PD5-08

Circulating Tumor DNA (ctDNA) Dynamics From Patients With ER+, HER2- Advanced Breast Cancer in the Phase 3 EMBER-3 Trial

Scan the QR code for a list of all Lilly content presented at the congress.

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from SABCSfi and the author of this poster.

Other company and product names are trademarks of their respective owners.

Francois-Clement Bidard[1], Komal Jhaveri[2], Sung-Bae Kim[3], Eriko Tokunaga[4], Philippe Aftimos[5], Cristina Saura[6], Joyce O'Shaughnessy[7], Nadia Harbeck[8], Guiseppe Curigliano[9,10], Antonio Llombart-Cussac[11], Elgene Lim[12], Seock-Ah Im[13], Hiroko Bando[14], Patrick Neven[15], Shawn T. Estrem[16], Bastien Nguyen[16], Shanshan Cao[16], Monish Ram Makena[16], Bhardwaj Desai[16], Lisa A. Carey[17]

[1]Institut Curie, Paris, France, [2]Memorial Sloan Kettering Cancer Center, New York, USA; Weill Cornell Medical College, New York, USA, [3]University of Ulsan College of Medicine, Seoul, Republic of Korea, [4]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan, [5]Institut Jules Bordet, Brussels, Belgium, [6]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [7]Baylor University Medical Center, Dallas, USA, [8]Ludwig Maximilians University Munich University Hospital, Munich, Germany, [9]University of Milan, Milan, Italy, [10]European Institute of Oncology, IRCCS, Milan, Italy, [11]Universidad Católica de Valencia, Valencia, Spain, [12]Garvan Institute of Medical Research, St Vincent's Hospital, University of New South Wales, NSW, Australia, [13]Seoul National University Hospital, Seoul, Republic of Korea, [14]University of Tsukuba, Tsukuba, Japan, [15]University Hospitals Leuven, Louvain, Belgium, [16]Eli Lilly and Company, Indianapolis, USA, [17]University of North Carolina at Chapel Hill, Chapel Hill, USA

Study was sponsored by Eli Lilly and Company

OBJECTIVE

Exploratory analyses of circulating tumor DNA (ctDNA) dynamics from baseline to cycle 2 day 1 (C2D1) conducted across all EMBER-3 arms, stratified by estrogen receptor 1 gene mutation (*ESR1*m) status at baseline

CONCLUSIONS

- Early ctDNA dynamics were consistent with the primary progression-free survival (PFS) results showing that patients who achieved a molecular response (MR) had a longer PFS
- Among all patients or patients with *ESR1*m detected at baseline, ctDNA reduction (MRR) was improved with imlunestrant vs. standard of care endocrine therapy (SOC ET) and for imlunestrant + abemaciclib vs. imlunestrant alone
- Although the ctDNA mean variant allele frequency (VAF) decline of ≥50% (MR) at C2D1 was associated with improved PFS, the allocated treatment remained a key determinant of patient outcomes

San Antonio Breast Cancer Symposium (SABCS) 48th Annual Meeting; San Antonio, TX; December 9-12, 2025

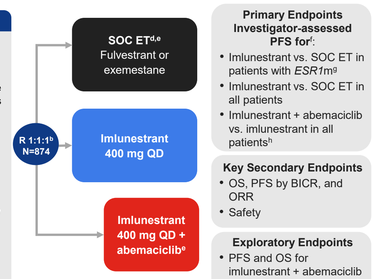
francois-clement.bidard@curie.fr

BACKGROUND

- Imlunestrant is a next-generation, brain-penetrant, oral SERD and pure ER antagonist[1]
  - Imlunestrant was recently FDA–approved for patients with ER+, HER2-, *ESR1*-mutated advanced breast cancer (ABC) with disease progression following at least 1 line of ET[2]
- In the Phase 3 EMBER-3 trial[3]
  - Imlunestrant demonstrated significant improvement in PFS vs. standard of care endocrine therapy (SOC ET; fulvestrant or exemestane) in patients with *ESR1*m (HR=0.62; 95% CI, 0.46-0.82)
  - The addition of abemaciclib to imlunestrant provided a statistically significant and clinically meaningful improvement in PFS compared with imlunestrant alone in all patients (HR=0.57; 95% CI, 0.44-0.73), regardless of *ESR1*m status
- Here we explore the association between PFS and ctDNA before treatment and after 1 month on treatment among patients in all arms of the EMBER-3 trial

METHODS

Study Design



[a]A GnRH agonist was required in men and premenopausal women; [b]Enrollment into imlunestrant + abemaciclib started with Protocol Amendment A (at which point 122 patients had been randomized across imlunestrant and SOC ET); [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 Guardant360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h]Analysis conducted in all concurrently randomized patients.

Note: Patients were enrolled from October 2021 to November 2023 across 195 sites in 22 countries.

ANALYSIS

- Plasma samples were obtained at baseline and after 4 weeks of treatment (C2D1)
- Samples were sequenced using the Guardant360 assay, covering 74 genes
- ctDNA dynamics were assessed by:
  - MR, defined as a decrease of ≥50% in VAF of ctDNA at C2D1 vs. baseline
  - MRR, defined as the percentage of patients who experienced an MR
- Median PFS was estimated using the Kaplan-Meier method and treatment effect was compared using the Cox proportional hazards model between patients with and without a ≥50% reduction in ctDNA levels from baseline to C2D1

Data cutoff: June 24, 2024.

REFERENCES

1. Bhagwat SV, et al. *Cancer Res.* 2025; 85:777-790.
2. INLURIYO (imlunestrant) [package insert]. Indianapolis, IN: Eli Lilly and Company, 2025.
3. Jhaveri KL, et al. *N Engl J Med.* 2025; 392:1189-1202.

ACKNOWLEDGMENTS

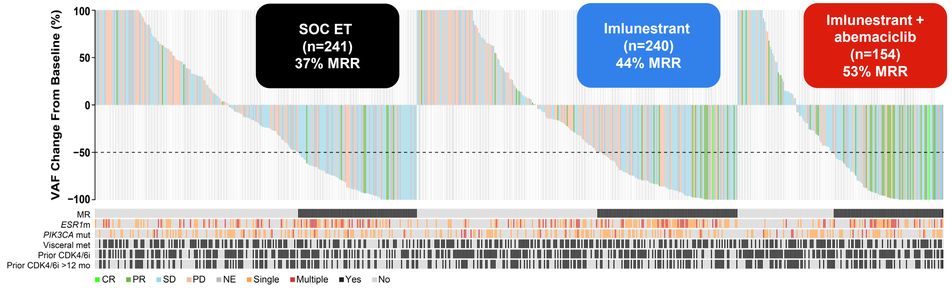
We thank the clinical trial participants and their families/caregivers for participating in this trial. We also thank the investigators and support staff who participated in this work

Medical writing assistance was provided by Heather Taft, PhD, of Envision Catalyst, an Envision Medical Communications agency, a part of Envision Pharma Group, and was funded by Eli Lilly and Company

Abbreviations: ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; C2D1, cycle 2 day 1; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; CR, complete response; ctDNA, circulating tumor DNA; ER, estrogen receptor; ESR1, estrogen receptor 1 gene; ESR1m, ESR1 mutation; ET, endocrine therapy; FDA, Food and Drug Administration; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mo, month; met, metastases; MR, molecular response; MR-ESR1, MR for ESR1; MRR, MR rate; MRR-ESR1, MRR using ESR1m only; mut, mutation; N, no; NE, not evaluable; NGS QC, next-generation sequencing quality control; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PIK3CA, phosphoinositide 3-kinase 3 catalytic subunit a; PR, partial response; QD, once daily; R, randomized; SD, stable disease; SERD, selective estrogen receptor degrader; SOC, standard of care; VAF, variant allele frequency; Y, yes

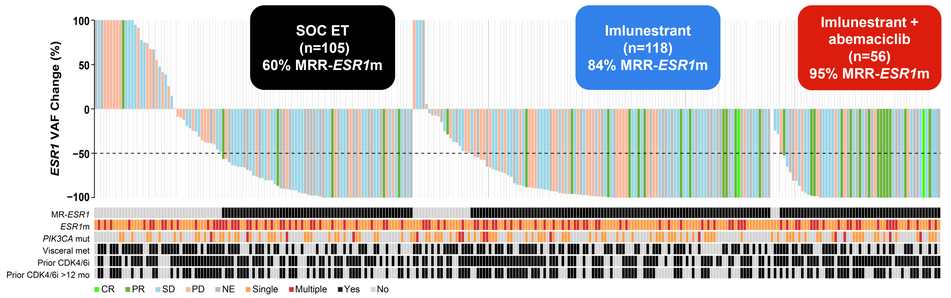
RESULTS

A Higher MRR Was Observed Among Patients Who Received Imlunestrant + Abemaciclib Than for SOC ET or Imlunestrant Monotherapy

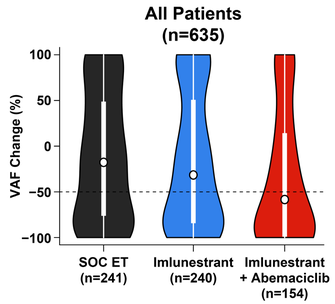


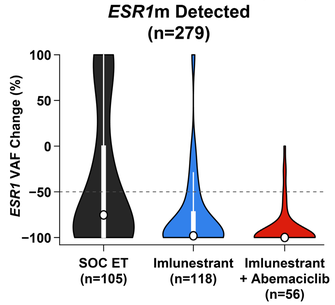
- *ESR1* and *PIK3CA* were the most commonly altered genes
- MRR was higher among patients who received imlunestrant, with an additional MRR benefit for combination treatment

In Patients With *ESR1*m, Imlunestrant With or Without Abemaciclib Led to a Higher Overall Decline in VAF and a Strong MRR-*ESR1*m Compared With SOC ET



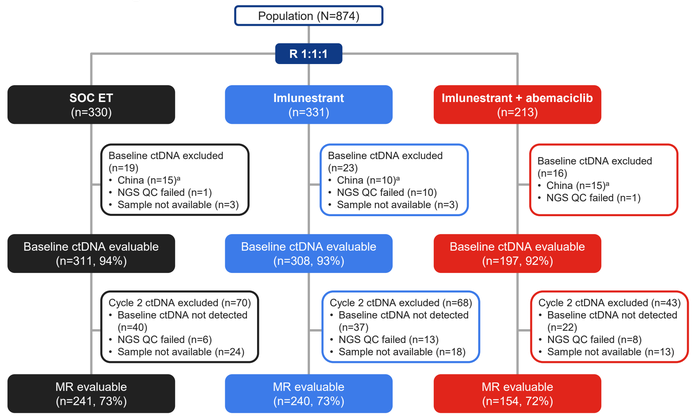
Patients Who Received Imlunestrant + Abemaciclib Experienced the Greatest Decline in VAF





Notes: In the violin plots, black outlined circles indicate the median; white boxes indicate the first and third quartiles; whiskers extend 1.5 times the interquartile range; widths of violin plots indicate kernel density of values.

CONSORT Diagram



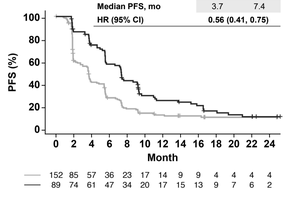
Across treatment arms, a similar attrition rate was observed with a similar frequency of detectable ctDNA and a high overall detection rate of 87.9%
Most patients (~70%) were MR evaluable, with ctDNA detected at baseline and C2D1 evaluable

[a]Patients from China were excluded due to regulations regarding sharing of genomic data.

Patients Experiencing an MR Had a Longer PFS in All Arms

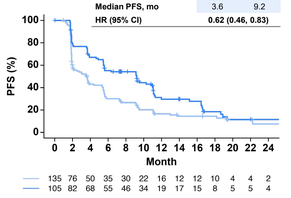
SOC ET (n=241)

	No MR	MR
Events, n (%)	126 (82.9)	70 (78.7)
Median PFS, mo	3.7	7.4
HR (95% CI)	0.56 (0.41, 0.75)	



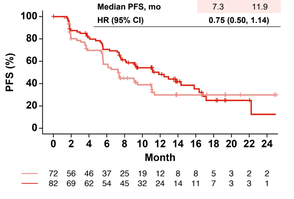
Imlunestrant (n=240)

	No MR	MR
Events, n (%)	108 (80.0)	76 (72.4)
Median PFS, mo	3.6	9.2
HR (95% CI)	0.62 (0.46, 0.83)	



Imlunestrant + abemaciclib (n=154)

	No MR	MR
Events, n (%)	44 (61.1)	47 (57.3)
Median PFS, mo	7.3	11.9
HR (95% CI)	0.75 (0.50, 1.14)	



Copyright ©2025 Eli Lilly and Company. All rights reserved.