A NATALEE data–based machine learning model to predict distant recurrence and treatment effect in real-world patients with HR+/HER2– early breast cancer without CDK4/6 inhibitor treatment

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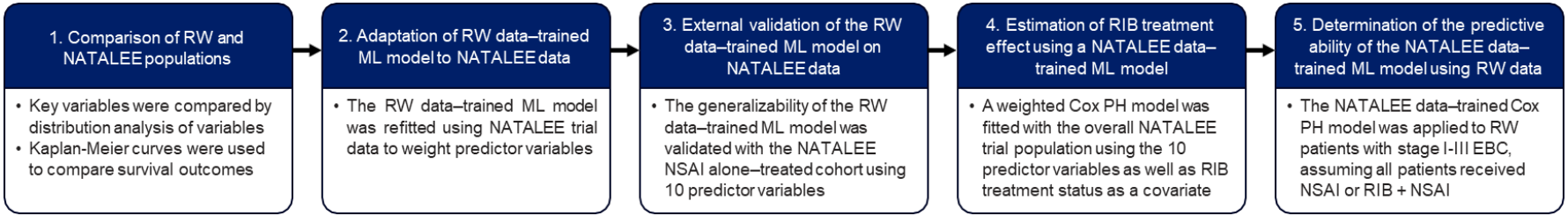
Introduction

- Despite standard-of-care adjuvant endocrine therapy (ET), many patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) early breast cancer (EBC) still experience distant recurrence (DR)[1-3]
- The phase 3 NATALEE trial demonstrated a statistically significant invasive disease-free survival benefit with ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) vs NSAI alone in patients with high-risk HR+/HER2− EBC,[3] with a sustained benefit after all patients were off RIB (HR, 0.72; 95% CI: 0.61-0.84; P<.0001)[4]
- We previously trained a machine learning (ML) model on real-world (RW) data that was able to accurately predict DR risk (concordance index [C-index], 0.86; integrated Brier score [IBS], 0.05)[5]
- This study aimed to externally validate this model using NATALEE data and assess whether RIB treatment effect can be predicted in an RW cohort of patients with HR+/HER2− EBC

Methods (1 of 2)

- Previously, an elastic net–penalized Cox proportional hazards (PH) model was trained with data from RW patients aged ≥18 years in the US-based, electronic health record–derived deidentified Flatiron Health Research Database6 with stage I-III HR+/HER2− EBC who had undergone surgery and initiated adjuvant ET, but not cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) treatment (1 January 2011 to 30 April 2024)[5]
- To validate and extend the ML model, the current analysis was conducted in 5 steps (**Figure 1**), using NATALEE trial data (data cutoff: 29 April 2024)

Figure 1. Study design



EBC, early breast cancer; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor positive; ML, machine learning; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; RW, real world.

Methods (2 of 2)

- The Harrell C-index (0.5-1.0; 1.0 = perfect concordance) and IBS (0-0.25; 0 = perfect concordance) were used to compare predicted vs actual outcomes for each model; *P* values were determined by Wald test and are reported at the α=0.05 level

IBS, integrated brier score.

Results (1 of 8)

Characteristics and DR in the RW and NATALEE NSAI alone populations

- A total of 7842 RW patients with stage I-III HR+/HER2– EBC who initiated adjuvant ET but not CDK4/6i treatment in the Flatiron Health database were eligible according to the inclusion and exclusion criteria[5]
  - Given that the NATALEE trial does not include patients with stage I EBC, only RW patients with stage II/III disease were included in analysis of cohort similarity
- Baseline characteristics in patients who received ET in the NATALEE NSAI alone treatment arm (n=2441)[4] were similar to those of the RW patients with stage II/III EBC (n=3276), except for age (median, 62 years in RW patients, 52 years in NATALEE NSAI patients; **Figure 2**)
- The percentage of patients free from DR at 48 months was 92.2% (382 DR events) in the RW cohort with stage II/III EBC and 87.3% (246 DR events) in the NATALEE NSAI alone arm cohort (**Figure 3**)

CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; DR, distant recurrence; EBC, early breast cancer; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor positive; NSAI, nonsteroidal aromatase inhibitor; RW, real world

Results (2 of 8)

Characteristics and DR in the RW and NATALEE NSAI alone populations

Figure 2. Characteristics of the RW population with stage II/III EBC and NSAI alone–treated NATALEE population

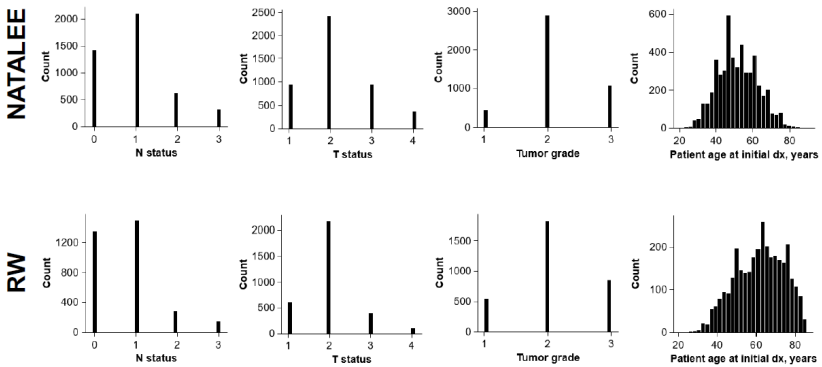
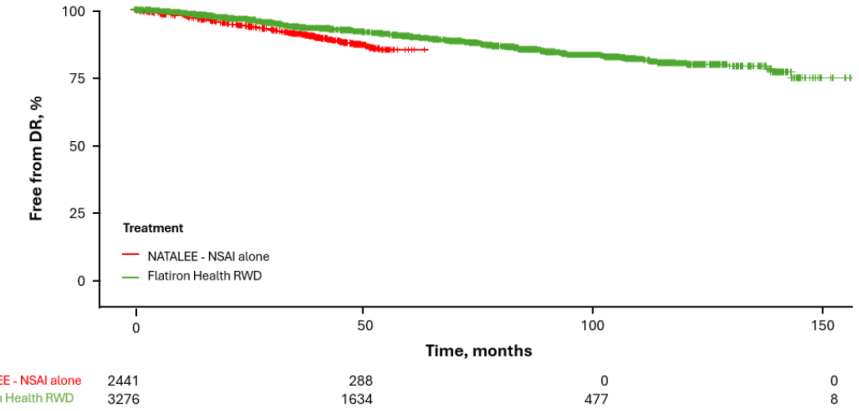


Figure 3. Percentage free from DR of the RW population with stage II/III EBC and NSAI alone–treated NATALEE population



NATALEE - NSAI alone	2441	288	0	0
Flatiron Health RWD	3276	1634	477	8

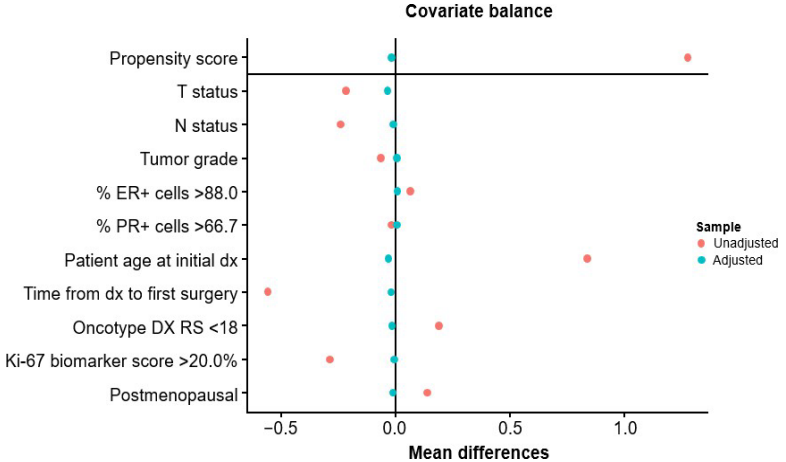
[a]Index date was at the start of adjuvant treatment for the RW population and at randomization for the population from the NATALEE trial (which allowed up to 12 months of prior ET at randomization).
DR, distant recurrence; dx, diagnosis; EBC, early breast cancer; N, nodal; NSAI, nonsteroidal aromatase inhibitor; RW, real world; RWD, real-world data; T, tumor.

Results (3 of 8)

External validation of the RW data–trained ML model on NATALEE data

- The ML model developed on data for RW patients with stage I-III EBC was retrained with weighting of the 10 predictor variables based on differences between the RW population with stage II/III EBC and overall NATALEE population (**Figure 4**)

Figure 4: Adjustment by weighting of predictor variables for population differences in the RW patients with stage II/III EBC vs the overall NATALEE cohort



DX, diagnosis; EBC, early breast cancer; ER, estrogen receptor; ML, machine learning; N, nodal; PR, progesterone receptor; RS, recurrence score; RW, real world; T, tumor.

Results (4 of 8)

External validation of the RW data–trained ML model on NATALEE data

- Post weighting, the ML model was externally validated on the NATALEE NSAI alone arm cohort, with lower but still discriminatory performance (C-index, 0.66; IBS, 0.06)
  - Sensitivity analyses yielded similar results with model training on only patients with stage II/III EBC in the RW cohort (C-index, 0.65; IBS, 0.06) or without variable weighting (C-index, 0.66; IBS, 0.06)

EBC, early breast cancer; IBS, integrated brier score; ML, machine learning; NSAI, nonsteroidal aromatase inhibitor; RW, real world.

Results (5 of 8)

Development of NATALEE data–trained ML models to predict DR risk to validate the modeling approach and to predict RIB treatment effect

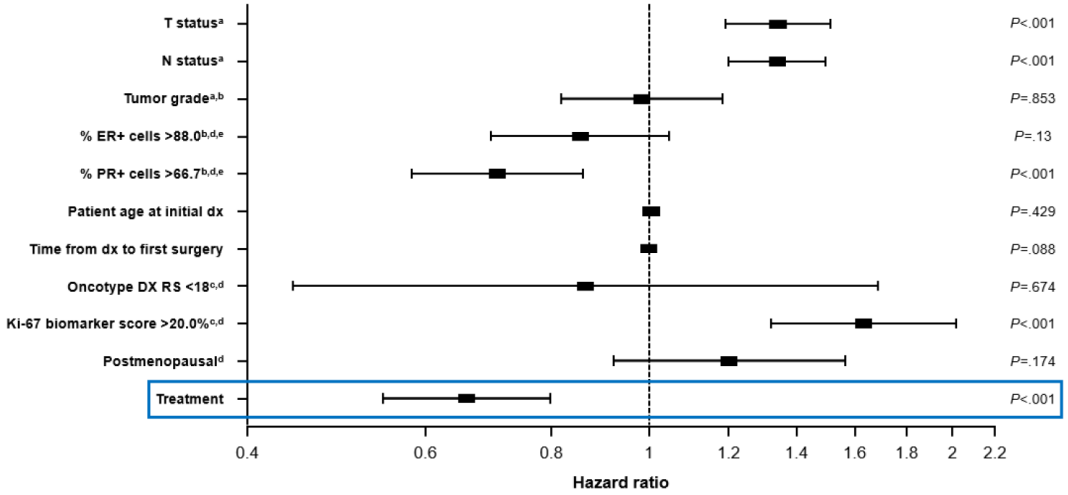
- To further validate this ML approach, another elastic net–penalized ML model developed with the same 10 predictor variables was trained on the NATALEE NSAI alone treatment arm, yielding a similar DR prediction accuracy (C-index, 0.70; IBS, 0.06)
- A weighted Cox PH model that included RIB treatment status as an additional 11th predictor variable trained on the overall NATALEE cohort also had a good predictive ability for DR risk (C-index, 0.68; IBS, 0.06)
  - The HRs for the contribution of the 10 variables used in previous model training indicated that the variables remained predictive (**Figure 5**), showing a similar direction and magnitude for each variable as in the original model[5]
- RIB treatment had an HR of 0.66 (95% CI: 0.55-0.80) in this model, representing a 34% reduction in relative DR risk with RIB + NSAI vs NSAI in the NATALEE cohort across the follow-up period (**Figure 5**)

DR, distant recurrence; HR, hormone receptor; IBS, integrated brier score; ML, machine learning; NSAI, nonsteroidal aromatase inhibitor; PH, proportional hazards; RIB, ribociclib.

Results (6 of 8)

Development of NATALEE data–trained ML models to predict DR risk to validate the modeling approach and to predict RIB treatment effect

Figure 5: Treatment effect of RIB on relative DR risk in the overall NATALEE trial population



Blue box: Treatment was included as an 11th predictor variable in model training. [a]Ordinal variable treated as continuous. Linear assumption supported by data. Hazard ratio indicates change with one step of variable (eg, N0 to N1). [b]Multivariate imputation by chained equations used to impute missing values. [c]Unknown/not documented category created when summarizing baseline variables with >30% missing data was excluded from model analyses. [d]Binary variable indicating condition that is met. Hazard ratio indicates change associated with meeting stated condition. [e]Cutoff associated with recurrence according to ML decision tree method.

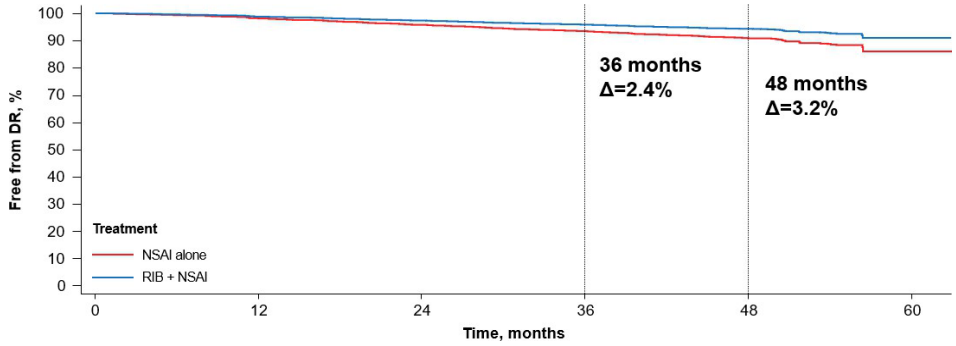
DR, distant recurrence; dx, diagnosis; ER, estrogen receptor; ML, machine learning; N, nodal; PR, progesterone receptor; RIB, ribociclib; RS, recurrence score; T, tumor.

Results (7 of 8)

NATALEE data–trained ML model application to RW cohort to predict the RIB treatment effect in an RW population

- Application of the weighted NATALEE data–trained ML model to the overall RW cohort (patients with stage I-III EBC and without CDK4/6i treatment) resulted in a predicted 2.4% reduction in absolute DR risk with RIB treatment at 36 months, and this reduction in absolute DR risk increased to 3.2% at 48 months (**Figure 6**)
  - Sensitivity analysis performed by training an unweighted Cox PH model on the NATALEE population produced a similar predicted reduction in absolute DR risk (36 months, 2.4%; 48 months, 3.2%)

Figure 6: Treatment effect of RIB on absolute DR risk in the RW population



Weighted NATALEE data–trained Cox PH model using the overall NATALEE population to predict absolute DR risk in an RW population, assuming all patients were treated with RIB + NSAI or NSAI alone.
CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; DR, distant recurrence; ML, machine learning; NSAI, nonsteroidal aromatase inhibitor; PH, proportional hazards; RIB, ribociclib; RW, real world.

Results (8 of 8)

Limitations

- Inherent RW data variability, as well as the use of a US-centric database, could lead to unexpected bias in model performance
- Potential differences in variables (definitions, missingness, etc) and in index date definition in RW and NATALEE populations should be noted
- These limitations could affect the accuracy of the NATALEE data– trained model when applied to the RW cohort, so the results should be interpreted with caution and further validated

RW, real world.

Key Findings and Conclusions

- This analysis validated an RW data–trained ML model[5] using NATALEE trial data to predict distant recurrence in RW patients with HR+/HER2– EBC
- Additionally, a NATALEE data–trained model was able to predict DR and RIB treatment effect in RW patients with HR+/HER2– EBC
- These findings support the use of both RW and clinical trial data in personalized prediction of DR risk and treatment benefit
- This approach can inform optimization of clinical decision-making in the HR+/HER2– EBC population
- Developing models with more extensive and diverse data and additional clinical and genomic variables may improve model performance and generalizability
- This NATALEE-trained ML model has the potential to estimate individual RW benefit from CDK4/6i treatment and guide treatment personalization for patients

CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; DR, distant recurrence; EBC, early breast cancer; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor positive; ML, machine learning; RIB, ribociclib; RW, real world.

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