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Early reporting of efficacy endpoints and its potential impact: Clinical part

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EORTC Breast Group Chair

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

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learning to care

DISCLOSURES

Consultant/Ad Board:

Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Teva

RISKS OF EARLY STOPPING/REPORTING TRIALS

- **High probability of overestimation of the magnitude of treatment effect**
- **Moderate probability of underestimation of the magnitude of treatment effect (long natural history; e.g. RT effects in breast cancer)**
- **Repeated interim analyses at short intervals raise concern about data reliability**
- **Long-term benefits and long term toxicities unknown/partially known**
- **Lack of safety data if enrollment is stopped**
- **Impact of crossover on overall survival results, if allowed**
- **Influence on other ongoing trials**

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original article

Annals of Oncology 19: 1347–1353, 2008
doi:10.1093/annonc/mdn042
Published online 27 February 2008

Stopping a trial early in oncology: for patients or for industry?

F. Trotta[1], G. Apolone[2], S. Garattini[2] & G. Tafuri[1,3]*

[1]*Italian Medicines Agency (AIFA), Rome;* [2]*Mario Negri Institute for Pharmacological Research, Milan, Italy;* [3]*Utrecht University, Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands*

Between 1997-2007, 25 RCTs testing new anti-cancer drugs stopped early because of benefit at interim analysis

- Result of early report**: stop enrollment 48%**; disclosure of results 20%; crossover to treatment group 12%; crossover to treatment group+ stop enrolment: 12%
- Increase in > 50% of prematurely stopped trials from 2004 to 2007
- 3300 patients/events across all studies were spared
- More than 78% of the RCTs were registration trials

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JOURNAL OF CLINICAL ONCOLOGY

STATISTICS IN ONCOLOGY

Stopping or Reporting Early for Positive Results in Randomized Clinical Trials: The National Cancer Institute Cooperative Group Experience From 1990 to 2005

Edward L. Korn, Boris Freidlin, and Margaret Mooney

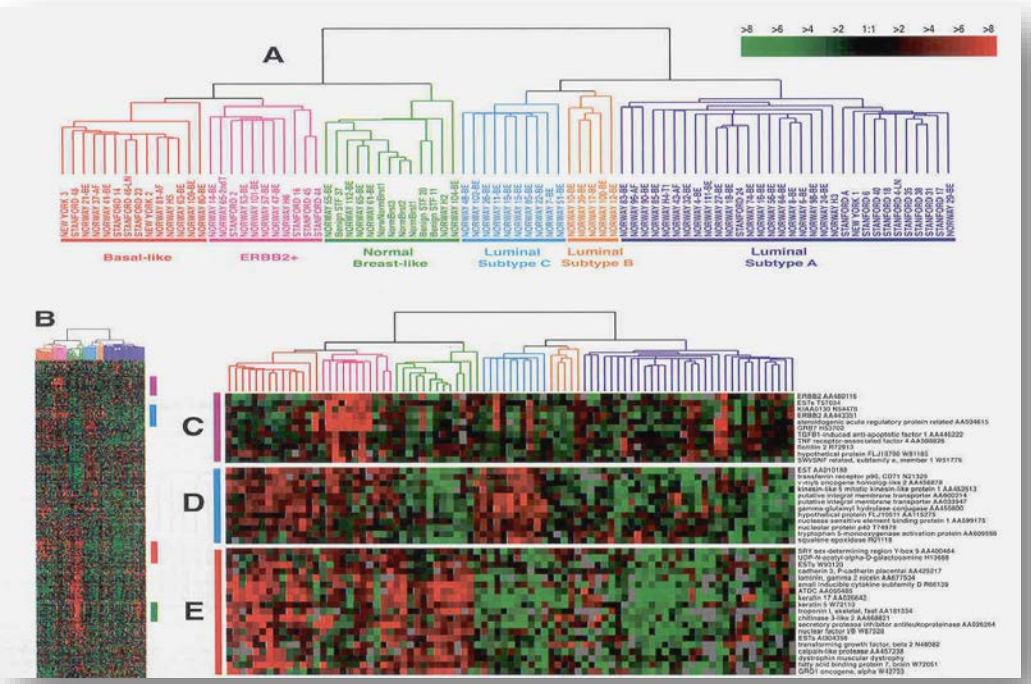
From 1990-2005, 27 studies from National Cancer Institute Cooperative Group Trials stopped early due to a positive result.

In 17 trials, the treatment effect at last FU was similar or slightly smaller than the one reported earlier.

Table 3. Latest OS Results for Trials in Table 2 Whose Primary End Point Was Not OS

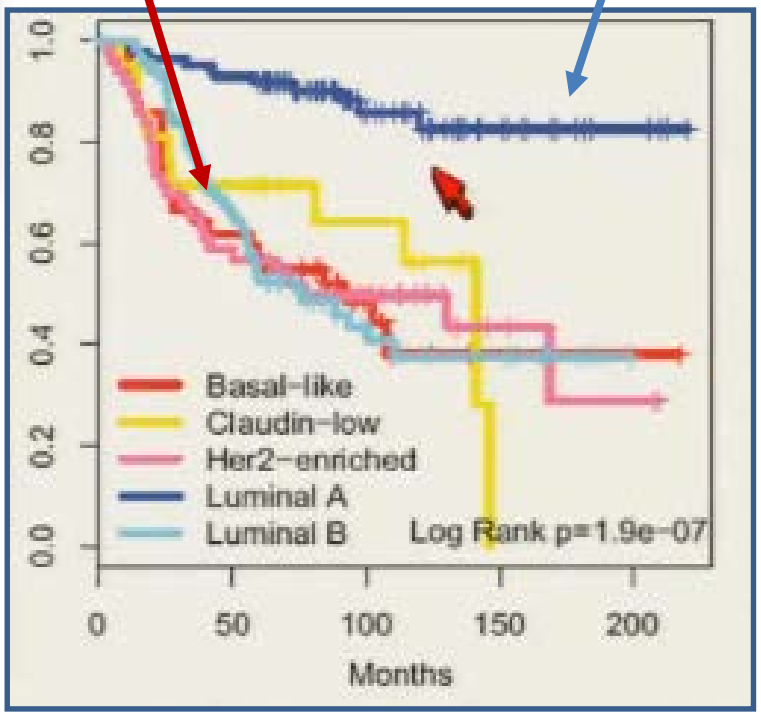
Trial Identifier	Treatment Effect	95% CI for HR or Difference in Rates	*P*
CLB-9011	Median OS: 66 *v* 56 months	Not applicable	.10
SWOG-8892	5-year OS: 67% *v* 37%	Not available	.001
E2491	5-year OS: 69% *v* 45%; difference = 24%	13.4% to 34.6%	.0001
SWOG-8814	HR = 0.83	0.69 to 0.99	.04
CLB-9344	HR = 0.82	0.71 to 0.95	.0064
CCG-5942	3-year OS: 98% *v* 99%; difference = −1%	−3.3% to 1.3%	.90
RTOG-9413	4-year OS: 84.7% *v* 84.3%; difference = 0.4%	−4.6% to 5.4%	.94
SWOG-S9701	HR = 0.84	0.61 to 1.16	.30
NCCTG-9741	HR = 0.66	0.54 to 0.82	.0001
NCIC-MA17	HR = 0.82	0.57 to 1.19	.3
ECOG-1496	HR = 0.51	0.25 to 1.04	.06
CCG-1961	HR = 0.64	0.47 to 0.87	.005
E2997	2-year OS: 79% *v* 80%; difference = −1%	−14.3 to 12.3*	.69
NSABP-B-31/NCCTG-N9831	HR = 0.63	0.49 to 0.81	.0004
ECOG-2100	HR = 0.88	0.74 to 1.05	.16
NCIC-MA21	47 *v* 65 deaths	Not applicable	.09†

MOLECULAR (RE-)CLASSIFICATION OF BREAST CANCER



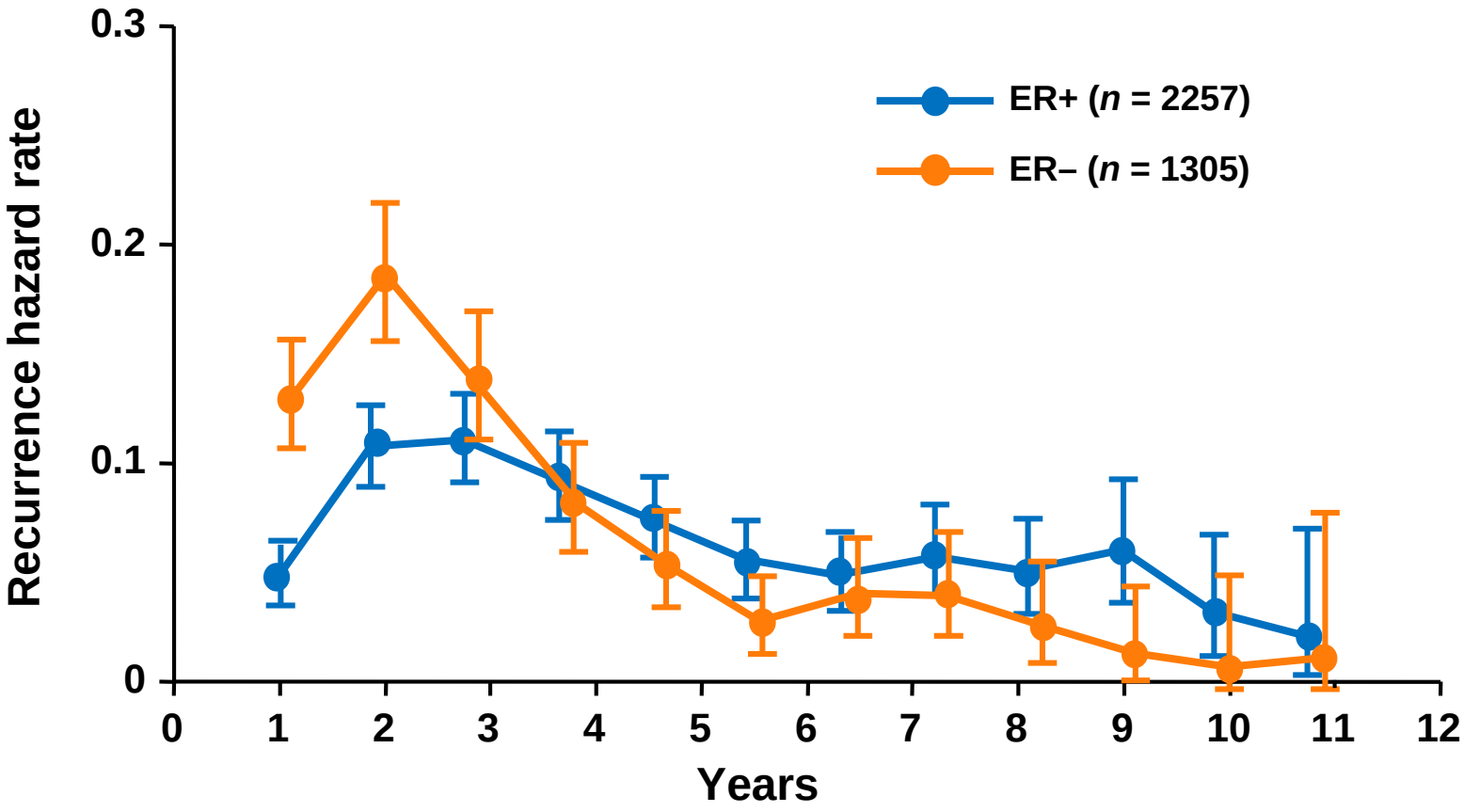
Relapse earlier

Relapse later



Perou et al, Nature, 2000
Sorlie et al, PNAS 2001
Sortiriou, PNAS 2003
Hu et al, BMC, Genomics 2006
Herschkowitz et al, GB 2007
Parker et al, JCO 2009

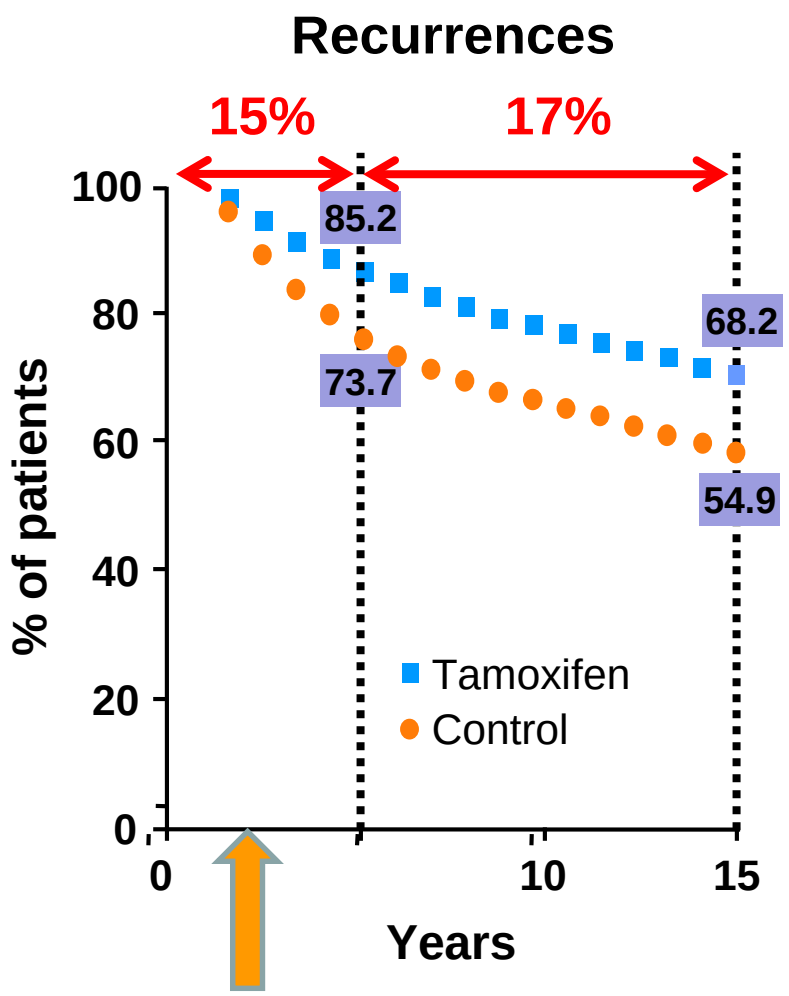
Annual Risk of Recurrence by ER Status

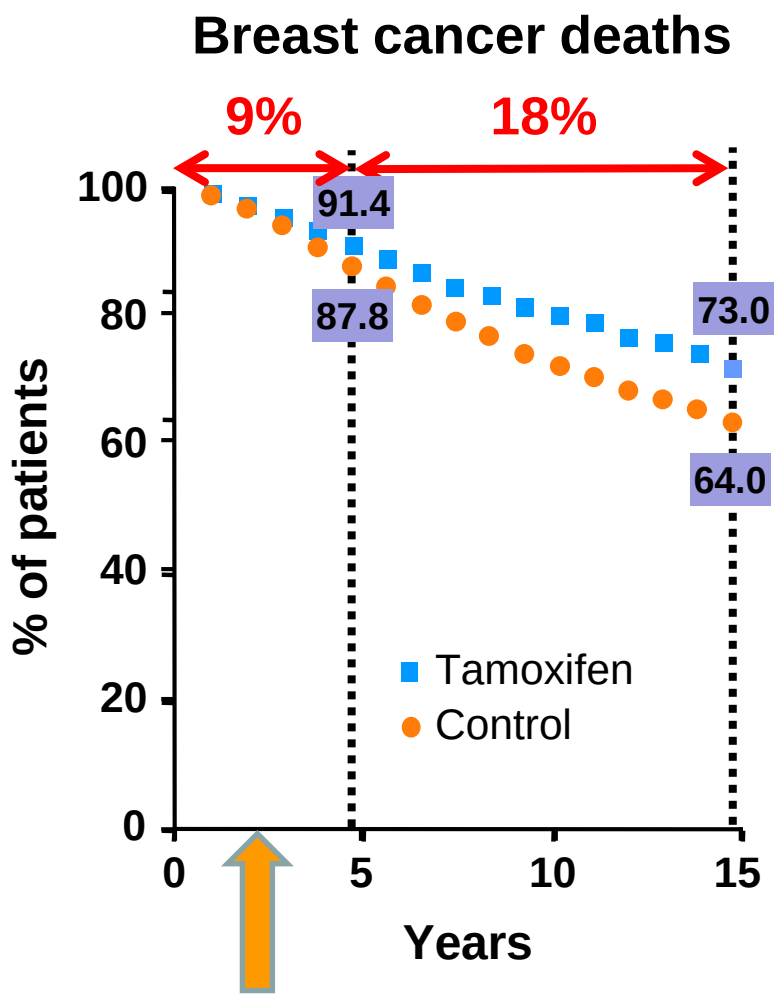


- **Over half of breast cancer recurrences occur >5 years post-surgery!**
- **The annual risk of late recurrence is particularly high in ER+ tumors (5.2% between years 5 and 8, 4.6% between years 8 and 12).**

Saphner T et al., J Clin Oncol 1996

More than Half of all Breast Cancer Recurrences and Deaths Occur Post- 5y Tamoxifen

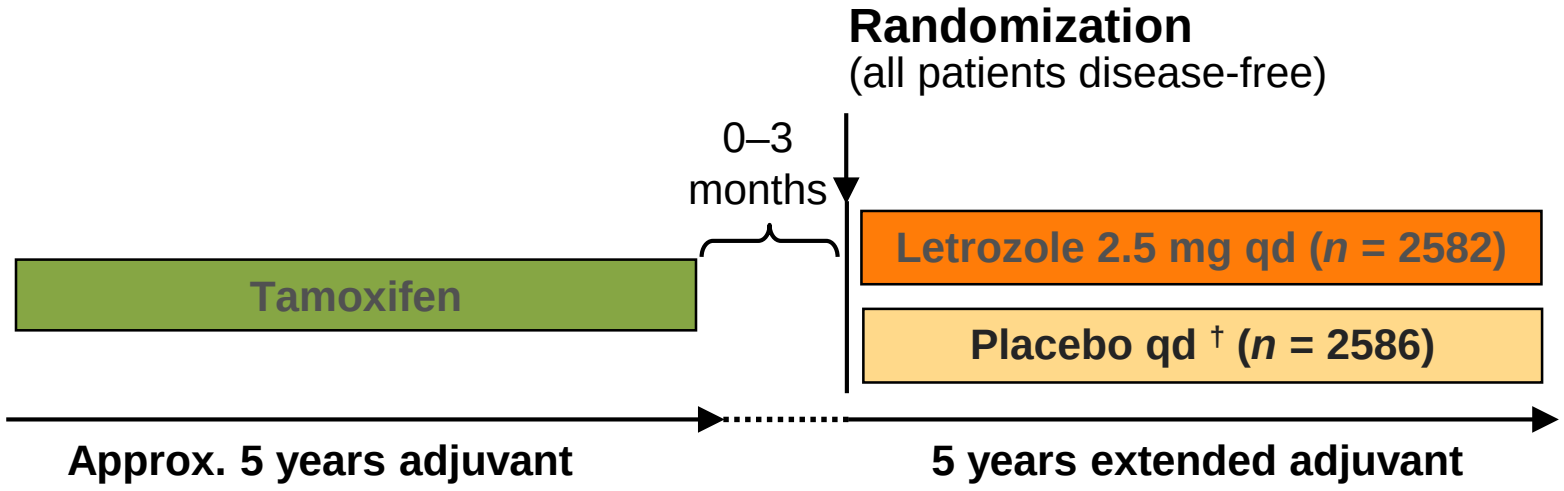




EBCTCG, Lancet. 2005

1st EXAMPLE

MA.17: Trial Design



- **Eligibility criteria: postmenopausal at randomization, HR+, recurrence-free, completed 4.5–6 year Tamoxifen, ECOG PS 0–2**
- **Primary endpoint: DFS (breast- only events)**
- **Secondary endpoints: OS, rate of contralateral BC, safety, QoL,**
- **Sub-studies: BMD/bone markers, lipid profile**

MA.17: Reports

Year	Author	Journal	Title
2003	Goss et al	NEJM	**A randomised trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early- stage breast cancer**
2005	Goss et al	JNCI	**Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17**
2008	Ingle et al	AnnOnc	**Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17**
2008	Goss et al	JCO	**Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen**
2012	Jin et al	JCO	**Longer-Term Outcomes of Letrozole Versus Placebo After 5 Years of Tamoxifen in the NCIC CTG MA.17. Trial: Analyses Adjusting for Treatment Crossover**

2003: first results

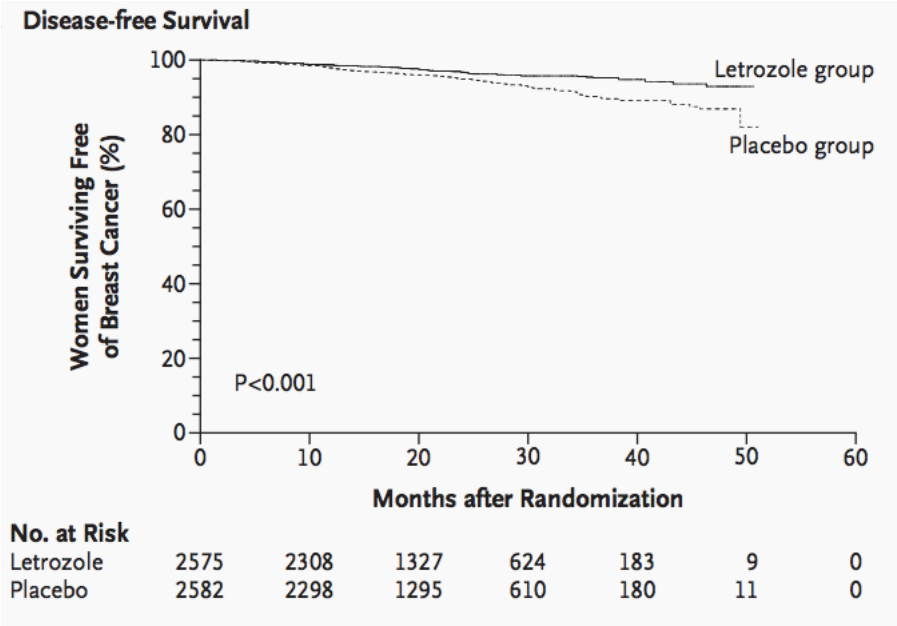
Median follow-up 2.4 y

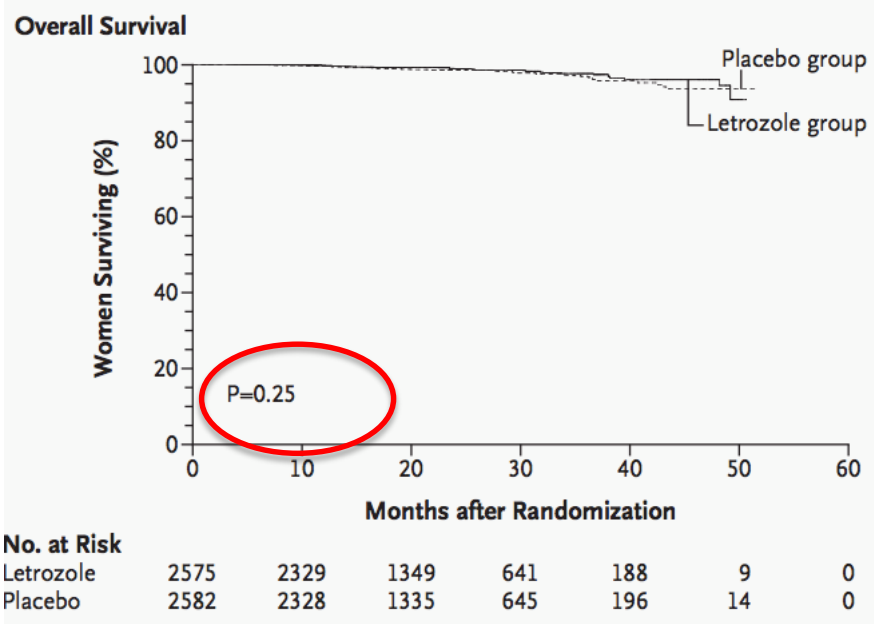
207 events (40%)

Event	HR	95%CI	p value
DFS 4y	0.57	0.43- 0.75	.00008
OS 4y	0.61	0.47-0.79	< .001

Unblinding

Expeditious report





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Planned Subgroup analysis according to LN status

	DFS	Distant DFS	OS
Node + patients	HR 0.61* (95% CI, 0.45-0.84)	HR 0.53* (95% CI, 0.36-0.78)	HR 0.61* (95% CI, 0.38-0.98)
Node – patients	HR 0.45* (95% CI, 0.27-0.75)	HR 0.63 (95% CI, 0.31-1.27)	HR 1.52 (95% CI, 0.76-3.06)

- A similar reduction in local recurrences, new primaries, and distant recurrences occurred in N – and N+ patients, with OS benefit observed only in N-positive patients.
- Extremely low rate rate than 70 years.

Not surprising!
They relapse earlier; therefore: higher rate of events

Goss et al. Proc ASCO 2004, Goss et al., JNCI 2005

Courtesy Cuffer

Consequences of MA-17 early reporting

Trial stopped

Patients offered crossover

Similar trials closed before completing accrual

Fortunately, FU of patients continued

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2005 Update: 247 events (only 40 more events!)

Letrozol benefit for DFS 4y

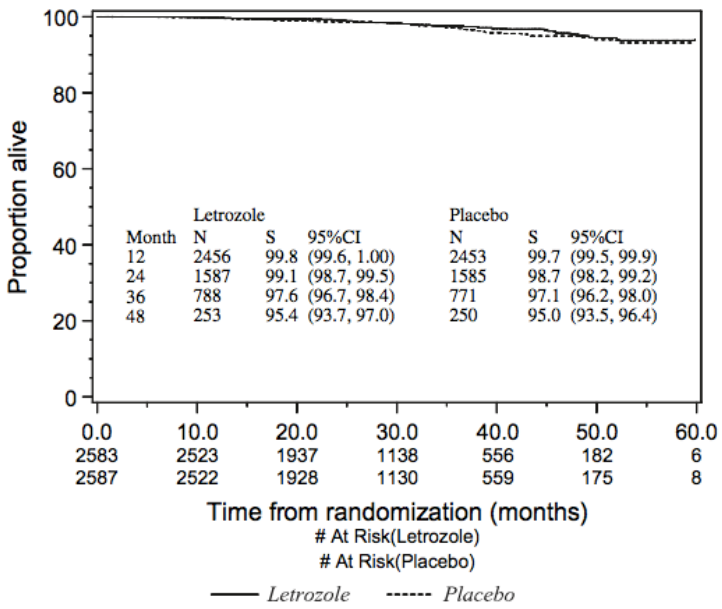
94.4% versus 89.8%

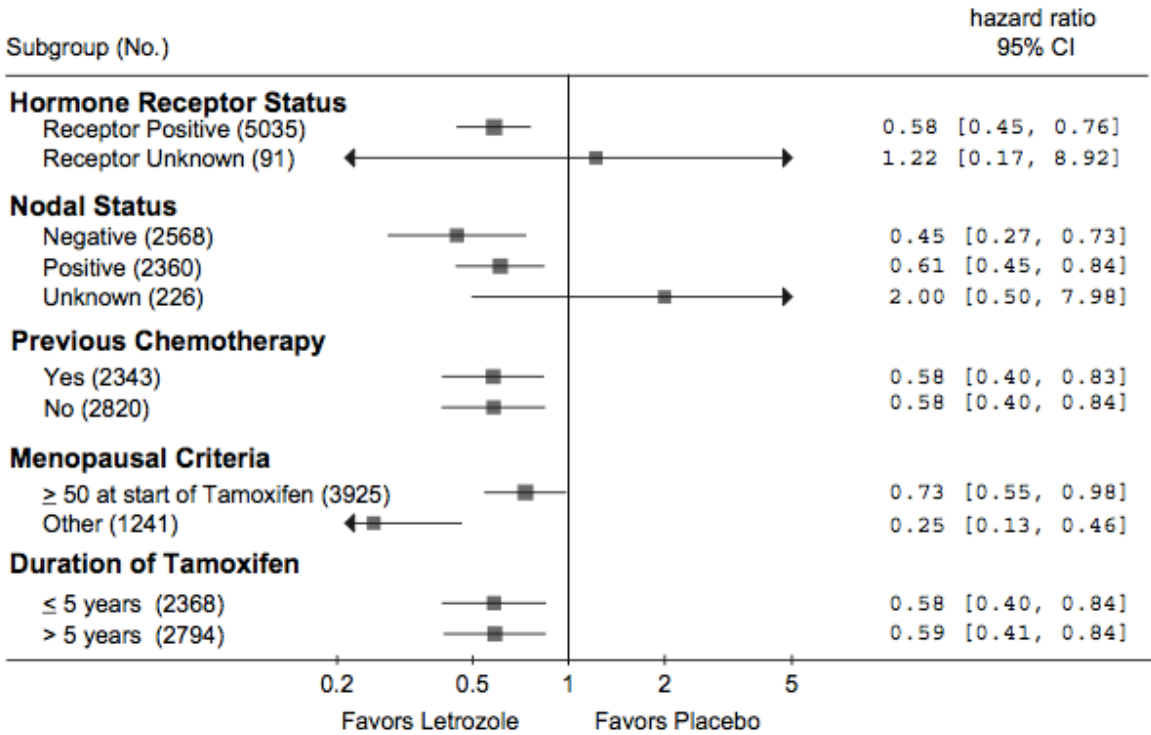
HR= 0.58 (95%CI: 0.45-0.76) (similar to 0.57)

Absolute reduction in recurrence 4.6%

Treatment with extended AI received Guideline recommendation

No OS difference





2008 Update: Intent to treat analysis

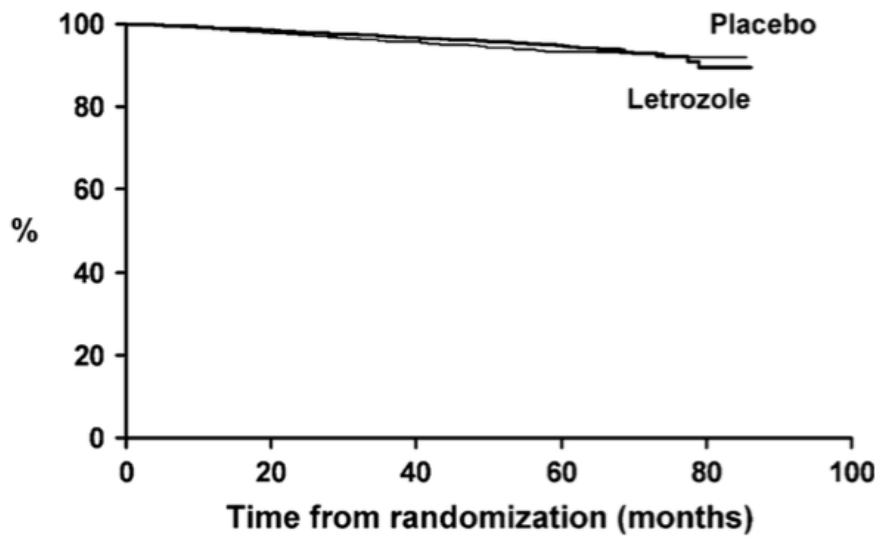
Median follow-up 64 months (over 5 years)

DFS 4y benefit

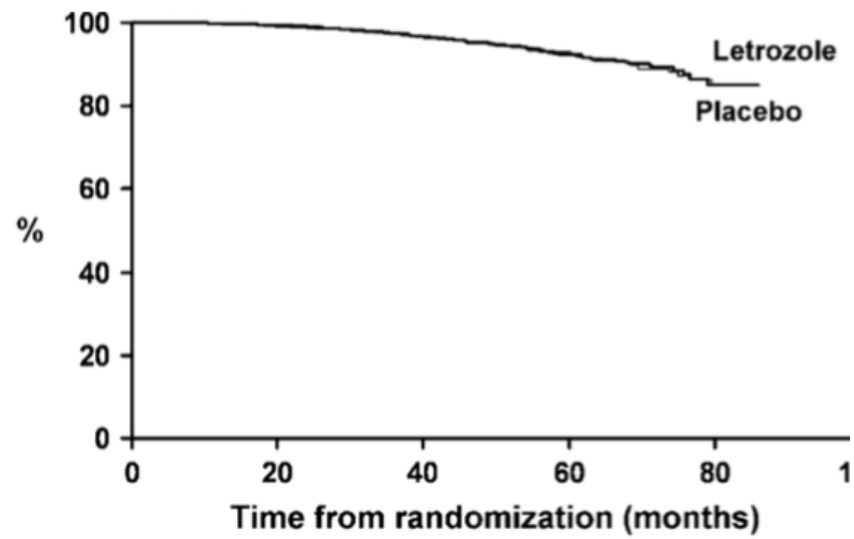
94.3% versus 91.4%: 2.9% absolute benefit (LOWER)

HR= 0.68 (95%CI: 0.55-0.83) (LOWER than before 0.58)

No OS difference (95.1% in both)



ozole	2,583	2,463	1,821	730	55	0
ebo	2,587	2,399	1,758	626	60	0



zole	2,583	2,512	1,881	755	58
bo	2,587	2,482	1,874	694	64

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2008 Update: Cohort analysis of patients on Placebo who were offered Letrozol

2012 Update: Long-term outcomes: exploratory analysis adjusting treatment crossover

Median FUP 64 months and 60% of crossover

Inverse probability of censoring weighted (IPCW) Cox model/

Cox model with time-dependent covariates

DFS HR= 0.52 (95%CI: 0.45-0.61)

OS HR= 0.61 (95%CI: 0.52-0.71)

No definite conclusion about OS

Consequences of MA-17 early reporting

B-33: Accrual

Opened:	May, 1 2001
Target Accrual:	3000 pts
Accrual in 10/03:	1598 pts (53.3%)

Accrual stopped in October 2003 after disclosure of results from the NCIC MA.17 trial

Consequences of MA-17 early reporting

B-33 Plan After Disclosure of NCIC MA-17 Results

- In October 2003 the NSABP DMC decided to permanently stop accrual and to unblind the study
- Offer exemestane to patients in the placebo group free of charge
- Offer continuation of exemestane to patients in the exemestane group for a total of 5 years
- Notification of investigators and patients
- Rapid amendment of the study to implement the DMC recommendations

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Consequences of MA-17 early reporting

B-33: Trial Status Post Unblinding

- Accrual of 3,000 pts was needed to detect a 21.3% reduction in hazard rate with a power of 80% (two-sided 0.05-level log-rank test).
- At the time of unblinding, 1598 pts had been randomized (1577 eligible)
- Upon unblinding, 560 of 783 pts on EXE continued EXE (72%)
- Of 779 pts on PLAC, 344 switched to EXE (44%)
- Median follow up for this ITT analysis: 30 mos

Consequences of MA-17 early reporting

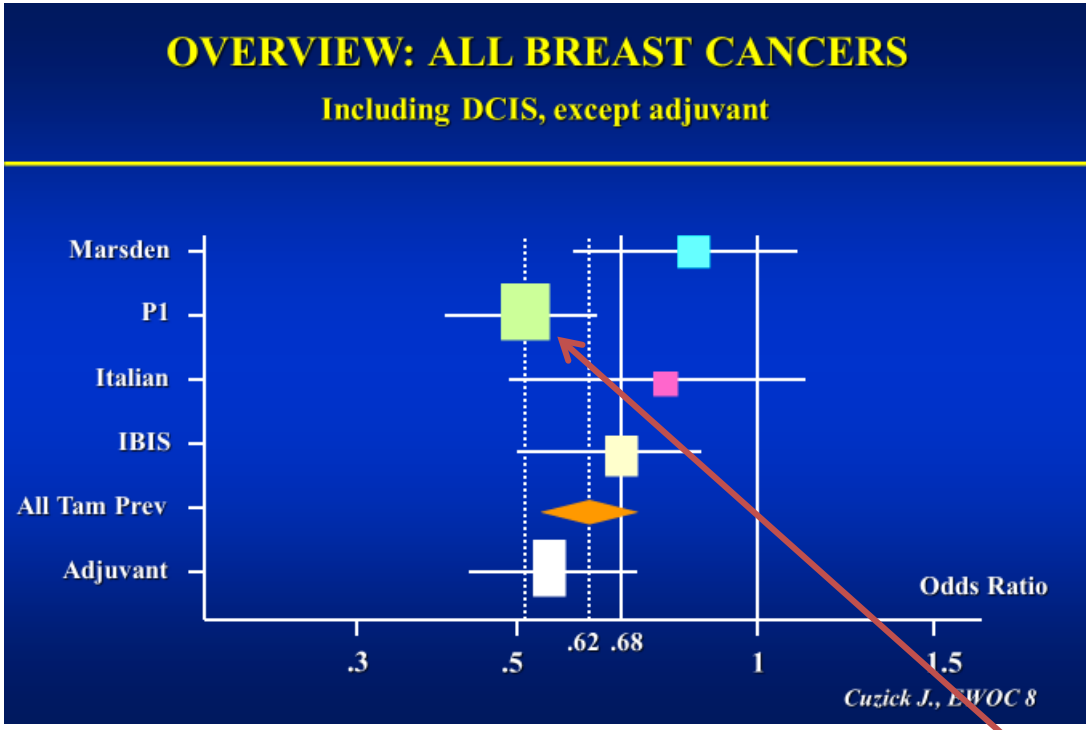
Consequences of MA-17 early reporting

ATTENTION: Stopping the trial was a IDMC recommendation and was as per definition in the protocol

WOULD YOU HAVE STOPPED THE TRIAL?

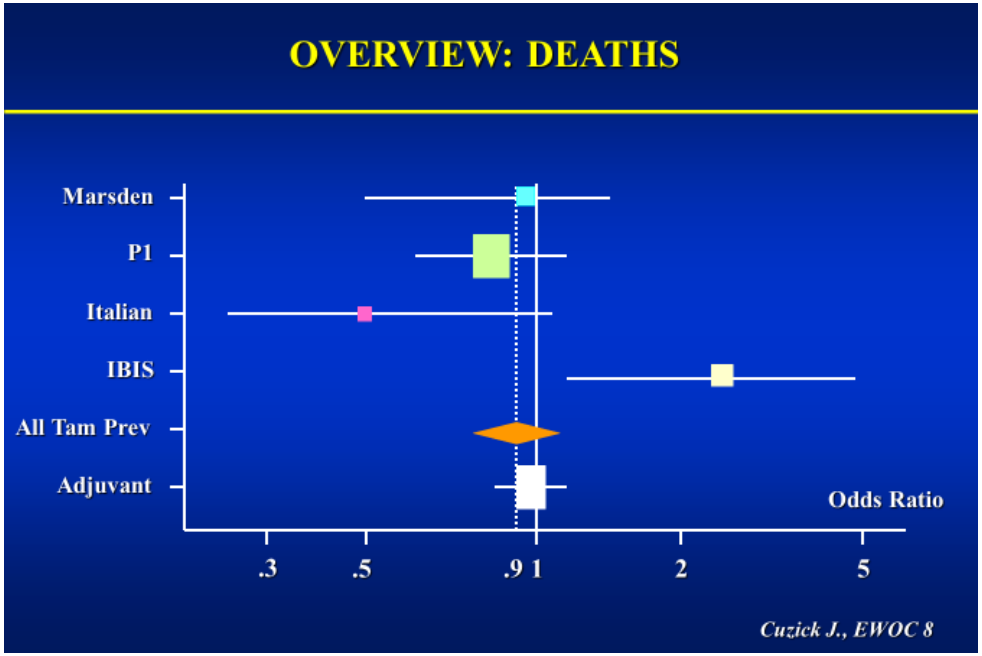
Consequences of early reporting in CHEMOPREVENTION

2nd EXAMPLE



Very large study, with potential to provide definite conclusions BUT reported earlier and stopped

Consequences of early reporting in CHEMOPREVENTION



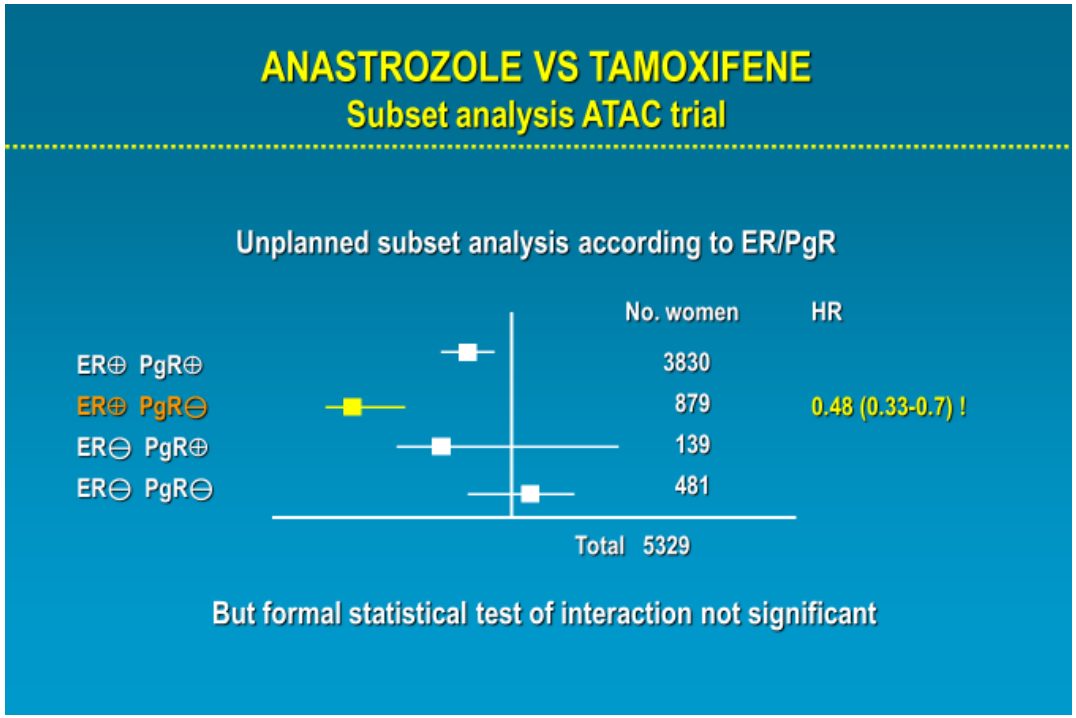
CONSEQUENCIES:

1) The effect of chemoprevention on the incidence of breast cancer is known but not the true effect on mortality

2) Overall uptake of chemoprevention is low

Consequences of early reporting & subgroup analysis in TRANSLATIONAL RESEARCH

3rd EXAMPLE



- **NOT CONFIRMED IN BIG 1-98 nor TEAM STUDIES**
- **Never reproduced**

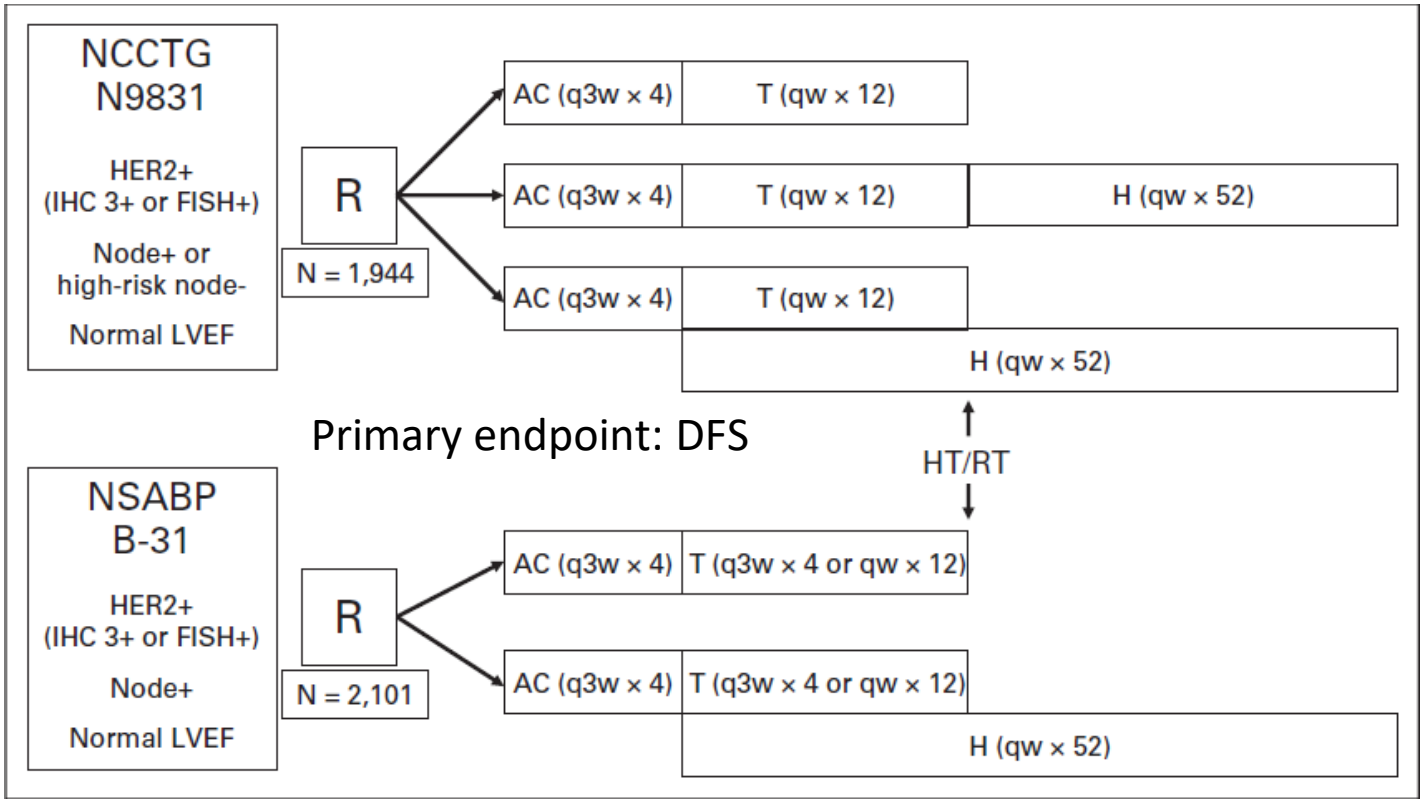
CONSEQUENCIES:

It influenced reimbursement and availability of AIs in Belgium for years

IS IT ALWAYS WRONG TO STOP A TRIAL EARLIER?

What happens when the new treatment benefit is substantially superior ?

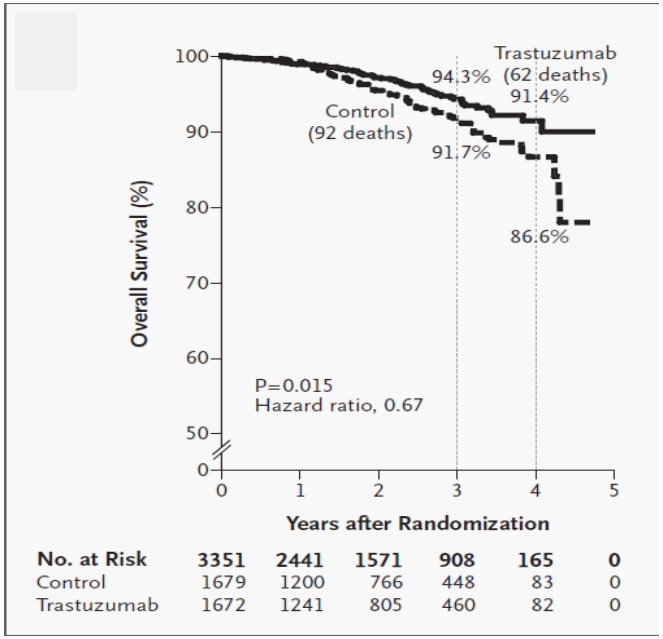
NCCTG N9831/NSABP B-31 trials: effect of adjuvant trastuzumab



NCCTG N9831/NSABP B-31 trial

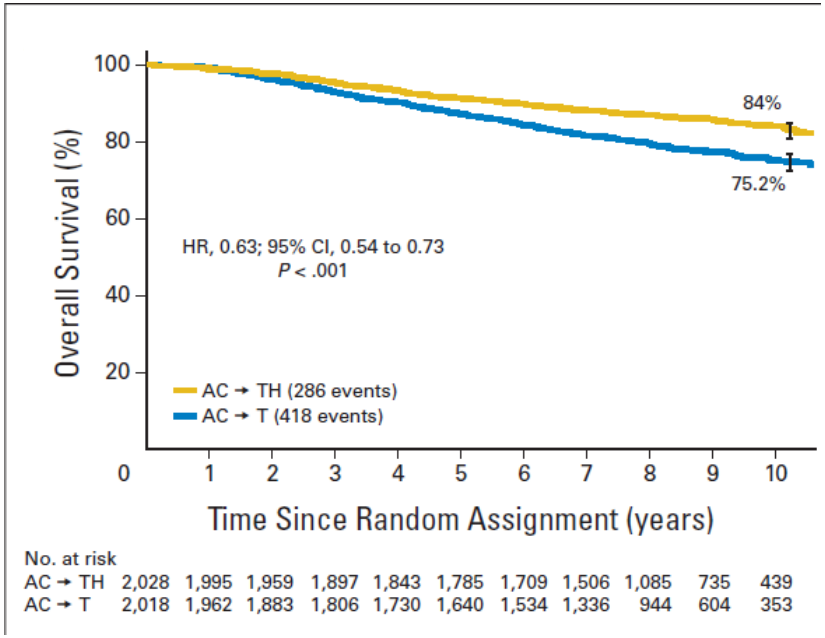
- Trial starting date May 2003 vs End of enrolment Nov 2004 vs Date of publication Oct 2005
- **81% of Patients accrued When Trial Stopped/Reported**
- DSMC yes
- Sample size: 710 Planned vs 394 at Interim Analysis
- Primary endpoint used in interim analysis: DFS
- **Interim analysis consequences: Stop enrolment and disclosures of results**

NCCTG N9831/NSABP B-31 trial: OS



Romond et al. N Engl J Med 2005;353:1673-84.

% Information	Treatment effect	*P*
55	HR=0,67	.015



Perez et al. J Clin Oncol 32:3744-3752.

% Information	Treatment effect	*P*
99	HR=0,63	<.001

Updated analysis confirmed the results.
Early reporting allowed for fewer patients to be treated in the control arm, crossover, earlier approval of drug.

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EARLY REPORTING OF TRIALS RISKS & BENEFITS

POTENTIAL BENEFITS

1) Expose less patients to the least effective therapy
2) Expose less patients to unnecessary toxicity
3) Offer patients assigned to the control arm the better therapy, through crossover
4) Save resources that can be redirected to other relevant questions

POTENTIAL HARMS

1) Probability of overestimate the true treatment effect
2) Probability to underestimate the true treatment effect
3) Loss of possibility to assess accurately long term outcomes such as OS and late toxicities
4) Implications for other ongoing trials

VERY BIG THANK YOU!

Joana Ribeiro, MD

Berta Sousa, MD