Utility of the 70-gene MammaPrint Assay for Prediction of Benefit From Extended Letrozole Therapy (ELT) in the NRG Oncology/ NSABP B-42 Trial

Priya Rastogi, MD,[1,2,3] Hanna Bandos, PhD,[1,3] Peter C Lucas, MD, PhD,[1,2,3] Laura J van 't Veer, PhD,[4] Jia-Perng Wei, PhD,[4] Charles E Geyer, Jr, MD,[1,5] Louis Fehrenbacher, MD,[1,6] Mark L Graham, MD,[1,7] Stephen K.L. Chia, MD,[1,8] Adam M Brufsky, MD, PhD,[1,2,3] Janice M Walshe, MD,[1,9] Gamini S Soori, MD,[1,10] Shaker R Dakhil, MD,[1,11] Soonmyung Paik, MD,[1,12] Sandra M Swain, MD,[1,13] Andrea Menicucci, PhD,[4] Shiyu Wang, MS,[4] M. William Audeh, MD, [4] Norman Wolmark, MD,[1,2,3] Eleftherios P Mamounas, MD,[1,14]

[1]NSABP/NRG Oncology, Pittsburgh, PA; [2]UPMC Hillman Cancer Center, Pittsburgh, PA; [3]University of Pittsburgh, Pittsburgh, PA; [4]Agendia, Irvine, CA; [5]Houston Methodist Cancer Center, Houston, TX; [6]Kaiser Permanente Oncology Clinical Trials Northern CA, Novato, CA; [7]Waverly Hematology Oncology, Cary, NC; [8]British Columbia Cancer Agency, Vancouver, BC, Canada, [9]Cancer Trials Ireland, and St. Vincent's University Hospital, Dublin, Ireland; [10]Missouri Valley Cancer Consortium/Florida Cancer Specialists, Fort Myers, FL; [11]Wichita NCORP Via Christi Regional Medical Center, Wichita, KS; [12]Yonsei University College of Medicine, Seoul, Republic of South Korea; [13]Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC; [14]Orlando Health Cancer Institute, Orlando, FL

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Disclosures

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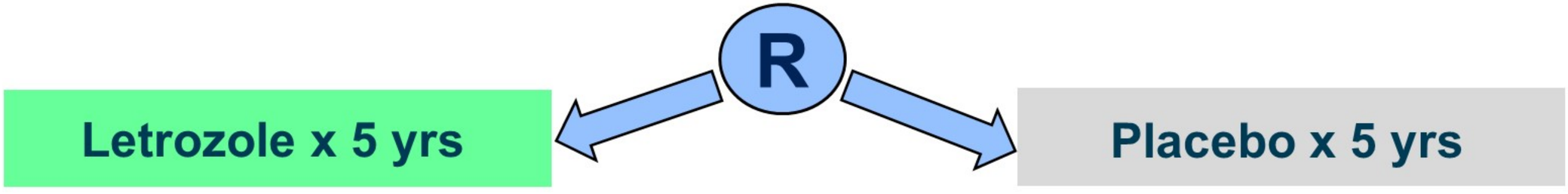
NSABP B-42

- Postmenopausal pts with ER+ or PR+ breast cancer
- Stage I, II, or IIIa invasive BC at diagnosis
- Disease-free after 5 yrs of endocrine therapy

AI x 5 yrs **or** TAM x ≤ 3 years → AI to Complete 5 yrs

Stratification:

Pathological nodal status (Negative, Positive)
Prior adjuvant TAM (Yes, No)
Lowest BMD T score: spine, hip, femur (>-2.0, ≤-2.0 SD)



NSABP B-42: Summary

- **Ten-year results (SABCS 2019) and further updated as of 04/30/2020**
  - **Statistically significant improvement in DFS with extended L therapy: HR=0.85, p=0.01, 3.3% absolute improvement**
  - **No significant difference in overall survival with L *v* P**
  - **Extended L provided statistically significant reduction in:**
    - **BCFI events: HR=0.75, p=0.003, 2.7% absolute improvement**
    - **DR: HR=0.72, p=0.01, 1.8% absolute improvement**

- **Genomic classifiers that predict risk of late recurrence and/or benefit from extended endocrine therapy may further assist with the decision to recommend extended aromatase inhibitor therapy**

MammaPrint Risk: Background

LR: Low Risk

No/low chemo benefit

MINDACT prospective validation: Clin-high / MP LOW Risk may avoid chemotherapy in certain subgroups for LN- and LN+ disease

(Cardoso et al. NEJM 2016 and Piccart et al. Lancet Oncol 2021)

HR: High Risk

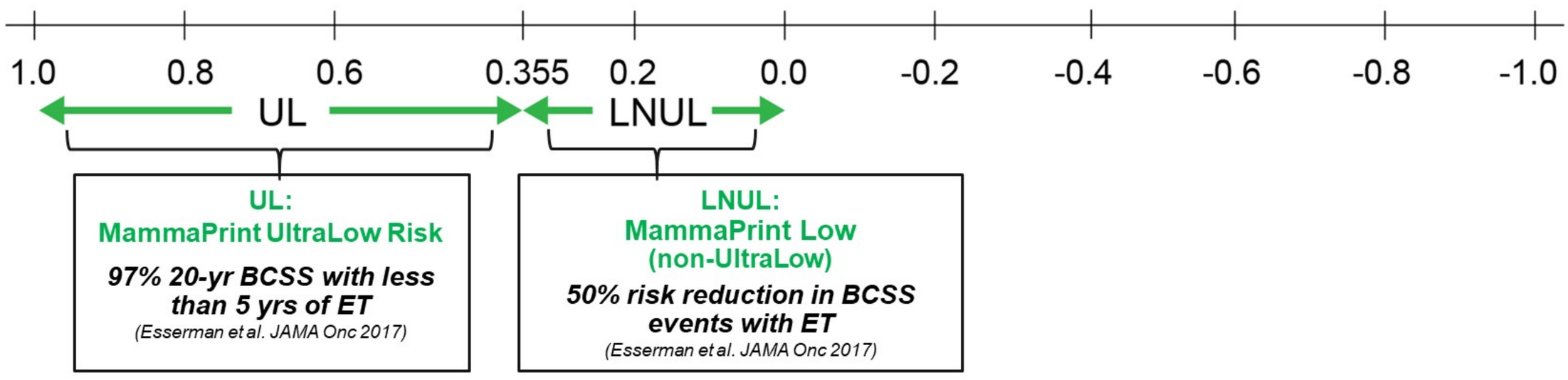
Chemo benefit

MINDACT prospective validation: Clin-high / MP HIGH have highest risk

(Piccart et al. Lancet Oncol 2021)

Chemosensitivity and increased pCR rates for MP HIGH Risk

(Whitworth et al. Ann Surg Oncol 2014 and SABCS 2020)



UL:
MammaPrint UltraLow Risk

97% 20-yr BCSS with less than 5 yrs of ET

(Esserman et al. JAMA Onc 2017)

LNUL:
MammaPrint Low (non-UltraLow)

50% risk reduction in BCSS events with ET

(Esserman et al. JAMA Onc 2017)

MP: MammaPrint
pCR: pathological complete response
BCSS: breast cancer specific survival
ET: endocrine therapy
CT: chemotherapy

Patients and Methods

- All eligible B-42 pts with clinical follow-up and available FFPE primary tumor tissue were included
- MP assay scores were generated by Agendia, blinded to clinical outcome
- Results were merged with clinical data for analyses
- Clinical cutoff date was April 30, 2020
- Median follow-up time is 10.4 yrs

Objectives

- **Primary**
  - Utility of the MP assay to identify pts who are likely to benefit or not benefit from extended letrozole therapy (ELT) for DR
- **Secondary**
  - Utility of the MP assay to identify pts who are likely to benefit or not benefit from ELT for DFS and BCFI
  - Determine distribution of MP-H, MP-L and MP-UL

- **Additional objectives on the effect of clinical and pathologic co-variables and MP assay in identifying patients likely to benefit from ELT will be the subject of future analyses**

Endpoints

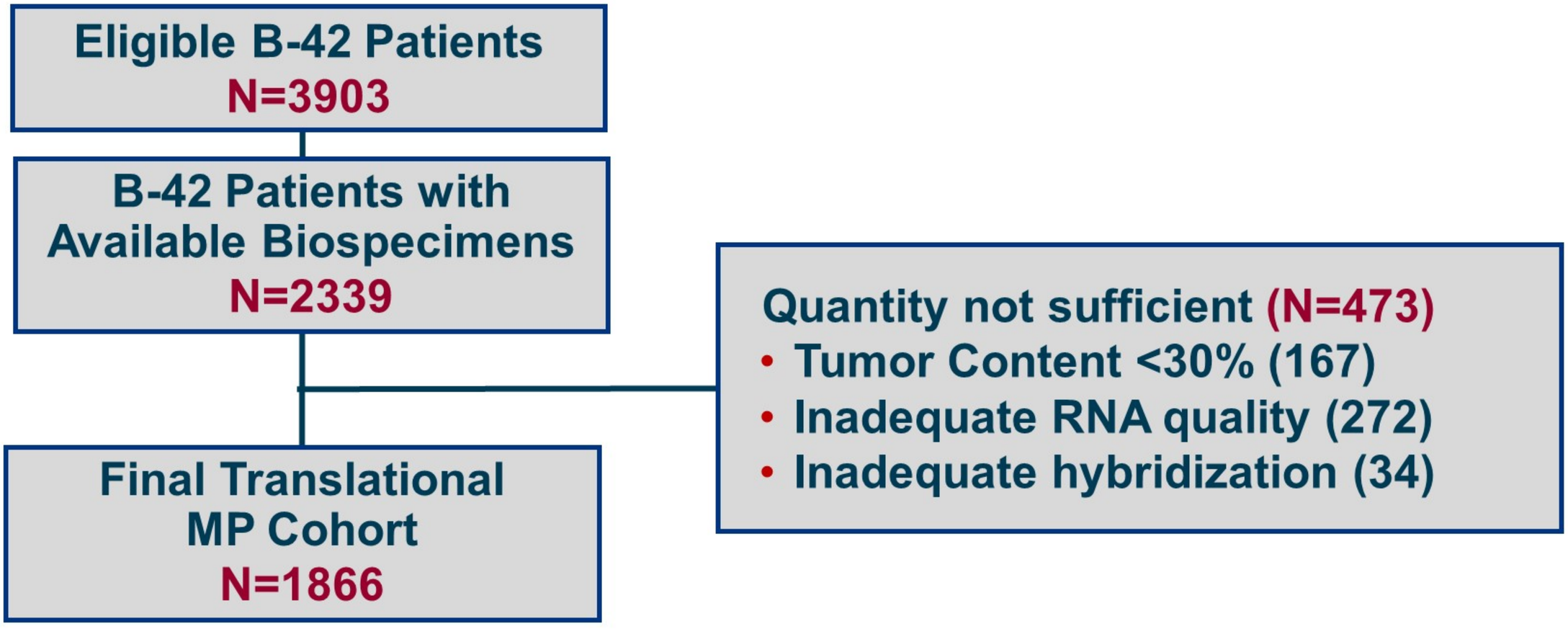
- **Primary**
  - **DR – time from randomization to distant recurrence**
- **Secondary**
  - **DFS – time from randomization to breast cancer recurrence, second primary malignancy, or death**
  - **BCFI – time from randomization to BC recurrence or contralateral breast cancer as a first event**

* Time from randomization (ELT *vs.* placebo) in B-42 parent trial

Statistical Considerations

- Differences in primary and secondary endpoints between P and L groups were assessed by stratified log-rank tests
- Hazard ratios and corresponding 95% CIs were calculated based on stratified Cox proportional hazards model
- Likelihood ratio test evaluated treatment by MP risk group interaction
- KM estimates were used for illustration purposes
- Exploratory analyses were performed for MP-L subcategories

REMARK Diagram



Cohort Characteristics

Characteristics		Overall B-42 population (N=3903) %	Translational MP Cohort (n=1,866) %	Excluded B-42 cohort (n=2,037) %	P value*
Age at randomization, yrs					0.19
	<60	34.4	33.4	35.4	
	≥60	65.6	66.6	64.6	
Nodal status					0.25
	Negative	57.4	56.4	58.3	
	Positive	42.6	43.6	41.7	
Lowest BMD T-score					0.34
	≤ –2.0	24.4	25.1	23.8	
	>–2.0	75.6	74.9	76.2	
Received prior tamoxifen					0.81
	No	60.9	61.1	60.7	
	Yes	39.1	38.9	39.3	
Surgery type					0.36
	Lumpectomy	60.8	60.1	61.5	
	Mastectomy	39.2	39.9	38.5	

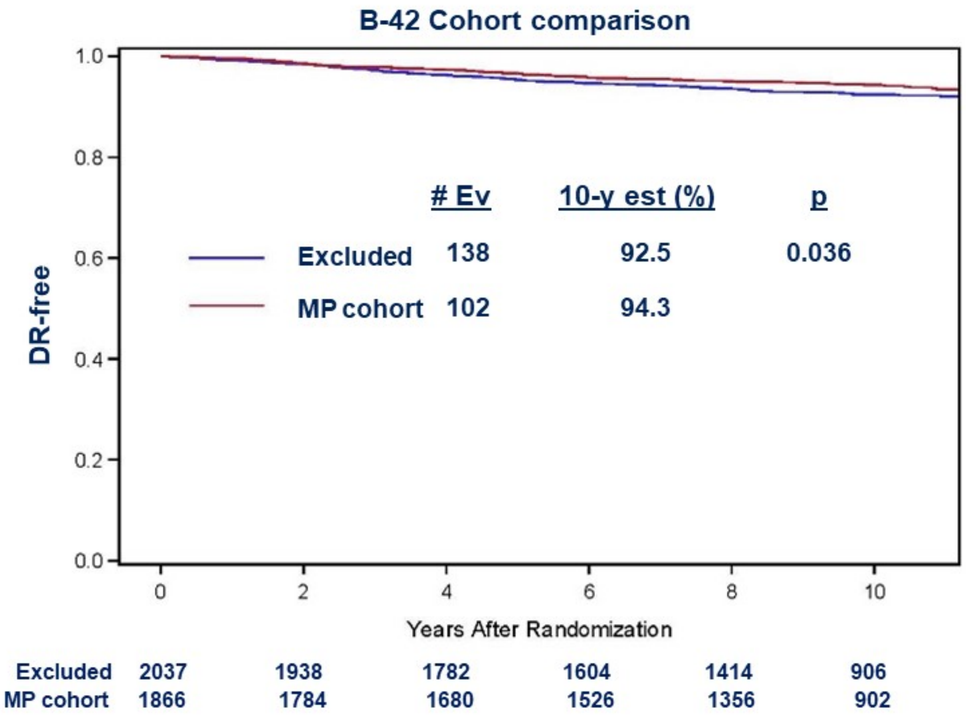
* p-value for comparison of the translational MP cohort to the excluded B-42 cohort

Cohort Characteristics (cont.)

Characteristics		Overall B-42 population (N=3903) %	Translational MP Cohort (n=1,866) %	Excluded B-42 cohort (n=2,037) %	P value*
Treatment					0.30
	Placebo	50.0	50.9	49.2	
	Letrozole	50.0	49.1	50.8	
HER2 status					0.04
	Positive	14.3	14.0	14.6	
	Negative	77.9	79.3	76.7	
	Unknown	7.8	6.7	8.7	
MP risk group					
	High		37.8		
	Low		62.2		
	UL			13.5	
	LNUL			48.7	

* p-value for comparison of the translational MP cohort to the excluded B-42 cohort

Cohort Characteristics (cont.)



Event	# events in the translational MP cohort	HR (95% CI) Translational MP cohort (n=1866)	HR (95% CI) Excluded B-42 cohort (n=2037)
DR*	102	0.50 (0.33,0.75)	0.92 (0.66,1.29)
DFS	457	0.81 (0.68,0.98)	0.89 (0.74,1.06)
BCFI	207	0.70 (0.53,0.93)	0.80 (0.62,1.04)

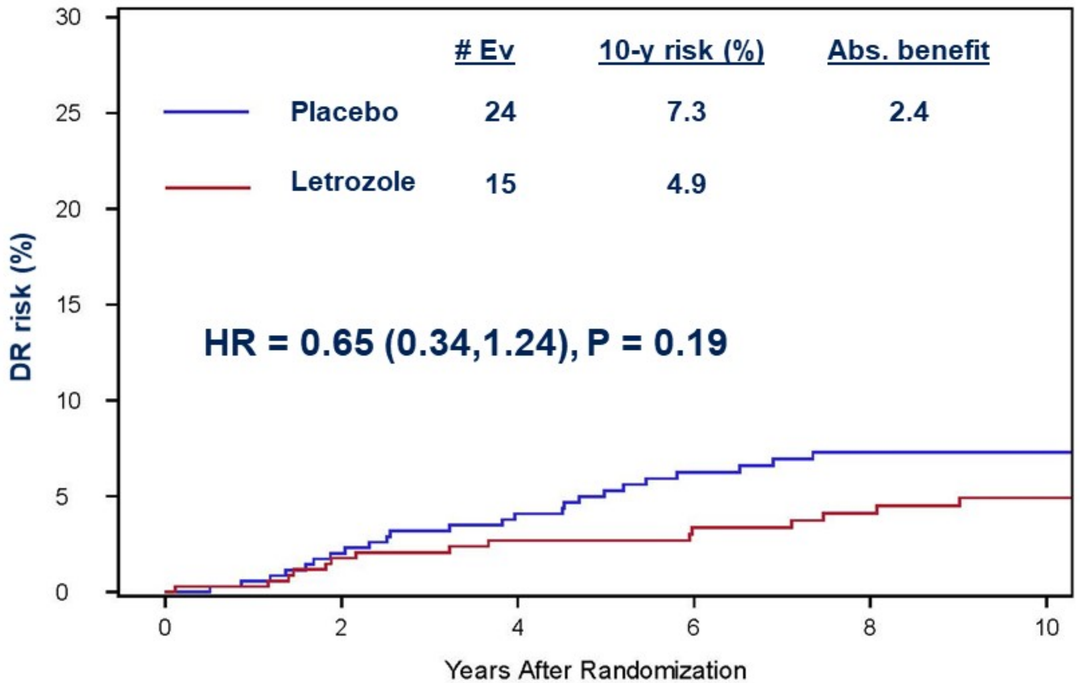
*statistically significant difference in ELT effect between the two cohorts (treatment-by-inclusion status interaction p=0.03)

Compared to the excluded B-42 population, MP cohort had:

- **slightly better prognosis in terms of DR (p=0.036)**
- **a more pronounced ELT effect for DR (p=0.03)**

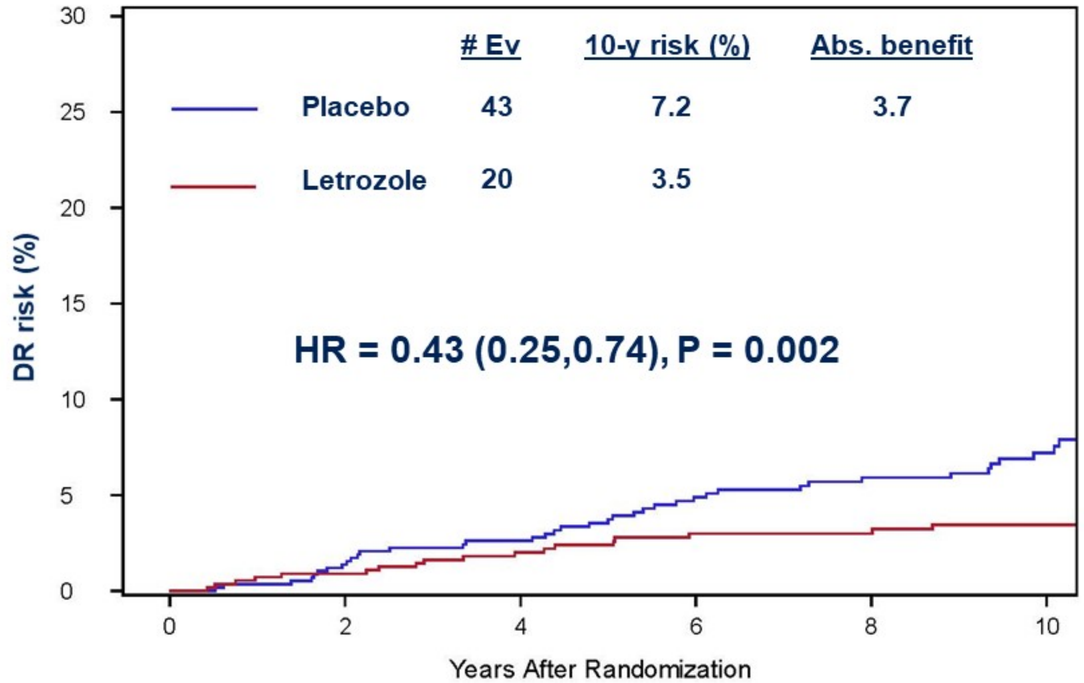
Results:
Primary Endpoint: DR

MP-High



Placebo	354	337	321	289	249	164
Letrozole	352	328	312	283	247	156

MP-Low



Placebo	596	570	532	483	434	290
Letrozole	564	549	515	471	426	292

Test for treatment-by-MP risk group Interaction p=0.38

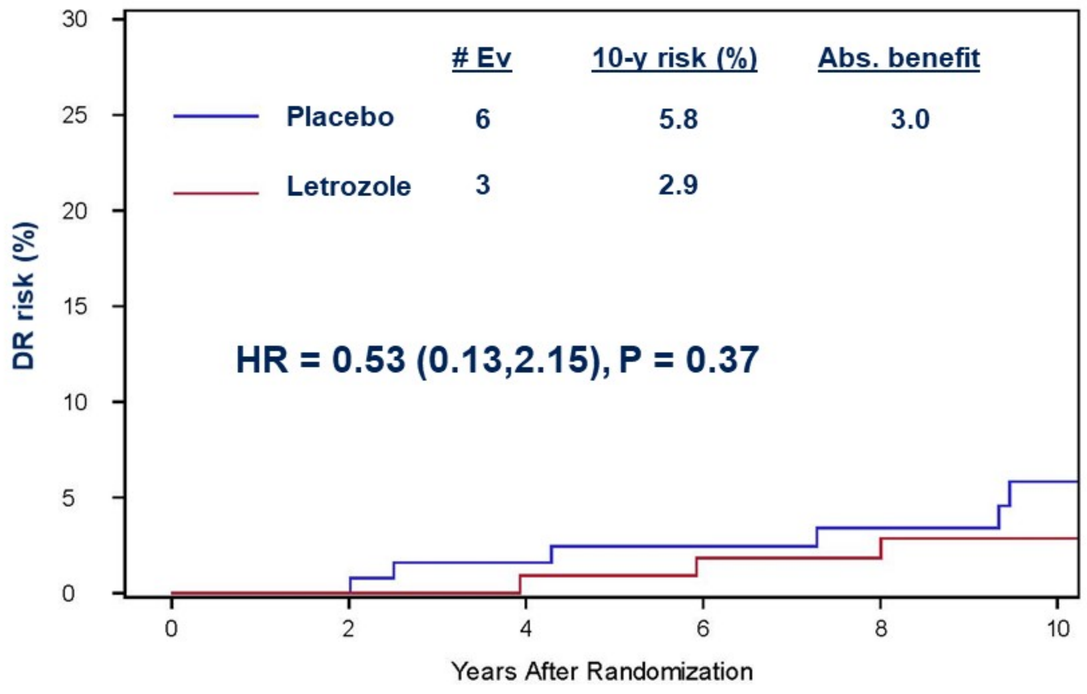
Results:
Summary of Secondary Endpoints

Endpoint	MP	10-yr risk Letrozole (%)	10-yr risk Placebo (%)	Absolute benefit (%)	HR (95%CI)	p	P interaction
DFS events	**Low**	20.3	28.1	7.8	**0.67** (0.52,0.85)	**<0.001**	**0.015**
	High	28.8	27.2	-1.6	**1.10** (0.82,1.47)	**0.55**	
BCFI	**Low**	8.4	15.4	7.0	**0.51** (0.35,0.74)	**<0.001**	**0.006**
	High	14.6	11.6	-3.0	**1.15** (0.74,1.79)	**0.53**	

- **Absolute benefit of L *vs.* P was limited to MP-L for both DFS and BCFI**
- **Tests for treatment-by-MP risk group interaction were statistically significant**

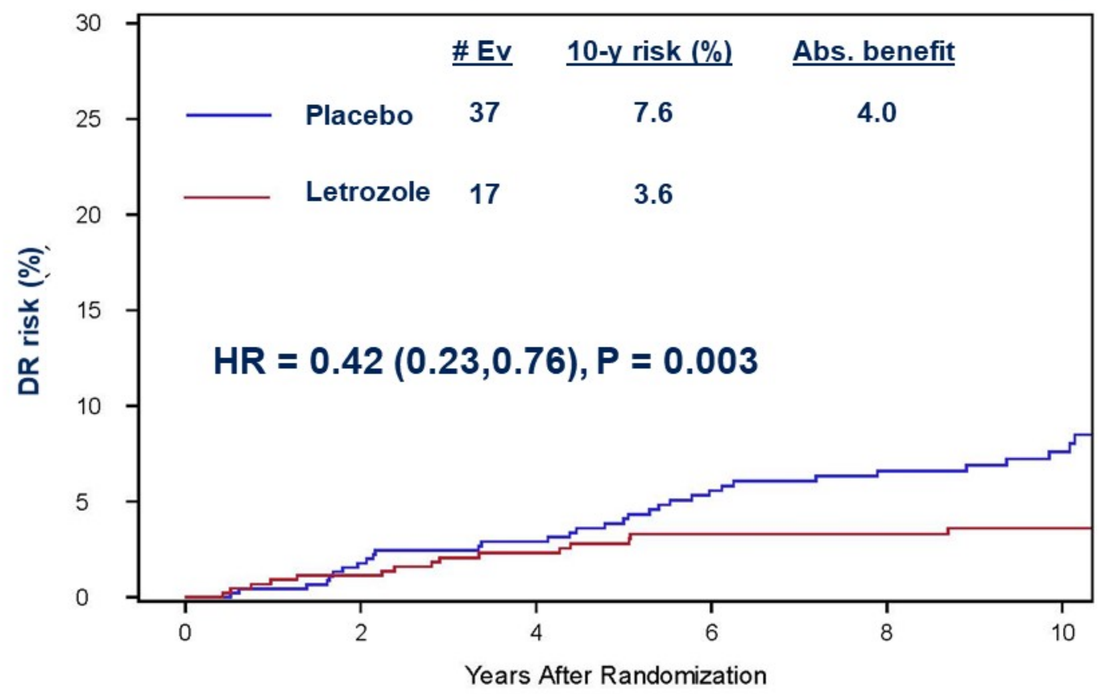
Results: DR by subcategories of LR

MP UL (UltraLow)



Placebo	133	128	118	105	98	62
Letrozole	119	118	110	105	96	64

MP LNUL (Low, non-UltraLow)



Placebo	463	442	414	378	336	228
Letrozole	445	431	405	366	330	228

Test for treatment-by-MPL risk subgroup interaction p=0.66

Results: Secondary Endpoints by Subcategories of LR

Endpoint	MP	10-yr risk Letrozole (%)	10-yr risk Placebo (%)	Absolute Benefit (%)	HR (95%CI)	p	P interaction
DFS	**UL**	17.5	19.3	1.8	**0.82** (0.45,1.48)	**0.50**	**0.52**
	LNUL	21.1	30.6	9.5	**0.64** (0.49,0.83)	**<0.001**	
BCFI	**UL**	7.3	11.4	4.1	**0.67** (0.28,1.65)	**0.38**	**0.59**
	LNUL	8.7	16.6	7.9	**0.48** (0.32,0.73)	**<0.001**	

- **The 10-yr absolute benefit of L *vs.* P was stronger in LNUL than in UL for both DFS and BCFI**
- **Tests for treatment-by-MPL risk subgroup interaction were not statistically significant**

B-42: Summary

- Statistically significant extended letrozole therapy benefit was observed for MP-L, but not MP-H
- The treatment-by-risk group interaction was not statistically significant for DR, but it was for DFS and BCFI:
  - Absolute benefit of ELT in MP-L :

    ΔDR 3.7% (p=0.002); ΔDFS 7.8% (p<0.001); ΔBCFI 7.0%, (p<0.001)
- The benefit appears to be stronger in MP-LNUL than in MP-UL, but the treatment by low-risk subgroup interaction was not statistically significant
  - MP-LNUL represents 48.7% of the total translational MP cohort

B-42: Conclusions

- These results have clinical implications for the utility of MP in patient selection for extended endocrine therapy
- Further confirmation in similar datasets of extended endocrine therapy would be important
- Future analyses of the B-42 MP translational cohort incorporating clinical-pathologic characteristics, such as LN status, could further optimize patient selection

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