(Neo-) adjuvant endocrine therapy

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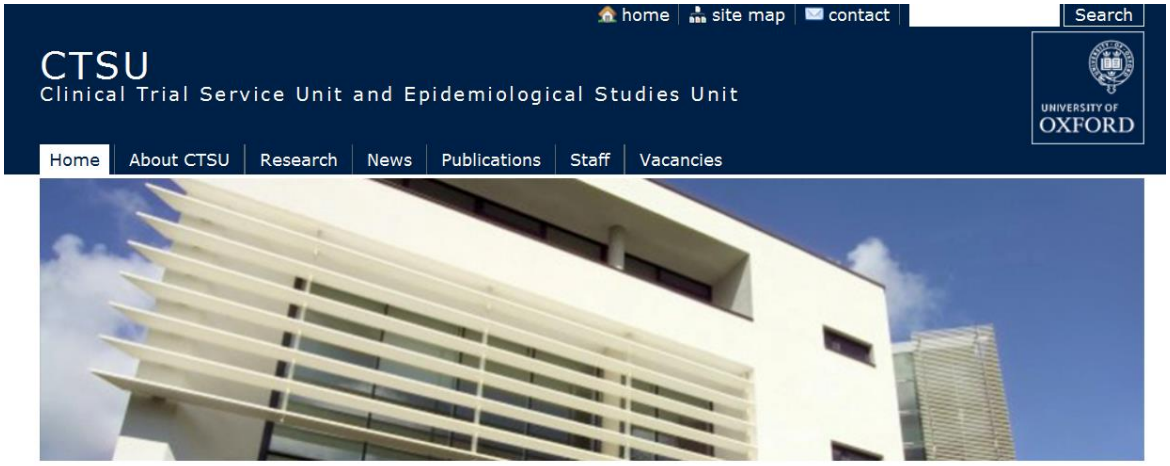
ESO Breast Cancer Program Coordinator
ESMO Board of Directors & Chair NR Committee
Chair EORTC-Breast Cancer Group

EORTC European Organisation for Research and Treatment of Cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

European School of Oncology
learning to care

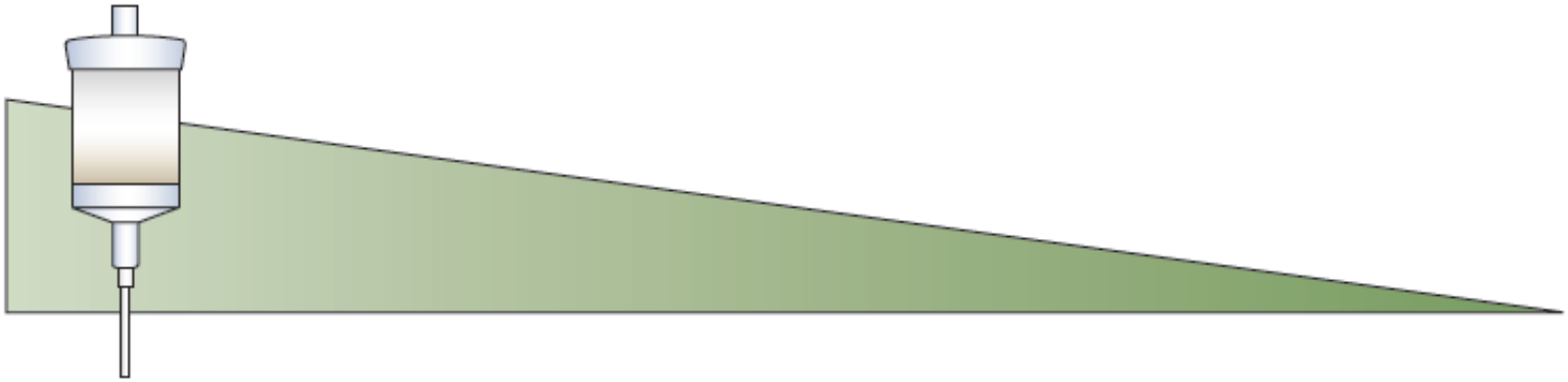


Individual trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) ("Oxford Overview")

St. Gallen 2015
Tailoring Therapy: Towards Precision Treatment of Patients with Early Breast Cancer

EARLY BREAST CANCER: WHO CAN AVOID ADJUVANT CT?



In favor of adjuvant chemotherapy

- ER negative
- Ductal histology
- Grade 3
- High proliferation
- High uPA and PAI1
- Basal and *HER2* positive
- High MammaPrint® or Oncotype DX® or GGI

Against adjuvant chemotherapy

- ER positive
- Lobular histology
- Grade 1
- Low proliferation
- Low uPA and PAI1
- Luminal A
- Low MammaPrint® or Oncotype DX® or GGI

Figure 2 | The chemosensitivity of a breast tumor depends on many factors. In individual treatment-decision making all these factors should be taken into consideration as well as the patient's risk of recurrence and risk of adverse effects, the likely benefit of adjuvant systemic therapy, and the patient's preferences. Abbreviations: ER, estrogen receptor; GGI, genomic grade index.

Bedard & Cardoso, Nat. Rev. Clin. Oncol. 8, 272–279 (2011)

EARLY BREAST CANCER: WHO NEEDS ADJUVANT ET?

All ER+ EARLY BREAST CANCER patients!

Until the early 90's: decision was based on menopausal status:
All post-menopausal: Yes
All pre-menopausal: No

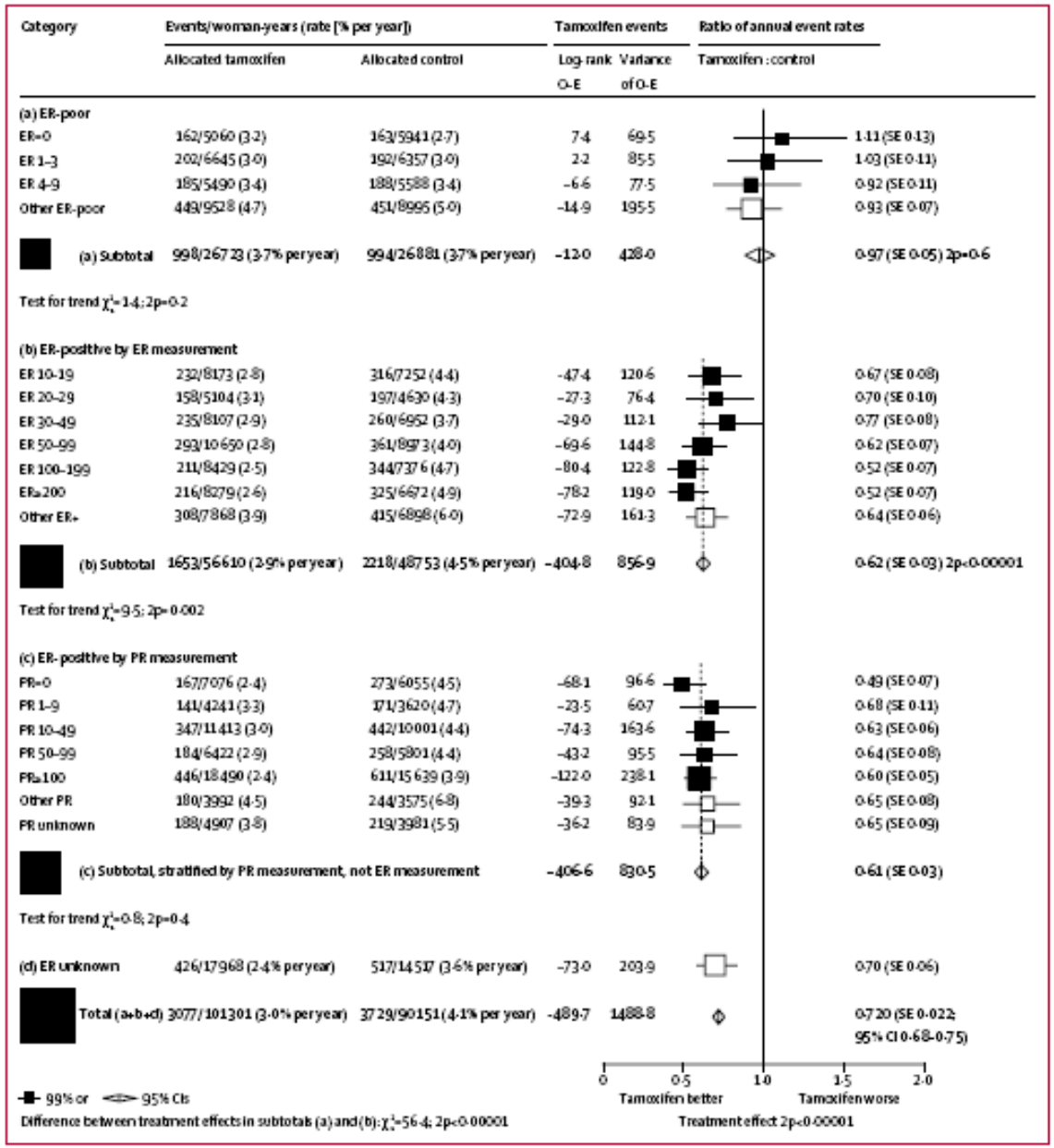


Figure 2: Relevance of quantitative ER and PR measurement (fmol/mg cytosol protein) to the tamoxifen versus control recurrence rate ratio
Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen. Other ER poor includes ER-negative by immunohistochemistry and ER unspecified, but less than 10 fmol/mg. ER=oestrogen receptor. PR=progesterone receptor. O-E=observed minus expected.

- **ER the only predictive factor**
- **Levels of positivity also important**

EBCTCG, The Lancet 2011

WHICH TYPE OF ENDOCRINE THERAPY?

Messages from the EBCTCG overview & individual trials

✓Efficacy of 5 years Tam

Study	Treatment arms/ Population (n)	Median FU	Recurrence	Mortality
Tamoxifen 5 years				
Overview 2011[76]	TAM 5 y vs no TAM 10 645 ER+	15 y	RR 0.53 [SE 0.03] years 0–4 RR 0.68 [SE 0·06] years 5–9 2p<0·00001 RR 0.97 [SE 0.10] years 10–14	RR 0.71 [SE 0.05] years 0–4, RR 0.66 [SE 0.05] years 5–9 RR 0.68 [SE 0.08] years 10–14 p<0·0001

CARRY-OVER EFFECT

Ribeiro, Sousa and Cardoso, ECCO-ESMO 2013 Educational Book

WHICH TYPE OF ENDOCRINE THERAPY?

Messages from the EBCTCG overview & individual trials

✓Efficacy of Aromatase Inhibitors: Upfront

Study	Treatment arms/ Population (n)	Median FU	Recurrence	Mortality
AIs 5 years				
ATAC	TAM 5y vs ANA 5y 3116/ 3125	120 months	HR= 0·91 (95% CI 0·83-0·99) p = 0·04	0.97 (95% CI 0.88–1.08) p = 0·6
BIG 1.98	TAM 5y vs LET 5y 2459/ 2463	76 months	HR=0·88 (95% CI 0·78–0·99) p = 0.03	HR 0.87 (95% CI 0.75-1.02) p = 0.08
TEAM	EXE 5y vs TAM 2-3y followed EXE 2-3y 4868/4898	5.1 y	HR=0·97 (0·88–1·08) p=0·60	HR=1.00 (0·89–1·14) p>0.9
Meta-analysis	Cohort 1 AIs initial monotherapy vs TAM 9,856	5.8 y	9.6% AI *v* 12.6% TAM 2.9% absolute decrease (SE 0.7%) 2*P* <.00001	4.8% AI *v* 5.9% TAM **1.1% (SE =0.5%) absolute decrease** 2*P* =0 .1
MA.27	EXE 5y vs ANA 5y 7,576	4.1y	HR=1.02 (95% CI, 0.87 to 1.18) *P* =0 .85	HR=0.93 (95% CI,0.77 - 1.13) P= 0 .46

Ribeiro, Sousa and Cardoso, ECCO-ESMO 2013 Educational Book

✓Efficacy of Tam & Aromatase Inhibitors in Sequence

Study	Treatment arms/ Population (n)	Median FU	Recurrence	Mortality
AIs and Tamoxifen in switching strategies				
BIG 1.98	LET 5 y TAM 2 y followed by LET 3 y LET 2 y followed by TAM 3 y 1546/ 1548/ 1540	71 months	HR=1·05 (95% CI 0·84–1·32) HR=0·96 (95% CI 0·76–1·21)	HR=1.13 (95% CI 0·83–1·53) HR=0.90 (95% CI 0·65–1·24)
ABCSG-8/ARNO 95	TAM 5y vs Tam f 2y followed by ANA for 3 years	28 months	HR=0·60 (0·44–0·81) p=0·0009	p=0·16
ITA	TAM 5y vs Tam f 2y followed by ANA	128 months	HR=0·64 (0·44–0·94) p = 0.023	HR=0.72 (0·44–1.17) p = 0.3
IES	TAM 5y vs Tam f 2-3y followed by EXE 2-3y	55·7 months	HR=0·76 (95% CI 0.66–0·88) p=0·0001	HR 0.·85 (95% CI 0·71–1·02) p=0·08
Meta-analysis	Cohort 2 AIs T after 2-3 y of TAM vs TAM 9,015	3.9y	5.0% AI *v* 8.1% TAM 3.1% absolute decrease (SE 0.6%) 2*P* <.00001	1.7% AI *v* 2.4% TAM **0.7% (SE =0.3%) absolute decrease** 2*P* =0 .2

Ribeiro, Sousa and Cardoso, ECCO-ESMO 2013 Educational Book

PREDICTIVE MARKERS FOR ENDOCRINE THERAPY

- ER (Tam and AIs)
- PgR (Tam and AIs)
- HER-2
- PROLIFERATION (Ki67)
- Bcl-2 (Tam)
- AIB-1 (Tam)
- ER-beta (Tam)
- MTA1s (Tam)
- Cyclin E (Tam)
- Intratumoral Aromatase (AIs)
- Genomic signatures
- ER mutation

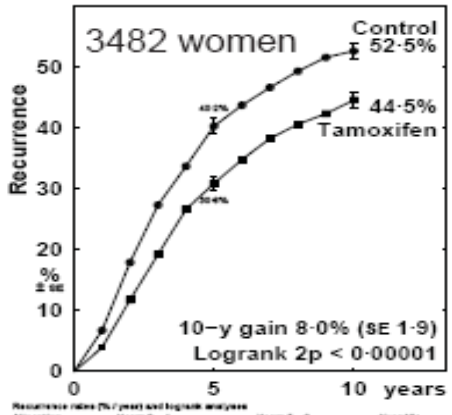
- HR are the only predictive factors with Level 1 evidence for ET

- NO BIOMARKER CAN HELP DECIDE BETWEEN TAM & AI

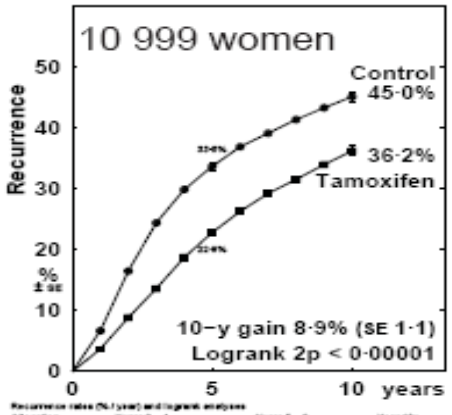
DURATION OF ENDOCRINE THERAPY

p 2: 10-year recurrence & breast cancer mortality, ER+ disease: 1, 2 or 5 years tam.

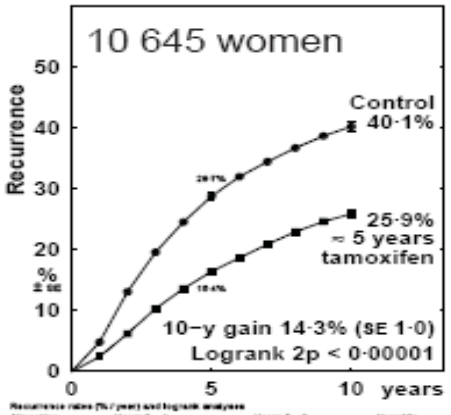
1 year tamoxifen vs. Not
RECURRENCE
ER+



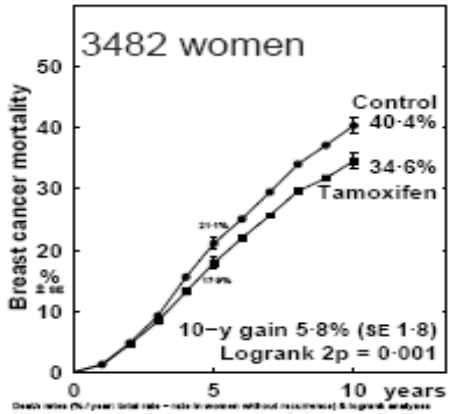
2 years tamoxifen vs. Not
RECURRENCE
ER+



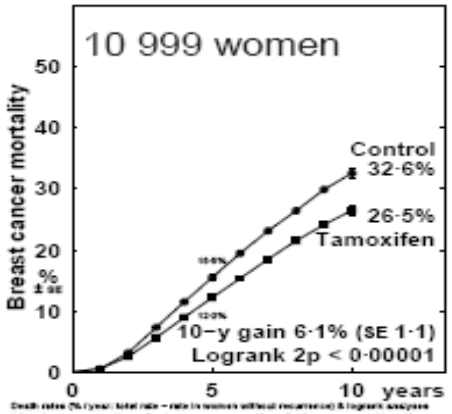
≈ 5 years tamoxifen vs. Not
RECURRENCE
ER+



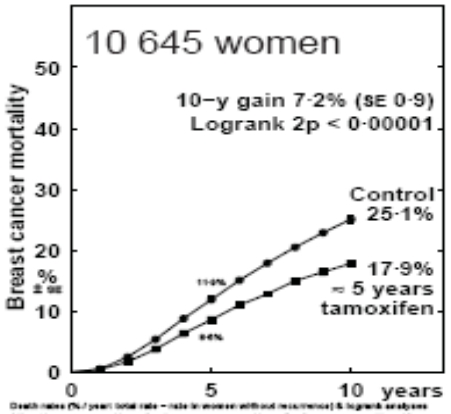
1 year tamoxifen vs. Not
BREAST CANCER MORTALITY
ER+



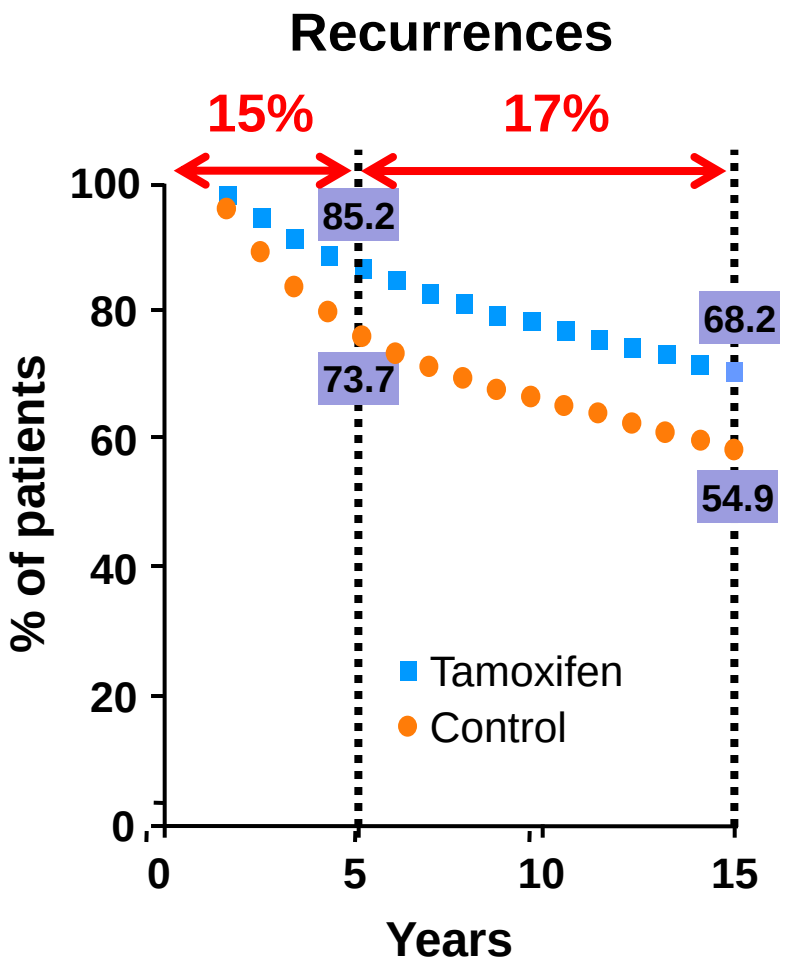
2 years tamoxifen vs. Not
BREAST CANCER MORTALITY
ER+

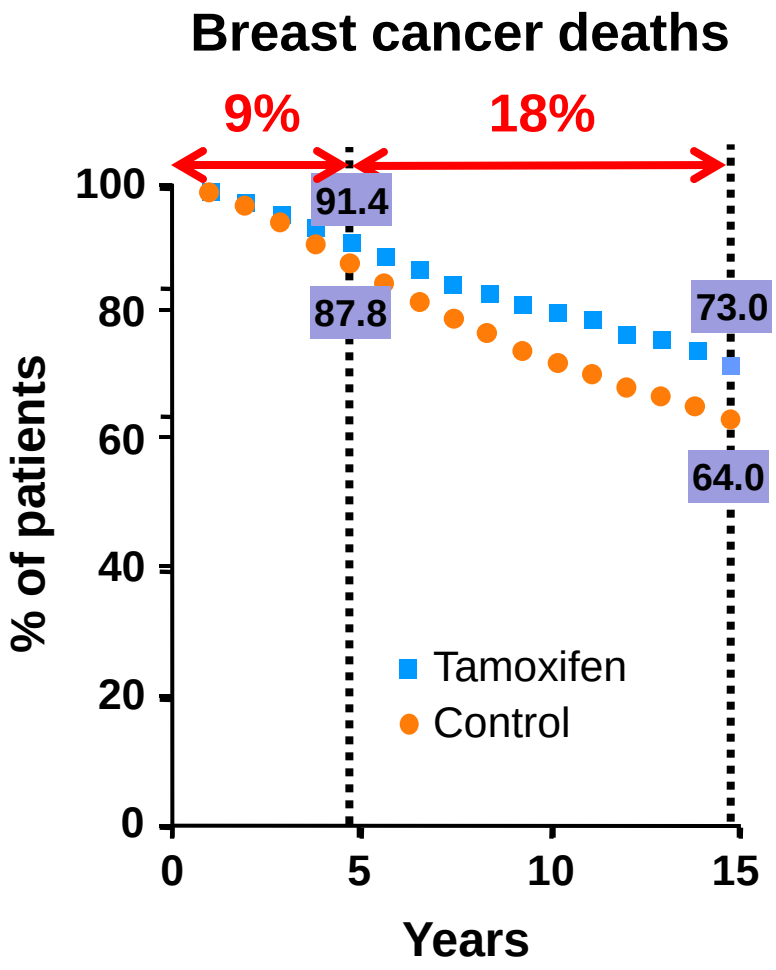


≈ 5 years tamoxifen vs. Not
BREAST CANCER MORTALITY
ER+



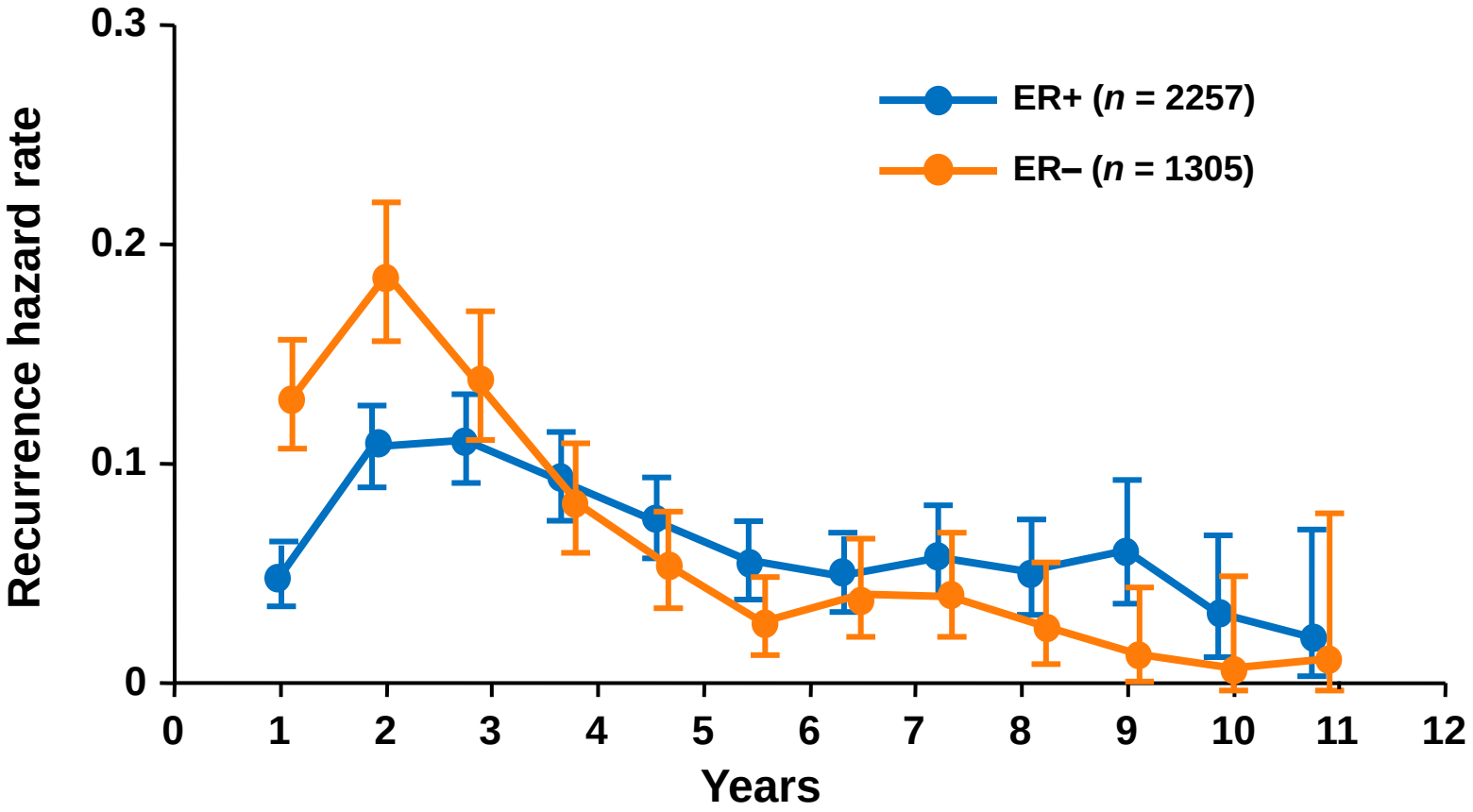
More than Half of all Breast Cancer Recurrences and Deaths Occur Post- 5y Tamoxifen





EBCTCG, Lancet. 2005

Annual Risk of Recurrence by ER Status



- Over half of breast cancer recurrences occur >5 years post-surgery!
- The annual risk of late recurrence is particularly high in ER+ tumors (5.2% between years 5 and 8, 4.6% between years 8 and 12).

Hormone receptor positivity is a strong predictor for late recurrence !

Saphner T et al., J Clin Oncol 1996

✓Efficacy of Extended (> 5 years) Adjuvant Strategies

Study	Treatment arms/ Population (n)	Median FU	Recurrence	Mortality
ATLAS	TAM 5y vs TAM 10y 3428/ 3418	NR	RR=0·90 (95% CI 0.79–1·02) 5-9y RR=0·75 (95% CI 0·62–0·90) later RR 0·84, 95% CI 0·76–0·94;p=0·002 in ER+	RR=0.97 (95% CI 0·79–1·18) 5–9 y RR= 0·71 (95% CI 0·58–0·88) later 639 deaths *vs* 722 deaths, p=0·01 in ER+
NSABP-B14	TAM 5y vs TAM >5y 579/ 593	7 y	DFS = 82% TAM 5y vs 78% TAM >5y *p*= .03	OS7Y = 94% TAM 5y vs 91% TAM >5y; *p*= .07
aTTOM	TAM 5y vs TAM 10y 6,934	4.2 y	415 vs 442 recurrences RR=0.94 (95% CI 0.81–1.09); p=0.4	NA
MA.17	TAM 5y followed LET 5y vs TAM 5y 2594/ 2593	30 ms	HR= 0·58 (95% CI 0·45–0·76) *p* <.001	HR=0·82(95% CI 0·57–1.19) *p* =0.03
NSABP-B33	TAM 5y followed EXE 5y vs TAM 5y 779/ 786	30 ms	DFS 4y 91% *v* 89% RR=0·68 (p=0·07)	16 deaths *vs* 13 *p* =0.1
ABCSG-6a	TAM 5y followed ANA 3y vs TAM 5y 469/ 387	62 ms	HR= 0·62 (95% CI 0·40–0·96) p=0.031	HR= 0·89 (95% CI 0·59–1·34) p=0.57

Ribeiro, Sousa and Cardoso, ECCO-ESMO 2013 Educational Book

MA.17: DFS by Menopausal Status

- Premenopausal (n=889)
  - < 50 years of age with menses, but underwent subsequent bilateral oophorectomy or became amenorrhoic during adjuvant Cht or Tam.
- Postmenopausal (n=4,277)

All patients	Premenopausal (n=889)	Postmenopausal (n=4,277)
HR= 0.57; p ≤ 0.001	**Absolute benefit 10.1% HR = 0.25 p<0.0001**	**Absolute benefit 3.3% HR = 0.69 p = 0.0008**

Women who had been premenopausal at diagnosis experienced significantly greater benefit of extended letrozole in terms of DFS; significant interaction between treatment and menopausal status (p = 0.03).

Goss PE et al. SABCS 2009; Goss PE et al., Ann Oncol 2013

MA.17R: Reduced Risk of Recurrence With Extending Adjuvant Letrozole Beyond 5 Yrs in Postmenopausal Women With Early-Stage Breast Cancer

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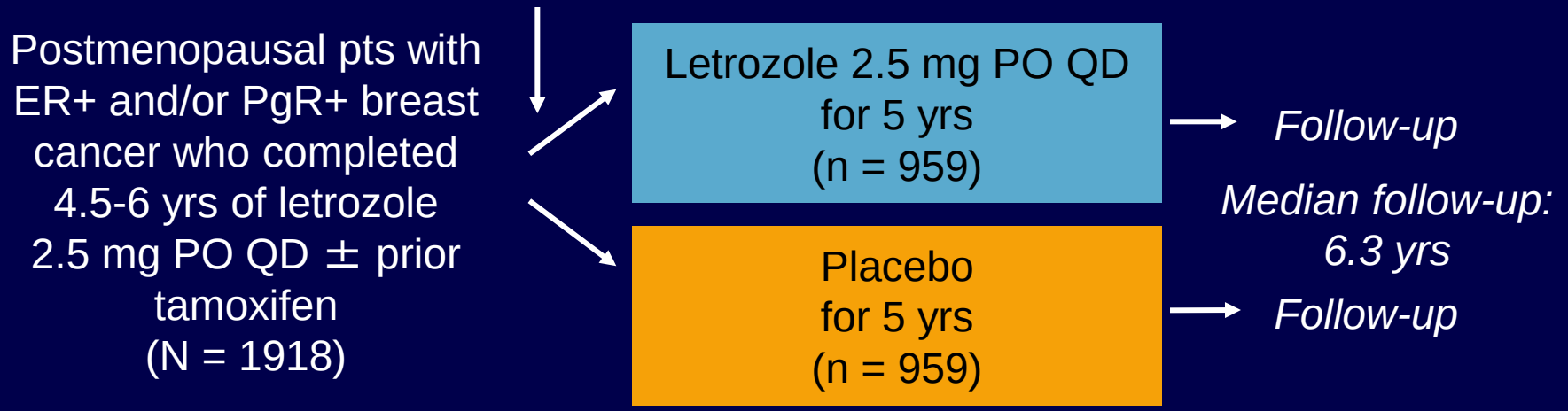
CLINICAL CARE OPTIONS®
ONCOLOGY

MA.17R: Study Design

Stratification by lymph node status at diagnosis, prior adjuvant chemotherapy, interval between last AI dose and randomization, duration of prior tamoxifen



- Primary endpoint: DFS (from randomization)
- Secondary endpoints: OS, CBC, safety, QoL

Goss PE, et al. ASCO 2016. Abstract LBA1.

Slide credit: clinicaloptions.com

MA.17R: DFS and OS After Median Follow-up of 6.3 Yrs

DFS Outcomes	Letrozole	Placebo	HR (95% CI)	*P* Value
Overall 5-yr DFS, %	95	91	0.66 (0.48-0.91)	.01
Events, n (%)	67 (7.0)	98 (10.2)		
New contralateral breast cancers, n (%)	13 (1.4)	31 (3.2)		.007
Locoregional recurrences, n	19	30		
Distant recurrences, n	42	53		
Bone recurrences, n	28	37		

- DFS benefit of extended letrozole in all prespecified subgroups
- 5-yr OS: 93% vs 94% (HR: 0.97; *P* = NS)

Goss PE, et al. ASCO 2016. Abstract LBA1.

Slide credit: clinicaloptions.com

MA.17R: Conclusions

- MA.17R first study to demonstrate benefit of extending AI treatment beyond 5 yrs
  - Letrozole treatment for 10 yrs decreased risk of disease recurrence by 34%
    - Majority of benefit in reduction of contralateral breast cancer
  - No new toxicities observed
  - Bone health remains important in weighing risks/benefits
  - Treatment extension did not adversely impact QoL
- OS not improved by extending letrozole beyond 5 yrs
- Investigators note that AIs readily available worldwide, and introducing 10 yrs of AI therapy as standard of care should improve global burden of breast cancer

Goss PE, et al. ASCO 2016. Abstract LBA1.

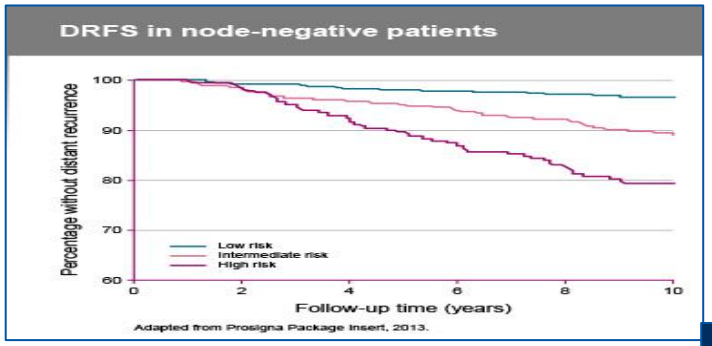
Slide credit: clinicaloptions.com

EARLY BREAST CANCER: WHO NEEDS EXTENDED ADJUVANT ET?

All ER+ EARLY BREAST CANCER patients with sufficient high risk??!

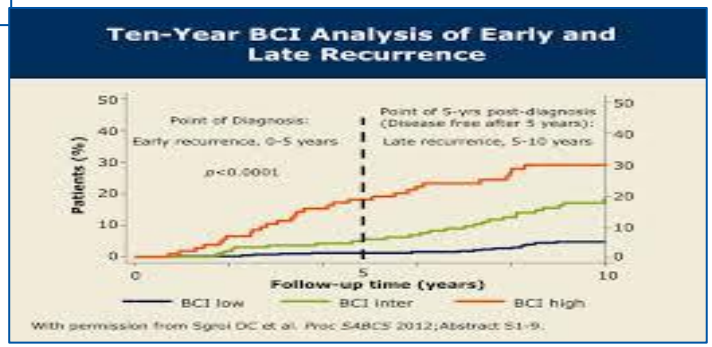
- No proven biomarker
- Role of some genomic signatures for determination of late relapses risk?!

PAM 50 (Prosigna Breast Cancer Assay)



Endopredict /Endopredict Clin

Breast Cancer Index (BCI)



Meta-analysis on Five or More Years of Adjuvant Tamoxifen: Safety Profile

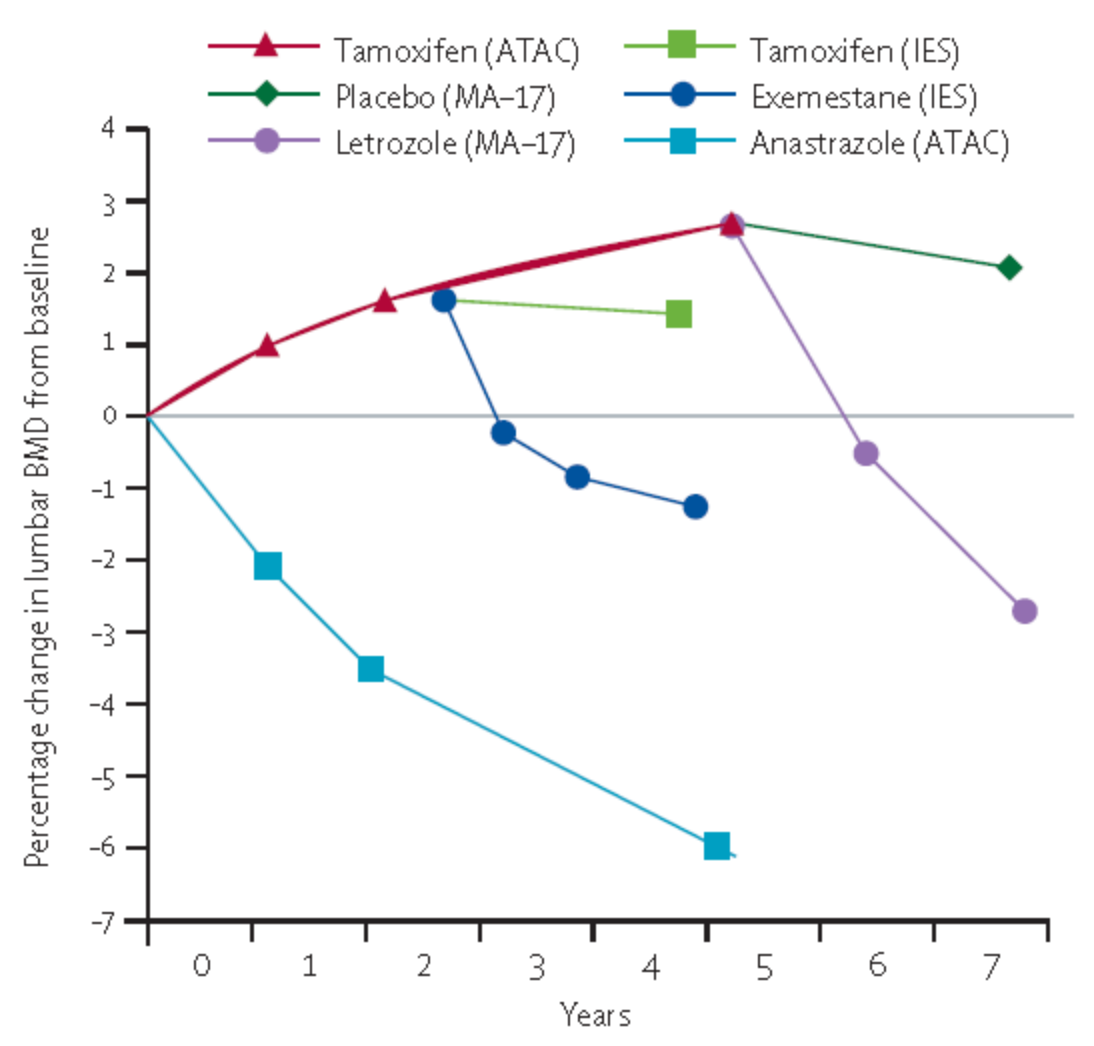
Extended adjuvant Tamoxifen:

- Higher incidence of hot flushes, vaginal discharge and fluid retention.
- Higher incidence of thromboembolic events.
- Significant increase in endometrial carcinoma (OR 2.06, p< 0.001) , absolute risk increase from 1.1 to 2.2%; without significant influence on death from endometrial cancer.

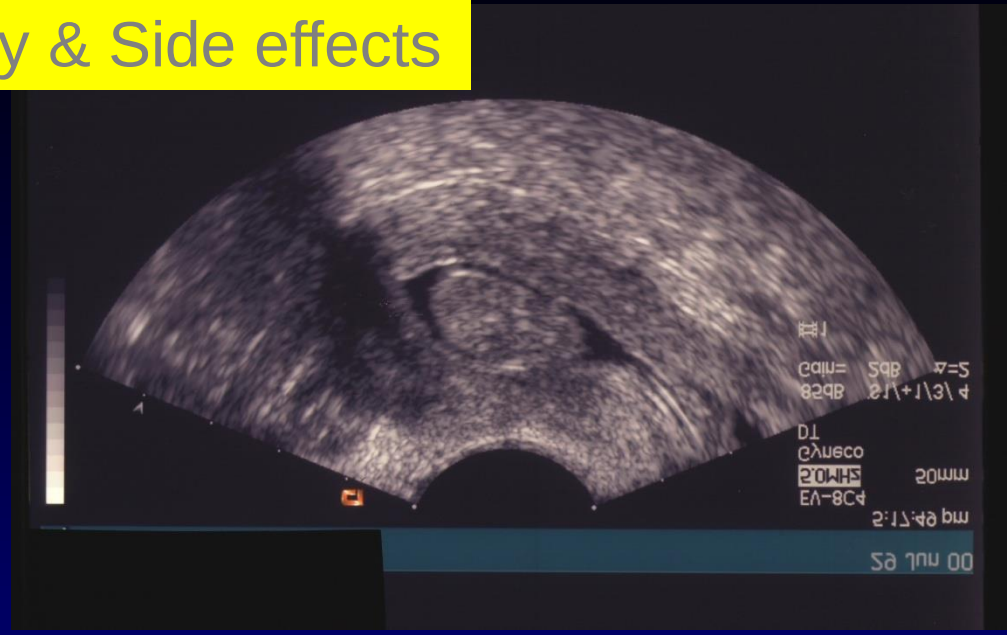
- Non- significant reduction in death from cardiovascular diseases (OR 0.89, p=0.25), absolute reduction from 3.2 to 2.8%;
- No association between extended Tamoxifen and other (non-endometrial) second cancers.

Al-Mubarak M et al.,PLOS One 2014

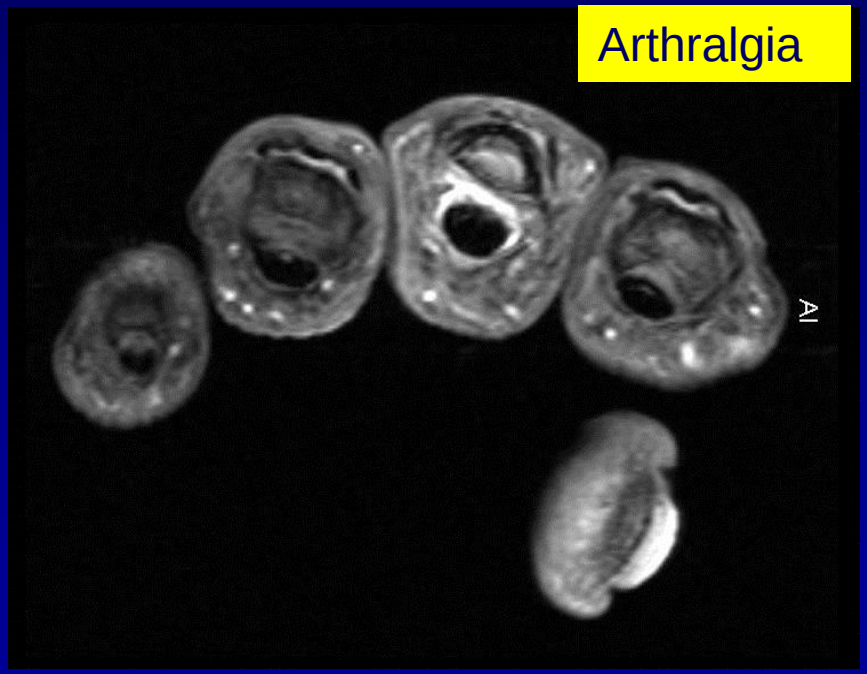
Estimated bone loss with AI's Comparing different strategies



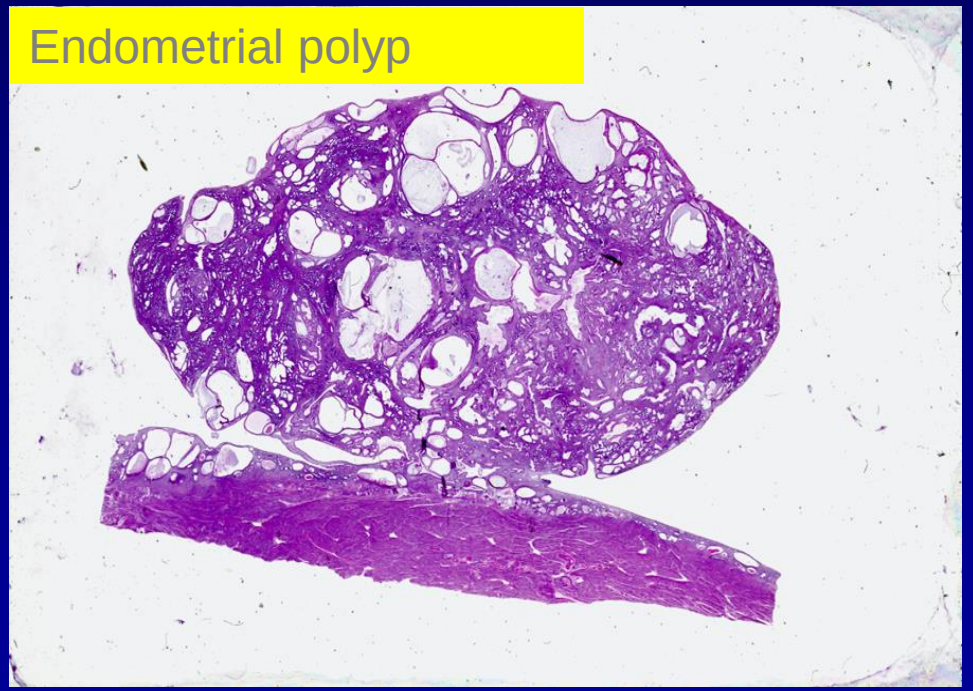
Co-Morbidity & Side effects



Arthralgia



Endometrial polyp



MBC UZ Leuven Abstr. 4056, Neuven et al

Cognitive Function in Postmenopausal Women Receiving Adjuvant Letrozole or Tamoxifen for Breast Cancer in the BIG 1-98 Trial

Karin Ribi, Kelly-Anne Phillips, Zhuoxin Sun, Alisa Stephens, Alastair Thompson, Vernon Harvey, Beat Thürlimann, Fatima Cardoso, Olivia Pagani, Alan S. Coates, Aron Goldhirsch, Karen N. Price, Richard D. Gelber, Jürg Bernhard

IBCSG International Breast Cancer Study Group

BIG

ADJUVANT ENDOCRINE THERAPY WITH AN A.I. : COMPLIANCE AND COST ISSUES

Treatment with an AI will often necessitate:

- ✓ **Earlier initiation of lipid-lowering drugs, antihypertensives and aspirin to reduce cardiac and cerebrovascular events**
- ✓ **Earlier initiation of medication for osteopenia/osteoporosis**
- ✓**The use of pain medication, such as anti-inflammatory for myalgia / arthralgia**

- ✓**Routine follow-up of lipids**
- ✓**Monitoring of blood pressure**
- ✓**Routine assessment of bone mineral density & frequently preventative therapy**

Courtesy of M. Trudeau

ENDOCRINE THERAPY: POSTMENOPAUSAL

Can some patients be adequately treated with TAMOXIFEN alone?

YES (98% vs 2%)

Factors arguing for inclusion of an AI at some point are:

- **Involvement of 4 or more nodes (97.6% vs 2.4%)**
- **Grade 3 or high Ki-67 (97.7% vs 2.3%)**

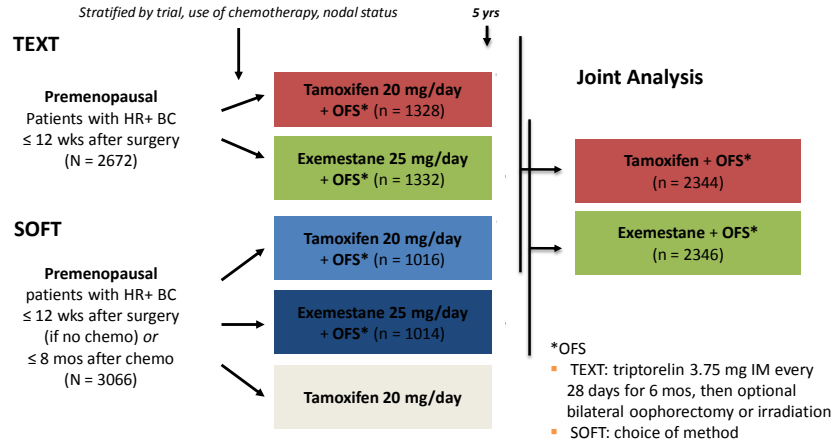
If an AI is used, should it be started upfront:

- **In patients at higher risk? (95.5 vs 4.5%)**
- **In all patients? (47.5 vs 52.5)**

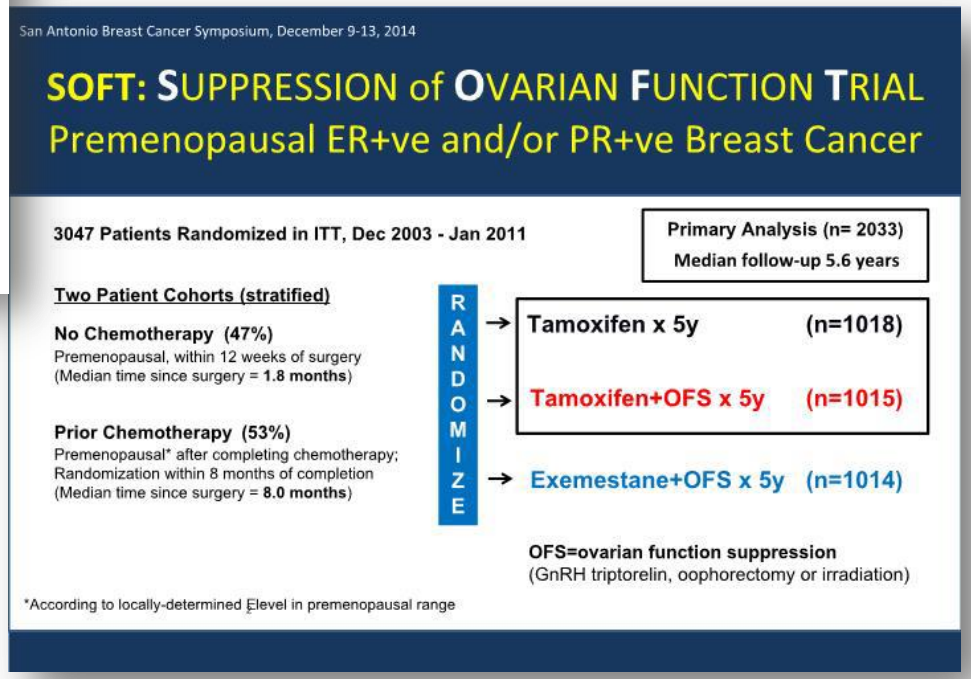
Can upfront AI be switched to TAM after 2 yrs? YES (75% vs 22.5%)

ROLE OF OFS & AI IN PREMENOPAUSAL WOMEN
TEXT & SOFT Trials

TEXT and SOFT Trials: Comparison of Tamoxifen or Exemestane With OFS

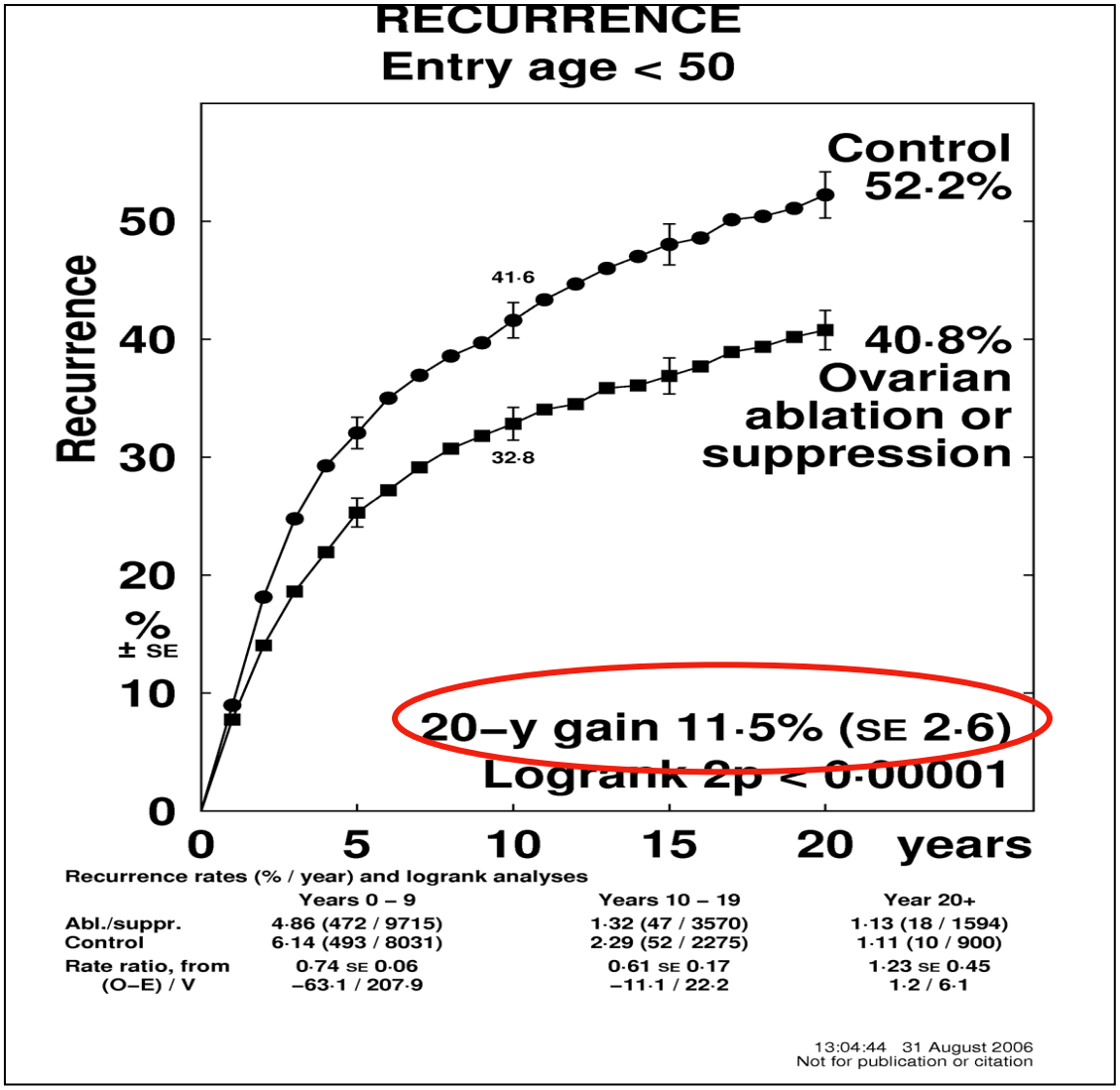


Pagani O, et al. ASCO 2014. Abstract LBA1.



Francis et al, N Engl J Med, 2015

OFS/OFA Meta-analysis EBCTCG 2006



- About 12% LESS RECURRENCES in PTS NOT TREATED WITH CT

- Not selected for ER!

San Antonio Breast Cancer Symposium, December 9-13, 2014

SOFT: SUPPRESSION of OVARIAN FUNCTION TRIAL
Premenopausal ER+ve and/or PR+ve Breast Cancer

3047 Patients Randomized in ITT, Dec 2003 - Jan 2011

Primary Analysis (n= 2033)
Median follow-up 5.6 years

Two Patient Cohorts (stratified)

No Chemotherapy (47%)
Premenopausal, within 12 weeks of surgery
(Median time since surgery = **1.8 months**)

Prior Chemotherapy (53%)
Premenopausal* after completing chemotherapy;
Randomization within 8 months of completion
(Median time since surgery = **8.0 months**)

RANDOMIZE

→ **Tamoxifen x 5y** (n=1018)

→ **Tamoxifen+OFS x 5y** (n=1015)

→ **Exemestane+OFS x 5y** (n=1014)

OFS=ovarian function suppression
(GnRH triptorelin, oophorectomy or irradiation)

CT DECISION WITH PHYSICIAN

*According to locally-determined level in premenopausal range

Francis et al, N Engl J Med, 2015

San Antonio Breast Cancer Symposium, December 9-13, 2014

Primary Analysis: Patient Characteristics

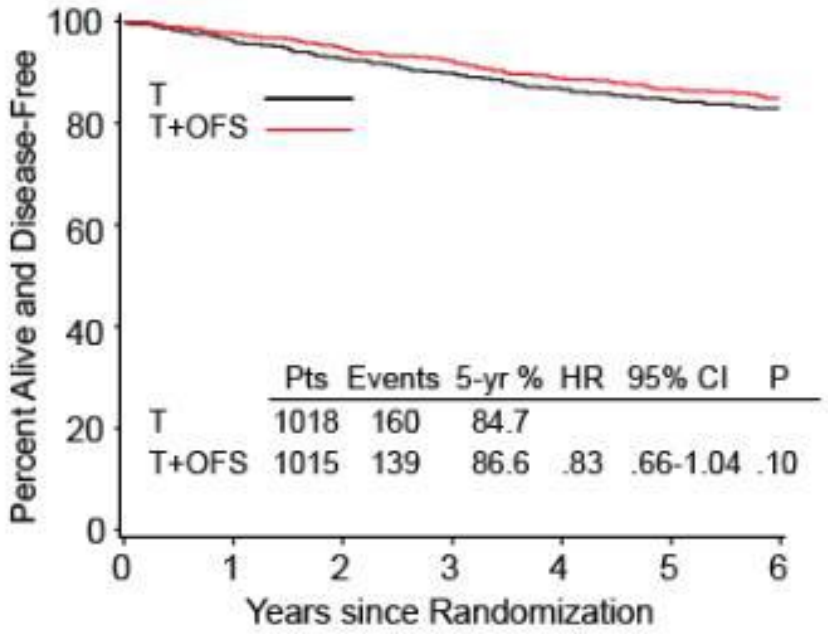
	No chemo 47% (n=949)	Prior Chemo 53% (n=1084)	Overall (n=2033)
Median age	46 y	40 y	43 y
Lymph Node +ve	9%	57%	35%
Tumor > 2 cm	14%	47%	32%
Grade 1	41%	14%	27%
Grade 3	7%	35%	22%
HER2+ve	4%	18%	12%
Median time since surgery	1.8 mo	8.0 mo	3.2 mo

Francis et al, N Engl J Med, 2015

San Antonio Breast Cancer Symposium, December 9-13, 2014

Primary Analysis: Disease-free Survival

5.6 years median follow-up



N= 2083

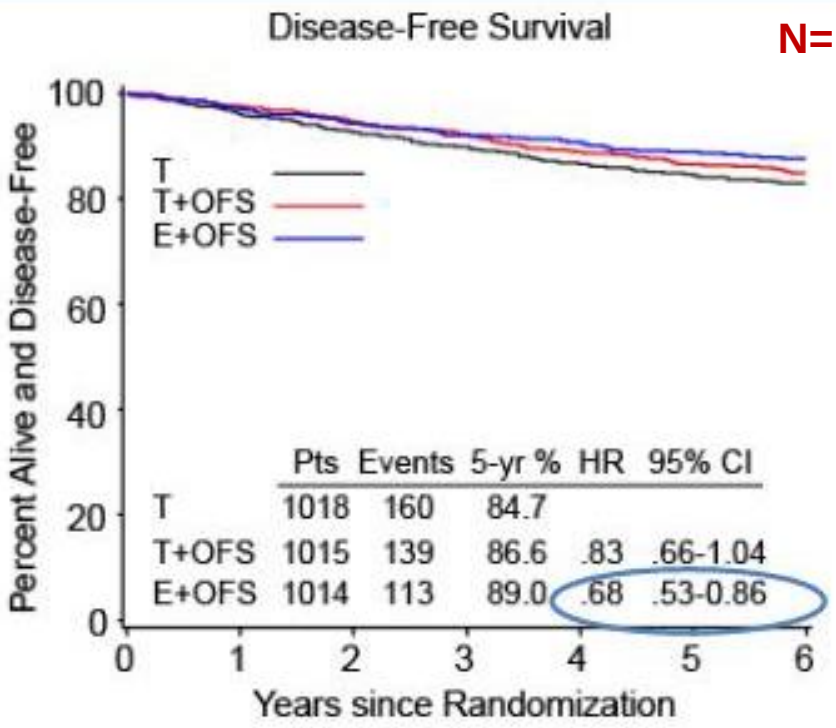
Primary analysis in overall population not significant (p=0.10)

Multivariable Cox model HR=0.78 (95% CI 0.62-0.98) p=0.03

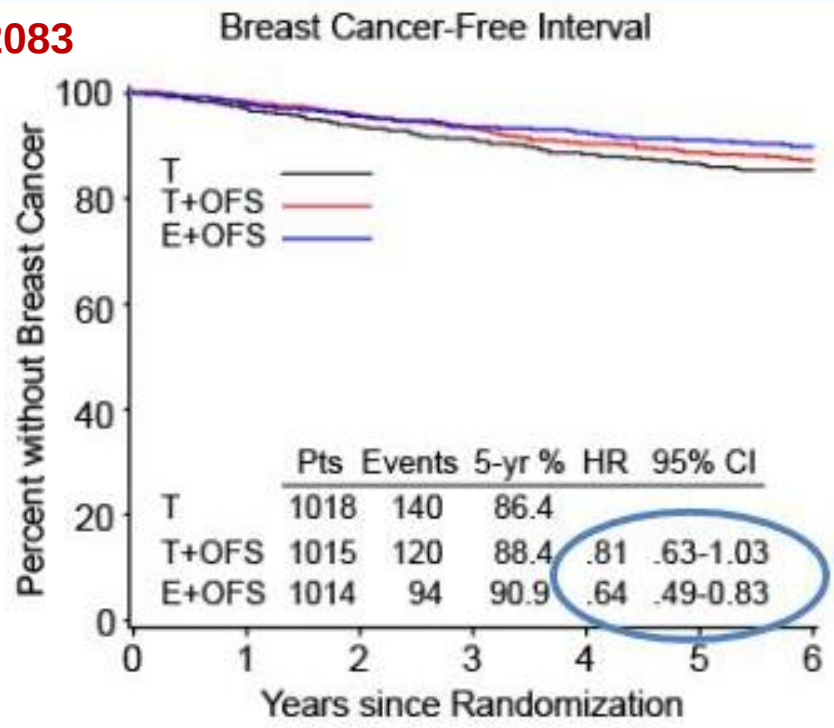
Francis et al, N Engl J Med, 2015

Francis et al, N Engl J Med, 2015

Secondary Objectives



N= 2083



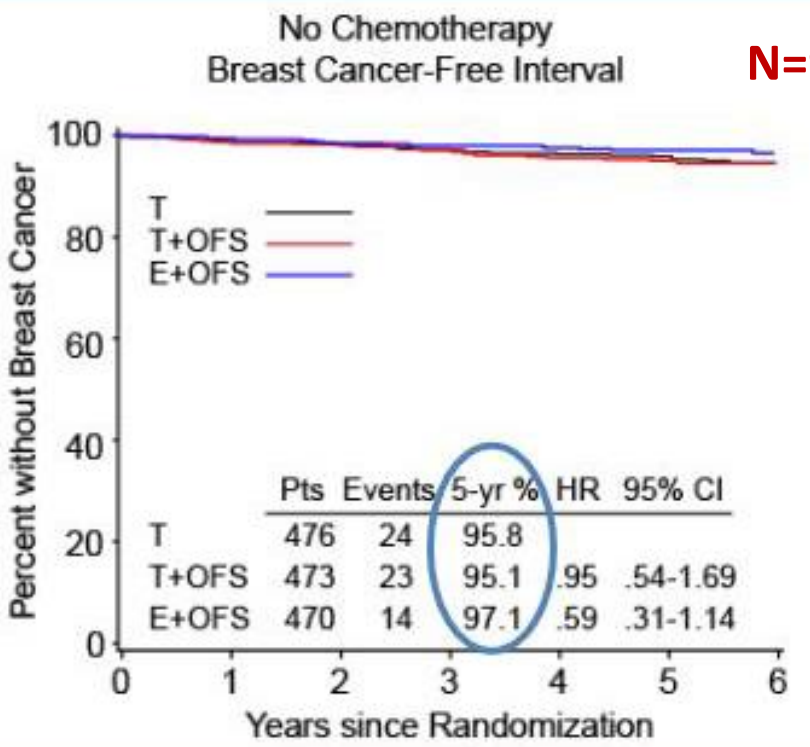
T+OFS v T: 19% relative reduction in BC recurrence, p=0.09

E+OFS v T: 36% relative reduction in BC recurrence, 5y BCFI >90%

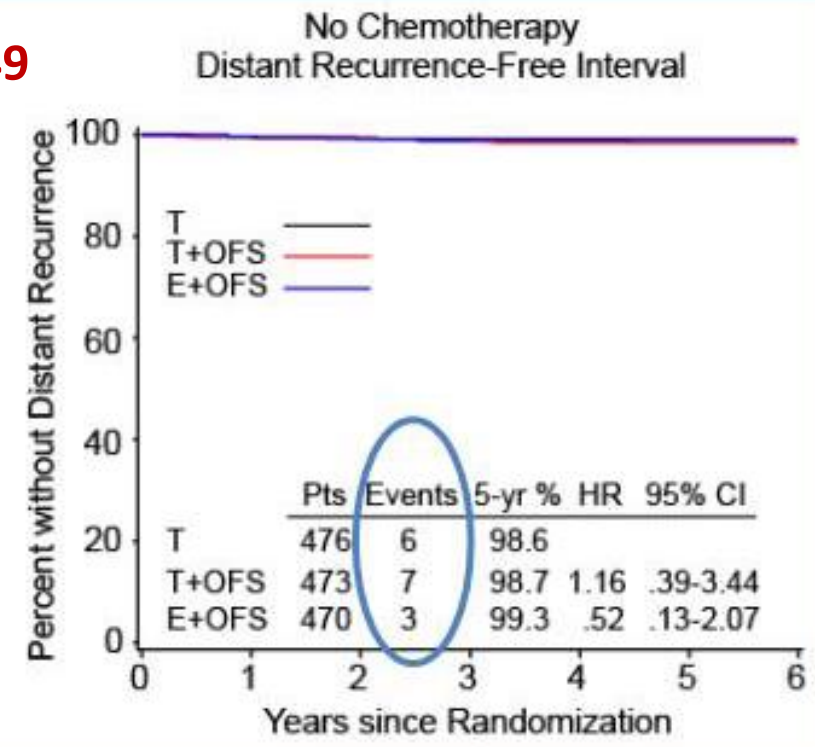
DFS	
TAM + OFS	No Benefit
E + OFS	4,3% (HR .68)

BCFI	
TAM + OFS	No Benefit
E + OFS	4,5% (HR .64)

Premenopausal No Chemotherapy



N=949



Cohort selected for low risk clinicopathologic features

90% ≥ age 40yr, 91% node negative, 85% tumor ≤ 2cm, 41% grade 1

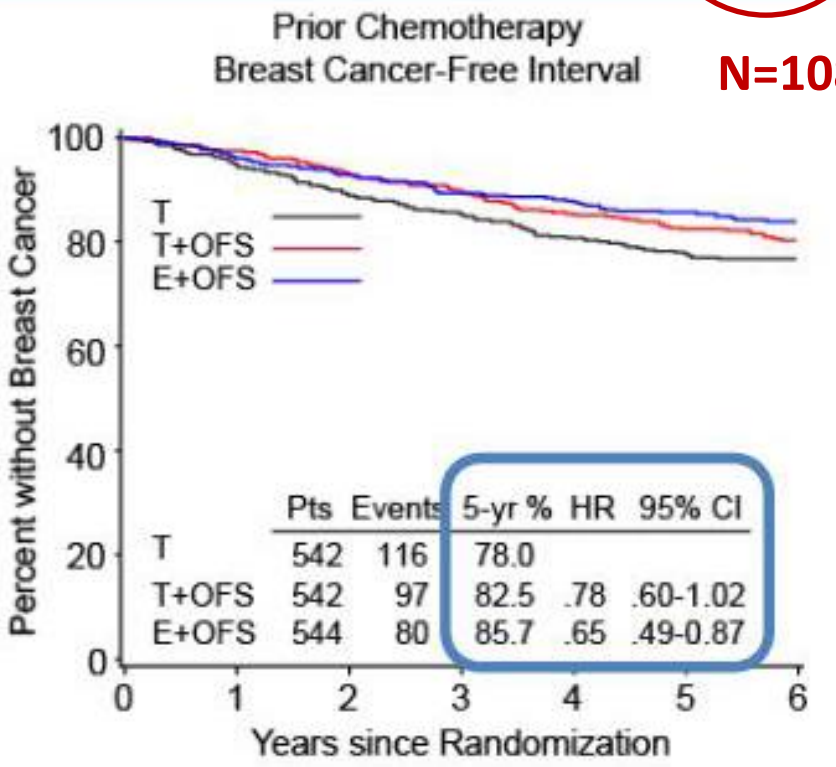
Excellent outcome – 1% Mortality ; 1.4% DRFI

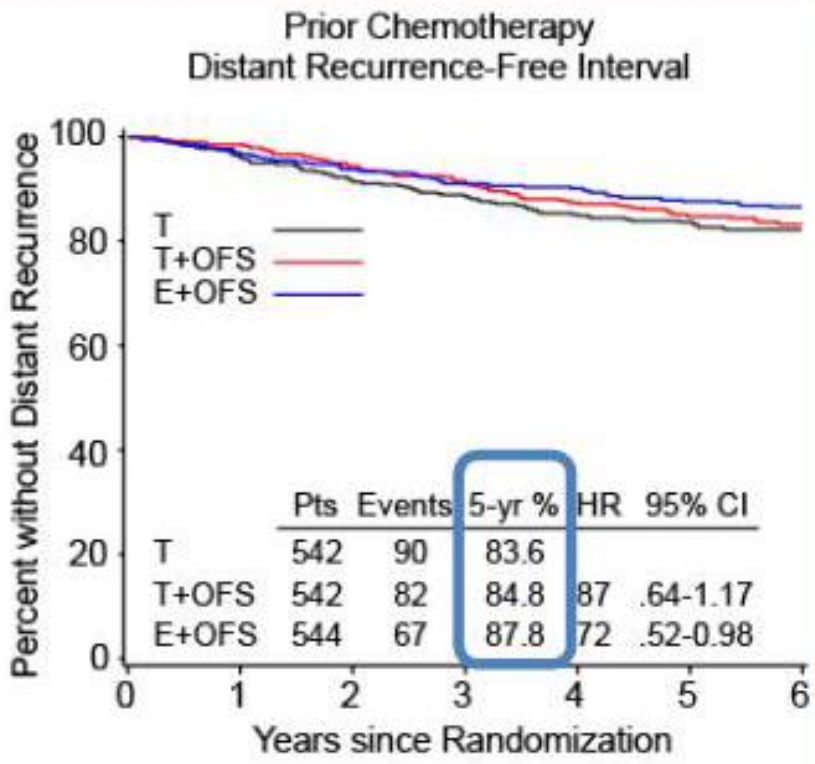
Francis et al, N Engl J Med, 2015

Francis et al, N Engl J Med, 2015

Premenopausal after Prior Chemotherapy

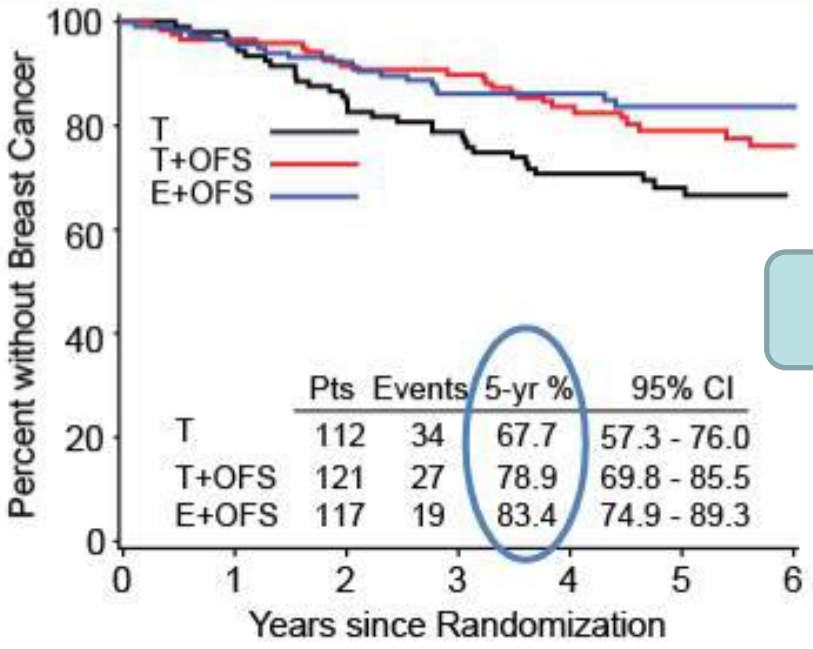
N=1084





Absolute improvement at 5 years – HR (95% CI)		
	T+OFS vs T	E + OFS vs T
BCFI	4,5% .78(.60-1.02)	7,7% .65(.49-.87)
DRFI	1,2% .87(.64-1.17)	4,2% .72(.52-.98)

All women < 35 years of age



N=350

94% received CT

	Absolute improvement at 5 years – HR (95% CI)	
	T+OFS vs T	**E + OFS vs T**
BCFI	**11,2%**	**15,7%**

Francis et al, N Engl J Med, 2015

SOFT Trial: CONCLUSIONS

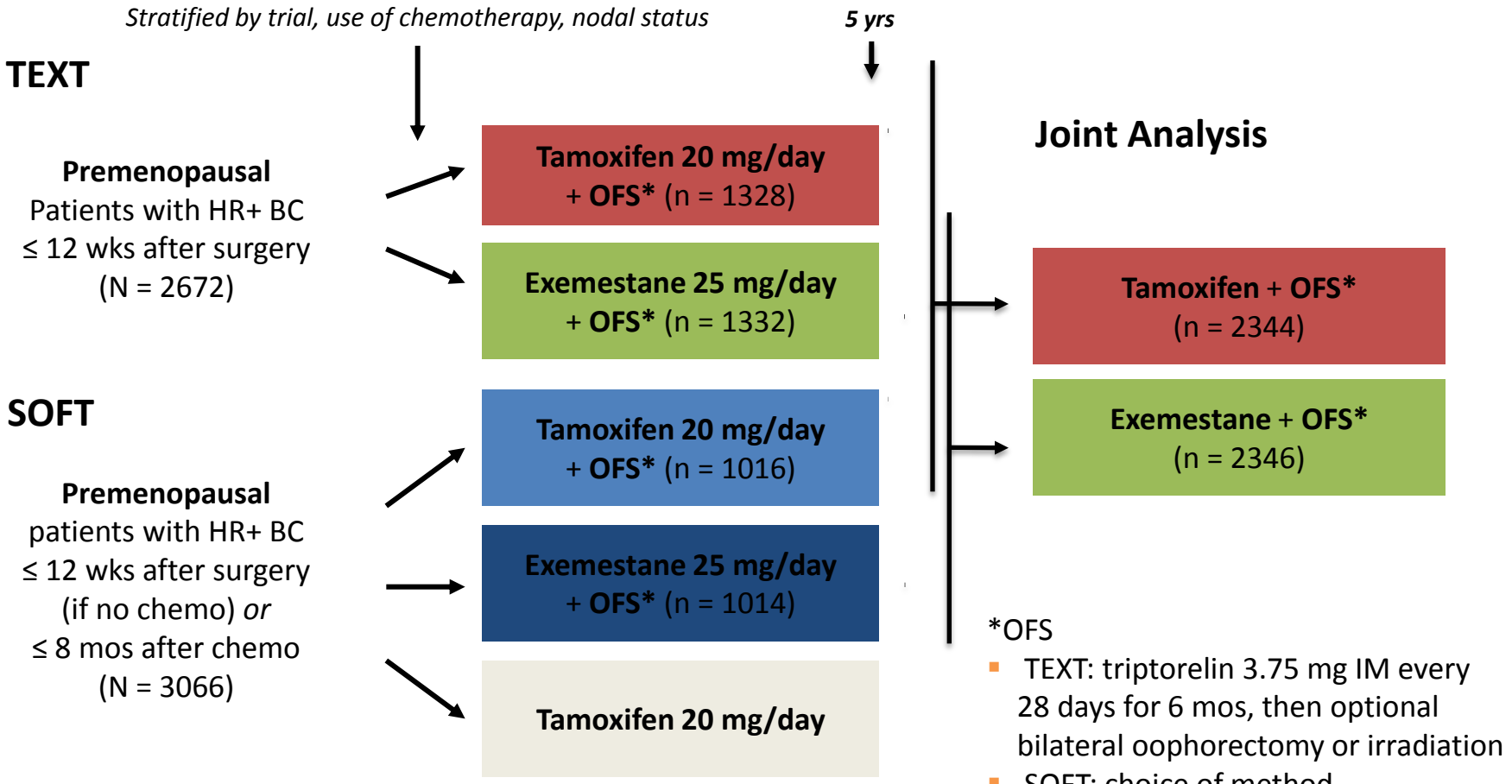
STRENGTHS:

1) LARGE, PROSPECTIVE, RANDOMIZED TRIAL
2) PRAGMATIC APPROACH TO USE OF CT
3) PROVIDES EVIDENCE THAT IN SOME PATIENTS WITH BETTER PROGNOSIS TAMOXIFEN ALONE IS A VERY GOOD TREATMENT
4) GIVES SUPPORT TO USE OF OFS IF NO AMENORRHEA IS OBTAINED WITH CT
5) HELPS DEFINING THE ROLE OF AIs IN PREMENOPAUSAL PATIENS, TOGETHER WITH THE TEXT TRIAL

OPEN QUESTIONS:

1) PATIENTS RECEIVING CT (higher risk) WITH AMENORRHEA
2) PATIENTS RECOVERING MENSES AFTER 8 MONTHS
3) <35 years AND no need for CT
4) OPTIMAL DURATION OF OFS: are 5 years really necessary ?
5) WILL RESULTS CHANGE WITH LONGER FU (ER+ disease); NEED FOR OS RESULTS

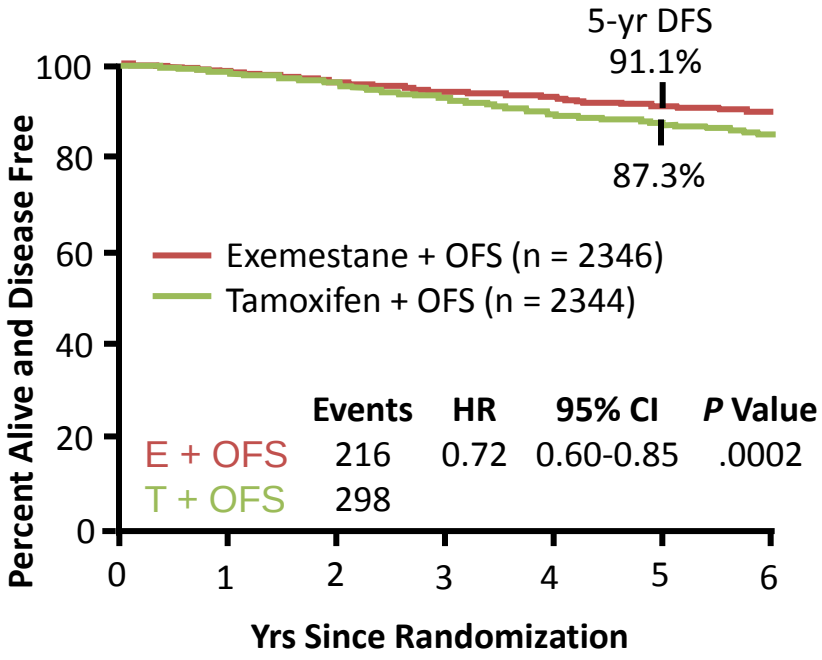
Combined analysis TEXT and SOFT Trials: Comparison of Tamoxifen or Exemestane With OFS

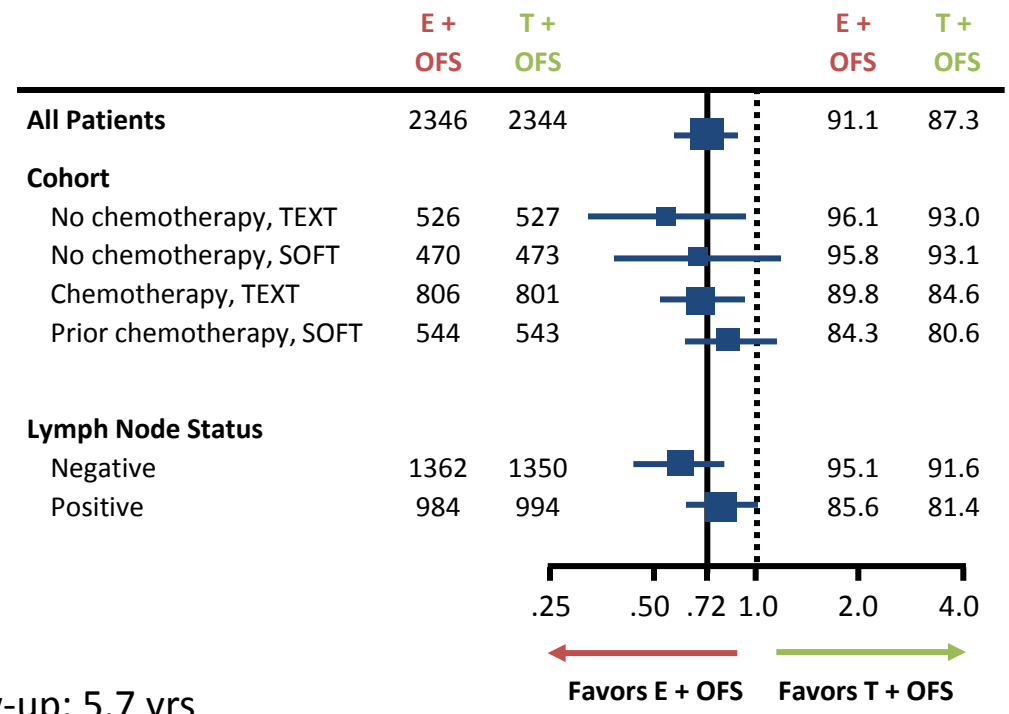


Pagani et al, N Engl J Med, 2014

Exemestane With Ovarian Function Suppression Improved DFS

Difference 3.8% at 5 yrs





Median follow-up: 5.7 yrs

60% of first failures involved distant sites, including soft tissue, bone, and viscera

% of first failures involved distant sites, including soft tissue, bone, and viscera

Pagani et al, N Engl J Med, 2014

Combined analysis TEXT and SOFT: Conclusions

- **Exemestane + OFS significantly improved DFS, BCFI, and DRFI vs tamoxifen + OFS and it represents now a new treatment option for premenopausal women with early HR+ BC**
- **No significant difference in OS based on preliminary follow-up**
- **Safety profile of exemestane + OFS similar to that seen with AIs in postmenopausal women**
- **Highly effective endocrine therapy alone offers excellent prognosis for some premenopausal women with HR+ BC**
- **Long-term follow-up is necessary**

Pagani et al, N Engl J Med, 2014

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

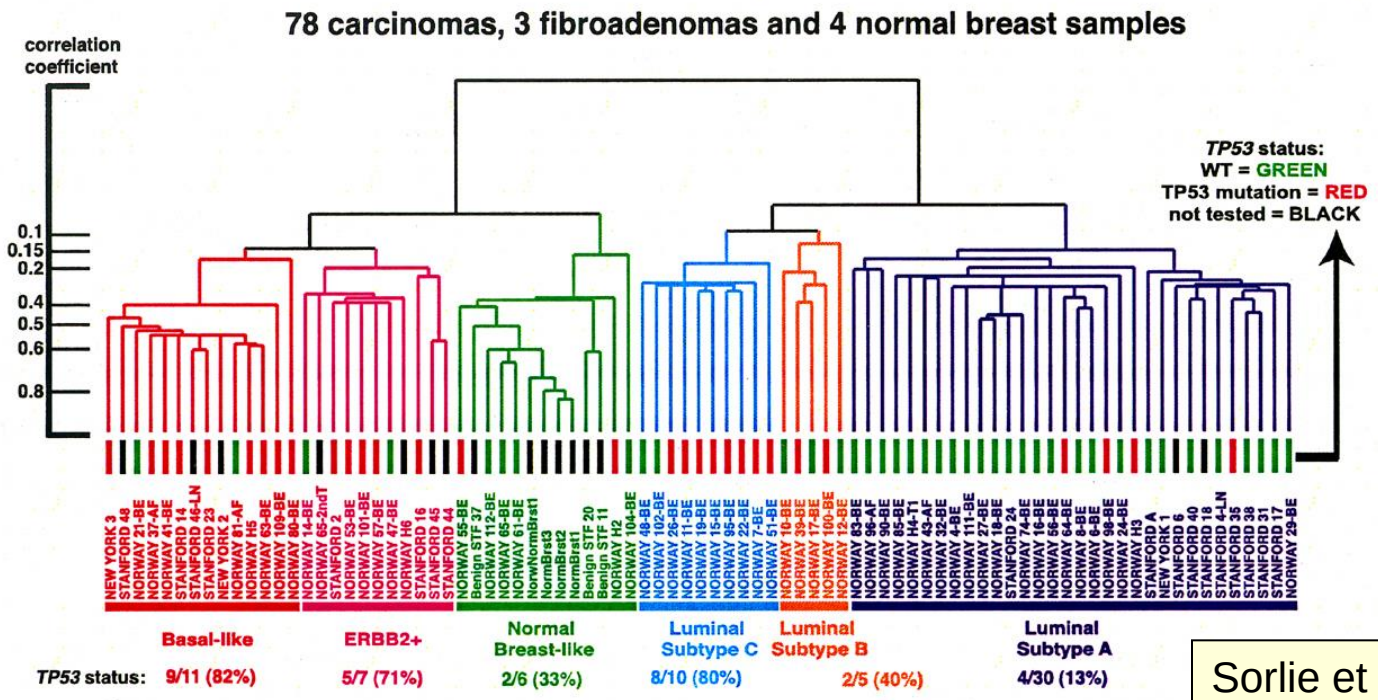
SAFETY RESULTS and CONCLUSIONS

- Incidence of grade 3-4 AEs was similar (31% with EXE + OFS vs. 29% with TAM + OFS)
- Early cessation of all assigned treatments was more frequent with EXE + OFS (16% vs. 11% with TAM + OFS)
- EXE + OFS compared with TAM + OFS improves DFS and breast cancer-free interval
- No significant difference in OS
- Subsequent analysis of SOFT on the need for OFS will be presented at SABCS 2014

- **Taken into account that anastrozole + OFS showed detrimental effects on OS in ABCSG-12 at longer follow-up, tamoxifen remains the standard treatment for premenopausal women. However, several factors need to be considered, i.e. the choice of LHRH agonist, duration of endocrine therapy, different patient characteristics, and the use and timing of chemotherapy**

- **Exemestane + OVARIAN FUNCTION SUPPRESSION might be an option for women with contraindications for tamoxifen**

DFS, disease-free survival; EXE, exemestane; OFS, ovarian function suppression; TAM, tamoxifen, OS, overall survival; AEs, adverse events; SABCS, San Antonio Breast Cancer Symposium; ABCSG, Austrian Breast and Colorectal Cancer Study Group; LHRH, luteinizing hormone-releasing hormone



Sorlie et al *PNAS* 2001

pCR% depends on cellular type and on **molecular type**

N=22
10 pCR (45%)
61 genes signature

N=20
9 pCR (45%)
no signature identified

N=28
2 pCR

Rouzier et al. Clin Cancer Res 2005

Endocrine Therapy Neoadjuvant Clinical Trials

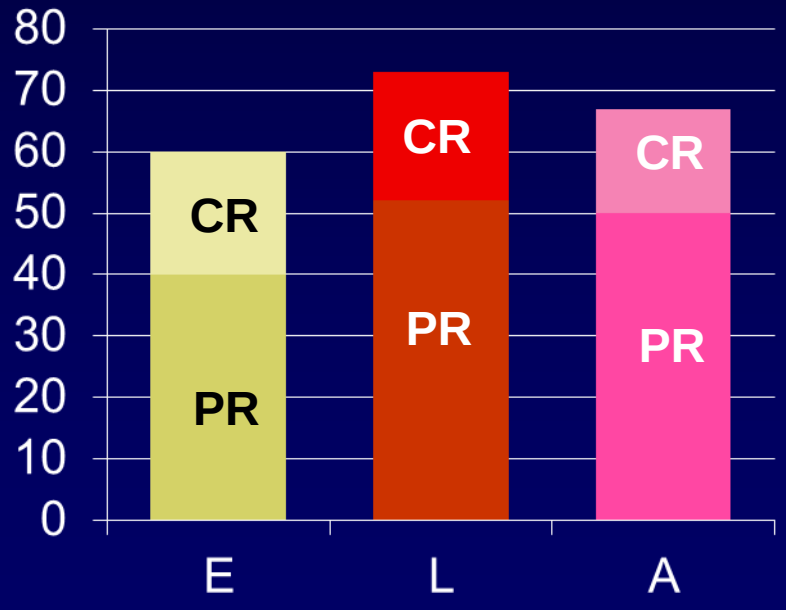
Aromatase Inhibitors (AIs) vs Tamoxifen

	Drug	N	Clinical Response	US Response	Increase BCS	
P024[1]	Letrozole	154	55%	35%	45%	*P* = .022
4 months	Tamoxifen	170	36%	25%	35%	
IMPACT[2]	Anastrozole	113	37%	24%	46%	*P* = .03
3 months	Tamoxifen	108	36%	20%	22%	
	Both	109	39%	28%	26%	
PROACT[3]	Anastrozole	228	50%	40%	38%	ns
3 months	Tamoxifen	223	46%	35%	30%	

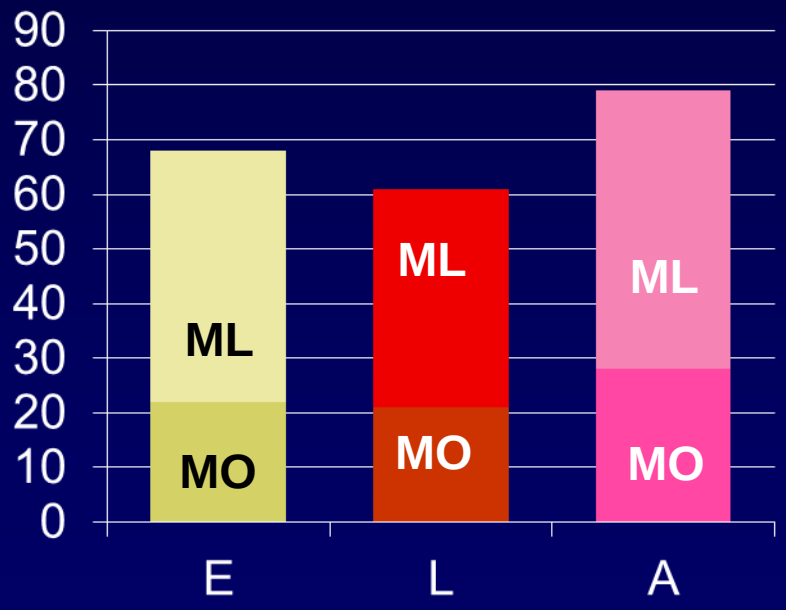
1. Ellis M, et al. *Breast Cancer Res Treat.* 2007;105(Suppl 1):33-43. 2. Smith IE, et al. *J Clin Oncol.* 2005;23(22):5108-5116. 3. Cataliotti L, et al. *Cancer*. 2006;106(10):2095-2103.

Neoadjuvant Aromatase Inhibitors Promote Breast Conservation: ACOSOG Z1031 Trial

Clinical Response, %



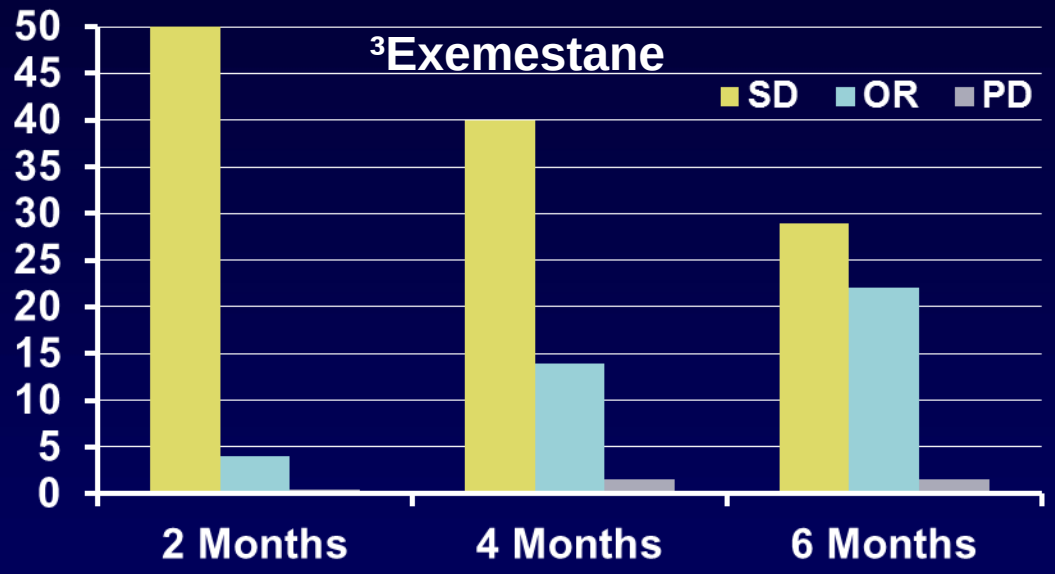
Breast Conservation, %



ML, marginal for lumpectomy; MO, mastectomy only at baseline

Ellis M, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S1-2.

Duration of Neoadjuvant Endocrine Therapy



[2]Duration letrozole	% CR
3 months	9.5
6 months	29
12 months	36

Response to treatment as evaluated by mammography.
OR, objective response; PD, progressive disease; SD, stable disease.

"Conclusion: Over half of patients become BCS-eligible within 4 months of preoperative letrozole treatment. While prolonged treatment for up to 8 months can result in further tumor volume reduction in some patients, there is no clear optimum for treatment duration"[1]

1. Paepke S, et al. *BMC Cancer.* 2008;8:62. 2. Renshaw L, et al. *Breast Cancer Res Treat.* 2004;88(Suppl 1): Abstract 204. 3. Barnadas A, et al. *Br J Cancer.* 2009;100(3):442-449

NEO-ADJUVANT ENDOCRINE THERAPY

Is neoadjuvant endocrine therapy without cytotoxics a reasonable option for postmenopausal patients with endocrine responsive disease? **YES 87.9%**

If yes, for which duration?

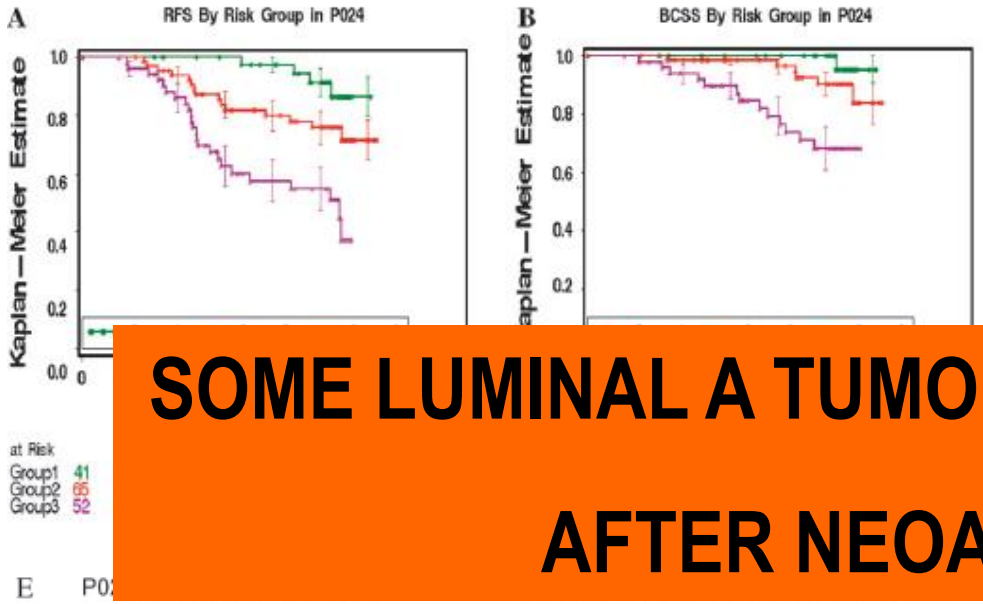
1. **1 – 2 weeks "window" prior to surgery 71%**
2. **3 – 4 months 3.6%**
3. **4 – 8 months 42.9%**
4. **Until maximal response 42.9%**
9. **Abstain 3.6%**

Ki67 Changes With Endocrine Neoadjuvant Can Surrogate for Results in Adjuvant?

Drug Comparison	Neoadjuvant Trial	Ki67 Results	Adjuvant Trial	Efficacy Results
Let vs Tam	P024 (n = 185)	Mean Ki67 @ 4 mos RFS L > T	BIG 1-98 (n = 8010)	L > T
Ana vs Tam vs Tam+Ana	IMPACT (n = 259)	Mean Ki67 @ 2/12 weeks: RFS A>T or AT	ATAC (n = 9366)	A > T or A+T
Ana vs Let vs Exe	ACOSOG Z1031 (n = 266)	Mean Ki67 @12-16 weeks. No Diff	MA 27 (n = 7576)	A = E

POTENTIAL PREDICTIVE ROLE OF CHANGE IN Ki67 AFTER NEOADJUVANT ET

PREOPERATIVE ENDOCRINE PROGNOSTIC INDEX (PEPI)



Model built on only 158 pts P024 study
Validated in 203 pts IMPACT study
Needs further validation

SOME LUMINAL A TUMORS BECAME LUMINAL B AFTER NEOADJUVANT AI

E P02

Risk score	0	1-3	4+	Total
Relapse	4(10%)	15(23%)	25(48%)	44
Chemo	5(12%)	24(37%)	28(54%)	57
Total	41	65	52	158

Risk Score	0	1-3	4+	Total
Relapse	1(3%)	5(5%)	13(17%)	19
Chemo	1(3%)	21(22%)	26(35%)	48
Total	31	97	75	203

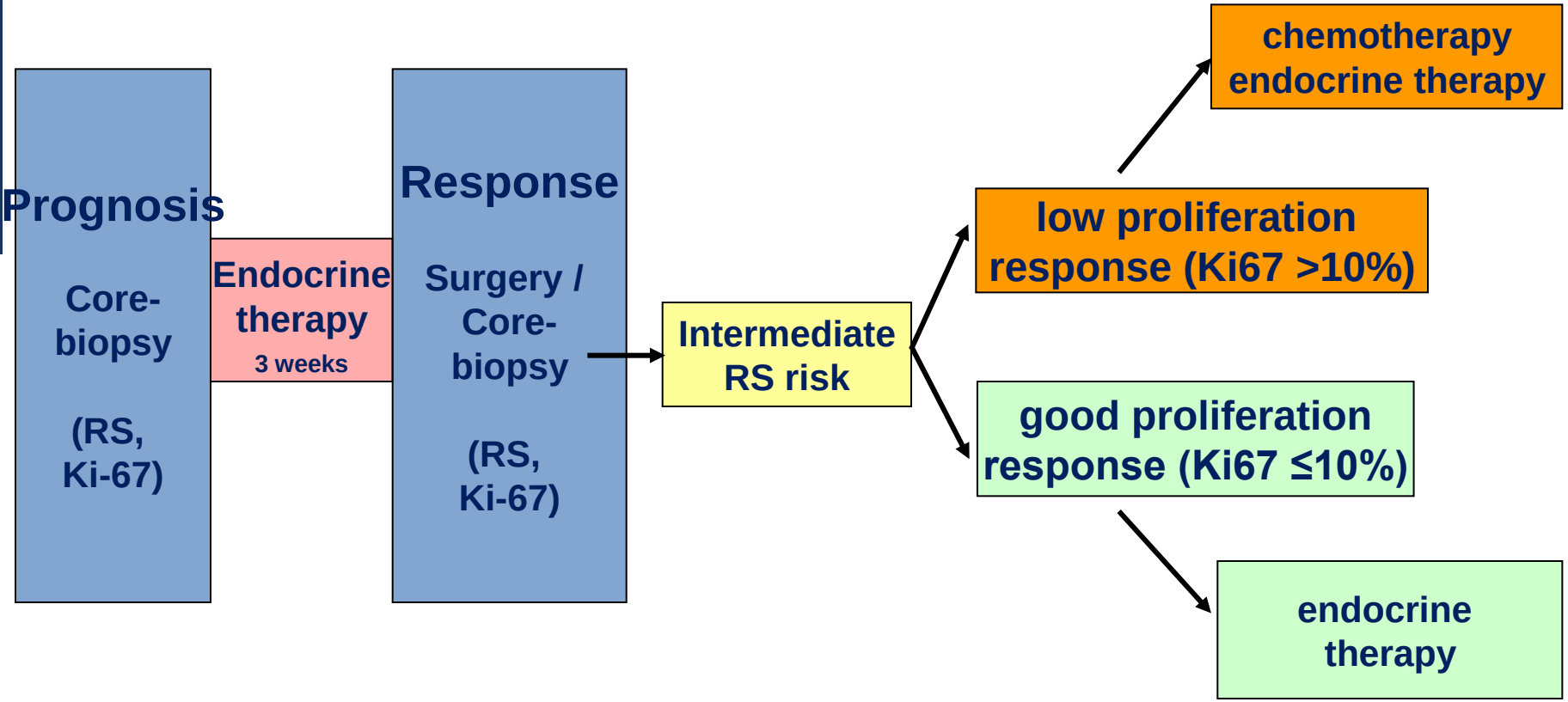
May help decision of adjuvant therapy:
PEPI Group 1 (0): No adjuvant CT needed
PEPI Group 3 (≥4): Adjuvant CT needed
PEPI Group 2 (1-3): unknown

Ellis et al, JNCI 2008

Table 4. The preoperative endocrine prognostic index*

Pathology, biomarker status	RFS		BCSS	
	HR	Points	HR	Points
Pathological tumor size				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki67 level				
0%–2.7% (0–1†)	—	0	—	0
>2.7%–7.3% (1–2†)	1.3	1	1.4	1
>7.3%–19.7% (2–3†)	1.7	1	2.0	2
>19.7%–53.1% (3–4†)	2.2	2	2.7	3
>53.1% (>4†)	2.9	3	3.8	3
ER status, Allred score				
0–2	2.8	3	7.0	3
3–8	—	0	—	0

WSG-ADAPT Trial: HR+ Subprotocol



Principal investigators: N. Harbeck (LKP), Munich; U. Nitz, Mönchengladbach

(courtesy Nadia Harbeck)

Hofmann et al, Trials 2013

POSITIVE Trial: "The Baby Trial"

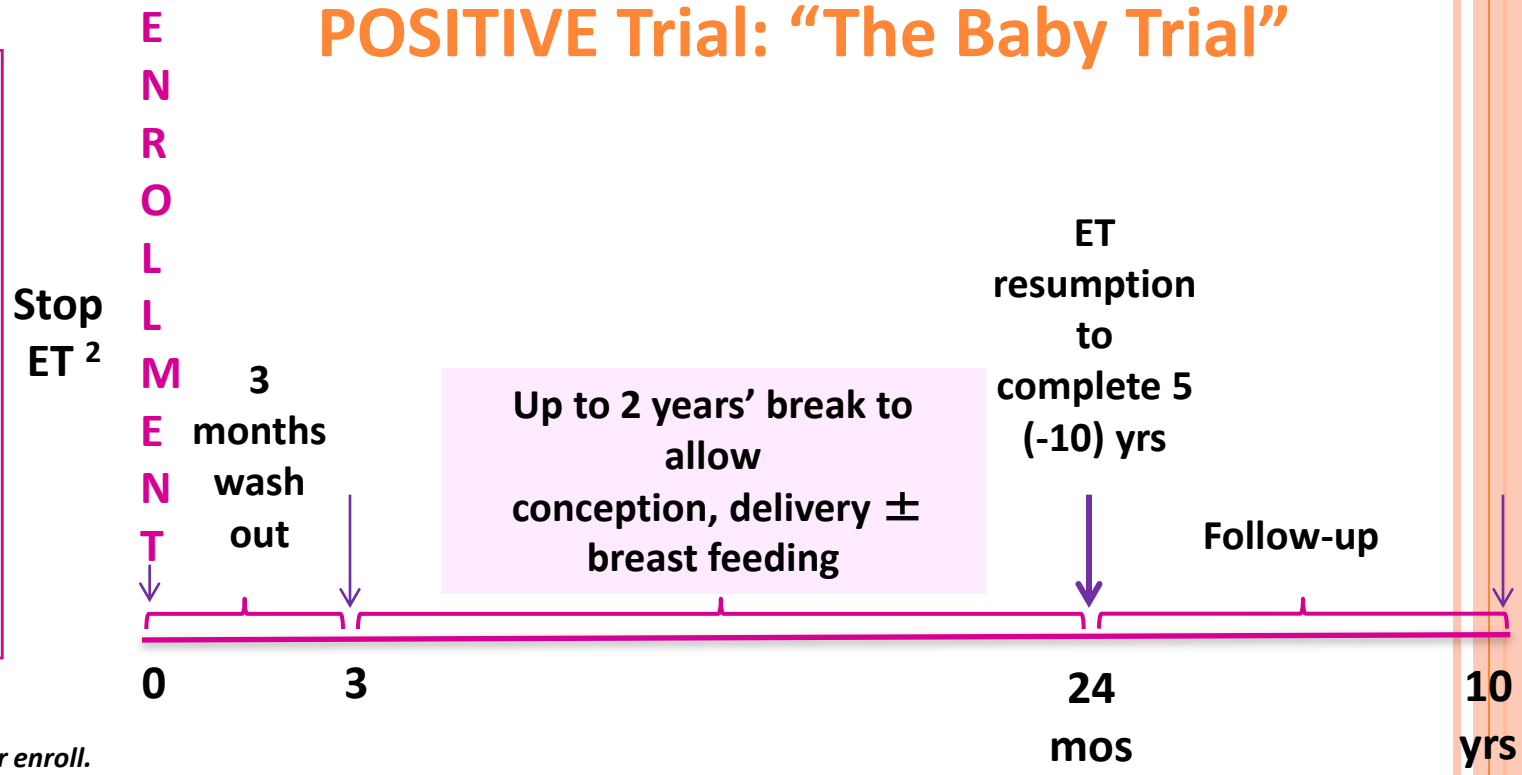
Screening/eligibility:

Patients with **ER+** early breast cancer

≥ 18 and ≤42 years at enrollment

Completing 18-30 months of ET (SERMs alone, GnRH analogue + SERM or AIs) [1]

Pregnancy desire



[1] ± CT

[2] *No more than 1 month prior enroll.*

Translational research

- Ovarian function evaluation
- Uterine evaluation
- Circulating tumor DNA (ctDNA)
- Genomic evaluation of primary breast tumor

Psycho-oncology companion – psychological distress, fertility concerns, decisional conflict

BIG Breast International Group

NABCG The North American Breast Cancer Group

IBCSG

OPEN QUESTIONS

- No predictive markers to discriminate between Tam & AI

- Optimal duration for the individual patient (> 5 years…)

- Best strategy for extended adjuvant (10 y Tam; 10 y AI, sequence, “sandwich”, …)

- Role of ovarian suppression/ablation for the individual patient: STILL OPEN QUESTION until OS data; Optimal duration of OFS?

- Resistance!