CARCINOMA DELLA MAMMELLA
La scelta del trattamento adiuvante: utilità clinica dei tests genomici

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TREATMENT INDIVIDUALIZATION: WHY?

100 BC patients

20% HER2+ BC

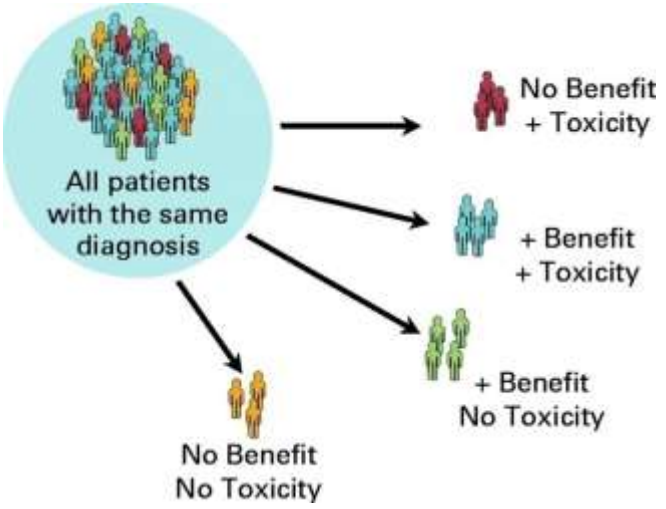
15% TN BC

65 HR+/HER2- BC patients

5% ≥4 Node positive

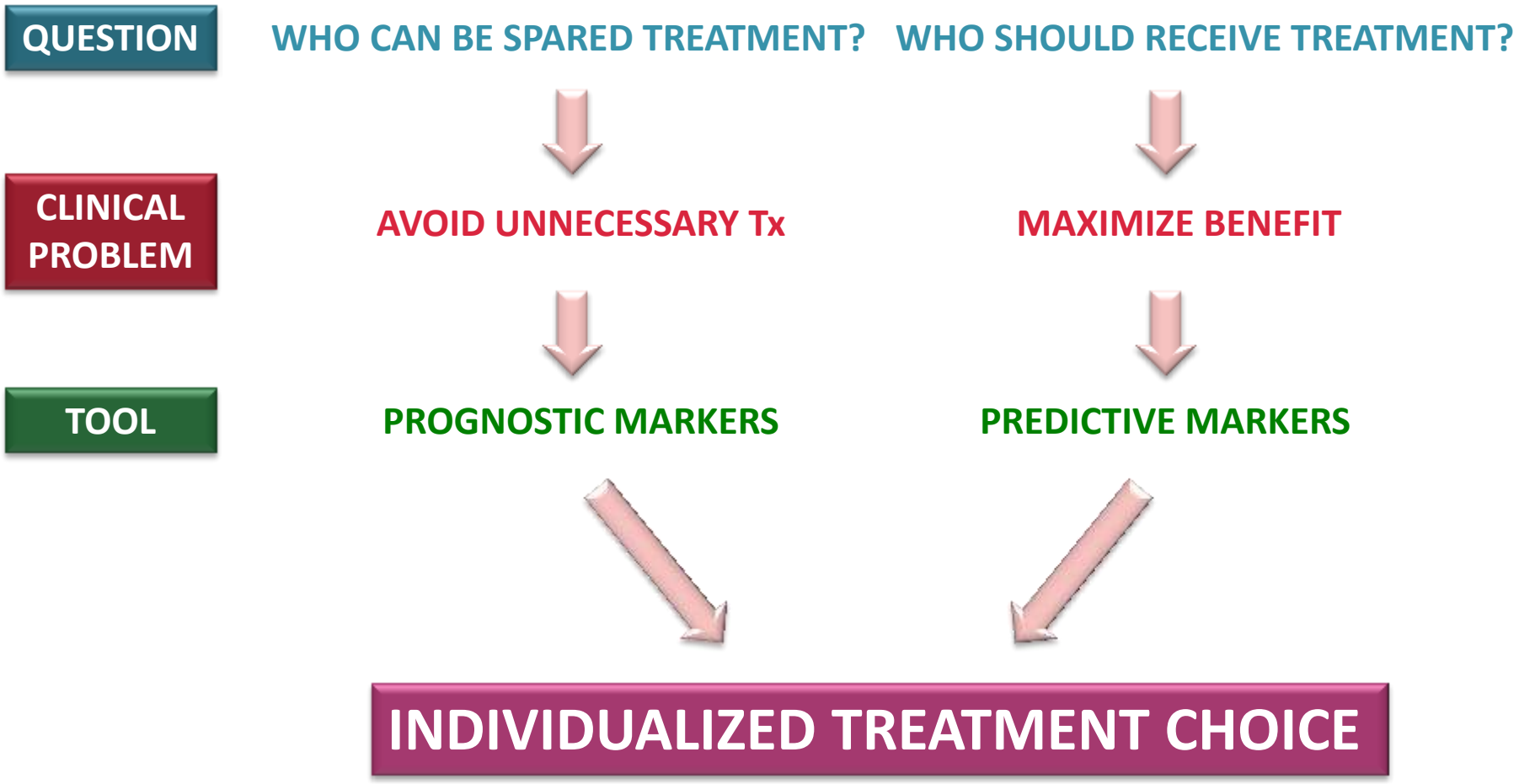
2-3% too frail for CT

≈50 HR+/HER2- BC PATIENTS POTENTIALLY CANDIDATE TO ADJUVANT CHEMOTHERAPY



Walgren et al. *JCO* 2005;23:7342-7349

THE ROAD TO TREATMENT INDIVIDUALIZATION



CLINICAL UTILITY OF A PROGNOSTIC BIOMARKER

Clinical validity

Predict baseline prognosis

Correlation of score with outcome

Clinical utility

Who can be spared chemotherapy?

Actionable: use results for patient benefit.

Prognosis is so good that the relative benefit, if any, would translate into a not clinically relevant absolute gain

*A biomarker-based test is judged to have clinical utility if use of the test is associated with a **favorable balance of benefits to harms** compared with treatment of the patients in the absence of the biomarker test result.*

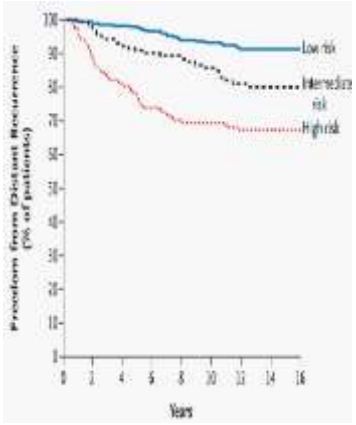
Absolute distant recurrence risk	Relative risk reduction with CT	Absolute % of pts who will benefit from CT	Fatal, life-threatening, permanent CT toxicity rate
50-60%	30%	**15-20%**	**2-3%**
10-15%	30%	**2-3%**	**2-3%**

Harris et al., JCO 2016

GENOMIC PROFILING AND PROGNOSIS FOR HR+/HER2- PATIENTS

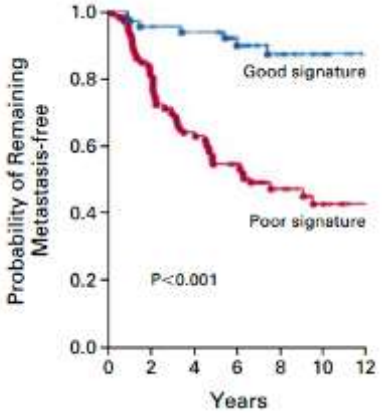
All tests have at least level IB evidence for HR+/HER2-, T1-2 and N0-1 early BC

OncotypeDX



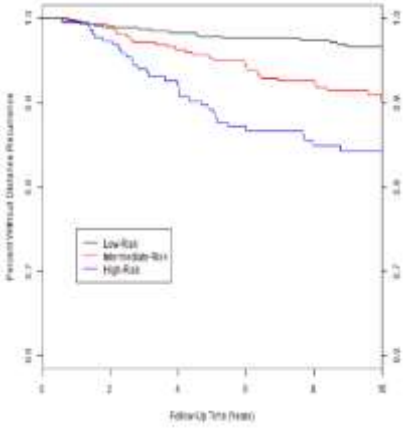
Paik NEJM 2006

MammaPrint



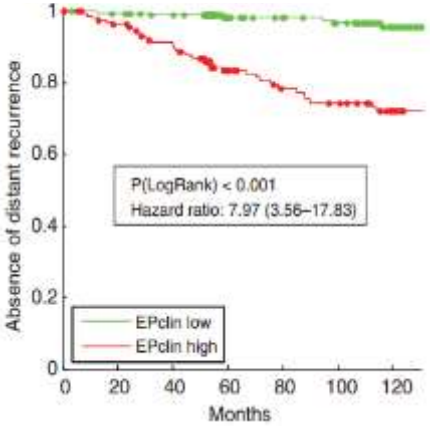
Vijver NEJM 2002

PAM50 ROR



Dowsett JCO 2013

EndoPredict



Filipits CCR 2011

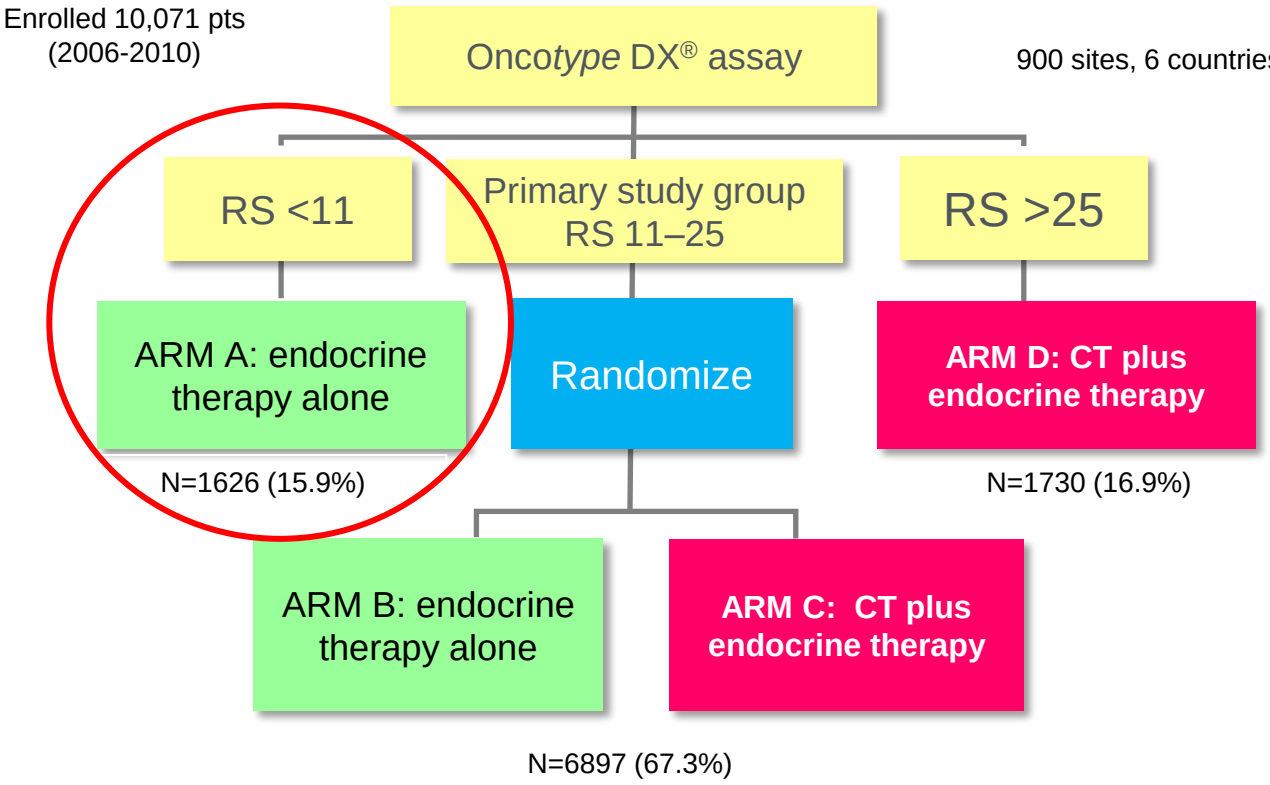
(include tumor size+nodal status)

DATA FROM PROSPECTIVE RANDOMIZED TRIALS DESIGNED TO TEST THE MARKER – LEVEL 1A

Trial Assigning IndividuaLized Options for Treatment (Rx), or TAILORx

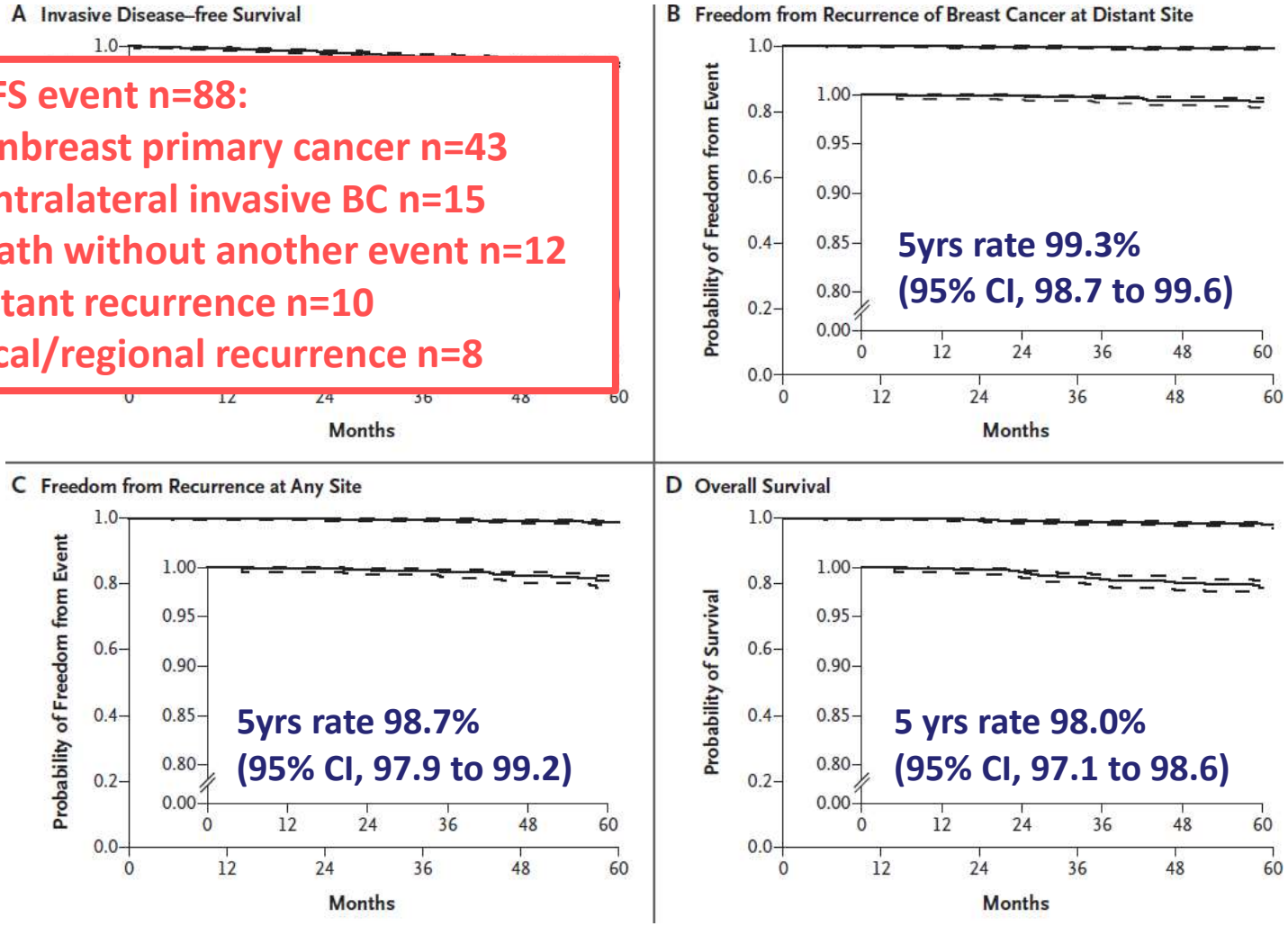
HR+/HER2-, N-negative
T1c-2 any grade or T1b and G2/3

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

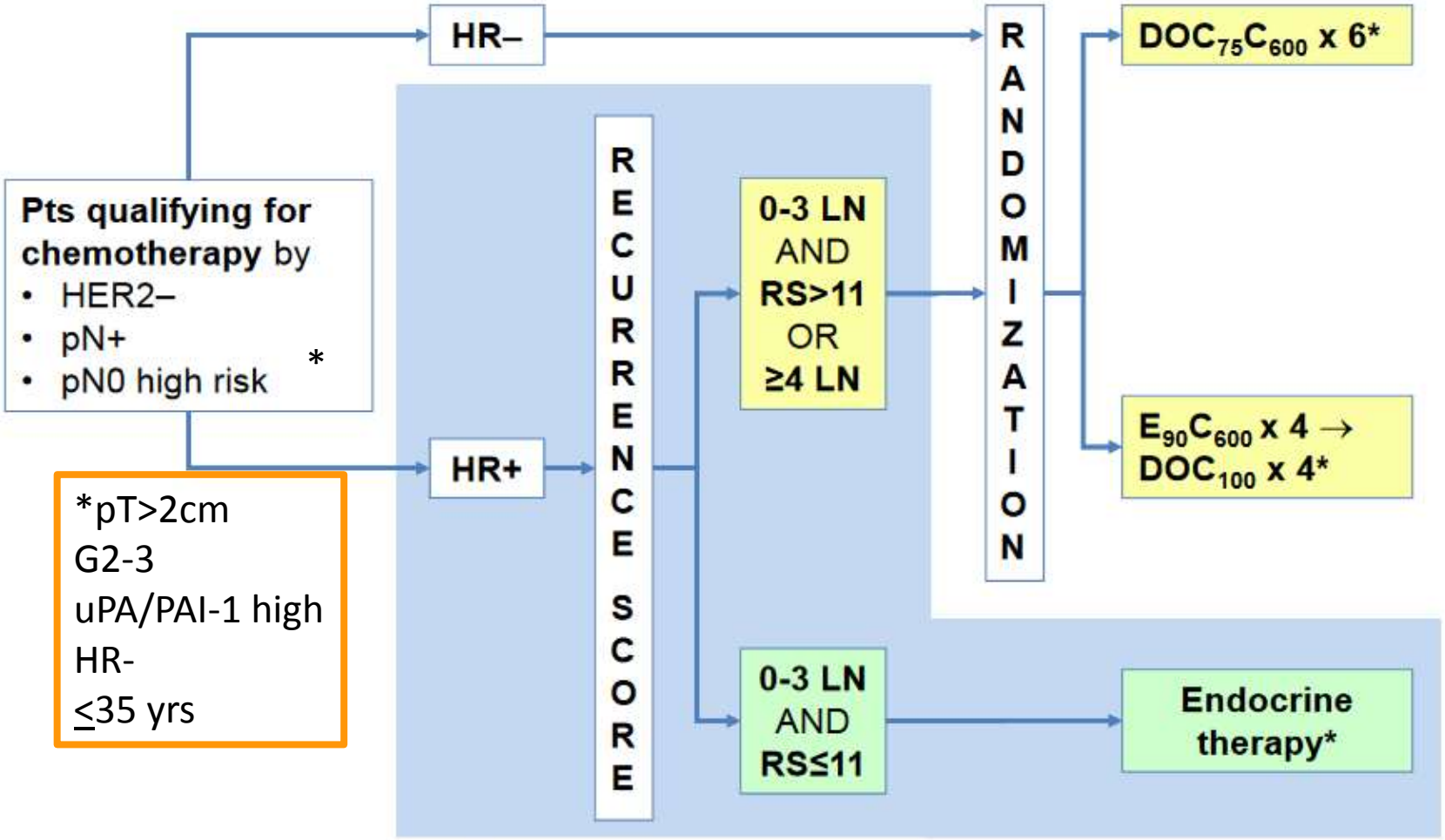
TailorX: prognosis of RS low patients



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

Sparano J, et al. N Engl J Med 2015

WSG-PlanB: trial design

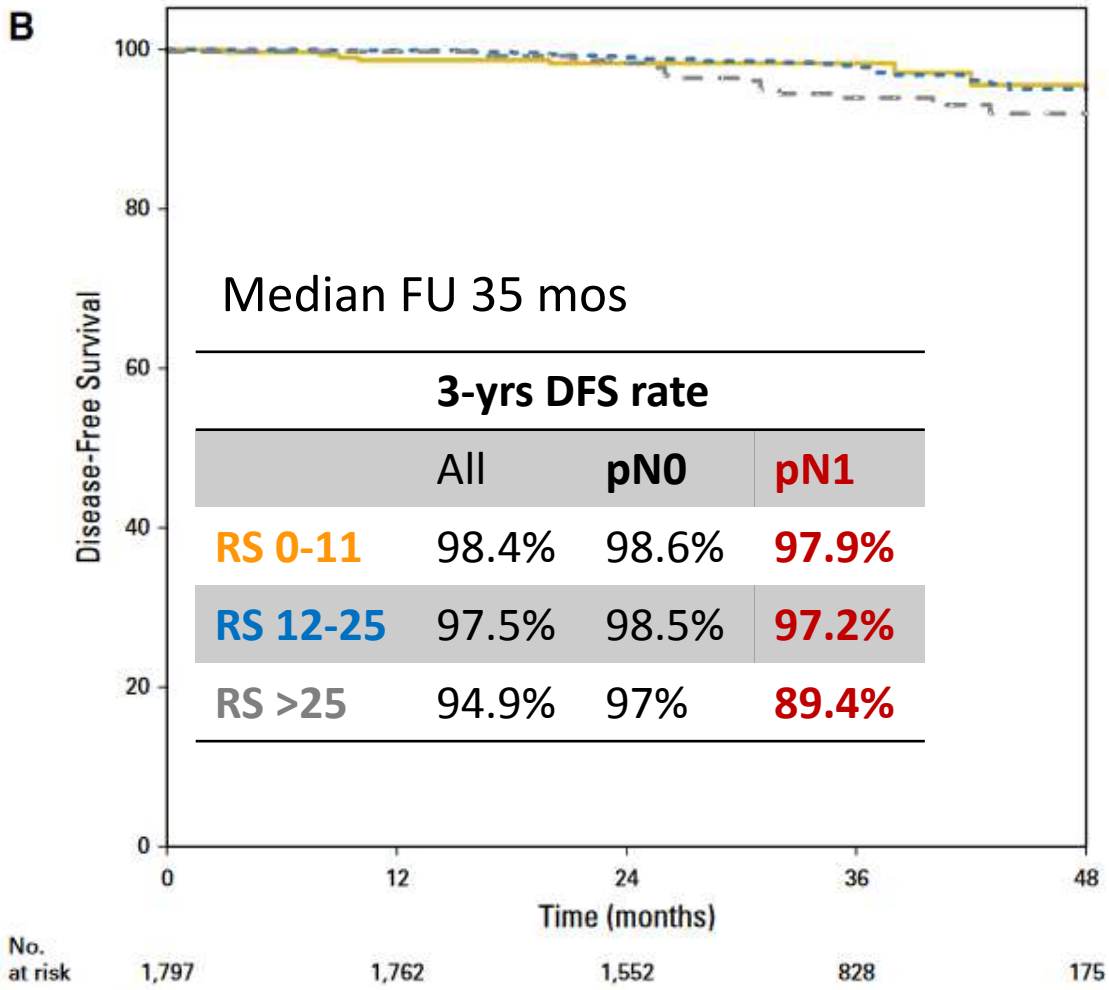


Nitz U et al. SABCS 2014; Poster P4-11-01.

*endocrine and radiotherapy according to national guidelines

WSG planB trial

DFS of pN0 and pN1 pts treated according to RS

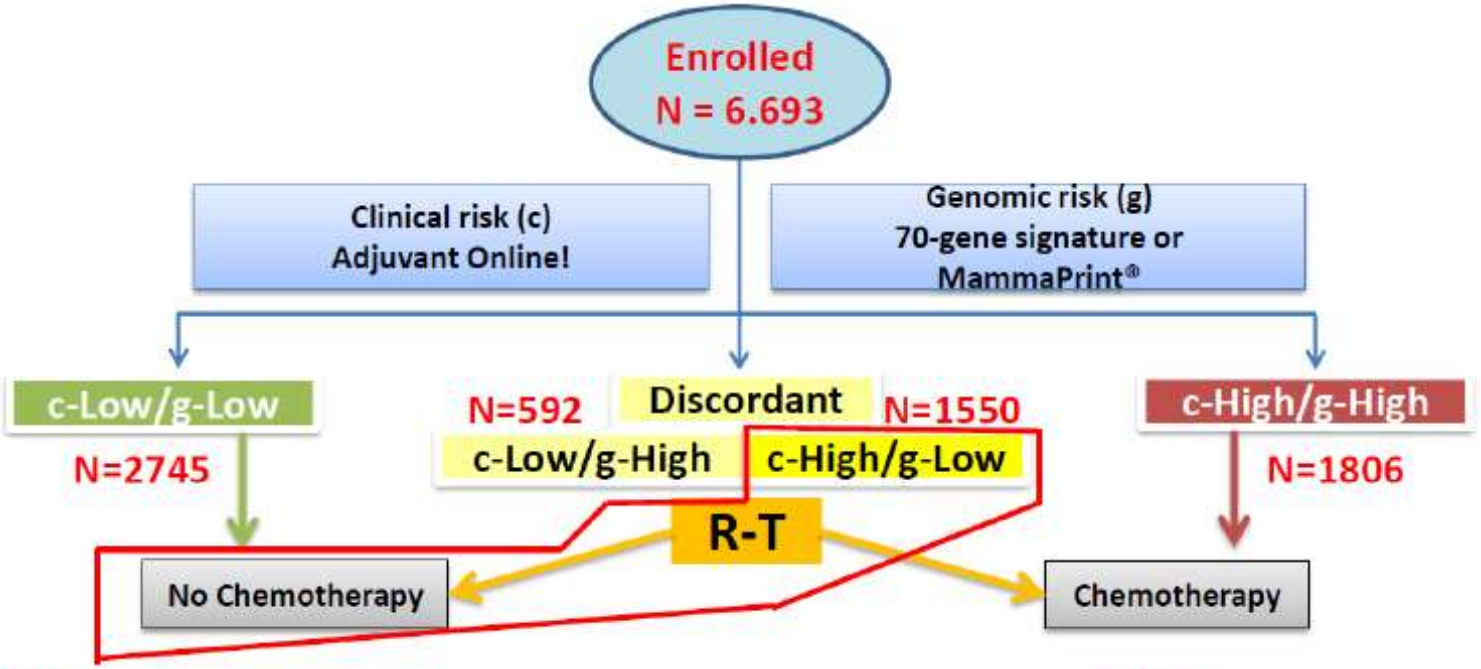


Median FU 35 mos

	3-yrs DFS rate		
	All	pN0	pN1
RS 0-11	98.4%	98.6%	97.9%
RS 12-25	97.5%	98.5%	97.2%
RS >25	94.9%	97%	89.4%

Gluz O, JCO 2016

MINDACT TRIAL: PRIMARY ANALYSIS POPULATION



Primary endpoint: Distant metastasis free survival (DMFS) at 5 years

Null hypothesis: 5-year DMFS rate in PT population = 92%

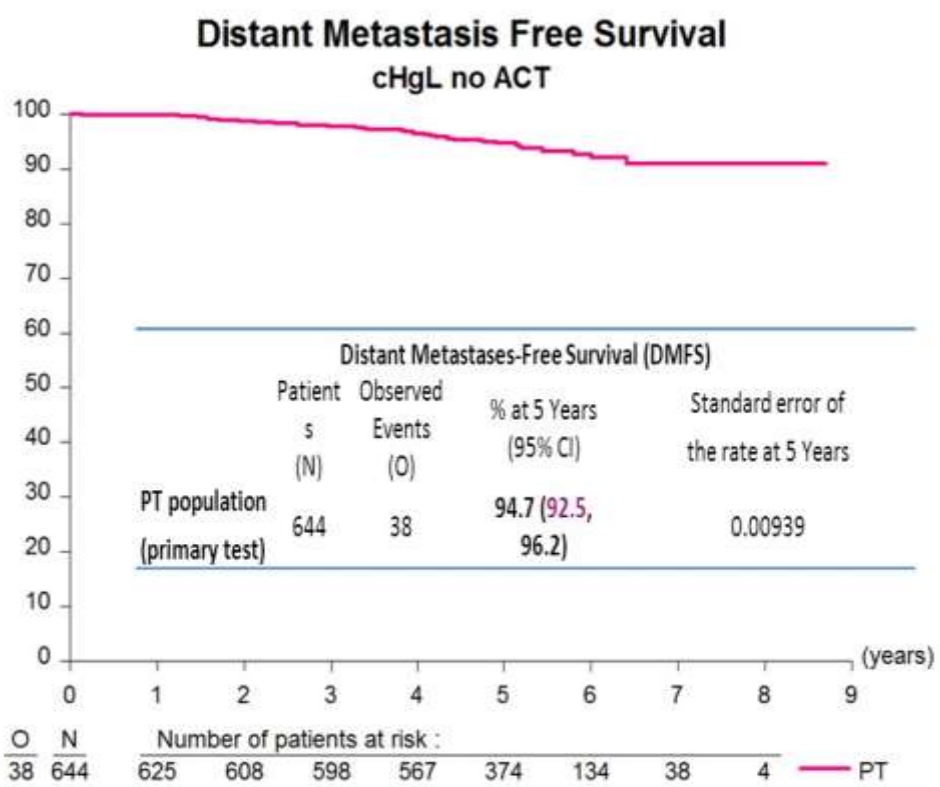
ha: 2.5% (1-sided)

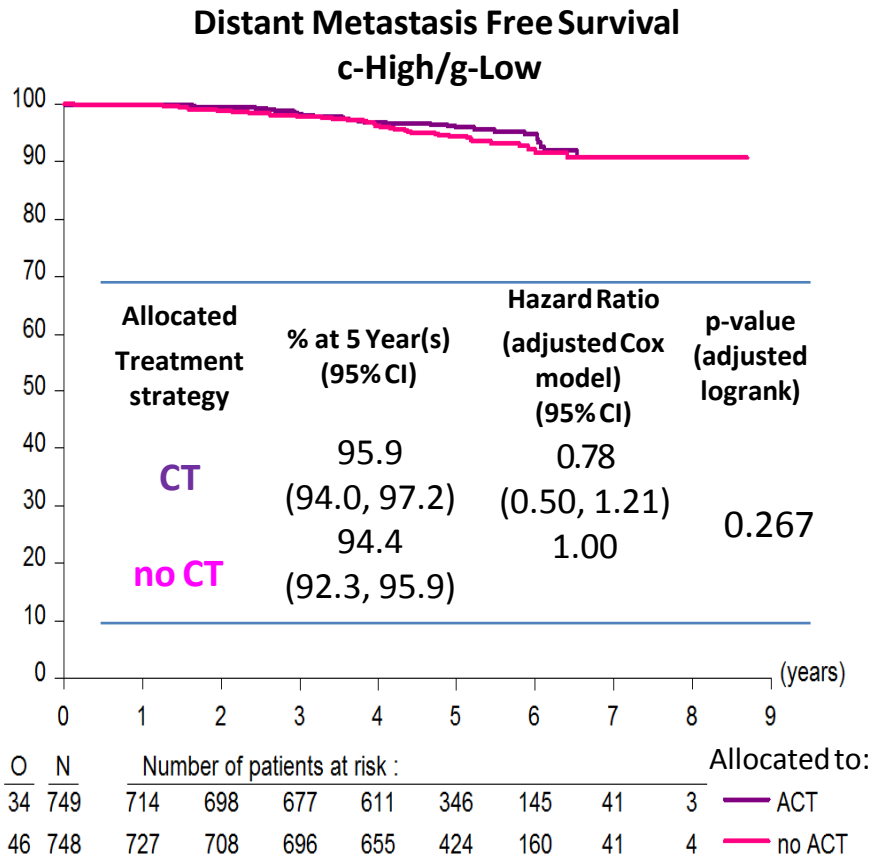
Power: 80% when true 5-year DMFS rate=95%

Cardoso et al. NEJM 2016

MINDACT TRIAL: PRIMARY ANALYSIS

The primary statistical test (DMFS at 5Y)





Null Hypothesis: set at 92%

Observed 5Y DMFS = 94.7%

95% CI ≈ 92.5 – 96.2%

RECOMMENDATIONS FOR PROGNOSTIC MULTIANALYTE TESTS IN ER+/HER2- BC

Test	ASCO	NCCN[a]	ESMO[b]	St. Gallen[b] group	EGTM[c]
uPA/PAI-1	LN−	NR	LN−, LN+	LN−, LN+	LN−
Oncotype DX	LN−	LN−, LN+	LN−, LN+	LN−, LN+	LN−, LN+
MammaPrint	NR	NR	LN−, LN+	LN−, LN+	LN−, LN+
Prosigna	LN−	NR	LN−, LN+	LN−, LN+	LN−, LN+
EndoPredict	LN−	NR	LN−, LN+	LN−, LN+	LN−, LN+
BCI	LN−	NR	NR	LN−, LN+	LN−

Certain variability also in LoE and SOR: different interpretation of published data, grading systems, timing for literature review

Duffy MJ, EJC 2017

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Oncotype DX	LN−	LN−, LN+	LN−, LN+	LN−, LN+	LN−, LN+
MammaPrint	NR	NR	LN−, LN+	LN−, LN+	LN−, LN+
Prosigna					
EndoPredict					
BCI	LN−	NR	NR	LN−, LN+	LN−

Test decentralizzati, eseguiti da vari laboratori nel mondo

Certain variability also in LoE and SOR: different interpretation of published data, grading systems, timing for literature review

Duffy MJ, EJC 2017

READY FOR PRIME TIME?

Breast Cancer—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

Armando E. Giuliano, MD[1]; James L. Connolly, MD[2]; Stephen B. Edge, MD[3]; Elizabeth A. Mittendorf, MD, PhD[4]; Hope S. Rugo, MD[5]; Lawrence J. Solin, MD[6]; Donald L. Weaver, MD[7]; David J. Winchester, MD[8]; Gabriel N. Hortobagyi, MD[9]

TABLE 8. Examples of Revisions to Breast Cancer Staging Using Biomarkers and Oncotype DX

T	N	M	G	HER2	ER	PR	SEVENTH EDITION ANATOMIC STAGE/ PROGNOSTIC GROUP	EIGHTH EDITION PROGNOSTIC STAGE GROUP
Biomarkers								
1	0	0	1	−	−	−	IA	IIA
1	0	0	3	−	+	−	IA	IIA
3	1-2	0	1	+	+	+	IIIA	IB
Oncotype DX recurrence score- < 11 for ER-positive tumors								
2	0	0	Any	−	+	Any	IIA	IB
1-2	1	0	Any	−	+	Any	IIA/IIB	IB
0-2	2	0	1-2	+	+	+	IIIA	IB

Ongoing prospective randomized trials assessing predictive value of multigene tests

TAILORx

Oncotype DX
N0
RS 11-25: randomization between CT+HT and HT

RxPONDER

Oncotype DX
N1
RS≤25: randomization between CT+HT and HT

OPTIMA

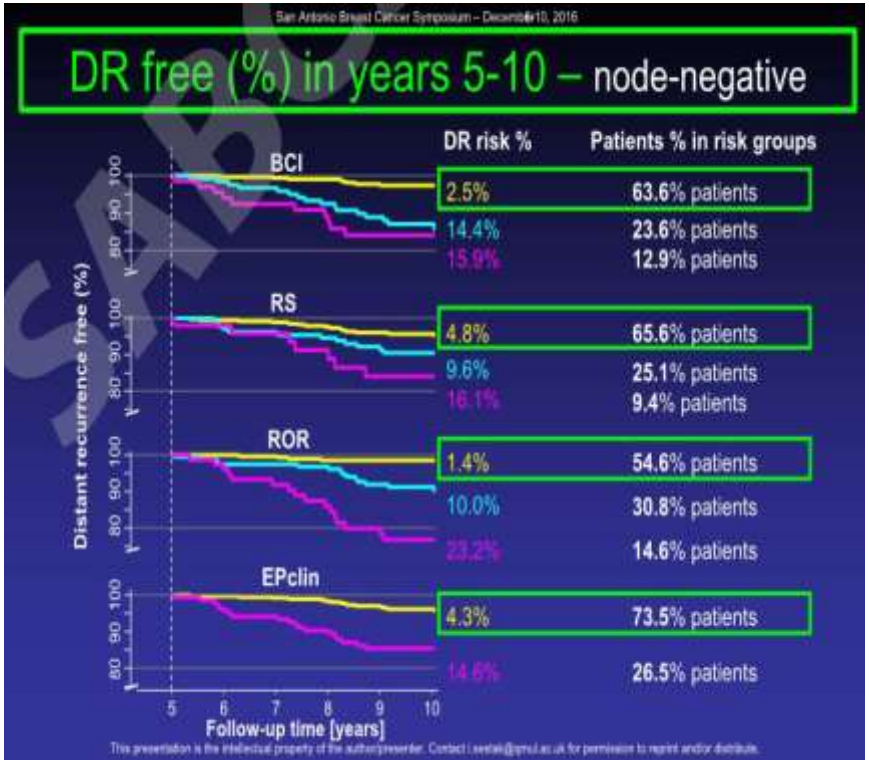
Prosigna (ROR)
N1-2 or N0 and T≥3cm
Randomization: CT vs test-directed therapy (CT+HT if Prosigna high; HT if Prosigna low)

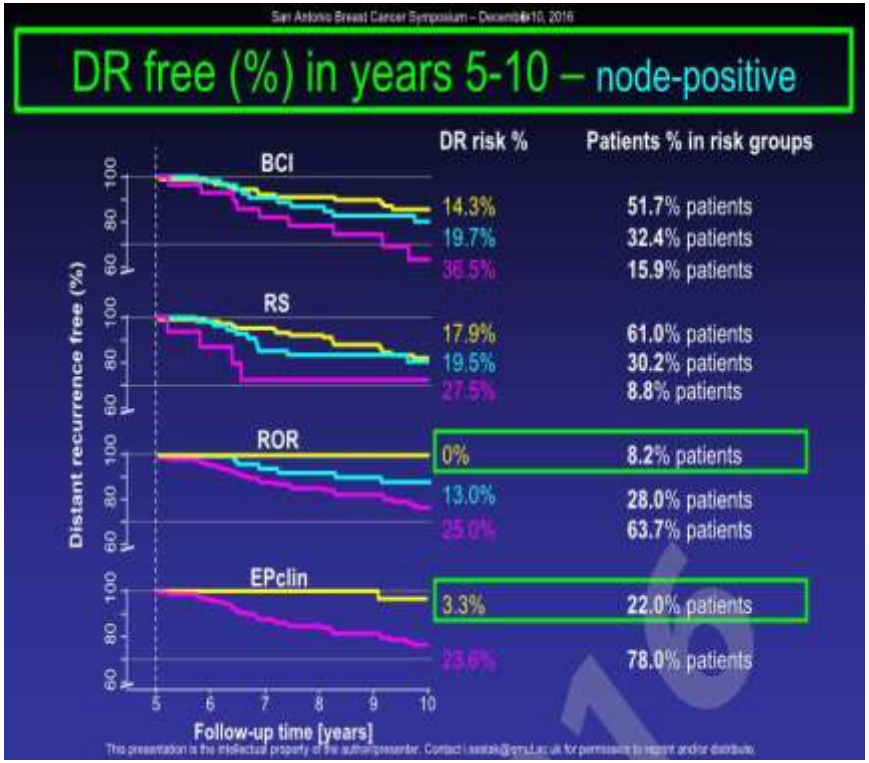
UNIRAD

EndoPredict
N1
EPClin score ≥ 3.32867: randomization between adding or not everolimus to HT after 1 disease-free year with HT

PREDICTION OF LATE RECURRENCES

data from TRANSATAC study





- N-: All signatures identify patients with low risk of late recurrences
- **N+: ROR and EpClin identify patients with low risk of late recurrences**

CAVEAT: ROR cut-off points estimated in TRANSATAC and incorporation of certain clinical variables is important

MULTIGENE TESTS: SUMMARY OF EVIDENCE

- All provide prognostic information independent of traditional factors.
- Majority validated in ER+/HER2-, N- BC patients, some also found to be prognostic in N1 pts.
- Only OncotypeDx and Mammaprint have been tested in prospective randomized trials (some studies ongoing for other tests).
- Included in major guidelines as **prognostic** tools to be integrated with traditional factors.
- Traditional prognostic factors (T, N, grade) should be accurately determined (included in risk scores or may modify absolute patient risk)
- None can be recommended at this stage for predicting response to chemotherapy.
- None can be recommended at this stage to decide on extended adjuvant ET (Endopredict and Prosigna better than others to estimate late recurrence risk*).

**Dubsky P, 2013; Sestak I, J Clin Oncol 2015*

HOW DO TESTS IMPACT ON CLINIC PRACTICE?

Prospective study of the impact of the Prosigna assay on adjuvant clinical decision-making in unselected patients with estrogen receptor positive, human epidermal growth factor receptor negative, node negative early-stage breast cancer

Miguel Martín ✉, Milagros González-Rivera, Serafín Morales, Juan de la Haba-Rodriguez, Lucía González-Cortijo, Luis Manso, Joan Albanell, Antonio González-Martín, Sónia González, Angels Arcusa, Luis de la Cruz-Merino, Federico Rojo, María Vidal, Patricia Galván, Elena Aguirre, Cristina Morales, Sean Ferree, Kristen Pompilio, Maribel Casas, Rosalía Caballero, Uxue Goicoechea, Eva Carrasco, Steven Michalopoulos, John Hornberger & Aleix Prat

200 unselected postmenopausal pts
ER+/HER2- early breast cancer
T1-T2 (<5 cm) and N0
enrolled in 15 Spanish hospitals
between June 2013 and January 2014

	Low ROR		Intermediate ROR		High ROR		TOTAL	
	N=101	(%)	N=66	(%)	N=33	(%)	N=200	(%)
HT to CHT	0	(0.0)	9	(13.6)	9	(27.3)	18	(9.0)
CHT to HT	13	(12.9)	9	(13.6)	0	(0.0)	22	(11.0)
Total	13	(12.9)	18	(27.3)	9	(27.3)	40	(20.0)

Figure 1. Patients receiving chemotherapy by Risk Group

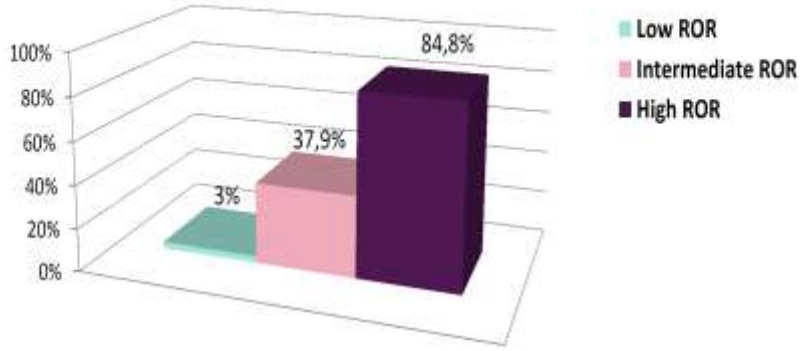


Table 2. Change in physician perception after Prosigna

	Same confidence (%)	More confidence (%)	Less confidence (%)
Confidence with prognosis (subtype, risk of recurrence)	101 (54.6)	74 (40.0)	10 (5.4)
Confidence with intended treatment	96 (51.9)	77 (41.6)	12 (6.5)

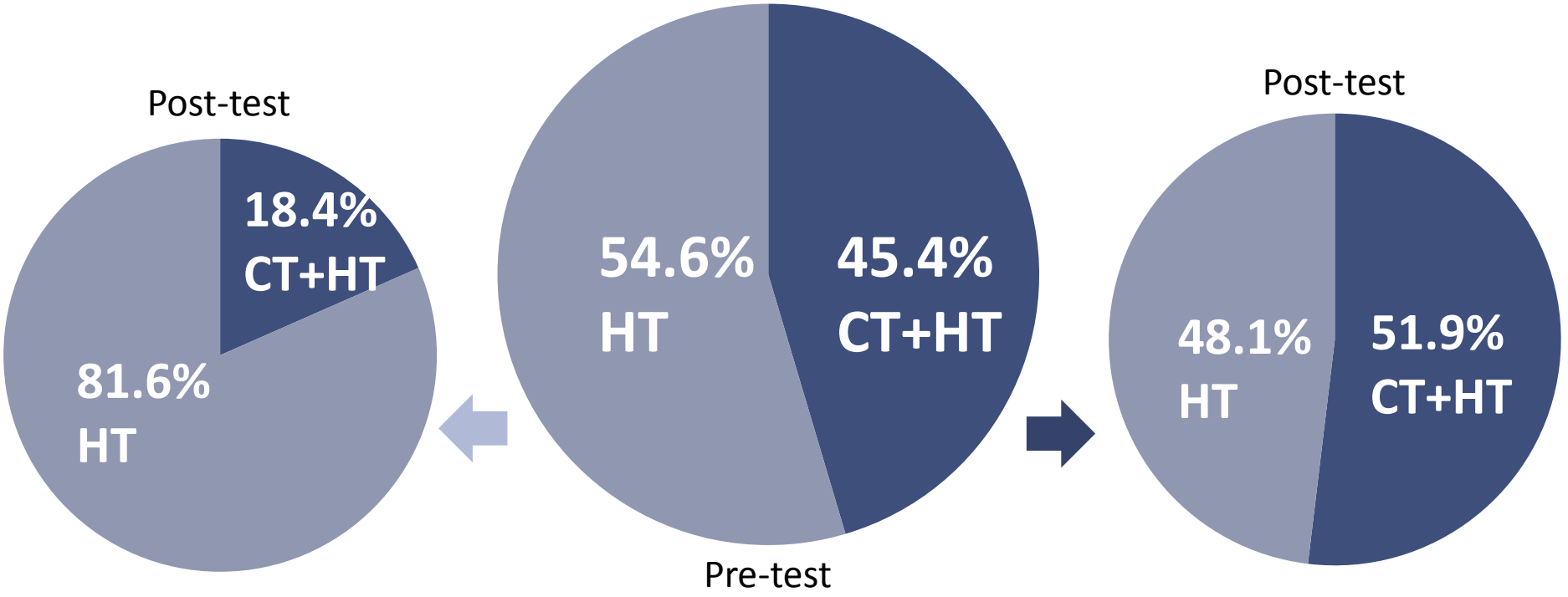
Martin M, Curr Med Res Opin. 2015

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



Overall, 31.9% had a recommendation change posttesting → 26% CT net reduction

01-109 Italian Decision Impact Study – BREAST-DX Italy

Impact of the Onco*type* DX® Breast Cancer Assay on Resources Optimization and Treatment Decisions for Women with Estrogen Receptor-Positive, Node-Negative and Node-Positive Breast Carcinoma: a prospective Italian multicenter study.

PROGRAMMA PER LA RICERCA INNOVAZIONE E HTA (PRIHTA) – REGIONE DEL VENETO

Coordinatore: Istituto Oncologico Veneto IRCCS, Padova

PI: Prof. PierFranco Conte

Trial Office/Data Centre: Servizio Sperimentazioni Cliniche e Biostatistica, IOV (Gian Luca De Salvo)

STUDY DESIGN

1. PROSPECTIVE REGISTRATION OF ALL CONSECUTIVE ER+, HER2-, N0-1 (0 to 3 positive nodes), T1-3 BC PATIENTS

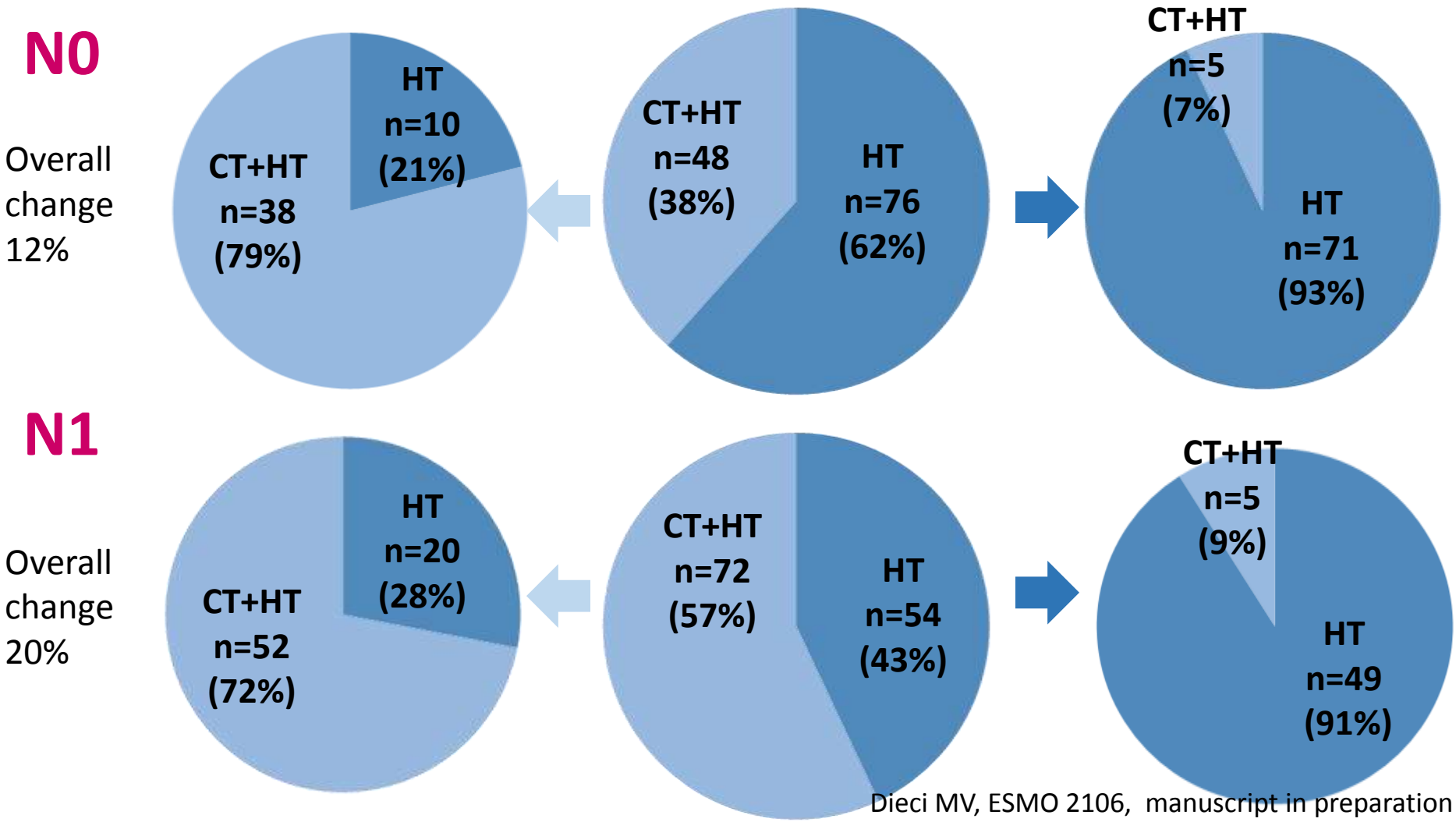
2. CATEGORIZATION IN RISK GROUPS BASED ON TRADITIONAL PROGNOSTIC FACTORS ACCORDING TO PROTOCOL CRITERIA

Low-Risk	Intermediate-Risk	High-Risk
At least 4 of: G1; T1a-b; Ki67 <15%; N0; ER >80%	Not classified as low or high risk.	At least 4 of : G3; T≥2; Ki67 >30%, N1; ER <30%

3. ONCOTYPE DX PROPOSED TO INTERMEDIATE-RISK PATIENTS ONLY

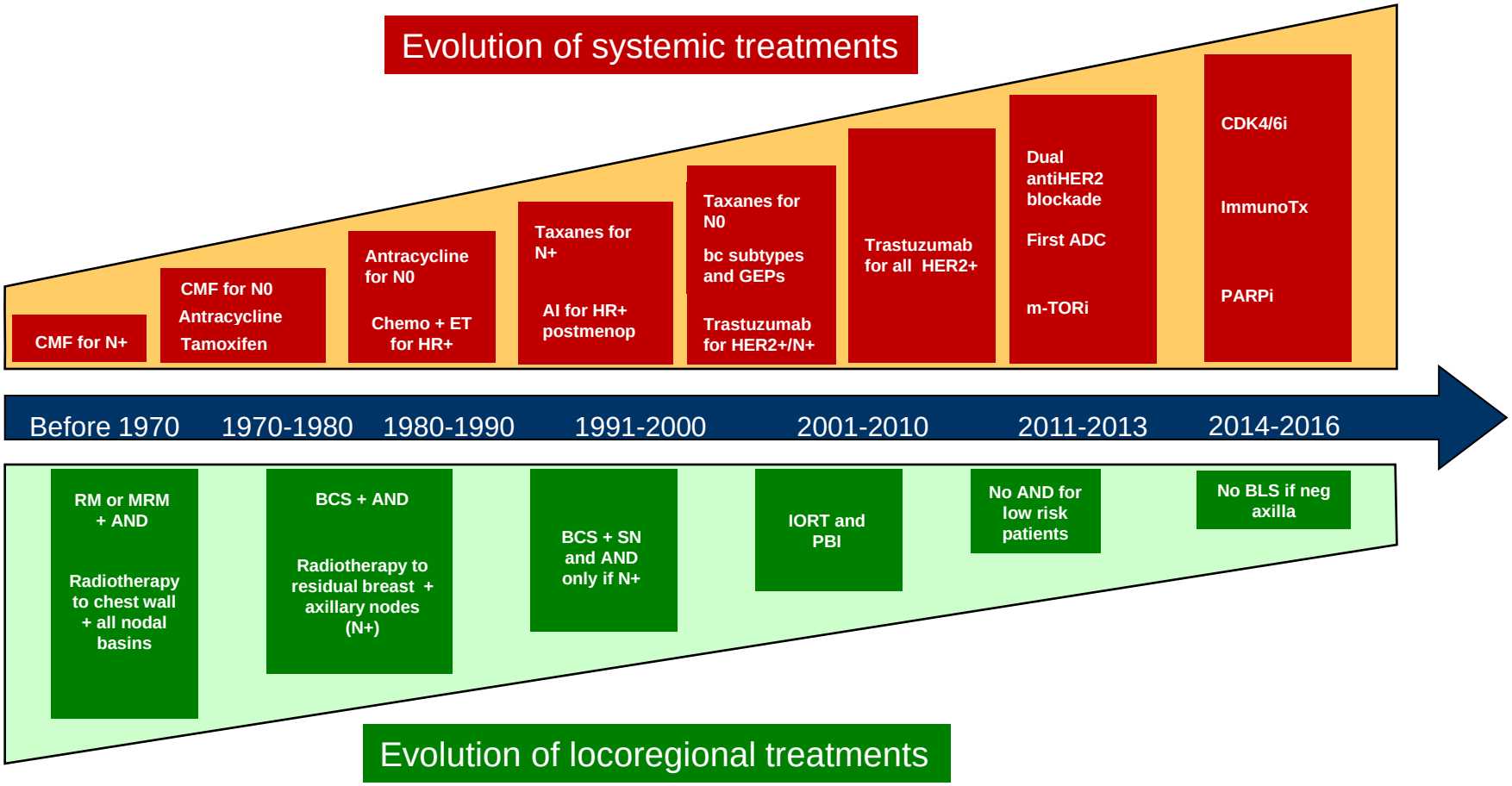
Data collected: pre-RS treatment recommendation; post-RS treatment recommendation; treatment that was actually started;. post-RS physician's perception of test utility.

Shift in post-RS recommendation by pre-RS recommendation



Dieci MV, ESMO 2106, manuscript in preparation

Breast cancer management over time



NEED NEW/BETTER PROGNOSTIC FACTORS!!!

Grazie dell'attenzione

gaia.griguolo@iov.veneto.it