New Endocrine and Targeted Agents for the Treatment of Hormone Receptor Positive, HER2 Negative Breast Cancer

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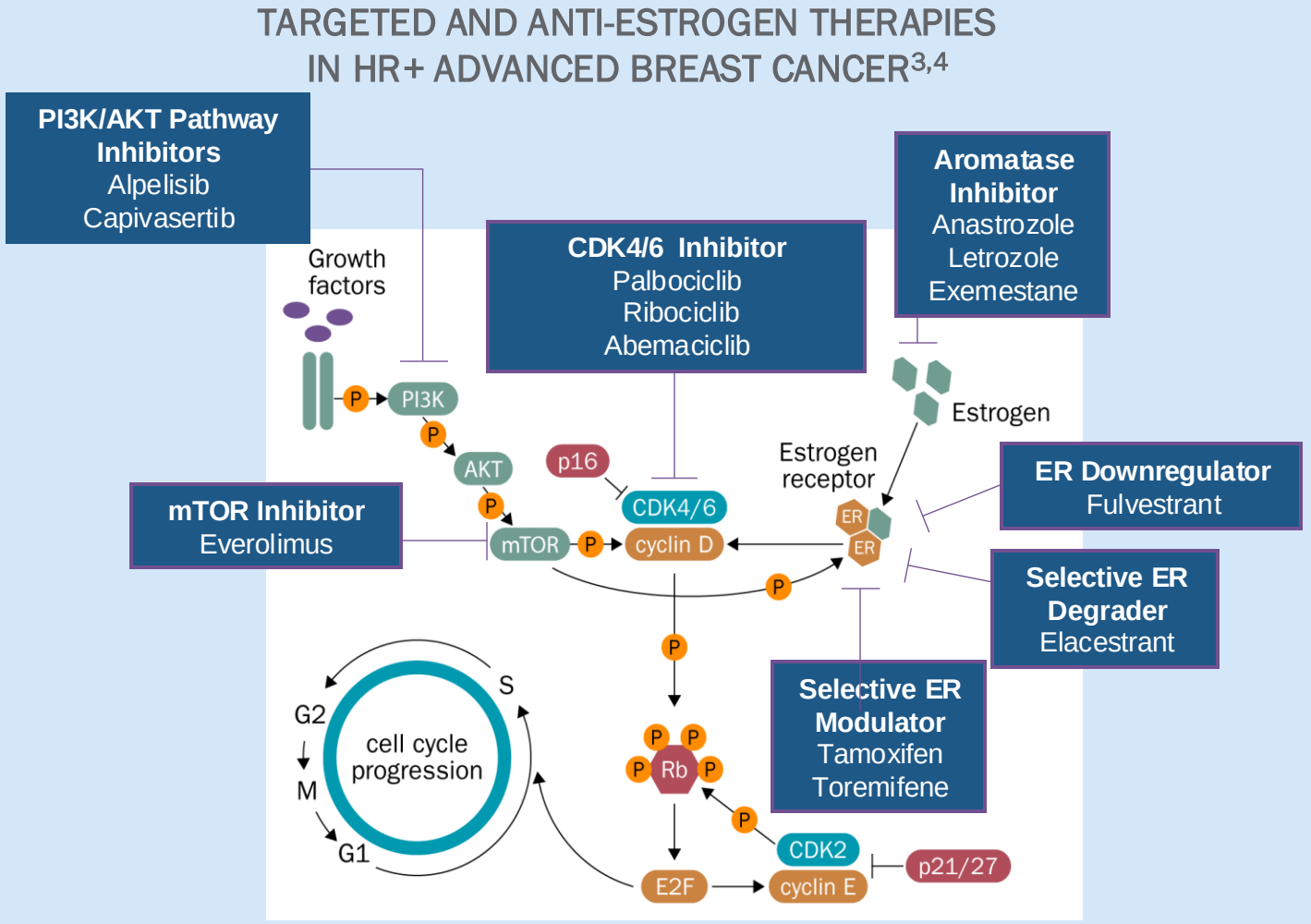
Targeting HR+/HER2– Breast Cancer

- 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]



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.

NCCN Guidelines Update: HR+/HER2– MBC

Setting	Preferred Regimens	Other Recommended Regimens (First and Subsequent Lines)
First line	AI + CDK4/6 inhibitor ▪ AI + ribociclib (Category 1) ▪ AI + abemaciclib ▪ AI + palbociclib	Selective ER downregulator ▪ Fulvestrant ▪ Elacestrant for *ESR1*mut tumors Selective ER downregulator (fulvestrant, Category 1) + nonsteroidal AI (anastrozole, letrozole) (Category 1) Nonsteroidal AI ▪ Anastrozole ▪ Letrozole Selective ER modulator ▪ Tamoxifen Steroidal aromatase inactivator ▪ Exemestane
	Fulvestrant + CDK4/6 inhibitor ▪ Fulvestrant + ribociclib (Category 1) ▪ Fulvestrant + abemaciclib (Category 1) ▪ Fulvestrant + palbociclib	
Second line	Fulvestrant + CDK4/6 inhibitor, if CDK4/6 inhibitor not previously used (Category 1)	
	▪ Alpelisib + fulvestrant for *PIK3CA* activating mutations (Category 1) ▪ Capivasertib + fulvestrant for *PIK3CA/AKT1/PTEN* activating mutations (Category 1)	
	Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)	

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.3.2024. Accessed June 25, 2024.

CDK4/6i + ET Recommended for 1L HR+/HER2– mBC[1]

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– MBC[10]
- 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 toxicity[11]

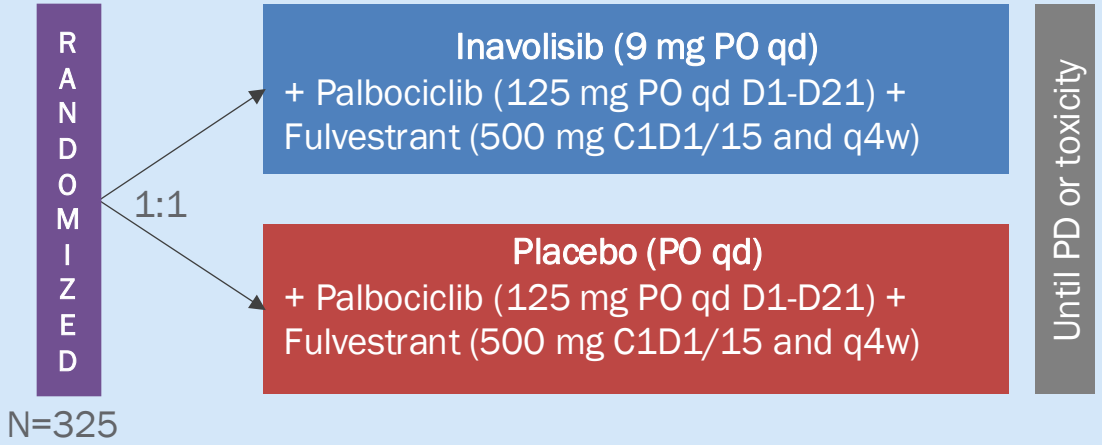
[a] 1L ET; up to 1 prior line of CT permitted in advanced setting (14% of patients had received CT in advanced setting). [b] *P*-value did not reach threshold for statistical significance.

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

- *PIK3CA*mut, 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%



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

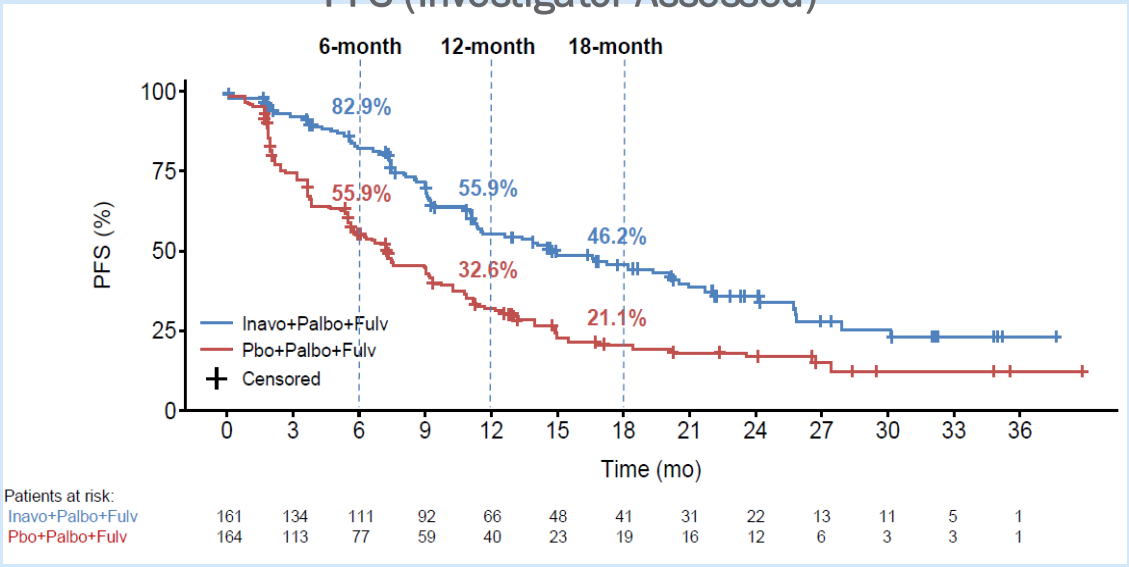
Patient Characteristics, %		Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
Median age (range), years		53.0 (27-77)	54.5 (29-79)
Race	Asian	38%	38%
	Black/African American	0.6%	0.6%
	White	58%	59%
ECOG PS	0	62%	65%
	1	37%	35%
Postmenopausal at randomization		57%	63%
Visceral disease		82%	78%
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.

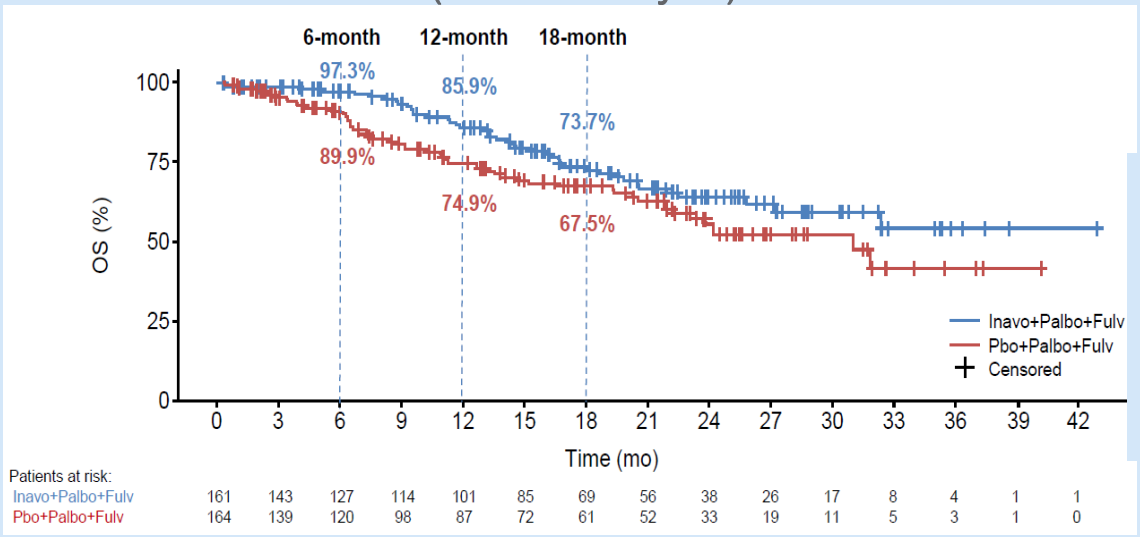
Jhaveri K, et al. SABCS 2023. Abstract GS03-13.

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

PFS (Investigator Assessed)



OS (Interim Analysis)[a]



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

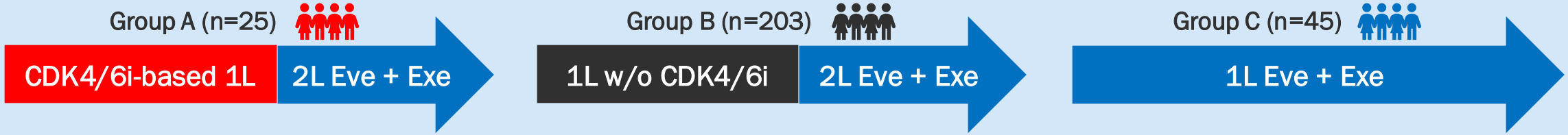
Overview of AEs, %	Inavo + Palbo + Fulv (n=162)	Pbo + Palbo + Fulv (n=162)
Any AEs	99%	100%
Grade 3-4 AEs	88%	82%
Grade 5 AE[a]	4%	1%
Serious AE	24%	11%
Leading to discontinuation	7%	0.6%
Inavolisib/placebo	6%	0.6%
Palbociclib	5%	0
Fulvestrant	3%	0
Leading to dose modification/ interruption of treatment	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.

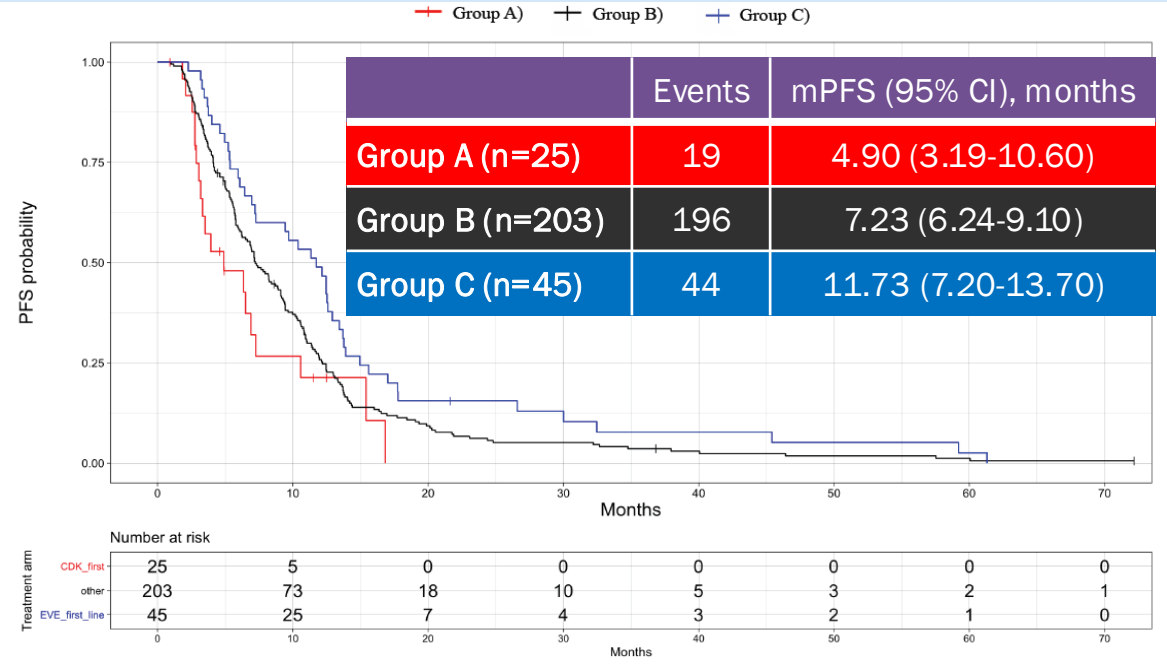
Jhaveri K, et al. SABCS 2023. Abstract GS03-13.

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

STUDY DESIGN

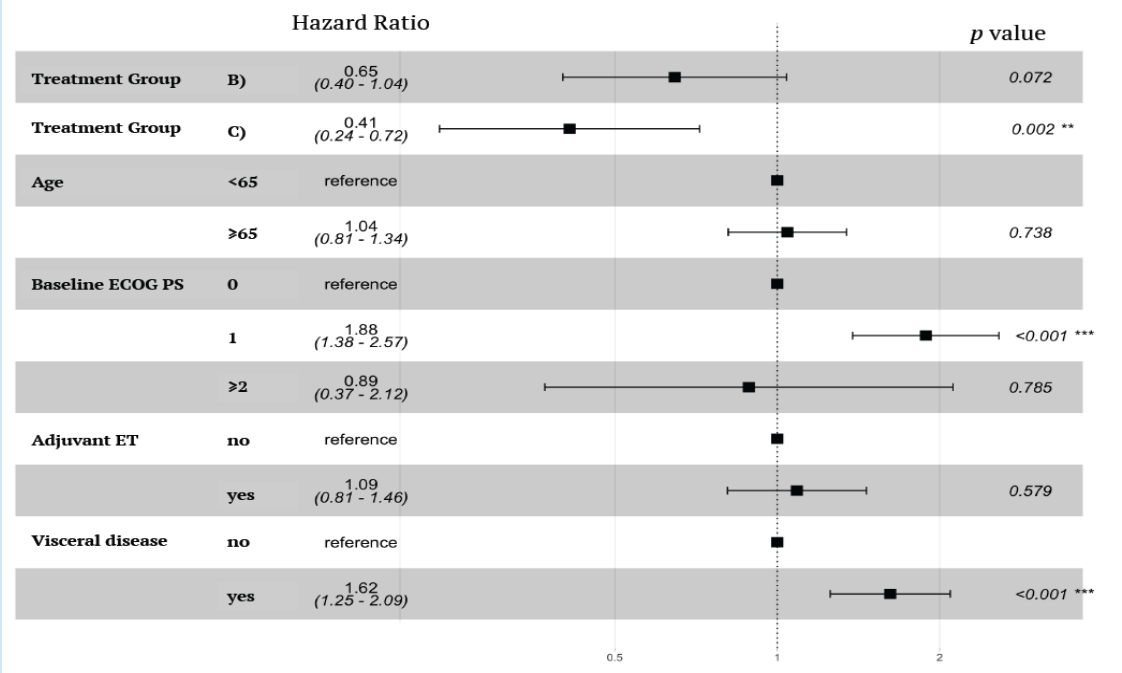


PFS Based on Treatment Group



	Events	mPFS (95% CI), months
Group A (n=25)	19	4.90 (3.19-10.60)
Group B (n=203)	196	7.23 (6.24-9.10)
Group C (n=45)	44	11.73 (7.20-13.70)

PFS According to Treatment or Other Variables

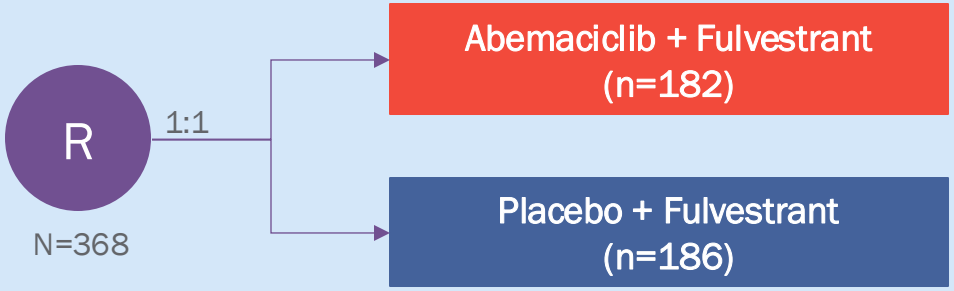


Nichetti F, et al. ESMO 2020. Abstract 337P.

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



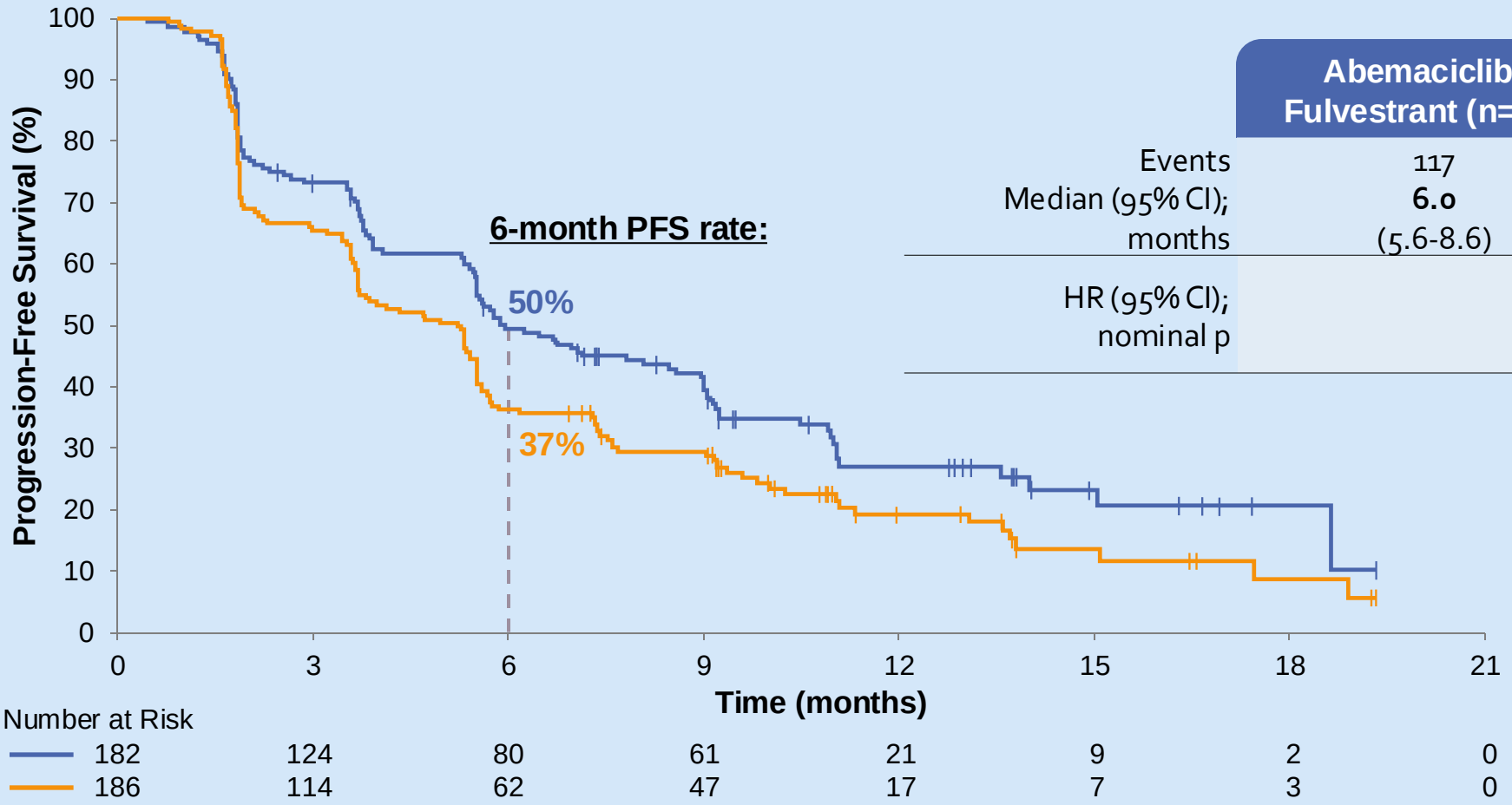
Primary endpoint: PFS (INV)
Key secondary endpoints: OS, PFS by BICR, ORR, CBR, DCR, DoR, safety, PK, and PRO

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.

Kalinsky K, et al. ASCO 2024. Abstract LBA1001.

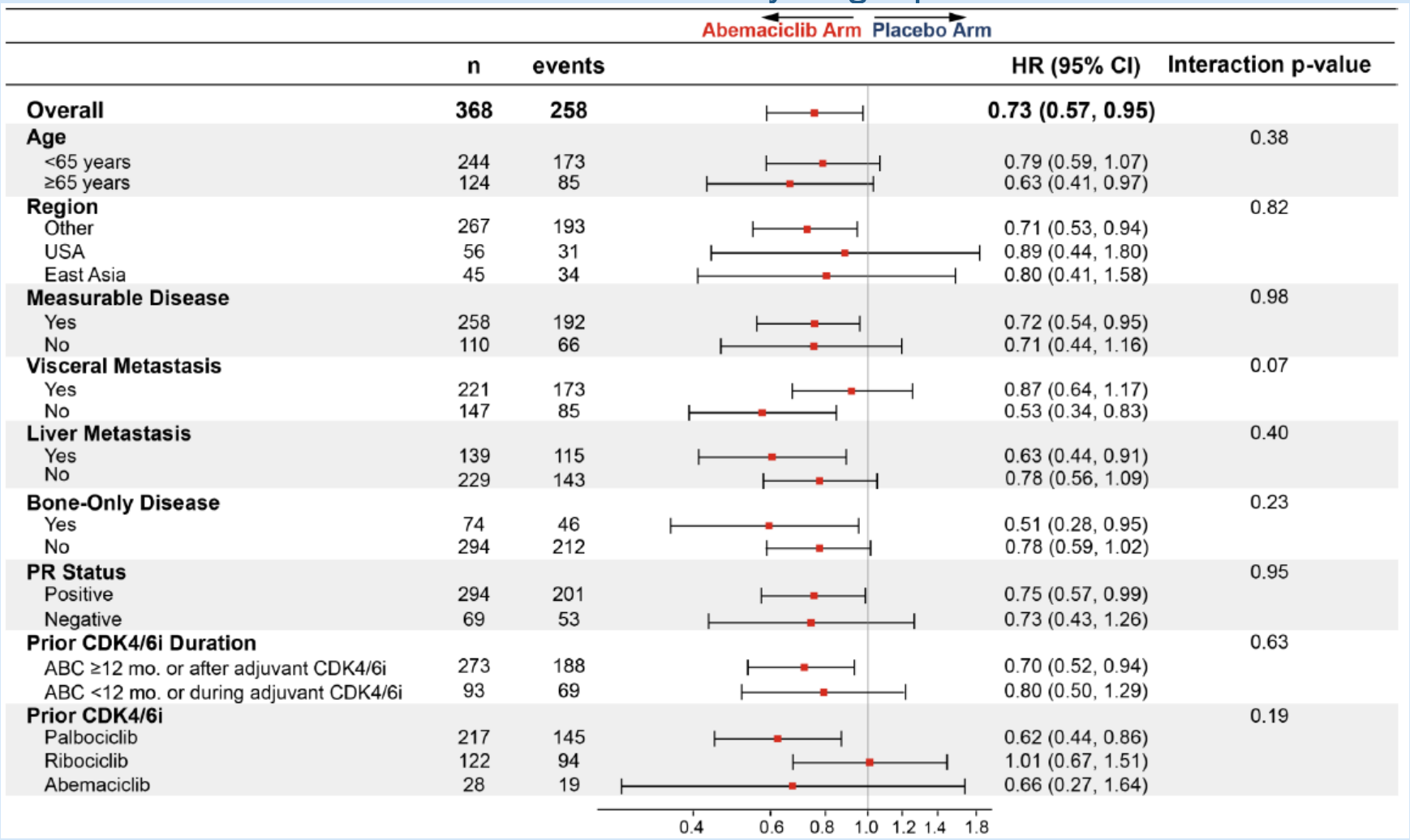
postMONARCH Phase 3 Trial: Abemaciclib + Fulvestrant vs Fulvestrant for HR+/HER2– MBC Post CDK4/6i



	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	

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

INV-Assessed PFS by Subgroup



	n	events	HR (95% CI)	Interaction p-value
Overall	**368**	**258**	**0.73 (0.57, 0.95)**	
Age				0.38
<65 years	244	173	0.79 (0.59, 1.07)	
≥65 years	124	85	0.63 (0.41, 0.97)	
Region				0.82
Other	267	193	0.71 (0.53, 0.94)	
USA	56	31	0.89 (0.44, 1.80)	
East Asia	45	34	0.80 (0.41, 1.58)	
Measurable Disease				0.98
Yes	258	192	0.72 (0.54, 0.95)	
No	110	66	0.71 (0.44, 1.16)	
Visceral Metastasis				0.07
Yes	221	173	0.87 (0.64, 1.17)	
No	147	85	0.53 (0.34, 0.83)	
Liver Metastasis				0.40
Yes	139	115	0.63 (0.44, 0.91)	
No	229	143	0.78 (0.56, 1.09)	
Bone-Only Disease				0.23
Yes	74	46	0.51 (0.28, 0.95)	
No	294	212	0.78 (0.59, 1.02)	
PR Status				0.95
Positive	294	201	0.75 (0.57, 0.99)	
Negative	69	53	0.73 (0.43, 1.26)	
Prior CDK4/6i Duration				0.63
ABC ≥12 mo. or after adjuvant CDK4/6i	273	188	0.70 (0.52, 0.94)	
ABC <12 mo. or during adjuvant CDK4/6i	93	69	0.80 (0.50, 1.29)	
Prior CDK4/6i				0.19
Palbociclib	217	145	0.62 (0.44, 0.86)	
Ribociclib	122	94	1.01 (0.67, 1.51)	
Abemaciclib	28	19	0.66 (0.27, 1.64)	

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 ≤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 *PIK3CA*mut		Without *PIK3CA*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%

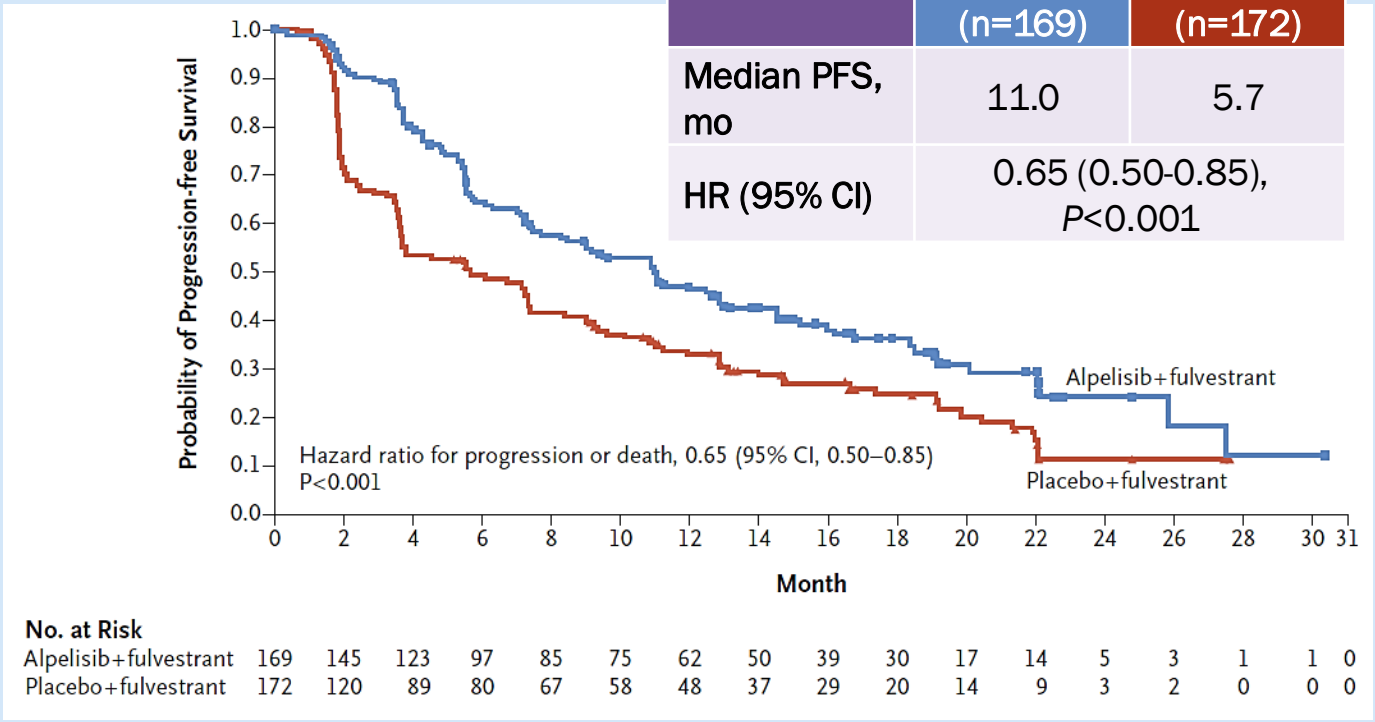
[a] HbA1c levels was an amendment to the original protocol implemented after the start of the study to lower rates of treatment discontinuation.[2] [b] Administered as intramuscular injection on days 1 and 15 of cycle 1 and on day 1 of subsequent cycles.

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

PFS Analysis	Alpelisib + Fulvestrant (n=169)	PBO + Fulvestrant (n=172)
Median PFS, mo	11.0	5.7
HR (95% CI)	0.65 (0.50-0.85), *P*<0.001	



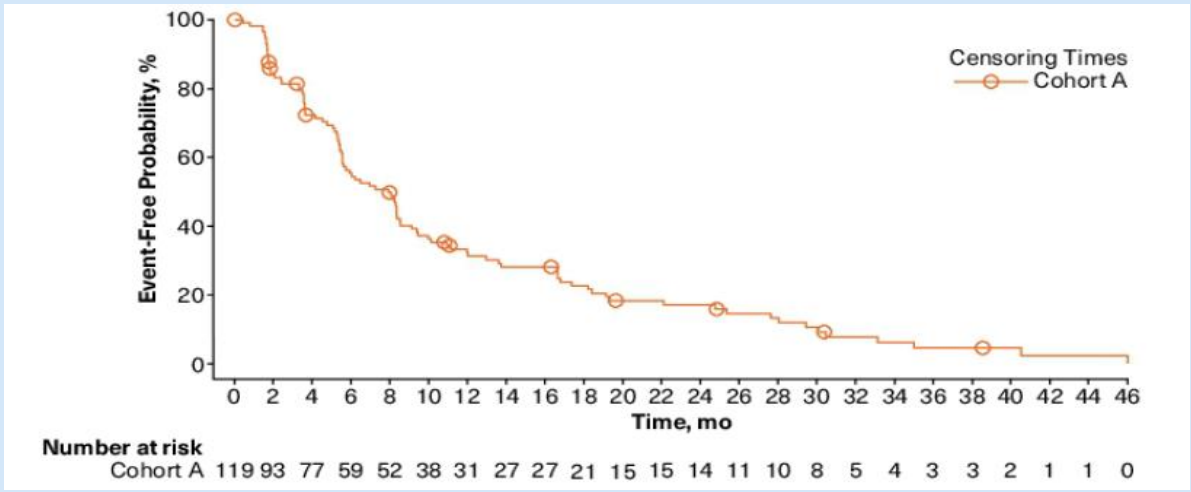
- Alpelisib + fulvestrant demonstrated improved PFS vs placebo + fulvestrant in patients with *PIK3CA*-mutated, HR+/HER2– advanced breast cancer who received prior endocrine therapy
- Key grade 3/4 AEs of concern in the alpelisib + fulvestrant vs placebo + fulvestrant arms were hyperglycemia (37% vs 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

Andre F, et al. *N Engl J Med.* 2019;380(20):1929-1940.

BYLieve Phase 2 Trial of Alpelisib + ET in PIK3CAmut HR+ MBC Post-CDK4/6i

Cohort A PFS

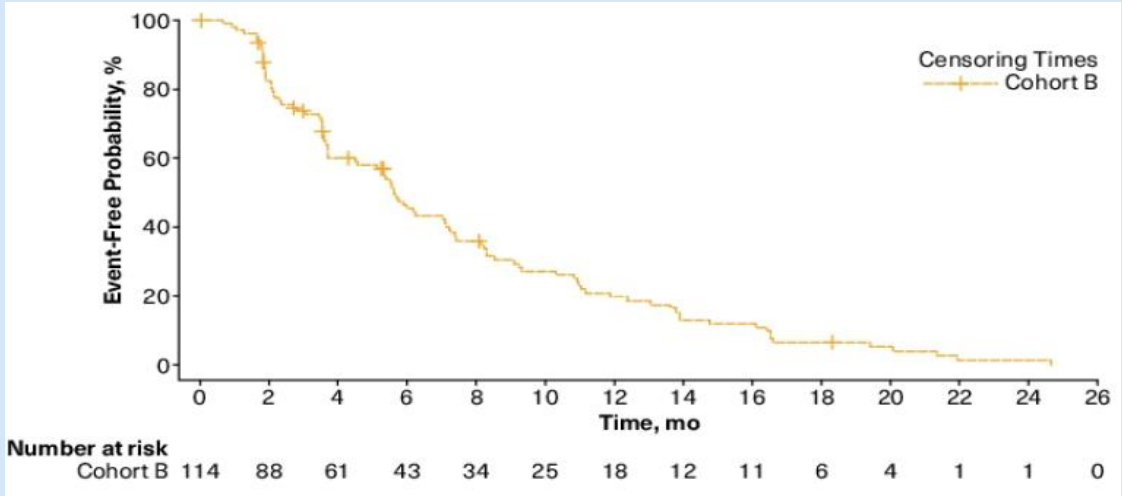
Alpelisib + Fulvestrant in Patients Who Received CDK4/6i + AI



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



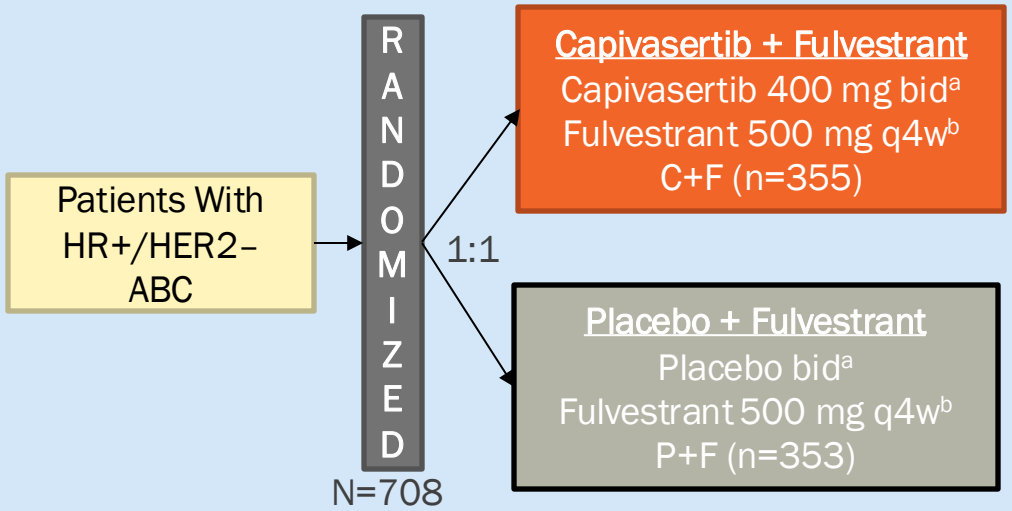
Cohort B PFS	A+L (n=114)
Events, n (%)	97 (85.1)
Median follow-up, mo	5.19
Median PFS, mo (95% CI)	5.6 (3.7-7.1)
Cohort B OS	
Events, n (%)	66 (57.9)
Median follow-up, mo	25.33
Median OS, mo (95% CI)	29.0 (24.5-34.8)

Chia S, et al. ASCO 2023. Abstract 1078.

CAPItello-291 Phase 3 Trial of Capivasertib + 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

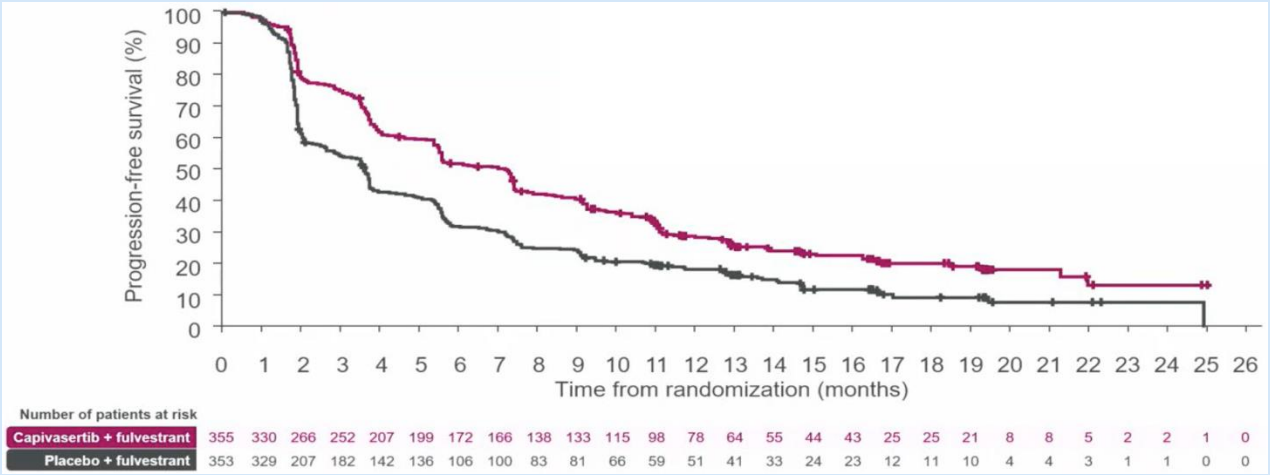
Patient Characteristics, n (%)		Overall Population C+F (n=355)	Overall Population P+F (n=353)	AKT Pathway Altered C+F (n=155)	AKT Pathway Altered P+F (n=134)
Median age (range), years		59 (26-84)	58 (26-90)	58 (36-84)	60 (34-90)
Metastatic sites	Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
	Liver[d]	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
HR status[e]	ER+/PR+	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
	ER+/PR–	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
	Unknown	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
Endocrine resistance	Primary	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
	Secondary	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)
Prior endocrine therapy for ABC	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
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)	67 (50.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)
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.

Turner NC, et al. SABCS 2022. Abstract GS3-04.

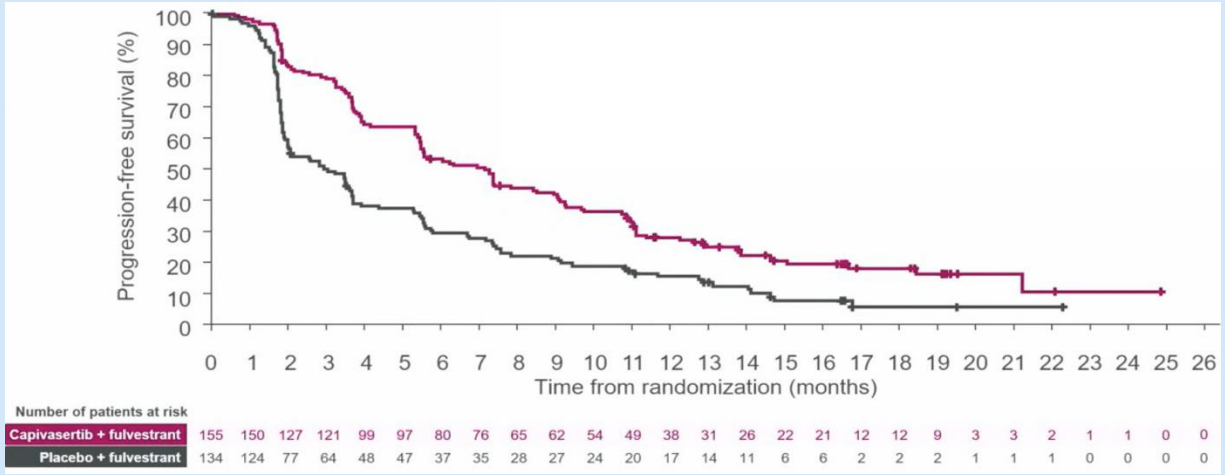
CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Primary Endpoint

PFS by Investigator in Overall 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	

PFS by Investigator in the AKT Pathway-Altered Population



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	

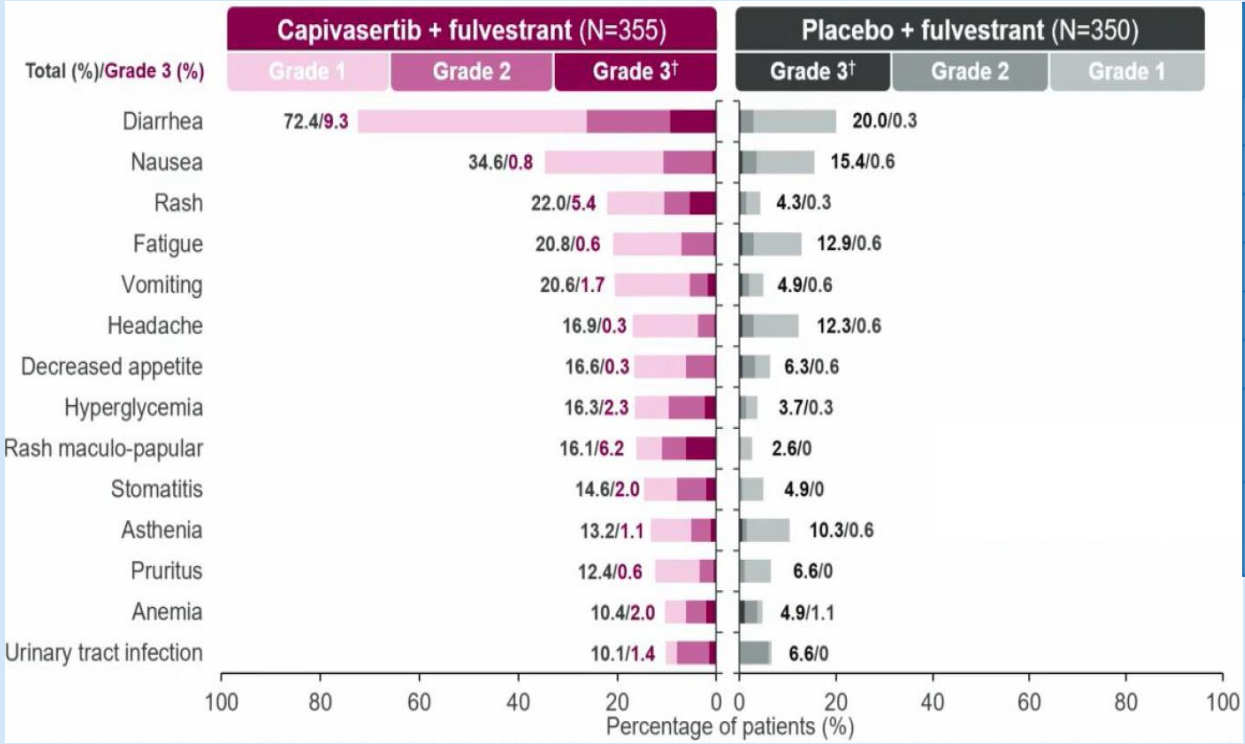
- PFS benefit was observed in all key subgroups, including regardless of prior use of CDK4/6i and liver metastases

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

Turner NC, et al. SABCS 2022. Abstract GS3-04.

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)

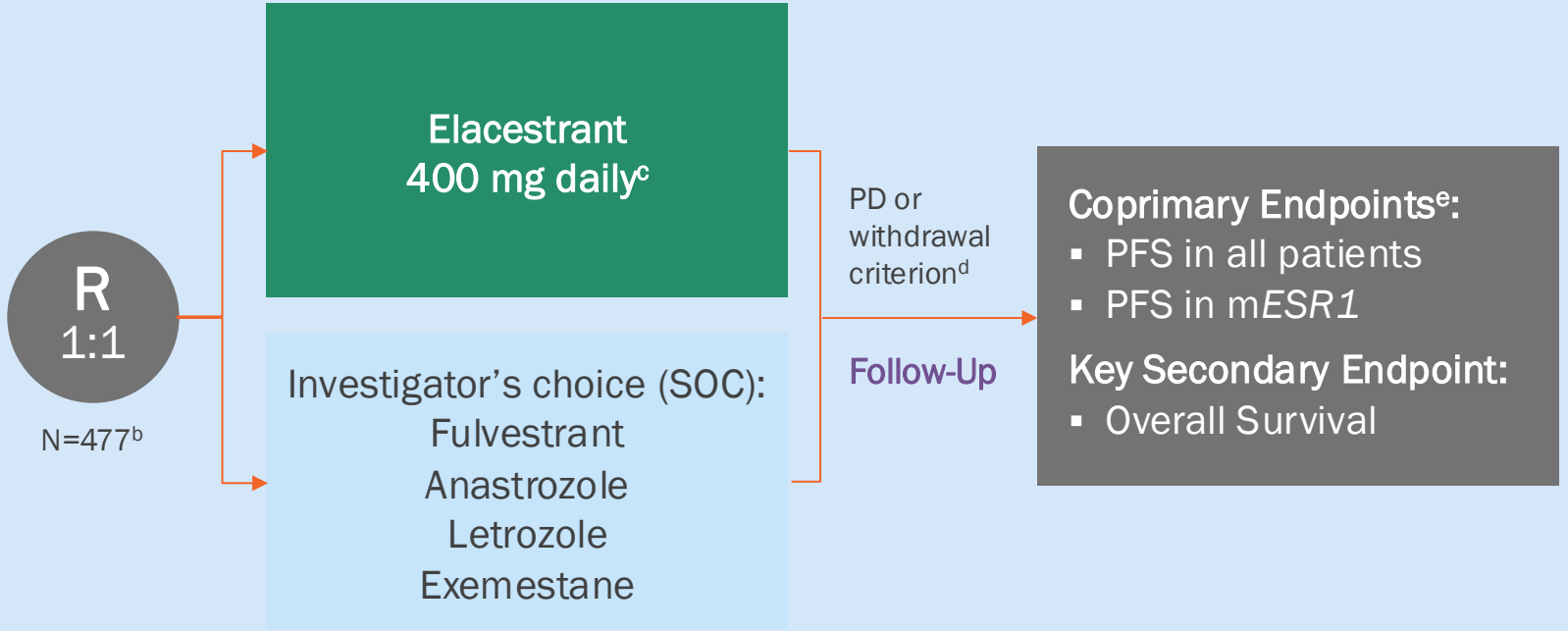
[a] Grade 5 events included acute myocardial infarction, cerebral hemorrhage, pneumonia aspiration, and sepsis (all n=1) in the C+F group and COVID-19 (n=1) in the P+F group. No grade 5 events were classified as related to C/P by local investigator. The safety analysis population included all patients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

Turner NC, et al. SABCS 2022. Abstract GS3-04.

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:

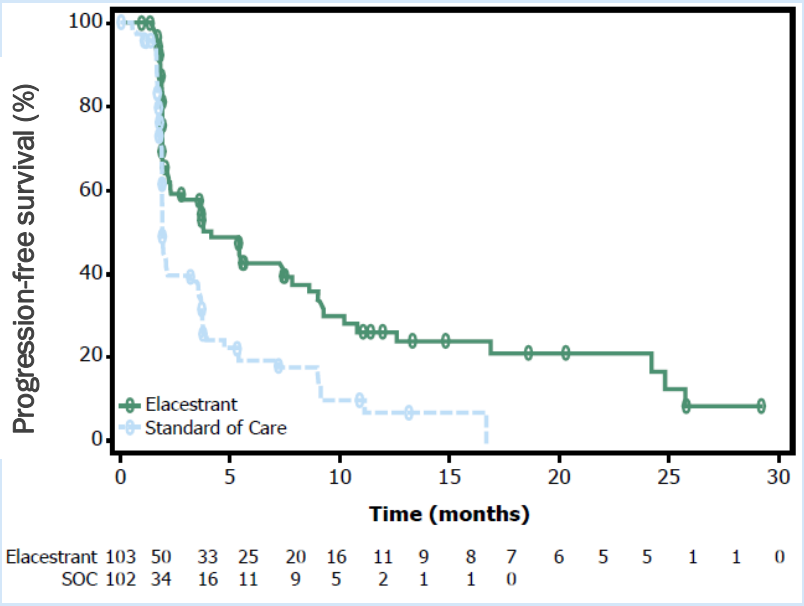
- *ESR1*-mutation status[f]
- Prior treatment with fulvestrant
- Presence of visceral metastases

[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.

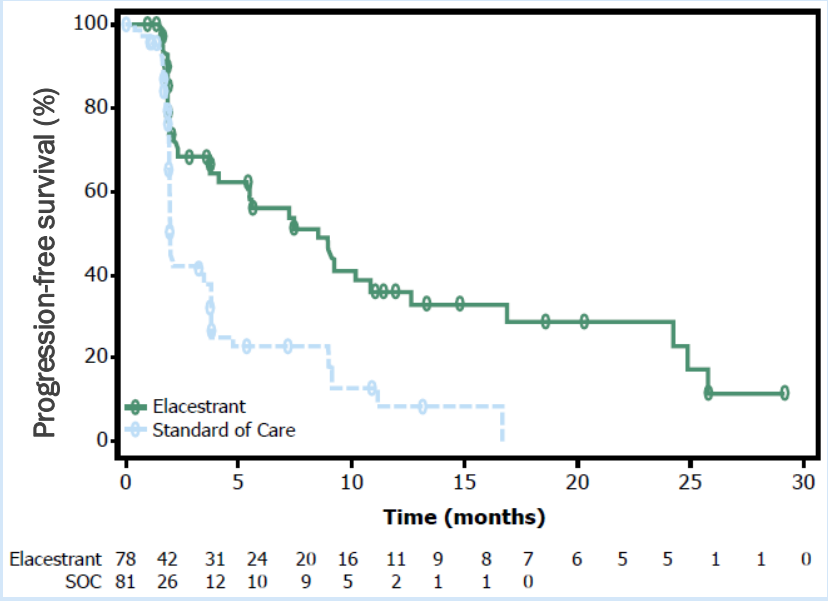
EMERALD: PFS in the *mESR1* Population* by Duration of CDK4/6i

At least 6 mo



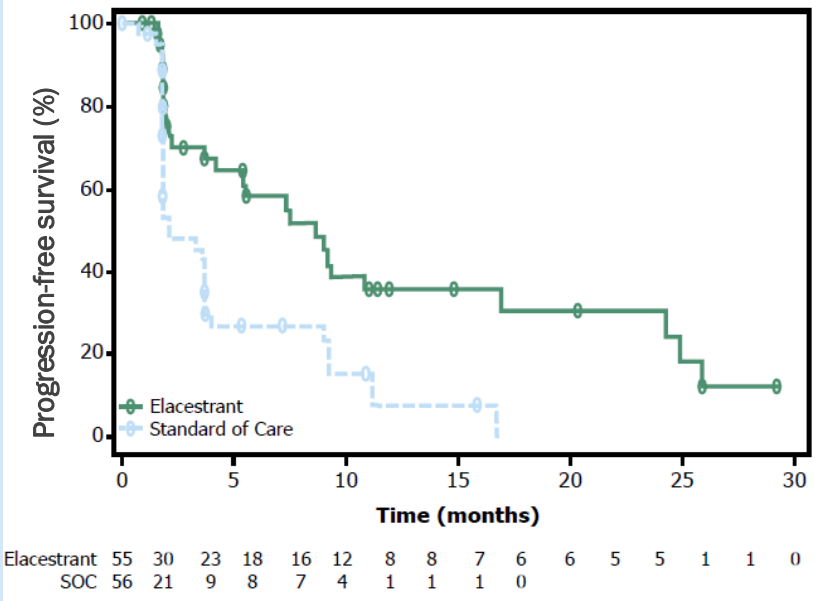
At least 6 mo	Elacestrant (n=103)	SOC (n=102)
Median PFS, mo (95% CI)	**4.14** (2.20-7.79)	**1.87** (1.87-3.29)
PFS rate at 12 mo, % (95% CI)	26.02 (15.12-36.92)	6.45 (0.00-13.65)
HR (95% CI)	**0.517** (0.361-0.738)	

At least 12 mo



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



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.

Bardia A, et al. SABCS 2022. Abstract GS3-01.

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

Most Common AEs (≥10%)

	Elacestrant (n=237)		SOC (n=229)	
AE, %	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

Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246-3256.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

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

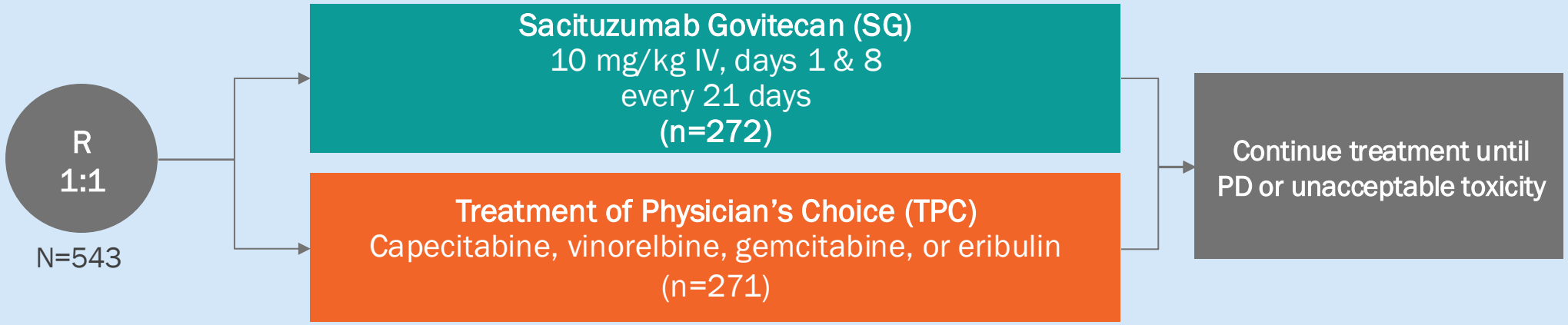
HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	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.

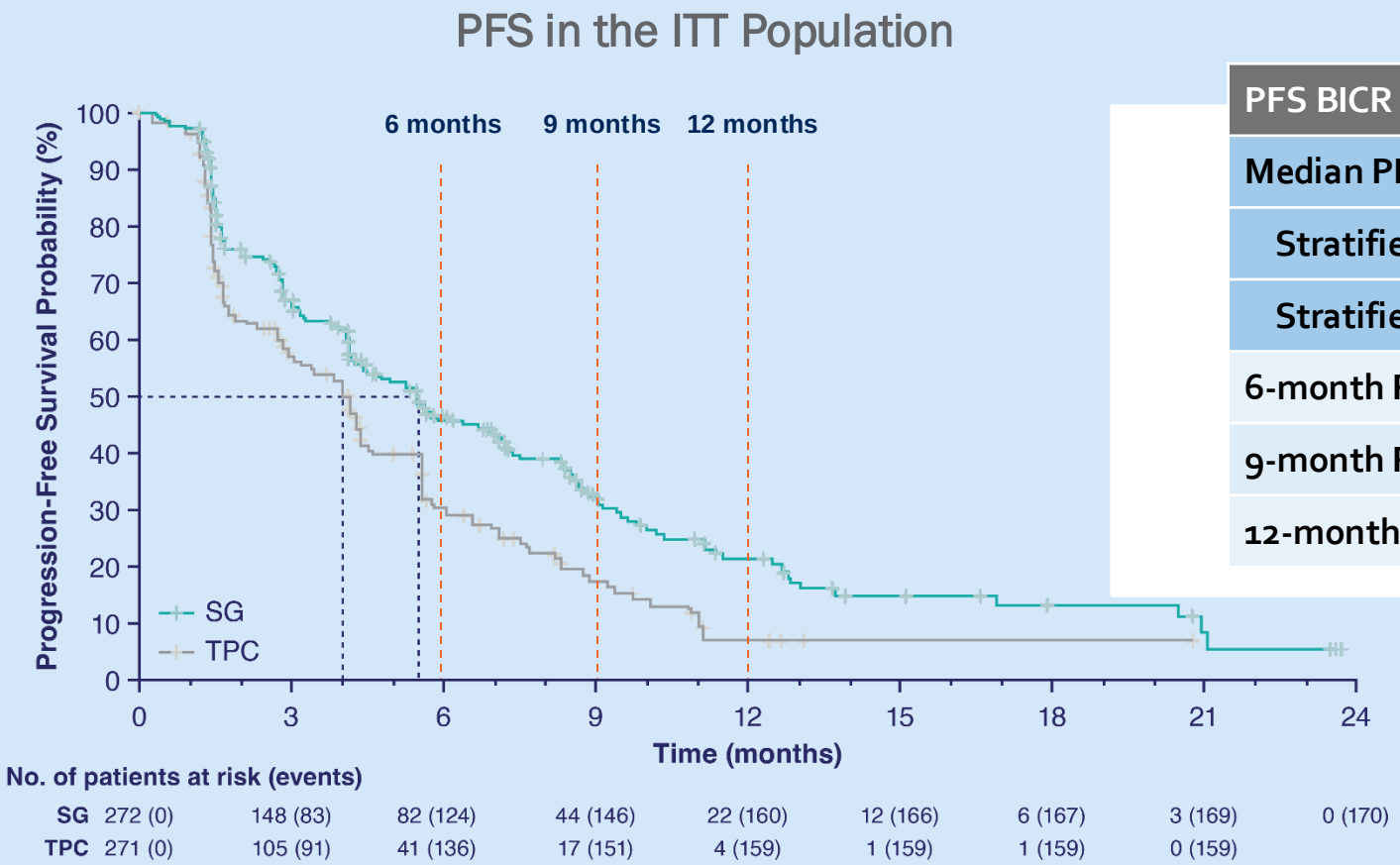
Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365-3376.

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)

Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365-3376.

TROPiCS-02: PFS (Primary Endpoint)

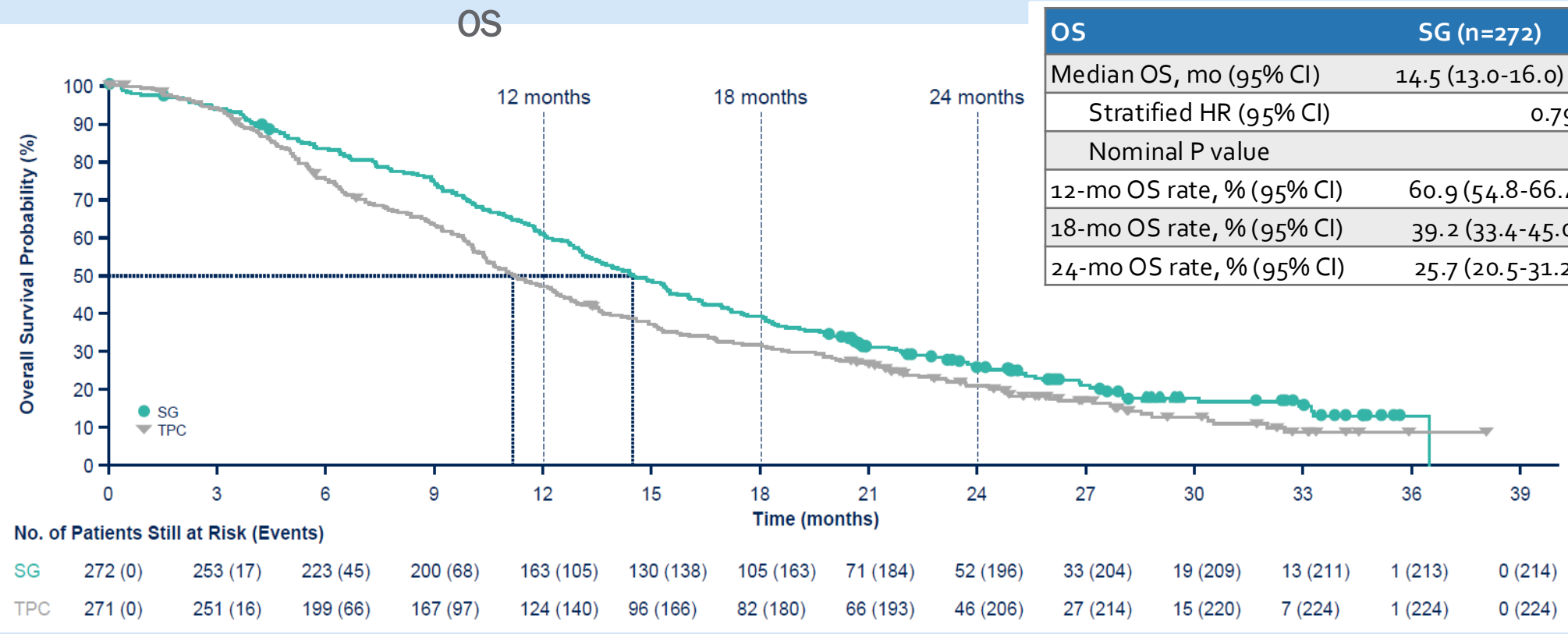


PFS BICR	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2-7.0)	4.0 (3.1-4.4)
Stratified HR (95% CI)	**0.66** (0.53-0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-month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

- 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

Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365-3376.

TROPiCS-02: OS (Final Update)



OS	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	0.79 (0.65-0.95)	
Nominal P value	0.0133	
12-mo OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-mo OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-mo OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

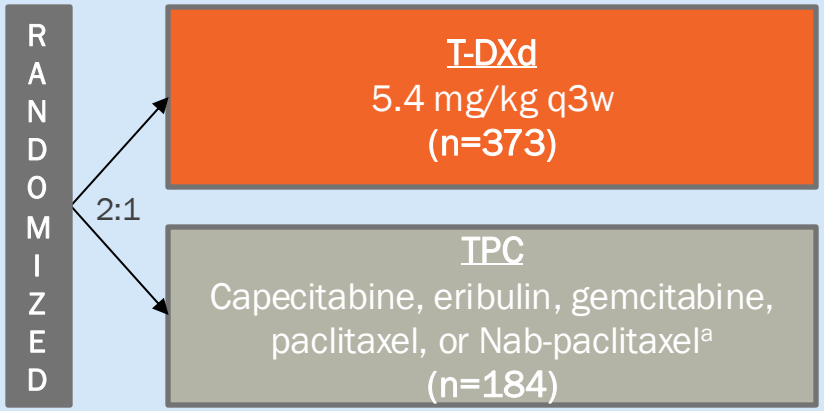
- SG demonstrated a statistically significant improvement in OS vs TPC with 21% reduction in the risk of death; having met statistical significance, no further formal statistical testing of OS will occur
- Patients who received SG survived a median of ***3.2 months longer*** than those who received TPC

1. Rugo HS, et al. ESMO 2022. Abstract LBA76. 2. Tolaney SM, et al. ASCO 2023. Abstract 1003. 3. Bardia A, et al. ASCO 2023. Abstract 1082.

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



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)	95 (58)	215 (58)	106 (58)
	2+/ISH-	138 (42)	68 (42)	158 (42)	78 (42)
HR positive,[c] n (%)		328 (99)	162 (99)	333 (89)	166 (90)
ECOG PS, n (%)	0	187 (56)	95 (58)	200 (54)	105 (57)
	1	144 (44)	68 (42)	173 (46)	79 (43)
Metastases at baseline, n (%)	Brain	18 (5)	7 (4)	24 (6)	8 (4)
	Liver	247 (75)	116 (71)	266 (71)	123 (67)
	Lung	98 (30)	58 (36)	120 (32)	63 (34)
Prior lines of Chemo (MBC setting)	Median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
	≥3, n (%)	3 (0.9)	0	6 (1.6)	0
Prior lines of ET (MBC setting)	Median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
	≥3, n (%)	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)	Targeted	259 (78)	132 (81)	279 (75)	140 (76)
	CDK4/6i	233 (70)	115 (71)	239 (64)	119 (65)

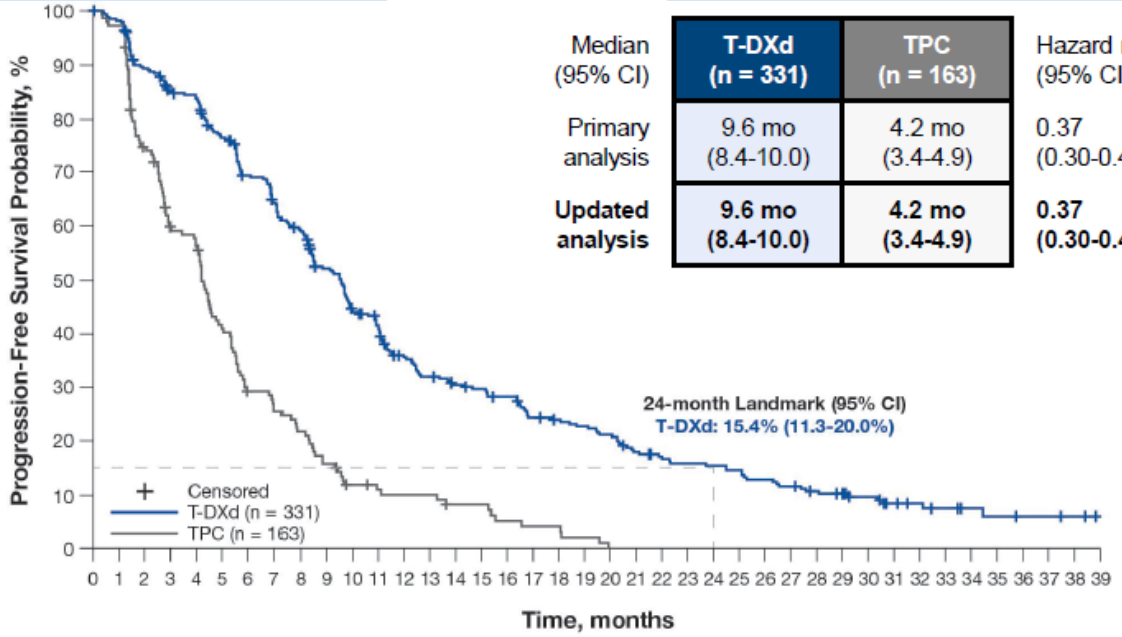
Data cutoff date: March 1, 2023.

[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.

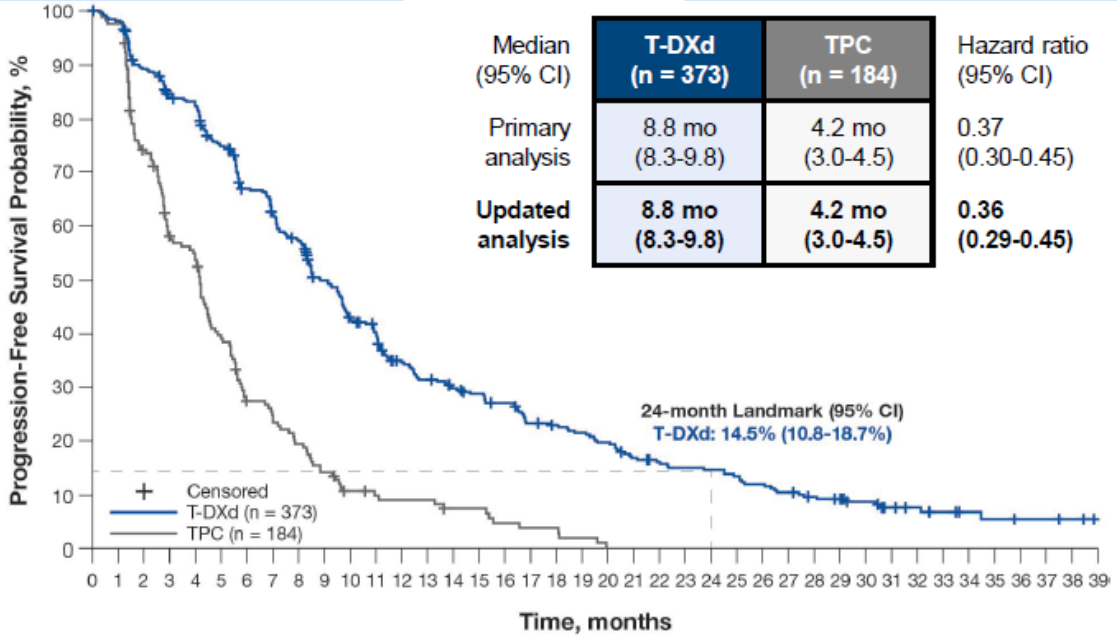
Updated Survival Results From DESTINY-Breast04 Phase 3 Trial of T-DXd vs TPC in HER2-Low MBC: PFS (Primary Endpoint)

PFS in HR+ Cohort (by Investigator[a])



Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**

PFS in All Patients (by Investigator[a])



Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**

Data cutoff date: March 1, 2023.

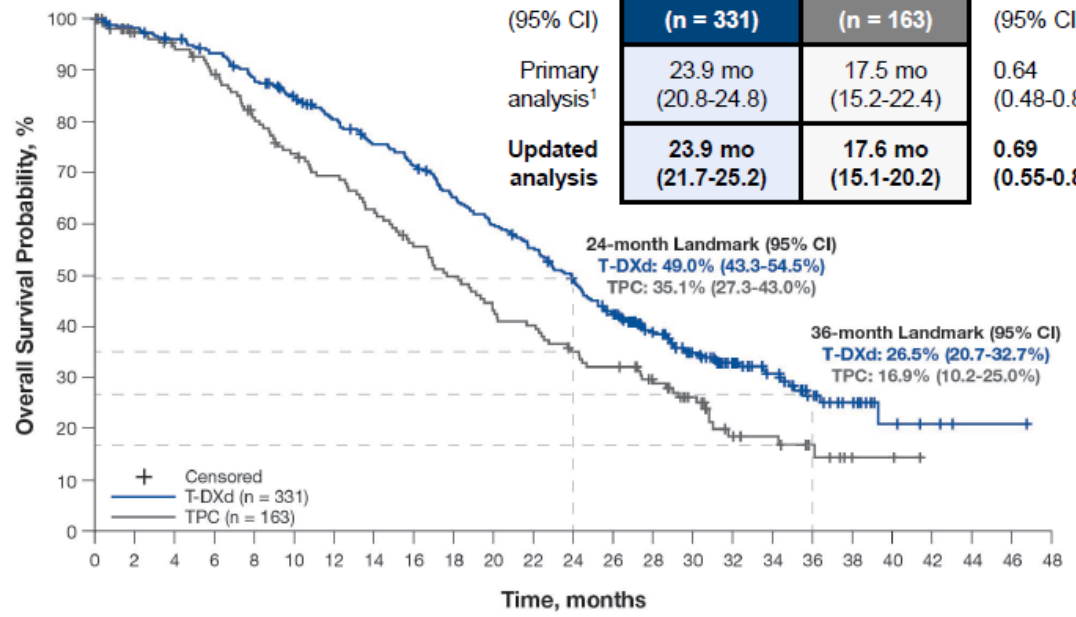
[a] PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (HR 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (HR 0.50).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

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



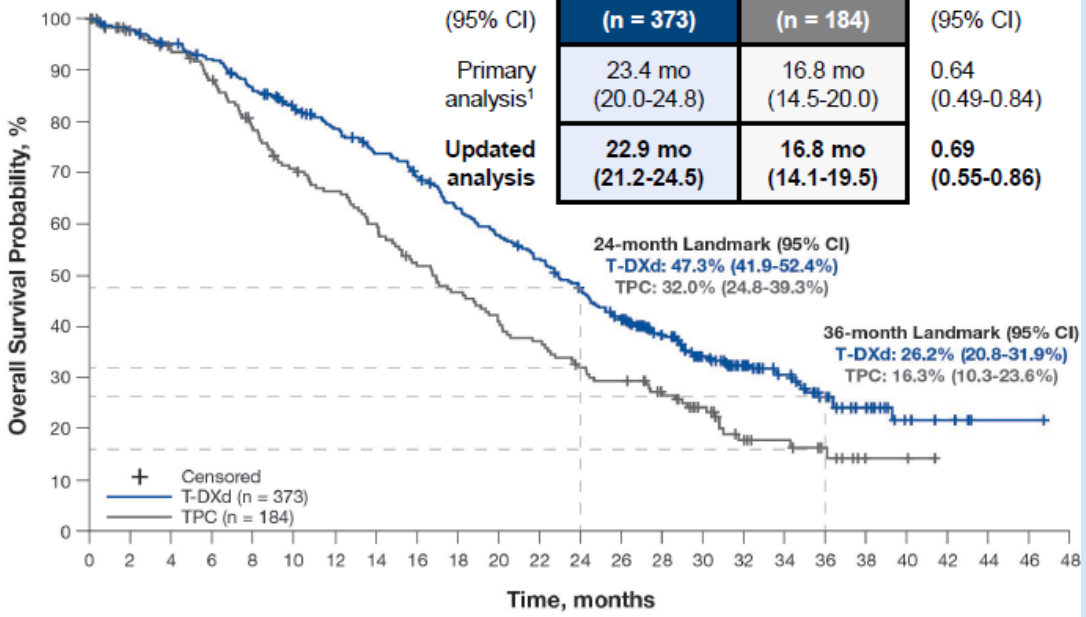
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 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

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 306 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 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)

Data cutoff date: March 1, 2023.

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

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

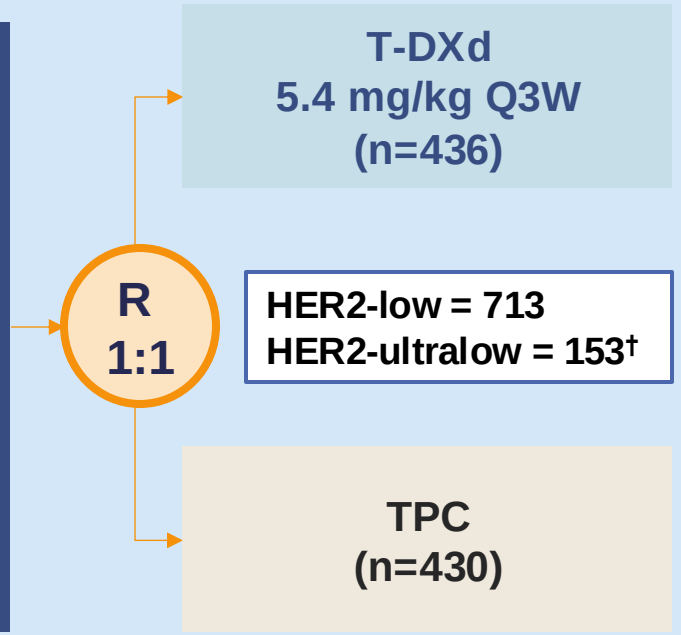
OR

- 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 straining)
- Prior taxane in the non-metastatic setting (yes vs no)



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

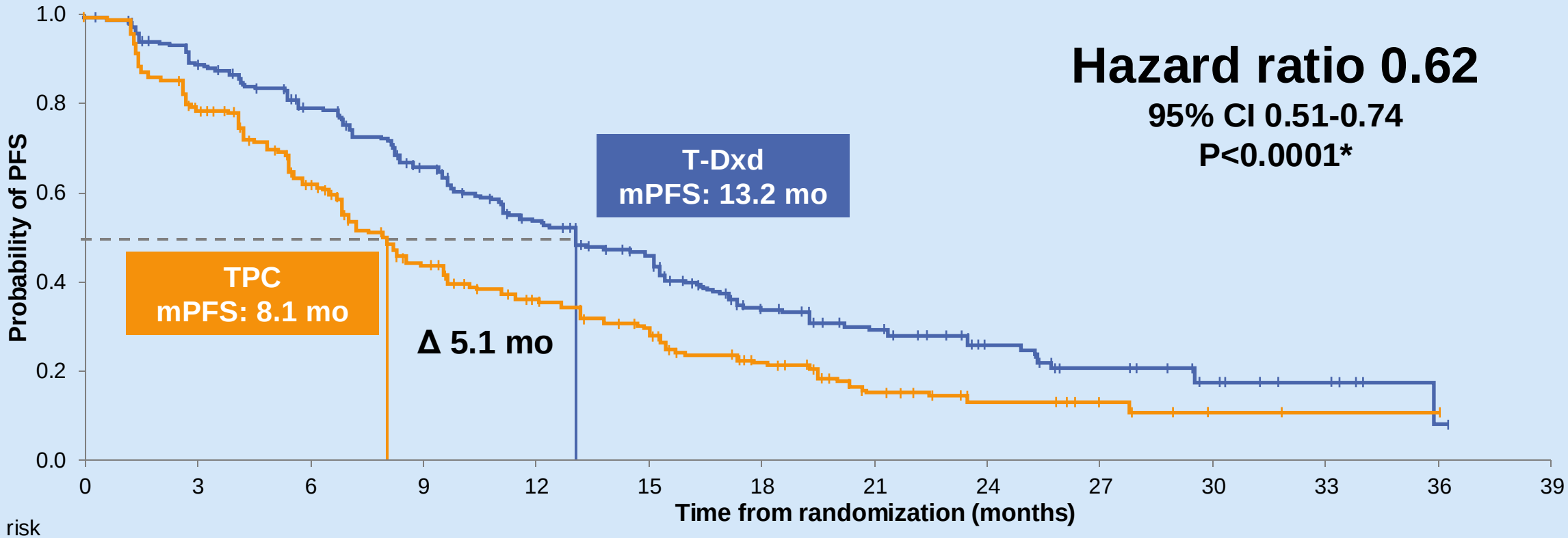
- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

*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 kinsase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; IHC, immunochemistry; 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/NCTo0094425 (Accessed May 13, 2024)

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



No. at risk

T-Dxd	359	310	265	213	163	131	72	49	28	17	10	6	1	0
TPC	354	254	192	118	85	65	37	19	10	6	2	1	1	0

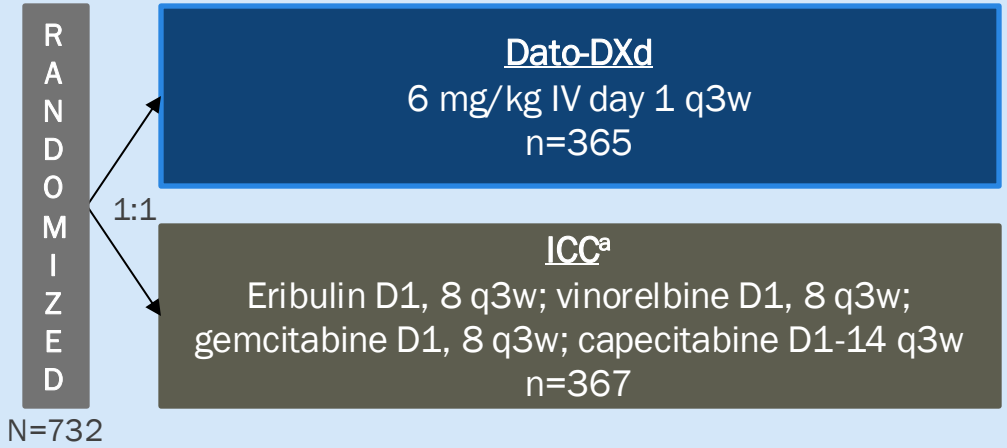
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*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-Breast01 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

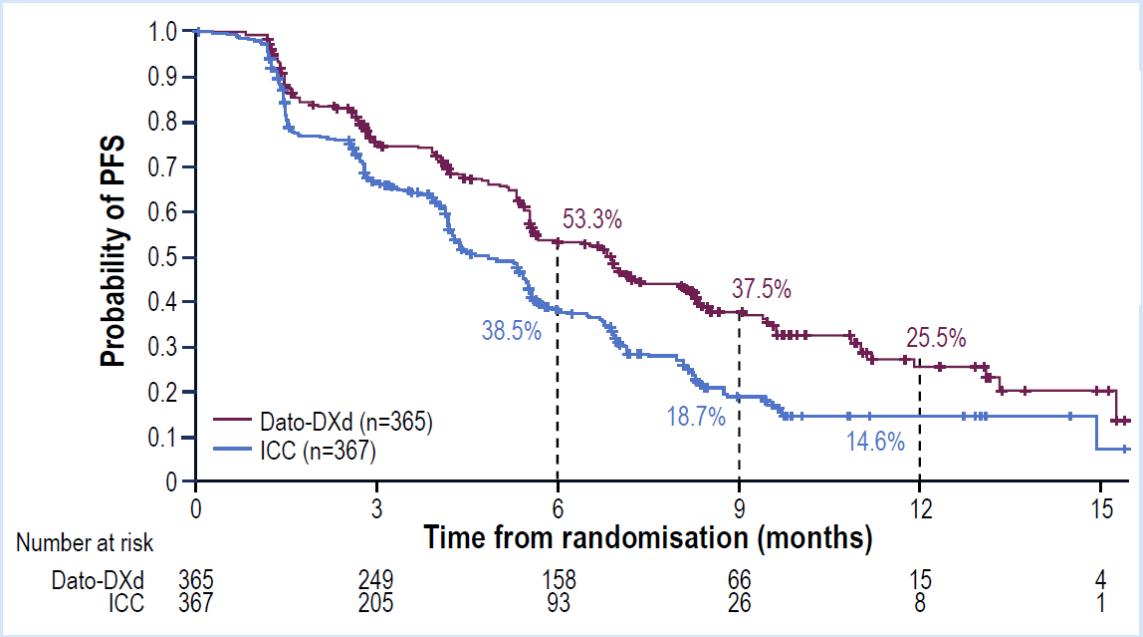
Patient Characteristics, n (%)		Dato-DXd (n=365)[b]	ICC (n=367)[c]
Median age (range), years		56 (29-86)	54 (28-86)
Race	Black or African American	4 (1)	7 (2)
	Asian	146 (40)	152 (41)
	White	180 (49)	170 (46)
	Other	35 (10)	38 (10)
Ethnicity	Hispanic or Latino	40 (11)	43 (12)
	Not Hispanic or Latino	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).

Bardia A, et al. ESMO 2023. Abstract LBA11.

TROPION-Breast01 Phase 3 Trial of Dato-DXd vs CT in HR+/HER2– MBC: PFS (Primary Endpoint)

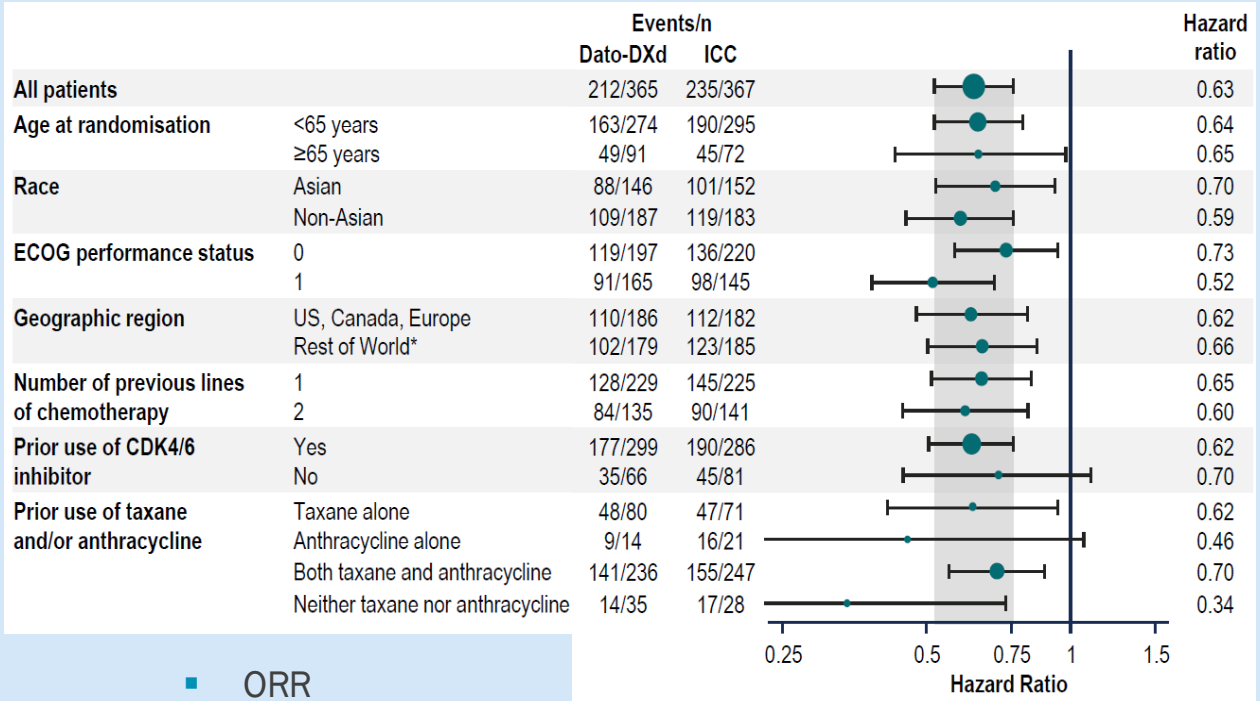
PFS by BICR: Primary Endpoint



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)

Bardia A, et al. ESMO 2023. Abstract LBA11.

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)

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

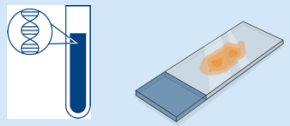
- Median treatment duration: 6.7 mo (Dato-DXd), 4.1 mo (ICC)
- Most TRAEs were grade 1-2 and manageable
- Oral mucositis/stomatitis led to discontinuation in 1 patient in the Dato-DXd group
- Most ocular events were dry eye; 1 patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related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

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 AESIs were grade 1-2; there were fewer grade ≥3 TRAEs and fewer TRAEs leading to dose interruption/reduction with Dato-DXd compared with ICC

Bardia A, et al. ESMO 2023. Abstract LBA11.

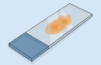
Treatment Paradigm for HR+/HER2– MBC



1st LINE → 2nd LINE → 3rd LINE → 4th LINE







	1st LINE	2nd LINE	3rd LINE	4th LINE
Wild Type	ET + CDK4/6i	ET + CDK4/6i ET + mTORi	ET + mTORi T-Dxd/Chemo	ADC/Chemo
PIK3CA	ET + CDK4/6i + PI3Ki	ET + PI3Ki	ET + PI3Ki	
AKT1, PTEN, PIK3CA		ET + AKTi	ET + AKTi	
ESR1		SERD (Elacestrant)	SERD (Elacestrant)	
gBRCA1/2			PARPi	PARPi

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THANK YOU!!!!!!!!!!