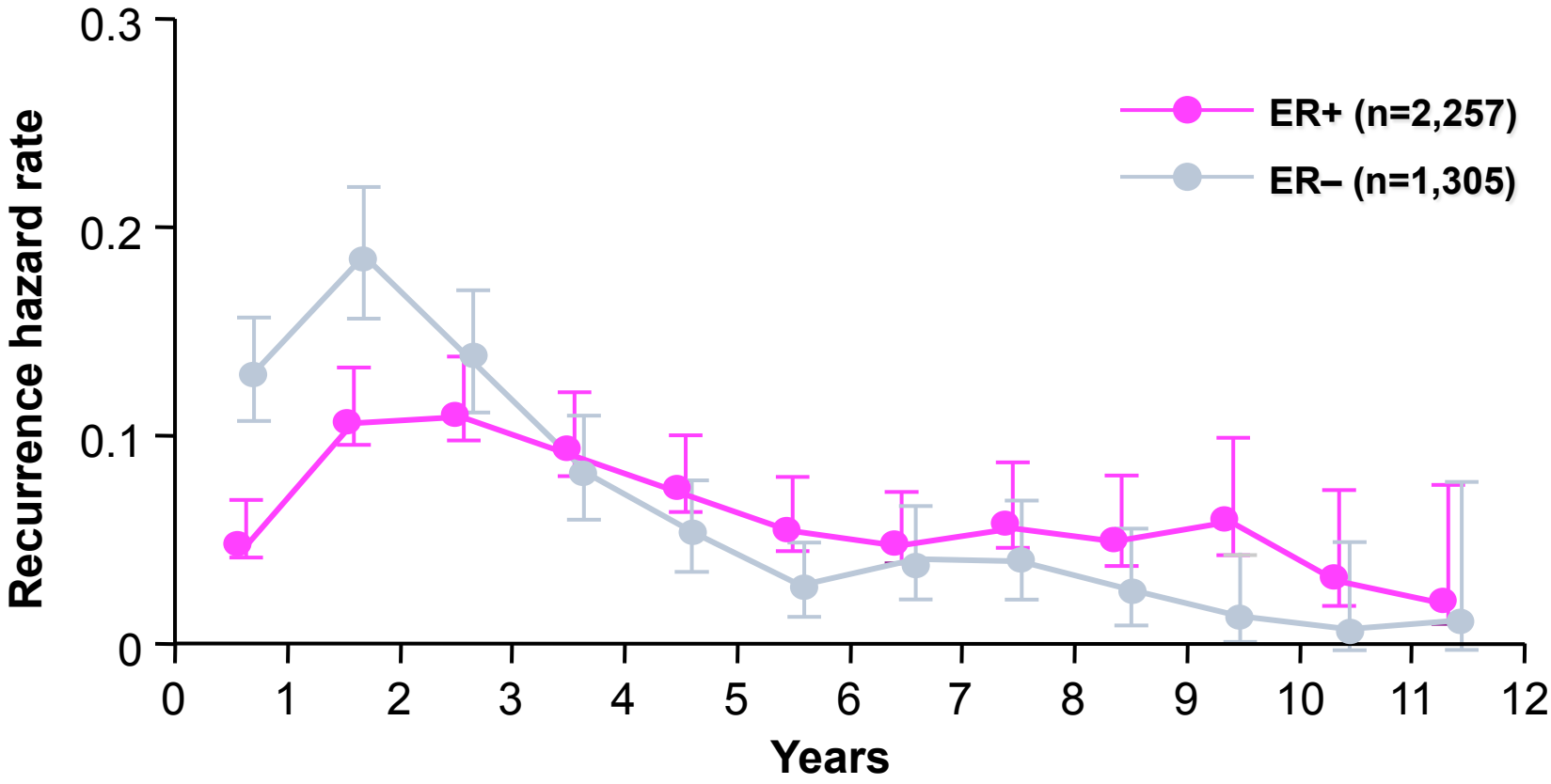
ORMONOTERAPIA ADIUVANTE: QUALE LA DURATA OTTIMALE?

MARIANTONIETTA COLOZZA

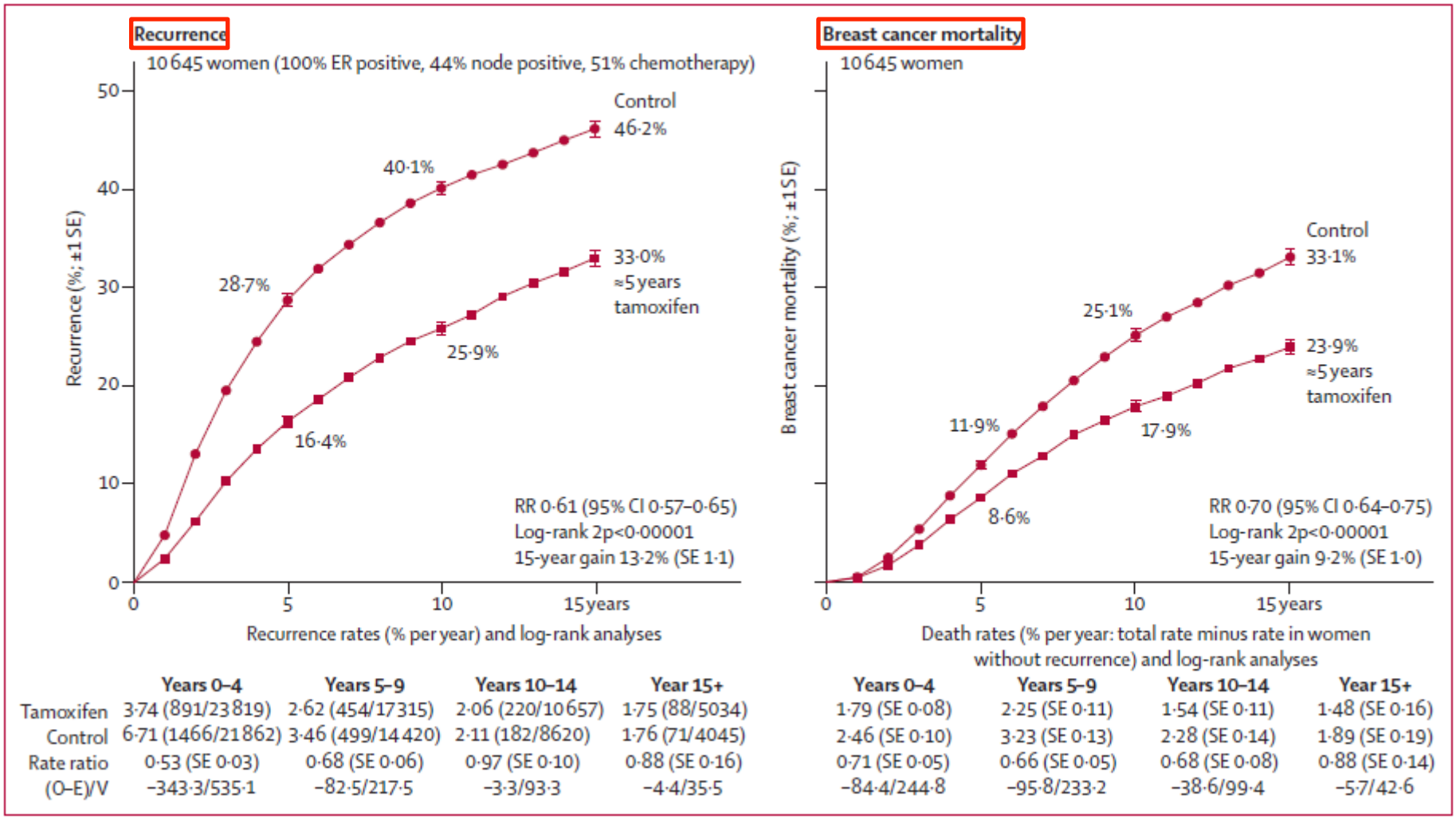
THE NATURAL HISTORY OF HORMONE RECEPTOR-POSITIVE BREAST CANCER IS VERY LONG



- A substantial proportion of breast cancer recurrences occur >5 years post surgery
- The annual risk of late recurrence is higher in ER+ tumors

Saphner et al J Clin Oncol,1996;14:2738

BREAST CANCER RECURRENCES AND DEATHS POST-TAMOXIFEN



	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5

Years 0–4	Years 5–9	Years 10–14	Year 15+
1·79 (SE 0·08)	2·25 (SE 0·11)	1·54 (SE 0·11)	1·48 (SE 0·16)
2·46 (SE 0·10)	3·23 (SE 0·13)	2·28 (SE 0·14)	1·89 (SE 0·19)
0·71 (SE 0·05)	0·66 (SE 0·05)	0·68 (SE 0·08)	0·88 (SE 0·14)
−84·4/244·8	−95·8/233·2	−38·6/99·4	−5·7/42·6

EBCTCG Lancet, 2011;378: 771-784

RELAPSES AFTER 5 YEARS

Thinking about late relapses using the 2000 Oxford overview

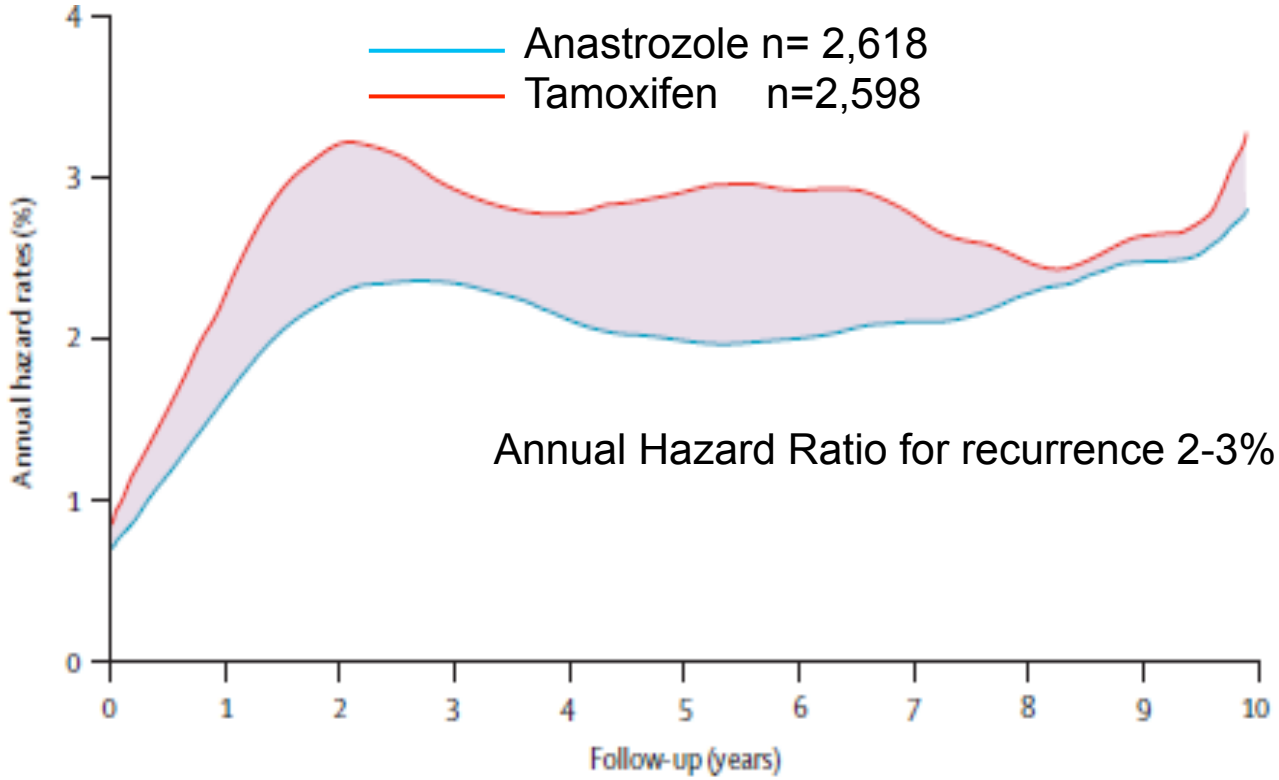
Annual Hazard Rate
Average annual risk observed (in % per yr)

	Treatment Category	Years 0-10	Years 5-10
N-	Control	3.6	2.0
	Tamoxifen	2.0	1.8
N+	Control	7.8	5.5
	Tamoxifen	5.1	4.7

Courtesy of P. Ravdin

LATE RECURRENCE REMAINS A CHALLENGE AS EARLY TREATMENT IMPROVES

ATAC trial 10 year analysis



Even with recent advances, including aromatase inhibitors and trastuzumab, there appears to be persistent risk of late recurrence

Cuzick J et al. Lancet Oncol 2010;11:1135-1141

RATIONALE FOR EVALUATING TO EXTEND ADJUVANT ENDOCRINE THERAPY FOLLOWING 5 YEARS

- The majority of patients are disease free at the time of tamoxifen or AI discontinuation but recurrences continue to occur over prolonged periods of time

- Over half of the recurrences and over two-thirds of the deaths occur after the first 5 years of follow up

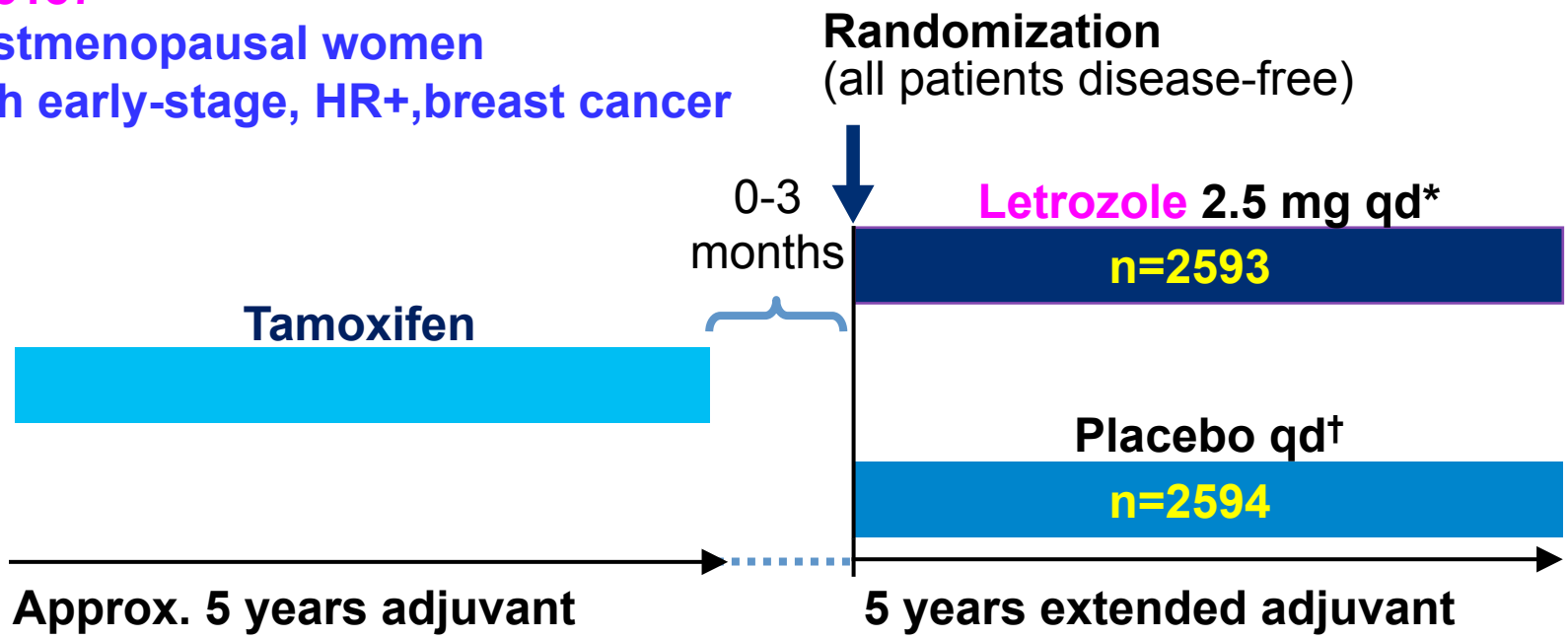
- The majority of the recurrences are still hormone-sensitive

MA.17

Trial Design

Phase III double-blind

N=5187
Postmenopausal women
with early-stage, HR+,breast cancer



PRIMARY END POINT: DFS

SECONDARY END POINTS: OS, annual incidence rate of contralateral tumor, safety, QoL, and DDFS

Substudies: BMD/bone markers, lipid profile

*n=2582 (efficacy), 2563 (safety); †n=2586 (efficacy), 2573 (safety).
BMD = bone mineral density, QoL= quality of life

MA.17 TRIAL
PATIENT DEMOGRAPHICS

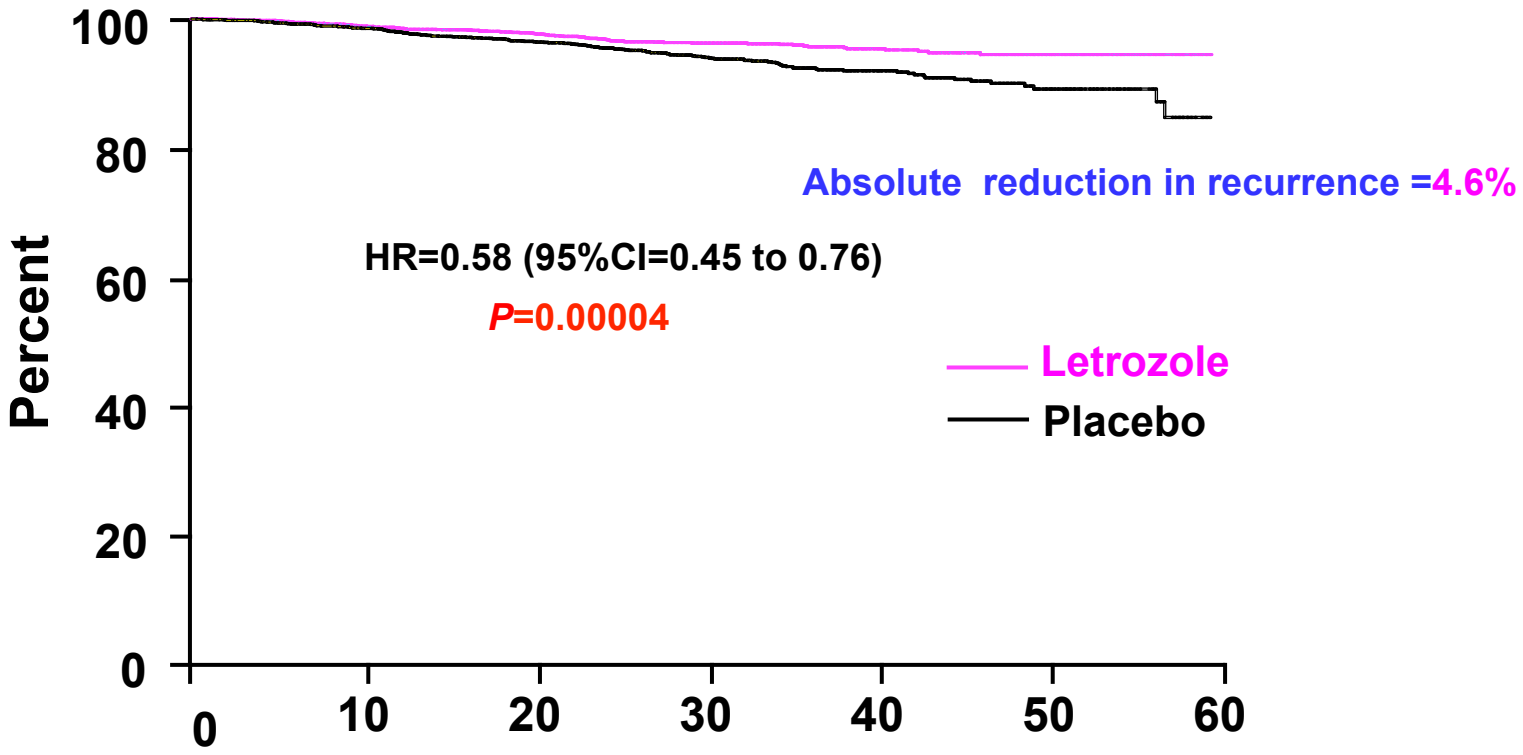
	LETROZOLE (n=2583)	PLACEBO (n=2587)
Median age (y)	62	62
ER+ and/or PgR+ (%)	97	97
ECOG 0 (%)	90	90
T1 (%)	**58**	**58**
Node-negative (%)	**50**	**49**
Breast-conserving surgery (%)	57	58
Radiotherapy (%)	60	59
Chemotherapy (%)	46	45

Goss PE et al. JNCI 2005; 97: 1262-1271

MA.17 TRIAL

DFS

LETROZOLE SIGNIFICANTLY REDUCED THE RISK OF RECURRENCE BY 42%



No. at risk (Letrozole)	2583	2497	1905	1110	541	176	6
No. at risk (Placebo)	2587	2489	1874	1075	519	164	8

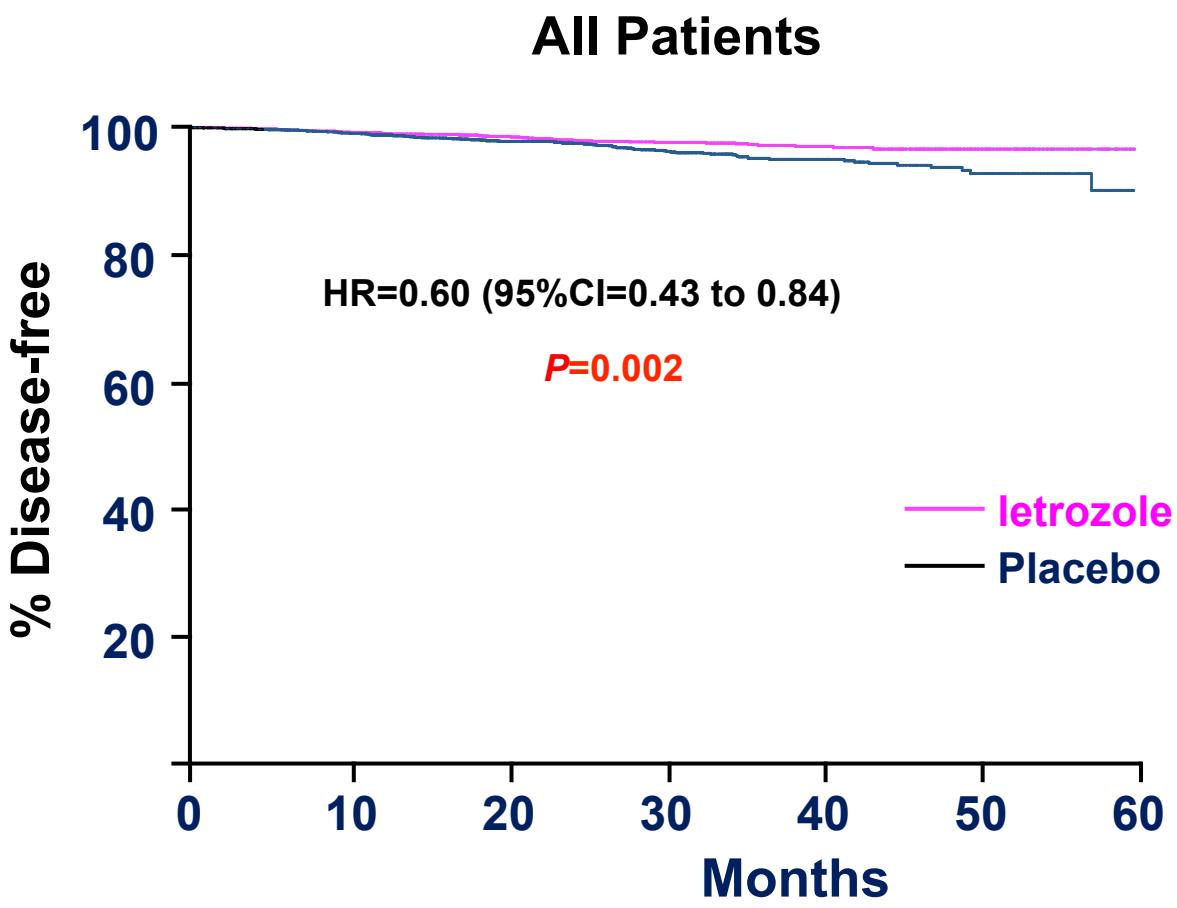
Median follow-up 2.5 years

Goss PE et al. JNCI 2005; 97: 1262-1271

MA.17 TRIAL

DISTANT DFS

LETROZOLE SIGNIFICANTLY REDUCED THE RISK OF DISTANT METASTASES BY 40%



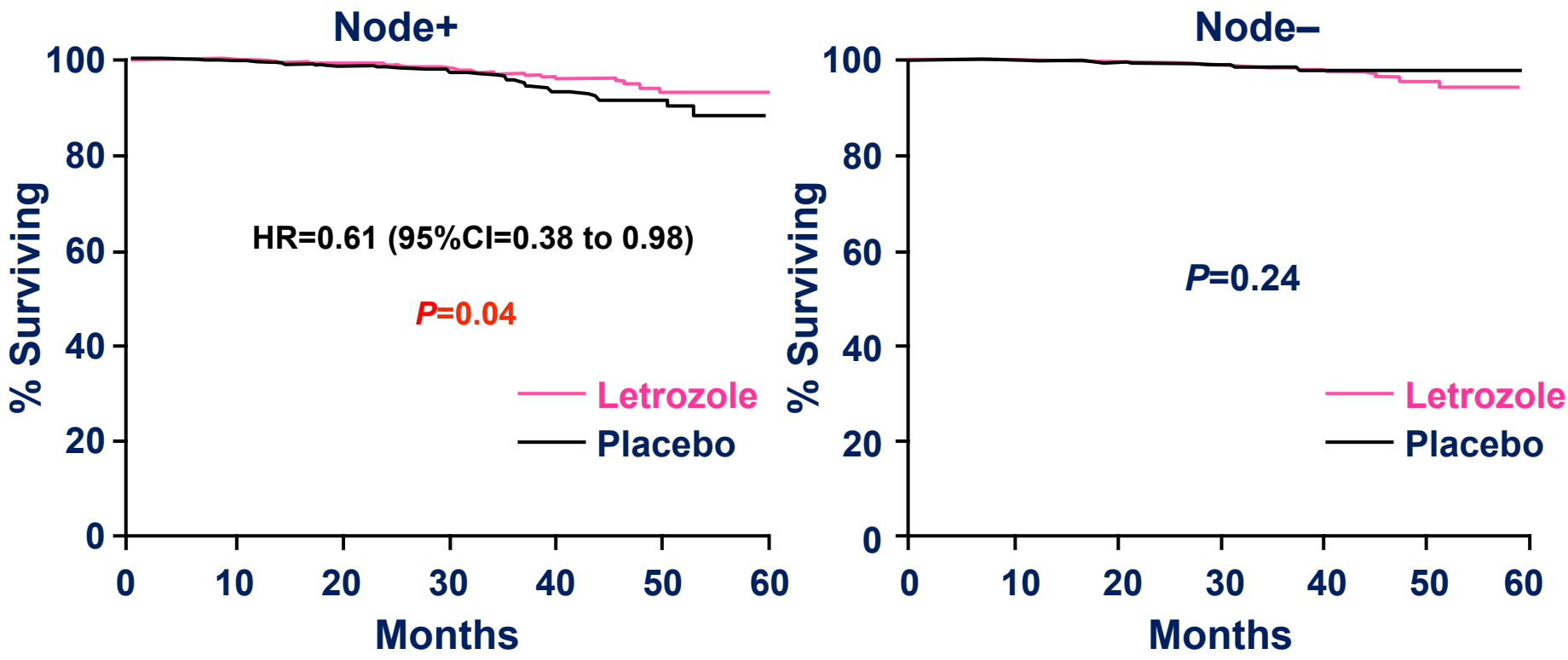
No. at risk (Letrozole)	2583	2497	1905	1110	541	176	6
No. at risk (Placebo)	2587	2489	1874	1075	519	164	8

Goss PE et al. JNCI, 2005; 97: 1262-1271

MA.17 TRIAL

OVERALL SURVIVAL

LETROZOLE DECREASED MORTALITY BY 39% IN NODE-POSITIVE PATIENTS



No. at risk:

letrozole	1171	1144	875	508	255	81	3
Placebo	1189	1157	877	500	243	75	3

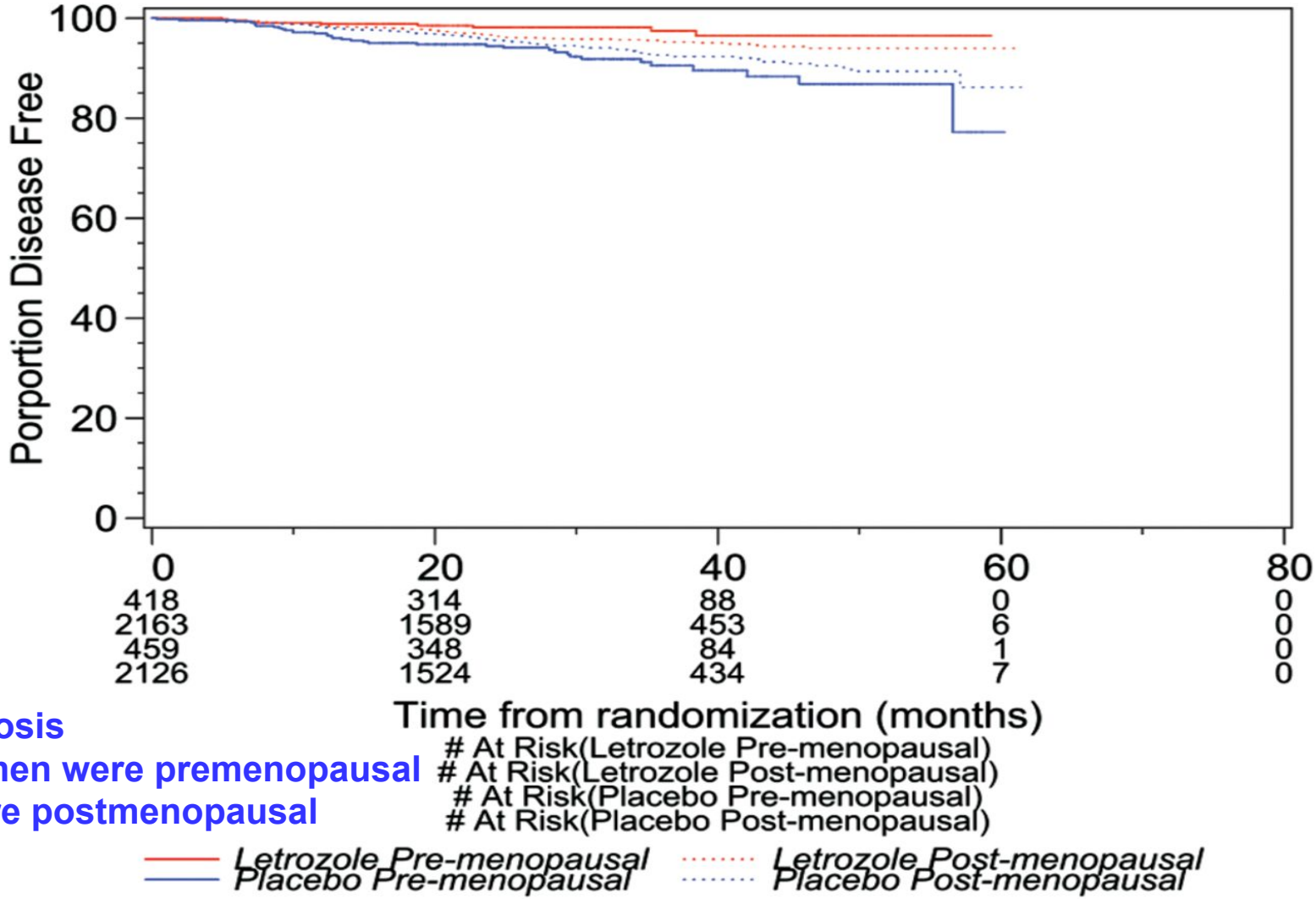
1292	1265	972	572	275	93	3
1276	1250	964	571	283	93	5

While OS was not improved in node-negative patients, a similar reduction in local recurrences, new primaries, and distant recurrences occurred as in the node-positive patients

Goss PE et al. JNCI 2005; 97: 1262-1271

MA.17 TRIAL

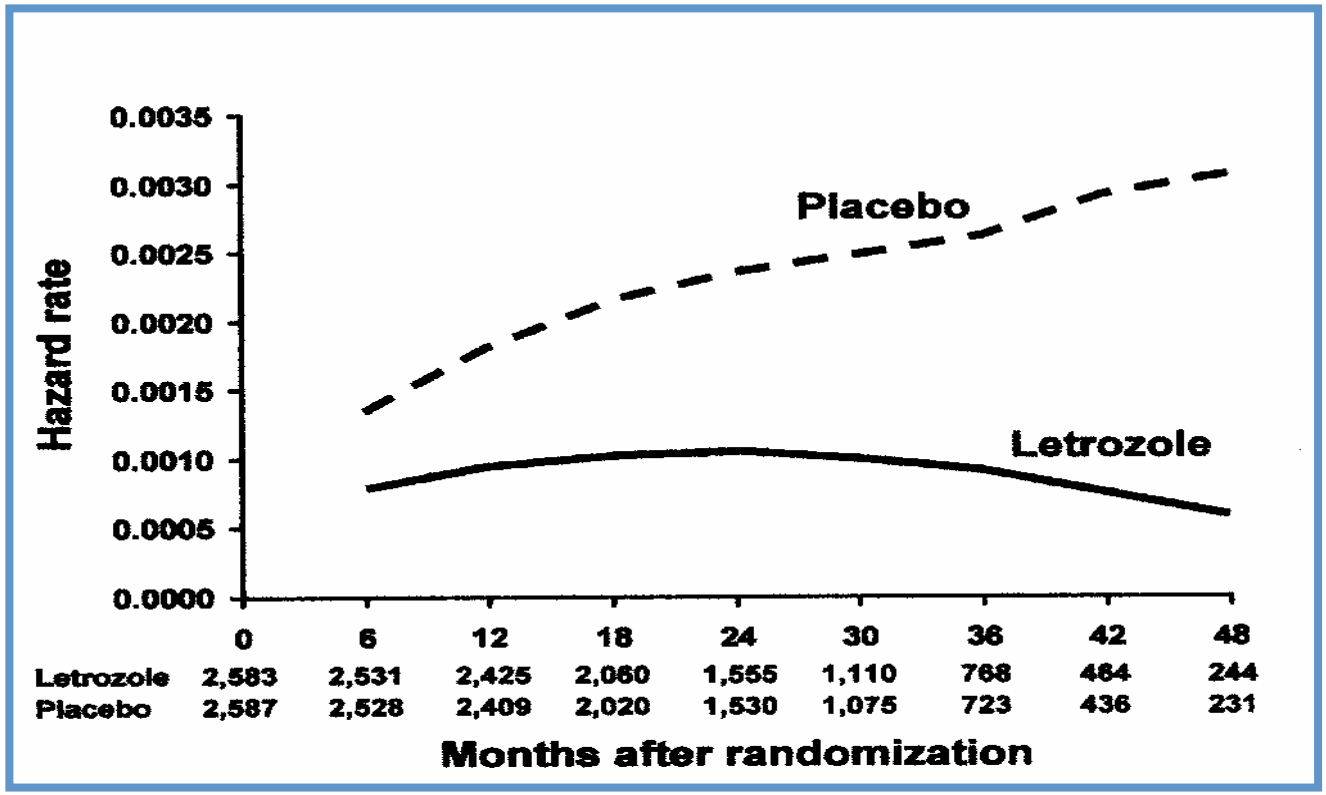
Kaplan–Meier curves for DFS by treatment and menopausal status



At diagnosis
877 women were premenopausal
4289 were postmenopausal

Goss P E et al. Ann Oncol, 2013;24:355-361

HAZARD RATES FOR EVENTS IN DFS FOR PATIENTS RANDOMIZED IN TRIAL MA.17



- Curves continue to diverge over time
- Risk of recurrence on placebo increased over time – 3% in year 9

Ingle et al. BCRT 2006;99:295-300

EXTENDED THERAPY WITH AI

SUMMARY OF TRIAL RESULTS

STUDY	No. pts	RX	FU months	HR recurrence (95% CI)	Abs diff.
MA17 Phase III double-blind placebo-controlled JNCI 05	5187	Tam x 5->Plac x 5 Tam x 5->Let x 5	64	ITT 0.68 (0.56-0.83) p<.001	4.0%
NSABP B33* Phase III double-blind placebo-controlled JCO 08	1598	Tam x 5->Plac x5 Tam x 5->Exe x 5	30	4-year DFS 0.68 p=.07	2%
ABCSG 6a Phase III open label JNCI 07	856	Tam x 5->no treat Tam x 5->Ana x 3	62.3	0.62 (0.40-0.96) p<.031	4.7%

*The trial was closed to accrual early following the publication of MA.17 trial results

ONGOING STUDIES TO ESTABLISH OPTIMAL DURATION OF AI THERAPY

~20,000 pts will be studied

- **NSABP B42**
  - Letrozole 5y vs placebo;
    N = 3,800
- **SALSA**
  - Anastrozole 2y vs 5y;
    N = 3,500
- **SOLE**
  - Letrozole 5y continuous vs intermittent
    N=4,800
- **Dutch**
  - Anastrozole 3y vs 6y;
    N = 1,800
- **GIM4**
  - Letrozole 2y vs letrozole 5y;
    N = 4,000

FIRST TRIALS EVALUATING EXTENDED TAMOXIFEN IN THE ADJUVANT SETTING

ECOG trial

indefinite tamoxifen vs 5 years

194 patients

- suggestion that tamoxifen continuation **may be better**

SCOTTISH trial

indefinite vs 5 years

342 patients

- indefinite tamoxifen was **worse**

NSABP B-14 trial

re-randomization to additional 5 years

1152 patients

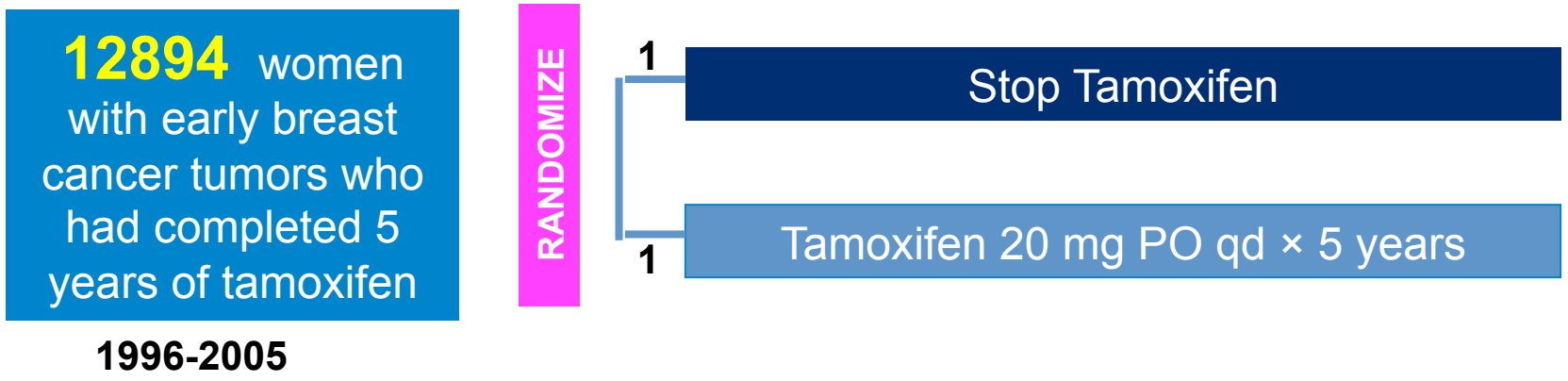
- indefinite tamoxifen was **worse**

TOTAL NUMBER OF ENROLLED PATIENTS: 1,688

Tormey et al. JNCI 2001; Stewart et al. JNCI 2001; Fisher et al. JNCI 2001

ATLAS TRIAL

Adjuvant Tamoxifen Longer Against Shorter



6846 women with ER-positive disease included in analyses of main effects on recurrence and breast cancer mortality

Side-effects among all women with positive,negative, or unknown ER status

ATLAS TRIAL

PATIENT DEMOGRAPHICS

6846 women with ER-positive disease

Geographical distribution:

25% Asia/mid-East, **28%** Latin America,**47%** **Europe/US/ANZ/South Africa**

Nodal status:

53% **node-negative**, **27%** N 1-3, **16%** N4 or more, **4%** unknown

T size:

48% **1-20mm**, **38%** 20-50mm, **7%** >50mm, **6%** unknown

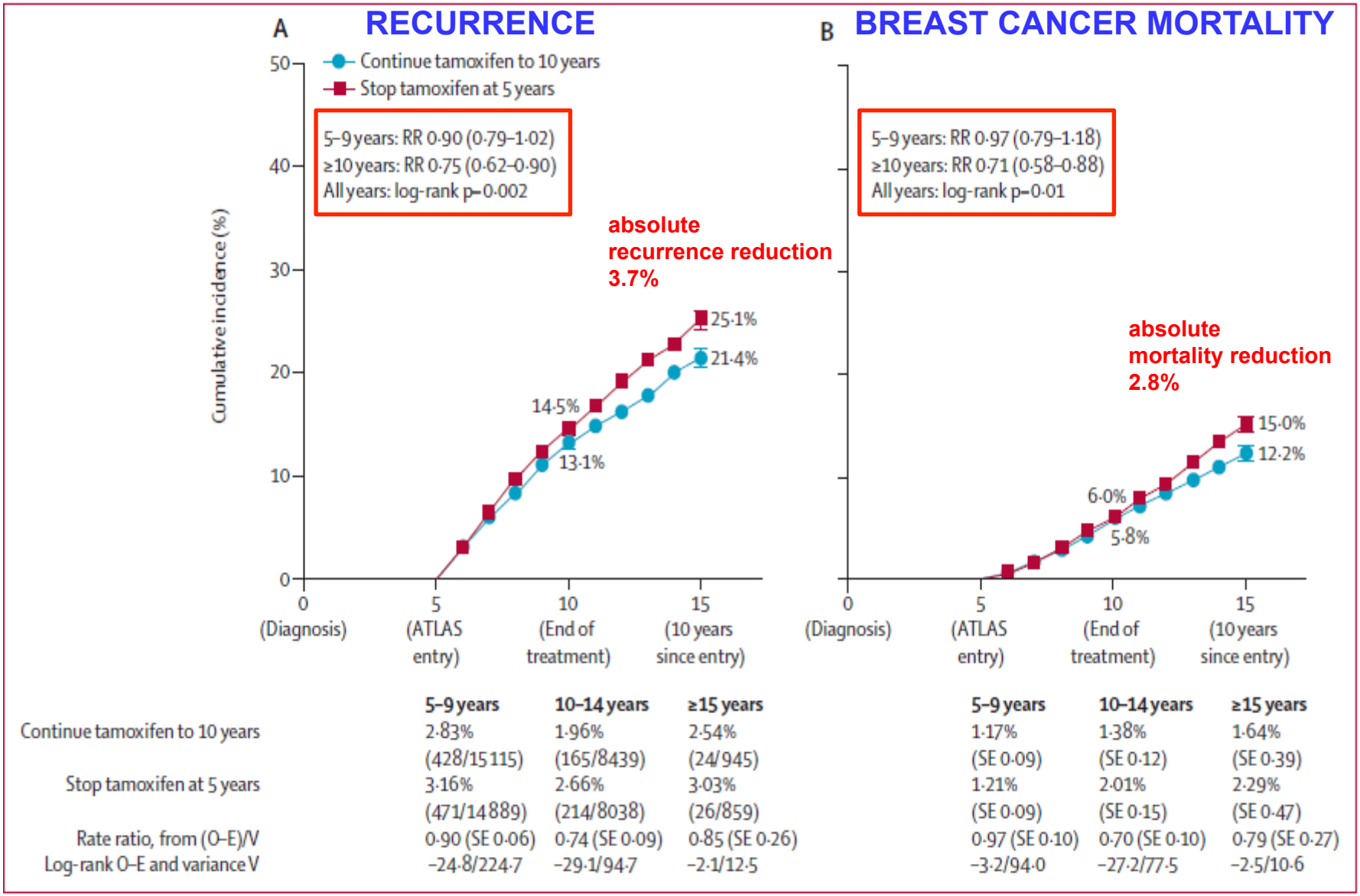
Menopausal status:

89% **postmenopausal** ,**9%** premenopausal, **2%** perimenopausal or unknown

7.6 yrs follow-up: compliance, recurrence, death

Davies C et al. Lancet, 2013; 381:805-916

ATLAS TRIAL



	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	−24·8/224·7	−29·1/94·7	−2·1/12·5	−3·2/94·0	−27·2/77·5	−2·5/10·6

Davies C et al. Lancet 2013; 381: 806-816

ER-POSITIVE DISEASE
5 YRS TAMOXIFEN *vs* 0, AND 10 YRS *vs* 5 YRS
EVENT RATE RATIOS (95%CIs), BY TIME PERIOD FROM DIAGNOSIS

	A: effects in meta-analyses of the trials of 5 years of tamoxifen *vs* none[1] (n=10 645)	B: effects in the ATLAS trial of continuing tamoxifen to 10 years *vs* stopping at 5 years (n=6846)	C: estimated effects in a trial of 10 years of tamoxifen *vs* none (product of A and B)
Recurrence			
0–4 years	0·53 (0·48–0·57)*	1	0·53 (0·48–0·57)*
5–9 years	0·68 (0·60–0·78)*	0·90 (0·79–1·02)	0·61 (0·51–0·73)*
≥10 years	0·94 (0·79–1·12)	0·75 (0·62–0·90)†	0·70 (0·54–0·91)†
Breast cancer mortality			
0–4 years	0·71 (0·62–0·80)*	1	0·71 (0·62–0·80)*
5–9 years	0·66 (0·58–0·75)*	0·97 (0·79–1·18)	0·64 (0·50–0·82)‡
≥10 years	0·73 (0·62–0·86)‡	0·71 (0·58–0·88)§	0·52 (0·40–0·68)*

(A) Trials of 5 years of tamoxifen (n=10 645; ~80% complied). (B) ATLAS trial of 10 years *vs* 5 years of tamoxifen (n=6846; ~80% difference in tamoxifen use [figure 2]). (C) Hypothetical trial of 10 years of tamoxifen *vs* none (with ~80% compliance). Two-sided p values in this table relate to particular time periods; values elsewhere combine all time periods. ER=oestrogen receptor. *p<0·00001. †p<0·01. ‡p=0·0001. §p=0·0016.

10 yrs tam. reduces breast cancer mortality by a third in first decade & half in second decade

Davies C et al. Lancet 2013; 381: 806-816

ATLAS TRIAL
RESULTS

RECURRENCE: 617 vs 711 women (2p=0.002)

BREAST CANCER MORTALITY: 331 vs 397 (2p=0.01)

OVERALL MORTALITY: 639 vs 722 (2p=0.01)

Recurrence and breast cancer mortality:
little effect during years 5-9
benefit mainly after year 10

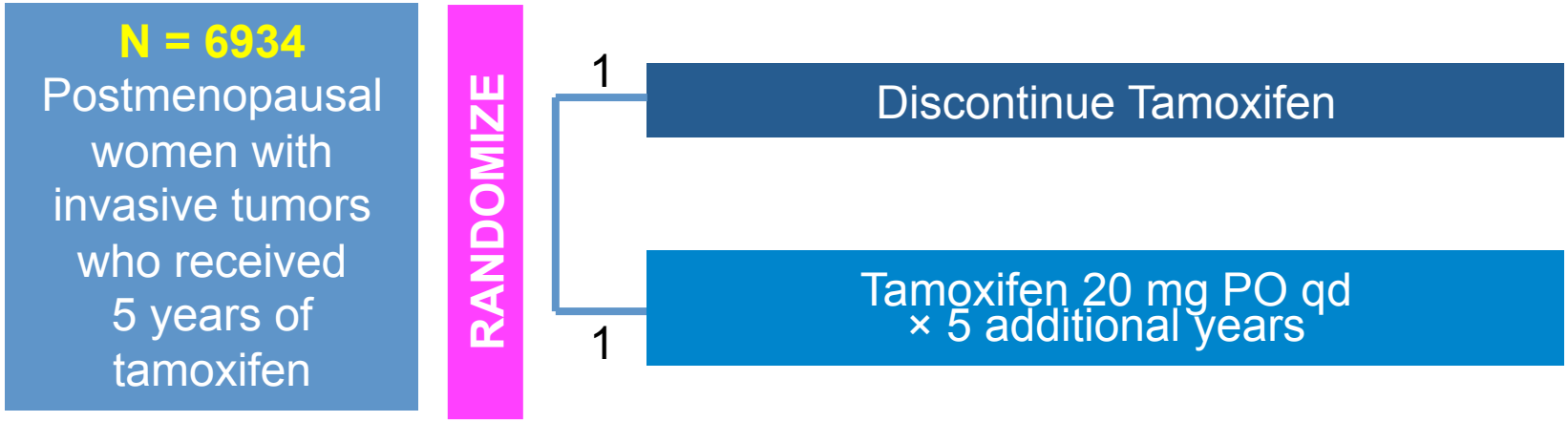
Cumulative risk of endometrial cancer during years 5-14 was:
3.1% (mortality 0.4%) for women allocated to continue tamoxifen vs
1.6% (mortality 0.2%) for controls

SIDE EFFECTS AND MAIN EFFECTS OF 10 YRS TAMOXIFEN ON 15-YR MORTALITY IN META-ANALYSIS AND ATLAS TRIAL

	5 yrs tam *vs* 0 meta-analysis	10 yrs tam *vs* 5 ATLAS trial	10 yrs tam *vs* 0 (by addition)
Endometrial cancer & PE mortality	0.2% loss	0.2% loss	0.4% loss
Breast cancer mortality	9% gain	3% gain	12% gain

Estimated effects of 10 yrs tamoxifen *vs* 0 on 15-yr mortality: absolute gain ~30 x absolute loss

aTTom TRIAL
Adjuvant Tamoxifen To Offer More

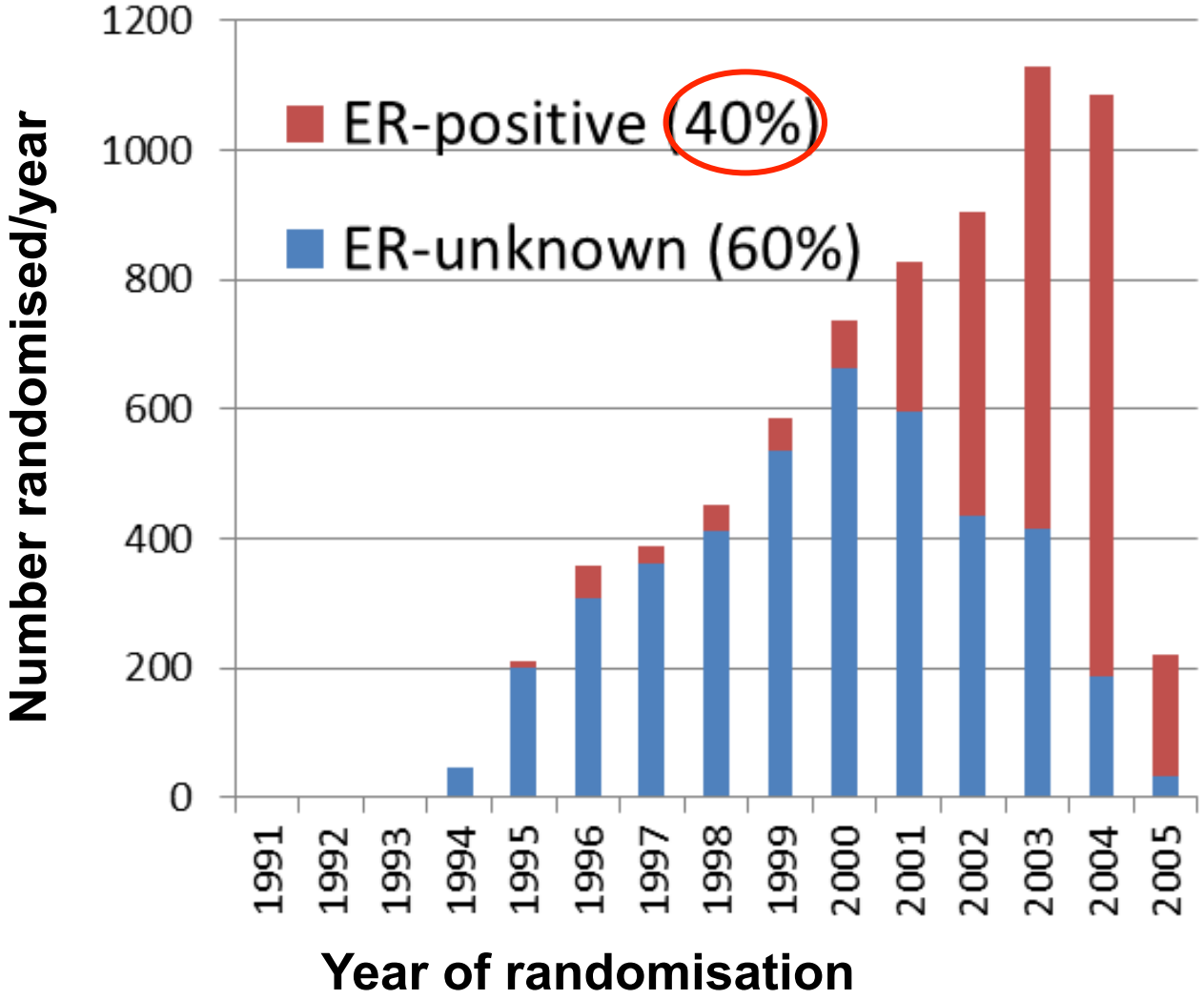


OBJECTIVES of aTTom (with its international counterpart ATLAS):

- **Randomise at least 20,000 women between 10 and 5 years of tamoxifen (to reliably detect, or reliably refute, a 2-3% improvement in survival)**
- **Follow-up randomised women for at least 15 years (because 10 or more years is needed to see full benefits from longer tamoxifen*)**

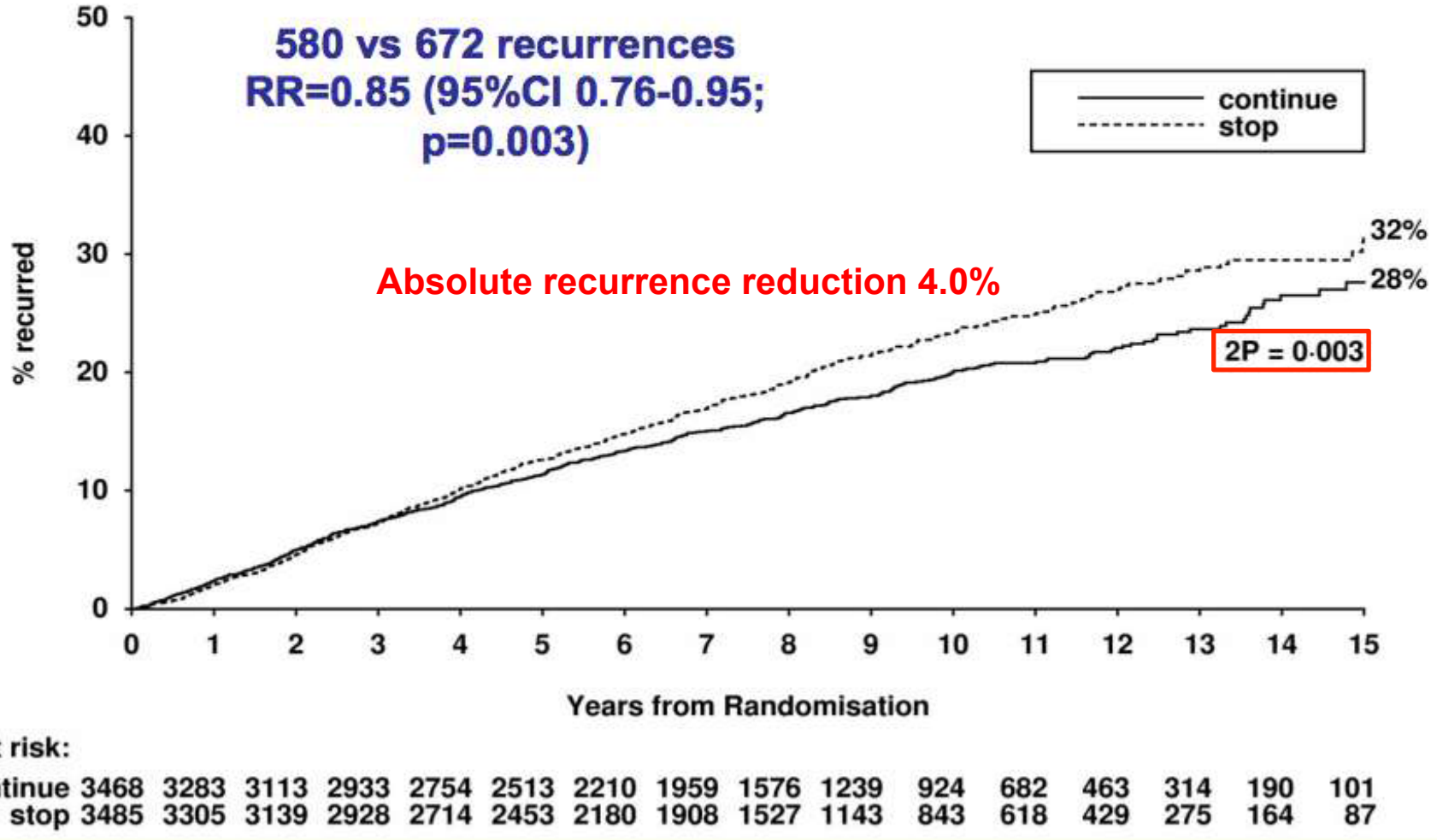
Peto R, Five Years of Tamoxifen – or More? JNCI 1996

aTTom - RECRUITMENT BY ER STATUS



Courtesy of R. Gray

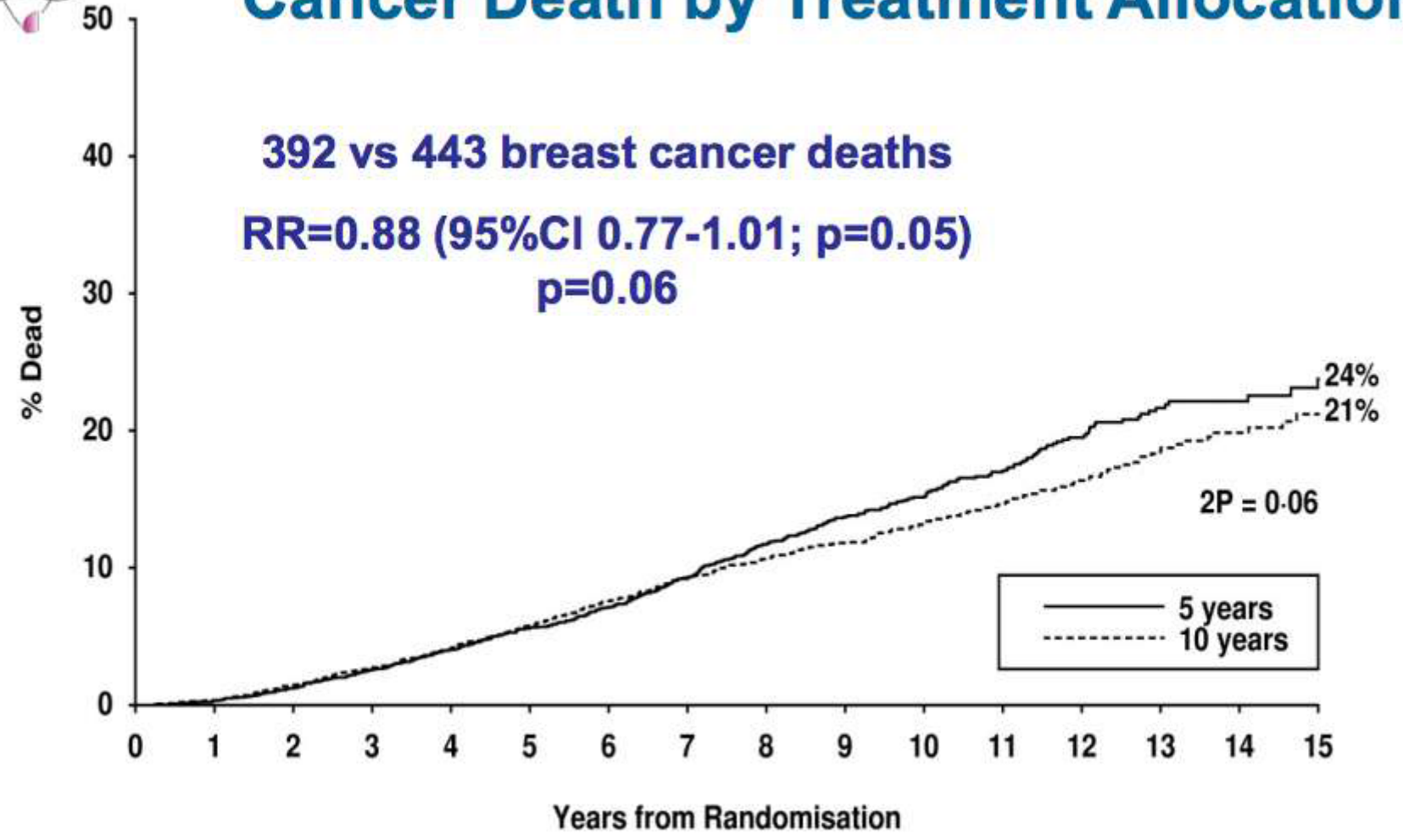
10 vs 5 Years of Tamoxifen: Recurrence by Treatment Allocation



10 vs 5 years of Tamoxifen: Breast Cancer Death by Treatment Allocation

392 vs 443 breast cancer deaths

RR=0.88 (95%CI 0.77-1.01; p=0.05)
p=0.06



At risk:

5 years	3485	3399	3293	3145	2981	2748	2482	2206	1785	1347	1013	743	520	334	207	116
10 years	3468	3384	3275	3143	2972	2753	2474	2207	1804	1419	1066	794	551	369	226	130

aTTom TRIAL
RESULTS

RECURRENCE: 580 vs 672 women (2p=0.003)

BREAST CANCER MORTALITY: 404 vs 452 (2p=0.06)

OVERALL MORTALITY: 885 vs 939 (2p=0.2)

Recurrence and breast cancer mortality:
little effect during years 5-9;
benefit mainly after year 10

aTTom TRIAL

MAIN RISK: ENDOMETRIAL CANCERS:

Absolute hazard 0.5%

	10 years	5 years	Rate ratio (95%CI)	P-value
Endometrial cancers	102 (2.9%)	45 (1.3%)	2.20 (1.31-2.34)	p<0.0001
Endometrial cancer death	37 (1.1%)	20 (0.6%)	1.83 (1.09-3.09)	p=0.02

Gray R, et al. J Clin Oncol. 2013;31 (suppl; abstract 5)

ER+ 10 yrs vs 5 yrs BREAST CANCER MORTALITY rate ratio* by period in aTTom and ATLAS

	10 yrs tam vs 5 aTTom (n=6934 ER+/UK)	10 yrs vs 5: ATLAS * (n=10543 ER+/UK)	10 yrs vs 5: aTTom & ATLAS combined (n=17477 ER+/UK)
years 5-9	**1.08** (0.85-1.38)	**0.92** (0.77-1.09)	**0.97** (0.84-1.15)
years 10+	**0.75**† (0.63-0.90)	**0.75**§ (0.63-0.90)	**0.75**† (0.65-0.86)
All years	**0.88**‡ (0.74-1.03)	**0.83**‡ (0.73-0.94)	**0.85**‡ (0.77-0.94)
	†p=0.007 ‡p=0.1	§p=0.002 ‡p=0.004	†p=0.00004 ‡p=0.001

*Inverse−variance−weighted estimate of the effect in ER+.(ATLAS, *Lancet* 2013)

ER+ 10 yrs vs 5 years OVERALL SURVIVAL
Rate ratio* by period in aTTom and ATLAS

	10 yrs tam. Vs 5: aTTom & ATLAS combined (n17477 ER+/unknown)
years 5-9	**0.99** (0.89-1.10)
years 10+	**0.84ł** (0.77-0.93)
All years	**0.91‡** (0.84-0.97)

ł p=0.0007
‡p=0.008

* Inverse-variance -weighted estimate of the effect in ER+ (Atlas, Lancet 2013)

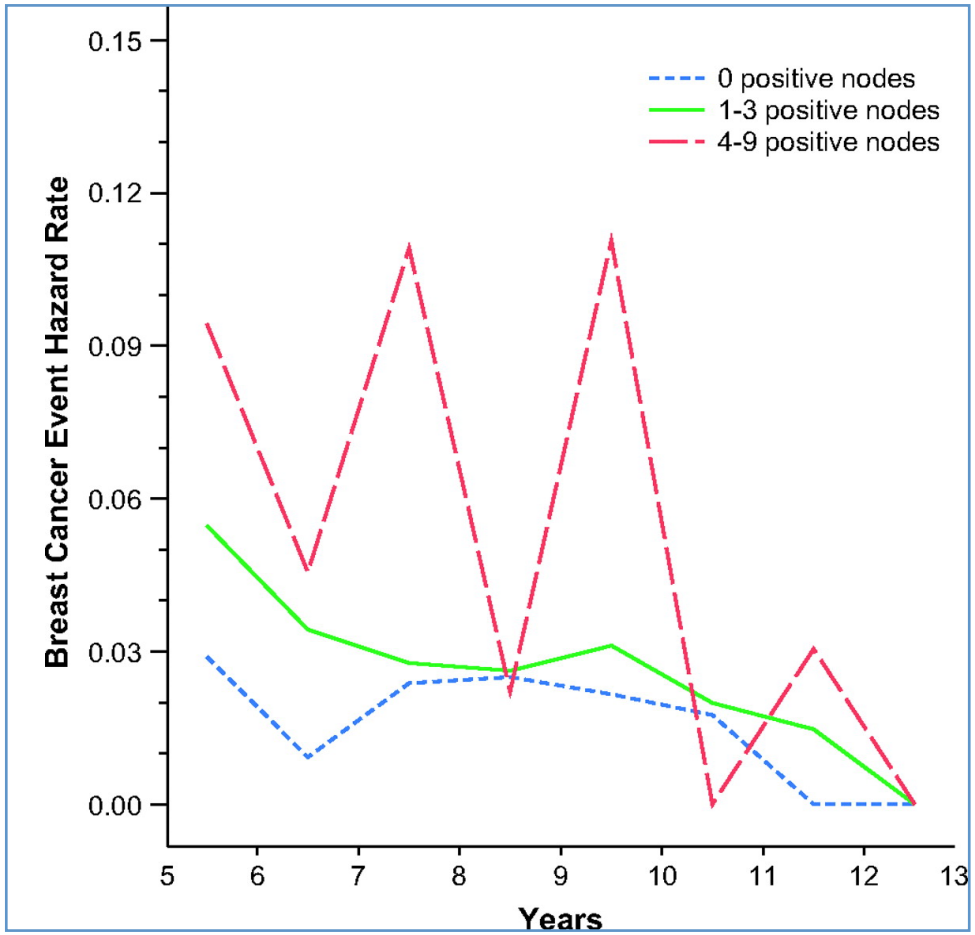
HOW CAN WE IDENTIFY PATIENTS AT HIGH RISK OF RECURRENCE BEYOND 5 YEARS?

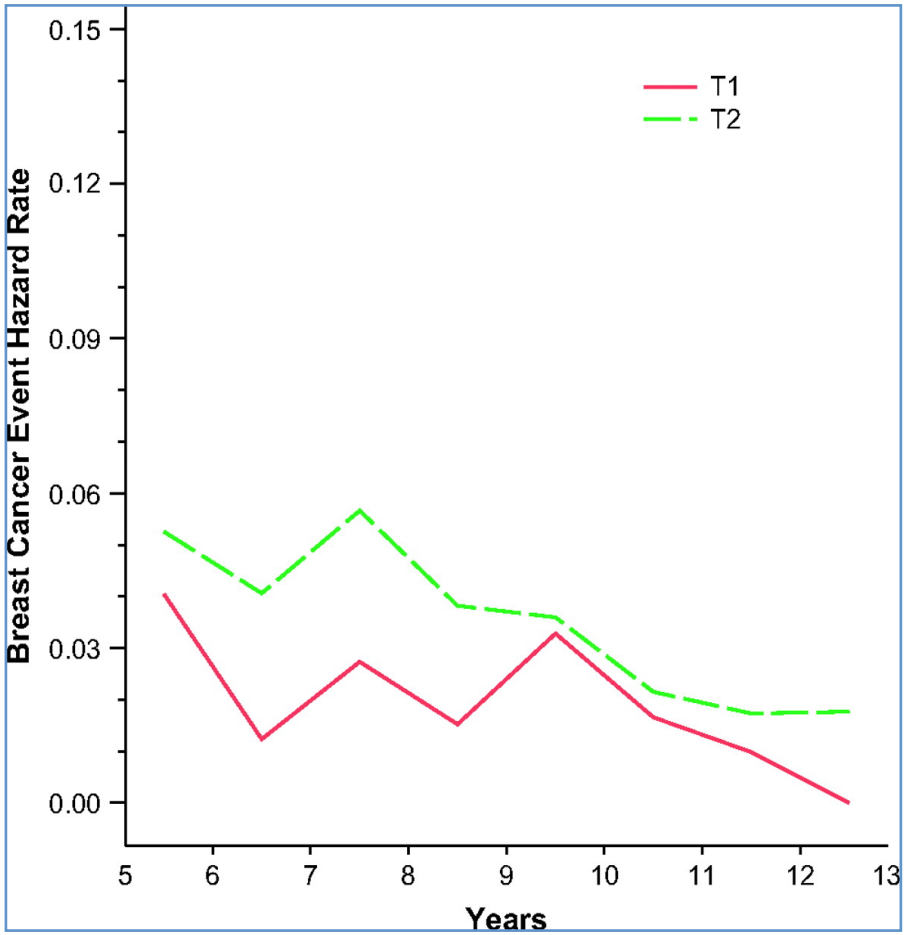
TUMOR BURDEN

STAGE MATTERS
FOR EARLY AND LATE RECURRENCE

BREAST CANCER EVENT HAZARD RATES YEARS 5 TO 13 AFTER DIAGNOSIS

1,086 postmenopausal women, stage I-IIIA BC, tamoxifen treated for 5 years and disease free
median age 64 yrs, ER+ 83%, ER unknown 17% N+ 53%, BCS and RT 51%, adjuvant CT 22%

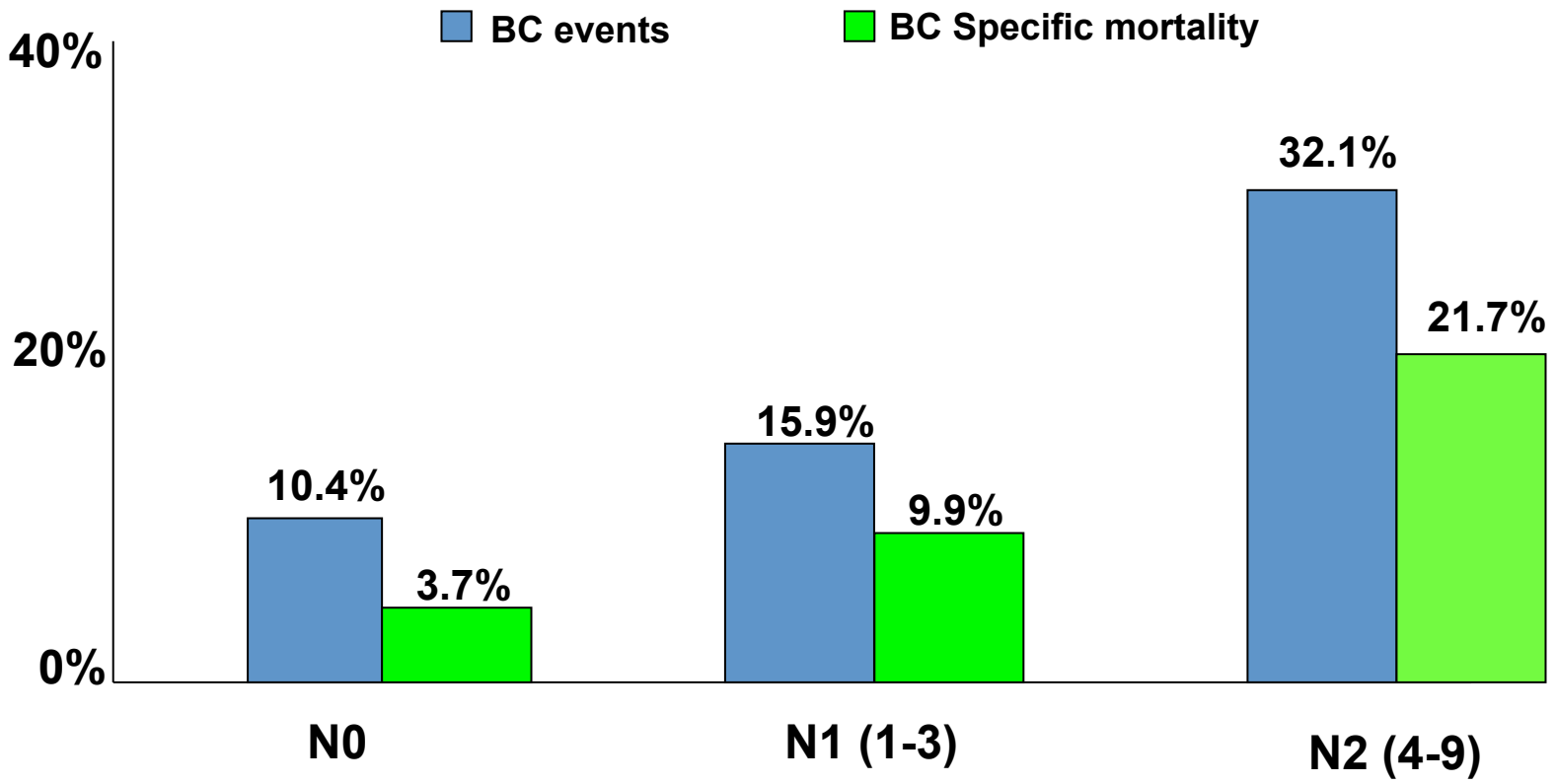




Median follow-up **10.5 yrs**

Konnecke HF et al. Ann Oncol 2007;18:45-51

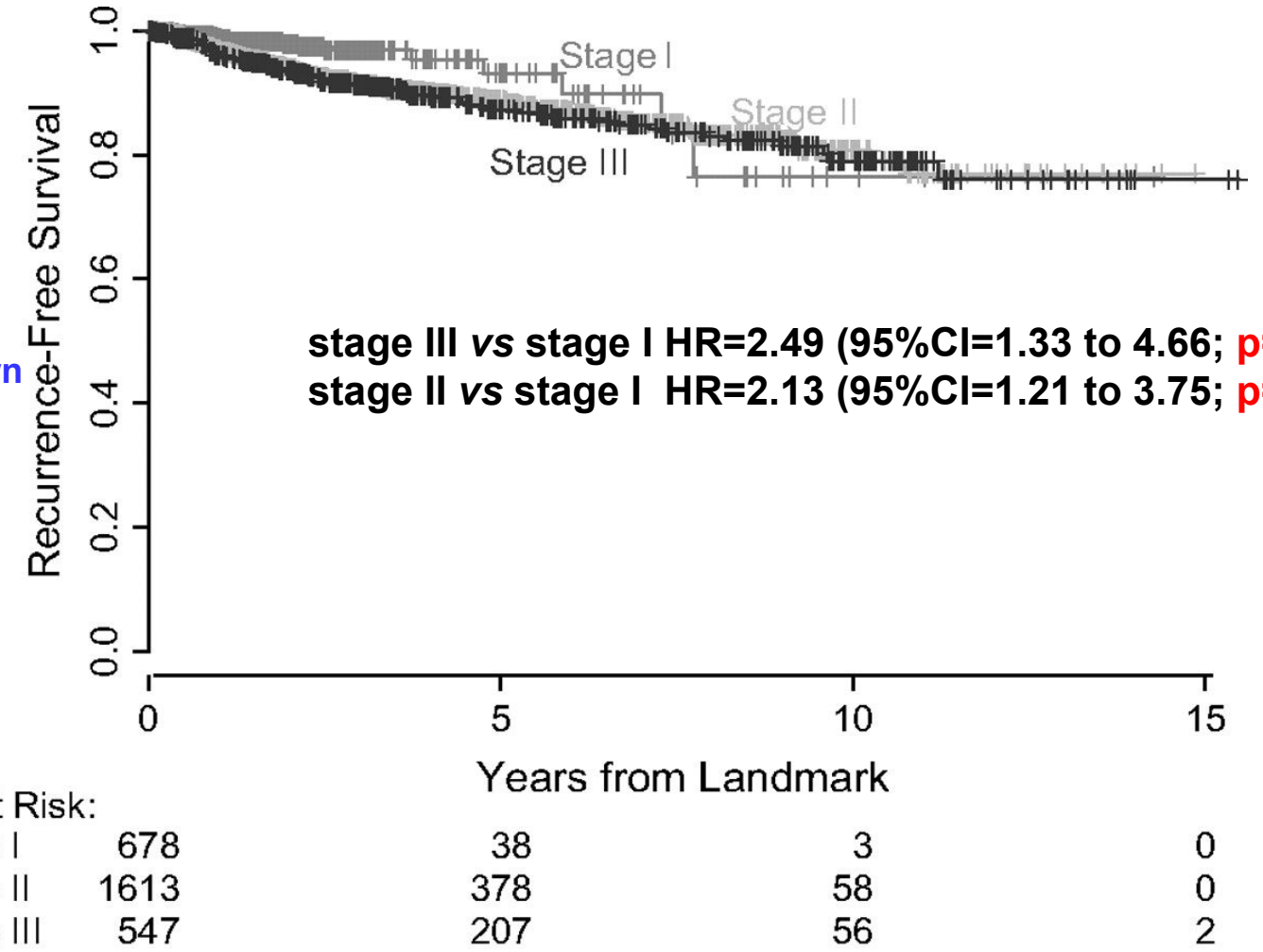
KAPLAN-MEIER BREAST CANCER-SPECIFIC MORTALITY AND EVENT RATES AT 10 YEARS FOLLOWING 5 YEARS OF TAMOXIFEN ACCORDING TO NODAL STAGE



Konnecke HF, *et al.* Ann Oncol 2007,18:45

KAPLAN–MEIER ANALYSIS OF RESIDUAL RECURRENCE-FREE SURVIVAL ACCORDING TO STAGE AT DIAGNOSIS

2838 pre and postmenopausal patients with Stage I-III BC HR+,HR- & unknown



stage III *vs* stage I HR=2.49 (95%CI=1.33 to 4.66; p=.004)
stage II *vs* stage I HR=2.13 (95%CI=1.21 to 3.75; p=.009)

Residual recurrence-free survival calculated from the landmark of 5 years from the start of adjuvant or neoadjuvant systemic therapy to the date of first disease recurrence or last follow-up

Brewster A M et al. JNCI 2008;100:1179-1183

TUMOR BIOLOGY

- **How do tumor subtypes (luminal A vs B) affect rates?**

  - Can gene expression profiling help us here?

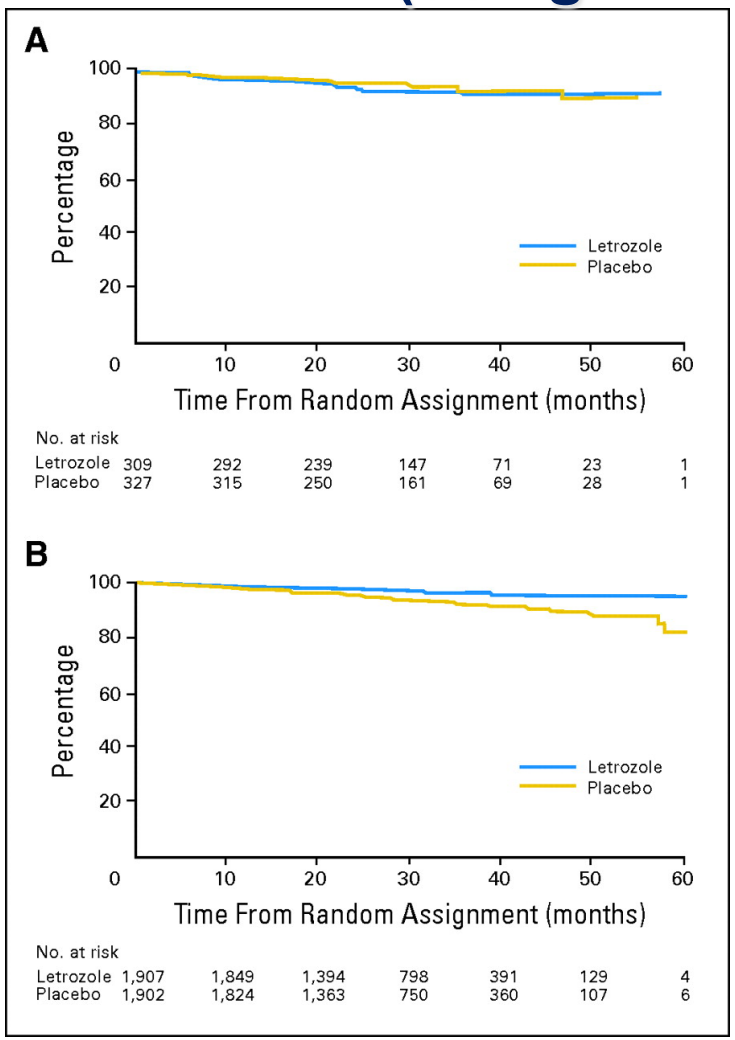
- **How can we better understand tumor dormancy and endocrine resistance mechanisms?**

EXTENDED ADJUVANT THERAPY IS BENEFICIAL IN LUMINAL A CANCERS

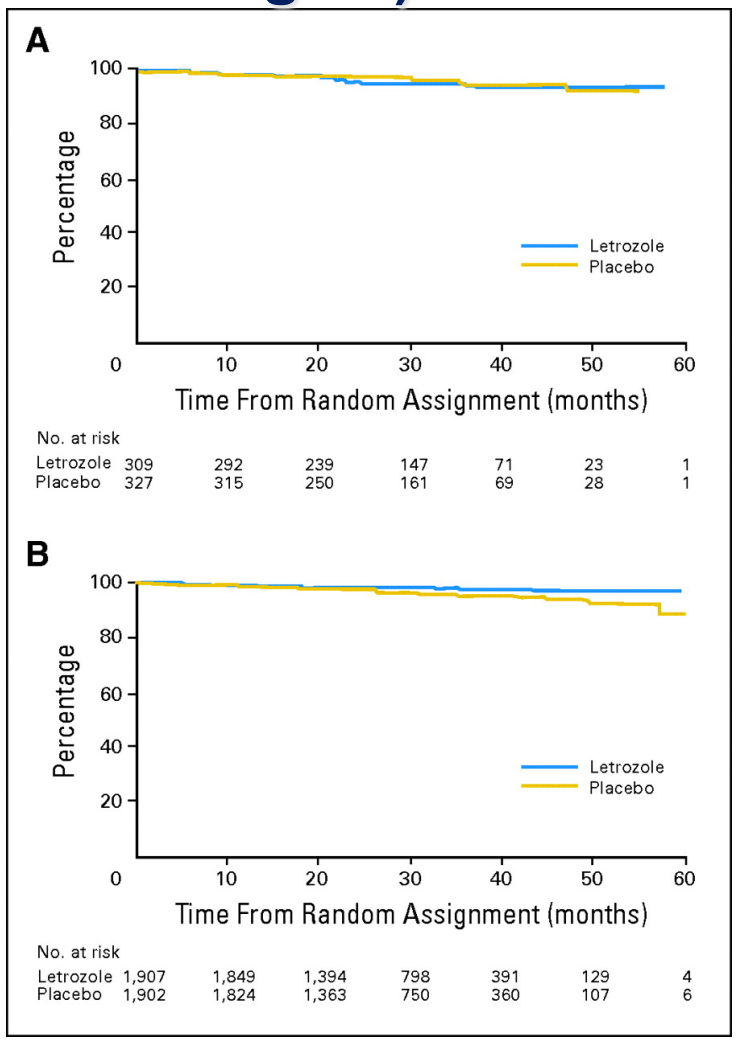
(using PR as a surrogate)

ER+PR-

ER+PR+



Disease free survival



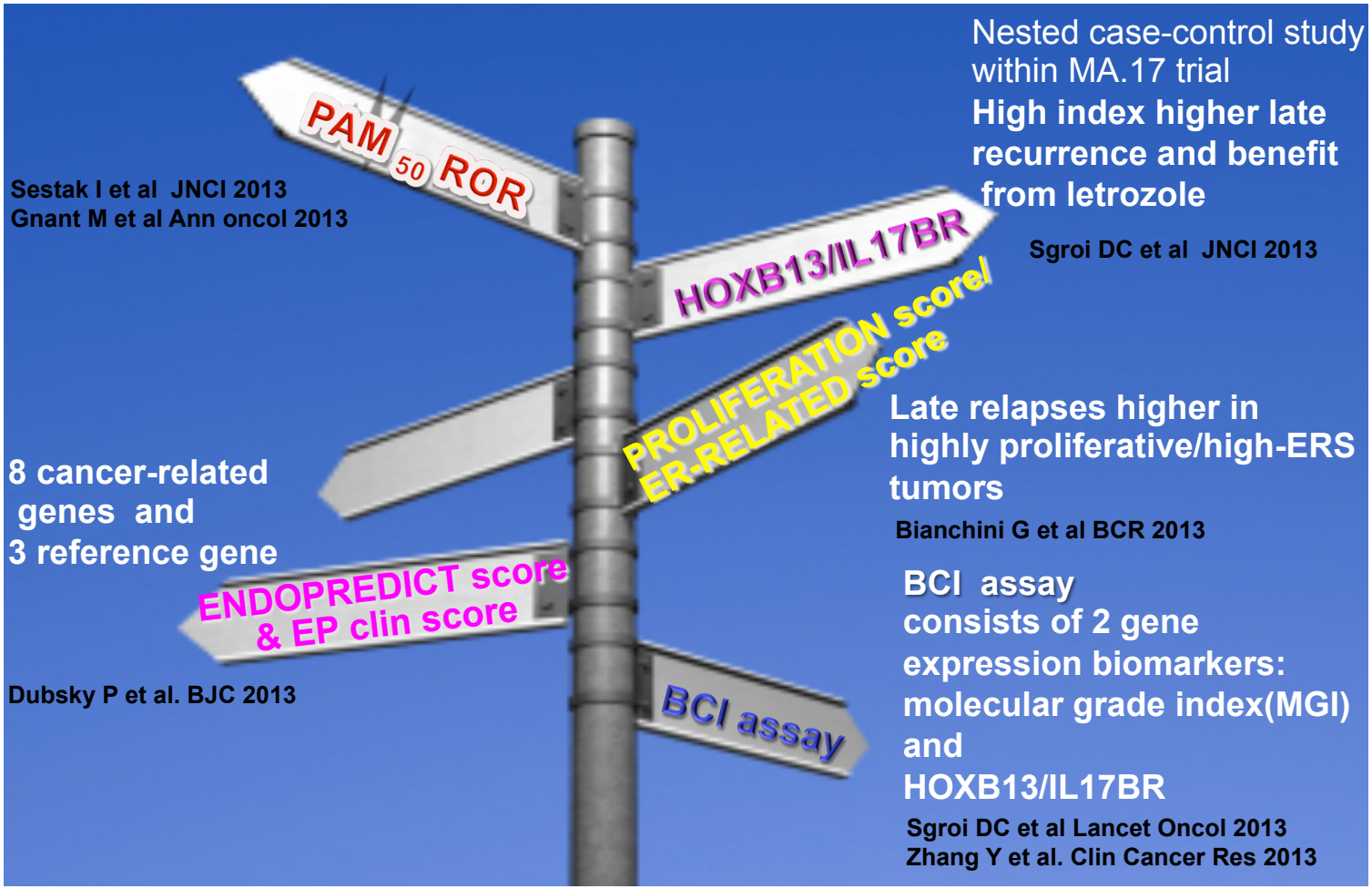
Distant disease free survival

LUMINAL B

LUMINAL A

Goss P et al. J Clin Oncol 2007;25:2006-2011

WHICH GENE EXPRESSION PROFILE FOR LATE RECURRENCE?



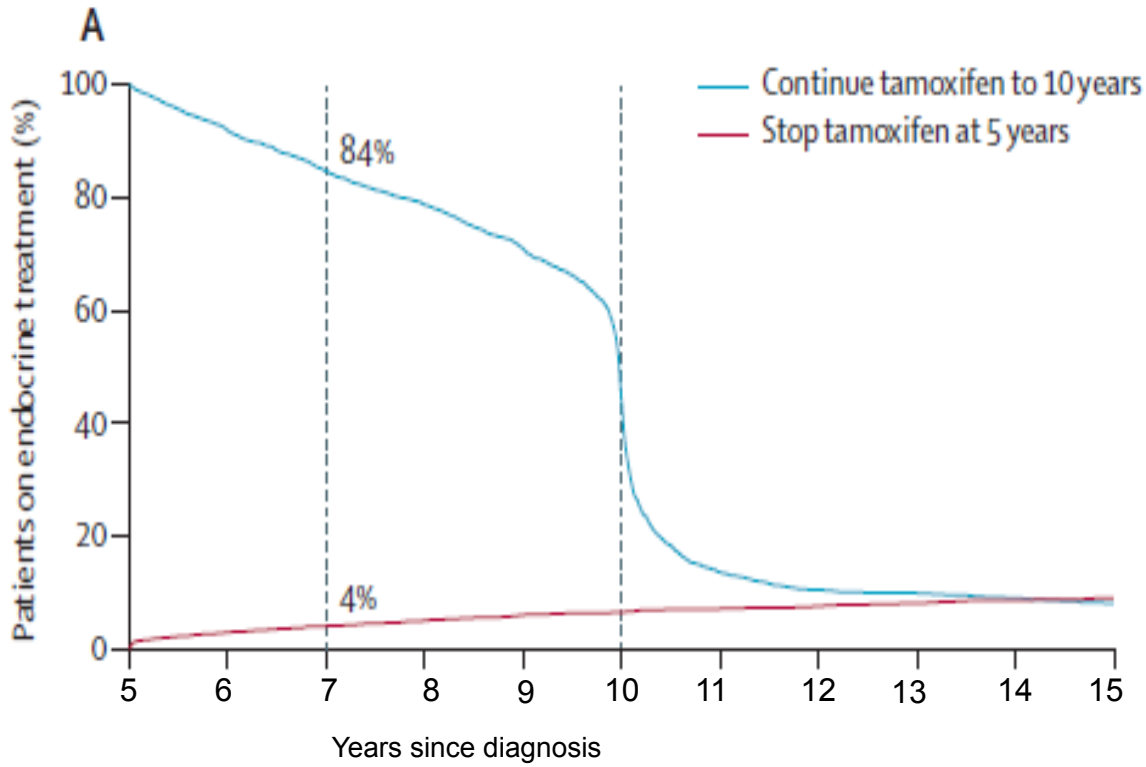
The majority of studies retrospectively analyzed archived samples from prospective trials of endocrine therapy for 5 years in postmenopausal women, node-negative, not treated with chemotherapy

CO-MORBIDITY AND AGE

(PROJECTED SURVIVAL)

ATLAS TREATMENT COMPLIANCE

2 years after randomization



Davies C et al. Lancet 2013; 381: 806-816

COMPLIANCE TO ADJUVANT HORMONAL THERAPY

- Compliance outside trials is not strong even for initial endocrine therapy (tamoxifen/AI)
  - A systematic review of 29 studies of adjuvant endocrine therapy showed: prevalence of adherence **from 41 to 72%** and discontinuation **from 31 to 73%** at the end of 5 years of treatment (Murphy CC et al. BCRT 2012)

  - In a prospective open-label phase-III trial comparing 2.5 with 5 years of extended adjuvant letrozole (IDEAL trial) in 1215 patients at 2.5 years overall non-compliance probability was **18.4%**(Fontein DBY et al. EJSO 2012)

- ATLAS conditions on women who have been compliant for 5 years so would be expected to be more compliant than those in the first 5 years

HAZARD RATIO IMPROVEMENT

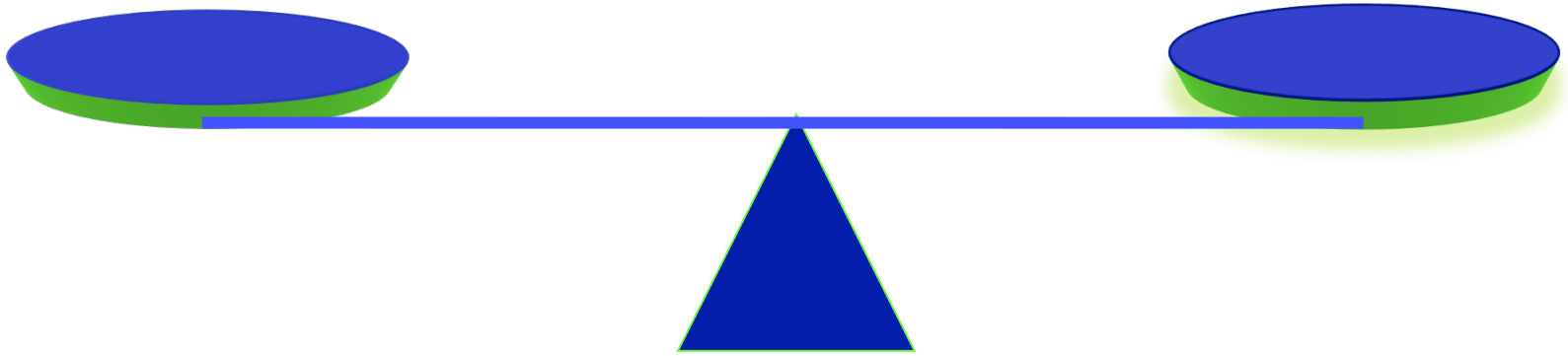
is not informative without taking into account

ABSOLUTE BASELINE RISKS

PERSONALIZED RISKS

ADVERSE EVENTS

ABSOLUTE BENEFITS



PATIENT PREFERENCE

EXTENDED ENDOCRINE THERAPY OPTIONS LARGELY DRIVEN BY MENOPAUSAL STATUS AND PRIOR TREATMENT

Options for postmenopausal women	Options for women with amenorrhea	Options for premenopausal women
Continue tamoxifen if contraindication, intolerance, or lack of availability of AI	Switch to AI after tamoxifen	Continue tamoxifen
Begin tamoxifen if completing 5 years of an AI (*indirect evidence)*	If continued ovarian function, continue tamoxifen	**Stop or take a break**
These data do not provide support for continuing AI beyond 5 years	**Stop or take a break**	
Stop or take a break		

Partridge A ASCO 2013