San Antonio Breast Cancer Symposium (SABCS) 47th Annual Meeting; San Antonio, TX; December 10-13, 2024

IMLUNESTRANT, AN ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADER (SERD), AS MONOTHERAPY AND COMBINED WITH ABEMACICLIB, FOR PATIENTS WITH ER+, HER2- ADVANCED BREAST CANCER (ABC), PRETREATED WITH ENDOCRINE THERAPY (ET): RESULTS OF THE PHASE 3 EMBER-3 TRIAL

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Disclosure Information

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I have the following relevant financial relationships to disclose:

Employee of: Memorial Sloan Kettering Cancer Center

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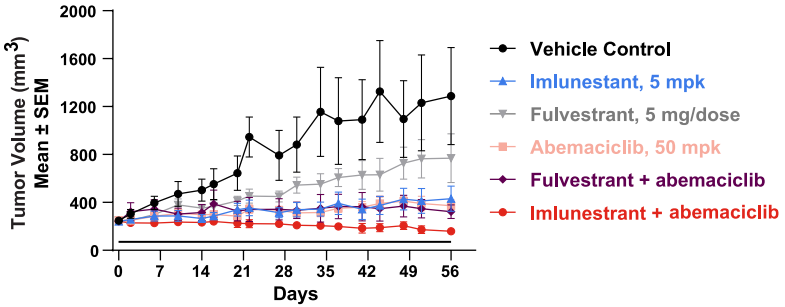
Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

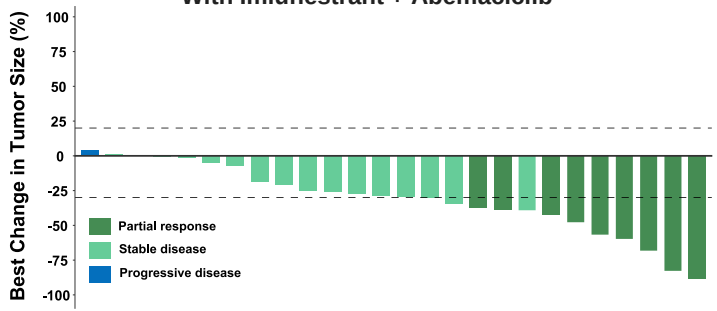
Background

- **ER and CDK4/6 are critical oncogenic pathways of ER+, HER2- ABC**
- **ET + CDK4/6i are essential therapies for ER+, HER2- ABC[1]**
  - Continued suppression of ER and CDK4/6 beyond progression on CDK4/6i + ET may be important for improved patient outcomes, regardless of *PIK3CA* or *ESR1*m
  - Abemaciclib has shown benefit in CDK4/6i-naïve[2] & CDK4/6i-pretreated patients[3]
- **Fulvestrant is the only SERD broadly approved as monotherapy and in combination, but**
  - **Efficacy** is **limited** in patients with *ESR1*m
  - Requires **intramuscular administration[4]**
    - Often painful & burdensome to patients,[5] when oral options are generally preferred[6]
- **Elacestrant is an oral SERD with dose-dependent mixed ER agonist/antagonist activity approved as monotherapy for patients with *ESR1*m[7]**
- **Imlunestrant is a next-generation, brain-penetrant, oral SERD and pure ER antagonist that delivers continuous ER inhibition**

In Vivo Efficacy in CTG-1260 *ESR1 D538G* Model[8]



EMBER Phase 1 trial: Tumor Response in Patients Treated With Imlunestrant + Abemaciclib[9]



ABC, advanced breast cancer; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; SEM, standard error of the mean.

1. Gradishar WJ. *J Natl Compr Canc Netw*. 2023;21(5.5):1-4; 2. VERZENIO (abemaciclib) [package insert]. Eli Lilly and Company; 2023; 3. Kalinsky K, et al. *J Clin Oncol*. 2024;42(Suppl 17):abstract LBA1001; 4. Robertson JFR, Harrison M. *Br J Cancer*. 2004;90(Suppl 1):S7-S10; 5. Cox AC, Fallowfield LJ. *Eur J Oncol Nurs*. 2007;11(1):43-48; 6. Eek D, et al. *Patient Prefer Adherence*. 2016;10:1609-1621; 7. Beumer JH, Foldi J. *Cancer Chemother Pharmacol*. 2023;92(2):157-163; 8. VandeKopple M, et al. Poster presented at ESMO Breast Cancer Congress; Berlin, Germany; May 11-13, 2023. Poster 41P; 9. Data on file. March 9, 2023.

EMBER-3 Study Design

ER+, HER2- ABC

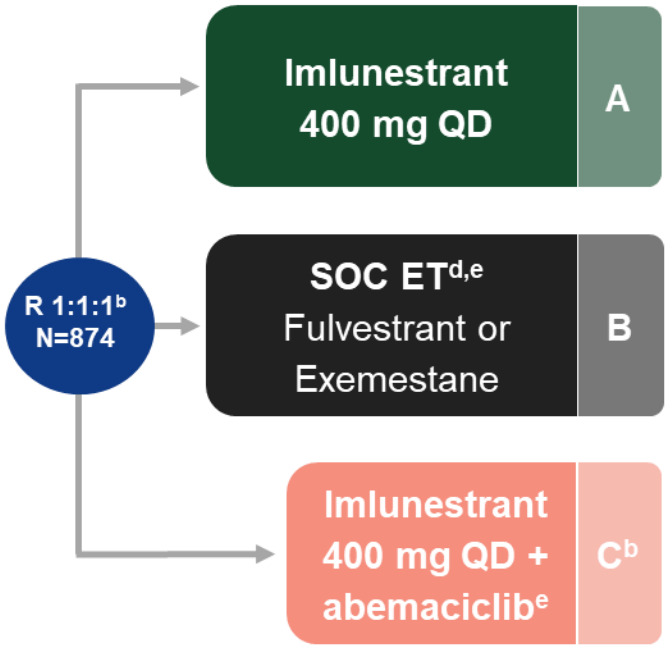
Men and Pre-[a]/Post-menopausal women

Prior therapy:

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification Factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]



Primary Endpoints

Investigator-assessed PFS for[f]:

- A vs B in patients with *ESR1*m[g]
- A vs B in all patients
- C vs A in all[h] patients

Key Secondary Endpoints

- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

- PFS and OS for C vs B in all[h] patients

ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 to November 2023 across 195 sites in 22 countries. [a] A GnRH agonist was required in men and premenopausal women; [b] Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c] East Asia vs United States/European Union vs others; [d] Investigator's choice; [e] Labeled dose; [f] Scans every 8 weeks for the first 12 months, then every 12 weeks; [g] *ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h] Analysis conducted in all concurrently randomized patients.

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Statistical Considerations

- **A graphical approach was used to control the overall type I error rate at 1-sided 0.025**
- **Alpha was initially assigned to the first PFS analysis of imlunestrant vs SOC ET**
  - 0.02 alpha assigned to patients with *ESR1*m (192 PFS events, 97%[a] power to detect a HR of 0.57)
  - 0.005 alpha assigned to all patients (480 PFS events, 76%[a] and 91%[b] power to detect a HR of 0.74)
- **Analysis of imlunestrant + abemaciclib vs imlunestrant[c] was only tested if one of the imlunestrant vs SOC ET endpoints was significant**
  - 80%[b] power, with 248 PFS events, to detect a target HR of 0.7
- **OS was only tested if the corresponding PFS endpoint was significant**

*ESR1*m, *ESR1* mutation; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SOC ET, standard of care endocrine therapy. [a] At initial alpha; [b] At full alpha after recycling; [c] Analysis conducted in all concurrently randomized patients.

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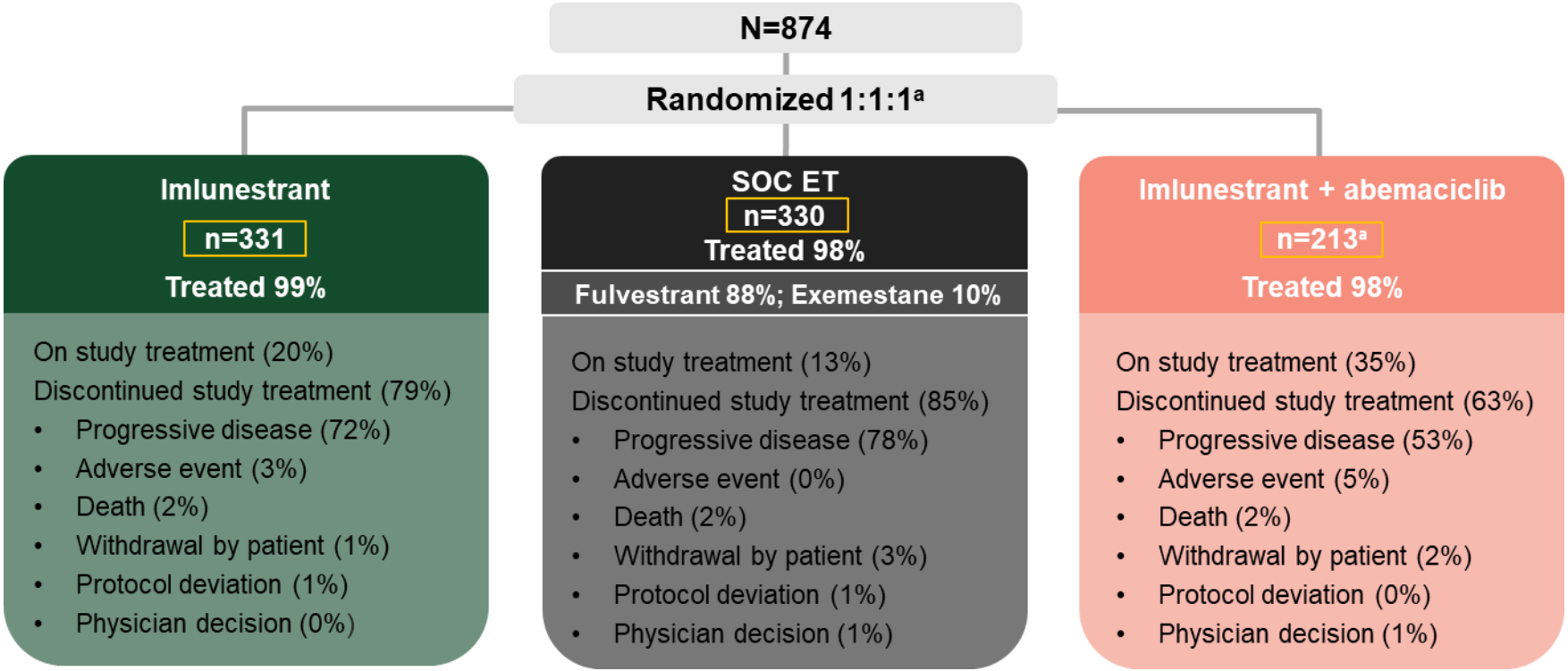
Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Patient Disposition



SOC ET, standard of care endocrine therapy. Data cutoff date: June 24, 2024. [a] Enrollment into the imlunestrant + abemaciclib arm started with Protocol Amendment A (at which point 122 patients had been randomized across the imlunestrant and SOC ET arms).

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Baseline Demographic and Disease Characteristics

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Median age, years (range)		61 (28-87)	62 (27-89)	62 (36-87)
Female, %		99	99	99
Post-menopausal, %		84	86	86
Race, %	White	56	58	52
	Asian	28	29	34
	Black or African American	3	2	4
Region, %	East Asia	25	26	31
	North America/ Western Europe	38	39	45
	Other	37	36	24
PR-positive, %		78	79	74
***ESR1* mutation, %[a]**		42	36	32
PI3K pathway mutations, %[b]		39	39	41

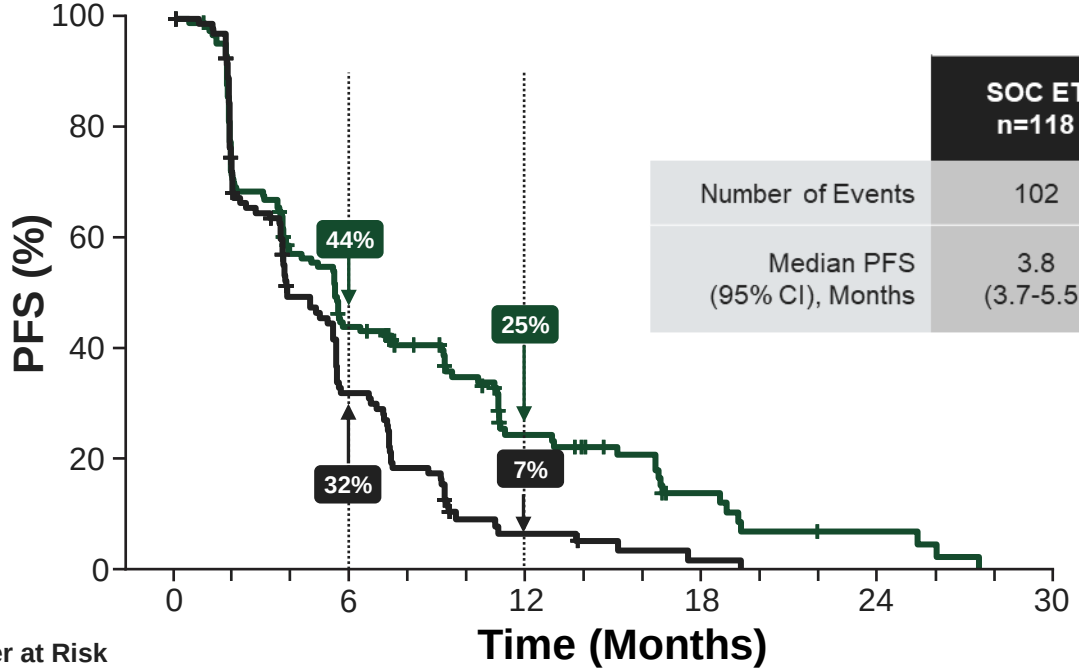
Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Site of metastases, %	Visceral	57	54	56
	Liver	32	30	27
	Bone-only	22	26	24
Endocrine resistance, %[c]	Primary	8	11	8
	Secondary	92	89	93
Most recent ET, %[d]	Adjuvant	32	34	30
	ABC	63	63	68
Previous CDK4/6i, %	Overall	59	57	65
	Adjuvant	4	5	3
	ABC	55	53	62
Previous CDK4/6i therapy, %[e]	Palbociclib	61	69	65
	Ribociclib	29	27	27
	Abemaciclib	10	4	7

Baseline characteristics were generally well balanced including in patients with *ESR1*m[f]

CDK4/6i, CDK4/6 inhibitor; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; PR, progesterone receptor; SOC ET, standard of care endocrine therapy. [a] Samples were analyzed by Guardant360 CDx, except for patients from China where samples were analyzed by OncoCompass Target assay, Burning Rock Biotech; [b] Includes single nucleotide variants and insertions/deletions of *PIK3CA, AKT1* or *PTEN* analyzed by Guardant 360 ctDNA assay. This analysis excludes patients from China or with unknown *ESR1*m status; [c] Per ESO-ESMO International Consensus Guidelines for ABC (ABC 6 and 7); [d] Adjuvant ET = First-line; ABC = Second-line; [e] Percentages calculated based on the numbers of patients who received prior CDK4/6i therapy (imlunestrant, n=195; SOC ET, n=189; imlunestrant + abemaciclib, n=139); [f] Data available in the online supplementary slides.

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Primary Endpoint: Imlunestrant vs SOC ET
Investigator-assessed PFS in Patients with *ESR1*m



	SOC ET n=118	Imlunestrant n=138
Number of Events	102	109
Median PFS (95% CI), Months	3.8 (3.7-5.5)	5.5 (3.9-7.4)

HR, 0.62 (95% CI, 0.46-0.82)[a] p<0.001

Number at Risk

SOC ET	118	74	51	33	19	7	5	3	2	1	0	0	0	0	0	0
Imlunestrant	138	95	74	56	45	35	22	18	15	8	4	4	3	2	0	0

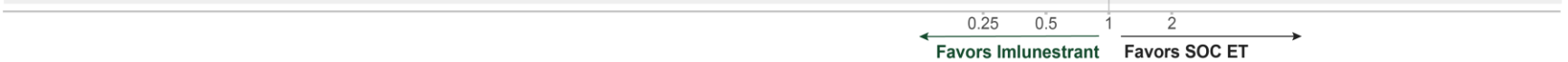
Imlunestrant led to a 38% reduction in the risk of progression or death in patients with *ESR1*m

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; RMST, restricted mean survival time; SOC ET, standard of care endocrine therapy. The median follow-up was 16.7 months in the imlunestrant arm and 13.8 months in the SOC ET arm.
[a] Due to evidence of non-proportional hazards, a sensitivity analysis of PFS using RMST was conducted. Estimated RSMT at 19.4 months was 7.9 months (95% CI 6.8-9.1) in the imlunestrant arm vs 5.4 months (95% CI 4.6-6.2) in the SOC ET arm [difference 2.6 months (1.2.-3.9)].

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Investigator-assessed PFS by Subgroup: Consistent Imlunestrant Benefit Across Subgroups in Patients with *ESR1*m

Subgroup		Imlunestrant No. of Events/Total No.	SOC ET No. of Events/Total No.	Hazard Ratio (95% CI)	Interaction *p*-value
Patients with *ESR1* mutation		109/138	102/118	0.62 (0.46, 0.82)	
Investigator's choice of ET	Exemestane	3/4	4/6	0.53 (0.09, 3.00)	**0.950**
	Fulvestrant	106/134	98/112	0.61 (0.46, 0.81)	
Age	<65 years	74/91	69/78	0.61 (0.44, 0.86)	**0.859**
	≥65 years	35/47	33/40	0.57 (0.34, 0.95)	
Region	East Asia	23/30	23/26	0.47 (0.25, 0.89)	**0.284**
	North America/Western Europe	51/63	44/54	0.77 (0.51, 1.17)	
	Other	35/45	35/38	0.50 (0.31, 0.82)	
No. of metastatic sites	1	24/35	26/35	0.53 (0.30, 0.94)	**0.901**
	2	36/45	35/39	0.61 (0.37, 0.99)	
	≥3	49/58	41/44	0.63 (0.41, 0.98)	
Visceral metastasis	No	39/54	42/51	0.51 (0.32, 0.79)	**0.612**
	Yes	70/84	60/67	0.68 (0.47, 0.98)	
Liver metastasis	No	58/81	59/71	0.58 (0.40, 0.83)	**0.679**
	Yes	51/57	43/47	0.64 (0.41, 0.99)	
Bone-only metastasis	No	92/111	79/88	0.65 (0.47, 0.89)	**0.439**
	Yes	17/27	23/30	0.42 (0.22, 0.80)	
Previous CDK4/6 inhibitor	No	29/45	31/33	0.42 (0.25, 0.72)	**0.246**
	Yes	80/93	71/85	0.72 (0.52, 1.01)	
Line of therapy in advanced setting	First-line	19/30	21/23	0.48 (0.25, 0.92)	**0.599**
	Second-line	88/106	81/95	0.66 (0.48, 0.90)	
PI3K pathway mutation status	Detected	59/72	48/57	0.62 (0.41, 0.93)	**0.732**
	Not detected	50/64	54/61	0.61 (0.41, 0.91)	

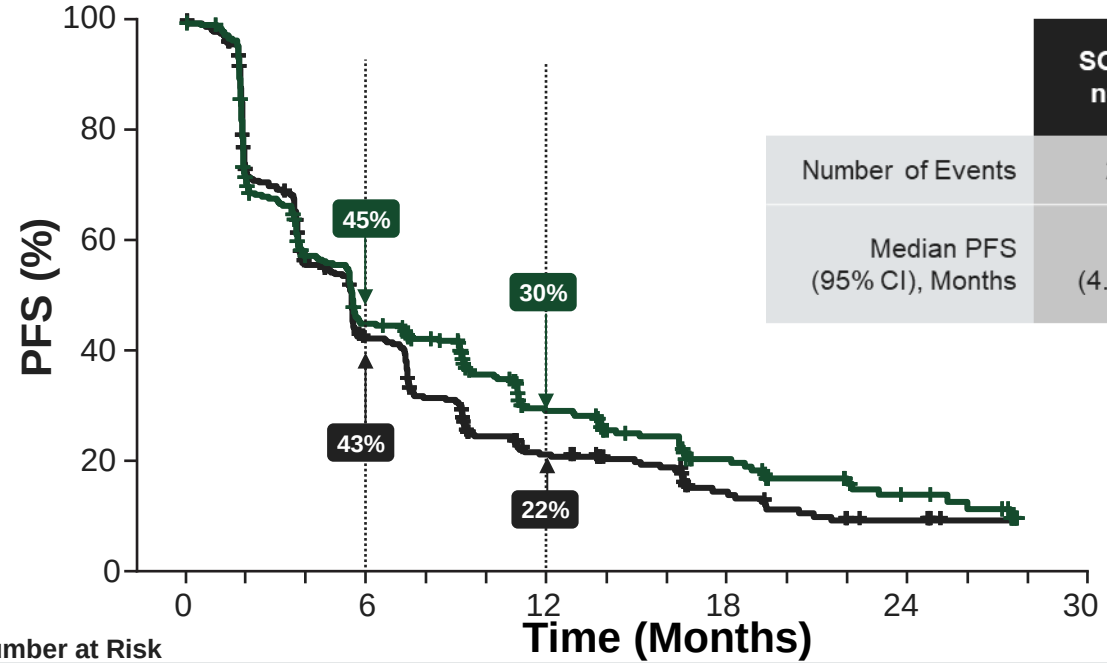


ET, endocrine therapy; SOC ET, standard of care endocrine therapy. First-line: most recent ET = adjuvant; Second-line: most recent ET = ABC. The total number of patients may not add up due to missing data in certain subgroups.

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Primary Endpoint: Imlunestrant vs SOC ET
Investigator-assessed PFS in All Patients



	SOC ET n=330	Imlunestrant n=331
Number of Events	253	237
Median PFS (95% CI), Months	5.5 (4.6-5.6)	5.6 (5.3-7.3)

HR, 0.87 (95% CI, 0.72-1.04) p=0.12

Prespecified Critical HR < 0.84[a]

Number at Risk

SOC ET	330	221	165	122	89	63	51	41	38	23	17	14	10	2	0	0
Imlunestrant	331	225	173	135	118	89	62	47	43	30	20	19	13	10	0	0

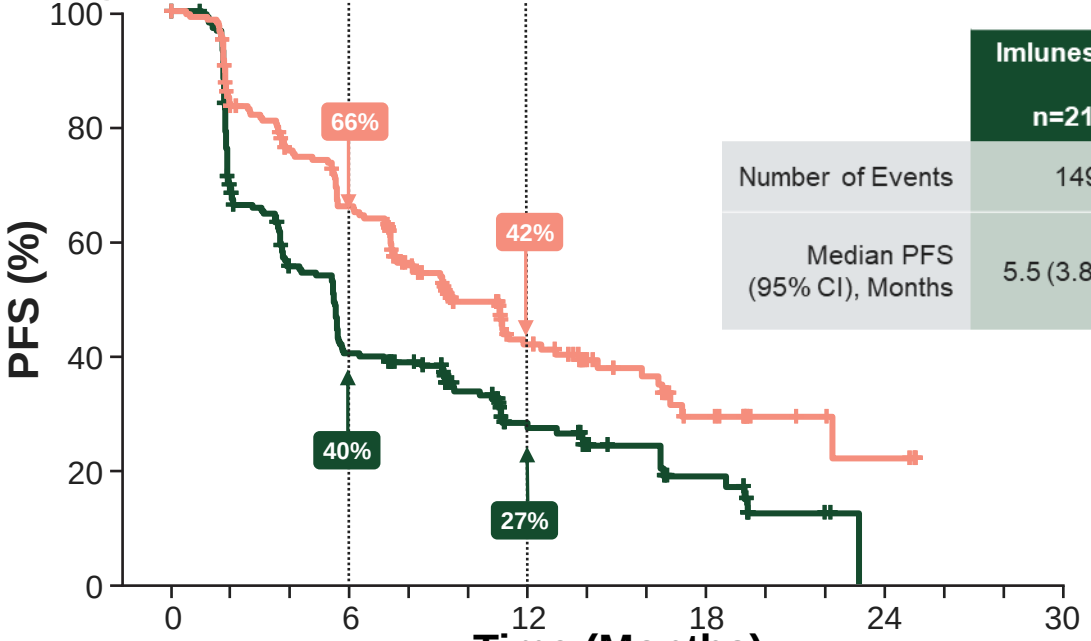
PFS difference of imlunestrant vs SOC ET in all patients did not reach significance

- The majority subgroup of patients without *ESR1*m showed no difference in PFS (HR=1.00; 95% CI, 0.79-1.27)[b]

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; PFS, progression-free survival; SOC ET, standard of care endocrine therapy. The median follow-up was 16.6 months in the imlunestrant arm and 16.8 months in the SOC ET arm.
[a] At full alpha; [b] Data available in supplementary slide 24.

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Primary Endpoint: Imlunestrant + Abemaciclib vs Imlunestrant Investigator-assessed PFS in All Patients



	Imlunestrant n=213[a]	Imlunestrant + Abemaciclib n=213
Number of Events	149	114
Median PFS (95% CI), Months	5.5 (3.8-5.6)	9.4 (7.5-11.9)

HR, 0.57
(95% CI, 0.44-0.73)
p<0.001

Number at Risk

Imlunestrant	213	140	106	77	67	48	29	20	18	10	3	2	0	0	0	0
Imlunestrant + Abemaciclib	213	165	141	122	96	72	48	29	25	13	6	5	3	0	0	0

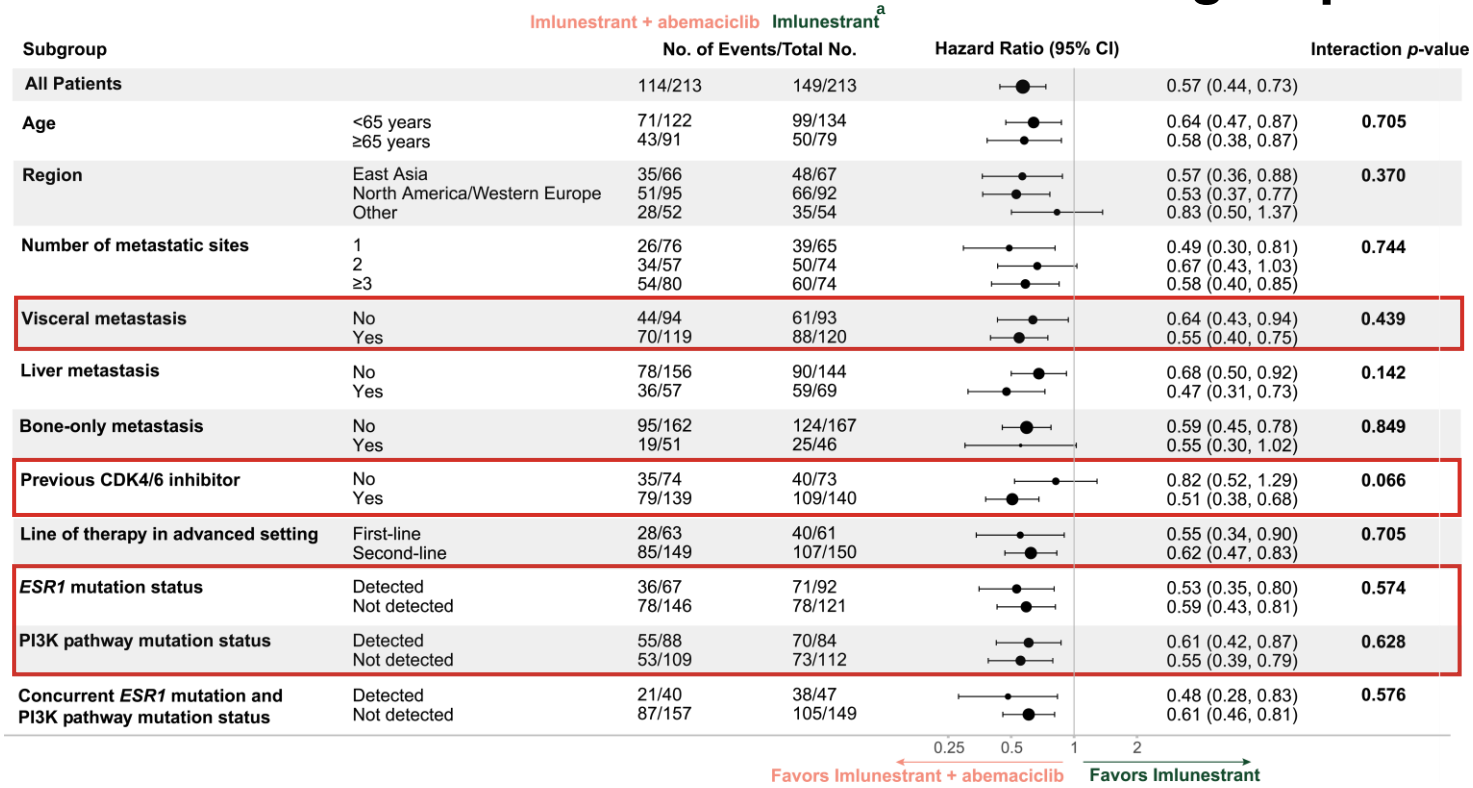
Imlunestrant + abemaciclib led to a 43% reduction in the risk of progression or death over imlunestrant alone in all patients

CI, confidence interval; HR, hazard ratio. [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm.
The median follow-up was 13.5 months in the imlunestrant + abemaciclib arm and 13.7 months in the imlunestrant arm.

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Investigator-assessed PFS by Subgroup: Consistent Imlunestrant + Abemaciclib Benefit Across Subgroups



CI, confidence interval. First-line: most recent ET was adjuvant; Second-line: most recent ET was ABC. The total number of patients may not add up due to missing data in certain subgroups. Patients without *ESR1*m include 8 with unknown *ESR1*m status (imlunestrant + abemaciclib, n=1; Imlunestrant, n=7).

[a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm.

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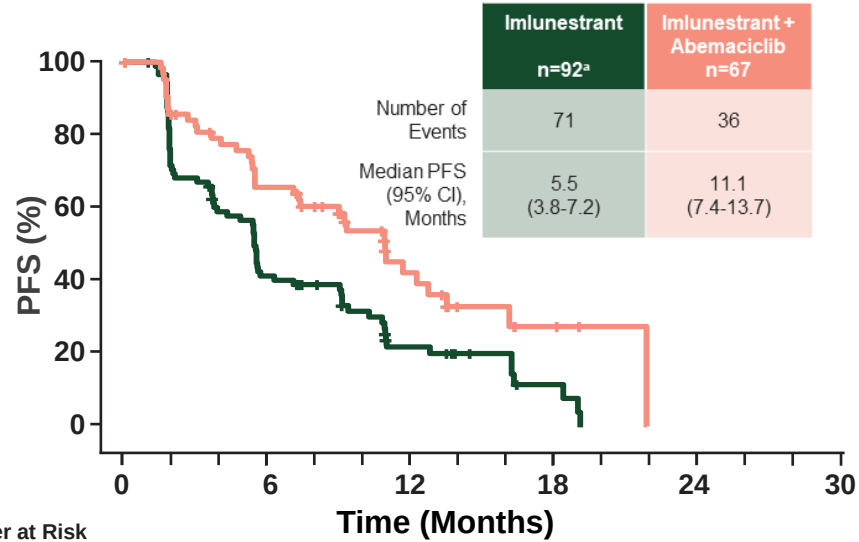
Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Subgroup Analysis: Imlunestrant + Abemaciclib vs Imlunestrant Investigator-assessed PFS by *ESR1m* status

Patients with *ESR1*m

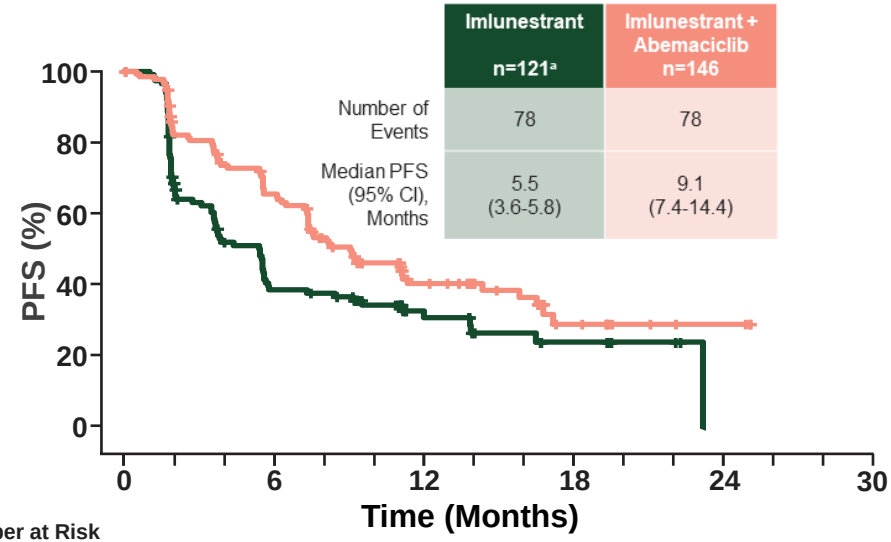


Number at Risk

Imlunestrant	92	62	50	35	28	20	12	9	7	3	0	0	0	0	0	0
Imlunestrant + Abemaciclib	67	54	47	39	33	22	14	7	6	3	1	1	0	0	0	0

HR, 0.53 (95% CI, 0.35-0.80)

Patients without *ESR1*m



Number at Risk

Imlunestrant	121	78	56	42	39	28	17	11	11	7	3	2	0	0	0	0
Imlunestrant + Abemaciclib	146	111	94	83	63	50	34	22	19	10	5	4	3	0	0	0

HR, 0.59 (95% CI, 0.43-0.81)

Consistent benefit of imlunestrant + abemaciclib regardless of *ESR1*m status

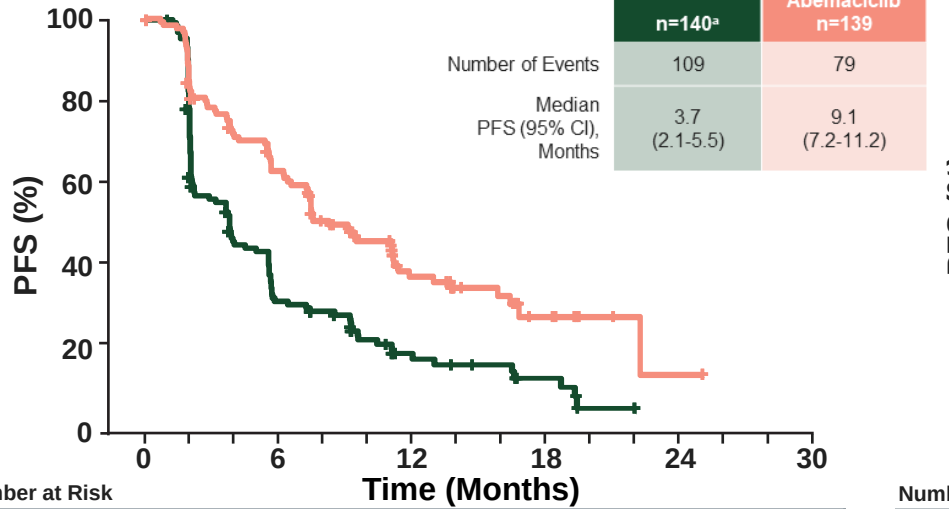
CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; PFS, progression-free survival. [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm. Patients without *ESR1*m include 8 with unknown *ESR1*m status (imlunestrant + abemaciclib, n=1; Imlunestrant, n=7).

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Subgroup Analysis: Imlunestrant + Abemaciclib vs Imlunestrant Investigator-assessed PFS in Key Clinical Subgroups

Patients with prior CDK4/6i treatment



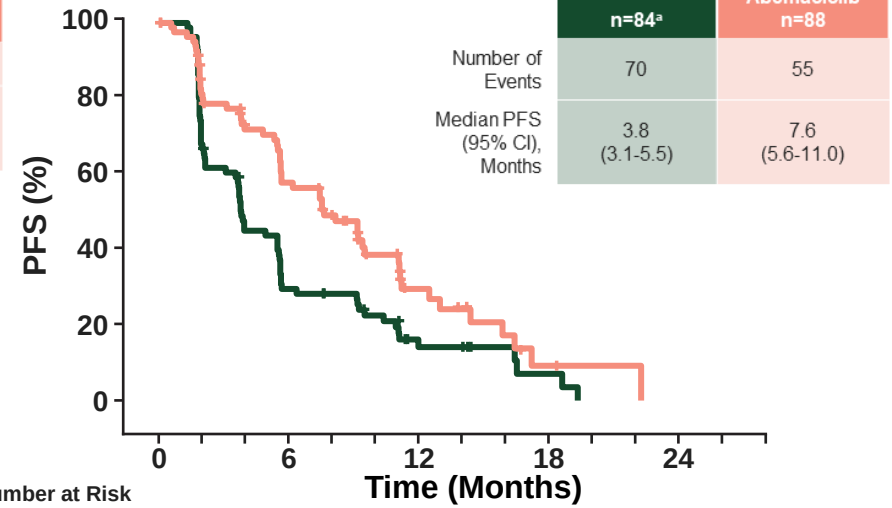
	Imlunestrant n=140[a]	Imlunestrant + Abemaciclib n=139
Number of Events	109	79
Median PFS (95% CI), Months	3.7 (2.1-5.5)	9.1 (7.2-11.2)

Number at Risk

Imlunestrant	140	79	56	39	32	21	13	11	10	6	1	0	0	0	0	0
Imlunestrant + Abemaciclib	139	105	87	76	58	43	29	19	17	8	3	2	1	0	0	0

HR, 0.51 (95% CI, 0.38-0.68)

Patients with PI3K pathway mutation[b]



	Imlunestrant n=84[a]	Imlunestrant + Abemaciclib n=88
Number of Events	70	55
Median PFS (95% CI), Months	3.8 (3.1-5.5)	7.6 (5.6-11.0)

Number at Risk

Imlunestrant	84	53	35	23	20	15	7	5	4	2	0	0	0	0	0
Imlunestrant + Abemaciclib	88	62	51	41	32	19	11	8	5	2	1	1	0	0	0

HR, 0.61 (95% CI, 0.42-0.87)

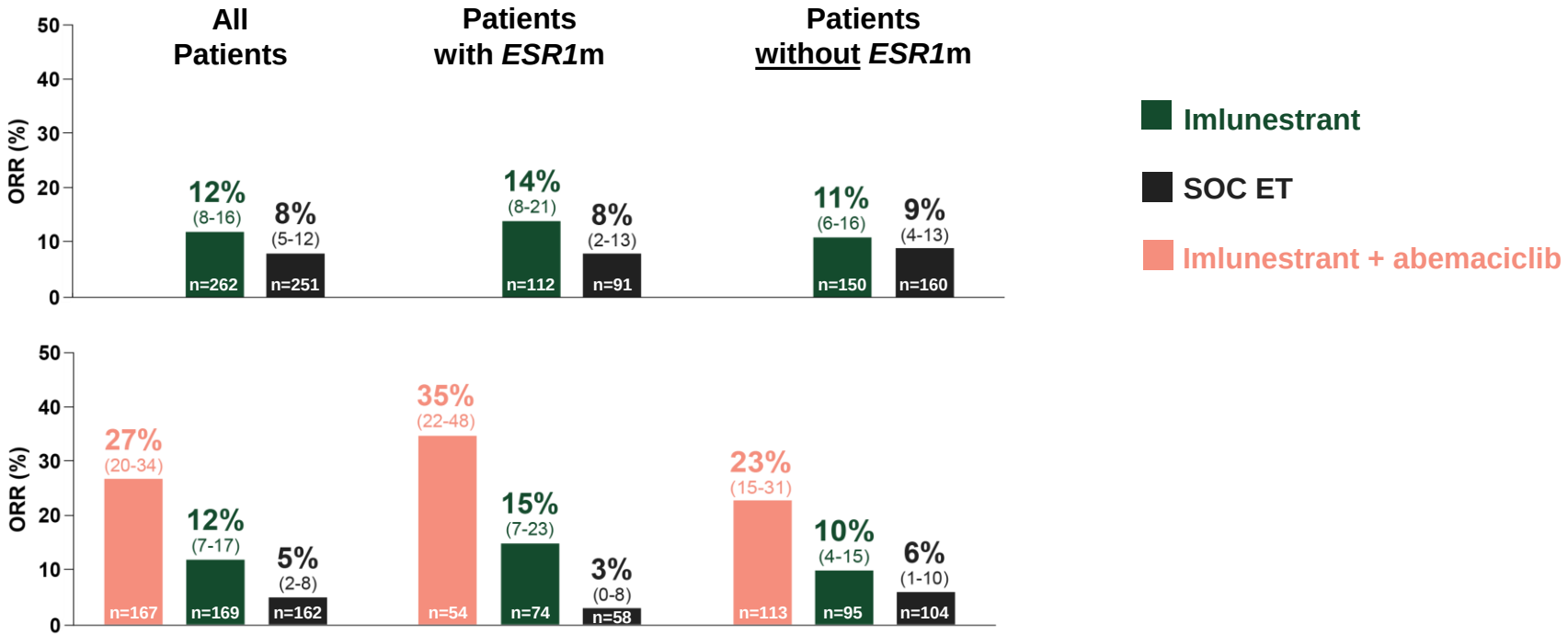
Consistent benefit of imlunestrant + abemaciclib across key clinical subgroups

CDK4/6i, CDK4/6 inhibitor; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival. [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm. [b]Includes single nucleotide variants and insertions/deletions of *PIK3CA, AKT1* or *PTEN* analyzed by Guardant 360 ctDNA assay.

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Secondary Endpoint: Investigator-assessed ORR in Patients with Measurable Disease

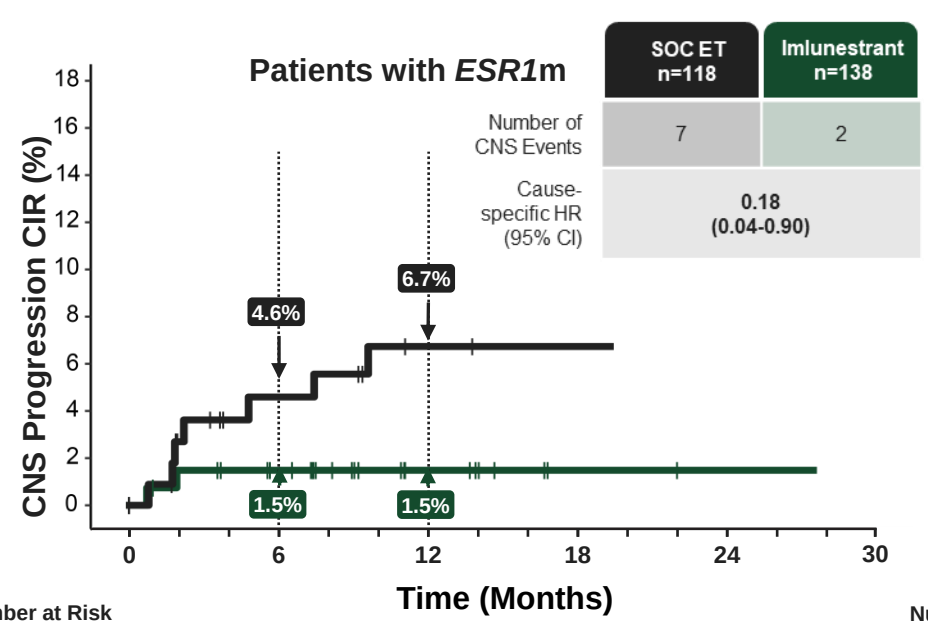


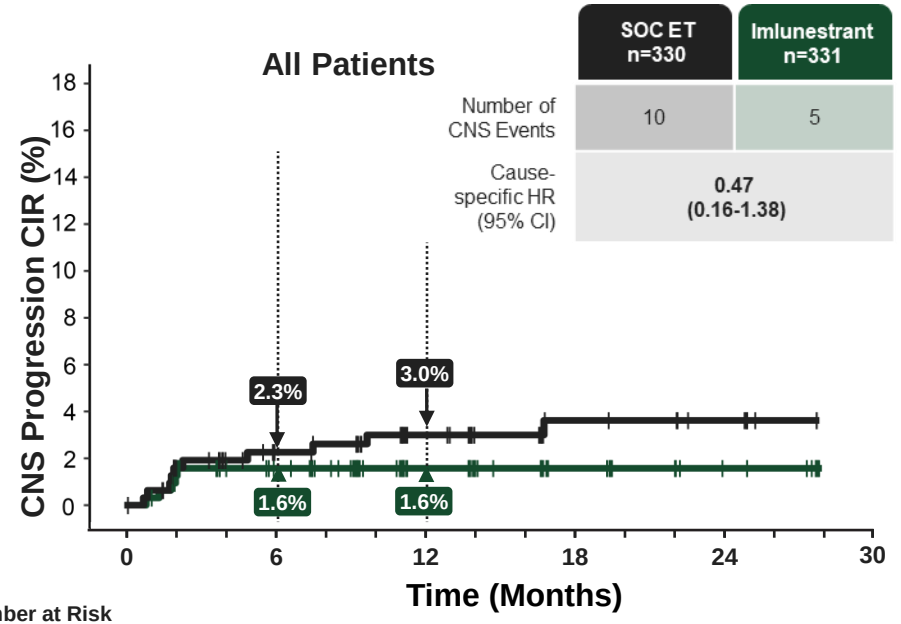
*ESR1*m, *ESR1* mutation; ORR, objective response rate; SOC ET, standard of care endocrine therapy. Patients without *ESR*1m include those with unknown *ESR1*m status (top bars: imlunestrant, n=13; SOC ET, n=7; bottom bars: imlunestrant + abemaciclib, n=1; Imlunestrant, n=7; SOC ET, n=4). Bottom bars: analyses confined to the imlunestrant/SOC ET population concurrently randomized. The values indicated in parentheses represent the 95% confidence intervals.

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Posthoc Exploratory Analysis: Imlunestrant vs SOC ET
Cumulative Incidence Rates of CNS Progression





Number at Risk

SOC ET	0	3	4	5	6	7	7	7	7	7	7	7	7	7	7	7
Imlunestrant	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Number at Risk

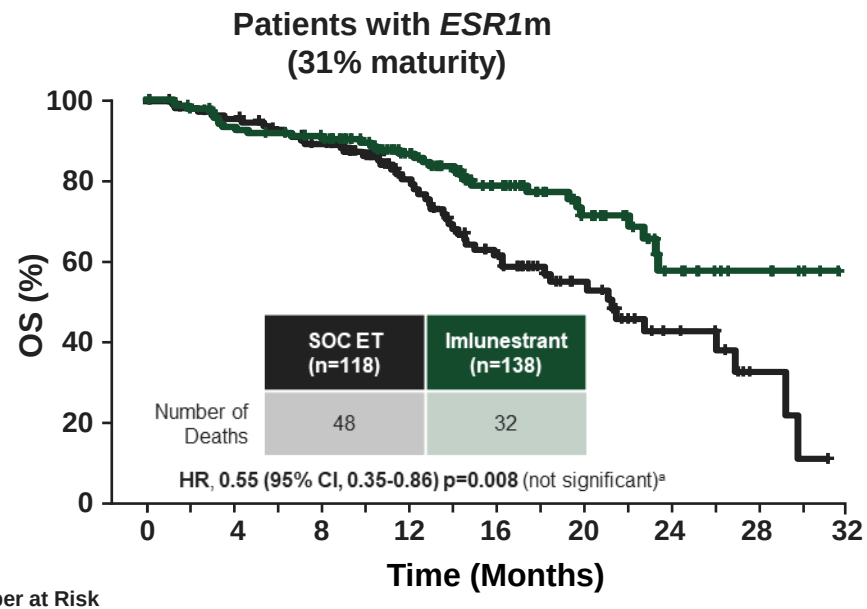
SOC ET	0	5	6	7	8	9	9	9	9	10	10	10	10	10	10	10
Imlunestrant	0	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5

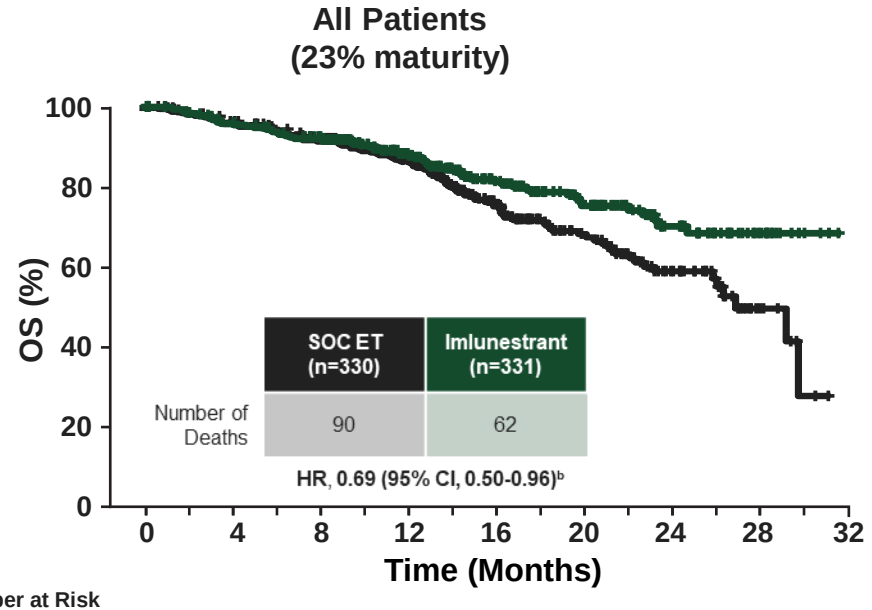
Trend towards lower rates of CNS progression with imlunestrant
HR estimate should be interpreted with caution given the low event rate

*ESR1*m, *ESR1* mutation; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; SOC ET, standard of care endocrine therapy. Baseline CNS imaging was required in all patients, serial CNS imaging was required only in patients with CNS metastases at baseline, otherwise performed as clinically indicated.
11 of 15 events were due to new lesions (imlunestrant, n=3; SOC ET, n=8); and 4 of 15 events were due to progressing existing lesions (imlunestrant, n=2; SOC ET, n=2).

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Interim Overall Survival





Number at Risk

SOC ET	118	112	108	102	96	82	66	54	44	32	25	16	12	8	3	1	0
Imlunestrant	138	132	124	121	116	100	85	74	57	45	34	24	13	8	6	2	0

Number at Risk

SOC ET	330	316	305	293	276	241	202	168	134	102	85	62	47	27	8	2	0
Imlunestrant	331	318	300	289	275	237	200	166	135	107	85	64	45	28	17	3	0

- In patients <u>without</u> *ESR1*m: maturity 18% (HR=0.87; 95% CI, 0.54-1.40)[c]
- In all patients within the combination therapy comparison: maturity 15% (HR=1.34; 95% CI, 0.81-2.21)[c]

*ESR1*m, *ESR1* mutation; CI, confidence interval; HR, hazard ratio; OS, overall survival. Maturity is defined as the total number of events divided by the total number of patients. [a] Did not meet prespecified boundary for statistical significance; [b] Statistical significance was not inferentially tested due to not meeting the PFS endpoint; [c] Prespecified subgroup analysis, not inferentially tested, data available in the online supplementary slides.

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Safety and Tolerability

TEAEs in ≥ 10% of Patients, %	Imlunestrant n=327		SOC ET n=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	83	17	84	21
Fatigue[a]	23	<1	13	1
Diarrhea	21	<1	12	0
Nausea	17	<1	13	0
Arthralgia	14	1	14	<1
AST increased	13	1	13	1
Back pain	11	1	7	<1
ALT increased	10	<1	10	1
Anemia[a]	10	2	13	3
Constipation	10	0	6	<1

Patients with ≥ 1 SAE, %		10	12
Dose reductions due to AE, %		2	0
Discontinuations due to AE, %		4	1
Deaths due to AE on study, %		2	1
Injection Site Reaction[a]	TEAE, n/N (%)[b]	NA	27/292 (9%)
	PRO-CTCAE, n/N (%)[c]	NA	201/278 (72%)

Generally favorable safety profile

TEAEs in ≥ 20% of Patients, %	Imlunestrant + abemaciclib n=208	
	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	98	49
Diarrhea	86	8
Nausea	49	2
Neutropenia[a]	48	20
Anemia[a]	44	8
Fatigue[a]	39	5
Vomiting	31	1
Leukopenia[a]	26	4
Hypercreatinemia[a]	22	1
Abdominal pain[a]	20	2
Decreased appetite	20	1

Patients with ≥ 1 SAE, %	17
Dose reductions due to AE, %[d]	39
Discontinuations due to AE, %	6
Deaths due to AE on study, %	1

Safety consistent with the known abemaciclib profile

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; PRO-CTAE, Patient Reported Outcomes-Common Terminology Criteria for AEs; SAE, serious AEs; TEAE, treatment-emergent AE. [a] Consolidated term; [b] N is the number of evaluable patients who received fulvestrant; [c] N is the number of evaluable patients who completed the PRO-CTCAE survey (answered "yes" or "no" to injection site pain, swelling, or redness). [d] Dose reduction of imlunestrant alone: 2%; abemaciclib alone: 23%; both drugs: 14%

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

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Conclusions

Imlunestrant monotherapy

- **Significantly improved PFS vs SOC ET in patients with *ESR1*m (HR=0.62; 95% CI, 0.46-0.82)** but did not reach statistical significance in the overall population (HR=0.87; 95% CI, 0.72-1.04)
- Consistent benefit across key subgroups, secondary and exploratory endpoints, and sensitivity analyses
- OS analyses were immature and ongoing
- **Favorable safety** profile; no oral SERD specific safety signals (eg, ocular or cardiac)

Imlunestrant + abemaciclib

- **Significantly improved PFS vs imlunestrant in all patients (HR=0.57; 95% CI, 0.44-0.73), regardless of *ESR1*m status, achieving a 9.4-month PFS (95% CI, 7.5-11.9),** with consistent benefit across key subgroups
- **Predictable safety**, comparable to prior studies of fulvestrant + abemaciclib with a **low discontinuation rate (6%)** relative to available combination regimens (13-26%)[1,2]

Imlunestrant, as monotherapy or combined with abemaciclib, provides an all-oral targeted therapy option after progression on ET for patients with ER+, HER2- ABC

1. André F, et al. *Ann Oncol*. 2021;32(2):208-217; 2. Turner NC, et al. *N Engl J Med*. 2023;388(22):2058-2070.

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

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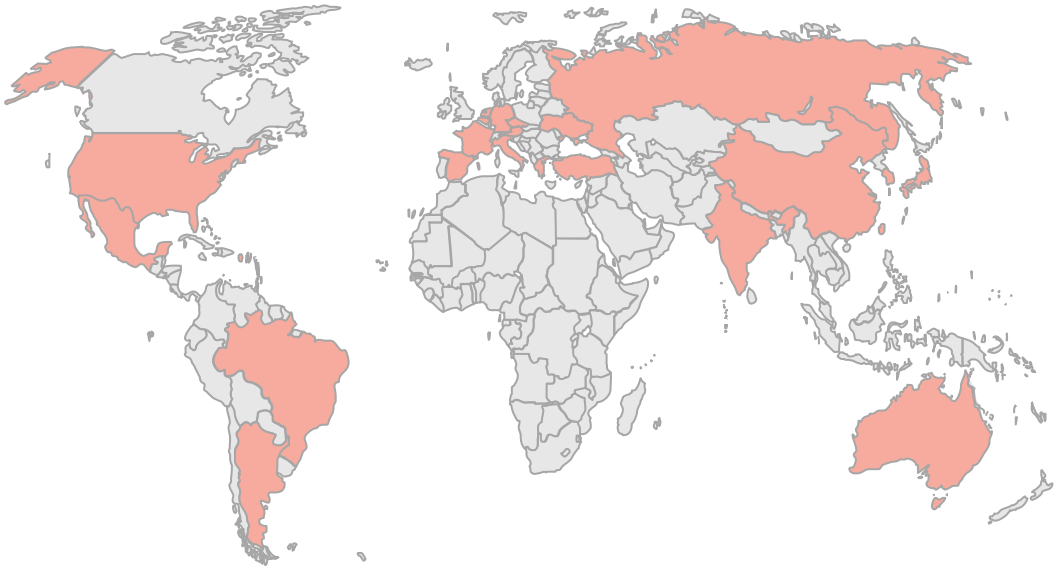
Acknowledgements

We thank the 874 clinical trial participants and their families/caregivers from 195 sites in 22 countries for participating in this trial



- We thank the investigators and their support staff who participated in this work
- We are very grateful for the time and efforts of the EMBER-3 Steering Committee
- This study was sponsored by Eli Lilly and Company

San Antonio Breast Cancer Symposium (SABCS) 47th Annual Meeting; San Antonio, TX; December 10-13, 2024

Supplemental Slides

IMLUNESTRANT, AN ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADER (SERD), AS MONOTHERAPY AND COMBINED WITH ABEMACICLIB, FOR PATIENTS WITH ER+, HER2- ADVANCED BREAST CANCER (ABC), PRETREATED WITH ENDOCRINE THERAPY (ET): RESULTS OF THE PHASE 3 EMBER-3 TRIAL

Demographics and Baseline Characteristics

Characteristic		Imlunestrant		SOC ET		Imlunestrant + abemaciclib
		All n=331	*ESR1*m n=138	All n=330	*ESR1*m n=118	All n=213
Median age, years (range)		61 (28-87)	61 (28-85)	62 (27-89)	60 (33-85)	62 (36-87)
Female, %		99	100	99	100	99
Post-menopausal, %		84	88	86	89	86
Race, %	White	56	58	58	64	52
	Asian	28	25	29	26	34
	Black or African American	3	5	2	3	4
Region, %	East Asia	25	22	26	22	31
	North America/ Western Europe	38	46	39	46	45
	Other	37	33	36	32	24
Progesterone receptor-positive, %		78	79	79	82	74
***ESR1* mutation, %[a]**		42	100	36	100	32
PI3K pathway mutations, %[b]		39	52	39	48	41

Baseline characteristics were also generally well balanced in patients with *ESR1*m

*ESR1*m, *ESR1* mutation; SOC ET, standard of care endocrine therapy. [a] Samples were analyzed by Guardant360 CDx, except for patients from China where samples were analyzed by OncoCompass Plus assay (Burning Rock Biotech); [b] Includes single nucleotide variants and insertions/deletions of *PIK3CA*, *AKT1* or *PTEN* analyzed by Guardant 360 ctDNA assay. This analysis excludes patients from China or with unknown *ESR1*m status.

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Disease Characteristics and Previous Therapies

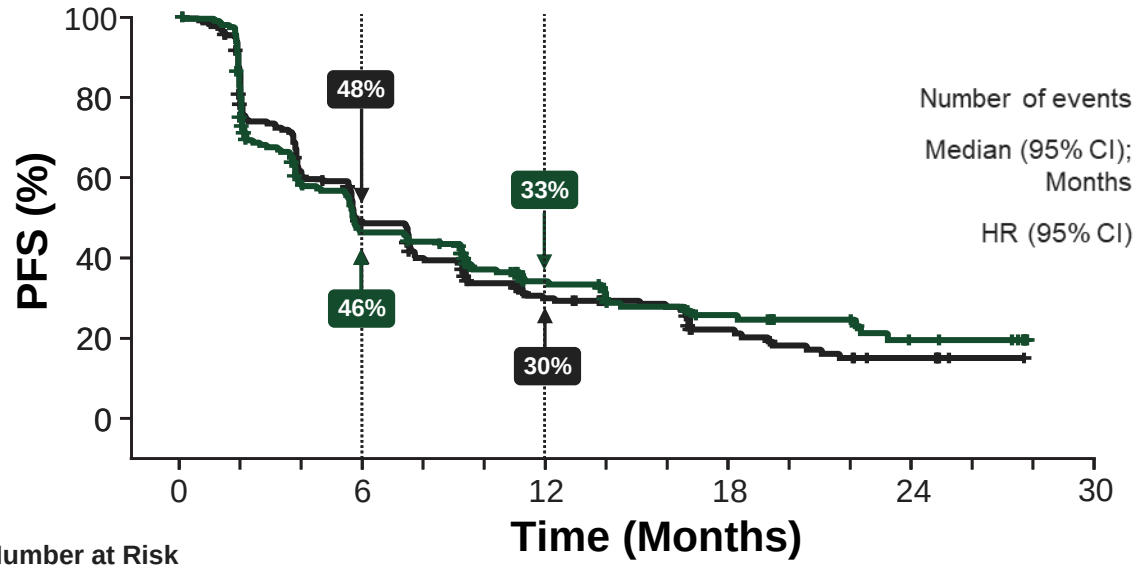
Characteristic		Imlunestrant		SOC ET		Imlunestrant + abemaciclib
		All n=331	*ESR1*m n=138	All n=330	*ESR1*m n=118	All n=213
Site of metastases, %	Visceral	57	61	54	57	56
	Liver	32	41	30	40	27
	Bone-only	22	20	26	25	24
Endocrine resistance, %[a]	Primary	8	0	11	0	8
	Secondary	92	100	89	100	93
Most recent ET, %[b]	Adjuvant	32	21	34	20	30
	ABC	63	73	63	77	68
Previous CDK4/6i, %	Overall	59	67	57	72	65
	Adjuvant	4	2	5	3	3
	ABC	55	65	53	70	62
Previous CDK4/6i therapy, %[c]	Palbociclib	61	69	69	72	65
	Ribociclib	29	24	27	26	27
	Abemaciclib	10	8	4	2	7

Baseline characteristics were also generally well balanced in patients with *ESR1*m

CDK4/6i, CDK4/6 inhibitor; *ESR1*m, *ESR1* mutation; SOC ET, standard of care endocrine therapy. [a] Per ESO-ESMO International Consensus Guidelines for ABC (ABC 6 and 7); [b]Adjuvant ET = First-line; ABC = Second-line; [c] Percentages calculated based on the numbers of patients who received prior CDK4/6i therapy (imlunestrant, n=195; SOC ET, n=189; imlunestrant + abemaciclib, n=139).

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Exploratory Analysis: Investigator-assessed PFS Imlunestrant vs SOC ET in Patients <u>without</u> *ESR1*m



	SOC ET n=212	Imlunestrant n=193
Number of events	151	128
Median (95% CI); Months	5.7 (5.5-7.4)	5.6 (4.4-9.1)
HR (95% CI)	1.00 (0.79-1.27)	

Number at Risk

SOC ET	212	147	114	89	70	56	46	38	36	22	17	14	10	2	0	0
Imlunestrant	193	130	99	79	73	54	40	29	28	22	16	15	10	8	0	0

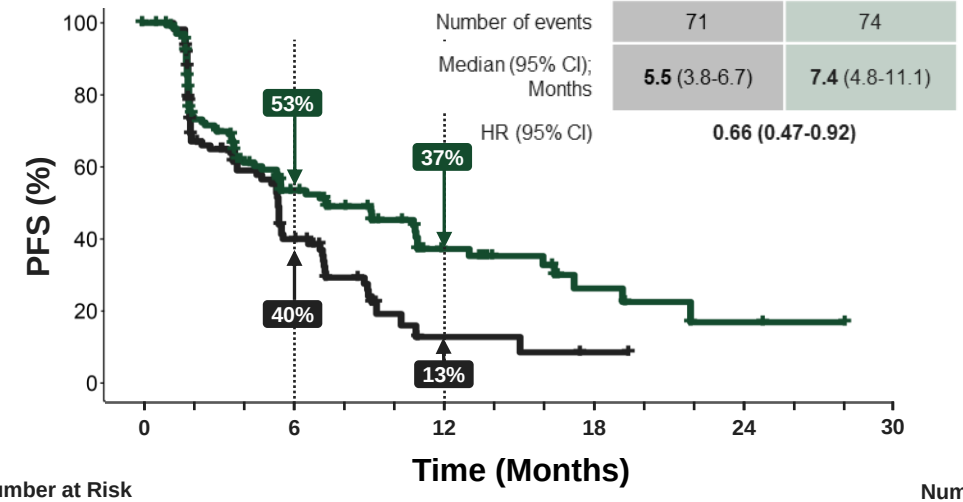
No difference in PFS observed between imlunestrant and SOC ET in patients <u>without</u> *ESR1*m

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; PFS, progression-free survival; SOC ET, standard of care endocrine therapy. Patients without *ESR1*m include 20 patients with unknown *ESR1*m status (Imlunestrant, n=13; SOC ET, n=7)

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Secondary Endpoint: Imlunestrant vs SOC ET
BICR-assessed PFS

Patients with *ESR1*m

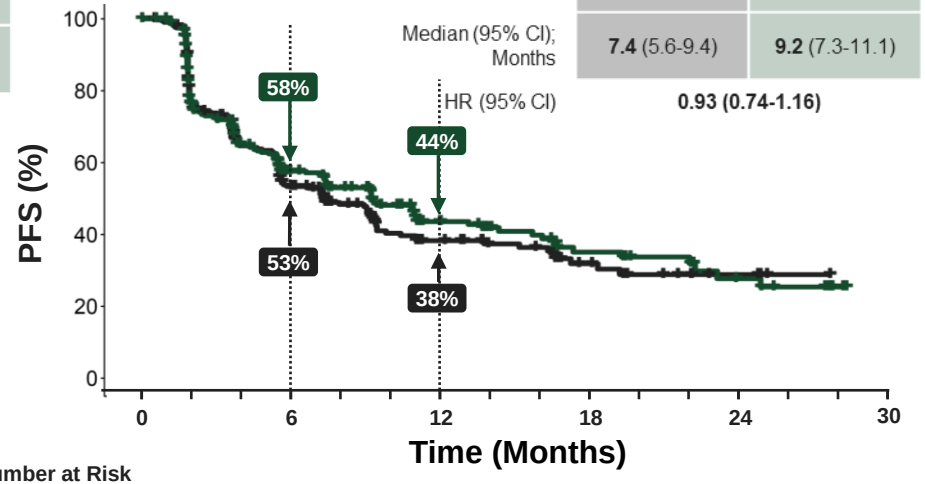


	SOC ET n=118	Imlunestrant n=138
Number of events	71	74
Median (95% CI); Months	**5.5** (3.8-6.7)	**7.4** (4.8-11.1)
HR (95% CI)	**0.66 (0.47-0.92)**	

Number at Risk

SOC ET	118	66	47	30	18	6	3	3	2	1	0	0	0	0	0	0
Imlunestrant	138	91	67	50	41	30	20	15	14	7	4	4	2	1	1	0

All Patients



	SOC ET n=330	Imlunestrant n=331
Number of events	159	160
Median (95% CI); Months	**7.4** (5.6-9.4)	**9.2** (7.3-11.1)
HR (95% CI)	**0.93 (0.74-1.16)**	

Number at Risk

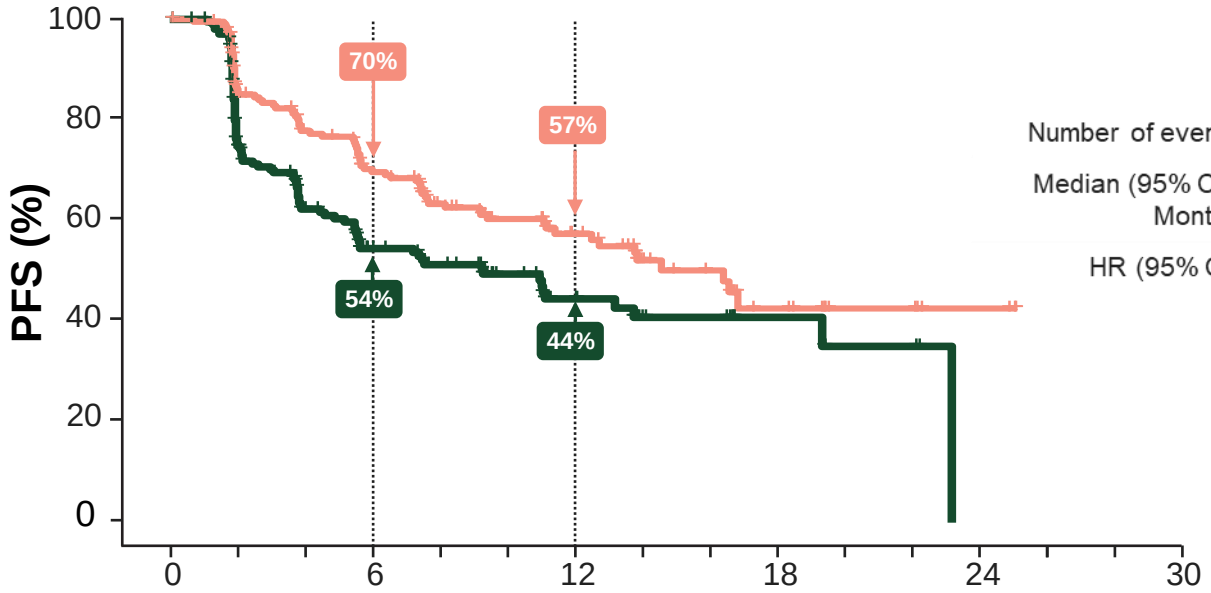
SOC ET	330	209	151	115	89	59	48	38	36	22	16	14	10	2	0	0
Imlunestrant	331	219	166	129	108	78	54	41	38	26	19	19	12	8	2	0

PFS by BICR is consistent with investigator assessment

BICR, blinded independent central review; CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Secondary Endpoint: Imlunestrant + Abemaciclib vs Imlunestrant BICR-assessed PFS in All Patients



	Imlunestrant n=213[a]	Imlunestrant + abemaciclib n=213
Number of events	97	81
Median (95% CI); Months	9.2 (5.5-13.7)	14.5 (11.4-NR)
HR (95% CI)	0.62 (0.45-0.84)	

Number at Risk

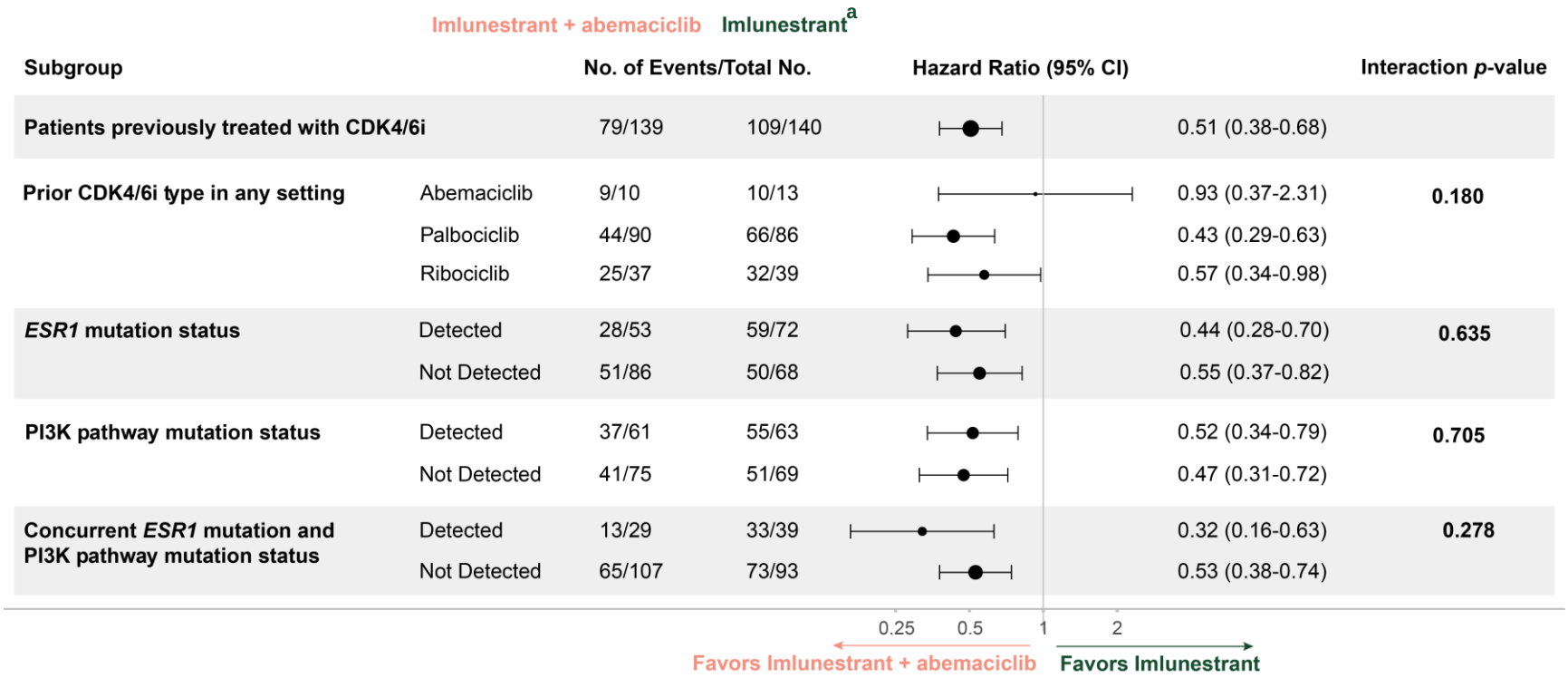
Imlunestrant	213	136	97	72	59	42	25	15	14	7	3	3	0	0	0	0
Imlunestrant + Abemaciclib	213	157	135	115	90	71	48	27	23	12	6	6	3	0	0	0

BICR results were consistent with investigator assessment

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NR, not reached. [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Investigator-assessed PFS by Subgroup in Patients Previously treated with CDK4/6 inhibitor: Consistent Benefit of Imlunestrant + Abemaciclib

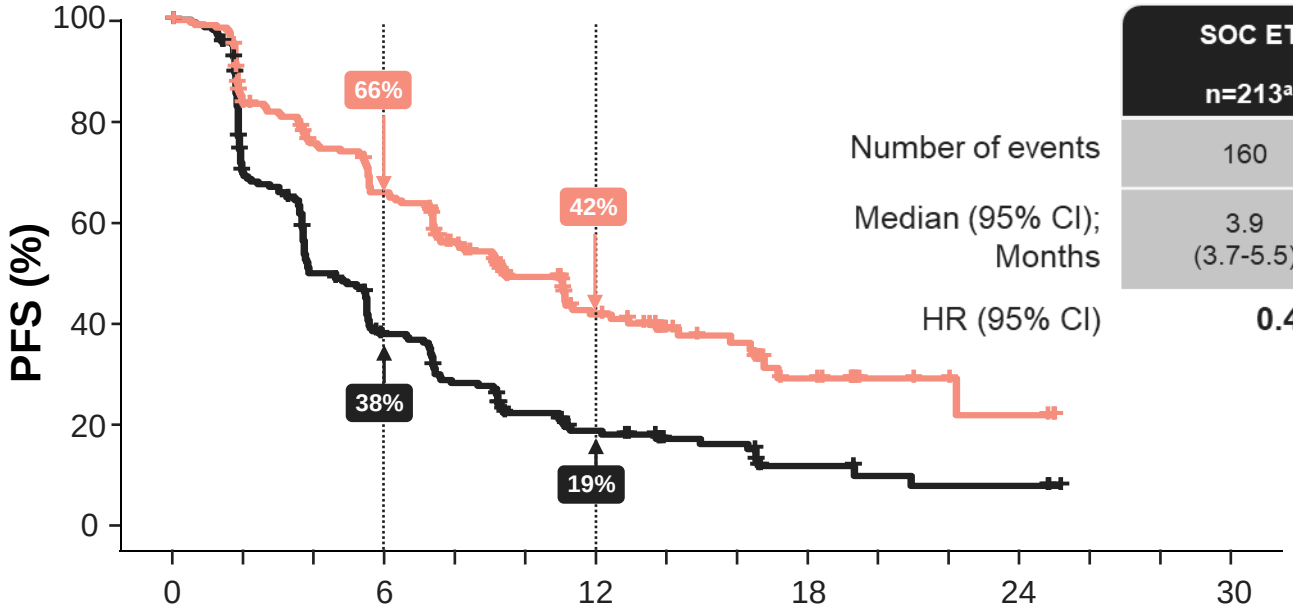


Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

CI, confidence interval; [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Exploratory Endpoint: Imlunestrant + Abemaciclib vs SOC ET Investigator-assessed PFS in All Patients



	SOC ET n=213[a]	Imlunestrant + abemaciclib n=213
Number of events	160	114
Median (95% CI); Months	3.9 (3.7-5.5)	9.4 (7.5-11.9)
HR (95% CI)	**0.46 (0.36-0.60)**	

Number at Risk

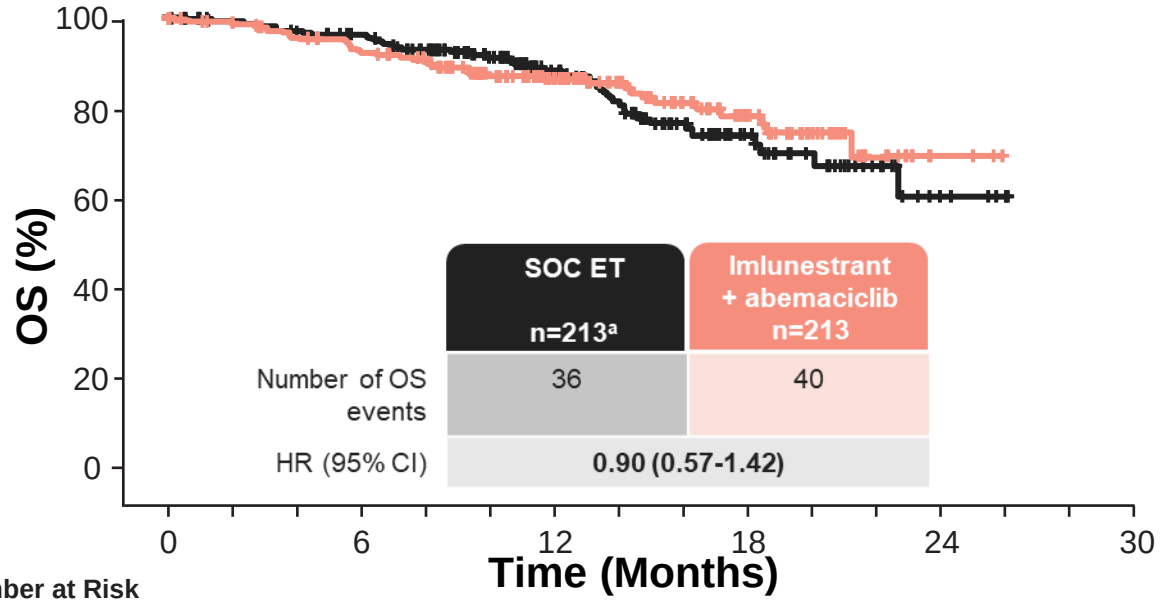
SOC ET	213	133	93	67	49	34	25	17	16	7	5	4	4	0	0	0
Imlunestrant + Abemaciclib	213	165	141	122	96	72	48	29	25	13	6	5	3	0	0	0

Imlunestrant + abemaciclib led to a 54% reduction in the risk of progression or death in all patients

CI, confidence interval; HR, hazard ratio; SOC ET, standard of care endocrine therapy. [a] Efficacy analyses confined to the SOC population concurrently randomized to imlunestrant + abemaciclib treatment arm

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Secondary Endpoint: Imlunestrant + Abemaciclib vs SOC ET OS in All Patients



Number at Risk

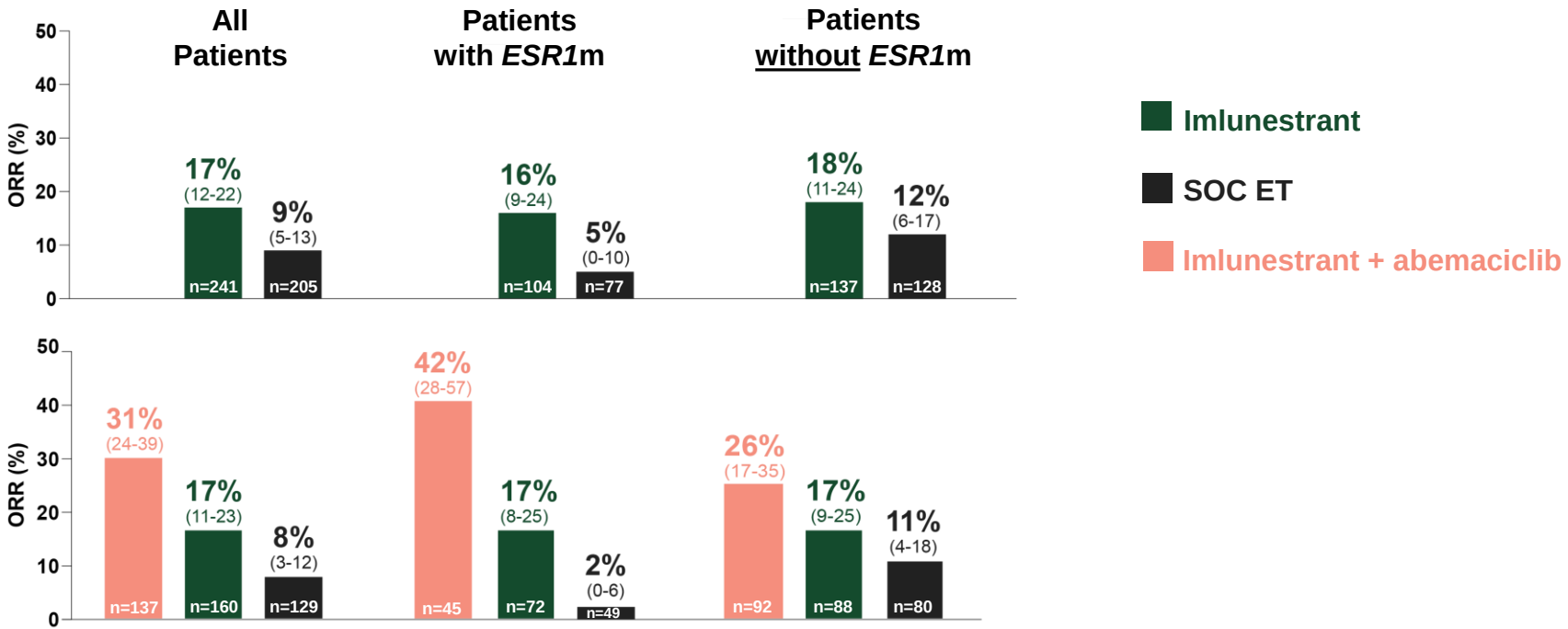
SOC ET	213	203	197	190	175	148	115	88	61	38	26	14	6	2	0	0
Imlunestrant + Abemaciclib	213	206	195	187	176	140	117	88	64	46	25	11	3	0	0	0

Maturity: 18% in concurrently enrolled patients

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio. Maturity is defined as the total number of events divided by the total number of patients.
[a] Efficacy analyses confined to the SOC population concurrently randomized to imlunestrant + abemaciclib treatment arm

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Secondary Endpoint: BICR-assessed ORR In Patients with Measurable Disease

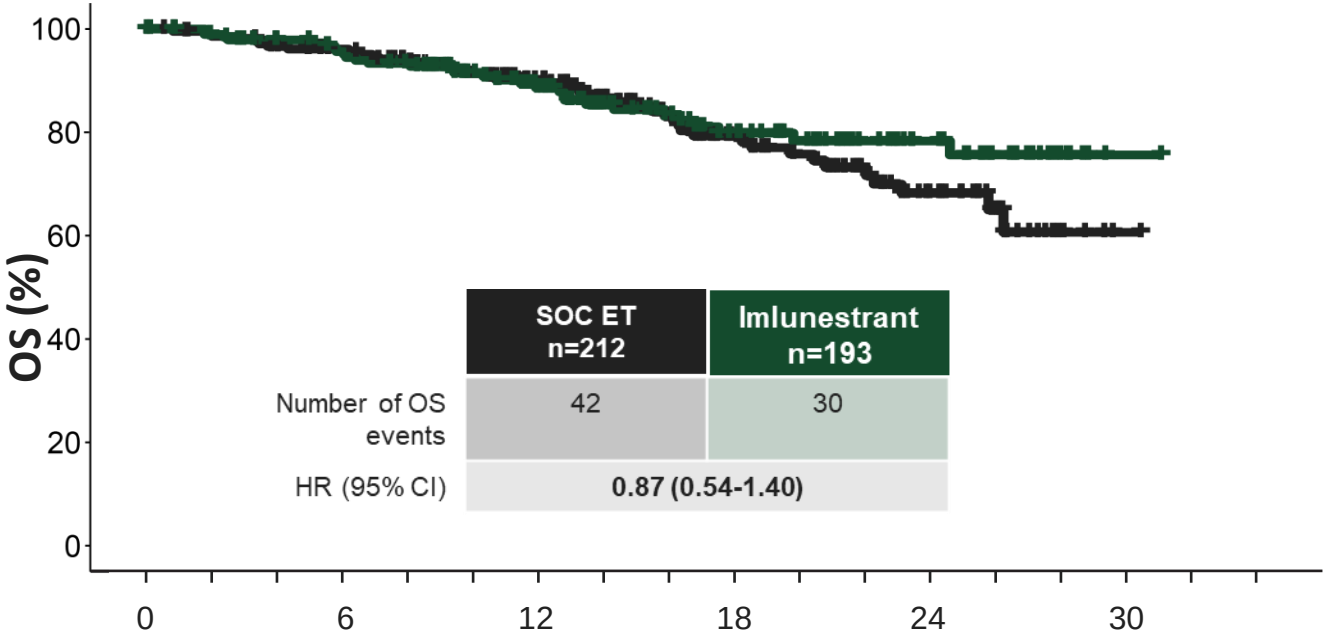


BICR, blinded independent central review; *ESR1*m, *ESR1* mutation; ORR, objective response rate; SOC ET, standard of care endocrine therapy. Patients without *ESR1*m include those with unknown *ESR1*m status (top bars: imlunestrant, n=13; SOC ET, n=7; bottom bars: imlunestrant + abemaciclib, n=1; Imlunestrant, n=7; SOC ET, n=4). Bottom bars: analyses confined to the imlunestrant/SOC ET population concurrently randomized. The values indicated in parentheses represent the 95% confidence intervals.

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Exploratory Analysis: Imlunestrant vs SOC ET
Interim Overall Survival in Patients <u>without</u> *ESR1*m



Number at Risk

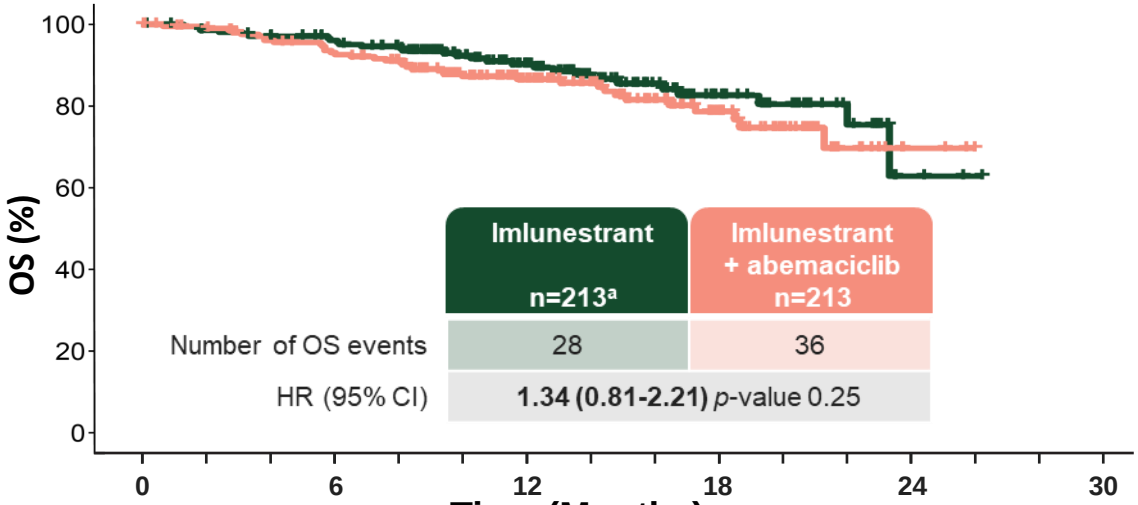
SOC ET	212	204	197	191	180	159	136	114	90	70	60	46	35	19	5	1	0	0
Imlunestrant	193	186	176	168	159	137	115	92	78	62	51	40	32	20	11	1	0	0

Maturity: 18% in patients <u>without</u> *ESR1*m

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio. Maturity is defined as the total number of events divided by the total number of patients. Patients without *ESR1*m include 20 patients with unknown *ESR1*m status (Imlunestrant, n=13; SOC ET, n=7).

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Secondary Endpoint: Imlunestrant + Abemaciclib vs Imlunestrant OS in All Patients



Number at Risk																
Imlunestrant	213	205	197	190	180	144	113	87	65	43	30	15	3	1	0	0
Imlunestrant + Abemaciclib	213	206	195	187	176	140	117	88	64	46	25	11	3	0	0	0

Maturity: 15% in concurrently enrolled patients

CI, confidence interval; HR, hazard ratio. Maturity is defined as the total number of events divided by the total number of patients. [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm.

Jhaveri, et al.; SABCS 2024

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Safety and Tolerability

TEAEs in ≥ 20% of patients, %	Imlunestrant + abemaciclib n=208		Imlunestrant n=327		MONARCH 2[1] Abemaciclib + fulvestrant n=441	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade 3
Patients with ≥ 1 TEAE	98	49	83	17	99	55
Diarrhea	86	8	21	<1	86	13
Nausea	49	2	17	<1	45	3
Neutropenia[a]	48	20	5	2	46	24
Anemia[a]	44	8	10	2	29	7
Fatigue[a]	39	5	23	<1	40	3
Vomiting	31	1	9	1	26	1
Leukopenia[a]	26	4	5	1	28	9
Hypercreatinemia[a]	22	1	3	<1	12	1
Abdominal pain[a]	20	2	9	<1	35	3
Decreased appetite	20	1	8	<1	27	1

Patients with ≥ 1 SAE, %[b]	17	10	22
Dose reductions due to AE, %	39[c]	2	43
Discontinuations due to AE, %	6	4	16
Deaths due to AE on study, %	1	2	2

Safety was consistent with known imlunestrant and abemaciclib profiles & compared favorably to fulvestrant + abemaciclib from MONARCH 2

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event. [a] Consolidated term; [b] SAE occurring on study and within 30 days of study treatment discontinuation; [c] Dose reductions: imlunestrant alone, 2%; abemaciclib alone, 23%; imlunestrant + abemaciclib, 14%. 1. Sledge GW Jr, et al. *J Clin Oncol*. 2017;35(25):2875-2884.

Data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858