

# A Multimodal-Multitask Deep Learning Model Trained in NSABP B-42 and Validated in TAILORx for Late Distant Recurrence Risk in HR+ Early Breast Cancer

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# Disclosure Information

## Eleftherios P. Mamounas, MD

- I have the following relevant financial relationships to disclose:
  - **Consultant for:** Merck, Genentech, Exact Sciences, Novartis, Astra Zeneca, Eli Lilly, GE Healthcare, Biotheranostics, Delphi Diagnostics
  - **Speaker's Bureau for:** Merck
  - **Honoraria from:** Novartis, Exact Sciences, Astra Zeneca
  - **Stockholder in:** Moderna

# The NSABP B-42 Trial

- Postmenopausal pts with ER+ or PR+ BC
- Stage I-IIIa at diagnosis
- Disease-free after 5 years of ET

AI or TAM → AI for 5 Years

## STRATIFICATION

Pathologic nodal status (-/+)  
Prior adjuvant TAM (Yes, No)  
Lowest BMD T score: (>-2.0, ≤-2.0 SD)

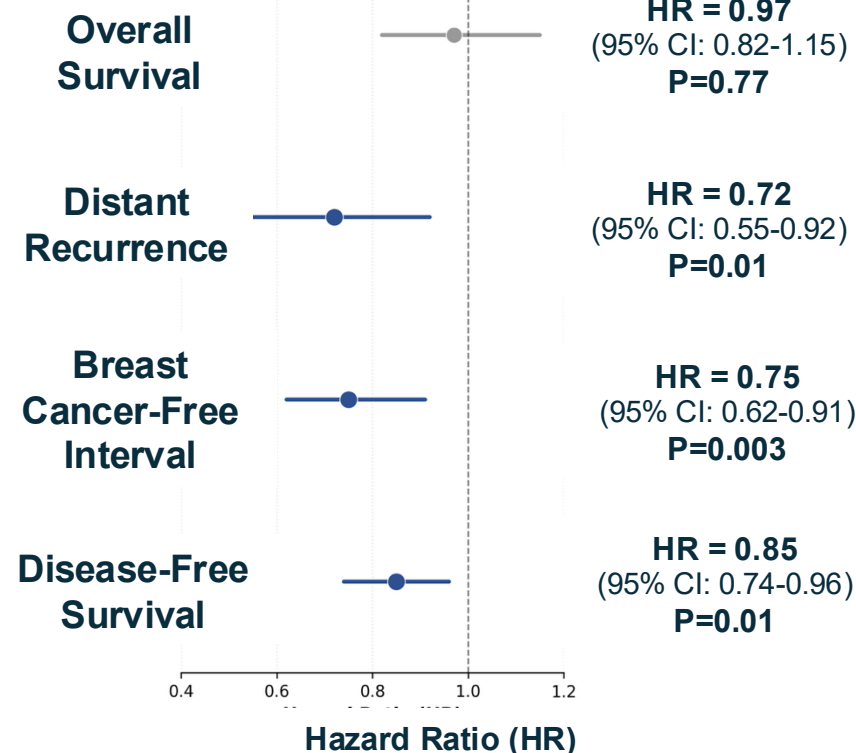
**R**

Letrozole x 5 yrs

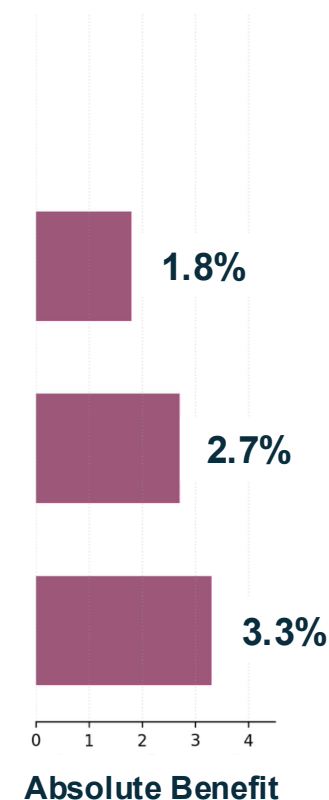
Placebo x 5 yrs

## 10-Year Results

### Extended Letrozole Therapy Efficacy Outcomes



### Absolute Benefit

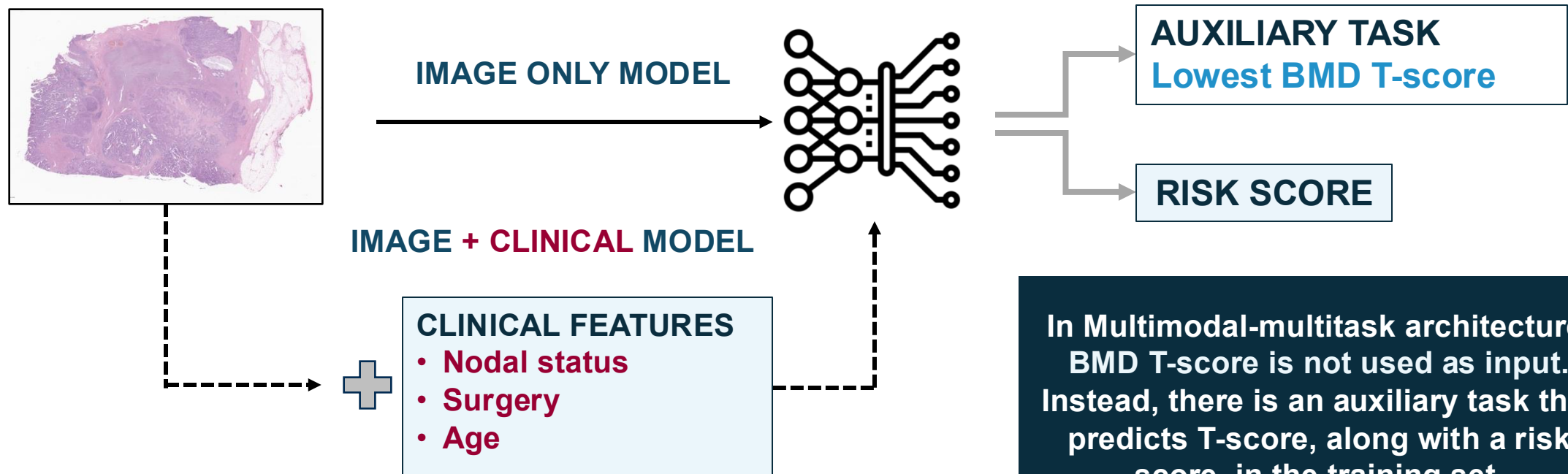


Favors ELT      Favors Placebo

# Image Only, Multimodal, and Multi-modal Multi-task (M3T) Models for Risk Prediction

B-42 Translational Cohort: **2271**

Training/Evaluation: **5-fold cross validation**



## MODEL INPUT

- Image only model input: H&E
- Multimodal model: H&E + clinical
- Multimodal-multitask (M3T) model: H&E + clinical as input and T-Score as additional target variable

In Multimodal-multitask architecture, BMD T-score is not used as input. Instead, there is an auxiliary task that predicts T-score, along with a risk score, in the training set.

T-score is not needed for test cases.

# Comparison of Model Prognostic Performance

Model	Low Risk 10-yr DR estimate (%)	High Risk 10-yr DR (%)	Absolute Difference (%)	HR (95% CI)	P value
Image only	2.72	8.5	5.79	3.419 (2.241–5.215)	<0.001
Multimodal	2.09	9.22	7.13	4.507 (2.863–7.096)	<0.001
Multimodal-multitask (M3T)	1.69	9.63	7.95	5.710 (3.500–9.317)	<0.001

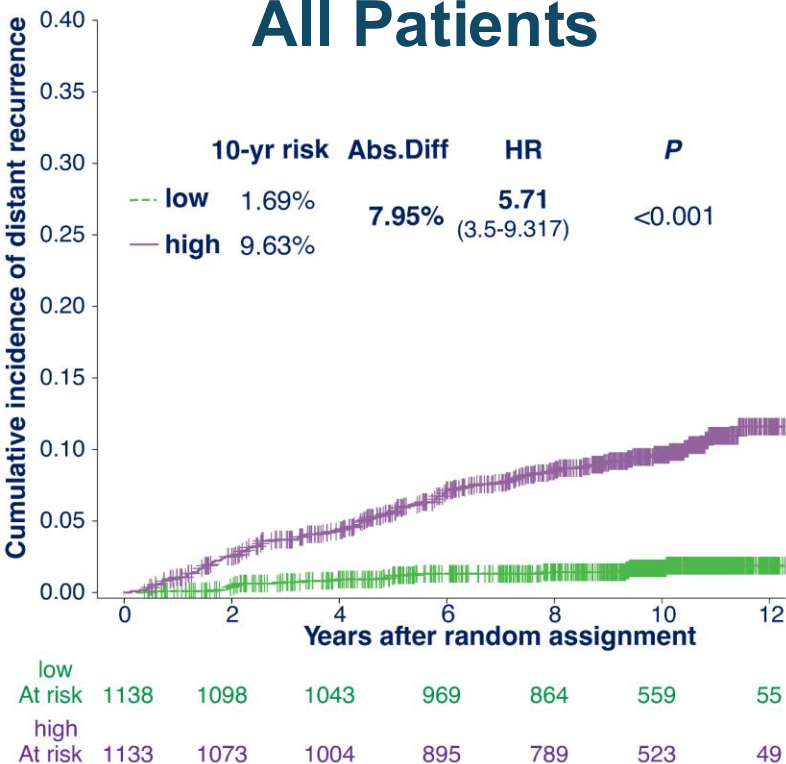
- **Multimodal-multitask model achieved the strongest risk discrimination (HR = 5.71, 95% CI 3.50–9.32), followed by the multimodal and image-only models.**
- The absolute risk difference between low- and high-risk groups increased from **5.8%** (image-only) to **7.1%** (multimodal) and **8.0%** (multimodal-multitask)
- **Similar patterns were observed within both the ELT and placebo groups.**



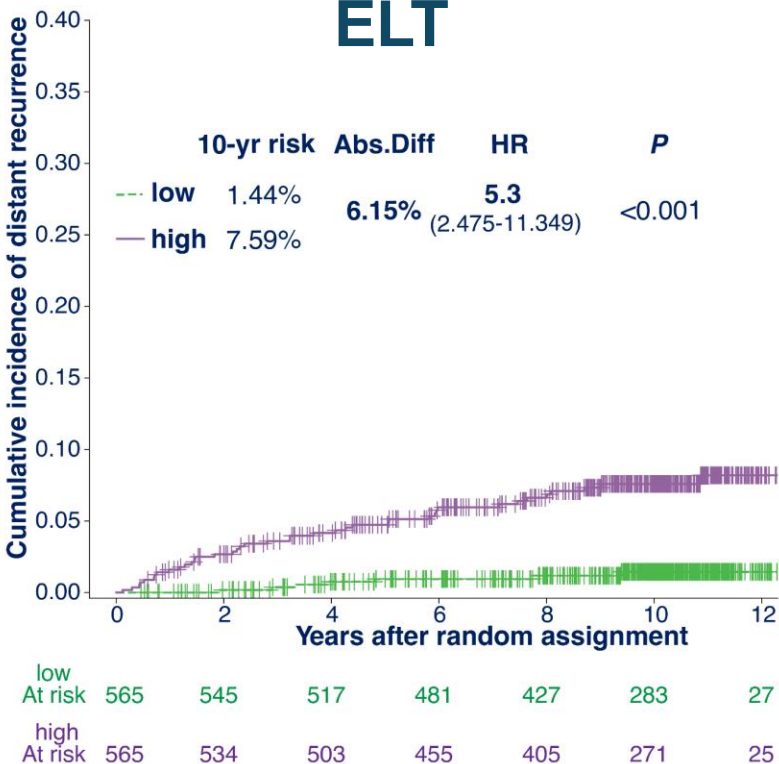
# M3T Model Shows Robust 10-Year Risk Stratification Independent of Treatment

## Multimodal-multitask Model (M3T)

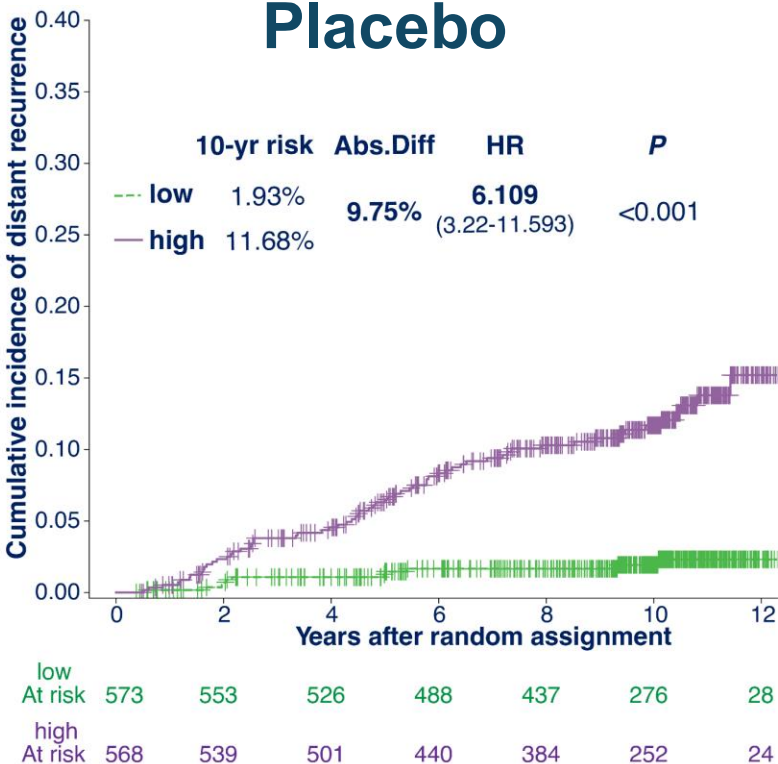
### All Patients



### ELT



### Placebo



The M3T model yielded a 10-year absolute risk difference of 7.95% between high and low-risk patients and shows strong prognostic performance independent of treatment.

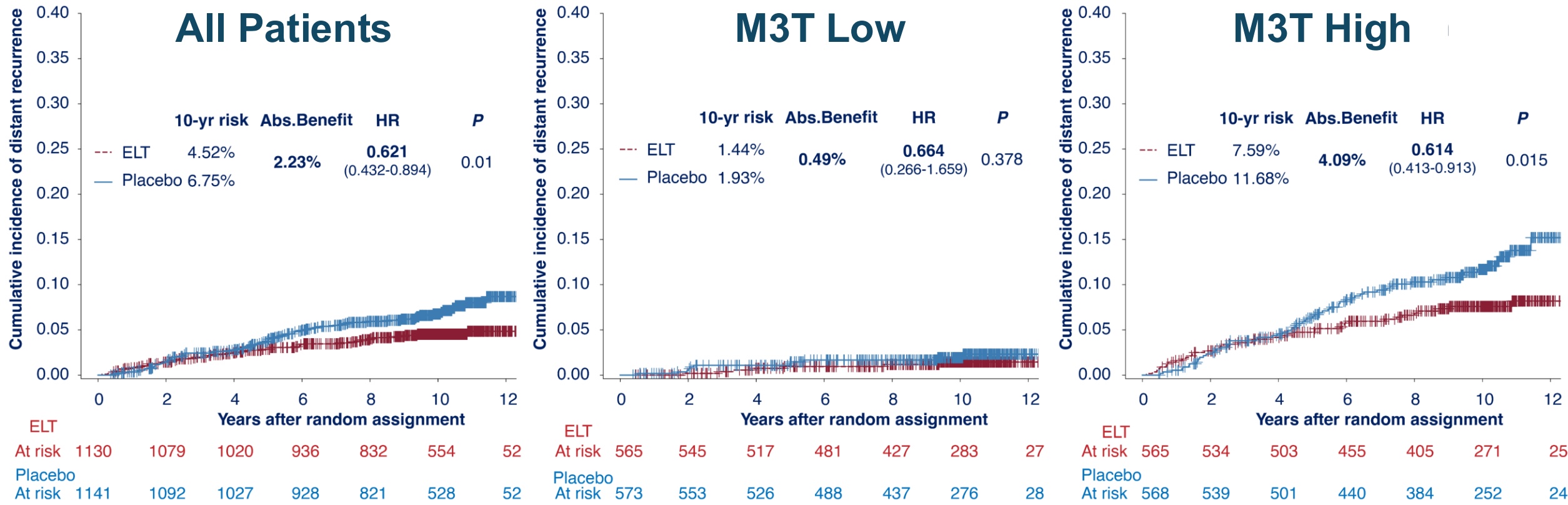
# Multivariable Cox Analysis for Image-only Model Risk Score

Covariate	Level	HR [95% CI]	P value
Treatment	Placebo	1	0.017
	ELT	<b>0.642</b> (0.446–0.923)	
Image-only	Low	1	<0.001
	High	<b>2.761</b> (1.799–4.238)	
Pathologic nodal status	Negative	1	<0.001
	Positive	<b>2.324</b> (1.573–3.435)	
Surgery type	Lumpectomy	1	<0.001
	Mastectomy	<b>2.146</b> (1.479–3.115)	

In multivariable Cox analysis adjusting for clinical features, risk label from the **Image-only model** remained an **independent prognostic factor**.

Additional multivariable Cox analysis using the **M3T-predicted risk label** showed an even **stronger prognostic effect (HR ≈ 3.58)**.

# M3T Model Suggests a Subgroup More Likely to Benefit from Extended Letrozole Therapy

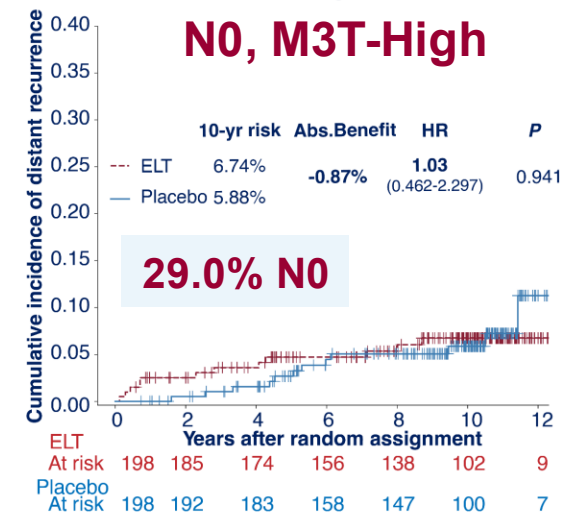
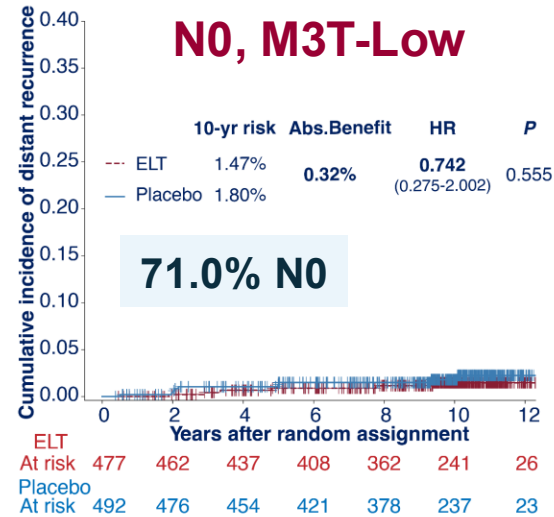
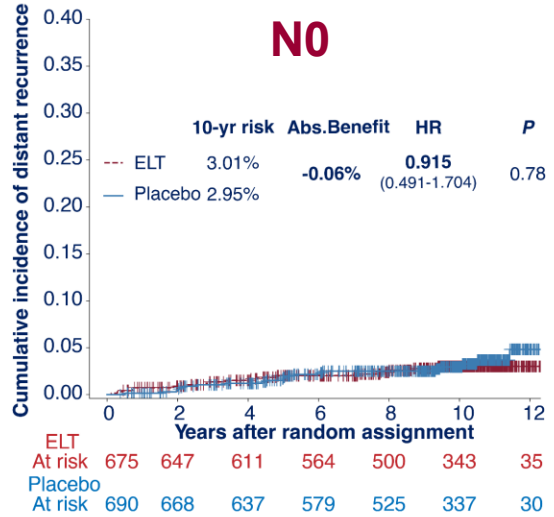


The M3T model showed greatest risk stratification and the largest absolute ELT benefit in the high-risk group  
There was no statistically significant treatment interaction by risk category.

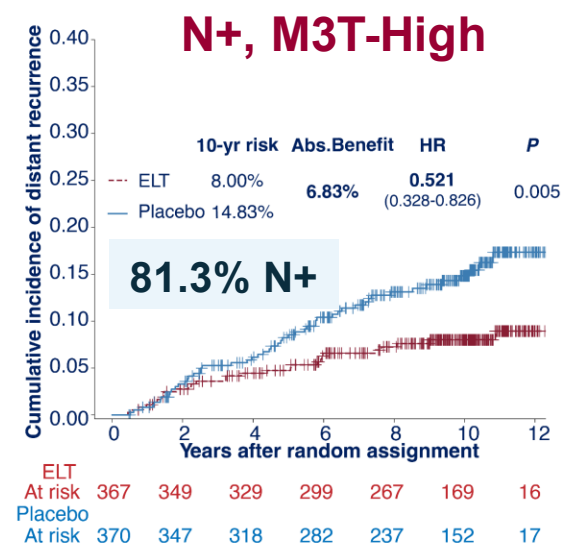
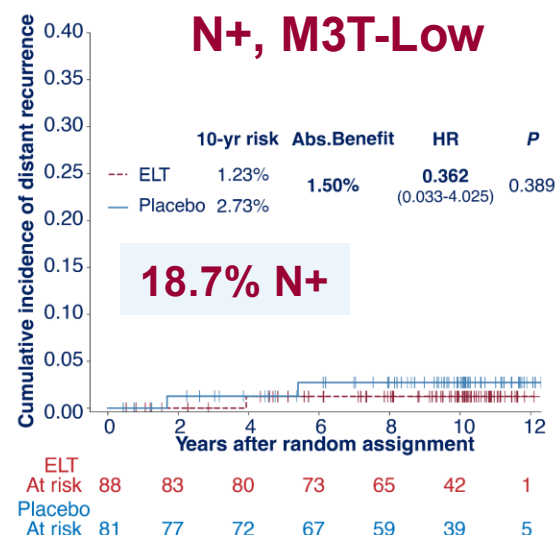
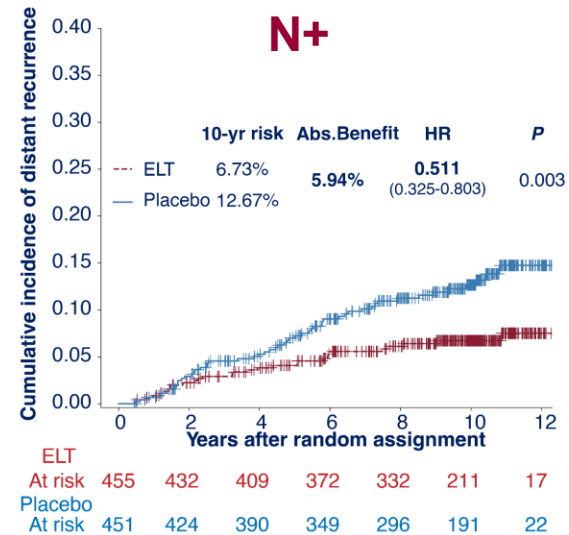


# M3T Reclassifies 18.7% N+ Patients as Low Risk and 29% N0 Patients as High Risk

## Path. Node Negative



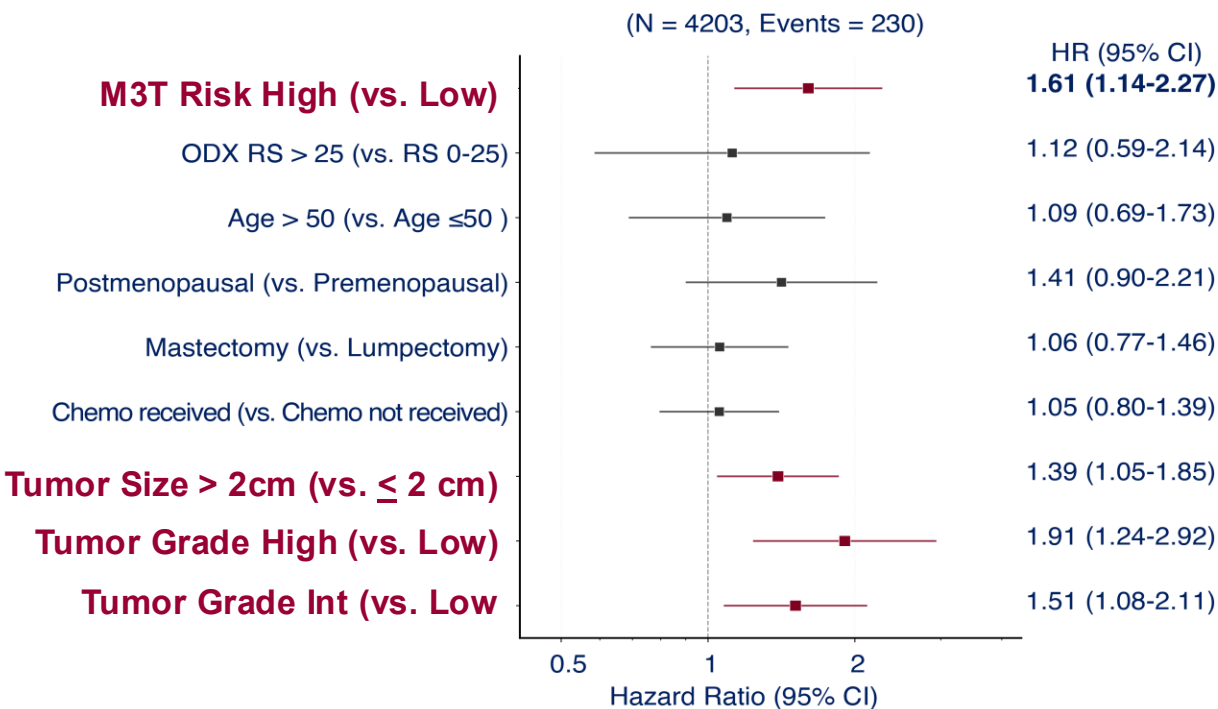
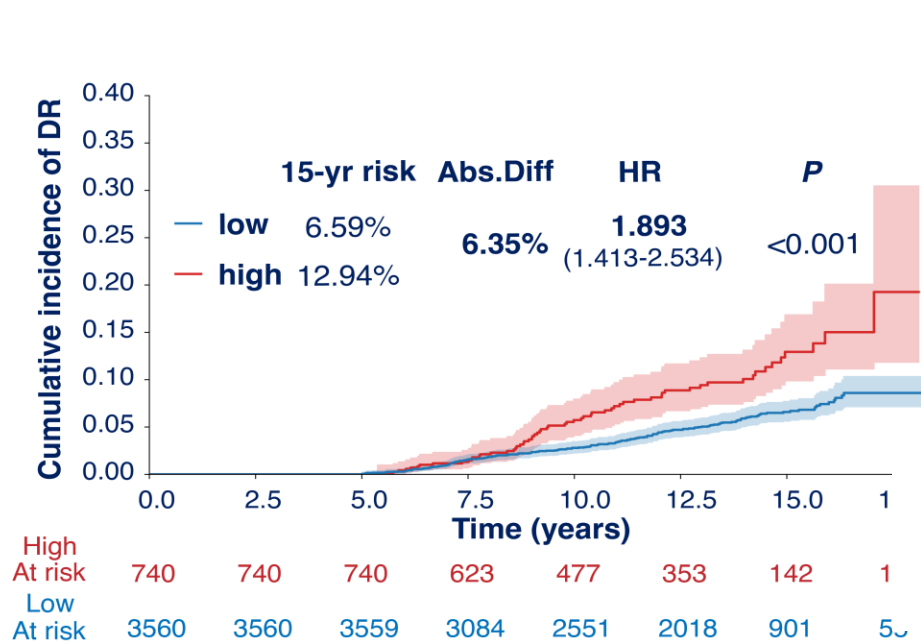
## Path. Node Positive



# External Validation of the M3T Model in TAILORx: Prediction of Risk of Late Distant Recurrence

N=4,300

Late DR (LDR): Patients with  $\geq 4.5$  yrs of ET and disease-free at 5 yrs



**M3T risk label provides independent prognostic information** beyond age, tumor size, grade, RS, surgery type, treatment type, and menopausal status.

# Conclusions

- In NSABP B-42, the **M3T Model** showed the **strongest prognostic performance** and identified low-risk patients, unlikely to obtain meaningful ELT benefit.
- Subset analyses by nodal status demonstrated potential treatment guidance beyond standard clinicopathologic factors
- **External validation in TAILORx** confirmed **independent late DR prognostication**.
- The M3T Model provides a **scalable, cost-effective alternative** to genomic assays using routine H&E and clinical data.

# Acknowledgements

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