

Genomic Assays in Early Breast Cancer

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Which patients with HR+/HER2- Breast Cancer Benefit from Adjuvant Chemotherapy?



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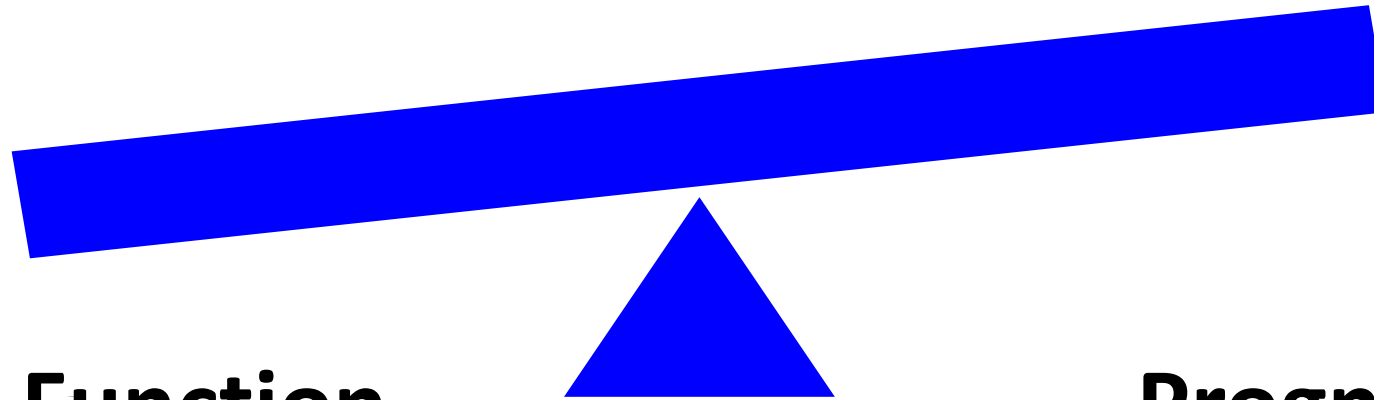
Adjuvant Systemic Therapy for Breast Cancer: Decision making

**Risks:
Adverse Events**

**Benefits:
Risk Reduction**

**Organ Function,
Age, Co-morbidities**

**Prognostic &
Predictive Factors**



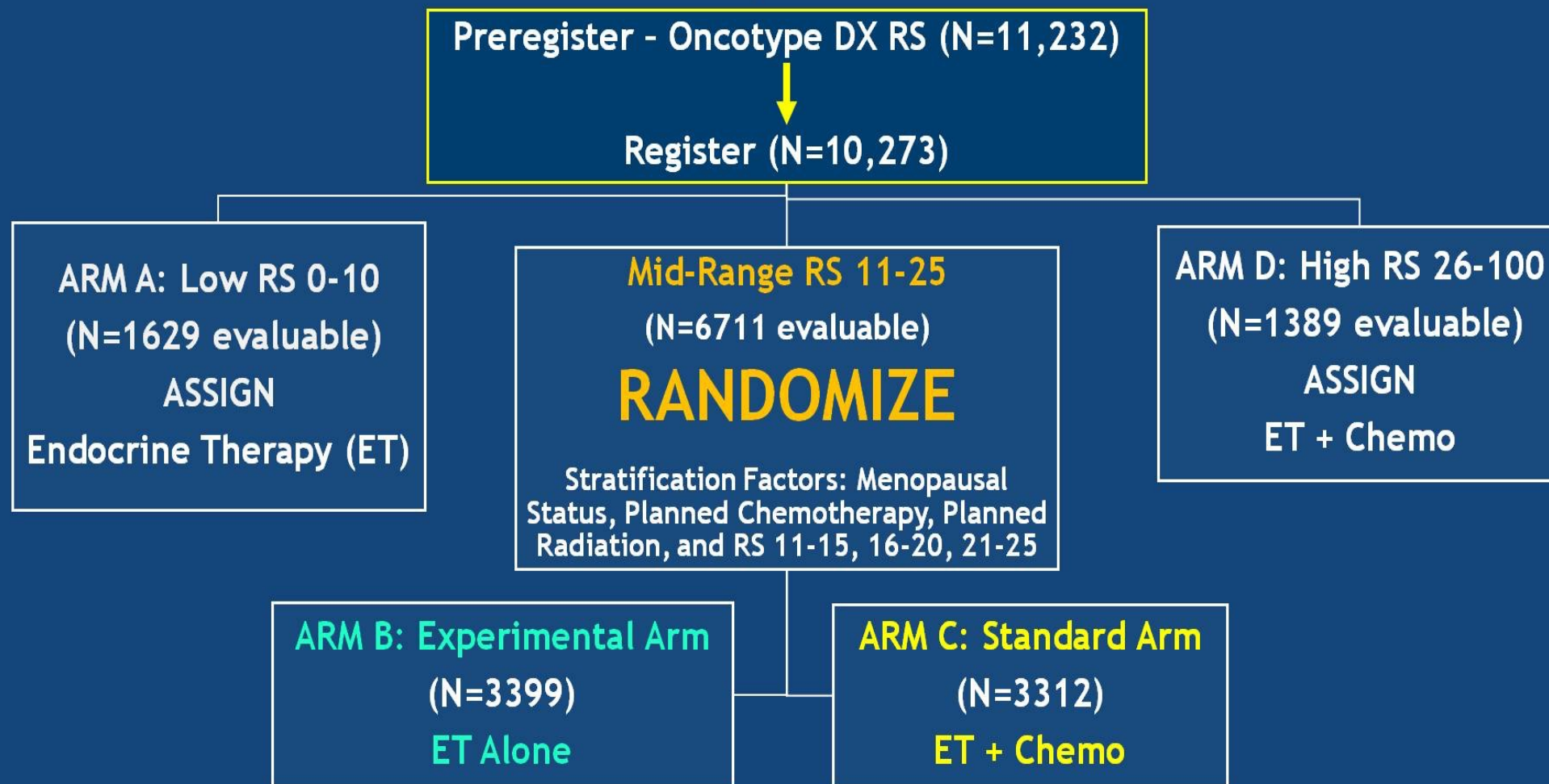
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TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010



TAILORx Results - ITT Population: All Arms (A,B,C & D)



9-Year Event Rates

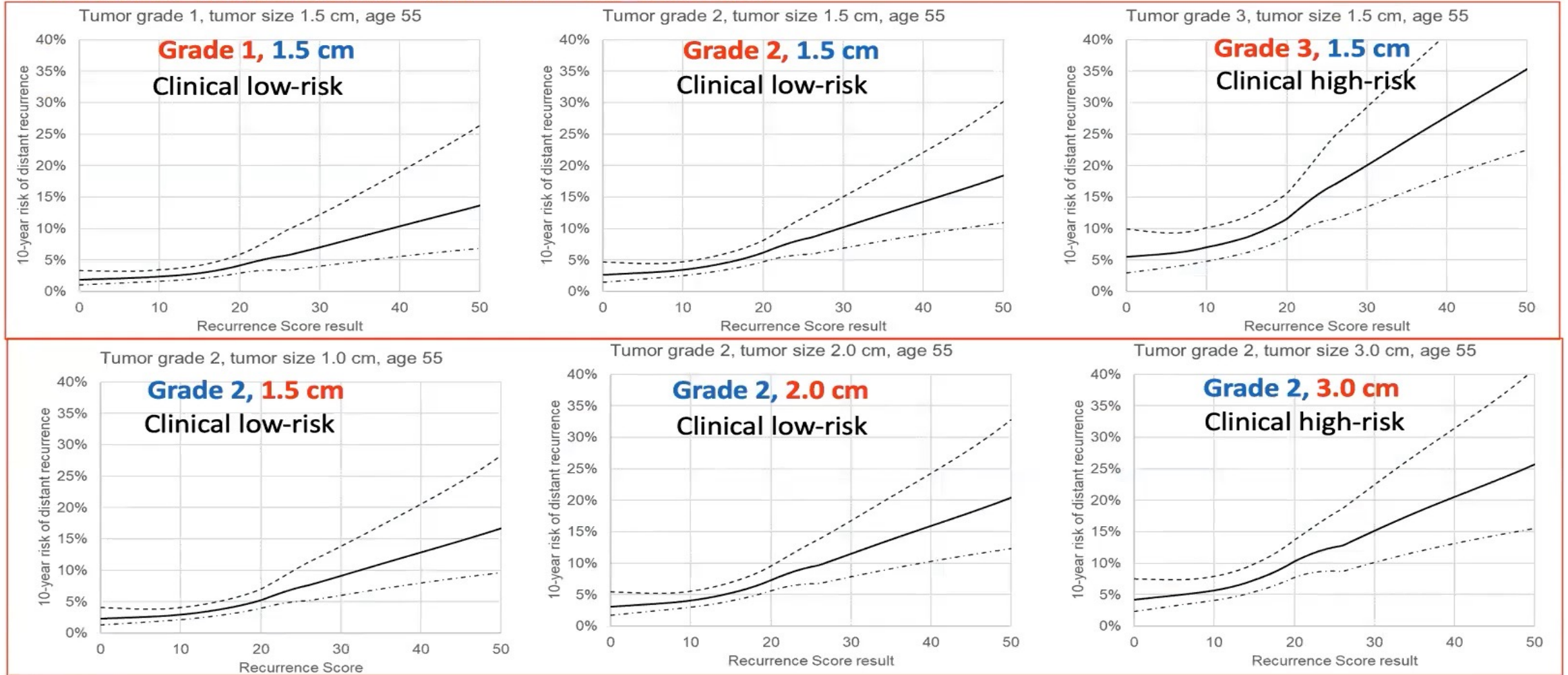
- **RS 0-10 (Arm A)**
 - 3% distant recurrence with ET alone
- **RS 11-25 (Arms B & C)**
 - 5% distant recurrence rate overall
 - $\leq 1\%$ difference for all endpoints
 - IDFS (83.3 vs. 84.3%)
 - DRFI (94.5 vs. 95.0%)
 - RFI (92.2 vs. 92.9%)
 - OS (93.9 vs. 93.8%)
- **RS 26-100 (Arm D)**
 - 13% distant recurrence despite chemo + ET

Adding in Clinical Risk Can Inform Individualized Risk: Women ≤ 50 yrs & RS 16-25 Stratified by RS and Clinical Risk

	Estimated Absolute Chemo Benefit <u>Not Stratified</u> by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit <u>Stratified</u> by Clinical Risk
RS 16-20 (N=886)	$\Delta +1.6\%$ (\pm SE 1.9%)	Low	671 (76%)	$\Delta -0.2\%$ (\pm SE 2.1%)
		High	215 (24%)	$\Delta +6.5\%$ (\pm SE 4.9%)
RS 21-25 (N=476)	$\Delta +6.5\%$ (\pm SE 3.7%)	Low	319 (67%)	$\Delta +6.4\%$ (\pm SE 4.9%)
		High	157 (33%)	$\Delta +8.7\%$ (\pm SE 6.2%)

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19
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 *Low Risk = Tumor < 1 cm & high grade; Tumor < 2 cm & int. grade; Tumor < 3 cm & low grade

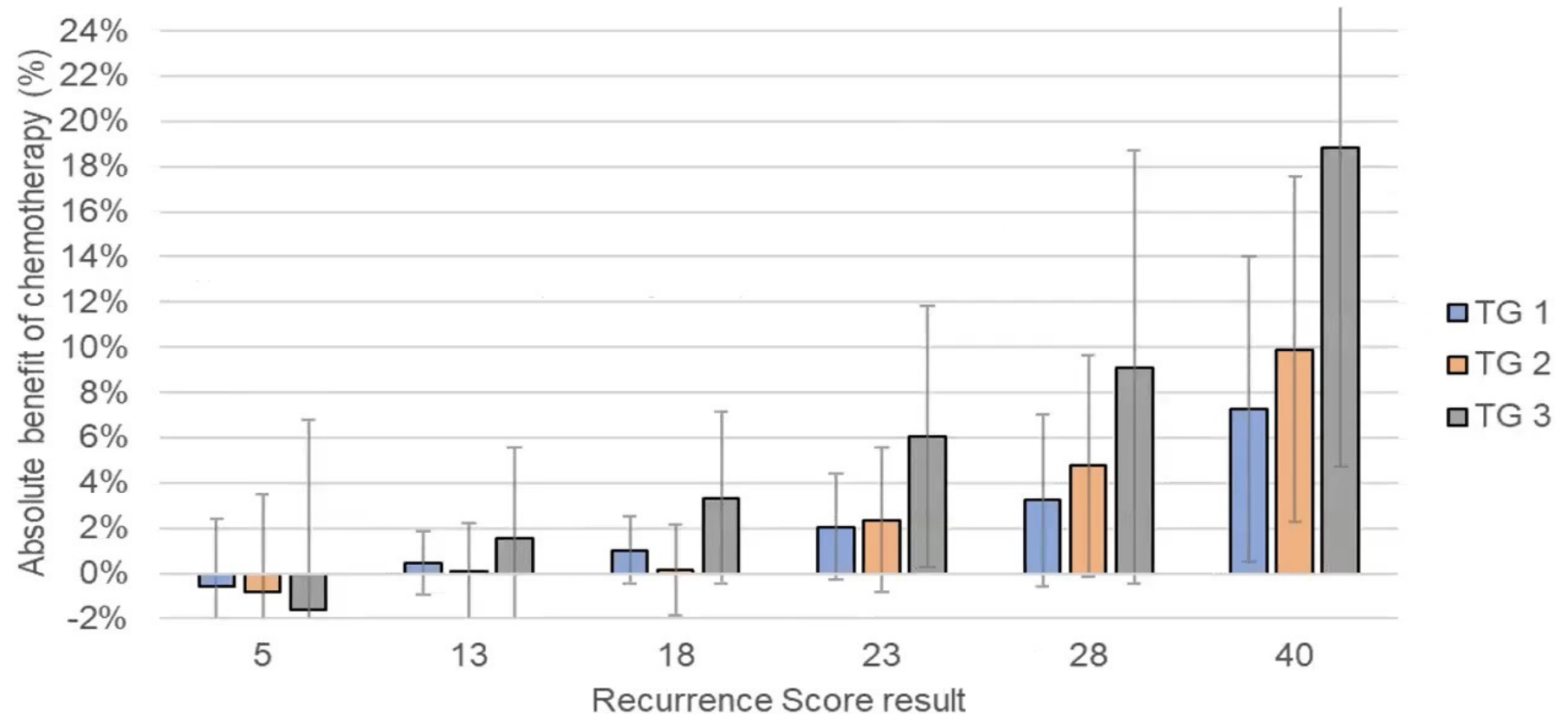
Results – prognosis: RSClin™ 10-year distant recurrence risk estimates (95% CI) Impact of tumor grade and size – 55 year old



Results—prediction: RSClin™ estimate of absolute CT benefit at 10 years (95% CI) Tumor grade series

Tumor size 1.5 cm, age 55

- Greater CT benefit with higher RS irrespective of grade.
- More absolute CT for higher grade tumors due to the higher underlying recurrence risk



Slide 9

RSCLin: Tool Available for patients with HR+/HER2-, LN- Breast Cancer

RSCLin™ Educational Tool

User Input

14

Oncotype DX
Breast Recurrence Score® Result

Tumor Size (cm): 2.2
Tumor Grade (Differentiation): 2
Planned Hormonal Treatment: Tamoxifen
Patient Age At Surgery: 46

Calculation Estimates

When patient specific characteristics are added to the Oncotype DX Breast Recurrence Score result, the following risk estimate provide additional information on your patient:

Individualized distant recurrence risk at 10 years

7% (95% CI: 5% – 9%)

Individualized absolute chemotherapy benefit

<1% (95% CI: -3% – 4%)

- ✓ Important Considerations:
- ✓ Only applies to node-negative disease
- ✓ Subgroups limited, such as very young women 4.6% in TAILORx
- ✓ No validation set for prediction in patients with node-negative breast cancer

RxPONDER Schema

Key Entry Criteria

- Women age ≥ 18 yrs
- ER and/or PR $\geq 1\%$, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

R
E
G
I
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Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

R
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N = 5,000 pts

Arm 1:
Chemotherapy Followed by
Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

Stratification Factors

Recurrence Score: 0-13 vs. 14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

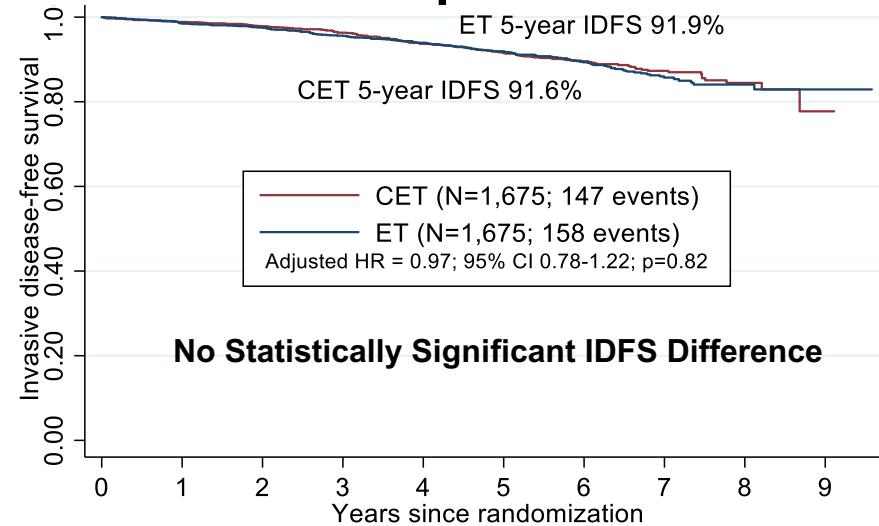


Baseline Characteristics by Treatment Arm

Baseline variable	Endocrine Therapy (n=2,506)	Chemotherapy (n=2,509)	Overall (n=5,015)
Race			
White	64.9%	66.4%	65.7%
Black	4.8%	5.1%	5.0%
Asian	6.8%	6.1%	6.5%
Other/Unknown	23.5%	22.3%	22.9%
Hispanic			
Yes	13.0%	11.9%	12.4%
No	67.6%	68.9%	68.3%
Unknown	19.4%	19.3%	19.3%
Menopausal status			
Premenopausal	33.2%	33.2%	33.2%
Postmenopausal	66.8%	66.8%	66.8%
Recurrence Score			
RS 0-13	42.7%	42.9%	42.8%
RS 14-25	57.3%	57.1%	57.2%
Nodal Dissection			
Full ALND	62.7%	62.5%	62.6%
Sentinel nodes only	37.4%	37.5%	37.4%
Positive Nodes			
1 node	65.9%	65.0%	65.5%
2 nodes	24.9%	25.7%	25.3%
3 nodes	9.2%	9.2%	9.2%
Grade			
Low	24.6%	24.7%	24.7%
Intermediate	64.1%	66.1%	65.1%
High	11.3%	9.2%	10.3%
Tumor size			
T1	58.5%	57.7%	58.1%
T2/T3	41.5%	42.3%	41.9%

IDFS Stratified by Menopausal Status

Postmenopausal

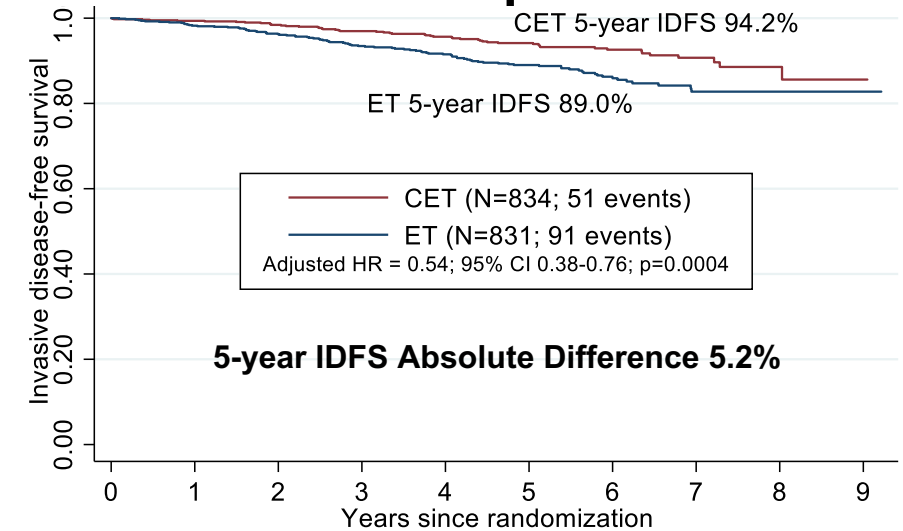


Number at risk										
CET	1675	1514	1400	1268	1113	943	585	287	88	3
ET	1675	1567	1462	1308	1167	975	601	298	104	9

IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Premenopausal



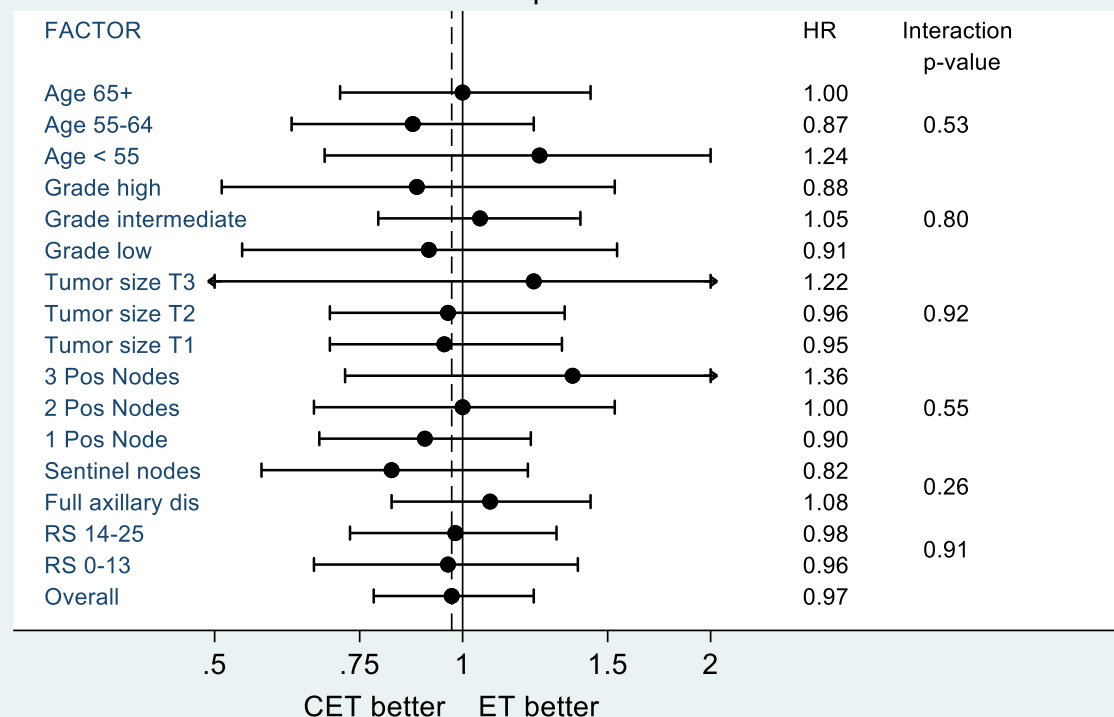
Number at risk										
CET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2

IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

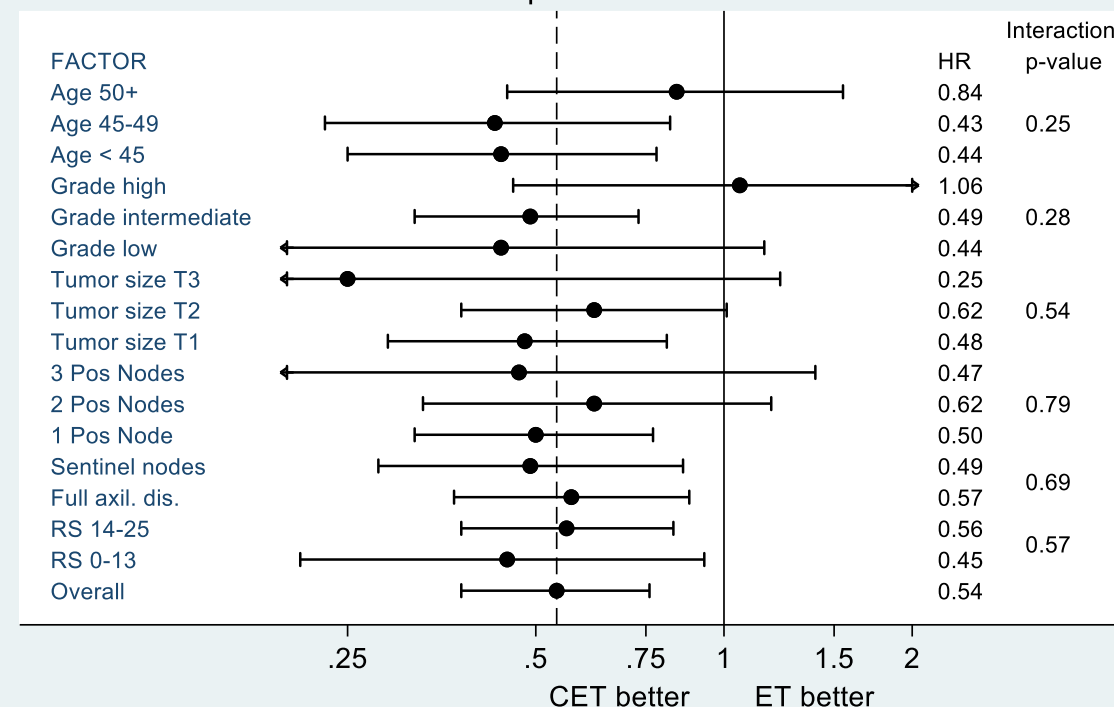
Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

Forest Plots of IDFS by Menopausal Status

Forest Plot of IDFS CET vs. ET Hazard Ratio and 95% CI
Postmenopausal Women



Forest Plot of IDFS CET vs. ET Hazard Ratio and 95% CI
Premenopausal Women



Landmarked Exploratory Analysis for IDFS in Premenopausal Women on Endocrine Therapy arm:
Ovarian Function Suppression (n=126) vs. no Ovarian Function Suppression (n=647) at 6 months: HR 0.73 (95% CI: 0.39-1.37), p=0.33

RxPONDER Conclusions

- ✓ **Postmenopausal women with 1-3 positive nodes and RS 0-25 can likely safely forego adjuvant chemotherapy without compromising IDFS**
 - ✓ **This will save tens of thousands of women the time, expense, and potentially harmful side effects that can be associated with chemotherapy infusions**
- ✓ **Premenopausal women with positive nodes and RS 0-25 likely benefit significantly from chemotherapy**



TransATAC:

Not All Genomic Assays Are the Same!

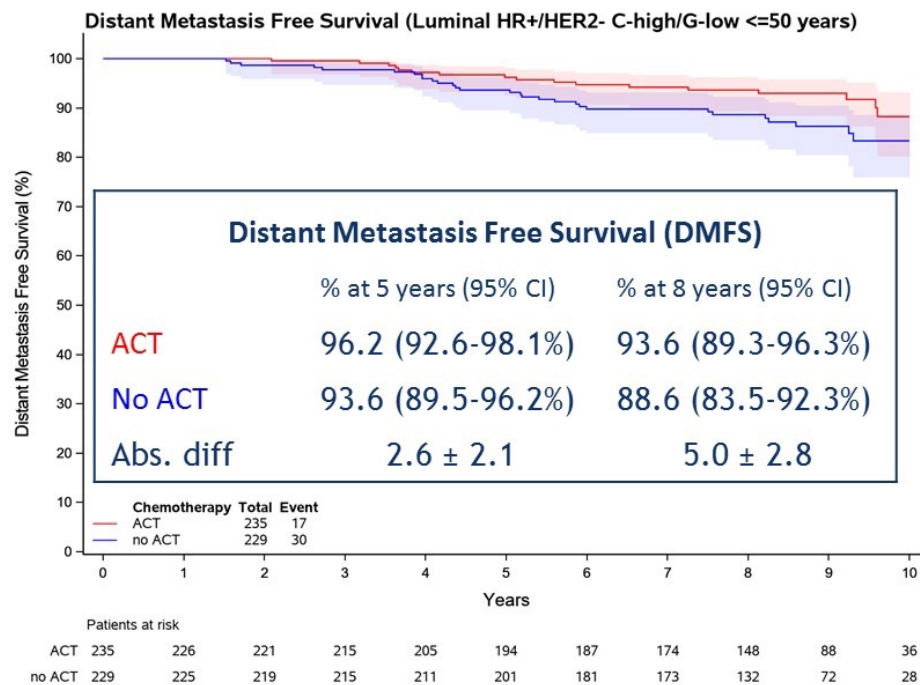
Table 3. Univariate HRs and C Indexes for All Prognostic Signatures According to Nodal Status During Years 5 to 10

Gene Signature	Patient Group			
	Node-Negative Disease (n = 535)		Node-Positive Disease (n = 154)	
	HR (95% CI) ^a	C Index (95% CI)	HR (95% CI) ^a	C Index (95% CI)
CTS	1.95 (1.43-2.65)	0.721 (0.654-0.788)	1.61 (1.05-2.47)	0.644 (0.534-0.753)
IHC4	1.59 (1.16-2.16)	0.660 (0.576-0.745)	1.20 (0.79-1.81)	0.579 (0.460-0.697)
RS	1.46 (1.09-1.96)	0.585 (0.467-0.702)	1.24 (0.81-1.90)	0.555 (0.418-0.693)
BCI	2.30 (1.61-3.30)	0.749 (0.668-0.830)	1.60 (1.04-2.47)	0.633 (0.514-0.751)
ROR	2.77 (1.93-3.96)	0.789 (0.724-0.854)	1.65 (1.08-2.51)	0.643 (0.528-0.758)
EPclin	2.19 (1.62-2.97)	0.768 (0.701-0.835)	1.87 (1.27-2.76)	0.697 (0.594-0.799)

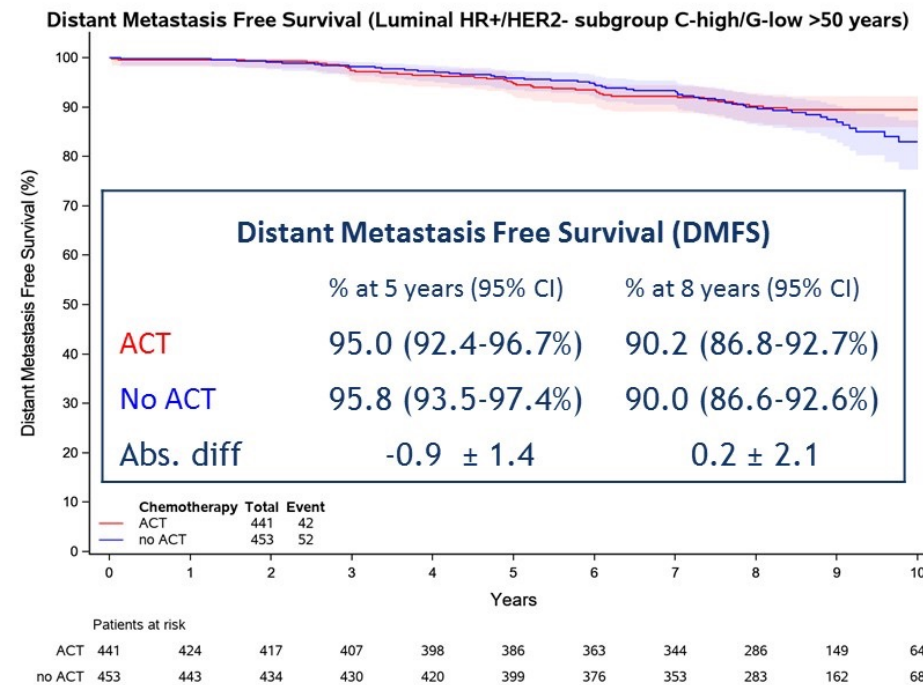
DMFS in C-High / G-Low risk patients with luminal cancers (**HR+/HER2-**) stratified by **age** **ITT** population

Age ≤50 years

Age >50 years



5% difference

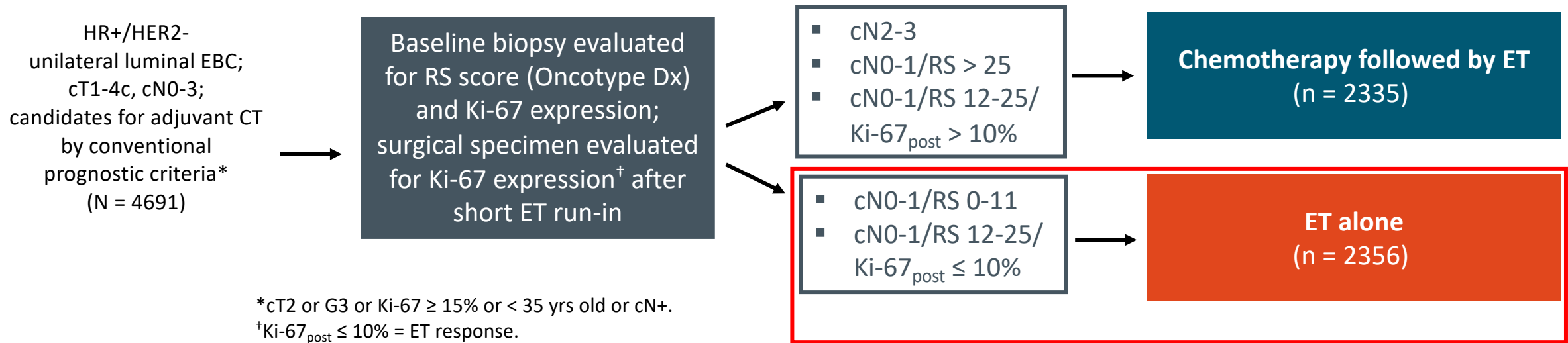


NO difference

Role of genomic assays as indicators of neoadjuvant response in HR+/HER2-?

ADAPT HR+/HER2-: Adjuvant ET ± Chemotherapy in Intermediate/High-Risk, HR+/HER2- Luminal EBC

- 2-part, prospective phase III trial
 - Part 1: Current analysis evaluated prognostic impact of RS < 26 and Ki-67 decrease after short-course of preoperative ET in the ET alone arm and is not a randomized comparison



- **Primary endpoint: 5-yr iDFS**

- **Part 1: noninferiority for pN0-1/RS 12-25/Ki-67_{post} ≤ 10% vs pN0-1/RS 0-11**

- Key secondary endpoints: dDFS, OS, translational research

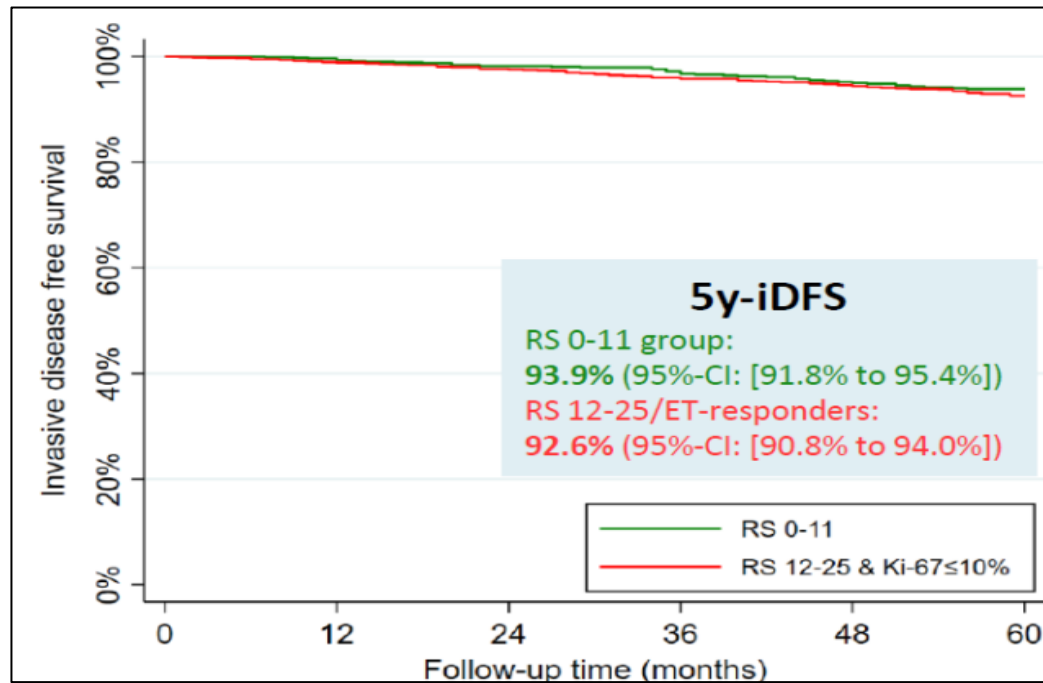
ADAPT HR+/HER2-: Baseline Characteristics

Characteristic	ITT Population of ET Alone Patients (n = 2290)	
	pN0-1/RS 0-11 (n = 868)	pN0-1/RS 12-25/ Ki-67 _{post} ≤ 10% (n = 1422)
Median age, yrs	57	58
▪ ≤ 50 yrs of age, n (%)	260 (30.0)	332 (23.3)
Premenopausal status, n (%)	300 (34.6)	374 (26.3)
Tumor stage pT2-4, n (%)	300 (34.6)	543 (38.2)
Nodal status pN1, n (%)	208 (24.0)	389 (27.4)
Grade 3, n (%)	114 (13.1)	306 (21.5)
Median Ki-67, %	15	15
Positive PgR, n (%)	823 (94.8)	1251 (88.0)

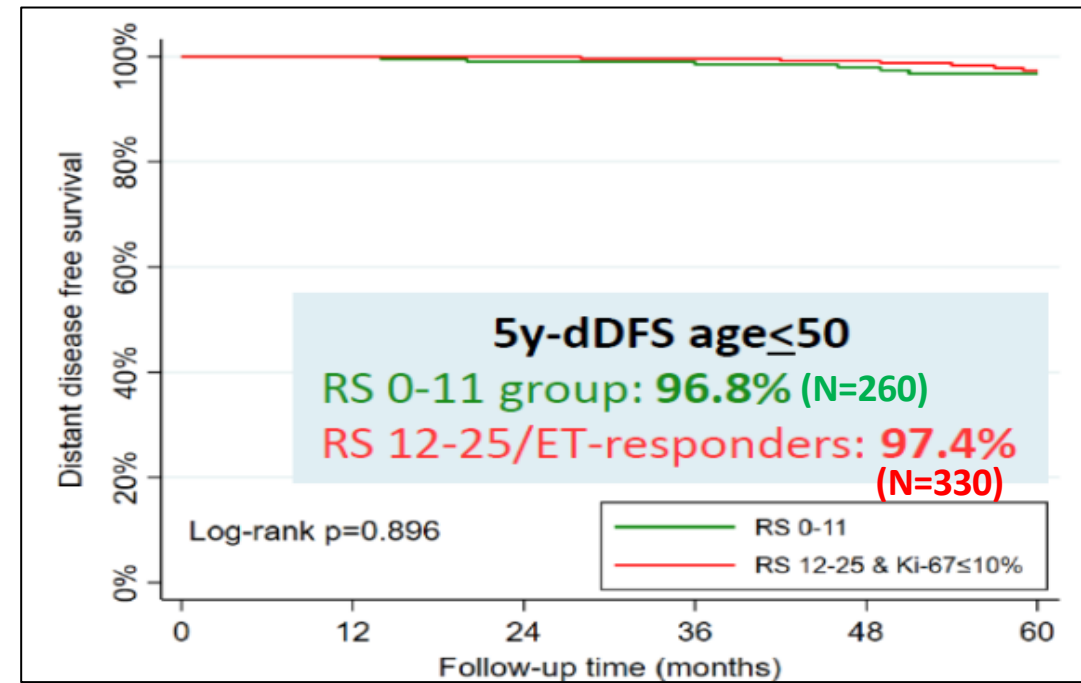
- Median follow-up: 60 mos (range: 0-91)

5-year iDFS not significantly different by non-inferiority threshold between the two RS cohorts overall or by age groups

5-year iDFS whole ITT population

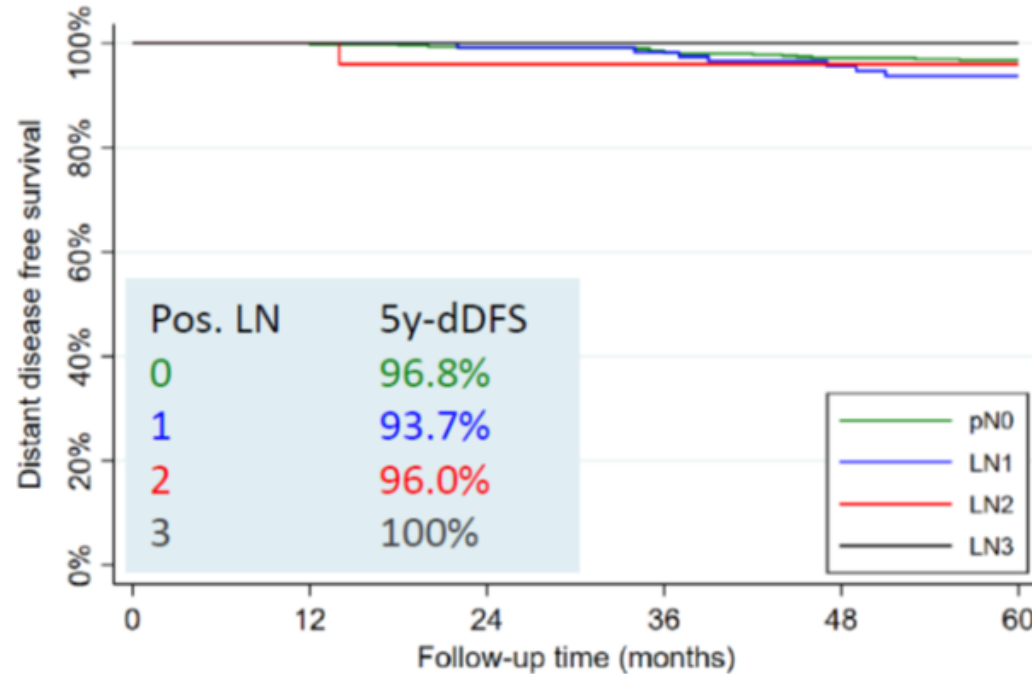


Distant disease-free survival age ≤ 50



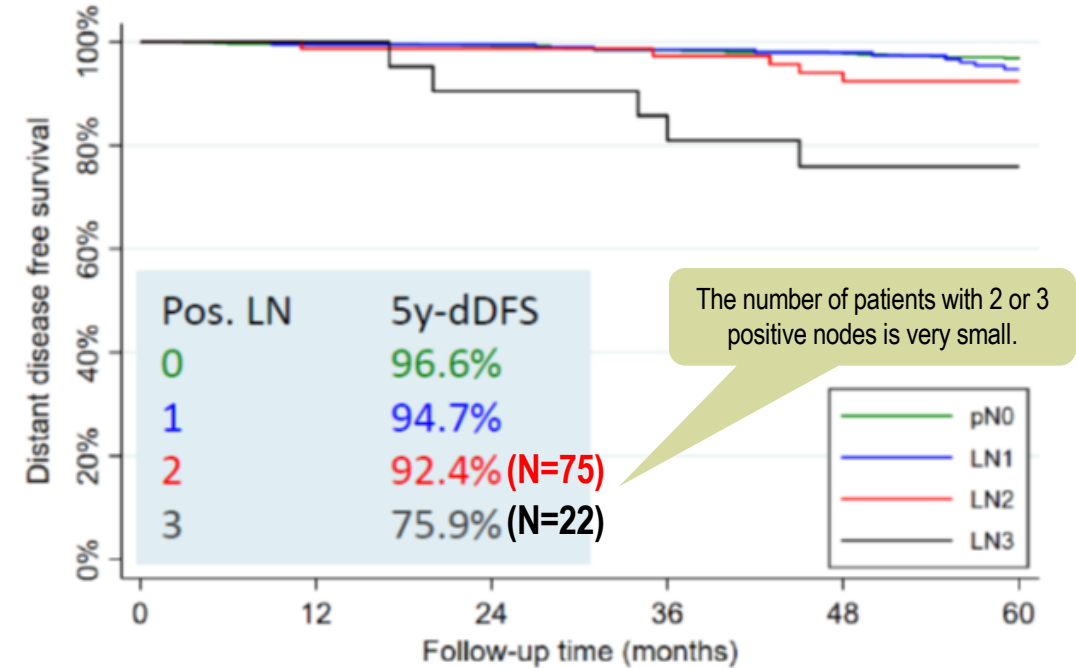
Distant disease-free survival by number of nodes involved in the two Recurrence Score cohorts

RS 0-11



Number at risk						
pN0	657	611	552	520	478	339
LN1	126	122	120	113	103	74
LN2	29	25	23	22	22	20
LN3	10	10	10	10	9	6

RS 12-25/Ki67 response



Number at risk						
pN0	1027	946	840	770	714	520
LN1	219	204	199	183	174	117
LN2	75	73	72	68	58	43
LN3	22	22	19	18	15	9