Caris CapeAI, An Artificial Intelligence Model of ER+ Breast Cancer Response to Capecitabine

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GEICAM spanish breast cancer group

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ESMO 2026

CARIS LIFE SCIENCES

[1]Disclosures: personal fees for advisory board participation, invited speaker activities, and writing engagements from AstraZeneca, Guardant Health, Lilly, Menarini-Stemline, MSD, Novartis, Pfizer, Pierre Fabre, and Roche. Institutional research grants from AstraZeneca and Roche. Principal investigator for studies sponsored by AstraZeneca, Gilead, Pfizer, and Roche.

INTRODUCTION

- Estrogen receptor-positive (ER+) breast cancer (BC) accounts for ~70-80% of all BC cases with many patients developing therapy resistance and metastatic disease.
- Capecitabine has long-remained a chemotherapy-backbone for hormone therapy-refractory metastatic BC (MBC)[1].
- However, response to capecitabine is highly heterogeneous with some patients achieving durable response and others showing eventual disease progression despite presenting with similar clinical disease[2,3].
- This variability highlights the lack of clinically-implementable predictive biomarkers for the efficacy of conventional chemotherapeutics, including capecitabine[4,5].
- Accurate and robust identification of patients who would derive the most therapeutic benefit from capecitabine while sparing the potential non-responders from unwarranted toxicity is crucial to improve patient outcome and quality of life.

OBJECTIVE

To develop and evaluate the potential of a novel machine learning approach, Caris® CapeAI, to model the response of patients with metastatic ER+ breast cancer to capecitabine therapy by molecular feature capture, and to support the clinical use of AI models to characterize patient prognosis and to potentially guide therapy selection

MATERIALS & METHODS

Clinical cohorts:

1) ***Caris Life Sciences real-world clinical dataset***: 885 ER+/- BC primary (41%), metastatic (57%), and local recurrence (2%) samples treated with capecitabine, with available whole-exome and whole-transcriptome sequencing (WTS) data.
   - *Feature selection and model training cohort*: N=619 (70%)
   - *Testing/validation cohort*: N=266 (30%)
2) ***PEARL clinical trial dataset***: An independent external validation cohort of 141 ER+/HER2− primary (82%) and metastatic (18%) BC samples from 140 capecitabine control arm patients of the GEICAM/2013-02 phase III trial; 59 patients (80% primary; 20% metastatic) met the quality threshold cutoffs: DNA - >300x coverage depth; RNA-seq - > 3 million total mapped reads

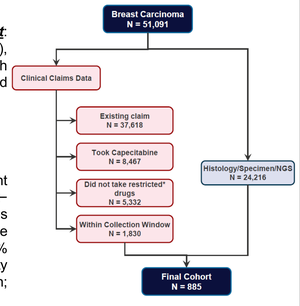

Figure 1. Caris® CapeAI patient cohort filtration

*olaparib, talazoparib, herceptin, trastuzumab, tucatinib, pertuzumab, neratinib, gemcitabine, irinotecan, bortezomib, bicalutamide, durvalumab, and enzalutamide.

Prediction model development and evaluation:

- Caris® CapeAI was developed using nested cross-validation and ensemble learning, implemented with Light Gradient Boosting Methods (LightGBM) in a regression framework.
- Molecular marker identification and characterization was performed via whole-exome and WTS, from the Caris MI Tumor Seek Hybrid™ assay in the Caris clinicogenomic database.
- The model was trained to map patient outcomes using time-to-next-treatment (TTNT) and overall survival (OS) as primary endpoints in the Caris cohort and externally validated in the PEARL cohort.

RESULTS

Table 1. Caris BC Cohort demographics

CapeAI BC Cohort (N = 885)	ER- (N=419)	ER+ (N=466)
Median Age (range) [n]	62 (23 – 90+)	59 (24 – 90+)
Male	1 (0.2%)	7 (1.5%)
Female	418 (99.8%)	459 (98.5%)
White	198 (61.3%)	287 (74.5%)
African American	90 (27.9%)	52 (13.5%)
Asian/Pacific Islander	13 (4.0%)	19 (4.9%)
Other	22 (6.8%)	27 (7.0%)
Hispanic/Latino	47 (14.5%)	33 (8.9%)
Not Hispanic/Latino	278 (85.5%)	337 (91.1%)

Table 1. Demographic data of the Caris BC cohort, stratified by ER status.

Table 2: Top 20 model features in Caris BC cohort

Gene	Feature Type	Gene	Feature Type
MAP7	Expression	*PLS1*	Copy Number
NOC2L	Expression	*TBL2*	Expression
CYYR1	Copy Number	*PTDSS1*	Expression
ZNF506	Copy Number	*CGB7*	Copy Number
BRD7	Copy Number	*C1orf226*	Copy Number
CPNE4	Copy Number	*PAPD5*	Copy Number
LPCAT3	Copy Number	*TOMM40L*	Expression
FBL	Copy Number	*CNTN4*	Copy Number
TSKU	Expression	*FLRT1*	Copy Number
NEK11	Copy Number	*ZNF682*	Copy Number

Table 2. Top 20 molecular features extracted from the Caris BC cohort. 9,370 molecular features were examined in the Caris® BC database and the top 100 features were extracted and used for model training. *Of the top 100 features, only the top 20 are shown here.*

Figure 2. Capecitabine response prediction using CapeAI in the Caris ER+ BC cohort

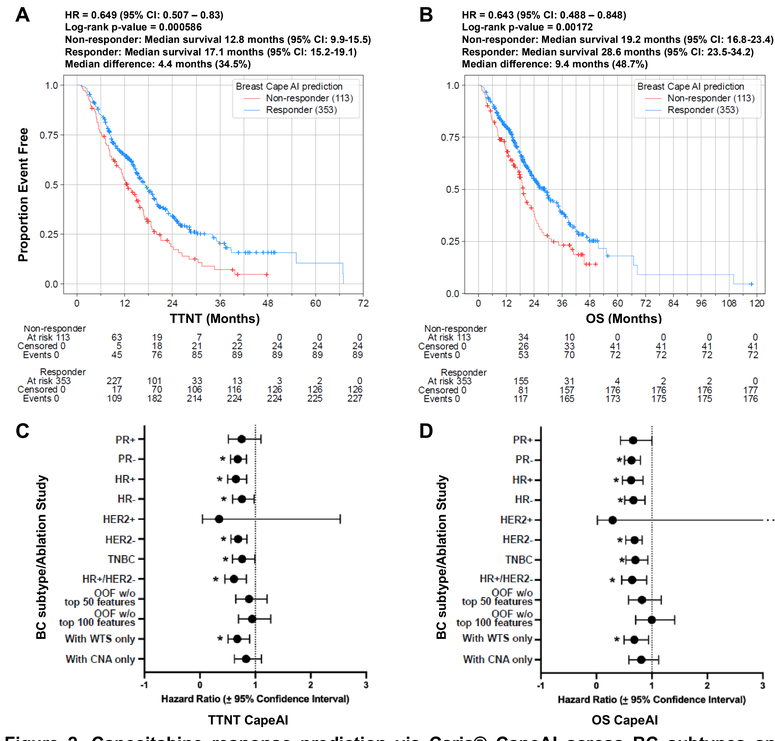

Figure 2. Capecitabine response prediction via Caris® CapeAI across BC subtypes and ablation studies in the Caris ER+ BC cohort. Caris® CapeAI model performance of predicted non-responders (n = 113, red) and predicted responders (n = 353, blue) by time to next treatment (TTNT) (**A**) and overall survival (OS) (**B**) in ER+ BC. CapeAI model performance was also examined in predicted non-responders vs. responders by other BC subtypes (PR+, HR+, HER2+, TNBC, HR+/HER2-) and model ablation studies. Data are presented as TTNT (**C**) or OS (**D**) by HR + 95% CI. Significance shown as * p < 0.05. OOF: Out-of-Fold; CNA: Copy number alteration

Figure 3. Capecitabine response prediction using CapeAI in the PEARL ER+/HER2- BC cohort

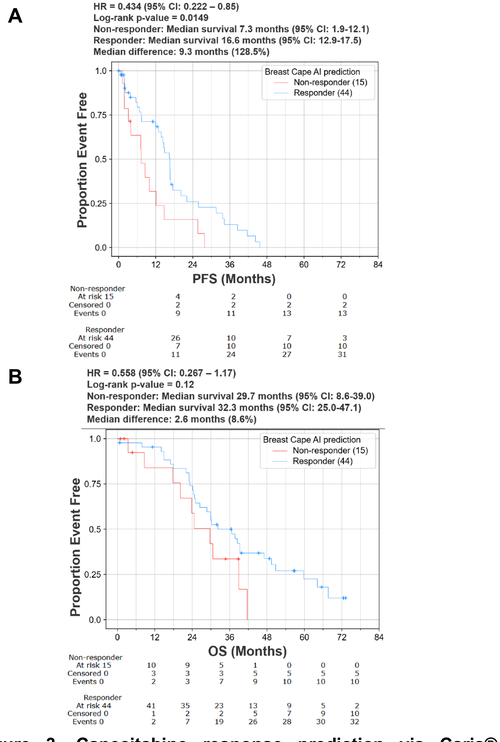

Figure 3. Capecitabine response prediction via Caris® CapeAI in PEARL ER+/HER2- BC cohort. PEARL trial patient data meeting quantity/quality standards were analyzed for progression-free survival (PFS) (**A**) and OS (**B**) by CapeAI predicted non-responder vs. responder. Predicted responders showed significantly longer PFS, but not OS, than non-responders. log-rank p-value, p<0.05 considered significant.

CONCLUSIONS AND SIGNIFICANCE

- Leveraging a deep clinicogenomic database in conjunction with whole transcriptome, whole exome, and hybrid NGS approaches, our CapeAI model provides capecitabine outcome stratification in ER+ BC patients.
- In ER+ BC, CapeAI-predicted responders showed clinically meaningful improvements in survival and showed consistent performance in an independent PEARL clinical trial cohort, supporting the potential utility of AI-models in guiding capecitabine use in ER+ BC.
- While precision oncology has transformed the clinical use of targeted agents, chemotherapeutic agents remain largely excluded from this shift, a key clinical gap our study directly addresses.

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ACKNOWLEDGMENTS

We thank all patients and their families for their participation in this study. We also acknowledge the contributions of all investigators and study support staff at the participating sites, as well as the teams at GEICAM and Caris Life Sciences.

This trial was sponsored by the GEICAM Spanish Breast Cancer Group, with support from Pfizer Inc. and AstraZeneca, which provided fulvestrant.

This work was supported by Caris Life Sciences.