Ruolo della soppressione ovarica in aggiunta al tamoxifene in premenopausa

Quale ruolo nella pratica clinica?

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What are the Questions?

- For premenopausal women with hormone responsive early stage breast cancer, how much is enough?
  - Should all/any women have their ovaries suppressed?
    - SOFT
  - If OFS, tamoxifen or an AI?
    - SOFT and TEXT combined analysis
  - In whom can we avoid chemotherapy?
    - No randomized trial
    - Inferential data from SOFT/TEXT and ABCSG12
  - Is the bang worth the buck?
    - Toxicity in SOFT

  - ***How long should hormone therapy be given***
  - ***What is the role of adjuvant bisphosphonates?***

Breast Cancer in Premenopausal Women

- Most frequent cancer diagnosis in women worldwide
- Most common cause of cancer death
- Age at diagnosis in the US (estimates for 2013)
  - 21% in women < age 50 (~49,000)
  - 4.7% in women < age 40 (~11,000)
  - Hormone receptor positive still the most common subtype
  - Incidence, particularly in younger women, has increased in the last decade

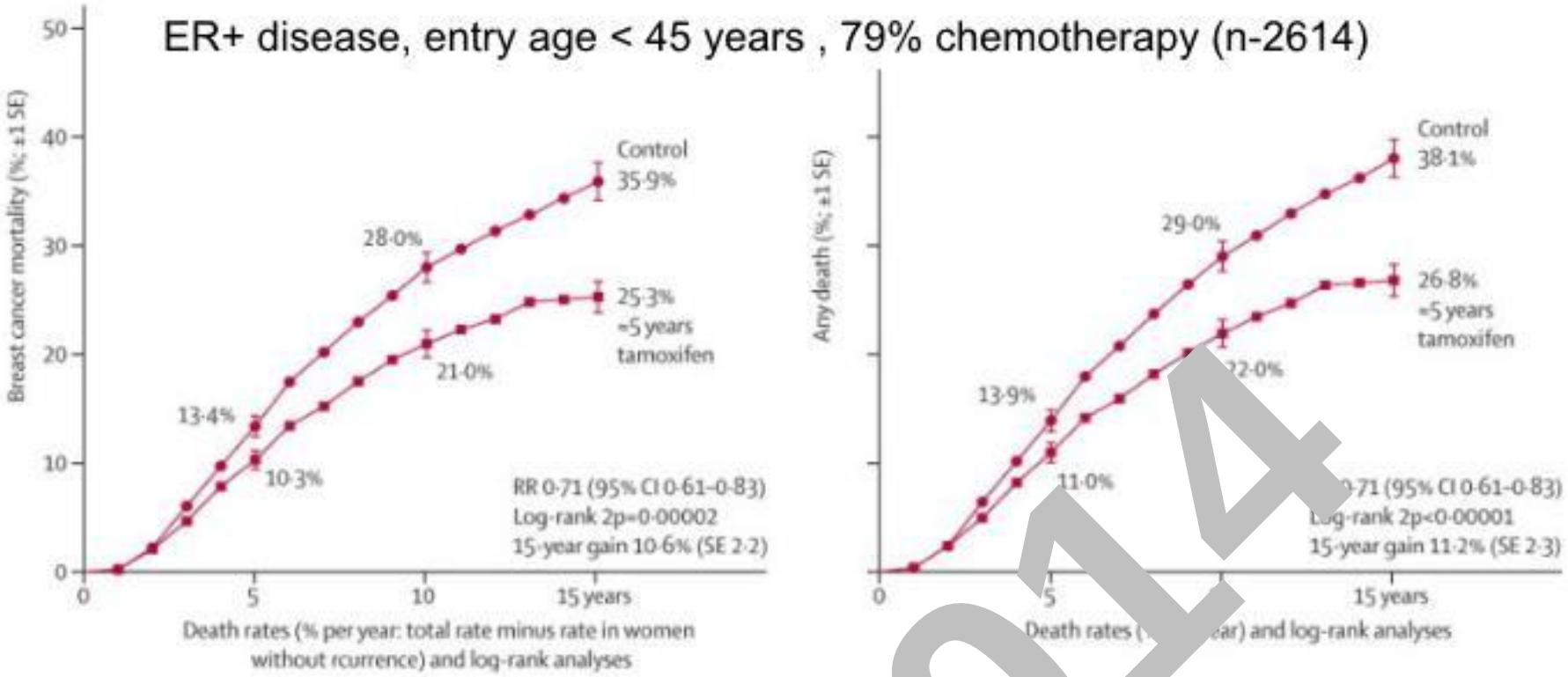
DEFINITION OF MENOPAUSE

Clinical trials in breast cancer have utilized a variety of definitions of menopause. Menopause is generally the permanent cessation of menses, and as the term is utilized in breast cancer management includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following:

- **Prior bilateral oophorectomy**
- **Age ≥60 y**
- **Age <60 y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range**
- **If taking tamoxifen or toremifene, and age <60 y, then FSH and plasma estradiol level in postmenopausal ranges**

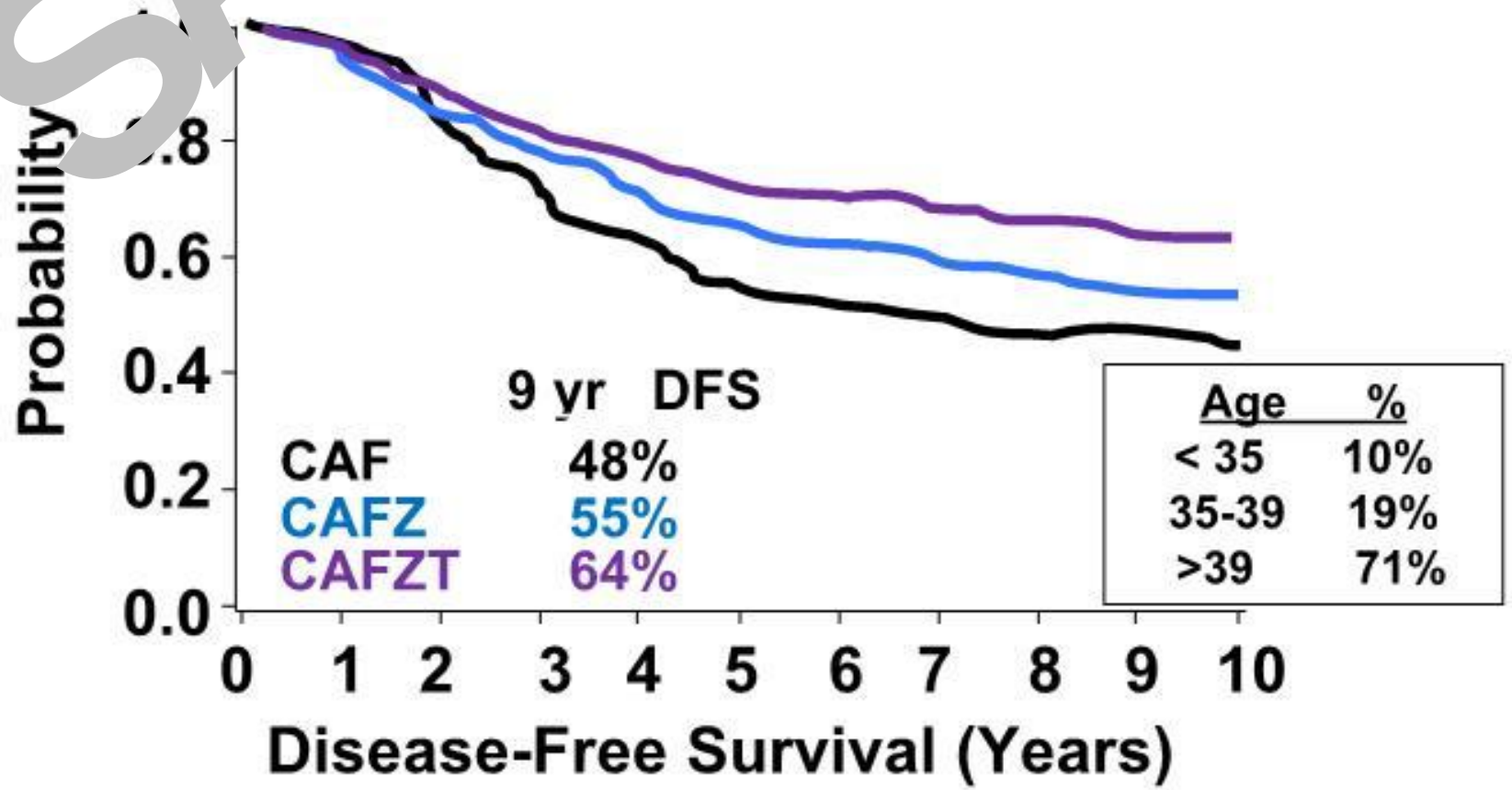
It is not possible to assign menopausal status to women who are receiving an LHRH agonist or antagonist. In women premenopausal at the beginning of adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status as ovarian function may still be intact or resume despite anovulation/amenorrhea after chemotherapy. For these women with therapy-induced amenorrhea, oophorectomy or serial measurement of FSH and/or estradiol are needed to ensure postmenopausal status if the use of aromatase inhibitors is considered as a component of endocrine therapy.

Outcome at 15 years with Tamoxifen



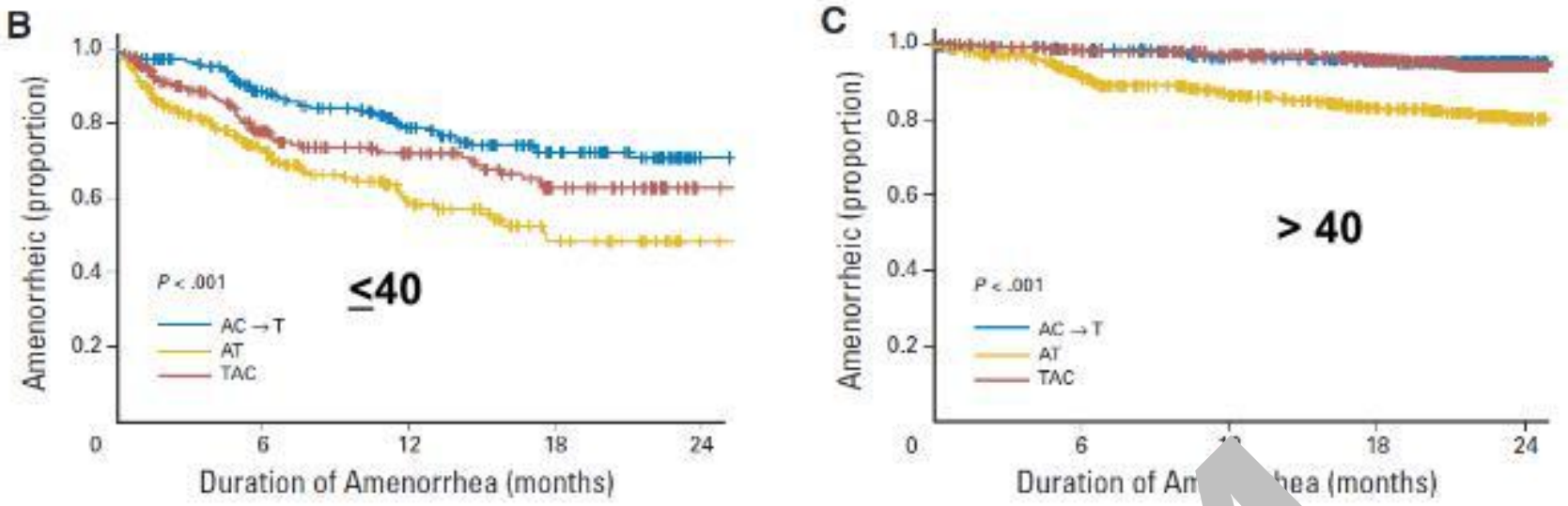
EBCTCG, Lancet 2011

Disease-Free Survival for Women Under 40 Years: E5188 INT 0101 (n=436/1500, all N+)



Davidson et al. J Clin Oncol, 2005

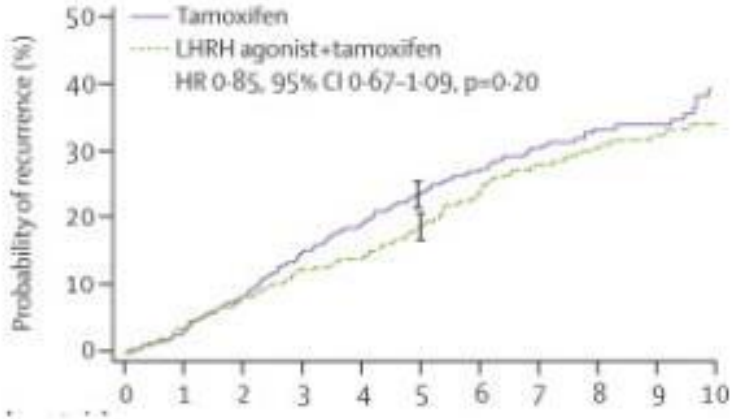
NSABP B30: Impact of Type of Chemotherapy and Age on Amenorrhea and Outcome



- NSABP B30 substudy (Swain et al, NEJM 2010)
  - 1885 women, N+, receiving chemotherapy
    - In women with ER+ disease:
      - Amenorrhea for ≥ 6 months predicted improved OS (HR 0.52, P=0.002) and DFS (0.51, P<0.001)

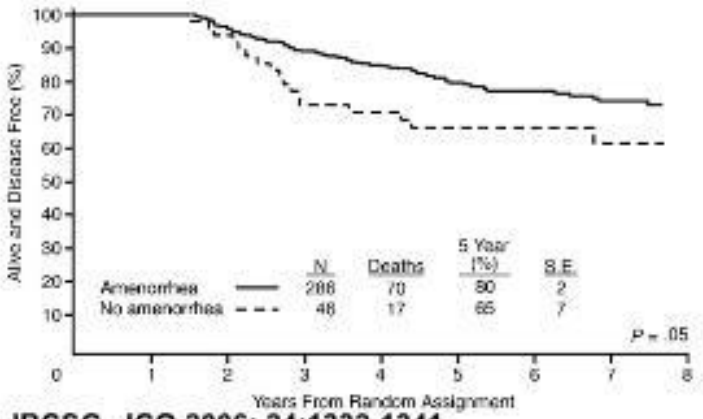
Ganz et al. J Clin Oncol 2011; Swain et al. NEJM 2010

The Paradox of Tamoxifen and OFS



Cuzick J, et al. Lancet 2004;369:1711

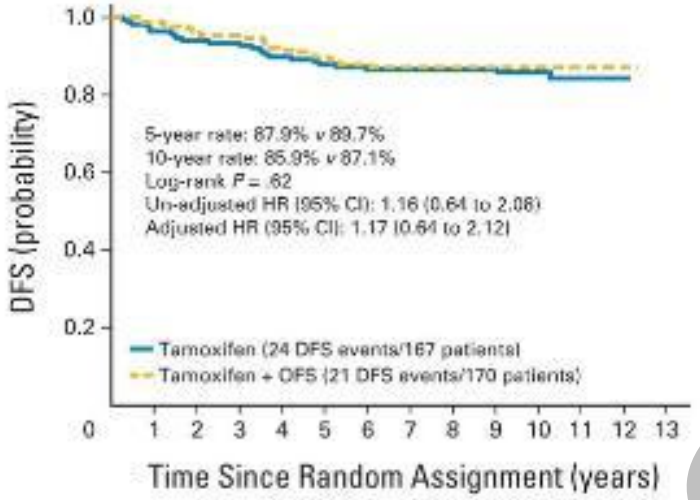
IBCSG 13-93



IBCSG, JCO 2006; 24:1332-1341

B

E3193 Tamoxifen ± OFS (no chemo)

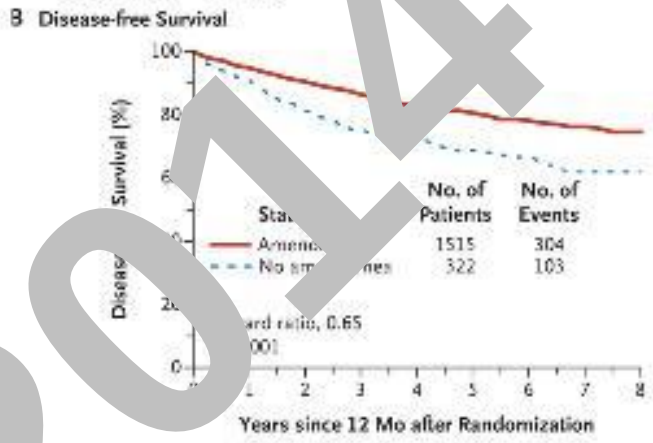


No. at risk

Tamoxifen	167	161	155	154	147	141	136	131	130	118	69	24	2	0
Tamoxifen + OFS	170	166	160	156	148	141	137	133	124	105	65	21		0

Tevaarwerk A J et al. JCO 2014;32:3948-39

NSABP B-30



Swain SM et al. N Engl J Med 2010;363:2268-2270.

Meta-Analysis of LHRH Agonists as Adjuvant Therapy for Premenopausal Women with HR+ Breast Cancer

- 9,022 women with HR+ disease; 6.8 years med FU
- Tamoxifen +/- LHRH agonist
  - No significant decrease in risk of recurrence (HR .85) or death after recurrence (HR 0.84)
- Chemotherapy +/- tamoxifen: addition of LHRH agonist provides modest benefit
  - Reduction in risk of recurrence of 12.2% (HR .88)
  - Reduction in risk of death after recurrence of 15.1% (HR .85)
- As effective as chemotherapy regimens used in these trials (no taxanes, mostly non-anthracycline)
  - Suboptimal use of tamoxifen

Cuzick et al; LHRH Meta-analysis Group. Lancet 2007;369:1714

Meta-analysis of LHRH agonists as adjuvant treatment in premenopausal patients with ER + breast cancer: Recurrence risk by age

<35 years	**HR 0.66**
35-39 years	**HR 0.77**
• 40-44 years	HR 0.96
• 45-49 years	HR 1.03
• ≥ 50 years	HR 0.85

N=9022

Significant interaction for recurrence of **age** for addition of LHRH agonist to chemotherapy with or without tamoxifen (p=0.046)

Lancet. 2007;369:1714

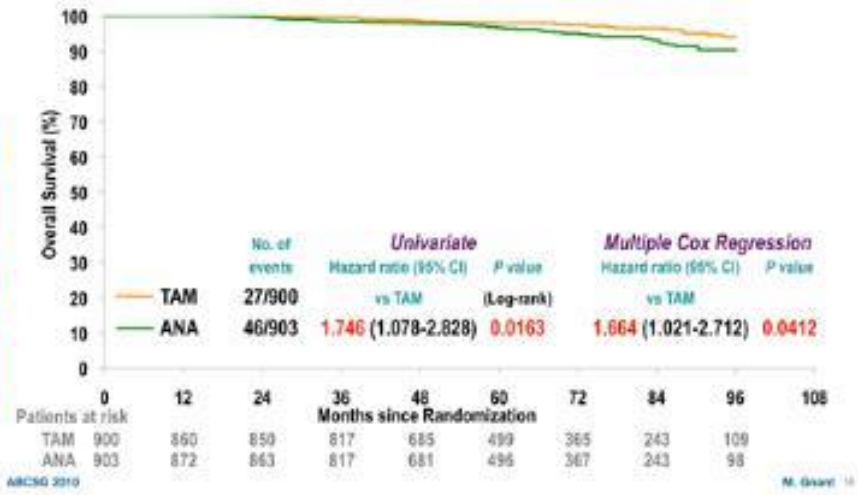
ABCSG-12 Trial Desig[illegible]

- Recruitment 1999-2006
- 1.803 premenopausal patie[illegible]
- Stage I&II, <10[illegible]des, ER+ [illegible]r P[illegible]
- Duration of trea[illegible]nt[illegible]rs
- Pre-operative Ch[illegible] allo[illegible]
- Bone [illegible]ntil Ju[illegible]

Surge[illegible] (+RT[illegible]) → Go[illegible] [illegible]g q2[illegible] → Randomize 1 : 1 : 1 : 1

- Tamoxifen 20 mg/d
- Tamoxifen 20 mg/d + Zoledronic Acid 4mg q6m
- Anastrozol 1 mg/d
- Anastrozol 1 mg/d + Zoledronic Acid 4mg q6m

Overall Survival: ANA *vs.* TAM



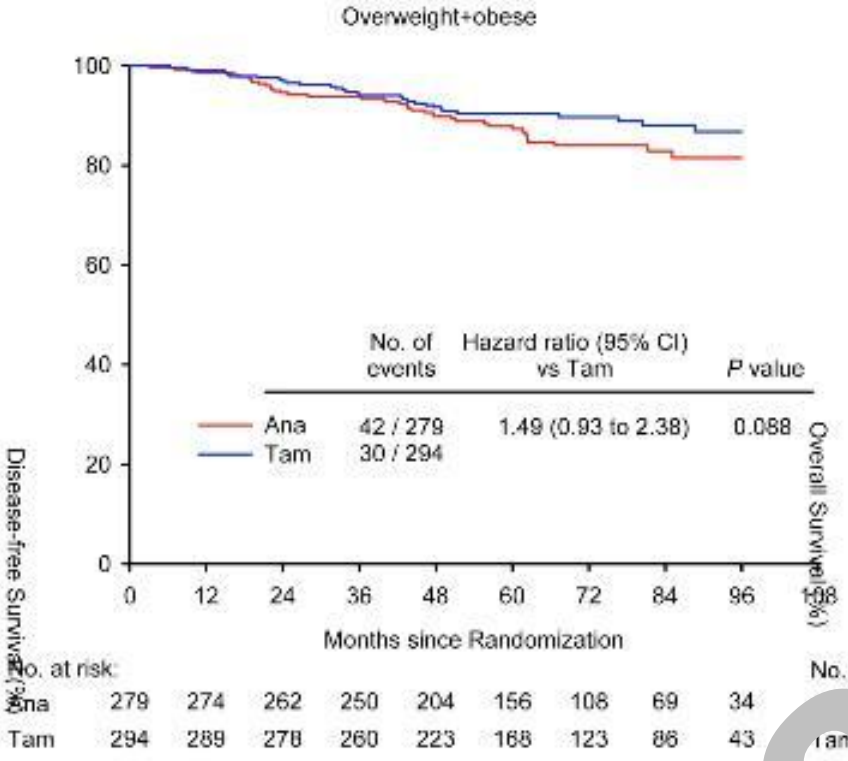
- Patient/tumor characteristics
  - 23% ≤ 40 yrs of age
  - 76% T1, 30% node +, 20% grade 3
- 95% of women are alive at 7.9 years median FU
- Worse survival with AI
  - Inadequate OFS?
- Role of zoledronate?
  - At 8 years, numerical advantage but loss of significance for DFS & OS

Gnant et al, Ann Oncol 2014

ABCSG-12 BMI

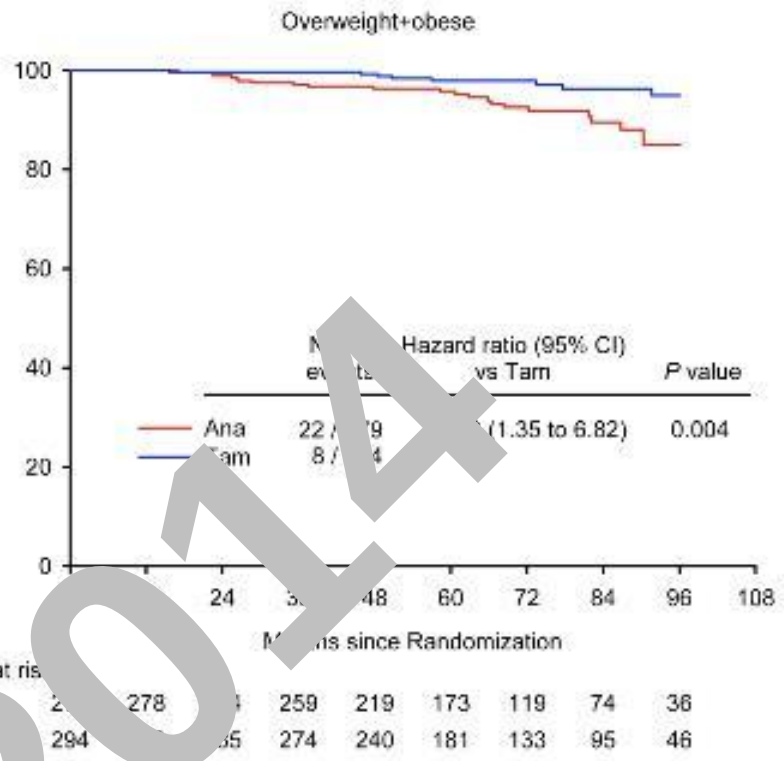
Predictive Impact of BMI – Overweight/Obese

Disease Free Survival



Cox Model
Hazard Ratio: 1.47 CI 95% (0.90-2.40) p=0.12

Overall Survival



Cox Model
Hazard Ratio: 3.23 CI 95% (1.39-7.53) p=0.006

Pfeiler et al, JCO 2011

TEXT and SOFT Designs

Enrolled 1[illegible]03-[illegible]

Pr[illegible]
≤ 12 weeks after surgery
Planned OFS
No planned chemo
OR planned chemo

RANDOMIZE

TEXT: 2672

- Tamoxifen+OFS x 5 yr
- Exemestane+OFS x 5 yr

Joint Analysis
N=4690

Median FU
5.7 years

SOFT Primary Analysis
N=2033

Premenopausal
≤ 12 weeks after surgery
No chemo
OR
Remain premenopausal ≤ 8 mos after chemo

RANDOMIZE

SOFT: 3047

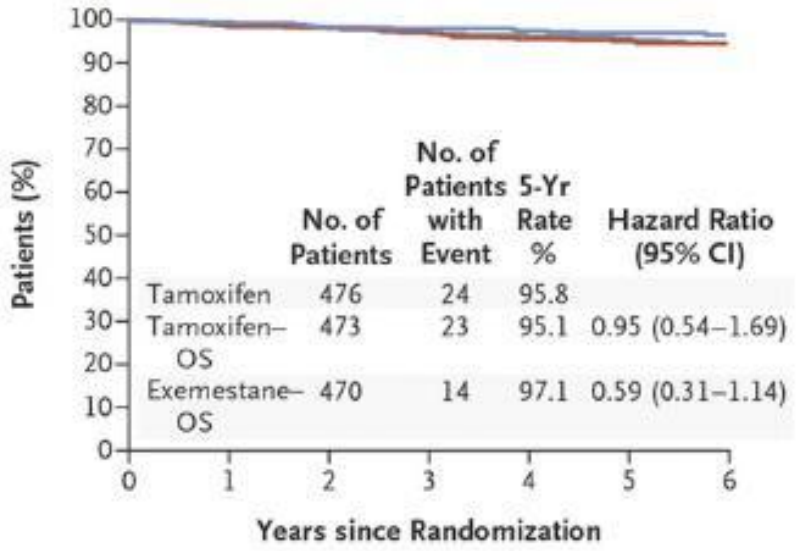
- Tamoxifen x 5 yrs (1018)
- Tamoxifen+OFS x 5 yr (1015)
- Exemestane+OFS x 5 yr (1014)

Median FU
5.6 years

Pagani et al, ASCO 2014 + NEJM 2014, Francis et al, SABCS 2014 + NEJM 2014

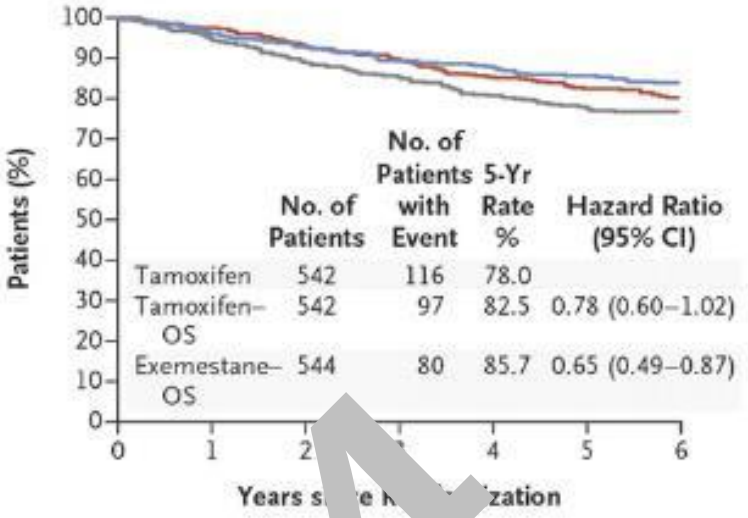
Resolving the Paradox:
SOFT / TEXT
The role of ovarian suppression in premenopausal ER+ breast cancer

No Chemotherapy, Freedom from Breast Cancer



	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	476	24	95.8	
Tamoxifen–OS	473	23	95.1	0.95 (0.54–1.69)
Exemestane–OS	470	14	97.1	0.59 (0.31–1.14)

Chemotherapy, Freedom from Breast Cancer



	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	542	116	78.0	
Tamoxifen–OS	542	97	82.5	0.78 (0.60–1.02)
Exemestane–OS	544	80	85.7	0.65 (0.49–0.87)

Clinical Assessment	Low Risk	r Risk
Chemotherapy	No	es
Benefit from OFS	No	es

DFS: women < 35 years old

Tam	68%
Tam + OFS	79%
Exe + OFS	83%

Francis PA et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1412379

Results:
Biology and Risk Drive Benefit of Ovarian Suppression

- BCFI in premenopausal women who retain ovarian production of estrogen following adjuvant chemotherapy
  - T + OFS > T
  - E + OFS >> T
- This difference is even greater in women < 35 yrs of age

Endpoint		Absolute improvement at 5 years HR (95% CI)	
		T + OFS v. T	E + OFS v. T
Premenopausal after chemo	BCFI	4.5% 0.78 (.60-1.02)	7.7% 0.65 (.49-.87)
	DRFI	1.2% 0.87 (,64 17)	4.2% 0.72 (.52-.98)
BCFI in < 35 yo (94% received chemo)		11.% 	15.7%

DRFI: distant recurrence free interval BCFI: breast cancer free interval;'

TEXT / SOFT Joint Analysis

Endpoint		Absolute improvement at 5 years
		E + OFS vs T + OFS
All patients combined	BCFI	4%
	DRFI	1.8%
No chemotherapy (TEXT only)	BCFI	3% (HR 0.41)
		TEXT vs SOFT
Premenopausal after/with chemo	BCFI	5.5 vs 3.9%
	DRFI	3.4 vs 2.6%

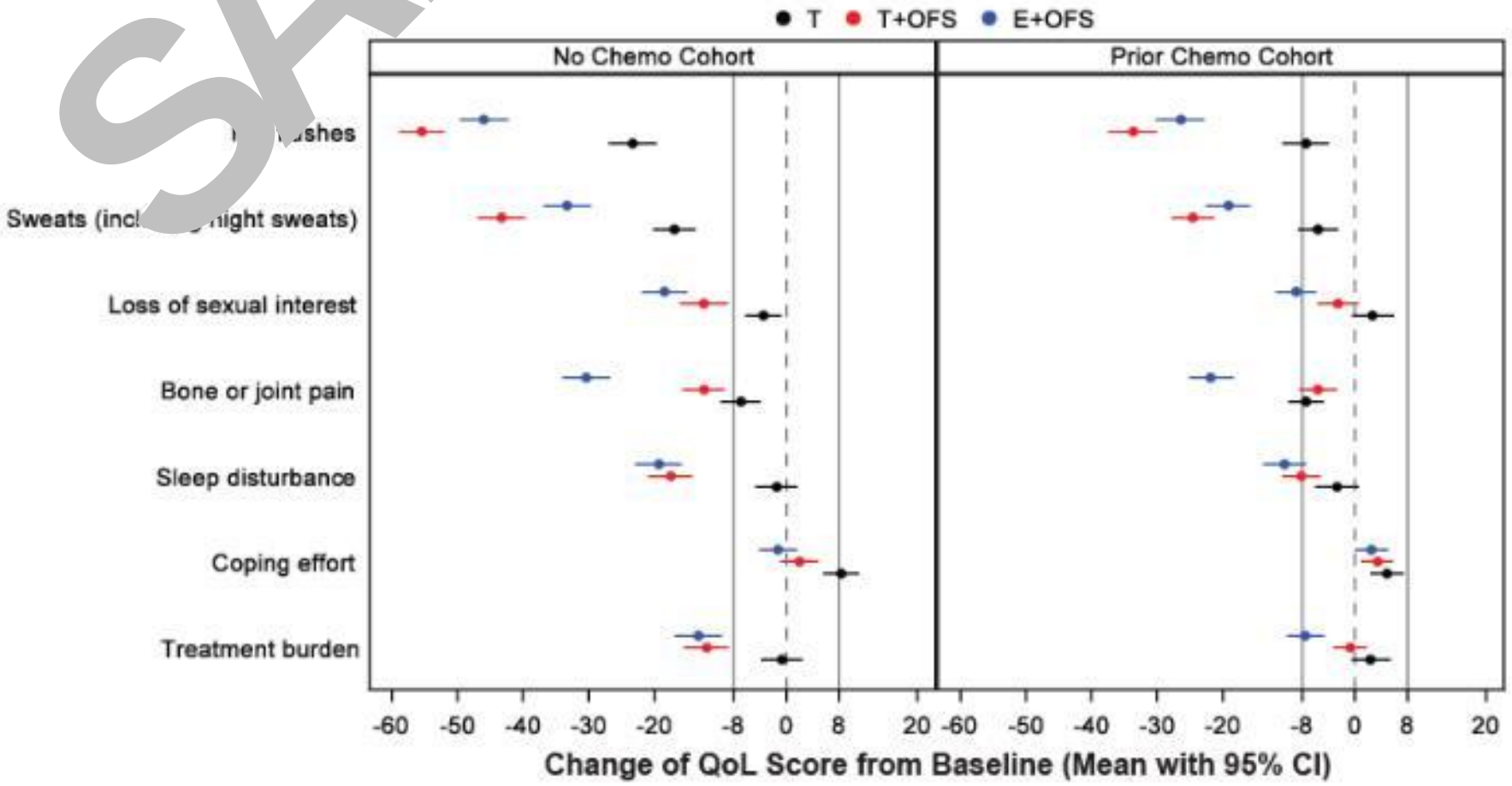
- TEXT, no chemotherapy: 21% node positive, 16% < 40, 19% T > 2 cm

Cost of Treatment: Toxicity

- **15% stopped OFS by 2 years, 22% by 3 years.**
- **Provider reported, clinically important**
  - Depression reported in ~ 50%, 4% severe, 5% increase with OFS
  - Increase in menopausal symptoms, osteoporosis, insomnia most marked
- **Patient reported (85% of trial population)**
  - No difference in global QOL with use of OFS in primary analysis despite differences in endocrine symptoms
    - Global QOL indicators do not reflect important endocrine effects
  - Endocrine differences are less pronounced after 2 years
    - Compliance or adjustment to menopause?
  - Endocrine toxicity overall less in women with prior chemotherapy

Ribi et al, SABCS 2014

Treatment Effect: by Cohort



(± 8 is the minimal clinically meaningful change of QoL scores)

Ribi et al, SABCS 2014

Take Home Points and Additional Thoughts

- Successful international collaboration
  - Accrual period 8 years
- Rigorous definition of menopausal status
- Clear and stringent definition of hormone receptor positive disease
  - >10% by IHC
- Long follow-up planned; tissue analyses offer great potential
- Excellent and careful assessment of patient reported outcomes

- Its still early! Short follow-up for distant recurrence and ov[illegible] survival
- Attention needs to be paid to management of toxicity
  - Endocrine symptoms
  - Depression
  - Hypertension
  - Bone health
- Risk vs benefit requires individuali[illegible]on

- Role of genomic tests in decisio[illegible] making [illegible]or i[illegible]termediate risk patients?

Advising Patients on Ovarian Suppression: risk stratification

Risk	Higher typically stage II or III, intermediate-high grade		Intermediate Higher anatomic stage, lower risk biology; lower stage, higher risk biology	Lower typically stage I, lower-grade
Age	< 35	40+		40+
Chemo?	Yes	Yes*		No
OFS	Yes	Discuss		No
Tablet	Tamoxifen or AI			Tamoxifen

*more likely to experience chemotherapy-induced amenorrhea

Advising Patients on Ovarian Suppression: risk stratification

Risk	Higher typically stage II or III, intermediate-high grade		Intermediate Higher anatomic stage, lower risk biology; lower stage, higher risk biology	Lower typically stage I, lower-grade
Age	< 35	40+	Variable	40+
Chemo?	Yes	Yes*	±	No
OFS	Yes	Discuss	?	No
Tablet	Tamoxifen or AI		Tamoxifen	Tamoxifen

*more likely to experience chemotherapy-induced amenorrhea

201[illegible] New Algorithm for Premenopausal Hormone Receptor Positive Disease?

Premenopausal
Hormone receptor positive
early stage breast cancer

No chemotherapy

Low risk
Smaller tumors
Node negative
Grade 1
Older

T x at least 5 years

Duration?

Intermediate risk
Low grade but larger tumor
Low grade but node positive

Chemo + OS/T or E?
OS + endocrine rx?

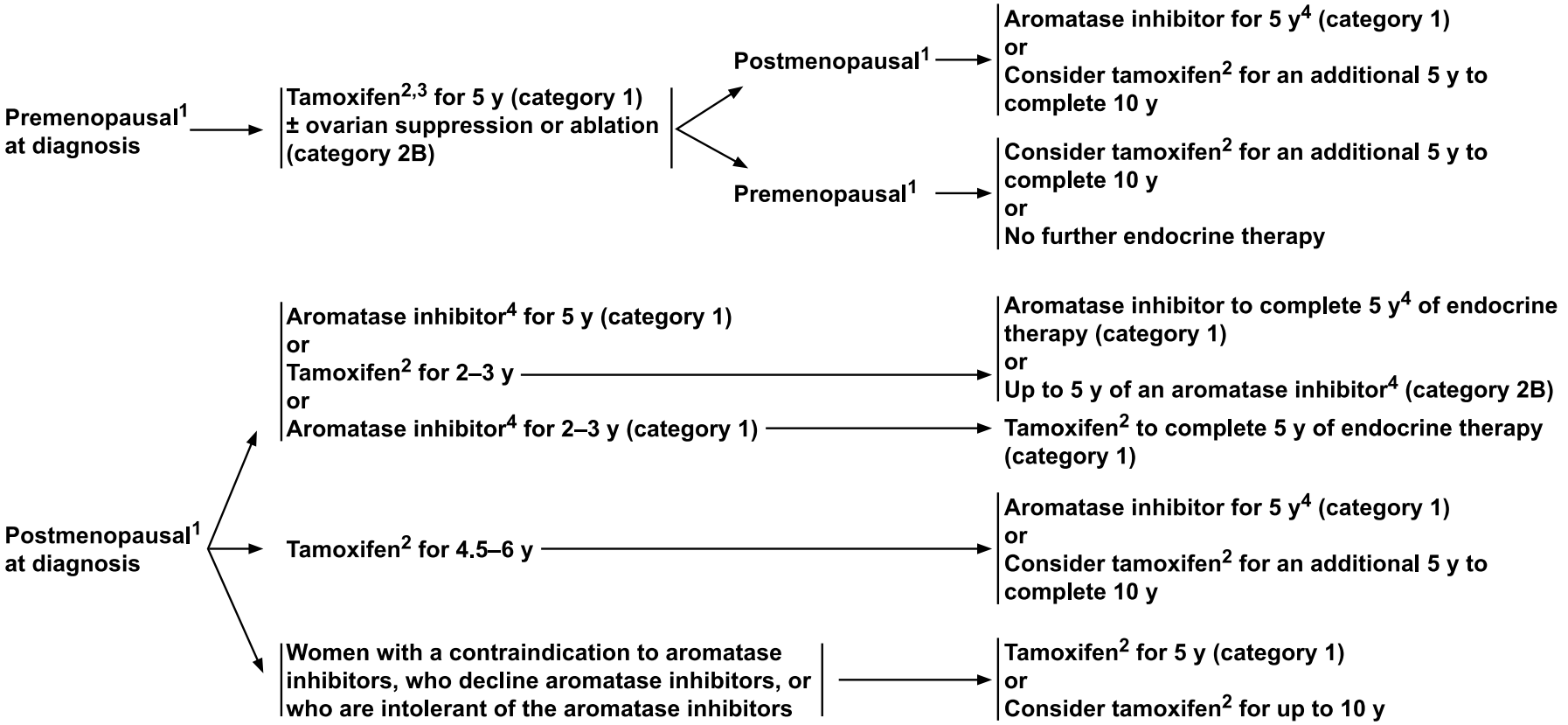
Chemotherapy

High risk
Larger tumors
Node positive
Grade 3
Younger

OS + T or E > T
(particularly in < 35 yo)

OS + E > OS + T

ADJUVANT ENDOCRINE THERAPY



[1] See Definition of Menopause (BINV-L).

[2] Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

[3] Aromatase inhibitor for 5 y + ovarian suppression may be considered as an alternative option based on SOFT and TEXT clinical trial outcomes. Pagani O, Regan M, Walley B, et al. Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2014; 371:107-118.

[4] The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and neoadjuvant settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.