Letrozole Monotherapy vs. Tamoxifen Monotherapy or vs. Letrozole in Sequence with Tamoxifen for Postmenopausal Women with Endocrine-Responsive Early Breast Cancer

BIG 1-98/IBCSG 18-98

Henning Mouridsen

for the BIG 1-98 Collaborative Group

Coordinated by the

International Breast Cancer Study Group
Disclosure

• BIG 1-98 is coordinated by the International Breast Cancer Study Group and financed by Novartis
• Henning Mouridsen has received fees from Novartis for advisory boards and lectures
<table>
<thead>
<tr>
<th>Country</th>
<th>Code</th>
<th>Participants</th>
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<tbody>
<tr>
<td>Argentina</td>
<td>123</td>
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<td>Netherlands</td>
<td>94</td>
<td>TOTAL 8028</td>
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</table>
BIG 1-98 Overall Design

2-Arm Option

- A: Tamoxifen
  - N=911
- B: Letrozole
  - N=917

N=1,828 Enrolled
1998-2000

4-Arm Option

- A: Tamoxifen
  - N=1548
- B: Letrozole
  - N=1546
- C: Tamoxifen + Letrozole
  - N=1548
- D: Letrozole + Tamoxifen
  - N=1540

N=8,010*

*ITT: excludes 18 patients who withdrew consent and did not receive study treatment

Previous Analyses:
Is 5 years Let superior to 5 years Tam as initial therapy?
- Primary Core Analysis (PCA), Median follow-up 26 months
- Monotherapy Arm Analysis, Median follow-up 51 months

Stratify
- Institution
- CT (Adjuvant/Neoadjuvant)
  - Prior
  - None
  - Concurrent

Randomize

4-YEARS
0 2 5

N=911
N=917
N=1548
N=1546
N=1548
N=1540

International Breast Cancer Study Group
SABCS 2008
Summary of Previous Analyses

The PCA and monotherapy analyses showed that 5 years upfront letrozole is significantly superior to 5 years of upfront tamoxifen in terms of

– Disease-Free Survival
– Time to Distant Recurrence

*Coates et al, J Clin Oncol 2007;25:486-92*
BIG 1-98
New Data to Be Presented

• Monotherapy update
  – Protocol-specified, 10-years from start of study
  – Median follow-up 76 months

• Sequential therapy vs. letrozole
  – Protocol-specified final efficacy analysis
    (DSMC October 2008)
  – Median follow-up 71 months
BIG 1-98 Monotherapy Update
Median Follow-up 76 months

2-Arm Option
- A: Tamoxifen, N=911
- B: Letrozole, N=917

4-Arm Option
- A: Tamoxifen, N=1548
- B: Letrozole, N=1546
- C: Tamoxifen, N=1548
- D: Letrozole, N=1546

N=1,828 Enrolled 1998-2000
N=3,094 Enrolled 1999-2003
N=4,922
BIG 1-98 Monotherapy Update

• 2005 results of Let superiority led to unblinding of Tam-alone arm
• 619 (25.2%) patients selectively crossed over to Let
  • Mostly in years 3-5
  • Median duration Let after crossover 18 mos.
• This complicates comparisons with Tam alone
• The comparison of Tam vs. Let was done by
  • Intent-to-treat (ITT)
  • Censoring at crossover
### BIG 1-98 Monotherapy Update

**Median Follow-up 76 months**

#### Disease-free Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Events Letrozole</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>ITT P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat*</td>
<td>509</td>
<td>0.88</td>
<td>0.78–0.99</td>
<td>0.03</td>
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<tr>
<td>Censored</td>
<td>565</td>
<td>0.84</td>
<td>0.74–0.95</td>
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#### Overall Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Events Letrozole</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>ITT P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat</td>
<td>303</td>
<td>0.87</td>
<td>0.75–1.02</td>
<td>0.08</td>
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<tr>
<td>Censored</td>
<td>343</td>
<td>0.81</td>
<td>0.69–0.94</td>
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</table>

#### Time to distant recurrence

<table>
<thead>
<tr>
<th>Group</th>
<th>Events Letrozole</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>ITT P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat</td>
<td>257</td>
<td>0.85</td>
<td>0.72–1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Censored</td>
<td>298</td>
<td>0.81</td>
<td>0.68–0.96</td>
<td></td>
</tr>
</tbody>
</table>

*Let: Tam: breast cancer events, 321:363; second (non breast) malignancy, 101:115; deaths without prior cancer event, 87:87
BIG 1-98
New Data to Be Presented

• Monotherapy update
  – Protocol-specified, 10-years from start of study
  – Median follow-up 76 months

• Sequential therapy vs. letrozole monotherapy
  – Protocol-specified, final efficacy analysis (DSMC October 2008)
  – Median follow-up 71 months
BIG 1-98 Sequential Therapy

2-Arm Option
A: Tamoxifen
B: Letrozole

4-Arm Option
A: Tamoxifen, N=1548*
B: Letrozole, N=1546
C: Tamoxifen, Letrozole, N=1548
D: Letrozole, Tamoxifen, N=1540

N=6,182 Enrolled 1999-2003

*612 patients (39.5%) selectively crossed over to letrozole after the tamoxifen arm was unblinded. The present analysis includes only 3 blinded arms (B, C, D)

Is a sequence of agents superior to letrozole monotherapy?
BIG 1-98 Sequential Therapy
Two Pairwise Comparisons

- 3 blinded arms
- Sequential vs. letrozole monotherapy
- Evaluated from randomization
- Median Follow Up 71 mos.
- 99% confidence intervals to account for multiple comparisons
BIG 1-98 Sequential Treatment Disease-Free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts</th>
<th>Events</th>
<th>5-year DFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole</td>
<td>1546</td>
<td>248</td>
<td>87.9</td>
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<tr>
<td>Let→Tam</td>
<td>1540</td>
<td>236</td>
<td>87.6</td>
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<tr>
<td>Tam→Let</td>
<td>1548</td>
<td>259</td>
<td>86.2</td>
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</table>

Number at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts</th>
<th>Years from randomization</th>
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<tbody>
<tr>
<td>Letrozole</td>
<td>1546</td>
<td>0, 1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>Let→Tam</td>
<td>1540</td>
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Sequential Treatment Comparisons
Median Follow-up 71 months

Tam→Let vs. Let

Hazard Ratio (99% CI)
0.5 0.75 1 1.25 1.5
DFS
OS
TDR*
Favors Tam→Let Favors Letrozole

Let→Tam vs. Let

Hazard Ratio (99% CI)
0.5 0.75 1 1.25 1.5
DFS
OS
TDR*
Favors Let→Tam Favors Letrozole

*Time to distant recurrence
Breast Cancer Events

Tam→Let vs. Let

Overall

By Nodal Status*

*42% of the population is node positive; 58% node negative
Breast Cancer Events

Let→Tam vs. Let

Overall

By Nodal Status*

*42% of the population is node positive; 58% node negative
Conclusions

For postmenopausal women with endocrine-responsive breast cancer

• Updated results of BIG 1-98 suggest superior overall survival with letrozole compared with tamoxifen

• Adjuvant endocrine therapy should start with letrozole especially for patients at higher risk for early recurrence

• Patients commenced on letrozole can be switched after 2 years to tamoxifen, if required

• Safety is consistent with known safety profiles of each agent (data not shown)

• Improved therapeutic approaches beyond five years are required to control late relapses
Thanks to…

- The patients participating in the trial
- The principal investigators
- The co-investigators, data managers, nurses, study coordinators
- The cooperative groups
- The IBCSG Data and Safety Monitoring Committee
- The trial monitors/audit teams
- Novartis