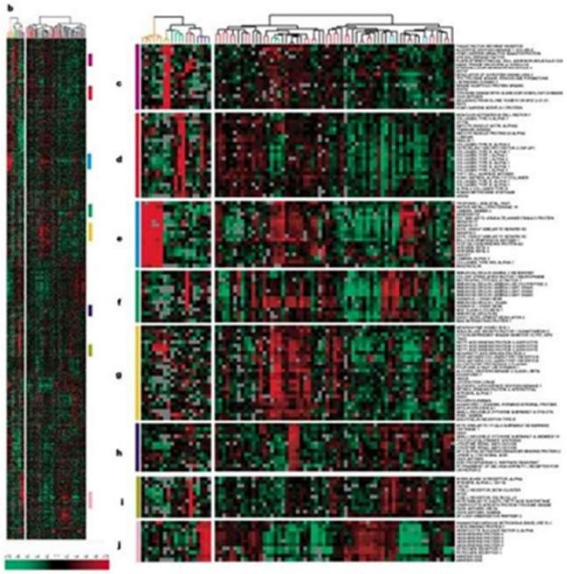
Predictive and Prognostic Biomarkers Using Genomic Profile in Early Breast Cancer

D. Constanza Guaqueta MD

Breast Medical Oncologist

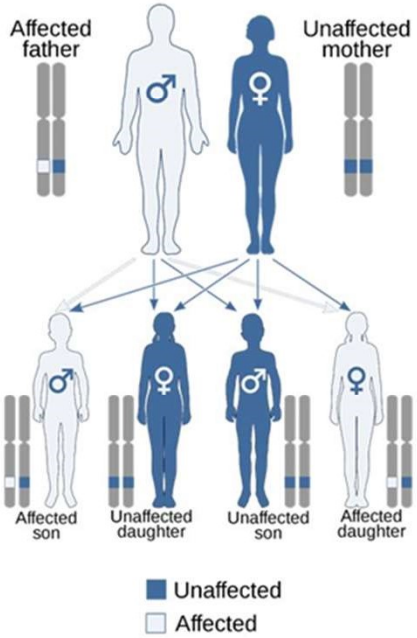
Memorial Cancer Institute

TUMOR TRANSCRIPTOME



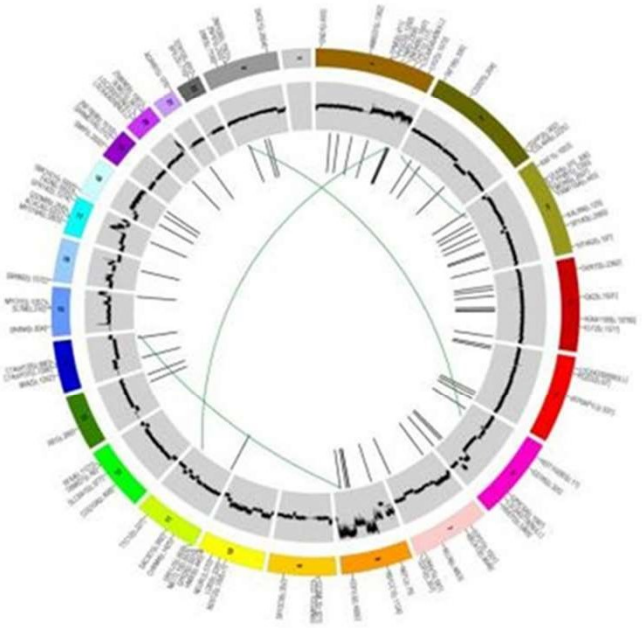
Nucleic Acid: Somatic tumor RNA
Source: Tumor biopsy
Timing: baseline diagnosis
Readout: patterns of
gene expression
genes: 6 to ~ 100

GERMLINE GENETICS



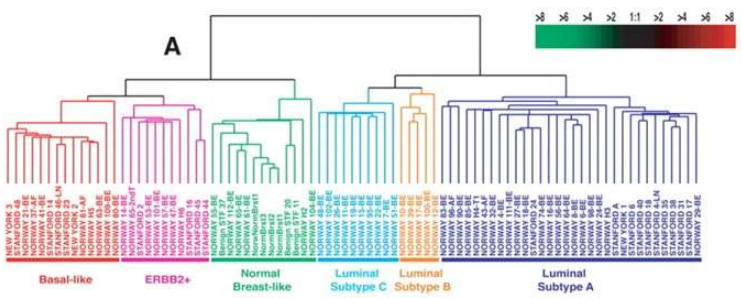
Nucleic Acid: Germline DNA
Source: "normal" tissue (e.g. blood)
Timing: At diagnosis, when mutation
suggested by FH, or at stage IV
Readout: mutations in genes
predisposing to cancer
genes: Variable from 2 (BRCA1/2) to > 25
depending on possible syndromes

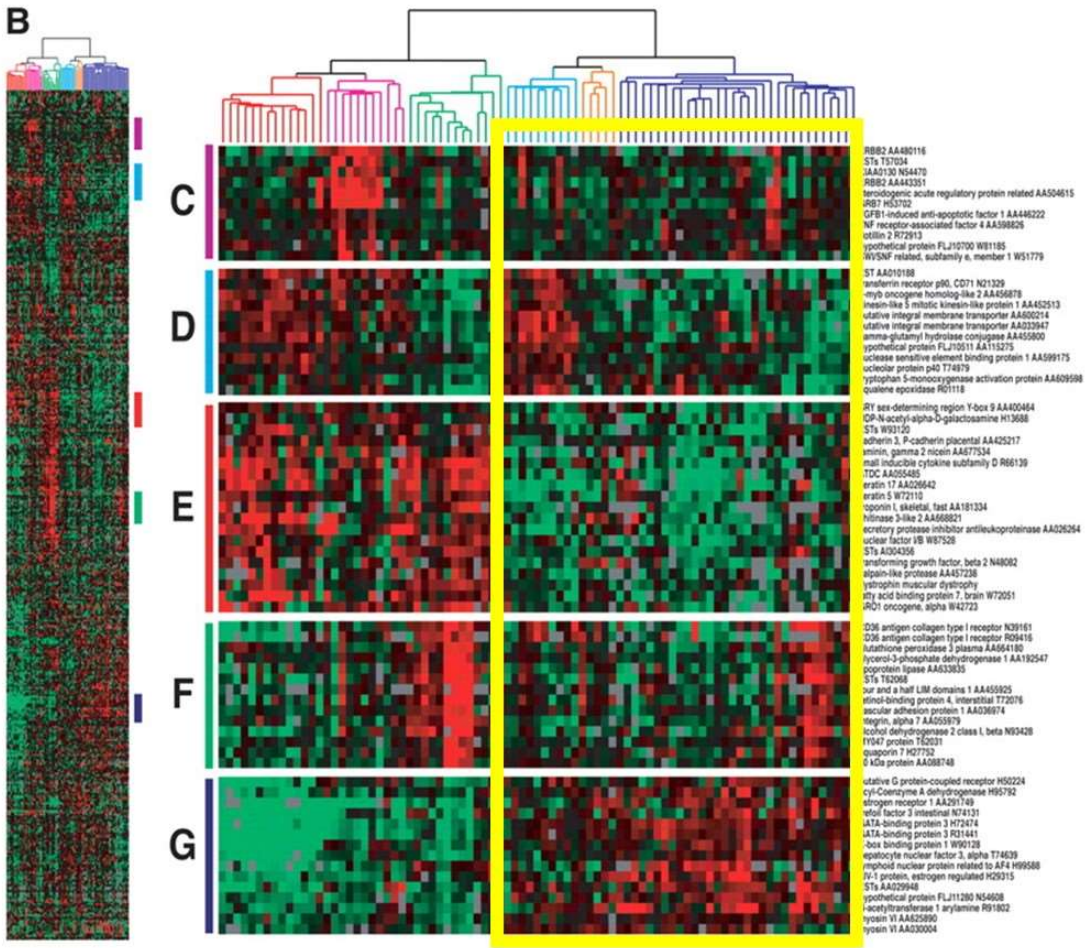
TUMOR GENOME



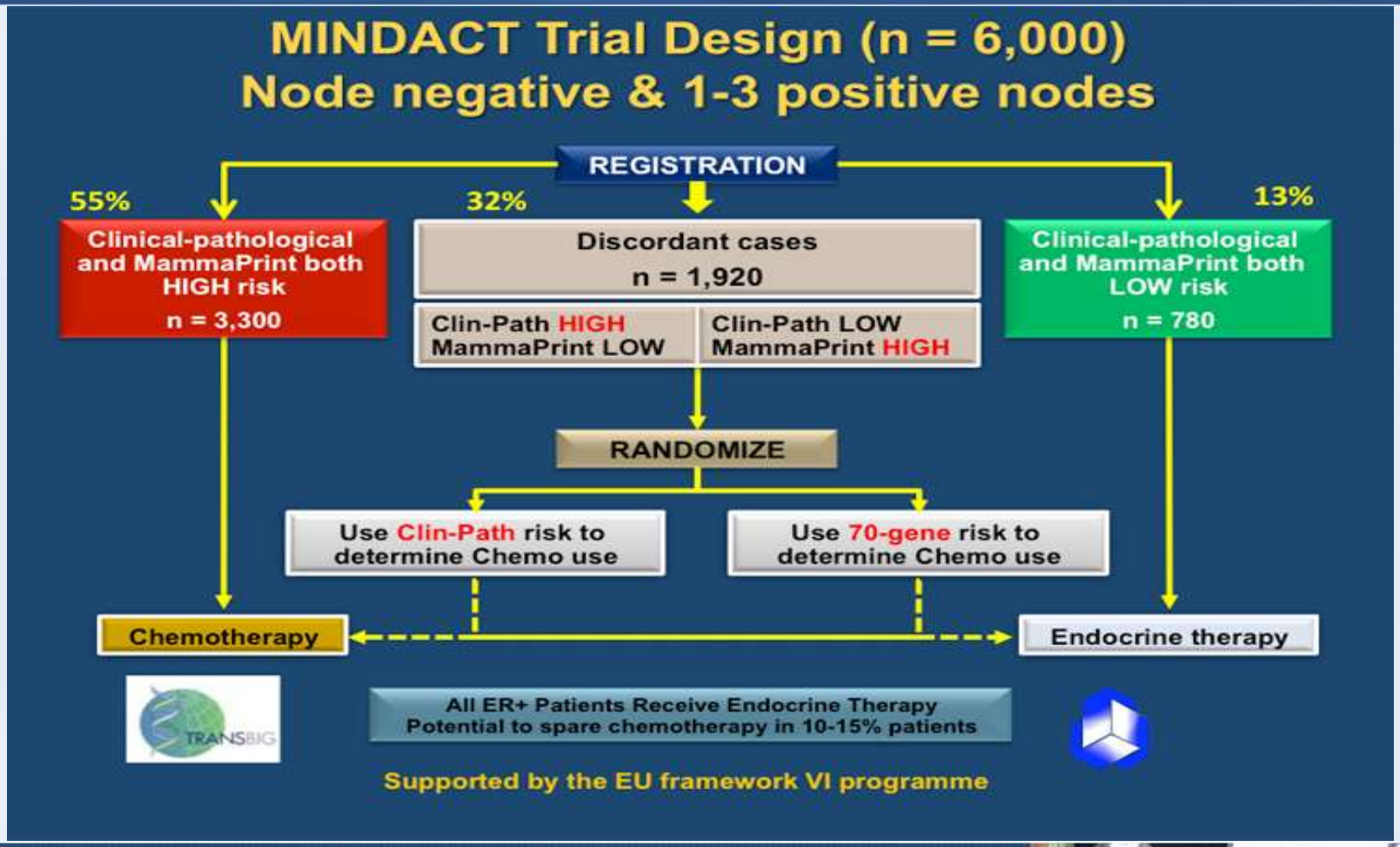
Nucleic Acid: Somatic tumor DNA
Source: Tumor biopsy or cell-free DNA
Timing: Metastatic recurrence & serially
Readout: somatic changes in tumor DNA at
baseline and over time
genes: ~ 500

Gene expression patterns of 85 experimental samples analyzed by hierarchical clustering using the 476 cDNA intrinsic clone set.





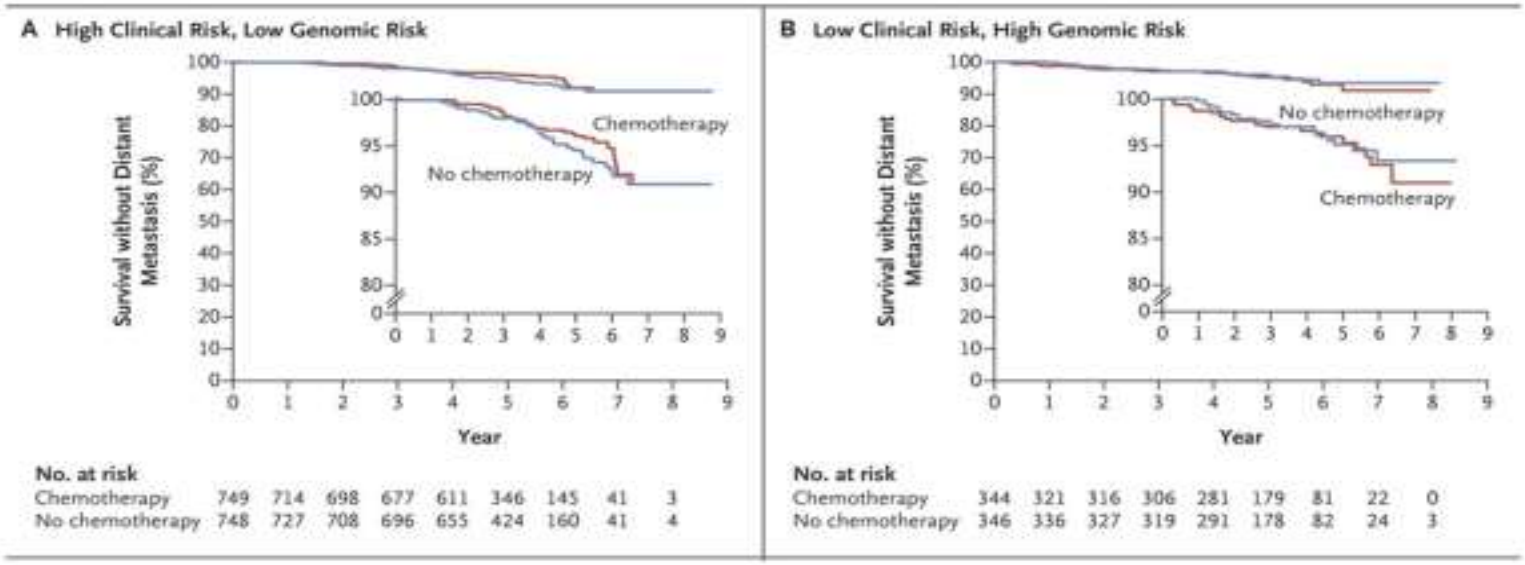
Therese Sørlie et al. PNAS 2001;98:19:10869-10874


MINDACT Trial Design (n = 6,000)
Node negative & 1-3 positive nodes
REGISTRATION
55%
Clinical-pathological and MammaPrint both HIGH risk
n = 3,300
32%
Discordant cases
n = 1,920
Clin-Path HIGH MammaPrint LOW
Clin-Path LOW MammaPrint HIGH
13%
Clinical-pathological and MammaPrint both LOW risk
n = 780
RANDOMIZE
Use Clin-Path risk to determine Chemo use
Use 70-gene risk to determine Chemo use
Chemotherapy
Endocrine therapy
TRANSBIG
All ER+ Patients Receive Endocrine Therapy
Potential to spare chemotherapy in 10-15% patients
Supported by the EU framework VI programme

MINDACT RESULTS Cardoso et al. NEJM 2016

Clinical Genomic	Low Low	Low High	High Low	High High
No.	2745	592	1550	1806
N+	6%	3%	48%	26%
T < 2 cm	96%	98%	42%	52%
Grade 3	2%	15%	29%	76%
ER+ Luminal	96%	79%	90%	50%
TNBC	0%	9%	1%	31%
HER2+	4%	12%	8%	19%
5 year DDFS	97.6%	94.8%	95.1%	90.6%
Δ DFS with chemo		2.2% HR .74, p NS	3.0% HR .64, p 0.026	

MINDACT: Survival without Distant Metastasis, Disease-free Survival, and Overall Survival in the Two Discordant-Risk Groups, According to Randomized Treatment.



Cardoso F et al.
N Engl J Med 2016;375:717-729.

Clinical Risk

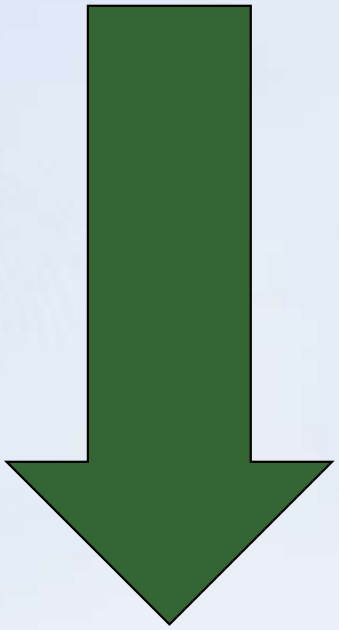
Low Clinical Risk:

- Tumor <3cm + Low Grade
- Tumor <2cm + Int. Grade
- Tumor<1cm + High Grade

High Clinical Risk:

Those that do not meet Low risk criteria

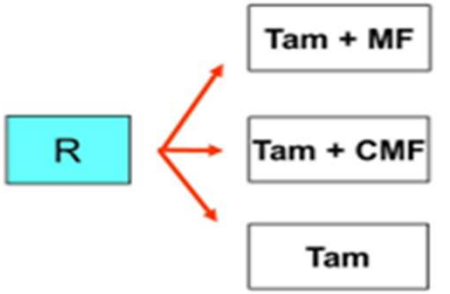
IMPACT OF 70 GENE SIGNATURE IN HIGH CLINICAL RISK GROUP

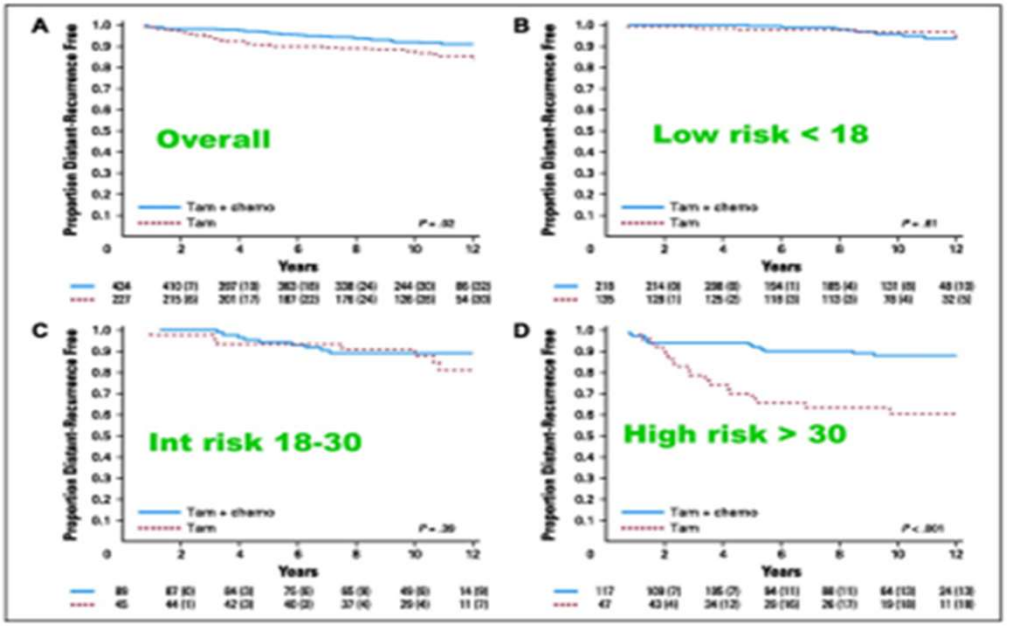


46%

Chemotherapy use

NSABP B-20
Outcome by Recurrence Score





Paik S, et al. *J Clin Oncol*. 2006;24(23):3726-3734.

TAILORx: Treatment Assignment & Randomization

Accrued Between April 2006 - October 2010

Key Eligibility Criteria
- Node-negative
- ER-pos, HER2-neg
- T1c-T2 (high-risk T1b)

Preregister - Oncotype DX RS (N=11,232)

Register (N=10,273)

Statistical Design
- Non-inferiority - IDFS
- HR 1.332 (90 vs. 87% 5-yr DFS)
- Type I 10%, type II 5%
- Full info– 835 IDFS events

ARM A: Low RS 0-10
(N=1629 evaluable)
ASSIGN
Endocrine Therapy (ET)

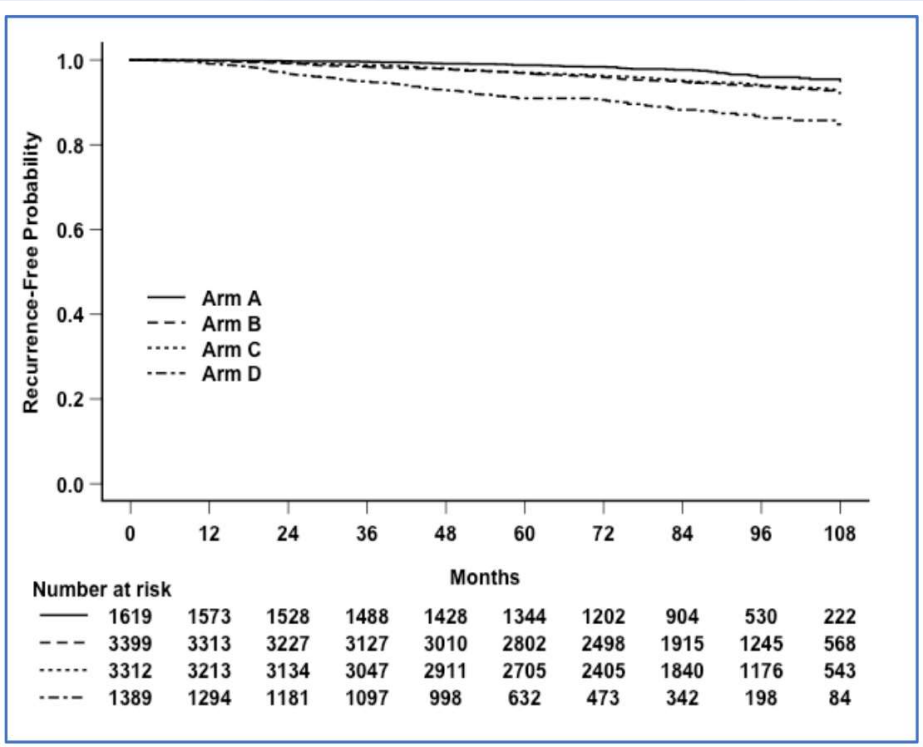
Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo

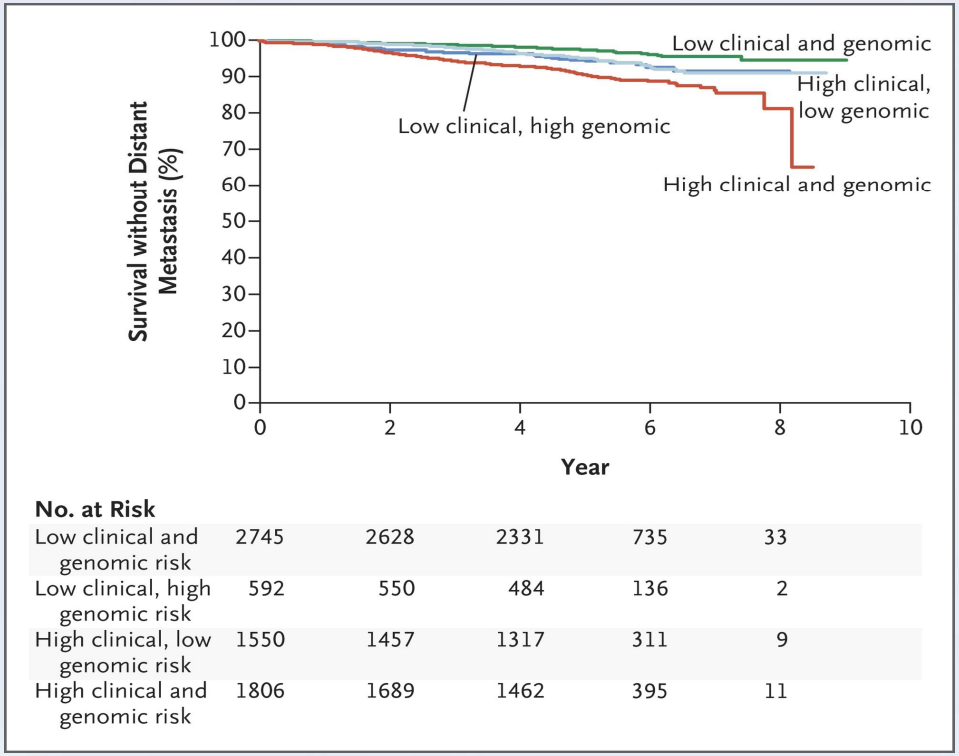
ARM B: Experimental Arm
(N=3399)
ET Alone

ARM C: Standard Arm
(N=3312)
ET + Chemo

PROSPECTIVE STUDIES IN ENDOCRINE THERAPY ALONE IN LOW GENOMIC RISK, EARLY BREAST CANCER



TAILORx Sparano J, et al. NEJM 2018; 379:111-121

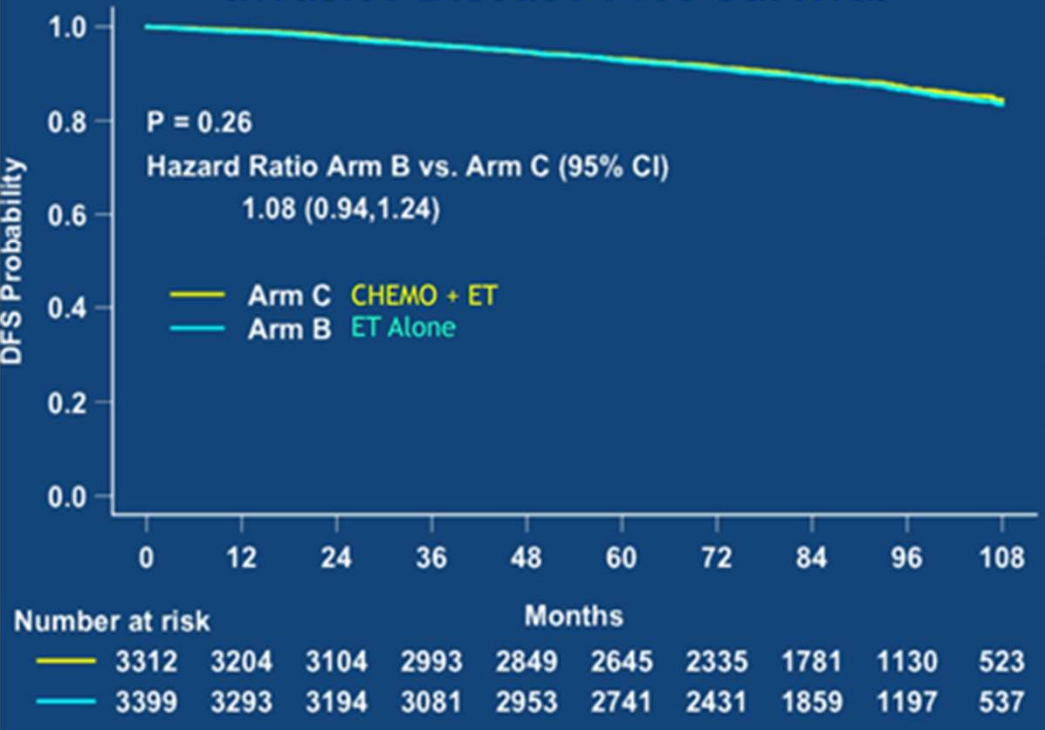


MINDACT Cardoso F, et al. NEJM 2016; 375: 717-729

TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as first event, of which 199 (23.8%) were distant

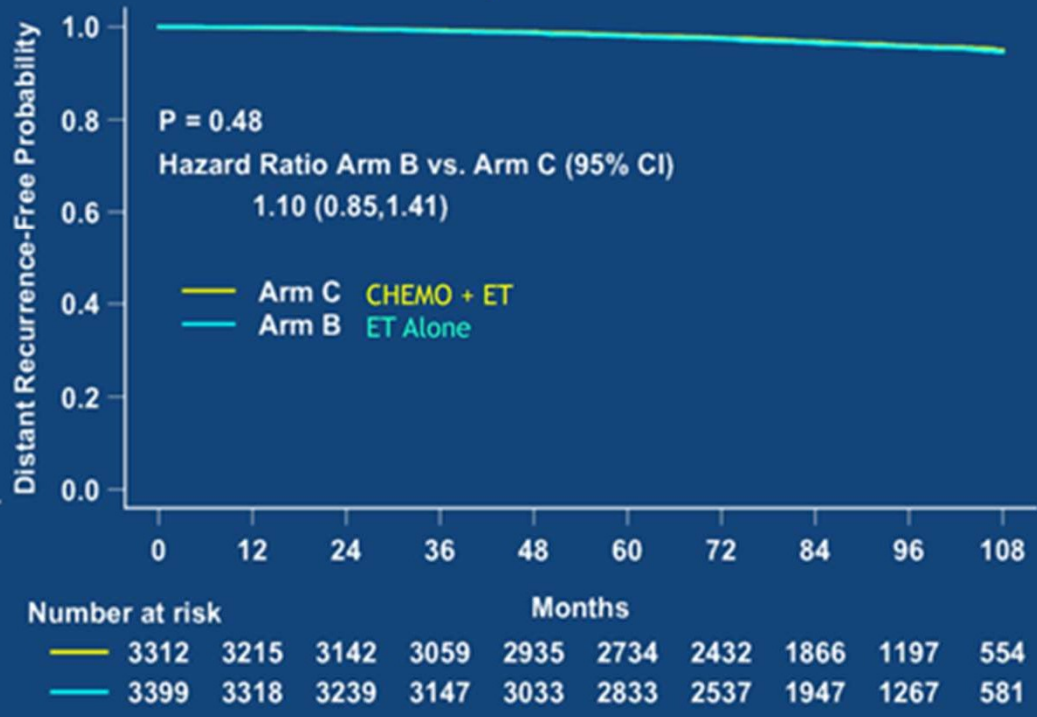
Primary Endpoint
Invasive Disease-Free Survival



Number at risk

Arm C	3312	3204	3104	2993	2849	2645	2335	1781	1130	523
Arm B	3399	3293	3194	3081	2953	2741	2431	1859	1197	537

Secondary Endpoint
Distant Relapse-Free Interval



Number at risk

Arm C	3312	3215	3142	3059	2935	2734	2432	1866	1197	554
Arm B	3399	3318	3239	3147	3033	2833	2537	1947	1267	581

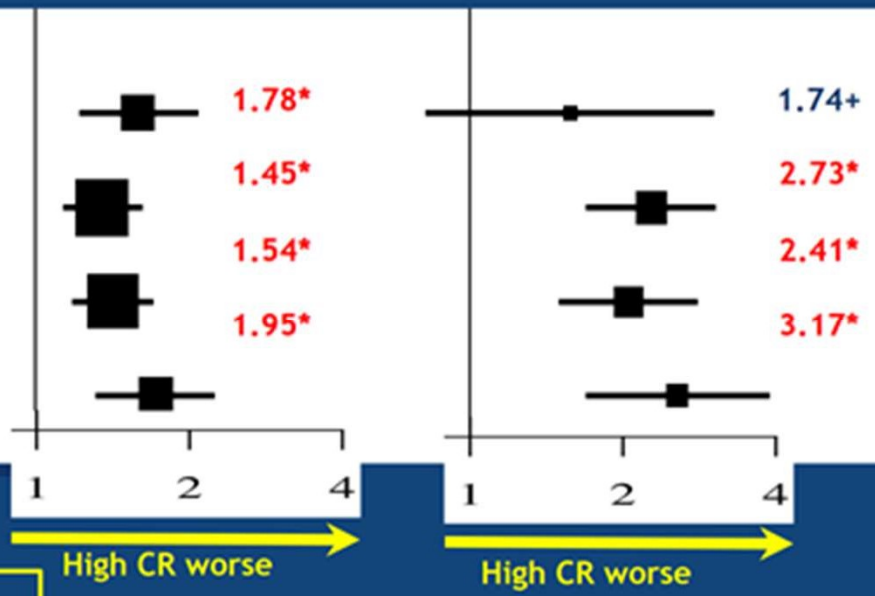
Sparano et al. N Engl J Med 2018; 379(2):111-121

TAILORx Results: Association between continuous RS 11-25 and 9 year distant recurrent rate stratified by age

TAILORx: Impact of Clinical Risk (CR) on Prognosis by RS Group

(N=9427) 30% clinical high risk & 70% clinical low risk

Grouped by RS	Total #/#IDFS/DR events	IDFS Hazard Ratio	DRFI Hazard Ratio
All Patients (n=9427)			
RS <= 10: Endocrine Therapy	1572/176/ 30	1.78*	1.74+
RS 11–25: Endocrine Therapy	3282/422/127	1.45*	2.73*
RS 11–25: Chemoendocrine Therapy	3214/389/113	1.54*	2.41*
RS > 25: Chemoendocrine Therapy	1359/184/ 96	1.95*	3.17*



Multivariate model for distant recurrence in RS 11-25 group:
(N=6496 cases and 240 distant recurrences):

- Clinical risk: HR for high vs. low risk 2.42, p<0.001
- Continuous RS: HR 1.08, p<0.001 (HR for a 1 point higher RS)

Hazard ratio > 1 - high clinical risk worse
+95% CI overlap 1
*95% CI don't overlap 1

Sparano et al. N Engl J Med 2019;380(25):2395-2405.

Clinical Risk

Low Clinical Risk:

- Tumor <3cm + Low Grade
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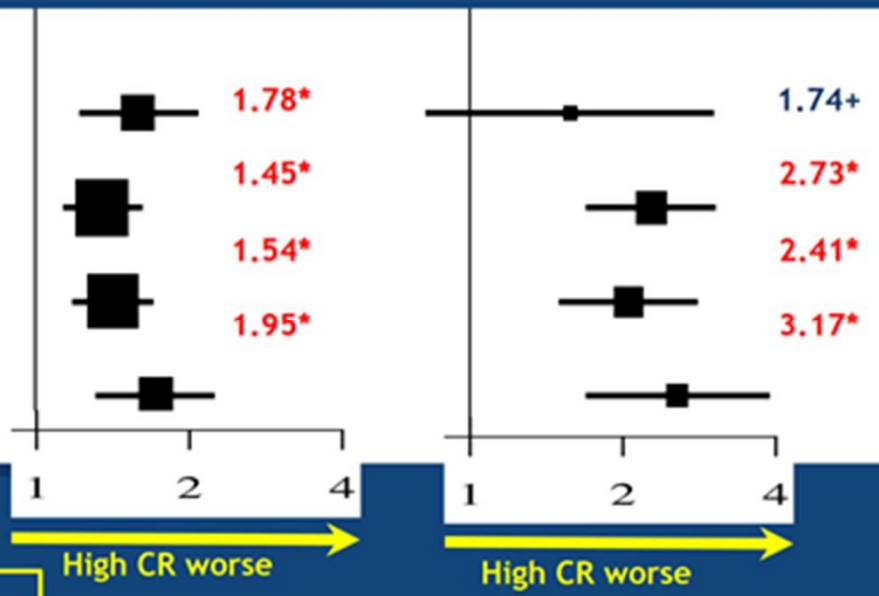

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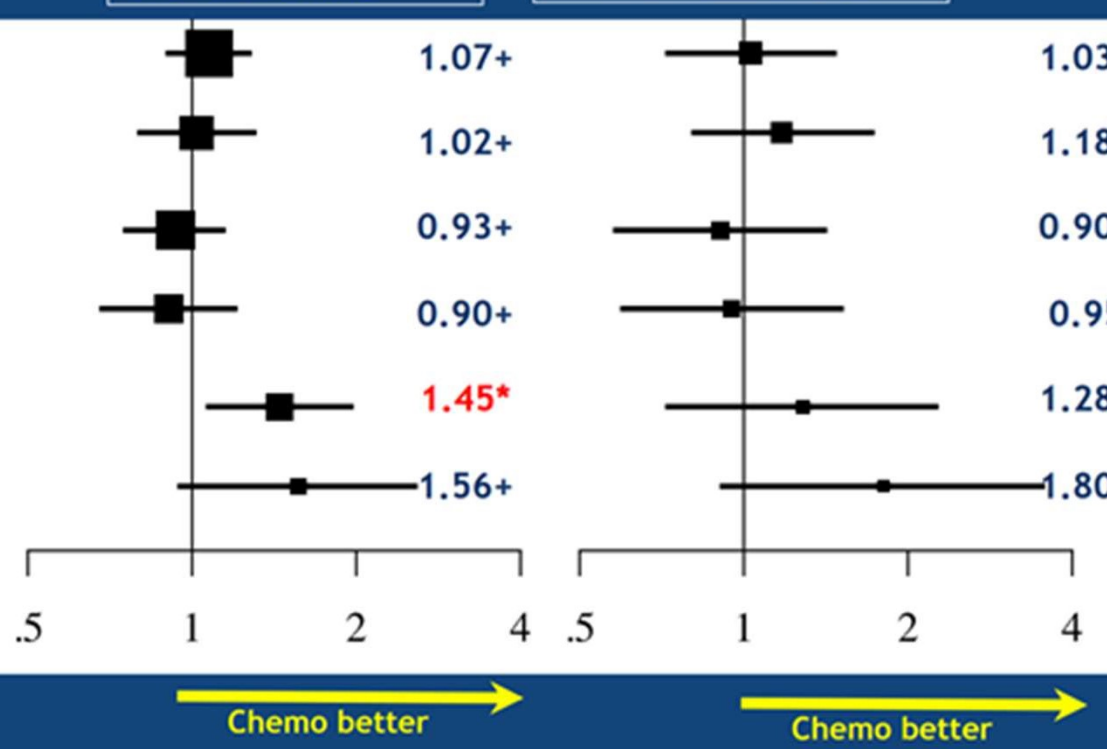
Sparano et al. N Engl J Med 2019;380(25):2395-2405.

TAILORx: Impact of Clinical Risk (CR) on Prediction of Chemotherapy Benefit by Age in RS 11-25 Group (ET vs. Chemo +ET)

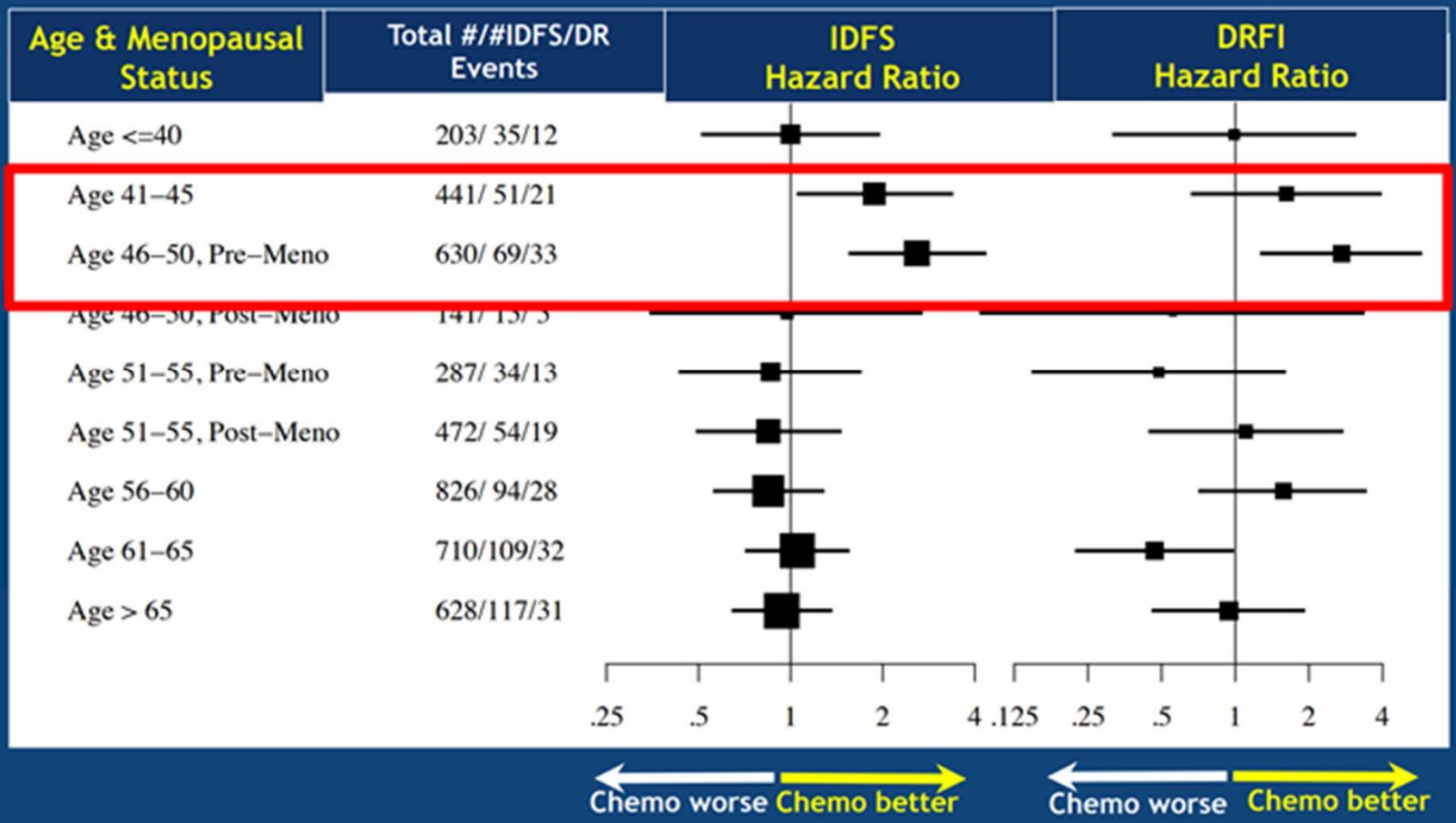
Grouped by Clinical Risk and Age	Total #/#IDFS/DR events	IDFS Hazard Ratio	DRFI Hazard Ratio
All Patients, Low Clinical Risk	4799/541/129	1.07+	1.03+
All Patients, High Clinical Risk	1697/270/111	1.02+	1.18+
Age > 50, Low Clinical Risk	3173/361/ 80	0.93+	0.90+
Age > 50, High Clinical Risk	1180/204/ 73	0.90+	0.95
Age <= 50, Low Clinical Risk	1626/180/ 49	1.45*	1.28+
Age <= 50, High Clinical Risk	517/ 66/ 38	1.56+	1.80+



Hazard ratio > 1 - chemo better
+95% CI overlap with 1
*95% CI don't overlap 1

Sparano et al. N Engl J Med 2019;380(25):2395-2405.

TAILORx: Exploratory Analysis - Impact of Age and Menopausal Status on Chemotherapy Benefit for RS 16-25



Sparano et al. N Engl J Med 2019;380(25):2395-2405.

TAILORx – ITT Population: Potential Chemotherapy benefit in women ≤ 50 yrs (N=2216) in RS 11-25

- **RS 16-25 - some chemo benefit**
  - RS 16-20: 9% fewer IDFS events, including 2% fewer distant recurrences
  - RS 21-25: 6% fewer IDFS events, mainly consisting of fewer distant recurrences
- **RS 0-15 - good prognosis with endocrine therapy**
  - 3% distant recurrence with ET alone
  - no evidence for chemo benefit in RS 11-15

TAILORx: CTS5 in All Patients and According to Subgroups

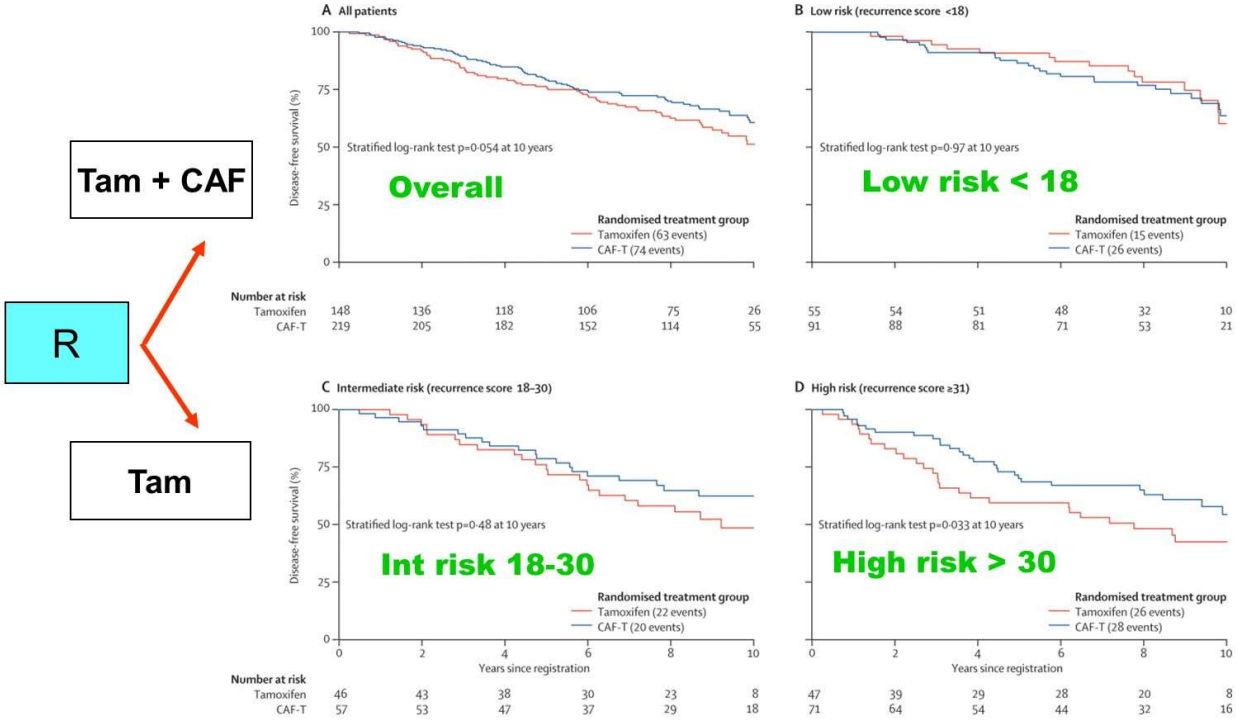
CTS5	RS	Treatment	HR	*p*-value
All patients (n = 7,353)	0-100	ET/CET	1.57	<0.0001
Arm A (n = 1,323)	0-10	ET	1.34	0.19
Arm B (n = 2,746)	11-25	ET	1.50	0.002
Arm C (n = 2,655)	11-25	CET	1.56	0.0003
Arm D (n = 629)	26-100	CET	1.90	0.004
Age ≤50 years (n = 2,259)	0-100	ET/CET	1.35	0.046
Age >50 years (n = 5,094)	0-100	ET/CET	1.78	<0.0001

ET = endocrine therapy; CET = chemo-ET

- Overall, CTS5 was highly prognostic for late distant recurrence (DR) stratified for assigned chemotherapy arm (HR = 1.57, $p < 0.0001$).
- Looking at each arm separately, CTS5 did not predict late DR in women with RS 0-10 and ET (arm A), but provided strong prognostic information for late DR in arms B (RS 11-25, ET), C (RS 11-25, CET), and D (RS 26-100, CET).
- CTS5 strongly predicted late DR in women >50 years (HR = 1.78, $p < 0.0001$), but to a lesser extent in women aged 50 years or younger (HR = 1.35, $p = 0.046$).

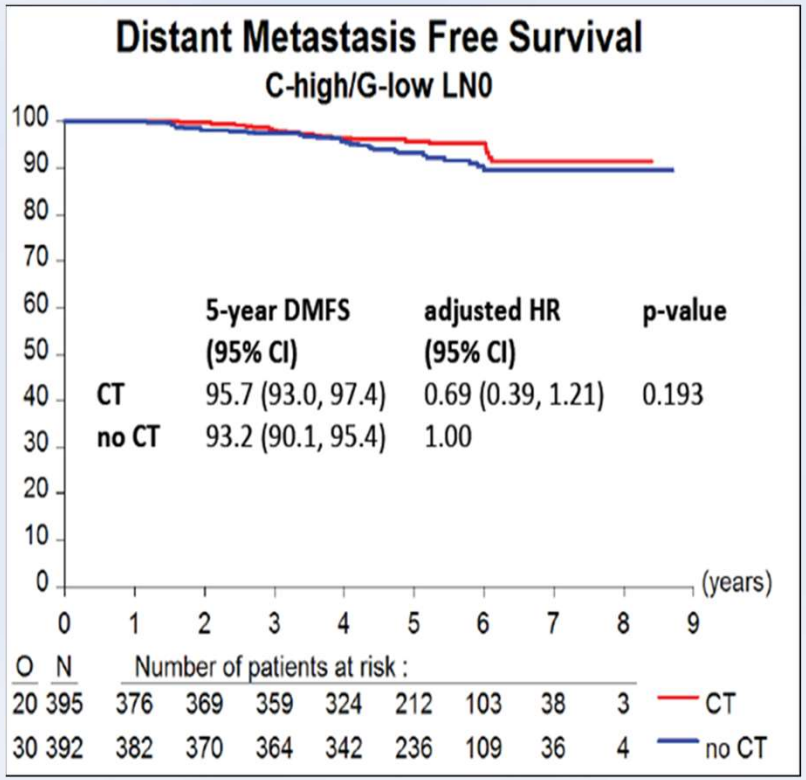
Sestak I et al. San Antonio Breast Cancer Symposium 2019;Abstract GS4-03.

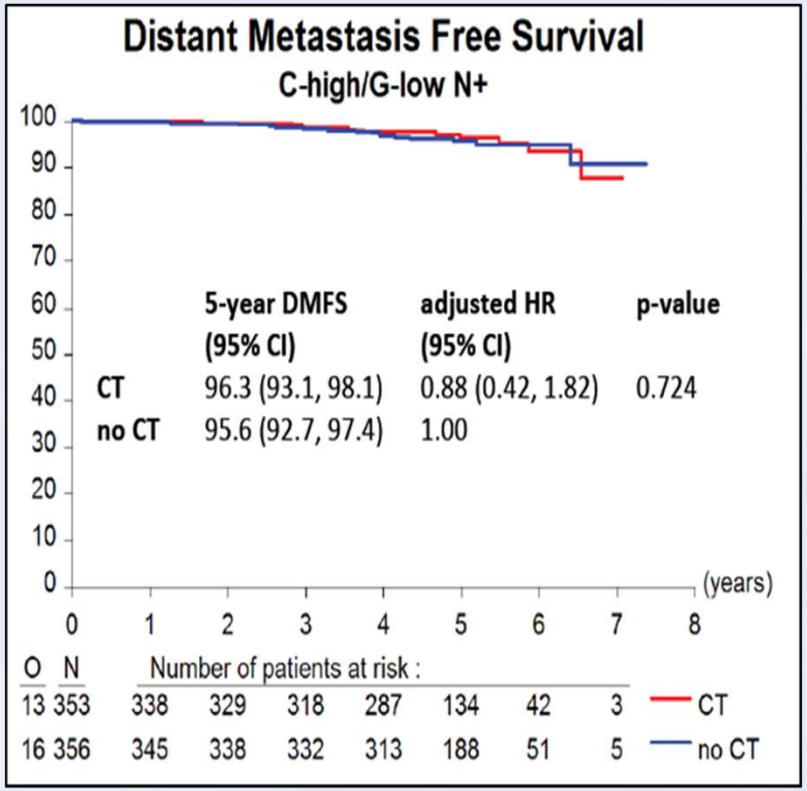
SWOG 8814: ER+ LN+, TAM ± CAF Chemotherapy



Albain KS, et al. *Lancet Oncol*. 2010;11(1):55-65.

MINDACT TRIAL





Take home message