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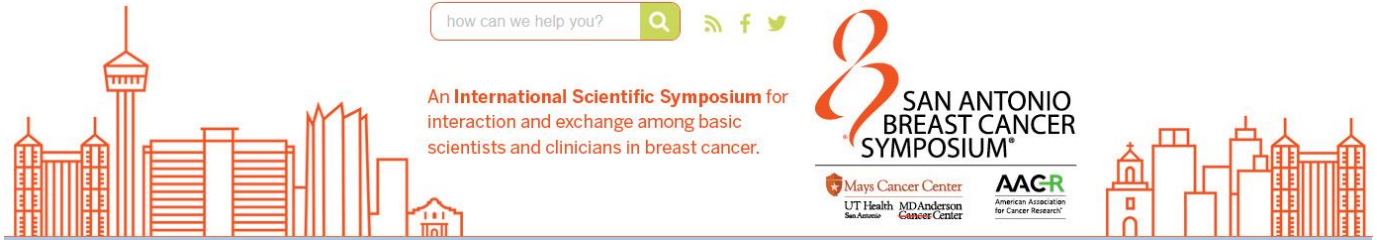
Neues zur Therapie des metastasierten Mammakarzinoms



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Universitäres Centrum für Tumorerkrankungen
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Conflict of Interest (COI)

- Forschungsunterstützung:
  - AstraZeneca, BioNTech, Eisai, Genentech, Novartis, Pantarhei Bioscience, Pfizer, Pierre-Fabre, Roche, SeaGen
- Vortragsstätigkeit:
  - AstraZeneca, Daiichi Sankyo, Eisai, GILEAD, Lilly, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, SeaGen
- Beratertätigkeit:
  - AstraZeneca, BioNTech, Daiichi Sankyo, Eisai, GILEAD, Lilly, MSD, Novartis, Pantarhei Bioscience, Pfizer, Pierre-Fabre, Roche, SeaGen

ER-positiv?

MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy for HR+, HER2- advanced breast cancer

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MONARCH 3 Study Design

Eligibility Criteria:

- HR+, HER2- ABC
- Postmenopausal
- Metastatic or locoregionally recurrent disease with no prior systemic therapy in this setting
- If (neo)adjuvant ET administered, a disease-free interval of >12 months since completion of ET
- ECOG PS ≤1

N=493

Randomization 2:1

abemaciclib 150 mg PO BID +
anastrozole 1 mg or
letrozole 2.5 mg PO QD until PD[a]

placebo PO BID +
anastrozole 1 mg or
letrozole 2.5 mg QD until PD[a]

Primary endpoint[6]
Investigator-assessed PFS

Key secondary endpoints
Overall survival, response rates, safety

Exploratory endpoint
Chemotherapy-free survival

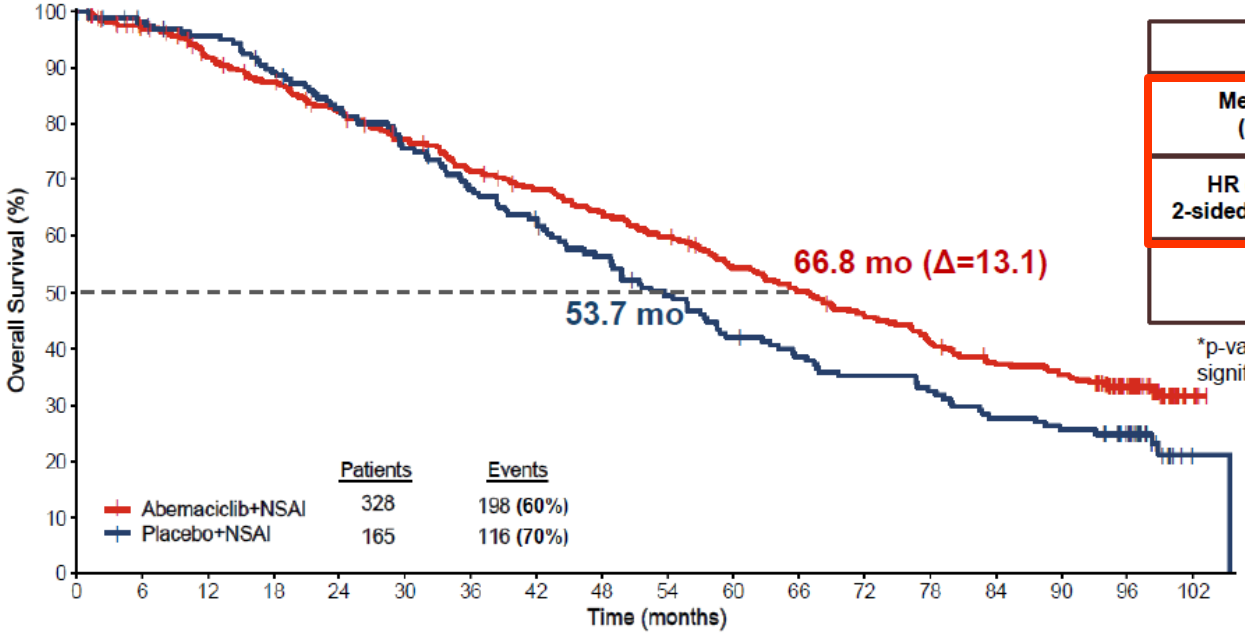
Stratification factors
- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

MONARCH 3 enrolled from November 2014 to November 2015 in 158 centers from 22 countries

[a]per physician's choice: 79.1% received letrozole, 19.9% received anastrozole

[6]Goetz MP, et al. *J Clin Oncol.* 2017;35(32):3638-3646

OS in the ITT Population



	abemaciclib + NSAI	placebo + NSAI
Median OS (months)	66.8	53.7
HR (95% CI) 2-sided *P* value	0.804 (0.637-1.015) p=0.0664*	

Final OS Analysis
Data cut: 29 Sep 2023

*p-value did not reach threshold (0.034) for statistical significance at this final analysis

Number at Risk

Abemaciclib+NSAI	328	304	281	266	247	229	211	199	187	174	156	144	131	117	104	99	66	6
Placebo+NSAI	165	155	149	138	127	116	104	95	84	73	62	56	51	47	40	37	28	1

Abemaciclib in combination with a NSAI resulted in longer OS compared to NSAI alone; however, statistical significance was not reached. The observed improvement in median OS was 13.1 months.

Post-Discontinuation Therapy

Parameter, n (%)*	abemaciclib + NSAI N=328	placebo + NSAI N=165
Patients who received subsequent systemic therapy	234 (71)	142 (86)
Endocrine therapy	196 (60)	121 (73)
Chemotherapy	136 (41)	102 (62)
Targeted agent therapy	94 (29)	80 (48)
Other	39 (12)	29 (18)
Patients who received a CDK4/6 inhibitor in any subsequent line	38 (12)	52 (32)
Palbociclib	25 (8)	41 (25)
Abemaciclib	10 (3)	7 (4)
Palbociclib + abemaciclib	2 (<1)	2 (1)
Ribociclib	1 (<1)	2 (1)

* Denominator used to calculate % corresponds to ITT population. 284 (86.6%) in the abemaciclib arm and 154 (93.3%) in the placebo arm entered the post-treatment discontinuation follow-up.

During follow-up, many patients received additional therapies post-progression which can impact OS.

Long-Term Safety of Abemaciclib

	abemaciclib + NSAI N=327		placebo + NSAI N=161	
TEAEs ≥30% in abemaciclib arm, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any	323 (99)	227 (69)	152 (94)	46 (29)
Diarrhea	273 (83)	32 (10)	55 (34)	2 (1)
Neutropenia	153 (47)	90 (28)	3 (2)	2 (1)
Fatigue	144 (44)	7 (2)	58 (36)	0
Nausea	137 (42)	4 (1)	37 (23)	2 (1)
Anemia	115 (35)	31 (9)	16 (10)	2 (1)
Abdominal pain	108 (33)	6 (2)	27 (17)	2 (1)
Vomiting	106 (32)	5 (2)	24 (15)	4 (2)

No new safety signals were observed with long-term use of abemaciclib.

Conclusions

- With a median follow-up of 8.1 years, abemaciclib in combination with a NSAI resulted in numerically longer OS compared to NSAI alone; however, statistical significance was not reached
  - Clinically meaningful improvement in median OS: 13.1 months (66.8 vs 53.7 months) in the ITT and 14.9 months (63.7 vs 48.8 months) in the subgroup with visceral disease
- The previously demonstrated PFS benefit persists, with substantial differences well beyond 5 years
  - Median PFS improvement: 14.3 months
  - 6-year PFS rates: 23.3% vs 4.3% for abemaciclib vs placebo
- Abemaciclib delayed subsequent receipt of chemotherapy (median improvement of 16.1 months)
- No new safety concerns were observed with prolonged exposure to abemaciclib
- These results continue to support the use of abemaciclib in combination with NSAI as first-line therapy in HR+, HER2- ABC and are consistent with results previously shown

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PARSIFAL-LONG: Extended follow-up of hormone receptor-positive/HER2-negative advanced breast cancer patients treated with fulvestrant and palbociclib vs letrozole and palbociclib in the PARSIFAL study

Antonio Llombart Cussac[1,2], José Manuel Pérez-García[1,3], Meritxell Bellet[4], Florence Dalenc[5], Miguel Gil-Gil[6], Manuel Ruiz-Borrego[7], Joaquín Gavila[8], Peter Schmid[9], Pilar Zamora[10], Duncan Wheatley[11], Eduardo Martínez-de Dueñas[12], Kepa Amillano[13], Antonio Anton[14], Paul Cottu[15], Gemma Viñas[16], Thierry Petit[17], Petra Tesarová[18], Juan Cueva[19], Marco Colleoni[20], Maria Purificación Martínez del Prado[21], Raquel Andres[22], Elena Aguirre[23], Marta Díaz[1], Susana Vitorino[1], Miguel Sampayo-Cordero[1], Javier Cortés[1,3,25]

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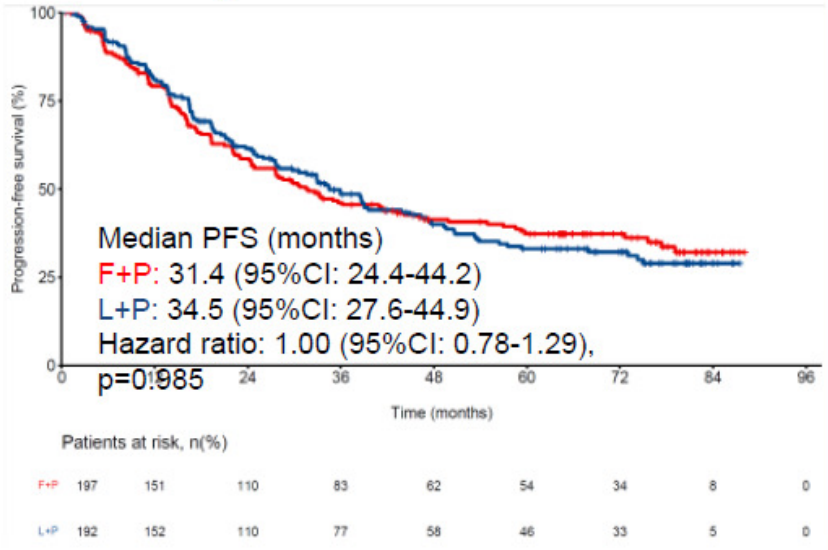
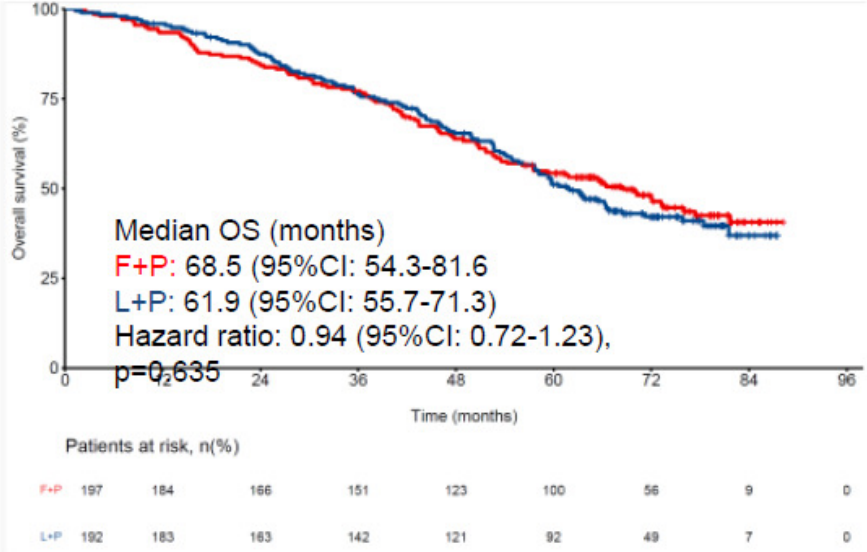
Results: Extended PFS and OS by treatment arm (n= 389)

Median follow-up: 59.7 months. Data cutoff: May 2023.

Progression-Free Survival



Overall Survival (OS)



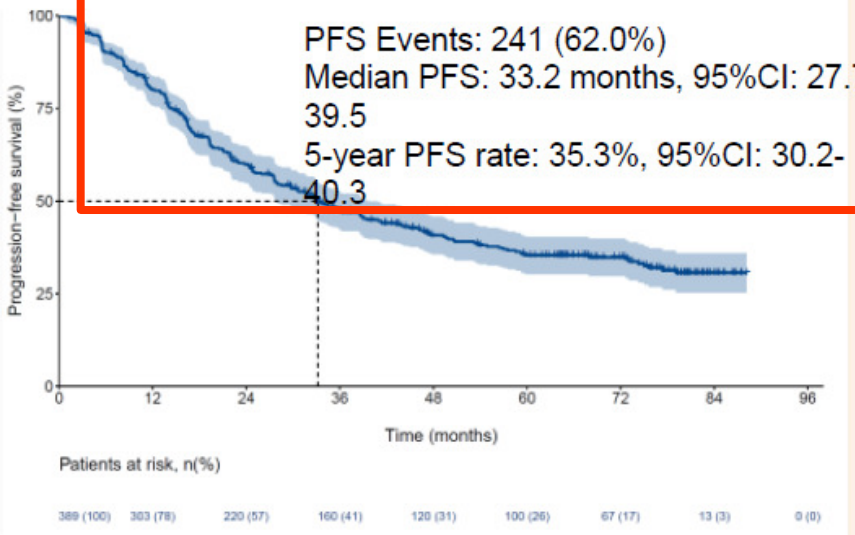
F: fulvestrant; L: letrozole; n (%), number of patients (percentage based on N); N: number of patients; OS: overall survival; P: palbociclib; PFS: progression-free survival

Results: PFS and OS of both cohorts combined (n=389)

Median follow-up: 59.7 months

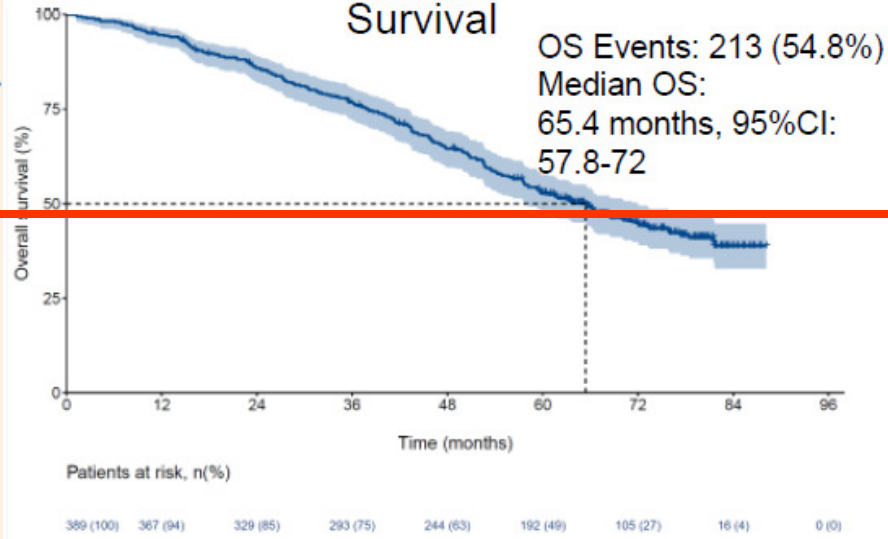
Progression-Free Survival

PFS Events: 241 (62.0%)
Median PFS: 33.2 months, 95%CI: 27.7-39.5
5-year PFS rate: 35.3%, 95%CI: 30.2-40.3



Overall Survival

OS Events: 213 (54.8%)
Median OS:
65.4 months, 95%CI: 57.8-72



n (%), number of patients (percentage based on N); N: number of patients; OS: overall survival; PFS: progression-free survival

Conclusions

- Extended follow-up confirmed no difference between letrozole and fulvestrant when combined with palbociclib
- mPFS was 33.2 months (95%CI, 27.7-39.5) and mOS was 65.4 mo (95%CI, 57.8-72.0), which is consistent with data for other CDK4/6 inhibitors
- Additional follow-up is planned with a data cutoff date of January 2024
- Early progression (<12 months) on a CDK4/6i regimen is a strong clinical marker of a less favorable outcome

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Inavolisib or placebo in combination with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer: Phase III INAVO120 primary analysis

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Presenting author: Prof. Komal L. Jhaveri, M.D., F.A.C.P.
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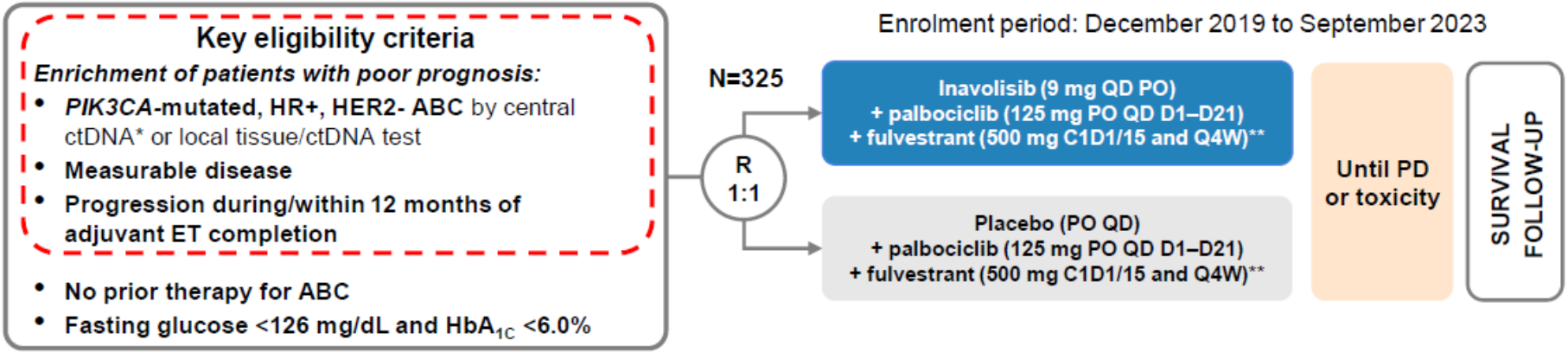
Background

- More effective treatments for patients with *PIK3CA*-mutated, HR+, HER2- ABC are needed[1]
- PI3Kα inhibitors to date have faced challenges with safety and tolerability[2,3]
- Inavolisib is a highly potent and selective PI3Kα inhibitor that also promotes the degradation of mutant p110α, which may improve the therapeutic window[4,5]
- Preclinical data demonstrated substantial synergy between PI3K and CDK4/6 inhibition with ET in *PIK3CA*-mutated xenograft models by deepening responses and blocking routes to resistance[4,6,7]
- Clinically, in a Phase I study (NCT03006172), the triplet of inavolisib, palbociclib and fulvestrant had a manageable safety profile, lacked DDI, and demonstrated promising preliminary antitumor activity in *PIK3CA*-mutated, HR+, HER2- ABC[6]
- INAVO120 (NCT04191499) is a Phase III, randomized, double-blind, placebo-controlled study that assessed inavolisib or placebo with palbociclib + fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2- ABC who recurred on or within 12 months of adjuvant ET

1. Cardoso F, *et al. Ann Oncol* 2020;**31**:1623–1649; 2. André F, *et al. N Eng J Med* 2019;**380**:1929–19:40; 3. Dent S, *et al. Ann Oncol* 2021;**32**:197–207; 4. Hong R, *et al.* SABCS 2017 (Poster PD4-14); 5. Edgar K, *et al.* SABCS 2019 (Poster P3-11-23); 6. Herrera-Abreu MT, *et al. Cancer Res* 2016;**76**:2301–2313; 7. Vora SR, *et al. Cancer Cell* 2014;**26**:136–149; 8. Bedard P, *et al.* SABCS 2020 (Poster PD1-02). ABC, advanced breast cancer; DDI, drug–drug interaction.

INAVO120 study design



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.

Demographics and baseline disease characteristics

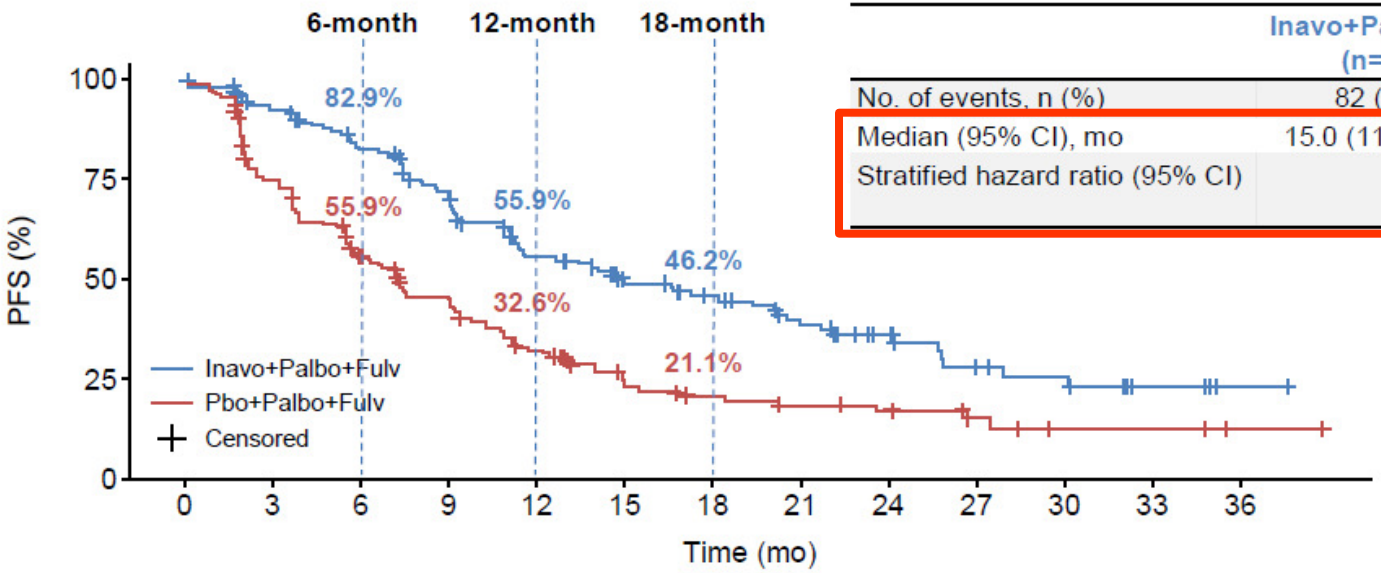
	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Age (year)		
Median	53.0	54.5
Min–Max	27–77	29–79
Sex, n (%)		
Female	156 (96.9)	163 (99.4)
Race, n (%)		
Asian	61 (37.9)	63 (38.4)
Black or African American	1 (0.6)	1 (0.6)
White	94 (58.4)	97 (59.1)
ECOG PS, n (%)		
0	100 (62.1)	106 (64.6)
1	60 (37.3)	58 (35.4)
Menopausal status at randomization, n (%)		
Premenopausal	65 (40.4)	59 (36.0)
Postmenopausal	91 (56.5)	104 (63.4)

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Number of organ sites, n (%)		
1	21 (13.0)	32 (19.5)
2	59 (36.6)	46 (28.0)
≥3	81 (50.3)	86 (52.4)
Visceral disease, n (%)*	132 (82.0)	128 (78.0)
Liver	77 (47.8)	91 (55.5)
Lung	66 (41.0)	66 (40.2)
Bone only†	5 (3.1)	6 (3.7)
ER‡ and PgR status, n (%)		
ER+/PgR+	113 (70.2)	113 (68.9)
ER+/PgR-	45 (28.0)	45 (27.4)
Endocrine resistance, n (%)**		
Primary	53 (32.9)	58 (35.4)
Secondary	108 (67.1)	105 (64.0)

301 (92.6%) pts were enrolled per ctDNA testing (284 [94.4%] central, 17 [5.6%] local) and 24 (7.4%) were enrolled per local tissue testing

* "Visceral" (yes/no) refers to lung, liver, brain, pleural, and peritoneal involvement; † Patients with evaluable bone-only disease were not eligible; patients with disease limited to the bone but with lytic or mixed lytic/blastic lesions, and at least one measurable soft-tissue component per RECIST 1.1, may be eligible. ‡ Defined as 10% per ASCO-CAP guidelines. ** Endocrine resistance was defined per 4th ESO–[ESMO] International Consensus Guidelines for Advanced Breast Cancer. Primary resistance: Relapse while on the first 2 years of adjuvant endocrine therapy. Secondary resistance: Relapse while on adjuvant endocrine therapy after at least 2 years or relapse within 12 months of completing adjuvant endocrine therapy. ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor, Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo; PgR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumors.

Primary endpoint: PFS (investigator-assessed)



	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

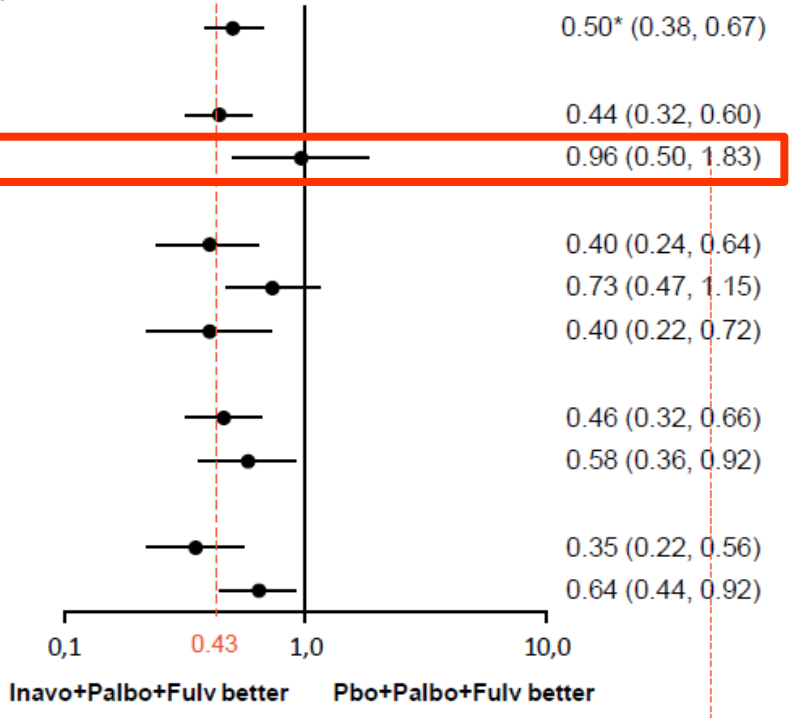
Median follow-up: **21.3 months**

CCOD: 29th September 2023

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

PFS (investigator-assessed) in key subgroups 1/2

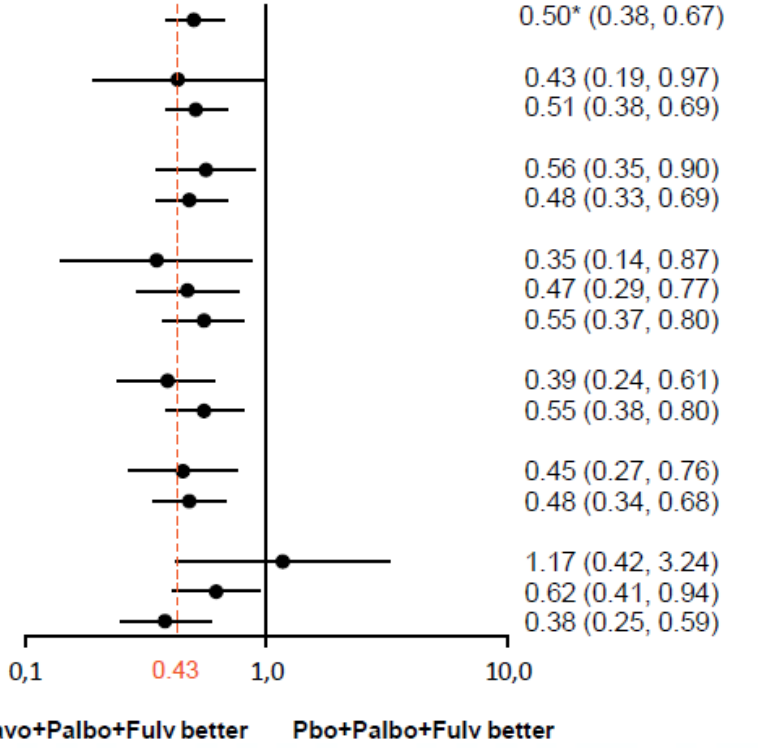
	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv		Hazard ratio (95% CI)
	n	Median (mo)	n	Median (mo)	
All patients	161	15.0	164	7.3	0.50* (0.38, 0.67)
Age, years					
<65	136	16.6	130	7.2	0.44 (0.32, 0.60)
≥65	25	9.3	34	10.7	0.96 (0.50, 1.83)
Region					
Asia	56	14.6	58	5.8	0.40 (0.24, 0.64)
North America/Western Europe	63	13.8	64	9.3	0.73 (0.47, 1.15)
Other	42	21.0	42	5.6	0.40 (0.22, 0.72)
ECOG PS at baseline					
0	100	16.6	106	7.4	0.46 (0.32, 0.66)
1	60	11.4	58	5.6	0.58 (0.36, 0.92)
Menopausal status at randomization					
Premenopausal	65	20.1	59	6.5	0.35 (0.22, 0.56)
Post-menopausal	91	13.4	104	7.5	0.64 (0.44, 0.92)



* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Fulv, fulvestrant; Inavo, inavolisib; mo, months, Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

PFS (investigator-assessed) in key subgroups 2/2

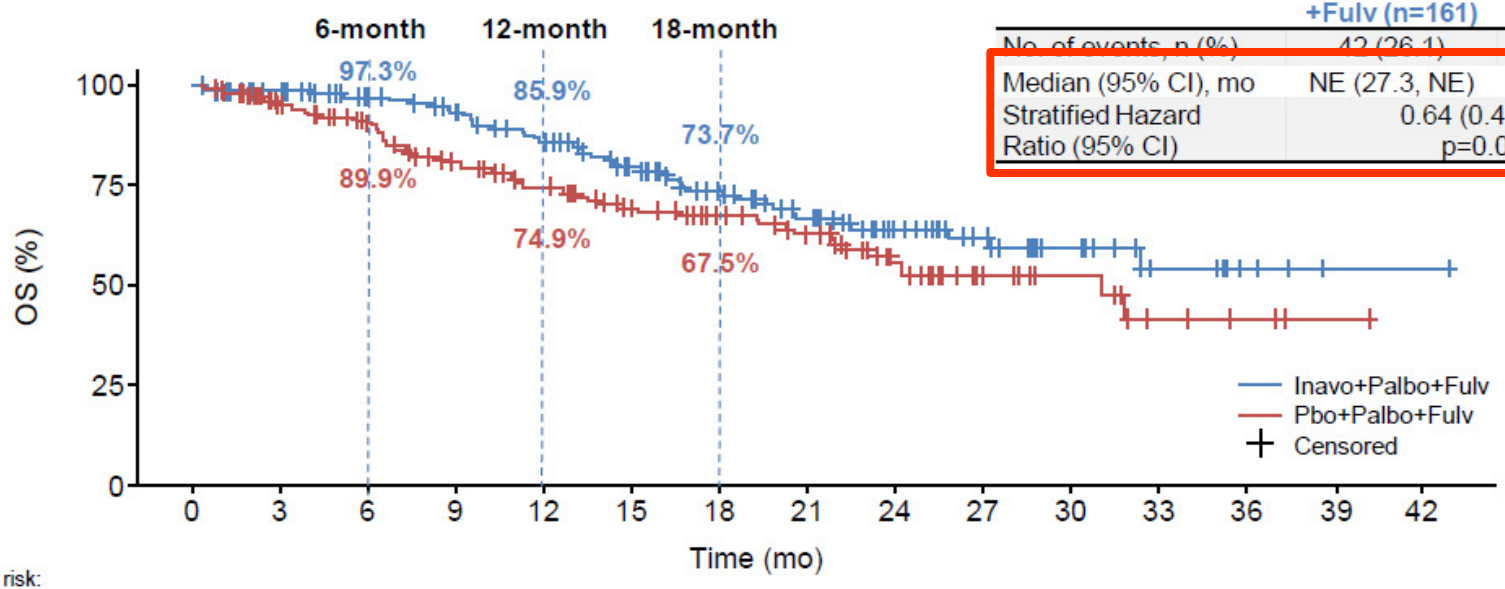
	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv		Hazard ratio (95% CI)
	n	Median (mo)	n	Median (mo)	
All patients	161	15.0	164	7.3	0.50* (0.38, 0.67)
Visceral disease					
No	29	25.8	36	7.4	0.43 (0.19, 0.97)
Yes	132	13.8	128	7.2	0.51 (0.38, 0.69)
Liver metastasis at enrollment					
No	84	24.2	73	11.3	0.56 (0.35, 0.90)
Yes	77	11.0	91	5.6	0.48 (0.33, 0.69)
Number of metastatic organs at enrollment					
1	21	20.2	32	7.4	0.35 (0.14, 0.87)
2	59	18.2	46	7.4	0.47 (0.29, 0.77)
≥3	81	14.1	86	7.3	0.55 (0.37, 0.80)
Endocrine resistance					
Primary	53	11.4	58	3.7	0.39 (0.24, 0.61)
Secondary	108	18.2	105	9.7	0.55 (0.38, 0.80)
HR status					
ER+/PgR-	45	11.1	45	5.6	0.45 (0.27, 0.76)
ER+/PgR+	113	18.2	113	7.4	0.48 (0.34, 0.68)
Prior (neo)adjuvant endocrine therapy					
Aromatase inhibitor and tamoxifen	18	11.0	19	12.9	1.17 (0.42, 3.24)
Aromatase inhibitor only	60	10.9	71	5.8	0.62 (0.41, 0.94)
Tamoxifen only	82	21.0	73	7.4	0.38 (0.25, 0.59)



* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

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

Key secondary endpoint: Overall survival (interim analysis)



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Patients at risk:

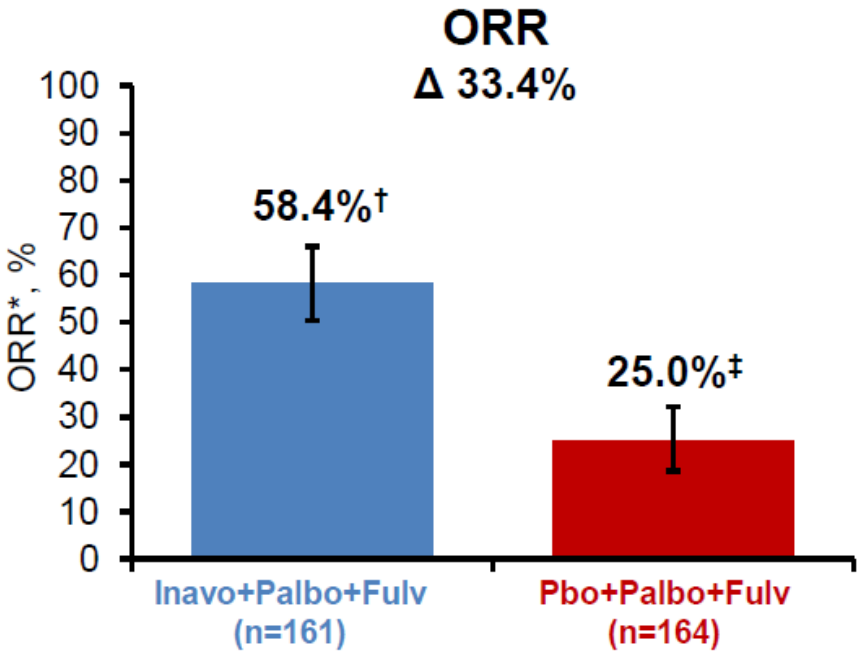
Inavo+Palbo+Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo+Palbo+Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

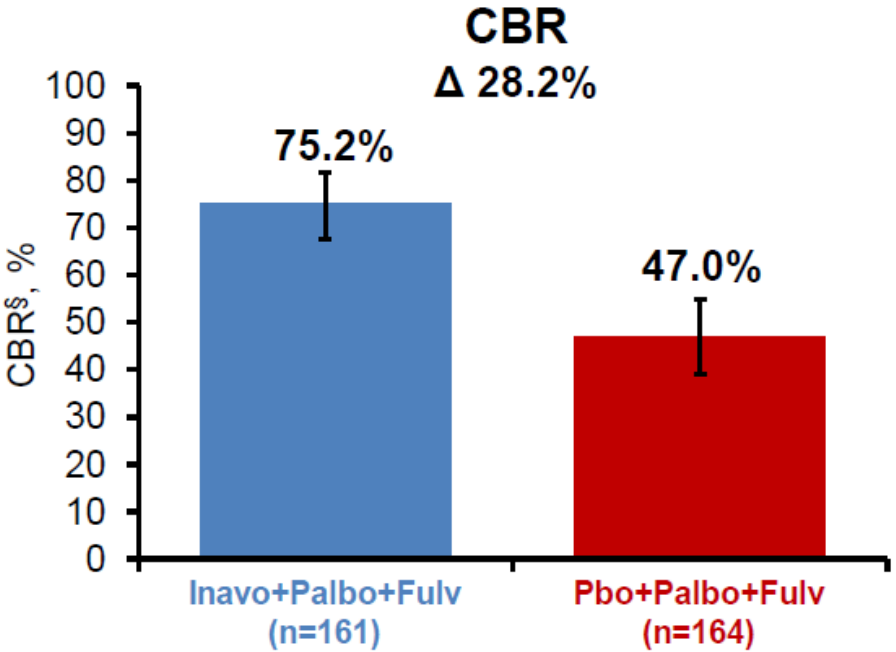
Median follow-up: **21.3 months**

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.

Secondary endpoints: ORR and CBR (investigator-assessed)





* Patients with a CR or PR on two consecutive occasions ≥4 weeks apart per RECIST v1.1. † Seven patients with CR, 87 patients with PR. ‡ One patient with CR, 40 patients with PR, 79 patients with SD, 34 patients with PD, and 10 with missing status. § Patients with a CR, PR, and/or SD for ≥24 weeks per RECIST v1.1. CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; Inavo, inavolisib; ORR, objective response rate; Palbo, palbociclib; Pbo, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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.

Overview of adverse events

Patients with ≥1 AE, n (%)	Inavo+Palbo+Fulv (n=162)	Pbo+Palbo+Fulv (n=162)
All, n (%)	160 (98.8%)	162 (100%)
Grade 3–4 AE	143 (88.3%)	133 (82.1%)
Grade 5 AE*	6 (3.7%)	2 (1.2%)
Serious AE	39 (24.1%)	17 (10.5%)
AEs leading to discontinuation of treatment	11 (6.8%)	1 (0.6%)
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)
Palbociclib	8 (4.9%)	0
Fulvestrant	5 (3.1%)	0
AEs leading to dose modification/interruption of treatment	134 (82.7%)	121 (74.7%)
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)
Palbociclib	125 (77.2%)	116 (71.6%)
Fulvestrant	52 (32.1%)	34 (21.0%)

AES were assessed per CTCAE V5

* None of the grade 5 AEs were reported as related to study treatment by investigators. The grade 5 AEs reported were cerebral hemorrhage; cerebrovascular accident, gastrointestinal hemorrhage, acute coronary syndrome, death and COVID-19 in the inavo+palbo+fulv arm and COVID-19 pneumonia and cardiac arrest in the pbo+palbo+fulv arm.

AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

INAVO120 summary and conclusions

- Addition of inavolisib to palbociclib + fulvestrant demonstrated a **statistically significant and clinically meaningful improvement in PFS** in patients with *PIK3CA*-mutated, HR+, HER2- ABC who recurred on or within 12 months of adjuvant ET
  - Median PFS more than doubled from 7.3 to 15.0 mo, with a stratified **hazard ratio of 0.43** (95% CI 0.32, 0.59; p<0.0001)
- **OS trend** at this first interim analysis: stratified **hazard ratio 0.64** (95% CI 0.43, 0.97)
- Inavolisib + palbociclib + fulvestrant had a **manageable safety profile**, consistent with the safety profiles of the individual drugs with no new safety signals and with a low discontinuation rate

Inavolisib in combination with palbociclib and fulvestrant may represent a new standard of care for patients with *PIK3CA*-mutated, HR+, HER2- ABC

ABC, advanced breast cancer; CI, confidence interval; mo, months; OS, overall survival; PFS, progression-free survival.

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AACR American Association for Cancer Research

Randomized phase 3 study of datopotamab deruxtecan vs chemotherapy for patients with previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative breast cancer: Results from TROPION-Breast01

Aditya Bardia,[1] Komal Jhaveri,[2] Seock-Ah Im,[3] Michelino De Laurentiis,[4] Binghe Xu,[5] Sonia Pernas,[6] Giuliano Borges,[7] David W. Cescon,[8] Masaya Hattori,[9] Yen-Shen Lu,[10] Noelia Martínez Jañez,[11] Erika Hamilton,[12] Shusen Wang,[13] Junji Tsurutani,[14] Kevin Kalinsky,[15] Lu Xu,[16] Sabrina Khan,[17] Neelima Denduluri,[17] Hope S. Rugo,[18]* Barbara Pistilli[19]*

*Contributed equally.

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Background

- **Chemotherapy** is utilised widely for management of **endocrine-resistant HR+/HER2– MBC**, but can be associated with **low response rate**, **poor prognosis**, and **significant toxicity** including myelosuppression and peripheral neuropathy, highlighting need for better therapies in this setting[1–5]
- **Dato-DXd** is a **TROP2-directed ADC**, that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells,[6] and has several unique properties:
  - Optimized drug to antibody ratio ≈ 4
  - Stable linker-payload
  - Tumor-selective cleavable linker
  - Bystander antitumor effect
- **Primary results** from phase 3 **TROPION-Breast01** study presented at ESMO 2023[7] demonstrated:
  - **Statistically significant and clinically meaningful improvement in PFS by BICR with Dato-DXd compared with ICC:** HR 0.63 (95% CI 0.52–0.76); P<0.0001
  - OS data not mature, but trend favoring Dato-DXd observed: HR 0.84 (95% CI 0.62–1.14)
  - ORR (by BICR): 36.4% in the Dato-DXd arm versus 22.9% in the ICC arm
- Here we present additional **efficacy, safety** and **QoL** results from TROPION-Breast01

ADC, antibody-drug conjugate; BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HER2–, human epidermal growth factor receptor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; MBC, metastatic breast cancer; ICC, investigator's choice of chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; Topo-I, topoisomerase I; TROP2, trophoblast cell surface antigen 2.

1. Kuderer NM, et al. *Nat Rev Clin Oncol* 2022;19:681–97; 2. Gennari A, et al. *Ann Oncol* 2021;32:1475–1495; 3. Wolff AC, et al. *J Clin Oncol* 2023;41:3867–72; 4. Moy B, et al. *J Clin Oncol* 2023;41:1318–20; 5. Moy B, et al. *J Clin Oncol* 2022;40:3088–90; 6. Okajima D, et al. *Mol Cancer Ther* 2021;20:2329–40; 7. Bardia A, et al. *Ann Oncol* 2023;34(suppl_2):S1264–5.

TROPION-Breast01 Study Design[1]

Randomized, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, PROs

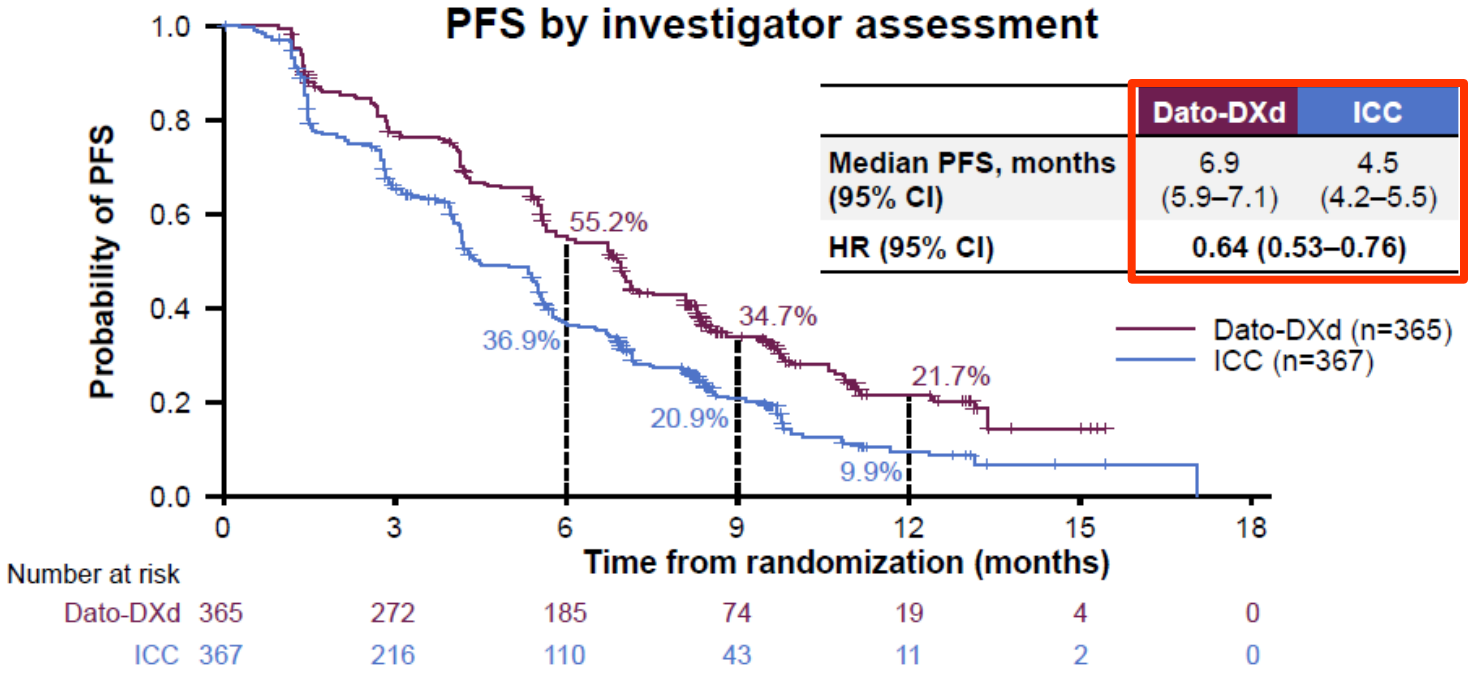
Randomization stratified by:
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m² IV on Days 1 and 8, Q3W; vinorelbine, 25 mg/m² IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m² IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m² orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice). CDK4/6, cyclin-dependent kinase 4/6; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in-situ hybridization; IV, intravenous; PD, progressive disease; PROs, patient-reported outcomes; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; TFST, time to first subsequent therapy.

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

Progression-Free Survival



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	**0.64 (0.53–0.76)**	

PFS by BICR (primary endpoint)[1]: Median 6.9 vs 4.9 months; HR 0.63 (95% CI 0.52–0.76); P<0.0001

Data cut-off: 17 July 2023.

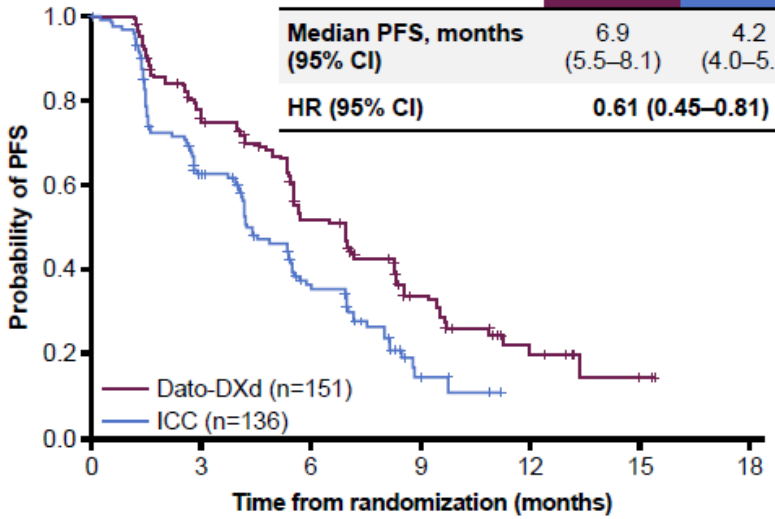
1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

PFS by BICR in Subgroups

Prior CDK4/6 Inhibitor

Prior duration of CDK4/6 inhibitor: ≤12 months

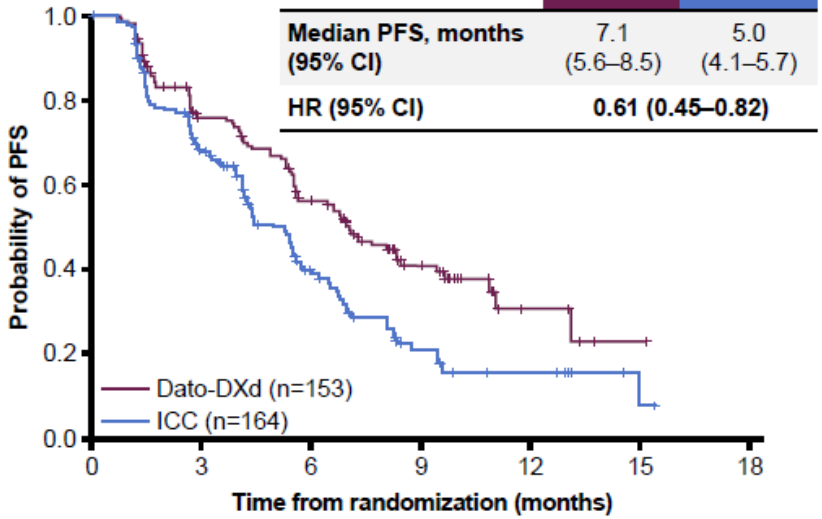
	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.5–8.1)	4.2 (4.0–5.5)
HR (95% CI)	0.61 (0.45–0.81)	



No. at risk							
Dato-DXd	151	106	63	26	8	2	0
ICC	136	74	35	7	0	0	0

Prior duration of CDK4/6 inhibitor: >12 months

	Dato-DXd	ICC
Median PFS, months (95% CI)	7.1 (5.6–8.5)	5.0 (4.1–5.7)
HR (95% CI)	0.61 (0.45–0.82)	



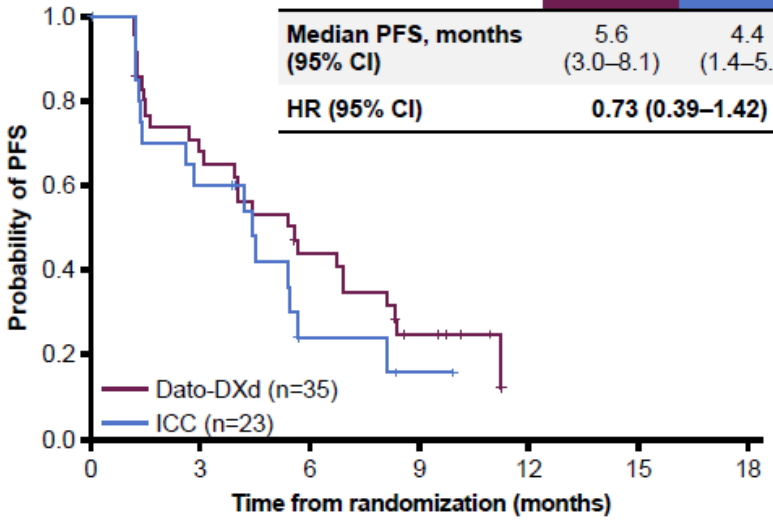
No. at risk							
Dato-DXd	153	102	70	28	6	1	0
ICC	164	90	40	13	7	1	0

PFS by BICR in Subgroups

Brain metastases

Brain metastases at study entry: Yes*

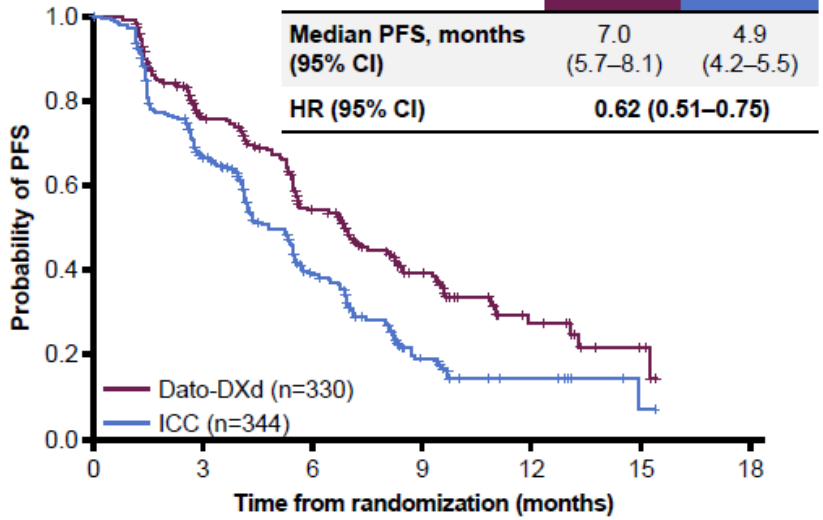
	Dato-DXd	ICC
Median PFS, months (95% CI)	5.6 (3.0–8.1)	4.4 (1.4–5.7)
HR (95% CI)	0.73 (0.39–1.42)	



No. at risk					
Dato-DXd	35	23	14	6	0
ICC	23	12	3	1	0

Brain metastases at study entry: No

	Dato-DXd	ICC
Median PFS, months (95% CI)	7.0 (5.7–8.1)	4.9 (4.2–5.5)
HR (95% CI)	0.62 (0.51–0.75)	



No. at risk							
Dato-DXd	330	226	144	60	15	4	0
ICC	344	193	90	25	8	1	0

*Study inclusion criteria permitted enrollment of patients with clinically inactive brain metastases, who required no treatment with corticosteroids or anticonvulsants.

Overall Safety Summary

TRAEs, n (%)[1]	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	157 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

- Most common TRAEs leading to dose interruption:
  - Dato-DXd: fatigue*, infusion-related reaction, ILD, stomatitis (each 1%)
  - ICC: neutropenia† (17%), leukopenia‡ (3%)
- No TRAEs led to discontinuation in ≥1% of patients in either arm
- One treatment-related death in the ICC arm due to febrile neutropenia

*Fatigue includes the preferred terms of fatigue, asthenia, and malaise. †Neutropenia includes the preferred terms neutropenia and neutrophil count decreased.
‡Leukopenia includes the preferred terms of white blood cell count decreased and leukopenia.
ILD, interstitial lung disease; TRAEs, treatment-related adverse events.

1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

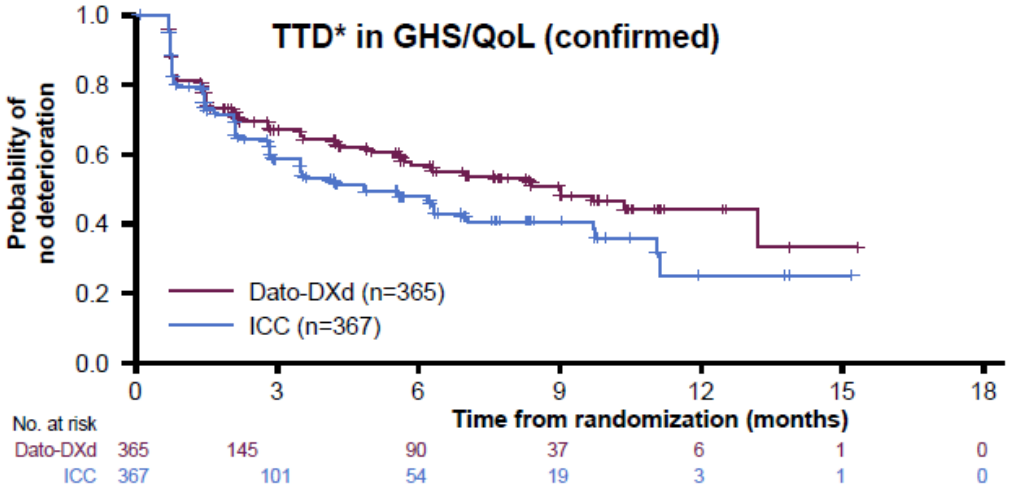
Adverse Events of Clinical Interest

Neutropenia*	Dato-DXd (n=360)	ICC (n=351)
Treatment-related neutropenia*, n (%)		
Any grade	39 (11)	149 (42)
Grade ≥3	4 (1)	108 (31)
Leading to dose interruption	0	60 (17)
Leading to dose reduction	1 (0.3)	45 (13)
Leading to dose discontinuation	0	1 (0.3)
G-CSF usage, n (%)		
On treatment	10 (3)	81 (22)
Post-treatment†	1 (0.3)	30 (8)

Stomatitis‡	Dato-DXd (n=360)	ICC (n=351)
Treatment-related stomatitis‡, n (%)		
Any grade	180 (50)	46 (13)
Grade 3	23 (6)	9 (3)
Leading to dose interruption	5 (1)	3 (1)
Leading to dose reduction	44 (12)	5 (1)
Leading to dose discontinuation	1 (0.3)	0

*Neutropenia includes the preferred terms neutropenia and neutrophil count decreased. Treatment-related febrile neutropenia occurred in 0 patients in the Dato-DXd arm and 8 patients (2.3%; all grade ≥3) in the ICC arm.
†Administered after discontinuation of study treatment.
‡As part of the Oral Care Protocol specified in the study protocol, daily use of prophylaxis with a steroid-containing mouthwash (e.g., dexamethasone oral solution or a similar mouthwash regimen using an alternative steroid advocated by institutional/local guidelines) was highly recommended.
G-CSF, granulocyte colony stimulating factor.

TTD in Global Health Status/Quality of Life



TTD*	Median TTD, months (first instance)		HR (95% CI)	Median TTD, months (confirmed)		HR (95% CI)
	Dato-DXd	ICC		Dato-DXd	ICC	
GHS/QoL	3.4	2.1	0.85 (0.68–1.06)	9.0	4.8	0.76 (0.58–0.98)

*TTD in pain, physical functioning and GHS/QoL are secondary endpoints. The primary analysis was based on time to first deterioration, defined as the time from date of randomization to date of first deterioration. Sensitivity analysis was based on time to confirmed deterioration, which required deterioration to be confirmed at a subsequent timepoint. Deterioration was defined as change from baseline that reached a clinically meaningful deterioration threshold (16.6 for GHS/QoL and pain, 13.3 for physical functioning). GHS/QoL, global health status/quality of life; TTD, time to deterioration.

Conclusions

- TROPION-Breast01 met its dual primary PFS endpoint, demonstrating statistically significant and clinically meaningful improvement in PFS (by BICR) with Dato-DXd compared with ICC
  - Investigator-assessed PFS was consistent with PFS by BICR
  - Median PFS improvement observed regardless of prior duration of CDK4/6 inhibitor or brain metastases
  - Time to first subsequent therapy was longer with Dato-DXd compared with ICC
- Overall, Dato-DXd demonstrated a favorable safety profile compared with ICC
  - Patients receiving Dato-DXd had fewer grade ≥3 TRAEs and fewer dose interruptions/reductions vs ICC
  - Treatment-related stomatitis with Dato-DXd was generally low grade and manageable
  - Neutropenia was the most common TRAE with ICC, which frequently led to dose interruption/reduction, and one death
- Time to deterioration in quality of life was delayed in the Dato-DXd arm compared with ICC

Overall, results support Dato-DXd as a potential new therapeutic option for patients with endocrine-resistant metastatic HR+/HER2– breast cancer

HER2-positiv?

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HER2CLIMB-02: Primary Analysis of a Randomized, Double-blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-positive Metastatic Breast Cancer

Sara A. Hurvitz, MD
Fred Hutchinson Cancer Center, Seattle, WA, USA

Sherene Loi, Joyce O'Shaughnessy, Alicia F. C. Okines, Sara M. Tolaney, Joohyuk Sohn, Cristina Saura, Xiaofu Zhu, David Cameron, Thomas Bachelot, Erika P. Hamilton, Giuseppe Curigliano, Antonio C. Wolff, Nadia Harbeck, Norikazu Masuda, Linda Vahdat, Khalil Zaman, Frances Valdes-Albini, Margaret Block, Timothy Pluard, Tira J. Tan, Chelsea D. Gawryletz, Arlene Chan, Philippe L. Bedard, Rinat Yerushalmi, Binghe Xu, Konstantinos Tryfonidis, Michael Schmitt, Diqiong Xie, Virginia F. Borges

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

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

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 at two-sided alpha level of 0.05. 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]

NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Accessed Oct 5, 2023.
a Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were not eligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.
b Subsequent OS analyses are planned upon 80% and 100% of required events for the final OS analysis.
1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PO, orally; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors.
Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.

Demographics and Baseline Characteristics

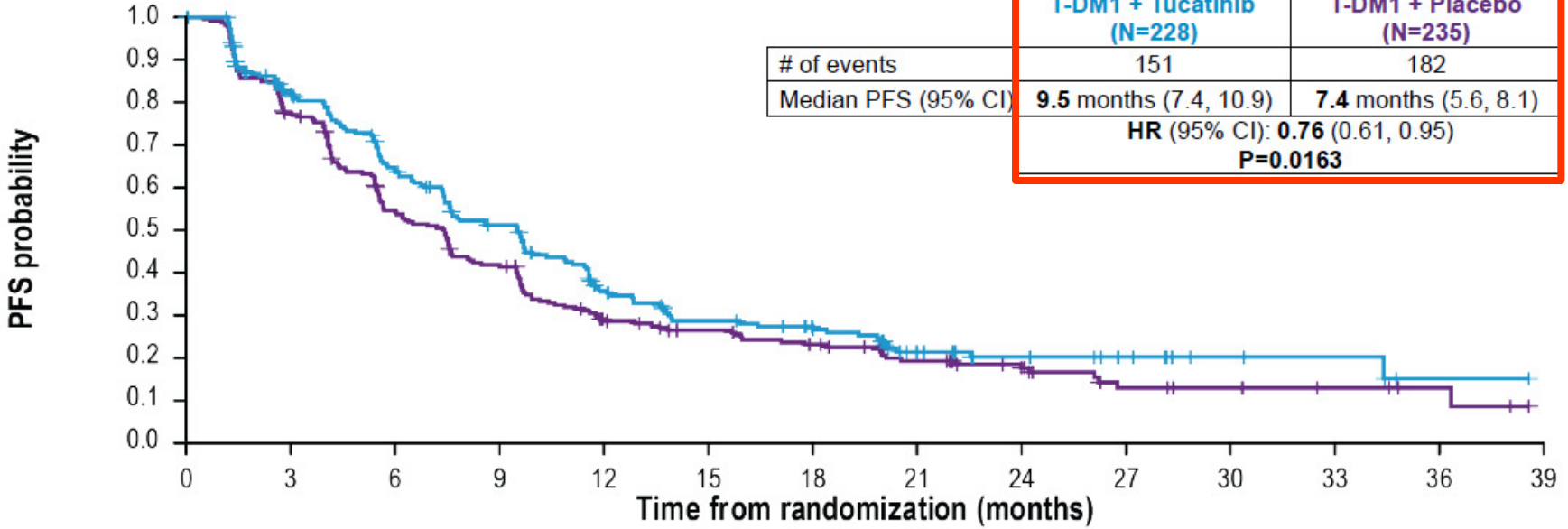
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Median age, years (range)	55.0 (26-83)	53.0 (27-82)
Female sex, n (%)	226 (99.1)	235 (100)
Geographic region, n (%)		
North America	105 (46.1)	93 (39.6)
Europe/Israel	53 (23.2)	77 (32.8)
Asia-Pacific	70 (30.7)	65 (27.7)
Hormone-receptor status, n (%)		
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)

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (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)

a Includes 2 patients with missing brain metastases data.
b Five patients in T-DM1 + Tucatinib arm and 7 patients in T-DM1 + Placebo arm had unknown stage.
ECOG, Eastern Cooperative Oncology Group; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Progression-Free Survival

	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**	



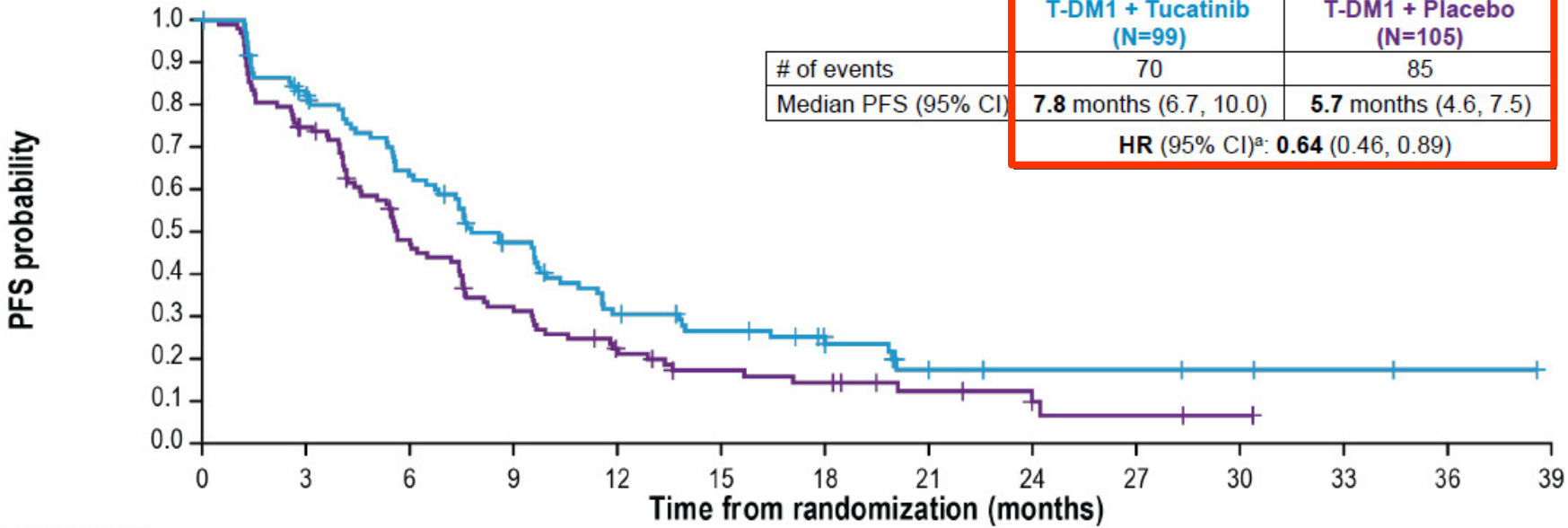
Patients at risk

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

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

PFS in Patients with Brain Metastases

	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (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)[a]: **0.64** (0.46, 0.89)	

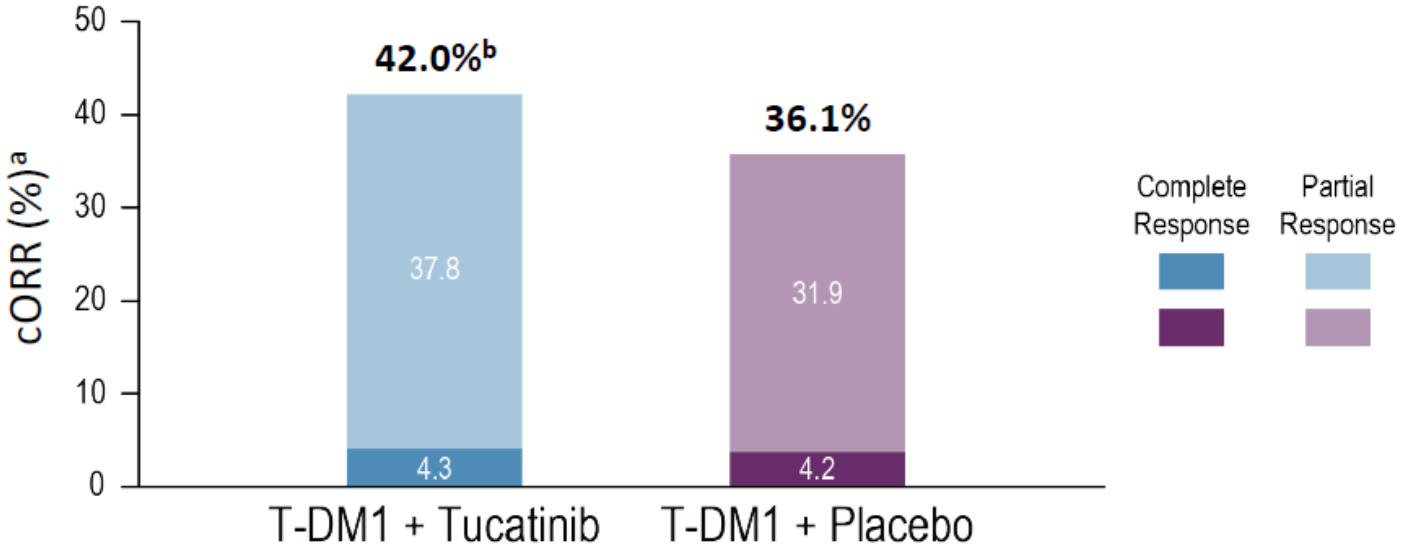


Patients at risk

T-DM1 + Tucatinib	99	76	57	40	25	20	15	6	4	4	3	2	1	0
T-DM1 + Placebo	105	75	46	30	18	12	10	6	3	2	1	0	0	0

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

Confirmed Objective Response Rate



a The outcome was not formally tested. Only patients with measurable disease were included in the analysis (N=188 for T-DM1 + Tucatinib arm and N=191 for T-DM1 + Placebo arm).
b Percentages for complete and partial response do not add up to the cORR due to rounding.
cORR, confirmed objective response rate; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Overall Safety Summary

	T-DM1 + Tucatinib (N=231) n (%)	T-DM1 + Placebo (N=233) n (%)
Any TEAE	230 (99.6)	233 (100)
Grade ≥3 TEAE	159 (68.8)	96 (41.2)
Any TESAE	70 (30.3)	52 (22.3)
TEAE leading to death	3 (1.3)	2 (0.9)
Discontinued tucatinib or placebo due to TEAE	40 (17.3)	16 (6.9)
Discontinued T-DM1 due to TEAE	47 (20.3)	26 (11.2)

Median duration of tucatinib or placebo treatment: 7.4 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo
Median duration of T-DM1 treatment: 7.5 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo

Most common TEAEs (≥2%) leading to tucatinib or placebo discontinuation (T-DM1 + Tucatinib vs T-DM1 + Placebo):
- ALT increased (2.6% vs 0%)

Most common TEAEs (≥2%) leading to T-DM1 discontinuation (T-DM1 + Tucatinib vs T-DM1 + Placebo):
- ALT increased (2.2% vs 0%)
- Thrombocytopenia (2.2% vs 0%)
- Interstitial lung disease (0% vs 2.1%)

ALT, alanine aminotransferase; T-DM1, trastuzumab emtansine; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
Date of data cutoff: Jun 29, 2023.

Adverse Events of Interest

- Hepatic TEAEs
  - Grade ≥3 hepatic TEAEs[a] greater in T-DM1 + Tucatinib arm (28.6% vs 7.3%), primarily due to AST/ALT elevations
  - No Hy's law cases were identified
  - 85% of all-grade hepatic TEAEs in T-DM1 + Tucatinib arm resolved or returned to grade 1, with median of 22 days to resolution[b]
- Diarrhea
  - Grade ≥3 events reported in 4.8% of T-DM1 + Tucatinib arm and 0.9% of T-DM1 + Placebo arm
  - No grade ≥4 events were reported in either arm

Dose Modifications Due to Hepatic TEAEs

	T-DM1 + Tucatinib (N=231) n (%)	T-DM1 + Placebo (N=233) n (%)
Tucatinib or placebo dose holds	76 (32.9)	26 (11.2)
Tucatinib or placebo dose reductions	46 (19.9)	12 (5.2)
Treatment discontinuation		
Tucatinib or placebo	16 (6.9)	5 (2.1)
T-DM1	18 (7.8)	5 (2.1)

Dose Modifications Due to Diarrhea

	T-DM1 + Tucatinib (N=231) n (%)	T-DM1 + Placebo (N=233) n (%)
Tucatinib or placebo dose holds	9 (3.9)	2 (0.9)
Tucatinib or placebo dose reductions	9 (3.9)	1 (0.4)
Treatment discontinuation		
Tucatinib or placebo	1 (0.4)	0
T-DM1	0	0

a Hepatic TEAEs refer to terms from the drug-related hepatic disorders - comprehensive search SMQ (narrow).
b For T-DM1 + Placebo arm, 75% of all-grade hepatic TEAEs resolved or returned to grade 1, with median of 22 days to resolution.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; SMQ, standardized Medical Dictionary for Regulatory Activities Queries; T-DM1, trastuzumab emtansine; TEAEs, treatment-emergent adverse events.
Date of data cutoff: Jun 29, 2023.

Conclusions

- Adding tucatinib to T-DM1 significantly improved PFS in patients with previously treated HER2+ LA/MBC
  - Median PFS was 9.5 vs 7.4 months (HR, 0.76; P=0.0163)
  - PFS HRs for prespecified subgroups were consistent with that of the overall population
  - Median PFS for patients with brain metastases was 7.8 vs 5.7 months (HR, 0.64)
  - OS data are immature
- Types of adverse events were consistent with those previously reported for tucatinib and T-DM1
  - Higher rate of hepatic events in the T-DM1 + Tucatinib arm; the events were generally transient, manageable, and reversible
- This is the second randomized study including patients with brain metastases demonstrating that a tucatinib-containing regimen delays disease progression in HER2+ LA/MBC

HR, hazard ratio; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TEAEs, treatment-emergent adverse events.

Triple-negativ?

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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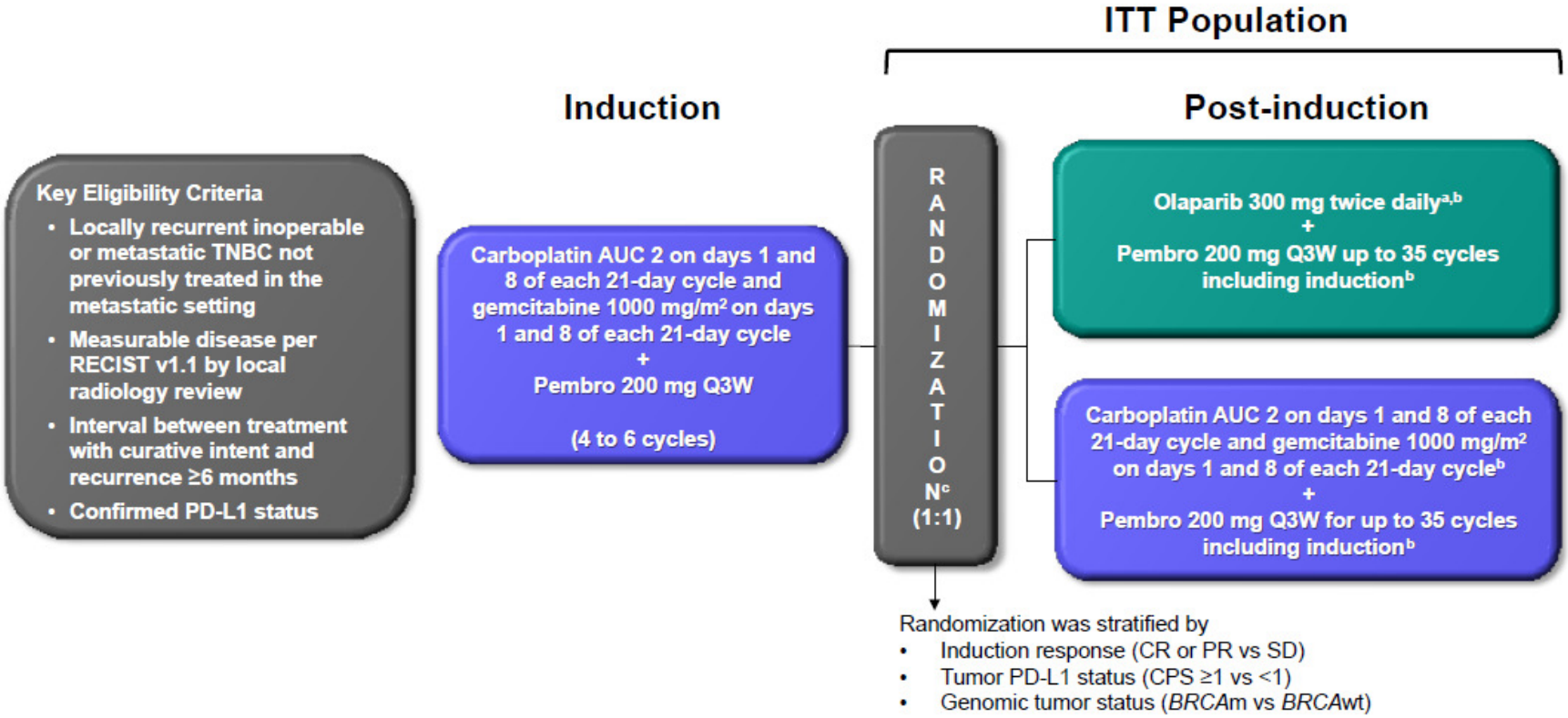
KEYLYNK-009 (NCT04191135): Study Design



[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).

Baseline Characteristics: ITT Population

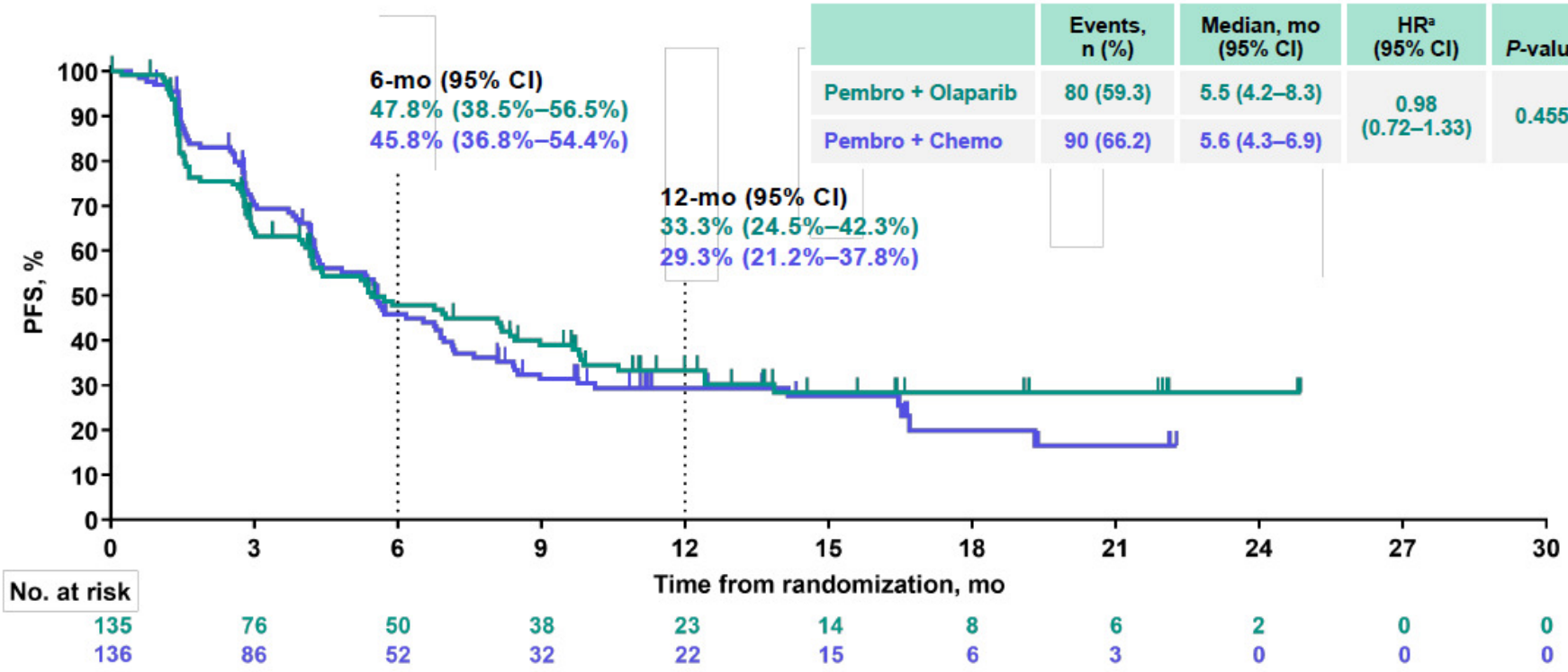
Characteristic, n (%)	Pembro + Olaparib n = 135	Pembro + Chemo n = 136
Age, median (range), y	54 (25–82)	52 (30–80)
ECOG PS 1	48 (35.6)	45 (33.1)
Postmenopausal	96 (71.1)	94 (69.1)
PD-L1 status[a]		
PD-L1 CPS ≥1	106 (78.5)	105 (77.2)
PD-L1 CPS <1	29 (21.5)	31 (22.8)
PD-L1 CPS ≥10	65 (48.1)	65 (47.8)
PD-L1 CPS <10	69 (51.1)	71 (52.2)
BRCA mutation[b]	29 (21.5)	30 (22.1)
HRD ≥33[c]	83 (61.5)	77 (56.6)
Disease status		
Metastatic, de novo	47 (34.8)	37 (27.2)
Metastatic, recurrence	87 (64.4)	96 (70.6)
Locally recurrent inoperable	1 (0.7)	3 (2.2)
Response at randomization		
CR/PR	95 (70.4)	96 (70.6)
SD	39 (28.9)	40 (29.4)

[a]PD-L1 assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx 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 × 100).

[b]BRCA status was determined in tumor for the purpose of this analysis; blood testing will be conducted at a later time. [c]Myriad MyChoice CDx® Plus was used to determine HRD; ≥33 is used as a cutoff for HRD based on Merck internal validation.

Data cutoff date: December 15, 2022.

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.

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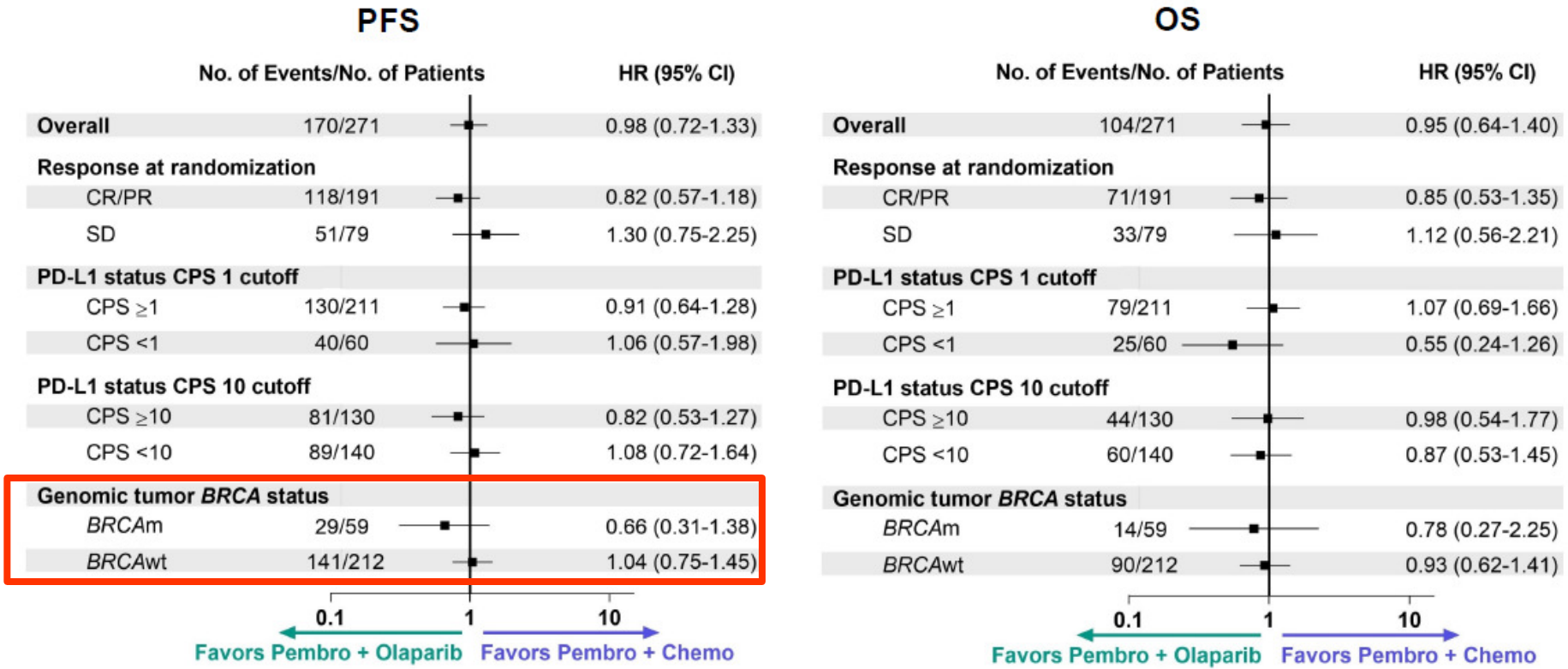
PFS and OS in Key Patient Subgroups: ITT Population



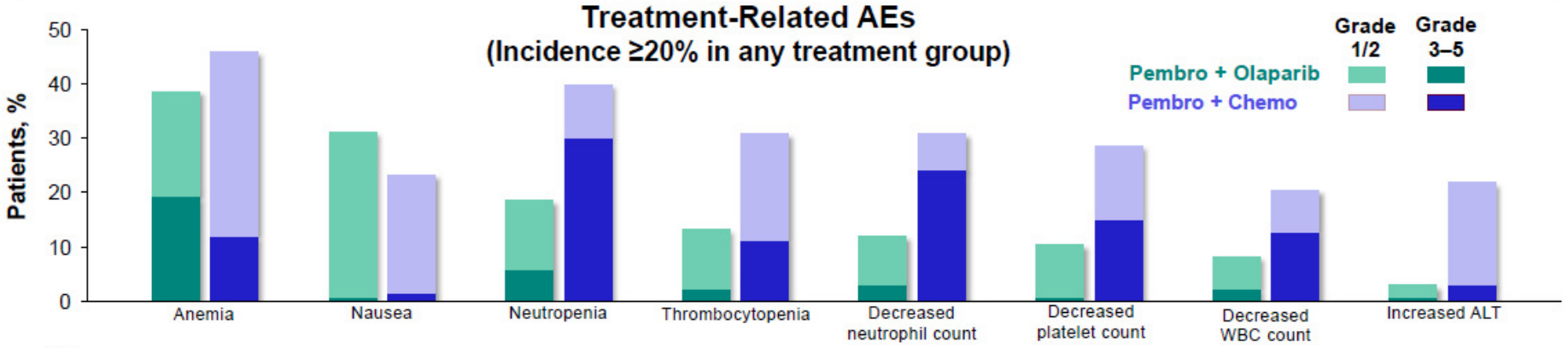
Data cutoff date: December 15, 2022.

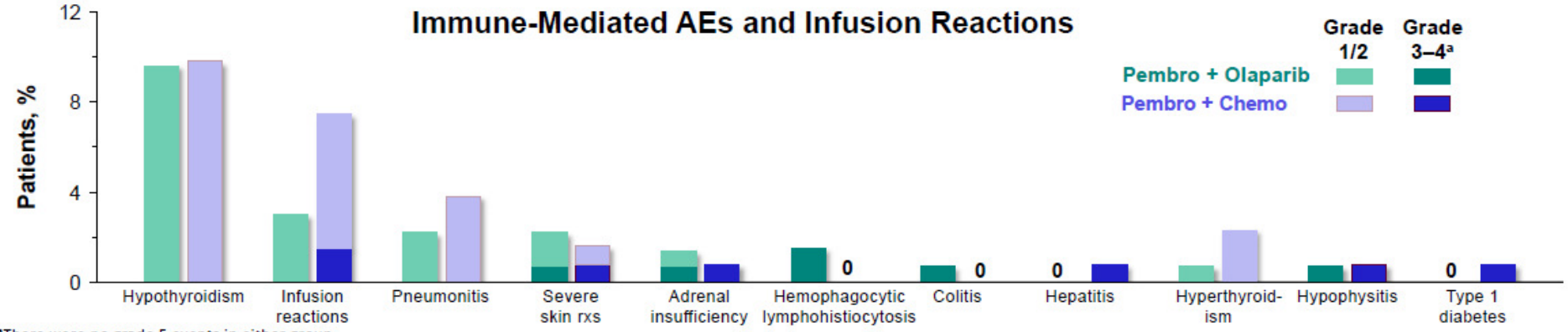
Adverse Events Summary (As-Treated Population)

	Pembro + Olaparib n = 135	Pembro + Chemo n = 133
Treatment-related AEs		
Any grade treatment-related AEs	114 (84.4)	128 (96.2)
Grade 3–5 treatment-related AEs	44 (32.6)[a]	91 (68.4)[b]
Treatment-related AEs leading to discontinuation of any treatment	12 (8.9)	26 (19.5)
Immune-Mediated AEs and Infusion Reactions[c]		
Any grade	26 (19.3)	31 (23.3)
Grade 3/4[d]	6 (4.4)	6 (4.5)
Led to discontinuation of any treatment	0	4 (3.0)

Data are n (%) of patients.
[a]There were no grade 5 events in the pembro + olaparib group.
[b]2 patients had grade 5 events in the pembro + chemo group (gastrointestinal hemorrhage and thrombotic thrombocytopenic purpura, n = 1 each).
[c]Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator.
[d]There were no grade 5 events in either group.
Data cutoff date: December 15, 2022.

Adverse Events (As-Treated Population)





[a]There were no grade 5 events in either group.

Data cutoff date: December 15, 2022.

Summary and Conclusions

- After induction pembrolizumab plus chemotherapy for metastatic TNBC, pembrolizumab plus olaparib in an unselected population with responding or stable disease did not improve PFS compared to continued pembrolizumab plus chemotherapy
  - HR for PFS: 0.98 (95% CI, 0.72–1.33; 1-sided *P*-value = 0.4556)
  - HR for OS: 0.95 (95% CI, 0.64–1.40)
- In patients with t*BRCA*m, there was a positive trend for PFS and OS for those receiving pembrolizumab plus olaparib vs pembrolizumab plus chemotherapy
- The treatment-related AE profile observed in patients treated with pembrolizumab plus olaparib was consistent with the known safety profiles of both monotherapies
  - A lower incidence of treatment-related AEs was reported in patients receiving pembrolizumab plus olaparib vs pembrolizumab plus chemotherapy
- Stopping chemotherapy in patients with responding or stable disease and treating with continued maintenance pembrolizumab plus olaparib showed similar efficacy outcomes compared with continued chemotherapy and pembrolizumab and resulted in a more favorable safety profile

Zusammenfassung

- **MONARCH 3:** Abemaciclib mit nicht signifikanter OS Verlängerung (+13,1 Monate; HR 0,804 n.s.)
- **PARSIFAL-LONG:** OS ET + Palbociclib 65,4 Monate
- **INAVO120:** Inavolisib verlängert PFS (+7,7 Monate; HR 0,43)
- **TROPION-Breast01:** DATO-DXd verlängert PFS (+2,4 Monate; HR0,64)
- **HER2CLIMB-02:** Tucatinib verlängert PFS (+2,1 Monate; HR 0,76
- **KEYLYNK-009:** Erhaltungstherastherapie mit Pembrolizumab + Olaparib nach Induktionschemotherapie vergleichbar effektiv

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