PS2-07-24

Circulating Tumor DNA Biomarker Analyses of a Phase 1/2 Study Evaluating Vepdegestrant, a PROTAC Estrogen Receptor Degrader, in ER+/HER2- Advanced Breast Cancer

Seth A Wander,[1] Hyo S Han,[2] Erika P Hamilton,[3] Sara A Hurvitz,[4] Michael Lachowicz,[5] Wendy Wu,[5] John Corradi,[5] Anna C Van Acker,[5] Madeline A Dorso,[5] Elizabeth Duperret,[5] Shaparak Lonning,[6] Sam Dychter,[6] Cynthia Ma[7]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA; [2]Moffitt Cancer Center, Tampa, FL; [3]Breast Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN; [4]Fred Hutch Cancer Center, Seattle, WA; [5]Arvinas Operations, Inc., New Haven, CT; [6]Pfizer, Inc., San Diego, CA; [7]Washington University School of Medicine, St. Louis, MO

Objective

- To report exploratory biomarker analyses of circulating tumor DNA (ctDNA) among patients with previously treated estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who received vepdegestrant, an oral PROteolysis TArgeting Chimera (PROTAC) ER degrader in a phase 1/2 study

Key Findings

- Of 138 patients with ctDNA samples analyzed with the F1LCDx platform (all had received vepdegestrant ≥100 mg/day), 59% were positive for *ESR1* mutations (*ESR1*m; D538G 30%; Y537S 28%; Y537N 16%; E380Q 6%; L536P 4%; L536R 4%)
- Baseline ctDNA measures were associated with clinical outcomes among patients with *ESR1*m-positive tumors treated with vepdegestrant
  - When analyzed as single variables, neither the *ESR1*m variant allele frequency (VAF) nor the overall tumor fraction (TF; % of cell-free DNA [cfDNA] originating from tumor) at baseline was associated with clinical benefit rate (CBR) or progression-free survival (PFS)
  - However, when the baseline *ESR1*m VAF was normalized to the baseline TF, a higher *ESR1*m VAF/TF ratio was significantly associated with a better CBR (P=0.005) and PFS (hazard ratio [HR]:0.23; 95% CI: 0.09–0.62; P=0.004)
- Vepdegestrant induced robust reductions in *ESR1*m VAF and TF in patients with *ESR1*m-positive tumors
  - Reductions in the *ESR1*m VAF were observed across the Y537X, D538X and L536X variants; 87% of *ESR1*m alleles decreased ≥50% from baseline at cycle (C) 1 day (D) 28
  - 70.8% of patients had ≥50% reductions in TF from baseline at C1D28
- Larger changes in TF were associated with better clinical outcomes among patients with *ESR1*m-positive tumors
  - The median percentage change in TF from C1D1 to C1D28 was −99.2% in patients with clinical benefit vs −50.4% in patients without clinical benefit (P<0.001)
  - PFS was significantly longer among patients with a molecular response (MR; defined as ≥50% reduction in TF from C1D1 to C1D28) vs those without MR (HR: 0.18; 95% CI: 0.09, 0.37; P<0.0001)

Conclusions

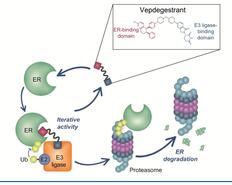
- Patients with a higher baseline *ESR1*m VAF/TF, a likely indicator of *ESR1*m clonality, had better clinical outcomes with vepdegestrant than patients with lower *ESR1*m VAF/TF
- Greater decreases in ctDNA TF at the end of C1 were associated with increased likelihood of achieving clinical benefit and prolonged PFS
- These exploratory analyses may provide clinically useful insights on patient responses to vepdegestrant and add to the growing body of evidence on the use of ctDNA in decisions around treatment continuation for patients with ER+/HER2- advanced breast cancer

San Antonio Breast Cancer Symposium (SABCS)
San Antonio, TX, USA; December 9-12, 2025

Background

- Vepdegestrant is an oral PROteolysis TArgeting Chimera (PROTAC) ER degrader that directly binds E3 ligase and ER to trigger ubiquitination of the ER and its subsequent degradation by the proteasomal system (**Figure 1**)[1,2]
- This mechanism of action differs from that of selective estrogen receptor degraders (eg, fulvestrant), which indirectly result in ER degradation secondary to inducing conformational changes and/or immobilization of ER[1]
- In preclinical studies, vepdegestrant induced ≥90% degradation of wild-type and mutant ER protein, inhibited proliferation of ER-dependent breast cancer cell lines, and induced complete inhibition of tumor growth in murine models of ER+ breast cancer[2]
- In a first-in-human, phase 1/2 study (NCT04072952), vepdegestrant showed encouraging clinical activity and was well tolerated in heavily pretreated patients with ER+/HER2- advanced breast cancer[3-5]
- A subsequent phase 3 trial (VERITAC-2; NCT05654623) demonstrated statistically significant and clinically meaningful prolongation of PFS assessed by blinded independent central review with vepdegestrant vs fulvestrant (HR: 0.57; 95% CI: 0.42–0.77; P<0.001) in patients with ER+/HER2- advanced breast cancer and *ESR1*m-positive tumors after previous treatment with endocrine therapy plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i)[6]
- Here, we report exploratory biomarker analyses from the phase 1/2 study (NCT04072952) in heavily pretreated patients with ER+/HER2- advanced breast cancer

Figure 1: MOA of vepdegestrant



ER=estrogen receptor; MOA, mechanism of action.

Methods

Study Design

- This multicenter, open-label study included a 3+3 dose escalation (phase 1; vepdegestrant doses: 30−700 mg daily) and dose expansion (phase 2; vepdegestrant 200 mg or 500 mg once daily)
- Key eligibility criteria were:
  - ER+/HER2- metastatic, recurrent, or locally advanced unresectable breast cancer
  - ≥1 prior CDK4/6i
  - ≥2 (phase 1) or ≥1 (phase 2) prior endocrine therapies
  - ≤3 prior lines of chemotherapy
- The primary (safety and tolerability) and secondary (PK and antitumor activity) endpoints of this study were reported previously[3-5]

Exploratory ctDNA analyses

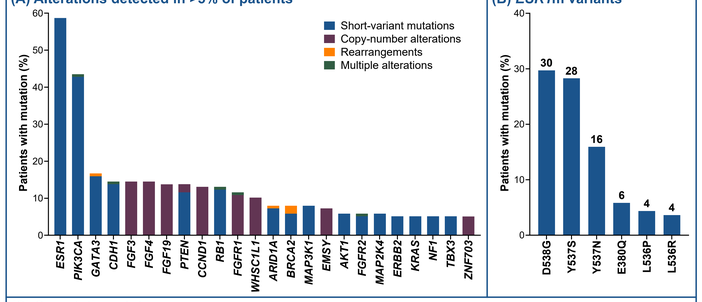
- We conducted exploratory analyses of the pooled phase 1/2 dataset
- Baseline (C1D1) and on-treatment (C1D28) cfDNA samples from patients treated with vepdegestrant (all at doses ≥100 mg/day) were analyzed using F1LCDx from Foundation Medicine
- Baseline and on-treatment changes in *ESR1*m VAF and TF (percentage of cfDNA that originates from the tumor) were assessed in association with clinical benefit (complete response [CR], partial response [PR], or stable disease [SD] for ≥24 weeks) and PFS among patients with *ESR1*m-positive tumors
- Clinical benefit data were analyzed by Firth's penalized logistic regression and Wilcoxon rank sum test and PFS data were analyzed using Cox regression

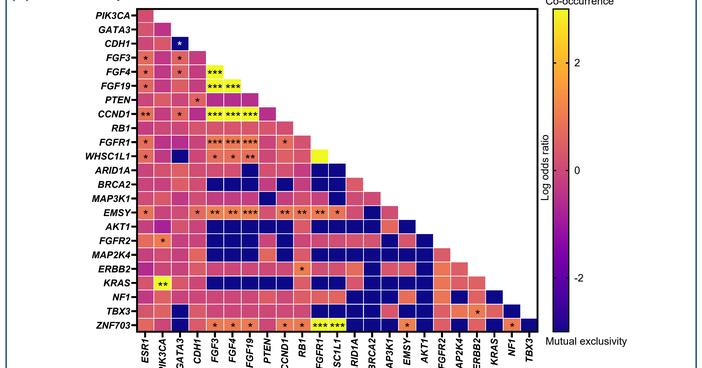
Results

Prevalence of gene alterations

- Among 154 patients treated with vepdegestrant, 138 had ctDNA samples analyzed with the F1LCDx platform (all had received vepdegestrant ≥100 mg/day)
- The most common gene alterations were short-variant mutations in *ESR1* (59%) and *PIK3CA* (43%; **Figure 2A**); the most common *ESR1* variants were D538G (30%), Y537S (28%), and Y537N (16%; **Figure 2B**)
- *ESR1*m weakly co-occurred with gene amplifications in *CCND1*, *FGF3/4/19*, *FGFR1*, *WHSC1L1*, and *EMSY* (**Figure 2C**)
- Co-occurrence of *PIK3CA* and *KRAS* mutations was common, whereas *CDH1* and *GATA3* mutations were usually mutually exclusive (**Figure 2C**)
- Amplicons of genes with close chromosomal proximity had high rates of co-occurrence (eg, *CCND1*, *FGF3*, *FGF4* and *FGF19* on chromosome 11q13 and *FGFR1*, *WHSC1L1* and *ZNF703* on chromosome 8p11-12; **Figure 2C**)

Figure 2: Prevalence of and co-occurrence of gene alterations at baseline (n=138)





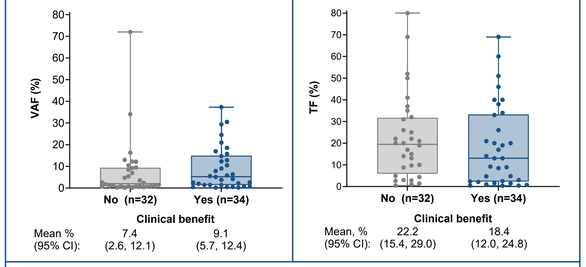
Baseline prevalence of (**A**) gene alterations occurring in >5% of patients and (**B**) specific *ESR1* variants (VUS were excluded), and (**C**) co-mutation plot showing co-occurrence of gene alterations (n=138 for all panels). Samples from 13 patients in the phase 1 study were analyzed using an older 70-gene FMI panel and were excluded these analyses. Panel A excludes CHIP genes (*ASXL1, ATM, CBL, CHEK2, DNMT3A, JAK2, MLL2, MYD88, SF3B1, TET2, TP53, U2AF1*). In panel C, the log odds ratio set was to 3 for complete co-occurrence (odds ratio=infinity) and -3 for complete mutual exclusivity (odds ratio=0). *P<0.05, **P<0.005, ***P<0.0005 by Fisher's exact test.
CHIP=clonal hematopoiesis of indeterminate potential; *ESR1*m=estrogen receptor 1 gene mutation; VUS=variants of unknown significance

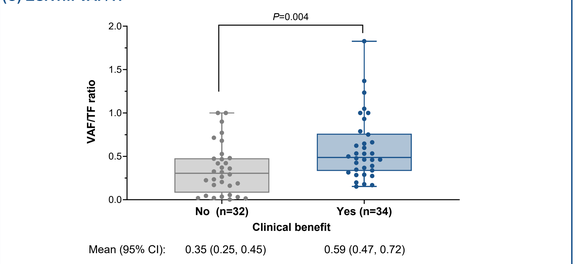
Exploratory ctDNA analyses among patients with *ESR1*m tumors

Baseline ctDNA levels and clinical outcomes during vepdegestrant treatment

- When analyzed as single variables, neither the *ESR1*m VAF nor the overall TF at baseline was associated with the CBR (**Figure 3A-B**)
- However, when baseline *ESR1*m VAF was normalized to baseline TF, a higher VAF/TF ratio was significantly associated with better CBR (P=0.004; **Figure 3C**)
- PFS was not associated with baseline *ESR1*m VAF or TF when analyzed as single variables, but the ratio of *ESR1*m VAF to TF was correlated with PFS (**Table 1**)

Figure 3: Baseline ctDNA levels by clinical response





(**A**) *ESR1*m VAF, (**B**) overall TF, and (**C**) ratio of *ESR1*m VAF to TF at baseline in patients with and without clinical benefit. Clinical benefit was defined as complete response, partial response, or stable disease for ≥24 weeks. P value shown is from Wilcoxon rank sum test. P=0.005 using logistic regression.
*ESR1*m=estrogen receptor 1 gene mutation; TF=tumor fraction; VAF=variant allele fraction.

Table 1: Effects of baseline TF, *ESR1*m VAF, and *ESR1*m VAF/TF on PFS

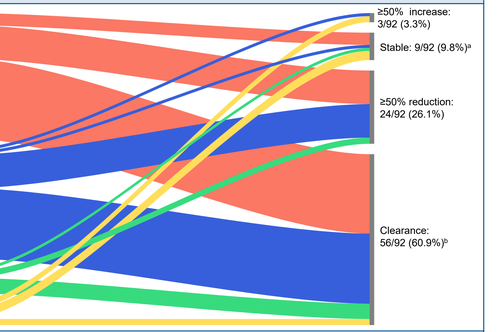
Baseline ctDNA parameter	n	HR (95% CI)	P value
*ESR1*m VAF	66	0.25 (0.01–5.68)	0.382
TF	66	1.49 (0.34–6.44)	0.595
*ESR1*m VAF/TF	66	0.23 (0.09–0.62)	0.004

ctDNA=circulating tumor DNA; *ESR1*m=estrogen receptor 1 gene mutation; HR=hazard ratio; PFS=progression-free survival; TF=tumor fraction; VAF=variant allele frequency.

Change from baseline in ESR1m VAF and TF and clinical outcomes

- Reductions in *ESR1*m VAF were observed after 1 cycle of vepdegestrant treatment, with 87% of mutant alleles showing ≥50% reduction from baseline at C1D28 (**Figure 4**)

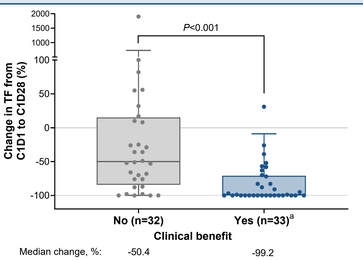
Figure 4: *ESR1*m VAF changes from C1D1 to C1D28



Sankey diagram of *ESR1*m VAF changes from C1D1 to C1D28 in patients with hotspot *ESR1* mutations. Data are shown per mutant allele; multiple mutant alleles may be present in 1 patient.
[a]Stable was defined as <50% change from baseline. [b]Clearance was defined as a 100% decrease from baseline.
C=cycle; D=day; *ESR1*m=ESR1 gene mutation; VAF=variant allele frequency.

- Robust reductions in TF were observed at the end of C1, with 70.8% of patients experiencing ≥50% reduction in TF from baseline at C1D28
- Patients who experienced clinical benefit (CR, PR, or SD for ≥24 weeks) had significantly greater reductions in TF from baseline to C1D28 than patients without clinical benefit (P<0.001; **Figure 5**)
- Patients with MR (≥50% reduction in TF from C1D1 to C1D28) had significantly longer PFS than those without MR (HR: 0.18; 95% CI: 0.09, 0.37; P<0.0001)

Figure 5: Change in TF and clinical benefit



Change in TF from C1D1 to C1D28 by clinical response in patients with TF>0 at baseline. Clinical benefit was defined as complete response, partial response, or stable disease for ≥24 weeks. P value indicated is from Wilcoxon rank sum test. Logistic regression also yielded P<0.001.
[a]1 patient did not have C1D28 results.
C=cycle; D=day; TF=tumor fraction.

References

1. Hamilton EP, et al. Target Oncol. 2025;20(3):431-444.
2. Gough SM, et al. Clin Cancer Res. 2024;30(16):3549-3563.
3. Hamilton E, et al. SABCS 2021; San Antonio, TX. PD13-08.
4. Hamilton E, et al. Annals Oncol. 2023;34 (S2): S344.
5. Hurvitz S, et al. Cancer Res. 2024;84(S9):PO3-05-08.
6. Campone M, et al. N Engl J Med. 2025;393(6):556-68.

Acknowledgments: We thank the patients who participated in this study and their caregivers, as well as the investigators, researchers, and coordinators who contributed to this study. This study was sponsored by Arvinas Estrogen Receptor, Inc, in collaboration with Pfizer, Inc. Medical writing support was provided by Lela Creutz, PhD of Arvinas Operations, Inc.

Contact: Seth Wander; SWANDER@mgh.harvard.edu