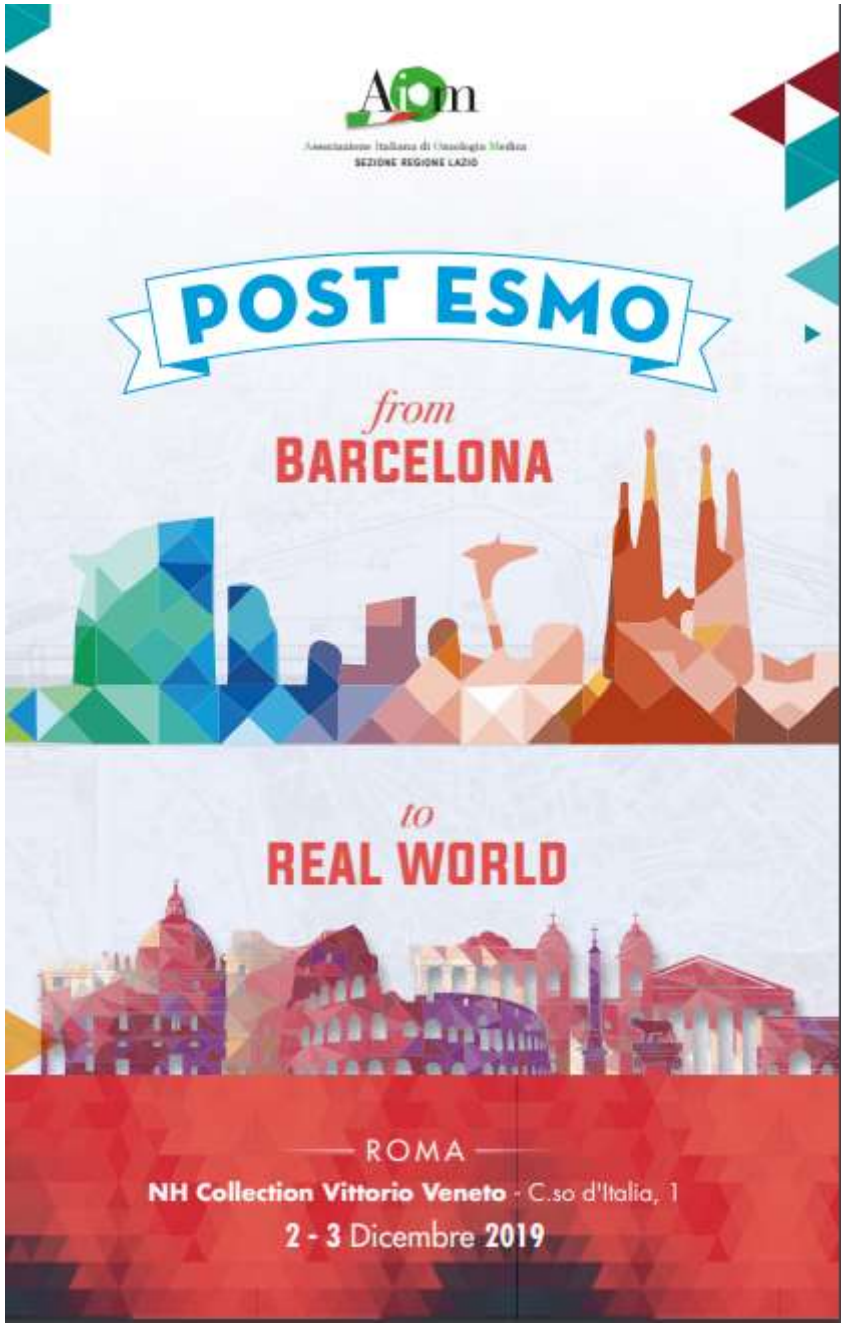


POST-ESMO
The gene signatures in early disease

Francesco Cognetti
Roma

Disclosures

Honoraria for Consultancy and Advisory Board from:

Abbott, Celgene, Glaxo Smith Kline, Roche, Bayer, Novartis, Amgen, Pfizer, Astrazeneca, Eisai, Merck-Serono, Boheringer Ingelheim, MSD, Bristol Meyers Squibb, Takeda, Astellas, Eli Lilly, Genomic Health

Prognostic Versus Predictive Biomarkers

Prognostic Biomarker

A prognostic biomarker provides information on a cancer outcome (eg, disease recurrence, disease progression)

Predictive Biomarker

A biomarker is predictive if the treatment effect is different for biomarker-positive patients compared with biomarker-negative patients
(at least 2 comparison groups are needed)

To determine whether a biomarker is potentially predictive, a formal test for an interaction between the biomarker, treatment group, and outcome must be statistically significant (*P* <0.05)

Ballman. *J Clin Oncol*. 2015.

Adjuvant Treatment Decisions Are Driven by Both Prognostic and Predictive Factors

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

- Age
- Nodal status
- Tumor size
- Tumor Grade
- HER2
- ER/PR
- Other multigene signature assays
- **Multigene Panel Assays**

Predictive factors: determine degree of response to a specific therapy

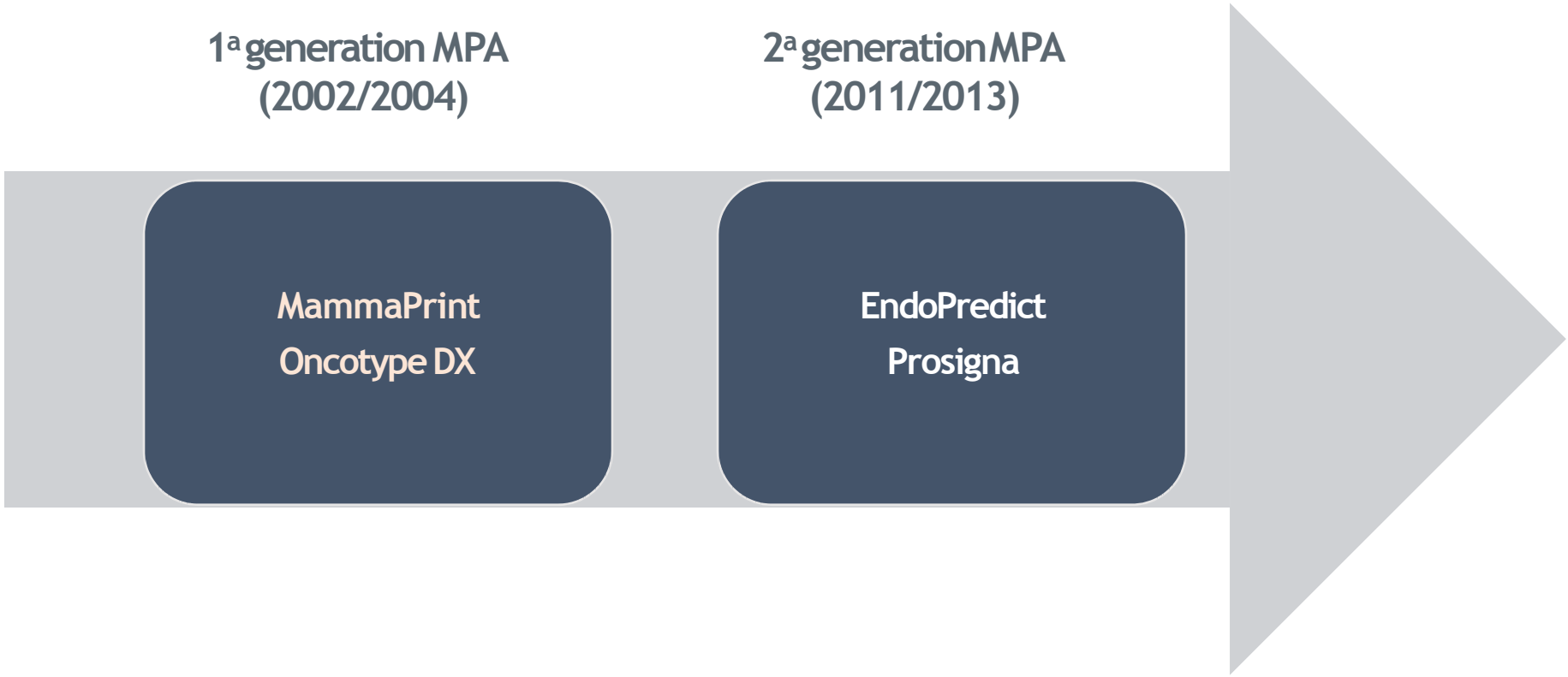
- ER
- HER2
- **Multigene Panel Assays**

Oncotype DX Breast Recurrence Score is the only genomic assay that is both prognostic and predictive of chemotherapy benefit

ER: estrogen receptor
PR: progesterone receptor
HER2: human epidermal growth factor receptor 2

Ballman. *J Clin Oncol*. 2015.

The available MPAs



The MPAs are not created equal

MPAs differ each other for genes selection and technology quantification

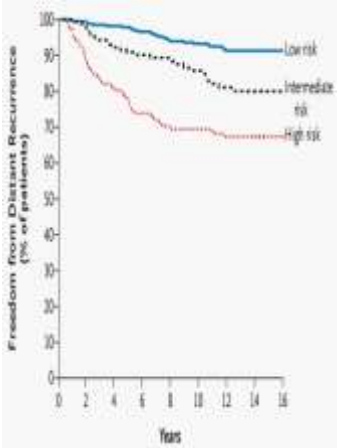
At individual level, MPAs provide different pts risk categorization

The MPAs are not interchangeable

Biologically predictable, clinically perplexing

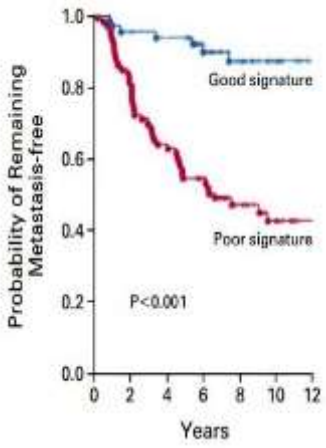
Cinical Validation Trials

OncotypeDX



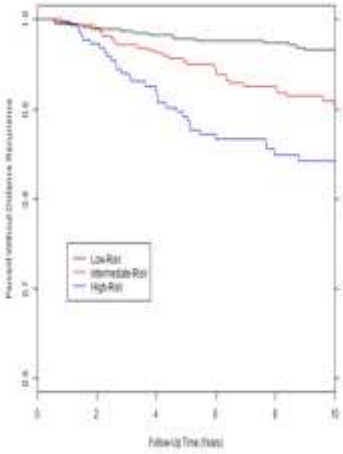
NSABP B-14
NSABP B-20
TransATAC
SWOG 8814
TAILORx (P)
RxPONDER (P)

MammaPrint



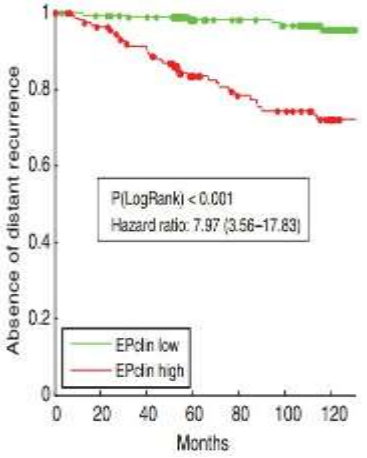
TRANSBIG
RASTER (P)
MINDACT (P)

Prosigna



TranATAC
ABCSG 8
OPTIMA (P)

EndoPredict



ABCSG 6
ABCSG 8
ATAC
GEICAM 9906
GEICAM 2003-02

Endopredict Predictive Ability

- No prospective, RCT to test the marker.
- An indirect, non comparison analysis suggested the different benefit of CT and ET according to the EPclin score
- **Endopredict's ability to select pts for CT is based solely on its prognostic capabilities**

Prosigna Predictive Ability

- Prosigna Score score provides prognostic information based on molecular intrinsec subtypes and risk of recurrence
  - Identifies node negative and node-positive patients at sufficiently low risk to be spared chemotherapy

- **Prosigna's ability to select pts for CT is based solely on its prognostic capabilities.**

MAMMAPRINT PREDICTIVE ABILITY

- The predictive ability of Mammaprint for the benefit of adj CT has not been prospectively demonstrated, as the MINDACT was not powered to directly compare outcomes b/w CT vs no CT in the C/G discordant groups.

- **For now, Mammaprint's ability to select pts for CT is based solely on its prognostic capabilities (level LoE1A for prognosis)**

RS PREDICTIVE ABILITY (ONCOTYPE DX)

- The predictive ability of RS to ascertain the futility of adding adj CT to ET in midrange risk (11-25) has been prospectively demonstrated, consistently with a strong NPV

- Conversely, the predictive ability of RS to ascertain the benefit of adj CT in high risk (>25) or the benefir of adj ET in low risk (<11) has not been proven in a prospective RCT (no PPV)

The Italian Real Life Utilization and Decision Impact of Oncotype Dx BC RS Assay

PONDx

- **Aims:**
- Describe the use of Oncotype DX in conditions that reflect the current clinical practice of Italian referral centers under simulated reimbursement conditions.
- Describe the patient population for which the test is recommended.
- Describe the impact of the Recurrence Score on the therapeutic decision.

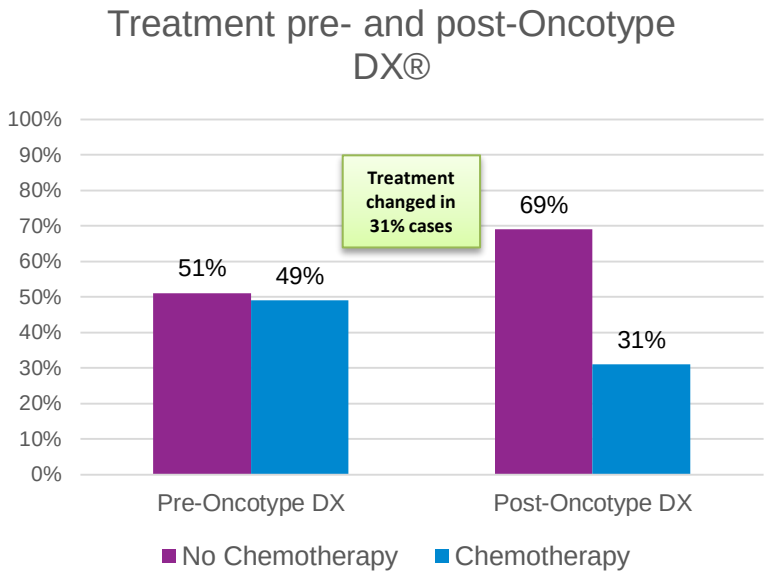
27 italian **centers** :
11 in Lombardia, 11 in Lazio, 2 in Campania, 1 in Emilia Romagna,1 in the Marche and 1 in Abruzzo.

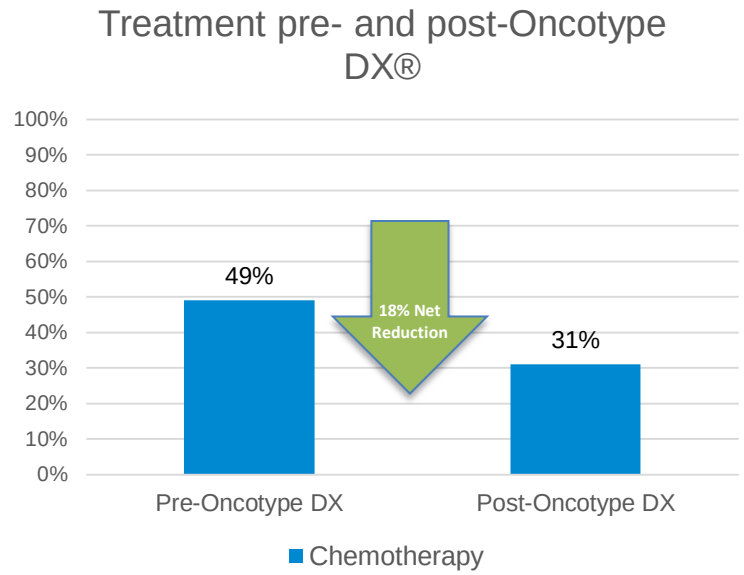
1674 pazienti

Duration of study: **01 March 2016-31 December 2017**

PONDx survey

Decision making impact analysis

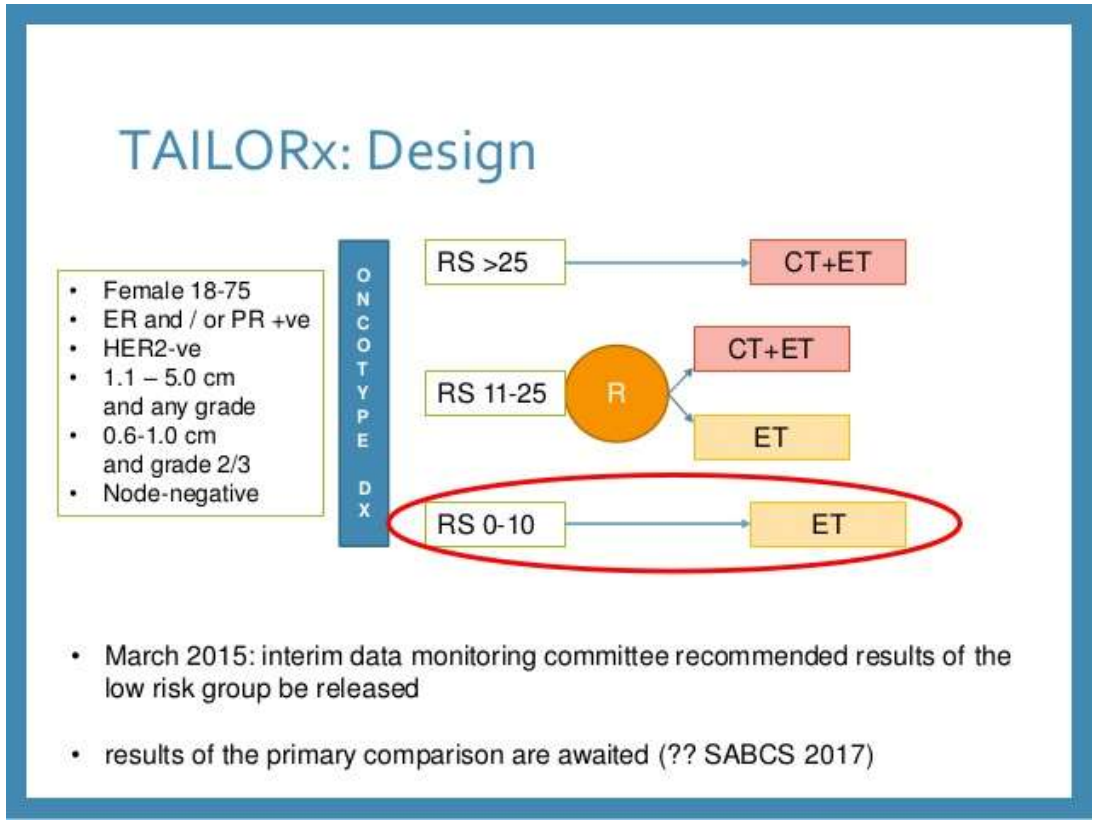




Nearly one-third of patients (31%) had a change in their decision on adjuvant chemotherapy

Oncotype DX led to a net reduction of 18% in the use of chemotherapy

TAILORx Design: Statistical Analysis Plan for Breast Recurrence Score® 11-25 Group



TAILORx Design: Statistical Analysis Plan for Breast Recurrence Score® 11-25 Group

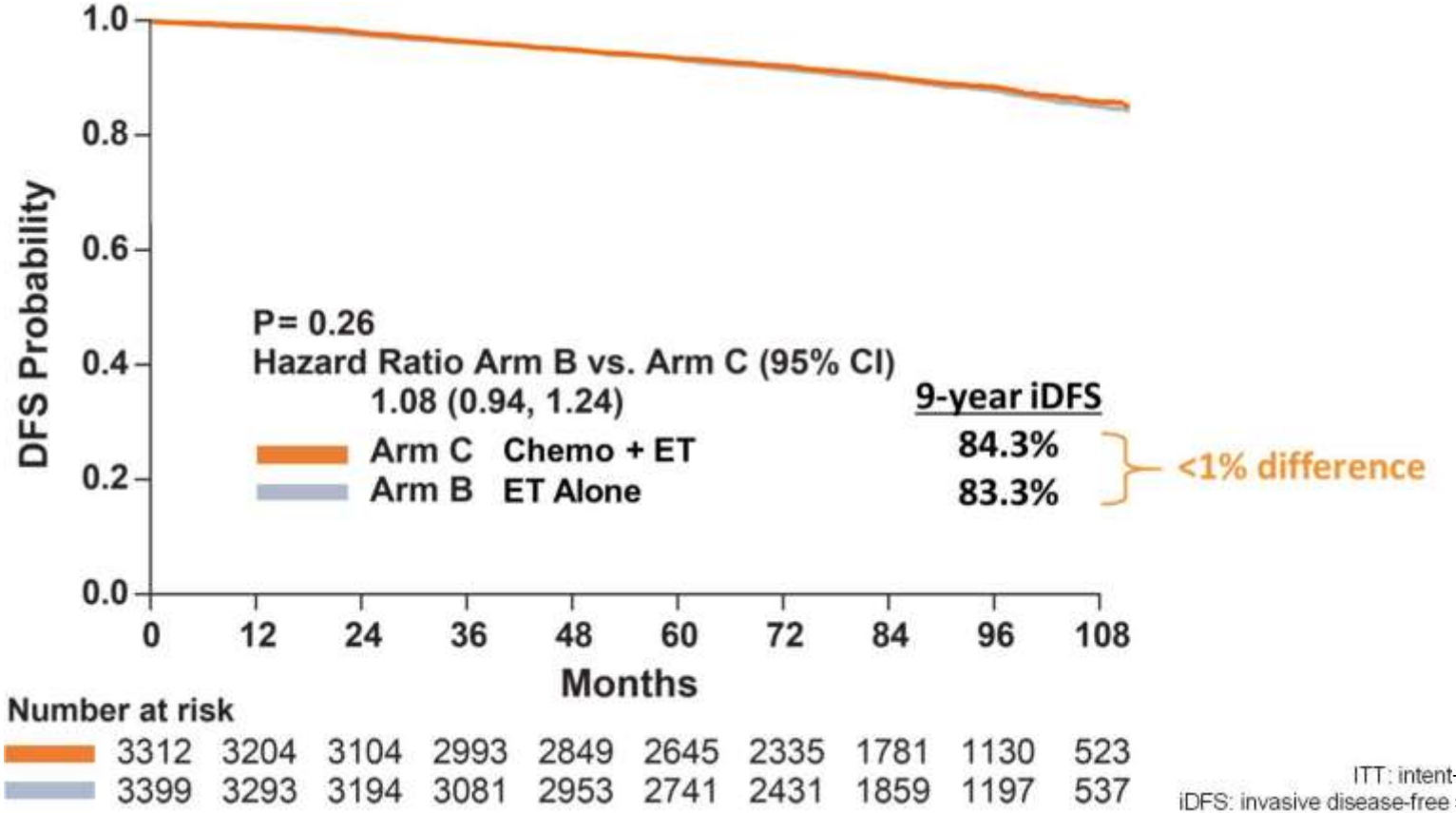
- Primary endpoint was invasive disease-free survival (iDFS)
  - Secondary endpoints included distant recurrence-free interval, relapse-free interval, and overall survival
- Noninferiority design for randomized arms
  - Arm B: experimental (endocrine therapy alone) compared to Arm C: standard of care (chemoendocrine therapy)
  - Final analysis after 835 prespecified iDFS events were reached

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

TAILORx Results: Endocrine Therapy Alone Was Not Inferior to Chemoendocrine Therapy in Patients With RS 11-25 (Arms B & C)

Primary Endpoint: 9-Year Invasive Disease-Free Survival (iDFS) in ITT Population

836 iDFS events after median follow-up of 7.5 years



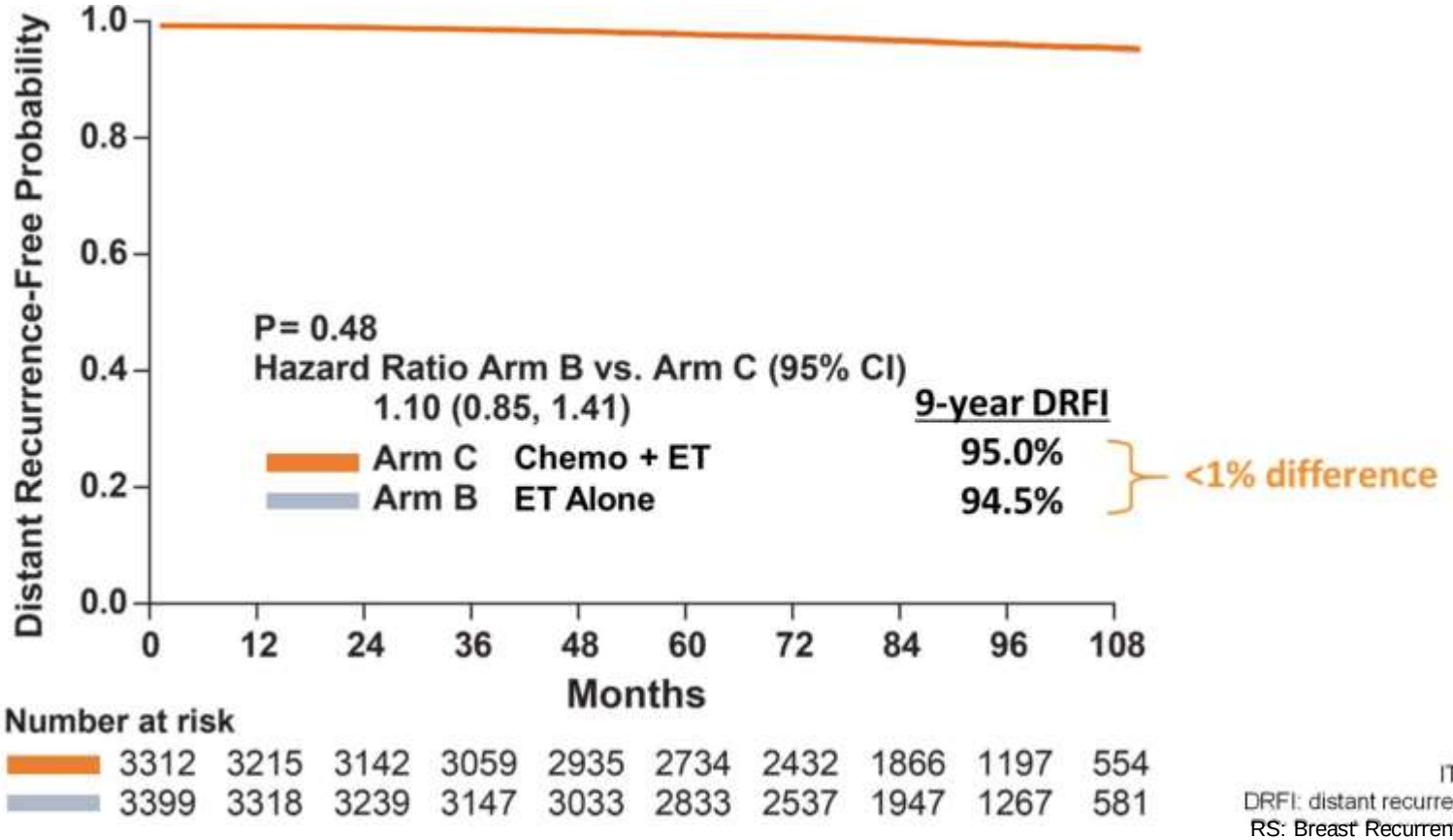
ITT: intent-to-treat
iDFS: invasive disease-free survival
RS: Breast Recurrence Score® result
ET: endocrine therapy

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

TAILORx Results: Patients With RS 11-25 (Arms B & C) Have a Very Low Risk of Distant Recurrence

Secondary Endpoint: 9-Year Distant Recurrence–Free Interval in ITT Population

199 of 836 (23.8%) were distant recurrences

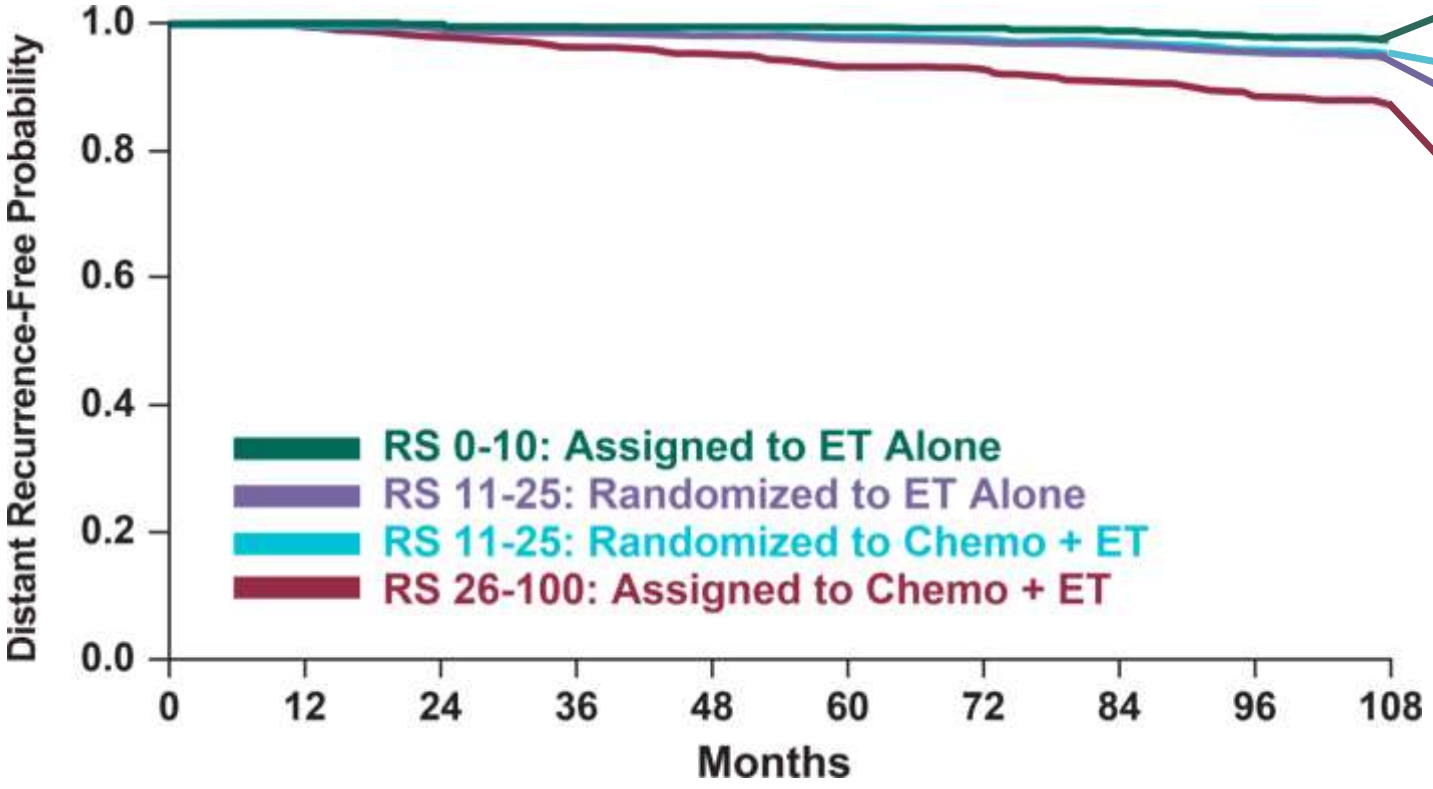


ITT: intent-to-treat
DRFI: distant recurrence–free interval
RS: Breast Recurrence Score® result
ET: endocrine therapy

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

TAILORx Results: Patients in Arms A, B & C With Recurrence Score® Results 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

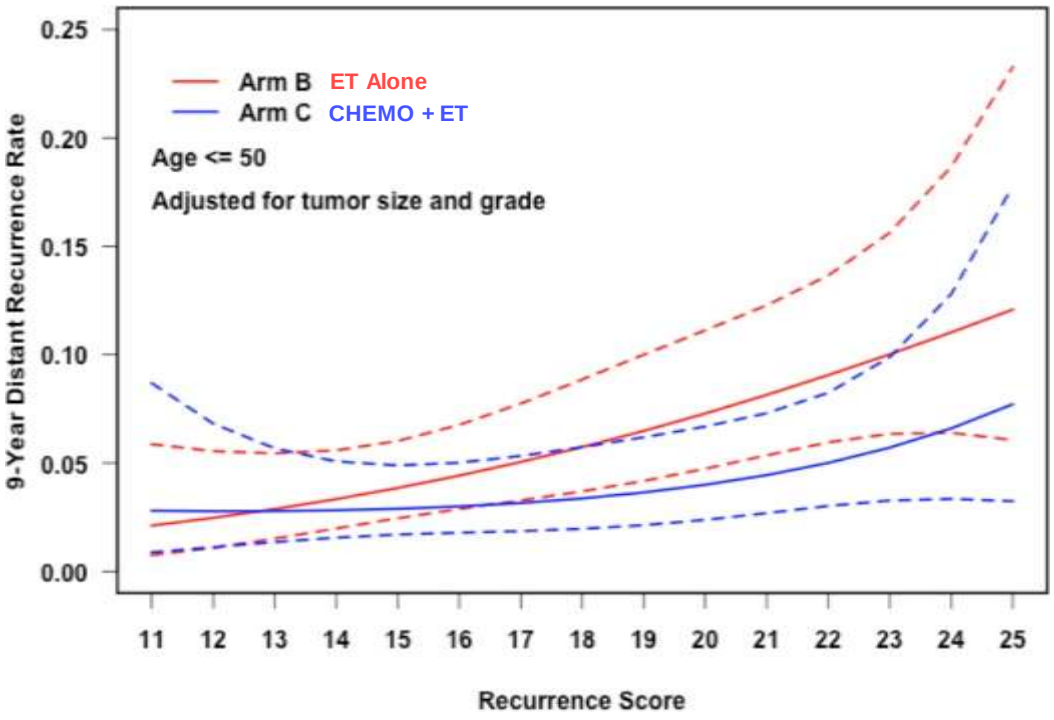
Patients in Arm D experienced a higher rate of distant recurrence at 13% despite chemoendocrine therapy

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

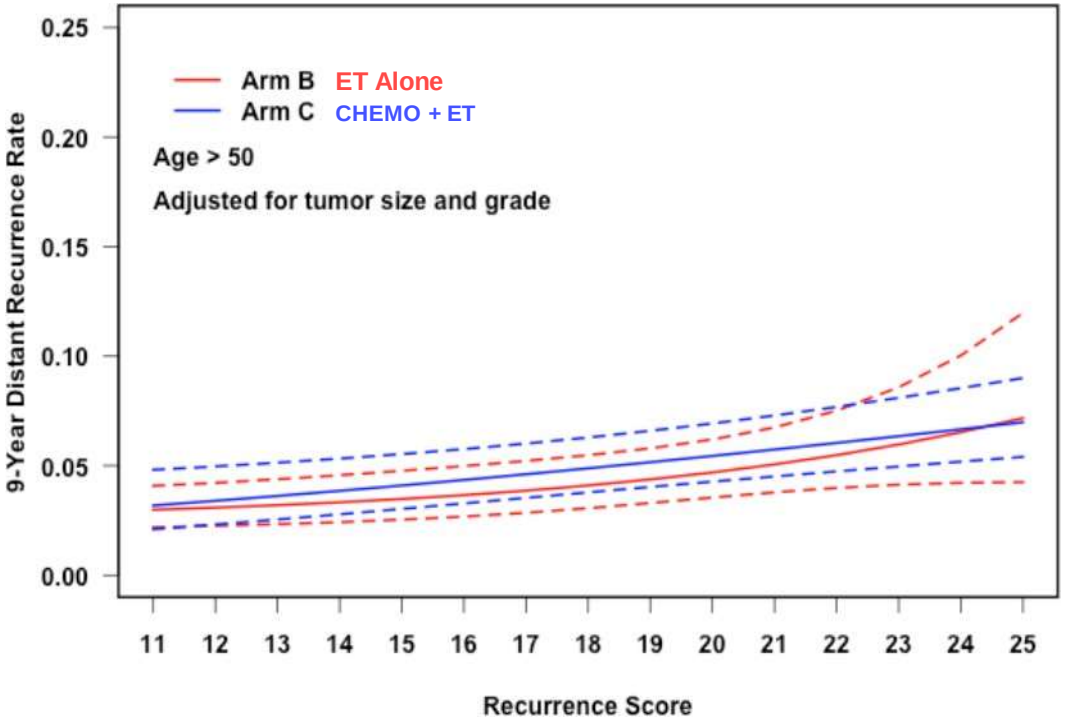
ET: endocrine therapy
ITT: intent-to-treat
RS: Recurrence Score® result

TAILORx Results: Association Between Continuous Recurrence Score® Results 11-25 and 9-Year Distant Recurrence Rate by Treatment Arms Stratified by Age

≤50 Years (n=2216)



>50 Years (n=4495)



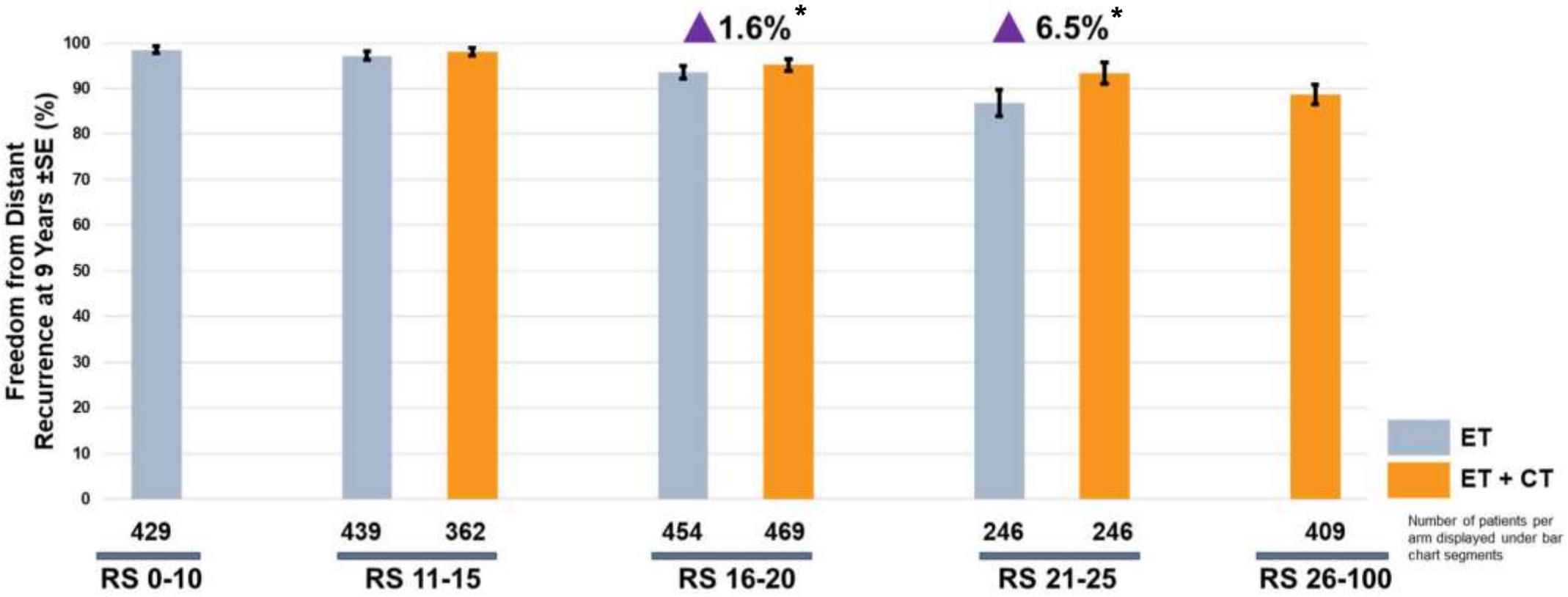
The magnitude of chemotherapy benefit in patients ≤50 years increases with increasing Recurrence Score result, but was not statistically significant

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

ET: endocrine therapy

TAILORx Results: A Small Chemotherapy Benefit is Seen in Women ≤50 Years (N = 3054) With Recurrence Score® Results 16-20 and 21-25

9-Year Freedom From Distant Recurrence



*These differences in distant recurrences, while not statistically significant, may be clinically significant.

ITT: intent-to-treat
ET: endocrine therapy
CT: chemotherapy
RS: Recurrence Score results

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

TAILORx Results: Oncotype DX Breast Recurrence Score® Prevents Over- and Undertreatment of Patients

		Recurrence Score	
		0-25	26-100
Clinical Risk*	Low (n = 6615)	**91%**	9%
	High (n = 2812)	73%	**27%**

Would have been undertreated

Would have been overtreated

*low clinical risk defined by low grade and tumor size ≤ 3 cm, intermediate grade and tumor size ≤ 2 cm, and high grade and tumor size ≤ 1 cm; high clinical risk defined as all other cases with known values for grade and tumor size

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

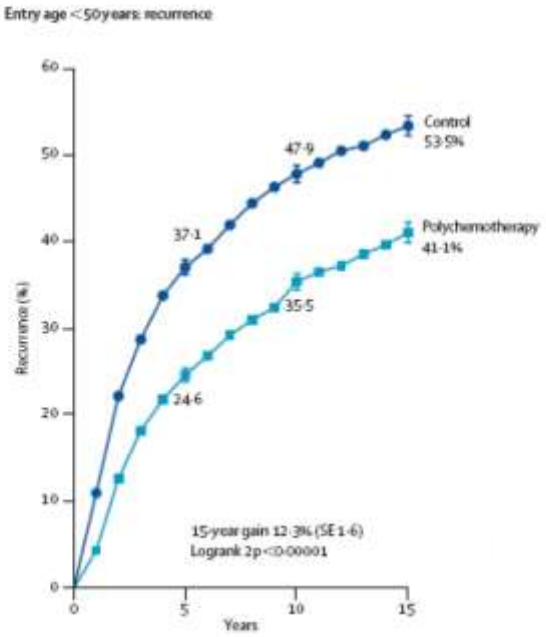
Are lower distant recurrence rates in women ≤50 years with Recurrence Scores® 16-25 due to chemotherapy benefit or ovarian suppression?

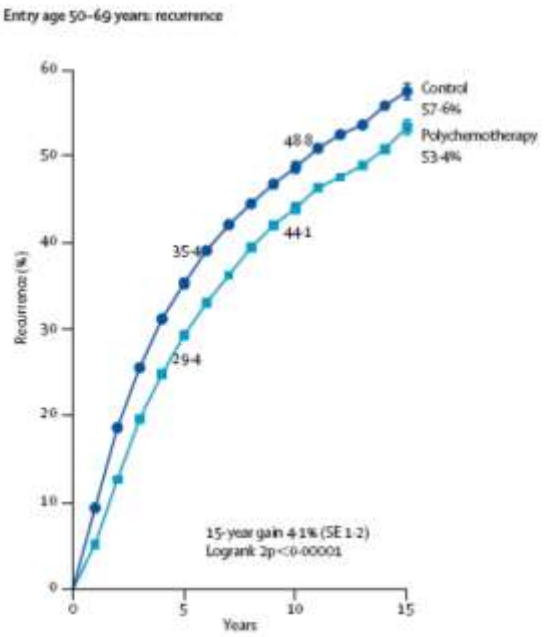
Endocrine Therapy Received in Premenopausal Women in TAILORx

	Recurrence Score 0-10	Recurrence Score 11-25		Recurrence Score 26 or Higher
	Arm A Endocrine Therapy	Arm B Endocrine Therapy	Arm C Chemoendocrine	Arm D Chemoendocrine
Endocrine Therapy (Premenopausal)	(n=478)	(n=1212)	(n=1203)	(n=407)
AI	32 (7%)	53 (4%)	110 (9%)	41 (10%)
OFS	17 (4%)	62 (5%)	33 (3%)	21 (5%)
OFS and AI	32 (7%)	124 (10%)	94 (8%)	31 (8%)
Tam	238 (50%)	558 (46%)	461 (38%)	177 (43%)
Tam and AI	146 (31%)	394 (33%)	482 (40%)	117 (29%)
Other	1 (0%)	5 (0%)	2 (0%)	1 (0%)
None Reported	12 (3%)	16 (1%)	21 (2%)	19 (5%)

Premenopausal – included ovarian suppression in 15%

Chemotherapy Reduces the Risk of Recurrence During the First 5 Years Only





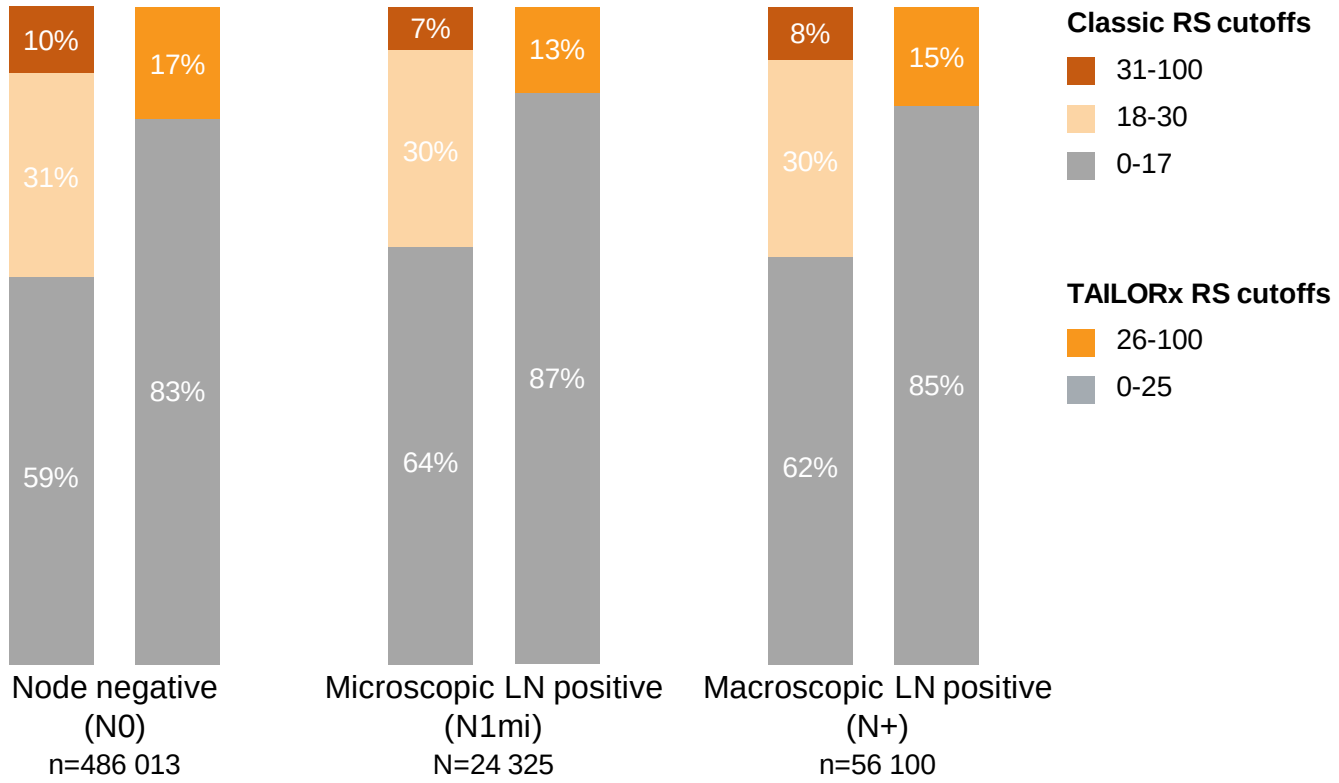
Absolute Difference in Recurrence over Time			
	5yrs	10yrs	15yrs
<50 years	12.5%	12.4%	12.4%
50-59 years	6.0%	4.7%	4.2%

EBCCTG. *Lancet* 2006.

Using the Recurrence Score® in Node-Positive Disease after TAILORx

Lymph Node Status Does Not Predict Tumor Biology

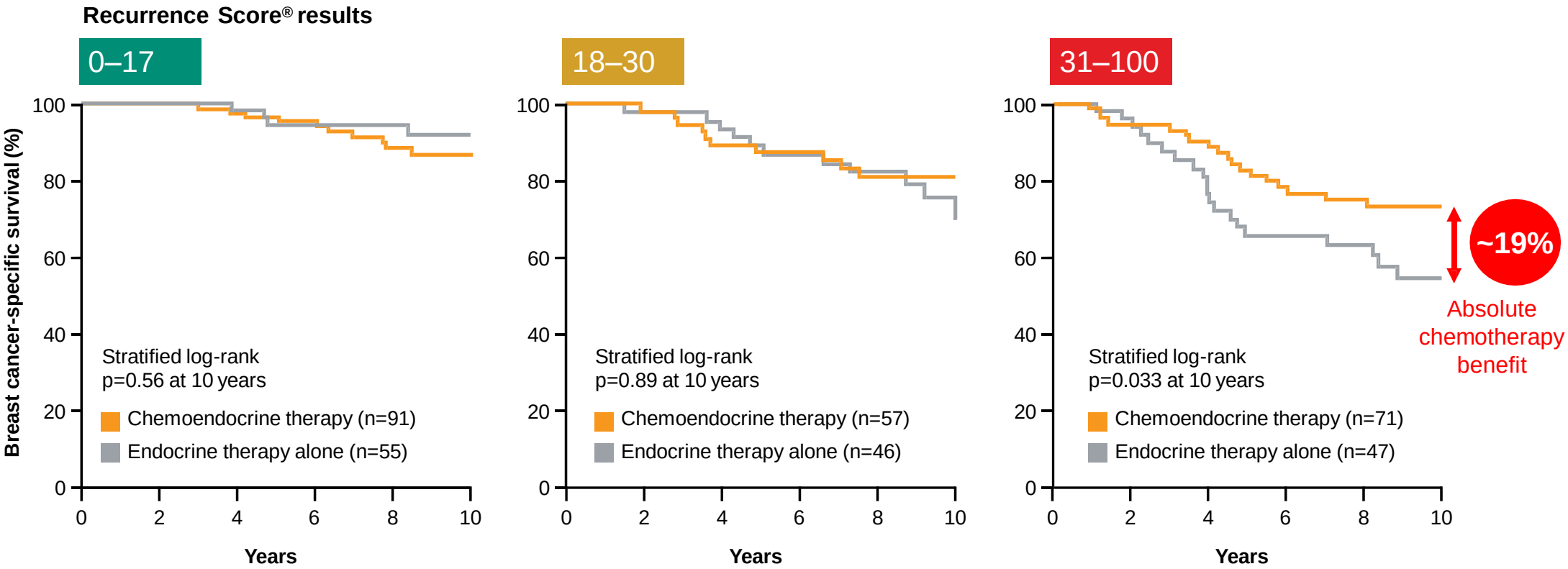
Genomic Health Clinical Laboratory (2004-2017), N=610,350



- 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

SWOG 8814: Recurrence Score® Result Predicts Chemotherapy Benefit in Node-Positive Patients



No benefit to chemotherapy for low Recurrence Score results

Interaction *P* = 0.029

Strong benefit to chemotherapy for high Recurrence Score results

Albain et al. *Lancet Oncol*. 2010.

NCCN Guidelines® for Breast Cancer

Node-Positive, Hormone Receptor-Positive, HER2-Negative Invasive Breast Cancer

Node-positive
- pN1mi (≤2 mm axillary node metastasis)
- N1 1-3 nodes

→

Patients who are candidates for chemotherapy:
- Consider multigene assay to assess prognosis and determine chemotherapy benefit

→

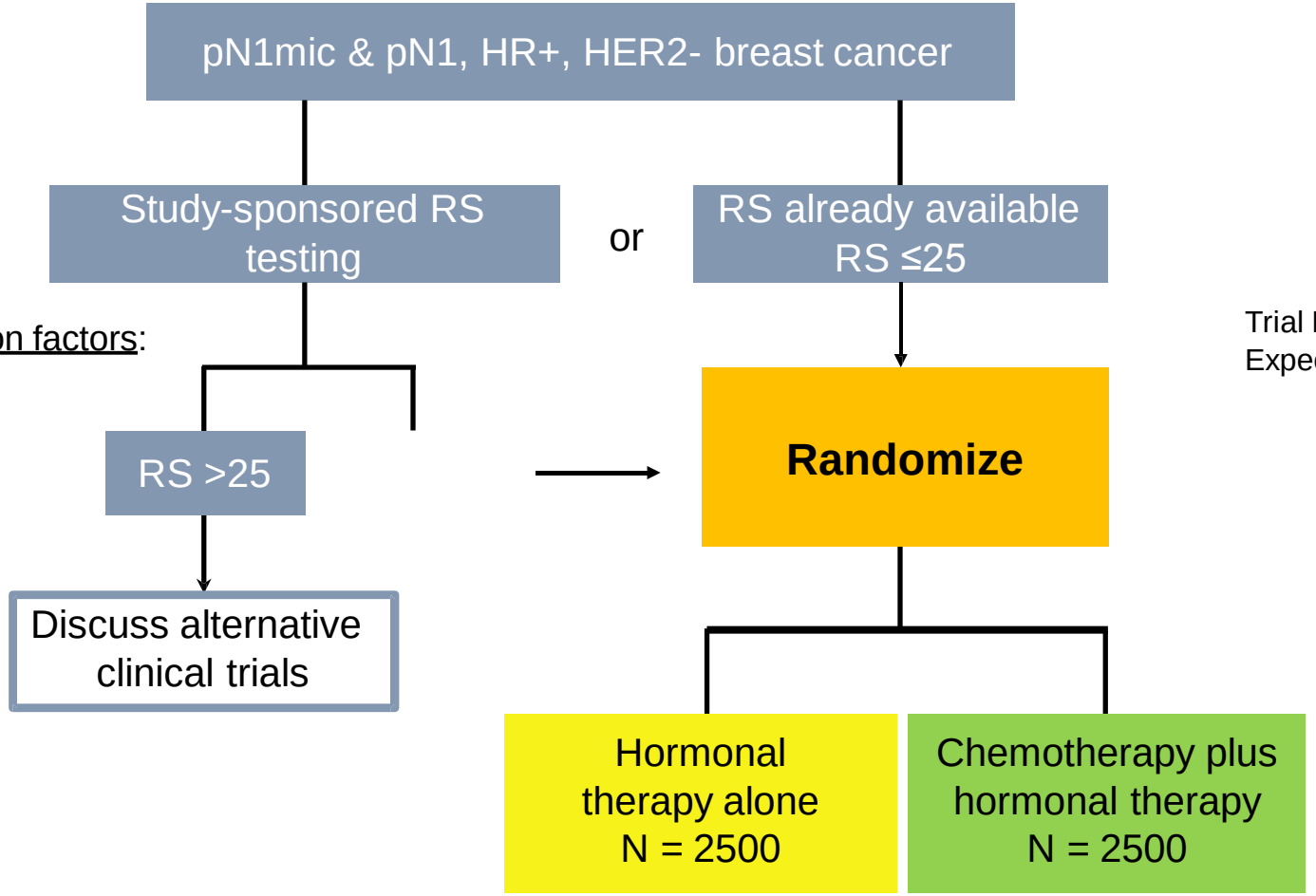
Adjuvant endocrine therapy
or
Adjuvant chemotherapy followed by endocrine therapy*

***Because of a higher risk of distant recurrence, patients with 1-3 positive lymph nodes and RS of ≥18 shouldbe considered for adjuvant chemotherapy**

NCCN Guidelines note that multigene assays such as the Oncotype DX Breast Recurrence Score® test can be considered in select patients with 1-3 positive ipsilateral axillary lymph nodes to guide the addition of chemotherapy to standard hormonal therapy based on retrospective, predictive data[1]

[1]Albain et al. *Lancet Oncol*. 2010.

Oncotype DX Breast Recurrence Score® Test for Treatment Decisions in Node-Positive Disease: RxPONDER Trial Schema



Randomization stratification factors:

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

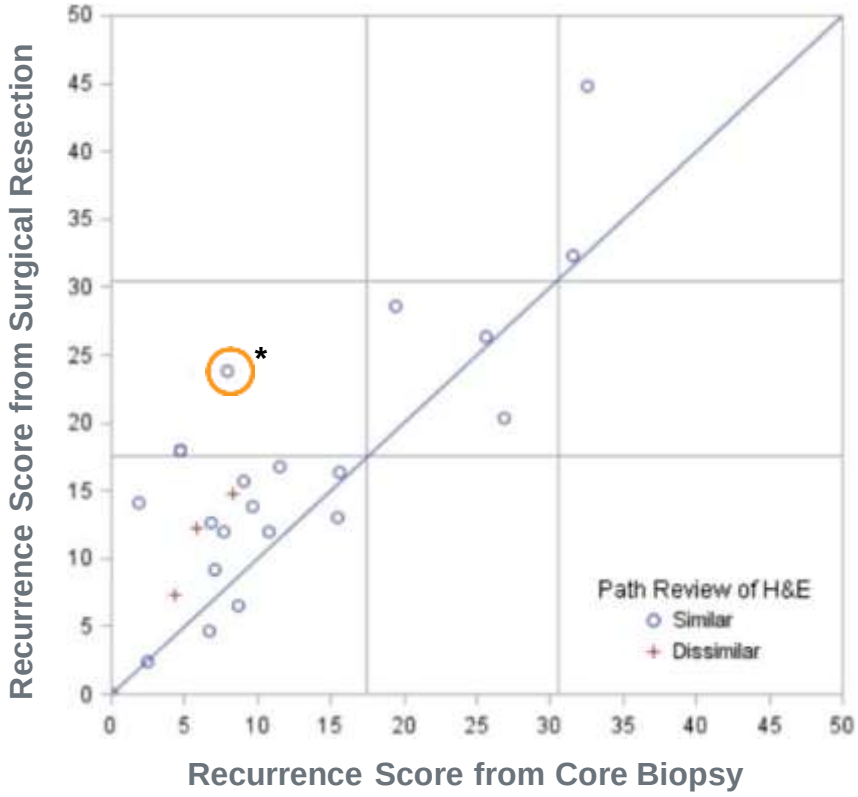
Trial Initiated: January 2011
Expected Completion: 2022

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

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

Value of Genomic Testing in Neoadjuvant Setting

High Degree Of Concordance Between Recurrence Score® Results Generated From Core Needle Biopsies And Surgical Excisions



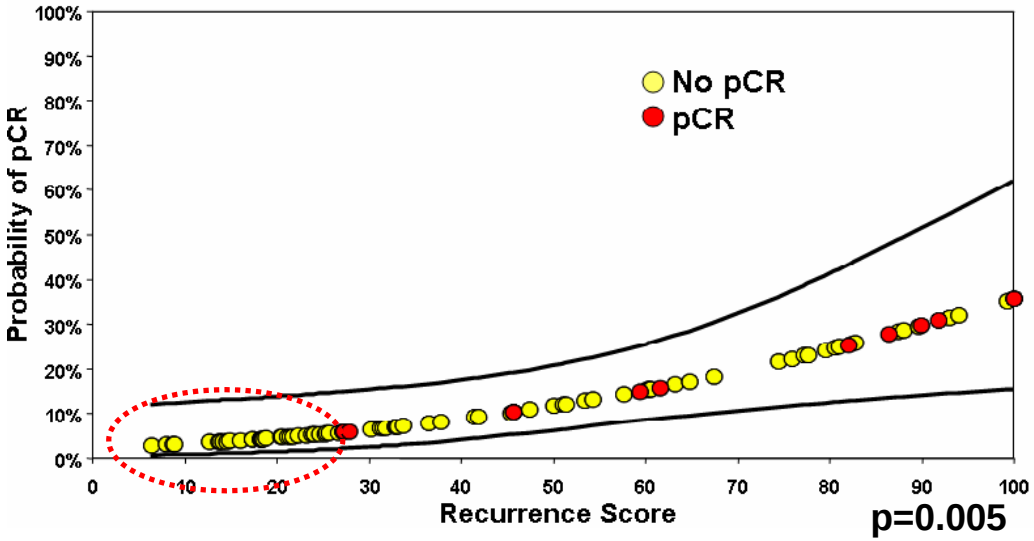
*Potentially clinically meaningful change in risk group

Group	N	Pearson's r	Concordance Correlation	Paired Differences (resection – core)	
				Mean	95% CI
Similar H&E	21	0.83	0.76	3.9	1.2, 6.6
All Patients	24	0.83	0.76	4.1	1.7, 6.4

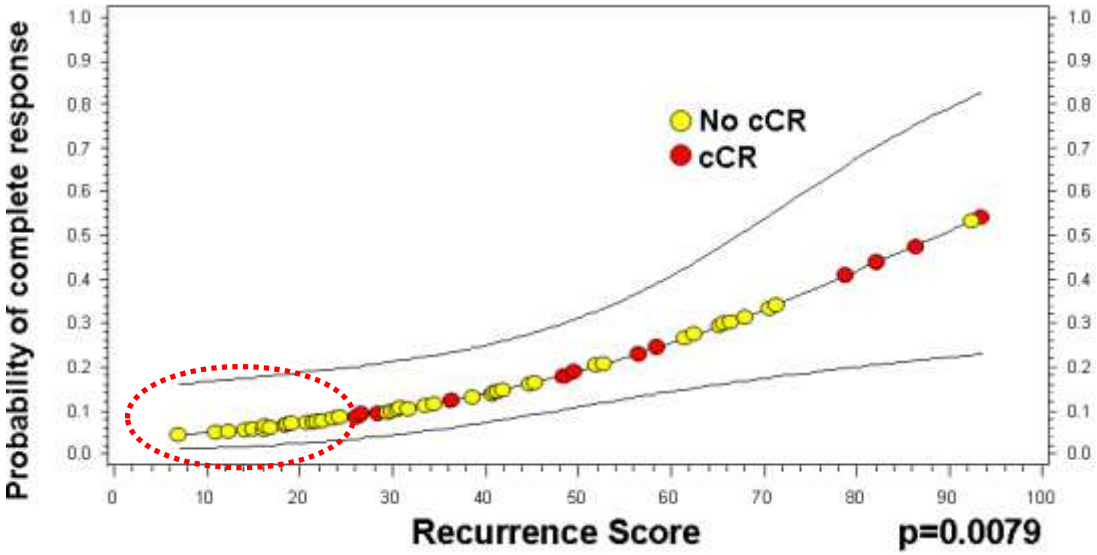
Stull et al. SABCS 2011.

Patients with Low Recurrence Score® Result Are Less Likely to Respond to Neoadjuvant Chemotherapy

Neoadjuvant
Anthracyline-Taxane Treatment
(N=89)



Neoadjuvant
Docetaxel Treatment
(N=72)



Gianni L, et al. *J Clin Oncol*. 2005;23(29):7265-7277.
Chang JC, et al. *Breast Cancer Res Treat*. 2008;108 (2):233-240.

Neoadjuvant Studies Supporting Chemotherapy Benefit with Recurrence Score® 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%

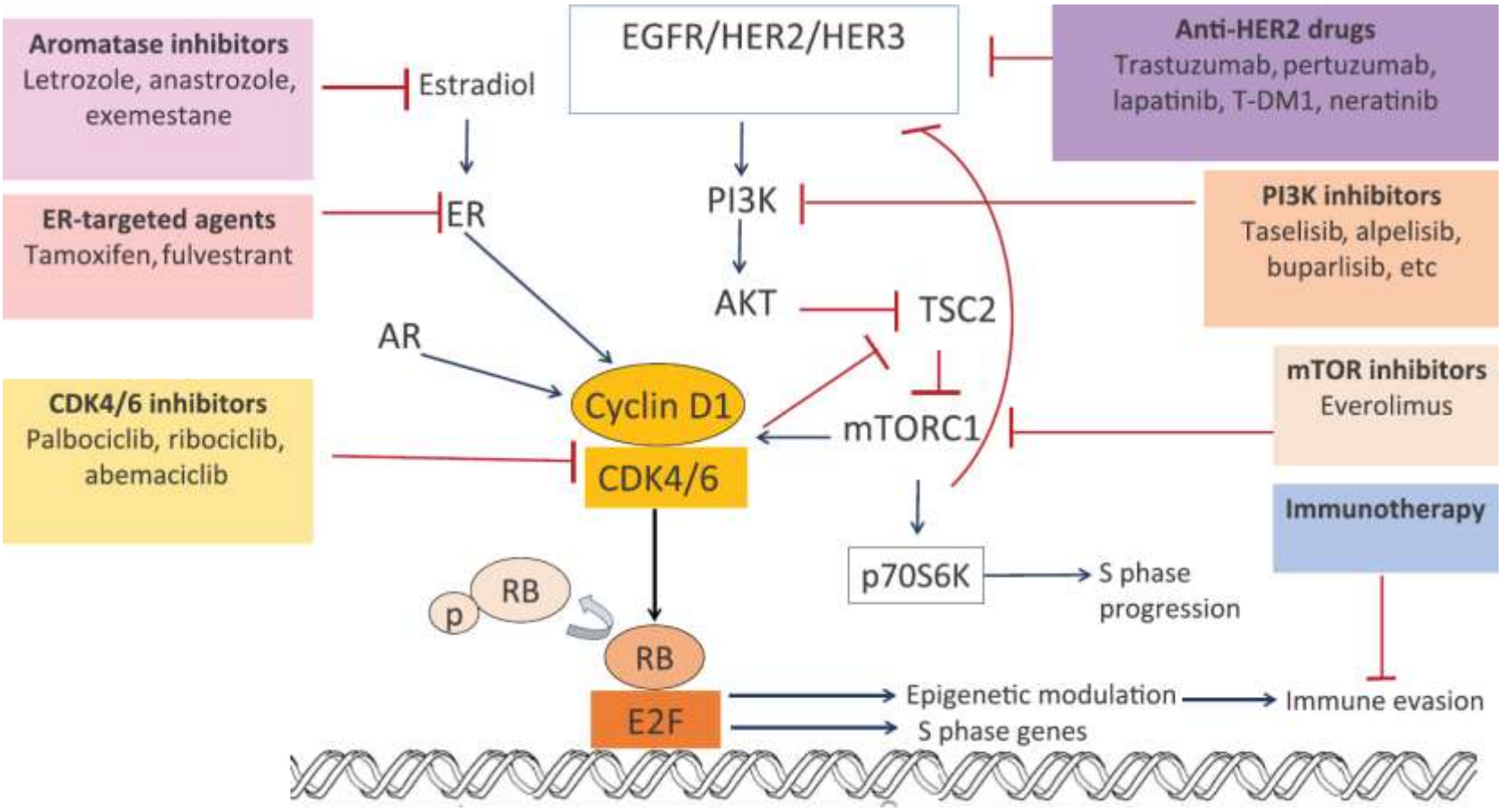
RS: Breast Recurrence Score® result
CT: chemotherapy
pCR: pathologic complete response

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

Conclusion

- ✓ MPAs are not created equal and are not interchangeable
- ✓ MPAs provide more prognostication than prediction, but OncotypeDX tested the marker in the midrange risk (11-25)
- ✓ The integration of genomic and clinical information may provide a more accurate estimation of prognosis for individual patients than could be provided by either the genomic or clinical information alone

Potential Combination Targeted Therapies for HR+ Breast Cancer



Pernas et al. *Ther Adv Med Oncol.* 2018,

RegioneLombardia
LA GIUNTA

DELIBERAZIONE N° XI / 1986 Seduta del 23/07/2019

LOW RISK: AT LEAST 4 OF THIS	HIGH RISK: AT LEAST 4 OF THIS
G1	G3
T1	T3-4
KI67 <15%	KI67 >30%
ER 80%	ER <30%
N0	N+

It is possible to reduce 50-75% chemotherapy prescription

TAILORx Results: Oncotype DX Breast Recurrence Score® Prevents Over- and Undertreatment of Patients

		Clinical Risk*	
		Low	High
Recurrence Score	0-25 (n = 8068)	**75%**	**25%**
	26-100 (n = 1359)	**43%**	**57%**

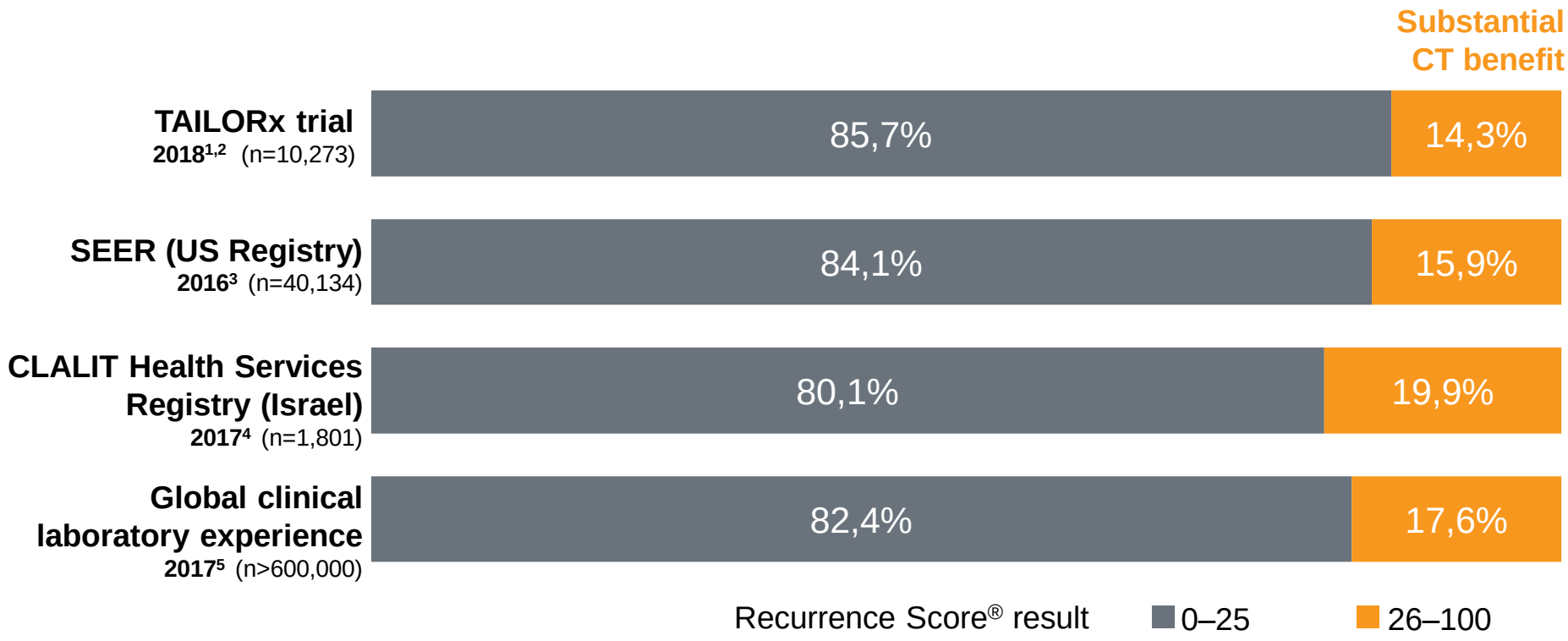
Would have been overtreated

Would have been undertreated

*low clinical risk defined by low grade and tumor size ≤ 3 cm, intermediate grade and tumor size ≤ 2 cm, and high grade and tumor size ≤ 1 cm; high clinical risk defined as all other cases with known values for grade and tumor size

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

Oncotype DX Breast Recurrence Score® Assay Consistently Identifies Patients Who Benefit From Chemotherapy

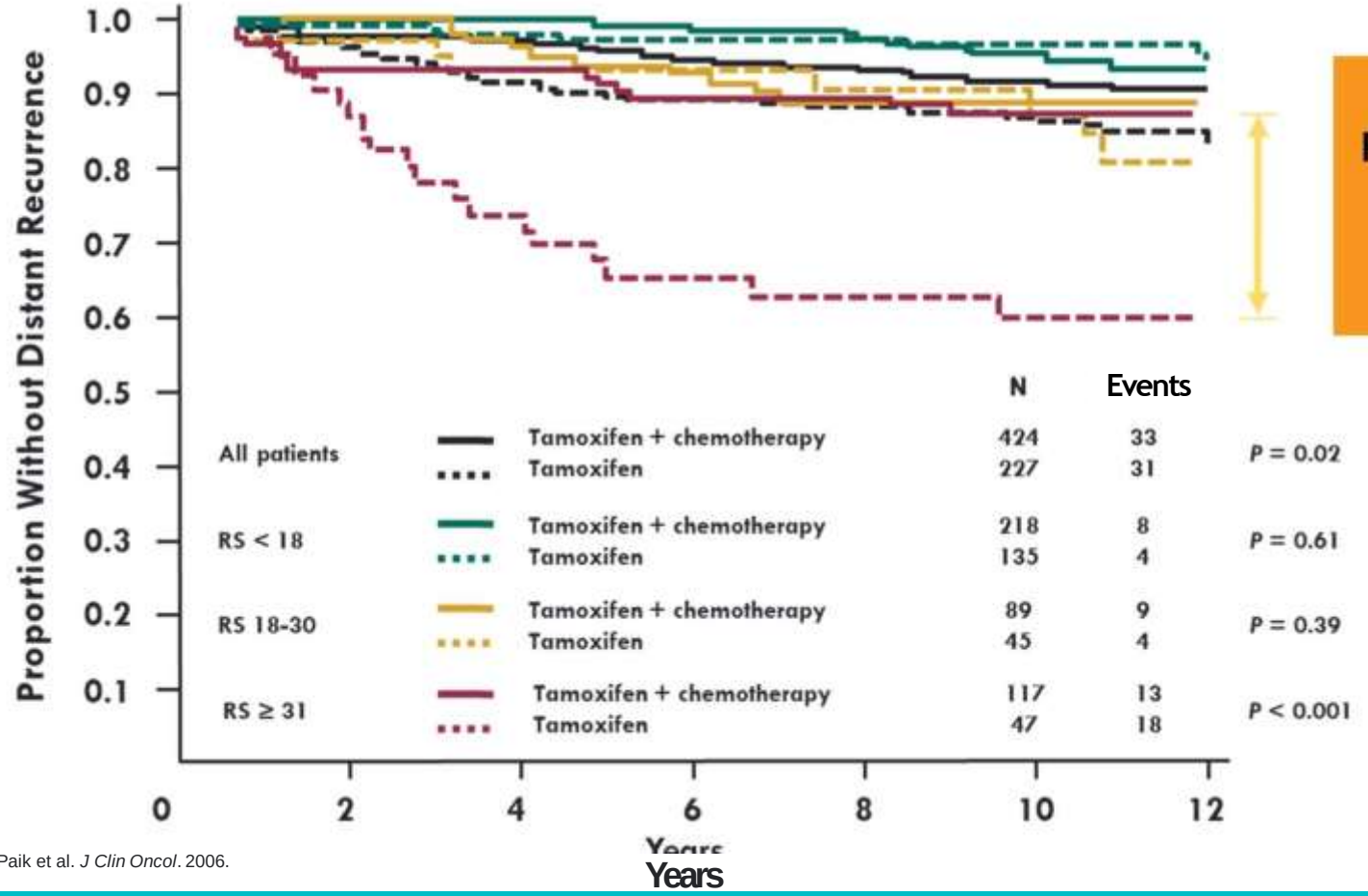


*HR+, HER2–, Node-negative
**Adding patients age ≤50 years and RS 21–25 would represent an additional 5%

Sparano et al. *N Engl J Med.* 2015. Sparano et al. *N Engl J Med.* 2018. Petkov et al. *npj Breast Cancer.* 2016. Stemmer et al. *npj Breast Cancer.* 2017. Blohmer et al. ESMO 2017. Abstract 192P.

Breast Recurrence Score® 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.

RS: Recurrence Score result