Use of Gene Expression Profile in a 42-year old patient with stage II luminal BC: In favour!

JEROEN MEBIS

JESSAZIEKENHUIS-UHASSELT

LIMBURGS ONCOLOGISCH CENTRUM

Disclosures

Scientific grants: Pierre Fabre, Astra Zeneca, Gilead, Sanofi, MSD, GSK

Consultancy fees: Seagen, Amgen, BMS, Ocare Pharma

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Introduction

Anatomic Staging Groupings

When T is…	And N is…	And M is…	The Stage Group is…
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB

oncotype DX® Breast Recurrence Score

mammaprint

Prosigna BREAST CANCER ASSAY

EndoPredict®

BREAST CANCER INDEX™

Criteria Belgium: EBC, pN0-pN1, Her2- ER+; ≥5cm; ≥ 45 yr; clin high risk.

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Oncotype DX® test development: Demonstrating the prognostic and predictive value in HR+, HER2- early breast cancer[1–6]

	N0	N1/N+
Clinical validation for **prognosis** (retrospective analysis)	**NSABP B-14**[1] N=668	**TransATAC**[2] N=306
Clinical validation for chemotherapy benefit **prediction** (retrospective analysis)	**NSABP B-20**[3] N=651	**SWOG8814**[4] N=367
Clinical utility (prospective, randomized studies)	**TAILORx**[5] N=10 273 NCT00310180	**RxPONDER**[6] N=5018 NCT01272037

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSABP, National Surgical Adjuvant Breast and Bowel Project.

1. Paik S, et al. N Engl J Med 2004; 351:2817-2826; 2. Dowsett M, et al. J Clin Oncol. 2010;28:1829-34; 3. Paik, S. et al. J. Clin. Oncol. 2006;24:3726–3734; 4. Albain K, et al. Lancet Oncol. 2010;11:55–65; 5. Sparano J, et al. N Engl J Med. 2018;379:111-121; 6. Kalinsky K, et al. N Engl J Med 2021;385:2336-2347.

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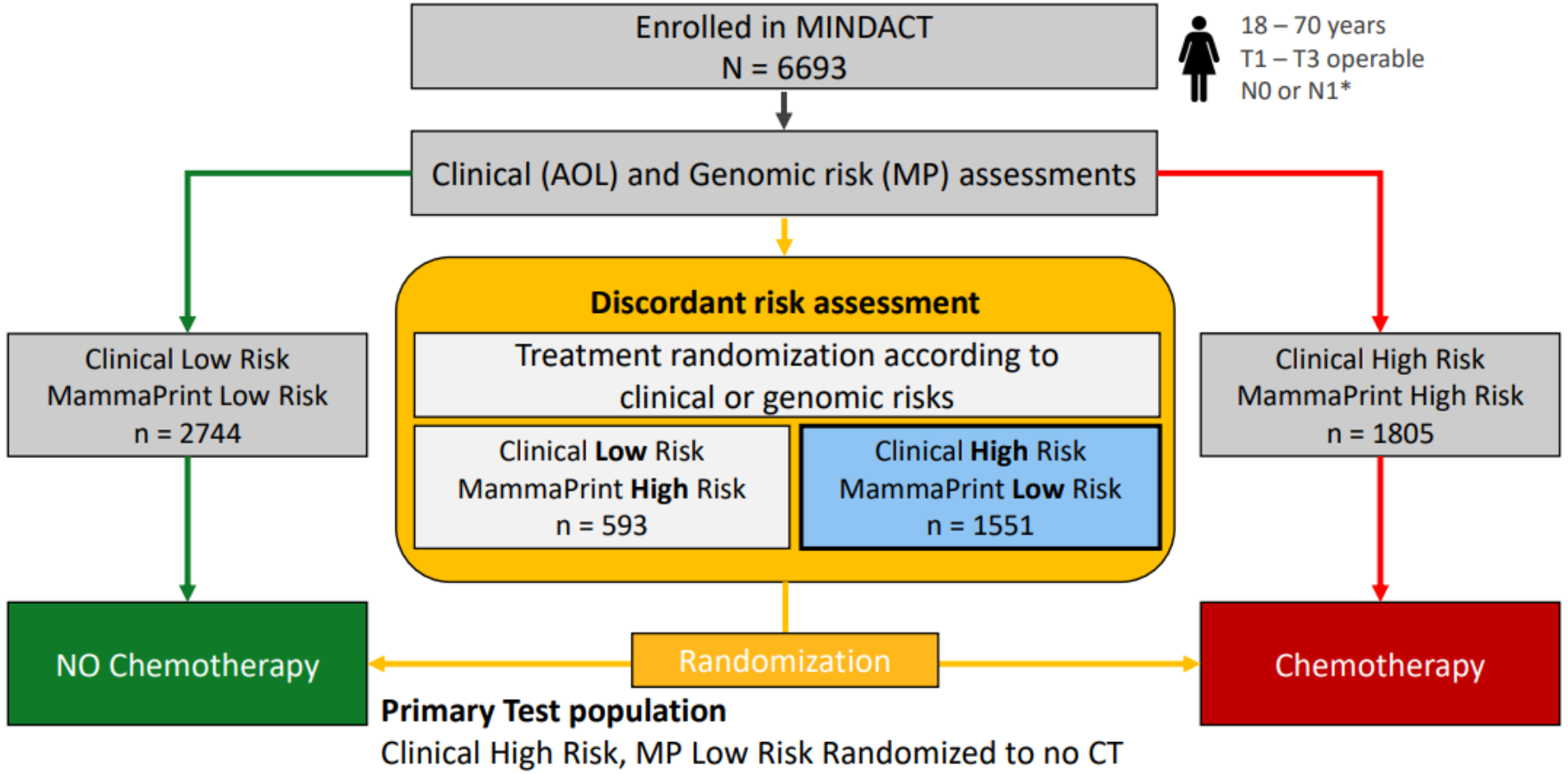
MINDACT study design



Primary Test population

Clinical High Risk, MP Low Risk Randomized to no CT

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*up to 3 positive axillary nodes, as per the 2009 protocol amendment.
AOL, Adjuvant! Online; CT, chemotherapy; MP, MammaPrint.

Adapted from Piccart et al. Lancet Oncol. 2021.

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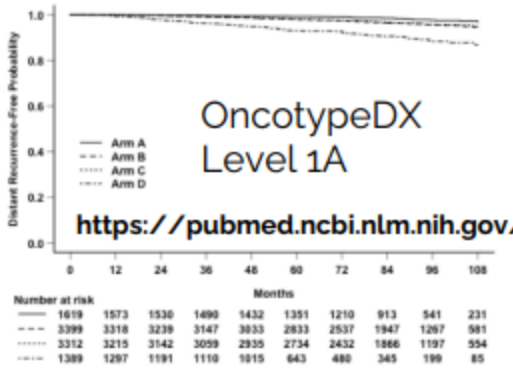
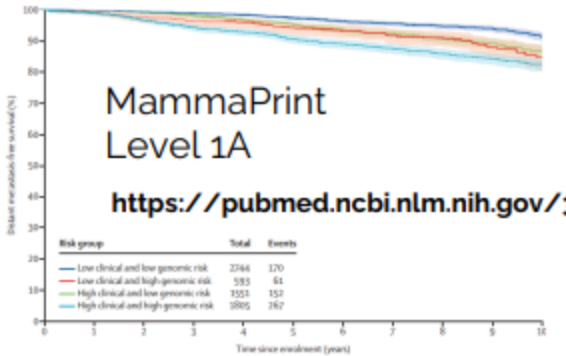
1. Predicting Prognosis



OncotypeDX
Level 1A

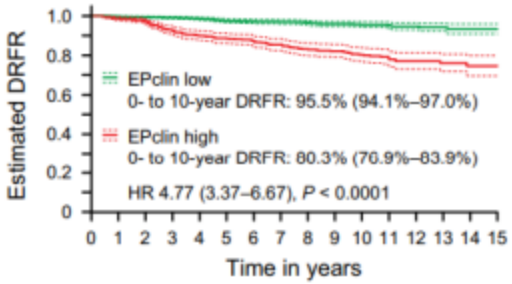
https://pubmed.ncbi.nlm.nih.gov/29860917/



MammaPrint
Level 1A

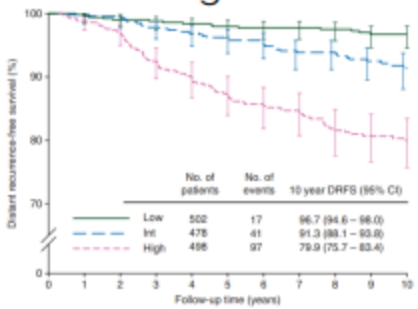
https://pubmed.ncbi.nlm.nih.gov/33721561/

EndoPredict – 1B



https://pubmed.ncbi.nlm.nih.gov/31064782/

Prosigna – 1B



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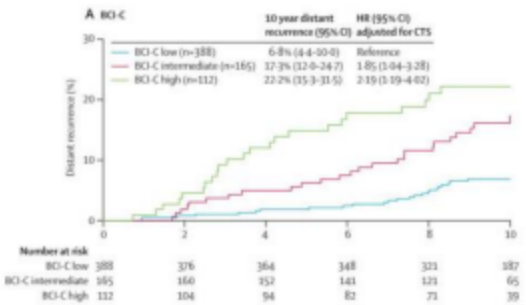
BCI – 1B



https://pubmed.ncbi.nlm.nih.gov/24035531/

PARIS 2022 ESMO congress

Aleix Prat, MD PhD

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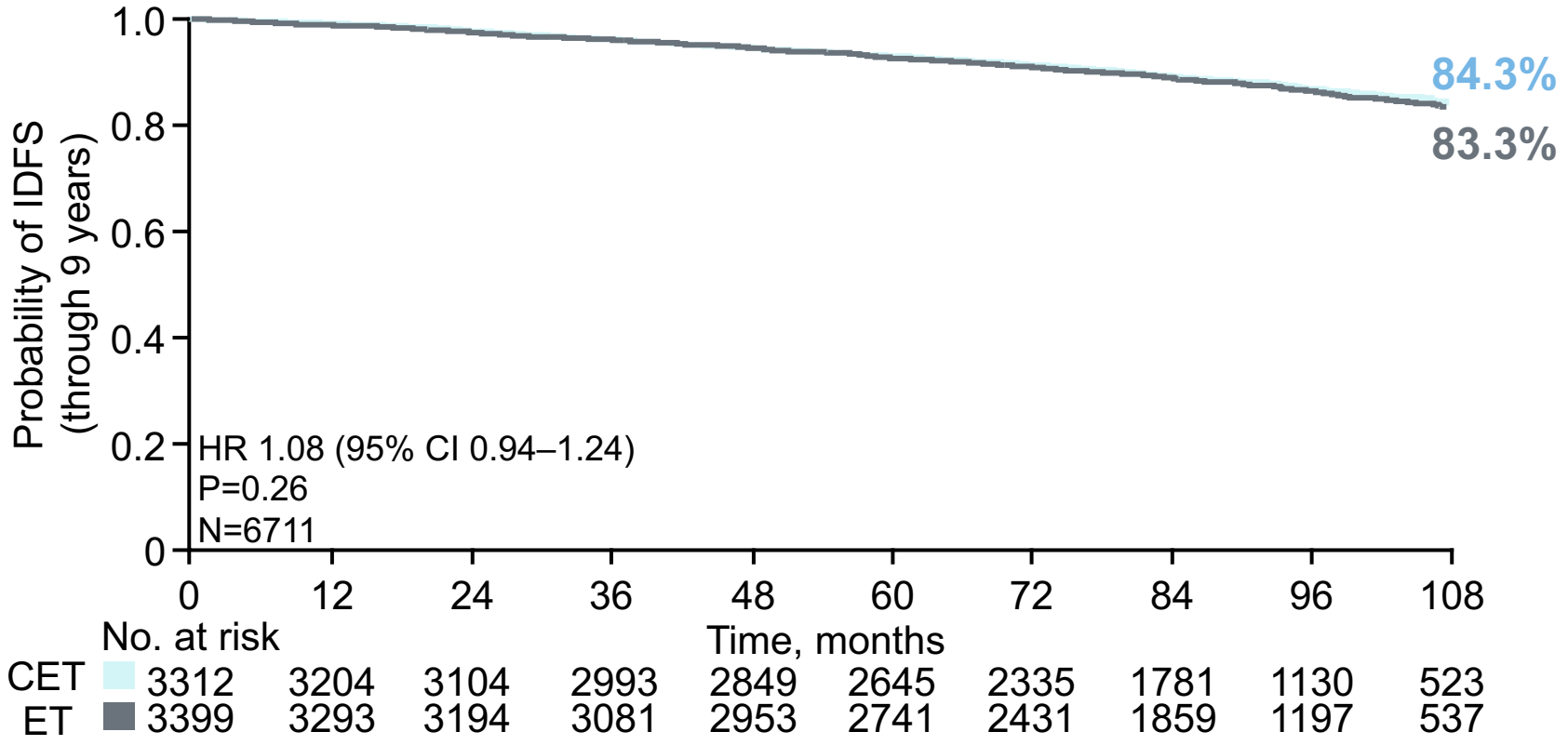
Permission obtained from A. Prat

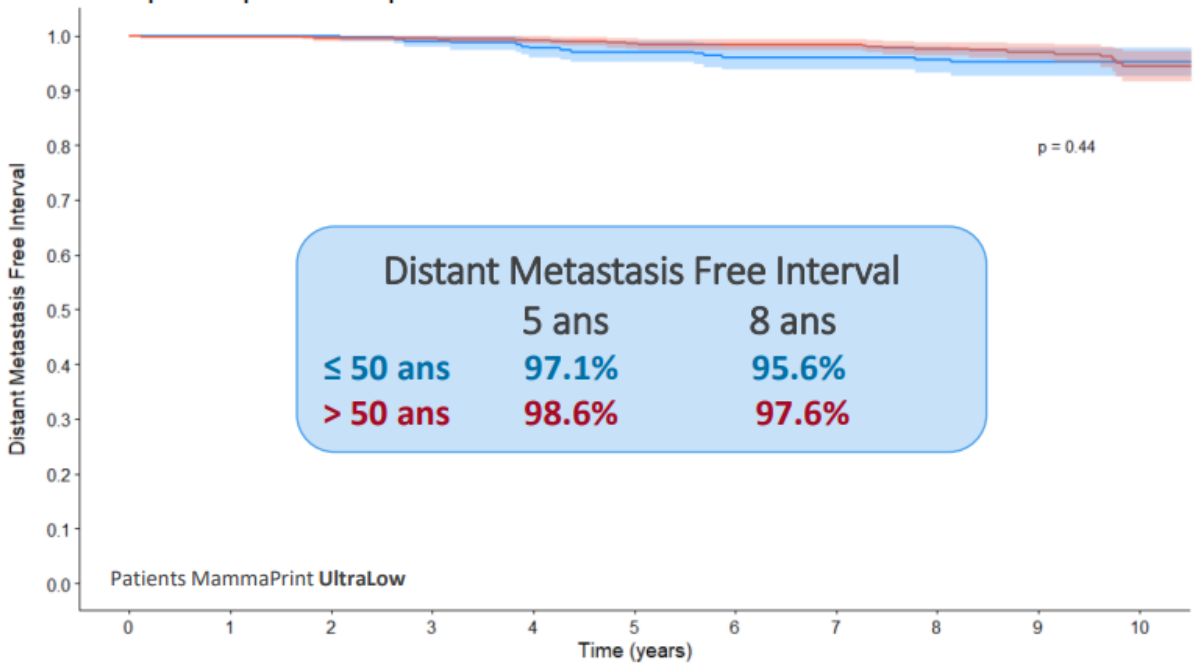
In patients with RS® results 11–25, endocrine therapy was non-inferior to chemoendocrine therapy for IDFS



CET, chemoendocrine therapy; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival.
Sparano J, et al. N Engl J Med. 2018;379:111–121.

MINDACT –MammaPrint **UltraLow Risk** 50 years old or younger

Premenopausal patients represents about 30% of MammaPrint UltraLow risk in MINDACT



Distant Metastasis Free Interval	5 ans	8 ans
≤ 50 ans	97.1%	95.6%
> 50 ans	98.6%	97.6%

Premenopausal patients with a MammaPrint UltraLow Risk have a great long-term prognosis regardless of age

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Lopes Cardozo, et al., JCO. 2022.

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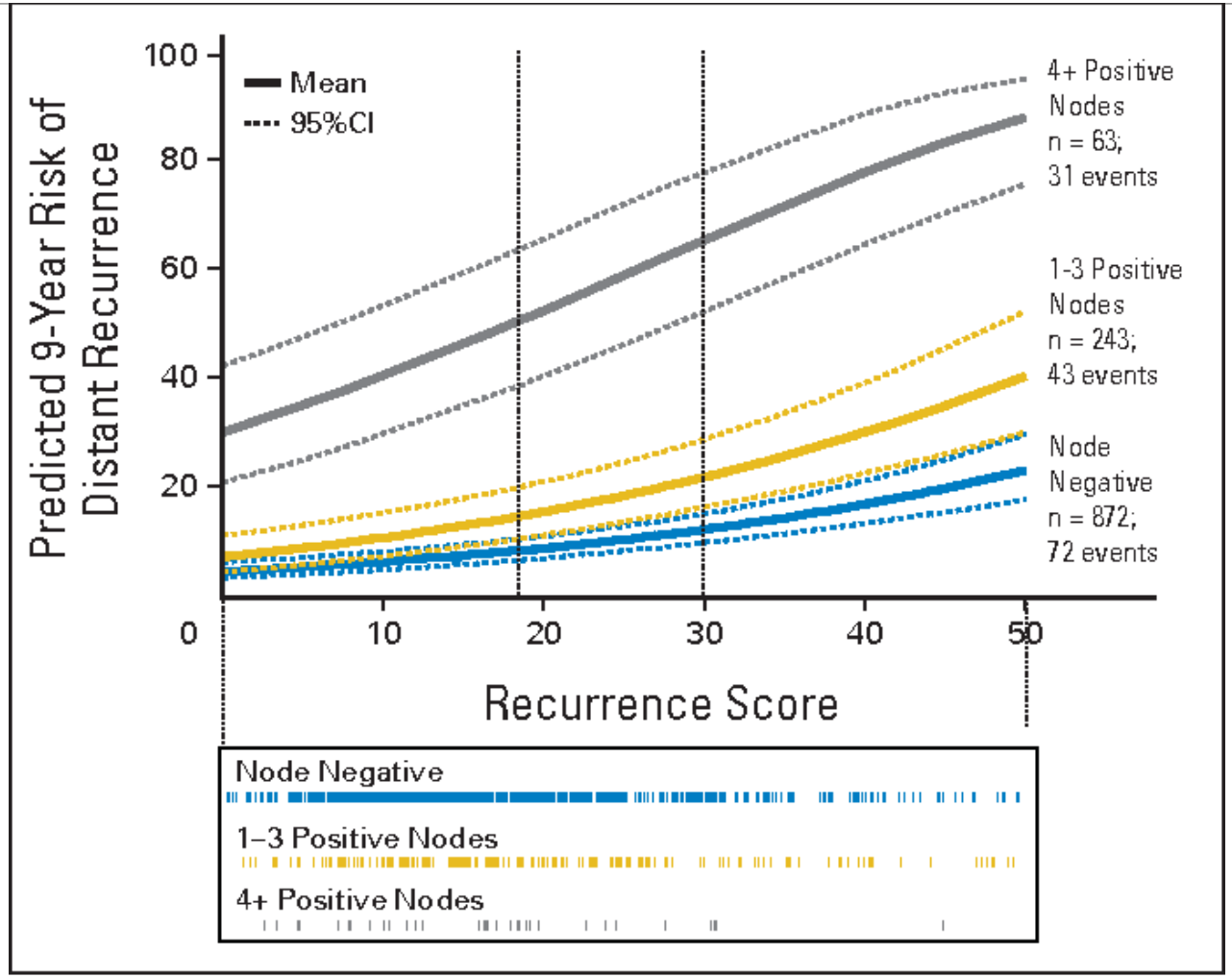
Prognosis: Stage (N) also important!



TransATAC: Oncotype DX

Dowsett et al, JCO 2010

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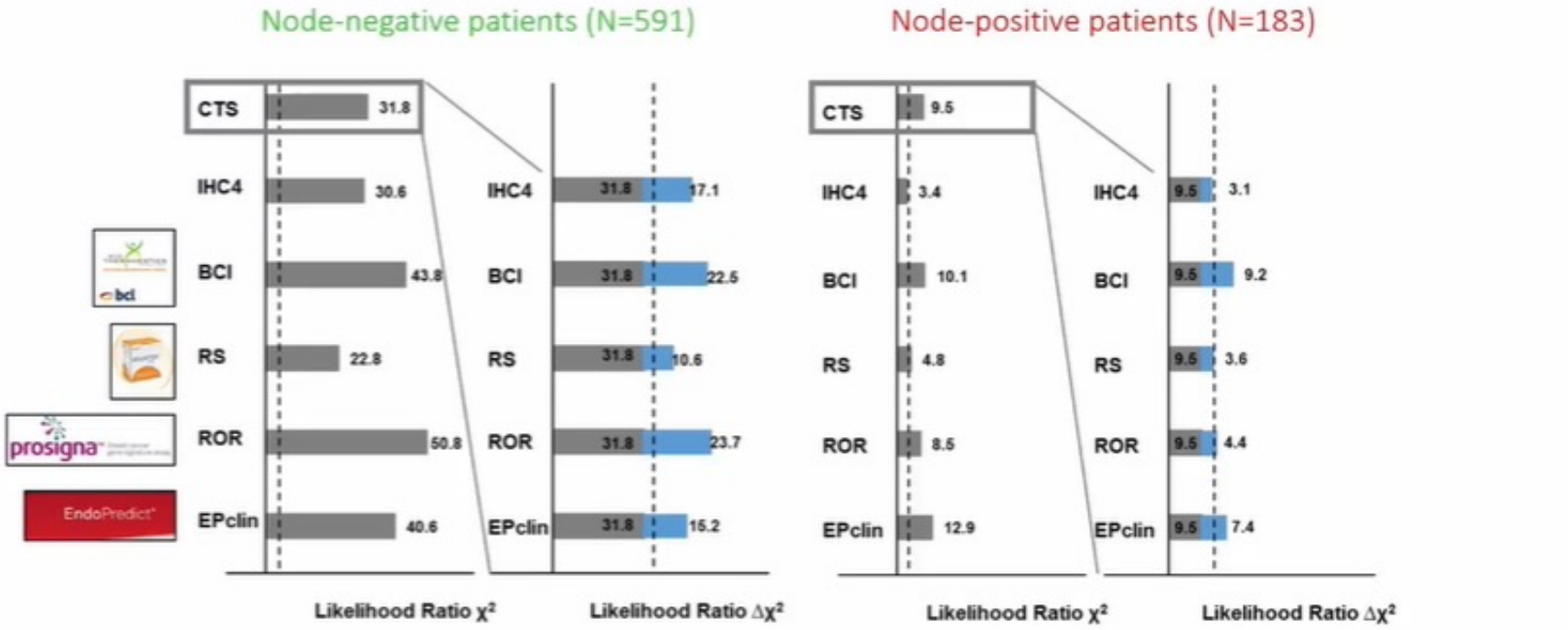
Each signature *provided significantly more information* than the Clinical Treatment Score (CTS) – TransATAC study



CTS: information on ***age, nodal status, tumor size, grade and treatment*** (tamoxifen vs anastrozole)

Sestak I et al., JAMA Oncol 2018

Conclusions

The prognostic signatures evaluated provided significant information to help determine appropriate candidates consisting of patients with ER-positive, *ERBB2*-negative breast cancer, for whom chemotherapy and extended endocrine therapy might not be indicated. In patients with node-negative disease, all multigene signatures provided significant and clinically meaningful prognostic information beyond clinical factors. The combination of clinical and molecular information enhanced prognostic performance, particularly for women with node-positive disease. All signatures performed similarly during the first 5 years of follow-up, but we found differences during years 5 to 10, when these tests may be valuable for decision making with regard to extended endocrine treatment.

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2. Indirect prediction of (chemo)therapy benefit

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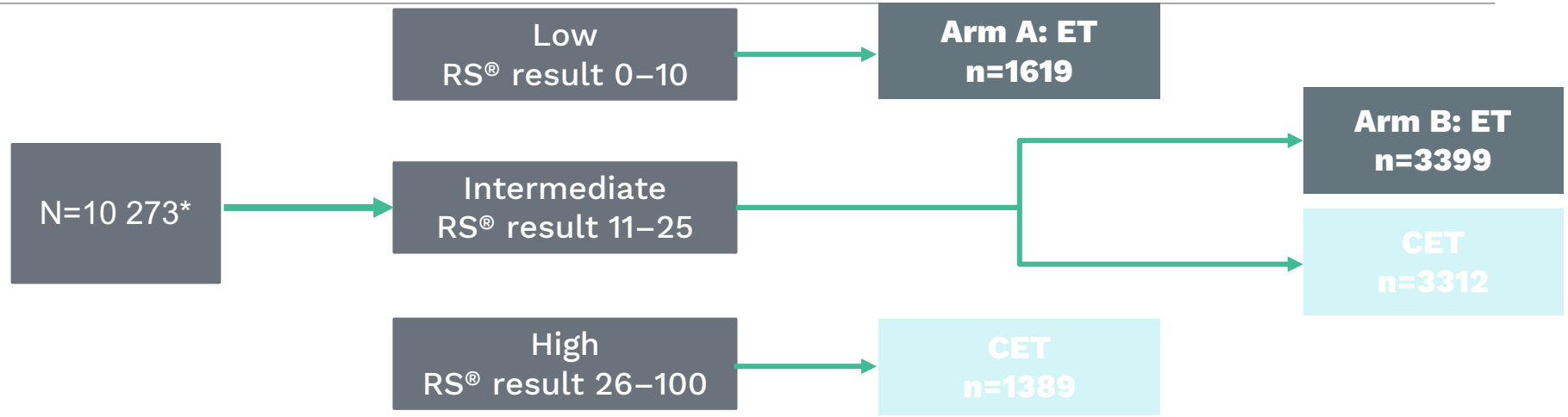
TAILORx: Study design

Study Design

Patients

- Invasive early breast cancer
- N0
- HR+, HER2-
- 18–75 years old
- Tumor size 1.1–5.0 cm (or 0.5–1.0 cm and intermediate-high grade)



Objective

- Determine whether chemotherapy is beneficial for women with a mid-range RS® result of 11–25
- Prospectively confirm that a low RS® result of 0–10 is associated with a low rate of distant recurrence when patients are treated with endocrine therapy alone

Primary Endpoint

- IDFS at 9 years
- Non-inferiority design for RS® results 11–25 randomized to ET alone versus CET

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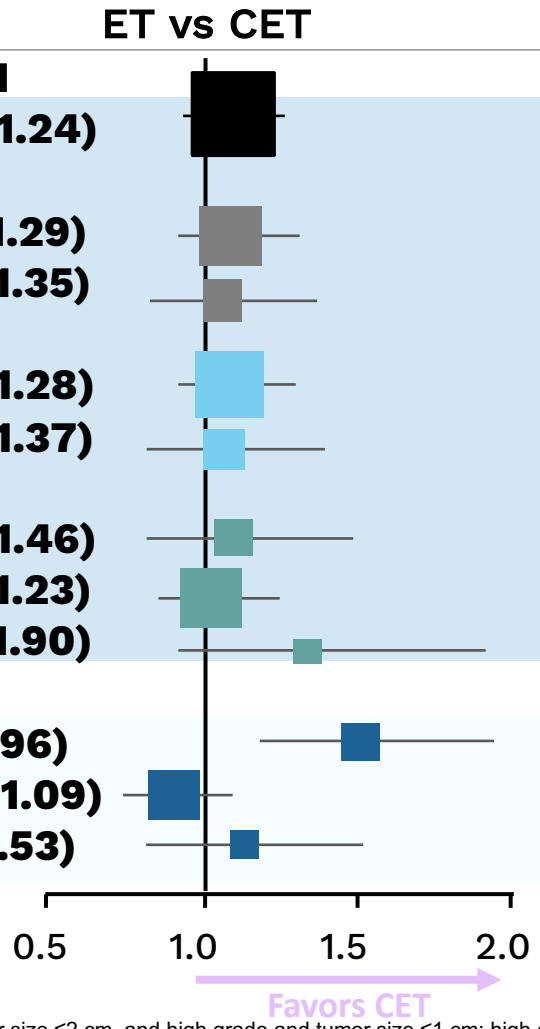
*554 patients were excluded due to ineligibility, did not have follow-up information, or did not have trial-period information; patients have been accrued between April 2006 and October 2010.
CET, chemoendocrine therapy; ET, endocrine therapy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease-free survival; RS®, Recurrence Score®
Sparano J, et al. N Engl J Med. 2018;379:111–121.

Most classical clinical parameters do not predict chemotherapy benefit for patients with RS® results 11–25

Group	n	HR	95% CI
RS® result 11–25	6711	1.08	(0.94–1.24)
Clinical risk			
Low*	4799	1.08	(0.91–1.29)
High	1697	1.05	(0.82–1.35)
Tumor size			
≤2 cm	5122	1.08	(0.92–1.28)
>2 cm	1587	1.06	(0.82–1.37)
Grade			
Low	1893	1.09	(0.82–1.46)
Intermediate	3721	1.02	(0.85–1.23)
High	884	1.32	(0.92–1.90)
Age			
≤50 years	2216	1.51	(1.17–1.96)
51–65 years	3545	0.89	(0.73–1.09)
>65 years	950	1.12	(0.81–1.53)



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

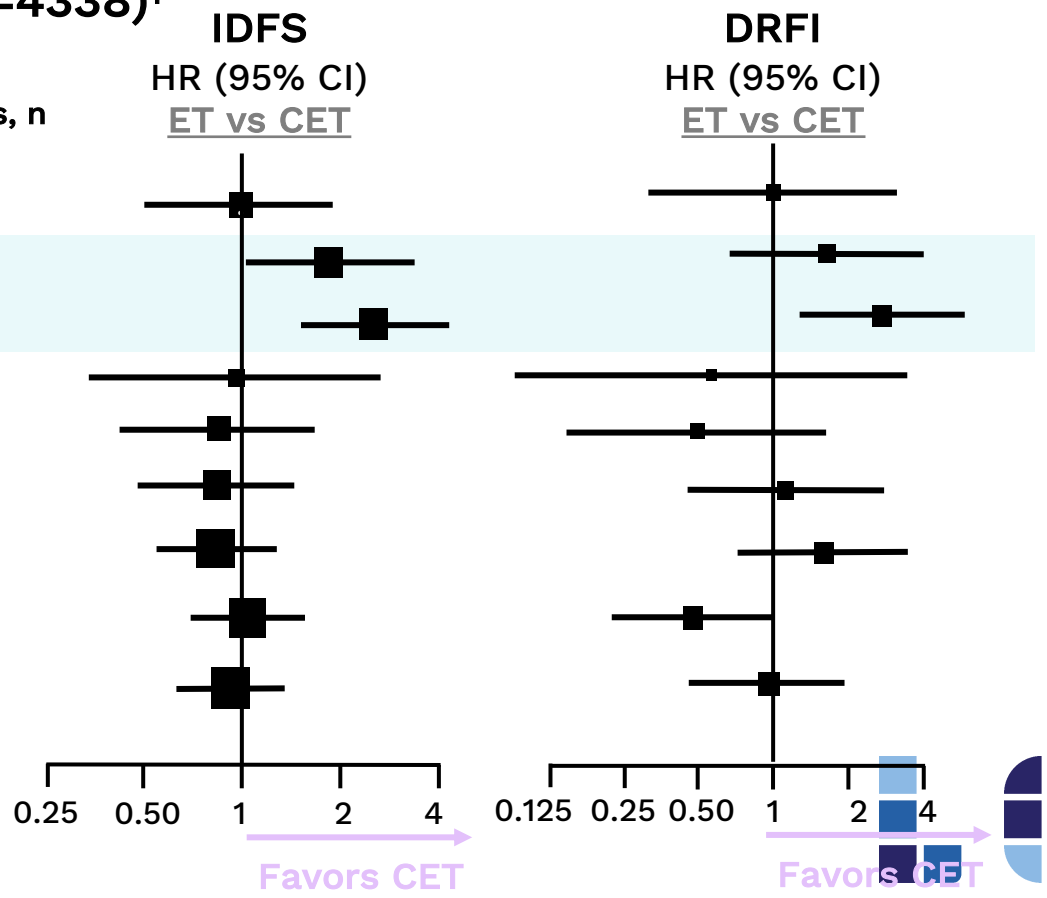
Younger patients (aged ≤50 years) with an RS® result of 11–25 may derive some benefit from chemotherapy

*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.
CET, chemoendocrine therapy; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; RS®, Recurrence Score®.
Sparano J, et al. N Engl J Med. 2018;379:111–121.

Chemoendocrine therapy benefit for patients with RS® results 16–25 was limited to premenopausal women aged between 41 and 50 years

Chemoendocrine therapy benefit by age and menopausal status in patients with RS® results 16–25 (N=4338)[1]

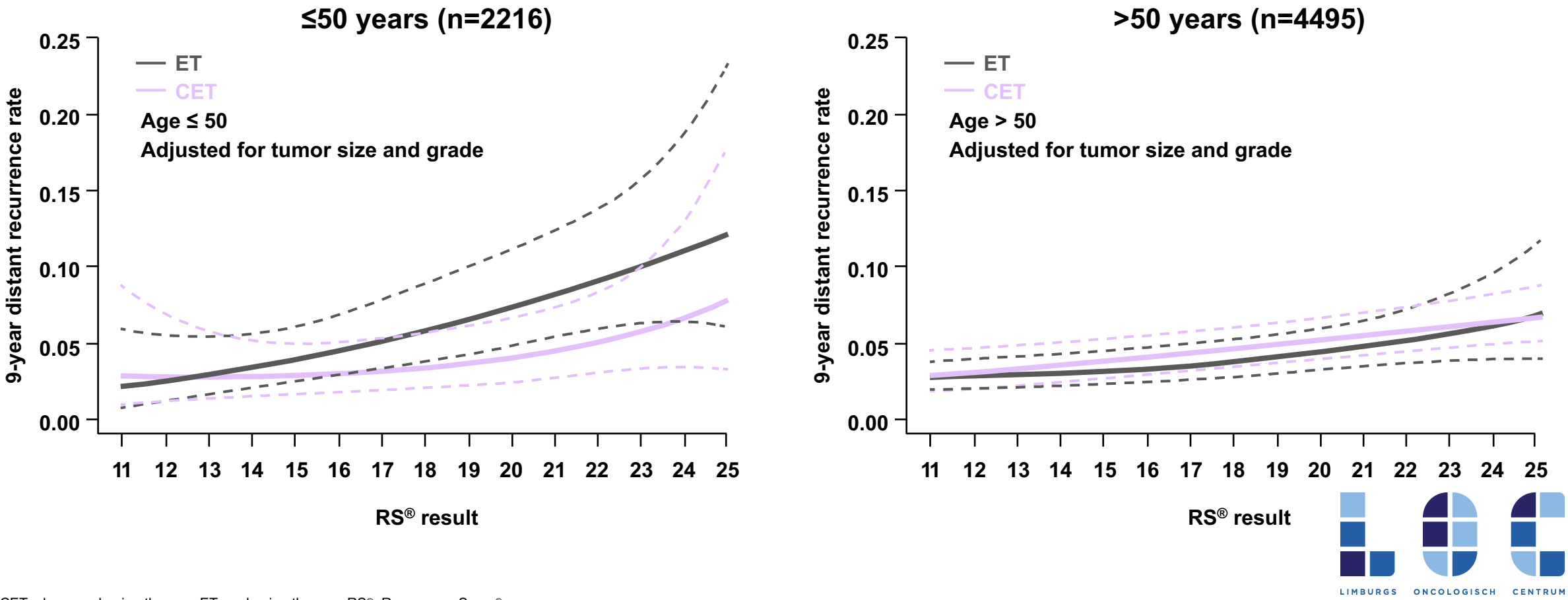
Age, years	Patients, n	IDFS events, n	DRFI events, n
<40	203	35	12
41–45	441	51	21
46–50 premenopausal	630	69	33
46–50 postmenopausal	141	15	5
51–55 premenopausal	287	34	13
51–55 postmenopausal	472	54	19
56–60	826	94	28
61–65	710	109	32
>65	628	117	31



CET, chemoendocrine therapy; CI, confidence interval; DRFI, distant recurrence-free interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; RS®, Recurrence Score®.

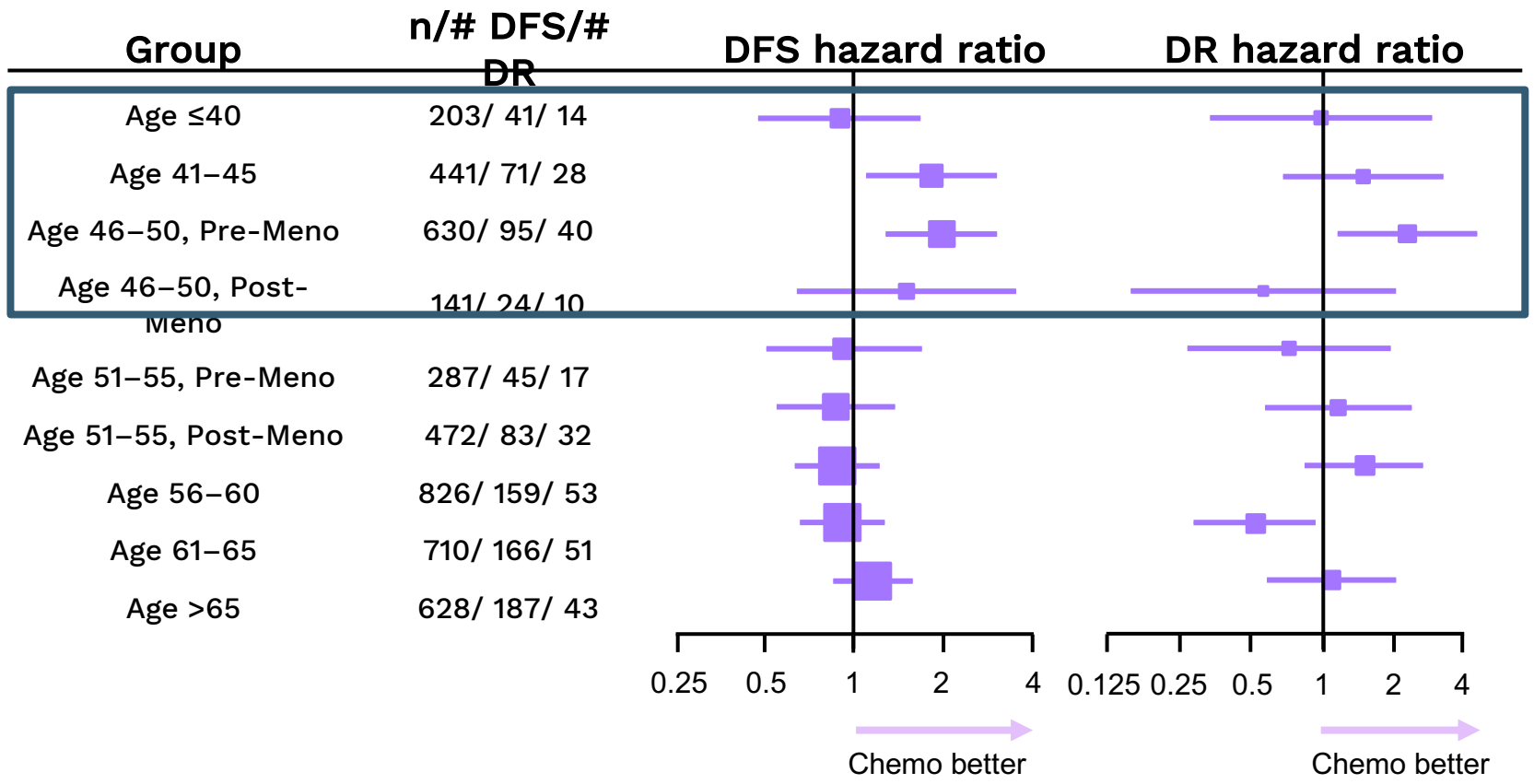
Sparano J, et al. N Engl J Med. 2019;380:2395–2405

Patients aged ≤50 years had a greater benefit from chemoendocrine therapy as their RS® result increased, although this was not significant (exploratory analysis)



CET, chemoendocrine therapy; ET, endocrine therapy; RS®, Recurrence Score®.
Sparano J, et al. N Engl J Med. 2018;379:111–121.

Effect of age and Recurrence Score® result on chemotherapy benefit



CET, Chemo-endocrine therapy; ET, Endocrine therapy; DR, distant relapse; DRFI, distant relapse-free survival; RS®, Recurrence Score® result.
Sparano JA, et al. Clin Cancer Res. 2023;83:GS1-05 (Presented SABCS 2022).

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Effect of age, Recurrence Score® result and clinical risk on chemotherapy benefit

12-Year DRFI rates in age ≤ 50 years and RS® 16–25

	Estimated absolute chemotherapy benefit not stratified by clinical risk	Clinical risk	No.	Estimated absolute chemotherapy benefit stratified by clinical risk
RS® 16–20 (N=886)	Δ +0.6% (±SE 2.1%)	Low	671 (76%)	Δ -0.5% (±SE 2.2%)
		High	215 (24%)	Δ +3.1% (±SE 5.4%)
RS® 21–25 (N=476)	Δ +7.8% (+SE 3.4%)	Low	319 (67%)	Δ +5.9% (±SE 3.4%)
		High	157 (33%)	Δ +11.7% (±SE 7.2%)

DRFI, distant relapse-free survival; RS®, Recurrence Score® result; SE, standard error.
Sparano JA, et al. Clin Cancer Res. 2023;83:GS1-05 (Presented SABCS 2022)

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Oncotype DX Breast Recurrence Score® Report - Example

N0
N1 RxPONDER and SWOG- 8814

	RS® result 0–10	RS result 11–15	RS result 16–20	RS result 21–25	RS result 26–100
>50 years N0* **Postmenopausal N1***	No CT benefit	No CT benefit	No CT benefit	No CT benefit	Substantial CT benefit
≤50years N0*	No CT benefit	No CT benefit	~0.6% CT benefit	~7.8% CT benefit	Substantial CT benefit
Premenopausal N1*	2.9% CT benefit				Substantial CT benefit**

* **Node-negative** (N0) patients: TAILORx analyses were performed by age and demonstrated patients ≤ 50 years derived some clinically meaningful benefit from CT at 9 years starting with an RS® result of 16;
Node-positive (N1) patients: RxPONDER data were analysed according to menopausal status and demonstrated that premenopausal patients with RS® results 0-25 overall derived benefit from chemotherapy at 5 years.

** Benefit of chemotherapy for premenopausal N1 patients with RS® results 26-100 has not been formally assessed in a randomised study. The benefit derived from chemotherapy was significant for RS results 0-13 and 14-25 in the RxPONDER study and it is inferred to be significant for patients with RS result 26-100

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

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. 5. Kalinsky et al, SABCS 2020 GS3-00; 6. Albain et al Lancet 2010

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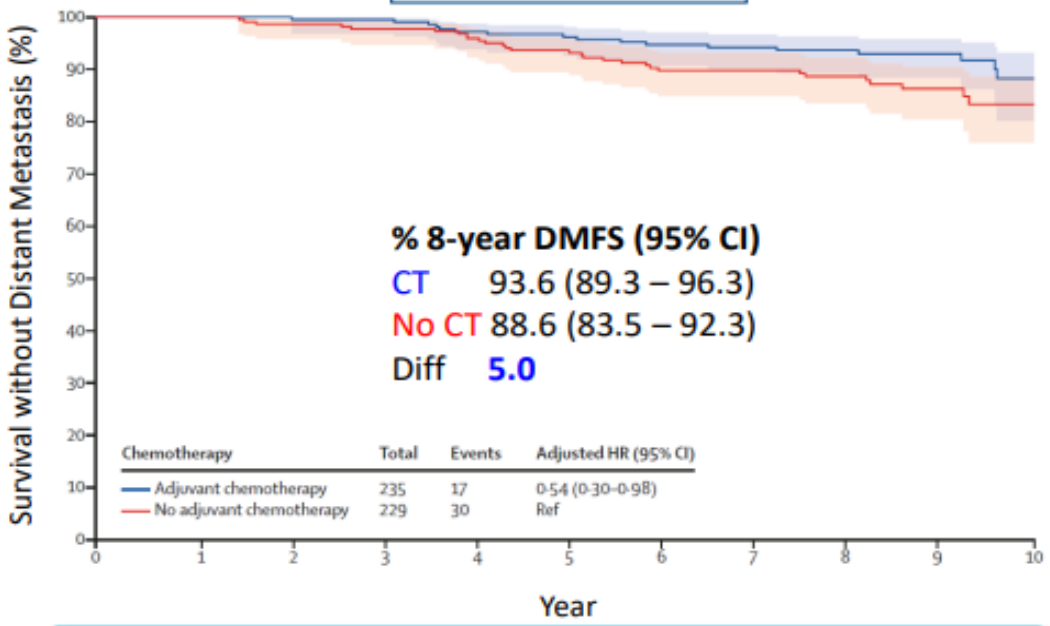
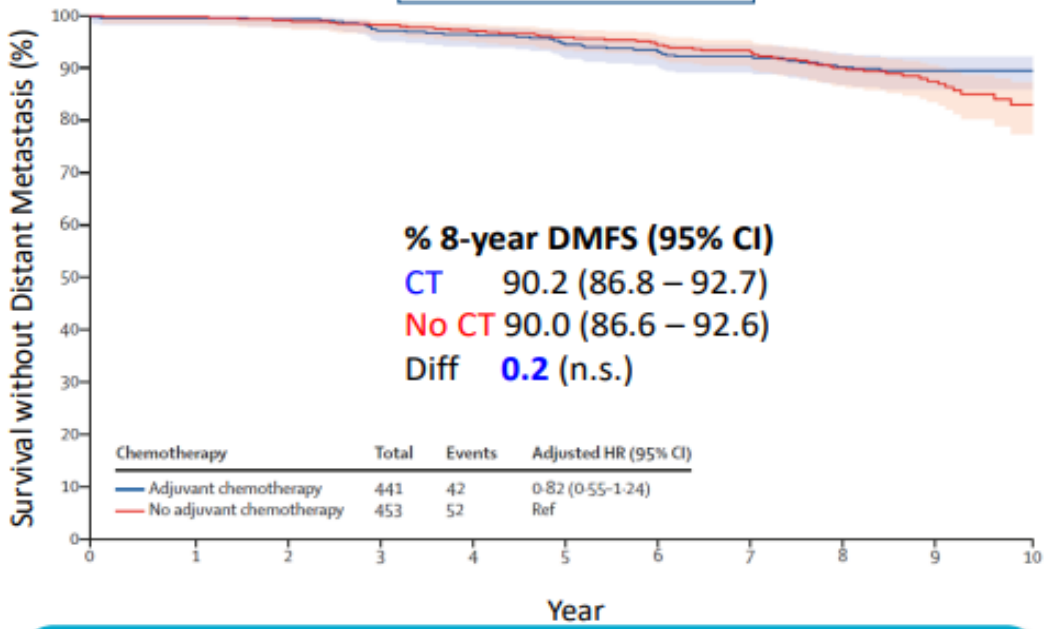
MINDACT – Predefined exploratory analyses by age

Patients ≤ 50 years old



Women ≤50years with a MammaPrint Low Risk result appear to benefit from chemotherapy, likely due to secondary OFS

Patients > 50 years old



Women >50years with a MammaPrint Low Risk result do not benefit from adjuvant chemotherapy

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Piccart et al. Lancet Oncol. 2021.

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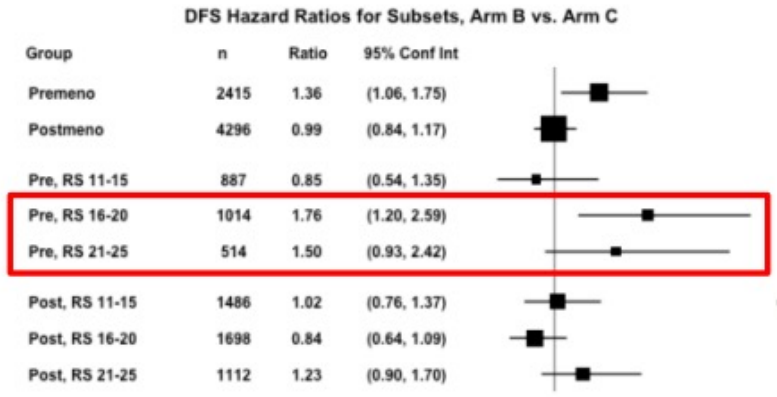
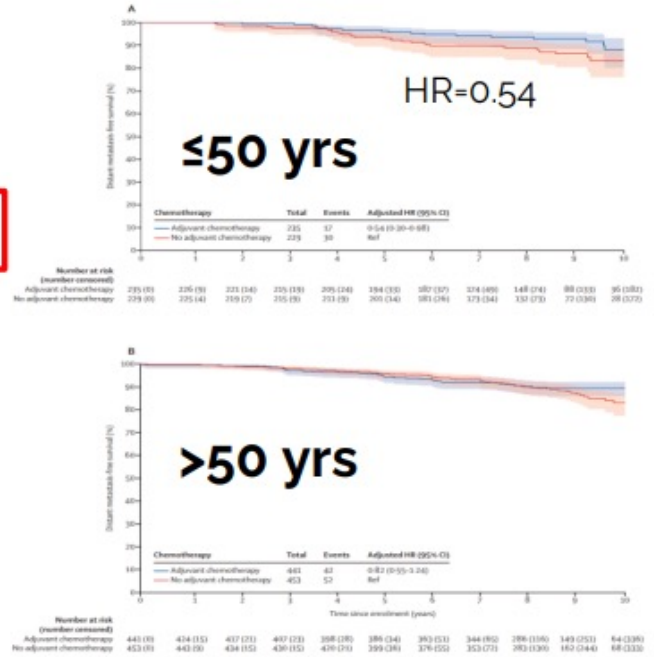
TailorX



Sparano et al, NEJM 2018

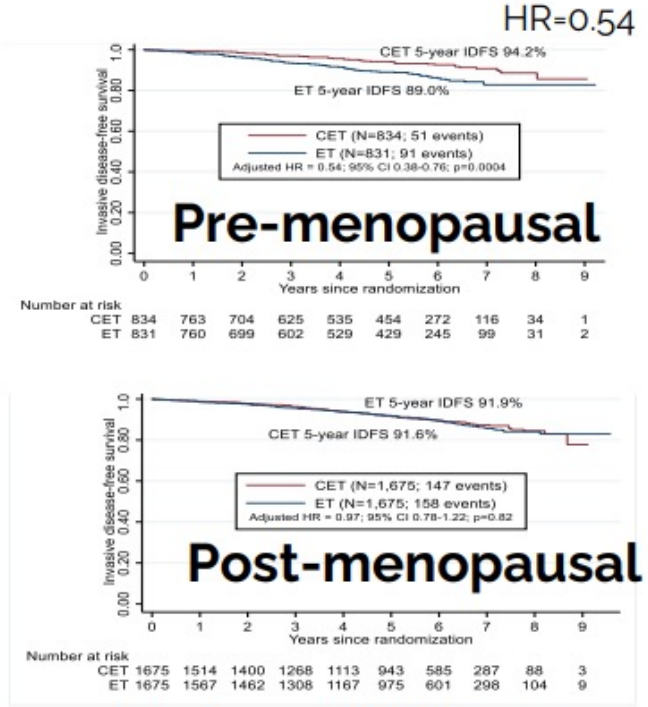
Note: use of LHRH analogs was 20% or less

MINDACT



Piccart et al. Lancet Oncol 2021

RxPONDER



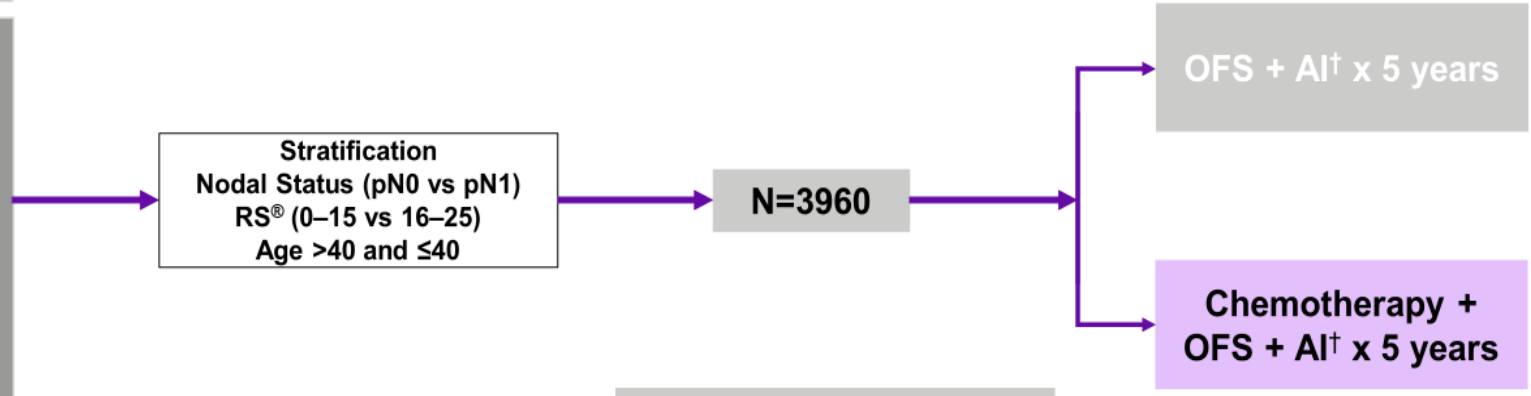
Kalinsky et al, SABCS 2020

OFSET Chemo (NRG-BR009) – Study Schema

Using the Breast Recurrence Score® Test to help identify mechanism of chemotherapy benefit in premenopausal patients

Study Design

- Premenopausal
- Age ≥18 years
- ECOG PS 0,1
- Resected T1–3, N0–1, M0 Breast Cancer
- ER and/or PR+ and HER2-
- pN0 RS® 16–20 plus high clinical risk* or RS® 21–25
- pN1 with RS® 0–25



Primary Endpoint

- IBCFS

Secondary Endpoints

- OS, DRFI, BCFI, PRO/QoL, compliance with endocrine therapy, correlative science studies

*Superiority trial; †Tamoxifen can be used if AI not tolerated
AI, Aromatase inhibitor; BCFI: Breast cancer-free interval; DRFS, distant relapse-free survival; EBC, Early breast cancer; ECOG PS, Eastern Cooperative Oncology Group Performance status; HER2-, human epidermal growth factor receptor 2; IDFS, invasive disease-free survival; OFS, Ovarian function suppression; OS, overall survival; PRO/QoL: Patient reported outcomes/Quality of Life; RS®, Recurrence Score®.
Mamounas T. Report from the Breast Cancer Working Group Meeting. Presented at: NRG Oncology Summer Meeting; July 21-23, 2022; Chicago, IL. Accessed March 2023. https://bit.ly/3WA3NVg

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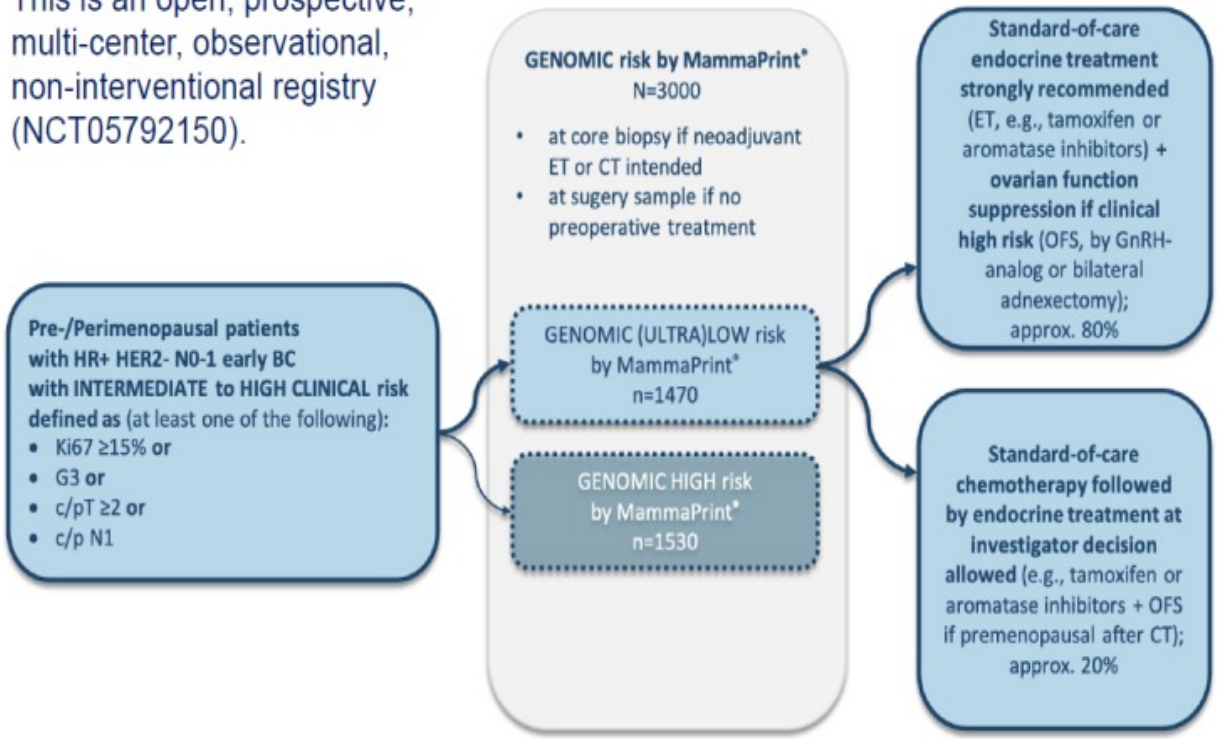
PROOFS Registry

Pre /perimenopausal patients with HR+/HER2 early breast cancer with intermediate to high clinical and low genomic risk, optimally treated by endocrine treatment plus ovarian function (OFS) or chemotherapy followed by endocrine treatment

Trial Design

This is an open, prospective, multi-center, observational, non-interventional registry (NCT05792150).



Trial sponsored by the German Study Group (WSG)

Open for inclusion

Adapted from Fischer et al. ESMO Breast Cancer 2023.

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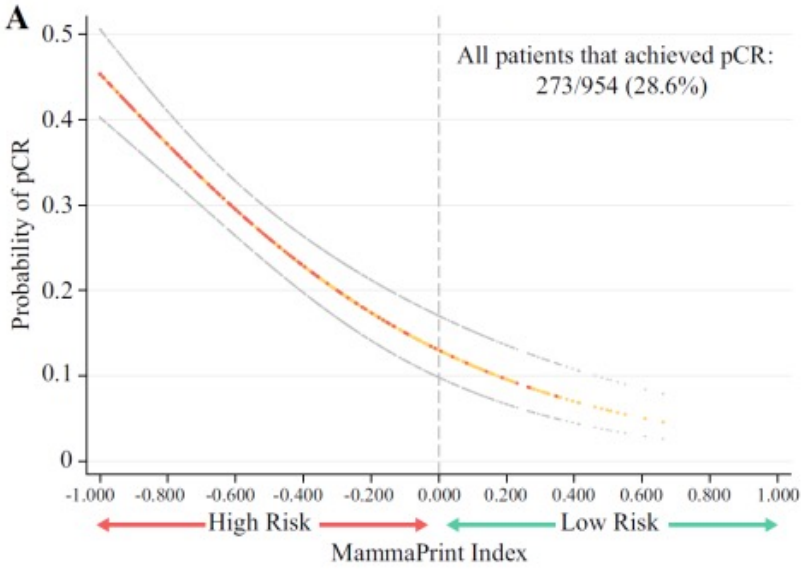
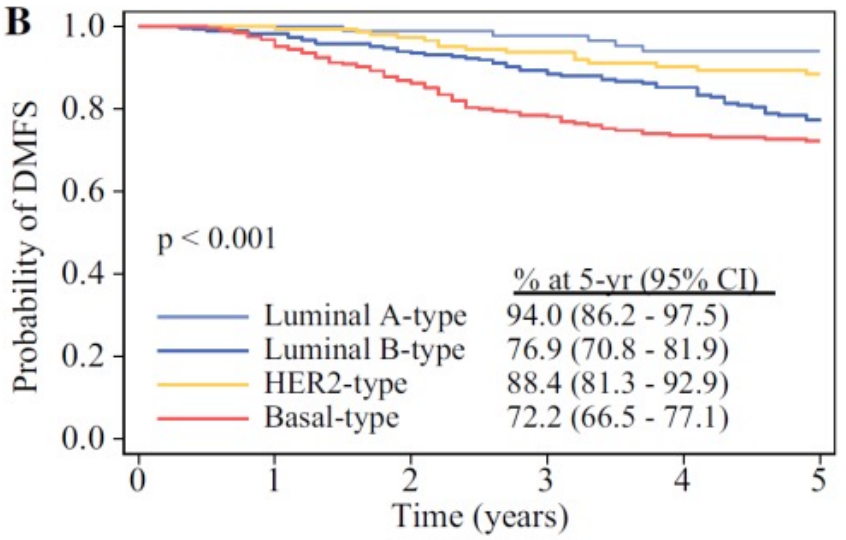
3. Even more information

MammaPrint **High Risk** and benefits of neoadjuvant chemotherapy in NBRST





Increasing MammaPrint High Risk is predictive of the sensitivity to chemotherapy
Patients with Luminal B cancer (MP High) have a poorer prognosis despite neoadjuvant chemotherapy

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Whitworth, et al. ASO. 2022

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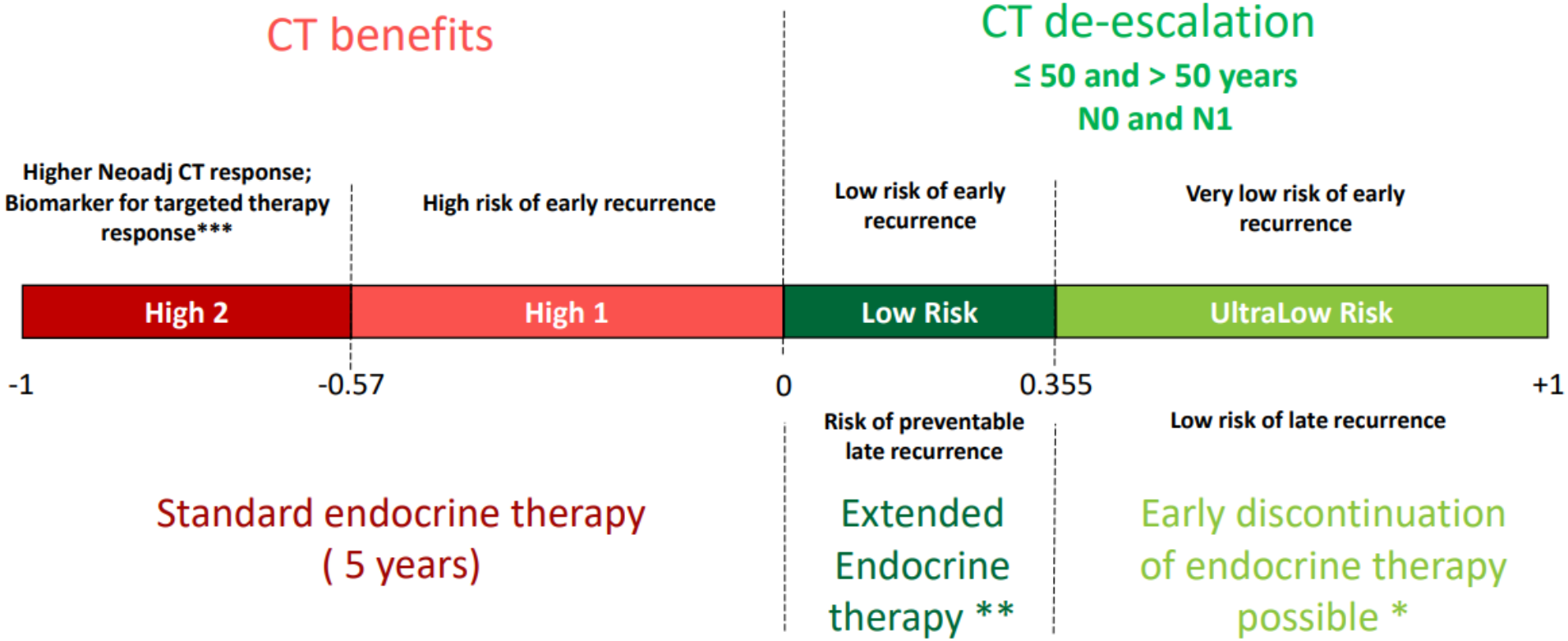
MammaPrint Index

A specific risk for each patient



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* Postmenopausal women with breast cancer HR+ HER2- N0, particularly with adherence issues
** Postmenopausal women with breast cancer HR+ HER2- N0/N1
*** Increased sensitivity to Carboplatin, Immunotherapies, PARPi

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Conclusion

GEP test, provides extra useful prognostic information independently of age

Pre-menopausal pts with pN0:

- Genomic low risk (RS 0-15)/MP ultra low: No chemo
- Genomic intermediate risk (RS16-25)/MP low: Chemo vs LHRH+AI
- Genomic high-risk (RS26-..)/MP high: Chemoendocrino therapy

Conclusion: It helps in providing more personalised care!

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Breast Cancer Debate of the year

Friday 26th January 2024

Use of Gene Expression Profile in a 42 y old patient with stage II luminal BC

- *In favour – **J. MEBIS (UHasselt)***
- *Not in favour - **M. IGNATIADIS (I. Jules Bordet – HUB)***
- *Discussion/Questions - **all***

Michail Ignatiadis MD, PhD
Institut Bordet & Université Libre de Bruxelles (U.L.B.)
Hôpital Universitaire de Bruxelles (HUB)

INSTITUT JULES BORDET INSTITUUT

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Debate is over!

Belgian Cancer Registry

- home
- belgian cancer registry
- cancer registration
  - standard cancer registration
  - web based cancer registration
  - specific project registrations
    - ntrk-inhibitor
    - stereotactic radiotherapy
    - complex surgery
    - gep breast
    - barrett esophagus - rfa
    - paediatrics - late effects
    - belgian transplant registry (btr)
    - innovative radiotherapy
    - effect
    - ralp
    - head and neck
  - transcan eranet
  - quality of life

GEP breast

Gene Expression Profiling (GEP) in breast cancer

A convention was concluded between the RIZIV/INAMI and recognised breast clinics for the reimbursement of 'Gene Expression Profiling (GEP)' tests for a specific group of patients with early breast cancer. These GEP tests determine the genetic profile of the tumour to assess the susceptibility to adjuvant chemotherapy whereby unnecessary chemotherapy can be avoided. More information about this convention can be found on the website of the RIZIV/INAMI.

The convention defines the target group as followed:

- Patients with early breast cancer, first diagnosis, with maximum 3 affected lymph nodes, a tumour of maximum 5 cm, HER2-, ER+ and/or PR+, menopausal or at least 45 years old, and clinically high risk based on a generally accepted algorithm as used, for example, in the MINDACT study or the Magee score.

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Is there any subgroup that we should use GEP in a 42-year old stage II luminal BC ?

Stage	Tumor	Node	Metastasis
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	AnyT	N3	M0
IV	AnyT	AnyN	M1

Tis = *in situ*, mi = micrometasis

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No GEP if T0N1, T1N1, T2N1!

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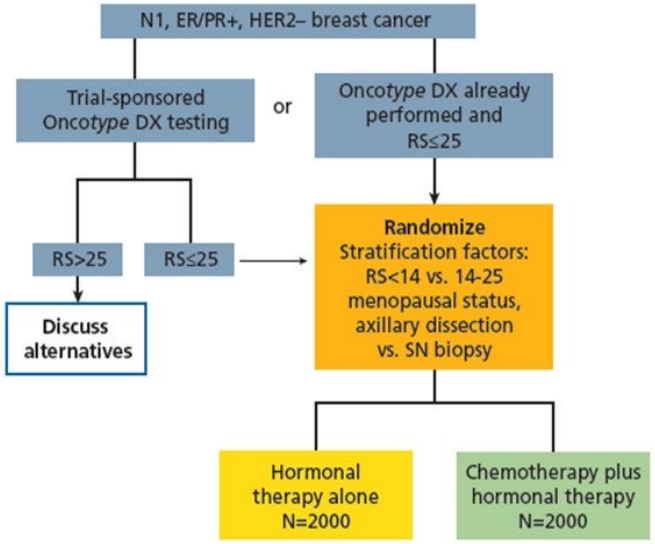
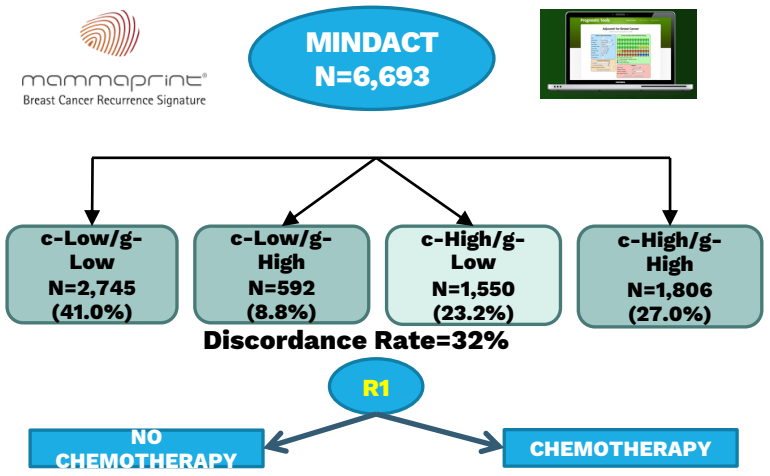
Is there any benefit from chemotherapy in clinically high risk breast cancer patients with “genomic low” tumors?

RxPONDER
RS ≤ 25
Node positive (1-3 N+)
N=5083



Kalinsky et al., N Engl J Med 2021

MINDACT
MammaPrint low
48% 1-3 N+ ; 50% T >2 cm
N=1550

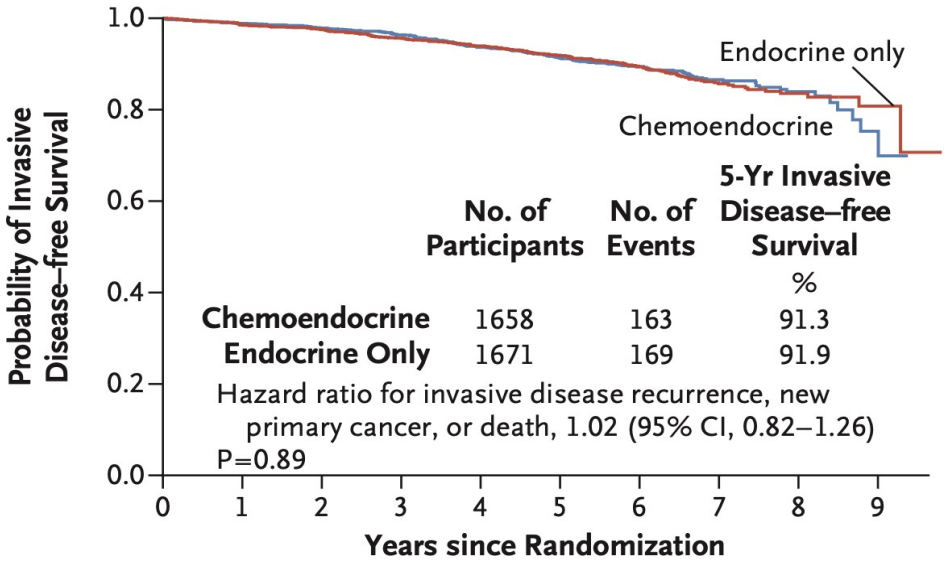


Piccart et al., Lancet Oncol 2021

LIMBURGS ONCOLOGISCH CENTRUM

No benefit of chemotherapy for postmenopausal pts

RxPONDER

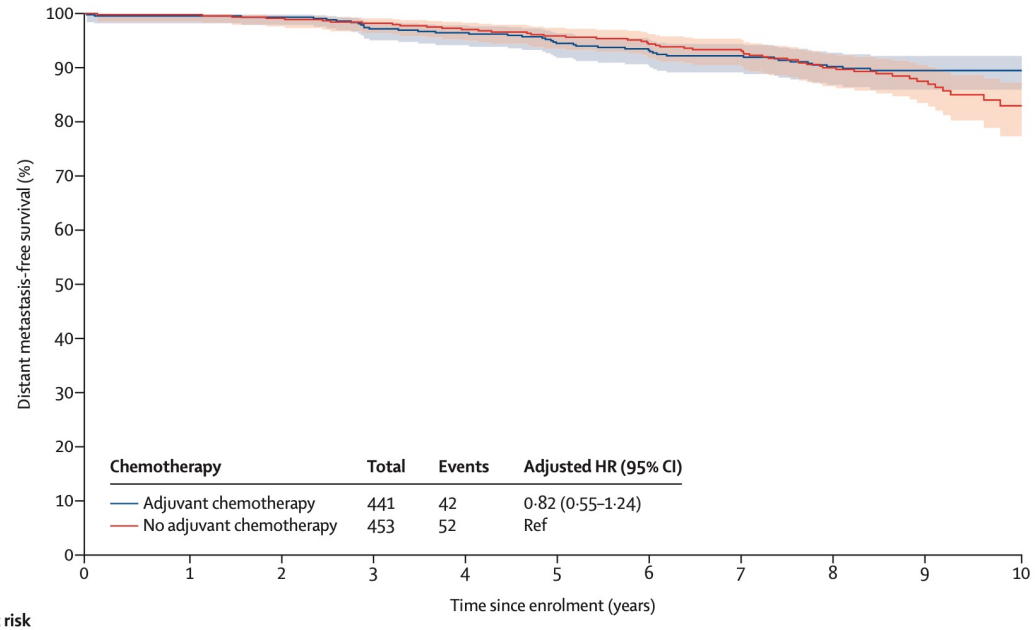


No. at Risk

Chemoendocrine group	1658	1515	1413	1298	1145	993	659	358	129	14
Endocrine-only group	1671	1568	1474	1343	1196	1030	679	364	137	21

Kalinsky et al., N Engl J Med 2021

MINDACT



Number at risk (number censored)

Adjuvant chemotherapy	441 (0)	424 (15)	417 (21)	407 (23)	398 (28)	386 (34)	363 (51)	344 (65)	286 (116)	149 (251)	64 (336)
No adjuvant chemotherapy	453 (0)	443 (9)	434 (15)	430 (15)	420 (21)	399 (36)	376 (55)	353 (72)	283 (130)	162 (244)	68 (333)

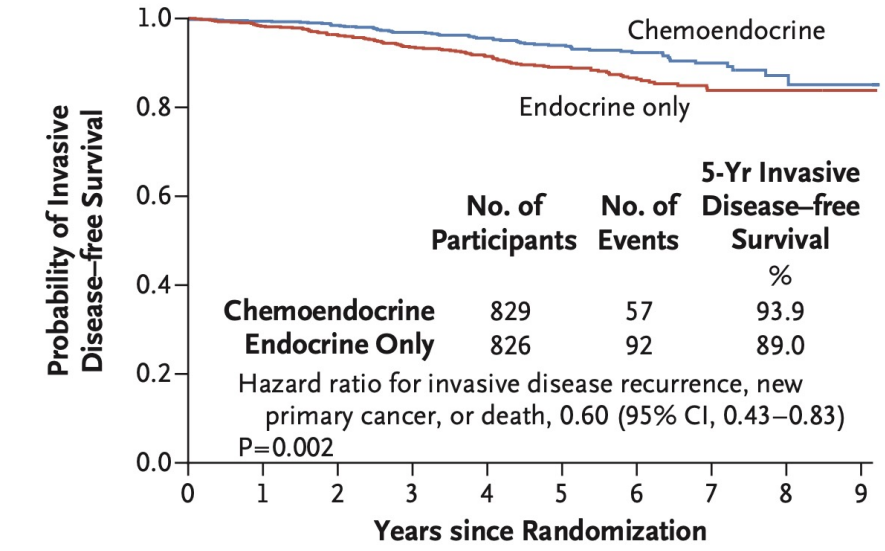
Piccart et al., Lancet Oncol 2021

LIMBURGS ONCOLOGISCH CENTRUM

Benefit of chemotherapy for premenopausal patients

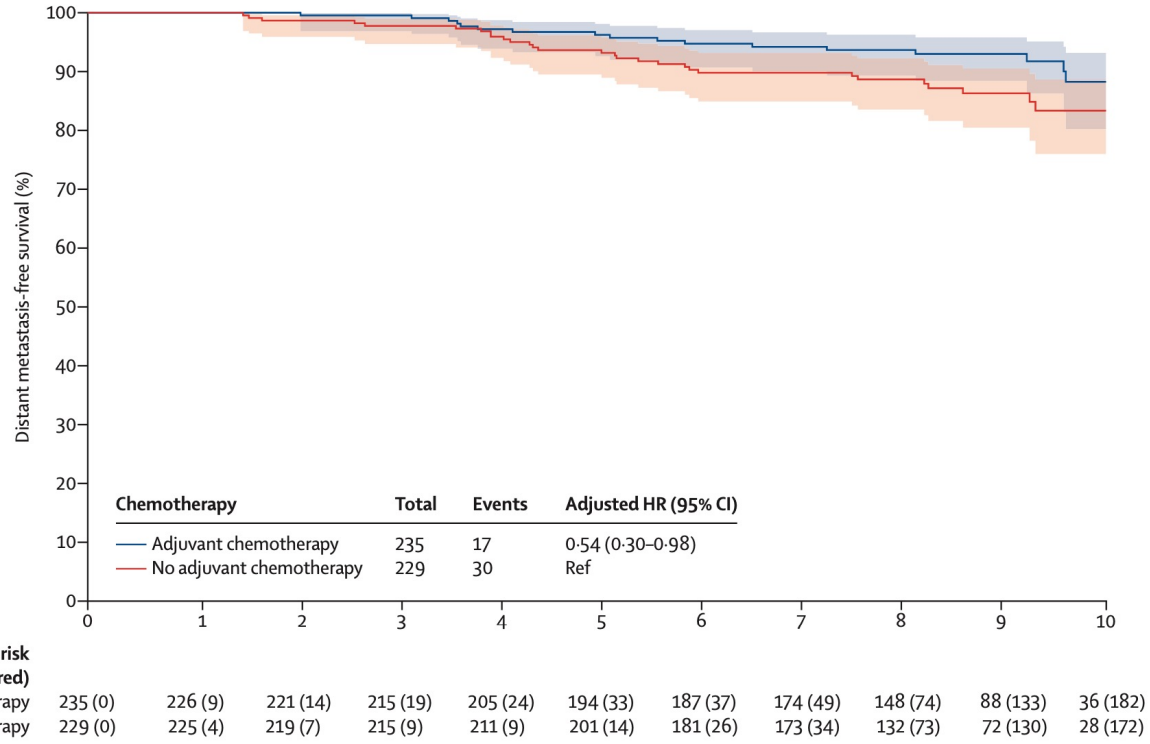
RxPONDER

12.7% received OFS



Kalinsky et al., N Engl J Med 2021

MINDACT



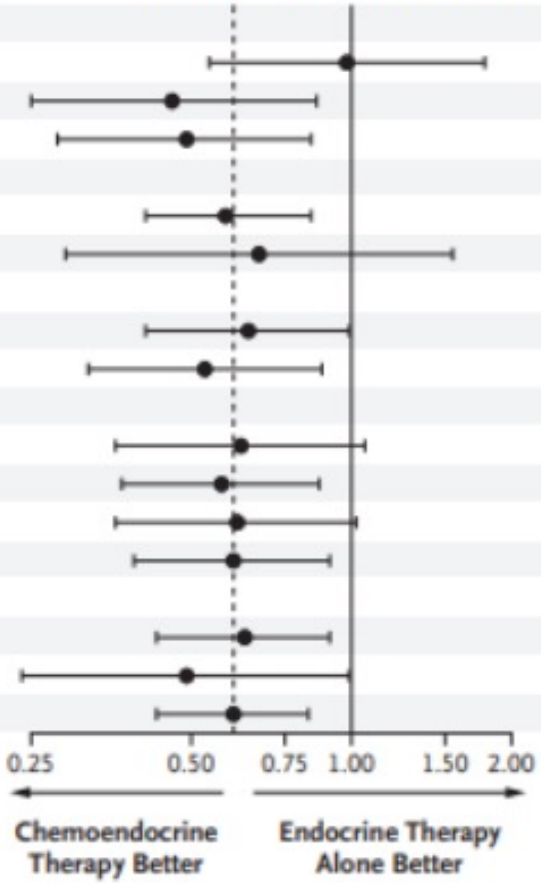
Piccart et al., Lancet Oncol 2021

LIMBURGS ONCOLOGISCH CENTRUM

Benefit of chemotherapy for premenopausal patients (RxPONDER)

B Premenopausal Women

Subgroup	No. of Participants	No. of Events	Hazard Ratio for Invasive Disease Recurrence, New Primary Cancer, or Death (95% CI)
Age			
≥50 yr	509	44	0.98 (0.54–1.78)
45–49 yr	615	46	0.46 (0.25–0.86)
<45 yr	531	59	0.49 (0.28–0.84)
Grade			
Intermediate or high	1280	125	0.58 (0.41–0.84)
Low	357	23	0.67 (0.29–1.55)
Tumor size			
T2 or T3	728	80	0.64 (0.41–0.99)
T1	925	69	0.53 (0.32–0.88)
Nodes			
2 or 3 positive	574	55	0.62 (0.36–1.06)
1 positive	1081	94	0.57 (0.37–0.87)
Sentinel node	556	60	0.61 (0.36–1.02)
Full axillary lymph-node dissection	1099	89	0.60 (0.39–0.91)
Recurrence score			
14–25	1015	113	0.63 (0.43–0.91)
0–13	640	36	0.49 (0.24–0.99)
Overall	1655	149	0.60 (0.43–0.83)



Kalinsky K et al NEJM 2021

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ULB

iris

No GEP if T3N0

Only 1,2% of 6693 patients in the MINDACT trial[1]

Only 0,002% of the 9719 of the TailorX trial[2]

[1]Cardoso F et al NEJM 2016, [2]Sparano J et al NEJM 2018

What about T2N0?

If you trust your pathology no GEP for T2N0 grade 3 & for T2N0 grade 1

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women with T2N0 grade 1 tumor without chemo

https://rconnect.dfci.harvard.edu/CompositeRiskSTEPP/

Characteristics Summary

Characteristics

Age
- < 35
- 35-39
- 40-44
- 45-49
- ≥ 50

No. of Positive Nodes
- 0
- 1-3
- ≥ 4

Tumor Size, cm
- Unknown
- ≤ 2cm
- > 2cm

Tumor Grade
- 1
- 2
- 3

ER Expression
- < 50%
- ≥ 50%

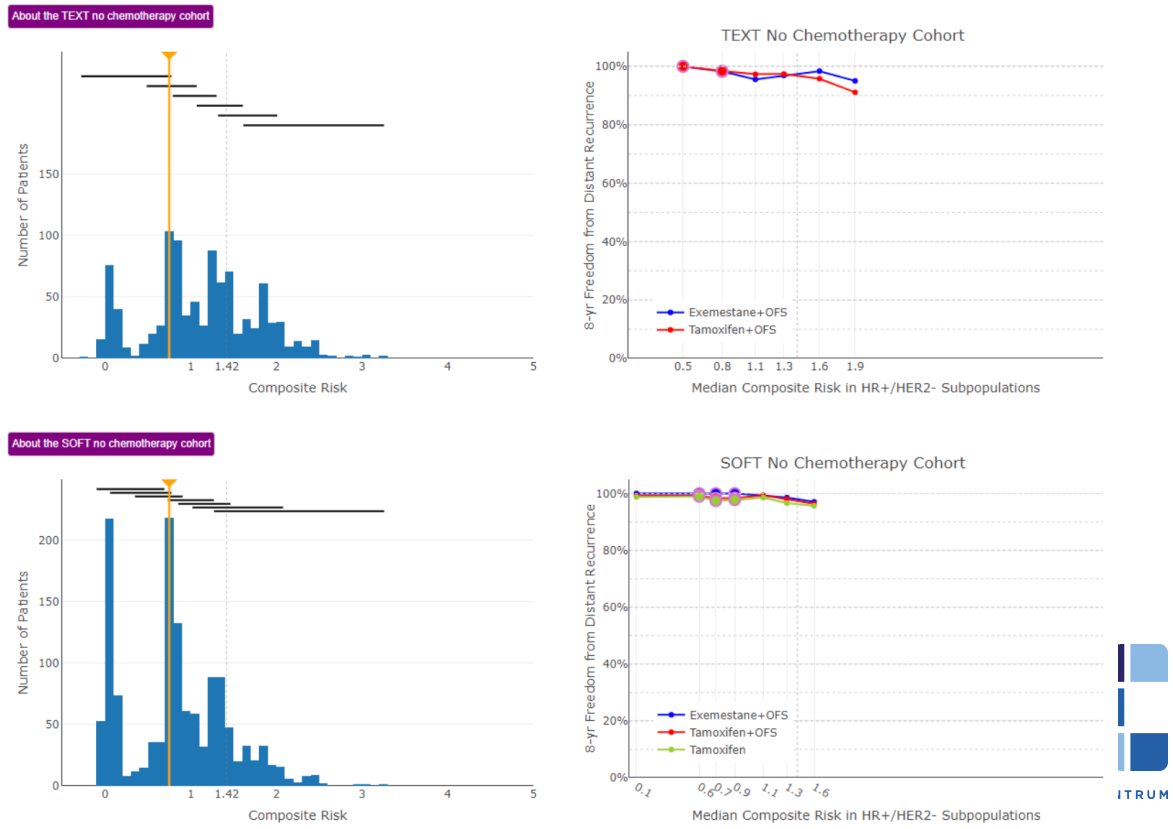
PgR Expression
- < 20%
- 20-49%
- ≥ 50%

Ki-67 Expression
- < 14%
- 14-19%
- 20-25%
- ≥ 26%

Composite risk

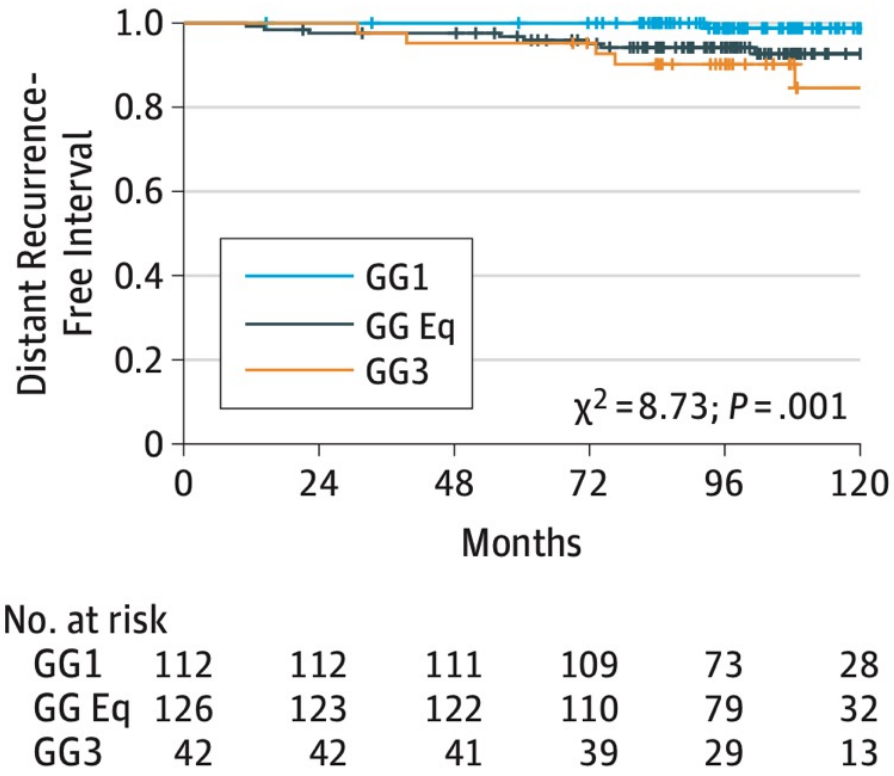
0.75

Input Suggestion



What about T2N0, histological grade 2?

Validation in BIG 1-98 in ER+/HER2-, *HG 2*, N0



Ignatiadis M et al., JAMA Oncol, 2016

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Why is there a benefit in pre but not in post-menopausal patients only?
Direct effect of chemo?
Ovarian suppression?

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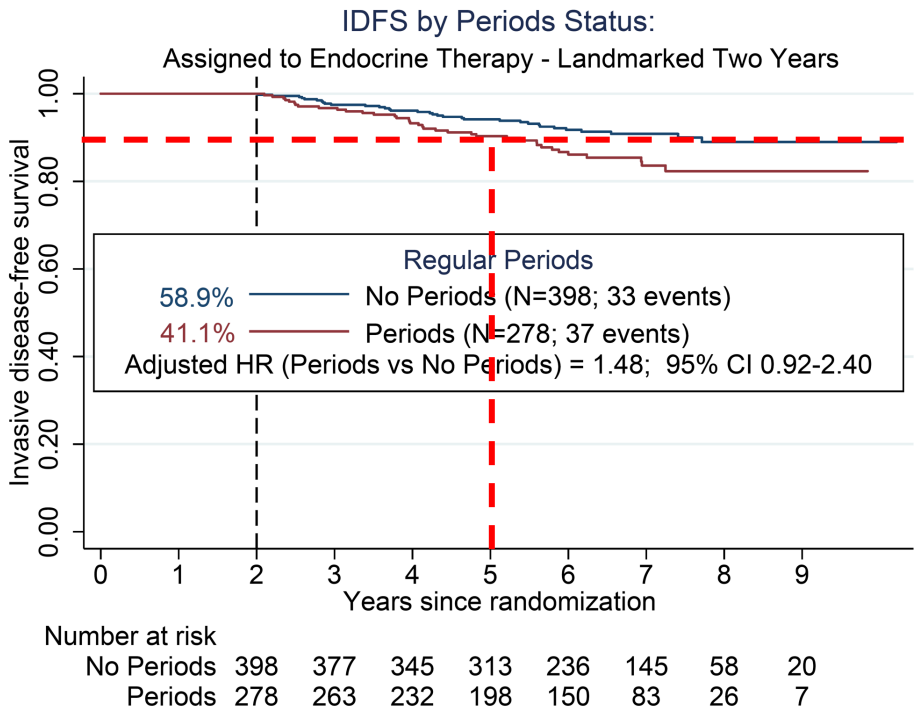
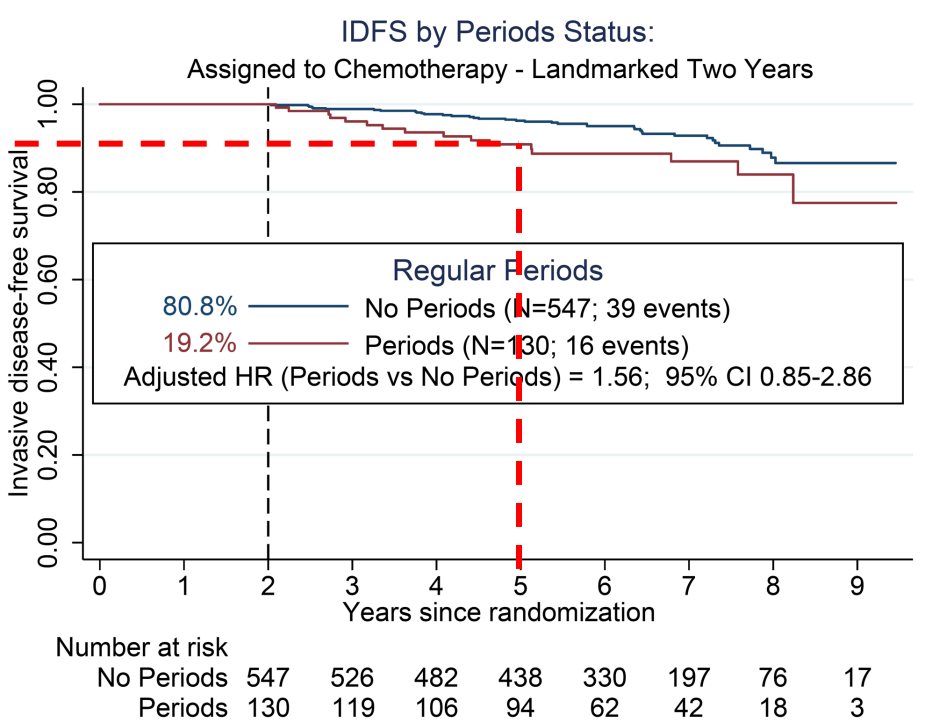
Numerically improved IDFS in premenopausal pts no longer having regular menstrual periods in both Tx arms

Endocrine Tx alone (N=676)



Chemo then Endocrine Tx (N=677



N1 NRG-BR009

OFSET Chemo (NRG-BR009) – Study Schema

Using the Breast Recurrence Score® Test to help identify mechanism of chemotherapy benefit in premenopausal patients

Study Design

- Premenopausal
- Age ≥18 years
- ECOG PS 0,1
- Resected T1–3, N0–1, M0 Breast Cancer
- ER and/or PR+ and HER2-
- pN0 RS* 16–20 plus high clinical risk* or RS* 21–25
- pN1 with RS* 0–25

Stratification
Nodal Status (pN0 vs pN1)
RS* (0–15 vs 16–25)
Age >40 and ≤40

N=3960

OFS + AI† x 5 years

Chemotherapy + OFS + AI† x 5 years

Primary Endpoint

- IBCFS

Secondary Endpoints

- OS, DRFI, BCFI, PRO/QoL, compliance with endocrine therapy, correlative science studies

*Superiority trial; †Tamoxifen can be used if AI not tolerated
AI, Aromatase inhibitor; BCFI: Breast cancer-free interval; DRFS, distant relapse-free survival; EBC, Early breast cancer; ECOG PS, Eastern Cooperative Oncology Group Performance status; HER2-, human epidermal growth factor receptor 2; IDFS, Invasive disease-free survival; OFS, Ovarian function suppression; OS, overall survival; PRO/QoL: Patient reported outcomes/Quality of Life; RS®, Recurrence Score®.
Mamounas T. Report from the Breast Cancer Working Group Meeting. Presented at: NRG Oncology Summer Meeting; July 21-25, 2022; Chicago, IL. Accessed March 2025. https://bit.ly/3WA3NVg

.OGISCH CENTRUM

Conclusions

For the majority of premenopausal women <45 years of age with stage II luminal breast cancer, no GEP is needed

One can consider GEP in the subgroup of premenopausal women with pT2N0, HG2 tumors

The value of chemotherapy in premenopausal women with ClinHigh GenLow tumors treated with OFS+AI is currently under investigation

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