#982 Machine Learning predicts early tumor progression in Hormone Receptor-positive, Human Epidermal growth factor Receptor 2-negative(HR+/HER2-) advanced breast cancer (aBC) patients treated with first-line endocrine therapy (ET) plus Cyclin Dependent Kinase 4/6 inhibitors (CDK4/6i).

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BACKGROUND

- CDK4/6i combined with ET reshaped the first-line treatment paradigm for HR+/HER2- advanced Breast Cancer (aBC).
- **Early progression** (tumor progression within 6 months from treatment initiation) occurred in 20-30% of cases in pivotal trial, and remains a major clinical challenge.
- Precociously identifying early progressors may lead to the use of alternative, potentially effective, treatments.
- **Machine learning and deep learning** (ML/DL) demonstrated significant capability in the use of clinical data predict clinical outcomes in oncology.

The aim of this study is to investigate the impact of early tumor progression (i.e., PFS <6 months) on survival outcomes, and to leverage the use of ML/DL to build a model to predict the individual risk of early progression.

METHODS

- Dataset: **PALMARES-2** (NCT06805812), multicenter, retrospective-prospective, observational Italian study enrolling HR+/HER2- aBC patients treated with 1L ET+CDK4/6i; 4337 patients enrolled at the 2nd study data cut-off (Jan 2025).
- Objectives: to **characterize early progressor patients** (PFS <6 months) in terms of clinical and biological characteristics, treatment patterns and survival outcomes; to **build a ML/DL model** to predict the risk of early tumor progression using baseline features.
- Statistical methods: chi-square and Wilcoxon rank sum test to test distributions across groups; univariable Cox regression model to test the impact of early progression on real-world time to chemotherapy (rwTTC) and overall survival (rwOS).
- Model input: **106 clinical and pathological real-world data** (RWD), **15 laboratory** (LAB) variables. Missing data imputed through bagged tree-based method; undersampling and SMOTE oversampling applied to address class imbalance; feature selected based on filters (missing >30%, near-zero variance) and MRMR algorithm, then normalized (min-max).
- ML/DL models: 6 ML architectures, i.e. **logistic regression** with elastic net penalisation (glmnet), **random forest** (RF), **XGBoost** (XGB), **averaged neural network** (avNNet), **multilayer perceptron** (MLP) and **tabular foundation model** (tabPFN) were trained to predict the risk of early progression, using real-world data (RWD) and the combination of RWD and laboratory (LAB) features with **early fusion** (concatenation) and **late fusion** (stacking) as model input. Best hyperparameters were selected based on 10-fold cross-validatio results. Model performances were evaluated on a test set (20% of the overall population) and on an independent cohort of patients from Istituto Nazionale dei Tumori, Milan. SHAP values were computed for model explainability and then plotted.

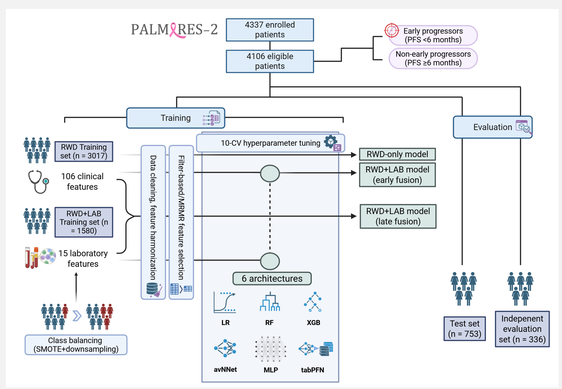


Figure 1. *Study workflow.*

RESULTS

Characteristic	Overall N = 4,106	Non-early progressors N = 3,584	Early progressors N = 522	p-value
Age	62 (53, 71)	62 (53, 71)	61 (53, 71)	0.6
Sex				0.6
Man	49 (1.2%)	44 (1.2%)	5 (1.0%)	
Woman	4,057 (99%)	3,540 (99%)	517 (99%)	
Histology				0.5
CLI	757 (19%)	657 (19%)	100 (19%)	
NST	2,996 (74%)	2,607 (74%)	389 (75%)	
Other	301 (7.4%)	269 (7.6%)	32 (6.1%)	
ER expression (%)	90 (85, 95)	90 (85, 95)	90 (80, 95)	<0.001
PgR expression (%)	40 (5, 80)	50 (5, 80)	20 (0, 70)	<0.001
Ki67 expression (%)	20 (15, 30)	20 (15, 30)	25 (15, 40)	<0.001
HER2 status				0.7
0	1,721 (43%)	1,506 (44%)	215 (43%)	
Low	2,244 (57%)	1,956 (56%)	288 (57%)	
Disease presentation				<0.001
De novo metastatic	1,363 (33%)	1,257 (35%)	106 (20%)	
Endocrine Resistant	1,349 (33%)	1,062 (30%)	287 (55%)	
Endocrine Sensitive	1,394 (34%)	1,265 (35%)	129 (25%)	
ECOG PS				<0.001
0	2,988 (77%)	2,661 (78%)	327 (67%)	
1	769 (20%)	637 (19%)	132 (27%)	
≥2	134 (3%)	104 (3%)	30 (6%)	
Menopausal status				0.4
Postmenopausal	3,347 (82%)	2,914 (81%)	433 (83%)	
Premenopausal	759 (18%)	670 (19%)	89 (17%)	
Liver Metastasis	869 (21%)	653 (18%)	216 (41%)	<0.001
Bone Metastasis	2,868 (70%)	2,493 (70%)	375 (72%)	0.3

Table 1*. Patient baseline characteristics by early tumor progression.*

Early progressors characteristics and survival outcomes

- Among 4106 evaluable pts, 522 (12.7%) experienced early tumor progression.
- Early progressors were more likely to have lower tumor estrogen receptor (ER) and progesterone receptor (PgR) expression, higher Ki67 expression, endocrine-resistant disease, worse ECOG PS and liver metastases (P <0.001, **Table 1**).
- Early progressors had significantly worse rwTTC (median 5.3 vs 43.3 months, P <0.001) and rwOS (median 21.4 vs 73.0 months, P <0.001) when compared to pts who did not experience early progression.
- 16.5% of early progressors did not receive any subsequent treatment due to rapid clinical deterioration or patient death, compared to 8.3% of non-early progressors.

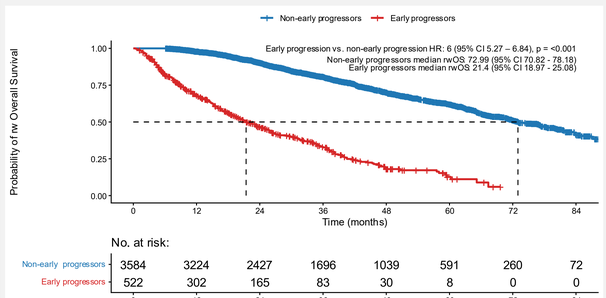


Figure 2. *Kaplan-Meier curve showing the impact of early progression on OS. HR resulted from univariable Cox regression model is showed in the Figure.*

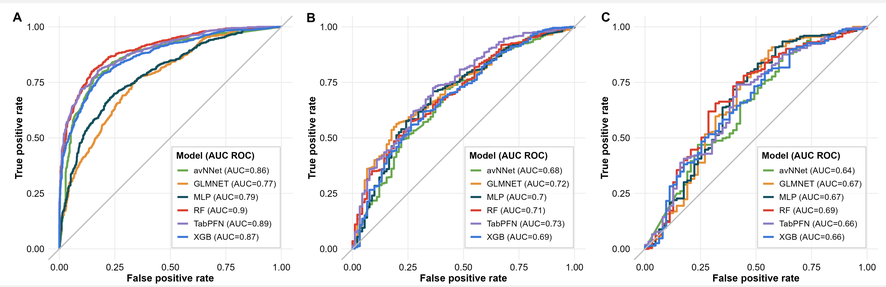


Figure 3. *ROC curves of the 6 ML/DL models across training (cross-validation; A), test (B) and independent validation cohort (C).*

Model development

- Model performances in terms of balanced accuracy, sensitivity and specificity on training (cross-validation), test and independent validation are reported in **Table 2**, while the receiver operating characteristic (ROC) curves with the corresponding area under the curves (AUCs) are shown in **Figure 3**. All models achieved consistent performances, with balanced accuracies ranging between 0.59 and 0.68 on test set and between 0.57 and 0.66 on independent validation set.
- The addition of laboratory values as model input did not improve model performances (**Table 2**).

Model	Input data	Balanced Accuracy	Balanced Accuracy	Balanced Accuracy
		Training set	Test set	Independent validation
LR	RWD	0,71	0,66	0,64
RF	RWD	0,82	0,65	0,59
XGB	RWD	0,79	0,62	0,6
avNNet	RWD	0,8	0,62	0,6
MLP	RWD	0,68	0,62	0,59
TabPFN	RWD	0,81	0,64	0,61
LR	RWD+LAB (early fusion)	0,77	0,62	0,66
RF	RWD+LAB (early fusion)	0,84	0,61	0,6
XGB	RWD+LAB (early fusion)	0,81	0,59	0,57
avNNet	RWD+LAB (early fusion)	0,84	0,63	0,57
MLP	RWD+LAB (early fusion)	0,67	0,62	0,59
TabPFN	RWD+LAB (early fusion)	0,81	0,61	0,62
LR	RWD+LAB (late fusion)	0,73	0,64	0,65
RF	RWD+LAB (late fusion)	0,84	0,63	0,57
XGB	RWD+LAB (late fusion)	0,48	0,62	0,59
avNNet	RWD+LAB (late fusion)	0,82	0,61	0,59
MLP	RWD+LAB (late fusion)	0,71	0,63	0,59
TabPFN	RWD+LAB (late fusion)	0,79	0,68	0,6

Table 2*. Model results of the 6 ML/DL architectures using RWD, RWD and LAB features with early modality fusion and RWD and LAB features with late modality fusion across training, test end independent validation cohorts.*

Figure 4. *rwPFS curves showing in the subgroups of patients categorized based on quartiles prediction in CV training set (A) and in the early vs. non-early progressors defined based on the fourth quartile in test (B).*

Model calibration and explainability

- Model-derived probabilities in the training set were stratified into quartiles, and survival outcomes across these risk groups were compared, confirming the model's ability to identify groups of patients with markedly different outcomes (**Figure 4A**); patients in the highest risk quartile exhibited especially poor prognosis, as confirmed in the test set (6-months PFS rate: 25 vs. 9.4%; **Figure 4B**).
- Endocrine-resistant disease, presence of liver metastases and tumor ER and PgR expression were among the most influencing features of the best model (glmnet trained on RWD; **Figure 5**).
- Early progressors obtained higher model risk scores, demonstrating good model calibration (**Figure 6**).

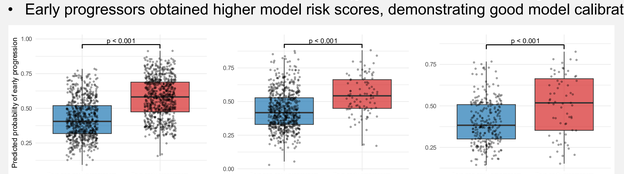


Figure 6. *Distribution of model predictions on CV training (A), test (B) and independent validation set (C) among true early vs. non-early progressors*

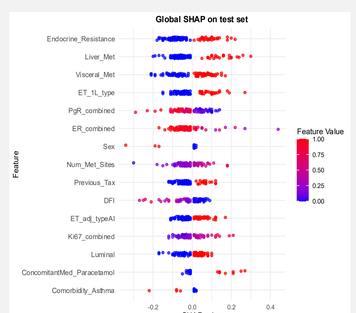


Figure 5. *Global explainability SHAP plot. Each dot corresponds to one patient. The x-axis indicates whether the feature increases (right) or decreases (left) the predicted risk; color represents the magnitude of the feature value.*

Early tumor progression is associated with remarkably lower OS and higher attrition rate after first-line treatment. We developed the first, explainable ML model to predict the individual risk of early progression in HR+/HER2- aBC patients treated with first-line ET+CDK4/6i. If prospectively validated, this model could serve as a tool to identify candidate for treatment escalation.

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DISCLOSURES: Invited speaker for Novartis, Pfizer, MSD.

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