PROFFERED PAPERS EARLY BREAST CANCER
Abstracts 245O, 246O, LBA10

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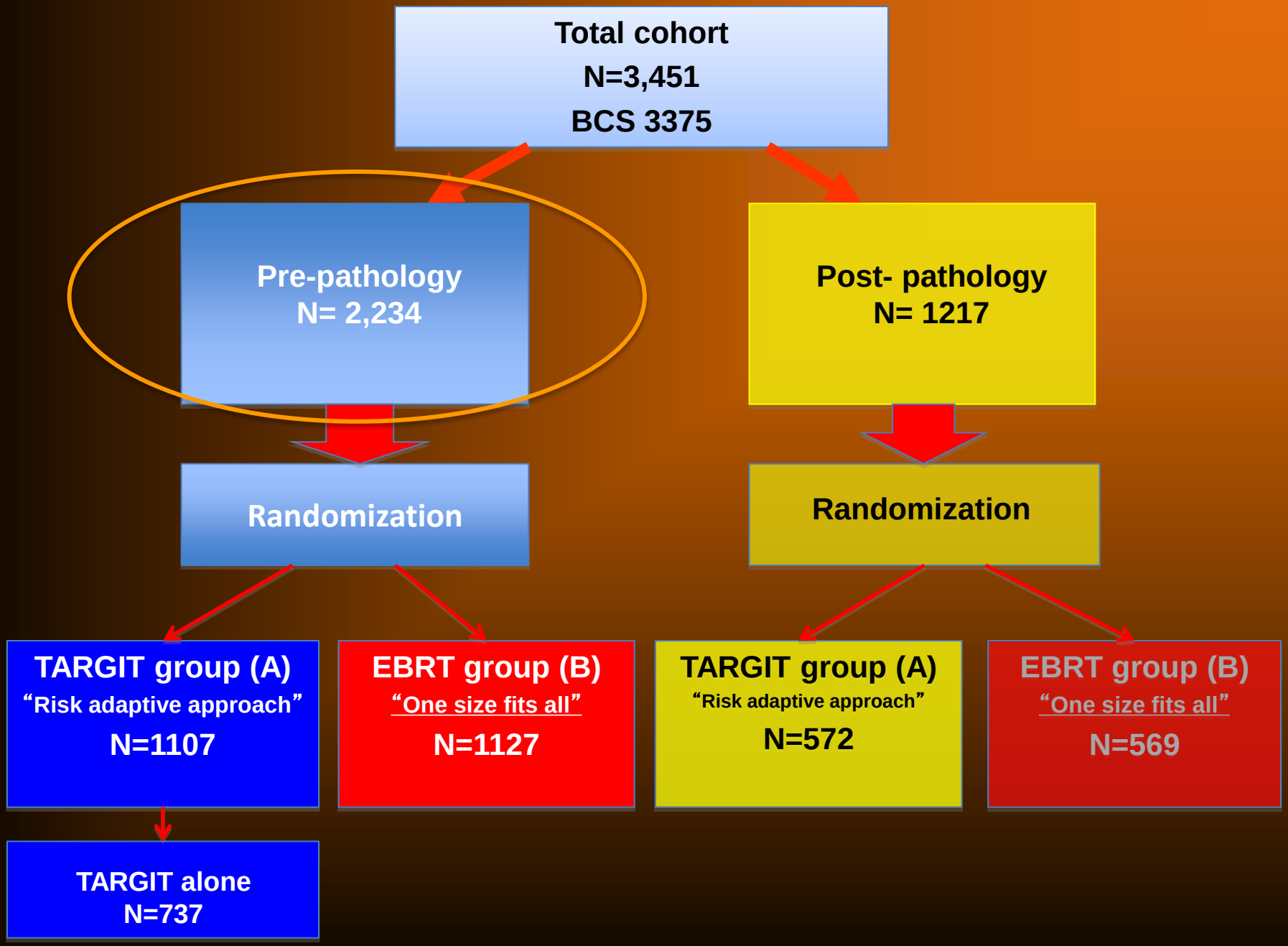
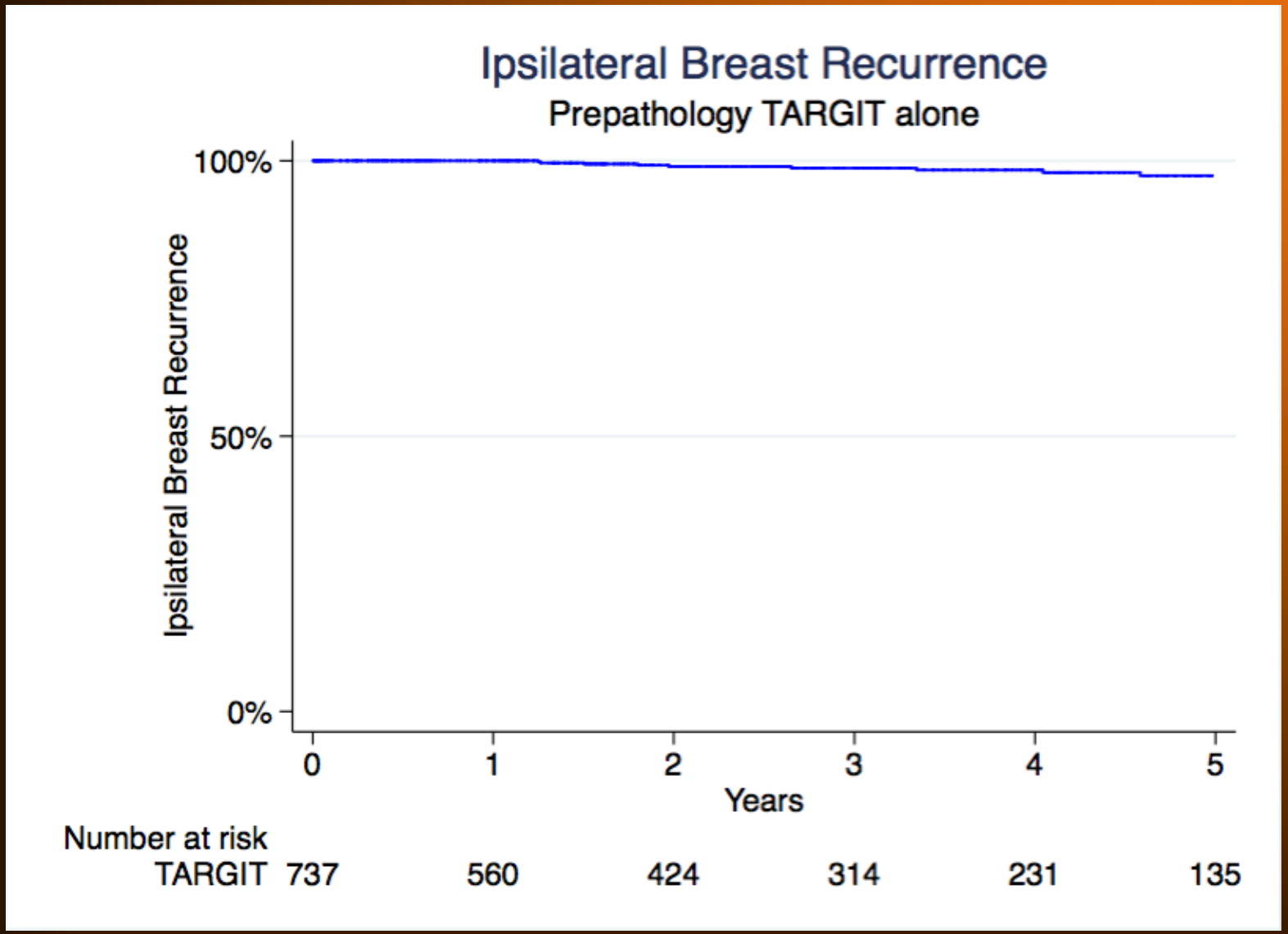
EORTC
European Organisation for Research and Treatment of Cancer

European School of Oncology
learning to care

Breast cancer being treated with Breast Conserving Surgery




Ipsilateral Breast Recurrence
Prepathology TARGIT alone
100%
50%
0%
Ipsilateral Breast Recurrence
0
1
2
3
4
5
Years
Number at risk
TARGIT 737 560 424 314 231 135

Relevant findings

- The BC mortality in this low risk group is low
- Contralateral disease is more common that ILR outside IQ

Limitations

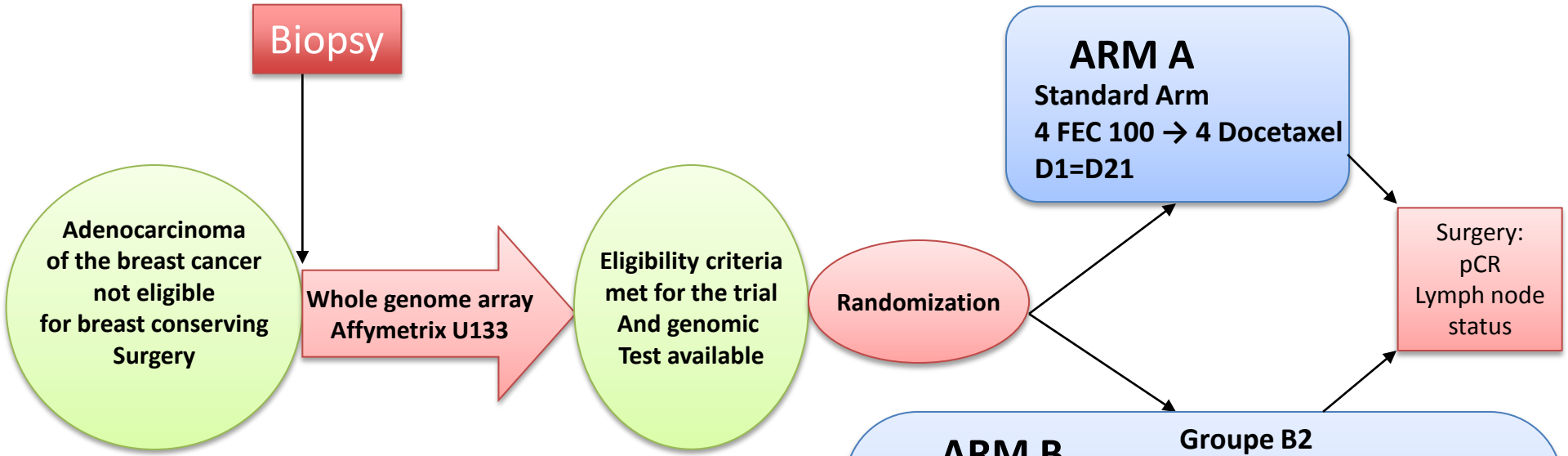
- It's a highly selected low risk population
- Does not address the role of "slightly larger" surgery
- Need to wait for final comparison with whole breast RT
- Need <u>(much) longer FU</u>

Comments

- **64% were screen-detected**
  - **If not screen-detected, most probably more advanced & not amenable to this much less invasive loco-regional treatments**
  - **One can not and should not infer from this trial the benefits of breast cancer screening**
- **Importance of all cause mortality outcomes in trials of screening: agree!**

REMAGUS 04 Trial design

Phase III randomized trial : standard neoadjuvant chemotherapy vs a genomic-driven neoadjuvant chemotherapy



Clinical Eligibility criteria

- HER2 neg
- no multifocality
- cT1-cT3 tumor
- no metastases
- normal lab value
- LVEF >50%

Sample Eligibility criteria

- 30% cancer cells
- RIN>6,
- RNA content > 2ug

TOP2A >500 (sensitive to anthracyclines)

VIENNA 2012 ESMO congress

www.esmo2012.org

(N° EudraCT: 2008-005534-70).

OBJECTIVES

- **Evaluate whether whole genome array approach is feasible in the context of daily practice**
- **Evaluate Diagonal Linear Discriminant Analysis–30 (DLDA-30) probe set model as predictor of resistance to neoadjuvant CT with a better sensitivity than standard parameters[1]**
- **Evaluate TOP2A amplification as a predictor for the efficacy of anthracyclines-based CT[2]**
- **Evaluate whether the use of a genomic score (DLD30) combined with TOP2A level could improve neoadjuvant chemotherapy efficacy.**

1 Hess et al, J Clin Oncol 2006

2 Di Leo A et al, Lancet Oncol 2011

- **Evaluate whether whole genome array approach is feasible in the context of daily practice**

•Whole genome array is feasible within 15 days in a multicentric setting

•The success rate for genomic analysis was 61% (142/232) for the eligible patients and 67% for the screened population.

•Main sources of loss of samples are low % tumor cell in biopsy and RNA quality

EORTC 10041 BIG 3-04 trial MINDACT TRIAL DESIGN
6,000 Node - & 1-3 N+ women

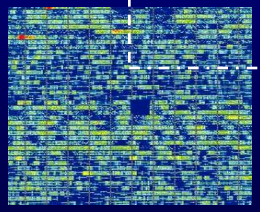
Evaluate Clinical-Pathological risk and 70-gene signature risk

55%
N=3300
Clinical-pathological and 70-gene both HIGH risk

32%
Discordant cases
Clin-Path HIGH 70-gene LOW
Clin-Path LOW 70-gene HIGH
N=1920
R-T
Use Clin-Path risk to decide Chemo or not
Use 70-gene risk to decide Chemo or not

13%
N=780
Clinical-pathological and 70-gene both LOW risk

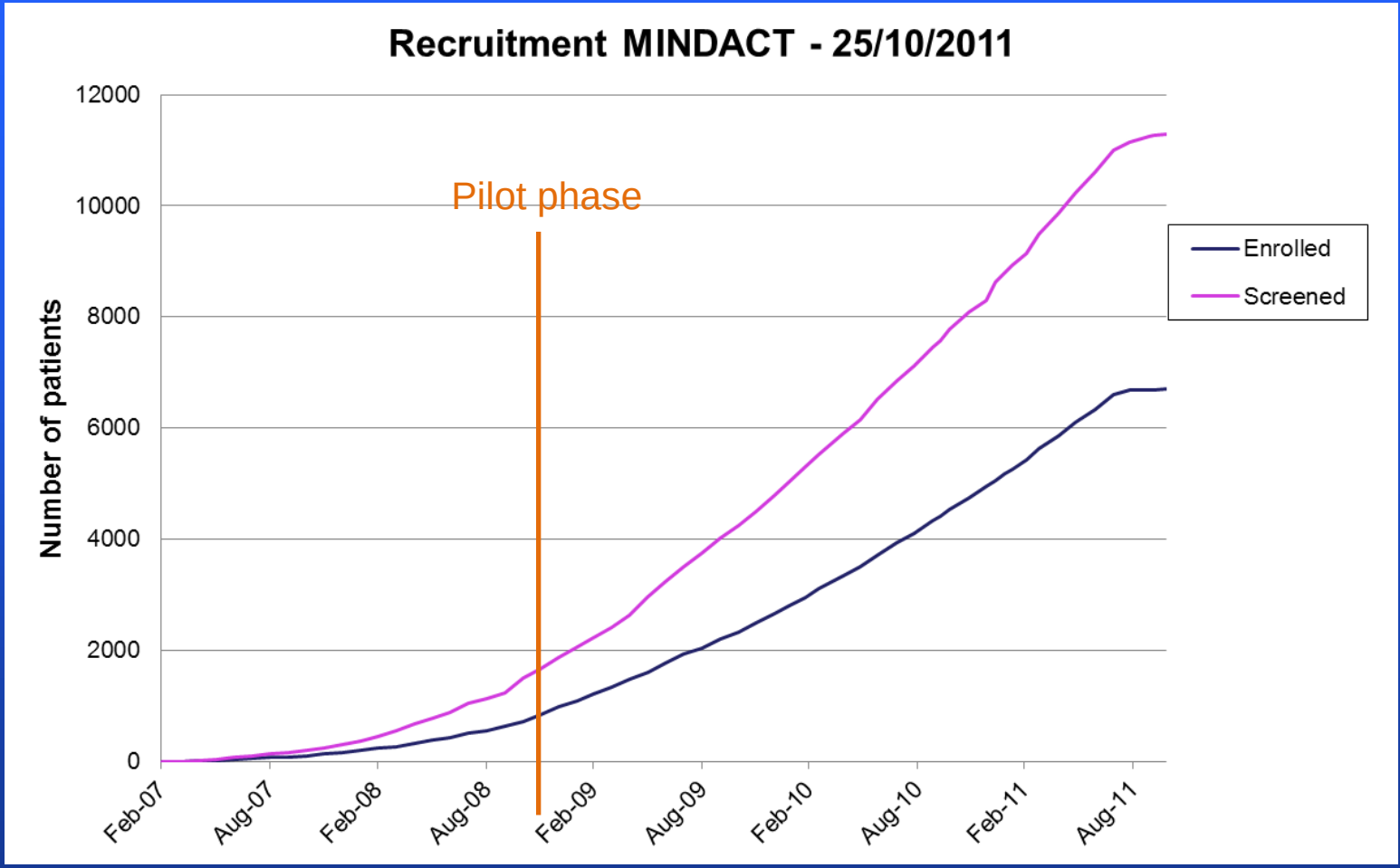
Chemotherapy



Endocrine therapy

Potential CT sparing in 10-15% pts

MINDACT – final accrual curve



	Registered	Screened	Enrolled
Number of patients	11291	11291	6694 (59.3%)

Reasons for non enrollment (4200 pts registered but not enrolled)

Eligibility criteria

Criteria	Number of patients
Sample damaged or defrosted	1
<30% (<50% pre amend.) tumor cells Bad RNA quality and quantity	976
Unsuccessful genomic test	11
"Clinical-related" reasons	3212

Cut-off date for all included data: 02/03/2011

- **Evaluate whether whole genome array approach is feasible in the context of daily practice**

TAKE-HOME MESSAGES

- **Genome arrays are feasible in a real-time basis and in a multicentric and multinational setting**
- **The success rate is linked to quality of samples making logistics set-up, pathologists training/learning curve crucial**

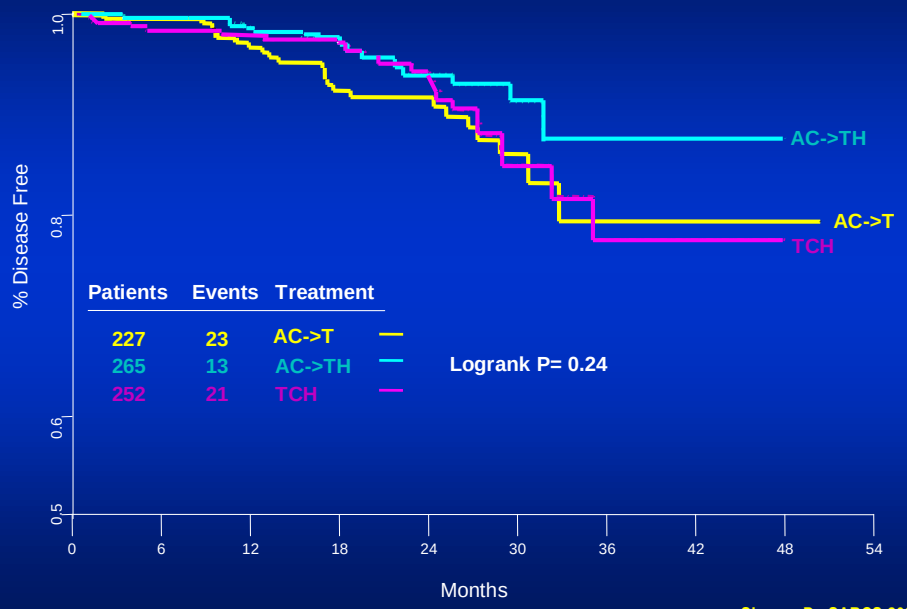
- **Evaluate TOP2A amplification as a predictor for the efficacy of anthracyclines-based CT**

TAKE-HOME MESSAGES

- **Non-anthracyclines-based regimen with very low pCR rate (4%)**

- **Role of Topo-II-A as a predictive marker for anthracyclines: still not ready for clinical practice**

DFS CO-AMPLIFIED TOPO II BY ARM



Slamon D., SABCS 2005

AC → TH

>>

AC → T or TCH

Anthracyclines & trastuzumab are imp

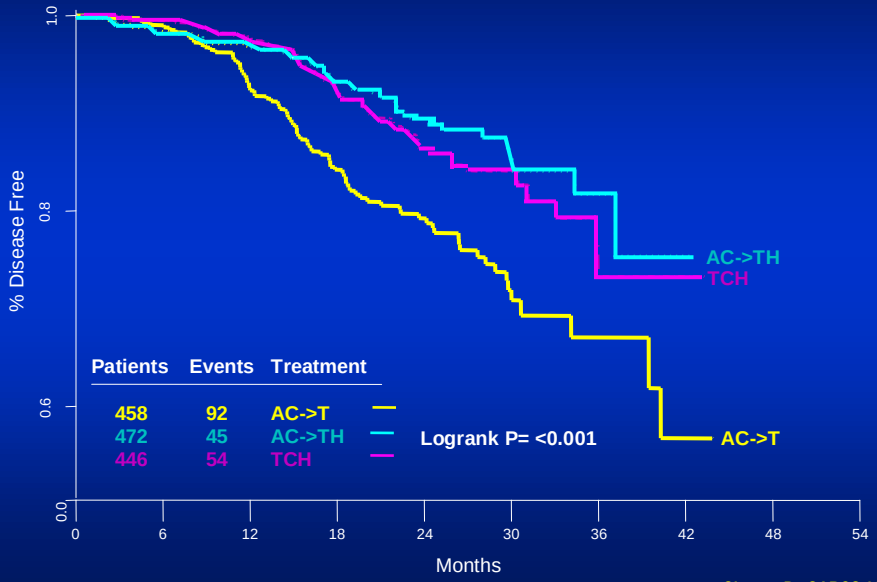
AC → TH & TCH

>>

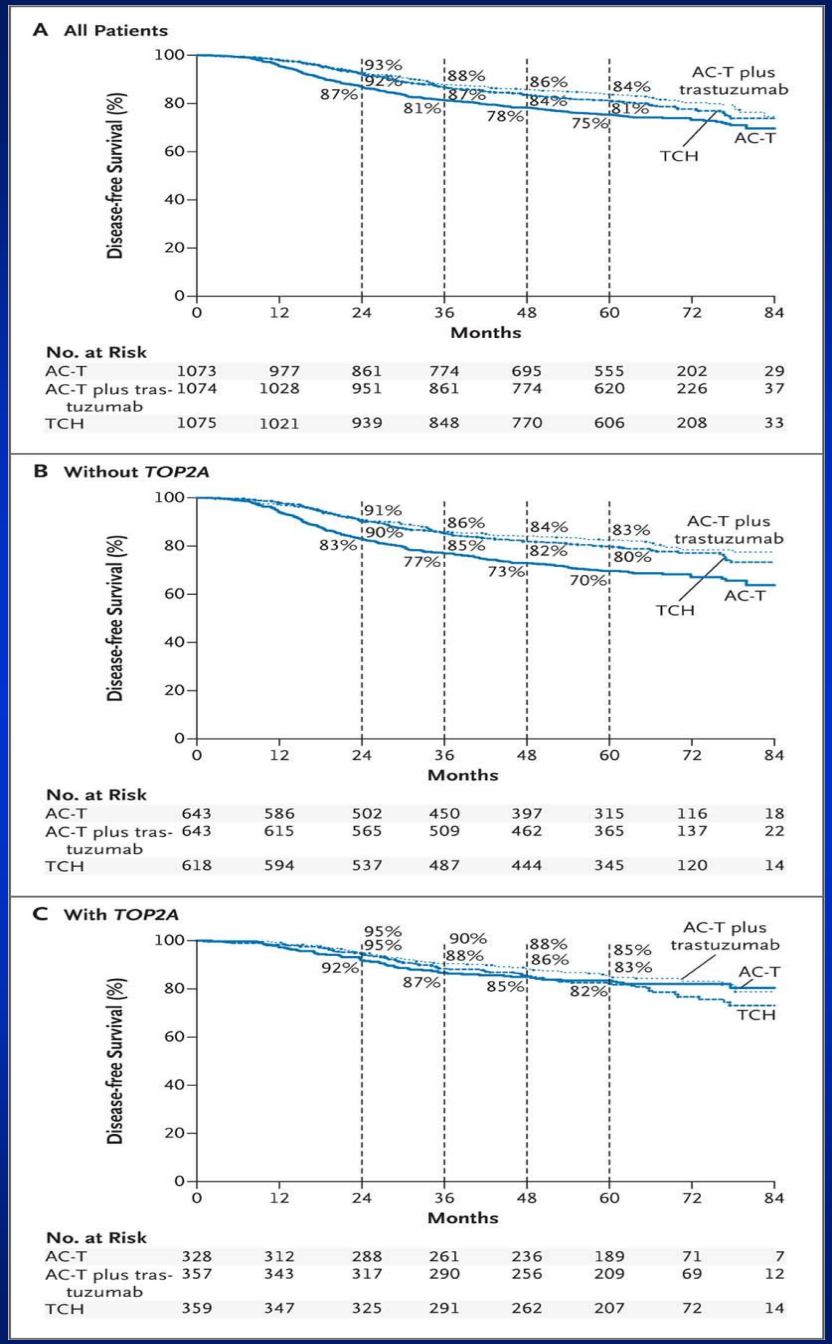
AC → T

Only trastuzumab is imp

DFS NON CO-AMPLIFIED TOPO II BY ARM



Slamon D., SABCS 2005



DFS in all patients
(TCH numerically not statistically inferior to A-based; trial hypothesis (superiority) NOT proven!)

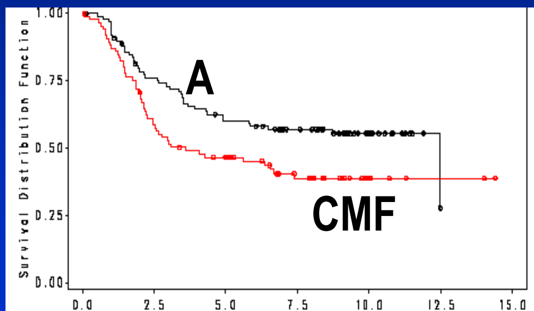
DFS in patients without *TOP2A* co-amplification
(TCH "less" inferior to A-based)

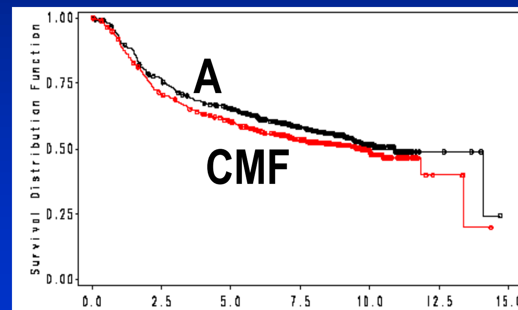
DFS in patients with *TOP2A* co-amplification
(A-based clearly superior)

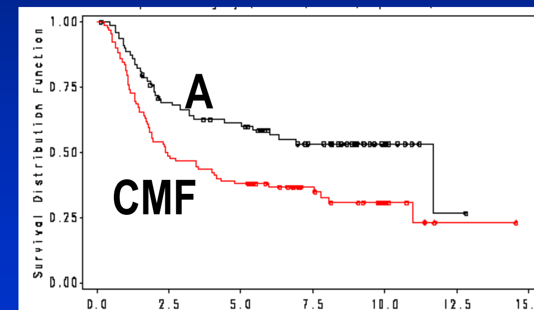
Slamon D et al. N Engl J Med 2011;365:1273-1283

DFS AND OS BY TOPO IIA STATUS KAPLAN-MEIER CURVES

DFS

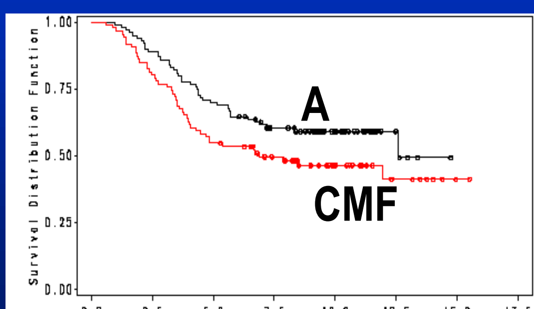


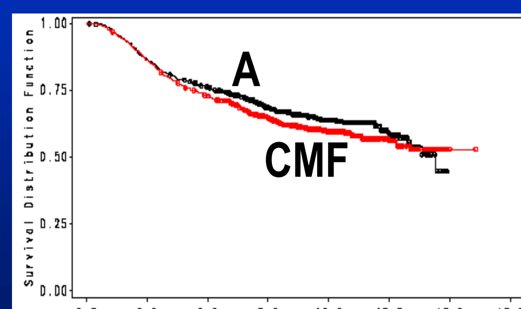


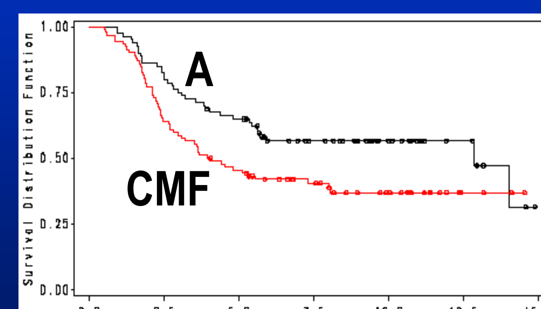


Amplified | **Normal** | **Deleted**

OS







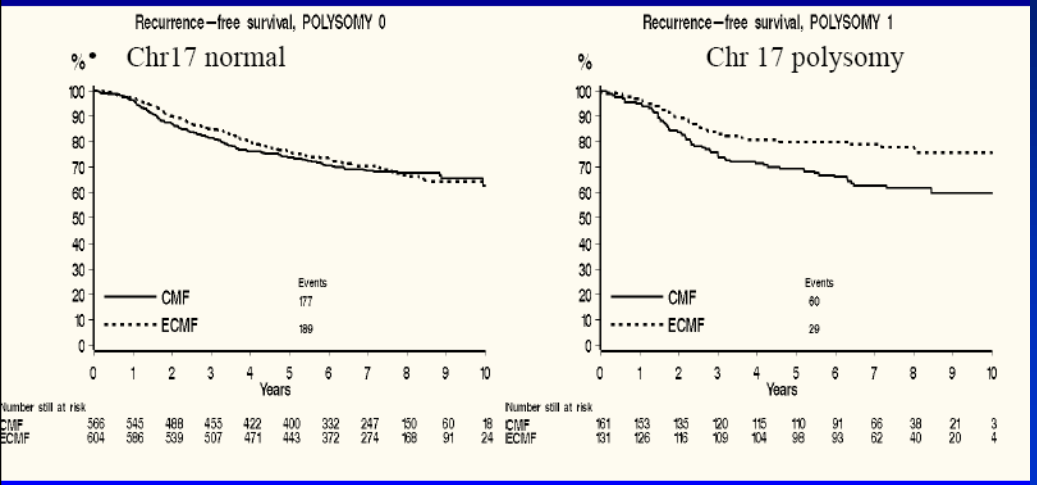
CONCLUSIONS

- The results of this planned interim analysis show that HER-2 and topo IIα genes have a clinically modest and a statistically borderline value in predicting sensitivity to anthracyclines in early breast cancer patients

- Caveats: 1) lack of reproducibility in topo IIα scores by FISH in 30.8% (38/123) of cases submitted to the central lab; 2) trials heterogeneity

- Exploratory analysis:
  1) In HER-2+ patients benefit from anthracyclines seems to be independent of topo IIα gene status
  2) Anthracyclines benefit does not seem to be confined to HER-2 positive patients
  3) Topo IIα protein levels might be a relevant predictive marker independently of gene status

Polysomy 17 predicts anthracycline benefit in the NEAT study (RFS)



•*Test for interaction: HR 0.59 (0.35-0.98) p*= 0.04

N = 1462

CHOMOSOME 17 POLYSOMY:

the true predictor of anthracycline benefit?

HER-2 & Topo-II maybe surrogates for ch17 polysomy

Polysomy: duplication of Ch17

- **Duplication of genes without amplification**
- **Associated with chromosomal instability**

Courtesy J Bartlett, SABCS08

Polysomy (N = 1462)		
	Ch 17 Norm	Ch 17 Poly
HER2 –ve	968 (84%)	190 (16%)
HER2 Amp	202 (66%)	**102 (34%)****
TOP2A –ve	1069 (85%)	250 (19%)
TOP2A amp	101 (71%)	**42 (29%)***
TOP2A –ve	1121 (85%)	200 (15%)
TOP2A Del	49 (35%)	**92 (65%)****

* p = 0.004, ** p<0.0001

- **Evaluate Diagonal Linear Discriminant Analysis–30 (DLDA-30) probe set model as predictor of resistance to neoadjuvant CT with a better sensitivity than standard parameters**

TAKE-HOME MESSAGES

- **DLD30+ score seems a good new predictive marker of response to CT: associated with an increased likelihood of pCR (36% versus 3% for DLD30-) but not a discriminator between different CT regimens**

- **Factors associated with pCR: DLD30+, ER and tumor grade**

- **Evaluate whether the use of a genomic score (DLD30) combined with TOP2A level could improve neoadjuvant chemotherapy efficacy**

TAKE-HOME MESSAGES

- **The overall pCR rate was 22%. No difference between genomic driven arm and standard CT arm (pCR rates: 22 % and 21% respectively).**

- **Evaluate whether the use of a genomic score (DLD30) combined with TOP2A level could improve neoadjuvant chemotherapy efficacy**

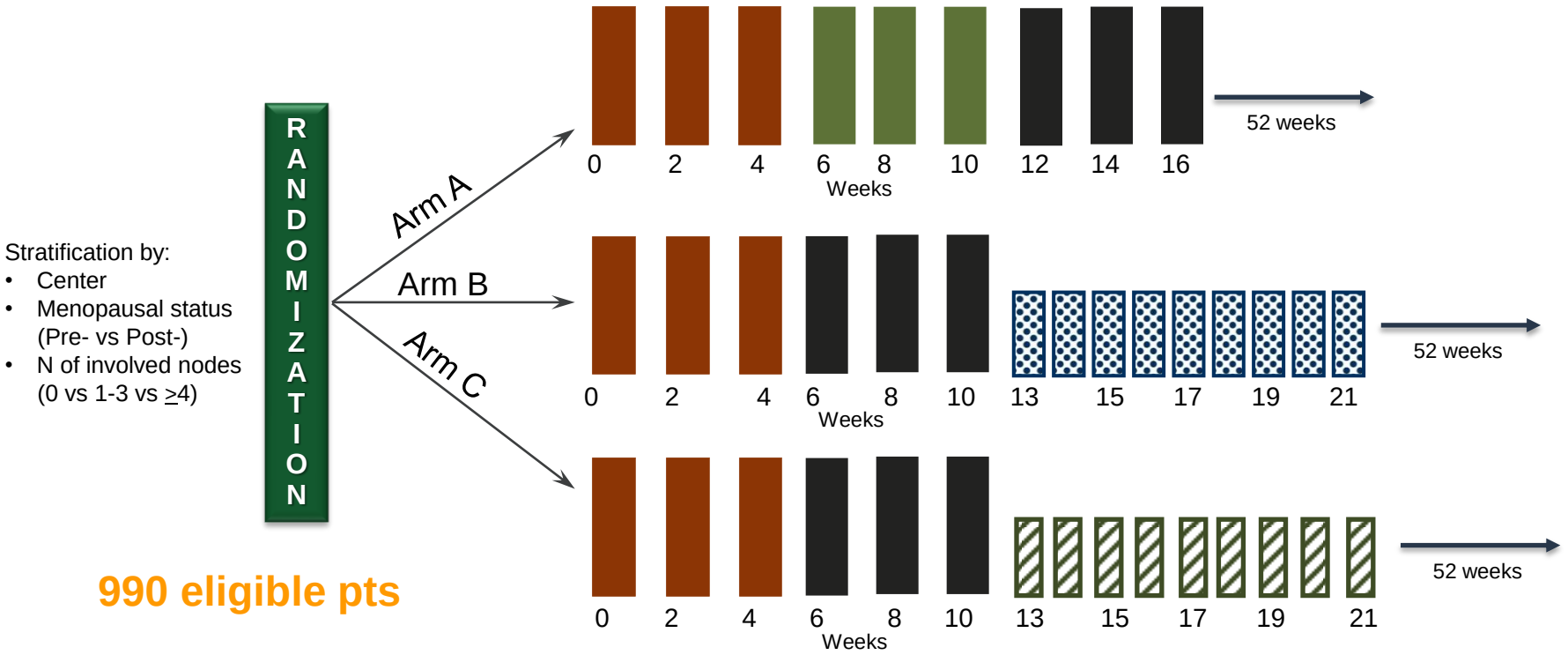
TAKE-HOME MESSAGES

- **There is still NO factor available for clinical use allowing for a tailoring of the type of neoadjuvant CT to the individual patient!**

- **Therefore: neoadjuvant CT regimens should be the standard ones (as in adjuvant) i.e. Anthracyclines and Taxanes, no other cytotoxic agents, no extra number of cycles.**

HE 10/05

(ACTRN 12610000151033)



Limitations

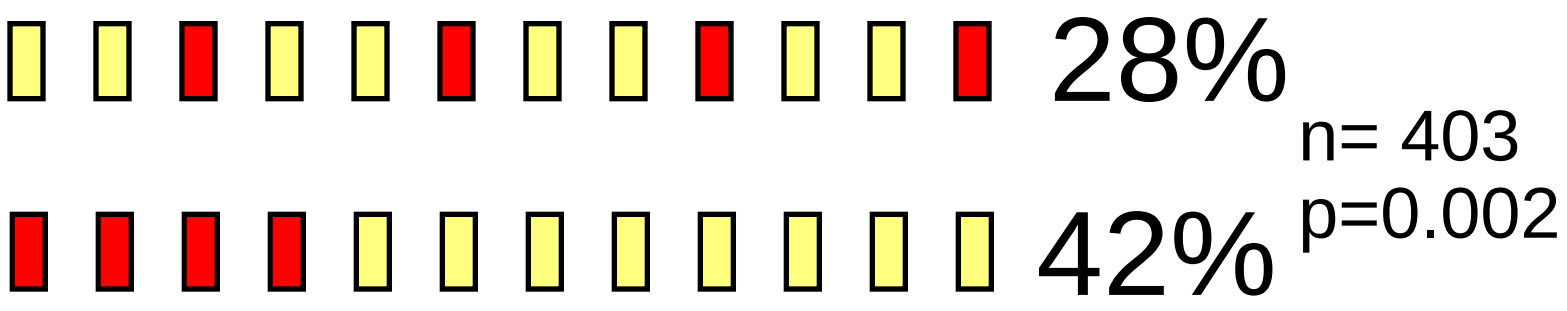
- **Acceptable control arm?**
- **Relatively small adjuvant trial (~1000 pts) and too many variables**
- **Dose dense but also dose intense regimens**
- **All BC subtypes included (about 75% ER+ & about 28% HER-2+)**

Relevant findings

- **Low rate of recurrence with all 3 regimens**
  - **Taxanes matter**
  - **Dose matters**
  - **Interval (dose dense) matters**
  - **Sequential regimens matters**

- **Toxicity acceptable in all 3 regimens but ARM A overall better tolerated (less discontinuations: 5.8% vs. 13.2% vs. 14.9%)**

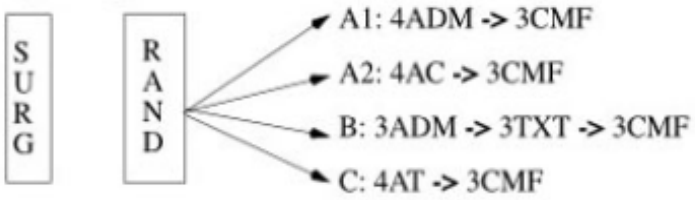
Sequential or alternating Rx
10 year disease-free survival



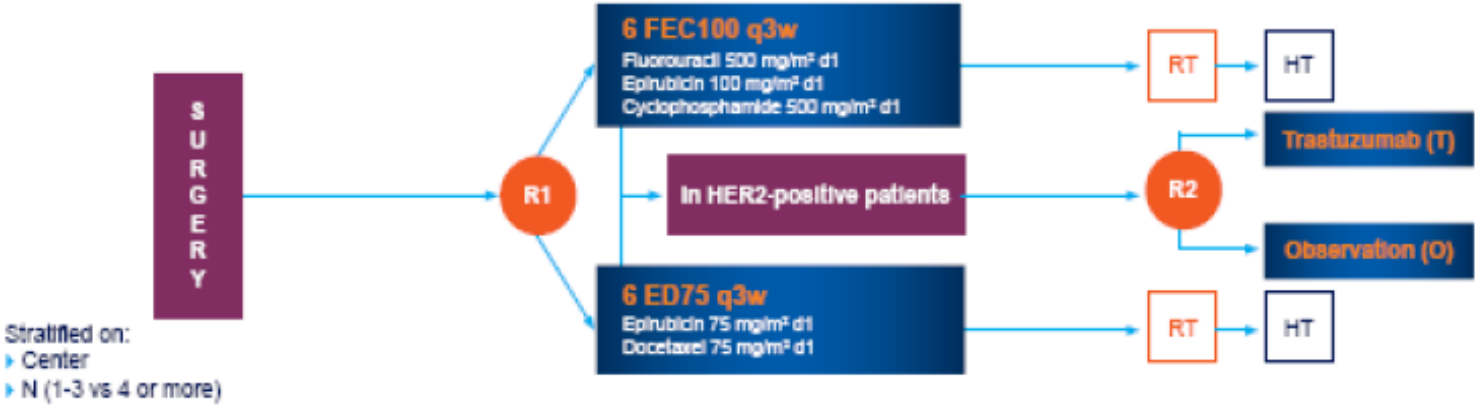
From Bonadonna et al: JAMA 1995; 273; 542-547

Sequential taxanes > combination in EBC

- BIG 2-98: DFS (HR 0.84) and OS (HR 0.79) better for arm B (A -> T) vs C (A+T)
  - Exploratory: no benefit of taxanes in triple negative



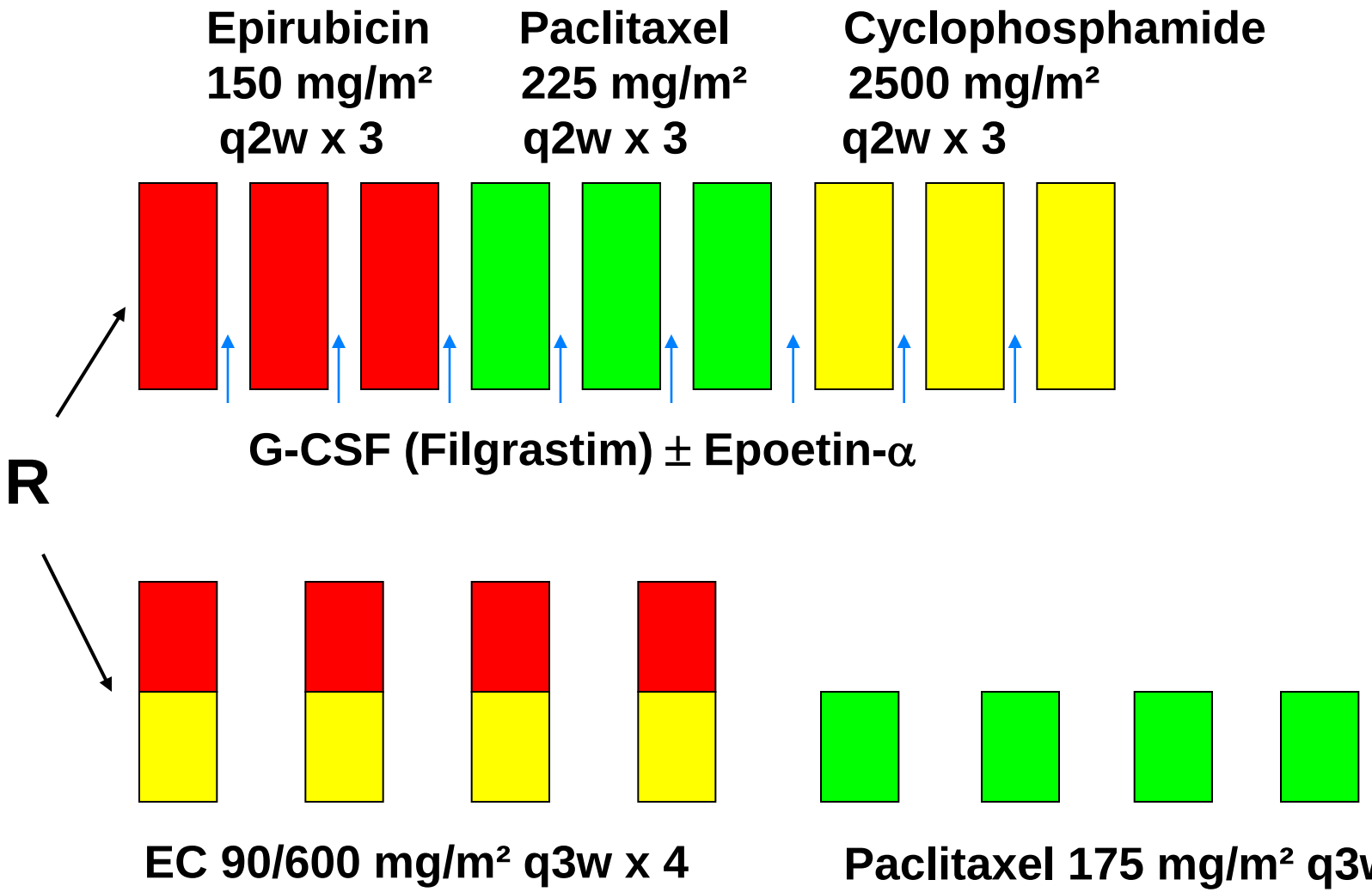
- PACS04: DFS and OS similar



Di Leo et al. SABCS 2009; Abstract 601; Roché et al. SABCS 2009; Abstract 602

AGO-Trial ETC vs. EC→T

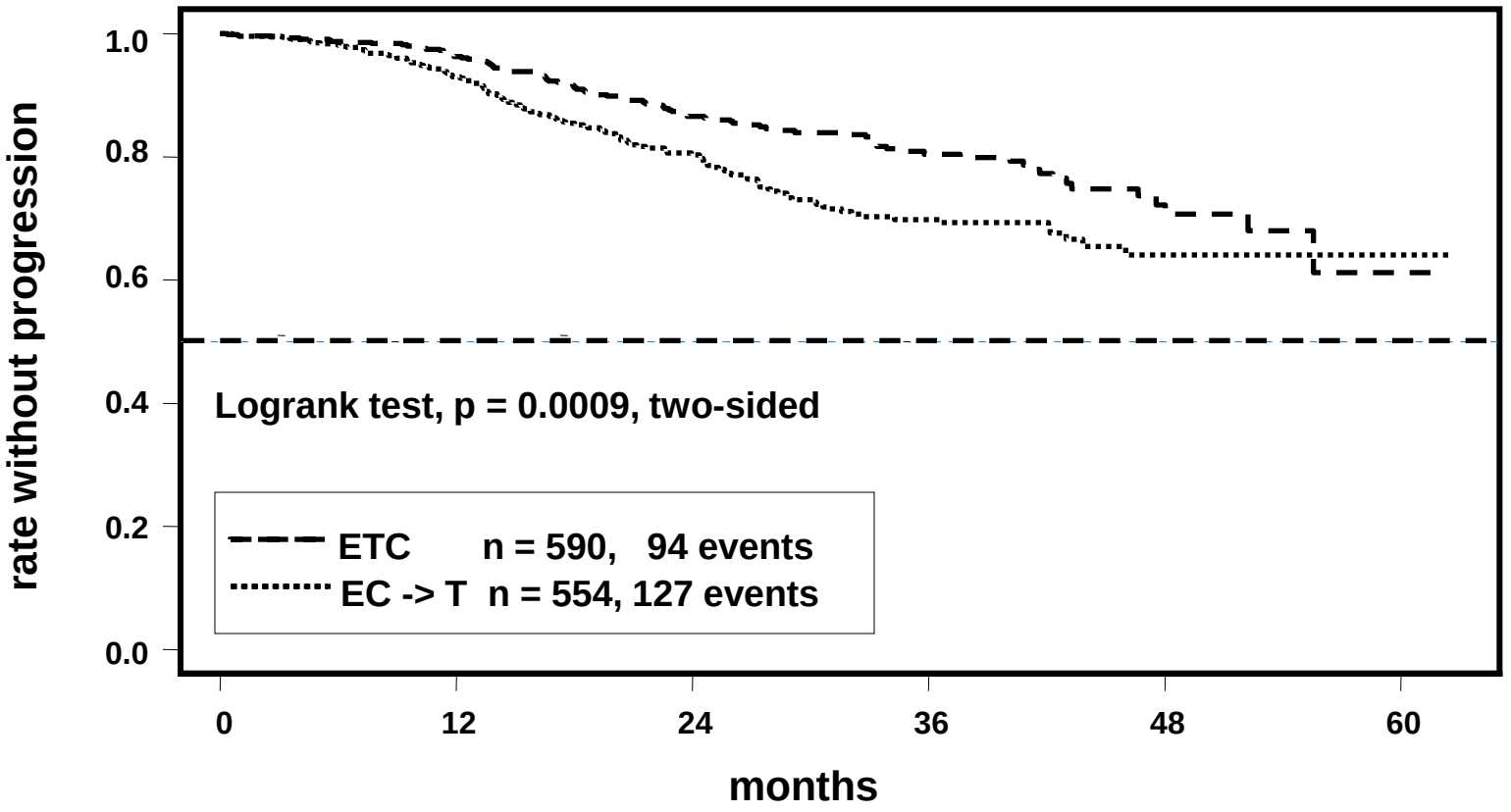
in patients with ≥4+ lymph nodes



Möbus, VJ et al: Proc ASCO 2004 Abs 513

AGO-Trial ETC vs EC→T

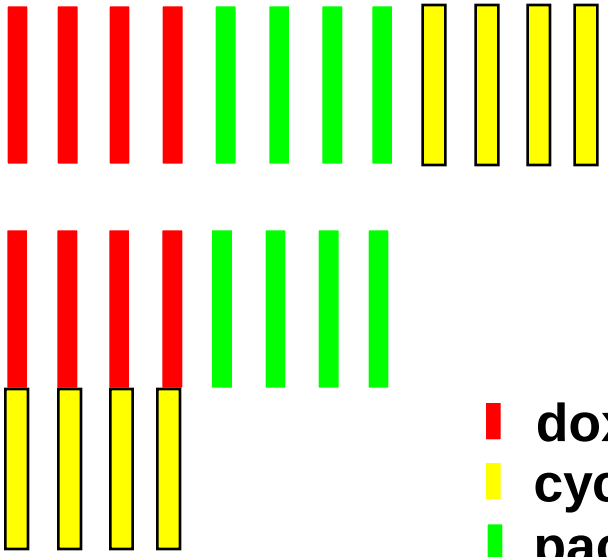
Time to relapse by therapy



Möbus, VJ et al: Proc ASCO 2004 Abs 513

Intergroup Node (+) Trial

CALGB 9741 – 2 x 2 Factorial Design



	q 2 wk (w/G-CSF)	q 3 wk
	22 weeks	33 weeks
	14 weeks	21 weeks

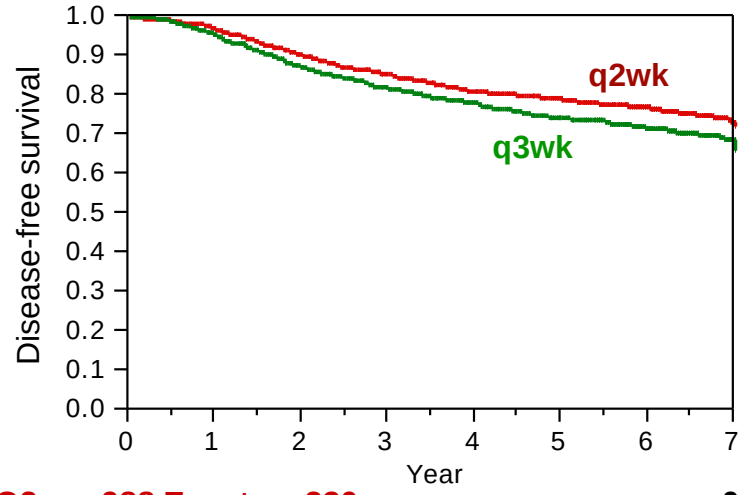
- doxorubicin 60 mg/m^2
- cyclophosphamide 600 mg/m^2
- paclitaxel 175 mg/m^2 over 3 hours

Radiation therapy and tamoxifen follow as appropriate

Accrued 9/97-3/99 with n=2005

M. Citron, et al. JCO 2003

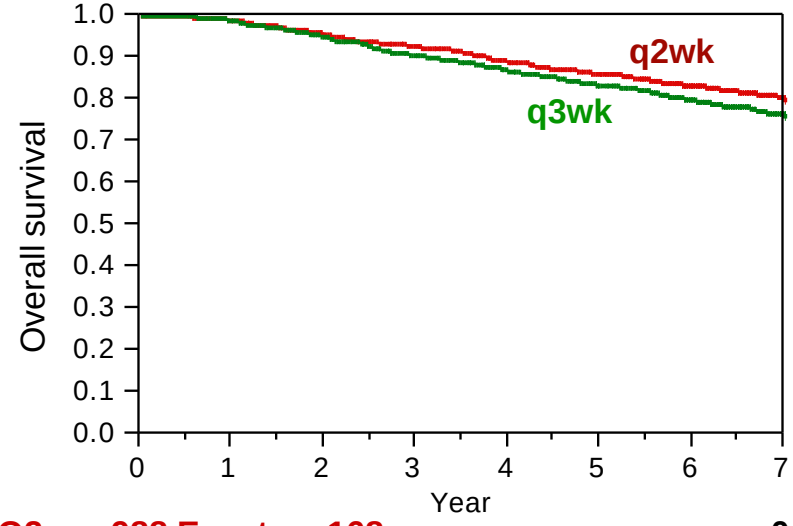
DFS by Dose Density (Q2 vs Q3)
11/30/2005



Q2 n = 988 Events = 230
Q3 n = 984 Events = 278

p = 0.012

OS by Dose Density (Q2 vs Q3)
11/30/2005

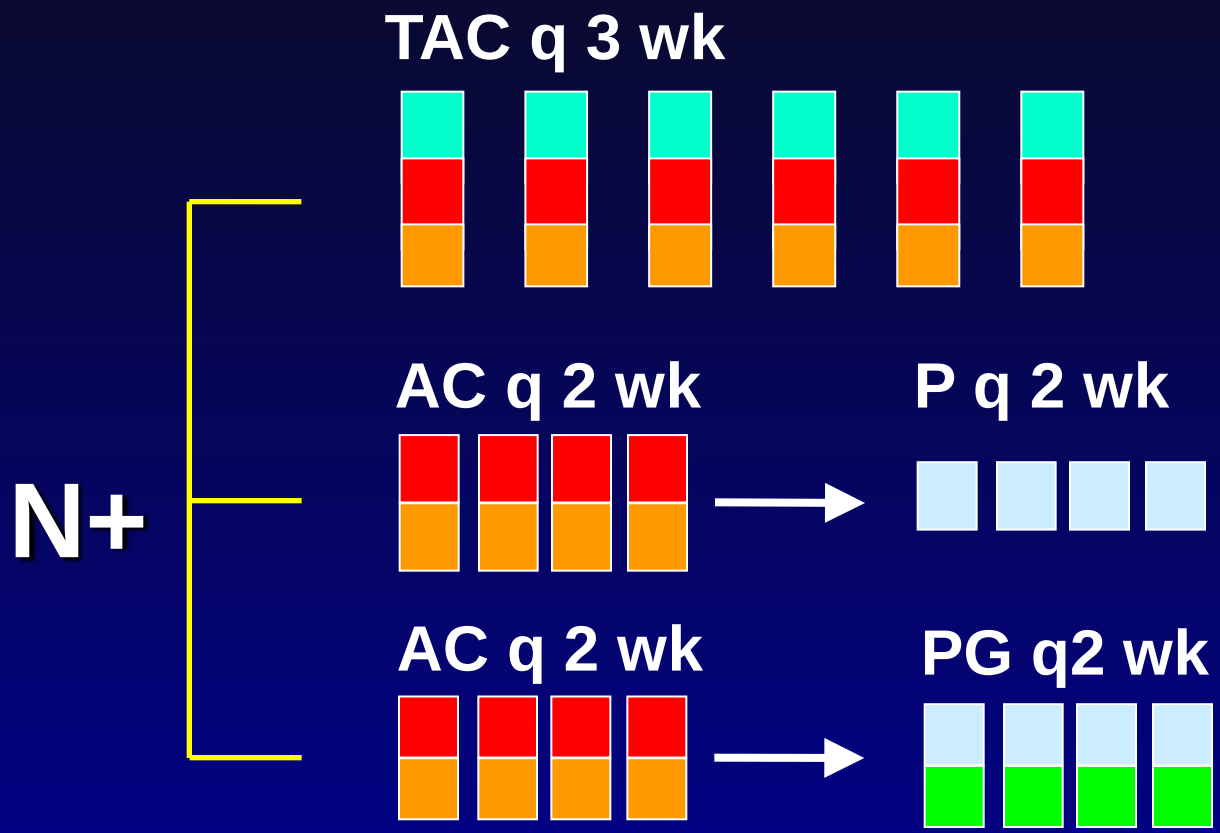


Q2 n = 988 Events = 168
Q3 n = 984 Events = 202

p = 0.049

NSABP B-38
Schema

Stratification: # nodes, Hormone receptor, Surgery and RT



All arms pegfilgrastim or filgrastim

EPO: rec for Hgb ≤ 11 gm/dl

ER positive: hormonal therapy for 5 yrs after chemo

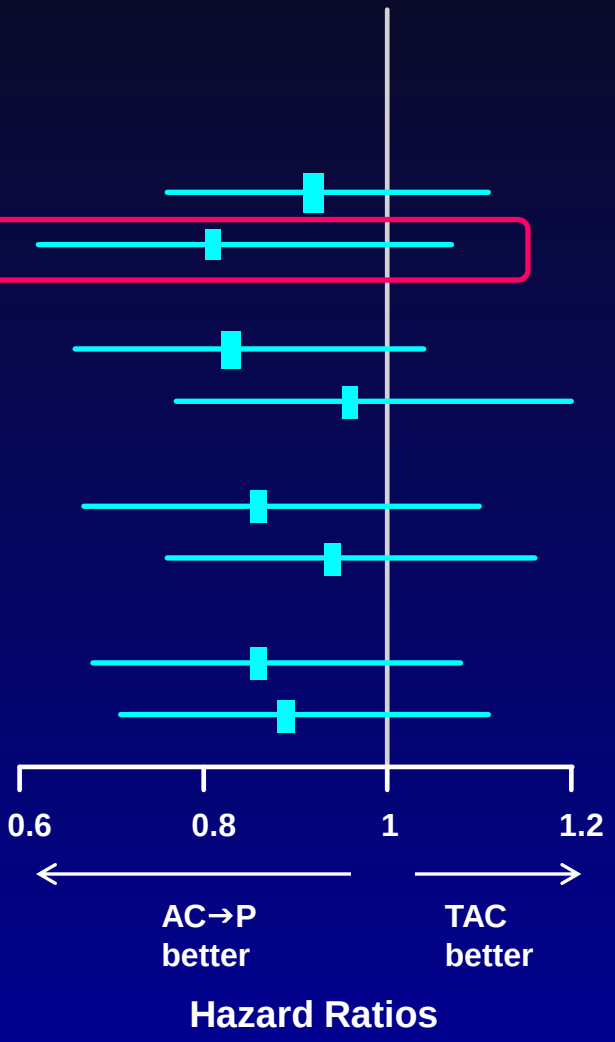
NSABP B-38
Disease-Free Survival (DFS)

- **Five-year DFS:**
  - TAC: 80.1% (95% CI = 78, 82)
  - DD AC→P: 82.2% (95% CI = 80.2, 84)
  - DD AC→PG: 80.6% (95% CI = 78.5, 82.5)
- **Pairwise comparisons:**
  - DD AC→PG vs. TAC: HR=0.93 (p=0.39)
  - DD AC→PG vs. DD AC→P: HR=1.07 (p=0.41)
  - DD AC→P vs. TAC: HR=0.87 (p=0.074)

NSABP B-38
Hazard Ratios for DFS

AC→P vs TAC

Subgroup	No. of Patients	Hazard Ratio *
ER Positive	3853	0.91
ER Negative	988	0.82
LN 1-3	3218	0.82
LN ≥ 4	1623	0.96
Lumpectomy	2411	0.87
Mastectomy	2250	0.91
No or local RT	2439	0.86
Regional RT	2269	0.88



** Adjusted for randomization factors*

NSABP B-38
Deaths on Treatment (N)

Grade	TAC (1612)	AC→P (1623)	AC→PG (1612)
5	13	5	7

P=0.2