Sono utili i test genomici per la valutazione della prognosi?

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Disclosures

Scientific advisory board, meeting, congress:

Celgene,
Lilly,
Novartis,
Roche,
Pfizer,
Astra Zeneca

My Outline

- How to show the relationship between Genomic Test and Prognosis?
- From predictive test to prognostic test: is it possible?
- Point on locally advanced disease and prognosis by genomic test
- Metastatic disease and genomic: towards a response through biomarkers

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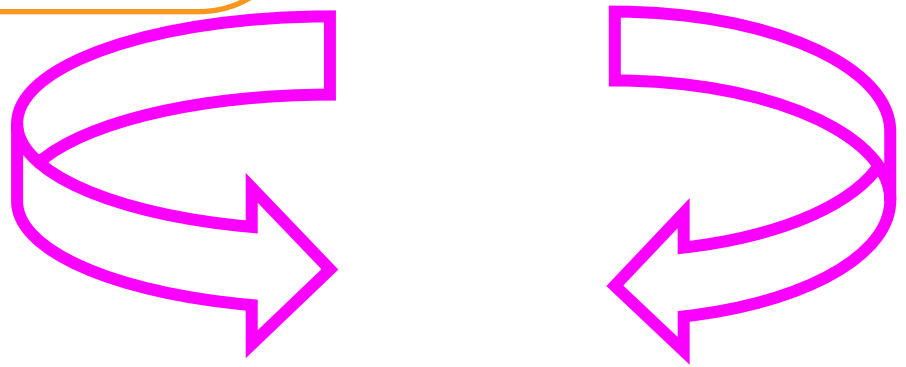
Prognostic Versus Predictive Value

Prognostic Test/Biomarker

A prognostic test/biomarker provides information on a cancer outcome

(disease recurrence, disease progression, death for cancer)



Ballman. *J Clin Oncol*. 2015

Adjuvant Treatment Decisions Are Driven by Both Prognostic and Predictive Factors

Prognostic factors: information on outcomes (eg, recurrence rate)

- Age
- Nodal status
- Tumor size
- Tumor Grade
- HER2
- ER/PR

Predictive factors: degree of response to a specific therapy

- ER
- HER2
-

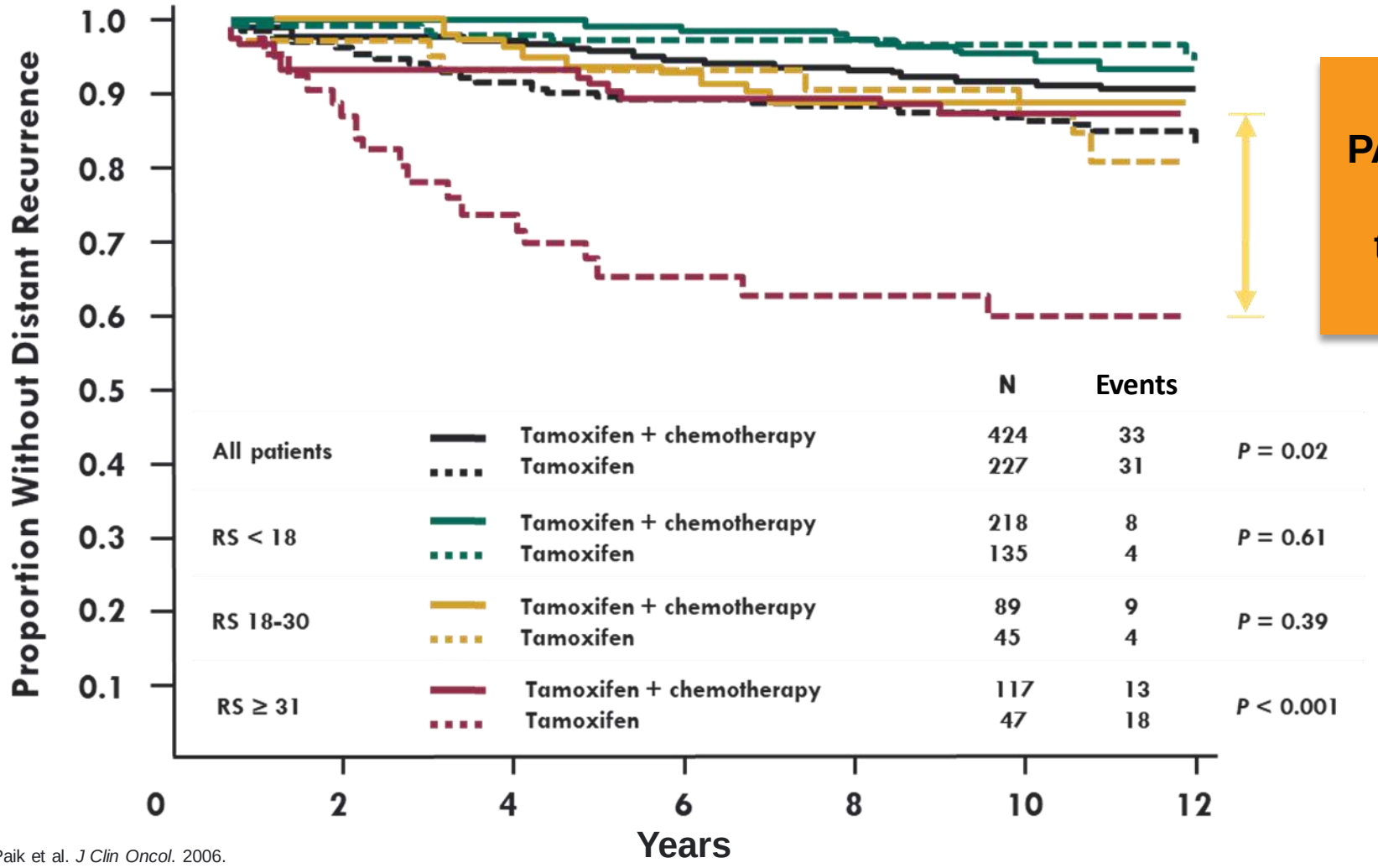
What do we have over?

2

Ballman. *J Clin Oncol.* 2015.

BRS Test Predicts Those Patients Who Do and Do Not Derive Benefit From Chemotherapy

NSABP B-20: Validation Study for Prediction in Node-Negative Patient Population

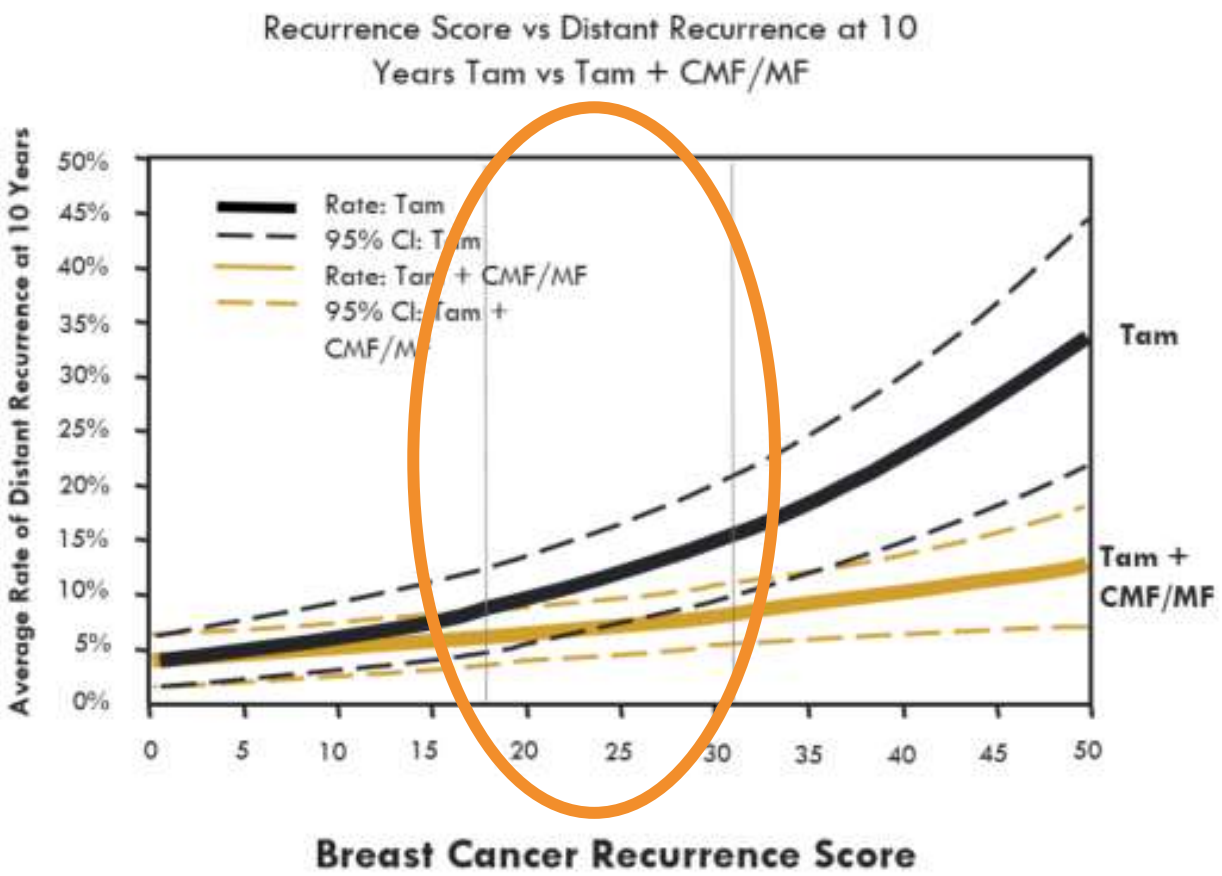


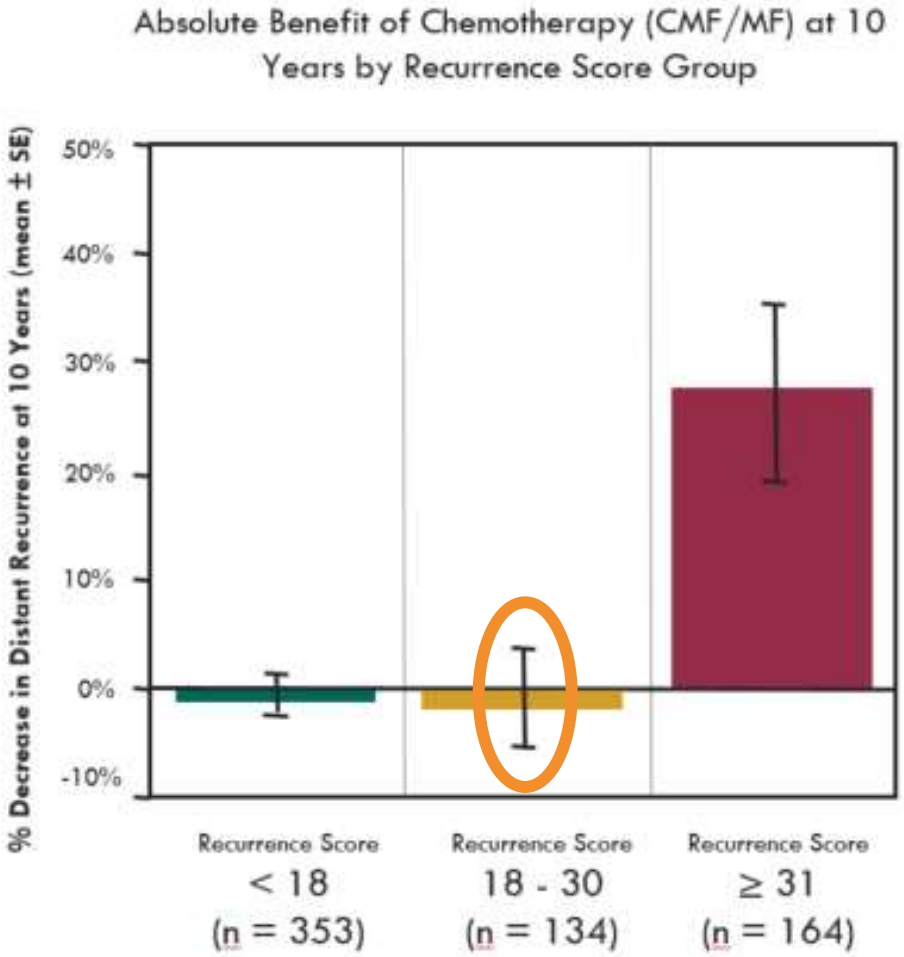
PATIENTS WITH HIGH RS ≥31
28% absolute benefit from tamoxifen + chemotherapy

Interaction *P* = 0.038

Paik et al. *J Clin Oncol*. 2006.

Rationale for Investigating Chemotherapy Benefit in Intermediate Oncotype DX Breast RS

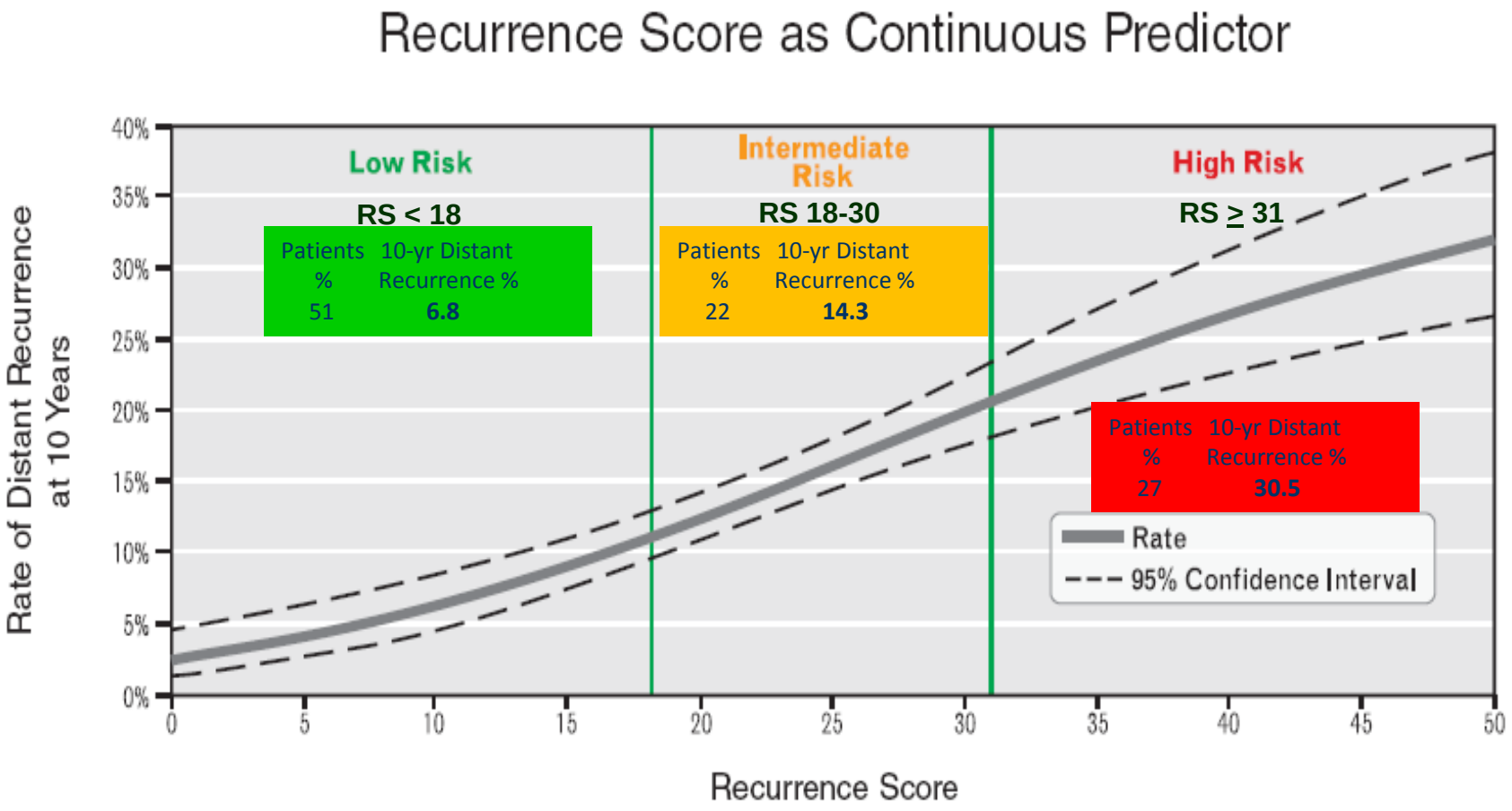




Paik et al. *J Clin Oncol.* 2006.

The RS is a continuous predictor of the Risk of Distant Recurrence
NSABP-14 CLINICAL VALIDATION

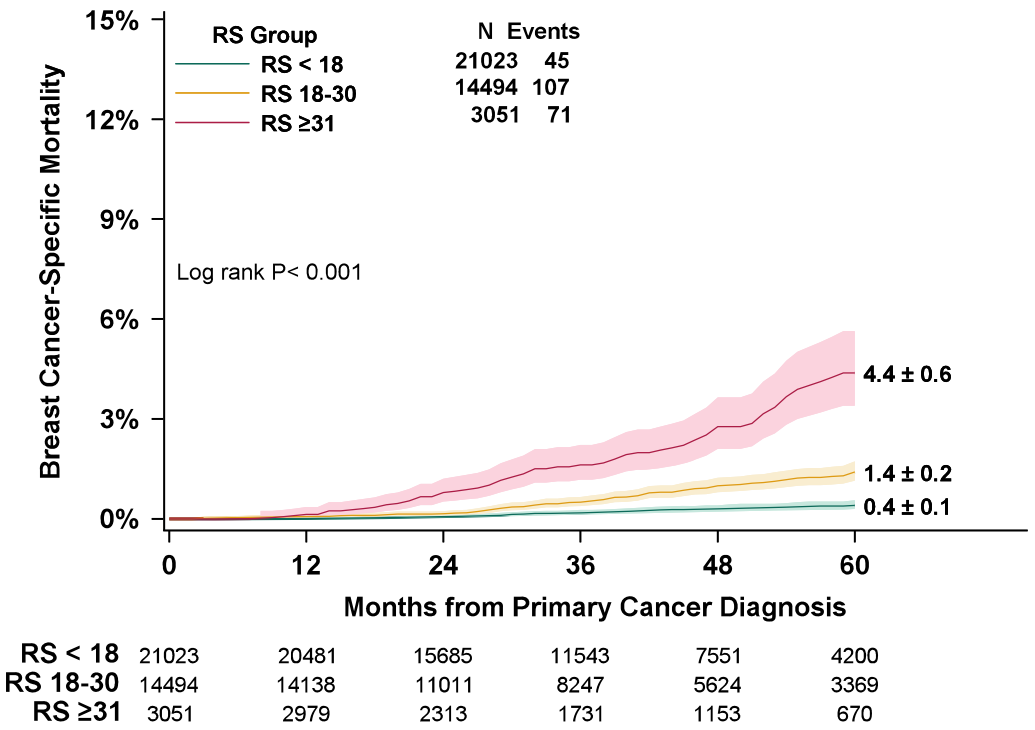
668 pts (stage I-II, N-, ER+ treated with 5 yrs of TAM)

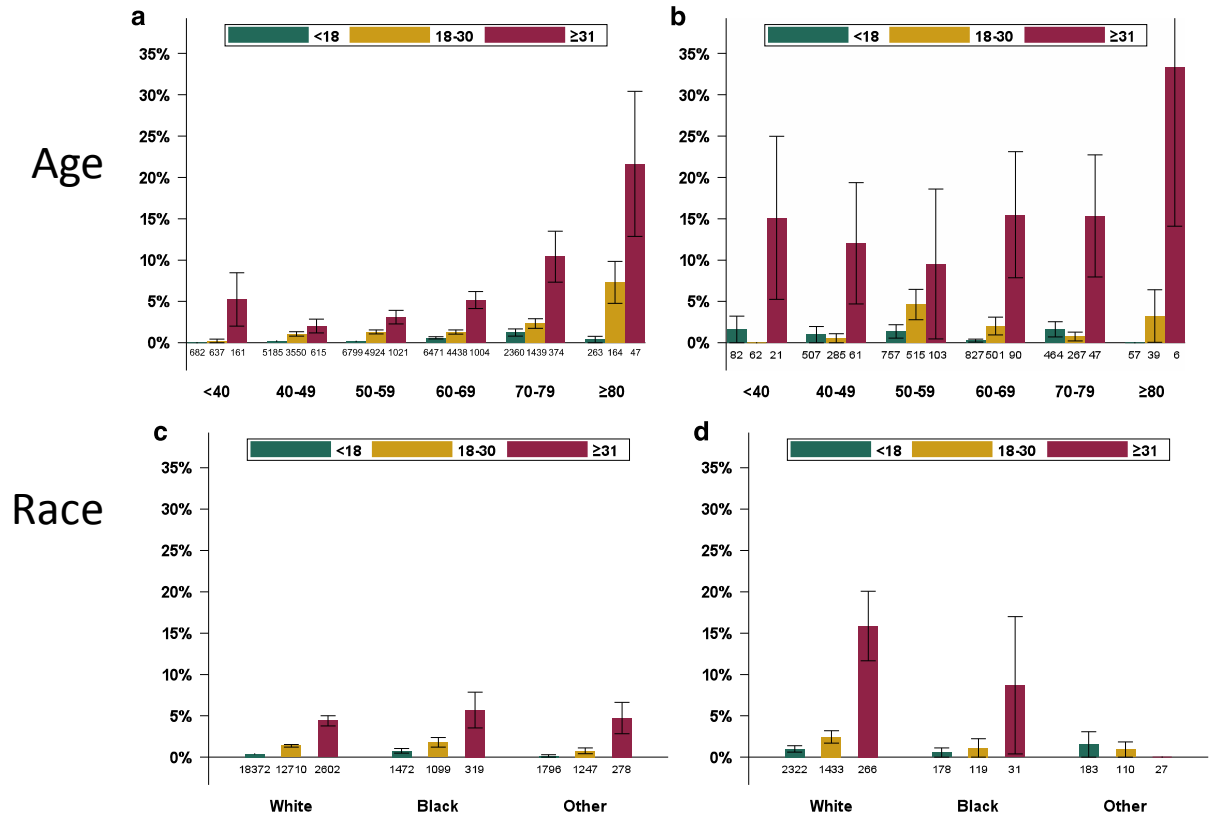


Paik S, NEJM 351(27):2817, 2004

Recurrence Score group was significantly prognostic
BC specific mortality

38.568 pts

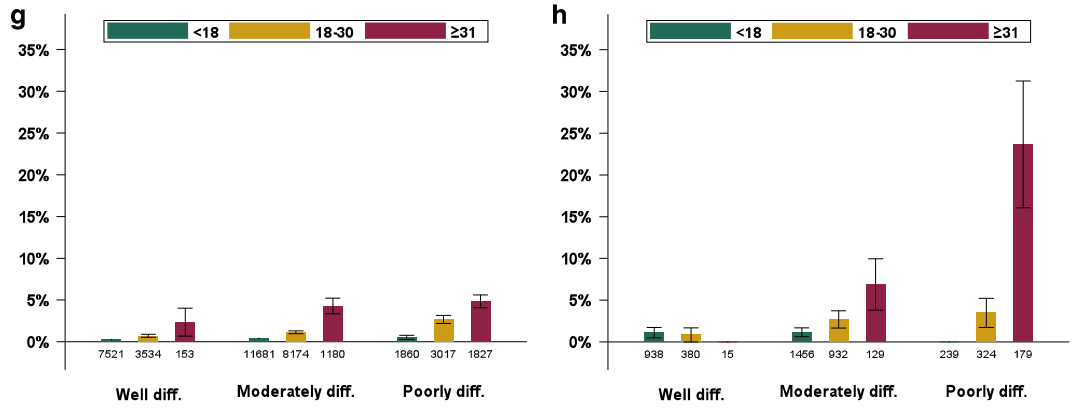




Petkov et al, npj Breast 2016

Recurrence Score group was significantly prognostic
BC specific mortality
38,568 pts

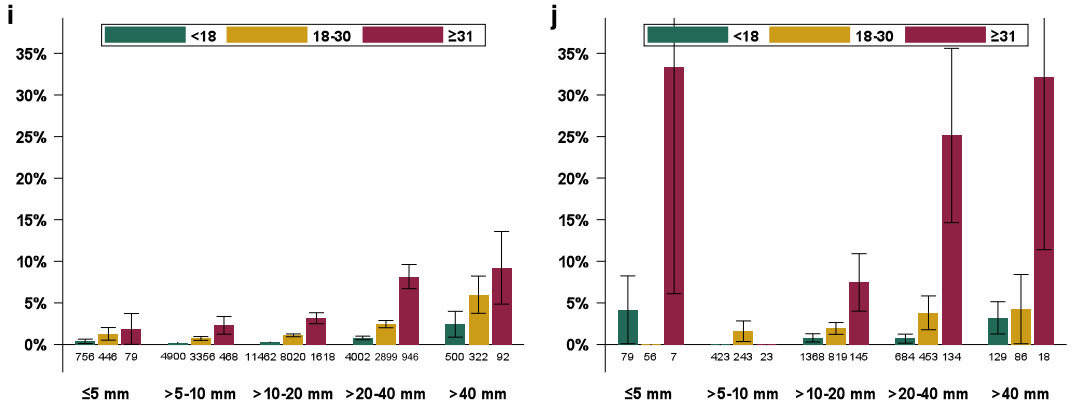
Grade



Characteristic	*Effect*	*Unadjusted HR (95% CI)*	*Unadjusted P value*[a]	*Adjusted HR (95% CI)*	*Adjusted P value*[a]
RS group (versus RS < 18)	RS 18–30	3.1 (2.3, 4.3)	< 0.001	3.0 (2.1, 4.2)	< 0.001
	RS ⩾ 31	11.0 (7.8, 15.5)		7.8 (5.3, 11.6)	

RS > 31 higher probability of BCSM

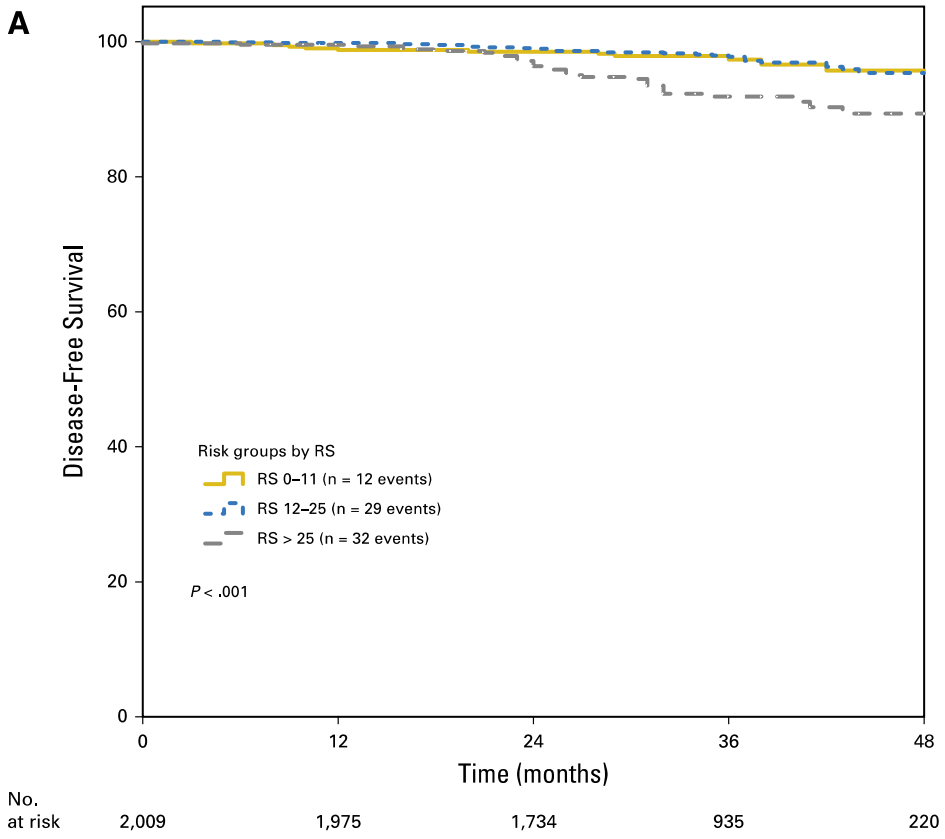
Size Tumor



Petkov et al, npj Breast 2016

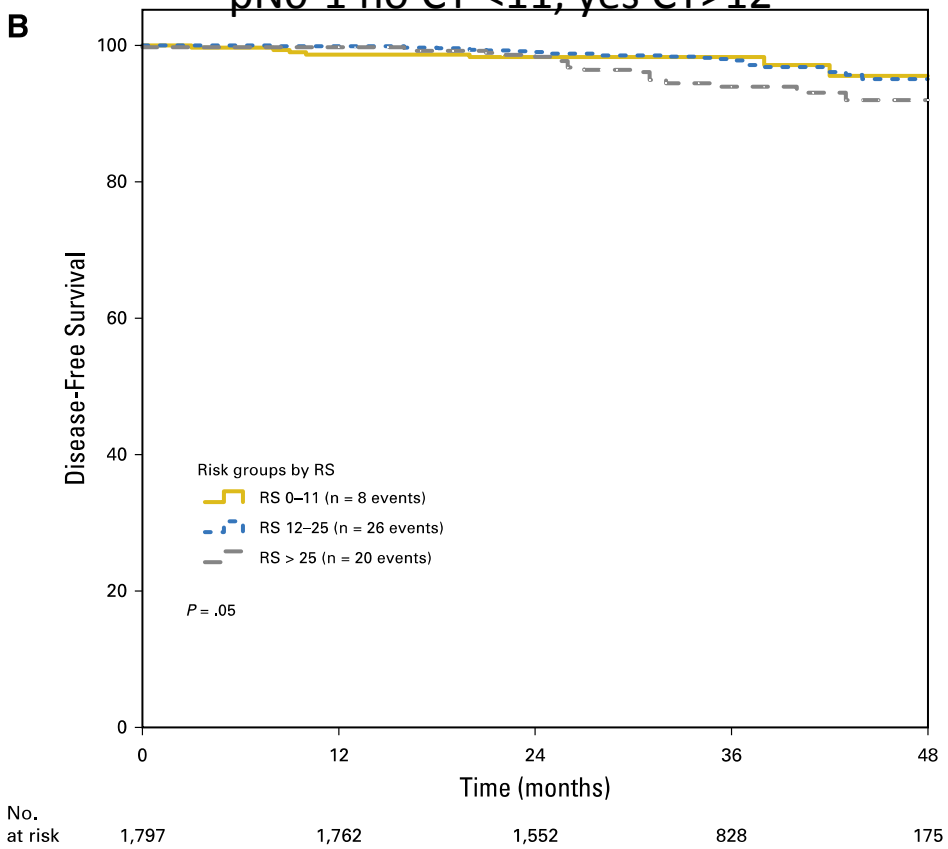
3198 pts

Gluz et al, jCO 2016



3-year DFS was **92%** (95% CI, 89.0% to 94.8%) in patients with high RS versus **98%** (95% CI, 96.8% to 98.8%) in pts with intermediate RS and **97%** in patients with RS < 11 (95% CI, 95.6% to 99.1%; p .001

pN0-1 no CT <11, yes CT>12



3-year DFS was **95%** within the RS > 25 group (95% CI, 91.4% to 98.4%) versus **97.5%** (95% CI, 95.9% to 99.0%) within RS 12 to 25 group and **98%** (95% CI, 97.0% to 99.8%) within the RS < 11 group (P = .05 for RS > 25 v others

PAM50 signature and long-term breast cancer survival

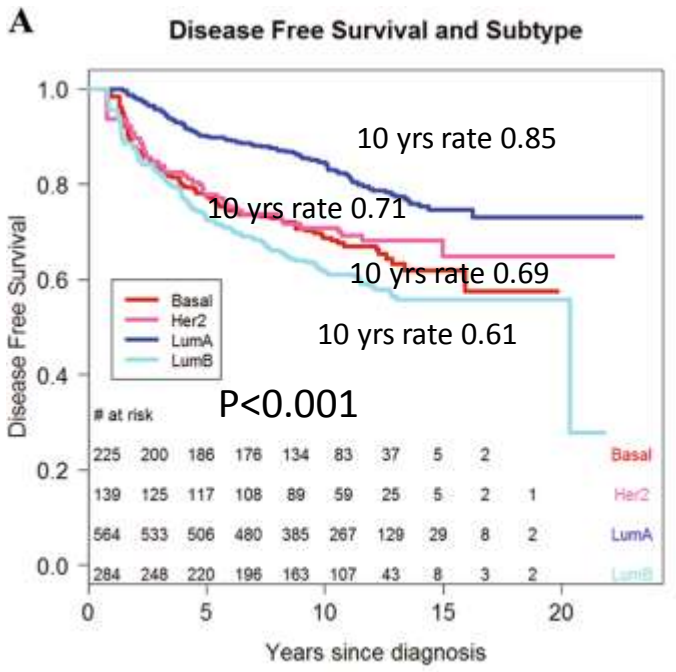
Distribution of PAM50 subtypes by clinical characteristics (15 yrs follow up)

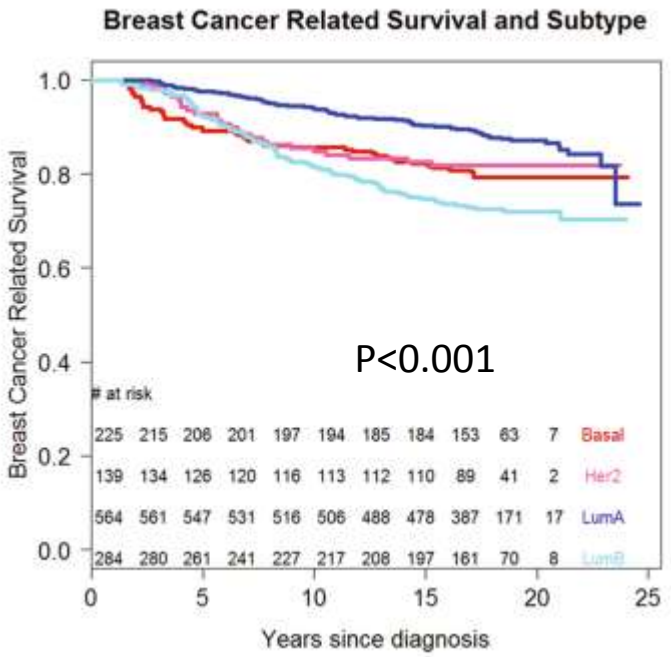
		45%	23%	18%	11%	3%	
		Luminal A %	Luminal B %	Basal-like %	Her2%	Normal %	*P*
	N	564	284	225	139	41	
Cancer stage							<0.0001
I	453	55.6	17.7	15.9	8.2	2.6	
IIA	432	42.4	22.9	20.1	11.1	3.5	
IIB	144	34.7	26.4	20.1	15.3	3.5	
IIIA	166	37.4	31.3	13.3	13.9	4.2	
IIIC	58	29.3	25.9	25.9	15.5	3.5	
Tumor grade							<0.0001
Well-differentiated	159	80.5	12	2.5	1.3	3.8	
Moderately-diff	496	57.3	26.6	4.8	7.9	3.4	
Poorly diff	497	17.9	23.9	37.4	18.1	2.6	
Unspecified	101	62.4	13.9	10.9	7.9	5	
Mean age at diagnosis (SE)		52.8 (0.4)	50.8 (0.5)	48.2 (0.6)	50.5 (0.8)	49.6 (1.2)	<0.0001
Menopausal status at diagnosis							0.02
Pre-menopausal		40.3	25	19.9	10.9	3.9	
Post-menopausal		49.7	20.3	16.3	11.3	2.7	

ER+/Her2–
=
ER+ tumors

ER+/Her2+ split across Her2-enriched (34%) Luminal A (29%) Luminal B (31%)

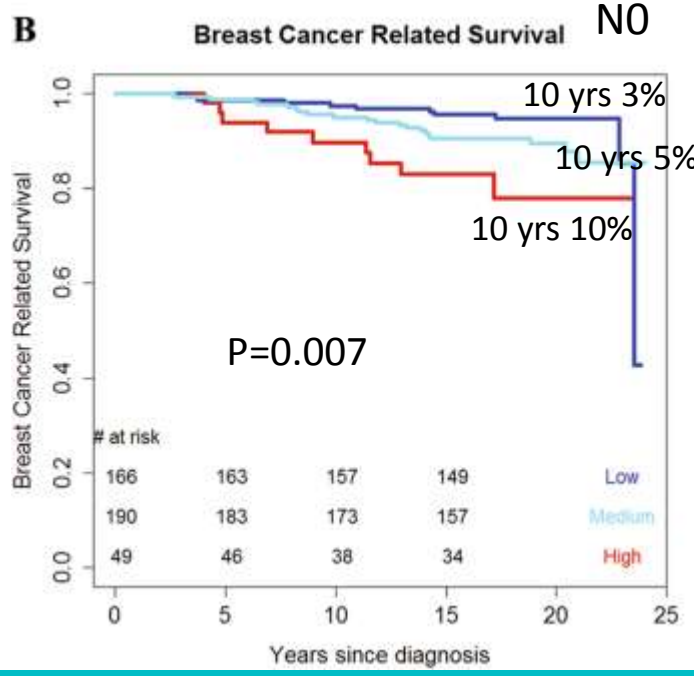
Pu et al Br Cancer Res Treat 2019

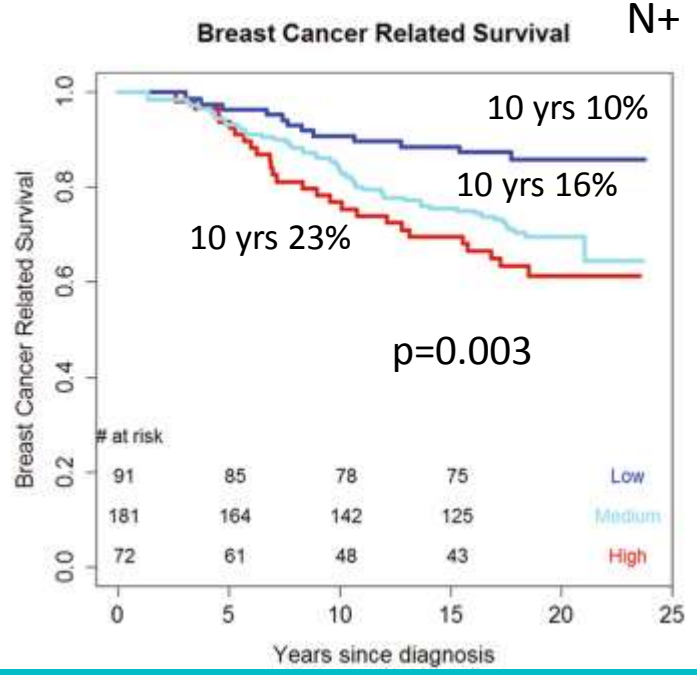




1253 pts

Prognostic value of PAM50 subtypes over clinical factors in an independent breast cancer cohort with long-term follow-up

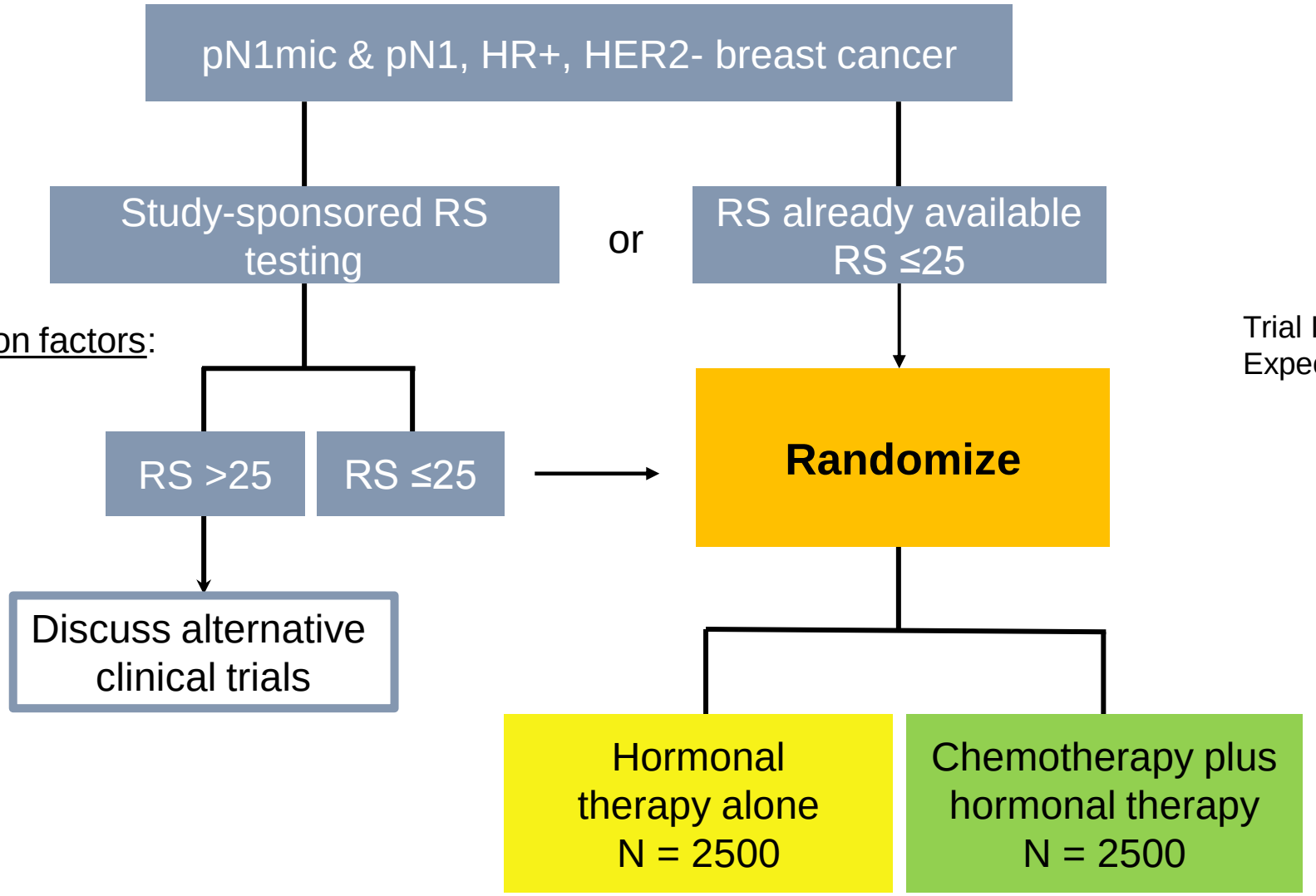




Pam50 intrinsic subtype is independently prognostic for long-term breast cancer survival, irrespective of menopausal status

Pu et al Br Cancer Res Treat2019

Node-Positive Disease: RxPONDER Trial Schema



Randomization stratification factors:

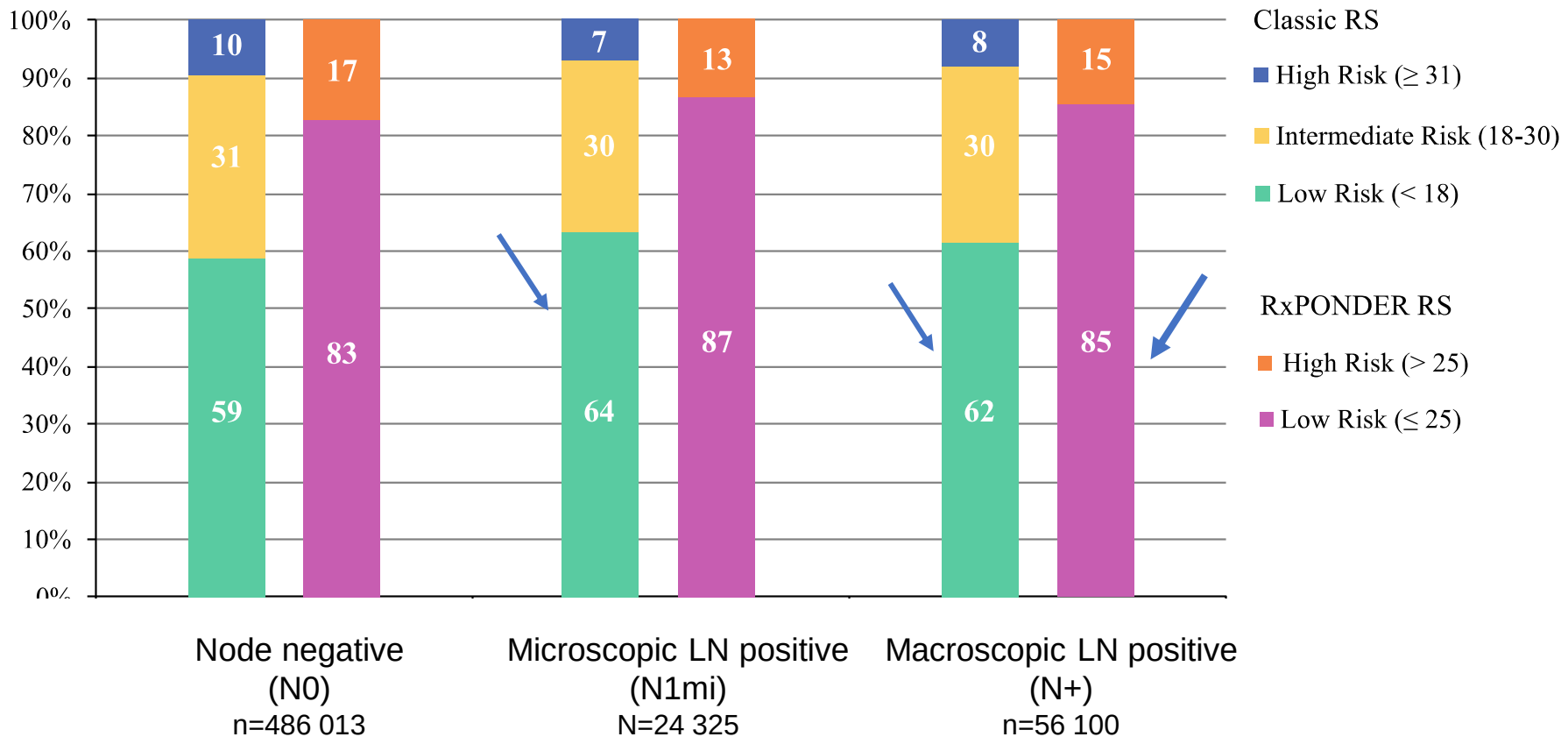
- RS <14 vs 14-25
- Menopausal status
- Axillary dissection vs sentinel node biopsy

Trial Initiated: January 2011
Expected Completion: 2022

Ramsey et al. *Contemp Clin Trials*. 2013.

pN1mi: micrometastases
pN1: 1-3 positive nodes
RS: Recurrence Score® result

Lymph Node Status Does Not Predict Tumor Biology
(2004-2017), N=610.350



- With classic low risk cutoff RS 0-17, 64% N1mi and 62% of N1 patients can be spared chemotherapy
- If RxPONDER shows no chemotherapy benefit with RS ≤25, 87% N1mi and 85% N1 patients can be spared chemotherapy

Bello et al. *Ann Surg Oncol.* 2018

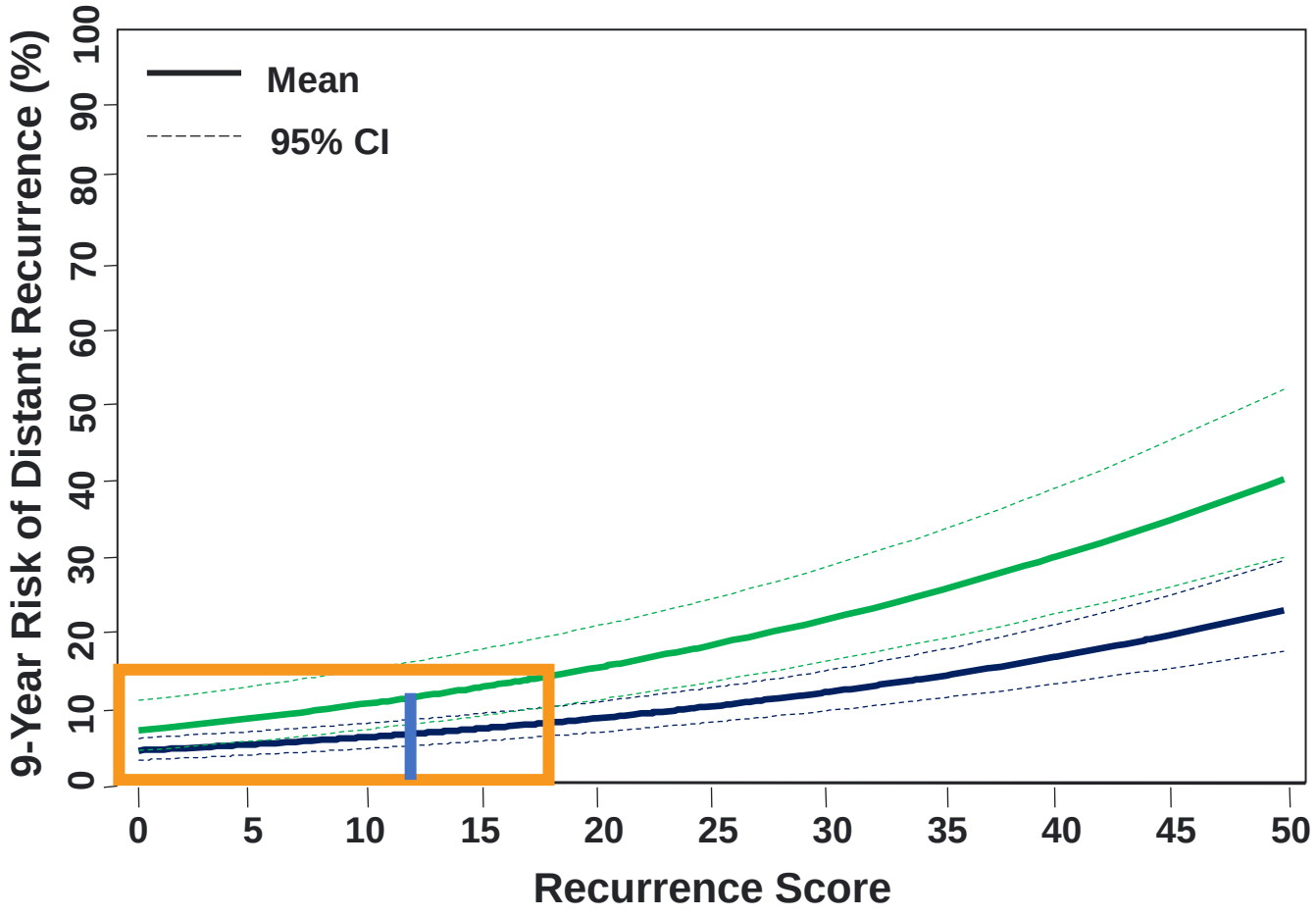
Node-Positive (N1mi/1-3 LN+)

	Study	Type of Study	N	Study Design	Endpoints
Level IA Evidence	**transATAC**	Prospective–retrospective; validation	306 (all N+)	ANA vs TAM vs ANA+TAM	9-year proportion DR-free
	SWOG 8814	Prospective–retrospective; validation	367 (all N+)	TAM vs CAF→T vs CAFT	10-year DFS in TAM-alone arm
	WSG PlanB	Prospective outcomes	930 (1-3 N+)	RS < 12: ET RS 12-25: ET vs CT RS ≥ 26: CT	5-year DFS 5-year DDFS
	Clalit	Prospective outcomes	709 (all N+)	Population-based registry	5-year DR 5-year BCSD
	SEER	Prospective outcomes	6,483 (N1mi/1-3 N+)	Population-based registry	5-year BCSM

Good Outcomes in Patients With Low-Risk RS Results Without Chemotherapy

Mamounas et al. *npj Breast Cancer.* 2016.; Nitz et al. *Breast Cancer Res Treat.* 2017.; Stemmer *npj Breast Cancer.* 2017.; Roberts et al. *Breast Cancer Res Treat*. 2017.

TransATAC



A low Recurrence Score result (<18) indicates a low risk of recurrence for patients with 1-3 positive nodes

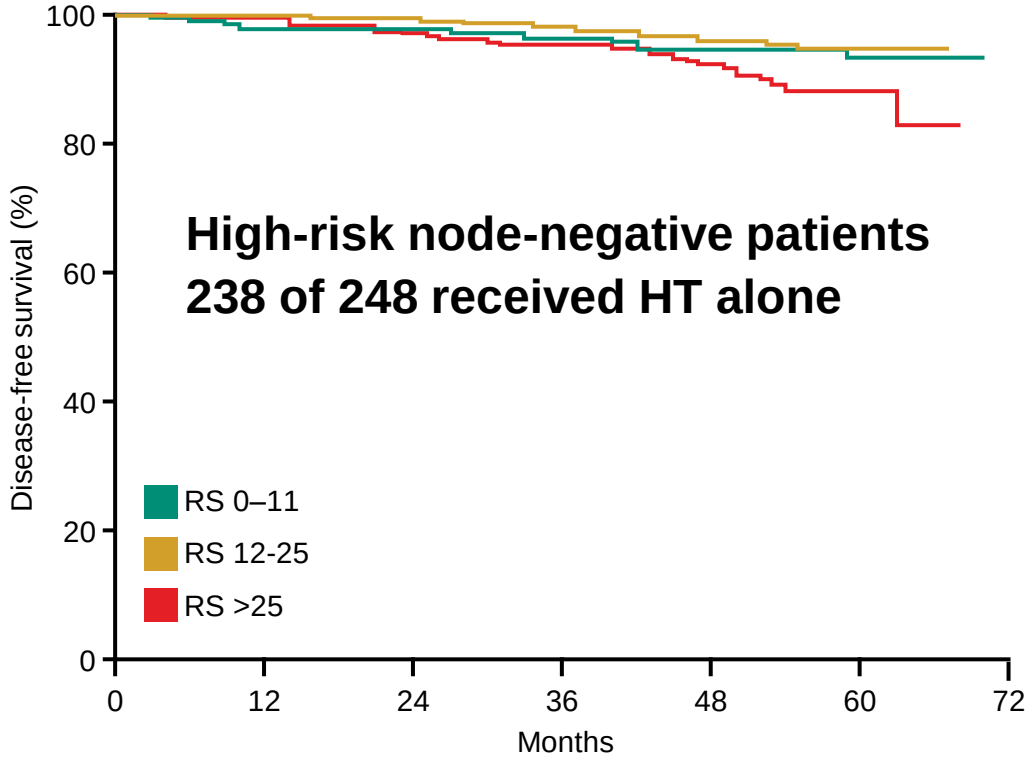
1-3 Positive nodes
n = 243

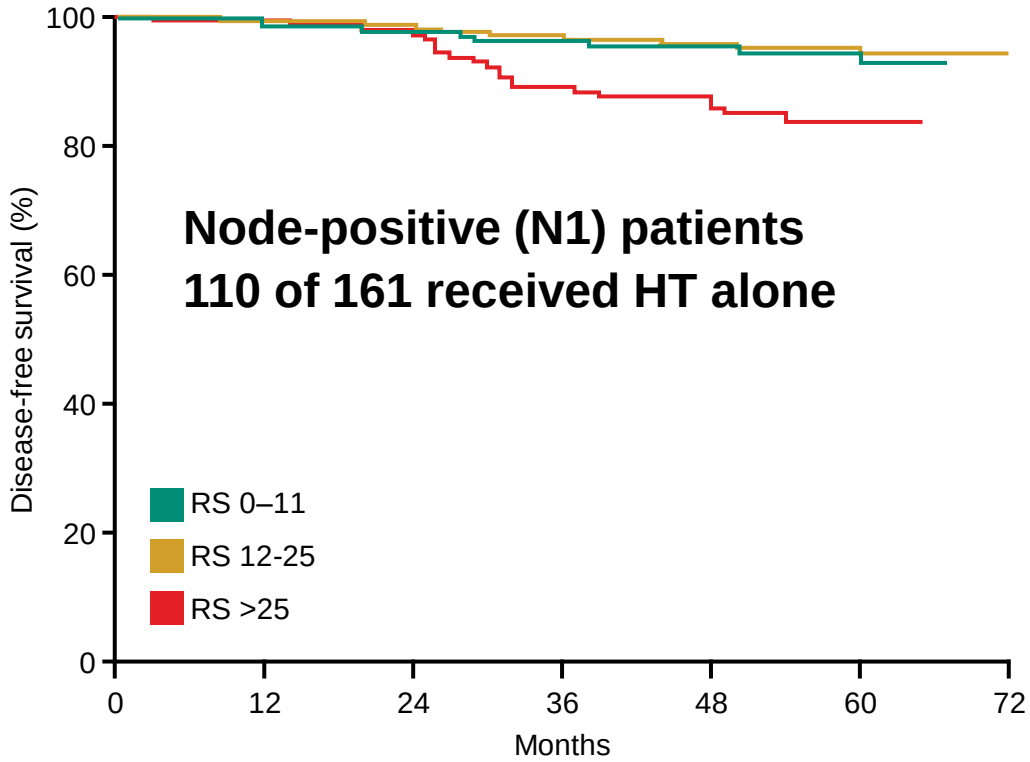
Node-negative
n = 872

RS Result Risk-Stratifies Node-Positive Patients Using Hormone Therapy Alone

Dowsett et al. *J Clin Oncol*. 2010.

West German Study Group PlanB Trial: High-Risk N0 and N1 Patients With RS 0-11 Do Equally Well With ET Alone





5-year disease-free survival was 94% in high-risk N0 and N1 patients with Recurrence Score results 0-11 and treated with hormone therapy alone

Nitz et al. *Breast Cancer Res Treat.* 2017

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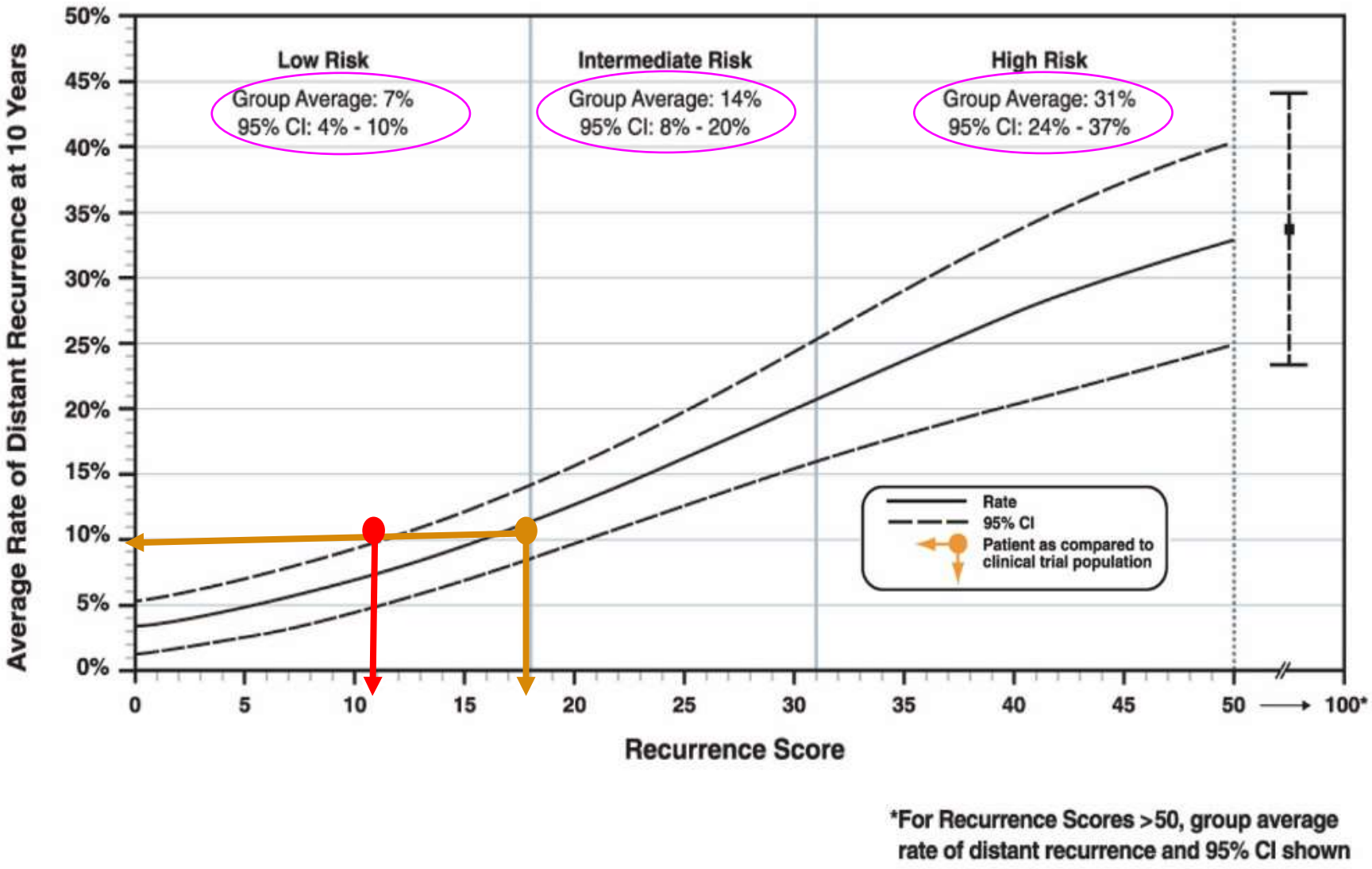
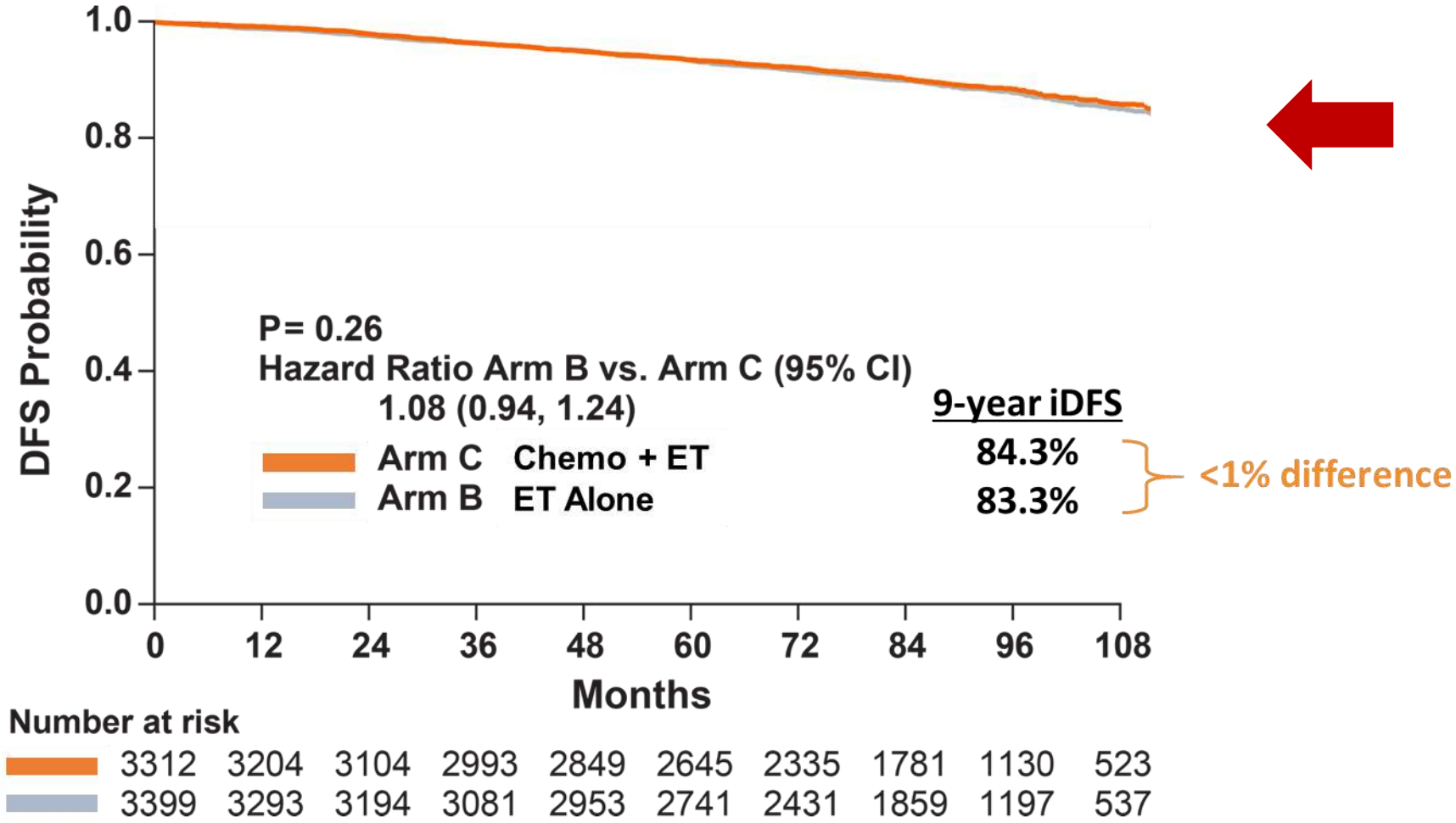

Low Risk
Group Average: 7%
95% CI: 4% - 10%
Intermediate Risk
Group Average: 14%
95% CI: 8% - 20%
High Risk
Group Average: 31%
95% CI: 24% - 37%
Rate
95% CI
Patient as compared to clinical trial population
Average Rate of Distant Recurrence at 10 Years
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0
5
10
15
20
25
30
35
40
45
50
100*
Recurrence Score
*For Recurrence Scores >50, group average rate of distant recurrence and 95% CI shown

TAILORx
ET Alone Was Not Inferior to CT/ET in RS 11-25

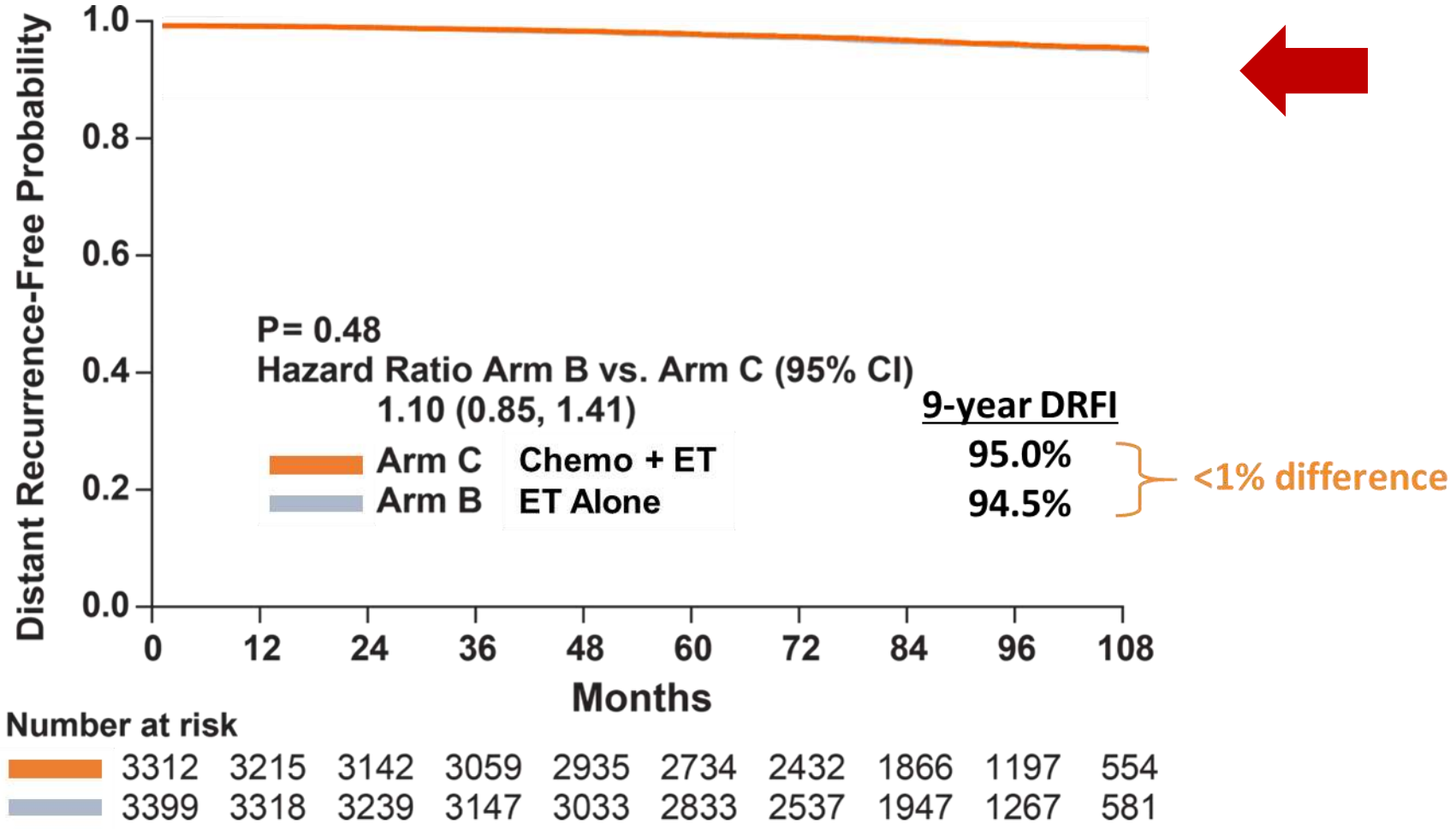
836 iDFS events after median follow-up of 7.5 years



Sparano et al. *N Engl J Med.* 2018.

TAILORx
Very Low Risk of Distant Recurrence in RS 11-25

199 of 836 (23.8%) were distant recurrences

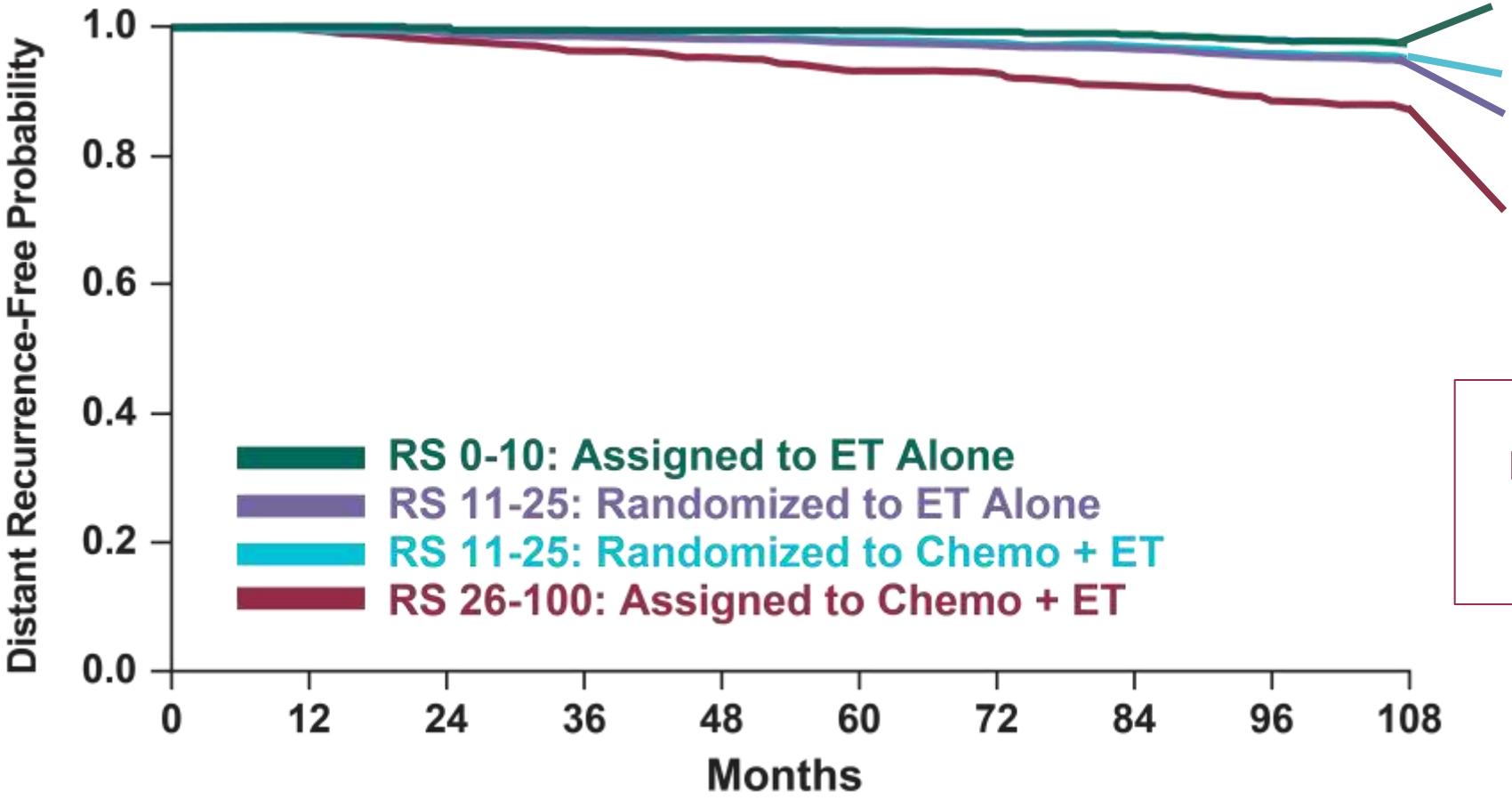


Sparano et al. *N Engl J Med.* 2018.

TAILORx

Arms A, B & C With RS 0-25 Have ≤5% Risk of Distant Recurrence at 9 Years

9-Year Event Rates – ITT Population: All Arms



Arm **A**: ET alone (RS 0-10)
3% Distant recurrence rate

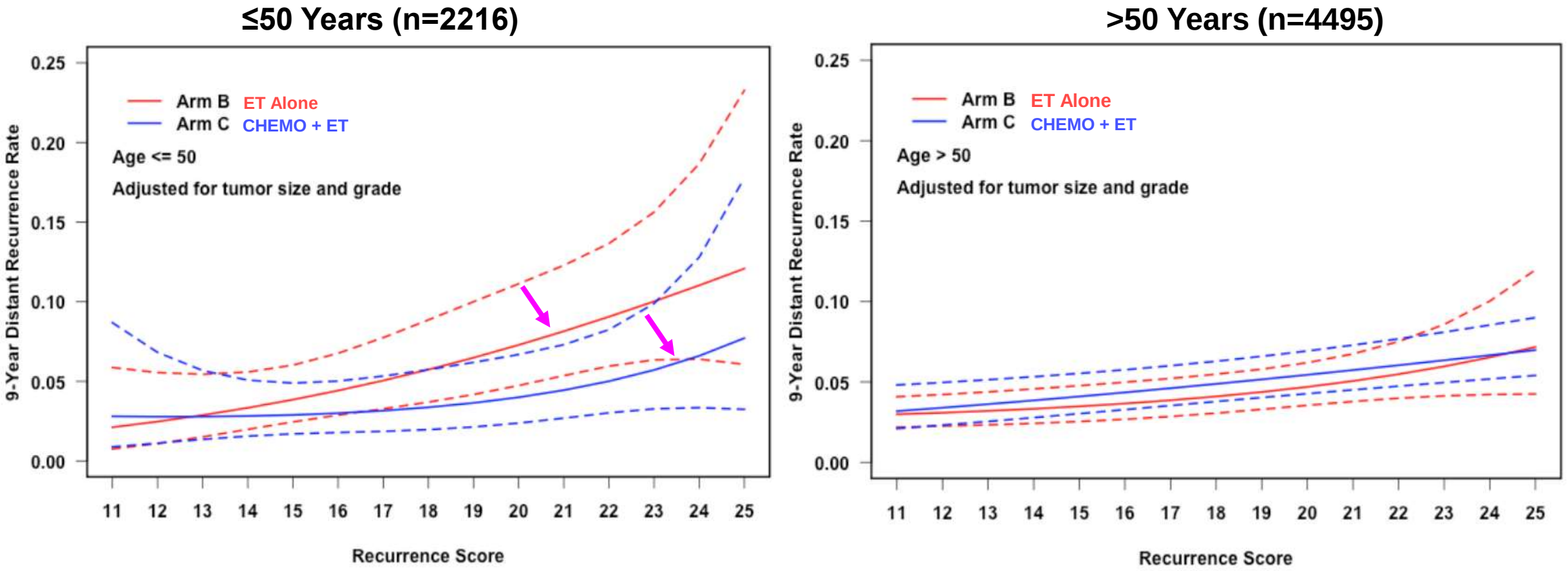
Arms **B** & **C**: Randomized (RS 11-25)
5% Distant recurrence rate overall

Arm **D**: Chemoendocrine (RS 26-100)
13% Distant recurrence rate

Patients in Arm D experienced a higher rate of distant recurrence at 13% despite chemoendocrine therapy

Sparano et al. *N Engl J Med.* 2018.

TAILORx and the Age



The magnitude of chemotherapy benefit in patients ≤50 years increases with increasing Recurrence Score result, but was not statistically significant

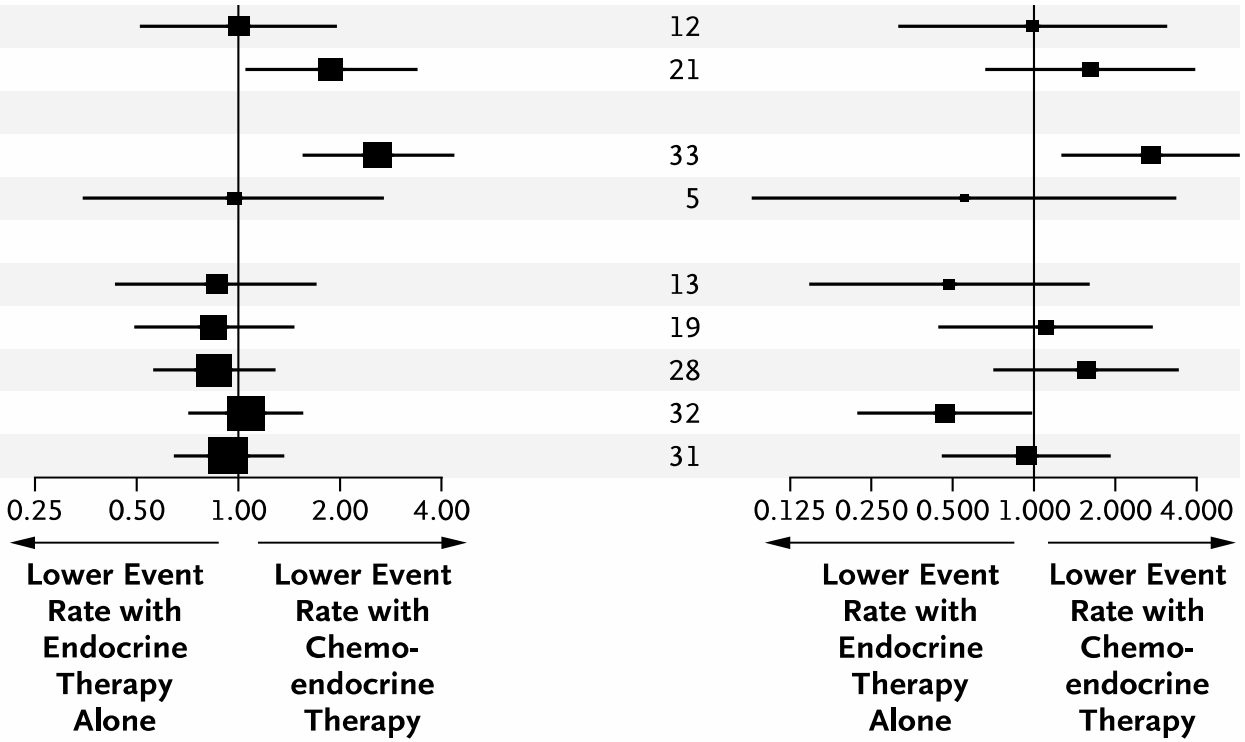
Sparano et al. *N Engl J Med.* 2018.

ET: endocrine therapy

Effect of Age and Menopausal Status on Chemotherapy Benefit

RS 16-25

Subgroup	No. of Patients	No. of Events	No. of Distant Recurrences
≤40 Yr of age	203	35	12
41–45 Yr of age	441	51	21
46–50 Yr of age			
Before menopause	630	69	33
After menopause	141	15	5
51–55 Yr of age			
Before menopause	287	34	13
After menopause	472	54	19
56–60 Yr of age	826	94	28
61–65 Yr of age	710	109	32
>65 Yr of age	628	117	31



Sparano et al, NEJM 2019

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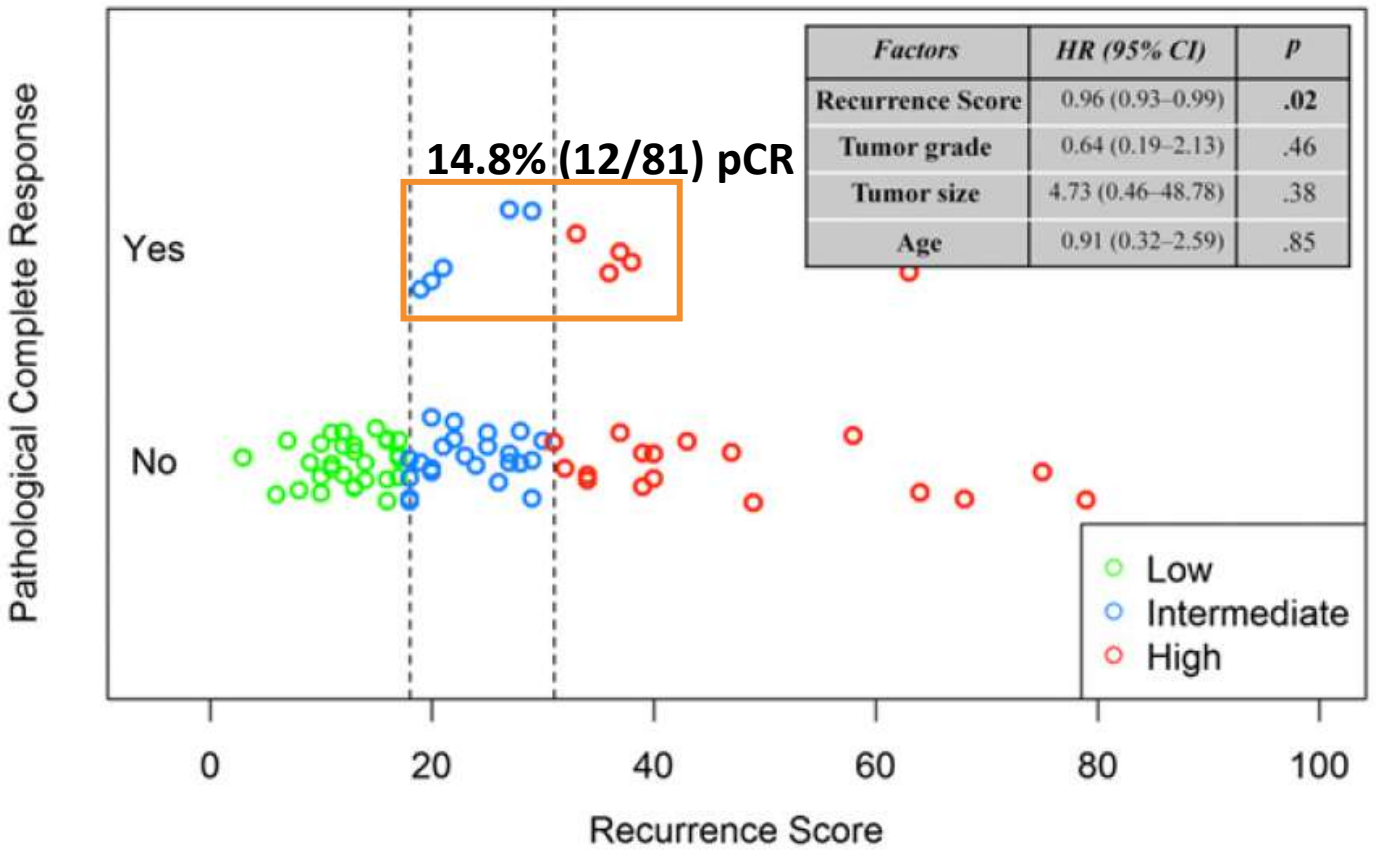
What about prognostic value of Genomic Testing in Neoadjuvant Setting?

pCR and RS



Factors	HR (95% CI)	P
Recurrence Score	0.96 (0.93–0.99)	.02
Tumor grade	0.64 (0.19–2.13)	.46
Tumor size	4.73 (0.46–48.78)	.38
Age	0.91 (0.32–2.59)	.85

RS was the only significant predictor of pCR

Pivot et al. Oncologist. 2015.

Neoadjuvant Studies Supporting Chemotherapy Benefit with RS Group 26-100

Neoadjuvant Chemotherapy

			pCR Rate	
Study	**Type of Study**	**N**	**RS 0-25**	**RS 26-100**
Gianni et al.	Neoadjuvant CT	89	0%	12%
Zelnak et al.	NACT vs NAHT	46	0%	22%
Yardley et al.	Neoadjuvant CT	108	0%	26%
Bear et al.	NACT vs NAHT	64	0%	14%

Sparano et al. *J Clin Oncol.* 2008; Gianni L, et al. *J Clin Oncol*. 2005; Chang JC, et al. *Breast Cancer Res Treat*. 2008; Zelnak AB, et al. *J Clin Oncol*. 2013; Yardley DA, et al. *Breast Cancer Res Treat*. 2015; Bear HD, et al. J *Surg Oncol*. 2017

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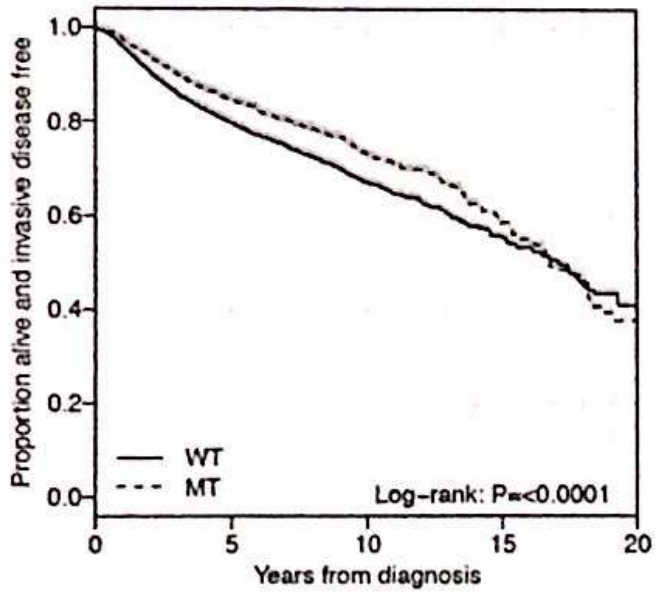
MADRID 2017 ESMO congress

PIK3CA mt BCs & prognosis in early stage disease n=10,319

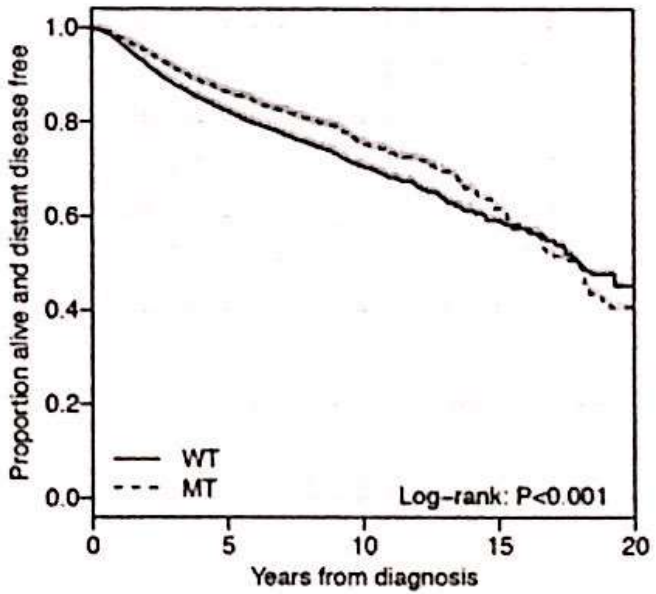
PIK3CA mutants had better outcomes than WT HR = 0.77 [95%CI: 0.71 – 0.84], p < 0.001, independent of subtype and location

Invasive disease free surival



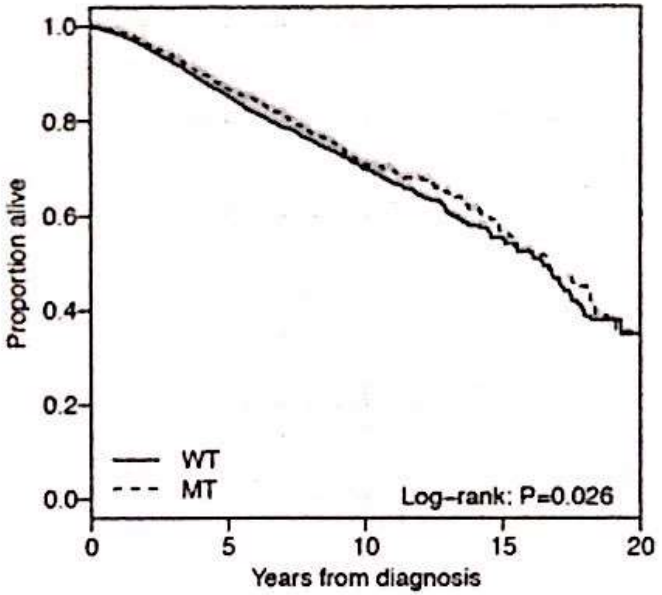
WT	6720	4496	699	164	21
MT	3143	2300	346	105	17

Distant disease free surival



WT	6574	4562	697	169	23
MT	3123	2318	335	108	18

Overall surival



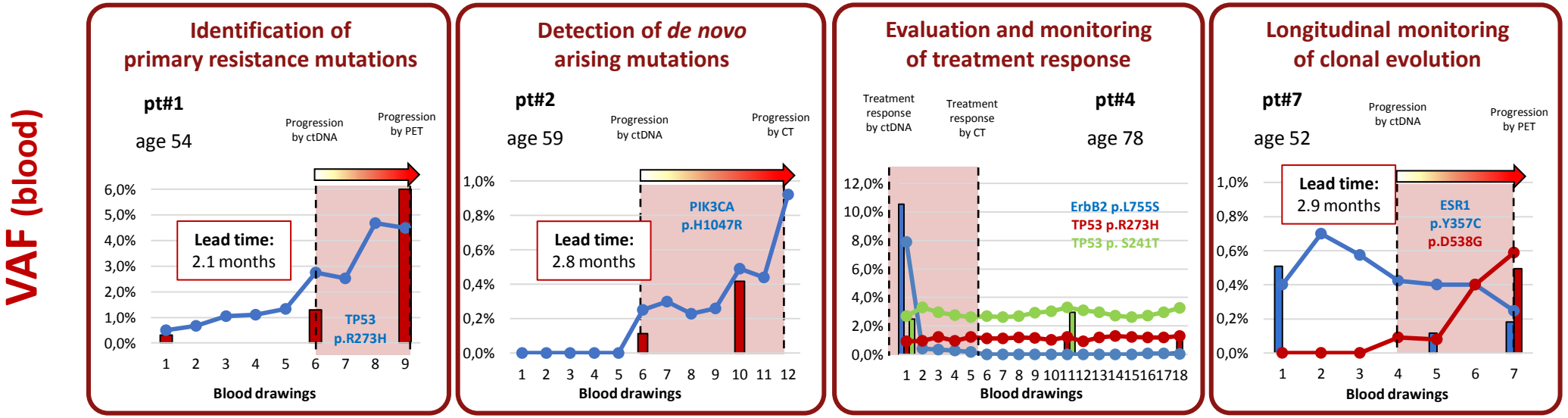
WT	6530	4685	634	137	9
MT	3048	2324	293	93	11

Pooled analysis of 10,319 patients from 19 studies, Median OS FU 7yrs .

Zardavas et al, submitted

LiquERB: the GIM21 project
when prediction become prognosis

LiqBreastTrack trial: preliminary results (II)



ctDNA present at time 0, and slowly going up

ctDNA **NOT** present at time 0, but de novo appearing some time after the beginning of treatment

ultra-fast clearance

intersecting ctDNA trajectories

resistance (primary)

resistance (acquired/adaptive)

sensitivity (best responders)

sensitivity & resistance (bi-clonal ear-marking)

Fabi, oral communication

THANK YOU for Your Attention