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

F. Cardoso, MD
Director, Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal
ESMO Board of Directors & NR Committee Chair
ESO Breast Cancer Program Coordinator
EORTC Breast Group Chair
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
Stopping a trial early in oncology: for patients or for industry?

F. Trotta¹, G. Apolone², S. Garattini² & G. Tafuri¹,³*

¹Italian Medicines Agency (AIFA), Rome; ²Mario Negri Institute for Pharmacological Research, Milan, Italy; ³Utrecht 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
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>
<thead>
<tr>
<th>Trial Identifier</th>
<th>Treatment Effect</th>
<th>95% CI for HR or Difference in Rates</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLB-9011</td>
<td>Median OS: 66 v 56 months</td>
<td>Not applicable</td>
<td>.10</td>
</tr>
<tr>
<td>SWOG-8892</td>
<td>5-year OS: 67% v 37%</td>
<td>Not available</td>
<td>.001</td>
</tr>
<tr>
<td>E2491</td>
<td>5-year OS: 69% v 45%; difference = 24%</td>
<td>13.4% to 34.6%</td>
<td>.0001</td>
</tr>
<tr>
<td>SWOG-8814</td>
<td>HR = 0.83</td>
<td>0.69 to 0.99</td>
<td>.04</td>
</tr>
<tr>
<td>CLB-9344</td>
<td>HR = 0.82</td>
<td>0.71 to 0.95</td>
<td>.0064</td>
</tr>
<tr>
<td>CCG-5942</td>
<td>3-year OS: 98% v 99%; difference = −1%</td>
<td>−3.3% to 1.3%</td>
<td>.90</td>
</tr>
<tr>
<td>RTOP-9413</td>
<td>4-year OS: 84.7% v 84.3%; difference = 0.4%</td>
<td>−4.6% to 5.4%</td>
<td>.94</td>
</tr>
<tr>
<td>SWOG-S9701</td>
<td>HR = 0.84</td>
<td>0.61 to 1.16</td>
<td>.30</td>
</tr>
<tr>
<td>NCCTG-9741</td>
<td>HR = 0.66</td>
<td>0.54 to 0.82</td>
<td>.0001</td>
</tr>
<tr>
<td>NCIC-MA17</td>
<td>HR = 0.82</td>
<td>0.57 to 1.19</td>
<td>.3</td>
</tr>
<tr>
<td>ECOG-1496</td>
<td>HR = 0.51</td>
<td>0.25 to 1.04</td>
<td>.06</td>
</tr>
<tr>
<td>CCG-1961</td>
<td>HR = 0.64</td>
<td>0.47 to 0.87</td>
<td>.005</td>
</tr>
<tr>
<td>E2997</td>
<td>2-year OS: 79% v 80%; difference = −1%</td>
<td>−14.3% to 12.3%</td>
<td>.69</td>
</tr>
<tr>
<td>NSABP-B-31/NCCTG-N9831</td>
<td>HR = 0.63</td>
<td>0.49 to 0.81</td>
<td>.0004</td>
</tr>
<tr>
<td>ECOG-2100</td>
<td>HR = 0.88</td>
<td>0.74 to 1.05</td>
<td>.16</td>
</tr>
</tbody>
</table>
| NCIC-MA21        | 47 v 65 deaths       | Not applicable                       | .09†
MOLECULAR (RE-)CLASSIFICATION OF BREAST CANCER

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

Relapse earlier

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

Recurrences

15% 17%

Breast cancer deaths

9% 18%

EBCTCG, Lancet. 2005
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
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Journal</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Goss et al</td>
<td>NEJM</td>
<td>A randomised trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer</td>
</tr>
<tr>
<td>2005</td>
<td>Goss et al</td>
<td>JNCI</td>
<td>Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17</td>
</tr>
<tr>
<td>2008</td>
<td>Goss et al</td>
<td>JCO</td>
<td>Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen</td>
</tr>
<tr>
<td>2012</td>
<td>Jin et al</td>
<td>JCO</td>
<td>Longer-Term Outcomes of Letrozole Versus Placebo After 5 Years of Tamoxifen in the NCIC CTG MA.17. Trial: Analyses Adjusting for Treatment Crossover</td>
</tr>
</tbody>
</table>
2003: first results
Median follow-up 2.4 y
207 events (40%)

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS 4y</td>
<td>0.57</td>
<td>0.43-0.75</td>
<td>.00008</td>
</tr>
<tr>
<td>OS 4y</td>
<td>0.61</td>
<td>0.47-0.79</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Unblinding
Expeditious report
Planned Subgroup analysis according to LN status

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>Distant DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node + patients</td>
<td>HR 0.61* (95% CI, 0.45-0.84)</td>
<td>HR 0.53* (95% CI, 0.36-0.78)</td>
<td>HR 0.61* (95% CI, 0.38-0.98)</td>
</tr>
<tr>
<td>Node – patients</td>
<td>HR 0.45* (95% CI, 0.27-0.75)</td>
<td>HR 0.63 (95% CI, 0.31-1.27)</td>
<td>HR 1.52 (95% CI, 0.76-3.06)</td>
</tr>
</tbody>
</table>

➢ 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 rates of AI discontinuation, overall 20%, zero in pts older 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
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%

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)
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

<table>
<thead>
<tr>
<th>B-33: Accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opened:</strong></td>
</tr>
<tr>
<td><strong>Target Accrual:</strong></td>
</tr>
<tr>
<td><strong>Accrual in 10/03:</strong></td>
</tr>
</tbody>
</table>

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
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

No significant difference
Lost possibility for confirmatory trial

WHY is confirmatory trial important?

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>779</td>
<td>52</td>
</tr>
<tr>
<td>Exemestane</td>
<td>783</td>
<td>37</td>
</tr>
</tbody>
</table>
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

Very large study, with potential to provide definite conclusions
BUT reported earlier and stopped
Consequences of early reporting in CHEMOPREVENTION

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

ANASTROZOLE VS TAMOXIFENE
Subset analysis ATAC trial

Unplanned subset analysis according to ER/PgR

<table>
<thead>
<tr>
<th>ER+ PgR+</th>
<th>ER+ PgR-</th>
<th>ER- PgR+</th>
<th>ER- PgR-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3830</td>
<td>879</td>
<td>139</td>
<td>481</td>
<td>5329</td>
</tr>
</tbody>
</table>

HR: 0.48 (0.33-0.7)!

But formal statistical test of interaction not significant

CONSEQUENCES:

It influenced reimbursement and availability of AIs in Belgium for years

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

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