



FONDAZIONE MICHELANGELO

Stopping a cancer trial early: is it really for the benefit of patients? What about the quality of data?

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I have no relevant relationships to disclose

Randomized clinical trials

They are typically designed with a specific accrual period (e.g. 2 years) and a subsequent follow-up time long enough (e.g. 5 years) to ensure sufficient information to reject with high probability (power) the null hypothesis of treatment equivalence when, in fact, the treatment differs by a specified amount

Randomized clinical trials

Monitoring interim efficacy results is important for stopping trials early for unexpectedly large treatment differences, or for “negative” differences suggesting a positive result at the end of the trial would be extremely unlikely

Reasons to Consider Premature Termination of a Clinical Trial

➤ **Non controversial**

- excessive toxicity
- changes in standard of care
- poor accrual

➤ **Possibly controversial**

- futility

➤ **Highly controversial**

- apparent higher efficacy of the experimental arm

Why 'early' or 'interim' analysis?

The specific aim of 'early' or 'interim' analyses is to **reduce the period required to determine the benefit** of an applied treatment

While this motivation is important, these analyses are not totally unbiased and they require careful evaluation and proper statistical considerations in that

they should properly predict long-term results

How should interim results be interpreted?

- Information about treatment efficacy is more limited in an early analysis than in a final analysis
- In particular, there are concerns that treatment effects seen early may not be real or may be overly optimistic
 - limited follow-up duration
 - early transient effects in patients with worse prognosis

Methodological Issues

- Clinical studies are usually designed to answer a primary aim, phrased in terms that FFP/DFS distributions in two treatment groups are equivalent (null hypothesis)

Methodological Issues

- The alternative hypothesis is that FFP/DFS is prolonged in either of the two treatment groups
 - √ 60% vs 67% at 3 years
at the 0.05 level (type I error)
 - √ median FFP 3 years vs 5.5 years
at the 0.05 level (type I error)

Methodological Issues

- Fleming et al. showed that the type I error can be as great as 26% if a statistical significance test is performed every 3 mos of a 3-year trial comparing two identical treatments

Nominal Two-Sided Significance Levels for Interim Monitoring that Maintain Overall Type I Error Level of 0.05

| Analysis # | Pocock | Peto Haybittle | O'Brien and Fleming | Fleming |
|--------------|--------------|-------------------|---------------------------|---------------|
| 1 | 0.016 | 0.0027 | 0.00001 | 0.0051 |
| 2 | 0.016 | 0.0027 | 0.0013 | 0.0061 |
| 3 | 0.016 | 0.0027 | 0.008 | 0.0073 |
| 4 | 0.016 | 0.0027 | 0.023 | 0.0089 |
| Final | 0.016 | 0.049 | 0.041 | 0.0402 |

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

F. Trotta e al, Ann Oncol 2008

Method: 1/1997 to 10/2007

Medline retrieval

93 relevant reports identified

25 selected for analysis

Type of stop: stop enrolment 16

disclosure of results 5

cross experimental arm 3

others 1

Final analysis results: same 22, different 1, NA 2

Registration trial 12, non registration trial 13

The National Cancer Institute Cooperative Group Experience From 1990-2005

Korn et al, JCO April 2009

A total of 27 Phase III trials identified that were stopped or reported early for positive results
Accrual completed in 19; stopped in 8 of 27

< 80%* information
= 9

**%info: observed events to
events required at final analysis*

With additional
Follow-up data
= 18
↓
Treatment effect
similar or only
slightly smaller
= 17

Choice of the Primary End Point

- The primary end point for an adjuvant trial in breast cancer is usually considered DFS
- The possibility exists that at the early stopping/release there are insufficient numbers of events for the non-primary end point OS
- In addition, allowing cross-over treatment to the experimental arm because of early positive results on DFS may influence the OS survival data

The National Cancer Institute Cooperative Group Experience From 1990-2005

Korn et al, JCO April 2009)

Studies with adjuvant therapy in early breast cancer

| | |
|-------------|--|
| EST-3189 | CAF vs 16 week multidrug regimen in N+ ER- tumors |
| SWOG-8814 | TAM vs CAF+TAM vs CAF→TAM in postmenopause, N+ ER+ tumors |
| CALGB-9344 | AC (st vs int vs high) paclitaxel in N+ tumors |
| NCIC-MA17 | Letrozole vs placebo in postmenopause after at least 5 years of adjuvant AI |
| NSABP-B31 | AC→P trastuzumab |
| NCCTG-N9831 | in HER2+, N+ or high-risk N- tumors |
| NCIC-MA21 | EC(G-CSF)→P vs AC→P (vs CEF) |

The National Cancer Institute Cooperative Group Experience From 1990-2005

Korn et al, JCO April 2009)

1 of 6 with premature closure of enrolment
(NSABP-B31/NCCTG-N9831)

↓
5 of 6 had DFS as primary objective

↓
5 of 6 with reported additional follow-up

↓
4 of 5 with additional follow-up had similar
outcomes as reported at interim

↓
3 of 4 studies reported statistically
significant OS benefit

The National Cancer Institute Cooperative Group Experience From 1990-2005

Korn et al, JCO April 2009)

| | First reported | | | Follow-up | | |
|-------------|----------------|--------------------------|----------|-----------|--------------------------|----------|
| | %info | effect | P | % info | effect | P |
| EST-3189 | 62 | 3-yr OS 84% vs 73% | 0.005 | 90 | 4-yr OS 78% vs 71% | 0.10 |
| SWOG-8814 | 81 | HR = 0.66 | 0.002 | 120 | HR = 0.76 | 0.002 |
| CALG-9011 | 25 | HR = 0.79 | 0.013 | 59 | HR = 0.83 | 0.0023 |
| NCIC-MA17 | 40 | HR = 0.57 | 0.00008 | 48 | HR = 0.58 | < 0.001 |
| NSABP-B31 | 55 | HR = 0.48 | < 0.0001 | 87 | HR = 0.49 | < 0.0001 |
| NCCTG-N9831 | | | | | | |
| NCIC-MA21 | 58 | HR = 0.60 | 0.0006 | NA | NA | NA |

%info: observed events to events required at final analysis

The National Cancer Institute Cooperative Group Experience From 1990-2005

Korn et al, JCO April 2009)

Overall survival

| | | |
|--------------------------|-----------|--------|
| SWOG-8814 | HR = 0.83 | 0.04 |
| CALG-9011 | HR = 0.82 | 0.0064 |
| NCIC-MA17 | HR = 0.82 | 0.30 |
| NSABP-B31 NCCTG-N9831 | HR = 0.63 | 0.0004 |
| NCIC-MA21 | NR | NR |

The National Cancer Institute Cooperative Group Experience From 1990-2005

Korn et al, JCO April 2009)

Only study had OS as primary end point (EST-3189)

3-yr OS = 84% vs 70.8%, $P = 0.005$ (62% information available)

4- yr OS = 78.1% vs 71.4%, $P = 0.10$ (90% information available)

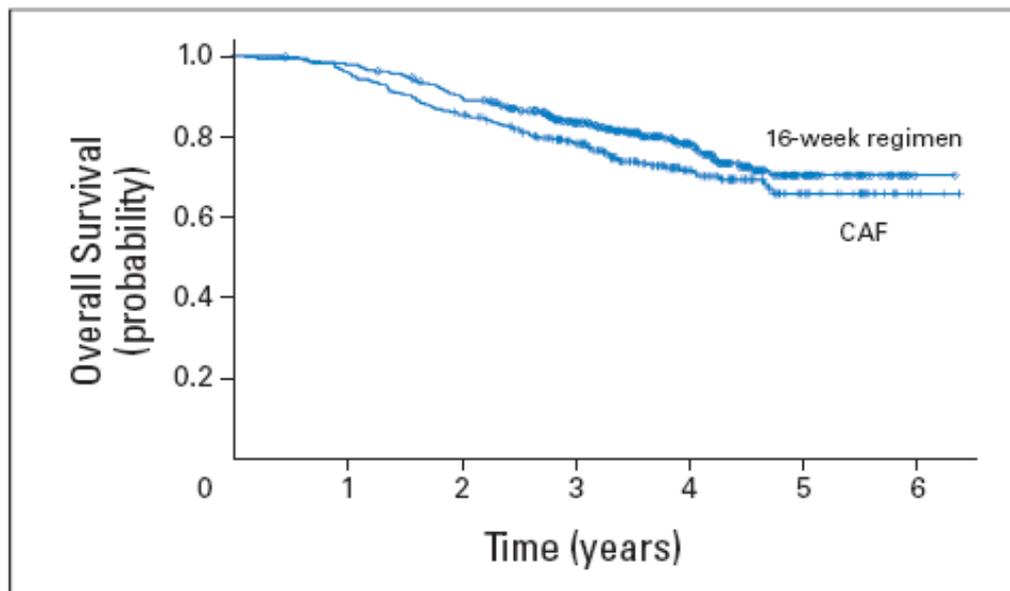


Fig 2. Overall survival curves from EST-3189 (control treatment = cyclophosphamide, doxorubicin, and fluorouracil [CAF]; experimental treatment = 16-week regimen; $P = .10$). (Reprinted from Fig 2 with permission.¹⁴)

**Important
Statistical significance
vanished, but there was
no direct patient arm**

Early vs Late Results: Remarks

- It has been noted that the treatment effect in a study that stops or is released early for positive results is, on average, higher than the true treatment effect
- However, it is also true that the treatment effect observed for a study concluded and reported at its regularly scheduled end (e.g. at 5 years) may be, on average, higher than the treatment effect observed at a later follow-up (e.g. 10 years)

Premature Termination/ Early Release Consequences

- Immature data may change with further follow-up because data from the initial patients enrolled may be not representative of the general population of patients
- Release of early data may prohibit the collection of meaningful data on long-term benefits or adverse events if this release results in a change in care for patients currently on the clinical trial (e.g. cross-over)

ORIGINAL ARTICLE

Adjuvant Docetaxel or Vinorelbine with or without Trastuzumab for Breast Cancer

Heikki Joensuu, M.D., Pirkko-Liisa Kellokumpu-Lehtinen, M.D., Petri Bono, M.D., Tuomo Alanko, M.D., Vesa Kataja, M.D., Raija Asola, M.D., Tapio Utriainen, M.D., Riitta Kokko, M.D., Akseli Hemminki, M.D., Maija Tarkkanen, M.D., Taina Turpeenniemi-Hujanen, M.D., Sirkku Jyrkkiö, M.D., Martti Flander, M.D., Leena Helle, M.D., Seija Ingalsuo, M.D., Kaisu Johansson, M.D., Anna-Stina Jääskeläinen, M.D., Marjo Pajunen, M.D., Mervi Rauhala, M.D., Jaana Kaleva-Kerola, M.D., Tapio Salminen, M.D., Mika Leinonen, M.Sci., Inkeri Elomaa, M.D., and Jorma Isola, M.D., for the FinHer Study Investigators*

CONCLUSIONS

Adjuvant treatment with docetaxel, as compared with vinorelbine, improves recurrence-free survival in women with early breast cancer. A short course of trastuzumab administered concomitantly with docetaxel or vinorelbine is effective in women with breast cancer who have an amplified *HER2/neu* gene. (International Standard Randomised Controlled Trial number, ISRCTN76560285.)

Adjuvant Docetaxel or Vinorelbine with or without Trastuzumab for Breast Cancer

Women who had verified HER2-positive cancer were randomly assigned to receive or not to receive trastuzumab. Nine trastuzumab infusions were administered at one-week intervals; the first

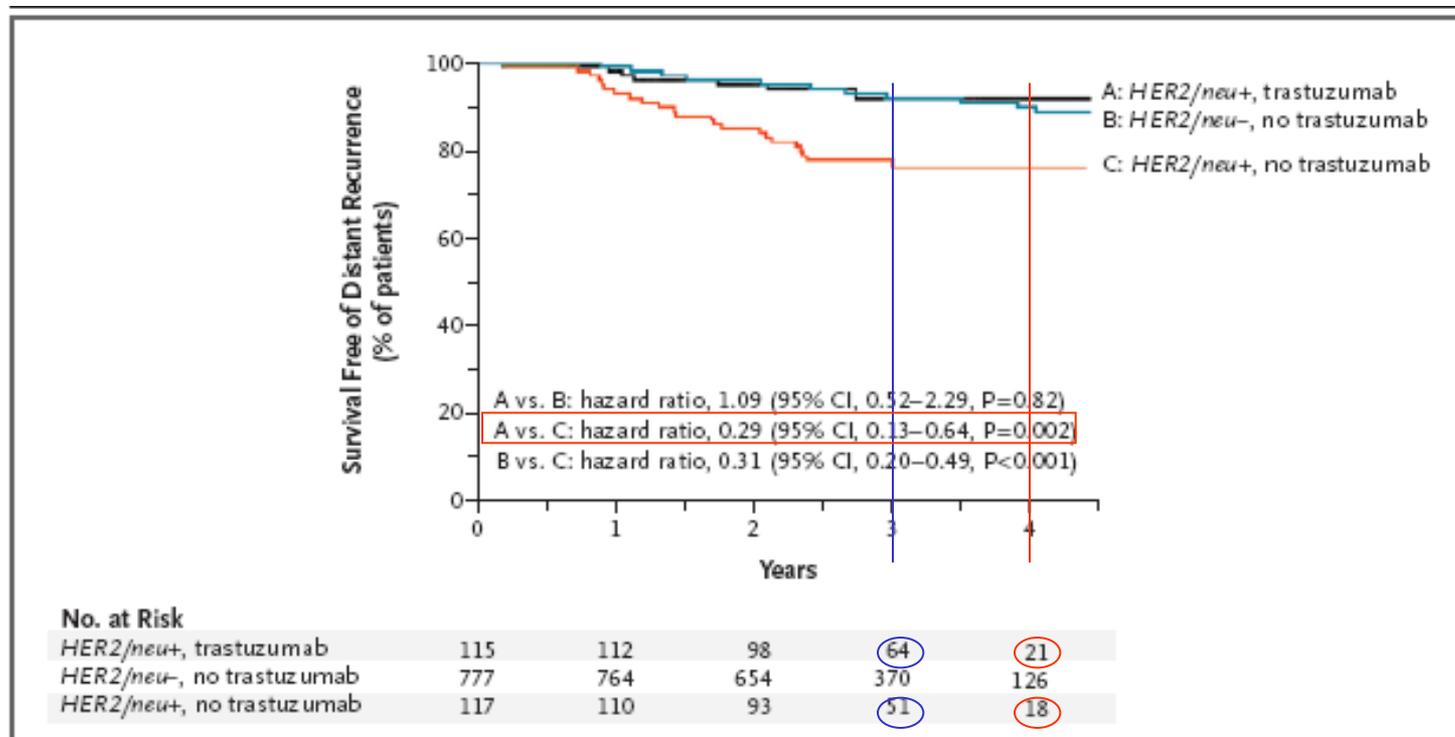


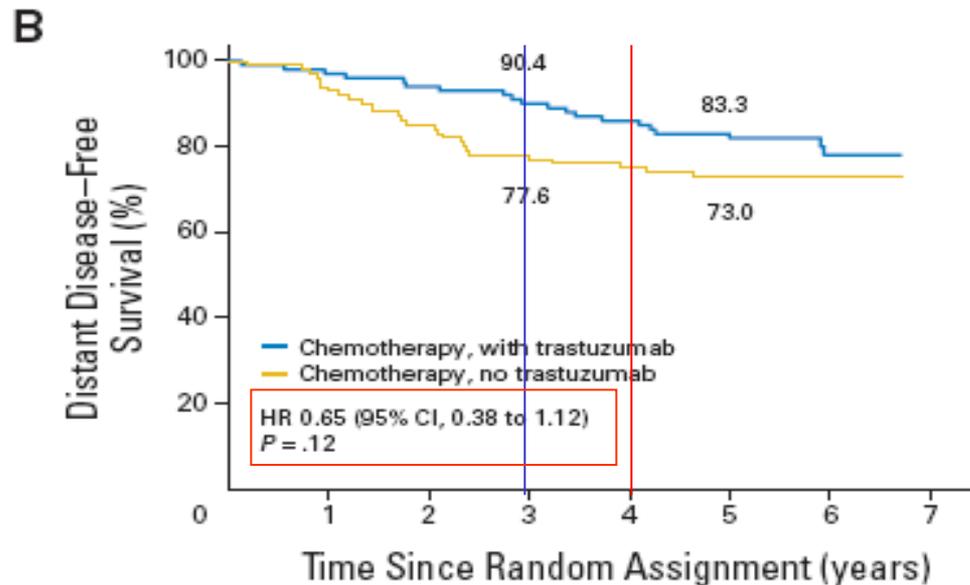
Figure 3. Effect of HER2/neu Amplification and Trastuzumab on the Kaplan–Meier Estimates of Survival Free of a First Distant Recurrence of Breast Cancer.

CI denotes confidence interval.

JCO December 2009

Fluorouracil, Epirubicin, and Cyclophosphamide With Either Docetaxel or Vinorelbine, With or Without Trastuzumab, As Adjuvant Treatments of Breast Cancer: Final Results of the FinHer Trial

Heikki Joensuu, Petri Bono, Vesa Kataja, Tuomo Alanko, Riitta Kokko, Raija Asola, Tapio Utriainen, Taina Turpeenniemi-Hujanen, Sirkku Jyrkkiö, Kari Möykkynen, Leena Helle, Seija Ingalsuo, Marjo Pajunen, Mauri Huusko, Tapio Salminen, Päivi Auvinen, Hannu Leinonen, Mika Leinonen, Jorma Isola, and Pirkko-Liisa Kellokumpu-Lehtinen



| No. at risk | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|------------------------------|-----|-----|-----|-----|----|----|----|---|
| Chemotherapy, trastuzumab | 115 | 112 | 108 | 104 | 98 | 70 | 29 | 0 |
| Chemotherapy, no trastuzumab | 116 | 109 | 98 | 90 | 86 | 54 | 26 | 0 |



HERA trial design

Women with locally determined HER2-positive invasive early breast cancer

Surgery + (neo)adjuvant CT RT

Centrally confirmed IHC 3+ or FISH+ and LVEF \geq 55%

Randomisation

Observation

1 year trastuzumab
8 mg/kg \rightarrow 6 mg/kg
3-weekly schedule

2 years trastuzumab
8 mg/kg \rightarrow 6 mg/kg
3-weekly schedule

After ASCO 2005,
option of crossover
to trastuzumab

HER2, human epidermal growth factor receptor 2; CT, chemotherapy; RT, radiotherapy;
IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridisation; LVEF, left ventricular ejection fraction



DFS and OS over time

Median follow-up
(% follow-up time
after selective
crossover)

DFS benefit

No. of DFS events
H 1 year vs
observation

Median follow-up
(% follow-up time
after selective
crossover)

OS benefit

No. of deaths
H 1 year vs
observation

2005¹
1 year
(0%)



127 vs 220
 $p < 0.0001$

2005¹
1 year
(0%)



29 vs 37
 $p = 0.26$

2006²
2 years
(4.3%)



218 vs 321
 $p < 0.0001$

2006²
2 years
(4.1%)



59 vs 90
 $p = 0.0115$

2008
4 years
(33.8%)



369 vs 458
 $p < 0.0001$

2008
4 years
(30.9%)



182 vs 213
 $p = 0.1087$

0 Favours 1 Favours no 2
trastuzumab HR trastuzumab

0 Favours 1 Favours no 2
trastuzumab HR trastuzumab

Premature Termination/ Early Release Consequences

- A full understanding of the circumstances at the time of stopping is important
- Between the moment of making the decision to stop/release and locking the database, substantial and corrected data may become available
- Such data cleaning may justify a pause before any final decision

Early vs Late Results: Remarks

- Can a trial be stopped on the basis of secondary end points?
- Probably not, unless
 - the secondary end point is safety (no harm to the patients)
 - the secondary end point results provide convincing evidence of great public health importance

Early vs Late Results

- It is important in clinical trials that a well-informed **Independent Data Monitoring Committee** review interim results
- This approach helps to protect
 - patients by having the interim results carefully evaluated by an experienced group of individuals
 - the study from the damage that ensues from misinterpretation of interim results

Independent Data Monitoring Committee (IDMC)

The primary responsibility of the IDMC is to monitor the risk/benefit ratio for patients participating in the trial

The IDMC will operate independently of the Sponsor and participating investigators
Members of the IDMC should disclose any potential conflict of interest for the trial they are asked to monitor

Independent Data Monitoring Committee (IDMC)

Members of the IDMC should make any of the following recommendations

- Continuation of the trial without modification
- Continuation with modification (considering any interim safety and/or efficacy data or other general issues related to the trial)
- Discontinuation (or temporary suspension) of recruitment

Early vs Late Results

- For trials with well-designed interim monitoring plans the ability of early stopping/release because of positive results is an important component of the trial
- This will allow the scientific community and the patients to benefit as soon as possible from study conclusions
- However, it is imperative that early release be **followed by updated and detailed information on DFS, OS and late adverse events**

Essentials of a Clinical Trial

➤ Design

- Important clinical end point(s), scientific and ethical issues
- Accurate and detailed statistical plan including accurate, appropriate and detailed rules for interim analyses

Essentials of a Clinical Trial

➤ Reporting

➤ Critical details of

➤ **when**

➤ **why**

➤ **under what guidelines**

➤ **by whom**

the trial was stopped or early released