EMBER-3: Study of Imlunestrant Alone or in Combination With Abemaciclib for Patients With ER+, HER2- ABC Following Progression on Previous ET

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Background

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

R 1:1:1[b] N=874

- **Imlunestrant 400 mg QD** — A
- **SOC ET[d,e]** Fulvestrant or Exemestane — B
- **Imlunestrant 400 mg QD + abemaciclib[e]** — C[b]

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 patients[h]

Key Secondary Endpoints

- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

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

Enrolled October 2021 to November 2023 across 243 sites in 22 countries.
[a]GnRH agonist required in men and premenopausal women. [b]Enrollment to Arm C started with amendment A (at which point 122 patients had been randomized across Arms A and B). [c]East Asia vs North America/EU vs Others. [d]Investigators' choice. [e]Labelled 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 Guardant 360® cfDNA assay and Burning Rock Biotech OncoCompass™ plus assay for patients from China (n=40). [h]Analysis conducted in all concurrently randomized patients.

- Demographics and baseline characteristics were well balanced at study entry
- Overall, ~37% of patients harbored an *ESR1*m and ~60% had previously received a CDK4/6i

Conclusions

- **Imlunestrant led to a statistically significant improvement in PFS vs SOC ET in patients with *ESR1*m (HR=0.62, 95% CI=0.46-0.82), but not in all patients with ER+, HER2- ABC (HR=0.87, 95% CI=0.72-1.04)**
- **Imlunestrant + abemaciclib demonstrated a statistically significant improvement in PFS vs imlunestrant alone in all patients (HR=0.57, 95% CI=0.44-0.73), regardless of *ESR1*m status**
- **Treatment effect of imlunestrant monotherapy in the *ESR1*m population and imlunestrant plus abemaciclib in the overall population across key subgroups and the secondary endpoints of ORR and PFS by BICR (not shown) supported the primary outcomes**
- **The safety profile associated with imlunestrant monotherapy was favorable with a low discontinuation rate and similar to that of SOC ET; the safety profile of imlunestrant in combination with abemaciclib was comparable to that of fulvestrant plus abemaciclib**

Reference: SABCS 2024 Presentation. Komal L. Jhaveri, et al. Abstract GS1-01: 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, and includes data from Jhaveri et al. NEJM. 2024; 10.1056/NEJMoa2410858

Abbreviations: 1L=first line; ABC=advanced breast cancer; AE=adverse event; AI=aromatase inhibitor; BICR=blinded independent central review; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CI=confidence interval; ctDNA=circulating tumor DNA; ER=estrogen receptor; ET=endocrine therapy; EU=European Union; GnRH=gonadotropin-releasing hormone; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; m=mutation; N/A=not applicable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QD=once daily; R=randomized; SOC=standard of care; TEAE=treatment-emergent adverse event.

ClinicalTrials.gov identifier: NCT04975308

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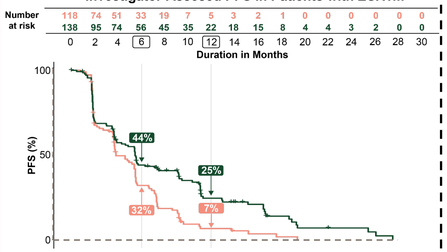
Results: Primary Endpoints

Imlunestrant vs SOC ET

Investigator-Assessed PFS in Patients with *ESR1m*

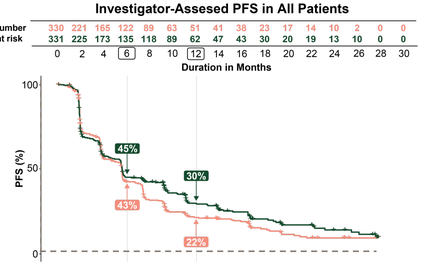


	Imlunestrant n=138	SOC ET n=118
Events, n	109	102
Median (95% CI); months	5.5 (3.9-7.4)	3.8 (3.7-5.5)
HR (95% CI); p value	0.62 (0.46-0.82) p<.001	

- Statistical significance was met
- Imlunestrant led to a **38%** reduction in the risk of progression or death

Imlunestrant vs SOC ET

Investigator-Assessed PFS in All Patients

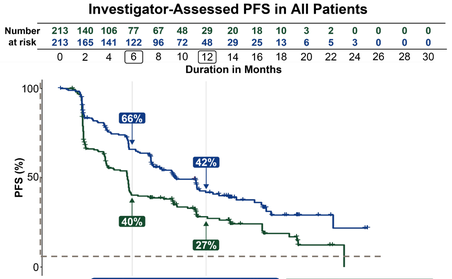


	Imlunestrant n=331	SOC ET n=330
Events, n	237	253
Median (95% CI); months	5.6 (5.3-7.3)	5.5 (4.6-5.6)
HR (95% CI); p value	0.87 (0.72-1.04) P=.12	

- Statistical significance was not reached in all patients
- The majority subgroup of patients without *ESR1*m showed no difference in PFS

Imlunestrant vs Imlunestrant-Abemaciclib

Investigator-Assessed PFS in All Patients



	Imlunestrant + Abemaciclib n=213	Imlunestrant n=213[a]
Events, n	114	149
Median (95% CI); months	9.4 (7.5-11.9)	5.5 (3.8-5.6)
HR (95% CI); p value	0.57 (0.44-0.73) p<.001	

- Statistical significance was met
- Imlunestrant + abemaciclib led to a **43%** reduction in the risk of progression or death

[a]Efficacy analyses confined to the imlunestrant population (n=213) concurrently randomized with the imlunestrant + abemaciclib treatment arm.

Safety and Tolerability

Parameters – number (%)	Imlunestrant n=327 Any Grade	Imlunestrant n=327 Grade ≥3	SOC ET n=324 Any Grade	SOC ET n=324 Grade ≥3
Patients with ≥1 TEAE	83	17	84	21
Top 3 Most Frequent TEAEs, %				
Fatigue[a]	23	<1	13	1
Diarrhea	21	<1	12	0
Nausea	17	<1	13	0
Dose reductions due to AE, %	2		0	
Discontinuations due to AE, %	4		1	
Deaths due to AE on study, %	2		1	
Injection Site TEAE, n/N(%)[b]	N/A		27/292 (9%)	
Reaction[a] PRO-CTCAE, n/N (%)[c]	N/A		201/279 (72%)	

Generally favorable safety profile

Parameters – number (%)	Imlunestrant + Abemaciclib n=208 Any Grade	Imlunestrant + Abemaciclib n=208 Grade ≥3
Patients with ≥1 TEAE	98	49
Top 3 Most Frequent TEAEs, %		
Diarrhea	86	8
Nausea	49	2
Neutropenia[a]	48	20
Dose reductions due to AE, %[d]	39	
Discontinuations due to AE, %	6	
Deaths due to AE on study, %	1	

Consistent with the known abemaciclib profile

[a]Consolidated term. [b]N=Evaluable patients received fulvestrant. [c]N=Evaluable patients completed patient-reported outcome survey (yes/no to injection site pain, swelling, or redness). [d]Dose reduction of imlunestrant alone: 2%; abemaciclib alone: 23%; both drugs: 14%.

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

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