Adjusting for Selective Crossover in Analyses of Letrozole Versus Tamoxifen in the BIG 1-98 Trial

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Disclosures

• BIG 1-98 is coordinated by the International Breast Cancer Study Group (IBCSG) for the BIG.
• Novartis, the manufacturer of letrozole, distributed study drugs and provided financial support to IBCSG but imposed no restrictions on the investigators with respect to trial data.
• Statistical analysis partially supported by NCI grant CA-75362 to IBCSG Statistical and Data Management Center.
What is Selective Crossover?

- Special case of *non-adherence to a randomized treatment* following the report of *positive trial results*: control group patients selectively cross over to the experimental treatment.

- *Disturbs the randomized comparison* in updated analyses performed subsequent to the first results.

- BIG 1-98, adjuvant trastuzumab trials.
Randomized Clinical Trial

Randomized Trial

CONTROL

Randomize

EXPERIMENTAL

Primary Result (ITT)

Follow-up

Experimental Superior DFS

Positive primary result leads to ethical imperative to allow patients in control group to receive experimental treatment
Randomized Clinical Trial

Randomized Trial

CONTROL

Follow-up

EXPERIMENTAL

Primary Result (ITT)

Experimental Superior DFS

Further Follow up

Selective crossover

Updated Result

Update DFS

Analyze for OS
Paradigm Shift

Randomized clinical trial → Observational study
Intent-to-Treat Modelling – account for treatment selection

Goal: Determine the best estimate of benefit of experimental treatment had there been no selective crossover
BIG 1-98 Monotherapy Update
76 months median follow-up (NEJM 2009)

Includes only patients randomized to monotherapy
(directly updates Coates et al., J Clin Oncol 2007 at 51 mos. MFU)
Selective Crossover in Tamoxifen Arm of BIG 1-98

- First report Jan 2005: Let vs. Tam HR for DFS=0.81 (95% CI 0.70-0.93)
- 25% crossed over
- 7% of total follow up
- Average 18 months on Let
- Patient and disease characteristics that contribute to outcome also influence selective crossover
Switching to AI after 2-3 yrs of tamoxifen prolongs OS.

### Cohort 2: Trials of switch from tamoxifen to AI

**Switching to AI after 2-3 yrs of tamoxifen**

**Cohort 2:**

**Trials of switch from tamoxifen to AI**

**Results:**

- **Switching to AI after 2-3 yrs of tamoxifen**
  - Prolongs OS

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**Meta-Analysis of Breast Cancer Outcomes in Adjuvant Trials of Aromatase Inhibitors Versus Tamoxifen**

Ingle JN et al. AIs vs tamoxifen as adjuvant therapy for postmenopausal women with ER-positive breast cancer: meta-analyses of randomized trials of monotherapy and switching strategies. SABCS 2008, abstract #12.
BIG 1-98 Monotherapy Update

76 months median follow-up (NEJM 2009)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>5-Yr % Let</th>
<th>5-Yr % Tam</th>
<th>ITT P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free Survival, Intent-to-treat</td>
<td>0.88 (0.78–0.99)</td>
<td>85.6</td>
<td>82.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Overall Survival, Intent-to-treat</td>
<td>0.87 (0.75–1.02)</td>
<td>91.8</td>
<td>90.9</td>
<td>0.08</td>
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<tr>
<td>Time to distant recurrence, Intent-to-treat</td>
<td>0.85 (0.72–1.00)</td>
<td>92.4</td>
<td>90.1</td>
<td>0.05</td>
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Favors Letrozole  Favors Tamoxifen
BIG 1-98 Monotherapy Update

76 months median follow-up (NEJM 2009)

### Hazard Ratio

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intent-to-treat</th>
<th>Censored</th>
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Favors Letrozole Favors Tamoxifen
Inverse Probability of Censoring Weighted Analysis (IPCW)

- Weight the follow up for the women who stay on tamoxifen so that they account not only for themselves but also for the censored follow up of matched patients who cross over.

- Weights determined by matching characteristics, both baseline and across time, for the women who do and do not cross over.
  
  - Better estimate of treatment effect than ITT in the presence of selective crossover.
  - Assumes all important confounders of both crossover and outcome are used to estimate weights.

Robins JM, Finkelstein DM. Biometrics 2000; 56:779-88
# Overall Survival

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Mo/Yr Presented</th>
<th>Median Follow Up (mos.)</th>
<th>Number of Events</th>
<th>HR [Let:Tam] (95% CI)</th>
</tr>
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<tr>
<td>ITT</td>
<td>1/05</td>
<td>26</td>
<td>358</td>
<td>.86 (.70-1.06)</td>
</tr>
<tr>
<td>ITT</td>
<td>12/08</td>
<td>76</td>
<td>646</td>
<td>.87 (.75-1.02)</td>
</tr>
<tr>
<td>Censored</td>
<td>12/08</td>
<td>74⁺</td>
<td>641⁺</td>
<td>.81 (.69-.94)</td>
</tr>
<tr>
<td>IPCW*</td>
<td>Today</td>
<td>74⁺</td>
<td>641⁺</td>
<td>.83 (.71-.97)</td>
</tr>
</tbody>
</table>

* Follow up censored at selective crossover: 641 events and 74 mos. median follow up.

* The weighting adjusts for factors associated with OS and with selective crossover, including baseline factors such as age, nodal status, tumor grade, and time-varying performance status.
BIG 1-98 Monotherapy Update
Including IPCW Analyses

Disease-free Survival
- Intent-to-treat: Hazard Ratio 0.88 (0.78–0.99)
- Censored: Hazard Ratio 0.84 (0.74–0.95)
- IPCW: Hazard Ratio 0.85 (0.76–0.96)

Overall Survival
- Intent-to-treat: Hazard Ratio 0.87 (0.75–1.02)
- Censored: Hazard Ratio 0.81 (0.69–0.94)
- IPCW: Hazard Ratio 0.83 (0.71–0.97)

Time to distant recurrence
- Intent-to-treat: Hazard Ratio 0.85 (0.72–1.00)
- Censored: Hazard Ratio 0.81 (0.68–0.96)
- IPCW: Hazard Ratio 0.81 (0.69–0.96)

Favors Letrozole  Favors Tamoxifen
Conclusions

• Because of selective crossover and based on external evidence showing the benefit of switching from tamoxifen to an aromatase inhibitor, the ITT analysis on updated data from BIG 1-98 is inaccurate and no longer relevant for patient care.

• Modeling methods such as IPCW should be used to estimate outcome that would have been observed had there been no selective crossover.

• BIG 1-98 provides evidence of a statistically significant (p<0.05) overall survival benefit for 5 years of letrozole compared with 5 years of tamoxifen.
Thanks to...

- The patients participating in the trial
- The investigators, data managers, nurses, study coordinators, statisticians
- The cooperative groups
- The trial monitors/audit teams
- Novartis