Overview

Saturday, March 23rd

Module 1: 7:30 AM – 9:10 AM — Hodgkin and Non-Hodgkin Lymphoma

Module 2: 9:30 AM – 10:20 AM — Gynecologic Cancers

Module 3: 10:20 AM – 11:10 AM — Localized Breast Cancer; SABCS 2023 Review

Module 4: 11:10 AM – 12:00 PM — Metastatic HER2-Positive and Triple-Negative Breast Cancer; SABCS 2023 Review

Module 5: 12:30 PM – 1:20 PM — Prostate Cancer

Module 6: 1:20 PM – 2:10 PM — Urothelial Bladder Cancer

Module 7: 2:10 PM – 3:00 PM — Renal Cell Carcinoma

Module 8: 3:20 PM – 4:10 PM — Targeted Therapy for Non-Small Cell Lung Cancer

Module 9: 4:10 PM – 5:00 PM — Nontargeted Treatments for Lung Cancer

Third Annual National General Medical Oncology Summit

Agenda

Module 1: Ovarian Cancer; Role of HER2-Directed Therapy in Gynecologic Cancers — Dr O'Malley

Module 2: Endometrial Cancer and Cervical Cancer — Dr Monk

Agenda

Module 1: Ovarian Cancer; Role of HER2-Directed Therapy in Gynecologic Cancers — Dr O'Malley

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OVARIAN CANCER; ROLE OF HER2-DIRECTED THERAPY IN GYNECOLOGIC CANCERS

David O'Malley, MD

Director & Professor, Division of Gynecologic Oncology in Obstetrics and Gynecology
John G. Boutselis Chair in Gynecologic Oncology
Ovarian Cancer Clinical Trial Advisor, GOG Partners

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Creating a cancer-free world. One person, one discovery at a time.




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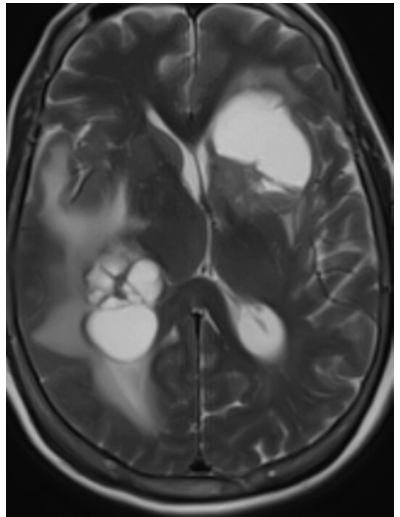
Advisory Committees and Consulting Agreements (Personal Fees)	AbbVie Inc, Adaptimmune, Agenus Inc, Arcus Biosciences, Arquer Diagnostics, AstraZeneca Pharmaceuticals LP, Atossa Therapeutics, Cardiff Oncology, Celcuity, Clovis Oncology, Corcept Therapeutics, Duality Biologics, Eisai Inc, Elevar Therapeutics, Exelixis Inc, F Hoffmann-La Roche Ltd, Genelux Corporation, Genentech, a member of the Roche Group, GSK, ImmunoGen Inc, Imvax Inc, InterVenn Biosciences, InxMed, Iovance Biotherapeutics, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Laekna Therapeutics, Leap Therapeutics Inc, Luzsana Biotechnology, Merck, Mersana Therapeutics Inc, MSD, Myriad Genetic Laboratories Inc, Novartis, Novocure Inc, OncoC4, Onconova Therapeutics Inc, Regeneron Pharmaceuticals Inc, Replimune, Roche Diagnostics, R-Pharm US, Seagen Inc, Sorrento Therapeutics, Sumitomo Dainippon Pharma Oncology Inc, Sutro Biopharma, Tarveda Therapeutics, Toray Industries Inc, Trillium Therapeutics Inc, Umoja Biopharma, VBL Therapeutics, Verastem Inc, Vincerx Pharma, Xencor, Zentalis Pharmaceuticals
Contracted Research (Institution Received Funds)	AbbVie Inc, Advaxis Inc, Agenus Inc, Alkermes, Aravive Inc, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Clovis Oncology, Deciphera Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Exelixis Inc, F Hoffmann-La Roche Ltd, Genentech, a member of the Roche Group, Genmab US Inc, GSK, ImmunoGen Inc, Incyte Corporation, Iovance Biotherapeutics, Karyopharm Therapeutics, Leap Therapeutics Inc, Merck, Mersana Therapeutics Inc, MSD, Novartis, Novocure Inc, OncoC4, OncoQuest Inc, Pfizer Inc, Predictive Oncology Inc, Prelude Therapeutics, Regeneron Pharmaceuticals Inc, Rubius Therapeutics, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Sutro Biopharma, Tesaro, A GSK Company, Verastem Inc
Nonrelevant Financial Relationships	GOG Foundation Inc, Ludwig Institute for Cancer Research Ltd, National Cancer Institute, NRG Oncology, RTOG, SWOG

Case

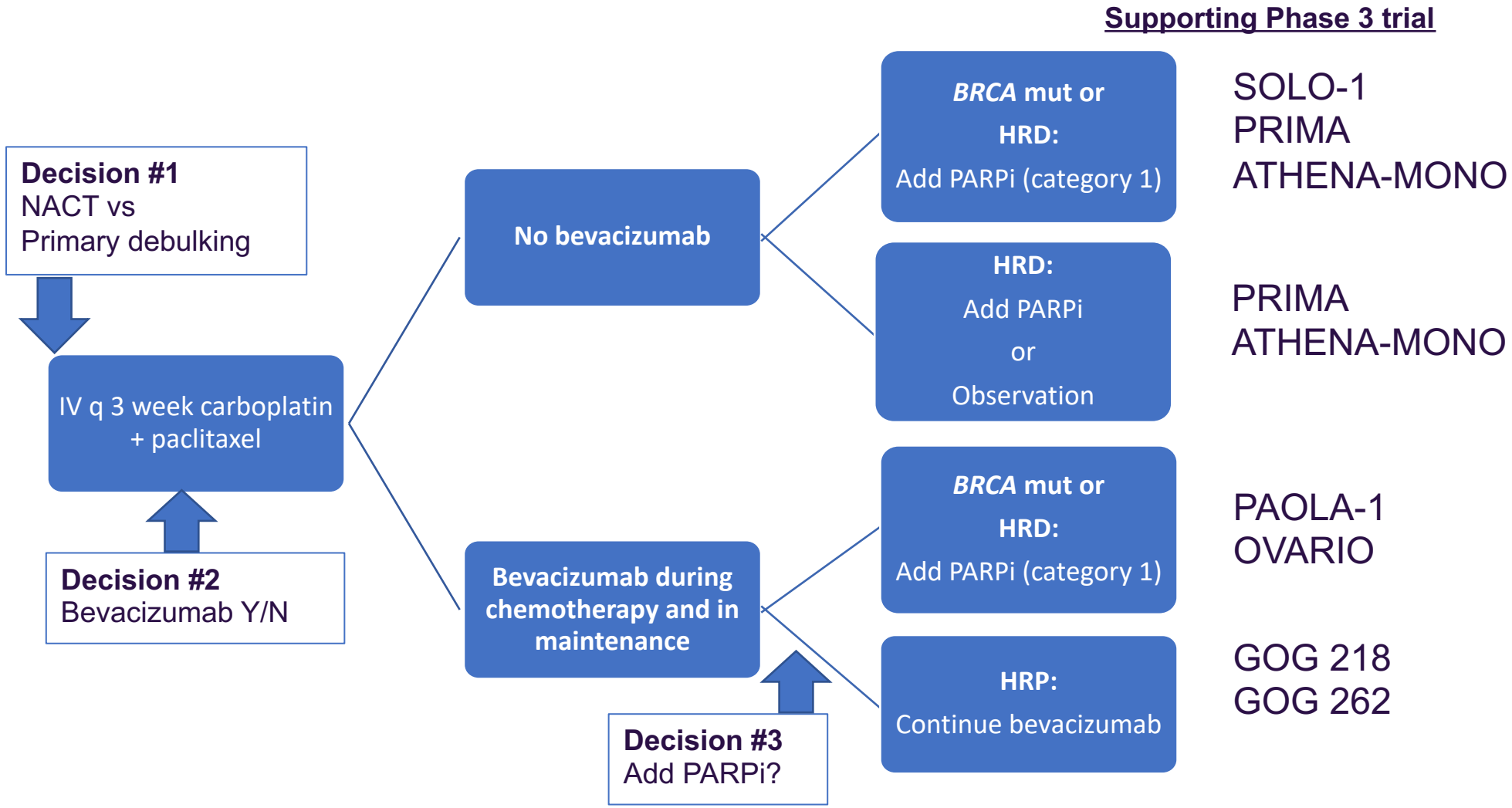
- 2013: TAH, BSO, pelvic and paraaortic lymphadenectomy, omentectomy . Found to have a high grade serous carcinoma of the ovary - initially IIIB
- Completed 6 cycles of Carbo/paclitaxel - dose dense
- NED for 4+ years when presented with multi-focal recurrence– biopsy proven.
  - NGS, MMR Testing - no clinically actionable mutations
- 2018: Carbo/gemcitabine x 6 cycles
- Recurred 4 months later
- Clinical trial Olaparib and AZD x 2 months
- CT Chest/Abdomen/Pelvis: Disease progression with new supraclavicular lymphadenopathy, worsening intra-thoracic lymphadenopathy, and worsening peritoneal carcinomatosis.
- Jan 2019: Clinical trial with IMGN853 (mirvetuximab) & Bevacizumab
- C27 delayed 2 weeks due to Grade 2 neuropathy, mirvetuximab reduced to 5 mg/kg
- Received 35 cycles of mirvetuximab + Bev - clinical trial closed
  - Persistent PR (87% improvement)
- 2021: Started Compassionate Use of mirvetuximab and Bev (commercial supply) - single patient compassionate use trial.
- October, 2022: Completed 46 (11 compassionate use) total cycles of mirvetuximab/Bev
- **Elected for Chemo Holiday after nearly 4 years of therapy**
- May, 2023 Presented with multiple brain mets



Agenda

- Up-front PARPi
  - Use of clinical characteristics and other factors to select among available PARPi maintenance
- Strategies to support continuation of treatment in patients receiving up-front PARPi maintenance
- PROC
  - Mirvetuximab
  - R-DXd
- T-DXd in Gyn cancers

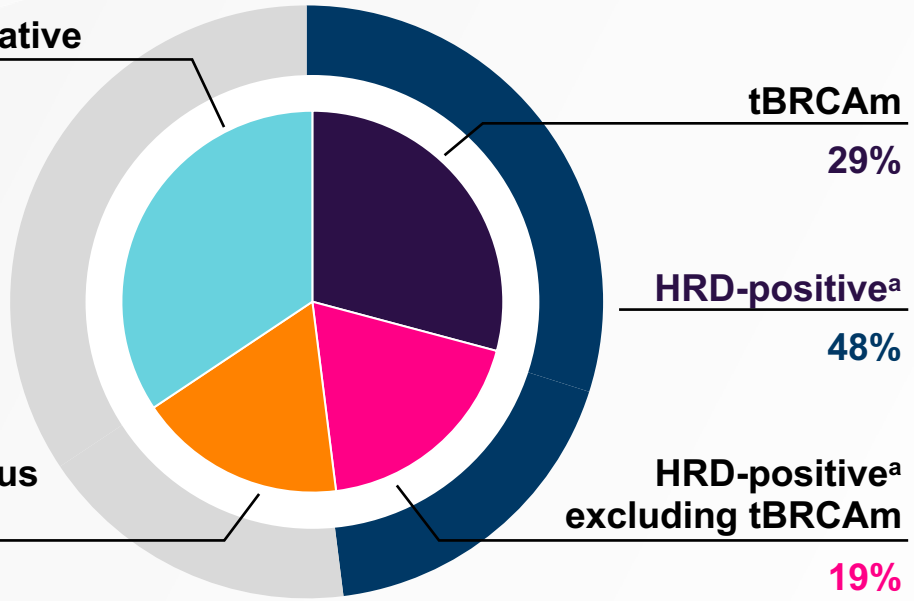
Integrated Maintenance Treatment Paradigm for Use in 1-L Ovarian Cancer (2022)



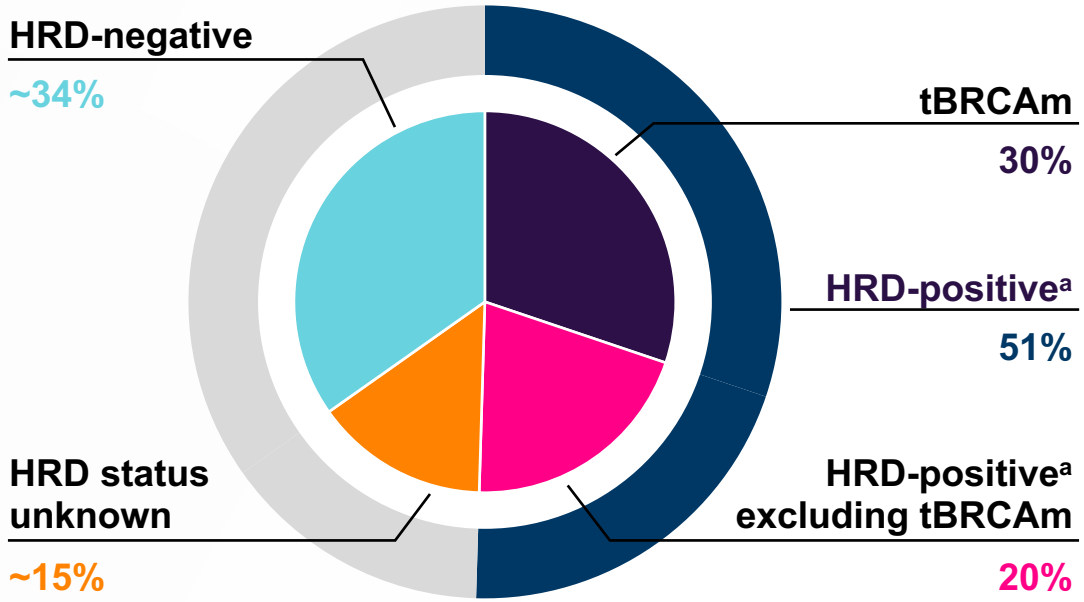
1. NCCN guidelines. Ovarian Cancer Version 1, 2024.

HRD (Homologous recombination deficiency)

PAOLA-1[1]

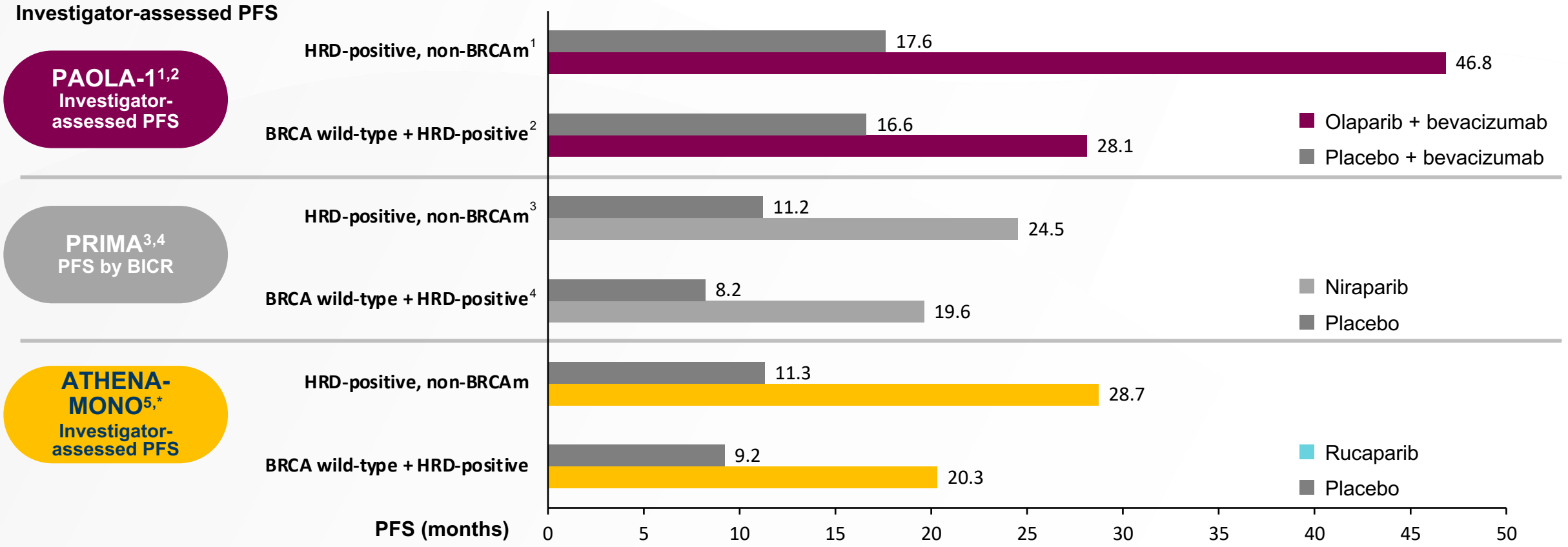


PRIMA[2]



1. Ray-Coquard I, et al. Presented at European Society for Medical Oncology Congress; 27th September – 1st October 2019; Barcelona, Spain; abstract LBA2_PR; 2. González-Martin A, et al. *N Engl J Med* 2019;381:2391–2402

PARPi clearly benefit in HRD+



1. Ray-Coquard I, et al. Presented at European Society for Medical Oncology Congress; 9th–13th September 2022; Paris, France; 2. Ray-Coquard I, et al. *N Engl J Med* 2019;381:2416–2428;
3. Gonzales-Martin A, et al. Presented at European Society for Medical Oncology Congress; 9th–13th September 2022; Paris, France; abstract #530P; 4. González-Martín A, et al. Presented at European Society of Gynaecological Oncology Congress; 2nd–5th November 2019; Athens, Greece; abstract #4627; 5. Monk JM, et al. *J Clin Oncol* 2022.
doi: http://ascopubs.org/doi/full/10.1200/JCO.22.01003 [Epub ahead of print]

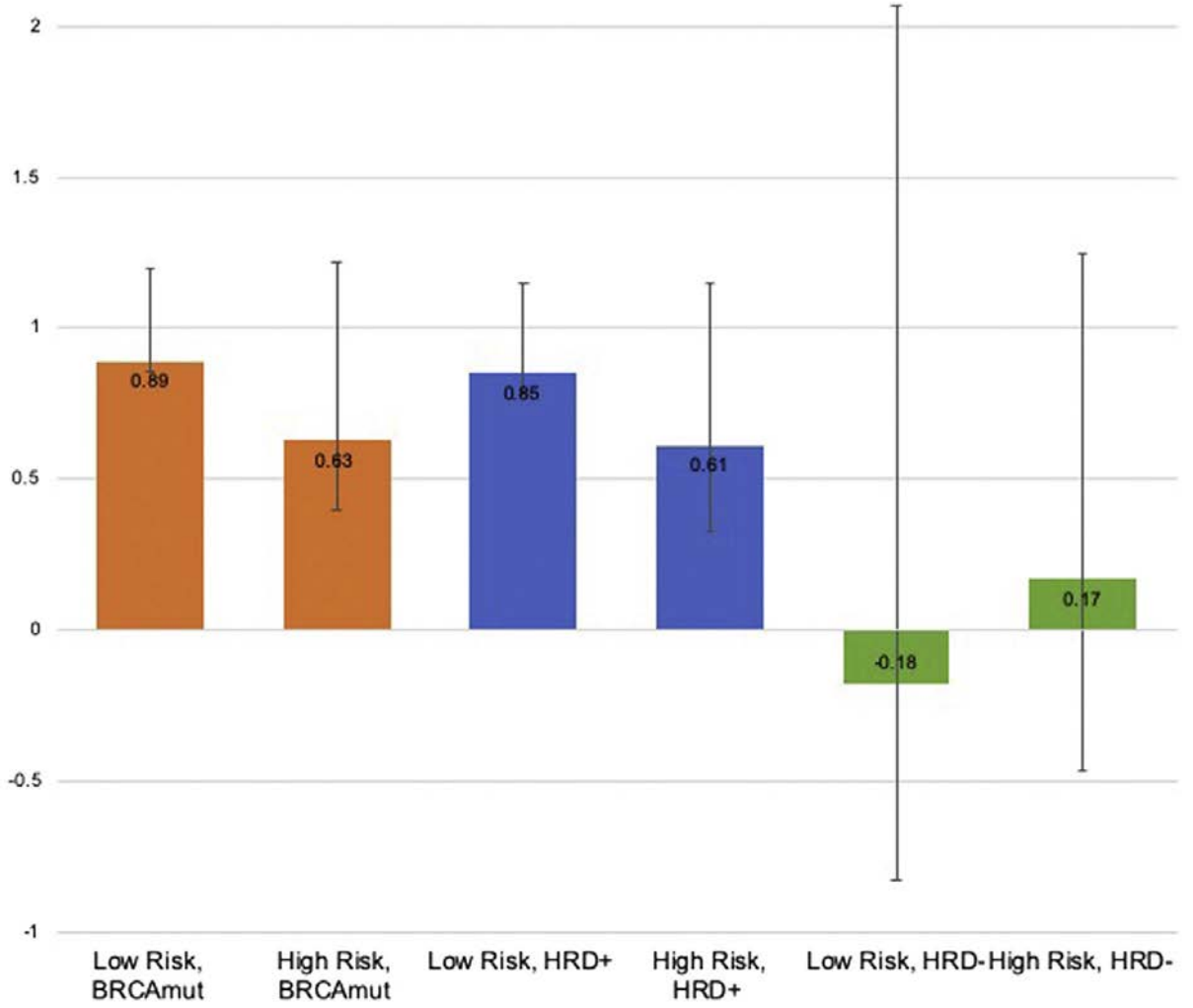
Is there a low-risk advanced ovarian cancer?

Clinical Opinion ajog.org

Is there a "low-risk" patient population in advanced epithelial ovarian cancer?: a critical analysis

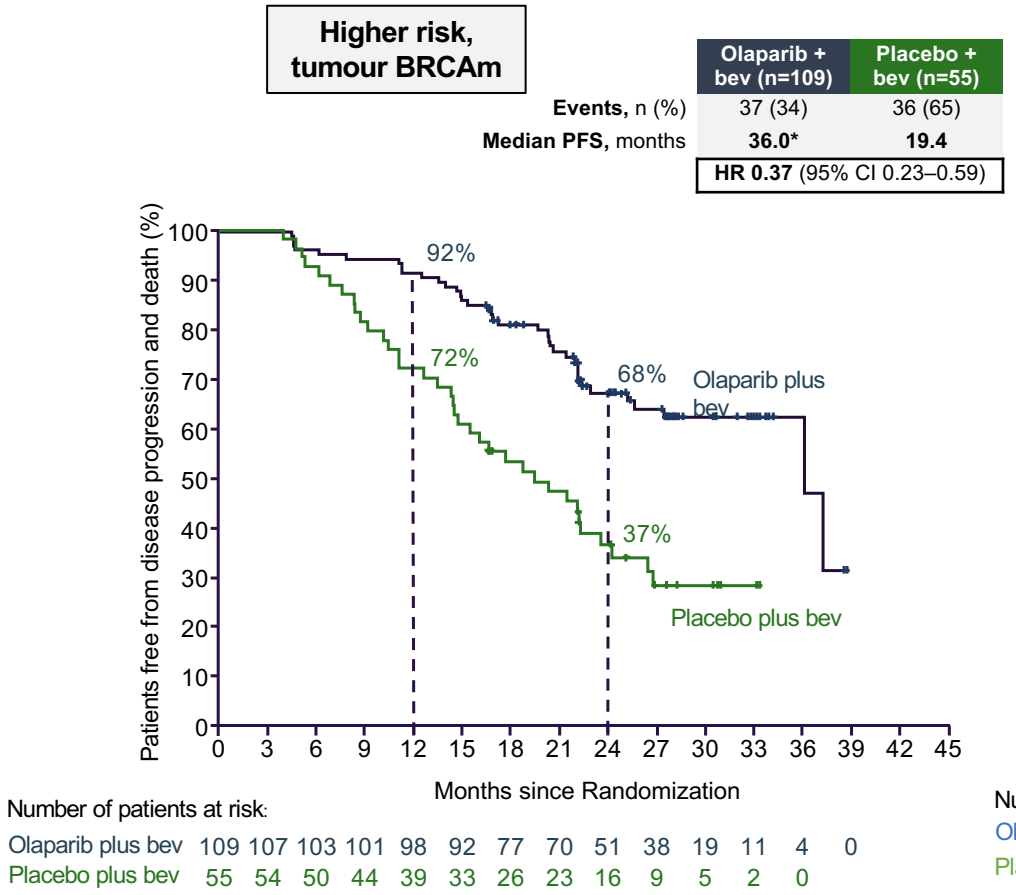
Laura M. Chambers, DO, MS; David M. O'Malley, MD; Robert L. Coleman, MD; Thomas J. Herzog, MD

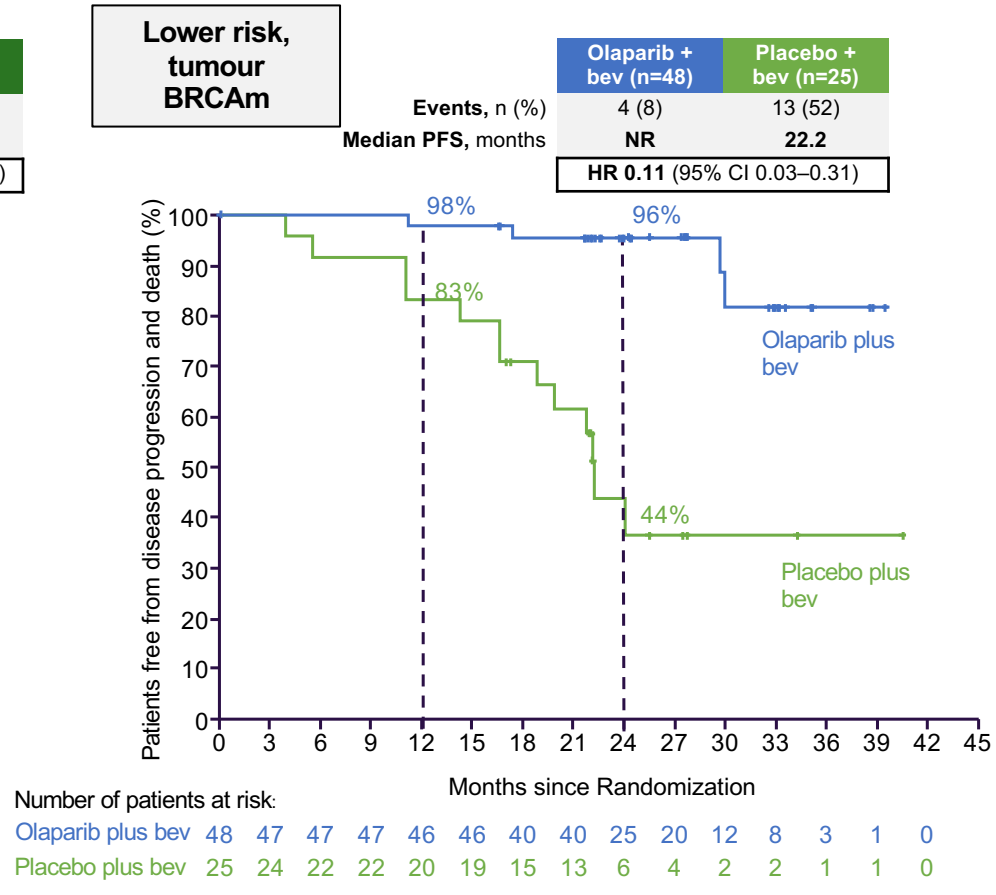
FIGURE
Impact of treatment (1-HR) with bevacizumab and olaparib on PFS in PAOLA-1 prognostic subgroups



AJOG Nov 2022

PAOLA-1
Exploratory Analysis on PFS by clinical risk- BRCAm patients

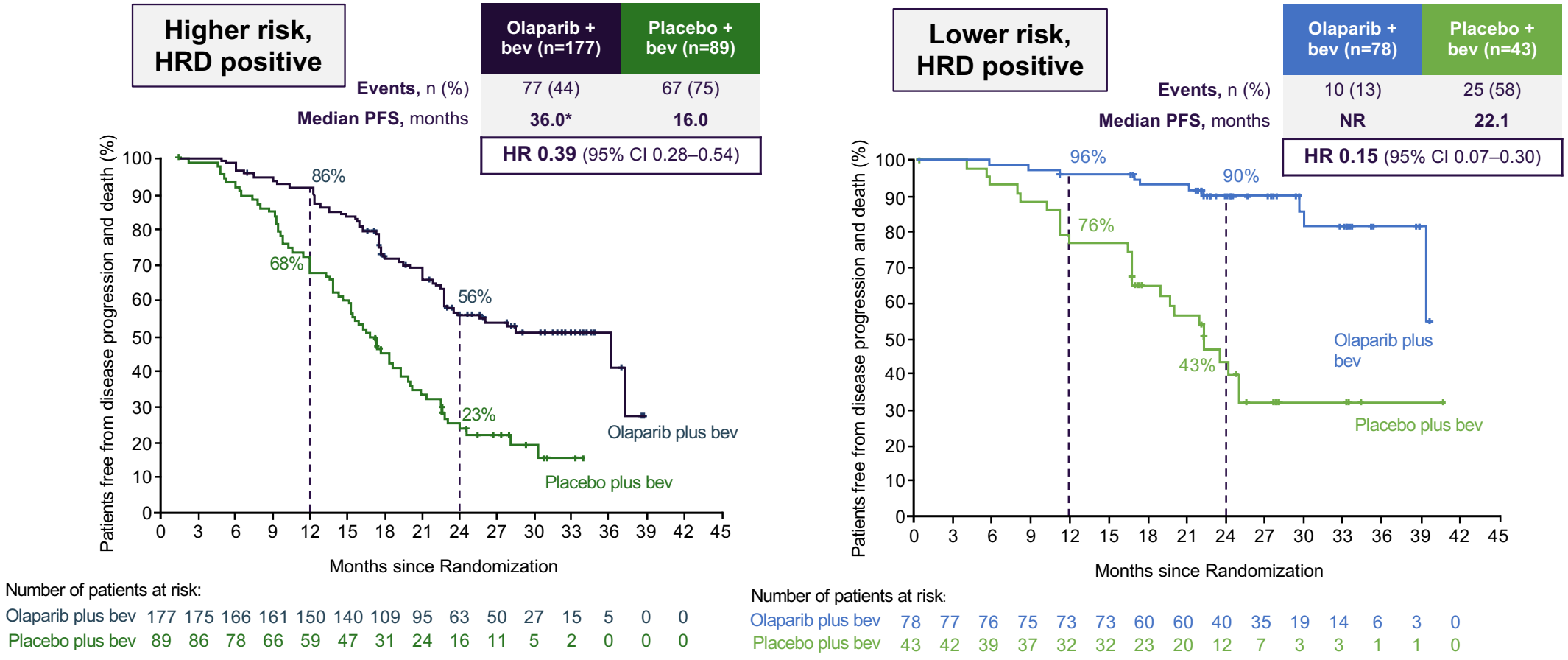




- Harter et al Gyn Onc 2022

*Unstable median due to lack of events
NR, not reached

PAOLA-1
Exploratory Analysis on PFS by clinical risk - HRD+ patients

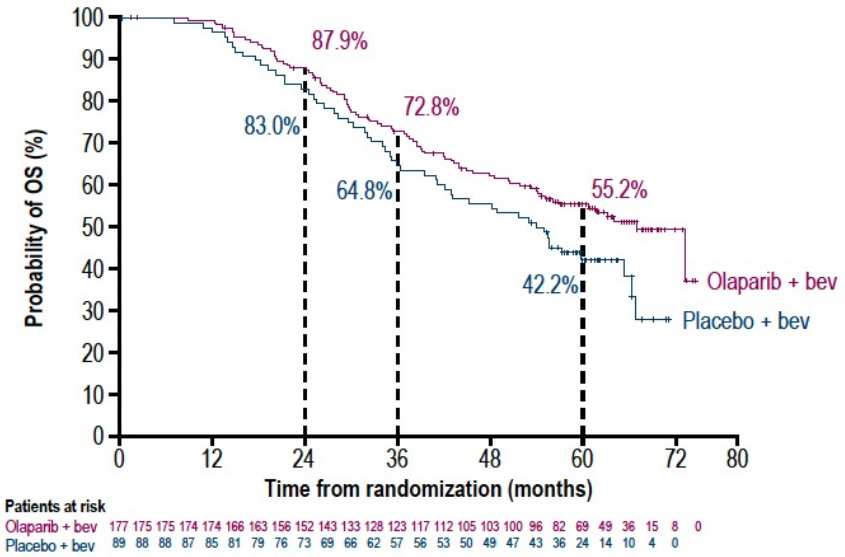


*Unstable median due to lack of events

- Harter et al Gyn Onc 2022

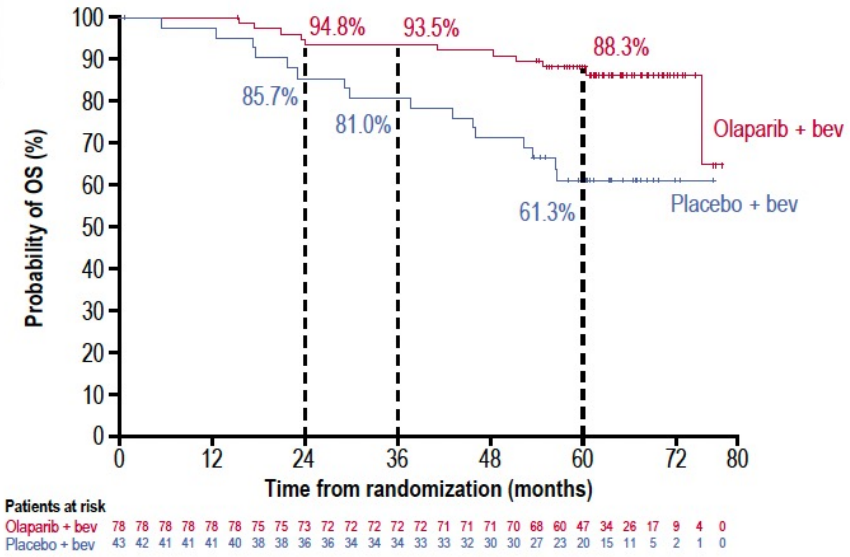
5-year OS by clinical risk in HRD-positive patients

Higher risk



	Olaparib + bevacizumab (n=177)	Placebo + bevacizumab (n=89)
Events, n (%)	82 (46.3)	53 (59.6)
Median OS, months	67.0*	54.0
5-year OS rate, %	55.2	42.2
	HR 0.70 (95% CI 0.50–1.00)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	18.6	56.2

Lower risk

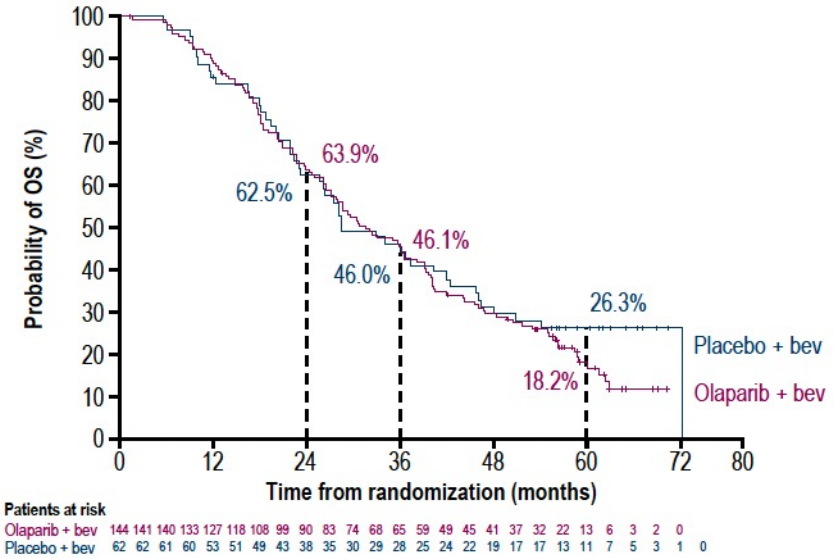


	Olaparib + bevacizumab (n=78)	Placebo + bevacizumab (n=43)
Events, n (%)	11 (14.1)	16 (37.2)
Median OS, months	NE	NE
5-year OS rate, %	88.3	61.3
	HR 0.31 (95% CI 0.14–0.66)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	14.1	39.5

Lorusso D, et al. Presented at ESMO Gynaecological Cancers Meeting, 2023; Lorusso D et al. Int J Gynecol Cancer 2023

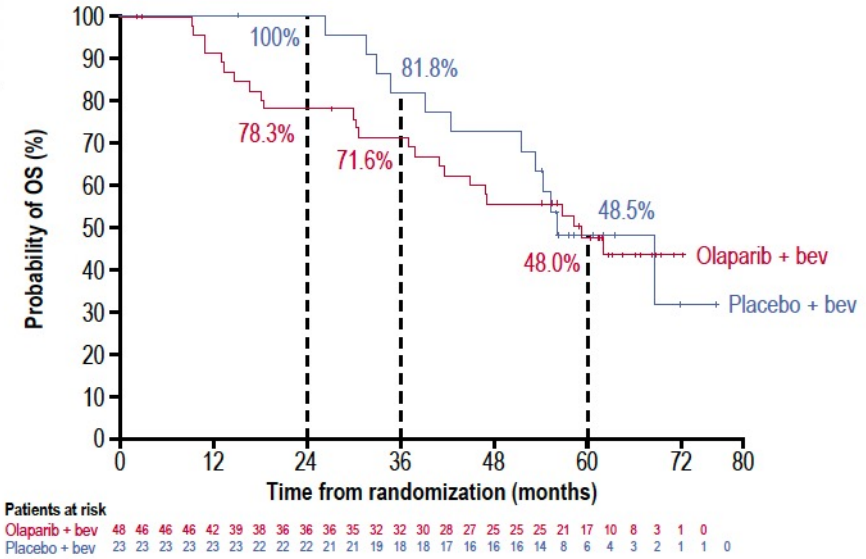
5-year OS by clinical risk in HRD-negative patients

Higher risk



	Olaparib + bevacizumab (n=144)	Placebo + bevacizumab (n=62)
Events, n (%)	116 (80.6)	46 (74.2)
Median OS, months	31.6	28.5
5-year OS rate, %	18.2	26.3
	HR 1.15 (95% CI 0.82–1.63)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	22.2	33.9

Lower risk



	Olaparib + bevacizumab (n=48)	Placebo + bevacizumab (n=23)
Events, n (%)	24 (50.0)	12 (52.2)
Median OS, months	59.3	56.2
5-year OS rate, %	48.0	48.5
	HR 1.14 (95% CI 0.58–2.38)	
Patients receiving a PARP inhibitor during any subsequent treatment, %	29.2	56.5

Lorusso D, et al. Presented at ESMO Gynaecological Cancers Meeting, 2023; Lorusso D et al. Int J Gynecol Cancer 2023

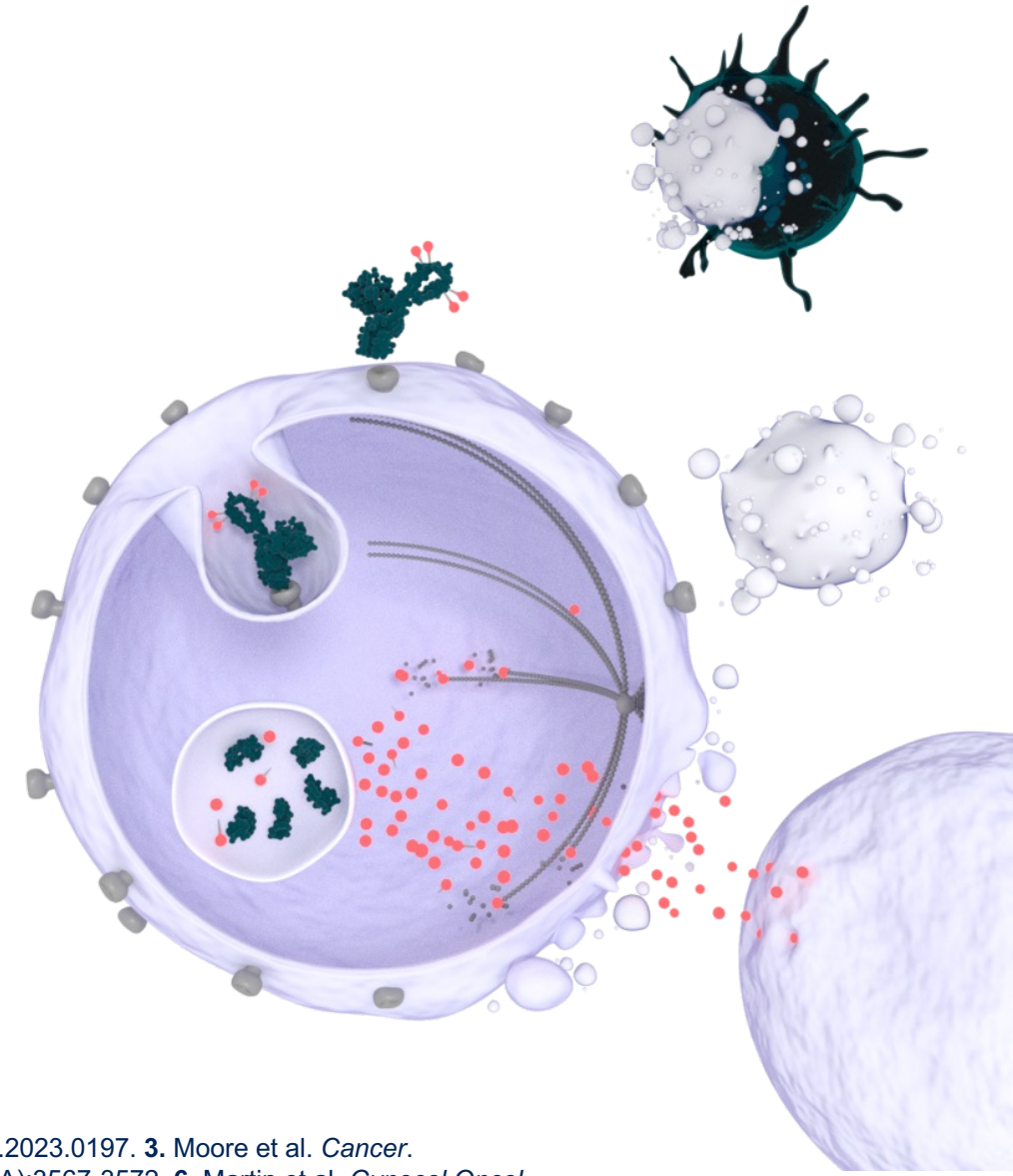
Practical Considerations for PARPi – Compliance with Therapy

- Education of expectations – messaging:
  - This is oral chemo – targeted chemo, but chemo
  - It may take us a few months to figure out the dose
  - Be honest with us, so we can help your symptoms
  - If you are struggling we will help figure it out
  - Tell us if you are not taking your medications
- Rx for anti-emetics for all
- Comply with recommended lab intervals
- Fatigue*
  - Don’t forget basic work-up but not delay intervention while work up is taking place
  - Discuss non-pharmacologic interventions
    - Exercise
    - Yoga
    - Sleep/Wake Cycles
    - Cognitive-Behavioral Therapy
    - Pain Control
  - Consider utilization of pharmacologic (Methylphenidate 5-10 mg at breakfast and lunch)

*NCCN 2024

Background

- No randomized phase 3 trial has shown an overall survival (OS) benefit of a novel therapy in platinum-resistant ovarian cancer (PROC)[1, 2]
- **Mirvetuximab soravtansine (MIRV) is an ADC comprising a FRα-binding antibody, cleavable linker, and maytansinoid DM4, a potent tubulin-targeting agent[3,4]**
- FRα is expressed in ~90% of ovarian carcinomas,[5, 6] with 35-40%[7] of PROC tumors exhibiting high FRα expression (≥75% of tumor cells positive with ≥2+ intensity)[8]
- MIRV demonstrated an ORR of 32% and mDOR 6.9 months in the single-arm study SORAYA[8] of BEV pre-treated PROC to support accelerated approval by the FDA[9]
- MIRASOL is the confirmatory, randomized, global phase 3 trial designed to support approval worldwide



1. Pujade-Lauraine et al. *J Clin Oncol*. 2014;32(13):1302-1308. **2.** Richardson et al. *JAMA Oncol.* 2023;10.1001/jamaoncol.2023.0197. **3.** Moore et al. *Cancer*. 2017;123(16):3080-3087. **4.** Ab et al. *Mol Cancer Ther*. 2015;14(7):1605-1613. **5.** Markert et al. *Anticancer Res.* 2008;28(6A):3567-3572. **6.** Martin et al. *Gynecol Oncol.* 2017;147(2):402-407. 7. Data on file. **8.** Matulonis et al. *J Clin Oncol*. 2023:41(13):2436-2445. **9.** U.S. FOOD & DRUG ADMINISTRATION. BLA ACCELERATED APPROVAL. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761310Orig1s000ltr.pdf. Accessed May 23, 2023.

MIRASOL (NCT04209855) – Study Design[1,2]

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

Patient Population
(N=453)

Enrollment and Key Eligibility
Platinum-resistant disease
(PFI ≤6 mo)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

High-grade serous histology

1º platinum-refractory disease excluded (primary PFI <3 mo)

1-3 prior lines of therapy

Prior BEV and PARPi allowed

Patients with BRCA mutations allowed

1:1 Randomization

Treatment Regimen-Experimental

MIRV
(6 mg/kg AIBW Q3W)

Treatment Regimen-Control

Investigator's Choice Chemotherapy
(Paclitaxel, PLD, or Topotecan)

Stratification Factors
IC chemo: paclitaxel, PLD, or topotecan
Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint
PFS by INV
(BICR sensitivity analysis)

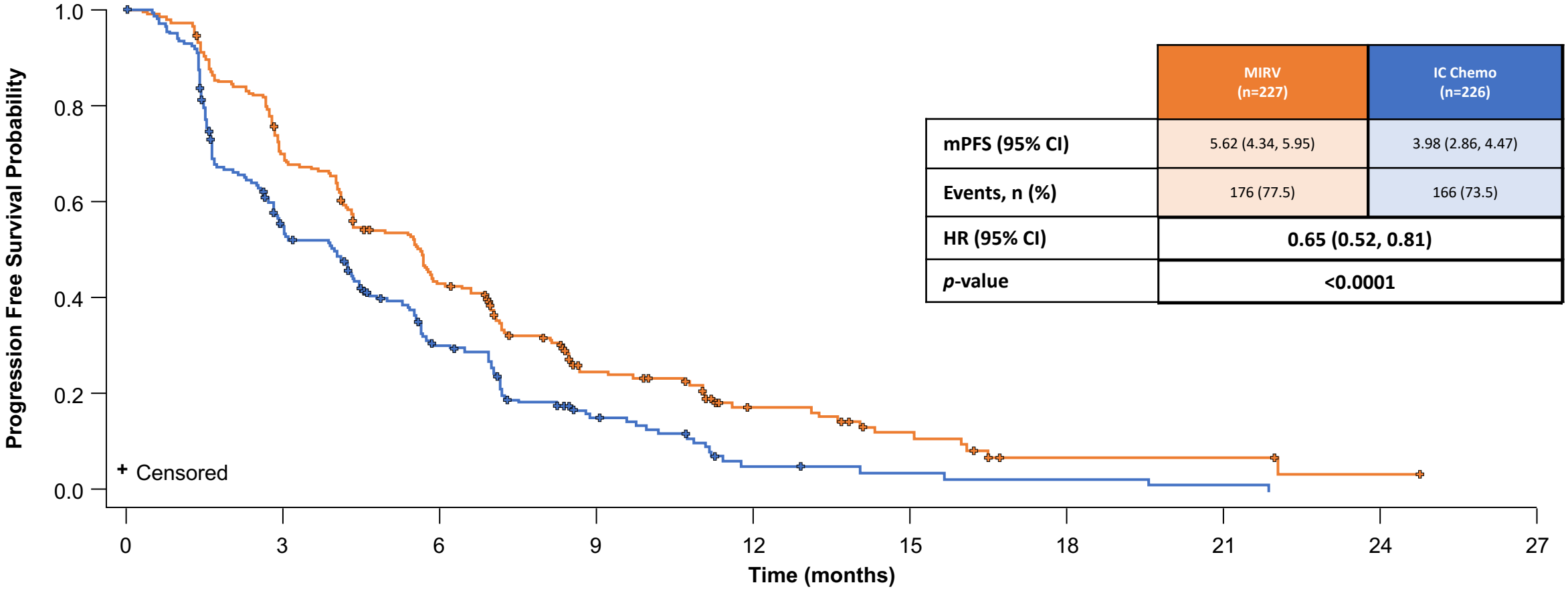
Key Secondary Endpoints
1) ORR by INV
2) OS
3) PROs[a]

Secondary Endpoints
Safety and tolerability
DOR
CA-125 response[b]
PFS2

AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.
[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.
[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

MIRASOL Primary Endpoint: Progression-Free Survival by Investigator



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	**0.65 (0.52, 0.81)**	
***p*-value**	**<0.0001**	

No. Participants at Risk

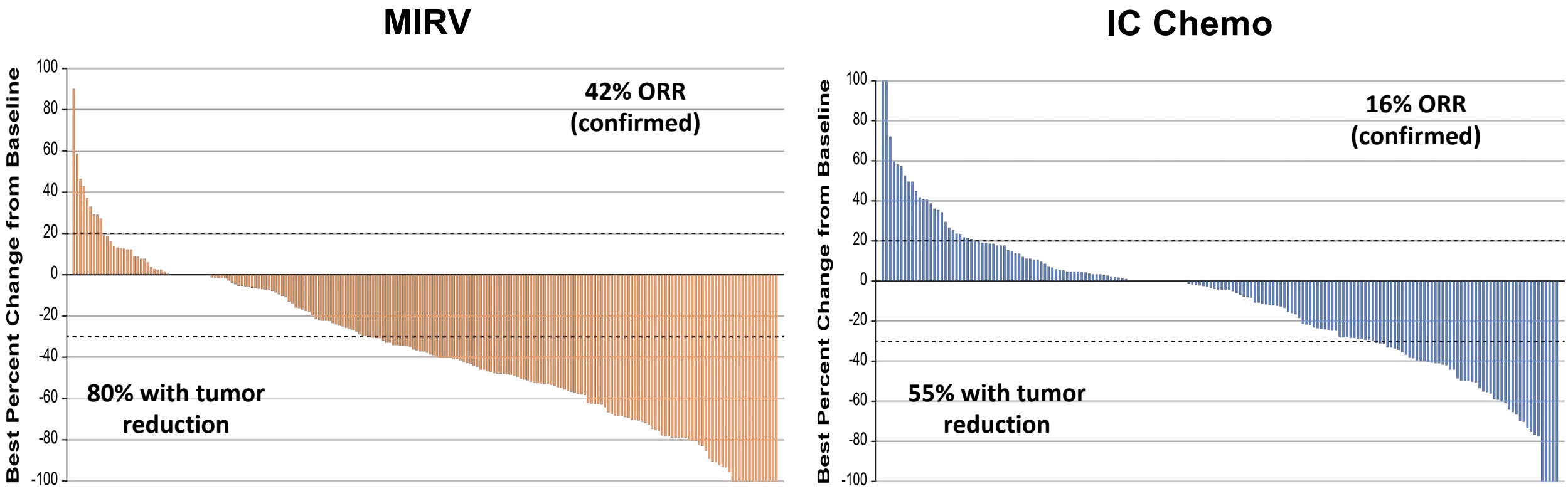
MIRV	227	151	89	38	18	10	3	3	1	0
IC Chemo	226	98	48	19	5	3	2	1	0	

Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

Moore et al ASCO 2023; Moore et al NEJM 2023.

MIRASOL: Maximum Percentage Change in Target Lesion Size from Baseline by Investigator (N=453)

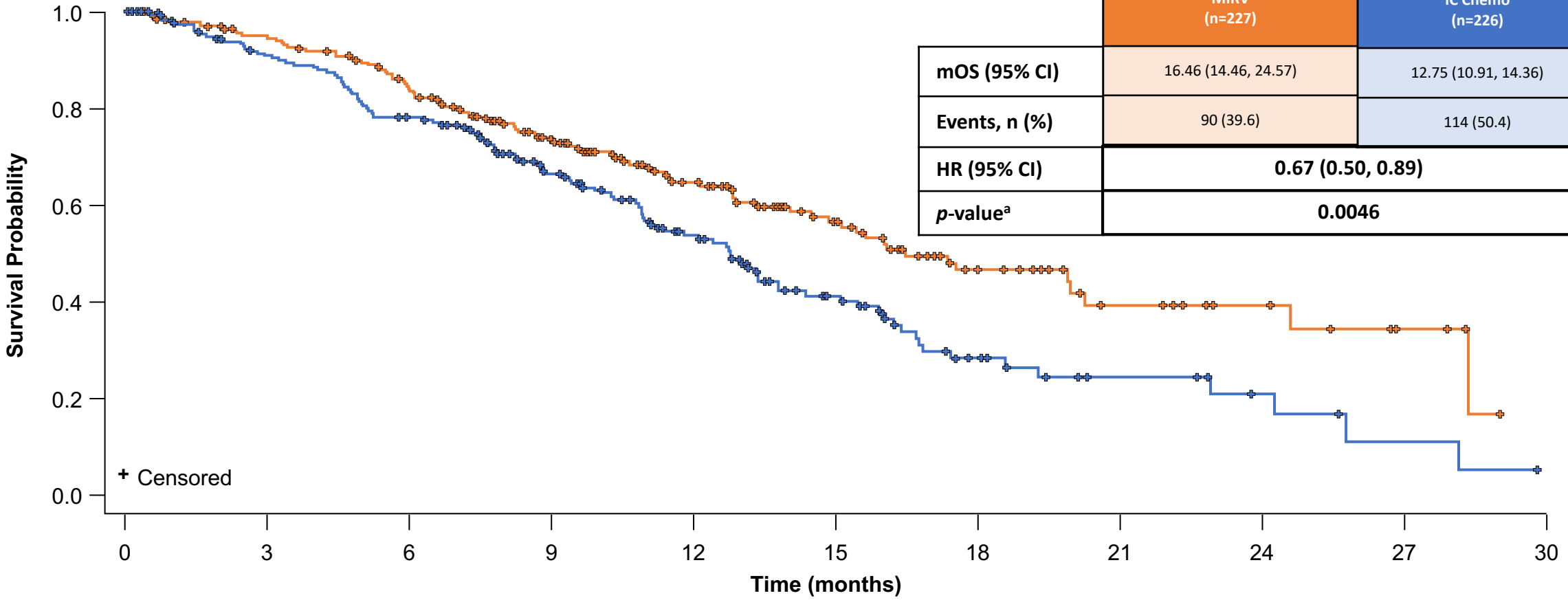


Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate.

Moore et al ASCO 2023; Moore et al NEJM 2023.

MIRASOL: Overall Survival

	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	**0.67 (0.50, 0.89)**	
***p*-value[a]**	**0.0046**	



No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

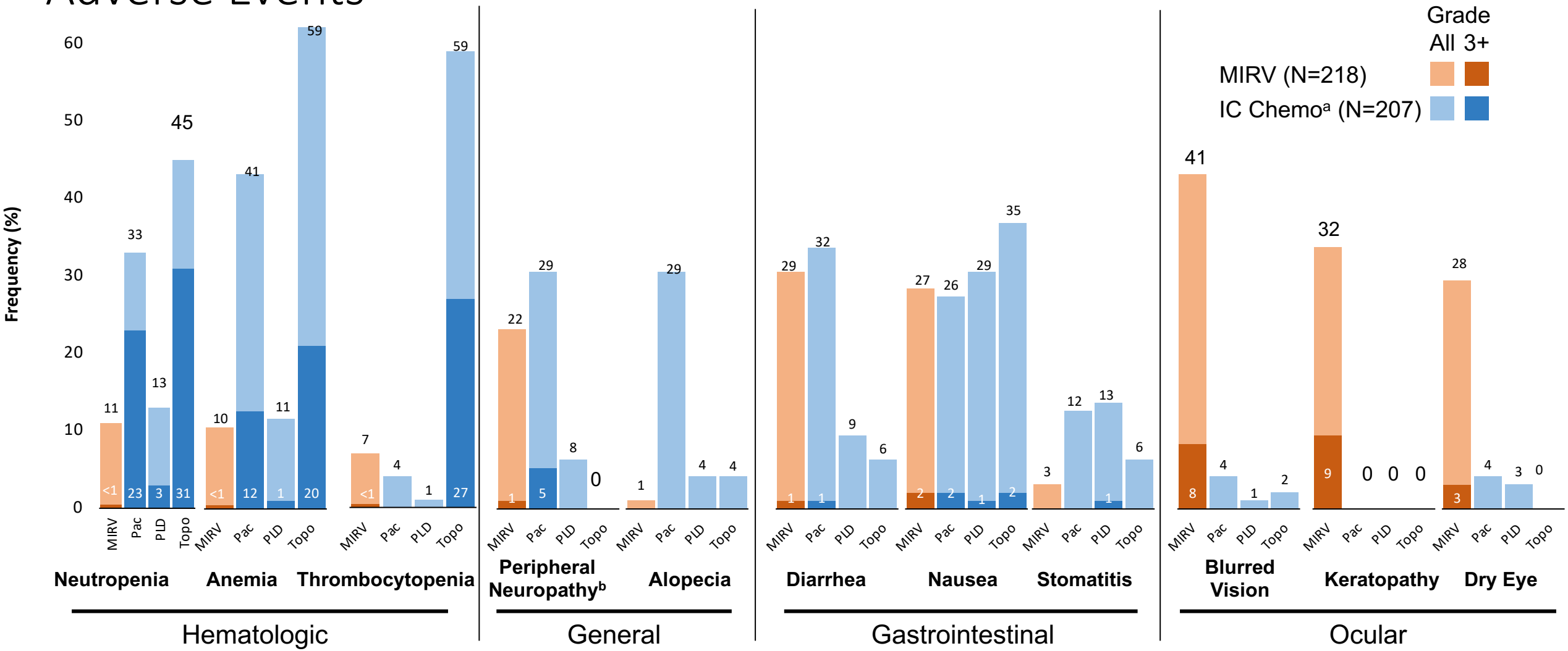
Data cutoff: March 6, 2023; median follow-up time: 13.11 months

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio.

[a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

Moore et al ASCO 2023; Moore et al NEJM 2023.

MIRASOL Differentiated Safety Profile: Treatment-Emergent Adverse Events



Data cutoff: March 6, 2023

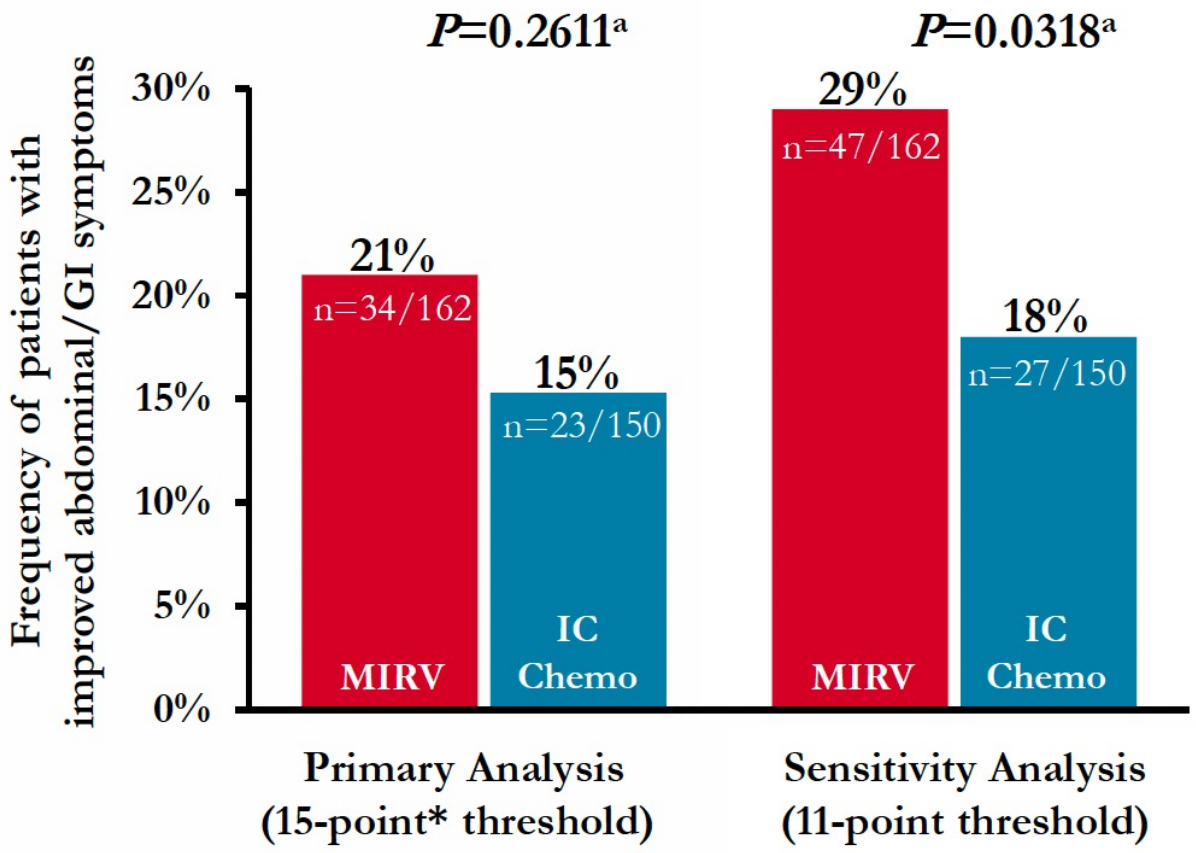
MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

[a]Pac n=82 (39%), PLD n=76 (37%), Topo n=49 (24%). [b]Grade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

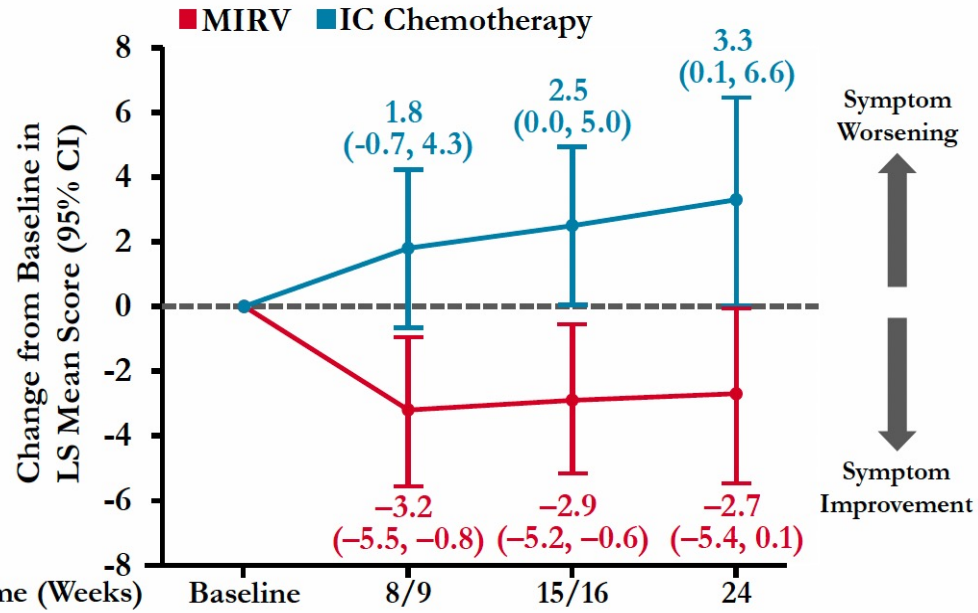
Moore et al ASCO 2023

PRO - MIRASOL

Figure. Responder Analysis for OV28 abdominal/GI symptom subscale scores by treatment group at week 8/9



Figure†. Change from baseline in EORTC QLQ-OV28 Abdominal/GI scale – ITT Population



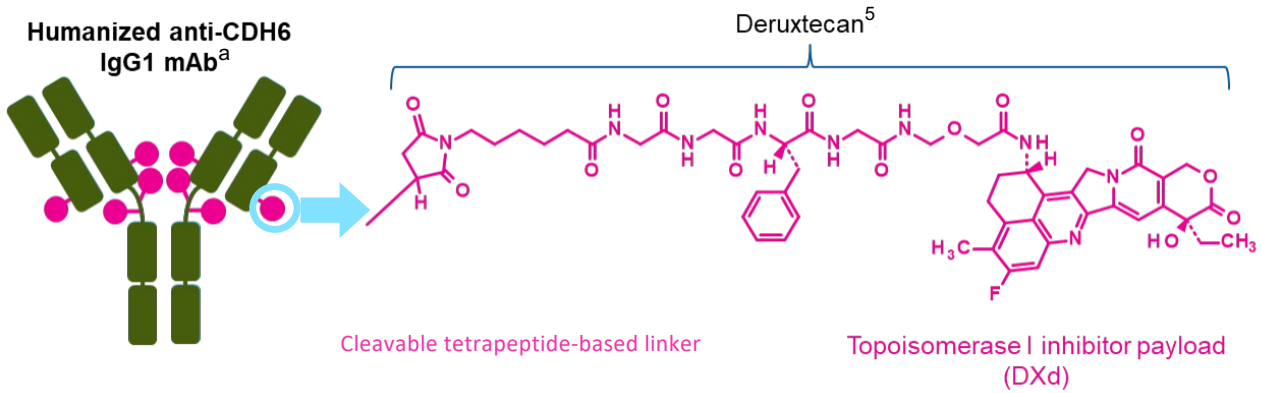
MIRV, n	185	141	93	53
IC Chemotherapy, n	180	123	54	37
Treatment difference[a]	-	−5.0	−5.4	−6.0
(95% CI)	-	(−8.3, −1.6)	(−8.9, −2.0)	(−10.2, −1.8)
P-value	-	0.0041	0.0020	0.0056

Konecny et al SGO 2024

Background

- The emergence of platinum resistance in recurrent OVC is inevitable; these patients have a clear need for novel treatments[1]
- Mirvetuximab soravtansine-gynx received accelerated approval from the FDA for the treatment of patients with platinum-resistant, FRα-positive OVC (ORR: 31.7%, median DOR: 6.9 months)[2]
- Expression of CDH6 is observed in ~65–85% of patients with OVC[3,4]
- **Raludotatug deruxtecan (R-DXd; DS-6000) is a CDH6-directed ADC composed of three parts: a humanized anti-CDH6 IgG1 mAb, covalently linked to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker[5]**

R-DXd was designed with 7 key attributes



- Payload mechanism of action: topoisomerase I inhibitor[5,b]
- High potency of payload[5,b]
- High drug-to-antibody ratio ≈8[5,b]
- Payload with short systemic half-life[6,b,c]
- Stable linker-payload[5,b]
- Tumor-selective cleavable linker[5,b]
- Bystander antitumor effect[5,b]

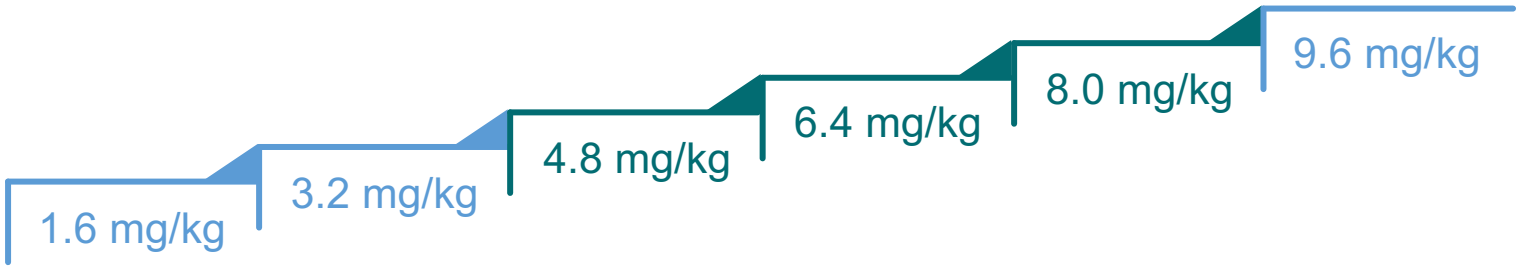
[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.
ADC, antibody–drug conjugate; CDH6, cadherin 6; DOR, duration of response; DXd, deruxtecan; FDA, United States Food and Drug Administration; FRα, folate receptor alpha; IgG1, immunoglobulin G1; mAb, monoclonal antibody; ORR, objective response rate; OVC, ovarian cancer.

1. Richardson DL, et al. *JAMA* Oncol. 2023;9:851–859; 2. ELAHERE™ (mirvetuximab soravtansine-gynx) prescribing information. Accessed September 1, 2023; 3. Bartolomé RA, et al. *Mol Oncol*. 2021;15:1849–1865;
4. Shintani D, et al. *Gynecol Oncol*. 2022;166(Suppl. 1):S116; 5. Suzuki H, et al. *Ann Oncol*. 2021;32(Suppl. 5):S361–S375; 6. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185.

First-in-human phase 1 study of R-DXd (NCT04707248)[1,2]

Subgroup analysis of patients with OVC who received R-DXd at 4.8–8.0 mg/kg[a]

Part A
Dose escalation: R-DXd IV Q3W



Part B
Dose expansion: R-DXd IV Q3W

- OVC cohort: 4.8 mg/kg
- OVC cohort: 6.4 mg/kg
- OVC cohort: 5.6 mg/kg
- OVC cohort: 8.0 mg/kg

Enrollment criteria:

- Advanced/metastatic OVC not amenable to SOC therapy
- ECOG PS 0–1
- Prior taxane and platinum-based chemotherapy
- No previous CDH6-targeting agents or ADCs with a linked topoisomerase I inhibitor
- **Patients were not selected based on tumor CDH6 expression**

Key primary objectives:

- Safety and tolerability
- Determine MTD and RDEs for dose expansion
- Determine ORR per RECIST v1.1 for dose expansion

Key secondary objectives:

- PK: ADC, total anti-CDH6 antibody, and the DXd payload
- Antitumor activity per RECIST v1.1
- Immunogenicity

[a]4.8–8.0 mg/kg R-DXd dose cohorts were initially prioritized for dose expansion due to a favorable benefit/risk profile.

ADC, antibody–drug conjugate; CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; ORR, objective response rate; OVC, ovarian cancer; PK, pharmacokinetics; Q3W, every 3 weeks; RDE, recommended doses for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care.

1. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT04707248. Accessed July 20, 2023; 2. Data on file. Daiichi Sankyo, Inc. DS6000-A-U101 protocol, version 3; 2020.

Safety profile of R-DXd is manageable

Patients with OVC who received R-DXd at 4.8–8.0 mg/kg

Overview of TEAEs

	n (%) N=60
Any TEAEs	57 (95.0)
TEAE with CTCAE Grade ≥3	31 (51.7)
TEAE associated with drug discontinuation	9 (15.0)
TEAE associated with dose interruption	22 (36.7)
TEAE associated with dose reduction	15 (25.0)
Any treatment-related CTCAE Grade ≥3 TEAE	22 (36.7)
Treatment-related TEAE associated with death	2 (3.3)[a]

- 3.3% (2/60) of patients in the 4.8–8.0 mg/kg cohort experienced Grade 5 ILD; both occurred in the 8.0 mg/kg cohort and were adjudicated as treatment-related
- 8.9% (4/45) of patients in the 4.8–6.4 mg/kg cohort experienced ILD (all Grade 2), of which 2 were adjudicated as treatment-related
- As of October 2022, the 8.0 mg/kg cohort was closed due to a higher incidence of serious and Grade ≥3 TEAEs and lack of a favorable benefit/risk ratio[b]
- Further dose assessment is ongoing at three doses: 4.8, 5.6 and 6.4 mg/kg

Data cutoff: July 14, 2023.

[a]Grade 5 ILD. [b]6/15 (40.0%) patients in the 8.0-mg/kg OVC cohort experienced serious and Grade ≥3 TEAEs.

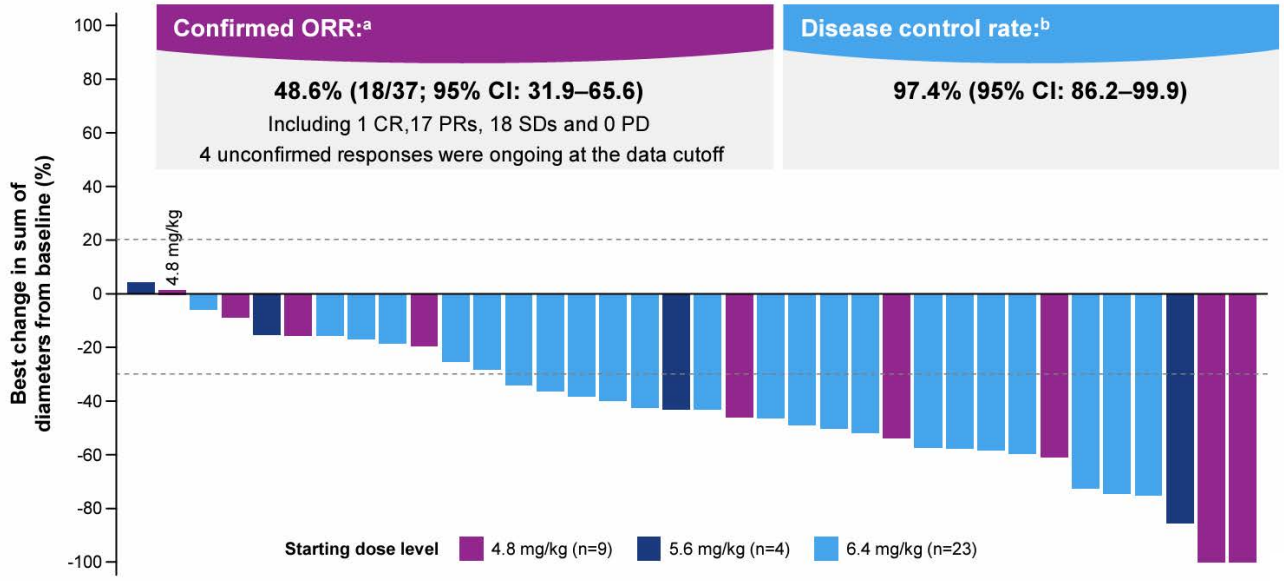
CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; OVC, ovarian cancer; TEAE, treatment-emergent adverse event.

Most common (≥10%) treatment-related TEAEs

Preferred term	n (%) N=60	
	All grades	Grade ≥3
Nausea	35 (58.3)	1 (1.7)
Fatigue	27 (45.0)	2 (3.3)
Vomiting	20 (33.3)	1 (1.7)
Anemia	17 (28.3)	11 (18.3)
Decreased neutrophil count	15 (25.0)	7 (11.7)
Diarrhea	16 (26.7)	1 (1.7)
Decreased appetite	15 (25.0)	1 (1.7)
Decreased platelet count	10 (16.7)	3 (5.0)
Alopecia	7 (11.7)	0
Malaise	6 (10.0)	0

Updated Efficacy and Safety 4.6-6.4 mg/kg

Preliminary antitumor activity of R-DXd is promising in heavily pretreated patients with OVC receiving doses of 4.8–6.4 mg/kg



Data cutoff: July 14, 2023.

[a]The evaluable population (n=37) included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason prior to the first post-baseline tumor assessment with change from baseline in target tumor size assessed per RECIST 1.1; one patient with no target lesion at baseline was excluded from the ORR dataset. [b]CR + PR + SD (per RECIST 1.1) ≥5 weeks. Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan were included in the waterfall plot: 7 patients had no post-baseline scans to date; 1 patient had no measurable lesions at baseline; 1 patient discontinued treatment and had no post-baseline scan.

CI, confidence interval; CR, complete response; OVC, ovarian cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

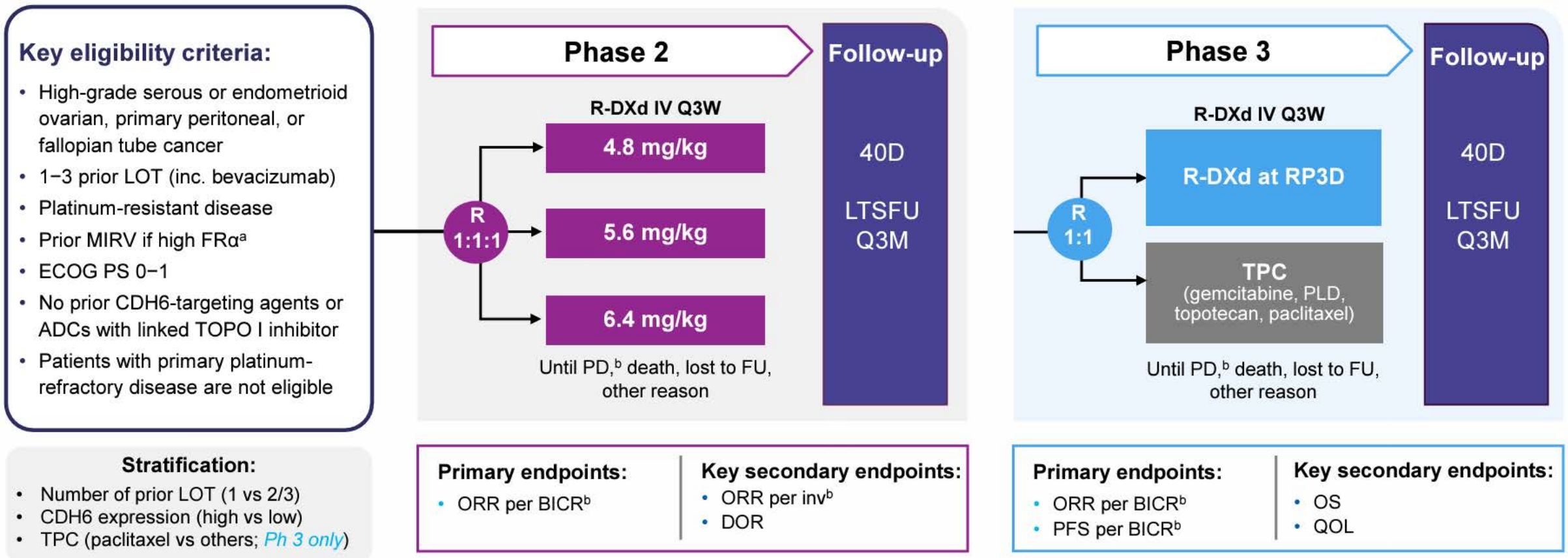
Overall safety summary

	4.8–6.4 mg/kg R-DXd N=45
Any TEAE, n (%)	42 (93.3)
Grade ≥3	20 (44.4)
Treatment-related TEAE, n (%)	41 (91.1)
Grade ≥3	12 (26.7)
Grade 5	0
Any SAE, n (%)	11 (24.4)
Grade ≥3	10 (22.2)
Treatment-related SAE, n (%)	4 (8.9)
Grade ≥3	3 (6.7)
Grade 5	0
Dose modifications,[a] n (%)	
Drug discontinuation	5 (11.1)
Dose interruption	14 (31.1)
Dose reduction	7 (15.6)

- Drug-related ILD/pneumonitis was reported in 2 patients, who received a starting dose of 6.4 mg/kg. Both cases were Grade 2

Moore et al, SGO 2024

REJOICE-Ovarian01: Phase 2/3 randomized study of R-DXd in platinum-resistant OVC (NCT06161025)



Moore et al, SGO 2024

DESTINY-PanTumor02: a Phase 2 study of T-DXd for HER2-expressing solid tumors

An open-label, multicenter study (NCT04482309)

Key eligibility criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd
5.4 mg/kg Q3W

40 per cohort[b]

- Endometrial cancer
- Cervical cancer
- Ovarian cancer
- Bladder cancer
- Other tumors[c]
- Biliary tract cancer
- Pancreatic cancer

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analysis

- Subgroup analyses by HER2 status

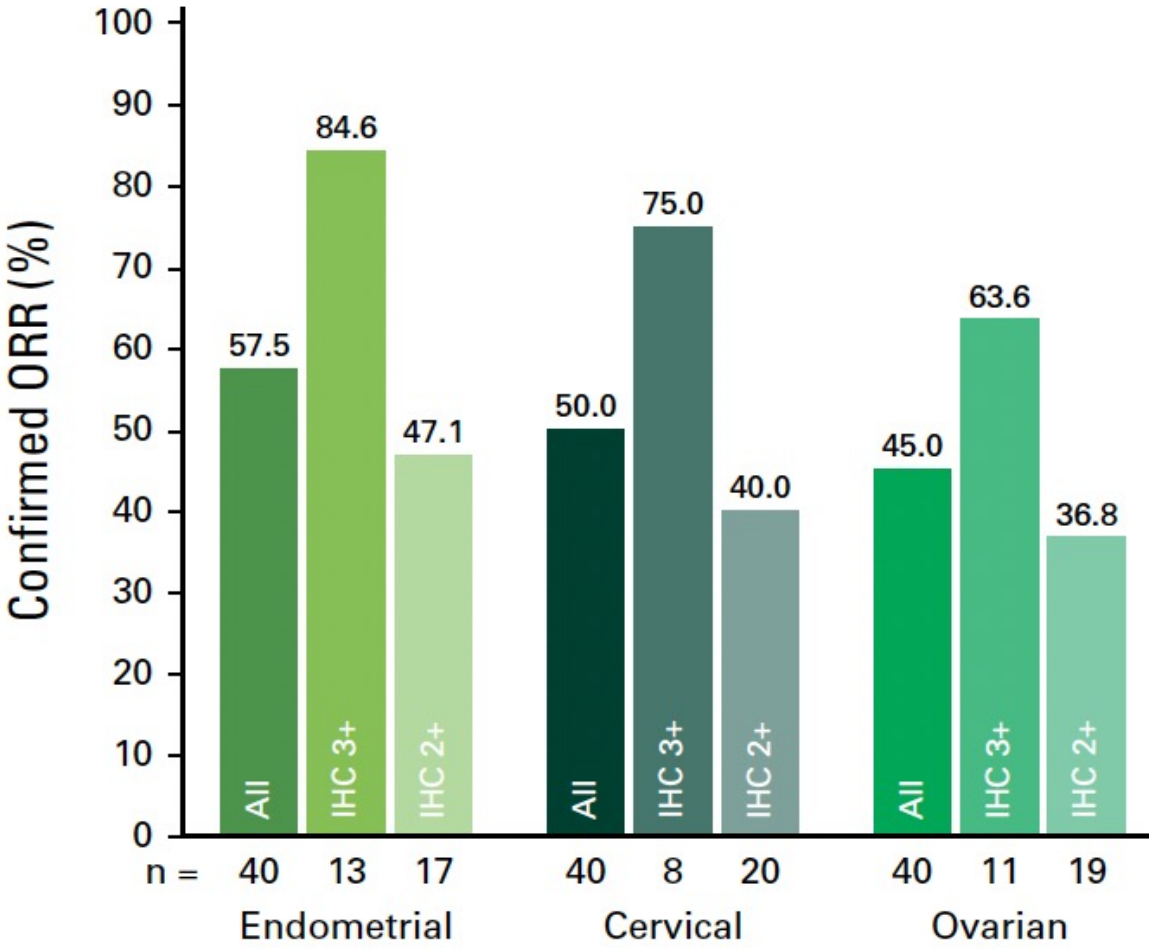
Primary analysis
data cutoff: Jun 8, 2023
Median follow up: 12.75 mo

Baseline characteristics

- 267 patients received treatment; 202 (75.7%) based on local HER2 testing
  - 111 (41.6%) patients were IHC 3+ based on HER2 test (local or central) at enrollment, primary efficacy analysis (all patients)
  - **75 (28.1%) patients were IHC 3+ on central testing**, sensitivity analysis on efficacy endpoints (subgroup analyses)
- Median age was 62 years (23–85) and **109 (40.8%) patients had received ≥3 lines of therapy**

Meric-Bernstam F, et al.,JCO 2023
Meric-Bernstam F, et al ESMO 2023

DESTINY-PanTumor02 T-DXd – Algebra Help from my Daughter



Endometrial – 23 responders
- HER2 3+: 11/13 (84.6%)
- HER2 2+: 8/17 (47.1%)
- All: 23/40 (57.5%)
- 4 – 1+; 5 – 0; 1 – (unk)nown
- **HER2 unk/0/1+: 4/10 (40%)**

Cervical – 20 responders
- HER2 3+: 6/8 (75%)
- HER2 2+: 8/20 (40%)
- All: 20/40 (50%)
- 8 – 1+; 4 – 0
- **HER2 0/1+: 6/12 (50%)**

Ovarian – 18 responders
- HER2 3+: 7/11 (63.6%)
- HER2 2+: 7/19 (36.8%)
- All: 18/40 (45%)
- 5 – 1+; 5 – 0
- **HER2 0/1+: 4/10 (40%)**

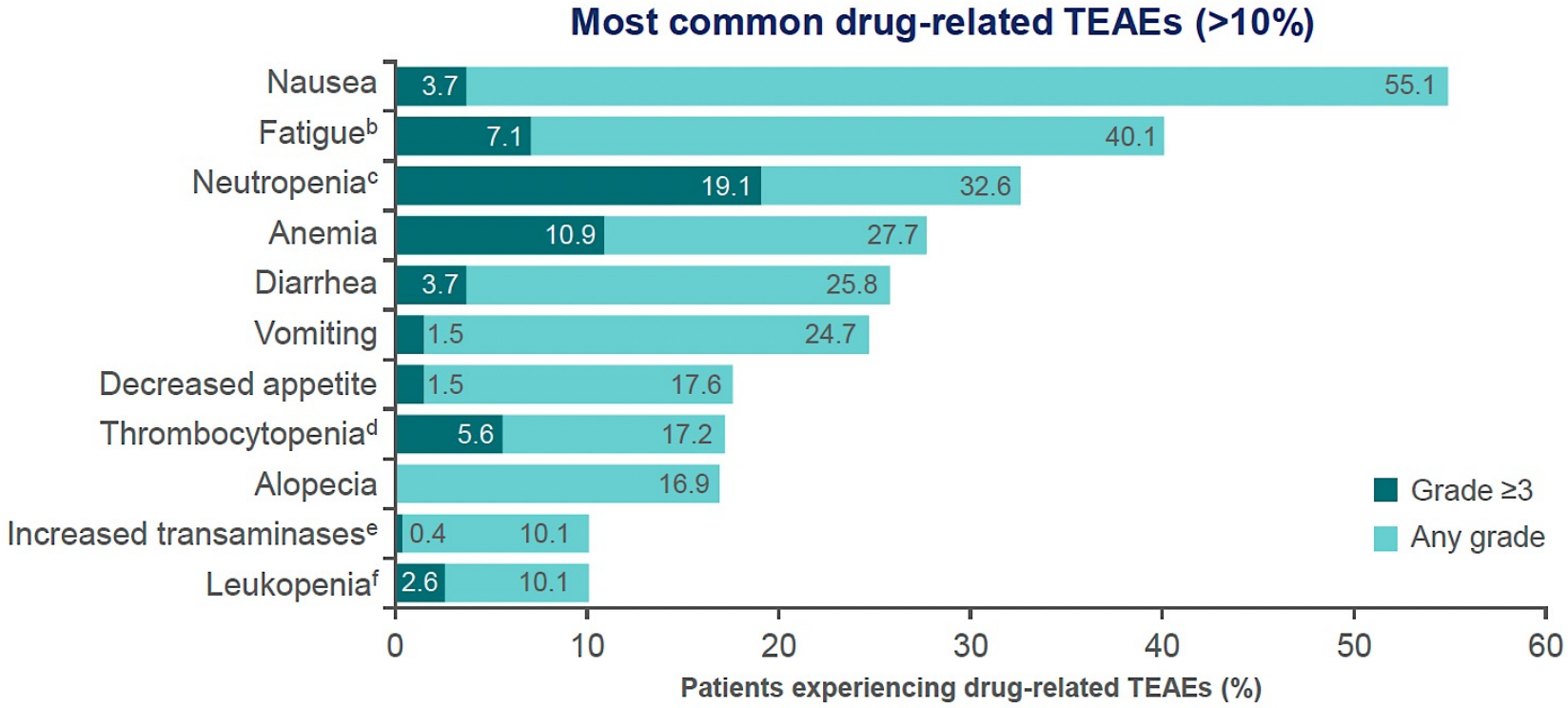
Meric-Bernstam F, et al JCO 2023
Meric-Bernstam F, et al ESMO 2023

Data of # of HER2 unknown, 0, 1+ found in supplement

DESTINY-PanTumor02 T-DXd

Safety summary

n (%)	All patients (N=267)
Any drug-related TEAEs	226 (84.6)
Drug-related TEAEs Grade ≥3	109 (40.8)
Serious drug-related TEAEs	36 (13.5)
Drug-related TEAEs associated with dose discontinuations	23 (8.6)
Drug-related TEAEs associated with dose interruptions	54 (20.2)
Drug-related TEAEs associated with dose reductions	54 (20.2)
Drug-related TEAEs associated with deaths	4 (1.5)[a]



ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	7 (2.6)	17 (6.4)	1 (0.4)	0	3 (1.1)	28 (10.5)

a: Included pneumonia (n=1), organizing pneumonia (n=1), pneumonitis (n=1), and neutropenic sepsis (n=1).

Meric-Bernstam F, et al JCO 2023

Meric-Bernstam F, et al 2023 ESMO Annual Meeting

Agenda

Module 1: Ovarian Cancer; Role of HER2-Directed Therapy in Gynecologic Cancers — Dr O'Malley

Module 2: Endometrial Cancer and Cervical Cancer — Dr Monk

TREATMENT OF ADVANCED AND RECURRENT ENDOMETRIAL CANCER (EC) and Cervical Cancer(CC) March 2024

Bradley J. Monk, MD, FACS, FACOG
Florida Cancer Specialists and Research Institute
Medical Director Late-Phase Clinical Research
West Palm Beach, FL 33401
bradley.monk@flcancer.com

Vice President and Member Board of Directors GOG-Foundation
Director GOG-Partners
bmonk@gog.org

DISCLOSURES

Consulting Agreements	Acrivon Therapeutics, Adaptimmune, Agenus Inc, Akeso Biopharma Co Ltd, Amgen Inc, Aravive Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Clovis Oncology, Eisai Inc, Elevar Therapeutics, Genentech, a member of the Roche Group, Genmab US Inc, Gradalis Inc, Hengrui Therapeutics Inc, ImmunoGen Inc, Iovance Biotherapeutics, Karyopharm Therapeutics, Laekna Therapeutics, Merck, Merck KGaA, Mersana Therapeutics Inc, Myriad Genetic Laboratories Inc, Novartis, Novocure Inc, OncoC4, Panavance Therapeutics, Pfizer Inc, Pieris Pharmaceuticals Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Seagen Inc, Sorrento Therapeutics, Tesaro, A GSK Company, VBL Therapeutics, Verastem Inc, Zentalis Pharmaceuticals
Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, Genentech, a member of the Roche Group, ImmunoGen Inc, Merck, Myriad Genetic Laboratories Inc, Tesaro, A GSK Company
Nonrelevant Financial Relationship	US Oncology Research

What's Your Approach?

- Prior Carboplatin + Paclitaxel
- Grade 3 endometrioid adenocarcinoma
- MSI-H
- CPI-naïve
- HER2 IHC3+
- What if HER2 expression was IHC2+?
- **What do you discuss with the patient?**

Discussion

What's Your Approach?

- Recurrent cervical carcinoma
- IO-naïve
- How do you decide on a 2L regimen?
  - ADC (eg, TV)
  - IO (eg, pembrolizumab or cemiplimab in Europe)
- What if she was IO exposed?
- **What do you discuss with the patient?**

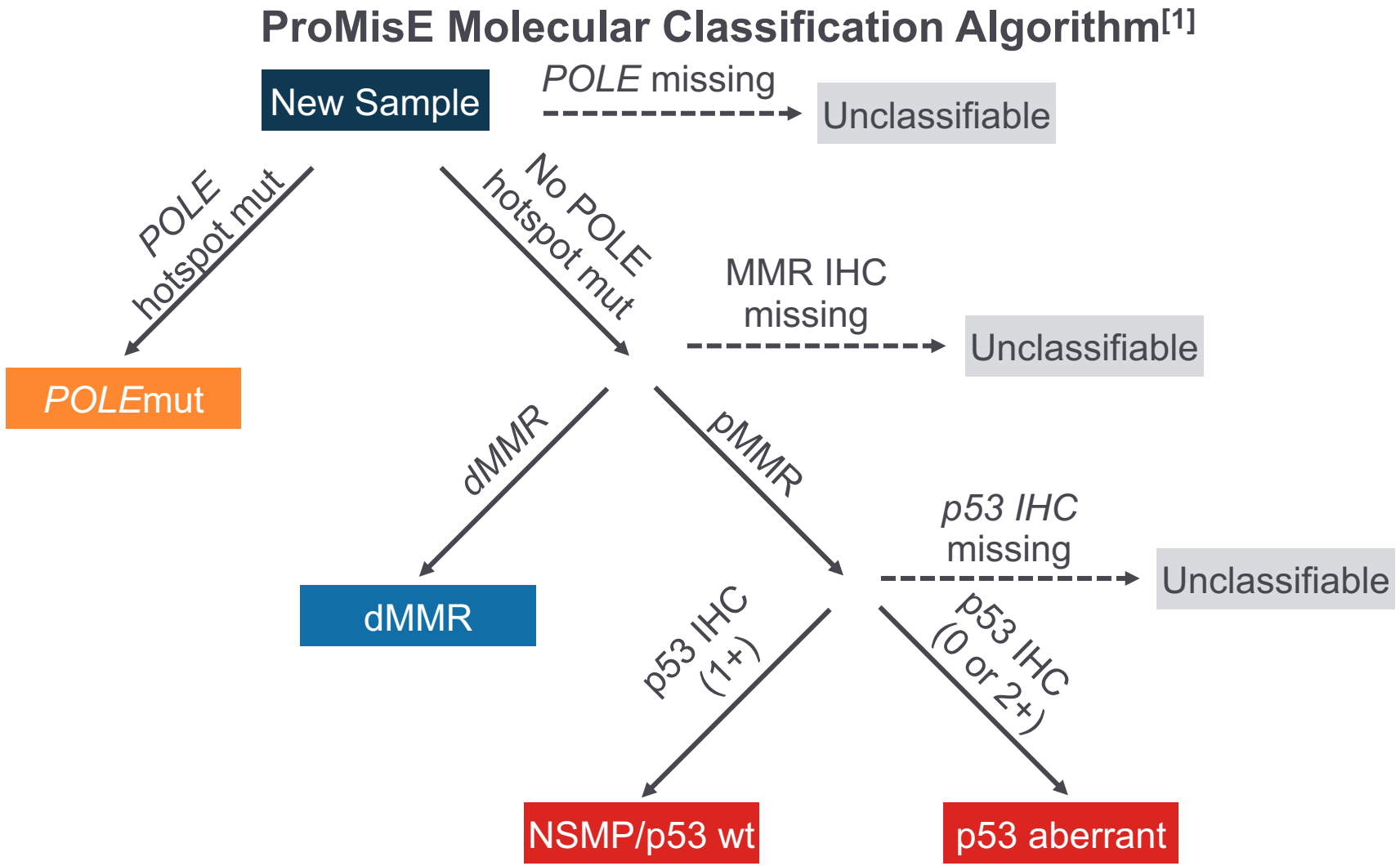
Discussion

Overview

- Update clinical trial data from recent oncology and gynecologic oncology conferences
- Update regulatory environment in EC and CC
- Defining context for personalized medicine

EC, endometrial cancer; irAE, immune-related adverse event.

Molecular Profiling in Newly Diagnosed EC



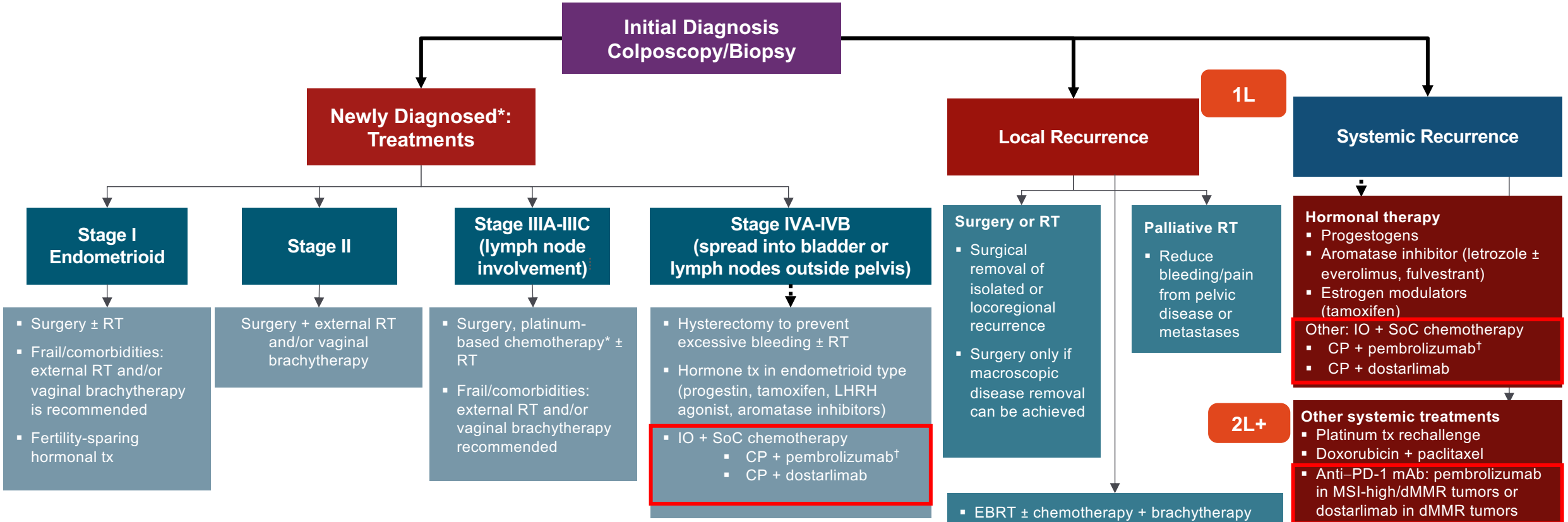
Recommended molecular profiling in newly diagnosed EC[2]

- MMR status[2] (presence or absence of MLH1, PMS2, MSH2, and MSH6 proteins[3])
- *POLE* status (if feasible)[2] or if status would influence adjuvant treatment[3]
  - May be lower priority for **very low-risk** EC[3]
- p53 status[2]
- ER/PR expression[2]
- HER2 amplification[2]

dMMR, mismatch repair deficient; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mut, mutated; NSMP, no specific molecular profile; pMMR, proficient MMR; PR, progesterone receptor; TMB-H, tumor mutational burden-high; wt, wild type.

1. Walsh CS, et al. Gynecol Oncol. 2023;168:48-55; 2. NCCN®. Uterine Neoplasms (v1.2024). 2023. Accessed November 30, 2023. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf; 3. Berg HG, et al. Br J Cancer. 2023;128:647-655; 3. Jamieson A, et al. J Natl Compr Canc Netw. 2023;21:210-216.

Current Use of Immune Checkpoint Inhibitors in Advanced EC



*Paclitaxel, carboplatin, doxorubicin or liposomal doxorubicin, and docetaxel. †Not FDA approved for this indication.

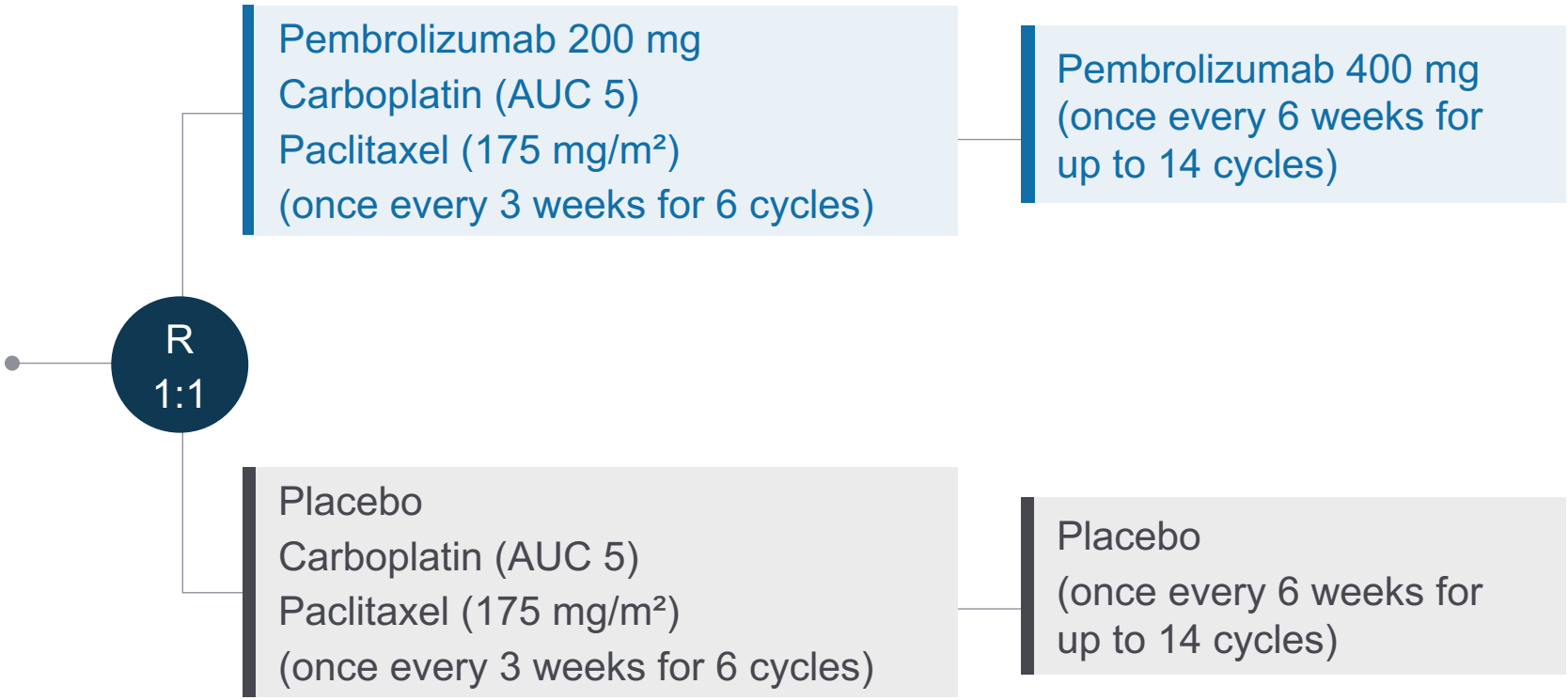
NCCN. Clinical practice guidelines in oncology. Uterine cancer. Version 1.2024.

Phase 3 Trial of Pembrolizumab Plus Chemotherapy in EC
NRG-GY018 Study Design

Key eligibility criteria (N = 816)

- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent EC **(excluding carcinosarcoma)**
- Known MMR status
- Prior adjuvant chemotherapy allowed if completed ≥ 12 months before study

Outcomes were stratified by dMMR (n = 225) vs pMMR (n = 591) status



Primary endpoint: PFS by investigator
Secondary endpoints: Safety, ORR, DOR, OS, PRO/QOL

AUC, area under the curve; DOR, duration of response; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; QOL, quality of life.
Eskander RN, et al. Ann Oncol. 2023;34(2_suppl): Abstract LBA43; Eskander RN, et al. N Engl J Med. 2023;388:2159-2170.

Phase 3 Trial of Dostarlimab Plus Chemotherapy in Advanced EC
RUBY/ENGOT-EN6/GOG-3031/NSGO Study Design

Key eligibility criteria

- Stage III/IV or first recurrent EC (**carcinosarcoma, clear cell, serous, or mixed histology**)
- Low potential for cure by RT or surgery alone or combined
- No systemic therapy or recurrence or PD ≥ 6 months after therapy

R
1:1

Dostarlimab 500 mg (n = 245)
Carboplatin (AUC 5)
Paclitaxel (175 mg/m²)
(once every 3 weeks for 6 cycles)

→ Dostarlimab 1000 mg (once every 6 weeks for up to 3 years)

Placebo (n = 249)
Carboplatin (AUC 5)
Paclitaxel (175 mg/m²)
(once every 3 weeks for 6 cycles)

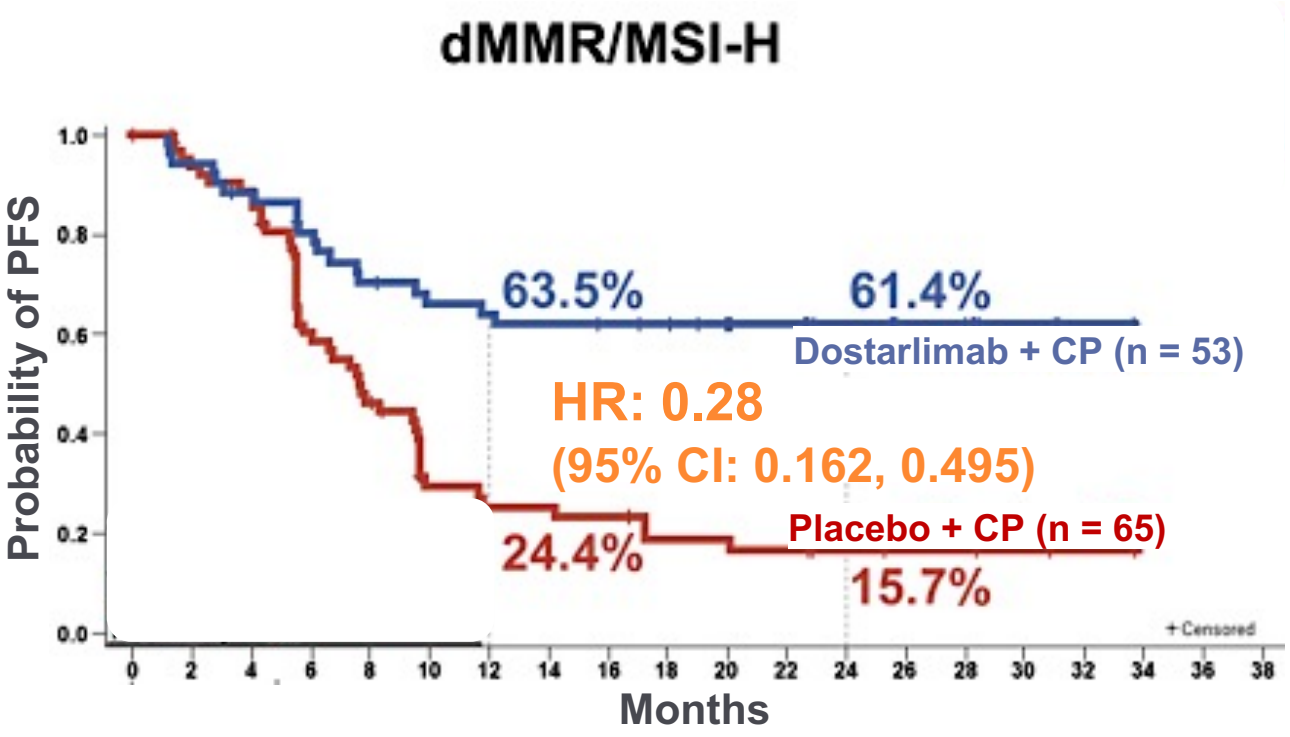
→ Placebo (once every 6 weeks for up to 3 years)

Primary endpoints: PFS by investigator, OS
Secondary endpoints: PFS by BICR, PFS2, ORR, DOR, DCR, HR-QOL/PRO, safety

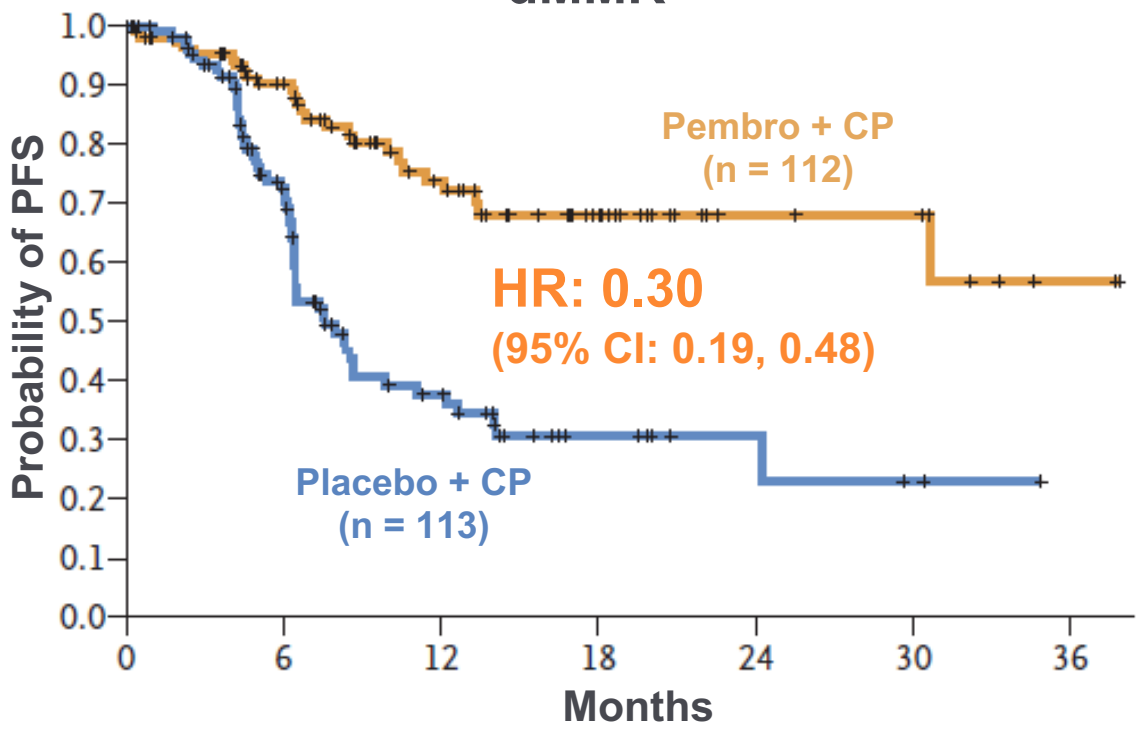
BICR, blinded independent central review; DCR, disease control rate; HR-QOL, health-related QOL; PD, progressive disease; RT, radiation therapy.
Mirza MR, et al. Ann Oncol. 2023;34(2_suppl): Abstract 740MO.

PFS in dMMR Cohorts in the NRG-GY018 and RUBY Trials

RUBY[1]



NRG-GY018[2]



PFS outcomes in the dMMR cohort were similar in both trials, with a 70% reduction in the risk of PD or death with pembrolizumab and a 72% reduction with dostarlimab

CP, carboplatin-paclitaxel; pembro, pembrolizumab.

1. Mirza MR, et al. Ann Oncol. 2023;34(2_suppl 2): Abstract 740MO; 2. Eskander RN, et al. N Engl J Med. 2023;388:2159-2170.

OS in RUBY Trial

Press release

For media and investors only

Issued: 30 October 2023, London UK

Phase III RUBY trial of dostarlimab plus chemotherapy meets endpoint of overall survival in patients with primary advanced or recurrent endometrial cancer

- Statistically significant and clinically meaningful overall survival benefit observed in the overall population in the trial
- Dostarlimab plus chemotherapy is the only immuno-oncology combination regimen to show an overall survival benefit in this patient population

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"A clinically meaningful OS benefit was observed in the mismatch repair proficient (MMRp) / microsatellite stable (MSS) patient subgroup"

https://www.gsk.com/en-gb/media/press-releases/phase-iii-ruby-trial-of-jemperli-dostarlimab-plus-chemotherapy-meets-endpoint-of-overall-survival-in-patients-with-primary-advanced-or-recurrent-endometrial-cancer/

All-comer FDA Action Date June 21, 2024.

NEWS RELEASE

FDA Grants Priority Review to Application for Pembrolizumab Plus Chemotherapy as Treatment for Primary Advanced or Recurrent Endometrial Carcinoma

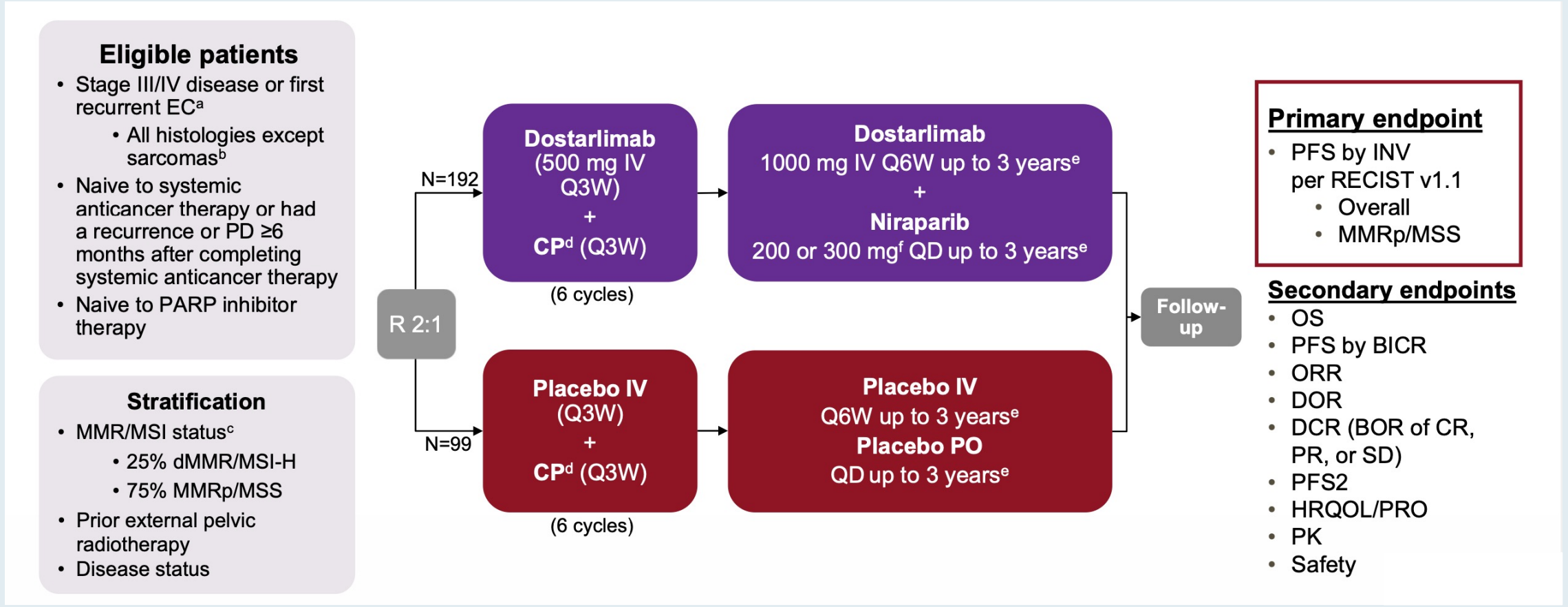
2/20/2024

Acceptance based on results from the pivotal Phase 3 NRG-GY018 trial

Health authorities in Israel, Canada, Australia, Singapore and Brazil will review this application as part of Project Orbis

https://www.merck.com/news/fda-grants-priority-review-to-mercks-application-for-keytruda-pembrolizumab-plus-chemotherapy-as-treatment-for-primary-advanced-or-recurrent-endometrial-carcinoma/

Phase III ENGOT-EN6-NSGO/GOG-3031/RUBY Part 2 Study Design

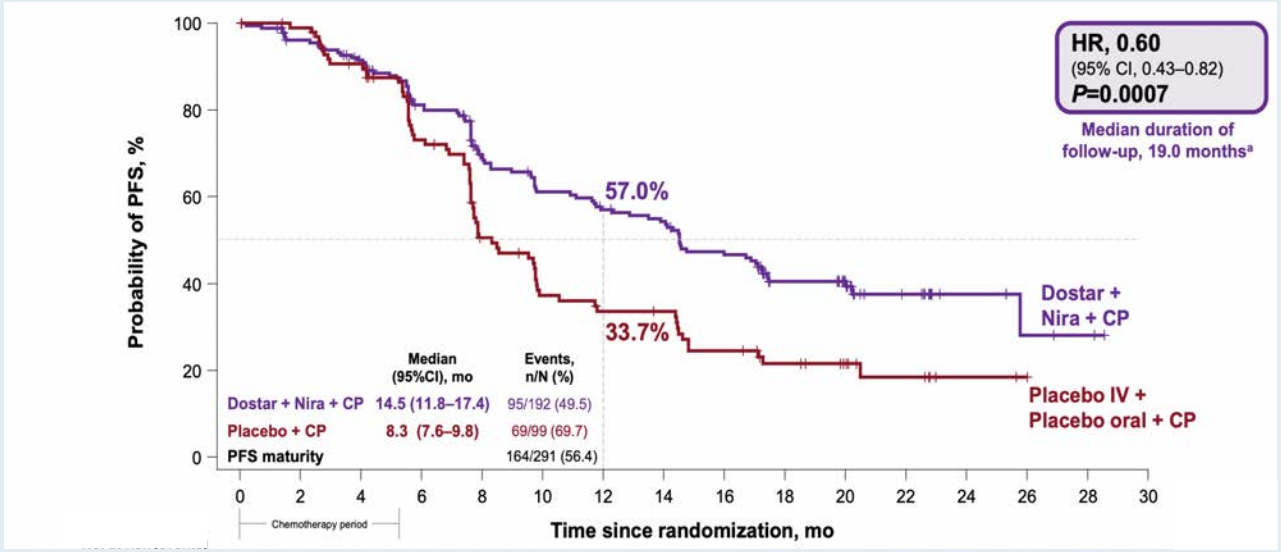


CP = carboplatin/paclitaxel

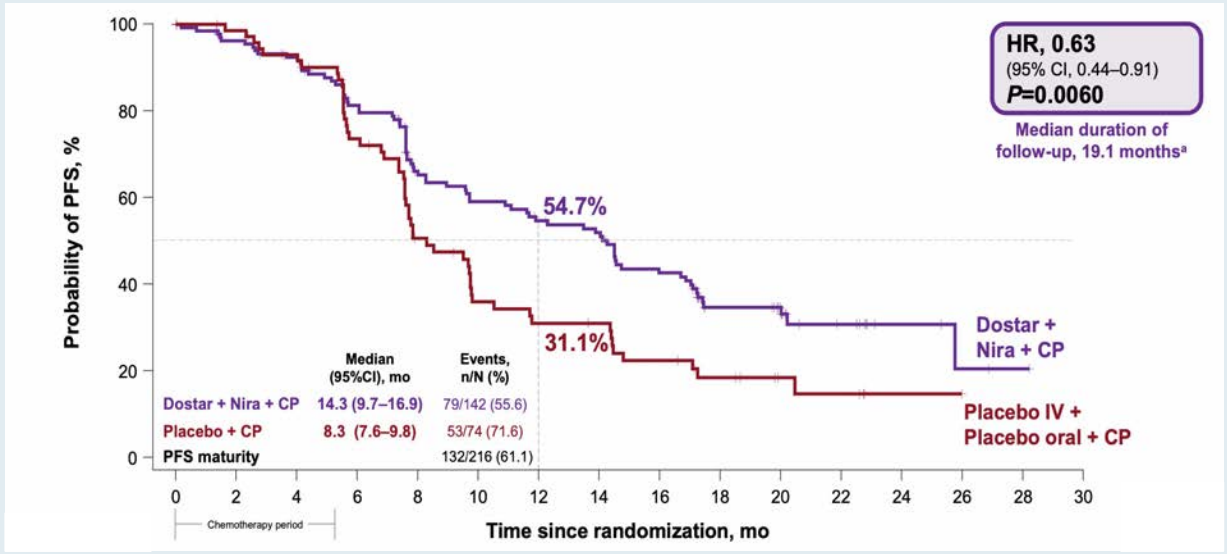
Mirza et al. SGO 2024

Phase III RUBY Part 2: PFS by Subgroup

Overall Population



MMRp/MSS Population

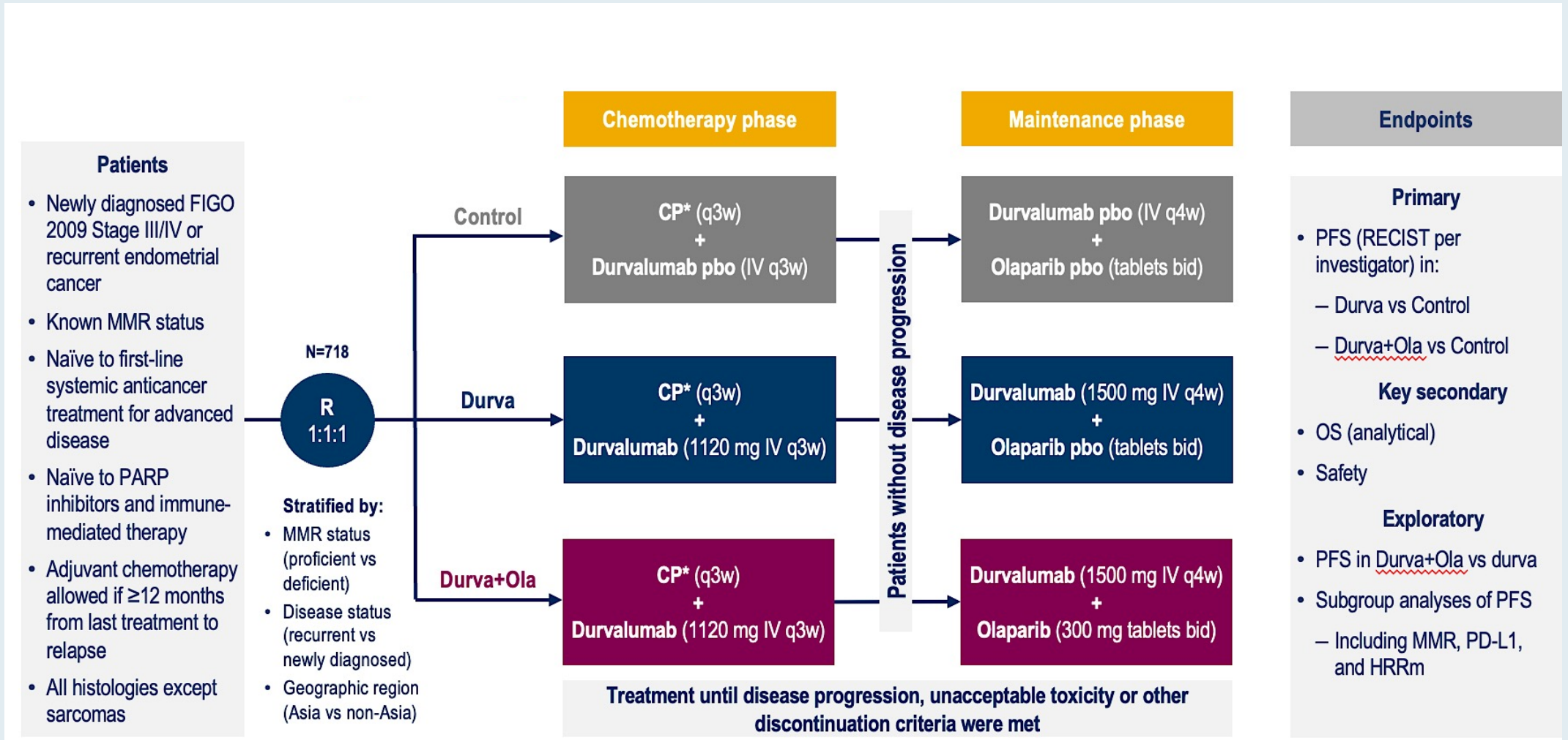


MMRp = mismatch repair proficient; MSS = microsatellite stable

Mirza et al. SGO 2024

RTP RESEARCH TO PRACTICE

Phase III DUO-E Study Design



*Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg per mL/min and paclitaxel 175 mg/m^2.
bid, twice daily; CP, carboplatin/paclitaxel; durva, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation; IV, intravenously; ola, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

MADRID 2023 ESMO congress

Shannon N. Westin

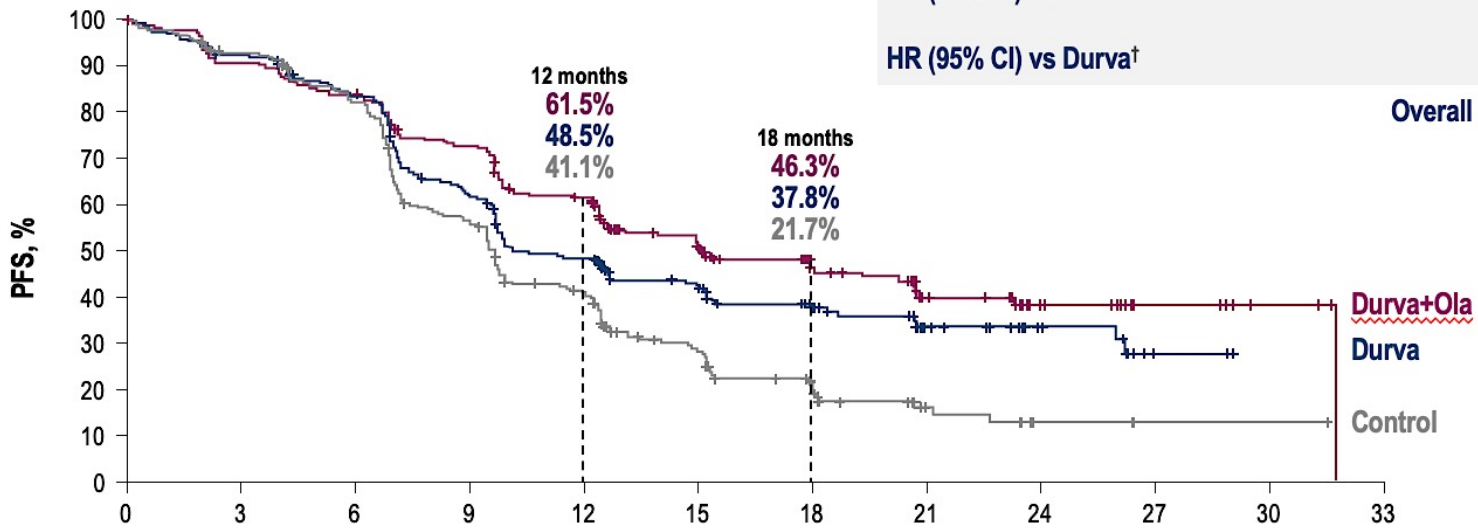
Westin SN et al. *J Clin Oncol* 2024;42(3):283-99.

RTP RESEARCH TO PRACTICE

Phase III DUO-E: PFS in ITT Population

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%



No. at risk												
Durva+Ola	239	214	198	169	139	95	51	30	16	7	3	0
Durva	238	211	188	138	105	69	45	26	13	5	0	0
Control	241	213	184	125	86	45	26	10	3	1	1	0

The median (range) duration of follow-up for PFS was 12.6 (0.0–31.6), 15.4 (0.0–29.1), and 15.4 (0.0–31.7) months in censored patients for the Control, Durva, and Durva+Ola arms, respectively. PFS rates were estimated by the KM method. *CI for median PFS is derived based on the Brookmeyer–Crowley method; †The primary PFS analysis for each comparison was performed separately. The HR and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. The *P* value was calculated using a log-rank test stratified by MMR and disease status. ITT, intent-to-treat; KM, Kaplan–Meier.

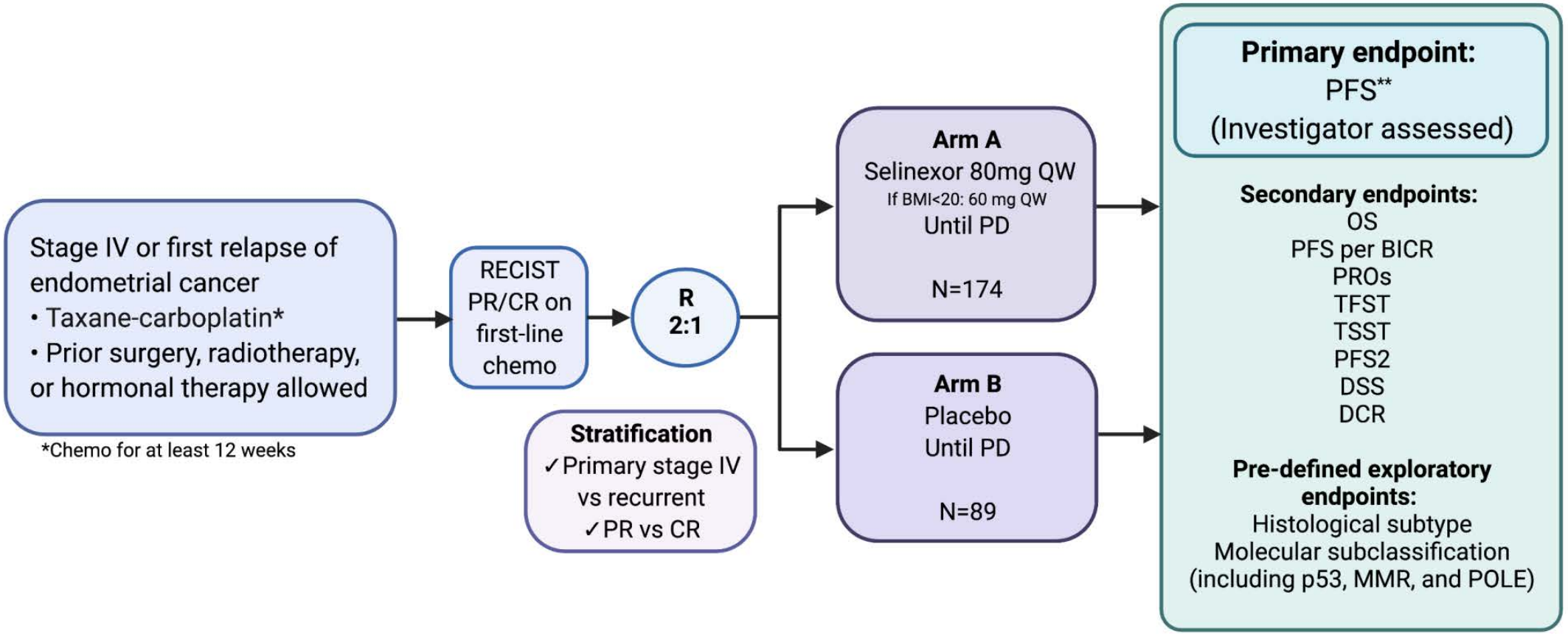
MADRID 2023 ESMO congress

Shannon N. Westin

Westin SN et al. *J Clin Oncol* 2024;42(3):283-99.

RTP RESEARCH TO PRACTICE

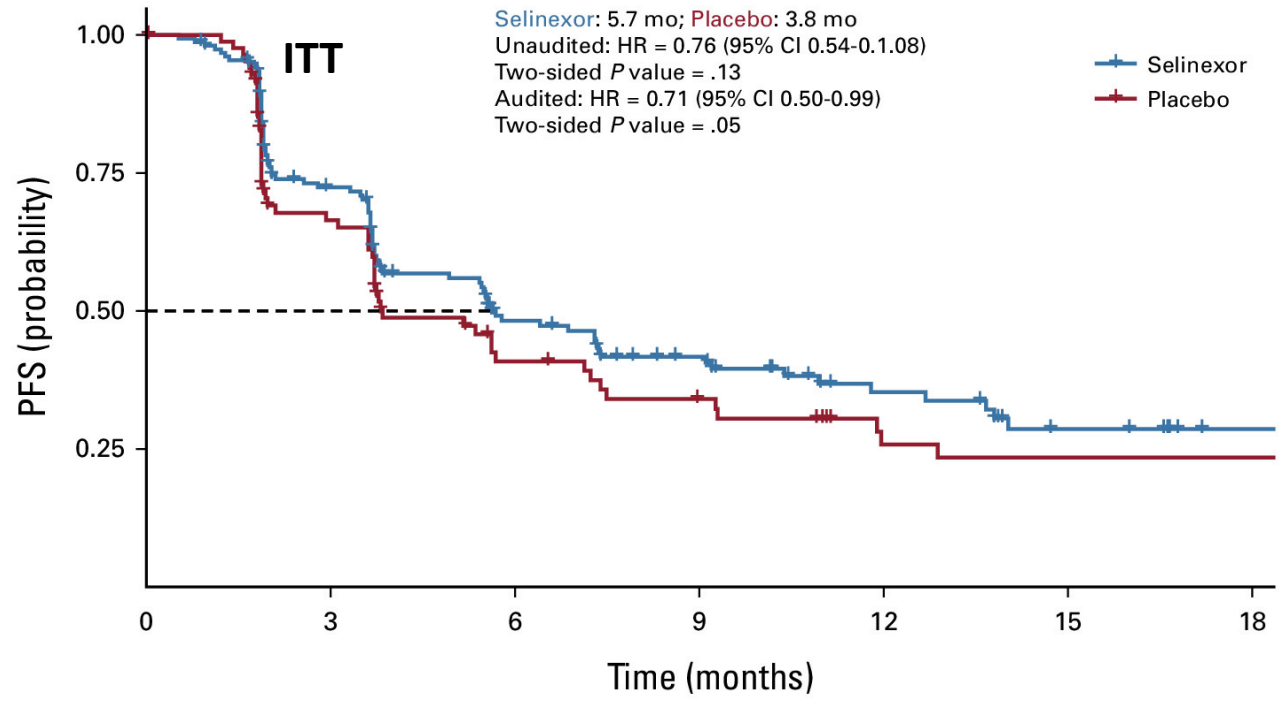
Phase III ENGOT-EN5/GOG-3055/SIENDO Study Design

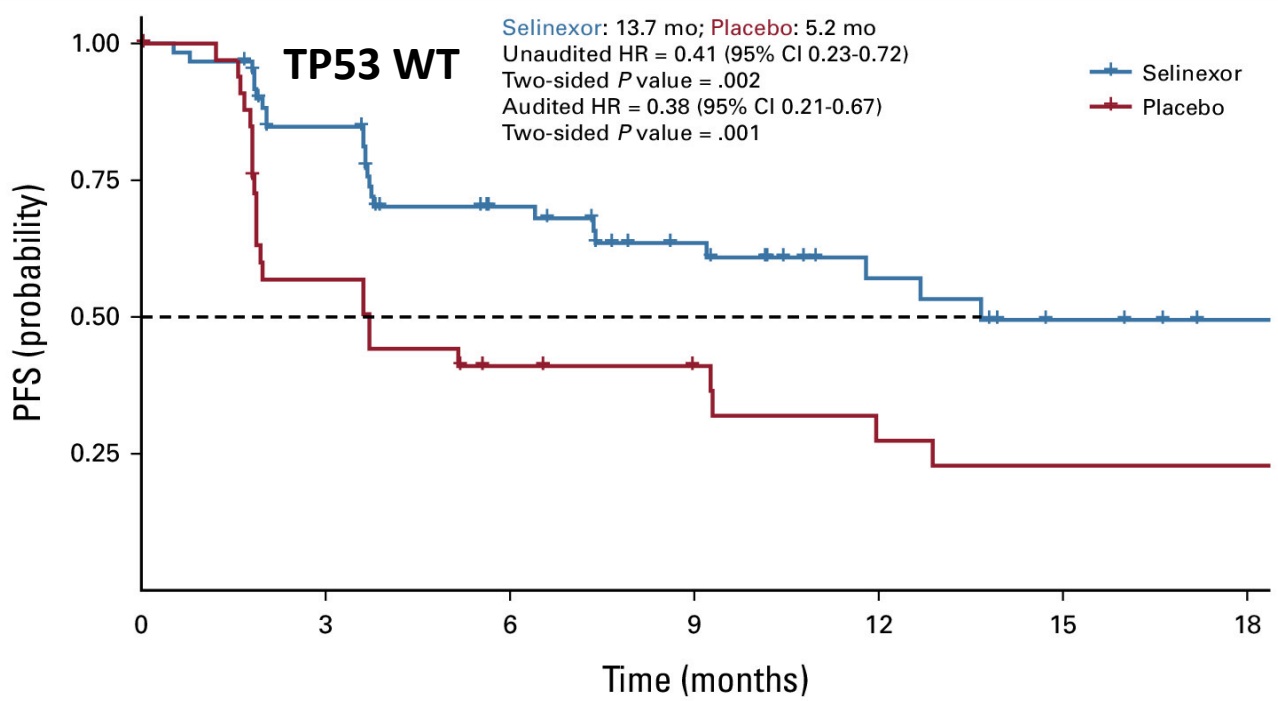


**140 PFS events needed to provide 80% power to detect a hazard ratio of 0.6 (median PFS 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.

Vergote I et al. *J Clin Oncol* 2023;41(35):5400-10.

Phase III SIENDO Trial: PFS in ITT and TP53-WT Populations





Vergote I et al. *J Clin Oncol* 2023;41(35):5400-10.

Treat pMMR EC According to Guidelines/FDA Approvals

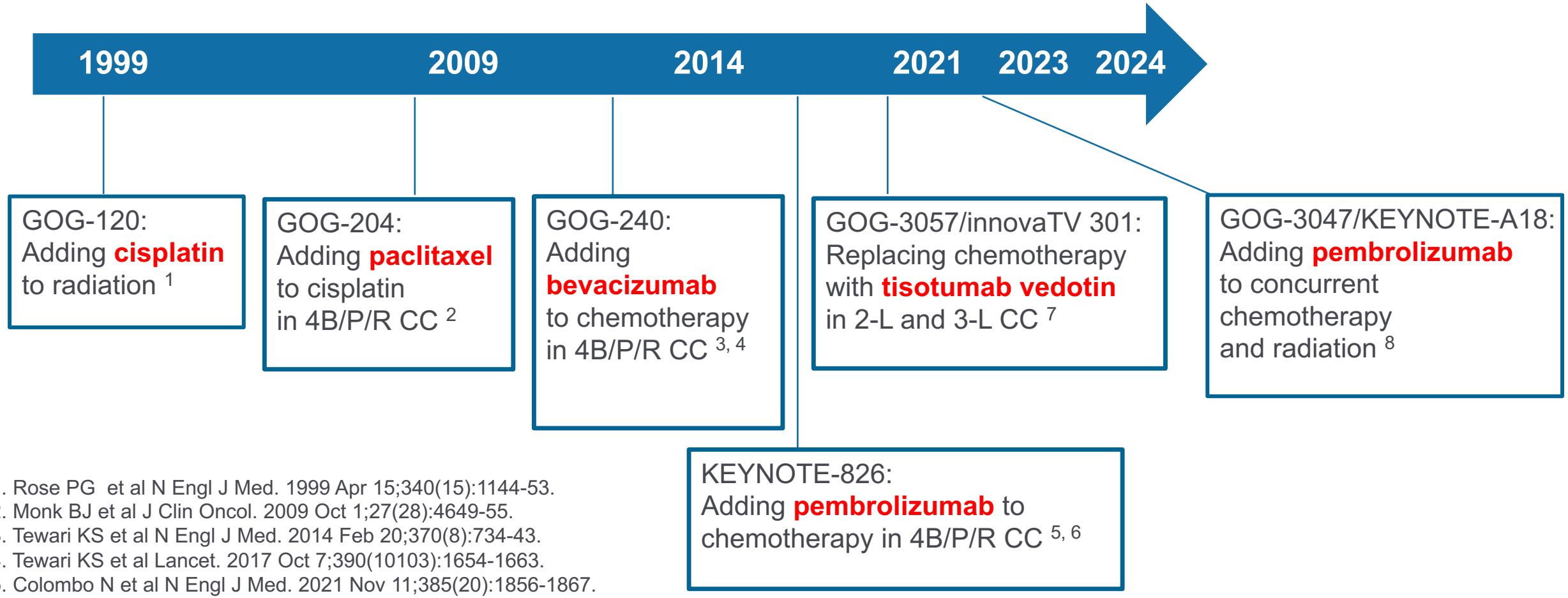
NCCN guidelines include dostarlimab/CP and pembrolizumab/CP as category 1 regimens for primary therapy, and either is an option for pMMR EC[a]

NCCN guidelines for systemic therapy do not include atezolizumab/CP or the durvalumab/olaparib/CP regimen, and more data are needed to confirm efficacy

[a]Pembrolizumab is not recommended for patients with carcinosarcoma.

NCCN®. Uterine Neoplasms (v.1.2024). 2023. Accessed November 30, 2023. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

Six Practice Changing Phase 3 Trials in Cervical Cancer



1. Rose PG et al N Engl J Med. 1999 Apr 15;340(15):1144-53.
2. Monk BJ et al J Clin Oncol. 2009 Oct 1;27(28):4649-55.
3. Tewari KS et al N Engl J Med. 2014 Feb 20;370(8):734-43.
4. Tewari KS et al Lancet. 2017 Oct 7;390(10103):1654-1663.
5. Colombo N et al N Engl J Med. 2021 Nov 11;385(20):1856-1867.
6. Monk BJ et al J Clin Oncol. 2023 Dec 20;41(36):5505-5511.
7. Vergote I et al ESMO 2023.
8. Lorusso D et al ESMO 2023.

ENGOT-cx11/GOG-3047/KEYNOTE-A18: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

- FIGO 2014 stage IB2-IIB (node-positive disease) or FIGO 2014 stage III-IVA (either node-positive or node-negative disease)
- RECIST 1.1 measurable or non-measurable disease
- Treatment naïve

Stratification Factors

- Planned EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT)
- Stage at screening (stage IB2-IIB vs III-IVA)
- Planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQ2D])

R
1:1
N = 1060

Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy
+
Pembrolizumab 200 mg Q3W for 5 cycles

Pembrolizumab 400 mg Q6W for 15 cycles

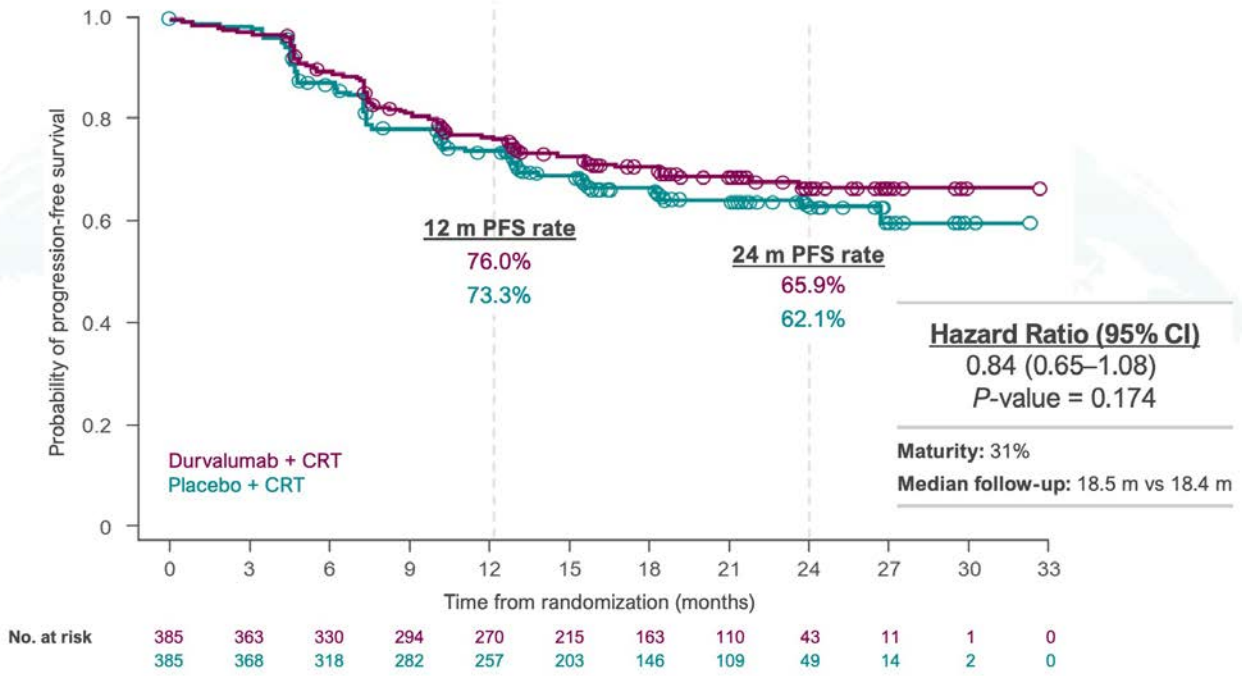
Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy
+
Placebo Q3W for 5 cycles

Placebo Q6W for 15 cycles

[a]A 6th cycle was allowed per investigator discretion. EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; Gy, grays; IMRT, intensity-modulated radiotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; VMAT, volumetric-modulated arc therapy. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

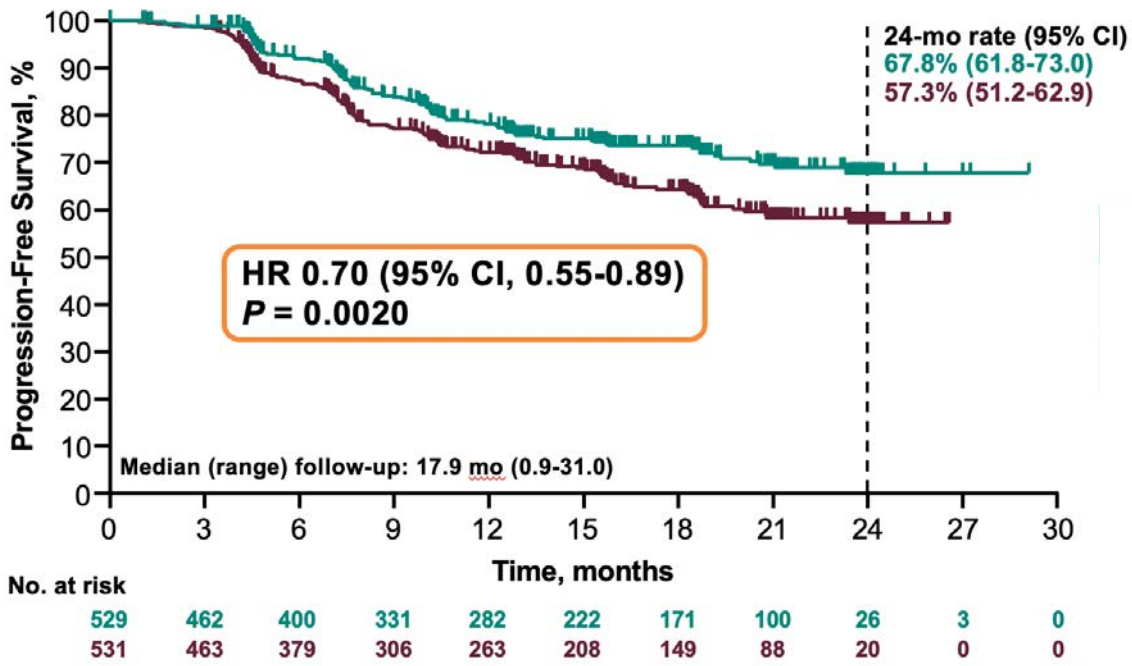
Adding Immune Checkpoint Inhibitors CCRT in LACC

Durvalumab in CALLA



Monk BJ et al IGCS 2023 Abstract 001/504
Lancet Oncol. 2023 Dec;24(12):1334-1348

Pembrolizumab in KEYNOTE-A-18



Lorusso D et al ESMO 2023 LBA 3172

MADRID 2023 ESMO congress

Discussant Bradley J. Monk

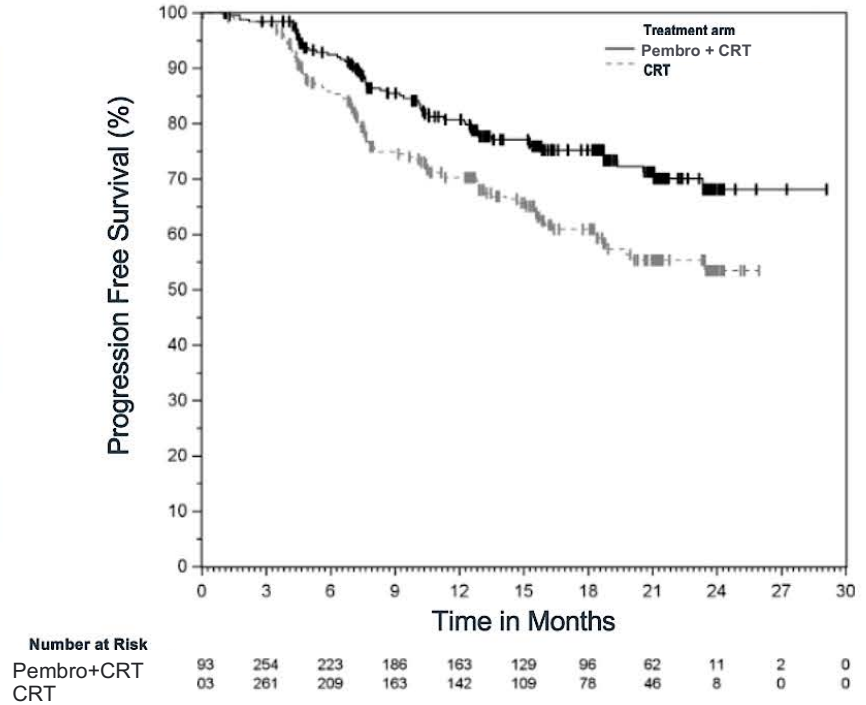
KEYNOTE-A18/GOG-3047: Efficacy in Patients with FIGO2014 Stage III-IVA Cervical Cancer

- In an exploratory subgroup analysis for the 462 patients (44%) with FIGO 2014 Stage IB2-IIB disease, the PFS HR estimate was 0.91 (95% CI: 0.63-1.31).
- OS data were not mature at the time of PFS analysis, with 10% deaths in the overall population.

	Pembro 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=293	Placebo with CRT n=303
PFS by Investigator		
Number of patients with event (%)	61 (21%)	94 (31%)
Median in months (95% CI)	NR (NR, NR)	NR (18.8, NR)
12-month PFS rate (95% CI)	81% (75, 85)	70% (64, 76)
Hazard ratio* (95% CI)	0.59 (0.43, 0.82)	

* Based on the unstratified Cox proportional hazard model

Kaplan-Meier Curve for PFS in KEYNOTE-A18 (Patients with FIGO 2014 Stage III IVA Cervical Cancer)



Pembrolizumab Prescribing information Jan 12, 2024

Incremental Improvements in Survival (OS) in Treating First-Line Cervical Cancer with Combinations and Biomarkers

Chemotherapy backbone (platinum + taxane) [2009]

Adding bevacizumab [2014]

Adding pembrolizumab [2021 IA1 / 2023 Final]

GOG-204 established the global standard with a median OS of 12.9 months[1]

ORR = 29%

GOG-240 added bevacizumab in eligible patients with a median OS of 17.5 months[2]

ORR = 48%

KEYNOTE-826 added pembrolizumab in PD-L1 positive (CPS ≥1%) median OS 28.6 months [3]

ORR = 69%

1. Monk BJ et al J Clin Oncol. 2009 Oct 1;27(28):4649-55.
2. Tewari KS et al Lancet. 2017 Oct 7;390(10103):1654-1663.
3. Monk BJ et al KEYNOTE-826 Final analysis. Presented at ASCO, 2023.

Evolution of Treatment of Stage 4B, Persistent, Recurrent Cervical Cancer (First-line)

The Past:

- GOG-204 (cisplatin + paclitaxel)
    - JCOG 0505 (non-inferiority of carboplatin and 3 hour paclitaxel)
- GOG-240 (addition of bevacizumab)

The Present:

- KEYNOTE-826 (addition of pembrolizumab)
- BEATcc (addition of atezolizumab)

Florida Cancer Specialists: Research and Clinical Trials

Majority of new cancer drugs approved for use in U.S. were studied in clinical trials with FCS' participation.

Over 160 highly-trained specialists & staff

Well-established relationships with companies at forefront of developing new therapies

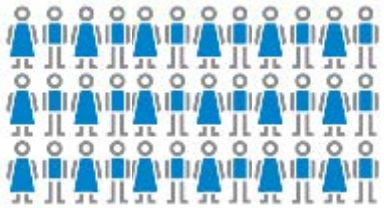
37 Research Office Locations in 21 Counties

SARASOTA · LAKE MARY · LAKE NONA

3 Phase 1 Drug Development Units

More than **300** trials available at any given time

11,000



Patients Enrolled Since Inception of the Research Program

Patients That Have Accessed Novel Therapies Through the DDU to Date

2,700

Patients Treated Per Year on Clinical Trials

600+

FLORIDA CANCER SPECIALISTS & Research Institute

The Annual
National General Medical Oncology Summit

Saturday, March 23, 2024

Moderator

Neil Love, MD

Faculty

Emmanuel S Antonarakis, MD
Ibiayi Dagogo-Jack, MD
Matthew D Galsky, MD
Edward B Garon, MD, MS
Erika Hamilton, MD
Eric Jonasch, MD
Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Matthew Lunning, DO
Kami Maddocks, MD
Rana R McKay, MD
Bradley J Monk, MD
David M O'Malley, MD
Joyce O'Shaughnessy, MD
Brian Rini, MD
Jonathan E Rosenberg, MD
Hope S Rugo, MD
Helena Yu, MD
Andrew D Zelenetz, MD, PhD

Overview

Saturday, March 23rd

Module 1: 7:30 AM – 9:10 AM — Hodgkin and Non-Hodgkin Lymphoma

Module 2: 9:30 AM – 10:20 AM — Gynecologic Cancers

Module 3: 10:20 AM – 11:10 AM — Localized Breast Cancer; SABCS 2023 Review

Module 4: 11:10 AM – 12:00 PM — Metastatic HER2-Positive and Triple-Negative Breast Cancer; SABCS 2023 Review

Module 5: 12:30 PM – 1:20 PM — Prostate Cancer

Module 6: 1:20 PM – 2:10 PM — Urothelial Bladder Cancer

Module 7: 2:10 PM – 3:00 PM — Renal Cell Carcinoma

Module 8: 3:20 PM – 4:10 PM — Targeted Therapy for Non-Small Cell Lung Cancer

Module 9: 4:10 PM – 5:00 PM — Nontargeted Treatments for Lung Cancer

Agenda

Module 1: Localized HER2-Positive and Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 2: Localized ER-Positive Breast Cancer — Dr Kalinsky

Module 3: SABCS 2023 Review — Dr Kaklamani

Agenda

Module 1: Localized HER2-Positive and Triple-Negative Breast Cancer — Dr O’Shaughnessy

Module 2: Localized ER-Positive Breast Cancer — Dr Kalinsky

Module 3: SABCS 2023 Review — Dr Kaklamani

Localized HER2-Positive and Triple-Negative Breast Cancer (BC); Role of PARP Inhibitors in Localized BC

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

Escalating and De-Escalating Therapy for Early-Stage TNBC

Disclosures

Advisory Committees and Consulting Agreements	AbbVie Inc, Agendia Inc, Aptitude Health, AstraZeneca Pharmaceuticals LP, Carrick Therapeutics, Daiichi Sankyo Inc, Eisai Inc, Fishawack Health, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Ontada, Pfizer Inc, Pierre Fabre, Puma Biotechnology Inc, Roche Laboratories Inc, Samsung Bioepis, Sanofi, Seagen Inc, Stemline Therapeutics Inc

30 yo woman with a g*BRCA1* mutation and Triple Negative EBC

- A 30 yo obese woman with a known g*BRCA1* mutation and a h/o 10 years of use of a levonorgestrel-eluting IUD, was newly married and was planning for pregnancy. Her mother was a 20-year ovarian cancer survivor
- She underwent her first screening MRI and was found to have a 1.8 cm mass in the UOQ of her right breast, with no adenopathy. Biopsy showed grade 3 TNBC (ER 0, PR 0, HER2 0, Ki-67 90%) with moderate stromal TIL
- She was treated with 4 cycles of preoperative docetaxel 75 and carboplatin AUC 6 with scalp cooling and good tolerability, working full-time, and MRI after 4 cycles showed complete resolution of the breast mass
- She underwent bilateral mastectomy with implant reconstruction and had a pCR in breast with no tumor or fibrosis seen in 2 SLNs
- She is doing well 2 years out and is proceeding with her plans for pregnancy

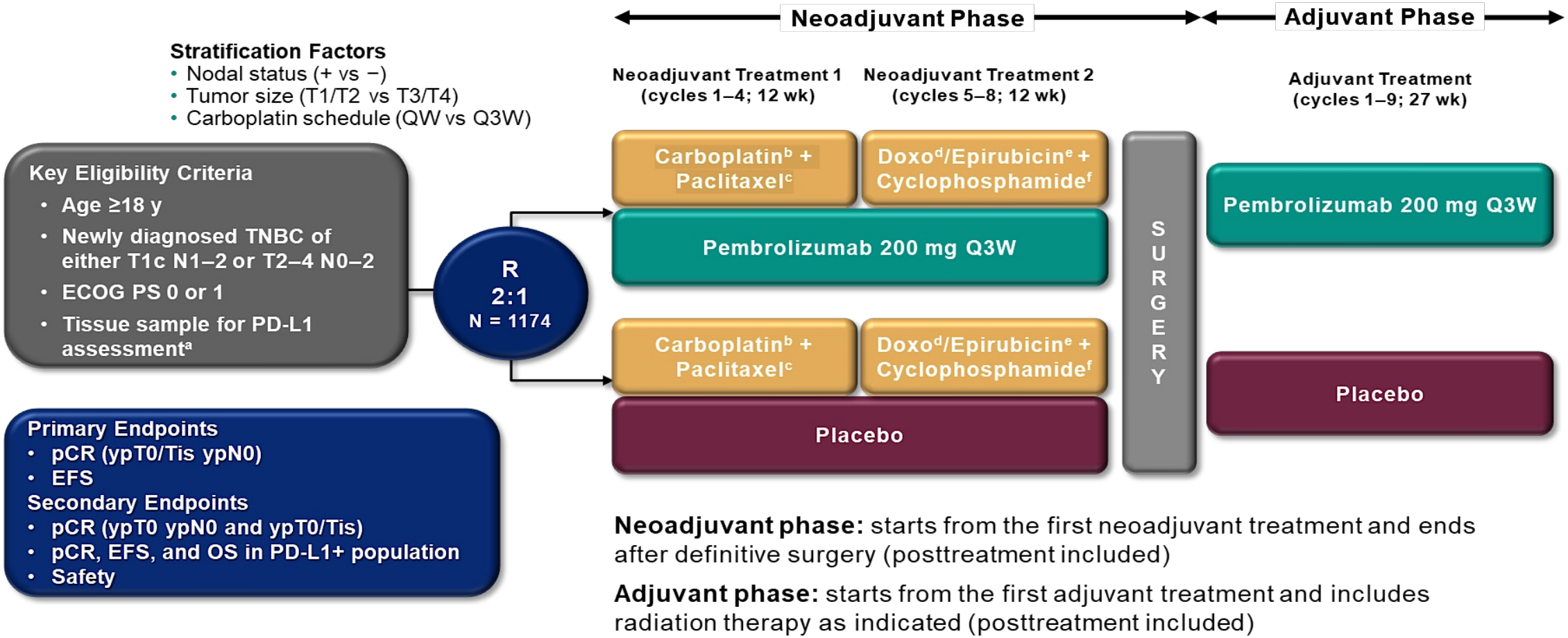
NCCN Guidelines V4.2023

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Negative[b]	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[c] • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[c] • TC (docetaxel and cyclophosphamide) • Olaparib, if germline *BRCA1/2* mutations[d,e] • High-risk[f] TNBC: Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab • TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[e] Capecitabine	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[c] • Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)	**Other Recommended Regimens:** • AC followed by docetaxel every 3 weeks[c] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Select patients with TNBC:[g,1] ▸ Paclitaxel + carboplatin (various schedules) ▸ Docetaxel + carboplatin[g,1] (preoperative setting only)

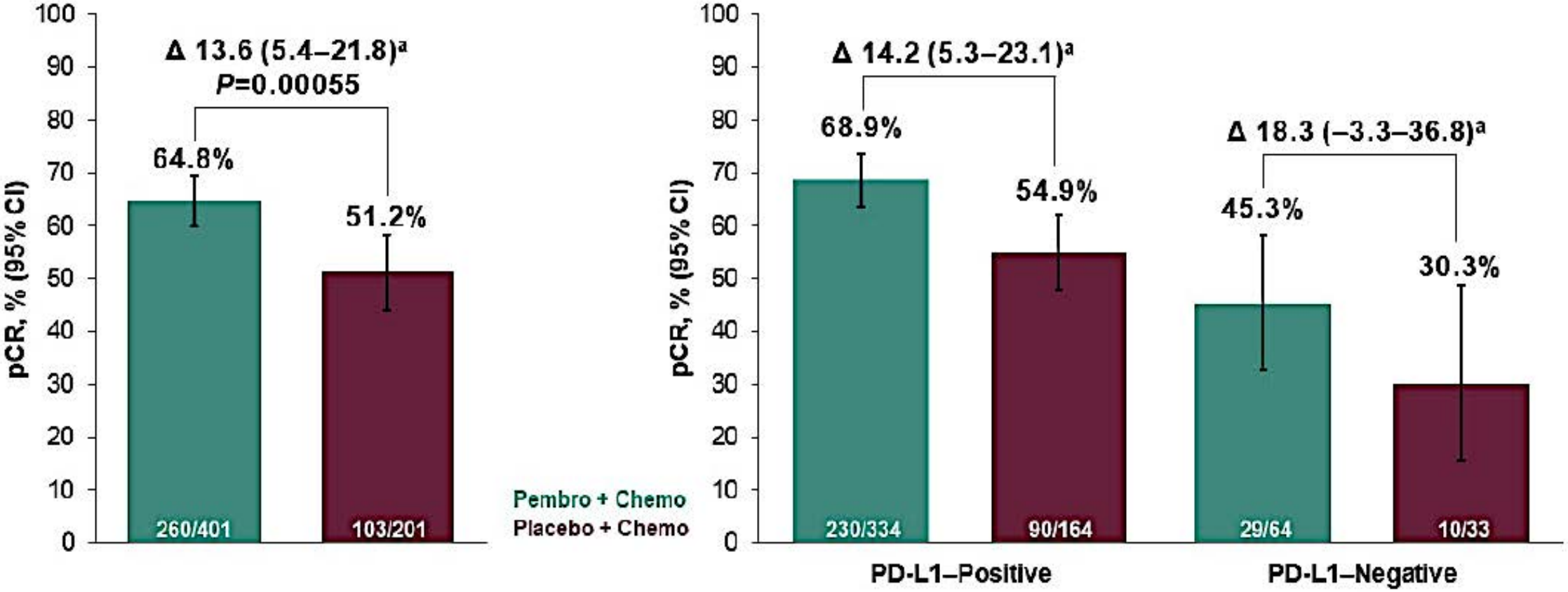
KN-522 study:

EFS results after a median follow-up of 63.1 months, including results in key subgroups and EFS event types



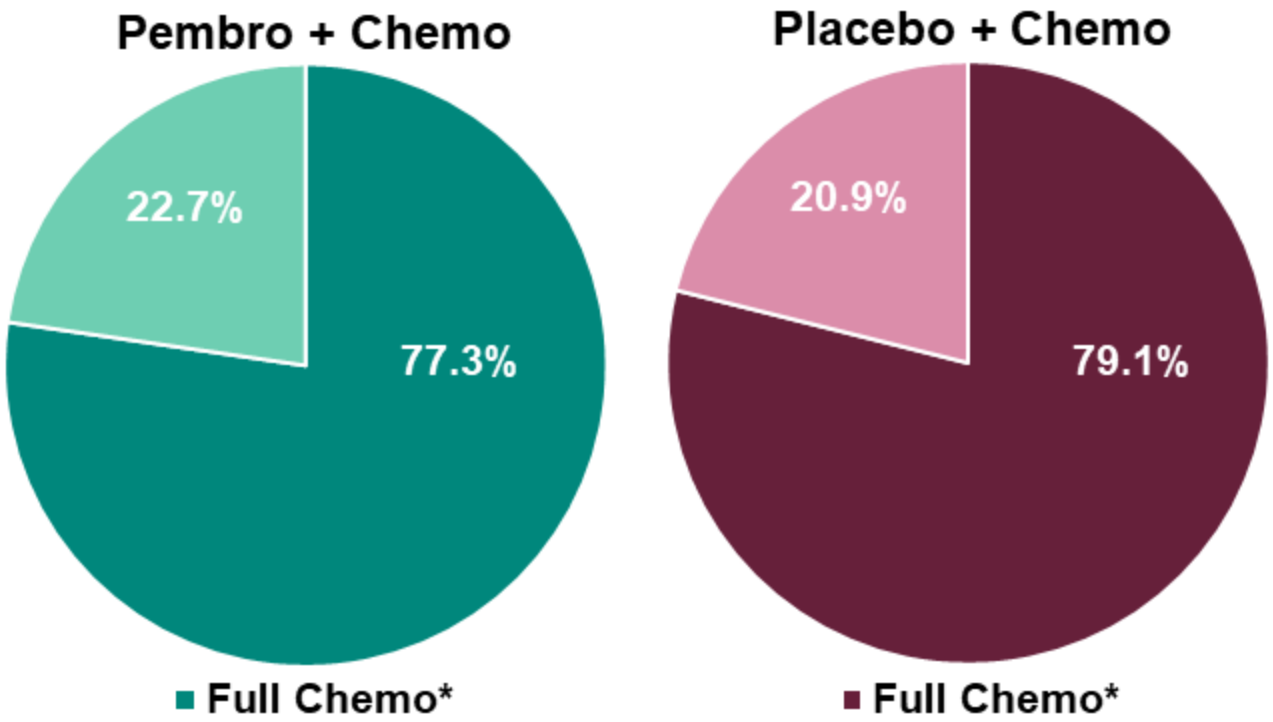
Schmid P, et al. SABCS 2023

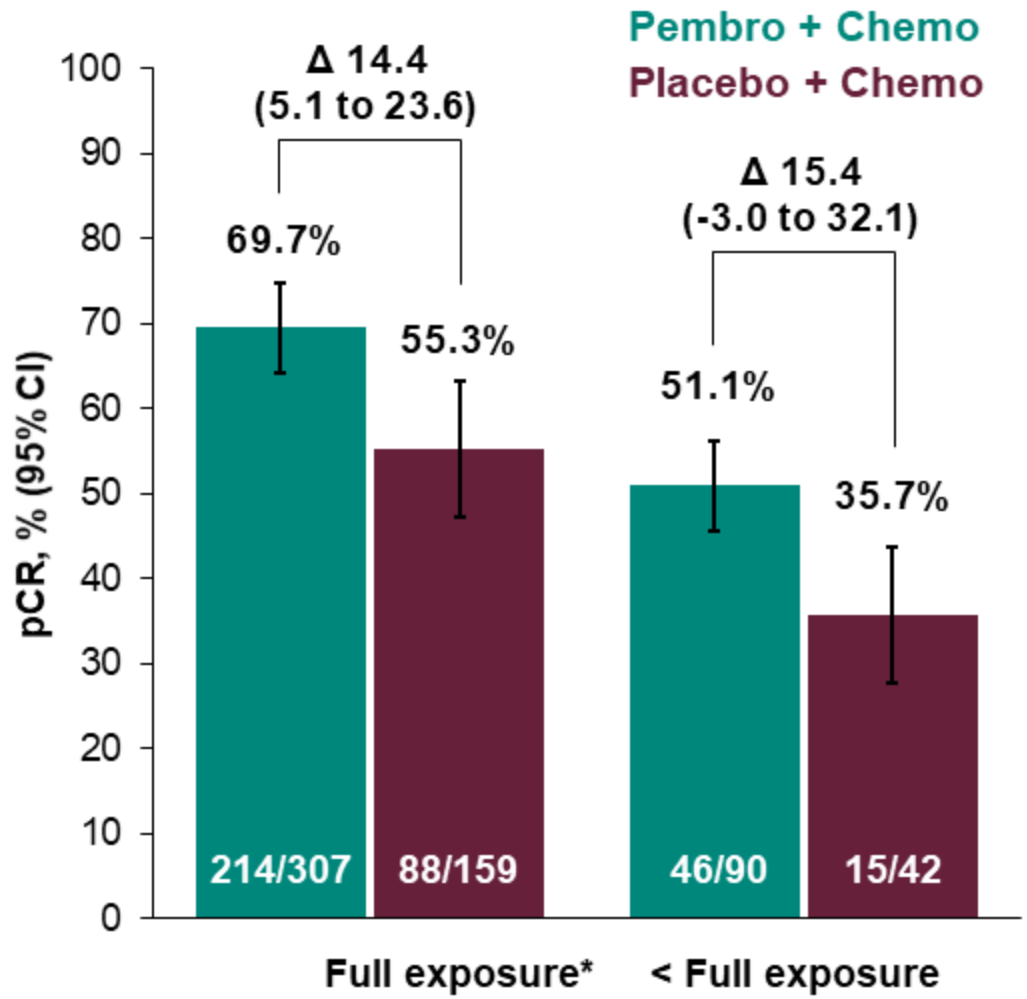
KN-522: pCR endpoint



Schmid P et al. ESMO 2019

pCR by Exposure to Chemotherapy





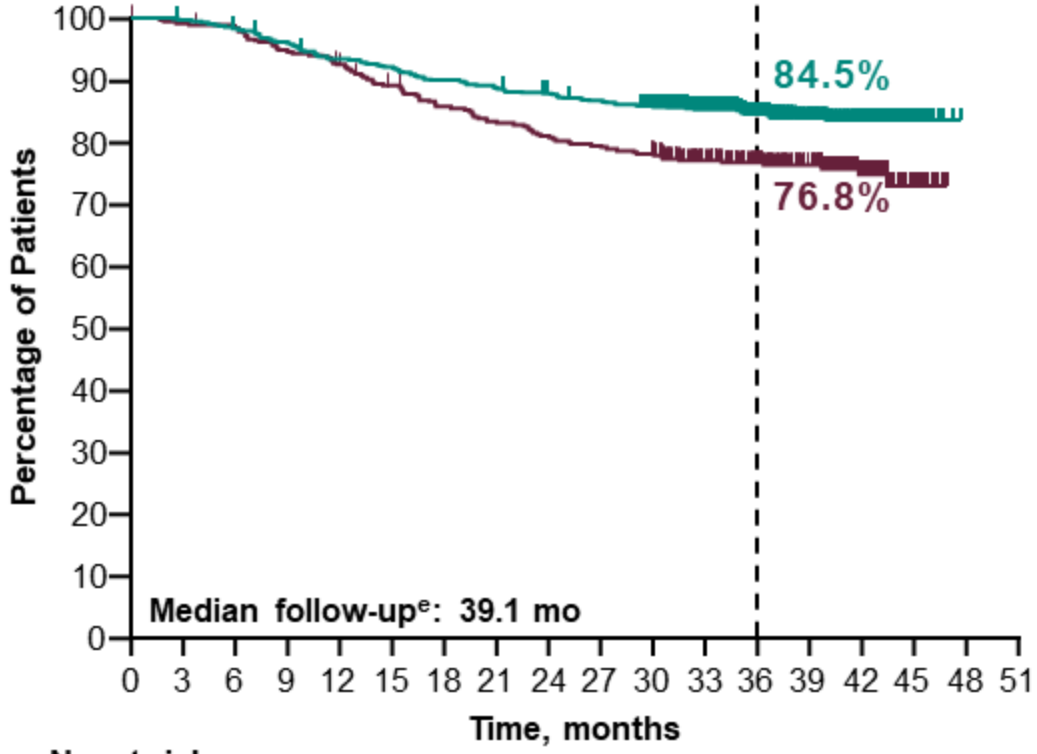
*Full chemotherapy exposure = (Paclitaxel Weekly 10-12 doses) and (Carboplatin Weekly 10-12 doses or Carboplatin Q3W 4 doses) and (Doxorubicin Q3W 4 doses or Epirubicin Q3W 4 doses) and (Cyclophosphamide Q3W 4 doses); regardless of exposure to pembrolizumab.

Post-hoc analysis. Data cutoff date: September 24, 2018.

Schmid et al, SABCS 2023

KEYNOTE-522: EFS at IA4 & IA6

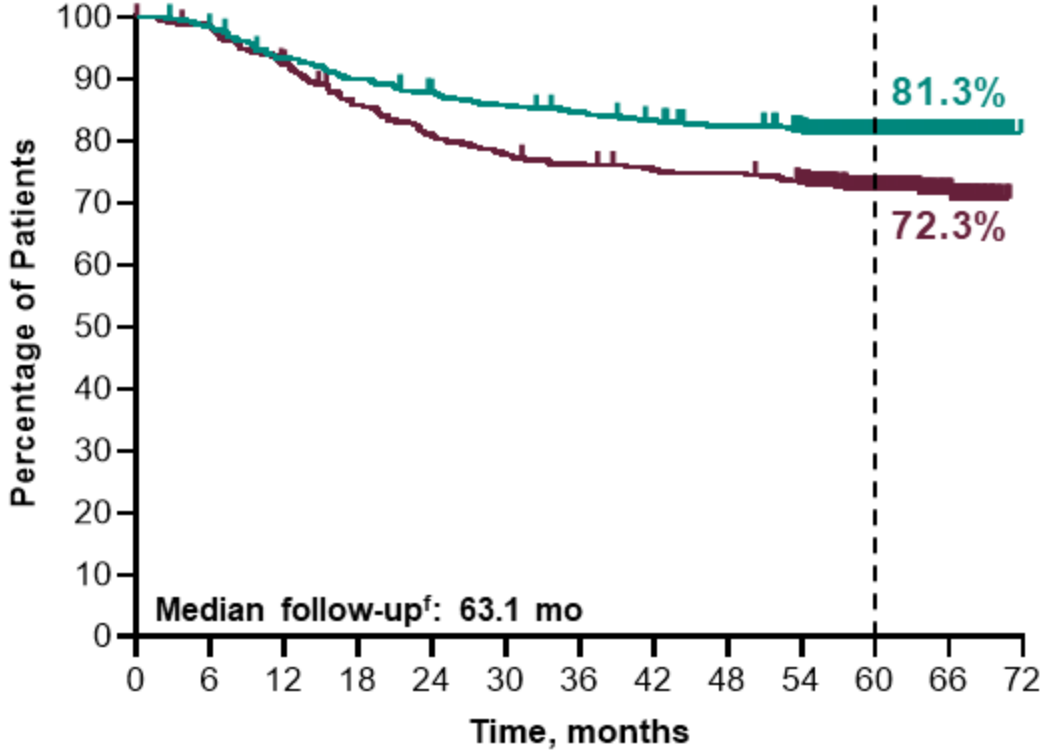
IA4[a]	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48-0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



No. at risk

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

IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49-0.81)
Placebo + Chemo/Placebo	27.7%	

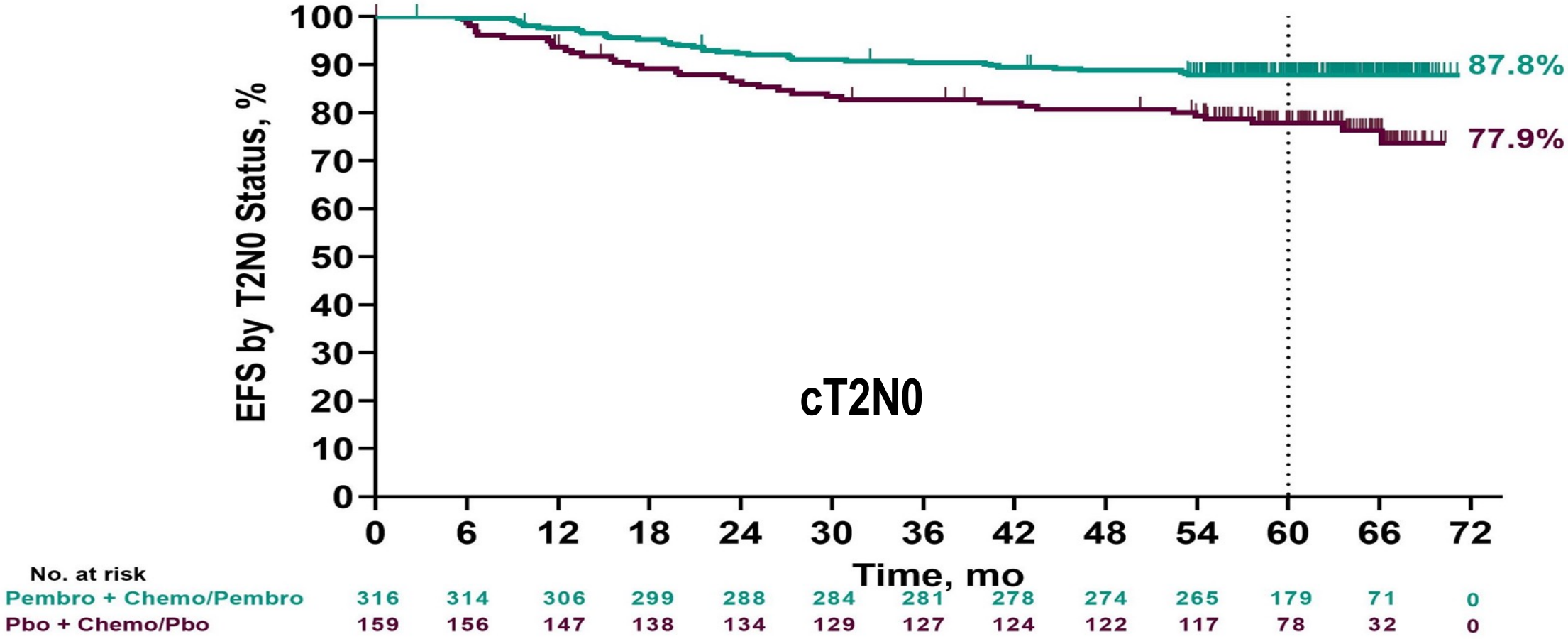


No. at risk

784	769	728	702	681	665	654	643	631	612	411	162	0
390	382	358	329	311	299	292	286	284	274	189	79	0

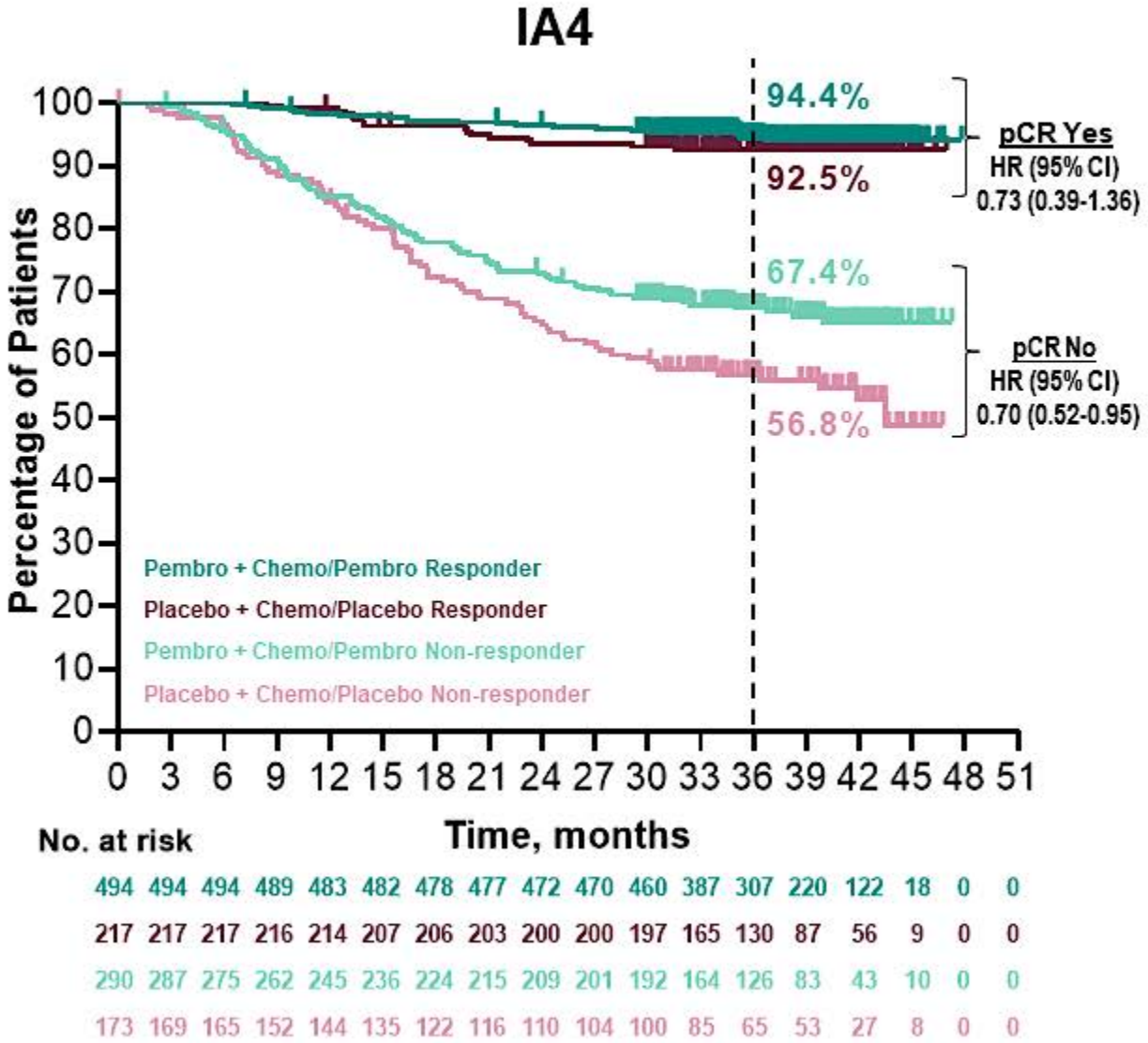
[a]The 4th prespecified interim analysis of EFS was calendar-driven planned to occur ~48 months after the first participant was randomized. [b]The 6th prespecified interim analysis of EFS was calendar-driven planned to occur ~72 months after the first participant was randomized. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary of 0.00517 was crossed. [e]Defined as the time from randomization to the data cutoff date of March 23, 2021. [f]Defined as the time from randomization to the data cutoff date of March 23, 2023.

KN-522 study

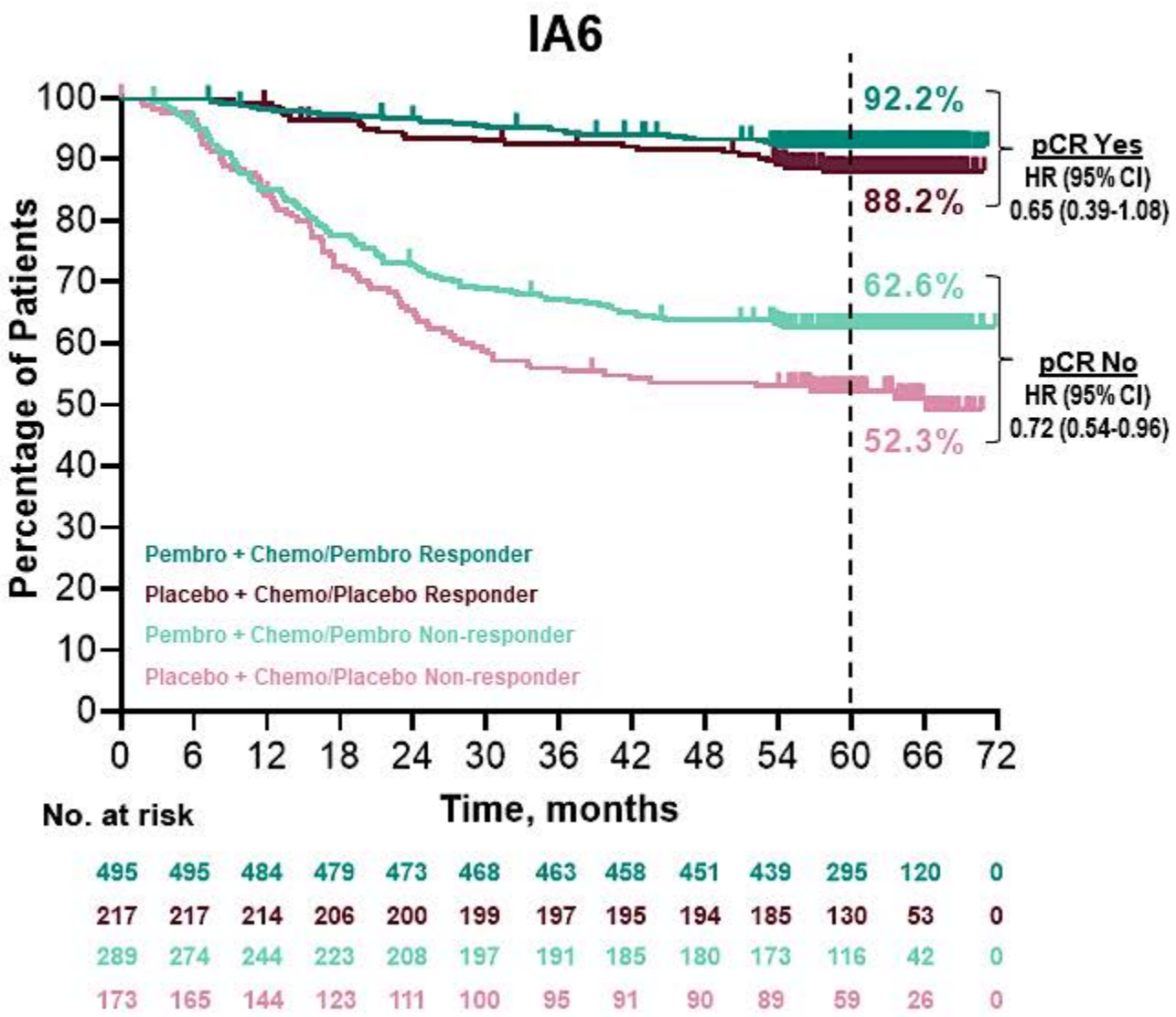


Schmid P, et al. SABCS 2023

KEYNOTE-522: EFS by pCR (ypT0/Tis ypN0) at IA4 & IA6



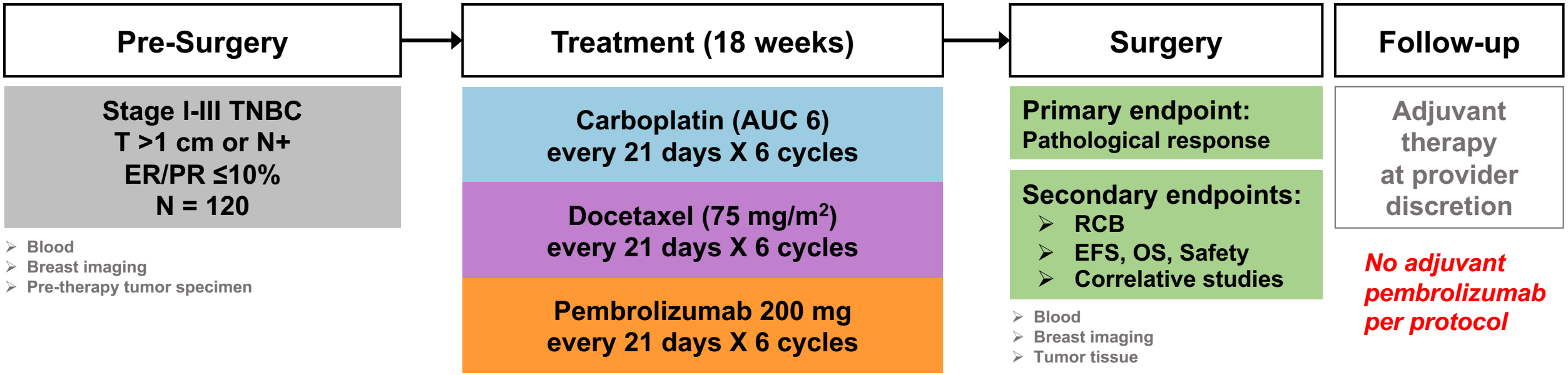
Data cutoff date: March 23, 2021.



Data cutoff date: March 23, 2023.

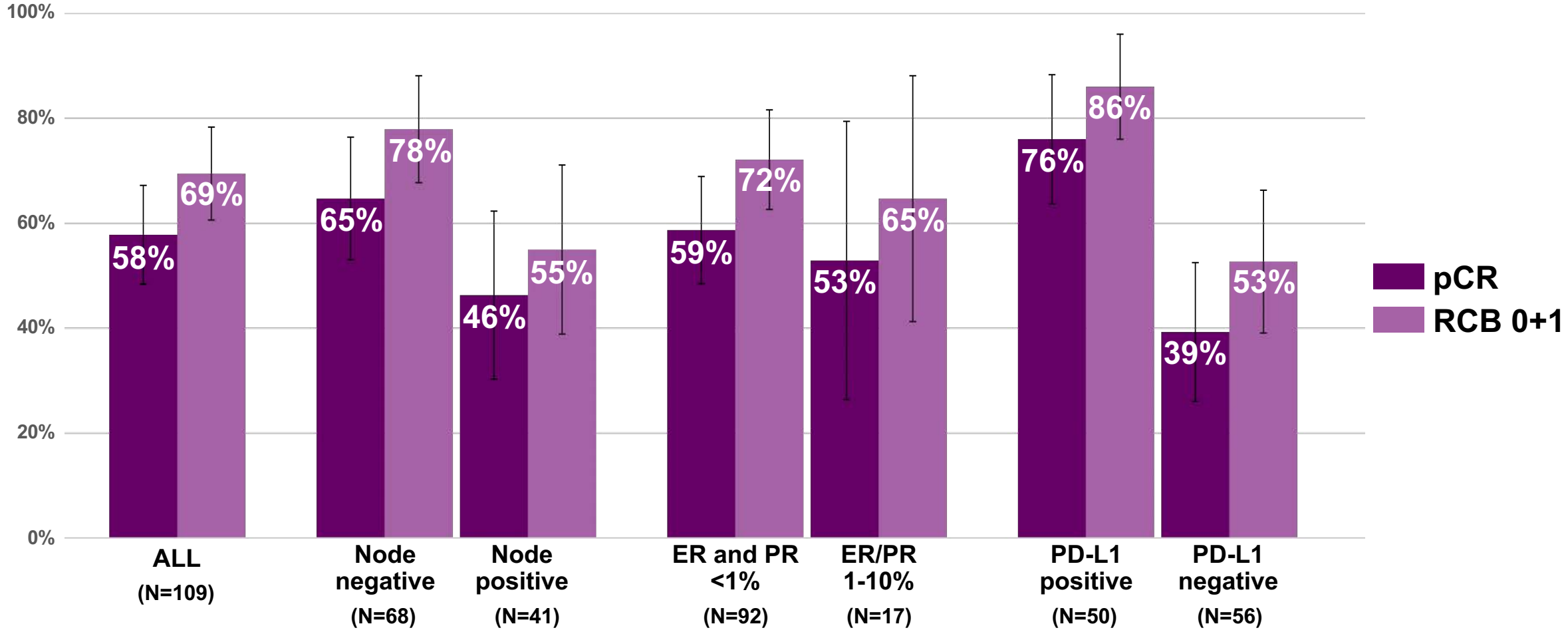
Schmid et al, ESMO 2023

Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)



Sites: University of Kansas and Baylor University Medical Center

RESULTS: Pathologic response



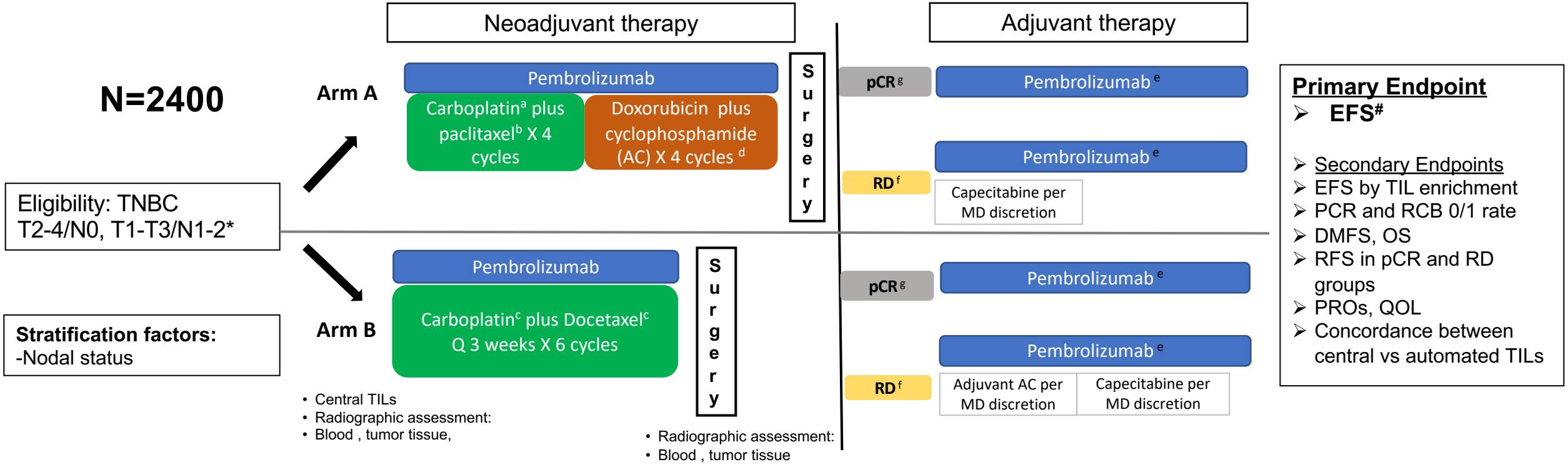
- No patients had disease progression during neoadjuvant treatment.
- Among patients with stage II-III disease and ER & PR IHC <1%, pCR and RCB 0+1 rates were 59% and 69%, respectively.
- pCR in TNM stage I, II, and III disease was 69%, 59%, and 43%, respectively.

Error bars represent 95% binomial confidence intervals

S2212: Anthracycline free chemoimmunotherapy adapted to pCR (SCARLET)

Randomized non-inferiority trial

Hypothesis: In patients with early stage TNBC, carboplatin-taxane chemoimmunotherapy is non-inferior to taxane-platinum-anthracycline-based chemoimmunotherapy



*T4/N+ , any N3 and inflammatory breast cancer excluded

[a]Carboplatin QW or Q3W, [b] Paclitaxel QW.

[c] Carboplatin Q3W, Docetaxel Q3W

[d] AC every 2 or 3 weeks

[e] Total duration of neo plus adjuvant pembrolizumab = 51 weeks

[f] Adjuvant Olaparib per MD discretion in gBRCA+ allowed

[g] No Further Adjuvant chemotherapy.

#adjusted for nodal status and TIL enrichment

Clinicaltrials.gov NCT05929768

SWOG CANCER RESEARCH NETWORK

OlympiA: Study Design

- Local genetic testing or on-study central screening (Myriad Genetics)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2 negative (HR+ or TNBC)
- Stage II-III breast cancer or lack of pCR to NACT

Neoadjuvant group
- *TNBC:* non-pCR
- *HR+:* non-pCR and CPS+EG score ≥3

≥6 cycles Neoadjuvant chemotherapy → **Surgery** → **± Radiotherapy**

Adjuvant group
- TNBC: ≥ pT2 or ≥ pN1
- *HR+:* ≥4 positive lymph nodes

Surgery → **≥6 cycles Adjuvant chemotherapy** → **± Radiotherapy**

Olaparib
300 mg twice daily for 1 year

1:1 randomization N=1836

Placebo
twice daily for 1 year

Primary endpoint
- IDFS by STEEP system

Secondary endpoints
- DDFS
- OS
- *BRCA1/2*-associated cancers
- Symptom/health-related QoL
- Safety

Stratification factors
- HR+ vs TNBC
- Neoadjuvant vs adjuvant
- Prior platinum-based chemotherapy (yes vs no)

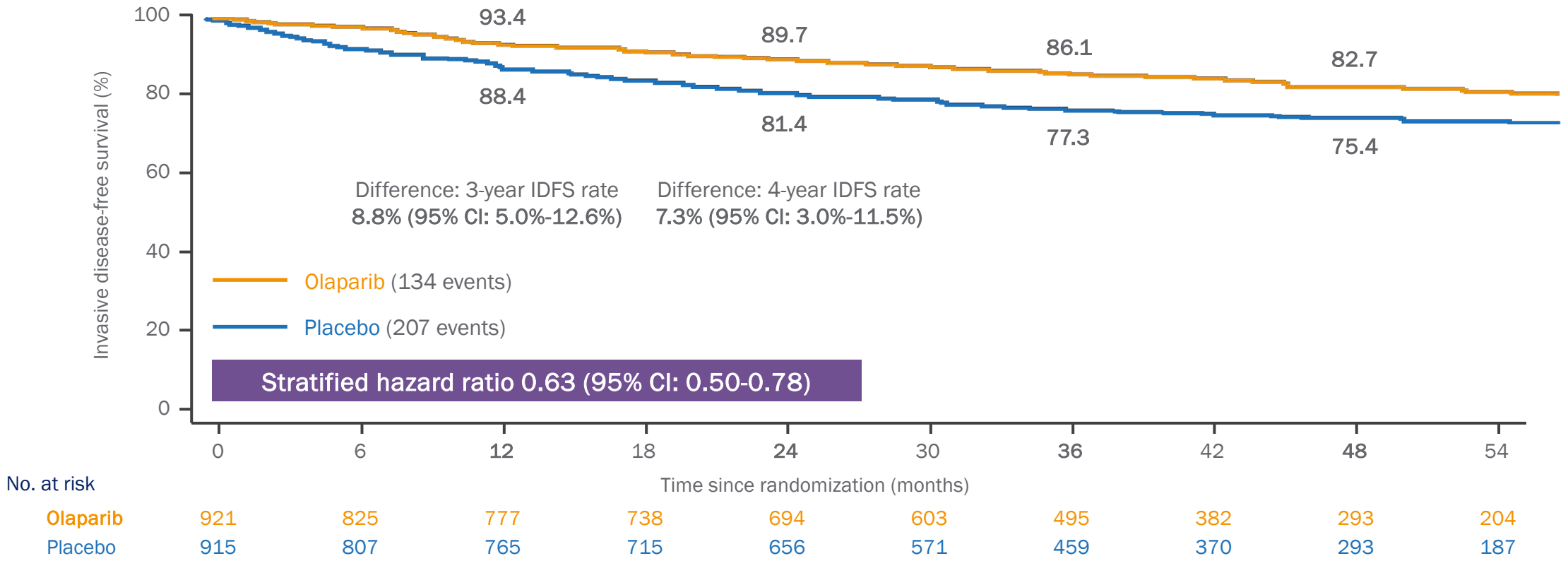
Concurrent adjuvant therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd adjuvant chemotherapy

HR+ defined as ER and/or PgR positive (IHC staining ≥1%).

Triple negative defined as ER and PgR negative (IHC staining <1%).

Tutt A, et al. ASCO 2021. Abstract LBA1.

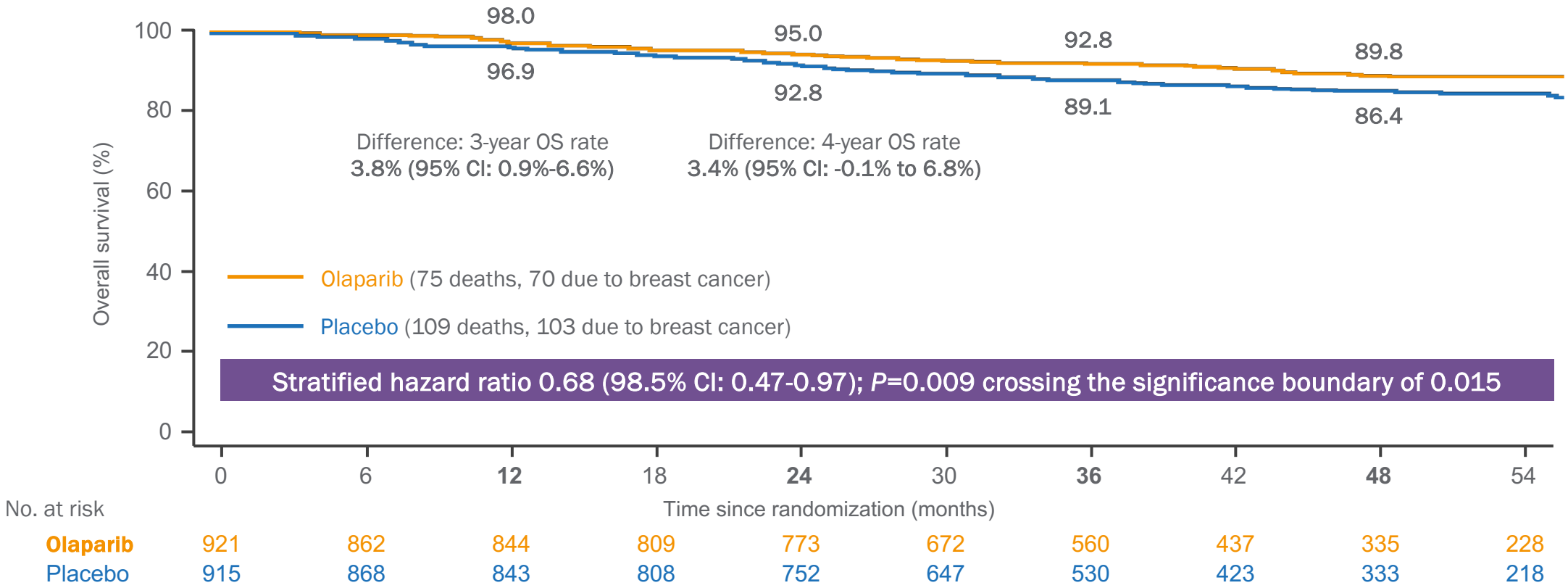
OlympiA: Analysis of IDFS (ITT) at OS IA2



No. at risk										
Olaparib	921	825	777	738	694	603	495	382	293	204
Placebo	915	807	765	715	656	571	459	370	293	187

Tutt A, et al. ESMO Virtual Plenary 2022. Abstract VP1-2022; Geyer C et al. Ann Oncol 2022;33(12):1251-68.

OlympiA: OS IA2 (ITT)



No. at risk

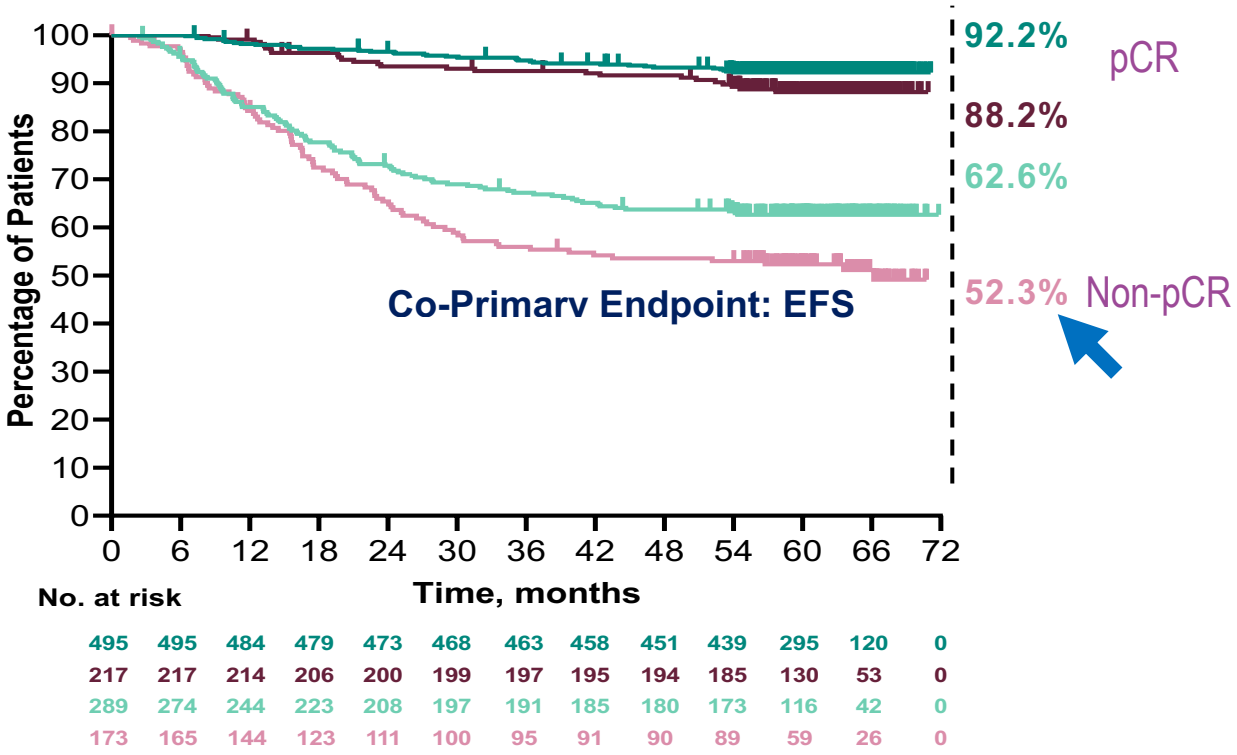
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

98.5% confidence intervals are shown for the hazard ratio because *P*<0.015 is required for statistical significance.

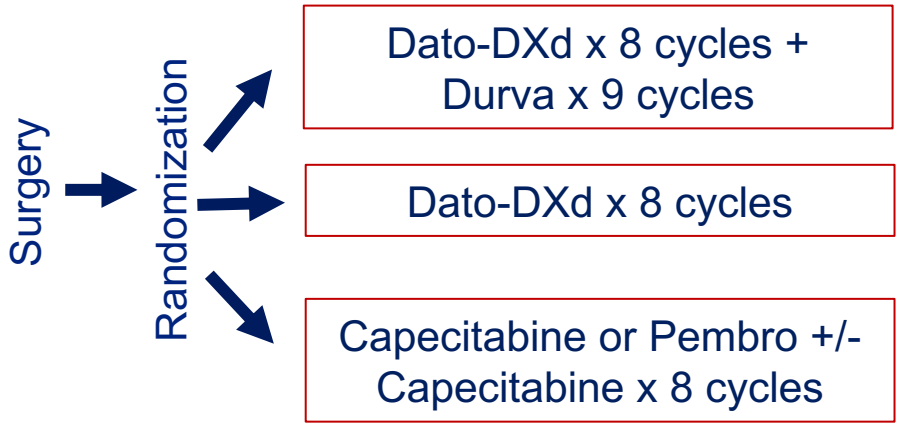
Tutt A, et al. ESMO Virtual Plenary 2022. Abstract VP1-2022; Geyer C et al. Ann Oncol 2022;33(12):1251-68.

Do More if Residual Dz After Neoadjuvant Chemo + IO?

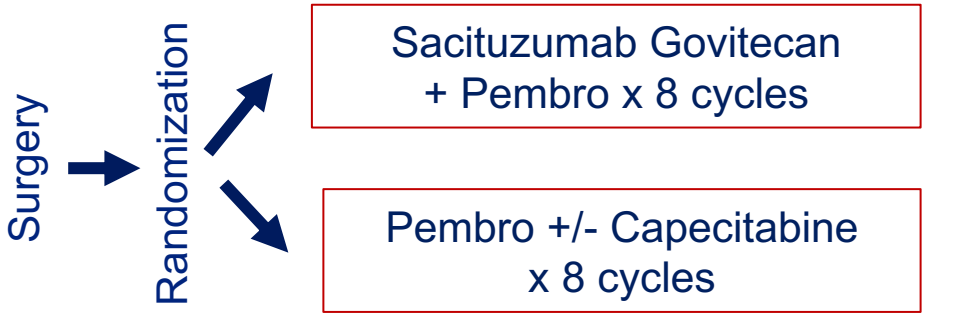
KEYNOTE-522 (=1174): Neo + Adj IO



TROPION-Breast03 (n=1433)



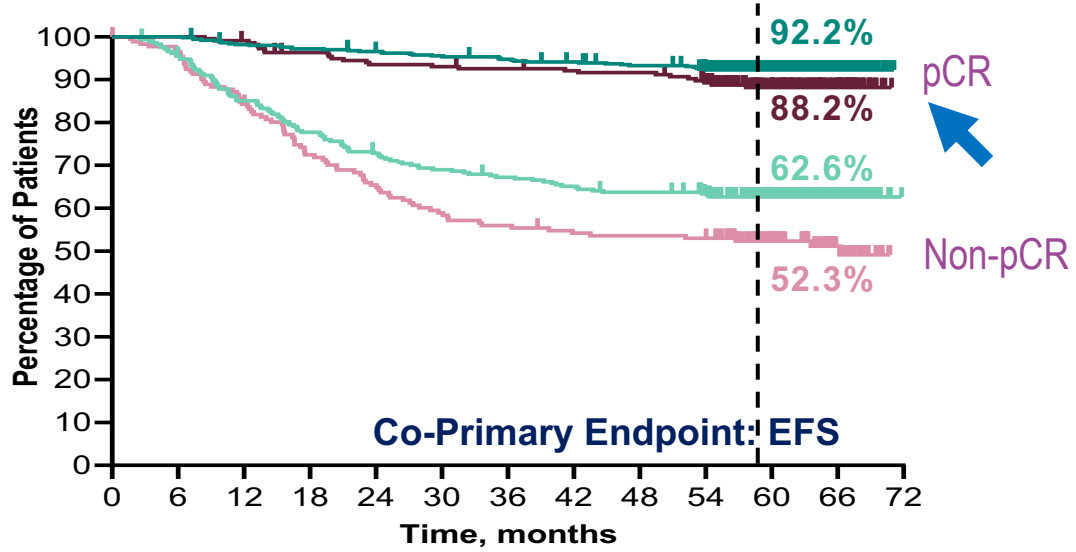
OptimICE-RD (n=1514)



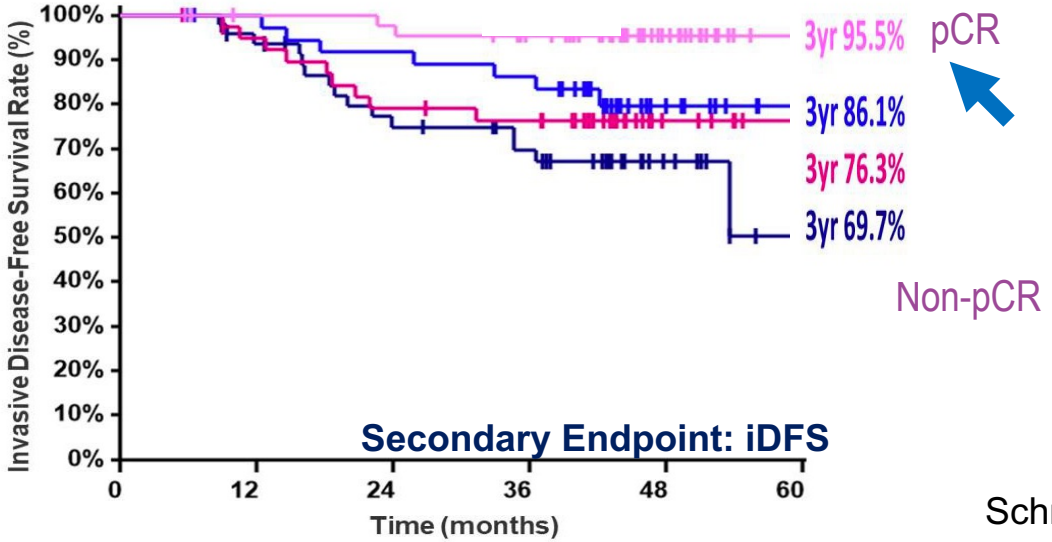
Residual Disease after neo chemo +/- IO

Do Less if pCR After Neoadjuvant Chemo + IO?

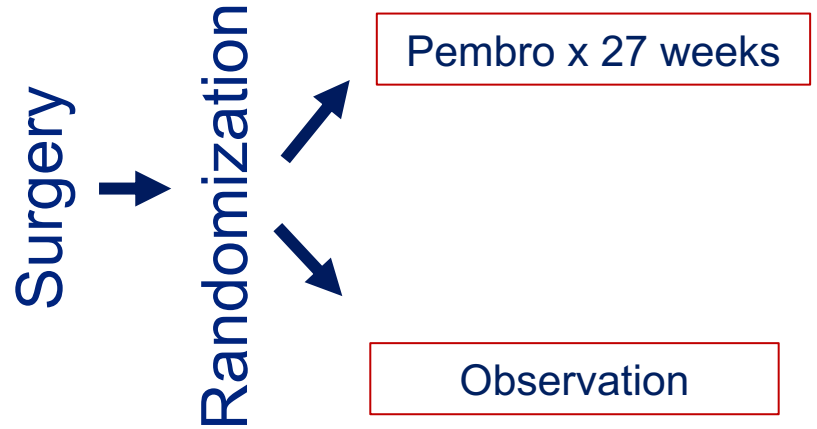
KEYNOTE-522 (n=1174): Neo + Adj IO



GeparNuevo (n=174): Neo IO



OptimICE-PCR (n=1295)

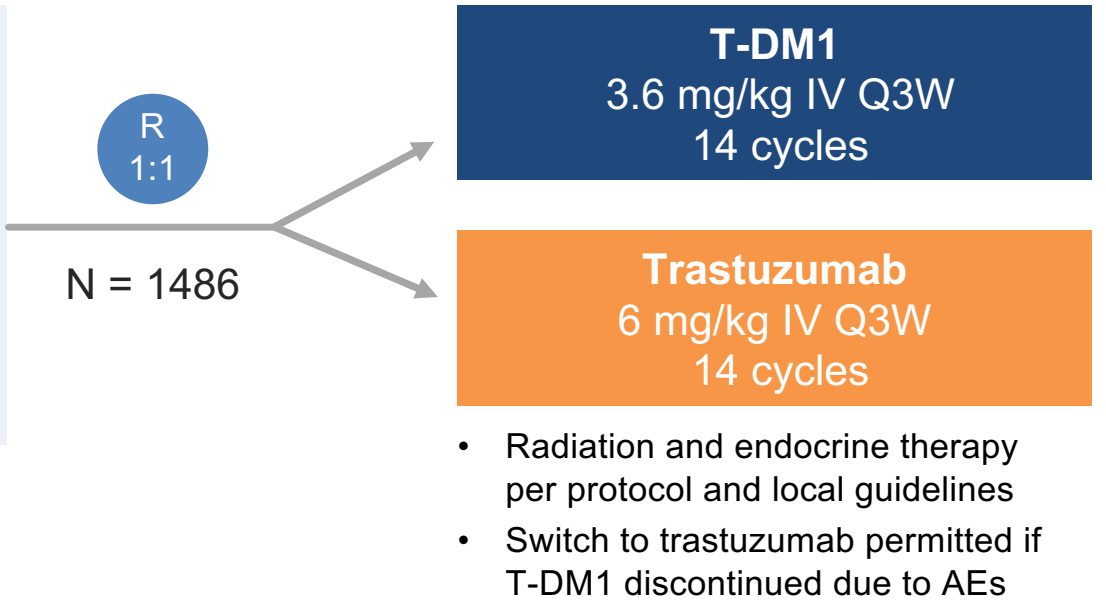


Schmid P et al ESMO 2023; Loibl S Annals of Oncology et al 2022

Escalating and De-Escalating Therapy for HER2-Positive EBC

KATHERINE study design

- Prior neoadjuvant therapy consisting of:
  - Minimum 6 cycles of chemotherapy
  - Minimum 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



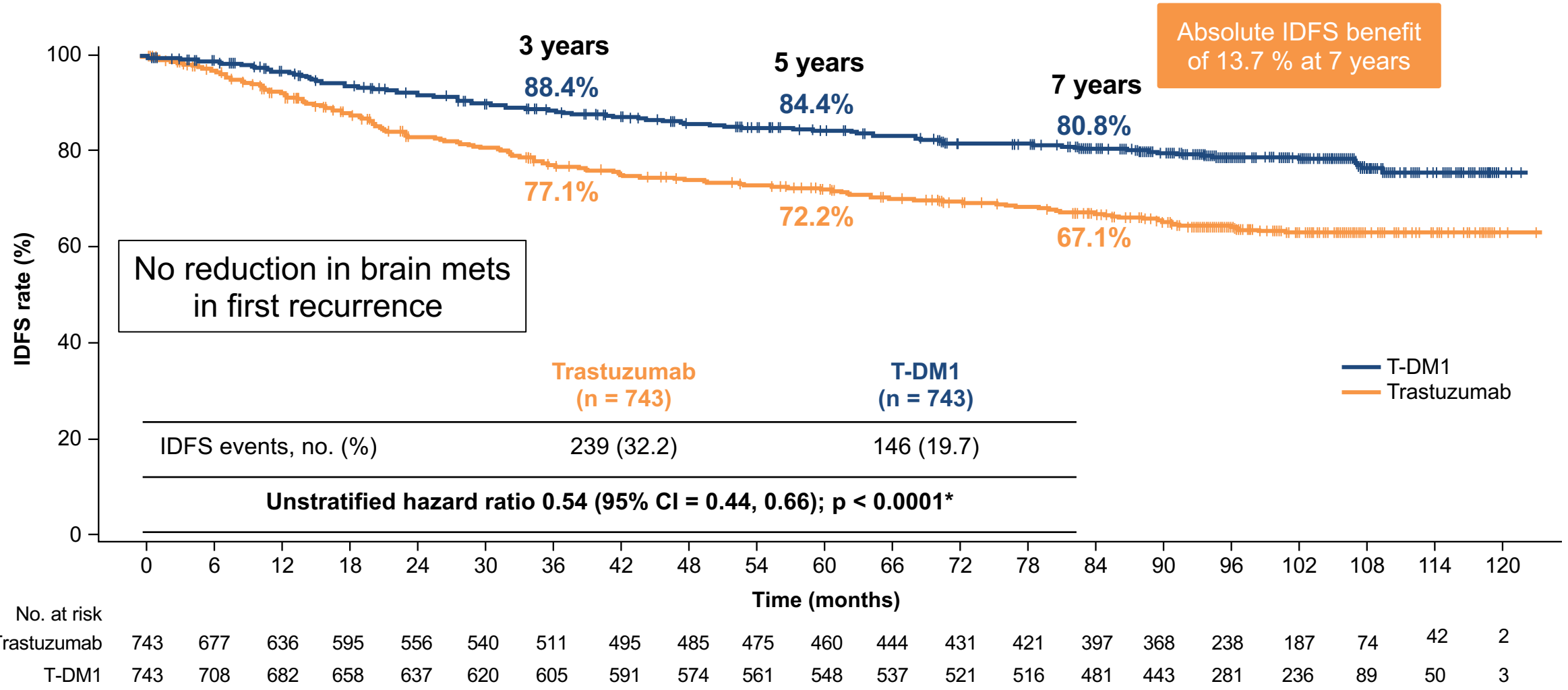
- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL
- **Stratification factors:** Clinical stage at presentation (inoperable vs operable), HR status, preoperative HER2-directed therapy, pathologic nodal status after preoperative therapy

AE, adverse event; DFS, disease-free survival; DRFI, distant recurrence-free interval; HR, hormone receptor; IDFS, invasive disease-free survival; IV, intravenous; OS, overall survival; Q3W, every 3 weeks; QoL, quality of life; R, randomized; T-DM1, ado-trastuzumab emtansine.

Adapted from *N Engl J Med*, von Minckwitz *et al.*, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)

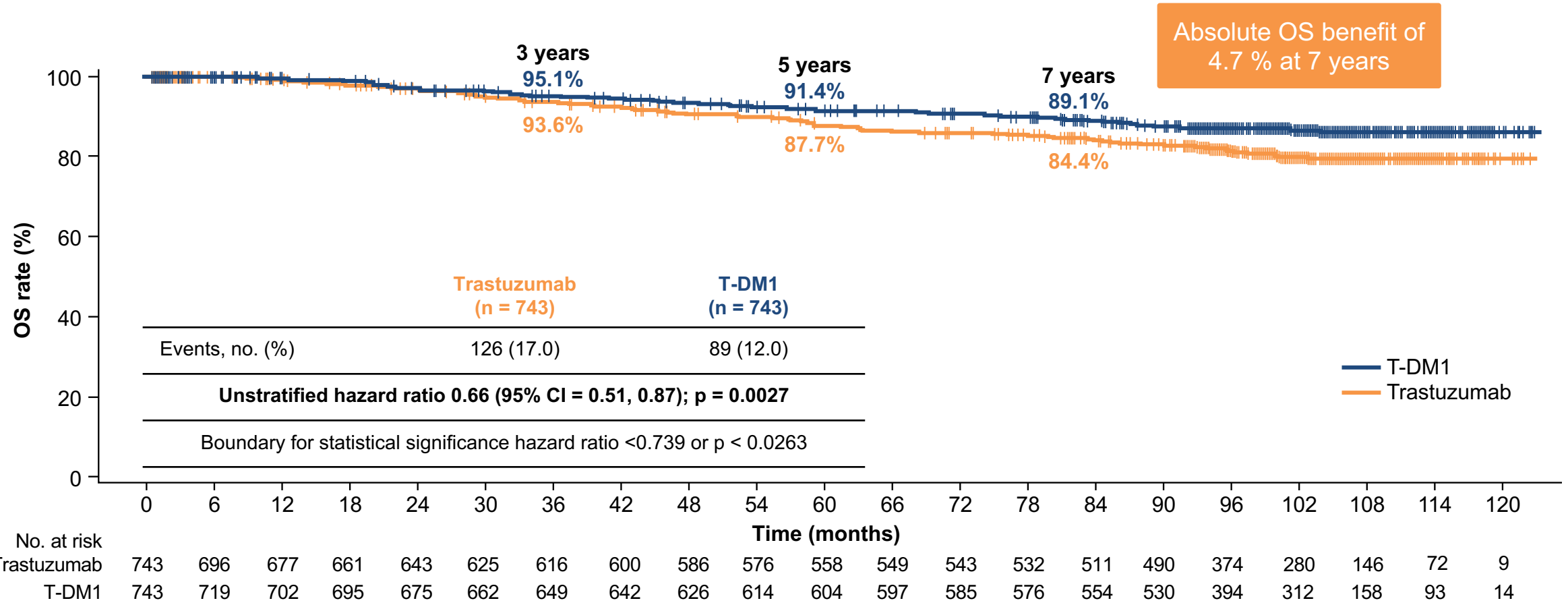


No. at risk																				
Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
T-DM1	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3

* 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. SABCS 2023

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)

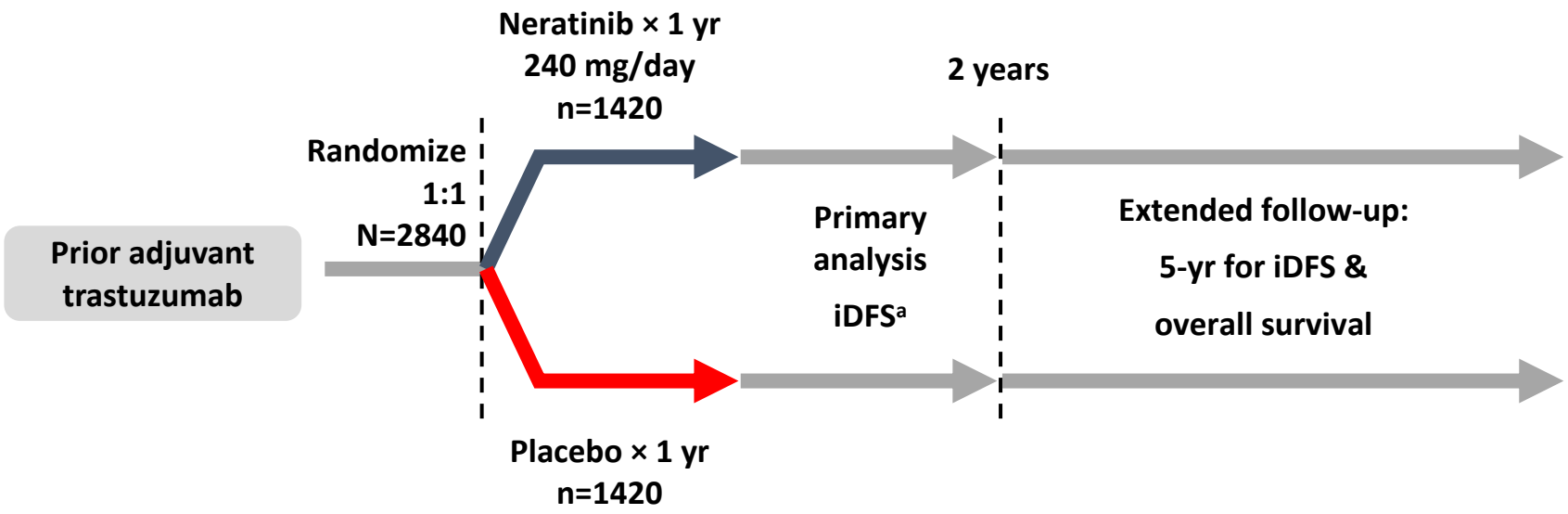


Significant reduction in risk of death by 34% with T-DM1

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

Loibl S, et al. SABCS 2023

ADJUVANT NERATINIB: ExteNET STUDY



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

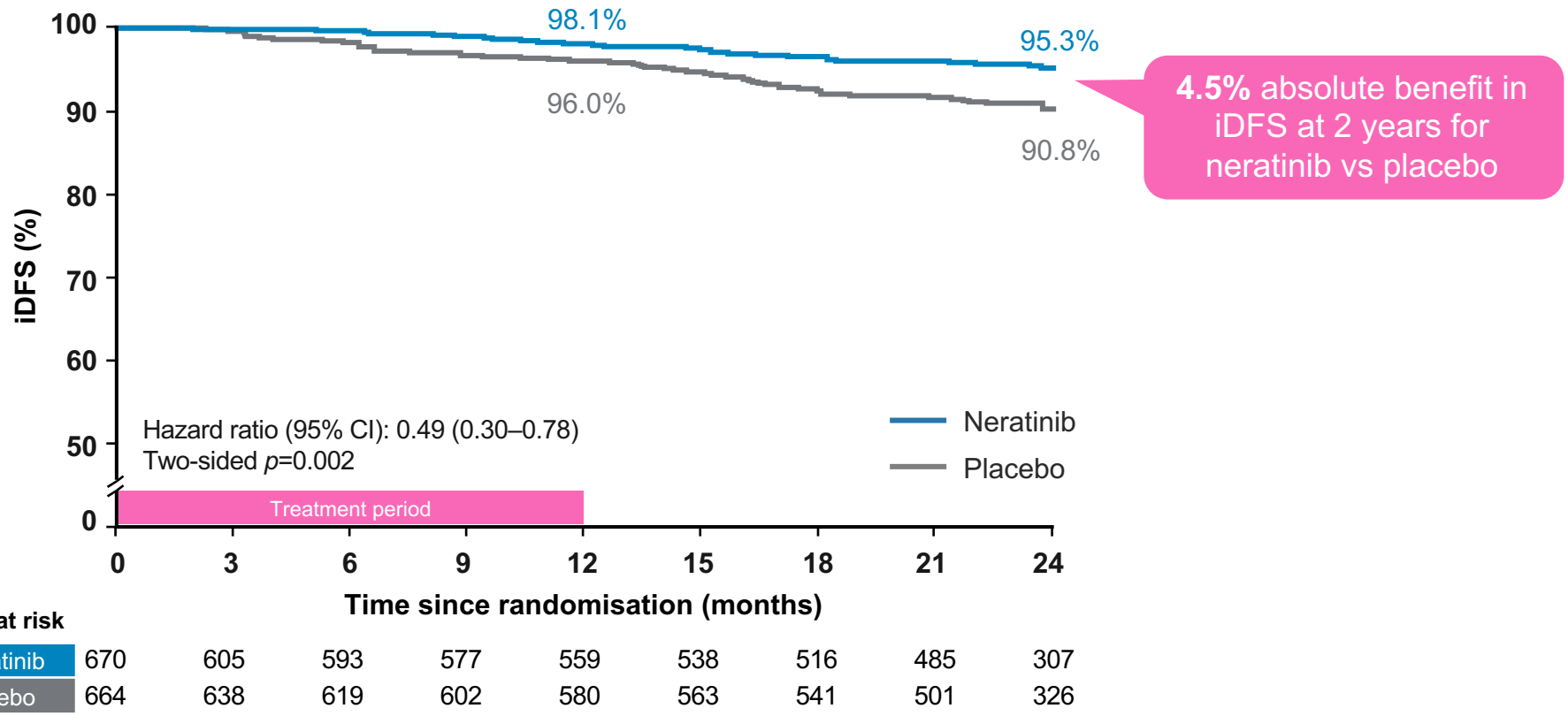
Secondary endpoints: overall survival, DFS-DCIS, distant DFS, time to distant recurrence, CNS metastases, safety,

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

Study blinded: Until primary analysis; OS remains blinded

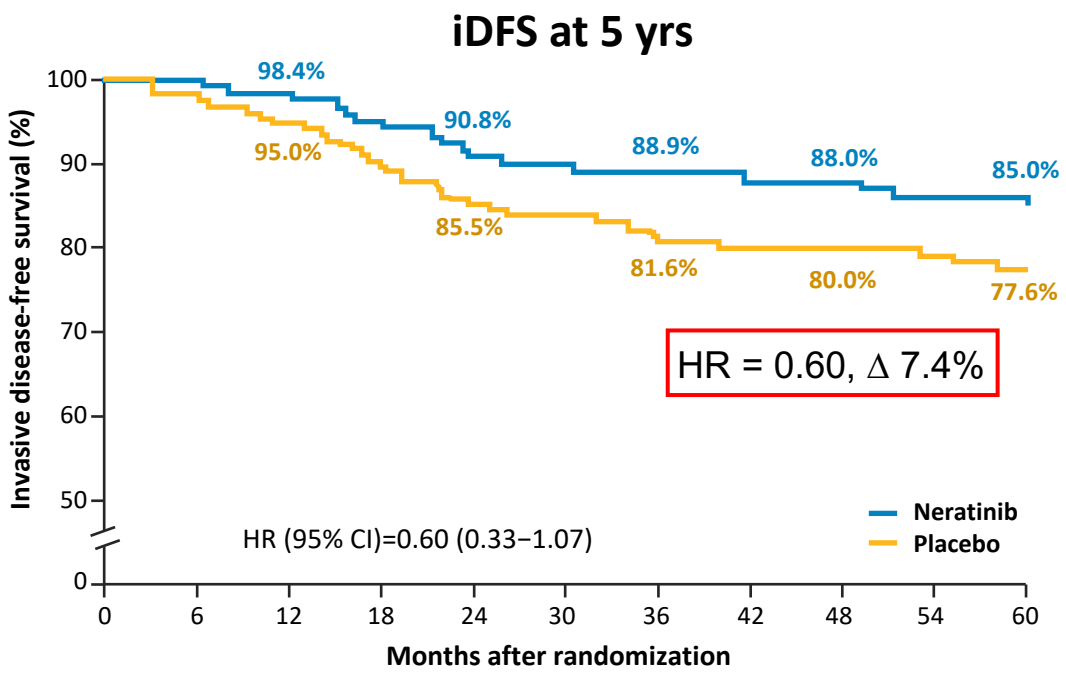
Neratinib significantly improves 2-year iDFS in the HR+/≤1 year population[1,a]

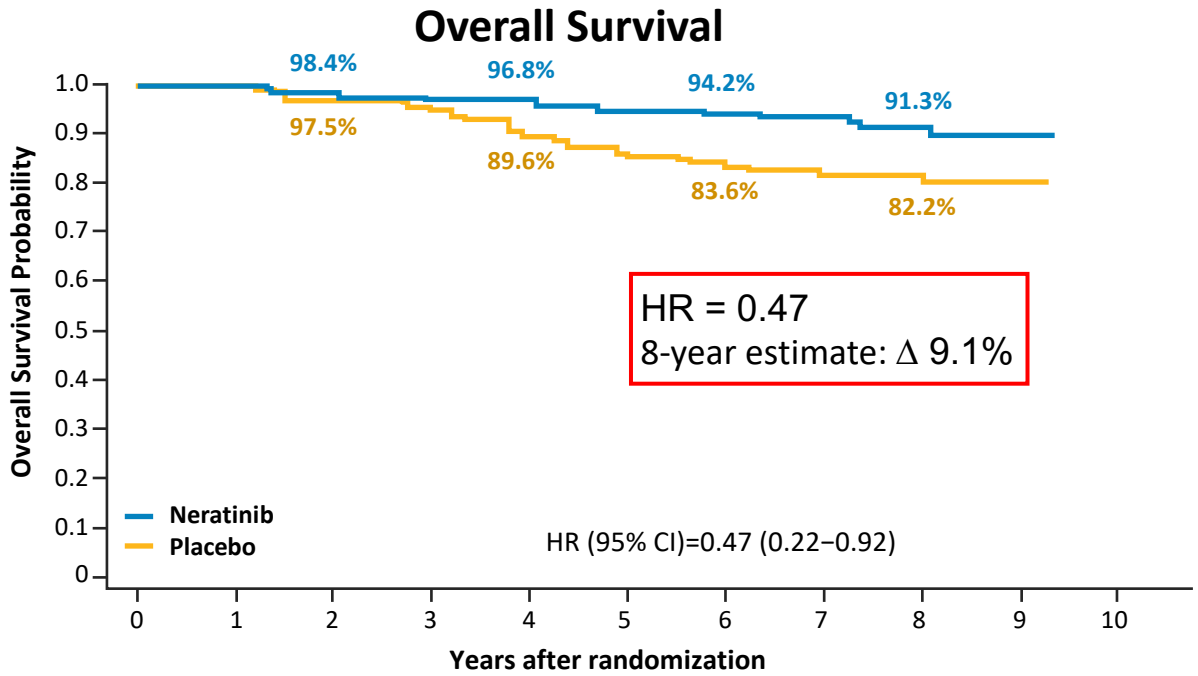
ExteNET: iDFS at 2 years in patients with HER2+/HR+ eBC who completed prior trastuzumab-based therapy ≤1 year from randomisation



[a] Patients with HER2+/HR+ eBC who completed prior trastuzumab-based therapy ≤1 year from randomisation. Data were derived from a descriptive subgroup analysis.[2]
95% of patients with HER2+/HR+ disease had concomitant endocrine therapy. Data cut-off, July 2014.
CI, confidence interval; eBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; ITT, intention to treat.
1. Chan A, et al. *Clin Breast Cancer* 2021;21:80–91.e7; 2. Martin M, et al. *Lancet Oncol* 2017;18:1688–700.

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

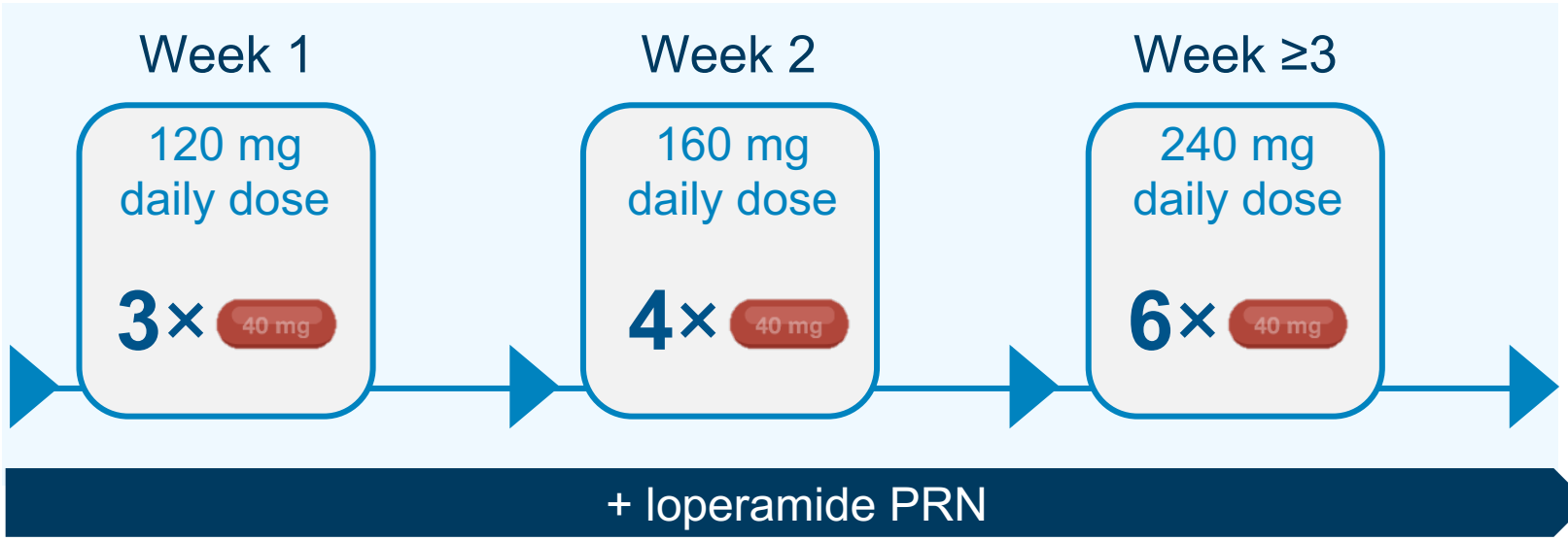
*Small Ns

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.

Recommendations for minimizing diarrhea with neratinib

Neratinib dose escalation



93% of patients (56/60) in the DE1 cohort of the CONTROL study escalated to the full dose of neratinib at Week ≥3

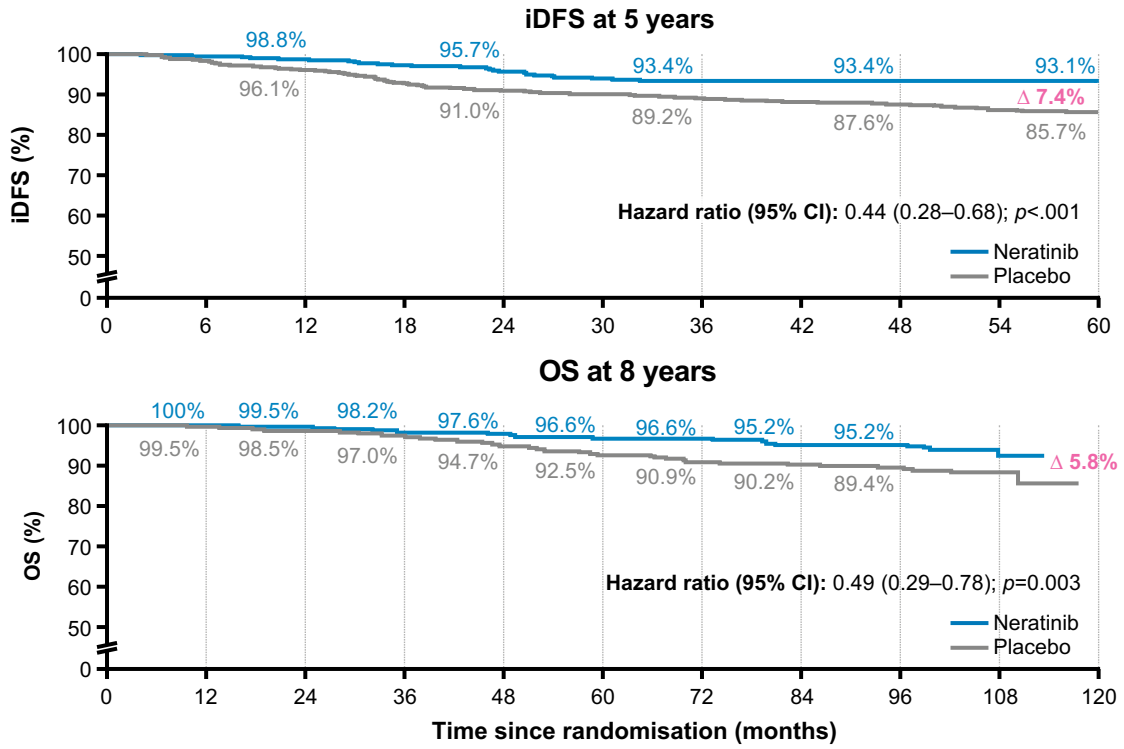
- In the CONTROL study, no patients in the neratinib DE1 cohort discontinued due to diarrhea after the first month

[a] Based on CONTROL data set published by Barcenas CH, et al. *Ann Oncol* 2020;31:1223–30.
DE, dose escalation; PRN, as needed.

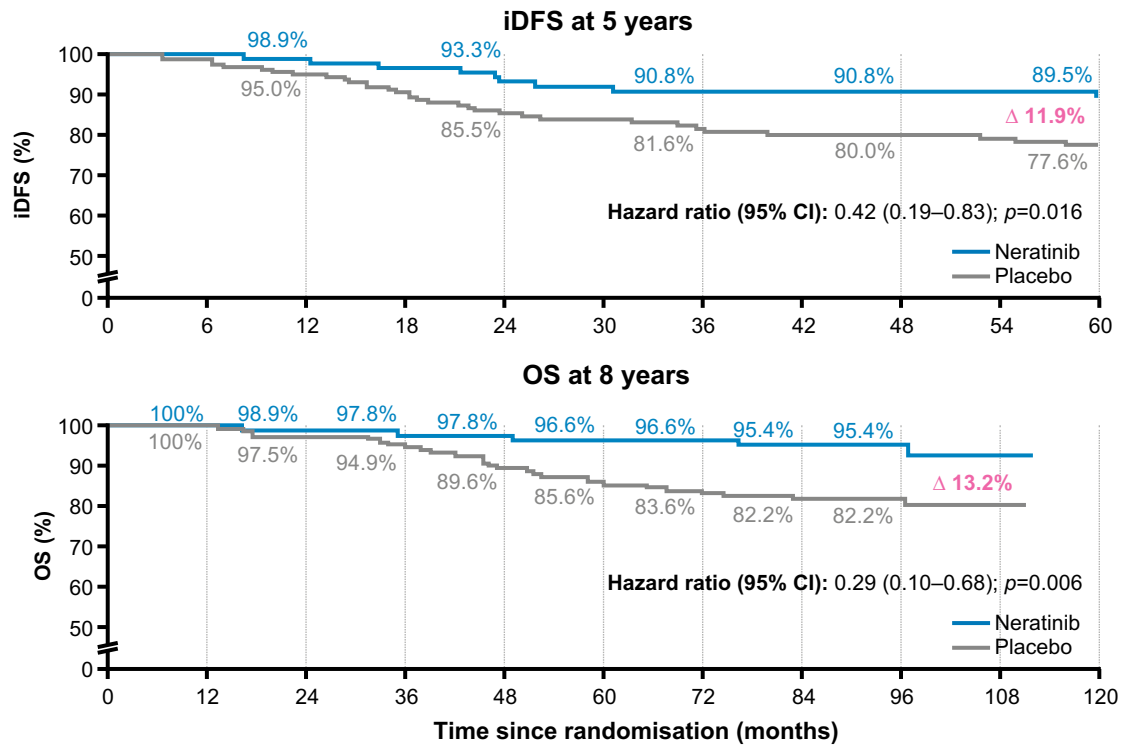
Impact of Adherence on Efficacy in the ExteNET Study With Extended Adjuvant Neratinib: iDFS and OS in Patients Who Received Neratinib Treatment for ≥ 11 Months

Patients who complete the recommended 1-year duration of extended adjuvant neratinib therapy* have an absolute benefit, with 5-year iDFS improved from 5.1%[1] (HR+ / ≤1 year population) to 7.4%[2] and from 7.4%[1] % (HR+ / ≤1 year no pCR population) to 11.9%[2]

ExteNET: HR+ / ≤1 year population (EMA label population)†
≥11 months of neratinib treatment[2]



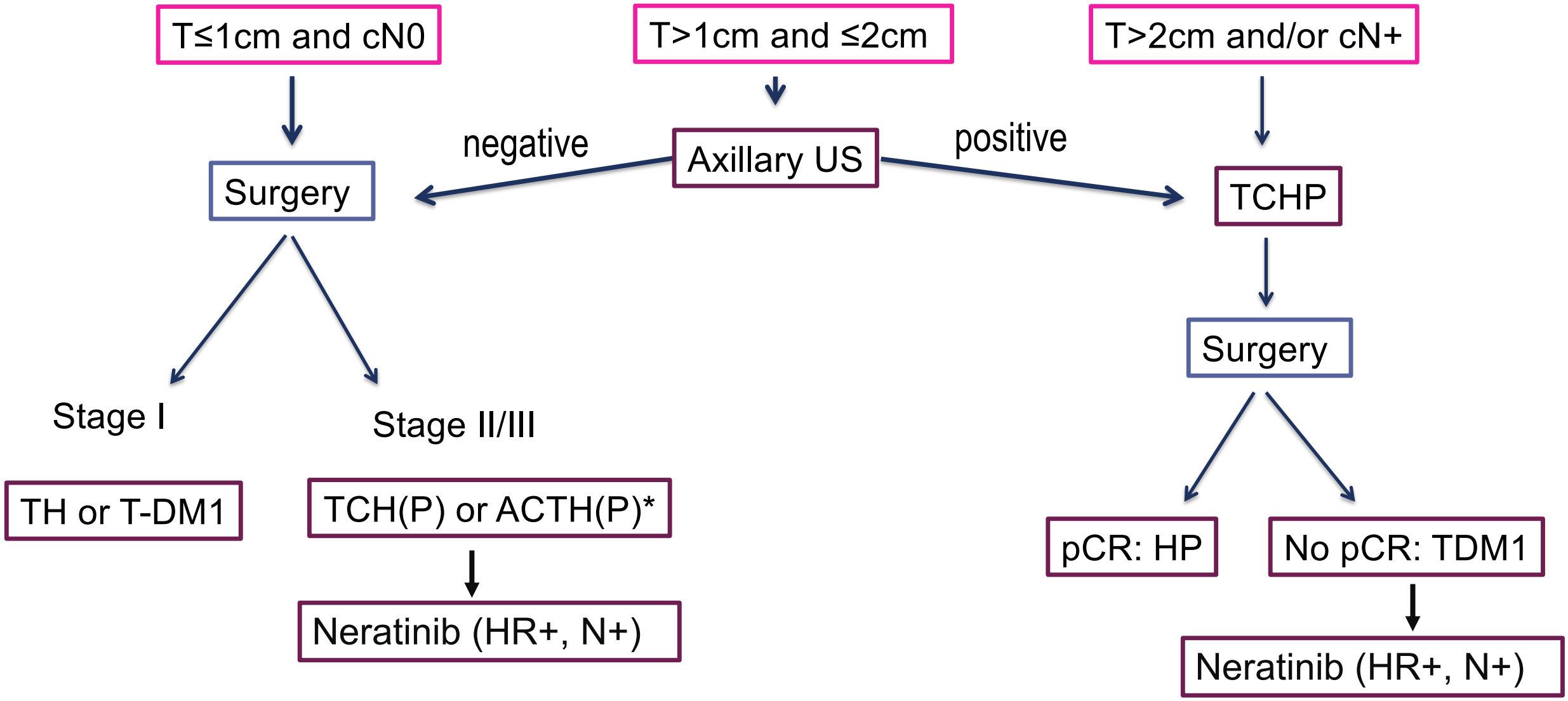
ExteNET: HR+ / ≤1 year, no pCR population‡
≥11 months of neratinib treatment[2]



*Defined as ≥11 months of therapy or ended treatment due to disease recurrence in the neratinib group versus all randomised patients in the placebo group;
†HR+ and ≤1 year after prior trastuzumab; ‡HR+ and ≤1 year after prior trastuzumab with residual disease post-neoadjuvant therapy (no pCR).

1. Chan A. et. al. Clin Breast Cancer.2021;21:80-91; 2. Moy B, et al. ASCO Annual Meeting. 4–8 June 2021; Poster 540.

HER2+ Early Breast Cancer Algorithm



*Depending on Nodal Status

Agenda

Module 1: Localized HER2-Positive and Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 2: Localized ER-Positive Breast Cancer — Dr Kalinsky

Module 3: SABCS 2023 Review — Dr Kaklamani

Localized ER-Positive BC

Kevin Kalinsky, MD, MS
Professor of Medicine
Director, Division of Medical Oncology
Louisa and Rand Glenn Family Chair in Breast Cancer Research
Winship Cancer Institute at Emory University

Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Menarini Silicon Biosystems, Merck, Mersana Therapeutics Inc, Myovant Sciences, Puma Biotechnology Inc, Seagen Inc, Takeda Pharmaceuticals USA Inc
Consulting Agreement	Merck
Contracted Research	Ambrx, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Novartis
Nonrelevant Financial Relationship	ADC Therapeutics (spouse)

Patient Case

- 65 yo postmenopausal woman with a grade III 1.5 cm ER 100%, PR 80%, HER2 1+ IDC presents to your office. She is s/p lumpectomy + SLNB. She is noted to have 2/3 lymph nodes involved. Systemic imaging normal.

- An oncotype returns with Recurrence Score of 21.

- What systemic therapy do you recommend for her?

CA209-7FL study design

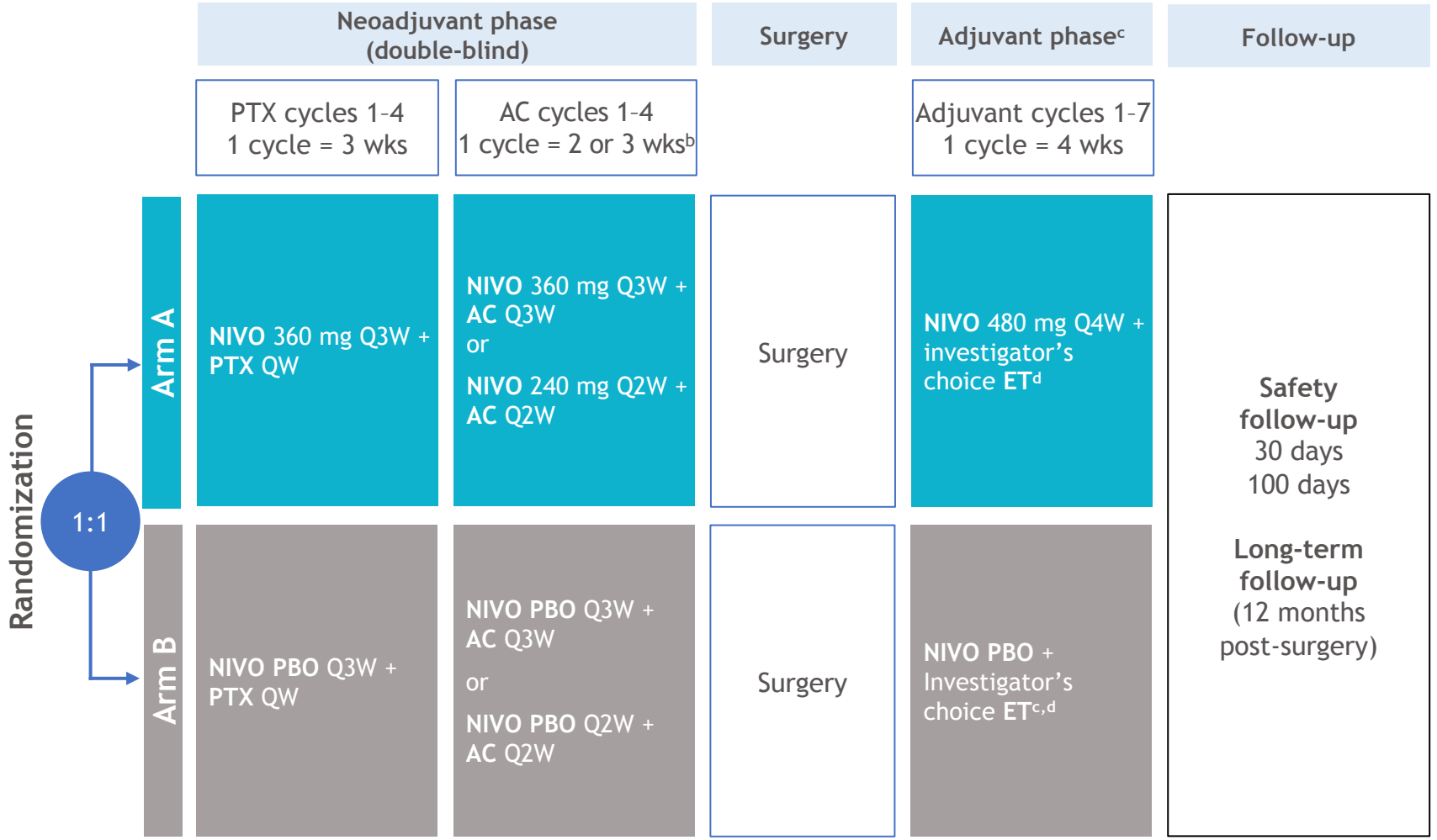
Screening

Key inclusion criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c (tumor size 2 cm only)-T2, cN1-cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1-10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0-1

Stratification factors

- PD-L1 IC (≥ 1% or < 1%) by SP142
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)



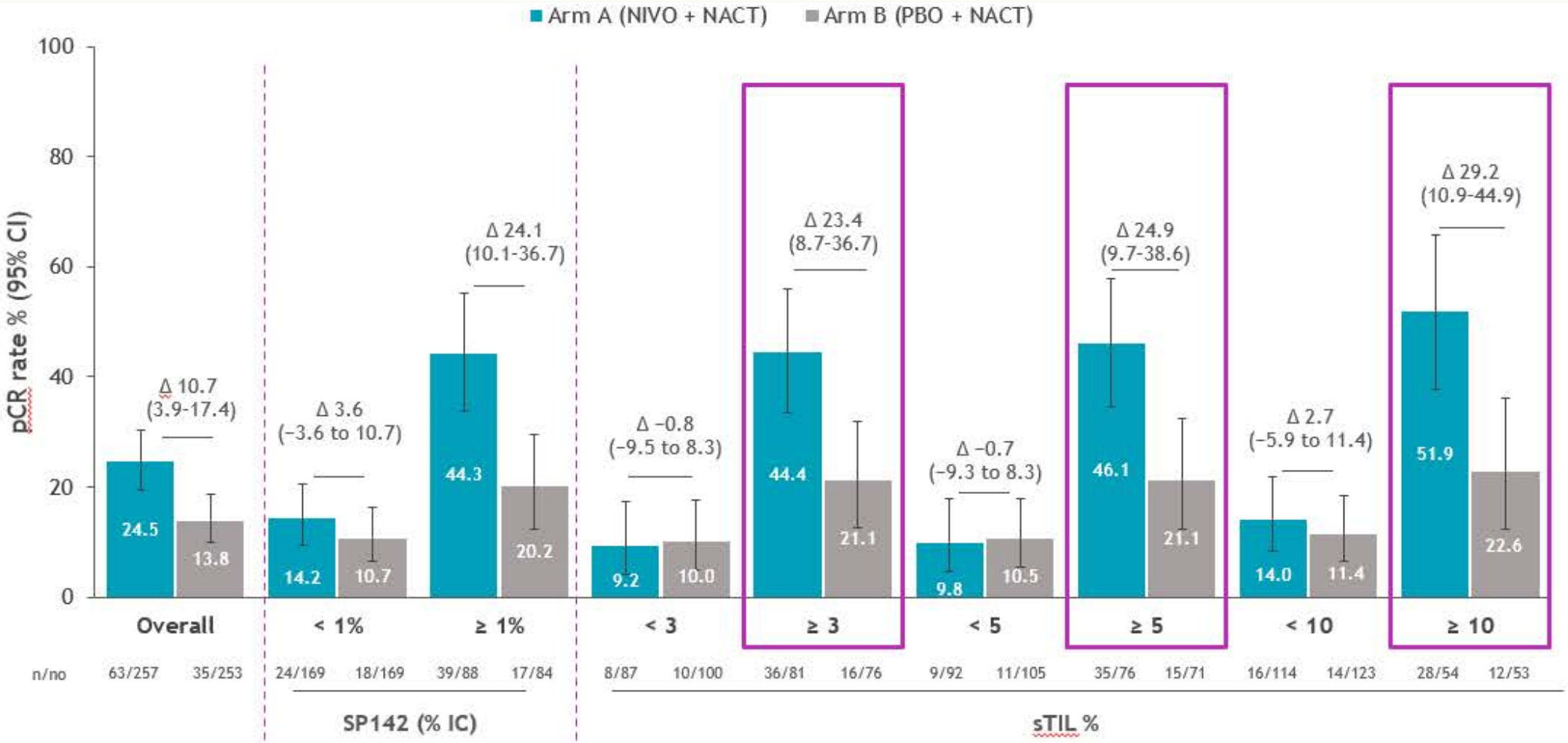
- [a]Grade was determined locally by investigator. [b]Investigator's choice: anthracycline dosing frequency of Q2W or Q3W for AC cycles determined by the investigator. [c]After protocol amendment 3, the study was unblinded in the adjuvant phase; participants in arm B did not receive NIVO PBO. [d]Available ET agents included tamoxifen, letrozole, anastrozole, and exemestane.
- AC, anthracycline + cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2-negative; IC, immune cell; N, lymph node involvement; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1; PTX, paclitaxel; QXW, every X weeks; SP142, Ventana PD-L1 SP142 assay; T, size and extent of primary tumor; wk, week.

Patient baseline characteristics in mITT population (n = 510) and in BEP (n = 349)

	Arm A: NIVO + NACT		Arm B: PBO + NACT	
	mITT population (n =257)	Patients with quantifiable PD-L1 28-8 CPS (n = 180)	mITT population (n = 253)	Patients with quantifiable PD-L1 28-8 CPS (n = 169)
Median age, years (range)	50 (24–78)	51 (25–78)	51 (23–79)	51 (23–79)
ECOG PS, n (%)				
0	221 (86)	161 (90)	222 (88)	149 (88)
1	36 (14)	19 (11)	31 (12)	20 (12)
Tumor grade,[a] n (%)				
Grade 2	6 (2)	4 (2)	1 (< 1)	1 (1)
Grade 3	251 (98)	176 (98)	252 (> 99)	168 (99)
Stage[b] (TNM classification[1]), n (%)				
Stage II	135 (53)	87 (48)	138 (55)	92 (54)
Stage III	118 (46)	90 (50)	105 (42)	68 (40)
Not assigned/reported	4 (2)	3 (2)	7 (3)	6 (4)
Ki67, n (%)				
< 20%	72 (28)	72 (40)	72 (28)	71 (42)
≥ 20%	107 (42)	107 (59)	97 (38)	93 (55)
Not reported	78 (30)	1 (1)	84 (33)	5 (3)
Axillary nodal status, n (%)				
Positive	205 (80)	147 (82)	201 (79)	137 (81)
Negative	52 (20)	33 (18)	52 (21)	32 (19)
AC dose-frequency chemotherapy regimen,[c] n (%)				
Q2W	132 (51)	89 (49)	134 (53)	86 (51)
Q3W	125 (49)	91 (51)	119 (47)	83 (49)

[a]Locally assessed. [b]Arm B included 1 patient with stage I disease and 2 patients with stage IV disease. [c]GnRH agonist therapy was allowed for ovarian preservation.
28-8 CPS, Dako 28-8 assay using CPS algorithm; AC, anthracycline + cyclophosphamide; BEP, biomarker evaluable population; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; mITT, modified intent-to-treat; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1; QXW, every X weeks; TNM, TNM staging system (T, size and extent of primary tumor; N, extent of spread to the lymph nodes; M, presence of metastasis). 1. AJCC Cancer Staging Manual; 8th edition, 3rd printing, Amin MB, Edge SB, Greene FL, et al. (Eds), Springer, Chicago 2018.

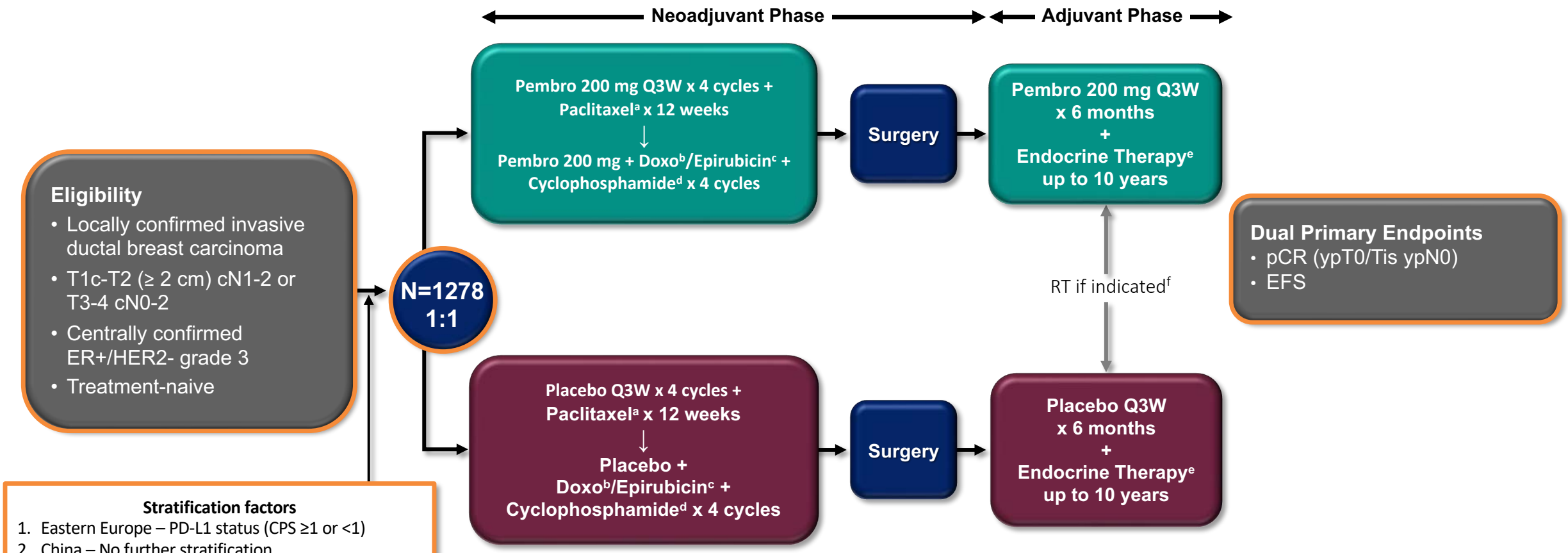
pCR by PD-L1 status determined by SP142 (IC%) and sTIL (cutoffs 3%, 5%, 10%)[a]



- The benefit of NIVO was increased in patients with sTIL > 1% or greater; the data for RCB 0/1 were consistent

[a]Exploratory biomarker/analysis. N = 344; Median sTIL % (min-max): 1 (1-98); mean sTIL % (SD): 14.49 (24.35). IC, immune cell; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; no, subpopulation total; PBO, placebo; pCR, pathological complete response; RCB, residual cancer burden; SD, standard deviation; SP142, Ventana PD-L1 SP142 assay; sTIL, stromal tumor-infiltrating lymphocyte.

KEYNOTE-756 Study Design (NCT03725059)



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

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

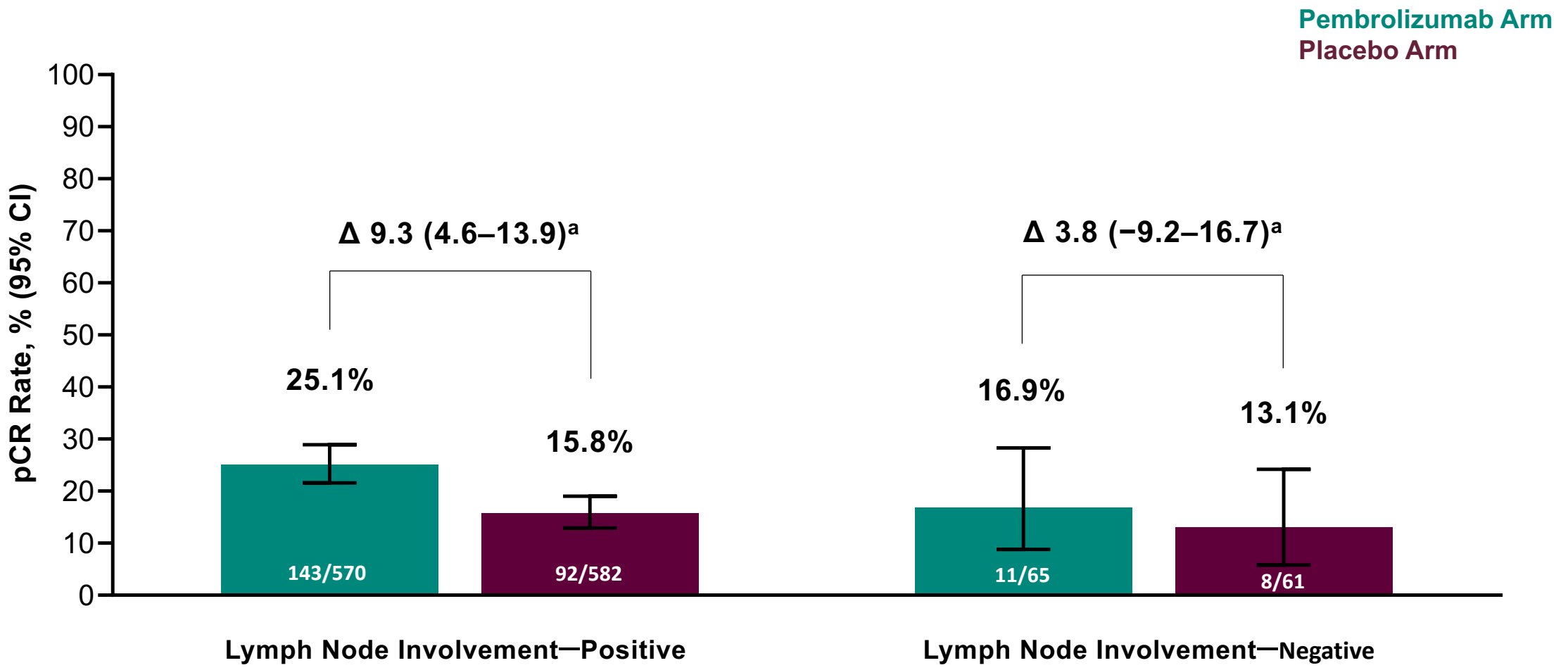
[a]Paclitaxel dose was 80 mg/m^2 QW. [b]Doxorubicin dose was 60 mg/m^2 Q3W. [c]Epirubicin dose was 100 mg/m^2 Q3W. [d]Cyclophosphamide dose was 600 mg/m^2 Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

Baseline Characteristics, ITT Population

Characteristic, n (%)	All Participants[a], N = 1278	
	Pembrolizumab Arm N = 635	Placebo Arm N = 643
Age, median (range), yrs	49 (24-82)	49 (19-78)
ECOG PS 1	65 (10.2)	55 (8.6)
PD-L1[b] CPS ≥1	482 (75.9)	489 (76.0)
PD-L1 CPS ≥10	253 (39.8)	259 (40.3)
China / Eastern Europe / all other countries	88 (13.9) / 139 (21.9) / 408 (64.3)	91 (14.2) / 130 (20.2) / 422 (65.6)
Overall disease stage		
II	399 (62.8)	408 (63.5)
III	236 (37.2)	235 (36.5)
Anthracycline schedule		
Q3W	415 (65.4)	425 (66.1)
Q2W	183 (28.8)	187 (29.1)
Not started	37 (5.8)	31 (4.8)
Tumor size		
T1/T2	402 (63.3)	413 (64.2)
T3/T4	233 (36.7)	230 (35.8)
Nodal involvement		
Positive	570 (89.8)	582 (90.5)
Negative	65 (10.2)	61 (9.5)
ER positivity ≥10%	601 (94.6)	600 (93.3)

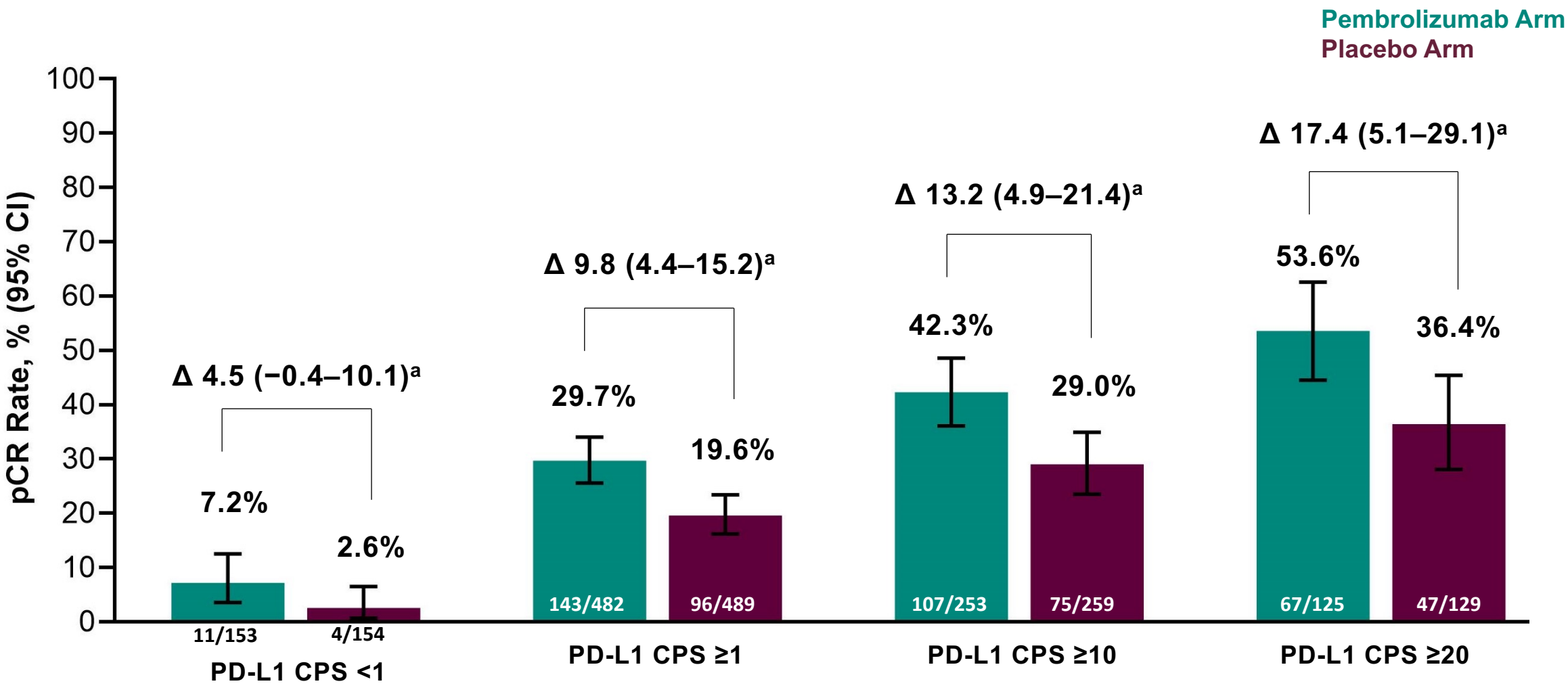
[a]All participants had centrally confirmed grade 3 disease. [b]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100). Data cutoff date: May 25, 2023.

Pathological Complete Response at IA1 by Lymph Node Involvement



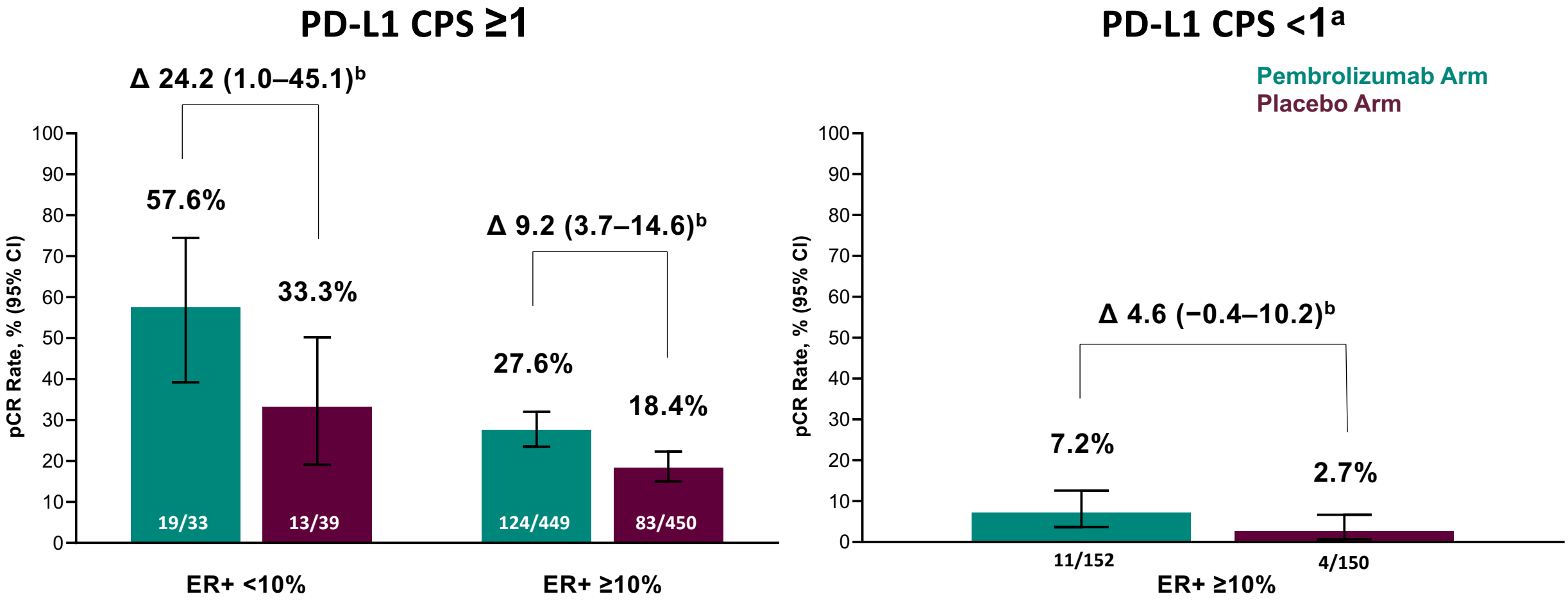
[a]Estimated treatment difference based on Miettinen & Nurminen method (unstratified). Data cutoff date: May 25, 2023.

Pathological Complete Response at IA1 by PD-L1 Expression Level



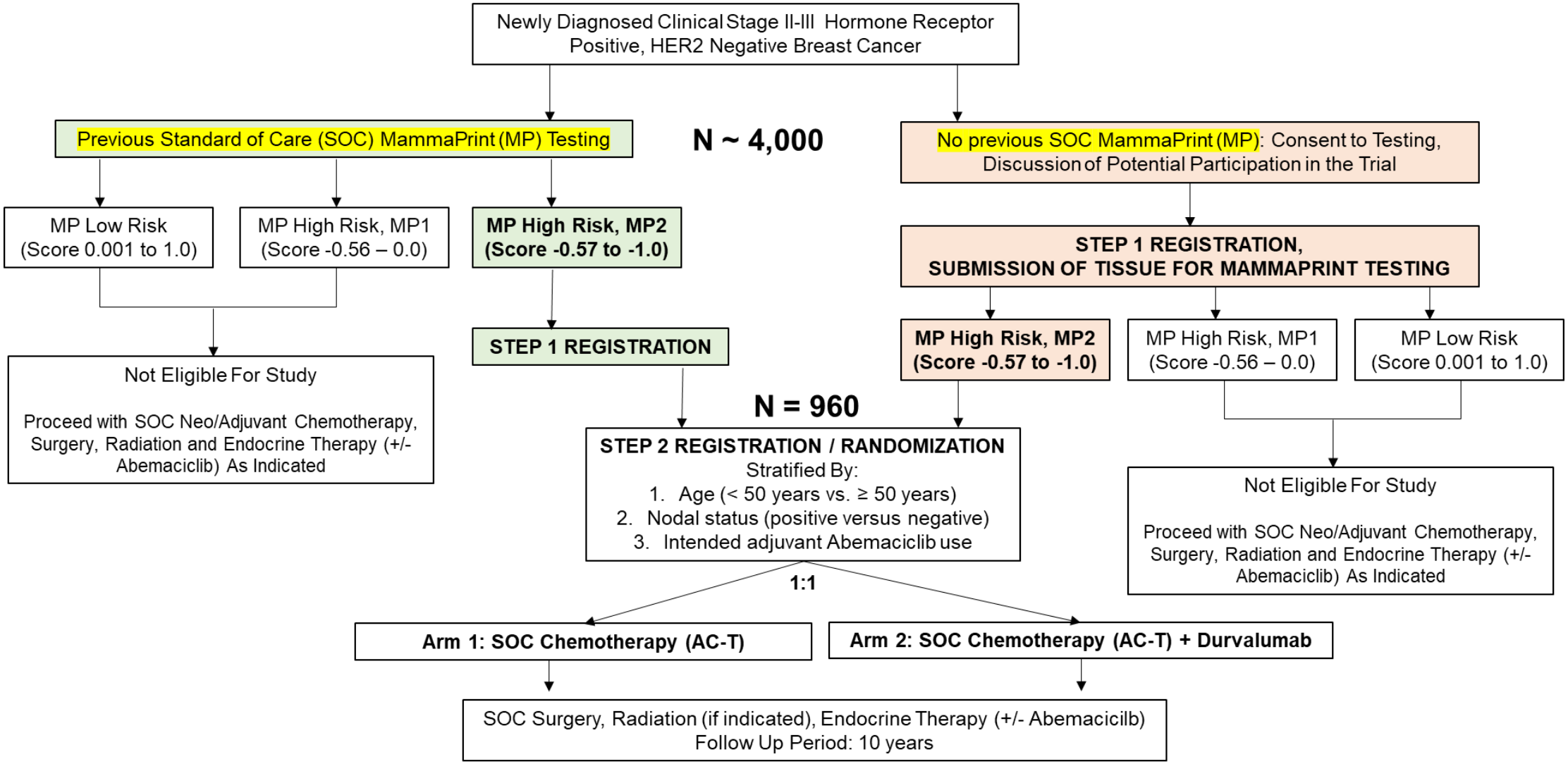
[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by geographic region (China vs Eastern Europe vs all other countries). Data cutoff date: May 25, 2023.

Pathologic Complete Response at IA1 by ER Status and PD-L1 Expression



[a]No pCR in patients with a PD-L1 CPS <1 with ER+ <10% (pembrolizumab arm, n = 1; placebo arm, n = 4). [b]Estimated treatment difference based on Miettinen & Nurminen method (unstratified).
Data cutoff date: May 25, 2023.

S2206 Schema



RxPONDER Schema

Key Entry Criteria

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

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

Arm 1:
Chemotherapy Followed by
Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

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

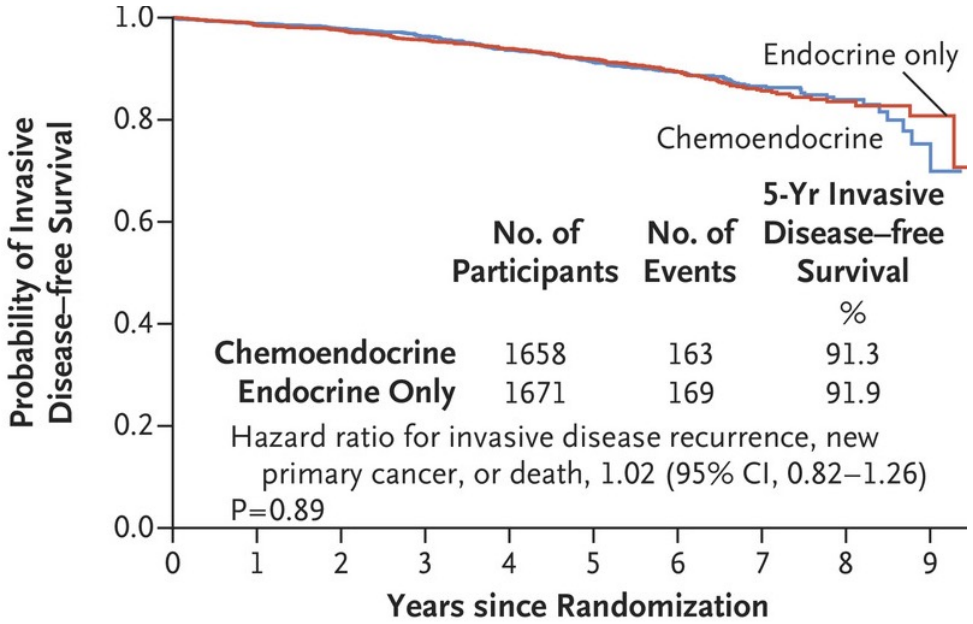
RxPONDER Population

T1	58%	T3	5%
1 LN+	66%	3 LN+	9%
Grade 2	64%	Grade 3	10%
40-49 yrs	21%	< 40 yrs	3%

Kalinsky K et al, NEJM 2021

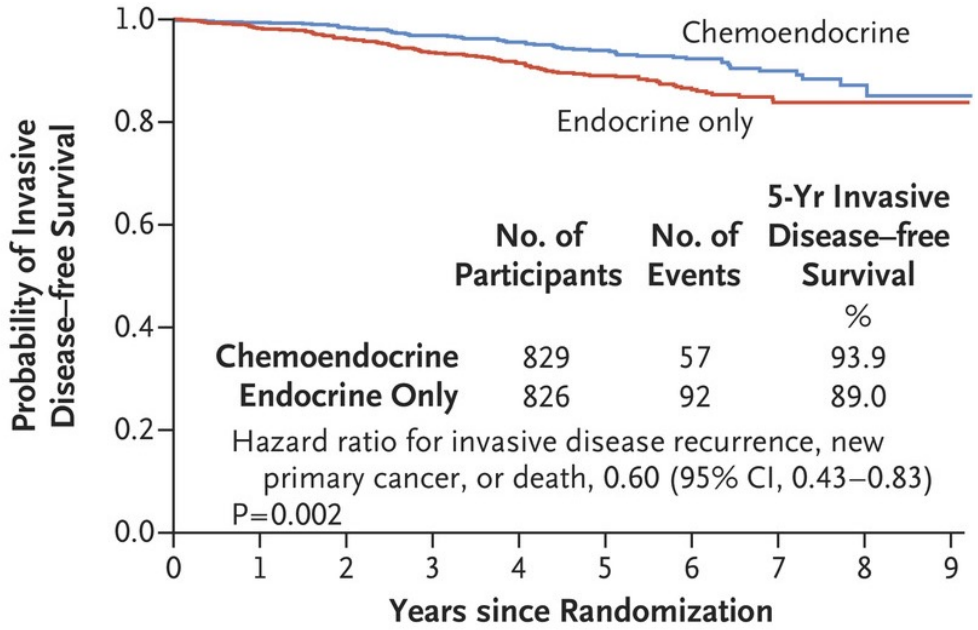
RxPONDER: Chemo Benefit Different by Menopausal Status if RS 0-25

Postmenopausal (2/3rd Trial)



What about if > 3 Lymph Nodes?

Premenopausal (1/3rd Trial)



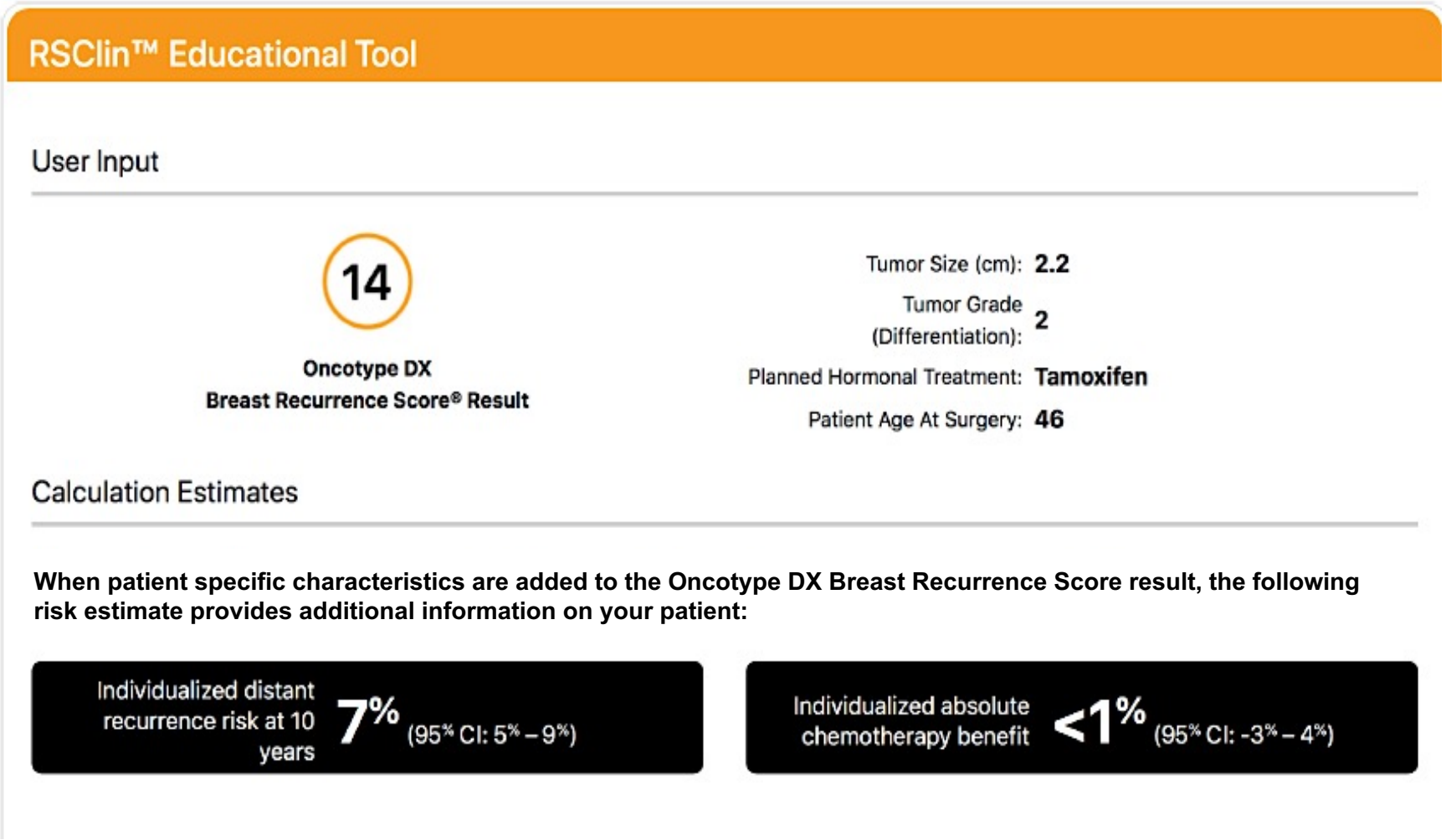
Why the Chemo Benefit?

OFS rate low (~ 16% in ET only)

postmenopausal: LMP > 12 mo or BSO; premenopausal: LMP < 6 mo; if neither: age 50 as cutoff

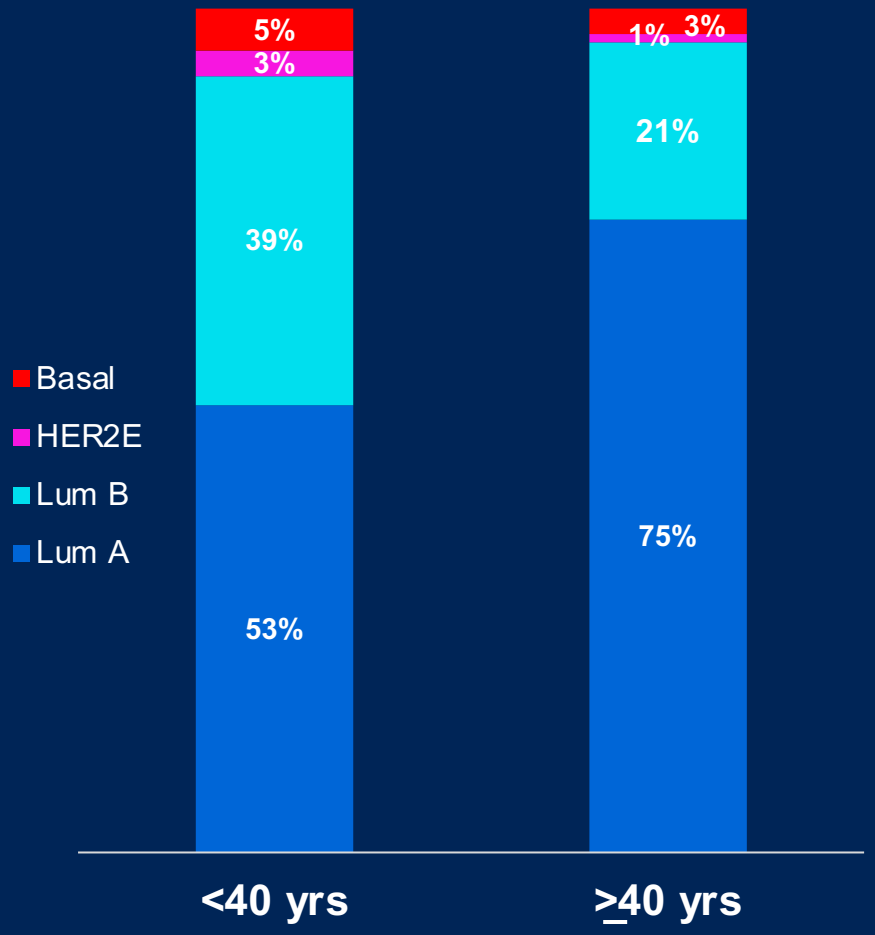
Kalinsky K et al, NEJM 2021

RSClin Tool for LN- Breast Cancer



- **Clinical-pathologic features inform risk**
- RSClin updates for late distant recurrence (P01-02-02)
- RSClin in LN+ in development

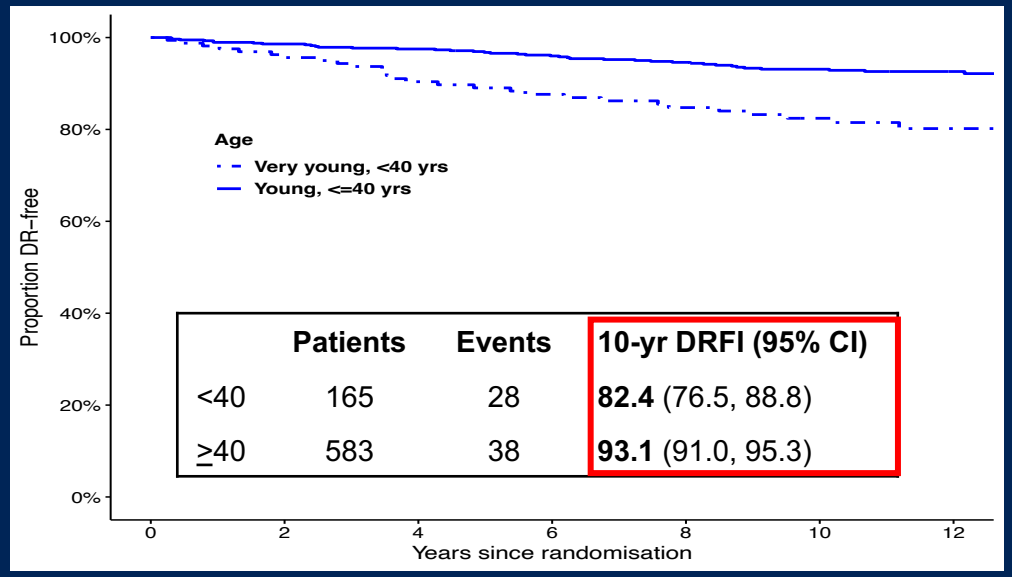
Very Young Women Have More Luminal B Tumors and Do Worse



* p= 0.005

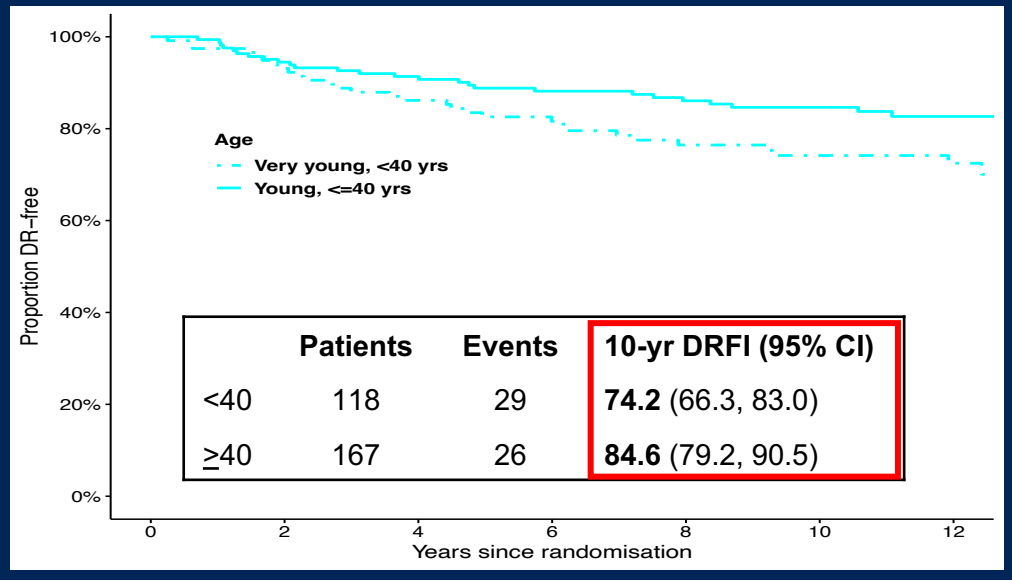
Higher HRD, Copy Number Alteration in Younger Women

Luminal A, <40yr vs ≥40yr



	Patients	Events	10-yr DRFI (95% CI)
<40	165	28	**82.4** (76.5, 88.8)
≥40	583	38	**93.1** (91.0, 95.3)

Luminal B, <40yr vs ≥40yr

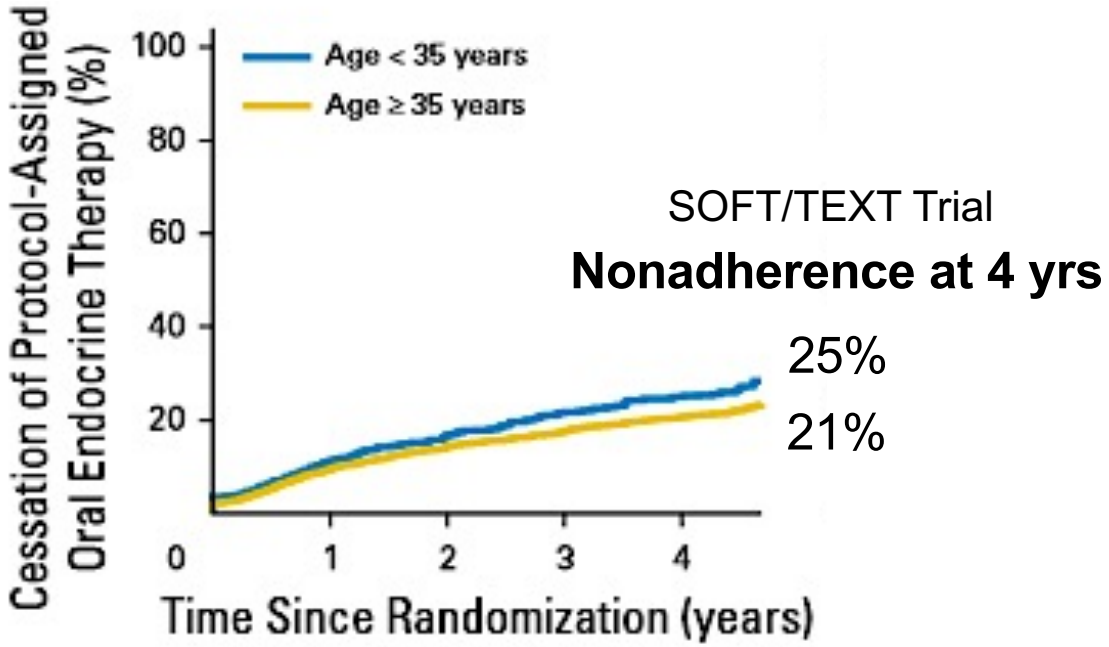


	Patients	Events	10-yr DRFI (95% CI)
<40	118	29	**74.2** (66.3, 83.0)
≥40	167	26	**84.6** (79.2, 90.5)

Luen SJ et al, Annals Oncology 2023; Brown LC et al, ASCO Meeting 2023

Not all patients are adherent to ovarian suppression

~ 20% nonadherent to oral ET



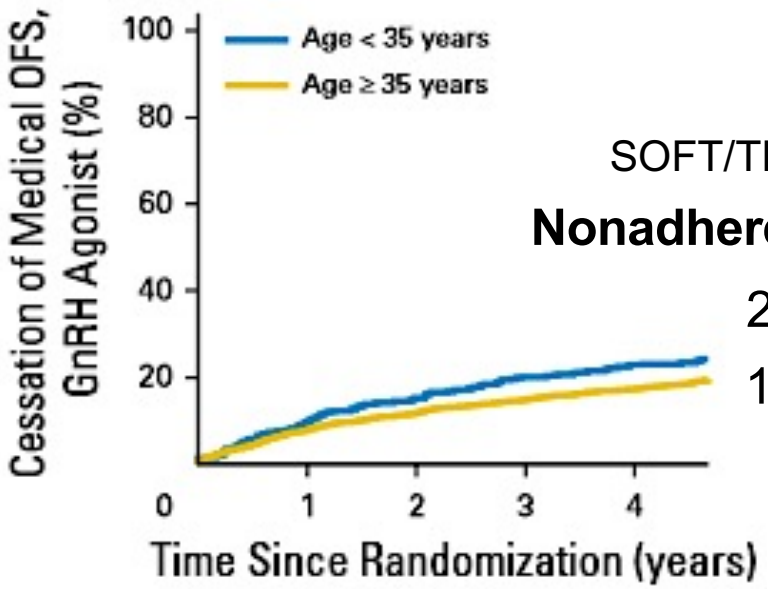
SOFT/TEXT Trial

Nonadherence at 4 yrs

25%

21%

~ 20% nonadherent to medical OFS



SOFT/TEXT Trial

Nonadherence at 4 yrs

23%

17%

ASTRA Trial: Early Discontinuation of 2 yrs OFS: 25.9%

Real World: < 40 yo highest rate of ET discontinuation

Saha P et al, JCO 2017; Kim HA et al JCO 2020: Hershman DL et al JCO 2010

BR009: Schema (N=3960)

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

Stratification

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

Randomization

CDK4/6 inh allowed

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

* Tamoxifen can be used if AI is not tolerated

monarchE and NATALEE: Schemas

monarchE: Abemaciclib x 2 yr

Randomization

- AI or tamoxifen +/- OFS
- Abemaciclib 150 mg po BID
- AI or tamoxifen +/- OFS

- ✓ N2
- ✓ N1 **and** T3, Grade 3, or Ki-67 ≥ 20%
- ✓ No N0

NATALEE: Ribociclib x 3 yr

Randomization

- NSAI +/- OFS
- Ribociclib 400 mg po QD 21 days on/ 7 days off
- NSAI +/- OFS

- ✓ N2
- ✓ N1
- ✓ N0 **and** Grade 3
- ✓ N0 **and** Grade 2 **and** Ki-67 > 20% or high genomic score

~30% pts early-stage tumors eligible for NATALEE and not monarchE

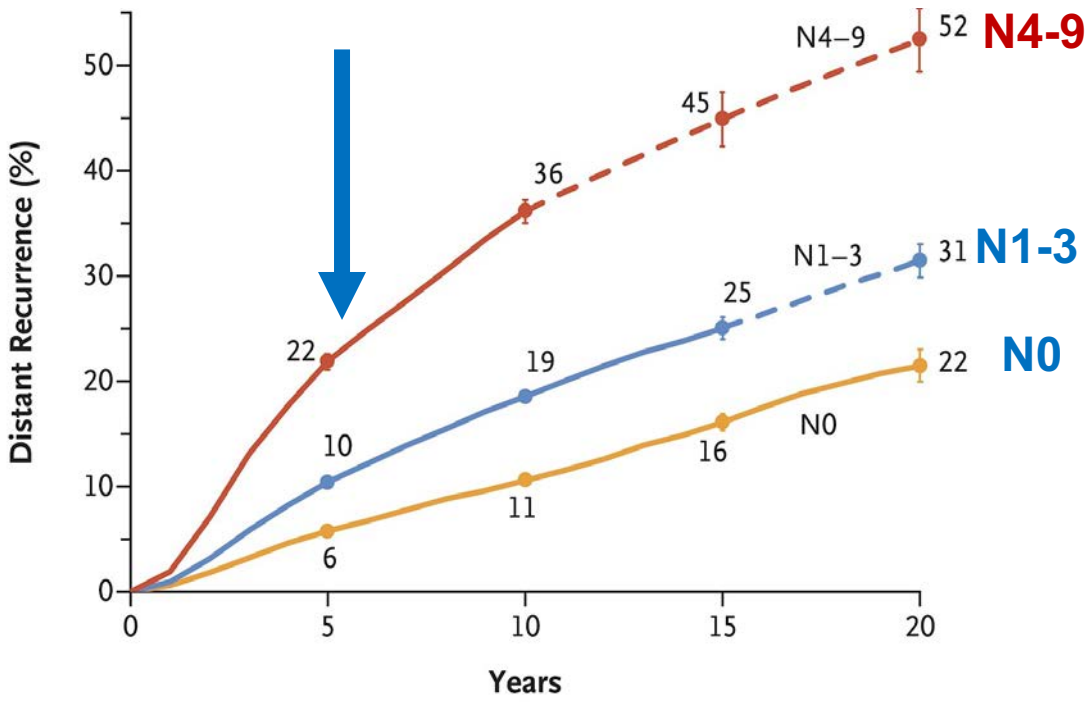
NSAI = Non-Steroidal Aromatase Inhibitor; OFS = Ovarian Function Suppression

Johnston S et al ESMO 2023; Slamon D et al ASCO 2023; Slamon D et al Ther Adv Med Oncol 2023

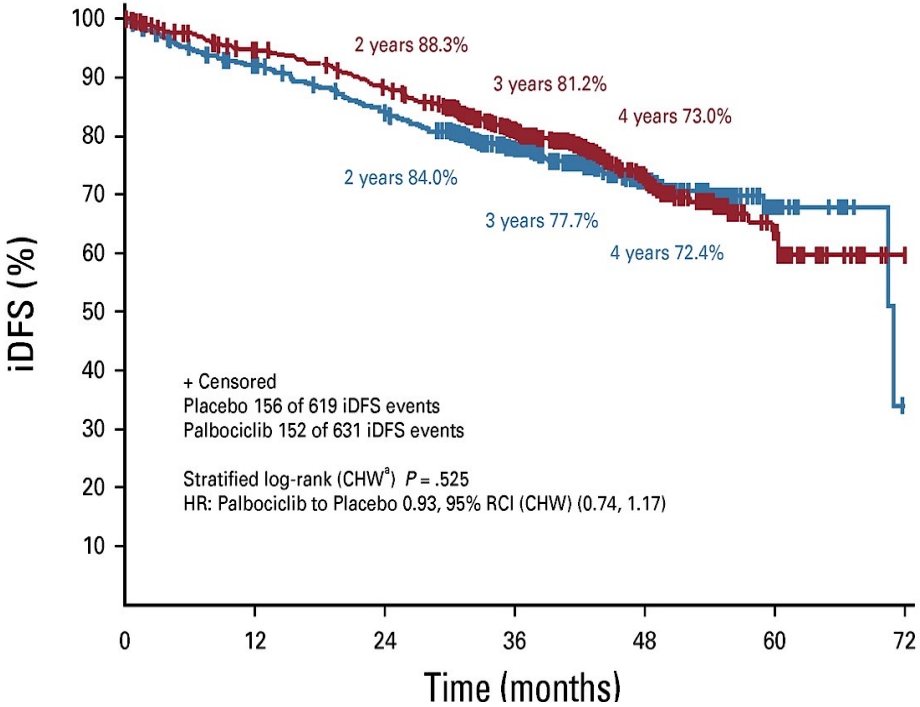
monarchE and NATALEE: Duration of Follow Up is Critical

Trial	iDFS Median Follow-up	Completed Time Period
monarchE	54 months	100% (2 year)
NATALEE	33.3 months	42.8% (3 year)

Impact on Late Recurrence?

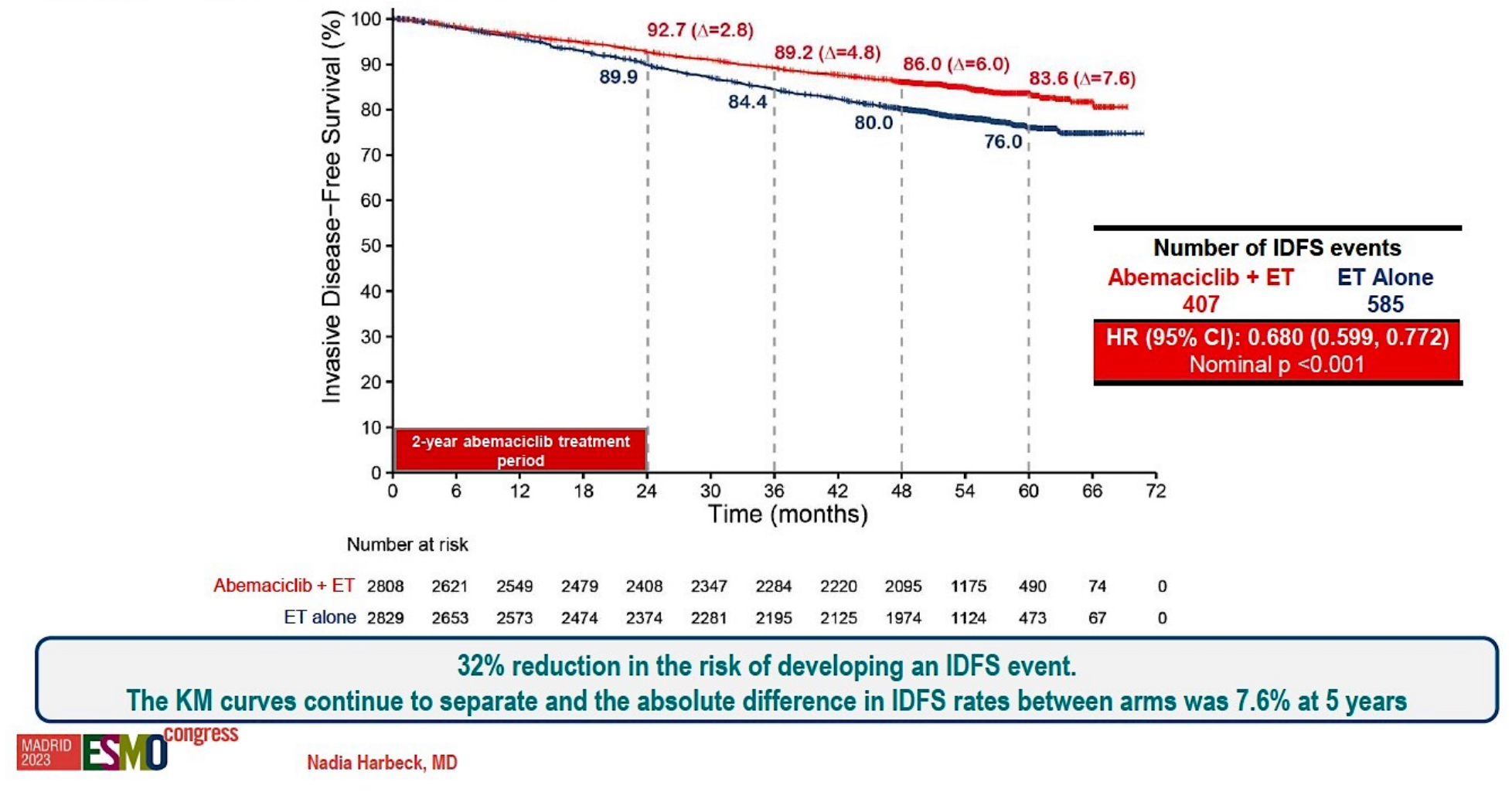


No Carry-Over Effect with Palbociclib



Pan et al NEJM 2017; Lloibl al JCO 2021; Johnston S et al Lancet Oncology 2023; Hortobagyi G et al SABCS 2023

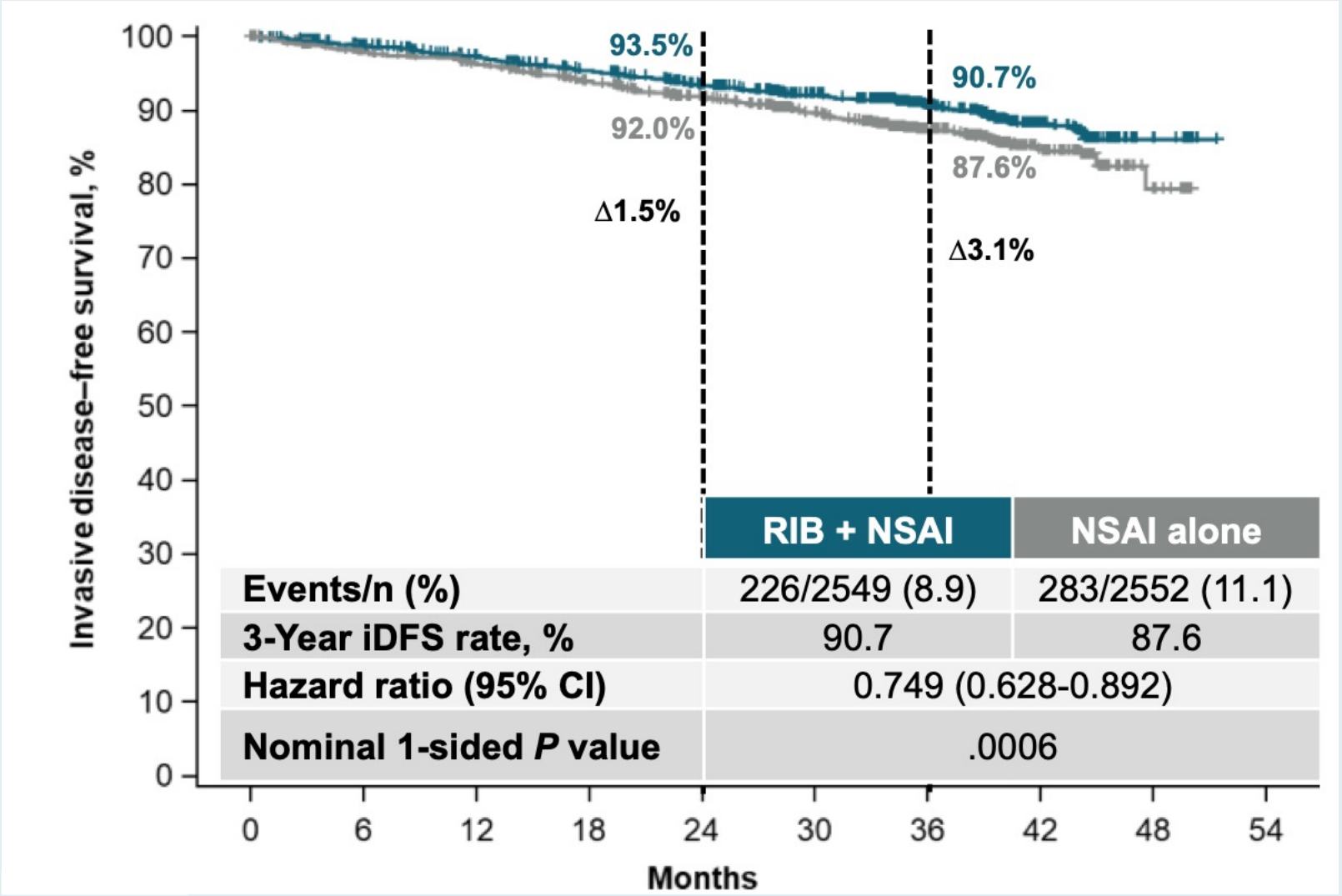
monarchE Trial: Abemaciclib Improved IDFS in the ITT Population



IDFS = invasive disease-free survival; ET = endocrine therapy

Harbeck N et al. ESMO 2023;Abstract LBA17.

NATALEE Trial: Ribociclib Significantly Improved IDFS

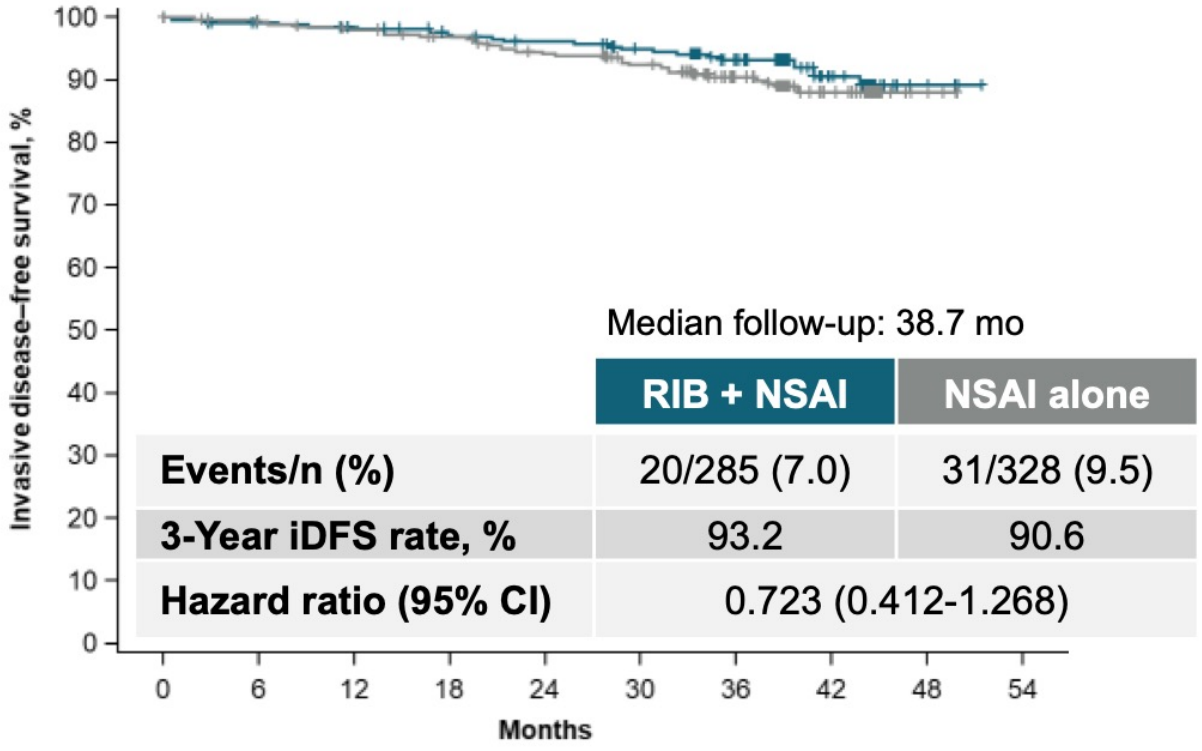


NSAI = nonsteroidal aromatase inhibitor

Hortobagyi GN et al. SABCS 2023;Abstract GS03-03.

NATALEE: Ribociclib Significantly Improved IDFS Regardless of Nodal Status

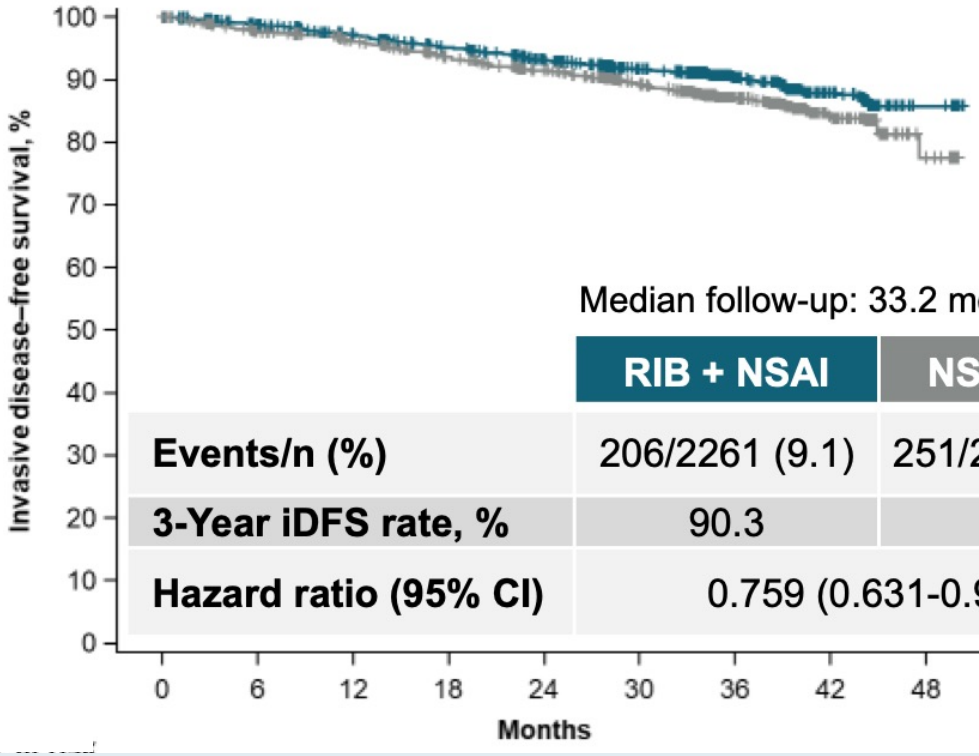
N0



Median follow-up: 38.7 mo

	RIB + NSAI	NSAI alone
Events/n (%)	20/285 (7.0)	31/328 (9.5)
3-Year iDFS rate, %	93.2	90.6
Hazard ratio (95% CI)	0.723 (0.412-1.268)	

N1-N3



Median follow-up: 33.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	206/2261 (9.1)	251/2219 (11.3)
3-Year iDFS rate, %	90.3	87.1
Hazard ratio (95% CI)	0.759 (0.631-0.912)	

Hortobagyi GN et al. SABCS 2023;Abstract GS03-03.

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Localized HER2-Positive and Triple-Negative Breast Cancer — Dr O'Shaughnessy

Module 2: Localized ER-Positive Breast Cancer — Dr Kalinsky

Module 3: SABCS 2023 Review — Dr Kaklamani

SABCS 2023 Review

Virginia Kaklamani, MD DSc
Professor of Medicine
Leader, Breast Oncology Program

Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center

Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Gilead Sciences Inc, Lilly, Menarini Group, Puma Biotechnology Inc, TerSera Therapeutics LLC
Contracted Research	Eisai Inc
Data and Safety Monitoring Board/Committee	Sanofi
Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Novartis, Pfizer Inc, Seagen Inc

Can we improve patient outcomes with lifestyle interventions?

Higher BMI Linked To:

- Increased breast cancer mortality
- Increased risk of second cancers

The Breast Cancer Weight Loss Trial (BWEL)

3136 Participants

Key Eligibility*

- Stage II-III Breast Cancer
- HR+/HER-2- or TNBC
- Diagnosed w/in past 14 months
- Completed with surgery and any chemotherapy and/or radiation
- BMI ≥ 27 kg/m2

*Patients planning on taking medications for the purpose of weight loss and/or undergoing a surgical weight loss procedure within 2 years were not eligible

Randomize

- **Health Education + 2-year Telephone-Based Weight Loss Intervention**
- **Health Education Alone**

Primary Objective:

Assess the impact of a weight loss intervention (WLI) on IDFS

- Key secondary endpoint: weight change

Chan et al. IJC 2022; Ligibel et al, ASCO 2023

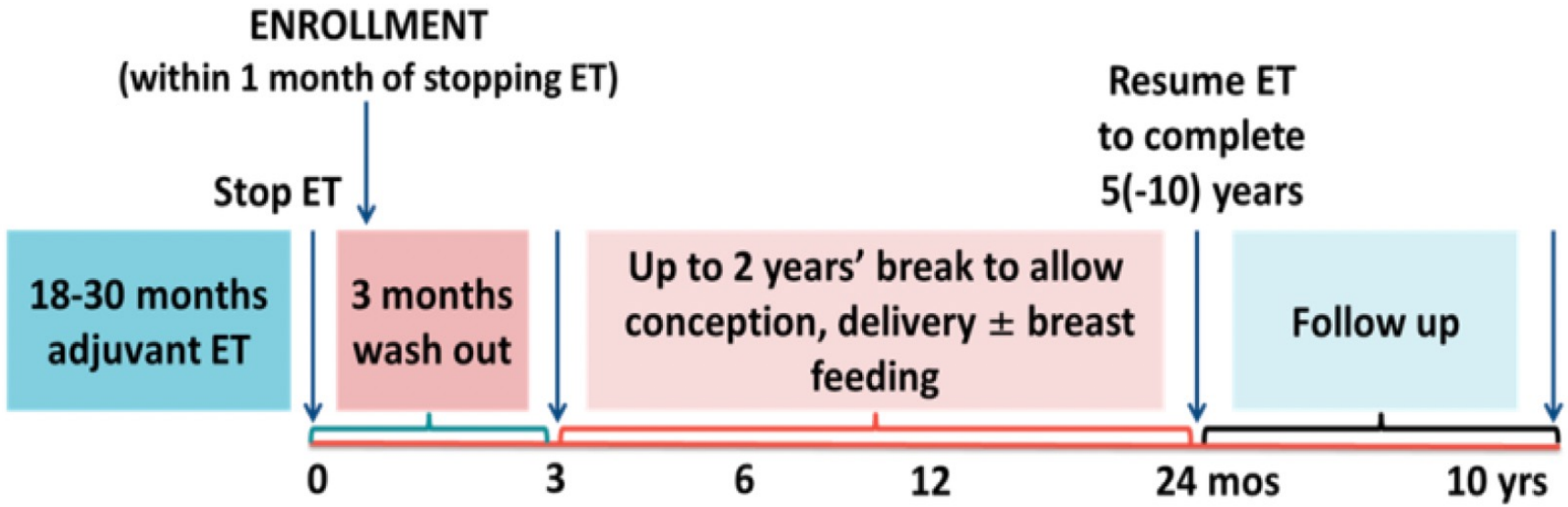
BWEL Weight Loss

	CONTROL (n=1173)	WLI (n=1222)	P VALUE
Absolute Weight Change at 6-months	+ 0.2 kg	- 4.4 kg	<0.0001
% Weight Change at 6-months	+ 0.3%	- 4.8%	<0.0001
Absolute Weight Change at 12-months	+ 0.7kg	- 4.4kg	<0.0001
% Weight Change at 12-months	+ 0.9%	- 4.8%	<0.0001

Ligibel et al, ASCO 2023

POSITIVE Trial Menses and ART Outcomes

- Prospective, international, multicenter, single-arm trial



Key Eligibility Criteria

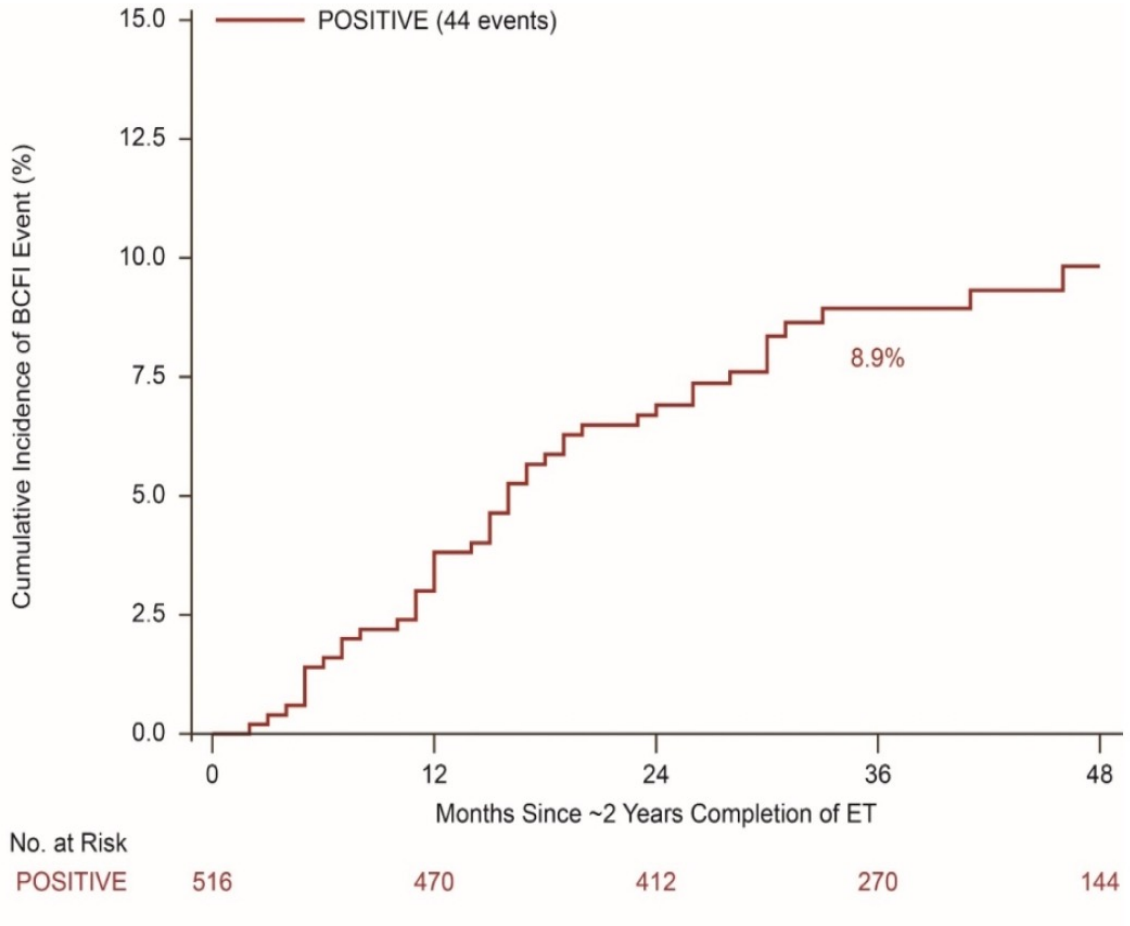
- Premenopausal women stage I-III HR+ BC
- Wishing to become pregnant
- Age ≤42 years at study entry
- At least 18 months and no more than 30 months of prior adjuvant ET
- No clinical evidence of recurrence

N=516

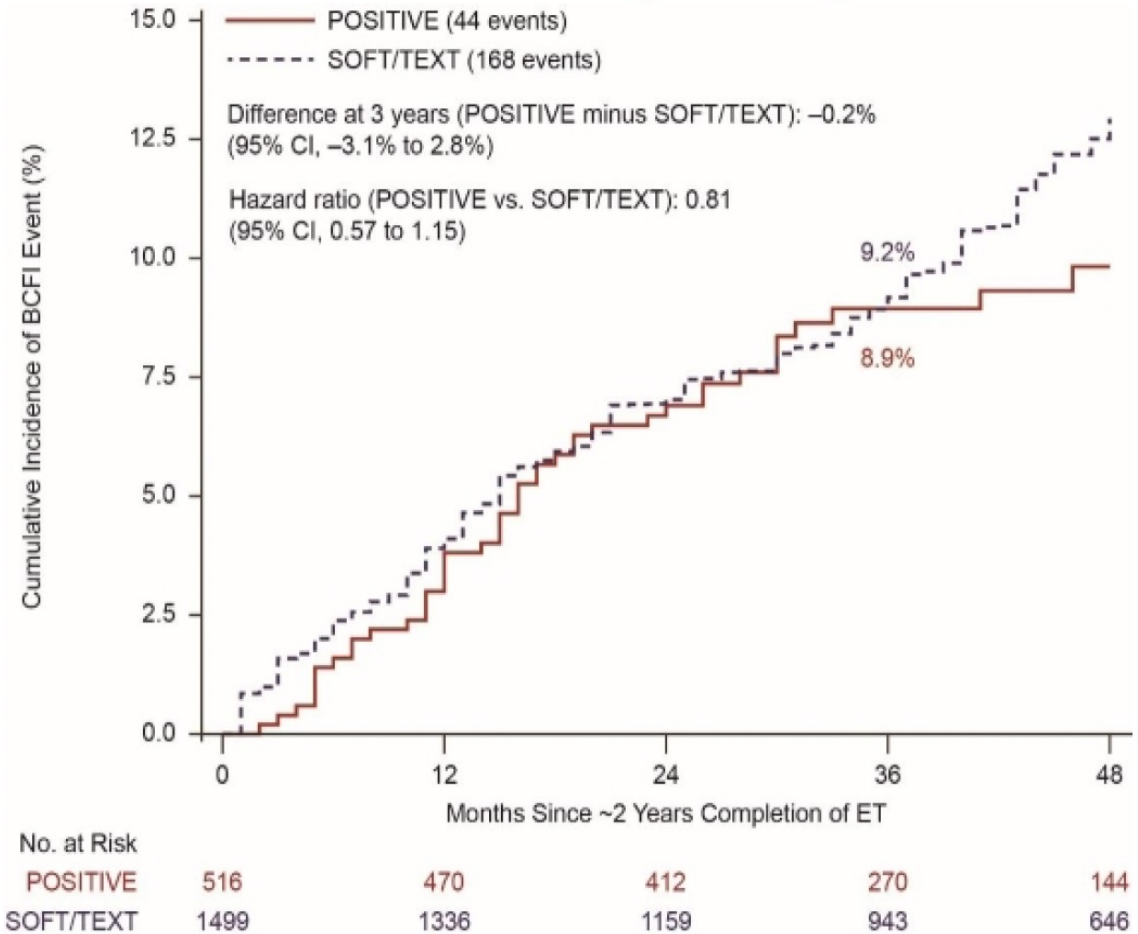
Partridge AH, et al. SABCS 2022; NEJM 2023; Azim et al, SABCS 2023

POSITIVE Trial Breast Cancer Outcomes

BCFI- POSITIVE only



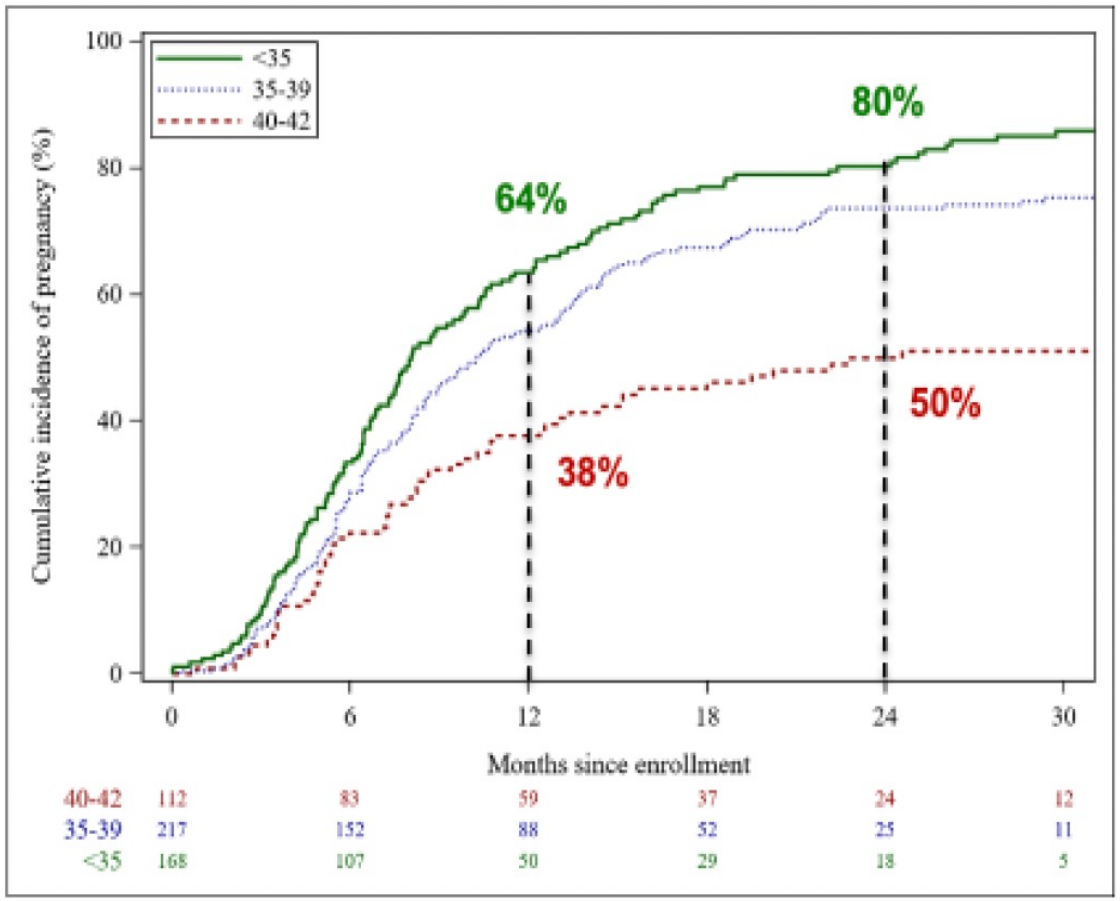
BCFI- SOFT and TEXT matching analyses



Partridge AH, et al. SABCS 2022; NEJM 2023

POSITIVE Trial- Time to Pregnancy

368 patients (74%) reported at least one pregnancy



Multivariable Fine and Gray competing risk model	sHR (95% CI)
Chemo + GnRHa vs Chemo alone	1.29 (0.94 – 1.79)
None vs Chemo alone	1.05 (0.85 – 1.32)
35-39 vs <35	0.74 (0.59 – 0.93)
40-42 vs <35	0.40 (0.29 – 0.56)
SERM+OFS vs SERM only	0.94 (0.71 – 1.24)
AI+OFS vs SERM only	0.94 (0.67 – 1.33)
Prior birth: Yes vs No	0.94 (0.72 – 1.23)
Irregular vs Persistent amenorrhea	1.17 (0.85 – 1.63)
Normal vs Persistent amenorrhea	1.01 (0.78 – 1.32)

Azim et al, SABCS 2023

POSITIVE Trial- Use of ART and Chance of Pregnancy

Multivariate logistic regression model	OR (95% CI)
35-39 vs <35	0.50 (0.29 - 0.86)
40-42 vs <35	0.16 (0.08 - 0.29)
Ovarian stimulation for IVF after enrollment vs No ART	0.85 (0.48 - 1.50)
Cryopreserved embryo transfer * vs No ART	2.41 (1.17 - 4.95)
Other ART vs No ART	1.80 (0.92 - 3.57)
Chemotherapy + GnRHa vs Chemotherapy no GnRHa	1.41 (0.70 - 2.82)
None vs Chemotherapy without GnRHa	1.10 (0.70 - 1.75)

* 82% of patients reported at least 1 pregnancy

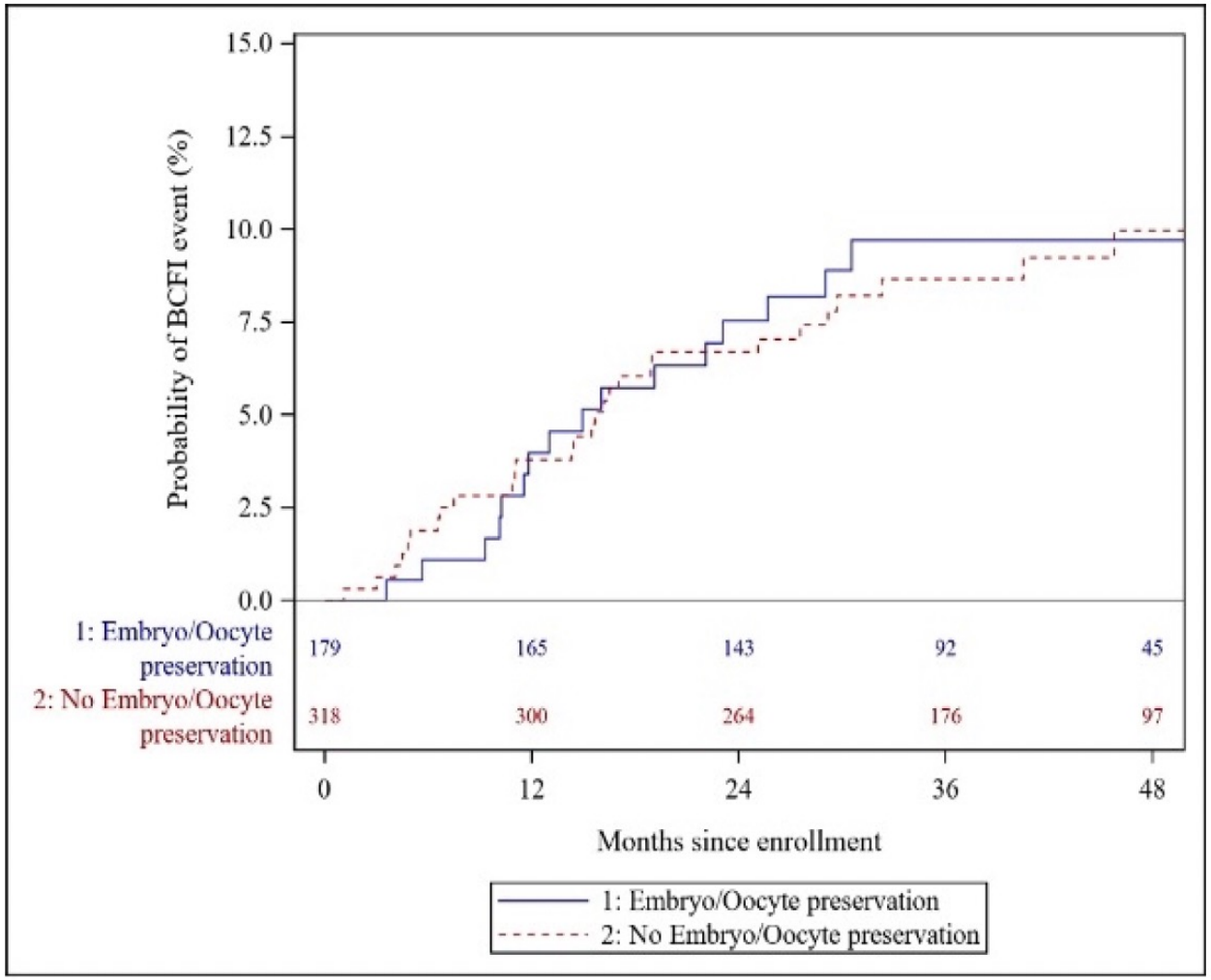
Azim et al, SABCS 2023

POSITIVE Trial- Ovarian Stim for FP and BC Outcome

As part of embryo/oocyte cryopreservation - at breast cancer diagnosis (N=179; 36%)

At 3-years, BCFI-events cumulative incidence

- **9.7%** (95% CI: 6.0% to 15.4%) for the 179 patients who underwent ovarian stimulation
- **8.7%** (95% CI: 6.0% to 12.5%) for the 318 patients who did not



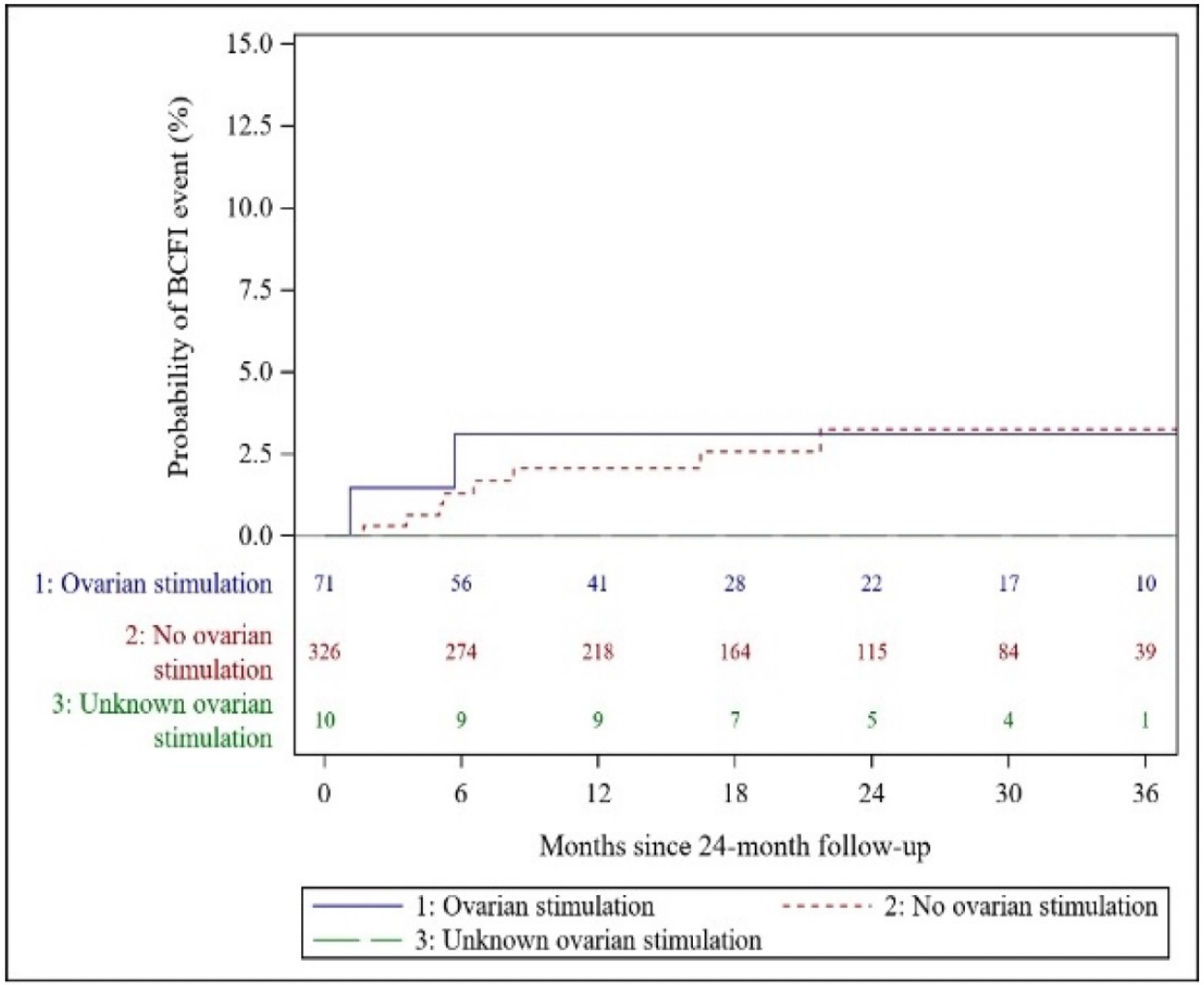
Azim et al, SABCS 2023

POSITIVE Trial- Ovarian Stim on Study and BC Outcome

As part of ART - after enrollment (N=80; 16%)

- **397 patients alive and BC free at 24-months (landmark analysis)**
  - 2 BC events amongst 71 patients in the ovarian stimulation group
  - 8 BC events amongst 326 patients in the non-ovarian stimulation group

SMALL NUMBERS!



Azim et al, SABCS 2023

The Annual
National General Medical Oncology Summit

Saturday, March 23, 2024

Moderator

Neil Love, MD

Faculty

Emmanuel S Antonarakis, MD
Ibiayi Dagogo-Jack, MD
Matthew D Galsky, MD
Edward B Garon, MD, MS
Erika Hamilton, MD
Eric Jonasch, MD
Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Matthew Lunning, DO
Kami Maddocks, MD
Rana R McKay, MD
Bradley J Monk, MD
David M O'Malley, MD
Joyce O'Shaughnessy, MD
Brian Rini, MD
Jonathan E Rosenberg, MD
Hope S Rugo, MD
Helena Yu, MD
Andrew D Zelenetz, MD, PhD

Overview

Saturday, March 23rd

Module 1: 7:30 AM – 9:10 AM — Hodgkin and Non-Hodgkin Lymphoma

Module 2: 9:30 AM – 10:20 AM — Gynecologic Cancers

Module 3: 10:20 AM – 11:10 AM — Localized Breast Cancer; SABCS 2023 Review

Module 4: 11:10 AM – 12:00 PM — Metastatic HER2-Positive and Triple-Negative Breast Cancer; SABCS 2023 Review

Module 5: 12:30 PM – 1:20 PM — Prostate Cancer

Module 6: 1:20 PM – 2:10 PM — Urothelial Bladder Cancer

Module 7: 2:10 PM – 3:00 PM — Renal Cell Carcinoma

Module 8: 3:20 PM – 4:10 PM — Targeted Therapy for Non-Small Cell Lung Cancer

Module 9: 4:10 PM – 5:00 PM — Nontargeted Treatments for Lung Cancer

Agenda

Module 1: HER2-Positive Metastatic Breast Cancer — Dr Hamilton

Module 2: Metastatic Triple Negative Breast Cancer — Dr Rugo

Module 3: SABCS 2023 Review — Dr Kaklamani

Agenda

Module 1: HER2-Positive Metastatic Breast Cancer — Dr Hamilton

Module 2: Metastatic Triple Negative Breast Cancer — Dr Rugo

Module 3: SABCS 2023 Review — Dr Kaklamani

HER2-Positive Metastatic BC (mBC)

Erika Hamilton, MD
Director, Breast Cancer Research
Chair, Breast Executive Committee
Sarah Cannon Research Institute, Nashville, TN

March 2024

SCRI Sarah Cannon Research Institute

Disclosures

Consulting Agreements — Payment Made to Institution	Accutar Biotechnology Inc, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Ellipses Pharma, Entos Pharmaceuticals, Fosun Pharma, Genentech, a member of the Roche Group, Gilead Sciences Inc, Greenwich LifeSciences Inc, Jazz Pharmaceuticals Inc, Lilly, Mersana Therapeutics Inc, MphaR, Novartis, Olema Oncology, Orum Therapeutics, Pfizer Inc, Stemline Therapeutics Inc, Theratechnologies, Tubulis, Zentalis Pharmaceuticals
Contracted Research — Payment Made to Institution	AbbVie Inc, Accutar Biotechnology Inc, Acerta Pharma — A member of the AstraZeneca Group, ADC Therapeutics, Akesobio Australia Pty Ltd, Amgen Inc, Aravive Inc, ArQule Inc, Artios, Arvinas, AstraZeneca Pharmaceuticals LP, AtlasMedx Inc, BeiGene Ltd, Black Diamond Therapeutics Inc, Bliss Biopharmaceutical, Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, Compugen, Context Therapeutics, Cullinan Oncology, Curis Inc, CytomX Therapeutics, Daiichi Sankyo Inc, Dantari, Deciphera Pharmaceuticals Inc, Duality Biologics, eFFECTOR Therapeutics Inc, Ellipses Pharma, Elucida Oncology Inc, EMD Serono Inc, FUJIFILM Pharmaceuticals USA Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, H3 Biomedicine, Harpoon Therapeutics, Hutchison MediPharma, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Inspirna, InventisBio, Jacobio Pharmaceuticals Group Co Ltd, Karyopharm Therapeutics, K-Group Beta, Kind Pharmaceuticals LLC, Leap Therapeutics Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Lycera, MacroGenics Inc, Marker Therapeutics Inc, Mersana Therapeutics Inc, Merus BV, Molecular Templates, Myriad Genetic Laboratories Inc, Novartis, NuCana, Olema Oncology, OncoMed Pharmaceuticals Inc, Onconova Therapeutics Inc, Oncothyreon, ORIC Pharmaceuticals, Orinove Inc, Orum Therapeutics, Pfizer Inc, PharmaMar, Pieris Pharmaceuticals Inc, Pionyr Immunotherapeutics, Plexxikon Inc, Prelude Therapeutics, ProfoundBio, Radius Health Inc, Regeneron Pharmaceuticals Inc, Relay Therapeutics, Repertoire Immune Medicines, Seagen Inc, Sermonix Pharmaceuticals, Shattuck Labs, Stemcentrx, Sutro Biopharma, Syndax Pharmaceuticals Inc, Syros Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, Tolmar, Transcenta, Treadwell Therapeutics, Verastem Inc, Zenith Epigenetics, Zymeworks Inc
Nonrelevant Financial Relationship	Verascity Science

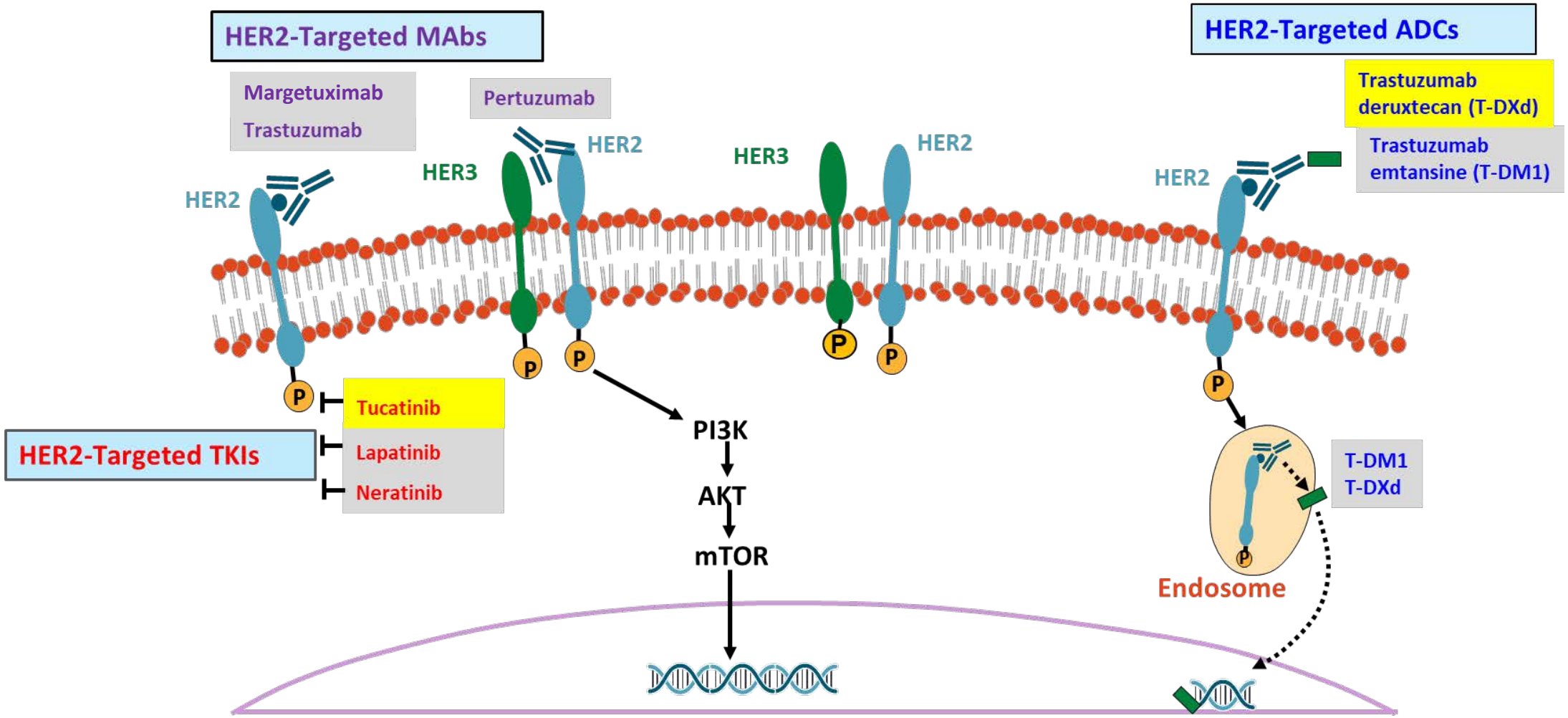
Case – A 36-year-old woman with de novo HER2-positive mBC

- Patient is a biologist who studies bats. She has a 4- and 2-year-old.
- She is diagnosed with de novo metastatic HER2 amplified breast cancer (liver, nodes, single brain met) at age 36.
  - HER2 FISH ratio 13.3 from liver biopsy, ER0, PR 0.
- Receives SRS to brain lesion.
- Receives THP x 8 cycles
  - Taxane dropped out and continues HP for 16 months.
  - Progresses with a new liver lesion and 3 new <1cm brain mets.
- Completes SRS to the brain lesions.
- Enrolls on HER2CLIMB and receives cape/tras/tucatinib.
  - Dose reduces capecitabine from 1500 mg BID to 1500 mg q am and 1000 mg qpm after 1st cycle.
  - Continues on this regimen for 13 months.
- Receives T-DXd.
  - Holds in cycle 4 for G1 ILD, resumes after 28 days.
  - Continues on this regimen now for 14 months.

Agenda

- Key studies evaluating the use of tucatinib-based therapy and trastuzumab deruxtecan (T-DXd) in HER2-positive mBC
- Incidence of brain metastases in patients with HER2-positive mBC
- CNS activity observed with T-DXd and tucatinib-based therapy
- Treatment algorithm for patients with HER2+ MBC

FDA approved targeted therapies for HER2+ breast cancer (2024)



Gajria. Expert Rev Anticancer Ther. 2011;
Pernas. Ther Adv Med Oncol. 2019

Tucatinib

SCRI Sarah Cannon Research Institute

HER2CLIMB: Phase III registration trial with tucatinib

Tucatinib is a HER2-specific TKI - 1000 fold more specific for HER2 vs EGFR

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

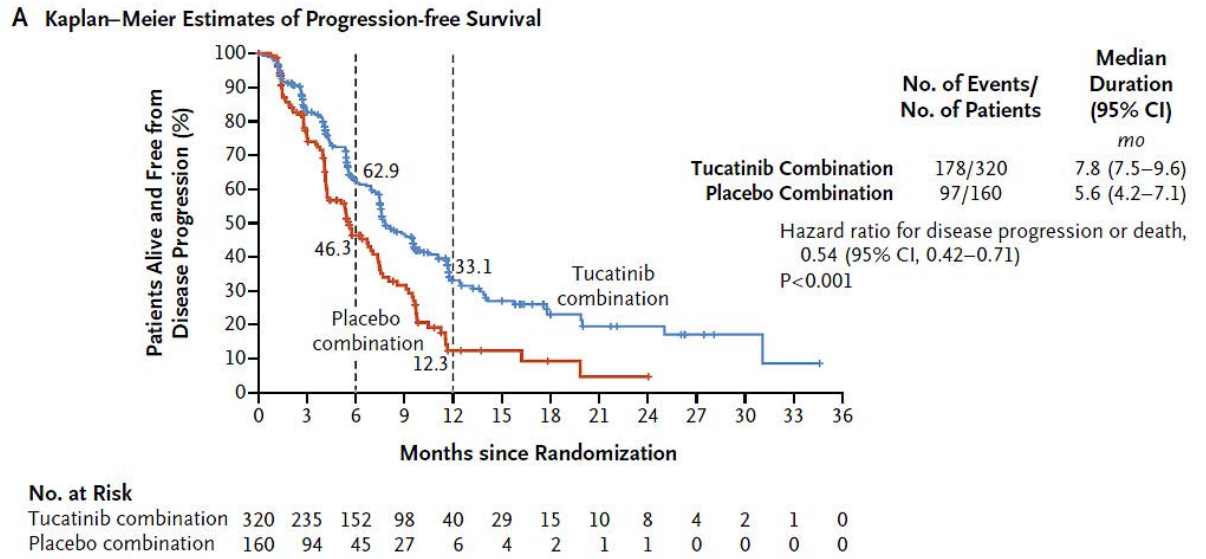
Placebo + Trastuzumab + Capecitabine
(21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

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

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

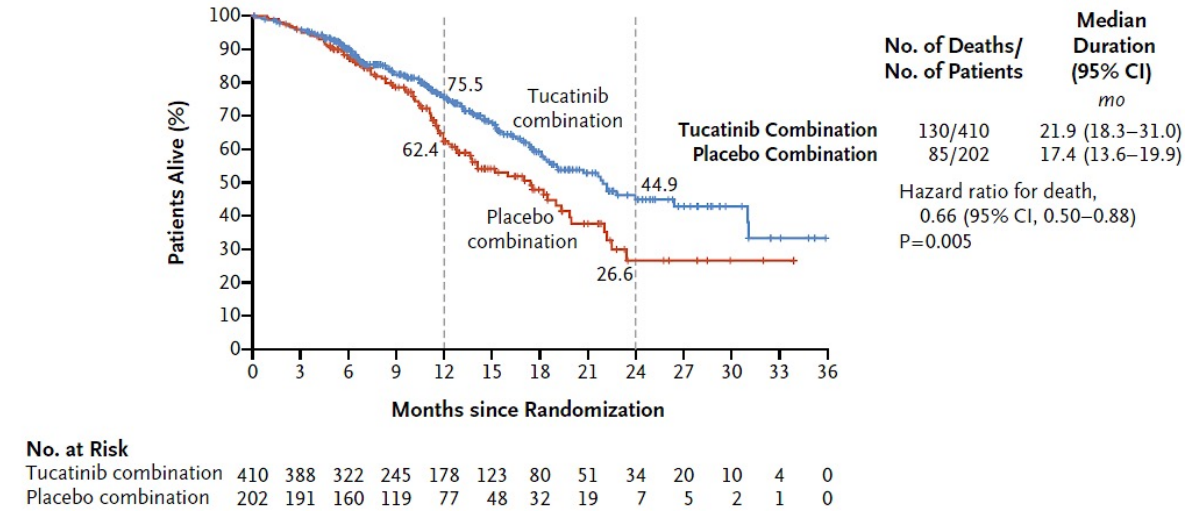
HER2CLIMB: Tucatinib improved PFS and OS in ITT



PFS by BICR
N=480*

Risk of progression or death was reduced by 46%
95% CI: 0.42 to 0.71, P<0.001

7.8 months vs 5.6 months



Overall Survival
N=612

Risk of death was reduced by 34%
95% CI: 0.50 to 0.88, P=0.005

21.9 months vs 17.4 months

April 17, 2020: Tucatinib in combination with trastuzumab and capecitabine received FDA approval for pts with HER2+ MBC, including pts with brain mets, who have received one or more prior anti-HER2 therapies in the metastatic setting

Murthy RK et al NEJM 2019

HER2CLIMB-02: T-DM1 +/- Tucatinib

- HER2+ LA/MBC with progression after trastuzumab and taxane in any setting[a]
- ECOG PS ≤1
- Previously treated stable, progressing, or untreated brain metastases not requiring immediate local therapy

N≈460

R 1:1

Stratification factors:
- Line of treatment for metastatic disease (1L vs other)
- Hormone receptor status (positive vs negative)
- Presence or history of brain metastases (yes vs no)
- ECOG PS (0 vs 1)

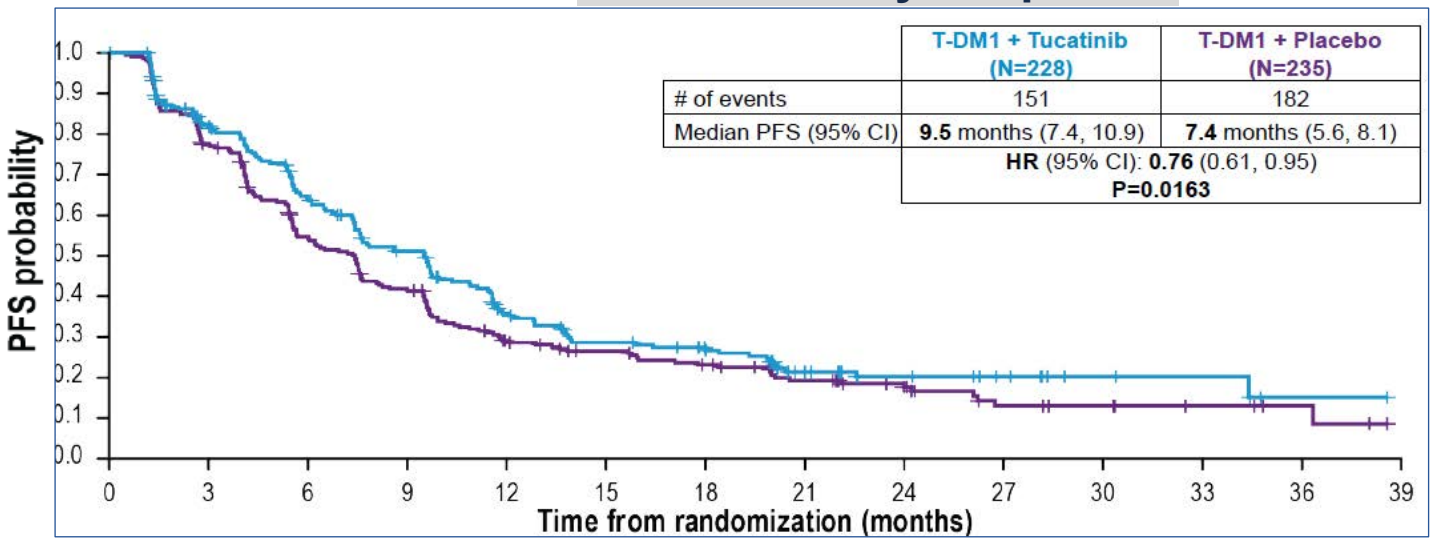
T-DM1 + Tucatinib

T-DM1 3.6 mg/kg IV and Tucatinib 300 mg PO BID

T-DM1 + Placebo

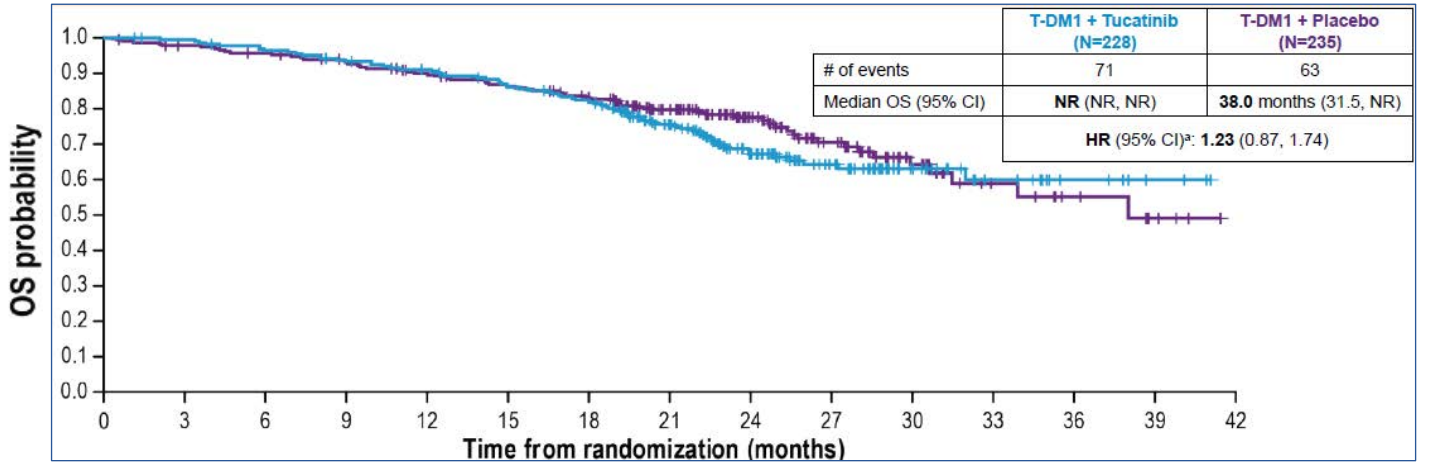
T-DM1 3.6 mg/kg IV and Placebo PO BID

PFS – Primary endpoint



	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
	HR (95% CI): **0.76** (0.61, 0.95) **P=0.0163**	

Overall survival



	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	71	63
Median OS (95% CI)	**NR** (NR, NR)	**38.0** months (31.5, NR)
	HR (95% CI)[a]: **1.23** (0.87, 1.74)	

Adding tucatinib to T-DM1 significantly improved PFS in ITT and in pts with brain metastases

OS data are immature

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Hurvitz SA et al SABCS 2023

Trastuzumab deruxtecan (T-DXd)

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DESTINY-Breast02: T-DXd vs TPC in ≥2L HER2+ MBC

Trastuzumab deruxtecan (T-DXd) was approved by the FDA on Dec 20, 2019 for treatment of HER2+ MBC after ≥2 prior anti-HER2 regimens based on data from DESTINY-Breast01

DESTINY-Breast02 was the confirmatory randomized trial with T-DXd in patients with refractory HER2+ MBC

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

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

R 2:1

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

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

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

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

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

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

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

Patient population

	T-DXd	TPC
Median priors for MBC #(range)	2 (0-10)	2 (1-8)
Prior pertuzumab	78.3%	77.2%
Prior endocrine therapy	40.4%	43.1%

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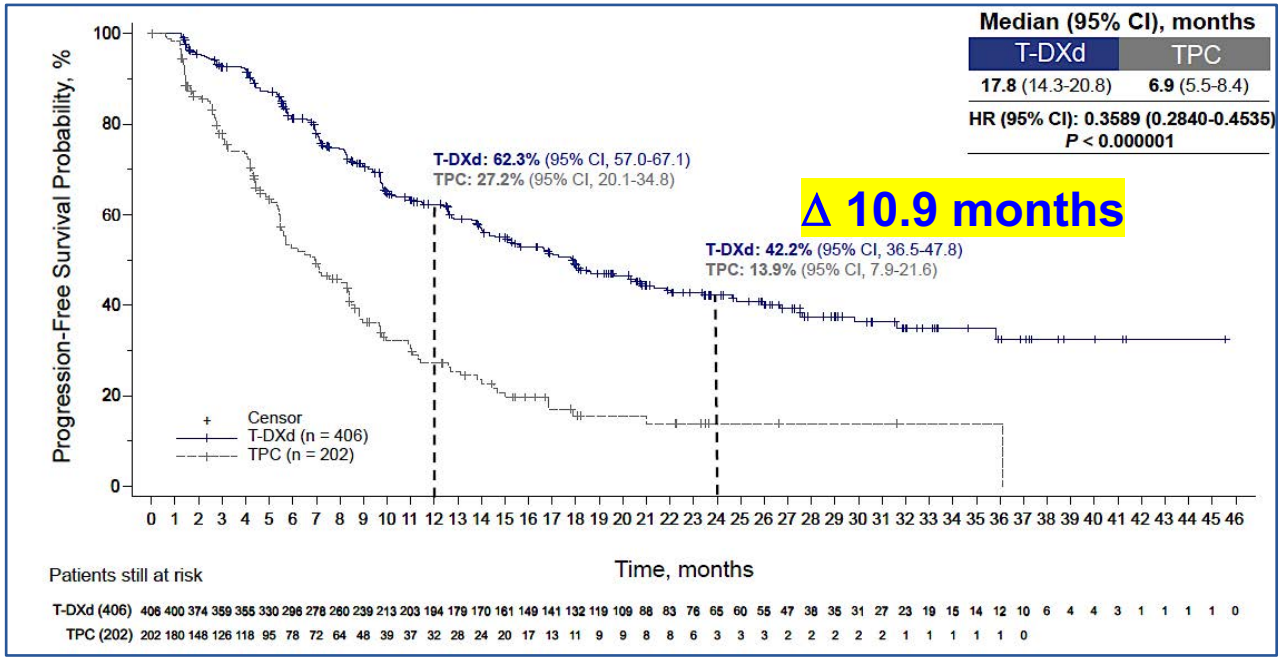
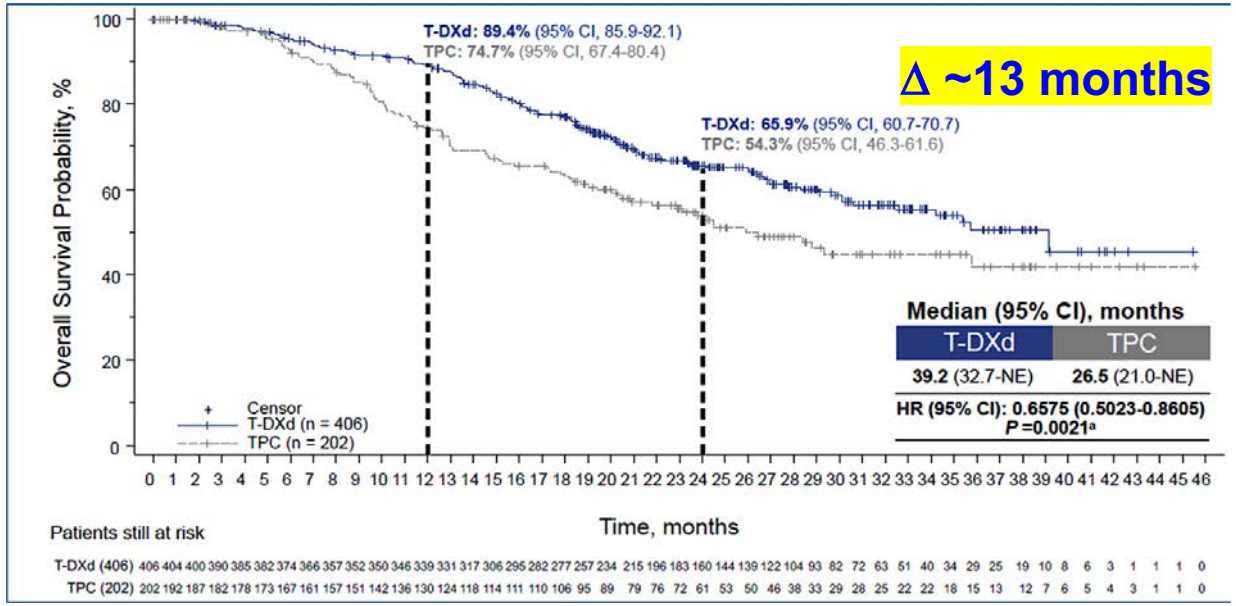
*Modi S et al. *New Engl J Med* 2020;382:610-621
Krop IA et al. SABCS 2022, GS2-01

DESTINY-Breast02: Efficacy endpoints

PFS – Primary endpoint



Overall survival



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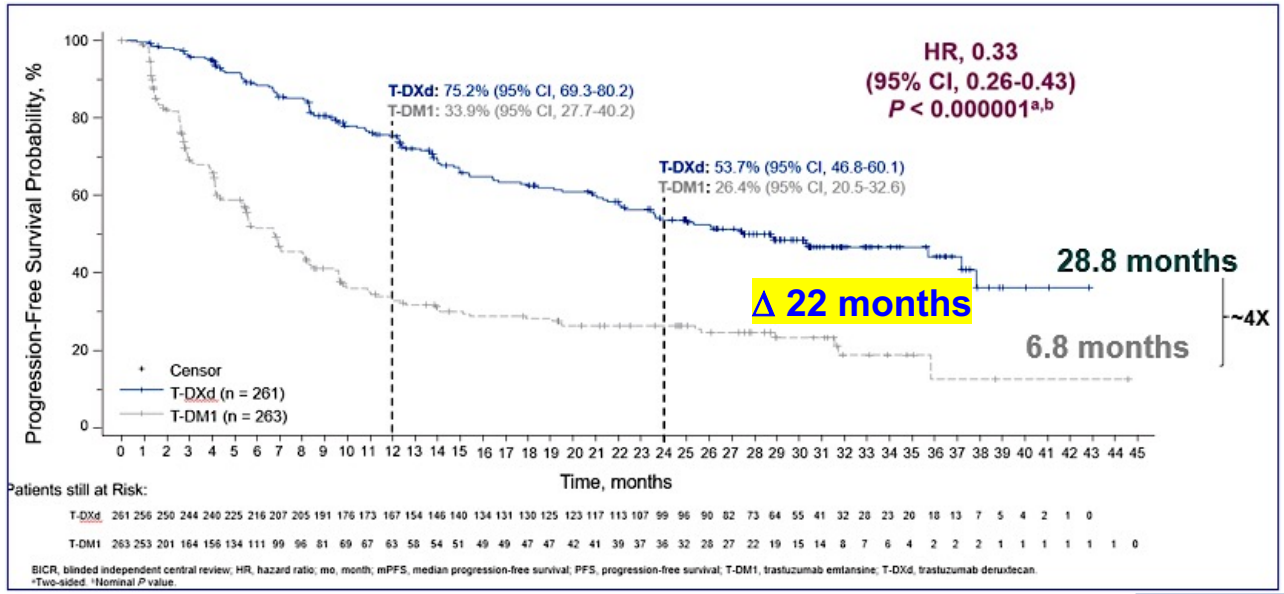
Andre F et al. *Lancet* 2023 May 27;401(10390):1773-85; Krop IA et al. SABCS 2022, GS2-01

DESTINY-Breast03: Phase 3 trial of T-DXd vs T-DM1 in 2L HER2+ MBC

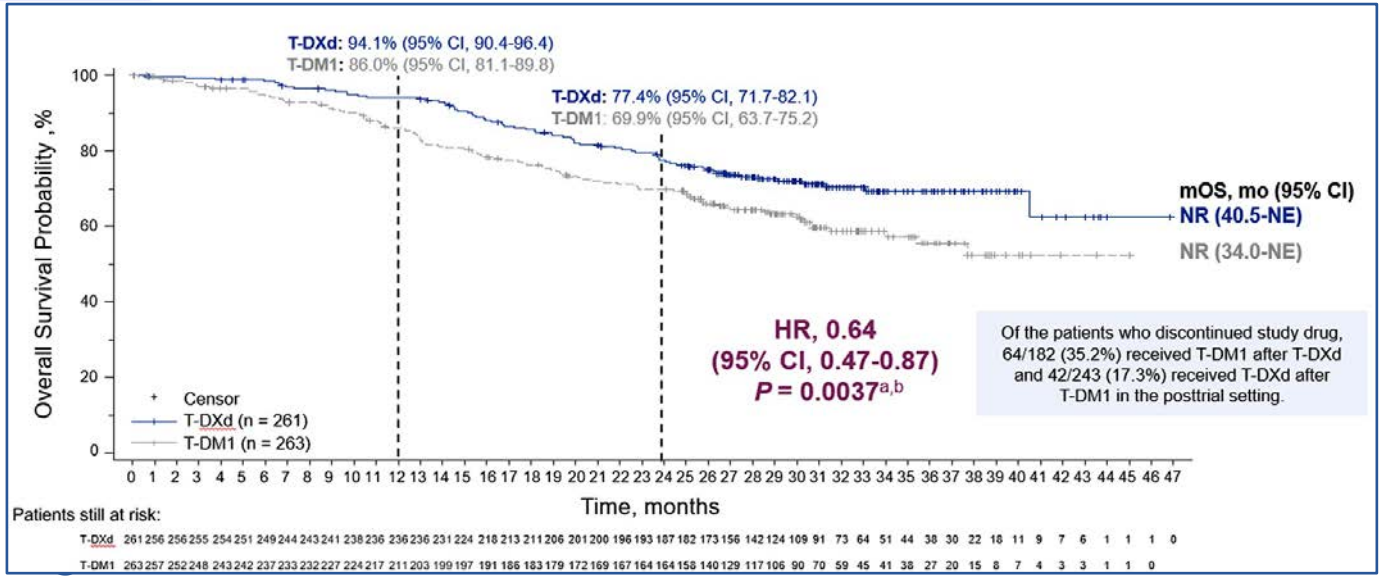
PFS – Primary endpoint



BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
aTwo-sided. bNominal *P* value.

Trastuzumab deruxtecan (T-DXd) was approved by the US FDA on May 6, 2022 for treatment of HER2+ MBC after 1 prior anti-HER2 regimen for MBC or relapse ≤6 months from (neo)adjuvant anti-HER2 treatment

Overall survival



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Cortes J et al. ESMO 2021; Hurvitz SA et al. *Lancet* 2023;401:105-17; Hurvitz SA et al. SABCS 2022, GS2-02

Drug-Related TEAEs[a] Reported in ≥20% of Patients in Either Treatment Arm

	T-DXd n = 257		T-DM1 n = 261	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	189 (73.5)	17 (6.6)	72 (27.6)	1 (0.4)
Fatigue	118 (45.9)	16 (6.2)	76 (29.1)	2 (0.8)
Vomiting	114 (44.4)	4 (1.6)	15 (5.7)	1 (0.4)
Neutropenia	111 (43.2)	51 (19.8)	30 (11.5)	8 (3.1)
Alopecia	97 (37.7)	1 (0.4)	7 (2.7)	0
Anemia	82 (31.9)	16 (6.2)	37 (14.2)	11 (4.2)
Leukopenia	79 (30.7)	17 (6.6)	21 (8.0)	2 (0.8)
Decreased appetite	68 (26.5)	3 (1.2)	34 (13.0)	0
Thrombocytopenia	65 (25.3)	19 (7.4)	137 (52.5)	65 (24.9)
Diarrhea	61 (23.7)	1 (0.4)	11 (4.2)	2 (0.8)
Constipation	60 (23.3)	0	25 (9.6)	0

- Most drug related AEs were hematologic or GI related
- Any grade nausea was the most common AE with T-DXd

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse events.
Selected TEAEs (and preferred terms included): anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased); neutropenia (neutrophil count decreased, neutropenia); thrombocytopenia (platelet count decreased, thrombocytopenia); fatigue (fatigue, asthenia, malaise).
[a]Based on nonclinical data, clinical data, epidemiology data, and reported data from drugs in a similar class (anti-HER2 therapies), selected TEAEs for T-DXd were reviewed for additional characterization.

HER2+ brain metastases (T-DXd)

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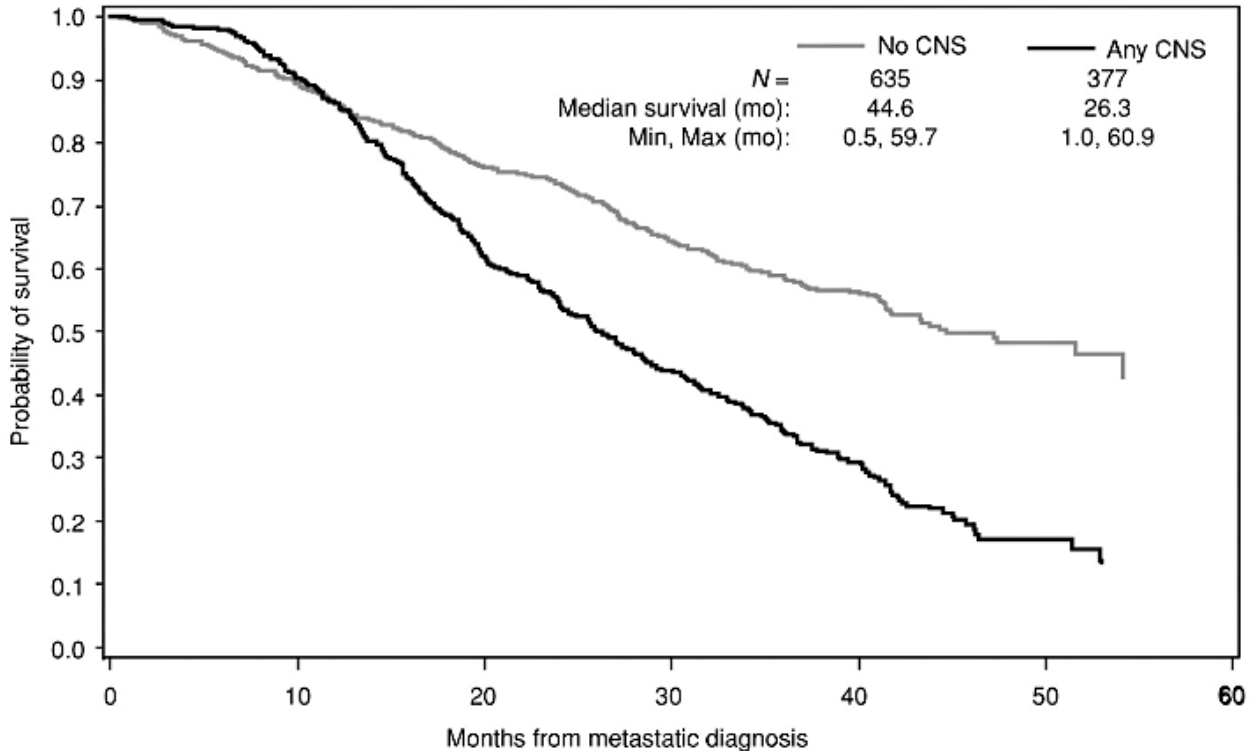
Incidence and survival of patients with HER2+ MBC and brain metastases

- The registHER study enrolled 1023 patients with HER2+ MBC
- 377 patients had CNS mets – 37%

Estimated survival for patients with and w/o CNS mets



Patients with CNS mets had poor survival outcomes

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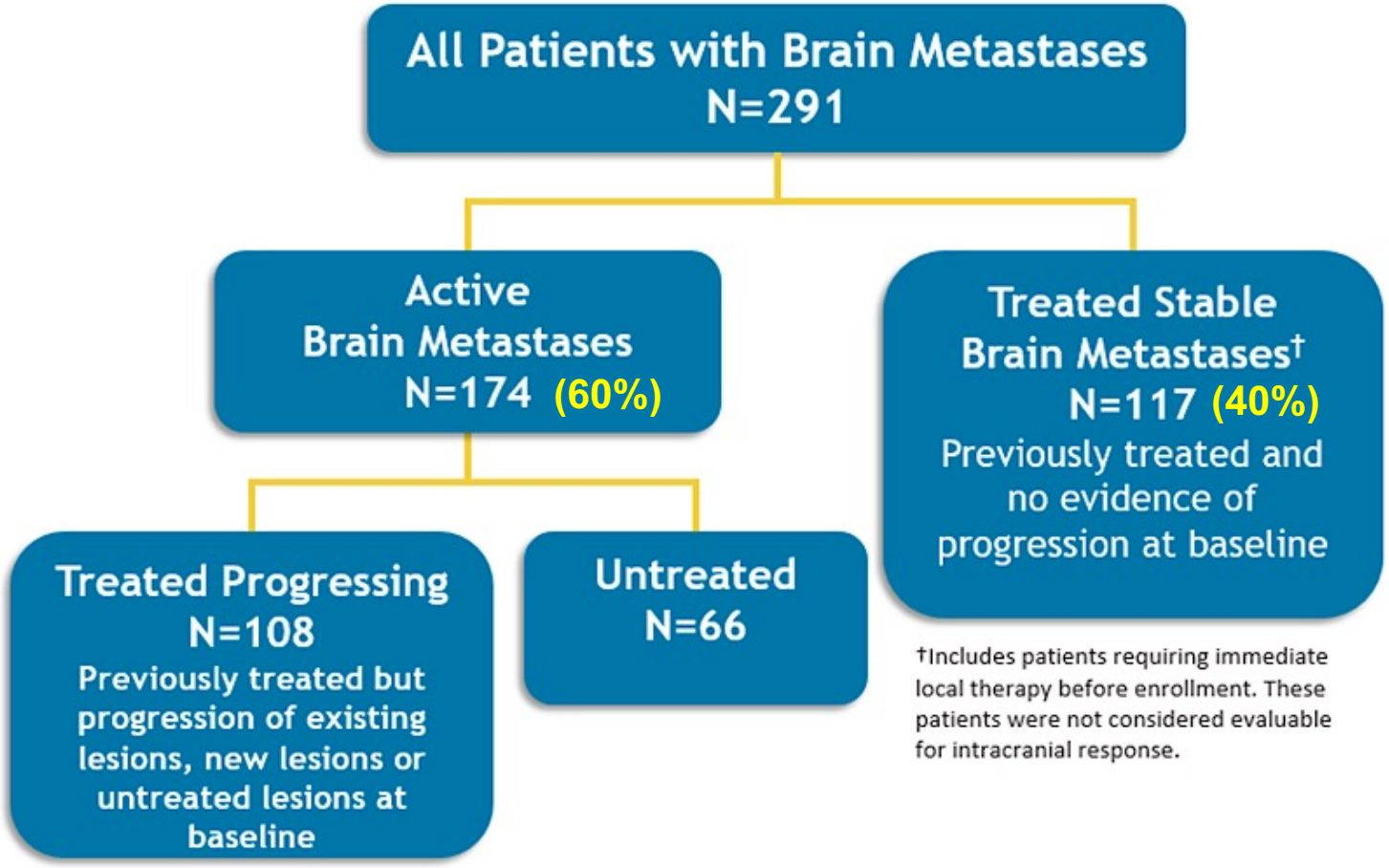
Brufsky A et al. Clin Cancer Res 2011

HER2CLIMB: CNS mets subset

48% of the patients enrolled on the trial had brain mets

- Brain MRI at baseline for all patients
- Brain MRI for brain metastases patients every 6 weeks in first 24 weeks, every 9 weeks thereafter
- Eligible brain metastases patients:
  - Not requiring immediate local therapy
  - Requiring local therapy during screening could be eligible after washout*

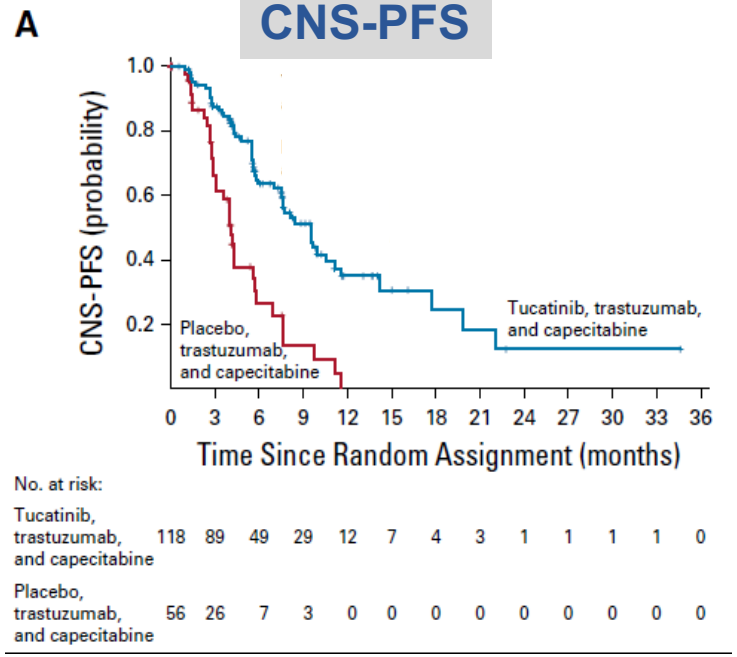


†Includes patients requiring immediate local therapy before enrollment. These patients were not considered evaluable for intracranial response.

*These patients were included in the Treated Stable group for analysis.

HER2CLIMB: CNS data in patients with brain mets

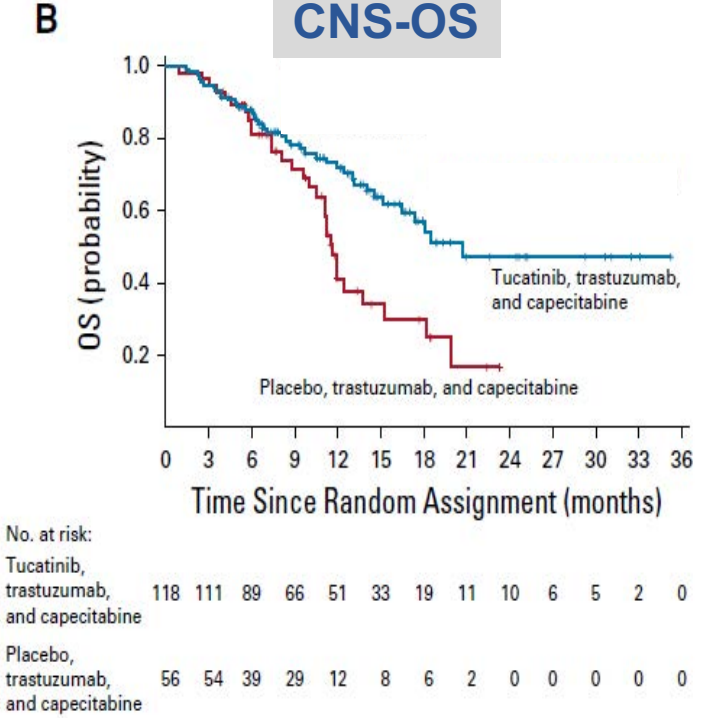
CNS-PFS



	Median PFS (months)
Tucatinib arm	9.5
Placebo arm	4.1
	HR 0.36 p <0.00001

Risk of progression or death in patients with active brain mets was reduced by 64%

CNS-OS



	Median OS (months)
Tucatinib arm	20.7
Placebo arm	11.6
	HR 0.49 p 0.004

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

In a separate analysis*, it was shown that the risk of developing new brain lesions or death was reduced by 48% in pts treated with tucatinib

Lin NU et al. JCO 2020
*Bachelot T et al ESMO 2020

T-DXd for tx of brain mets (HER2+/HER2-low MBC)

DEBBRAH Study

Trastuzumab-deruxtecan
(5.4 mg/kg) every 3 weeks until disease progression or unacceptable toxicity

A Multicenter, Open-Label, Single-Arm, Multicohort Phase II Clinical Trial of Trastuzumab Deruxtecan (DS-8201a) in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced Breast Cancer with Brain Metastases and/or Leptomeningeal Carcinomatosis

Step 1: Single cohort

HER2-positive MBC pts with stable CNS Disease

8 patients

Step 2: 4 Cohorts

- *Cohort 2: HER2[3+] or [+low] with untreated BM* — 10 pts
- *Cohort 3: HER2[3+] & BM progression after local treatment* — 7 pts
- *Cohort 4: HER2[+low] & BM progression after local treatment* — 7 pts
- *Cohort 5: HER2[3+] or [+low] & meningeal carcinomatosis.* — 7 pts

Primary Objective: 16 weeks CNS PFS

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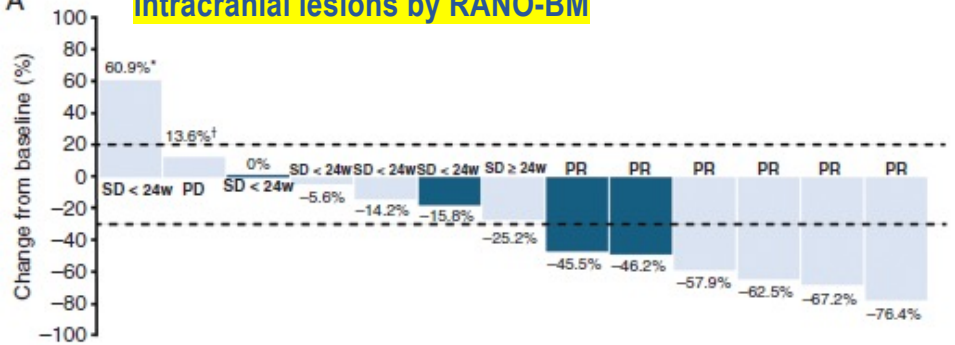
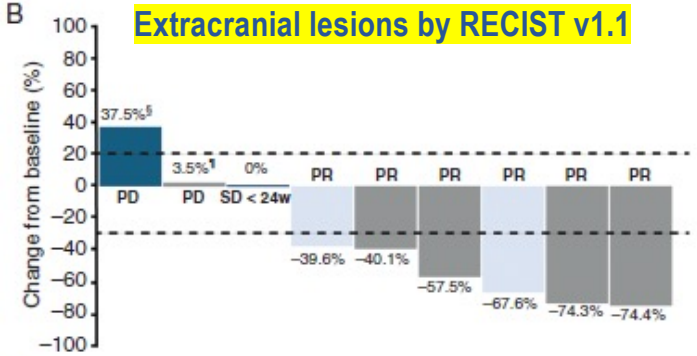
Braga S et al MedSIR project 2020

DEBBRAH: Efficacy in pts with brain mets

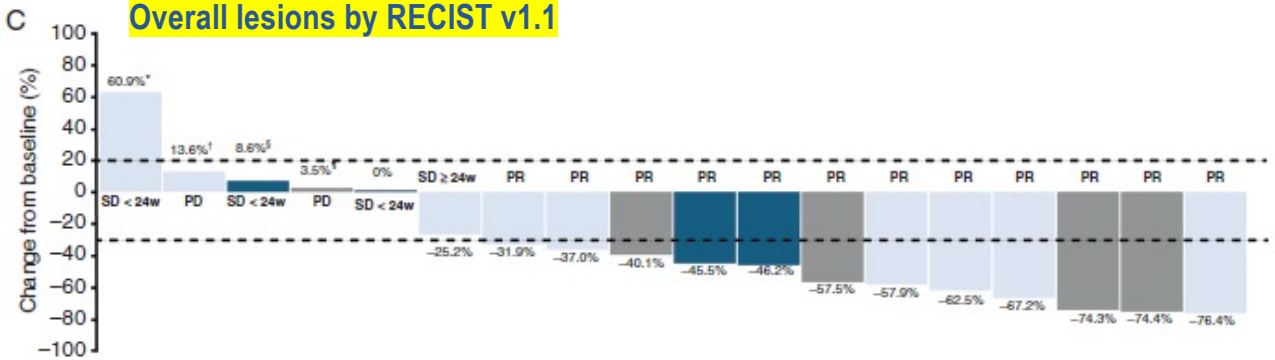
A **Intracranial lesions by RANO-BM**



B **Extracranial lesions by RECIST v1.1**



C **Overall lesions by RECIST v1.1**



		ORR	DCR
Cohort 1	HER2+ MBC stable BM	80%	80%
Cohort 2	HER2+/HER2-low untx BM	50%	100%
Cohort 3	HER2+ BM - PD after local tx	66.7%	89.9%

Progression free survival at 6 mo: 78.7%

Progression free survival at 9 mo: 61.4%

Encouraging intracranial & extracranial activity with T-DXd in pretreated HER2+ MBC with stable/active brain mets

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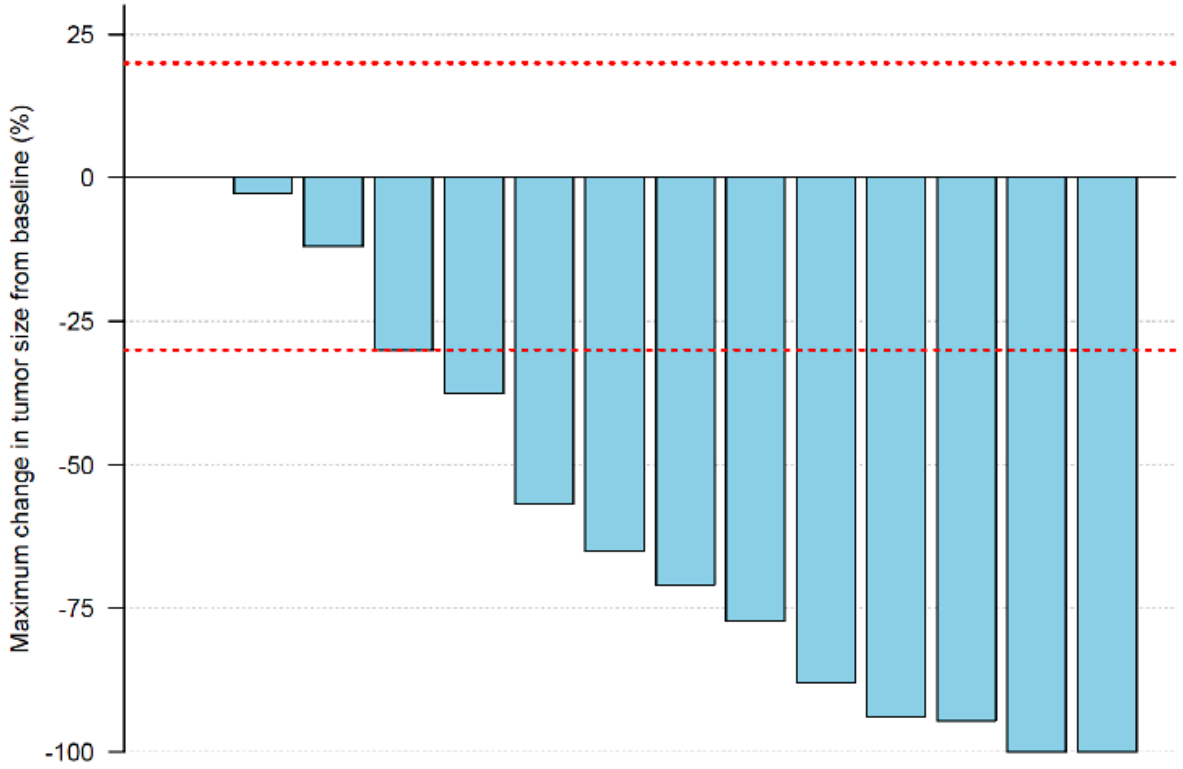
Perez-Garcia JM et al. Neuro-oncology 2023

TUXEDO-1: T-DXd for *active* HER2+ brain mets

Patient population: HER2+ MBC with active brain mets; previously treated with trastuzumab and pertuzumab; prior T-DM1 allowed

Primary endpoint: ORR by RANO-BM criteria

ORR in ITT (n=15): 73.3%

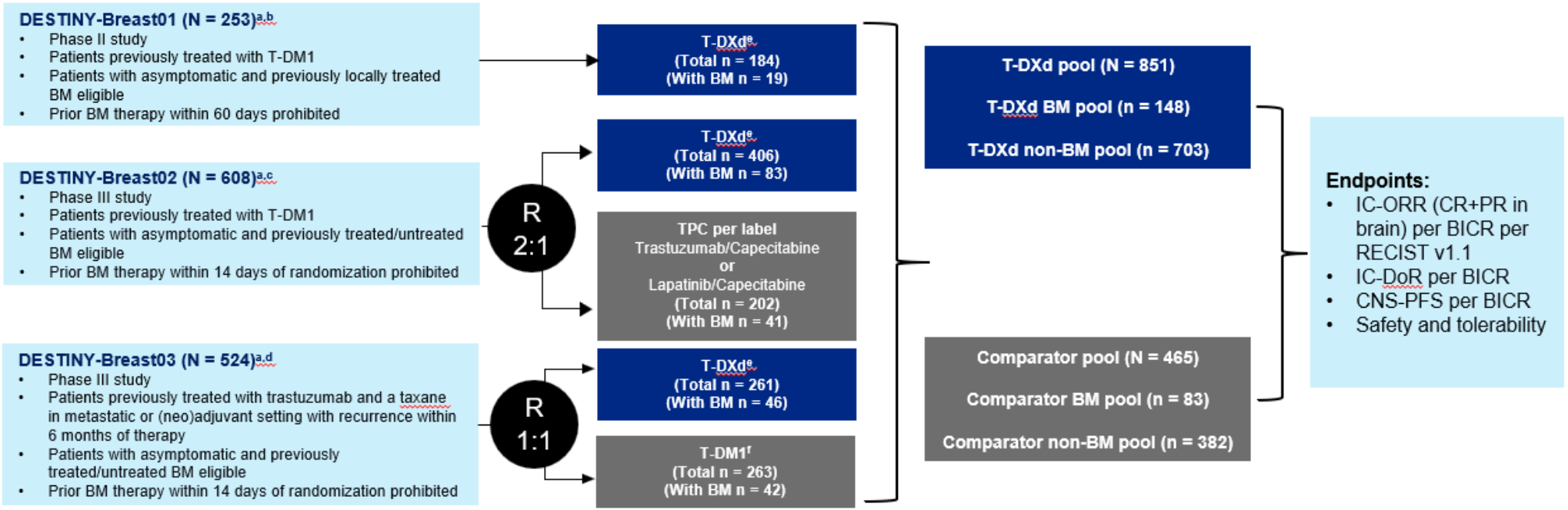


Secondary endpoints

- Clinical Benefit Rate (CR+PR+SD ≥6 months): 13/15 (86.7%) in the ITT population and 13/14 (92.9%) in the PP population
- Median OS not reached
- Extracranial Response Rate:
  - Pts. with extracranial metastases at baseline (*n*=13): PR 5/13 (27.8%)
  - Pts with measurable extracranial disease at baseline (*n*=8): PR 5/8 (62.5%)

Bartsch R et al. ESMO Breast 2022

Pooled analysis of T-DXd in pts with HER2+ brain mets from DESTINY-Breast01, -02 and -03



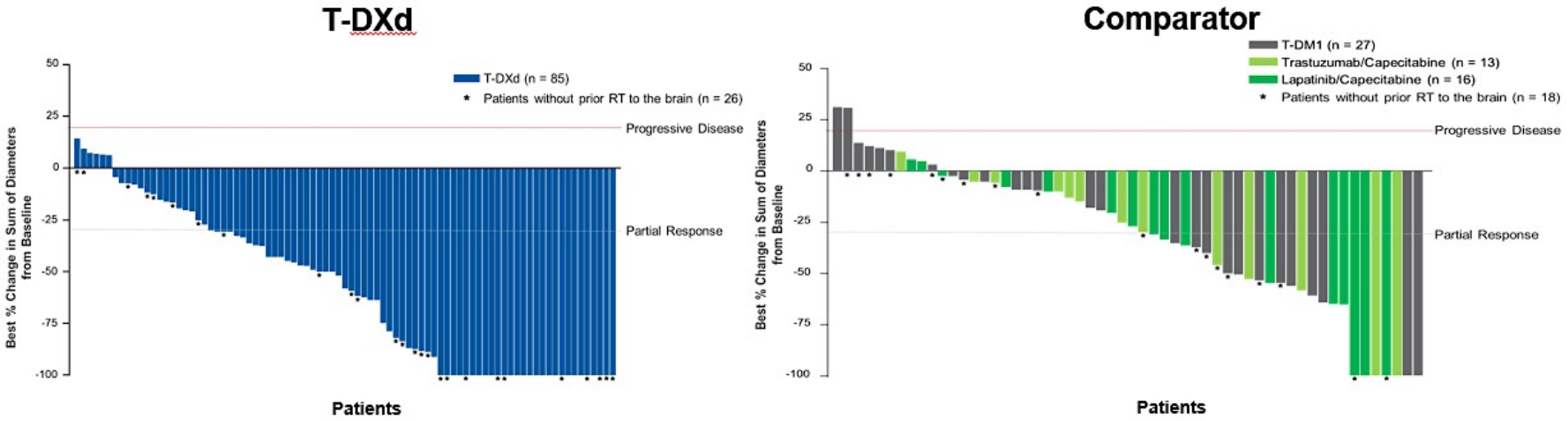
- **The BM and non-BM pools were determined by BICR at baseline among all patients based on mandatory brain CT/MRI screening**

Patient characteristics

- ✓ 94-96% of pts in the brain mets pool had visceral disease
- ✓ patients with BM were heavily pretreated with a median of 3 prior systemic regimens in the metastatic setting
- ✓ In both T-DXd and comparator pools, of the patients with BMs at baseline, ~70% had treated/stable BMs and ~30% had untreated/active BMs

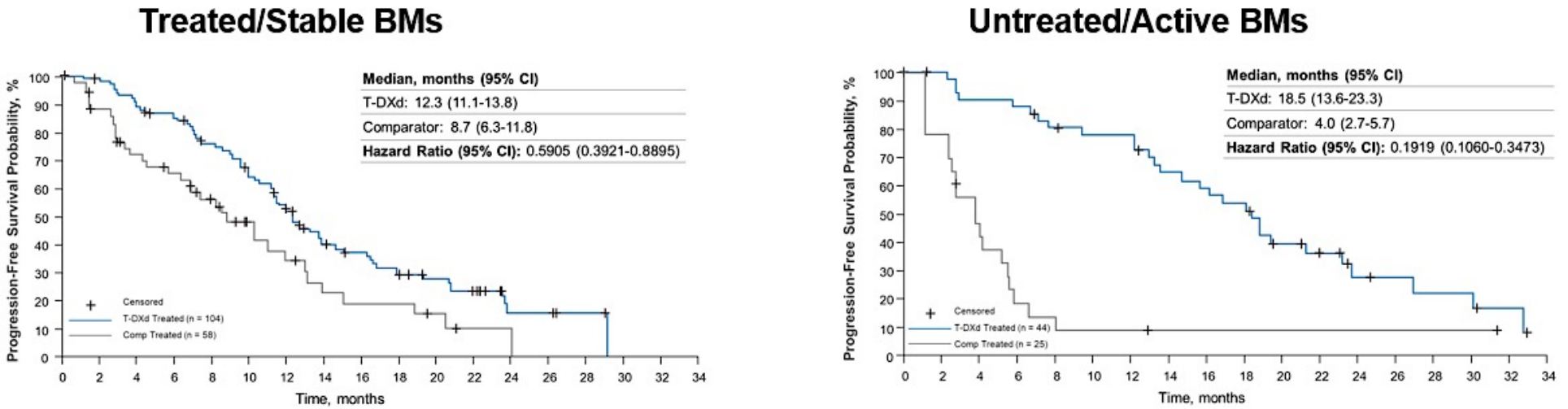
Efficacy of T-DXd vs comparator pool

Best Percentage Change from Baseline in Sum of Diameters of CNS Tumors



- **The shrinkage of BMs in response to T-DXd was more prominent, whereas in the comparator pool, BMs showed less of a response**

Exploratory CNS-PFS per BICR



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Hurvitz SA et al. ESMO 2023

Safety and summary

n, (%)	T-DXd Pool (N = 845)		Comparator Pool (N = 456)	
	BM Pool (n = 146)	Non-BM Pool (n = 699)	BM Pool (n = 83)	Non-BM Pool (n = 373)
Any drug-related TEAE	138 (94.5)	691 (98.9)	78 (94.0)	330 (88.5)
Drug-related TEAEs grade ≥3	63 (43.2)	324 (46.4)	30 (36.1)	140 (37.5)
Drug-related serious TEAEs	19 (13.0)	87 (12.4)	6 (7.2)	29 (7.8)
Drug-related TEAEs associated with discontinuation	21 (14.4)	121 (17.3)	6 (7.2)	21 (5.6)
Drug-related TEAEs associated with dose reduction	31 (21.2)	172 (24.6)	22 (26.5)	105 (28.2)
Drug-related TEAEs associated with an outcome of death	0	7 (1.0)	0	0

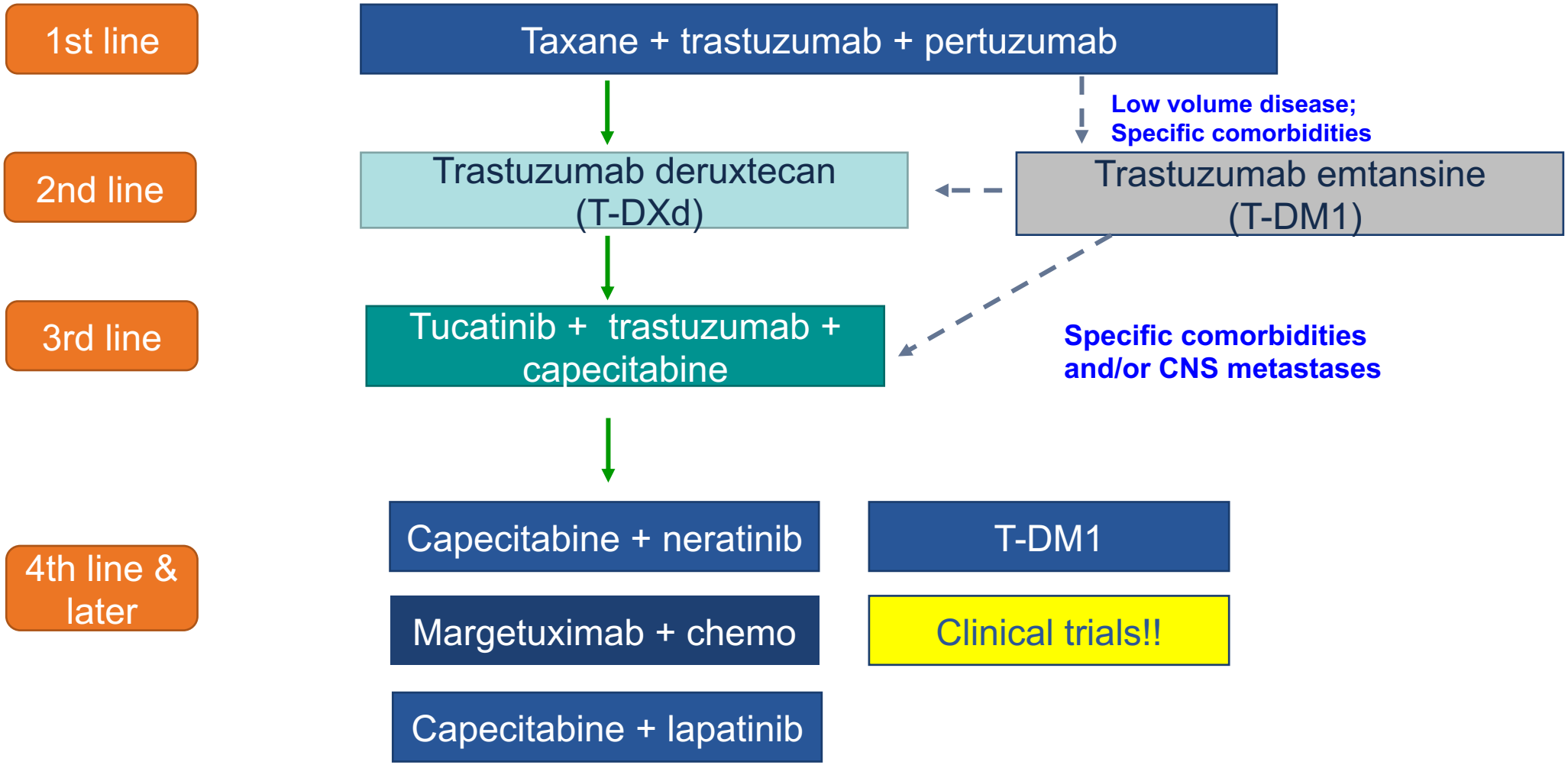
- T-DXd demonstrated robust intracranial (IC) responses in patients with treated/stable and active BMs vs comparator
  - Stable BMs:
    - IC-ORR: 45.2% vs 27.6%
  - Active BMs:
    - IC-ORR: 45.5% vs 12.0%

- Numerically longer median CNS-PFS was observed in patients with treated/stable and active BMs randomized to T-DXd vs comparator
  - Stable BMs: 12.3 vs 8.7 months
  - Active BMs: 18.5 vs 4.0 months

- The safety profile of T-DXd in patients with BMs was acceptable, generally manageable, and similar to the safety profile in the overall patient population

Hurvitz SA et al. ESMO 2023

Current treatment algorithm for HER2+ MBC



Agenda

Module 1: HER2-Positive Metastatic Breast Cancer — Dr Hamilton

Module 2: Metastatic Triple Negative Breast Cancer — Dr Rugo

Module 3: SABCS 2023 Review — Dr Kaklamani

UCSF Helen Diller Family Comprehensive Cancer Center

Metastatic Triple Negative BC (mTNBC)

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

Disclosures

Consulting Agreements	Daiichi Sankyo Inc, Eisai Inc, Napo Pharmaceuticals Inc, Viatris
Contracted Research	Ambrx, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, F Hoffmann-La Roche Ltd, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Merck, Novartis, OBI Pharma Inc, Pfizer Inc, Stemline Therapeutics Inc

Case Presentation

- 40 yo woman presents with a left breast mass
  - Imaging shows a 2cm mass with one enlarged axillary node
  - Biopsy of breast and node: grade 3 IDC, ER/PR negative, HER2 IHC 0
    - Ki67 in breast 70%
- Staging CT CAP
  - Multiple liver lesions
  - Biopsy + IDC, same histology and markers
  - Liver enzymes are normal; she feels well
- Breast biopsy sent for NGS and CPS testing; genetic testing performed
  - TP53 loss, FGFR2 mutation
  - CPS: 12
  - Germline testing: BRCA1 pathogenic mutation
- Started on nab-paclitaxel and pembrolizumab
  - After 8 cycles of 2 weeks on, one week off imaging shows resolution of the liver lesions
  - She continues pembrolizumab maintenance
    - Olaparib added after extensive discussion

KEYNOTE-355 Study Design (NCT02819518)

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression[a]
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

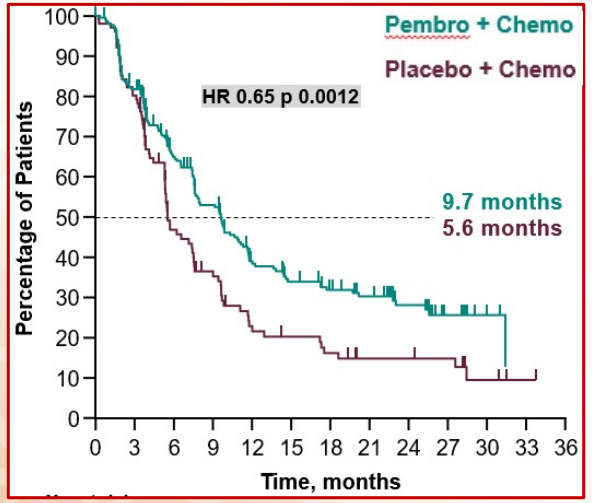
R 2:1

- Pembrolizumab[b] + Chemotherapy[c]
- Placebo[d] + Chemotherapy[c]

→ Progressive disease[e]/cessation of study therapy

Stratification Factors:
- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥1 or CPS <1)[f]
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

PFS: PD-L1 CPS ≥10

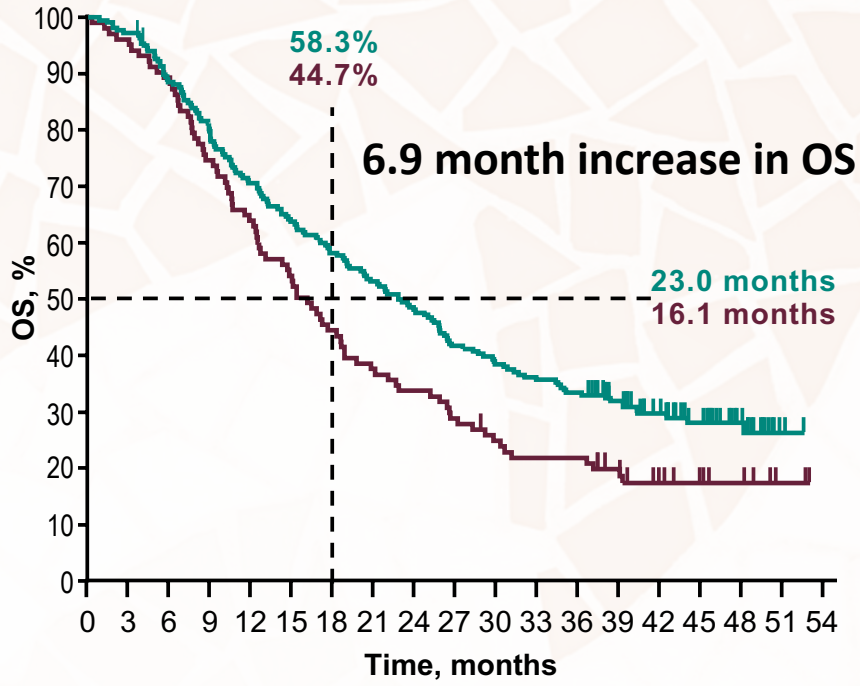


Prespecified *P* value boundary of 0.00411 met

38% of pts

OS: PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		



No. at risk

220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

Cortes et al, Lancet 2020; Rugo et al, ESMO 2021; Cortes et al, NEJM 2022

KEYNOTE-355: PFS and OS in Patients Treated With Pembrolizumab Plus Chemotherapy Who Had CR, PR, or SD ≥24 Weeks

Analysis Population	N	Median Pembro Treatment Duration (range), mo	Median Chemo Treatment Duration (range), mo	Median (95% CI) PFS[a], mo	Median (95% CI) OS[a], mo
All patients as treated					
Patients who discontinued chemo before pembro[b]	92	14.1 (4.2–29.5)	6.0 (2.6–25.3)	14.5 (11.9–20.2)	32.9 (27.4–38.3)
Overall	317	9.4 (0.0–32.2)	7.9 (0.3–45.8)	11.6 (9.9–12.3)	26.4 (23.5–29.7)
PD-L1 CPS ≥1					
Patients who discontinued chemo before pembro[b]	70	15.3 (4.2–29.5)	5.9 (2.6–24.7)	18.7 (14.4–NR)	34.5 (27.9–NR)
Overall	249	9.4 (0.0–32.2)	8.2 (1.4–45.8)	11.7 (9.9–13.9)	26.6 (23.5–30.5)
PD-L1 CPS ≥10					
Patients who discontinued chemo before pembro[b]	46	20.8 (4.9–29.5)	6.8 (3.5–24.7)	36.7 (17.3–NR)	NR (34.3–NR)
Overall	143	11.1 (0.0–32.2)	8.5 (3.0–45.8)	14.4 (11.3–17.7)	34.4 (26.7–42.5)

NR, not reached.
[a]Per Kaplan-Meier method.
[b]Received pembrolizumab plus chemotherapy, achieved a best overall response of CR, PR, or SD lasting ≥24 weeks, and received their last dose of chemotherapy >21 days before their last dose of pembrolizumab.
Data cutoff date: June 21, 2021.

Rugo et al, ESMO Breast 2023

KEYNOTE-355: PFS and OS in Patients Treated With Pembrolizumab Plus Chemotherapy Who had Immune-Mediated AEs[a]

Analysis Population	N	Median Pembro Treatment Duration (range), mo	Median Chemo Treatment Duration (range), mo	Median (95% CI) PFS[b], mo	Median (95% CI) OS[b], mo
All patients as treated					
Patients who had immune-mediated AEs	**149**	**8.8 (0.0–29.0)**	**7.2 (0.3–41.7)**	**9.7 (8.0–11.6)**	**23.9 (20.6–28.6)**
All	562	5.6 (0.0–32.2)	5.1 (0.0–48.8)	7.5 (6.3-7.7)	17.2 (15.3–19.0)
PD-L1 CPS ≥1					
Patients who had immune-mediated AEs	**109**	**8.8 (0.7–29.0)**	**7.3 (1.0–34.8)**	**9.8 (8.0–16.5)**	**26.3 (21.2–32.7)**
All	421	5.9 (0.0-32.2)	5.1 (0.0-48.8)	7.6 (6.6-8.0)	17.6 (15.5–19.5)
PD-L1 CPS ≥10					
Patients who had immune-mediated AEs	**64**	**10.4 (0.8–29.0)**	**8.4 (2.3–34.8)**	**11.8 (9.5–NR)**	**35.6 (26.3–NR)**
All	219	7.6 (0.0-32.2)	5.8 (0.0-45.8)	9.7 (7.6-11.3)	22.8 (18.8–26.2)

[a]Only treated patients in the part 2 pembrolizumab plus chemotherapy group were analyzed. [b]Per Kaplan-Meier method.
Data cutoff date: June 15, 2021.

Rugo et al, ESMO Breast 2023

OlympiAD

Patient Population
- HER2– MBC
  - ER+ and/or PR+ or
  - TNBC
- Deleterious or suspected deleterious g*BRCA*m
- ≤2 prior chemotherapy lines in metastatic setting
- Prior anthracycline and taxane
- HR+ patients who have progressed on ≥1 endocrine therapy, or not suitable
- If patients had received platinum
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

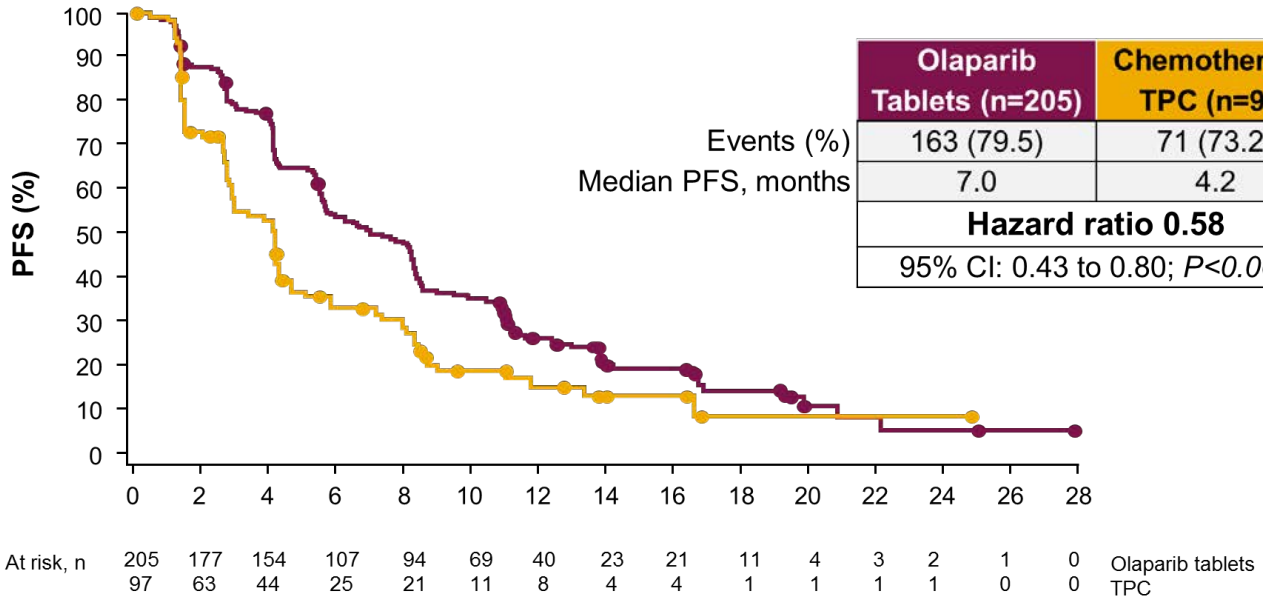
Randomized 2:1 (N=302)

Olaparib tablets 300 mg BID

Chemotherapy TPC
- Capecitabine
- Eribulin
- Vinorelbine

Treat until progression

Primary Endpoint	Secondary Endpoints
PFS (RECIST 1.1, BICR)	• OS • Time to second progression or death • ORR • Global HRQoL (EORTC-QLQ-C30) • Safety and tolerability



	Olaparib Tablets (n=205)	Chemotherapy TPC (n=97)
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
Hazard ratio 0.58		
95% CI: 0.43 to 0.80; *P<0.001*		

EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:
- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

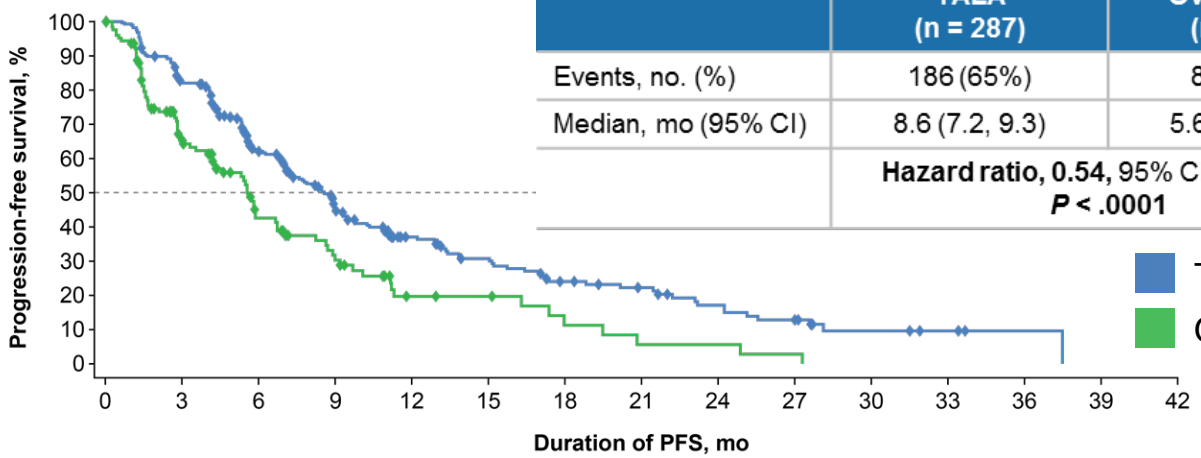
R 2:1

Talazoparib 1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

Physician's choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine

Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

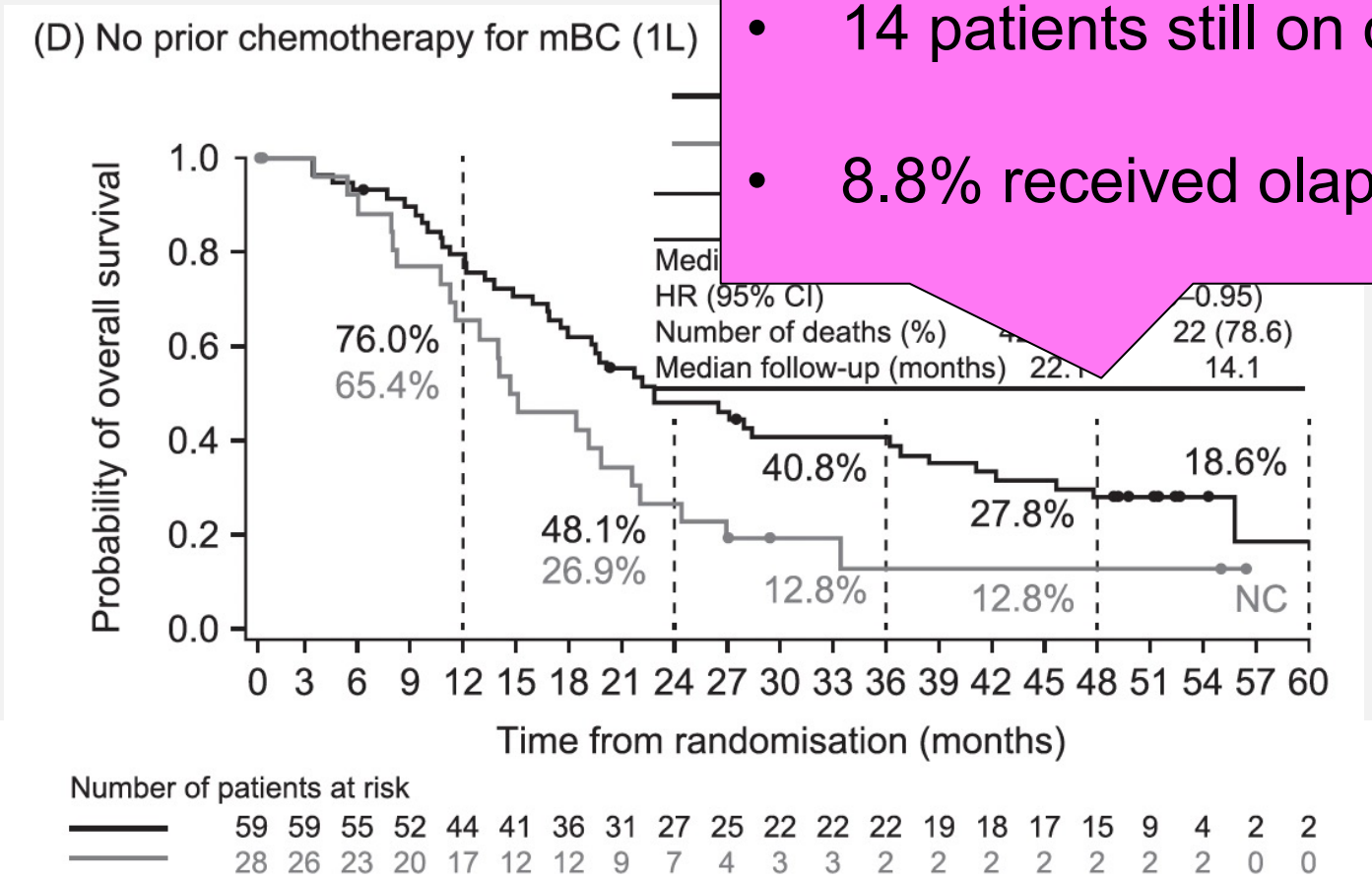
No. at risk (events/cumulative events)

TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

Litton JK et al. *N Engl J Med.* 2018;379(8):753-763.
Robson M et al. *N Engl J Med.* 2017;377(6):523-533.

OlympiAD Extended Follow-Up

- No statistically significant differences in survival curves in:
  - Overall population and > 1 lines of chemotherapy in metastatic setting
  - Tissue receptor subtype
  - Prior exposure to platinums
- No new safety signal – No AML/MDS



- 14 patients still on olaparib
- 8.8% received olaparib > 3 years

Robson M et al.
Eur J Cancer, 2023

Additional Data

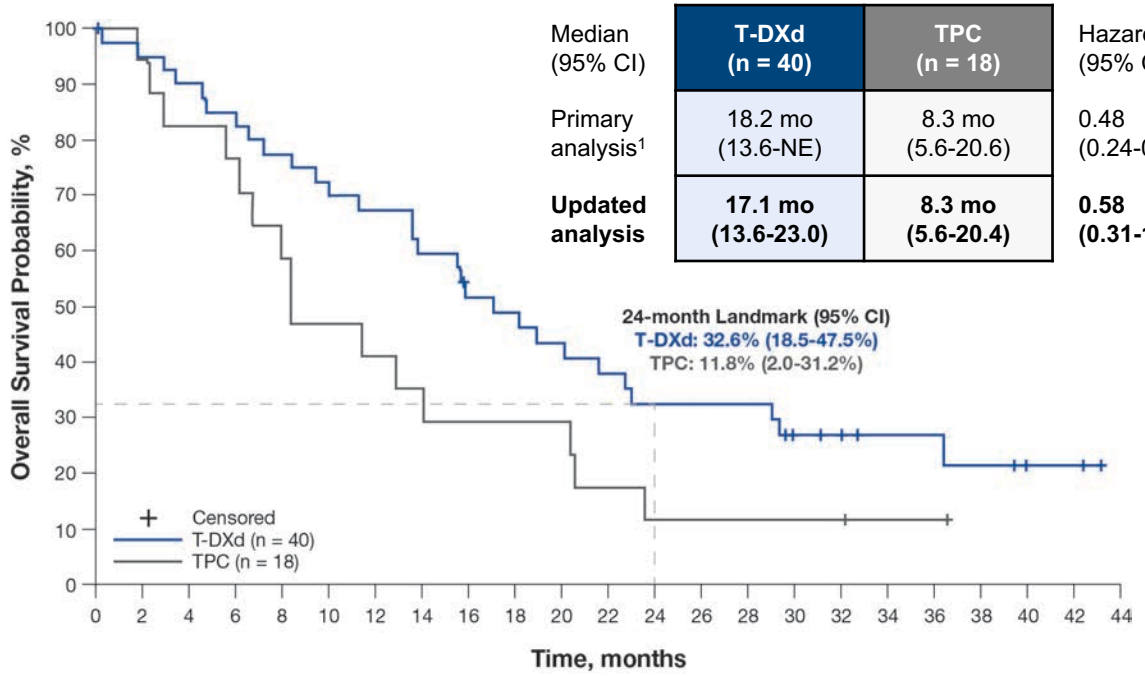
- Supports PARPi maintenance
  - BROCADE 3
    - Paclitaxel/carboplatin +/- Veliparib in gBRCA mutated MBC
      - 136/337 on PCV and 58/172 on PCP stopped chemo before PD and continued veliparib or placebo blinded monotherapy
    - mPFS from randomization was 25.7 mo on V vs 14.6 mo on P
  - KEYLYNK-009
    - Pembrolizumab/olaparib after induction pembrolizumab/chemo for locally advanced/metastatic TNBC
    - In the tBRCA mutant cohort, there was a trend for improved PFS and OS in patients continuing on olaparib/pembro maintenance vs pembro/chemo
- PARPi in pts with BRCA somatic mutations
    - Olaparib Expanded
      - 8/16/PR

Dieras et al, Lancet Oncol 2020; Han et al, Ann Oncol 2022; Rugo et al, SABCS 2023; Tan et al, JCO 2020

DESTINY-Breast04: Efficacy in the HR− Cohort (Exploratory Analyses)

Overall Survival

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**



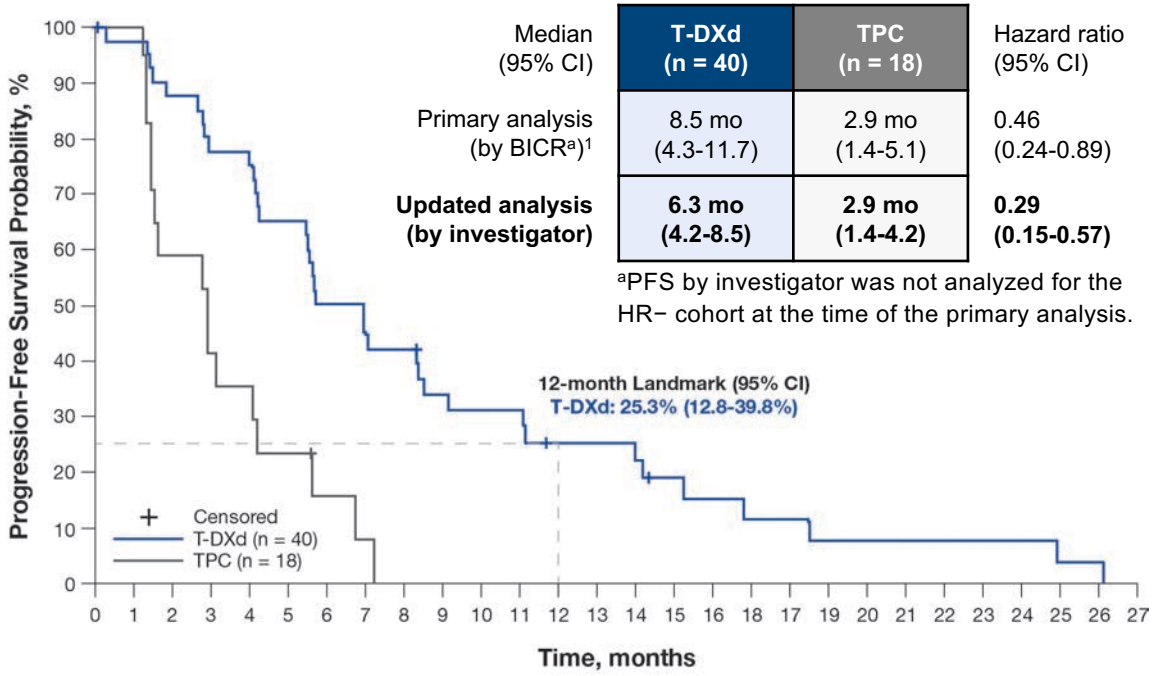
Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

Progression-Free Survival (by Investigator)

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.



Patients still at risk:

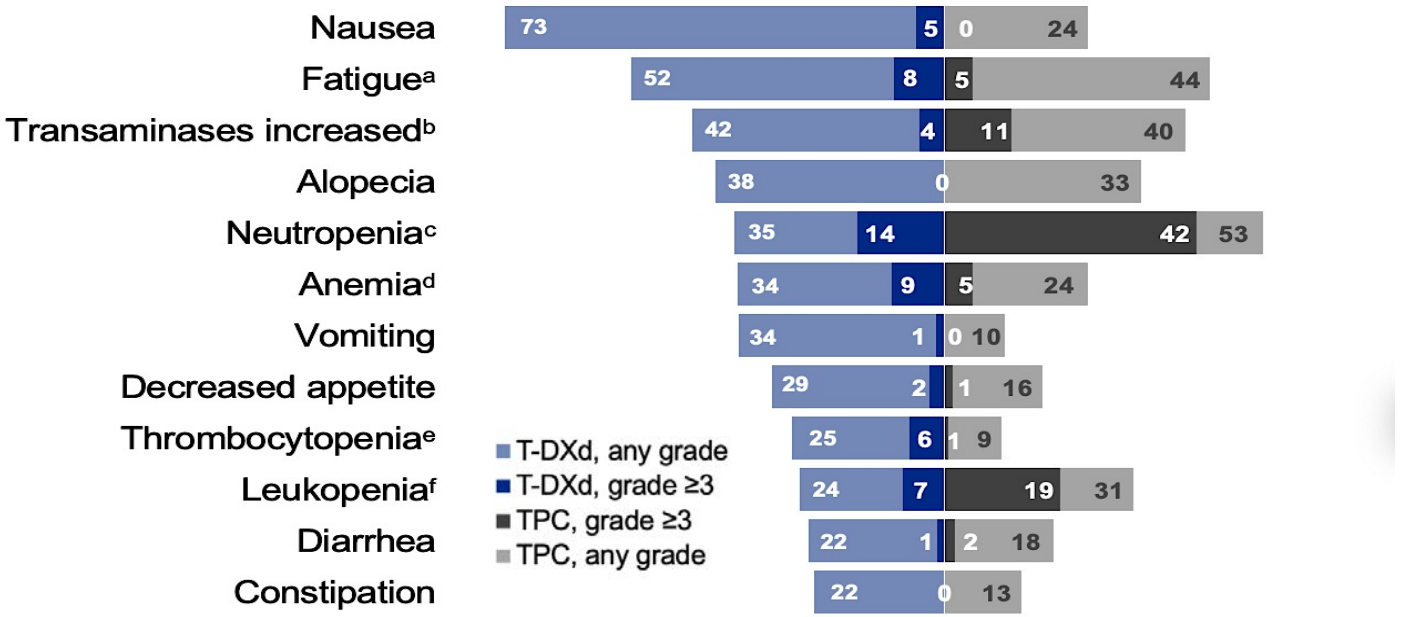
T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- Median FU now 32 months vs 18.4 at primary analysis
- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

BICR, blinded independent central review; HR, hormone receptor; mo, month; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi et al, NEJM 2022; ESMO 2023

DESTINY-Breast04 Adverse Events: Overall Population

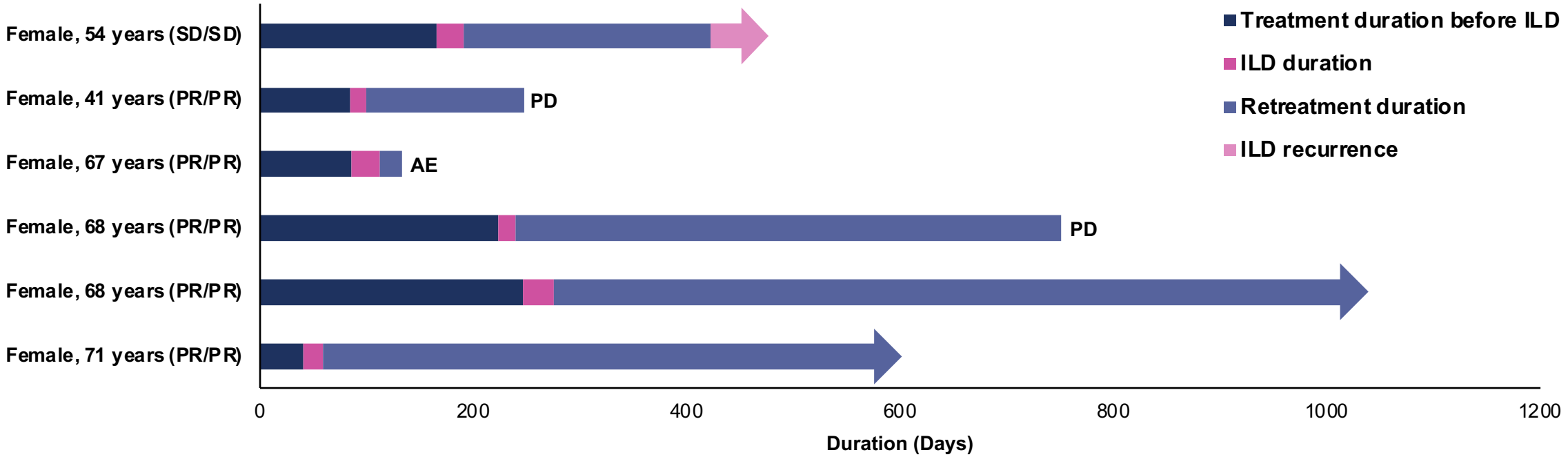


Percent of Patients Experiencing Drug-Related TEAE

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure, n (%)						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

Modi et al, NEJM 2022; ESMO 2023

Re-Treatment with T-DXd in Patients After Occurrence of Grade 1 ILD



- 6 patients with grade 1 ILD (as assessed by investigator) were re-treated after resolution; 1 of these patients had a second ILD event that was adjudicated as grade 2 by the adjudication committee at re-occurrence
  - At DCO, 1 patient discontinued due to an AE; 2 patients discontinued due to PD; 3 patients remained on T-DXd

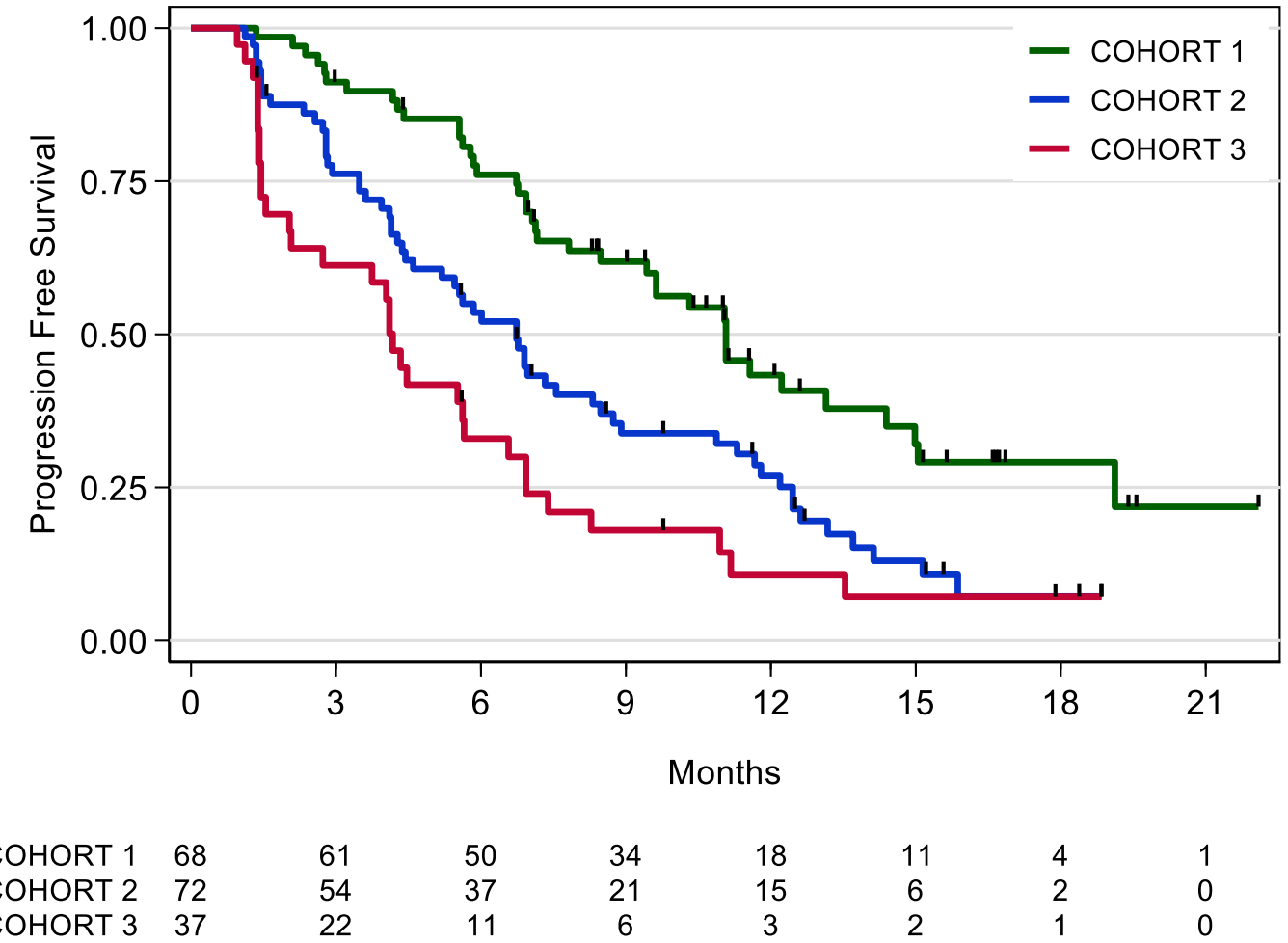
AE, adverse event; DCO, data cutoff; ILD, interstitial lung disease; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

Rugo et al, ESMO Breast 2023

DAISY: PFS with T-DXd according to HER2 expression

Data cutoff: Oct 19, 2021	Cohort 1 HER2 IHC 3+ or IHC 2+/ISH+ (n=68)	Cohort 2 HER2 IHC 2+/ISH- or IHC 1+ (n=72)	Cohort 3 HER2 IHC 0 (n=37)
Median PFS (mths) (95% CI)	11.1 (8.5–14.4)	6.7 (4.4-8.3)	4.2 (2-5.7)
HR (95% CI)	0.53 (0.34-0.84)	1.00	1.96 (1.21-3.15)
***p*-value**	***p* <0.0001**		

	Median PFS	Median OS
(HR+)	4.5 months	11.6 months
(HR-)	2.1 months	10.3 months



THE PFS IS DIFFERENT BETWEEN THE THREE COHORTS *p* <0.0001

Median follow up: 15.6 months

Mosele et al, Nature Medicine 2023

NCT04132960

Testing Trastuzumab Deruxtecan in HER2 'Ultralow' DESTINY-Breast06

Key differences with DB-04:

- Includes IHC0 (ultralow, n=150))
- Larger (n=850)
- Restricted to HR+ disease
- Chemo-naïve patients

Status: Completed accrual

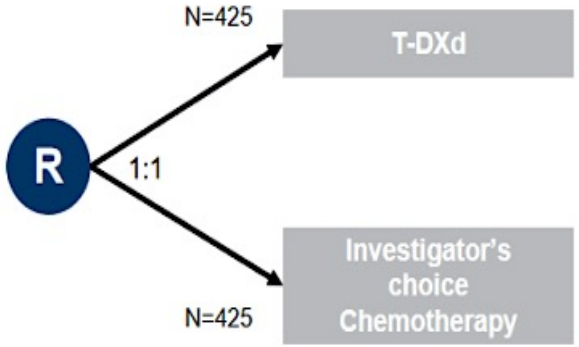
POPULATION

- Advanced/metastatic breast cancer after progression on 2 prior ETs
- HR+
- HER2 IHC 0+ or 1+ or 2+ (determined based on central IHC assessment of archival tissue collected at time of diagnosis of first metastatic disease or later)

Stratification factors:

- Prior CDK4/6 inhibitor
- HER2 IHC 2+ v. 1+ v. 0+
- Prior taxane in non-metastatic setting

TREATMENT



- Chemotherapy options: capecitabine, paclitaxel, nab-paclitaxel
- Treatment continues until progressive disease or toxicity
- HER2 IHC 0+ defined by any IHC staining up to 10% of tumor cells
- Futility analysis in HER2 IHC 0+ cohort will be done

ENDPOINTS

Primary:

- PFS (BICR) in HER2 IHC 1+/2+ population

Key Secondary:

- OS in HER2 IHC 1+/2+ population
- PFS in ITT population
- OS in ITT population

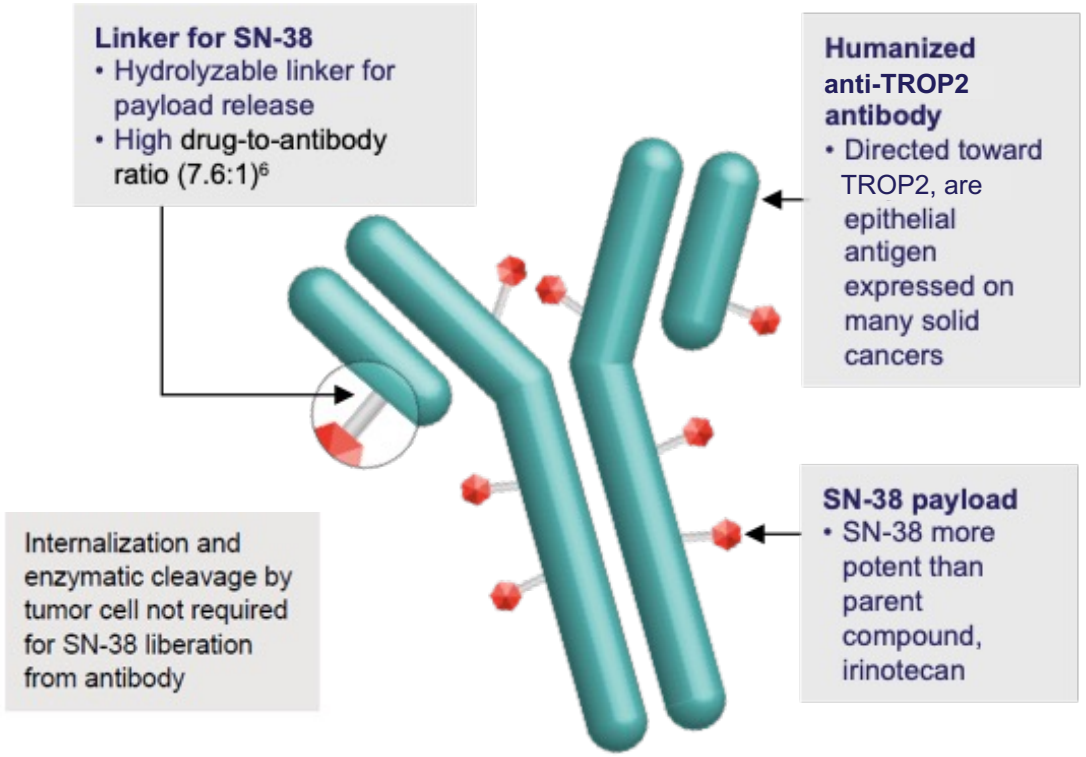
Secondary:

- PFS (investigator assessed) in HER2 IHC 1+/2+
- ORR and DOR of HER2 IHC 1+/2+ and ITT populations
- Safety and tolerability
- Symptoms, functioning and HRQoL

Exploratory:

- PRO
- Pharmacodynamic biomarkers

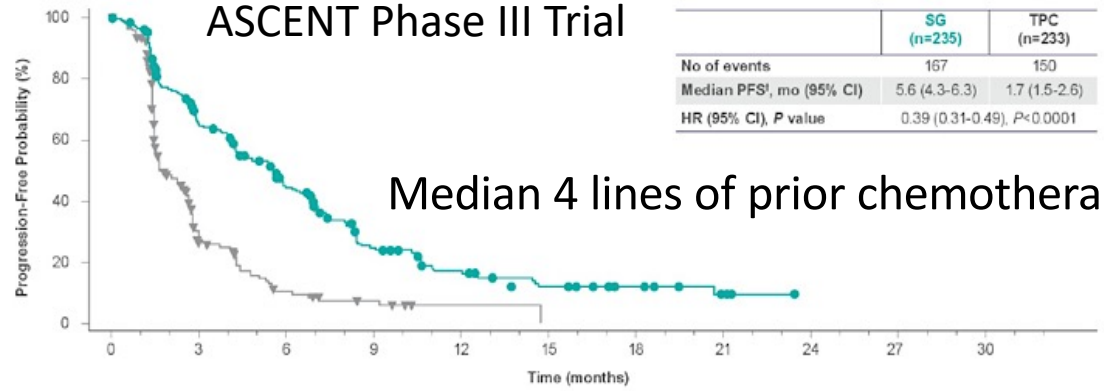
Sacituzumab Govitecan (SG): First-in-Class TROP2–Directed ADC



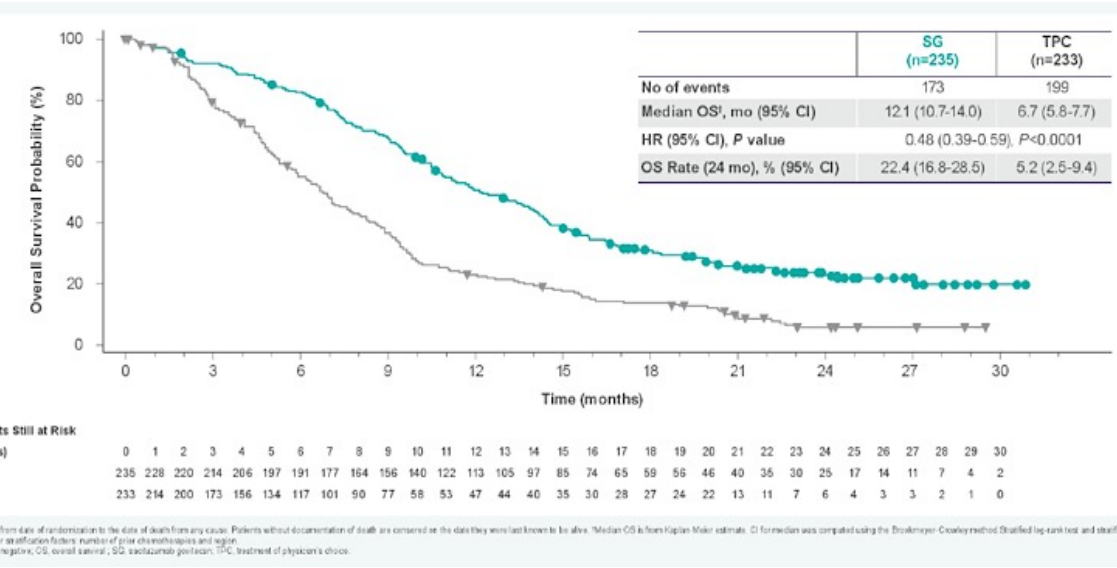
- TROP2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- **Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), FN (6% vs 2%)**
  - G-CSF: 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
  - No severe CV toxicity, no grade >2 neuropathy or grade >3 ILD with SG

ASCENT Phase III Trial

Median 4 lines of prior chemotherapy



	SG (n=235)	TPC (n=233)
No of events	167	150
Median PFS[1], mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.39 (0.31-0.49), *P*<0.0001	



	SG (n=235)	TPC (n=233)
No of events	173	199
Median OS[1], mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	0.48 (0.39-0.59), *P*<0.0001	
OS Rate (24 mo), % (95% CI)	22.4 (16.8-28.5)	5.2 (2.5-9.4)

Bardia et al. *NEJM*, 2021.

ASCENT and TROPiCS-02: Safety Outcomes by UGT1A1 Status

UGT1A1

- ✓ Variants affect enzymatic function, causing reduced metabolic capacity
- ✓ Over 50% of individuals may harbor an UGT1A1 polymorphism, dependent on genetic ancestry

	ASCENT		TROPiCS-02	
SG patients (n=250)	UGT1A1 Status n(%)	Dose Intensity (%)	UGT1A1 Status n(%)	Dose Intensity (%)
*1/*1 (wt)	113 (44)	99.8	104 (38)	99
*1/*28	96 (37)	99.5	119 (44)	98
*28/*28	34 (13)	99.8	25 (9)	94

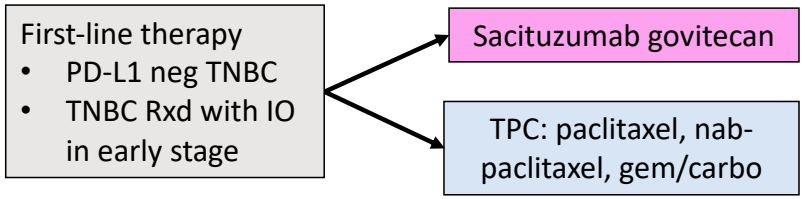
Grade ≥3 TEAEs Overall (%)	SG (n=268)
Neutropenia	52
Diarrhea	10
Anemia	8
Febrile neutropenia	6

	ASCENT			TROPiCS-02		
Grade ≥3 TEAEs By UGT1A1 Status (%)	*1/*1 (wt)	*1/*28	*28/*28	*1/*1 (wt)	*1/*28	*28/*28
Neutropenia	53	47	59	45	57	64
Diarrhea	10	9	15	6	13	24
Anemia	4	6	15	6	8	8
Febrile neutropenia	3	5	18	6	7	4
Growth factor for neutropenia (initiated on/after first dose) overall 54%						
				33	49	11

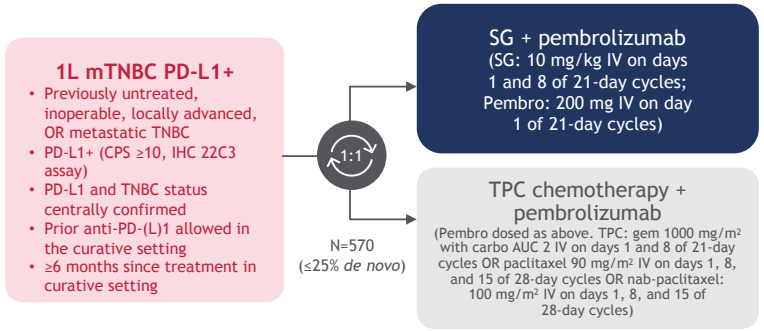
ASCENT: Treatment discontinuation due to TRAEs more common in *28 homozygous genotype

Nelson, RS, et al. *Cancers.* 2021;13:1566.
Rugo, HS, et al. *npj Breast Cancer.* 2022;8:98.
Marmé, F, et al. *Annals of Oncol.* 2023;8(1suppl_4):101223-101223.
Rugo, et al. Lancet 2023.

ASCENT-03 (NCT05382299): PD-L1 negative
N=540

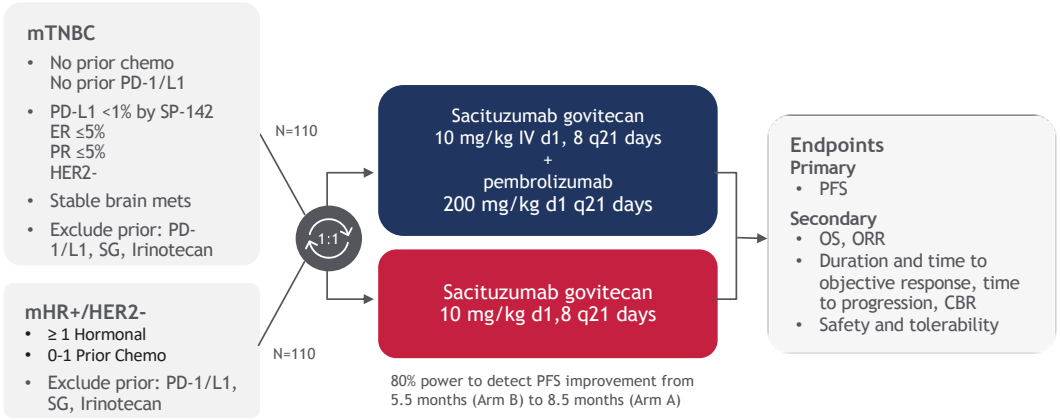


ASCENT-04 (NCT05382286): PD-L1 positive
N=570

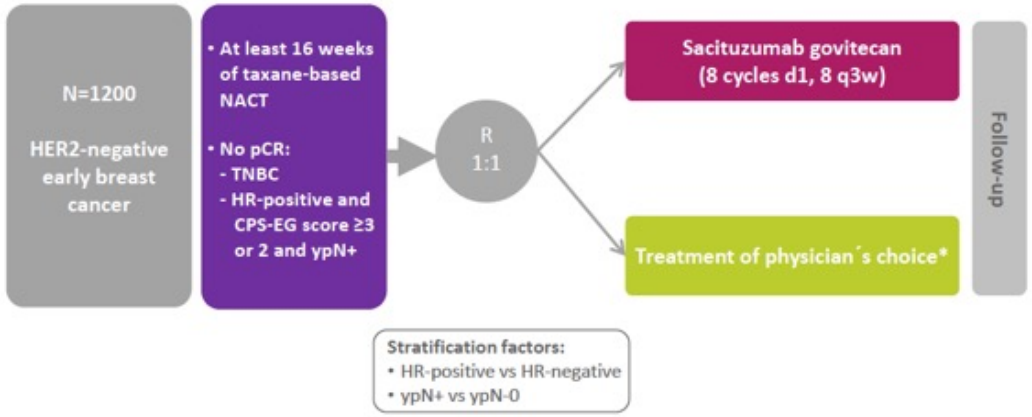


Saci-IO TNBC and HR+: Sacituzumab govitecan +/− pembrolizumab in 1L PD-L1− mTNBC and HR+

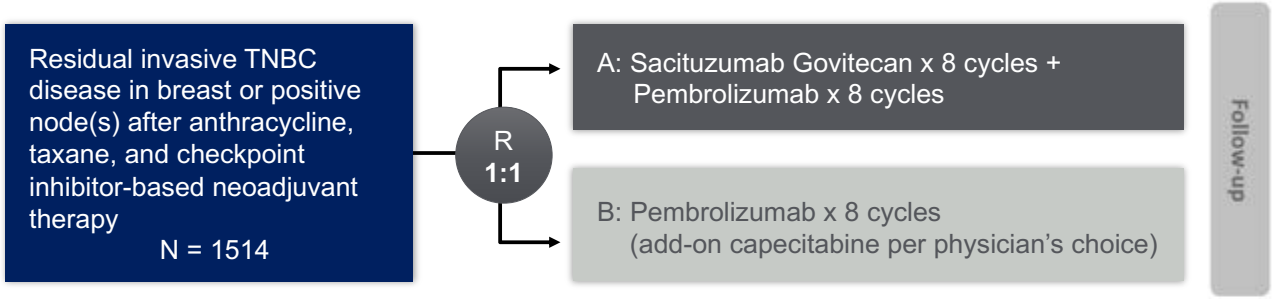
Garrido-Castro/Tolaney



GBG: SASCIA Post-Neoadjuvant Trial
NCT04595565



Phase III Trial: OptimICE-RD/ASCENT-05
Residual disease in TNBC



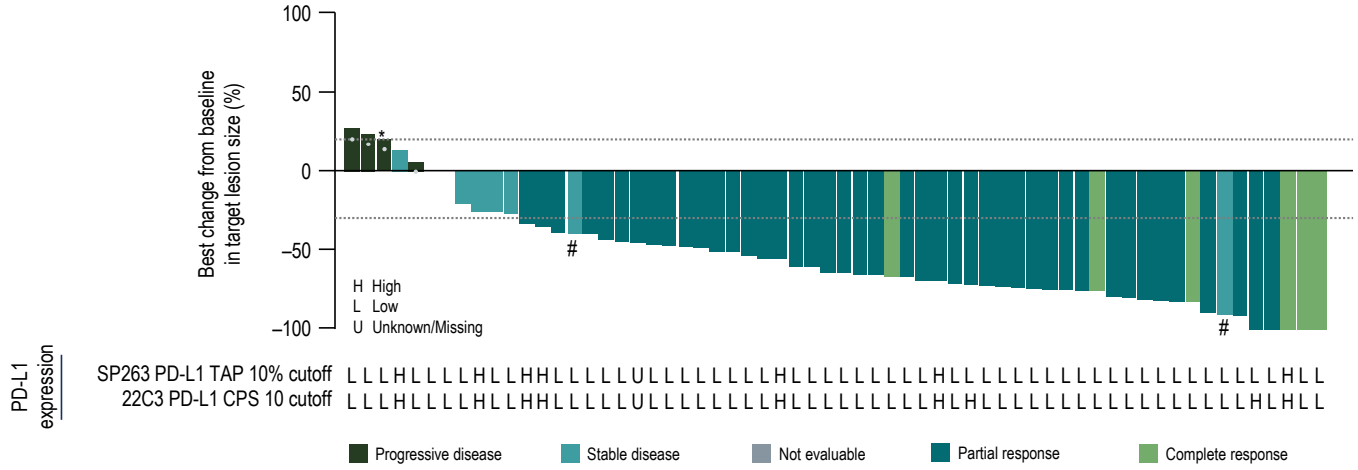
PI: Sara Tolaney; Alliance Foundation Trial

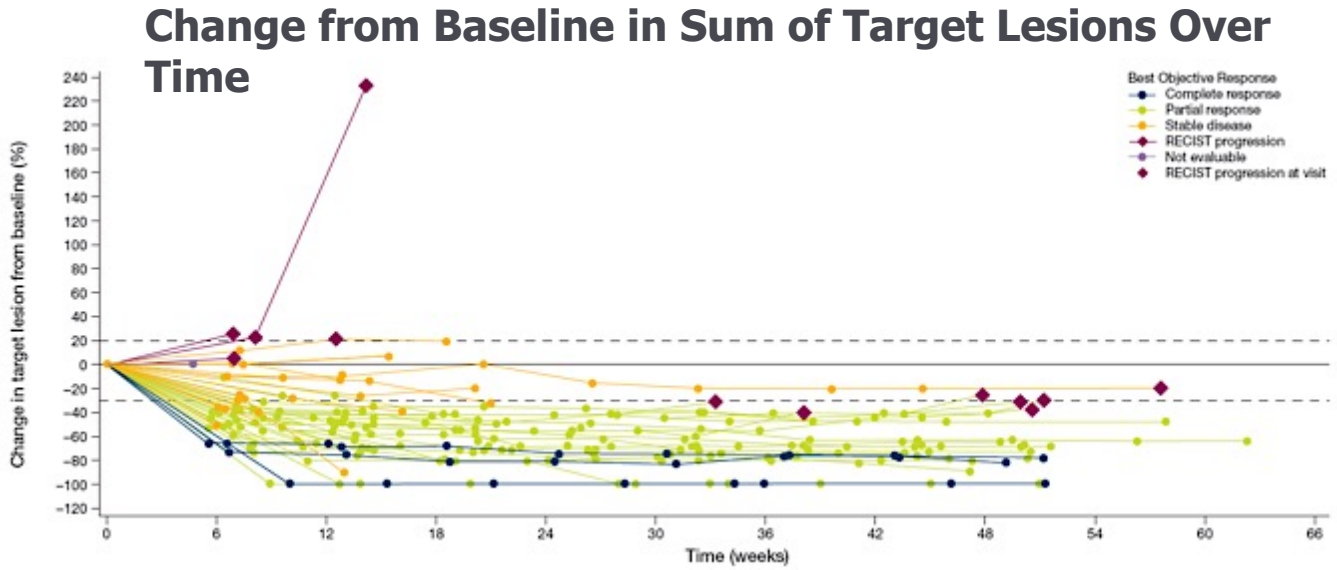
BEGONIA Trial: Dato-DXd + Durvalumab

- 1st line TNBC
  - N=62;
  - Median FU 11.7 mo
  - Durable responses
    - Median FU 13.8 mo, DOR 15.5 mo
  - Adverse events
    - 57% grade 3/4 AEs; 16% d/c due to AEs
    - Stomatitis (65%), rash (32%), dry eye (21%), hypothyroidism (14.5%), keratitis (14.5%)
      - 11% Gr3/4 stomatitis
    - **ILD/pneumonitis in 5% (3)**
      - **All grade 1-2**

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





Schmid et al, ESMO 2023; SABCS 2022; PD11-09

TROPION-Breast02 (n=625)

NCT05374512

Key eligibility criteria:

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1 / PD-L1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:

- Geographic location
- DFI (*de novo* vs DFI ≤12 months vs DFI >12 months)

Dual primary endpoint:
PFS (BICR) and OS

Secondary endpoints:
PFS (inv), ORR, DoR, safety

1:1

- Dato-DxD
- Investigator's choice of chemotherapy

- 1st line therapy for TNBC
- PD-L1 negative

TROPION-Breast05 (n=625)

NCT06103864

Key Eligibility Criteria

- Previously untreated locally recurrent inoperable or metastatic TNBC
- ECOG PS 0 or 1
- Measurable disease as defined by RECIST 1.1
- Adequate haematologic and end-organ function
- PD-L1 centrally confirmed
- PD-L1 positive by 22C3 assay CPS ≥ 10 IHC
- No systemic steroids
- No active autoimmune diseases
- No active brain metastases
- DFI ≥ 6 months since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed

Stratification Factors

- DFI history (de novo versus prior DFI 6 to 12 months[a] versus prior DFI > 12 months)
- Geographic location (US/Canada/Europe versus Dato-DXd Monotherapy Enrolling Countries versus Rest of World)
- Prior PD-1/PD-L1 treatment for early stage TNBC (yes versus no)

N=625

1:1:1[c]

Arm 1
Dato-DXd
6.0 mg/kg IV Q3W
+
Durvalumab
1120 mg IV Q3W
(n=275)

Arm 2
Investigator's Choice Chemotherapy[b]
+
Pembrolizumab
200 mg IV Q3W
(n=275)

Arm 3
Dato-DXd
6.0 mg/kg IV Q3W
(n=75)[d]

Primary endpoint:
PFS (BICR)

Key secondary endpoint:
OS

Secondary endpoints including:
PFS (inv), ORR, DoR, CBR, TTD, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints including:
TROP2

a DFI 6 to 12 months capped at 20%.
b Chemotherapy options include paclitaxel (90 mg/m² IV on days 1, 8, and 15, Q4W), nab-paclitaxel (100 mg/m² IV days 1, 8, and 15, Q4W) or gemcitabine 1000 mg/m² IV + carboplatin AUC 2 IV days 1 and 8 Q3W.
c Once approximately 75 participants are randomised to Arm 3, this cohort will close, and all countries will continue with a 1:1 randomisation strategy for Arms 1 and 2.
d In selected countries only.

TROPION-Breast03 (n=1075)

NCT05629585

N=1075
Stage I-III TNBC
Residual disease after at least 6 cycles of neoadjuvant chemotherapy

R
1:1:1

- Datopotamab deruxtecan x 8 cycles Durvalumab x 9 cycles
- Datopotamab deruxtecan x 8 cycles
- Capecitabine x 8 cycles OR Pembrolizumab x 9 cycles OR Cape + Pembro

TROPION-Breast04 (n=1728)

NCT06112379

Neoadjuvant therapy for TNBC

- Durvalumab + Dato-DXd x 8 cycles followed by surgery; durva x 9 cycles postop vs KN522

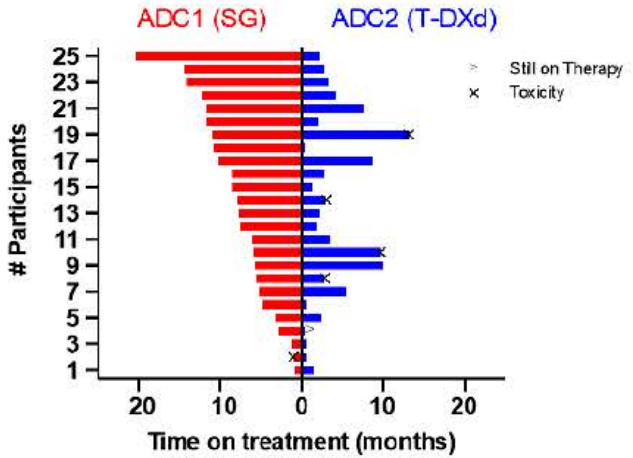
HR−/HER2-low efficacy data (n=28)

SG → T-DXd (n=25, 89.3%)

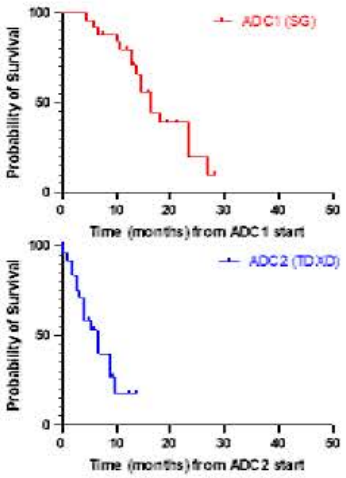
- Median lines of therapy for MBC prior to SG: 2.0 (range 0-5)
- Intervening therapies between ADCs: 40.0%

	ADC1 (SG)	ADC2 (T-DXd)
ORR (CR+PR) by investigator assessment, %	68.0%	35.0%
CBR (CR + PR + SD) by investigator assessment, %	80.0%	45.0%
Median rwPFS, months	7.8	2.8
Median rwOS from time of each ADC start, months	16.5	6.5

rwPFS



rwOS

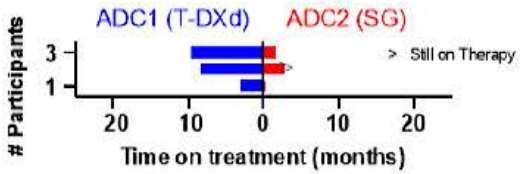


T-DXd → SG (n=3, 10.7%)

- Median lines of therapy for MBC prior to T-DXd: 3.0 (range 1-5)
- Intervening therapies between ADCs: 66.7%

	ADC1 (T-DXd)	ADC2 (SG)
ORR (CR+PR) by investigator assessment, %	33.3%	0.0%
CBR (CR + PR + SD) by investigator assessment, %	66.7%	50.0%
Median rwPFS, months	undetermined	
Median rwOS from time of each ADC start, months	undetermined	

rwPFS



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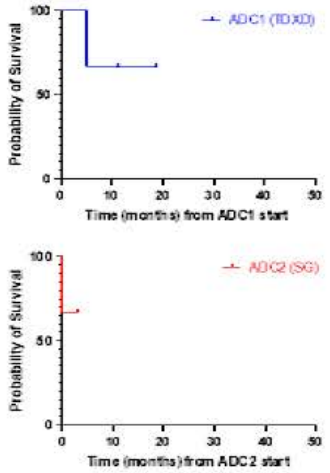


Huppert L, et al. SABCS 2023. Abstract PS08-04

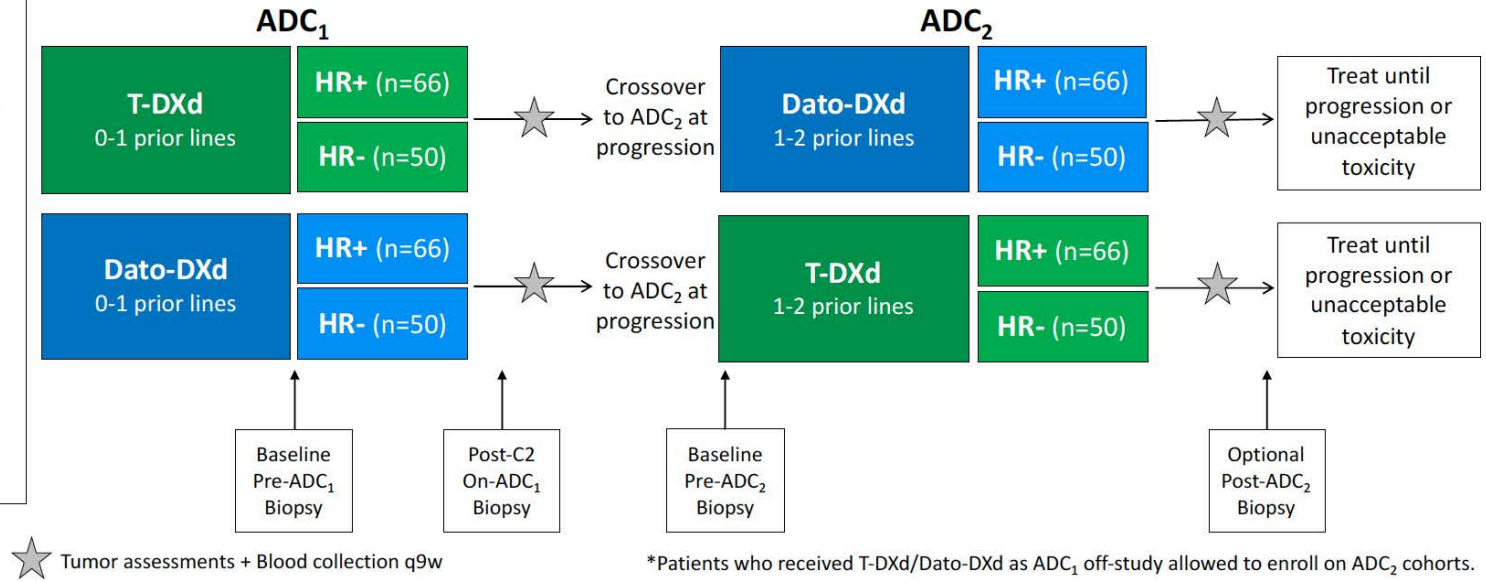
TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd (TRADE DXd).
PI: Ana Garrido-Castro

Eligibility:

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

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

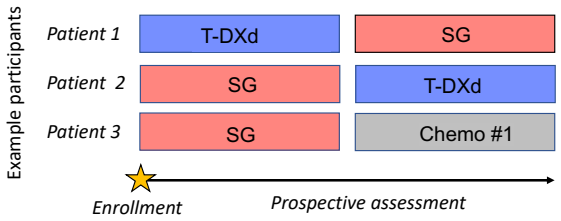
Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR



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

Registry Sequencing Study: Laura Huppert UCSF

Cohorts 1 & 2: Enrollment Prior to ADC #1



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

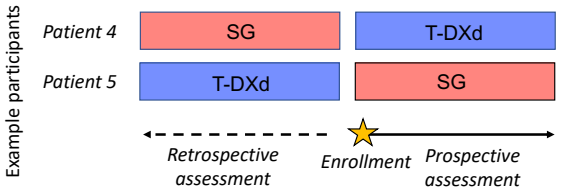
Cohort 2: TNBC, HER2 low
~25 patients

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

Objectives/considerations:

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

Cohorts 3 & 4: Enrollment Prior to ADC #2



Cohort 3: HR+/HER2-
~25 patients

Cohort 4: TNBC
~15 patients

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

Objectives/considerations:

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

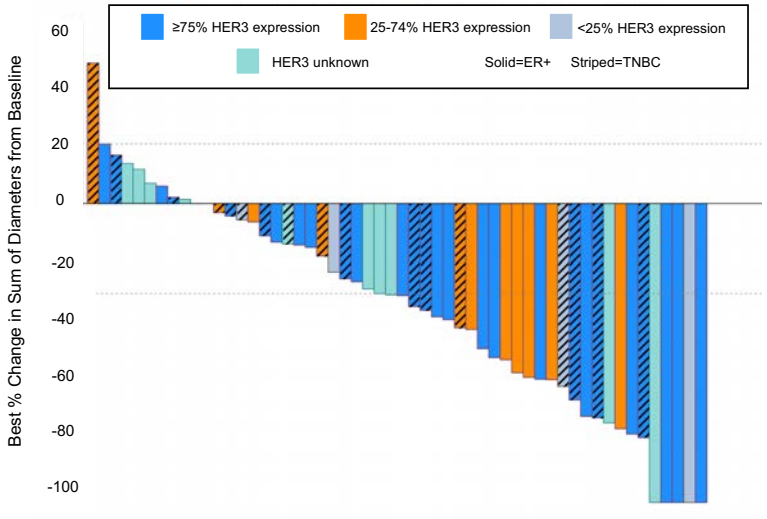
Patritumab Deruxtecan: Phase 2 Study of HER3-DXd in MBC

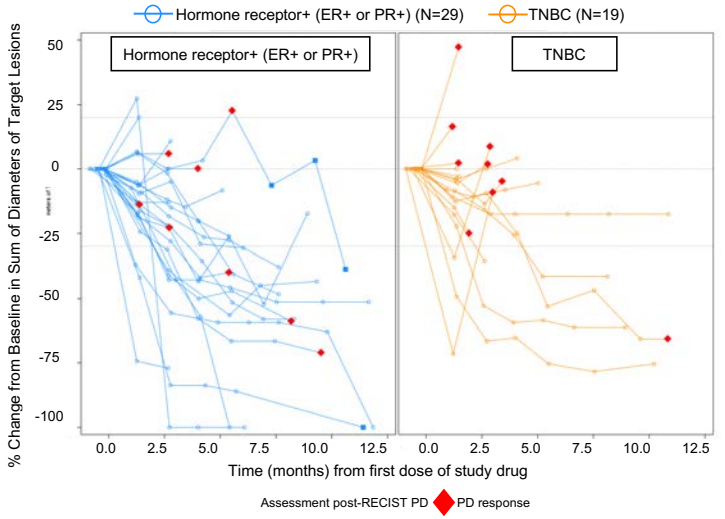
- 60 pts:
  - HR+: Prior CDKi, 0-2 chemo
  - TN: 1-3 chemo
  - 29 HR+/19 TN (n=48)
  - 64% HER3 ≥75%; 8% <25% (n=47)
- ORR 35%, CBR 43%,
  - No relationship to HER3 expression
- DOR ≥ 6mo: 47.6% in responders (n=10)
- Most common AE:
  - Nausea/diarrhea/fatigue
  - TEAE: 2 ILD, 1 low plt

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

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

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



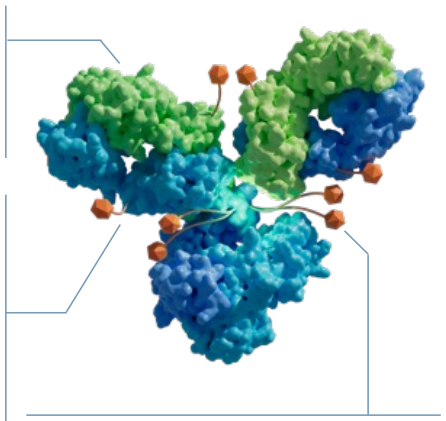


Hamilton et al, ASCO 2023

Phase 2: 2L SKB264 (MK-2870) for Metastatic TNBC

Antibody
- hRS7, a recombinant humanized anti-TROP2 antibody with high affinity

Linker
- A sulfonyl pyrimidine-CL2A-carbonate linker
- Irreversible linker with proprietary design
- Favorable stability in circulation system for better therapeutic window
- Releasing payload in acidic environment relying on hydrolysis
- Bystander effect



Payload
- Novel Topo I inhibitor (Belotecan derivative named KL610023)
- The average of DAR: 7.4 (range: 7~8)

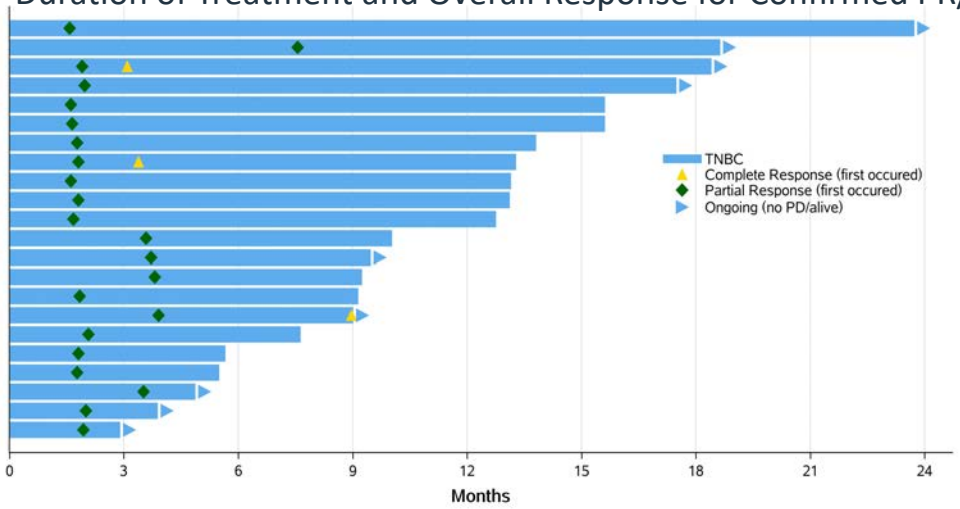
Summary of Treatment-related Adverse Events (TRAEs)

TRAEs	Total (N=59), n (%)	
	All Grade	≥Grade 3
TRAEs	59 (100)	35 (59.3)
Treatment-related SAEs	17 (28.8)	16 (27.1)
TRAEs associated with dose delay	28 (47.5)	20 (33.9)
TRAEs associated with dose reduction	8 (13.6)	6 (10.2)
TRAEs associated with dose discontinuation	3 (5.1)	2 (3.4)
TRAEs associated with death	0	0
TRAEs in any grade ≥30% or ≥ grade 3 ≥5% of patients, by preferred term		
Anaemia	49 (83.1)	13 (22)
White blood cell count decreased	45 (76.3)	14 (23.7)
Neutrophil count decreased	40 (67.8)	15 (25.4)
Stomatitis	27 (45.8)	4 (6.8)
Vomiting	24 (40.7)	0
Platelet count decreased	23 (39.0)	10 (16.9)
Nausea	21 (35.6)	0
Rash	21 (35.6)	2 (3.4)
Lymphocyte count decreased	18 (30.5)	4 (6.8)
Alanine aminotransferase increased	18 (30.5)	0

Yin Y, et al. SABCS 2023. PS08-08

Response and survival outcomes (by investigator)	**Overall (N=59)**	**TROP2 high expression (H-score > 200, N=32)**
ORR, % (95% CI)	42.4 (29.6, 55.9)	53.1 (34.7, 70.9)
Confirmed PR/CR, n (%)	22 (37.3)	16 (50)
DCR, % (95% CI)	76.3 (63.4, 86.4)	81.3 (63.6, 92.8)
mDoR, months (range)	11.5 (3.7 to 22.1+)	11.1 (3.7 to 22.1+)
mPFS, months (95% CI)	5.7 (3.8, 9.1)	5.8 (3.7, 13.3)
OS, months (95% CI)	16.8 (12.7, NE)	NE (9.7, NE)
12-month OS rate, %	65.0	65.3
24-month OS rate, %	39.5	57.3

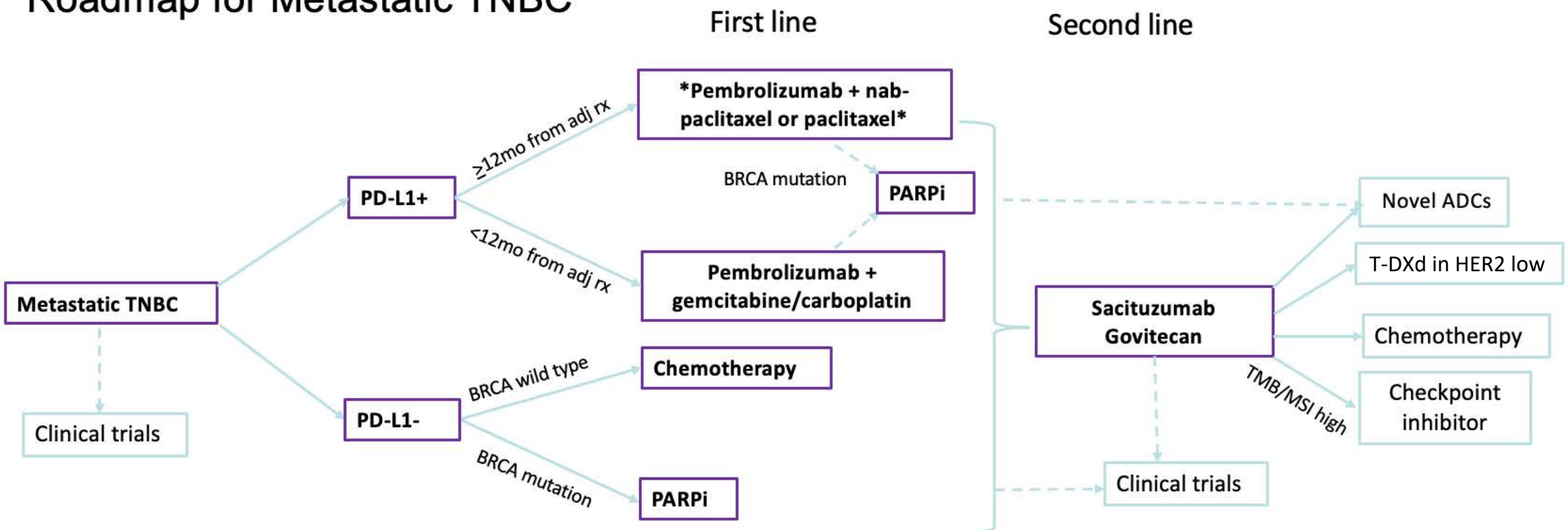
Duration of Treatment and Overall Response for Confirmed PR/CR



Conclusions

- Advances in mTNBC
  - ADCs
  - Better understanding of immunotherapy
- Next steps
  - Optimizing treatment in earlier lines of therapy for ADCs
  - Combinations with immunotherapy to enhance efficacy
  - New ADCs!

Roadmap for Metastatic TNBC



Agenda

Module 1: HER2-Positive Metastatic Breast Cancer — Dr Hamilton

Module 2: Metastatic Triple Negative Breast Cancer — Dr Rugo

Module 3: SABCS 2023 Review — Dr Kaklamani

SABCS 2023 Review

Virginia Kaklamani, MD DSc
Professor of Medicine
Leader, Breast Oncology Program

Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center

Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Gilead Sciences Inc, Lilly, Menarini Group, Puma Biotechnology Inc, TerSera Therapeutics LLC
Contracted Research	Eisai Inc
Data and Safety Monitoring Board/Committee	Sanofi
Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Novartis, Pfizer Inc, Seagen Inc

Current landscape of ADCs in HER2-negative MBC

	HR+/HER2- BC			TNBC	
ADC trials in MBC	**DESTINY-Breast04**	**TROPION-Breast01**	**TROPiCS-02**	**DESTINY-Breast04**	**ASCENT**
Treatment arms	T-DXd (HER2) vs TPC	Dato-DXd (TROP2) vs TPC	SG (TROP2) vs TPC	T-DXd (HER2) vs. TPC	SG (TROP2) vs. TPC
HER2 status	1+, 2+/ISH-	0, 1+, 2+/ISH-	0, 1+, 2+/ISH-	1+, 2+/ISH-	0, 1+, 2+/ISH-
Prior chemotherapy for MBC	1-2	1-2	2-4	1-2	≥1
Median PFS HR (95% CI)	9.6 vs 4.2 mo. HR 0.37 (0.30-0.56)	6.9 vs 4.9 mo. HR 0.63 (0.52-0.76)	5.5 vs 4.0 mo. HR 0.65 (0.53-0.81)	6.3 vs 2.9 mo. HR 0.29 (0.15-0.57)	5.6 vs 1.7 mo. HR: 0.41 (0.32-0.52)
Median OS HR (95% CI)	23.9 vs 17.6 mo. HR 0.69 (0.55-0.87)	N/A HR 0.84 (0.62–1.14)	14.5 vs 11.2 mo. HR 0.79 (0.65-0.95)	17.1 vs 8.3 mo. HR 0.58 (0.31-1.08)	12.1 vs 6.7 mo. 0.48 (0.38-0.59)
ORR	52.6% vs 16.3%	36.4% vs 22.9%	21% vs 14%	50.0% vs 16.7%	35% vs 5%

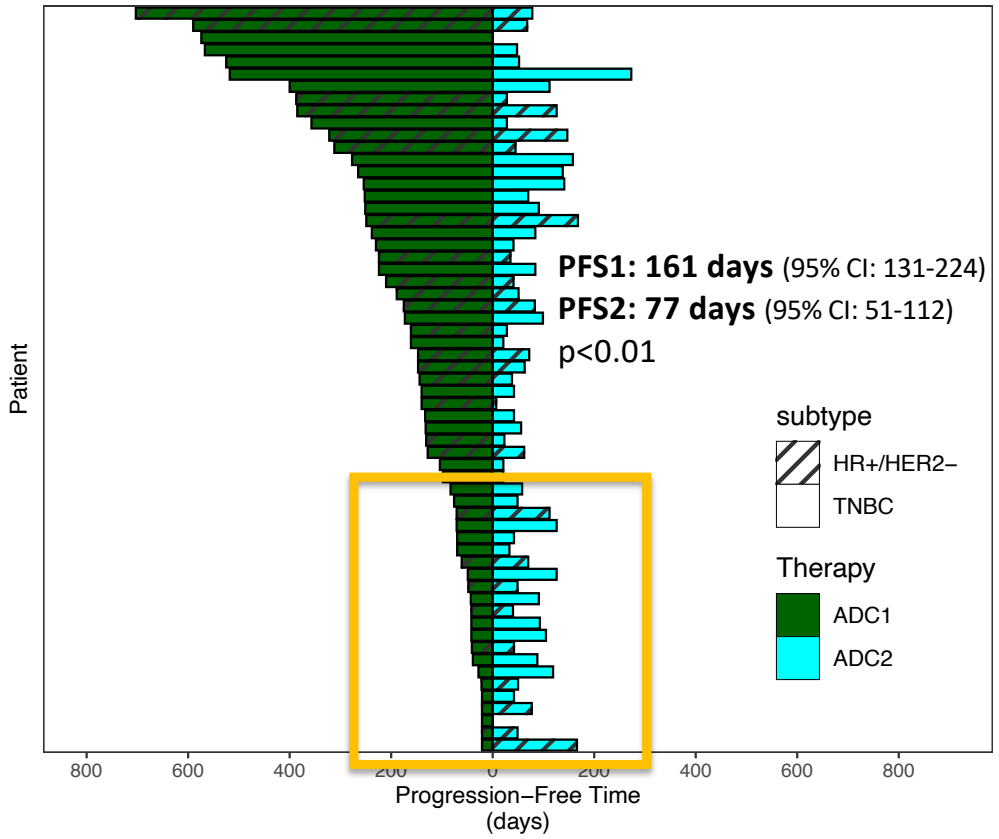
1. Is there a preferred initial ADC?

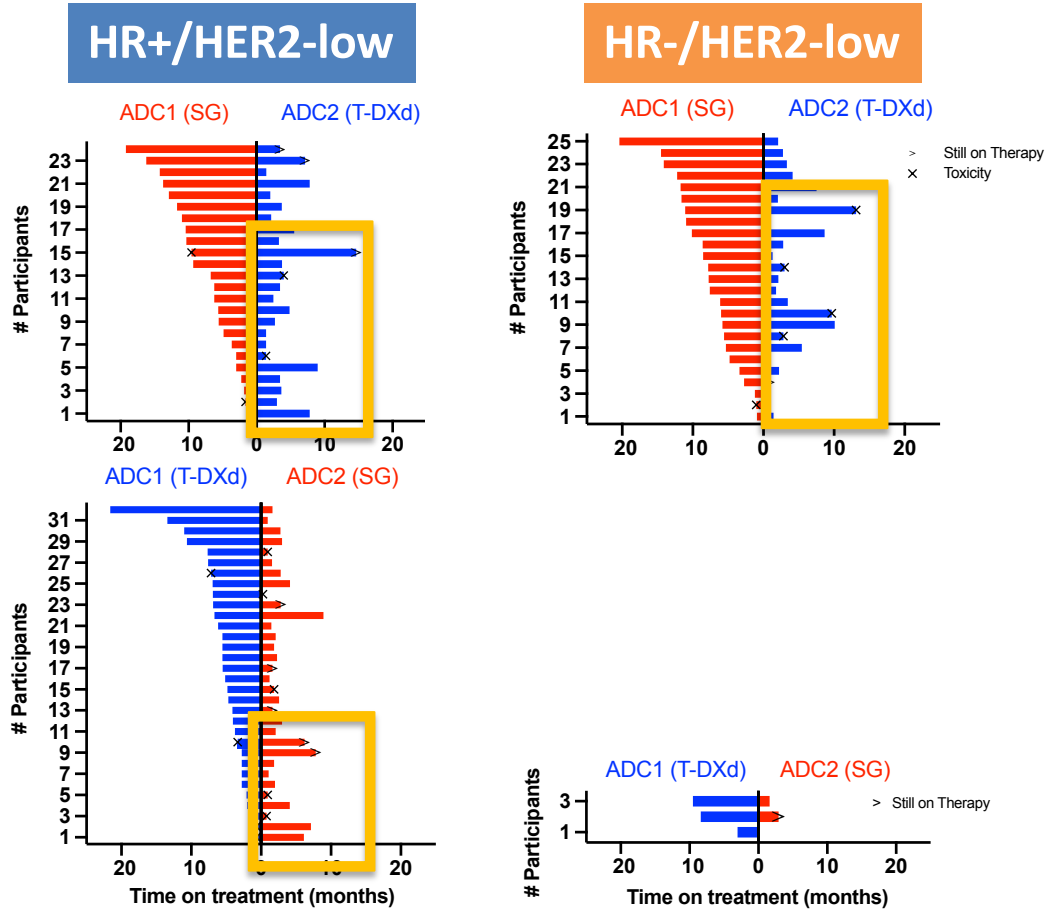
2. Is there a role for sequencing of ADCs?

Modi S et al. ESMO 2023; Bardia A et al. ESMO 2023; Tolaney S et al. ASCO 2023; Bardia A et al. NEJM 2021.

Is there benefit with ADC2 after ADC1?

- Significantly shorter median TTP with ADC2 vs ADC1: >, ≈, or < than other standard therapy (i.e., chemotherapy)?
- How to identify patients who appear to derive similar or greater benefit from ADC2 than ADC1?

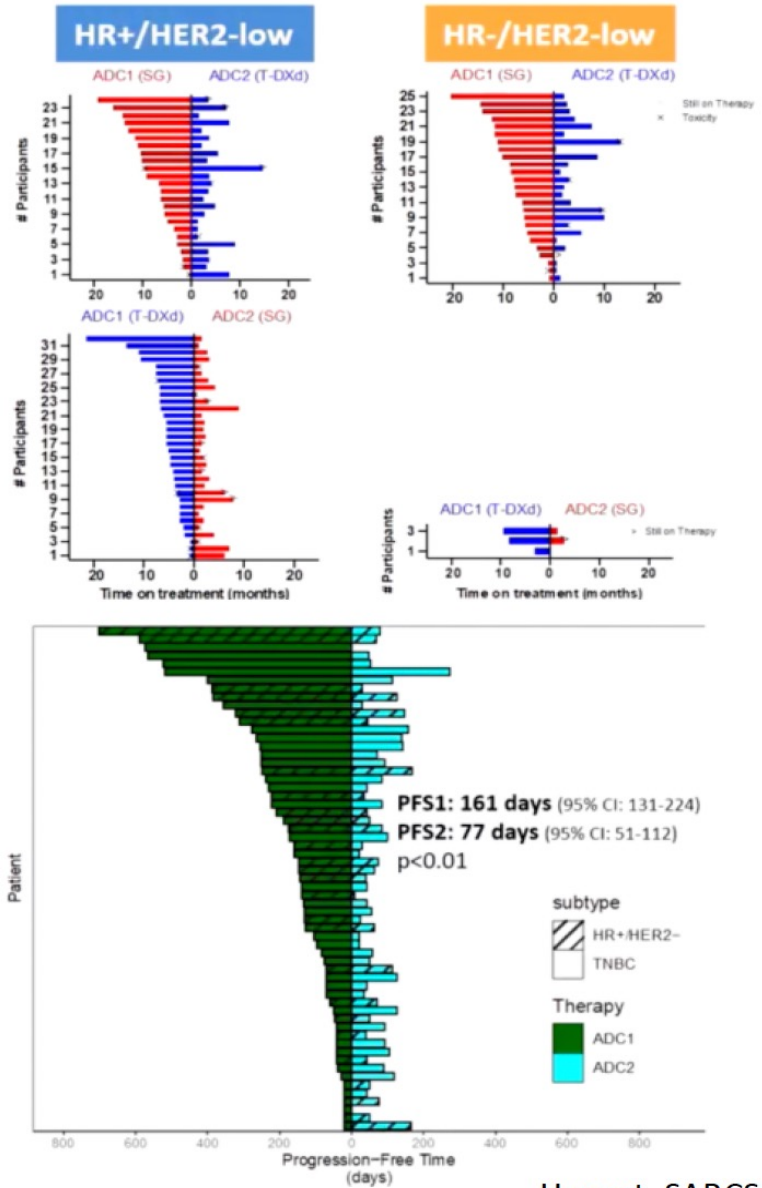




Abelman RO et al. SABCS 2023; Huppert LA et al. SABCS 2023.

ADC after ADC?

- Current data limited by its retrospective nature
  - Patient heterogeneity, selection and indication bias, differences in # lines of treatment, not immediate sequencing, etc.
  - Clinical trials are needed
- Today the best sequence is unclear → individualize
- **Data suggest that after ADC1, ADC2 has shorter duration of response in most (but not all) patients**
  - mPFS2 is shorter, but how it compares to chemotherapy?
  - How to identify?
  - Trop 1 variant as possible mechanism of resistance?



Hupert, SABCS 2023
Abelman, SABCS 2023

Is there a preferred sequence of TROP2/HER2 ADCs?

Median PFS			Abelman et al.		Poumeaud et al.		Huppert, Mahtani et al.	
HR+	SG → T-DXd	ADC1 (SG)	N=7	8.3 mo	N/A		N=24	8.0 mo
		ADC2 (T-DXd)		5.6 mo				3.7 mo
	T-DXd → SG	ADC1 (T-DXd)	N=11	4.9 mo	N=56	2.7 mo	N=32	5.5 mo
		ADC2 (SG)		1.7 mo		2.3 mo		2.6 mo
HR-	SG → T-DXd	ADC1 (SG)	N=14	7.7 mo	N=100	4.9 mo	N=25	7.8 mo
		ADC2 (T-DXd)		2.8 mo		3.2 mo		2.8 mo
	T-DXd → SG	ADC1 (T-DXd)	N=7	1.4 mo	N/A		N=3	NR
		ADC2 (SG)		3.1 mo				NR

ADCs in Breast Cancer- Some questions

Testing and Biomarkers

- How to best select patients?
  - Her2-low, How low?, Trop2?

Sequencing

- What is the best sequence?
  - Among Her2-low patients, in what order should T-DXd and SG be used?
  - Similar sequence for patients with HR+ and HR- BC?
- Will ADCs move to 1st line?
- How will we incorporate new agents (Dato-DXd)?

Resistance

- What are the main mechanisms of resistance?
  - Impacting payload
  - Impacting target
- Can we use sequential agents that have similar payloads?
- Will combinations be more effective?

How to optimize the use of ADCs for the benefit of our patients?

Advances in TNBC

- Until recently, the treatment of patients with TNBC was limited to chemotherapy, however, in recent years, immunotherapy and ADCs have significantly impacted the treatment options for patients with advanced TNBC.
  - Pembrolizumab
  - Sacituzumab Govitecan
  - Trastuzumab Deruxtecan
- Several studies are assessing the safety and efficacy of combining immunotherapy and ADCs

The Annual
National General Medical Oncology Summit

Saturday, March 23, 2024

Moderator

Neil Love, MD

Faculty

Emmanuel S Antonarakis, MD
Ibiayi Dagogo-Jack, MD
Matthew D Galsky, MD
Edward B Garon, MD, MS
Erika Hamilton, MD
Eric Jonasch, MD
Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Matthew Lunning, DO
Kami Maddocks, MD
Rana R McKay, MD
Bradley J Monk, MD
David M O'Malley, MD
Joyce O'Shaughnessy, MD
Brian Rini, MD
Jonathan E Rosenberg, MD
Hope S Rugo, MD
Helena Yu, MD
Andrew D Zelenetz, MD, PhD

We are taking a short break!

The program will resume at 12:30 PM ET

Up Next…

Drs Emmanuel Antonarakis and Rana McKay discuss the management of prostate cancer

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