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Imlunestrant, an oral selective estrogen receptor degrader, as monotherapy and combined with abemaciclib, in recurrent/advanced ER-positive endometrioid endometrial cancer: Results from the phase 1a/1b EMBER study

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HIGHLIGHTS

- Imlunestrant orally once daily, as monotherapy and combined with abemaciclib, has a manageable safety profile.
- Preliminary evidence of antitumor activity was observed for imlunestrant as monotherapy and in combination with abemaciclib.
- The ORR, CBR and median PFS were numerically higher in the imlunestrant plus abemaciclib arm compared to the monotherapy arm.
- In the monotherapy arm, patients who achieved a molecular response had greater response rates and longer PFS.

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ABSTRACT

Objective. Imlunestrant is a next-generation oral selective estrogen receptor degrader designed to deliver continuous estrogen receptor (ER) target inhibition. EMBER is a phase 1a/b trial of imlunestrant, as monotherapy and combined with targeted therapy, in patients with ER+ advanced breast cancer or endometrioid endometrial

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cancer (EEC). This report focuses on patients with ER+ EEC.

Methods. EMBER used an i3 + 3 dose-escalation design to determine the recommended phase 2 dose (RP2D) followed by dose-expansion cohorts (1:1 randomization): imlunestrant monotherapy and imlunestrant plus abemaciclib (150 mg twice daily). Eligible patients had measurable disease and progression or recurrence after platinum-containing chemotherapy. Prior fulvestrant or aromatase inhibitor was not allowed. Secondary endpoints included safety, pharmacokinetics and antitumor activity.

Results. In total, 72 patients with a median of 2 prior anticancer therapies were treated. Among the 39 patients who received imlunestrant (400 mg [RP2D], $n = 33$; 800 mg, $n = 6$), the most common treatment-emergent adverse events (TEAEs) were grade 1–2 nausea (35.9 %), diarrhea (25.6 %), urinary tract infection (25.6 %), and abdominal pain (20.5 %). Overall response rate (ORR) was 10.3 %, clinical benefit rate (CBR) was 33.3 %, and median progression-free survival (mPFS) was 3.8 months (95 % CI, 1.8–6.7). Among the 33 patients who received imlunestrant (400 mg [RP2D], $n = 29$; 800 mg, $n = 4$) plus abemaciclib, the most common TEAEs were diarrhea (87.9 %), nausea (66.7 %), fatigue (48.5 %), and anemia (45.5 %). ORR was 18.2 %, CBR was 42.4 %, and mPFS was 6.8 months (95 % CI, 2.1–12).

Conclusion. Imlunestrant, as monotherapy and combined with abemaciclib, has a manageable safety profile with preliminary evidence of antitumor activity in patients with ER+ EEC.

1. Introduction

Estrogen receptor (ER) driven cancers, including breast and endometrial, are the most frequent cancers among women and a major cause of cancer-related deaths worldwide [1]. Most low to intermediate grade endometrioid endometrial cancers (EECs) are ER+ and are often treated with chemotherapy despite a poor response [2]. The standard of care for treatment of metastatic disease includes platinum-based chemotherapy, immunotherapy (with or without lenvatinib), or endocrine therapy (ET) [3].

Endocrine therapy for EEC includes progestins, aromatase inhibitors (AIs) such as letrozole, selective ER modulators (SERMs) such as tamoxifen, and selective ER degrader (SERDs) such as fulvestrant, with generally low response rate and clinical benefit [4–7]. Additionally, fulvestrant is poorly soluble, has no oral absorption, and requires intramuscular administration that is often painful and burdensome to patients [8,9].

In ER driven early and metastatic breast cancer, cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) have significantly improved outcomes, and emerging evidence suggests that combining ET and CDK4/6i could improve outcomes for patients with advanced or recurrent ER + EEC [10]. Recently, the combination of letrozole with CDK4/6i (abemaciclib, ribociclib, palbociclib) demonstrated durable activity in patients with ER+ EEC [3,11–13]. Although the combination of letrozole and CDK4/6i has shown promising results in ER+ ECC, it may not be the most effective treatment option. Clinical trials with AIs as monotherapy have shown little activity with a response rate of less than 10 % [14,15]. In addition, AIs inhibit the production of estrogen by blocking the aromatase enzyme leading to incomplete inhibition of the estrogen signaling pathway, which has been associated with worse clinical outcomes in breast cancer [16,17]. SERDs block and degrade ER leading to a more complete inhibition of the pathway [18]. This provides a compelling rationale for the evaluation of novel SERDs for use as monotherapy and combined with CDK4/6i in patients with EEC.

Imlunestrant is a next-generation oral SERD with pure antagonistic properties resulting in sustained inhibition of ER-dependent gene transcription and cell growth [19,20]. Preclinically, imlunestrant has shown favorable pharmacokinetic properties and efficient antitumor activity in both *ESR1*-mutant and wild-type (WT) models; its efficacy is enhanced when combined with targeted therapy [20]. The feasibility of combining abemaciclib and imlunestrant has been demonstrated in patients with ER+/human epidermal growth factor receptor 2- (HER2-) advanced breast cancer (ABC). At the recommended phase 2 dose (RP2D) of 400 mg once daily (QD), imlunestrant had favorable safety, pharmacokinetics, and encouraging preliminary antitumor activity with a median progression-free survival (PFS) of 7.2 months as monotherapy and 19.2 months when combined with abemaciclib [21].

Here we present the EEC data from the first-in-human EMBER study of imlunestrant as monotherapy and when combined with abemaciclib.

2. Methods

2.1. Study design

EMBER (NCT04188548) is a global, open-label study consisting of a dose-escalation (phase 1a) of imlunestrant monotherapy followed by dose-expansion cohorts (phase 1b) exploring imlunestrant as monotherapy and combined with other targeted therapy in patients with ER + (HER2- and HER2+) ABC or ER+ recurrent, persistent, or metastatic EEC. The detailed study design has been previously reported [21].

In phase 1a, imlunestrant was administered orally QD on an empty stomach as either capsules or tablets in dosing cohorts (200, 400, 600, 800 and 1200 mg) using the i3 + 3 design [22] to determine the RP2D in patients with ER+, HER2- ABC ($n = 74$) and ER+ EEC (n = 7). For the EEC phase 1b expansion, 72 patients were randomized 1:1 to receive imlunestrant monotherapy or combined with abemaciclib to allow for a balanced enrollment between cohorts (Fig. S1). Patients were stratified according to tumor grade (grade 1–2 or 3) and prior chemotherapy (1 or > 1). Abemaciclib was administered orally at the dose of 150 mg twice daily (BID). Study treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal. Imlunestrant dose interruptions for less than 28 days and dose reductions were allowed unless the patients were already at the lowest dose level of 200 mg. Abemaciclib dose modifications were determined by the investigator according to the label. The planned sample size was established as 40 patients for each phase 1b cohort to provide adequate precision for the safety and antitumor activity assessments, through estimated incidence rate including but not limited to AE percentage and response (CR/PR) rate (**Table S1**). An interim analysis was conducted to evaluate safety, efficacy, and PK once approximately 20 participants in each cohort had been randomized. Despite reassuring safety, the study stopped enrollment before reaching the targeted sample size based on evaluation of interim efficacy and the prioritization of breast cancer cohorts. To allow for a meaningful analysis, the 7 patients with ER+ EEC in phase 1a were combined with patients enrolled in the imlunestrant monotherapy cohort in the phase 1b expansion.

The study protocol was approved by ethical and institutional review boards in compliance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice Guideline, and applicable regulatory requirements.

2.2. Outcome measures

The primary objective was determination of the RP2D of imlunestrant monotherapy and when combined with targeted therapy. Key secondary endpoints included assessment of safety, tolerability, pharmacokinetics, overall response rate (ORR), clinical benefit rate (CBR), and PFS per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Exploratory objectives included evaluation of tumor biomarkers (p53 immunohistochemistry, *TP53* mutational status, and microsatellite instability (MSI)).

2.3. Patients

Eligible patients were 18 years of age or older with confirmed advanced, recurrent, or metastatic ER+ EEC of any histological grade. ER + was defined as ≥1 % ER+ tumor nuclei as determined by immunohistochemistry [23]. Cancers in these patients must have progressed after platinum-based chemotherapy, been deemed unsuitable for, or declined platinum-based chemotherapy. Other inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, adequate organ function, and measurable disease.

No prior fulvestrant or AI was allowed. The study initially allowed prior AI but was later amended to exclude it after 2 patients were enrolled. Complete eligibility criteria are available in the Protocol (Fig. S1).

2.4. Assessments

Study visits occurred weekly in the first month (phase 1a only) and then monthly. During these visits, the patients underwent physical, laboratory, cardiological, and ECOG PS assessments. Tumor assessments were conducted at the beginning of the study, followed by assessments every 8 weeks for the first 6 months, and then every 12 weeks until study discontinuation. Follow-up assessments were conducted approximately 30 days after treatment discontinuation, followed by long-term survival monitoring every 12 weeks. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs v5.0 and coded using the Medical Dictionary for Regulatory Activities.

Blood samples were collected in Cell-Free DNA BCT (Streck, La Vista, NE) for biomarker analysis, specifically circulating tumor DNA (ctDNA). The samples were collected at baseline, C2D1, and every odd cycle until progression. The Guardant360 assay (Guardant Health, Redwood City, CA) was used to perform somatic mutation analysis on the ctDNA samples collected on C1D1 and C2D1.

Available formalin-fixed paraffin-embedded (FFPE) archival tumor specimens were collected. Tumor p53 immunohistochemistry (antibody clone D07) was performed by NeoGenomics Laboratories (Aliso Viejo, CA, USA) and scored as normal (WT), overexpression (aberrant/mutant), complete absence (aberrant/mutant), or cytoplasmic only (aberrant/mutant). MSI detection was performed by HistoGeneX (Belgium) using the Promega OncoMate Dx MSI Analysis System (Madison, WI, USA) in FFPE specimens and whole blood samples.

2.5. Statistical analysis

All safety and efficacy analyses were based on the safety population, defined as patients who received at least one imlunestrant dose. All safety and efficacy analyses were conducted for patients treated with imlunestrant monotherapy (including phase 1a patients with EEC and phase 1b cohort E8) and imlunestrant+abemaciclib (phase 1b cohort E9), unless otherwise stated. ORR was defined as the proportion of patients with a best overall response (BOR) of complete response or partial response. CBR is defined as the proportion of patients with a BOR of CR, PR or stable disease for ≥24 weeks. PFS was calculated as time from enrollment/randomization until the first occurrence of documented investigator-assessed disease progression or death from any cause in the absence of progressive disease. Adverse events, ORR and CBR were descriptively analyzed by count and percentage, while for PFS, the standard Kaplan-Meier method was used to estimate the curves, median, and 2-sided 95 % CIs calculated by log-log method. The association between ctDNA molecular response and clinical benefit was analyzed using the Wilcoxon test.

3. Results

3.1. Population

Across the EMBER study, a total of 379 patients with ER+ ABC (n = 307) or EEC (n = 72) were treated with imlunestrant alone or in combination. Among the 72 patients with ER+ EEC, 39 received imlunestrant monotherapy (phase 1a, n = 7; phase 1b, n = 32) and 33 received imlunestrant plus abemaciclib. Patient demographics and baseline characteristics are presented in Table 1.

Overall, the median age was 64.5 years (range 29–87). In any setting, patients had a median of 2 prior anticancer therapies for EEC including prior ET (30.8 % vs 36.4 %), targeted therapy with pembrolizumab ± lenvatinib (12.8 % vs 24.2 %), and platinum-based therapy (97.4 % vs 93.9 %) in the monotherapy arm and imlunestrant plus abemaciclib arm, respectively. The remaining patients were not candidates for or otherwise declined platinum-based therapy. All patients were CDK4/

Table 1
Baseline demographics and disease characteristics.

	Imlunestrant	Imlunestrant + abemaciclib
	n = 39	n = 33
Median age, years (range)	62 (44–78)	67 (29–87)
Race, n (%)		
White	25 (64.1)	21 (63.6)
Asian	10 (25.6)	9 (27.3)
Black or African American	1 (2.6)	1 (3.0)
American Indian or Alaska Native	2 (5.1)	0
Native Hawaiian or other pacific islander	0	1 (3.0)
Menopausal status, n (%)		
Postmenopausal	39 (100.0)	32 (97.0)
Pre-menopausal	0	1 (3.0)
Baseline ECOG PS, n (%)		
0	20 (51.3)	15 (45.5)
1	19 (48.7)	18 (54.5)
ER Score, n/N[a] (%)		
ER score ≥ 10 %, n/N [a] (%)	13/15 (86.7)	15/15 (100.0)
ER score < 10 %, n/N [a] (%)	2/15 (13.3)	0
ESR1-mutations-detected at baseline, n/N (%)	1/36 (2.8)	1/32 (3.1)
Visceral metastasis, n (%)	30 (76.9)	27 (81.8)
Stage at study entry, n (%)		
III	1 (2.6)	3 (9.1)
IV	38 (97.4)	30 (90.9)
Histological diagnosis grade, n (%) [b]		
Grade 1	17 (43.6)	15 (45.5)
Grade 2	12 (30.8)	9 (27.3)
Grade 3	9 (23.1)	8 (24.2)
Median prior therapy in any setting, n (range)	2 (0–4)	2 (1–6)
No. of patients with prior therapy in any setting, n (%)	38 (97.4)	33 (100)
Chemotherapy	38 (97.4)	31 (93.9)
Platinum-based chemotherapy	38 (97.4)	31 (93.9)
Endocrine therapy	12 (30.8)	12 (36.4)
Tamoxifen	3 (7.7)	6 (18.2)
Megestrol acetate	3 (7.7)	4 (12.1)
Progestin	6 (15.4)	7 (21.2)
AI [a]	2 (5.1)	0
Targeted therapy (pembrolizumab ± lenvatinib), n (%)	5 (12.8)	8 (24.2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; n, number of patients.
[a] Patients with an evaluable ER score.
[b] Patients were enrolled in a prior protocol version where AI therapy was not excluded.

6i-naïve. It is worth noting that 2 patients (5.1 %) in the monotherapy arm had received prior AI.

At the cut-off date of August 14, 2023, 13 patients (17.6 %) were still receiving study treatment: 5 (12.5 %) on the imlunestrant monotherapy arm and 8 (23.5 %) on the imlunestrant plus abemaciclib arm. Patient disposition is shown in Fig. S2.

3.2. Safety

3.2.1. Imlunestrant monotherapy

Treatment-emergent AEs (TEAEs) and treatment-related AEs (TRAEs) are shown in Table 2. Thirty-eight patients (97.4 %) who received imlunestrant monotherapy had at least one TEAE; most commonly grade 1–2 nausea (35.9 %), diarrhea (25.6 %), urinary tract infection (UTI) (25.6 %), and/or abdominal pain (20.5 %). Grade ≥ 3 TEAEs were observed in 23.1 % of patients; abdominal pain (7.7 %) or blood creatinine increased (5.1 %) were most common (by grade in the **Table S2**).

The most frequently reported all-grade TRAEs were nausea (20.5 %), diarrhea (17.9 %), fatigue (12.8 %), and hot flashes (10.3 %). There were no grade ≥ 3 TRAEs. Dose reductions occurred in 5.1 % of patients and no patient discontinued due to AEs (**Table S4**).

3.2.2. Imlunestrant combined with abemaciclib

For recipients of imlunestrant plus abemaciclib, 100 % of patients ($n = 33$) presented at least one TEAE; the most common all-grade TEAEs and TRAEs were diarrhea (87.9 % and 84.8 %, respectively), nausea (66.7 % and 60.6 %), fatigue (48.5 % and 48.5 %) and anemia (45.5 % and 39.4 %). The most frequently reported grade ≥ 3 TEAEs were anemia (12.1 %), fatigue (9.1 %), neutropenia, thrombocytopenia, leukopenia, UTI, and acute kidney injury (6.1 %, each). Grade ≥ 3 TRAEs were reported for 9 patients (27.3 %), with anemia (9.1 %), thrombocytopenia (6.1 %), and fatigue (6.1 %) being the most common. Two (6.1 %) patients experienced grade 4 AEs (thrombocytopenia and colitis, 1 patient each). There were no grade 5 TRAEs (**Table S3**).

For patients receiving the combination of imlunestrant and abemaciclib, dose reductions due to AEs occurred in 42.4 % of patients (21.2 % reduced concurrently both imlunestrant and abemaciclib, 15.2 % had only the abemaciclib dose reduced, and 6.1 % had only the imlunestrant dose reduced). Three patients (9.1 %) discontinued

Table 2
Most common adverse events reported in ≥10 % of patients.

	Treatment-emergent adverse events				Treatment-related adverse events			
	Imlunestrant [a]		Imlunestrant + abemaciclib [b]		Imlunestrant [a]		Imlunestrant + abemaciclib [b]	
	n = 39		n = 33		n = 39		n = 33	
Parameters, n (%)	All	G ≥ 3	All	G ≥ 3	All	G ≥ 3	All	G ≥ 3
Patients with ≥1 adverse event	38 (97.4)	9 (23.1)	33 (100.0)	10 (30.3)	22 (56.4)	0	32 (97.0)	9 (27.3)
Gastrointestinal disorders								
Nausea	14 (35.9)	1 (2.6)	22 (66.7)	0	8 (20.5)	0	20 (60.6)	0
Diarrhea	10 (25.6)	0	29 (87.9)	1 (3.0)	7 (17.9)	0	28 (84.8)	1 (3.0)
Abdominal pain	8 (20.5)	3 (7.7)	9 (27.3)	1 (3.0)	3 (7.7)	0	2 (6.1)	0
Constipation	7 (17.9)	0	4 (12.1)	0	2 (5.1)	0	1 (3.0)	0
Vomiting	4 (10.3)	0	9 (27.3)	1 (3.0)	2 (5.1)	0	9 (27.3)	0
Hematological disorders								
Anemia	4 (10.3)	1 (2.6)	15 (45.5)	4 (12.1)	3 (7.7)	0	13 (39.4)	3 (9.1)
Neutropenia	1 (2.6)	0	7 (21.2)	2 (6.1)	1 (2.6)	0	7 (21.2)	1 (3.0)
Thrombocytopenia	0	0	9 (27.3)	2 (6.1)	0	0	8 (24.2)	2 (6.1)
Leukopenia	0	0	4 (12.1)	2 (6.1)	0	0	4 (12.1)	1 (3.0)
Liver disorders								
ALT increased	4 (10.3)	0	4 (12.1)	1 (3.0)	1 (2.6)	0	4 (12.1)	1 (3.0)
AST increased	3 (7.7)	0	4 (12.1)	1 (3.0)	1 (2.6)	0	4 (12.1)	1 (3.0)
Renal and urinary disorders								
UTI [c]	10 (25.6)	1 (2.6)	5 (15.2)	2 (6.1)	0	0	1 (3.0)	0
Blood creatinine increased	3 (7.7)	2 (5.1)	12 (36.4)	1 (3.0)	2 (5.1)	0	10 (30.3)	0
Acute kidney injury	1 (2.6)	1 (2.6)	4 (12.1)	2 (6.1)	0	0	2 (6.1)	1 (3.0)
Brain disorders								
Headache	5 (12.8)	0	3 (9.1)	0	2 (5.1)	0	1 (3.0)	0
Respiratory disorders								
Cough	6 (15.4)	0	4 (12.1)	0	0	0	0	0
Dyspnea	2 (5.1)	1 (2.6)	4 (12.1)	0	0	0	2 (6.1)	0
Pain								
Myalgia	4 (10.3)	0	2 (6.1)	1 (3.0)	1 (2.6)	0	2 (6.1)	1 (3.0)
Skin and subcutaneous disorders								
Pruritus	5 (12.8)	0	2 (6.1)	0	3 (7.7)	0	1 (3.0)	0
Rash [d]	4 (10.3)	0	5 (15.2)	0	2 (5.1)	0	1 (3.0)	0
Other								
Fatigue [e]	7 (17.9)	0	16 (48.5)	3 (9.1)	5 (12.8)	0	16 (48.5)	2 (6.1)
Hot flashes [f]	4 (10.3)	0	6 (18.2)	0	4 (10.3)	0	6 (18.2)	0
Decreased appetite	1 (2.6)	0	11 (33.3)	0	0	0	11 (33.3)	0
Weight decreased	1 (2.6)	0	8 (24.2)	0	0	0	5 (15.2)	0
Dysgeusia	1 (2.6)	0	5 (15.2)	0	1 (2.6)	0	5 (15.2)	0
Edema peripheral	0	0	5 (15.2)	0	0	0	1 (3.0)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; n, number of patients; UTI, urinary tract infection.
[a] 6 patients treated with imlunestrant 800 mg.
[b] 4 patients treated with imlunestrant 800 mg.
[c] The group term of UTI includes Bacteriuria; Urinary tract infection; Urinary tract candidiasis.
[d] The group term of rash includes rash, rash vesicular, rash maculo-papular, rash morbilliform, rash pruritic, rash pustular, rash erythematous, dermatitis acneiform.
[e] The group term of fatigue includes fatigue and asthenia.
[f] The group term of hot flashes includes hot flashes and flushing.

treatment with imlunestrant plus abemaciclib due to nausea, fatigue, and myalgia (**Table S4**).

3.3. Clinical activity

3.3.1. Imlunestrant monotherapy

The ORR was 10.3 % including one (2.6 %) complete response and 3 (7.7 %) partial responses. Stable disease was reported in 21 patients (53.8 %) while 12 (30.8 %) had progressive disease. The CBR was 33.3 %, median PFS was 3.8 months (95 % CI, 1.8–6.7), and the 6-month PFS rate was 35.7 % (Table 3, Fig. 1)

3.3.2. Imlunestrant combined with abemaciclib

The ORR was 18.2 % with all 6 patients showing partial response. Fifteen patients (45.5 %) had stable disease, 10 (30.3 %) had progressive disease, and 2 (6.1 %) were non-evaluable. The CBR was 42.4 %, median PFS was 6.8 months (95 % CI, 2.1–12.0), and the 6-month PFS rate was 50.4 % (Table 3, Fig. 1).

3.3.3. Individual responses to imlunestrant monotherapy and imlunestrant in combination with abemaciclib

A swimmer plot showing individual response is shown (Fig. S3), along with the characteristics of the patients who responded to therapy (**Table S5, Table S6**).

All patients presented with stage IV disease at study entry, the majority had low histological grade 1–2, and were exposed to 1 prior line of therapy. The metastatic sites were predominantly peritoneum and lung. In responding patients, duration of response ranged from 6.3 to 19.7 months in ER + EEC patients treated with imlunestrant monotherapy (**Table S5**), and 3.4–21.2 months in patients treated with imlunestrant in combination with abemaciclib (**Table S6**). Notably, the patient who reported a complete response was diagnosed with histologic grade 3 EEC and received imlunestrant monotherapy for almost two years.

3.4. Biomarkers analyses

Among the 72 patients with ER+ EEC, archival FFPE tumor samples from 51 patients (70.8 %) were tested for p53 expression by immunohistochemistry and 44 tumor samples (61.1 %) were molecularly classified for MSI. Additionally, plasma samples were collected at baseline (n = 68) for ctDNA (Table 4). Out of these, 59 patients (86.8 %) had detectable ctDNA.

Table 3
Efficacy.

	Imlunestrant	Imlunestrant + abemaciclib
	n = 39	n = 33
Best Overall Response, n (%)		
Complete Response	1 (2.6)	0
Partial Response	3 (7.7)	6 (18.2)
Stable Disease	21 (53.8)	15 (45.5)
Progressive Disease	12 (30.8)	10 (30.3)
Non-evaluable	2 (5.1)	2 (6.1)
Overall Response Rate, n (%) [a]	4 (10.3)	6 (18.2)
Clinical Benefit Rate, n (%) [b]	13 (33.3)	14 (42.4)
Disease Control Rate, n (%)	25 (64.1)	21 (63.6)
Median Treatment Duration, months (range)	3.9 (0.1–35.39)	5.5 (0.1–25.8)
Median Progression-free survival, months (95 % CI)	3.8 (1.8, 6.7)	6.8 (2.1, 12.0)
3-month progression-free survival, % (95 % CI)	66.7 (48.8, 79.5)	67.4 (47.9, 81.0)
6-month progression-free survival, % (95 % CI)	35.7 (20.6, 51.1)	50.4 (31.6, 66.5)
12-month progression-free survival, % (95 % CI)	17.9 (7.3, 32.1)	26.7 (11.1, 45.3)

[a] Clinical benefit rate defined as the proportion of patients who achieved a best overall response of complete response, partial response or stable disease for ≥24 weeks.
[b] Disease control rate defined as the proportion of patients who achieved a best overall response of complete response, partial response or stable disease.

3.4.1. Imlunestrant monotherapy cohort

Among the 3 patients who had tumor samples with aberrant p53 expression, one patient exhibited clinical benefit (stable disease ≥24 weeks). Similarly, of the 3 patients with MSI-high tumor samples, one patient exhibited clinical benefit (complete response).

Among the 36 patients in this cohort with baseline ctDNA data, 14 had a *TP53* mutation and out of these, 3 patients (21.4 %) exhibited clinical benefit. The baseline ctDNA analysis identified 4 patients with MSI-high disease. Notably, 3 of the 4 patients had grade 2 tumors, and the other had grade 1 tumor. All had ER expression ≥95 %. None of these patients showed clinical benefit.

Two of the 3 patients with aberrant p53 expression had *TP53* mutation detected by ctDNA. The patient without a *TP53* mutation had only one somatic mutation detected with a very low variant allele frequency (VAF) (0.23 %), indicating limited ctDNA shedding.

3.4.2. Imlunestrant combined with abemaciclib cohort

None of the 3 patients in this cohort who had tumor samples with abnormal p53 expression exhibited clinical benefit. One of the 3 patients with MSI-High disease showed clinical benefit (partial response).

Among the 32 patients with baseline ctDNA, 17 had *TP53* mutations, and 6 (35.3 %) of them exhibited clinical benefit. Of the 7 patients with MSI-High disease, 3 (42.8 %) demonstrated clinical benefit.

All 3 patients with abnormal p53 expression also had *TP53* mutations detected by ctDNA analysis.

Archival FFPE tumor samples were less likely to indicate an alteration in p53 compared to baseline ctDNA samples, within this limited data. There was no significant association observed between tumor-derived p53 and/or MSI status and clinical outcome.

3.5. Correlation of ctDNA dynamics with disease response

In the 24 patients who received imlunestrant monotherapy and had serial ctDNA samples available, clinical benefit and disease control (partial response + stable disease) were often associated with VAF declines at C2D1 (Fig. 2A). Patients who achieved a molecular response (decline ≥50 % ctDNA) had greater clinical benefit and longer PFS (8.3 months; 95 % CI, 4.8-NA) than those without (1.8 months; 95 % CI, 1.7–5.6) (Fig. 2B).

4. Discussion

Recurrent and advanced EEC remains a treatment dilemma. Currently, multiagent chemotherapy regimens are preferred in the first-line setting but not always well-tolerated by patients [3]. Moreover, patients who experience disease relapse have limited effective treatment options. The FDA approval of dostarlimab, pembrolizumab, and durvalumab have provided new treatment options with substantial benefit in the mismatch repair-deficient (dMMR)-MSI-high population [24,25]. Additionally, combining pembrolizumab with lenvatinib has been approved for those with non-MSI-high or dMMR advanced EEC tumors after progression on chemotherapy, however this combination is associated with significant toxicity and is difficult to tolerate [26,27].

For certain patients, ET alone or in combinations guided by biomarkers could be a treatment option [28]. Low-grade endometrioid histology and positive ER/PR tumor status are predictors of a positive response to ET [29,30]. This hormonally driven subtype is enriched in the *TP53* WT/Copy-number low group of the TCGA classification [31]. A previous study showed that combining ET and abemaciclib improved outcomes for HR+ ABC [32]. Given that both HR+ breast cancer and ER+ EEC are estrogen receptor driven, evaluating the potential benefit of

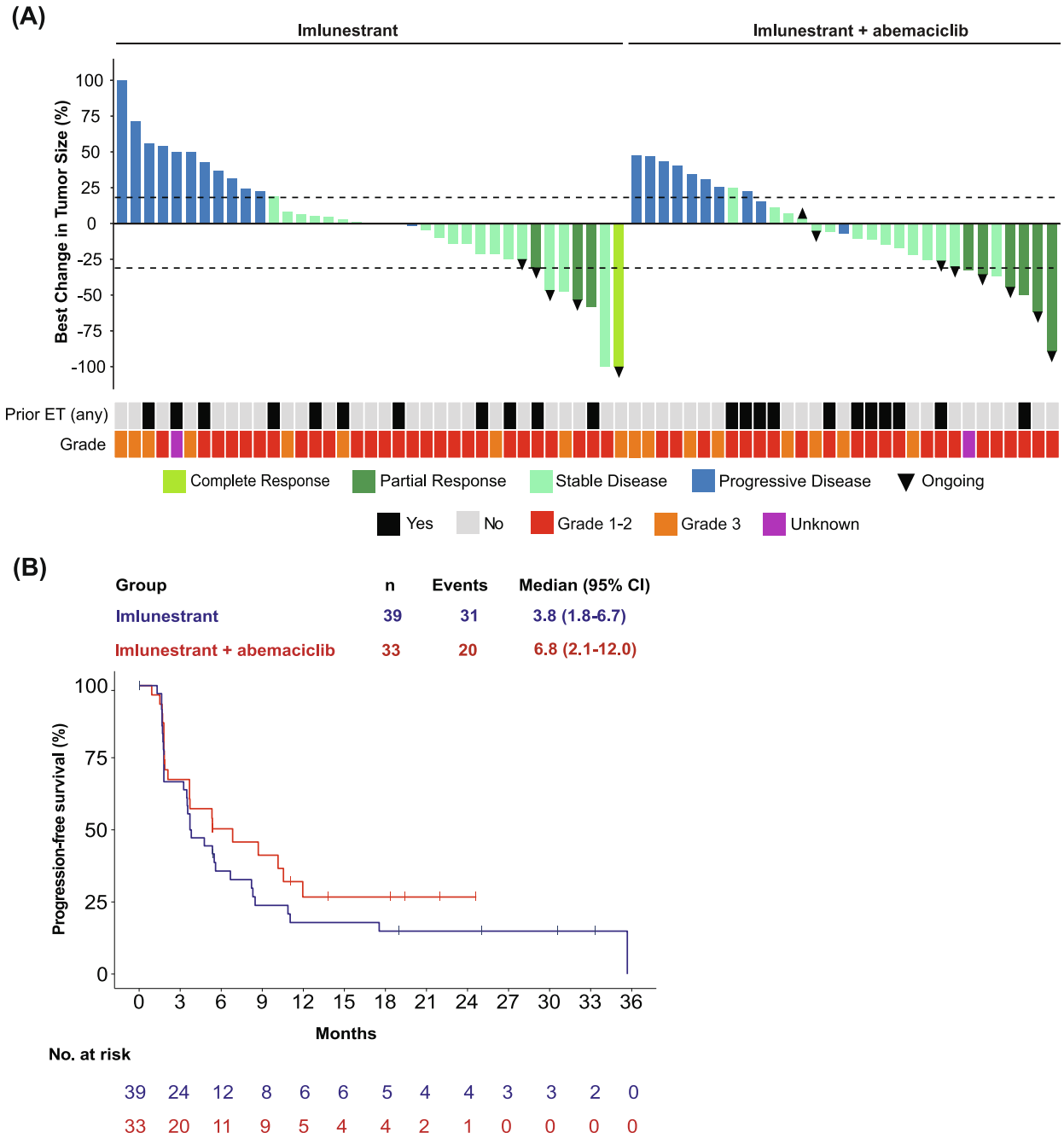

Fig. 1. (A) Waterfall plot for best percentage change in tumor size in patients with measurable disease who received imlunestrant monotherapy and imlunestrant in combination with abemaciclib. Each bar represents one patient. (B) Kaplan-Meier estimates of PFS. Abbreviations: CI, confidence interval; ET, endocrine therapy; G, grade (histological grade at diagnosis).

combining the CDK4/6i abemaciclib with ET, including an oral SERD, warrants investigation.

Here, we report results from the EMBER study, which evaluated imlunestrant as monotherapy and combined with abemaciclib in patients with ER+ EEC. EMBER is the first and only trial to demonstrate the feasibility and tolerability of the combination therapy of an oral SERD plus a CDK4/6i in patients with ER+ recurrent, persistent or metastatic EEC. In the dose escalation phase, imlunestrant monotherapy demonstrated a tolerable safety profile with no dose-limiting toxicity or toxicity-associated discontinuations at doses ranging from 200 to 1200 mg QD; 400 mg was declared as the RP2D. In patients with ER+/HER2- ABC, antitumor activity was observed with the RP2D (median PFS 7.2 months), including patients pre-treated with fulvestrant and/or CDK4/6i and those with tumors harboring *ESR1*-mutations [21].

In this study, 73.6 % of the patients had low-grade EEC, and most (95.8 %) had received platinum-based chemotherapy. *ESR1*-mutations were found to be quite rare, as only 2 patients had detectable *ESR1*-mutations at baseline. The low incidence of *ESR1*-mutation is in line with prior publications [33,34], which could be a reflection of low rates of prior AI in this cohort, as *ESR1*-mutations may develop in the course of treatment with AIs [33].

In patients with ER+ EEC who received imlunestrant monotherapy, the majority of TEAEs were grade 1–2, with 20.5 % having grade 3 TEAEs. Grade 4 TEAEs were observed in less than 3 % of patients and no grade 5 TEAEs were reported. The most frequent TEAEs were gastrointestinal

Table 4
Associations between biomarkers and clinical activity.

Biomarker	Imlunestrant	Imlunestrant + abemaciclib
	Clinical benefit	Clinical benefit
FFPE specimens		
Tested for p53, *n* =51		
Aberrant p53 expression, n/N (%)	1/3 (33.3)	0/3
Normal p53 expression, n/N (%)	10/25 (40.0)	9/20 (45.0)
Tested for MSI [a], *n* =44		
MSI-High, n/N (%)	1/3 (33.3)	1/3 (33.3)
MSS, n/N (%)	7/20 (35)	7/18 (38.9)
Baseline ctDNA, n (%)		
Tested for *TP53* mutation, n=68		
TP53 mutation, n/N (%)	3/14 (21.4)	6/17 (35.3)
TP53 mutation not detected, n/N (%)	8/22 (36.4)	7/15 (46.7)
Tested for MSI [a], *n* =68		
MSI-High, n/N (%)	0/4	3/7 (42.8)
MSS, n/N (%)	11/32 (34.4)	10/25 (40.0)

Abbreviations: FFPE, formalin-fixed paraffin-embedded; MSI, microsatellite instability; MSS, microsatellite stable.
[a] whole blood was also evaluated for MSI in the safety population.

toxicities (such as nausea, diarrhea, abdominal pain), UTI, and fatigue, which are observed with other drugs in the same class [35]. No patients discontinued due to AE. These results highlight the manageable safety profile of imlunestrant as a single agent in EEC.

Imlunestrant monotherapy demonstrated preliminary efficacy (ORR 10.3 %, CBR 33.3 %, mPFS 3.8 months [95 % CI, 1.8–6.7]) in previously treated patients with metastatic ER+ EEC. While noting the limitations of cross-trial comparisons, these EMBER data are comparable to fulvestrant reports of a median PFS of 2.3 months in patients with ER-positive advanced or recurrent EEC and to AIs with 7 % and 9.4 % response rates reported for anastrozole and letrozole, respectively [14,36,37]. Notably, there was evidence of clinical benefit in patients who had previously received hormonal therapy, including tamoxifen and progestins.

EMBER also explored the combination of imlunestrant with abemaciclib. The AEs of imlunestrant plus abemaciclib were consistent with its known safety profile previously reported in the ABC setting [21,38,39]. No new safety signals or unexpected toxicities were observed with the addition of abemaciclib, suggesting no additive toxicity effects. The most frequently reported TEAEs were diarrhea, nausea, fatigue, and anemia. The majority of TEAEs were grade 2 (57.6 %), with 21.2 % having grade 3 and 9.1 % having Grade 4 TEAEs. Although the incidence of SAEs is similar between treatment arms, the incidence of grade ≥ 3 TEAEs was higher compared to imlunestrant monotherapy, safety profile was predictable and manageable with medication and/or dose modifications [39].

Preliminary efficacy was observed with the combination regimen (ORR 18.2 %, CBR 42.4 %, and median PFS of 6.8 months). A recent phase 2 study of the combination of letrozole with abemaciclib reported a median PFS of 9.1 months and a 30 % ORR [11]. Cross trial comparisons are challenging, especially when comparing a single cohort of a multicohort phase 1a/b study not limited to EEC to results of a phase 2 EEC specific study. EMBER was a multi-cohort breast cancer trial focusing on safety of various combinations with imlunestrant, of which patients with ER + EEC represented a small portion of this trial (23 %). This combination has been incorporated into the NCCN guidelines as recommended therapies for ER+ recurrent or metastatic EEC [3]. Given the manageable safety profile of imlunestrant monotherapy and the combination with abemaciclib, as well as its preliminary efficacy in this phase 1 study, this combination could be investigated in future trials as an alternative ET backbone for patients intolerant to other ET.

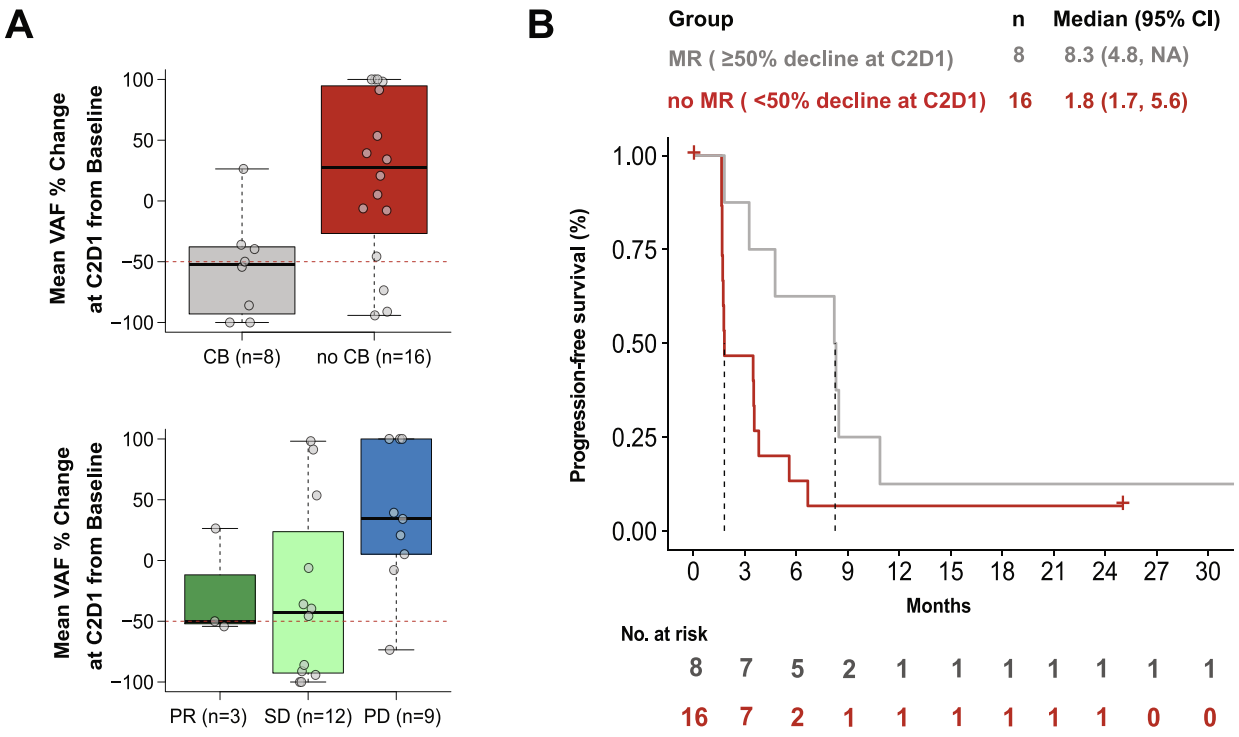

Fig. 2. ctDNA dynamics in patients who received imlunestrant monotherapy. (A) Mean VAF % change of all somatic mutations at C2D1 compared to baseline according to best overall response and clinical benefit in patients who received imlunestrant ($n = 23$). (B) PFS according to MR (≥ 50 % decline in VAF at C2D1) versus no MR (<50 % - 0 % decline in VAF at C2D1). Abbreviations: C2D1, Cycle 2 Day 1; CR, complete response; MR, molecular response; PD, progressive disease; PR, partial response; CB, clinical benefit; PFS, progression-free survival; SD, stable disease, VAF, variant allele frequency.

Exploratory biomarker assessments yielded noteworthy observations. Within the small ctDNA sequencing dataset from the monotherapy arm, ctDNA VAF decreases at C2D1 were generally associated with better clinical outcomes, supporting further investigation for incorporating early ctDNA dynamics analysis in this patient population [29]. Data from patients with aberrant tumor p53 expression or MSI-High status were insufficient to establish associations with treatment outcomes.

Likewise, significant associations between baseline *TP53* mutation or MSI-high status and clinical outcomes were not observed. However, molecular classification is encouraged in all endometrial carcinomas, especially high-grade tumors (IV, B) [40]. There was some discordance between the *TP53* mutation and MSI status when comparing the ctDNA assessment to tissue. Potential explanations for these differences include the collection of ctDNA at a different time than the tissue biopsy, limited sensitivity of ctDNA assessments due to the rate of tumor DNA shedding, and the absence of standardized criteria to define abnormal p53 expression.

Overall, our results indicate the potential benefit of hormonal and targeted therapies in EEC. In hormonally driven breast and prostate cancers, targeted and/or hormonal strategies are used up front and chemotherapy reserved for later lines. These strategies reflect the change in underlying cancer biology. As cancers progress, they trend towards an undifferentiated state and are less responsive to targeted/hormonal therapies. An intriguing possibility is the use of CDK4/6i and SERDs early in the treatment of ER+, *TP53* WT EEC, with potentially higher ORR and PFS, allowing the deferral of chemotherapy until these cancers become less responsive to ET.

5. Conclusion

Among patients with measurable, recurrent, persistent or metastatic ER+ EEC, imlunestrant, as monotherapy or imlunestrant combined with abemaciclib, has a manageable safety profile with preliminary evidence of efficacy. Notably, imlunestrant phase 3 studies are ongoing for the treatment of ER+, HER2- ABC and as adjuvant therapy in high-risk ER+, HER2- EBC (EMBER-3 NCT04975308 and EMBER-4 NCT05514054, respectively).

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Data availability

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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