San Antonio Breast Cancer Symposium Review

Update on Endocrine Therapy

Georgia Society of Clinical Oncology
January 10, 2015

Amelia B. Zelnak, M.D., M.Sc.
Assistant Professor of Hematology and Medical Oncology
Winship Cancer Institute
Emory University School of Medicine

Outline

• Invasive Lobular Carcinoma	S2-04, S2-05, S2-06
• Prevention	S3-07
• Male Breast Cancer	S6-05
• 1st line Fulvestrant	S6-04
• SOFT	S3-08, S3-09

Invasive Lobular Carcinoma

S2-04 Ciriello et al. Comprehensive Molecular Characterization of Invasive Lobular tumors

S2-05 Desmedt et al. Characterization and clincial relevance of genomic alterations defining lobular breast cancer

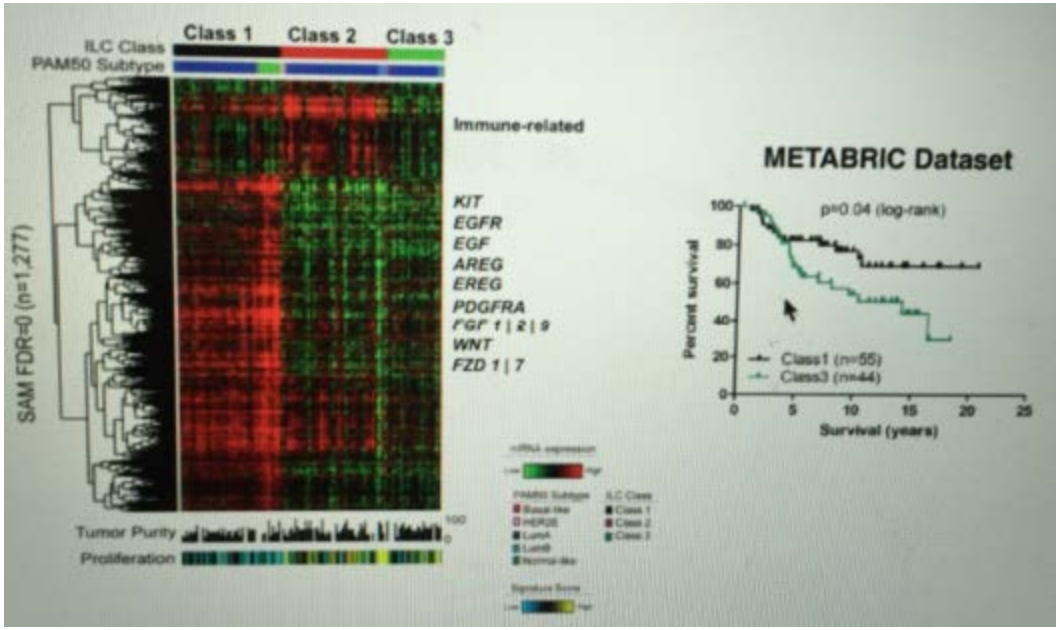
S2-06 Knauer et al. Survival advantage of anastrozole compared to tamoxifen for lobular breast cancer in the ABCSG-8 study

Invasive Lobular Carcinoma

- 5-15% of all invasive cancer
- Small, discohesive epithelial cells
- Mostly hormone receptor positive
- More late recurrences compared to invasive ductal carcinoma
- Wider metastatic pattern compared to ductal
  - ovaries, uterus, peritoneum, retroperitoneum, stomach, and intestine

Invasive Lobular Carcinoma: Ciriello et al

- 817 breast cancer samples, 127 lobular
- 83% of invasive lobular carcinoma were luminal A
- 3 mRNA subtypes, all with loss of E-cadherin



Invasive Lobular Carcinoma: Ciriello et al

- FoxA1, key modulator of ER-regulated transcription, was more commonly mutated in ILC compared to IDC (9% vs. 2%)
- PTEN loss of function mutations are more frequent with lobular cancers
- Luminal A ILC showed increased RTK/AKT activation compared to Luminal A IDC

Invasive Lobular Carcinoma: Desmedt et al

Patients and samples

N= 630 eligible patients

- 17 failed library prep 24 potentially contaminated
- 177 with lower coverage than pre-specified by power calculation according to cellularity

N= 413 patients with subs/indels

(36% with matched normal DNA; median coverage: 103x)

- 243 not fulfilling predefined QC

N= 170 patients with CN data

Invasive Lobular Carcinoma: Desmedt et al

Patient's characteristics (n=413)

Age (years)	%
<50	31.5
50 or >	68.5

Tumor size (cm)	%
< or = 2	45.5
>2	54.5

Nodal status	%
Negative	47.7
Positive	49.4
Unknown	2.9

Histological subtype	%
Classic	47.7
Alveolar	16.0
Solid	15.7
Mixed, non classic	13.8
Trabecular	6.8

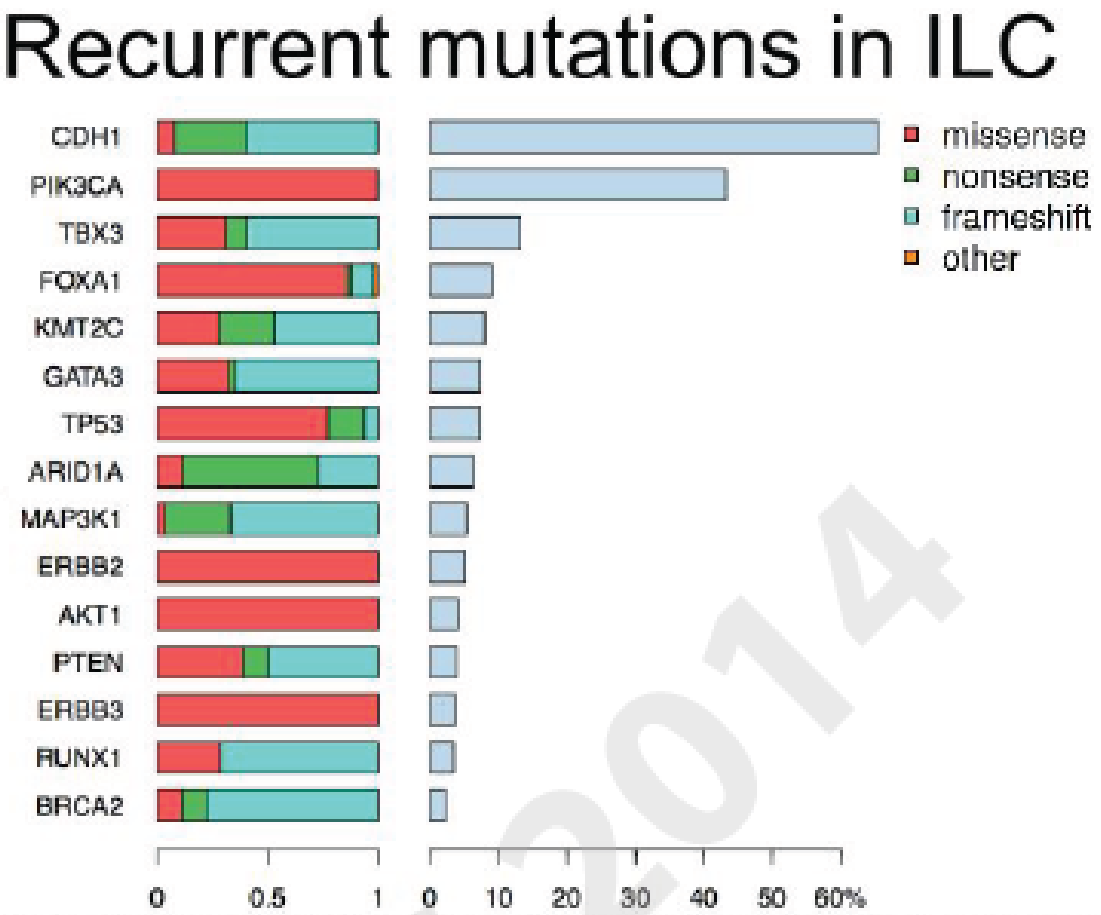
Receptor status	%
ER-	6.1
ER+ PgR-	20.8
ER+ PgR+	73.1

Ki67	%
<10	24.7
10-19	42.8
20 or >	30.0
Unknown	1.5

Her-2	%
Negative	93.7
Positive	5.8

Tumor grade	%
G1	11.4
G2	73.2
G3	15.3

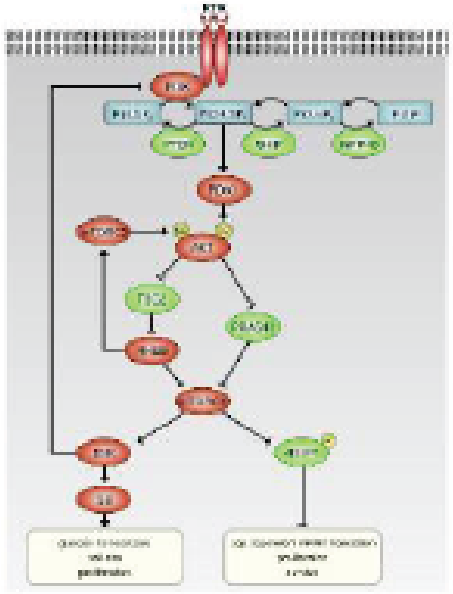
Invasive Lobular Carcinoma: Desmedt et al



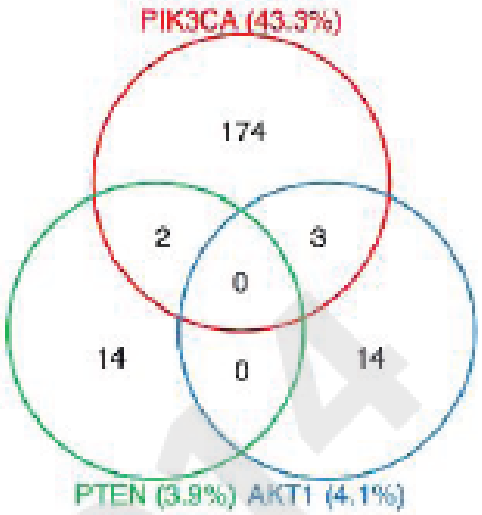
Invasive Lobular Carcinoma: Desmedt et al

SAN ANTONIO BREAST CANCER SYMPOSIUM

PI3K pathway dysregulation (50%)



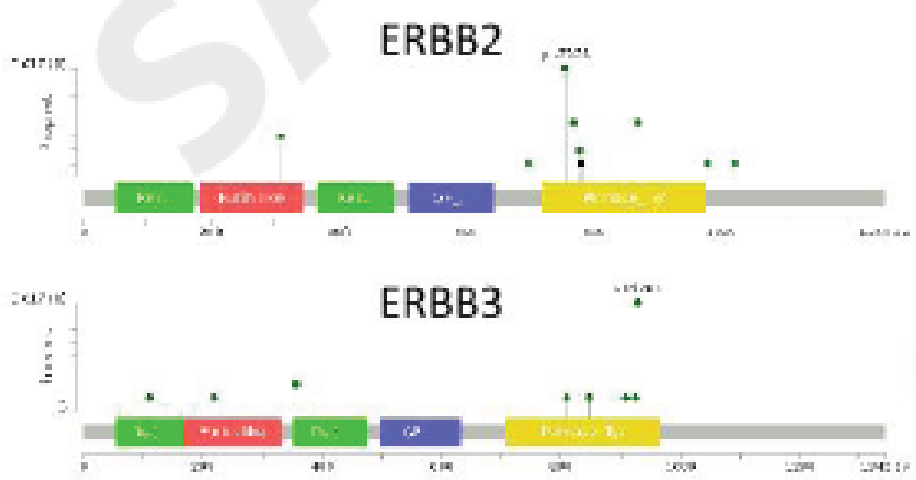
Barenbeek et al. 2013

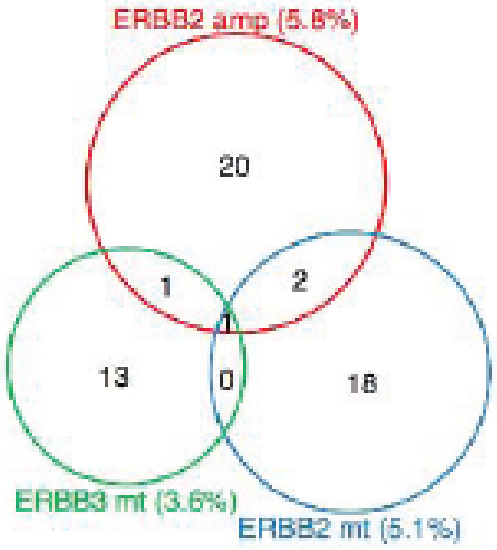


PI3K pathway dysregulated in 50% of lobular tumors, with mutations in PIK3CA, AKT1 and PTEN being mostly mutually exclusive

Invasive Lobular Carcinoma: Desmedt et al

ERBB2-ERBB3 (8.5%)

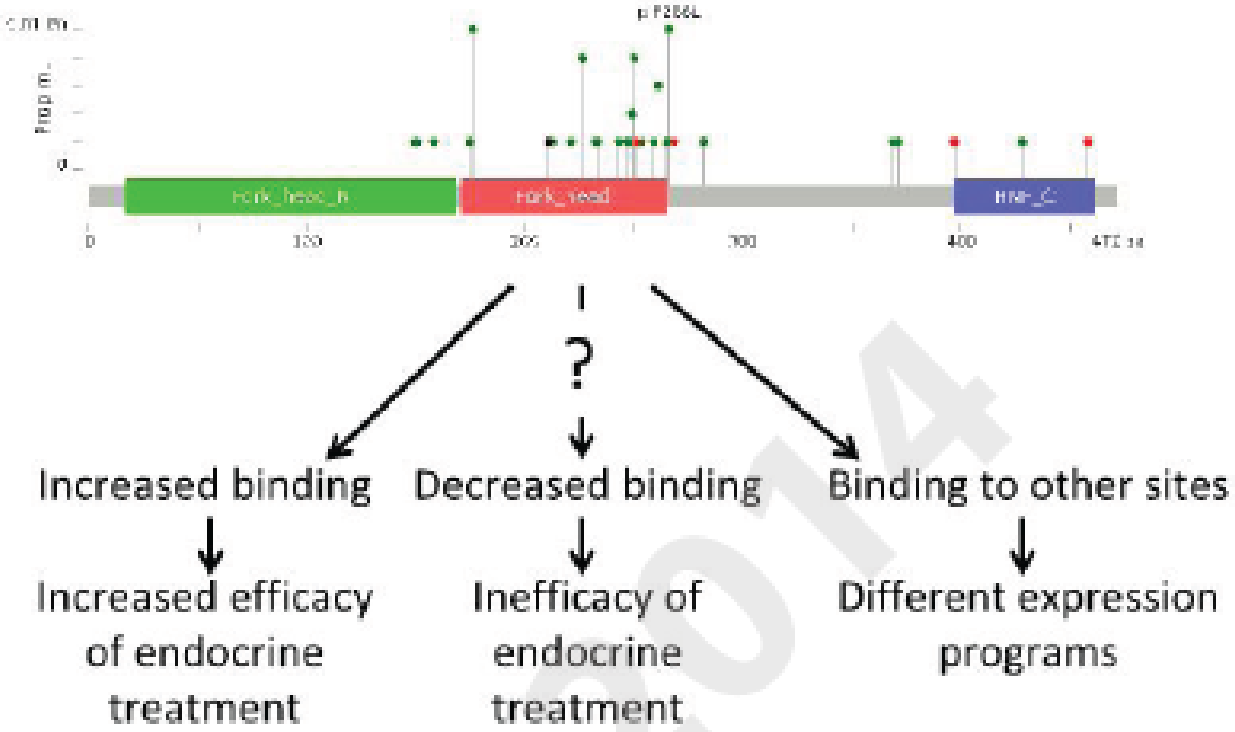




Oncogenic ERBB2/ERBB3 mutations could represent potential **therapeutic targets in lobular breast cancer.**

Invasive Lobular Carcinoma: Desmedt et al

FOXA1=ER-binding partner (9%)



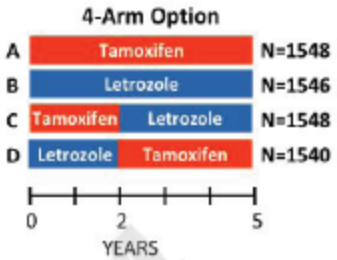
Survival Advantage of Anastrozole Compared to Tamoxifen for Lobular Breast Cancer in the ABCSG 8 Study

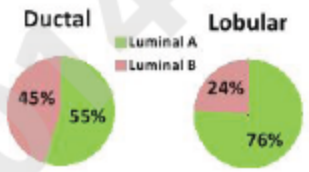
Michael Knauer

Christine Gruber, Otto Dietze, Richard Greil, Herbert Stöger, Margaretha Rudas, Zsuzsanna Bago-Horvath, Brigitte Mlineritsch, Werner Kwasny, Christian Singer, Peter Dubsky, Raimund Jakesz, Florian Fitzal, Günther Steger, Rupert Bartsch, Martin Filipits, Christian Fesl, Michael Gnant

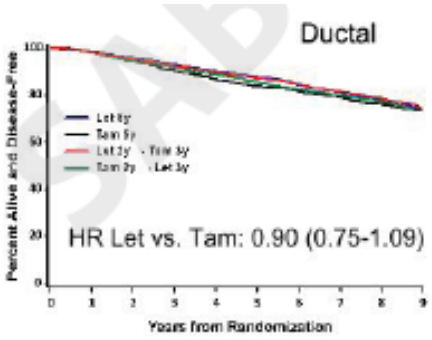
Invasive Lobular Carcinoma: BIG 1-98

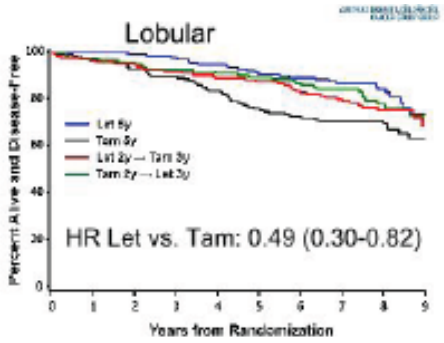
- Phase III 4-arm randomized study
- Substantial cross-over: 40%
- 8 years median follow-up[1]
- Patients: 3788 IDC vs. 502 ILC[2]





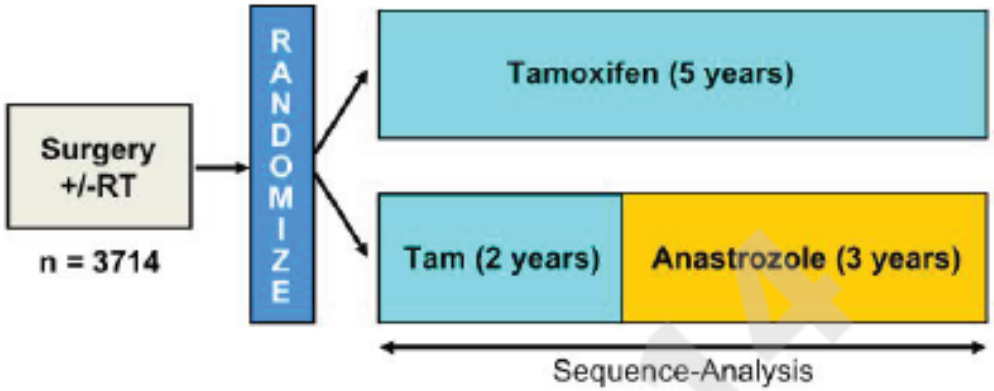
- Pathologic surrogates of intrinsic subtypes:
- ER+ and/or PgR+ and Her2-neg.
- Cut-off: Ki-67 14%





- IDC: no advantage for letrozole containing arms regarding DFS and OS
- ILC: only Letrozole 5y vs. Tamoxifen 5y significant:
  DFS HR 0.49 (0.30-0.82), OS HR 0.39 (0.20-0.76)

Study Design of ABCSG-8



Relevant inclusion criteria:

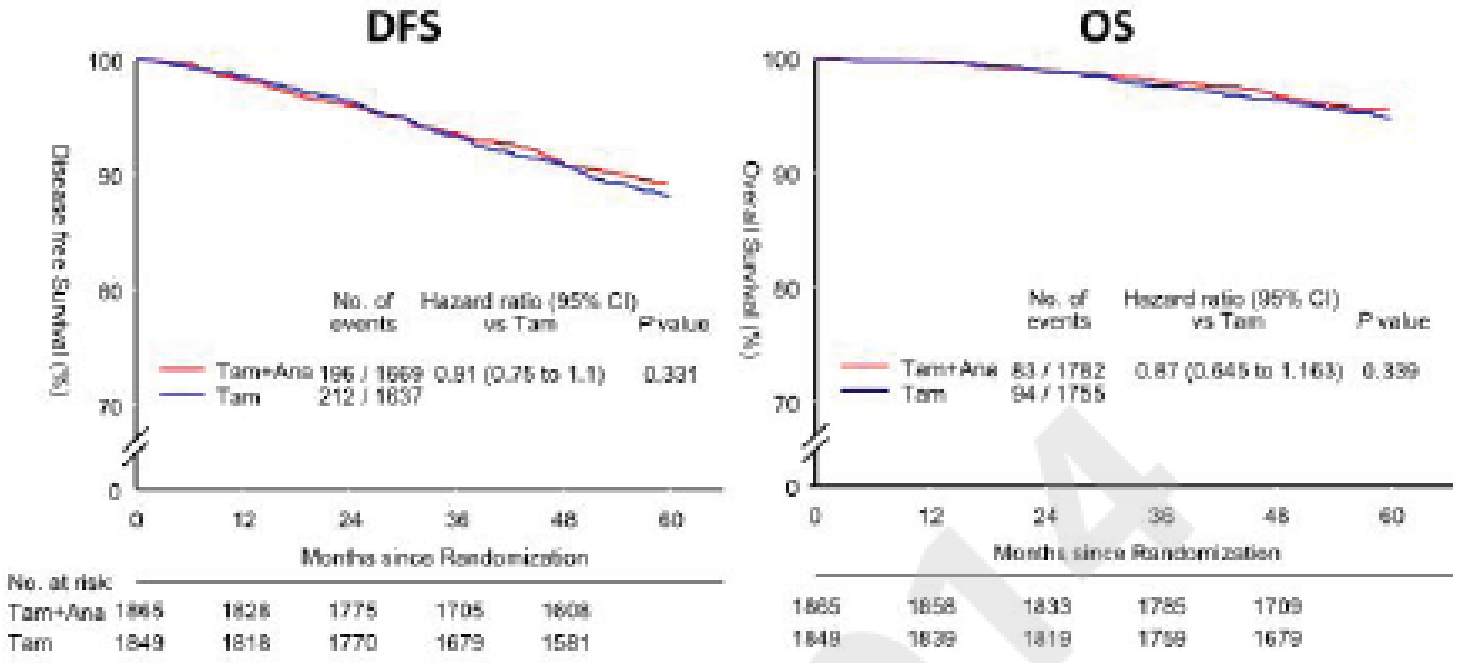
- Postmenopausal patients with endocrine-responsive cancer
- Grade 1/2
- No adjuvant chemotherapy

Patients	**3714**
Median age at surgery	**64**
T1	**75%**
N0	**75%**
Breast conserving surgery	**82%**
Radiotherapy	**70%**

- Low to intermediate risk population

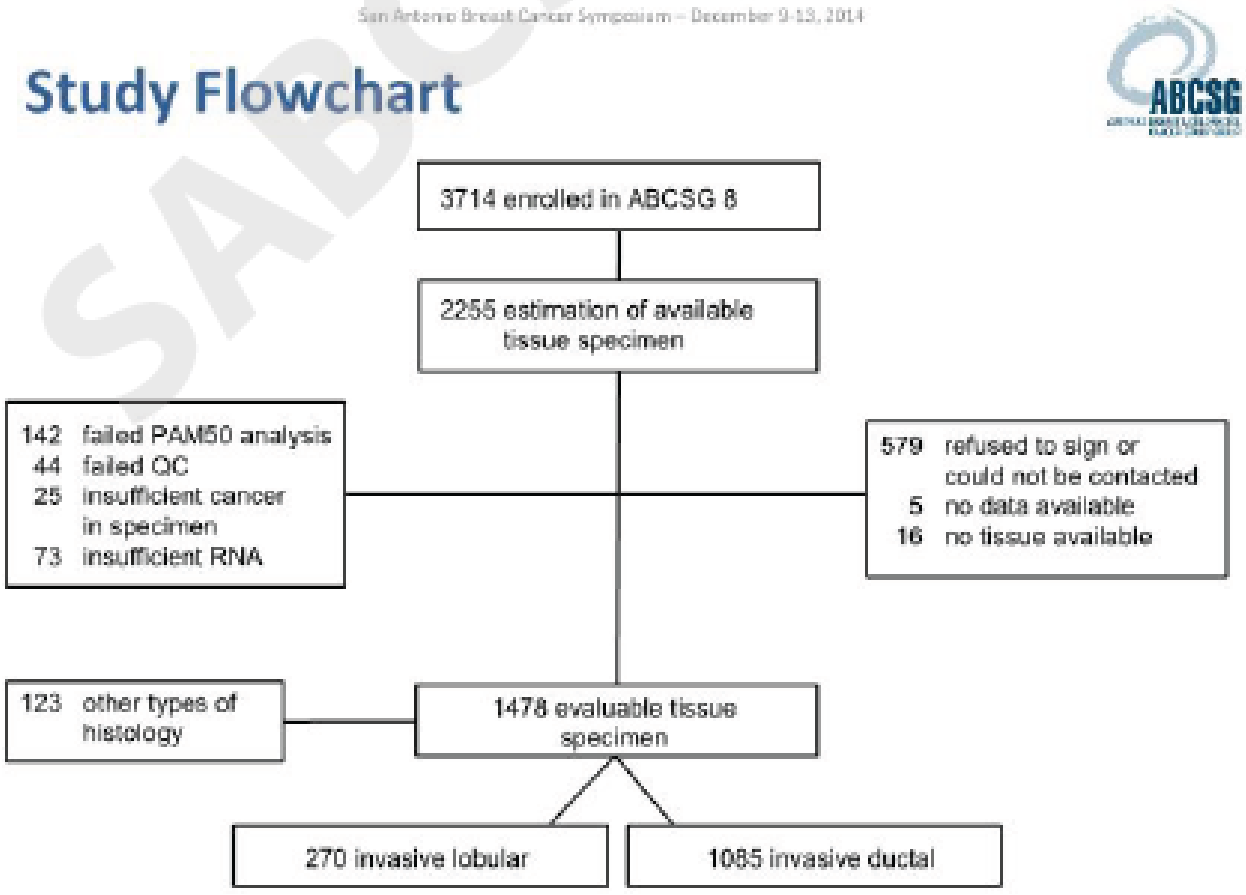
Dubsky P et al., J Clin Oncol 2012

Overall Results from ABCSG-8



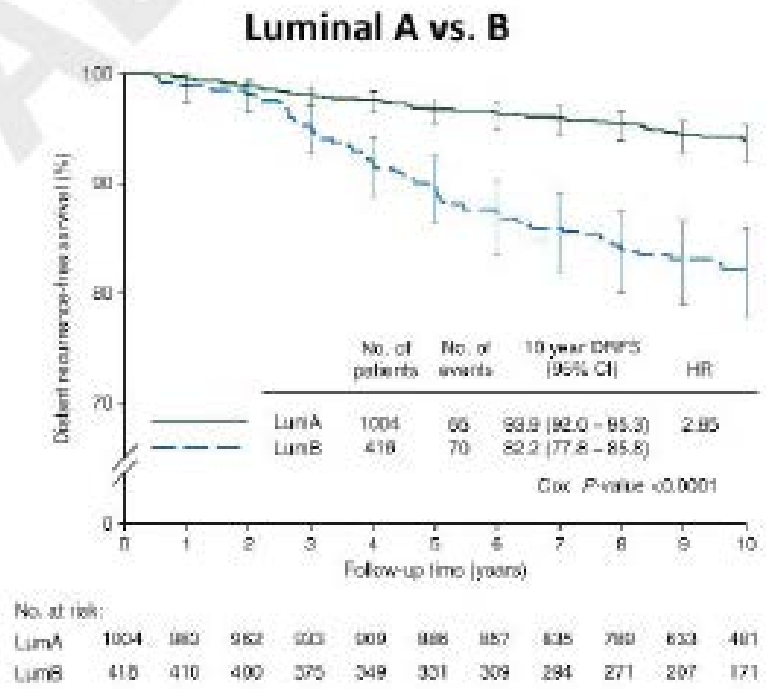
Distant disease-free survival (DDFS): HR 0.78 (0.60-0.996), p=0.046

Invasive Lobular Carcinoma: Knauer et al



Invasive Lobular Carcinoma: Knauer et al

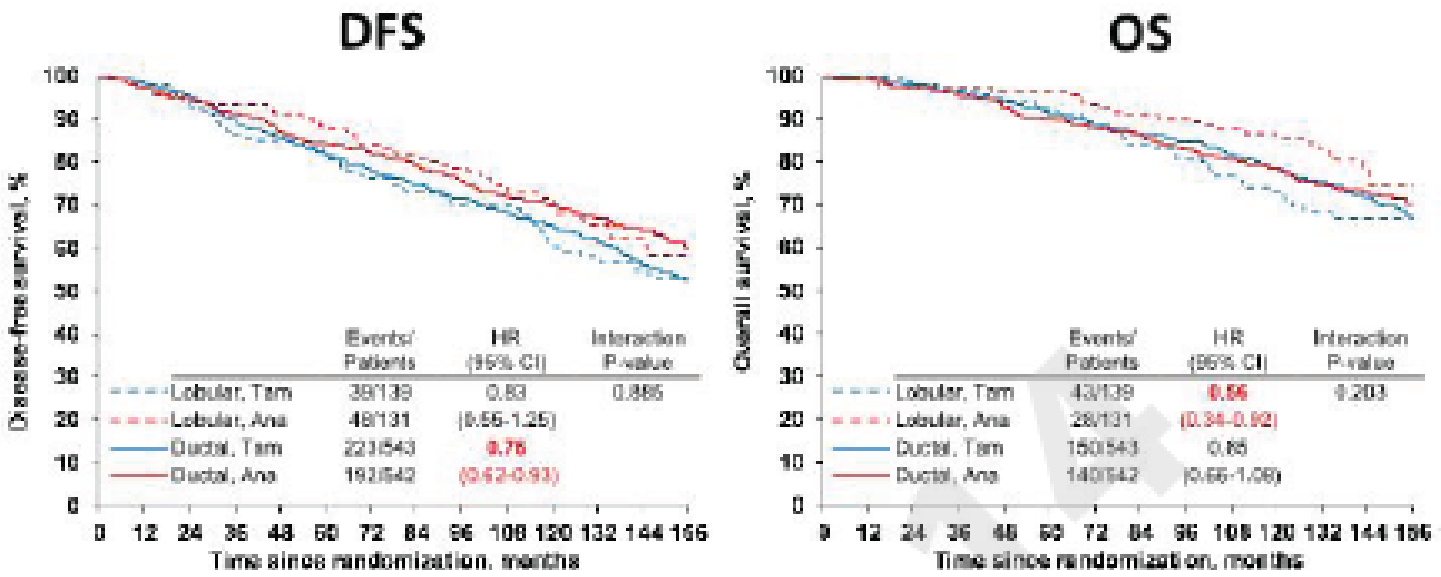
ABCSG 8 and PAM50: DDFS



Gnant M et al., Ann Oncol 2014

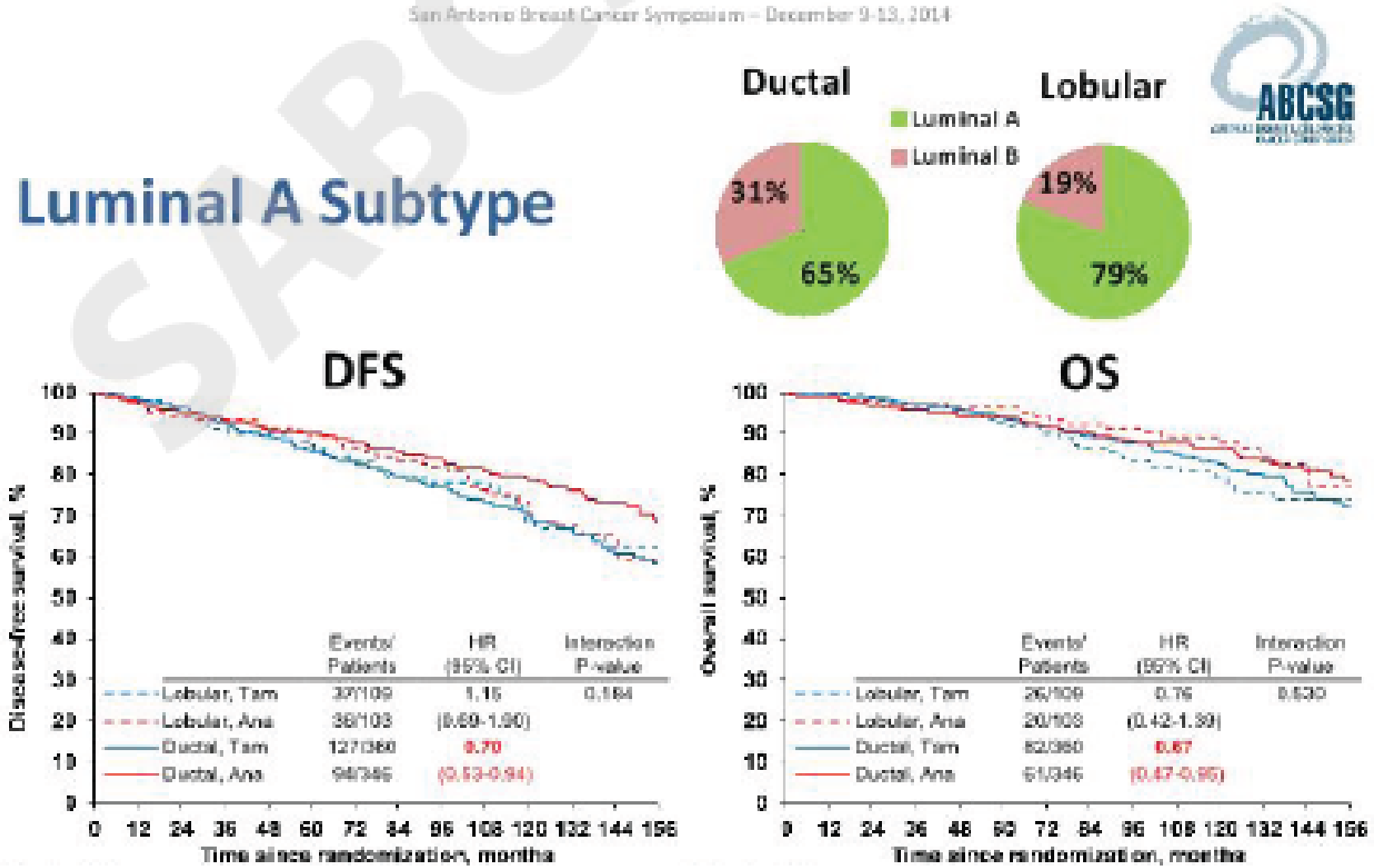
Invasive Lobular Carcinoma: Knauer et al

Overall Study Population



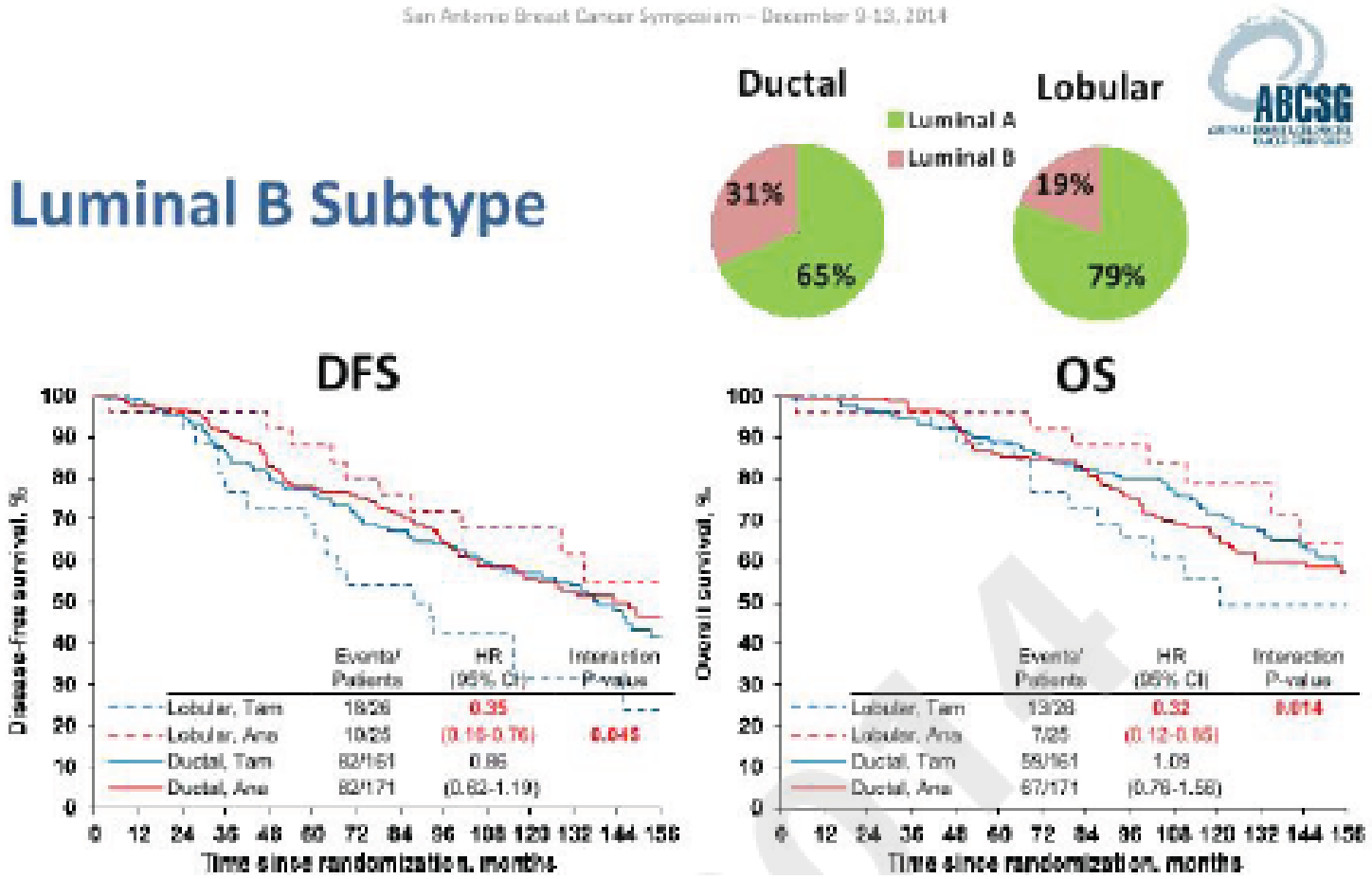
Among all patients with lobular cancers, anastrozole showed superior OS compared to tamoxifen

Invasive Lobular Carcinoma: Knauer et al



Benefit of anastrozole in DFS and OS was only significant among Luminal A Invasive Ductal Carcinoma

Invasive Lobular Carcinoma: Knauer et al



Benefit of anastrozole in DFS and OS was only significant among Luminal B Invasive Lobular Carcinoma

Conclusions regarding Lobular Cancers

- IDC and ILC are different on a genetic level
  - Potential implications for drug development and trial design
- Benefit of anastrozole over tamoxifen was different among IDC vs ILC
- Luminal A vs Luminal B: although data using PAM-50 or IHC surrogates is intriguing, still not ready to predict benefit from AI vs tamoxifen.

Extended long-term follow up of the IBIS-I breast cancer prevention trial

Jack Cuzick

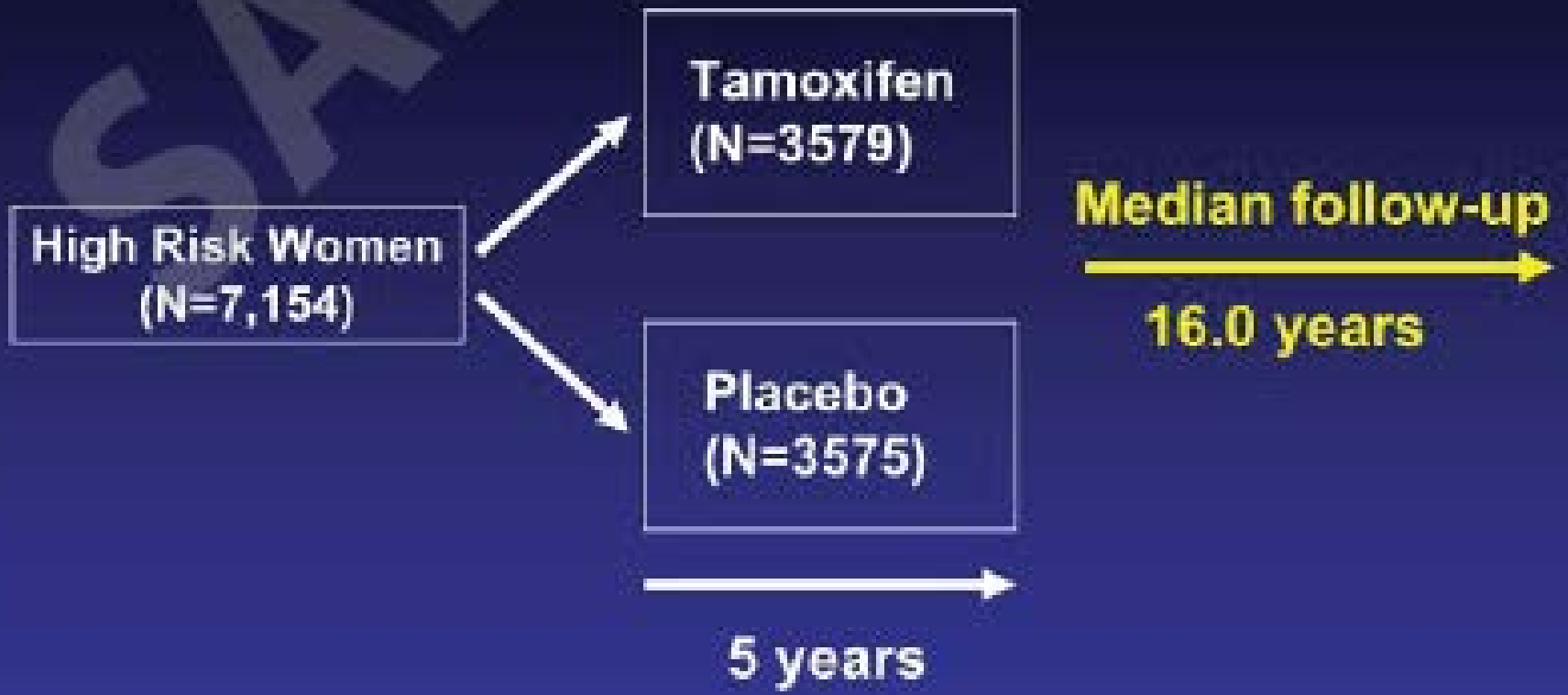
Ivana Sestak, Simon Cawthorn, Hisham Hamed,

Kaija Holli, Anthony Howell, John F. Forbes

on behalf of the IBIS-I investigators

Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University London, London, UK
Breast Care Centre, Southmead Hospital, Bristol, UK
Genesis Breast Cancer Prevention Centre, Manchester, UK
Guy's & St. Thomas Hospital, London, UK
University of Tampere, Tampere, Finland
University of Newcastle, Calvary Mater Hospital, Australia New Zealand Breast Cancer Trials Group Newcastle, Australia

IBIS-I study design

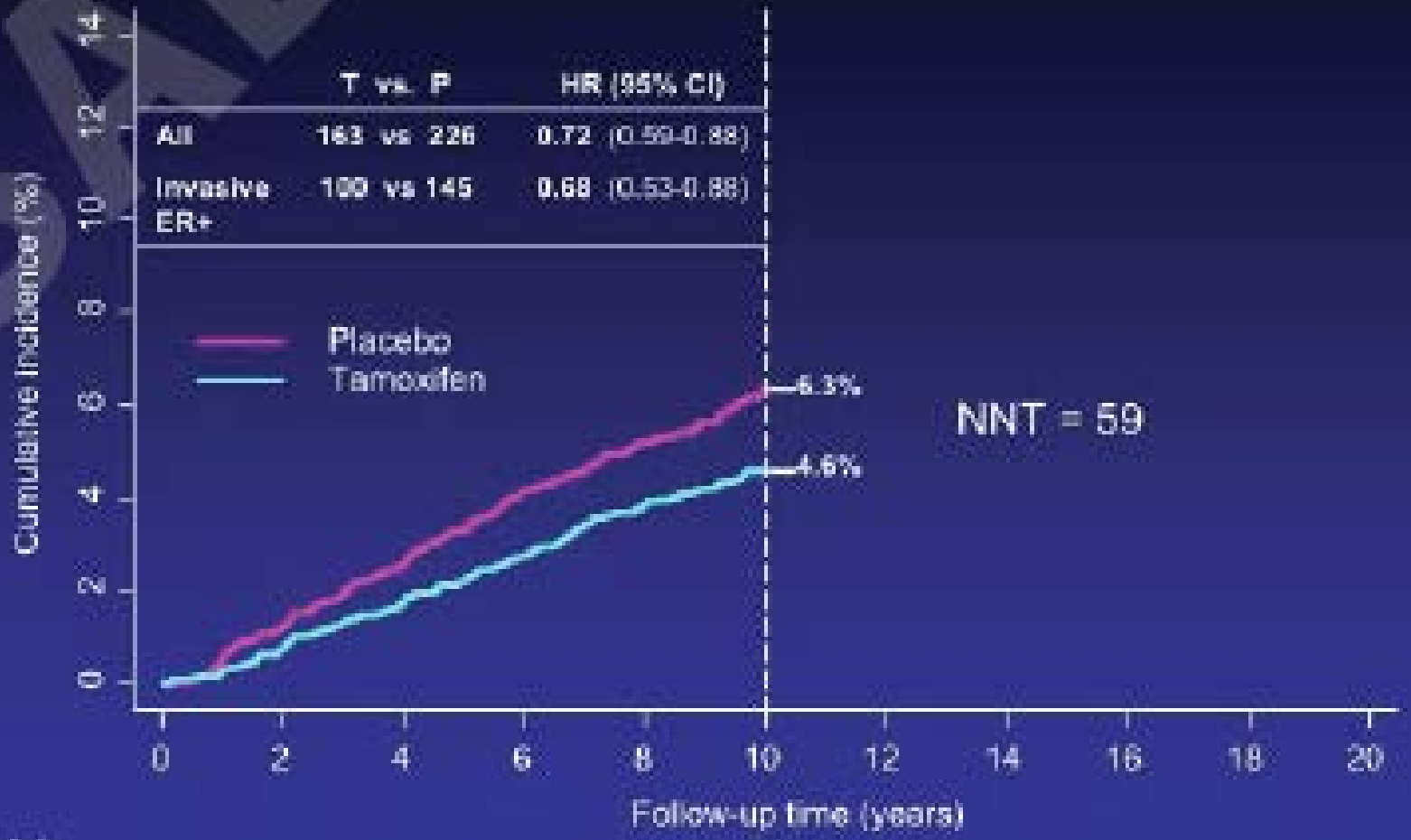


Endpoints: Primary: Breast cancer incidence (incl. DCIS)
Secondary: Other cancers, BC mortality, all cause mortality, adverse events

Baseline characteristics

	Placebo (N=3575)	Tamoxifen (N=3579)
Age (years), mean (SD)	50.8 (6.8)	50.8 (7.0)
BMI (kg/m^2), mean (SD)	26.9 (5.1)	27.0 (5.3)
Postmenopausal (%)	53.7%	54.1%
HRT use (%)		
During trial	49.5%	40.9%
Ex-users	10.6%	11.2%
Never users	49.5%	47.7%
Hysterectomy (%)	35.9%	34.4%

Cumulative incidence for all breast cancer

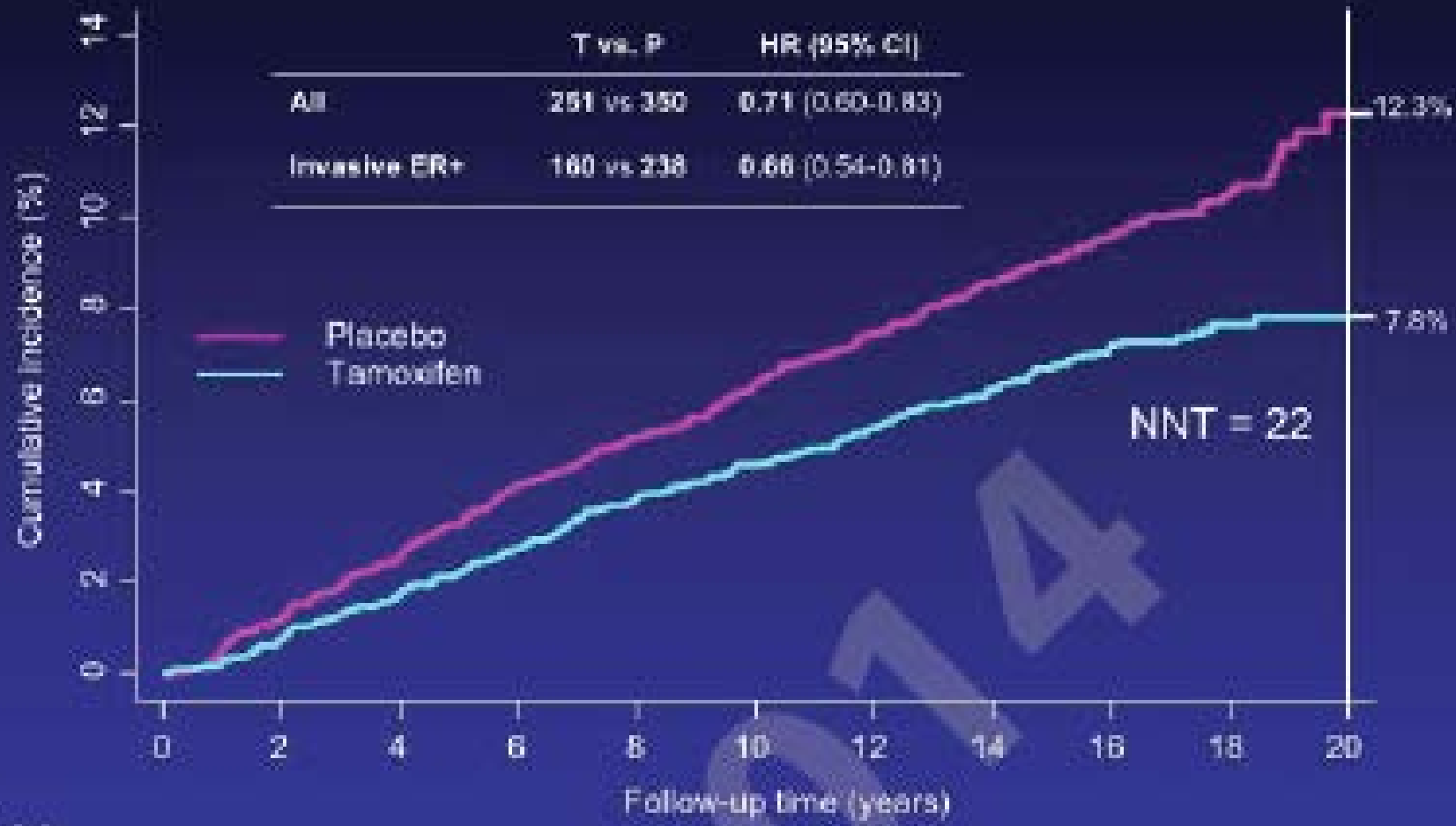


Number at risk

Placebo	3575	3527	3474	3410	3358	3296	3239	2850	1901	725	165
Tamoxifen	3579	3542	3495	3446	3385	3344	3293	2890	1918	748	168

Cumulative incidence for all breast cancer

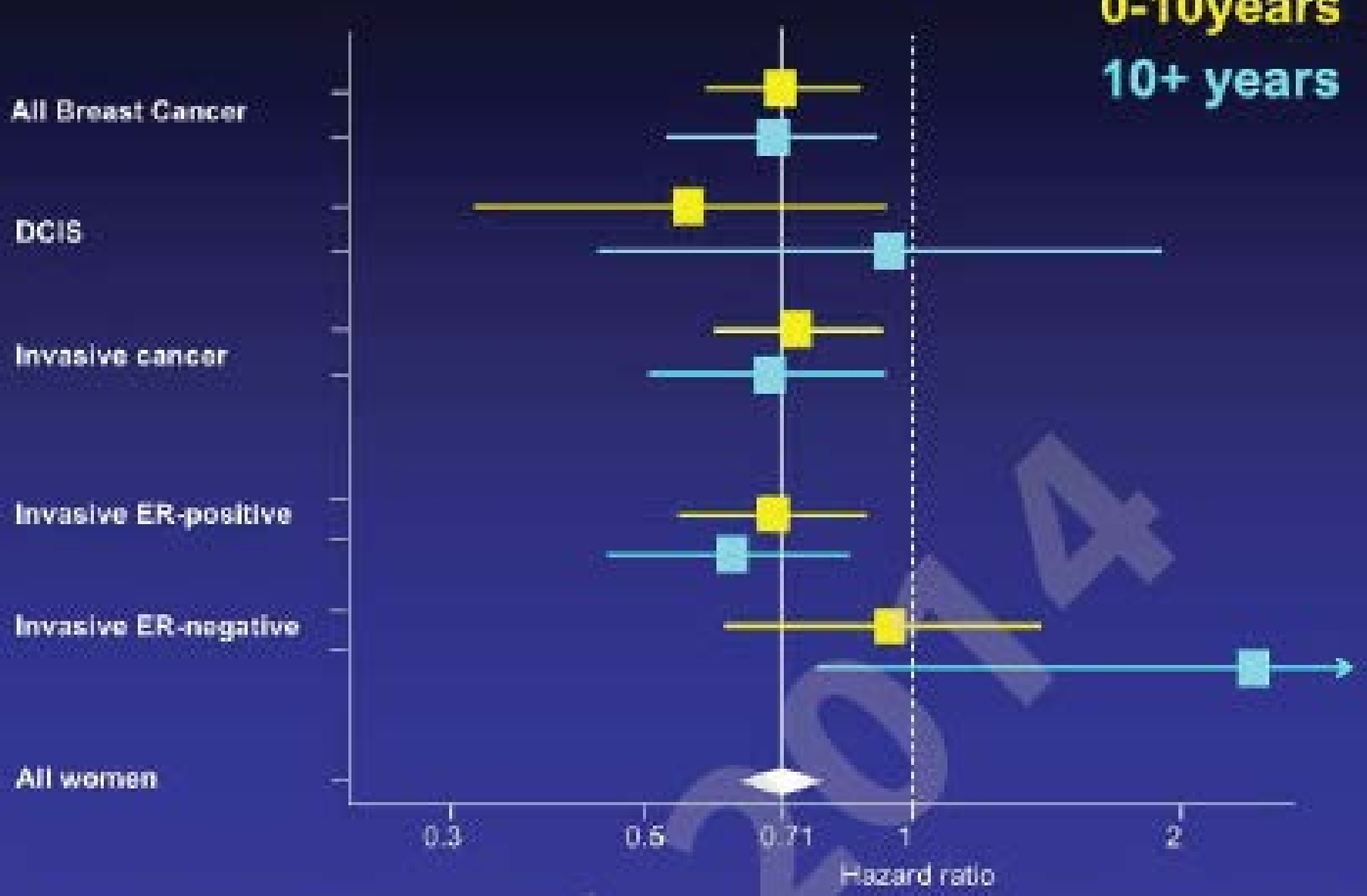
	T vs. P	HR (95% CI)
All	251 vs 350	0.71 (0.60-0.83)
Invasive ER+	160 vs 238	0.66 (0.54-0.81)



Number at risk

Placebo	3575	3527	3474	3410	3358	3296	3239	2850	1901	725	165
Tamoxifen	3579	3542	3495	3446	3385	3344	3293	2890	1918	748	168

Breast cancer subgroups



Other cancers

	Placebo (N=3575)	Tamoxifen (N=3579)		OR (95% CI)
Total	**315 (8.8%)**	**351 (9.8%)**	**+36**	**1.13 (0.96-1.32)**
Endometrial	20	29	+9	1.45 (0.79-2.71)
Non-melanoma skin	84	116	+32	1.39 (1.04-1.87)
All other	210	206		1.02 (0.83-1.25)
Colorectal	47	35	-12	0.74 (0.46-1.18)

Adverse events

	Placebo (N=3575)	Tamoxifen (N=3579)		OR (95% CI)
Pulmonary embolism (PE)	22	30	+8	1.37 (0.76-2.49)
DVT (without PE)	23	40	+17	1.75 (1.02-3.06)
Myocardial infarction	17	13	-4	0.76 (0.34-1.67)
Stroke/CVA	28	30	+2	1.07 (0.62-1.86)

Deaths

	Placebo (N=3575)	Tamoxifen (N=3579)		OR (95% CI)
Total	**166 (4.6%)**	**182 (5.1%)**	**+16**	**1.10 (0.88-1.37)**
Breast cancer	26	31	+5	1.19 (0.68-2.10)
Endometrial cancer	0	5	+5	
Other cancers	78	83	+5	1.06 (0.77-1.47)
Cardiac	14	12		
DVT/PE	3	4		
Stroke/CVA	12	10		
Other causes	33	37		

Summary

- After 20 years of follow up results show a clear long-term benefit of 5 years of tamoxifen for preventing breast cancer:

All breast cancer:	7.8% vs. 12.3%
Invasive ER-positive:	4.9% vs. 8.3%

Number Needed to Treat:

All breast cancer:	22
Invasive ER-positive:	29

- Effects larger for women not taking HRT during trial (38% vs. 12%, P=0.04)

Summary (cont.)

- No reduction in breast cancer mortality
  - Increase with tamoxifen seen after 10 years
  - With previous estimates of a potential 18% reduction, power only 12% to observe reduction in breast cancer mortality
  - Increase in ER-negative breast cancer after 10 years
- No increase seen in overall mortality after 10 years (95 vs. 96)
  - Non-significant increase in endometrial cancer deaths (5 vs. 0)
- Clear benefits of tamoxifen in reduction of breast cancer incidence, but uncertainty with respect to mortality impact

Characterization of male breast cancer: First results of the EORTC 10085/TBCRC/BIG/NABCG International Male BC Program

Fatima Cardoso, John Bartlett, Leen Slaets, Carolien van Deurzen, Elise van Leeuwen-Stok, Peggy Porter, Barbro Linderholm, Ingrid Hedenfalk, Carolien Schröder, John Martens, Jane Bayani, Christi van Asperen, Melissa Murray, Clifford Hudis, Lavinia Middleton, Joanna Vermeij, Stephanie Peeters, Judith Fraser, Monika Nowaczyk, Isabel T. Rubio, Stefan Aebi, Catherine Kelly, Kathryn Ruddy, Eric Winer, Cecilia Nisson, Lissandra Dal Lago, Larissa Korde, Kim Benstead, Danielle Van Den Weyngaert, Oliver Bogler, Theodora Goulioti, Nicolas Dif, Carlo Messina, Konstantinos Tryfonidis, Jan Bogaerts and Sharon Giordano.

San Antonio Breast Cancer Symposium
December 2014
San Antonio, TX, USA

Male Breast Cancer: Cardoso et al

San Antonio Breast Cancer Symposium, December, 2014

INTRODUCTION

- Rare disease **(< 1% of all male cancers; about 1% of all BC)**
- African countries with higher incidence (Uganda 5% and Zambia 15%)
- Literature: mainly case-control and retrospective studies with small numbers of pts
- **NO RANDOMIZED DATA!** All clinical trials to date closed for lack of accrual…
- Treatment strategies largely extrapolated from female BC
- **Incidence**:
  - U. S. incidence climbed through 2000, now steady
  - Nordic Cancer Registries: Stable rates
- **Mortality**: down by 28% (vs 52% for women)

Male Breast Cancer: Cardoso et al

MALE BC INTERNATIONAL PROGRAM: outline

Part 1: Retrospective part

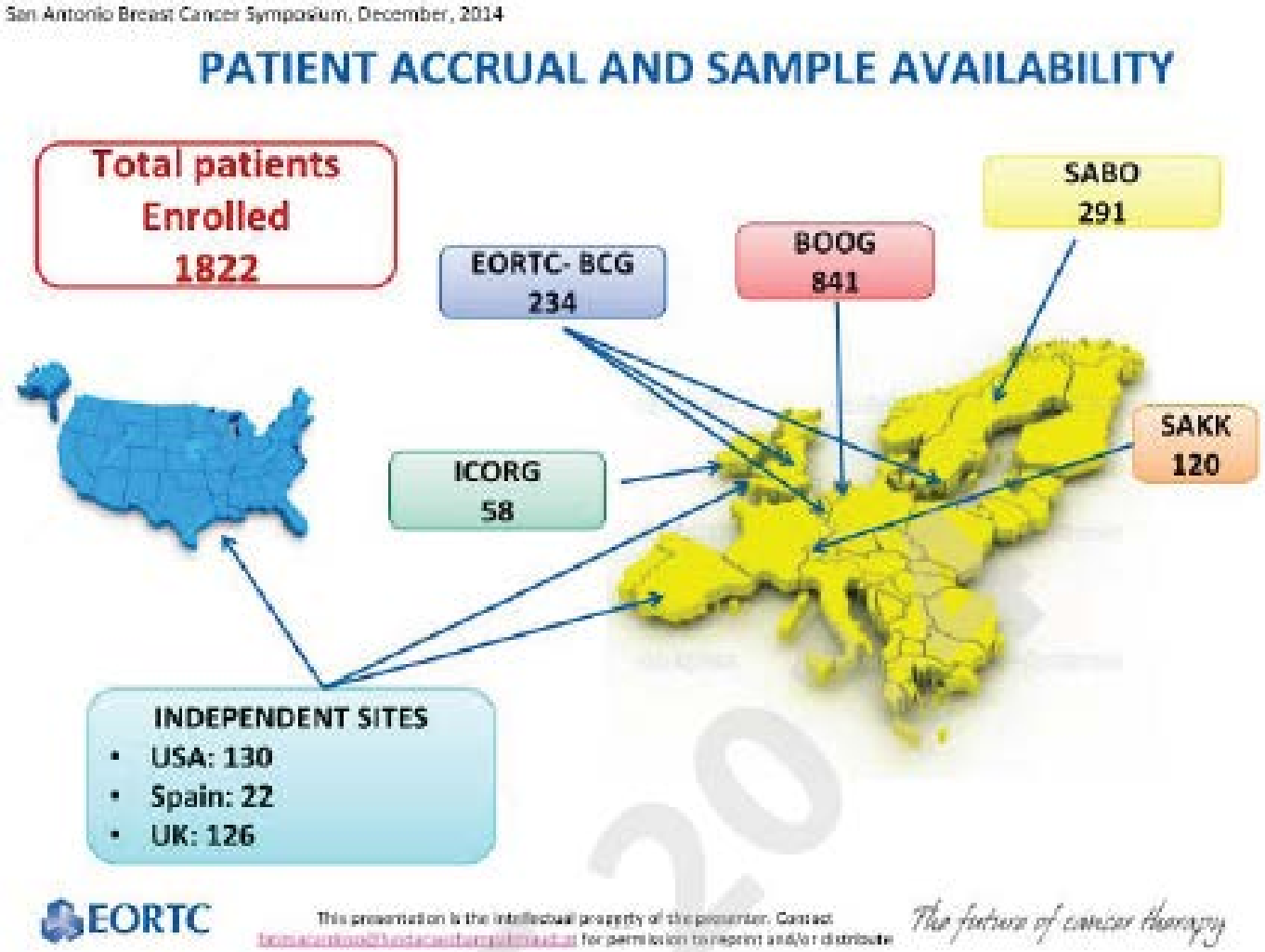
- **RETROSPECTIVE JOINT ANALYSIS** of all Male BC patients diagnosed and treated in the participating centres within the last 20 years
- Retrospective collection of tumor blocks and central analysis of tumor biology

Part 2: Prospective part

- **PROSPECTIVE INTERNATIONAL REGISTRY** of all Male BC cases in 30 months
- Simultaneous collection of biological material (tumor and blood) depending on funding (US, NL, Latin America, Sweden)
- Quality of Life sub-study

Part 3: Clinical trials in male breast cancer patients

Male Breast Cancer: Cardoso et al



Male Breast Cancer: Cardoso et al

San Antonio Breast Cancer Symposium, December, 2014

Baseline characteristics: Age and M status at diagnosis

N (%)	Period of diagnosis 1990-1995 (N=225)	1996-2000 (N=317)	2001-2005 (N=457)	2006-2010 (N=484)	Total (N=1483)
Age at diagnosis					
<= 40	5 (2.2)	4 (1.3)	8 (1.8)	7 (1.4)	**24 (1.6)**
41 - 50	18 (8.0)	31 (9.8)	28 (6.1)	40 (8.3)	**117 (7.9)**
51 - 65	63 (28.0)	97 (30.6)	144 (31.5)	148 (30.6)	**452 (30.5)**
66 - 75	77 (34.2)	93 (29.3)	134 (29.3)	147 (30.4)	**451 (30.4)**
> 75	62 (27.6)	92 (29.0)	143 (31.3)	142 (29.3)	**439 (29.6)**
M status					
M0	135 (60.0)	185 (58.4)	344 (75.3)	390 (80.6)	**1054 (71.1)**
M1	7 (3.1)	16 (5.0)	19 (4.2)	15 (3.1)	**57 (3.8)**
Mx	83 (36.9)	116 (36.6)	94 (20.6)	79 (16.3)	**372 (25.1)**

MEDIAN AGE AT DX (68.4 years) older than female BC

Male Breast Cancer: Cardoso et al

San Antonio Breast Cancer Symposium, December, 2014

Baseline characteristics: Nodal status for M0 pts

N (%)	Period of diagnosis 1990-1995 (N=135)	1996-2000 (N=184)	2001-2005 (N= 341)	2006-2010 (N=386)	Total (N=1054)
Nodal Status					
N0	75 (55.6)	99 (53.5)	184 (53.5)	234 (60.0)	592 (56.2)
N1	40 (29.6)	49 (26.5)	112 (32.6)	120 (30.8)	321 (30.5)
N2	7 (5.2)	9 (4.9)	20 (5.8)	17 (4.4)	53 (5.0)
N3	2 (1.5)	7 (3.8)	8 (2.3)	13 (3.3)	30 (2.8)
Nx	11 (8.1)	21 (11.4)	20 (5.8)	6 (1.5)	58 (5.5)

Higher % of N+ than in female BC

Male Breast Cancer: Cardoso et al

San Antonio Breast Cancer Symposium, December, 2014

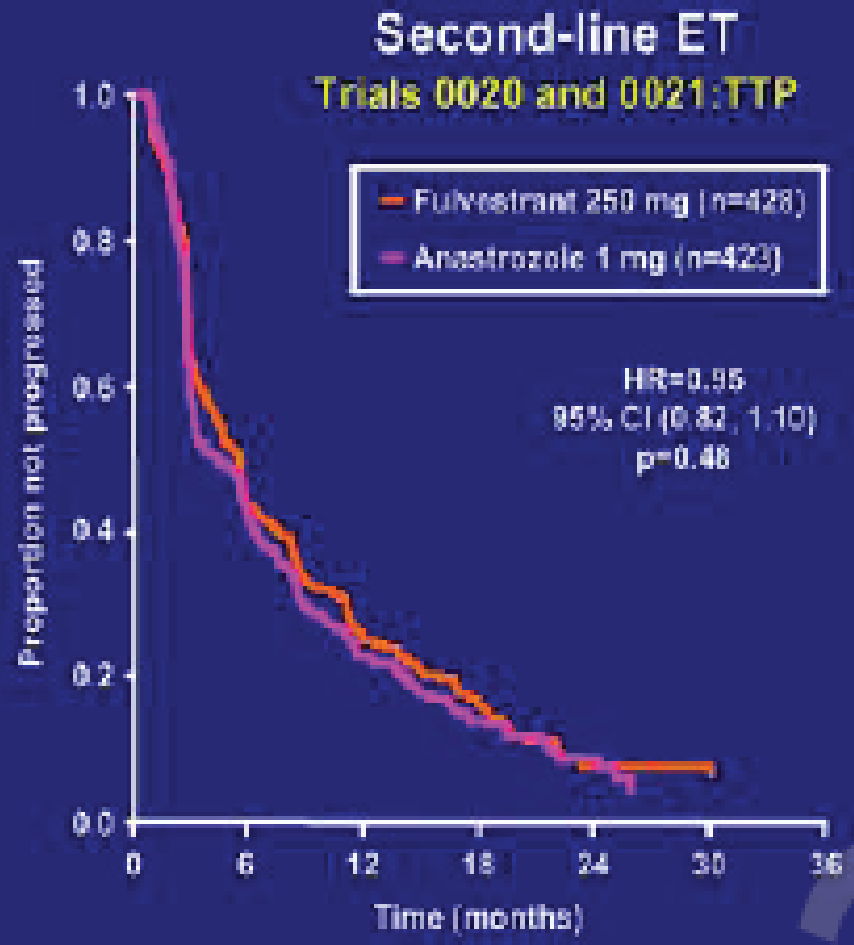
CONCLUSIONS (1)

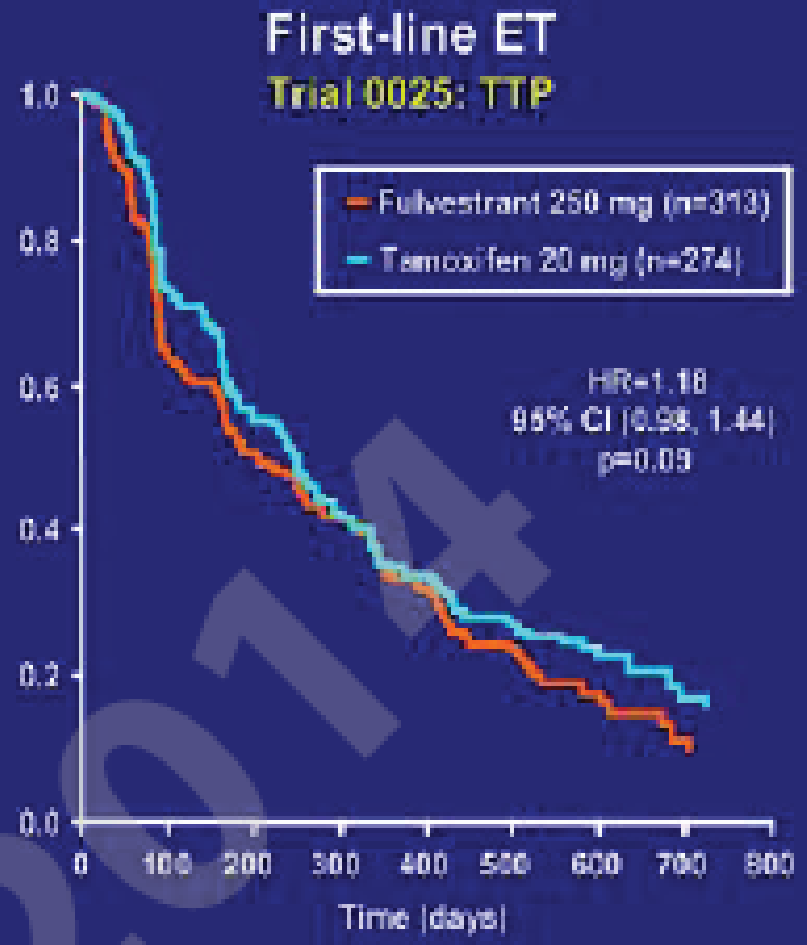
- 56% of patients had pT1 tumors but only 4% had BCS.
- Adjuvant radiotherapy mostly correctly provided but still 36% of N1 and 15% of N2 pts did not receive it.
- 30% of pts received adjuvant CT, mostly anthracyclines or anthracylines/taxanes-based.
- ER was highly + in >90% but adjuvant ET given in only 77% pts
- Usually tamoxifen was chosen but in over 5% of pts an AI or a sequence of AI-tamoxifen was given.
- Most common histological type was invasive ductal carcinomas of grade 2.
- Male BC is usually ER+, PR+ & AR+ and of luminal A- like subtype (9% HER2 positive & < 1% TNBC).

Fulvestrant 500 mg versus anastrozole as first-line treatment for advanced breast cancer: Overall Survival from the Phase II "FIRST" study

John F. R. Robertson, Antonio Llombart-Cussac, David Feltl, John Dewar, Marek Jasiówka, Nicola Hewson, Yuri Rukazenkov, Matthew J. Ellis

Background to FIRST: fulvestrant 250 mg studies





CI, confidence interval; ET, endocrine therapy; FIRST, Fulvestrant First-Line Study Comparing Endocrine Treatments; HR, hazard ratio; TTP, time to progression

Robertson et al. Cancer 2003
Howell et al. J Clin Oncol 2004

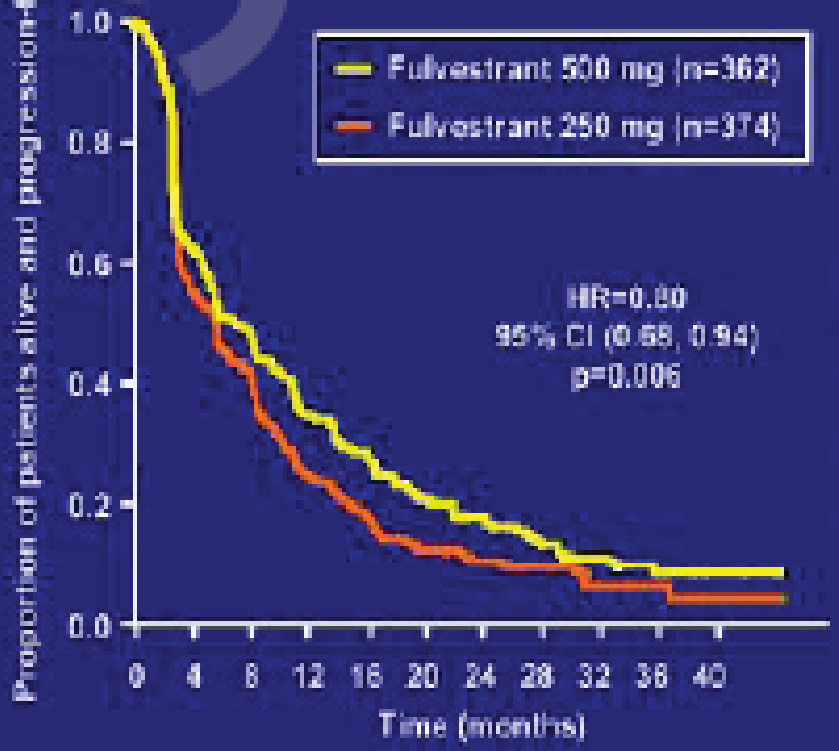
CONFIRM: fulvestrant 500 mg vs 250 mg

Second-line ET

(post-AI 42.5%; post-AO 57.5%)

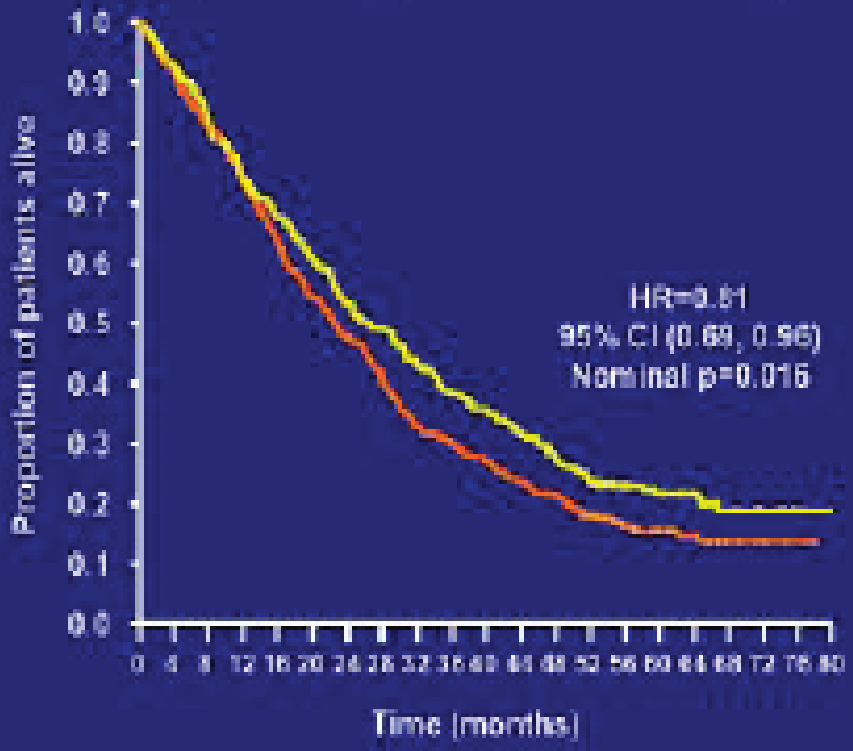
PFS

(Primary analysis)



OS

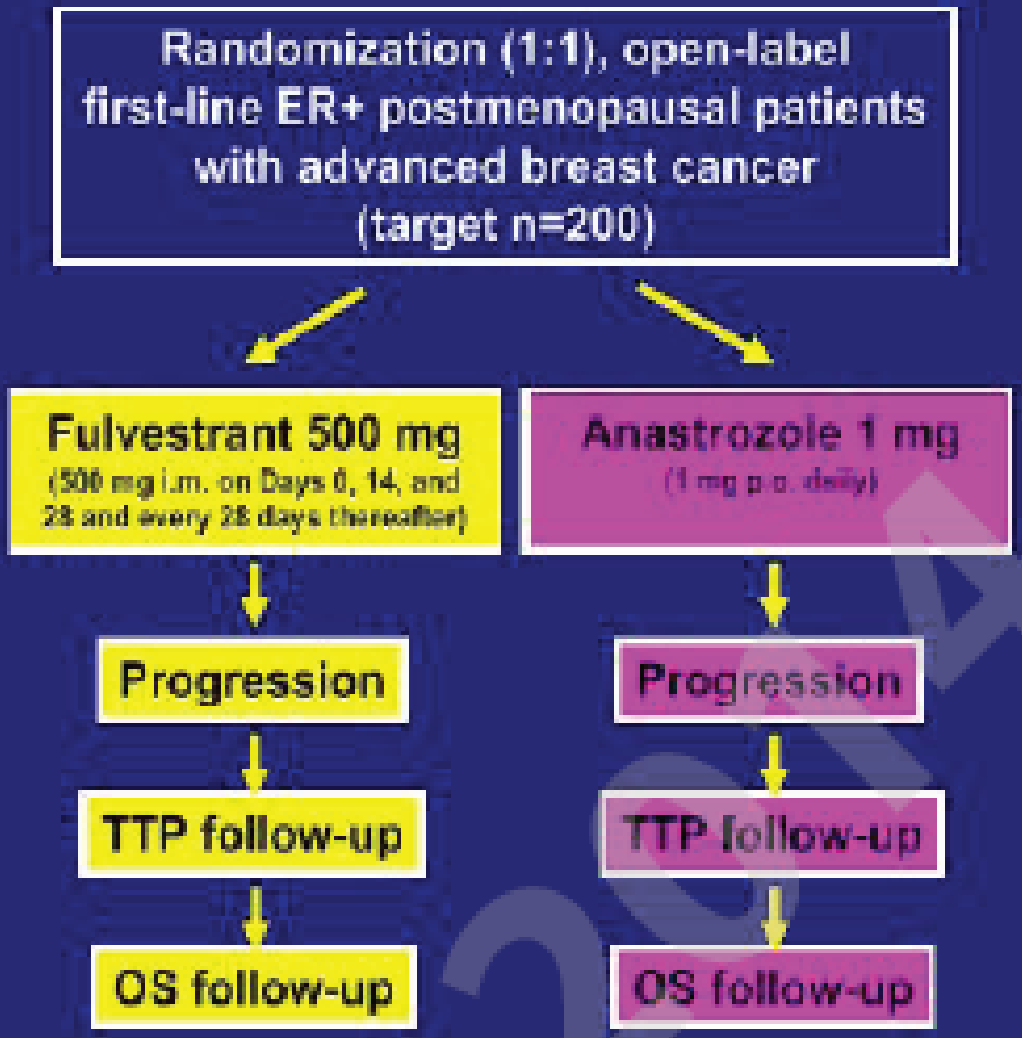
(Final analysis at 75% maturity)



CONFIRM, Comparison of Faslodex in Recurrent or Metastatic Breast Cancer; **PFS**, progression-free survival; **OS**, overall survival; **post-AI/AO**, received aromatase inhibitor/antiestrogen as last endocrine therapy

Di Leo et al. J Clin Oncol 2010
Di Leo et al. J Natl Cancer Inst 2014

FIRST: study design



Robertson et al. J Clin Oncol 2006
Robertson et al. Breast Cancer Res Treat 2012

OS, overall survival

Baseline characteristics

	Number (%) of patients	
	Fulvestrant 500 mg n=102	Anastrozole 1 mg n=103
Median age	66 years	68 years
Disease stage		
Locally advanced only	19 (18.6)	18 (17.5)
Metastatic	83 (81.4)	85 (82.5)
Measurable disease	89 (87.3)	93 (90.3)
Prior endocrine treatment		
No prior endocrine treatment	73 (71.6)	80 (77.7)
Completed endocrine treatment for early disease >12 months prior to randomization	28 (27.5)[a]	23 (22.3)
Prior adjuvant chemotherapy received for early breast cancer	29 (28.4)	25 (24.3)
Previously received chemotherapy and endocrine treatment	19 (18.6)	13 (12.6)

[a]In addition, one patient in the fulvestrant group received prior adjuvant endocrine treatment within 12 months of randomization

Robertson et al. J Clin Oncol 2009

Primary endpoint: clinical benefit rate

All randomized patients (n=205)

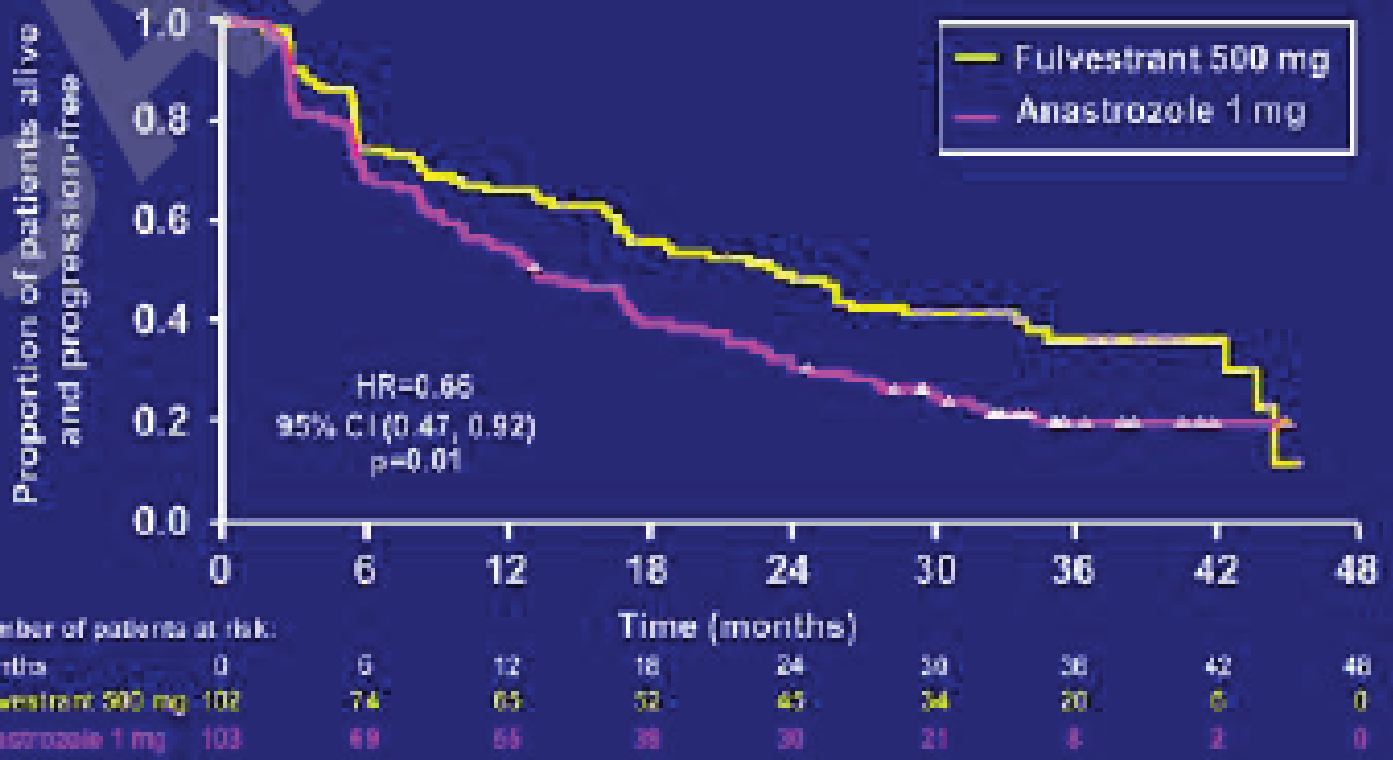
Clinical benefit rate				
Fulvestrant 500 mg % (total with CB/n)	Anastrozole 1 mg % (total with CB/n)	Odds ratio (95% CI)	p-value	Absolute difference (95% CI)
72.5% (74/102)	67.0% (69/103)	1.30 (0.72, 2.38)	0.386	5.6% (-7.8%, 15.8%)

Fulvestrant 500 mg was at least as effective as anastrozole for the primary endpoint of clinical benefit rate

CB, clinical benefit

Robertson et al. J Clin Oncol 2009

Time to progression
(TTP follow-up analysis)



	Fulvestrant 500 mg n=102	Anastrozole 1 mg n=103
Number of progressions (%)	63 (61.8)	79 (76.7)
Median (months)	23.4	13.1

After primary data cut-off, progression was determined by investigator opinion

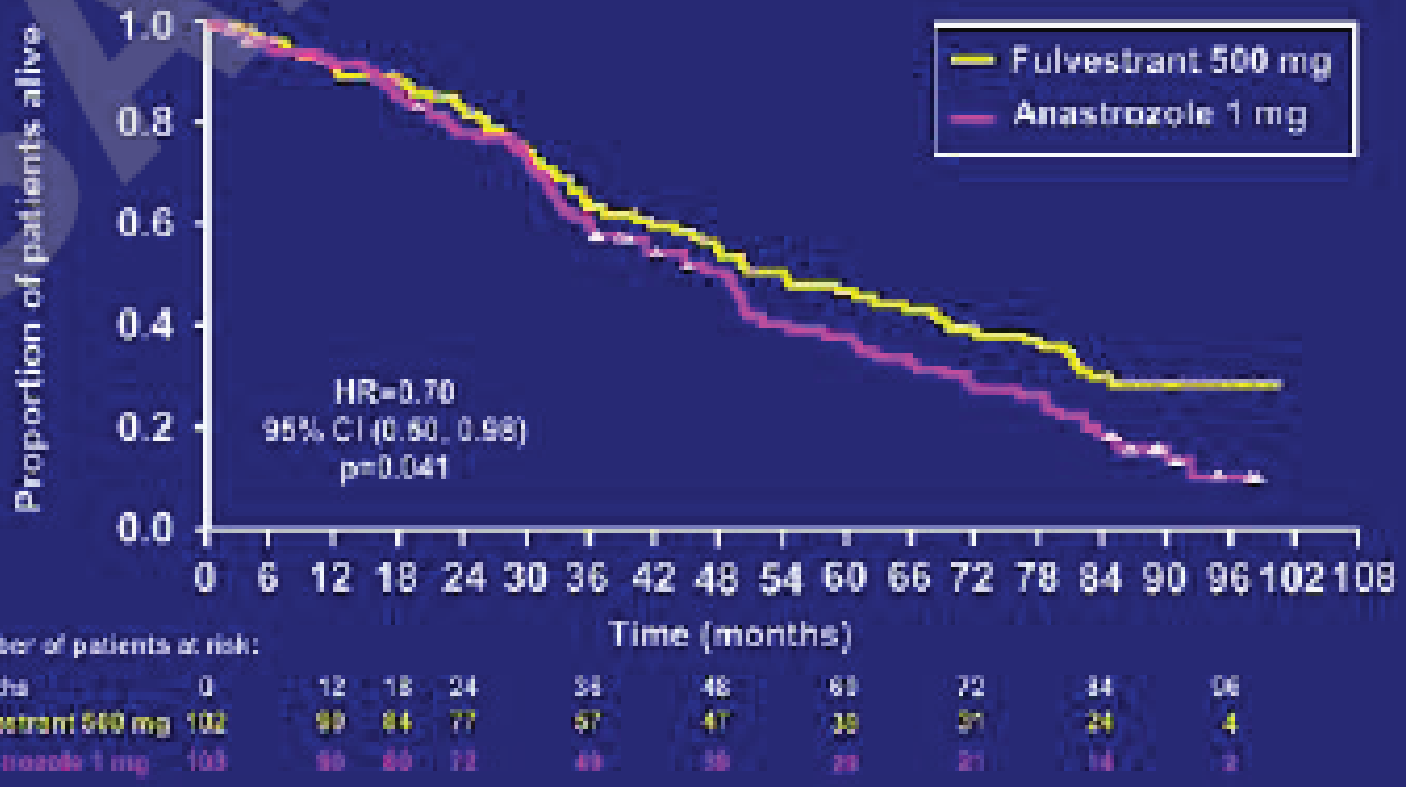
Robertson et al. Breast Cancer Res Treat 2012

Comparison of FIRST with Phase III studies of first-line endocrine monotherapy for ABC

	Bonneterre et al. *Cancer* 2001 (n=1021)		Mouridsen et al. *J Clin Oncol* 2001 (n=916)		Paridaens et al. *J Clin Oncol* 2008 (n=371)		FIRST (n=205)	
	Tam	Ana	Tam	Let	Tam	Exe	Ana	F500
Median TTP (months)	7.0	8.5	6.0	9.4	5.8	9.9	13.1	23.4

ABC, advanced breast cancer; Ana, anastrozole; Exe, exemestane; F500, fulvestrant 500 mg; Let, letrozole; Tam, tamoxifen

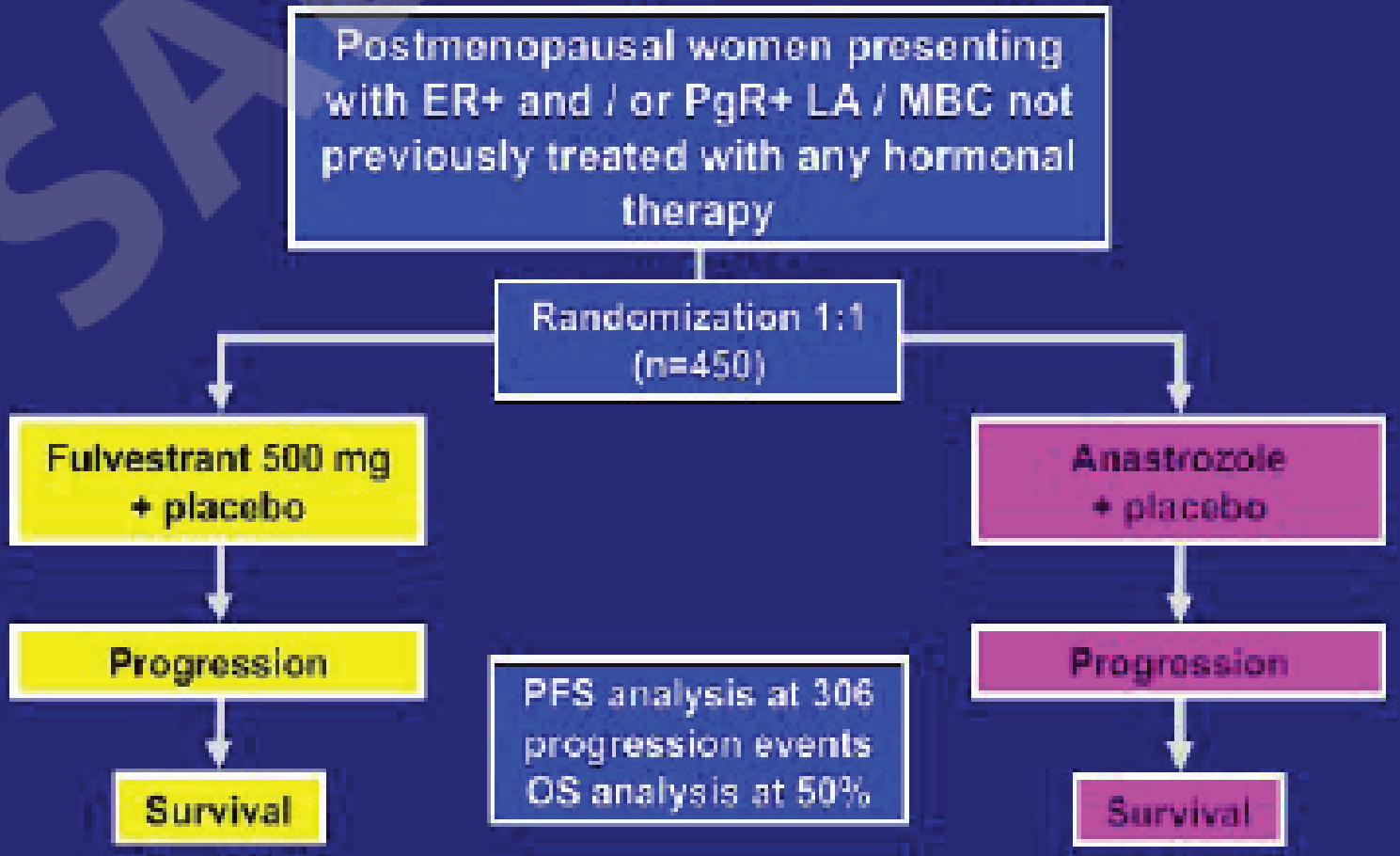
FIRST: overall survival analysis



	Fulvestrant 500 mg n=102	Anastrozole 1 mg n=103
Dead, n (%)	63 (61.8)	74 (71.8)
Median OS (months)	54.1	48.4

Patients not known to have died were right-censored at the last time they were known to be alive

Ongoing Phase III study: FALCON



FALCON, Fulvestrant and AnastrozoLe COmpared in hormonal therapy Naïve advanced breast cancer
ClinicalTrials.gov identifier: NCT01602380
LA / MBC, locally advanced / metastatic breast cancer

Randomized comparison of adjuvant tamoxifen plus ovarian function suppression versus tamoxifen in premenopausal women with hormone-receptor-positive (HR+) early breast cancer: The SOFT trial

Prudence Francis
for SOFT Investigators,
International Breast Cancer Study Group,
Breast International Group,
and North American Breast Cancer Group

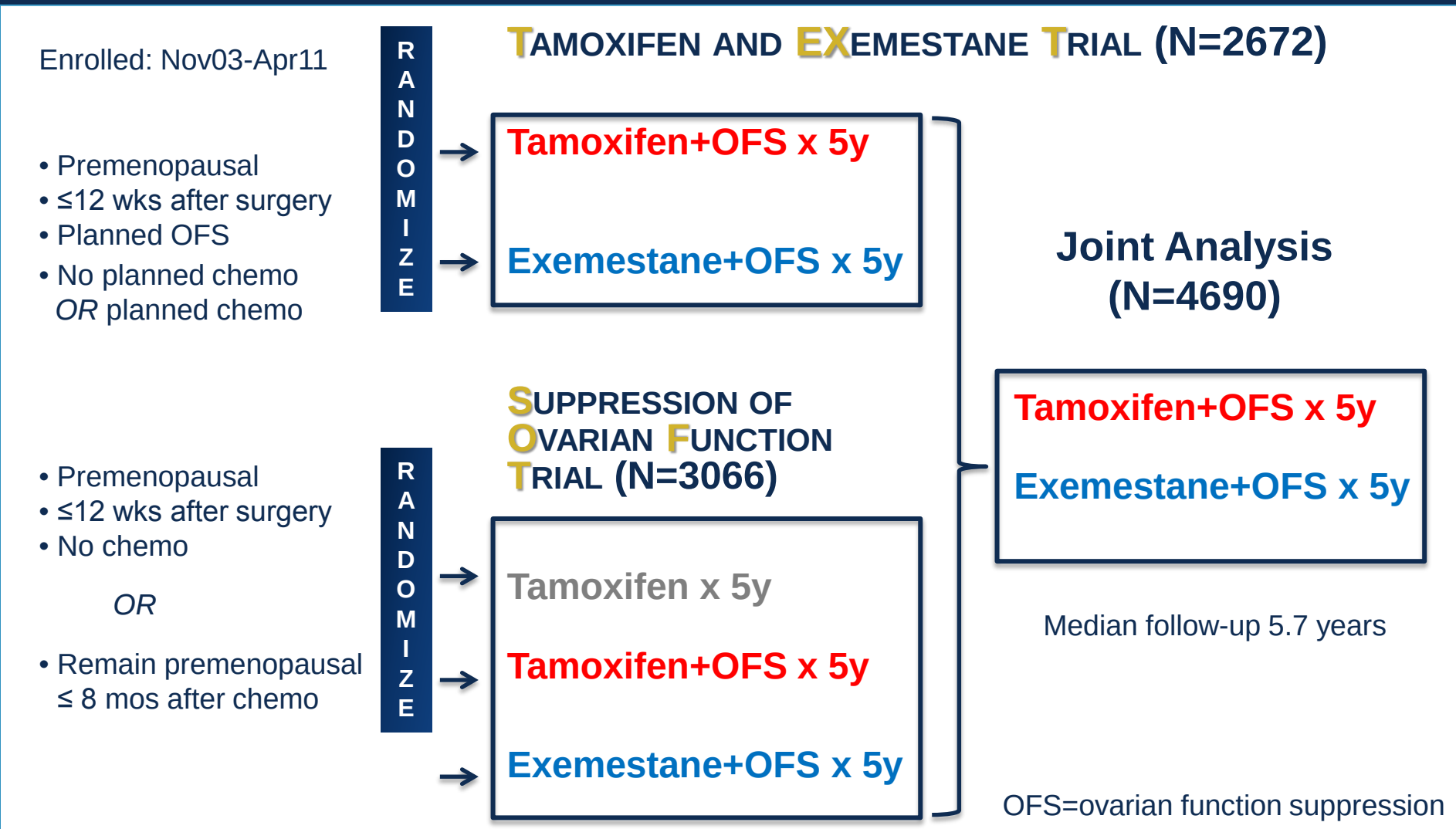
Premenopausal HR+ Early Breast Cancer

- Adjuvant tamoxifen for ≥ 5 years is recommended
- The value of ovarian function suppression or ablation (OFS) for women who receive tamoxifen (T) is uncertain
- Women who develop chemotherapy-induced ovarian suppression (amenorrhea) have a reduced risk of relapse
- Likelihood of chemotherapy-induced amenorrhea correlated with older age; less likely in women < 35 years age

Questions in Premenopausal Hormone-Receptor Positive Early Breast Cancer

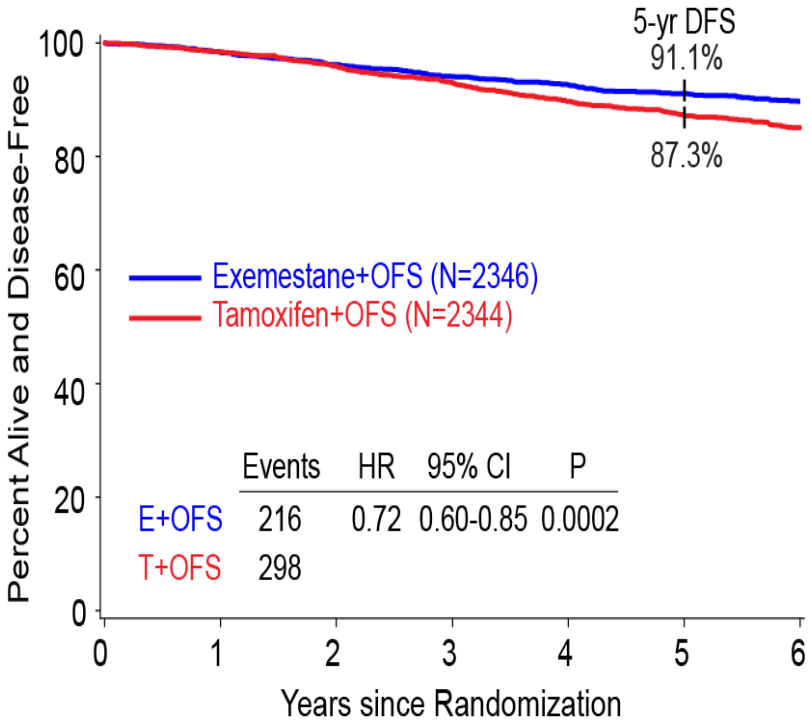
- What is the value of adding OFS to adjuvant tamoxifen in premenopausal women?
- What is role of adjuvant therapy with the aromatase inhibitor (AI) exemestane + OFS in premenopausal women ?

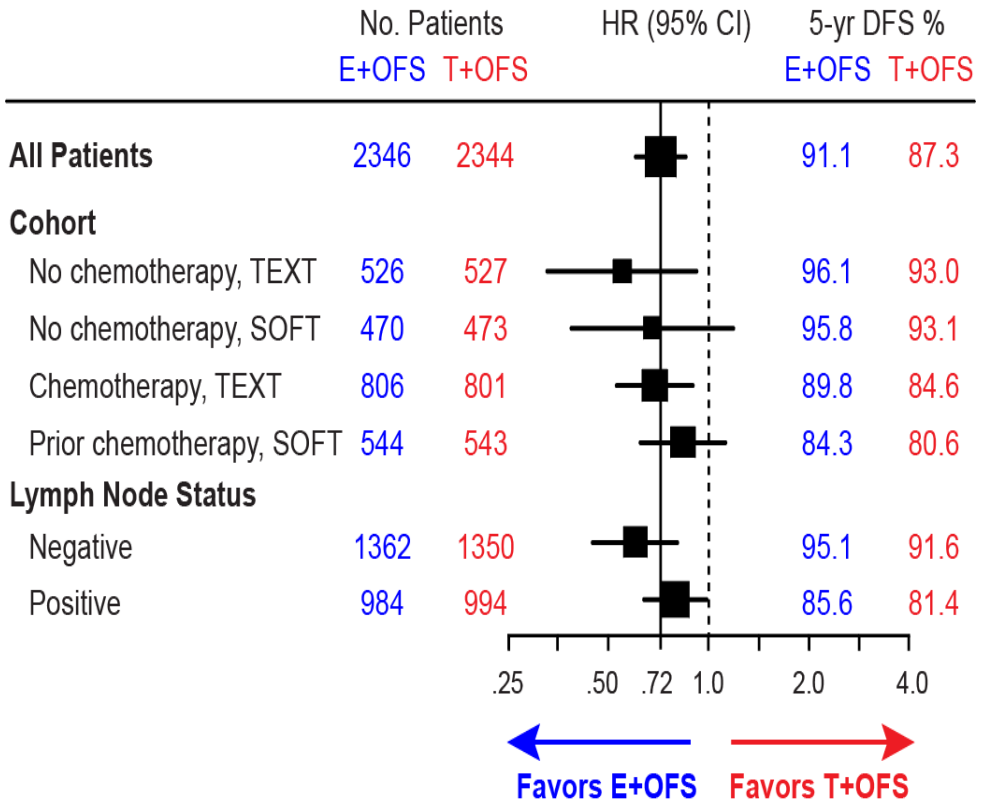
TEXT and SOFT Designs



Exemestane+OFS Improved DFS

Difference 3.8% at 5 years





5.7 years median follow-up

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)

*According to locally-determined E2 level in premenopausal range

Protocol Endpoints

Primary: Disease-free survival (DFS)

- invasive recurrence (local, regional, distant)
- invasive contralateral breast cancer
- second non-breast invasive malignancy
- death without prior cancer event

Secondary:

Breast cancer-free interval (BCFI)

- invasive recurrence or contralateral breast ca

Distant recurrence-free interval (DRFI)

Overall survival

Statistical Considerations

- ITT analysis, stratified by chemo (yes/no), nodal status (-/+)
- Original plan for three pair-wise comparisons to detect HR=0.75 with analysis after 783 DFS events (α=0.0167)
- Enrolled patients older, lower risk, better DFS than anticipated
- Protocol amendment 2011 (before efficacy data)

Statistical Considerations Post-Amendment

- Primary analysis: T+OFS vs T
- After median follow-up of at least 5 years
- Anticipated 186 DFS events, power 80% for HR=0.665 comparing T+OFS vs T (two sided α=0.05)
- Analysis according to use of prior chemotherapy (no/yes) was prospectively planned
- E+OFS vs T became secondary objective

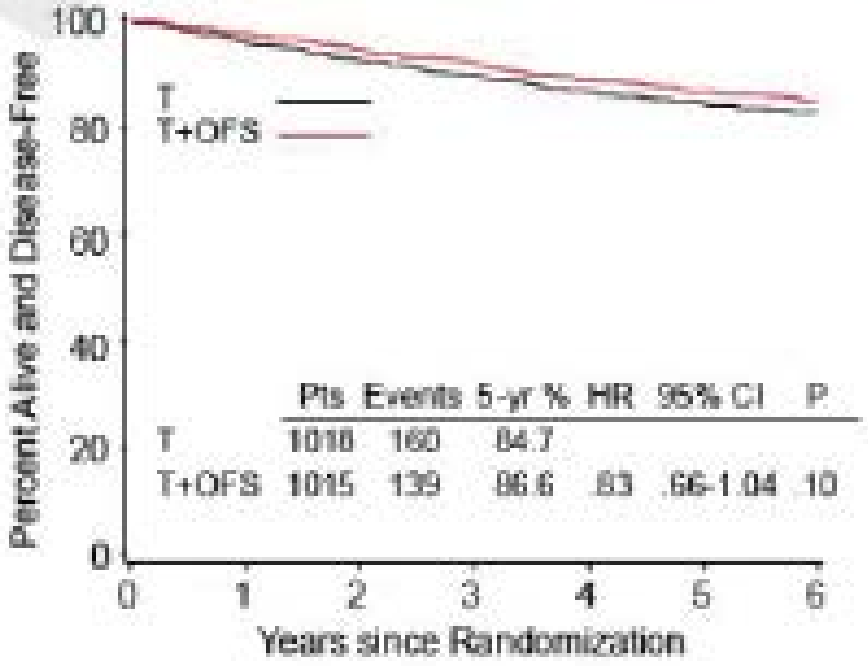
(E+OFS vs T+OFS by combined analysis with TEXT Pagani et al, NEJM 2014)

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

Primary Analysis: Disease-free Survival

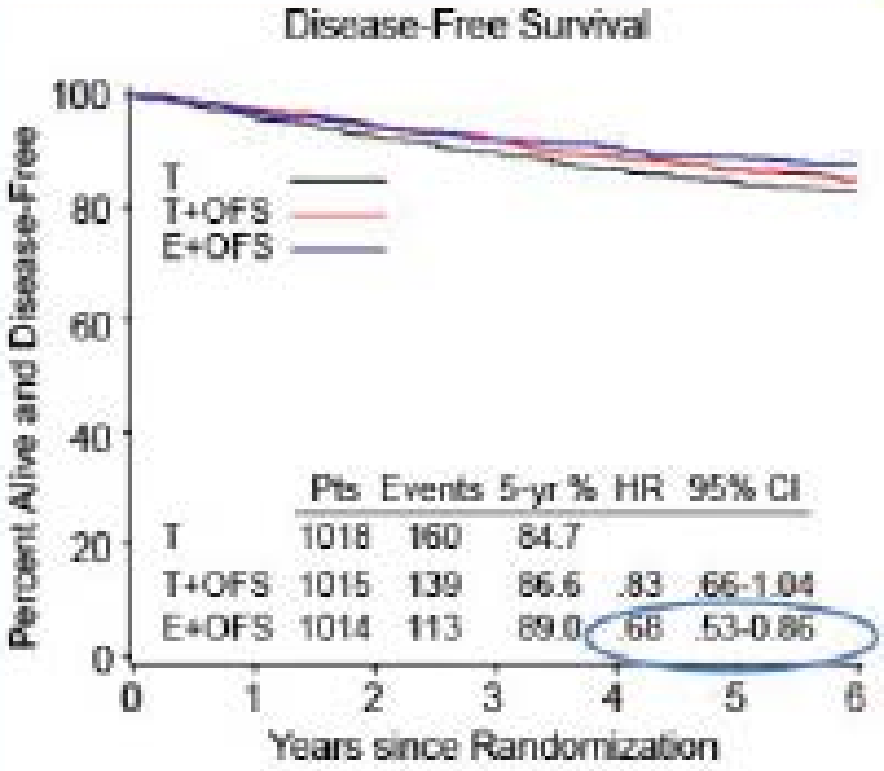
5.6 years median follow-up

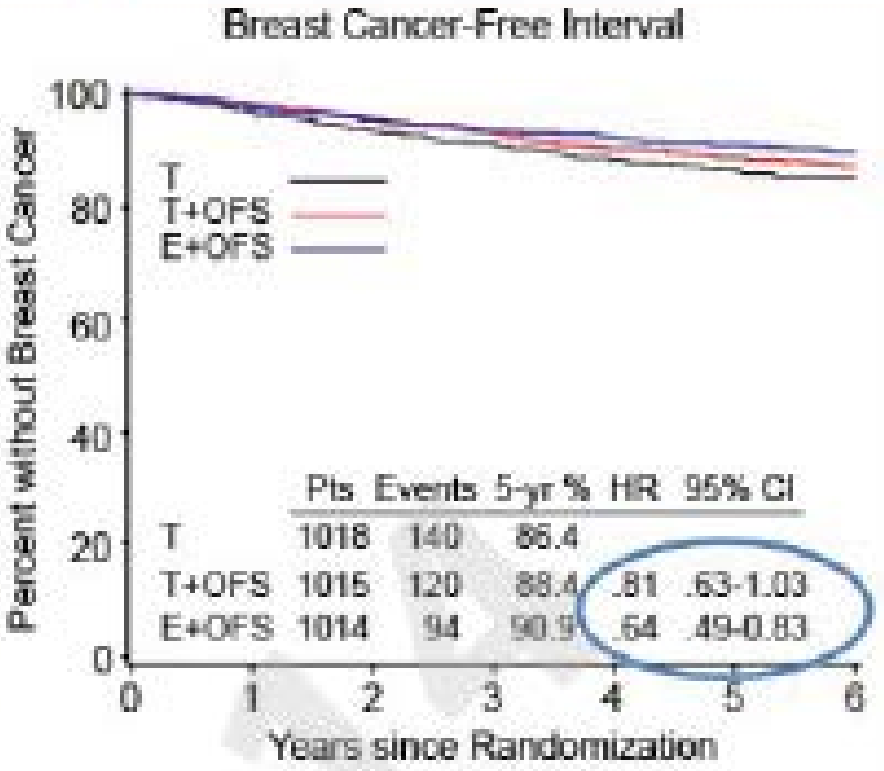


Primary analysis in overall population not significant (p=0.10)

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

Secondary Objectives

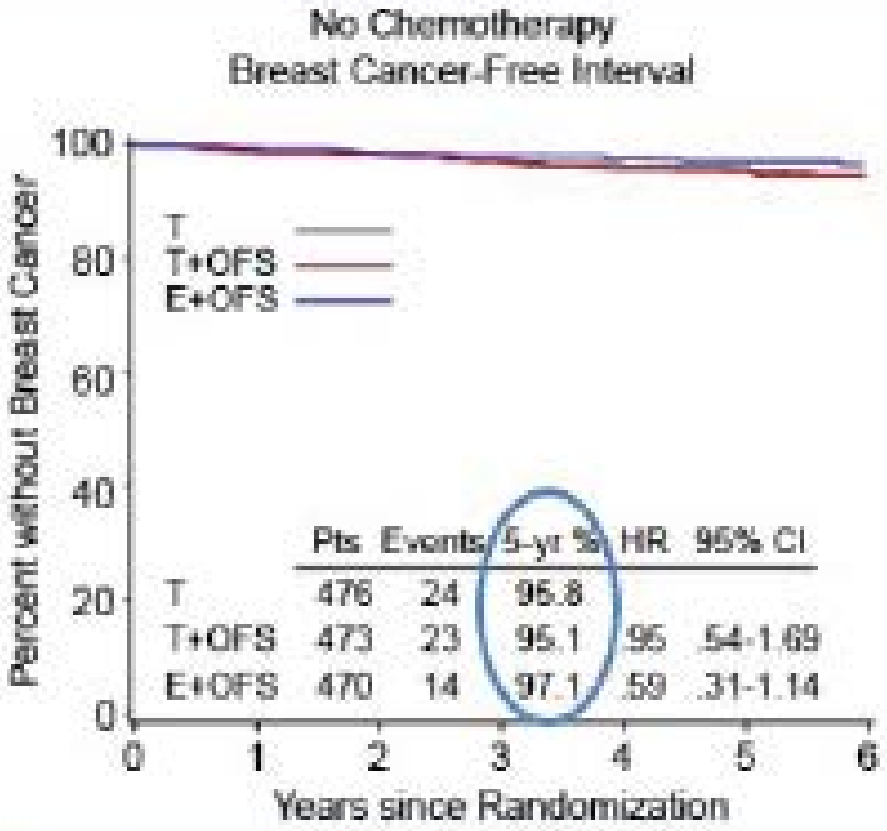


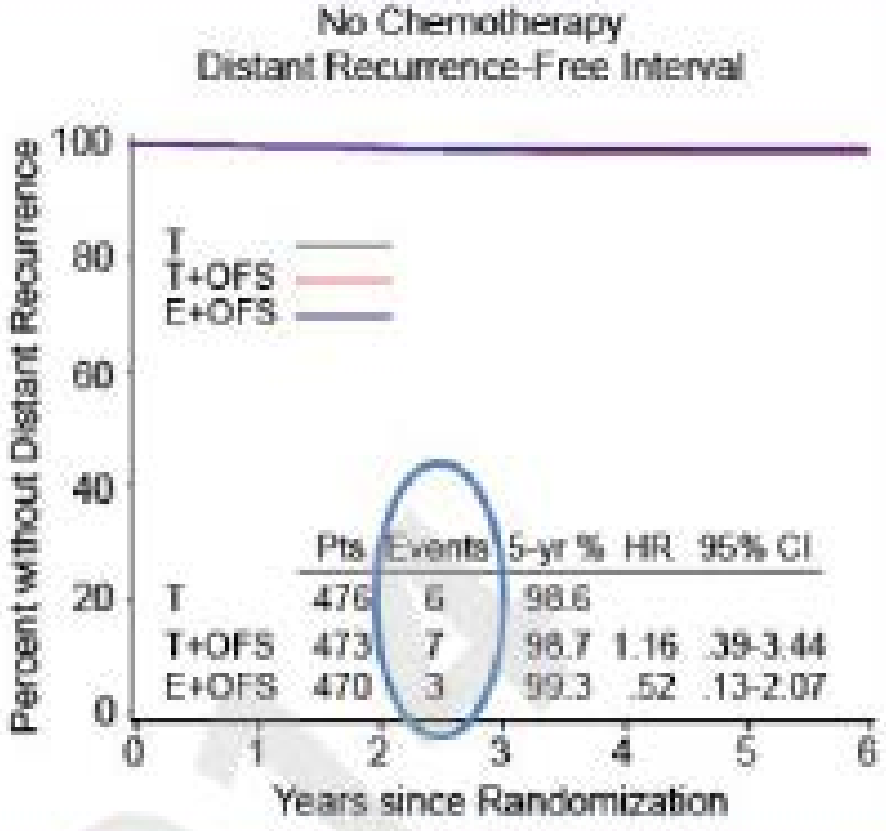


T+OFS v T: 19% relative reduction in BC recurrence, p=0.09

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

Premenopausal No Chemotherapy

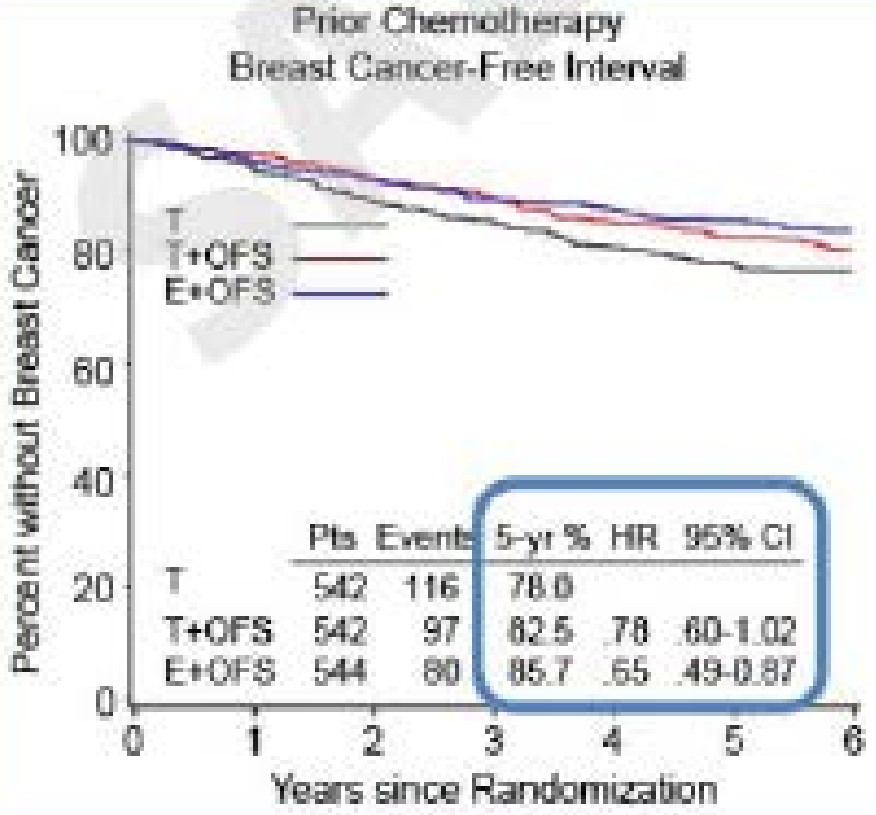


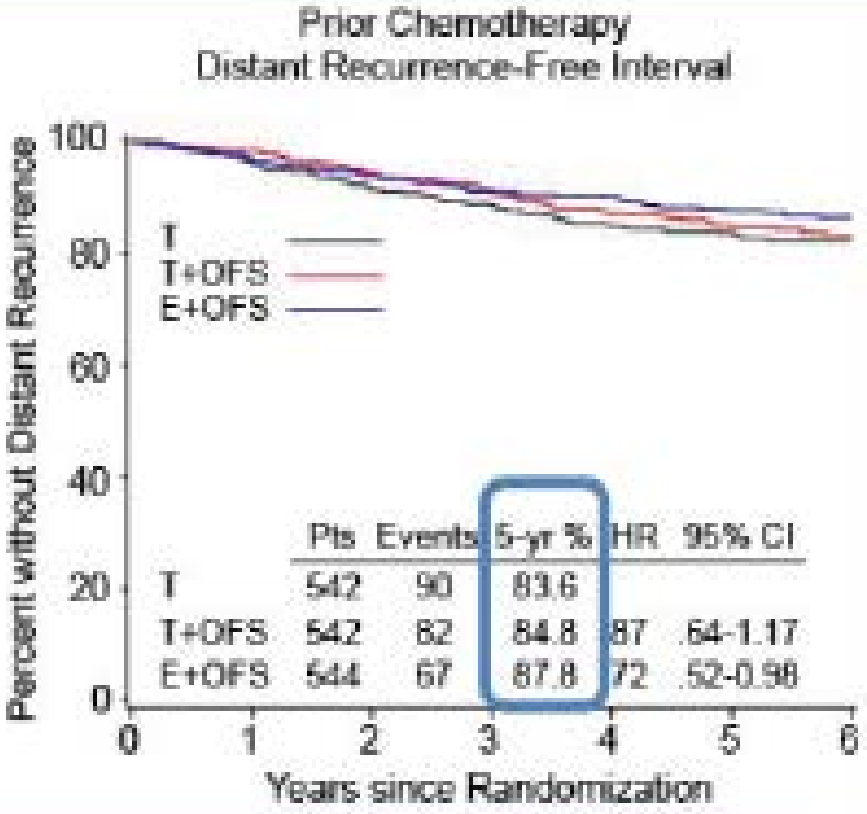


Cohort selected for low risk clinicopathologic features

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

Premenopausal after Prior Chemotherapy

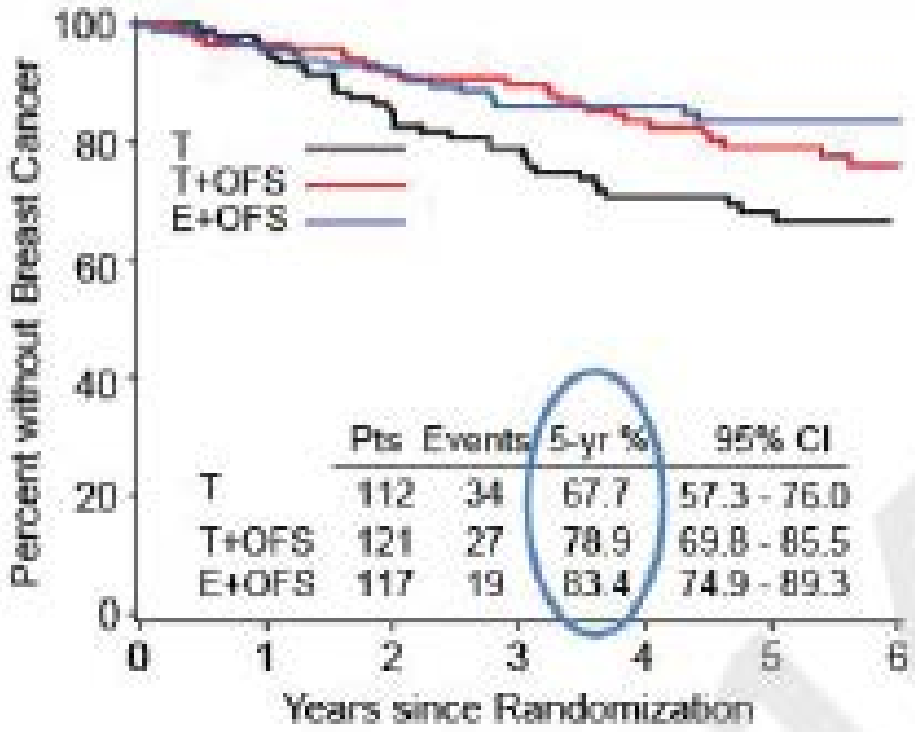




T+OFS v T: Absolute improvement in 5-yr BCFI of 4.5%

E+OFS v T: Absolute improvement in 5-yr BCFI of 7.7% and 5-yr DRFI of 4.2%

All women < 35 years of age



350 patients (11.5%) under age 35

94% received chemotherapy in this age group

Treatment Continuation

- 26% pts continuing some or all protocol-assigned treatment
- Overall 19% ceased tamoxifen early (+/- other Rx started)
- OFS entirely by GnRH agonist triptorelin for 81% patients
- Adherence with OFS
  - 91% at 1 year
  - 85% at 2 years
  - 78% at 4 years

Selected Adverse Events

	T+OFS (N=1005)		T (N=1006)	
CTCAE v3.0	**Grade 1-4**	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Hot flushes/flashes	93%	13%	80%	8%
Sweating	62%	--	48%	--
Libido decrease	47%	--	42%	--
Vaginal dryness	50%	--	42%	--
Depression	52%	4%	47%	4%
Insomnia	57%	5%	46%	3%
Musculoskeletal symptoms	75%	5%	69%	6%
Osteoporosis (% T< -2.5)	20% (6%)	0.3%	12% (3%)	0.1%
Hypertension	23%	7%	17%	5%
Glucose intolerance (diabetes)*	3%	1%	2%	0.3%
Hyperglycaemia*	5%	1%	2%	0.1%
Any Gr 3- 4 targeted AE	--	31%	--	24%

*Added during trial conduct, may be under-reported

SOFT: Conclusions

- The overall premenopausal population did not benefit from the addition of OFS -- some do very well with tamoxifen alone.
- For women at sufficient risk of recurrence to warrant adjuvant chemotherapy and who retained premenopausal estradiol, addition of OFS to tamoxifen reduced recurrence.
- OFS enables treatment with an aromatase inhibitor which further reduced recurrence in the higher-risk cohort.
- Addition of OFS increases menopausal symptoms, depression, hypertension, diabetes and osteoporosis.

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

Patient-reported endocrine symptoms, sexual functioning and quality of life (QoL) in the IBCSG SOFT trial

Karin Ribi
for SOFT Investigators,
International Breast Cancer Study Group,
Breast International Group,
and North American Breast Cancer Group

SOFT QoL Assessment

3047 Patients Randomized in ITT, Dec 2003 - Jan 2011

Primary Analysis (n=2033)

Two Patient Cohorts

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)

Median follow-up 67 months

OFS=ovarian function suppression

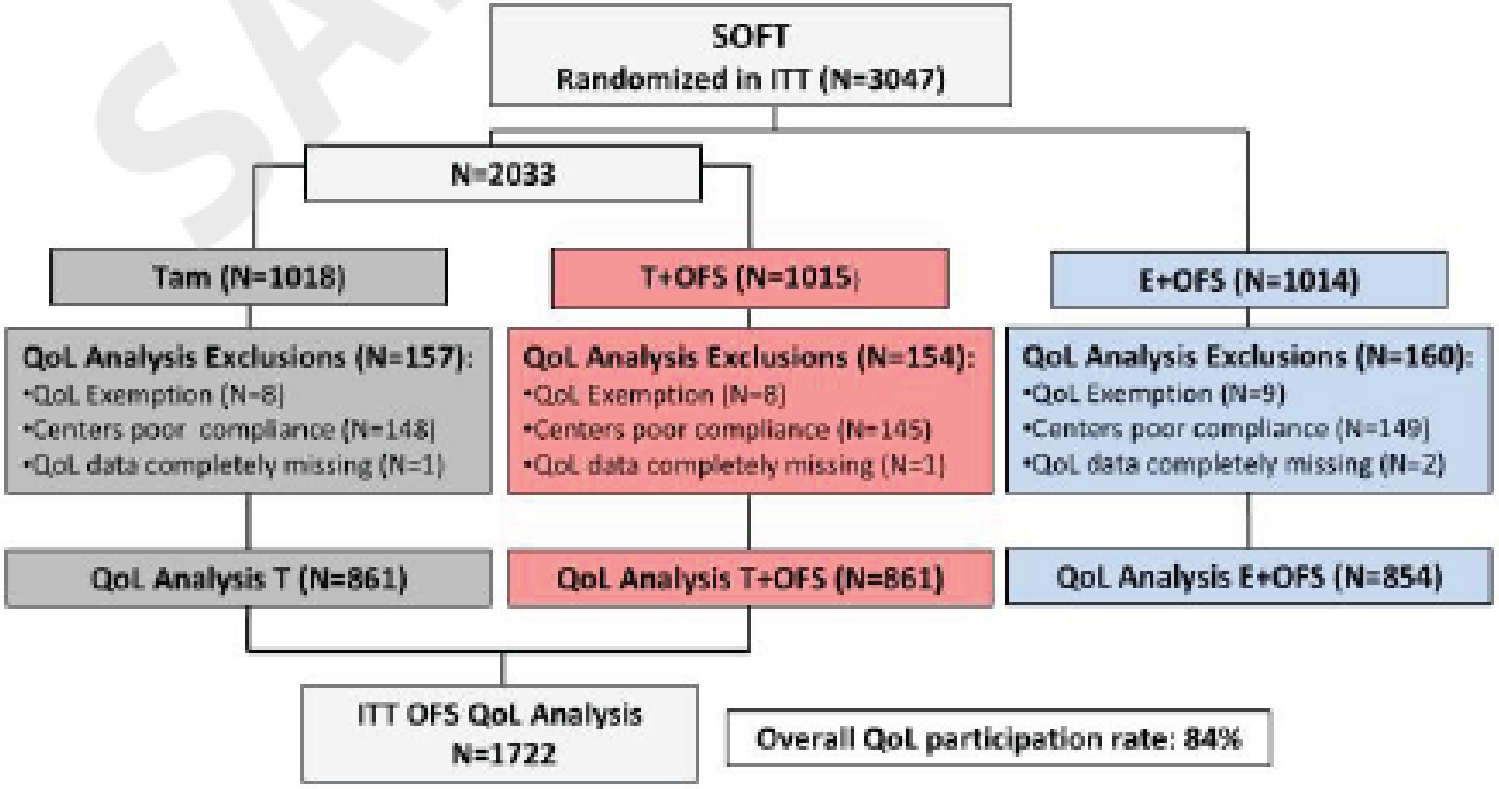
Treatment month

0 6 12 18 24 36 48 60

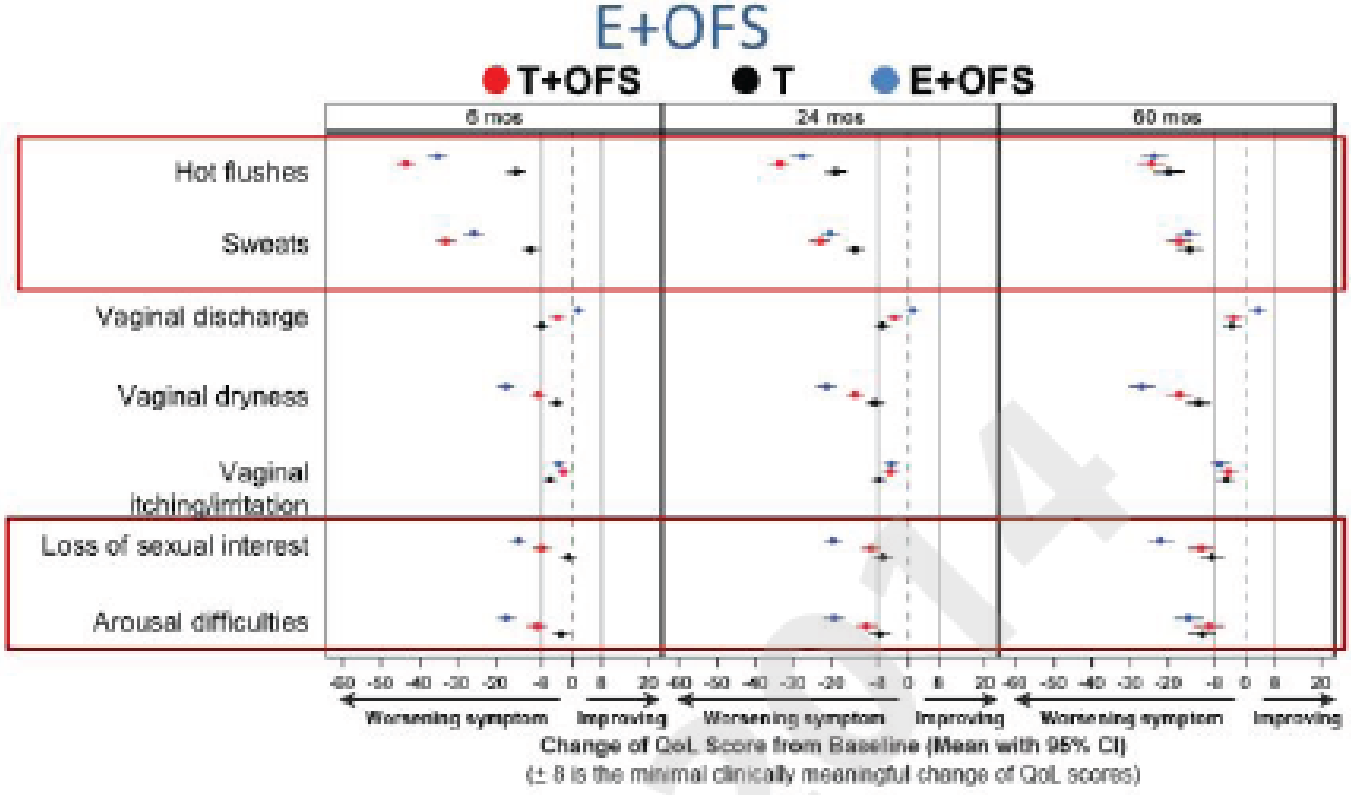
QoL assessment time points

*According to locally-determined E_2 level in premenopausal range

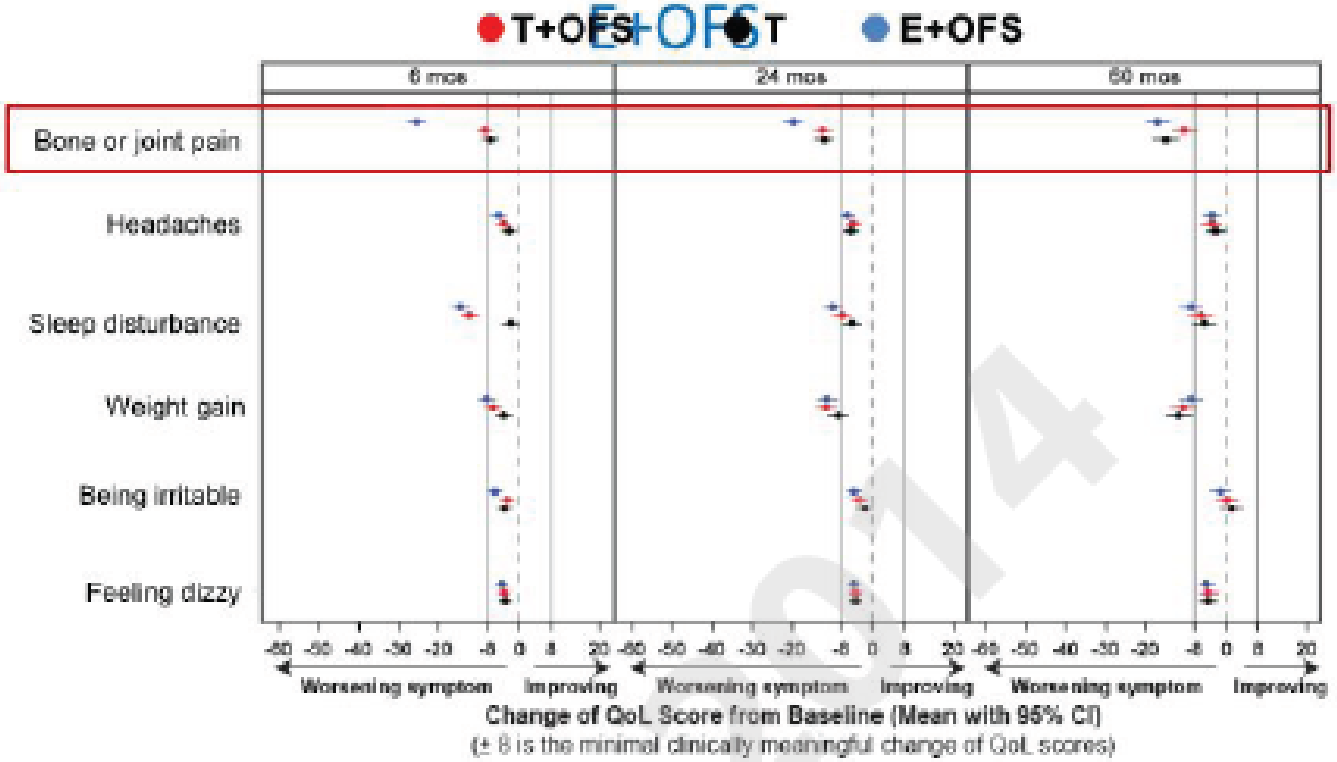
Patient Population



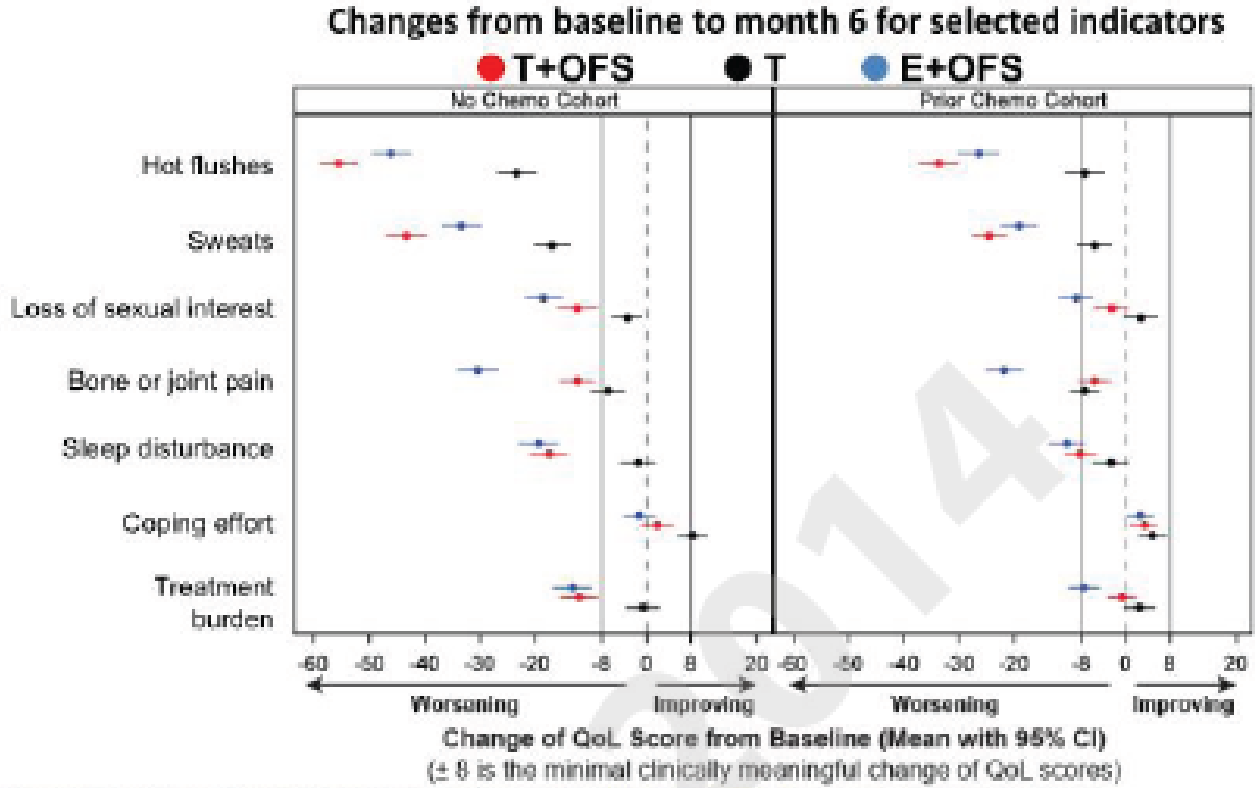
Treatment Effect: Symptoms



Treatment Effect: Symptoms (cont.)



Treatment Effect: by Cohort



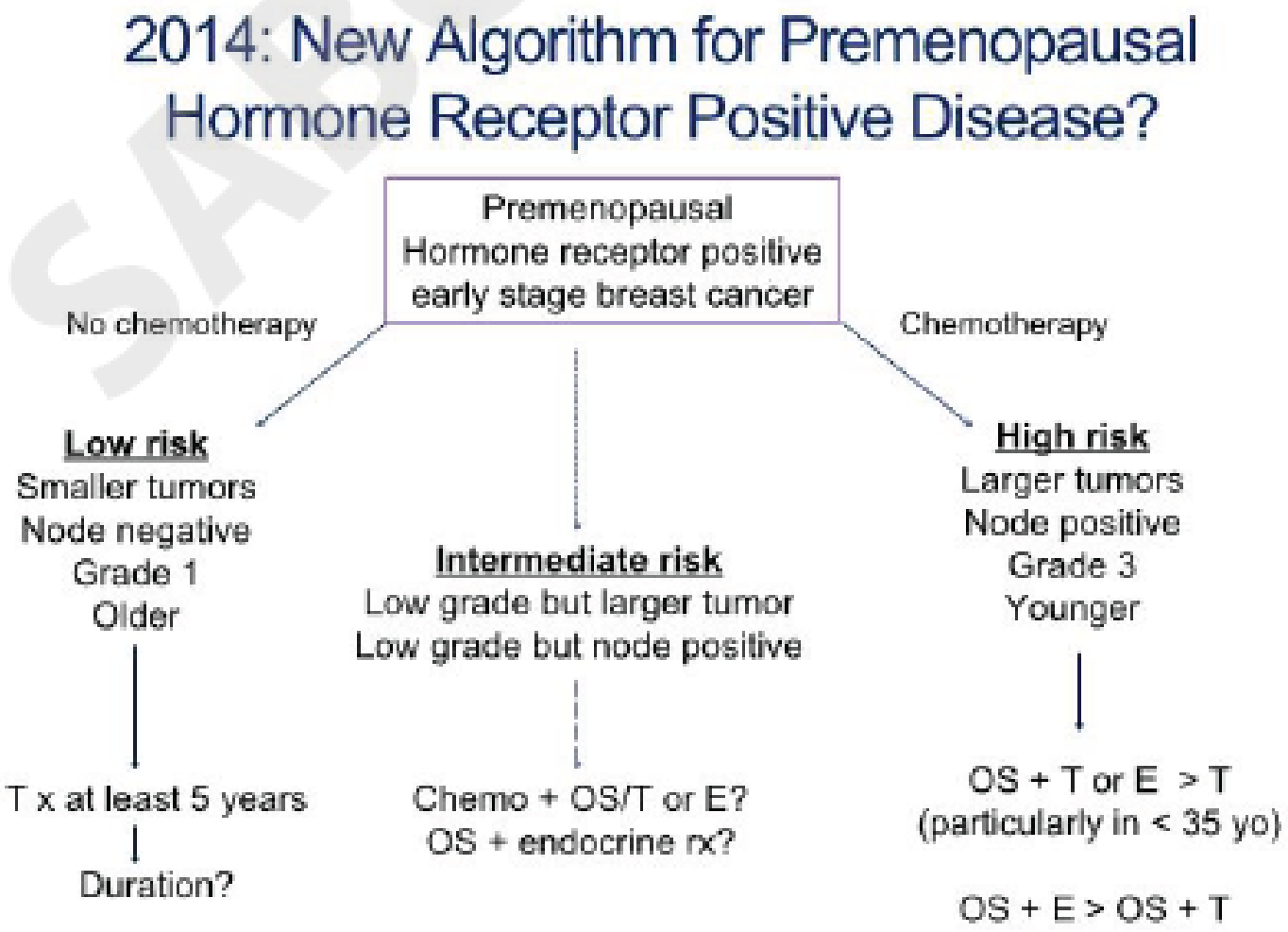
Conclusions

- Overall, patients receiving T+OFS experienced worse endocrine symptoms and sexual functioning than those receiving T alone.
- Most differences in symptoms between treatments were seen during the first 2 years of treatment, no longer apparent at 5 years.
- Global QoL did not differ between T+OFS and T alone.
- E+OFS vs. T+OFS showed differential effects on endocrine symptoms burden, but not on global QoL indicators.

Conclusions

- Less improvement in coping and greater treatment burden were seen with T+OFS vs. T in patients with no prior chemotherapy.
- For patients who received prior chemotherapy, differences in endocrine symptoms between T+OFS and T were less pronounced.
- The cohort of women receiving prior chemotherapy benefited most from OFS in terms of disease control.

Clinical Impact of SOFT/TEXT



Rugo SABCS 2014