Breast Cancer Debate of the Year

OFFICIAL best of SABCS

INSTITUT JULES BORDET

H.U.B HÔPITAL UNIVERSITAIRE DE BRUXELLES ACADEMISCHE ZIEKENHUIS BRUSSEL

BSMO

LICENSED BY ENCORE MEDICAL EDUCATION

The Motion :

Ovarian Function Suppression and Aromatase Inhibitor can replace Adjuvant Chemotherapy

in a 41yr young lady with cT2N0, 27mm,
gr 2, invasive ductal carcinoma of the breast (Ki67 20%)

Debate: Adjuvant chemotherapy

= Cytotoxic anti-cancer?

= Cytotoxic ovarian suppression?

Yes, I am in favor of the motion

P. Neven

MBC UZ Leuven

2023: This is an important topic, indeed

Unmed Need in ER+ HER2 - EBC

ALLIANCE Breast Committee members ranking top clinical research priorities

Tailoring therapy by clinical & molecular assays → omit adj chemotherapy

Tailoring extended adjuvant ET (pT1-2N1a)
Neoadjuvant therapy
Adherence intervention studies to improve outcome with existing drugs through adherence

My disclosures

Financial: None

Bias: 1. MINDACT not in UZL: + adj CT in *clin low risk lum BrCa* [iNPI < 3.5]
2. GEP-believer in some clin high risk pt, also <51 yrs; in-house GEP (MP)

		70-gene prognosis signature (n=427)		Discordant findings, n (%), 95% CI, kappa
		Good (n=219)	Poor (n=208)	
Clinical risk (NPI guidelines) grade 1 and grade 3 lesions (n=223)				
Low (n=87)		72	15	31 (13·9),10·0–19·1, 0·7085
Moderate or high (n=136)		16	120	..
Clinical risk (NPI guidelines) grade 2 lesions (n=204)				
Low (n=161)	< 3.5	103	58	86 (42·2), 35·6–49·0, 0·0091
Moderate or high (n=43)	>3.4	28	15	..

Table: Grade 1 and 3 and grade 2 breast cancers assessed by NPI and the 70-gene signature

RASTER: 427 LN-neg EBC,
161 **gr 2 +** NPI < 3.5 (Clin Low Risk)
36% = MP-high

MINDACT
70-gene prognosis signature

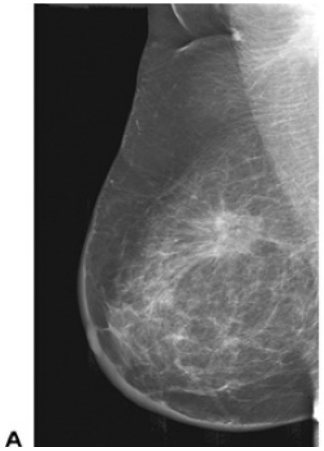
Bueno-de-Mesquita JM et al. Use of 70-gene signature to predict prognosis of patients with LN-neg breast cancer (RASTER). Lancet Oncol 2007; 8: 1079–87
P. Neven et al. Are gene signatures better than traditional clinical factors. Lancet Oncol 2008; 197-198
V. Van Belle et al. Qualitative assessment of the progesterone receptor and HER2 improves NPI. J Clin Oncol 2010 4129-34

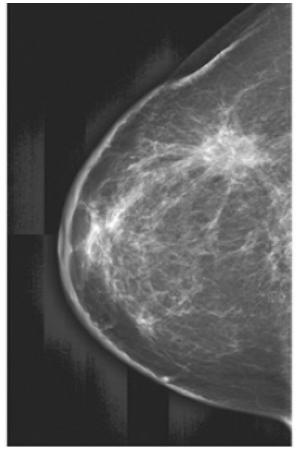
NPI = [0.2 x S] + N + G

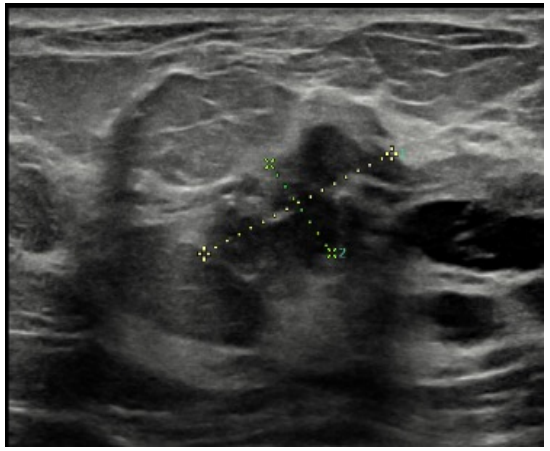
NPI = Nottingham Prognostic Index

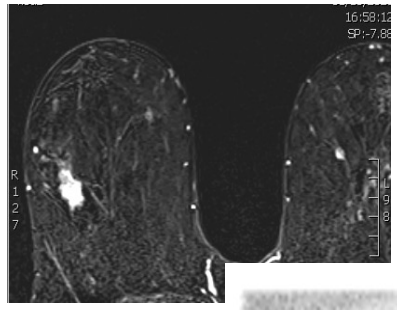
41yrs, fit, overweight

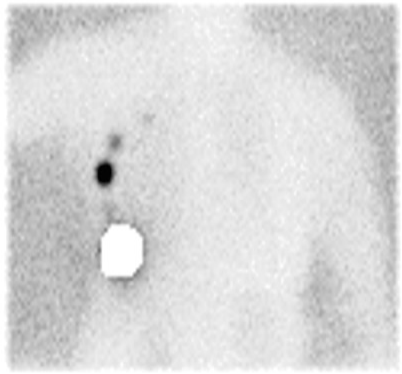
- **Screen detected mass** right breast
- Clinical examination:
  - Inspection: normal
  - Palpation:cnot well defined mobile mass, 10h, cT1N0M0
    Stopped oral CC-pill when CNB ‘cancer’











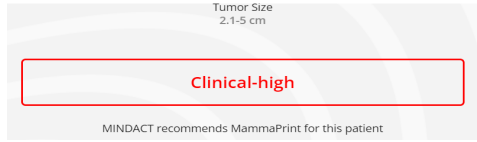
SLN mapping

WE + SLN : NST ductal adenoca
27mm; gr 2; mitotic score 1; Ki-20 %;
ER 8/8, PR 8/8, HER2 1+ (neg)
→pT2cN0 (sn); free margins; no-LVI

MOC/COM: Local radiotherapy
Anti-E: OFS + AI
(Bone agent)
IUD for contraception

Luminal B-like (borderline Ki-67)

NPI : 3,54 (intermediate risk)



Short discussion on 4m adj CT

Presentation outline :

ERA prior to GEP ←2019

Short discussion MOC/COM

ERA after GEP→2019

MINDACT & TAILORx

(The power of OFS + AI)

← 2019: lum B-like and 2 or more bad prognostic factors : Discuss 'adj CT-question'

Fill in: 41y, 27mm, LN-neg, grade 2, premenopausal, Ki-67 pos,
unknown mode detection, 5 yr tam, 3rd gen CT

Based on RWD

Results

Table | Curves | Chart | Texts | Icons

Select number of years since surgery you wish to consider:

5 | 10 | 15

This table shows the percentage of women who survive at least 10 years after surgery.

Treatment	Additional Benefit	Overall Survival %	Detected by	Screening	Symptoms	Unknown
Surgery only	-	85%	Surgery only	-		87%
+ Hormone therapy	3.9% (2.3% – 4.8%)	89%	+ Hormone therapy	3.3% (2.0% – 4.1%)		90%
+ Chemotherapy	3.1% (2.3% – 3.8%)	92%	+ Chemotherapy	2.6% (1.9% – 3.2%)		93%

If death from breast cancer were excluded, 98% would survive at least 10 years, and 2% would die of other causes.

Hormone (endocrine) therapy
= data only from the tamoxifen trials

MOC/COM UZ Leuven:
'borderline benefit of adj-CT'
To be discussed with patient but…

← 2019

Consider traditional clinical prognostic factors

ER & PR high

Screened breast cancer

Mitotic activity low

No LVI

Unifocal

CT-benefit PREDICT = **3.1 %** ~
-Detection mode +/- 0.5%
-Ki-67 +/- 1%

Can we trust *Ki-67/ Cut-off?

~ menstrual cycle; CC-stop

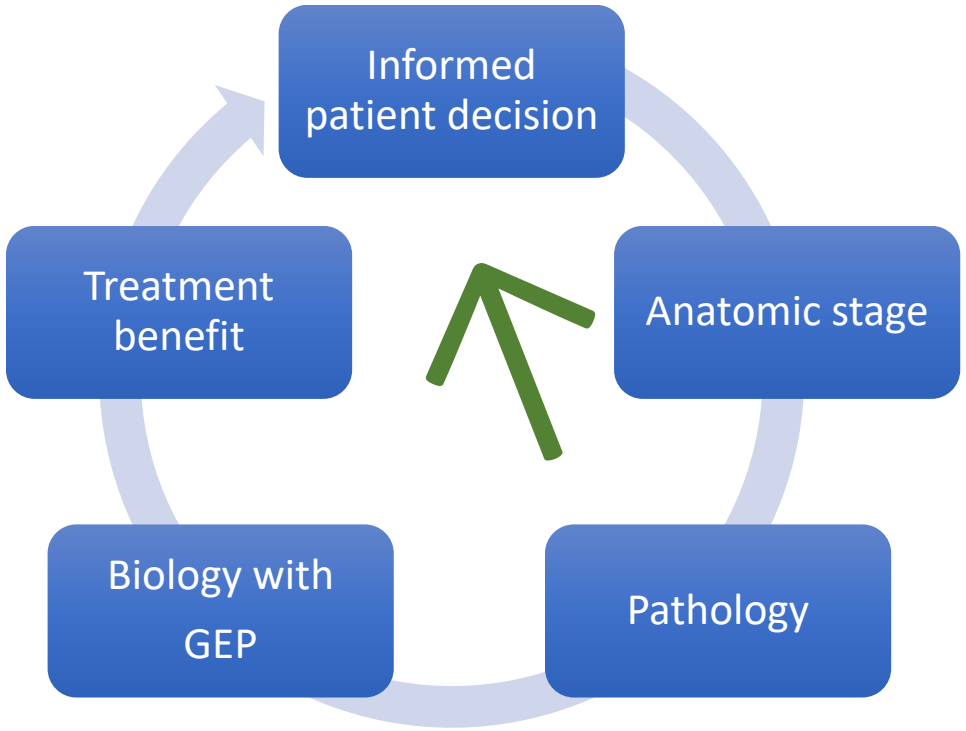
Horimoto et al. J Clin Path 2015 :Ki-67 : Higher expression on IHC in luteal phase.
Haynes P et al. NPJ Breast Cancer 2019: Menstrual cycle associated changes in hormone-related gene expression id ER-pos breast cancer

← 2019

1st fundamental question to consider CT in Lum ER+ HER2 neg EBC:

[prognostic] : Are there grade 2 pT2N0(sn) EBC with such a favorable outcome that benefit [predictive] of adj CT < side effects: Yes

adj CT > side effects: Yes



Recent Data

Text/SOFT

A large cohort without adj CT; 12yr DDFS > 90%

UZ Leuven database: 2000-2017 >5yr FU

[40-45y] ; grade 2 and **pT2**

199 no-adj chemotherapy: 3 metastatic events

43 adjuvant chemotherapy: 9 metastatic events

ERA after mature MINDACT & TAILORx data → 2019

mymammaprint

Tumor Size
2.1-5 cm

Clinical-high

MINDACT recommends MammaPrint for this patient

or Odx based on TAILORx!

MyMammaPrint.com

mammaprint®

It is recommended but…

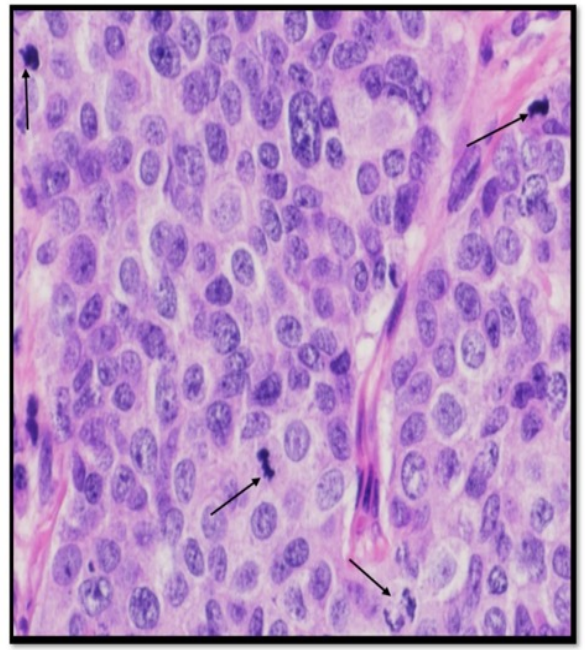
Sometimes not needed also in clinical high risk

Histopathology

Evaluation Oncotype DX® 21-Gene Recurrence Score and Clinicopathological Parameters: A single institutional experience

Tools to predict GEP results

Categories	Oncotype DX risk groups			
	Low Risk (0-10)	Intermediate risk (11-25)	High Risk (26-100)	X^2 *P*-value
Patient's Age (Years)				
<50	16 (17%)	56 (58%)	34 (25%)	1.1
≥50	65 (20%)	201(60%)	68 (20%)	0.6
Menopausal status				
Premenopausal	21 (17%)	74 (60%)	28 (23%)	0.4
Post-menopausal	60 (20%)	183 (60%)	64 (20%)	0.8
Tumour size (cm)				
≤ 2 cm	35 (18%)	111 (57%)	48 (25%)	2.3
> 2 cm	46 (19%)	146 (62)	44 (19%)	0.3
Tumour grade				
Grade 1	5 (20%)	20 (80%)	0 (0%)	104.1
Grade 2	63 (26%)	162 (67%)	16 (7%)	**<0.0001**
Grade 3	13 (8%)	75 (46%)	76 (46%)	
Mitoses score				
1	66 (28%)	167 (72%)	0 (0%)	146.6
2	11 (9%)	55 (47%)	52 (44%)	**<0.0001**
3	4 (5%)	35(44%)	40 (51%)	
Progesterone receptor status				
Negative ≤10	5 (4%)	55 (49%)	53 (47%)	66.6
Positive >10	76 (24%)	202 (64%)	39 (12%)	**<0.0001**



Supplementary figure 1: a reviewed BC case with many mitotic figures in one high power field.

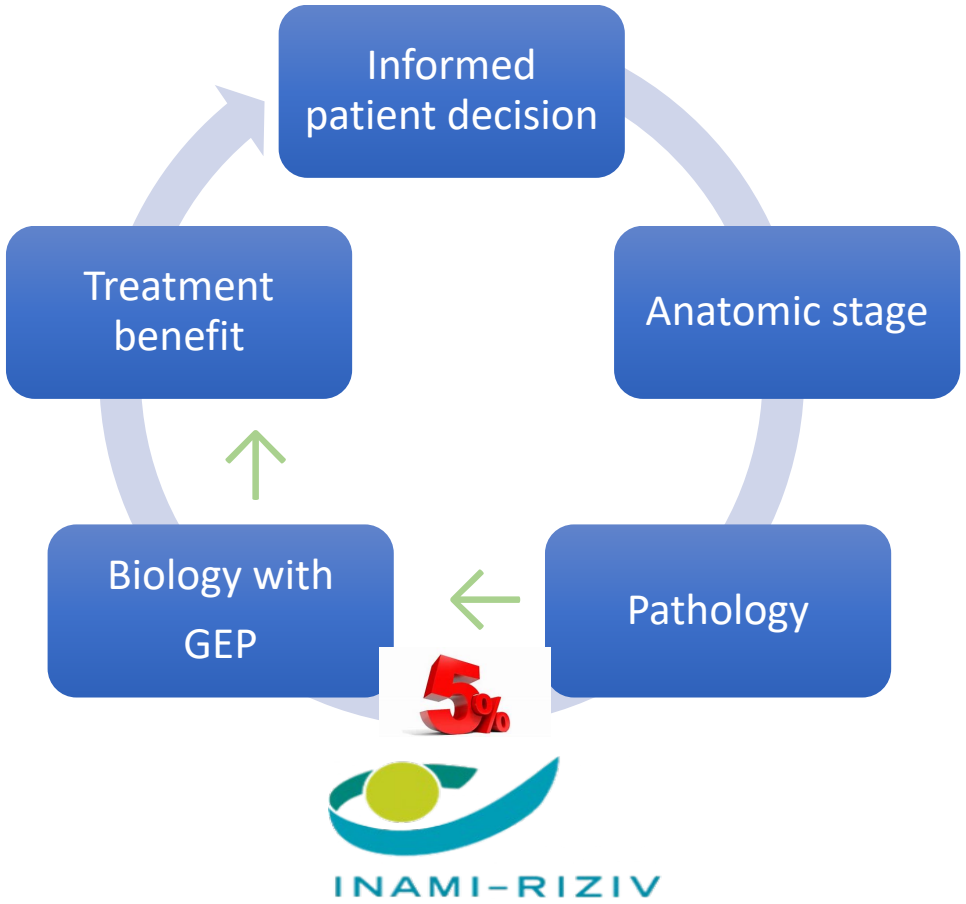
Relationship ODX risk and clinicopathological parameters
123 premenopausal luminal breast cancer

A. Lashen et al. 11 Jan 2023 ***https://doi.org/10.1111/his.14863***

The New Magee Equations estimating the Odx – RS
Slembrouck L. et al. Modern Pathology 2021

2nd fundamental question when testing/adding CT in Lum ER+ HER2 neg EBC: 41 yr gr 2 pT2N0(sn) EBC: RS 16-25/MP low?

Clin High Risk: How clin meaningful are CT-data by GEP (RCT)?



YES, UZL
GEP =
Addit Progn Tool
But Predictive?

From here onwards, the discussion might start→

… in premenopausal women with ER+ HER- EBC : 3 FACTS

FACT: GEP is developed in postmenopausal women

"premenopausal women remain an important subgroup for which recommendations based on GEP are ill-defined"

FACT: GEP results vary with menstrual cycle

"Further research on the reliability and interpretation of GEP in the premenopausal subgroup is necessary"

FACT: To predict CT-benefit, traditional clinicopathologic methods remain powerful with any GEP

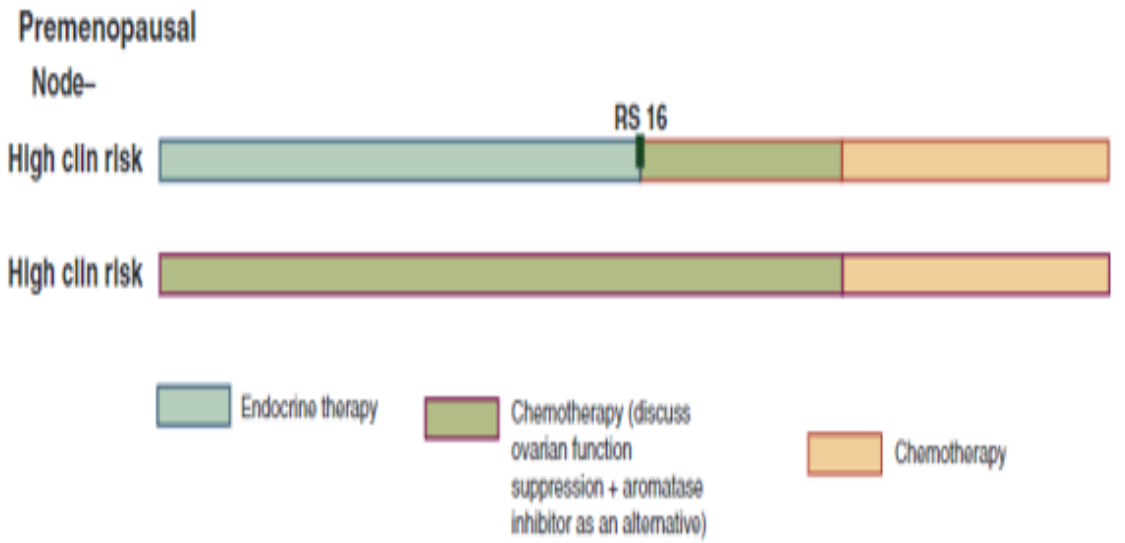
"a higher genomic risk can be insufficient predictive for CT-benefit over the best ET in <51 yrs"
→AS IN OUR PATIENT

With this knowledge…
and recent confusing guidelines

MyMammaPrint.com

mammaprint®

Evidence why better to discuss OFS + AI rather than chemotherapy



TAILORx data

MINDACT data

Piccart M, Kalinsky K. et al.

Ann Oncol 2022; 33: 668

41 yr; Gr 2; pT2N0(sn) ER+ HER2- = Clinical High Risk:
A critical interpretation of available CT-benefit data <51yrs

MammaPrint Genetic Low Risk = Adj CT if Genomic Low Risk

ASCO

Recommendation 1.9

If <51 yrs and clin high risk, don't use MammaPrint test to guide decisions for adj CT (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

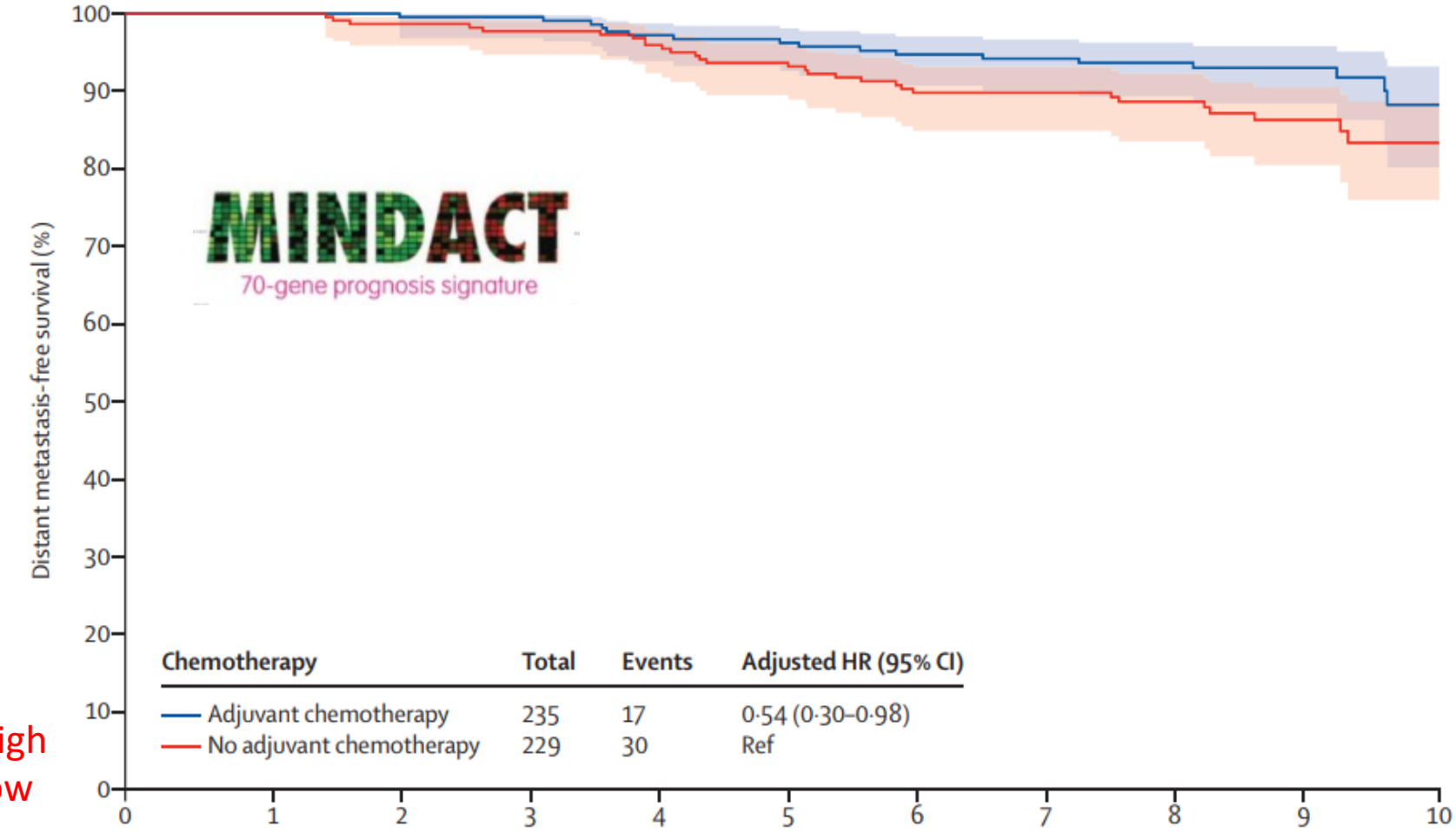
Think Twice When Giving Adj-CT

Because…

<51yrs : MammaPrint is out if Clin High & MP Low… because

In MINDACT there was a 5% benefit from adding CT to ET if < 51 years

So, Adj-CT



Clin High
MP Low

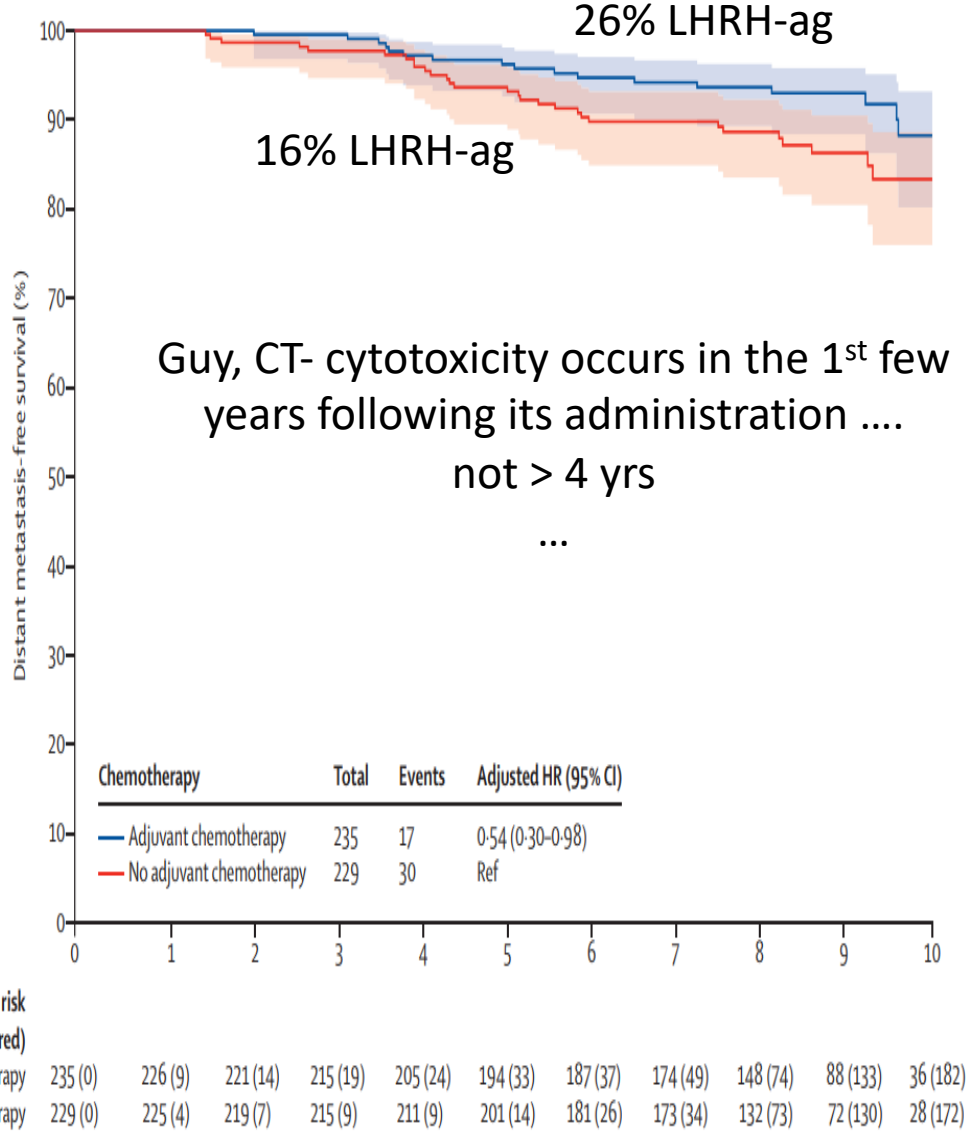
Number at risk (number censored)											
Adjuvant chemotherapy	235 (0)	226 (9)	221 (14)	215 (19)	205 (24)	194 (33)	187 (37)	174 (49)	148 (74)	88 (133)	36 (182)
No adjuvant chemotherapy	229 (0)	225 (4)	219 (7)	215 (9)	211 (9)	201 (14)	181 (26)	173 (34)	132 (73)	72 (130)	28 (172)

BUT

www.thelancet.com/oncology Vol 22 April 2021

Evidence that Adj CT = Indirect endocrine effect in 'premenopausal women'

MINDACT
70-gene prognosis signature



Guy, CT- cytotoxicity occurs in the 1st few years following its administration ….
not > 4 yrs
…

www.thelancet.com/oncology Vol 22 April 2021

TAILORx (RS 11-25 ET/ET + CT) : 16% LHRHag

Table 3. Estimated Survival Rates According to Recurrence Score and Assigned Treatment among Women 50 Years of Age or Younger in the Intention-to-Treat Population.*

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
Freedom from recurrence of breast cancer at a distant site		
Score of 16–20, endocrine therapy	98.1±0.7	93.6±1.4
Score of 16–20, chemoendocrine therapy	98.9±0.5	95.2±1.3
Score of 21–25, endocrine therapy	93.2±1.7	86.9±2.9
Score of 21–25, chemoendocrine therapy	96.4±1.2	93.4±2.3

TAILORx
Largest breast cancer treatment trial

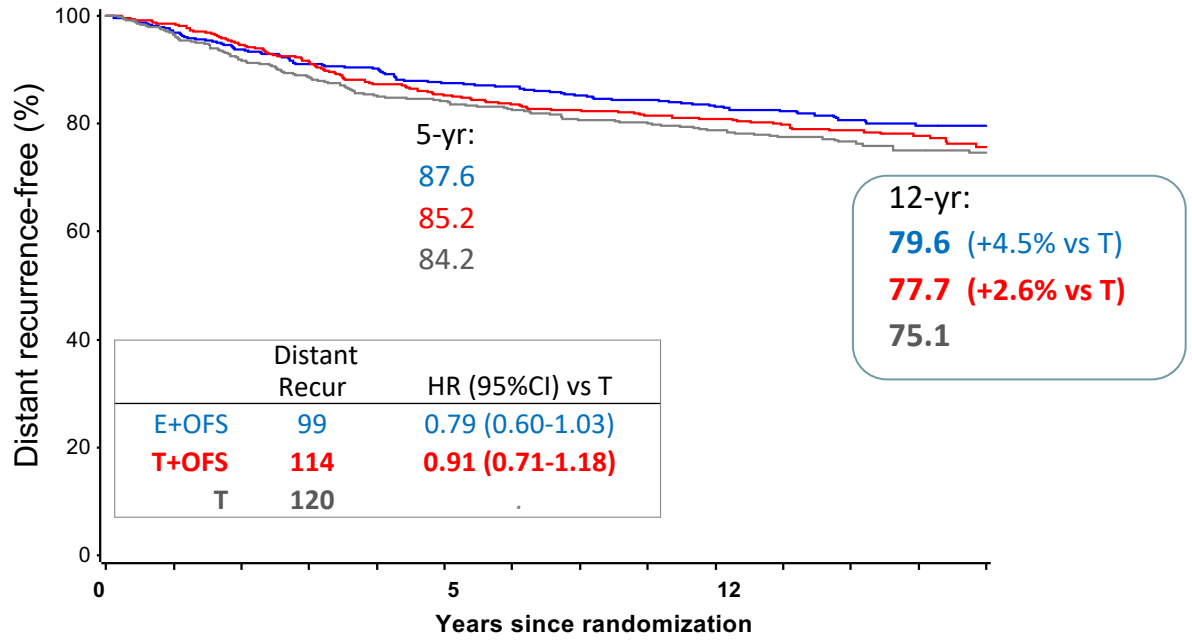
NEJM 379; 2 July 12, 2018

Guy, in SOFT, it took 4 yrs to see benefit from adding OFS to tam

The power of 'OFS': SOFT (high risk cohort) 12 yr med FU

*Subgroep Analyse**

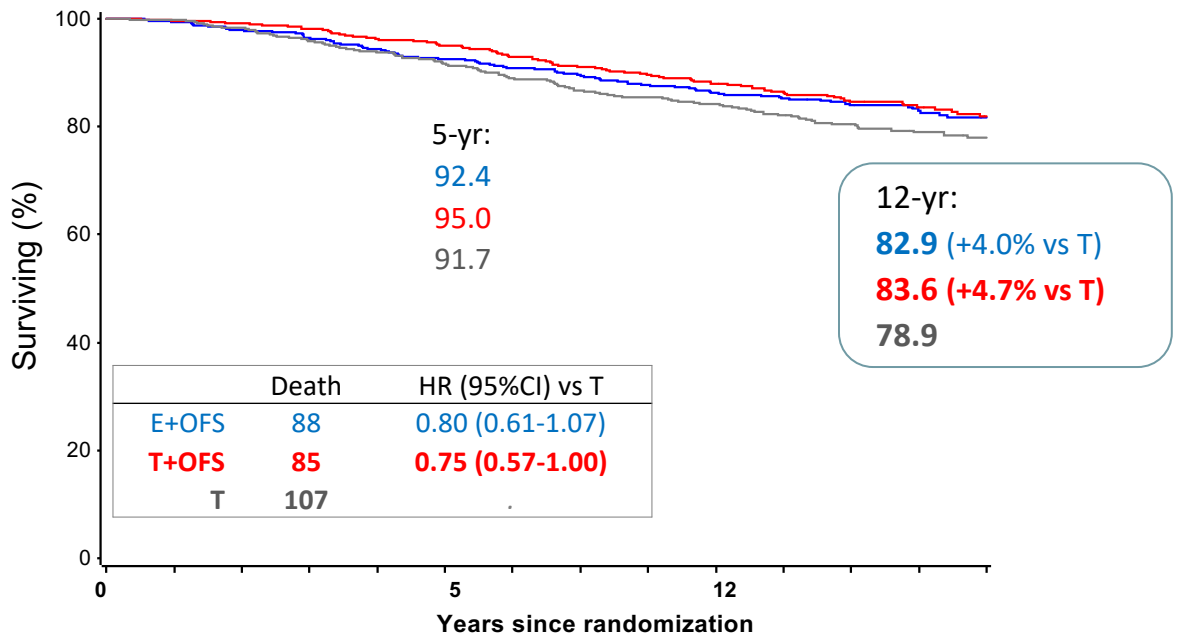
Distant Recurrence-free Interval



	Distant Recur	HR (95%CI) vs T
E+OFS	99	0.79 (0.60-1.03)
T+OFS	114	0.91 (0.71-1.18)
T	120	.

	0-5 years		>5 years	
	Recur	HR (95% CI) vs T	Recur	HR (95% CI) vs T
E+OFS:	65	0.77 (0.56-1.07)	34	0.81 (0.51-1.29)
T+OFS:	76	0.91 (0.67-1.24)	38	0.92 (0.59-1.44)
T:	81	.	39	.
At risk:	1628 pts	7131 pyfu	1257 pts	8005 pyfu

Overall Survival



	Death	HR (95%CI) vs T
E+OFS	88	0.80 (0.61-1.07)
T+OFS	85	0.75 (0.57-1.00)
T	107	.

	0-5 years		>5 years	
	Deaths	HR (95% CI) vs T	Deaths	HR (95% CI) vs T
E+OFS:	40	0.93 (0.61-1.43)	48	0.72 (0.50-1.05)
T+OFS:	26	0.60 (0.37-0.97)	59	0.86 (0.60-1.22)
T:	43	.	64	.
At risk:	1628 pts	7681 pyfu	1427 pts	9295 pyfu

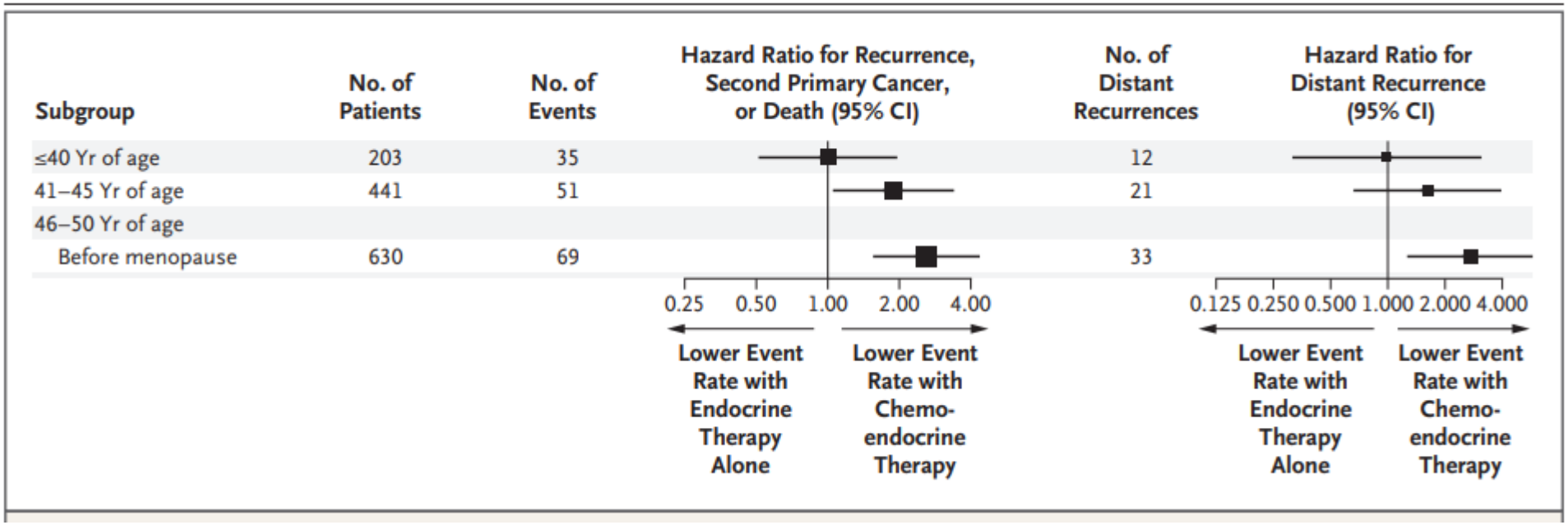
OS: Tam + OFS vs Tam: absolute gain in OS **4.7%** (0-5j)

*In complete SOFT cohort of 3047 pts: + OFS OS HR is 0.78 (0.60 – 1.01); *P*-value is 0.06

More evidence for
Indirect endocrine effect
of adj-chemotherapy

TAILORx: <51 yr & ODX RS 16 - 25: ET vs ET + CT.
Effect of Age and Menopausal Status on Chemotherapy Benefit

+ CT-benefit for distant recurrences most evident at 46-50 yrs = cytotoxic ovarian suppression effect

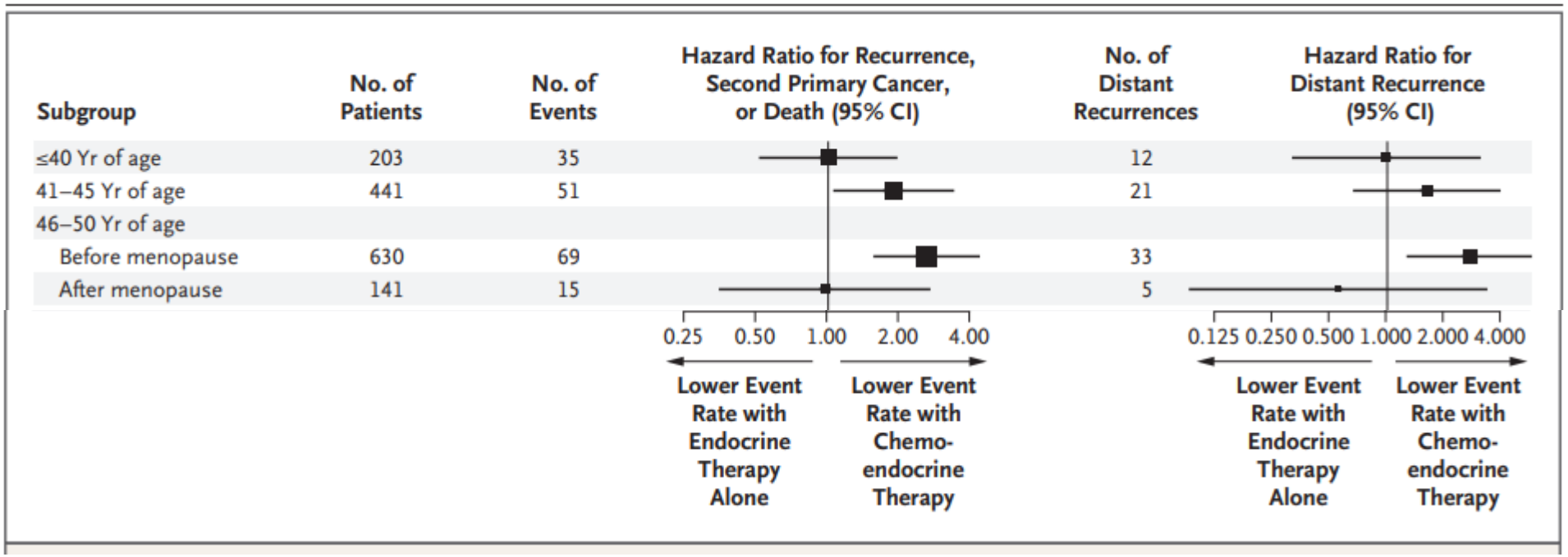


Estimated treatment HR (endocr vs. chemo endocr) and 95% CIs for rates of distant recurrence at 9 years (a HR >1 indicates chemo-endocrine therapy is better).

Follow-Up →March 2018;
reports NEJM 2018, 2019

TAILORx
Effect of Age and Menopausal Status on Chemotherapy Benefit

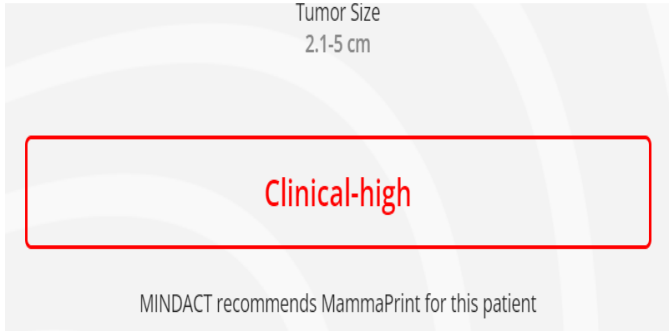
+ CT-benefit for distant recurrences at 46-50 yrs <u>but not if already in menopause</u>



Menopause age of 45-59 yrs: spontaneous cessation of menses > 12 months before registration

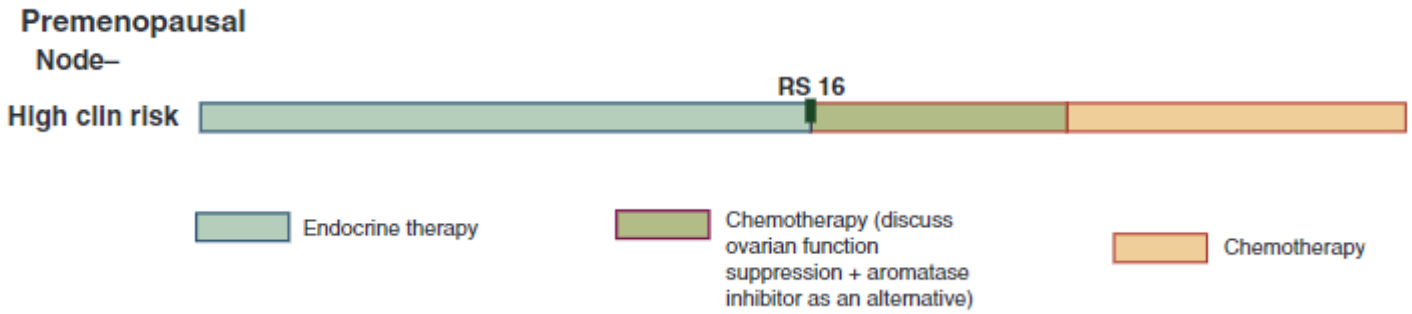
Follow-Up →March 2018;
reports NEJM 2018, 2019

mymammaprint



Value of GEP in LN-neg Lum BrCa
"Premenop" "<51y"

RS 16-25: Adj CT-benefit?
How Clinical Meaningful?



TAILORx data

Piccart M, Kalinsky K. et al.
Ann Oncol 2022; 33: 668

ASCO

Recommendation 1.1 & 1.3.

If <51 yrs & Oncotype DX RS 16 to 25, the clinician may offer chemo- endocrine therapy

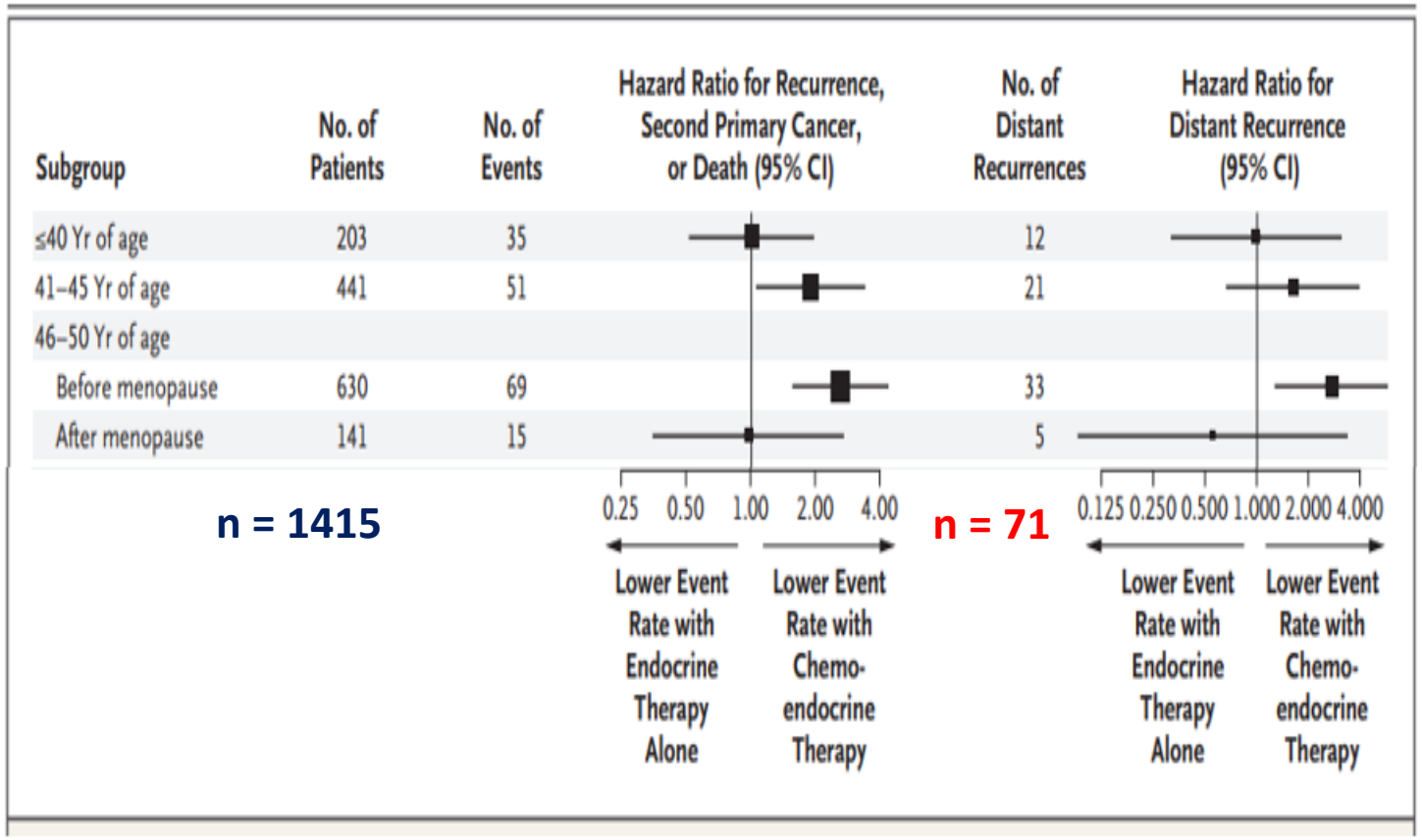
(Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

J Clin Oncol 2022; 40:1816-1837

TAILORx: <51 yrs

Subgroup of Subgroup Analysis…

Clinical Meaningful? ~ Number of distant metastatic events RS 16-25 <51 yrs



TAILORx RS 16-25 <51 yrs

n = 1415

	RS 16-20		RS 21-25	
	ET	CT-ET	ET	CT-ET
	454	469	246	246
	10	4	6	1
	8	8	8	5
Number of Distant → Events	17	10	17	9

n = 53

Suppl. Table S6 ‘1st event’
TAILORx: <51 yrs

Follow-Up →March 2018;
reports NEJM 2018, 2019

Effect of Clinical Risk on Prediction of Chemotherapy Benefit.

Subgroup of Subgroup of Subgroup Analysis…

Table 2. Recurrence, Second Primary Cancer, or Death, and Distant Recurrence at 9 Years, According to Use or Nonuse of Adjuvant Chemotherapy in Women Younger than 50 Years of Age, Stratified According to Recurrence Score and Clinical Risk (Intention-to-Treat Population).*

Variable	Clinical Risk	No. of Patients	Estimated Probability of Recurrence, Second Primary Cancer, or Death	Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)†	Estimated Probability of Distant Recurrence	Estimated Absolute Chemotherapy Benefit	Hazard Ratio for Distant Recurrence (95% CI)†
			percent		*percent*	*percentage points*	
Recurrence score of 16–20							
No chemotherapy	Low	328	19.6±3.1	1.89 (1.18–3.04)	4.6±1.5	−0.2±2.1	1.00 (0.44–2.28)
Chemotherapy	Low	343	9.5±1.8		4.8±1.5		
No chemotherapy	High	107	19.0±4.5	1.68 (0.76–3.72)	11.9±3.9	6.5±4.9	2.26 (0.70–7.34)
Chemotherapy	High	108	16.3±5.8		5.5±3.0		
Recurrence score of 21–25							
No chemotherapy	Low	158	19.7±4.5	1.38 (0.74–2.57)	11.4±3.9	6.4±4.9	3.16 (1.01–9.94)
Chemotherapy	Low	161	15.8±4.0		5.0±3.0		
No chemotherapy	High	75	26.4±5.4	2.63 (1.14–6.05)	18.8±5.0	8.7±6.2	1.86 (0.73–4.74)
Chemotherapy	High	82	11.4±3.8		10.1±3.7		

* Plus–minus values are Kaplan–Meier estimates ±SE.
† An estimated hazard ratio of greater than 1 indicates a higher recurrence rate with endocrine therapy alone than with chemoendocrine therapy. Confidence intervals have not been adjusted, and inferences drawn from the intervals may not be reproducible.

ET:	328*4.6/100 =	15
CT-ET:	343*4.8/100 =	16
ET:	107*11.9/100 =	12
CT-ET:	108*5.5/100 =	6
ET:	158*11.4/100=	18
CT-ET:	161*5.0/100=	8
ET:	75*26.4/100=	20
CT-ET:	82*11.4/100=	9
Total distant events	=	**104**

n = 104
Estimated probability?

So, in TAILORx what are the absolute number for CT-benefit, preventing metastatic events if high clinical risk?

It is confusing!

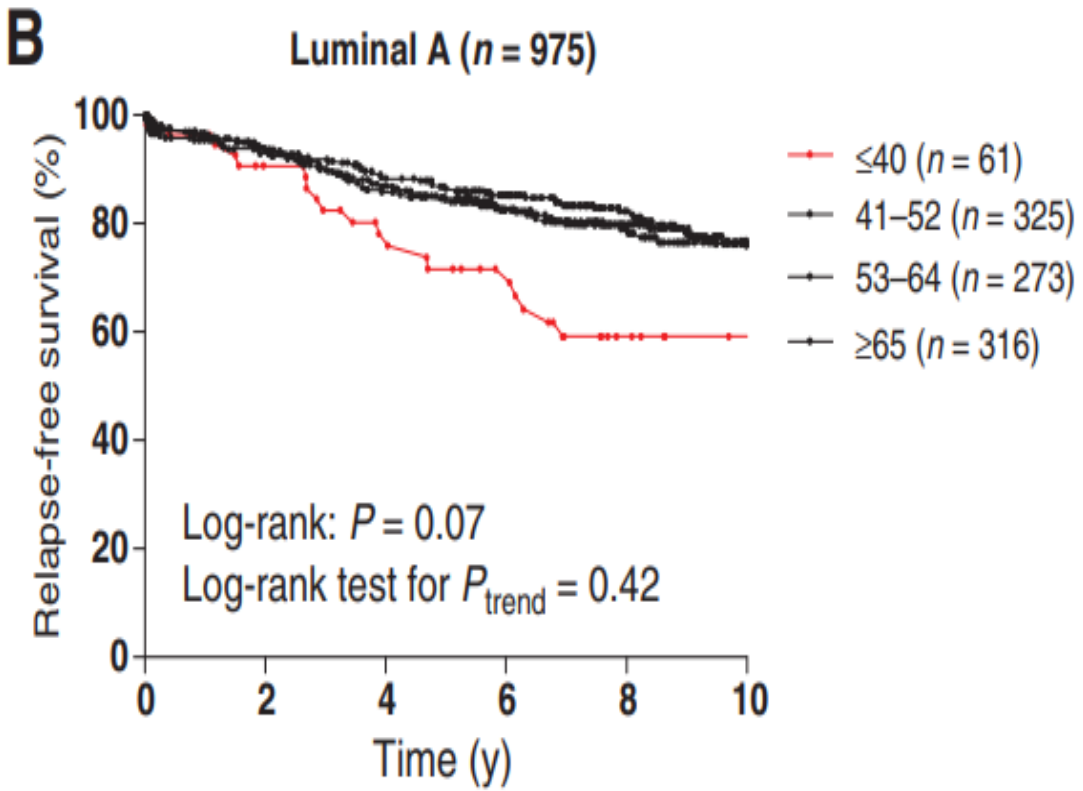
Follow-Up →March 2018;
reports NEJM 2018, 2019

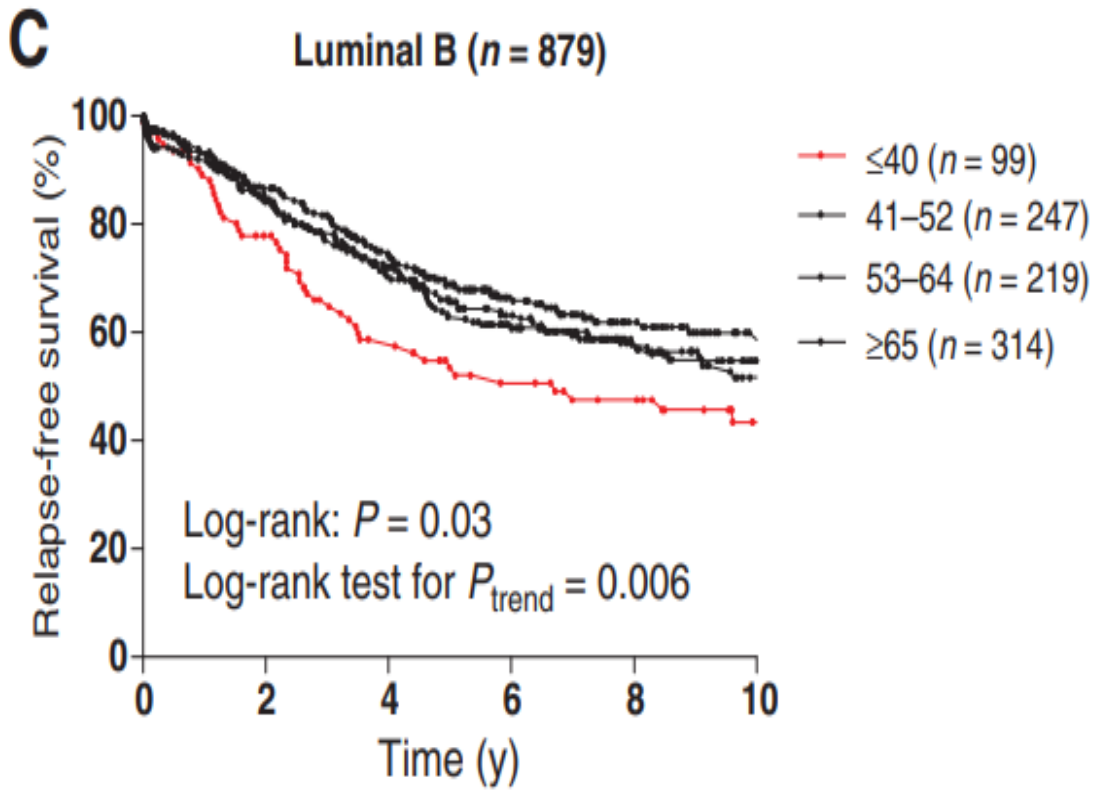
Guy, if you don't believe in GEP <51 yrs
…and you give adj CT in any clinical high risk Lum BrCa pt

"Luminal breast cancer in younger women is biologically different and more sensitive to adj chemotherapy"

Liège

I propose you read this article on the biology of breast cancer arising in young women using gene expression profiling it is especially < 41yrs that Lum BrCa are more aggressive





Azim HA Jr et al. Clin Cancer Res 2012; 18: 1341-51

To conclude my part in favor of motion:

In 2023, some women <51yr have too little benefit from adj-CT if gr 2, pT2N0 Lum-EBC

Uncertainties will need to be communicated to patients as part of informed shared decision making

Kevin
Many Thanks

We hope the audience does agree…

Oxford Debate

On argument might be inconsistencies between assays Lum A versus Lum B

prosigna® Breast cancer prognostic gene signature assay

“Agreement for genomic risk classification between tools is …as bad as agreement for tumor grade…”

mammaprint®

Genomic Health® oncotypeDX®

DOI 10.3310/hta20100

Breast Cancer Debate of the Year

OFFICIAL best of SABCS

INSTITUT JULES BORDET

H.U.B HÔPITAL UNIVERSITAIRE DE BRUXELLES ACADEMISCHE ZIEKENHUIS BRUSSEL

BSMO

LICENSED BY ENCORE MEDICAL EDUCATION

Ovarian Function Suppression and aromatase inhibitor can replace adjuvant chemotherapy…

NOT IN FAVOUR

Guy Jerusalem, MD, PhD

Conflicts of interest

- I’m a Medical Oncologist and I have been asked to defend the role of chemotherapy.
- I don’t like to see women suffering from severe side effects that can be easily stopped by the interruption of the treatment.
- My aim is to offer the highest chance of cure to my patients.

Chemotherapy-induced ovarian suppression

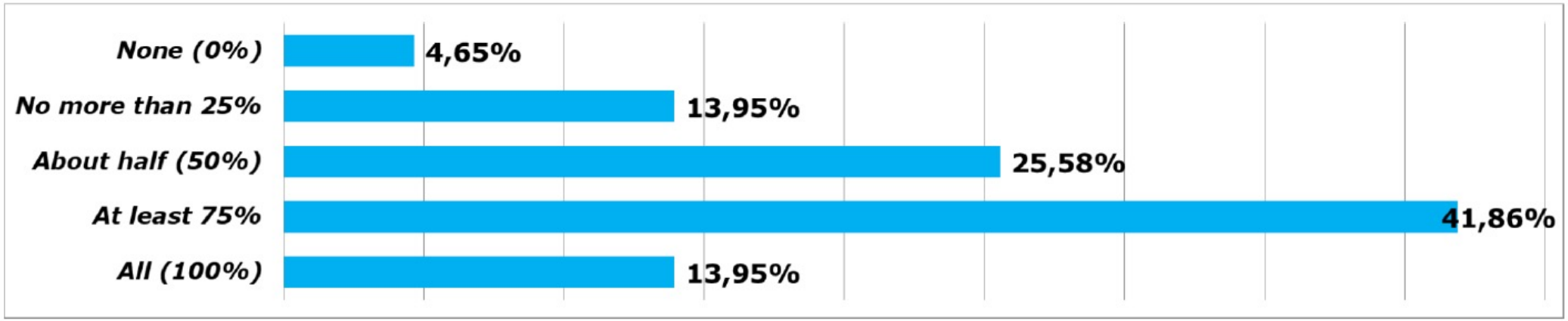
17TH ST.GALLEN INTERNATIONAL BREAST CANCER CONFERENCE 2021

Primary Therapy of Early Breast Cancer. Evidence, Controversies, Consensus.

17 – 21 March 2021, online worldwide

st gallen oncology conferences

The likely contribution of chemotherapy-induced ovarian suppression to the effectiveness of chemotherapy (as opposed to 'cytotoxic' effects of chemotherapy in premenopausal women with ER+ early stage breast cancers with favorable biological features such as ER/PR/grade/Ki67 or lower risk genomic signature) is best estimated as:



The debate should be focused!

- The question is NOT the role of castration or chemotherapy in any but in this specific case!
- ER positive breast cancers: a spectrum of disease

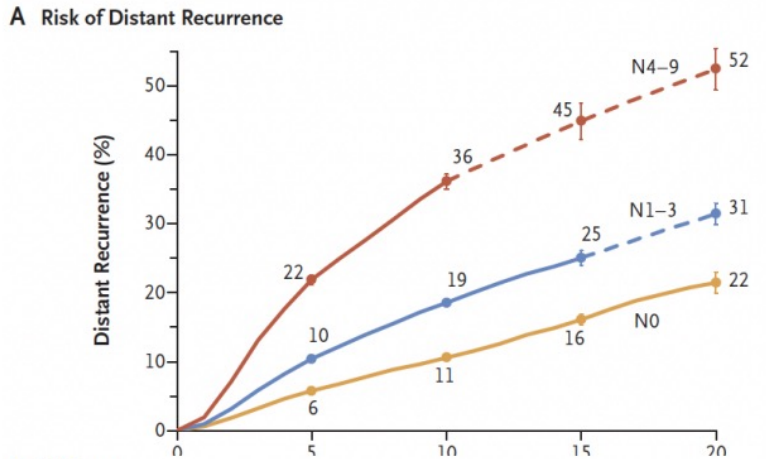
DEFINITION OF HIGH RISK ER+/HER2- EARLY BREAST CANCER

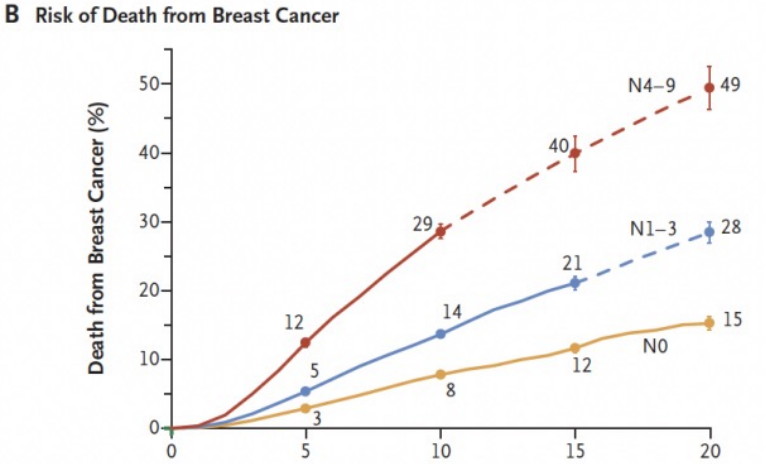
- Standard clinical pathologic features: age, tumor size, nodal status, ER expression, LV invasion, Tumor grade, KI67

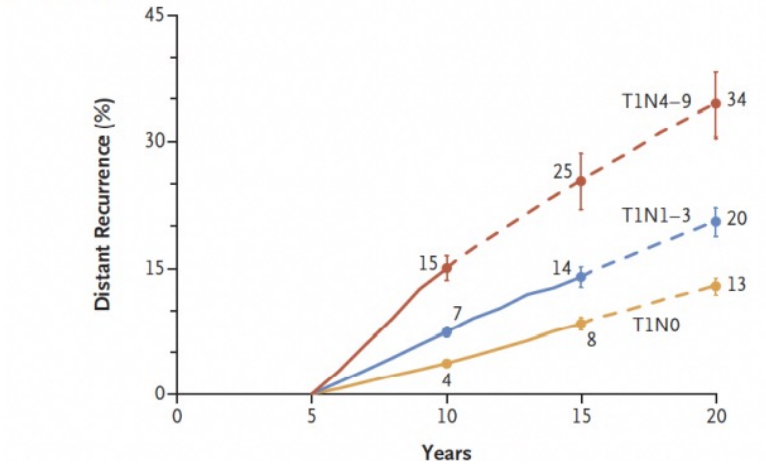
  41y old lady with a pT2(2.7cm)N0, grade II, invasive ductal carcinoma of the breast (KI67 20%)

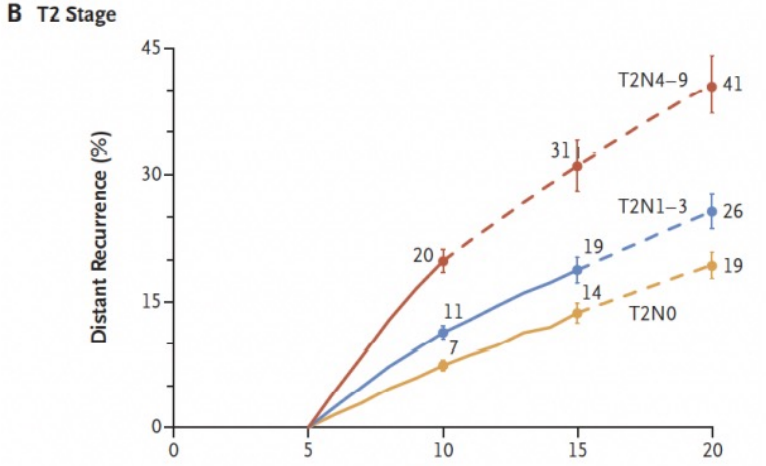
- Gene expression signatures: 21-gene RS>25 (Oncotype); 70-gene high-risk (Mammaprint); Molecular intrinsic subtype (luminal B, HER2-enriched and basal-like)
- Adaptive phenotypic response to ET (PEPI score, CPS+EG score)

20-YEAR RISK OF BREAST CANCER RECURRENCE AFTER STOPPING ENDOCRINE THERAPY









Pan H et al. NEJM 2017

Surrogate definitions of intrinsic subtypes of breast cancer

Intrinsic Subtype	Clinicopathological Surrogate	Prevalence
Luminal A	ER+ Her2- Ki67 <15% PR+	40%
	Low risk molecular signature	
Luminal B	ER+ Her2- Ki67>14% or PR -	20%
	High Risk molecular signature	
	ER+ Her2+ any Ki67/PR	
Her2	Her2 + ER- PR-	15 – 25%
Basal Like	TNBC	11 – 25%

A Goldhirsch et al, Ann Oncol, 2013

WHAT IS THE RECOMMENDED TREATMENT FOR LUMINAL EARLY BREAST CANCER?

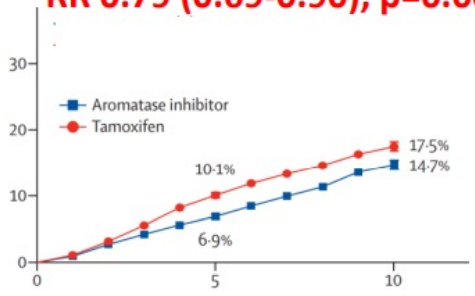
	Recommended treatment
Luminal-A like	ET alone in the majority of cases (CT only in selected cases)
Luminal B-like (HER2-negative)	CT followed by ET in the majority of cases
Luminal B-like (HER2-positive)	CT + anti-HER2 therapy followed by ET
HER2-positive	CT + anti-HER2 therapy
Triple-negative	CT

E de Azambuja, Brussels, June 2022, Adapted from Cardoso F et al., ESMO Clinical Practice Guidelines for Early Breast Cancer

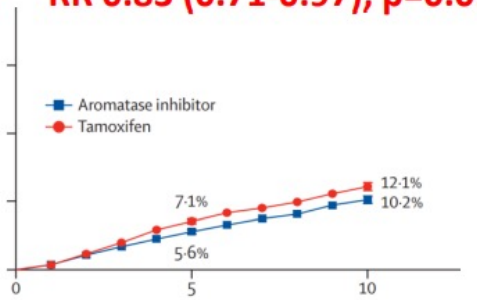
OFS + TAM vs OFS + AI in Premenopausal Patients

EBCTCG Meta-analysis, 4 randomized trials
ABCSG12, SOFT, TEXT, HOBOE
n=7030 pre-menopausal patients

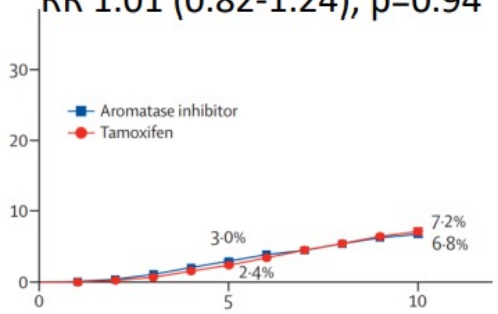
10Y Any recurrence
17.5 vs 14.7%, **Δ2.8%**
RR 0.79 (0.69-0.90), p=0.0005



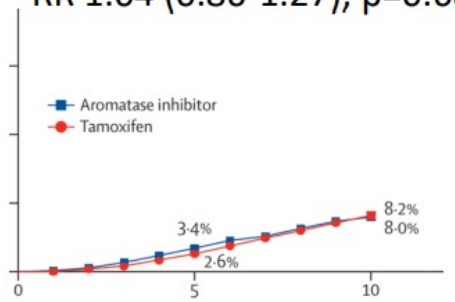
10Y Distant Recurrence
10.2 vs 12.1%, **Δ1.9%**
RR 0.83 (0.71-0.97), p=0.018



10Y Breast cancer mortality
7.2 vs 6.8%, Δ0.4%
RR 1.01 (0.82-1.24), p=0.94



10Y All cause mortality
8.2 vs 8.0%, Δ0.2%
RR 1.04 (0.86-1.27), p=0.68

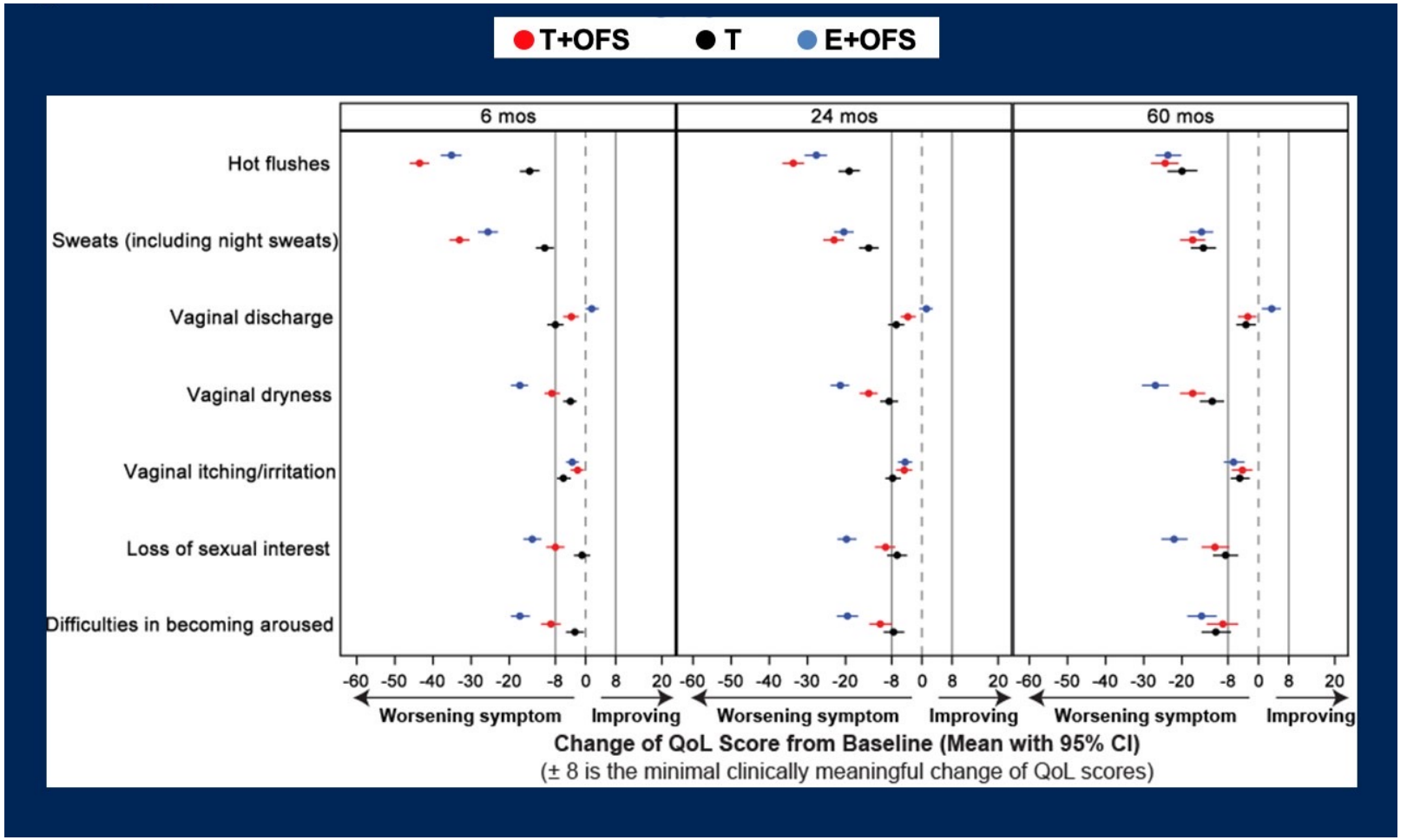


More bone fractures with AI vs tamoxifen (6.4% vs 5.1%, **Δ1.3%**)
Non-breast cancer deaths rare (0.9% vs 0.7% AI vs tam)
Endometrial cancers rare (0.2% vs 0.3% AI vs tam)

OFS + AI **reduces breast cancer recurrence** but not mortality compared to OFS + Tam. **May be considered in high risk patients** after weighing potential benefits and risks of fractures

EBCTCG, Lancet Oncol 2022

Ovarian function suppression: Symptoms



K Ribi SABCS 2004

Ovarian function suppression: Side effects

Toxicity from OFS is higher than evident from this trial

Addition of AI seems worse in our patient's clinical experience

…"the true impact of hormonal treatments in young women with active personal and professional lives may be well hidden between the lines of clinical trial data"…..

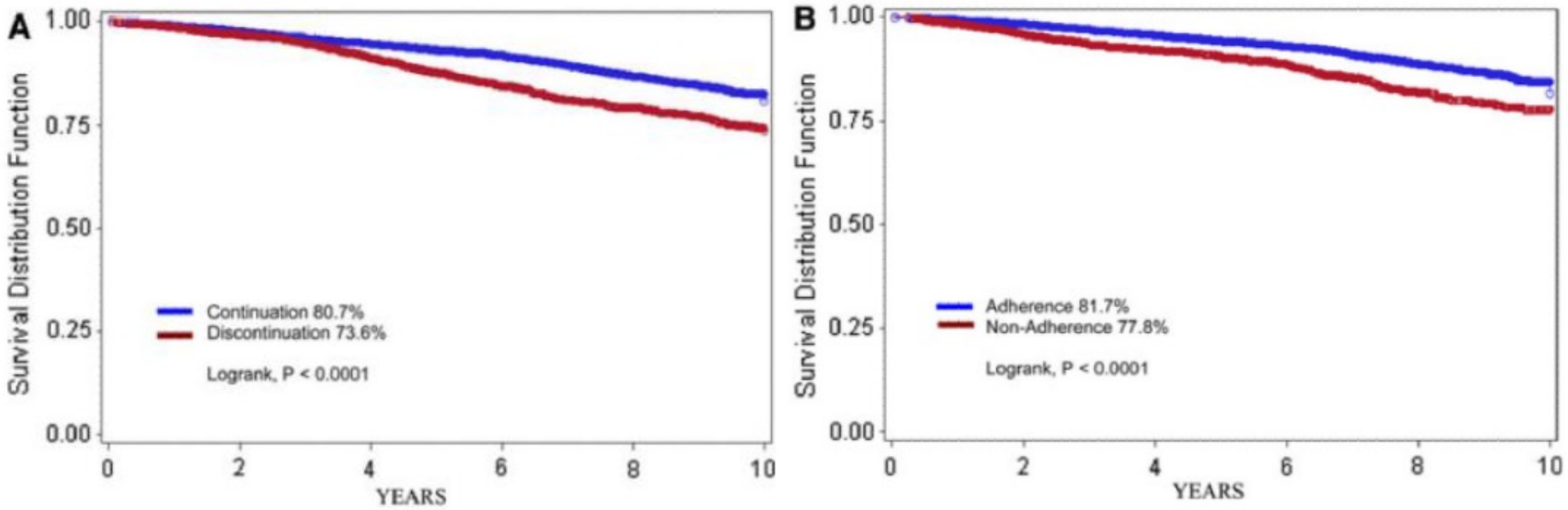
M Gnant Ann Oncol 2016, M Gnant ESMO BC, 2020

Endocrine therapy adherence

- In SOFT and TEXT 19.8% of women under age 35 stopped ALL protocol-related endocrine therapy early
- Claims-based analysis of adjuvant tamoxifen from 1990-1996
  - patients filled prescriptions for 87% of their first year
  - adherence deceased to 50% by year 4
  - younger women at higher risk of nonadherence
    - Toxicities
    - Desire for child-bearing

P Saha JCO 2017, A Partridge JCO 2003

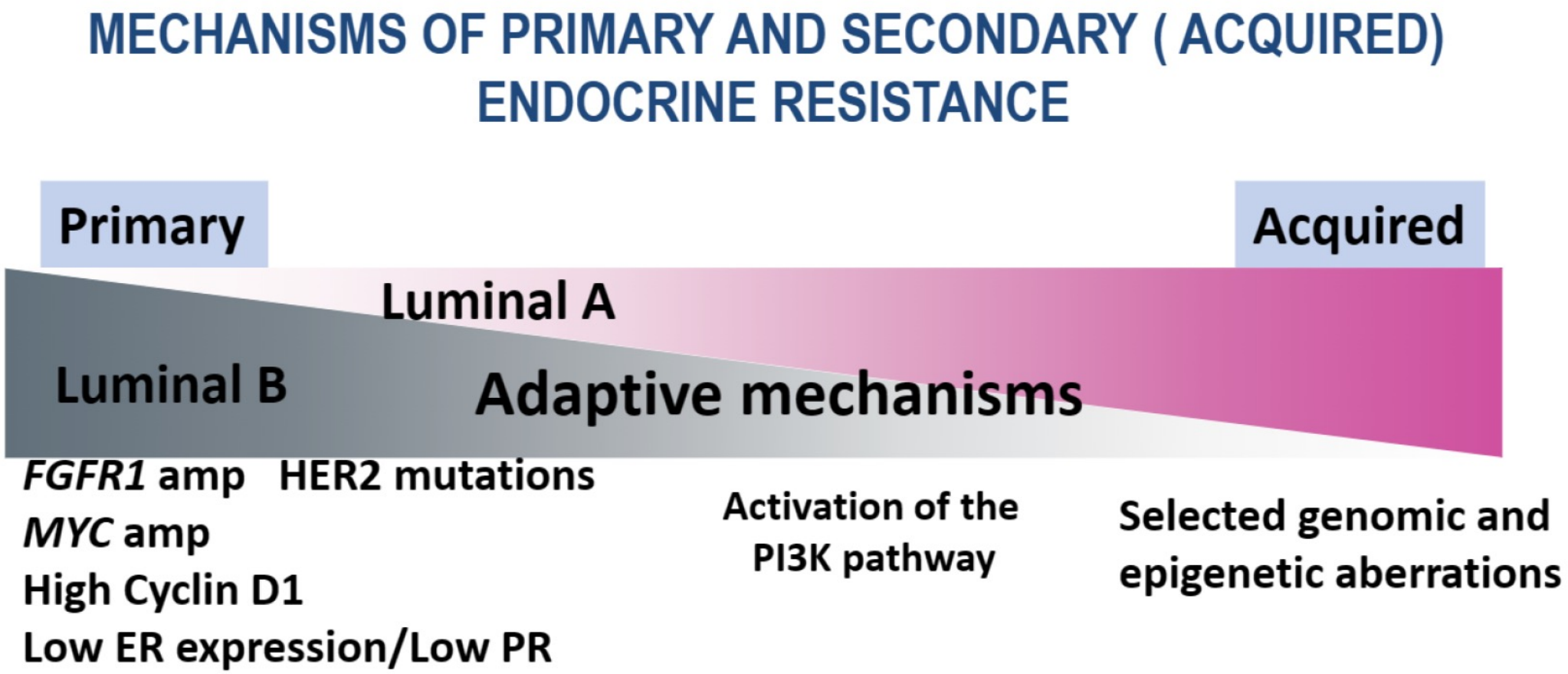
Early discontinuation and non-adherence: Increased mortality



Both early discontinuation and non-adherence to HT were common and associated with increased mortality. Interventions to improve continuation of and adherence to HT may be critical to improve BC survival.

D Hershman Breast Cancer Res Treat 2011

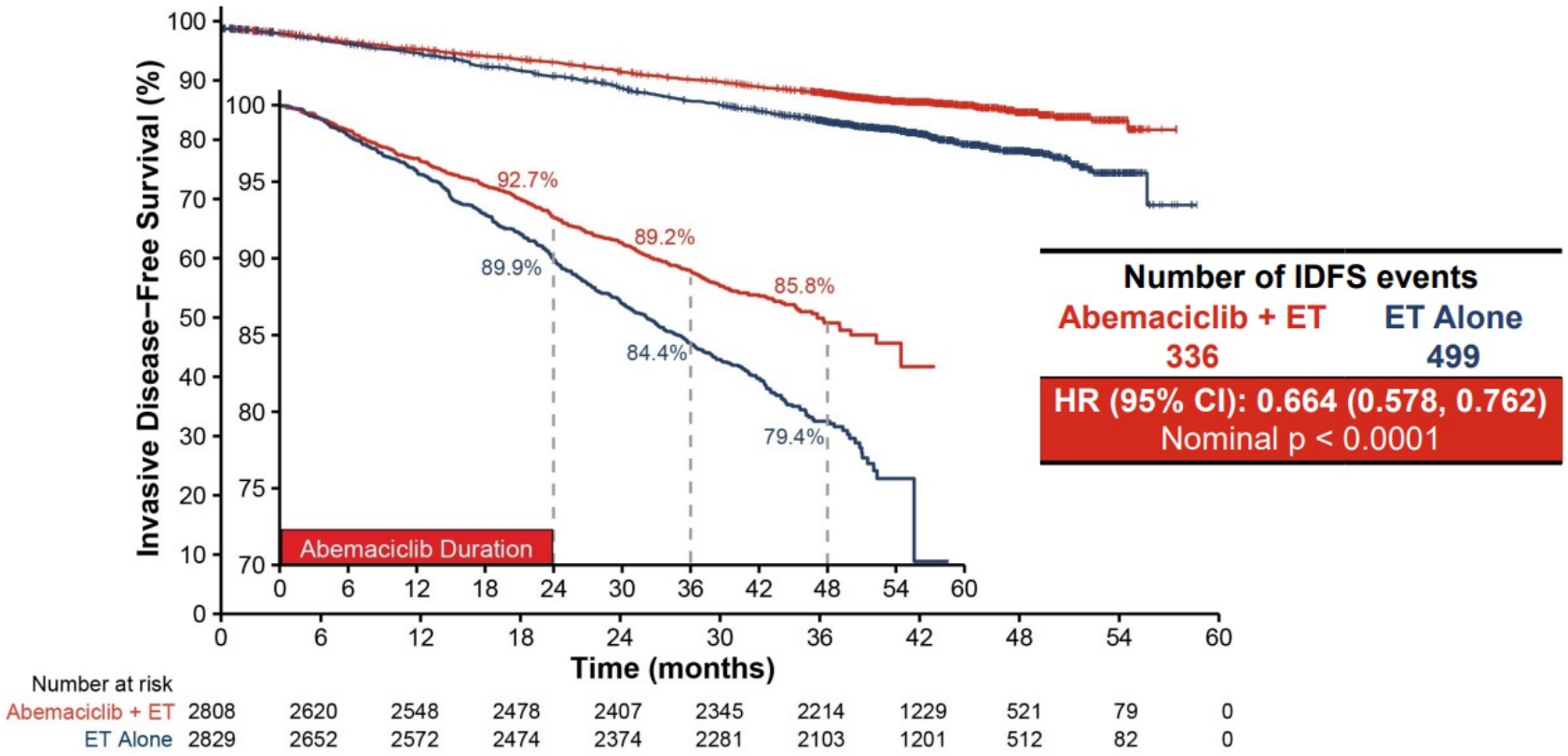
Endocrine resistance: A major issue



Jeselsohn R ESMO BC 2020

Preplanned monarchE OS interim analysis (including 4-year efficacy outcomes)

IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib

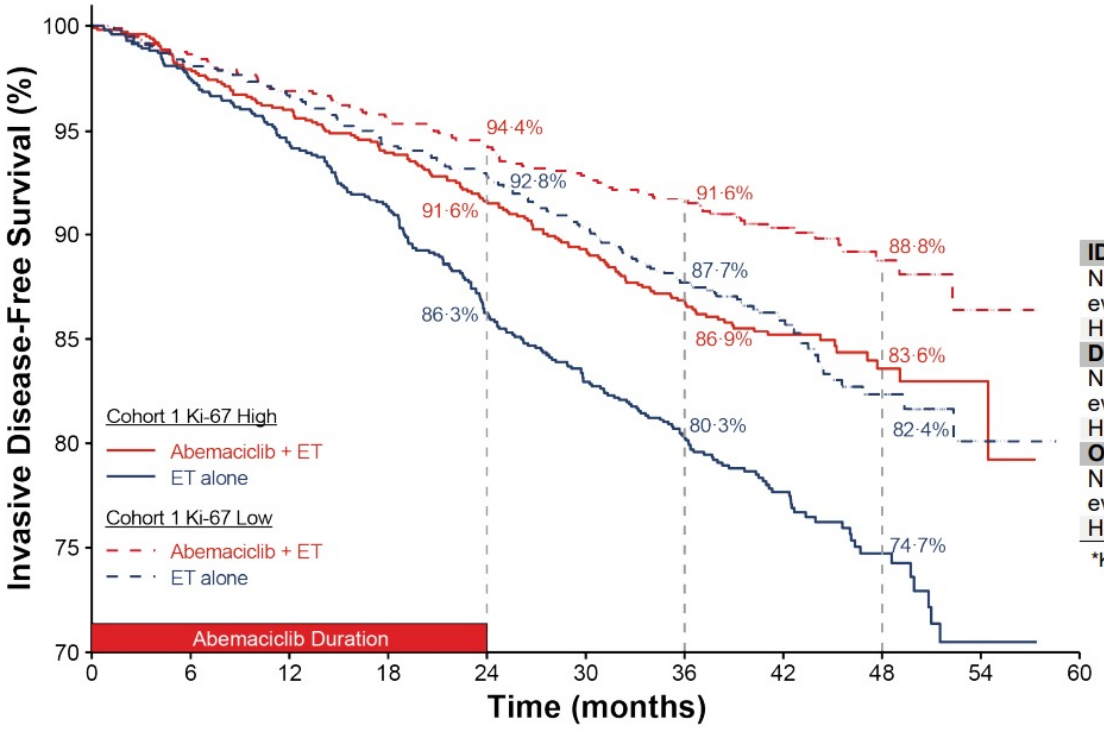


33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

Johnston S , SABCS 2022, GS 1-09

Preplanned monarchE OS interim analysis (including 4-year efficacy outcomes)

Ki-67 is Prognostic, but Not Predictive of Abemaciclib Benefit



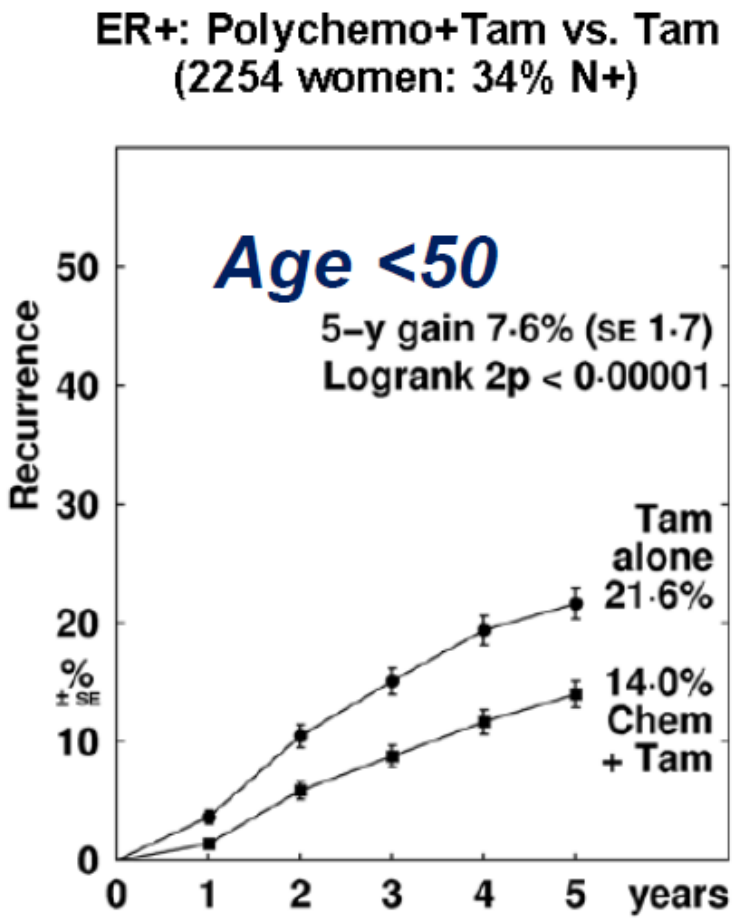
	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=1017	ET alone N=986	Abemaciclib + ET N=946	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of events, n	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

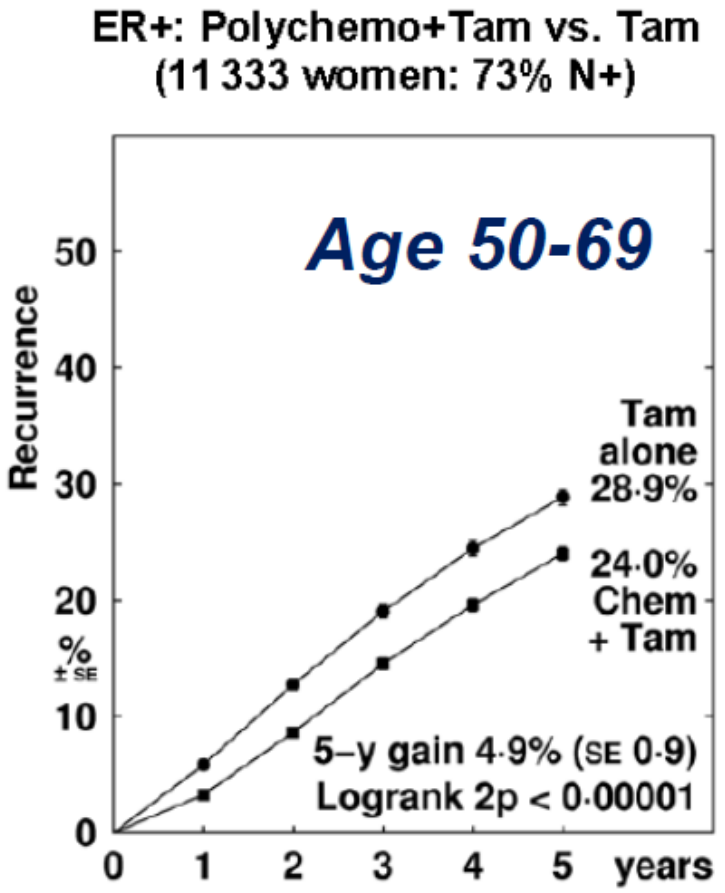
*Ki-67 value was missing in 1203 (23.5%) patients

Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index

Johnston S , SABCS 2022, GS 1-09

Does chemotherapy improves outcome?





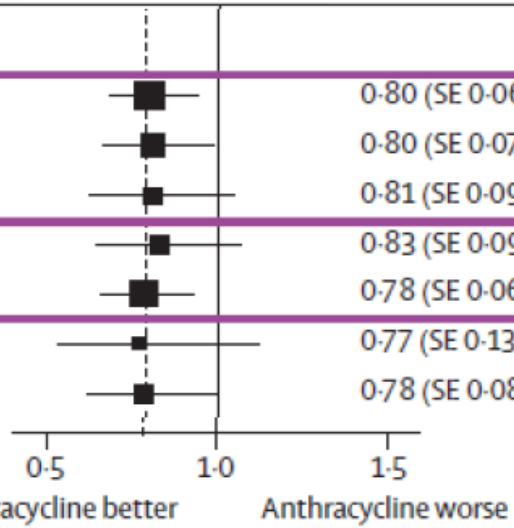
6 MONTHS OF ANTHRACYCLINES REDUCES THE ANNUAL BC DEATH BY ABOUT 38% (<50) AND 20% (>50)

EBCTCG. Lancet 2005

Chemotherapy benefits by age and ER

Anthracyclins versus nill, effect on Breast Cancer Mortality **= independent of ER and age**

	Deaths/women		Anthracycline deaths		Ratio of annual death rates
	Allocated anthracycline	Allocated control	Log-rank O–E	Variance of O–E	Anthracycline:Control
Subsets of ER+					
ER+, chemotherapy+endocrine *vs* endocrine	659/2622 (25·1%)	853/2675 (31·9%)	−56·2	247·0	0·80 (SE 0·06)
ER 10–99 fmol/mg	416/1371 (30·3%)	544/1442 (37·7%)	−35·3	162·5	0·80 (SE 0·07)
ER ≥100 fmol/mg	274/1146 (23·9%)	337/1160 (29·1%)	−20·6	95·6	0·81 (SE 0·09)
ER+, age <55 years	250/845 (29·6%)	316/943 (33·5%)	−19·4	102·4	0·83 (SE 0·09)
ER+, age 55–69 years	542/2071 (26·2%)	677/2055 (32·9%)	−53·9	215·3	0·78 (SE 0·06)
ER+, poorly differentiated	100/461 (21·7%)	120/477 (25·2%)	−12·2	45·8	0·77 (SE 0·13)
ER+, moderately/well differentiated	228/985 (23·1%)	286/1026 (27·9%)	−27·8	112·8	0·78 (SE 0·08)



■ 99% or ◁▷ 95% CI

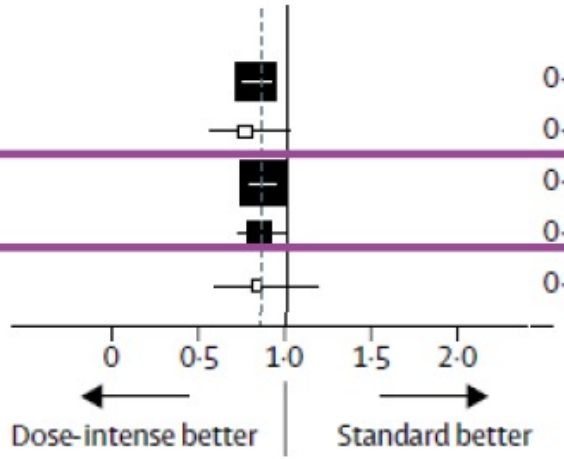
Global heterogeneity: χ^2_6 =5·8; p=0·4

EBCTCG. Lancet 2012

Dose dense chemotherapy benefits by age and ER

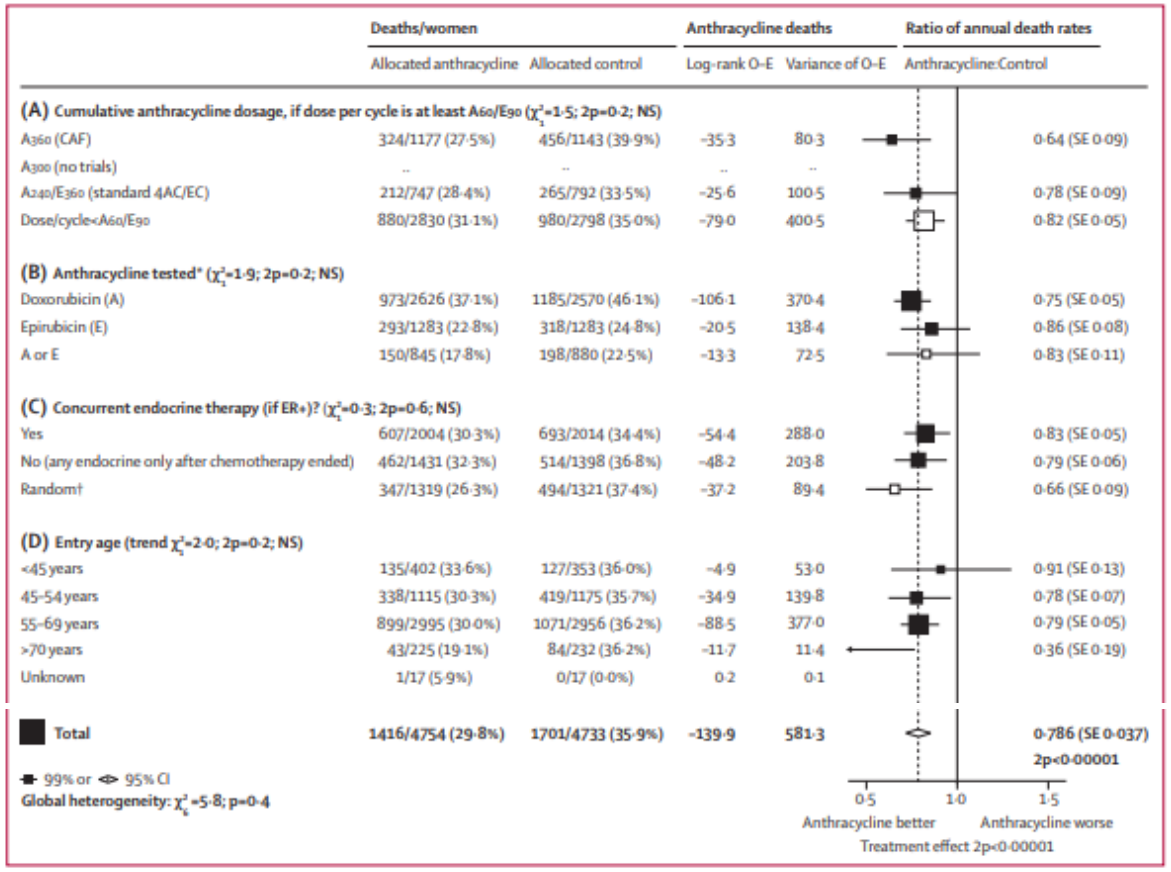
Dose dense versus not, effect on Breast Cancer Mortality **= independent of ER**

	Events/Women		Dose-intense events		Ratio of annual event rates	Rate ratio and CI
	Allocated Dose-intense	Allocated Standard	Logrank O–E	Variance of O–E	Dose-intense : standard	
(F) ER and PR status (χ^2_2=0·1; 2p>0·1; NS)						
ER negative, PR any	1394/4630 (30·1%)	1618/4695 (34·5%)	−125·7	673·7		0·83 (0·75–0·92)
ER?, PR any	163/659 (24·7%)	201/669 (30·0%)	−21·6	78·9		0·76 (0·57–1·02)
ER positive, PR positive	1786/9297 (19·2%)	1985/9267 (21·4%)	−127·3	898·1		0·87 (0·80–0·95)
ER positive, PR negative	490/1916 (25·6%)	563/1944 (29·0%)	−40·5	243·7		0·85 (0·72–1·00)
ER positive, PR?	107/557 (19·2%)	126/563 (22·4%)	−9·9	54·2		0·83 (0·59–1·18)



EBCTCG. Lancet 2019

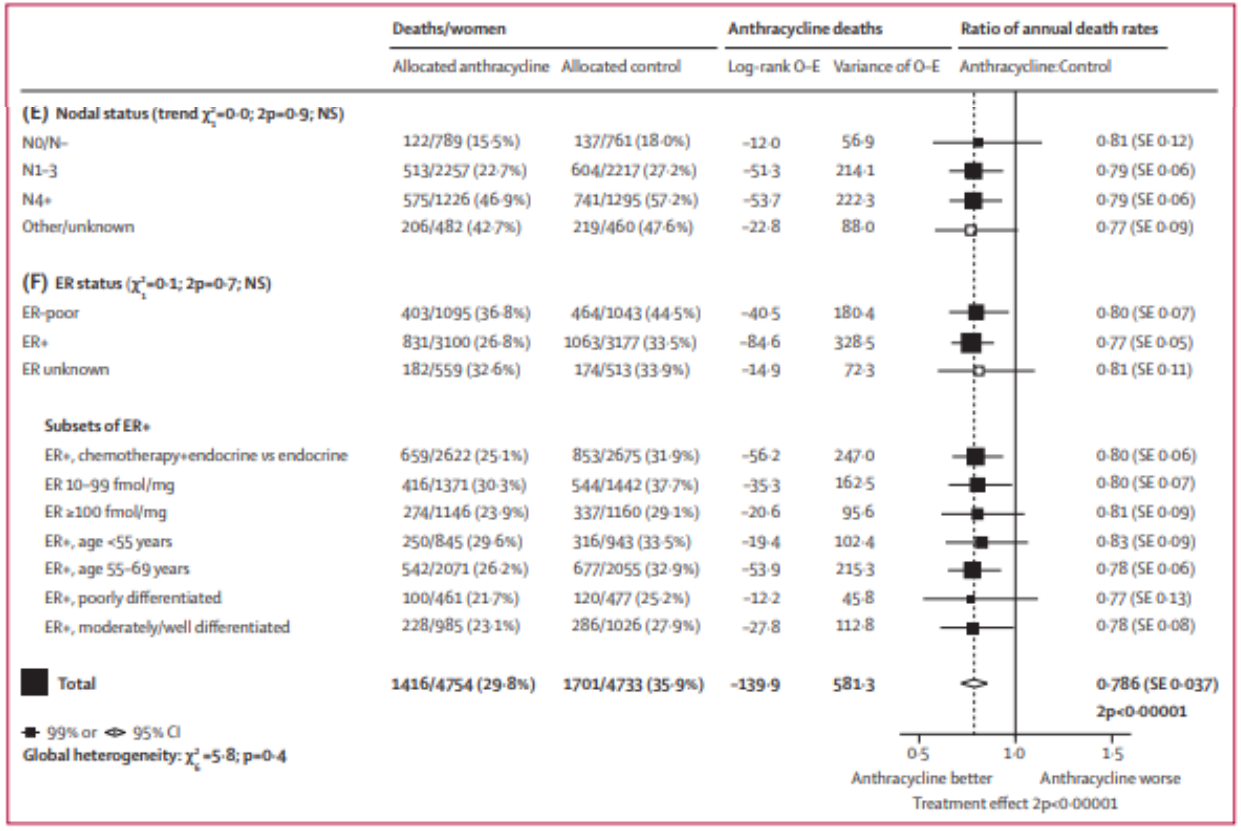
Does chemotherapy improves outcome?



	Deaths/women		Anthracycline deaths		Ratio of annual death rates
	Allocated anthracycline	Allocated control	Log-rank O–E	Variance of O–E	Anthracycline:Control
(A) Cumulative anthracycline dosage, if dose per cycle is at least A60/E90 (χ^2_1=1·5; 2p=0·2; NS)					
A360 (CAF)	324/1177 (27·5%)	456/1143 (39·9%)	−35·3	80·3	0·64 (SE 0·09)
A300 (no trials)	..	..	..	..	
A240/E360 (standard 4AC/EC)	212/747 (28·4%)	265/792 (33·5%)	−25·6	100·5	0·78 (SE 0·09)
Dose/cycle<A60/E90	880/2830 (31·1%)	980/2798 (35·0%)	−79·0	400·5	0·82 (SE 0·05)
(B) Anthracycline tested* (χ^2_1=1·9; 2p=0·2; NS)					
Doxorubicin (A)	973/2626 (37·1%)	1185/2570 (46·1%)	−106·1	370·4	0·75 (SE 0·05)
Epirubicin (E)	293/1283 (22·8%)	318/1283 (24·8%)	−20·5	138·4	0·86 (SE 0·08)
A or E	150/845 (17·8%)	198/880 (22·5%)	−13·3	72·5	0·83 (SE 0·11)
(C) Concurrent endocrine therapy (if ER+)? (χ^2_1=0·3; 2p=0·6; NS)					
Yes	607/2004 (30·3%)	693/2014 (34·4%)	−54·4	288·0	0·83 (SE 0·05)
No (any endocrine only after chemotherapy ended)	462/1431 (32·3%)	514/1398 (36·8%)	−48·2	203·8	0·79 (SE 0·06)
Random†	347/1319 (26·3%)	494/1321 (37·4%)	−37·2	89·4	0·66 (SE 0·09)
(D) Entry age (trend χ^2_1=2·0; 2p=0·2; NS)					
<45 years	135/402 (33·6%)	127/353 (36·0%)	−4·9	53·0	0·91 (SE 0·13)
45–54 years	338/1115 (30·3%)	419/1175 (35·7%)	−34·9	139·8	0·78 (SE 0·07)
55–69 years	899/2995 (30·0%)	1071/2956 (36·2%)	−88·5	377·0	0·79 (SE 0·05)
>70 years	43/225 (19·1%)	84/232 (36·2%)	−11·7	11·4	0·36 (SE 0·19)
Unknown	1/17 (5·9%)	0/17 (0·0%)	0·2	0·1	
Total	**1416/4754 (29·8%)**	**1701/4733 (35·9%)**	**−139·9**	**581·3**	**0·786 (SE 0·037)**
					2p<0·00001

■ 99% or ◇ 95% CI
Global heterogeneity: χ^2_6=5·8; p=0·4

0·5 1·0 1·5
Anthracycline better Anthracycline worse
Treatment effect 2p<0·00001



	Deaths/women		Anthracycline deaths		Ratio of annual death rates
	Allocated anthracycline	Allocated control	Log-rank O–E	Variance of O–E	Anthracycline:Control
(E) Nodal status (trend χ^2_1=0·0; 2p=0·9; NS)					
N0/N–	122/789 (15·5%)	137/761 (18·0%)	−12·0	56·9	0·81 (SE 0·12)
N1–3	513/2257 (22·7%)	604/2217 (27·2%)	−51·3	214·1	0·79 (SE 0·06)
N4+	575/1226 (46·9%)	741/1295 (57·2%)	−53·7	222·3	0·79 (SE 0·06)
Other/unknown	206/482 (42·7%)	219/460 (47·6%)	−22·8	88·0	0·77 (SE 0·09)
(F) ER status (χ^2_1=0·1; 2p=0·7; NS)					
ER-poor	403/1095 (36·8%)	464/1043 (44·5%)	−40·5	180·4	0·80 (SE 0·07)
ER+	831/3100 (26·8%)	1063/3177 (33·5%)	−84·6	328·5	0·77 (SE 0·05)
ER unknown	182/559 (32·6%)	174/513 (33·9%)	−14·9	72·3	0·81 (SE 0·11)
Subsets of ER+					
ER+, chemotherapy+endocrine vs endocrine	659/2622 (25·1%)	853/2675 (31·9%)	−56·2	247·0	0·80 (SE 0·06)
ER 10–99 fmol/mg	416/1371 (30·3%)	544/1442 (37·7%)	−35·3	162·5	0·80 (SE 0·07)
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ER+, age <55 years	250/845 (29·6%)	316/943 (33·5%)	−19·4	102·4	0·83 (SE 0·09)
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ER+, moderately/well differentiated	228/985 (23·1%)	286/1026 (27·9%)	−27·8	112·8	0·78 (SE 0·08)
Total	**1416/4754 (29·8%)**	**1701/4733 (35·9%)**	**−139·9**	**581·3**	**0·786 (SE 0·037)**
					2p<0·00001

■ 99% or ◇ 95% CI
Global heterogeneity: χ^2_6=5·8; p=0·4

0·5 1·0 1·5
Anthracycline better Anthracycline worse
Treatment effect 2p<0·00001

EBCTCG. Lancet 2012

What is the expected benefit in our patient?

Treatment Options

Hormone Therapy — No | 5 Years | 10 Years

Hormone (endocrine) therapy
Available when ER-status is positive

Chemotherapy — None | 2nd gen | 3rd gen

Treatment	Additional Benefit	Overall Survival %
Surgery only	-	85%
+ Hormone therapy	3.9% (2.3% – 4.8%)	89%
+ Chemotherapy	3.1% (2.3% – 3.8%)	92%

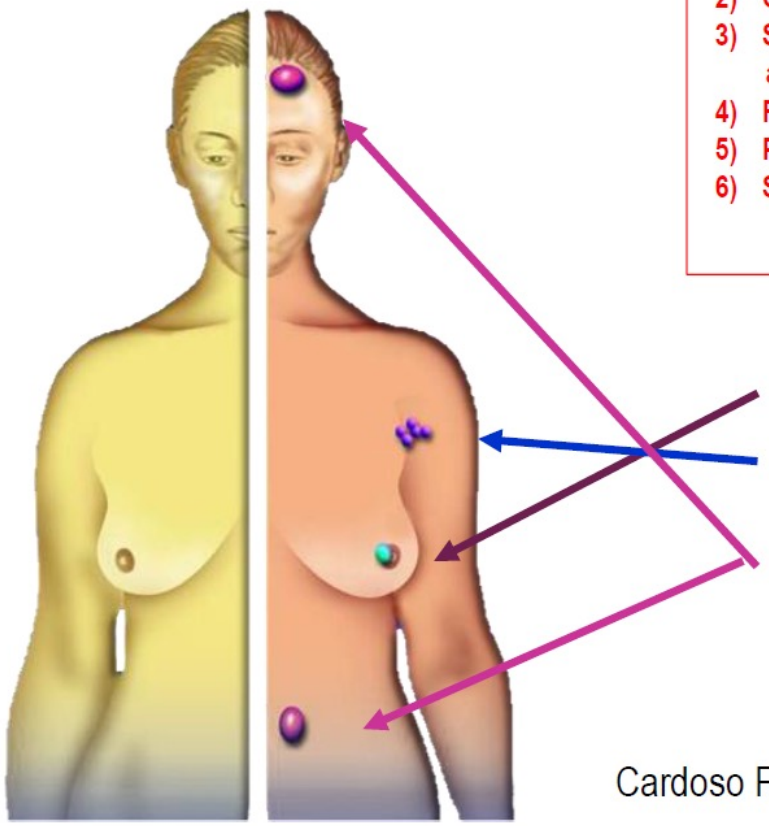
If death from breast cancer were excluded, 98% would survive at least 10 years, and 2% would die of other causes.

https://breast.predict.nhs.uk/tool, assessed JAN 6 2023

The opinion of the patient

Defining a role for chemothrapy depends on…

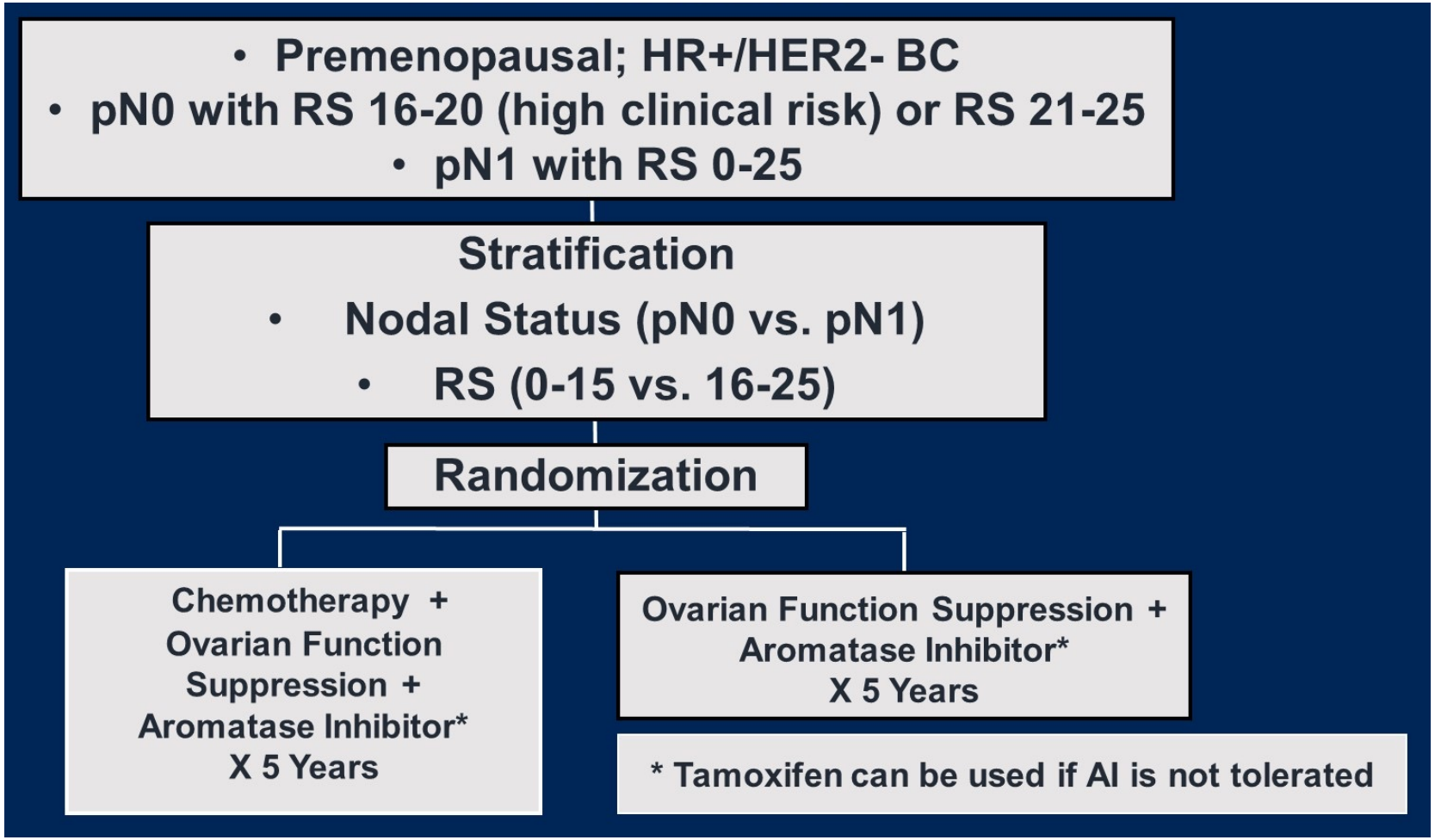
- **Tumour burden**
  - Tumour size
  - Grade
  - Histological subtypes
  - ER/PR and HER2 status
  - Presence of lymphovascular invasion
  - Proliferation (Ki-67)
- **Presumed responsiveness to endocrine therapy**
- **Patient's preference**



Patient's Concern:
1) Side effects of chemotherapy
2) QoL s.a. self-image
3) Suspend from work due to staying at home
4) Financial Toxicity
5) Psychological distress from CT
6) Some still recur after CT completion

Cardoso F. Annals of Oncology 2019

BR009: Trial Design



G Fleming. ASCO 2022

Take home messages

- Medicine is most frequently not black or white: chemotherapy or not, OFS or not, very high or very low risk…
- Treatment individualisation integrating tumor related and patient related factors.
- I recommand chemotherapy but not OFS for this particular patient.
- All the benefit doesn’t come from chemotherapy-induced OFS but probably some patients benefit more from the endocrine therapy effect and others more from the cytotoxic effect.

Thank you very much for your attention!