Γονιδιακές υπογραφές σε N0/N1 όγκους Oncotype DX - Mammaprint

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Adjuvant Therapy Recommendations for Breast Cancer in the Year 2000

SPECIAL ARTICLE

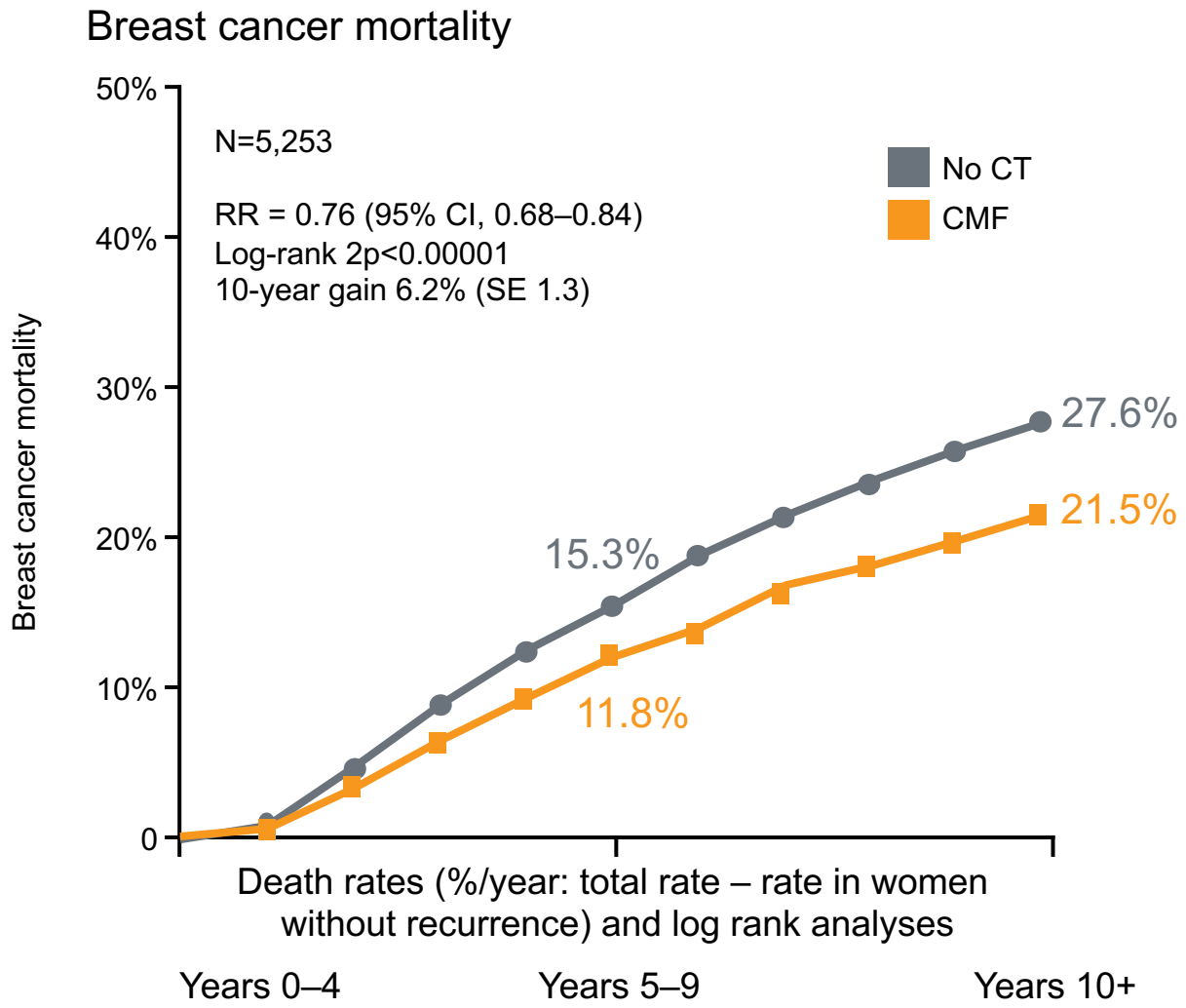
National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1–3, 2000

*National Institutes of Health Consensus Development Panel**

"…it is important to determine whether there are specific patient populations for whom it is reasonable to avoid the administration of cytotoxic chemotherapy. Unfortunately, very limited information is available to answer this important question".

J Natl Cancer Inst. 2001.

The vast majority of patients with early breast cancer do not benefit from adjuvant chemotherapy



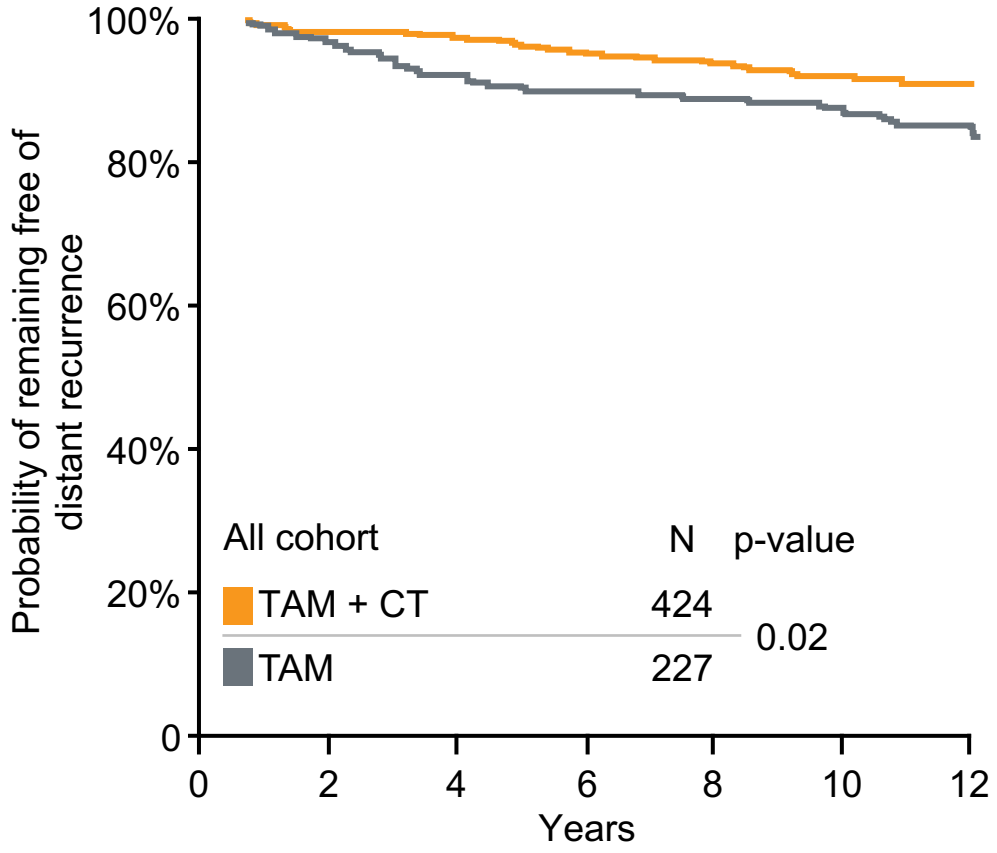
Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of randomised studies in trials CMF vs no chemotherapy (CT)

5,253 women, 66% N0, 34% N+

EBCTCG. *Lancet.* 2012.

CMF = cyclophosphamide, methotrexate and fluorouracil;
RR = event rate ratio

NSABP B-20: which ER-positive patients benefit from chemotherapy?



4% absolute benefit from chemotherapy

"…statistical analyses failed to identify a subgroup of patients with negative nodes and ER-positive tumors who failed to benefit from chemotherapy."

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

ER: estrogen receptor
TAM: tamoxifen

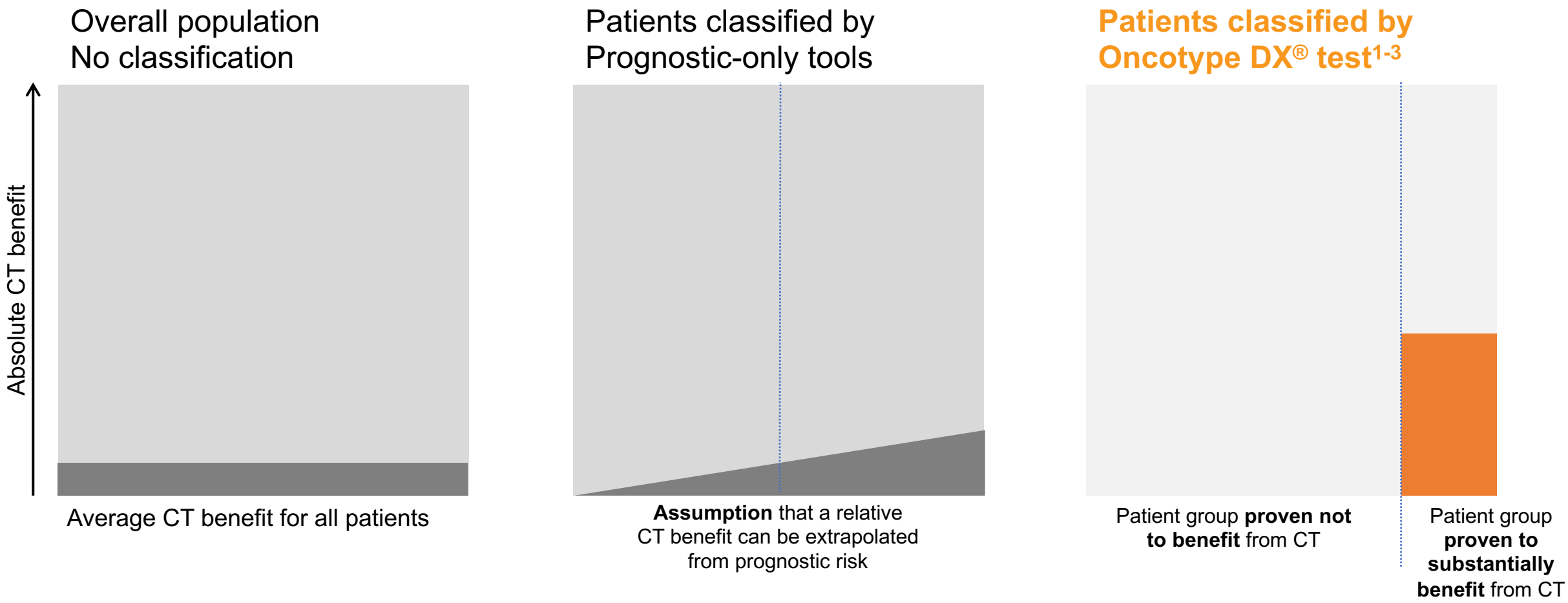
Prognostic versus predictive biomarkers[1]

Prognosis of disease progression	"A prognostic biomarker informs about a likely cancer **outcome** (e.g., disease recurrence, disease progression, death) independent of treatment received"[1]
Prediction of chemotherapy benefit	"A biomarker is predictive if the **treatment effect** (experimental compared with control) is different for biomarker-positive patients compared with biomarker-negative patients." [1]

To determine whether a **biomarker is predictive of treatment benefit**, a **formal test for an interaction** between the biomarker, treatment group, and outcome must be statistically significant (P <0.05) in the context of **a randomized study**[1]

1. Ballman. *J Clin Oncol*. 2015.

Moving from assumed to proven chemotherapy benefit



Population treatment benefit (area under curve) identical in all three scenarios

1. Sparano et al. *N Engl J Med.* 2018; 2. Geyer et al. *npj Breast Cancer* 2018; 3. Paik et al. *J Clin Oncol.* 2006.

Node Negative

The Oncotype DX Breast Recurrence Score® Test

Treatment Decisions in HR-Positive, Node-Negative Invasive Breast Cancer

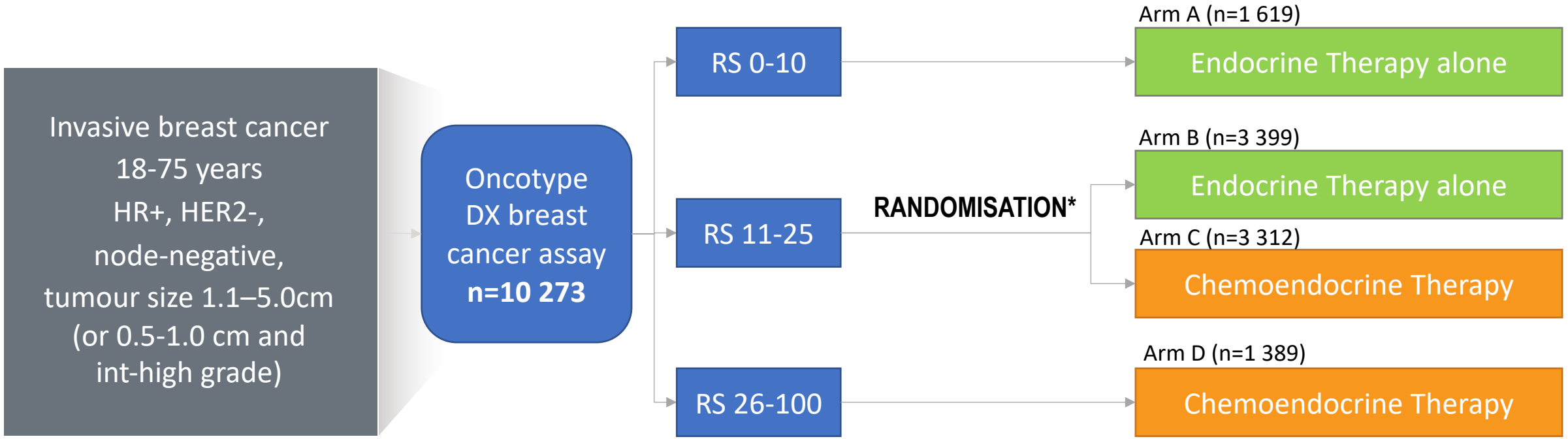
Trial Assigning IndividuaLized Options for TReatment: TAILORx

Phase 3 trial of chemoendocrine therapy versus endocrine therapy alone in HR-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene Recurrence Score®

NATIONAL CANCER INSTITUTE®

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

TAILORx study design



Primary endpoints:

- Invasive disease-free survival (iDFS)
- Non-inferiority design for Recurrence Score® 11-25 group randomized to endocrine therapy alone vs. chemoendocrine therapy

Exploratory analyses:

- Chemotherapy benefit in subgroups by Recurrence Score result, tumour size, grade, clinical risk, menopausal status and age

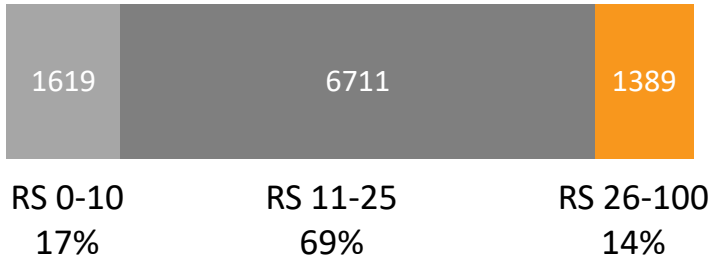
* Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25
RS: Recurrence Score® result

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

Patient population according to Recurrence Score® result groups in TAILORx[1]

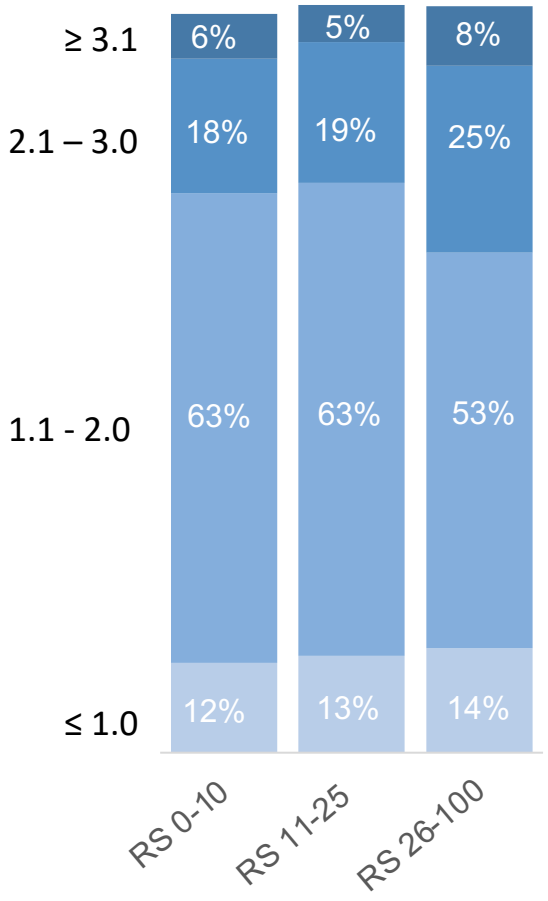
N0 TAILORx (Level 1A evidence)

Recurrence Score result distribution[1]

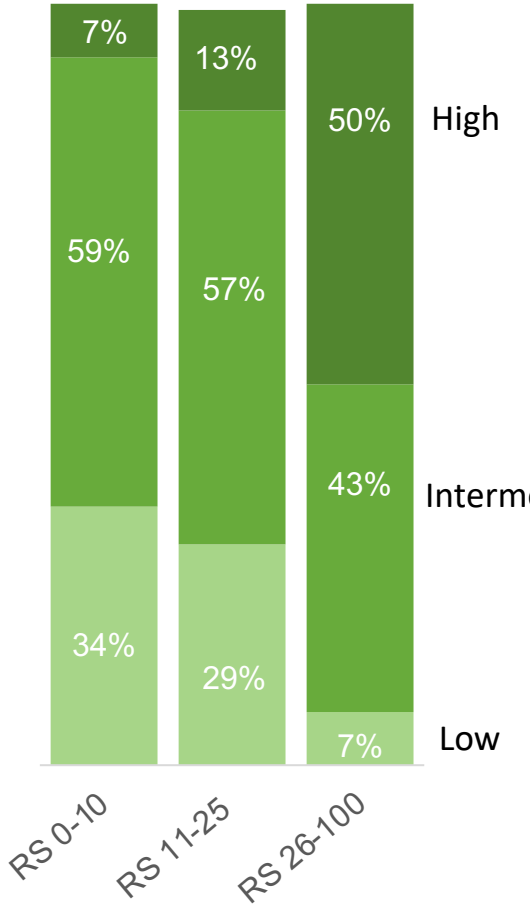


* Low clinical risk:
tumour size ≤3 cm and Grade 1
tumour size ≤2 cm and Grade 2
tumour size ≤1 cm and Grade 3
High clinical risk: all other cases with known values for grade and tumour size

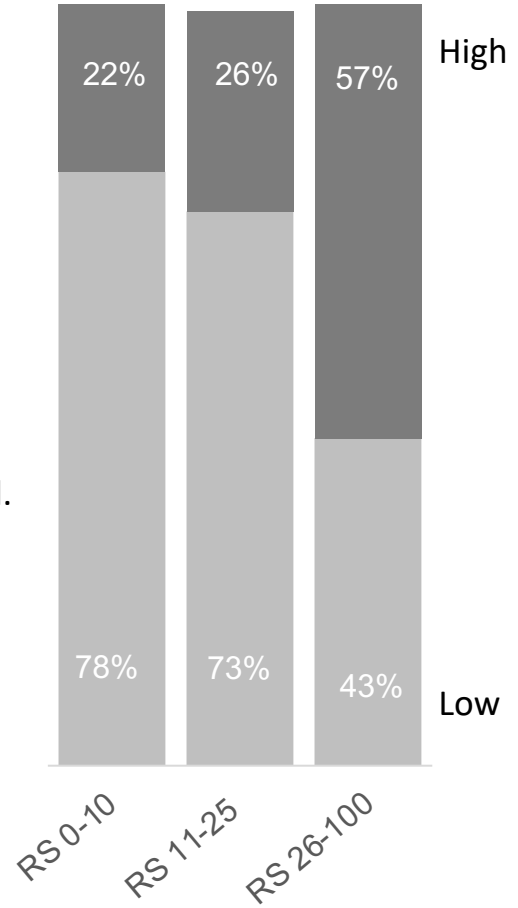
Tumour size (cm)



Tumour grade



Clinical risk*



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

RS: Recurrence Score result

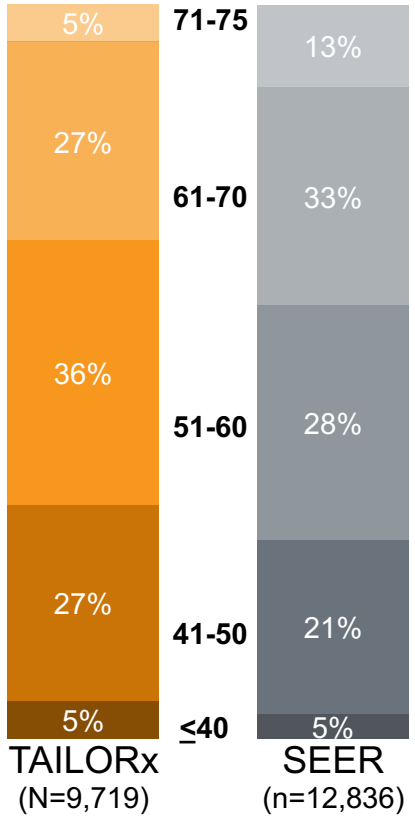
Comparable patient populations between TAILORx[1] and SEER registry

TAILORx included patients tested in clinical practice

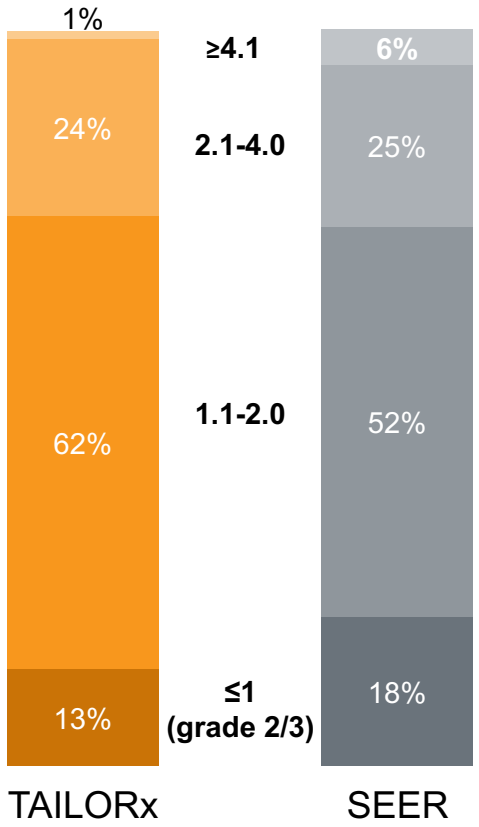
N0 TAILORx & SEER registry

Age distribution (years)

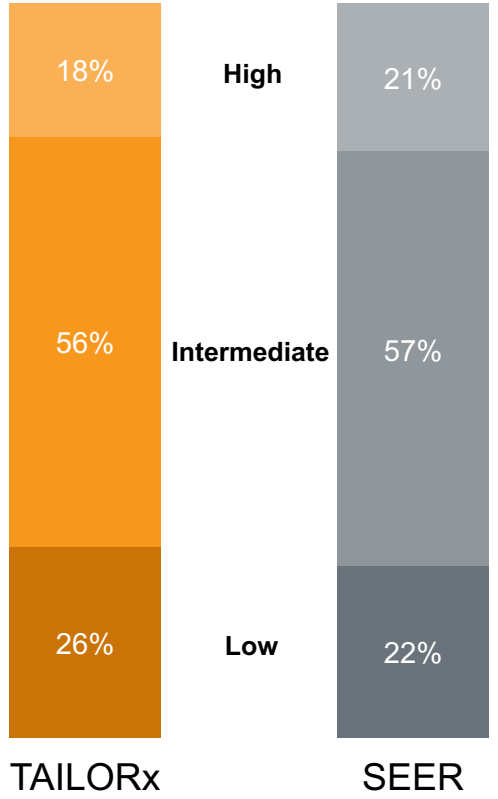
Median age = 56 (25-75)



Tumour size (cm)



Tumour grade

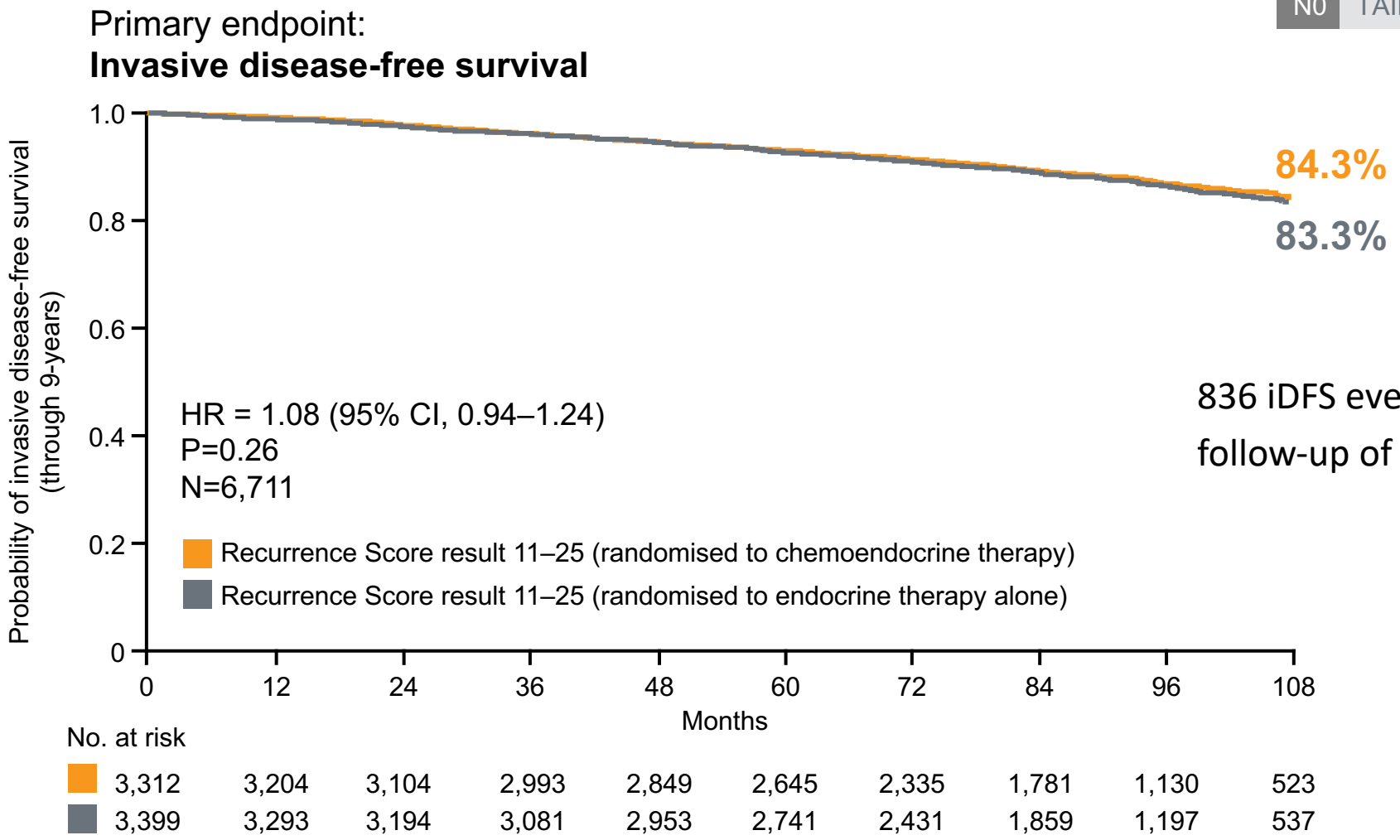


1. Sparano et al. *N Engl J Med.* 2018. SEER Database N-, HR+, HER2-. 2010.

SEER patients from 2010: HR-positive, HER2-negative breast cancer patients with clinicopathologic characteristics consistent with women eligible for TAILORx

TAILORx primary endpoint: endocrine therapy alone is non-inferior to chemoendocrine therapy in patients with Recurrence Score® results 11–25

N0 TAILORx (Level 1A evidence)



836 iDFS events after median follow-up of 7.5 years

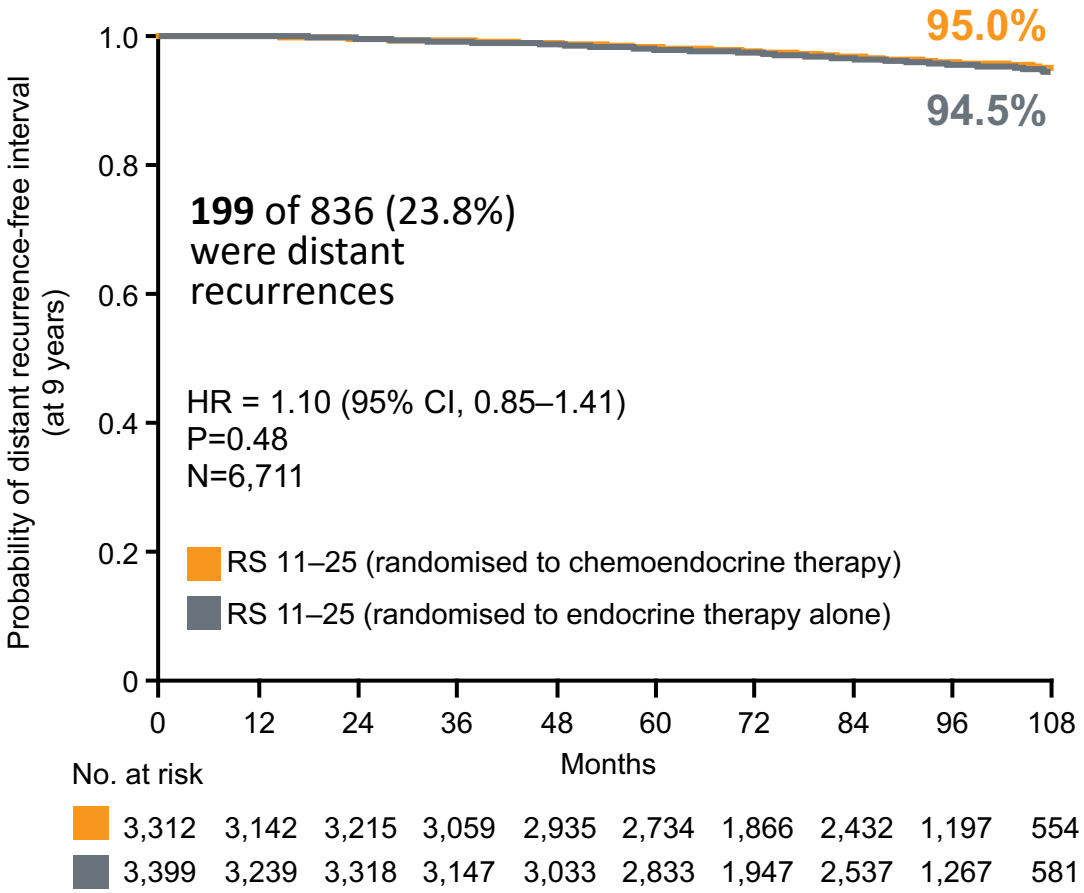
Sparano et al. *N Engl J Med.* 2018.

HR = hazard ratio; CI = confidence interval

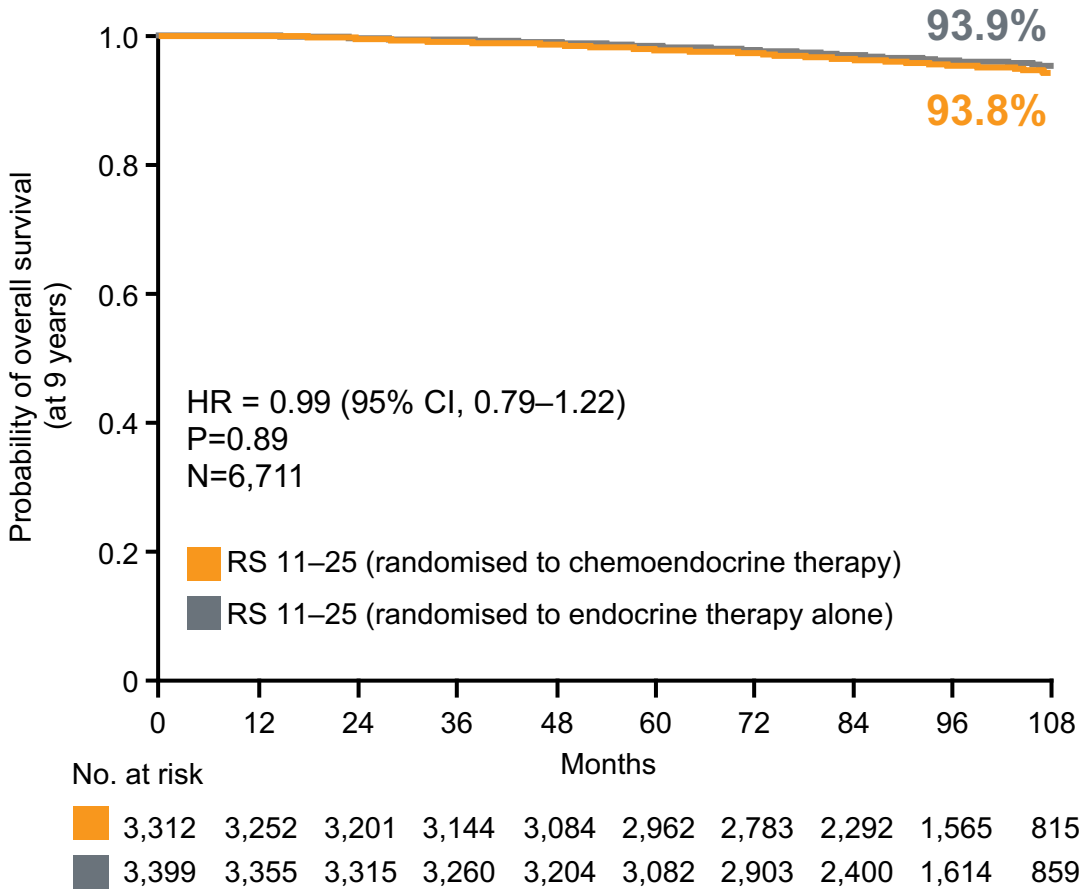
TAILORx secondary endpoints: endocrine therapy alone is non-inferior to chemoendocrine therapy for patients with Recurrence Score® results 11–25

N0 TAILORx (Level 1A evidence)

Secondary endpoint:
Distant recurrence-free interval



Secondary endpoint:
Overall survival



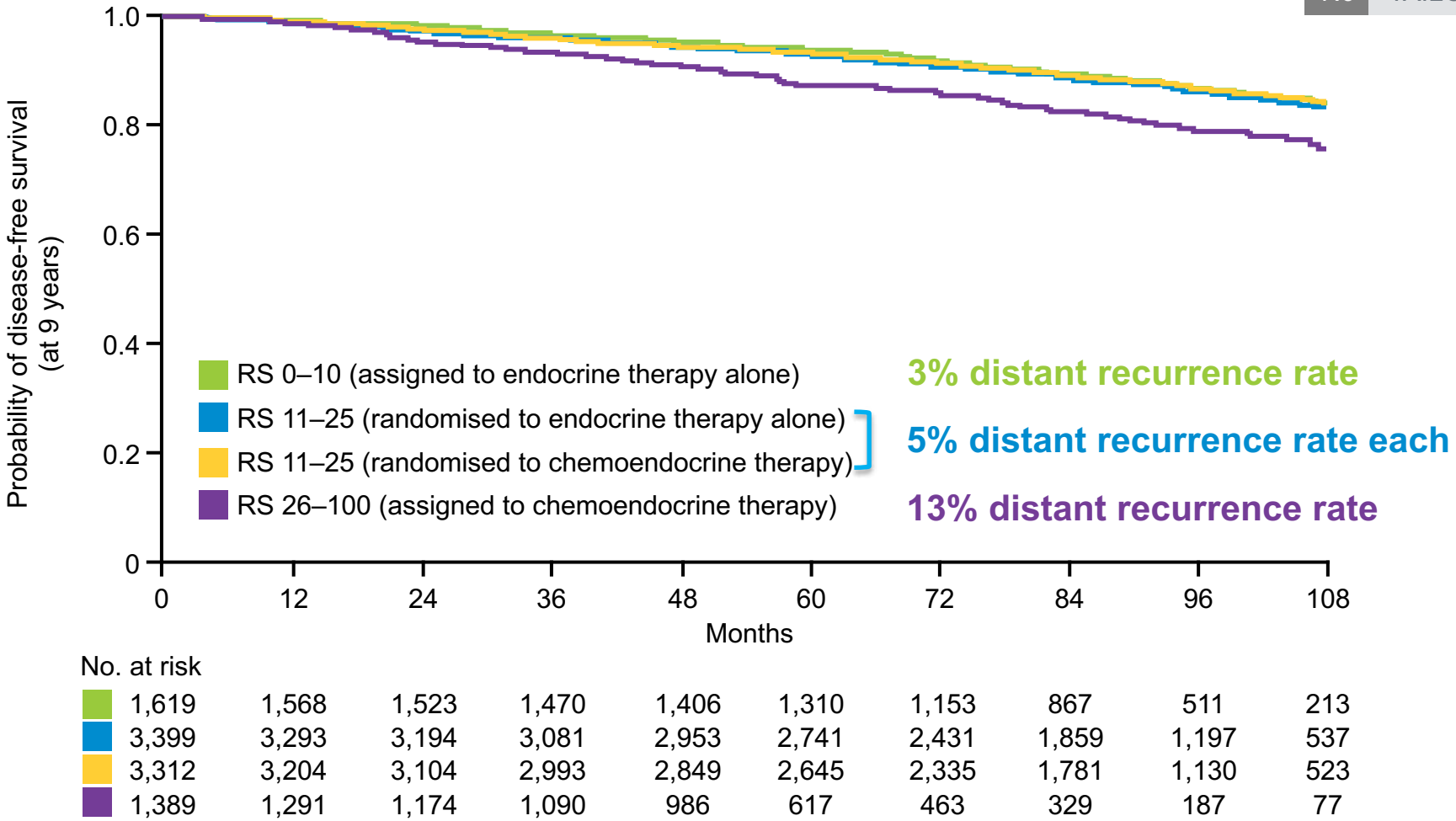
Sparano et al. *N Engl J Med.* 2018.

HR = hazard ratio; CI = confidence interval; RS = Recurrence Score result

Patients with Recurrence Score® results 0-25 have ≤5% risk of distant recurrence at 9 years[1,2]

TAILORx 9-year DFS event rates – ITT population

N0 TAILORx (Level 1A evidence)



1. Paik et al. *J Clin Oncol*. 2006; 2. Sparano. et al. *N Engl J Med.* 2018.

HR = hazard ratio; CI = confidence interval; HR+ = hormone receptor-positive; HER2– = human epidermal growth factor receptor 2-negative; N0 = node-negative; RS = Recurrence Score result

Implications for clinical practice based on TAILORx & NSABP B-20 results using the Oncotype DX Breast Recurrence Score® test

HR-positive, HER2-negative, node-negative patients[1-3]

Recurrence Score® Result	
0-25	26-100
No Chemotherapy Benefit[1-3]	Chemotherapy Benefit[1,2]

1. Sparano et al. *J Clin Oncol.* 2008; 2. Geyer et al. *Npj Breast Canc* 2018: 3. Sparano et al. *N Engl J Med.* 2018.;

HR: hormone receptor
HER2: human epidermal growth factor receptor 2

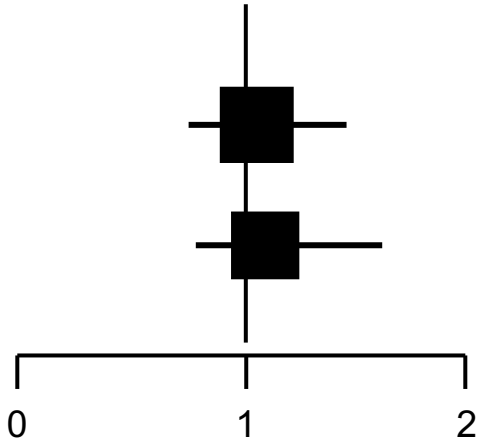
Clinical risk does NOT correlate with chemotherapy benefit in the Recurrence Score® result 11-25 group[1,2]

TAILORx Exploratory analysis

N0 TAILORx exploratory

Distant Recurrence-Free Interval (DRFI)
hazard ratios for subsets, ET vs CT-ET therapy

Group	N (%)	Ratio	95% CI
Low clinical risk	4799 (74%)	1.03	(0.72, 1.46)
High clinical risk	1697 (26%)	1.10	(0.75, 1.62)



Low clinical risk:

- tumour size ≤3 cm and Grade 1
- tumour size ≤2 cm and Grade 2
- tumour size ≤1 cm and Grade 3

High clinical risk: All other cases with known values for grade and tumour size

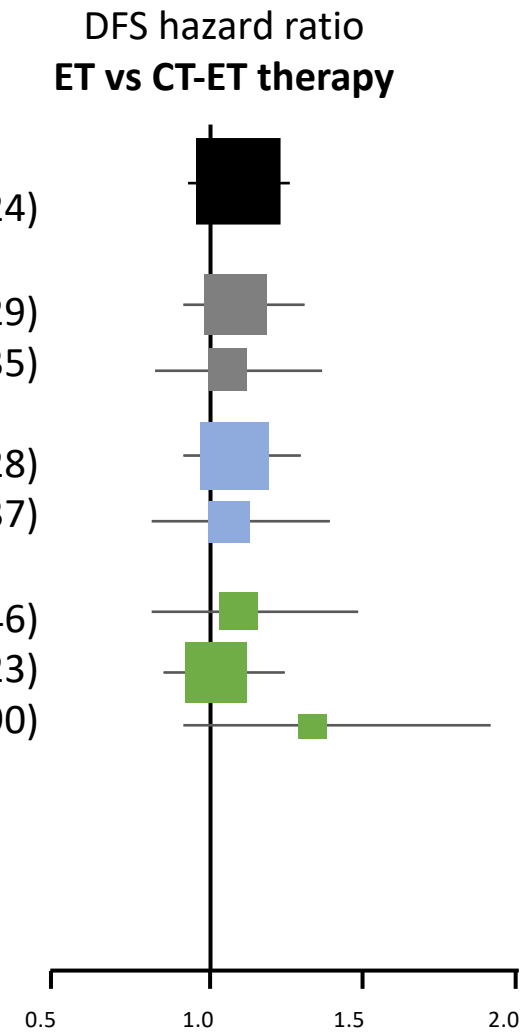
1. Sparano et al. *N Engl J Med* 2018; 2. Sparano et al. *N Engl J Med* 2019

Classical clinical parameters do NOT predict chemotherapy benefit in the Recurrence Score® result 11-25 group

TAILORx Exploratory analyses

N0 TAILORx exploratory

Group	n	ratio	95% CI
Overall	6711	1.08	(0.94, 1.24)
Clinical risk low	4799	1.08	(0.91, 1.29)
Clinical risk high	1697	1.05	(0.82, 1.35)
Tumour size ≤ 2cm	5122	1.08	(0.92, 1.28)
Tumour size > 2cm	1587	1.06	(0.82, 1.37)
Grade low	1893	1.09	(0.82, 1.46)
Grade intermed	3721	1.02	(0.85, 1.23)
Grade high	884	1.32	(0.92, 1.90)



No statistically significant chemotherapy treatment interactions were found in any of these subgroups

Low clinical risk:

- tumour size ≤3 cm and Grade 1
- tumour size ≤2 cm and Grade 2
- tumour size ≤1 cm and Grade 3

High clinical risk: all other cases with known values for grade and tumour size

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

Risks of over- and undertreatment in the TAILORx study[1]

N0 TAILORx study

High clinical risk patients

Clinical risk[a]	Recurrence Score® result 0–25	26–100
Low (n=6,615)	91%	9%
High (n=2,812)	**73%** (2042)	27%

Would have been overtreated[±]

Low clinical risk patients

Recurrence Score result	Clinical risk[a] Low	High
0–25 (n=8,068)	75%	25%
26–100 (n=1,359)	**43%** (589)	57%

Would have been undertreated[±]

a. low clinical risk defined by low grade and tumour size ≤3cm, intermediate grade and tumour size ≤2cm, and high grade and tumour size ≤1cm; high clinical risk defined as all other cases with known values for grade and tumour size
± Assuming that adjuvant chemotherapy would have been recommended because of the high clinical risk.

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

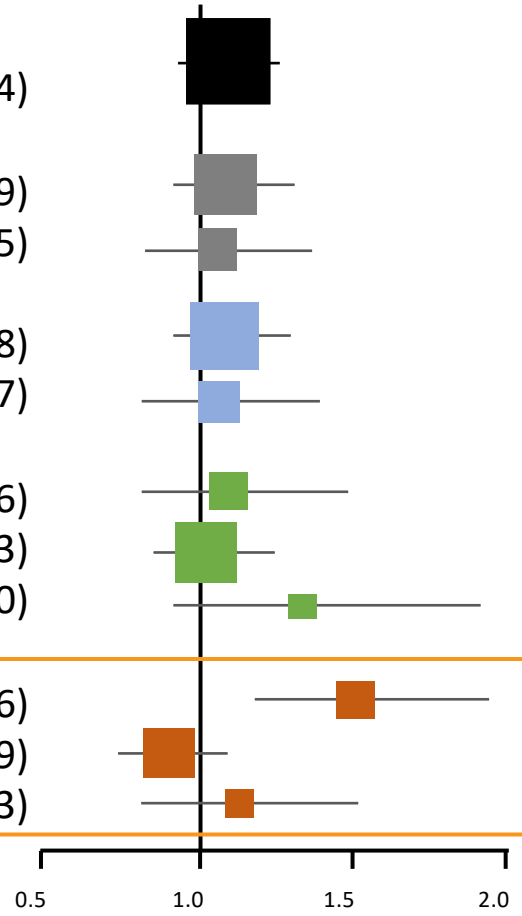
Classical clinical parameters do not predict chemotherapy benefit while younger patients (age ≤50) may derive some benefit from chemotherapy

TAILORx Exploratory analyses

N0 | TAILORx exploratory

DFS hazard ratio
ET vs CT-ET therapy

Group	n	ratio	95% CI
Patients RS 11-25	6711	1.08	(0.94, 1.24)
Clinical risk low	4799	1.08	(0.91, 1.29)
Clinical risk high	1697	1.05	(0.82, 1.35)
Tumour size ≤ 2cm	5122	1.08	(0.92, 1.28)
Tumour size > 2cm	1587	1.06	(0.82, 1.37)
Grade low	1893	1.09	(0.82, 1.46)
Grade intermed.	3721	1.02	(0.85, 1.23)
Grade high	884	1.32	(0.92, 1.90)
Age ≤ 50	2216	1.51	(1.17, 1.96)
Age 51-65	3545	0.89	(0.73, 1.09)
Age >65	950	1.12	(0.81, 1.53)



No statistically significant chemotherapy treatment interactions were found in any of these subgroups

Younger patients (age ≤50) may derive some benefit from chemotherapy in the RS 11-25

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

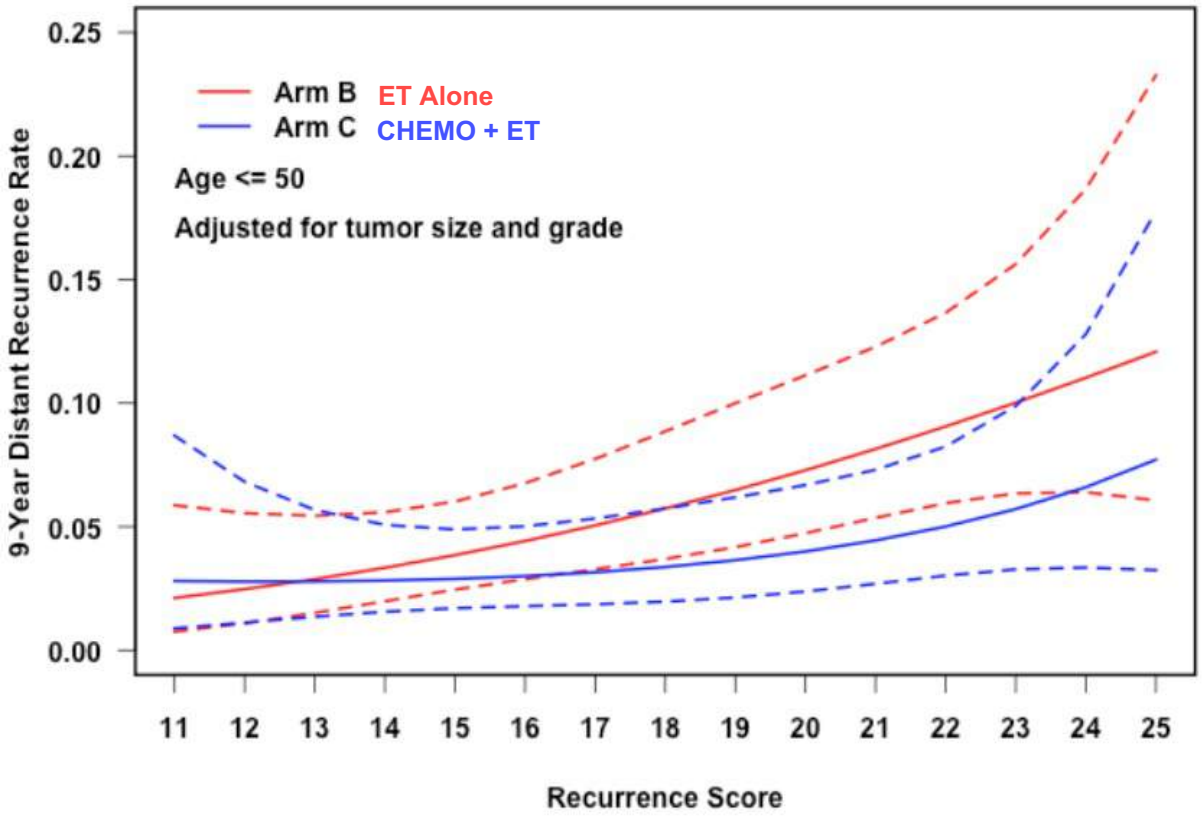
Sparano et al. *N Engl J Med* 2018, Supplement

TAILORx results: association between continuous Recurrence Score® results 11-25 and distant recurrence rate by treatment arms stratified by age

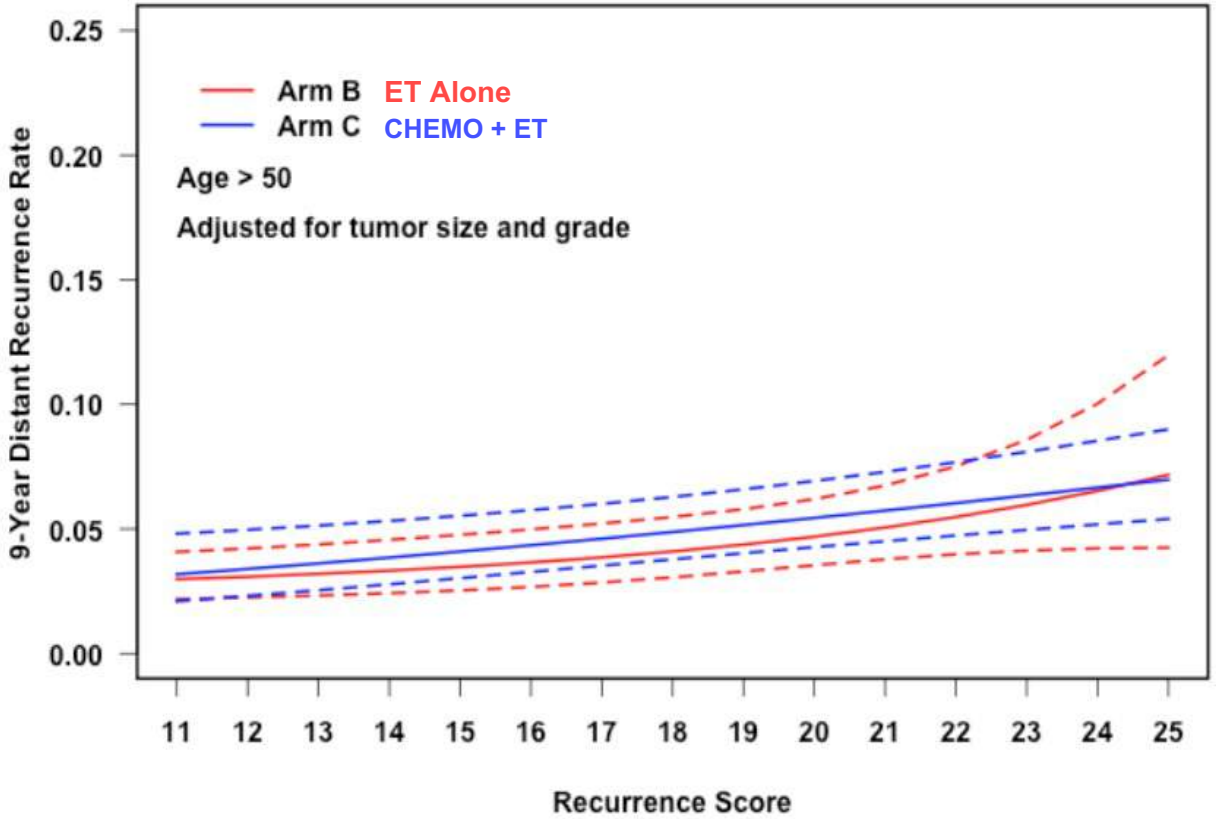
TAILORx Exploratory analysis

N0 | TAILORx exploratory

≤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 exploratory subgroup analysis reinforces evidence to predict with precision which patients are more likely to benefit from chemotherapy[1-4]

N0 TAILORx exploratory

Total patients N=9719	RS 0-10 n=1619	RS 11-15 n=2373	RS 16-20 n=2712	RS 21-25 n=1626	RS 26-100 n=1389
Age >50 years n=6665 (69%)	No CT Benefit n=1190 (12%)	No CT Benefit n=1572 (16%)	No CT Benefit n=1789 (18%)	No CT Benefit n=1134 (12%)	**CT Benefit** n=980 (10%)
Age ≤50 years n=3054 (31%)	No CT Benefit n=429 (4%)	No CT Benefit n=801 (8%)	**~1.6% CT Benefit** n=923 (9%)	**~6.5% CT Benefit** n=492 (5%)	**CT Benefit** n=409 (4%)

Patients ≤50 years

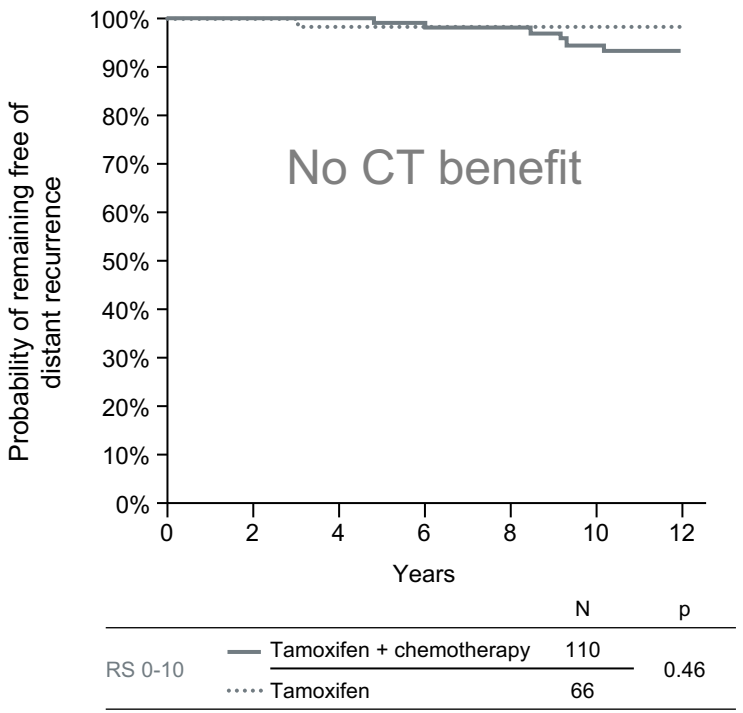
Low clinical risk	7% of all patients **No CT benefit**	3% of all patients **~6.4% CT benefit**
High clinical risk	2% of all patients **~6.5% CT benefit**	2% of all patients **~8.7% CT benefit**

RS= Recurrence Score® result

1. Sparano et al. *N Engl J Med*. 2018; 2. Paik et al. *J Clin Oncol*. 2006; 3. Sparano and Paik. *J Clin Oncol*. 2008; 4. Sparano et al. *N Engl J Med* 2019.

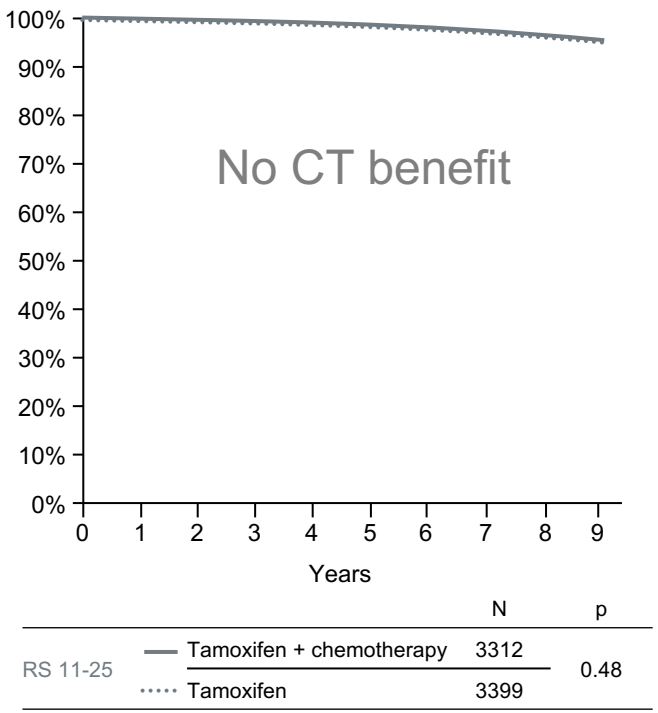
Recurrence Score® result precisely identifies two groups of patients: those who will benefit from & those who can be spared chemotherapy

Recurrence Score® Results **0-10**
NSABP B-20[1,2] (Level 1B evidence)



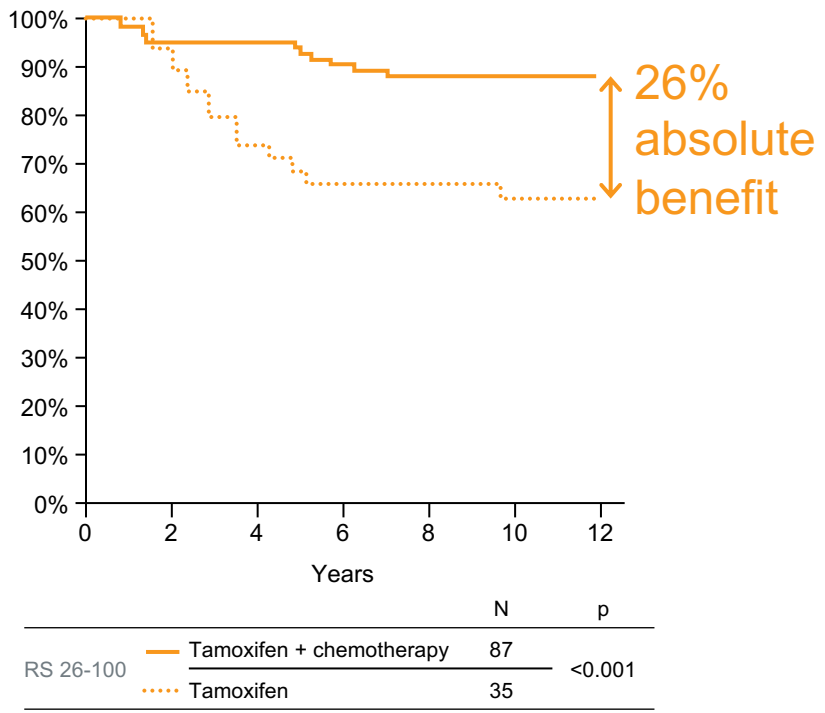
		N	p
RS 0-10	Tamoxifen + chemotherapy	110	0.46
	Tamoxifen	66	

Recurrence Score® Results **11-25**
TAILORx[3] (Level 1A evidence)



		N	p
RS 11-25	Tamoxifen + chemotherapy	3312	0.48
	Tamoxifen	3399	

Recurrence Score® Results **26–100**
NSABP B-20[1,2] (Level 1B evidence)



		N	p
RS 26-100	Tamoxifen + chemotherapy	87	<0.001
	Tamoxifen	35	

~ 80% of the patients*[3-8]

~ 20% of the patients*[3-8]

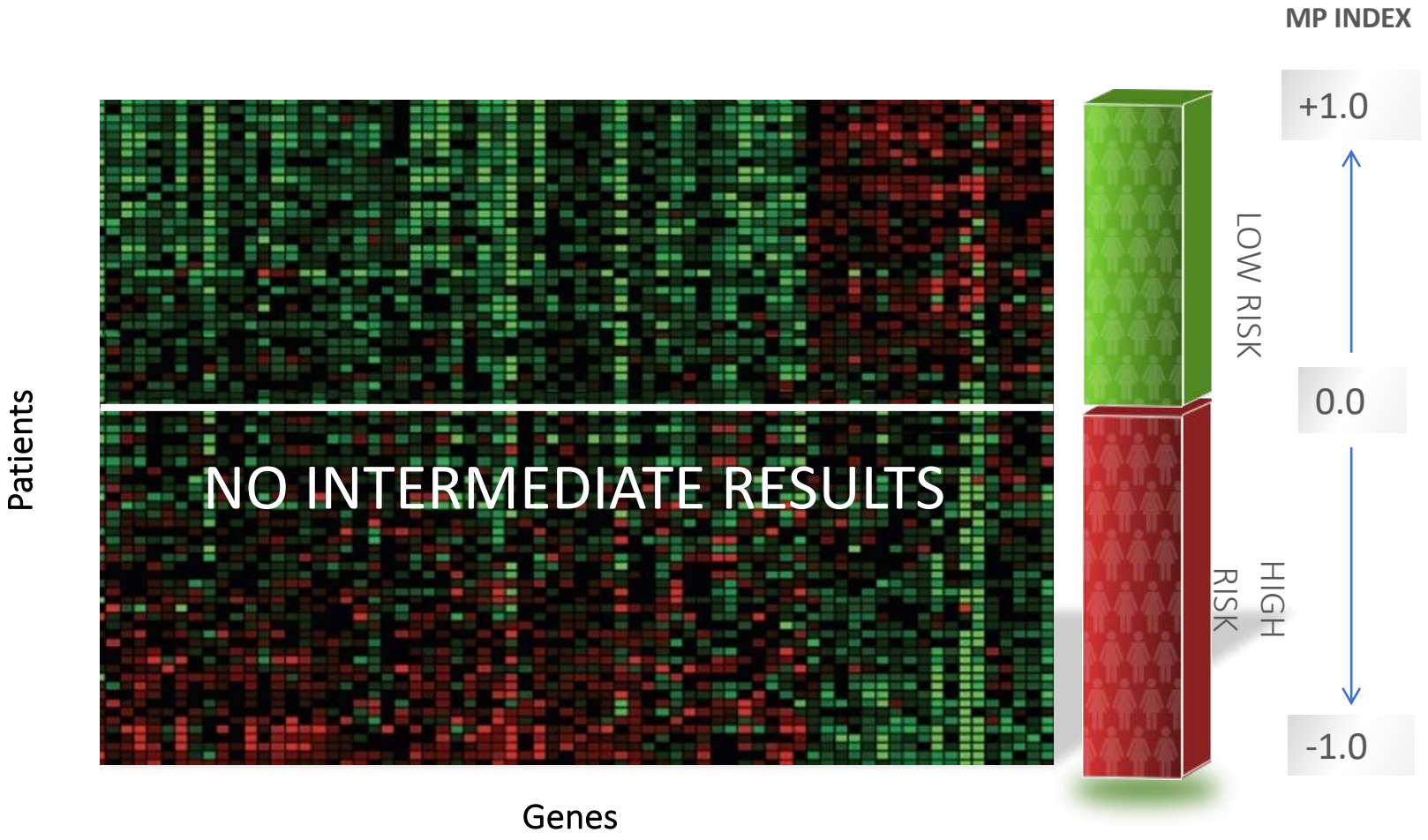
*HR+, HER2-, node-negative, early-stage, invasive breast cancer

1. Paik et al. *J Clin Oncol*. 2006; 2. Geyer et al. npj *Breast Cancer* 2018; 3. Sparano et al. *N Engl J Med*. 2018; 4. Hortobagyi et al. *SABCS* 2018; 5; Sparano et al. *N Engl J Med.* 2015;
6. Petkov et al. *npj Breast Cancer.* 2016; 7. Stemmer et al. *npj Breast Cancer.* 2017; 8. Blohmer et al. *ESMO* 2017.

Mammaprint

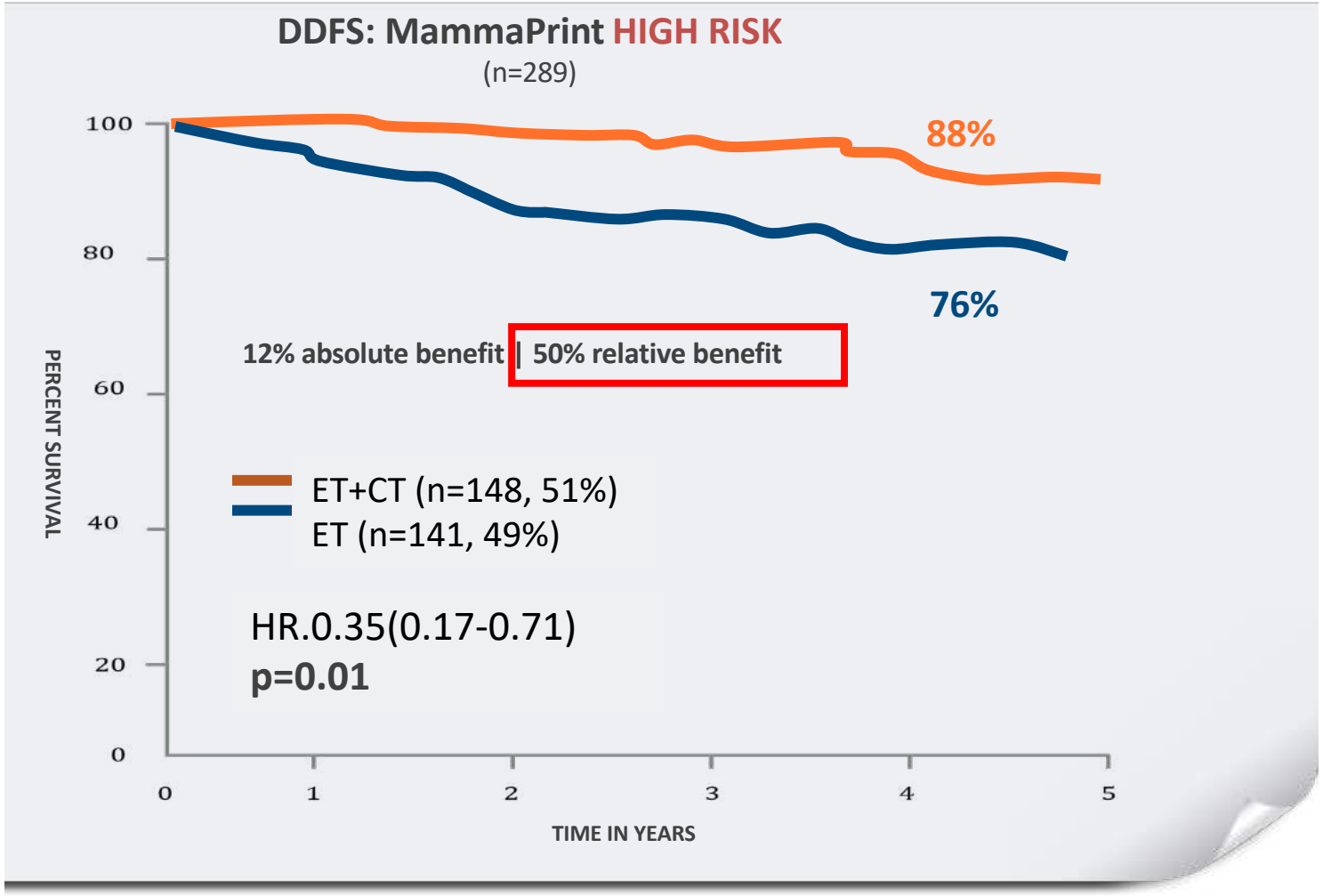
MammaPrint provides true binary results

Clinical classification threshold set by determination of largest population of Low Risk patients that can withhold CT and not suffer adverse consequence.



Buyse et al., Jrnl of the NCI. 2006;98(17):1183-92

MammaPrint HIGH RISK patients Benefit from Chemotherapy



Combined Clinical High and Low Risk

N= 541

Chemotherapy:

- Anthracycline-based (n=194)
- Taxane-containing (n=21)
- CMF (n=11)

Knauer et al. 2010, Breast Cancer Res Treat

MINDACT Primary Test and End Point

Primary test:

- The trial was designed as a non-inferiority trial to assess whether

  C-high / G-low patients could safely omit chemotherapy

Primary endpoint:

- Distant Metastasis Free Survival (DMFS) at 5 years
- Significant (positive trial) if 92% is excluded from the lower bound of the confidence interval in the untreated (no CT) arm of the C-high / G-low group.

Randomize patients with clinical and genomic risk disagreement

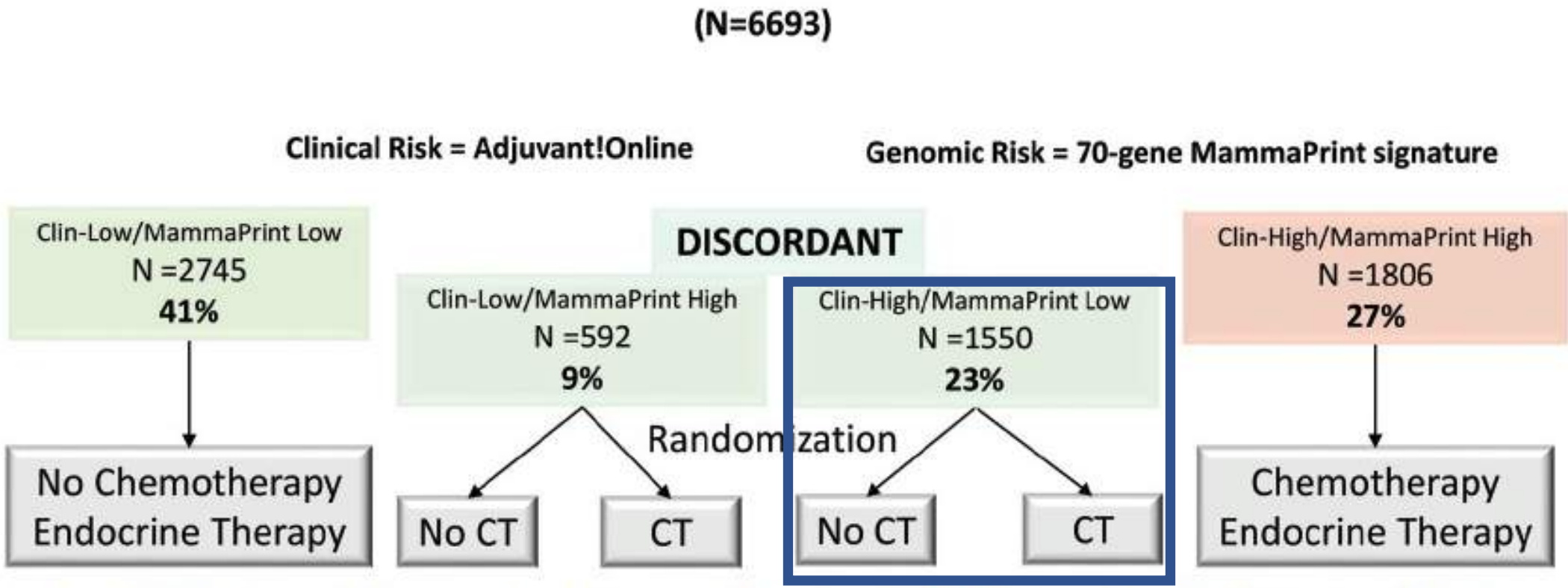
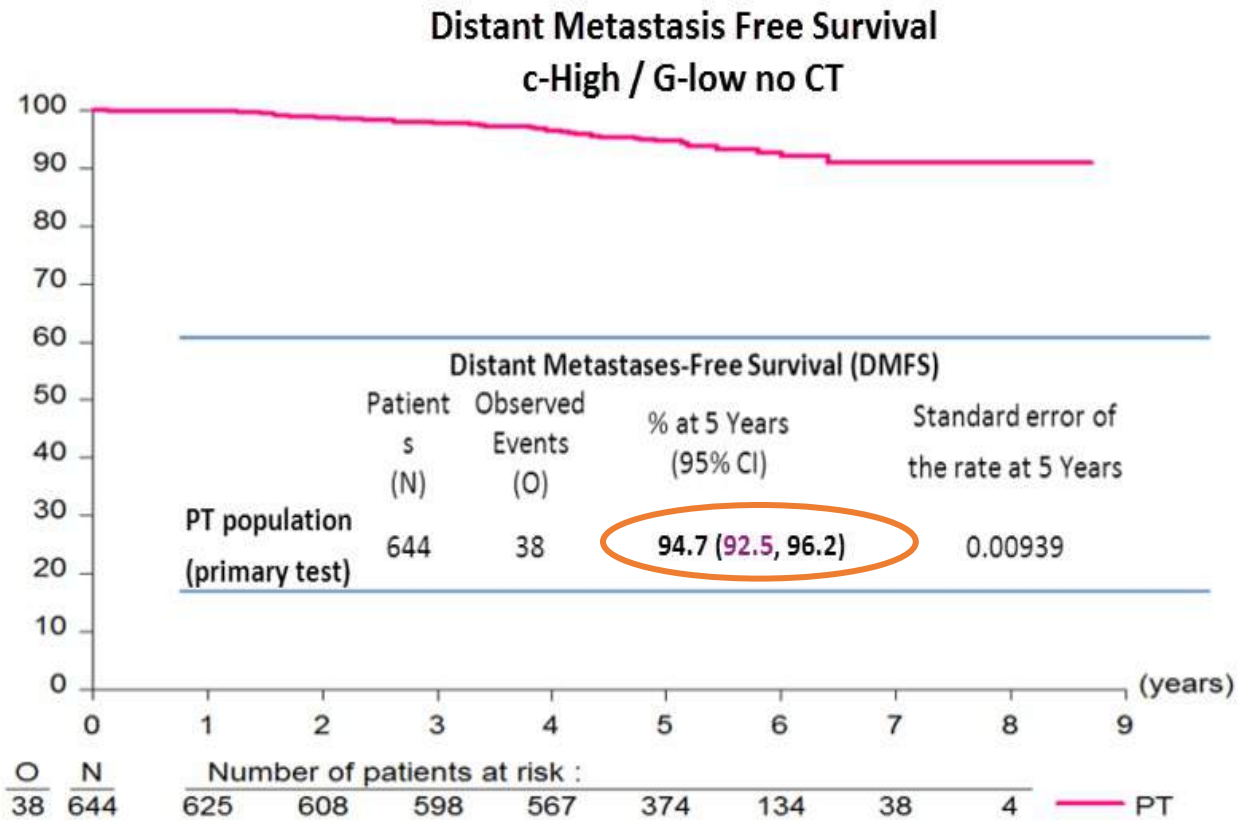


Figure 2. Distribution of Clinical Risk and Genomic Risk in the MINDACT Trial. From Ref. 3 Cardoso (2016).

MINDACT Primary Test Analysis:
C-high / G-low (MP Low) group- No CT, 100% compliance



Primary Test Population, C-high / G-low tumors:

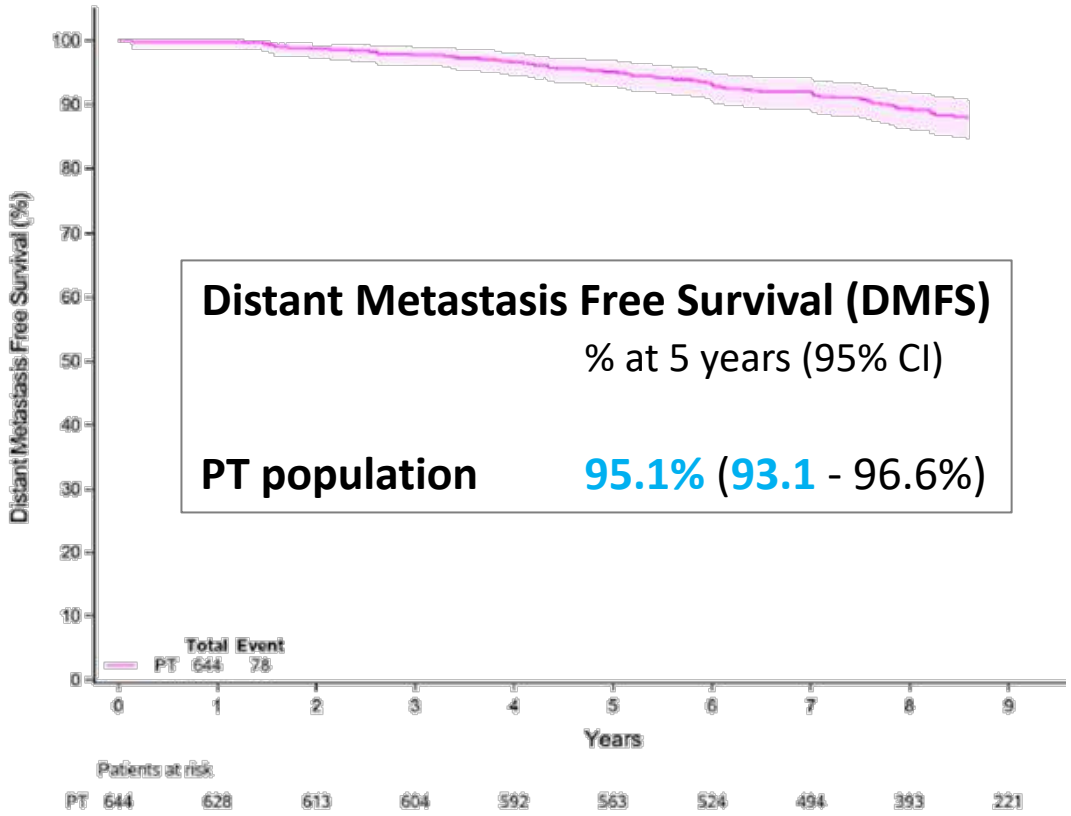
- 58% >2cm
- 93% Grade II or III
- 48% LN+ 1-3
- 98% HR+

- 5-Year DMFS for the C-high / G-low (MP Low) group with no CT= **94.7%** (CI: 92.5 – 96.2%). **60% of the patients**.
- Excludes 92%, positive outcome met.

MINDACT Primary Test Analysis:

C-high / G-low (MP Low) group- No CT, 100% compliance

Long term: 90.4% of the patients 5-yr DMFS without CT



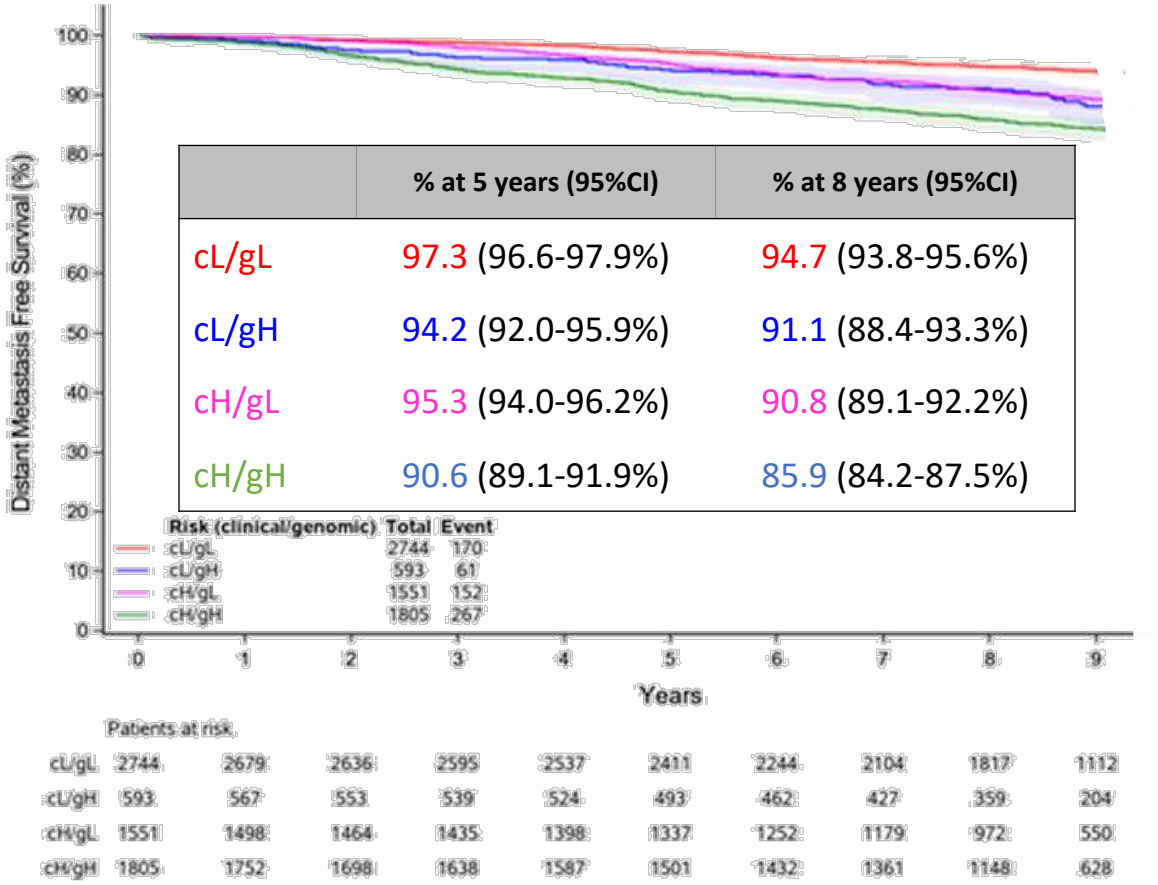
Primary Test (PT) Results:

- **95.1%** 5-yr DMFS without CT for clinically high/MP Low Risk patients
  - Lower bound 95% CI exceeds 92%
- **Confirmation of primary results with more mature follow-up**

Adapted from Cardoso, F., et al. ASCO 2020. *J Clin Oncol 38: 2020 (suppl; abstr 506)*

MINDACT confirms the long-term clinical utility of MammaPrint

5-yr and 8-yr DMFS outcomes across MINDACT risk groups



	% at 5 years (95%CI)	% at 8 years (95%CI)
cL/gL	97.3 (96.6-97.9%)	94.7 (93.8-95.6%)
cL/gH	94.2 (92.0-95.9%)	91.1 (88.4-93.3%)
cH/gL	95.3 (94.0-96.2%)	90.8 (89.1-92.2%)
cH/gH	90.6 (89.1-91.9%)	85.9 (84.2-87.5%)

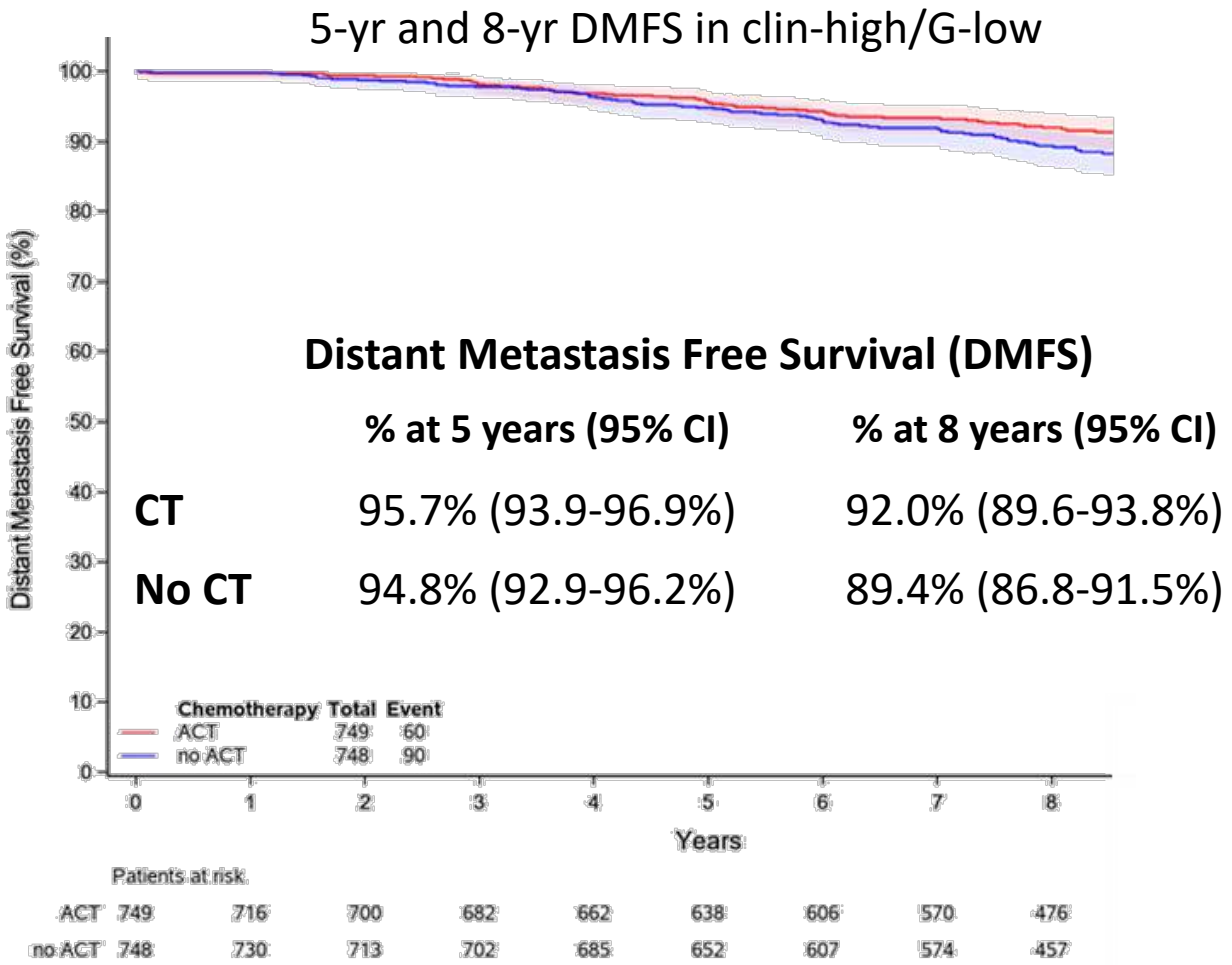
- 8.7y median FU, DMFS in 4 risk groups (**70.4% of the patients**)
- Excellent prognosis and low rate of events in all groups except Clinical High/Genomic High

Type of first event (n = 650)

- distant recurrences: 68.8%
- death of any cause: 31.2%

Adapted from Cardoso, F., et al. ASCO 2020. J Clin Oncol 38: 2020 (suppl; abstr 506)

Clinical High Risk / MammaPrint Low Risk (DMFS)* Chemotherapy vs No Chemotherapy

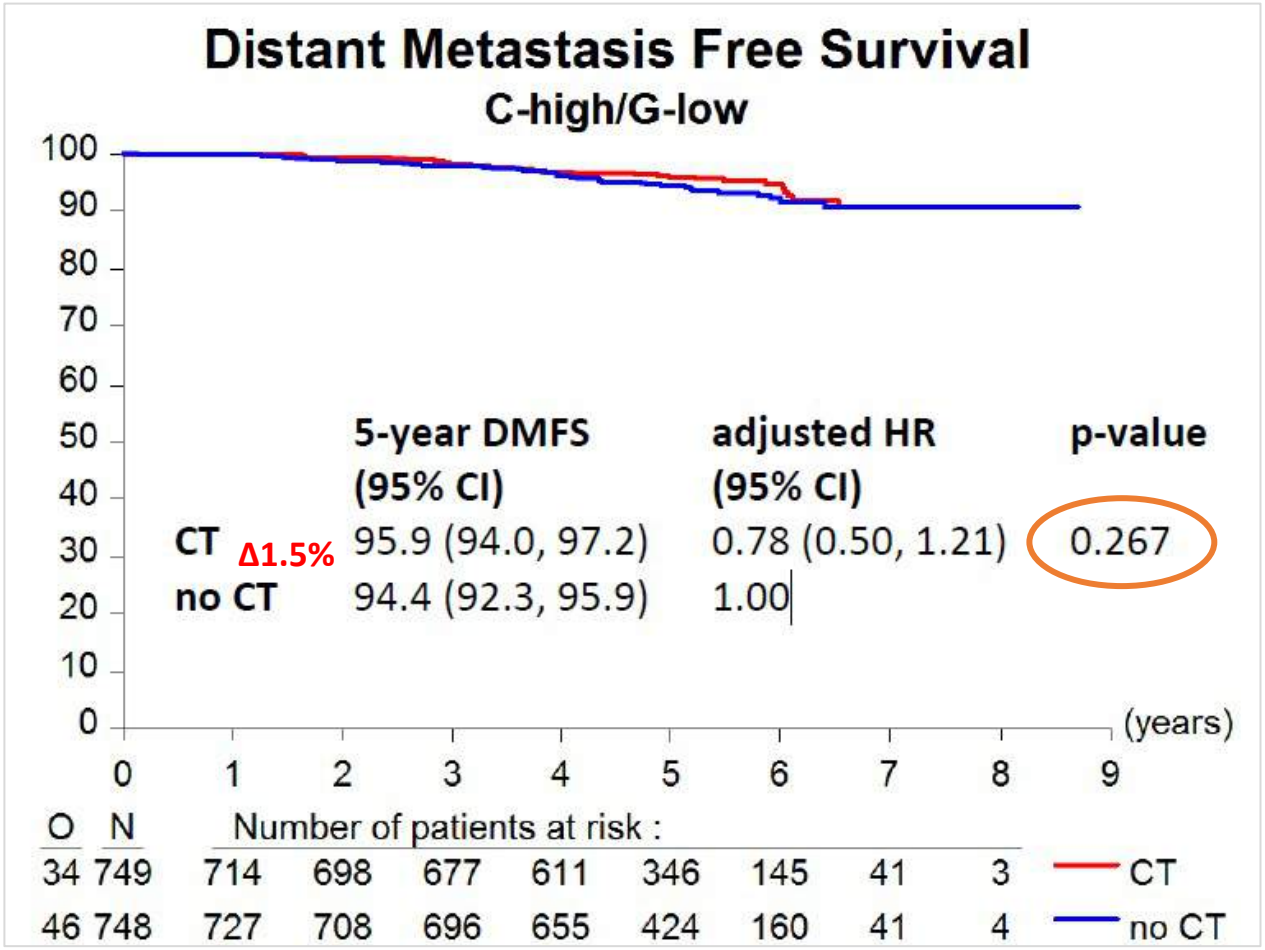


Absolute difference in DMFS between CT and no CT groups:

- 5 yr: **0.9** ± 1.1 % (90.4% of the patients)
- 8 yr: **2.6** ± 1.6 % (70.4% of the patients)

Adapted from Cardoso, F., et al. ASCO 2020. J Clin Oncol 38: 2020 (suppl; abstr 506)

Clinical High Risk / MammaPrint Low Risk (DMFS)* Chemotherapy vs No Chemotherapy

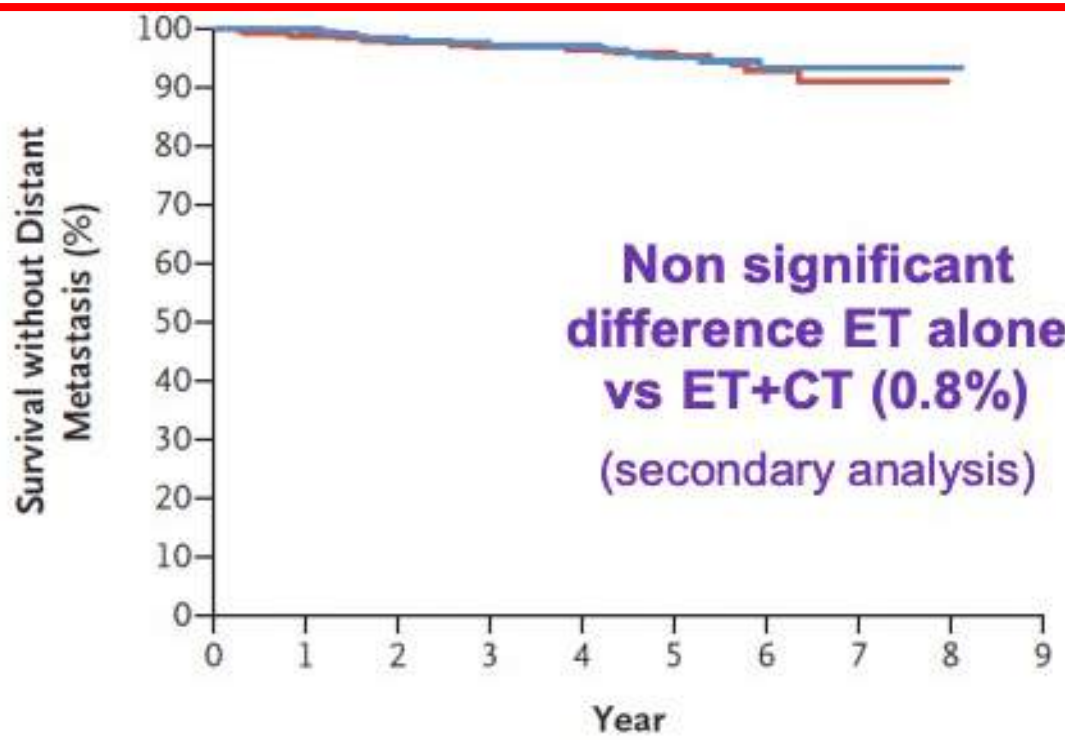


Adapted from Figure 2

- **No statistical difference** between CT vs no CT arms
- Excellent survival with no chemotherapy for patients with clinically high risk features **(94.4%)**

*(DMFS = distant metastases or deaths due to any cause)

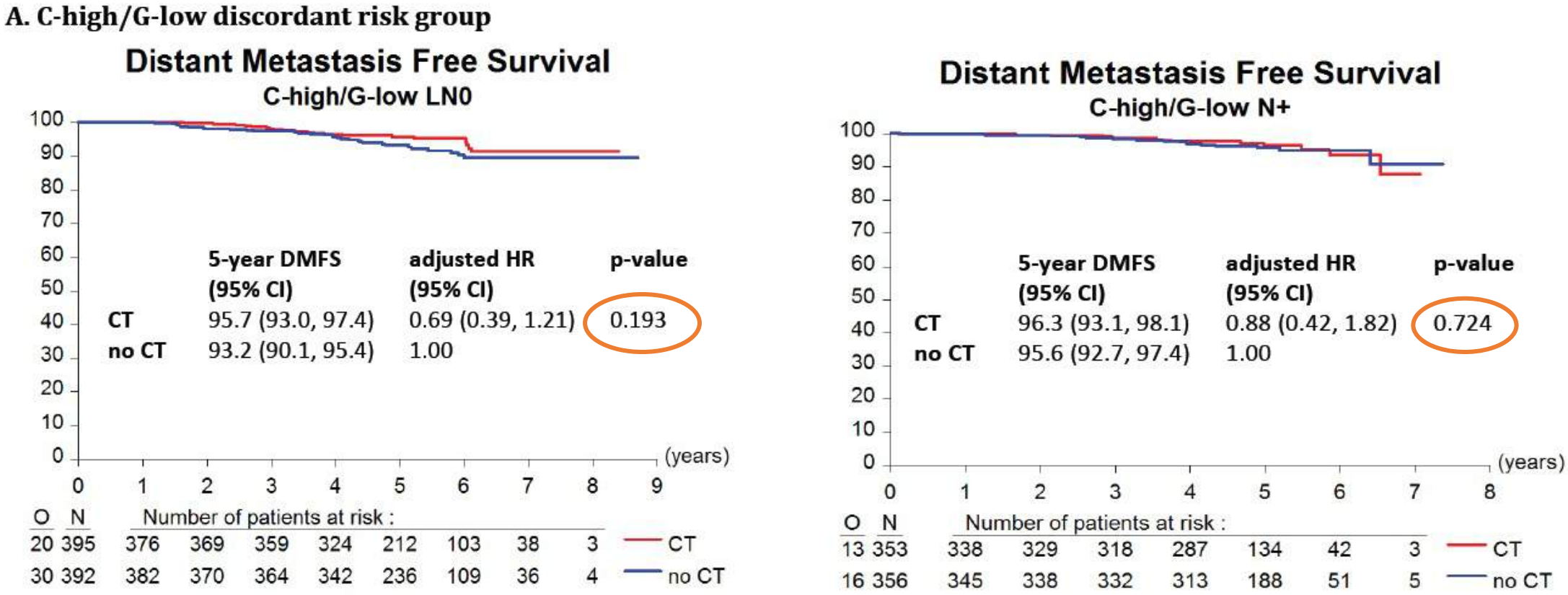
Clinical-low / MammaPrint-high risk (n=592)



No. at risk									
Chemotherapy	344	321	316	306	281	179	81	22	0
No chemotherapy	346	336	327	319	291	178	82	24	3

Cardoso F et al N Engl J Med 2016

Sub-group Analysis (ITT): LN Negative & LN Positive CT vs no CT in C-high / G-low group



- There is no statistical difference between CT vs no CT for MammaPrint Low Risk patients, even with positive lymph nodes
- LN positive MammaPrint Low Risk patients have 95.6% survival without chemotherapy

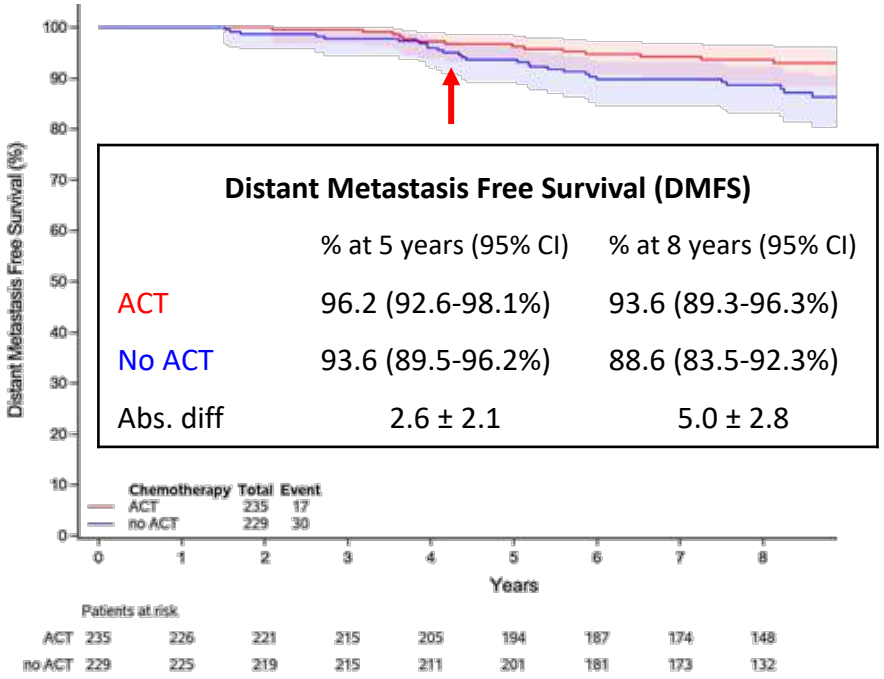
Figure S 2

Cardoso et al. 2016, NEJM

DMFS in C-High / G-Low risk (HR+/HER2-) patients stratified by age. ITT population

Age ≤50 years

DMFS in HR+/HER2-, c-high/G-low, ≤50 yrs



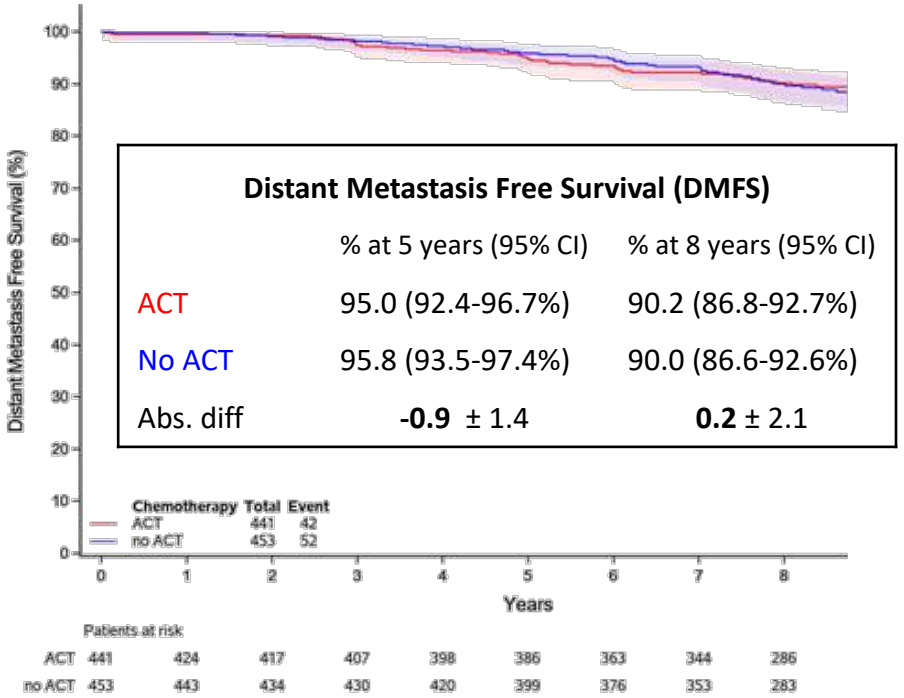
Distant Metastasis Free Survival (DMFS)

	% at 5 years (95% CI)	% at 8 years (95% CI)
ACT	96.2 (92.6-98.1%)	93.6 (89.3-96.3%)
No ACT	93.6 (89.5-96.2%)	88.6 (83.5-92.3%)
Abs. diff	2.6 ± 2.1	5.0 ± 2.8

2.6% difference @5yrs
5% difference @8yrs

Age >50 years

DMFS in HR+/HER2-, c-high/G-low, >50 yrs



Distant Metastasis Free Survival (DMFS)

	% at 5 years (95% CI)	% at 8 years (95% CI)
ACT	95.0 (92.4-96.7%)	90.2 (86.8-92.7%)
No ACT	95.8 (93.5-97.4%)	90.0 (86.6-92.6%)
Abs. diff	**-0.9** ± 1.4	**0.2** ± 2.1

NO Difference @5yrs
NO Difference @8yrs

Adapted from Cardoso, F., et al. ASCO 2020. *J Clin Oncol 38: 2020 (suppl; abstr 506)*

SABCS 2019

Clin-High, MMP-Low
≤ 50 yrs old
(n=452)

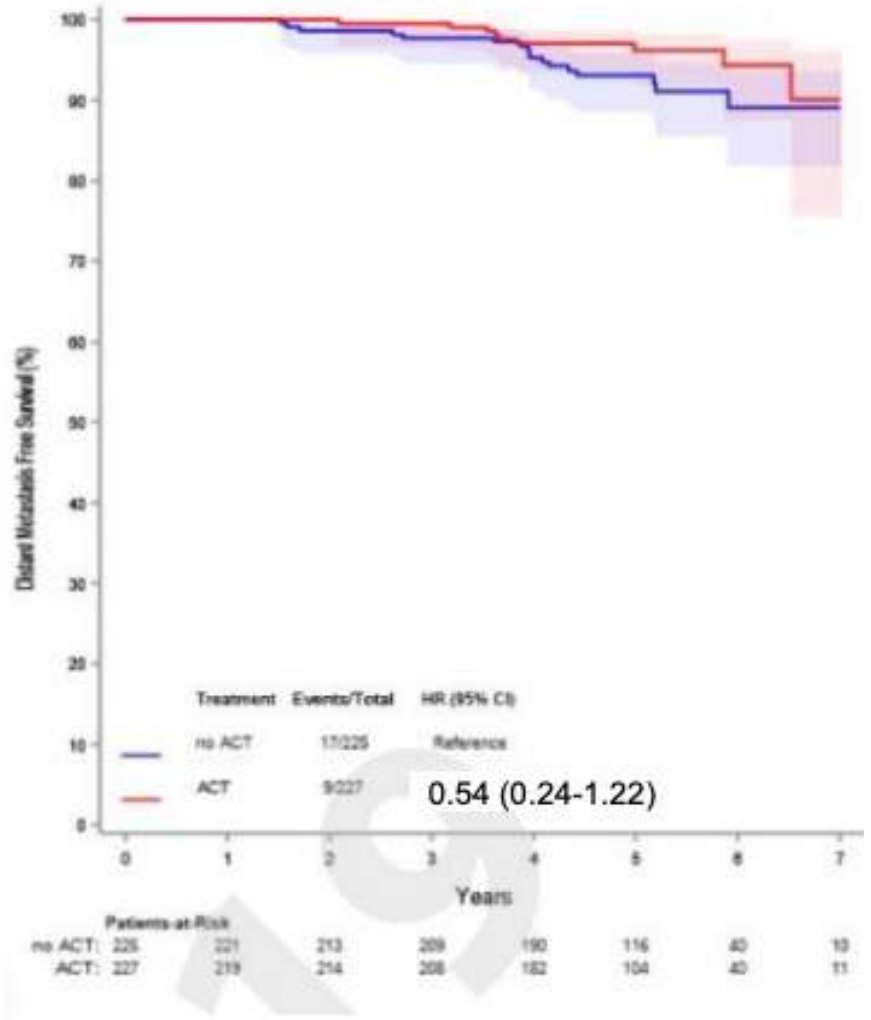
DMFS 5 years

	Event/Total	Hazard Ratio (95% CI)[Cox]	5-year Survival Estimates (95% CI)[KM]
Treatment			
no ACT	17/225	Reference	93.1 (88.6-95.8%)
ACT	9/227	0.54 (0.24-1.22)	96.1 (91.9-98.2%)

[KM]Kaplan-Meier method; [Cox]Cox model

3% difference

DMFS events (26): distant recurrences (24) and death any cause (2)

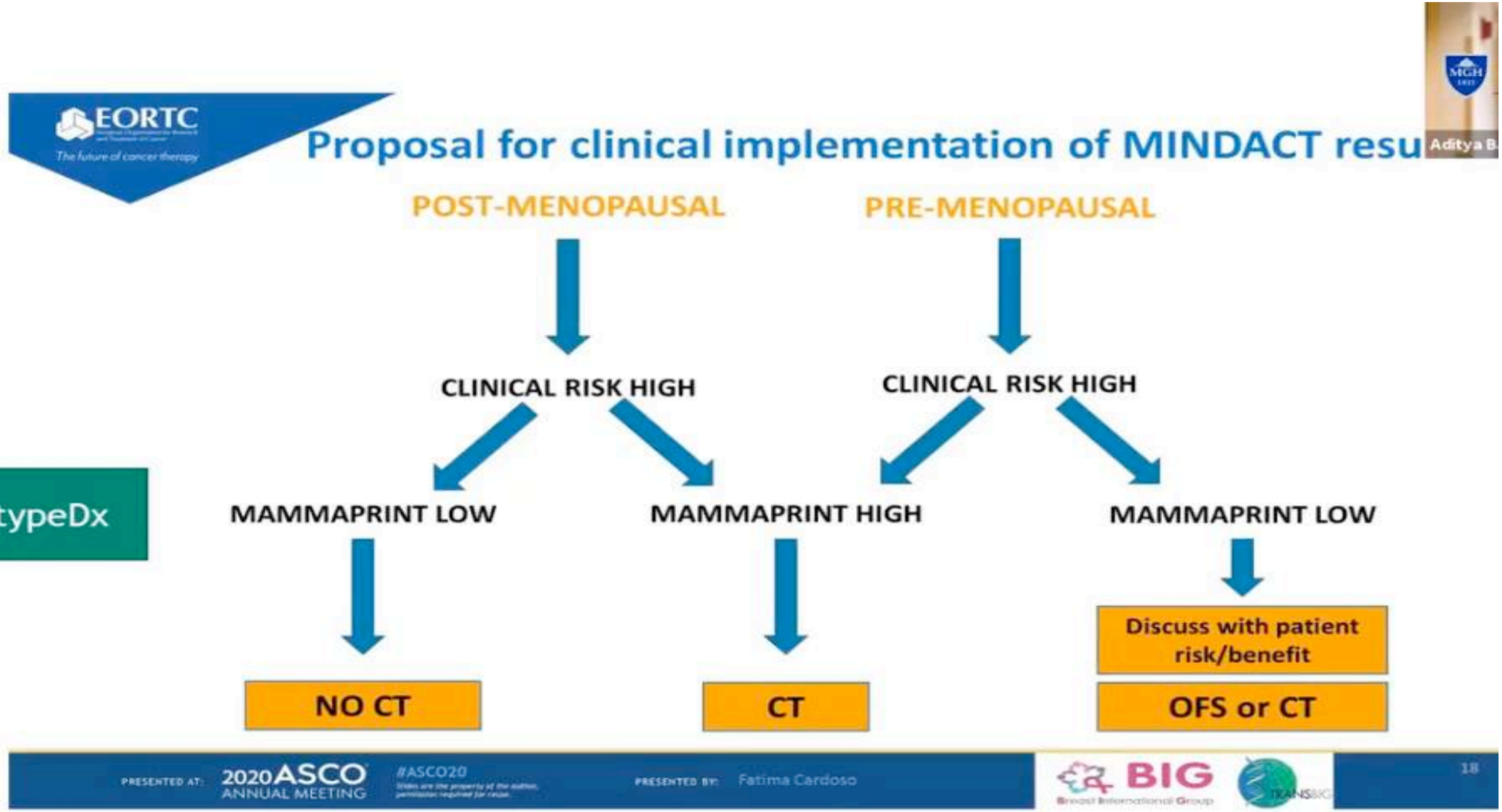


Cardoso F et al SABCS 2019

EORTC
The future of cancer therapy

CONCLUSIONS

- **At 8.7 years** medium FU, **the primary endpoint continues to be met in CT untreated C-High/G-Low risk women**, **confirming MINDACT as a positive de-escalation study**
- **At 8 years**, the estimated **DMFS gain for CT administration** in **C-High/G-Low is 2.6%** and must be balanced with CT harmful side effects
- **Omitting CT** in C-High/G-Low **postmenopausal women** continues to be **safe** (DMFS gain 0.2% ± 2.3%), and a **fully preserved performance of MammaPrint** to forego adjuvant CT is demonstrated.
- In **premenopausal women** the **difference** seen might be **clinically relevant** (DMFS gain 5% ± 2.8%); **importantly, this effect may possibly be related to chemotherapy-induced ovarian function suppression.**
- Overall in the **C-Low/G-High** risk patients, there is no advantage of guiding treatment based on the genomic risk
- Results remain valid for both **LN-negative** and **LN(1-3)positive** patients


EORTC
The future of cancer therapy
Proposal for clinical implementation of MINDACT resu
Aditya B
POST-MENOPAUSAL
PRE-MENOPAUSAL
CLINICAL RISK HIGH
CLINICAL RISK HIGH
OncotypeDx
MAMMAPRINT LOW
MAMMAPRINT HIGH
MAMMAPRINT LOW
Discuss with patient risk/benefit
NO CT
CT
OFS or CT
PRESENTED AT: 2020 ASCO ANNUAL MEETING
#ASCO20
PRESENTED BY: Fatima Cardoso
BIG
Breast International Groups
18

SABCS 2019 Mammaprint

Guidelines

NCCN Guidelines Version 6.2020 Breast Cancer N0

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NCCN Guidelines Version 6.2020
Invasive Breast Cancer

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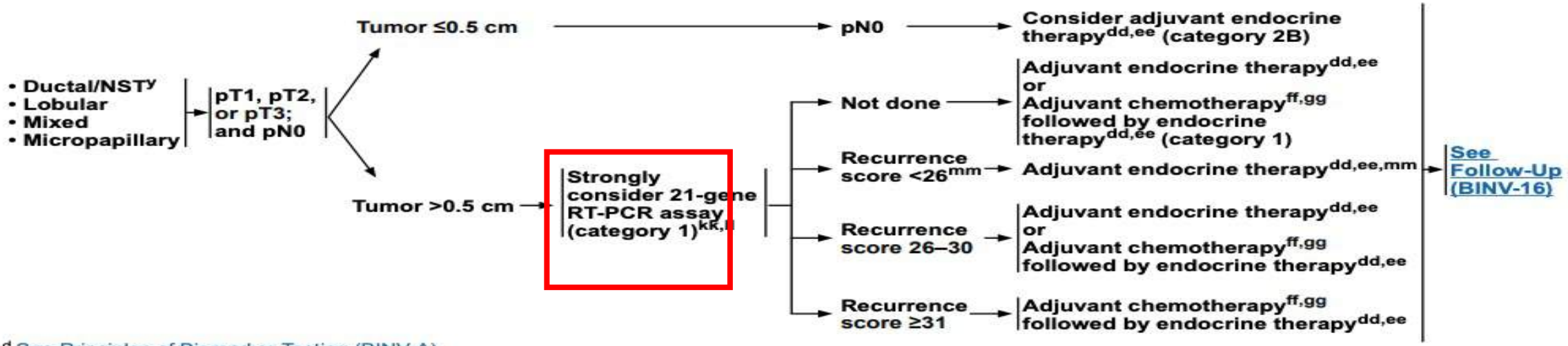
SYSTEMIC ADJUVANT TREATMENT: NODE-NEGATIVE - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE[d,v,cc]



[d] See Principles of Biomarker Testing (BINV-A).
[v] See Special Considerations for Breast Cancer in Men (BINV-J).
[y] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[cc] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data in the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers. This should be considered in decision-making for other adjuvant therapy and overall treatment pathway. See Principles of Biomarker Testing (BINV-A).
[dd] Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.
[ee] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).

[ff] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).
[gg] There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.
[kk] Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Gene Expression Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-N).
[ll] Patients with T1b tumors with low-grade histology and no lymphovascular invasion should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.
[mm] In women 50 years of age or younger with a recurrence score of 16–25, an exploratory analysis from the TAILORx study demonstrated a potential benefit to chemotherapy in younger patients. See Discussion.

NCCN Guidelines Version 6.2020 Breast Cancer N+

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Invasive Breast Cancer

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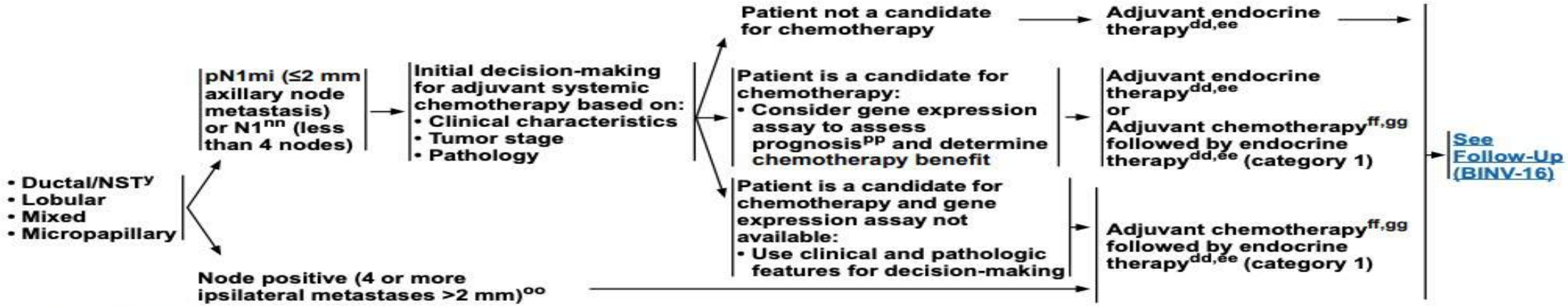
SYSTEMIC ADJUVANT TREATMENT: NODE-POSITIVE - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE[d,v,cc]



[d] See Principles of Biomarker Testing (BINV-A).
[v] See Special Considerations for Breast Cancer in Men (BINV-J).
[y] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[cc] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers. This should be considered in decision-making for other adjuvant therapy and overall treatment pathway. See Principles of Biomarker Testing (BINV-A).
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[ee] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).
[ff] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).
[gg] There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.
[nn] In N1mi and N1, gene expression assays are prognostic and not proven to be predictive of chemotherapy benefit but can be used to identify a low-risk population that when treated with proper endocrine therapy may derive little absolute benefit from chemotherapy. Regarding the 21-gene RT-PCR assay, a secondary analysis of a prospective trial suggests that the test is predictive for women with 1–3 involved ipsilateral axillary lymph nodes. Other gene expression assays have not proven to be predictive of chemotherapy benefit.
[oo] There are few data regarding the role of gene expression assays in women with four or more ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.
[pp] See Gene Expression Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-N).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 6.2020 Breast Cancer N+

gg There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

nn In N1mi and N1, gene expression assays are prognostic and not proven to be predictive of chemotherapy benefit but can be used to identify a low-risk population that when treated with proper endocrine therapy may derive little absolute benefit from chemotherapy. Regarding the 21-gene RT-PCR assay, a secondary analysis of a prospective trial suggests that the test is predictive for women with 1–3 involved ipsilateral axillary lymph nodes. Other gene expression assays have not proven to be predictive of chemotherapy benefit.

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Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus	Recurrence Risk and Treatment Implications
21-gene (Oncotype Dx) (for pN0 or node negative)	Yes	Yes	Preferred	1	BINV-N (2 of 4)
21-gene (Oncotype Dx) (for pN+ or node positive)	N/A* *awaiting results of RxPONDER study	Yes	Other	2A	BINV-N (2 of 4)
70-gene (MammaPrint) (for node negative and 1–3 positive nodes)	Not determined	Yes	Other	1	BINV-N (3 of 4)
50-gene (PAM 50) (for node negative and 1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3 of 4)
12-gene (EndoPredict) (node negative and 1–3 nodes)	Not determined	Yes	Other	2A	BINV-N (3 of 4)
Breast Cancer Index (BCI)	Not determined	Yes	Other	2A	BINV-N (3 of 4)

ASCO Guidelines Mammaprint

ASCO guidelines	MammaPrint
High Clinical risk **Node negative**	➔ *(Update of 2016 recommendation 1.7)* **If a patient has ER/PgR-positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay (MammaPrint; Agendia, Irvine, CA) may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. (Strong Recommendation; EB-H)**
Low Clinical risk **Node negative**	➔ *(Update of 2016 recommendation 1.7)* **If a patient has ER/PgR-positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay should *NOT* be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy since women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high risk cancer. (Strong Recommendation; EB-H)**
High Clinical risk **1-3 Node+**	➔ *(Update of 2016 recommendation 1.7)* **If a patient has ER/PgR-positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay may be used in patients with 1-3 positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. (Moderate Recommendation; EB-H)** • However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node.
Low Clinical risk **1-3 Node+**	➔ *(Update of 2016 recommendation 1.7)* **If a patient has ER/PgR-positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay should *NOT* be used in patients with 1-3 positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population. (Moderate Recommendation; IC-L)**

New ASCO 2019 Guidelines establish TAILORx-defined cutoffs for determining chemotherapy benefit in node-negative breast cancer[1]

ASCO guidelines description[1]	Guidance	Level of evidence and strength of recommendation
Recommendation 1.1.1. "For patients older than 50 years and whose tumors have Oncotype DX recurrence scores <26 and for patients ≤50 years whose tumors have Oncotype DX recurrence scores <16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone"	**RS 0-25 & >50 years** **RS 0-15 & ≤50 years** May offer **endocrine** therapy alone	*Type: **evidence-based***, benefits outweigh harms *Evidence quality: **high;*** *Strength of recommendation: **strong***
Recommendation 1.1.2. "For patients ≤50 years with Oncotype DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy"	**RS 16-25 & ≤50 years** May offer **chemoendocrine** therapy	*Type: **evidence-based***, benefits outweigh harms; *Evidence quality: **intermediate;*** *Strength of recommendation: **moderate***
Recommendation 1.1.4. "Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores of 26 to 30"	**RS 26-30** May offer **chemoendocrine** therapy	*Type: **informal consensus***; *Evidence quality: **insufficient;*** *Strength of recommendation**: moderate***
Recommendation 1.1.3. "Patients with Oncotype DX recurrence scores of >30 should be considered candidates for chemoendocrine therapy"	**RS 31-100** Should consider **chemoendocrine** therapy	*Type: **evidence-based***, benefits outweigh harms; *Evidence quality: **high;*** *Strength of recommendation: **strong***

1. Andre et al. *J Clin Oncol.* 2019.


ΕΥΧΑΡΙΣΤΩ


Together
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More
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