Fourth Annual
National General Medical Oncology Summit

Saturday, March 1, 2025

Moderator

Neil Love, MD

Faculty

Rahul Aggarwal, MD
Aditya Bardia, MD, MPH
Mitesh J Borad, MD
Virginia F Borges, MD, MMSc
Harold J Burstein, MD, PhD
Rashmi Chugh, MD
Christopher Flowers, MD, MS
Jonathan Goldman, MD
Nicole Lamanna, MD
Natasha B Leighl, MD, MMSc
Amit Mahipal, MD, MPH
William K Oh, MD
David M O'Malley, MD
Joyce O'Shaughnessy, MD
Krish Patel, MD
Richard F Riedel, MD
Kerry A Rogers, MD
Simron Singh, MD, MPH
Brian M Slomovitz, MD
Jonathan Strosberg, MD

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Co-Moderators

Sunil Gandhi, MD
Maen Hussein, MD
Mary Li, MD, PhD
Vikas Malhotra, MD
Bradley J Monk, MD
Frank Rodriguez, MD
Savan Shah, MD
Faye Yin, MD

Disclosures for Moderator Neil Love, MD

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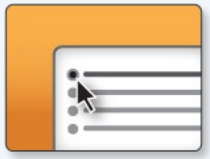
Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the premeeting survey.

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

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

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from this weekend 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.

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Fourth Annual National General Medical Oncology Summit

Module 1: HER2-Positive, Triple-Negative and Localized Breast Cancer

HER2-Positive Breast Cancer — Dr O'Shaughnessy

Triple-Negative Breast Cancer (TNBC) — Dr Bardia

Personalizing Adjuvant Therapy for Patients with HR-Positive Breast Cancer — Dr Borges

Current Role of CDK4/6 Inhibitors in the Localized Setting — Dr Burstein

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Current Role of CDK4/6 Inhibitors in the Localized Setting — Dr Burstein

HER2+ Breast Cancer

Joyce O'Shaughnessy, MD

Baylor University Medical Center

Texas Oncology

Sarah Cannon Research Institute

Dallas TX

Disclosures

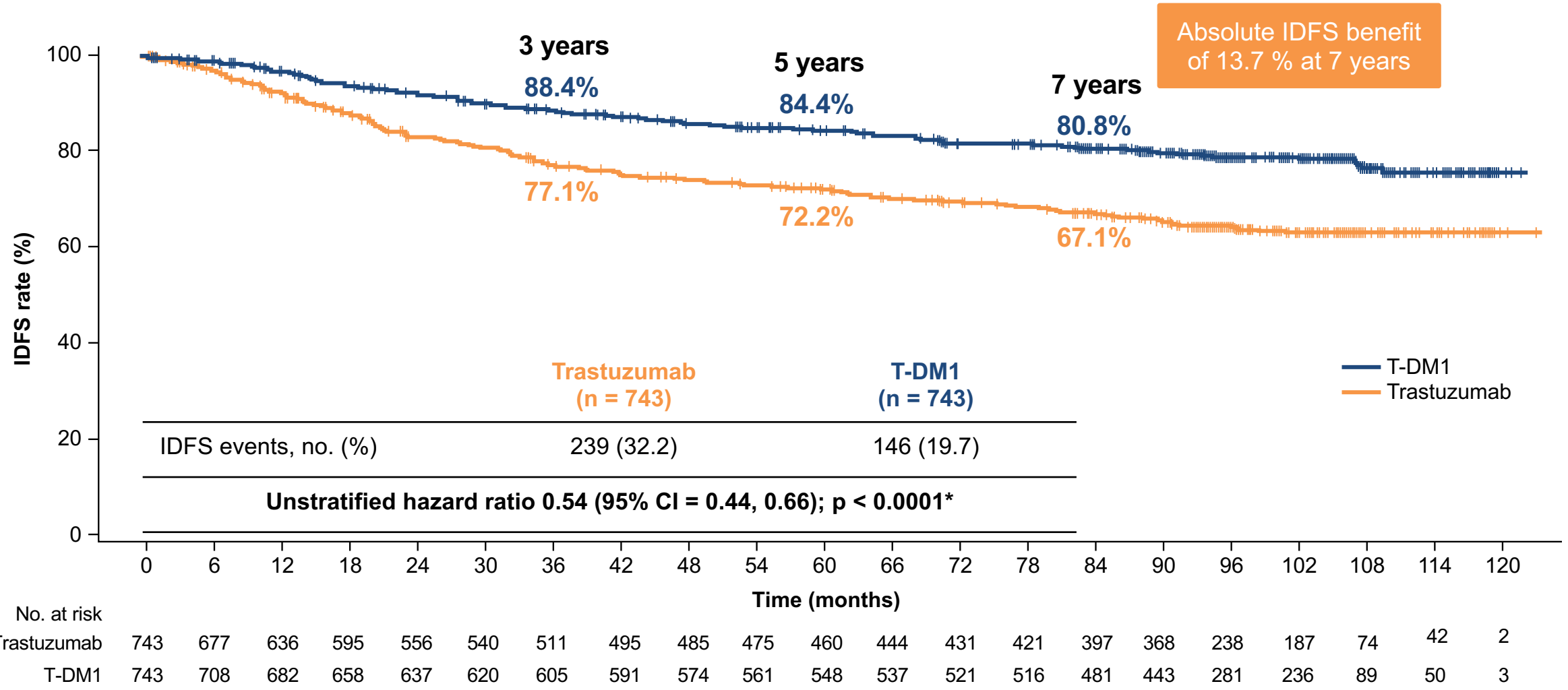
Advisory Committees and Consulting Agreements	Aadi Bioscience, Agendia Inc, Amgen Inc, Aptitude Health, AstraZeneca Pharmaceuticals LP, BioNTech SE, Bristol Myers Squibb, Daiichi Sankyo Inc, Duality Biologics, Eisai Inc, Ellipses Pharma, Exact Sciences Corporation, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Guardant Health, HiberCell, Jazz Pharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Pfizer Inc, Pierre Fabre, Puma Biotechnology Inc, Roche Laboratories Inc, Sanofi, Seagen Inc, Stemline Therapeutics Inc, Summit Therapeutics, Tempus, TerSera Therapeutics LLC

NEOADJUVANT PERTUZUMAB/TRASTUZUMAB (3 REGIMENS FDA APPROVED 9/2013)

	NEOSPHERE[1]	TRYPHAENA[2]	TRYPHAENA[2]
Treatment	Pertuzumab, Trastuzumab, Docetaxel THP x 4 FEC x 3 post-op)	Docetaxel/Carbo/ Trastuzumab/ Pertuzumab TCHP x 6	 FEC x 3 → THP x 3
N	107	77	75
ypT0/is ypN0 (%)	39.3	63.6	54.6

1. Gianni L, et al. *Lancet Oncol*. 2012;13(1):25-32.
2. Schneeweiss A, et al. *Ann Oncol*. 2013;24(9):2278-84.

KATHERINE IDFS Final Analysis; Median Follow-up 8.4 Years (101 months)



No. at risk																				
Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
T-DM1	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3

* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Loibl S et al. 2023 SABCS. GS03-12.

Should small HER2+ tumors get preop therapy?

Pathologic nodal status with upfront surgery in HER2+ cancers

	DF/BCC, No./total no. (%)			
	Upfront surgery patients, *N* = 368		NAC patients, *N* = 211	
	pN+, *N* = 73 (19.8%)	*p*	ypN+, *N* = 26 (12.3%)	*p*
Clinical tumor category		< .001[c]		.719
T1mic	6/48 (10.4)		–	
T1a	3/26 (11.5)		–	
T1b	7/87 (8.0)		1/7 (14.3)	
T1c	38/154 (24.7)		5/30 (16.7)	
T2	19/53 (35.8)		20/174 (11.5)	

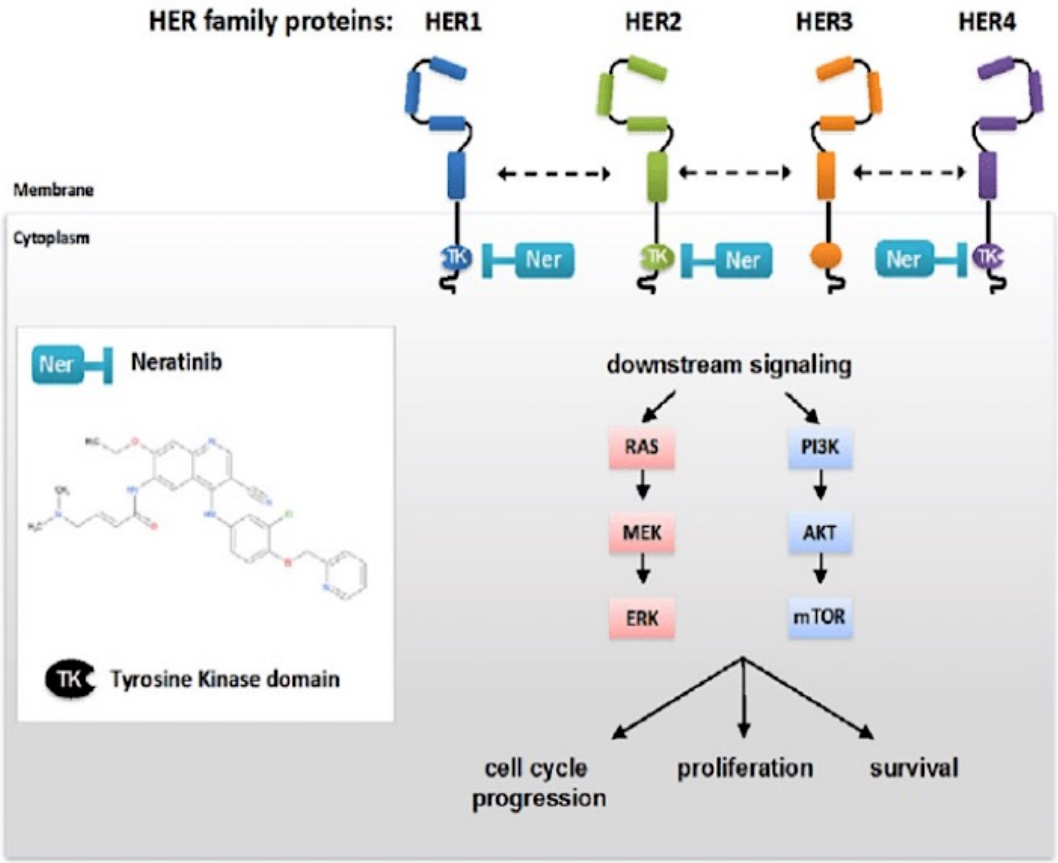
- Up to 25% of T1c tumors will be node positive, and therefore should be getting preoperative therapy
- Should we do axillary US upfront on all clinically node-negative patients and if negative, then take to surgery, and give adjuvant TH, or give preop TH for these pts?
  - RFI 97.5% suggests may not need more than TH for almost all pts, so could lead to overtreatment

Axillary Ultrasound for clinically node-negative stage I patients is critical for decision-making

Weiss A et al, Cancer. 2023;129(12):1836-1845.

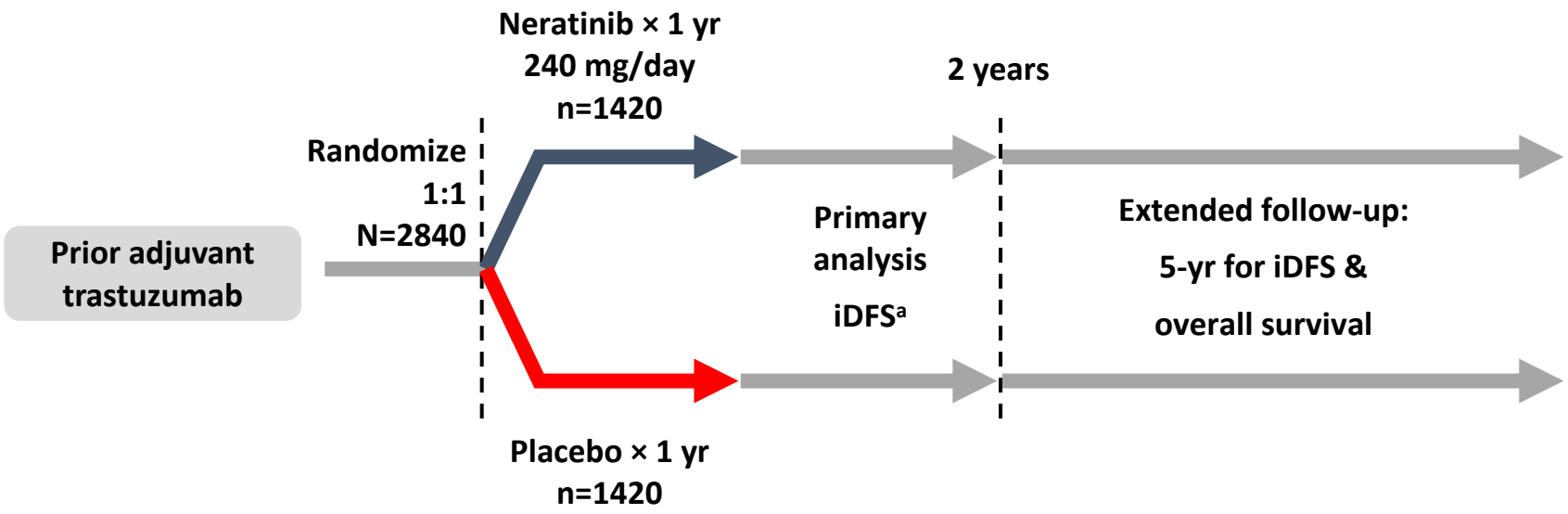
Neratinib

- Potent, irreversible-binding inhibitor of the ErbB family
  - Inhibits signal transduction through EGFR, HER2, HER4
- FDA approved for extended adjuvant therapy of early-stage HR+/HER2+ breast cancer (<1 yr from completion of prior adjuvant trastuzumab
- Active systemically alone or when combined with chemotherapy[1-7]
- On NCCN guidelines for treatment of metastatic disease in combination with capecitabine



[1]Burstein et al. *J Clin Oncol* 2010; [2]Awada A et al. *JAMA Oncol* 2016; [3]Chow LW et al *Br J Cancer* 2013, [4]Awada A et al. *Ann Oncol* 2013; [5]Saura C et al. *J Clin Oncol* 2014; [6] Awada A et al. *JAMA Oncol* 2016; [7]Saura C et al. *J Clin Oncol* 2020

ADDING NERATINIB: EXTENET STUDY



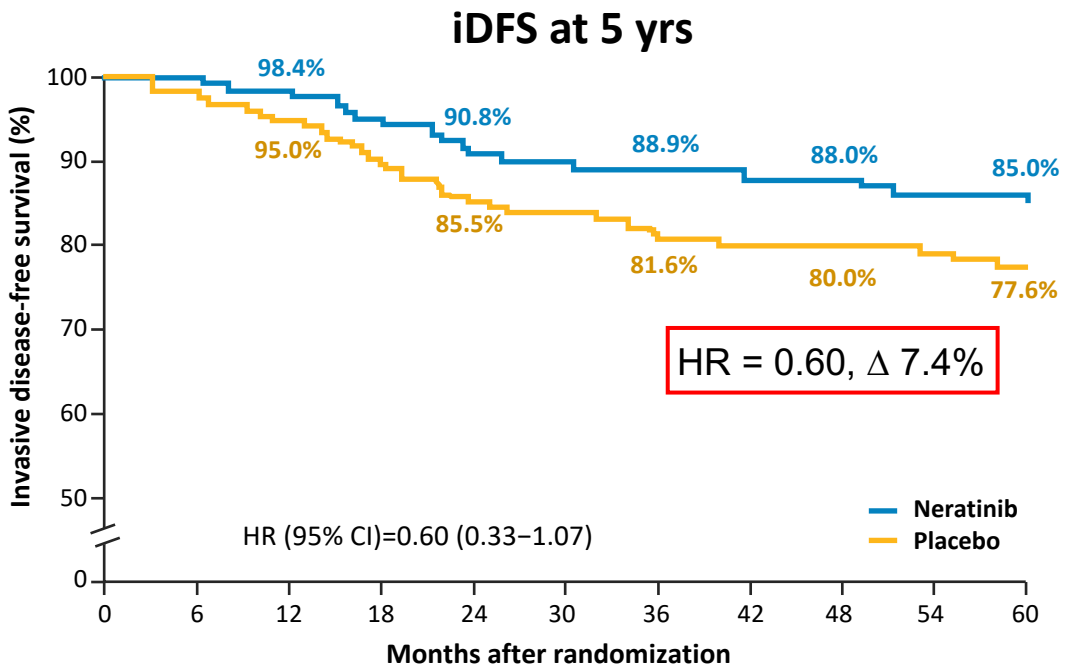
Primary endpoint: invasive disease-free survival (iDFS)[a]

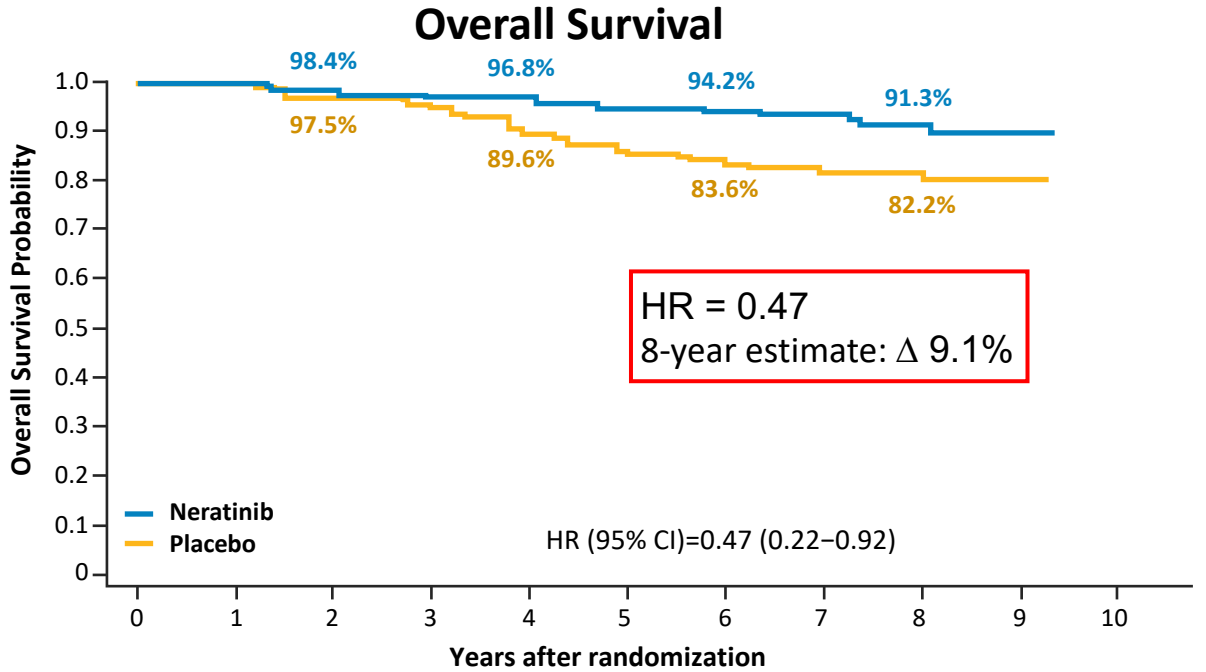
Secondary endpoints: overall survival, DFS-DCIS, distant DFS, time to distant recurrence, CNS metastases, safety,

Stratification: nodes 0, 1-3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

Study blinded: Until primary analysis; OS remains blinded

ExteNET: No pCR Post Neoadjuvant Therapy HR+, ≤1 Year from Trastuzumab (N=295)





No. at risk

Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

No. at risk

Neratinib	131	126	121	116	113	110	106	100	60	14	0
Placebo	164	161	156	143	135	129	123	115	65	12	0

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

Descriptive Analysis: Cumulative Incidence of CNS recurrences at first site of mets at 5 years HR+/≤1-year population (*n*=1334)

Subgroup	Cumulative Incidence of CNS recurrences at 5 years, %	
	Neratinib	Placebo
	%	%
All patients (*n*=1334)	0.7	2.1
Prior neoadjuvant therapy		
No (*n*=980)	0.7	1.5
Yes (*n*=354)	0.7	3.7
pCR status[1]		
No (*n*=295)	0.8	3.6
Yes (*n*=38)*	0	5

*Small Ns

1. Among the 354 patients who had received neoadjuvant therapy, 295 had no pCR, 38 patients achieved a pCR, and 21 patients had no outcome reported
CI, confidence interval; CNS, central nervous system; NE, not estimated; pCR, pathologic complete response

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

To date no agent has shown a difference in CNS Recurrences at first site of metastasis

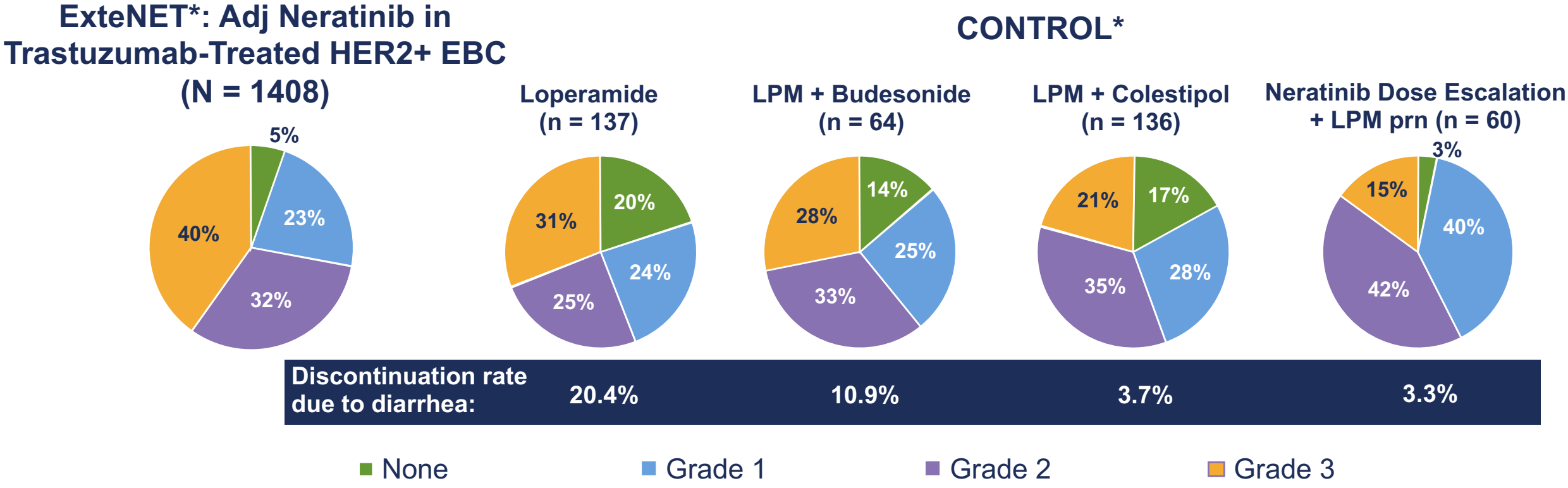
Trial Population	CNS Recurrences, %	CNS Recurrences, %
ALLTO (3 years) ITT, L+T , T->L, L, T* (N=5190)	Trastuzumab: 2	Trastuzumab +Lapatinib: 2
APHINITY (3 years) ITT (N=4,805)	Placebo: 2	Pertuzumab: 2
KATHERINE (3 years) ITT (high risk, No pCR) (N=1,486)	Trastuzumab: 5.1	T-DM1: 7

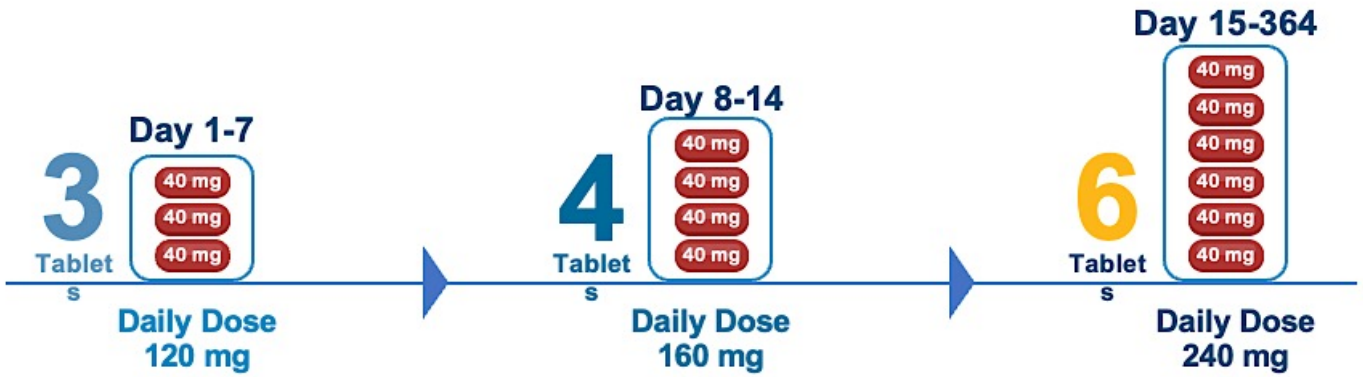
Caveat: Cross Trial Comparisons
Patients in KATHERINE are at higher risk of recurrence

*ALTTO reported the same rate for all 4 arms, 2 are shown here

Piccart-Gebhart, et al. *J Clin Oncol*. 2016;34(10) 1034-42.
von Minckwitz et al. *N Engl J Med*. 2017;377:122-131.
von Minckwitz et al. *N Engl J Med*. 2019;380(7) 617-628.

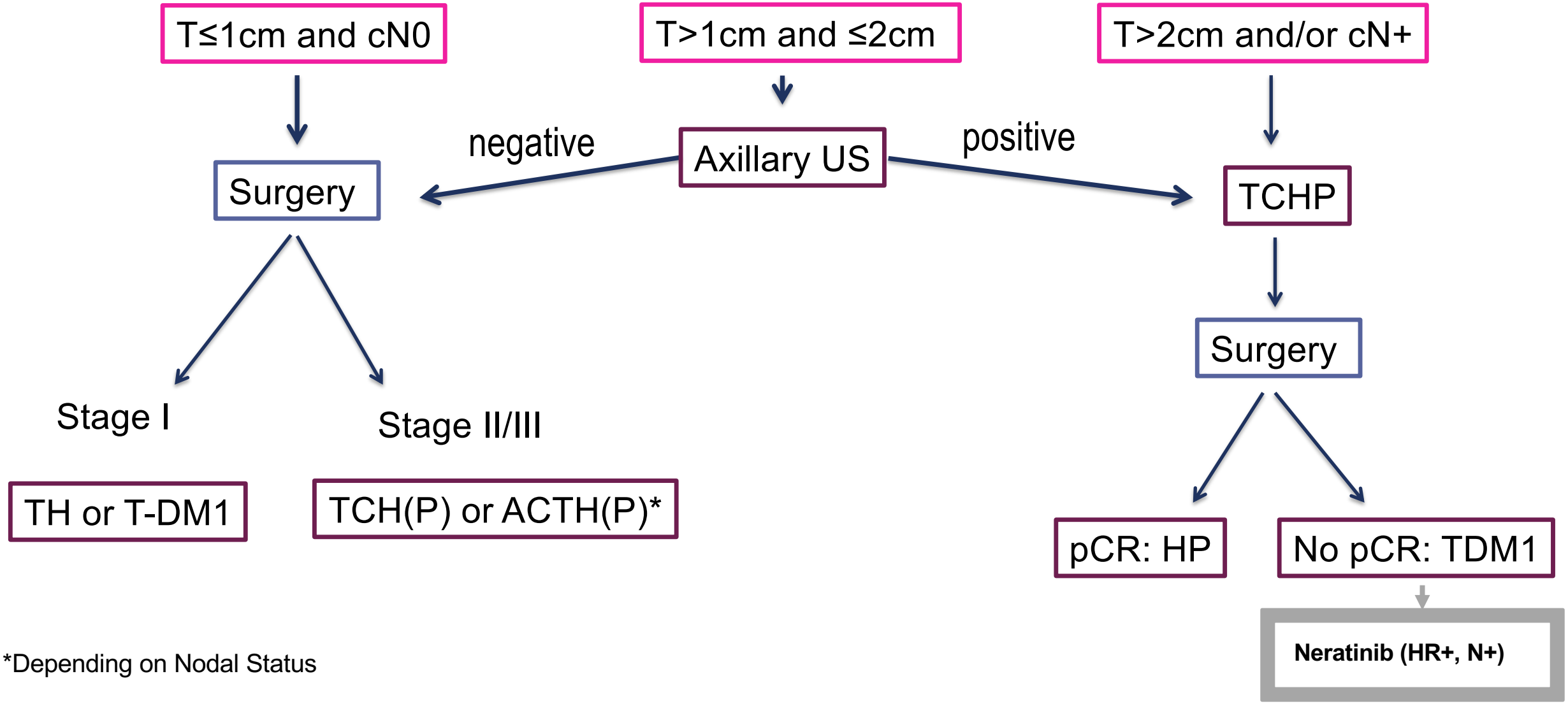
ANTIDIARRHEAL PROPHYLAXIS REDUCES DIARRHEA WITH NERATINIB: CONTROL TRIAL





Chan et al. SABCS 2019. Abstract P5-14-03.
Chan at al. Lancet Oncol. 2016;17(3):367-377.
Hurvitz S, et al. SABCS 2017.

HER2+ Early Breast Cancer Algorithm



*Depending on Nodal Status

HER2+ MBC AFT-38 PATINA Study Design

Pre-Study

- Histologically confirmed HR+HER2+ MBC
- No prior treatment in the advanced setting beyond induction treatment
- 6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane

Key eligibility criteria

- Completion of induction chemotherapy and no evidence of disease progression (i.e. , CR, PR, or SD)

N=518

R* 1:1

Palbociclib (125 mg PO QD D1-D21)
Trastuzumab ± Pertuzumab + Endocrine therapy†

Trastuzumab ± Pertuzumab + Endocrine therapy†

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification Factors

- Pertuzumab Use (Yes vs. No)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (Yes vs. No, including denovo)*
- Response to induction therapy (CR or PR vs. SD) by investigator assessment*
- Type of endocrine therapy (Fulvestrant vs. AI)

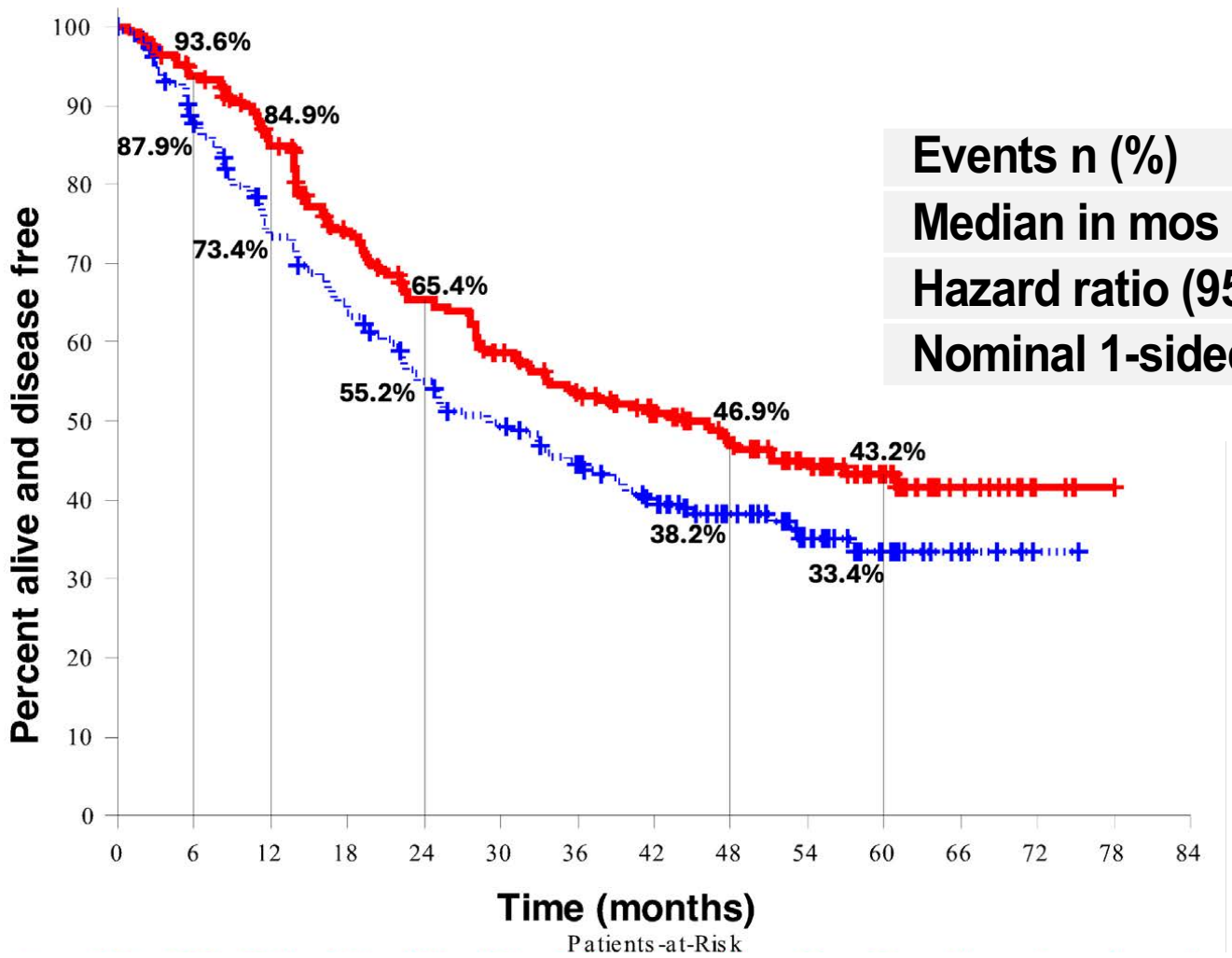
97% used pertuzumab

Prior trastuzumab 71%

ORR 69%

Metzger O et al. SABCS 2024

Investigator-Assessed PFS



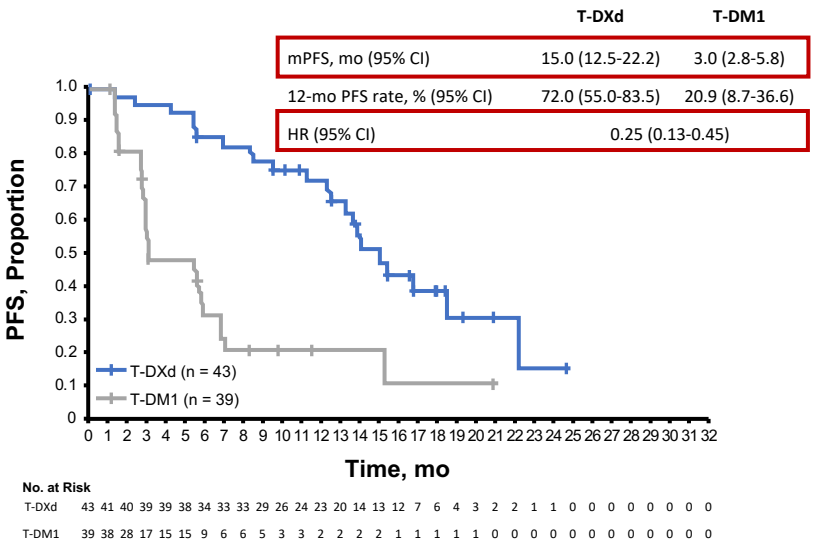
	Palbo + Anti-HER2 and ET	+ Anti-HER2 and ET
Events n (%)	126/261	136/257
Median in mos (95% CI)	44.3	29.1
Hazard ratio (95% CI)	0.74 (0.58–0.94)	
Nominal 1-sided *P* value	0.0074	

This is quite high!

Metzger O et al. SABCS 2024

DESTINY-Breast03: PFS in Patients With and Without Brain Metastases1-4

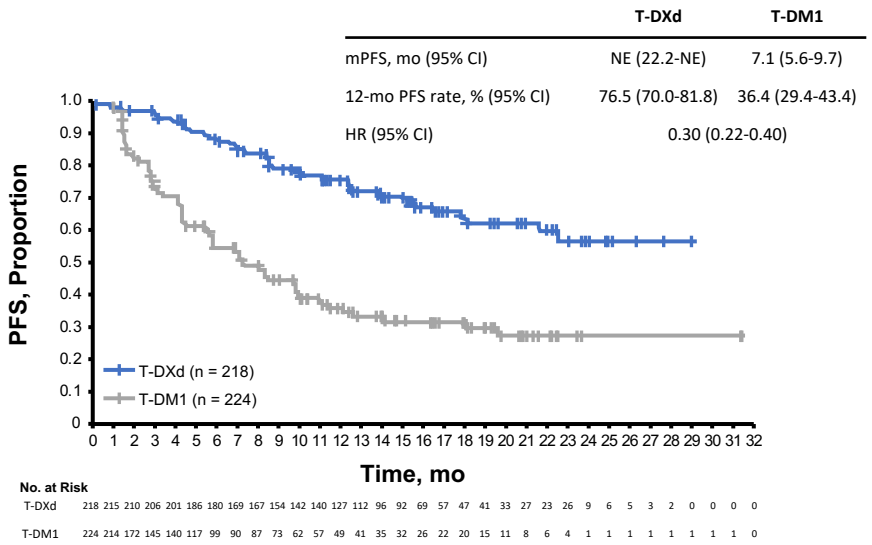
Brain Metastases at Baseline



In patients with brain metastases at baseline, PD was observed:

- In 48.8% (21/43) treated with T-DXd vs 69.2% (27/39) with T-DM1
- In the brain in 42.9% (9/21) treated with T-DXd vs 40.7% (11/27) with T-DM1

No Brain Metastases at Baseline



In patients without brain metastases at baseline, PD was observed:

- In 28.9% (63/218) treated with T-DXd vs 57.1% (128/224) with T-DM1
- In the brain in 6.3% (4/63) treated with T-DXd vs 0.8% (1/128) with T-DM1

1. Cortés J et al. 2021 ESMO Congress. Abstract LBA1. 2. Cortés J et al. *N Engl J Med.* 2022;386(12):1143-1154.
3. Hurvitz SA et al. 2021 SABCS. Presentation GS3-01. 4. Hurvitz SA et al. *Lancet.* 2023;401(10371):105-117.

Brain Metastases May Go Undetected

- **Asymptomatic brain metastases occur in 15-36% of patients with HER2+ mBC[1-3]**
- Up to **50% of patients** with HER2+ MBC **may develop brain metastases** during the course of their disease[4-7]

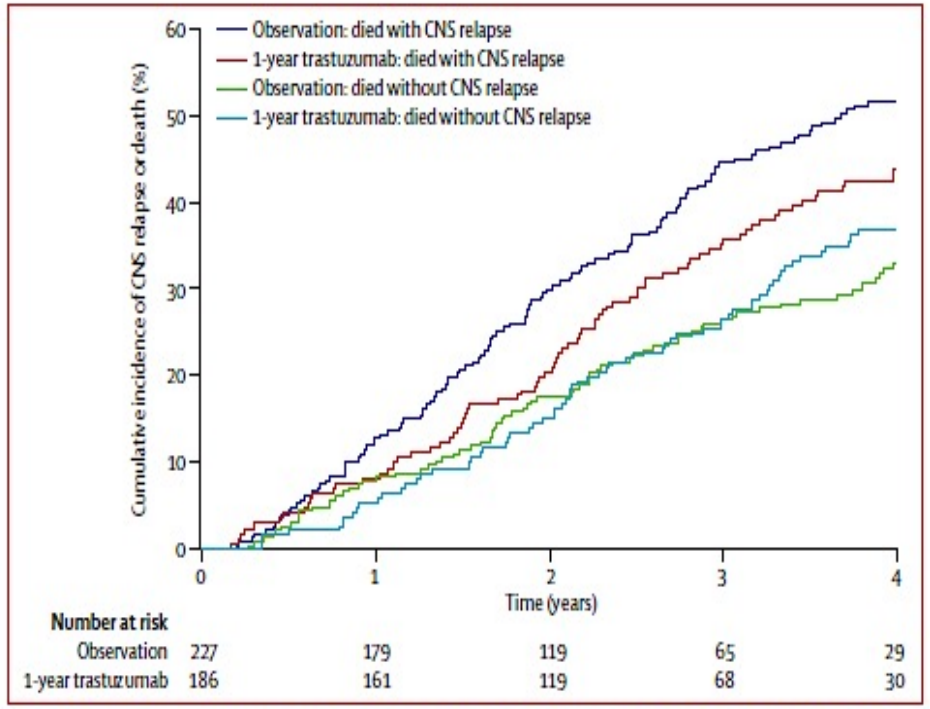


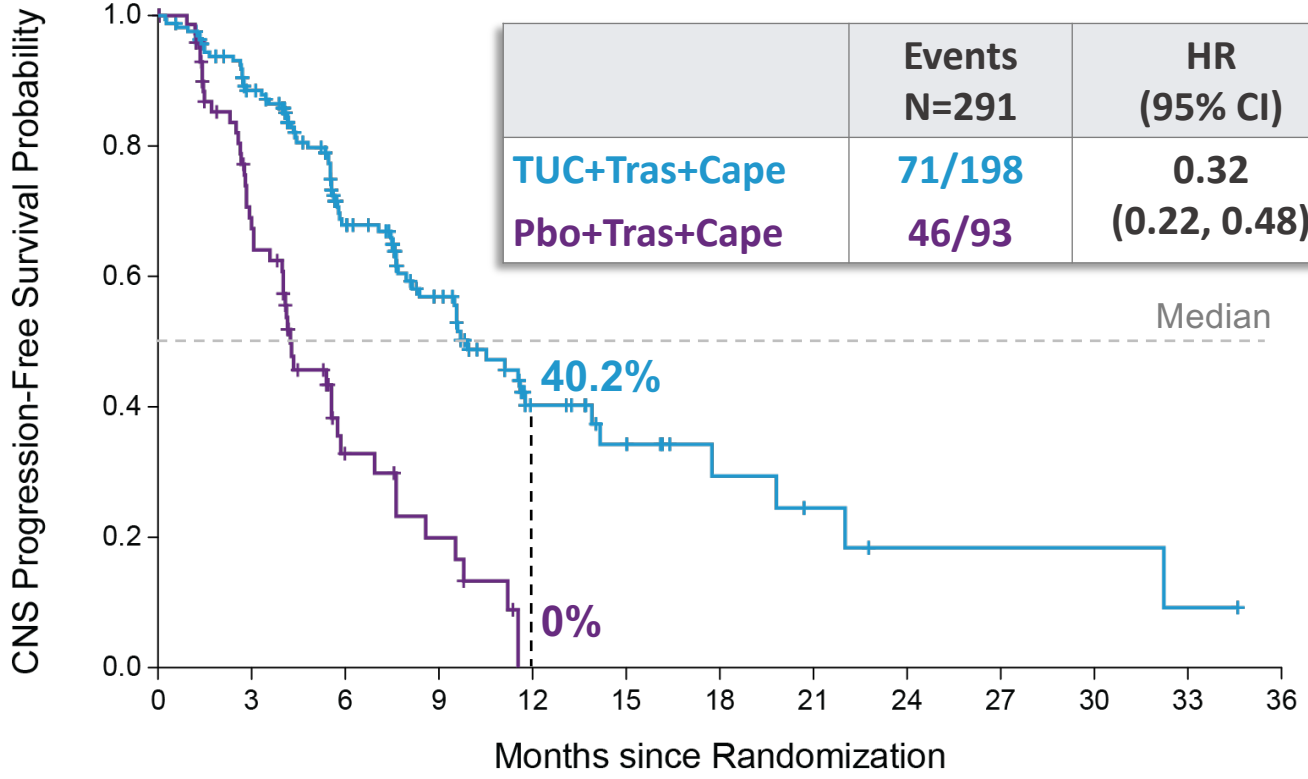
Figure 2: **Competing risks analysis of cumulative incidence of CNS relapse in the 413 patients who had died for whom forms were returned**

Curves for both groups are shown for the cumulative incidence of the competing events of death without CNS relapse at any time, and for CNS-relapse reported any time before death. Time axis not drawn beyond 4 years, because numbers at risk are small. DFS=disease-free survival.

- Continuous risk over time

1. Brufsky AM, et al. *Clin Cancer Res*. 2011;17:4834–4843. **2.** Miller KD, et al. *Ann Oncol.* 2003;14:1072-1077. **3.** Niwińska A, et al. *Int J Radiat Oncol Biol Phys.* 2010;77:1134-1139.
4. Olson EM et al. *Breast*. 2013;22:525-531. **5.** Bendell JC et al. *Cancer*. 2003;97:2972-2977. **6.** Freedman RA et al. *J Clin Oncol*. 2019;37:1081-1089.
7. Pestalozzi BC et al. *Lancet Oncol*. 2013;14:244-248.

HER2CLIMB Trial: CNS-PFS Benefit in Patients with Brain Metastases



	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	71/198	0.32 (0.22, 0.48)	<0.00001
Pbo+Tras+Cape	46/93		

No. at Risk													
TUC+Tras+Cape	198	132	74	45	18	11	6	4	2	2	2	1	0
Pbo+Tras+Cape	93	41	11	6	0	0	0	0	0	0	0	0	0

Risk of CNS progression or death was reduced by 68% in patients with brain metastases

One-year CNS-PFS (95% CI):	
TUC+Tras+Cape 40.2% (29.5, 50.6)	Pbo+Tras+Cape 0%
Median CNS-PFS (95% CI):	
9.9 months (8.0, 13.9)	4.2 months (3.6, 5.7)

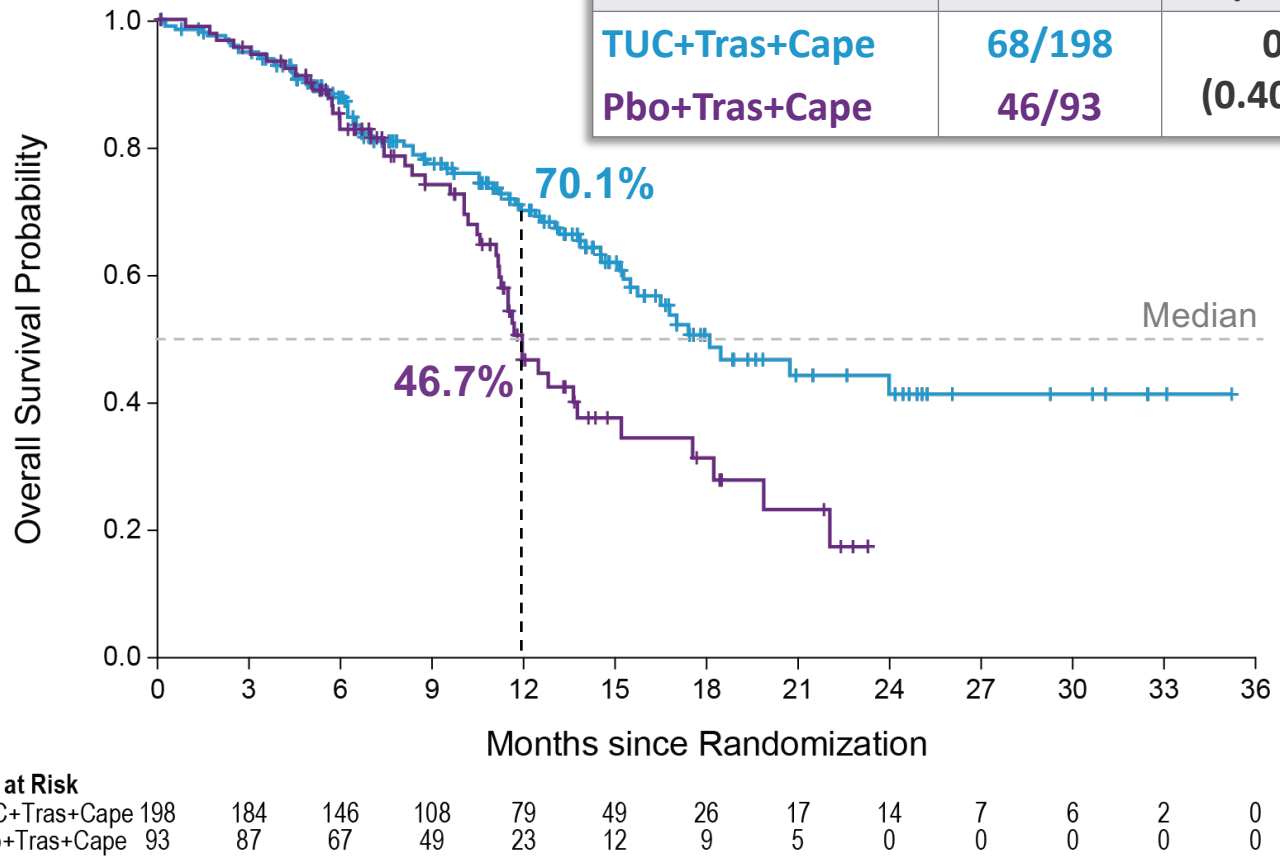
Stable BrMets:	13.9 mos	5.6 mos
Active BrMets:	9.5 mos	4.1 mos

CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment.
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.

Lin et al. *J Clin Oncol*. 2020;38(23):2610-2619.

HER2CLIMB Trial: OS Benefit in Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		



Risk of death was reduced by 42% in patients with brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape 70.1% (62.1, 76.7)	Pbo+Tras+Cape 46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

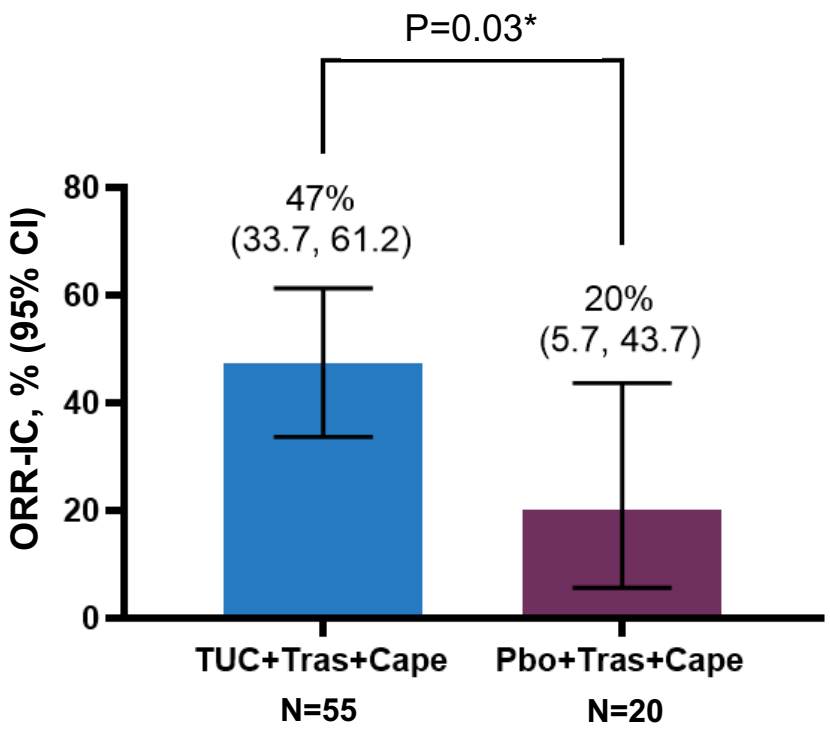
Stable BrMets:	15.7 mos	13.6 mos
Active BrMets:	20.7 mos	11.6 mos

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.

Lin et al. *J Clin Oncol*. 2020;38(23):2610-2619.

HER2CLIMB Trial: Intracranial Response Rate in Patients with Active Brain Metastases and Measurable Intracranial Lesions

Confirmed Objective Response Rate (RECIST 1.1)



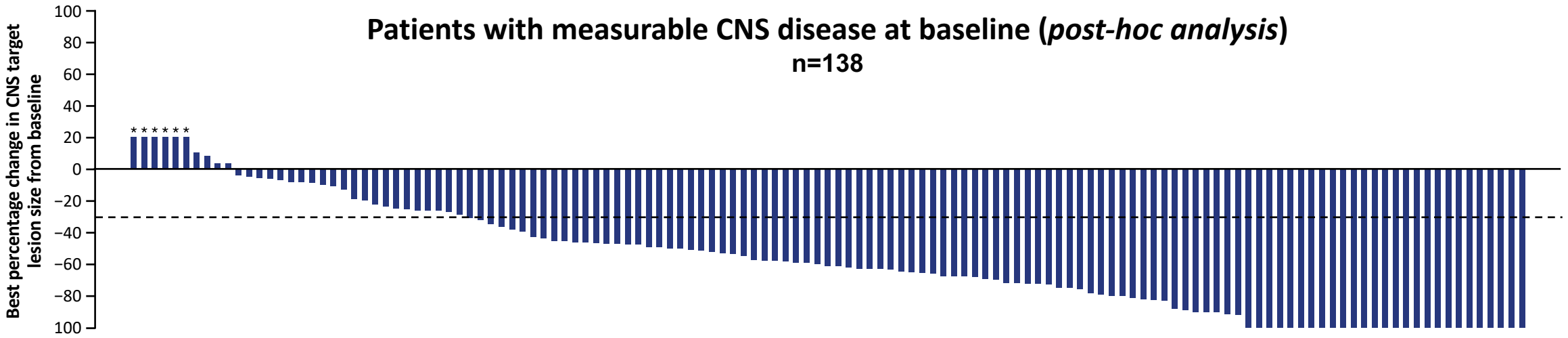
*Stratified Cochran-Mantel-Haenszel P value

Lin et al. *J Clin Oncol*. 2020;38(23):2610-2619.

	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).

DESTINY-Breast12 Trial Baseline BMs: CNS ORR



Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs (n=61)	Active BM subgroups: Untreated (n=23) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=38) *Post-hoc analysis*
Confirmed CNS ORR, % (95% CI)	71.7 (64.2, 79.3)	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD

BM, brain metastasis; CI, confidence interval; CNS, central nervous system; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan

Harbeck N et al. *Nat Med*. 2024 Dec;30(12):3717-3727.

COMPASSHER2 TRIALS

Eligibility:
Stage II or IIIA HER2+ BC (T2-3, N0-2)

- cN0 eligible if ≥ 2.0 cm
- cN1-2 eligible ≥ 1.5cm
- ER+ and ER- eligible

REGISTRATION

Preoperative Phase: all patients

THP x 4 Cycles
Paclitaxel qwk x12
OR
Docetaxel q3 wk x4
with
Trastuzumab (H)
& Pertuzumab (P) q3 wk x4

* nab-pacl allowed

SURGERY

pCR (ypT0/Tis ypN0) *40%*

No pCR *60%*

Arm A: pCR (no invasive disease)

EA1181
CompassHER2-pCR

- Complete 1 yr HP
- Radiation and endocrine Rx (if appropriate)

ECOG-ACRIN cancer research group
Reshaping the future of patient care

A011801
CompassHER2-RD

Alliance for Clinical Trials in Oncology

Grp 1: pre-op THP-> AC, Cb/HP x 4
Grp 2: pre-op TCHP, *AC-THP* -> no further chemo

Eligibility
HER2+ RD
ER- & ER+
(ER+ must be N+)
(~30% of A011801 expected to come from EA1181)

Registration

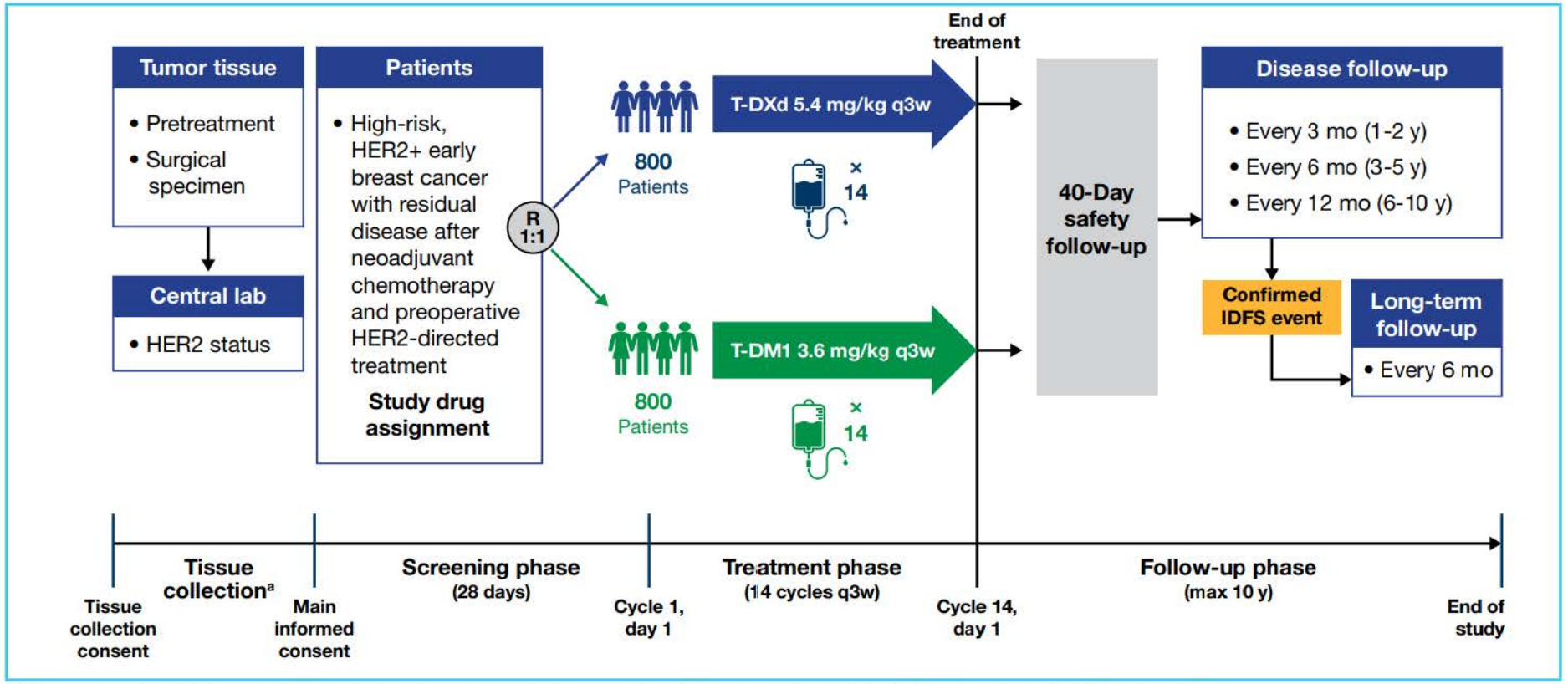
R

T-DM1 x 14 doses

T-DM1/tucatinib x 14 doses

DESTINY-Breast05 phase 3 trial

DESTINY-Breast05: A Multicenter, Open-Label, Randomized Phase 3 Trial Comparing the Efficacy and Safety of T-DXd vs T-DM1 in High-Risk Patients With HER2-Positive, Residual, Invasive Breast Cancer After Neoadjuvant Therapy (N≈1600)



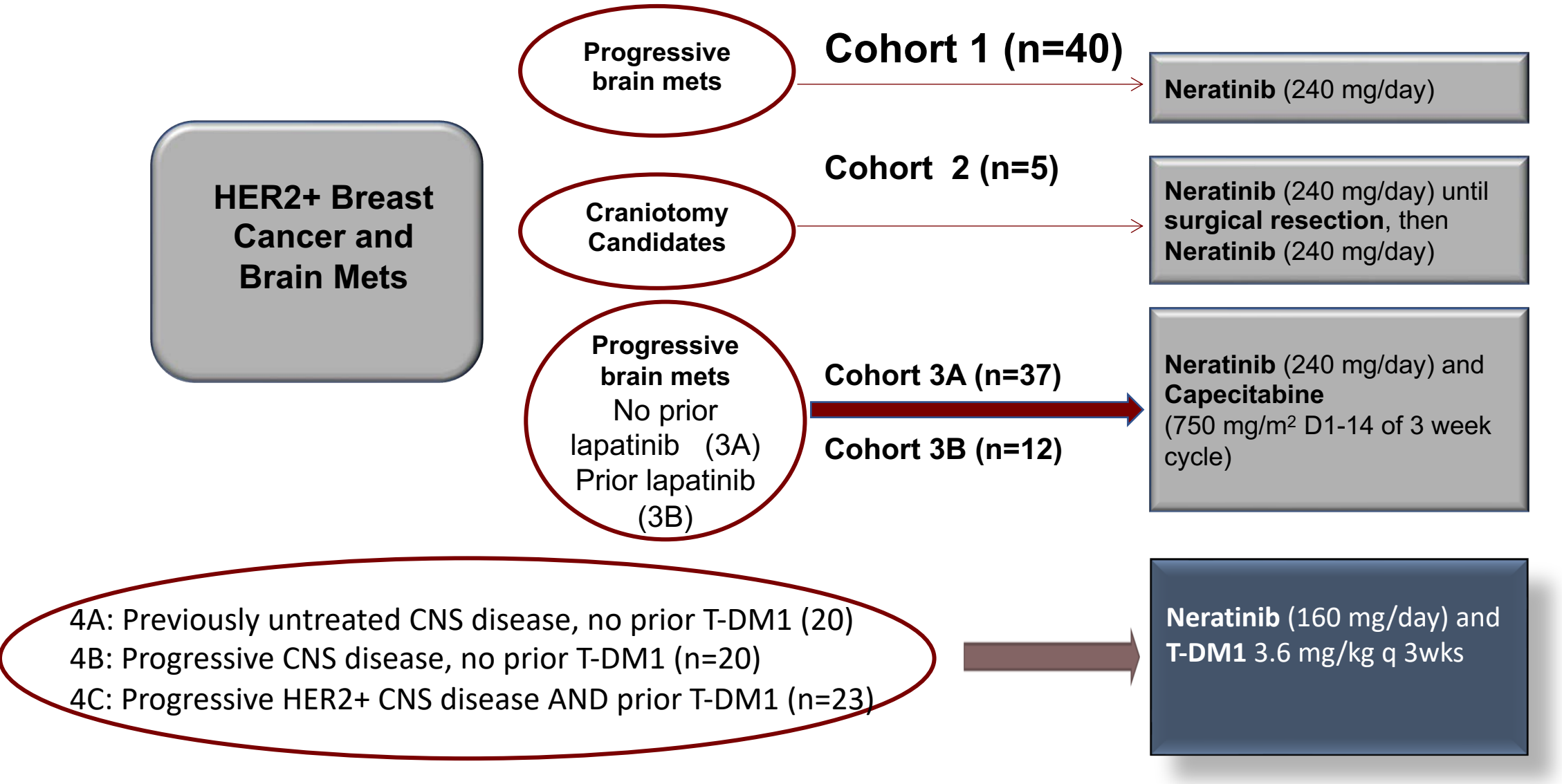
HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; lab, laboratory; max, maximum; q3w, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a] Patients may move into the main screening phase before HER2 status results are available from the central laboratory.

– **Inoperable** breast cancer at presentation

– Operable breast cancer at presentation with **node–positive (ypN1-3) disease** after neoadjuvant therapy

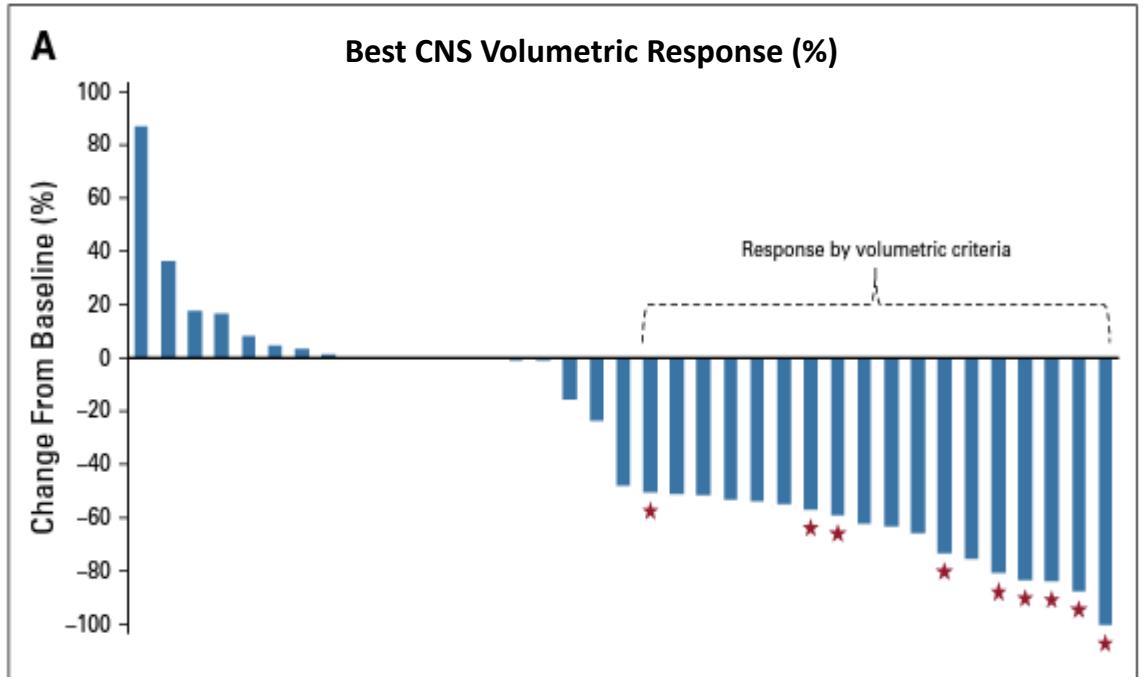
Geyer et al. SABCS 2020;Abstract OT-03-01.

TBCRC 022: A Phase II Trial of Neratinib for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases



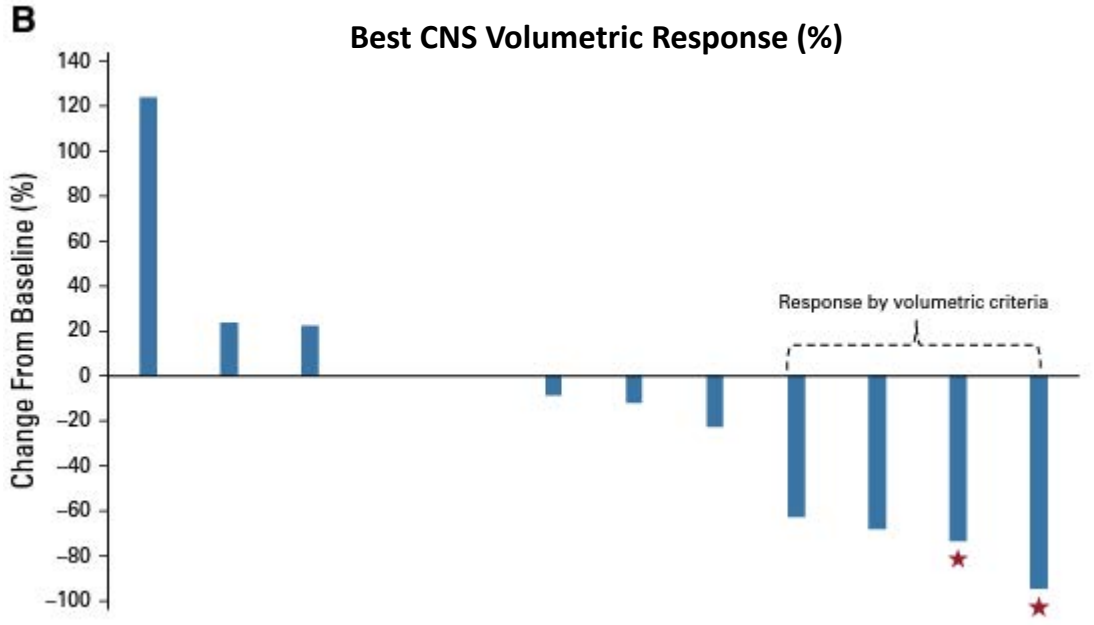
TBCRC 022 Cohort 2 – Neratinib/Capecitabine

Cohort 3A (lapatinib naïve)



CNS ORR = 49% (n=37)

Cohort 3B (lapatinib exposed)



CNS ORR = 33% (n=12)

┼ **No patient had clear increase in steroid use, non-target lesions, non-CNS lesions, or worsening neurological symptoms at time**

Freedman et al. *J Clin Oncol* 2019;37(13):1081-1089

HER2+ Breast Cancer Summary

- Neoadjuvant therapy in Stage 2 or 3 disease – T1cN0 reasonable as well
- T-DM1 improves OS post-neoadjuvant therapy in pts with residual disease
- Neratinib for HR+ pts with residual disease at high risk of recurrence

- Palbociclib maintenance therapy with ET + HP 1L MBC – 15 mo gain in PFS
- T-DXd improves OS 2L and has high CNS activity for established brain mets
- HER2CLIMB Tucatinib improves OS in ITT and brain mets populations
- Later line neratinib + capecitabine for pts HER2+ brain mets

- CompassHER2 RD and DB-05 are evaluating tucatinib and T-DXd in EBC pts with RD – need reduction in CNS and other recurrences

Discussion Question

- A 65-year-old woman with ER-negative, HER2-positive metastatic breast cancer receives first-line THP and then develops asymptomatic disease progression with multiple brain metastases. Regulatory and reimbursement issues aside, which systemic treatment would you recommend?

Discussion Questions

- Have you or would you administer trastuzumab deruxtecan (T-DXd) and hold off on radiation therapy for a patient with HER2-positive mBC with several small untreated asymptomatic brain metastases?

- How, if at all, do you integrate olanzapine into the management of T-DXd-related nausea and vomiting?

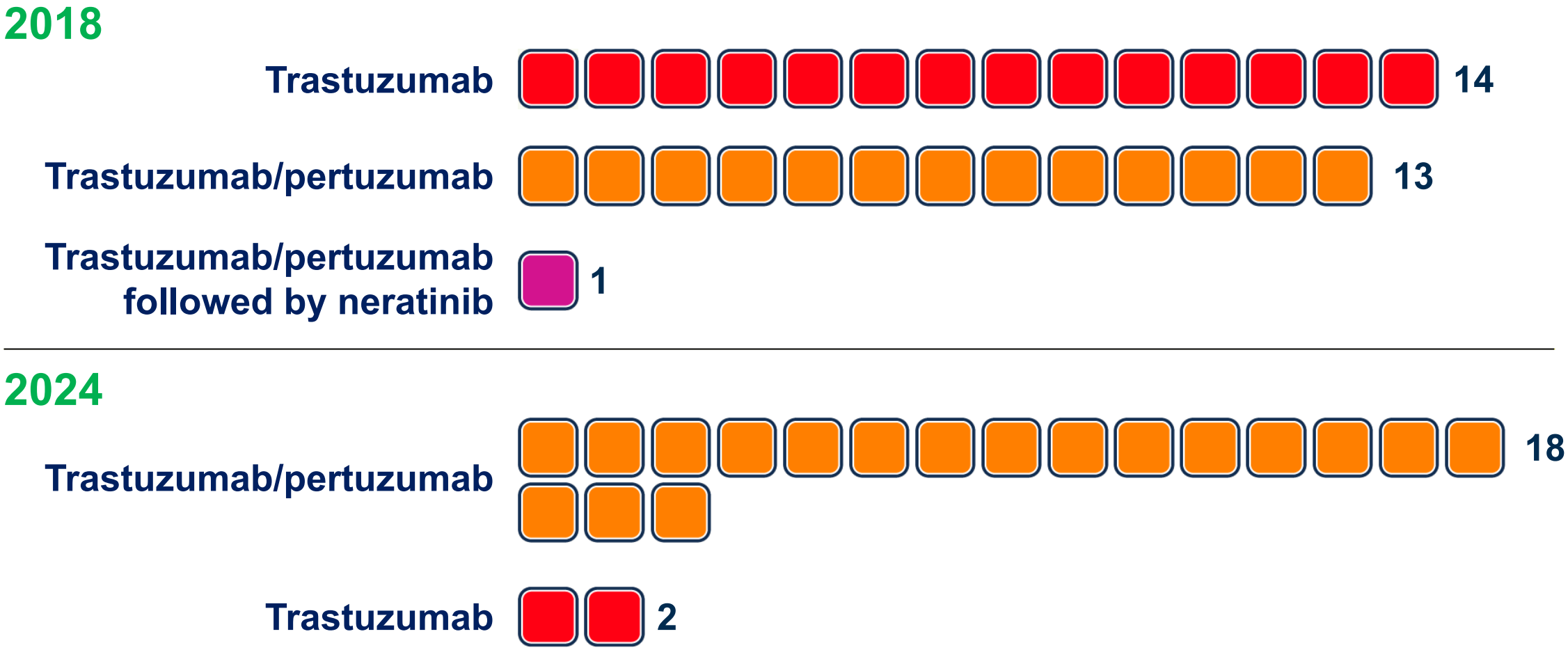
2018 and 2024 Surveys of Clinical Investigator (CI) Use of Postoperative Systemic Therapy After Prior Neoadjuvant Treatment of HER2-Positive Breast Cancer (HER2+ BC)

Abstract: P3-11-20

Thursday, December 12, 2024
12:00 PM – 2:00 PM

What adjuvant anti-HER2 treatment would you most likely recommend in the following scenario?

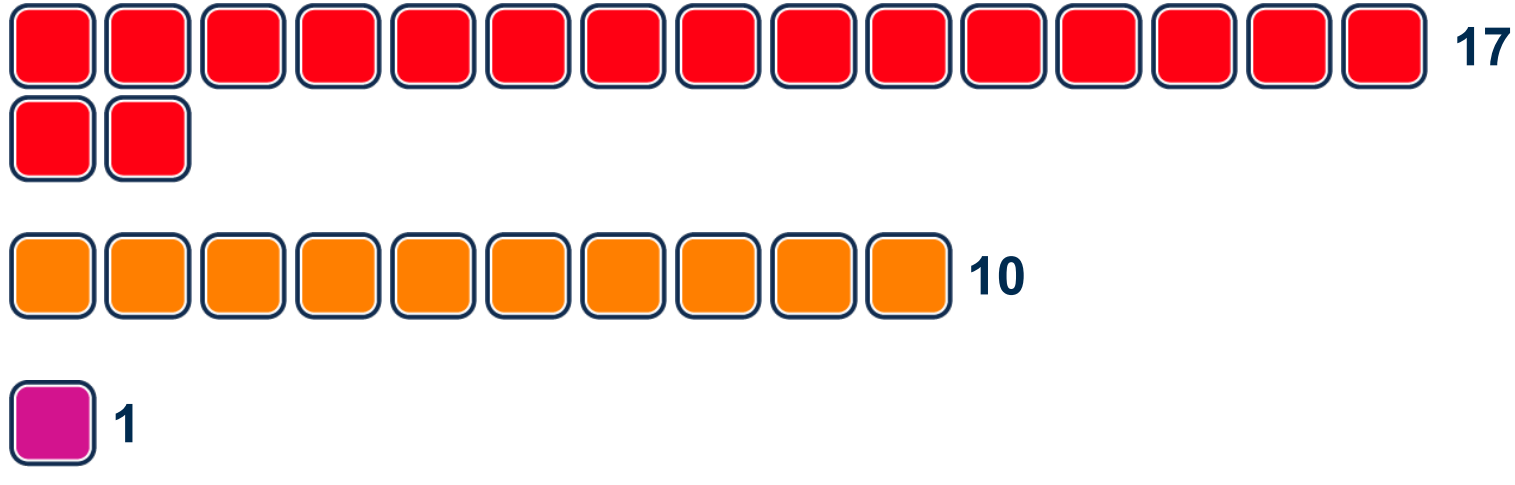
HER2-positive, ER-negative
Neoadjuvant docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP)
Pathologic complete response (pCR) at surgery



What adjuvant anti-HER2 treatment would you most likely recommend in the following scenario?

HER2-positive, ER-positive
Neoadjuvant TCHP
pCR at surgery

2018

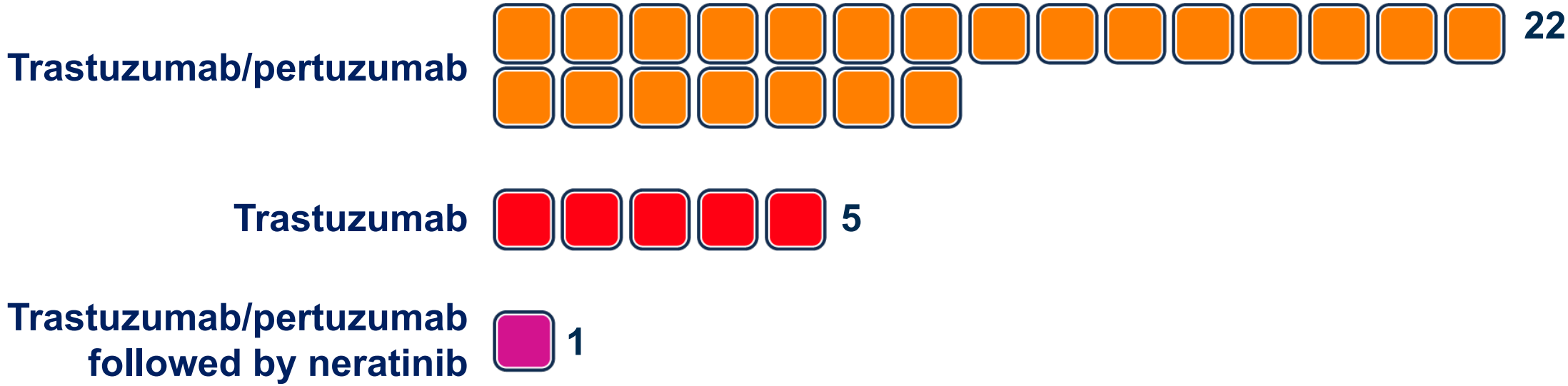


2024

What adjuvant anti-HER2 treatment would you most likely recommend in the following scenario?

HER2-positive, ER-negative
Neoadjuvant TCHP
Minimal residual disease at surgery

2018

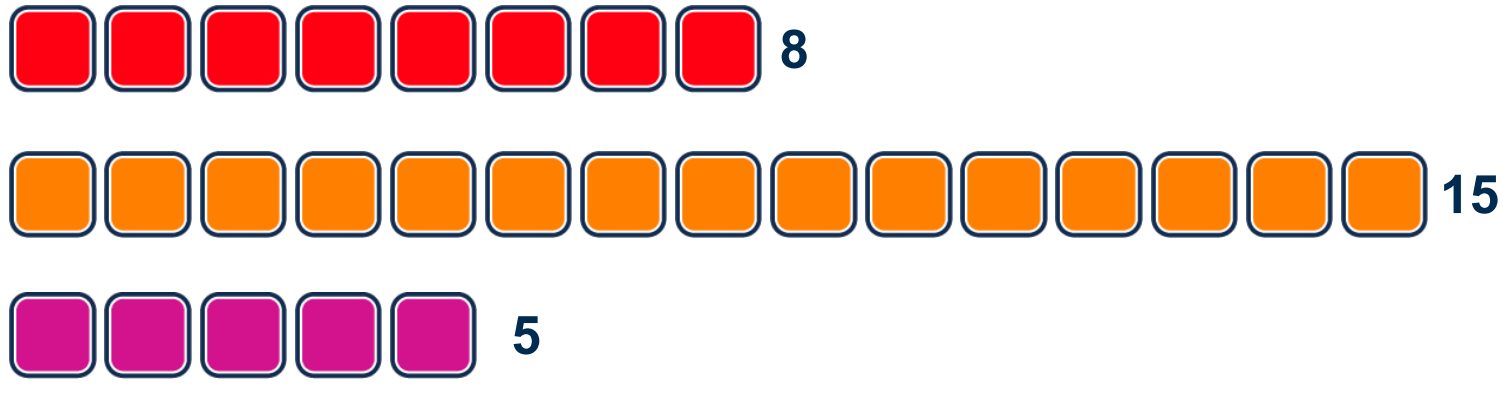


2024

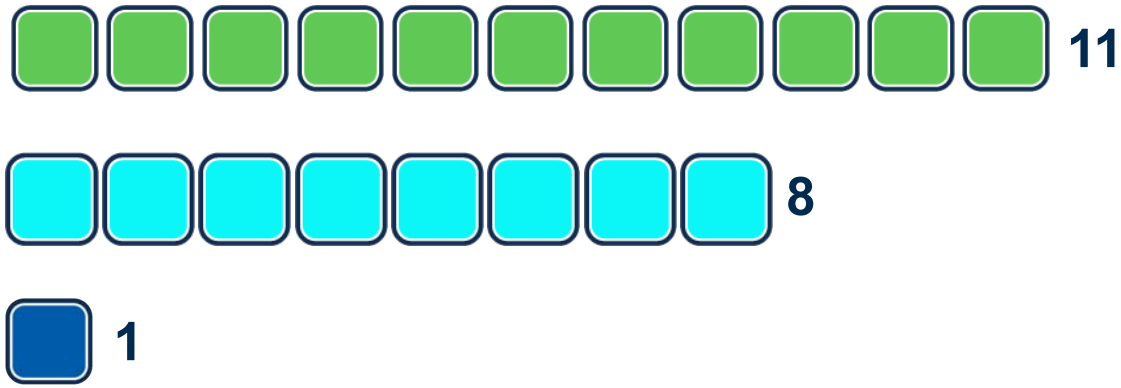
What adjuvant anti-HER2 treatment would you most likely recommend in the following scenario?

HER2-positive, ER-positive
Neoadjuvant TCHP
Minimal residual disease at surgery

2018



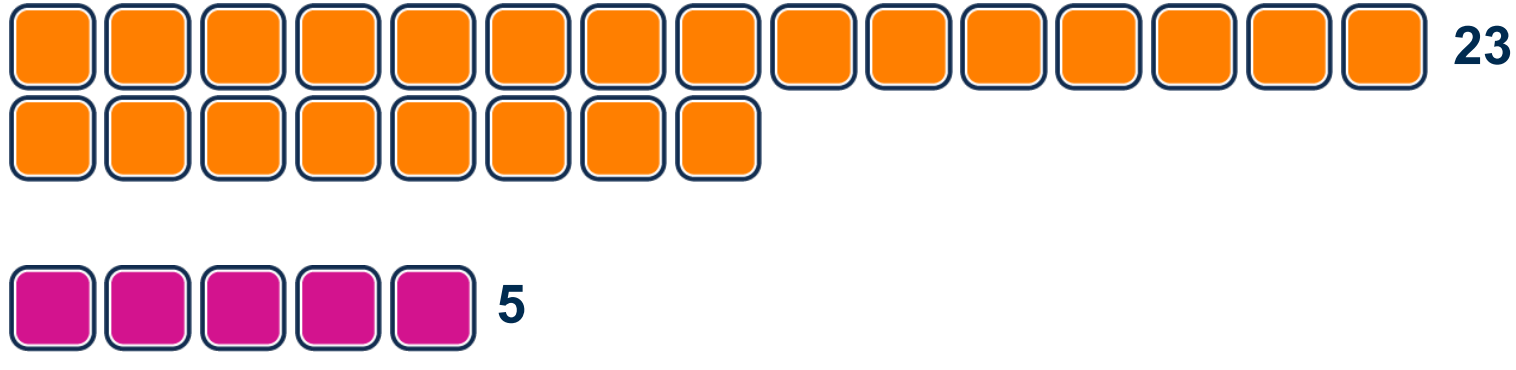
2024



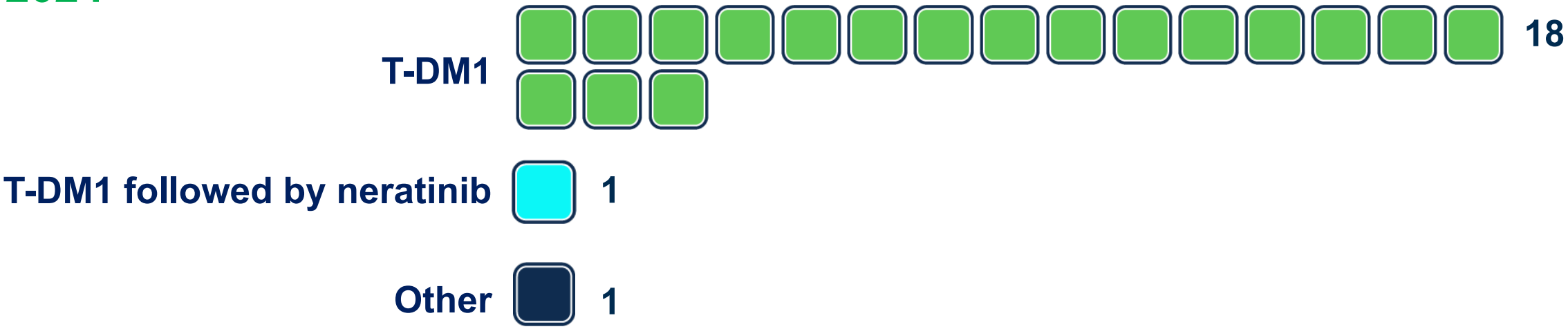
What adjuvant anti-HER2 treatment would you most likely recommend in the following scenario?

HER2-positive, ER-negative
Neoadjuvant TCHP
Macroscopic residual disease at surgery

2018



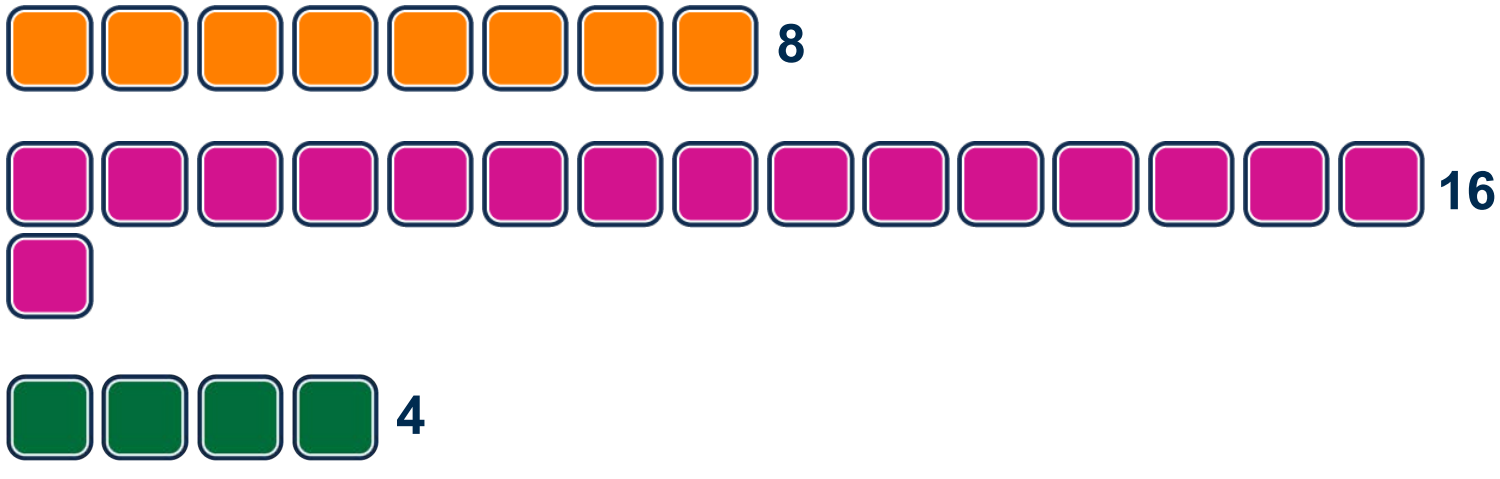
2024



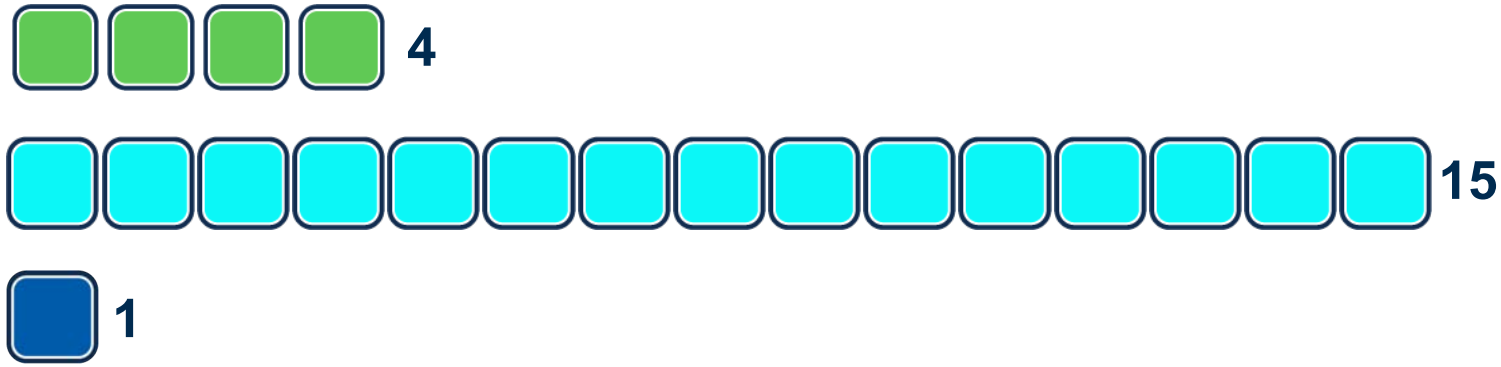
What adjuvant anti-HER2 treatment would you most likely recommend in the following scenario?

HER2-positive, ER-positive
Neoadjuvant TCHP
Macroscopic residual disease at surgery

2018



2024



Module 1: HER2-Positive, Triple-Negative and Localized Breast Cancer

HER2-Positive Breast Cancer — Dr O'Shaughnessy

Triple-Negative Breast Cancer (TNBC) — Dr Bardia

Personalizing Adjuvant Therapy for Patients with HR-Positive Breast Cancer — Dr Borges

Current Role of CDK4/6 Inhibitors in the Localized Setting — Dr Burstein

Triple-Negative Breast Cancer (TNBC)

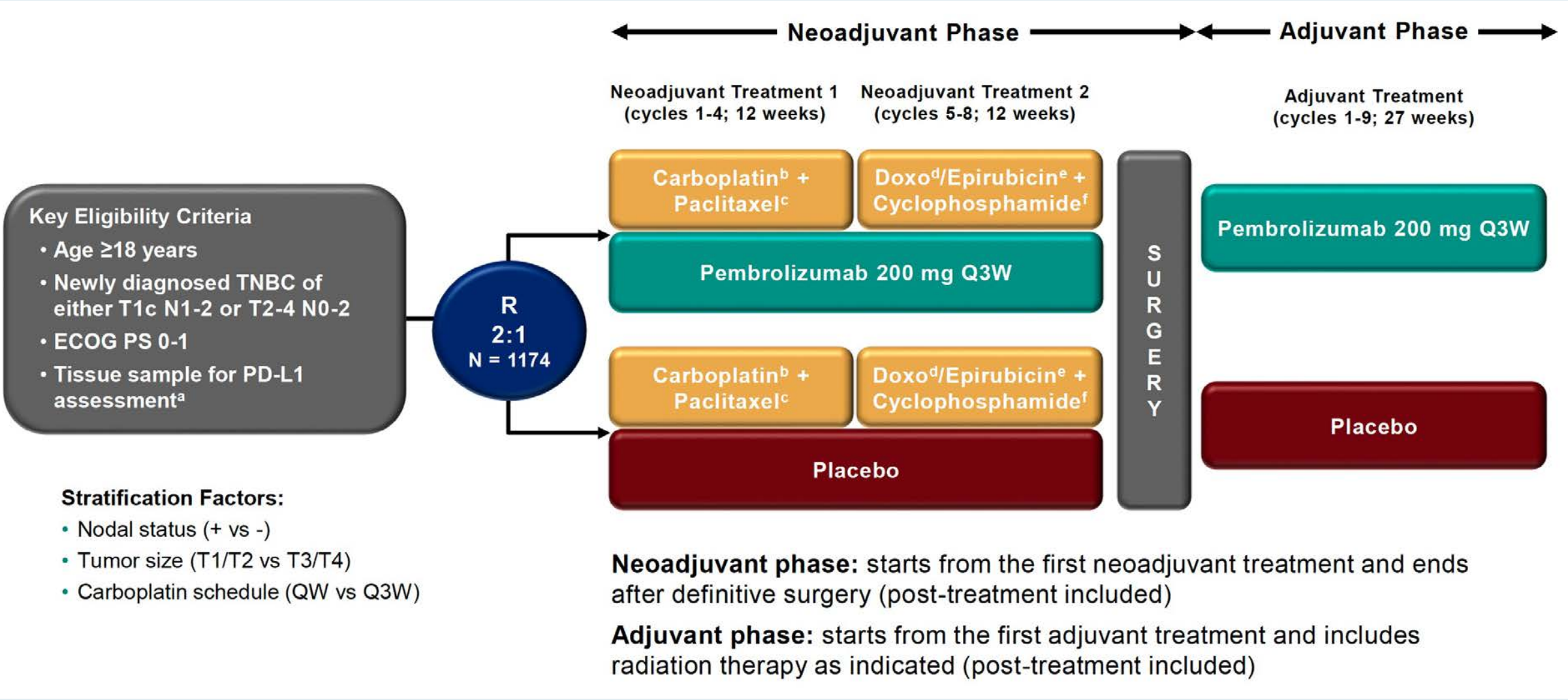
Aditya Bardia, MD, MPH
UCLA Health Jonsson Comprehensive Cancer Center
Los Angeles, California

Disclosures

Consulting Agreements and Contracted Research	Alyssum Therapeutics, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Menarini Group, Merck, Novartis, Pfizer Inc, Sanofi

RTP
RESEARCH
TO PRACTICE

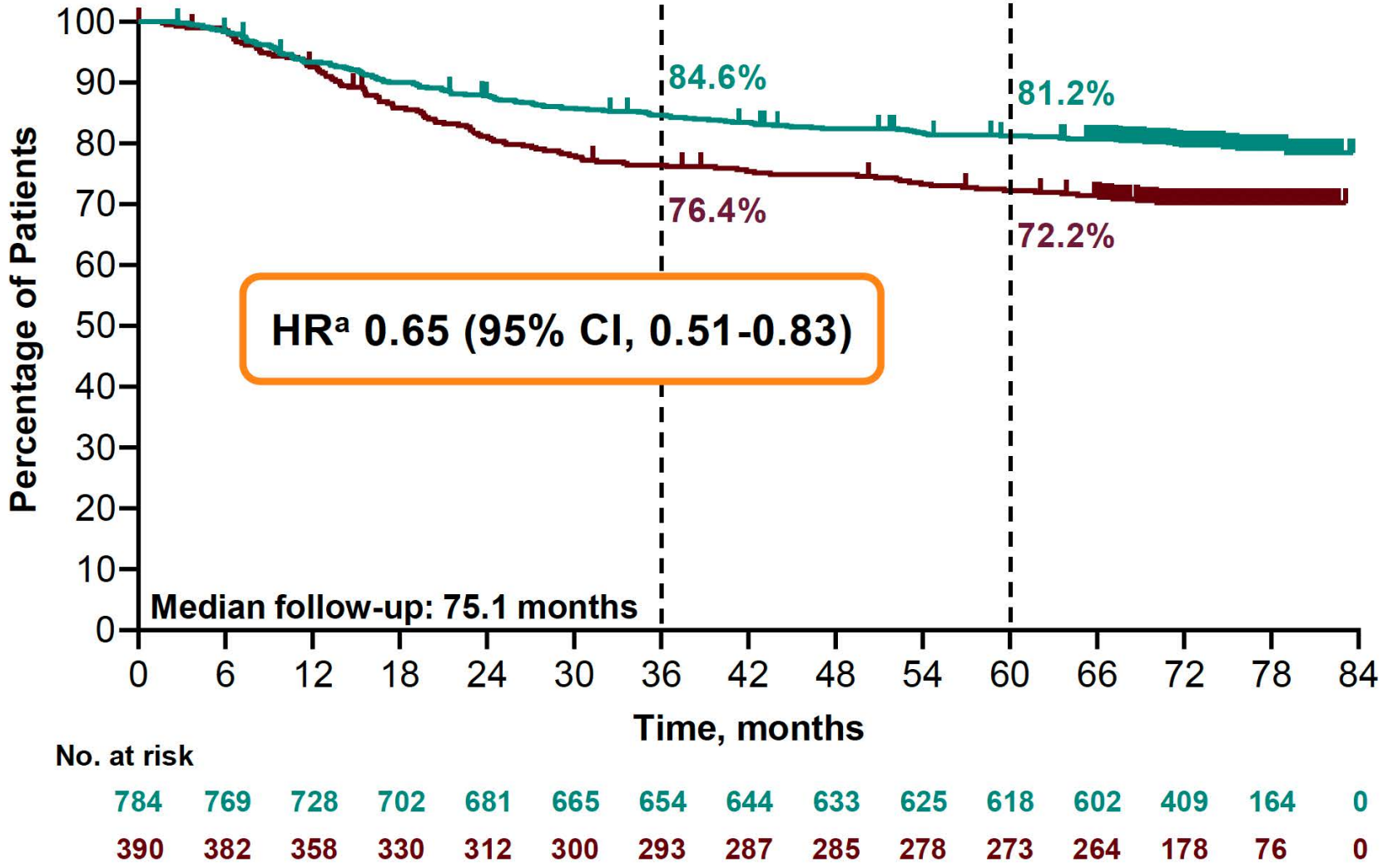
KEYNOTE-522 Trial: Perioperative Pembrolizumab with Chemotherapy



Schmid P et al. ESMO 2024;Abstract LBA4.

RTP RESEARCH TO PRACTICE

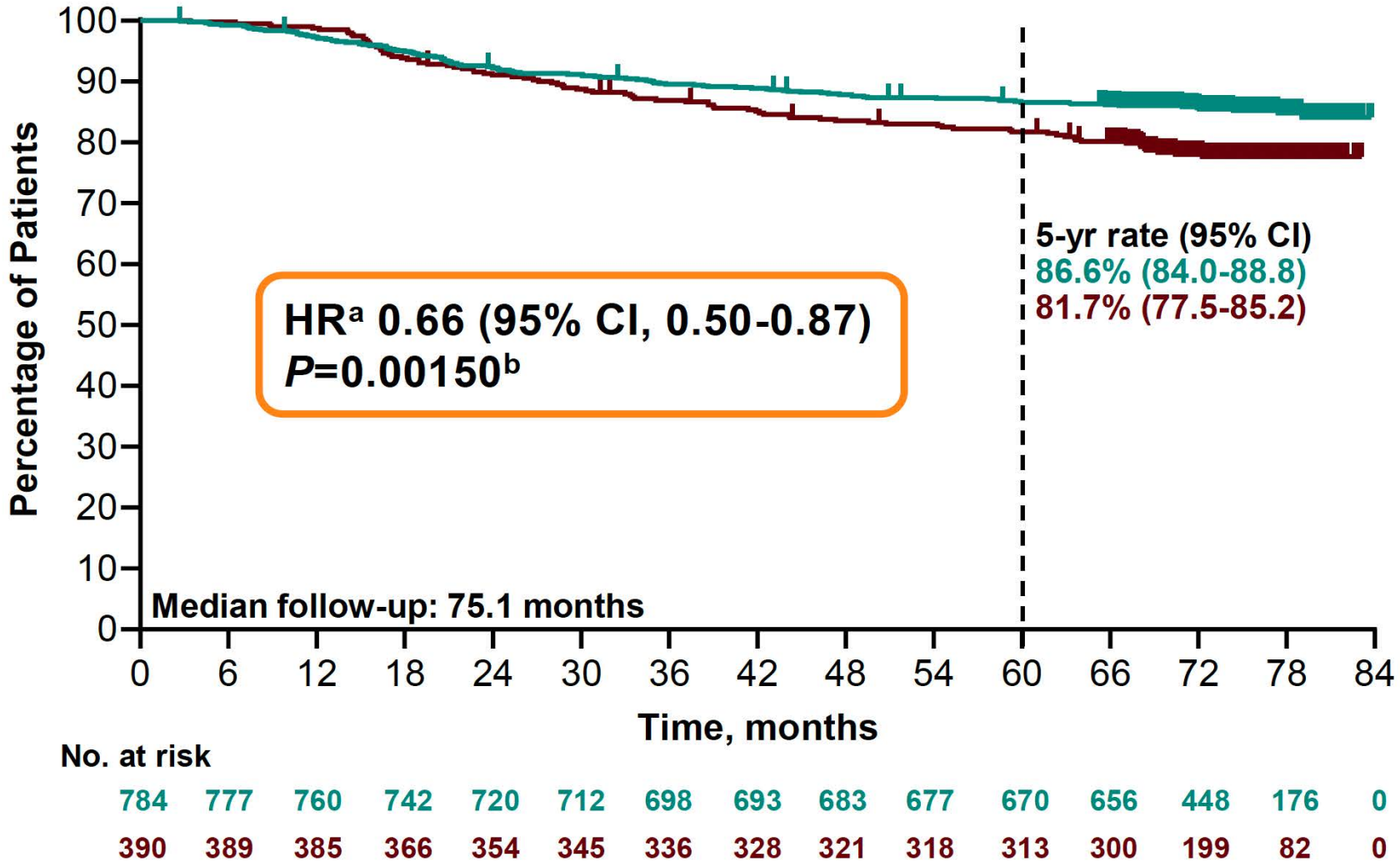
KEYNOTE-522: Perioperative Pembrolizumab/Chemotherapy – Event-Free Survival



	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

Schmid P et al. ESMO 2024;Abstract LBA4.

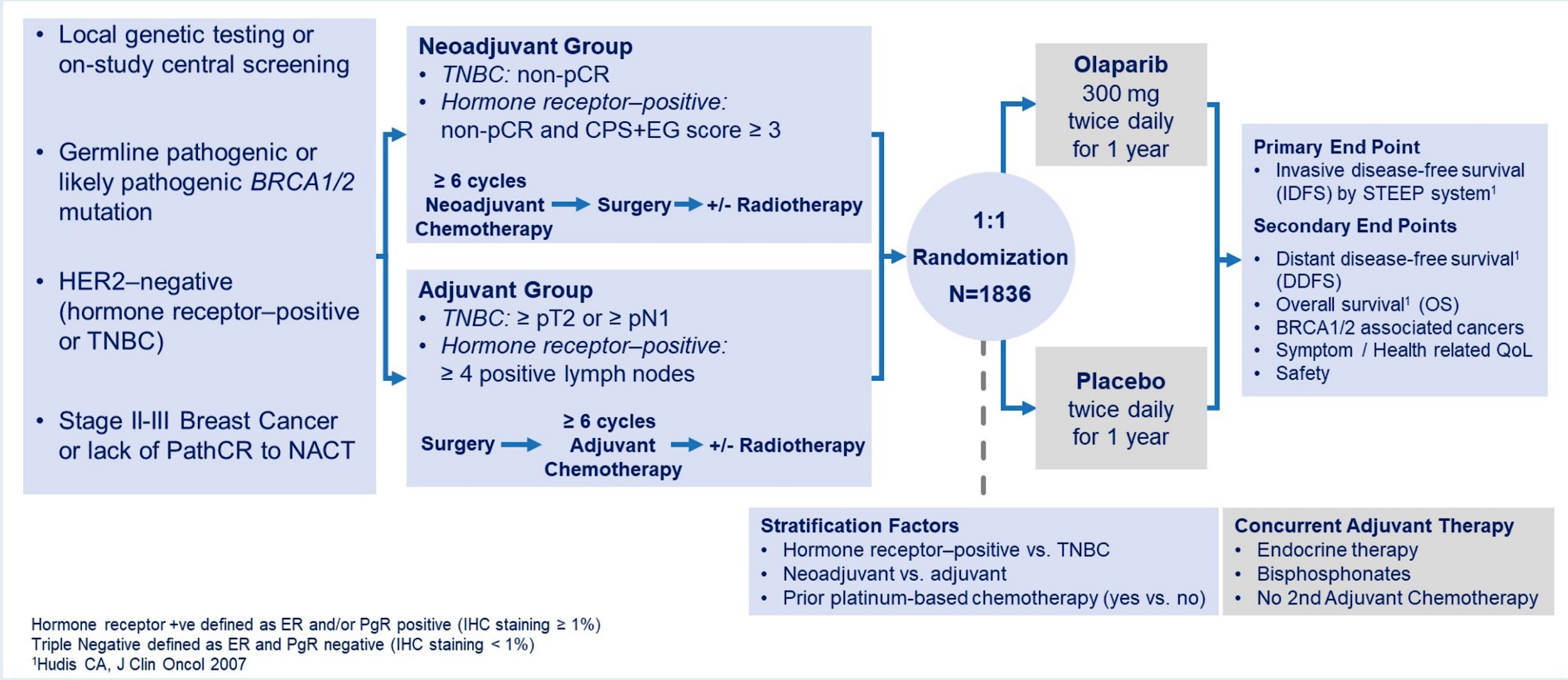
KEYNOTE-522: Perioperative Pembrolizumab/Chemotherapy – Overall Survival



	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

Schmid P et al. ESMO 2024;Abstract LBA4.

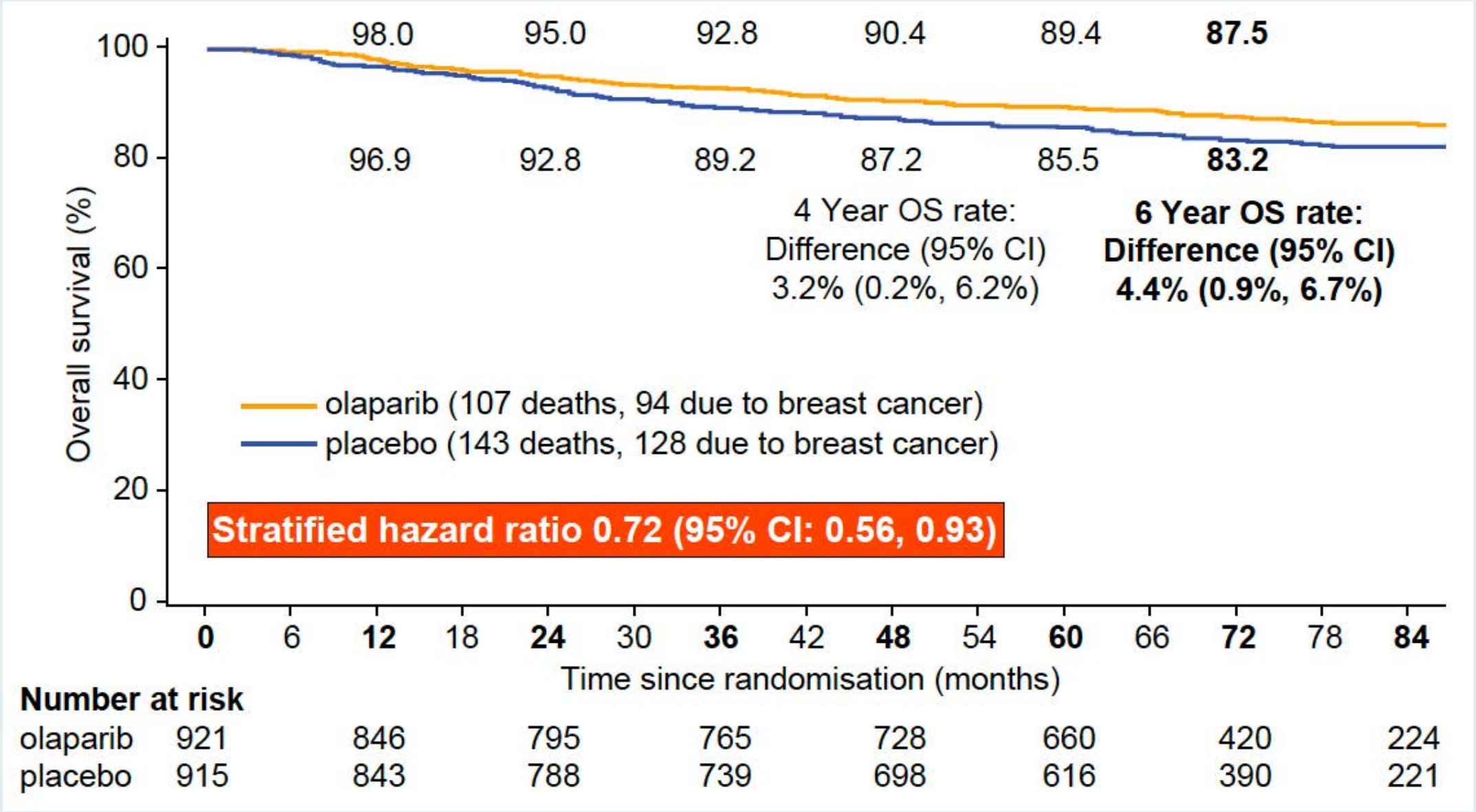
OlympiA Phase III Trial of Adjuvant Olaparib



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

Tutt A et al. ASCO 2021;Abstract LBA1.

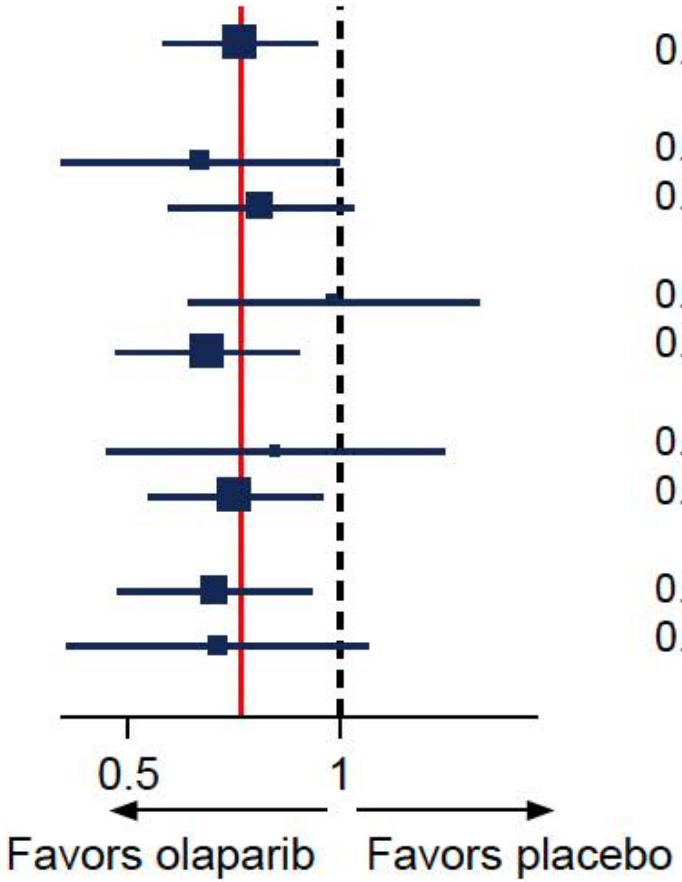
OlympiA Phase III Trial of Adjuvant Olaparib – OS



Garber J et al. San Antonio Breast Cancer Symposium 2024;Abstract GS1-09.

Adjuvant Olaparib – Subgroup Analyses of OS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	P value for heterogeneity
	Number of patients with a death/total number			
All patients	107/921	143/915	0.725 (0.563 – 0.930)	NA
Prior Chemo				
Adjuvant	31/461	48/455	0.638 (0.402 – 0.997)	0.49
Neoadjuvant	76/460	95/460	0.774 (0.571 – 1.045)	
Prior Platinum				
Yes	35/247	34/238	0.979 (0.610 – 1.574)	0.15
No	72/674	109/677	0.653 (0.483 – 0.876)	
HR status				
HR+/HER2–	24/168	28/157	0.814 (0.469 – 1.404)	0.67
TNBC	83/751	115/758	0.713 (0.536 – 0.944)	
BRCA				
BRCA1	64/579	94/588	0.667 (0.484 – 0.914)	1.00
BRCA2	28/235	38/216	0.676 (0.412 – 1.098)	
BRCA1/2 both	0/2	0/3	NC	



Garber J et al. San Antonio Breast Cancer Symposium 2024;Abstract GS1-09.

Adjuvant Olaparib – Long-Term Safety

	Olaparib (N = 911)		Placebo (N = 904)	
	Current	Previous*	Current	Previous*
Adverse event leading to death[1]	**5 (<1%)**	*[2 (<1%)]*	**10 (1.1 %)**	*[4 (<1%)]*
Adverse event of special interest at any time	**57 (6.3%)**	*[31 (3.4%)]*	**84 (9.3%)**	*[51 (5.6%)]*
On treatment AESIs[2]	**14 (1.5%)**	*[14 (1.5%)]*	**28 (3.1%)**	*[27 (3.0%)]*
AESI > 30 days after last dose	**44 (4.8%)**	*[18 (2.0%)]*	**57 (6.3%)**	*[24 (2.7%)]*
MDS/AML	**4 (0.4%)**	*[2 (0.2%)]*	**6 (0.7%)**	*[3 (0.3%)]*
Pneumonitis	**9 (1.0%)**	*[9 (1.0%)]*	**13 (1.4%)**	*[12 (1.3%)]*
New primary malignancy	**45 (4.9%)**	*[21 (2.3%)]*	**68 (7.5%)**	*[36 (4.0%)]*

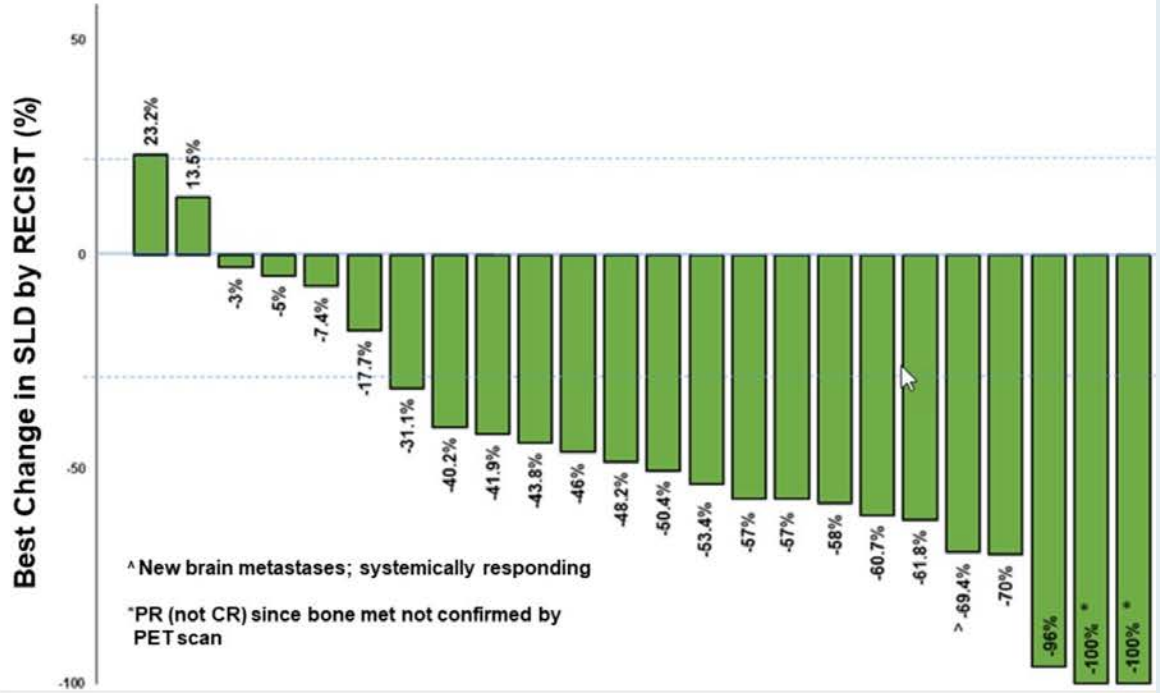
*Previous data from OS IA2. *AML acute myeloid leukemia; MDS myelodysplastic syndrome*

Garber J et al. San Antonio Breast Cancer Symposium 2024;Abstract GS1-09.

Phase II Study of Olaparib in mBC with gPALB2 Mutations

gPALB2 N=24	
Best Response	**Responses (rate, %)**
Complete Response (CR)	1 (4%)
Partial Response (PR)	17 (71%)
Stable Disease (SD)	5 (21%)
Progressive Disease (PD)	1 (4%)
ORR = 75% (18/24, 80%-CI: 60%-86%)	
CBR (18 wks) = 83% (20/24, 90%-CI: 66%-94%)	

Datacut May 3, 2024



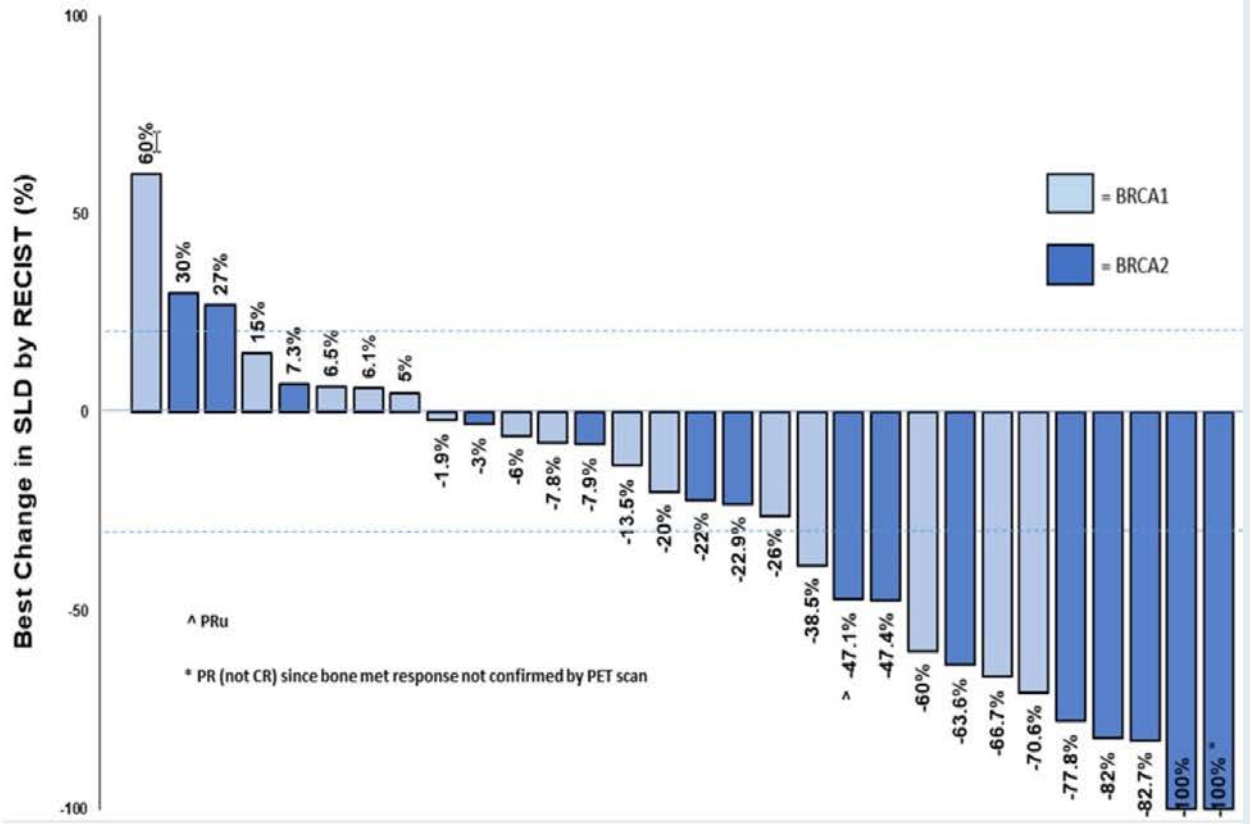
Tumor subtype	Responses
TNBC	2/2
ER+/HER2-neg	13/19
HER2+	3/3

Tung NM et al. ASCO 2024;Abstract 1021.

Phase II Study of Olaparib in mBC with sBRCA1/2 Mutations

sBRCA1/2 N=30	
Best Response	**Responses, (rate, %)**
Complete Response (CR)	1 (3%)
Partial Response (PR)^	10 (33%)
Stable Disease (SD)	13 (43%)
Progressive Disease (PD)	6 (20%)
ORR = 37% (11/30, 80%-CI: 25%-50%)	
CBR (18 wks) = 53% (16/30, 90%-CI: 37%-69%)	

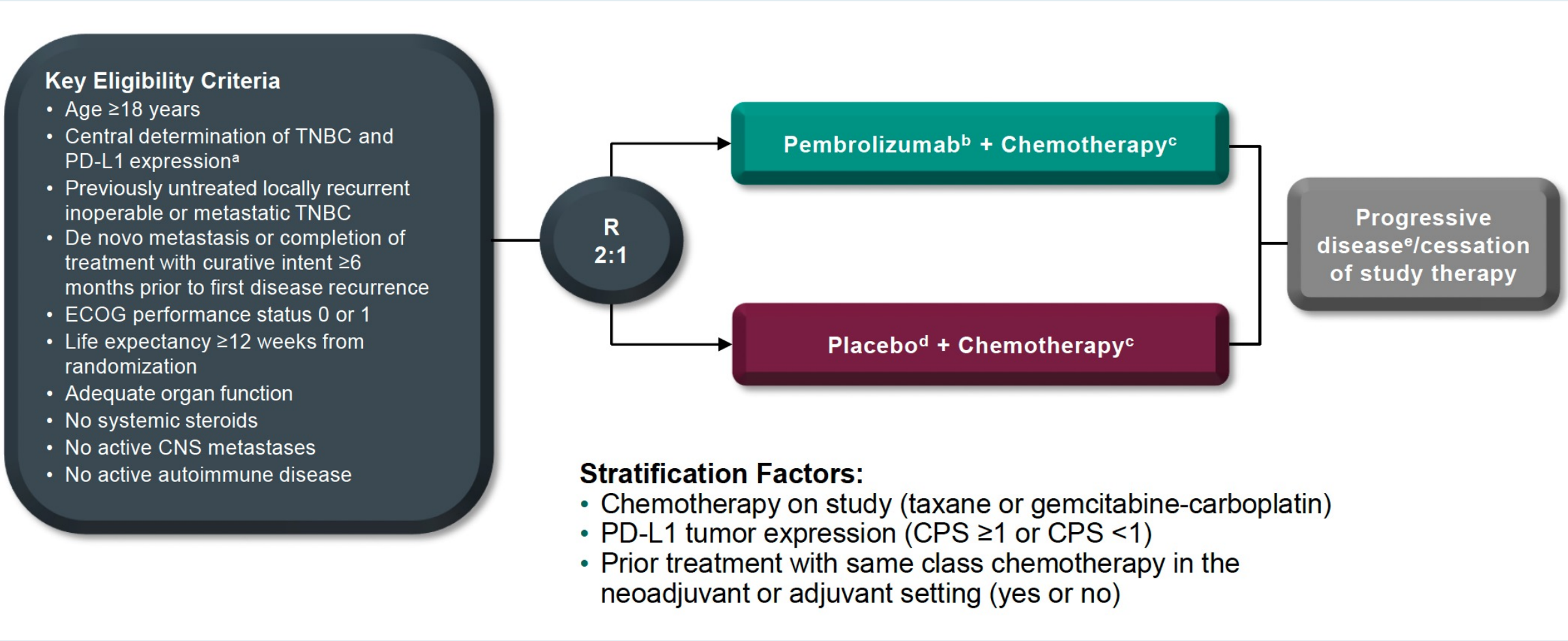
^ 1 unconfirmed PR did not count for ORR or CBR



Datacut May 3,, 2024

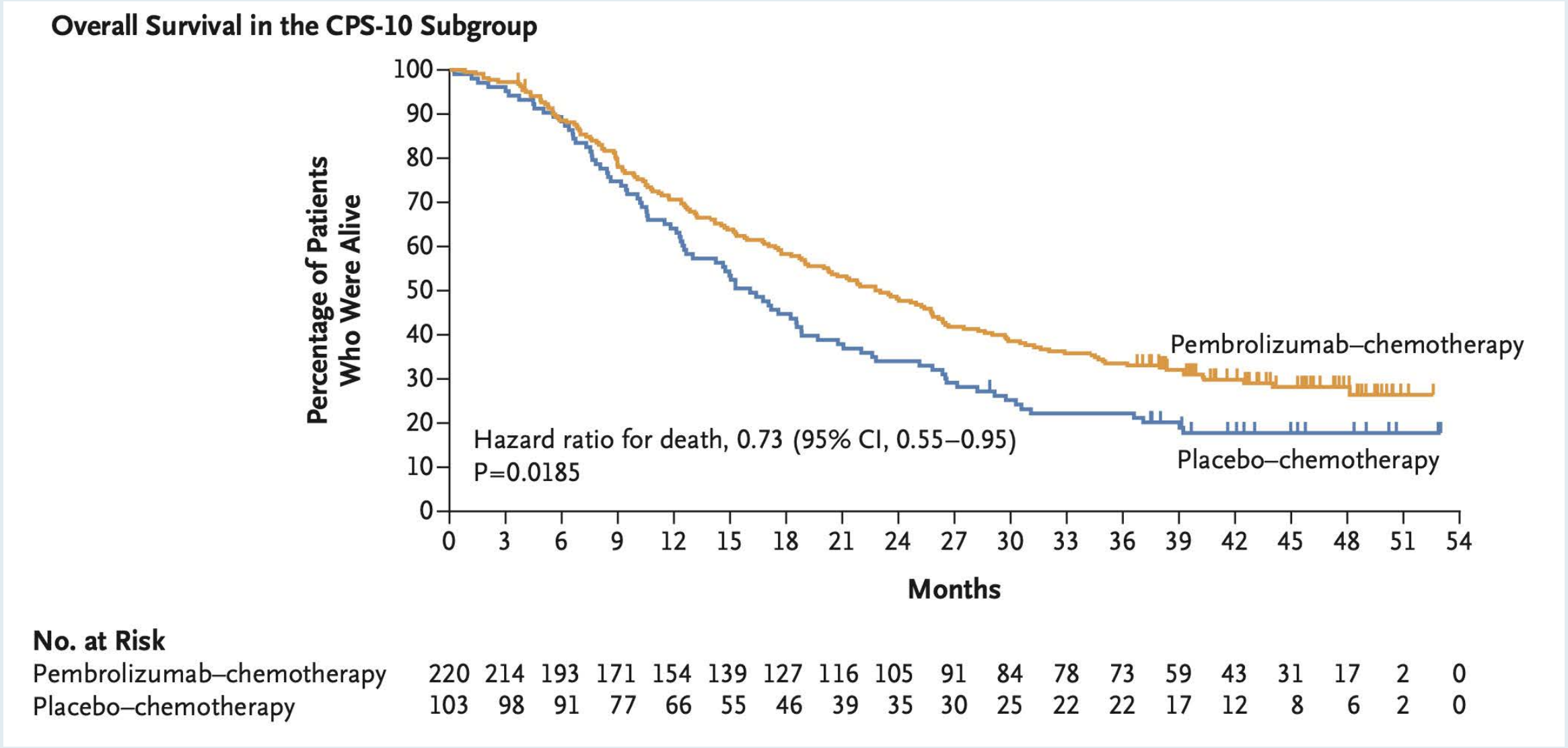
Tung NM et al. ASCO 2024;Abstract 1021.

KEYNOTE-355 Trial: Pembrolizumab with Chemotherapy



Rugo H et al. ESMO 2021;Abstract LBA16.

KEYNOTE-355: Pembrolizumab/Chemotherapy – OS

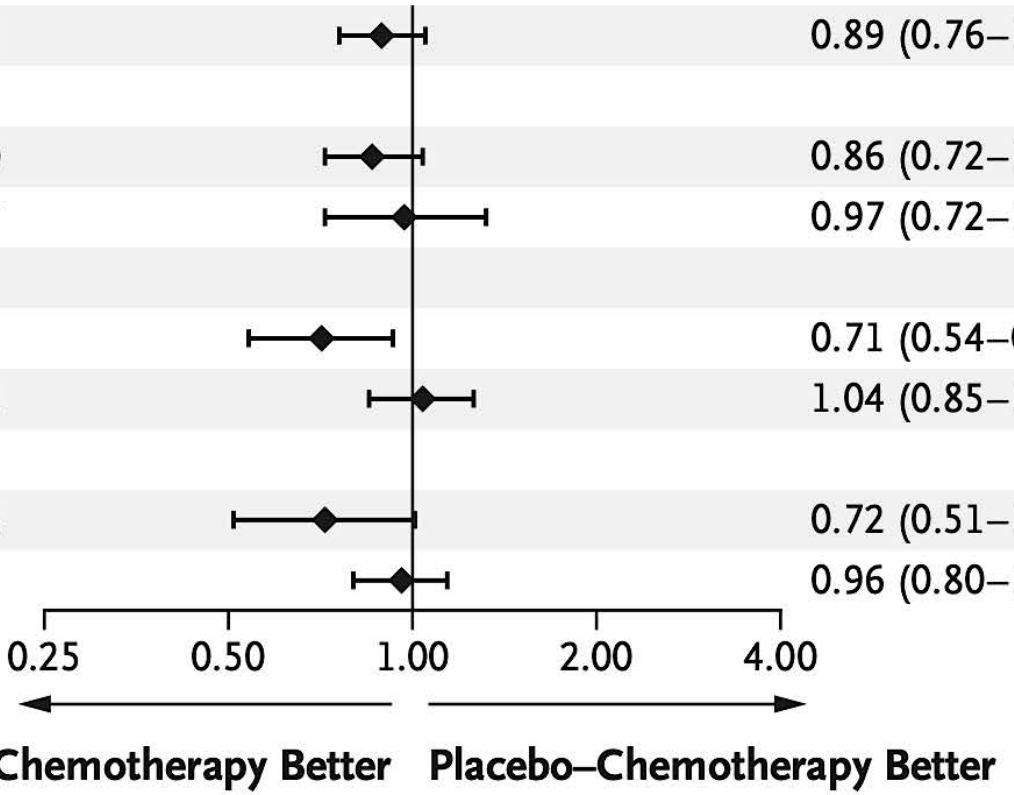


CPS = PD-L1 combined positive score

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

KEYNOTE-355: Pembrolizumab/Chemotherapy – Subgroups

Subgroup	No. of Patients	Median Overall Survival		Hazard Ratio for Death (95% CI)
		Pembrolizumab–chemotherapy	Placebo–chemotherapy	
		mo		
Overall	847	17.2	15.5	0.89 (0.76–1.05)
PD-L1 CPS cutoff of 1				
CPS ≥1	636	17.6	16.0	0.86 (0.72–1.04)
CPS <1	211	16.2	14.7	0.97 (0.72–1.32)
PD-L1 CPS cutoff of 10				
CPS ≥10	323	23.0	16.1	0.71 (0.54–0.93)
CPS <10	524	14.7	15.2	1.04 (0.85–1.26)
PD-L1 CPS cutoff of 20				
CPS ≥20	204	24.0	15.6	0.72 (0.51–1.01)
CPS <20	643	15.9	15.5	0.96 (0.80–1.14)



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

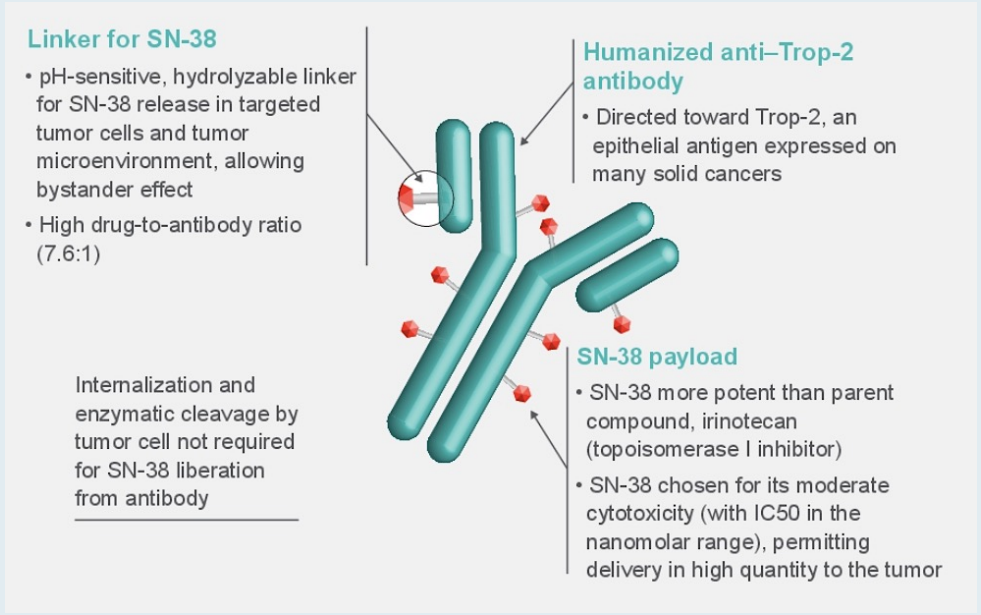
KEYNOTE-355: Pembrolizumab/Chemotherapy – Safety

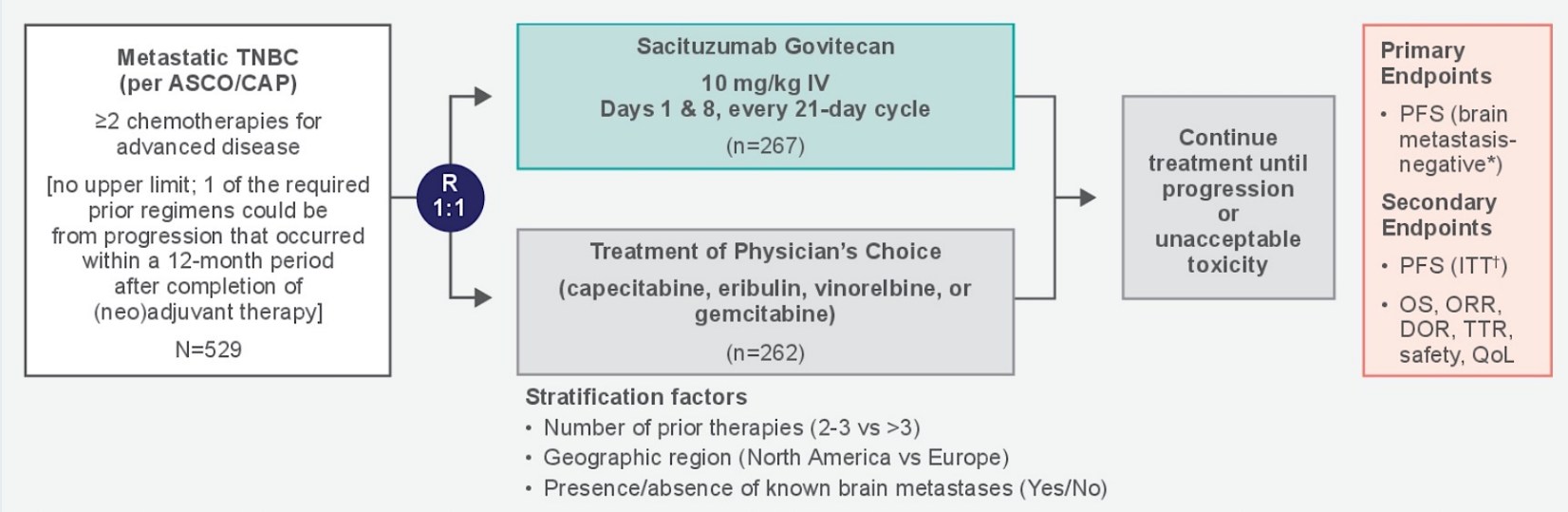
Table 1. Adverse Events.*

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

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

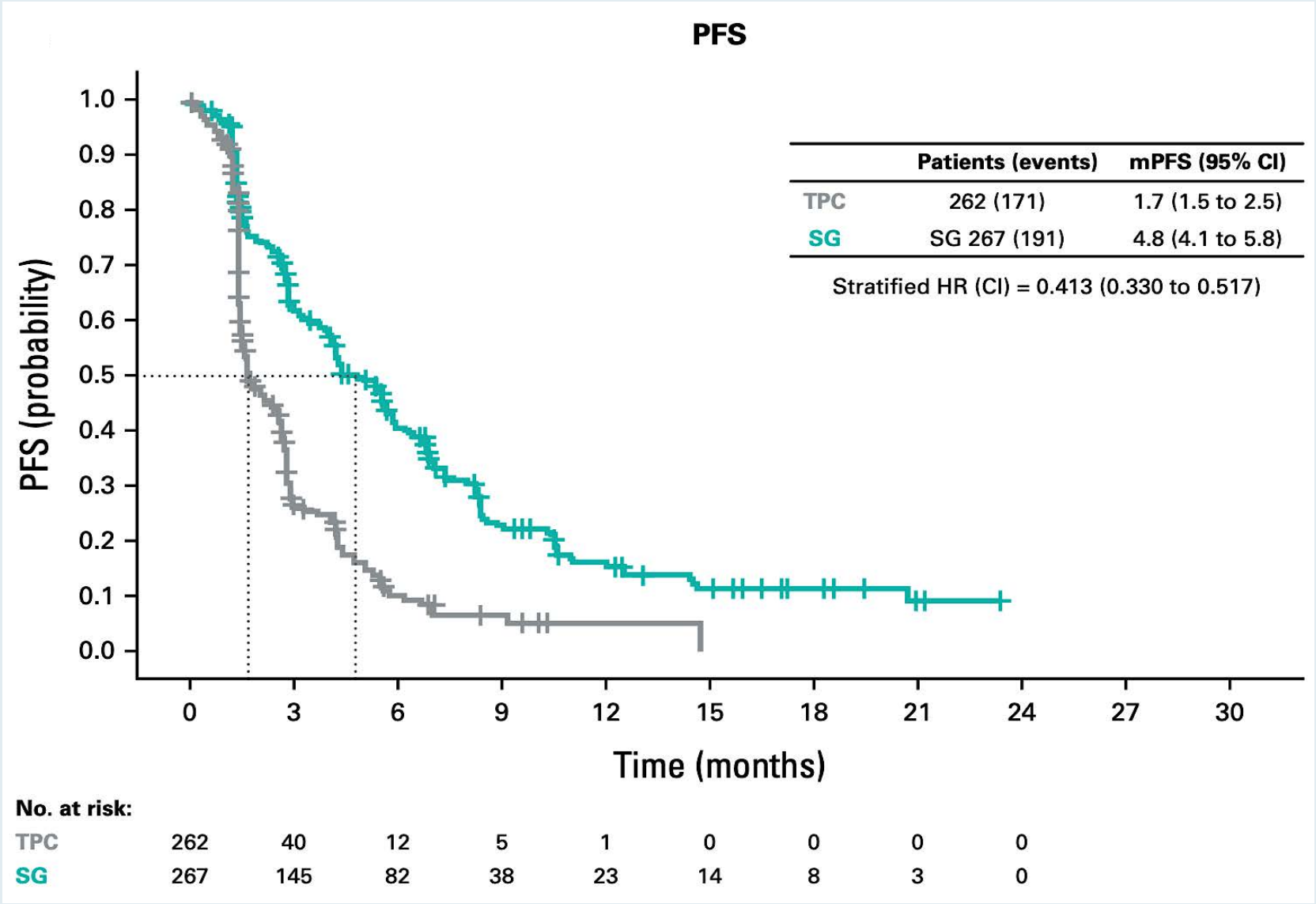
Phase III ASCENT Trial: Sacituzumab Govitecan





Bardia A et al. ASCO 2022;Abstract 1071.

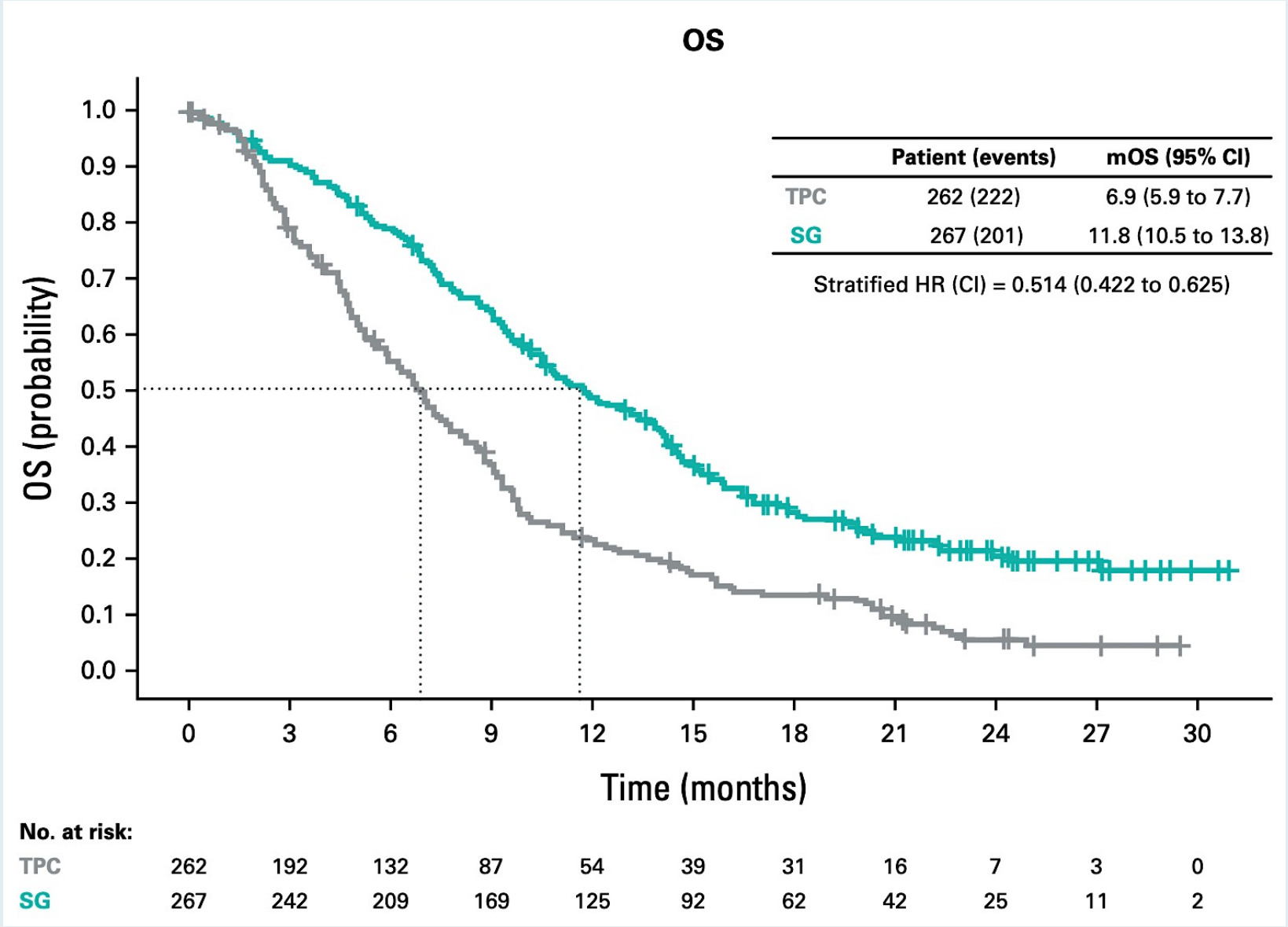
Phase III ASCENT: Sacituzumab Govitecan (SG) – Progression-Free Survival (PFS)



TPC = treatment of physician's choice

Bardia A et al. *J Clin Oncol* 2024;42(15):1738-44.

Phase III ASCENT: Sacituzumab Govitecan – Overall Survival (OS)



mOS = median OS

Bardia A et al. *J Clin Oncol* 2024;42(15):1738-44.

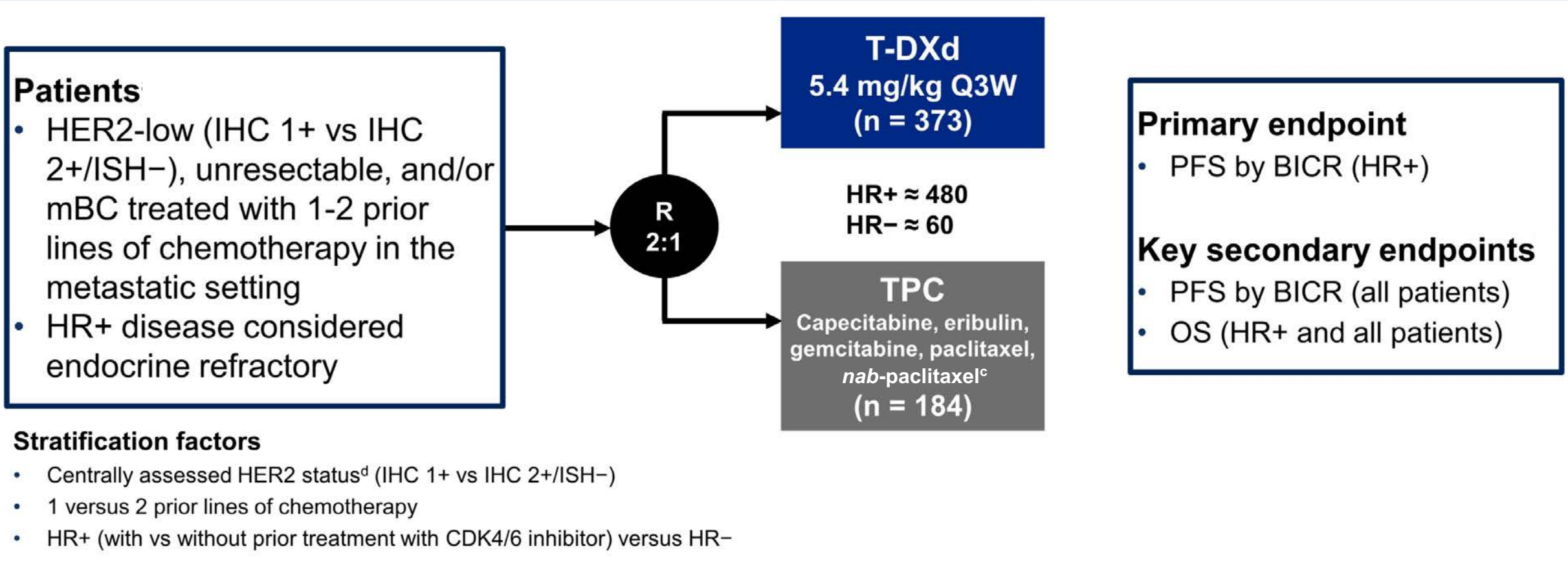
Phase III ASCENT: Sacituzumab Govitecan – Safety

TRAE*		SG (n=258)			TPC (n=224)		
		All grade (%)	Grade 3 (%)	Grade 4 (%)	All grade (%)	Grade 3 (%)	Grade 4 (%)
Hematologic	Neutropenia†	163 (63)	88 (34)	45 (17)	96 (43)	45 (20)	29 (13)
	Anemia	89 (35)	20 (8)	0	53 (24)	11 (5)	0
	White blood cell count decreased	33 (13)	18 (7)	2 (1)	22 (10)	9 (4)	2 (1)
	Febrile neutropenia	15 (6)	12 (5)	3 (1)	5 (2)	4 (2)	1 (<1)
Gastrointestinal	Diarrhea	153 (59)	28 (11)	0	27 (12)	1 (<1)	0
	Nausea	147 (57)	6 (2)	1 (<1)	59 (26)	1 (<1)	0
	Vomiting	75 (29)	3 (1)	1 (<1)	23 (10)	1 (<1)	0
Other	Alopecia	119 (46)	0	0	35 (16)	0	0
	Fatigue	115 (45)	8 (3)	0	68 (30)	12 (5)	0

TRAE = treatment-related adverse event

Bardia A et al. ASCO 2022;Abstract 1071.

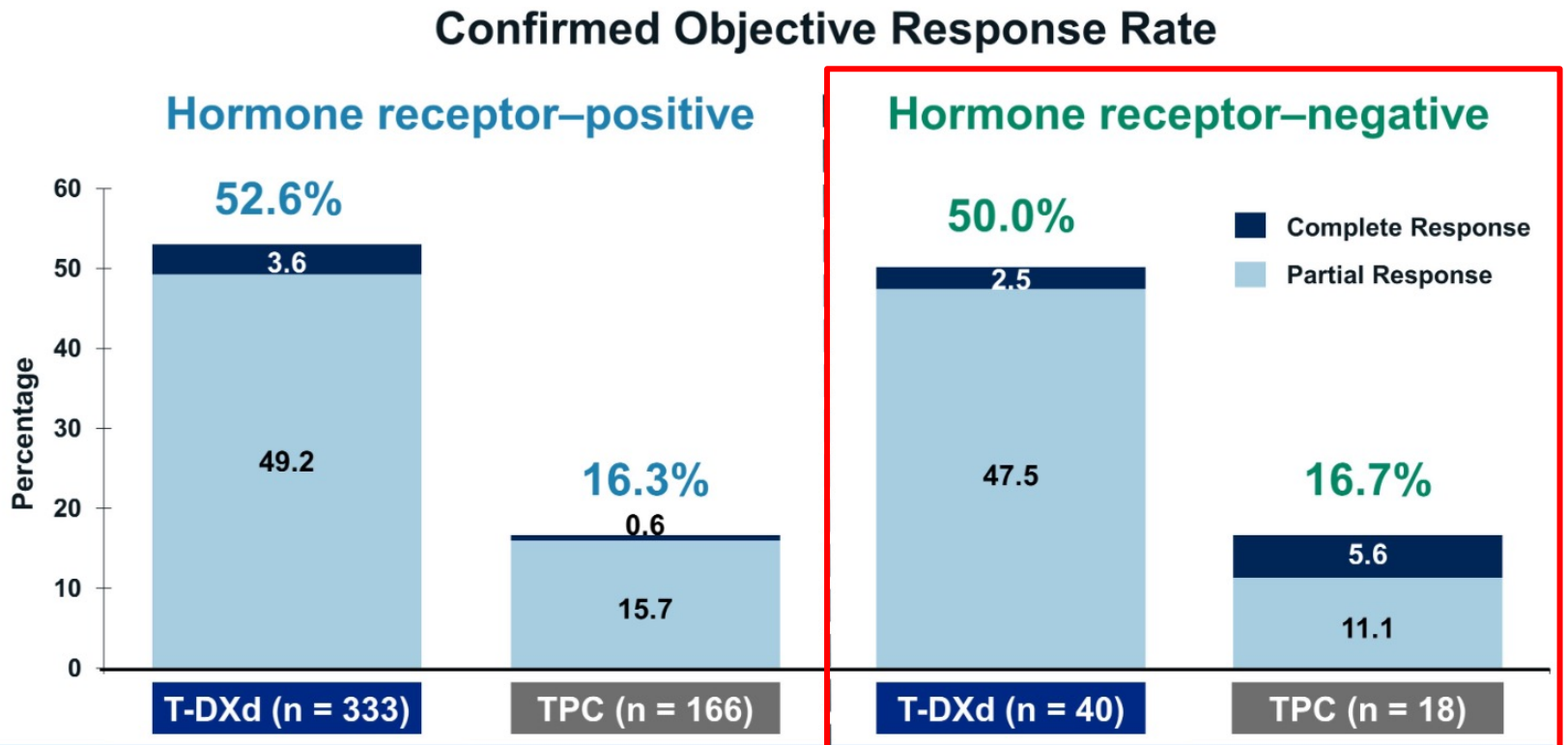
DESTINY-Breast04 Study Design



T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice; BICR = blinded independent central review

Modi S et al. ASCO 2022;Abstract LBA3.

DESTINY-Breast04: HR-Negative Cohort – Response

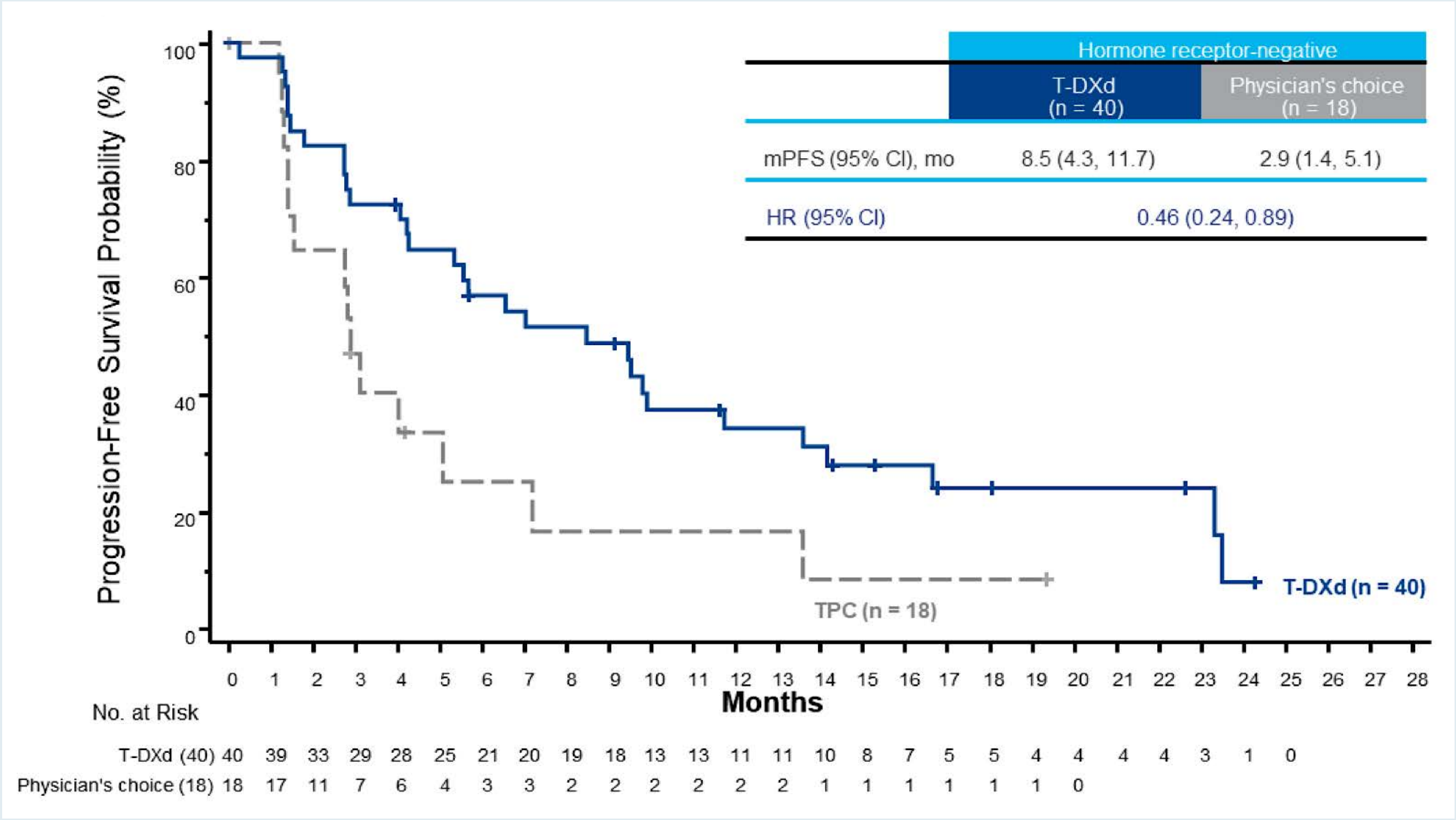


	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Modi S et al. ASCO 2022;Abstract LBA3.

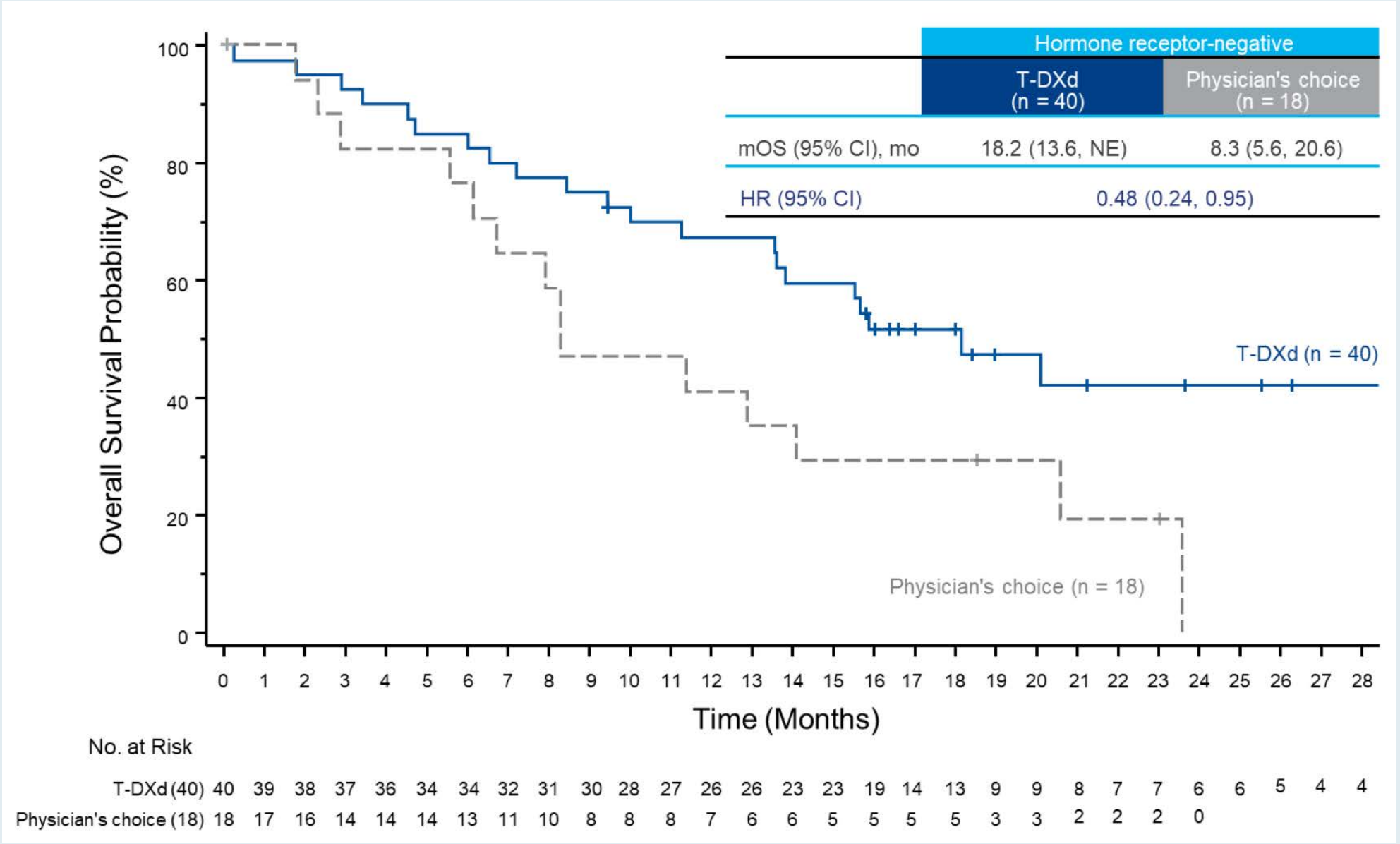
RTP RESEARCH TO PRACTICE

DESTINY-Breast04: HR-Negative Cohort – PFS



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

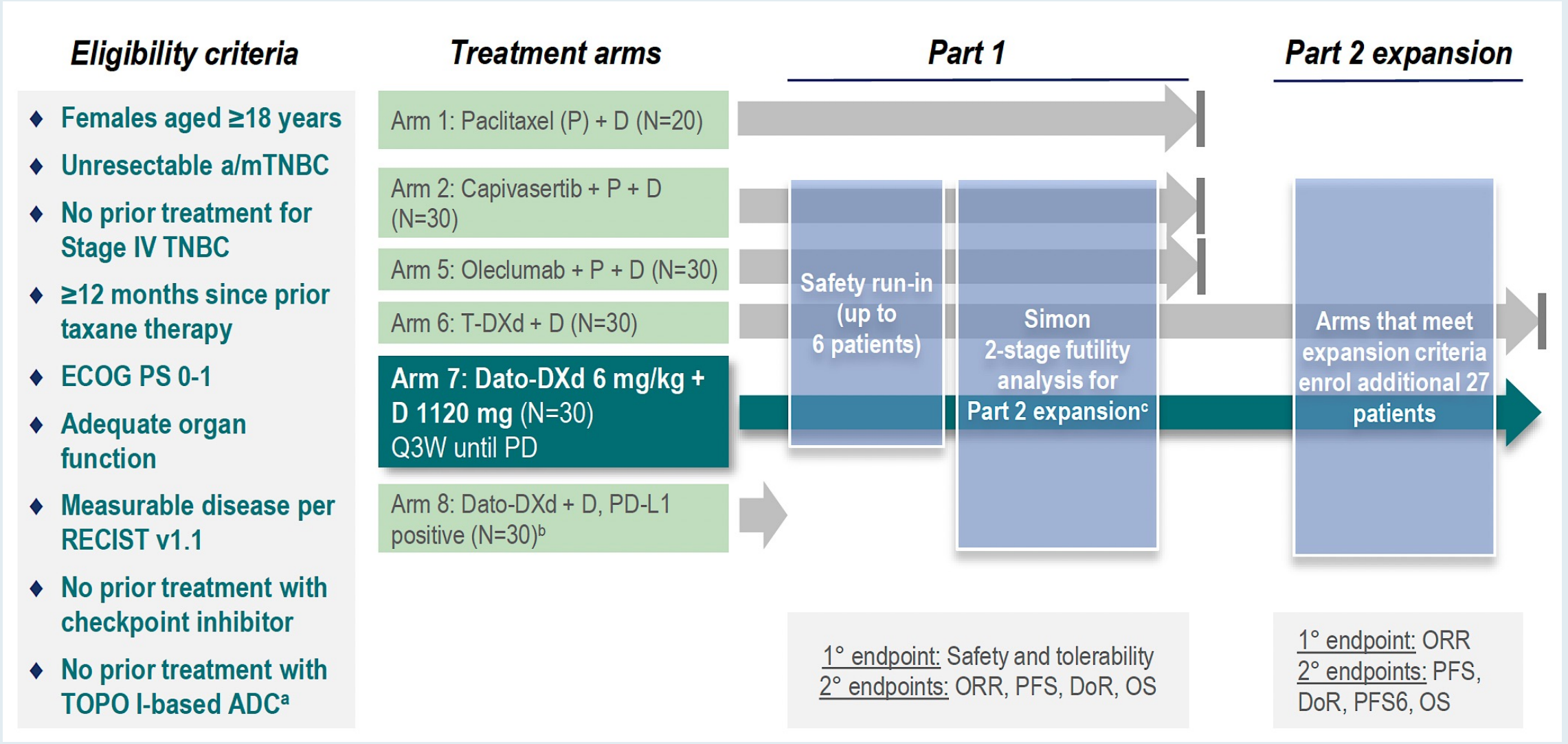
DESTINY-Breast04: HR-Negative Cohort – OS



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

RTP RESEARCH TO PRACTICE

BEGONIA: A Phase Ib/II Study of Datopotamab Deruxtecan (Dato-DXd) with Durvalumab (D) as First-Line Treatment for Metastatic TNBC



a/m = advanced or metastatic; ADC = antibody-drug conjugate; PD = disease progression

Schmid P et al. ESMO 2023;Abstract 379MO.

BEGONIA: First-Line Dato-DXd with Durvalumab – Response

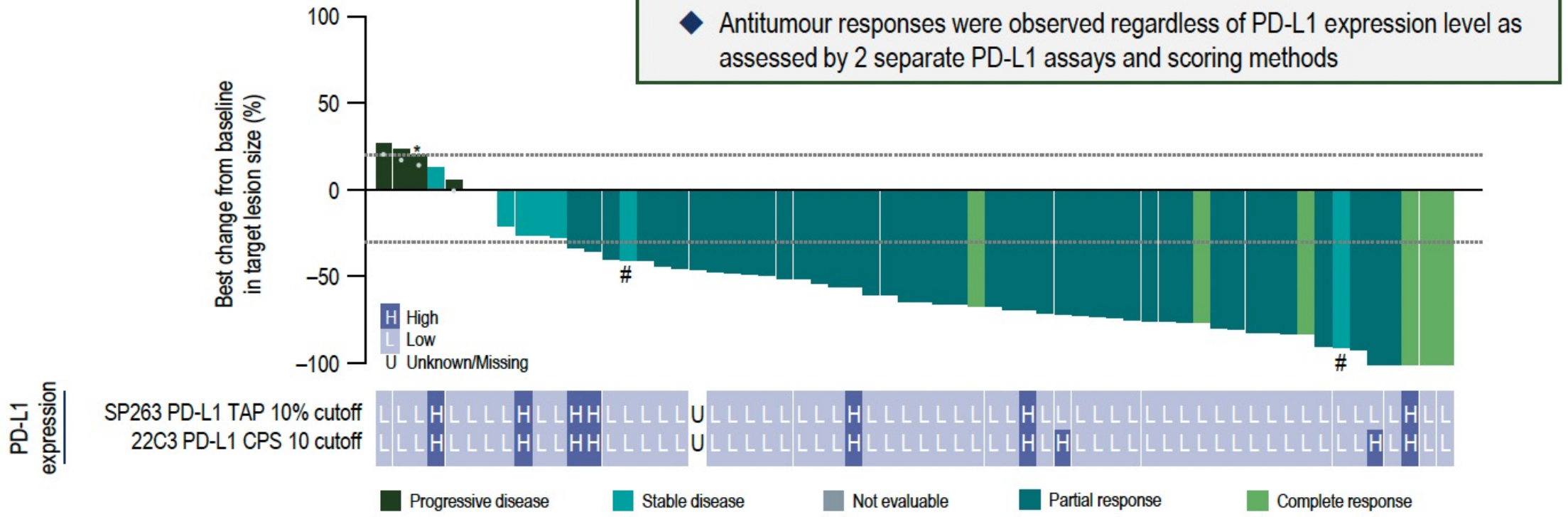
MADRID 2023 ESMO congress

BEGONIA Arm 7: Dato-DXd + Durvalumab

Antitumour Responses in 1L a/mTNBC

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods

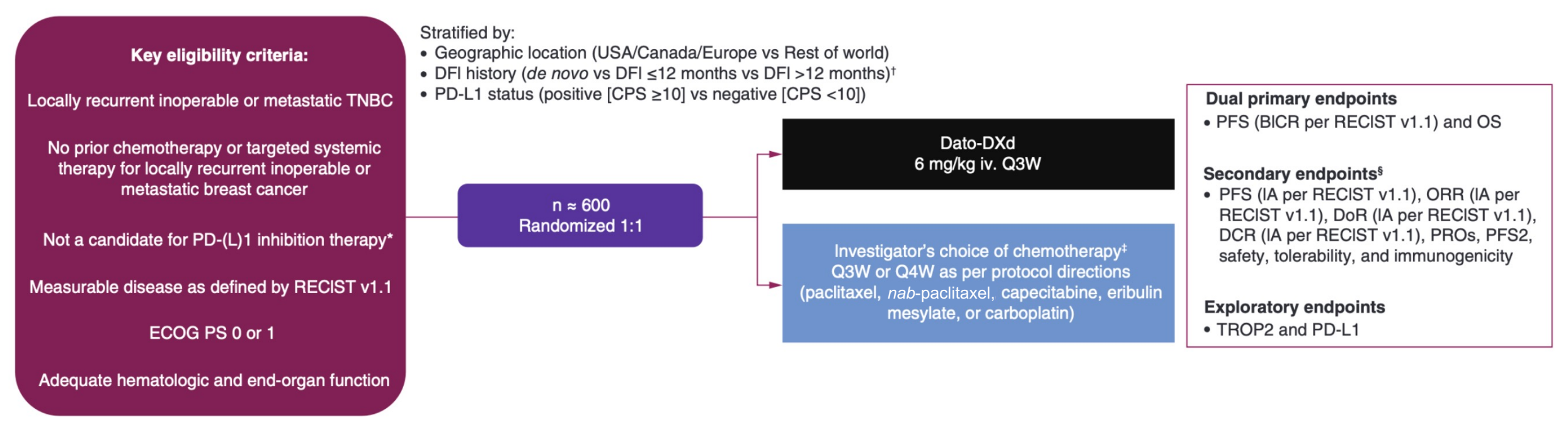


ORR = objective response rate; CR = complete response; PR = partial response

Schmid P et al. ESMO 2023;Abstract 379MO.

RTP RESEARCH TO PRACTICE

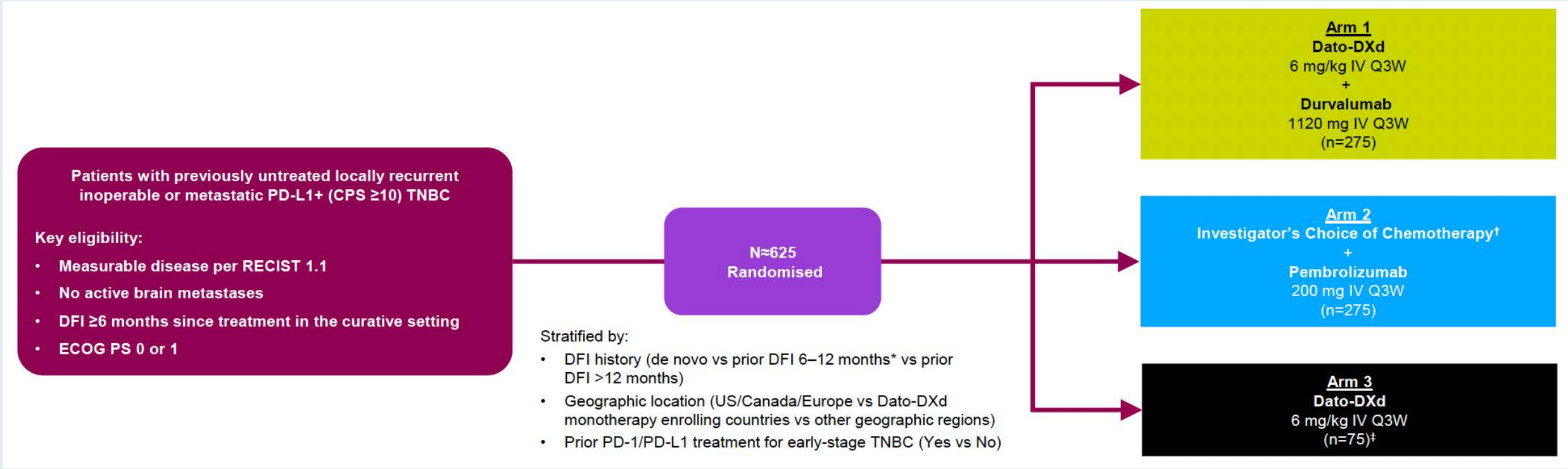
TROPION-Breast02 Trial: Dato-DXd for Previously Untreated Advanced TNBC Not Eligible for PD-1/PD-L1 Inhibitors



DFI = disease-free interval; CPS = combined positive score

Dent RA et al. *Future Oncol* 2023;19(35):2349-59.

TROPION-Breast05 Trial: Dato-DXd with or without Durvalumab for Advanced PD-L1-Positive (CPS ≥10) Previously Untreated TNBC



Schmid P et al. ESMO Breast 2024;Abstract 261TiP.

Discussion Question

- A 70-year-old woman with a 3.5-cm, ER/PR-positive, HER2-negative breast cancer is going to receive neoadjuvant systemic therapy. She has no relevant family history of cancer. Should BRCA testing be ordered for this patient?

Discussion Question

- Regulatory and reimbursement issues aside, what would be your preferred treatment approach for a 60-year-old patient with a germline PALB2 mutation and de novo metastatic triple-negative breast cancer that is PD-L1-negative?

First-Line Camizestrant Demonstrated a Statistically Significant and Clinically Meaningful Improvement in PFS for Advanced HR-Positive Breast Cancer with an Emergent ESR1 Tumor Mutation in the Phase III SERENA-6 Trial

Press Release: February 26, 2025

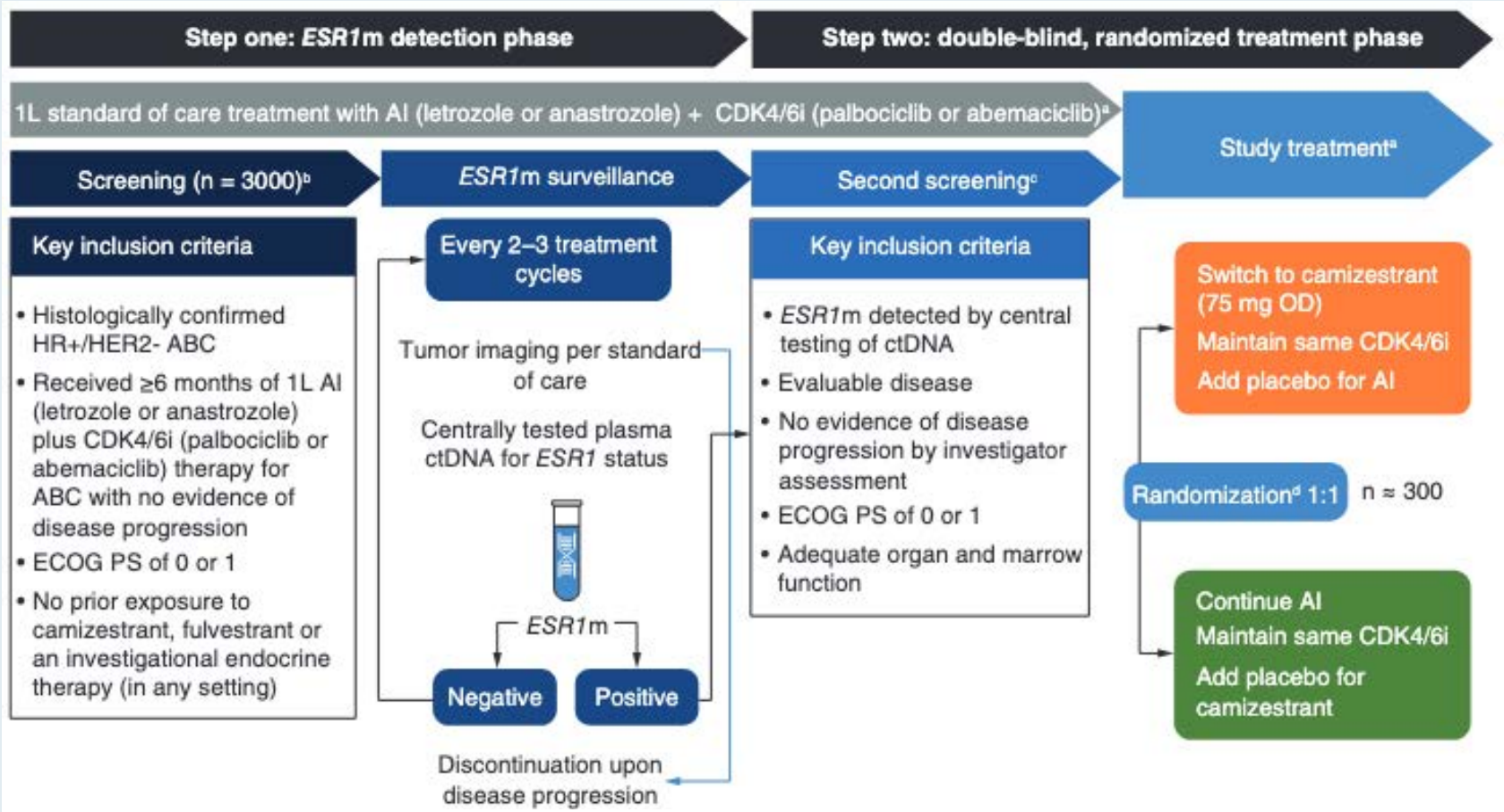
"Positive high-level results from a planned interim analysis of the SERENA-6 Phase III trial showed that camizestrant in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib, ribociclib or abemaciclib) demonstrated a highly statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS). The trial evaluated switching to the camizestrant combination versus continuing standard-of-care treatment with an aromatase inhibitor (AI) (anastrozole or letrozole) in combination with a CDK4/6 inhibitor in the 1st-line treatment of patients with hormone receptor (HR)-positive, HER2-negative advanced breast cancer whose tumours have an emergent *ESR1* mutation.

The key secondary endpoints of time to second disease progression (PFS2) and overall survival (OS) were immature at the time of this interim analysis. However, the camizestrant combination demonstrated a trend toward improvement in PFS2. The trial will continue as planned to further assess key secondary endpoints."

https://www.astrazeneca.com/media-centre/press-releases/2025/camizestrant-improved-pfs-in-1l-hr-breast-cancer.html.

RTP RESEARCH TO PRACTICE

SERENA-6 Phase III Study Design



[a]Premenopausal/perimenopausal women or male participants (if medically indicated) receive a concurrent monthly luteinizing-hormone-releasing hormone agonist (goserelin or leuprorelin).
[b]Patients who are screen failures for STEP 1 can be rescreened.
[c]Patients who are screen failures for STEP 2 can be rescreened after consultation with the Global Study Team.
[d]Randomization will be stratified by: disease site (visceral disease vs non-visceral disease); *ESR1*m status (detectable at first versus subsequent ctDNA tests); time from initiation of CDK4/6i + AI to randomization (<18 months vs ≥18 months); CDK4/6i.

Turner N et al. *Future Oncol* 2023;19(8):559-73.

RTP RESEARCH TO PRACTICE

Module 1: HER2-Positive, Triple-Negative and Localized Breast Cancer

HER2-Positive Breast Cancer — Dr O'Shaughnessy

Triple-Negative Breast Cancer (TNBC) — Dr Bardia

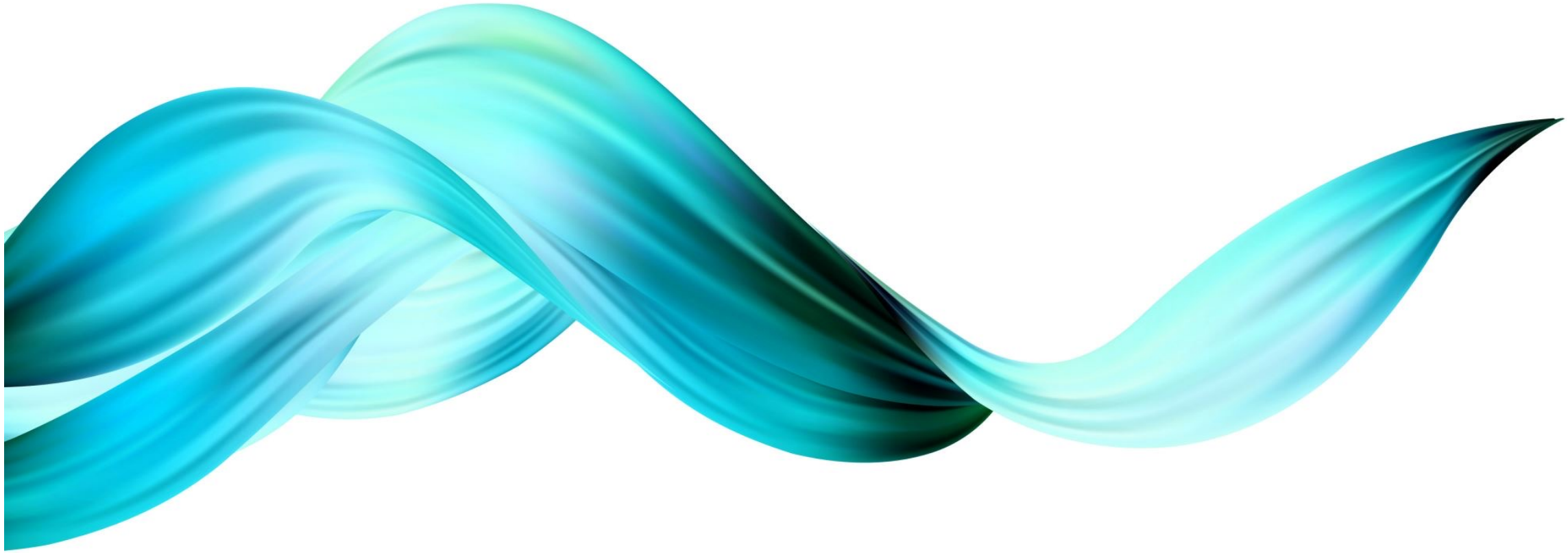
Personalizing Adjuvant Therapy for Patients with HR-Positive Breast Cancer — Dr Borges

Current Role of CDK4/6 Inhibitors in the Localized Setting — Dr Burstein

Personalizing the Use of Adjuvant Therapy for Patients with HR-positive Breast Cancer

Virginia F. Borges, MD, MMSc

University of Colorado Cancer Center



Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Olema Oncology, Pfizer Inc, Seagen Inc
Consulting Agreements	Gilead Sciences Inc, Olema Oncology
Contracted Research	Agendia Inc, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Gilead Sciences Inc, Olema Oncology, Pfizer Inc, Seagen Inc
Data and Safety Monitoring Boards/Committees	Pfizer Inc, Seagen Inc (HER2CLIMB-02 trial)
Nonrelevant Financial Relationships	Pearl Scientific LLC

Agenda

1. Genomic tools for (neo-) adjuvant choices
2. When to extend adjuvant endocrine therapy & decision tools available
3. Ovarian function suppression in premenopausal HR-positive BC
4. Preservation of fertility with OFS in YWBC

Adjuvant therapy decision making

HR+, HER2 neg EBC

Who needs chemo in 2025?

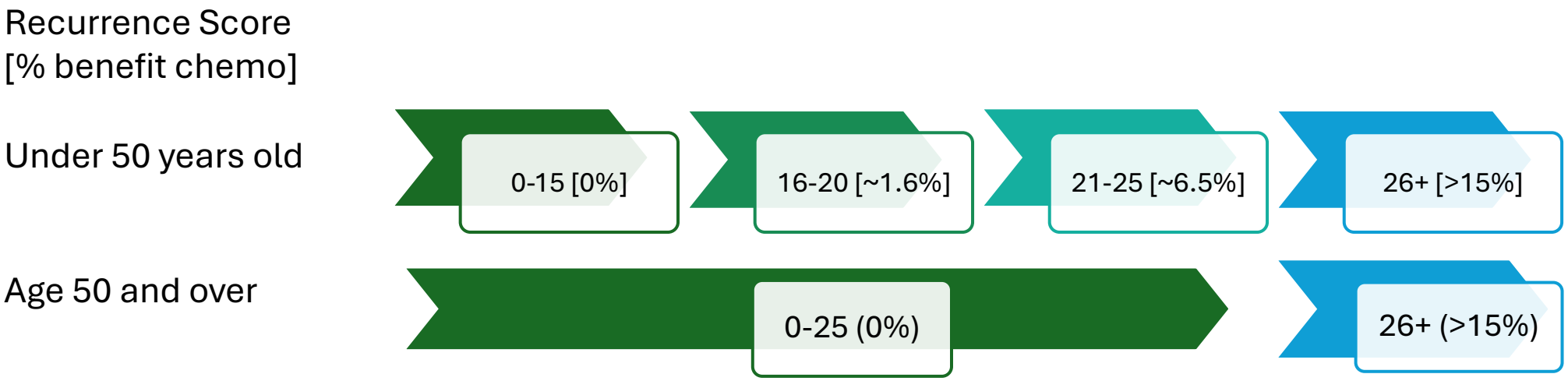
Best ET choices and for what duration?

Predictive/Prognostic Genomic Assays

Assay	RNA-Based Assays
Oncotype DX® Recurrence Score[1]	Uses RT-PCR to measure the expression of 21 genes—16 cancer-related genes and 5 reference genes—in a tumor sample
Prosigna® ROR-PT[2]	Analyzes the activity of 50 genes known as the PAM50 gene signature, along with clinical–pathologic features, to provide a prognostic score indicating the probability of cancer recurrence in the next 10 yr
MammaPrint®[3]	Analyzes the 70 most important genes associated with breast cancer recurrence from case/control studies of relapse within 5 yr
EndoPredict®[4]	Analyzes RNA expression of 8 target genes, 3 normalization genes, and 1 control gene, creating a 12-gene molecular score, which is then combined with clinical features of the tumor (tumor size and nodal status) to predict the 10-yr distant recurrence rate
Breast Cancer Index®[5]	Mix of 2 profiles—a select 2-gene ratio (*HOXB13:IL17BR*) and the molecular grade index representing 5 proliferation genes—to determine risk of late recurrence *Recommended by NCCN Guidelines as a predictive biomarker to inform the decision of extended adjuvant endocrine therapy*

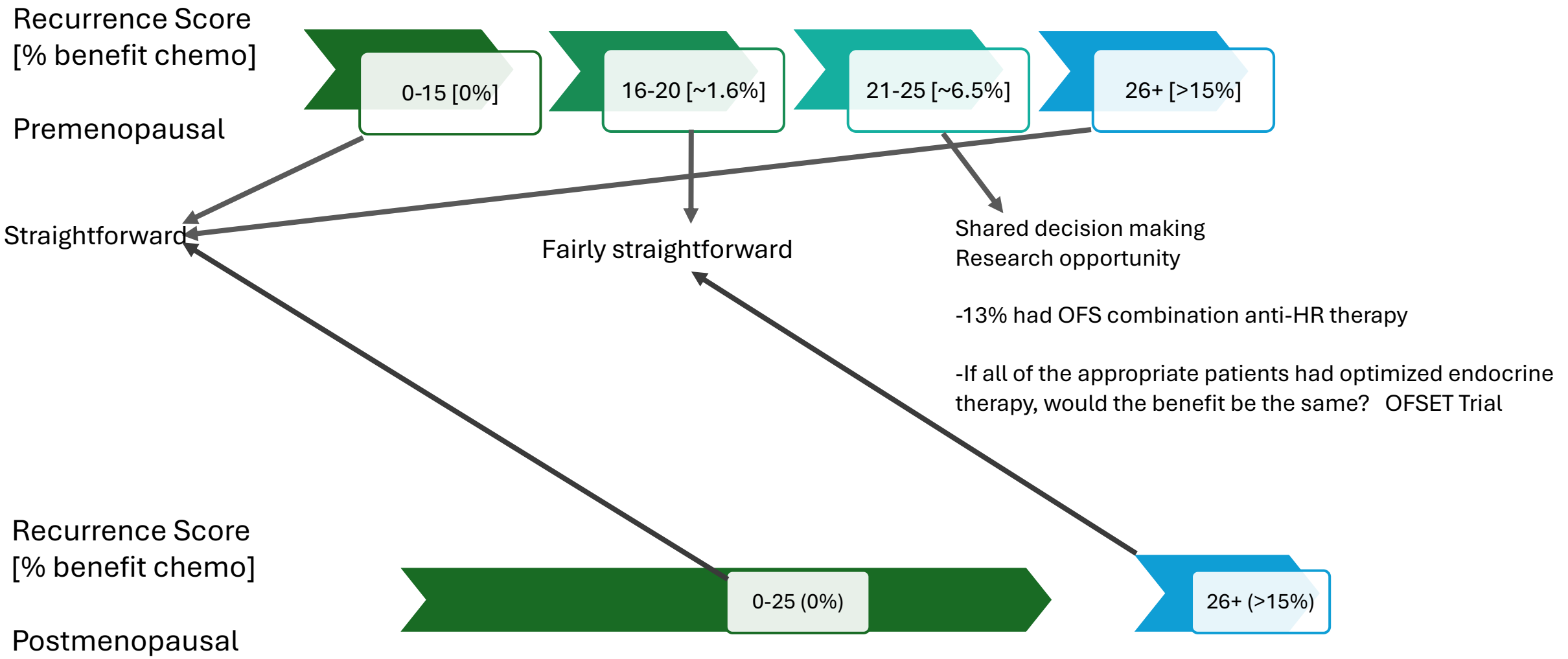
1. Paik. NEJM. 2004;351:2817. 2. Parker. JCO. 2009;27:1160. 3. Van't Veer, Nature. 2002;414:530.
4. Filipits. Clin Cancer Res. 2011;17:6012. 5. Ma. Cancer Cell. 2004;5:607.

TAILORx results overview for HR+ HER2- Node negative using 21 gene assay



J Sporano, et al. N Engl J Med 2018;379:111-21. DOI: 10.1056/NEJMoa1804710

TAILORx results interpretation for HR+ HER2 neg 21 gene assay



J Sporano, et al. N Engl J Med 2018;379:111-21. DOI: 10.1056/NEJMoa1804710

ER+ HER2– NODE+ Disease Best Use Strategy

Semi-personalized tumor genomic determination for need/benefit of chemo

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

Key Entry Criteria

- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by Endocrine Therapy Recommended

RANDOMIZATION

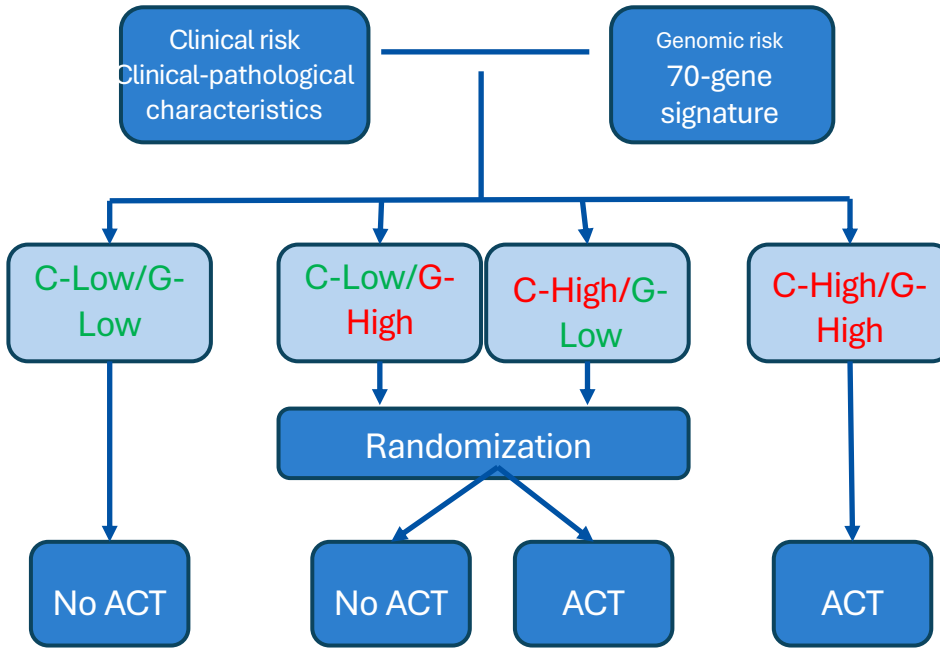
Arm 1:
Chemotherapy Followed by Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

N = 5,000 pts

Kalinsky (2021) N Engl J Med 2021; 385:2336-2347

MINDACT trial design



Cardoso (2016) NEJM;375:717-729. ;
Piccart (2021) Lancet Oncol. 2021; 22:476–488

Baseline Characteristics by Menopausal Status

Baseline variable	Postmenopausal (n=3,350)	Premenopausal (n=1,665)	Overall (n=5,015)
Age group			
< 40 years	0.2%	8.5% [141]	2.9%
40-49 years	1.9%	60.8%	21.5%
50-59 years	34.9%	30.5%	33.4%
60-69 years	45.7%	0.2%	30.6%
70+ years	17.3%	0%	11.6%
Recurrence Score			
RS 0-13	44.8%	38.7%	42.8%
RS 14-25	55.2%	61.3%	57.2%
Nodal Dissection			
Full ALND	60.7%	66.4%	62.6%
Sentinel nodes only	39.3%	33.6%	37.4%
Positive Nodes			
1 node	65.6%	65.3%	65.5%
2 nodes	25.1%	25.7%	25.3%
3 nodes	9.3%	9.0%	9.2%
Grade			
Low	26.0%	22.0%	24.7%
Intermediate	63.5%	68.3%	65.1%
High	10.6%	9.7%	10.3%
Tumor size			
T1	59.1%	56.2%	58.1%
T2/T3	41.9%	43.9%	41.9%

ER+ HER2– NODE+ Disease Best Use Strategy

Semi-personalized tumor genomic determination for need/benefit of chemo

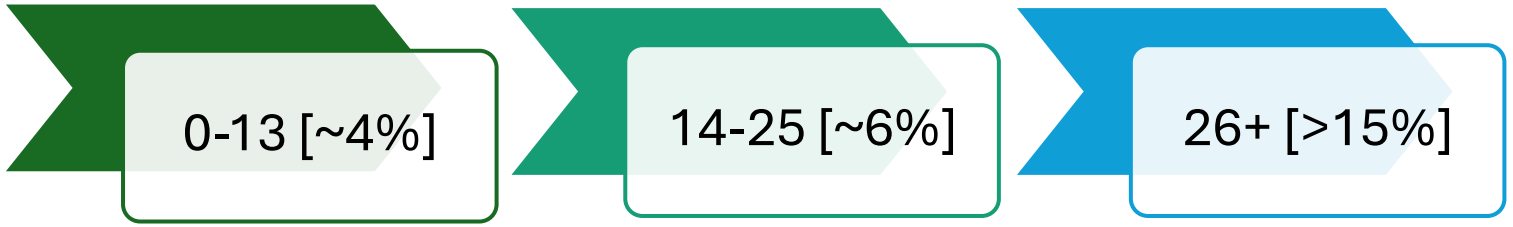
RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer

Recurrence Score
[% benefit chemo]

Postmenopausal

Recurrence Score
[% benefit chemo]

Premenopausal

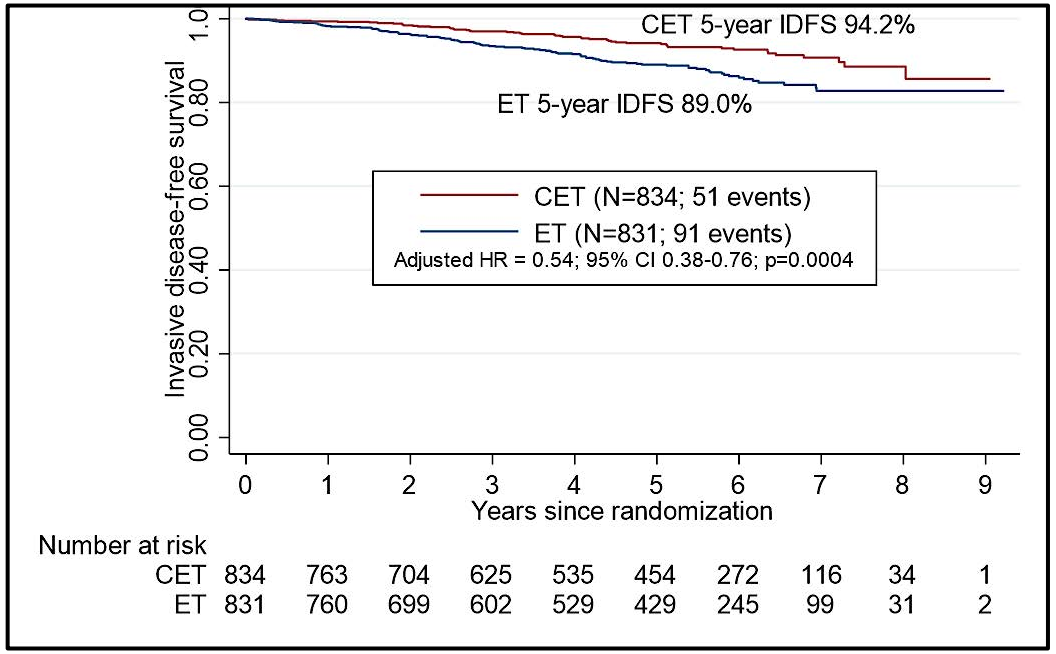


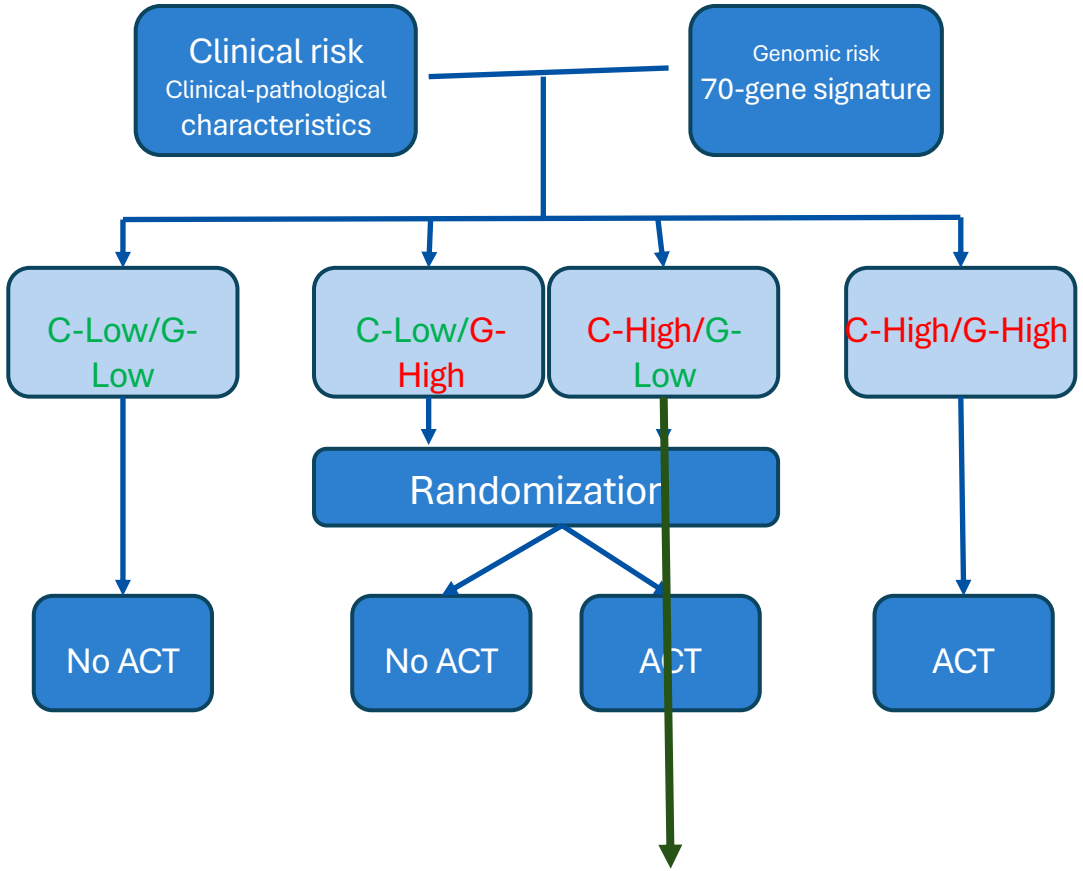
Kalinsky (2021) N Engl J Med 2021; 385:2336-2347

Premenopausal women benefit more from chemotherapy

- Premenopausal women with RS 0-25 had benefit from the addition of chemotherapy to endocrine therapy
  54% received Anthracycline regimen
- 46% decrease in IDFS events; benefit was observed across premenopausal subgroups
- 53% decrease in deaths, leading to a 5-year OS absolute improvement of 1.3%
- 1 node v 2-3 nodes – equal benefit at ~5% benefit

IDFS premenopausal women





ER+ HER2- N1 disease

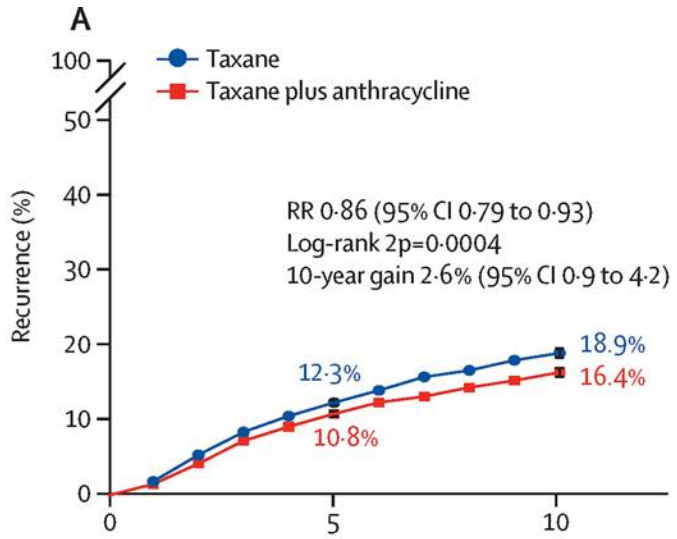
Women under 50 chemo/no chemo

93.6% v 88.6% [5% gain for chemo]

Kalinsky, et al N Engl J Med 2021; 385:2336-2347
DOI: 10.1056/NEJMoa2108873

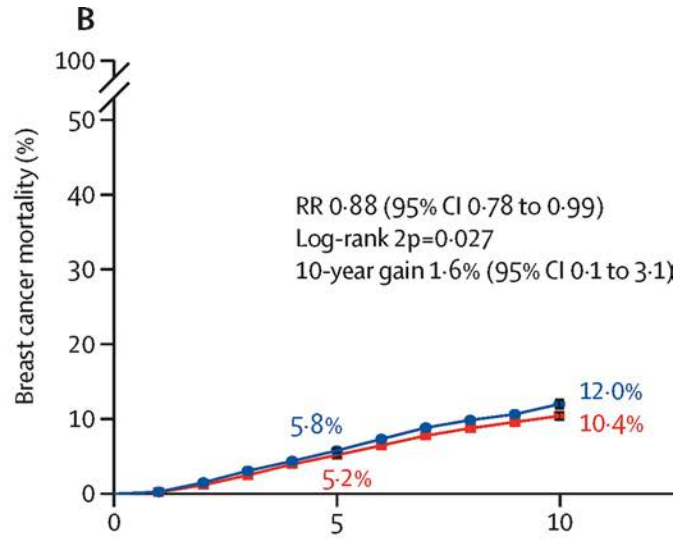
Genomic options for determining type of chemotherapy to use?

EBCCTG 2023: Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100,000 women from 86 randomized trials



Recurrence rates per year (% [events per woman-years]) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Taxane plus anthracycline	2·34% (900/38 514)	1·37% (158/11 575)	0·95% (4/420)
Taxane	2·63% (1008/38 389)	1·65% (188/11 388)	0·76% (3/396)
RR (95% CI)	0·87 (0·79–0·95)	0·80 (0·64–0·99)	1·83 (0·36–9·22)
(O–E) / V	–63·8/443·9	–19·1/83·3	0·9 / 1·5



Death rates per year (% [95% CI]: total rate–rate in participants without recurrence) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Taxane plus anthracycline	1·05% (0·95–1·15)	1·24% (1·04–1·44)	1·10% (0·14–2·06)
Taxane	1·15% (1·04–1·25)	1·42% (1·21–1·63)	1·38% (0·28–2·48)
RR (95% CI)	0·89 (0·78–1·02)	0·85 (0·68–1·06)	0·88 (0·26–2·92)
(O–E) / V	–24·4/208·8	–13·0/79·0	–0·4/2·7

<u>HR show improved outcomes if</u>:
<54
ER-
N+
High grade
Her2-

<u>HR cross 1.0 if:</u>
Age>54
ER+
Node 0
Low-med grade
Her2 positive

Impact of Anthracyclines in High Genomic Risk Node-Negative HR+/HER2- Breast Cancer

Nan Chen MD[a], Jincong Q Freeman MPH MS, Sudha Yarlagadda MD, Aishwarya Atmakuri, Kevin Kalinsky MD, Lajos Pusztai MD DPhil, Dezheng Huo MD PhD, Rita Nanda MD, Frederick M Howard MD[a]

[a] Department of Internal Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL, USA

Patient Characteristics

	T-AC n = 438	TC n = 2111
Age, mean (SD)	53.0 (9.3)	55.1 (9.1)
Menopausal Status, n (%)		
Postmenopausal	256 (58.4)	1359 (64.4)
Premenopausal	182 (41.6)	752 (35.6)
Tumor Size (mm), mean (SD)	19.6 (9.0)	17.7 (8.1)
Grade, n (%)		
Low	63 (14.4)	461 (21.8)
Medium	203 (46.3)	1096 (51.9)
High	159 (36.3)	504 (23.9)
PR Status		
Positive	348 (79.5)	1810 (85.7)
Negative	90 (20.5)	301 (14.3)

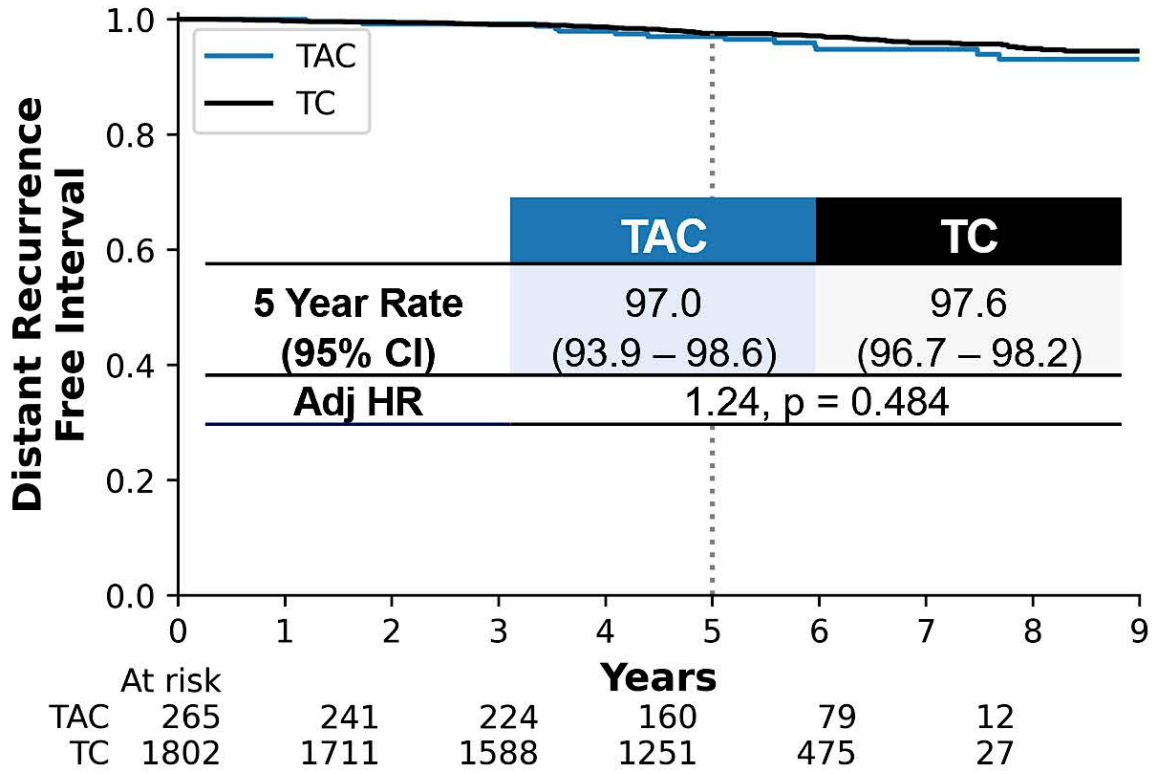
	T-AC n = 438	TC n = 2111
Recurrence Score, mean (SD)	29.6 (14.2)	22.3 (9.5)
Recurrence Score, n (%)		
11-25	196 (44.7)	1554 (73.6)
26-30	69 (15.8)	251 (11.9)
31-100	173 (39.5)	306 (14.5)
Chemotherapy Regimen, n (%)		
Dose dense AC-T	186 (42.5)	
Standard AC-T	110 (25.1)	
Concurrent TAC	57 (13.0)	
Other Anthracycline / Taxane	85 (19.4)	
TC		2111 (100.0)

Chen SABCS 2024

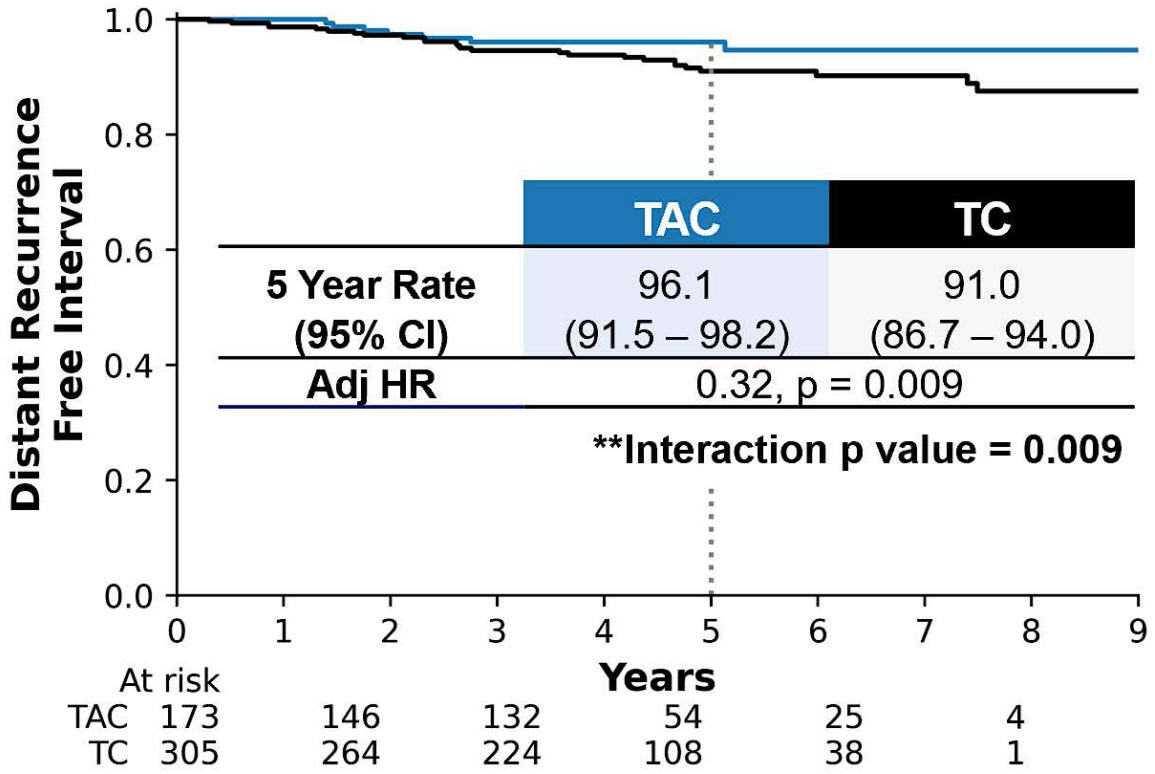
Primary Survival Outcome: Distant Recurrence-Free Interval at 5 years

Chen SABCS 2024

RS < 31



RS ≥ 31

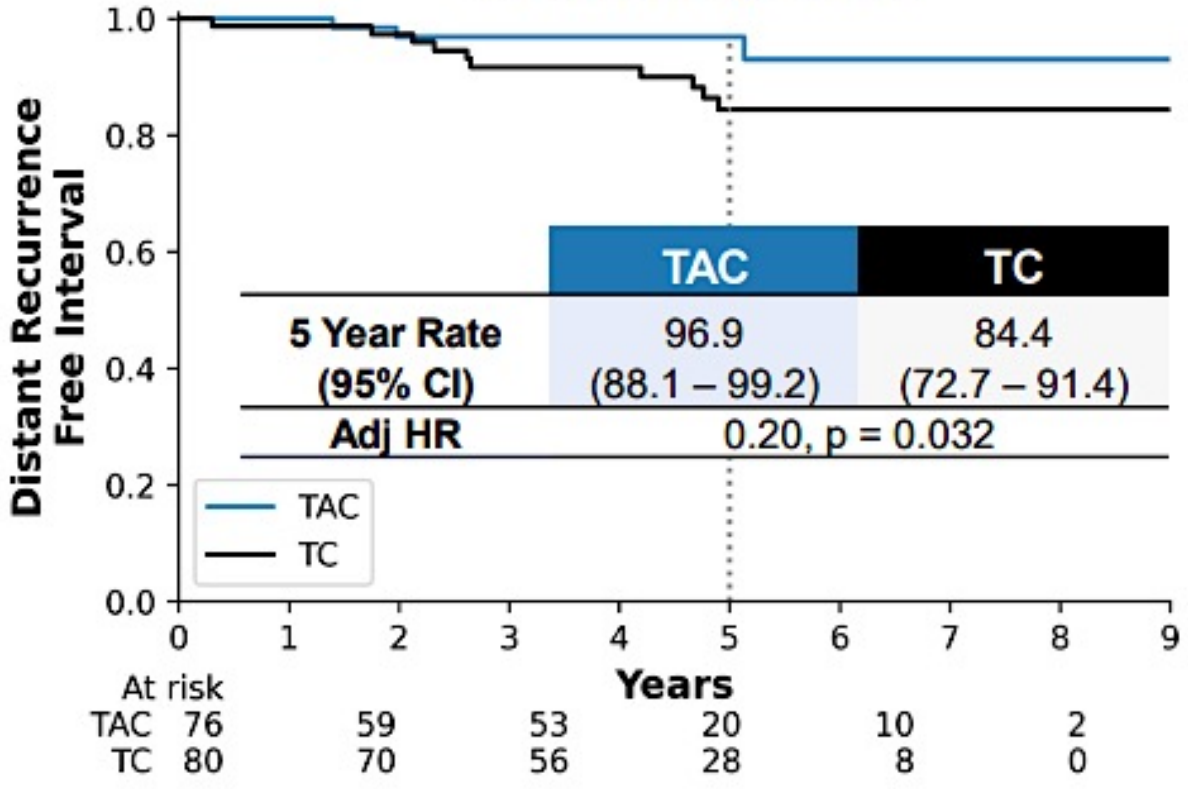


*Adjusted hazard ratios controlling for age, ER/PR status, RS, tumor size, treatment received, and interaction of treatment with RS

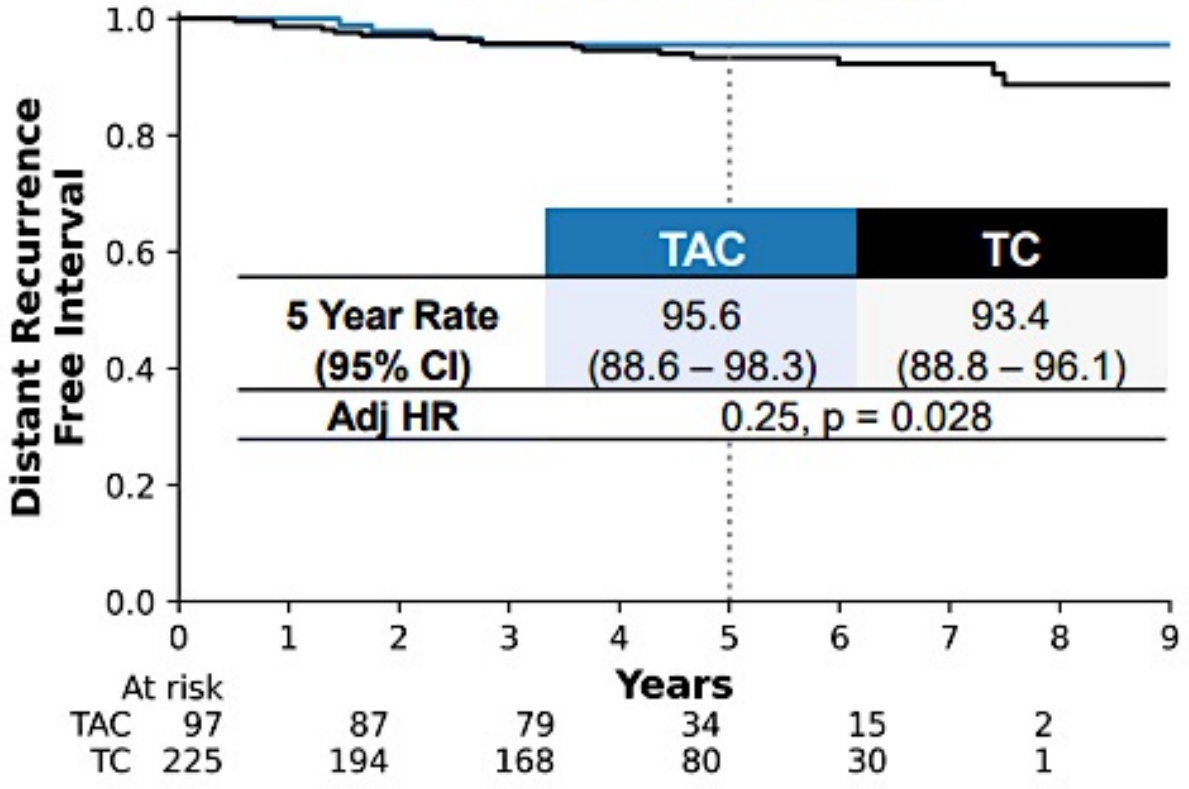
DRFI by Menopausal Status in RS ≥ 31

Chen SABCS 2024

Premenopausal



Postmenopausal

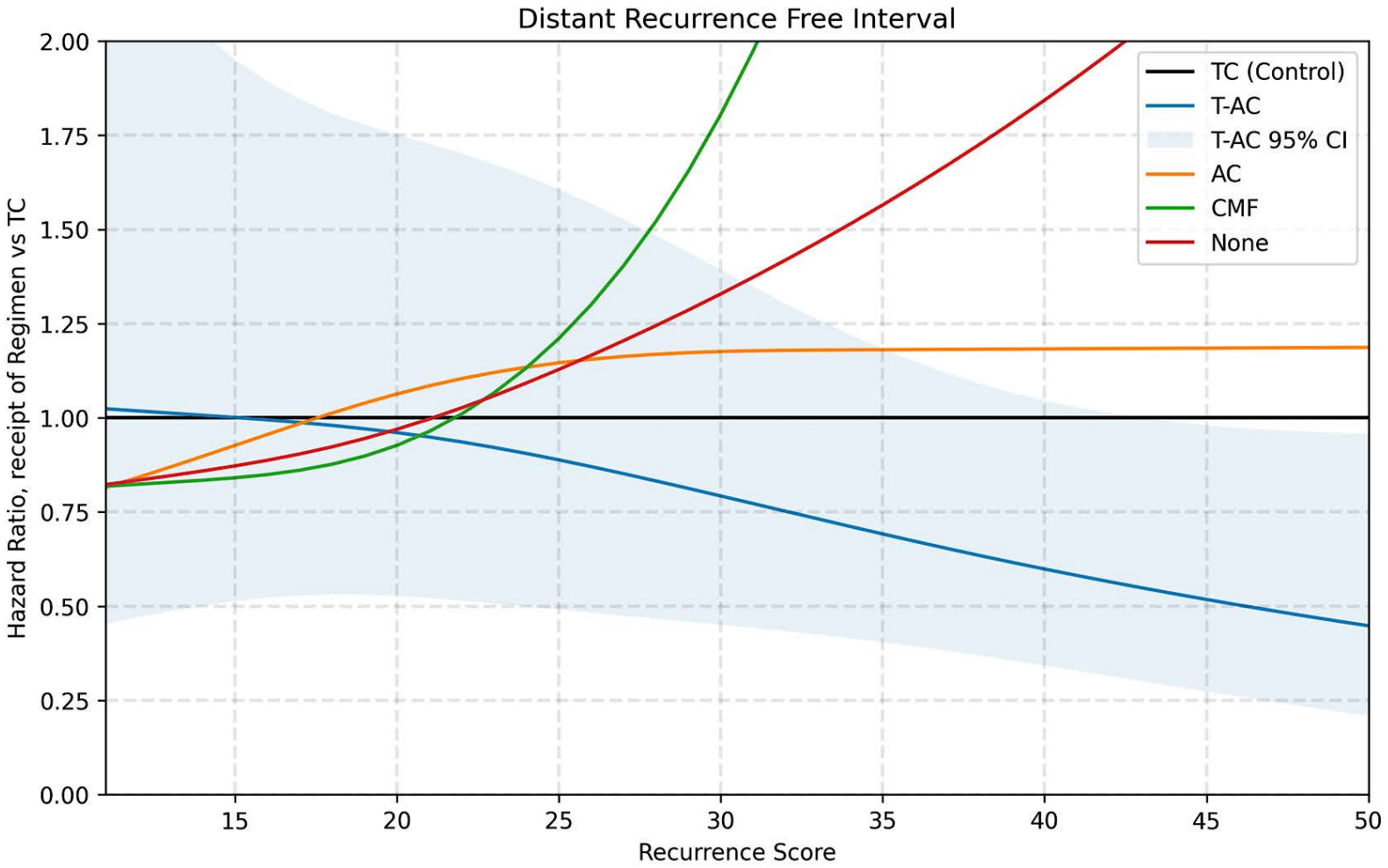


*Adjusted hazard ratios controlling for age, ER/PR status, RS, tumor size, treatment received in high RS population

Alternative Chemotherapy Regimens Have Decreased Benefit with Increasing RS

Chen SABCS 2024

RS	Adj HR, DRFI
15	1.00 (0.51 - 1.95)
20	0.96 (0.53 - 1.75)
25	0.89 (0.49 - 1.61)
30	0.79 (0.45 - 1.39)
35	0.69 (0.40 - 1.18)
40	0.60 (0.34 - 1.05)
45	0.52 (0.27 - 0.98)
50	0.45 (0.21 - 0.96)



My Conclusions:

This is in keeping with findings of

- EBCTCG Lancet 2023
  - Benefit of anthracyclines and taxanes for early breast cancer
- O'Shaughnessy ASCO 2024
  - Benefit of anthracyclines for Mammoprint H2/Luminal B type tumors

Consider using anthracycline containing regimen for individuals with LN- but >2cm tumors and Oncotype >31

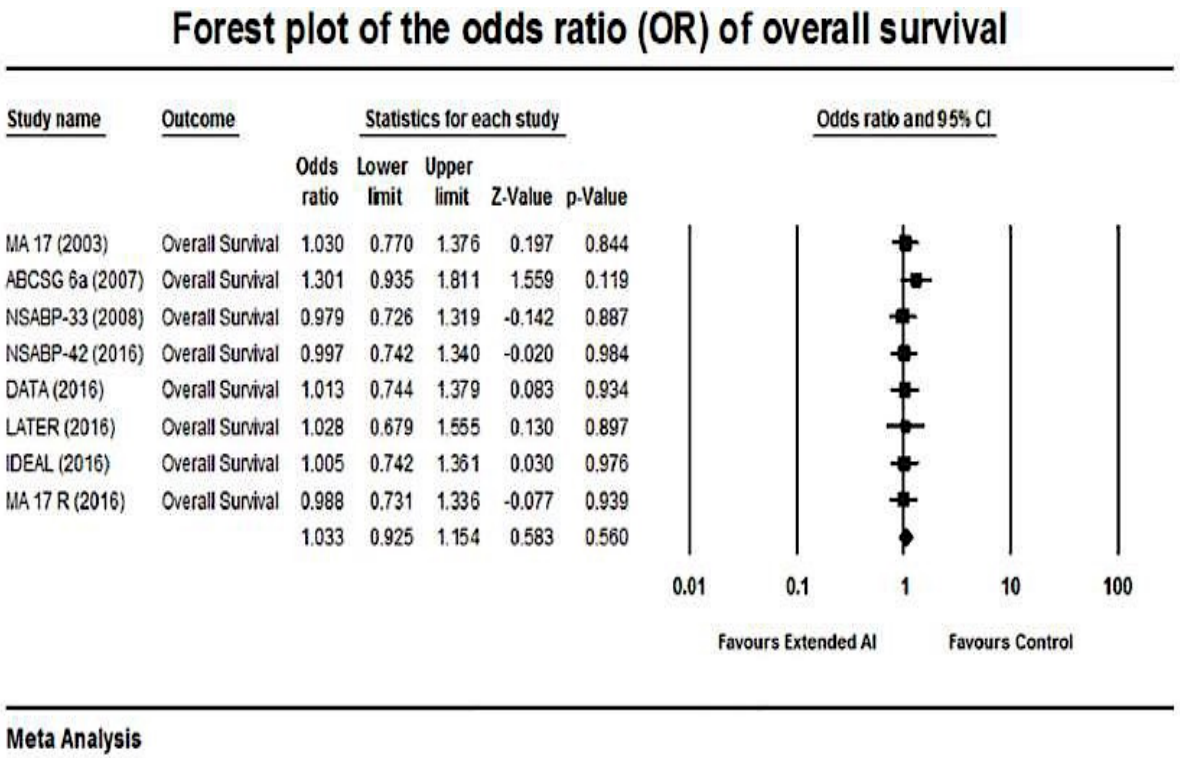
- Need to weigh risk/benefits of anthracyclines

Extention of Endocrine Therapy

Who benefits and how to decide?

Extended ET with Tam or AI and Disease-Free Survival and Overall Survival

Trial	Duration of Therapy (y)		N	Median Follow-up (y)	Disease-free Survival[1]	Absolute Benefit	Hazard Ratio or Rate Ratio (95% CI)
MA.17	TAM x 5y	→ Placebo x 5y → AI x 5y	2587 2583	2.5	89.8% 94.4%	4.6%	HR 0.58 (0.45-0.76) P<0.001
ABCSG 6A	TAM x 5y	→ Placebo x 3y → AI x 3y	469 387	5.2	88.2% 92.9%	4.7%	HR 0.62 (0.40-0.96) P=0.031
aTTom	AM x 5y	→ No treatment → TAM x 5y	3485 3468	10	68% 72%	4%	RR 0.85 (0.76-0.95) P=0.003
ATLAST	AM x 5y	→ No treatment → TAM x 5y	3418 3428	7.6	74.9% 78.6%	3.7%	RR 0.84 (0.76-0.94) p=0.002
NSABP B-42	AI x 5y	→ Placebo x 5y → AI x 5y	1983 1983	9.3	72.1% 76.1%	4%	HR 0.84 (0.74-0.96) P=0.011



Clement, Z et al. *Gland Surg* 2018;7(5):449-457

EBCTCG Meta-analysis

Effect of Prolonged Duration AI Therapy

- Meta-analysis of ~25,000 patients
- Five years of additional AI therapy reduced recurrence:
  1.1% in node-negative patients
  3.8%in those with 1 to 3 positive nodes
  7.7% in those with ≥4 positive nodes.

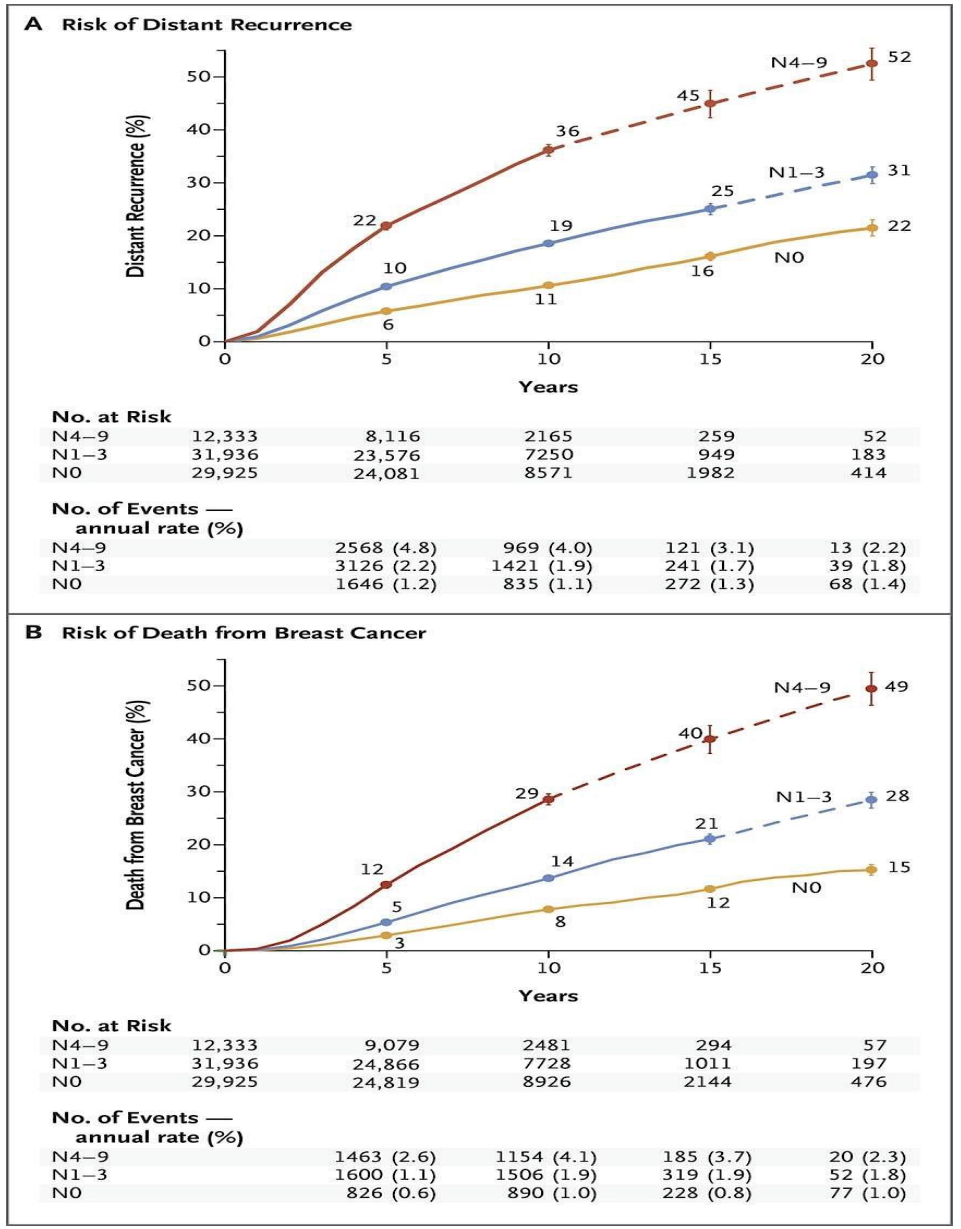
- The benefit was more pronounced in patients who received 5 years of tamoxifen alone compared with those who received prior adjuvant AI therapy.

Gray R, Early Breast Cancer Trialists' Collaborative Group. Cancer Res. 2019;79(4 suppl):GS3-03.

Association between Pathological Nodal Status and the Risk of Distant Recurrence or Death from Breast Cancer during the 20-Year Study Period.

Recurrences persist in HR+ breast cancer for +2 decades with 5 years of endocrine therapy; but *most* patients don't benefit from continuation.

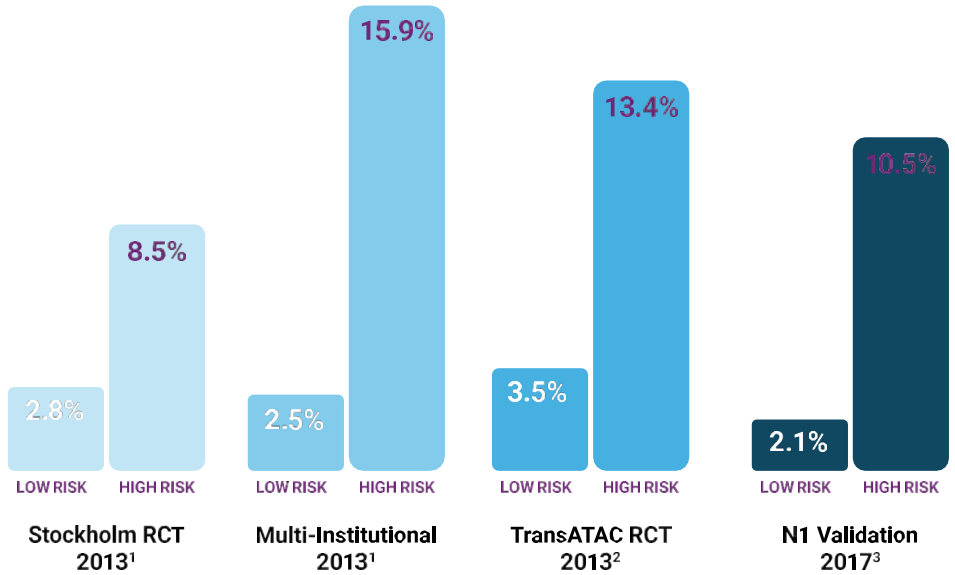
How do we choose?



The NEW ENGLAND JOURNAL of MEDICINE

BCI validation studies for prediction of benefit from extended therapy

Node Negative Validation (N0)			Node Positive Validation (N1, 1-3 positive nodes)
Stockholm RCT 2013	**Multi-Institutional 2013[1]**	**TransATAC RCT 2013[2]**	**N1 Validation 2017[3]**
Validation in Prospective RCT	Validation in Multi-Institutional Cohort	Validation in Prospective RCT & Head to Head with Oncotype Dx	Validation with Massachusetts General Hospital
317 Patients	358 Patients	665 Patients	
Post-Menopausal	Pre- and Post-Menopausal	Post-Menopausal	Pre- and Post-Menopausal
TAM	TAM	TAM or AI	or AI TAM



1. Zhang Y, et al. Clin Cancer Res. 2013;19(15):4196-205. **2.** Sgroi, et al., Lancet Oncology, 2013,14(11):1067-1076. **3.** Zhang Y et al. Clin Cancer Res. 2017 Dec 1;23(23):7217-7224.

Summary of BCI Clinical Evidence for Prediction of Endocrine Benefit

Study	N	Study Treatment(s)	Relative ROR: HR (95% CI)	*P* Value	Interaction *P* Value
Stockholm[1]	600	Adjuvant TAM vs none	H/I-High: 0.35 (0.19-0.65) H/I-Low: 0.67 (0.36-1.24)	.0005 .204	.003
MA.17*[2]	249	Extended AI vs placebo	H/I-High: 0.35 (0.16-0.75) H/I-Low: 0.68 (0.31-1.52)	.007 .035	.03
Trans-aTTom N+[3]	583	Extended TAM vs stop	H/I-High: 0.35 (0.15-0.86) H/I-Low: 1.07 (0.69-1.65)	.027 .768	.012
IDEAL[4]	908	5 yr vs 2.5 yr extended AI	H/I-High: 0.42 (0.21-0.84) H/I-Low: 0.95 (0.58-1.56)	.011 .835	.045
NSABP B-42	2179	5Y vs No	H/I-High: 0.29 (0.12-0.69) H/I-Low: 0.68 (0.33-1.39)	.003 0.28	0.55

1. Zhang. Clin Cancer Res. 2013; 19:4196. 2. Sgroi. J Natl Cancer Inst. 2013;105:1036.
3. Bartlett. Ann Oncol. 2019;30:1776. 4. Noordhoek. Clin Cancer Res. 2021;[Epub].

Breast Cancer Index NCCN Guidelines

If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI

(Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

If a patient has node-positive breast cancer with >/= 4 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI

(Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Optimizing ET for premenopausal women

Combination versus monotherapy?

27 trials identified (19,222 women randomized)

→ **200 women (2 trials) no data**

→ **4,021 women ineligible**

- 1305 postmenopausal
- 2760 ER-negative (44 postmenopausal)

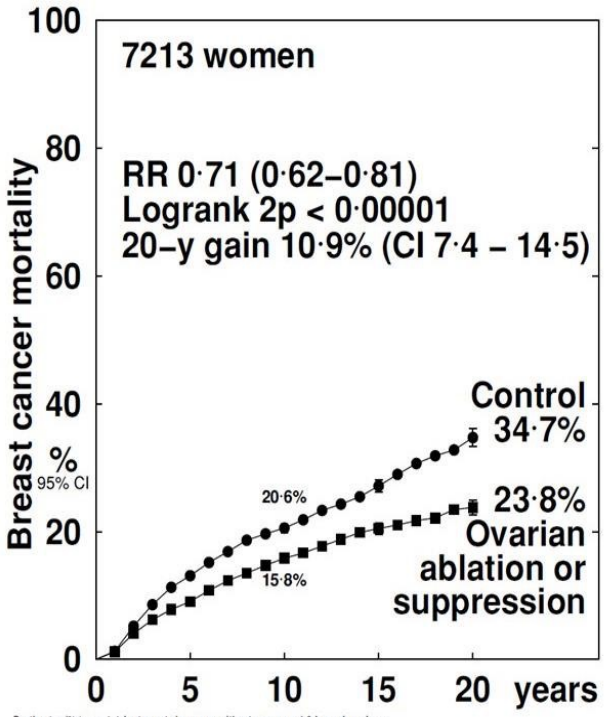
14,999 women (23 trials*) who were premenopausal at randomization

*2 trials included only postmenopausal women

Ovarian Ablation/Suppression vs. Not: Mortality

No chemotherapy or premenopausal after chemotherapy

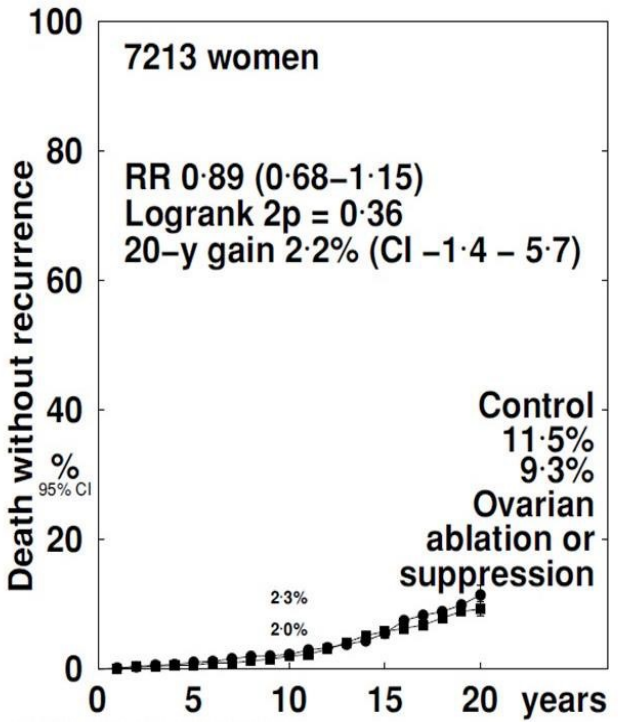
Breast cancer mortality



Death rates (%/year: total rate – rate in women without recurrence) and log-rank analyses

Allocation	Years 0 – 9	Years 10 – 19	Years 20+
Abl/suppr.	2.01 CI 1.84 – 2.18	1.18 CI 0.95 – 1.41	1.30 CI 0.93 – 1.68
Control	2.19 CI 2.01 – 2.37	1.78 CI 1.47 – 2.09	1.47 CI 1.01 – 1.93
Rate ratio, from	0.74 CI 0.63 – 0.66	0.58 CI 0.42 – 0.81	0.82 CI 0.43 – 1.56
(O – E)/V	-51.7/169.2	-19.5/35.9	-1.9/9.4

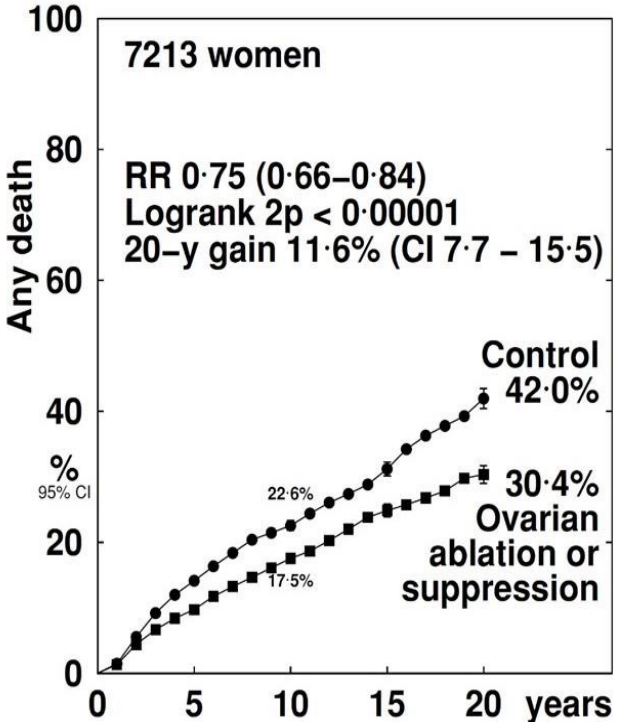
Death without recurrence



Death–without–recurrence–rates (%/year) and log-rank analyses

Allocation	Years 0 – 9	Years 10 – 19	Years 20+
Abl/suppr.	0.19 (49/25166)	0.73 (56/7648)	4.32 (146/3376)
Control	0.21 (50/23362)	0.86 (51/5905)	4.32 (106/2452)
Rate ratio, from	0.75 CI 0.46 – 1.22	0.89 CI 0.54 – 1.47	0.98 CI 0.67 – 1.44
(O – E)/V	-4.7/16.2	-1.8/15.4	-0.5/26.1

All cause mortality

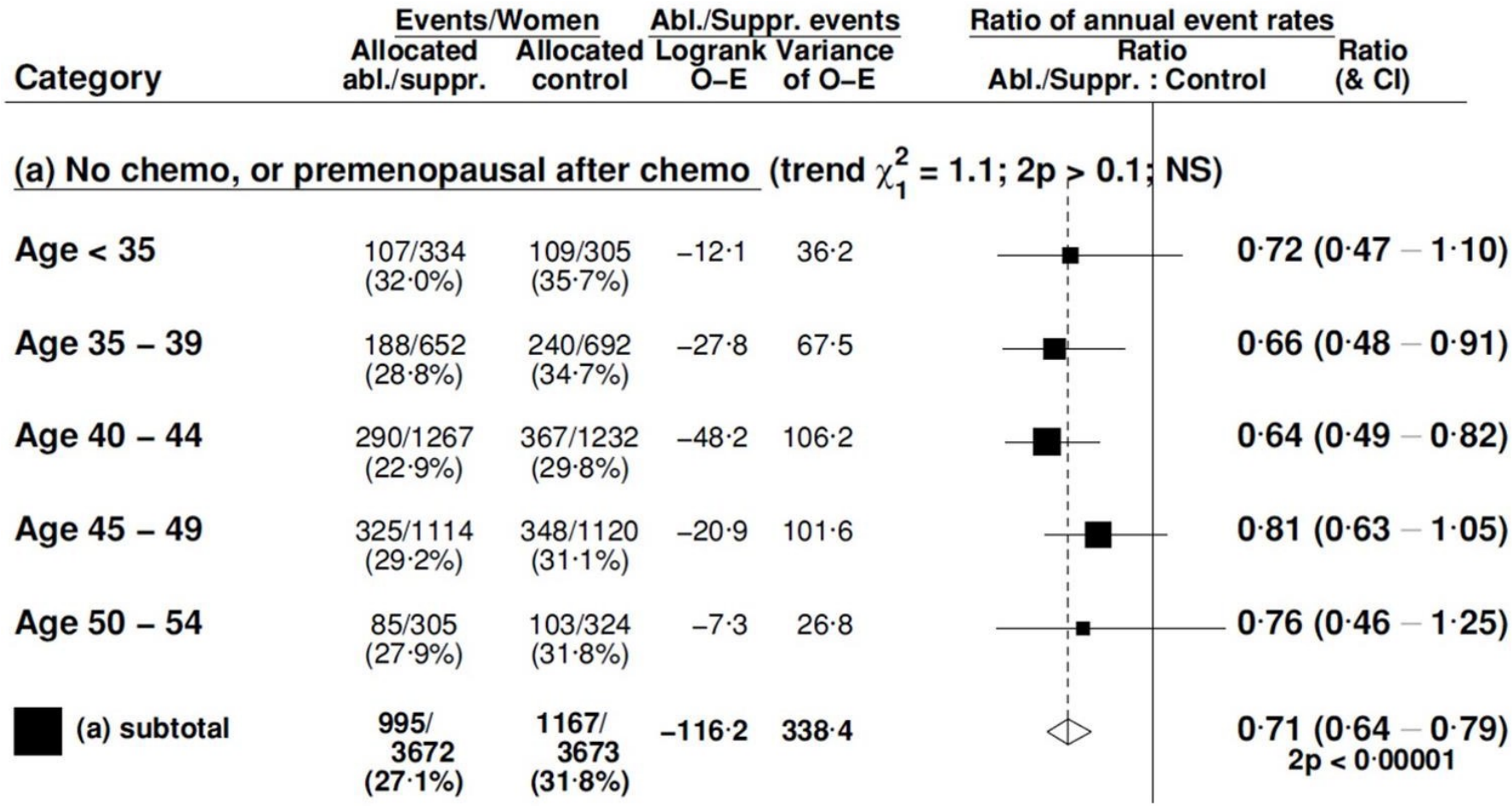


Death rates (%/year) and log-rank analyses

Allocation	Years 0 – 9	Years 10 – 19	Years 20+
Abl/suppr.	2.22 (602/27161)	1.89 (160/8488)	5.40 (193/3573)
Control	2.43 (628/25843)	2.55 (178/6991)	5.52 (145/2625)
Rate ratio, from	0.74 CI 0.64 – 0.85	0.66 CI 0.50 – 0.87	0.93 CI 0.67 – 1.30
(O – E)/V	-56.4/185.5	-21.3/51.3	-2.4/35.5

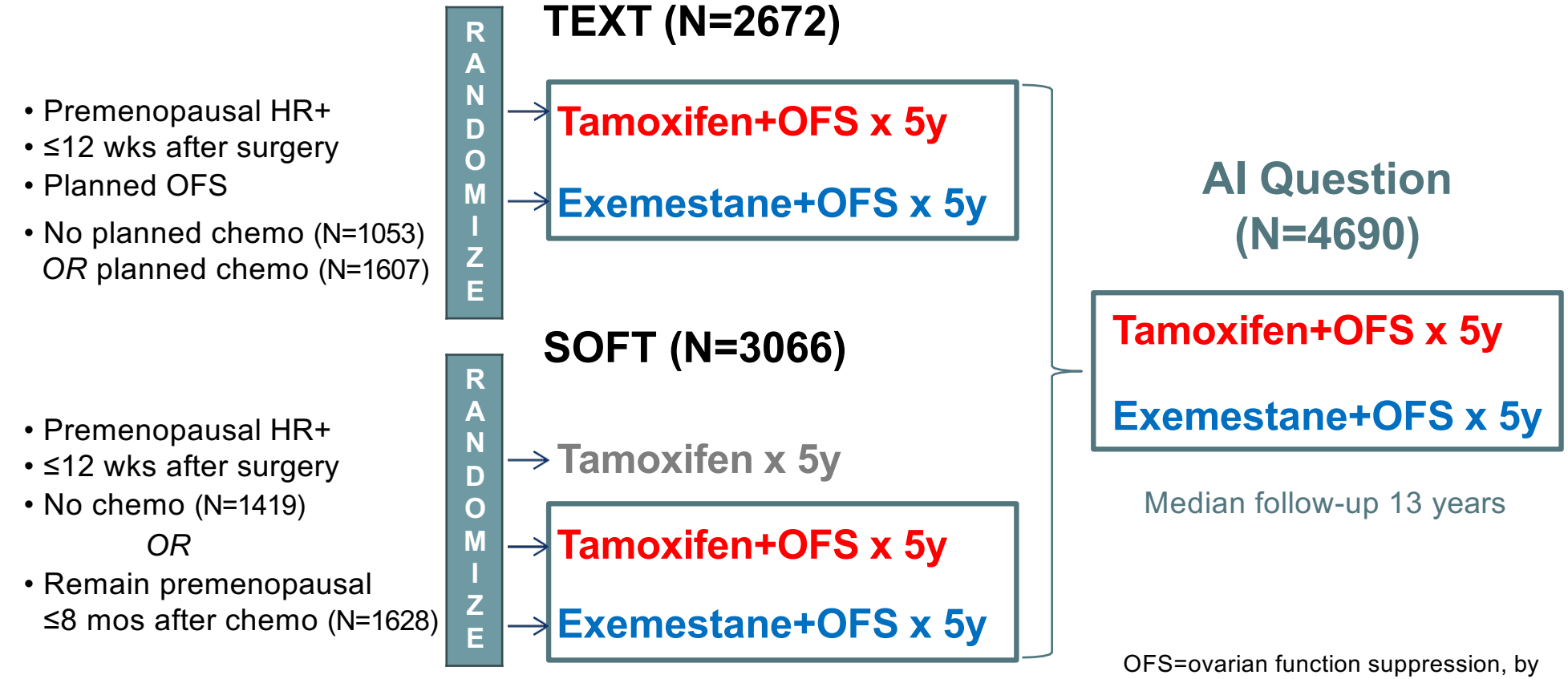
Ovarian Ablation/Suppression vs. Not: Recurrence by Age*

No chemotherapy or premenopausal after chemotherapy



TEXT and SOFT Trial Designs:

Effect of OFS as Adjuvant Therapy in ER+ Early Breast Cancer



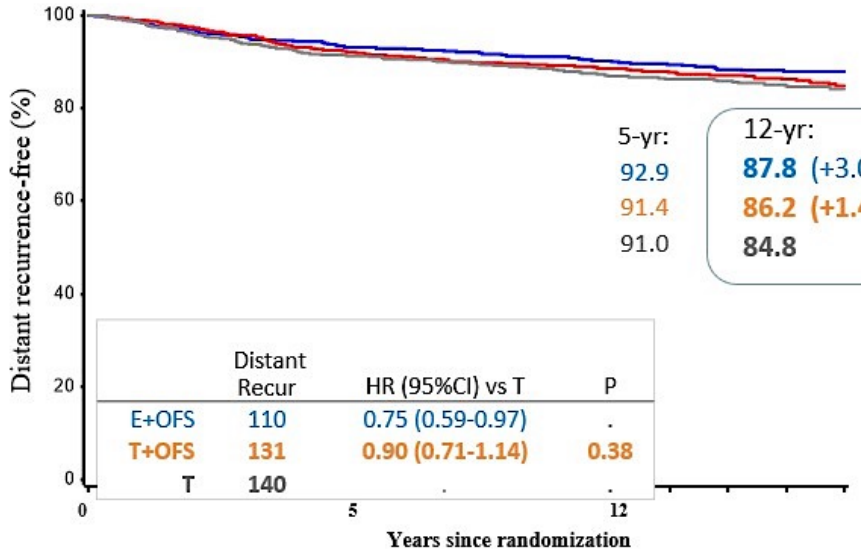
OFS=ovarian function suppression, by GnRH analogue triptorelin or oophorectomy

ER, estrogen receptor; HR, hormone receptor; mos, months; OFS, ovarian function suppression; by GnRh analogue triptorelin or oophorectomy.
Francis P et al. *N Engl J Med.* 2018;379:122-137. Francis P et al. J Clin Oncol. 2022;41(7):1370-1375.

OFS Question: SOFT Overall Population

(35% LN+; 12 Years Median Follow-up)

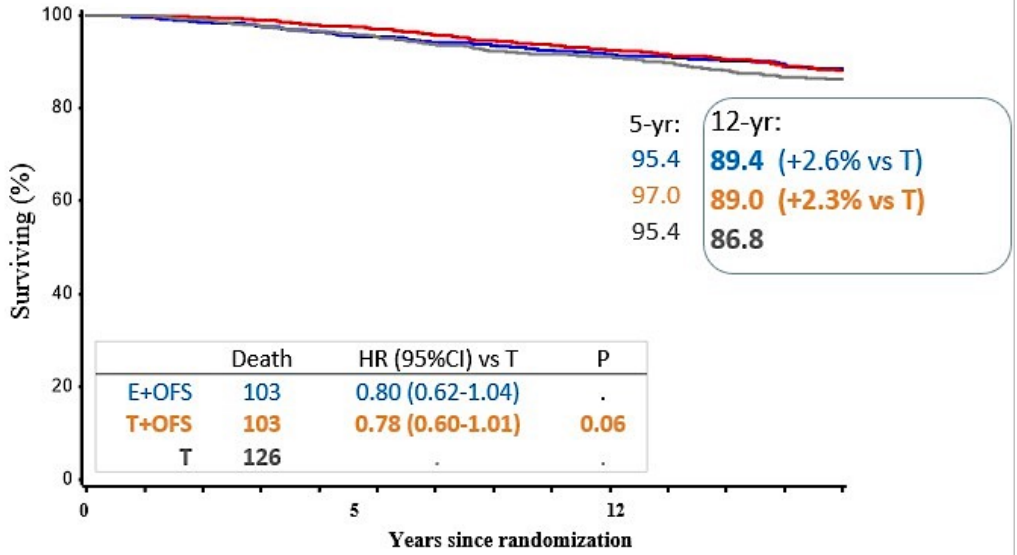
Distant recurrence-free survival



	Distant Recur	HR (95%CI) vs T	P
E+OFS	110	0.75 (0.59-0.97)	.
T+OFS	131	0.90 (0.71-1.14)	0.38
T	140	.	.

	0-5 years		>5 years	
	Recur	HR (95% CI) vs T	Recur	HR (95% CI) vs T
E+OFS:	68	0.76 (0.55-1.04)	42	0.74 (0.50-1.12)
T+OFS:	83	0.93 (0.69-1.25)	48	0.85 (0.58-1.26)
T:	87	.	53	.
At risk:	**3047** pts	13787 pyfu	2521 pts	16343 pyfu

Overall survival



	Death	HR (95%CI) vs T	P
E+OFS	103	0.80 (0.62-1.04)	.
T+OFS	103	0.78 (0.60-1.01)	0.06
T	126	.	.

	0-5 years		>5 years	
	Deaths	HR (95% CI) vs T	Deaths	HR (95% CI) vs T
E+OFS:	45	1.00 (0.66-1.51)	58	0.70 (0.50-0.98)
T+OFS:	29	0.63 (0.40-1.01)	74	0.86 (0.63-1.18)
T:	45	.	81	.
At risk:	**3047** pts	14524 pyfu	2745 pts	18383 pyfu

T+OFS vs T: absolute reductions in distant recurrence and death 1.4% and 2.3% at 12 years

E+OFS vs T: absolute reductions in distant recurrence and death 3.0% and 2.6% at 12 years

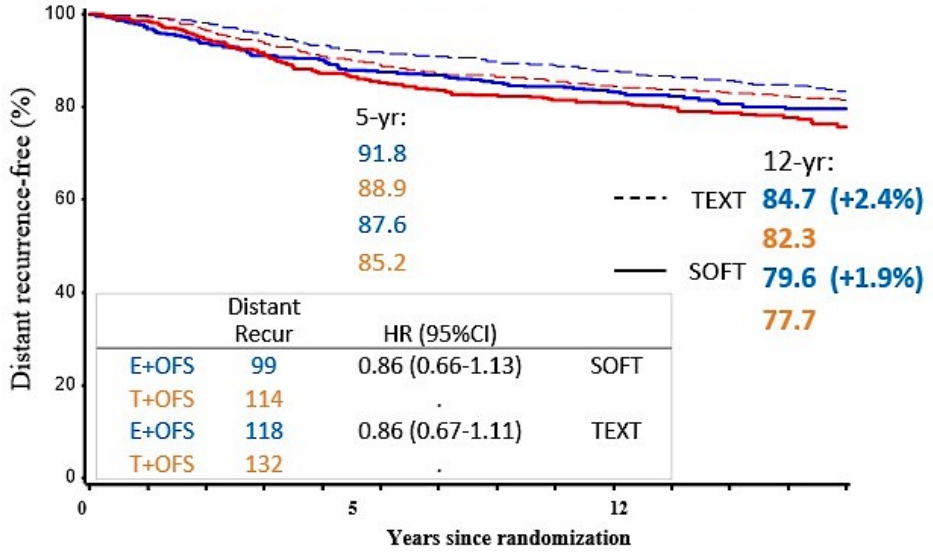
CI, confidence interval; E, exemestane; HR, hazard ratio; LN, lymph node; OFS, ovarian function suppression; T, tamoxifen.

Francis P et al. *J Clin Oncol.* 2022;41(7):1370-1375.

SOFT+TEXT: Chemotherapy Cohorts

(57% & 66% LN+; 13 Years Median Follow-up)

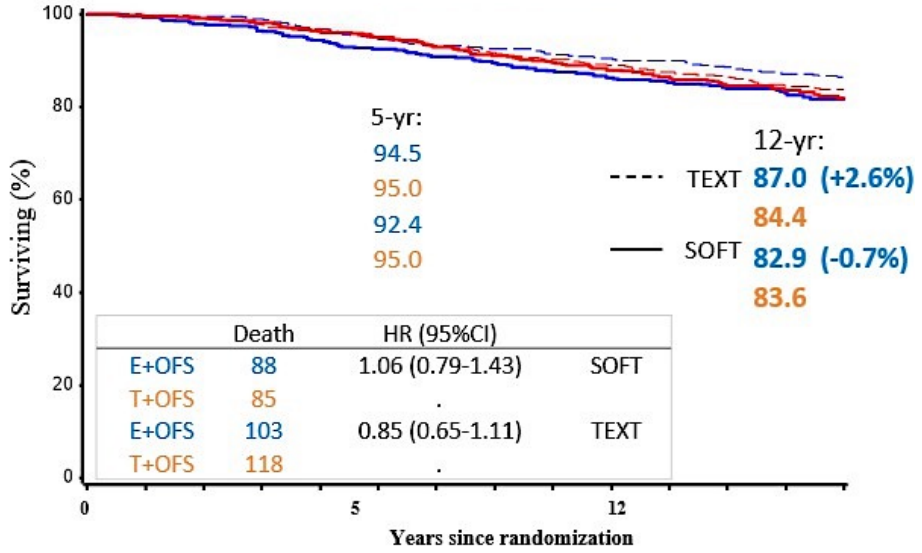
Distant recurrence-free interval



	Distant Recur	HR (95%CI)	
E+OFS	99	0.86 (0.66-1.13)	SOFT
T+OFS	114	.	
E+OFS	118	0.86 (0.67-1.11)	TEXT
T+OFS	132	.	

		0-5 years		>5 years	
		Recur	HR (95% CI)	Recur	HR (95% CI)
SOFT	E+OFS:	65	0.85 (0.61-1.19)	34	0.88 (0.56-1.41)
	T+OFS:	76	.	38	.
TEXT	E+OFS:	62	0.73 (0.52-1.01)	56	1.10 (0.75-1.61)
	T+OFS:	83	.	49	.
	At risk:	2694 pts	12086 pyfu	2166 pts	14702 pyfu

Overall survival



	Death	HR (95%CI)	
E+OFS	88	1.06 (0.79-1.43)	SOFT
T+OFS	85	.	
E+OFS	103	0.85 (0.65-1.11)	TEXT
T+OFS	118	.	

		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 and 2.4% TEXT at 12 years overall survival, -0.7% SOFT and +2.6% TEXT at 12 years

CI, confidence interval; E, exemestane; HR, hazard ratio; LN, lymph node; OFS, ovarian function suppression; T, tamoxifen.

Pagani O et al. *J Clin Oncol.* 2023;41(7):1376-1382.

Fertility Issues with chemotherapy

- If a women has never been pregnant, her fertility status is an unknown
  - Fertility declines after ~age 35, normally

- Modern chemotherapy regimens less frequently alter fertility than older ones, mostly due to alkylating dose changes
  - Delay of therapy for egg harvesting
  - Oocytes/ovarian tissue if No Acceptable Sperm on hand
  - *STRONG consideration to ovarian protection*

- *Post treatment pregnancy does NOT increase breast cancer recurrence risk [POSITIVE trial data, NEJM 2023]*

- Right now, is a REALLY BAD TIME for pregnancy, so fertility must be controlled in a definitive manner.

Breast Cancer: IPD Meta-analysis

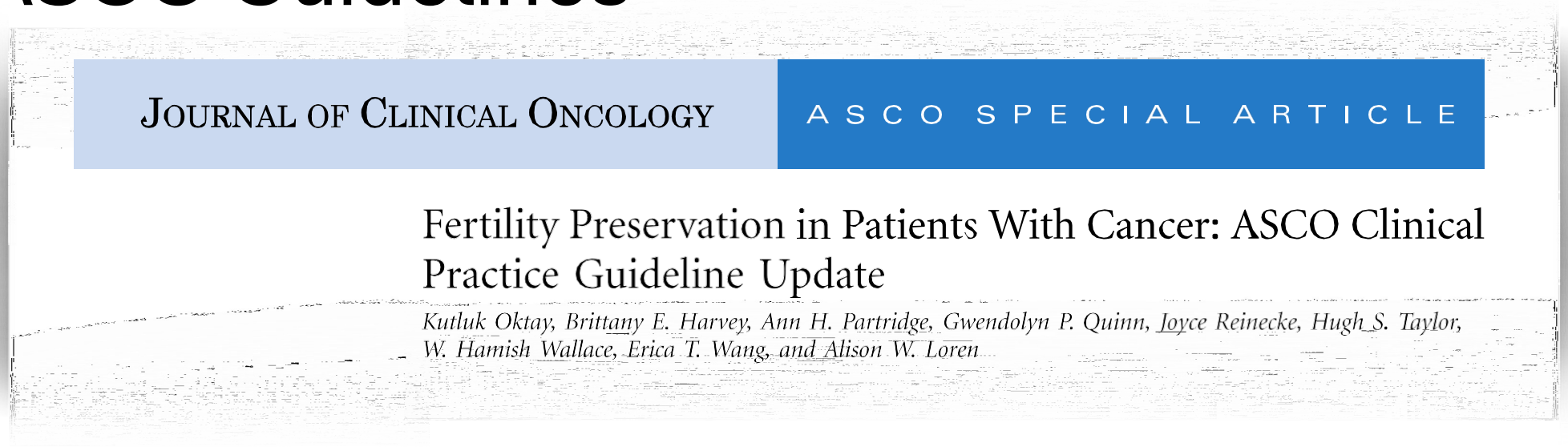
Study characteristics

	 PROMISE-GIM6[1,2]	 POEMS/SWOG S0230[3]	 Moffitt-led trial[4]	 GBG-37 ZORO[5]	 Anglo Celtic Group OPTION[6]
Definition of POI	No resumption of menstrual activity and postmenopausal levels of FSH and E2	Amenorrhea for the prior 6 months and postmenopausal levels of FSH	No maintenance of menses and no resumption of menses	No re-appearance of two consecutive menstrual periods within 21 to 35 days	Amenorrhea with elevated FSH
Timing of POI after chemotherapy	12 months	24 months	24 months	6 months	Between 12 and 24 months
Sample size	281	257	48	60	227
ER status for eligibility	ER-positive and ER-negative	ER-negative only	ER-positive and ER-negative	ER-negative only	ER-positive and ER-negative
Upper age limit for eligibility	≤ 45 years	≤ 49 years	≤ 44 years	≤ 45 years	None
Type of GnRHa	Triptorelin	Goserelin	Triptorelin	Goserelin	Goserelin

ER, estrogen receptor; FSH, follicle-stimulating hormone; GnRHa, gonadotropin-releasing hormone; POI, premature ovarian insufficiency.

1. Del Mastro L et al, *JAMA* 2011;306:269=76. 2. Lambertini M et al, *JAMA* 2015;314:2632-40. 3. Moore HCF et al, *N Eng J Med* 2015;372:923-32. 4. Munster P et al, *J Clin Oncol* 2012;30:533-38.
5. Gerber B et al, *J Clin Oncol* 2011;29:2334-41. 6. Leonard RCF et al, *Ann Oncol* 2017;28:1811-16.
Lambertini M et al. *J Clin Oncol.* 2018;36(19):1981-1990. San Antonio Breast Cancer Symposium, December 5-9, 2017.

ASCO Guidelines



"The Panel recognizes that, when proven fertility preservation methods are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. GnRHa should not be used in place of proven fertility preservation methods"

ASCO, American Society of Clinical Oncology; GnRHa, gonadotropin-releasing hormone agonist.
Oktay K et al. *J Clin Oncol.* 2018;36(19):1994-2001.

Discussion Questions

- Would you recommend adjuvant chemotherapy in addition to endocrine therapy for a 58-year-old postmenopausal patient with ER-positive, HER2-negative localized breast cancer, a 21-gene Recurrence Score of 20 and 2 positive nodes? What if she had a Recurrence Score of 8?

Module 1: HER2-Positive, Triple-Negative and Localized Breast Cancer

HER2-Positive Breast Cancer — Dr O'Shaughnessy

Triple-Negative Breast Cancer (TNBC) — Dr Bardia

Personalizing Adjuvant Therapy for Patients with HR-Positive Breast Cancer — Dr Borges

Current Role of CDK4/6 Inhibitors in the Localized Setting — Dr Burstein

Current Role of CDK4/6 Inhibitors in Early Stage Breast Cancer

Harold J. Burstein, MD, PhD

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Disclosures

No relevant conflicts of interest to disclose.

Adjuvant eBC Trials With CDK4/6 Inhibitors

	PALLAS[1,2]	monarchE[3,4]	PENELOPE-B[5,6]	NATALEE[7]
Sponsor/collaborator	ABCSG/AFT	Eli Lilly/NSABP	GBG/Pfizer/AGO/ NSABP/BIG	Novartis/TRIO
CDK4/6 inhibitor	Palbociclib	Abemaciclib	Palbociclib	Ribociclib
Sample size/sites	5760/406	4580/612	1250/267	5101/395
Design	Phase 3 randomized open label	Phase 3 randomized open label	Phase 3 randomized placebo-controlled	Phase 3 randomized open label
Patient population	Stage II-III (Stage IIA capped 1000 pts)	High-risk N+ plus 1 other risk factor (size, grade, Ki67)	Very high-risk with residual disease after neoadjuvant chemo (CPS-EG score ≥ 3 or 2 and N+)	Stage II-III
Duration of CDK4/6 therapy	**2 years (26 cycles)**	**2 years (26 cycles)**	**1 year (13 cycles)**	**3 years (39 cycles)**
Primary endpoint	iDFS	iDFS	iDFS	iDFS
Median duration of follow-up	43 months	42 months	43 months	28 months

This information is not presented to compare the efficacy or safety profile of the discussed products. No implication of superiority or inferiority is intended or should be inferred. Cross-trial comparisons are unreliable as they are likely to be confounded due to differences in study design and patient population.

AFT=Alliance Foundation Trials, LLC; AGO=German Gynecological Oncology Working Group; BIG=Breast International Group; GBG=German Breast Group; iDFS=invasive disease-free survival; NSABP=National Surgical Adjuvant Breast and Bowel Project; TRIO=Translation Research in Oncology.

1. PALLAS. Updated June 15, 2023. Accessed October 19, 2023. https://clinicaltrials.gov/ct2/show/NCT02513394 2. Mayer EL et al. 2020 ESMO Congress. LBA12. 3. monarchE. Updated July 14, 2023. Accessed October 19, 2023. https://clinicaltrials.gov/ct2/show/NCT03155997 4. Rastogi P et al. 2020 SABCS. GS1-01. 5. PENELOPE-B. Updated April 12, 2022. Accessed October 19, 2023. https://clinicaltrials.gov/ct2/show/NCT01864746 6. Loibl S et al. 2020 SABCS. 7. NATALEE. Updated October 3, 2023. Accessed October 19, 2023. https://clinicaltrials.gov/ct2/show/NCT03701334

PALLAS: Phase III open-label study of palbociclib and adjuvant endocrine therapy

Eligibility:
- Stage II-III HR+/HER2- breast cancer
- Completion of prior surgery, +/- chemo, RT
- Within 12 mo of diagnosis
- Within 6 mo of starting adjuvant endocrine treatment
- FFPE tumor block submitted

N=5,600

Stratification:
- **Stage** (IIA vs IIB/III)
- **Chemotherapy** (yes vs no)
- **Age** (≤50 vs >50)
- **Geographic region** (N. America vs Europe vs Other)

RANDOMIZE

1:1

Arm A
Palbociclib x 2 years
(125 mg qd, 3 wks on/1 wk off)
+
Endocrine Treatment*

Arm B
Endocrine Treatment

* Aromatase inhibitor or tamoxifen, +/- LHRH agonist

Primary Endpoint: invasive Disease-Free Survival (iDFS)

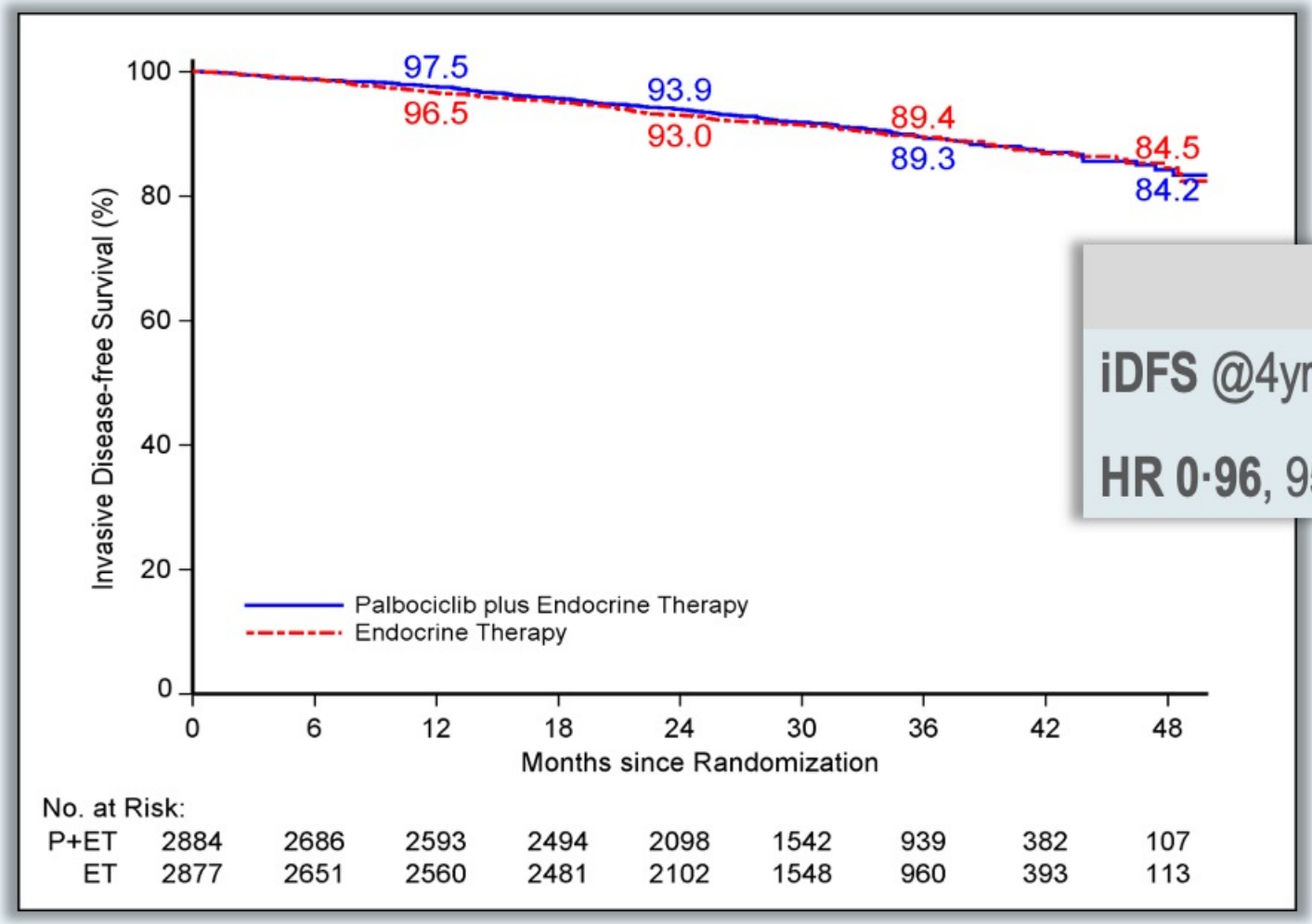
PALLAS
ABCSG 42 / AFT-05 / BIG 14-03

Sponsored by AFT and ABCSG, in cooperation with PrECOG, BIG, GBG, NSABP, and supported by Pfizer.

ABCSG ALLIANCE FOUNDATION TRIALS, LLC BIG Pfizer Oncology

Mayer et al. Lancet Oncol 2021; Gnant et al. JCO 2022

PALLAS: Primary Endpoint iDFS



	Palbociclib + ET	ET alone
iDFS @4yrs	84.2%	84.5%

HR 0·96, 95% CI 0·81-1·14; log-rank p = 0·65

253 vs 263 iDFS events, no difference in event categories (distant recurrences, second primaries, local, regional, contralateral, deaths without recurrence)

Efficacy population:
Intent-to-treat (ITT) principle, with patients withdrawing consent for all data excluded

At a median follow-up of 31 months, **no significant difference in 4-year iDFS** was observed

Study Design

N=1250
- HR+/HER2- breast cancer
- no pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

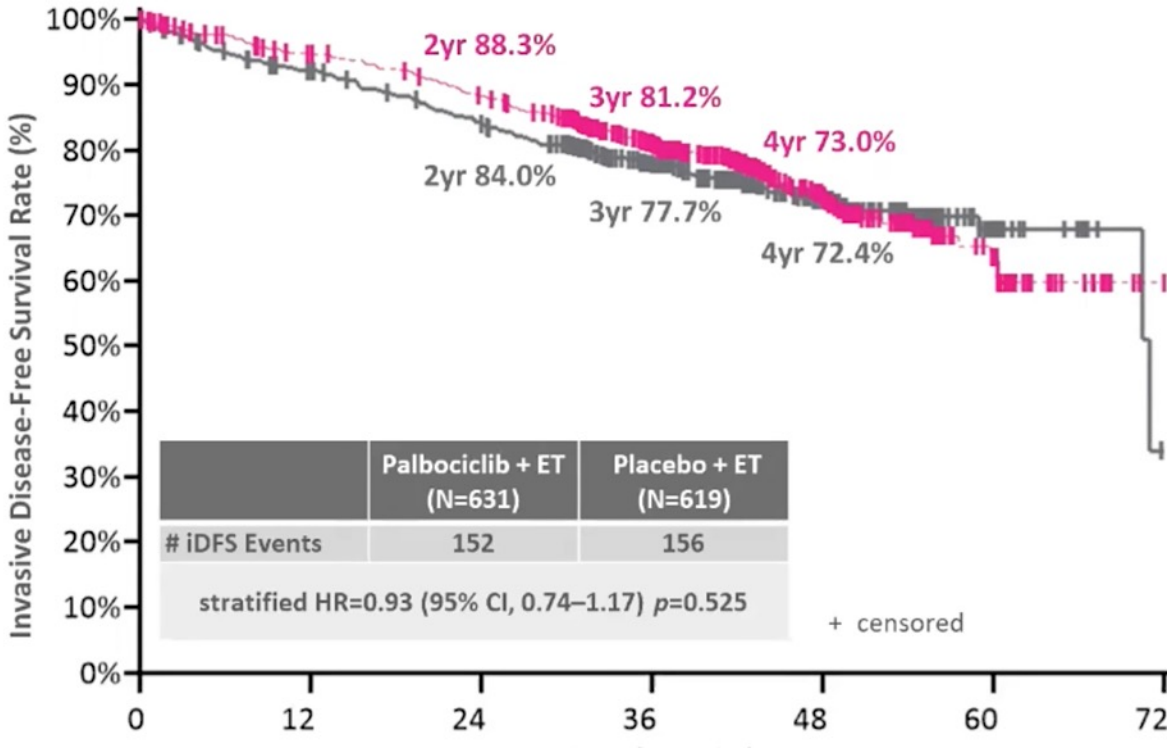
Primary Endpoint: iDFS

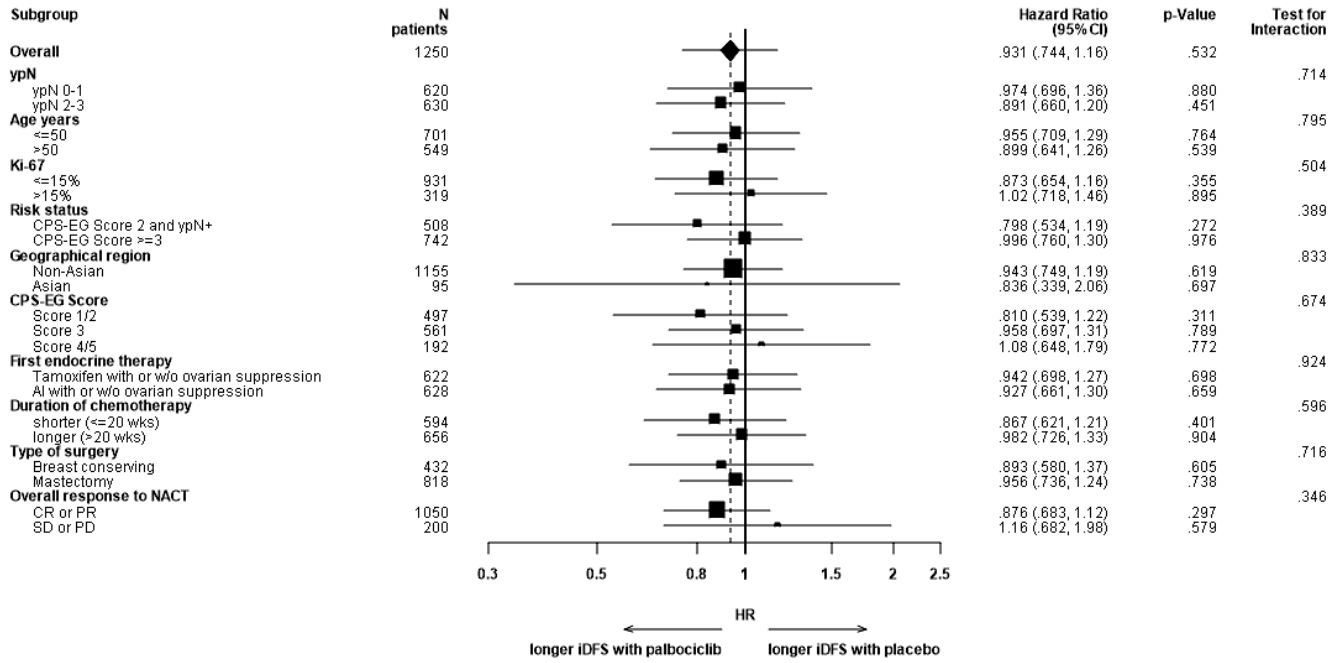
Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+

All patients will receive concomitantly endocrine therapy according to local standards

PENELOPE-B: ClinicalTrials.gov NCT01864746

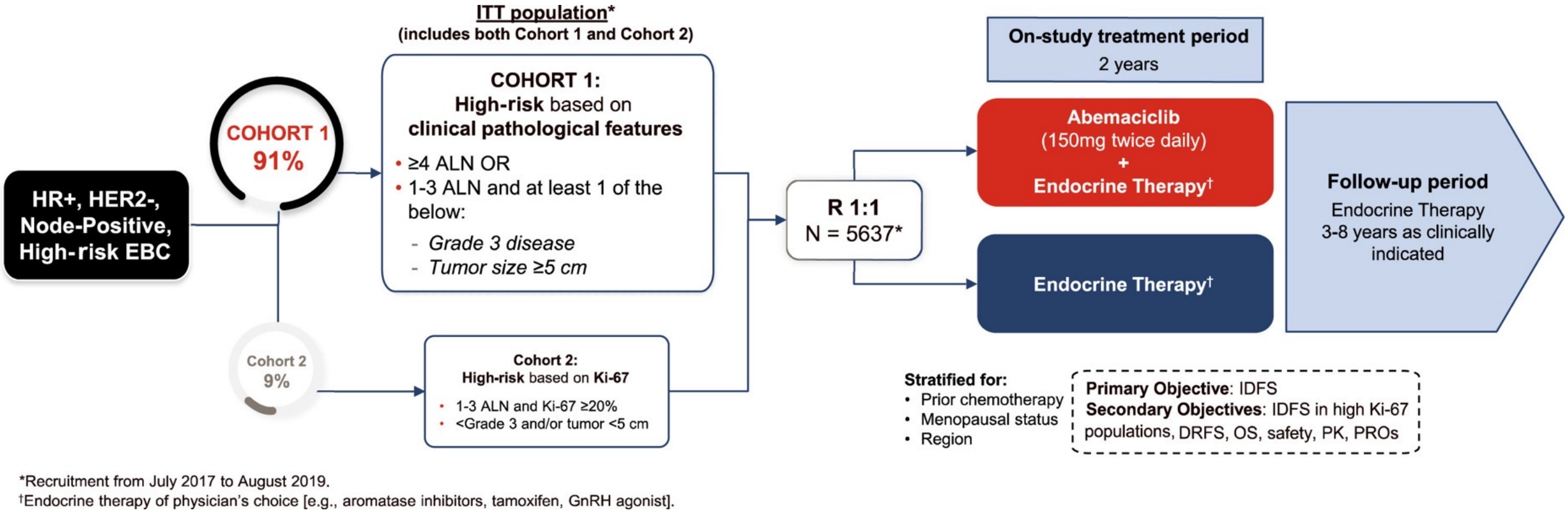
PENELOPE-B Efficacy





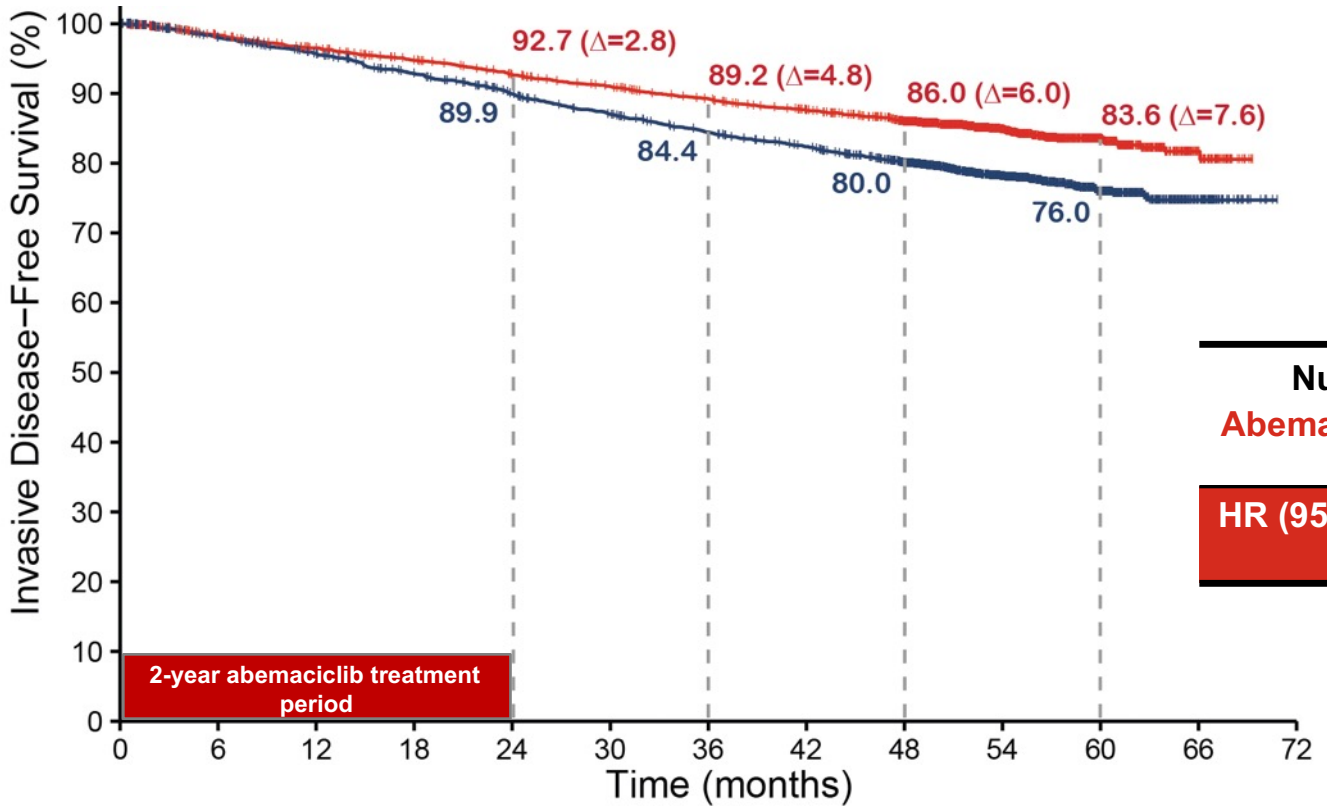
Loibl S et al. *J Clin Oncol*. 2021 May 10;39(14):1518-1530.

monarchE Study Design (NCT03155997)



*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

monarchE Primary Endpoint: Sustained IDFS Benefit in ITT at 5y



Number of IDFS events

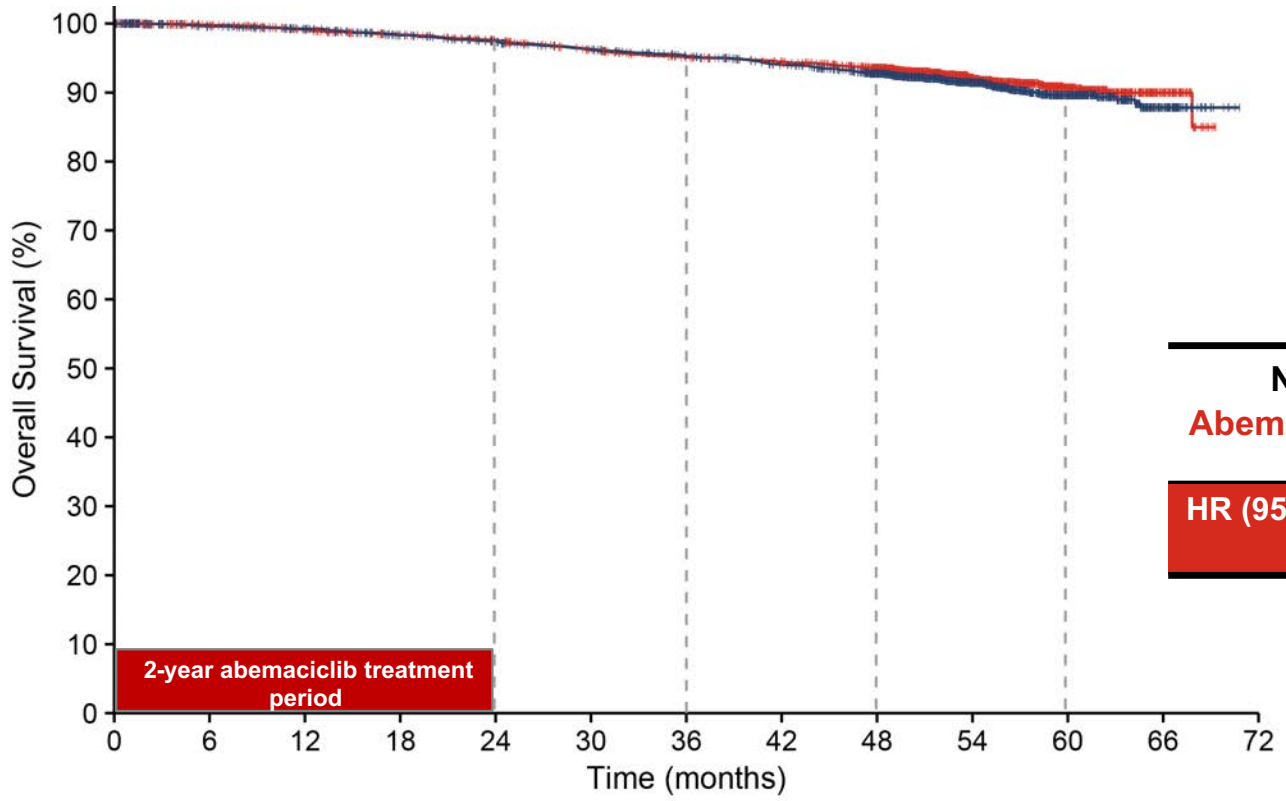
Abemaciclib + ET	ET Alone
407	585

HR (95% CI): 0.680 (0.599, 0.772)
Nominal p <0.001

32% reduction in the risk of developing an IDFS event.
The KM curves continue to separate and the absolute difference in IDFS rates between arms was 7.6% at 5 years

Nadia Harbeck, MD
ESMO, Madrid, Spain. 20 October 2023

monarchE: OS Update



Number of OS events

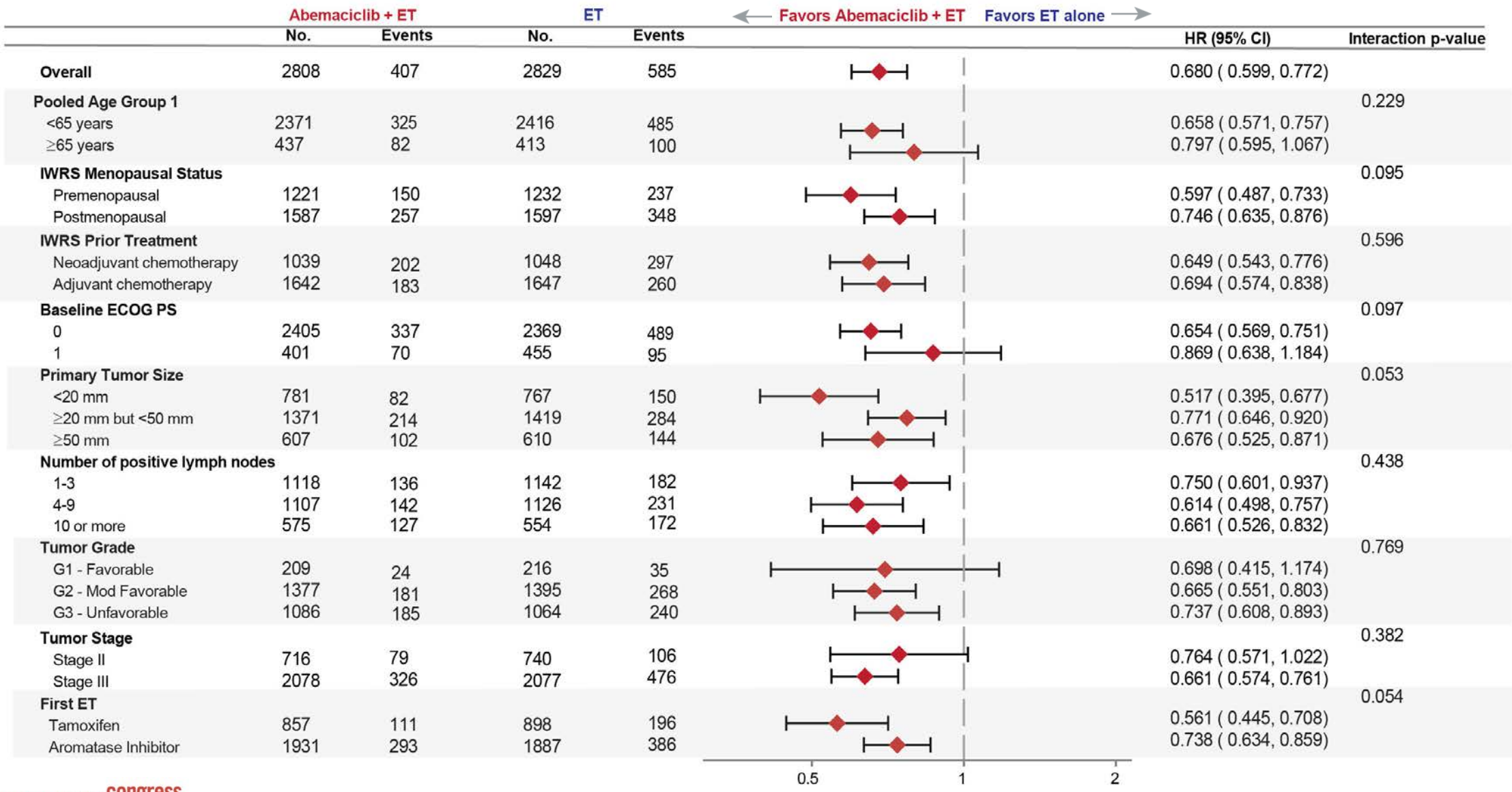
Abemaciclib + ET	ET Alone
208	234

HR (95% CI): 0.903 (0.749, 1.088)
p=0.284

At OS IA3 statistical significance was not reached for OS

Nadia Harbeck, MD
ESMO, Madrid, Spain. 20 October 2023

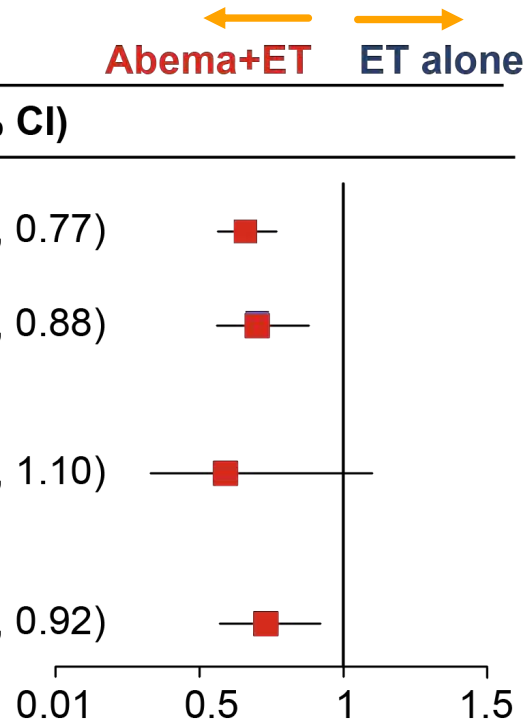
Consistent IDFS Benefit Observed in Selected Subgroups*



*Region of enrollment and Progesterone status data not shown

Treatment Benefit Observed in Inferred Oncotype DX® Risk Scores

	Abemaciclib + ET		ET Alone		
	Events/n (%)	4yr IDFS Rate (95% CI)	Events/n (%)	4yr IDFS Rate (95% CI)	HR (95% CI)
ITT	407/2808 (14%)	86.0 (84.7−87.3)	585/2829 (21%)	80.0 (78.5−81.6)	0.68 (0.60, 0.77)
Biomarker Subset	138/605 (23%)	77.4 (74.1−80.9)	182/585 (31%)	69.8 (66.1−73.7)	0.70 (0.56, 0.88)
Inferred Oncotype-RNA score <=25	18/173 (10%)	90.2 (85.8−94.9)	28/165 (17%)	84.2 (78.7−90.1)	0.59 (0.33, 1.10)
Inferred Oncotype-RNA score>25	120/432 (28%)	72.3 (68.1−76.8)	154/420 (37%)	64.1 (59.6−69)	0.73 (0.57, 0.92)



Interaction p-value (inferred Oncotype DX scores high and low) **= 0.532**

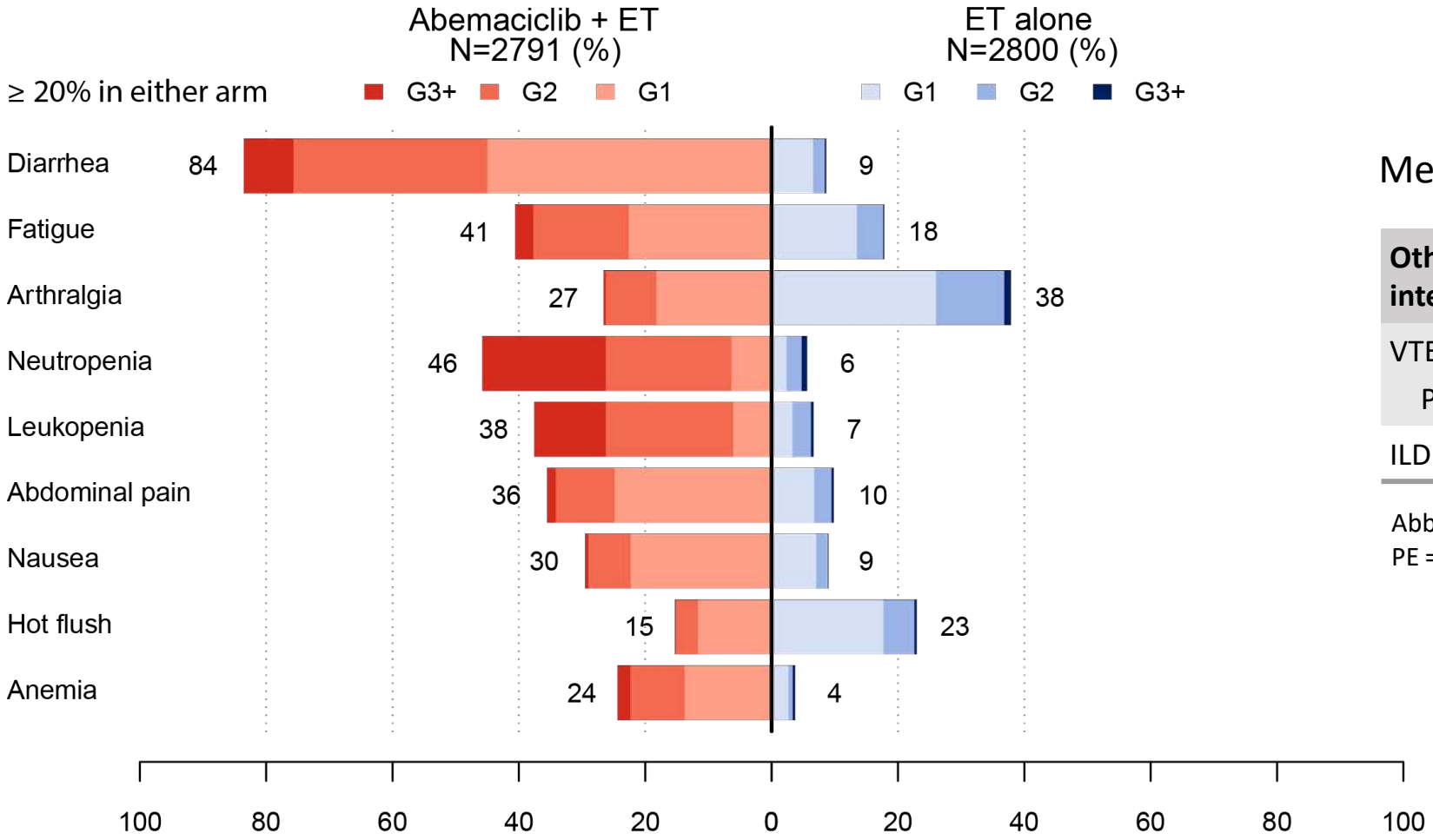
- The selected biomarker subset is enriched for IDFS events using case-cohort design
- IDFS rates are presented as indicative of relative prognosis across subtypes but do not inform the actúal risk of recurrence within each subtype because of IDFS enrichment

Older Patients Derived Similar Abemaciclib Benefit to ITT Population

	IDFS			DRFS		
	ITT	<65	≥65	ITT	<65	≥65
Events/N						
Abemaciclib + ET	**336**/2808	**270**/2371	**66**/437	**281**/2808	**230**/2371	**51**/437
ET alone	**499**/2829	**414**/2416	**85**/413	**421**/2829	**353**/2416	**68**/413
HR (95% CI)	**0.664** (0.578, 0.762)	**0.646** (0.554, 0.753)	**0.767** (0.556, 1.059)	**0.659** (0.567, 0.767)	**0.647** (0.548, 0.764)	**0.748** (0.520, 1.077)
Interaction p-value	NA	0.35		NA	0.49	
4-year rate, %						
Abemaciclib + ET	**85.8**	**86.5**	**82.0**	**88.4**	**88.8**	**86.1**
ET alone	**79.4**	**79.8**	**76.8**	**82.5**	**82.6**	**81.5**
Absolute benefit	**6.4**	**6.7**	**5.2**	**5.9**	**6.2**	**4.6**

Consistent results were observed in Cohort 1

monarchE: Toxicity



Median duration of abemaciclib: 23.7 mo

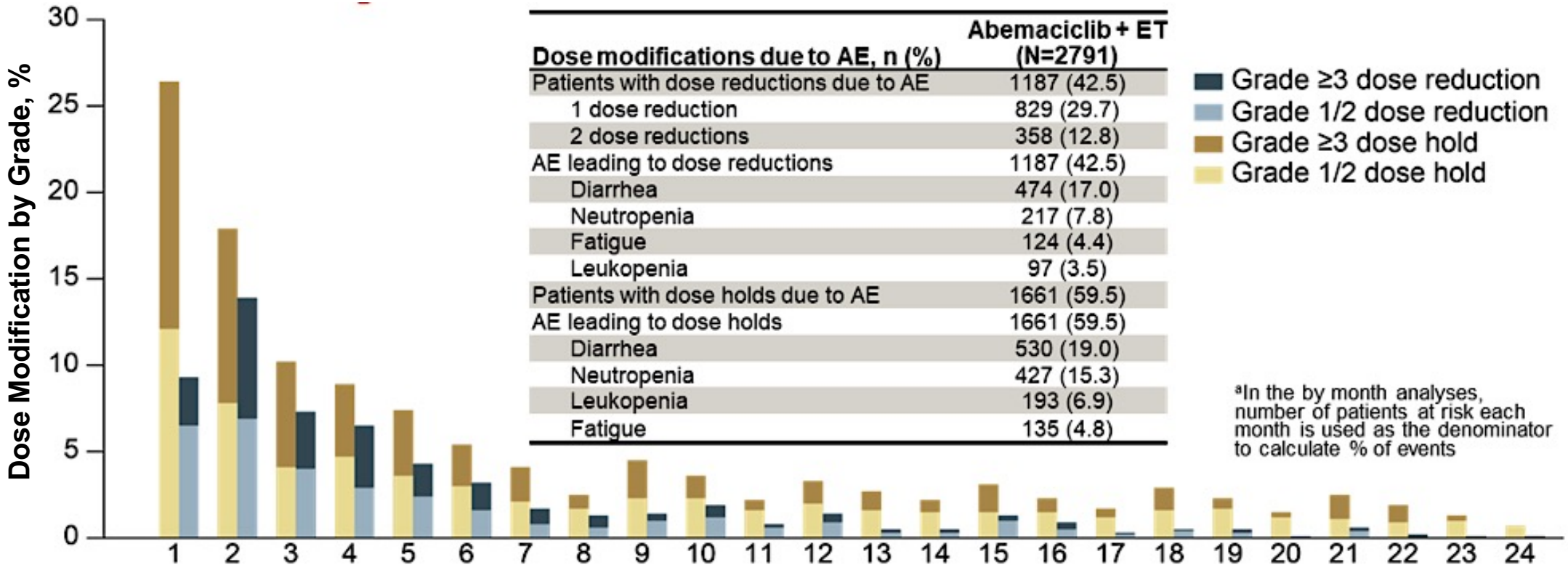
Other events of interest, any grade	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.6
PE	1.0	0.1
ILD	3.2	1.3

Abbreviations: VTE = venous thromboembolic event; PE = pulmonary embolism; ILD = Interstitial lung disease

Johnston SRD et al. *Lancet Oncol*. 2023;24(1):77-90.

monarchE: Dose Modifications Were Common and Occurred Early

- 42.5% required dose reduction, most frequently in first few months
- Most common toxicities leading to DR: diarrhea, neutropenia, fatigue



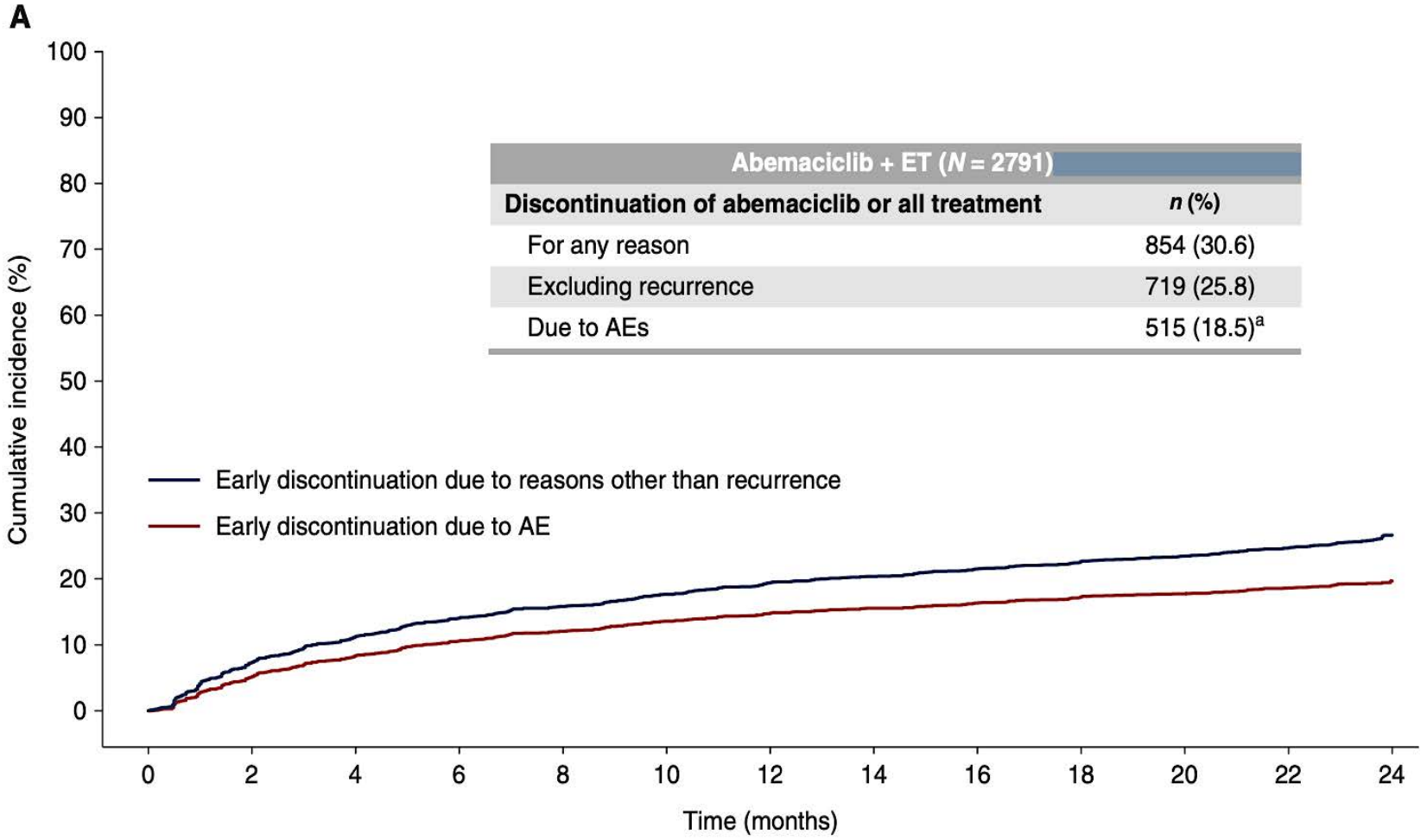
Dose modifications due to AE, n (%)	Abemaciclib + ET (N=2791)
Patients with dose reductions due to AE	1187 (42.5)
1 dose reduction	829 (29.7)
2 dose reductions	358 (12.8)
AE leading to dose reductions	1187 (42.5)
Diarrhea	474 (17.0)
Neutropenia	217 (7.8)
Fatigue	124 (4.4)
Leukopenia	97 (3.5)
Patients with dose holds due to AE	1661 (59.5)
AE leading to dose holds	1661 (59.5)
Diarrhea	530 (19.0)
Neutropenia	427 (15.3)
Leukopenia	193 (6.9)
Fatigue	135 (4.8)

[a]In the by month analyses, number of patients at risk each month is used as the denominator to calculate % of events

Rugo HS et al. *Ann Oncol.* 2022;33:616-627.

monarchE: Patient Disposition

- 30% discontinued abemaciclib early; most within the first 6 months of treatment
- 18.5% of discontinuation was due to AEs
- Over half did not have a prior dose reduction

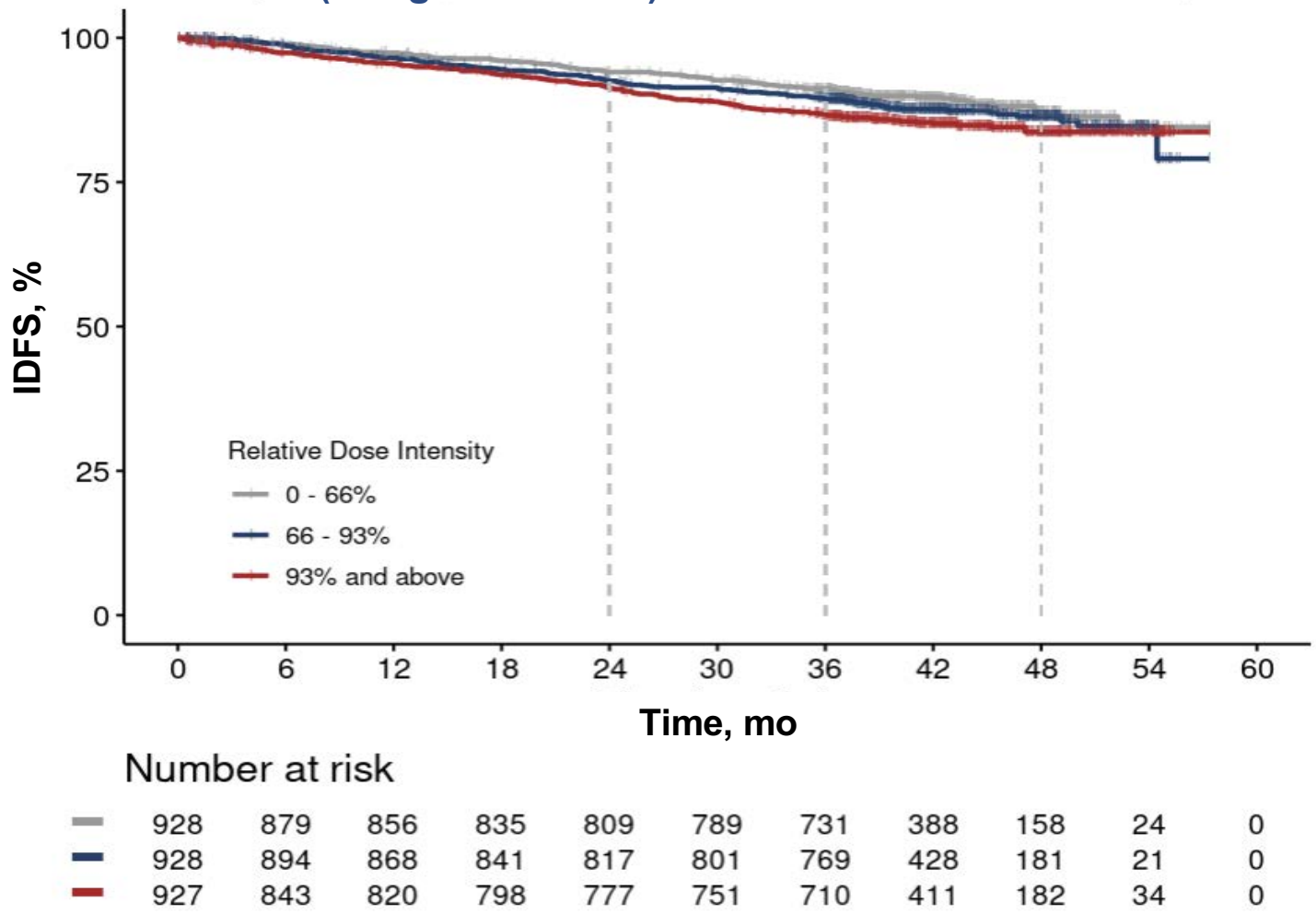


Abemaciclib + ET (*N* = 2791)	
Discontinuation of abemaciclib or all treatment	***n*** **(%)**
For any reason	854 (30.6)
Excluding recurrence	719 (25.8)
Due to AEs	515 (18.5)[a]

Rugo HS et al. *Ann Oncol.* 2022;33:616-627.

monarchE: Abemaciclib Benefit Is Maintained With Dose Modifications

IDFS according to RDI in patients treated with abemaciclib (all ages included)



- Dose adjustments result in lower relative dose intensity (RDI)[a]; to explore the impact of dose adjustments on abemaciclib efficacy:
  - Patients treated with abemaciclib were classified into three equal-sized subgroups by RDI
  - IDFS rates were estimated within each subgroup
- 4-y IDFS rates were generally consistent (87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest)
  - Similar findings were observed in patients treated with abemaciclib in cohort 1

[a] RDI is defined as the average daily dose of abemaciclib received over the treatment duration, relative to the full dose (150 mg BID).

1. Hamilton EP et al. ASCO 2023. Abstract 501.

NATALEE: Study Design and Methods

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **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]

RIB
400 mg/day
3 weeks on/1 week off
for 3 years

+

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

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

Primary End Point
- iDFS using STEEP criteria

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

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

Endpoints included in this presentation

Statistical comparisons were performed using a Cox proportional hazards model and the Kaplan-Meier method

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

Data cutoff: 29 April 2024

ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; RIB, ribociclib; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.

[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.

1. ClinicalTrials.gov. Accessed March 15, 2024. https://clinicaltrials.gov/ct2/show/NCT03701334. **2.** Slamon DJ, et al. Poster presented at: ASCO 2019. Poster TPS597. **3.** Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:1-16. **4.** Hortobagyi, G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

NATALEE: Broader Inclusion

AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]
Stage IA	T1N0	✗
Stage IB	T0N1mi	✗
	T1N1mi	✗
Stage IIA	T0N1	✓
	T1N1	✓
	T2N0	G3, or G2 with Ki-67 ≥ 20% or high genomic risk[c]
Stage IIB	T2N1	✓
	T3N0	✓
Stage IIIA	T0N2	✓
	T1N2	✓
	T2N2	✓
	T3N1	✓
	T3N2	✓
Stage IIIB	T4N0	✓
	T4N1	✓
	T4N2	✓
Stage IIIC	Any TN3	✓

Baseline characteristics

Parameter	RIB + NSAI n = 2549	NSAI Alone n = 2552	All Patients N = 5101
Age, median (min-max), years	52 (24-90)	52 (24-89)	52 (24-90)
Menopausal status, n (%)			
Men[a] and premenopausal women	1126 (44)	1132 (44)	2258 (44)
Postmenopausal women	1423 (56)	1420 (56)	2843 (56)
Anatomical stage,[b,c] n (%)			
Stage IIA	479 (19)	521 (20)	1000 (20)
Stage IIB	532 (21)	513 (20)	1045 (20)
Stage III	1528 (60)	1512 (59)	3040 (60)
Nodal status at diagnosis, n (%)			
NX	272 (11)	264 (10)	536 (11)
N0	694 (27)	737 (29)	1431 (28)
N1	1050 (41)	1049 (41)	2099 (41)
N2/N3	483 (19)	467 (18)	950 (19)
Prior ET, n (%)[d]			
Yes	1824 (72)	1801 (71)	3625 (71)
Prior (neo)adjuvant CT, n (%)			
Yes	2249 (88)	2245 (88)	4494 (88)
ECOG PS, n (%)			
0	2106 (83)	2132 (84)	4238 (83)
1	440 (17)	418 (16)	858 (17)

Dana-Farber Cancer Institute

Slamon DJ et al. ASCO 2023. Abstract LBA500.

Different Eligibility, Different Populations

NATALEE

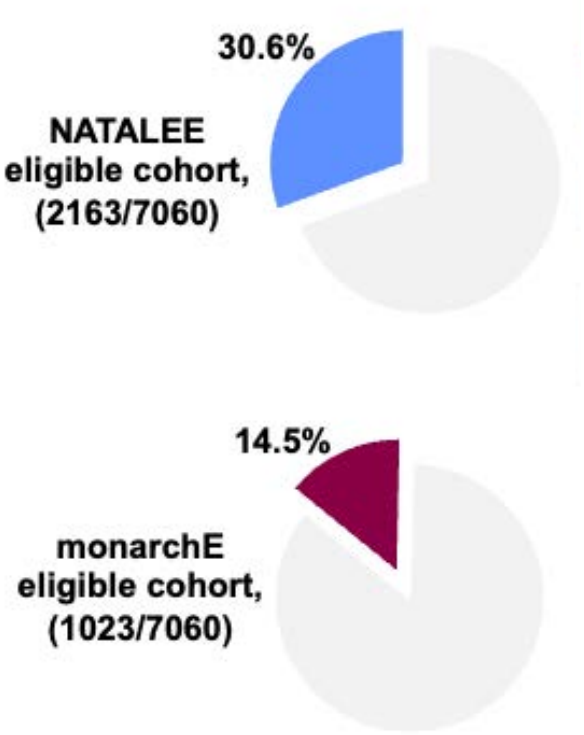
- N1, N2
- N0:
  - Grade 3
  - Grade 2 + high risk:
  - Ki-67 ≥ 20%
  - Onco*type* ≥ 26 or
  - High risk via genomic risk profiling

monarchE

- N2
- N1:
  - Grade 3
  - T ≥5 cm
  - Ki-67 ≥ 20%

AJCC Stage	TN	NATALEE	monarchE
Stage 1A	T1N0	X	X
Stage IB	T0N1mi	X	X
	T1N1mi	X	X
Stage IIA	T0N1	✓	X
	T1N1	✓	G3 or Ki67 ≥20%
	T2N0	G3, or G2 with Ki67 ≥20% or high genomic risk	X
Stage IIB	T2N1	✓	G3 or Ki67 ≥20%
	T3N0	✓	X
Stage IIIA	T0N2	✓	✓
	T1N2	✓	✓
	T2N2	✓	✓
	T3N1	✓	✓
	T3N2	✓	✓
Stage IIIB	T4N0	✓	X
	T4N1	✓	✓
	T4N2	✓	✓
Stage IIIC	AnyTN3	✓	✓

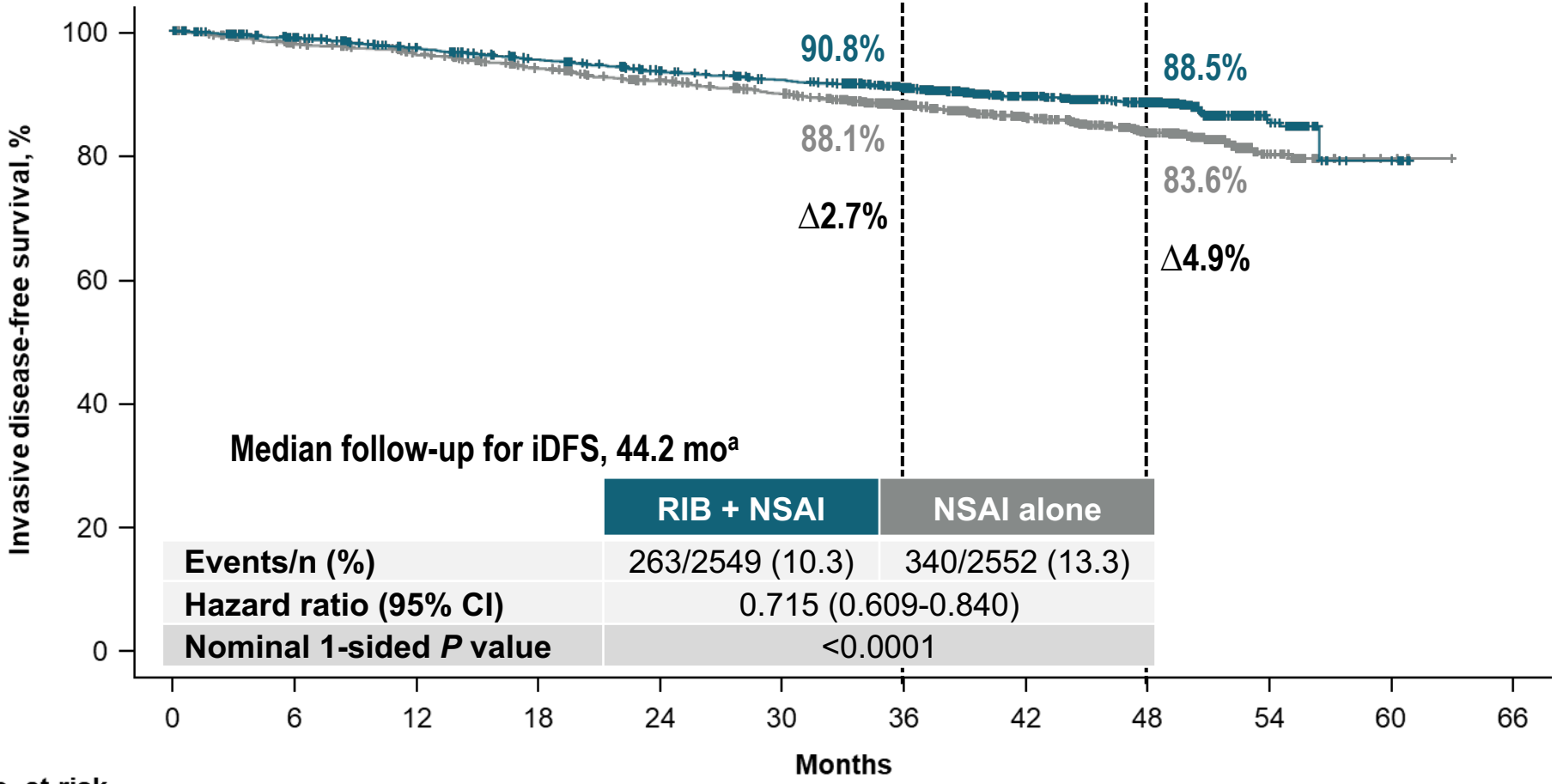
US EHR Analysis of HR+ eBC



Tarantino et al, ESMO 2024

iDFS in ITT Population

Significant iDFS benefit with RIB + NSAI after the planned 3-y treatment

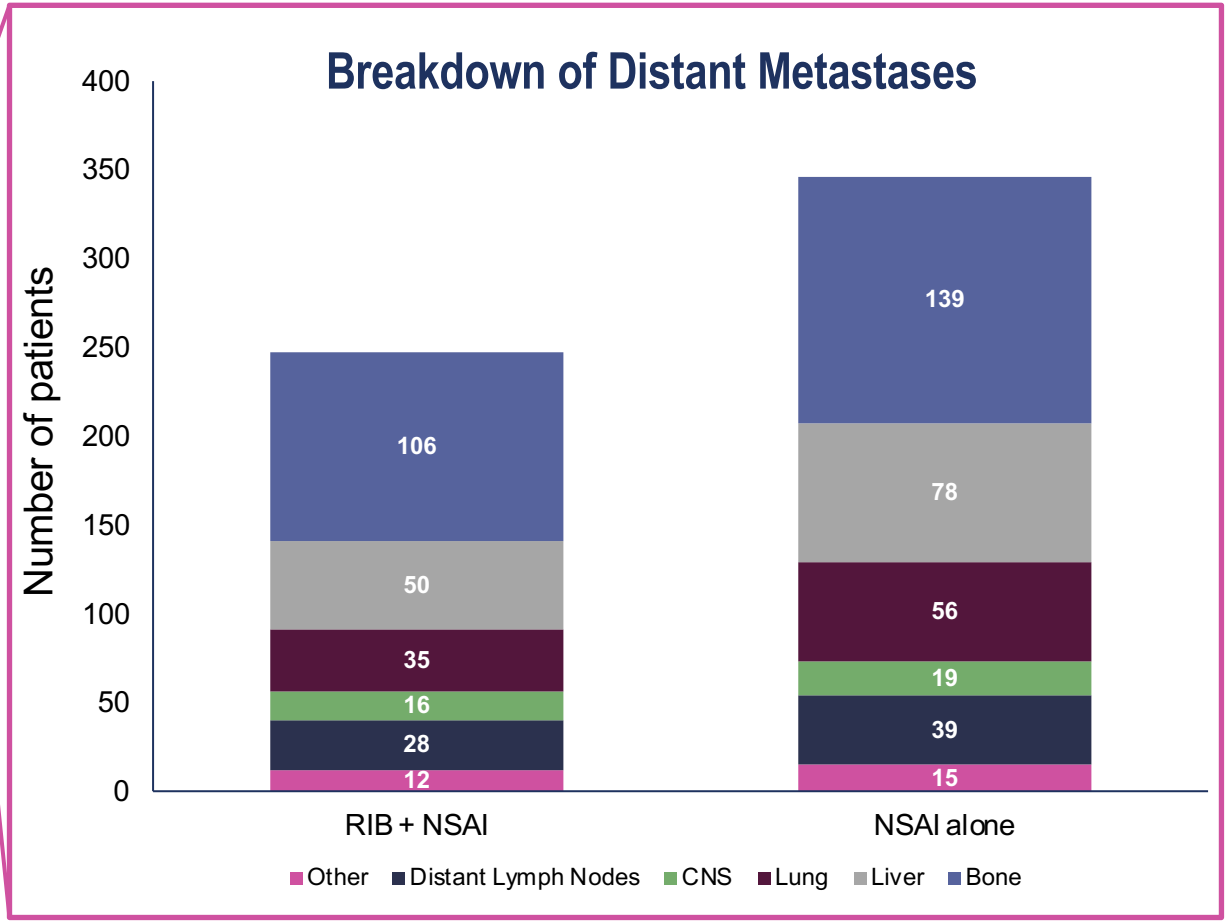


iDFS, invasive disease-free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

iDFS Events in ITT Population

The majority of iDFS events were distant recurrences, which were more common in the NSAI only arm

Type and site of first iDFS event, n (%)	RIB + NSAI n=2549	NSAI Alone n=2552
Distant recurrence	176 (6.9)	246 (9.6)
Local/regional invasive recurrence	25 (1.0)	49 (1.9)
Second primary nonbreast cancer	39 (1.5)	40 (1.6)
Death	17 (0.7)	11 (0.4)
Invasive contralateral breast tumor	11 (0.4)	10 (0.4)
Invasive ipsilateral breast tumor	8 (0.3)	9 (0.4)

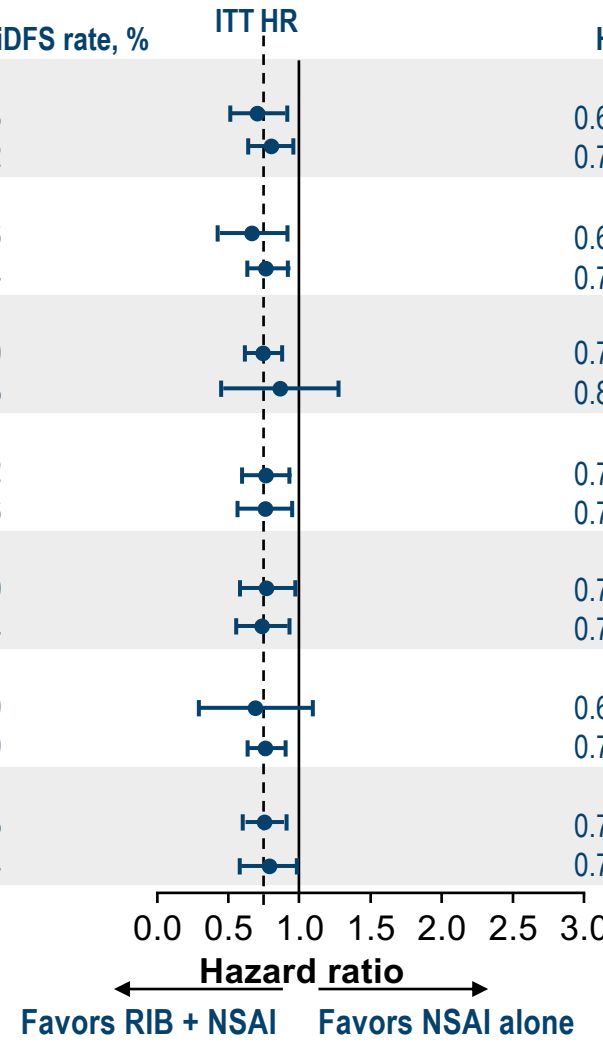


CNS, central nervous system; iDFS, invasive disease–free survival; ITT, intent to treat; NE, not estimable; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

iDFS Across Key Prespecified Subgroups

Consistent iDFS benefit across subgroups

Subgroup	RIB + NSAI Events/n	4-y iDFS rate, %	NSAI alone Events/n	4-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	99/1125	90.7	137/1132	85.3	0.677	0.523-0.877
Postmenopausal women	164/1424	86.8	203/1420	82.2	0.760	0.619-0.933
AJCC stage						
Stage II	62/1012	93.9	96/1034	89.6	0.644	0.468-0.887
Stage III	200/1527	84.3	244/1512	78.4	0.737	0.611-0.888
Prior CT						
Yes	238/2249	88.2	309/2245	83.0	0.715	0.604-0.846
No	25/300	90.7	31/307	87.5	0.827	0.488-1.401
Region						
North America/Western Europe/Oceania	151/1563	88.9	195/1565	84.2	0.726	0.587-0.898
Rest of world	112/986	88.0	145/987	82.6	0.722	0.564-0.925
Ki-67 status[a]						
Ki-67 ≤20%	106/1199	89.9	142/1236	85.9	0.737	0.573-0.948
Ki-67 >20%	113/920	86.3	149/937	80.4	0.709	0.555-0.905
Nodal status[b,c]						
N0	23/285	92.1	38/328	87.0	0.666	0.397-1.118
N1-N3	240/2261	88.0	301/2219	83.0	0.731	0.617-0.866
Prior ET						
Yes	176/1830	89.2	227/1807	84.5	0.718	0.589-0.874
No	87/719	86.7	113/745	81.4	0.752	0.568-0.994



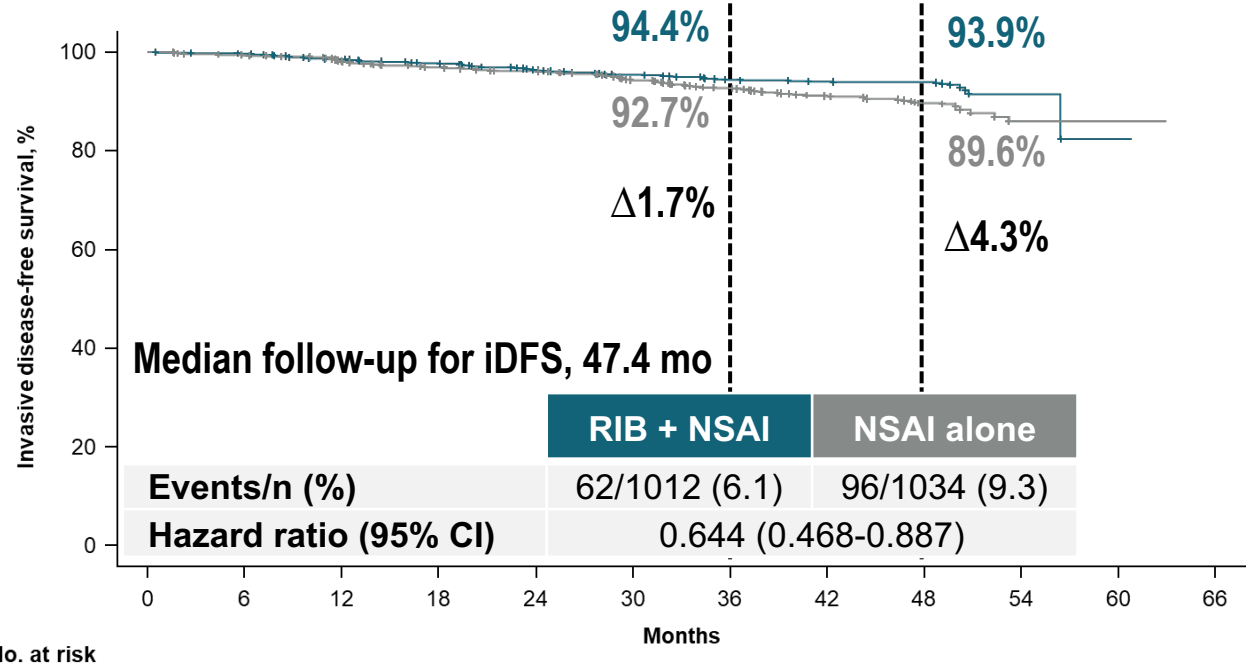
AJCC, American Joint Committee on Cancer; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease–free survival; ITT, intent to treat; N, node; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

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

iDFS by Stage

RIB + NSAI demonstrated an increased magnitude of iDFS benefit over time for stage II/III disease

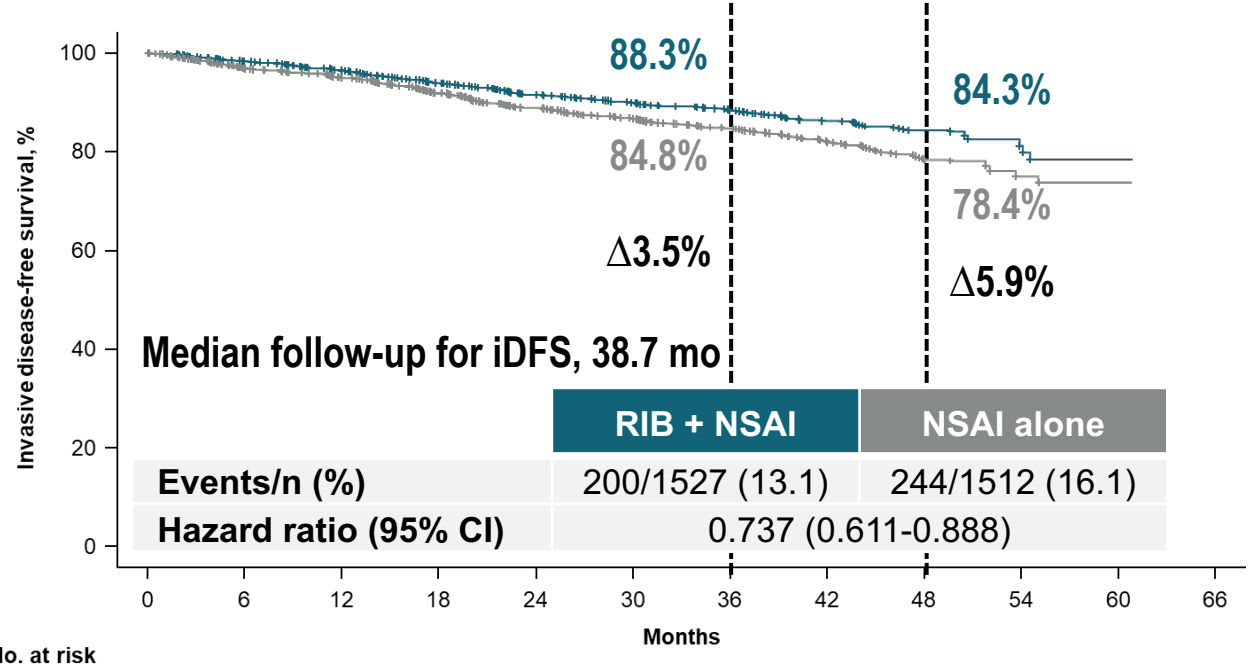
Stage II



	RIB + NSAI	NSAI alone
Events/n (%)	62/1012 (6.1)	96/1034 (9.3)
Hazard ratio (95% CI)	0.644 (0.468-0.887)	

No. at risk												
RIB + NSAI	1012	931	904	885	862	846	825	796	513	95	7	0
NSAI alone	1034	948	924	894	874	848	812	772	494	85	5	0

Stage III



	RIB + NSAI	NSAI alone
Events/n (%)	200/1527 (13.1)	244/1512 (16.1)
Hazard ratio (95% CI)	0.737 (0.611-0.888)	

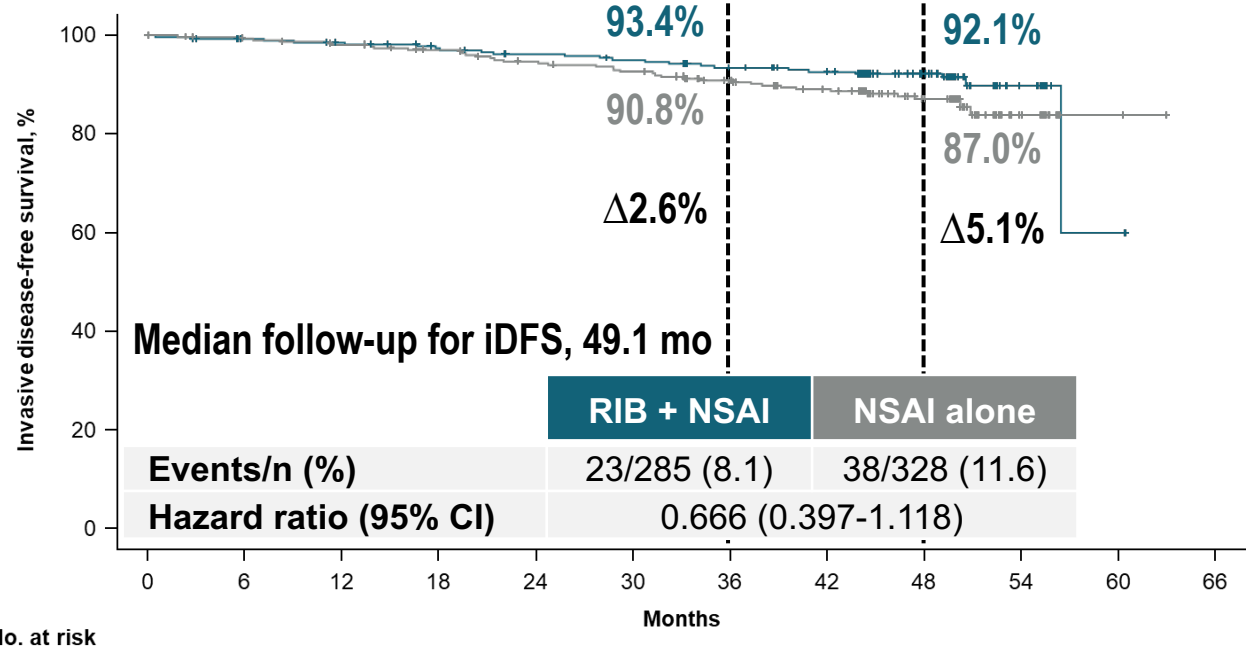
No. at risk												
RIB + NSAI	1527	1410	1362	1313	1262	1223	1009	676	398	60	1	0
NSAI alone	1512	1288	1240	1184	1128	1083	871	590	352	65	1	0

iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

iDFS by Nodal Status

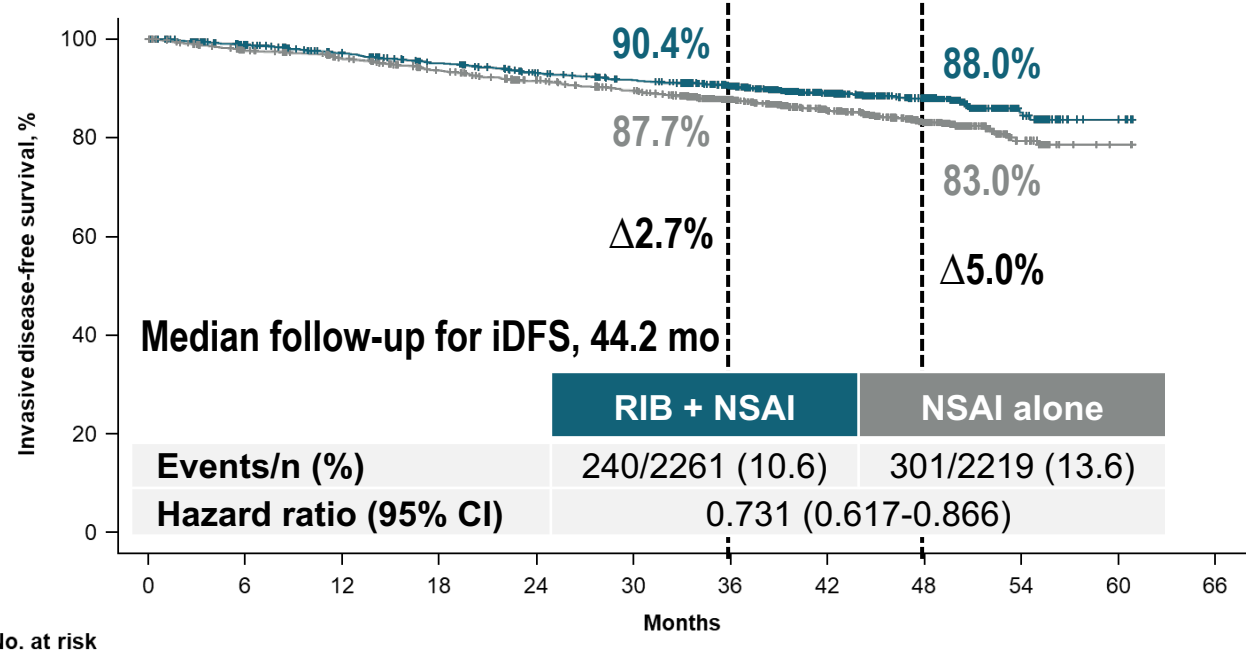
RIB + NSAI showed an increasing magnitude of iDFS benefit over time for patients with N0 or N1-3 disease

N0



No. at risk												
RIB + NSAI	285	262	258	250	244	240	230	221	156	37	2	0
NSAI alone	328	300	294	287	277	270	252	234	156	33	2	0

N1-3



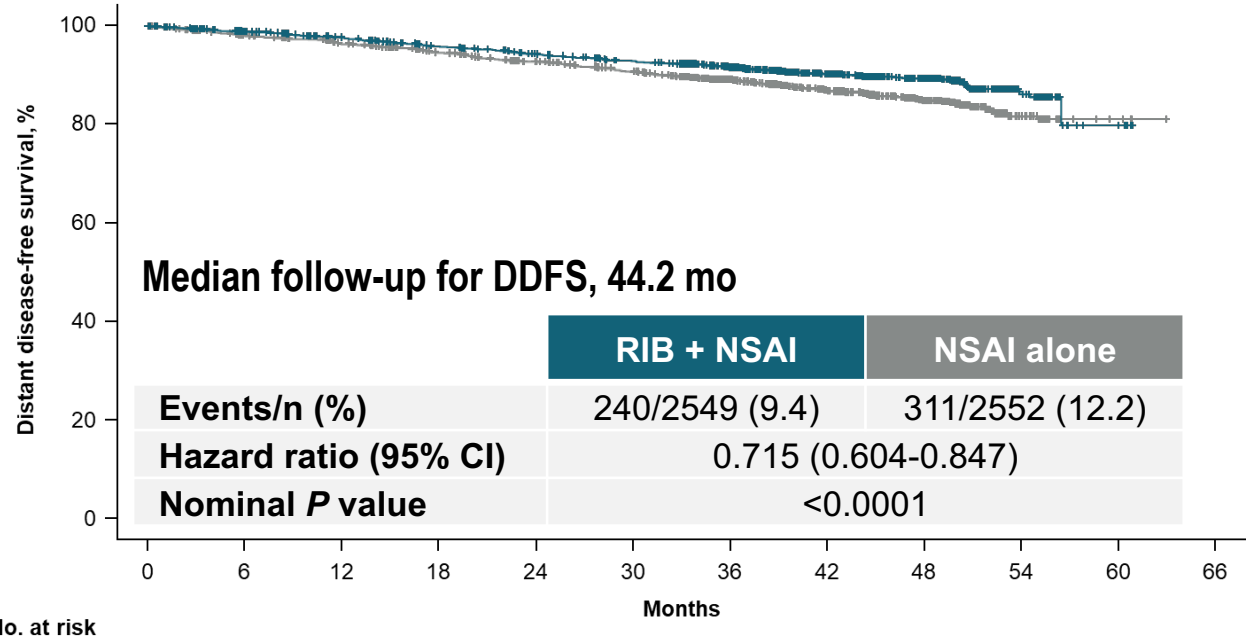
No. at risk												
RIB + NSAI	2261	2086	2014	1954	1886	1835	1612	1258	758	118	6	0
NSAI alone	2219	1937	1872	1793	1727	1663	1433	1130	689	117	4	0

iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Key Secondary Efficacy Endpoints

RIB + NSAI continued to improve DDFS and showed a positive trend for OS

DDFS

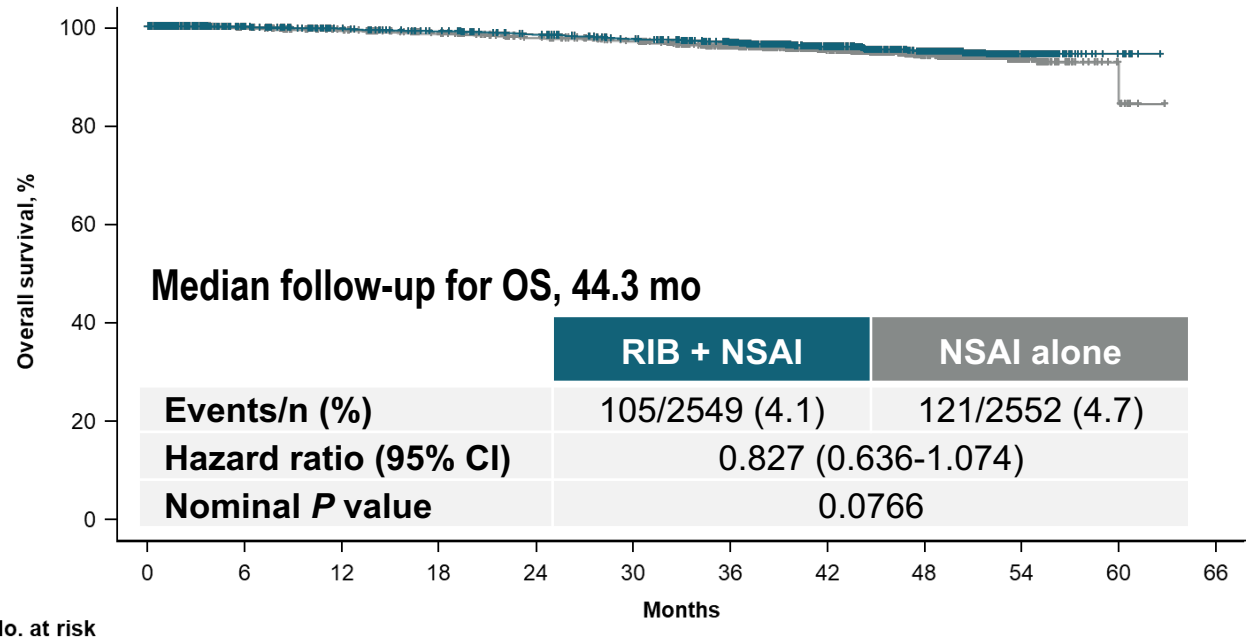


Median follow-up for DDFS, 44.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	240/2549 (9.4)	311/2552 (12.2)
Hazard ratio (95% CI)	0.715 (0.604-0.847)	
Nominal *P* value	<0.0001	

No. at risk												
RIB + NSAI	2549	2353	2282	2215	2146	2089	1854	1487	918	155	8	0
NSAI alone	2552	2244	2171	2093	2021	1949	1701	1376	856	152	6	0

OS



Median follow-up for OS, 44.3 mo

	RIB + NSAI	NSAI alone
Events/n (%)	105/2549 (4.1)	121/2552 (4.7)
Hazard ratio (95% CI)	0.827 (0.636-1.074)	
Nominal *P* value	0.0766	

No. at risk												
RIB + NSAI	2549	2404	2336	2300	2260	2217	2080	1648	1032	195	11	0
NSAI alone	2552	2302	2256	2210	2164	2117	1945	1571	991	204	13	0

DDFS, distant disease-free survival; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

Tolerability of Ribociclib at 400-mg Dose

	RIB + NSAI (n = 2,524)		NSAI Alone (n = 2,444)	
AESIs, %	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Neutropenia[a]	62.1	43.8	4.5	0.8
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	25.4	8.3	10.6	1.5
QT interval prolongation	5.2	1.0	1.2	0.5
ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis[d]	1.5	0	0.8	0.1
Other clinically relevant AEs,%				
Arthralgia	36.5	1.0	42.5	1.3
Nausea	23.0	0.2	7.5	0.04
Headache	22.0	0.4	16.5	0.2
Fatigue	21.9	0.7	12.7	0.2
Diarrhea	14.2	0.6	5.4	0.1
VTE	1.4	0.6	0.6	0.2

- The most frequent all-grade AEs (RIB + NSAI vs NSAI alone) leading to discontinuation were:
  - Liver-related AEs: 8.9% vs 0.1%
  - Arthralgia: 1.3% vs 1.9%
- Most of the AE discontinuations of RIB occurred early in treatment
  - Median time of discontinuation, 4 months

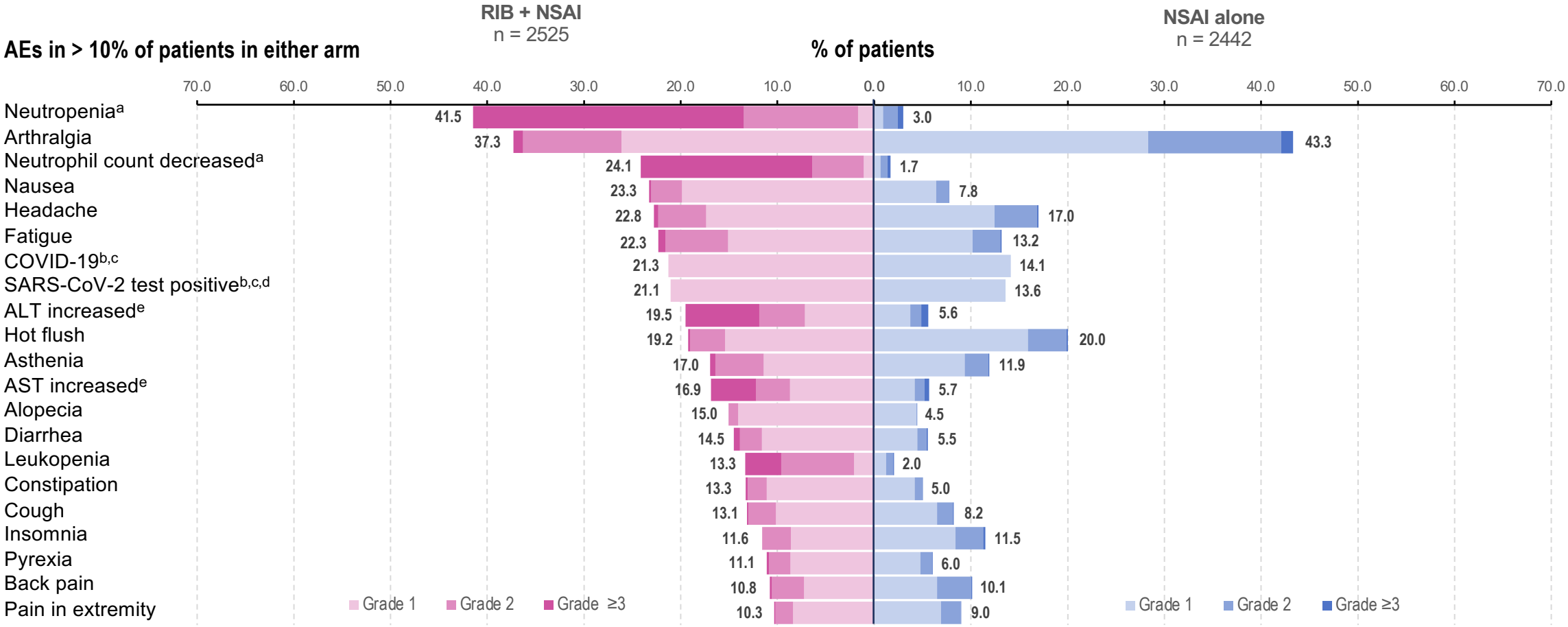
Lower rates of neutropenia and QTc prolongation than 600 mg dose, but no difference in grade 3 LFT abnormalities

[a] This is a grouped term that combines neutropenia and neutrophil count decreased. [b] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] This is a grouped term. [d] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease.

1. Slamon DJ et al. ASCO 2023. Abstract LBA500.

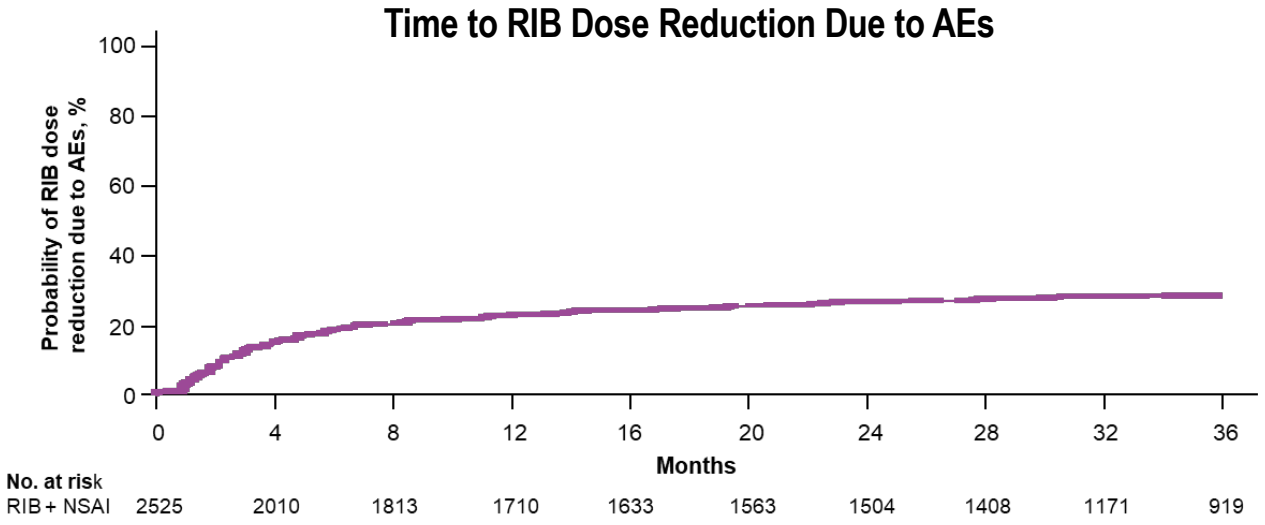
NATALEE: ADVERSE EVENTS

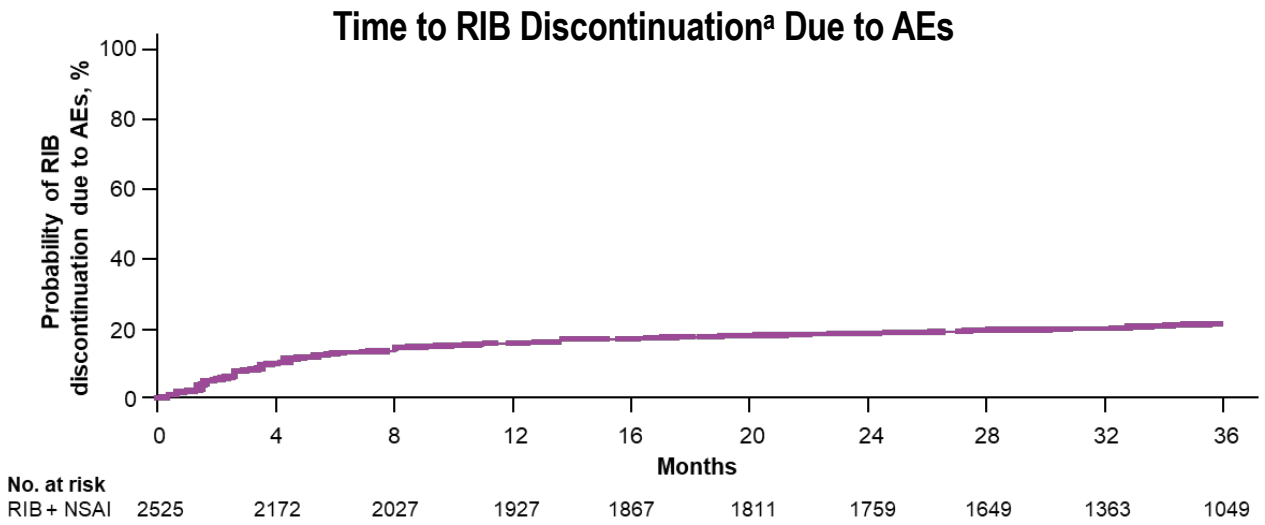
98.0% of patients on RIB + NSAI experienced AEs; similarly, 87.8% of patients on NSAI alone experienced AEs



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Included in the AESI grouping "neutropenia." [b] Only reported as all-grade events. [c] Included in the AESI grouping "infections." [d] Spontaneously reported (no solicited collection). [e] Included in the AESI grouping "hepatobiliary toxicity" and in the grouping "liver-related AEs" used hereafter.

NATALEE: AE-Related Dose Reduction and Discontinuation





- AE-related RIB dose reductions occurred in 22.8% of patients
  - Most commonly due to neutropenia (8.5%) and neutrophil count decreased (5.6%)
- Median time to AE-related RIB dose reduction: 3.15 months (range, 0.26-34.17 months)
- Median RDI during RIB treatment: 94%

- Most common AEs leading to discontinuation: ALT increased (7.1%) and AST increased (2.8%)
- Of 19.7% who discontinued due to AEs, 14.0% discontinued without prior dose reduction and 5.7% had their dose reduced before discontinuing
- Median time to AE-related RIB discontinuation: 4.17 months (range, 0.10-35.75 months)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; RDI, relative dose intensity; RIB, ribociclib.

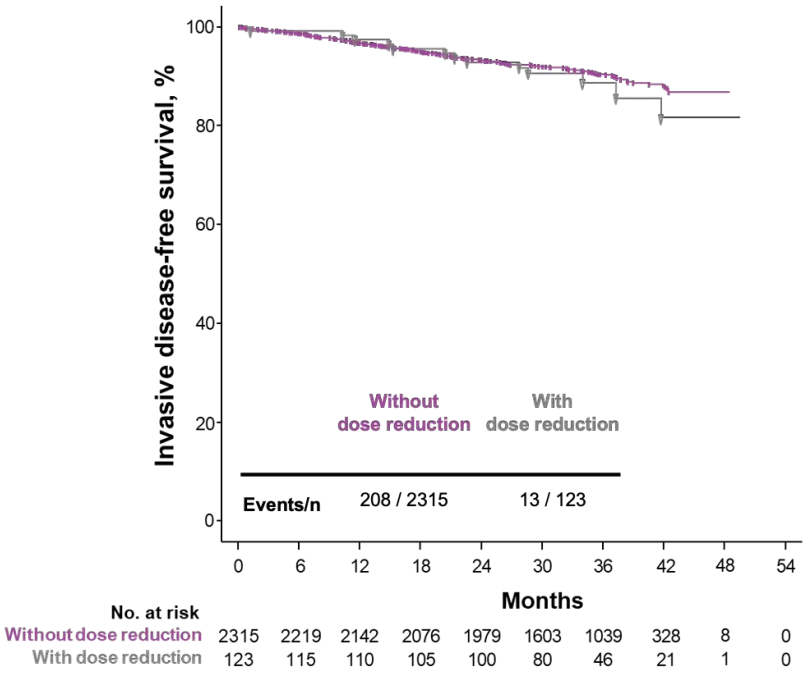
[a] Protocol required discontinuation for RIB dose interruption of > 28 days, or grade 4 AEs (except neutropenia and thrombocytopenia), or recurrent high-grade AEs.

Barrios C et al. 2024 ESMO Breast. Abstract 113MO.

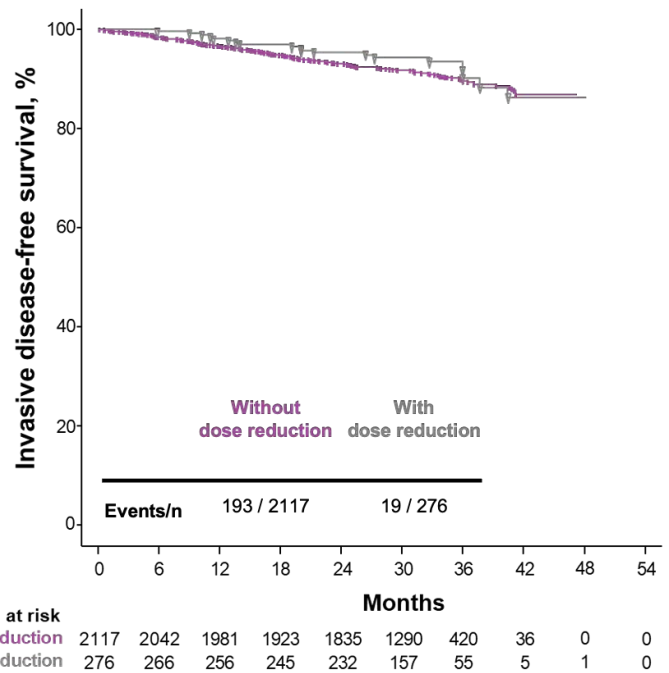
NATALEE: IDFS by Dose Reduction

Landmark analysis revealed that RIB dose reduction due to AEs did not impact efficacy

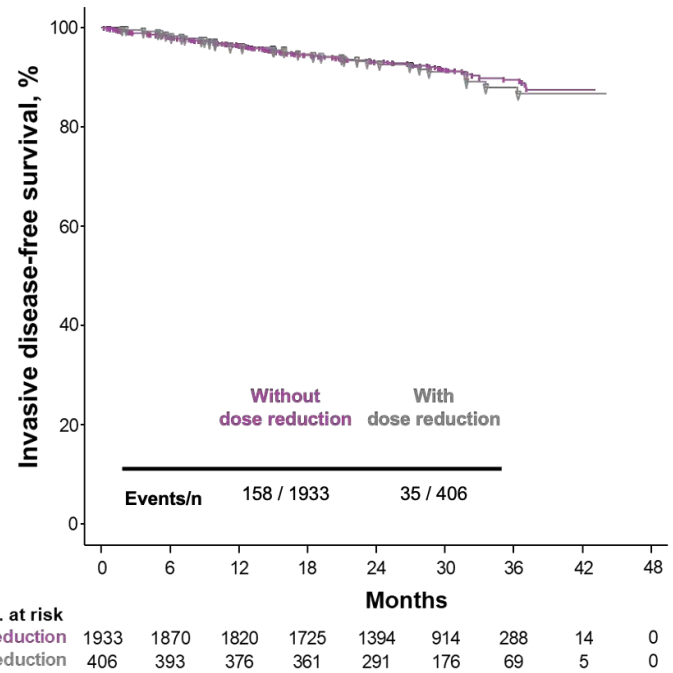
IDFS by Dose Reduction at 25th Percentile (1.87 mo)[a]



IDFS by Dose Reduction at 50th Percentile (3.17 mo)[a]



IDFS by Dose Reduction at 75th Percentile (7.28 mo)[a]



[a] Of dose reduction time, calculated from randomization.

1. Barrios C et al. 2024 ESMO Breast. Abstract 113MO.

How do we select an adjuvant CDK4/6 inhibitor?

ADJUVANT CDK 4/6 INHIBITORS IN ER+ EBC

Discontinuations due to Adverse Events – a clue to compliance

monarchE

- **18.5% discontinued Abemaciclib due to AE**
- Most frequent all-grade AEs leading to discontinuation:
  - Diarrhea: 5.3%
  - Fatigue: 2.0%
- Most of ABEMA AE discontinuations occurred early in treatment
  - Majority in 1st 3 months

Rugo HS, et al. Ann. Oncol. 2022; 33(6):616-27

NATALEE

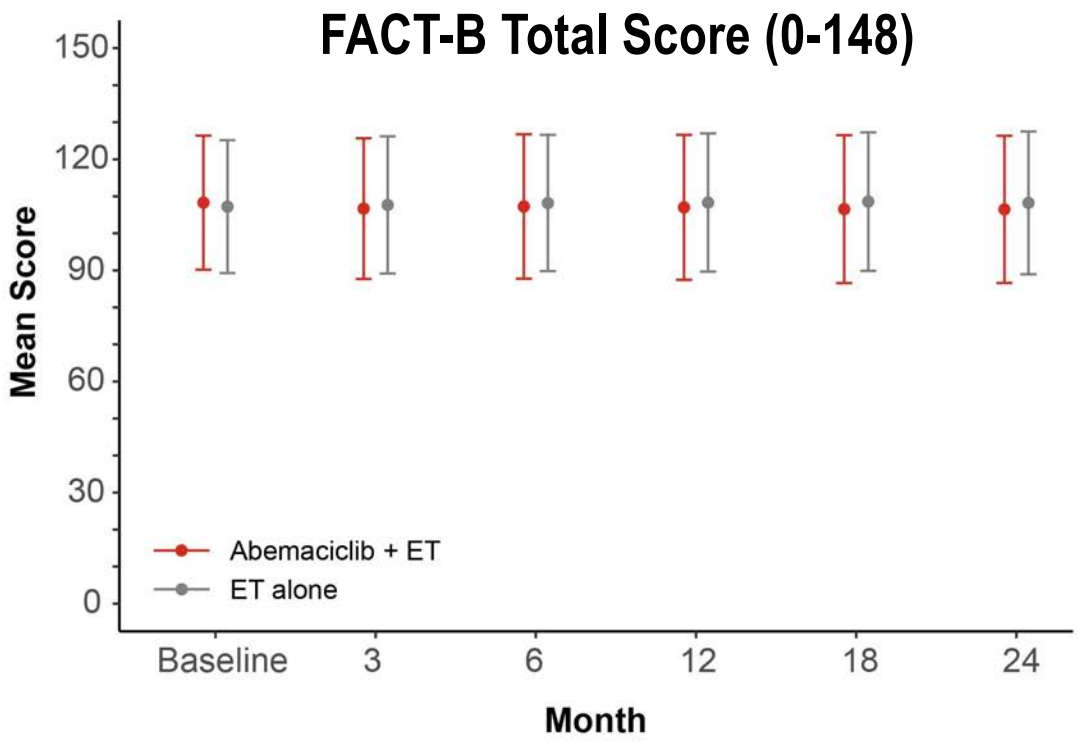
- **19% discontinued ribociclib due to AE**
- Most frequent all-grade AEs leading to discontinuation:
  - Liver-related AEs: 8.9%
  - Arthralgia: 1.3%
- Most of RIB AE discontinuations occurred early in treatment:
  - Median time of these discontinuations was 4 months

Slamon D, et al. ASCO 2023 LBA500

ADJUVANT CDK 4/6 INHIBITORS IN ER+ EBC

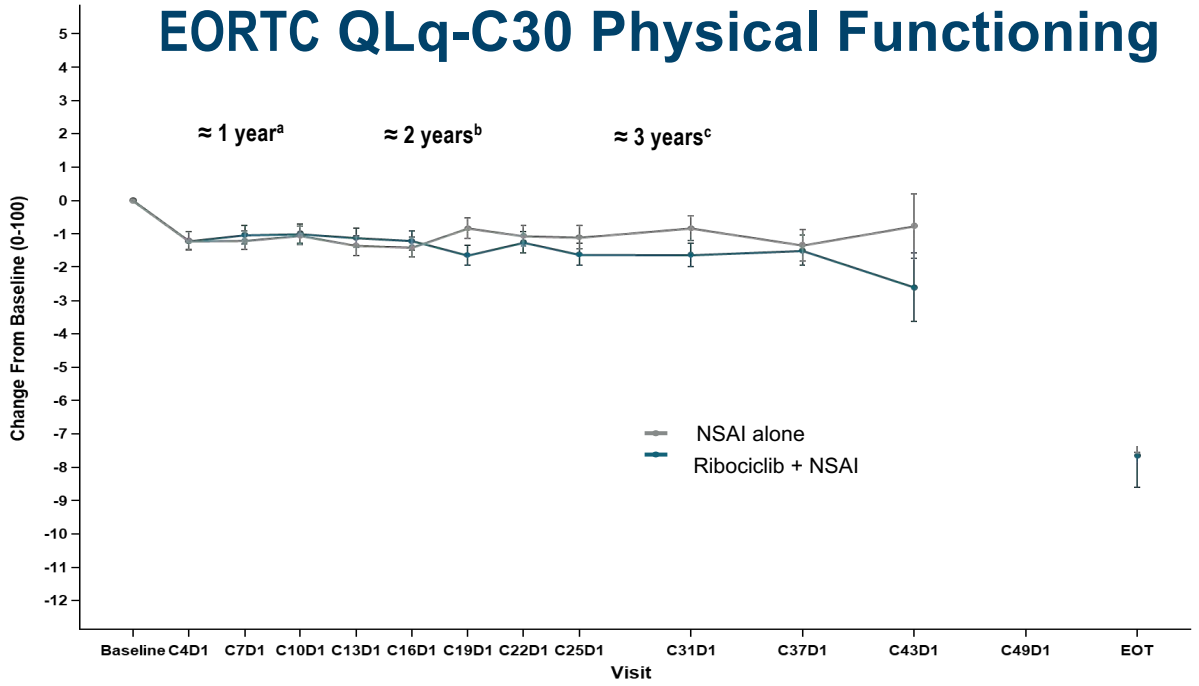
QOL scores maintained over time on treatment

monarchE



Harbeck N, et al. ESMO Breast 2023 Ann Oncol 8 (s4) 101219

NATALEE



Fasching P, et al. Virtual Plenary 2023

NEOADJUVANT CDK4/6i THERAPY

neoMONARCH

- Phase 2 study of abemaciclib, anastrozole or abema + anastrozole x 2w
- Then 14 weeks of abema + anastrozole

- Abema → complete cell cycle arrest in 68%

- 46% radiological response

- pCR rate of 4% in cohort of 224 patients

Hurvitz SA et al. *Clin Cancer Res* (2020) 26 (3): 566–580.

Adjuvant Trials of Oral SERDS vs Standard ET in ER+ HER2- tumors with higher risk of recurrence

Standard Endocrine Therapy (e.g. tam/OFS/AI)

INITIAL THERAPY

SERD

CAMBRIA-2 (n=5300), camizestrant; abema option
lidERA (n=4100), giredestrant; no CDK4/6i

Ongoing Endocrine Therapy (e.g. tam/OFS/AI)

AFTER 2-5 YRS STANDARD ET

SERD

CAMBRIA-1 (n=4300), camizestrant
ELEGANT (n=4220), elacestrant
EMBER-4 (n=6000), imlunestrant

At present, these trials are not designed to capture potential clinical interactions between SERDs and CDK4/6 inhibitors, and are vulnerable to unknown variations in frequency and timing of acquisition of ESR1mut (if that is a key subset) or other features of endocrine resistance which to date have been the contexts where SERDS > standard treatment

Summary: CDK4/6 inhibitors in early stage ER+ breast cancer

- **Abemaciclib and ribociclib have shown reduction in recurrence risk in higher risk breast cancer**
- **They differ in side effect profiles and durations of treatment**
- **It is not known which is better**
- **These drugs carry more toxicity than perhaps suggested by the clinical trials data**
- **To date, there is no OS benefit**
- **Not clear that neoadjuvant CDK4/6i therapy improves long-term tumor response or outcomes**

Discussion Questions

- Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor to a woman with HR-positive, HER2-negative localized breast cancer with a Grade 3, 3-cm tumor and no positive nodes?

- When administering a CDK4/6 inhibitor in the adjuvant setting, for how long do you generally continue treatment?

We are taking a short break!

The program will resume at 9:45 AM ET

Up Next…

Drs Simron Singh and Jonathan Strosberg
discuss the management of neuroendocrine tumors

RTP
RESEARCH
TO PRACTICE