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

Study Design:

ER+, HER2- ABC

Men & pre[a]/postmenopausal women
Prior therapy:
- **Adjuvant:** Recurrence on or within 12 months of completing AI ± CDK4/6i
- **ABC:** Progression on 1L AI ± CDK4/6i
- No other therapy for ABC

n=874
R 1:1:1[c]

- **Imlunestrant 400 mg QD**
- **SOC ET[d,e]** Fulvestrant or Exemestane
- **Imlunestrant 400 mg QD + Abemaciclib[b,e]**

Infographic Objective:
Present the primary outcome results of the EMBER-3 trial

Stratification Factors:
- Prior CDK4/6i therapy (yes/no)
- Visceral metastases (yes/no)
- Region[c]

Primary Endpoints
Investigator-Assessed PFS[f]:
- A vs B in patients with *ESR1*m[g]
- A vs B in all patients
- C vs A in all patients[h]

Secondary Endpoints:
- OS, PFS by BICR, and ORR
- CBR, DoR
- Safety

Exploratory Endpoints: PFS and OS
- C vs B in all patients[h]

Enrolled October 2021 to November 2023 across 243 sites in 22 countries.

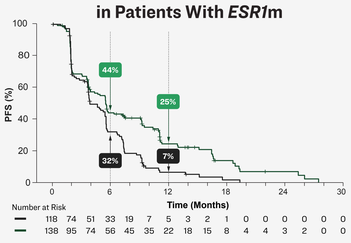
[a]GnRH agonist required in men and premenopausal women. [b]Enrollment to Arm C started with amendment A (at which point 122 patients had been randomized across Arms A and B). [c]East Asia vs North America/Western Europe vs Others. [d]Investigators' choice. [e]Labelled dose. [f]Scans every 8 weeks for the first 12 months, then every 12 weeks. [g]*ESR1*m status was centrally determined in baseline plasma by Guardant 360® ctDNA assay and Burning Rock Biotech OncoCompass™ plus assay for patients from China (n=40). [h]Analysis conducted in all concurrently randomized patients.

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

Results: Primary Endpoints

Imlunestrant vs SOC ET

Investigator-Assessed PFS in Patients With *ESR1*m

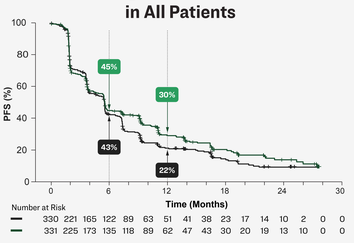


	SOC ET n=118	Imlunestrant n=138
Number of Events	102	109
Median PFS (95% CI); Months	3.8 (3.7-5.5)	5.5 (3.9-7.4)
HR (95% CI); p value	0.62 (0.46-0.82) p<0.001	

- 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

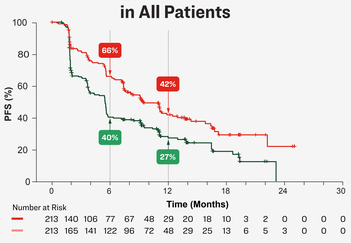


	SOC ET n=330	Imlunestrant n=331
Number of Events	253	237
Median PFS (95% CI); Months	5.5 (4.6-5.6)	5.6 (5.3-7.3)
HR (95% CI); p value	0.87 (0.72-1.04) p=0.12	

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

Imlunestrant + Abemaciclib vs Imlunestrant

Investigator-Assessed PFS in All Patients



	Imlunestrant n=213	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 (95% CI); p value	0.57 (0.44-0.73) p<0.001	

- 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

Top 3 Most Frequent TEAEs, %	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
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]	N/A		27/292 (9%)	
Injection Site Reaction[a] PRO-CTCAE, n/N (%)[c]	N/A		201/279 (72%)	

Generally favorable safety profile

Top 3 Most Frequent TEAEs, %	Imlunestrant + Abemaciclib n=208	
	Any Grade	Grade ≥3
Patients with ≥1 TEAE	98	49
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 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 + 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**

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

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.

Abbreviations: 1L=First-line; ABC=Advanced Breast Cancer; AE=Adverse Event; AI=Aromatase Inhibitor; BICR=Blinded Independent Central Review; CBR=Clinical Benefit Rate; CDK4/6i=Cyclin-dependent Kinase 4/6 Inhibitor; CI=Confidence Interval; ctDNA=Circulating Tumor DNA; DoR=Duration of Response; 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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