Temi aperti sui trattamenti adiuvanti: Malattia HR+/HER2-

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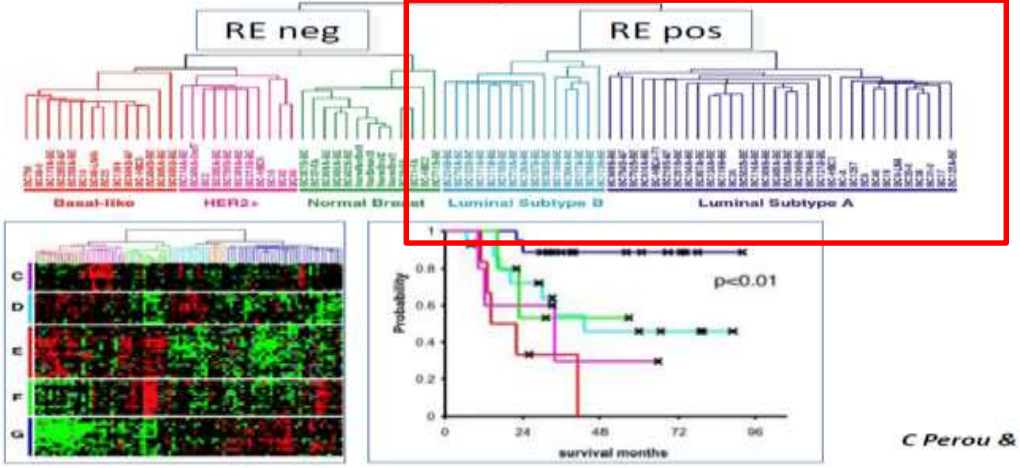
Outline

- Luminals
- Chemotherapy:
  - For who? What?
- Hormonotherapy:
  - Which? How long?

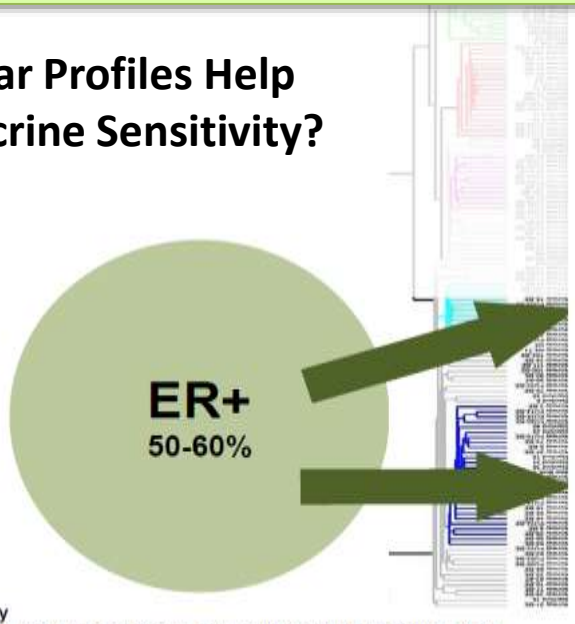
THE «LUMINALS»



C Perou & T Sorlie

- Luminal subtype can guide decision toward adjuvant chemotherapy
- Luminal subtype does not guide the choice of endocrine therapy

Can Molecular Profiles Help Define Endocrine Sensitivity?



Basal

HER2+

Luminal B → Pargu

Luminal A → E

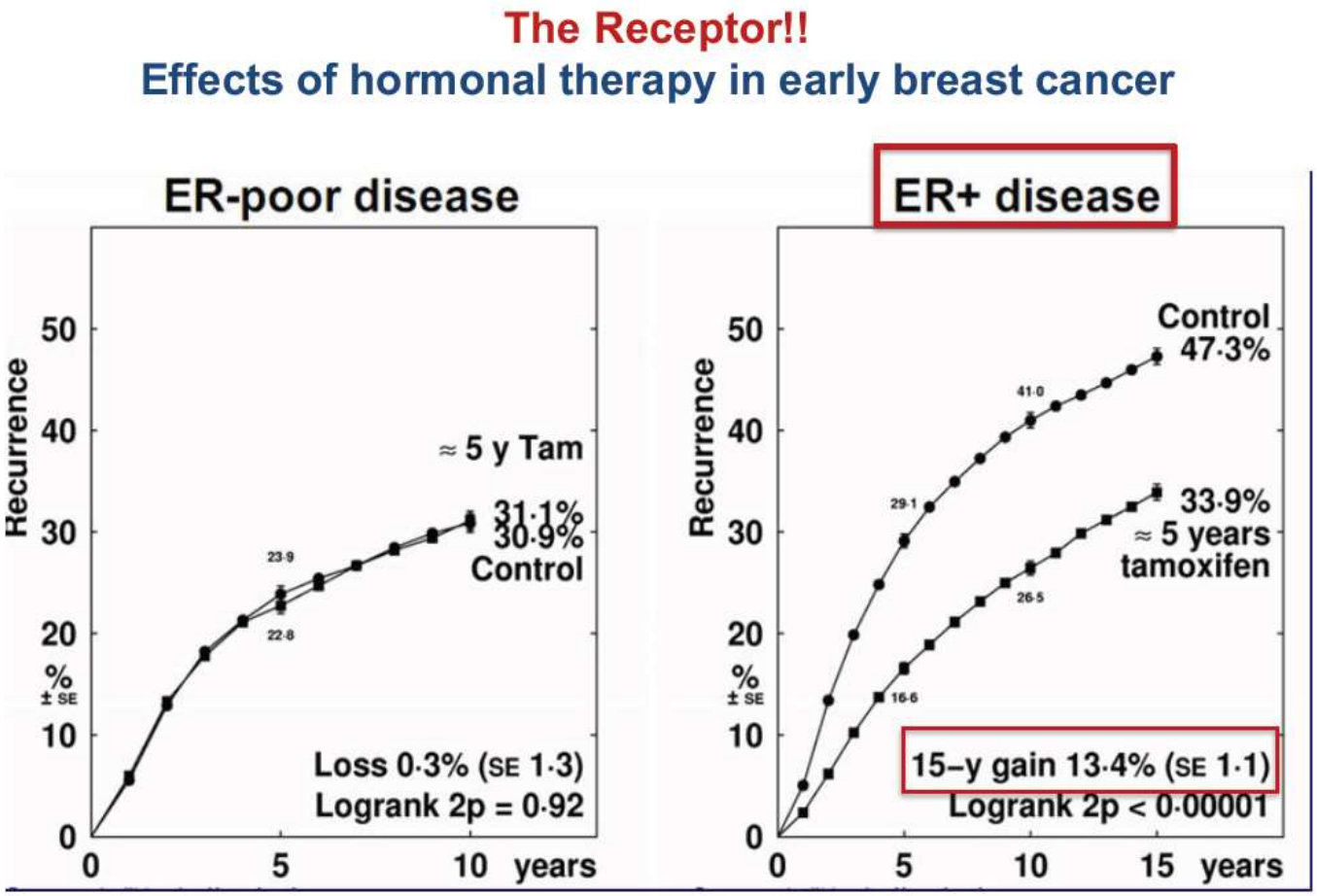
ET+CT

ET alone

ET, endocrine therapy

Sorlie T, et al. *Proc Natl Acad Sci U S A.* 2003;100(14):8418-8423.

Hormone therapy: When?



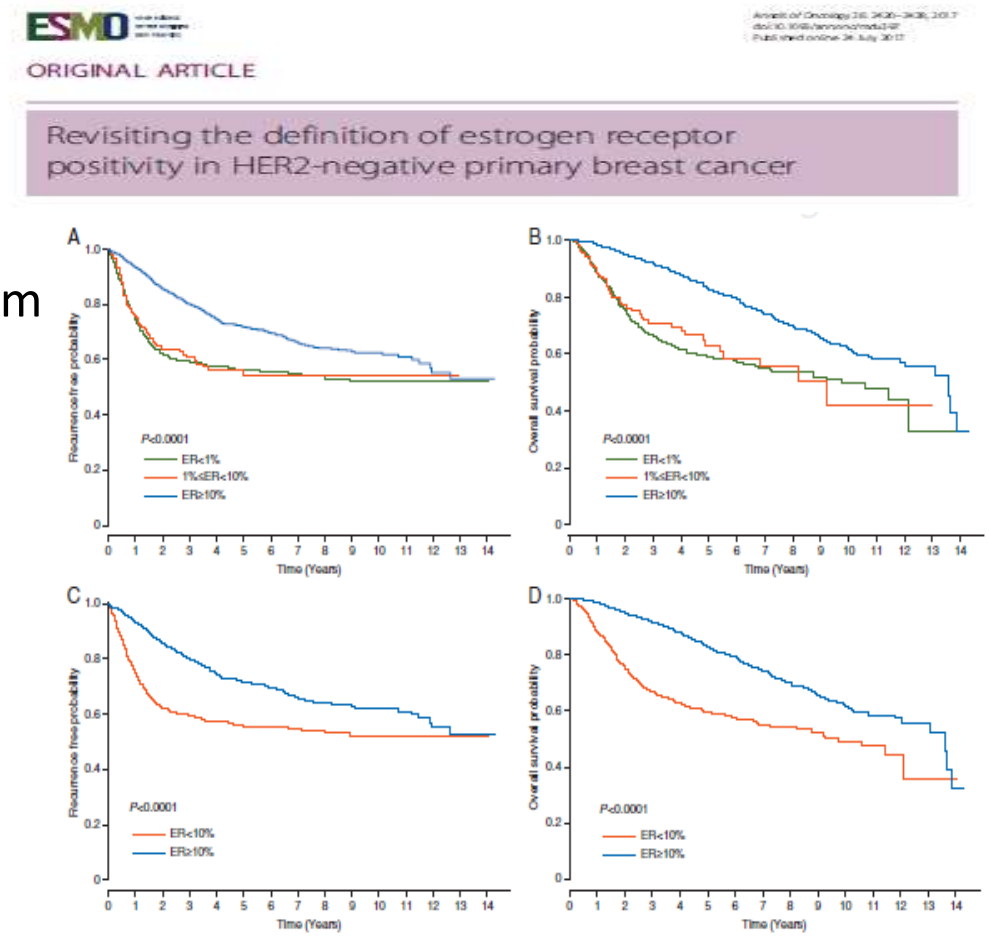
EBCTCG Lancet 2005

How to define ER+?

- Guidelines define BC HR+ if ≥ 1% cells stain positive for ER and/or PR

Senkus et al AnnOncol 26; 2015.
Hammond et al; JCO 2010

- ≥ 10% tumor cells ER+ benefit from adjuvant hormonal therapy
- Bordenline ER (1-9% cells) less certain benefit (if IHC is accurate)



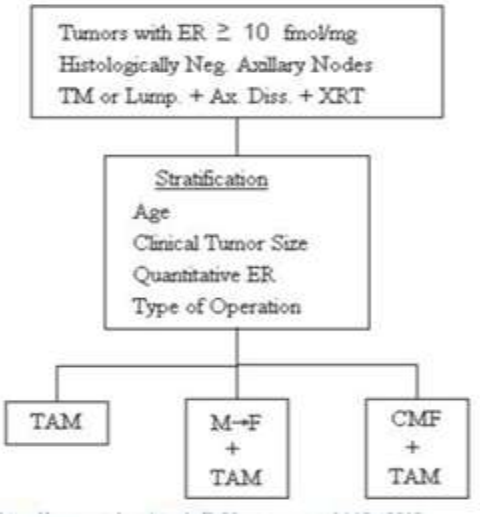
Fujii et Ann Oncol 2017

What do we need for chemo decision (Luminal cancers)

	Prognostic	Predictive (chemo)
Pathological variables	N, T, Grading, proliferation index, ER expression, HER2 status	?
Addional genomic tests	Genomic signatures (OncotypeDX™, Mammaprint®, Prosigna®, EpClin®, BCI™)	?

Chemotherapy for all?

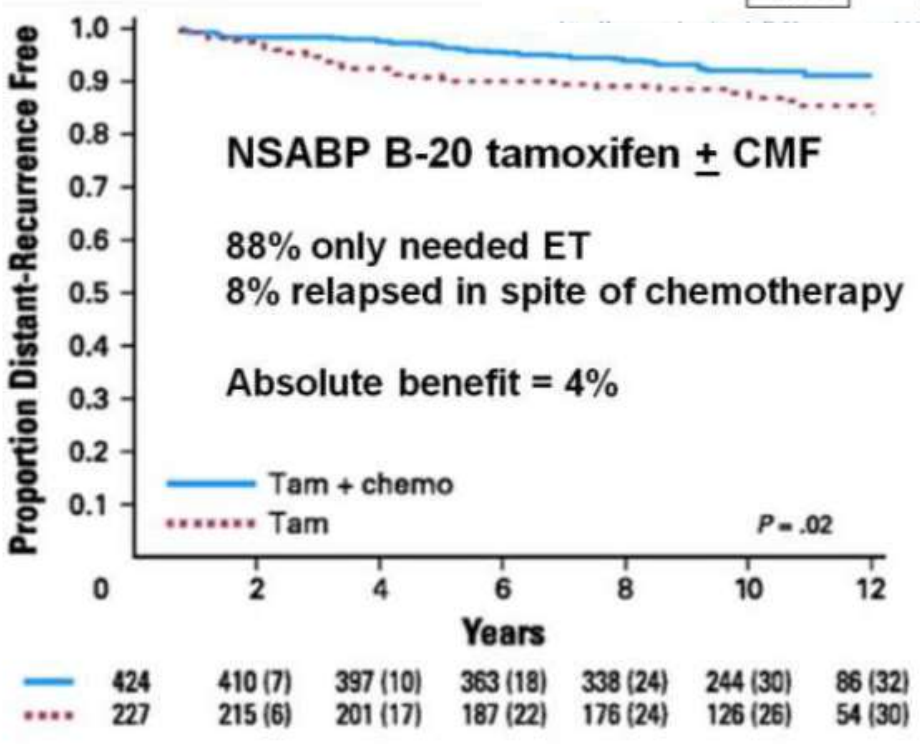
Women with tumors **≥1 cm** should all get chemotherapy



Adjuvant Therapy for Breast Cancer

National Institutes of Health
Consensus Development Conference Statement
November 1-3, 2000

ALL BENEFIT!

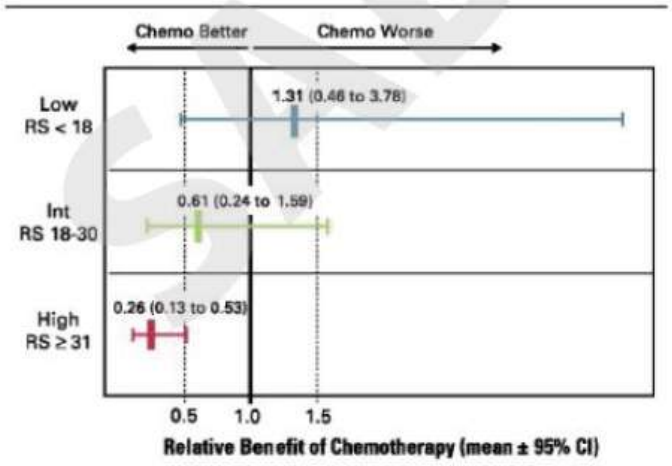


Paik et al, J Clin Oncol 2006

http://www.nsabp.pitt.edu/B-20.asp accessed 14Oct2018
& Fisher B, et al. JNCI 89.22:1673-1682, 1997

The same trial, 9 years after

2006 – Node Negative Disease: Genomic Assay-Stratified Outcomes And Said “Maybe Not All”.



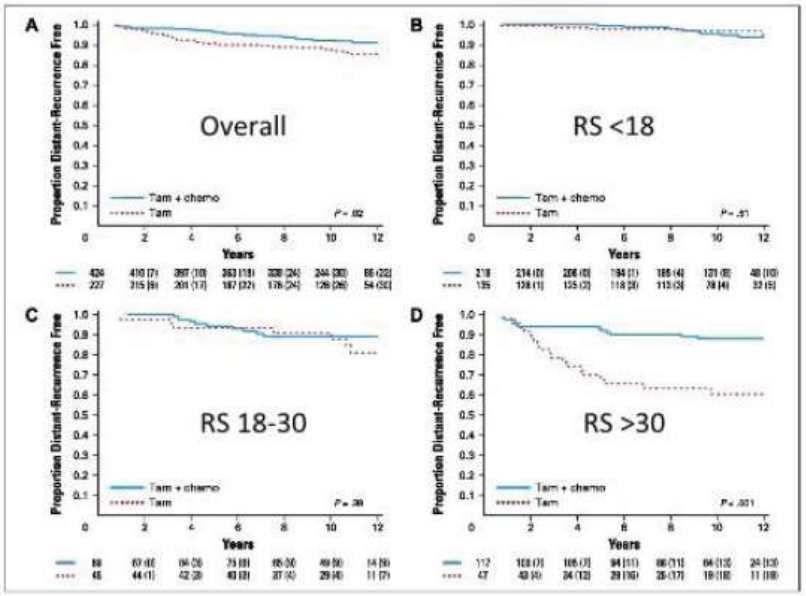


Fig 2. Kaplan-Meier plots for distant recurrence comparing treatment with tamoxifen (Tam) alone versus treatment with tamoxifen plus chemotherapy (Tam + chemo). (A) All patients; (B) low risk (recurrence score [RS] < 18); (C) intermediate risk (RS 18-30); (D) high risk (RS ≥ 31). The number of patients at risk and the number of distant recurrences (in parentheses) are provided below each part of the figure.

Paik S, et al. JCO 2006 Aug 10;24(23):3726-34

TailorX Design

2006-2010

Accrued 11,232
Registered 10,273

Recurrence Score Performed

Recurrence Score < 11
Hormonal therapy only
N=1629

Recurrence Score 11-25
Randomized to Hormonal or Hormonal + Chemo
N=6711

Recurrence Score >25
Hormonal therapy + chemo
N=1389

Sparano et al NEJM 2015 and 2018

TailorX Results

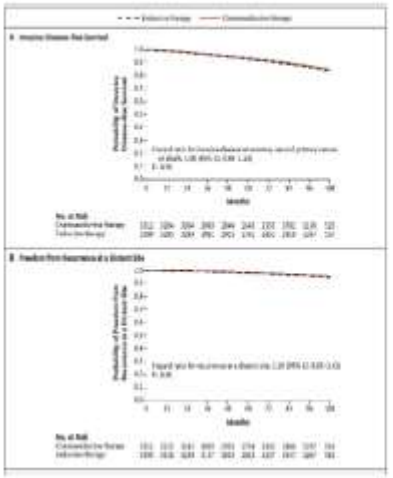
Recurrence Score 11-25
n=6621

Hormonal Rx

Chemotherapy and Hormonal Rx

Null hypothesis = no difference

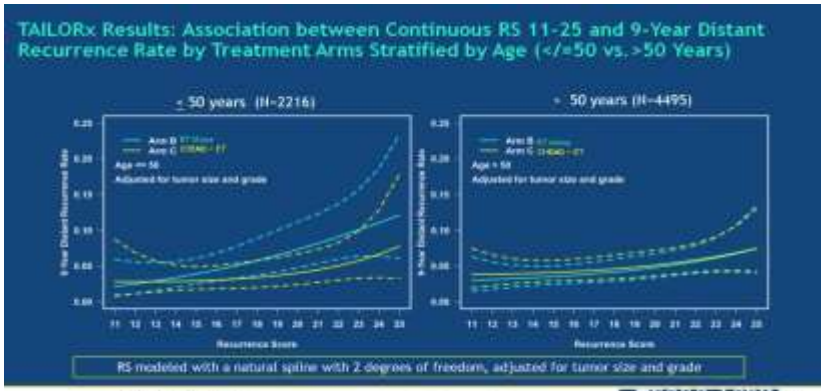
5 year IDFS of 87% vs 90% unacceptable and would disprove null hypothesis



- Age <50 = 33-34%
- Age <40 = 5%
- ER and PR positive = 92%
- T size 2.1-3 cm = 19%
- T size >3 cm = 5%
- Grade III: 13%
- Low clinical risk (per MINDACT criteria) = 74%

- **RS 16-25 (<50 YS)**
- **Some chemo benefit**

Estimate absolute Chemo Benefit	
RS 16-20 (N=886)	**Δ + 1.6% (+ SE 1.9%)**
RS 21-25 (N= 476)	**Δ + 6.5% (+ SE 3.7%)**



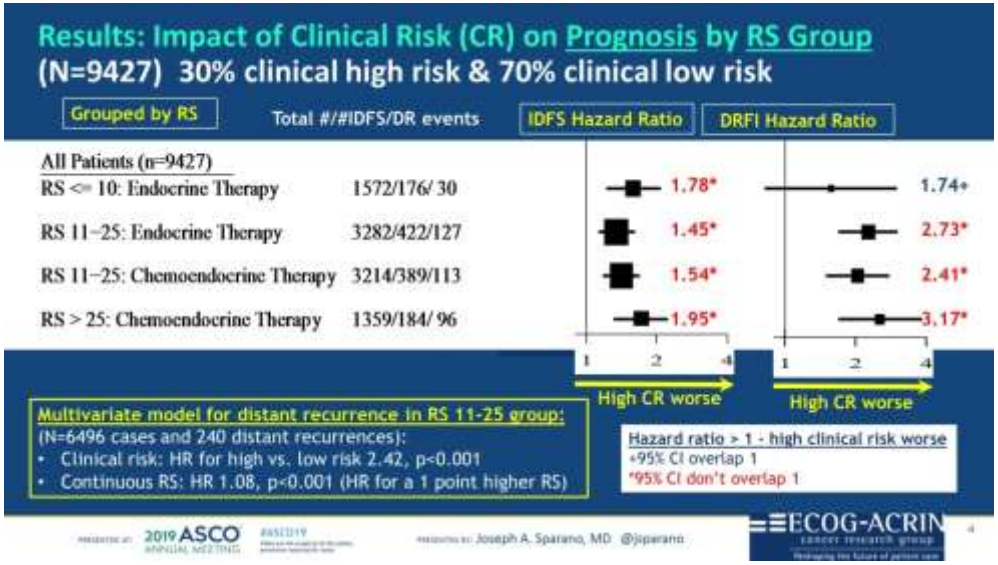
Is genomic profiling going to one day replace traditional clinical and pathological risk factor–based prognostication?

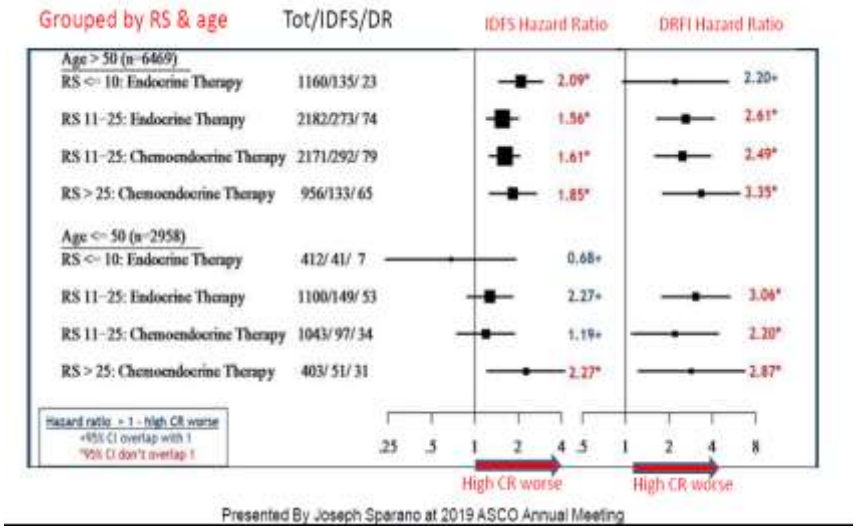
- A routine pathology—examining the levels of ER and PgR, looking at the grading of the tumor, at the proliferation indices, measures like Ki67—actually is really good in good hands at doing a very similar thing.

- Eventually, the genomic scores complement what the traditional pathology review shows
  - E.g. A tumors **with a score of 19** and lower grade still do a little better than tumors that are higher grade
  - Tumors that are strongly ER-positive still do better than tumors that are not so strongly ER-positive

Results: impact of Clinical Risk (CR) on prognosis by RS and age

- **Low risk**
  - Tumor ≤ 1 cm & high grade
  - Tumor ≤ 2 cm & int. grade
  - Tumor ≤ 3 cm & low grade
- **High risk** – not meeting low risk criteria





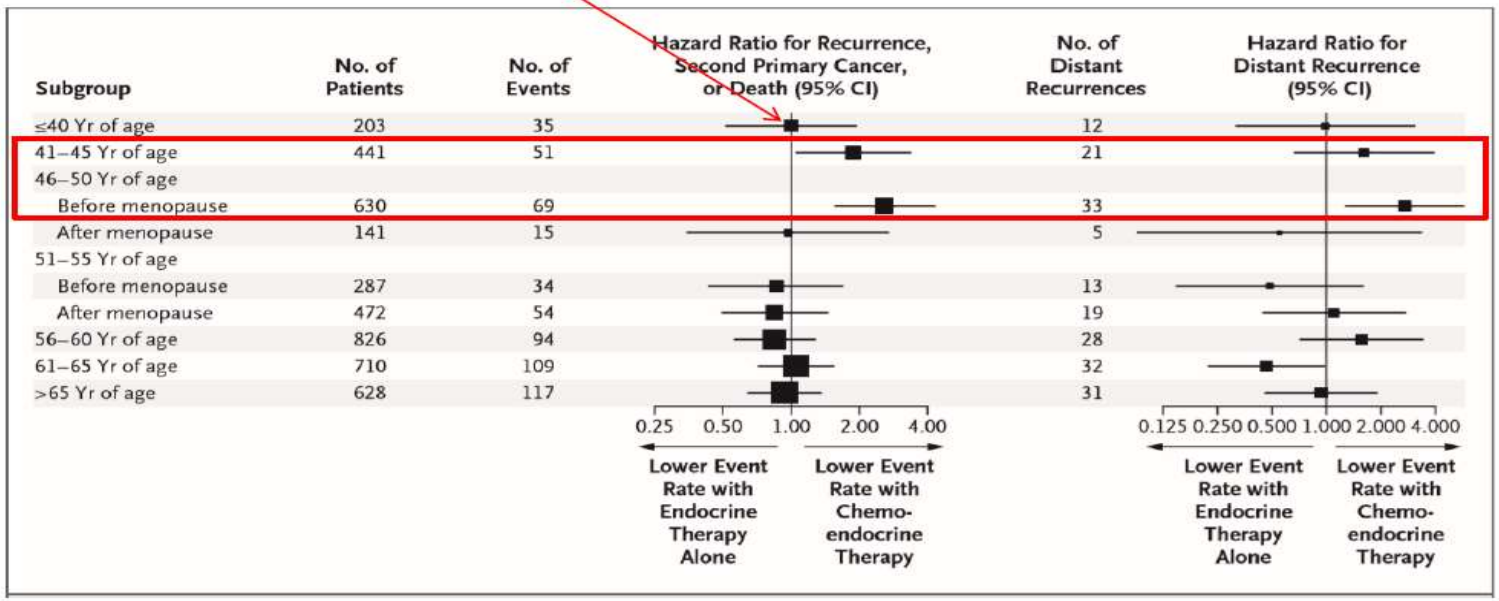
Presented By Joseph Sparano at 2019 ASCO Annual Meeting

Clinical risk provides additional prognostic information to RS for distant recurrence

- In RS 11-25 group irrespective of chemo use – 2.5-3x relative, 5% absolute Δ
- In RS 26-100 group treated with chemo + ET – 3x relative, 10% absolute Δ

Effect of Age and Menopausal Status on Chemotherapy Benefit

(RS 16-25)

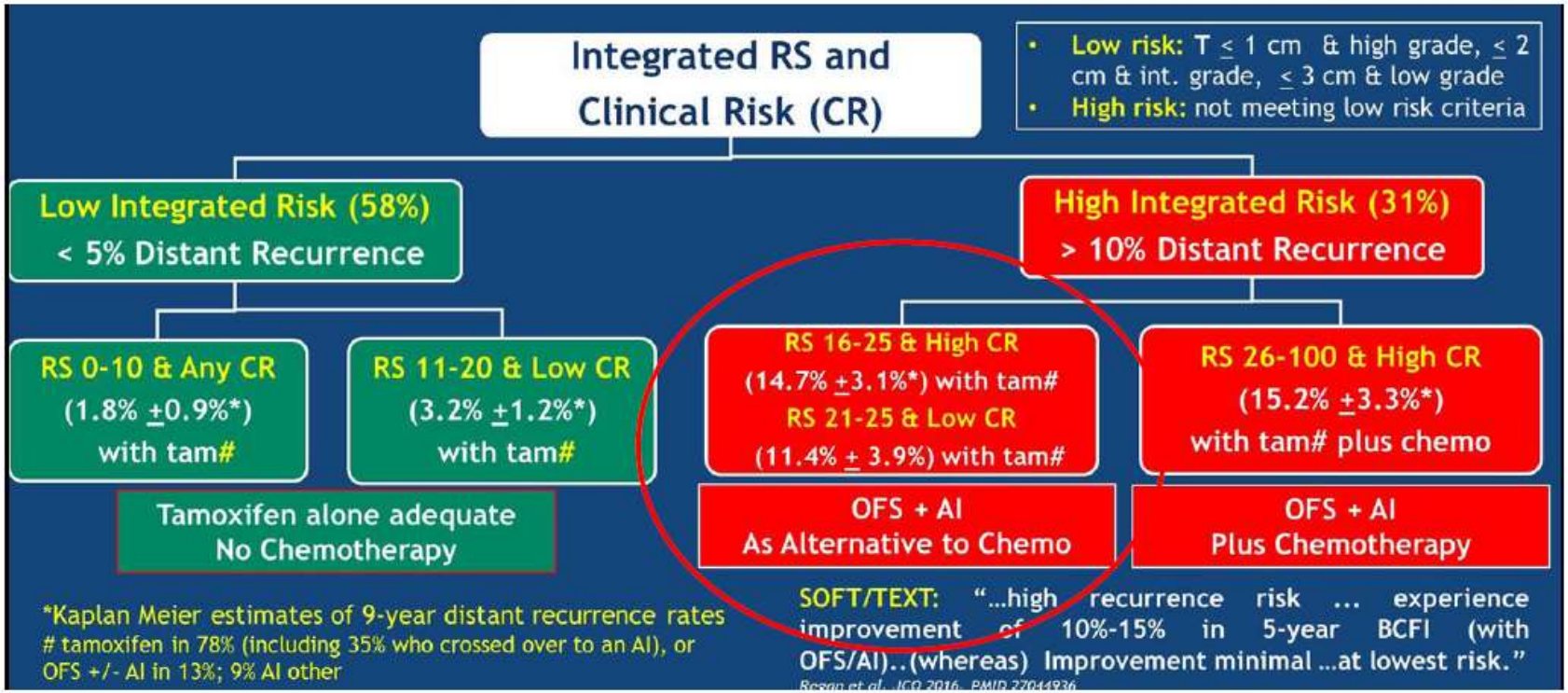


Sparano JA et al. N Engl J Med 2019;380:2395-405.

Absolute chemo benefit if premenopausal and age 45-50 with RS 16-25

Castration effect associated with cytotoxic therapy, rather than an effect in eradicating micrometastatic disease.

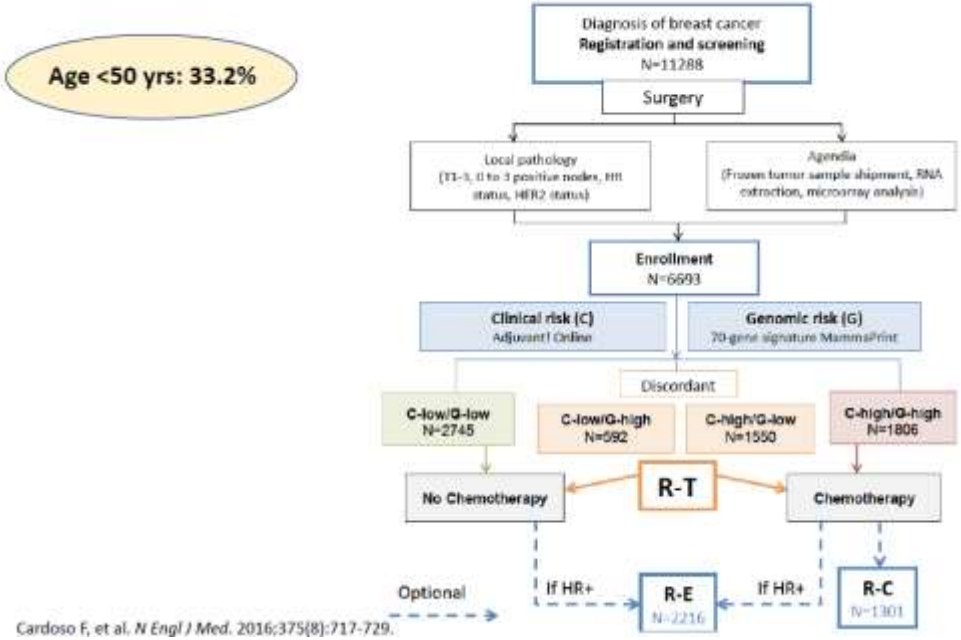
Potential Clinical Utility of Integrated RS and Clinical Risk for Guiding treatment in Women **< 50 years**



Is chemotherapy needed in Node + (1-3)

- Data will not be avaible from RxPonder for several years
- Are we going to treat all pts with 1-3+ Nodes with chemotherapy?
- MINDACT supports use of genomic assay in positive disease
- We can extrapolate results from TailorX (N0) and MINDACT (N+)
  - Not all studies can be conducted in all subsets of pts

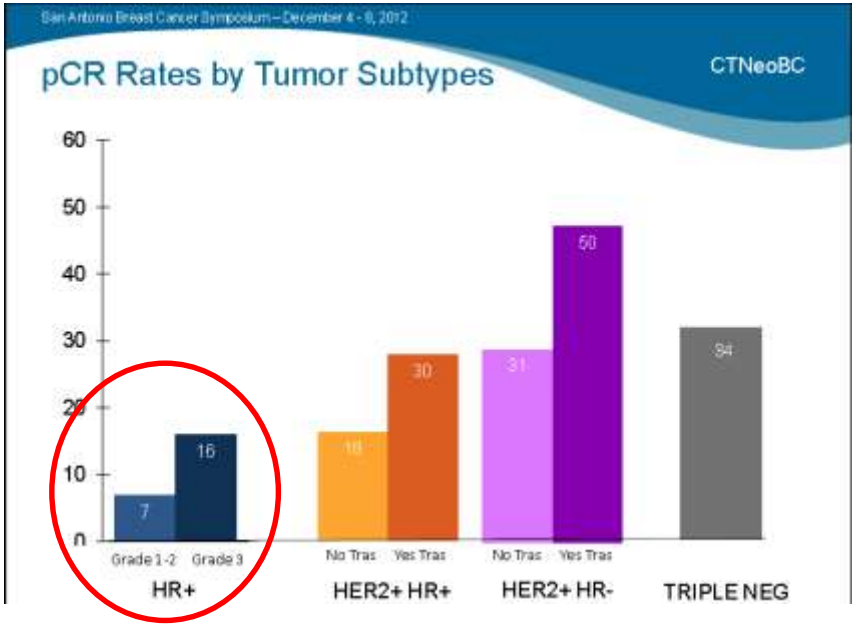
Prospective Validation of 70-Gene Expression Assay in Node-POSITIVE Patients: MINDACT



Cardoso F, et al. *N Engl J Med*. 2016;375(8):717-729.

Lesson learned from the neoadjuvant setting

ER-positive/HER2-negative carcinomas, especially of the lobular histology and luminal A-like subtype, are generally less responsive to primary CT and may benefit more from primary ET



Neoadjuvant treatment in ER+ BC treated with ET o CT:
Impact of recurrence score on response

	RS < 11	RS 11 to 25		RS > 25
Treatment	ET	ET	CT	CT
N	12	18	11	14
Clinical Response Rate	83%	50%	72%	93%
pCR	0%	0%	0%	14%

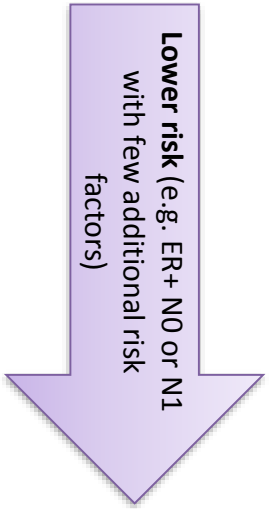
Bear HD, et al. J Surg Oncol 2017;115:917-23

Which chemo regimen, if chemo

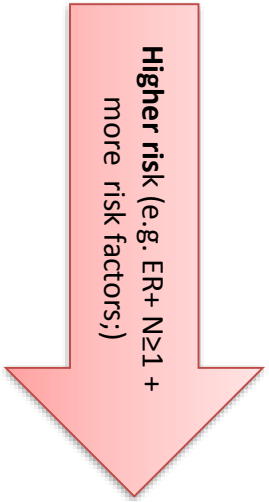
Indications for Chemotherapy

- ER+ and risk factors
  - grade 3 or
  - N≥2 or
  - pT≥3
  - high proliferation or
  - low ER/PgR or
  - high risk MGS

Preferred Regimens



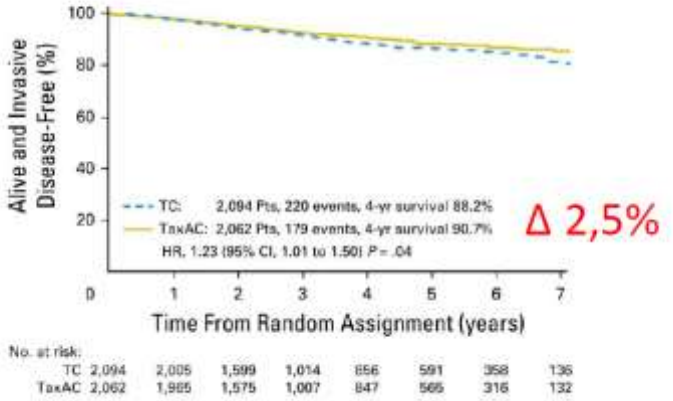
Anthracycline-free regimen (e.g. docetaxel + cyclophosphamide)

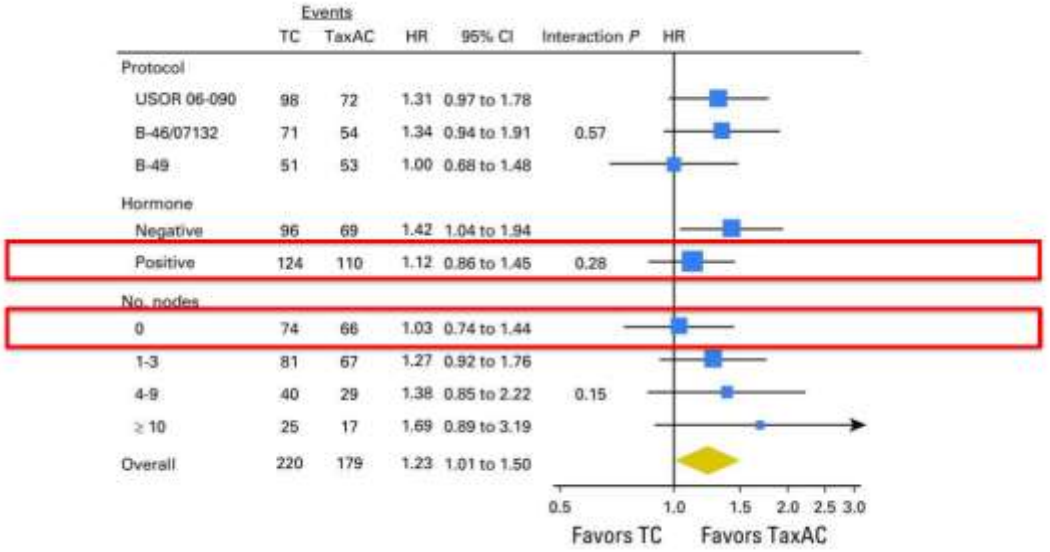


Anthracycline + taxane(e.g. AC →weekly paclitaxel, or TAC)

ABC trials: descalation?

Joint Analysis of 3 ABC Trials
TC vs TaxAC
4242 high risk pts





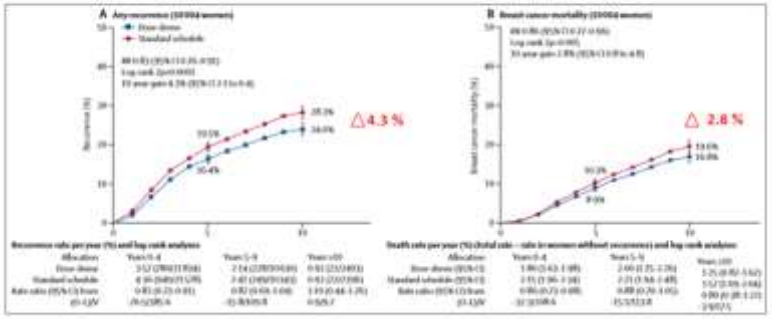
Blum et al JCO 2017

Dose dense regimens: escalation?

Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials

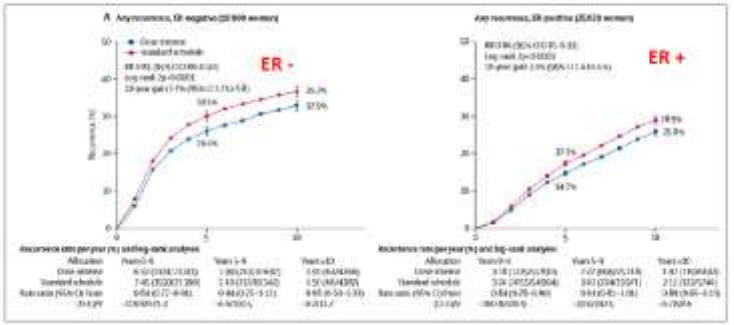
Summary

Dose-dense (2-weekly) chemotherapy versus the same chemotherapy given 3-weekly



Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Lancet 2019; 393: 1440–52

10-year recurrence by oestrogen receptor status



Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Lancet 2019; 393: 1440–52

CLINICAL PRACTICE GUIDELINES

The use of dose-dense schedules [with G-CSF support] should be considered, particularly in highly proliferative tumours

Aiom

NCCN National Comprehensive Cancer Network®

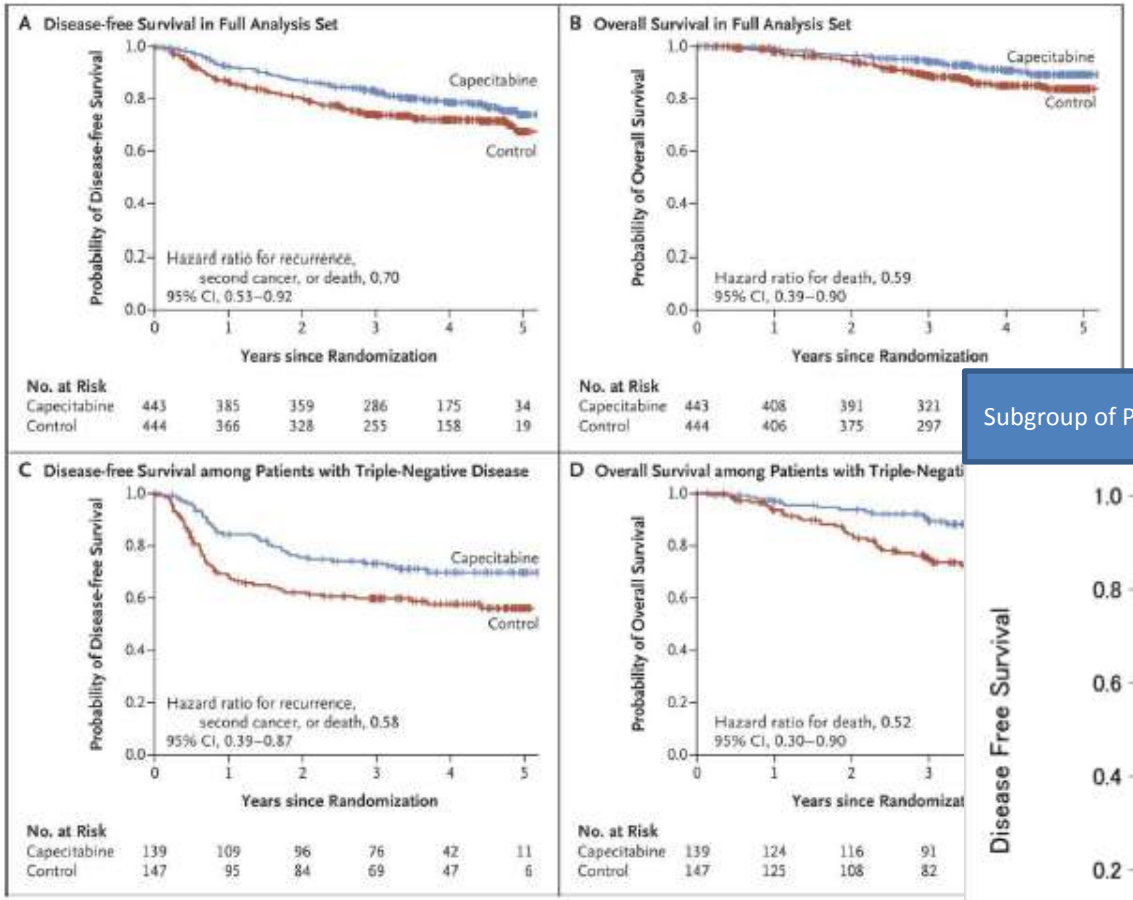
Impact of Cumulative Chemotherapy Dose on Survival With Adjuvant FEC-D Chemotherapy for Breast Cancer

Zachary Veitch, MSc, MD[a,b]; Omar F. Khan, MD[a]; Derek Tilley, MSc[c]; Patricia A. Tang, MD[a]; Domen Ribnikar, MD[b]; Douglas A. Stewart, MD[a]; Xanthoula Kostaras, MSc[c]; Karen King, MD[d]; and Sasha Lupichuk, MD[a]

- 1,302 women with stage I-III HER2-negative breast cancer, included in the Alberta Cancer Registry,received between 4 and 6 cycles of (FEC-D).
- Reduced doses of chemotherapy were received by 16% of patients, while the remaining 84% received at least 85% of their total intended chemotherapy dose.
- Patients who received at least 85% of their total chemotherapy dose had significantly higher 5-year DFS and OS compared to patients who received reduced doses
  - DFS; 86% vs 79%; P = .025
  - OS ; 89% vs 81%; P = .001
- Delayed dosing did not impact outcomes, nor did use of granulocyte colony stimulating factor (GCSF).

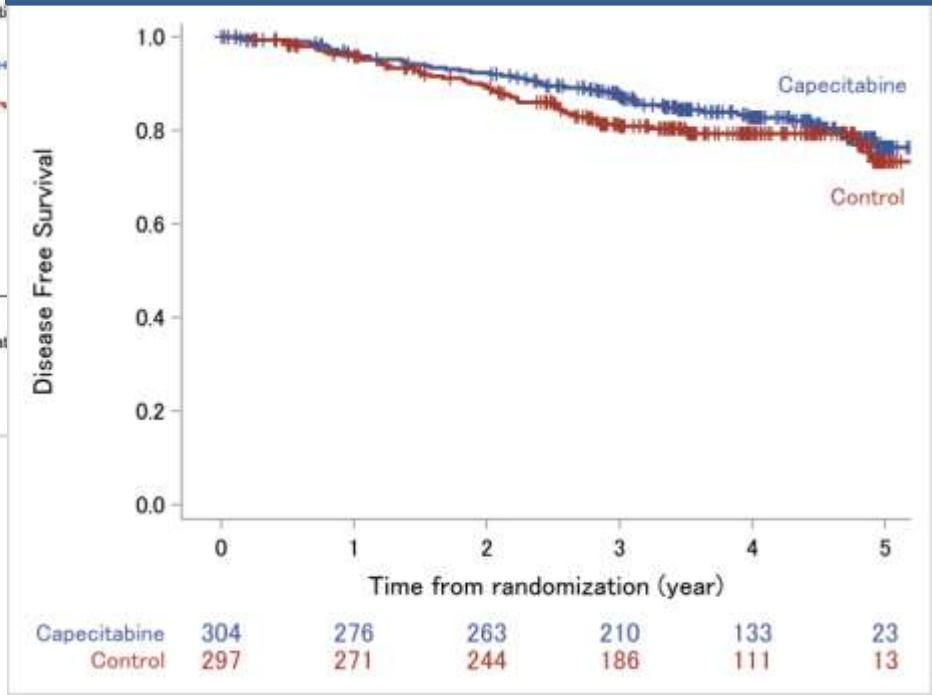
J Natl Compr Canc Netw. 2019;17:957-967

Adding capecitabine
Residual disease after neoadjuvant CT ?



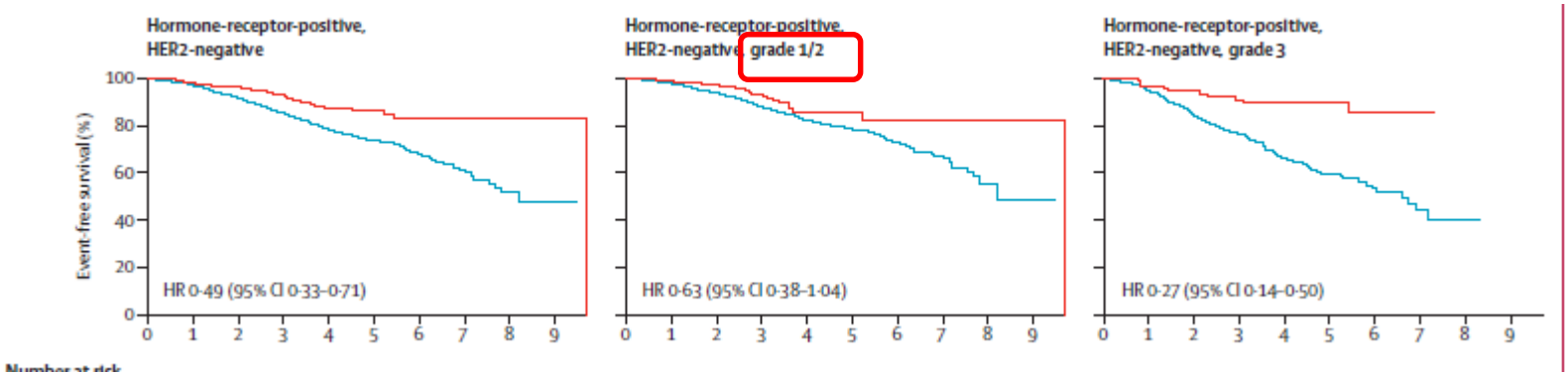
910 HER2- pts with RD and N+ after neoadjuvant chemotherapy

Subgroup of Patients with Hormone Receptor Positive Disease



Masuda, et al. NEJM 2017, ASCO 2018

pCR and long term clinical benefit in BC: the CTneoBC Pooled analysis (12 trials, 12000 pts)

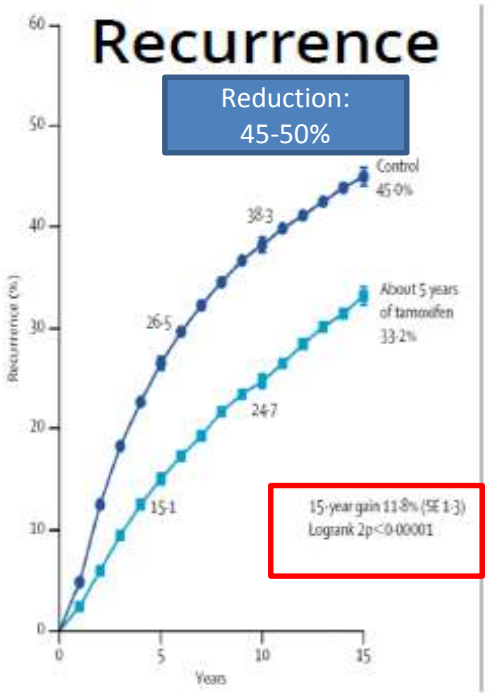


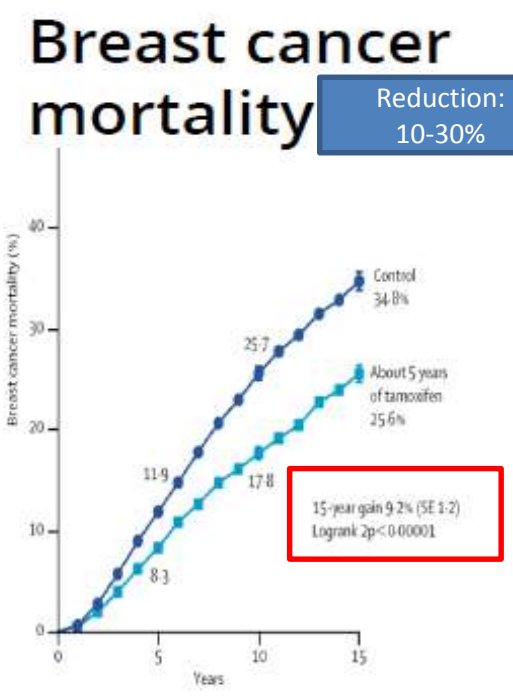
ER- positive Non pCRs do quite well after chemotherapy

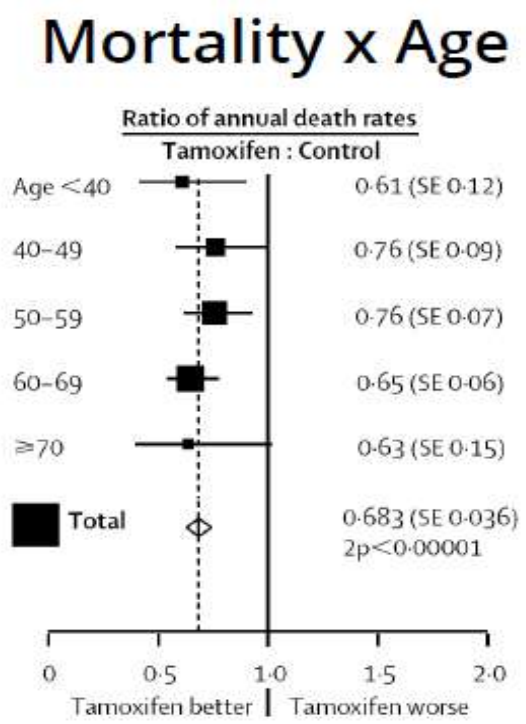
Selection of Adjuvant Endocrine Therapy

- Post-menopausal
  - Aromatase inhibitors
    - Drug of choice for most
      - Upfront x 5-10 ys
      - Sequential after tamoxifen x 2-3 years; total 5-10 ys
      - Sequential after tamoxifen x 5 years; total 10-15 ys
  - Tamoxifen
    - Appropriate for some pts; total 5-10 years
- Premenopausal
  - Tamoxifen 5-10 ys
  - Ovarian ablation (OFS) with tamoxifen or AI x 5 ys

Adjuvant Tamoxifen Prolongs Survival after ER+ Breast Cancer



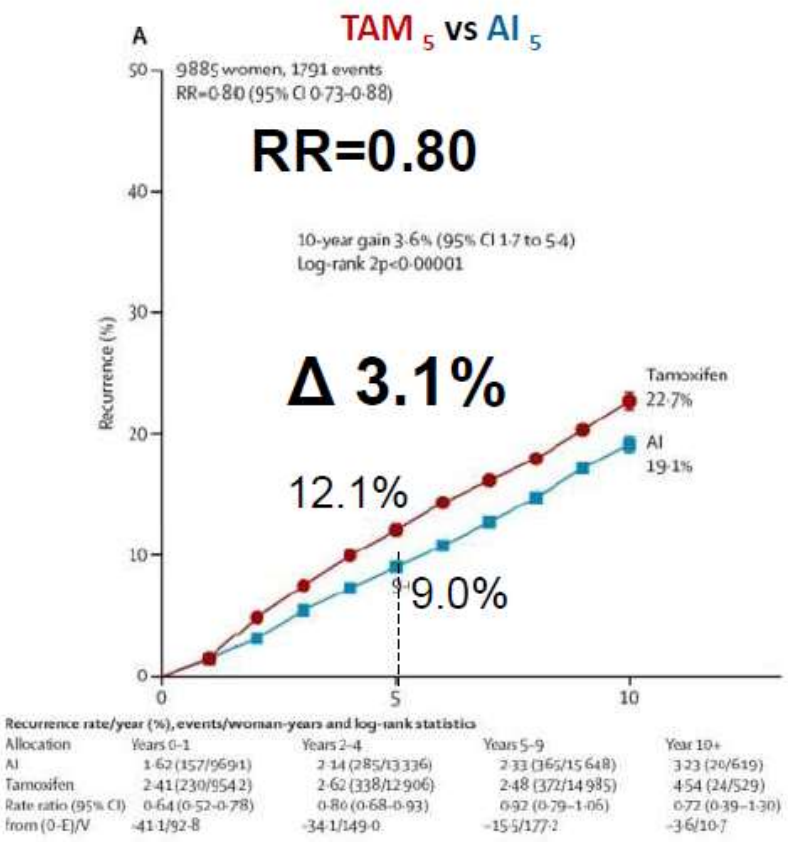




Similar *proportional* reduction of risk of recurrence in N0 and N+
Absolute DFS benefit @ 15 years: N–, 9.1%; N+, 16.1%

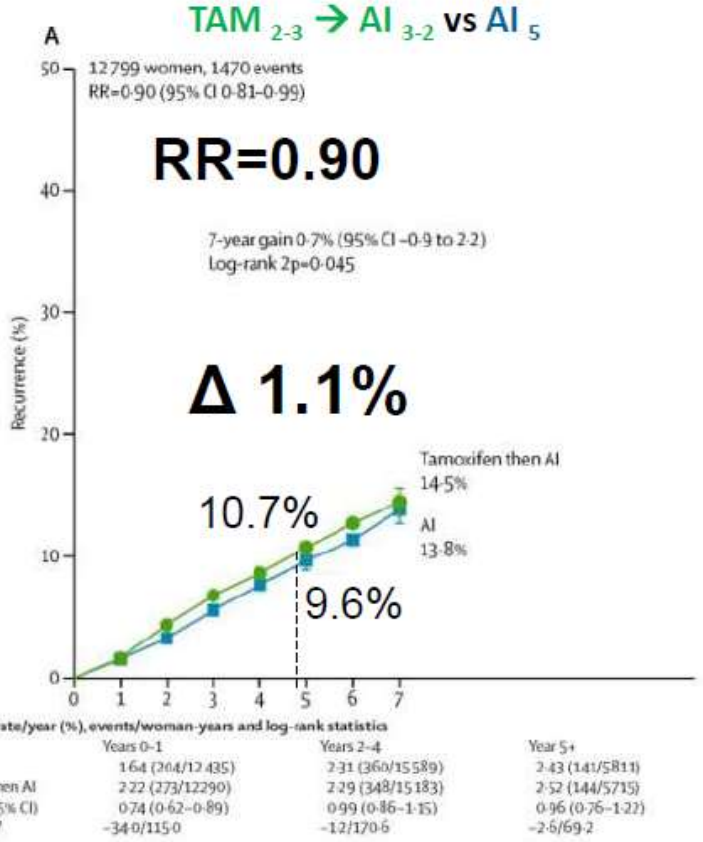
EBCTCG. Lancet 2005 365 1687

Patient-level meta-analysis of RCTs with endocrine therapy



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13 336)	2·33 (365/15 648)	3·23 (26/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12 906)	2·48 (372/14 985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O-E)/V	-41·1/92·8	-34·1/149·0	-15·5/177·2	-3·6/10·7

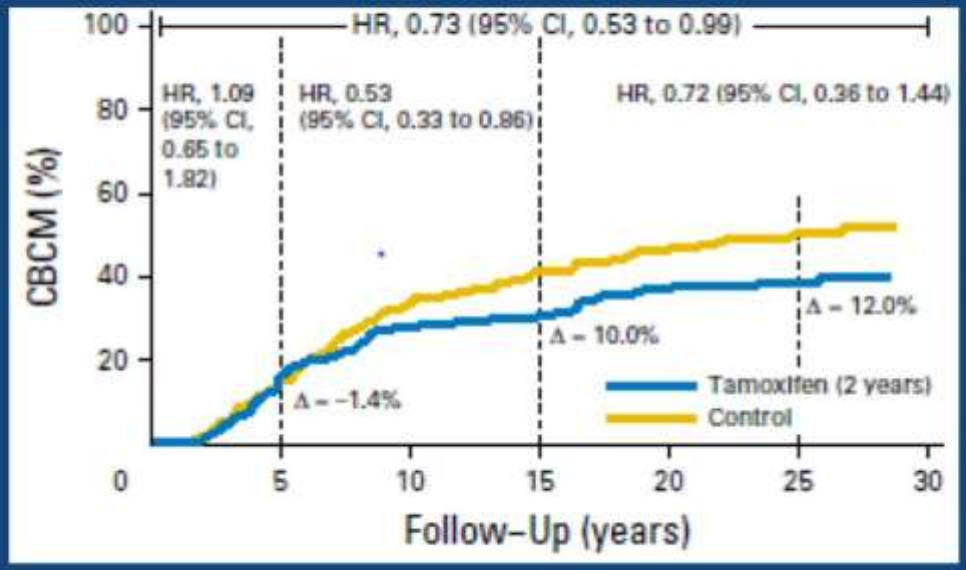


Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	1·64 (204/12 435)	2·31 (360/15 589)	2·43 (141/5811)
Tamoxifen then AI	2·22 (273/12290)	2·29 (348/15 183)	2·52 (144/5715)
Rate ratio (95% CI)	0·74 (0·62–0·89)	0·99 (0·86–1·15)	0·96 (0·76–1·22)
from (O-E)/V	-34·0/115·0	-1·2/170·6	-2·6/69·2

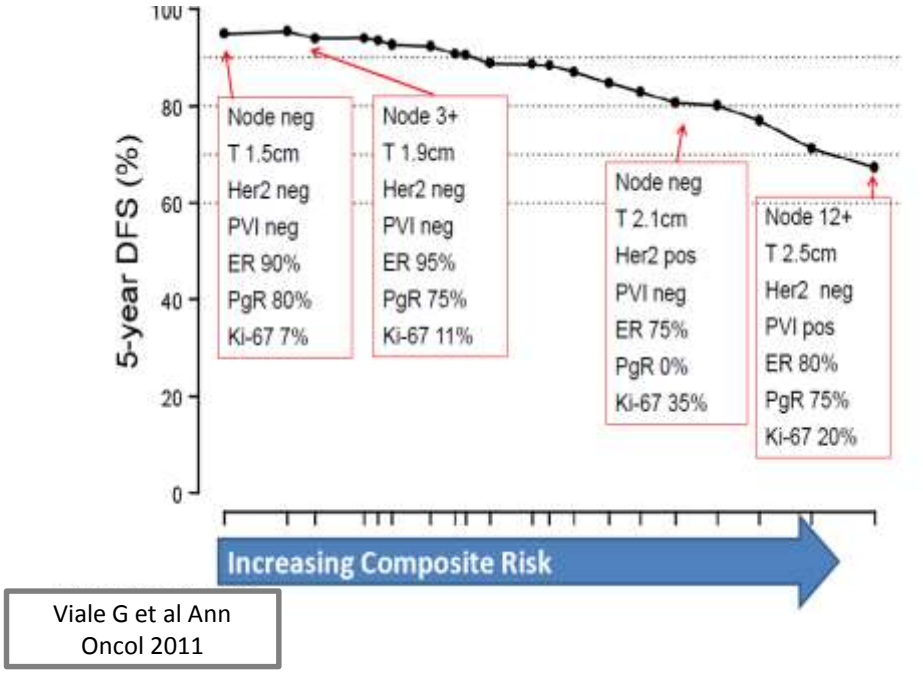
EBCTCG. Lancet 2015

Adjuvant Tamoxifen for 2 years Premenopausal ER+ve Reducing Breast Cancer Mortality @ 25 years!

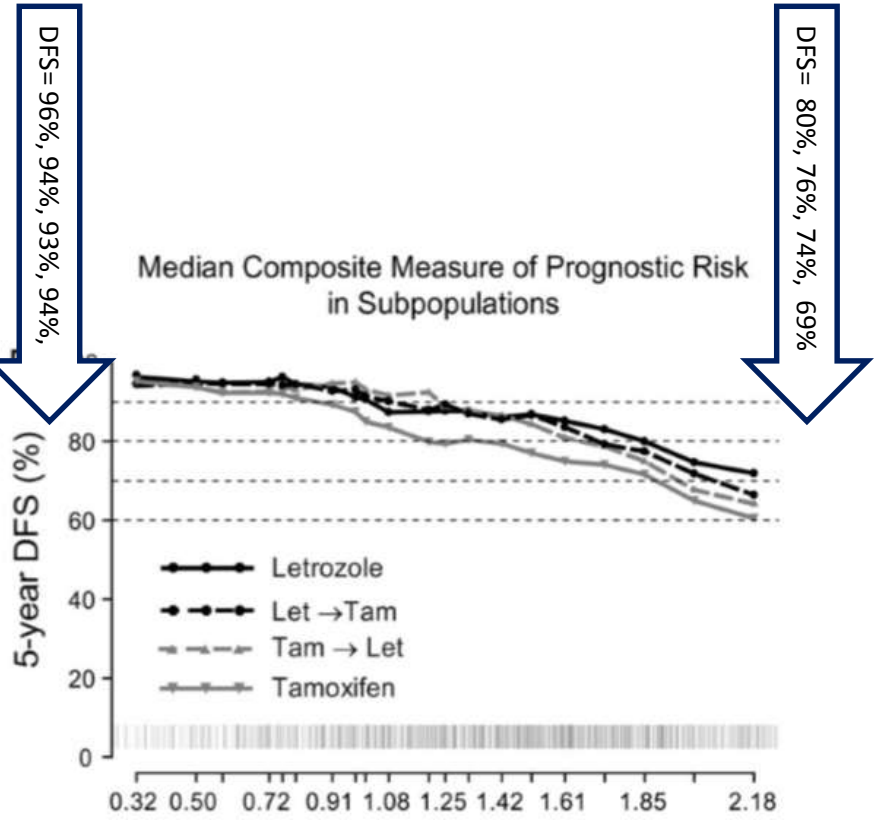


OK to stop
in case of severe intollerance

Which post-menopausasl patients benefit most from adjuvant aromatase inhibitors?



Viale G et al Ann Oncol 2011



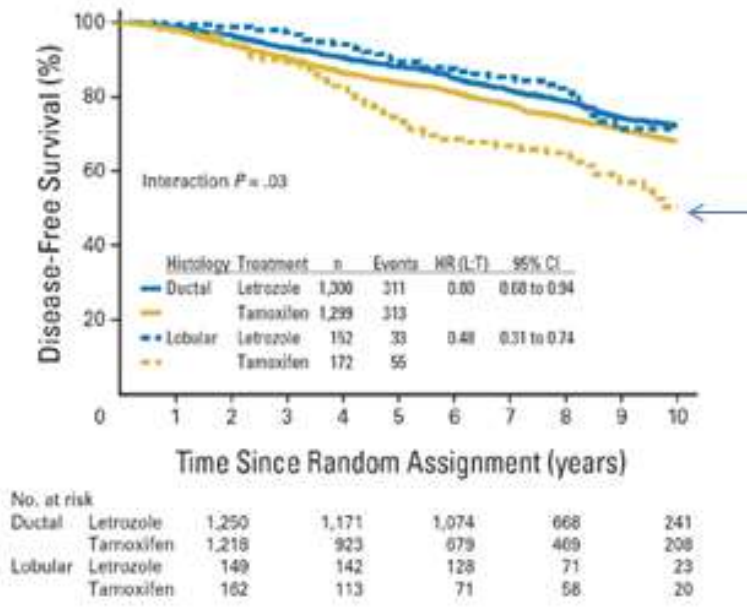
A composite measure of risk informs treatment selection better than individual biomarkers and supports the choice of 5 years of letrozole for patients at highest risk for recurrence.

Tamoxifen alone is still appropriate for some patients

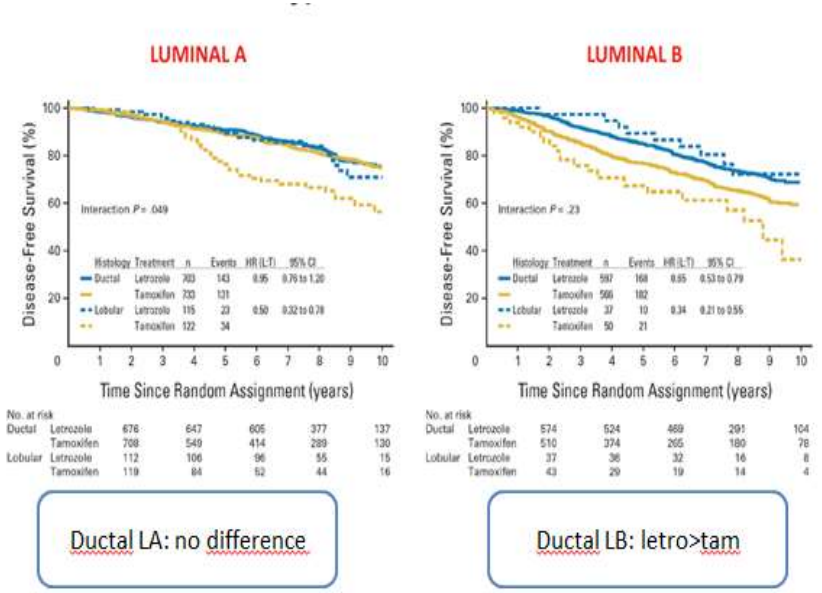
Better individual tollerability

Which post-menopausasl patients benefit most from adjuvant aromatase inhibitors?

Histology and letrozole effectiveness



Intrinsic subtypes and letrozole effectiveness



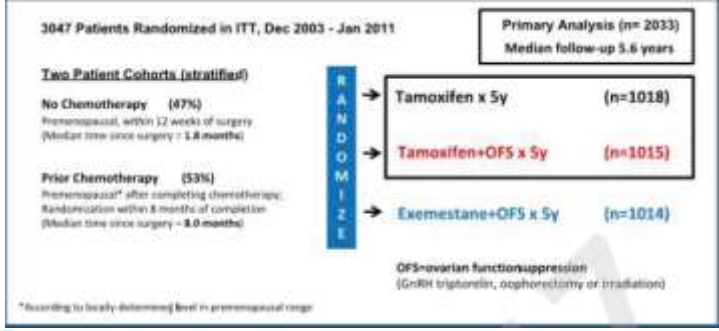
Ductal LA: no difference

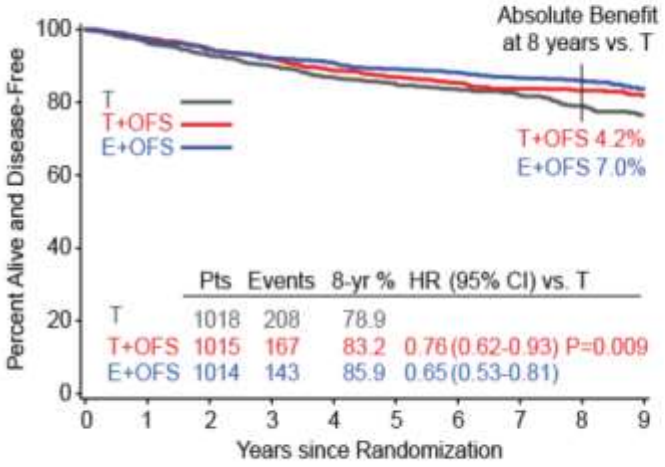
Ductal LB: letro>tam

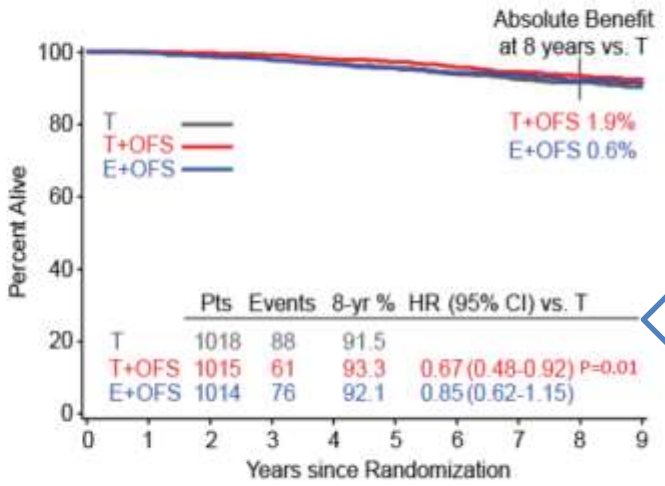
Metzger Filho O et al JCO 2015

Does ovarian function suppression/ablation (OFS) improve outcomes, and if so in which patients?

Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer







SOFT- 8 years update

T + OFS significantly improves DFS vs T-alone in overall population

- **Addition of OFS to TAM** significantly improves DFS and OS at 8 ys median FU in DFS in particular for < 35 yrs pts (HR=0.66)
- Population not receiving chemotherapy has a **low risk** of distant metastases at 8 yrs with TAM alone; however, they can derive some benefit from addition of OFS

8-year DFS (%)

	T	T + OFS	HR (T+OFS vs T)	E + OFS	HR (E+OFS vs T)
All	78.9	83.2	0.76 (0.62–0.93)	85.9	0.65 (0.53–0.81)
No chemo	87.4	90.6	0.76 (0.52–1.12)	92.5	0.58 (0.38–0.88)
Prior chemo	71.4	76.7	0.76 (0.60–0.97)	80.4	0.68 (0.53–0.88)
<35 yrs (n = 350)	64.3	73.0	0.66 (0.4–1.07)	77.4	0.52 (0.31–0.87)

Fleming G, et al. SABCS 2017: Abstract GS4-03.
Francis PA et al NEJM 2018

Quesito grade: soppressione ovarica + Tam (basso rischio)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

P.A. Francis, O. Pagani, G.F. Fleming, B.A. Walley, M. Colleoni, I. Láng, H.L. Gómez, C. Tondini, E. Ciruelos, H.J. Burstein, H.R. Bonnefoi, M. Bellet, S. Martino, C.E. Geyer, Jr., M.P. Goetz, V. Stearns, G. Pinotti, F. Puglisi, S. Spazzapan, M.A. Clement, L. Pavesi, T. Rubistaller, N.E. Davidson, R. Coleman, M. Debled, S. Buchholz, J.N. Ingle, E.P. Winer, R. Maibach, M. Rabaglio-Poretti, B. Ruepp, A. Di Leo, A.S. Coates, R.D. Gelber, A. Goldhirsch, and M.M. Regan, for the SOFT and TEXT Investigators and the International Breast Cancer Study Group*

N Engl J Med 2018;379:122-37.
DOI: 10.1056/NEJMoa1803164

OFS + Tam vs Tam, follow up mediano 8 anni:

- Confermato beneficio DFS
- Beneficio in OS
- Vantaggio evidente per le pazienti trattate con CT

Nelle donne in premenopausa con carcinoma mammario operato, recettori ormonali positivi, HER2 negativo, a basso rischio, è raccomandabile l'aggiunta della soppressione ovarica al tamoxifene?

Qualità Globale delle evidenze GRADE	2017 Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle donne in premenopausa con carcinoma mammario operato, recettori ormonali positivi, HER2 negativo, a basso rischio, l'aggiunta della soppressione ovarica al tamoxifene non dovrebbe essere presa in considerazione	Negativa Debole

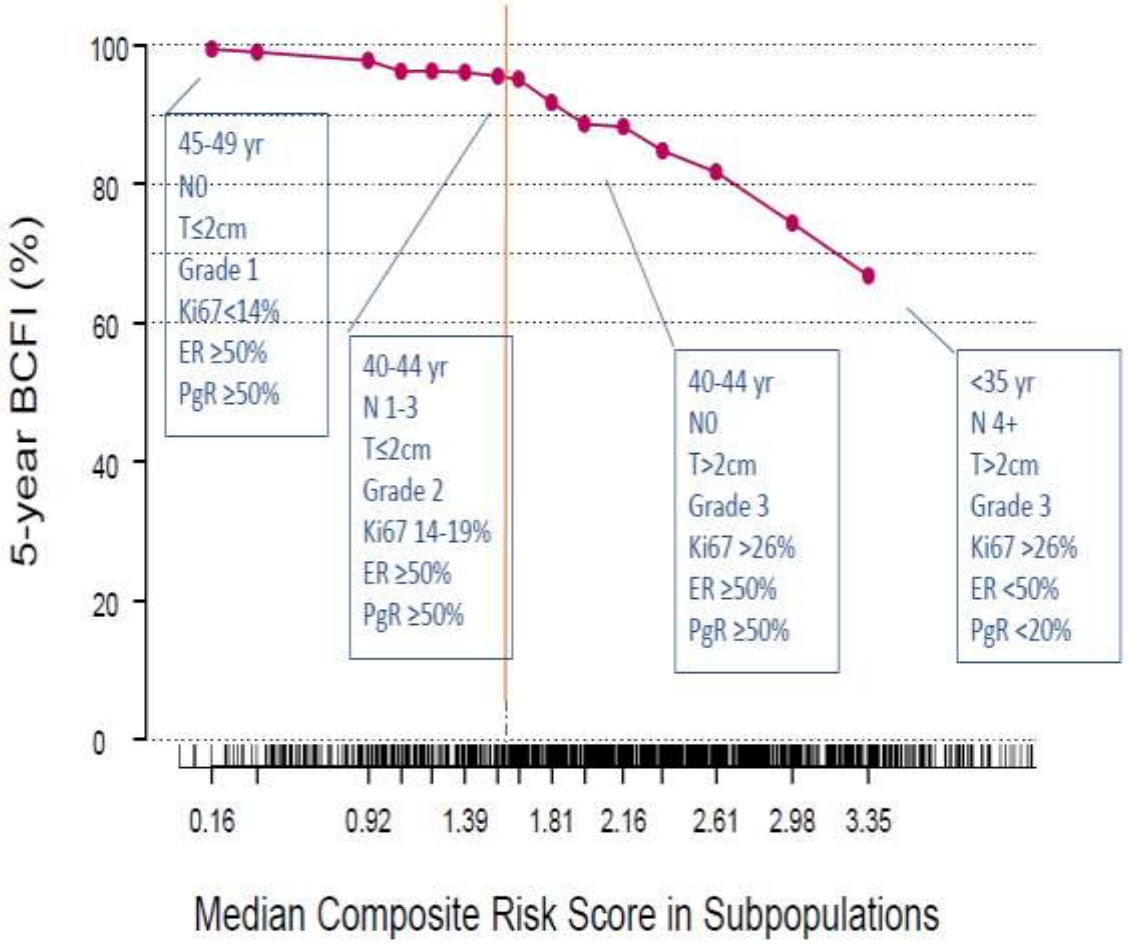
Leggere capitolo 15- Raccomandazioni prodotte secondo metodologia GRADE

Qualità Globale delle evidenze GRADE	2018 Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle donne in premenopausa con carcinoma mammario operato, recettori ormonali positivi, HER2 negativo, a basso rischio, l'aggiunta della soppressione ovarica al tamoxifene non dovrebbe essere presa in considerazione	Negativa Debole

Leggere capitolo 14- Raccomandazioni prodotte secondo metodologia GRADE

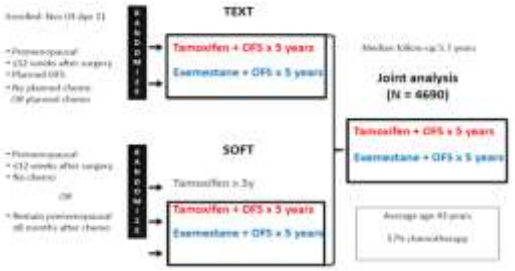
SOFT and TEXT HER2-negative population Composite risk and STEPP analysis

- Combined standard clinico-pathological features into a single value for each patient- a continuous, composite measure of recurrence risk: «composite risk»
- Age (5-ys groups), nodal status (0, 1-3, ≥4), T size (≤2, ≥2)
- ER (<50%, ≥50%), PgR (<20%, 20-49%, ≥50) ki67 (<14%, 14-19%, 20-25%, ≥26%)

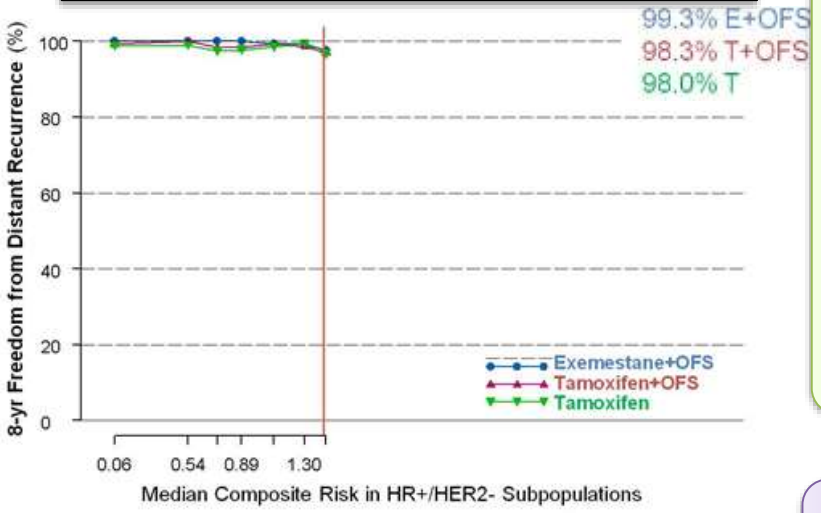


Regan et al; JCO 2016; ASCO 2018

Are aromatase inhibitors better than tam, if combined with OFS?

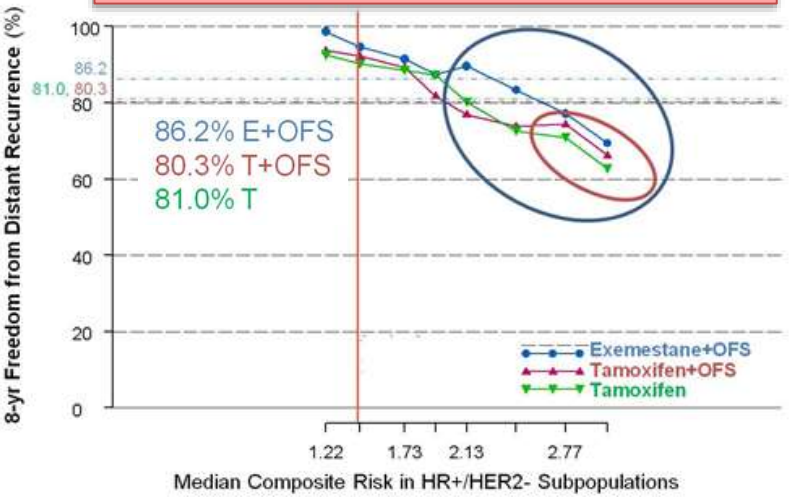


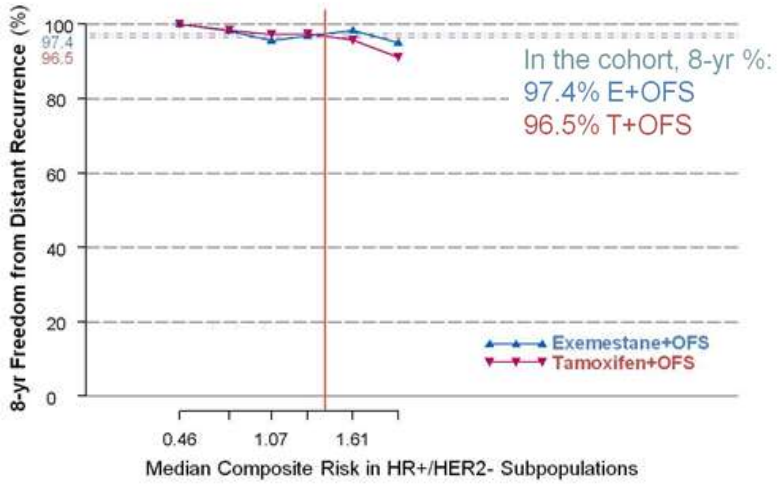
No Chemo



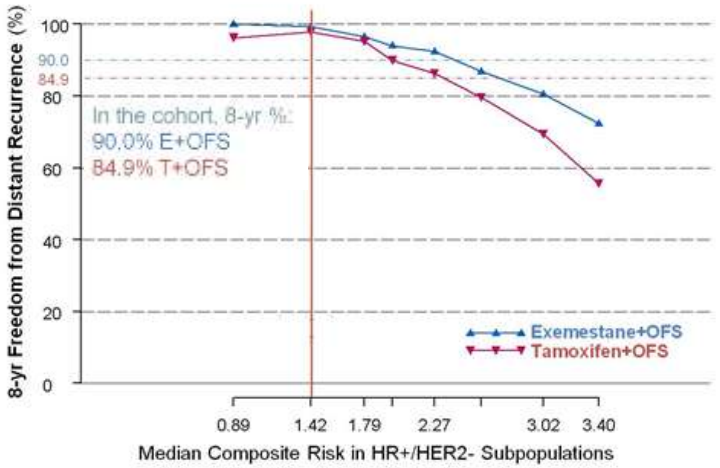
SOFT

Chemo





TEXT

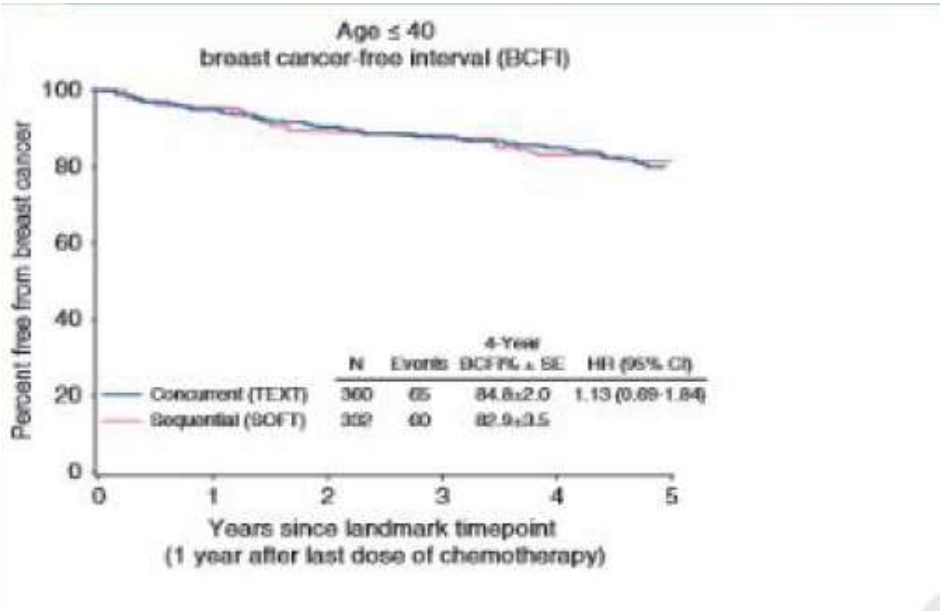


Regan et al; JCO 2016; ASCO 2018

Caution with IA

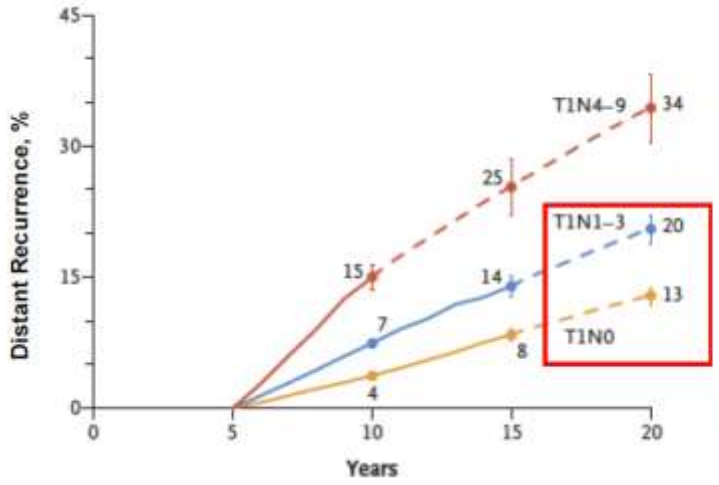
- Beware AI use in women < 50ys with chemotherapy-induced amenorrhea (unless LHRHa or Oophorectomy)-significant rates of ovarian recovery
- Prolonged amenorrhea on TAM is not equal menopause
- Tamoxifen reduces FSH and LH levels in postmenopausal women making determination of menopausal status more difficult
- The risk of OFR during treatment with AIs in amenorrheic women in their 40s is high, and AI therapy alone should be avoided in these patients.
- Concurrent use of LHRHa and chemotherapy is a safe option (provides some protection of ovarian function)

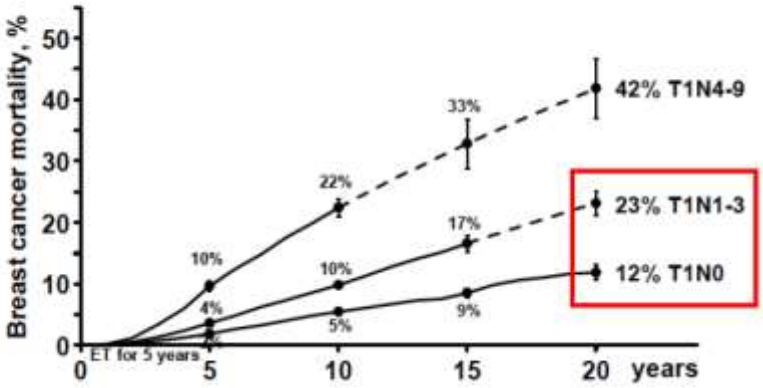
Non randomized comparative effectiveness modeling outcomes women ≤ 40 ER+ BC receinving chemotherapy and LHRH in TEXT (concurrent) or SOFT (sequential)



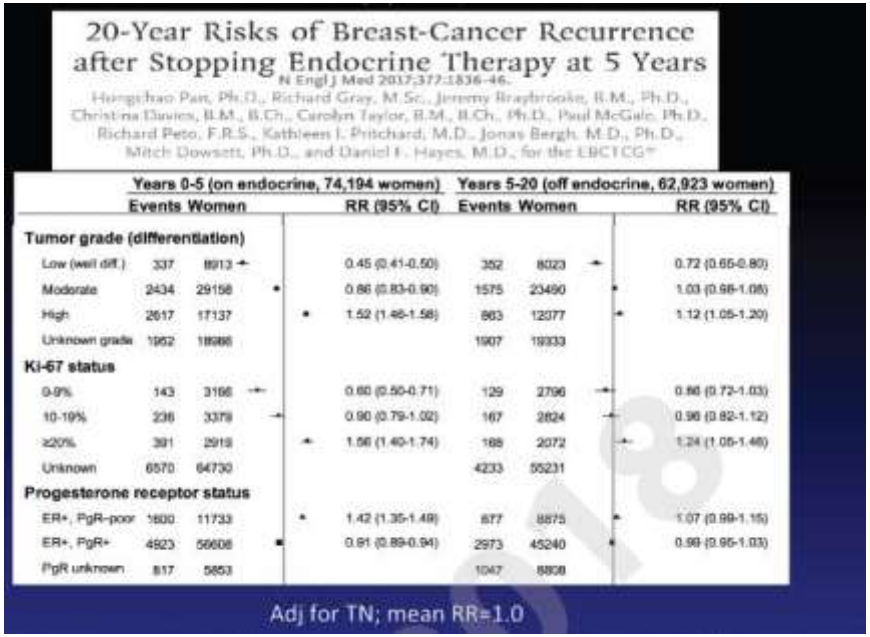
Smith et al JCO 2006
Guerrero et al Ann Oncol 2012
Krekow LK JCO 2016, 34.1594-600
Regan et al Ann Oncol 2017

Recurrence Risk After 5 Years of Adjuvant Endocrine Therapy





- After 5 years of adjuvant endocrine therapy, breast cancer recurrence continues to occur steadily from 5 years to 20 years
- Risk of DR and breast cancer mortality strongly correlates with original TN status (but also grading, ki67, PgR expression)



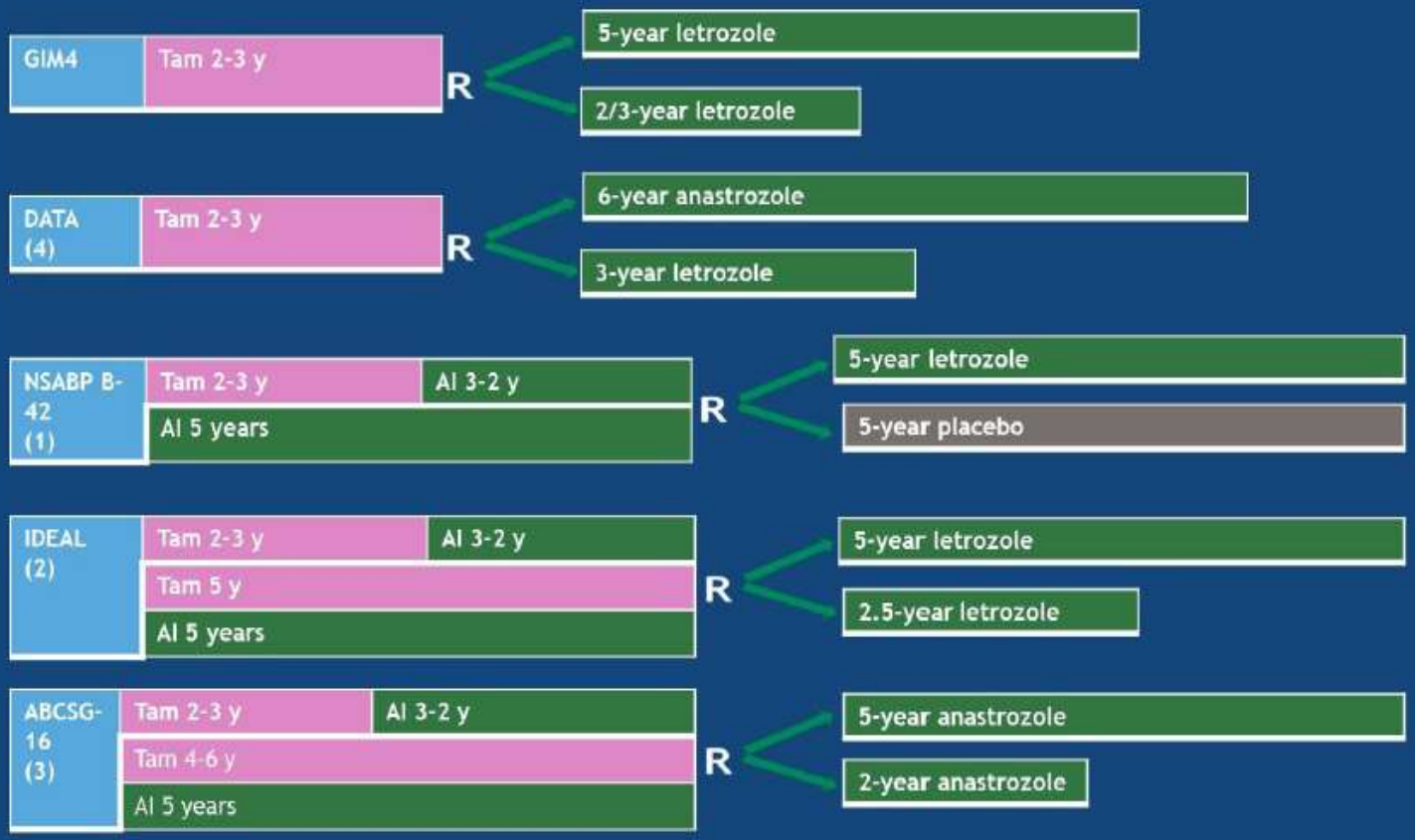
Pan H, et al. *N EnglJ Med.* 2017;377(19):1836-1846.

Extended Endocrine Therapy

- Extended endocrine therapy beyond 5 ys further reduced risk of recurrence
  - Absolute benefit low (1-3%)
  - Tamoxifen after tamoxifen: 1/3 relative reduction
  - AI after Tamoxifen: 1/2 relative reduction
  - AI after AI: controversial
- Extended endocrine therapy has additional toxicity

Goss : NEJM 2003; Mamounas JCO 2008; Jacketz JNCI 2007, Davies C et al . *Lancet* 2013; 381: 805–16.Gray R et al. ASCO 2013, abs 5

Extended adjuvant AI studies



ET duration, years	HR DFS
5 vs 7/8	0.81 (0.65-1.00)
5/6 vs 8/9	0.79 (0.62-1.02)
5 vs 10	0.85 (0.62-1.02)
7.5 vs 10	1.007 (0.87-1.16)
7 vs 10	0.92 (0.74-1.16)

1. Mamounas; Lancet Oncol. 2019; 20:88-99; 2. Blok; J Natl Cancer Inst 2018; 110:40-48; 3. Gnant; SABCS 2017;
2. 4. Tjan-Heijnen ; Lancet Oncol 2017; 18:1502-11

Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a meta-analysis of 22,192 women in 11 randomized trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Postmenopausal women with ER-positive (99%) or ER-unknown (1%) tumors in trials of:

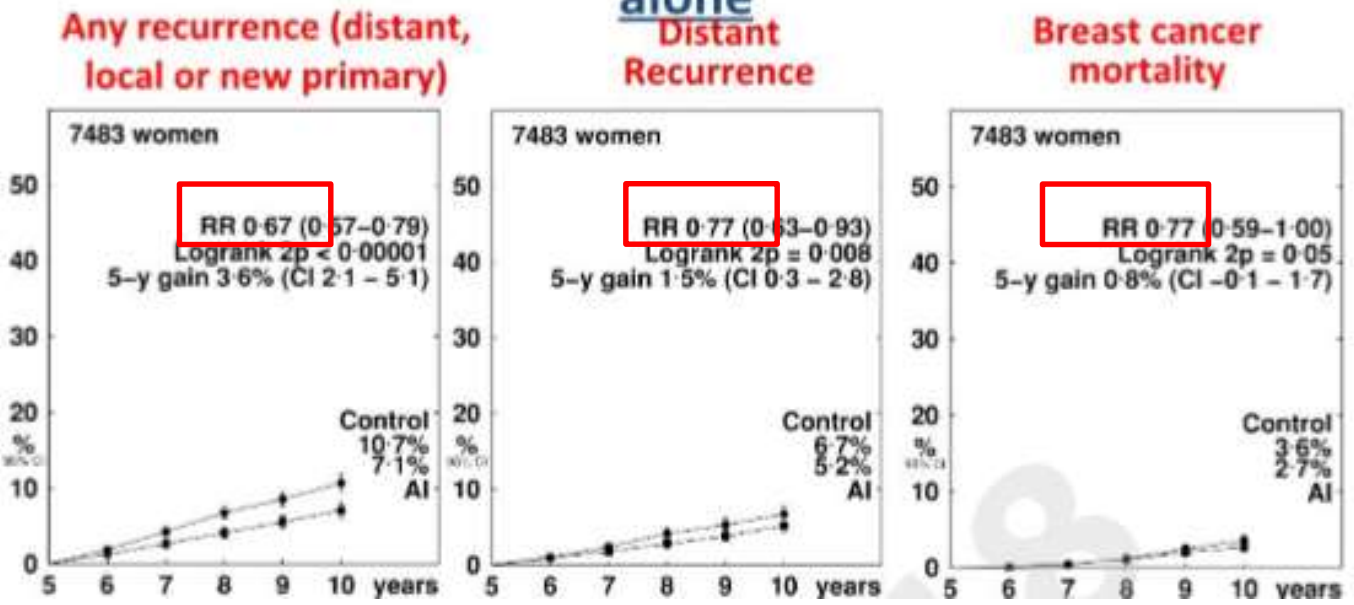
Any third-generation AI (exemestane, anastrozole, letrozole) vs no further adjuvant therapy **following**:

a) ≈ **5 years of tamoxifen alone** (n=7,500)

b) ≈ **5-10 years of tamoxifen then AI** (n=12,600)

c) ≈ **5 years of AI alone** (n=4,800)

(a) Trials of AI after ≈5 years of Tamoxifen alone



5-y gain: 3.6% (p <0.001)

5-y gain: 1.5% (p= 0.008)

5-y gain: 0.8% (p= 0.05)

Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a meta-analysis of 22,192 women in 11 randomized trials

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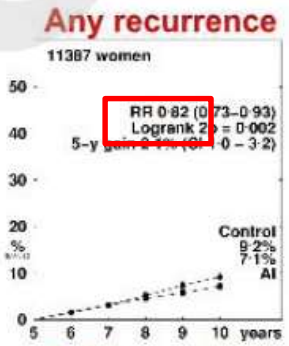
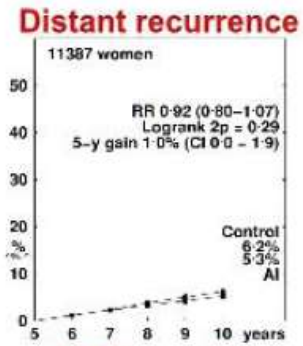
c) ≈ **5 years of AI alone** (n=4,800)

Gray SABCS 2018

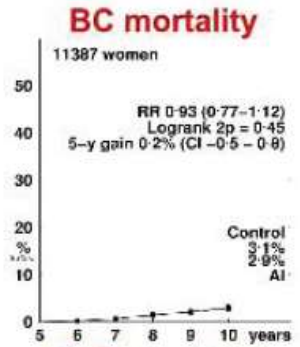
Tam→AI (5-10y) → extended AI



5-year gain: **2.1%** (p=0.002)

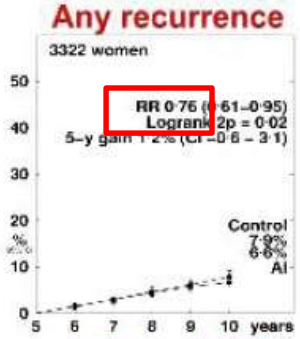


1.0% (p=0.29)

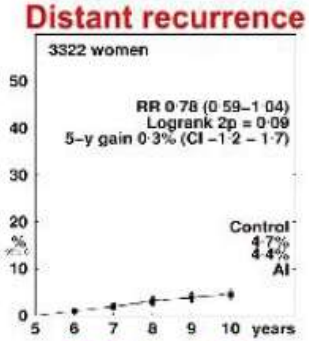


0.2% (p=0.45)

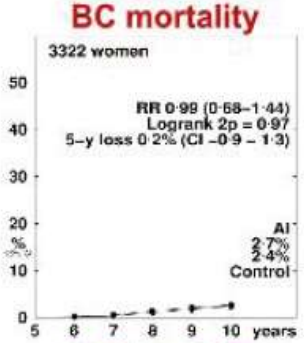
AI → extended AI



5-year gain: **1.2%** (p=0.02)



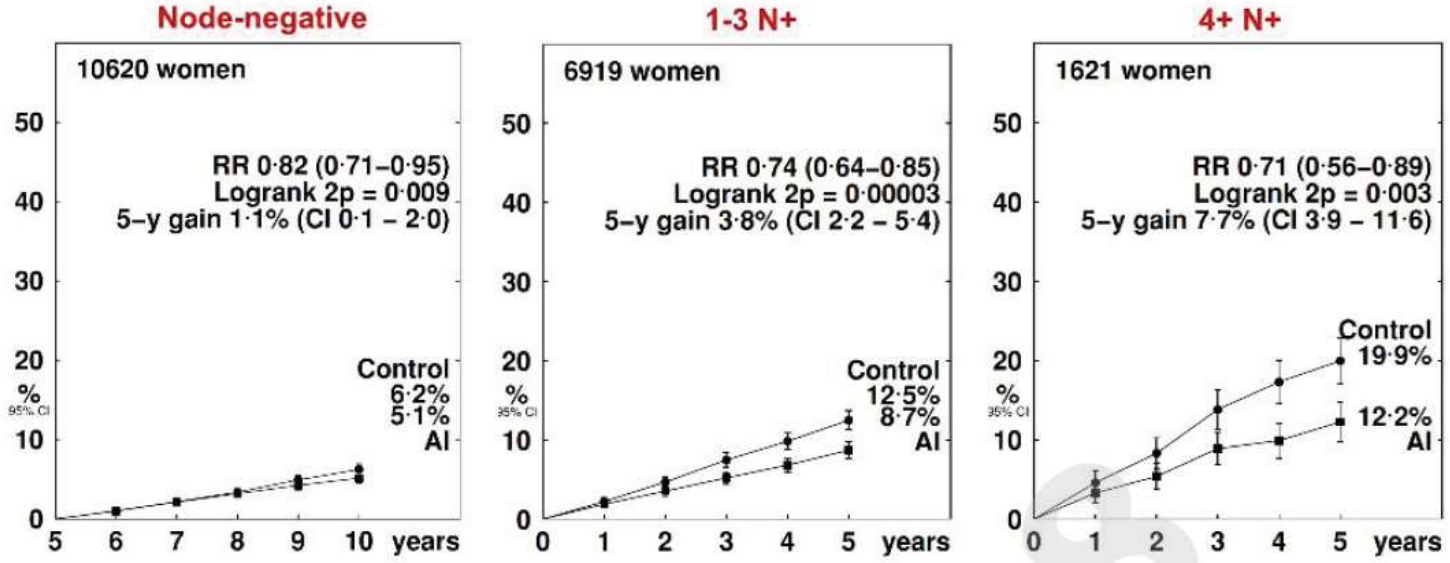
0.3% (p=0.09)



0.2% (p=0.97)

Gray SABCS 2018

Recurrence by nodal status – all trials



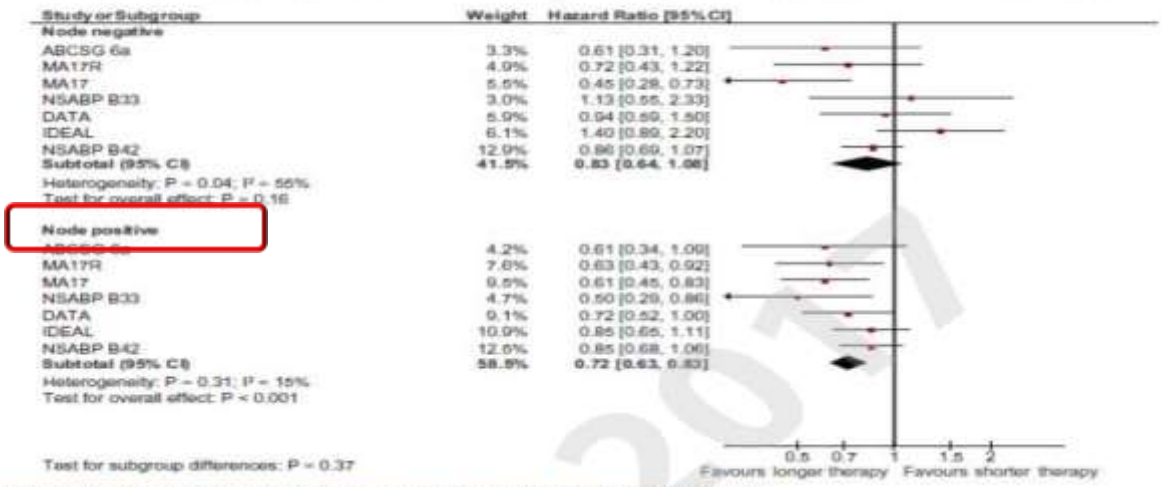
5-year gain:
1.1% (95% CI 0.1–2.0)

5-year gain:
3.8% (95% CI 2.2–5.4)

5-year gain:
7.7% (95% CI 3.9–11.6)

Meta-analysis: Extended AI Therapy

Forest Plot for Disease-free Survival According to Nodal involvement



Goldvaser et al, *Cancer Treatment Reviews* 60 (2017) 53–59

Toxicity of Extended Adjuvant Therapy With Aromatase Inhibitors in Early Breast Cancer: A Systematic Review and Meta-analysis

JOURNAL of the NATIONAL CANCER INSTITUTE
JNCI J Natl Cancer Inst (2018) 110(1): djx141

Hadar Goldvaser, Tristan A. Barnes, Boštjan Šeruga, David W. Cescon, Alberto Ocaña, Domen Ribnikar, Eitan Amir

Pooled absolute risk of adverse event

Trial	Cardiovascular disease		Fractures		Treatment discontinuation for AE		Second cancers		Death without recurrence	
	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH
ABCSG 6	+0.26	+385	−0.29	−345	+9.83	+11	NR	NR	+0.84	+120
MA.17	+0.21	+477	+0.71	+141	+1.29	+78	−0.27	−371	−0.19	−527
NSABP B-33	NR	NR	+1.01	+100	NR	NR	−0.01	−10 000	−0.64	+157
DATA	+0.58	+173	+2.35	+43	+8.57	+12	+0.61	164	NR	NR
IDEAL	+4.14	+25	+3.22	+32	+8.29	+13	NR	NR	NR	NR
MA.17R	+1.82	+55	+4.64	+22	+1.75	+58	NR	NR	+0.28	+358
NSABP B-42	+0.57	+176	+0.67	+150	+3.23	+31	−0.39	−257	+0.67	+150
Weighted pooled effect	+0.82	+122	+1.39	+72	+4.82	+21	−0.16	−625	+0.27	+371

Goldvaser et al JNCI 2018

Toxicity is an important reason for non-adherence

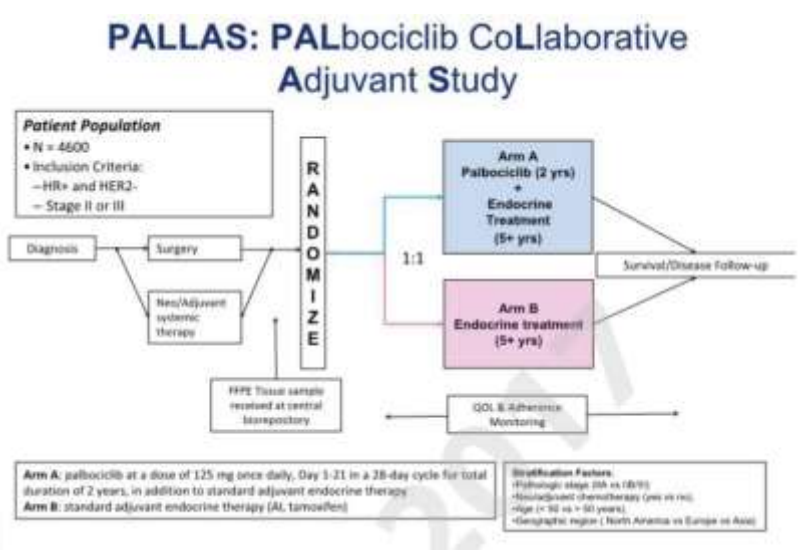
Extended Duration of Adjuvant Therapy For All?

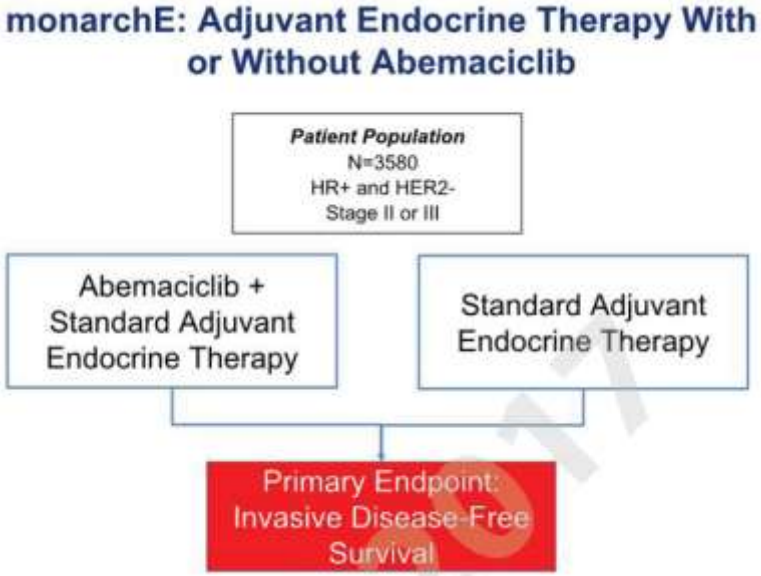
- Late recurrences are real
  - Baseline stage/grade/biomarkers are persistent prognostic factors and can be used to frame risk of late recurrence
- Treatment pros/cons
  - Benefits include lower distant recurrence and secondary prophylaxis
  - Side effects include ongoing familiar symptoms and bone health risks

Consider extended adjuvant endocrine therapy in:

Women with stage 3 cancers
Women with stage 2 cancers at higher risk, especially node-positive
Women with stage 1 cancers on individualized basis and with additional goal of secondary prevention
Especially patients who have tolerated treatment
Especially patients who started with tamoxifen

The future


PALLAS: PALbociclib CoLlaborative Adjuvant Study
Patient Population
• N = 4600
• Inclusion Criteria:
–HR+ and HER2-
– Stage II or III
Diagnosis
Surgery
Neo/Adjuvant systemic therapy
RANDOMIZE
1:1
Arm A
Palbociclib (2 yrs)
+
Endocrine Treatment
(5+ yrs)
Arm B
Endocrine treatment
(5+ yrs)
Survival/Disease Follow-up
FFPE Tissue sample received at central biorepository
QOL & Adherence Monitoring
Arm A: palbociclib at a dose of 125 mg once daily, Day 1-21 in a 28-day cycle for total duration of 2 years, in addition to standard adjuvant endocrine therapy
Arm B: standard adjuvant endocrine therapy (AI, tamoxifen)


monarchE: Adjuvant Endocrine Therapy With or Without Abemaciclib
Patient Population
N=3580
HR+ and HER2-
Stage II or III
Abemaciclib + Standard Adjuvant Endocrine Therapy
Standard Adjuvant Endocrine Therapy
Primary Endpoint:
Invasive Disease-Free Survival

Other possible strategies in adjuvant therapy

- Based on a meta-analysis data, the use of bisphosphonates as adjuvant treatment of postmenopausal women with breast cancer is indicated
- Zoledronic acid every 6 months for 5 years, or daily oral clodronate for 3 years.
- Denosumab has been shown to reduce bone-health related events in breast cancer patients and may reduce recurrence

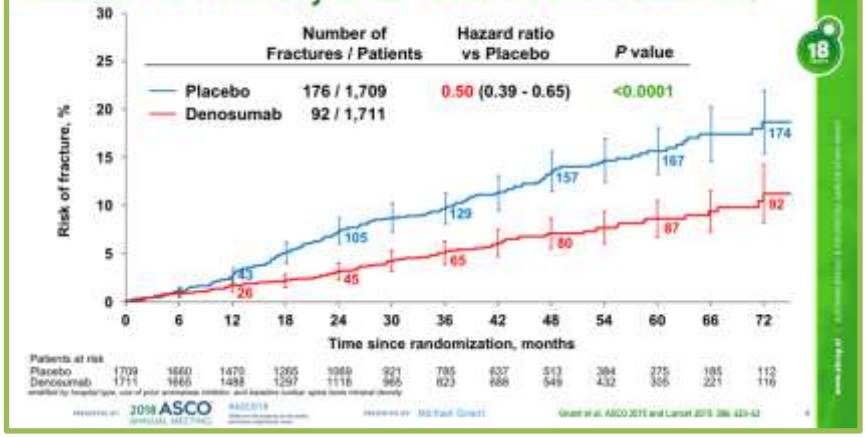
Effects of bisphosphonate treatment on recurrence in women with early breast cancer: a meta-analysis

- 41 randomised trials, 17,751 women
- There were no improvements in recurrence for premenopausal women
- In Post menopausal: 3.1% decrease in breast cancer mortality

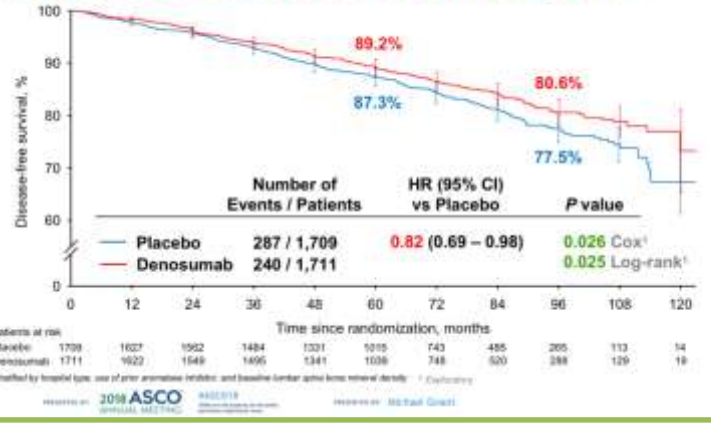
	No. events	HR	10 year gain	P value
Postmenopausal women (n = 10,540)				
Breast cancer mortality	1,107	0.83 (0.06)	3.1%	0.004
Breast cancer recurrence	1,809	0.86 (0.05)	3.0%	0.002
Distant recurrence	1,503	0.83 (0.05)	3.3%	0.0007
Bone recurrence	445	0.65 (0.08)	2.9%	0.00001
Other distant recurrence	1,058	0.93 (0.06)	0.7%	0.26

R Coleman, SABCS 2014, abstract S4-07

ABCSG-18 Primary End Point Results (ASCO 2015)



ABCSG-18 Results of the DFS ITT Analysis



Other possible strategies in adjuvant therapy

Counsel pts about importance of healthy lifestyle

- Obesity and BMI
  - Meta-analysis of 82 studies:
    - mortality HR 1.35 [1.24-1.47]; premenopausal: HR 1.75 [1.26-2.41]; postmenopausal: HR 1.34 [1.18-1.53];
- Nutrition
  - Dietary (LISA trial, Success C)
- Smoking and Alcohol
- Phisical activity

Chan et al; Ann Oncol 2014