Poster #2606

A liquid biopsy assay of estrogen receptor activity predicts response to giredestrant in ER+/HER2− advanced breast cancer

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BACKGROUND

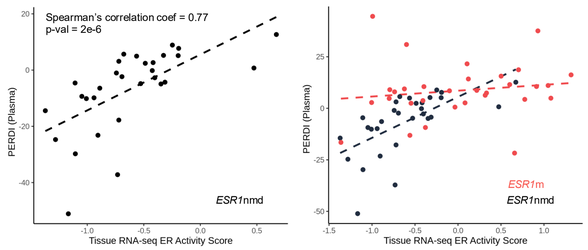
Endocrine resistance limits benefit durability in ER+/HER2- advanced breast cancer (aBC), particularly after CDK4/6 inhibition[1]. Prior studies have shown that tumor mRNA-based estrogen receptor (ER) activity predicts response to the oral SERD giredestrant and serves as a pharmacodynamic (PD) biomarker of ER pathway suppression[2,3,4]. However, tumor profiling requires serial biopsies which are often challenging in aBC. The Precede ER Dependence Index (PERDI) quantifies ER-driven cis-regulatory enhancer activity from circulating chromatin, enabling noninvasive monitoring of ER pathway dependence and treatment response.

METHODS

One milliliter of plasma from 94 ER+/HER2- aBC pre-treatment (tx) and 25 on-tx (giredestrant ± CDK4/6i ± atezolizumab) samples was profiled using Precede's comprehensive epigenomic liquid biopsy assay. PERDI scores were evaluable for 85 pre-tx and 19 on-tx samples. Baseline *ESR1* mutation (m) status was determined using the FoundationOne® Liquid CDx assay. PERDI concordance was assessed against tissue ER activity[3] from matched RNA-seq. Clinical response analyses were performed on patients treated with giredestrant ± CDKi ± atezolizumab. Plasma-based gene expression was inferred using Precede's gene expression prediction models that integrate enhancer, promoter and DNA methylation features.

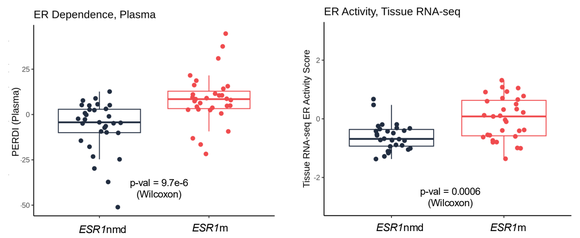
RESULTS

PERDI recapitulates tumor ER biology in plasma of ER+ aBC



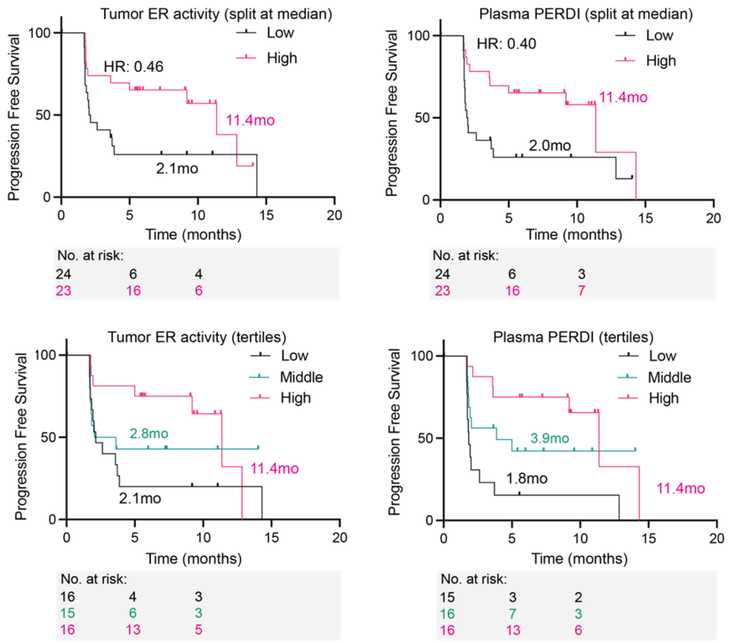
The Precede ER Dependent Index (PERDI) was validated against tissue-based RNA-seq to determine its accuracy in reflecting tumor ER signaling. In samples with no detectable *ESR1* mutation (*ESR1*nmd; left) and ctDNA fraction greater than 2%, plasma-based PERDI showed a strong positive correlation with tissue-based ER activity scores. The correlation between plasma and tissue metrics is notably more robust in the *ESR1*nmd population compared to the *ESR1*m (right, red).

Higher plasma PERDI is associated with *ESR1*m tumors



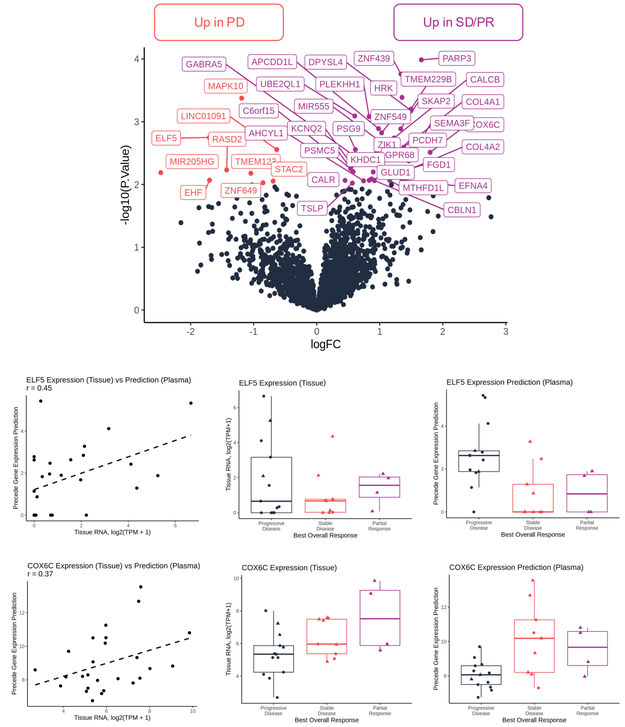
Baseline plasma-based PERDI scores (left) and ER activity scores derived from tissue RNA-seq (right) were compared across *ESR1* genotypes. Similar to tumor-based ER activity scores, PERDI consistently scored samples from patients with *ESR1*m disease significantly higher than those with no mutation detected. Significance was determined using the Wilcoxon rank-sum test.

Baseline plasma PERDI levels are associated with response to giredestrant



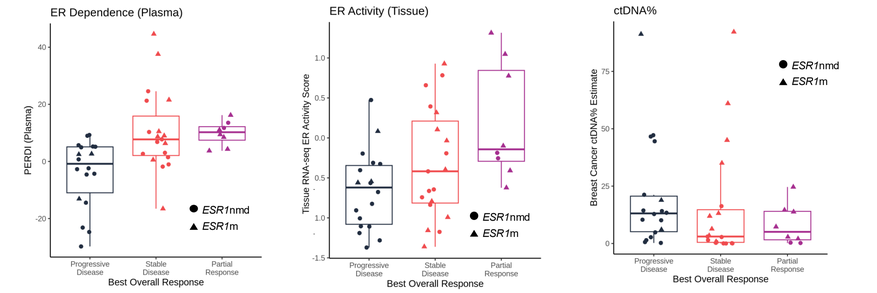
Progression free survival (PFS) was analyzed in patients with ER+/HER2- aBC (both *ESR1*m and *ESR*1nmd) who progressed on a CDK4/6i before receiving giredestrant alone or with a CDKi (either ribociclib, abemaciclib, or samuraciclib) ± atezolizumab. A median split of plasma-based PERDI (top right; HR=0.43; CI: 0.20-0.93) demonstrated association with PFS comparable to tissue-based tumor ER activity (top left). Patients in the PERDI-high group achieved a median PFS of 11.4 months, compared to only 2.0 months in the PERDI-low group. The association with PFS was further enhanced when comparing the top vs. bottom PERDI tertiles (bottom right, HR=0.19l; CI: 0.07–0.52).

Plasma-predicted expression scores reflect tumor biology driving ER+/HER2- aBC and associated with giredestrant response



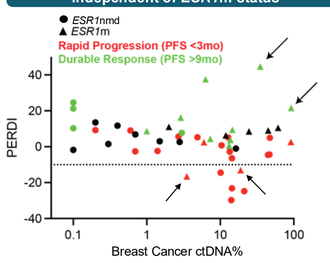
Expression predictions for >2000 disease-defining genes were generated using Precede's breast cancer specific gene expression models. Differential expression analysis was performed to identify specific biological pathways associated with clinical benefit, as defined by RECIST 1.1-evaluated Best Overall Response (BOR). A volcano plot (top) illustrates genes significantly upregulated in responders (purple; defined as Stable Disease [SD] or Partial Response [PR]) vs non-responders (orange; defined as Progressive Disease [PD]). *ELF5* expression, a known marker of ER independence, was found to be significantly higher in patients with progressive disease in both tissue RNA-seq and plasma-based predictions (middle). Plasma *ELF5* levels anti-correlated with overall outcome and ER dependence. Conversely, *COX6C*, a marker of ER dependency, showed enriched expression in responders.

Baseline plasma PERDI levels are associated with response to giredestrant



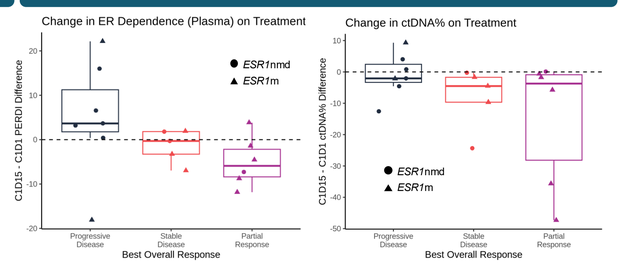
Samples evaluated in this cohort were obtained from patients with ER+/HER2- aBC following progression on a CDK4/6i. Patients were subsequently treated with giredestrant monotherapy or in combination with a CDKi (either ribociclib, abemaciclib, or samuraciclib) ± atezolizumab. PERDI scores (left) effectively distinguished between RECIST 1.1-evaluated clinical response groups at baseline, with patients exhibiting progressive disease showing the lowest scores and those with partial responses showing the highest. While PERDI showed a clear positive correlation clinical response, baseline tissue-based ER activity (middle) and plasma ctDNA levels (right) were less discriminative. Data points are stratified by *ESR1* mutation status (circles=negative, triangles=positive), demonstrating the predictive utility of PERDI across different genomic backgrounds.

Plasma PERDI resolves giredestrant response independent of *ESR1*m status



High ctDNA and low PERDI levels correlated with rapid disease progression (PFS <3 months; red markers). High PERDI scores predicted durable clinical benefit (PFS >9 months) even in patients with high ctDNA tumor fraction (green triangles denoted with arrows), suggesting PERDI captures biological sensitivity that ctDNA alone does not. PERDI effectively flagged rapid progression events, even in patients with *ESR1*m disease (red triangles denoted with arrows).

On-treatment plasma PERDI dynamics associate with giredestrant response



The delta in plasma PERDI scores was calculated between Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15) following treatment with giredestrant ± CDK4/6i ± atezolizumab. Negative values indicate a decrease in ER activity following treatment; dashed line plotted at 0 change for reference. Patients achieving a RECIST 1.1-evaluated partial response (right, in purple) exhibited the highest baseline PERDI scores, which were consistently repressed by C1D15. Conversely, progressors typically had low baseline PERDI scores that remained unsuppressed or even increased after treatment.

CONCLUSIONS

Non-invasive surrogate: Plasma PERDI reflects tumor ER biology in ER+/HER2-aBC. High baseline PERDI identified patients most likely to benefit from giredestrant-based therapy, including those with *ESR1*nmd disease.

Refined patient stratification: Plasma PERDI offers critical prognostic value independent of genotype and ctDNA burden, distinguishing endocrine-sensitive *ESR1*m disease and identifying patients capable of durable responses even in high-burden disease.

Functional readout: Early on-treatment PERDI suppression serves as a non-invasive pharmacodynamic marker of giredestrant response, while the broader platform has the potential to resolve specific transcriptional drivers of resistance.

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References:

1. Zhou et al. (2023) Front. Cell Dev. Biol., **11,** Article 148792
2. Collier et al. (2026) Nat Comm (in press), https://doi.org/10.1038/s41467-026-70335-0
3. Liang et al. (2026) Nat Comm (in press)
4. Guan et al. (2019) Cell, **178**:949-963.

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