I test genomici nelle pazienti con EBC HR+: quali test e in quali pazienti? Quali informazioni forniscono al clinico?

Maria Vittoria Dieci

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IOV - IRCCS

Rationale for treatment individualization for early HR+/HER2- BC patients

100 BC pts
20% HER2+ BC
15% TN BC

65 HR+/HER2- BC pts candidate to HT
5% ≥4 Node positive
2-3% too frail for CT

50 HR+/HER2- BC PATIENTS POTENTIALLY CANDIDATE TO ADJUVANT Ct + HT

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

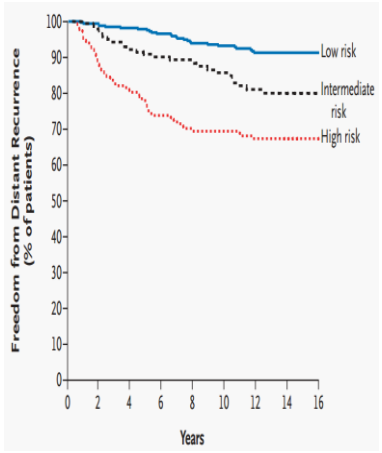
Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Catherine Van Poznak, Robert C. Bast, and Daniel F. Hayes

- CT produces the same proportional risk reduction in all patients (EBCTCG).
- This translates into different degrees of absolute benefit, depending on the individual estimate of absolute risk of recurrence.
- What is the threshold of absolute risk of recurrence that defines patients that can be safely spared CT?

Absolute distant recurrence risk at baseline	Relative risk reduction with CT	Absolute risk reduction from CT	Risk of Fatal, life-threatening, permanent CT toxicity
50-60%	30%	15-20%	2-3%
10-15%	30%	2-3%	2-3%

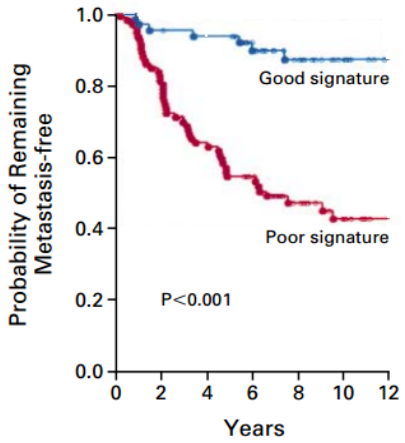
Multigene prognostic tests for HR+/HER2-

OncotypeDX



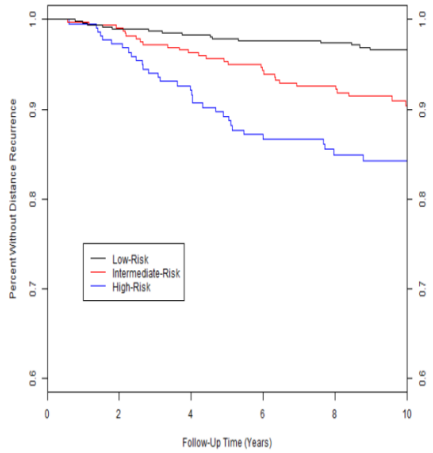
Paik NEJM 2006

MammaPrint



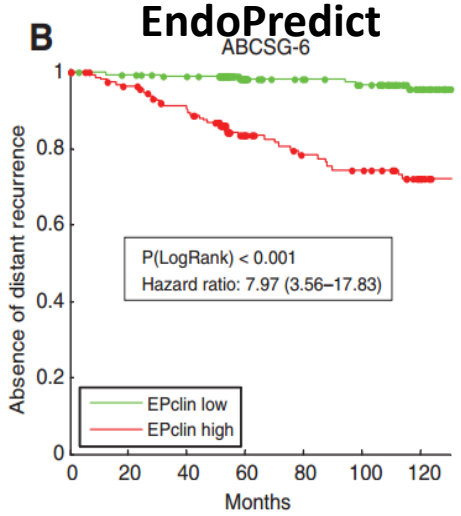
Vijver NEJM 2002

PAM50 ROR



Dowsett JCO 2013

EndoPredict



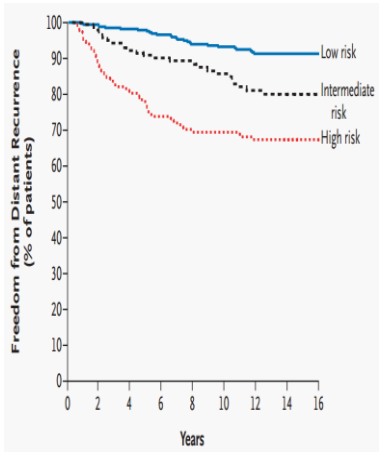
Filipits CCR 2011

(include tumor size+nodal status)

All have at least LoE1B as prognostic tests: results from ≥2 prospective trials analyzed retrospectively, not designed to test the marker

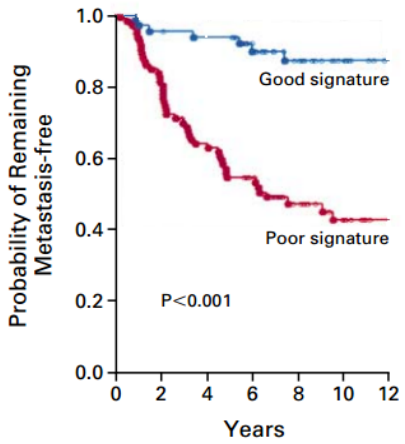
Multigene prognostic tests for HR+/HER2-

OncotypeDX



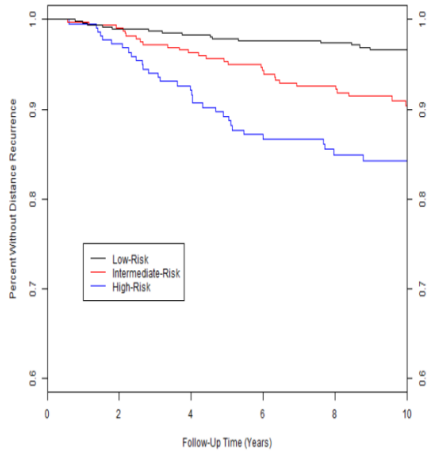
Paik NEJM 2006

MammaPrint



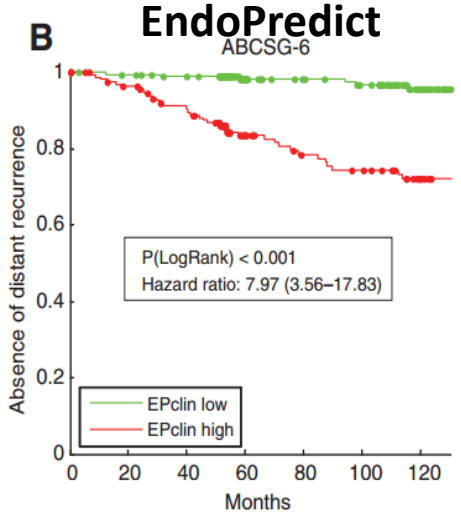
Vijver NEJM 2002

PAM50 ROR



Dowsett JCO 2013

EndoPredict

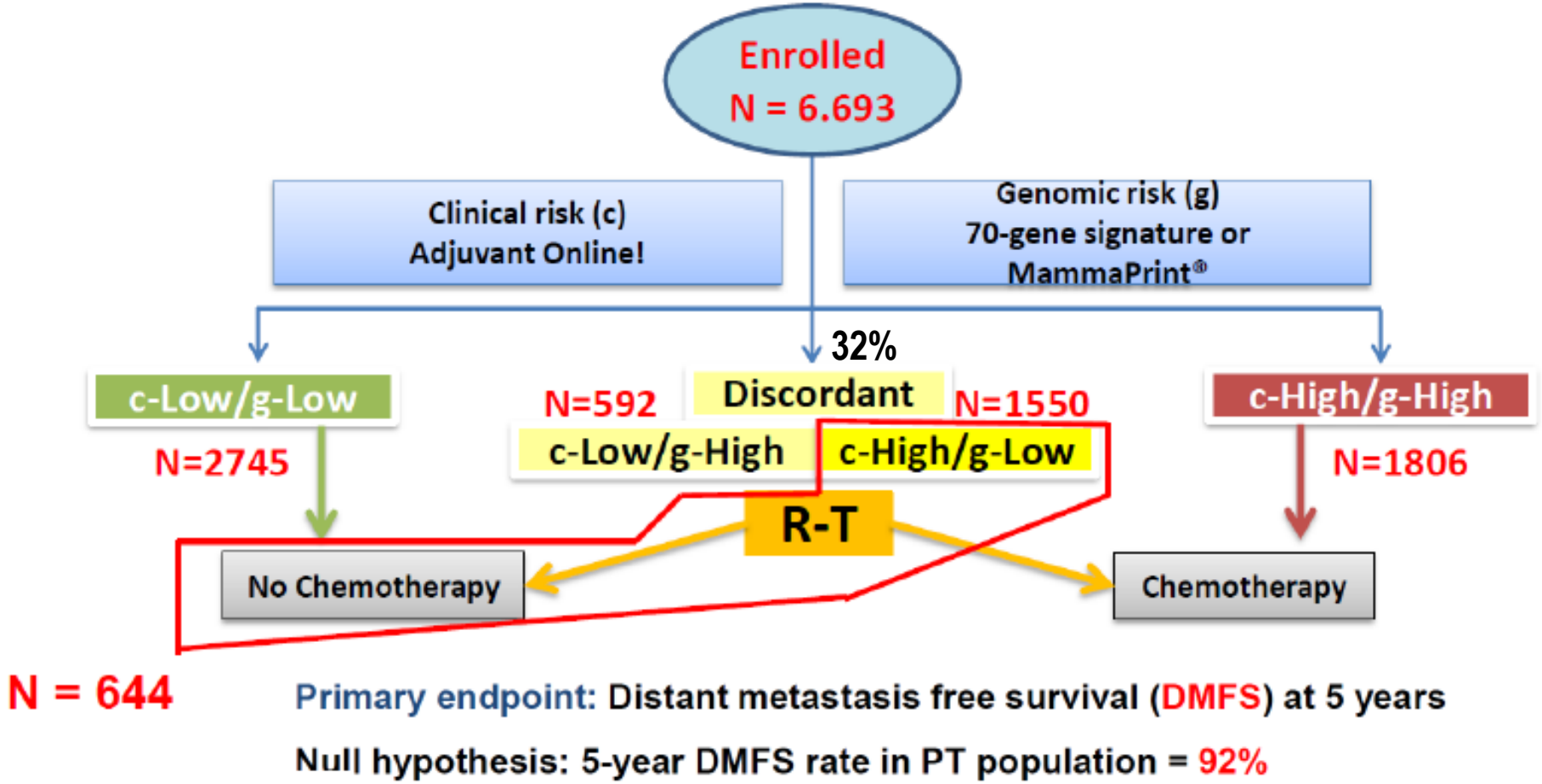


Filipits CCR 2011

(include tumor size+nodal status)

LoE1A: results from ≥1 prospective trial specifically designed to test the marker

MINDACT: Study Design

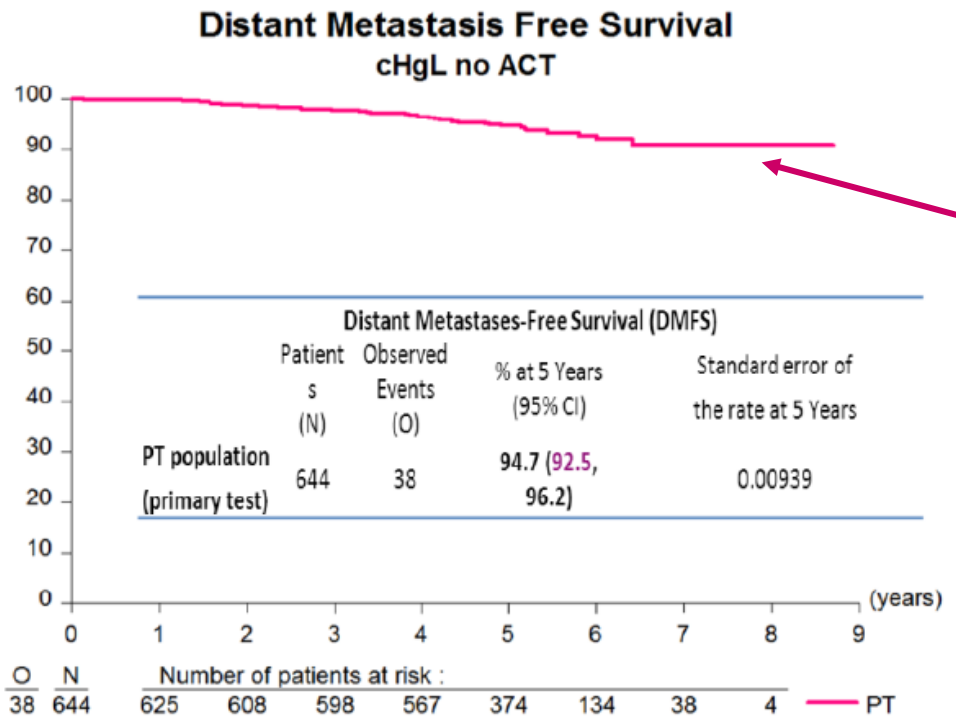


Cardoso F, NEJM 2016

MINDACT DISCORDANT GROUP: PRIMARY ENDPOINT

Median FU 5yrs

The primary statistical test (DMFS at 5Y)



N=1550 C-High/G-low
90% ER+/HER2-
52% N0
42% T<2cm
71% G1-2

N=644 no CT

Null Hypothesis: set at 92%

Observed 5Y DMFS = 94.7%

95% CI ≈ 92.5 – 96.2% excludes 92% !!!

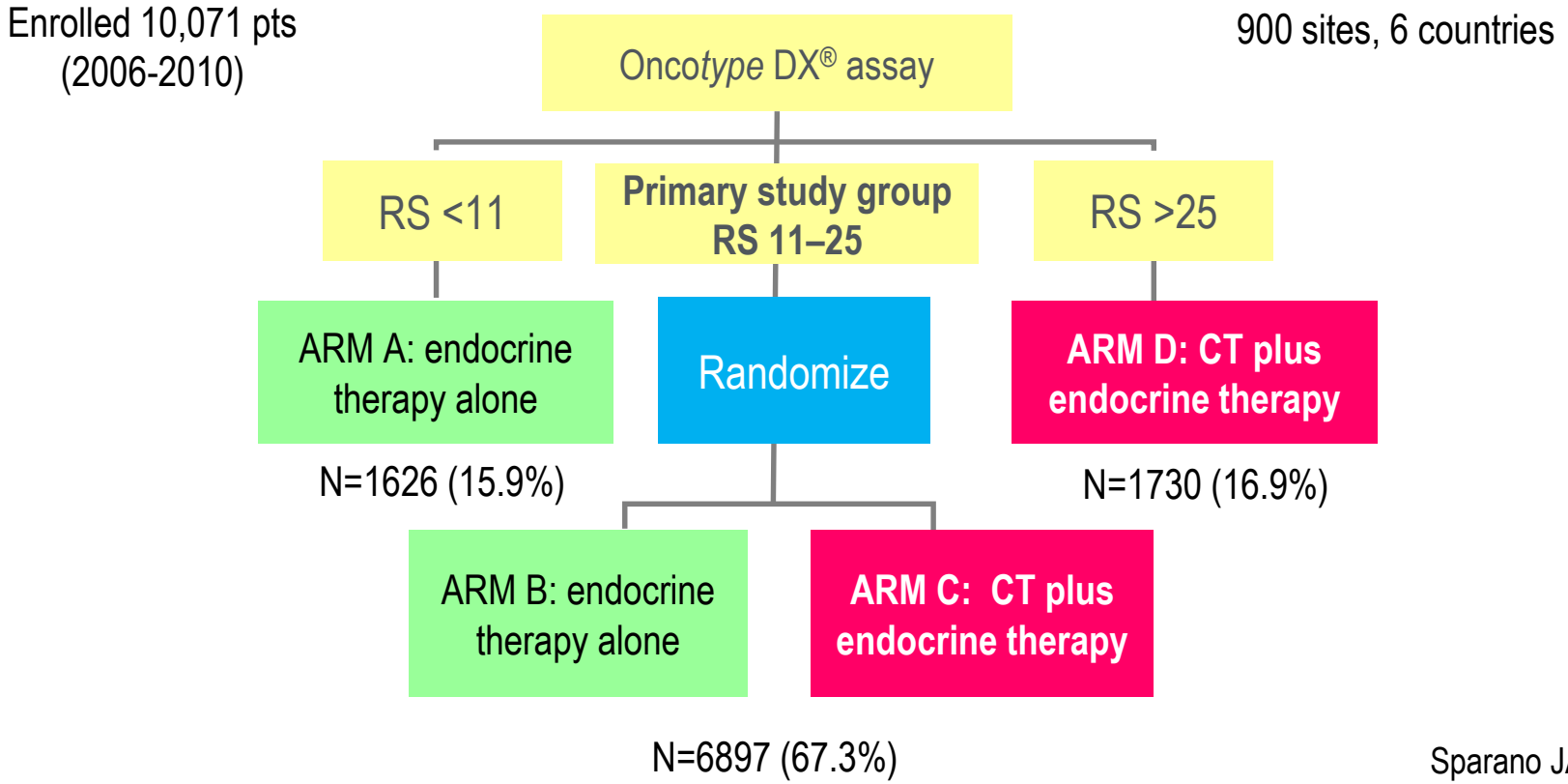
LoE 1A

Cardoso F, NEJM 2016

Trial Assigning IndividuaLized Options for Treatment (Rx) TAILORx

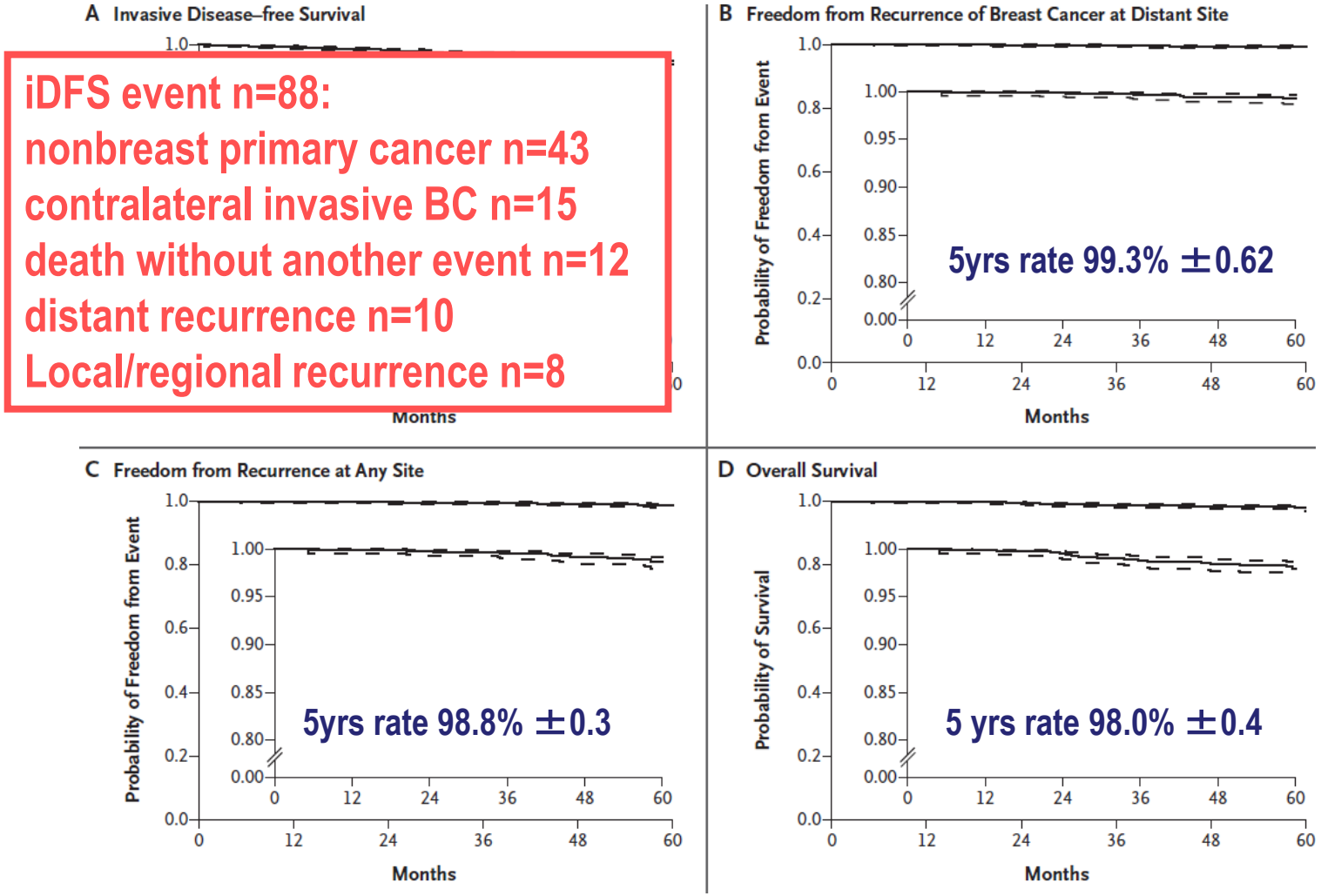
HR+/HER2-, N-negative
T1c-2 any grade or T1b and G2/3

Primary analysis: non-inferiority (iDFS) of HT vs CT+HT in women in the RS 11-25 group.



Sparano JA et al. *N Engl J Med* 2015

TailorX: prognosis of RS low patients



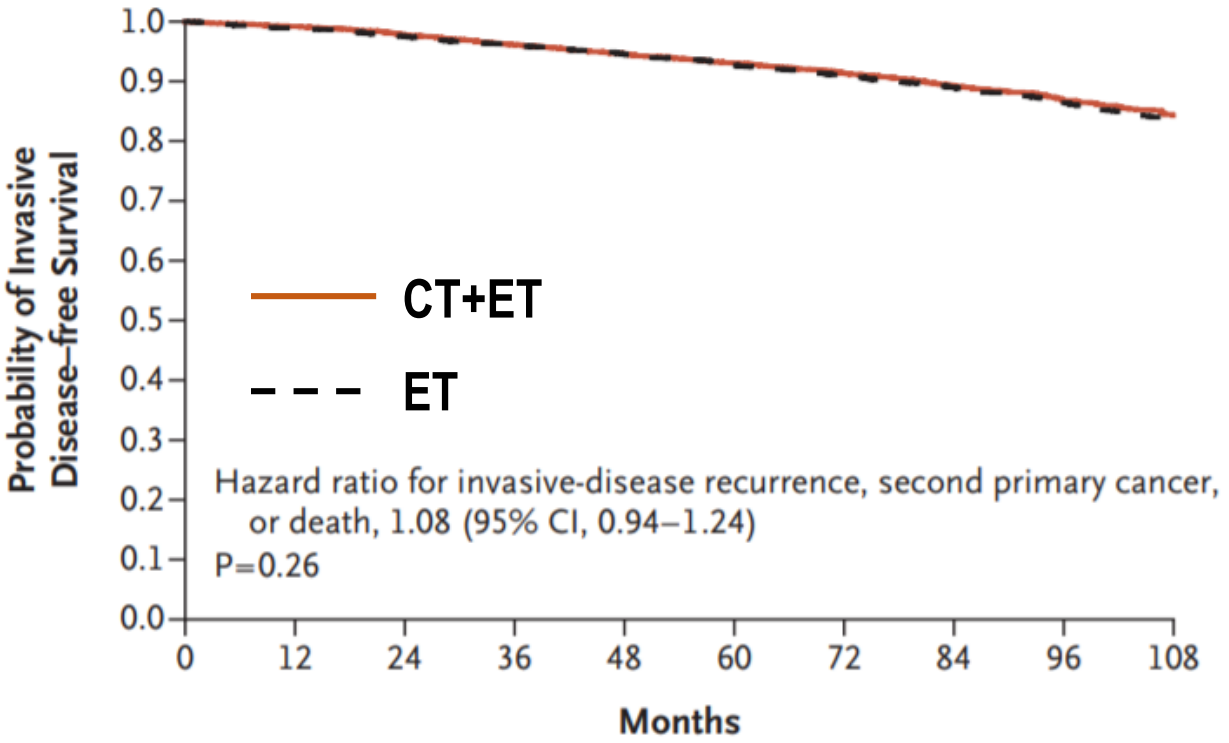
iDFS event n=88:
nonbreast primary cancer n=43
contralateral invasive BC n=15
death without another event n=12
distant recurrence n=10
Local/regional recurrence n=8

LoE 1A for N-

Sparano JA et al. *N Engl J Med* 2015; Sparano JA et al. *N Engl J Med* 2018

TailorX (N0): RS 11-25, primary endpoint

RS 11-25, randomized to CT+ET or ET alone n=6711



iDFS	5yrs %	9yrs %
ET	92.8 ±0.5	83.3 ±0.9
CT+ET	93.1 ±0.5	84.3 ±0.8

A 5-year rate of invasive disease–free survival of 90% with chemoendocrine therapy and of 87% or less with endocrine therapy alone, which corresponds to a 32.2% higher risk of an invasive disease recurrence, second primary cancer, or death as a result of not administering chemotherapy (hazard ratio, 1.322).

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

TailorX (N0): RS 11-25, other endpoints

	ET N=3399	CT+ET N=3312
Ipsilateral breast	38 (1.1)	31 (0.9)
Other locoregional relapse	39 (1.1)	31 (0.9)
Distant relapse	107 (3.1)	92 (2.8)
Contralateral BC	44 (1.3)	48 (1.4)
Second nonBC primary	145 (4.3)	146 (4.4)
Death	63 (1.9)	52 (1.6)
Total	436 (12.8)	400 (12.1)

Endpoints	5yrs %	9yrs %	HR (95% CI)
Freedom from distant relapse			
ET	98.0 ±0.3	94.5 ±0.5	1.10 (0.85-1.41)
CT+ET	98.2 ±0.2	95.0 ±0.5	ref
Freedom from any BC relapse			
ET	96.9 ±0.3	92.2 ±0.6	1.11 (0.90-1.37)
CT+ET	97.0 ±0.3	92.9 ±0.6	ref
Overall survival			
ET	98.0 ±0.2	93.9 ±0.5	0.99 (0.79-1.22)
CT+ET	98.1 ±0.2	93.8 ±0.5	ref

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

TAILORx: different cut-offs for young patients

All patients

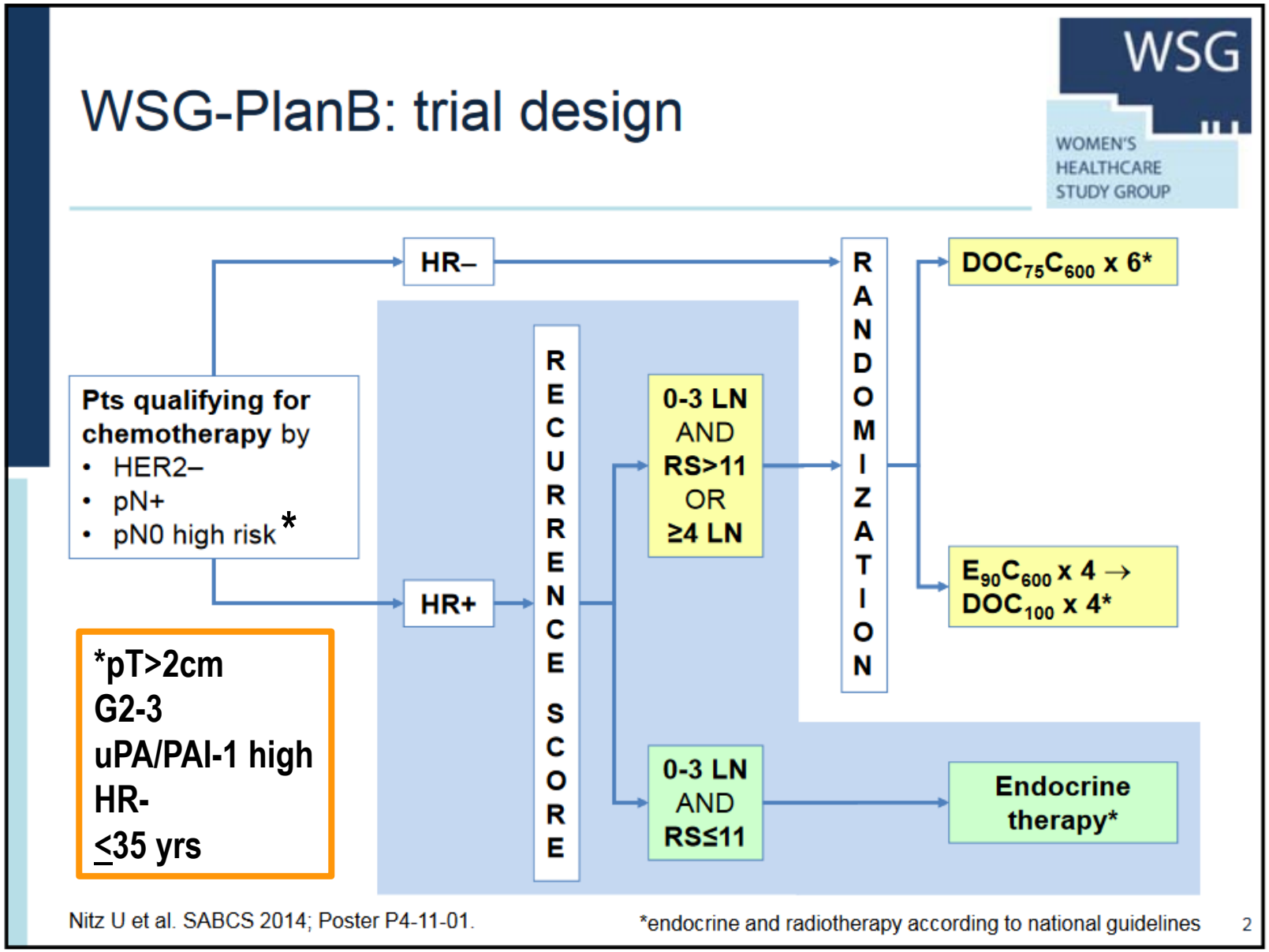
0-11	11-25	≥26
Good prognosis with ET: 94.0% iDFS 5 yrs	ET: 92.8% iDFS 5 yrs CT: 93.1% iDFS 5yrs	Assigned to CT + ET

Young patients (≤50 yrs), n=2216

0-11	11-15	16-20	21-25	≥26
Good prognosis with ET: 95.1% iDFS 5 yrs	ET: 95.1% iDFS 5 yrs CT: 94.3% iDFS 5yrs	ET: 92.0% iDFS 5 yrs CT: 94.7% iDFS 5yrs 9% fewer iDFS events with CT (2% distant)	ET: 93.2% iDFS 5 yrs CT: 96.4% iDFS 5yrs 6% fewer iDFS events with CT (mainly distant)	Assigned to CT+ET

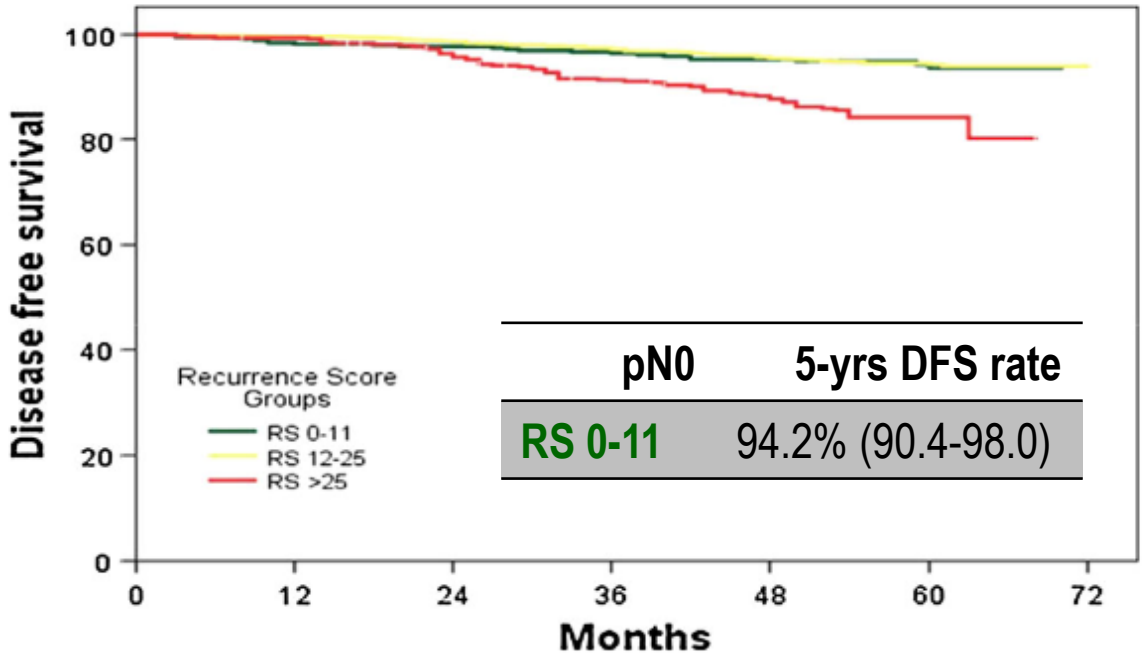
Sparano JA et al. *N Engl J Med* 2018

WSG planB: 5-yrs DDFS according to RS



WSG planB: 5-yrs DFS according to RS

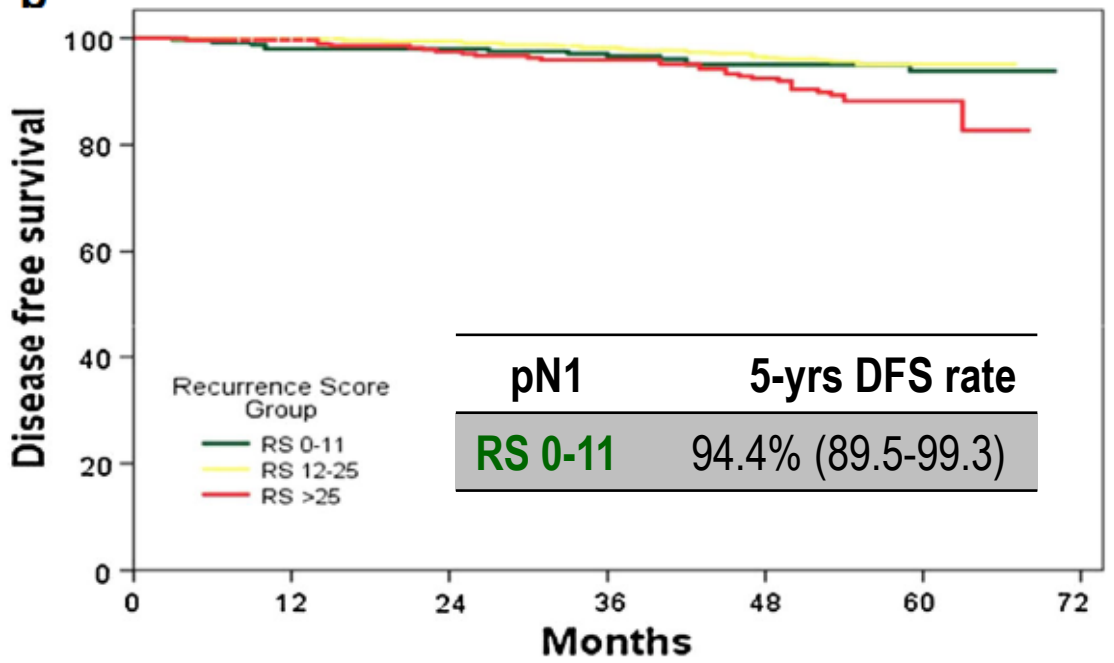
a



pN0	5-yrs DFS rate
RS 0-11	94.2% (90.4-98.0)

At-risk patients						
RS ≤ 11	439	429	407	353	295	134
RS 12-25	1200	1182	1182	1015	853	407
RS >25	478	472	472	380	320	142

b



pN1	5-yrs DFS rate
RS 0-11	94.4% (89.5-99.3)

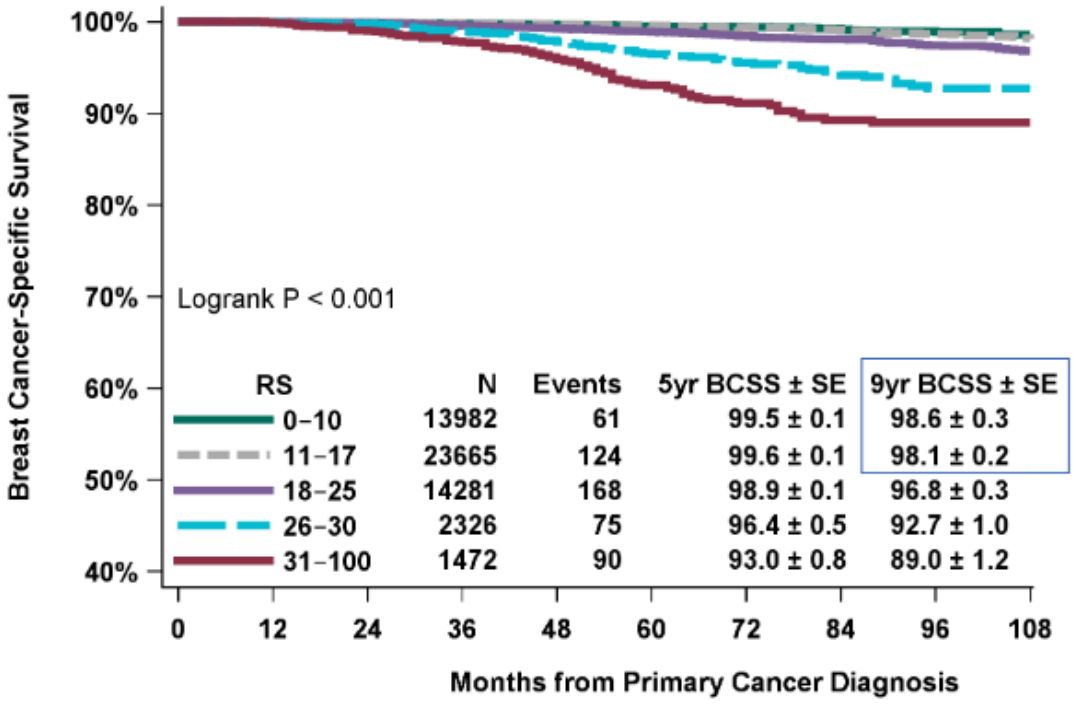
At-risk patients						
RS ≤ 11	248	240	227	198	166	72
RS 12-25	661	654	615	566	471	211
RS >25	283	280	258	247	235	89

Gluz O, Breast cancer Res Treat 2017

Breast Cancer-specific Mortality in Patients With Node-negative and Node-positive Breast Cancer Guided by the 21-gene Assay: A SEER-Genomic Population-based Study

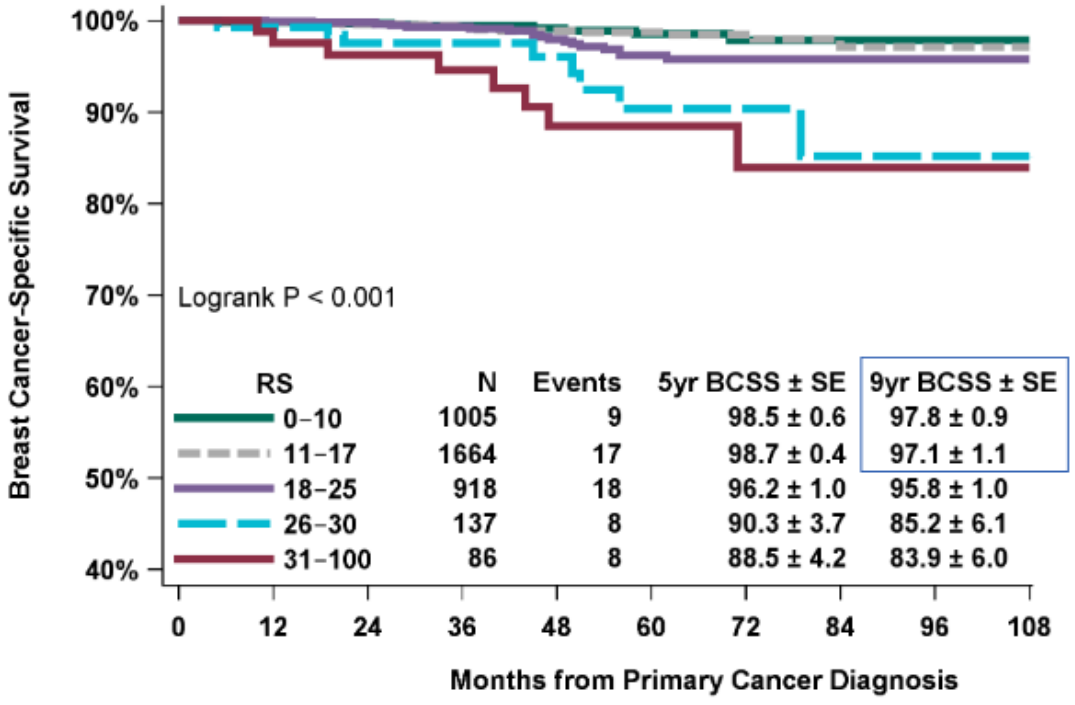
Patients treated with ET alone

(a) N0



RS	N	Events	5yr BCSS ± SE	9yr BCSS ± SE
0–10	13982	61	99.5 ± 0.1	98.6 ± 0.3
11–17	23665	124	99.6 ± 0.1	98.1 ± 0.2
18–25	14281	168	98.9 ± 0.1	96.8 ± 0.3
26–30	2326	75	96.4 ± 0.5	92.7 ± 1.0
31–100	1472	90	93.0 ± 0.8	89.0 ± 1.2

(c) N1



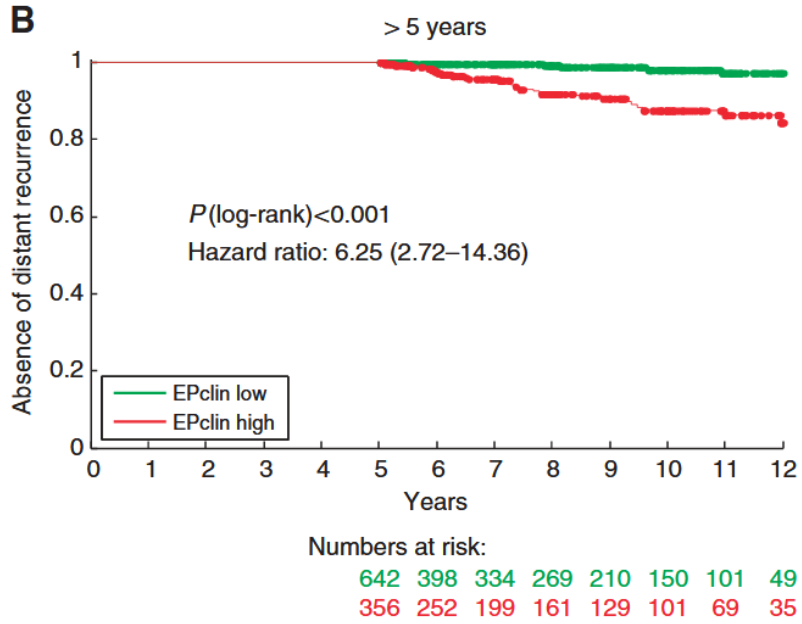
RS	N	Events	5yr BCSS ± SE	9yr BCSS ± SE
0–10	1005	9	98.5 ± 0.6	97.8 ± 0.9
11–17	1664	17	98.7 ± 0.4	97.1 ± 1.1
18–25	918	18	96.2 ± 1.0	95.8 ± 1.0
26–30	137	8	90.3 ± 3.7	85.2 ± 6.1
31–100	86	8	88.5 ± 4.2	83.9 ± 6.0

Hortobagyi G et al, SABCS 2018

Late recurrence prediction

EpClin

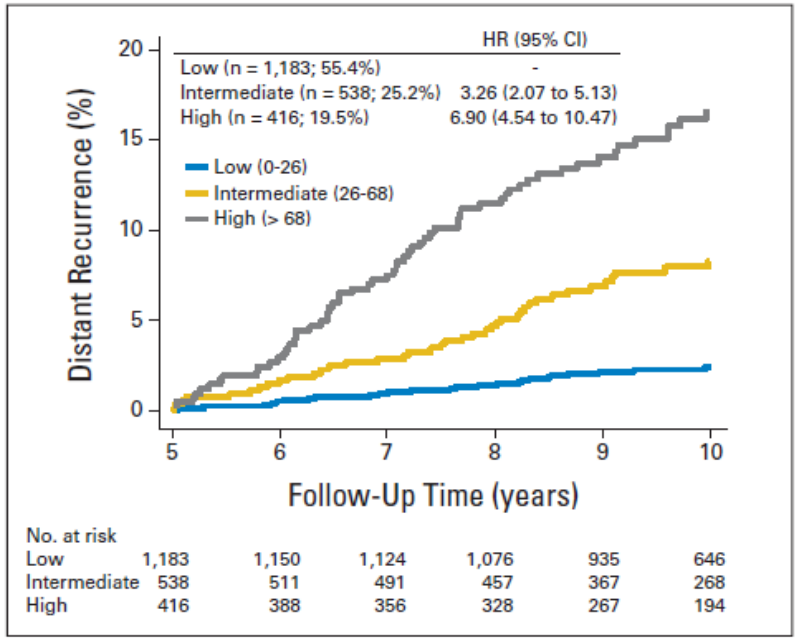
ABCSG-6/8



Dubsky P, Br J Cancer 2013

PAM50 ROR

ABCSG-8 and ATAC combined



Sestak I, J Clin Oncol 2015

Optimizing the use of genomic prognostic tests

- Which test to choose
- Genomic tests vs clinicopathological features
- For which patients

Poor agreement between tests at the individual level

Test	MammaPrint (low), Kappa statistic (95% CI)	Prosigna (low/intermediate), Kappa statistic (95% CI)	IHC4 (low/intermediate), Kappa statistic (95% CI)	IHC4-AQUA† (low/low-mid), Kappa statistic (95% CI)
Oncotype DX (recurrence score ≤25)	0.40 (0.30 to 0.49)	0.44 (0.33 to 0.54)	0.53 (0.41 to 0.65)	0.40 (0.30 to 0.51)
MammaPrint	–	0.53 (0.43 to 0.63)	0.33 (0.21 to 0.44)	0.42 (0.30 to 0.53)
Prosigna (low/intermediate)	–	–	0.39 (0.27 to 0.50)	0.43 (0.31 to 0.54)
IHC4 (low/intermediate)	–	–	–	0.60 (0.50 to 0.70)

*Kappa statistics are for agreement between categorization into combined low and intermediate risk vs high risk. CI = confidence interval.
†IHC4-AQUA mid risk and high risk are combined for this analysis.

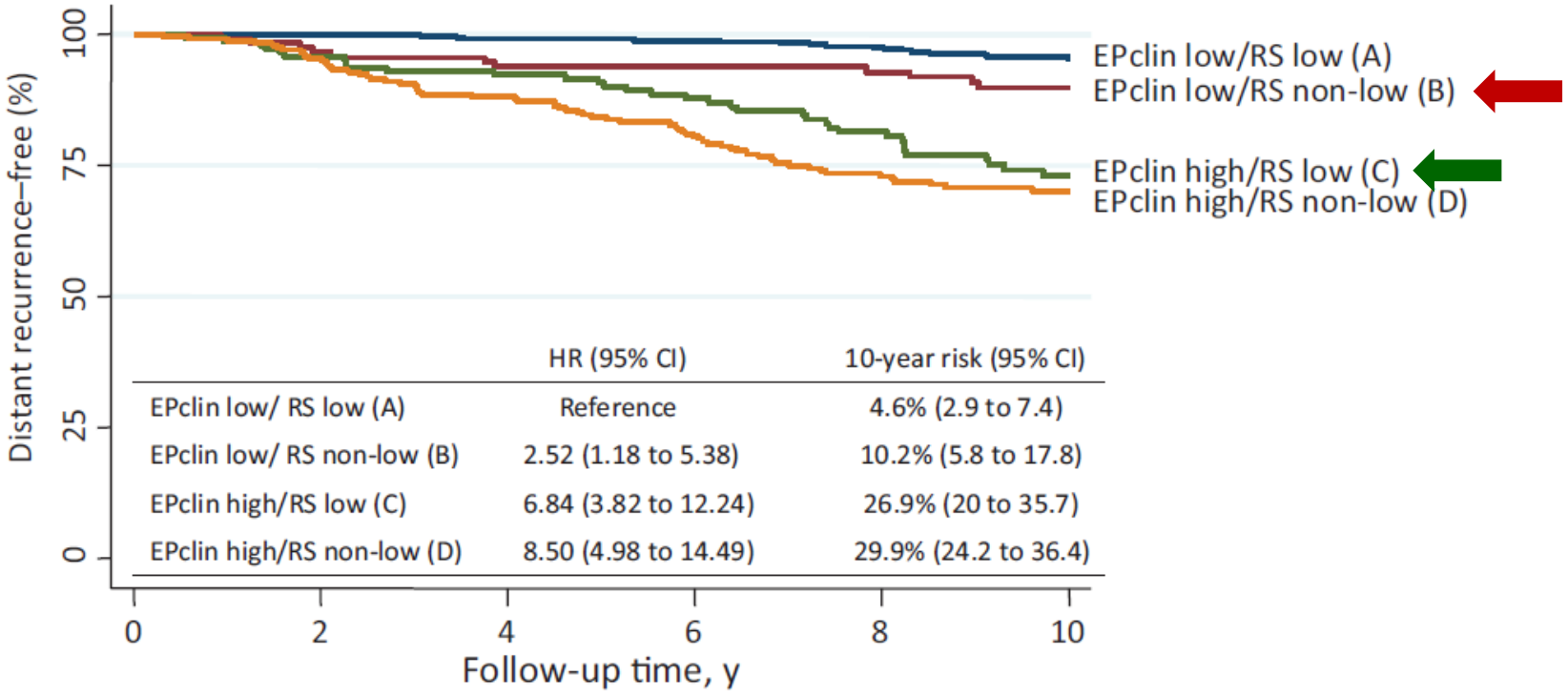
Two distinct tests may provide different risk classification for the same patient.

Is this variability in prognostic classification clinically acceptable?

Does this mean that some tests are better than others?

Bartlett et al., JNCI 2016

EpCLin vs OncotypeDX in TransATAC



	HR (95% CI)	10-year risk (95% CI)
EPclin low/ RS low (A)	Reference	4.6% (2.9 to 7.4)
EPclin low/ RS non-low (B)	2.52 (1.18 to 5.38)	10.2% (5.8 to 17.8)
EPclin high/RS low (C)	6.84 (3.82 to 12.24)	26.9% (20 to 35.7)
EPclin high/RS non-low (D)	8.50 (4.98 to 14.49)	29.9% (24.2 to 36.4)

- Difference between tests may be related, at least in part, to: inclusion of clinicopathological features in EpClin, differing ability to predict late recurrences
- Potential selection bias can not be excluded (n=928 out of the n=9366 enrolled in ATAC)
- Comparison studies on different clinical platforms may be useful

Buus R, JNCI 2016

Graphical Printout | **RSPC** (Recurrence Score - Pathology-Clinical)

RSPC Assessment of Node Negative , ER Positive Distant Recurrence Risk

User Input	
Oncotype DX® Breast Cancer Assay Recurrence Score®:	22
Planned Hormonal Treatment:	Aromatase Inhibitor
Patient age at surgery:	60
Tumor size (cm):	1.5
Tumor grade (differentiation):	Grade 2 (Moderate)

Results	
Risk of distant recurrence at 10 years:	9% (6%-11%)

T, N and G need to be accurately determined!!!

Graphical Printout | **RSPC** (Recurrence Score - Pathology-Clinical)

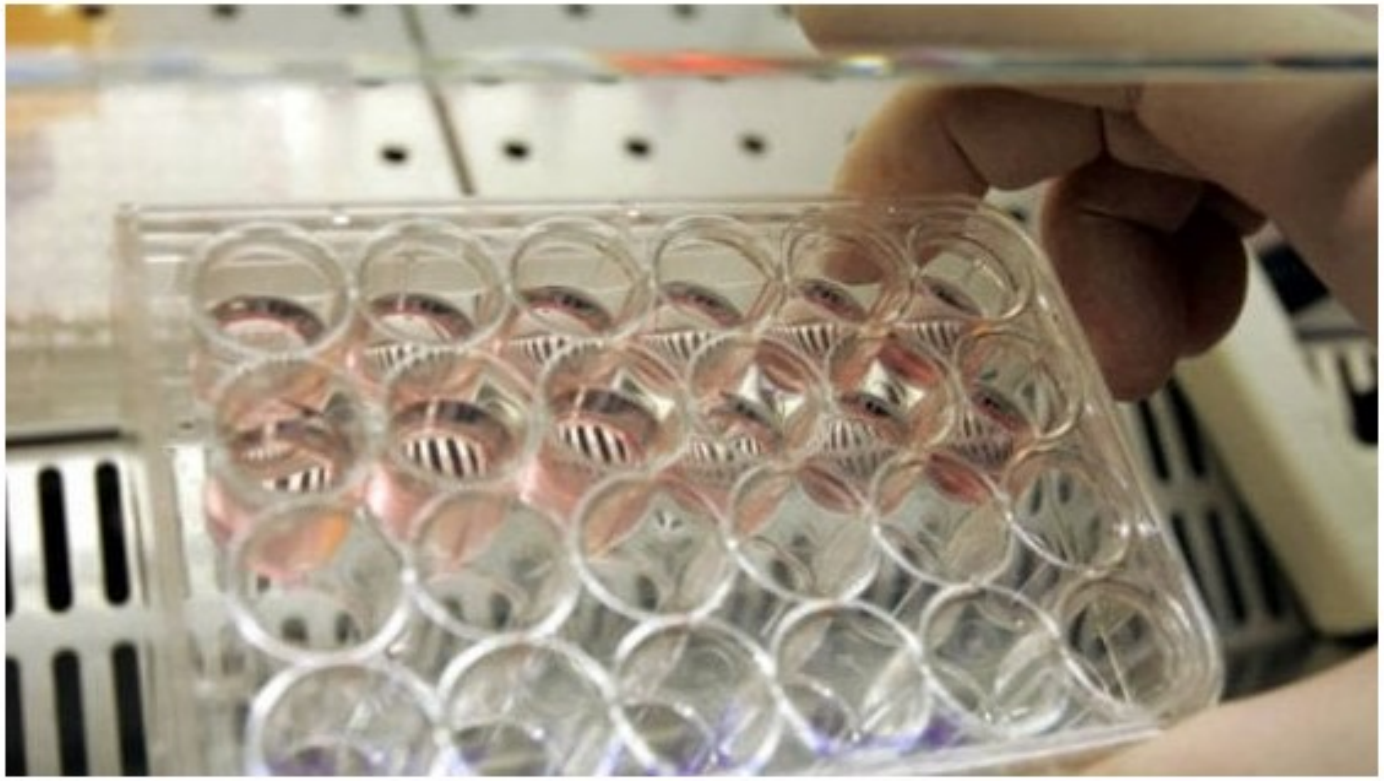
RSPC Assessment of Node Negative , ER Positive Distant Recurrence Risk

User Input	
Oncotype DX® Breast Cancer Assay Recurrence Score®:	22
Planned Hormonal Treatment:	Aromatase Inhibitor
Patient age at surgery:	50
Tumor size (cm):	1.5
Tumor grade (differentiation):	Grade 3 (Poor)

Results	
Risk of distant recurrence at 10 years:	18% (13%-24%)

TAILORx: Patients' characteristics

Tumore precoce al seno, un test per evitare la chemio nel 70% dei casi



Terapia su misura per le donne con un cancro alle prime fasi grazie allo screening di 21 geni. Sette pazienti su 10 possono essere trattate solo con la terapia ormonale

Sparano JA et al. *N Engl J Med* 2015

Original article

Results of PONDx, a prospective multicenter study of the Oncotype DX® breast cancer assay: Real-life utilization and decision impact in French clinical practice

Elsa Curtit [a,*], Jean-Michel Vannetzel [b], Jean-Claude Darmon [c], Sophie Roche [d], Hugues Bourgeois [d], Sylvain Dewas [e], Stéphanie Catala [f], Emile Mereb [g], Charlotte Furtos Fanget [h], Dominique Genet [i], Anne-Marie Forest [j], Céline Bernier [k], Xavier Pivot [l]

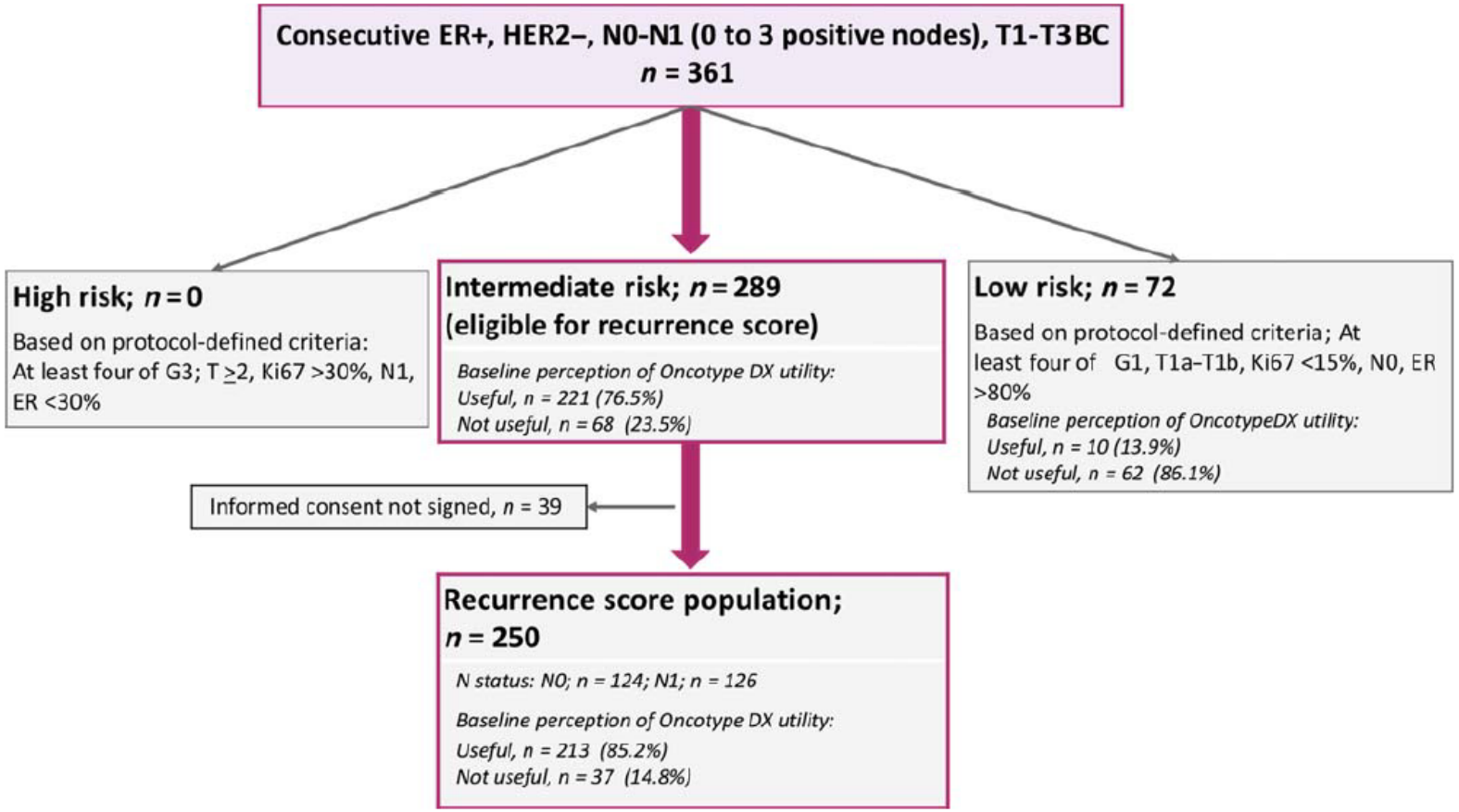
2019

Characteristics	% (n=866)
[redacted]	
T≤2cm	66%
[redacted]	
N0	71%
N1mic	8%
N1	23%
[redacted]	

*total of 752 with available data

- 66% rate of pre-test recommendation to CT+HT.
- 44% rate of post-test change in treatment decision.
- 37% net CT reduction.

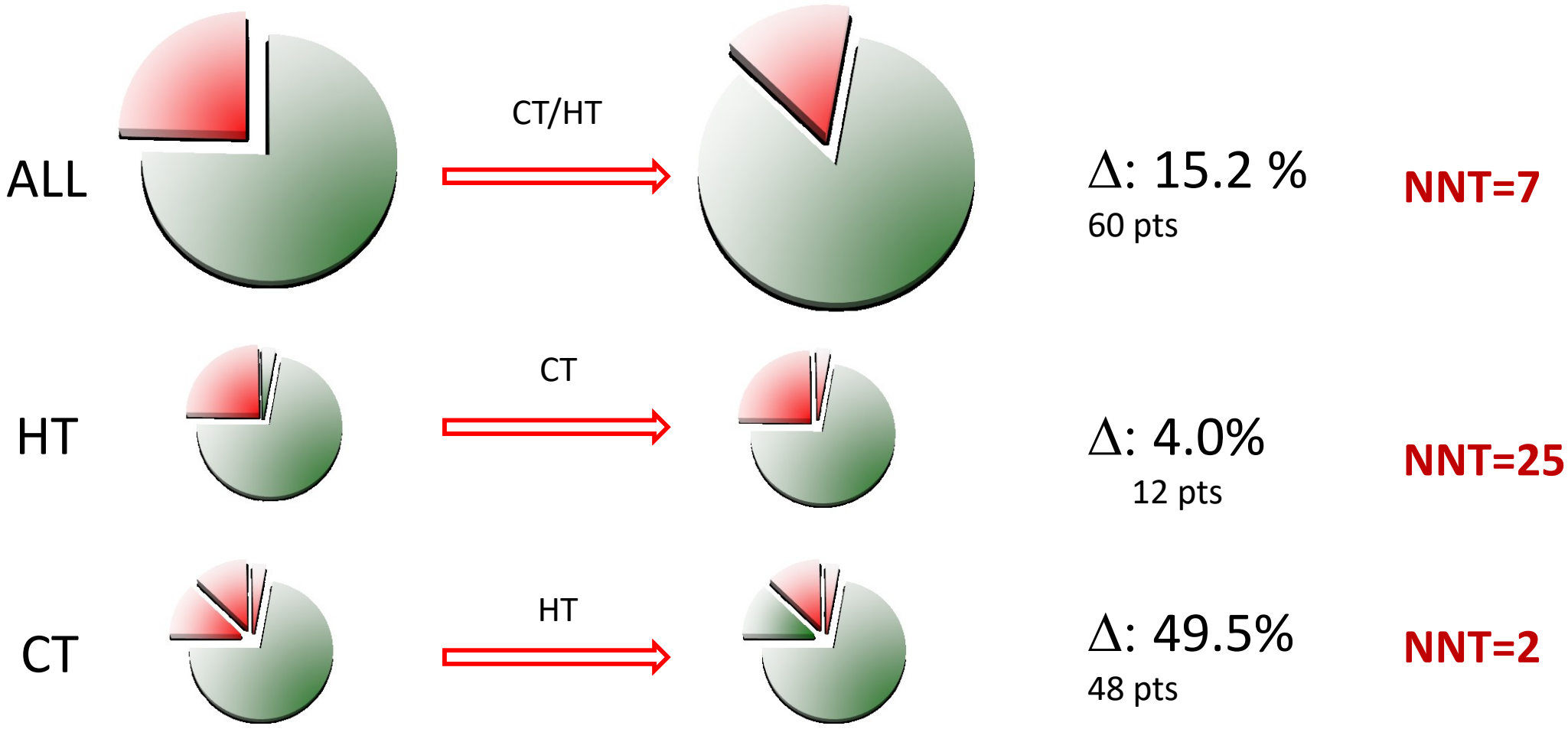
BREAST-DX Italy Study



- 52% of these patients were candidate to ET alone
- 16% rate of change in treatment recommendation
- 8% net reduction in CT recommendation

Dieci MV et al, Oncologist 2017

BONDx: Change of Recommendation



Zambelli A et al, AIOM 2018

ROXANE: P**R**ospective multicenter study to assess the impact of the **O**ncotype D**X**® Bre**a**st Ca**n**c**e**r Assay on Resources Optimization and Treatment Decisions for Women with Estrogen Receptor-Positive, Node-Negative and Node-Positive Breast Carcinoma

Prospective observational multicentric study
Sponsor: Istituto Oncologico Veneto IRCCS, Padova
Support: Genomic Health (RS tests free of charge)

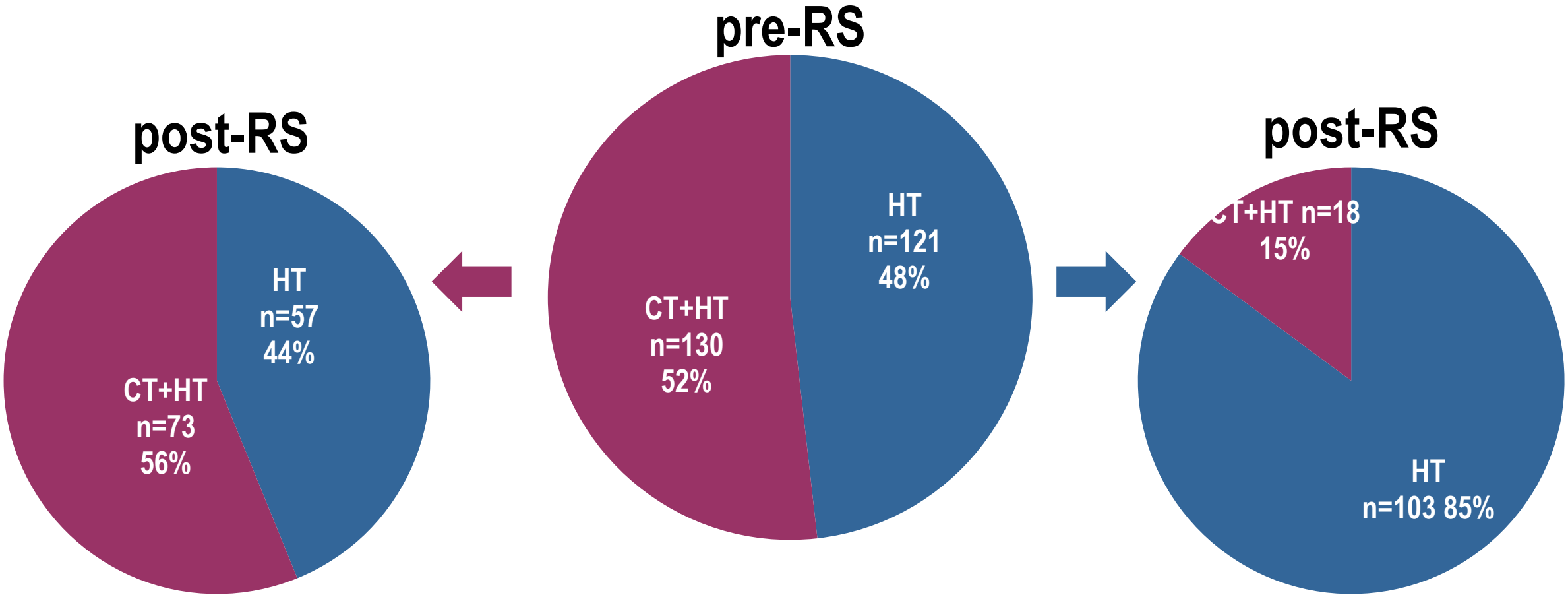
Rationale:

the impact of RS test on adjuvant treatment decisions in a scenario where, whenever physicians are unsure about treatment recommendation, the test is available

Patients' characteristics

	ALL (n=251), n(%)	N0 (n=152), n(%)	N1 (n=99), n(%)	P
Age >50 yrs	159 (63.3)	102 (67.1)	57 (57.6)	
Age ≤50 yrs	92 (36.6)	50 (32.9)	42 (42.4)	0.126
Premenopausal	105 (42.5)	61 (40.9)	44 (44.9)	
Postmenopausal	142 (57.5)	88 (59.1)	54 (55.1)	0.538
T ≤2cm	171 (69.0)	109 (72.2)	62 (63.9)	
T >2cm	77 (31.0)	42 (27.8)	35 (36.1)	0.170
Grade 1	17 (6.8)	8 (5.3)	9 (9.1)	
Grade 2	142 (56.6)	69 (45.4)	73 (73.7)	
Grade 3	92 (36.6)	75 (49.3)	17 (17.2)	<0.001
Ductal	214 (85.3)	130 (85.5)	84 (84.9)	
Lobular	28 (11.2)	15 (9.9)	13 (13.1)	
Other	9 (3.6)	7 (4.6)	2 (2.0)	0.429
Ki67%, median (range)	25 (2-75)	25 (2-75)	20 (2-57)	0.001
PgR pos	211 (84.1)	121 (79.6)	90 (90.9)	
PgR neg	40 (15.9)	31 (20.4)	9 (9.1)	0.012
Clin Low	73 (29.1)	67 (44.1)	6 (6.1)	
Clin high	178 (70.9)	85 (55.9)	93 (93.9)	<0.001

Change in recommendation by pre-RS indication



- Overall change in treatment recommendation: **30%** (75/251)
- Main change from CT+HT to HT: 77% (58/75)

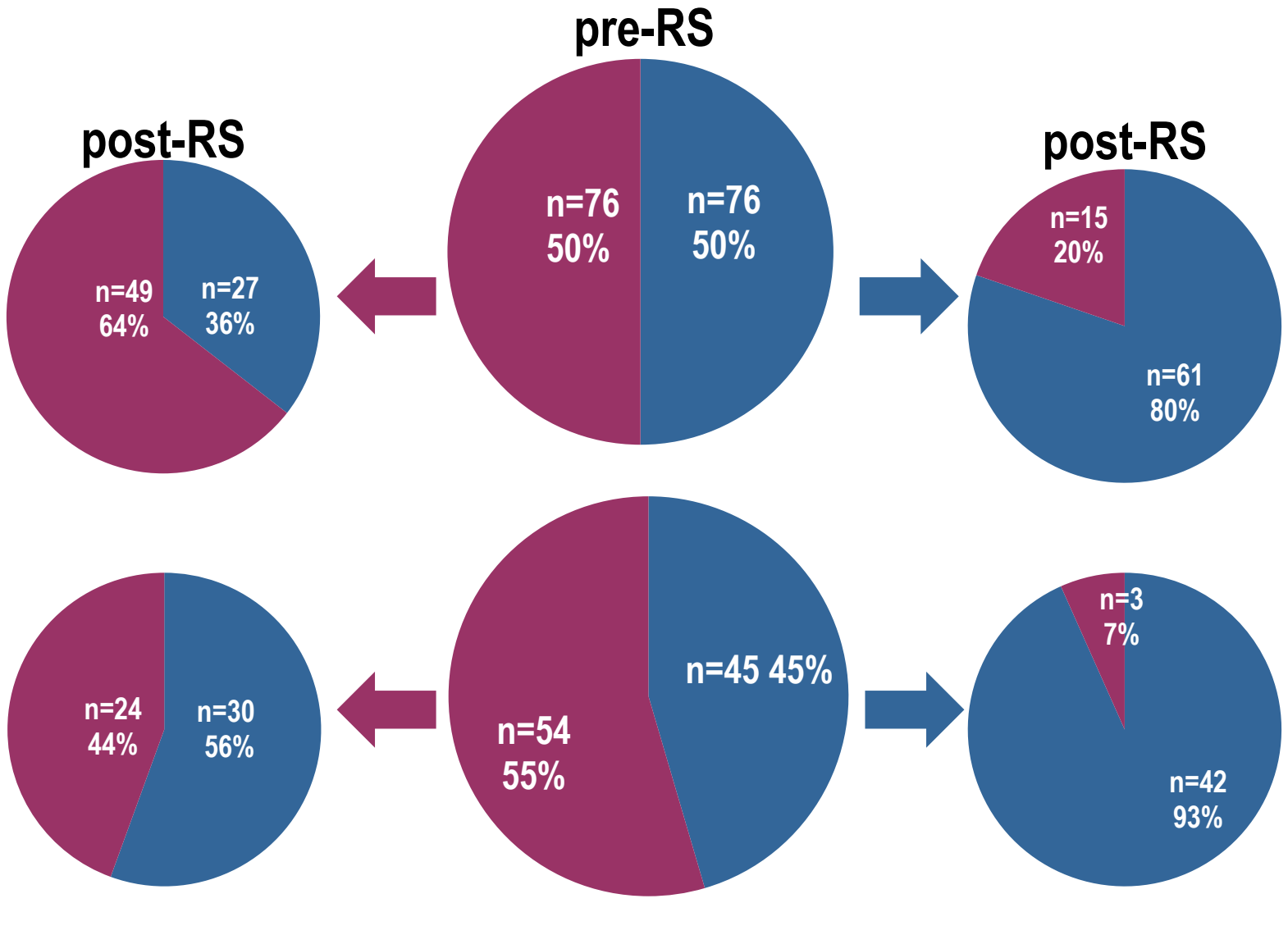
Change by pre-RS indication in N0 and N1 pts

N0

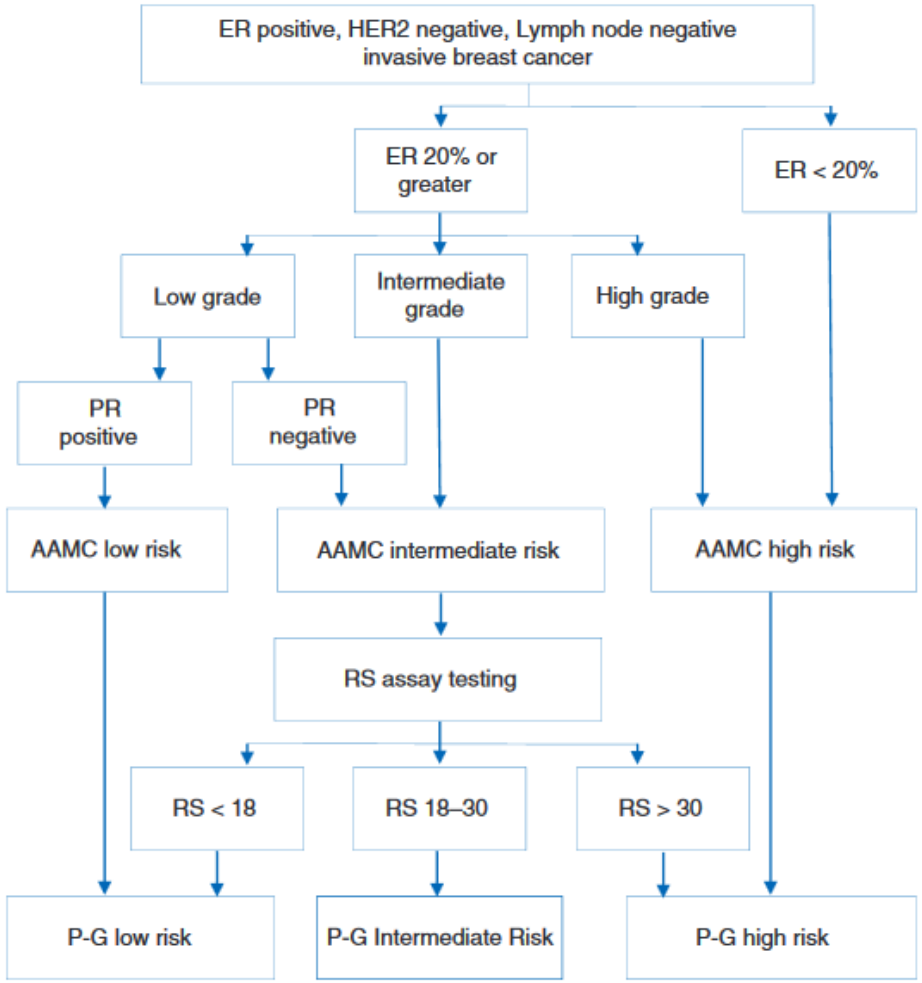
- Overall change: 28% (42/152).
- Main change from CT+HT to HT: 64% (27/42).

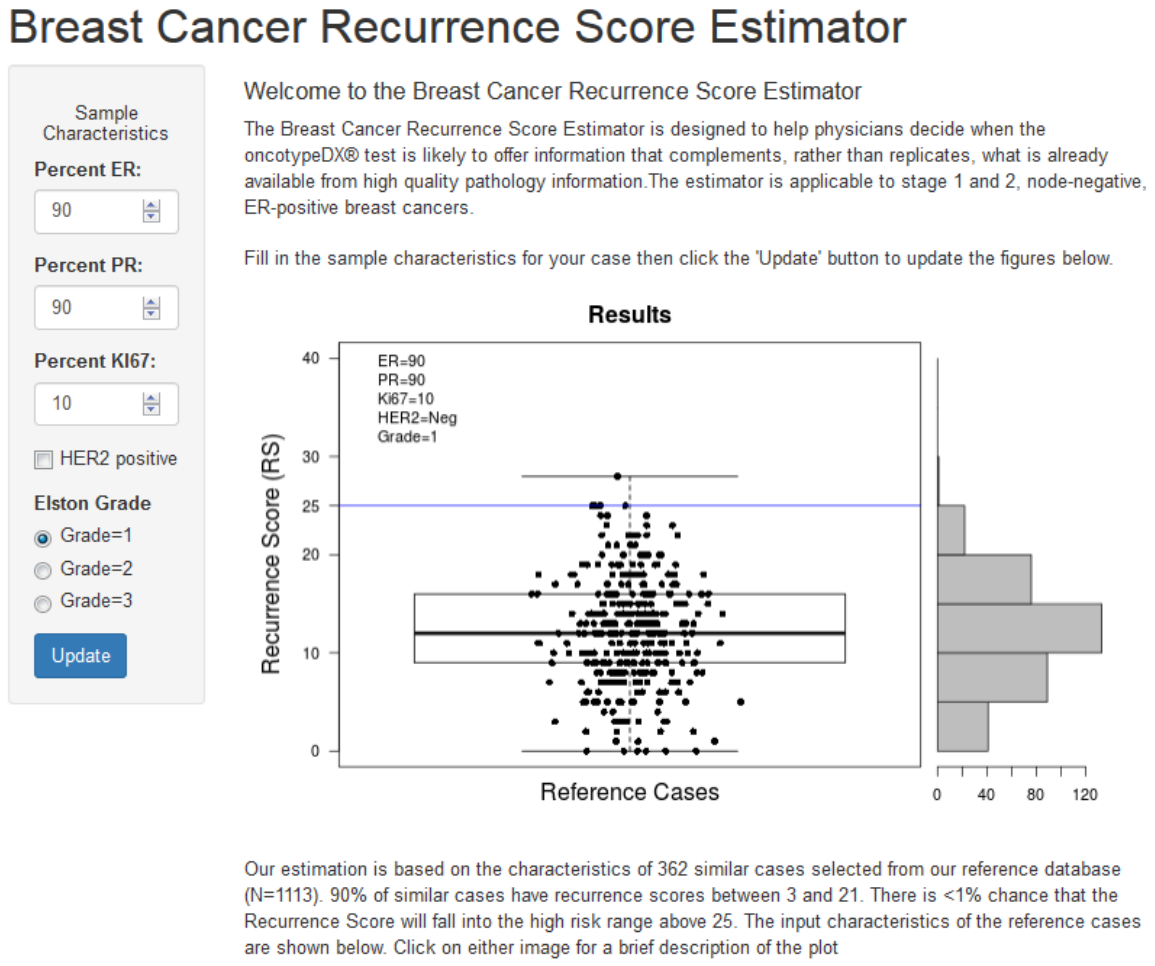
N1

- Overall change: 33% (33/99).
- Main change from CT+HT to HT: 91% (30/33).



Tools to guide RS use or predict RS results





Gage MM, Ann Oncol 2018

Kim H, J Clin Oncol 2016

Optimizing the use of genomic prognostic tests

- **ALWAYS** consider classical clinicopathological features

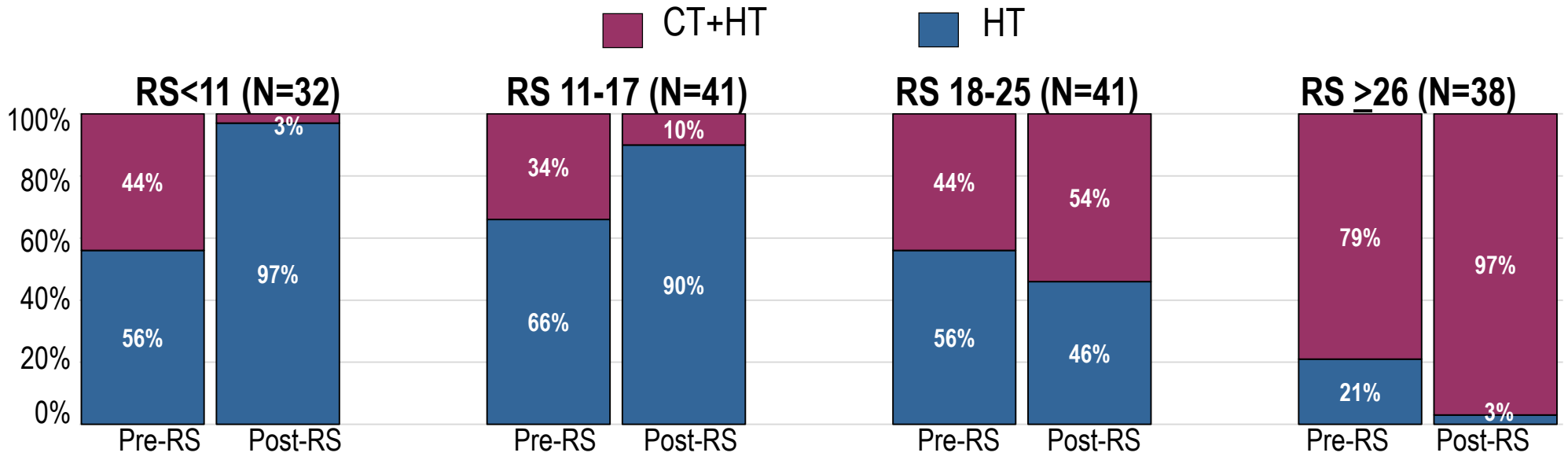
- It is challenging to provide a universally accepted definition of the patients for whom the test would be most useful:
  - Avoid offering the test to patients not suitable for chemotherapy
  - Avoid offering the test to patients at very low or very high risk for whom the decision is highly unlikely to change
  - ROXANE data show that Italian clinicians are able to identify patients for the use of tests in clinical practice

- Regulatory restrictions limit the use outside clinical studies in many countries
  - Differing Health Regulations and geographic heterogeneity influence clinical and economic impact:
    - Physician's confidence in classical clinicopathological biomarkers (i.e. Ki67)
    - Local clinical guidelines and policies
    - Chemotherapy-related costs
  - Collaboration with academia, health authorities, companies, patients on a local perspective

Pre- and post-RS recommendation by RS category

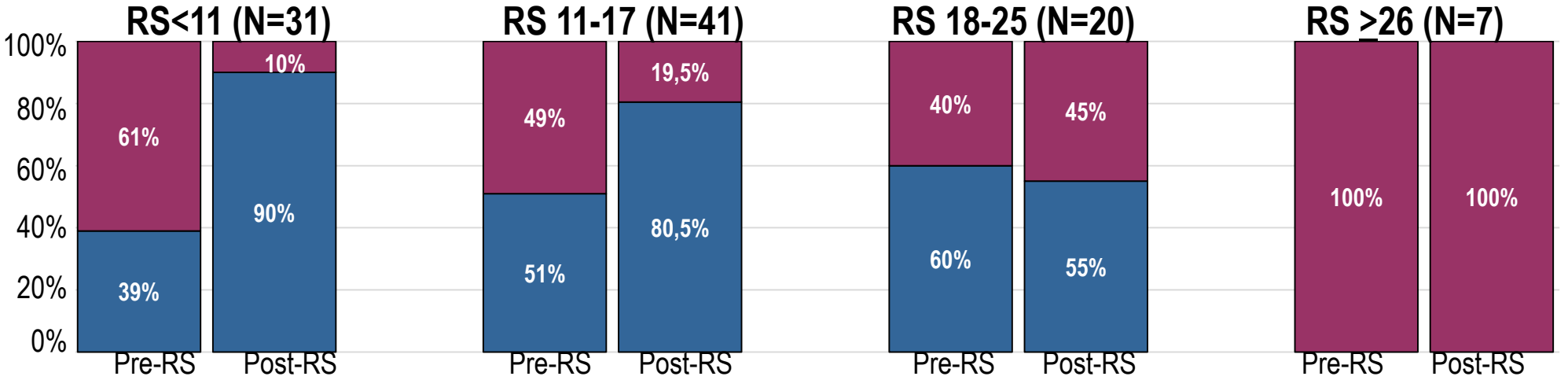
N0

Net CT reduction:
8% (50% to 42%)



N1

Net CT reduction:
28% (55% to 27%)



MINDACT: Clinical risk by modified Adjuvant!Online

ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
			1-3 positive nodes	≤ 2 cm	C-low
				2.1-5 cm	C-high
		moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high

- For N0, given the same G, T size discriminates between C-high and C-low

Cardoso F, NEJM 2016

MINDACT: Clinical risk by modified Adjuvant!Online

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				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high

- For N0, given the same G, T size discriminates between C-high and C-low
- All N+ (1-3) C-High (except from G1 and T≤2cm)

C-High
G1 pT 3.5 cm N0
G2 pT 2.1 cm N0
G2 T1.5cm N 1+
G3 pT 1.2 cm N0
G3 T 2.5cm N 2+

Cardoso F, NEJM 2016

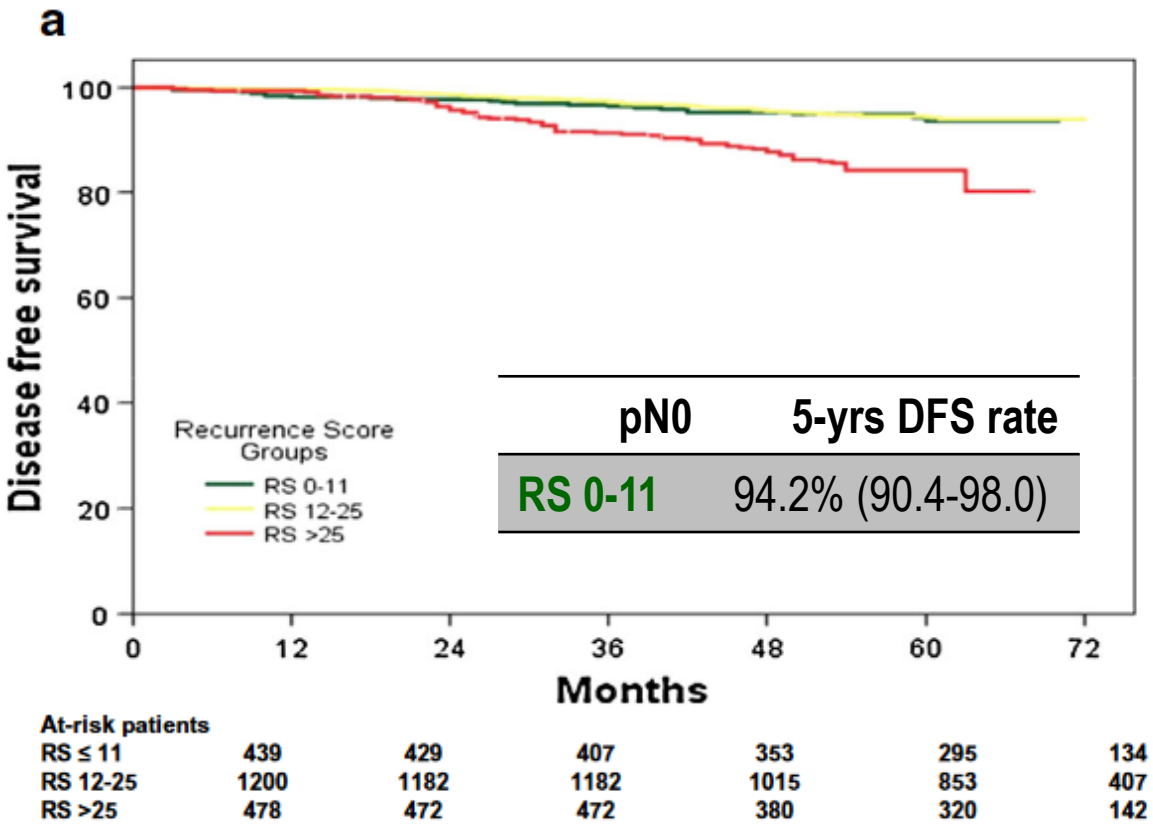
MINDACT: CT vs no CT in discordant groups

C-high/G-low	CT n=592		noCT n=636		HR	p
Outcome	*Events*	*Survival% 5yrs*	*Events*	*Survival% 5yrs*		
DMFS	22	96.7 (64.7-98)	37	94.8 (92.6-96.3)	0.65 (0.38-1.10)	0.11
DFS	39	93.3 (30.7-95.2)	66	90.3 (87.6-92.4)	0.64 (0.43-0.95)	0.03
OS	10	98.8 (97.4-99.5)	18	97.3 (95.6-98.4)	0.63 (0.29-1.37)	0.25

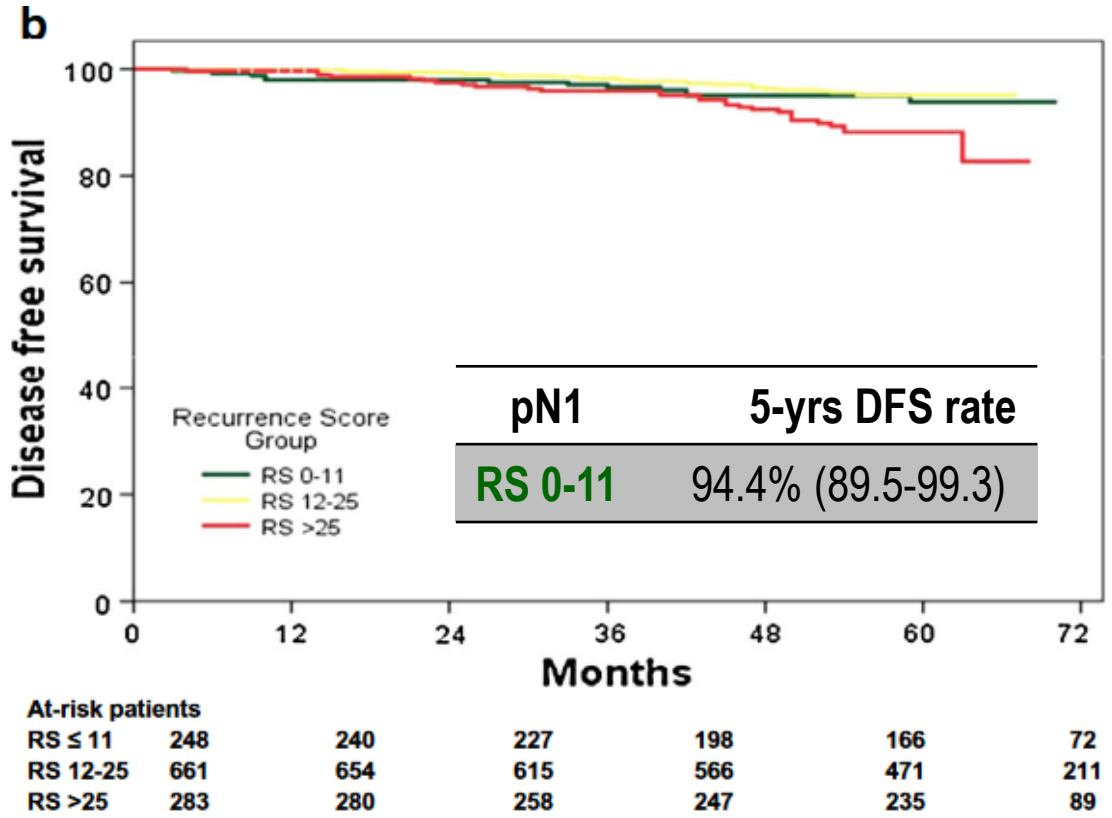
C-low/G-high	CT n=224		noCT n=254		HR	p
Outcome	*Events*	*Survival% 5yrs*	*Events*	*Survival% 5yrs*		
DMFS	11	96.1 (92.4-98.1)	14	93.9 (89.6-96.5)	0.90 (0.40-2.01)	0.80
DFS	17	92.7 (87.9-95.7)	25	90.5 (85.7-93.8)	0.74 (0.40-1.39)	0.36
OS	5	98.1 (94.9-99.3)	8	97.0 (93.8-98.6)	0.73 (0.23-2.24)	0.57

Cardoso F, NEJM 2016

WSG planB: 5-yrs DFS according to RS



pN0	5-yrs DFS rate
RS 0-11	94.2% (90.4-98.0)

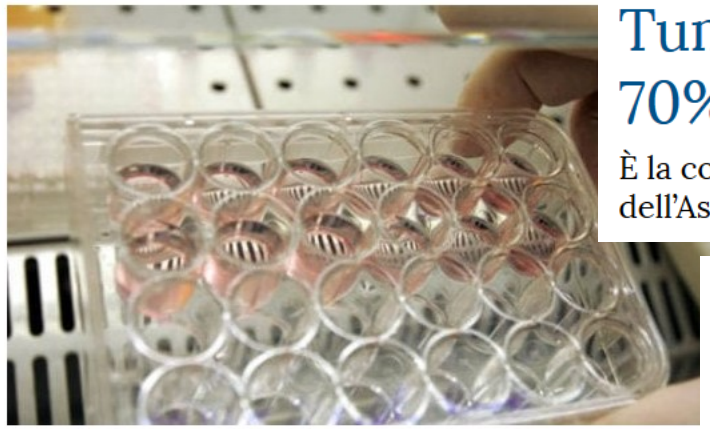


pN1	5-yrs DFS rate
RS 0-11	94.4% (89.5-99.3)

ALL (pN0/1/2/3) – all CT treated	5-yrs DFS rate
RS 12-25	94.3% (92.8-95.8)
RS >25	84.2% (80.6-87.8)

Gluz O, Breast cancer Res Treat 2017

Tumore precoce al seno, un test per evitare la chemio nel 70% dei casi



Tumore al seno, la chemio diventa evitabile nel 70% dei casi con un nuovo test genetico

È la conclusione di un maxi studio Usa di fase III presentato a Chicago al meeting annuale dell'Asco, l'American Society of Clinical Oncology

Terapia su misura per le donne con un cancro alle prime fasi grazie allo screening di 21 geni. Sette pazienti su 10 possono essere trattate solo con la terapia ormonale

Tumore del seno iniziale, la chemio evitabile nel 70% dei casi

Li individua test genetico. In Italia possibile per 3.000 pazienti l'anno

Cancro al seno, con un test il 70% delle donne può evitare la chemioterapia

Grazie a un test genomico si può prevedere il rischio di recidiva per le donne con un cancro al seno nella fase iniziale della malattia. Secondo lo studio, circ il 70% delle pazienti potrebbero evitare la chemioterapia (e tutti gli effetti collaterali) e sottoporsi alla sola terapia ormonale

Tumore seno. "Niente chemio nel 70% dei casi iniziali"

Chicago, ottimista il presidente degli oncologi americani ad Asco 2018. "Impatto positivo test su tumore chemio-free"

Tumore seno "chemio-free", possibile nel 70% dei casi in fase iniziale

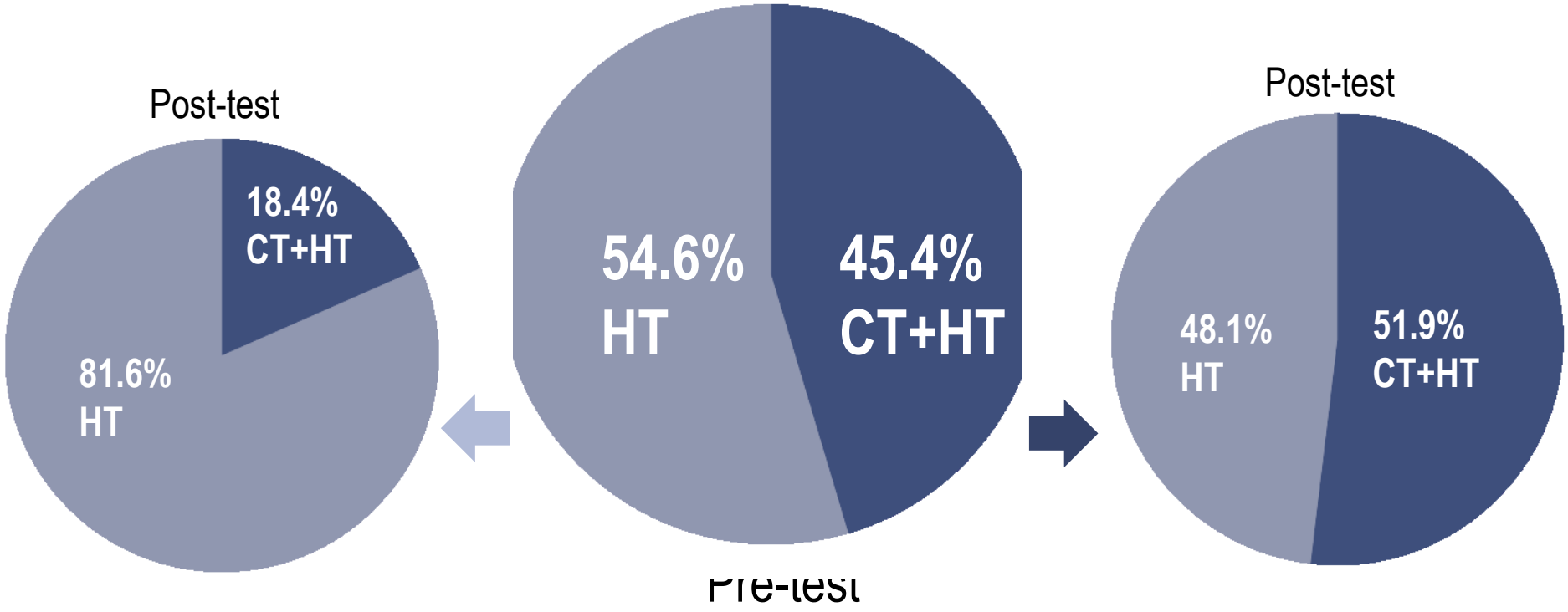
Secondo uno studio la svolta sarebbe resa possibile da un test diagnostico in grado di individuare quali siano le pazienti che non necessitano della chemio

Original Research

Pooled analysis of prospective European studies assessing the impact of using the 21-gene Recurrence Score assay on clinical decision making in women with oestrogen receptor–positive, human epidermal growth factor receptor 2–negative early-stage breast cancer

Joan Albanell [a,b,c,*], Christer Svedman [d], Joseph Gligorov [e], Simon D.H. Holt [f], Gianfilippo Bertelli [g], Jens-Uwe Blohmer [h], Roman Rouzier [i], Ana Lluch [j], Wolfgang Eiermann [k]

n=527, N-neg
G3: 13%



31.9% had a recommendation change post-test→ 26% CT net reduction