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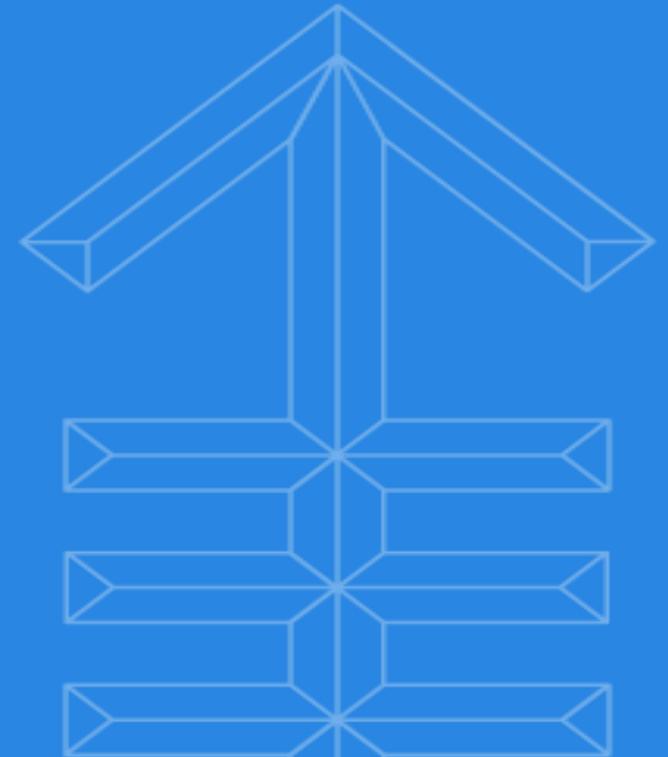
HR Positive Metastatic Breast Cancer – Are there forks in the road?

Neil M. Iyengar, MD

Associate Attending
Program Lead, MSK Healthy Living
Breast Medicine Service
Memorial Sloan Kettering Cancer Center
Associate Professor of Medicine
Weill Cornell Medicine
Associate Physician
Rockefeller University

✉ iyengarn@mskcc.org

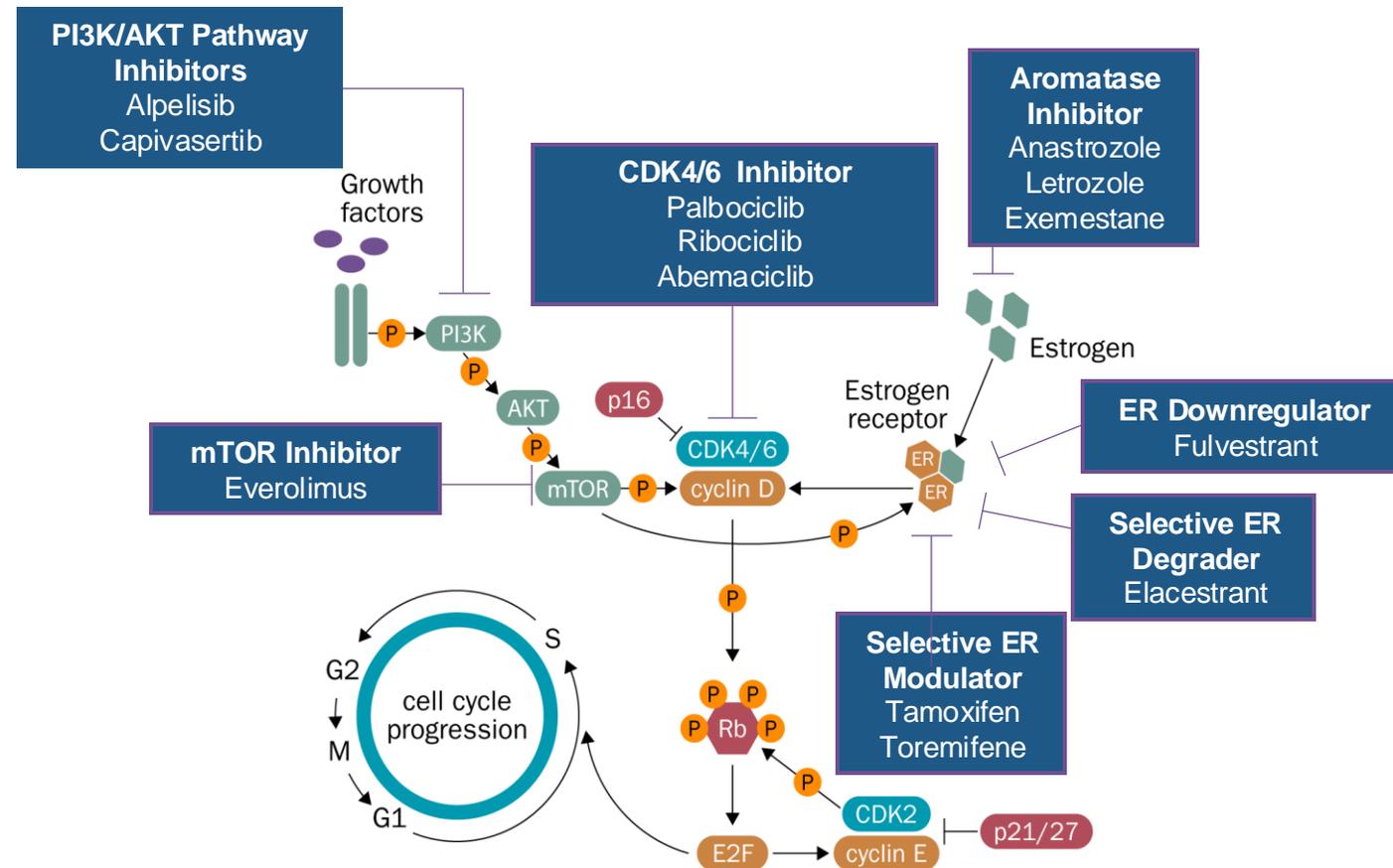
✉ [@Neil_Iyengar](https://twitter.com/Neil_Iyengar)



Targeting HR+/HER2– Breast Cancer

- HR+/HER2– breast cancer is the most common subtype, accounting for ~70% of breast cancers^{1,2}
- A significant portion of early-stage breast cancers will progress to metastatic disease
 - Among patients with metastatic HR+/HER2– breast cancer, the 5-year relative survival rate is ~30%
- While recent advances in endocrine therapy have improved prognosis in HR+/HER2– breast cancer, endocrine resistance remains a persistent concern^{3,4}
 - Most patients who initially respond to endocrine-based therapy develop resistance to it via multiple mechanisms^{3,4}

TARGETED AND ANTI-ESTROGEN THERAPIES IN HR+ ADVANCED BREAST CANCER^{3,4}



1. National Cancer Institute. Cancer Stat Facts: Female Breast Cancer Subtypes. Accessed July 20, 2022. <https://seer.cancer.gov/statfacts/html/breast-subtypes.html>. 2. Redig AJ, et al. *J Intern Med*. 2013; 274(2):113-126. 3. Portman N, et al. *Endocrine-Related Cancer*. 2019;26(1):R15-R30. 4. Brufsky AB, et al. *Oncologist*. 2018;23(5):528-539.

CDK4/6i + ET Recommended for 1L HR+/HER2– mBC¹

Phase 3 Study	PALOMA-2 ^{2,3}	MONALEESA-2 ^{4,5}	MONALEESA-7 ^{6,7}	MONARCH-3 ^{8,9}
CDK4/6 inhibitor + endocrine partner	Palbociclib + Letrozole	Ribociclib + Letrozole	Ribociclib + Tamoxifen, letrozole, or anastrozole	Abemaciclib + Letrozole or anastrozole
Comparator arm	Placebo + Letrozole	Placebo + Letrozole	Placebo + Tamoxifen, letrozole, or anastrozole	Placebo + Letrozole or anastrozole
Setting for HR+/HER2– mBC	1L	1L	1L ^a	1L
Median PFS, mo	27.6 vs 14.5 (HR, 0.56; P<0.0001)	25.3 vs 16.0 (HR, 0.57; P<0.0001)	23.8 vs 13.0 (HR, 0.55; P<0.0001)	29.0 vs 14.8 (HR, 0.54; P<0.0001)
Median OS, mo	53.9 vs 51.2 (HR, 0.96; P=0.3378)	63.9 vs 51.4 (HR, 0.76; P=0.008)	58.7 vs 48.0 (HR, 0.76)	66.8 vs 53.7 (HR, 0.80; P=0.07) ^b

- ET + CDK4/6i therapy demonstrates a consistent survival benefit as 1L therapy for HR+/HER2– MBC¹⁰
- Patients who progress on 1L ET + CDK4/6i can receive further lines of ET with or without targeted agents, but outcomes with subsequent endocrine-based therapy worsen with increasing lines of therapy^{10,11}
- Sequential single-agent chemotherapy is recommended for endocrine-resistant HR+/HER2– MBC; however, later-line chemotherapy has limited effectiveness and is associated with increased toxicity¹¹

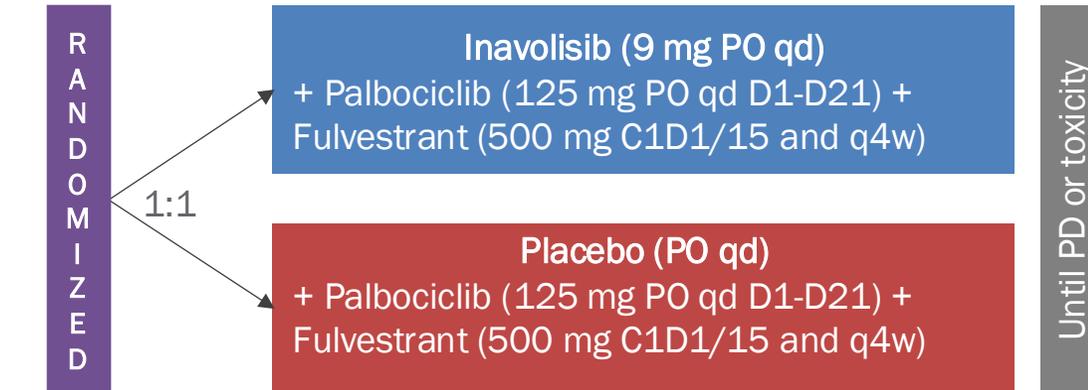
^a 1L ET; up to 1 prior line of CT permitted in advanced setting (14% of patients had received CT in advanced setting). ^b P-value did not reach threshold for statistical significance.

1. Burstein HJ, et al. *J Clin Oncol*. 2021;39(35):3959-3977. 2. Rugo HS, et al. *Breast Cancer Res Treat*. 2019;174(3):719-729. 3. Finn RS, et al. ASCO 2022. Abstract LBA1003. 4. Hortobagyi GN, et al. *Ann Oncol*. 2018;29(7):1541-1547. 5. Hortobagyi GN, et al. *N Engl J Med*. 2022; 386(10):942-950. 6. Tripathy D, et al. *Lancet Oncol*. 2018;19(7):904-915. 7. Lu Y-S, et al. *Clin Cancer Res*. 2022;28(5):851-859. 8. Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5. 9. Goetz M, et al. ESMO 2022. Abstract LBA15. 10. Burstein HJ, et al. *J Clin Oncol*. 2021;39(35):3959-3977. 11. Twelves C, et al. *Clinical Breast Cancer*. 2021;22(4):223-234.

Phase 3 INAVO120 Trial of Inavolisib in PIK3CAmut HR+/HER2- MBC

Key Eligibility Criteria

- PIK3CAmut, HR+, HER2- ABC by central ctDNA or local tissue/ctDNA test^a
- Measurable disease
- Progression during/within 12 months of adjuvant ET completion; no prior therapy for MBC
- Fasting glucose <126 mg/dL and HbA1c <6.0%



N=325

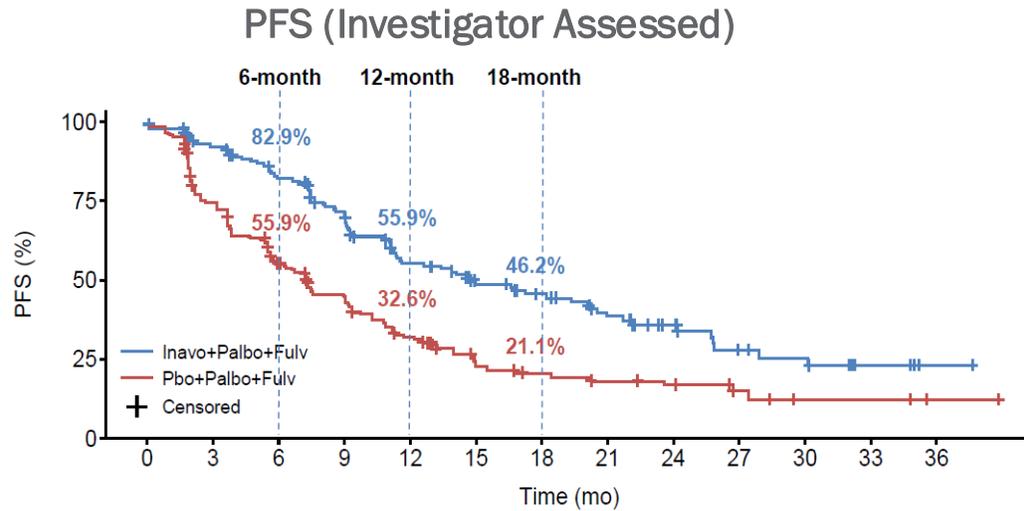
Primary endpoint: PFS by investigator

Secondary endpoints: OS (if PFS is positive), ORR, BOR, CBR, DOR, PROs

Patient Characteristics, %		Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
Median age (range), years		53.0 (27-77)	54.5 (29-79)
Race	Asian	38%	38%
	Black/African American	0.6%	0.6%
	White	58%	59%
ECOG PS	0	62%	65%
	1	37%	35%
Postmenopausal at randomization		57%	63%
Visceral disease		82%	78%
ER and PgR status	ER+/PgR+	70%	69%
	ER+/PgR-	28%	27%
Endocrine resistance	Primary	33%	35%
	Secondary	67%	64%
Prior (neo)adjuvant Chemo		82%	84%
Prior (neo)adjuvant ET	AI only	37%	43%
	Tamoxifen only	51%	45%
	AI and tamoxifen	11%	12%
Prior adjuvant CDK4/6i		1.9%	0.6%

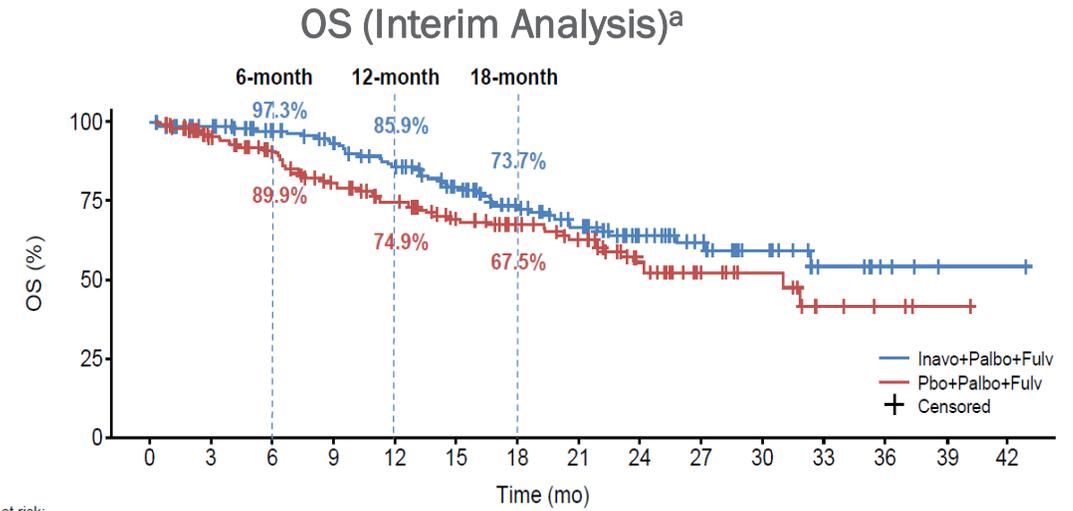
^a 301 patients (92.6%) were enrolled by ctDNA testing (284 central, 17 local); 24 (7.4%) were enrolled by local tissue testing.
Jhaveri K, et al. SABCS 2023. Abstract GS03-13.

Phase 3 INAVO₁₂₀ Trial of Inavolisib in PIK₃C_Amut HR+/HER2- MBC



Patients at risk:
 Inavo+Palbo+Fulv
 Pbo+Palbo+Fulv

Time (mo)	0	3	6	9	12	15	18	21	24	27	30	33	36
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



Patients at risk:
 Inavo+Palbo+Fulv
 Pbo+Palbo+Fulv

Time (mo)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
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

PFS	Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
PFS events, n (%)	82 (50.9)	113 (68.9)
Median PFS (95% CI), mo	15.0 (11.3-20.5)	7.3 (5.6-9.3)
Stratified HR (95% CI)	0.43 (0.32-0.59)	
P value	P<0.0001	

OS	Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
Events, n (%)	42 (26.1)	55 (33.5)
Median OS (95% CI), mo	NE (27.3-NE)	31.1 (22.3-NE)
Stratified HR (95% CI)	0.64 (0.43-0.97)	
P value	P=0.0338	

Data cutoff date: September 29, 2023. Median follow-up: 21.3 months.

^a The prespecified boundary for OS ($P=0.0098$ or $HR=0.592$) was not crossed at this interim analysis.

Jhaveri K, et al. SABCS 2023. Abstract GS03-13.

Phase 3 INAVO120 Trial of Inavolisib in PIK3CAmut HR+/HER2- MBC

AEs ≥20% Incidence in Either Group, %	Inavo + Palbo + Fulv (n=162)		Pbo + Palbo + Fulv (n=162)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Neutropenia	89%	80%	91%	78%
Thrombocytopenia	48%	14%	45%	4%
Anemia	37%	6%	36%	2%
Stomatitis/Mucositis	51%	6%	27%	0
Hyperglycemia	59%	6%	9%	0
Diarrhea	48%	4%	16%	0
Nausea	28%	<2%	17%	0
Rash	25%	0	17%	0
Decreased appetite	24%	<2%	9%	<2%
Fatigue	24%	<2%	13%	<2%
COVID-19	23%	<2%	11%	<2%
Headache	21%	<2%	14%	<2%
Leukopenia	17%	7%	25%	11%
Ocular toxicities	22%	0	13%	0

Overview of AEs, %	Inavo + Palbo + Fulv (n=162)	Pbo + Palbo + Fulv (n=162)
Any AEs	99%	100%
Grade 3-4 AEs	88%	82%
Grade 5 AE ^a	4%	1%
Serious AE	24%	11%
Leading to discontinuation	7%	0.6%
Inavolisib/placebo	6%	0.6%
Palbociclib	5%	0
Fulvestrant	3%	0
Leading to dose modification/interruption of treatment	83%	75%
Inavolisib/placebo	70%	35%
Palbociclib	77%	72%
Fulvestrant	32%	21%

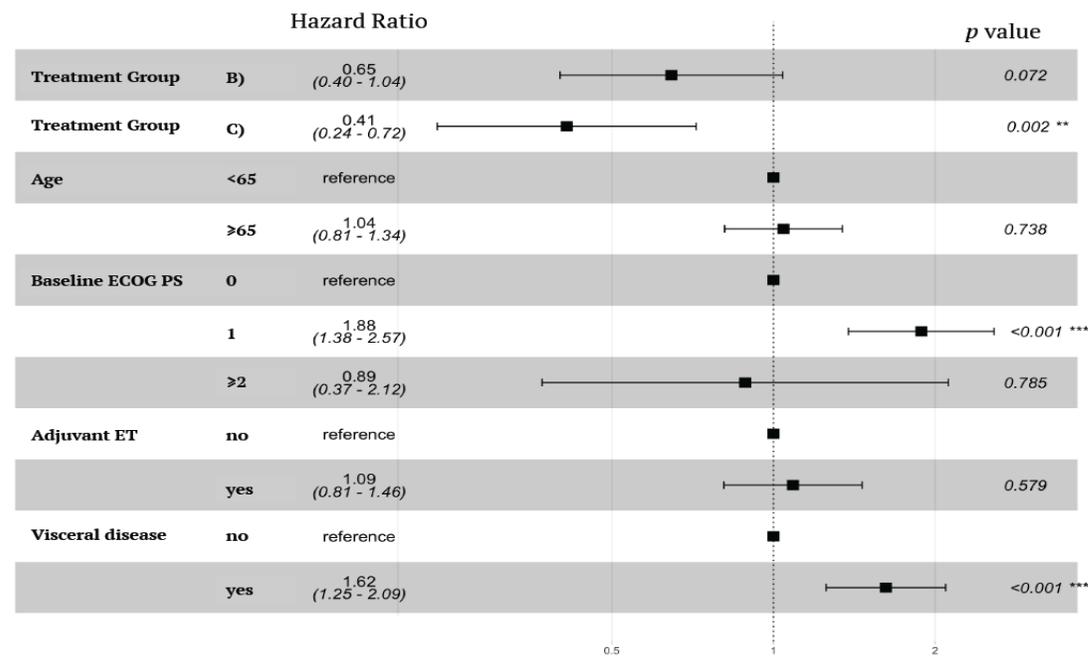
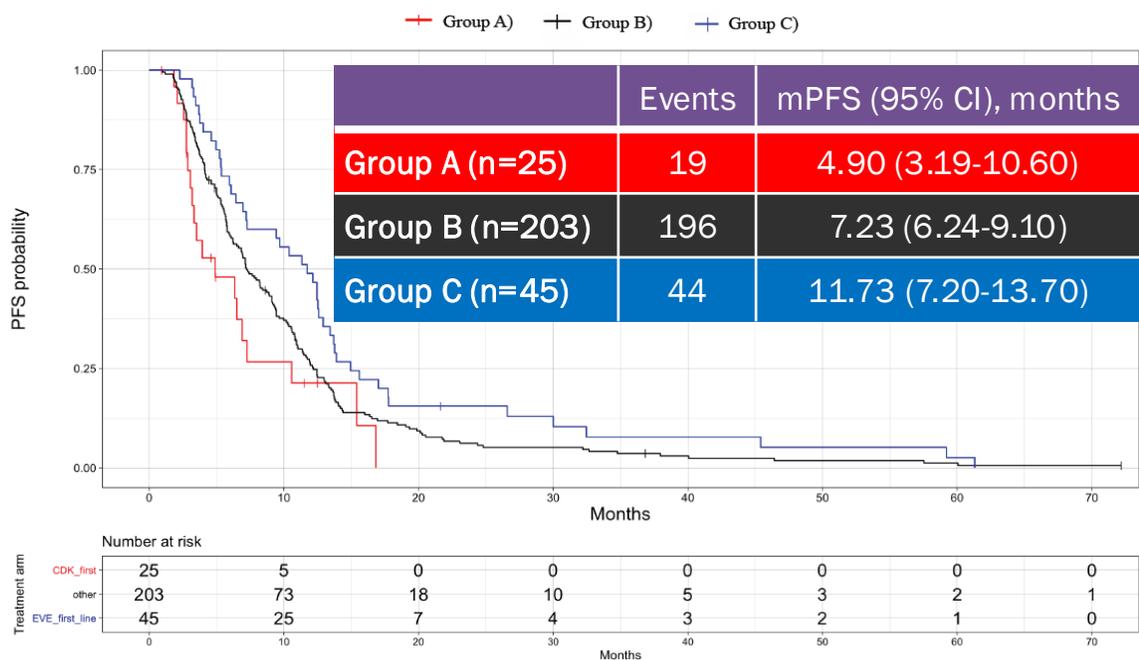
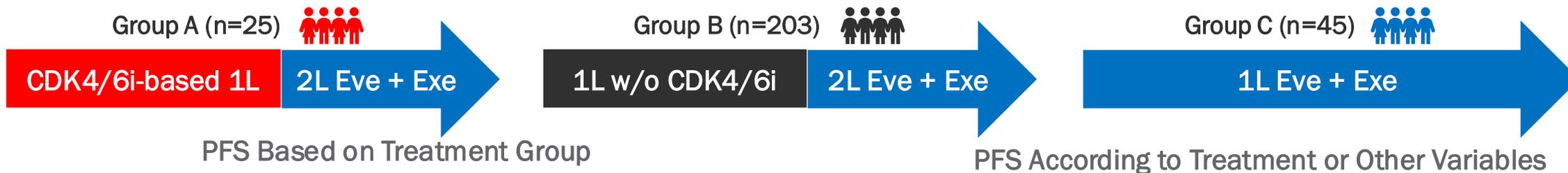
^a None of the grade 5 AEs were reported as related to study treatment by investigators.

NCCN Guidelines Update: HR+/HER2– MBC

Setting	Preferred Regimens	Other Recommended Regimens (First and Subsequent Lines)
First line	AI + CDK4/6 inhibitor <ul style="list-style-type: none"> AI + ribociclib (Category 1) AI + abemaciclib AI + palbociclib 	Selective ER downregulator <ul style="list-style-type: none"> Fulvestrant Elacestrant for <i>ESR1</i>mut tumors
	Fulvestrant + CDK4/6 inhibitor <ul style="list-style-type: none"> Fulvestrant + ribociclib (Category 1) Fulvestrant + abemaciclib (Category 1) Fulvestrant + palbociclib 	Selective ER downregulator (fulvestrant, Category 1) + nonsteroidal AI (anastrozole, letrozole) (Category 1) Nonsteroidal AI <ul style="list-style-type: none"> Anastrozole Letrozole
Second line	Fulvestrant + CDK4/6 inhibitor, if CDK4/6 inhibitor not previously used (Category 1)	Selective ER modulator <ul style="list-style-type: none"> Tamoxifen
	<ul style="list-style-type: none"> Alpelisib + fulvestrant for <i>PIK3CA</i> activating mutations (Category 1) Capivasertib + fulvestrant for <i>PIK3CA/AKT1/PTEN</i> activating mutations (Category 1) 	Steroidal aromatase inactivator <ul style="list-style-type: none"> Exemestane
	Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)	

EVERMET: Retrospective, Multicenter Evaluation of Everolimus + Exemestane Based on Previous Therapy

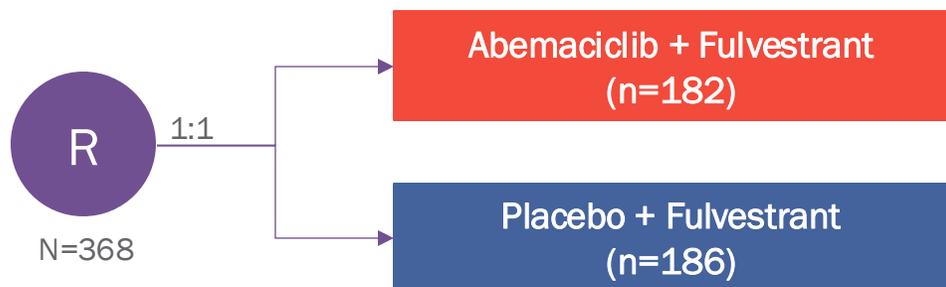
STUDY DESIGN



postMONARCH Phase 3 Trial: Abemaciclib + Fulvestrant vs Fulvestrant for HR+/HER2- MBC Post CDK4/6i

Key Eligibility Criteria

- HR+/HER2- ABC
- Men and pre/post-menopausal women
- Prior therapy:
 - Disease progression on CDK4/6i + AI as initial therapy in ABC setting or recurrence on/after CDK4/6i + ET in adjuvant setting
 - No other therapy for ABC



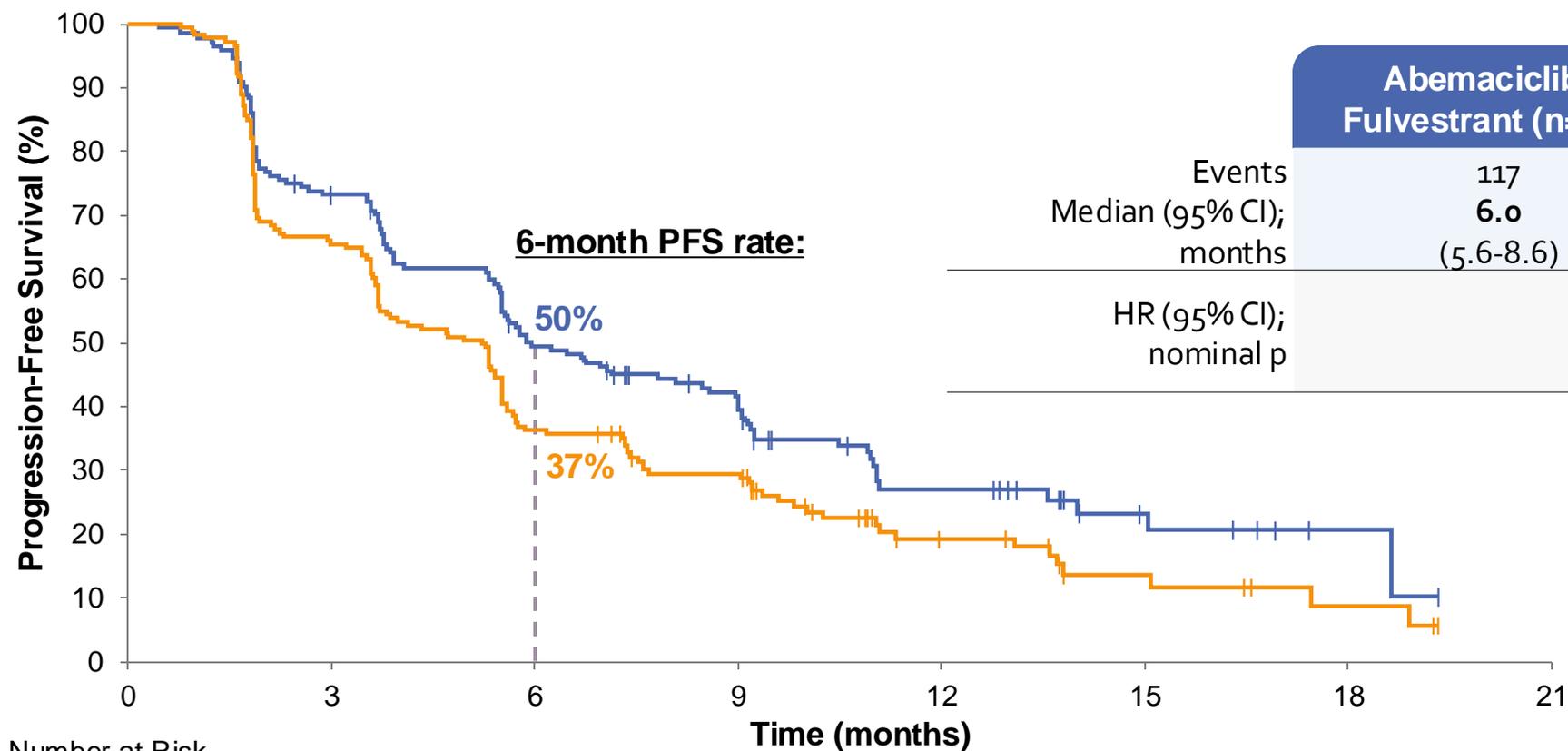
Primary endpoint: PFS (INV)

Key secondary endpoints: OS, PFS by BICR, ORR, CBR, DCR, DoR, safety, PK, and PRO

Patient Characteristics, %		Abemaciclib + Fulv (n=182)	Placebo + Fulv (n=186)
Median age (range), years		58 (27-86)	61 (28-85)
ECOG PS	0	57%	58%
	1	43%	43%
HR status	ER+	100%	99%
	PR+	79%	81%
Measurable disease		72%	68%
Visceral metastasis		62%	59%
Site of metastasis	Liver	37%	38%
	Bone-only	18%	23%
Prior CDK4/6i setting	ABC	100%	98%
	Adjuvant	0%	2%
Prior CDK4/6i	Palbociclib	59%	59%
	Ribociclib	34%	33%
	Abemaciclib	8%	8%
Prior CDK4/6i duration	≥12 months ^a	71%	77%
	<12 months ^b	29%	22%
Median prior CDK4/6i duration (mo; range) ^c		19 (2-110)	21 (3-87)

^a ≥12 months ABC or recurrence after EBC therapy. ^b 12 months ABC or recurrence on EBC therapy. ^c for ABC.

postMONARCH Phase 3 Trial: Abemaciclib + Fulvestrant vs Fulvestrant for HR+/HER2- MBC Post CDK4/6i



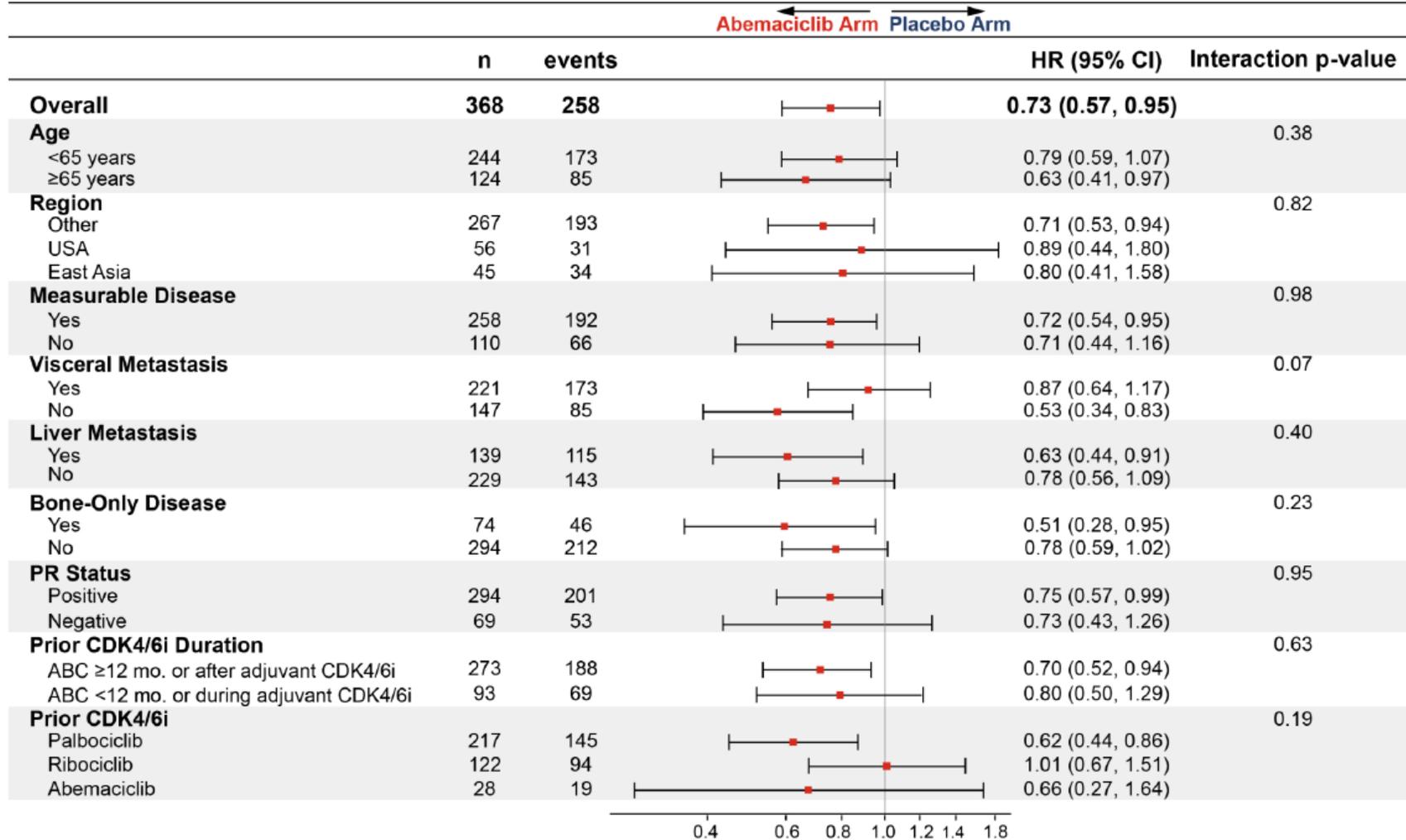
	Abemaciclib + Fulvestrant (n=182)	Placebo + Fulvestrant (n=186)
Events	117	141
Median (95% CI); months	6.0 (5.6-8.6)	5.3 (3.7-5.6)
HR (95% CI); nominal p	0.73 (0.57-0.95) 0.02	

Number at Risk

Time (months)	0	3	6	9	12	15	18	21
Abemaciclib + Fulvestrant (n=182)	182	124	80	61	21	9	2	0
Placebo + Fulvestrant (n=186)	186	114	62	47	17	7	3	0

postMONARCH Phase 3 Trial: Abemaciclib + Fulvestrant vs Fulvestrant for HR+/HER2- MBC Post CDK4/6i

INV-Assessed PFS by Subgroup



SOLAR-1 Phase 3 Trial of Alpelisib + Fulvestrant in HR+/HER2- MBC

Key Eligibility Criteria

- Eligible to receive ET after relapse or progression
- Received AI treatment in neo/adjuvant or metastatic setting
- No previous chemotherapy for advanced disease
- No previous fulvestrant or PI3K, AKT, or mTOR inhibitors
- **No type 1 or uncontrolled type 2 diabetes**
- **Fasting glucose \leq 140 mg/dL or HbA1c $<$ 6.5%^a**



Primary endpoint: PFS by investigator in patient cohort with *PIK3CA*-mutated cancer

Secondary endpoints: OS in patient cohort with *PIK3CA*-mutated cancer, PFS in patient cohort without *PIK3CA*-mutated cancer, ORR, CBR, safety

Stratification factors: Lung or liver metastases, prior CDK4/6i

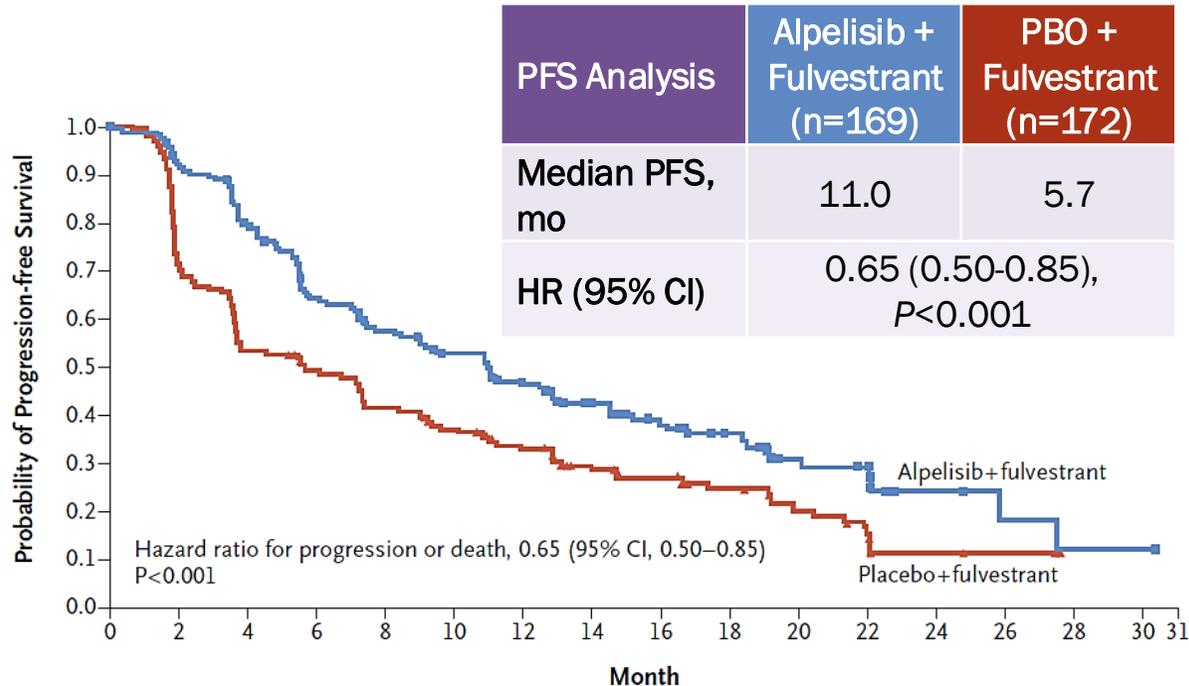
Patient Characteristics, n (%)		With <i>PIK3CA</i> mut		Without <i>PIK3CA</i> mut	
		A+F (n=169)	P+F (n=172)	A+F (n=115)	P+F (n=116)
Median age (range), years		63 (25-87)	64 (38-92)	62 (39-82)	63 (32-88)
Metastatic sites	Bone only	25%	20%	23%	20%
	Visceral	55%	58%	57%	64%
Endocrine status	Primary	14%	13%	27%	22%
	Secondary	71%	74%	57%	56%
	Sensitivity	12%	11%	14%	17%
Line of treatment in advanced disease	First line	52%	52%	62%	53%
	Second line	47%	48%	37%	46%
Prior treatment	Any CDK4/6i	5.3%	6.4%	6.1%	6.9%
	Chemotherapy	60%	62%	68%	62%

^a HbA1c levels was an amendment to the original protocol implemented after the start of the study to lower rates of treatment discontinuation.² ^b Administered as intramuscular injection on days 1 and 15 of cycle 1 and on day 1 of subsequent cycles.

1. Andre F, et al. *N Engl J Med*. 2019;380(20):1929-1940. 2. Rugo HS, et al. *Ann Oncol*. 2020;31(8):1001-1010.

SOLAR-1 Phase 3 Trial of Alpelisib + Fulvestrant in HR+/HER2- MBC

PIK3CA-Mutated Cohort



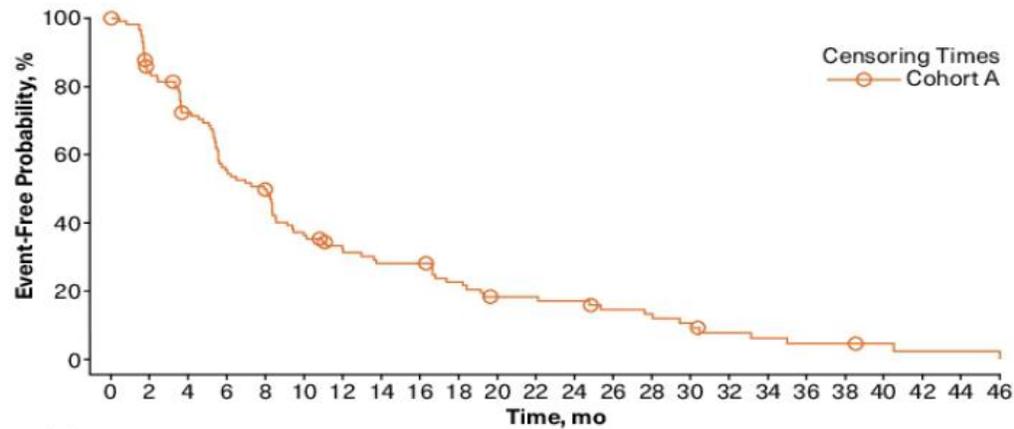
No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	31
Alpelisib+fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo+fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

- Alpelisib + fulvestrant demonstrated improved PFS vs placebo + fulvestrant in patients with *PIK3CA*-mutated, HR+/HER2- advanced breast cancer who received prior endocrine therapy
- Key grade 3/4 AEs of concern in the alpelisib + fulvestrant vs placebo + fulvestrant arms were hyperglycemia (37% vs 1%), rash (10% vs <1%), and diarrhea (7% vs <1%)
- The frequency of discontinuations due to AEs in the alpelisib + fulvestrant vs placebo + fulvestrant arms were 25% vs 4%, respectively

BYLieve Phase 2 Trial of Alpelisib + ET in PIK₃C_Amut HR+ MBC Post-CDK₄/6i

Cohort A PFS

Alpelisib + Fulvestrant in Patients Who Received CDK4/6i + AI

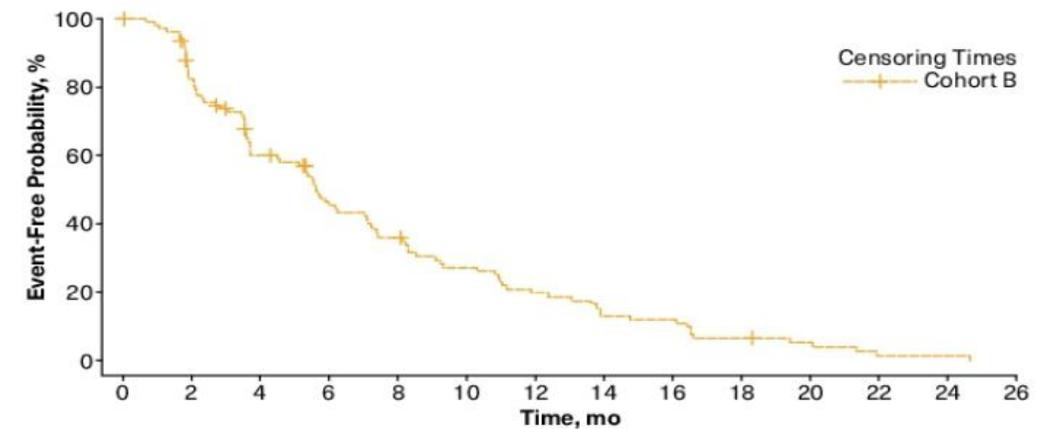


Number at risk
Cohort A 119 93 77 59 52 38 31 27 27 21 15 15 14 11 10 8 5 4 3 3 2 1 1 0

Cohort A PFS	A+F (n=119)
Events, n (%)	98 (82.4)
Median follow-up, mo	5.95
Median PFS, mo (95% CI)	8.0 (5.6-8.6)
Cohort A OS	
Events, n (%)	71 (59.7)
Median follow-up, mo	21.78
Median OS, mo (95% CI)	27.3 (21.3-32.7)

Cohort B PFS

Alpelisib + Letrozole in Patients Who Received CDK4/6i + Fulvestrant



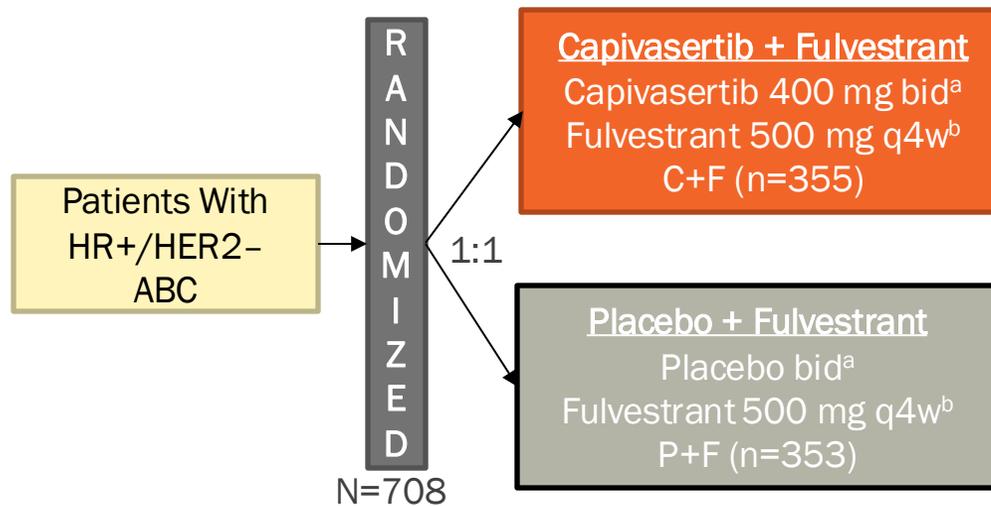
Number at risk
Cohort B 114 88 61 43 34 25 18 12 11 6 4 1 1 0

Cohort B PFS	A+L (n=114)
Events, n (%)	97 (85.1)
Median follow-up, mo	5.19
Median PFS, mo (95% CI)	5.6 (3.7-7.1)
Cohort B OS	
Events, n (%)	66 (57.9)
Median follow-up, mo	25.33
Median OS, mo (95% CI)	29.0 (24.5-34.8)

CAPitello-291 Phase 3 Trial of Capiivasertib + Fulvestrant in AI-Resistant HR+/HER2- MBC: Study Design and Patients

Key Eligibility Criteria

- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6i allowed (at least 51% required)
- HbA1c < 8.0%



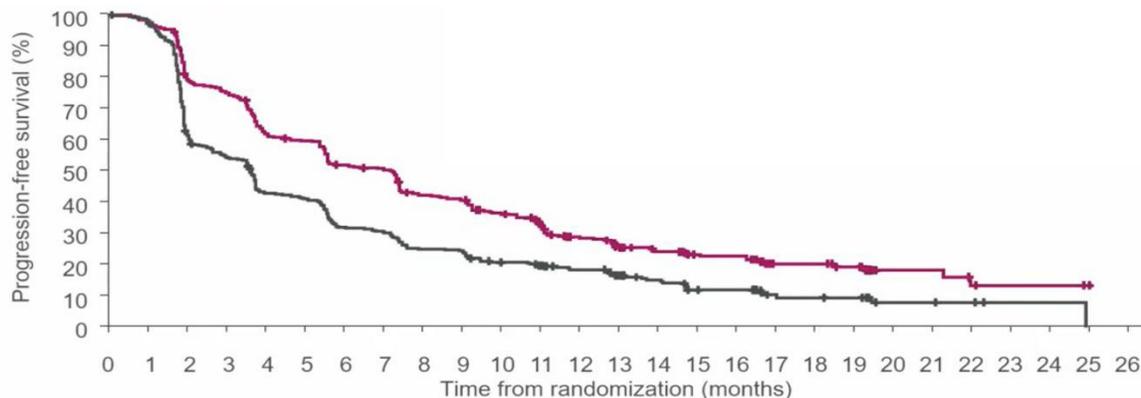
Dual primary endpoints: PFS by investigator in overall and in AKT pathway-altered tumors^c
Secondary endpoints: OS, ORR

Patient Characteristics, n (%)	Overall Population		AKT Pathway Altered	
	C+F (n=355)	P+F (n=353)	C+F (n=155)	P+F (n=134)
Median age (range), years	59 (26-84)	58 (26-90)	58 (36-84)	60 (34-90)
Metastatic sites	Bone only	51 (14.4)	52 (14.7)	25 (16.1)
	Liver ^d	156 (43.9)	150 (42.5)	70 (45.2)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)
HR status ^e	ER+/PR+	255 (71.8)	246 (69.7)	116 (74.8)
	ER+/PR-	94 (26.5)	103 (29.2)	35 (22.6)
	Unknown	5 (1.4)	4 (1.1)	4 (2.6)
Endocrine resistance	Primary	127 (35.8)	135 (38.2)	60 (38.7)
	Secondary	228 (64.2)	218 (61.8)	95 (61.3)
Prior endocrine therapy for ABC	0	40 (11.3)	54 (15.3)	14 (9.0)
	1	286 (80.6)	252 (71.4)	130 (83.9)
	2	29 (8.2)	47 (13.3)	11 (7.1)
Prior CDK4/6i for ABC	245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Prior CT	(Neo)adjuvant	180 (50.7)	170 (48.2)	79 (51.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)
AKT pathway alteration	155 (43.7)	134 (38.0)	-	-

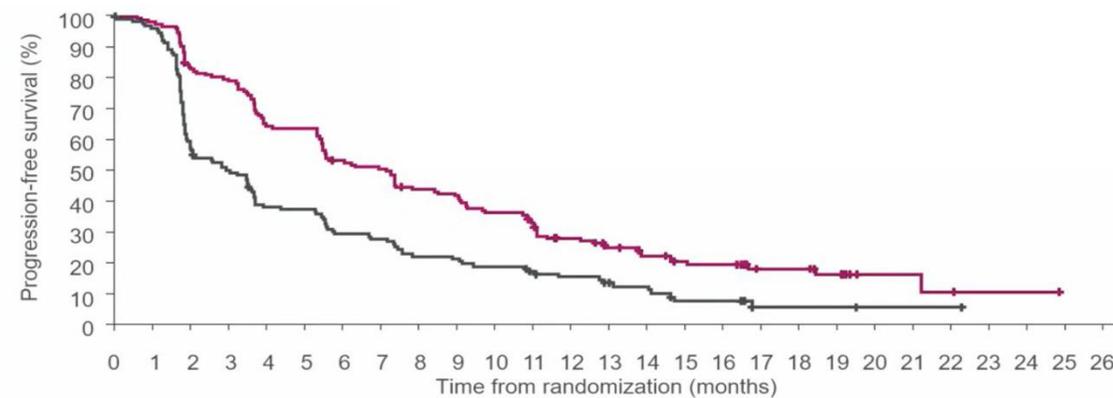
^a 4 days on, 3 days off. ^b Cycle 1, days 1 & 15; then q4w. ^c AKT pathway-altered tumors: ≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration. ^d Baseline stratification factor. ^e One patient in the C+F group was ER negative.

CAPitello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2- MBC: Primary Endpoint

PFS by Investigator in Overall Population



PFS by Investigator in the AKT Pathway-Altered Population



Overall Population	C+F (n=355)	P+F (n=353)
PFS events	258	293
Median PFS, mo (95% CI)	7.2 (5.5-7.4)	3.6 (2.8-3.7)
Adjusted HR (95% CI)	0.60 (0.51-0.71)	
Two-sided P value	<0.001	

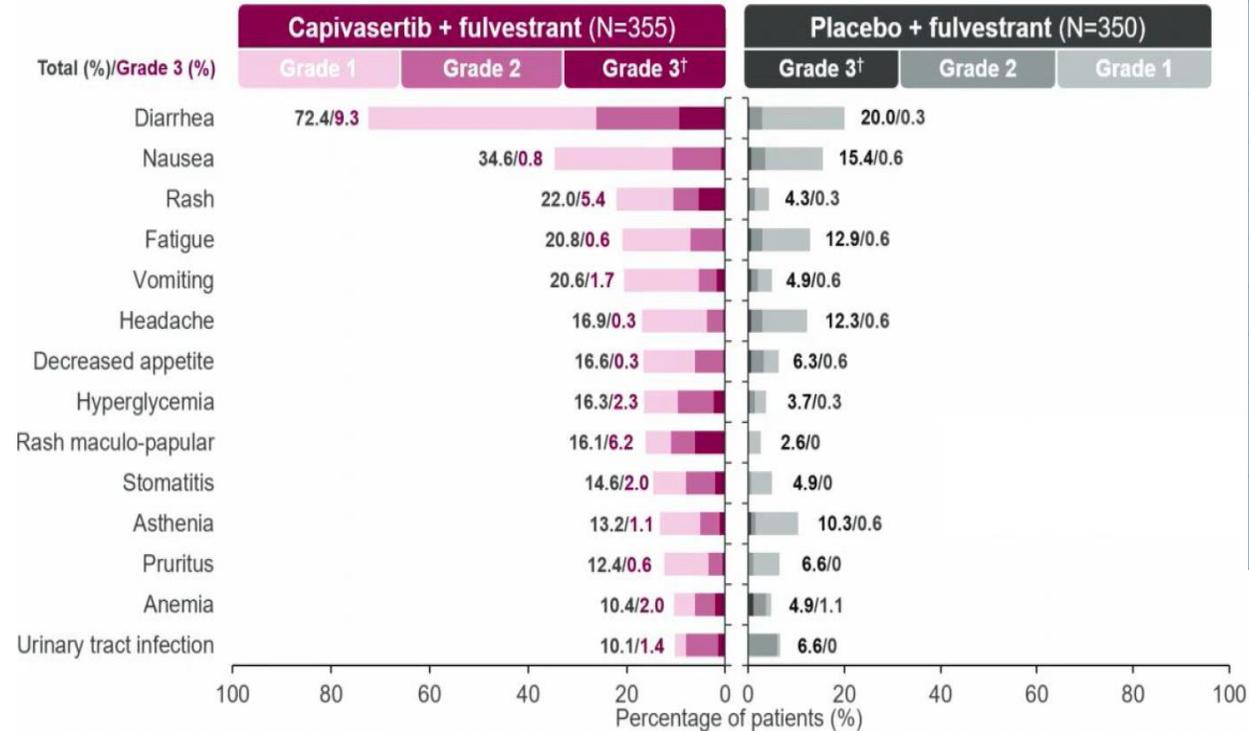
Overall Population	C+F (n=155)	P+F (n=134)
PFS events	121	115
Median PFS, mo (95% CI)	7.3 (5.5-9.0)	3.1 (2.0-3.7)
Adjusted HR (95% CI)	0.50 (0.38-0.65)	
Two-sided P value	<0.001	

- PFS benefit was observed in all key subgroups, including regardless of prior use of CDK4/6i and liver metastases

HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6i and geographic region.

CAPitello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2- MBC: Safety

AEs (>10% of Patients)



Safety Summary, n (%)	C+F (n=355)	P+F (n=350)
Any AE	343 (96.6)	288 (82.3)
Serious AE	57 (16.1)	28 (8.0)
AE leading to death ^a	4 (1.1)	1 (0.3)
AE leading to discontinuation	46 (13.0)	8 (2.3)
Discontinuation of C/P only	33 (9.3)	2 (0.6)
Discontinuation of both C/P and F	13 (3.7)	6 (1.7)
AE leading to dose interruption of C/P only	124 (34.9)	36 (10.3)
AE leading to dose reduction of C/P only	70 (19.7)	6 (1.7)

^a Grade 5 events included acute myocardial infarction, cerebral hemorrhage, pneumonia aspiration, and sepsis (all n=1) in the C+F group and COVID-19 (n=1) in the P+F group. No grade 5 events were classified as related to C/P by local investigator. The safety analysis population included all patients who received at least 1 dose of the study drug.

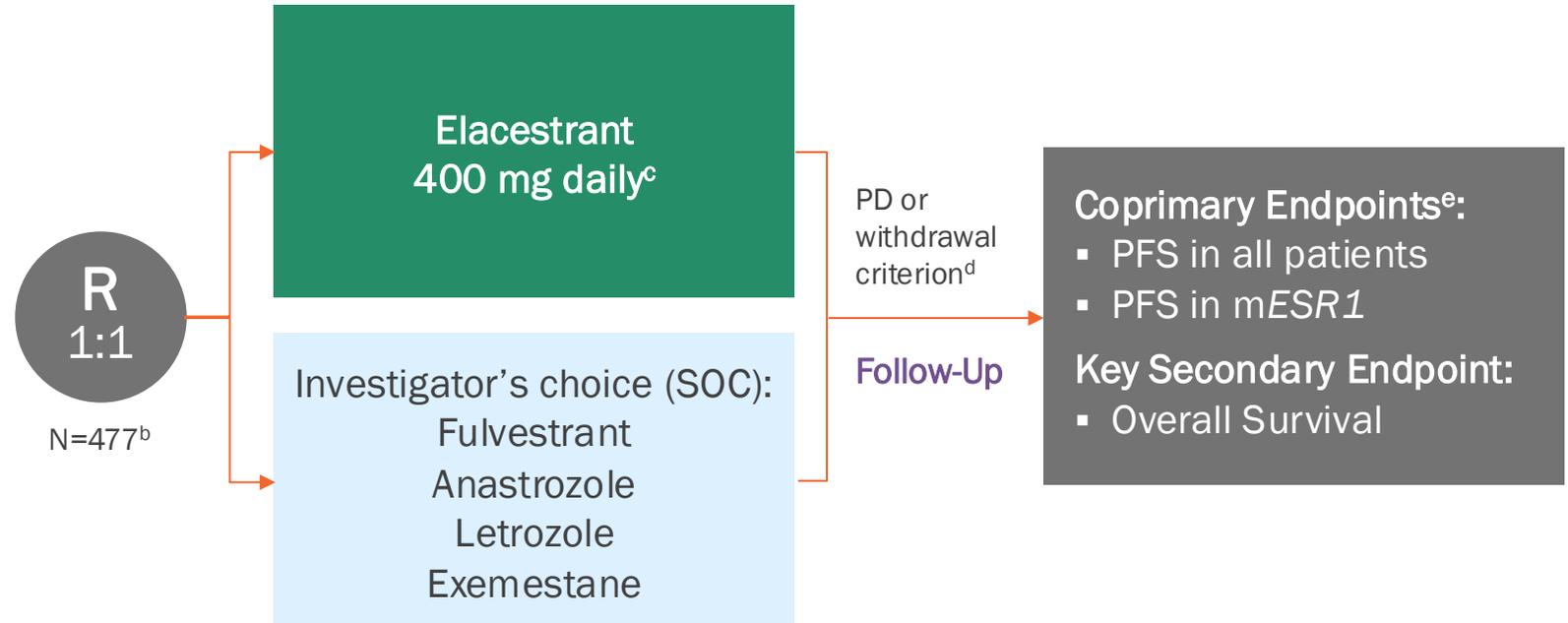
EMERALD: Phase 3 Trial of Elacestrant in ER+/HER2- MBC

Inclusion Criteria:

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,^a HER2-
- Progressed or relapsed on or after 1-2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0-1

Stratification Factors:

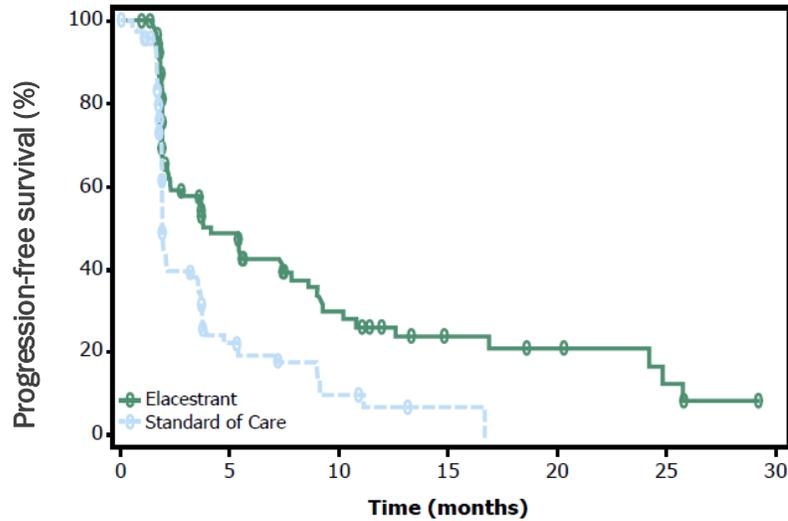
- *ESR1*-mutation status^f
- Prior treatment with fulvestrant
- Presence of visceral metastases



^a Defined as documentation of ER+ tumor with ≥1% staining by immunohistochemistry. ^b Patients were recruited from February 2019 to October 2020. ^c Protocol-defined reductions of elacestrant were permitted. ^d Restaging CT scans were performed every 8 weeks. ^e Per Blinded Independent Central Review. ^f *ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).
Bardia A, et al. SABCS 2021. Abstract GS2-02.

EMERALD: PFS in the *mESR1* Population* by Duration of CDK4/6i

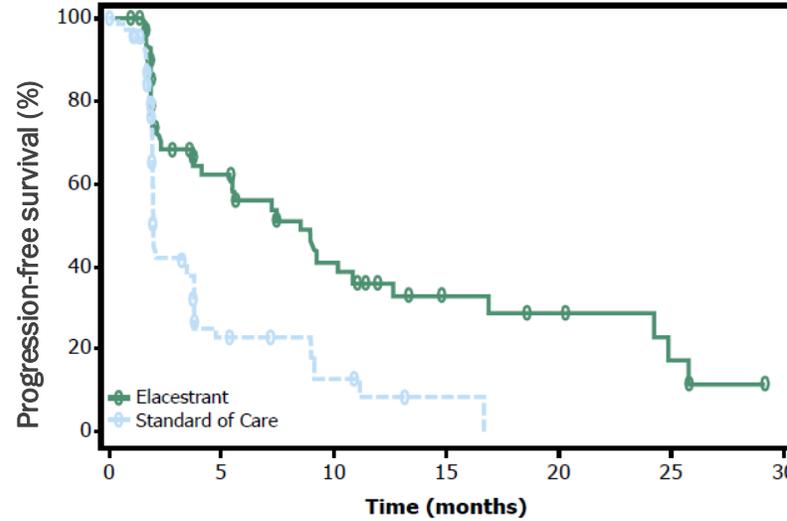
At least 6 mo



Elacestrant 103 50 33 25 20 16 11 9 8 7 6 5 5 1 1 0
SOC 102 34 16 11 9 5 2 1 1 0

At least 6 mo	Elacestrant (n=103)	SOC (n=102)
Median PFS, mo (95% CI)	4.14 (2.20-7.79)	1.87 (1.87-3.29)
PFS rate at 12 mo, % (95% CI)	26.02 (15.12-36.92)	6.45 (0.00-13.65)
HR (95% CI)	0.517 (0.361-0.738)	

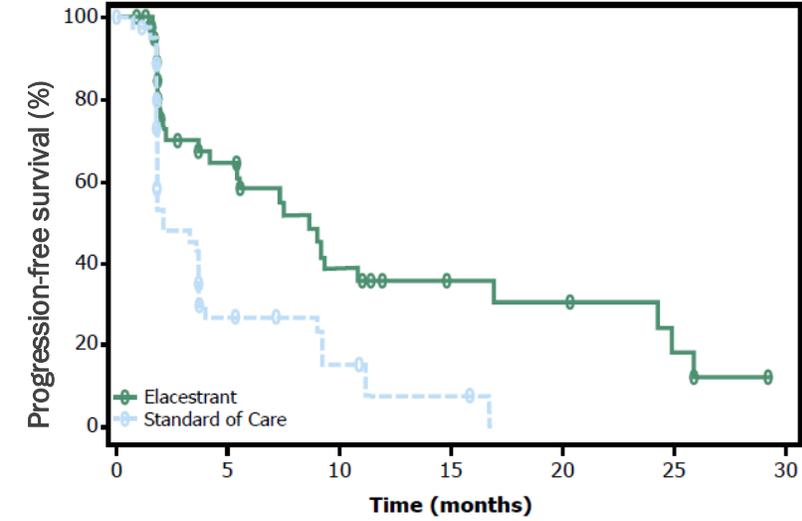
At least 12 mo



Elacestrant 78 42 31 24 20 16 11 9 8 7 6 5 5 1 1 0
SOC 81 26 12 10 9 5 2 1 1 0

At least 12 mo	Elacestrant (n=78)	SOC (n=81)
Median PFS, mo (95% CI)	8.61 (4.14-10.84)	1.91 (1.87-3.68)
PFS rate at 12 mo, % (95% CI)	35.81 (21.84-49.78)	8.39 (0.00-17.66)
HR (95% CI)	0.410 (0.262-0.634)	

At least 18 mo



Elacestrant 55 30 23 18 16 12 8 8 7 6 6 5 5 1 1 0
SOC 56 21 9 8 7 4 1 1 1 0

At least 18 mo	Elacestrant (n=55)	SOC (n=66)
Median PFS, mo (95% CI)	8.61 (5.45-16.89)	2.10 (1.87-3.75)
PFS rate at 12 mo, % (95% CI)	35.79 (19.54-52.05)	7.73 (0.00-20.20)
HR (95% CI)	0.466 (0.270-0.791)	

*Elacestrant is FDA approved for the treatment of ER+/HER2, *ESR1*-mutated advanced or MBC with disease progression following at least one line of endocrine therapy. The presence of *ESR1* mutation(s) in plasma is to be confirmed using an FDA-approved test; in EMERALD, *ESR1* mutational status was determined using the Guardant360 CDx assay on ctDNA from blood.

EMERALD: Phase 3 Trial of Elacestrant in ER+/HER2– MBC

Most Common AEs (≥10%)

AE, %	Elacestrant (n=237)		SOC (n=229)	
	All grades	Grade 3-4	All grades	Grade 3-4
Nausea	35%	2.5%	19%	0.9%
Fatigue	19%	0.8%	19%	0.9%
Vomiting	19%	0.8%	8.3%	0
Decreased appetite	15%	0.8%	9.2%	0.4%
Arthralgia	14%	0.8%	16%	0
Diarrhea	14%	0	10%	0.9%
Back pain	14%	2.5%	9.6%	0.4%
AST increased	13%	1.7%	12%	0.9%
Headache	12%	1.7%	11%	0
Constipation	12%	0	6.6%	0
Hot flush	11%	0	8.3%	0
Dyspepsia	10%	0	2.6%	0
ALT increased	9%	2.1%	10%	0.4%

Safety Summary

- AEs of any grade leading to discontinuation in the safety population occurred in **15 patients (6.3%)** in the elacestrant arm and **10 patients (4.4%)** in the SOC arm
- Elacestrant demonstrated a predictable and manageable safety profile consistent with other endocrine therapies

NCCN Guidelines®: Systemic Therapy Regimens for HR+/HER2–Endocrine Resistant Breast Cancer (Recurrent or Stage IV)



NCCN Guidelines Version 4.2023 Invasive Breast Cancer

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SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE^a

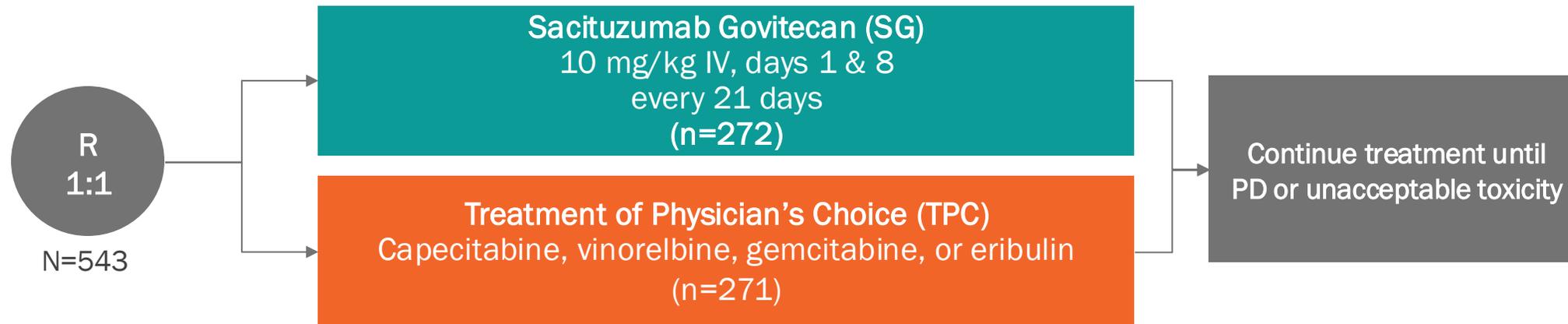
HR-Positive and HER2-Negative with Visceral Crisis [†] or Endocrine Refractory		
Setting	Subtype/Biomarker	Regimen
First Line	No germline <i>BRCA1/2</i> mutation ^b	Systemic chemotherapy see BINV-Q (5)
	Germline <i>BRCA1/2</i> mutation ^b	PARPi (olaparib, talazoparib) ^c (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative ^d	Fam-trastuzumab deruxtecan-nxki ^e (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan- nxki	Sacituzumab govitecan ^f (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)

[†] According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1625) for advanced breast cancer visceral crisis is defined as: "severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy."

TROPiCS-02: Phase 3 Trial of Sacituzumab Govitecan (SG) in HR+/HER2– MBC

Key Eligibility Criteria

- HR+/HER2– mBC^a (or locally recurrent inoperable) with PD after:
 - ≥1 endocrine therapy, taxane, and CDK4/6i in any setting
 - ≥2 to ≤4 lines of chemotherapy for metastatic disease
 - Measurable disease by RECIST 1:1



Primary Endpoint:

- PFS by BICR

Secondary Endpoints:

- OS, ORR, DOR, CBR by LIR and BICR, PRO, safety

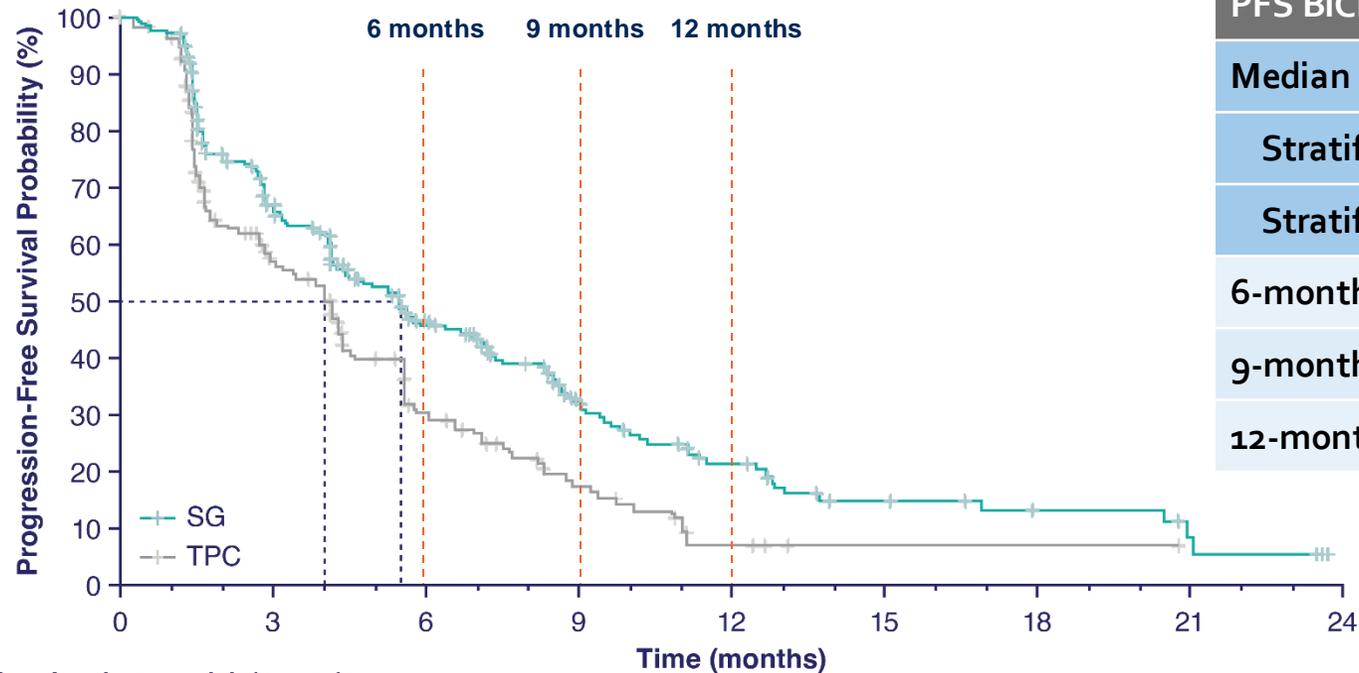
^a HER2–= IHC≤2+ or fluorescence in situ hybridization negative.

TROPiCS-02: Baseline Characteristics

Patient Characteristics		SG (n=272)	TPC (n=271)
Median age (range), years		57 (29-86)	55 (27-78)
ECOG PS, n (%)	0	116 (43)	126 (46)
	1	156 (57)	145 (54)
Visceral mets at baseline, n (%)		259 (95)	258 (95)
Liver mets, n (%)		229 (84)	237 (87)
Median time from initial MBC diagnosis to randomization (range), months		48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)		173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥ 6 months, n (%)		235 (86)	234 (86)
Prior CDK4/6i, n (%)	≤ 12 months	161 (59)	166 (61)
	> 12 months	106 (39)	102 (38)
	Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting (range), n		3 (0-8)	3 (1-5)

TROPiCS-02: PFS (Primary Endpoint)

PFS in the ITT Population



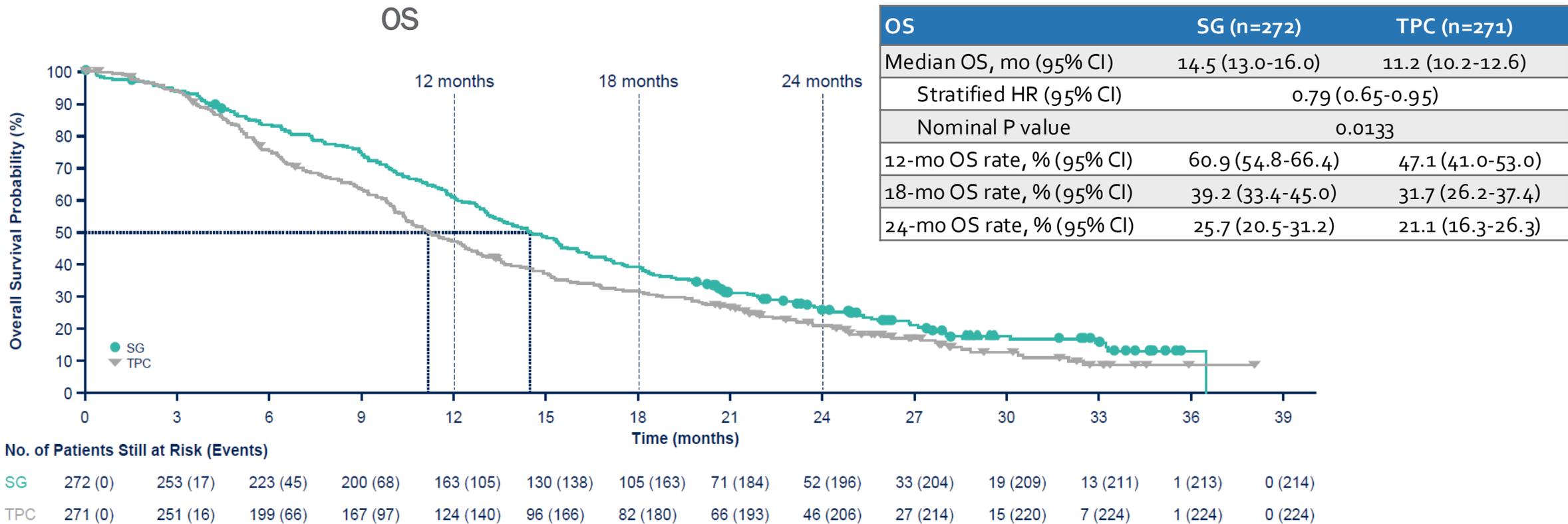
PFS BICR	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2-7.0)	4.0 (3.1-4.4)
Stratified HR (95% CI)	0.66 (0.53-0.83)	
Stratified Log Rank P value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2-28.1)	7.1 (2.8-13.9)

No. of patients at risk (events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

- In subgroup analyses, SG demonstrated a generally consistent PFS benefit across predefined subgroups, including patients with ≥ 3 prior chemotherapy regimens in the metastatic setting, visceral metastases, and age ≥ 65 years

TROPiCS-02: OS (Final Update)

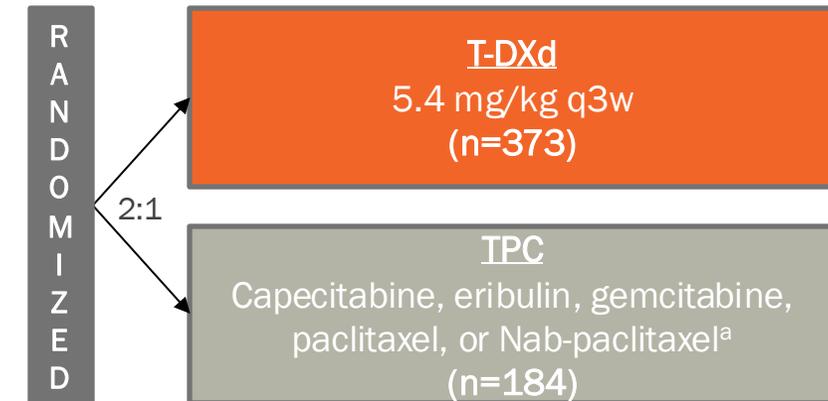


- SG demonstrated a statistically significant improvement in OS vs TPC with 21% reduction in the risk of death; having met statistical significance, no further formal statistical testing of OS will occur
- Patients who received SG survived a median of **3.2 months longer** than those who received TPC

Updated Survival Results From DESTINY-Breast04 Phase 3 Trial of T-DXd vs TPC in HER2-Low MBC: Study Design and Patients

Key Eligibility Criteria

- HER2-low (IHC 1+ or IHC 2+/ISH-) unresectable and/or MBC
- ≥1 prior line of Chemo in the metastatic setting
- ≥1 line of ET if HR+ MBC



N=557

Primary endpoint: PFS by BICR (HR+)

Key secondary endpoints^b: PFS by BICR (all patients), OS (HR+ and all patients)

Secondary endpoints: PFS by INV, ORR (BICR and INV), DoR (BICR), safety, PROs (HR+)

Patient Characteristics	HR+		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=373)	TPC (n=184)
Median age (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
HER2 status (IHC), n (%)	1+	193 (58)	215 (58)	106 (58)
	2+/ISH-	138 (42)	158 (42)	78 (42)
HR positive, ^c n (%)	328 (99)	162 (99)	333 (89)	166 (90)
ECOG PS, n (%)	0	187 (56)	200 (54)	105 (57)
	1	144 (44)	173 (46)	79 (43)
Metastases at baseline, n (%)	Brain	18 (5)	7 (4)	24 (6)
	Liver	247 (75)	116 (71)	266 (71)
	Lung	98 (30)	58 (36)	120 (32)
Prior lines of Chemo (MBC setting)	Median (range)	1 (0-3)	1 (0-2)	1 (0-3)
	≥3, n (%)	3 (0.9)	0	6 (1.6)
Prior lines of ET (MBC setting)	Median (range)	2 (0-7)	2 (0-6)	2 (0-7)
	≥3, n (%)	88 (27)	44 (27)	90 (24)
Prior targeted cancer therapy, n (%)	Targeted	259 (78)	132 (81)	279 (75)
	CDK4/6i	233 (70)	115 (71)	239 (64)

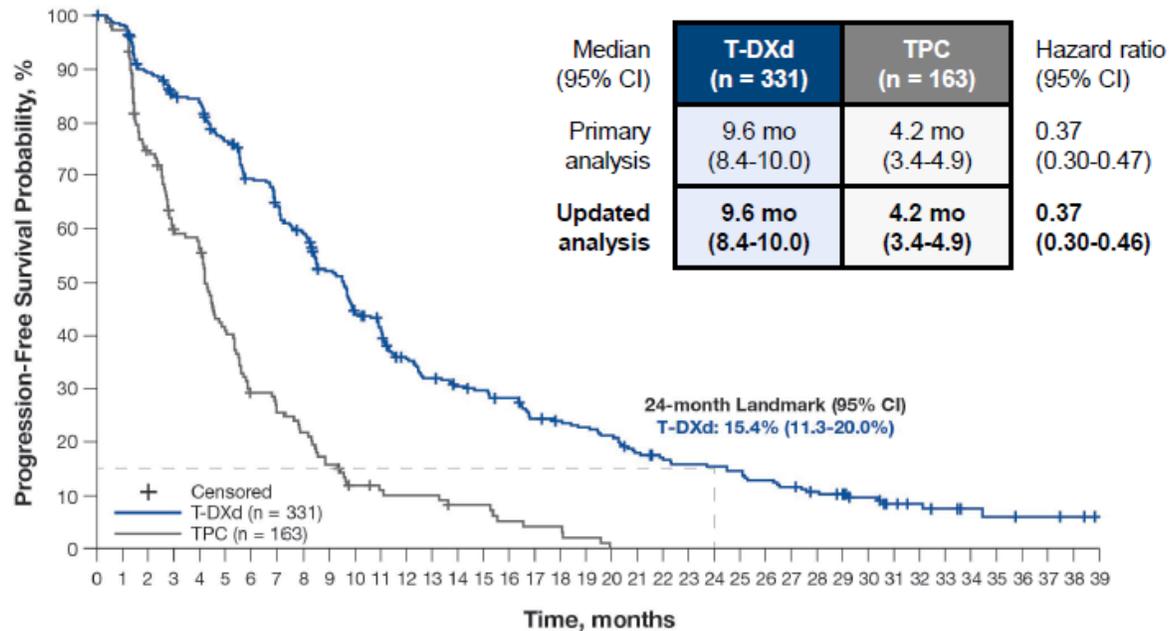
Data cutoff date: March 1, 2023.

^a TPC was administered according to the label. ^b Efficacy in the HR- cohort was an exploratory endpoint. ^c HR status was based on data collected using interactive web/voice response system at randomization, which includes mis-stratified patients.

1. Modi S, et al. ESMO 2023. Abstract 376O. 2. Modi S, et al. ASCO 2022. Abstract LBA3.

Updated Survival Results From DESTINY-Breast04 Phase 3 Trial of T-DXd vs TPC in HER2-Low MBC: PFS (Primary Endpoint)

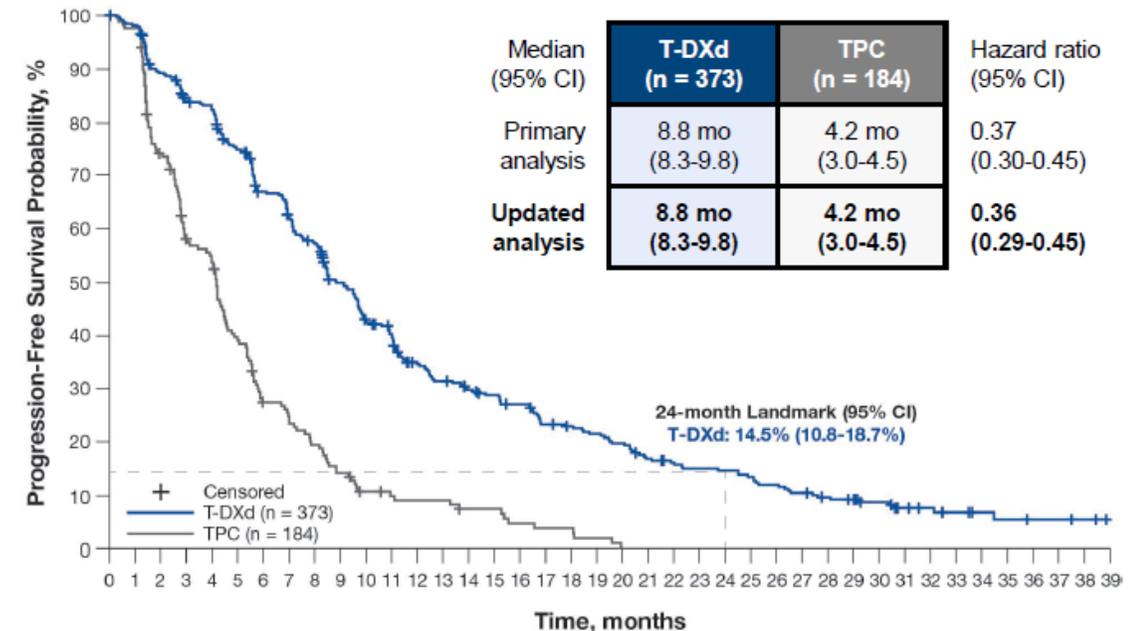
PFS in HR+ Cohort (by Investigator^a)



Patients still at risk:

T-DXd (n = 331) 331 323 290 272 267 241 215 198 181 154 129 119 98 85 82 79 74 63 60 57 53 44 40 37 36 34 30 27 23 21 16 11 9 7 5 4 3 3 2 0
TPC (n = 163) 163 143 107 83 76 56 39 34 29 21 14 12 11 11 8 8 5 4 4 4 2 0

PFS in All Patients (by Investigator^a)



Patients still at risk:

T-DXd (n = 373) 373 364 327 304 297 267 234 216 198 166 140 130 107 97 90 85 79 67 64 60 55 46 42 39 38 35 31 27 23 21 16 11 9 7 5 4 3 3 2 0
TPC (n = 184) 184 163 121 92 85 61 41 35 29 21 14 12 11 11 8 8 5 4 4 4 2 0

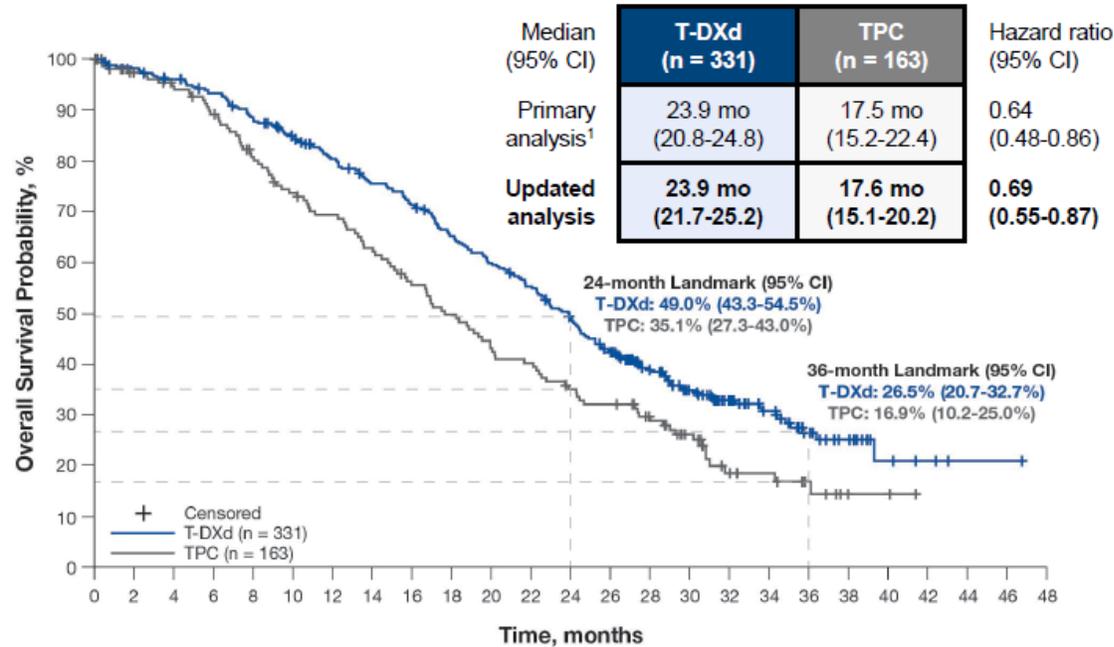
Data cutoff date: March 1, 2023.

^a PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (HR 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (HR 0.50). The updated analysis is based on PFS by investigator.

Modi S, et al. ESMO 2023. Abstract 376O.

Updated Survival Results From DESTINY-Breast04 Phase 3 Trial of T-DXd vs TPC in HER2-Low MBC: OS

OS in HR+ Cohort

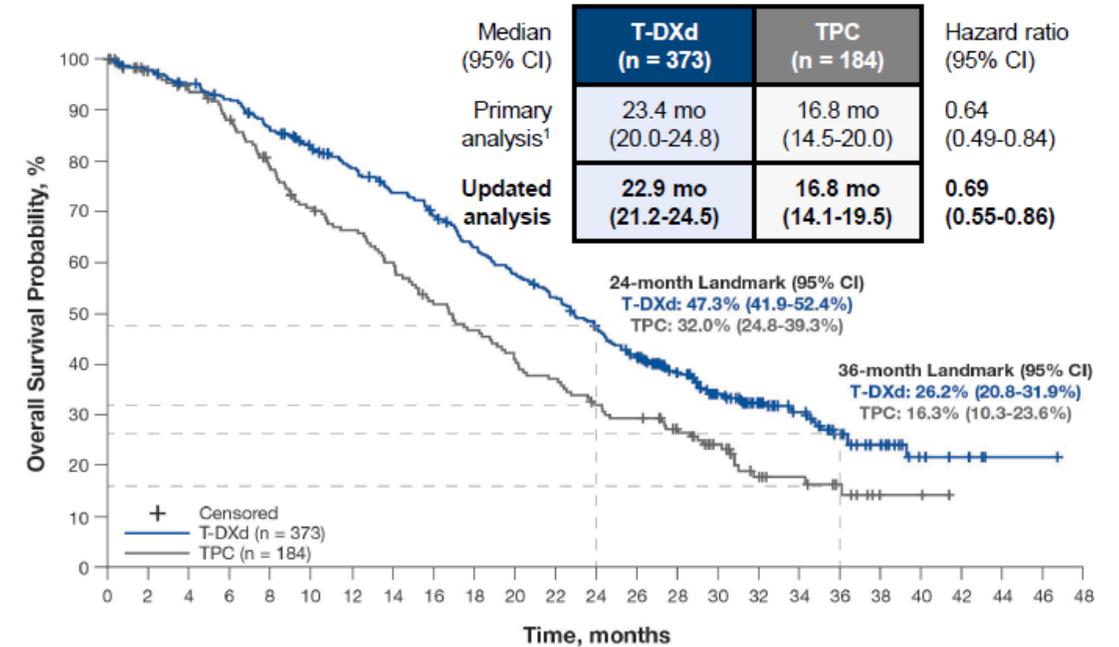


Patients still at risk:

T-DXd (n = 331) 331 325 325 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 100 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

OS in All Patients



Patients still at risk:

T-DXd (n = 373) 373 368 363 355 350 342 337 325 314 306 295 285 276 269 257 254 240 231 217 205 190 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 106 100 95 88 81 76 73 69 64 59 58 53 49 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

- OS benefit was observed across subgroups in HR+ cohort and in all patients (not shown)

DESTINY-Breast06: Phase 3, randomized, first line T-DXd vs TPC

Patient Population

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining)*
- Chemotherapy naïve in the mBC setting

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC

OR

- 1 line for mBC **AND**

- Progression ≤6 months of starting first-line ET + CDK4/6i

OR

- Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH- vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

T-DXd
5.4 mg/kg Q3W
(n=436)

R
1:1

HER2-low = 713
HER2-ultralow = 153[†]

TPC
(n=430)

Options: capecitabine,
nab-paclitaxel, paclitaxel

PRIMARY ENDPOINT

PFS (BICR) in HER2-low

KEY SECONDARY ENDPOINTS

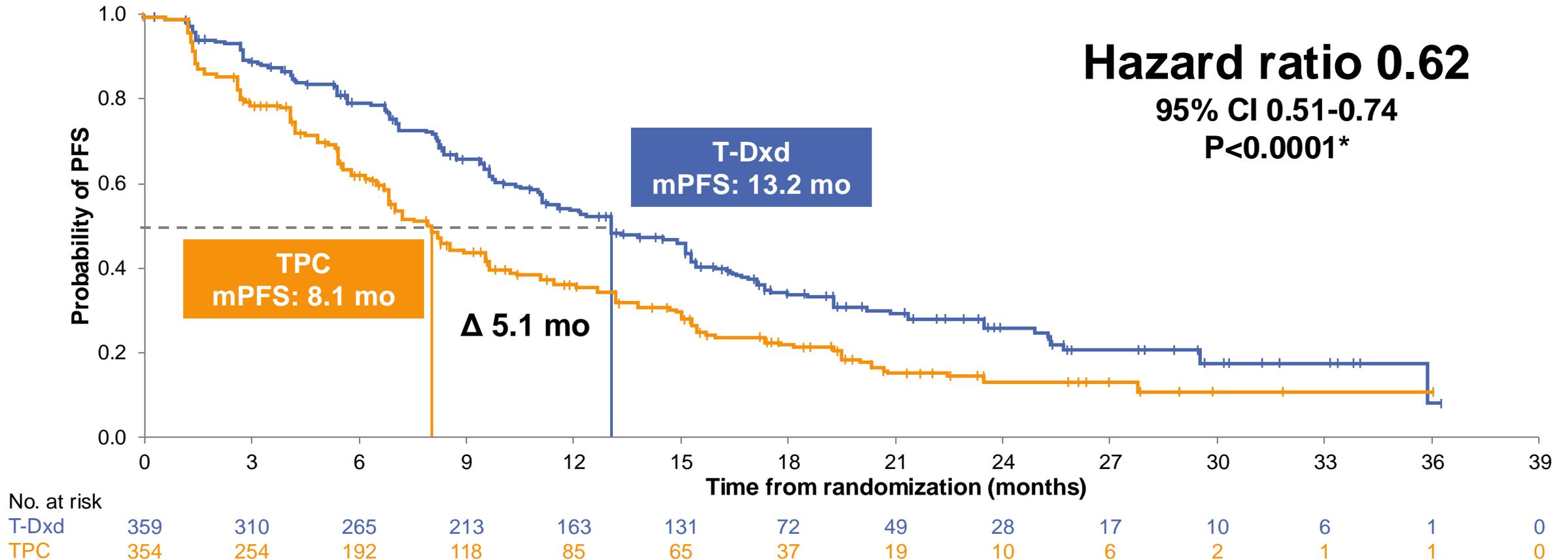
- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

OTHER SECONDARY ENDPOINTS

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes[‡]

*Study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint; partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+);[†]HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 as determined per central laboratory testing data); [‡]to be presented separately
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization, T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice
NCT04494425. Updated. April 12, 2024. Available from <https://clinicaltrials.gov/study/NCT0094425> (Accessed May 13, 2024)

DESTINY-Breast06: Phase 3, randomized, first line T-DXd vs TPC



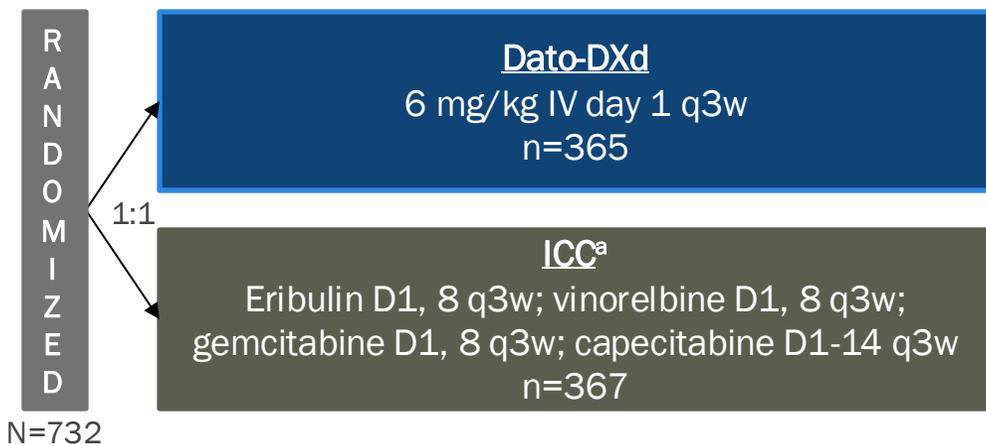
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
 BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

TROPION-Breasto1 Phase 3 Trial of Dato-DXd vs CT in HR+/HER2– MBC: Study Design and Patients

Key Eligibility Criteria

- HR+/HER2– EBC (HER2 IHC 0/1+/2+; ISH–)
- Progressed on and not suitable for ET
- 1-2 prior lines of CT in inoperable/metastatic setting
- ECOG PS 0-1



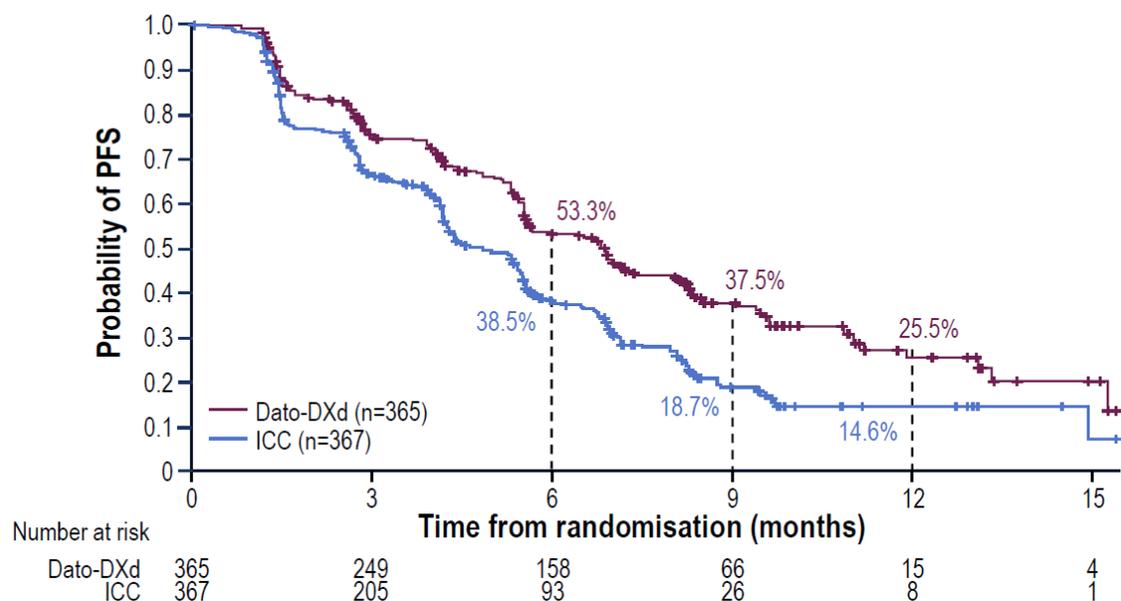
Dual primary endpoints: PFS by BICR per RECIST v1.1, OS
Secondary endpoints: ORR, PFS by investigator, safety

Patient Characteristics, n (%)		Dato-DXd (n=365) ^b	ICC (n=367) ^c
Median age (range), years		56 (29-86)	54 (28-86)
Race	Black or African American	4 (1)	7 (2)
	Asian	146 (40)	152 (41)
	White	180 (49)	170 (46)
	Other	35 (10)	38 (10)
Ethnicity	Hispanic or Latino	40 (11)	43 (12)
	Not Hispanic or Latino	322 (88)	318 (87)
Prior lines of CT	1	229 (63)	225 (61)
	2	135 (37)	141 (38)
Prior CDK4/6i		288 (82)	286 (78)
Prior taxane and/or anthracycline		330 (90)	339 (92)

^a Investigator's choice of chemotherapy (ICC) was administered as follows: eribulin, 1.4 mg/kg IV on D1, 8, q3w; vinorelbine, 25 mg/m² IV on D1, 8, q3w; gemcitabine 1000 mg/m² IV on D1, 8, q3w; capecitabine 1000 or 1250 mg/m² (dose per standard institutional practice) orally twice daily D1-14, q3w. ^b 360 patients received treatment with Dato-DXd. ^c 351 received treatment with ICC: eribulin (n=220); vinorelbine (n=38); capecitabine (n=76); gemcitabine (n=33).

TROPION-Breasto1 Phase 3 Trial of Dato-DXd vs CT in HR+/HER2- MBC: PFS (Primary Endpoint)

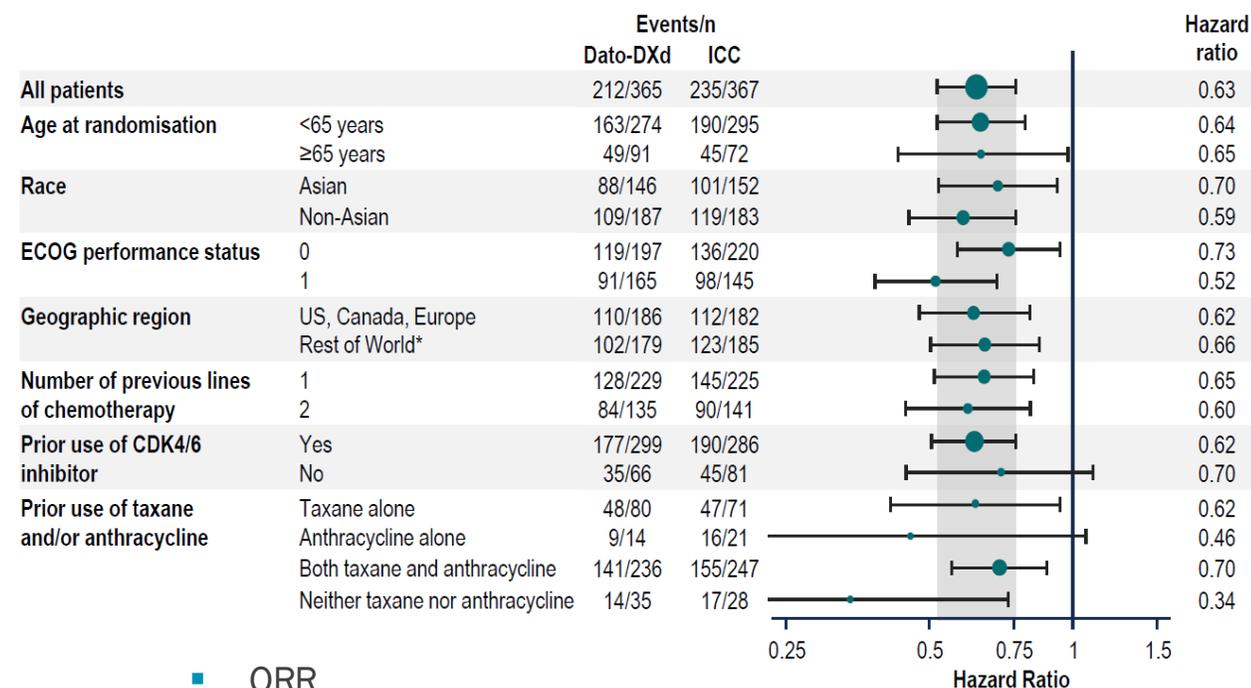
PFS by BICR: Primary Endpoint



PFS by BICR	Dato-DXd (n=365)	ICC (n=367)
Median PFS, mo (95% CI)	6.9 (5.7, 7.4)	4.9 (4.2, 5.5)
HR (95% CI)	0.63 (0.52, 0.76)	
P	<0.0001	

- Median study follow-up: 10.8 mo
- Median PFS by investigator: 6.9 vs 4.5 mo; HR 0.64 (95% CI: 0.53, 0.76)

PFS by BICR Across Subgroups



- ORR
 - Dato-DXd (n=365): **36.4%** (0.5% CR)
 - ICC (n=367): **22.9%**
- OS data not mature (median follow-up: 9.7 mo)
 - A trend favoring Dato-DXd was observed:
 - HR 0.84 (95% CI: 0.62, 1.14)

TROPION-Breast01 Phase 3 Trial of Dato-DXd vs CT in HR+/HER2– MBC: Safety & Conclusions

TRAEs, n (%)	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	105 (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)

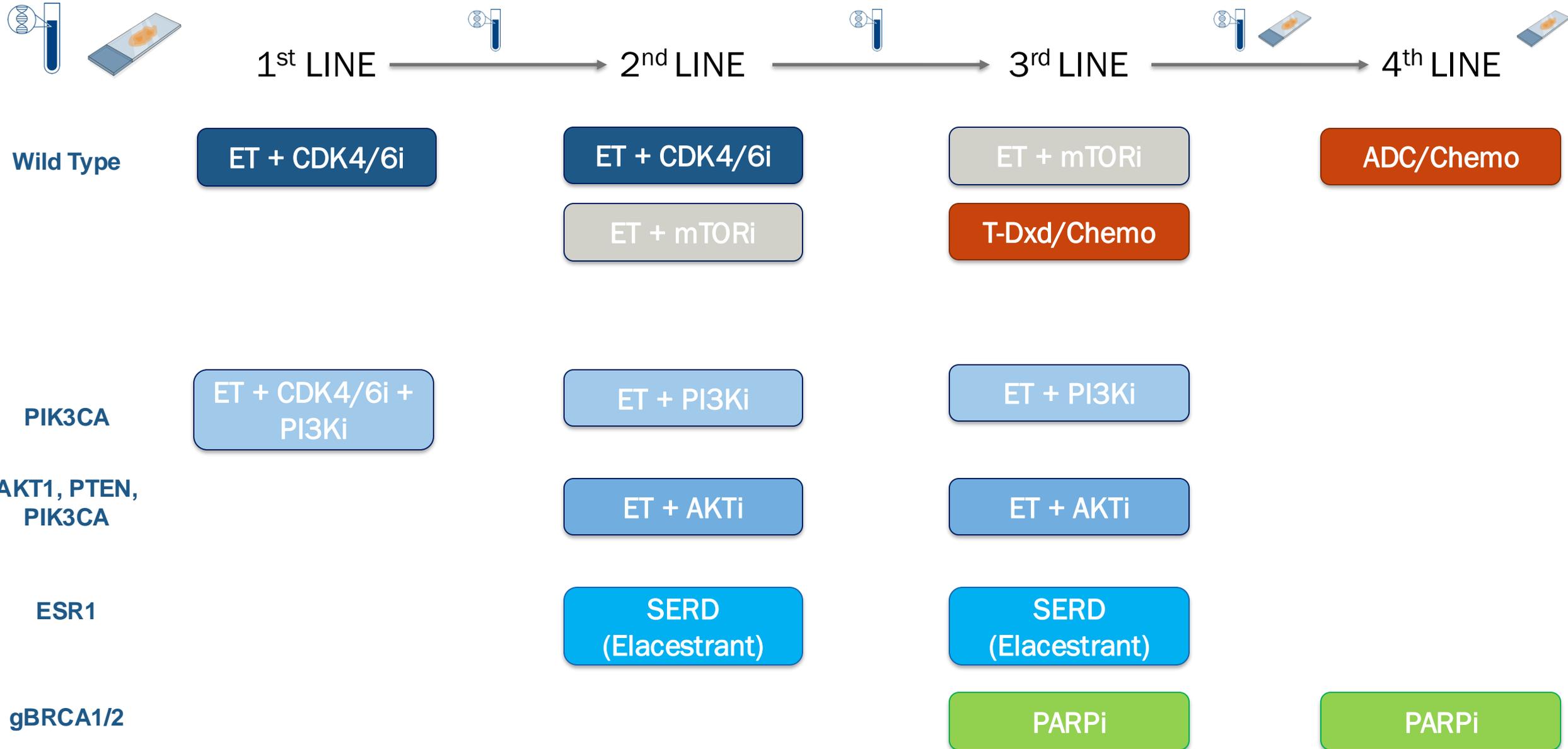
- Median treatment duration: 6.7 mo (Dato-DXd), 4.1 mo (ICC)
- Most TRAEs were grade 1-2 and manageable
- Oral mucositis/stomatitis led to discontinuation in 1 patient in the Dato-DXd group
- Most ocular events were dry eye; 1 patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related ILD rate was low, mainly grade 1/2: 9 (3%) all grades; 2 (1%) grade ≥3

TRAEs (in ≥15%), n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia	39 (11)	4 (1)	149 (42)	108 (31)
Dry eye	78 (22)	2 (1)	27 (8)	0
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Alopecia	131 (36)	0	72 (21)	0

Conclusions

- TROPION-Breast01 met its dual primary PFS endpoint, demonstrating statistically significant PFS improvement with Dato-DXd compared with ICC; PFS benefit was consistent across subgroups
- The safety profile of Dato-DXd was manageable, with no new safety signals; most AEs were grade 1-2; there were fewer grade ≥3 TRAEs and fewer TRAEs leading to dose interruption/reduction with Dato-DXd compared with ICC

Treatment Paradigm for HR+/HER2- MBC





Memorial Sloan Kettering
Cancer Center™

Thank you!

✉ iyengar@mskcc.org

✂ [@Neil_Iyengar](https://twitter.com/Neil_Iyengar)

