Adjuvant endocrine therapy for patients with non-invasive breast cancer

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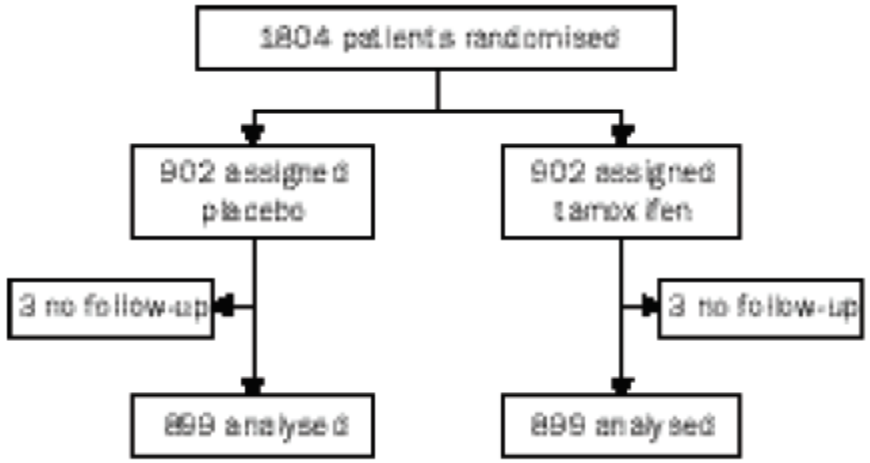
Studies on adjuvant ET in DCIS:

- **NSABP B-24 (1991-1994)**: What is the benefit of tamoxifen in addition to breast conservation and RT in patients with DCIS?
- **UK/ANZ DCIS trial (1990-1998)**: What is the benefit of tamoxifen in patients with DCIS after radical breast conservation?
- **NSABP B-35 (2003-2006):** Is anastrozole better and more safe than tamoxifen to prevent BC events in postmenopausal women with ER pos DCIS?
- **IBIS II trial (2003-2012):** Is anastrozole better than tamoxifen to prevent BC events in postmenopausal women with ER pos DCIS?
- **TAM-01 trial (2008-2015) :** Is there a benefit of low dose tamoxifen in preventing recurrence after breast intraepithelial neoplasi?

NSABP-B24 (1991-1994)



- DCIS or mixed DCIS and LCIS
- breast conservation
- doubled-blinded, placebo controlled
- tamoxifen 10 mg * 2/day
- positive margin in 25%
- all patients: RT 50 Gy/25 fx
- N=1804
- Median follow-up: 74 months

Bernard Fisher et al, Lancet 1999

NSABP-B24

Type of first event	Placebo group (n=899)			Tamoxifen group (n=899)			Rate ratio (95% CI) †	p
	Number of events	Cumulative incidence at 5 years (%)	Rate*	Number of events	Cumulative incidence at 5 years (%)	Rate*		
Breast cancer and non-breast cancer	169	16·7	38·12	126	12·6	27·50	0·72 (0·57–0·91)	0·006
All breast cancer								
Total	130	13·4	29·32	84	8·2	18·33	0·63 (0·47–0·83)	0·0009
Invasive‡	70	7·2	15·79	41	4·1	8·95	0·57 (0·38–0·85)	0·004
Non-invasive§	60	6·2	13·53	43	4·2	9·39	0·69 (0·46–1·04)	0·08
Ipsilateral-breast cancer								
Total	87	..	19·62	63	..	13·75	0·70 (0·50–0·98)	0·04
Invasive	40	4·2	9·02	23	2·1	5·02	0·56 (0·32–0·95)	0·03
Non-invasive	47	5·1	10·60	40	3·9	8·73	0·82 (0·53–1·28)	0·43
Contralateral-breast cancer								
Total	36		8·12	18		3·93	0·48 (0·26–0·87)	0·01
Invasive	23	2·3	5·19	15	1·8	3·27	0·63 (0·31–1·26)	0·22
Non-invasive	13	1·1	2·93	3	0·2	0·66	0·22 (0·04–0·81)	0·02
Breast cancer at regional or distant sites	7	..	1·58	3	..	0·66	0·42 (0·07–1·82)	0·32
Non-breast cancer								
Total	39	3·3	8·80	42	4·4	9·17	1·04 (0·66–1·65)	0·94
Second primary cancers other than endometrial cancer	26	..	5·86	25	..	5·46	0·93 (0·52–1·68)	0·91
Endometrial cancer	2	..	0·45	7	..	1·53	3·39 (0·64–33·42)	0·20
Deaths, no evidence of disease	11	..	2·48	10	..	2·18	0·88 (0·33–2·28)	0·94

*Rate per 1000 patients per year.
†Rate in tamoxifen group divided by rate in placebo group.
‡Includes ipsilateral-breast cancer, contralateral-breast cancer, and local, regional, and distant disease.
§Includes ipsilateral and contralateral non-invasive tumours.

37% reduction of all BC events (70% ipsilateral)

44% reduction of ipsilateral invasive BC

52% reduction of contralateral BC events

Bernard Fisher et al, Lancet 1999

NSABP-B24 (patients with known ER status of DCIS)

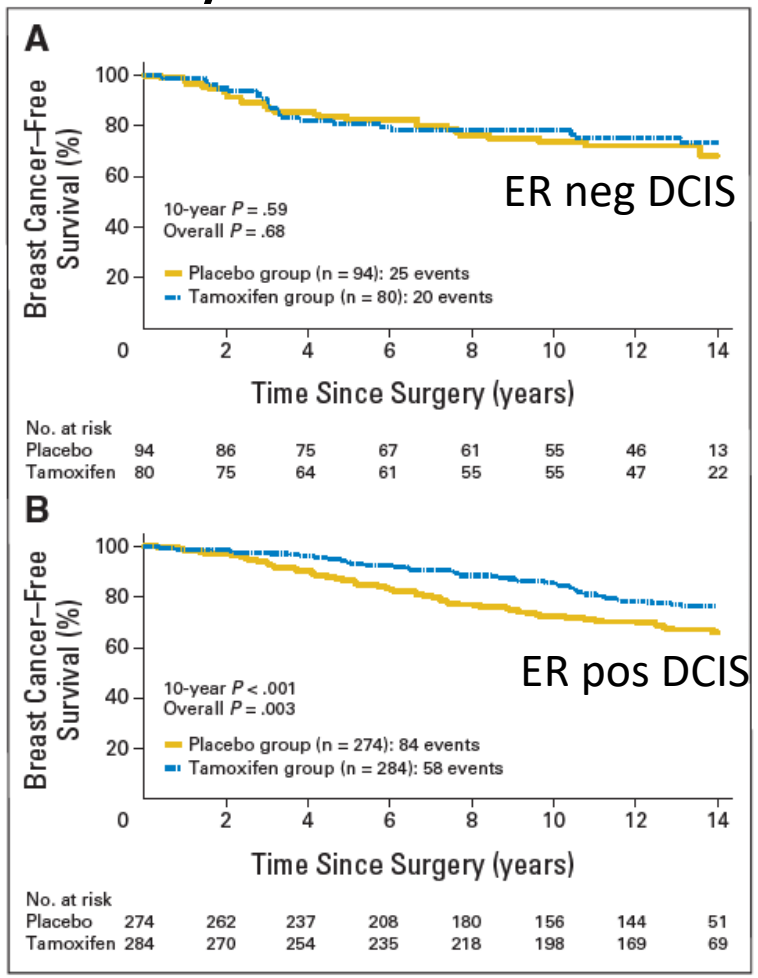


Fig 3. Kaplan-Meier curves showing probability of any subsequent breast cancer in patients with (A) estrogen receptor (ER) –negative and (B) ER-positive ductal carcinoma in situ (DCIS) treated with adjuvant placebo versus tamoxifen. Tamoxifen benefit (42% reduction in relative risk; $P = .001$) was restricted to ER-positive DCIS.

	Placebo (n = 368)		Tamoxifen (n = 364)				
Type of BC	No.	%	No.	%	HR*	95% CI	P†
ER positive							
Any							
BC	84	31	58	20	0.58	0.415 to 0.81	.0015
IBC	52	19	33	12	0.53	0.34 to 0.82	.005
DCIS	32	12	25	9	0.66	0.39 to 1.12	.12
Ipsilateral							
BC	47	17	39	14	0.68	0.44 to 1.03	.07
IBC	26	9	20	7	0.61	0.34 to 1.09	.10
DCIS	21	8	19	7	0.76	0.41 to 1.42	.39
Contralateral							
BC	32	11	18	6	0.50	0.28 to 0.88	.02
IBC	21	8	12	4	0.51	0.25 to 1.03	.06
DCIS	11	4	6	2	0.47	0.17 to 1.27	.14
ER negative							
Any							
BC	25	27	20	25	0.88	0.49 to 1.59	.68
IBC	14	15	9	11	0.69	0.30 to 1.59	.38
DCIS	11	12	11	14	1.15	0.50 to 2.65	.75
Ipsilateral							
BC	16	17	17	21	1.18	0.60 to 2.34	.63
IBC	6	6	7	9	1.24	0.42 to 3.70	.70
DCIS	10	11	10	13	1.15	0.48 to 2.75	.76
Contralateral							
BC	7	7	3	4	0.46	0.12 to 1.80	.35
IBC	6	6	2	3	0.36	0.07 to 1.77	.29
DCIS	1	1	1	1	1.15	0.07 to 18.44	1.00

42% reduction of all BC events

32% reduction of all ipsilateral BC events

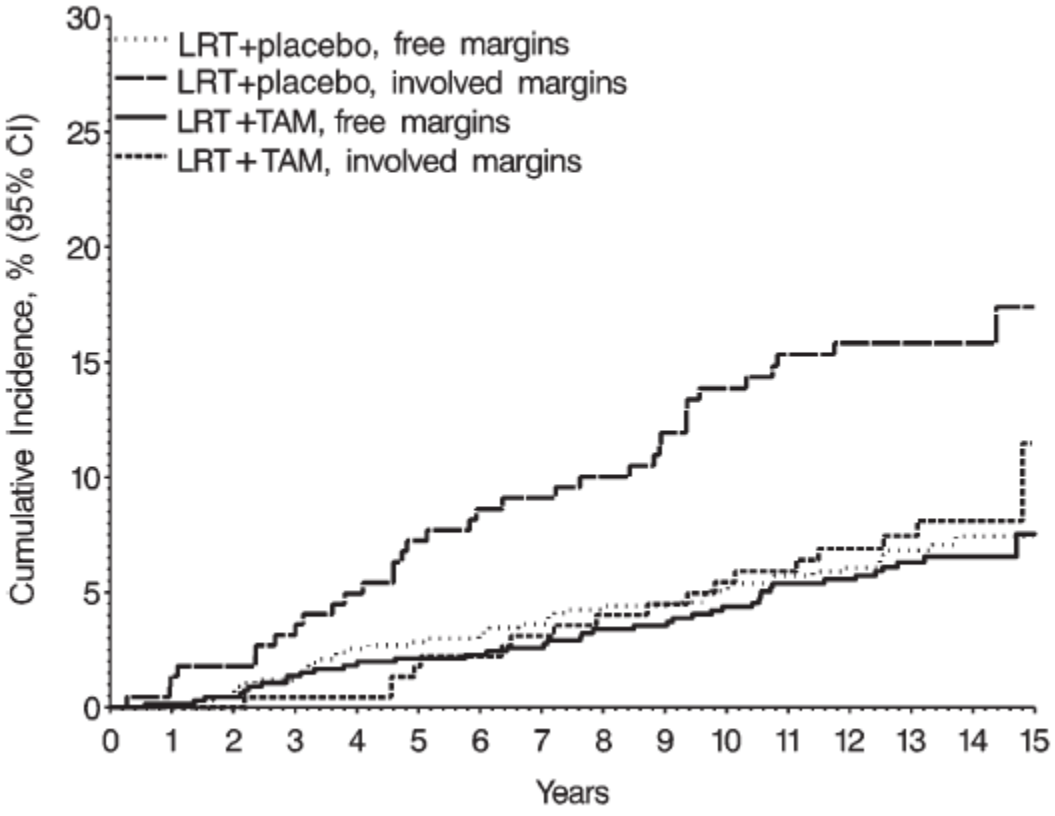
50% reduction of all contralateral BC events

non significant reduction of contralateral BC events (prevention)

D. Craig Allred, JCO 2012

NSABP-B24 (outcome based on margin)

Invasive ipsilateral breast tumor recurrence



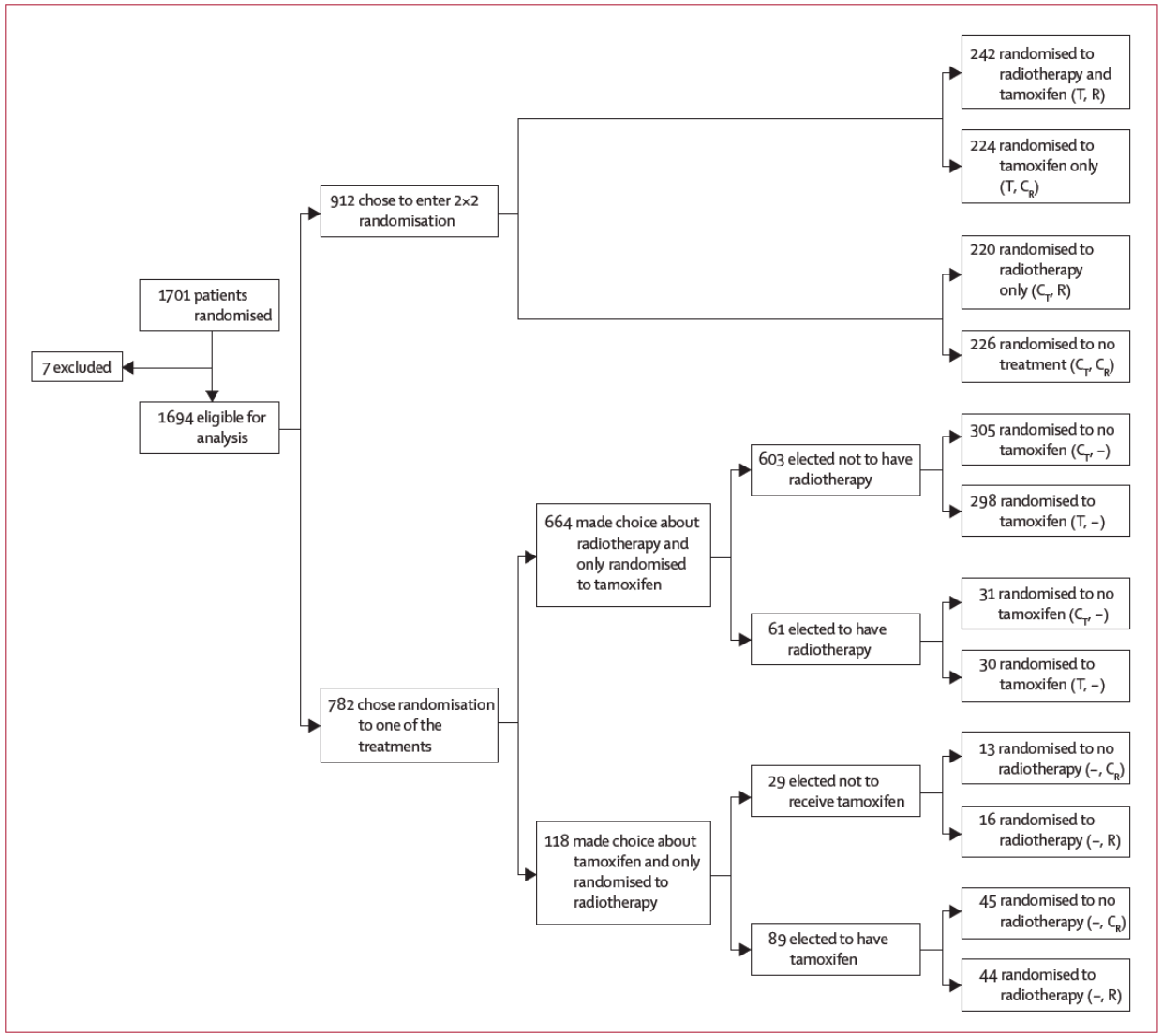
"The benefit of tamoxifen on ipsilateral breast tumor recurrence was in patients with involved margins"

BCS + RT, placebo, involved margin

BCS + RT, tamoxifen, involved margin

Wapnir IL et all J Natl Cancer Inst 2011

UK/ANZ DCIS trial (1990-1998)



- patients with DCIS suitable for breast conservation
- radical surgery
- ER status unknown
- randomized to 4 groups: RT, TAM, both or no adjuvant treatment
- N=1701 patients
- median follow-up: 12,7 years

Jack Cuzick et al, Lancet Oncol 2011

UK/ANZ DCIS trial

	No adjuvant treatment (n=544)	Tamoxifen alone (n=567)	Radiotherapy alone (n=267)	Radiotherapy and tamoxifen (n=316)	Total (n=1694)
Follow-up (woman-years)	5428	6017	3023	3545	18 013
Breast events	174 (32%)	135 (24%)	35 (13%)	32 (10%)	376 (22%)
DCIS	96 (18%)	72 (13%)	16 (6%)	13 (4%)	197 (12%)
Ipsilateral	86 (16%)	63 (11%)	14 (5%)	11 (3%)	174 (10%)
Contralateral	9 (2%)	4 (1%)	2 (1%)	2 (1%)	17 (1%)
Unknown	1	5	0	0	6
Invasive	72 (13%)	57 (10%)	16 (6%)	18 (6%)	163 (10%)
Ipsilateral	52 (10%)	49 (9%)	10 (4%)	11 (3%)	122 (7%)
Contralateral	20 (4%)	7 (1%)	5 (2%)	7 (2%)	39 (2%)
Unknown	0	1	1	0	2
Unknown	6 (1%)	6 (1%)	3 (1%)	1 (0%)	16 (1%)
Annual rate of breast events (%)	3·2%	2·2%	1·2%	0·9%	2·1%

Data are number (%). DCIS=ductal carcinoma in situ.

***Table 1*: New breast events**

Jack Cuzick et al, Lancet Oncol 2011

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UK/ANZ DCIS trial

Comparable to NSABP B-24

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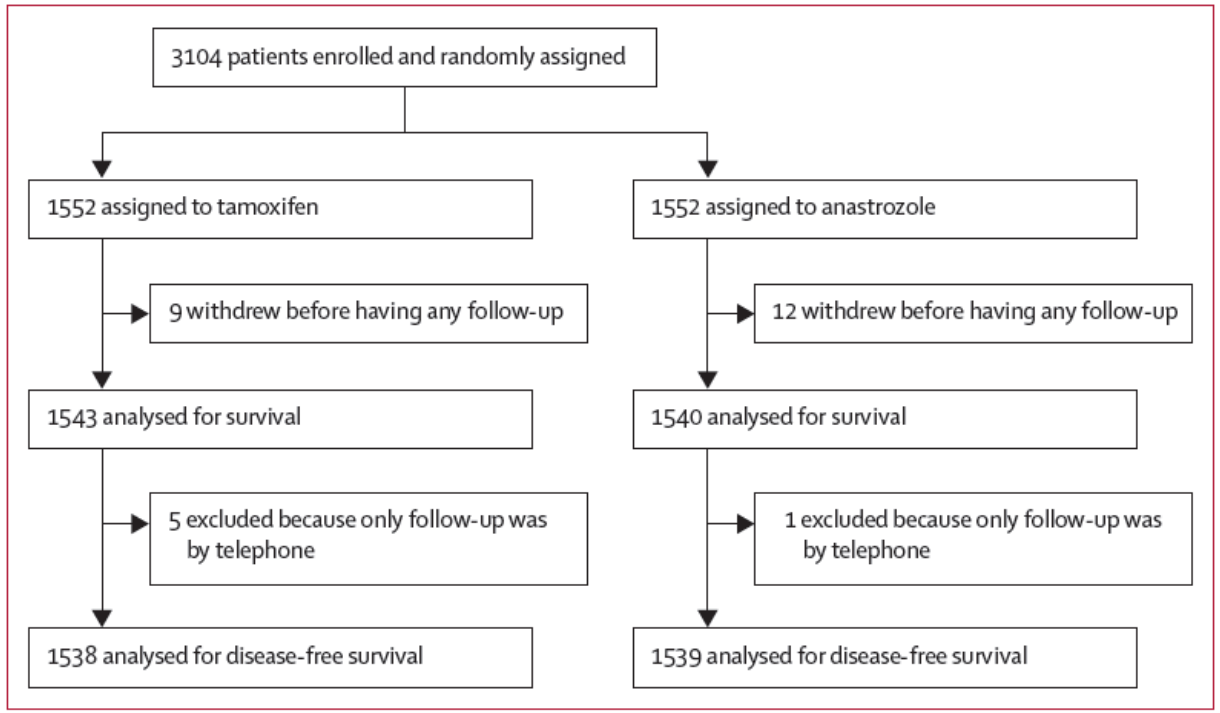
Jack Cuzick et al, Lancet Oncol 2011

NSABP B-35 (2003-2006)



- postmenopausal women with ER pos DCIS or mixed DCIS and LCIS
- breast conservation
- clear margins and negative nodes
- all patients: RT 50 Gy in 25 fx
- standard doses of tamoxifen and anastrozole for 5 years
- comparable side-effects
- N=3104
- median follow-up: 9 years

Margolese RG, Lancet 2016

NSABP B-35

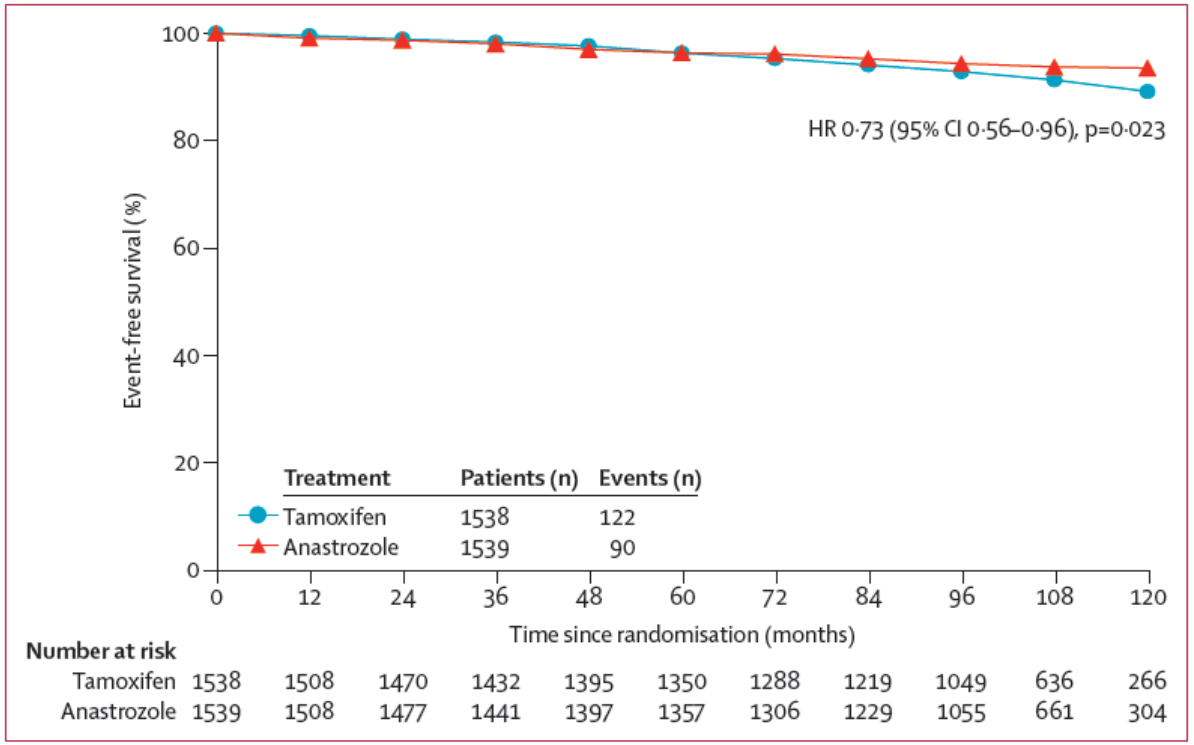


Figure 2: **Breast cancer-free interval**
HR=hazard ratio

	Patients (n)	Tamoxifen (n=1538)	Anastrozole (n=1539)	Hazard ratio (95% CI)	p value
Breast cancer-free interval events					
<60 years	1447	63	34	0·53 (0·35–0·80)	0·0026
≥60 years	1630	59	56	0·95 (0·66–1·37)	0·78
Disease-free survival events					
<60 years	1447	104	74	0·69 (0·51–0·93)	0·0151
≥60 years	1630	156	161	1·03 (0·83–1·28)	0·79

Table 3: **Breast cancer-free interval and disease-free survival events by age group**

The benefit of anastrozole was especially seen as a reduction of contralateral invasive BC

Margolese RG, Lancet 2016

IBIS II trial (2003-2012)

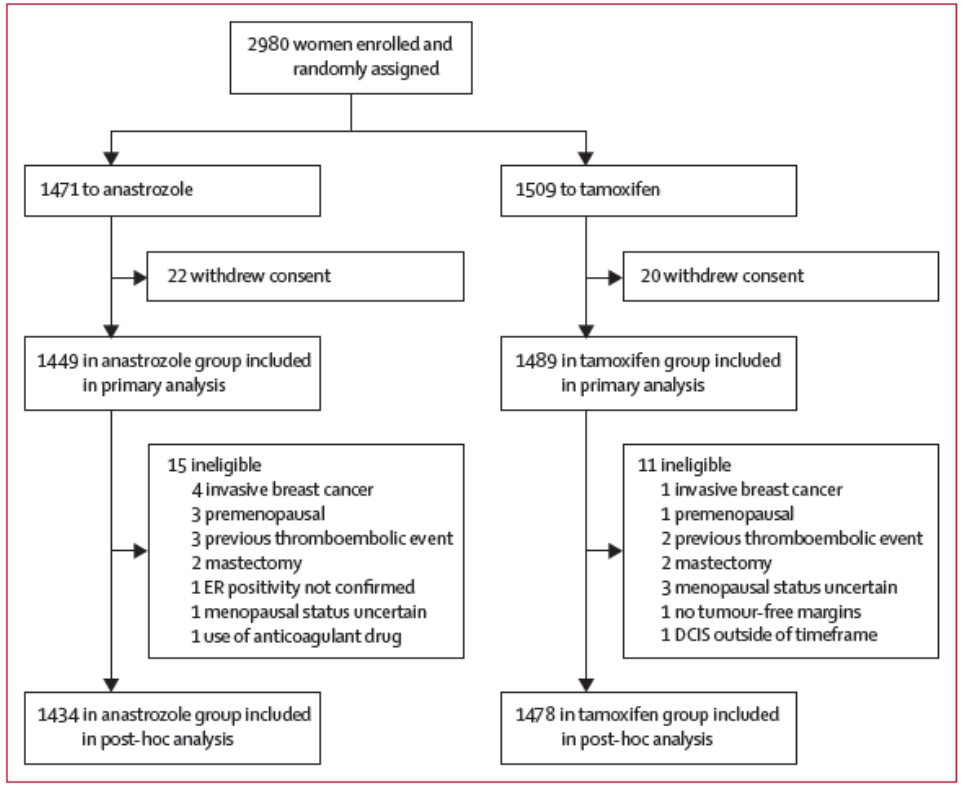


Figure 1: **Trial profile**
ER=oestrogen receptor. DCIS=ductal carcinoma in situ.

- postmenopausal women
- ER pos DCIS
- breast conservation
- 71% had RT (local practise)
- standard doses of tamoxifen and anastrozole
- comparable adverse events
- N=2980
- median follow-up: 7.2 years

John Forbes et al, Lancet 2016

IBIS II trial

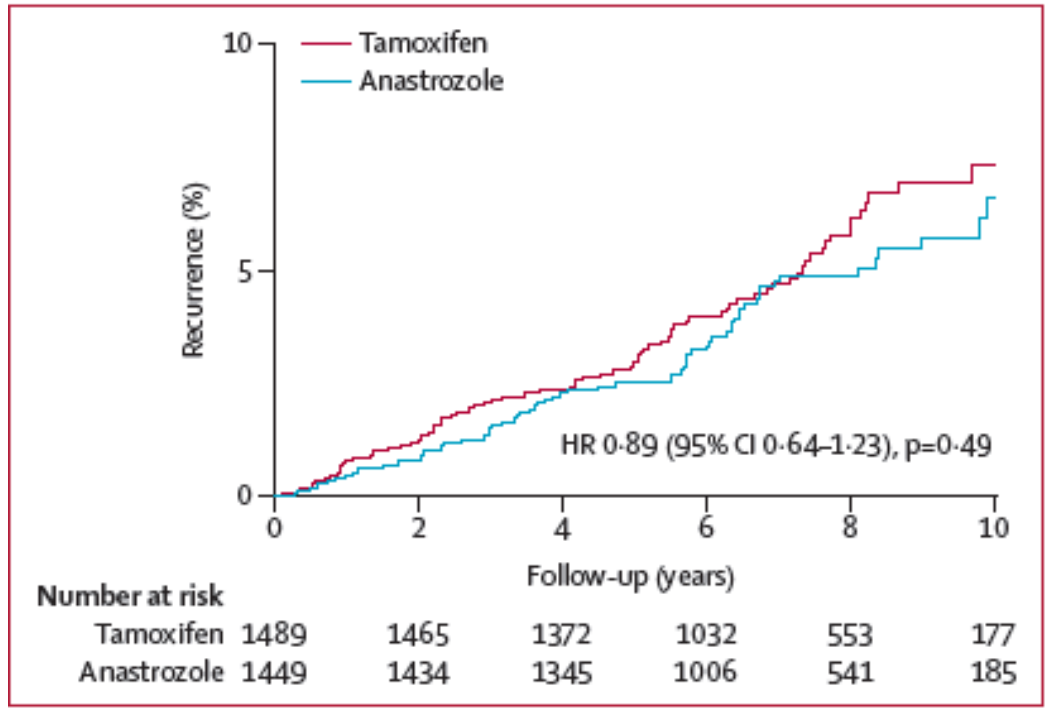


Figure 2: **Recurrence for all breast cancer according to treatment allocation**

	Anastrozole (n=1449)	Tamoxifen (n=1489)	Unadjusted analysis		Adjusted analysis*	
			HR (95% CI)	p value	HR (95% CI)	p value
All	67 (5%)	77 (5%)	0·89 (0·64–1·23)	0·49	0·83 (0·59–1·18)	0·31
Invasive†	37 (3%)	47 (3%)	0·80 (0·52–1·24)	0·32	0·72 (0·46–1·14)	0·16
Ipsilateral	20 (1%)	22 (1%)	0·93 (0·51–1·71)	0·82	0·77 (0·40–1·48)	0·44
Contralateral	17 (1%)	25 (2%)	0·69 (0·37–1·28)	0·24	0·68 (0·36–1·29)	0·24
DCIS	29 (2%)	30‡ (2%)	0·99 (0·60–1·65)	0·98	0·98 (0·57–1·69)	0·95
Ipsilateral	21 (1%)	23 (2%)	0·94 (0·52–1·69)	0·83	1·03 (0·55–1·91)	0·93
Contralateral	8 (<1%)	6 (<1%)	1·37 (0·47–3·94)	0·56	1·02 (0·33–3·18)	0·97

DCIS=ductal carcinoma in situ. HR=hazard ratio. *Adjusted for age, body-mass index, menopausal hormone therapy, grade, margins, and radiotherapy. †1 missing for invasiveness. ‡1 missing data for laterality.

Table 2: **All breast cancer, invasive, and DCIS recurrences according to treatment allocation**

2 years shorter follow-up than NSABP B-35!

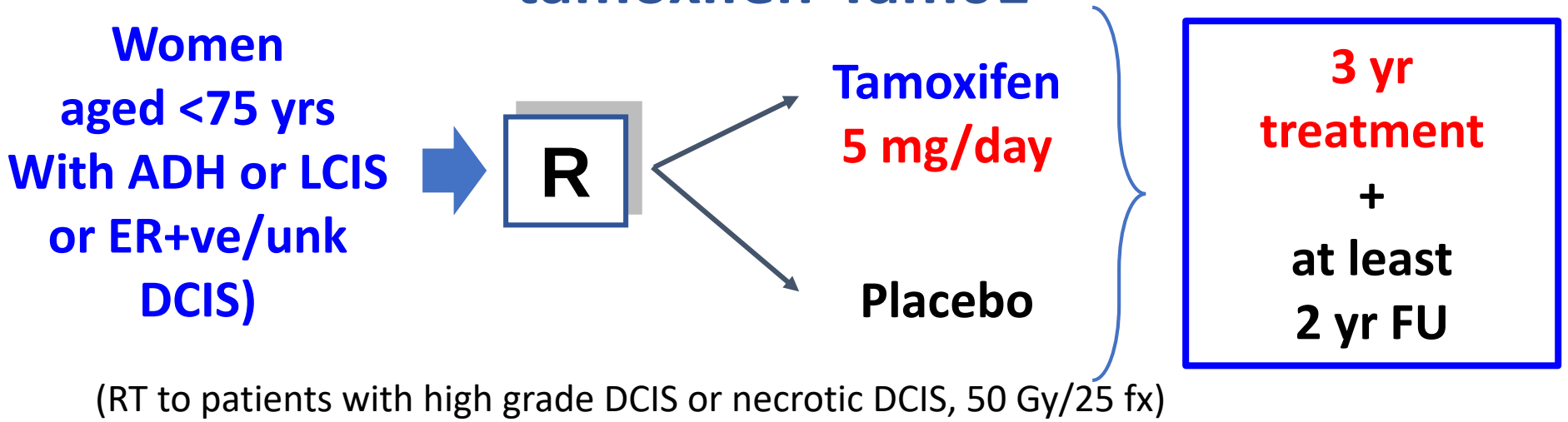
John Forbes et al, Lancet 2016

Only a small risk of recurrence after DCIS with modern treatment

- 98% of patient with DCIS alive after 5 years
- They all undergo routine mammography
- In case of recurrence, surgery can often cure the patient
- Many side-effects with endocrine treatment

- Therefore low dose tamoxifen (3 years) was testet in TAM-01:

Randomized placebo controlled trial of low dose tamoxifen-Tam01



(RT to patients with high grade DCIS or necrotic DCIS, 50 Gy/25 fx)

Primary endpoint: Incidence of invasive breast cancer or DCIS

- **500 participants enrolled from 14 centers in Italy**
- **Median follow up = 5.1 years (IQR 3.9-6.3)**
- **Primary events: 42**

Courtesy of Dr Emiel Rutgers

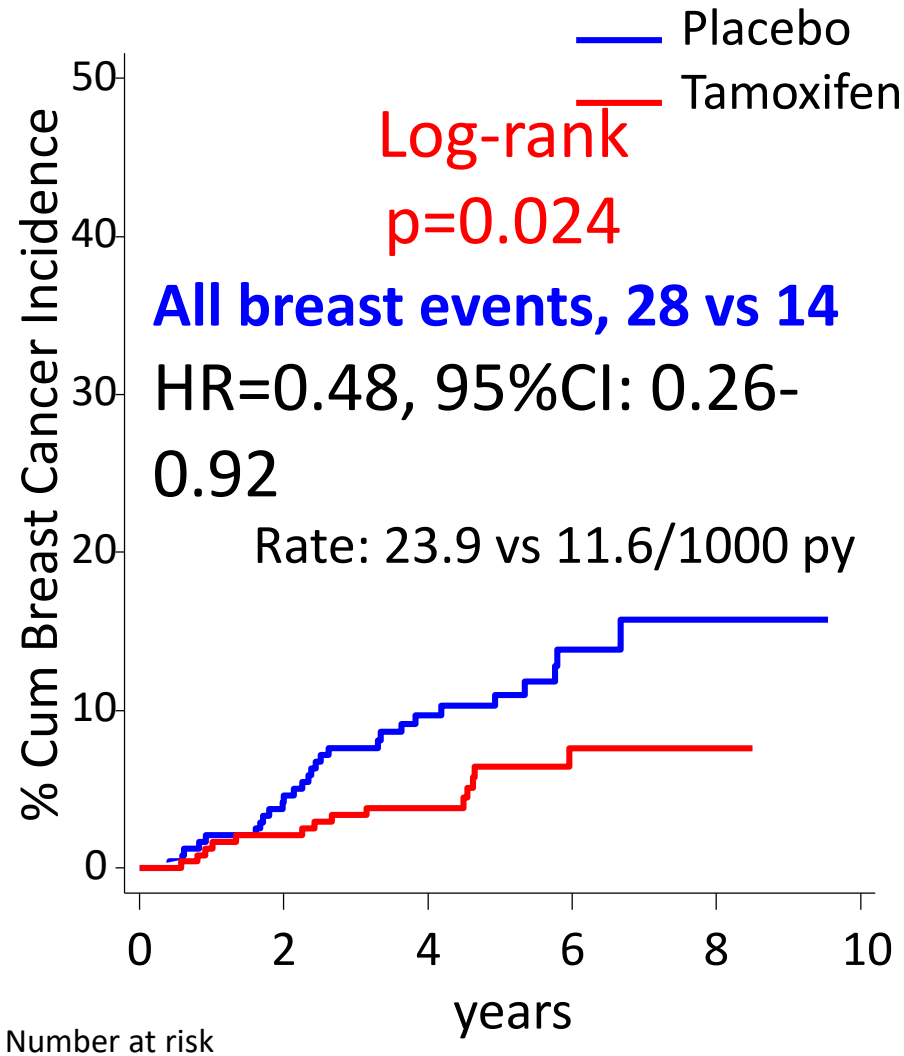
DeCensi et al. JCO, 2019

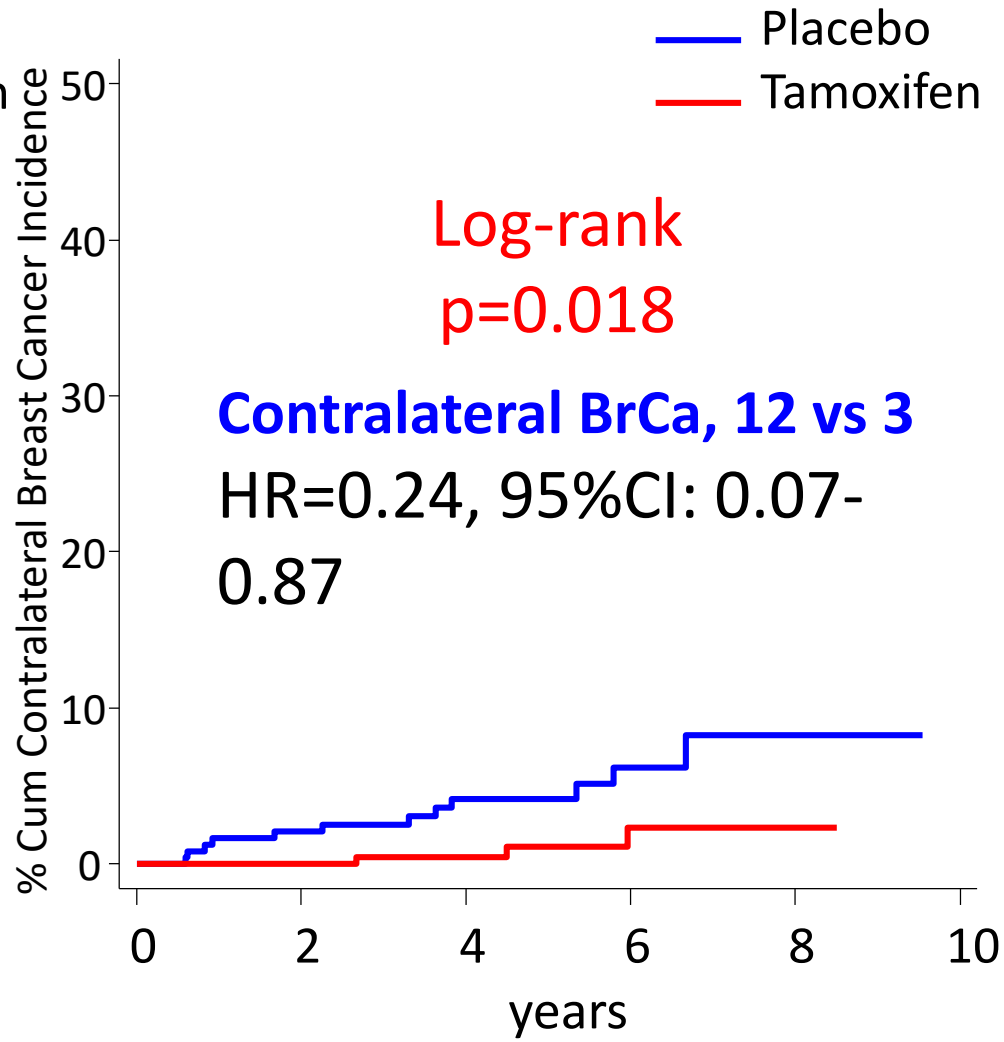
Main subject and tumor characteristics (n = 500)

	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 for DCIS, %	61	61

Courtesy of Dr Emiel Rutgers

DeCensi et al. JCO, 2019





Courtesy of Dr Emiel Rutgers

DeCensi A et al. JCO, 2019

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

Courtesy of Dr Emiel Rutgers

DeCensi A et al. JCO, 2019

Non serious Adverse Events

TABLE A2. Nonserious Adverse Events

Adverse Event	Tamoxifen (n = 249), No. (%)	Placebo (n = 246), No. (%)	*P**
Hot flashes	34 (13.7)	18 (7.3)	.03
Arthralgia	14 (5.6)	21 (8.5)	.22
Vaginal dryness	5 (2.0)	8 (3.3)	.42
Vaginal bleeding	10 (4.0)	3 (1.2)	.09
Headache	1 (0.4)	11 (4.5)	.003
Vaginal discharge	6 (2.4)	5 (2.0)	1.00
Endometrial polyps	7 (2.8)	4 (1.6)	.54
Muscle cramping/myalgia	6 (2.4)	4 (1.6)	.75

NOTE. The safety analysis included all patients who received at least one dose of drug or placebo (495 patients). Events that occurred in at least 2% of patients are reported. Patients may have had more than one event.

*Fisher's exact test.

DeCensi A et al. JCO, 2019

Summary (1)

- NSABP B-24: (70 % of recurrences were ipsilateral)
- BCS and RT: 5 year risk of:
  - 1) ipsilateral non-invasive recurrence (5.1%)
  - 2) ipsilateral invasive recurrence (4.2%)
  - 3) contralateral invasive tumor (2.3%)
  - 4) contralateral non-invasive tumor (1.1%)

- BCS and RT and TAM: 5 year risk of:
  - 1) ipsilateral non-invasive recurrence (3,9%)
  - 2) ipsilateral invasive recurrence (2.1%)
  - 3) contralateral invasive tumor (1.8%)
  - 4) contralateral non-invasive tumor (0.2%)

Benefit TAM if pos margins and ER pos DCIS

Benefit TAM (preventing)

Summary (2)

- UK/ANZ DCIS trial: benefit of tamoxifen: less non-invasive ipsilateral and less invasive contralateral BC events in no RT patients
- NSABP B-35: Anastrozole superior to tamoxifen in young postmenopausal women
- IBIS II trial: no difference between anastrozole and tamoxifen
- TAM-01 trial: Benefit of low dose tamoxifen in preventing all ipsilateral and contralateral BC events (only few event, no margin status, no routine RT)

Conclusion DCIS and systemic ET

- **What is the primary aim of the adjuvant treatment?**
- Ipsilateral BC events can be prevented by radical surgery and adjuvant RT. Tamoxifen should only be considered in:
  - ER pos DCIS and no RT and positive margins
  - young age and risk factors?
- Contralateral BC events can be prevented by tamoxifen and could be considered in
  - young age and risk factors?
- normal dose TAM and AI (5 years) and low dose TAM (3 years) can be used

thank you..