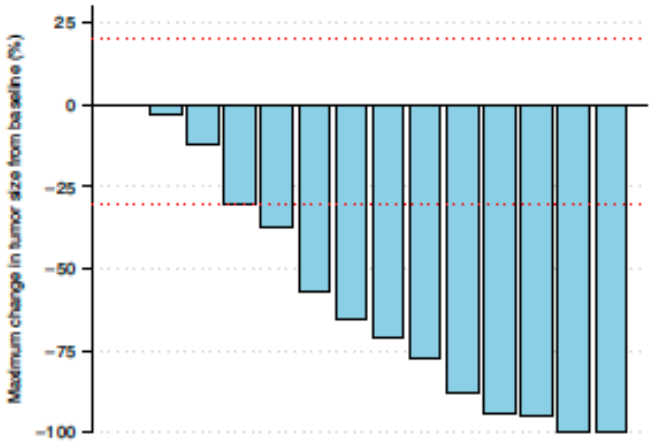
	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

Hurvitz SA et al. SABCS 2021;Abstract GS3-01.

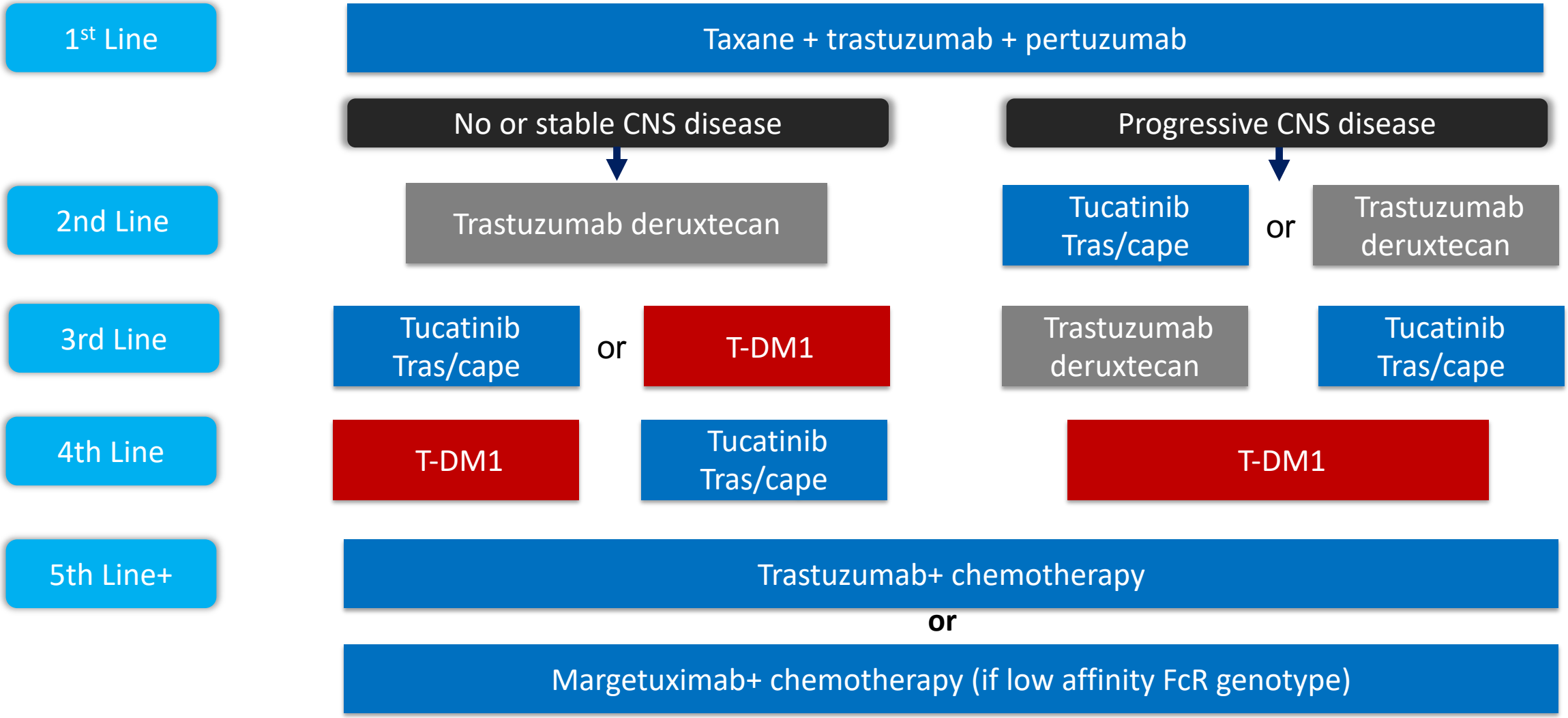
Trastuzumab Deruxtecan in patients with progressive brain metastases

- Case series
  - Newly diagnosed HER2+ BM or progression after prior local therapy
  - CNS objective response in 7 of 10 pts (70%)
- DEBBRAH study
  - HER2+ or HER2 low with progression after local therapy
  - Intracranial response (RANO BM) in 6 of 12 pts (50%)
- TUXEDO study
  - Newly diagnosed HER2+ BM or progression after prior local therapy
  - RANO RR: 73% (N=15)



Kabraji et al, SABCS 2021
Bartsch et al, Nat Med 2022 28:1840
Perez-Garcia JM et al. SABCS 2022;Abstract PD7-02

Approach to Therapy for Metastatic HER2+ disease



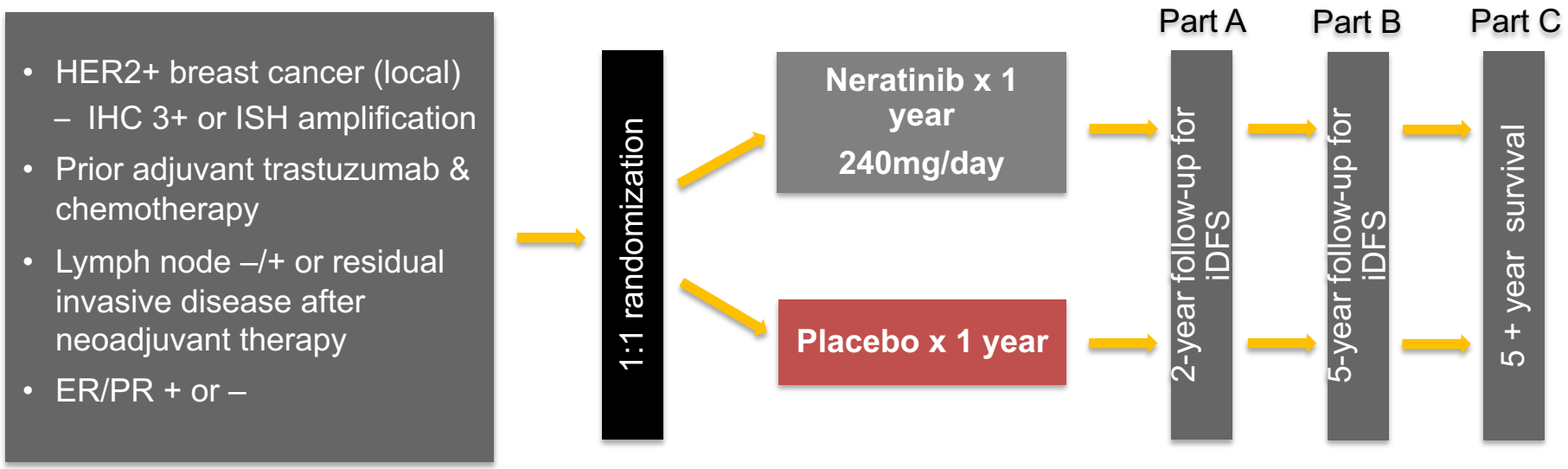
Adapted from Modi et al, ESMO 2021

Unanswered questions in HER2+ MBC

- What is the efficacy of T-DM1 after trastuzumab deruxtecan?
- Is there a role for neratinib or pyrotinib?
- What is comparative efficacy of T-DXd vs tucatinib in patients with active brain metastases?

Is there a role for neratinib for high risk HER2+ EBC?

ExteNET: Study design

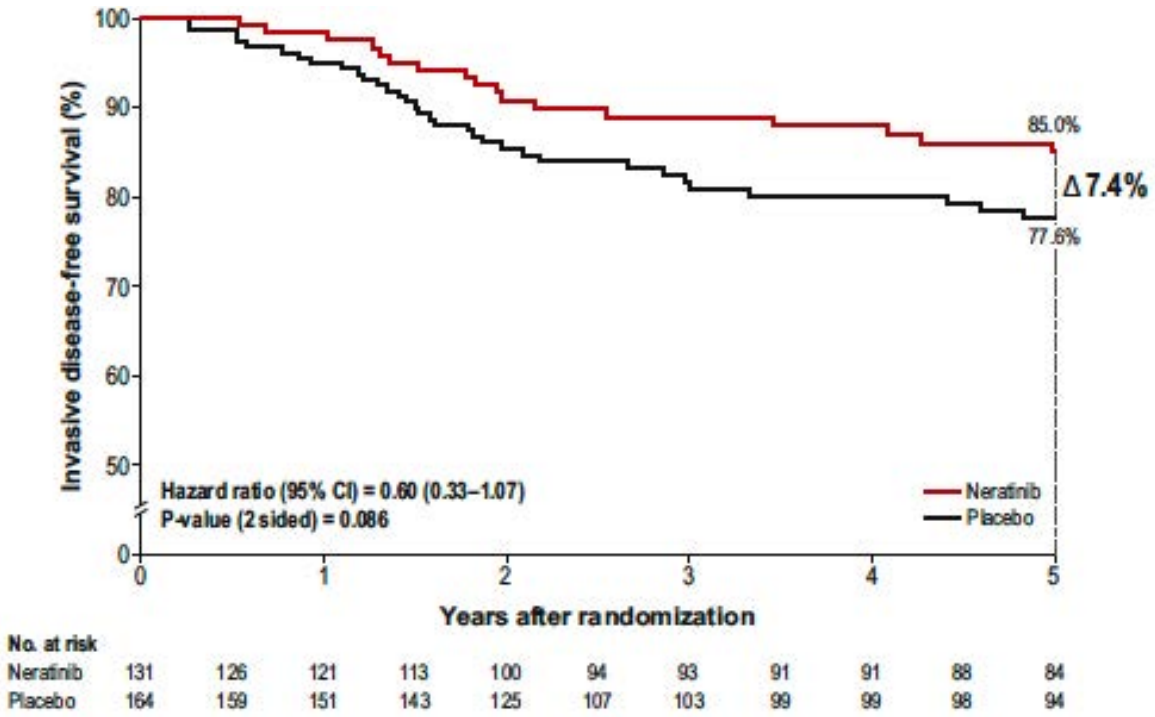


- Primary endpoint: invasive disease-free survival (iDFS)
- Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- Other analyses: biomarkers, health outcome assessment (FACT-B, EQ-5d)
- Stratified by: nodes 0, 1–3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

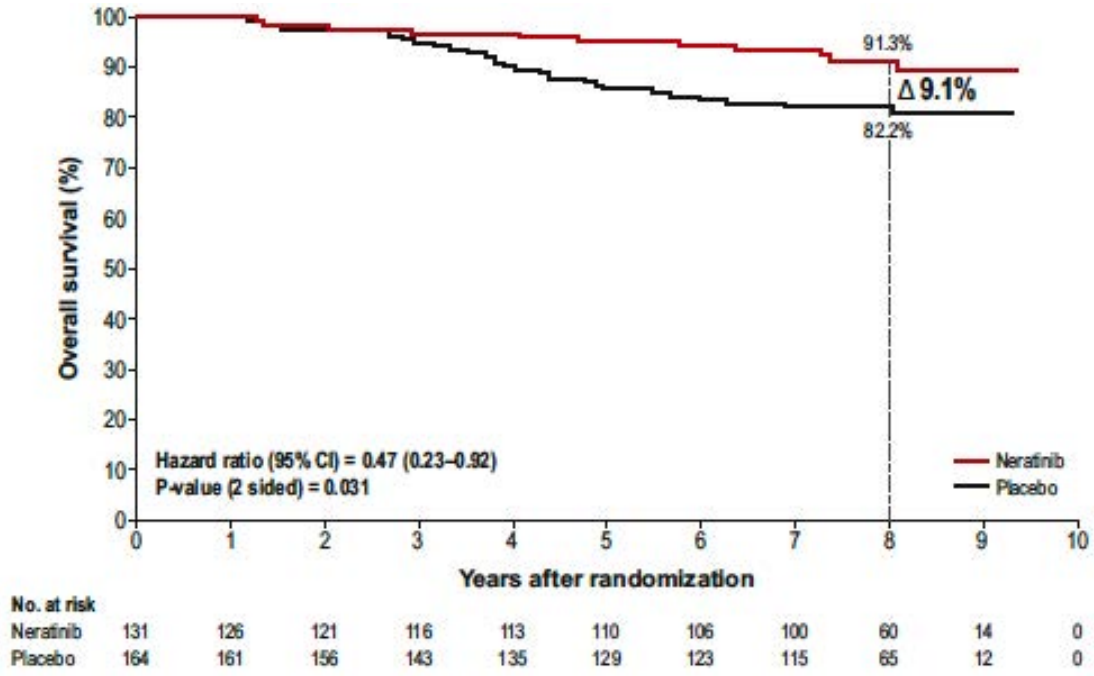
Chan et al, ASCO Breast 2015

Outcomes in HR+, ≤1 year from trastuzumab, and with residual disease after neoadjuvant therapy

iDFS at 5yrs



Overall Survival



Chan et al Clin Breast Cancer 2021 Feb;21(1):80-91.e7.

Cumulative incidence of CNS disease as 1st site of recurrence

Population or Subgroup	CNS Events (No. Patients)		Cumulative Incidence of CNS Recurrences at 5 Years, % (95% CI)	
	Neratinib	Placebo	Neratinib	Placebo
HR+/≤ 1-year population	4 (670)	12 (664)	0.7 (0.2–1.7)	2.1 (1.1–3.5)
Nodal status				
Positive	4 (540)	10 (539)	0.8 (0.3-2.0)	2.2 (1.1-3.8)
Negative	0 (130)	2 (125)	0 (NE)	1.9 (0.4-6.0)
Prior trastuzumab regimen				
Concurrent	2 (411)	8 (415)	0.6 (0.1-1.9)	2.3 (1.1-4.3)
Sequential	2 (259)	4 (249)	0.9 (0.2-3.0)	1.8 (0.6-4.3)
Adjuvant or neoadjuvant therapy				
Adjuvant	3 (508)	6 (472)	0.7 (0.2-2.0)	1.5 (0.6-3.0)
Neoadjuvant	1 (162)	6 (192)	0.7 (0.1-3.3)	3.7 (1.5-7.4)
pCR status[a]				
No	1 (131)	5 (164)	0.8 (0.1-4.0)	3.6 (1.3-7.8)
Yes	0 (17)	1 (21)	0 (NE)	5.0 (0.3-21.2)

Chan et al Clin Breast Cancer 2021 Feb;21(1):80-91.e7.

Who Should Receive Neratinib?

- Clear benefit (relative and absolute) in ER+HER2+ high risk patients
  - Must be balanced against significant toxicity risk
- No data giving neratinib after pertuzumab or T-DM1
  - All patients at sufficiently high risk to receive neratinib will have received pertuzumab and T-DM1
- So who should receive it?
  - Unclear, but my opinion is that it is reasonable option to consider in ER+ patients with multiple positive nodes after neoadjuvant therapy or multiple node positive patients who did not receive neoadjuvant therapy

Agenda

Module 1: Long-Term Management of HER2-Positive Breast Cancer — Dr Krop

Module 2: Optimizing the Management of ER-Positive Localized Breast Cancer — Dr Kalinsky

Module 3: Considerations in the Care of Patients with ER-Positive mBC — Dr Jhaveri

Module 4: Novel and Emerging Strategies for ER-Positive mBC — Dr Rugo

Module 5: Evolving Clinical Decision-Making for Localized Triple-Negative Breast Cancer (TNBC) — Dr O'Shaughnessy

Module 6: Recent Advances in the Treatment of Metastatic TNBC (mTNBC) — Prof Schmid

RTP RESEARCH TO PRACTICE

Ovarian function suppression to preserve fertility and prevent premature ovarian insufficiency; interrupting adjuvant hormonal therapy to attempt pregnancy

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

RTP
RESEARCH
TO PRACTICE

For premenopausal patients with ER-positive, HER2-negative BC who are about to receive adjuvant chemotherapy, do you generally offer the option of using ovarian function suppression during chemotherapy for fertility preservation or ovarian function preservation?

 Dr Jhaveri	Yes, for both	 Prof Schmid	Yes, for fertility preservation
 Dr Kalinsky	Yes, for both	 Dr Hurvitz	Yes, for fertility preservation
 Dr Krop	Yes, for both	 Dr Tolaney	Yes, for both
 Dr O'Shaughnessy	Yes, for both	 Dr Traina	Yes, for both
 Dr Rugo	Yes, for fertility preservation		

RTP RESEARCH TO PRACTICE

Have you offered or would you offer a premenopausal patient with ER-positive localized BC the opportunity to discontinue adjuvant endocrine therapy in order to become pregnant?

 Dr Jhaveri	I have not but would for the right patient	 Prof Schmid	I have
 Dr Kalinsky	I have	 Dr Hurvitz	I have
 Dr Krop	I have	 Dr Tolaney	I have
 Dr O'Shaughnessy	I have	 Dr Traina	I have
 Dr Rugo	I have		

RTP RESEARCH TO PRACTICE

2023 ASCO ANNUAL MEETING

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

Early Breast Cancer Trialists Collaborative Group (EBCTCG)

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

2023 ASCO ANNUAL MEETING

Thinking Differently About Breast Cancer in Young Women

Abstract Discussion: 503, 504 and 505

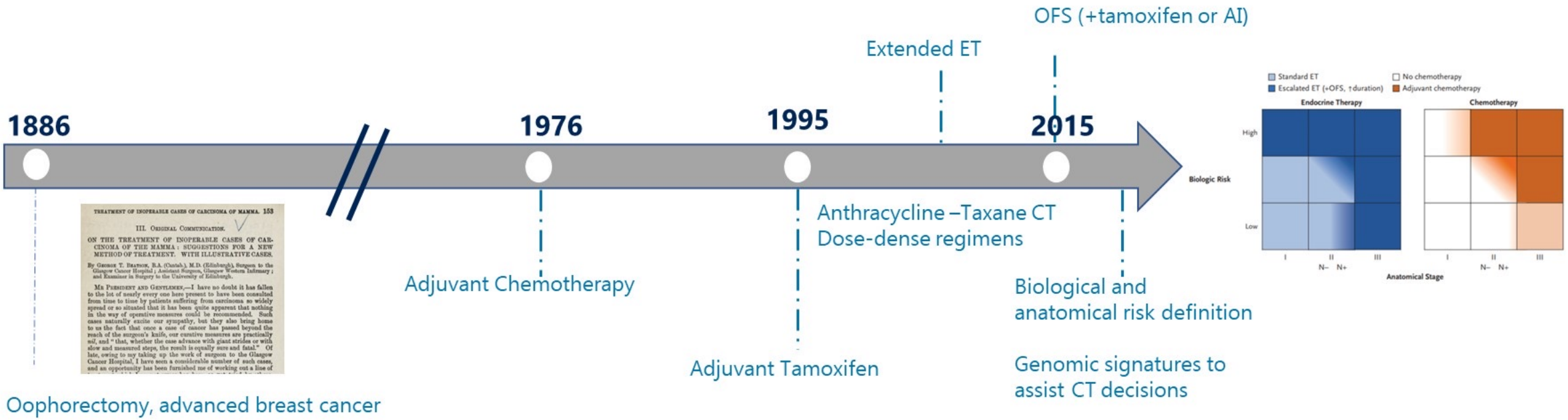
Ines Vaz-Luis

Breast Cancer Survivorship Group - INSERM Unit 981, Villejuif, France
Interdisciplinary Department for the Organization of Patient Pathways (DIOPP) - Gustave Roussy, Villejuif, France

Decision-Making & Standards of Care in Young Women

Moving towards Tailored Approaches

"Still Refining Adjuvant Therapy in Premenopausal Women: Not Too Much, Not Too Little"



ET: endocrine treatment, CT: chemotherapy, OFS: Ovarian function suppression AI: aromatase inhibitors, N-: node negative, N+: node positive

WolfF & Rugo, JCO, 2016; Burstein, NEJM 2020; Andre, JCO 2022

PRESENTED BY: Ines Vaz-Luis, Gustave Roussy - Villejuif, France

Decision-Making & Standards of Care in Young Women

Moving towards Tailored Approaches

OFFSET (NRG BR009)

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

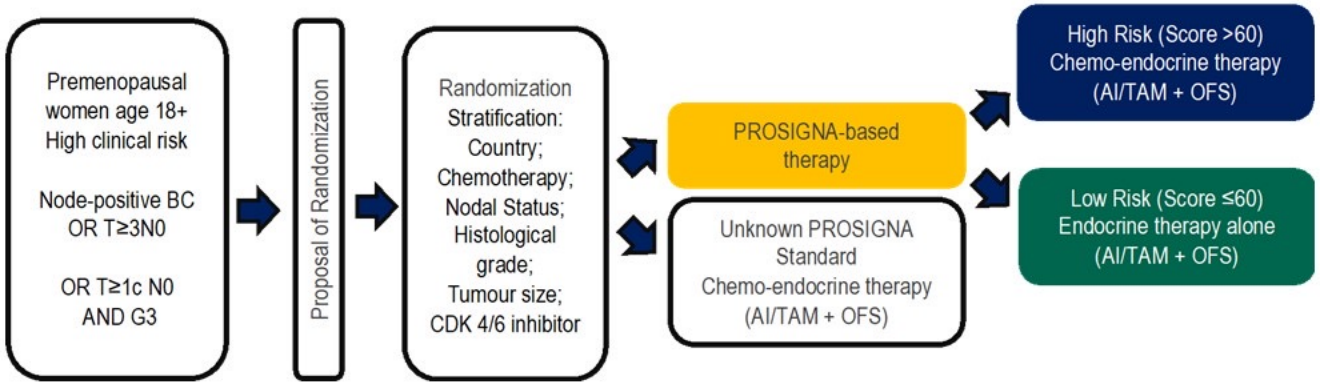
Stratification

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

Randomization

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

OPTIMA YOUNG



PRESENTED BY: Ines Vaz-Luis, Gustave Roussy - Villejuif, France

Selection of patients for adjuvant tamoxifen monotherapy

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

RTP
RESEARCH
TO PRACTICE

Which adjuvant treatment would you most likely recommend for a 30-year-old patient with ER-positive, HER2-negative, node-negative localized BC with a 21-gene RS of 8?

 Dr Jhaveri	Tamoxifen
 Dr Kalinsky	Tamoxifen
 Dr Krop	Tamoxifen
 Dr O'Shaughnessy	OFS and tamoxifen
 Dr Rugo	OFS and letrozole or anastrozole
 Prof Schmid	OFS and letrozole
 Dr Hurvitz	Tamoxifen
 Dr Tolaney	If ≤1 cm, tamoxifen; if larger or other high-risk features, consider adding OFS
 Dr Traina	Tamoxifen

OFS = ovarian function suppression/ablation

RTP RESEARCH TO PRACTICE

Utility of genomic assays in the neoadjuvant setting; management of node-positive disease in postmenopausal patients with low-risk Recurrence Scores

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

Have you ordered or would you order a genomic assay in the neoadjuvant setting to assist with clinical decision-making for a patient with ER-positive, HER2-negative localized BC?

 Dr Jhaveri	I have commonly	 Prof Schmid	I have occasionally or rarely
 Dr Kalinsky	I have occasionally or rarely	 Dr Hurvitz	I have occasionally or rarely
 Dr Krop	I have commonly	 Dr Tolaney	I have commonly
 Dr O'Shaughnessy	I have commonly	 Dr Traina	I have occasionally or rarely
 Dr Rugo	I have commonly		

RTP RESEARCH TO PRACTICE

In general, would you be comfortable withholding chemotherapy for a postmenopausal patient with ER-positive, HER2-negative localized BC, a 21-gene RS of 8 and 4 positive nodes?

 Dr Jhaveri	No	 Prof Schmid	No
 Dr Kalinsky	Yes, depending on age and comorbidities	 Dr Hurvitz	Yes, after a balanced discussion
 Dr Krop	Yes	 Dr Tolaney	No
 Dr O'Shaughnessy	Yes	 Dr Traina	No
 Dr Rugo	No		

RTP RESEARCH TO PRACTICE

Selection between abemaciclib and ribociclib in the adjuvant setting

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

RTP
RESEARCH
TO PRACTICE

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

 Dr Jhaveri	Yes, abemaciclib	 Prof Schmid	Yes, abemaciclib
 Dr Kalinsky	Yes, either abemaciclib or ribociclib	 Dr Hurvitz	Yes, ribociclib
 Dr Krop	Yes, abemaciclib	 Dr Tolaney	Yes, abemaciclib
 Dr O'Shaughnessy	Yes, abemaciclib	 Dr Traina	Yes, abemaciclib
 Dr Rugo	Yes, either abemaciclib or ribociclib		

RTP RESEARCH TO PRACTICE

2023 ASCO ANNUAL MEETING

Cyclin' Through the Inhibitors

in HR+/HER2- early breast cancer

Nadia Harbeck

Breast Center, Dept. OB&GYN, LMU University Hospital, Munich, Germany

Conclusions

- monarchE and NATALEE have reached their primary endpoint (iDFS) in interim analysis - abemaciclib and ribociclib improve iDFS in HR+/HER2- EBC
- Transfer to clinical practice still poses challenges
  - available evidence does not support replacing chemo by ET-based therapy (about 90% prior chemotherapy) - ADAPTcycle addresses this issue; completed, results pending
  - avoid early discontinuations by continuous support with proactive information and therapy management (including dose reductions) for the additional 2-3y therapy
- NATALEE as well as monarch-E need longer follow-up to ascertain the full benefit of adjuvant CDK 4/6i, particularly for individual subgroups
- PENELOPE-B shows high risk for recurrence in HR+/HER2- EBC patients with non-pCR and ctDNA detection – consistent with findings in other subtypes
  - ctDNA dynamics prognostic – adequately powered prospective trials needed to understand predictive benefit of ctDNA detection and clearance to optimize outcomes
  - Optimal test system, sampling times, and therapeutic interventions need to be explored

Adjuvant CDK 4/6i – Main Take-Aways

- **Good news for patients:** Abemaciclib and Ribociclib increase chances for cure in HR+/HER2- early breast cancer (EBC) with acceptable safety profile
- But: We still have work to do - further research is needed
  - Optimal therapy management to allow patients to complete intended therapy duration - eHealth support may be beneficial and empower patients
  - Identification of patients still at risk despite optimal adjuvant therapy
    - Define new therapy options for these patients
- CDK 4/6i use in EBC raises questions for MBC (e.g. re-challenge, sequencing)
- Given their different indications, efficacy data, and side effect profiles, all available CDK 4/6i are valuable therapy options for breast cancer patients

Potential utility of circulating tumor DNA assessment in breast cancer

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

RTP
RESEARCH
TO PRACTICE

Have you ordered or would you order a circulating tumor DNA assay to assist with clinical decision-making for a patient with BC?

 Dr Jhaveri	I have not and would not	 Prof Schmid	I have
 Dr Kalinsky	I have not and would not	 Dr Hurvitz	I have not and would not
 Dr Krop	I have not and would not	 Dr Tolaney	I have not and would not
 Dr O'Shaughnessy	I have in the metastatic setting only	 Dr Traina	I have
 Dr Rugo	I have		

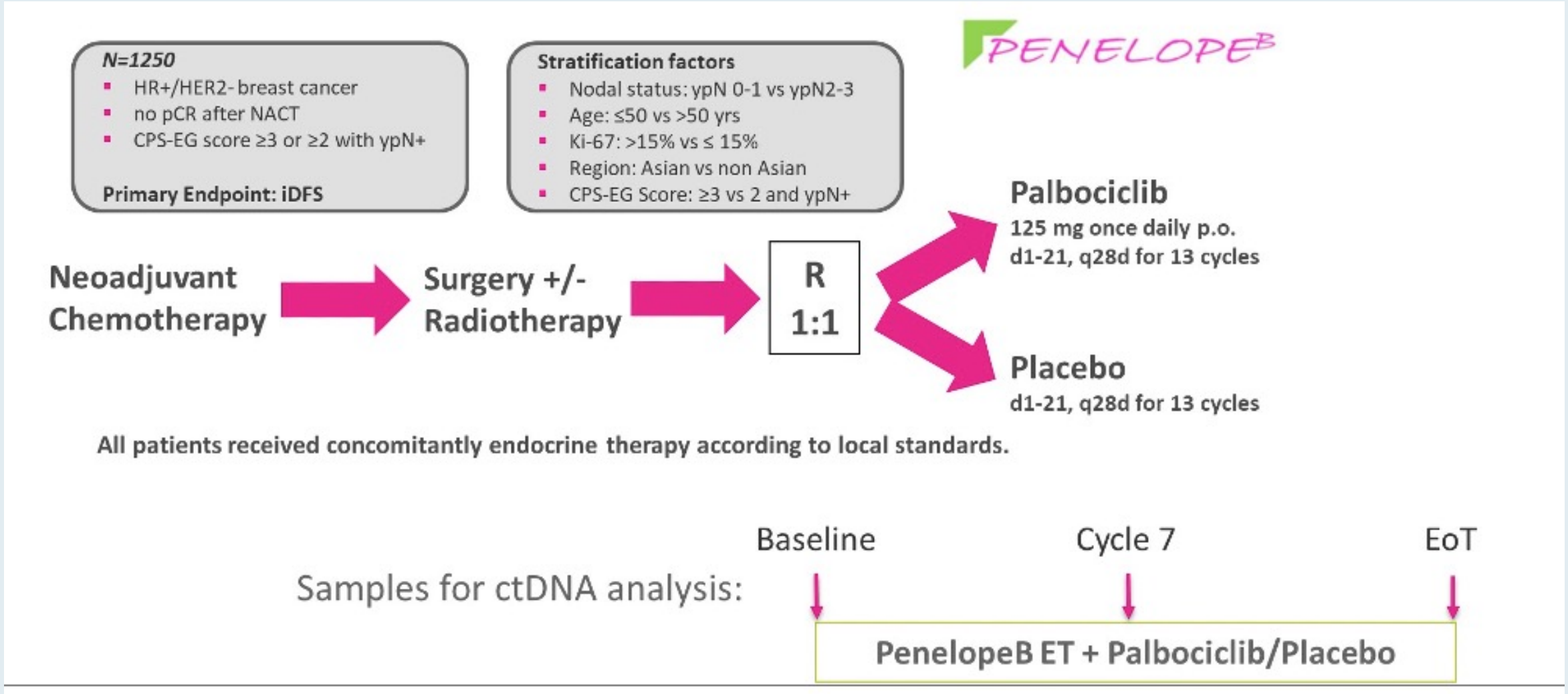
RTP RESEARCH TO PRACTICE

Detection of circulating tumor DNA following neoadjuvant chemotherapy and surgery to anticipate early relapse in ER positive and HER2 negative breast cancer: Analysis from the PENELOPE-B trial

Nicholas Turner, Frederik Marmé, Sung-Bae Kim, Hervé Bonnefoi, Jose Angel García-Sáenz, Antonio Antón Torres, Harry Bear, Hans Tesch, Mireia Melé Olivé, Nicole McCarthy, Josefina Cruz Jurado, Seock-Ah Im, Yuan Liu, Zhe Zhang, Karsten Weber, Bärbel Felder, Valentina Nekljudova, Toralf Reimer, Carsten Denkert, Sibylle Loibl

Abstract 502

PENELOPE-B: Trial Design



Turner N et al. ASCO 2023;Abstract 502.

ctDNA Analysis Methods

A tumor sample was exome sequenced, and up to 50 mutations were tracked in plasma using error-corrected sequencing for ctDNA detection (RaDaR assay).

Step 1

Patient's tumor sample (FFPE) is sent to the NeoGenomics laboratory

Step 2

Patient's tumor DNA is sequenced to determine the tumor's unique mutation profile

Step 3

A personalized RaDaR panel is designed for the patient

Step 4

After initial panel design, ctDNA is tested using blood samples and the patient's custom RaDaR panel

Step 5

Report is generated

Turner N et al. ASCO 2023;Abstract 502.

RTP RESEARCH TO PRACTICE

PENELOPE-B: Conclusions

- Detection of ctDNA following neoadjuvant chemotherapy, and surgery, is associated with a very high risk of early relapse suggesting limited efficacy of adjuvant endocrine therapy
  - Studies of clinical imaging and experimental therapy are warranted for these patients

- 'Sensitivity' for future relapse is imperfect, in particular for later relapses, in patients who had prior neoadjuvant chemotherapy and surgery
  - Response to prior neoadjuvant chemotherapy may reduce ctDNA detection rates
  - Sequential testing improves 'sensitivity' for relapse

- Although ctDNA analysis has been approved by Medicare, use is likely not appropriate in deciding whether to give adjuvant CDK4/6 inhibitor in patients otherwise eligible, after neoadjuvant chemotherapy

Turner N et al. ASCO 2023;Abstract 502.

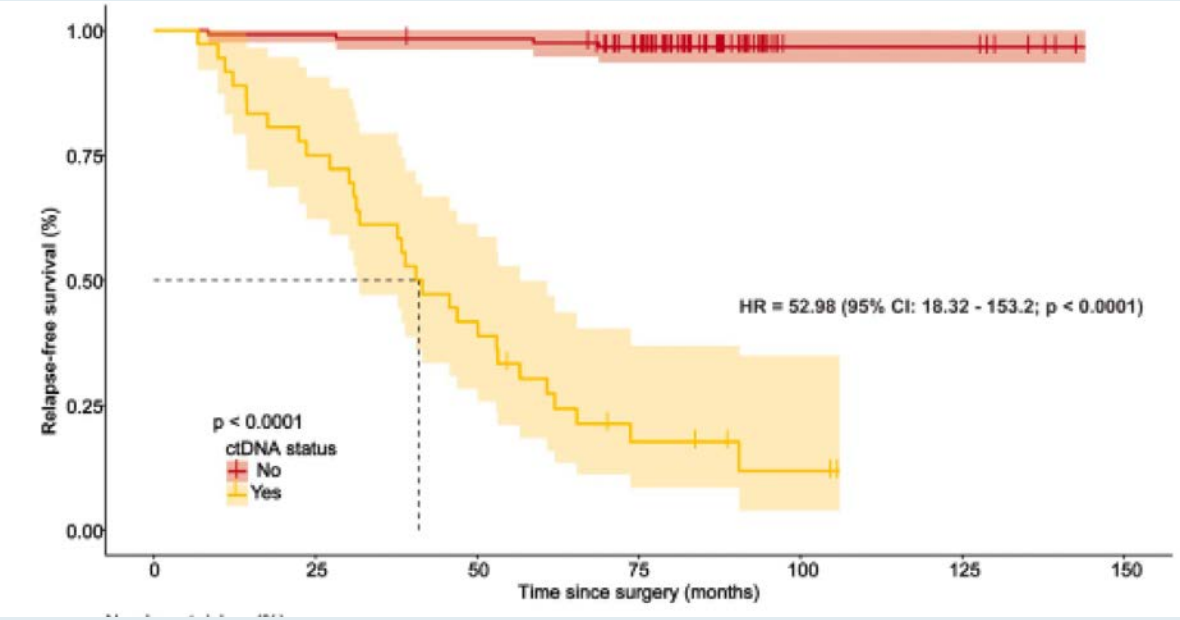
Serial Postoperative ctDNA Monitoring of Breast Cancer Recurrence

Shaw JA et al.

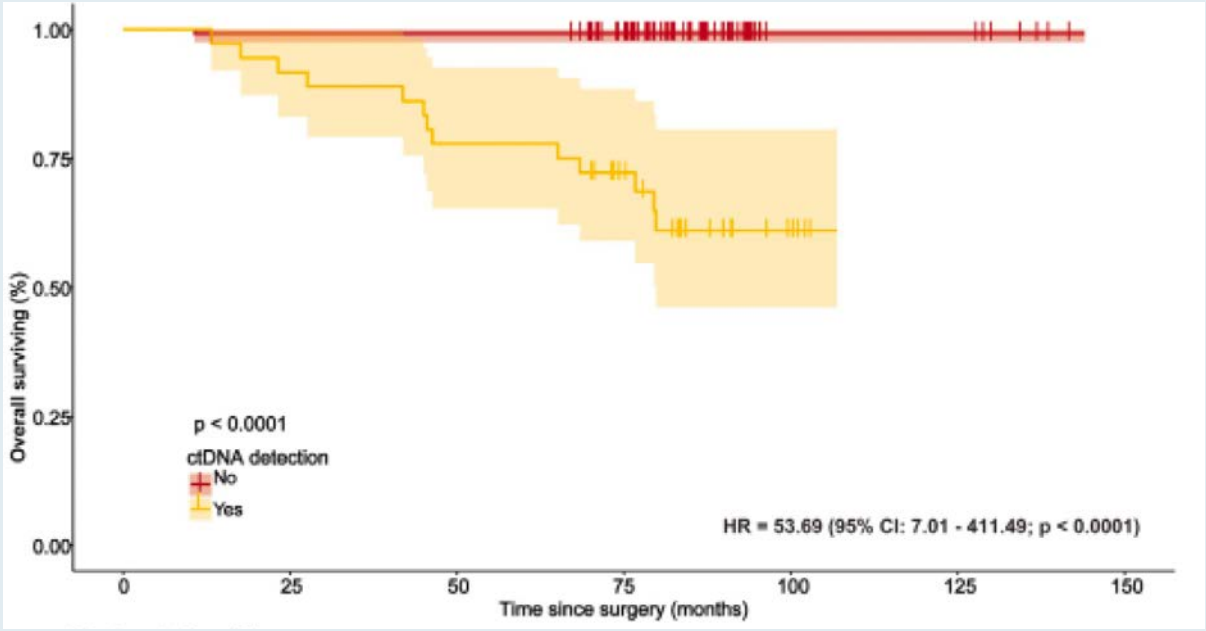
ASCO 2022;Abstract 562.

Exploratory Breast Lead Interval Study (EBLIS): ctDNA Detection in Serial Plasma Samples Predicts RFS and OS

RFS



OS



Shaw JA et al. ASCO 2022;Abstract 562.

RTP RESEARCH TO PRACTICE

Monitoring for Response and Recurrence n Neoadjuvant-Treated Hormone Receptor-Positive HER2-Negative Breast Cancer by Personalized Circulating Tumor DNA Testing

Magbanua MJM et al.

San Antonio Breast Cancer Symposium 2022;Abstract P5-05-05.

Optimizing the Management of ER-Positive Localized Breast Cancer

Kevin Kalinsky, MD, MS

RxPONDER Schema

Key Entry Criteria

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

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

Arm 1:
Chemotherapy Followed by
Endocrine Therapy

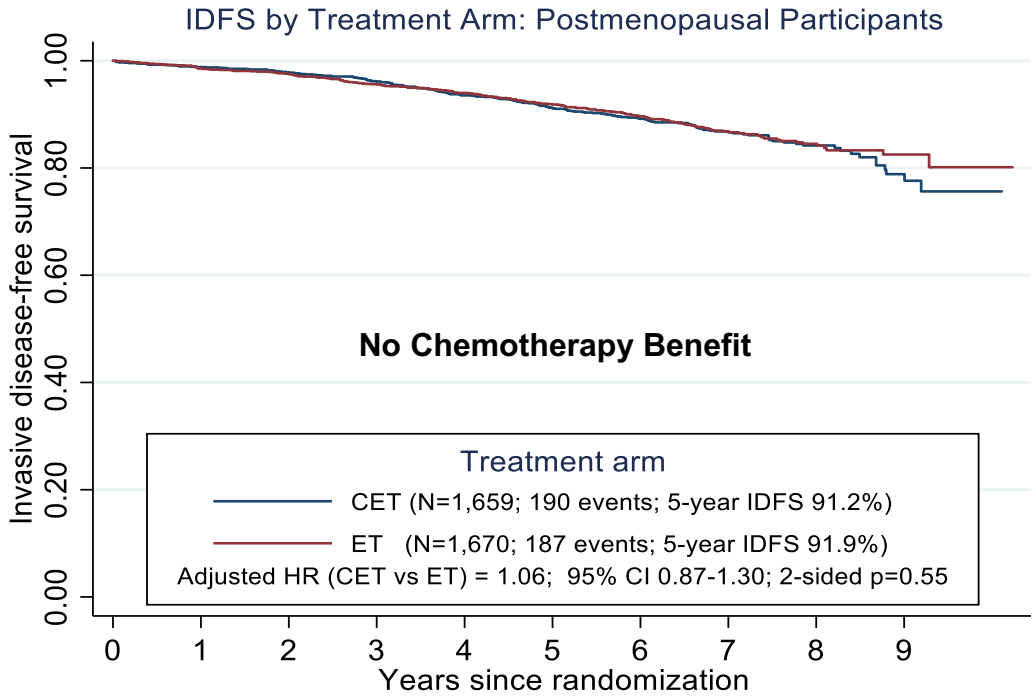
Arm 2:
Endocrine Therapy Alone

Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

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

Updated Analysis: Postmenopausal Women Have No Chemotherapy Benefit

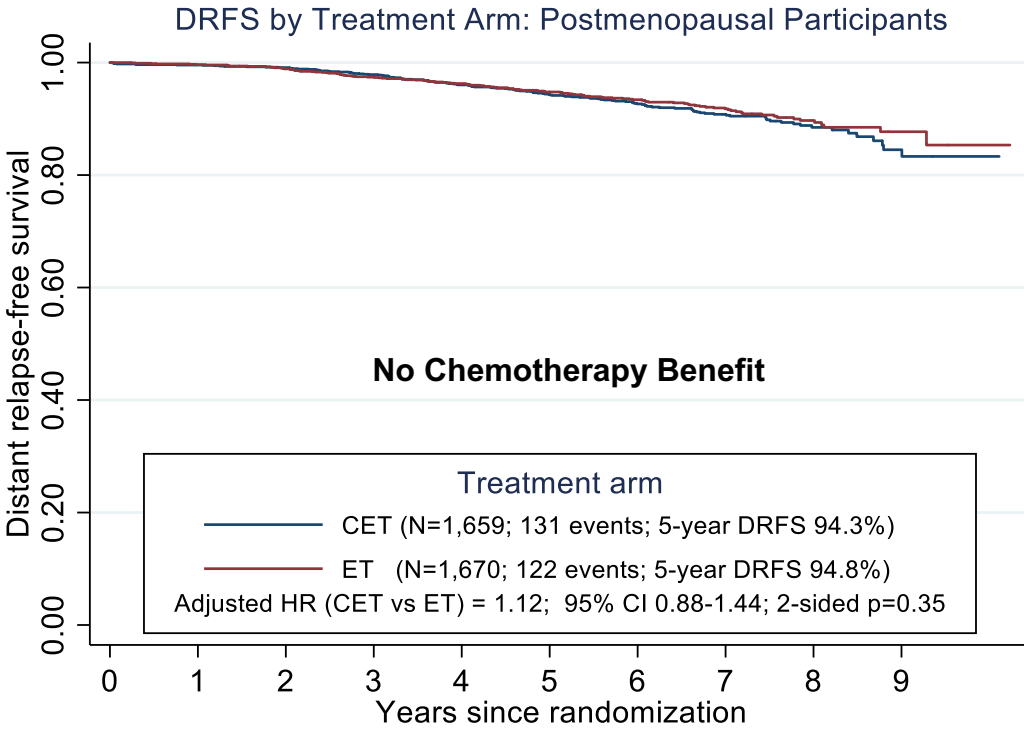
Invasive Disease-Free Survival



Number at risk

CET	1659	1557	1498	1427	1258	1118	848	540	243	64
ET	1670	1599	1550	1465	1314	1164	879	547	247	67

Distant Relapse-Free Survival

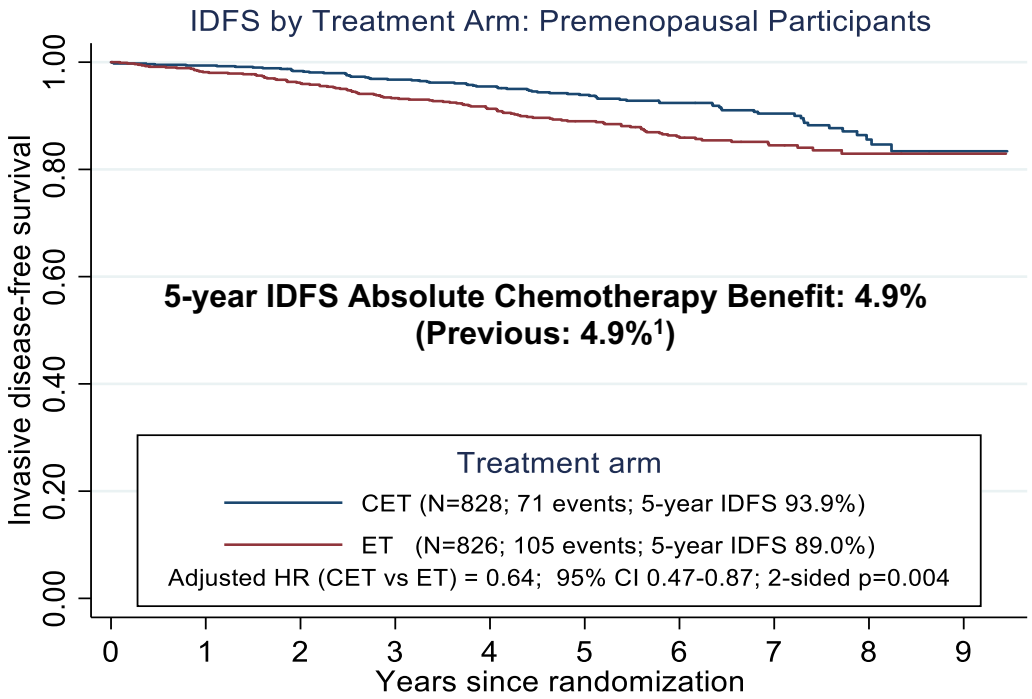


Number at risk

CET	1659	1567	1514	1448	1291	1152	884	571	261	71
ET	1670	1614	1569	1491	1345	1201	916	582	264	71

Updated Analysis: Premenopausal Women Have Chemotherapy Benefit

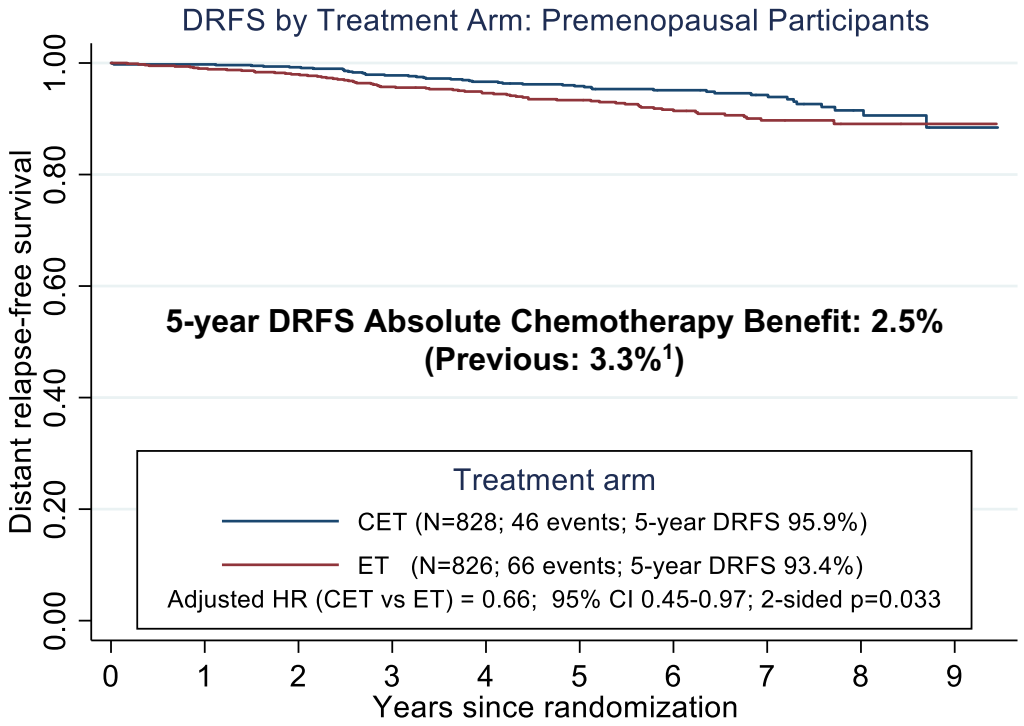
Invasive Disease-Free Survival



Number at risk

CET	828	783	754	706	632	561	408	252	99	21
ET	826	774	737	694	610	533	398	236	86	27

Distant Relapse-Free Survival

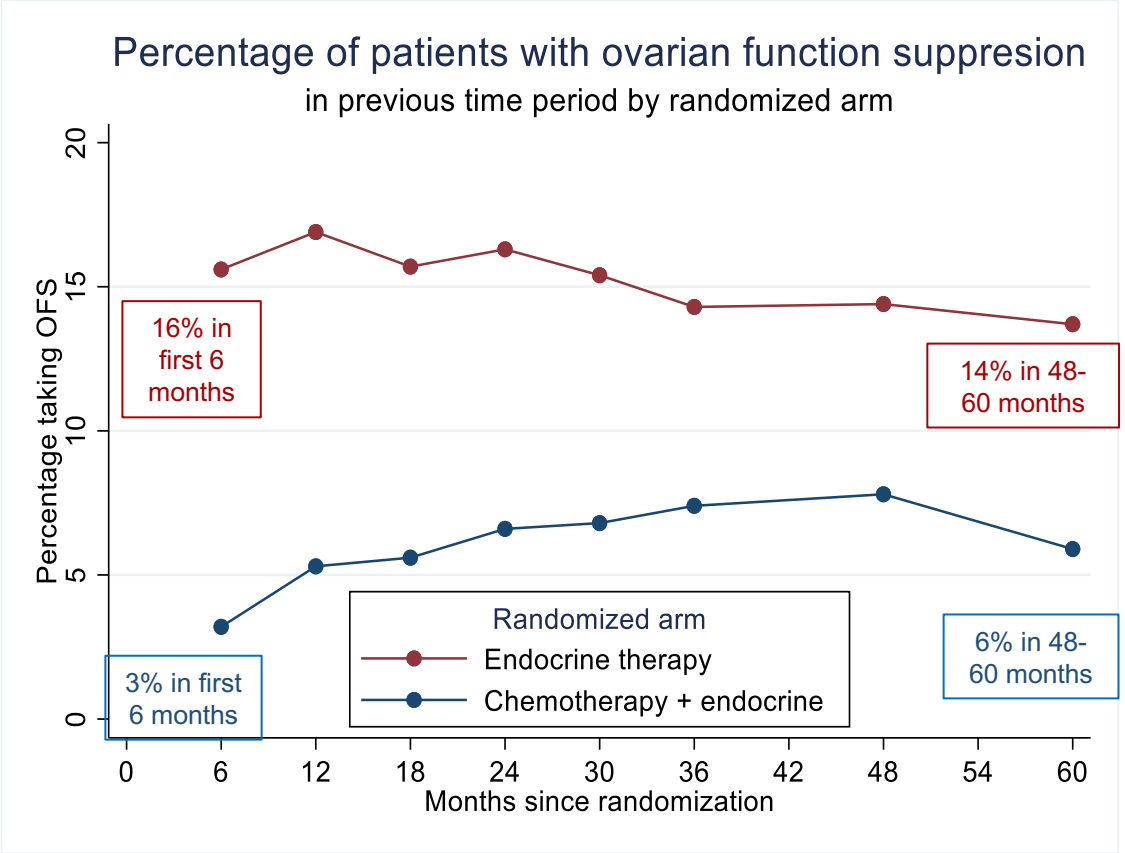


Number at risk

CET	828	786	761	714	641	575	421	266	106	22
ET	826	780	751	712	631	555	420	247	93	28

[1] Kalinsky et al, New England Journal of Medicine: December 1, 2021

OFS Rate in Premenopausal Pts in Tx Arms Over Time



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

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

BR009: Schema

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

Stratification

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

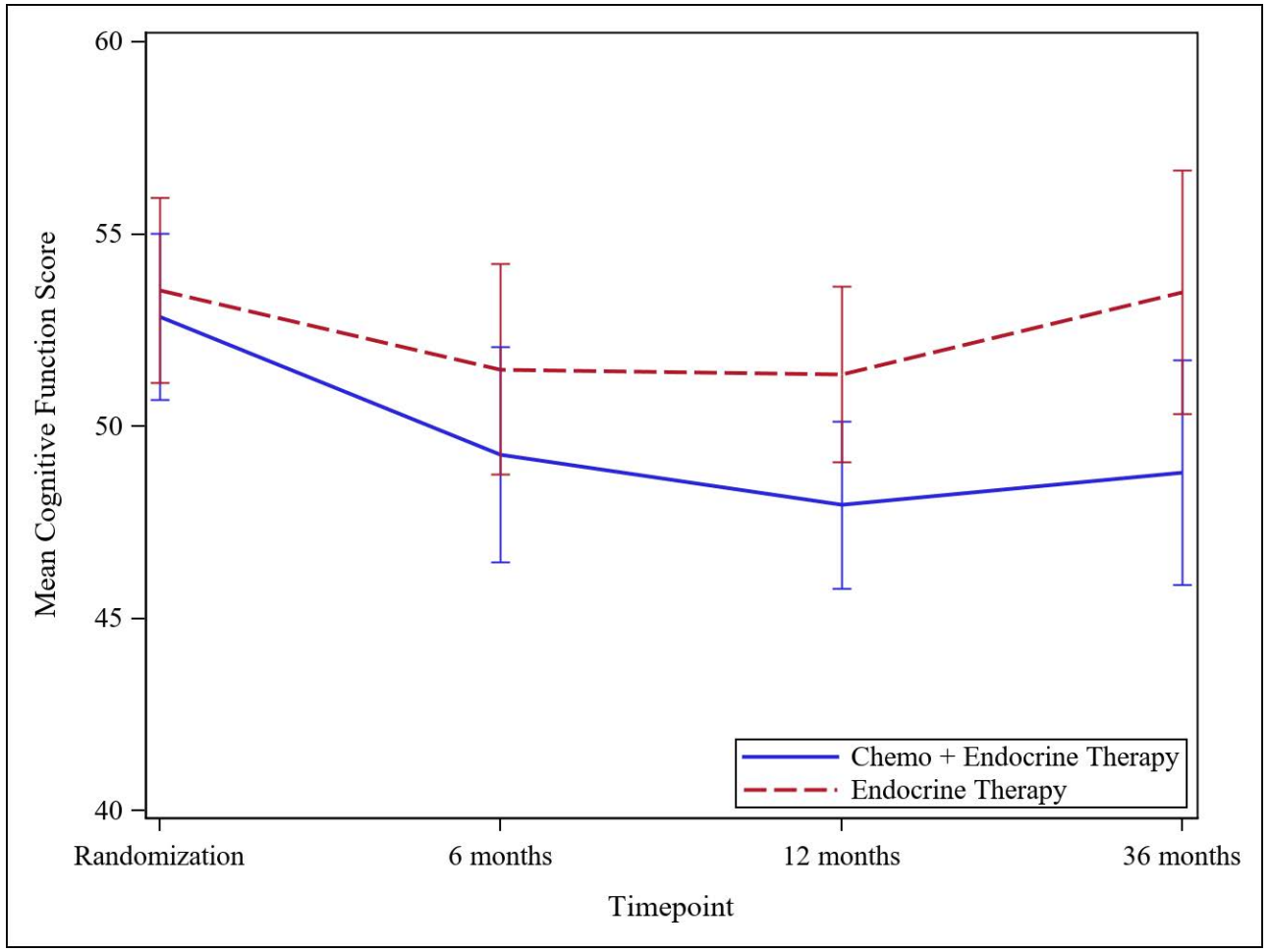
Randomization

N=3,960

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

* Tamoxifen can be used if AI is not tolerated

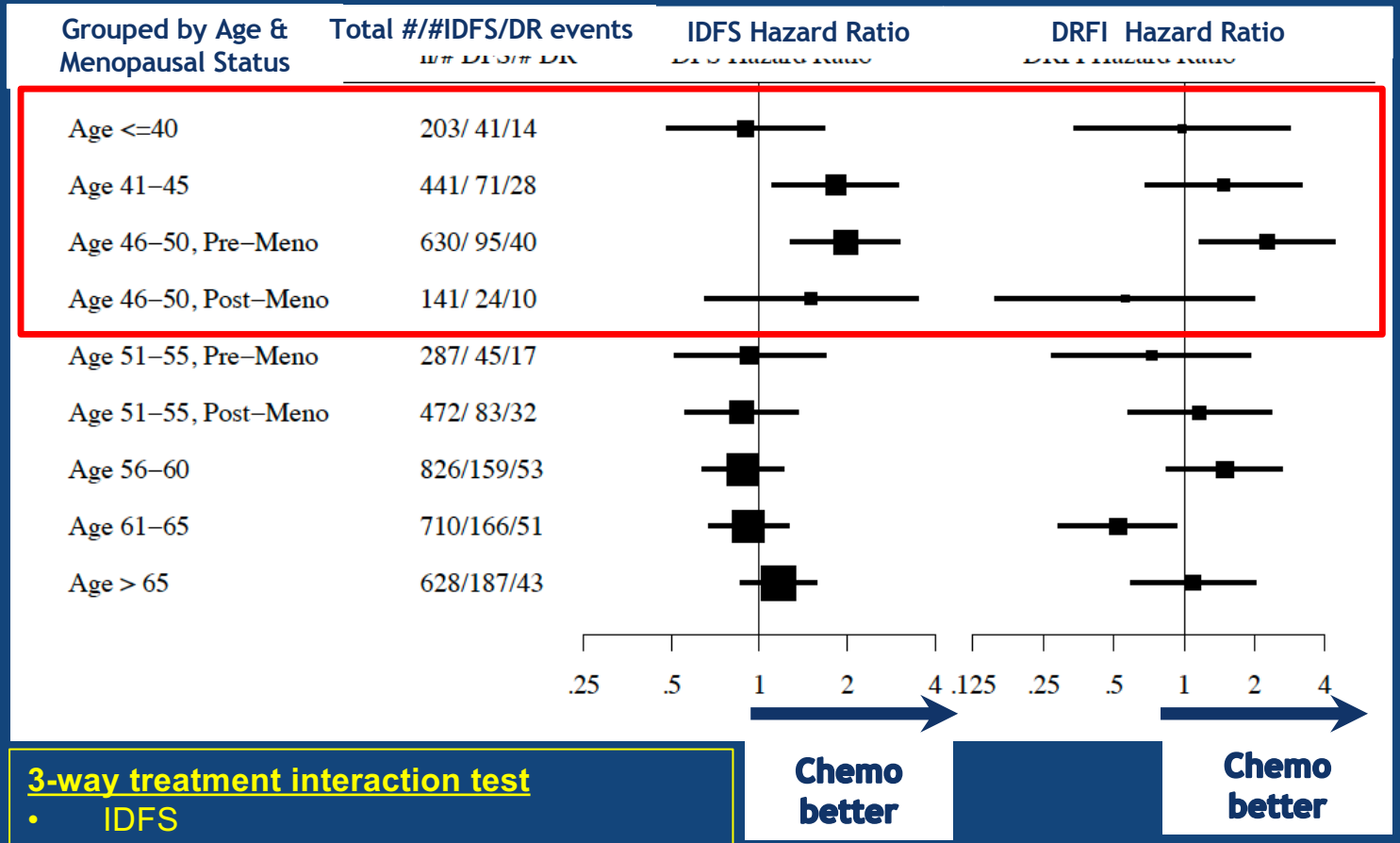
Mean Cognitive Function Score: Premenopausal



Total n=139	CET	65	43	44	36
	ET	74	55	56	39

Kang I et al. SABCS 2022;Abstract GS1-04.

TAILORx: Updated Analysis - Effect of Age, RS, and Clinical Risk on Chemotherapy Benefit (ITT Population)



3-way treatment interaction test

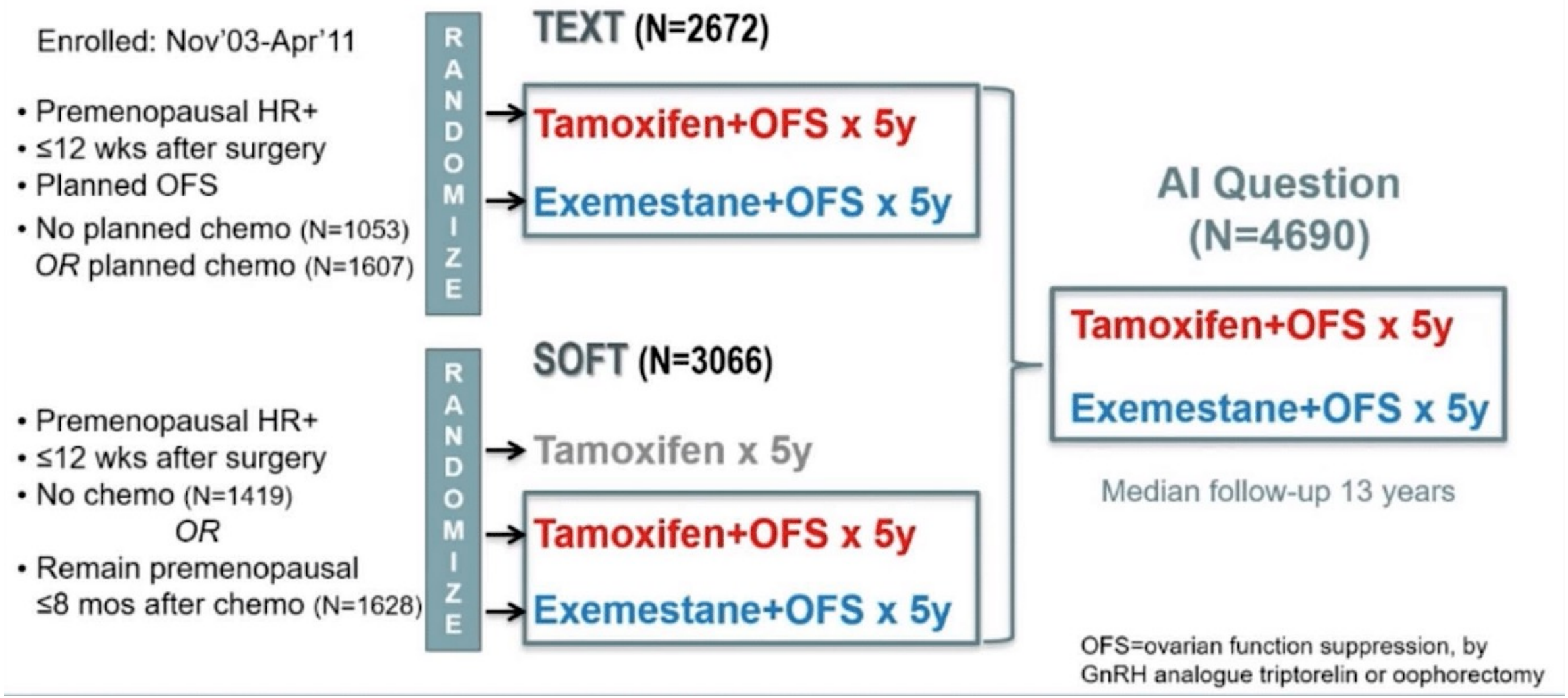
- IDFS
  - Chemo-Age-RS (p=0.007)
  - Chemo-Menopause-RS (p=0.06)
- DRFI
  - Chemo-Age-RS (p=0.43)
  - Chemo-Menopause-RS (p=0.26)

12-Year DRFI Rates in Age ≤ 50 Years & RS 16-25

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +0.4% (±SE 2.1%)	Low	671 (76%)	Δ -0.5% (±SE 2.2%)
		High	215 (24%)	Δ +3.1% (±SE 5.4%)
RS 21-25 (N=476)	Δ +7.8% (±SE 3.4%)	Low	319 (67%)	Δ +5.9% (±SE 3.4%)
		High	157 (33%)	Δ +11.7% (±SE 7.2%)

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

TEXT and SOFT Joint Analysis

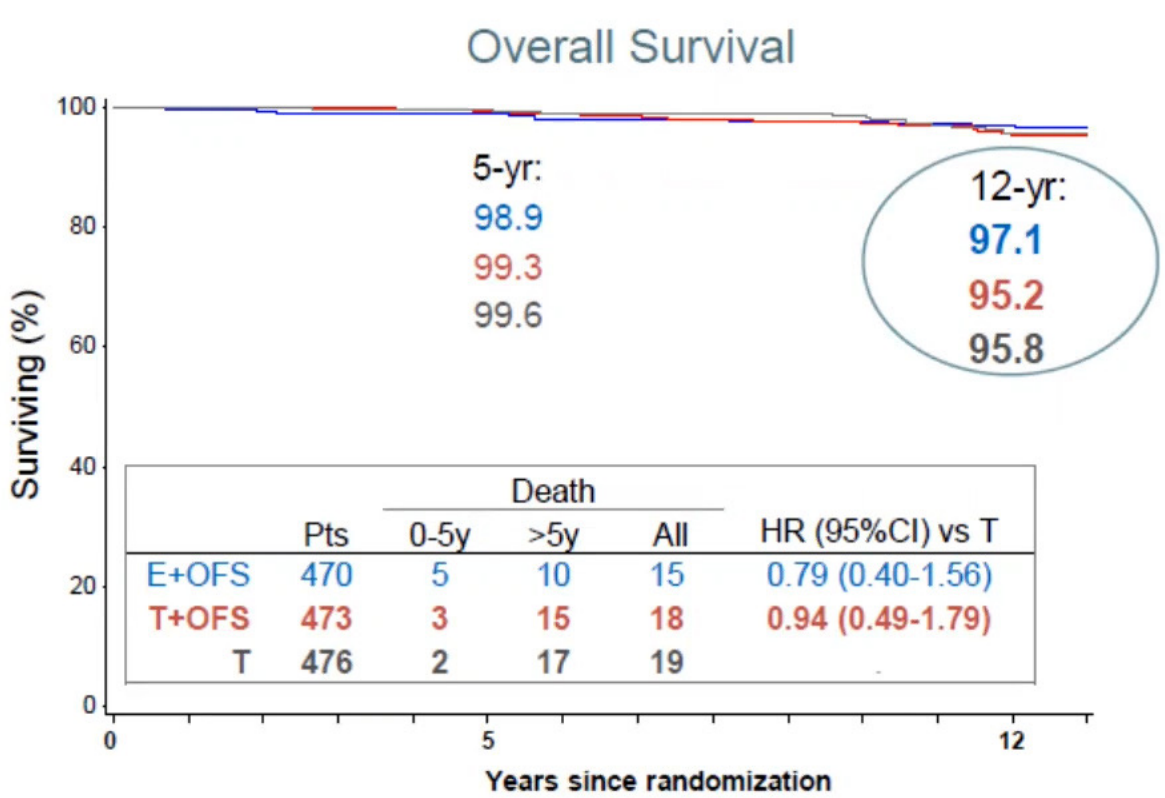


Regan M et al. SABCS 2021;Abstract GS2-05.

No Chemotherapy Groups

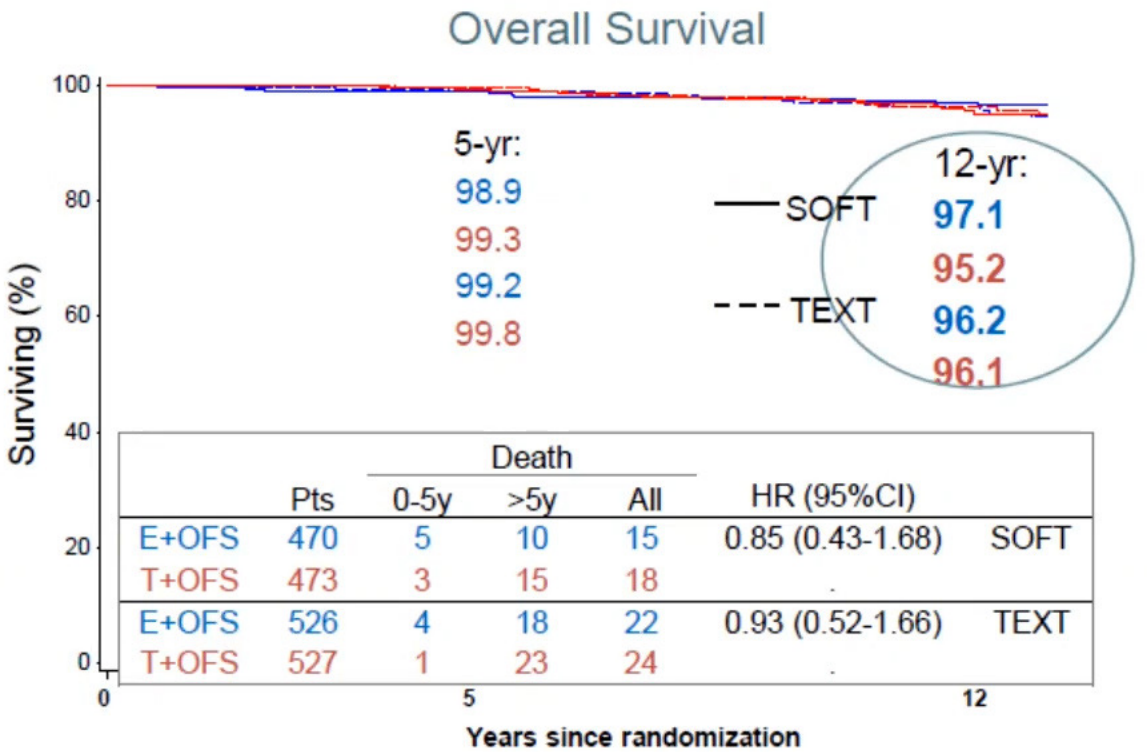
>95% of women surviving at 12 years

SOFT



	Pts	Death 0-5y	Death >5y	Death All	HR (95%CI) vs T
E+OFS	470	5	10	15	0.79 (0.40-1.56)
T+OFS	473	3	15	18	0.94 (0.49-1.79)
T	476	2	17	19	

SOFT/TEXT trials

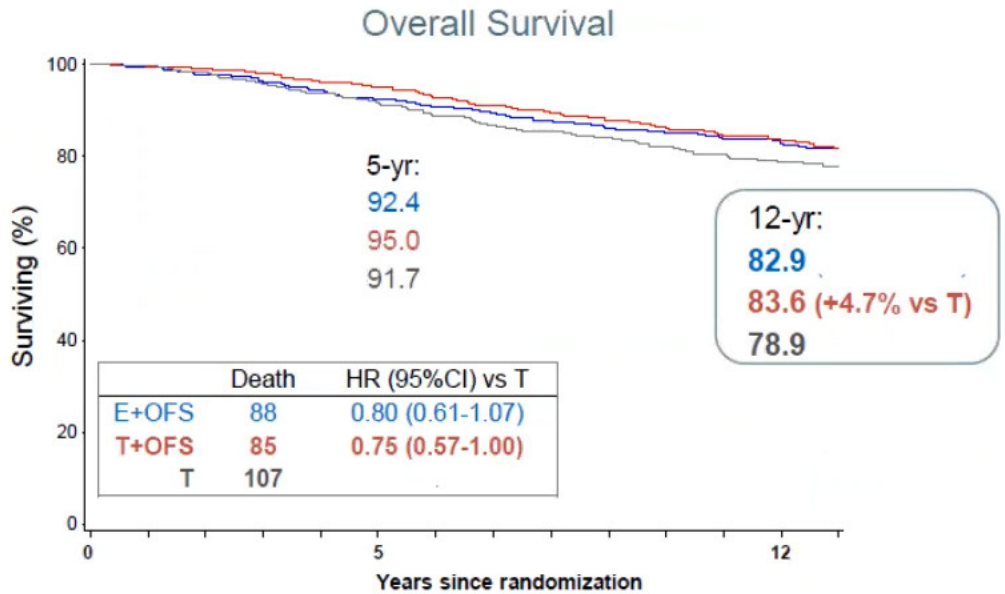


	Pts	Death 0-5y	Death >5y	Death All	HR (95%CI)	
E+OFS	470	5	10	15	0.85 (0.43-1.68)	SOFT
T+OFS	473	3	15	18	.	
E+OFS	526	4	18	22	0.93 (0.52-1.66)	TEXT
T+OFS	527	1	23	24	.	

Regan M et al. SABCS 2021;Abstract GS2-05.

Prior Chemotherapy Group

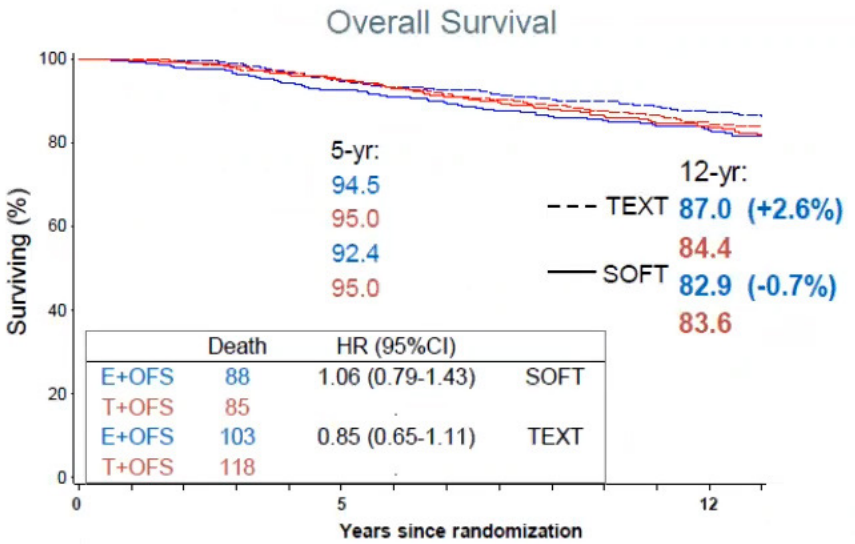
SOFT



	0-5 years		>5 years	
	Deaths	HR (95% CI) vs T	Deaths	HR (95% CI) vs T
E+OFS:	40	0.93 (0.61-1.43)	48	0.72 (0.50-1.05)
T+OFS:	26	0.60 (0.37-0.97)	59	0.86 (0.60-1.22)
T:	43	.	64	.
At risk:	1628 pts	7681 pyfu	1427 pts	9295 pyfu

T+OFS vs T: absolute reduction in distant recurrence, 2.6% at 12 years
reduction in death persists, absolute reduction 4.7% at 12 years
E+OFS vs T: reductions of 4.5% and 4.0%, at 12 years

SOFT/TEXT trials



		0-5 years		>5 years	
		Deaths	HR (95% CI)	Deaths	HR (95% CI)
SOFT	E+OFS:	40	1.57 (0.96-2.57)	48	0.84 (0.57-1.22)
	T+OFS:	26	.	59	.
TEXT	E+OFS:	42	1.10 (0.71-1.70)	61	0.74 (0.53-1.03)
	T+OFS:	38	.	80	.
	At risk:	2694 pts	12774 pyfu	2395 pts	16928 pyfu

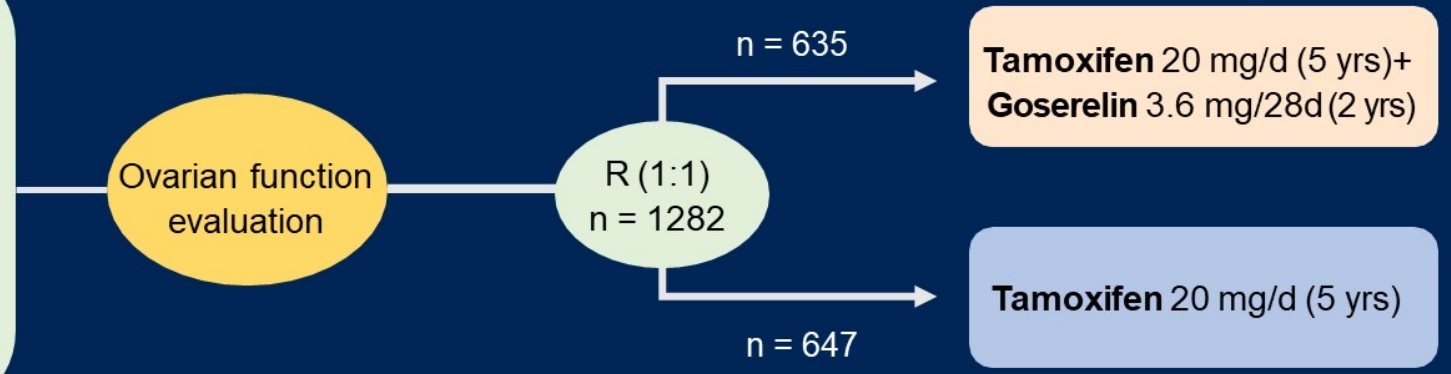
E + OFS vs T + OFS: reductions in distant recurrence 1.9% SOFT 2.4% TEXT at 12 years; OS -0.7% SOFT and + 2.6% TEXT at 12 years

Regan M et al. SABCS 2021;Abstract GS2-05.

ASTRRA study design

Inclusion criteria

- Premenopausal women
- Age ≤ **45** years
- ER+ stage I–III primary breast cancer
- Had been treated with definitive surgery and **chemotherapy**
- WHO performance status of 0–2



Ovarian function evaluation

- Serum FSH level ≥ 30 mIU/mL, menstruation
  - Evaluated every 6 months for 2 years
- Amenorrhea for 2 years
  - Permanent menopause group

    Excluded from the survival analysis

Endpoints

- Primary: Disease Free Survival (DFS)
- Secondary: Overall survival (OS)

Kim HA and Noh WC et al, JCO 2019

PRESENTED BY: Corresponding Author
Hee Jeong Kim MD, PhD
Professor, Asan Medical Center

Baek SY et al. ASCO 2022;Abstract 506.

Comparisons between ASTRRA and SOFT trials

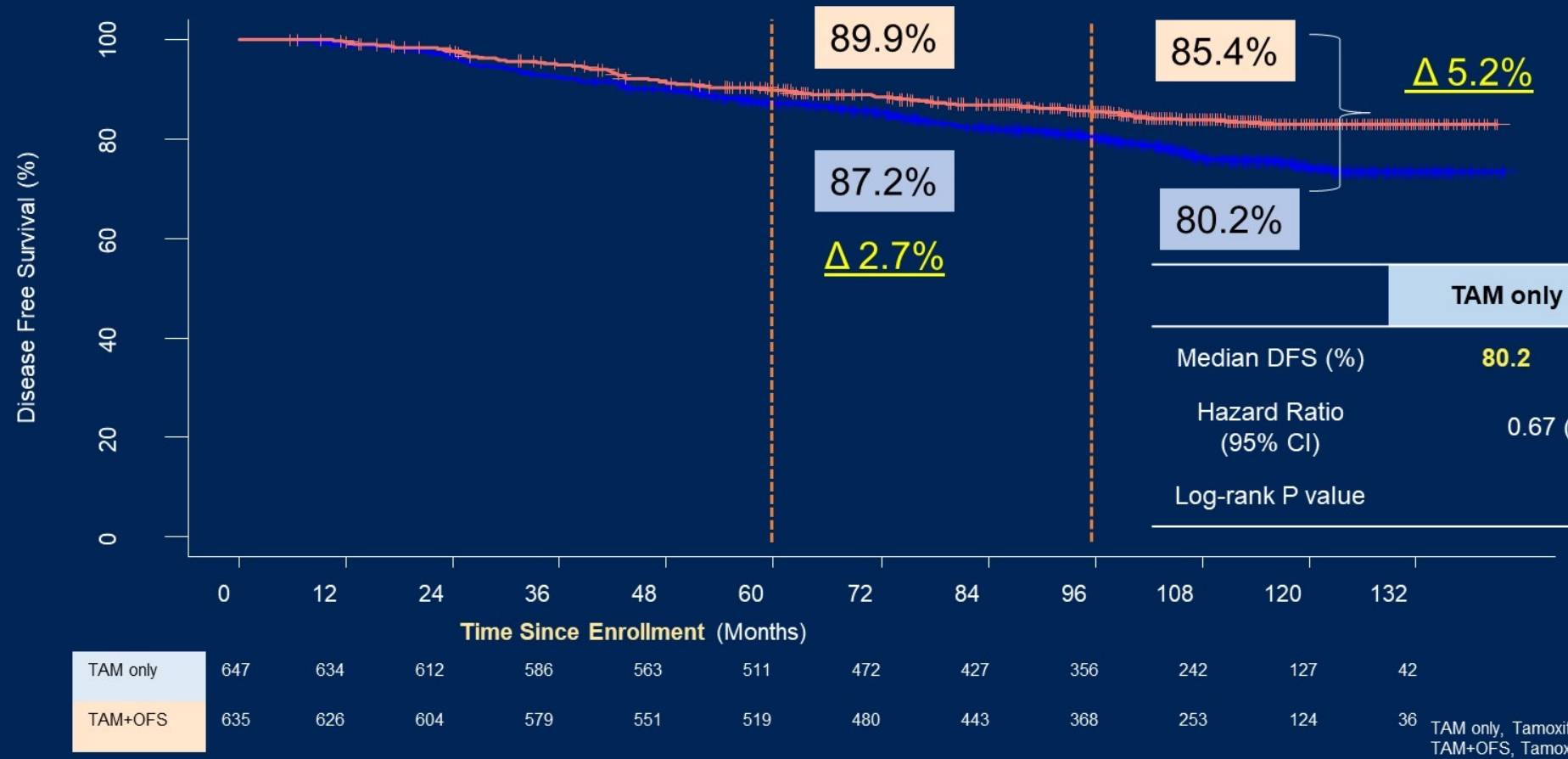
	ASTRRA	SOFT-chemotherapy
Age	45 or less	Premenopausal
Median age	40	40
Lymph node positivity	55%	57%
HER2 over expression	14%	19%
Periods of ovarian function evauation for randomization	2 years	8 month
Treatment durations of OFS	2 years	5 years

SOFT study: The Suppression of Ovarian Function Trial
OFS; Ovarian Function Suppression

Francis PA et al, NEJM 2015
Kim HA and Noh WC et al, JCO 2019

Baek SY et al. ASCO 2022;Abstract 506.

Primary Endpoint – Disease Free Survival



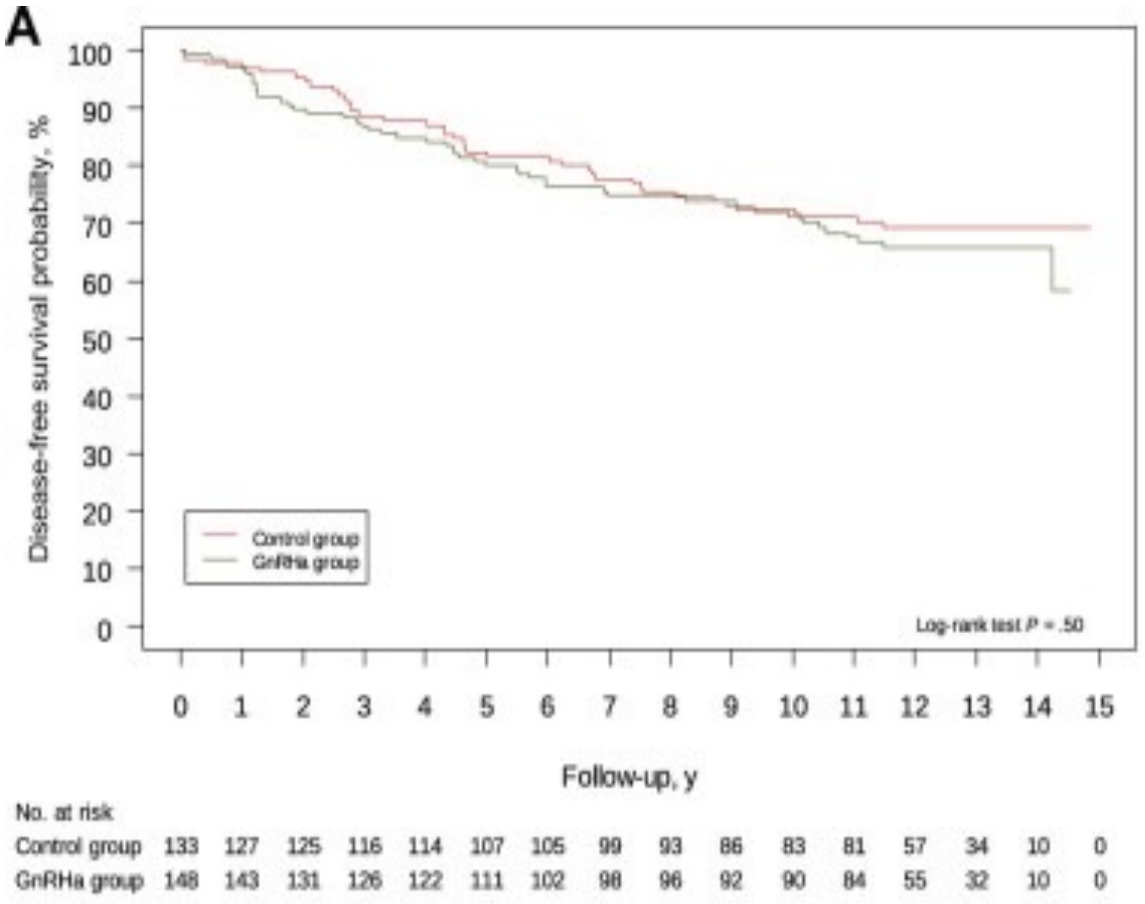
	TAM only	TAM + OFS
Median DFS (%)	80.2	85.4
Hazard Ratio (95% CI)	0.67 (0.514 to 0.869)	
Log-rank P value	0.0027	

TAM only, Tamoxifen only group
TAM+OFS, Tamoxifen plus ovarian function suppression group

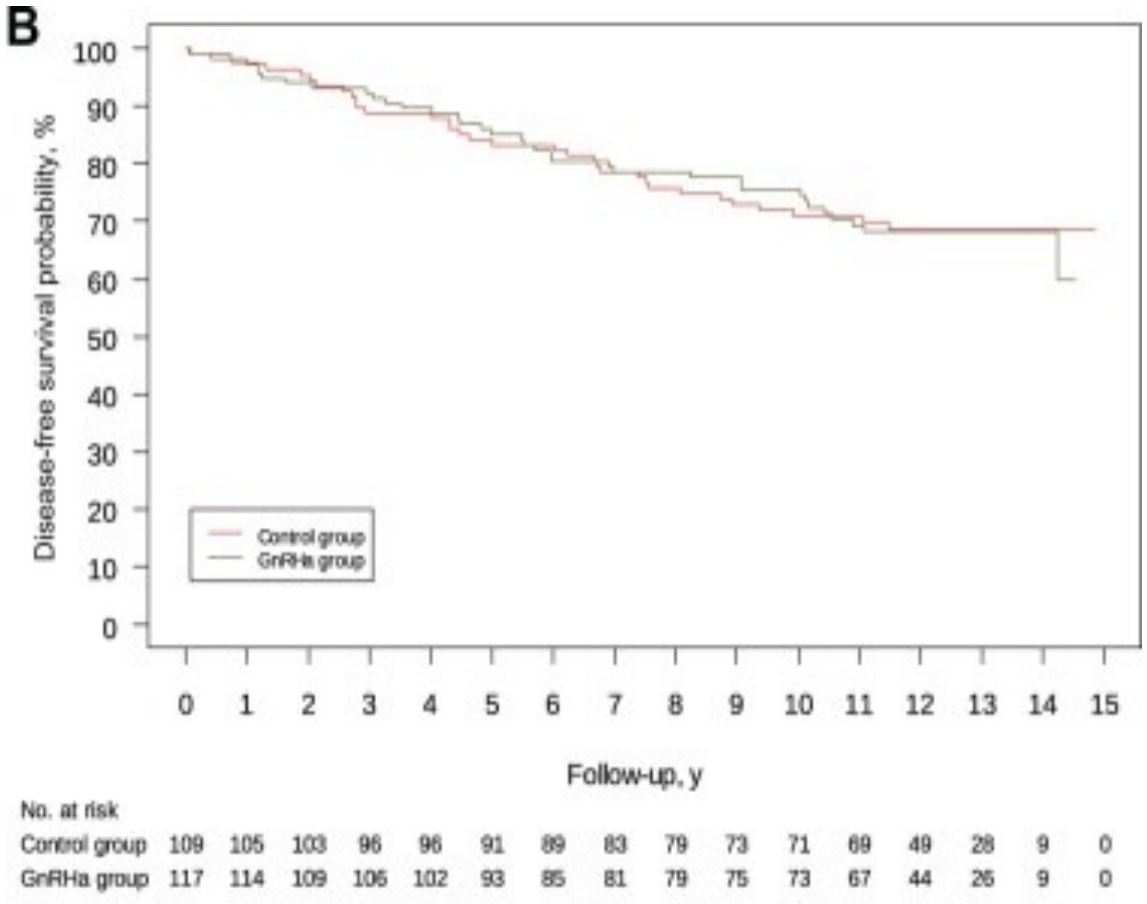
Baek SY et al. ASCO 2022;Abstract 506.

Long Term Safety with OFS During Chemo for Fertility (PROMISE-GIM6)

All Patients



HR+/HER2-



Lambertini et al JNCI 2022

monarchE Study Design (NCT03155997)

HR+, HER2-, node positive high-risk EBC

- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**

- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**

- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:

- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

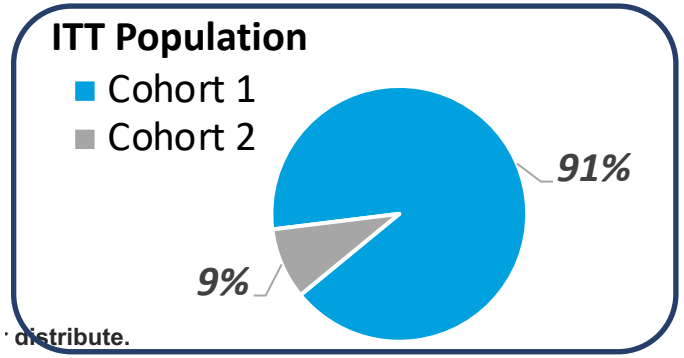
On-study treatment period
2 years

Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

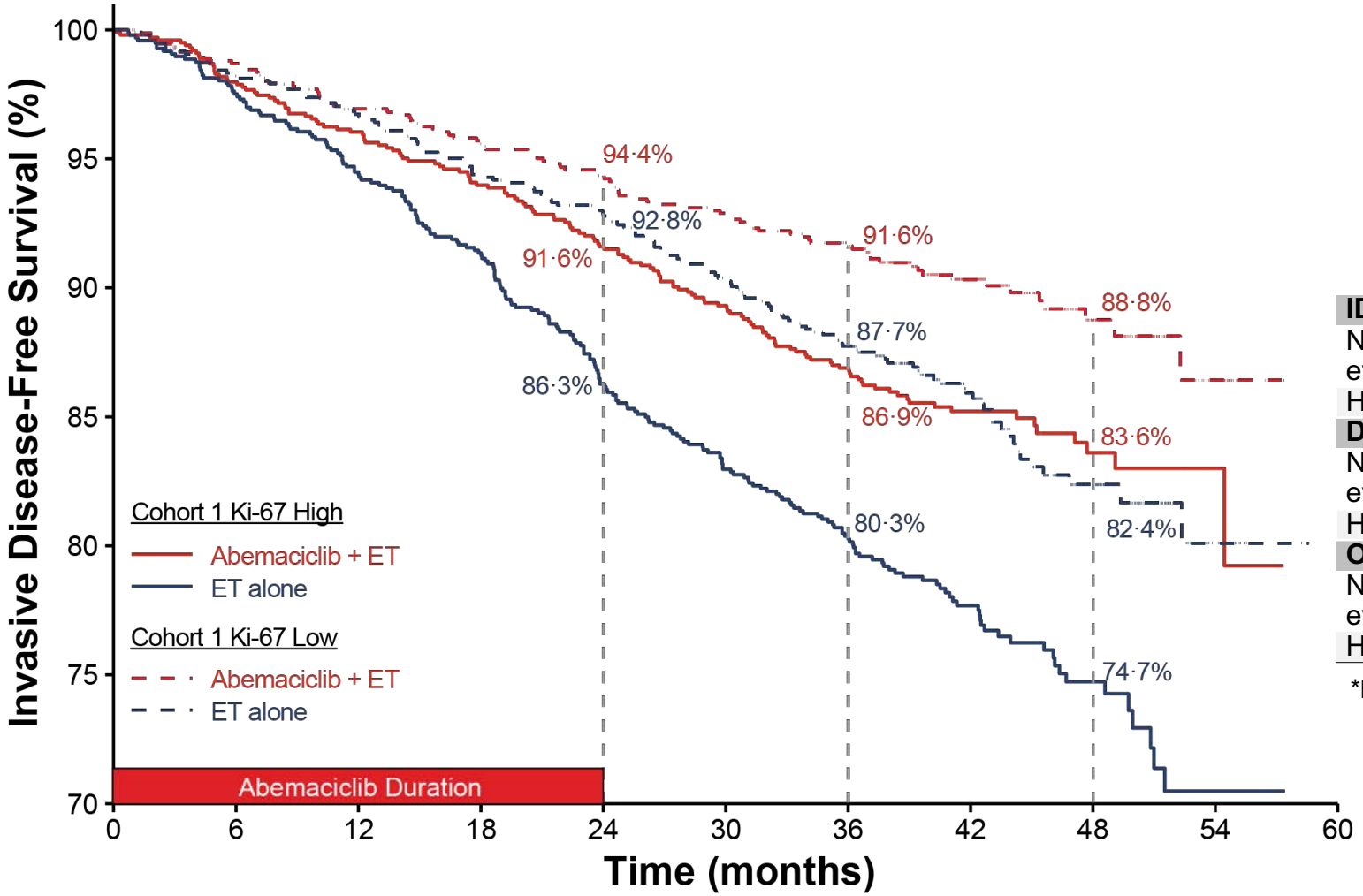
Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO



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

Ki-67 is Prognostic, but Not Predictive of Abemaciclib Benefit



	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=1017	ET alone N=986	Abemaciclib + ET N=946	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of events, n	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

*Ki-67 value was missing in 1203 (23.5%) patients

Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index

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

NATALEE study design[1,2]

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

N = 5101[b]

R 1:1[c]

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

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

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

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl) [abstract TPS597].

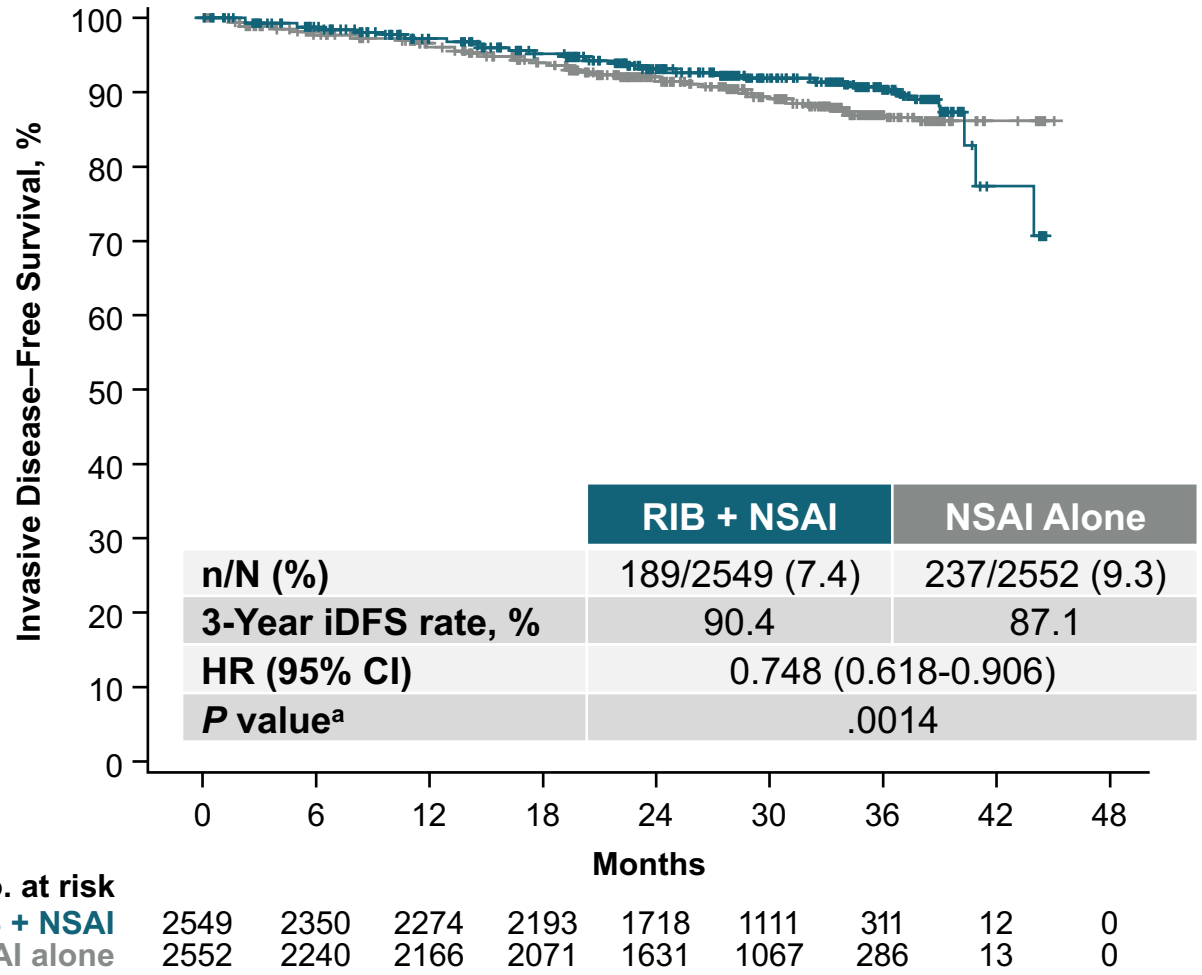
Patient disposition

Median follow-up of 34.0 months (minimum, 21 months)[a]

Parameter, n %	RIB + NSAI n = 2549	NSAI alone n = 2552
Patients treated	2526 (99)	2442 (96)
Patients with treatment ongoing[b]	1984 (78)	1826 (72)
Patients who discontinued NSAI	542 (21)	617 (24)
Primary reason for treatment discontinuation (NSAI)[c]		
Adverse Event	118 (5)	105 (4)
Patient/Physician decision	256 (10)	296 (12)
Disease relapse	142 (6)	186 (7)
Other[d]	13 (0.5)	15 (0.6)
Lost to follow-up	8 (0.3)	12 (0.5)
Death[e]	5 (0.2)	3 (0.1)
Patients who completed ribociclib treatment		
≥2 years (including ongoing)	1449 (57)	-
Completed 3 years RIB	515 (20)	-
Primary reason for early discontinuation of RIB[f]		-
Adverse Event	477 (19)	-

NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Randomization to data cutoff of January 11, 2023. [b] In the RIB + NSAI arm, the treatment is considered ongoing if the patient is continuing either study treatment. [c] All components of treatment are discontinued if NSAI is discontinued. [d] Includes protocol deviations. [e] Causes of death in the RIB + NSAI arm were COVID-19 pneumonia, pulmonary embolism, and traffic accident, and in patients who had previously discontinued RIB but remained on NSAI, the causes of death were cardiac arrest and brain edema; for patients in the NSAI alone arm, the causes of death were myocardial infraction, sepsis, and unknown. [f] RIB could be discontinued early due to AEs, all other reasons for discontinuations would require both components be discontinued and are captured above.

Ribociclib achieved highly significant iDFS benefit



	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

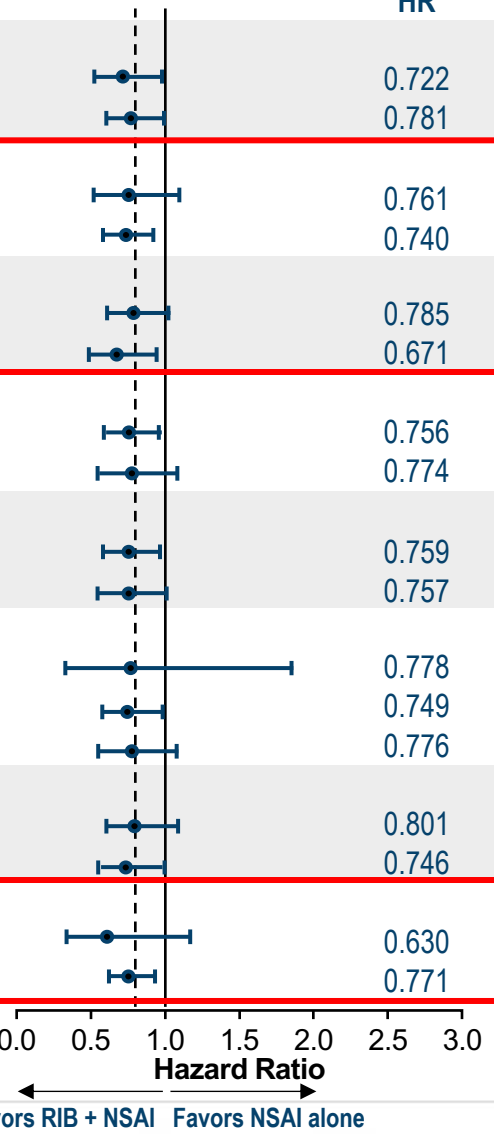
No. at risk									
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

- Median follow-up for iDFS was 27.7 months
- Based on the *P* value of 0.0014, the IDMC concluded that the results met the criteria to demonstrate statistically significant and clinically superior efficacy
- Absolute iDFS benefit with RIB + NSAI at 3 years was 3.3%
- Risk of invasive disease was reduced by 25.2% with RIB + NSAI vs NSAI alone
- Ongoing patients will remain on treatment and follow-up will continue as prespecified

iDFS, invasive disease–free survival; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value.

iDFS benefit was consistent across prespecified key subgroups

Subgroup	RIB + NSAI n = 2549	NSAI Alone n = 2552	HR	(95% CI)
Menopausal status				
Men and premenopausal women	71/1126	93/1132	0.722	(0.530-0.983)
Postmenopausal women	118/1423	144/1420	0.781	(0.613-0.997)
AJCC stage				
Stage II	49/1011	65/1034	0.761	(0.525-1.103)
Stage III	140/1528	172/1512	0.740	(0.592-0.925)
Prior CT				
Neoadjuvant	111/1085	132/1095	0.785	(0.610-1.011)
Adjuvant	63/1223	89/1220	0.671	(0.486-0.927)
Prior ET				
Yes	127/1824	157/1801	0.756	(0.598-0.955)
No	62/725	80/751	0.774	(0.556-1.079)
Region				
North America/Western Europe/Oceania	111/1563	139/1565	0.759	(0.591-0.974)
Rest of world	78/986	98/987	0.757	(0.562-1.019)
Histological grade at time of surgery				
Grade 1	9/213	12/217	0.778	(0.328-1.846)
Grade 2	102/1460	125/1432	0.749	(0.577-0.973)
Grade 3	61/684	78/702	0.776	(0.555-1.085)
Ki-67 status[a]				
Ki-67 ≤ 20%	76/1199	95/1236	0.801	(0.593-1.083)
Ki-67 > 20%	82/920	105/938	0.746	(0.559-0.996)
Nodal status[b,c]				
N0	16/285	28/328	0.630	(0.341-1.165)
N1-N3	173/2261	208/2219	0.771	(0.630-0.944)

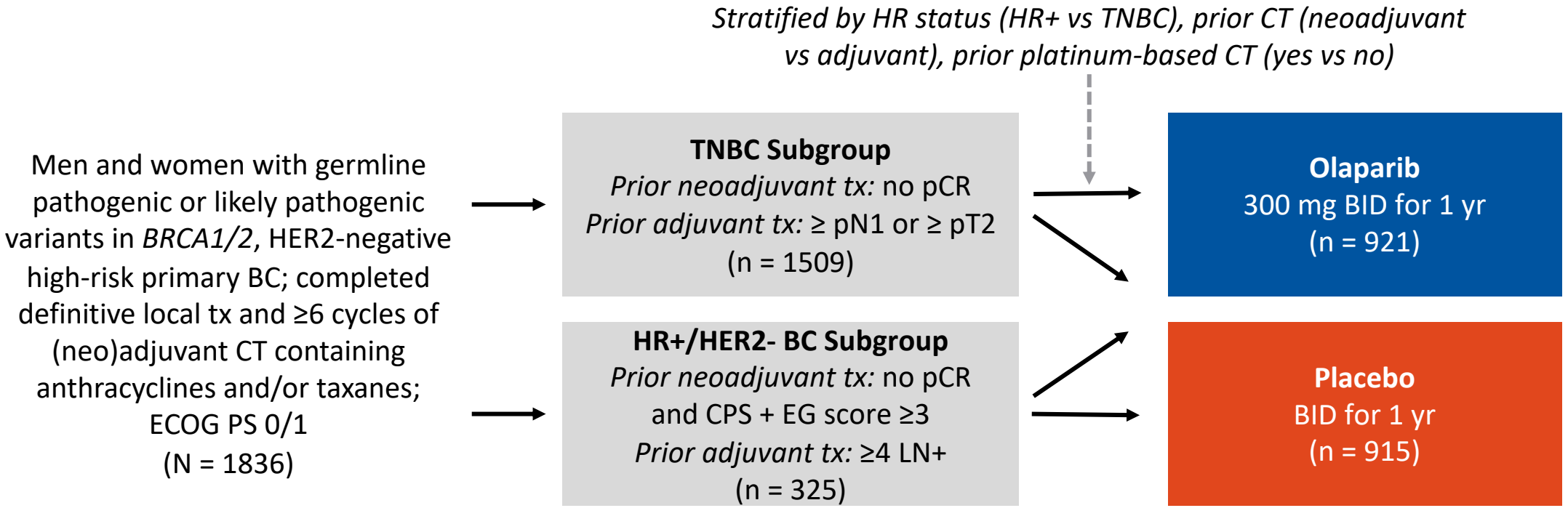


AJCC, American Joint Committee on Cancer; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

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

OlympiA: Adjuvant Olaparib for Germline *BRCA1/2*-Mutated HER2- Early Breast Cancer

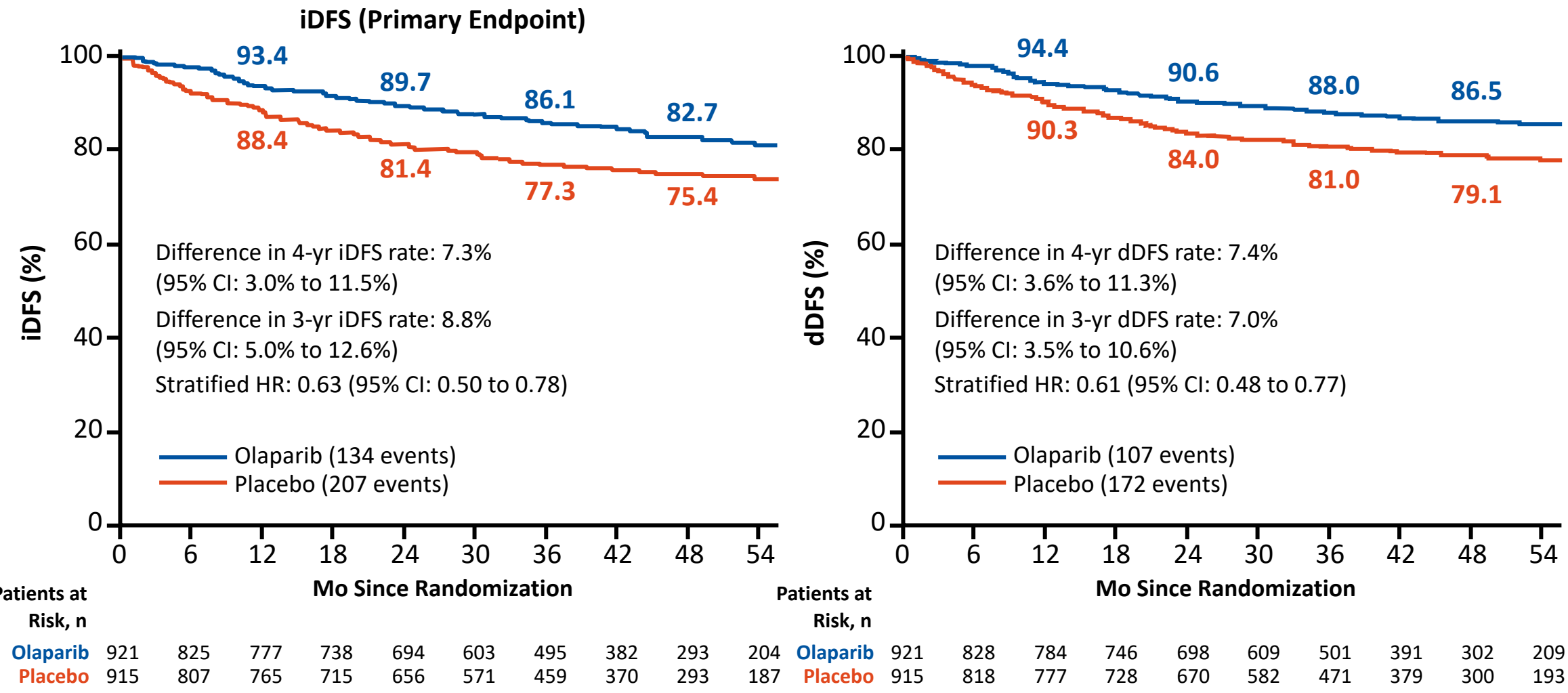
- Randomized, double-blind phase III trial



- Primary endpoint: invasive DFS
- Secondary endpoints: OS, distant DFS, incidence of new cancers, QoL

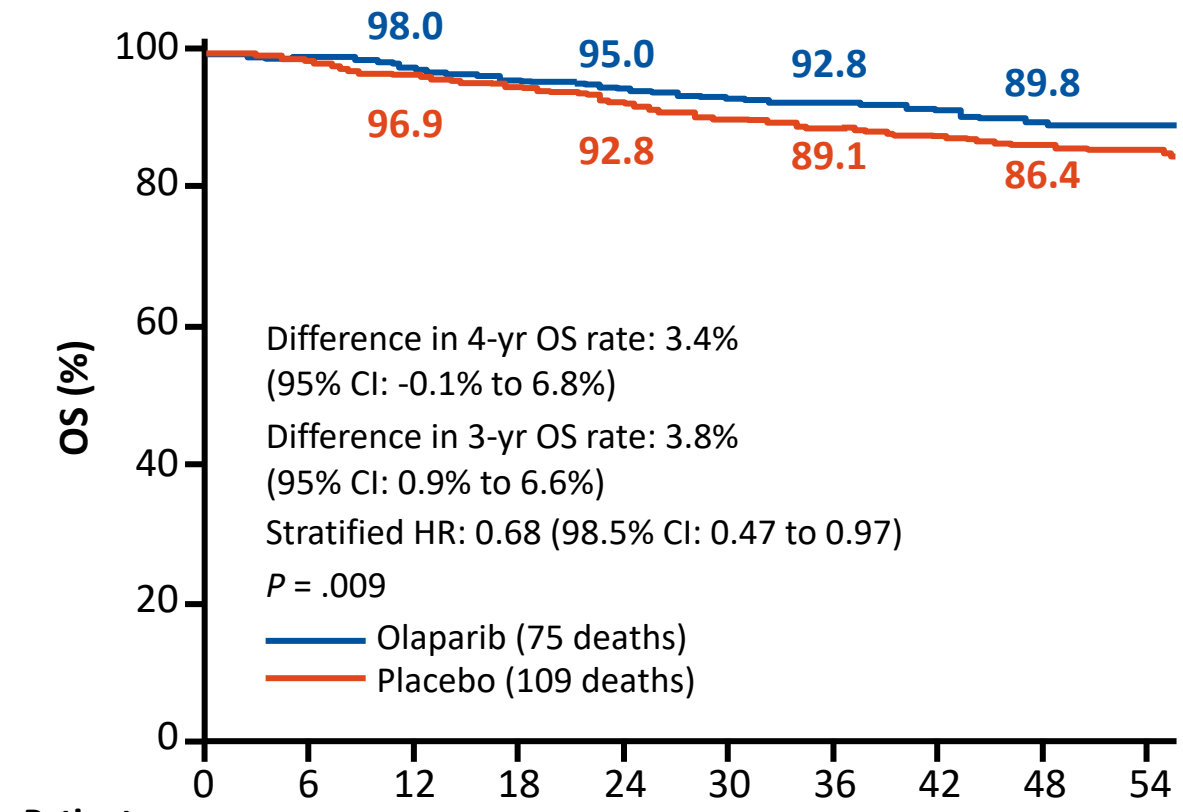
Tutt. NEJM. 2021;384:2394. Geyer CE et al. Ann Oncol.2022;33:1250.

OlympiA: Second Interim Analysis of iDFS and dDFS



Median follow-up: 3.5 yr

OlympiA: Second Interim Analysis of OS



Median follow-up: 3.5 yr

Geyer CE et al. Ann Oncol 2022;33:1250.

Agenda

Module 1: Long-Term Management of HER2-Positive Breast Cancer — Dr Krop

Module 2: Optimizing the Management of ER-Positive Localized Breast Cancer — Dr Kalinsky

Module 3: Considerations in the Care of Patients with ER-Positive mBC — Dr Jhaveri

Module 4: Novel and Emerging Strategies for ER-Positive mBC — Dr Rugo

Module 5: Evolving Clinical Decision-Making for Localized Triple-Negative Breast Cancer (TNBC) — Dr O'Shaughnessy

Module 6: Recent Advances in the Treatment of Metastatic TNBC (mTNBC) — Prof Schmid

Preference of CDK4/6 inhibitor in the metastatic setting

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

RTP
RESEARCH
TO PRACTICE

In general, which CDK4/6 inhibitor do you recommend in combination with endocrine therapy as first-line treatment for <u>postmenopausal</u> women with ER-positive, HER2-negative mBC?

 Dr Jhaveri	Ribociclib	 Prof Schmid	Ribociclib
 Dr Kalinsky	Ribociclib	 Dr Hurvitz	Ribociclib
 Dr Krop	Ribociclib	 Dr Tolaney	Ribociclib
 Dr O'Shaughnessy	Ribociclib	 Dr Traina	Ribociclib
 Dr Rugo	No preference		

In general, which CDK4/6 inhibitor do you recommend in combination with endocrine therapy as first-line treatment for premenopausal women with ER-positive, HER2-negative mBC?

 Dr Jhaveri	Ribociclib	 Prof Schmid	Ribociclib
 Dr Kalinsky	Ribociclib	 Dr Hurvitz	Ribociclib
 Dr Krop	Ribociclib	 Dr Tolaney	Ribociclib
 Dr O'Shaughnessy	Ribociclib	 Dr Traina	Ribociclib
 Dr Rugo	Ribociclib		

RTP RESEARCH TO PRACTICE

Sequencing of trastuzumab deruxtecan in ER-positive, HER2-low metastatic breast cancer

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

RTP
RESEARCH
TO PRACTICE

A woman who has completed 5 years of an adjuvant aromatase inhibitor for ER-positive, HER2 IHC 2+, FISH-negative BC develops asymptomatic, low-volume, nonvisceral metastases 3 years later. Regulatory and reimbursement issues aside, when would you most likely offer trastuzumab deruxtecan?

 Dr Jhaveri	After 1 line of chemotherapy	 Prof Schmid	After 1 line of chemotherapy
 Dr Kalinsky	After 1 line of chemotherapy	 Dr Hurvitz	After 1 line of chemotherapy
 Dr Krop	After 1 line of chemotherapy	 Dr Tolaney	After 1 line of chemotherapy
 Dr O'Shaughnessy	After 1 line of chemotherapy or after 2 lines of endocrine therapy	 Dr Traina	After 1 line of chemotherapy
 Dr Rugo	After 1 line of chemotherapy		

Considerations in the Care of Patients with ER-Positive mBC

Komal Jhaveri, MD, FACP
Associate Attending, Breast Medicine and Early Drug Development Service
Section Head, Endocrine Therapy Research Program
Clinical Director, Early Drug Development Service
Memorial Sloan Kettering Cancer Center

Associate Professor
Weill Cornell Medical College
New York, New York

Memorial Sloan Kettering Cancer Center

PFS in 1st and 2nd Line Treatment With CDK4/6 Inhibitors + ET

	1st LINE TREATMENT				≥ 2nd LINE TREATMENT		1st AND 2nd LINE TREATMENT
	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7	PALOMA-3	MONARCH-2	MONALEESA-3
Endocrine partner	Letrozole	Letrozole	Letrozole	Letrozole (or Tamoxifen) + LHRH agonist	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 Inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
Patients on study, n	666	668	493	672	521	669	726
Primary Endpoint = PFS (CDK4/6 inhibitor + ET vs. ET)							
HR	0.58	0.56	0.54	0.55	0.46	0.55	0.59
Median PFS, months	27.6 vs 14.5 (13.1 mo)	25.3 vs 16 (9.3 mo)	28.2 vs 14.8 (13.4 mo)	23.8 vs 13 (10.8 mo)	9.5 vs 4.6 (4.9 mo)	16.4 vs 9.3 (7.1 mo)	20.5 vs 12.8 (7.7 mo)
Secondary Endpoint = OS (CDK4/6 inhibitor + ET vs. ET)							
HR	0.956	0.76	0.754	0.76	0.81	0.78	0.75
Median OS, months	53.9 vs 51.2	63.9 vs 51.4	67.1 vs 54.5*	58.7 vs 40.9	34.9 vs 28.0	45.8 vs 37.25	52.2 vs 41.5

*** IA2**

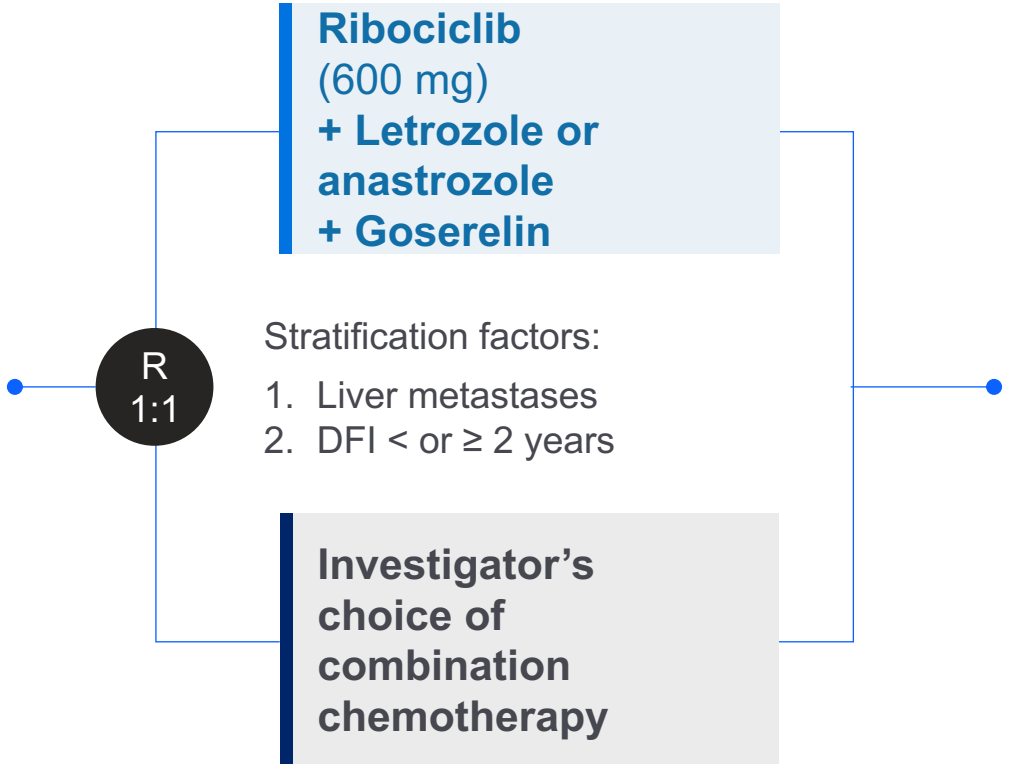
Cristofanilli et al, Lancet Oncology 2016; Finn et al, NEJM 2016; Hortobagyi et al, NEJM 2016; Tripathy et al, Lancet 2018; Sledge et al, JCO 2017; Goetz et al, ESMO 2022; Slamon et al, JCO 2018; Turner et al NEJM 2018; Sledge GW et al - JAMA Oncol. 2019; Slamon DJ, et al NEJM. Feb 2020; Rugo HS et al., Brain Cancer Res Treat. 2019; Finn et al ASCO2022, Neven et al ESMO Breast 2022 , Sledge et al SABCS 2022

Ribociclib + ET vs Chemotherapy in HR+/HER2− Advanced BC *RIGHT Choice*

Phase 2 study of ribociclib + goserelin with hormonal therapy vs physician choice chemotherapy in HR+/HER2− inoperable locally advanced or mBC

Eligibility criteria

- Pre/perimenopausal women
- HR+, HER2− ABC
- No prior systemic therapy for ABC
- Aggressive disease
  - Symptomatic visceral metastases
  - Rapid PD or impending visual compromise
  - Non-visceral disease
- ECOG PS ≤ 2
- Total bilirubin ≤ 1.5 ULN
- N = 222



Primary endpoint

- PFS

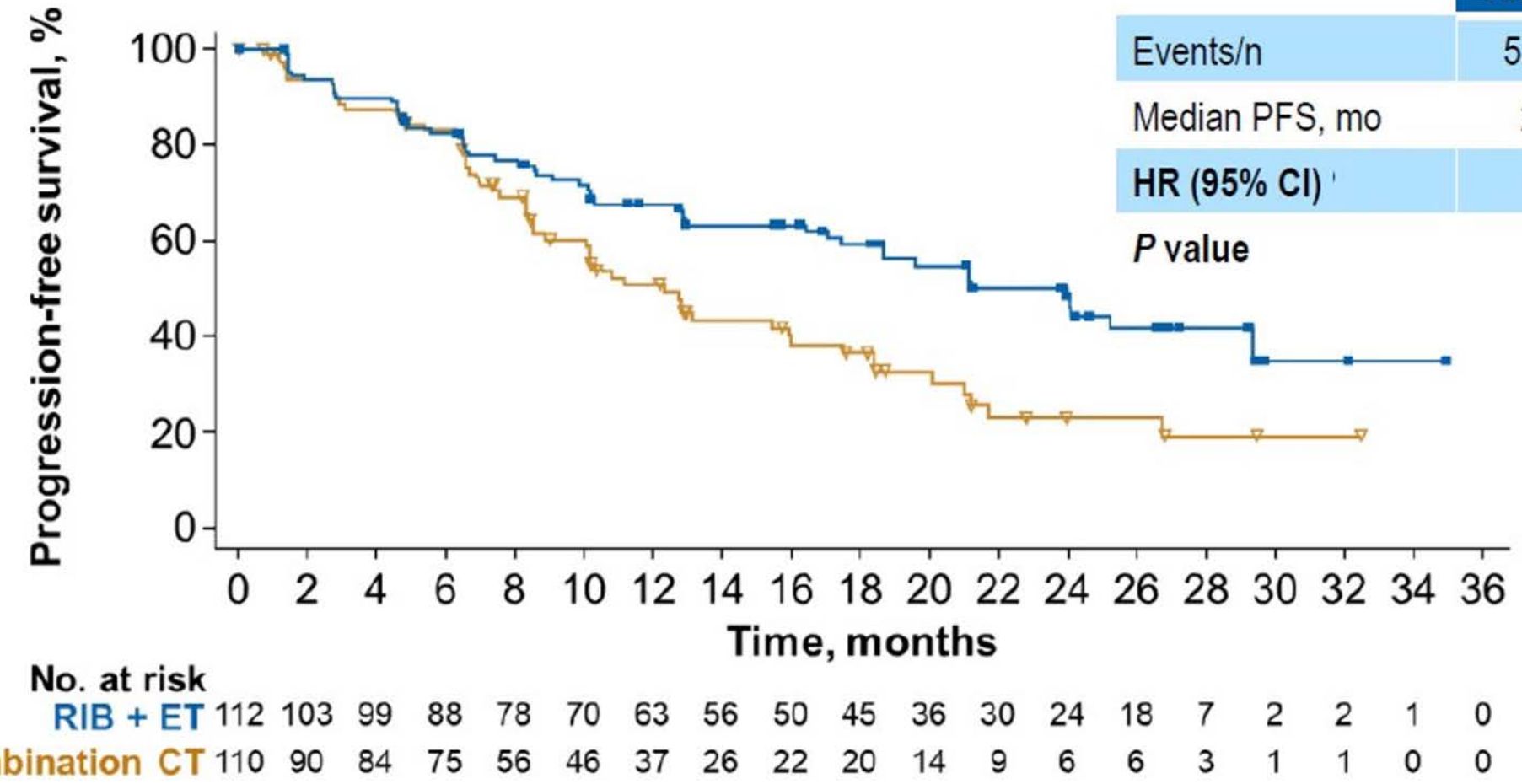
Secondary endpoints

- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

QOL, quality of life; TFR, treatment failure rate; TTF, time to treatment failure; ULN, upper limit of normal.

Lu Y-S, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS1-10.

RIGHT Choice
PFS

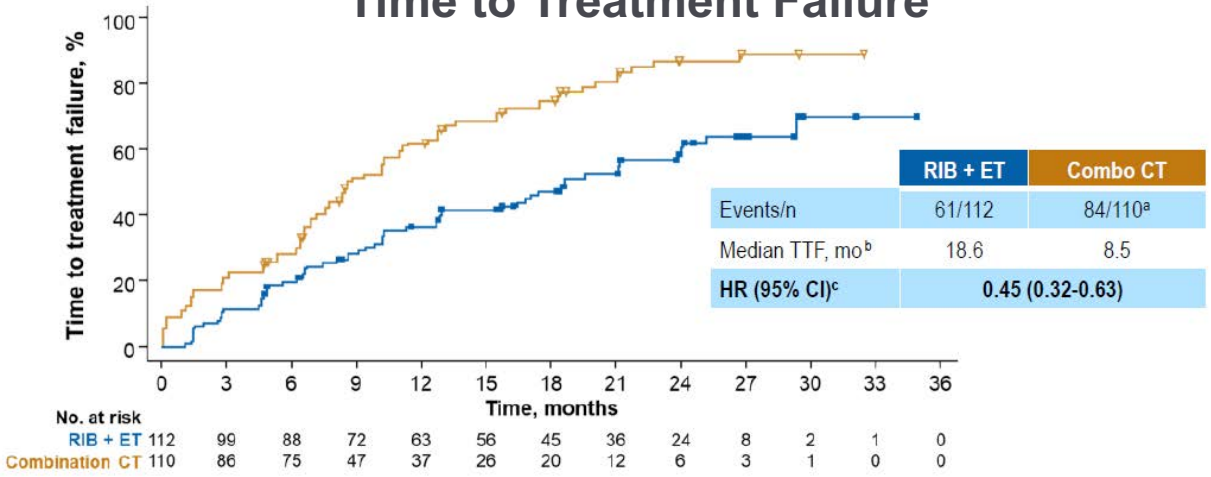


	RIB + ET	Combo CT
Events/n	52/112	58/110
Median PFS, mo	24.0	12.3
HR (95% CI)	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

Lu Y-S, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS1-10.

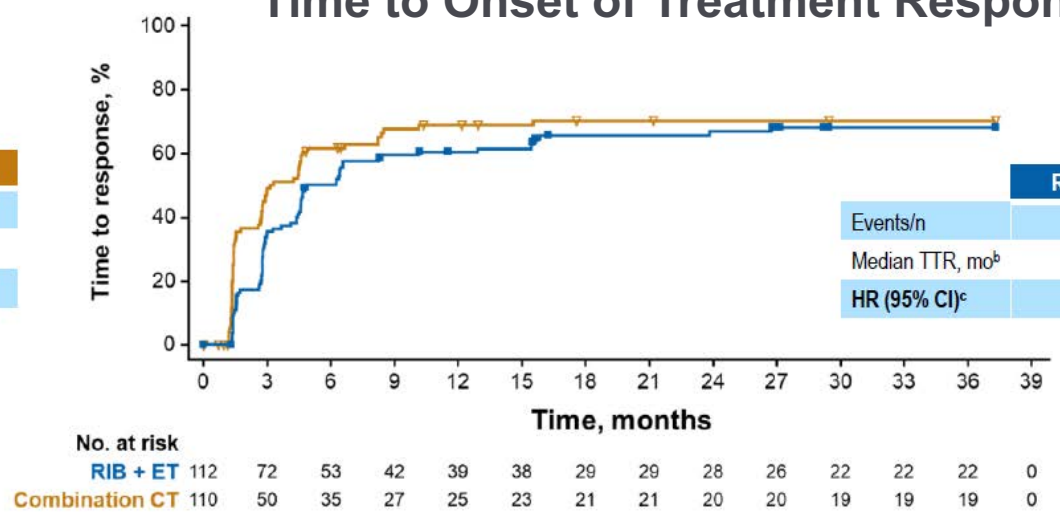
RIGHT Choice
TTF and Response

Time to Treatment Failure



	RIB + ET	Combo CT
Events/n	61/112	84/110[a]
Median TTF, mo[b]	18.6	8.5
HR (95% CI)[c]	0.45 (0.32-0.63)	

Time to Onset of Treatment Response



	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	0.78 (0.56-1.09)	

Dose Reductions

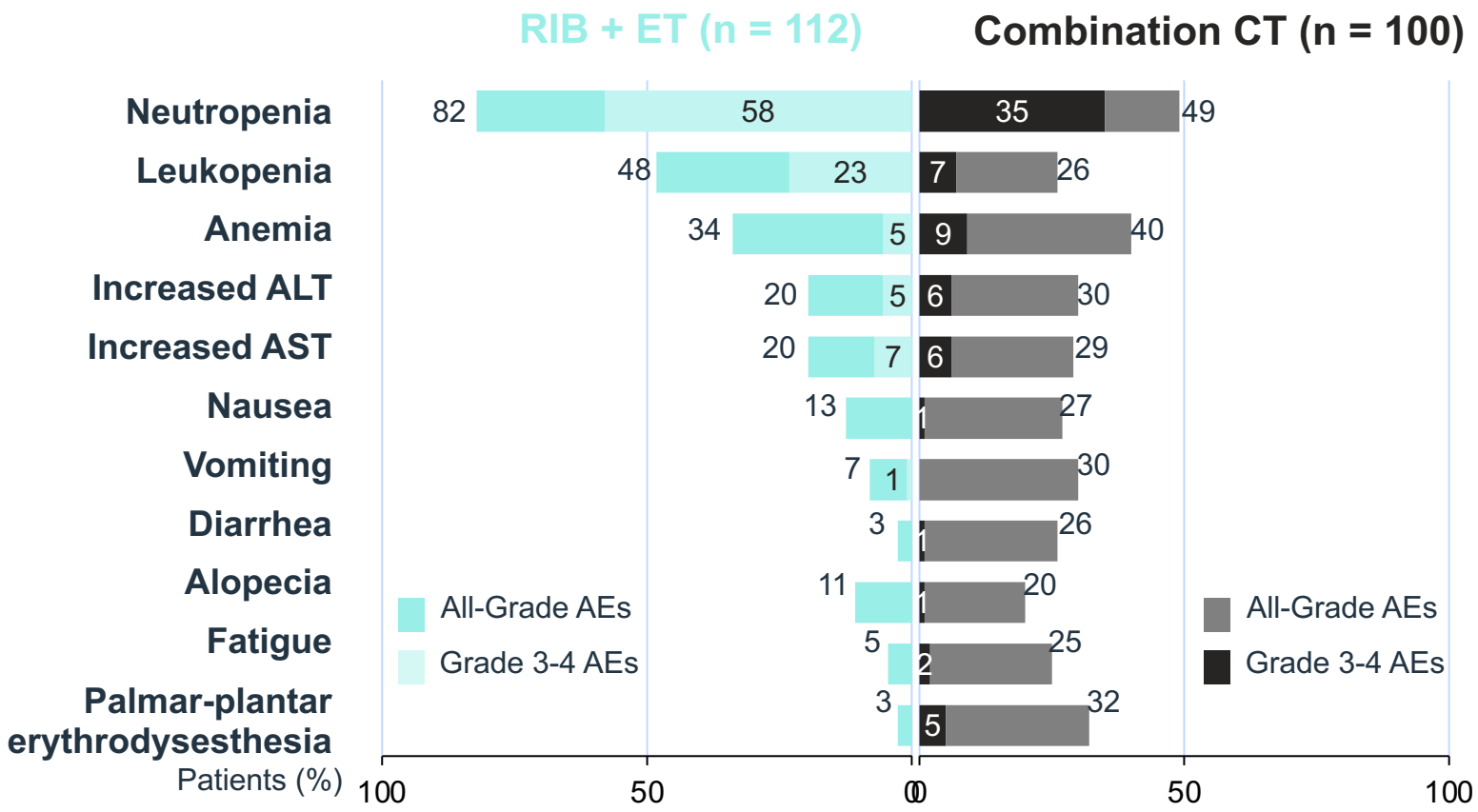
Parameter, n (%)	Ribociclib + ET (n = 112)	Combination CT (n = 100)
0	81 (72.3)	54 (54.0)
1	27 (24.1)	12 (12.0)
2	4 (3.6)	14 (14.0)
≥ 3	0	20 (20.0)

	Ribociclib + ET (n = 112)	Combination CT (n = 100)
ORR, %	65.2	60.0
CBR, %	80.4	72.7

Lu Y-S, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS1-10.

RIGHT Choice
Safety

AEs Irrespective of Causality



2 patients in ribociclib arm showed grade ≥ 3 QT prolongation

All-grade treatment-related serious AEs
- RIB + ET: 2/112
- Combo chemo: 8/100

All-grade serious AEs leading to discontinuation
- RIB + ET: 8/112
- Combo chemo: 23/100

Lu Y-S, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS1-10.

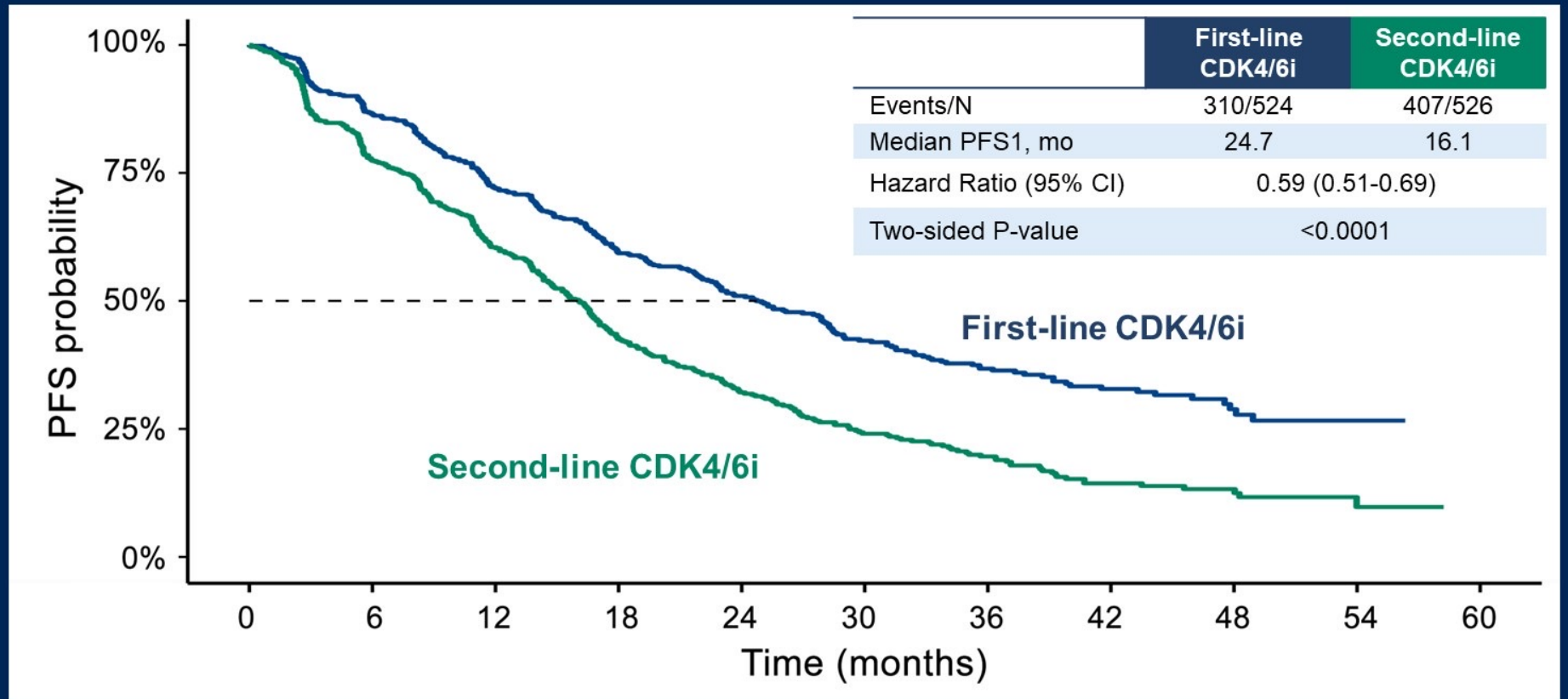
2023 ASCO ANNUAL MEETING

Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03)

Gabe Sonke, Annemiek van Ommen - Nijhof, Noor Wortelboer, Vincent van der Noort, Astrid Swinkels, Hedwig Blommestein, Aart Beeker, Karin Beelen, Lisanne Hamming, Joan Heijns, Aafke Honkoop, Paul de Jong, Quirine van Rossum - Schornagel, Christa van Schaik - van de Mheen, Jolien Tol, Cathrien Tromp - van Driel, Suzan Vrijaldenhoven, Elise van Leeuwen - Stok, Inge Konings, Agnes Jager

PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD

PFS1 analysis

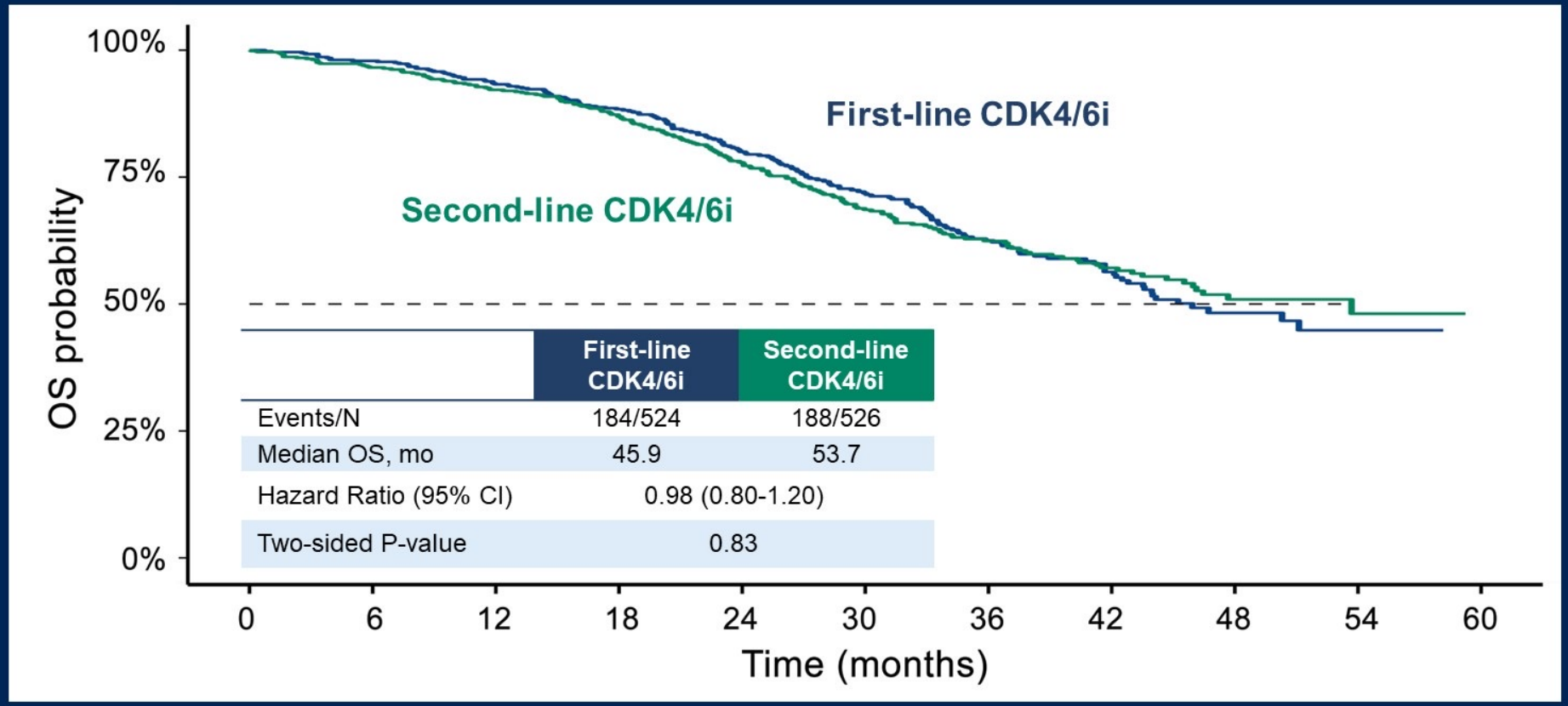


	First-line CDK4/6i	Second-line CDK4/6i
Events/N	310/524	407/526
Median PFS1, mo	24.7	16.1
Hazard Ratio (95% CI)	0.59 (0.51-0.69)	
Two-sided P-value	<0.0001	

First-line	524 (0)	451 (3)	374 (4)	285 (30)	202 (76)	137 (110)	101 (129)	63 (158)	27 (189)	4 (210)	0 (210)
Second-line	526 (0)	406 (2)	315 (4)	203 (25)	128 (54)	84 (68)	57 (81)	31 (93)	17 (105)	5 (114)	0 (119)

Numbers at risk (censored)

Overall survival analysis

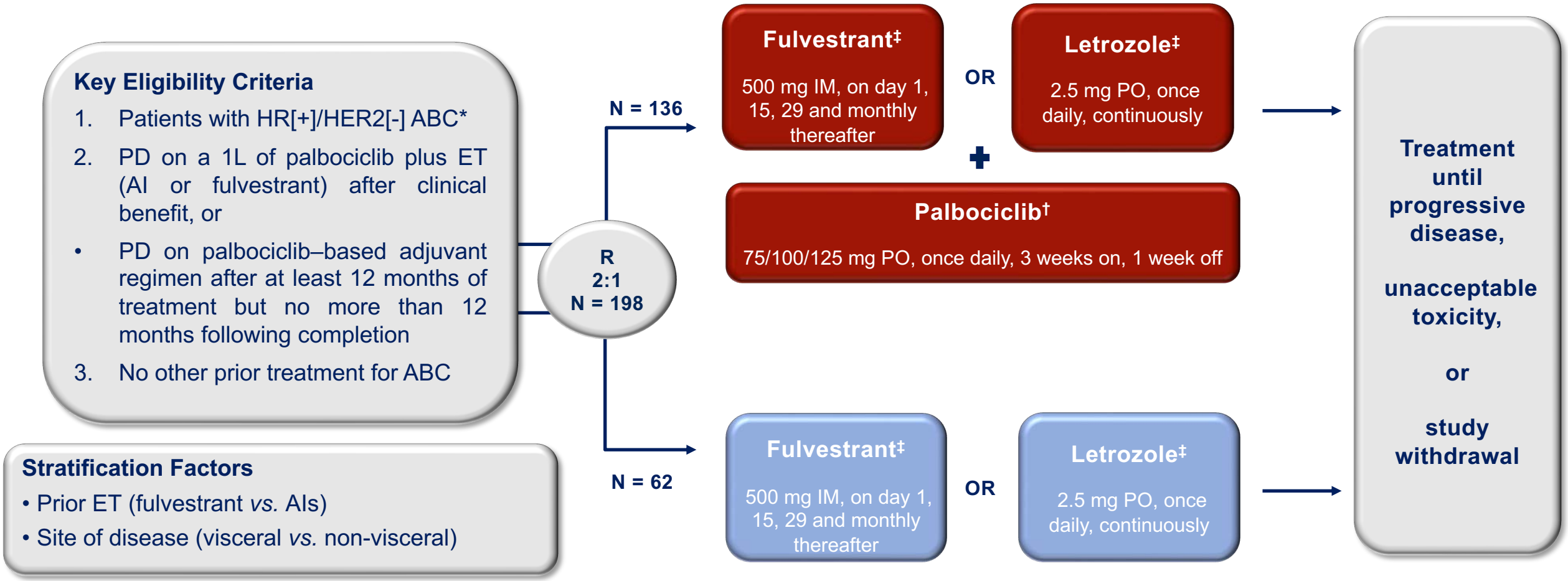


	First-line CDK4/6i	Second-line CDK4/6i
Events/N	184/524	188/526
Median OS, mo	45.9	53.7
Hazard Ratio (95% CI)	0.98 (0.80-1.20)	
Two-sided P-value	0.83	

First-line	524 (0)	510 (3)	485 (4)	427 (37)	324 (103)	240 (157)	171 (197)	104 (250)	42 (300)	7 (333)	0 (340)
Second-line	526 (0)	506 (2)	483 (2)	426 (32)	328 (89)	242 (139)	175 (186)	112 (236)	52 (287)	16 (322)	0 (338)

Numbers at risk (censored)

PALMIRA Study Design (NCT03809988)



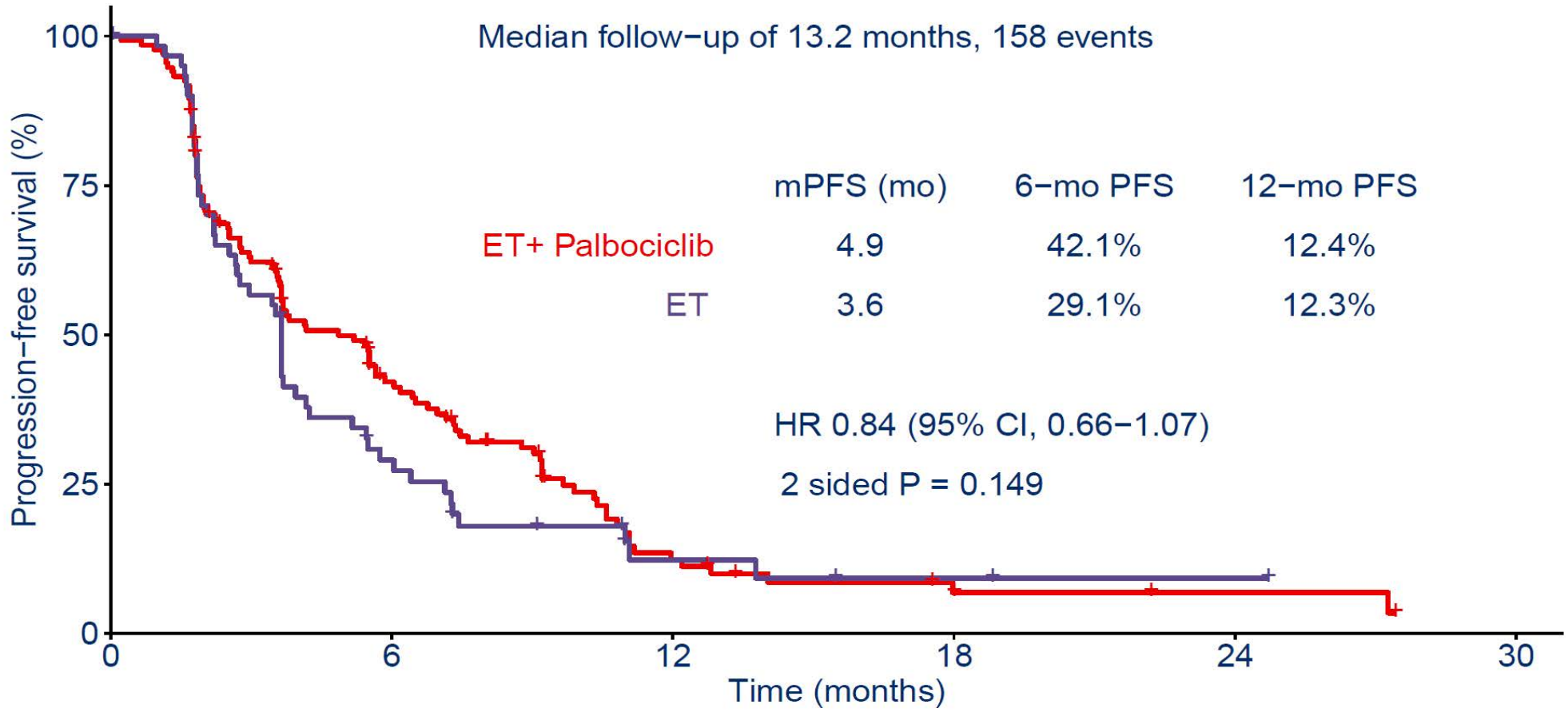
1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; ET: Endocrine therapy; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; IM: Intramuscular injection; PO: oral administration; PD: Progressive disease; R: Randomization.

*If pre-menopausal, ovarian function suppression method required.

†Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.

‡Administration of endocrine therapy was chosen depending on the prior administered agent.

Primary Objective: Investigator-assessed PFS (ITT Population)

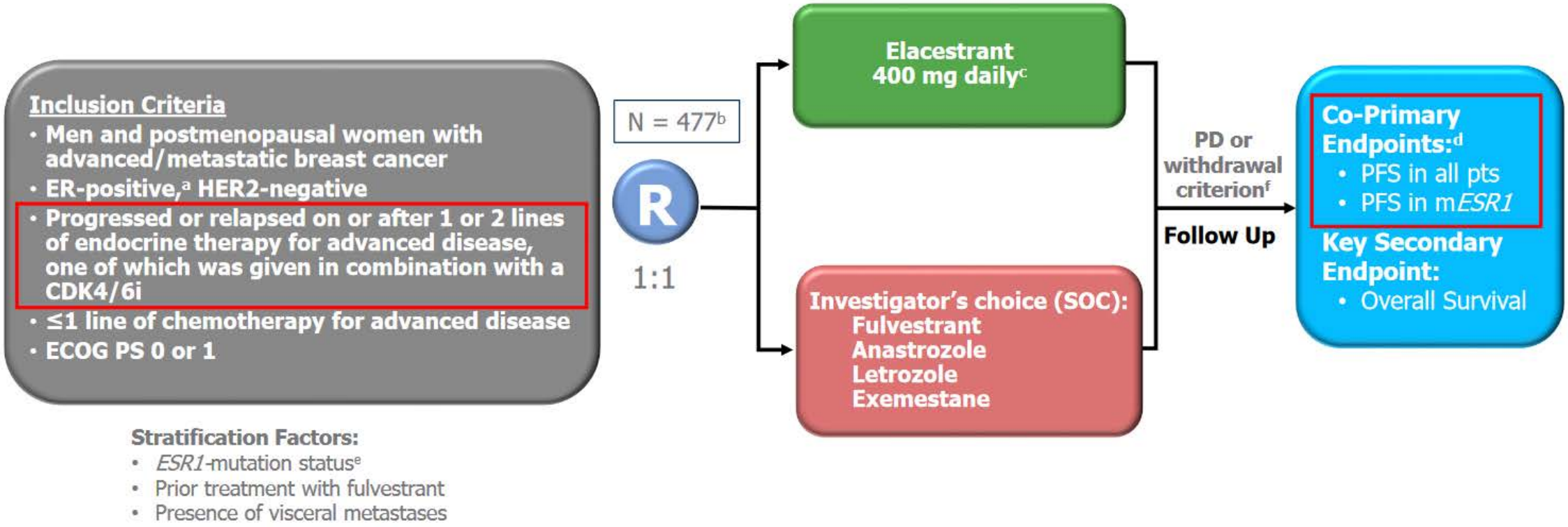


Patients at risk, n (%)

ET+Palbociclib	136 (100)	47 (35)	11 (8)	4 (3)	2 (1)	0 (0)
ET	62 (100)	16 (26)	4 (6)	2 (3)	1 (2)	0 (0)

CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

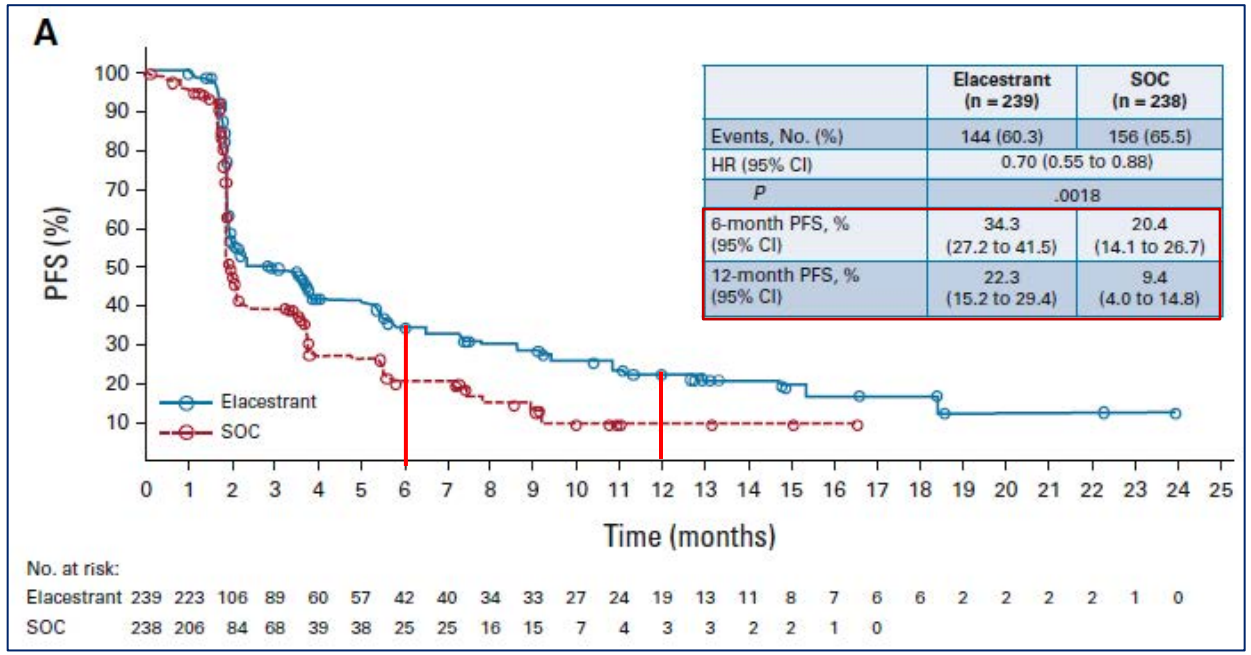
EMERALD:
Phase 3 Trial of Elacestrant vs ET in Post CDK4/6i Setting



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

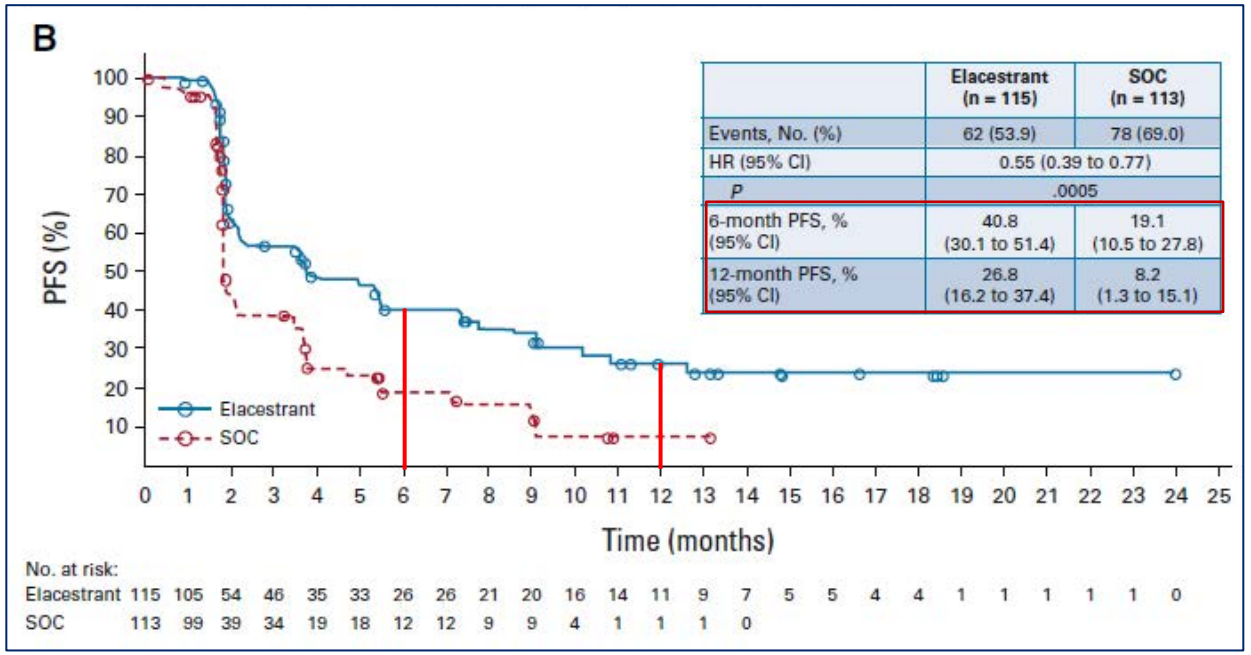
EMERALD Results: Elacestrant vs SOC
PFS Rate at 6 and 12 Months

All Patients



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

Patients with Tumors Harboring *mESR1*



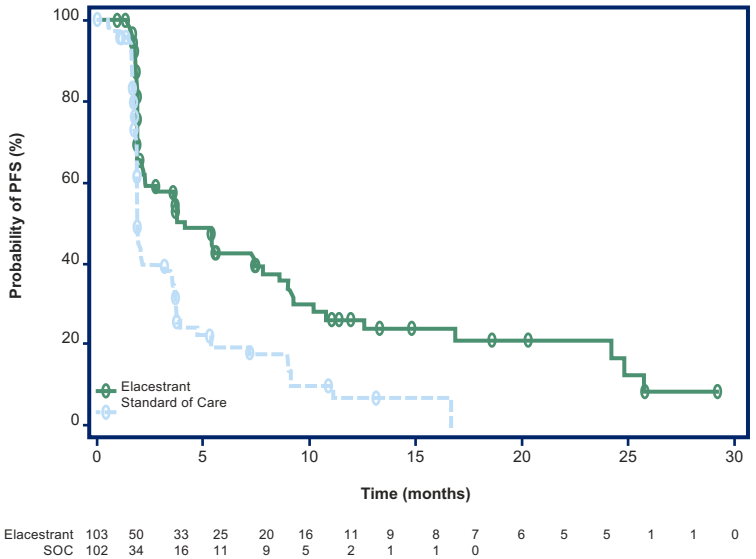
	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

Elacestrant demonstrated improved PFS versus SOC ET in patients with ER+/HER2- advanced/metastatic breast cancer following prior CDK4/6i therapy, particularly in *mESR1* cohort

Bidard FC et al. *J Clin Oncol*. 2022;JCO2200338.

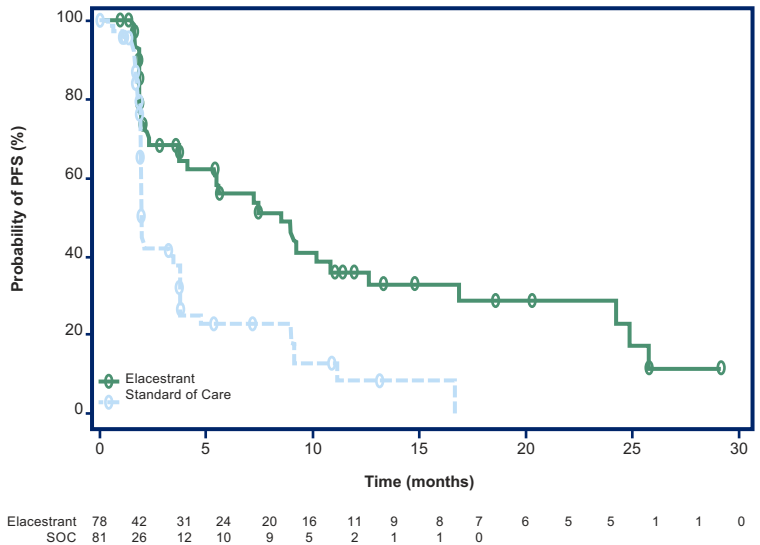
EMERALD Results: Elacestrant vs SOC
PFS by Duration of CDK4/6i in *mESR1* Cohort

≥ 6 Months CDK4/6i



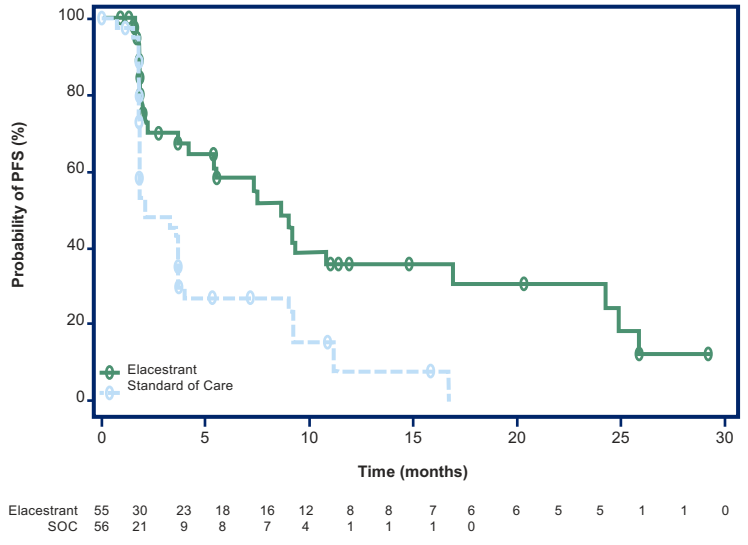
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

≥ 12 Months CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

≥ 18 Months CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

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

EMERALD: Elacestrant
Safety

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

AEs:

- Most AEs were grade 1 or 2
- Low-grade nausea was common in both treatment arms
- No grade 4 TRAEs

Treatment discontinuation:

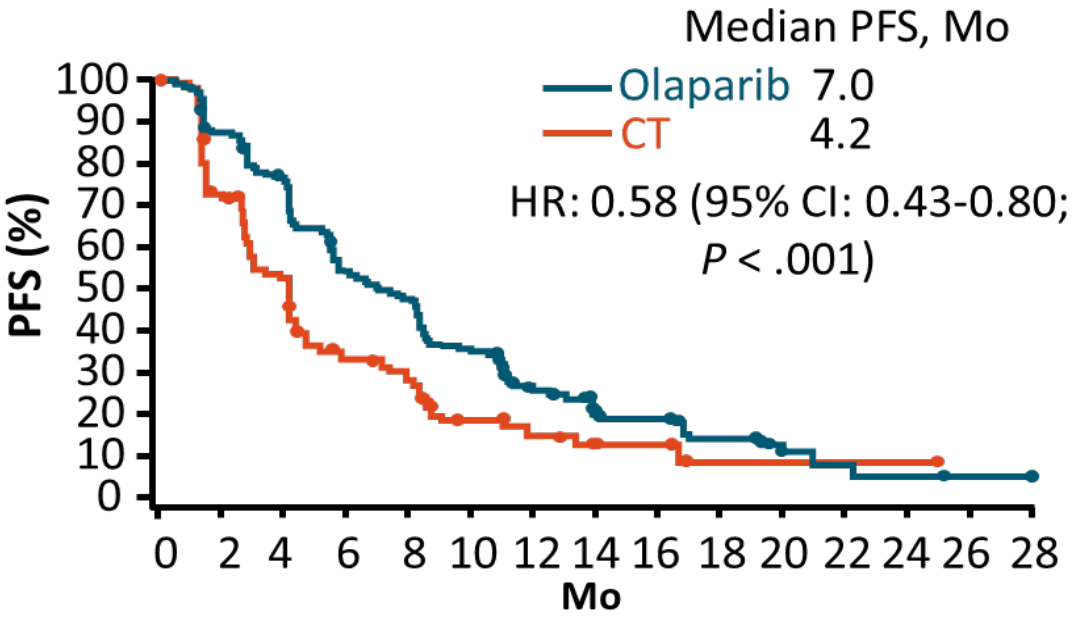
- Elacestrant: 3.4%
- SOC: 0.9%
- No hematologic safety signal was observed
- No incidence of bradycardia

Bardia A, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-01.

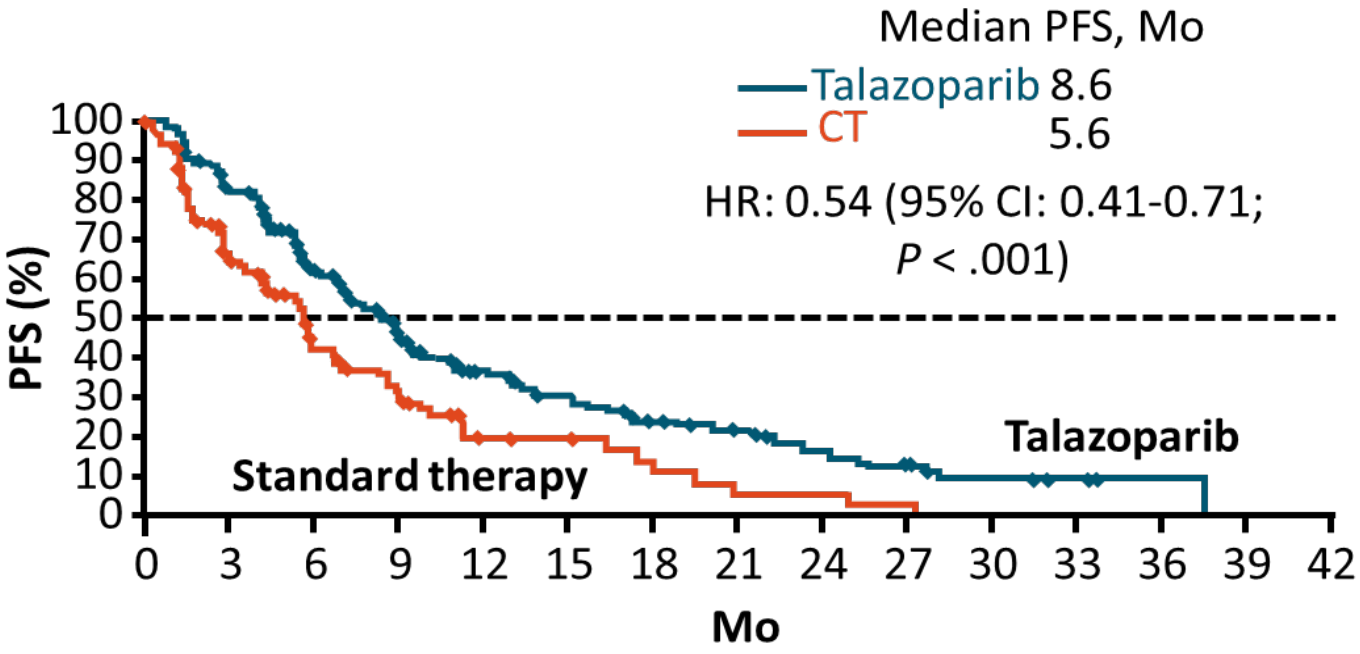
PARP Inhibitors FDA Approved for g*BRCA*-Mutated MBC

Improvement in PFS with PARP inhibitors compared with chemotherapy

Olaparib[a]
Phase 3 OlympiAD



Talazoparib[b]
Phase 3 EMBRACA



a. Robson M, et al. N Engl J Med. 2017;377:523-533; b. Litton JK, et al. N Engl J Med. 2018;379:753-763.

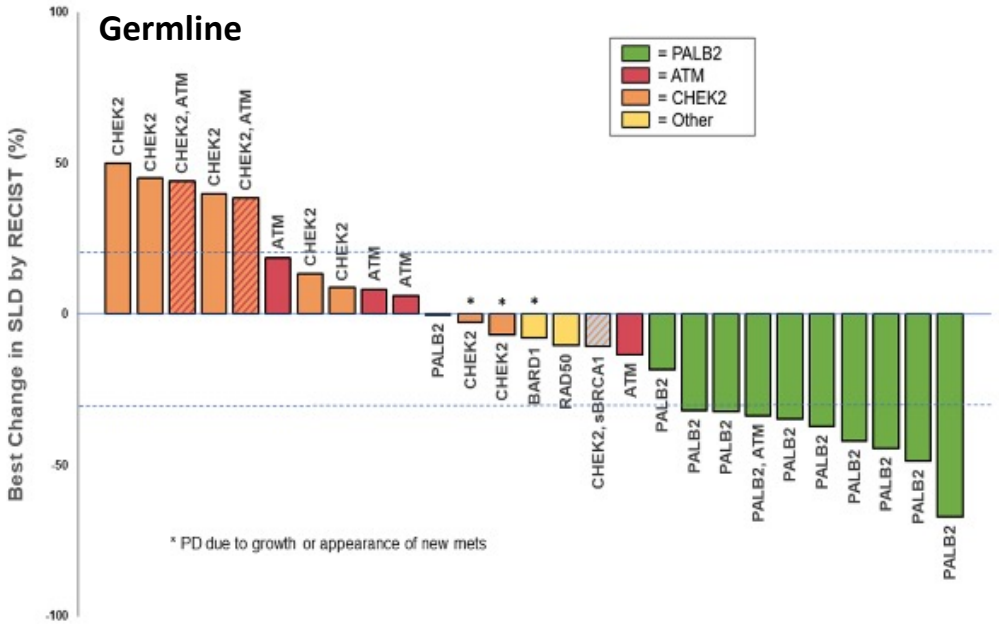
TBCRC 048: A Phase 2 Study of Olaparib in MBC With Germline or Somatic Mutations in Homologous Recombination Pathway Genes

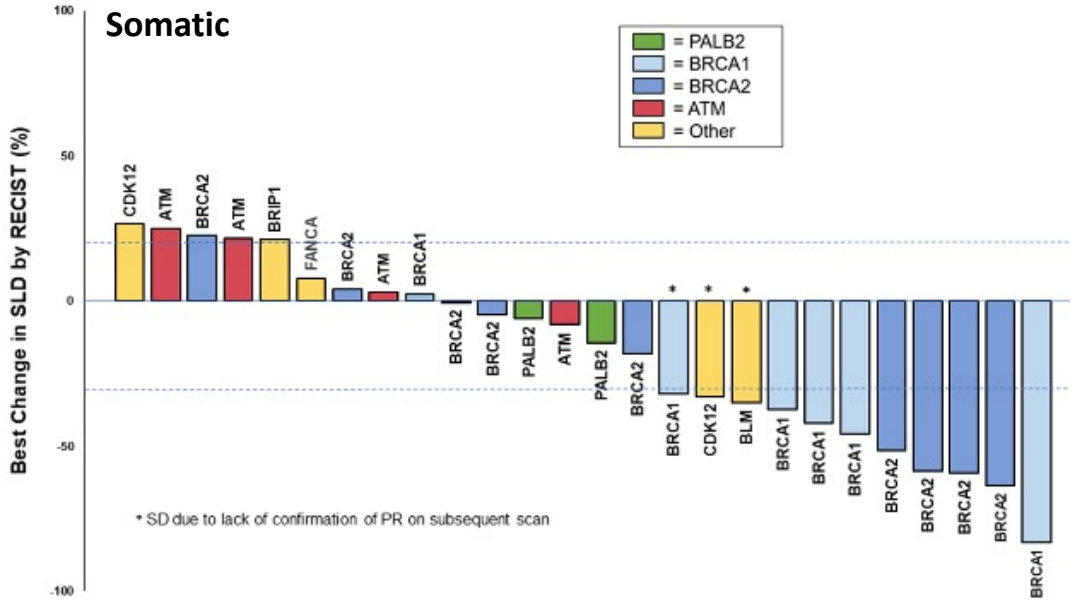
Germline (Cohort 1)		Somatic (Cohort 2)[4]	
• *CHEK2*[1,2]	n=8	• *sBRCA1*[5]	n=6
• *ATM*	n=4	• *sBRCA2*	n=9
• *ATM & CHEK2*[1]	n=2	• *ATM*[6]	n=4
• *PALB2*[3]	n=11	• *PAL2*	n=2
• *BARD1*	n=1	• *CDK12*	n=2
• *RAD50*	n=1	• *BRIP1*	n=1
		• *BLM*	n=1
		• *FANCA*	n=1

14 *ATM CHEK2*

15 *sBRCA1/2*

PALB2 N=13	*sBRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr Somatic: 0/2 – both SD* (limited assessments)	8/16 PR (50%)	0/13 germline 0/4 somatic

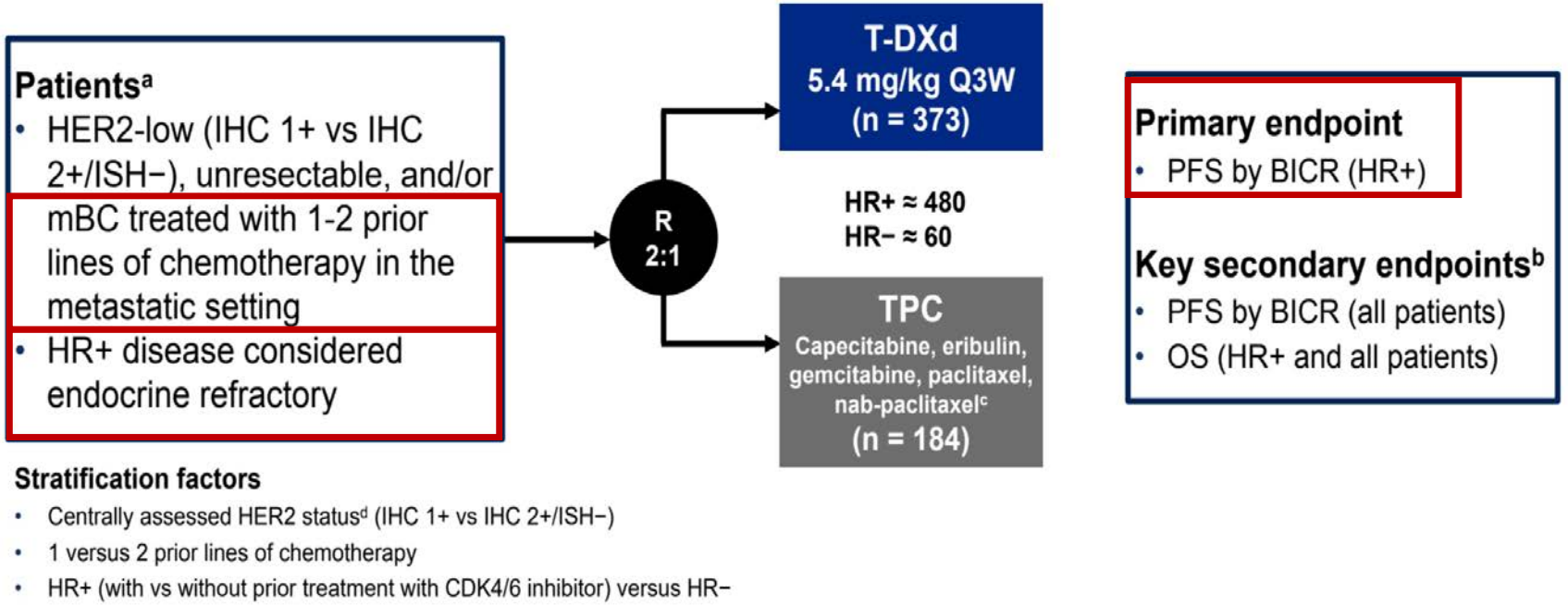




Tung NM, et al. *J Clin Oncol*. 2020;38:4274-4282.

DESTINY-Breast04: Trial Design

DESTINY-Breast04
Phase 3 trial initiated to confirm the benefit of targeting HER2-low expression in mBC



Modi S, et al. N Eng J Med. 2022;387:9-20.

DESTINY-Breast04: Population

60% HER2 1+, 40% HER2 2+ /ISH-

90% HR+ (n=499), 10% TNBC (n=58)

Median of 2 prior lines of ET and 1 chemo

70% of HR+ received prior CDK4/6i

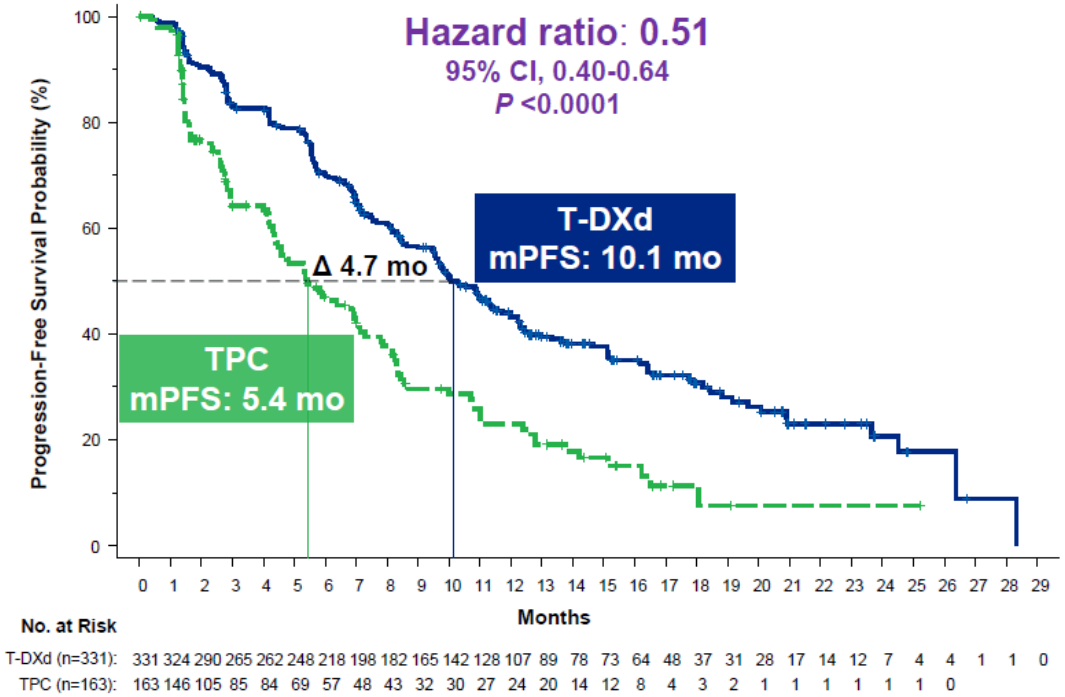
	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

Modi S, et al. N Eng J Med. 2022;387:9-20.

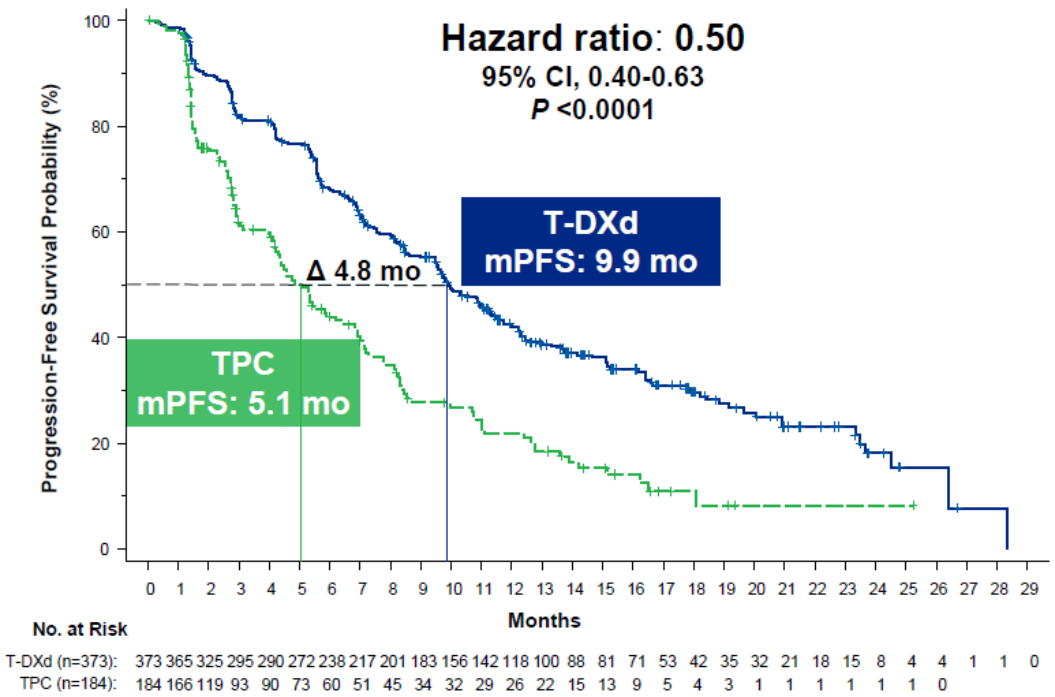
Trastuzumab Deruxtecan in HER2-Low MBC
DESTINY-Breast04 Phase 3: PFS

70% prior CDK4/6 inhibitors
Median 1 prior chemo

PFS in HR-Positive



PFS in All Patients



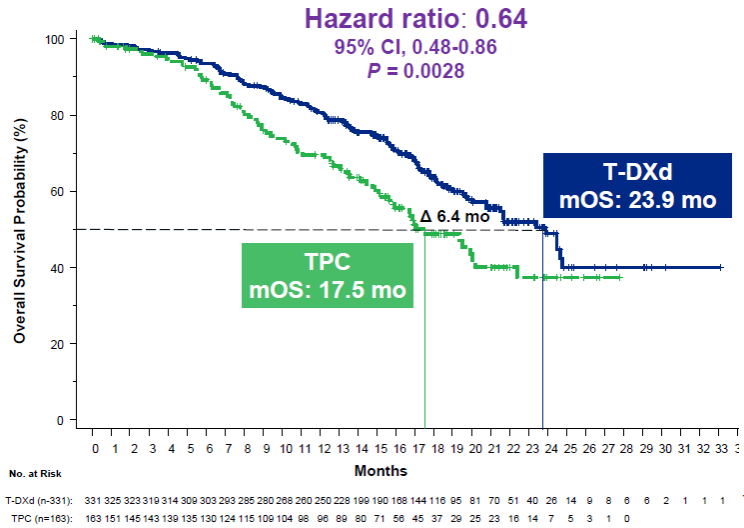
PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Cameron DA, et al. Presented at: 2020 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL. Abstract LBA3; Modi S, et al. N Engl J Med. 2022;387:9-20.

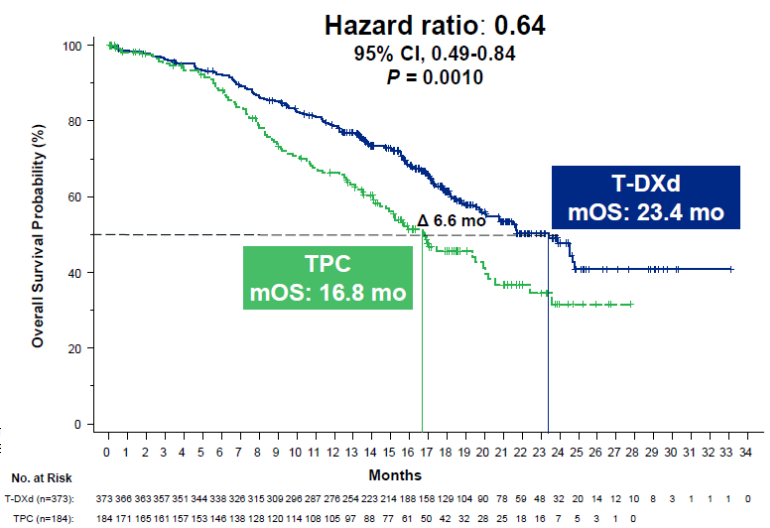
Trastuzumab Deruxtecan in HER2-Low MBC
DESTINY-Breast04 Phase 3: OS

2022 FDA Approved T-DXd as the new SOC For HER2 Low (1+ or 2+/ISH-) MBC

OS in HR-Positive



OS in All Patients



Response	HR-Positive		HR-Negative	
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Confirmed ORR, %	52.6	16.3	50.0	16.7
CR	3.6	0.6	2.5	5.6
PR	49.2	15.7	47.5	11.1
PD	7.8	21.1	12.5	33.3
NE	4.2	12.7	7.5	5.6
CBR, %	71.2	34.3	62.5	27.8
Median DOR, mo	10.7	6.8	8.6	4.9

Adjudicated as Drug-Related ILD/Pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

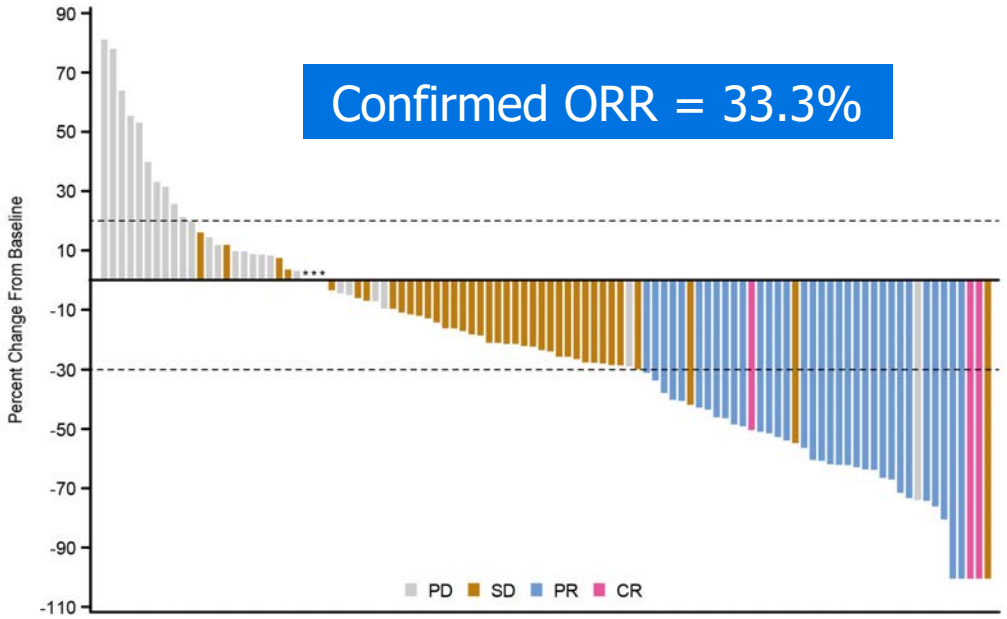
CBR, clinical benefit rate; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response.

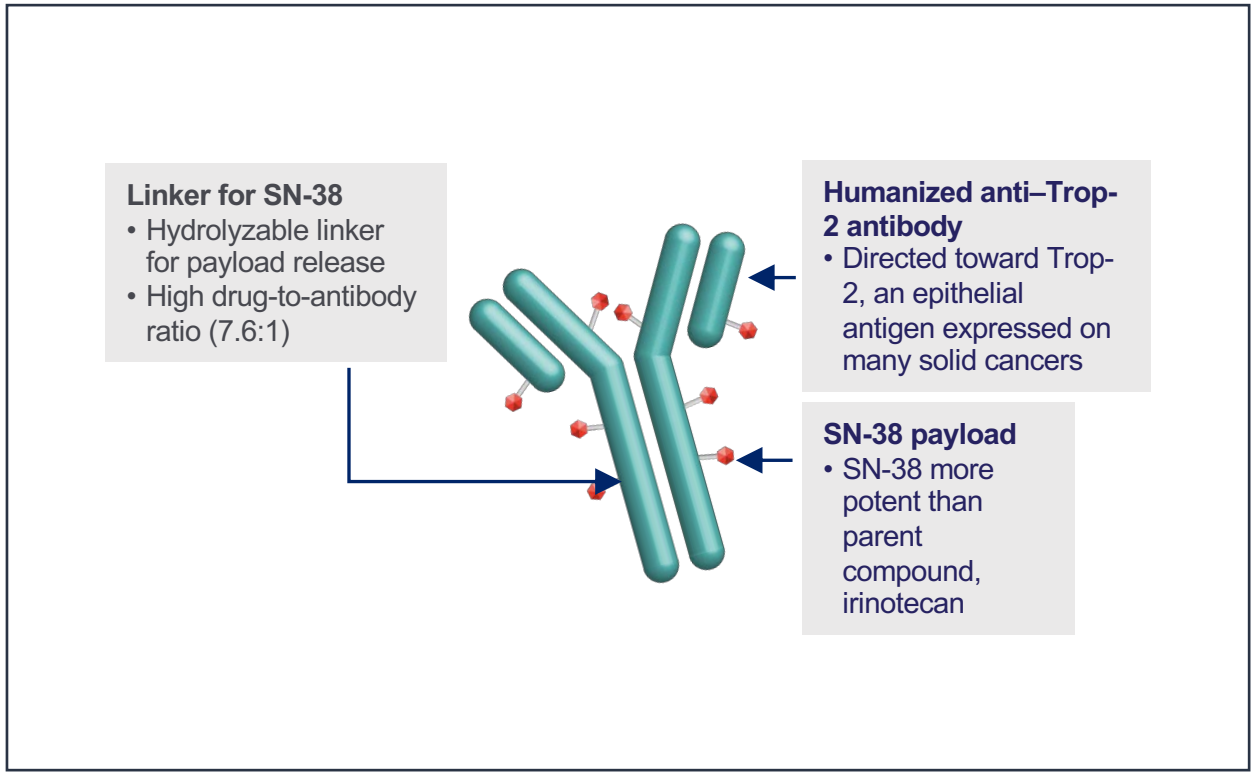
Cameron DA, et al. Presented at: 2020 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL. Abstract LBA3; Modi S, et al. N Engl J Med. 2022;387:9-20.

Targeting Trop-2 with Sacituzumab Govitecan

SG is an anti-Trop2 ADC with
- High drug-to-antibody ratio (7.6:1)
- Topoisomerase inhibitor payload (SN38)
- Ability to exert bystander effect

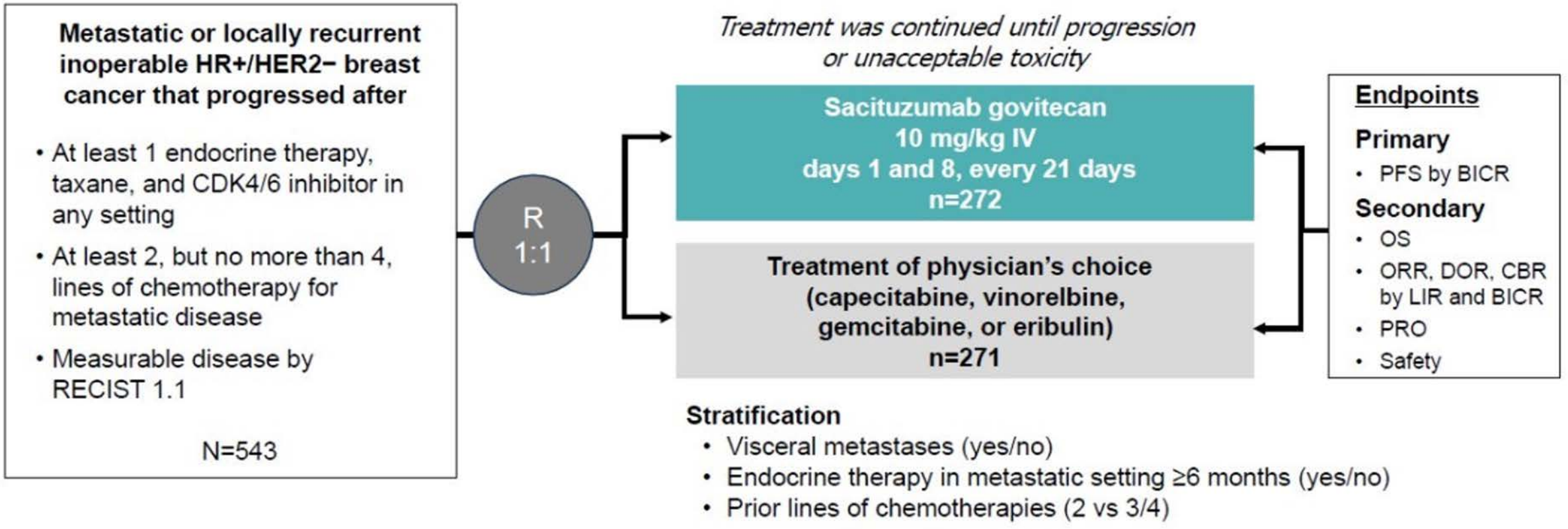
- Granted accelerated approval by the FDA for metastatic TNBC





Bardia A et al. *NEJM*. 2019; Nagayama, A et al, . Target Oncol. 2017

Sacituzumab Govitecan vs TPC in HR-Positive/HER2-Negative MBC
TROPiCS-02



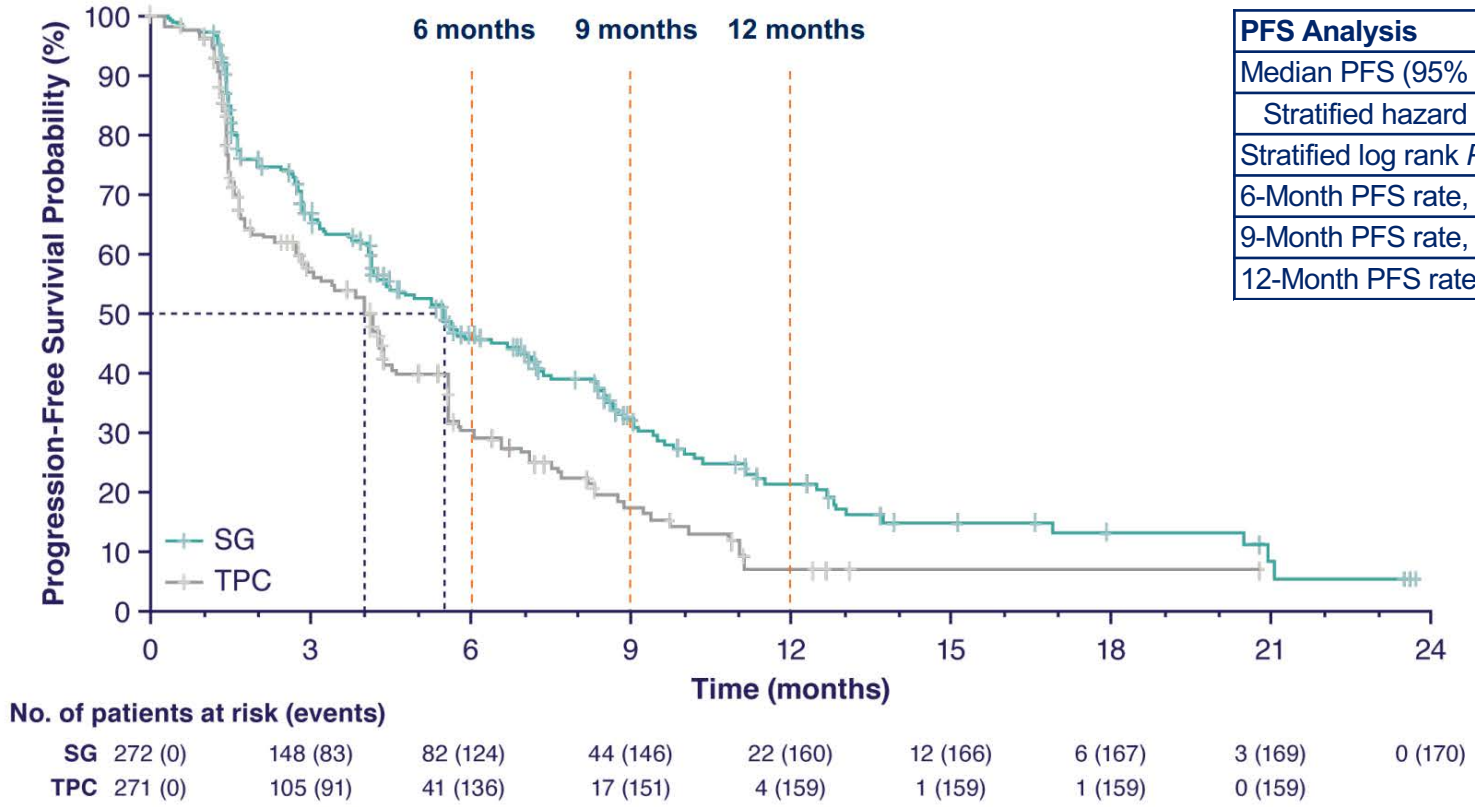
BICR, blinded independent central review; LIR, local investigator review; IV, intravenous; PRO, patient-reported outcomes; RECIST, Response Evaluation Criteria in Solid Tumors.

Rugo HS, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS5-11.

Sacituzumab Govitecan in HR-Positive/HER2-Negative MBC
TROPiCS-02 Phase 3: Efficacy

BICR-Assessed PFS in the ITT Population

98% prior CDK4/6 inhibitors
Median 3 prior chemo

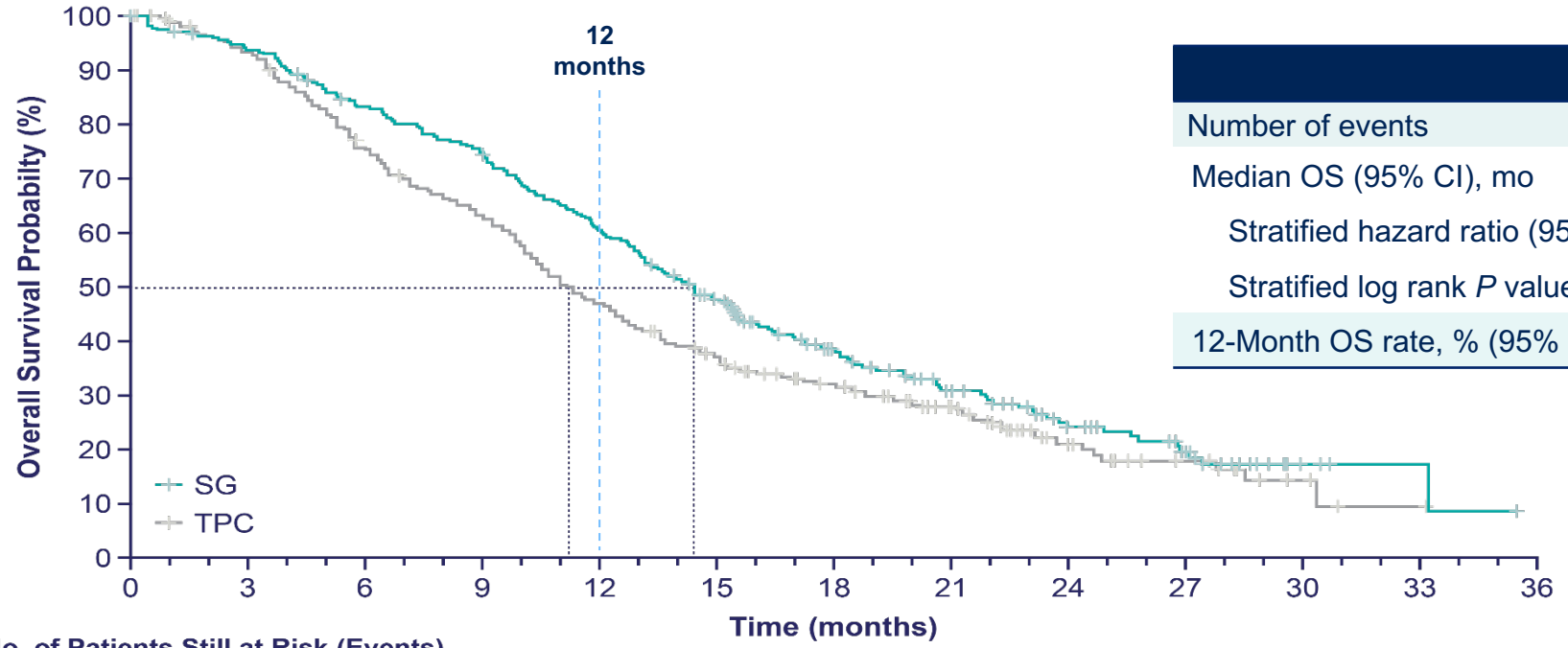


PFS Analysis	SG (n = 272)	TPC (n = 271)
Median PFS (95% CI), mo	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)
Stratified hazard ratio (95% CI)	0.66 (0.53-0.83)	
Stratified log rank *P* value	.0003	
6-Month PFS rate, % (95% CI)	46.1 (39.4, 52.6)	30.3 (23.6, 37.3)
9-Month PFS rate, % (95% CI)	32.5 (25.9, 39.2)	17.3 (11.5, 24.2)
12-Month PFS rate, % (95% CI)	21.3 (15.2, 28.1)	7.1 (2.8, 13.9)

- SG resulted in a 34% reduction in the risk of PD/death
- SG resulted in PFS benefit consistent across all subgroup analyses, including patients with
  - ≥ 3 prior chemotherapy regimens in the metastatic setting
  - Visceral metastases
  - Endocrine therapy for MBC ≥ 6 months

ITT, intention to treat; SG, sacituzumab govitecan.
Rugo H, et al. Presented at: 2020 ASCO Annual Meeting; May 29-31, 2020; Virtual. Abstract LBA1001.

TROPiCS-02
Key Secondary Endpoint: OS (Second Interim Analysis)



	SG (n = 272)	TPC (n = 271)
Number of events	191	199
Median OS (95% CI), mo	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)
Stratified hazard ratio (95% CI)	**0.79** (0.65, 0.96)	
Stratified log rank *P* value	.020	
12-Month OS rate, % (95% CI)	61 (55, 66)	47 (41, 53)

- SG showed statistically significant improvement in OS vs TPC with 21% reduction in the risk of death
- Patients who received SG survived a median of ***3.2 months longer*** than those who received TPC

Rugo H, et al. Presented at: Presented at: ESMO Congress 2022; September 9-13, 2022; Paris, France.; September 9-13, 2022; Paris, France.

Agenda

Module 1: Long-Term Management of HER2-Positive Breast Cancer — Dr Krop

Module 2: Optimizing the Management of ER-Positive Localized Breast Cancer — Dr Kalinsky

Module 3: Considerations in the Care of Patients with ER-Positive mBC — Dr Jhaveri

Module 4: Novel and Emerging Strategies for ER-Positive mBC — Dr Rugo

Module 5: Evolving Clinical Decision-Making for Localized Triple-Negative Breast Cancer (TNBC) — Dr O'Shaughnessy

Module 6: Recent Advances in the Treatment of Metastatic TNBC (mTNBC) — Prof Schmid

Selection of therapy for ER-positive metastatic breast cancer progressing on a CDK4/6 inhibitor; future role of capivasertib

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

RTP
RESEARCH
TO PRACTICE

A patient who has been receiving a CDK4/6 inhibitor with letrozole for ER-positive, HER2-negative mBC experiences disease progression after 18 months. Biomarker evaluation reveals an ESR1 mutation but is negative for PIK3CA. Regulatory and reimbursement issues aside, which systemic treatment would you most likely recommend?

 Dr Jhaveri	Elacestrant
 Dr Kalinsky	Elacestrant
 Dr Krop	Continue the CDK4/6 inhibitor and switch endocrine therapy
 Dr O'Shaughnessy	Elacestrant
 Dr Rugo	Elacestrant
 Prof Schmid	Continue the CDK4/6 inhibitor and switch endocrine therapy
 Dr Hurvitz	Elacestrant
 Dr Tolaney	Elacestrant
 Dr Traina	Elacestrant

RTP RESEARCH TO PRACTICE

A patient who has been receiving a CDK4/6 inhibitor with letrozole for ER-positive, HER2-negative mBC experiences disease progression after 18 months. Biomarker evaluation reveals a PIK3CA mutation but is negative for ESR1. Regulatory and reimbursement issues aside, which systemic treatment would you most likely recommend?

 Dr Jhaveri	Alpelisib/fulvestrant
 Dr Kalinsky	Alpelisib/fulvestrant
 Dr Krop	Alpelisib/fulvestrant
 Dr O'Shaughnessy	Alpelisib/fulvestrant
 Dr Rugo	Alpelisib/fulvestrant
 Prof Schmid	Alpelisib/fulvestrant
 Dr Hurvitz	Alpelisib/fulvestrant
 Dr Tolaney	Alpelisib/fulvestrant
 Dr Traina	Alpelisib/fulvestrant

RTP RESEARCH TO PRACTICE

A patient who has been receiving a CDK4/6 inhibitor with letrozole for ER-positive, HER2-negative mBC experiences disease progression after 18 months. Biomarker evaluation reveals a PIK3CA mutation and an ESR1 mutation. Regulatory and reimbursement issues aside, which systemic treatment would you most likely recommend?

 Dr Jhaveri	Clinical trial
 Dr Kalinsky	Alpelisib/fulvestrant
 Dr Krop	Alpelisib/fulvestrant
 Dr O'Shaughnessy	Alpelisib/fulvestrant
 Dr Rugo	Alpelisib/fulvestrant
 Prof Schmid	Alpelisib/fulvestrant
 Dr Hurvitz	Alpelisib/fulvestrant
 Dr Tolaney	Alpelisib/fulvestrant
 Dr Traina	Alpelisib/fulvestrant or elacestrant, depending on disease volume, symptoms, etc

RTP RESEARCH TO PRACTICE

If capivasertib were to become available, for which patients with ER-positive mBC would you prioritize its use?

 Dr Jhaveri	Depends if approval is for all comers or only for patients with alteration
 Dr Kalinsky	Suspect it will be approved regardless of PIK3CA mutation or PI3K alteration
 Dr Krop	Patients with AKT pathway alterations
 Dr O'Shaughnessy	Patients with CDK4/i and AI pre-treated disease and DP, regardless of PI3K/AKT mutation status
 Dr Rugo	Patients with alterations in the AKT signaling pathway
 Prof Schmid	2nd line after CDK4/6
 Dr Hurvitz	As 2nd line for all, regardless of PIK3CA or ESR1 mutation status, w/ fulvestrant
 Dr Tolaney	After DP on 1L AI + CDK4/6i w/AKT pathway alteration (AKT/PI3K/PTEN)
 Dr Traina	Would think about it for pts w/ PI3K and ESR1 WT as limited other options

AI = aromatase inhibitor; DP = disease progression

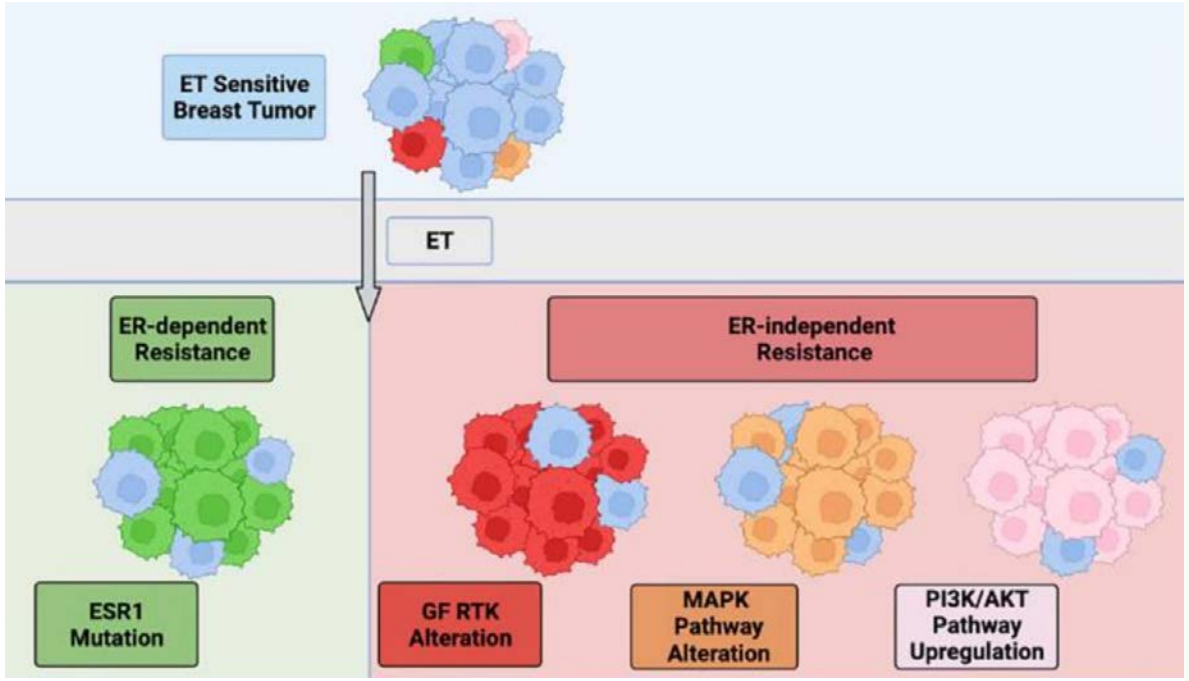
RTP RESEARCH TO PRACTICE

UCSF Helen Diller Family Comprehensive Cancer Center

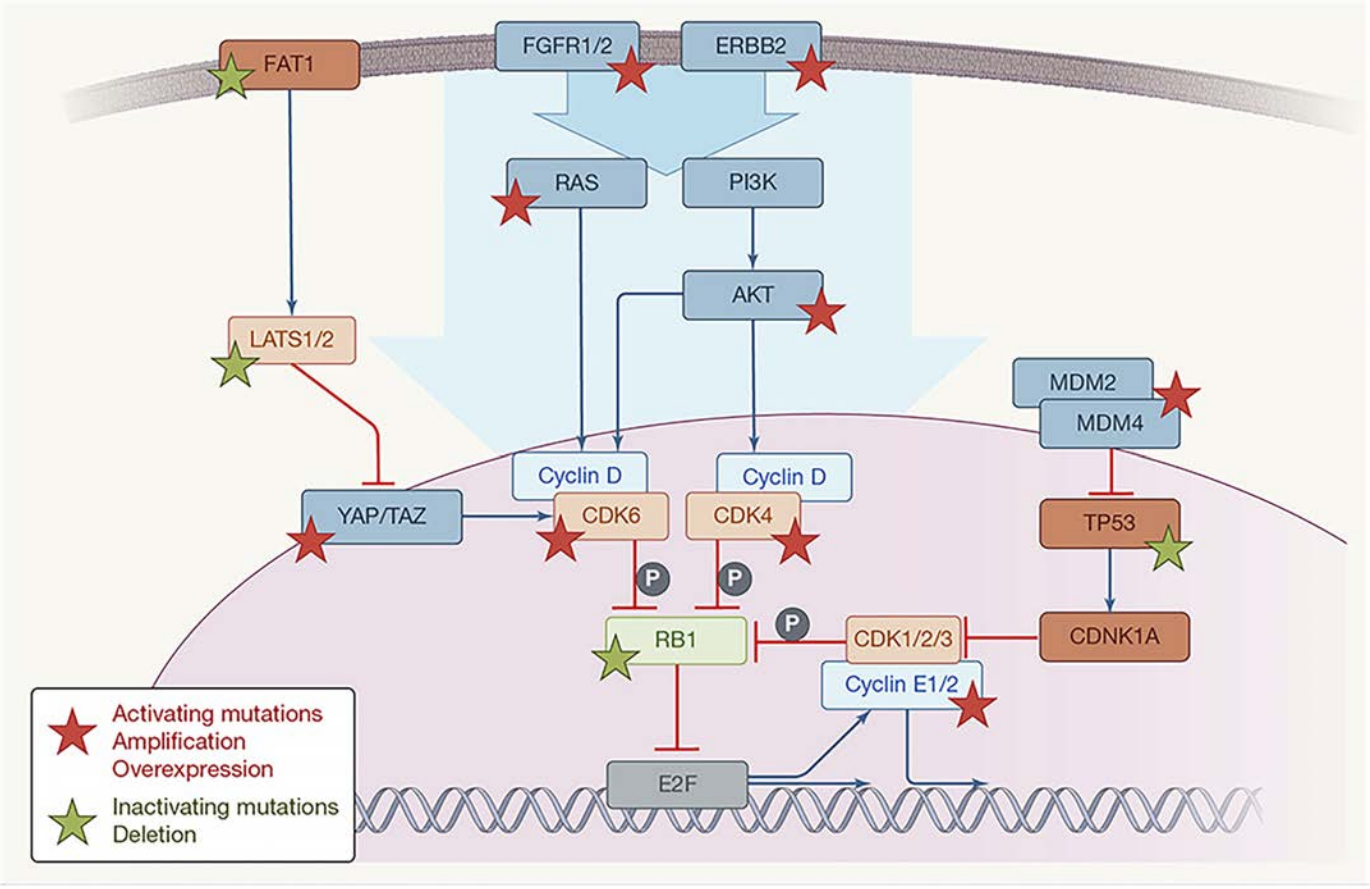
Novel Investigational Strategies for ER-Positive mBC

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

Resistance to ET + CDK4/6i: Now a High Unmet Need



ER dependent and independent mechanism of resistance



Major Mechanisms of Resistance to CDK4/6 Inhibitors

Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25
Álvarez-Fernández M, Malumbres M. *Cancer Cell*. 2020;37:514-529.

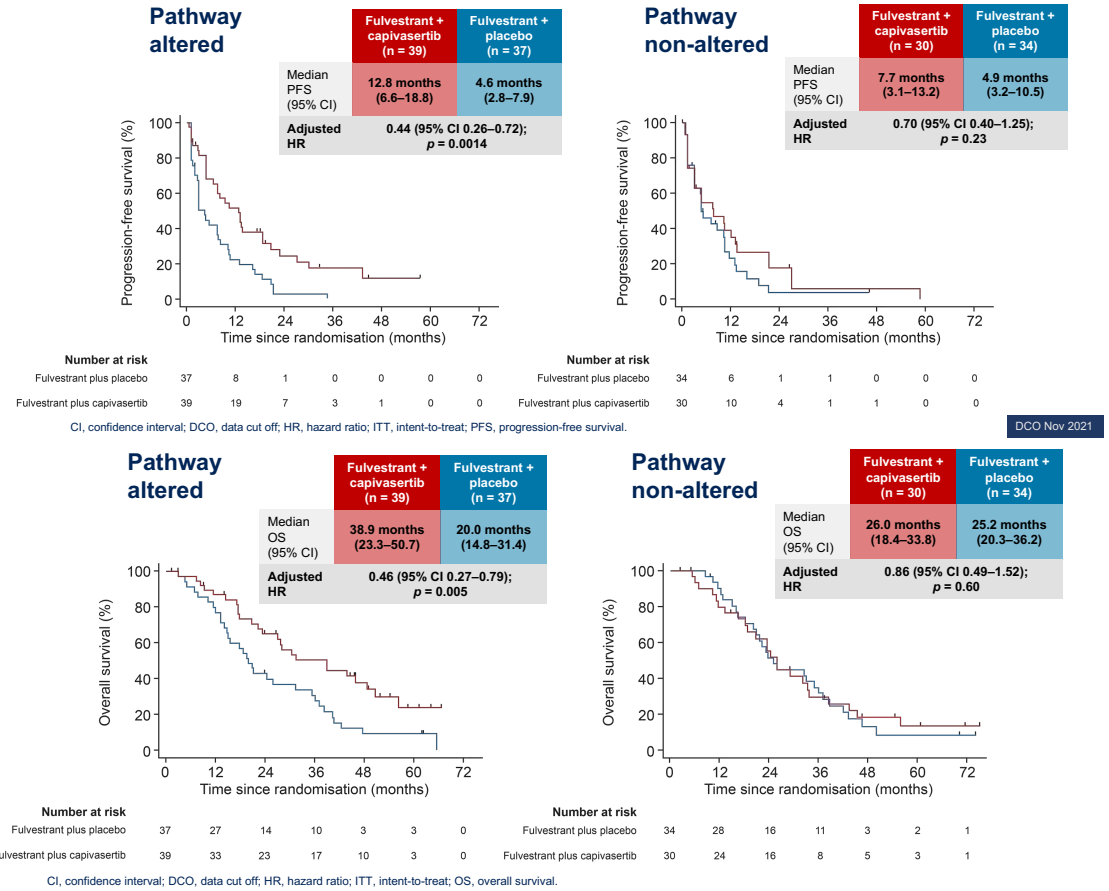
Inhibiting AKT

- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*
  - May also occur in cancers without these genetic alterations
  - AKT signalling implicated in development of ET resistance
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)

Turner et al, SABCS 2022; Jones RH, et al. Lancet Oncol 2020; Howell et al, Lancet Oncology 2022

Phase II FAKTION Trial

- Adding Capi to Fulv in PM women with AI resistant HR+ MBC (no prior CDKi) improved PFS and OS, with most benefit in altered population



CAPItello-291:

Phase III, randomized, double-blind, placebo-controlled study

Patients with HR+/HER2– ABC

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

R1:1 (N=708)

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

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

Dual primary endpoints

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

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Summary of Demographics

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

Turner et al, SABCS 2022

AKT Pathway Alterations

Alteration; n (%)			
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)

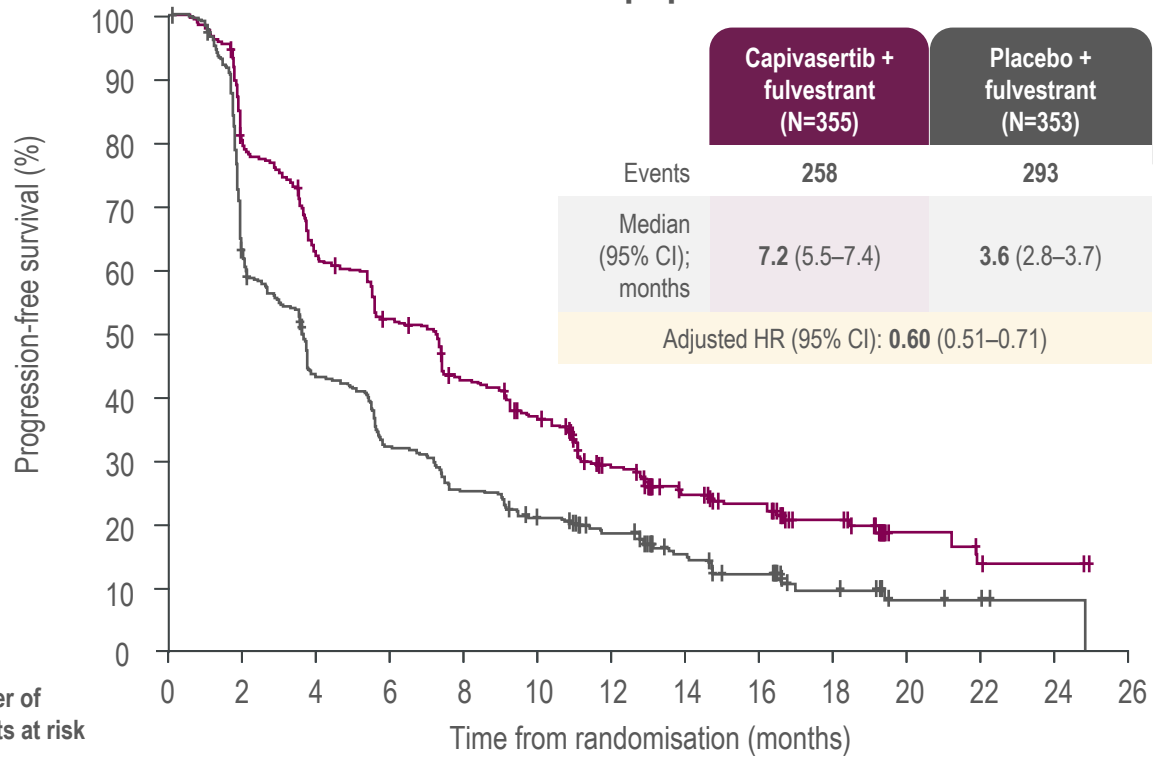
AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

Turner et al, SABCS 2022

Dual primary endpoint: PFS in overall and AKT pathway-altered populations[1]

Capivasertib plus fulvestrant provides a statistically significant and clinically meaningful improvement in PFS in the overall and the AKT pathway-altered populations

Overall population

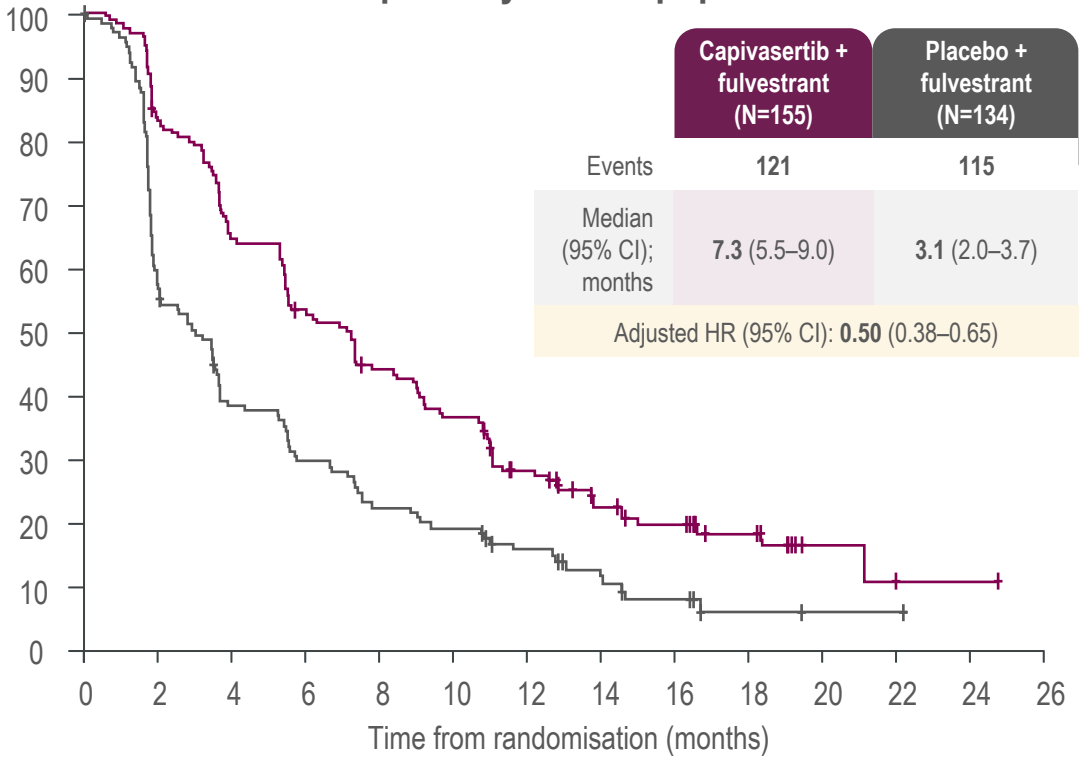


	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Events	258	293
Median (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI): **0.60** (0.51–0.71)		

Number of patients at risk

Capivasertib + fulvestrant	355	226	207	172	138	115	78	55	43	25	8	5	2	0
Placebo + fulvestrant	353	207	142	106	83	66	51	33	23	11	4	3	1	0

AKT pathway-altered population



	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Events	121	115
Median (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI): **0.50** (0.38–0.65)		

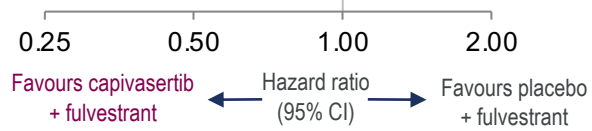
Capivasertib + fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo + fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

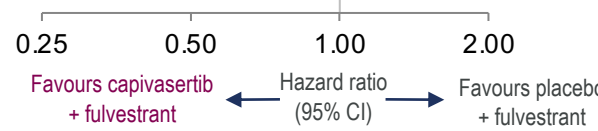
1. Turner et al. *Cancer Res* 2023;83(Suppl 5):GS3-04 abstract and presentation. + indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

Summary of PFS by subgroups

Consistent clinically meaningful benefit with capivasertib + fulvestrant was observed across clinically relevant subgroups in both the overall population and AKT pathway-altered population

		Overall population				AKT pathway-altered population			
			Median PFS, months				Median PFS, months		
		n	Capivasertib + fulvestrant	Placebo + fulvestrant		n	Capivasertib + fulvestrant	Placebo + fulvestrant	
Overall[a]		708	7.2	3.6		289	7.3	3.1	
Prior CDK4/6 inhibitor[b]	Yes	496	5.5	2.6		208	5.5	2.0	
	No	212	10.9	7.2		81	11.0	7.4	
Prior chemotherapy for ABC[b]	Yes	129	3.8	2.1		53	4.0	2.0	
	No	579	7.3	3.7		236	7.4	3.5	
Liver metastases at baseline[b]	Yes	306	3.8	1.9		123	5.5	1.8	
	No	402	9.2	5.5		166	9.1	3.7	



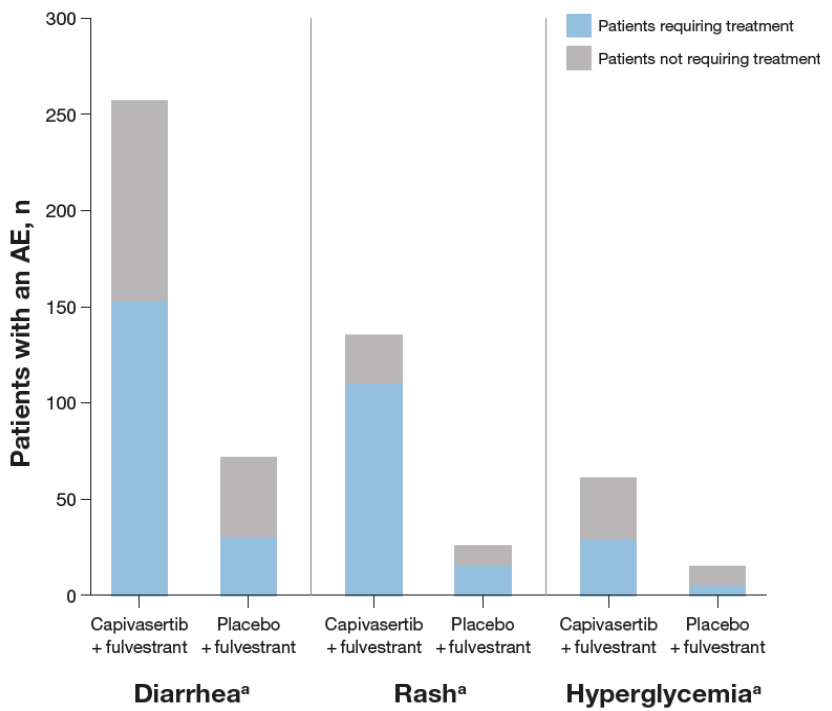


[a]HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region. [b]HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and geographic region (prior CDK4/6 inhibitor subgroup), the presence of liver metastases and prior use of CDK4/6 inhibitor (prior chemotherapy for ABC subgroup [overall population]) and prior use of CDK4/6 inhibitor only (prior chemotherapy for ABC subgroup [AKT pathway-altered population] and liver metastases subgroup).

Oliveira et al, ESMO BC 2023

CAPItello 291: Safety Analysis

AE; n (%)	Capivasertib + fulvestrant (n=355)					Placebo + fulvestrant (n=350)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AE	343 (96.6)	52 (14.6)	139 (39.2)	139 (39.2)	9 (2.5)	288 (82.3)	115 (32.9)	118 (33.7)	44 (12.6)	10 (2.9)
Diarrhea[a]	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	71 (20.3)	61 (17.4)	9 (2.6)	1 (0.3)	0
Rash[a]	135 (38.0)	57 (16.1)	35 (9.9)	43 (12.1)	0	25 (7.1)	19 (5.4)	5 (1.4)	1 (0.3)	0
Nausea	123 (34.6)	85 (23.9)	35 (9.9)	3 (0.8)	0	54 (15.4)	42 (12.0)	10 (2.9)	2 (0.6)	0
Fatigue	74 (20.8)	49 (13.8)	23 (6.5)	2 (0.6)	0	45 (12.9)	35 (10.0)	8 (2.3)	2 (0.6)	0
Vomiting	73 (20.6)	54 (15.2)	13 (3.7)	6 (1.7)	0	17 (4.9)	10 (2.9)	5 (1.4)	2 (0.6)	0
Headache	60 (16.9)	47 (13.2)	12 (3.4)	1 (0.3)	0	43 (12.3)	33 (9.4)	8 (2.3)	2 (0.6)	0
Hyperglycemia[a]	60 (16.9)	26 (7.3)	26 (7.3)	7 (2.0)	1 (0.3)	14 (4.0)	8 (2.3)	5 (1.4)	1 (0.3)	0
Decreased appetite	59 (16.6)	37 (10.4)	21 (5.9)	1 (0.3)	0	22 (6.3)	11 (3.1)	9 (2.6)	2 (0.6)	0
Stomatitis	52 (14.6)	24 (6.8)	21 (5.9)	7 (2.0)	0	17 (4.9)	15 (4.3)	2 (0.6)	0	0
Asthenia	47 (13.2)	29 (8.2)	14 (3.9)	4 (1.1)	0	36 (10.3)	31 (8.9)	3 (0.9)	2 (0.6)	0
Pruritus	44 (12.4)	32 (9.0)	10 (2.8)	2 (0.6)	0	23 (6.6)	19 (5.4)	4 (1.1)	0	0



AEs leading to:

- Discontinuation capi/pla: 9.3 vs 0.6%
- Interruption capi/pla: 34.9 vs 10.3%
- Dose reduction capi/pla: 19.7 vs 1.7%

Median time to onset, Days

- Diarrhea: 8 (2-22)
- Rash: 12 (10-15)
- Hyperglycemia: 15 (1-51)

AEs leading to discontinuation

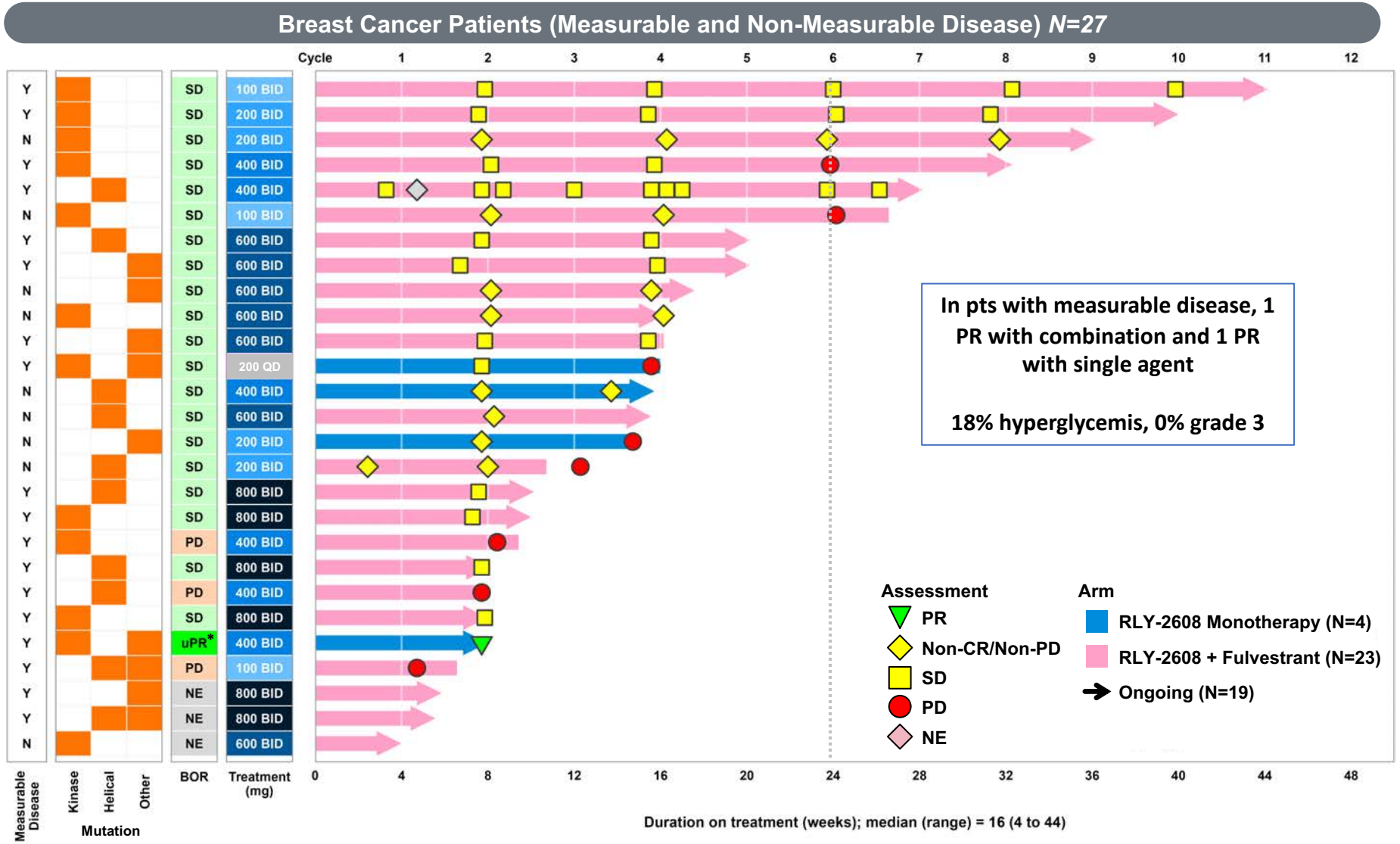
- Diarrhea: 2%
- Rash 4.5%
- Hyperglycemia: 0.3%

Rugo et al, ASCO 2023

Summary: Capivasertib and Fulvestrant

- Capivasertib/fulvestrant vs Pla/fulvestrant improved PFS in the overall population and in patients with tumor PIK3CA altered population; overall survival immature
- Efficacy in the subset of patients with non-altered tumors encouraging
  - Trial was not powered to look at this subgroup; small group with unknown mutation profile hard to take into account
- Benefit seen across subgroups including those with prior CDK4/6i & with visceral mets
- Safety
  - Overall well tolerated, low rate of hyperglycemia
- Data to be considered for regulatory approval
- Additional studies
  - **CAPItello-292** (NCT04862663): Fulvestrant/Palbociclib +/- Capi; now being evaluated with ribociclib and abemaciclib combinations
  - Additional studies with ipatasertib with similar designs
  - New PIK3CA inhibitors: Inavolisib, RLY-2608
    - Mutant selective (H1047): LOX783, STX-H1047-PI3Kα
    - And more!

RLY-2608: Disease Stabilization Across *PIK3CA* Breast Cancer Genotypes



19/27 patients (70%) ongoing

Duration on treatment:
- **Median: 16 weeks**
- **Range: 4 – 44 weeks**

21/24 RECIST evaluable patients (88%) had non-CR/non-PD, SD or response

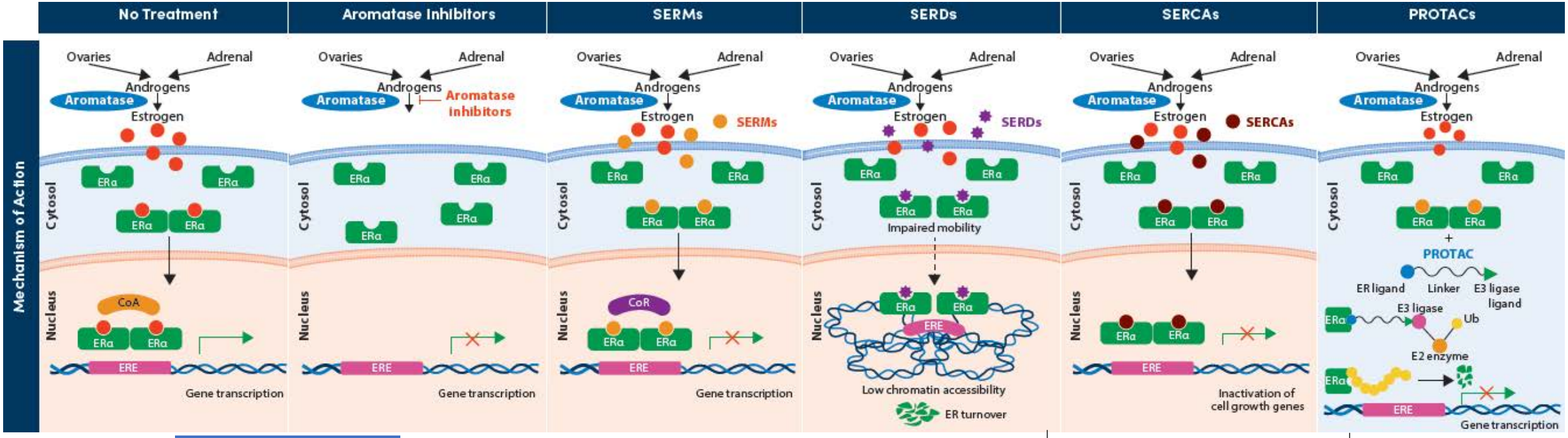
Most patients (7/8) discontinued due to progressive disease
- **No AEs leading to treatment discontinuation**

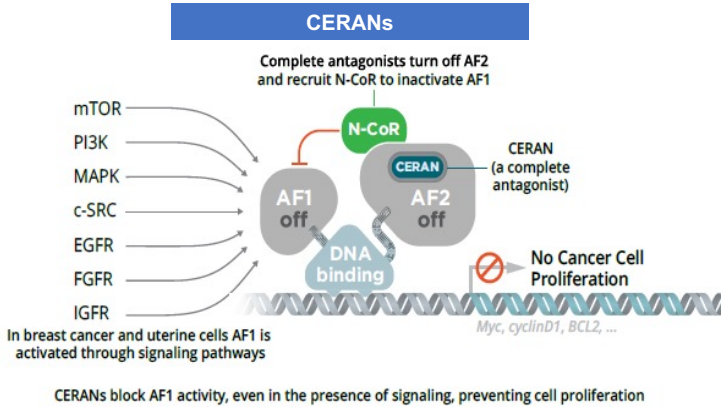
*Response confirmed after data cut-off

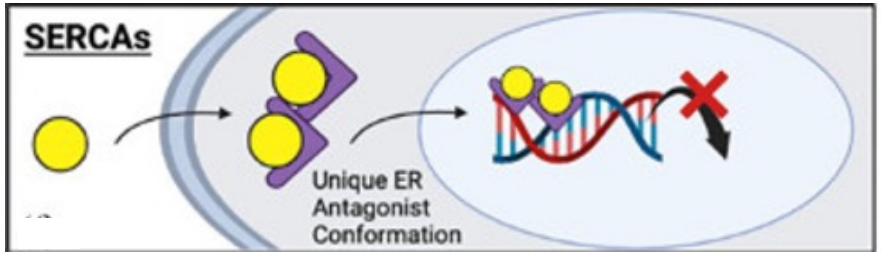
Varkaris AACR 2023

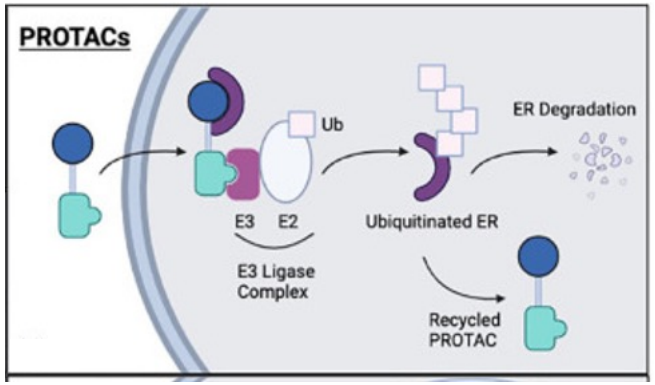
Preliminary data as of 03/09/2023

Mechanism of Action of New Endocrine Agents Targeting the ER Domain





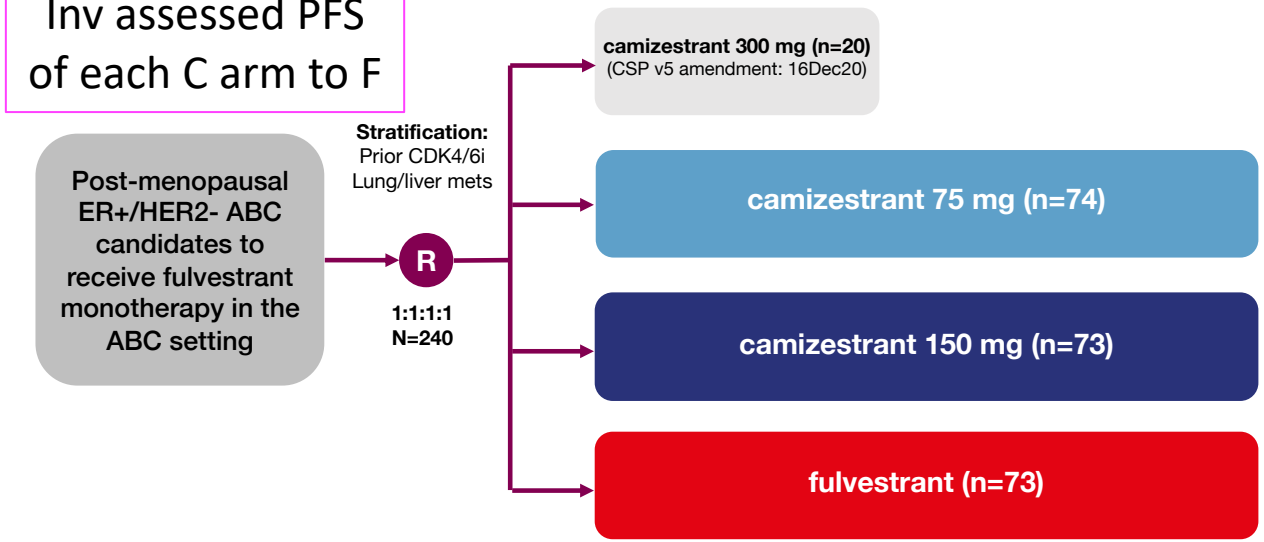




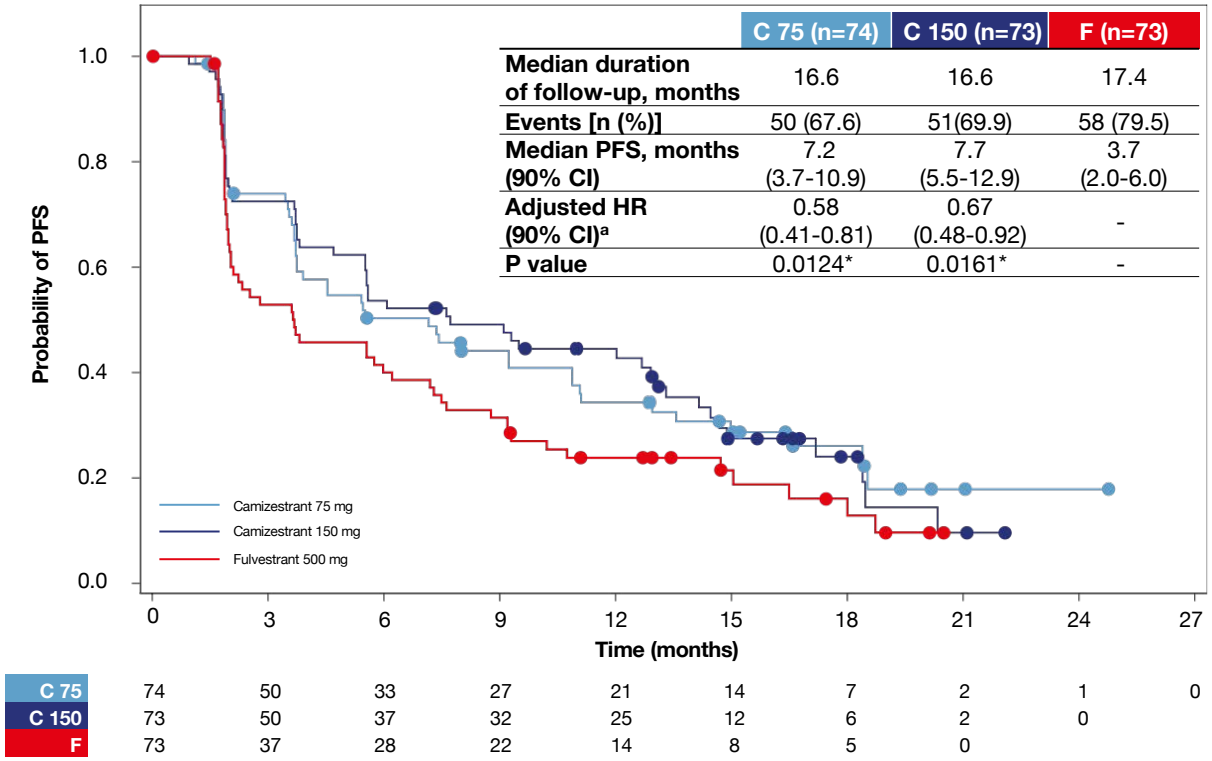
1. Hanker AB et al. *Cancer Cell.* 2020;37:496-513 2. Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25

SERENA-2 Phase 2 Trial: Camizestrant plus Fulvestrant

Primary endpt: Inv assessed PFS of each C arm to F



Primary endpoint: PFS by investigator assessment



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

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

Demographics

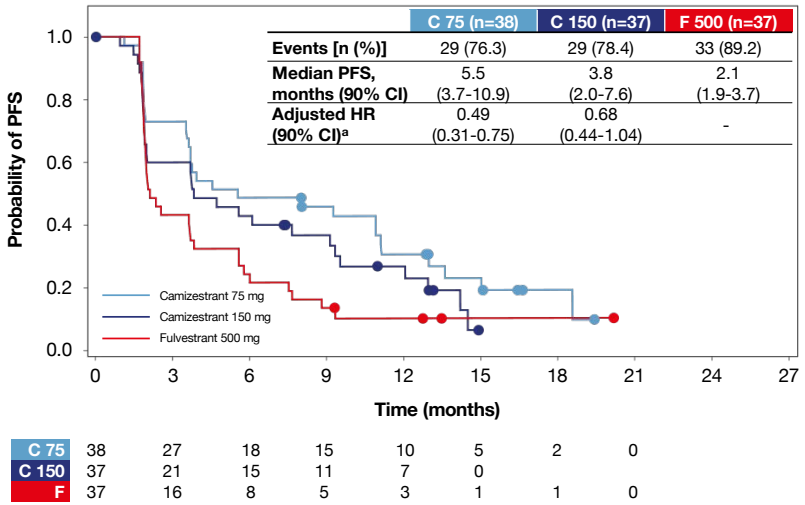
- 90-95% white
- Imbalance in liver (not visceral) mets: 31 v 41 vs 48%
- Imbalance in ESR1m: 30 v 36 v 48%
- 77% one line ET, 63% prior AI; 50% prior CDK4/6i
- Prior chemo for MBC: 22 v 12 v 26%

PFS by BICR: Significant discordance with inv PFS for 150 mg

	C 75 (n=74)	C 150 (n=73)	F (n=73)
Events [n (%)]	39 (52.7)	33 (45.2)	53 (72.6)
Median PFS, months (90% CI)	7.4 (4.5-10.9)	12.7 (9.3-18.4)	3.7 (2.0-3.8)
Adjusted HR (90% CI)[a]	0.56 (0.39-0.80)	0.47 (0.33-0.68)	-
P value	0.0079*	0.0004*	-

Oliveira et al, SABCS 2022

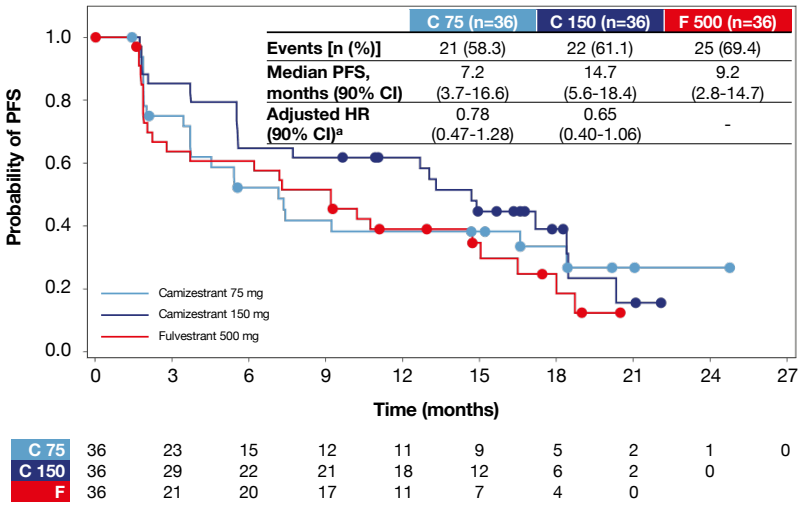
Prior CDK4/6i



	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-

C 75	38	27	18	15	10	5	2	0	
C 150	37	21	15	11	7	0			
F	37	16	8	5	3	1	1	0	

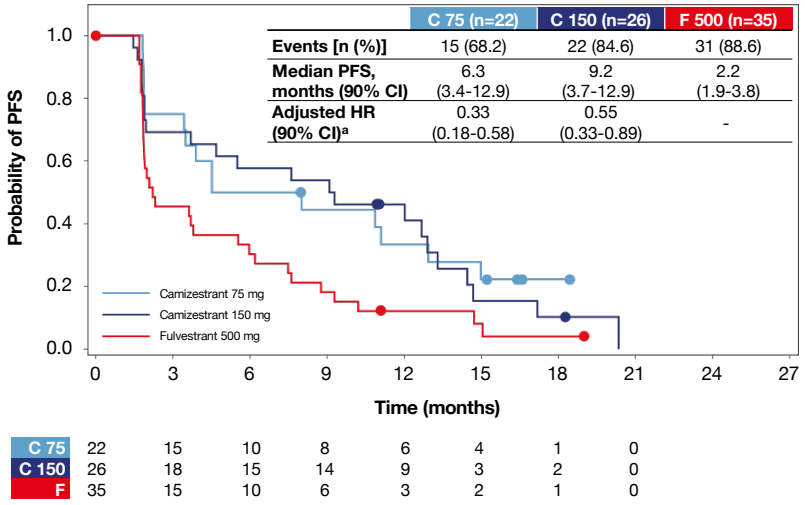
No prior CDK4/6i



	C 75 (n=36)	C 150 (n=36)	F 500 (n=36)
Events [n (%)]	21 (58.3)	22 (61.1)	25 (69.4)
Median PFS, months (90% CI)	7.2 (3.7-16.6)	14.7 (5.6-18.4)	9.2 (2.8-14.7)
Adjusted HR (90% CI)[a]	0.78 (0.47-1.28)	0.65 (0.40-1.06)	-

C 75	36	23	15	12	11	9	5	2	1	0
C 150	36	29	22	21	18	12	6	2	0	
F	36	21	20	17	11	7	4	0		

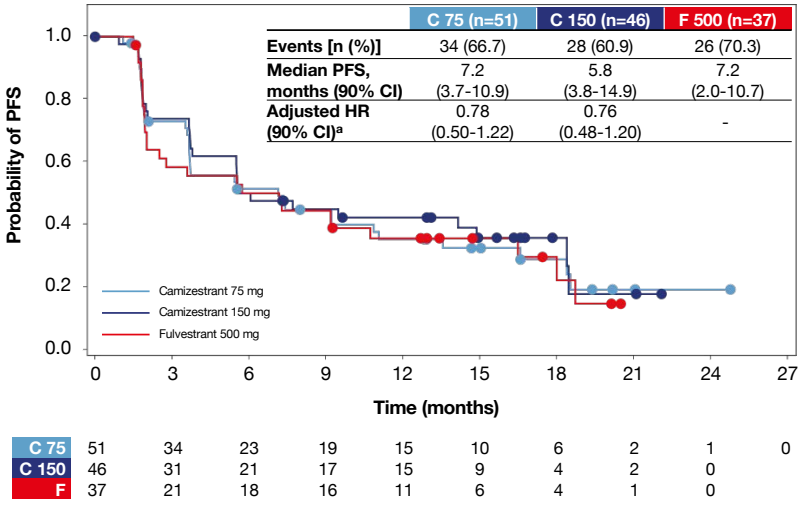
*ESR1*m detectable at baseline



	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

C 75	22	15	10	8	6	4	1	0
C 150	26	18	15	14	9	3	2	0
F	35	15	10	6	3	2	1	0

*ESR1*m not detectable at baseline



	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

Liver and/or lung mets

YES	C 75 (n=43)	C 150 (n=43)	F 500 (n=43)
Events [n (%)]	31 (72.1)	32 (74.4)	39 (90.7)
Median PFS, months (90% CI)	7.2 (3.6-11.1)	5.6 (3.7-9.1)	2.0 (1.9-3.6)
Adjusted HR (90% CI)[a]	0.43 (0.28-0.65)	0.55 (0.37-0.82)	-

NO	C 75 (n=31)	C 150 (n=30)	F 500 (n=30)
Events [n (%)]	19 (61.3)	19 (63.3)	19 (63.3)
Median PFS, months (90% CI)	5.5 (3.7-15.0)	14.5 (5.6-17.2)	9.2 (3.7-18.7)
Adjusted HR (90% CI)[a]	0.99 (0.57-1.69)	0.91 (0.53-1.56)	-

Biomarkers

- Camizestrant reduced ESR1 ctDNA to near zero by C2D1

Safety

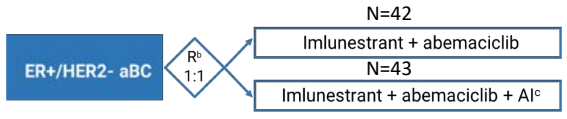
- Very low rate discontinuation
- Interruption TRAEs ~med 7 days: ~10%
- Very low rate of grade 3 AEs
- All grade AEs (low-high dose):
  - Photopsia: 12-25%
  - Sinus bradycardia: 5-26%
  - More fatigue, arthragia, AST/ALT elevation at higher dose

• Conclusion

- Met its primary endpoint
- No comment about dosing or imbalance in specific factors
  - Ph 3 trials ongoing
  - Dose: 75 mg

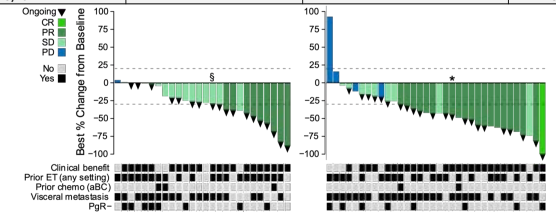
Oliveira et al, SABCS 2022

Imlunestrant: Phase Ia/b Trial



≤1 prior therapy for MBC, no prior CDK4/6i
ET sensitive disease (≥24 weeks on ET)

	Imlunestrant + abemaciclib N=42	Imlunestrant + abemaciclib + AI N=43	Total N=85
ORR, n/N (%)	9/28 (32)	20/34 (59)	29/62 (47)
Median TTR, months (min-max)	3.7 (1.6-10.9)	3.7 (1.7-7.1)	3.7 (1.6-10.9)
CBR, n/N (%)	30/42 (71)	34/43 (79)	64/85 (75)
12-month PFS, %	80	80	80



Demographics
- ESR1m: 7 v 10%
- Visceral mets: 50 v 65%
- De novo: 19 v 33%
- Measurable dse: 67 v 79%
- 70% Rxd in first line; 10% prior chemo
- Recurrence <12 mo adj Rx: 67 v 44%

RP2D Imlunestrant combined with abemaciclib
- 150 mg BID

Safety (all/gr3, averaged)
- Diarrhea: 92/10%
- Nausea: 59/0%
- Neutropenia: 41/14%

D/C for TRAE: 1%
Dose reduction for AE:
- Both: 6%
- Abema: 29%

Jhaveri et al, SABCS 2022

- PFS: small number of events; 80% prog free at 12 mos
- ctDNA: ORR/PFS assoc with decline
- No PK drug interaction with abemaciclib
- Phase III trials ongoing in metastatic and adjuvant settings

ARV-471 (PROTAC ER Degrader): VERITAC Phase II Expansion Trial

- ARV-471 directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER then proteasomal degradation
- ≥1 ET for MBC, a CDK4/6i
  - 35 pts at 200mg/d; 36 pts at 500 mg/d
  - 58% ESR1 mutations; 79% prior fulvestrant, 45% liver mets
- Primary toxicities: fatigue, nausea, but ≤grade 2
- PFS

	All Patients	
	200 mg QD (n=35)	Total (N=71)
Events, n (%)	24 (68.6)	41 (57.7)
mPFS, mo (95% CI)	3.5 (1.8–7.8)	3.7 (1.9–8.3)

	Mutant *ESR1*	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)
Patients with mutant *ESR1*	(n=19)	(n=22)	(n=41)
CBR, % (95% CI)	47.4 (24.4–71.1)	54.5 (32.2–75.6)	51.2 (35.1–67.1)

Median ER degradation was 69% (range: 28%–95%)

Phase 3 VERITAC-2 Trial
- Fulvestrant vs ARV471 200 mg/d

Hurvitz, **Schott** et al, SABC 2022

Additional Phase III SERD Trials for MBC: Examples

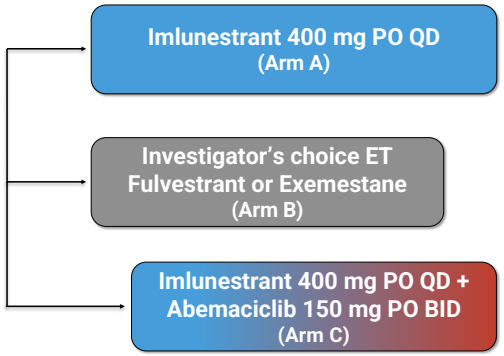
EMBER-3

1:1:1 Randomization
N = ~860

ER+, HER2-, Advanced Breast Cancer

- Relapsed on (neo) adjuvant/within 1 year of adjuvant AI, alone or in combination with a CDK4/6 inhibitor
  OR
- Progressed on 1L AI, alone or in combination with a CDK4/6 inhibitor
- Prior CDK4/6i treatment is expected if approved and reimbursed

Stratified for:
- Prior CDK4 & 6 inhibitor therapy
- Presence of visceral metastases
- Region

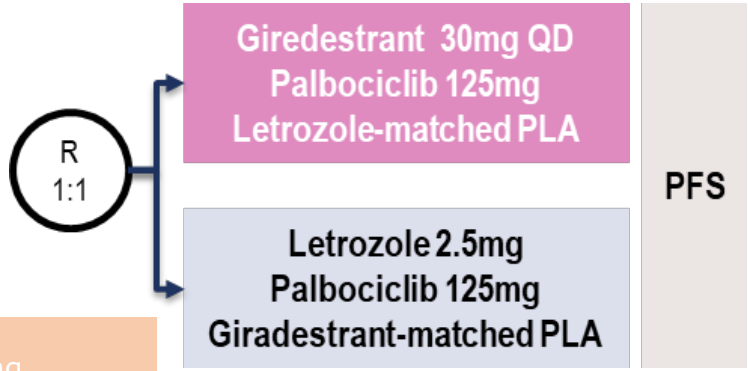


Primary Objectives:
- Investigator-assessed PFS for A vs B
- Investigator-assessed PFS for A vs B in the *ESR1*-mutation detected population
- Investigator-assessed PFS for C vs A (gated, i.e. only tested if A vs B is stat sig)

Secondary Objectives:
- OS (gated), PFS by BICR, ORR, CBR, DoR, PRO's

persevERA

N=978
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

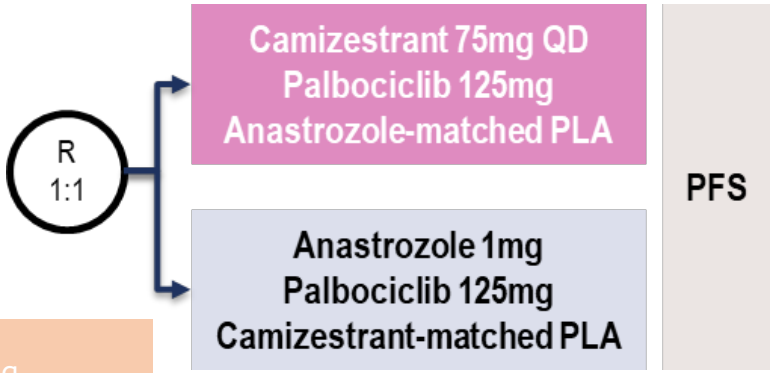


Recruiting

NCT04546009

SERENA-4

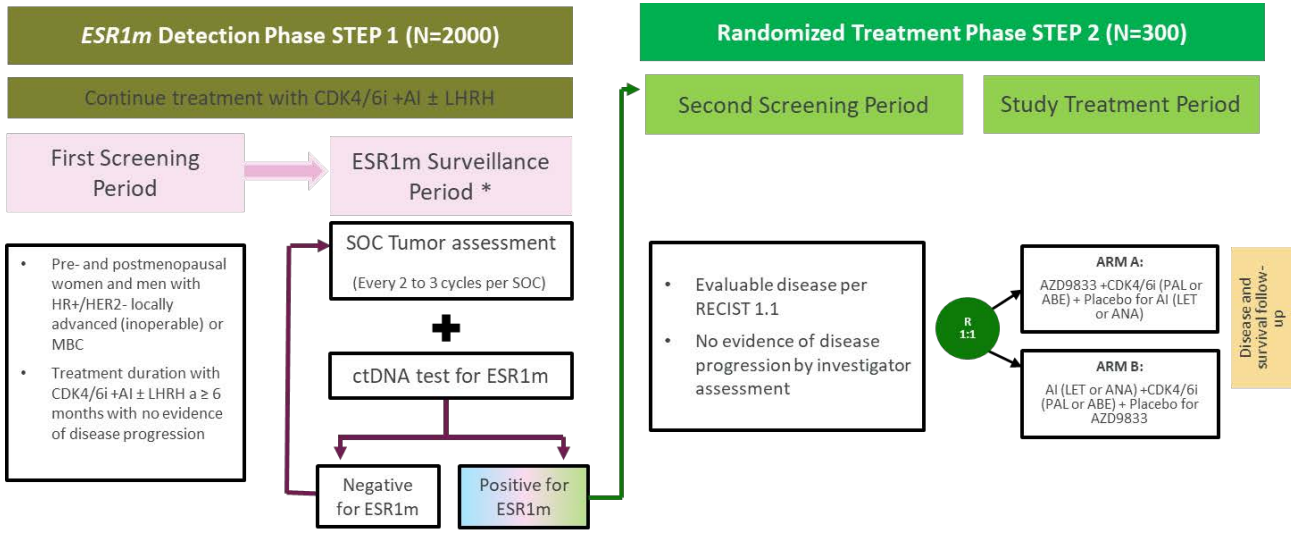
N=1342
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



Recruiting

NCT04711252

SERENA-6



CDK Inhibitors in Clinical Development

Drug	Target	Available and upcoming data	Trial
PF-07104091	CDK2	**ASCO 2023 #3010 (PD)**	NCT04553133
PF-07220060	CDK4	**ASCO 2023 #3009 (PD)**	NCT04557449
PF-06873600	CDK2/4/6	Hematologic and GI AEs; ORR 8% (Yap T et al, SABCS 2021)	NCT03519178 discontinued
PF-07220060 + PF-07104091	CDK4 + CDK2	Phase I/II study in progress	NCT05262400
BLU-222	CDK2	**ASCO 2023 #3095 (P)**	NCT05252416
Samuraciclib	CDK7	Combination with giredestrant Combination with elacestrant Phase II with fulvestrant	NCT04802759 TBD TBD
SY-5609	CDK7	GI AEs; activity in pancreatic cancer (ESMO 2021) Combo with Fulv in BC: **ASCO 2023 #3081 (P)**	NCT04247126
XL102	CDK7	GI AEs, combos ongoing (Patnaik A et al, SABCS 2022)	NCT04726332

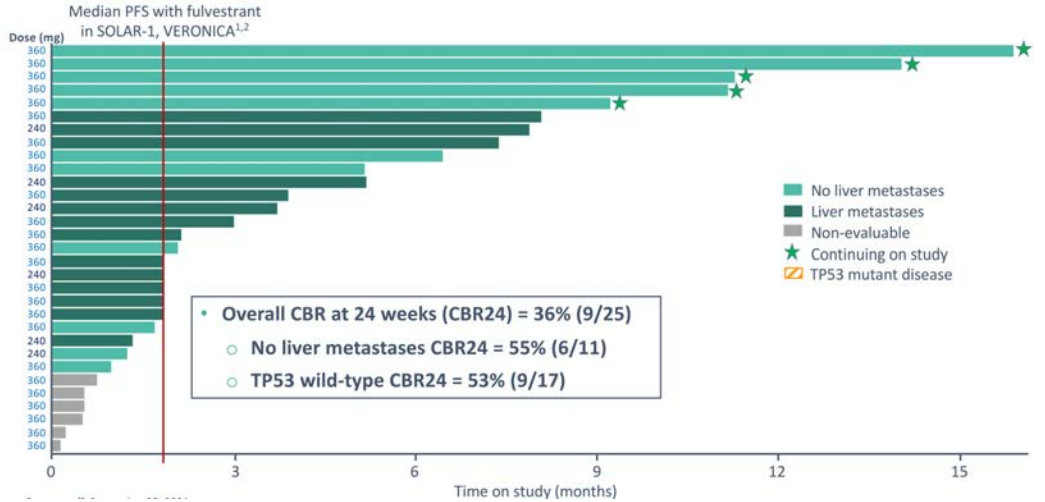
… and more to come

Phase I of Samuraciclib (CDK7 inhibitor)

Module 2A

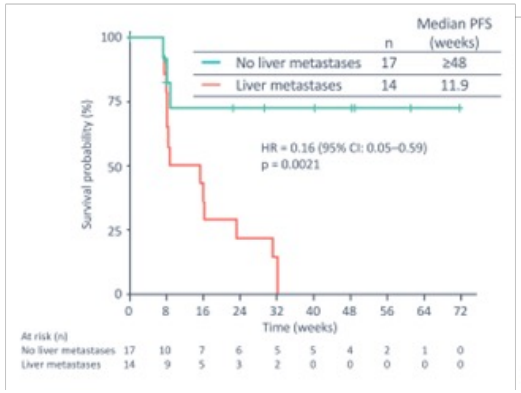
- Female, aged ≥18 years
- Histologically confirmed, metastatic or locally advanced, ER+ and/or PGR+, HER2- breast cancer
- Measurable disease
- Prior CDK4/6 inhibitor therapy
- No prior fulvestrant
- ≤1 line of chemotherapy or ≤2 lines of endocrine therapy for advanced breast cancer

→ **Samuraciclib 240 mg QD + fulvestrant 500 mg q4w (n=6)** → **Samuraciclib 360 mg QD + fulvestrant 500 mg q4w (n=25)**

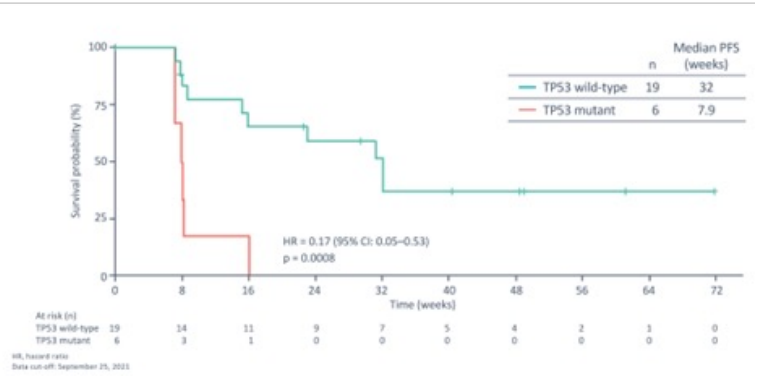


Adverse event	All grades, n (%)	Grade ≥3, n (%)
Diarrhea	28 (90)	6 (19)
Nausea	25 (81)	3 (10)
Vomiting	23 (74)	1 (3)
Fatigue	11 (36)	1 (3)
Decreased appetite	9 (29)	0
Abdominal pain	7 (23)	0
AST increased	4 (13)	0
Dysgeusia	4 (13)	0
Headache	4 (13)	0
Upper abdominal pain	4 (13)	0

PFS according to liver metastasis



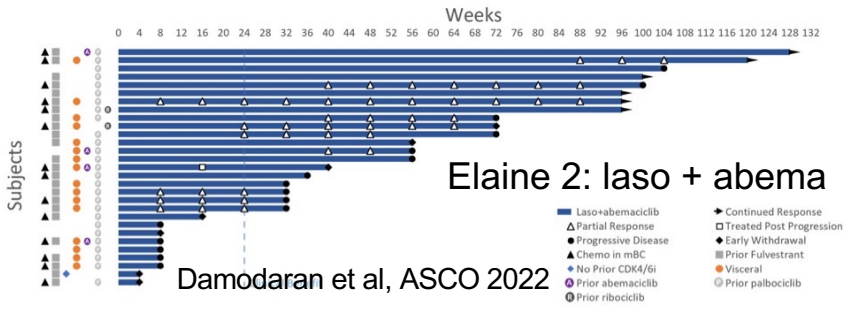
PFS according to TP53



Coombes RC et al, SABCS 2021

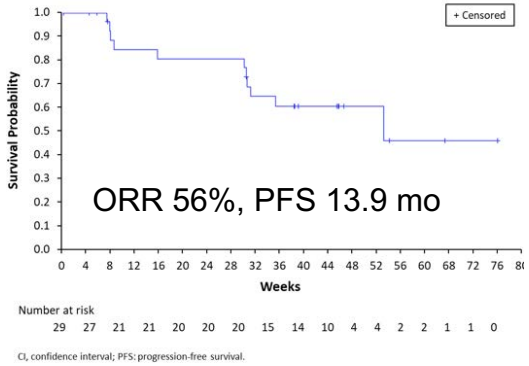
Other Investigational Endocrine Agents

- SARM: selective androgen receptor modulator
  - Enobosarm: ORR 48%, CBR 80%, and median PFS 5.5 months in AR+++ (n=24) (Palmieri et al, ASCO 2021)
    - Phase III ARTEST trial ongoing in 2-3rd line metastatic setting
    - Fast track designation by FDA
- SERM: Lasofoxifene
  - Phase III Elaine III: Fulv/abema vs Laso/abema, N=400



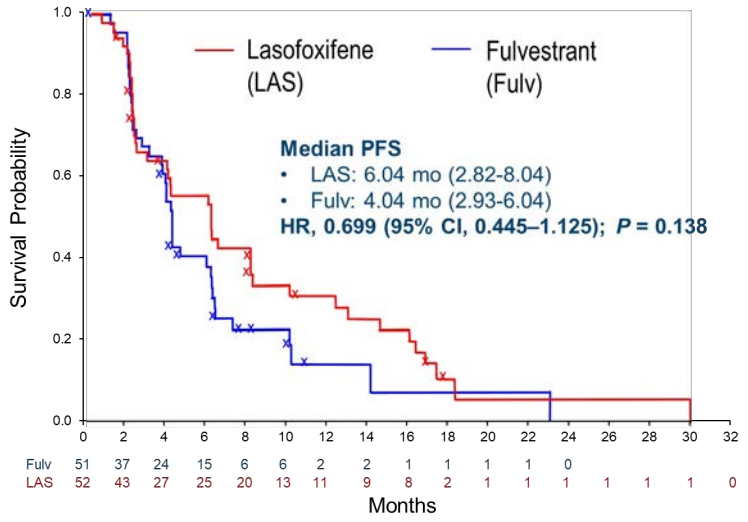
Damodaran et al, ASCO 2022

Elaine 2: laso + abema



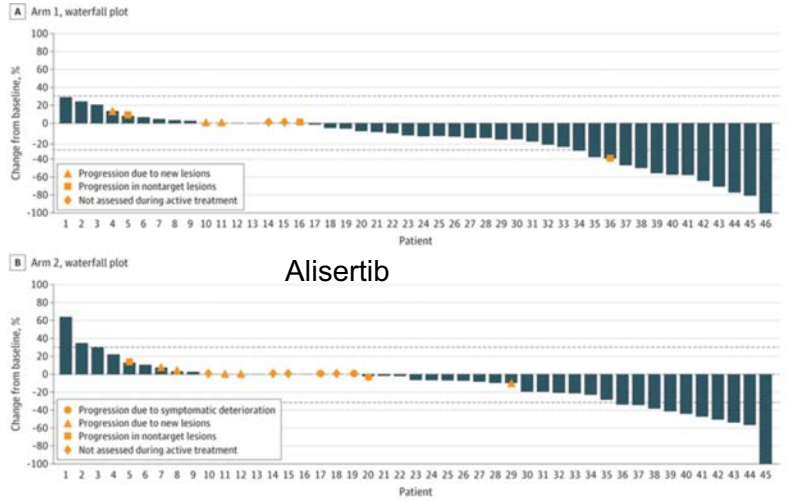
ORR 56%, PFS 13.9 mo

Lasofoxifene



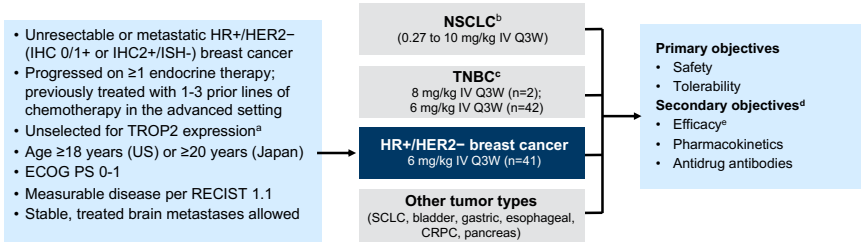
Elaine 1: Goetz et al, ESMO 2022; SABCS 2022

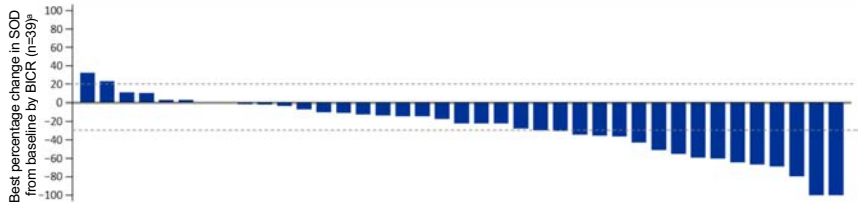
- Aurora Kinase A: alisertib (Haddad, JAMA 2023)
  - ORR alisertib alone (n=46): 19.6%; med DoR 15.1 mo; CBR 41.3%; mPFS 5.6 mo
  - Primary toxicity neutropenia



Alisertib

Phase 1 TROPION-PanTumor01: Datopotomab deruxtecan in HR+/HER2neg MBC





Meric-Bernstam et al, SABCS 2022

- N=41
  - Median of 2 prior chemo for MBC (Range: 1-6)
  - 95% prior CDKi
- Efficacy:
  - ORR (all PR): 27%;
  - CBR: 44%
  - Med PFS 8.3 mo
  - 59% alive for >1 year
- Safety (all Gr/≥Gr 3):
  - Stomatitis: 83/10%
  - Nausea: 56/0%
  - Alopecia: 37%
  - Pneumonitis: Gr 2 and 3 (2 pts)

Novel TROP2 ADC

Neoadjuvant in I-SPY2

TROPION-Breast01 (NCT05104866)[1,a]

Second/Third-Line Therapy for HR+/HER2- MBC

- HR+/HER2- inoperable/metastatic breast cancer with PD following 1 or 2 lines of chemotherapy (and progressed on or not suitable for ET)
- Targeted agents (inhibitors of mTOR, PD-1/PD-L1, CDK4/6, PARP) and ET do not count as prior lines of chemotherapy
- ≥1 measurable lesion
- FFPE tumor sample
- Adequate organ function

R
1:1

Dato-DXd
6 mg/kg IV Q3W
n = 350

Investigator's choice of chemotherapy
(eribulin, vinorelbine, capecitabine, or gemcitabine)
n = 350

Stratification
- 1 vs 2 previous lines of chemotherapy in the inoperable/metastatic setting
- Geographic location (US, Canada, EU vs rest of world)
- Previous CDK4/6i use

Primary endpoints
- PFS (BICR), OS

Secondary endpoints
- PFS (inv), ORR, DOR, DCR, PROs, safety, tolerability, PK, and immunogenicity

Exploratory endpoints
- TROP2 IHC

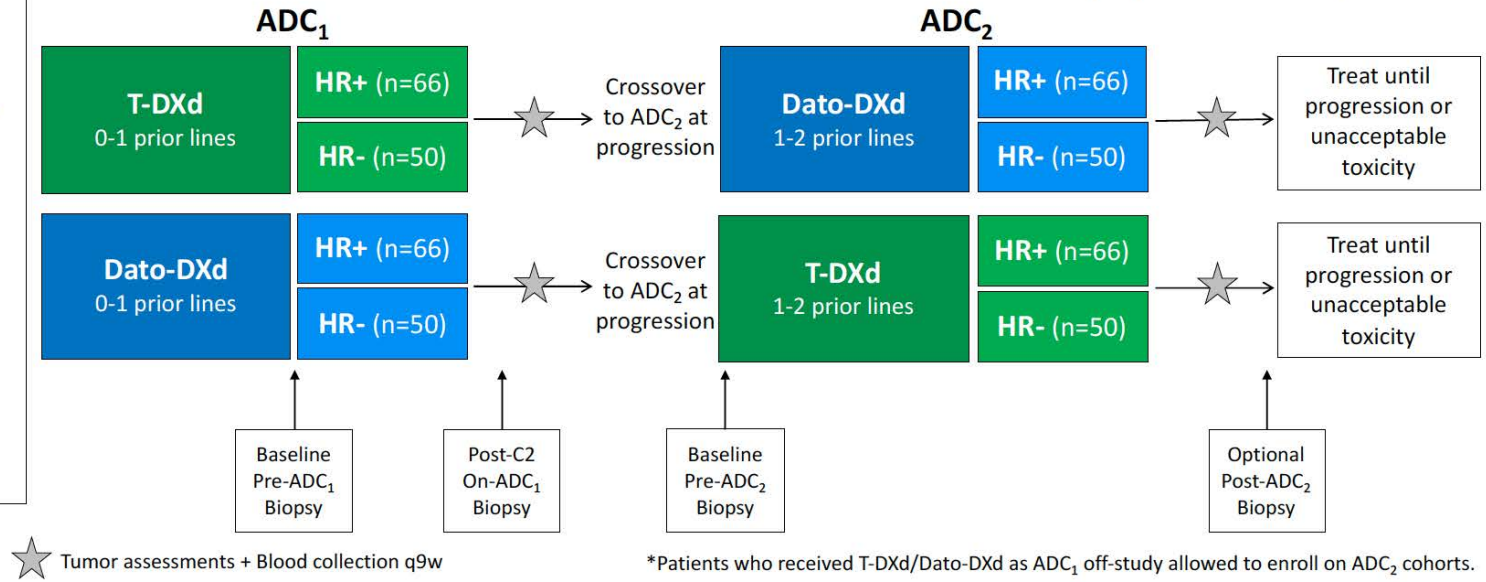
TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd (TRADE DXd).
PI: Ana Garrido-Castro

Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low BC: IHC 1+ or 2+/ISH- (any sample: primary or met)
- Measurable disease
- Prior endocrine therapy and CDK4/6 inhibitor for HR+ MBC
- Prior topo-I inhibitor allowed only in neo-/adjuvant setting(s) and if ≥12m elapsed since last dose to metastatic recurrence

*Randomization 1:1 to T-DXd or Dato-DXd as ADC_1 for allocation purposes.

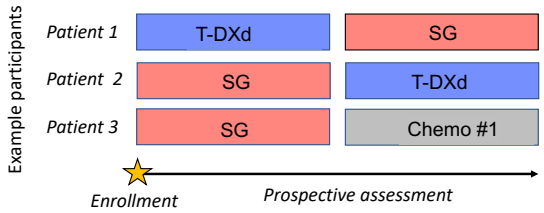
Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR



*Patients who received T-DXd/Dato-DXd as ADC_1 off-study allowed to enroll on ADC_2 cohorts.

Registry Sequencing Study:
Laura Huppert UCSF

Cohorts 1 & 2: Enrollment Prior to ADC #1



Cohort 1: HR+/HER2-HER2 low
~35 patients

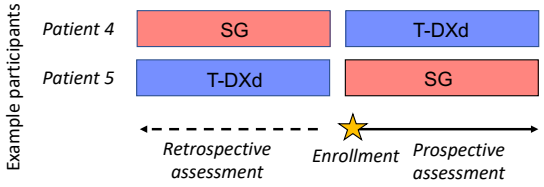
Cohort 2: TNBC, HER2 low
~25 patients

- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

Objectives/considerations:

- Allows for prospective assessment of ADC #1 and ADC #2 efficacy, including PRO data and collection of blood for translational endpoints
- Potential barrier: Patient not guaranteed to get ADC #2 (e.g., example patient #3 shown here)

Cohorts 3 & 4: Enrollment Prior to ADC #2



Cohort 3: HR+/HER2-
~25 patients

Cohort 4: TNBC
~15 patients

- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

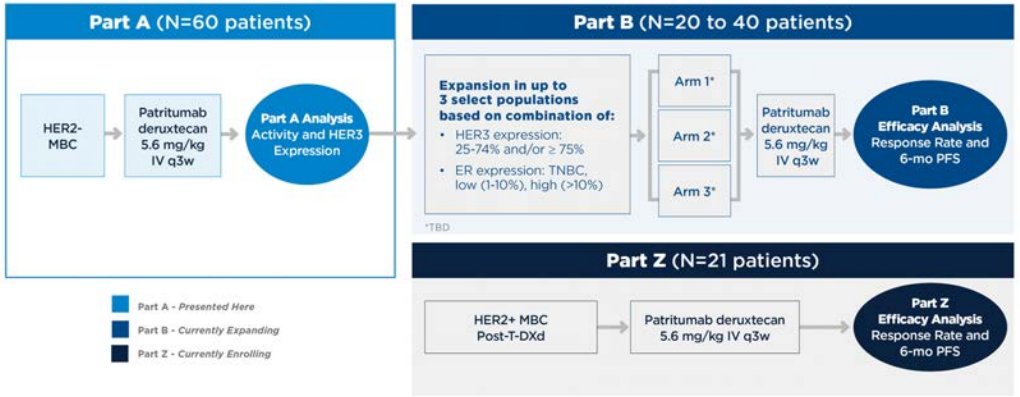
Objectives/considerations:

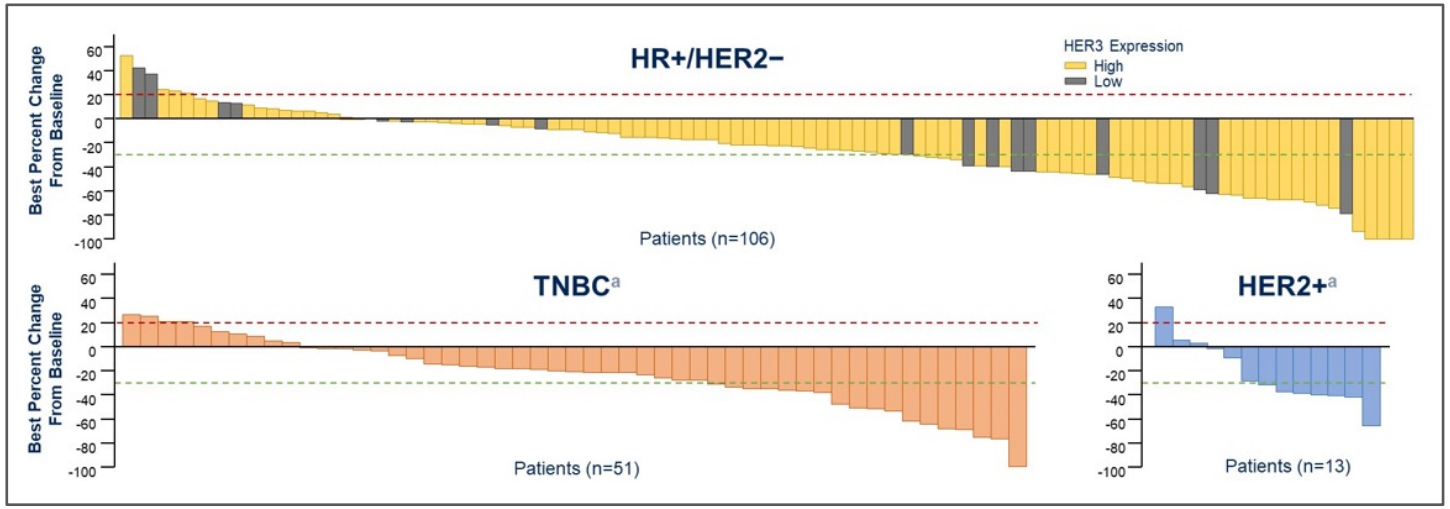
- Allows for prospective assessment of ADC #2 safety and efficacy, including PRO data and translational endpoints
- Allows for retrospective safety and efficacy of ADC #1

Patritumab deruxtecan: Activity in HER3-expressing MBC

- Patritumab deruxtecan: Anti HER3 Ab (Patritumab) connected to a Topo I payload (DXd) via a cleavable linker
- Data from expansion of a phase 1/2 trial in HER3 expressing MBC
  - Heavily pretreated patient population with median priors ranging from 2-6 depending on subtype

FDA Fast track designation for metastatic EGFR mutated NSCLC





- ✓ **Durable antitumor activity in all BC subtypes across the range of HER3 expression**
- ✓ **Manageable safety profile with low rates of treatment discontinuation**
- ✓ **Most common toxicities: GI and heme**
  - **10% discontinuation due to AEs**
  - **27% grade 3 thrombocytopenia**
  - **6.6% ILD; 1 death**

Subtype	ORR	Median DoR
HR+/HER2-	30%	7.2 mo
HER2+	23%	5.9 mo
TNBC	43%	8.3 mo

Krop I et al. ASCO 2022,

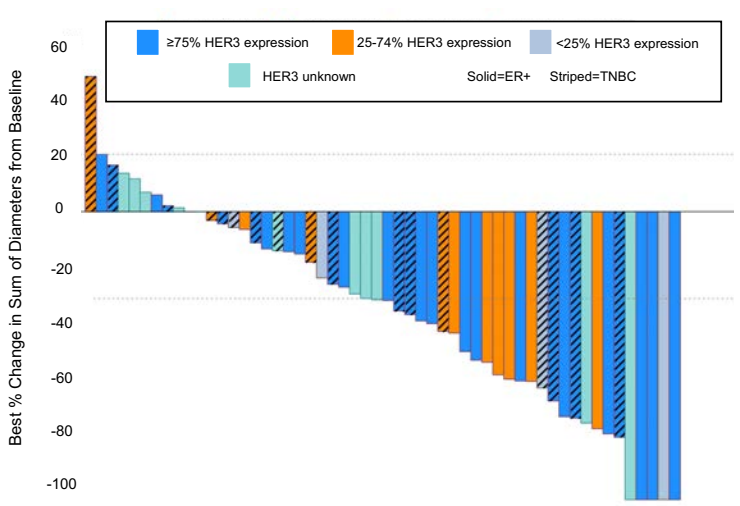
Data from Part A: HER3-DXd

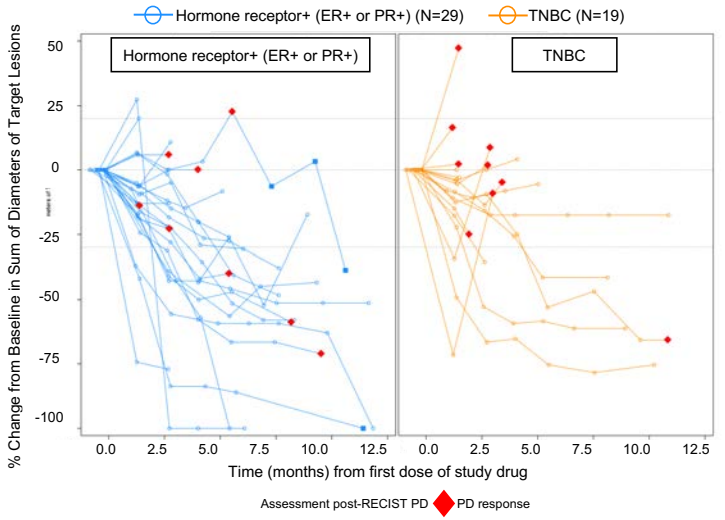
- 60 pts:
  - HR+: Prior CDKi, 0-2 chemo
  - TN: 1-3 chemo
  - 27HR+/19TN (n=48)
  - Med 3 prior regimens
  - 64% HER3 ≥75%; 8% <25% (n=47)
- ORR 35%, CBR 43%, DOR ≥ 6mo
  - No relationship to HER3 expression
- Med DOR: 10 mo
- Most common AE:
  - Nausea/diarrhea/fatigue
  - TEAE: 2 ILD, 1 low plt

	(N=60) n (%)
Number of Prior Systemic Regimens in Metastatic Setting	
1-2 prior regimens	24 (40.0)
3 or more prior regimens	36 (60.0)
Median (range)	**3 (1, 9)**
Type of Prior Regimens in the Metastatic Setting*	
Chemotherapy	54 (90.0)
PARP inhibitors	3 (5.0)
Immunotherapy	12 (20.0)
Sacituzumab govitecan	5 (8.3)

	HR+ (N=29)	TNBC (N=19)
ORR, n (%)	**12 (41.4)**	**4 (21.1)**
95% CI	(23.5, 61.1)	(6.1, 45.6)

	Any grade (N=60) n (%)	Grade 3/4 (N=60) n (%)
Any Adverse Event (AE)	56 (93.3)	19 (31.7)
Nausea	30 (50.0)	2 (3.3)
Fatigue	27 (45.0)	4 (6.7)
Diarrhea	22 (36.7)	3 (5.0)
Vomiting	19 (31.7)	1 (1.7)
Anemia	18 (30.0)	0
Alopecia	17 (28.3)	N/A
Hypokalemia	9 (15.0)	1 (1.7)
Decreased Appetite	8 (13.3)	0
Neutrophil Count Decreased**	7 (11.7)	3 (5.0)
White Blood Cell Count Decreased**	7 (11.7)	1 (1.7)





Hamilton et al, ASCO 2023

Agenda

Module 1: Long-Term Management of HER2-Positive Breast Cancer — Dr Krop

Module 2: Optimizing the Management of ER-Positive Localized Breast Cancer — Dr Kalinsky

Module 3: Considerations in the Care of Patients with ER-Positive mBC — Dr Jhaveri

Module 4: Novel and Emerging Strategies for ER-Positive mBC — Dr Rugo

Module 5: Evolving Clinical Decision-Making for Localized Triple-Negative Breast Cancer (TNBC) — Dr O'Shaughnessy

Module 6: Recent Advances in the Treatment of Metastatic TNBC (mTNBC) — Prof Schmid

Management of triple-negative localized breast cancer; selection of patients for adjuvant olaparib

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

RTP
RESEARCH
TO PRACTICE

In general, what would you recommend as adjuvant treatment for a patient with BRCA wild-type TNBC who has residual disease after neoadjuvant chemotherapy/pembrolizumab?

 Dr Jhaveri	Pembrolizumab + capecitabine
 Dr Kalinsky	Pembrolizumab + capecitabine
 Dr Krop	Pembrolizumab + capecitabine
 Dr O'Shaughnessy	Pembrolizumab + capecitabine
 Dr Rugo	Pembrolizumab + capecitabine
 Prof Schmid	Pembrolizumab + capecitabine
 Dr Hurvitz	Pembrolizumab + capecitabine
 Dr Tolaney	Pembrolizumab + capecitabine
 Dr Traina	Pembrolizumab + capecitabine

RTP RESEARCH TO PRACTICE

In general, what would you recommend as adjuvant treatment for a patient with TNBC and a germline BRCA mutation who has residual disease after neoadjuvant chemotherapy/pembrolizumab?

 Dr Jhaveri	Pembrolizumab + olaparib	 Prof Schmid	Pembrolizumab + olaparib
 Dr Kalinsky	Pembrolizumab + olaparib	 Dr Hurvitz	Pembrolizumab + olaparib
 Dr Krop	Pembrolizumab + olaparib	 Dr Tolaney	Pembrolizumab + olaparib
 Dr O'Shaughnessy	Pembrolizumab + olaparib	 Dr Traina	Pembrolizumab + olaparib
 Dr Rugo	Pembrolizumab + olaparib		

RTP RESEARCH TO PRACTICE

PARP inhibitor tolerability

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

RTP
RESEARCH
TO PRACTICE

In your experience, what is the approximate likelihood that a patient will be able to complete the full 1-year course of adjuvant olaparib?

 Dr Jhaveri	95%
 Dr Kalinsky	90%
 Dr Krop	15%
 Dr O'Shaughnessy	90%
 Dr Rugo	100%
 Prof Schmid	100%
 Dr Hurvitz	60%
 Dr Tolaney	95%
 Dr Traina	>90%

RTP
RESEARCH
TO PRACTICE

In general, do you initiate preemptive medication for nausea and vomiting when administering PARP inhibitors?

 Dr Jhaveri	No	 Prof Schmid	No
 Dr Kalinsky	No	 Dr Hurvitz	Yes
 Dr Krop	No	 Dr Tolaney	Yes
 Dr O'Shaughnessy	No	 Dr Traina	Yes
 Dr Rugo	No		

RTP
RESEARCH
TO PRACTICE

In general, when administering adjuvant olaparib to a patient with BC, do you discuss the risk of developing AML/MDS, and if so, do you provide an estimate of risk?

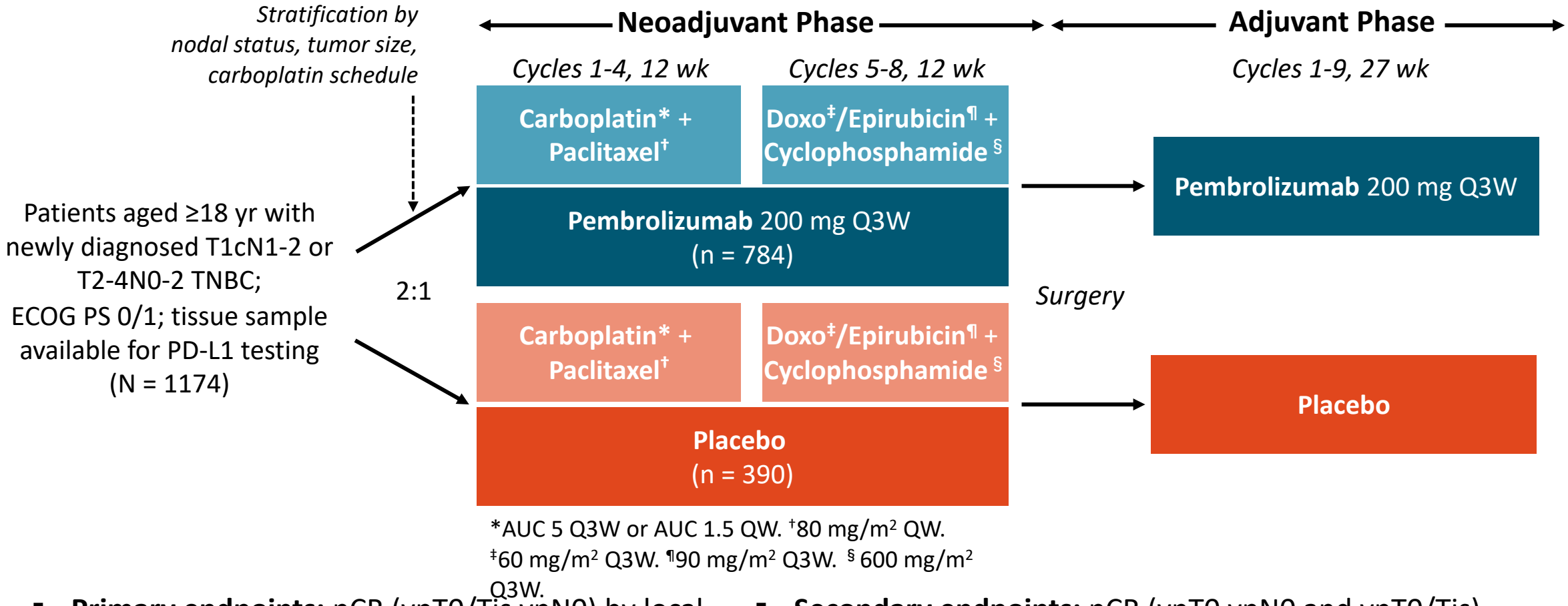
 Dr Jhaveri	No
 Dr Kalinsky	No
 Dr Krop	Yes, but I do not provide a risk estimate
 Dr O'Shaughnessy	Yes, but I do not provide a risk estimate
 Dr Rugo	Yes, specifically that there does not appear to be an increased risk
 Prof Schmid	Yes, but I do not provide a risk estimate
 Dr Hurvitz	Yes, very small (<5%)
 Dr Tolaney	Yes, <1%
 Dr Traina	Yes, <0.5%

RTP RESEARCH TO PRACTICE

Evolving Clinical Decision-Making for Localized Triple Negative Breast Cancer (TNBC)

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

KEYNOTE-522: Study Design

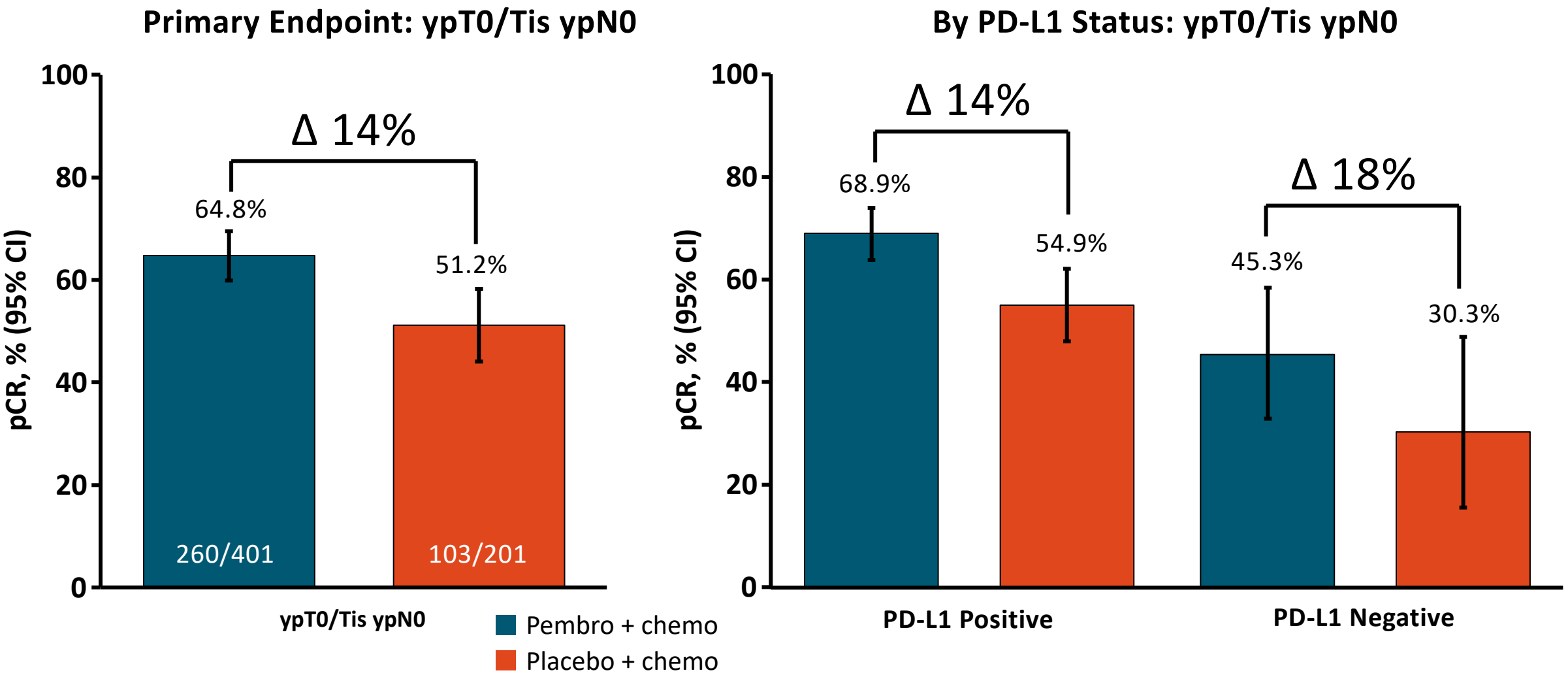


*AUC 5 Q3W or AUC 1.5 QW. †80 mg/m² QW. ‡60 mg/m² Q3W. ¶90 mg/m² Q3W. § 600 mg/m² Q3W.

- **Primary endpoints:** pCR (ypT0/Tis ypN0) by local review, EFS by local review
- **Secondary endpoints:** pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS, AE
- **Exploratory endpoints:** RCB, pCR by subgroups, EFS by pCR

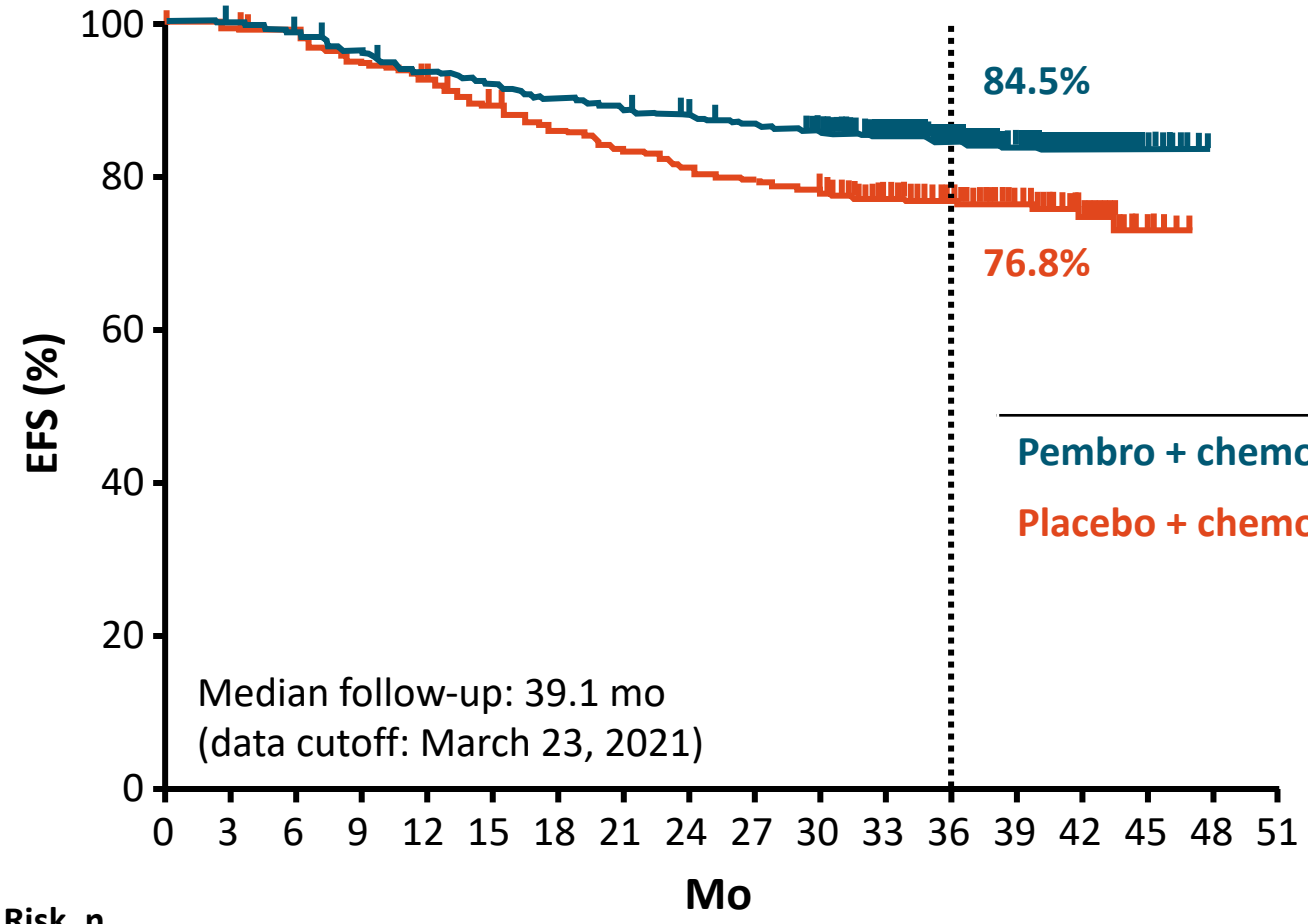
Schmid. NEJM. 2020;382:810.

KEYNOTE-522: pCR at IA1



Schmid. NEJM. 2020;382:810.

KEYNOTE-522: EFS at IA4



	Events, %	HR (95% CI)
Pembro + chemo	15.7	0.63 (0.48-0.82; *P* <.001*)
Placebo + chemo	23.8	

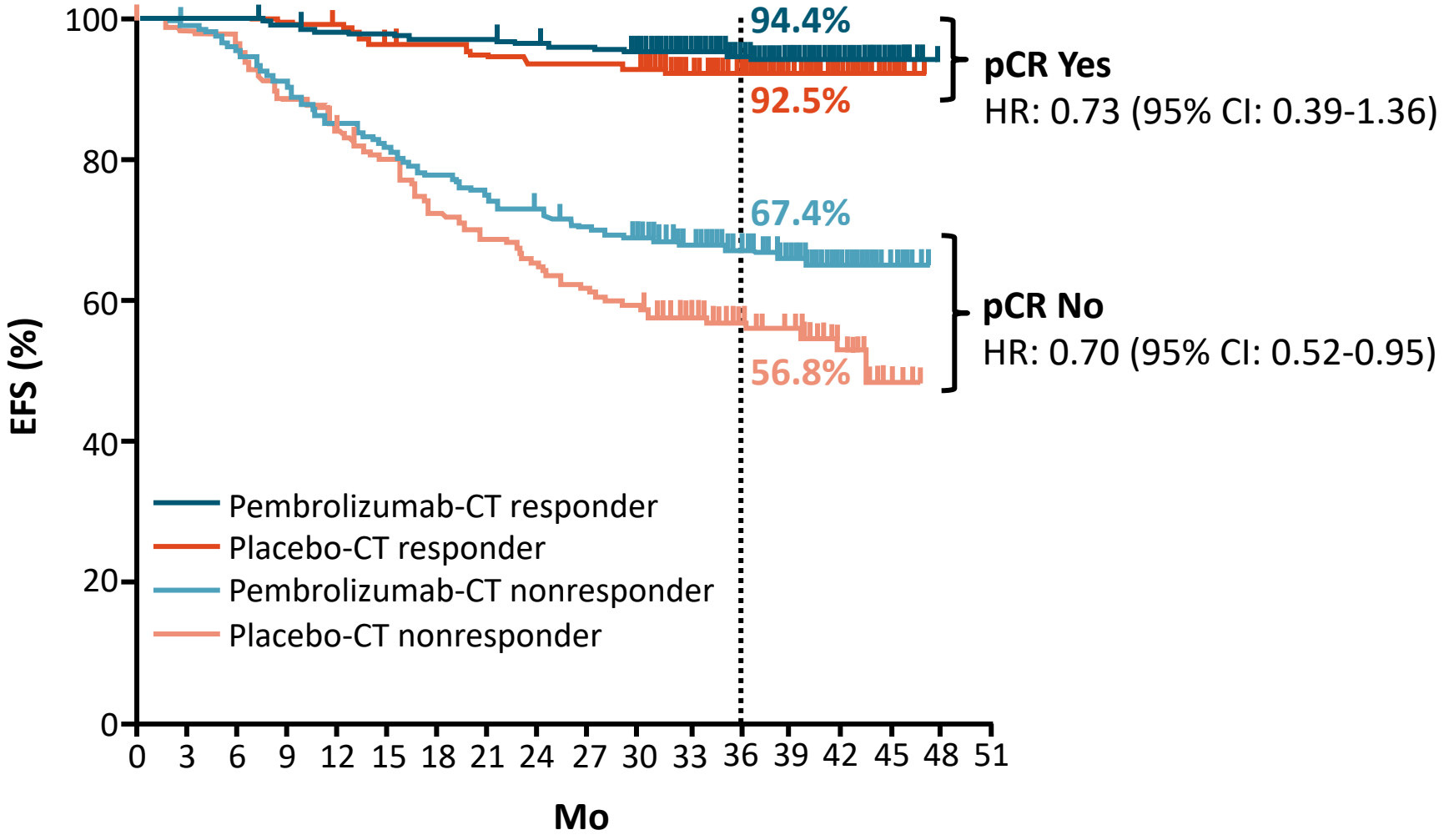
*Crossed prespecified boundary of *P* = .01034.

Patients at Risk, n

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

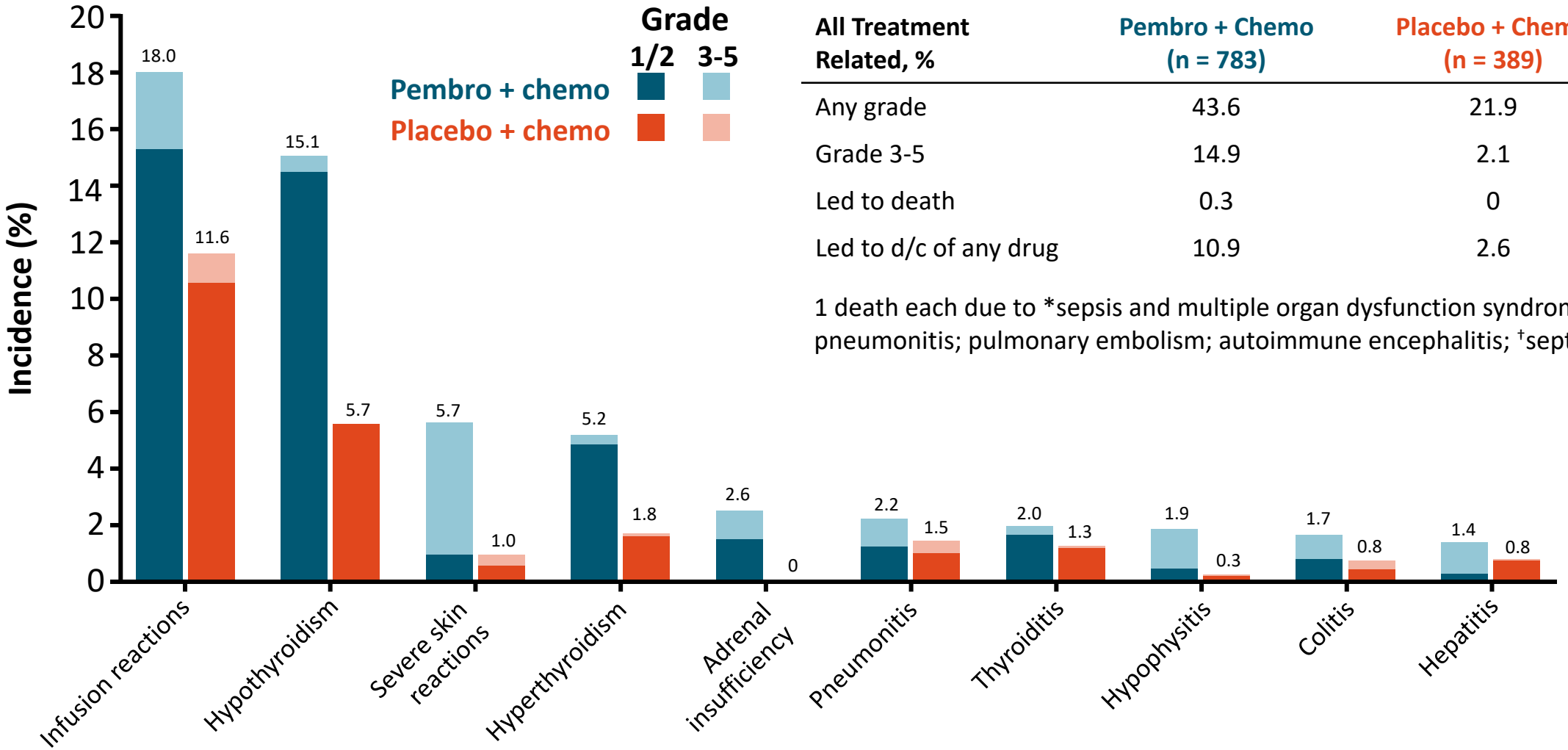
Schmid. NEJM. 2022;386:556.

KEYNOTE-522: EFS by pCR



Schmid. NEJM. 2022;386:556.

KEYNOTE-522: Immune-Related Adverse Events



All Treatment Related, %	Pembro + Chemo (n = 783)	Placebo + Chemo (n = 389)
Any grade	43.6	21.9
Grade 3-5	14.9	2.1
Led to death	0.3	0
Led to d/c of any drug	10.9	2.6

1 death each due to *sepsis and multiple organ dysfunction syndrome; pneumonitis; pulmonary embolism; autoimmune encephalitis; †septic shock.

Immune-Mediated AEs and Infusion Reactions With Incidence ≥10 Patients

Schmid. ESMO 2021. Abstr VP7_2021.

Phase II NeoPACT: Neoadjuvant Pembrolizumab + Carboplatin/Doxorubicin in TNBC

- Multicenter phase II trial evaluating de-intensified, anthracycline-free neoadjuvant tx for TNBC

Patients with stage I-III TNBC; T >1 cm or N+; ER/PR ≤10%; HER2 negative per ASCO/CAP guidelines (N = 115)

→ **Carboplatin** AUC 6 + **Docetaxel** 75 mg/m^2 + **Pembrolizumab** 200 mg Q21D x 6 → **Surgery** → *Follow-up; adjuvant therapy permitted (no pembrolizumab)*

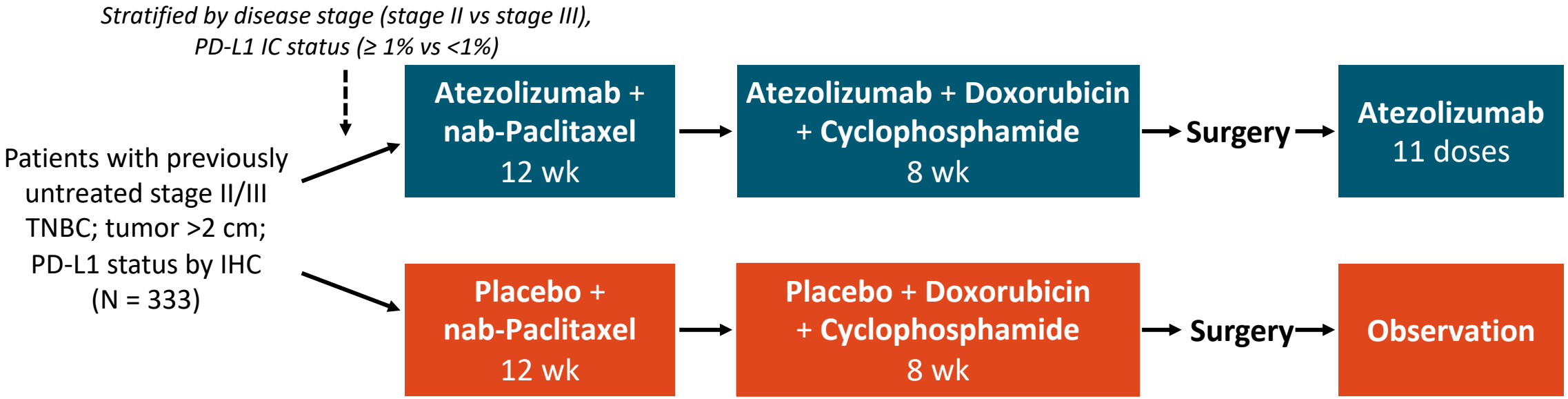
Primary Endpoint: pCR, %		Patients (N = 115)
All, % (95% CI)		58 (48-67)
TNM	▪ I ▪ II ▪ III	69 59 43
Nodal status	▪ Negative ▪ Positive	65 46
PD-L1 status	▪ Negative ▪ Positive	39 76

Secondary Efficacy Endpoints, %	Patients (N = 115)
RCB 0+1	69
2-yr EFS ▪ With pCR ▪ Without pCR	89 98 78
2-yr OS ▪ With pCR ▪ Without pCR	90 100 76

Sharma. ASCO 2022. Abstr 513.

IMpassion031: Addition of Atezolizumab to Neoadjuvant Chemotherapy in Stage II-III TNBC

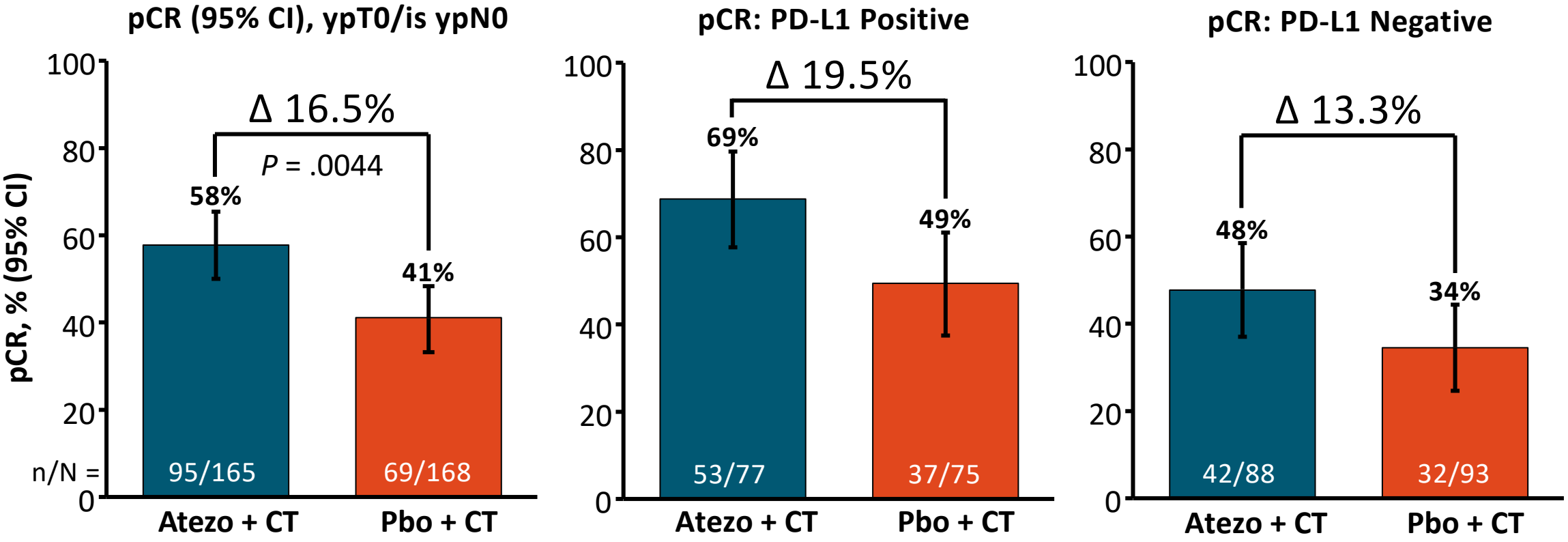
- Randomized, double-blind, placebo-controlled phase III trial



- **Primary endpoint:** pCR using AJCC staging system in ITT population and PD-L1+ subpopulation
- **Key secondary endpoints:** EFS, DFS, OS in all patients and PD-L1+ subpopulation, safety

Mittendorf. Lancet. 2020;396:1090. Harbeck. ESMO 2020. Abstr LBA11. NCT03197935.

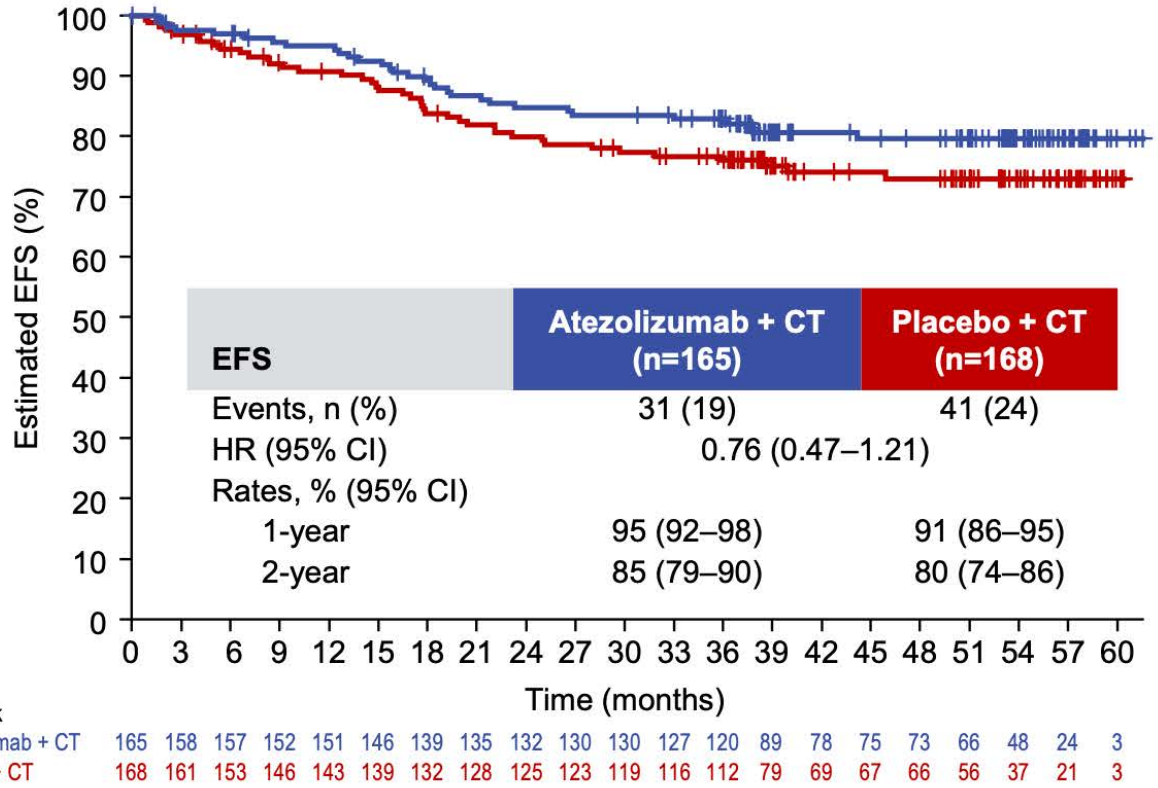
IMpassion031: pCR in ITT Population



Mittendorf. Lancet. 2020;396:1090. Harbeck. ESMO 2020. Abstr LBA11.

IMpassion031: EFS (ITT POPULATION AND SUBGROUPS)

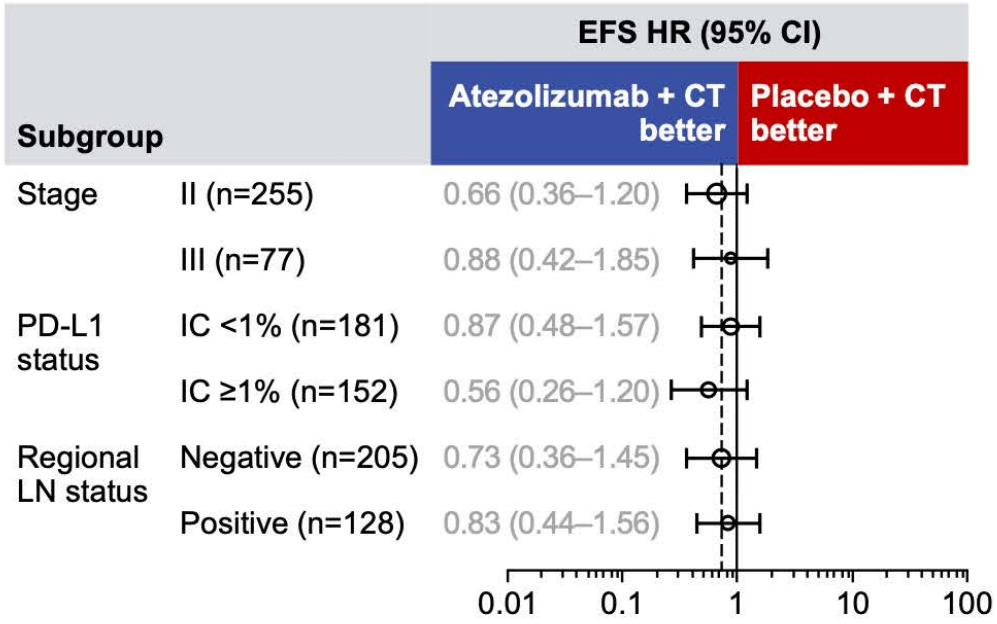
Atezolizumab provides significant pCR benefit and numerically improved EFS



EFS	Atezolizumab + CT (n=165)	Placebo + CT (n=168)
Events, n (%)	31 (19)	41 (24)
HR (95% CI)	0.76 (0.47–1.21)	
Rates, % (95% CI)		
1-year	95 (92–98)	91 (86–95)
2-year	85 (79–90)	80 (74–86)

No. at risk

Atezolizumab + CT	165	158	157	152	151	146	139	135	132	130	130	127	120	89	78	75	73	66	48	24	3
Placebo + CT	168	161	153	146	143	139	132	128	125	123	119	116	112	79	69	67	66	56	37	21	3

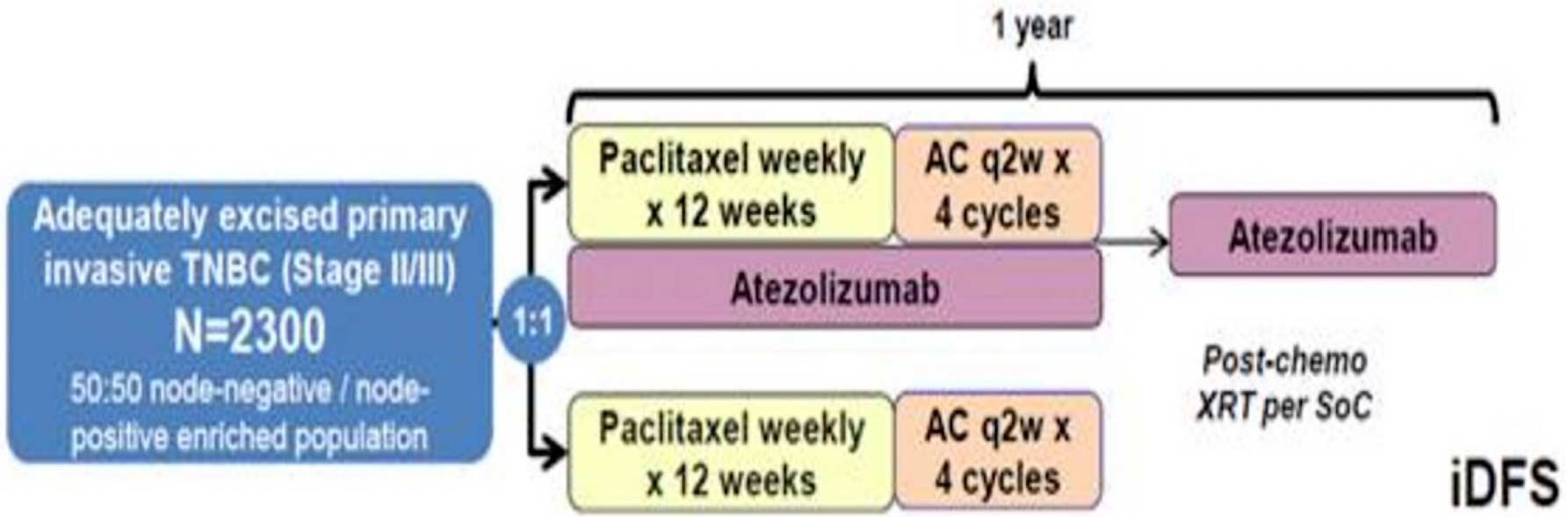


HR = hazard ratio

2023 ESMO BREAST CANCER

Barrios. ESMO Breast 2023. Abstr LBA1.

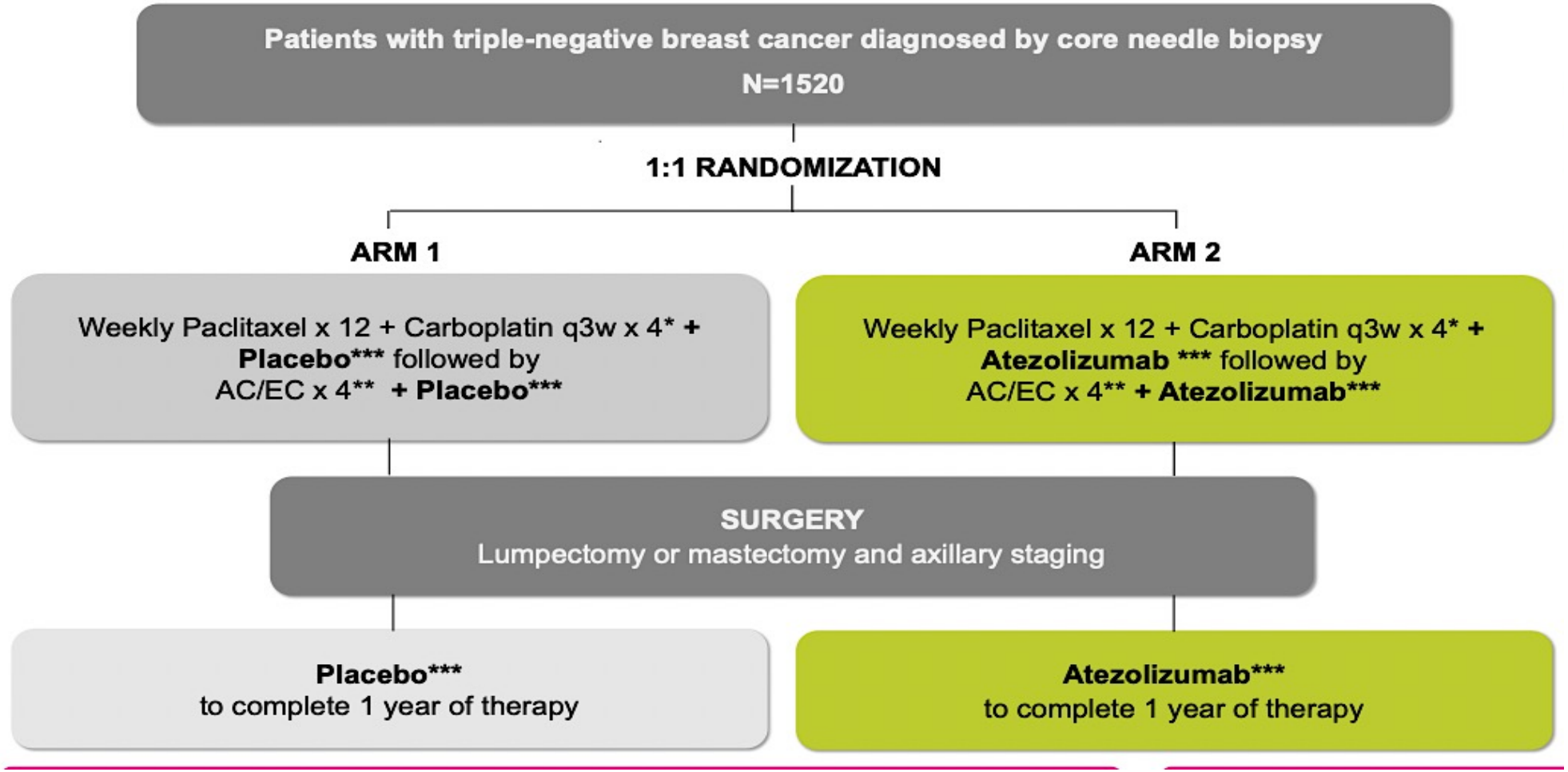
ALEXANDRA/IMpassion030 Futile for iDFS per DMC



X

NSABP B59/GBG 96-GeparDouze

Figure 1. GeparDouze Study Design



Who Should Be Tested for *BRCA1/2* Mutations?

Patients diagnosed at ANY AGE with breast cancer and any of the following:

- **To aid adjuvant therapy decision-making using olaparib in high-risk EBC**
- To aid systemic therapy decision-making using PARP inhibitors in the metastatic setting
- TNBC histology
- Lobular breast cancer and personal/family history of diffuse gastric cancer
- Male breast cancer
- ≥1 close male relative with breast cancer

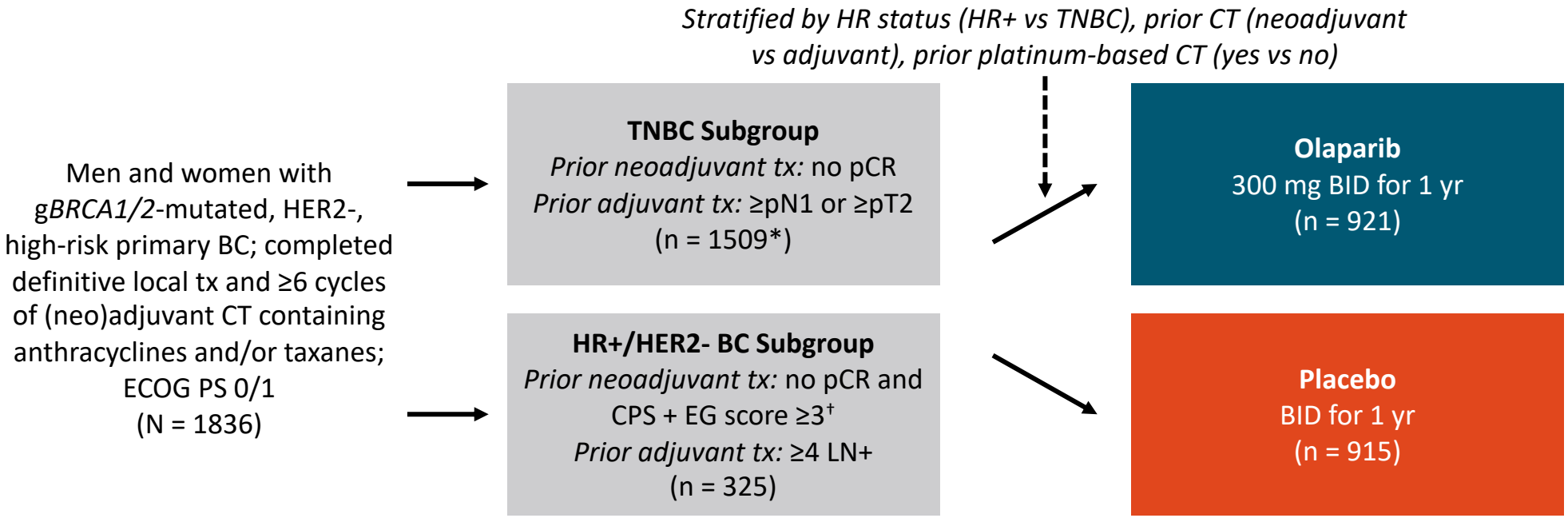
Patients with personal history of breast cancer and ≥1 of the following:

- Aged ≤45 yr at diagnosis
- Aged 46-50 yr at diagnosis, plus any:
  - Family history (unknown or limited)
  - Multiple primary breast cancers at any time interval
  - ≥1 close blood relative diagnosed at any age with breast, ovarian, pancreatic, or prostate cancer
- Aged ≥51 yr at diagnosis plus any of the following:
  - ≥1 close blood relative aged ≤50 yr with breast cancer
  - ≥1 close blood relative diagnosed at any age with ovarian or pancreatic cancer
  - Close male relative with breast cancer or high-risk prostate cancer
  - ≥3 total breast cancer diagnoses in patient/close blood relative
  - ≥2 blood relatives with breast or prostate cancer
- Ashkenazi Jewish ancestry

NCCN. Clinical practice guidelines in oncology: genetic/familial high-risk assessment: breast, ovarian, and pancreatic. v.2.2022. nccn.org. Accessed March 9, 2022.

OlympiA: Study Design

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



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

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

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

Tutt. NEJM. 2021;384:2394. NCT02032823.

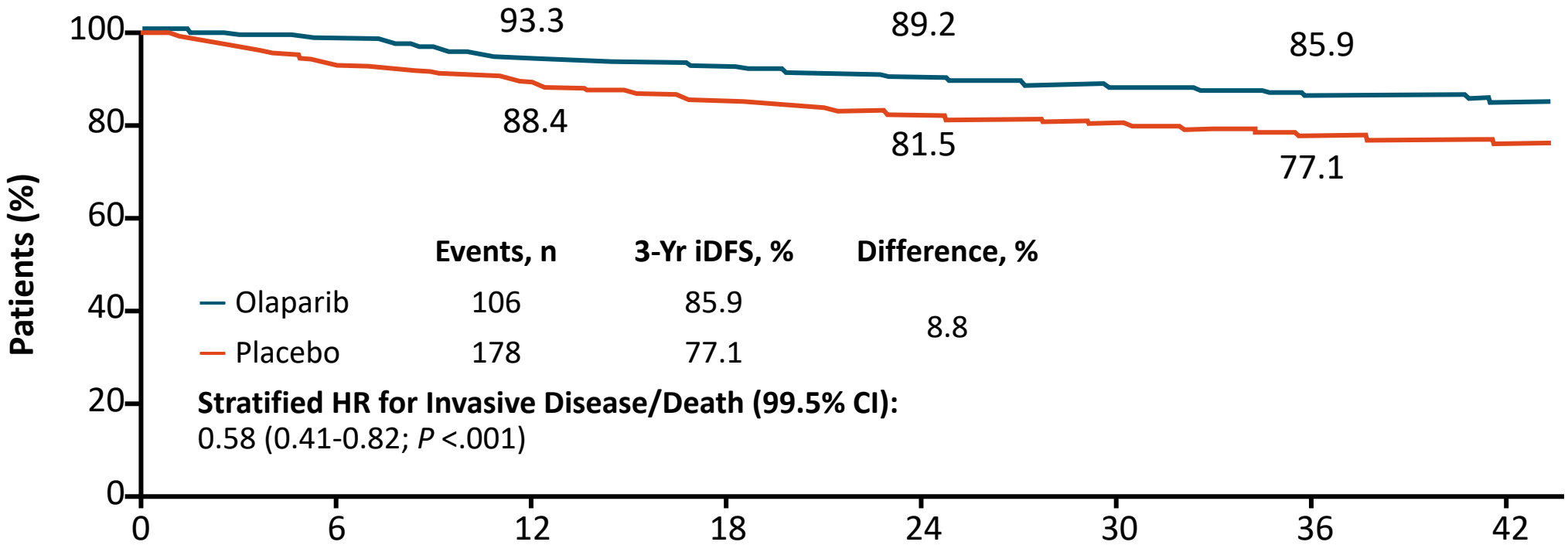
OlympiA: Baseline Patient Characteristics

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

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

Tutt. NEJM. 2021;384.2394.

OlympiA: Invasive Disease-Free Survival (ITT)

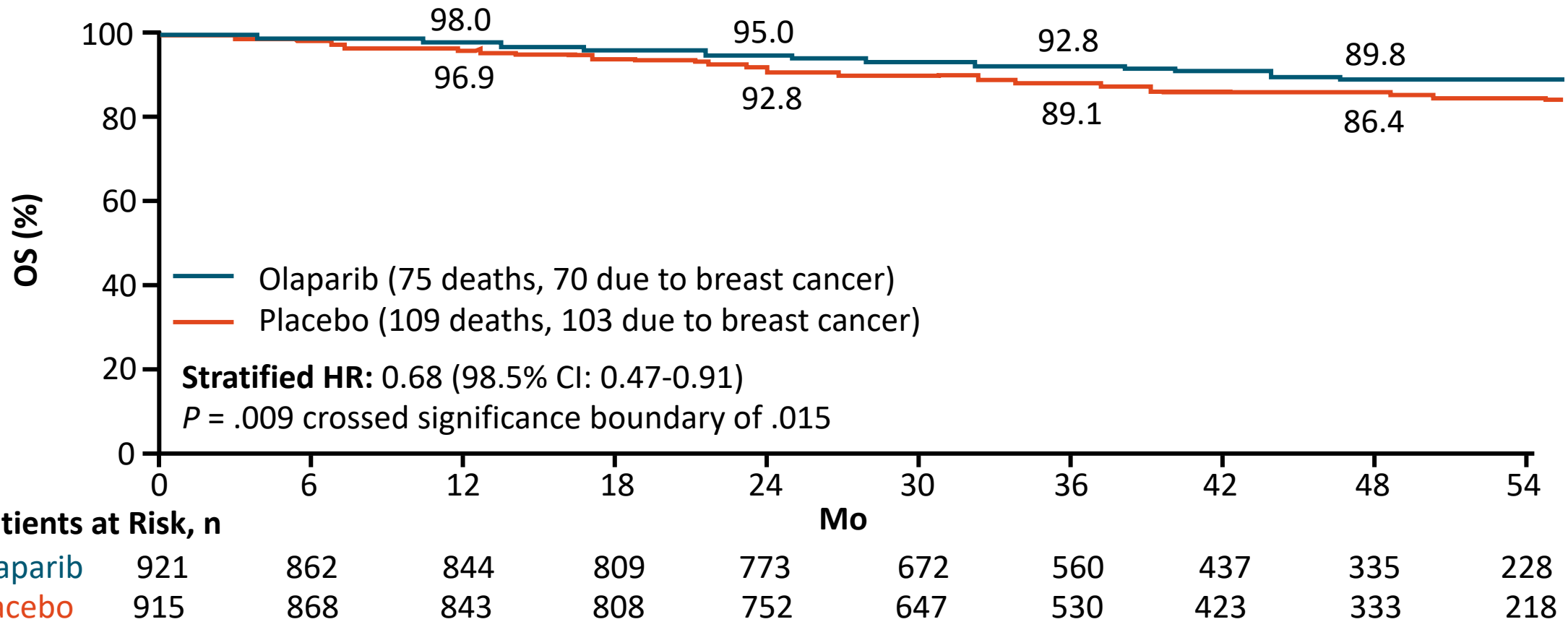


Patients at Risk, n

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

Tutt. NEJM. 2021;384:2394.

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



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

Tutt. ESMO 2022. Abstr VP1-2022.

OlympiA: AEs, Treatment Exposure, QoL

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

- In the olaparib arm, anemia was the most frequent AE at grade ≥3 in >1% patients
  - Transfusions: olaparib, 5.8%; placebo, 0.9%
- Median percentage of intended dose received: olaparib, 94.8%; placebo, 98.9%
- For the olaparib vs placebo arms:
  - Dose reductions: 25.0% vs 5.2%
  - Discontinuations due to AEs: 9.9% vs 4.2% (with olaparib, most commonly due to nausea, 2.0%; anemia, 1.8%; fatigue, 1.3%; decreased neutrophil count, 1.0%)
- No declines or clinically significant differences observed between arms in global health quality during tx

Tutt. NEJM. 2021;384:2394.

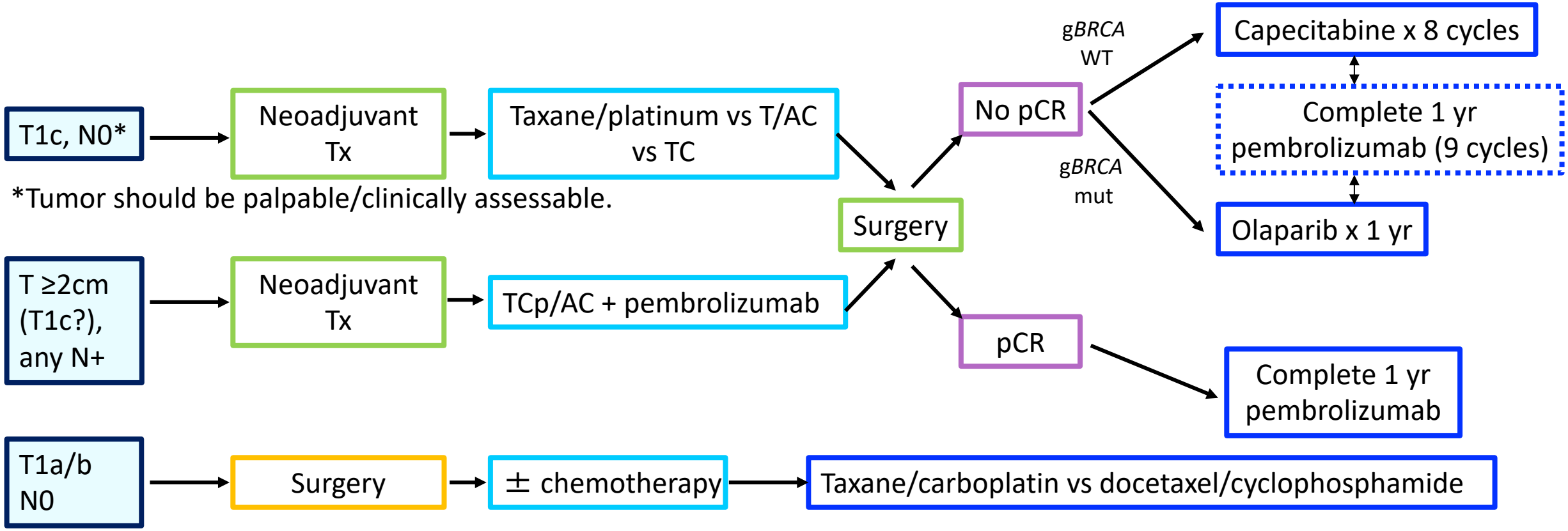
OlympiA: Safety

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

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

Tutt. NEJM. 2021;384:2394.

Considerations in the Treatment of Early-Stage TNBC

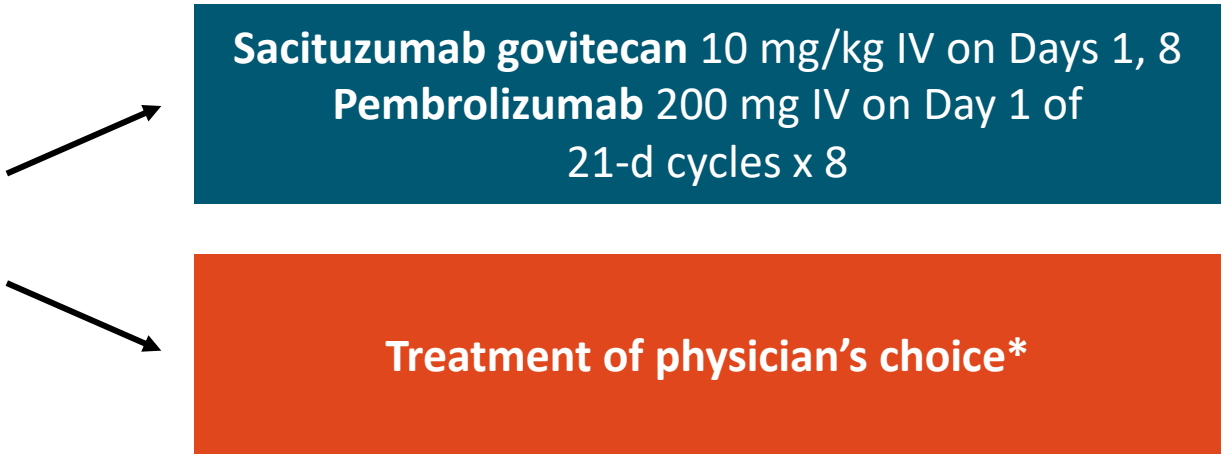


Upcoming NCTN Trials of Immunotherapy in Early TNBC

- **SWOG S2212 (SCARLET)**
  - Neoadjuvant taxane/carboplatin → AC + pembrolizumab vs docetaxel/carboplatin x 6 + pembrolizumab
- **Alliance A012103 (OptimICE-PCR)**
  - A randomized trial of adjuvant pembrolizumab continuation vs discontinuation in patients with stage II-III TNBC who achieved a pCR to neoadjuvant CT + CPI

Phase III ASCENT-05: Sacituzumab Govitecan + Pembro in TNBC With Residual Disease After Surgery + Neoadj Tx

Adults with residual invasive TNBC in breast/LNs after neoadjuvant therapy + surgery; removal of all clinically evident disease in breast/LNs; treated with RT; recovered from surgery and RT; samples available of both pre-neoadjuvant therapy diagnostic biopsy and resected residual invasive disease tissue; no known g*BRCA*m; ECOG PS 0/1 (N = 1514)

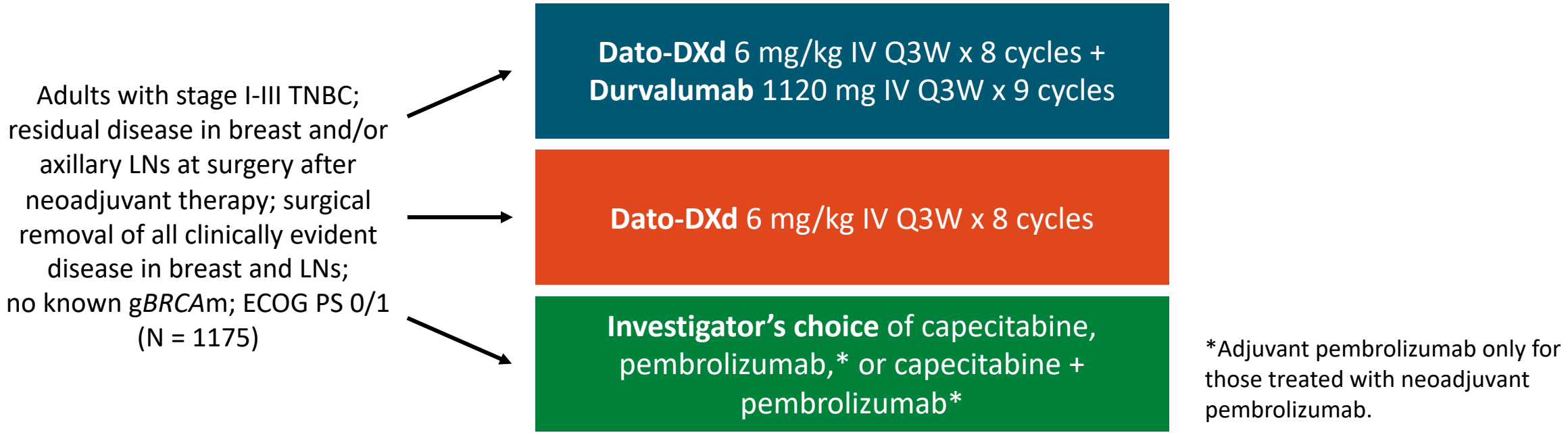


*Pembrolizumab ± capecitabine.

- **Primary endpoint:** iDFS
- **Secondary endpoints:** OS, dDFS, time to worsening of QoL, safety

NCT05633654.

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



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

NCT05629585.

Summary Triple Negative Breast Cancer

- Preop chemotherapy + pembrolizumab SOC for stage 2/3 TNBC (?T1cN0)
- SWOG/NCTN: Preop KN-522 vs 6 DCb + pembrolizumab -- de-escalate chemotherapy for pts with cCR post-preop taxane/Cb/pembrolizumab?
- Improving outcome efficacy of stage II/III TNBC pts with residual disease s/p KN-522 with sacituzumab + pembrolizumab or dato-DXd +/- durvalumab
- Need better understanding and therapeutic strategies for RCB 2/3 early stage TNBC pts

Agenda

Module 1: Long-Term Management of HER2-Positive Breast Cancer — Dr Krop

Module 2: Optimizing the Management of ER-Positive Localized Breast Cancer — Dr Kalinsky

Module 3: Considerations in the Care of Patients with ER-Positive mBC — Dr Jhaveri

Module 4: Novel and Emerging Strategies for ER-Positive mBC — Dr Rugo

Module 5: Evolving Clinical Decision-Making for Localized Triple-Negative Breast Cancer (TNBC) — Dr O'Shaughnessy

Module 6: Recent Advances in the Treatment of Metastatic TNBC (mTNBC) — Prof Schmid

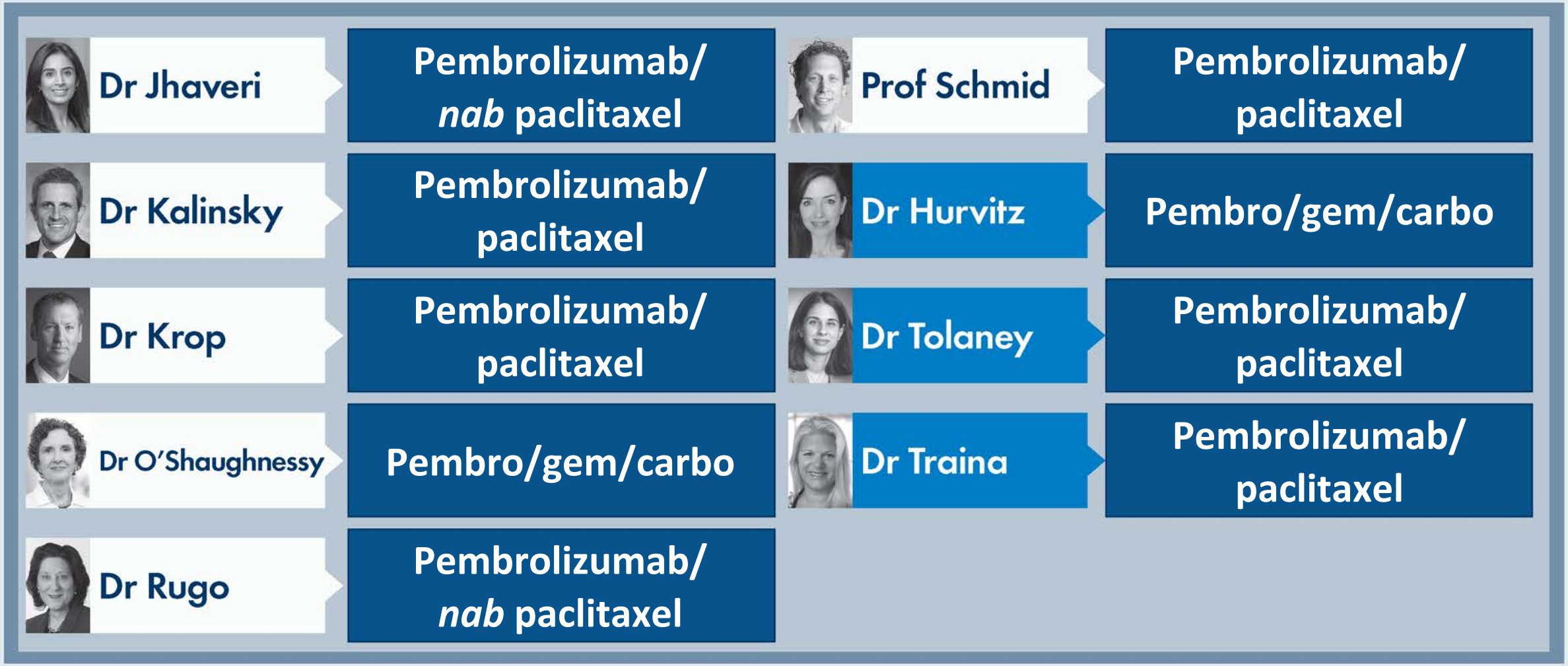
Selection of therapy for triple-negative metastatic breast cancer; sequencing of trastuzumab deruxtecan in ER-negative, HER2-low disease

Sara A Hurvitz, MD

Sara M Tolaney, MD, MPH

Tiffany A Traina, MD, FASCO

What would be your preferred treatment approach for a 60-year-old patient with BRCA wild-type de novo mTNBC with a PD-L1 CPS >10?



CPS = combined positive score; pembro = pembrolizumab; gem = gemcitabine; carbo = carboplatin

RTP RESEARCH TO PRACTICE

What would be your preferred treatment approach for a 60-year-old patient with a germline BRCA mutation and de novo mTNBC that is PD-L1-negative?

 Dr Jhaveri	Olaparib	 Prof Schmid	Olaparib or talazoparib
 Dr Kalinsky	Olaparib or talazoparib	 Dr Hurvitz	Nonplatinum chemotherapy
 Dr Krop	Olaparib	 Dr Tolaney	Olaparib
 Dr O'Shaughnessy	Olaparib	 Dr Traina	Olaparib
 Dr Rugo	Olaparib or talazoparib		

RTP RESEARCH TO PRACTICE

What would be your preferred treatment approach for a 60-year-old patient with a germline BRCA mutation and de novo mTNBC with a PD-L1 CPS >10?

 Dr Jhaveri	Pembrolizumab/ *nab* paclitaxel	 Prof Schmid	Pembro/gem/carbo
 Dr Kalinsky	Pembro/gem/carbo	 Dr Hurvitz	Pembrolizumab/ *nab* paclitaxel
 Dr Krop	Pembrolizumab/ paclitaxel	 Dr Tolaney	Pembro/gem/carbo
 Dr O'Shaughnessy	Pembro/gem/carbo*	 Dr Traina	Pembro/paclitaxel OR Pembro/gem/carbo
 Dr Rugo	Pembrolizumab/ *nab* paclitaxel*		

CPS = combined positive score; pembro = pembrolizumab; gem = gemcitabine; carbo = carboplatin

* Followed by maintenance pembrolizumab + olaparib

RTP RESEARCH TO PRACTICE

What treatment would you recommend next for a 60-year-old woman with mTNBC (BRCA wild type, PD-L1-positive) who experiences disease progression after 7 months of first-line pembrolizumab/paclitaxel?

 Dr Jhaveri	Sacituzumab govitecan	 Prof Schmid	Sacituzumab govitecan
 Dr Kalinsky	Sacituzumab govitecan	 Dr Hurvitz	Sacituzumab govitecan
 Dr Krop	Sacituzumab govitecan	 Dr Tolaney	Sacituzumab govitecan
 Dr O'Shaughnessy	Sacituzumab govitecan	 Dr Traina	Sacituzumab govitecan
 Dr Rugo	Sacituzumab govitecan		

RTP RESEARCH TO PRACTICE

A woman undergoes neoadjuvant chemotherapy and surgery for BRCA wild-type, ER-negative, HER2 IHC 2+, FISH-negative BC and develops asymptomatic, low-volume, nonvisceral metastases while receiving adjuvant capecitabine. Regulatory and reimbursement issues aside, when would you most likely offer trastuzumab deruxtecan?

 Dr Jhaveri	As third-line therapy	 Prof Schmid	As third-line therapy
 Dr Kalinsky	As second-line therapy	 Dr Hurvitz	As first-line therapy
 Dr Krop	As third-line therapy	 Dr Tolaney	As first-line therapy
 Dr O'Shaughnessy	As third-line therapy	 Dr Traina	As second-line therapy
 Dr Rugo	As second-line therapy		

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you offer trastuzumab deruxtecan to a patient with HER2 IHC 0 mBC who has exhausted all approved treatment options?

 Dr Jhaveri	No	 Prof Schmid	No
 Dr Kalinsky	Yes	 Dr Hurvitz	Yes
 Dr Krop	Yes	 Dr Tolaney	Yes
 Dr O'Shaughnessy	Yes	 Dr Traina	No
 Dr Rugo	Yes		

RTP RESEARCH TO PRACTICE

Reprogramming the options in metastatic TNBC

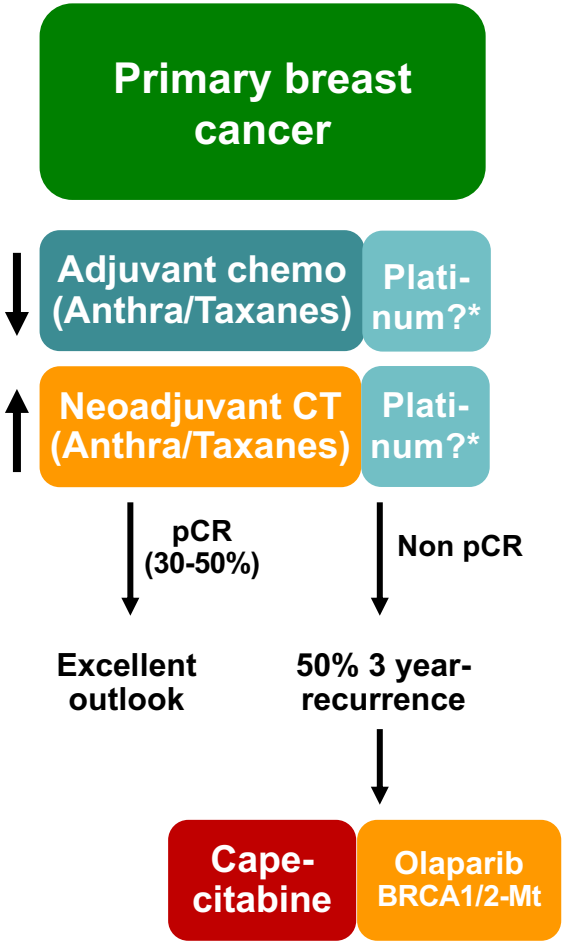
Professor Peter Schmid, MD PhD FRCP

Lead, Centre for Experimental Cancer Medicine

Barts Cancer Institute, St Bartholomew's Hospital
Queen Mary University of London

Triple Negative Breast Cancer – Management in 2018

Median OS for met. TNBC 12-15 months!



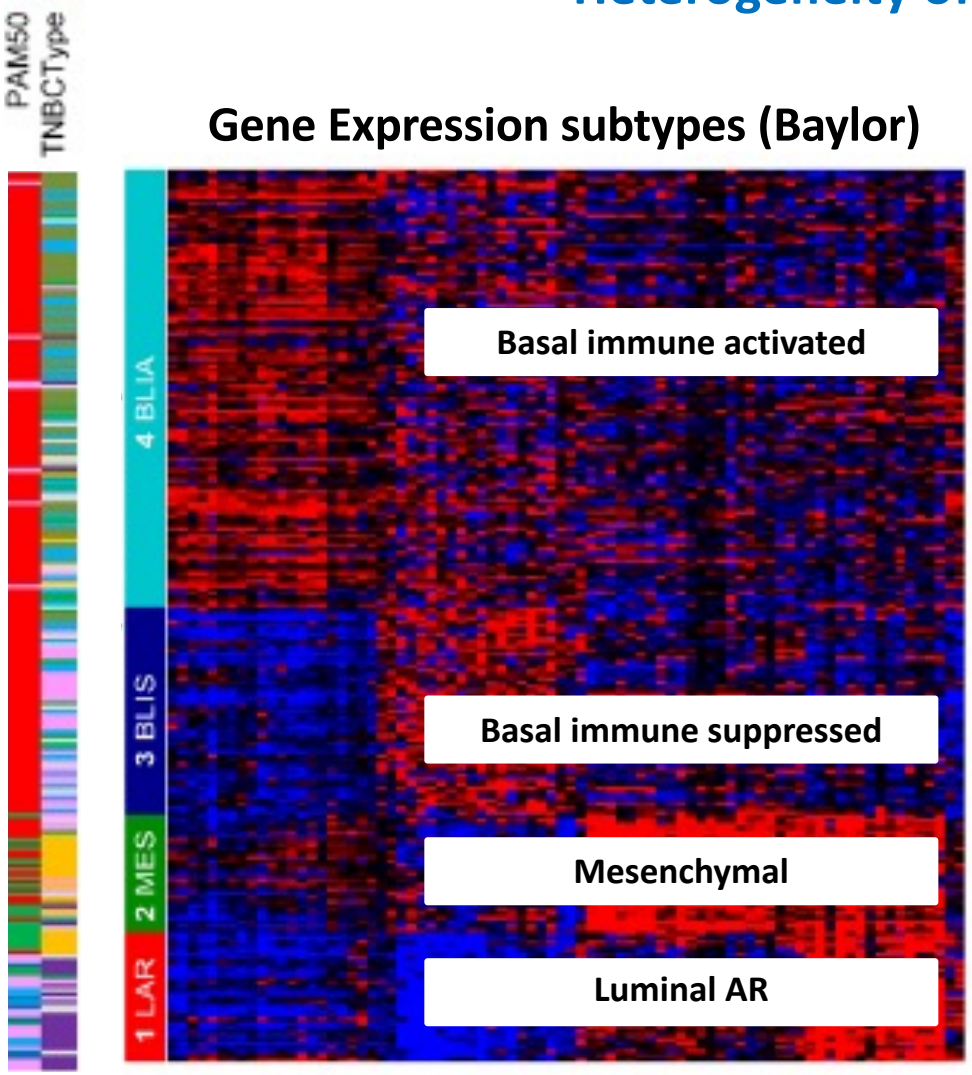
MBC 1st line	MBC 2nd line	MBC >2nd line
Taxanes (if DFI >1a)	Capecitabine	Eribulin
Platinum Combinations (CarboTax, GC)	Platinum Combinations (CarboTax, GC)	BSC or TPC
Taxanes + Bevacizumab	Eribulin	

* All patients? High-risk patients? Suboptimal responders? BRCA1/2 carriers?

Schmid P, Personal Communication

Understanding the Biology of TNBC

Heterogeneity of TNBC and Treatment Strategies



Gene Expression subtypes (Baylor)

Adapted from Burstein et al, CCR 2014

GE-Subtypes and Therapeutic Subgroups not aligned

ADC targets don't need to be oncogenic drivers

Target/Population

- PD-L1+
- gBRCA-Mt+
- TROP2
- HER2
- HER3
- LIV1
- ?
- AR+/LAR

Subgroups overlapping

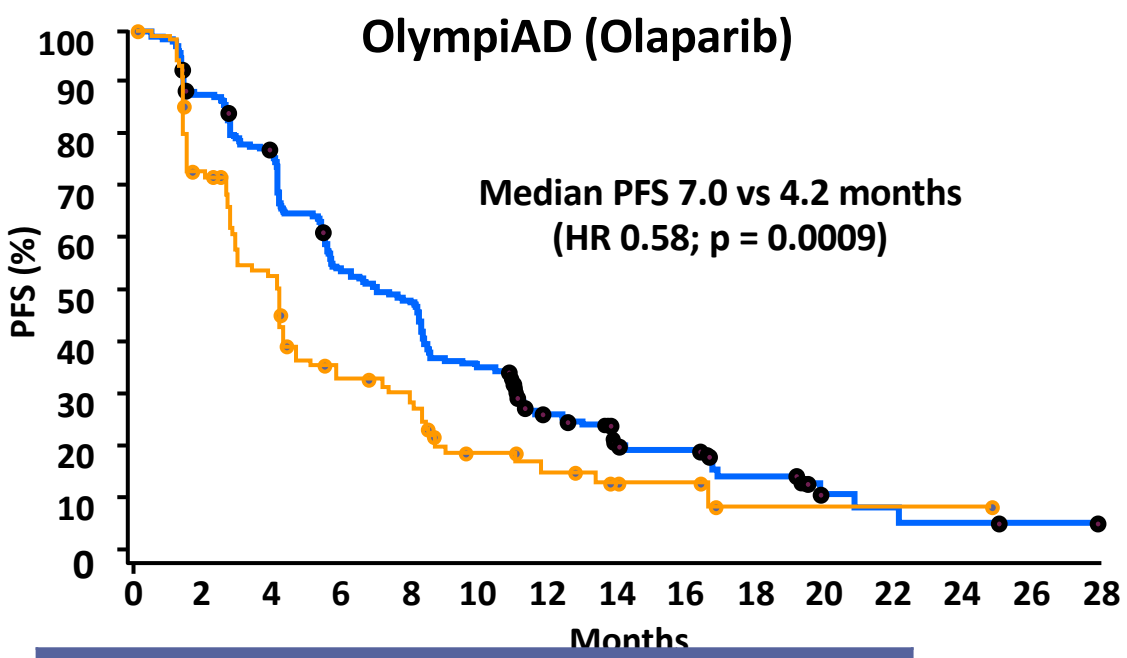
Therapeutic Strategies

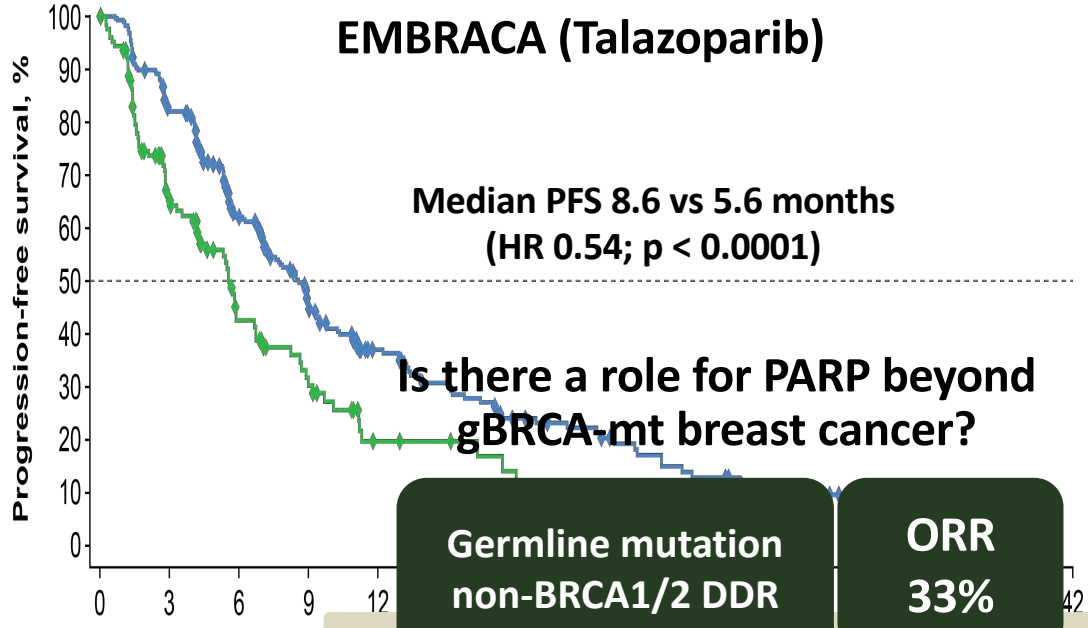
- Immunotherapy
- PARP inhibitors
- Antibody-Drug Conjugates
- AKT Inhibitors
- Anti-androgen

Schmid P, Personal Communication

Targeting PARP in breast cancer

Potential impact of platinum-based therapy on PARPi remains to be defined as trial excluded patients progressing on platinum-based therapy





RR	OlympiAD	EMBRACA
PARPi	60%	62.6%
Chemo	29%	27.2%

Carboplatin (TNT): ORR 68%

Is there a role for PARP beyond gBRCA-mt breast cancer?

Germline mutation non-BRCA1/2 DDR	ORR 33%
Somatic BRCA1/2-Mt or non-BRCA1/2 DDR	ORR 31%

Responses seen gPALB2 (82%) & sBRCA Mt (50%)

No responses seen in ATM or CHEK2 Mt

Tung, NM, et al. JCO 2020

Robson M, et al. NEJM 2017, Litton J, et al. NEJM 2018, Tutt A, et al Nature Med 2018

Immunotherapy in mTNBC provides OS benefit in PD-L1+

IMpassion130 study design

- 1L mTNBC
- Treatment-free ≥ 12m
- PDL1+/- as per SP142

R 1:1

Atezolizumab + *nab*-paclitaxel

Double blind; no crossover permitted

Placebo + *nab*-paclitaxel

Stratification factors:
- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status (SP142 ≥1% vs < 1%)

KEYNOTE-355 study design

- 1L mTNBC
- Treatment-free ≥6m
- PDL1+/- as per CPD(22C3)

R 2:1

Pembrolizumab + Chemotherapy*

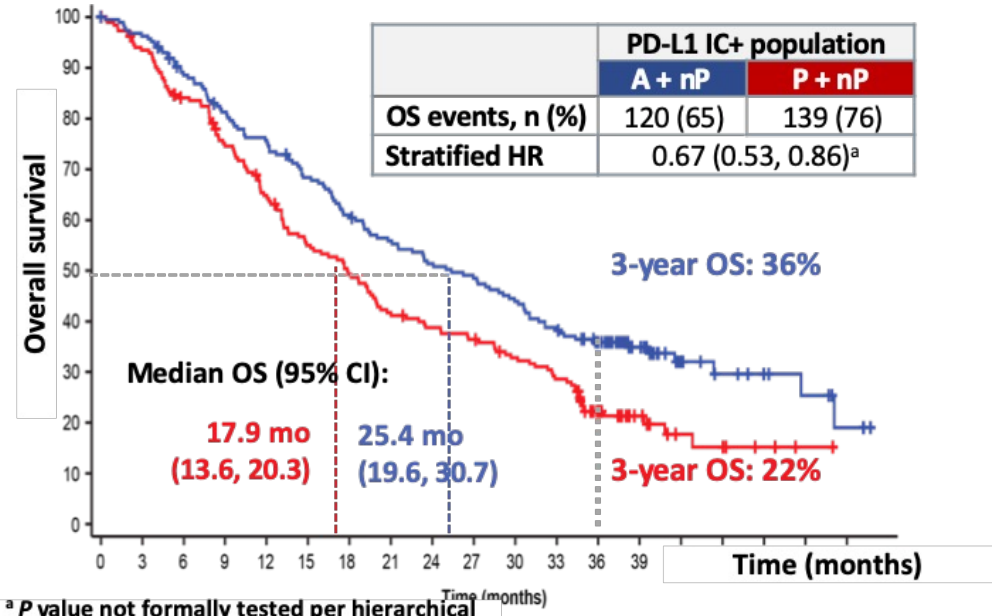
Double blind; no crossover permitted

Placebo + Chemotherapy*

Stratification factors:
- Prior therapy with same class chemo
- Chemo on study
- PD-L1 status (CPS ≥1 vs CPS <1)

*Nab-paclitaxel weekly or Paclitaxel weekly or Gemcitabine/Carboplatin

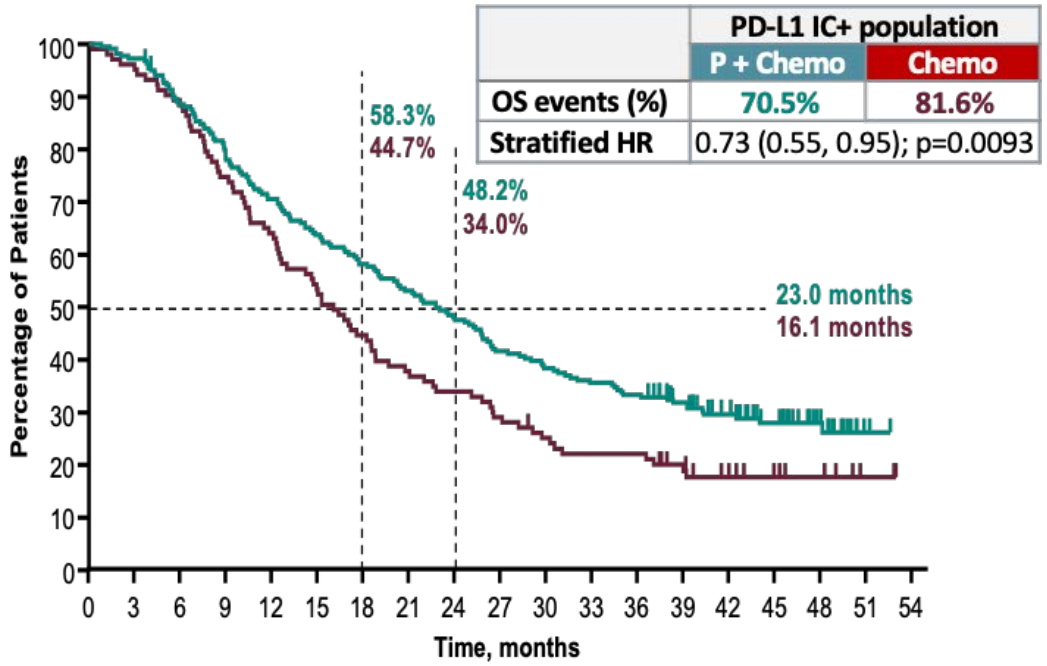
OS, SP142 ≥1%



	PD-L1 IC+ population	
	A + nP	P + nP
OS events, n (%)	120 (65)	139 (76)
Stratified HR	0.67 (0.53, 0.86)[a]	

[a] *P* value not formally tested per hierarchical study design.

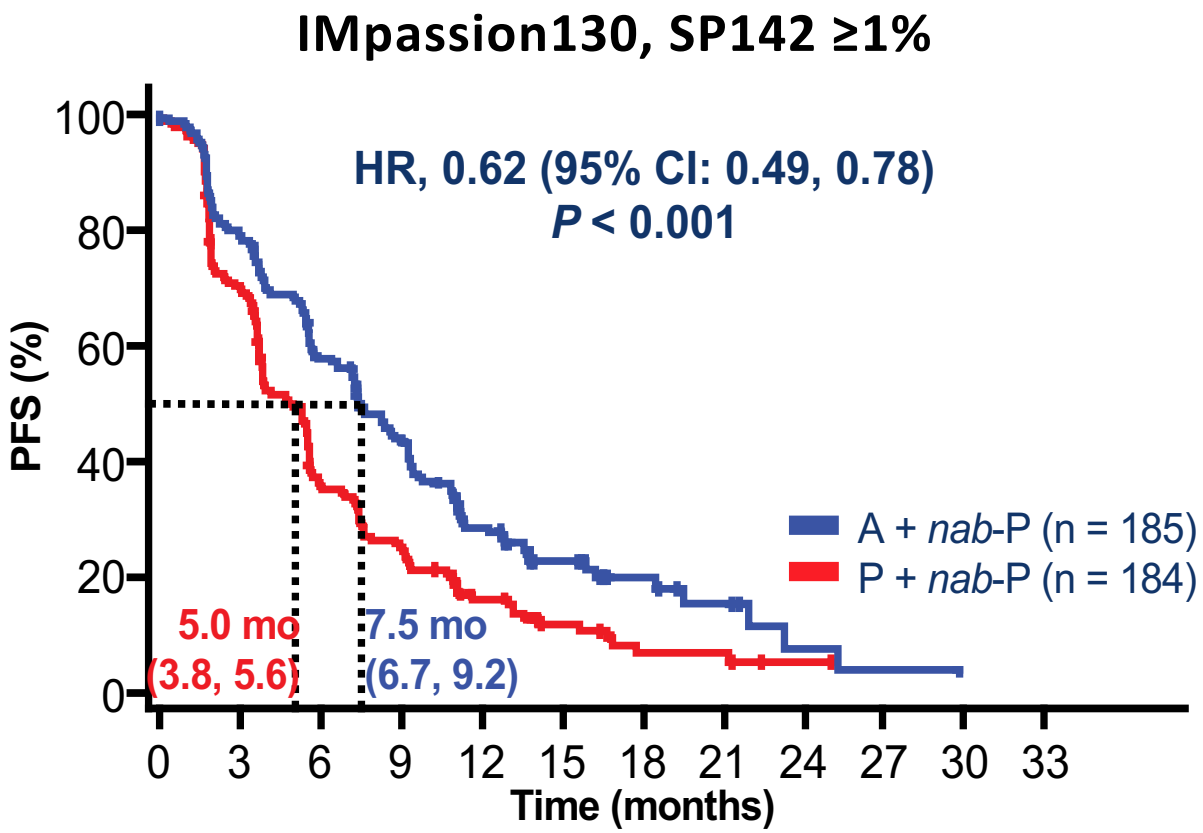
OS, CPS ≥10

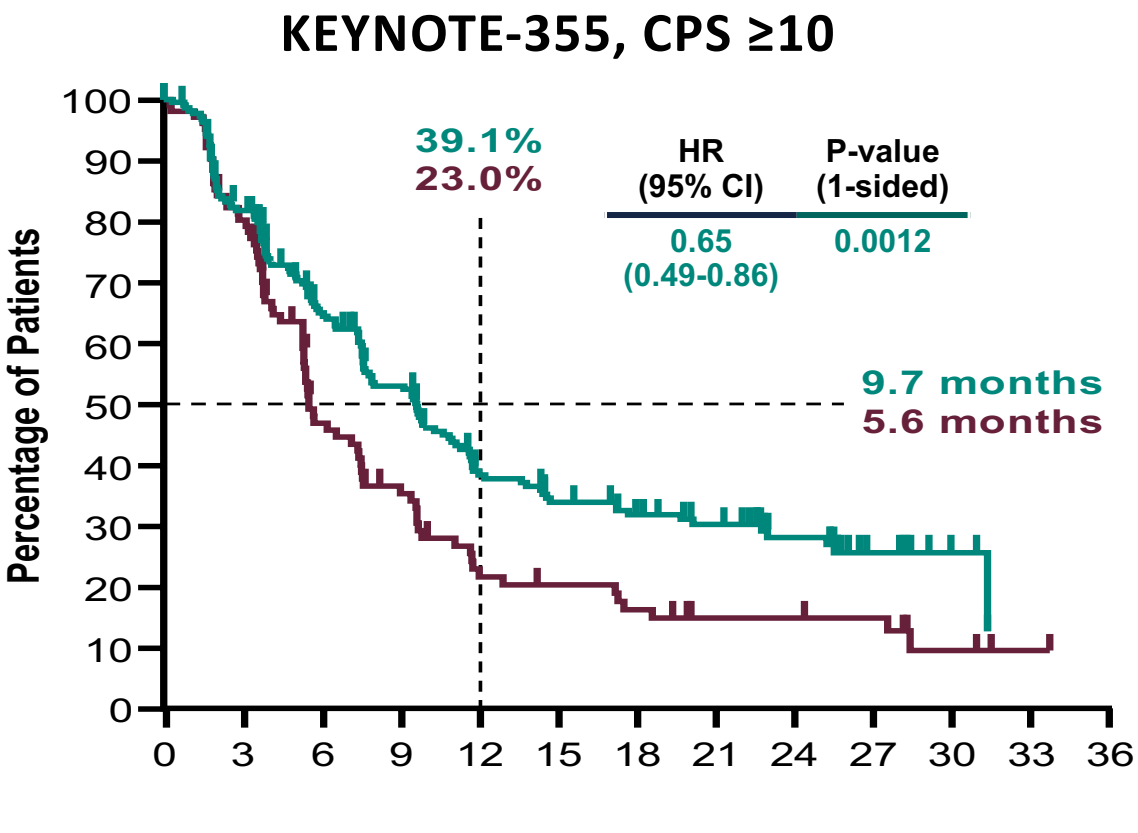


	PD-L1 IC+ population	
	P + Chemo	Chemo
OS events (%)	70.5%	81.6%
Stratified HR	0.73 (0.55, 0.95); p=0.0093	

Schmid, NEJM 2018; Emens LA, ESMO 2020; Cortes, SABCS 2021; Cortes NEJM 2022

Immunotherapy plus Chemo in 1L TNBC: Progression-free Survival





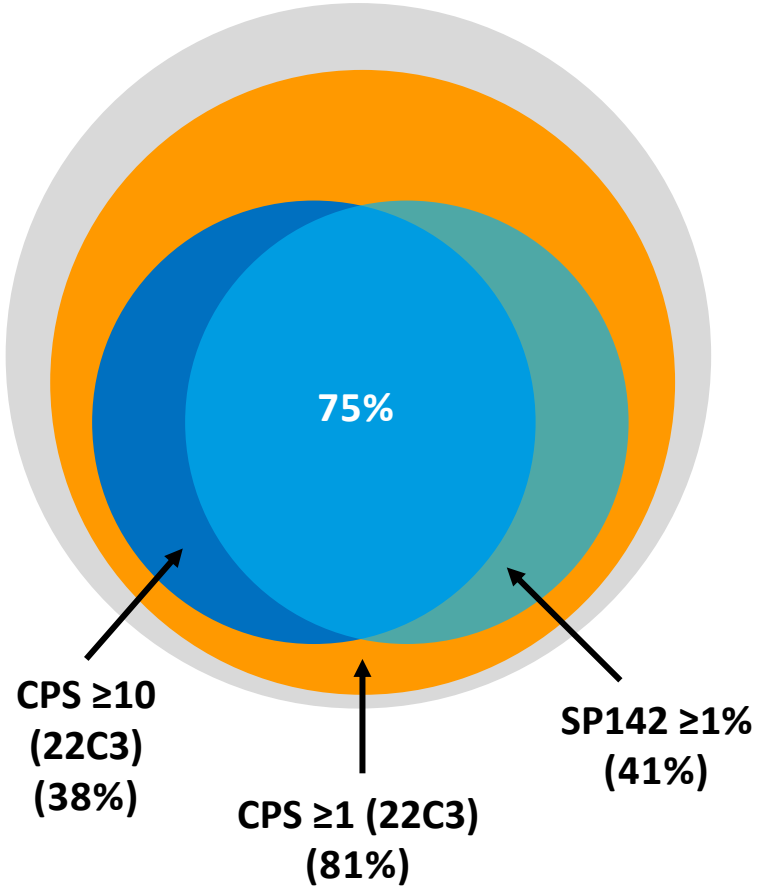
No benefit in "PD-L1 negative" (SP142<1% or 22C3 CPS<10)

Schmid P, et al NEJM 2018; Cortes J, et al, Lancet 2020

Who benefits from Immunotherapy in metastatic TNBC?

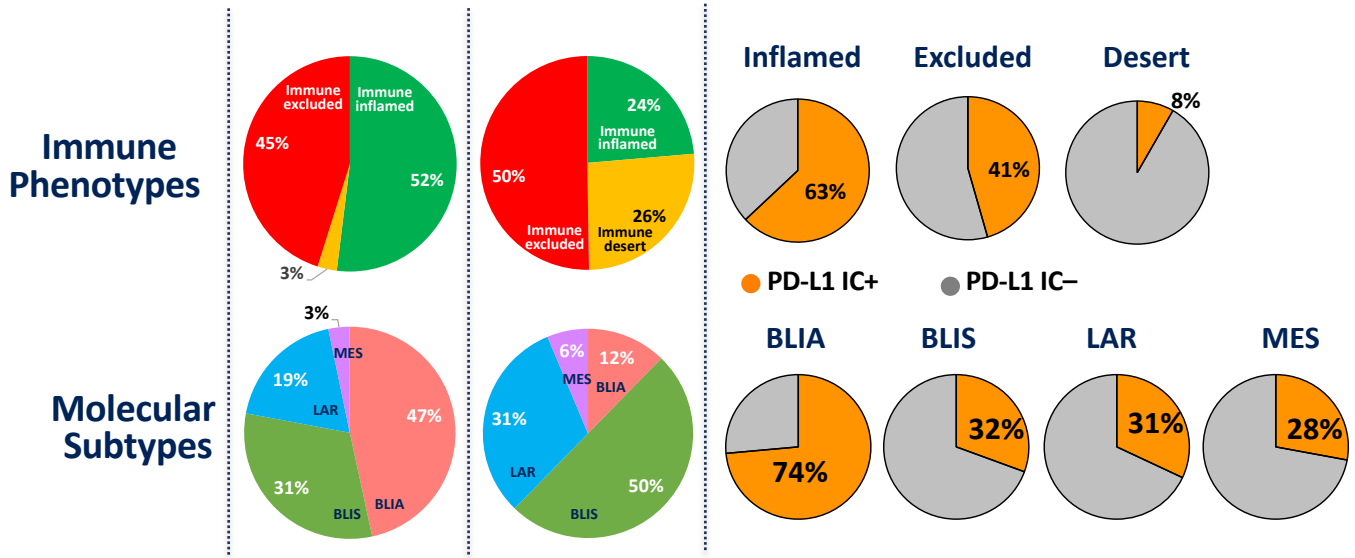
PD-L1 Subpopulations in TNBC

Defined by PD-L1 assays SP142 and 22C3



PD-L1 predicts outcome better than Immune/Molecular Subtypes

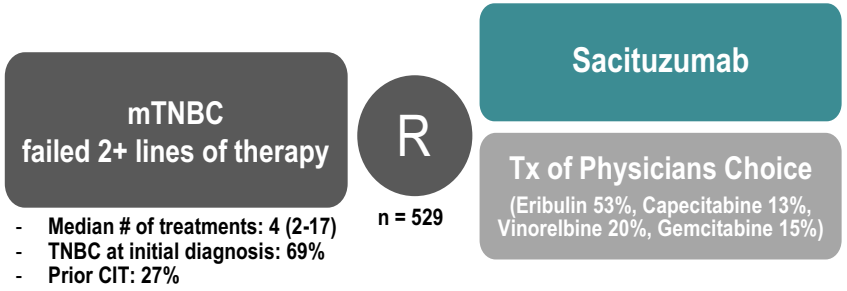
	IMpassion 130		KEYNOTE-355	
	PD-L1+	PD-L1-	PD-L1+	PD-L1-
PFS	0.62 (0.45-0.78)	0.94 (0.78-1.13)	0.65 (0.49-0.86)	0.94 (0.76-1.16)
OS	0.67 (0.53-0.86)	1.02 (0.84-1.24)	0.73 (0.55-0.95)	1.04 (0.85-1.26)



Schmid P, Personal Communication

Adapted from Emens LA. ASCO 2021

Trop2-ADCs in TNBC: Sacituzumab in pretreated mTNBC

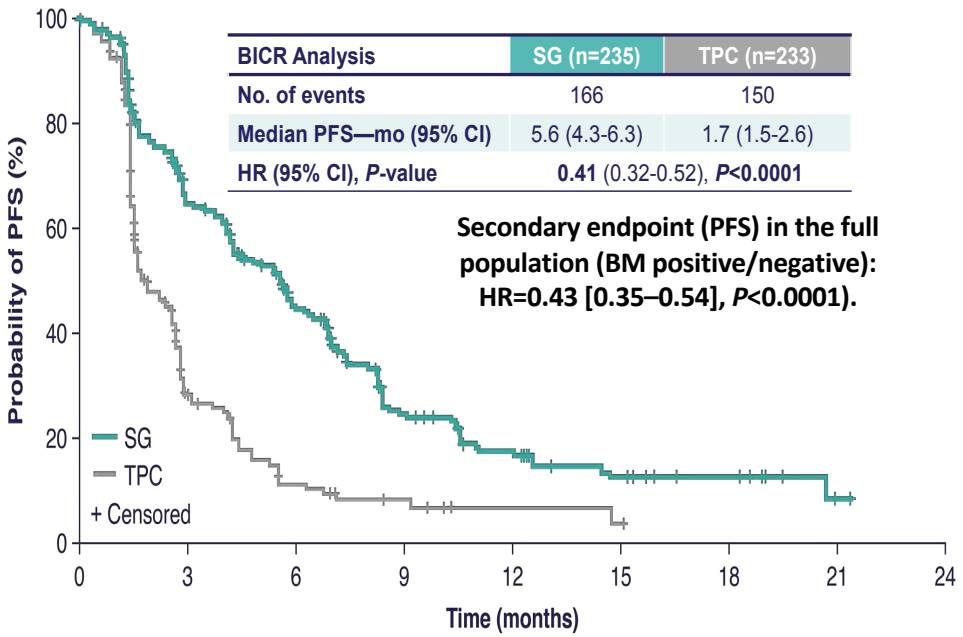


- Median # of treatments: 4 (2-17)
- TNBC at initial diagnosis: 69%
- Prior CIT: 27%

Primary Endpoint:
- PFS (central review)

Secondary Endpoints:
- PFS (including brain mets)
- OS, ORR, DOR
- Safety

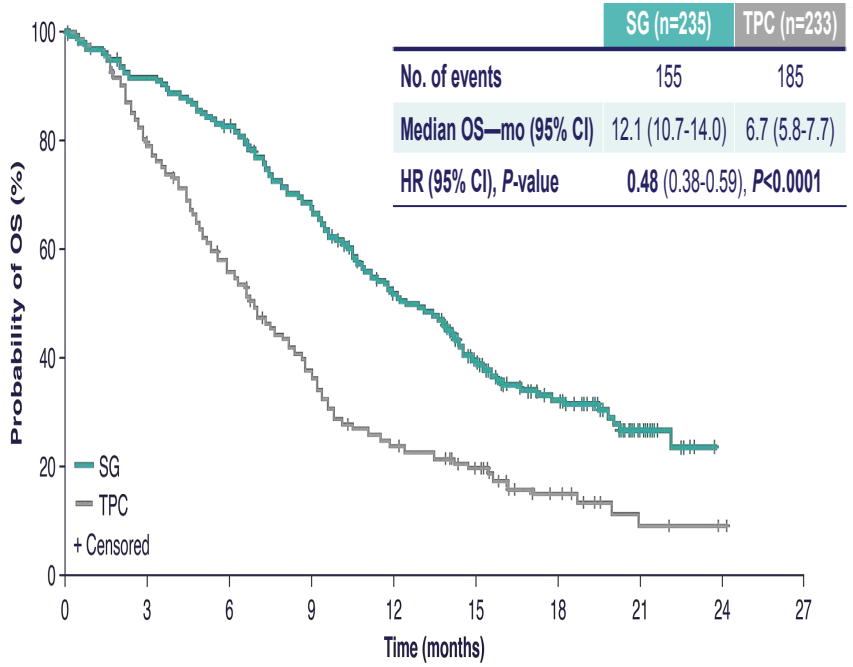
Progression-free Survival



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

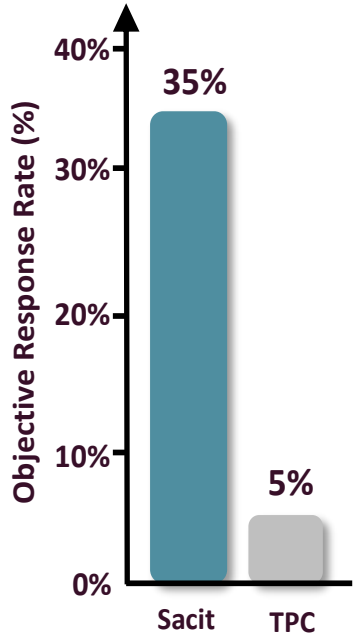
Secondary endpoint (PFS) in the full population (BM positive/negative): HR=0.43 [0.35–0.54], *P*<0.0001).

Overall Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Objective Response

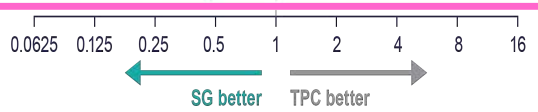


Bardia A, et al. NEJM 2021; Bardia A, et al Ann Oncol 2021.

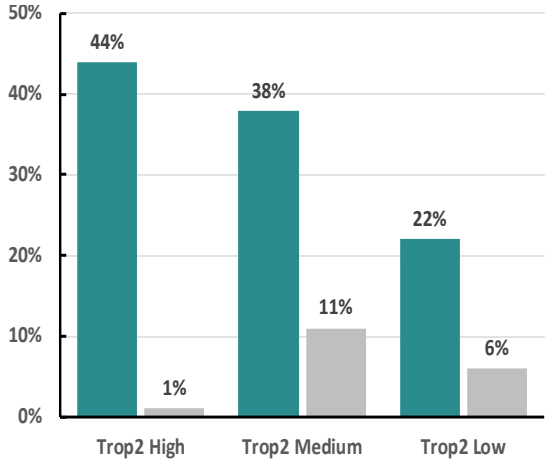
ASCENT: Progression-Free Survival by Subgroup

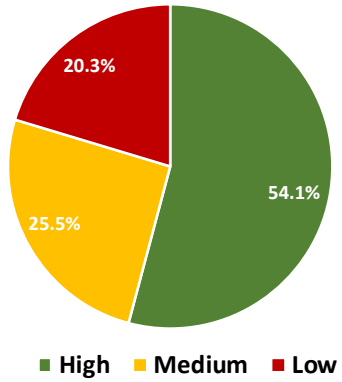
PFS by Subgroups

Subgroup	Median PFS, Months (95% CI) SG	TPC	HR (95% CI)	P value
Overall (n=468)	5.6 (4.3–6.3)	1.7 (1.5–2.6)	0.41 (0.33–0.52)	<0.0001
Age Group				
<65 (n=378)	4.6 (3.7–5.7)	1.7 (1.5–2.5)	0.46 (0.35–0.59)	<0.0001
≥65 (n=90)	7.1 (5.8–8.9)	2.4 (1.4–2.9)	0.22 (0.12–0.40)	<0.0001
Race				
White (n=369)	5.7 (4.3–6.8)	1.7 (1.5–2.6)	0.39 (0.30–0.51)	<0.0001
Black (n=56)	5.4 (2.8–7.4)	2.2 (1.5–2.9)	0.45 (0.24–0.86)	0.0152
Asian (n=18)	NE (1.3–NE)	1.5 (1.2–NE)	0.40 (0.08–2.08)	0.2781
Prior Therapies				
2-3 (n=330)	5.8 (4.2–7.1)	1.6 (1.5–2.5)	0.39 (0.29–0.52)	<0.0001
>3 (n=138)	5.6 (3.0–6.5)	2.5 (1.5–2.8)	0.48 (0.32–0.72)	0.0004
Region				
North America (n=298)	4.9 (4.0–6.3)	2.0 (1.5–2.6)	0.44 (0.33–0.60)	<0.0001
Rest of World (n=170)	5.9 (4.2–6.9)	1.6 (1.4–2.7)	0.36 (0.24–0.53)	<0.0001
Prior PD-L1/PD-1 use				
Yes (n=127)	4.2 (3.2–5.6)	1.6 (1.4–2.3)	0.37 (0.24–0.57)	<0.0001
No (n=341)	6.2 (4.9–7.1)	2.1 (1.5–2.7)	0.42 (0.32–0.56)	<0.0001
Liver Metastases				
Yes (n=199)	4.2 (2.8–5.8)	1.5 (1.4–2.4)	0.48 (0.34–0.67)	<0.0001
No (n=269)	6.8 (4.6–8.0)	2.3 (1.6–2.7)	0.36 (0.26–0.50)	<0.0001
Initial Diagnosis TNBC				
Yes (n=322)	5.7 (4.3–6.9)	1.6 (1.5–2.6)	0.38 (0.29–0.51)	<0.0001
No (n=146)	4.6 (3.7–6.9)	2.3 (1.5–2.8)	0.48 (0.32–0.72)	0.0004

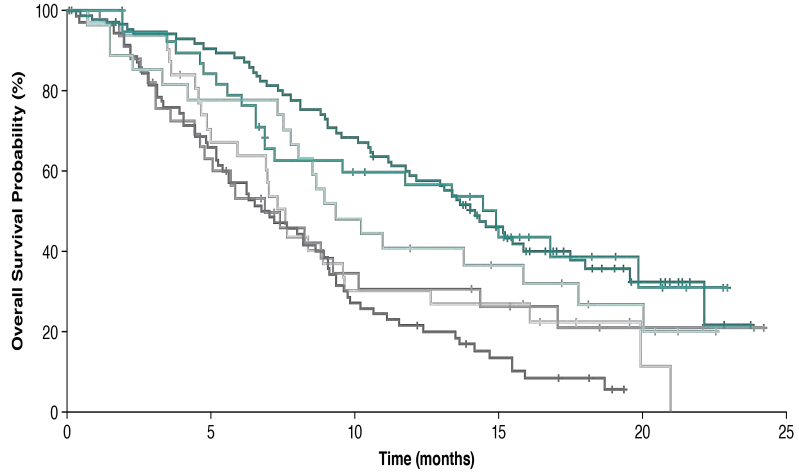


TROP2 Expression and Response



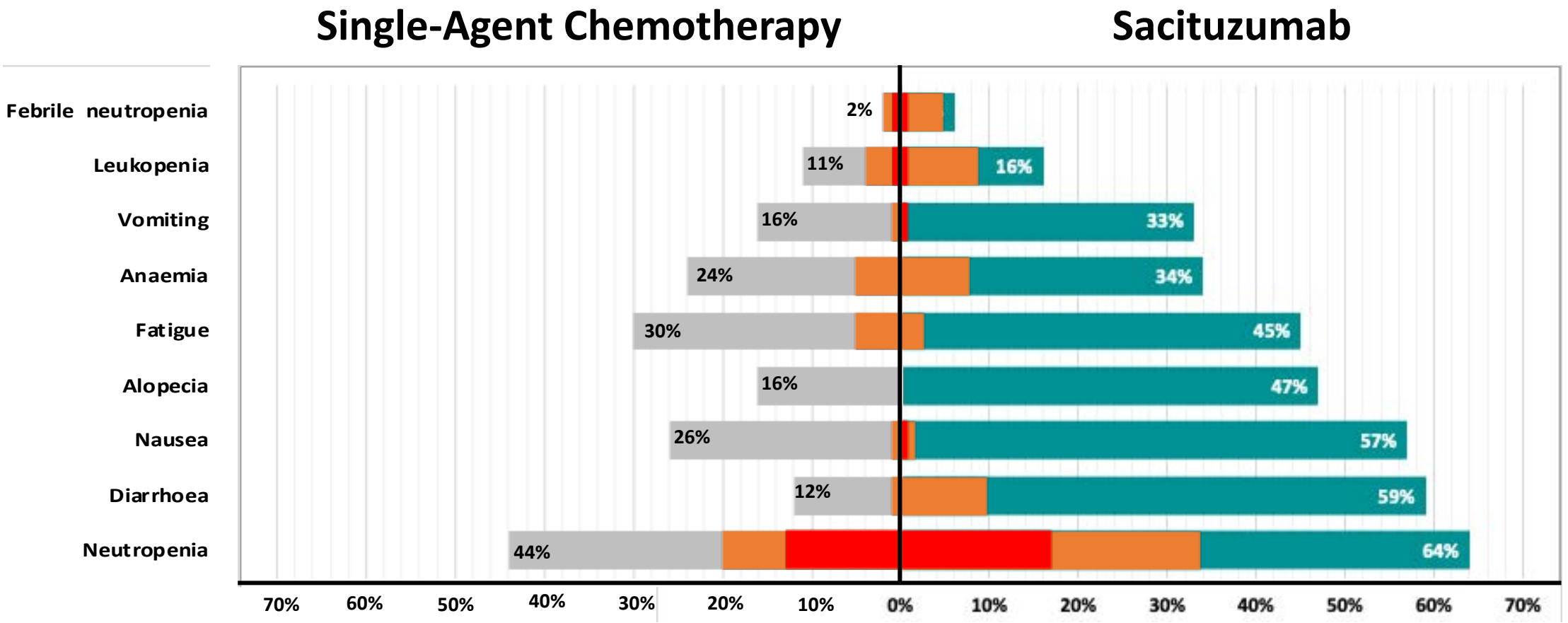


TROP2 Expression and OS



Bardia A, et al. ESMO 2020; Abstract LBA17.; Bardia A, et al, NEJM 2021

Sacituzumab vs TPC (ASCENT Trial): Safety



Adverse events of special interest in the ASCENT trial

~5% of patients in both arms discontinued for any adverse reaction[1]

- **Neutropenia or febrile neutropenia did not lead to any permanent discontinuation**
- **No patients discontinued treatment because of diarrhoea**

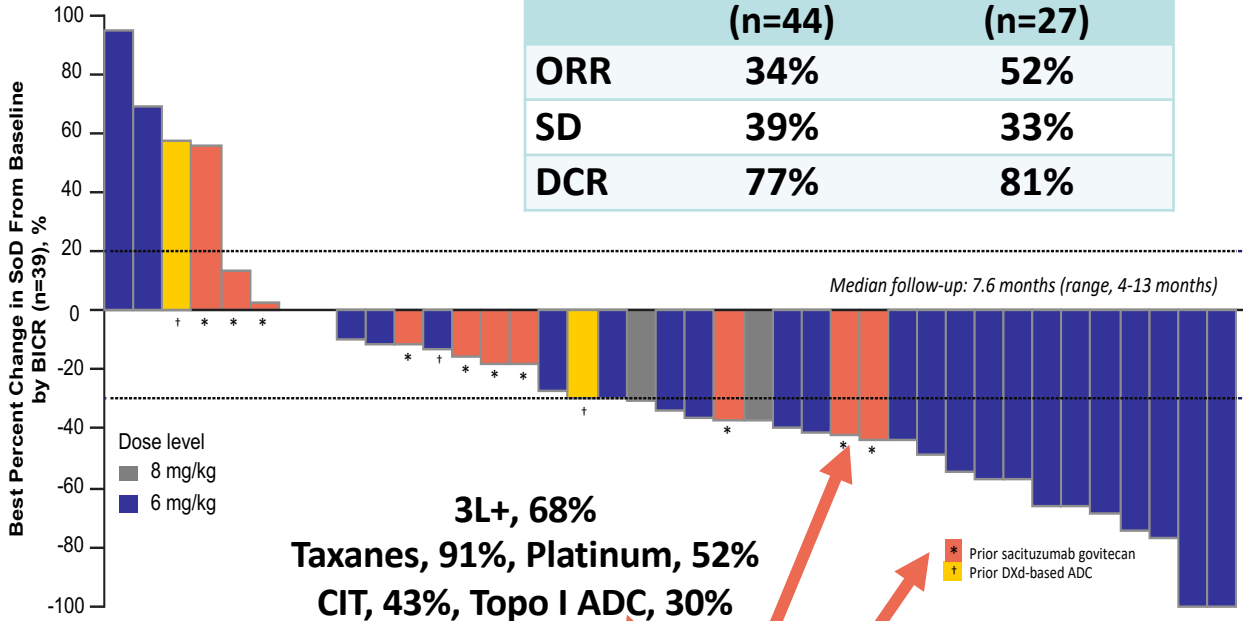
The most frequently reported AEs leading to dose reduction were neutropenia (6.3%) and diarrhoea (3.3%)[3]

Bardia A, et al. ESMO 2020; Abstract LBA17.; Bardia A, et al, NEJM 2021

Trop2-ADC: Dato-DXd (Datopotamab) in pretreated mTNBC

Anti-tumour response

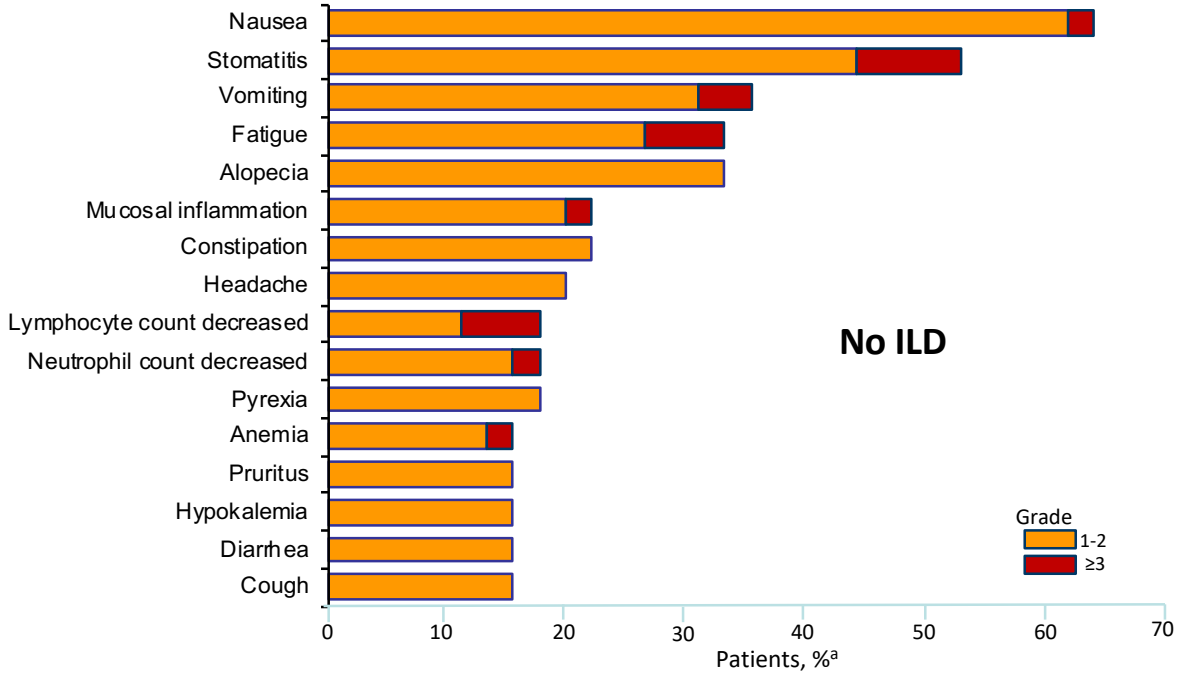
	All patients (n=44)	SG/DXd naïve (n=27)
ORR	34%	52%
SD	39%	33%
DCR	77%	81%



3L+, 68%
Taxanes, 91%, Platinum, 52%
CIT, 43%, Topo I ADC, 30%

ADC-Resistance: Target or Payload?

Safety



Krop I, et al. SABCS 2021

Trastuzumab Deruxtecan (T-DXd) in HER2-low MBC

- HER2-low MBC (IHC 1+ or IHC 2+/ISH−)
- 1-2 lines of chemo for MBC
- HR+ endocrine refractory

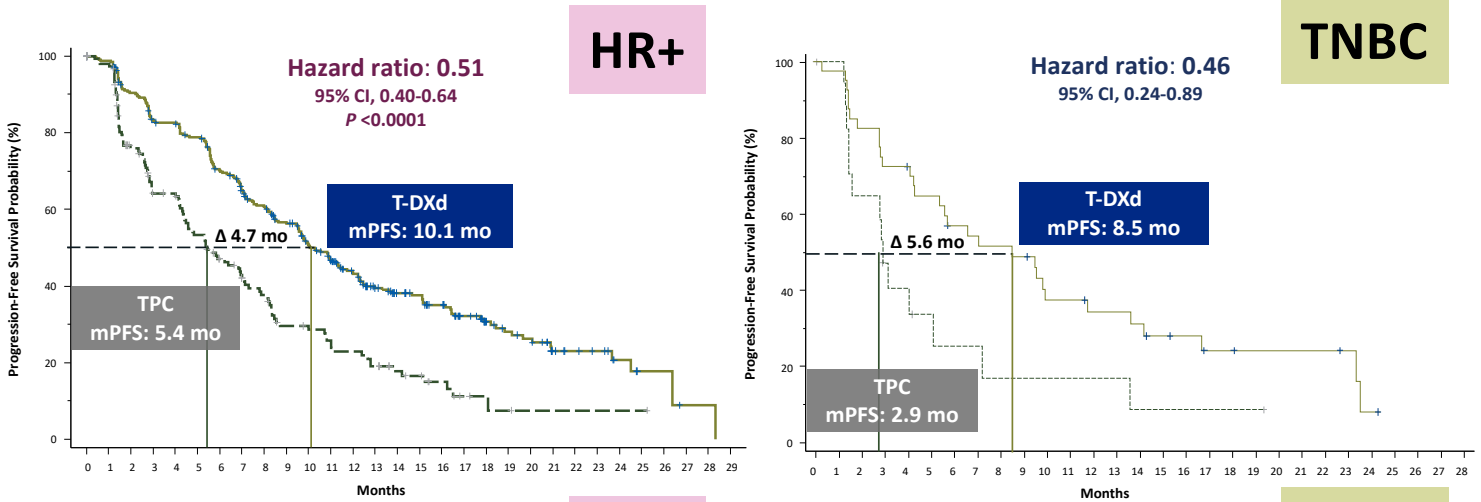
R 1:1

T-DXd
5.4 mg/kg Q3W

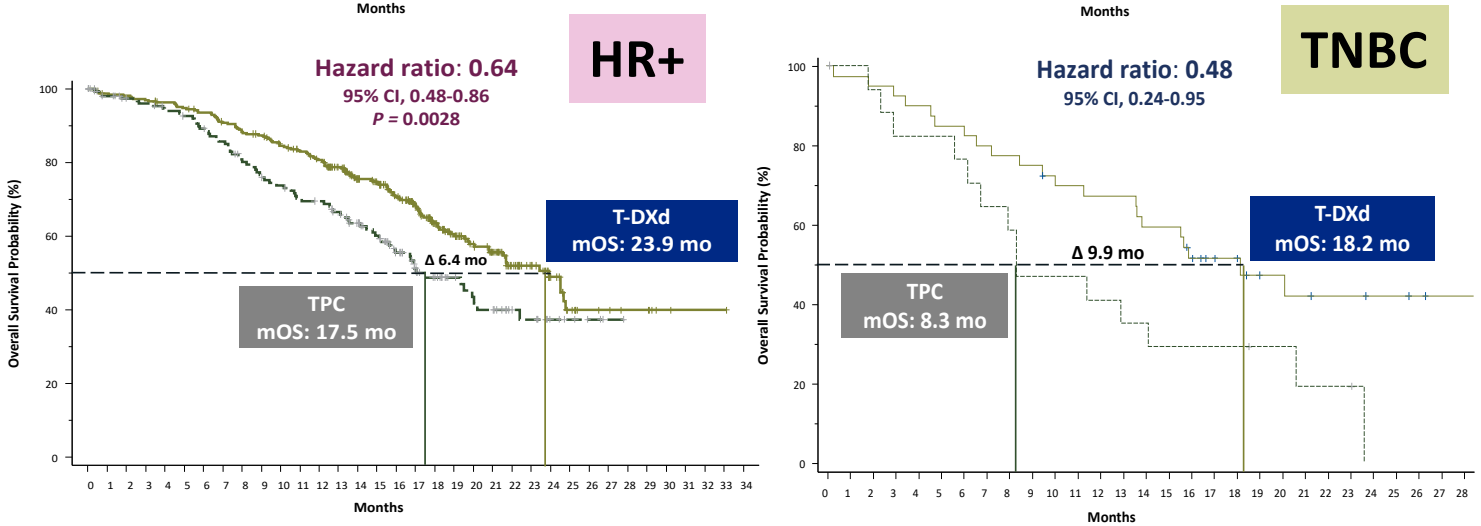
TPC
Capecitabine, eribulin, gemcitabine, (nab)paclitaxel

Stratification factors:
- Central HER2 (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (+/- prior CDK4/6i) vs HR−

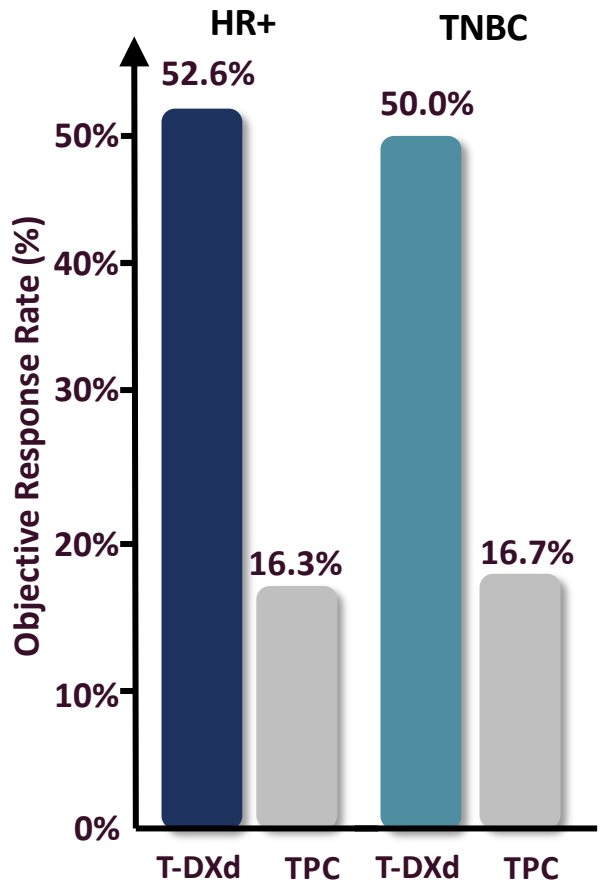
PFS



OS

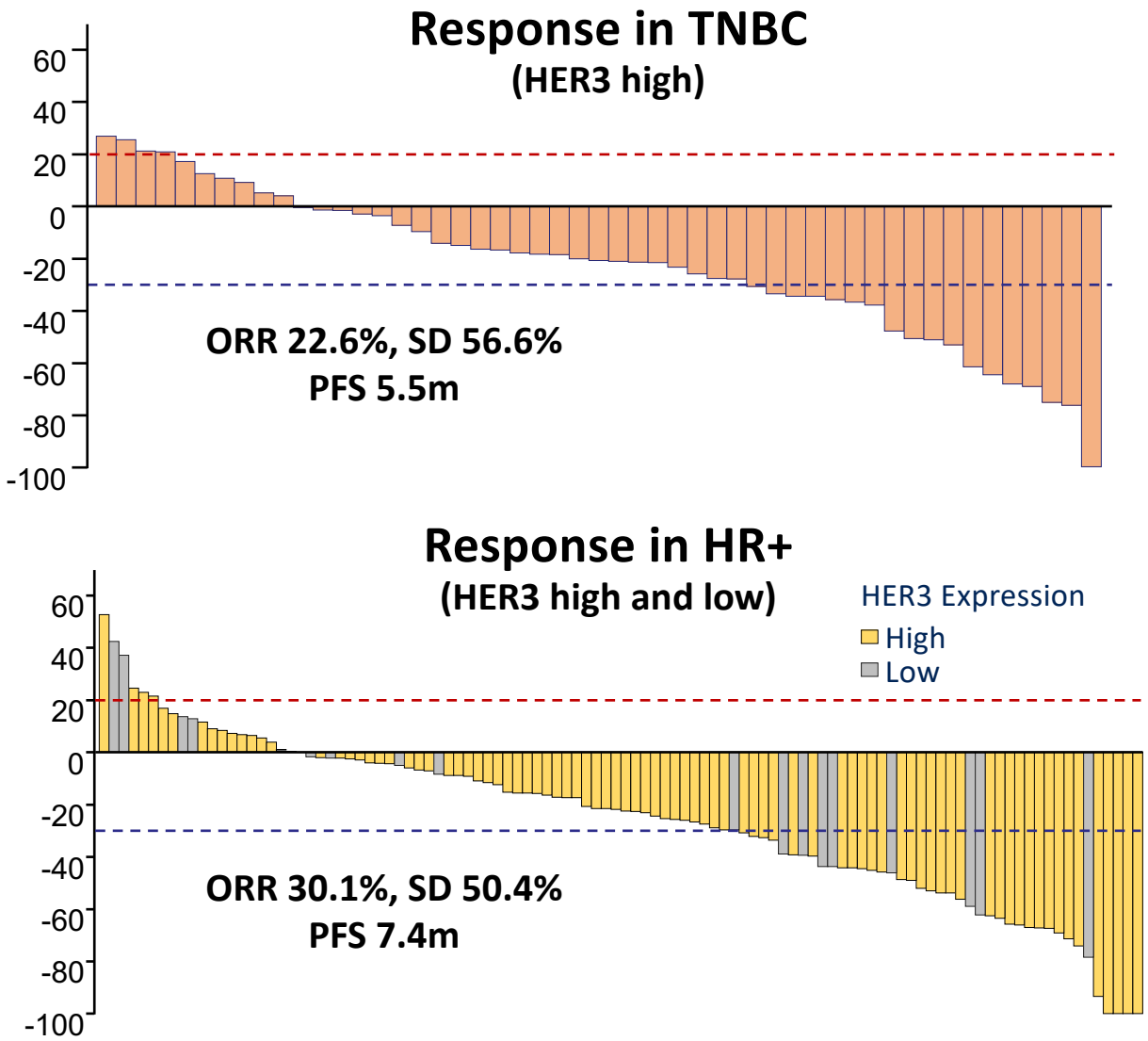


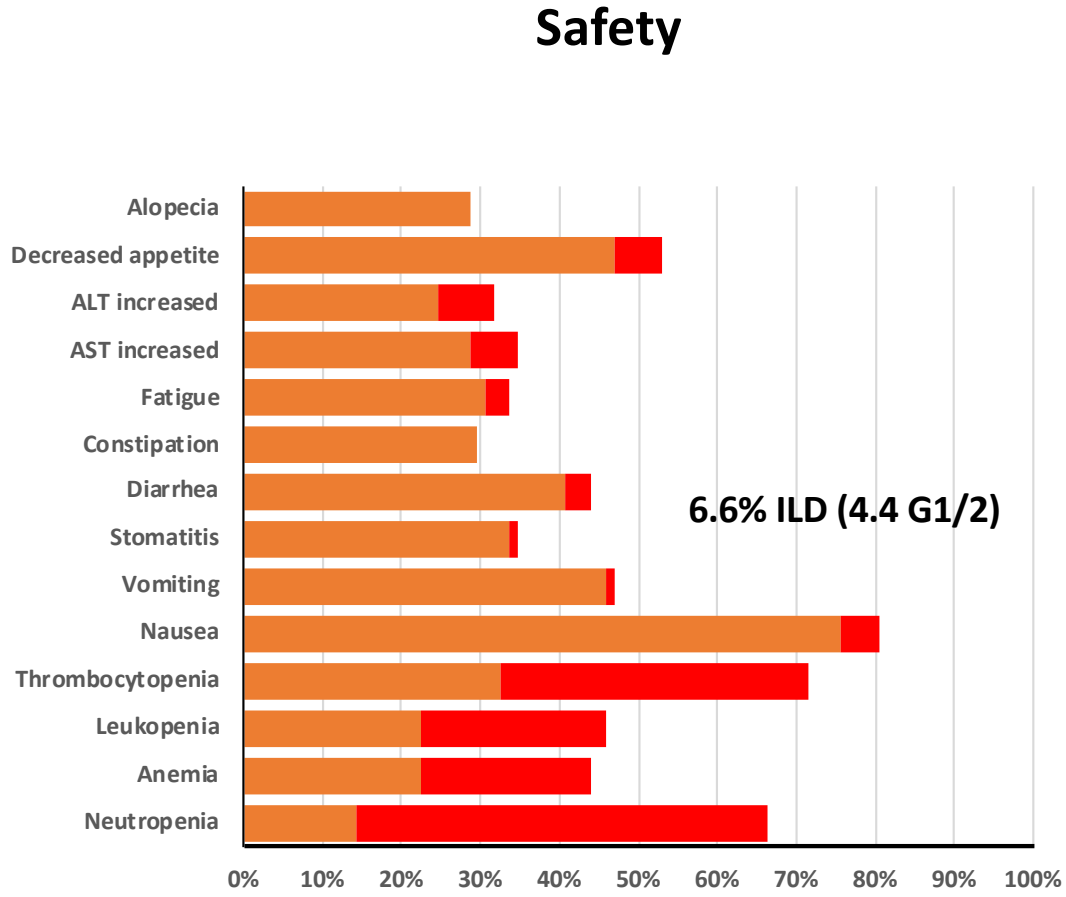
Objective response



Modi, NEJM 2022

HER3-ADC: Patritumab in pretreated MBC



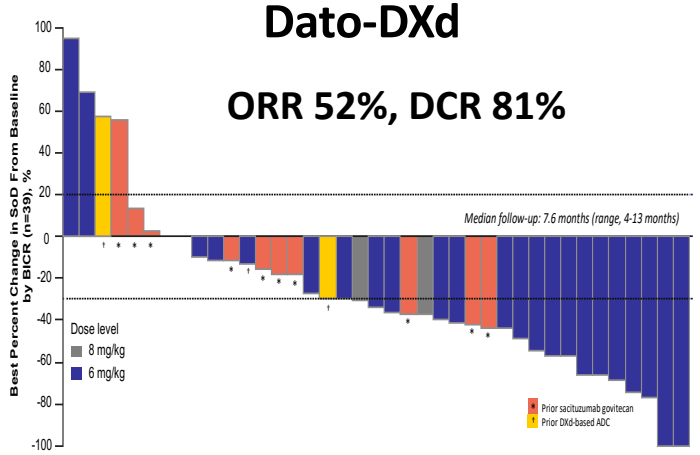


Krop I, et al. ASCO 2022

Targets for Antibody-Drug Conjugates in TNBC

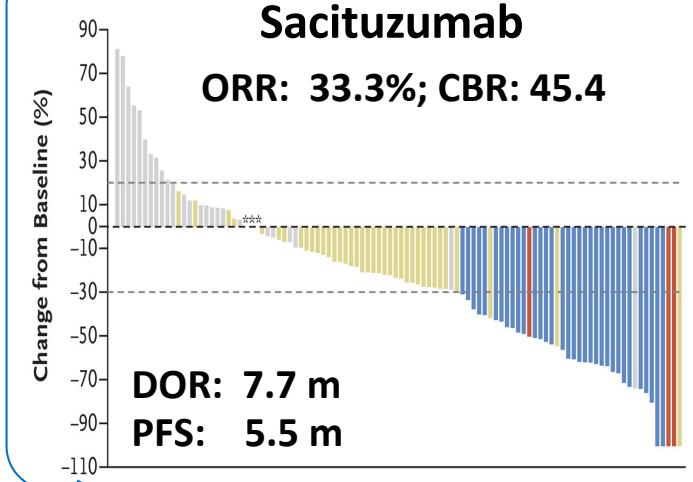
Dato-DXd

ORR 52%, DCR 81%



Sacituzumab

ORR: 33.3%; CBR: 45.4

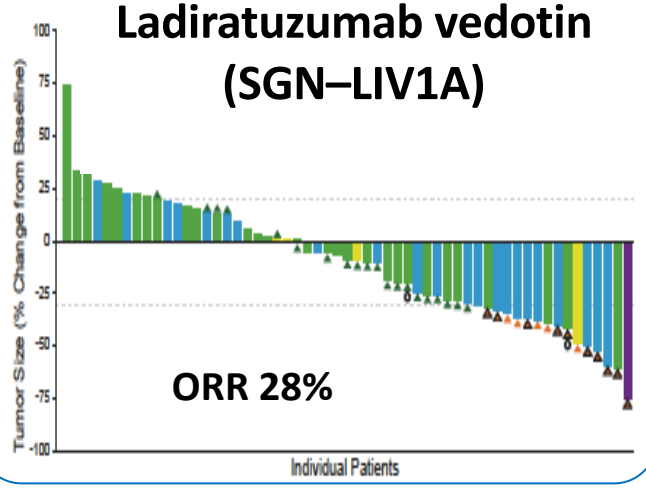


DOR: 7.7 m
PFS: 5.5 m

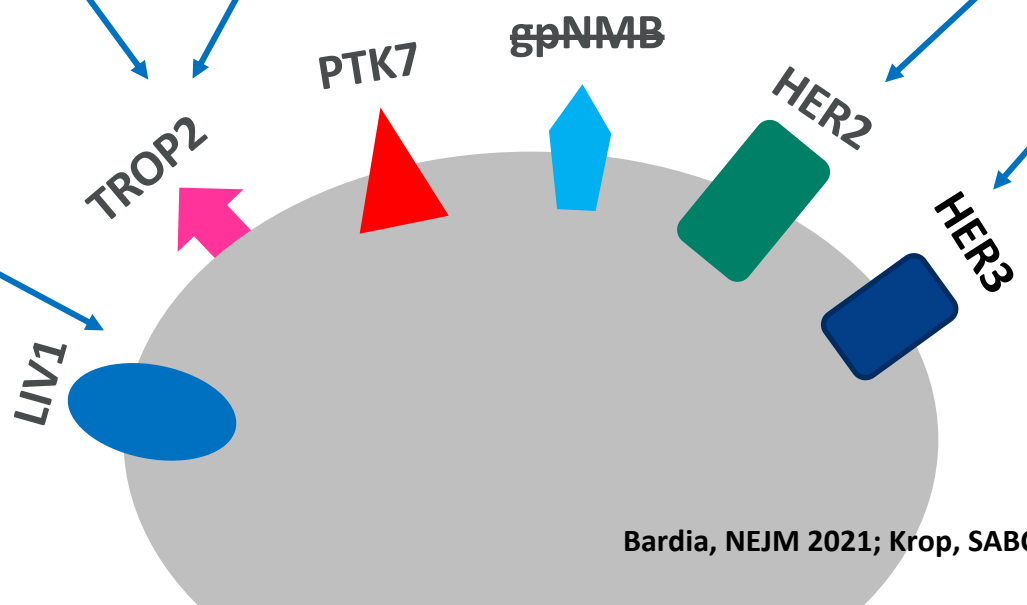
T-DXd

ORR 37%

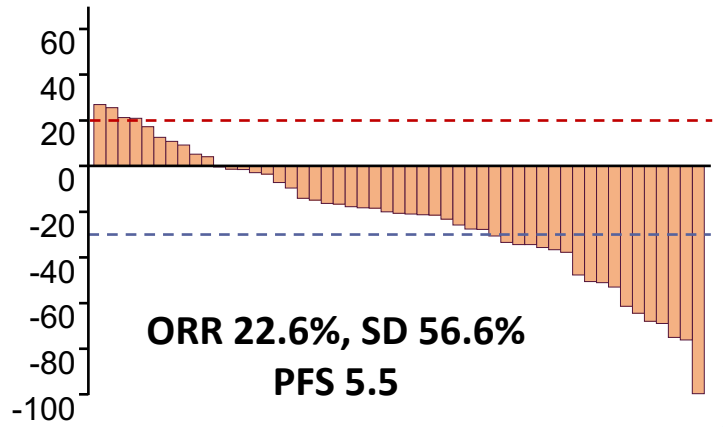
Ladiratuzumab vedotin (SGN–LIV1A)



ORR 28%



Patritumab DXd

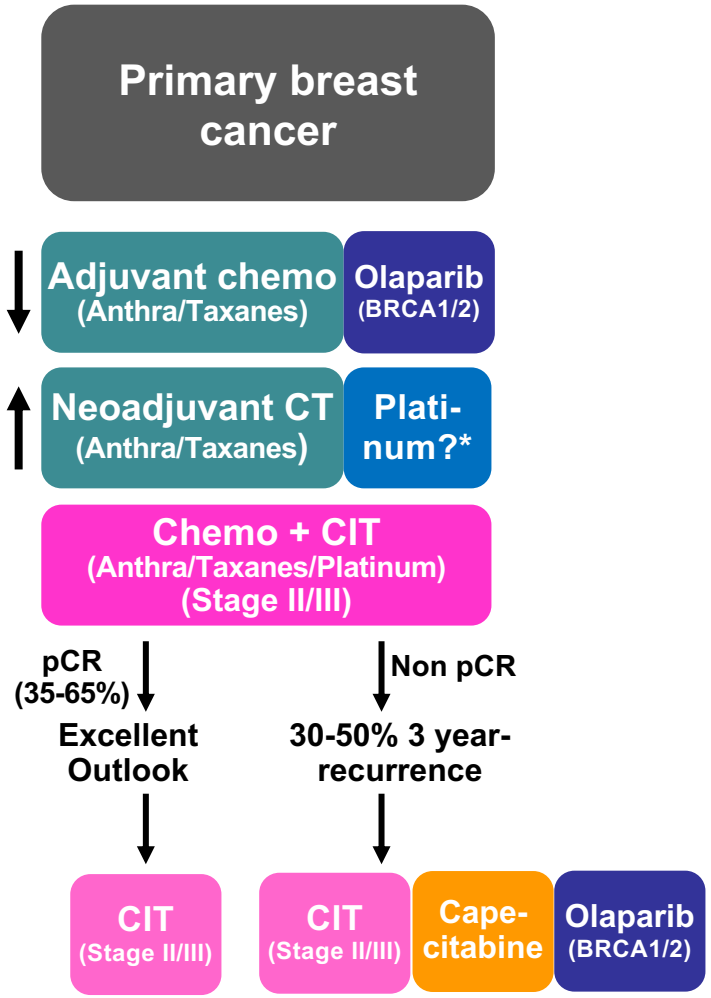


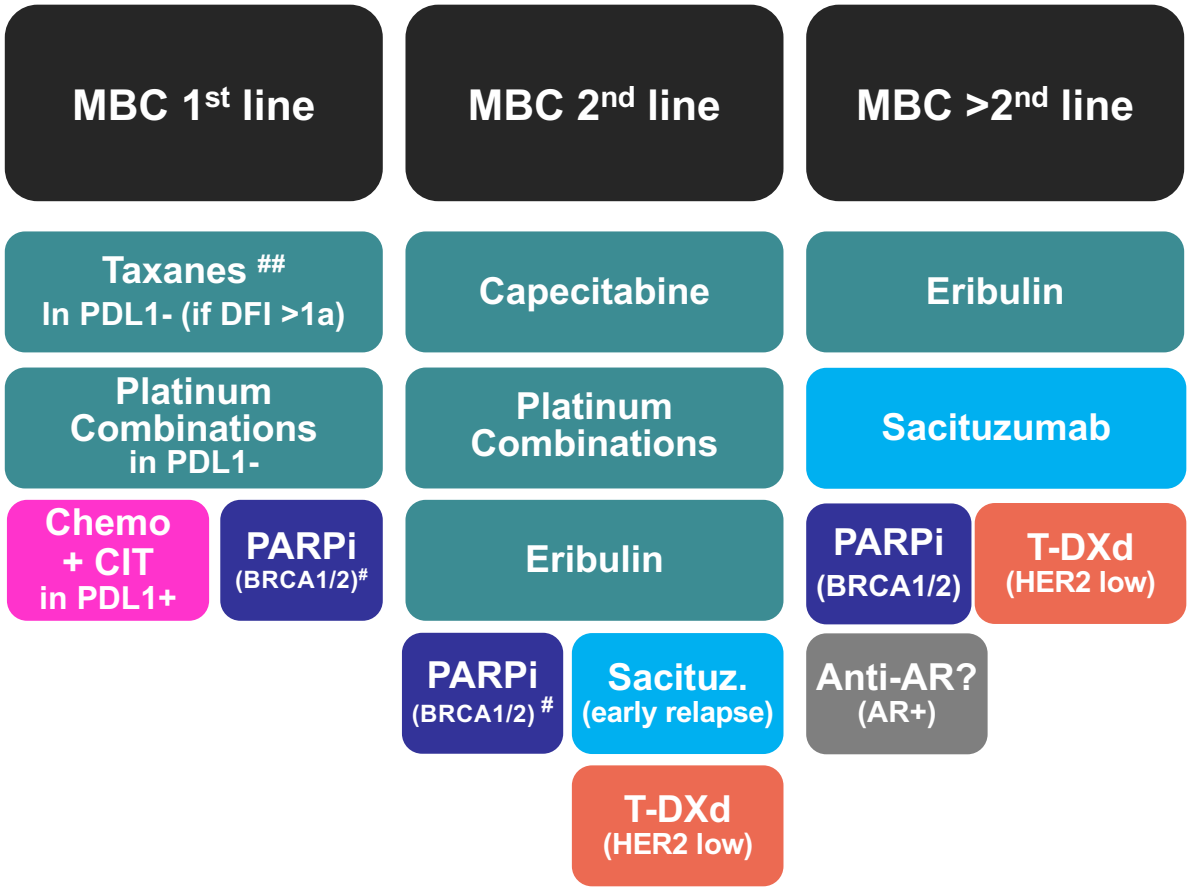
ORR 22.6%, SD 56.6%
PFS 5.5

Schmid P, Personal Communication

Bardia, NEJM 2021; Krop, SABCS 2021, Krop ASCO 2022, Modi JCO 2020 Tsai ESMO 2021

Triple Negative Breast Cancer – Management in 2022



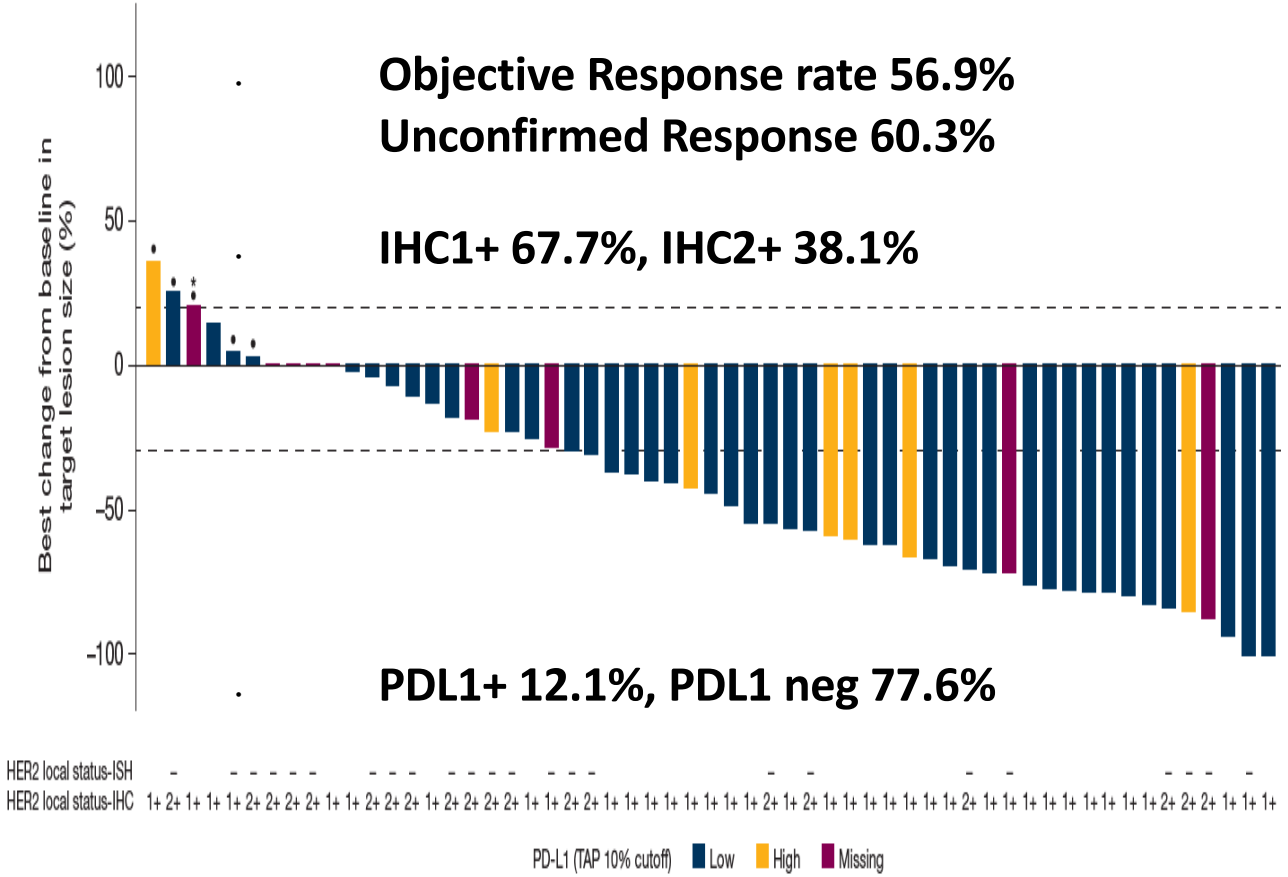


* All patients? High-risk patients? Suboptimal responders? BRCA1/2 carriers?
# limited to patients without progression on platinum, ## +/- Bevacizumab

Antibody-Drug Conjugates plus CPI/Chemotherapy

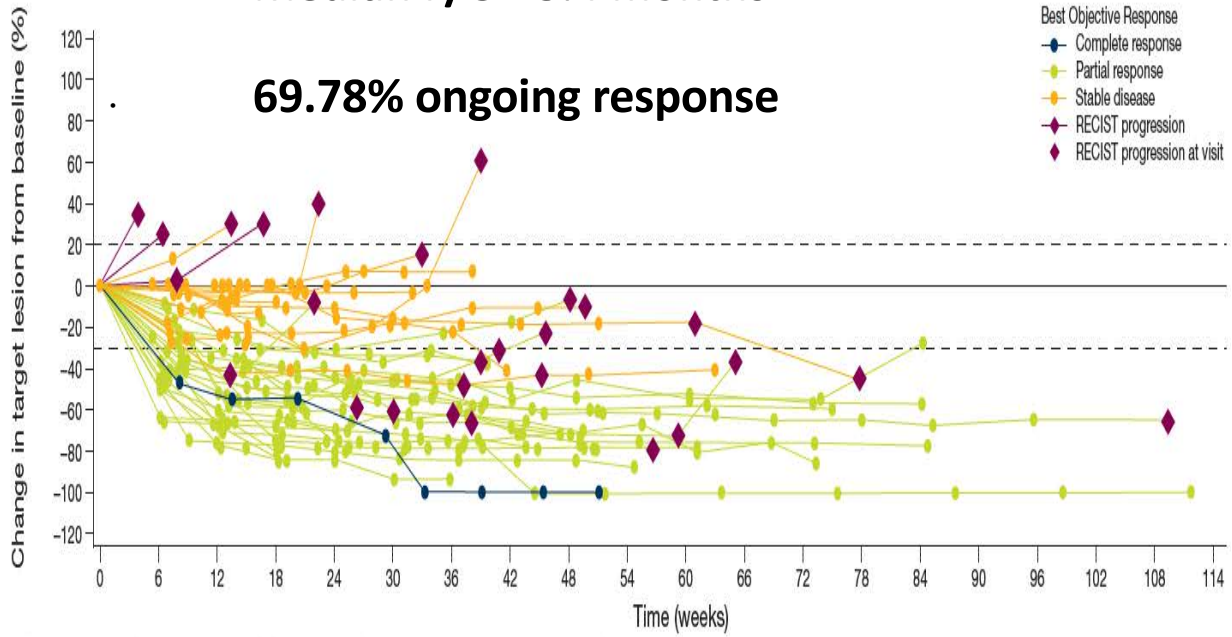
Trastuzumab-DXd (DS8201) plus Durvalumab in 1st line TNBC, HER2-low (IHC1+/2+)

- Objective Response rate 56.9%
- Unconfirmed Response 60.3%
- IHC1+ 67.7%, IHC2+ 38.1%
- PDL1+ 12.1%, PDL1 neg 77.6%



Dotted reference lines at -30% and 20% indicate thresholds for partial response and progressive disease, respectively.
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with progressive disease as best overall response.

- Median PFS 12.6 months
- Median F/U 13.4 months
- 69.78% ongoing response



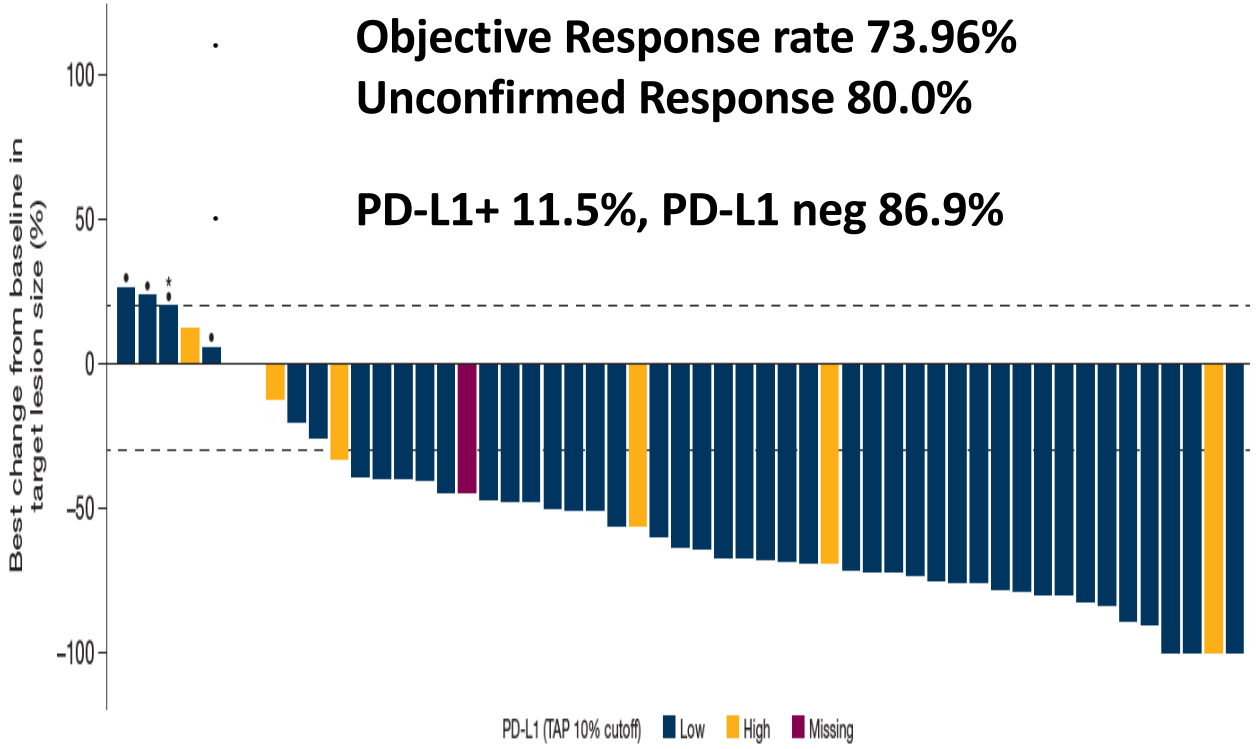
Dotted reference lines at -30% and 20% indicate thresholds for partial response and progressive disease, respectively.

Schmid, et al. SABCS 2022

Antibody-Drug Conjugates plus CPI/Chemotherapy

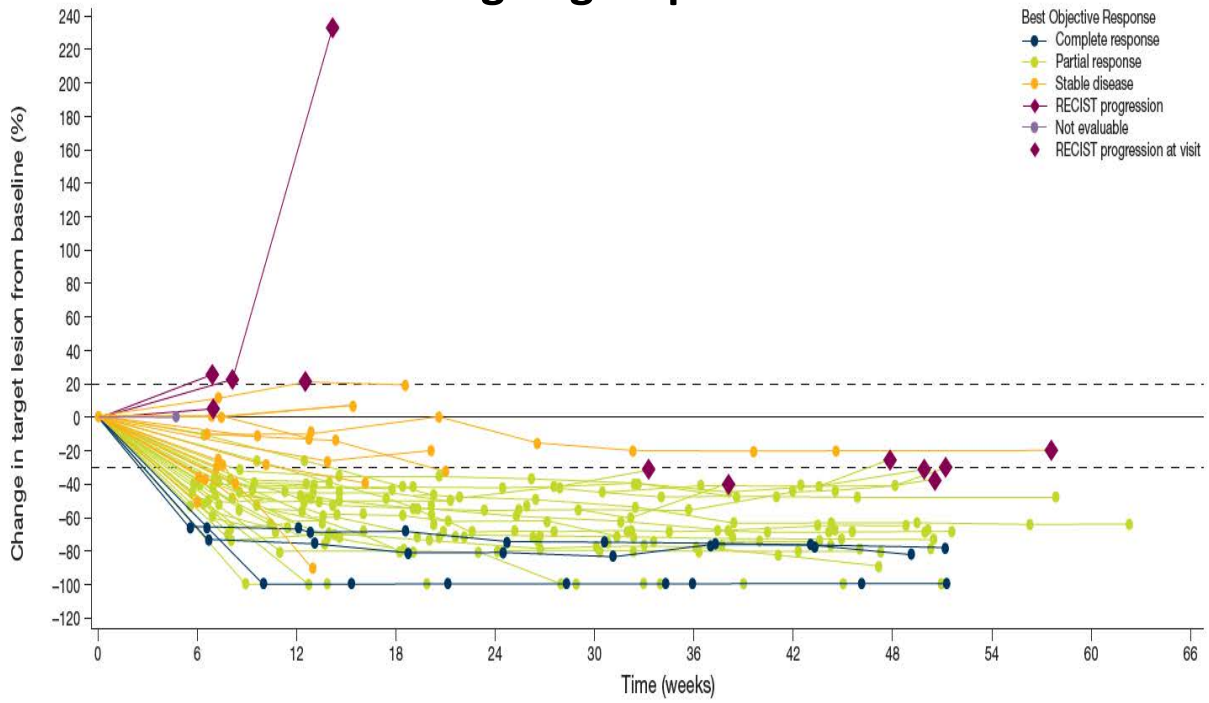
Dato-DXd plus Durvalumab in 1st line TNBC

- Objective Response rate 73.96%
  Unconfirmed Response 80.0%
- PD-L1+ 11.5%, PD-L1 neg 86.9%



n = 53.
Dotted reference lines at –30% and 20% indicate thresholds for partial response and progressive disease, respectively.
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with progressive disease as best overall response.

- Median F/U 7.2 months
- 69.78% ongoing response



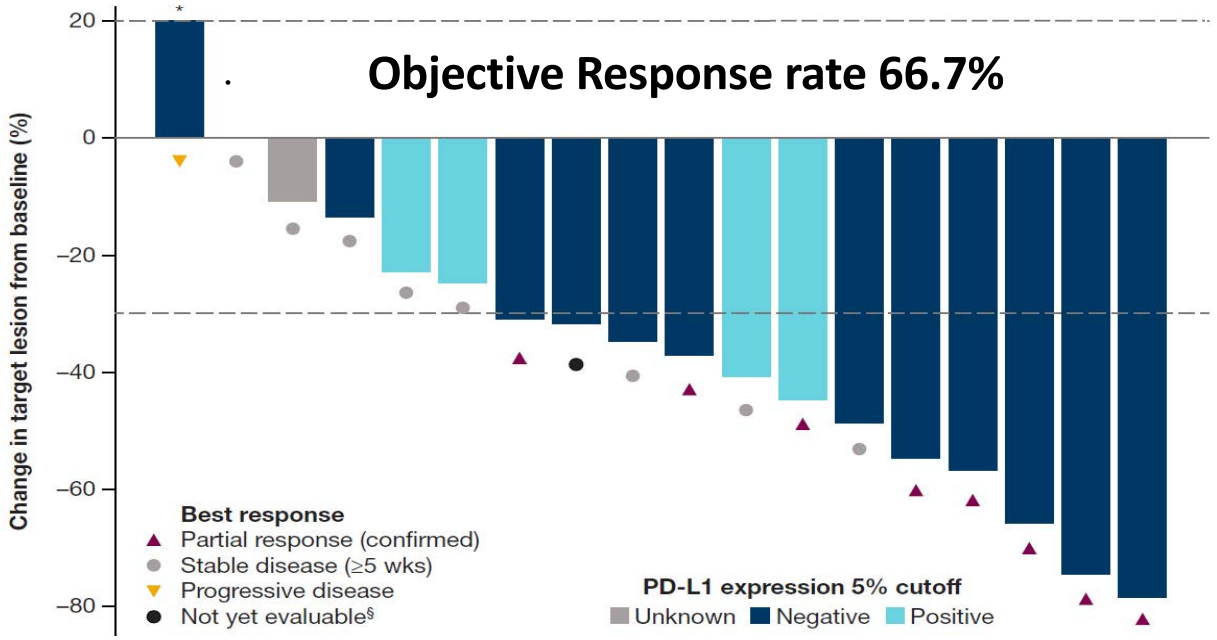
Dotted reference lines at –30% and 20% indicate thresholds for partial response and progressive disease, respectively.

Schmid, et al. SABCS 2022

Antibody-Drug Conjugates plus CPI/Chemotherapy

Trastuzumab-DXd (DS8201) plus Durvalumab

in 1st line TNBC, HER2-low (IHC1+/2+)

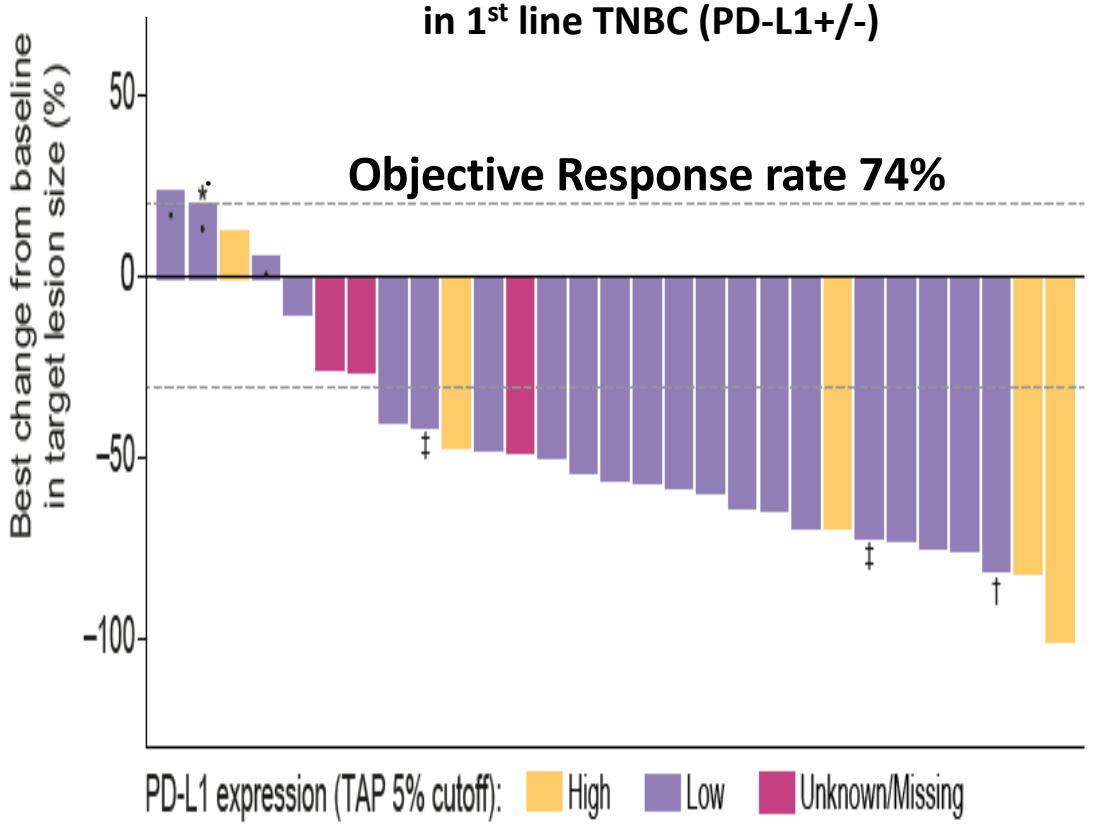


HER2 1+ 71%, HER2 2+ 29%
PD-L1+ 29%; PDL1- 62%

Schmid, et al. ASCO 2021

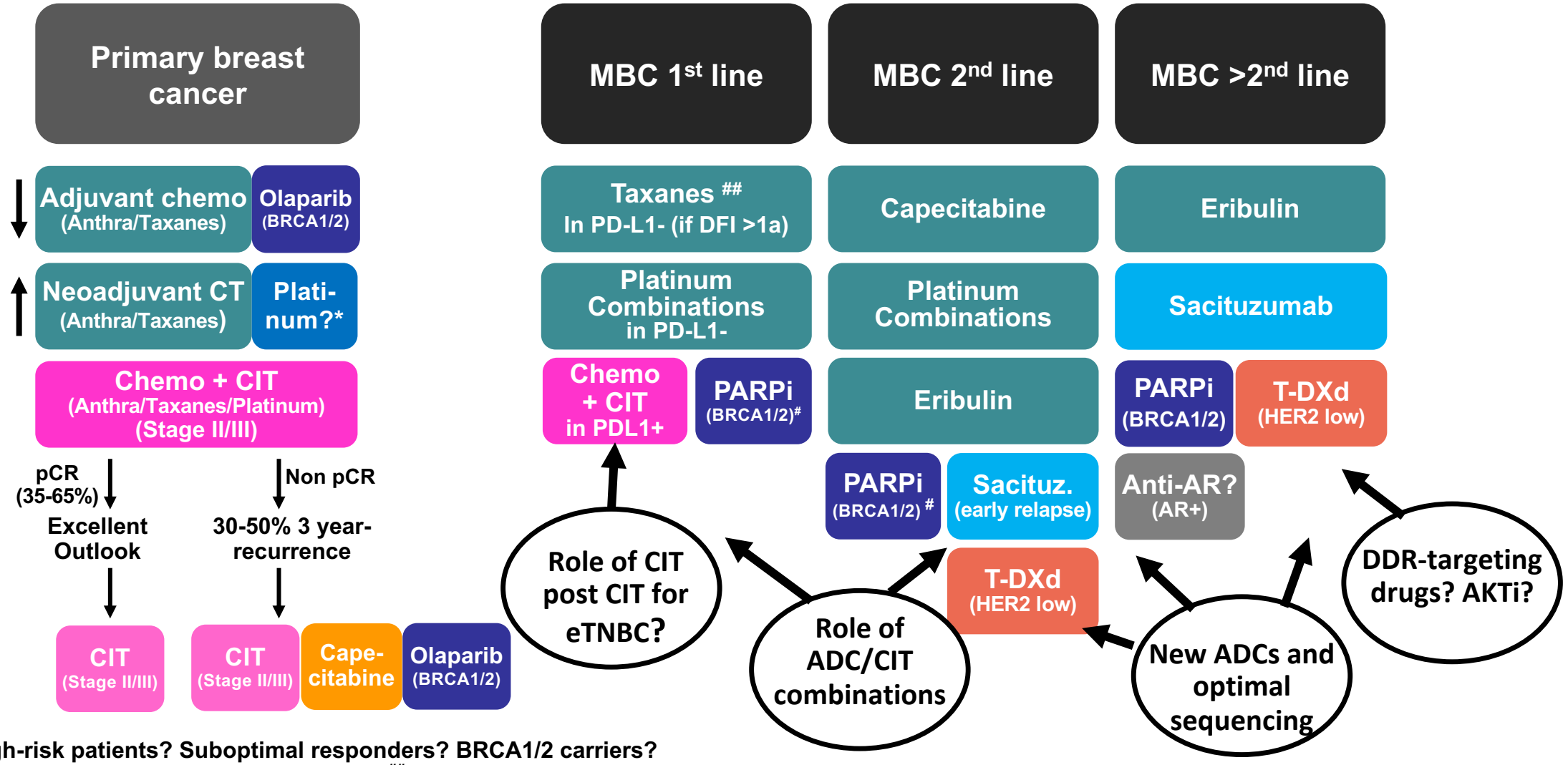
Dato-DXd plus Durvalumab

in 1st line TNBC (PD-L1+/-)



Schmid, et al. ESMO Breast 2022

Triple Negative Breast Cancer – Management in 2022



* All patients? High-risk patients? Suboptimal responders? BRCA1/2 carriers?
# limited to patients without progression on platinum, ## +/- Bevacizumab

Video Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Breast Cancer

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Monday, June 5, 2023

7:00 PM – 9:30 PM CT

Faculty

Komal Jhaveri, MD
Kevin Kalinsky, MD, MS
Ian E Krop, MD, PhD
Joyce O'Shaughnessy, MD
Hope S Rugo, MD
Prof Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Contributing Investigators

Sara A Hurvitz, MD
Professor of Medicine
Director, Breast Cancer Clinical Trials Program
Division of Hematology-Oncology
David Geffen School of Medicine at UCLA
Los Angeles, California

Tiffany A Traina, MD, FASCO
Vice Chair, Department of Medicine
Section Head, Triple-Negative Breast Cancer Clinical Research Program
Associate Attending Physician
Breast Medicine Service
Memorial Sloan Kettering Cancer Center
Associate Professor
Weill Cornell Medical College
New York, New York

Sara M Tolaney, MD, MPH
Chief, Division of Breast Oncology
Associate Director, Susan F Smith Center for Women's Cancers
Senior Physician
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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Investigator Perspectives on Available Research Findings and Challenging Questions in Renal Cell Carcinoma

A CME/MOC-Accredited Virtual Event Held in Conjunction with the 2023 ASCO Annual Meeting

Tuesday, June 6, 2023
7:00 AM – 8:00 AM CT

Faculty

David F McDermott, MD
Sumanta Kumar Pal, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

POSTMEETING SURVEY – Available Now

Clinicians in Attendance: The postmeeting survey is now available on the iPads for attendees in the room and on Zoom for those attending virtually. We appreciate your completing this survey before the end of the program.

Thank you for your input.

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

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

How to Obtain CME Credit

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

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

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