Abs GS03-01. Randomized trial of low dose tamoxifen to prevent recurrence of breast intraepithelial neoplasia. Study TAM01

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Disclosure

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AIFA, EU-TRANSCAN, AIRC, US NCI, Italian Ministry of Health, Umberto Veronesi Foundation, Berlucchi Foundation, International Breast Cancer Study Group, Indena SpA, Roche, Pfizer, Janssen, Novartis, Sanofi Aventis, Quintiles, Gilead, MacroGenics

Background

- **IEN** accounts for 15-25% of all breast neoplasms with heterogenous spectrum of disorders (ADH, DCIS, LCIS).
- **Dose de-escalation** now considered given lack of benefit of XRT+5 yr tamoxifen on mortality in DCIS.
- **Tamoxifen** side effects, including Endom Ca, DVT and menopausal symptoms, are a barrier for prevention.
- The **minimal active dose** of tamoxifen is unknown.
- **Our hypothesis:** a lower dose (5 mg/d) and a shorter duration (3y) was as effective and less toxic than 20 mg/d.

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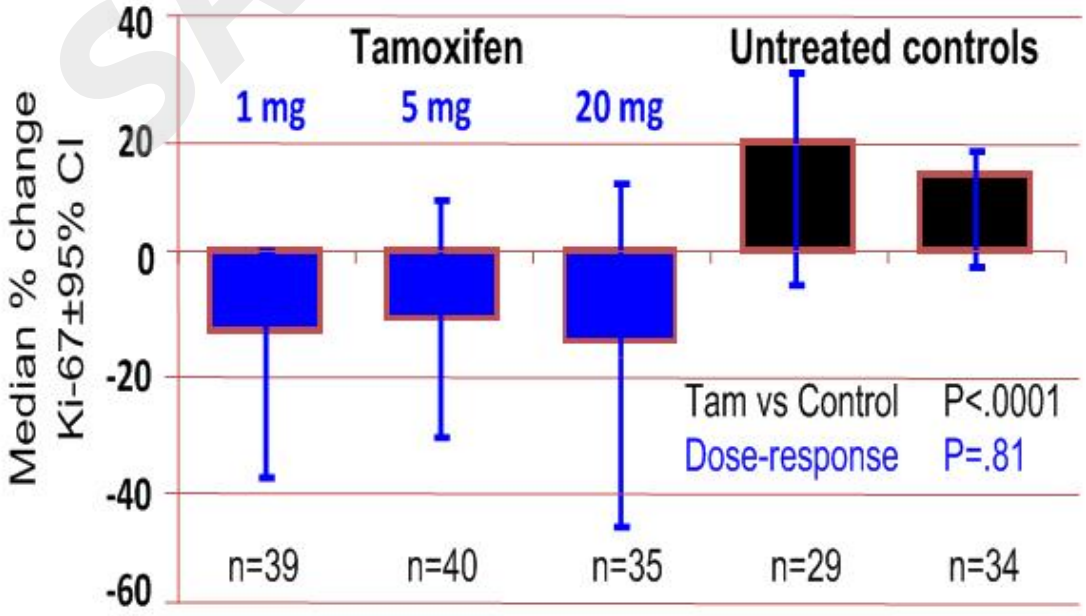
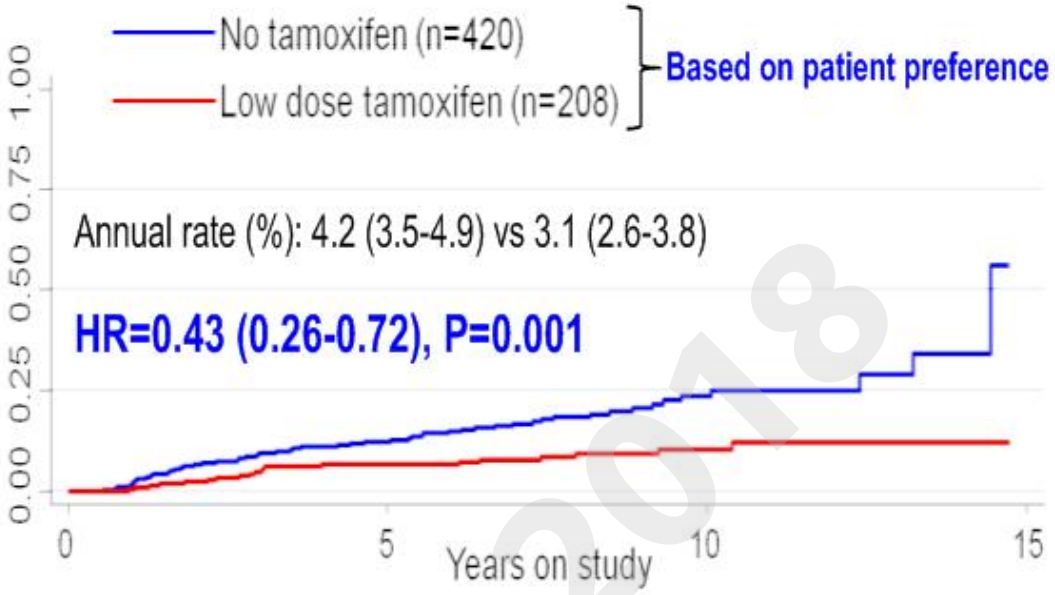
Lower doses non inferior to 20 mg/d in decreasing ki -67 in a randomized presurgical trial



DeCensi et al. *JNCI* 95: 779, 2003

Effect of 10 mg on alternate days on ipsilateral recurrence in high risk DCIS>50 yrs



Guerrieri Gonzaga et al. *Int J Cancer* 139:2127-34, 2016

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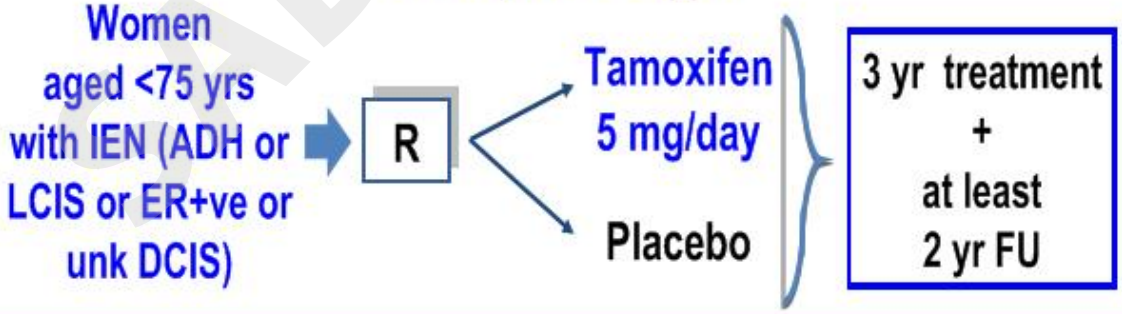
Study Design



Primary endpoint: Incidence of invasive breast cancer or DCIS

- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months, Mx every year
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42

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Main subject and tumor characteristics (n = 500)

	Tamoxifen N=253	Placebo N=247
Age, mean (SD)	54 (9.6)	54 (9.1)
Pre-menopausal, %	46	44
BMI, mean (SD)	25.7 (4.8)	25.3 (4.2)
ADH, %	20	20
LCIS, %	11	10
DCIS, %	69	70
ER/PR+ve/unknown, %	66 / 34	67 / 33
HER 2-neu 3+, %	8	9
Quadrantectomy/Mastectomy %	84 / 16	82 / 18
Radiotherapy, %	43	43

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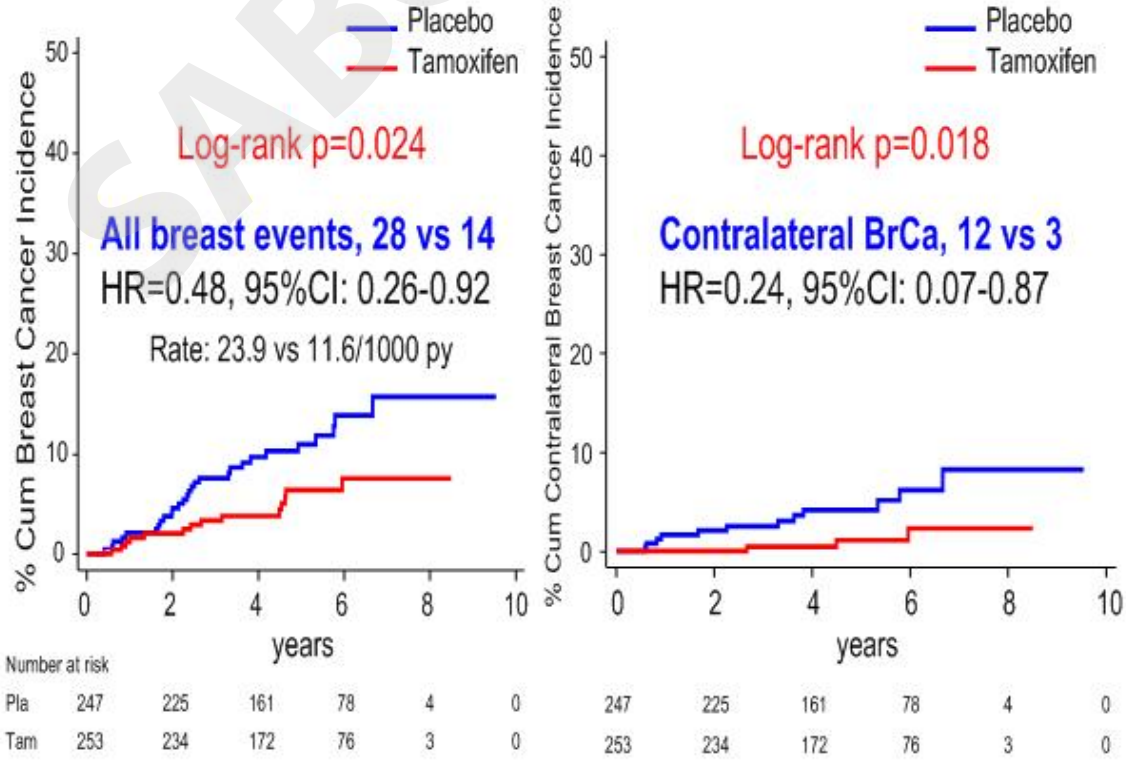

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Main tumor characteristics during the trial (n = 42)

	Tamoxifen (N=14)	Placebo (N=28)
Invasive	3	10
DCIS	11	18
Tumor diameter (mm), median (IQR)	10 (8-17)	16 (6-22)
ER (%), median (IQR)	83 (70-95)	90 (60-95)
PR (%), median (IQR)	60 (5-80)	23 (0-90)
HER2/neu 3+, %	20	16

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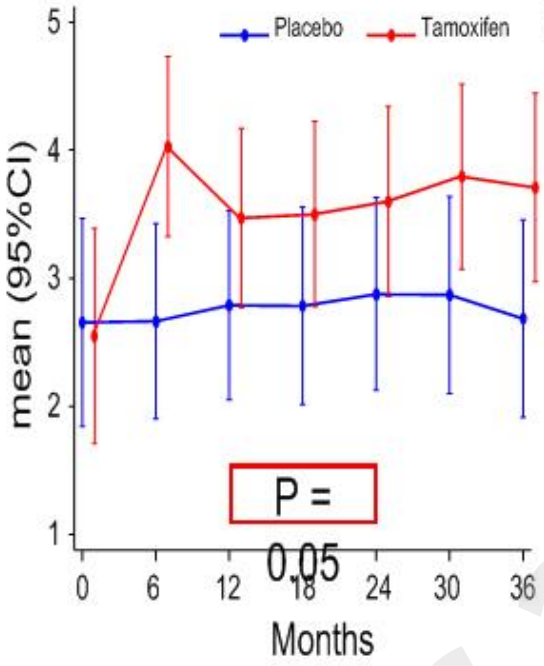
Serious adverse events

	Tamoxifen	Placebo
Endometrial cancer	1	0
DVT or PE	1	1
Other neoplasms	4	6
Coronary heart disease	2	2
Other	3	5
Death	1	2
Total	12	16

20 mg/d, expected Endometrial Cancer: **2.7**; DVT+PE: **2.4**[1]

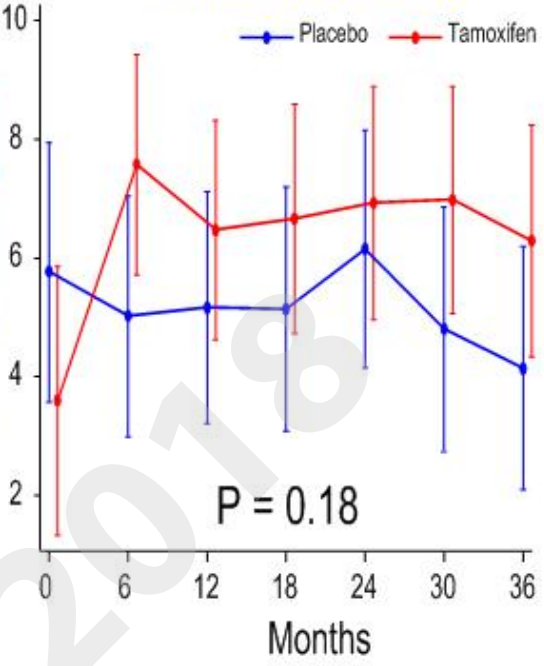
[1]NSABP-P1 trial (Fisher et al. *JNCI* 90:1371-88, 1998)

Daily hot flashes frequency



Daily hot flashes score

Frequency by Intensity



Sloan, Loprinzi et al. *JCO* 19:4280, 2001

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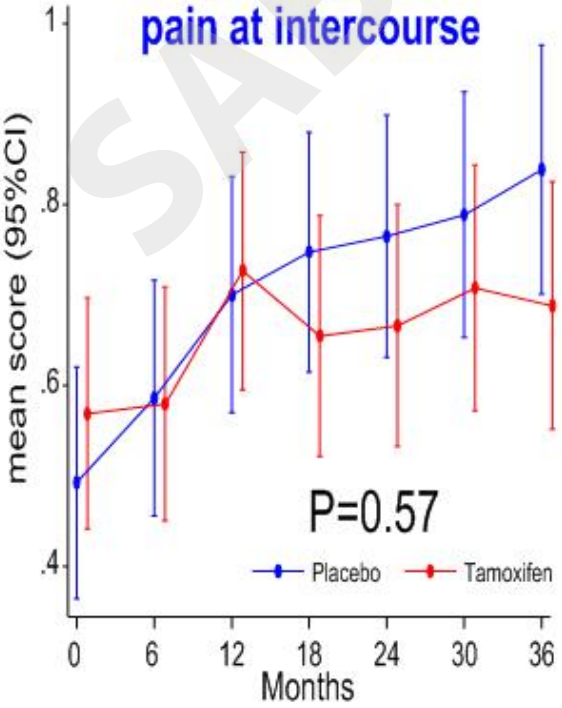
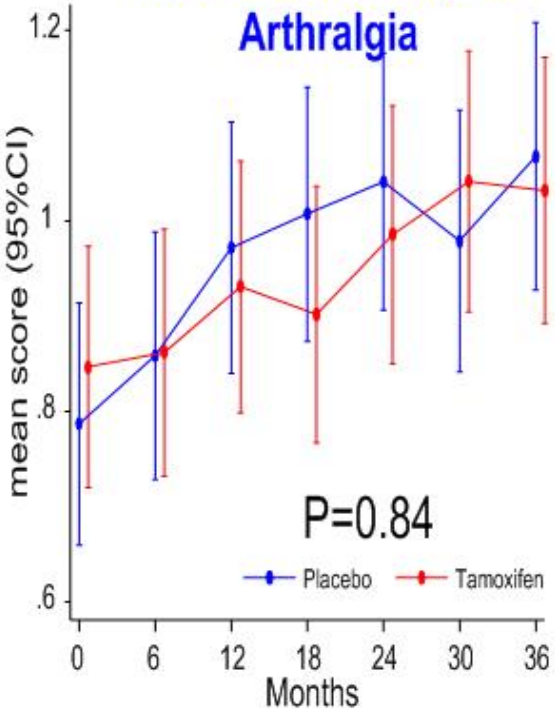
Vaginal dryness or pain at intercourse



Musculoskeletal pain/ Arthralgia



BCPSC, Stanton et al. *JNCI* 97:448-456, 2005

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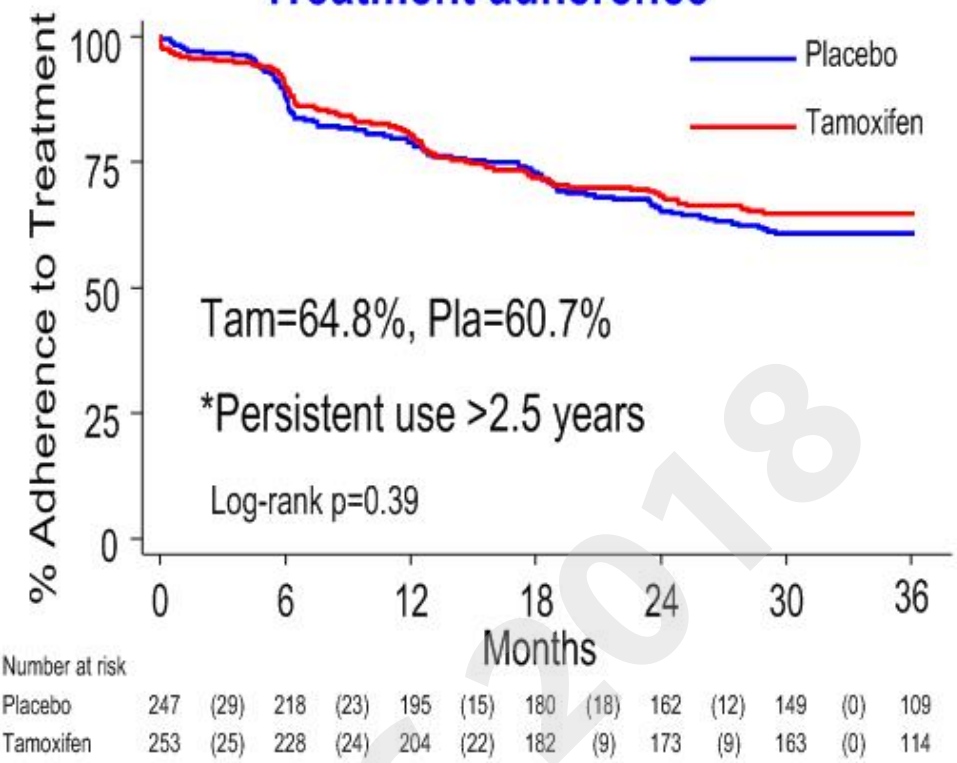
Treatment adherence*



Number at risk													
Placebo	247	(29)	218	(23)	195	(15)	180	(18)	162	(12)	149	(0)	109
Tamoxifen	253	(25)	228	(24)	204	(22)	182	(9)	173	(9)	163	(0)	114

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Estimate of treatment impact at 5 years

Number needed to treat*	22 (95% CI, 20-27)
Number needed to harm**	218 (95% CI, 193-265)
Likelihood of benefit	10 (218/22)

*5 year cumulative incidence of breast events: 6.4% on T and 11.0% on P
**5 year cumulative incidence of SAE: 0.87% on T and 0.41% on P

Conclusions

- Tamoxifen 5 mg/day for 3 years **halves the recurrence** of breast intraepithelial neoplasia in line with 20 mg/day (HR=0.58, 95% CI, 0.42-0.81)[1]
- Low dose Tamoxifen decreased contralateral breast cancer by 75%, suggesting a **strong preventive** potential
- Rate of endometrial cancer and DVT/PE on 5 mg (0.85/1000 py) **not different from placebo** and **2.5 times lower** than 20 mg[2]
- **Menopausal symptoms not worsened** except for a borderline effect on hot flashes
- Our results have external validity and are **generalizable**
- Tamoxifen **10 mg every other day** is **applicable in clinical practice from tomorrow!**

[1]Allred et al. NSABP B-24 trial. *JCO* 30:1268-73, 2012
[2]Fisher et al. NSABP-P1 trial. *JNCI* 90:1371-88, 1998

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