Treatment Approaches after CDK4/6 Inhibition in HR+/HER2-Negative MBC

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National Cancer Institute-Designated Comprehensive Cancer Center

Disclosures

Spouse, Stock: Grail, Array BioPharma and Pfizer (Prior Employee)

Advisory/Consulting: Eli-Lilly, Pfizer, Novartis, Eisai, AstraZeneca, Immunomedics, Merck, Seattle Genetics, and Cyclocel

Results for Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2[1]	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	No
MONALEESA-2[2]	Ribociclib	1st Line/AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7[3a]	Ribociclib	1st Line/AI or Tam	Pre/Peri	0.55	Yes	0.70	Yes
MONARCH-3[4]	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.75	No (@IA2)
PALOMA-3[5]	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2[6]	Abemaciclib	2nd Line/Fulv	Pre/Post	0.55	Yes	0.78	Yes
MONALEESA-3[7]	Ribociclib	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	0.72	Yes

a. Missing survival data (ie, pts who withdrew consent or were lost to follow-up) and were censored (assumed to be alive) at time of analysis: 13% in palbo+AI arm vs 21% in control arm.
b. 27% of patients in control arm went on to receive a CDK4/6i (24% received palbociclib).
c. PFS/OS data reported for approved AI subset.

AI indicates aromatase inhibitor; Fulv, fulvestrant; IA2, interim analysis 2; NR, not reported; Rx, therapy.

1. PALOMA-2: Finn R, et al. *N Engl J Med*. 2016;375:1925-1936; Rugo H, et al. *Breast Cancer Res Treat*. 2019;174:719-729. Finn R, et al. ASCO 2022. LBA1003. **2.** MONALEESA-2: Hortobagyi G, et al. *N Engl J Med*. 2016;375:1738-1748; Hortobagyi G, et al. *Ann Oncol*. 2018;29:1541-1547; Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR. **3.** MONALEESA-7: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915; Im S-A, et al. *New Engl J Med*. 2019;381:307-316. **4.** MONARCH-3: Goetz M, et al. *J Clin Oncol*. 2017;35:3638-3646; Johnson S, et al. NPJ *Breast Cancer. 2019;5:5*. Goetz MP, et al. ESMO 2022. Abstract LBA 15. **5.** PALOMA-3: Turner NC, et al. *New Engl J Med*. 2015;373:209-219; Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439; Turner NC, et al. *New Engl J Med*. 2015;373:1672-1673. **6.** MONARCH-2: Sledge G, et al. *J Clin Oncol*. 2017;35:2875-2884; Sledge G, et al. *JAMA Oncol*. 2020;6:116-124**. 7.** MONALEESA-3: Slamon D, et al. *J Clin Oncol*. 2018;36:2465-2472; Slamon D, et al. *New Engl J Med*. 2020;382:514-524.

What Do We Do After Progression on CDK 4/6i?

- **Performance of endocrine monotherapy therapy post cdk 4/6 is poor; role for novel endocrine agents?**

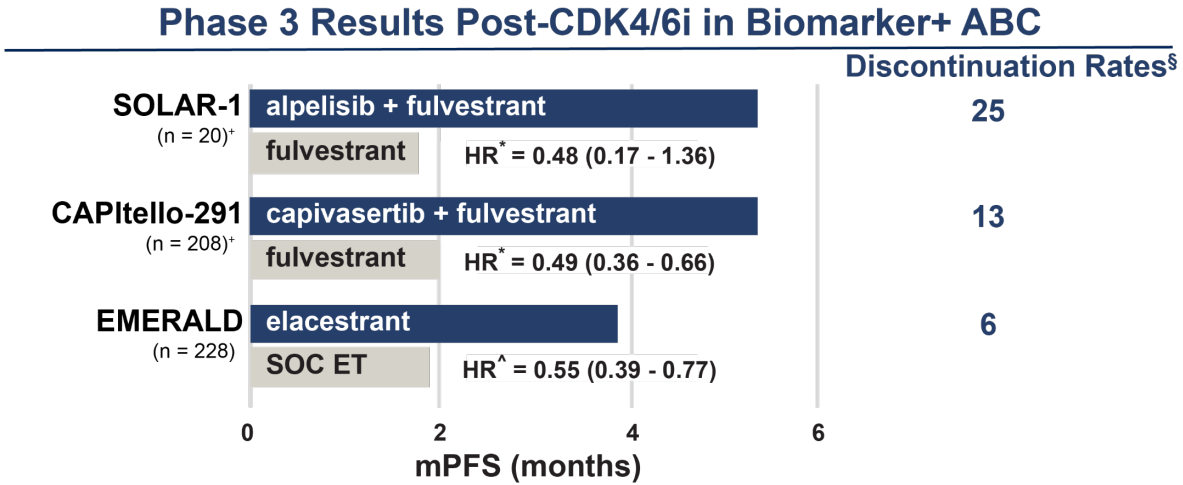
  -Single agent fulvestrant : median PFS ~ 2 months (EMERALD; VERONICA)
  -Elacestrant in *ESR1*m: 3.8 months (2.8 months in ITT; EMERALD)

- **Is there a role for continuation of cdk 4/6 inhibition beyond progression?**

- **Tackle endocrine resistance**
  - Targeting the PI3K-Akt-mTOR pathway (BOLERO-2, PreECOG, SOLAR-1, BYLieve, CAPItello 291)
  - Novel Endocrine Therapies

Background: Targeted Therapy Options Post 1L CDK4/6i

- Targeted therapy options are primarily confined to biomarker-positive (+) ABC (PI3K pathway altered, *ESR1* mutant)
- Despite this important progress, median PFS with these agents remains <6 months, absolute improvement generally limited to ~1-2 scan intervals, and toxicities vary



+Post CDK4/6i Subgroup, *Investigator PFS, ^BICR PFS, §ITT population

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Juric D. et al 2019 Proceedings of SABCS 79(4) Abstract nr GS3-08
Oliveira M. et al 2023 Annals of Oncology 8(1)
Turner N. et al 2023 N Engl J Med 388(22) 2058-2070
Bidard F. et al 2022 J Clin Oncology 40(28) 3246-32568

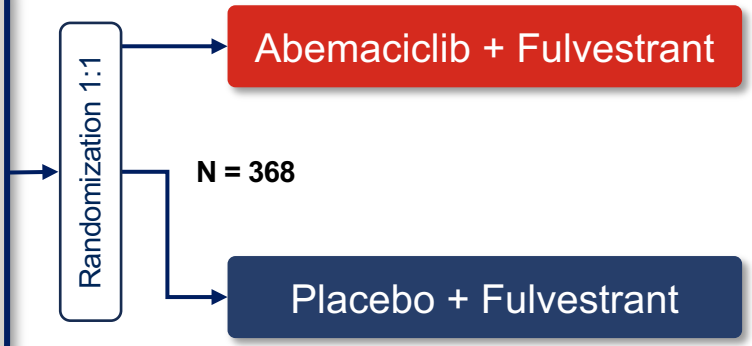
postMONARCH Study Design

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

Prior Therapy:
- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC



Primary Endpoint:
Investigator-Assessed PFS

Secondary Endpoints:
OS, PFS by BICR, ORR, CBR, DCR, DoR, Safety, PK & PRO

Stratification Factors:
- Duration of prior CDK4/6i
- Visceral metastases
- Geographic region

- Enrolled March 2022 to June 2023 across 96 centers in 16 countries
- Scans every 8 weeks for the first 12 months, then every 12 weeks
- Primary outcome targeted 251 events; interim analysis planned at ~70% of events
- Assuming a hazard ratio (HR) of 0.70, ~80% power to detect abemaciclib superiority, with a cumulative 2-sided type I error of 0.05
- Biomarker ctDNA analyzed by GuardantINFINITY assay

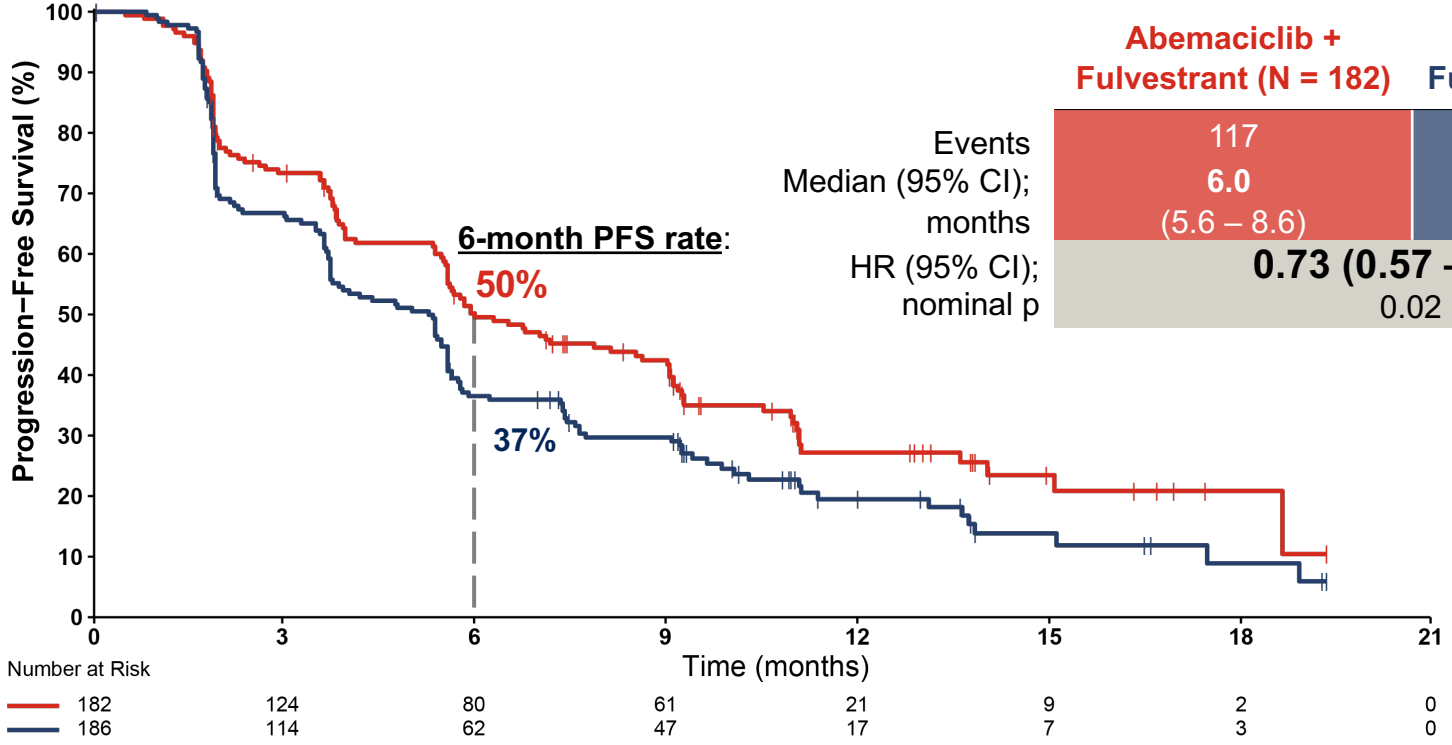
Balanced Baseline Patient & Disease Characteristics

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestrant N=186 (%)
Age	Median (range)	58 (27, 86)	61 (28, 85)
	< 65 years	69	63
	≥ 65 years	31	37
Gender	Female	99	100
ECOG	0	57	58
	1	43	43
Region	Other (includes EU)	73	72
	Asia	12	13
	USA	15	15
Race	White	82	82
	Asian	12	15
	Black/African American	4	2
Ethnicity	Not Hispanic/Latino	74	77
	Hispanic/Latino	15	15
HR Status	ER+	100	99
	PR+	79	81

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestant N=186 (%)
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*	71	77
	<12 months^	29	22
Median Prior CDK4/6i Duration (mo; range)#	All	19 (2, 110)	21 (3, 87)
	Palbociclib	19	23
	Ribociclib	15	18
	Abemaciclib	26	21

* ≥ 12 months ABC or recurrence after EBC therapy
^ < 12 months ABC or recurrence on EBC therapy
# for ABC

Primary Analysis: Abemaciclib Improved Investigator-Assessed PFS



	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	

Abemaciclib led to 27% reduction in the risk of developing PFS event

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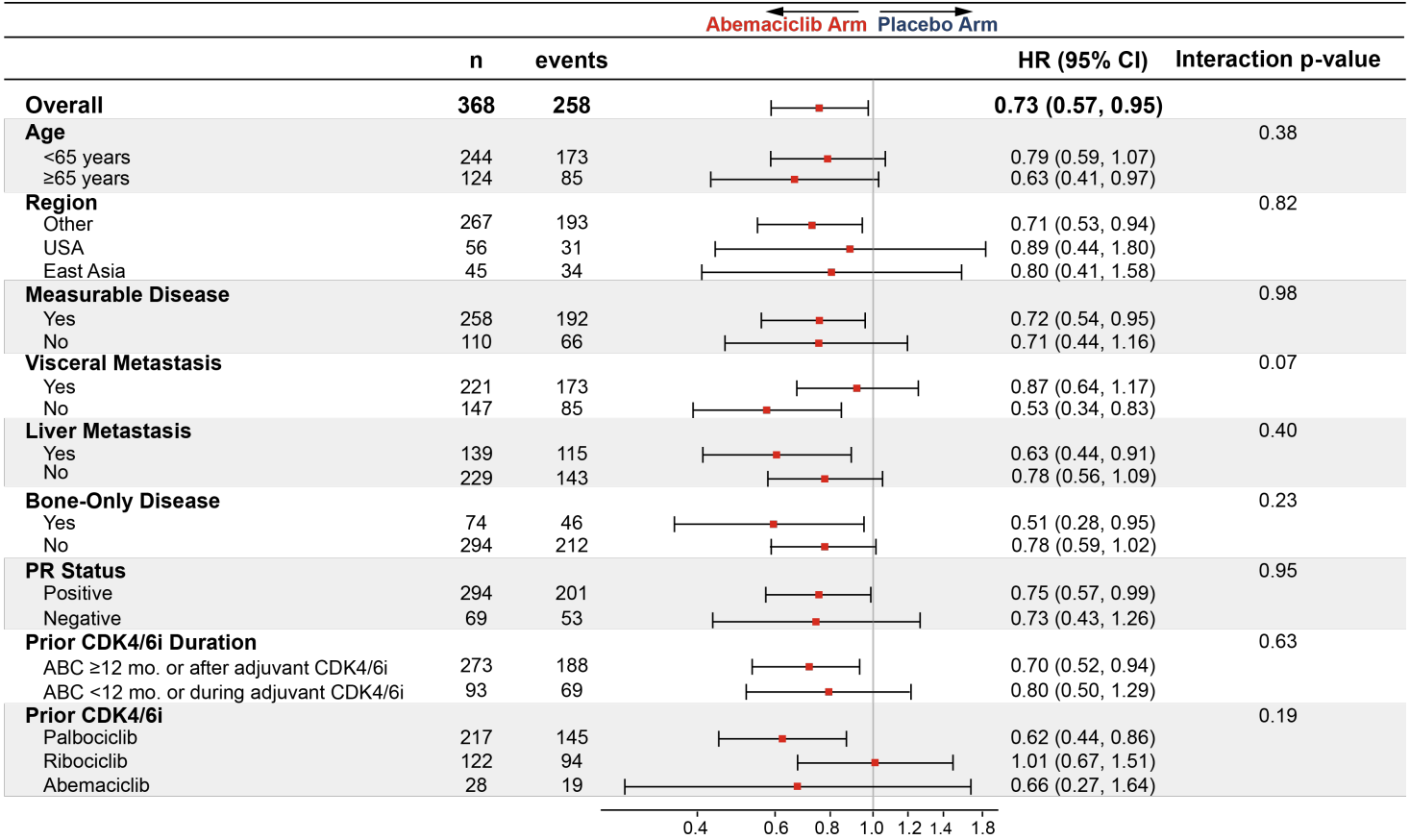
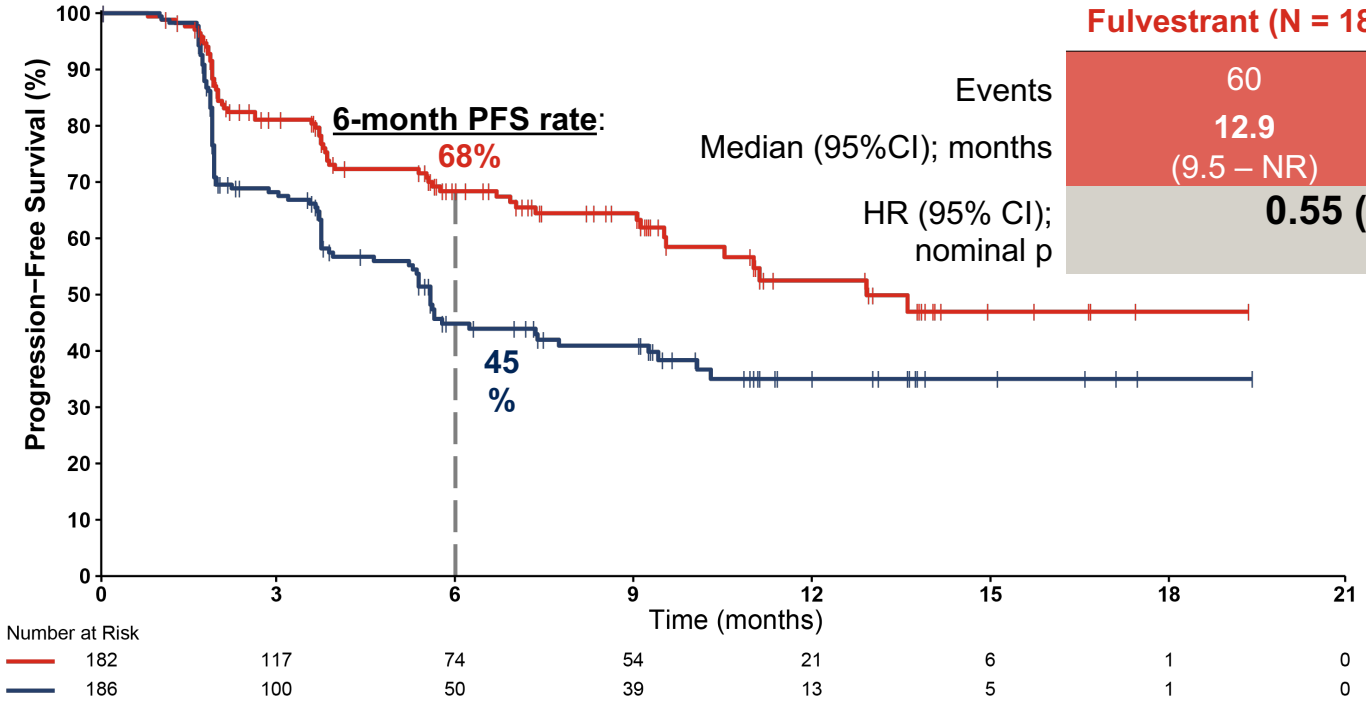
Investigator-Assessed PFS by Subgroup: Consistent Abemaciclib Effect Across Subgroups



Secondary Analysis: Abemaciclib Improved BICR-Assessed PFS



	Abemaciclib + Fulvestrant (N = 182)	Placebo + Fulvestrant (N = 186)
Events	60	92
Median (95%CI); months	**12.9** (9.5 – NR)	**5.6** (3.9 – 7.7)
HR (95% CI); nominal p	**0.55 (0.39 – 0.77)** 0.0004	

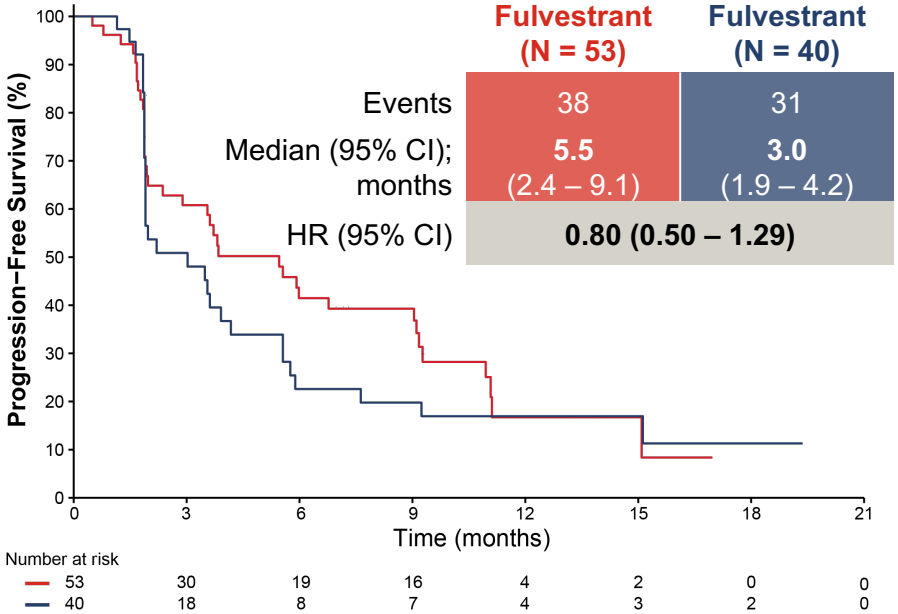
Estimates impacted by informative censoring (discordance with investigator events: **51% abemaciclib arm, 38% placebo arm**)

Abemaciclib led to 45% reduction in the risk of developing PFS event per BICR

BICR: Blinded Independent Central Review

Subgroup Analysis: Investigator-Assessed PFS by Prior CDK4/6i Duration

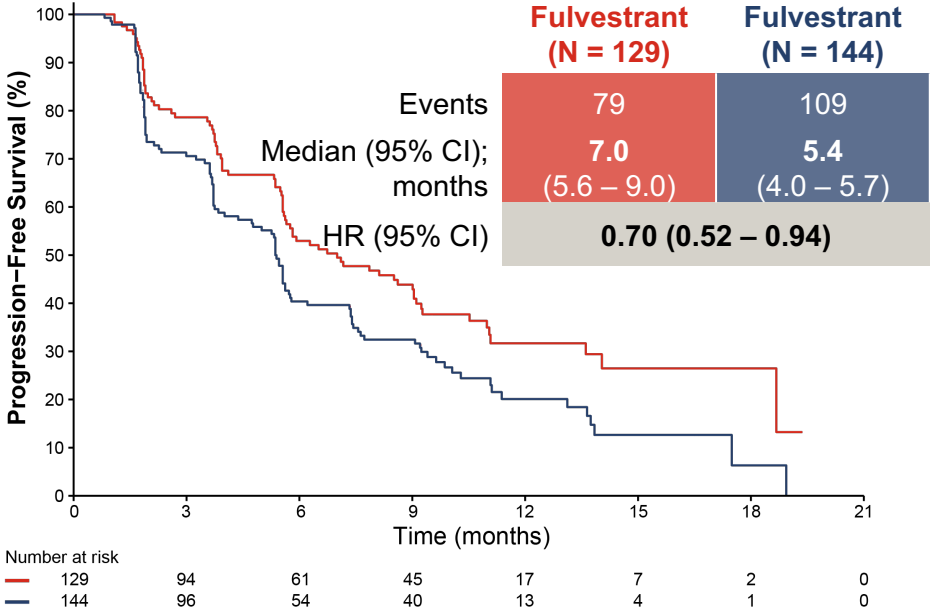
< 12 months^



	Abemaciclib + Fulvestrant (N = 53)	Placebo + Fulvestrant (N = 40)
Events	38	31
Median (95% CI); months	**5.5** (2.4 – 9.1)	**3.0** (1.9 – 4.2)
HR (95% CI)	**0.80 (0.50 – 1.29)**	

^ < 12 months ABC or recurrence on EBC therapy

≥ 12 months*



	Abemaciclib + Fulvestrant (N = 129)	Placebo + Fulvestrant (N = 144)
Events	79	109
Median (95% CI); months	**7.0** (5.6 – 9.0)	**5.4** (4.0 – 5.7)
HR (95% CI)	**0.70 (0.52 – 0.94)**	

* ≥ 12 months ABC or recurrence after EBC therapy

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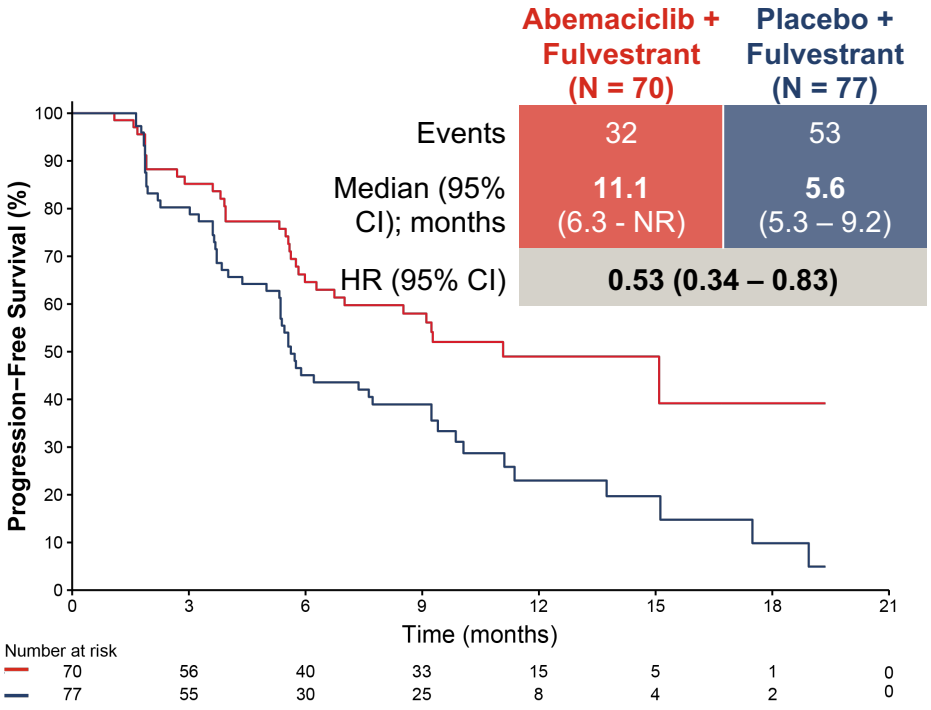
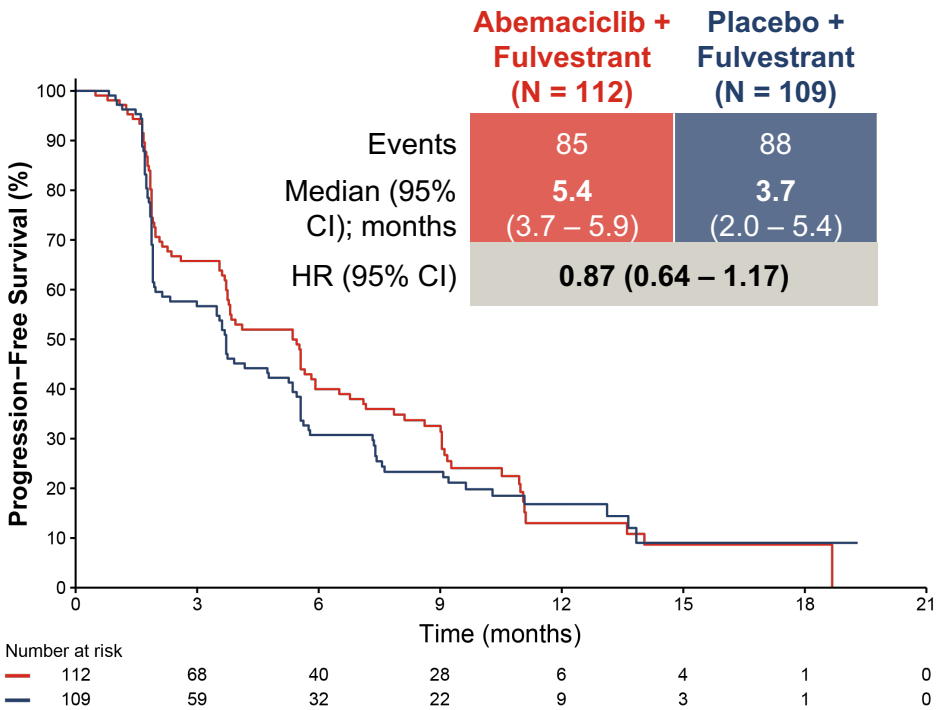
Subgroup Analysis: Investigator-Assessed PFS by Visceral Metastasis

No visceral metastasis



Visceral metastasis



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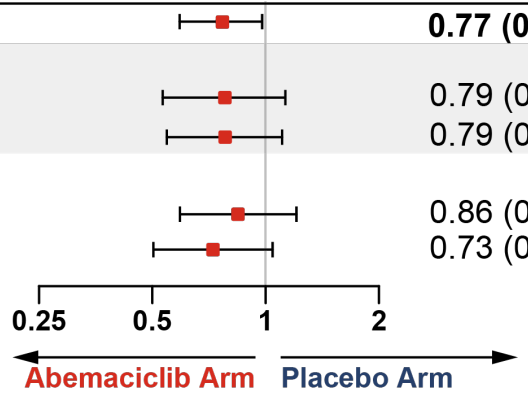
Exploratory: Consistent Effect Across Biomarker Subgroups

		Abemaciclib + Fulvestrant N=182	Placebo + Fulvestrant N=186
ctDNA Evaluable Population		161 (88%)	159 (85%)
Biomarker Status	*ESR1* mutation	40%	51%
	PIK3CA or *PTEN* or *AKT1* alteration	46%	52%

Subgroup	n	events	HR (95% CI)	Interaction p-value
ctDNA Evaluable Population	**320**	**230**	**0.77 (0.59 to 1.00)**	
ESR1				0.98
Detected	145	110	0.79 (0.54 to 1.15)	
Not detected	175	120	0.79 (0.55 to 1.13)	
PIK3CA* or *AKT1* or *PTEN				0.55
Detected	156	118	0.86 (0.60 to 1.23)	
Not detected	164	112	0.73 (0.51 to 1.06)	



Biomarker ctDNA by GuardantINFINITY assay

Conclusions

- postMONARCH is the first randomized, placebo-controlled Phase 3 study to demonstrate benefit of continued CDK4/6 inhibition beyond progression on a CDK4/6i

- Abemaciclib improved PFS in pts with HR+, HER2- ABC with disease progression on prior CDK4/6i + ET, despite the control arm performing better than expected
  - 27% risk reduction for developing a PFS event (HR: 0.73 [0.57- 0.95])
  - Consistent benefit across multiple prespecified and clinically relevant subgroups, including key biomarker subgroups
  - Consistent improvement across key secondary efficacy endpoints, including PFS by BICR and ORR
- Safety was consistent with the known abemaciclib profile and discontinuation rate was low

Abemaciclib + fulvestrant offers a targeted therapy option after disease progression on a CDK4/6i for patients with HR+, HER2- ABC, not selected for biomarker status

Phase 3 Capitello-291: Prior treatments

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression 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 CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Prior endocrine therapy for ABC; n (%)	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)
Previous CDK4/6 inhibitor for ABC; n (%)		245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy; n (%)	Adjuvant/neoadjuvant	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)

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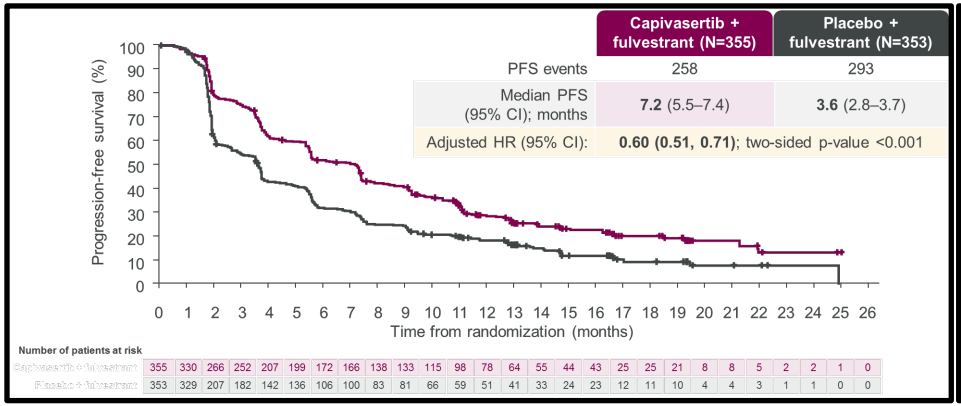
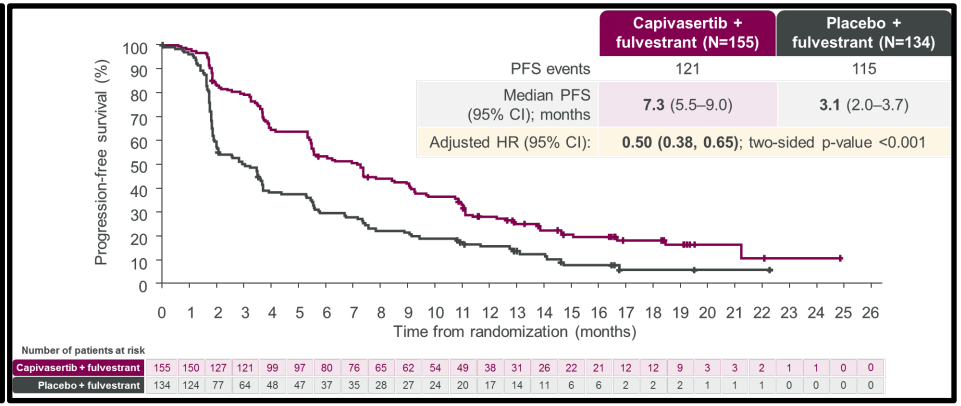
Phase 3 Capitello-291: Dual-primary endpoint: Investigator-assessed PFS in the overall population and AKT pathway-altered population



Overall population



AKT pathway-altered population

13% discontinuation, 20% dose reduction; most common AE: diarrhea , rash, nausea, fatigue
Diarrhea grade 3 : 9.3%
Rash grade 3 12%
Hyperglycemia grade 3 2.3%

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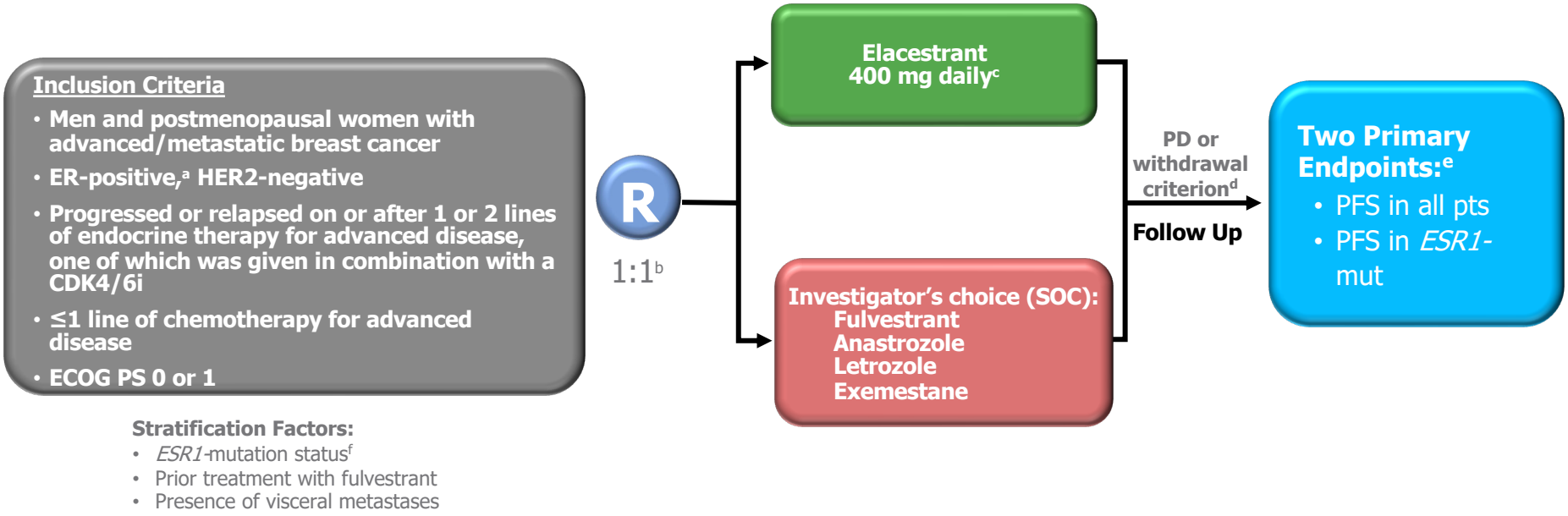
EMERALD Phase 3 Study Design



[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay.

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

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Baseline Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.0 (32-83)	63.0 (32-83)
Gender, n (%) Female Male	 233 (97.5) 6 (2.5)	 115 (100) 0	 238 (99.6) 1 (0.4)	 113 (100) 0
ECOG PS, n (%) 0 1 >1	 143 (59.8) 96 (40.2) 0	 67 (58.3) 48 (41.7) 0	 135 (56.5) 103 (43.1) 1 (0.4)	 62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6i, n (%)	239 (100)	115 (100)	239 (100)	113 (100)
Number of prior lines of endocrine therapy,** n (%) 1 2	 129 (54.0) 110 (46.0)	 73 (63.5) 42 (36.5)	 142 (59.4) 97 (40.6)	 69 (61.1) 44 (38.9)
Type of prior endocrine therapy, n (%)** **Fulvestrant** AI Tamoxifen	 **70 (29.3)** 193 (80.8) 19 (7.9)	 **27 (23.5)** 101 (87.8) 9 (7.8)	 **75 (31.4)** 194 (81.2) 15 (6.3)	 **28 (24.8)** 96 (85.0) 9 (8.0)
Number of prior lines of chemotherapy,** n (%) 0 1	 191 (79.9) 48 (20.1)	 89 (77.4) 26 (22.6)	 180 (75.3) 59 (24.7)	 81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

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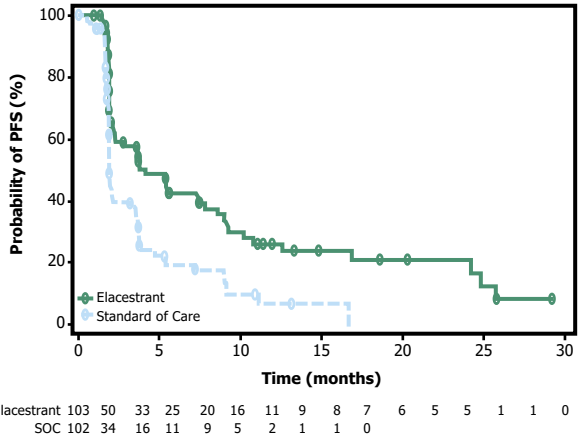
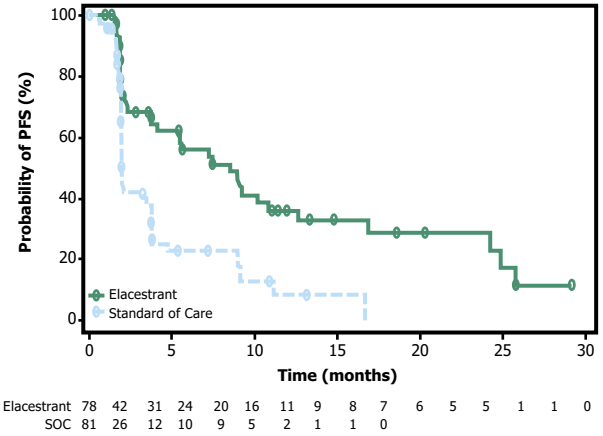
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



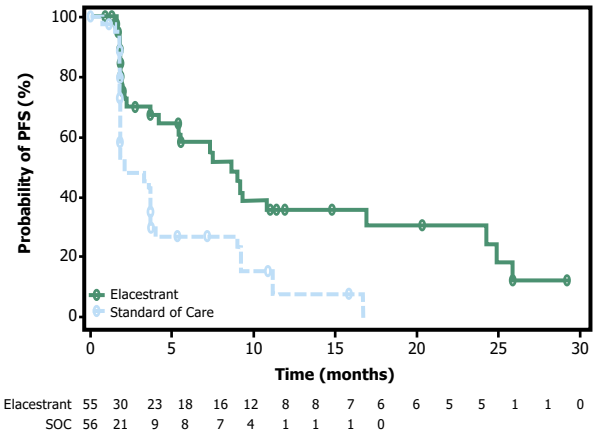
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

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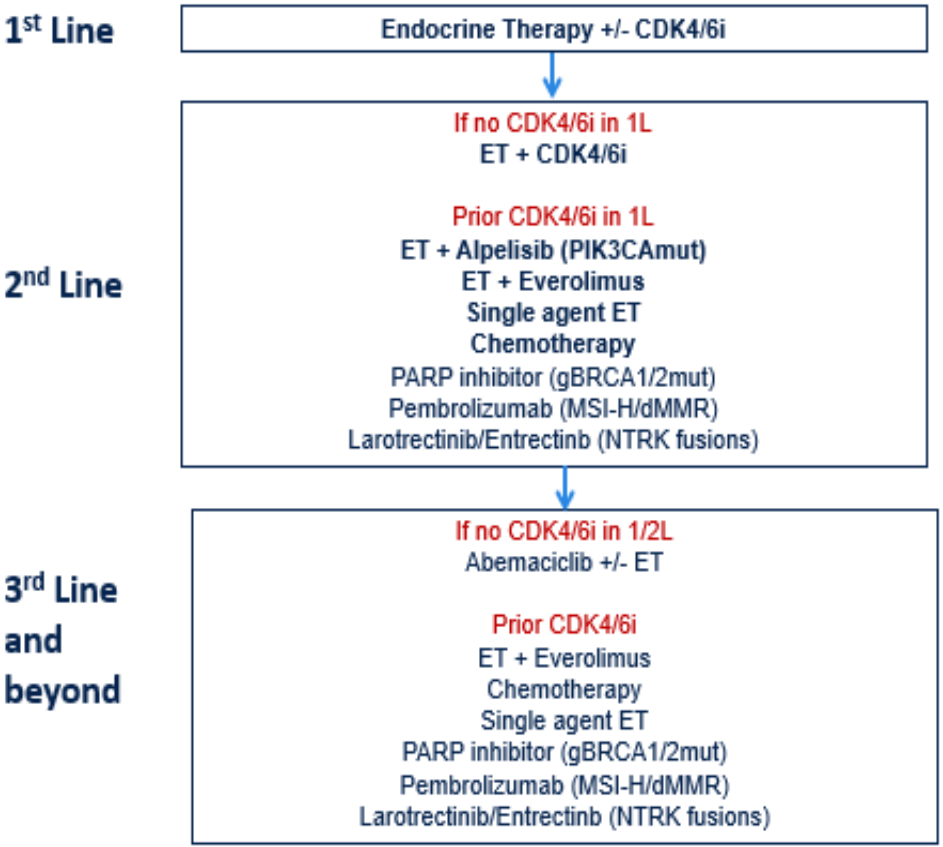
Emerald Toxicity

AEs[c] Occurring in ≥ 10% of Patients in Any Arm	Elacestrant		Total		Fulvestrant		AI	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)[d]	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	0	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)[e]	2 (0.8)	19 (8.3)	0	12 (7.5)	0	7 (10.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	0	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0	28 (17.4)	0	9 (13.2)	0
Diarrhea	33 (13.9)	0	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	0
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	0
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0	18 (11.2)	0	8 (11.8)	0
Constipation	29 (12.2)	0	15 (6.6)	0	10 (6.2)	0	5 (7.4)	0
Hot flush	27 (11.4)	0	19 (8.3)	0	15 (9.3)	0	4 (5.9)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0	4 (2.5)	0	2 (2.9)	0
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	0	6 (8.8)	1 (1.5)

Kaklamani VG, et al. ASCO Annual Meeting 2023 (abstr 1070)

Clinical pathway for treatment of ER+/HER2- MBC



- If ESR1 mutation: single agent elacestrant
- Switch ET + Abema if prior CDK4/6i and no targetable mutation.
- Fulvestrant + Capivasertib if PI3K pathway alteration (concern in uncontrolled diabetic)

- Sacituzumab if at least 2 prior lines of systemic tx
- ? ADC after ADC

Adapted from http://www.nccn.org/professionals/physician_gls/pdf/breast.pdfJM