Highlights of the Year 2023 : MBC

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January 2024

Disclosures

Advisory role: Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Hengrui, Innate, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Seattle Genetics, Menarini

Speaker fees: Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Seattle Genetics

Research grants to my Institute: BMS, Roche

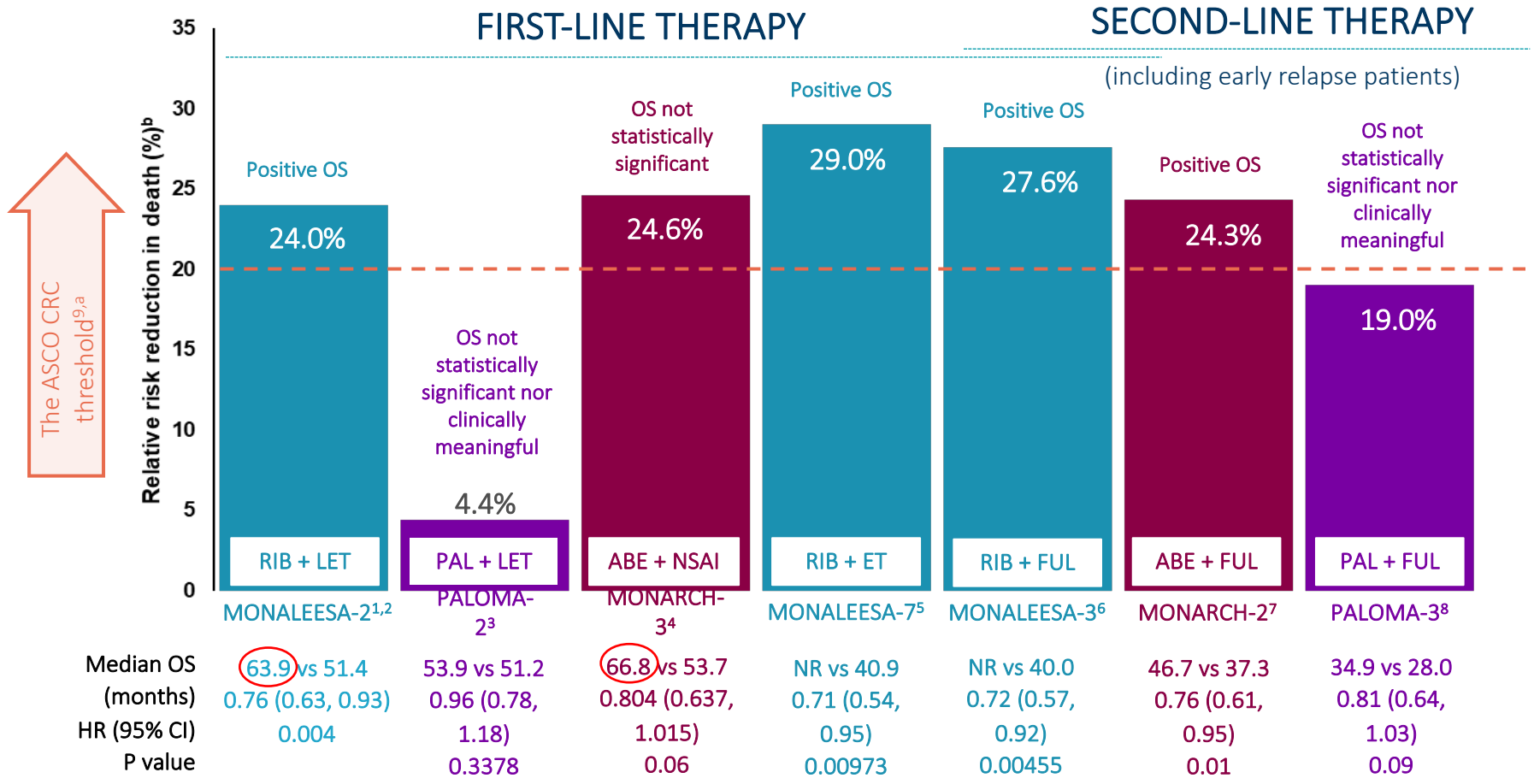
Plan of the Talk

- CDK 4/6i and beyond in the management of HR+/HER2 non amplified
- Triple positive MBC (including HR+/HER2 low)
- HER2 amplified tumors
- Triple negative MBC
- Conclusions and perspectives

Luminal MBC

Ribociclib and abemaciclib but not palbociclib have demonstrated a consistent significant OS benefit across phase 3 studies (although HR for PFS was the same)

Comparisons cannot be made in the absence of well-controlled, head-to-head studies



[a]The ASCO Cancer Research Committee defined incremental improvements in HR of OS ≥ 20% over standard therapy as a clinically meaningful outcome; the magnitude of benefit is based on hazard ratios and refers to the proportional improvement achieved with the addition of CDK4/6 inhibitors in comparison to the respective control groups. [b] As measured by 1 minus HR multiplied by 100.[c] P value did not reach threshold for statistical significance at this interim analysis of MONARCH 3. ABE, abemaciclib; ASCO, American Society of Clinical Oncology; CI, confidence interval; CRC, colorectal cancer; ET, endocrine therapy; FUL, fulvestrant; HR, hazard ratio; LET, letrozole; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PAL, palbociclib; PFS, progression fee survival; RIB, ribociclib.

1. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950; 2. Hortobagyi GN, et al. ESMO 2021. Oral LBA17_PR; 3. Finn RS, et al. ASCO 2022. LBA1003; 4. Goetz, et al. ESMO 2022. LBA15; 5. Im SA, et al. *N Engl J Med*. 2019;38:307-316.; 6. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524; 7. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124; 8. Turner NC, et al. *N Engl J Med*. 2018;15;379:1926-1936; 9. Ellis LM, et al. *J Clin Oncol*. 2014;32:1277-80.

First-line therapies for advanced luminal breast cancer: Important clinical questions and answers

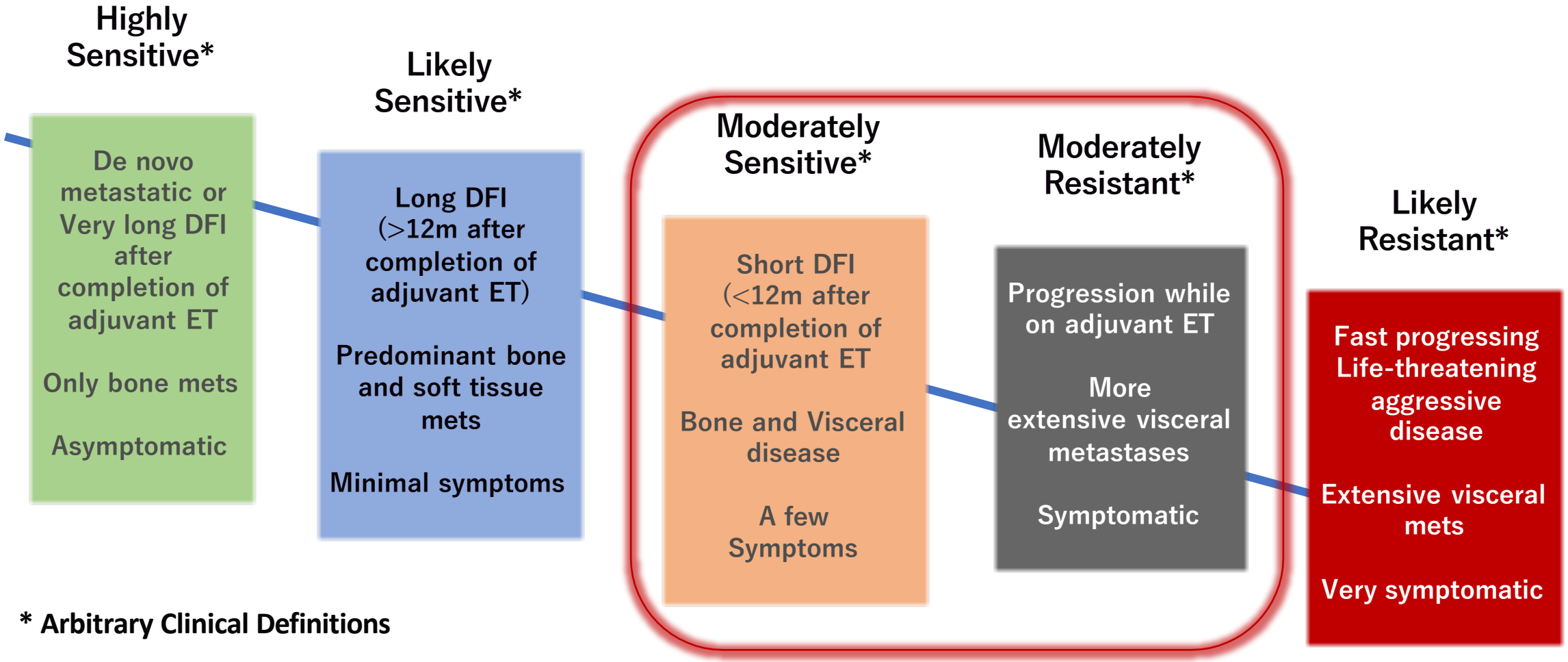
- 1. Should CDK4/6 inhibitors be used as first-line or later line therapy? → First-line (challenged by SONIA trial)[1]
- 2. Which ET should be prescribed in first-line in combination with a CDK4/6i? → AI whenever possible
  (PARSIFAL: AI = fulvestrant ± palbociclib)
- 3. In the presence of non-life-threatening visceral disease (lung + liver) which treatment strategy should be used? (ET + CDK4/6i or chemotherapy) → ET + CDK4/6i
- 4. In the presence of aggressive/life-threatening visceral disease which treatment strategy should be used? → ET + ribociclib with a close follow-up (RIGHT Choice trial)[2]
  (ET + ribociclib or combination chemotherapy)
- 5. Efficacy of CDK4/6i in gBRACA-mutated tumors ? → Less efficacy

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy.

1. Sonke GS, et al. *J Clin Oncol* 2023;41:LBA1000; 2. El Saghir NS, et al. *J Clin Oncol* 2023;41:1063.

Clinical Spectrum of HR+ Disease

(considering endocrine sensitivity)



* Arbitrary Clinical Definitions

Courtesy of Carlos Barrios-modified after Llombart-Cusac A, 2022

INAVO120 study design

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019-September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer. [1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; **Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

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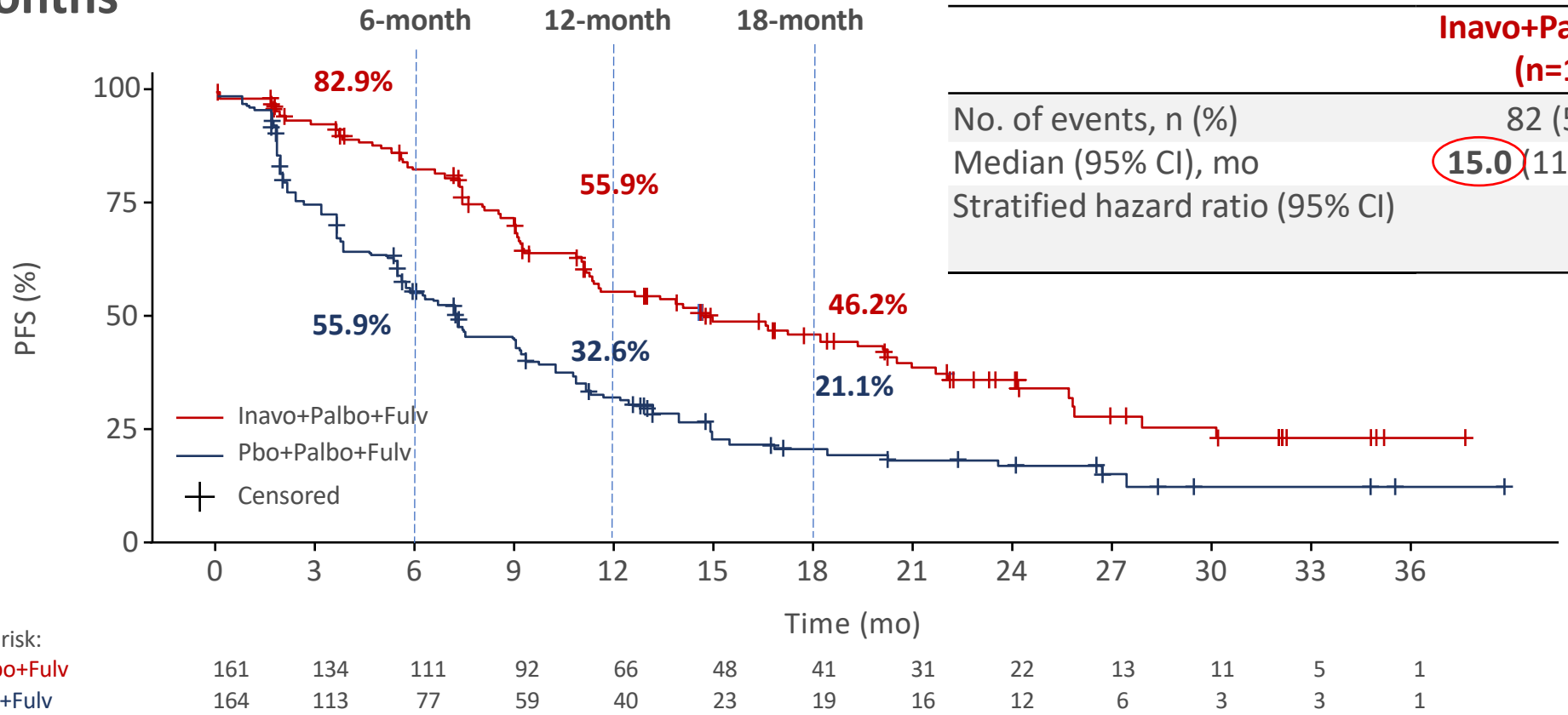
Primary endpoint: PFS (investigator assessed)

Median follow-up: **21.3 months**



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	**15.0** (11.3, 20.5)	**7.3** (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)** **p<0.0001**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

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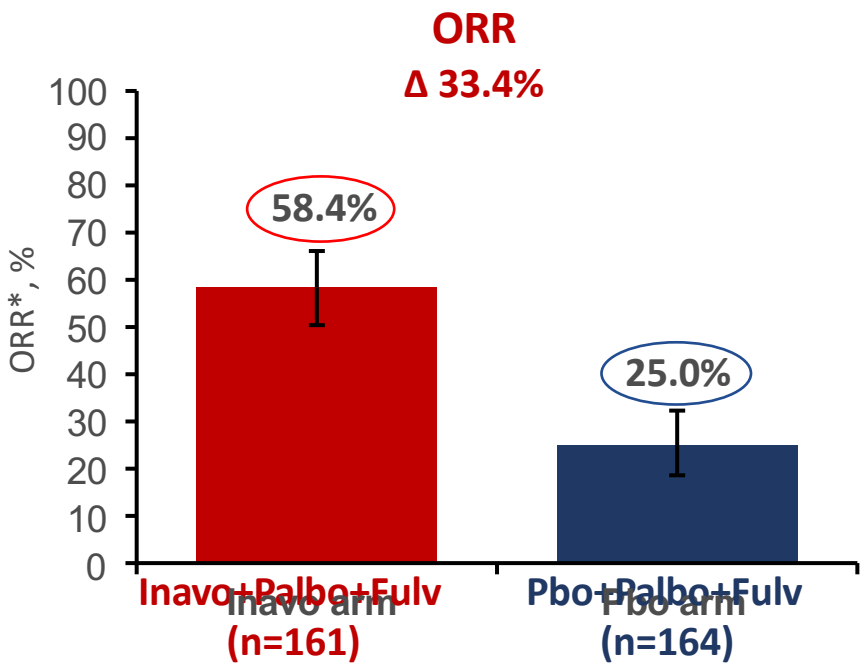
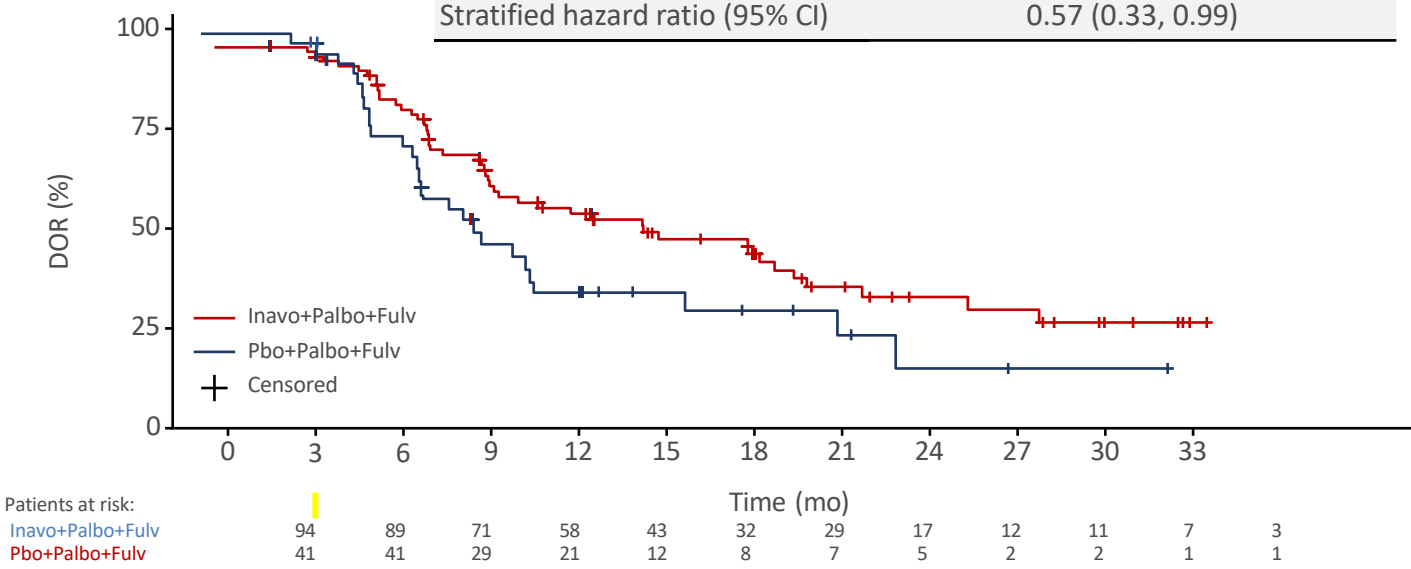
ORR and DOR



	Inavo+Palbo +Fulv (n=94)	Pbo+Palbo+Fulv (n=41)
No. of events, n (%)	46 (48.9)	27 (65.9)
Median (95% CI), mo	**18.4 (10.4, 22.2)**	**9.6 (7.4, 16.6)**
Stratified hazard ratio (95% CI)	0.57 (0.33, 0.99)	



Patients at risk:

Inavo+Palbo+Fulv	94	89	71	58	43	32	29	17	12	11	7	3
Pbo+Palbo+Fulv	41	41	29	21	12	8	7	5	2	2	1	1

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Adverse events with any grade AEs ≥20% incidence in either treatment group

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	**36 (22.2%)**	**0**	**21 (13.0%)**	**0**

Key AEs are shown in **bold.** AES were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

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Advanced luminal breast cancer beyond PD on ET + CDK4/6 inhibitor: Important clinical questions and answers

- **1. What is the role of tissue or liquid biopsy and NGS and when to test for predictive biomarkers (*PIK3CA*, *ESR1* and *BRCA* mutations and AKT alterations)** → After 1st line and after exposure to AI[1] (ESMO): Challenged by INAVO120 trial
- **2. Should CDK4/6i rechallenge be offered in patients pretreated with a CDK4/6i?** → Early data available (MAINTAIN, PACE and PALMIRA trials)[2–4]
- **3. What is the role of SERDs (e.g., elacestrant,…) in such patients?** → Emerald trial
- **4. What is the setting for exemestane + everolimus therapy?** → Later line endocrine therapy[5] (Retrospective trials)
- **5. What is the efficacy of a PIK3CA inhibitor in patients with *PIK3CA*-mut, pretreated with CDK4/6i?** → Phase 3 Study ongoing
- **6. What is the role of ADCs and PARPi (*BRCA*-mut tumors)?**

ADC, antibody-drug conjugate; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; NGS, next generation sequencing; SERD, selective estrogen receptor degrader.

1. Pascual J et al. *Ann Oncol* 2022;33:750–768; 2. Kalinsky K et al. *J Clin Oncol* 2023;41:4004–4013; 3. Mayer EL et al. SABCS 2022. Oral GS3-06; 4. Llombart-Cussac A et al. *J Clin Oncol* 2023;41:S1001–S1001; 5. Rozenblit M et al. *Breast Cancer Res* 2021;23:14.

Post CDK4/6 inhibitors: Proposed Therapeutic Algorithm

Key considerations

- Prior ET
- Type and response to prior CDK4/6i
- Prior ChT
- Germline or somatic mutations
- CTC/tumor load

Monarch E/NATALEE

AI + CDK4/6i (adjuvant/ recurrence on or within 6 months/1 year of stopping CDK4/6i

- **1. Mild PD tumor response to palbociclib** → FUL + RIBO (or Abema) – select patients (Maintain)
- **2. *ESR1* mutation (12 months prior CDK4/6i)** → ELA (Emerald)(FUL + CDK4/6i if no PD on AI +CDK4/6i(PADA))
- **3. *PIK3CA* mutation** → FUL + alpelisib (Bylieve)
- **4. AKT mutation** → FUL + capivasertib (CAPitello)
- **5. g*BRCA* mutation** → PARPi (OlympiAD; EMBARCA)
- **6. No mutations, response to prior ET** → Everolimus + exemestane (Retrospective data)
- **7. Imminent organ failure** → Chemotherapy (including ADCs)
- **8. HER2 low, ET failure** → T-Dxd (DESTINY-B04)
- **9. HER2 0, ET failure** → Sacituzumab govitecan (Tropics02); Datopotomab-deruxtecan (Tropion B01)

AI, aromatase inhibitor; ADC, antibody-drug conjugate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; CTC, circulating tumor cells; ELA, elacestrant; ET, endocrine therapy; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; PARPi, poly ADP ribose polymerase inhibitor; PD, progressive disease; RIBO, ribociclib; T-Dxd; trastuzumab deruxtecan.
PADA trial – find reference

Role of ADCs in HR+ Advanced Breast Cancer

	Destiny B04	Tropion B01	Tropics 02
ADC	Trastuzumab deruxtecan	Datopotomab deruxtecan	Sacituzumab Govitecan
Payload	Topoisomerase I	Topoisomerase I	Topoisomerase I
Target	HER-2	TROP-2	TROP-2
Drug to Antibody Ratio (DAR)	≈8:1	≈ 4:1	≈7:1
HER2 status	+1, +2	0, +1, +2	0, +1, +2
Prior lines CT	1-2	1-2	2-4
PFS vs. CT (months)	10.1 vs. 5.4 HR 0.51	6.9 vs. 4.9 HR 0.63	5.5 vs. 4.0 HR 0.66
ORR vs. CT (%)	53 vs. 16	36 vs. 23	21 vs. 14
OS vs. CT (months)	23.9 vs. 17.6 HR 0.69	NR (immature)	14.4 vs. 11.2 HR 0.79

Retrospective studies evaluating ADC sequencing

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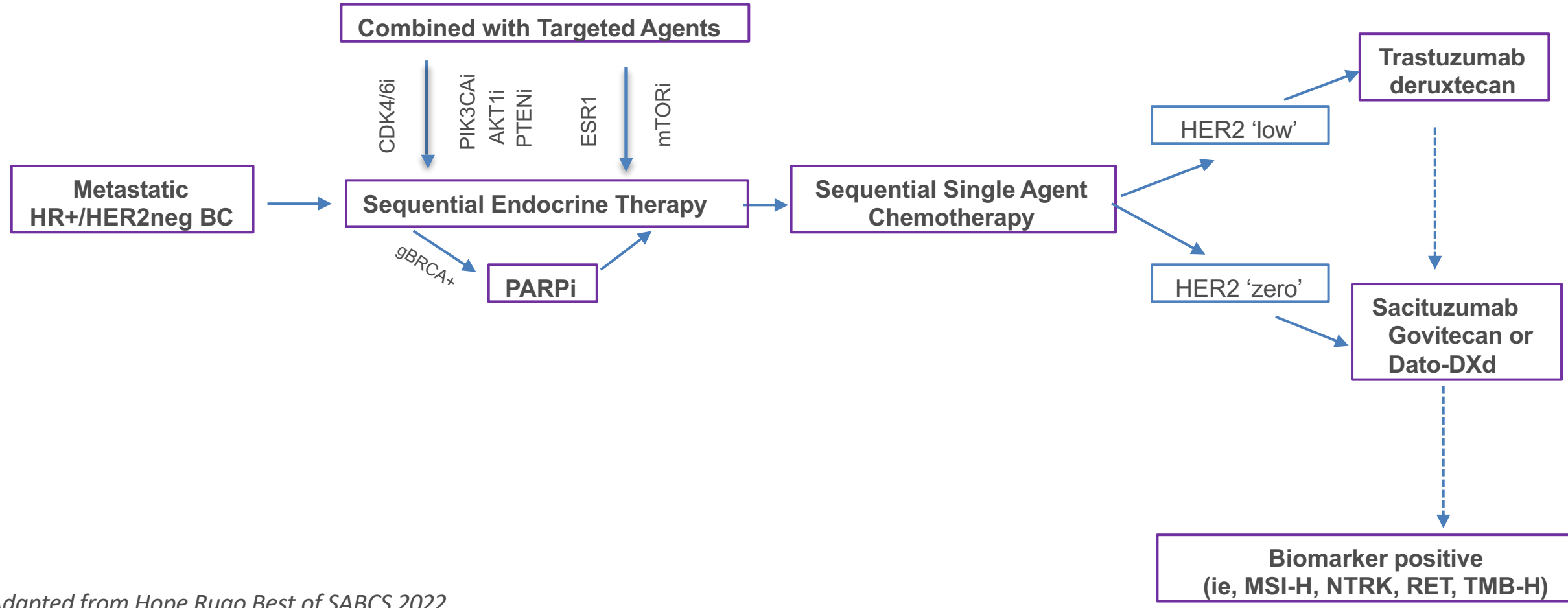
	Population	ADC 1	ADC 2	
Abelman	**n=68** HR+: 44%, TNBC: 56% Prior lines of treatment: 3-7	mTTP: 5.4mo	mTTP:2.5mo	Trop1 variant may drive resistance
Raghavendra	**n=33** Subtype data not available	PFS: SG: 4.6 mo. PFS: TDXd: 7.6 mo	PFS SG TDXd: 5.5mo PFS TDXd SG: 2.4 mo	Suggest superiority of T-DXd but unknown HR status
Huppert	**n=84** HR+/HER2-low: 67% HR-/HER2-low: 33% Prior lines of treatment: 2-4.5	TTNT SGTDXd: HR+ 8 mo HR- 7.8 mo TTNT TDXd SG: HR+ 5.5 mo HR- undetermined	TTNT SGTDXd: HR+ 3.7 mo HR:- 2.8 mo TTNT TDXd SG: HR+ 2.7mo HR- undetermined	All HER2-low expressing Longer PFS with ADC1 than ADC2
Poumeaud	**n= 179** HR+/HER2-low: 69% HR-/HER2-low: 31% Prior lines of treatment: 3-5 Prior ADC use: 64% received SG as ADC1	mPFS: 4.5 mo. mPFS HR+/HE2-low: 2.7 mo. (T-DXd) mPFS HR-/HE2-low: 4.9 mo. (SG)	. SG-T-DXd- PFS2: 3.1mo. T-DXd-GG: 2.2 mo.	In MV analysis **SG -->T-DXd was associated with improved outcomes** 50% primary resistance to ADC2

Treatment Sequencing in HR+/HER2- MBC



Adapted from Hope Rugo Best of SABCS 2022

Triple Positive MBC (Including HR+/HER2 low)

- ASPIRE trial (Frontline setting)
- DESTINY-Breast08 (HER2 low; HR+; no prior CT)
- Zanidatamab-based trial (Prior T, P, T-DM1)

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A Multicenter, Phase I/II Trial of Anastrozole, Palbociclib, Trastuzumab, and Pertuzumab in Hormone Receptor (HR)- Positive, HER2-Positive Metastatic Breast Cancer (ASPIRE)

Rima Patel[1], MD; Krystal Cascetta[1], MD; Paula Klein[1], MD; Erin Moshier[1], BS; Maryann Kwa[2], MD; Julie Fasano[1], MD; Anupama Goel[1], MD; Melissa Accordino[3], MD; Charles Shapiro[1], MD; Rita Vaccaro[1], RN; Laura Fiedler[1], MPH; Karen Meyer[1], PhD; Joseph A. Sparano[1], MD; Amy Tiersten[1], MD

[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]New York University Langone Medical Center, New York, NY; [3]Columbia University Medical Center, New York, NY

Trial Design

Key Eligibility Criteria

- Metastatic breast cancer with ER or PR positivity in ≥ 1% cells and HER2 positivity
- No prior systemic therapy for MBC
- Measurable or evaluable disease including bone metastasis only

PHASE I N=3-12	PHASE II N=30-43
Palbociclib: PO at increasing doses (100mg, 125mg) on Days 1-21, followed by 7 days off using a 3+3 design	**Palbociclib:** PO at MTD (125mg) on Days 1-21, followed by 7 days off
Anastrozole: 1mg PO once daily	**Anastrozole:** 1mg PO once daily
Trastuzumab: 8mg/kg loading dose, followed by 6mg/kg q21 days	**Trastuzumab:** 8mg/kg loading dose, followed by 6mg/kg q21 days
Pertuzumab: 840mg/kg loading dose, followed by 420mg/kg q21 days	**Pertuzumab:** 840mg/kg loading dose, followed by 420mg/kg q21 days
Primary Endpoint Maximum Tolerated Dose (MTD)	**Primary Endpoint** • Clinical benefit rate (CBR): sum of complete response, partial response, and stable disease for ≥ 6 months **Secondary Endpoints** • Progression free survival (PFS) • Objective response rate (ORR) • Safety

Clinical Response in IIT Cohort

Outcome	Patient Population (N=30)
Clinical benefit rate, % [95% CI]	**97%** [83, 100], p<0.0001
Objective response rate, % [95% CI]	**73%** [54, 88]
Complete Response	13% (4)
Partial Response	60% (18)
Stable Disease	23% (7)
Progressive Disease	0% (0)
Unevaluable	3% (1)
Median time to overall response, months [95% CI]	2.8 [2.7, 5.2]
Median duration of response, months [95% CI]	37.8 [14.0, Not Estimable]
Median follow up, months [95% CI]	30.3 [21.86,52.70]

Phase II portion was powered with 30 patients to show efficacy of combination if CBR exceeded 58%.

Trastuzumab deruxtecan (T-DXd) in combination with anastrozole or fulvestrant in patients with HER2-low HR+ advanced/metastatic breast cancer: a Phase 1b, open-label, multicenter, dose-expansion study (DESTINY-Breast08)

#RF02-03

Komal Jhaveri,[1] Fabrice André, Erika Hamilton, Peter Schmid, Carey K Anders, Laura Testa, Inna Ganshina, Yen-Shen Lu, Seock-Ah Im, Robyn R Young, Magdalena Wrona, Caron Lloyd, Yiwen Zhang, Sherene Loi

On behalf of the DESTINY-Breast08 investigators

[1]Memorial Sloan Kettering Cancer Center, New York, NY, US

Baseline characteristics and patients disposition

	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Median age, years (range)	55.0 (29.0–75.0)	65.5 (31.0–73.0)
Female, n (%)	21 (100.0)	20 (100.0)
Race, n (%)		
Asian	11 (52.4)	12 (60.0)
White	10 (47.6)	7 (35.0)
Black or African	0	1 (5.0)
HER2 status, n (%)		
IHC 1+	16 (76.2)	13 (65.0)
IHC 2+/ISH−	5 (23.8)	7 (35.0)
HR status, n (%)		
ER+ and PR+	14 (66.7)	10 (50.0)
ER+ and PR−	7 (33.3)	9 (45.0)
ER+ and PR missing	0	1 (5.0)
ECOG PS, n (%)		
0	12 (57.1)	17 (85.0)
1	8 (38.1)	3 (15.0)
2	1 (4.8)	0
Received no prior line of treatment for mBC, n (%)	7 (33.3)*	6 (30.0)†
Received a prior line as first line for mBC, n (%)	14 (66.7)‡	14 (70.0)§

n (%)	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Median duration of follow up, months (range)	20.2 (4.9–24.8)	15.2 (2.2–22.6)
Treatment ongoing	6 (28.6)	7 (35.0)
Patients who discontinued both IPs	15 (71.4)	13 (65.0)
Patients who discontinued T-DXd	15 (71.4)	16 (80.0)
AE	4 (19.0)	6 (30.0)
Subject decision	0 (0)	4 (20.0)
Objective disease progression	8 (38.1)	5 (25.0)
Subjective disease progression	3 (14.3)	2 (10.0)
Patients who discontinued ET	15 (71.4)	13 (65.0)

All patients received study drug

As of August 16, 2023, **6 patients** (28.6%) **in the T-DXd + ANA arm** and **7 patients** (35.0%) **in the T-DXd + FUL arm** were **ongoing study treatment**

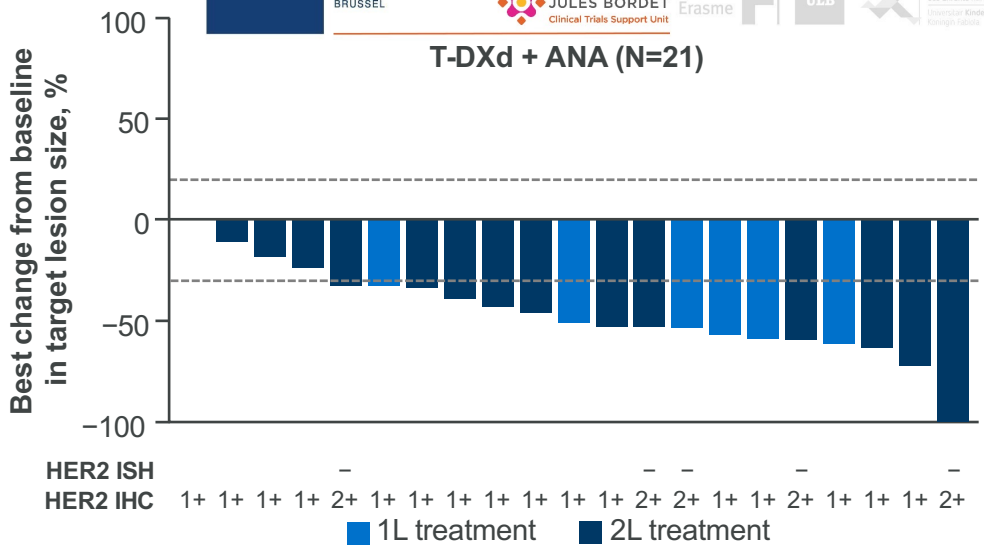
Disease progression was the leading reason for treatment discontinuation in both arms

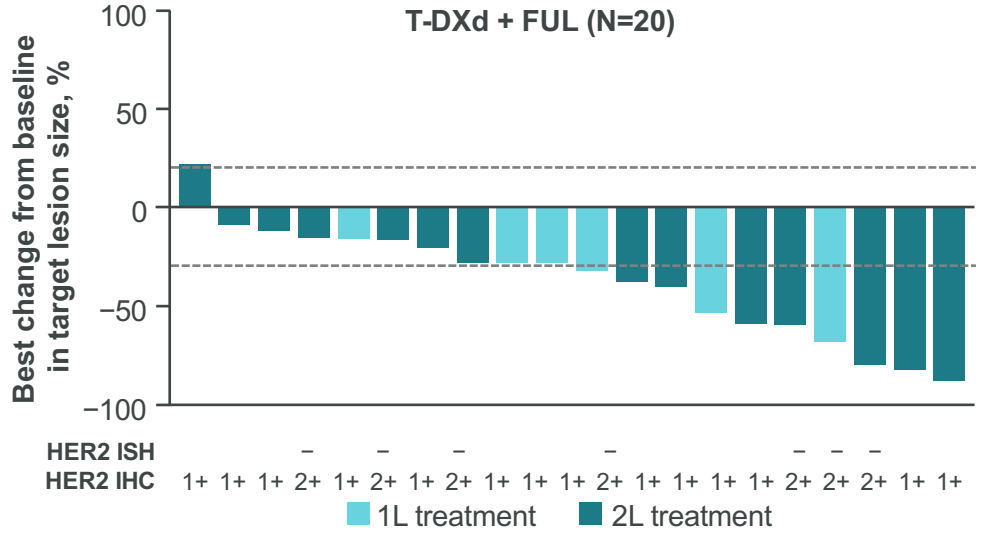
and three had de-novo mBC. ‡All patients received hormonal therapy with a targeted therapy. §11 patients received hormonal therapy with a targeted therapy and three received hormonal therapy alone
ER, estrogen receptor; IP, investigational product; PR, progesterone receptor

Efficacy overview

	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Confirmed ORR, % (95% CI)	71.4 (47.8, 88.7)	40.0 (19.1, 64.0)
Unconfirmed ORR, % (95% CI)	76.2 (52.8, 91.8)	50.0 (27.2, 72.8)
Median DOR, months (95% CI)*	9.8 (6.7, NE)	NE (4.1, NE)
Total PFS events, n (%)	14 (66.7)	7 (35.0)
Median PFS, months (95% CI)*	13.4 (8.5, 19.4)	NE (5.6, NE)
PFS rate at 6 months, % (95% CI)	80.7 (56.3, 92.3)	75.3 (46.4, 90.0)
PFS rate at 12 months, % (95% CI)	50.4 (27.5, 69.5)	52.7 (25.0, 74.4)

- Efficacy results need to be interpreted with caution owing to the small datasets
  - Of note, 15% of patients in the T-DXd + FUL arm withdrew consent and discontinued study treatment before disease progression





*NE signifies that median DOR/PFS was not reached for these patients at the time of DCO
Median DOR calculated using Kaplan-Meier technique. Target lesion size is the sum of diameters of target lesions, assessed by investigator per RECIST 1.1.
Best change in target lesion is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively. PFS was assessed by investigator per RECIST 1.1
1L, first line; 2L, second line; CI, confidence interval

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Primary Results From a Phase 2a Study of Zanidatamab in Combination With Palbociclib Plus Fulvestrant in HER2+ HR+ Metastatic Breast Cancer

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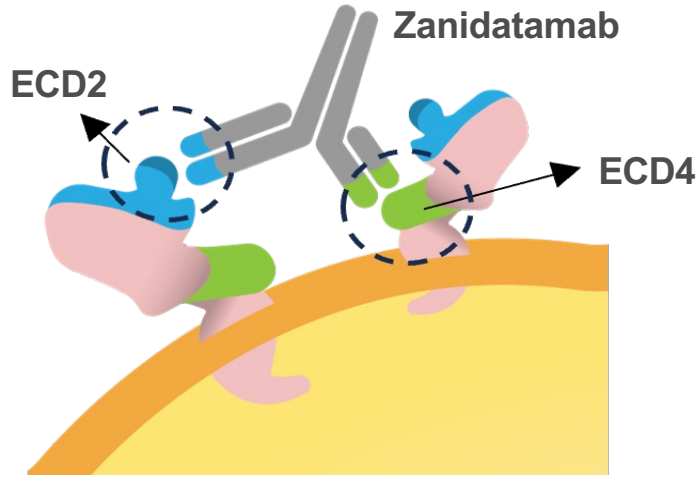
Background and Objective

- Prior studies with a HER2-targeting agent combined with an ER antagonist with or without a CDK 4/6 inhibitor have shown clinical benefit in patients with HER2+ HR+ mBC[1,2]
- Zanidatamab is a bispecific antibody that simultaneously binds two non-overlapping extracellular domains of HER2 (biparatopic binding) leading to[3]:
  - Receptor crosslinking, clustering, internalization, and downregulation
  - Inhibition of tumor cell signaling and proliferation by preventing HER2 dimerization
  - Immune-mediated antitumor effects including antibody-dependent cellular cytotoxicity and phagocytosis, and complement-dependent cytotoxicity

Zanidatamab binding to HER2[3]



Objective: To evaluate the safety and efficacy of zanidatamab in combination with palbociclib (CDK4/6 inhibitor) plus fulvestrant (ER antagonist) in HER2+ HR+ mBC

1. Tolaney SM, et al. *Lancet Oncol*. 2020;21(6):763-775. 2. Ciruelos E, et al. *Clin Cancer Res*. 2020;26(22):5820-5829. 3. Weisser NE, et al. *Nat Commun*. 2023;14(1):1394.

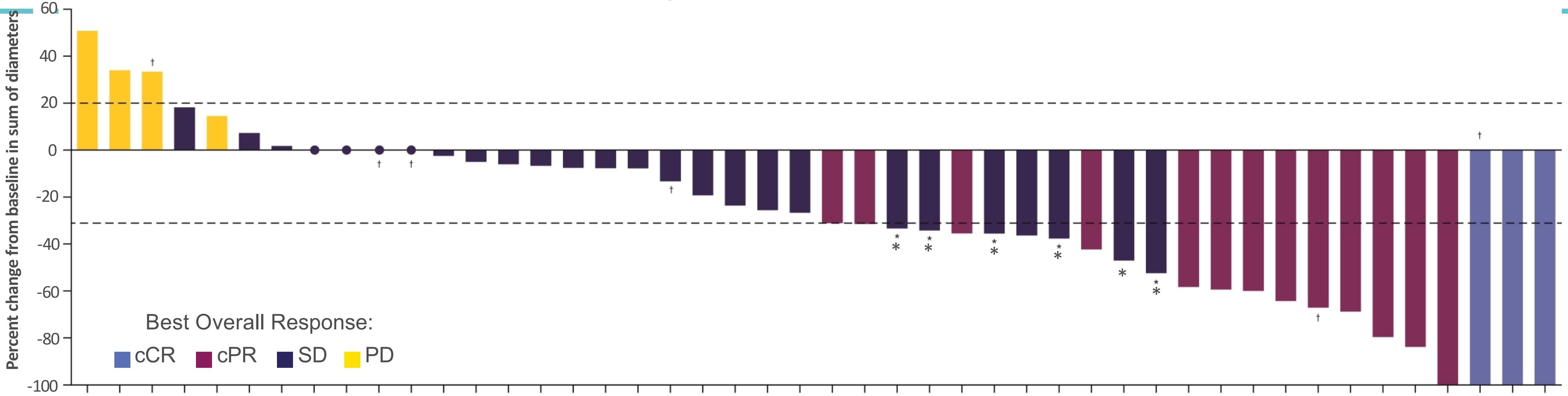
Efficacy and Duration of Treatment

- Median (range) follow-up time: 16 (2-32) months
- Median (range) duration of zanidatamab treatment: 8 (1-30) months

	All Patients (N=51)	ccHER2+ Subset (n=32)	non-ccHER2+ Subset (n=19)
PFS6, n (%) [95% CI]	34 (**67**) [52, 79]	22 (**69**) [50, 84]	12 (**63**) [38, 84]
Median PFS, months (95% CI)	12 (8, 15)	15 (9, 17)	8 (4, 9)
cORR, n (%) [95% CI][a]	16 (35) [21, 50]	14 (48) [29, 68]	2 (10) [1, 33]
cBOR, n (%)[a]			
CR	3 (6)	3 (10)	0 (0)
PR	13 (28)	11 (38)	2 (12)
SD	26 (56)	13 (45)	13 (76)
PD	4 (9)	2 (7)	2 (12)
DCR, n (%) [95% CI]	42 (91) [79, 98]	27 (93) [77, 99]	15 (88) [64, 98]
Median DOR, months (95% CI)[b]	15 (12, 25)	14 (11, 25)	NE (7, NE)[c]

[a]Evaluated in patients with measurable disease (n=46 all patients; n=29 ccHER2+ subset; n=17 non-ccHER2+ subset. [b]Evaluated in patients with a CR or PR (n=16 all patients; n=14 ccHER2+ subset; n=2 non-ccHER2+ subset). [c]Median DOR was 7.1 and 24.1 months for the 2 patients with a response in the non-ccHER2+ subset.

Efficacy of Treatment by Best Overall Response (All Patients With Measurable Disease)



Central IHC	1+	3+	1+	2+	2+	2+	1+	2+	2+	2+		1+	2+	2+	3+	0	1+	2+	2+	3+	1+	1+	2+	2+	3+	0	3+	3+	2+	2+	3+	3+	3+	2+	2+	2+	3+	3+	3+	2+	2+	3+	3+	3+	3	2
Central FISH	-	+	-	+	+	+		+	+	-			-	+	+	-	+	+		+	-	-	-	+	+	-	+	+	-	+	+	+	+	+		-	-	+	+	+	+	+	+	+	++	++
PAM50		LB		HE	HE		HE		LB	LB		HE						HE		HE	LB	LB	HE		HE	HE	HE	HE	LB	LB			HE	HE	LB		LB				HE	LB				HE
Prior fulv			Y			Y				Y	Y					Y			Y														Y						Y					Y		
Prior HER2 Trt[a]	DPX	DP CX	DP	DPC	DP CX	DP CX	DPC	DPL	PC LN	DP	DP	DLX	DP	DPC	DL	DPL	DP	DPC	DL	DP	DPC	DP	DP	DP CN	DPL	DPX	DPC	DP CM	DPX	DL	DP	DP	DPL	DLX	D	DP	DPX	DP	DP	DP	DP	DX	D	D	DP	DP

Prior HER2 trt[a]: C, tucatinib; D, T-DM1; L, lapatinib; M, margetuximab; N, neratinib; P, pertuzumab; X, T-DXd.

PAM50 subtype: HE, HER2-enriched; LB, luminal B.

*Indicates patients with unconfirmed partial responses. Dotted lines indicate -30% and +20% change in tumor size.

[a]All patients received prior trastuzumab and taxane.

HER2 Amplified tumors

- HERB TEA study (older patients)
- HER2-Climb 02 study

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A phase III study comparing trastuzumab emtansine with trastuzumab, pertuzumab, and docetaxel in older patients with advanced-stage HER2- positive breast cancer. (JCOG1607 HERB TEA study)

Akihiko Shimomura, Kenji Tamura, Keita Sasaki, Ryo Sadachi, Akihiko Suto, Masataka Sawaki, Yasuaki Sagara, Naohito Yamamoto, Tomoyuki Yoshiyama, Takako Hayashi, Eriko Tokunaga, Takashi Yamanaka, Chikako Shimizu, Tadahiko Shien, Hiroji Iwata

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JCOG Japan Clinical Oncology Group

Study Design

Primary endpoint:
Overall survival (OS)
Secondary endpoints:
Progression-free survival, Cumulative breast cancer specific survival, Response rate, Adverse events, Serious adverse events, Proportion of non-deteriorating of instrumental activities of daily living

- Older patients with advanced HER2-positive breast cancer
- No prior chemotherapy for MBC
- Over 65 years and old
- PS 0 to 2 (0 to 1 for over 75 y.o.)

R

N=148

Arm A: HPD arm (N=75)

Trastuzumab (6 mg/kg, loading dose 8 mg/kg)
+ Pertuzumab (420 mg, loading dose 840 mg)
+ Docetaxel (60 mg/m²) q3w
until PD

The dose up of Docetaxel (75 mg/m²) from the second cycle was allowed based on the data regarding safety during the first cycle.

Arm B: T-DM1 arm (N=73)

T-DM1 (3.6 mg/kg) q3w
until PD

*Planned sample size: 250 Pts. Terminated early at 148 Pts by interim analysis because the OS hazard ratio estimate exceeded the non-inferiority margin (data cutoff 12/22/2022). The data cutoff for this presentation is 6/15/2023.

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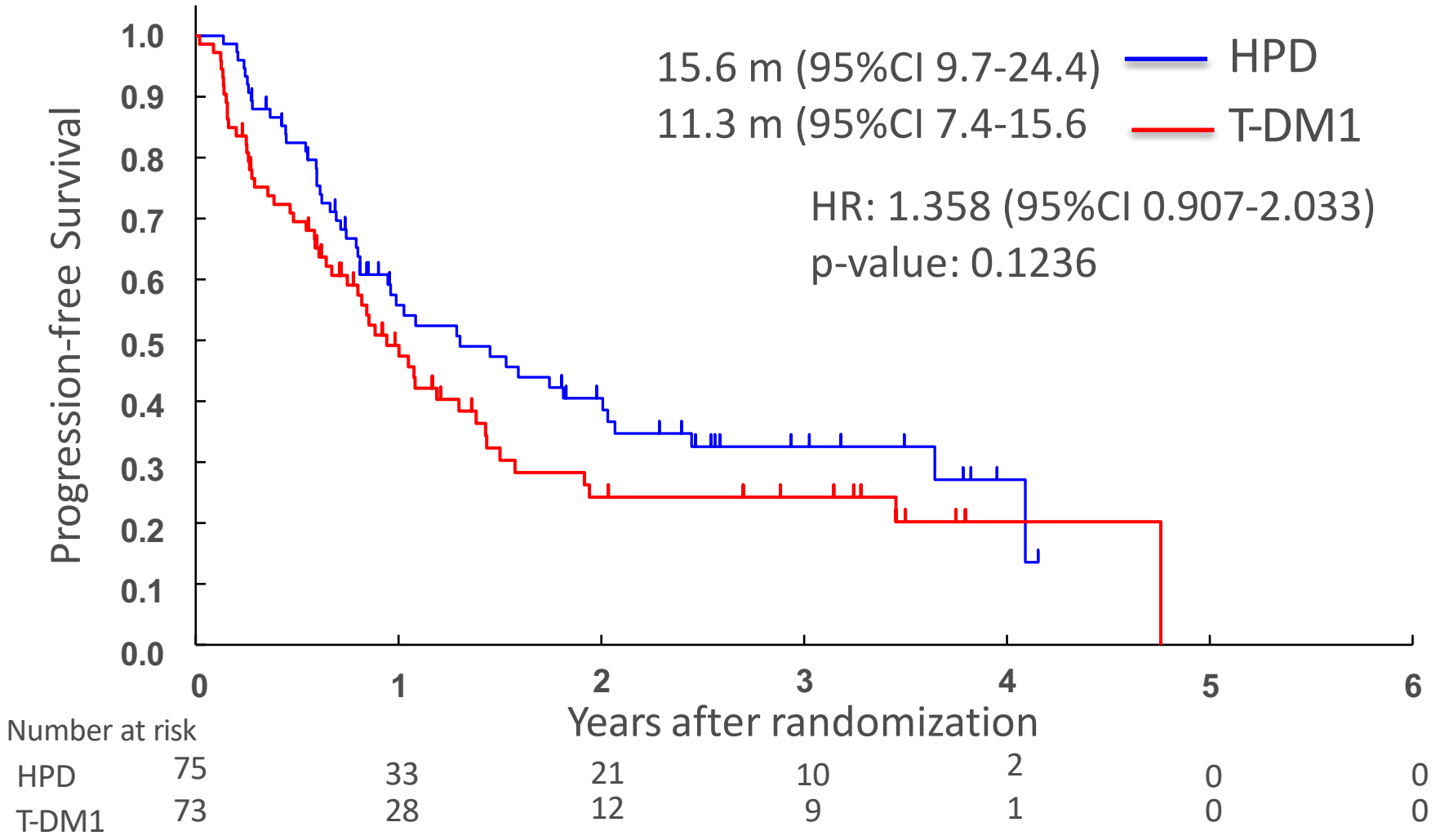
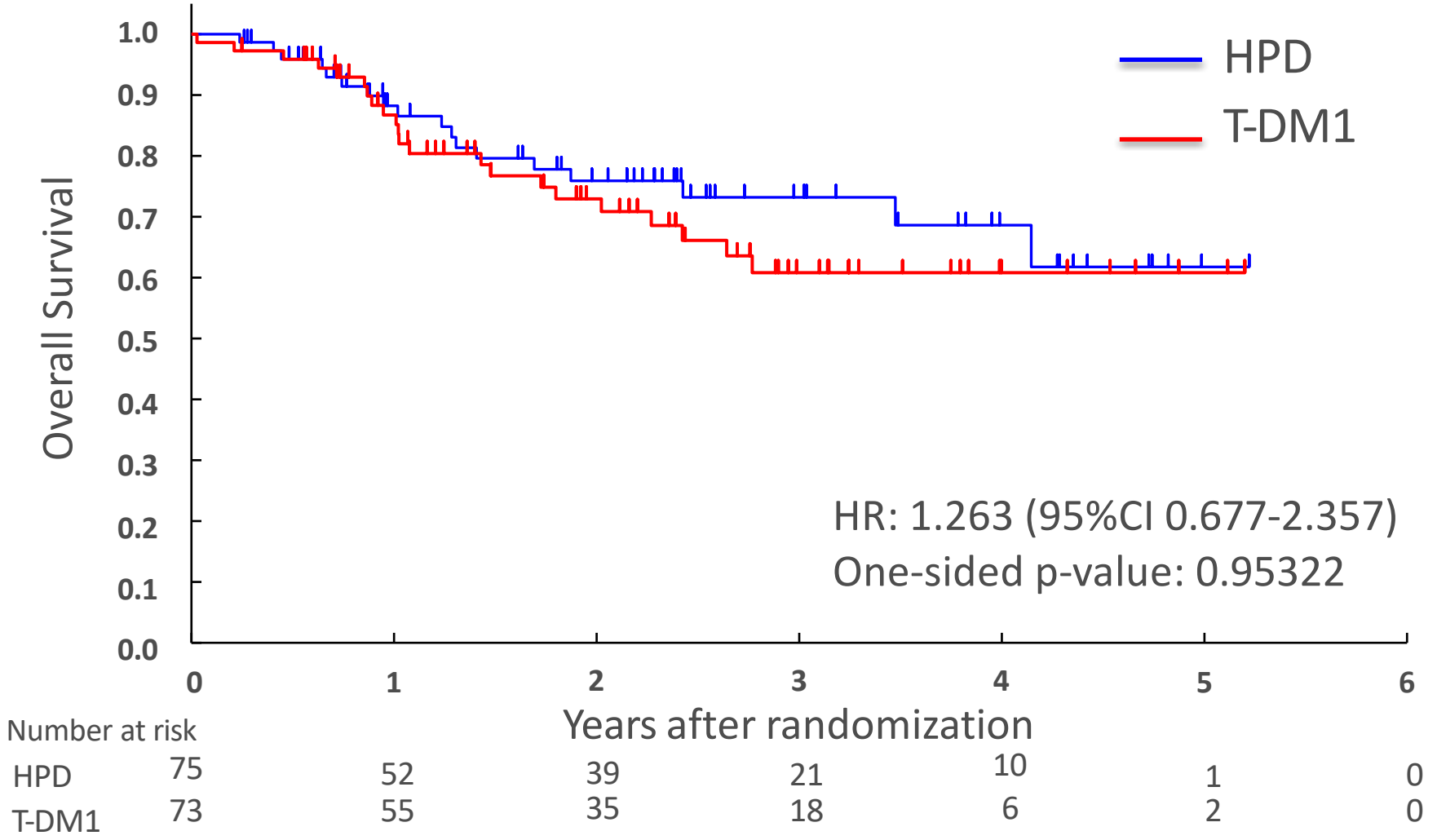
Progression-free Survival



Overall Survival



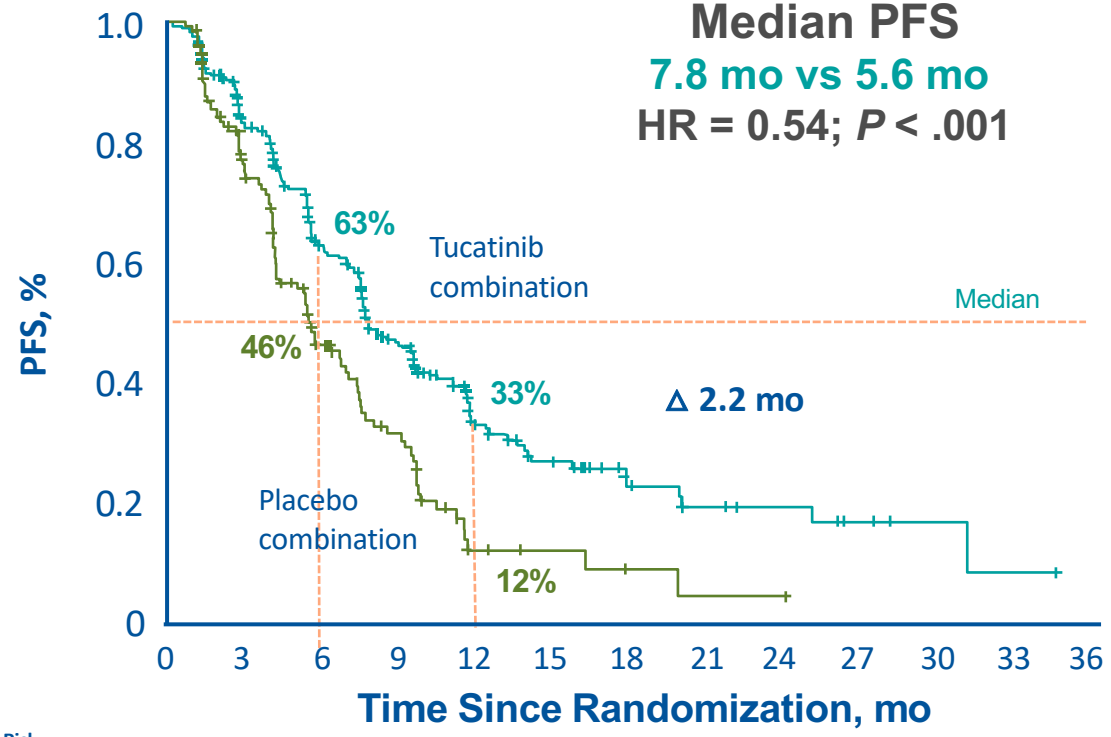
Conclusions

- T-DM1 failed to show non-inferiority to HPD in OS and PFS.
- Adverse events grade 3 and more are more frequent in the HPD arm, especially leukopenia, neutropenia, diarrhea, fatigue and appetite loss were common.
- HPD therapy is the standard of care as 1st line treatment for HER2-positive advanced breast cancer regardless of age.
- Detailed analysis, including geriatric assessment, is needed to identify the patient population for whom T-DM1 may be used as 1st line treatment.

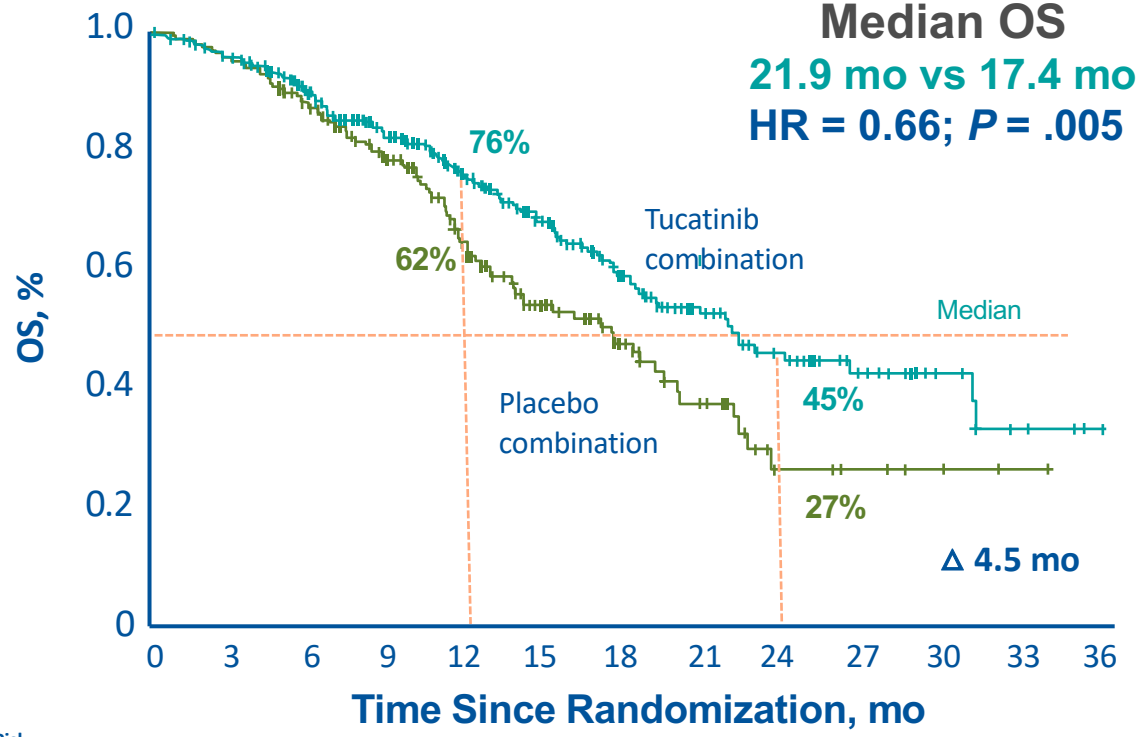
HER2CLIMB: Randomized Phase 2 Trial of Tucatinib[1]

Tucatinib + Capecitabine + Trastuzumab vs Capecitabine + Trastuzumab

Tucatinib Improves PFS and OS



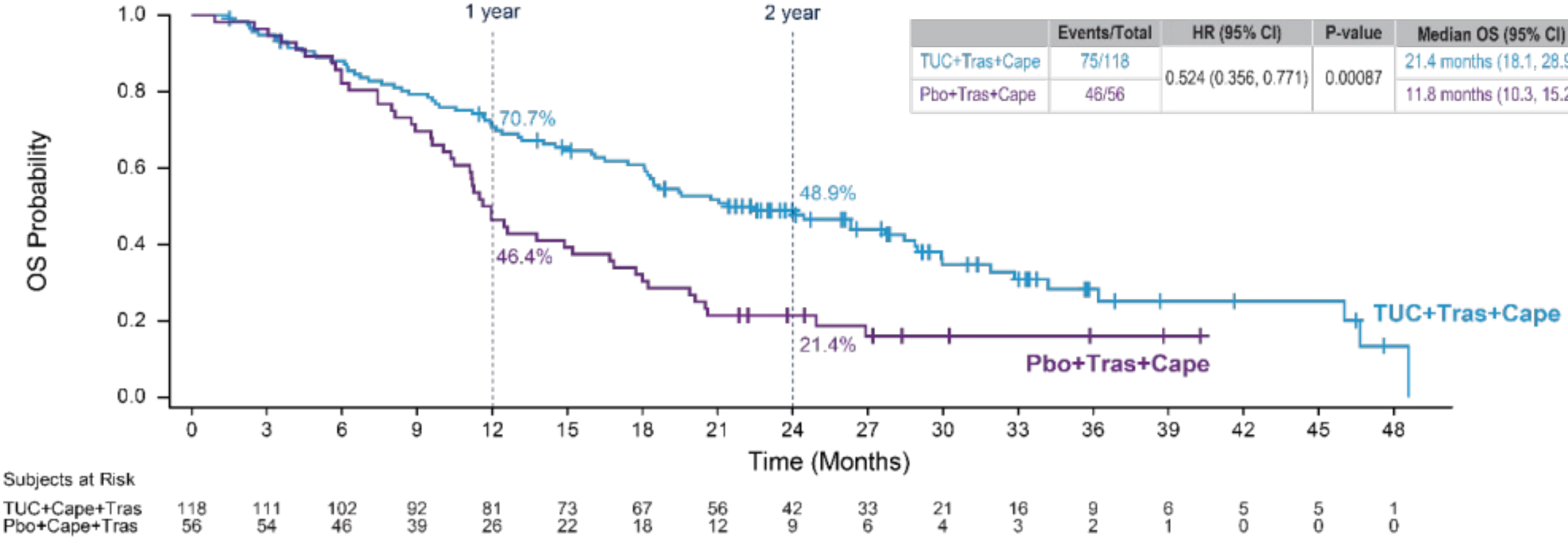
No. at Risk													
Tuc + tras + cape	320	235	152	96	40	29	15	10	8	4	2	1	0
Pbo + tras + cape	160	94	45	27	6	4	2	1	1	0	0	0	0



No. at Risk													
Tuc + tras + cape	410	388	322	245	178	123	80	51	34	20	10	4	0
Pbo + tras + cape	202	191	160	119	77	48	32	19	7	5	2	1	0

Murthy R, et al. *N Engl J Med*. 2020;382:597-609.

HER2CLIMB: OS for Patients With Active Brain Metastases



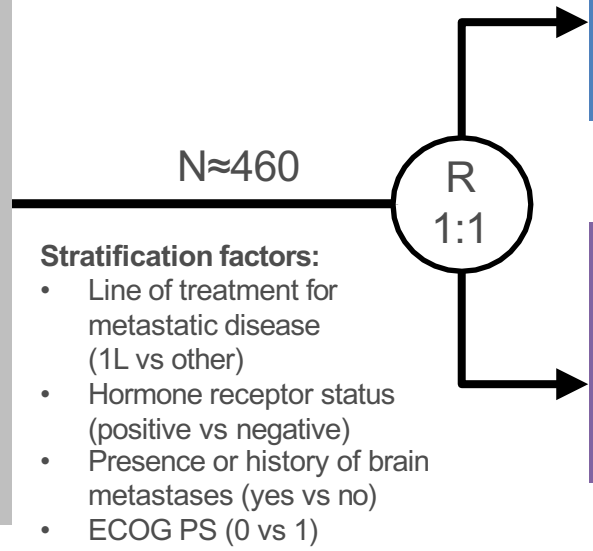
	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	75/118	0.524 (0.356, 0.771)	0.00087	21.4 months (18.1, 28.9)
Pbo+Tras+Cape	46/56			11.8 months (10.3, 15.2)

Median OS was 9.6 months longer in the tucatinib arm compared with the control arm in patients with active brain metastases.

Lin NU, et al. SABCS 2021. Abstract PD4-04.

HER2CLIMB-02 Study Design

- 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



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)

Tucatinib (TUC) + T-DM1

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

Placebo (PBO) + T-DM1

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

Outcomes

Primary
- PFS by investigator assessment per RECIST v1.1

Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7.
The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive[b].

HER2CLIMB-02: Demographics and Baseline Characteristics

	TUC + T-DM1 (N=228)	PBO + T-DM1 (N=235)
Median age, years (range)	55.0 (26-83)	53.0 (27-82)
Female sex, n (%)	226 (99.1)	235 (100)
Geographic region, n (%)		
North America	105 (46.1)	93 (39.6)
Europe/Israel	53 (23.2)	77 (32.8)
Asia-Pacific	70 (30.7)	65 (27.7)
Hormone-receptor status, n (%)		
Positive	137 (60.1)	140 (59.6)
Negative	91 (39.9)	95 (40.4)
ECOG performance status score, n (%)		
0	137 (60.1)	141 (60.0)
1	91 (39.9)	94 (40.0)

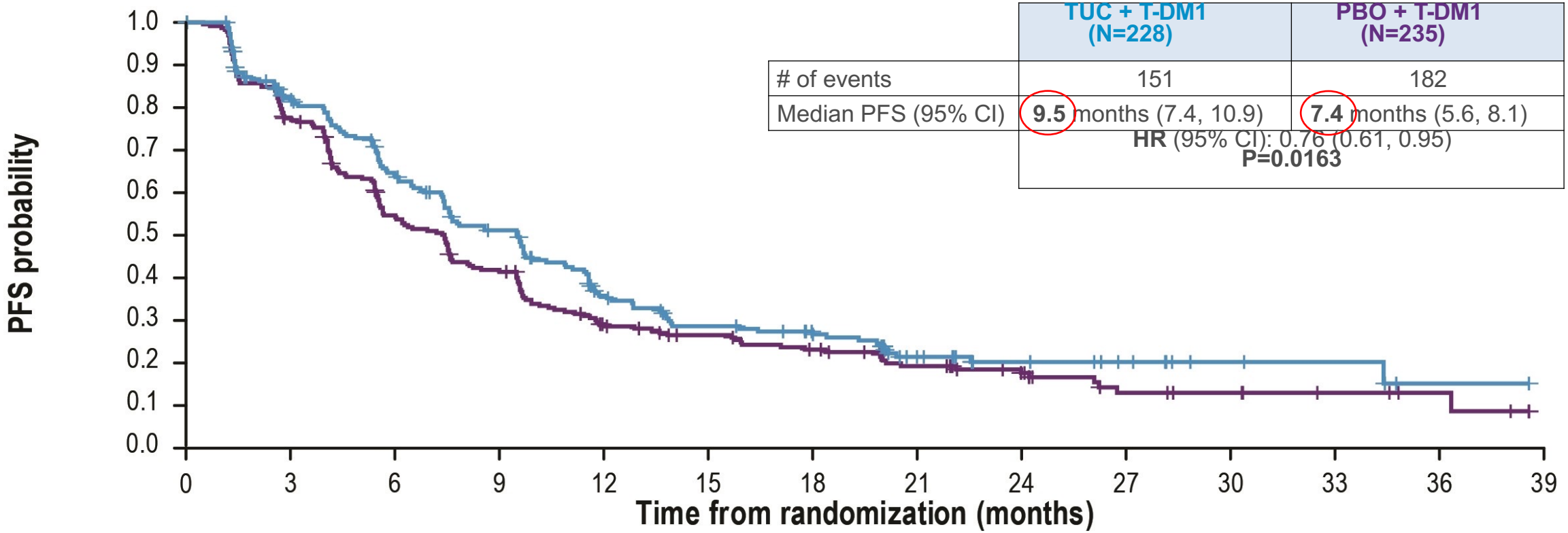
	TUC + T-DM1 (N=228)	PBO + T-DM1 (N=235)
Presence or history of brain metastases, n (%)		
Yes	99 (43.4)	105 (44.7)
Active	50 (21.9)	57 (24.3)
Treated stable	49 (21.5)	48 (20.4)
No[a]	129 (56.6)	130 (55.3)
Stage at initial diagnosis, n (%)[b]		
0-III	120 (52.6)	130 (55.3)
IV	103 (45.2)	98 (41.7)

HER2CLIMB-02: Prior Systemic Therapies

	TUC + T-DM1 (N=228)	PBO + T-DM1 (N=235)
Median prior lines of systemic therapy in metastatic setting (range)	1 (0-8)	1 (0-6)
Prior lines of systemic therapy in metastatic setting, n (%)		
0	29 (12.7)	33 (14.0)
1	146 (64.0)	150 (63.8)
2	36 (15.8)	31 (13.2)
≥3	17 (7.5)	21 (8.9)
Received prior pertuzumab treatment, n (%)	202 (88.6)	214 (91.1)
Received prior anti-HER2 TKIs, n (%)	3 (1.3)	5 (2.1)

HER2CLIMB-02: Progression-Free Survival

	TUC + T-DM1 (N=228)	PBO + T-DM1 (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**	



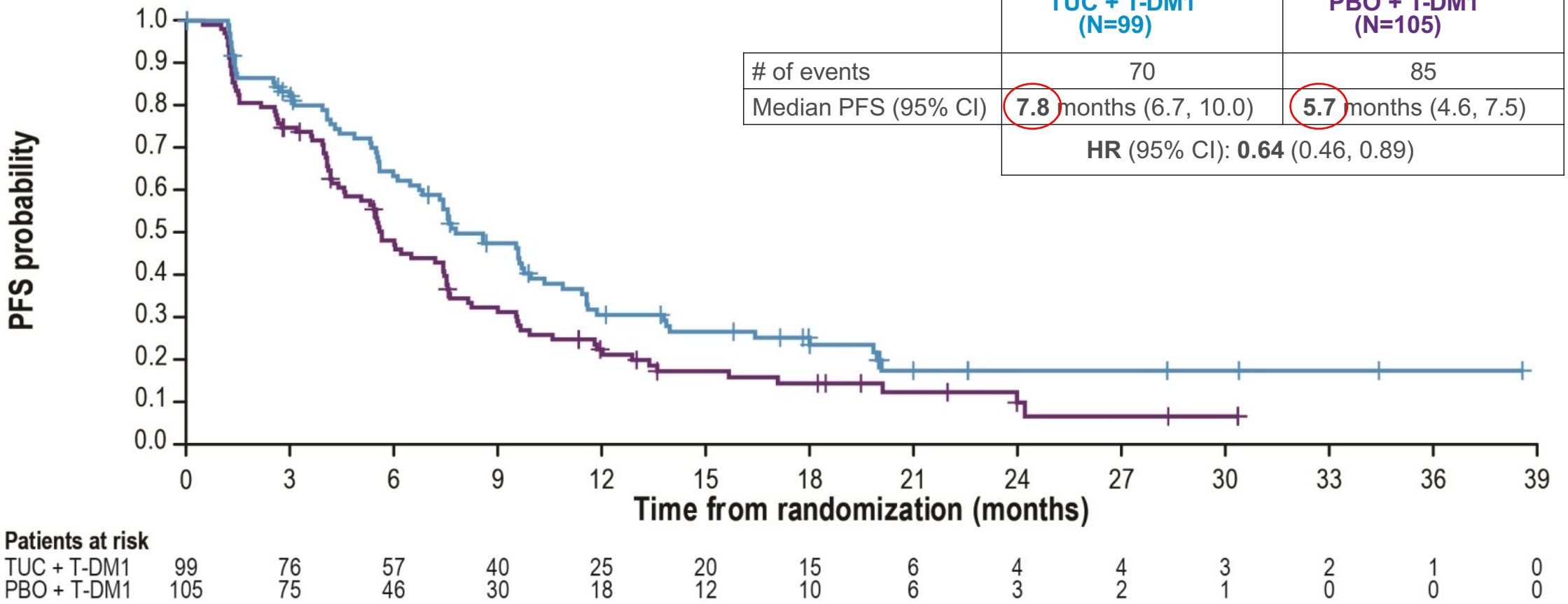
Patients at risk

TUC + T-DM1	228	165	126	96	62	47	40	22	14	10	5	4	1	0
PBO + T-DM1	235	177	120	91	58	48	40	29	19	10	8	5	3	0

HR, hazard ratio; PBO, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TUC, tucatinib.
Date of data cutoff: Jun 29, 2023.

HER2CLIMB-02: PFS in Patients with Brain Metastases[a]

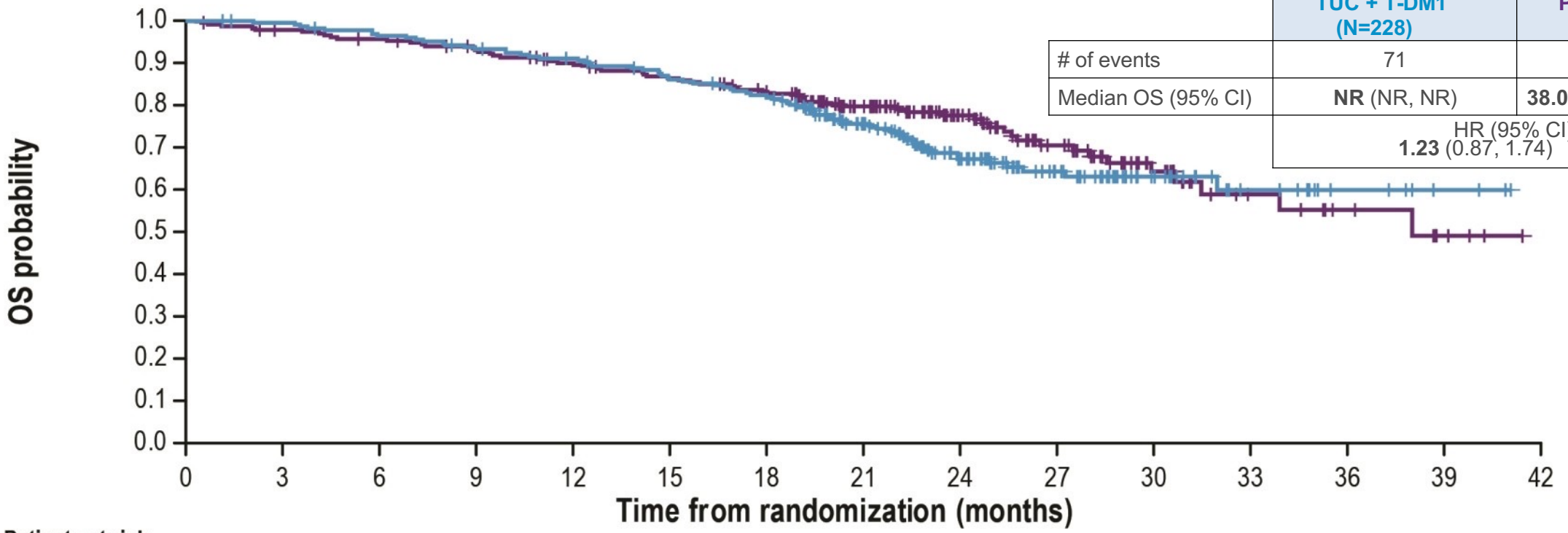
	TUC + T-DM1 (N=99)	PBO + T-DM1 (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
	HR (95% CI): **0.64** (0.46, 0.89)	



a The outcome was not formally tested.
HR, hazard ratio; PBO, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TUC, tucatinib.
Date of data cutoff: Jun 29, 2023.

HER2CLIMB-02: Overall Survival

	TUC + T-DM1 (N=228)	PBO + T-DM1 (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)	



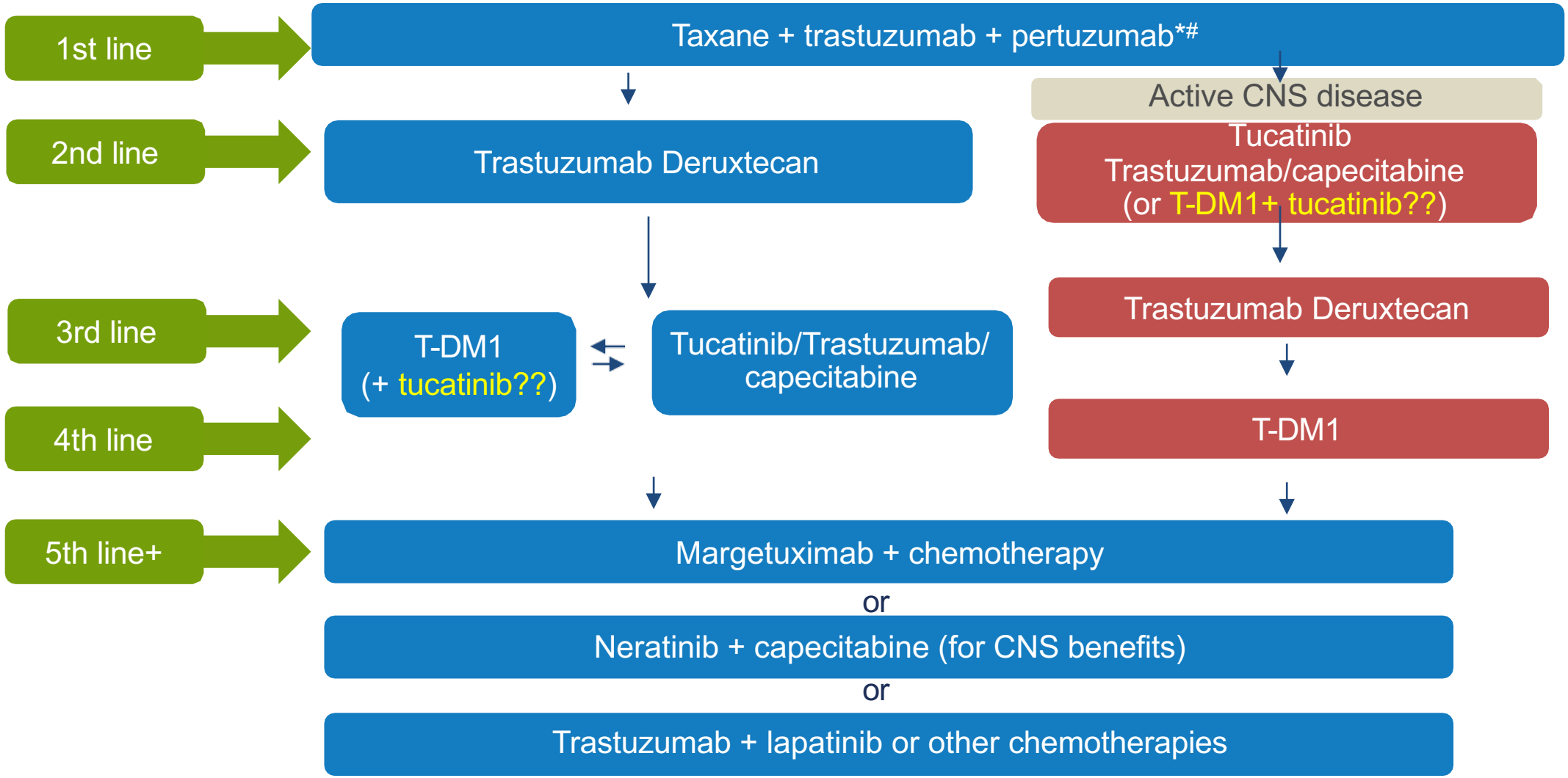
Patients at risk

TUC + T-DM1	228	225	217	209	202	189	180	132	89	55	30	16	7	3	0
PBO + T-DM1	235	227	221	212	201	191	180	135	90	58	32	16	10	4	0

Median follow-up was 24.4 months. As of data cutoff, 134 out of 253 (53%) prespecified events for the OS final analysis were observed. Interim OS results did not meet the prespecified crossing boundary of P=0.0041.

a The proportional hazard assumption was not maintained post-18 months, with heavy censoring on both arms.
HRs, hazard ratios; NR, not reached; OS, overall survival; PBO, placebo; T-DM1, trastuzumab emtansine; TUC, tucatinib.
Date of data cutoff: Jun 29, 2023.

Algorithm for Metastatic HER2+ Disease



*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

Slide adapted from Shanu Modi

Metastatic TNBC

- KEYLYNK-009 Study (Olaparib-based maintenance)
- BEGONIA study (Dato-DXd + Durvalumab; 1st line)

San Antonio Breast Cancer Symposium®, December 5–9, 2023

Pembrolizumab Plus Olaparib vs Pembrolizumab Plus Chemotherapy After Induction With Pembrolizumab Plus Chemotherapy for Locally Recurrent Inoperable or Metastatic TNBC: Randomized, Open-Label, Phase 2 KEYLYNK-009 Study

Hope S. Rugo[1]; Mark Robson[2]; Seock-Ah Im[3]; Florence Dalenc[4]; Eduardo Yañez Ruiz[5]; Young-Hyuck Im[6]; Sergii Kulyk[7]; Oleksandr Dudnichenko[8]; Néstor Llinás-Quintero[9]; Shigehira Saji[10]; Yasuo Miyoshi[11]; Nadia Harbeck[12]; Li Fan[13]; Jaime A. Mejia[13]; Vassiliki Karantza[13]; David W. Cescon[14]

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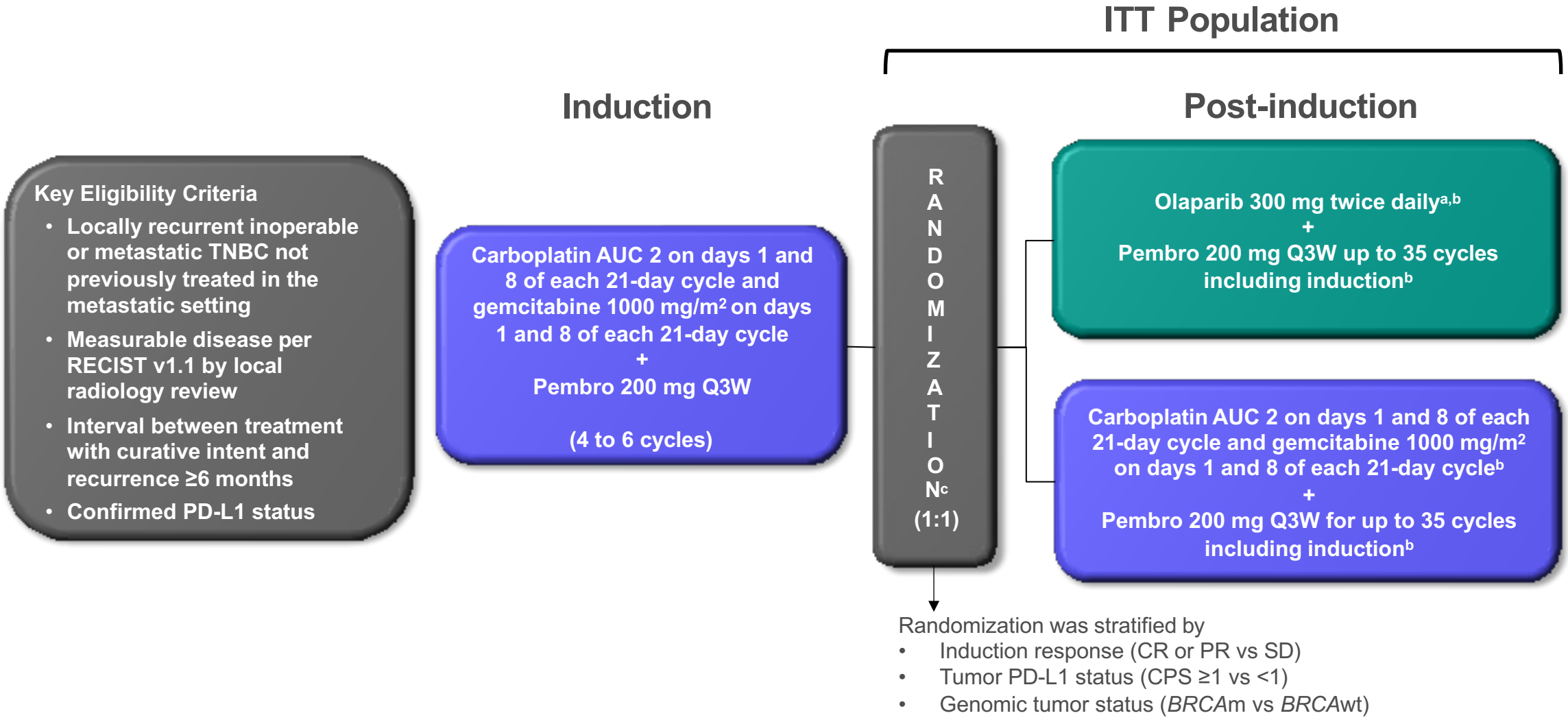
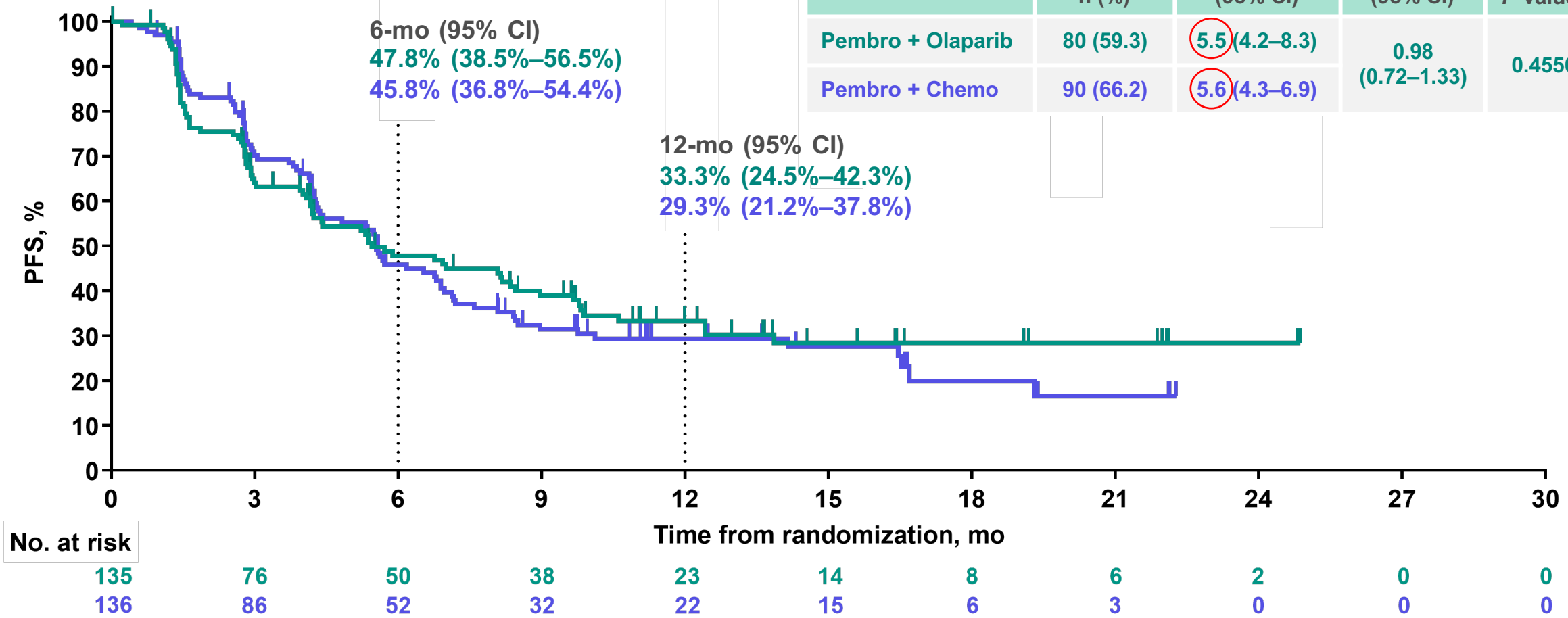
KEYLYNK-009 (NCT04191135): Study Design



[a]Olaparib was administered postinduction and given concurrently with pembrolizumab. [b]Until disease progression or unacceptable toxicity. [c]ITT population was determined from randomization (not from the time of enrollment).

PFS per RECIST v1.1 by BICR: ITT Population

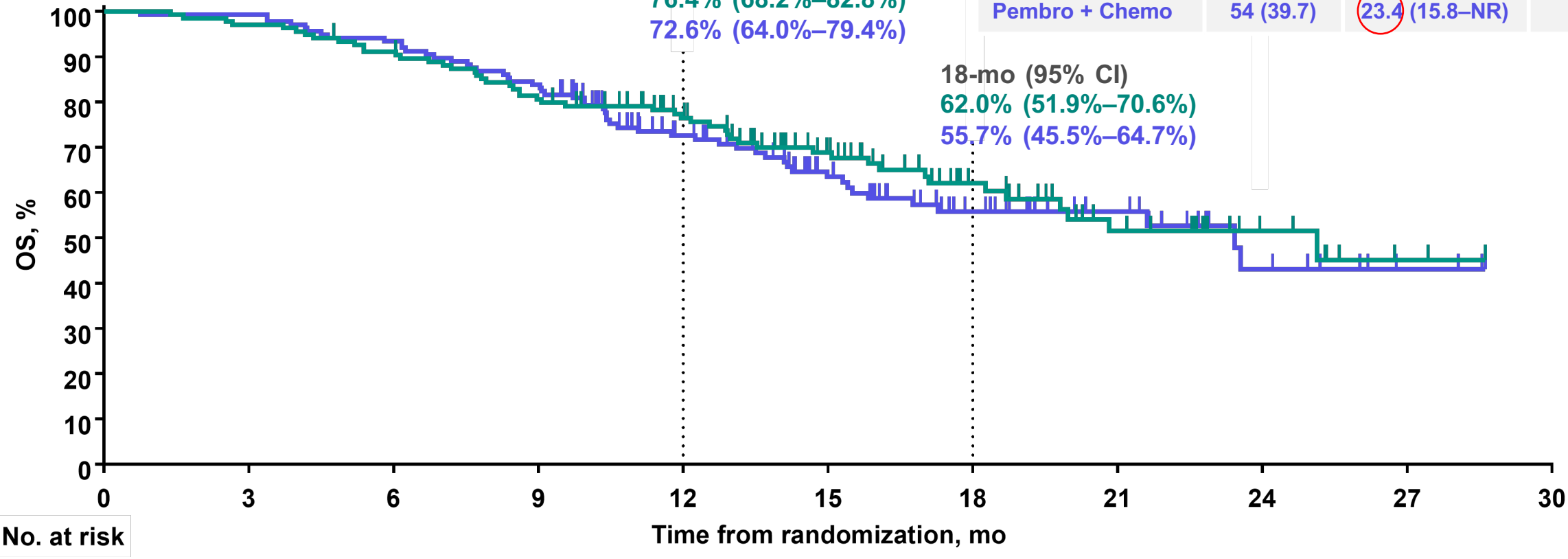
	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)	*P*-value[b]
Pembro + Olaparib	80 (59.3)	5.5 (4.2–8.3)	0.98 (0.72–1.33)	0.4556
Pembro + Chemo	90 (66.2)	5.6 (4.3–6.9)		



[a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy, tumor PD-L1 status, and *BRCA* status. [b]One-sided and based on log-rank test stratified by response to induction therapy, tumor PD-L1 status, and *BRCA* status.

Estimates of OS: ITT Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	50 (37.0)	25.1 (18.3–NR)	0.95 (0.64–1.40)
Pembro + Chemo	54 (39.7)	23.4 (15.8–NR)	



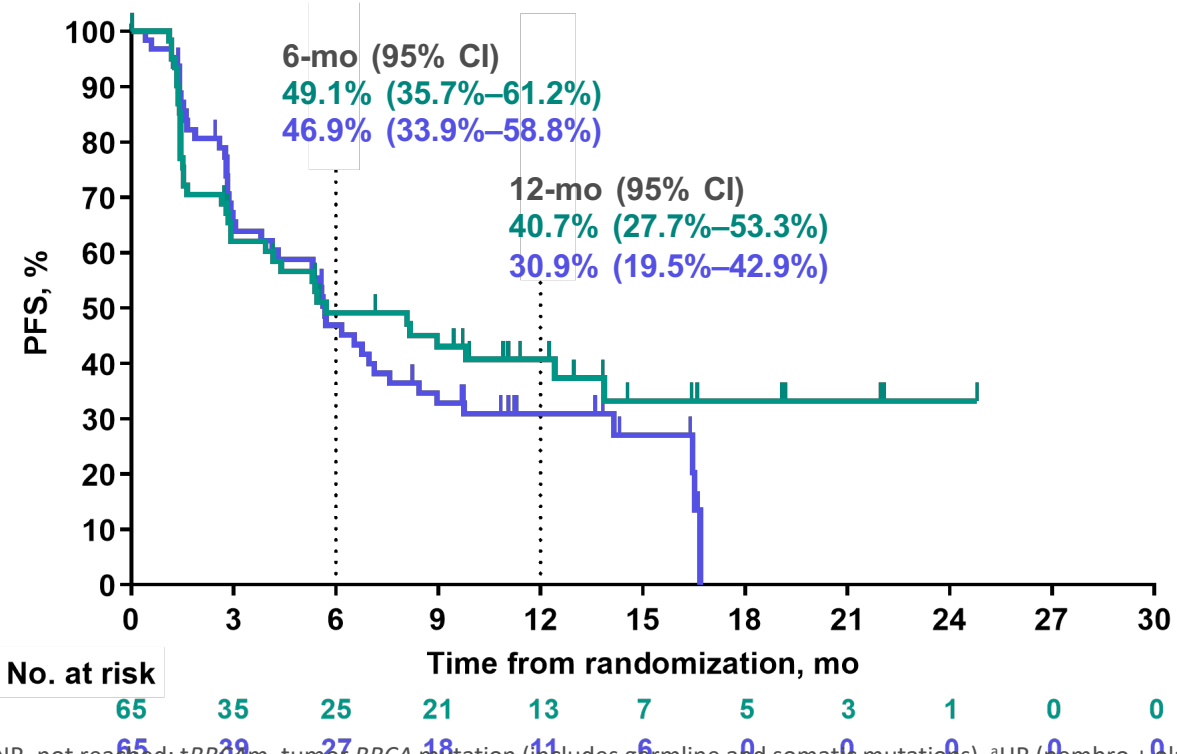
No. at risk										
135	131	122	107	87	59	36	20	9	2	0
136	135	127	114	79	54	32	21	9	3	0

NR, not reached. [a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy, tumor PD-L1 status, and *BRCA* status.

PFS per RECIST v1.1 by BICR: PD-L1 CPS ≥10 and t*BRCA*m

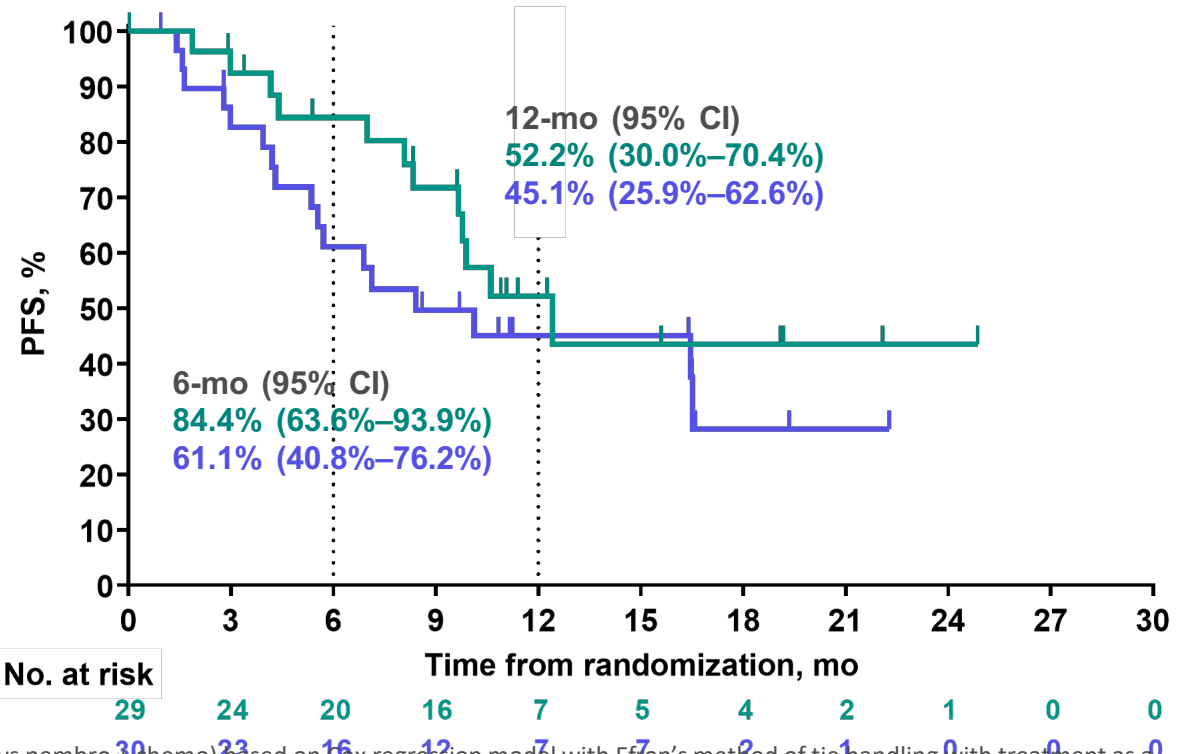
Tumor PD-L1 CPS ≥10 Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	36 (55.4)	5.7 (2.9–13.9)	0.92 (0.59–1.43)
Pembro + Chemo	45 (69.2)	5.7 (3.8–7.6)	



t*BRCA*m Population

	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	12 (41.4)	12.4 (8.3–NR)	0.70 (0.33–1.48)
Pembro + Chemo	17 (56.7)	8.4 (5.4–NR)	

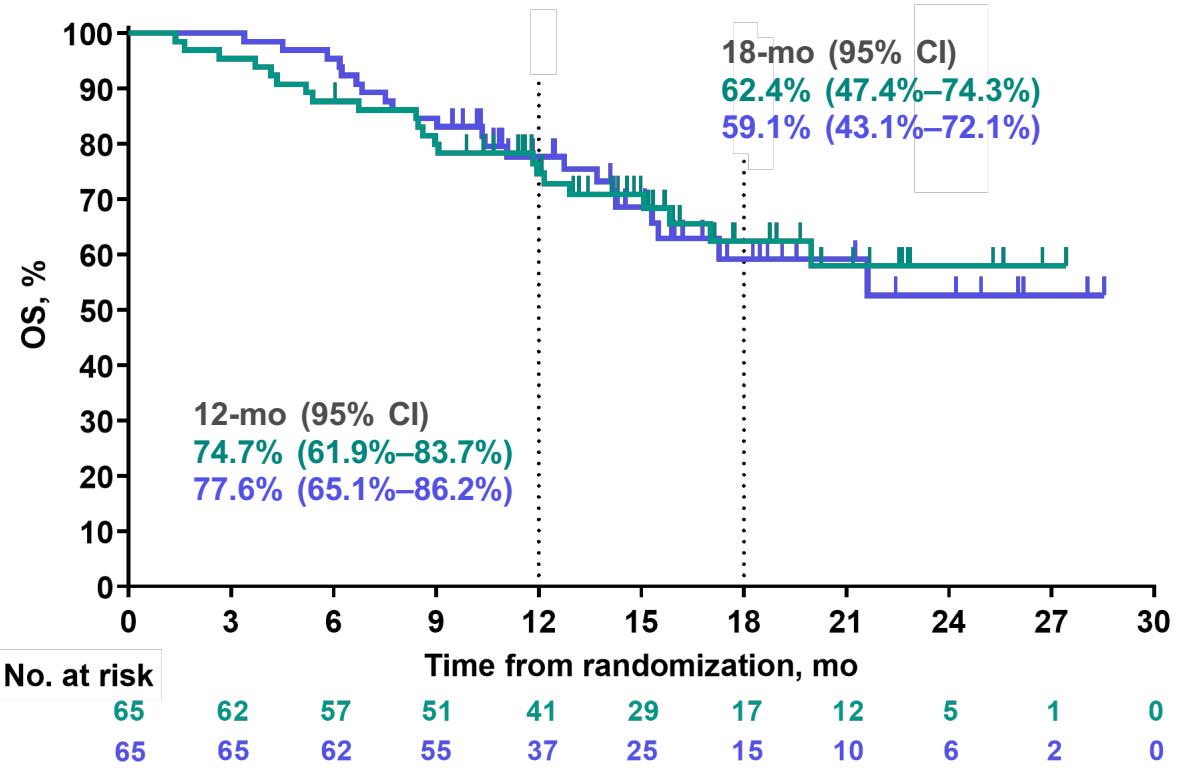


NR, not reached; t*BRCA*m, tumor *BRCA* mutation (includes germline and somatic mutations). [a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and *BRCA* status. [b]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and tumor PD-L1 status.

Estimates of OS: PD-L1 CPS ≥10 and t*BRCA*m

Tumor PD-L1 CPS ≥10 Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	22 (33.8)	NR (17.0–NR)	0.97 (0.53–1.76)
Pembro + Chemo	22 (33.8)	NR (15.5–NR)	

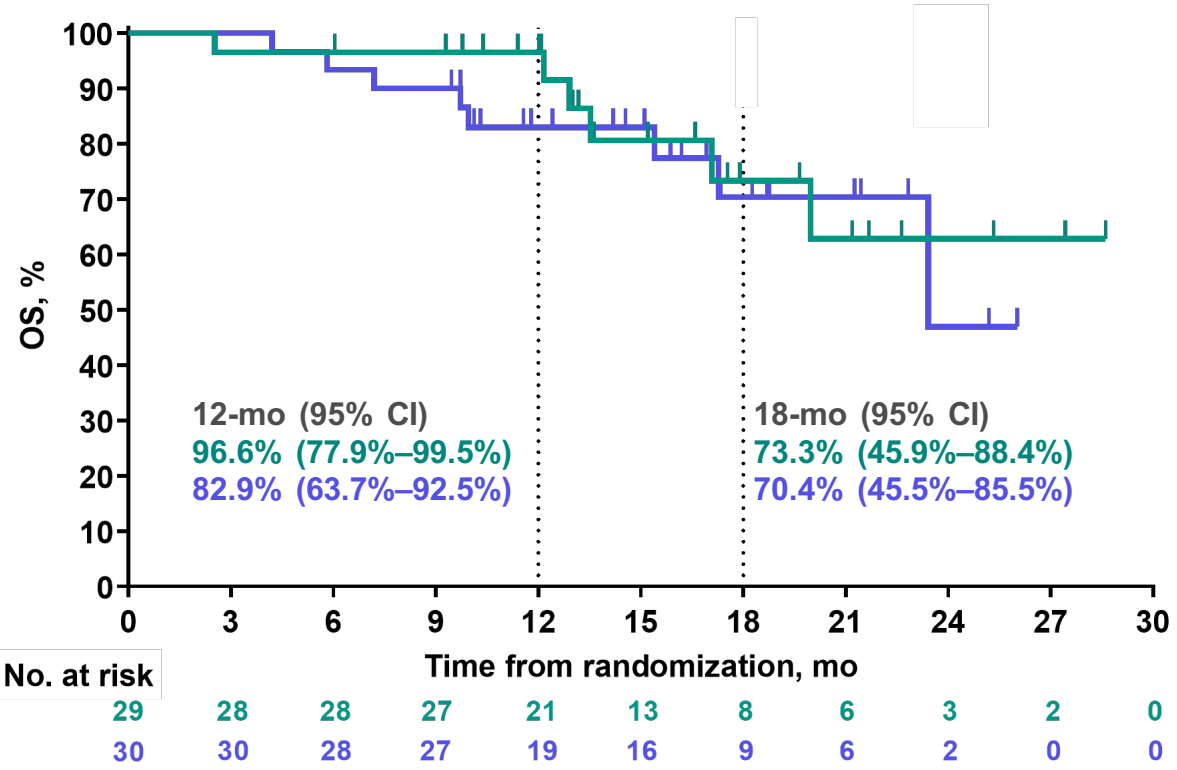


No. at risk

65	62	57	51	41	29	17	12	5	1	0
65	65	62	55	37	25	15	10	6	2	0

t*BRCA*m Population

	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	6 (20.7)	NR (17.1–NR)	0.81 (0.28–2.37)
Pembro + Chemo	8 (26.7)	23.4 (17.3–NR)	



No. at risk

29	28	28	27	21	13	8	6	3	2	0
30	30	28	27	19	16	9	6	2	0	0

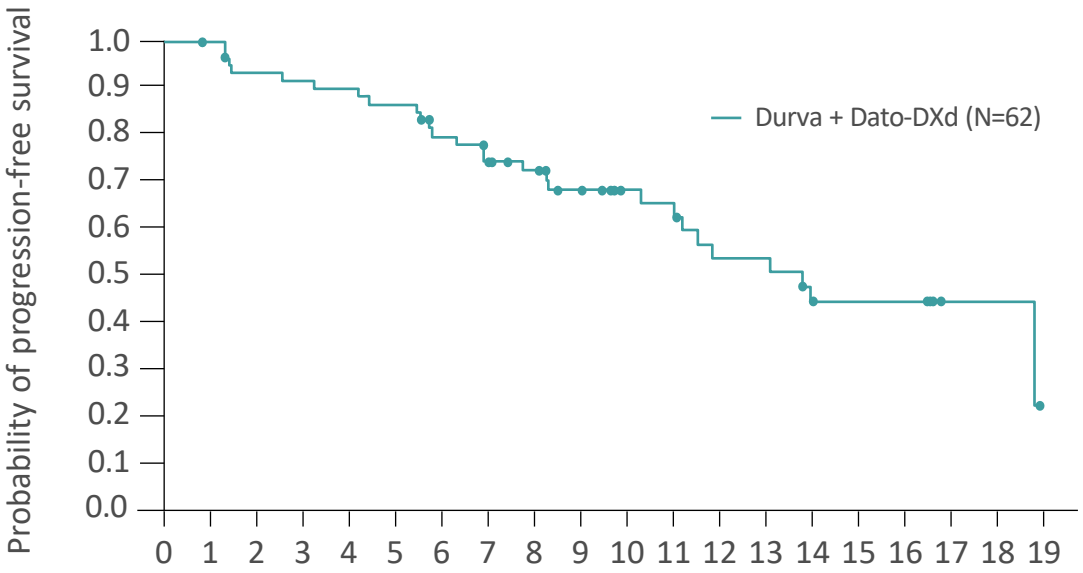
NR, not reached. [a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and *BRCA* status. [b]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and tumor PD-L1 status.

BEGONIA Arm 7: Dato-DXd + Durvalumab

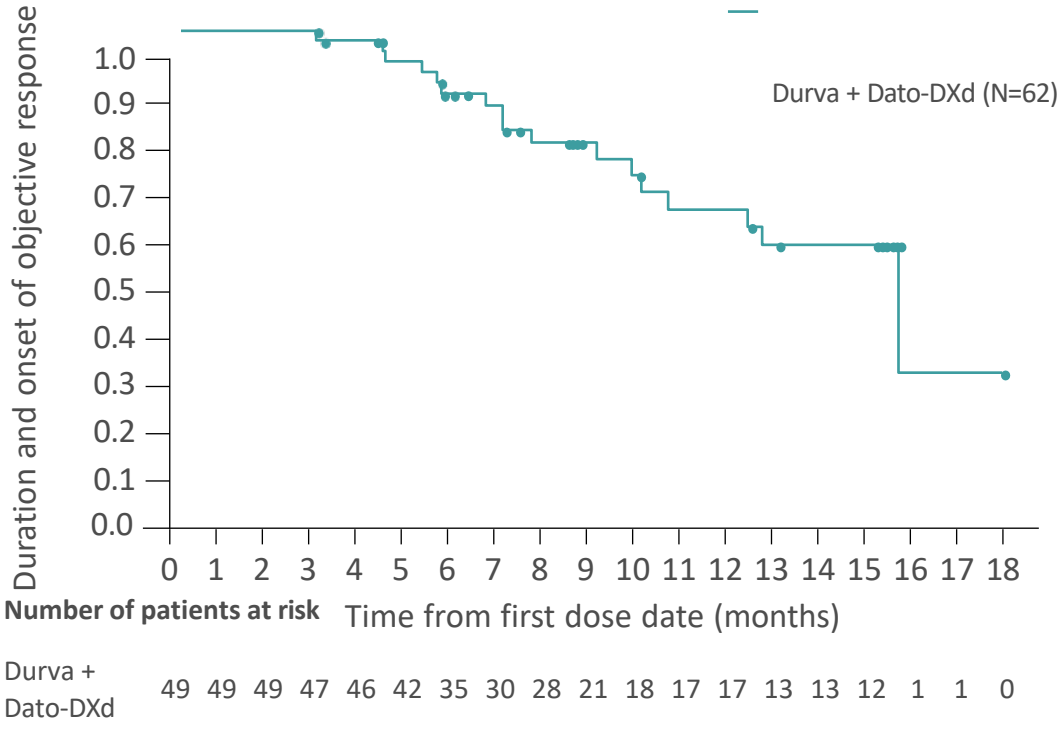
Antitumour Responses in 1L a/mTNBC (n=62)

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR Antitumor responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods

Median PFS was **13.8** months (95% CI, 11.0–NC)



Median DoR was **15.5** months (95% CI, 9.92–NC)



Kaplan-Meier analysis was performed. Circles indicate censored observations.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; PFS, progression-free survival.

Schmid, et al. ESMO 2023

Thank you