Clinical Trial Designs for First-line Hormonal Treatment of Metastatic Breast Cancer

Susan Honig, M.D.
Patricia Cortazar, M.D.
Rajeshwari Sridhara, Ph.D.
Acknowledgements

- John Johnson
- Alison Martin
- Grant Williams
- Julie Beitz
- Richard Pazdur
- Gang Chen
- George Chi
- Ning Li
- Dianne Spillman
- Ann Staten
Purpose

- To discuss the rationale and basis for past approvals of hormonal therapy for metastatic breast cancer
- To solicit input from the Committee in order to improve and standardize our approach
Hormone Drug Approval: Historical Perspective

- Should be distinguished from cytotoxic drug therapy
  - Toxicity
- Basis for approval of hormonal agents derived from NDAs for megestrol acetate, tamoxifen
Megestrol acetate (Megace)

- Approved 7/76 for “the palliative treatment of advanced carcinoma of the breast...”
- Basis of approval
  - Response rate (RR) in Phase II studies
  - Database of 116 patients
- No information available about time to progression (TTP), survival (OS)
- Historical controls
Tamoxifen

• Approved 12/77; many supplements
• Basis of approval:
  – RR in 14 Phase II studies
  – RR in literature reports from 9 other studies
  – Database 1164 patients
• No information available about TTP, OS
• Historical controls for the initial approval
Recent Approval Requirements for Hormonal Drugs

- Randomized clinical trials required
- Response rate adequate endpoint
  - Surrogate endpoint acceptable for treatments with modest toxicity
  - Response is attributed to drug effect, as cancer rarely shrinks without treatment
  - Used as FDA’s primary endpoint for traditional approval, not subpart H
Approval Requirements for Hormonal Drugs

- Survival not required
  - Lack of a demonstrated survival advantage for the control compared to no therapy
  - Non-inferiority for survival is a safety, not efficacy, endpoint

- TTP submitted, but not used as the sole basis of approval
Historical Standards for Approval

- Non-inferiority based on response rate
  - Lower limit of the 2-sided 95% CI for the difference in response between Drug A and Drug B should be ≤ 10%
- “Similarity” for TTP, OS
- Total database of about 1000 patients
Historical Standards for Approval

- Comparator frequently tamoxifen (RR 20%)
- Difference in response rate interpreted as
  - Ruling out inferiority by an absolute difference of 10% OR
  - Ruling out a loss of half of tamoxifen’s effect
Recent Approvals

• Will be summarized by Dr. Cortazar
Hormonal Treatment of Metastatic Breast Cancer

Approval Overview
Hormonal Drugs Approved in 2nd line Metastatic Breast Cancer

- Comparator: Megestrol acetate
- 1° Endpoints: Response rate, TTP
- Approvals: Anastrozole, Letrozole, Exemestane
Hormonal Drugs Approved in 1st line Metastatic Breast Cancer

- Tamoxifen
- Toremifene
- Anastrozole
- Letrozole
Toremifene: Fareston®

1st line Metastatic Breast Cancer

- Approved: October 1995
- Trials: 3 randomized Phase 3
- Comparator: Tamoxifen
- Sample size: 1526 patients in all trials
- 1° Endpoints: Response rate, TTP
- Designed to show non-inferiority in RR
Non-inferiority Trial Design

Protocol definition for non-inferiority was in terms of the lower bounds of the 95% C.I. for RR and TTP:

- Difference in RR (Tor – Tam) was not more than 10% worse than tam.
- TTP lower limit at least 0.80.
## Toremifene 1st line MBC Efficacy Results

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>U.S.</th>
<th>Nordic</th>
<th>East Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tor</td>
<td>Tam</td>
<td>Tor</td>
</tr>
<tr>
<td>60</td>
<td>21</td>
<td>31</td>
<td>60</td>
</tr>
<tr>
<td>20</td>
<td>19</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>RR (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-5.8, 10)</td>
<td></td>
<td></td>
<td>(-15, 3.1)</td>
</tr>
<tr>
<td>95% C.I.</td>
<td></td>
<td></td>
<td>(-9.5, 8.6)</td>
</tr>
<tr>
<td>TTP median months</td>
<td>5.6</td>
<td>7.3</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>5.8</td>
<td>10</td>
<td>5.1</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1.007</td>
<td>0.801</td>
<td>1.015</td>
</tr>
<tr>
<td>95% C.I.</td>
<td>(0.805, 1.259)</td>
<td>(0.643, 0.998)</td>
<td>(0.787, 1.311)</td>
</tr>
</tbody>
</table>
Statistical Issues

- Nordic Trial did not meet the protocol definition of non-inferiority (L.C.I. more than 10%)
- Nordic Trial had significantly worse TTP with TOR
- Lack of explanation for deviance in results
- Approved because of non-inferiority in RR and TTP in 2 of 3 trials
Anastrozole: Arimidex®
1st line Metastatic Breast Cancer

- Approved: September, 2000
- Trials: 2 randomized Phase 3
- Comparator: Tamoxifen
- Sample size: 1021 patients in all trials
- 1° Endpoints: Response rate, TTP
- Designed to show non-inferiority
Non-inferiority Trial Design

Non-inferiority was defined in terms of the lower bounds of the 95% C.I. for RR and TTP:

- Margin for RR was 10% (difference in RR A – Tam more than – 10%).
- Margin for TTP was 20% (HR Tam:A should be more than 0.80).
# Anastrozole 1st line MBC

## Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>Trial 0030</th>
<th>Trial 0027</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td><strong>A</strong> 1</td>
<td><strong>A</strong> 1</td>
</tr>
<tr>
<td></td>
<td><strong>T</strong> 20</td>
<td><strong>T</strong> 20</td>
</tr>
<tr>
<td>Response Rate (%)</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td><strong>Odds Ratio</strong></td>
<td>1.30</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Diff. (A-T)</strong></td>
<td>4.01</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>95% C.I.</strong></td>
<td>(-4.74, 12.78)</td>
<td>(-7.10, 7.74)</td>
</tr>
<tr>
<td>TTP median months</td>
<td>11</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>5.6</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>Hazard Ratio, 95% C.I.</strong></td>
<td>1.42 (1.11, 1.82)</td>
<td>1.01 (0.85, 1.20)</td>
</tr>
<tr>
<td><strong>P - value</strong></td>
<td><em>P = 0.006</em></td>
<td><em>P = 0.920</em></td>
</tr>
</tbody>
</table>
Letrozole: Femara®
1st line Metastatic Breast Cancer

- Approved: December, 2000
- Trial: 1 randomized Phase 3
- Comparator: Tamoxifen
- Sample size: 916 patients
- 1° Endpoint: TTP
- Designed to show superiority
# Letrozole 1<sup>st</sup> line MBC Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>Letrozole</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>2.5</td>
<td>20</td>
</tr>
<tr>
<td>TTP median months</td>
<td>9.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>95% C.I.</td>
<td></td>
<td>(0.60, 0.82)</td>
</tr>
<tr>
<td>P - value</td>
<td></td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>RR (%)</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td></td>
<td>1.71</td>
</tr>
<tr>
<td>95% C.I.</td>
<td></td>
<td>(1.26, 2.32)</td>
</tr>
<tr>
<td>P - value</td>
<td></td>
<td>P = 0.0006</td>
</tr>
</tbody>
</table>
Recent Approvals

- **Anastrozole**
  - RR: Non-inferior to tamoxifen
  - TTP:
    - Superior in study 030 [N ~ 350; 88% ER(+)]
    - Non-inferior in study 027 [45% ER(+)]
- **Letrozole** the first to demonstrate superiority with statistical significance for RR and TTP
  - N=916; 66% ER(+)
- No direct comparison of these agents
- Potential class effect?
Issues to consider: TTP

- Should TTP be the new primary endpoint for breast cancer?
  - Pros
    - Is TTP intrinsically more meaningful than RR?
  - Cons
    - Neither of the aromatase inhibitors may be acceptable for non-inferiority comparison. Neither has reproducibly demonstrated a TTP advantage.
    - No data available for TTP for other comparators
    - Sample size needed for a TTP non-inferiority analysis may be very large
Issues to consider: TTP

• Required information for TTP non-inferiority analysis
  – How to estimate treatment effect of comparator from historical data
    • Point estimate of the hazard ratio?
    • 95% CI?
    • More conservative or more liberal boundary?
  – What fraction of the effect should be retained?
Issues to consider: Response Rate

• Is response rate still an acceptable primary end point?
  – Does RR sufficiently identify efficacy in this setting?
Issues to consider: Response Rate

• Is non-inferiority to tamoxifen (or other approved first-line agent) still an acceptable basis for approval?
  – Pro: FDA has no comparative efficacy standard in most cases
  – Con: Letrozole’s RR > tamoxifen’s RR
Issues to consider: Response Rate

• Alternatively, is superiority to tamoxifen required?
  – By superiority in a direct comparison to tamoxifen OR
  – By non-inferiority comparison to letrozole
**Issues to consider: Response Rate**

- Required information for RR non-inferiority analysis, letrozole as comparator
  - Treatment effect size (RR 30% for letrozole)
  - What fraction of the effect should be retained?
    - Rule out 10% absolute difference in RR
      - Rule out RR < 20%
    - Retain 50% of the letrozole RR
      - Rule out RR < 15%
    - Retain some fraction of the letrozole advantage over tamoxifen
      - Letrozole RR - tamoxifen RR = 10%
      - Retain 50% or 75% of this difference
      - Rule out RR < 25%
Additional Concerns: Choice of endpoint

• Response rate
  – Must exclude patients with bone-only disease

• TTP
  – ODAC discussed difficulties in assessing TTP 6/99
  – Strengthened by blinded trials
Additional Concerns: Choice of endpoint

- **Response rate**
  - Must exclude patients with bone-only disease

- **TTP**
  - ODAC discussed difficulties in assessing TTP 6/99
  - Strengthened by blinded trials
Additional concerns: Non-inferiority trial designs

“Sloppiness obscures differences”

Robert Temple, M.D.
Additional concerns: Non-inferiority trial designs

- Independent substantiation of results particularly important for non-inferiority
- Special attention to study conduct important
  - Inclusion of patients with ER unknown status contributes to lack of observed difference
  - Inclusion of patients with bone-predominant disease makes response assessment difficult
  - Must adapt inclusion criteria as potential predictive factors are validated (her2-neu?)
Additional concerns:
Future applications

- Ongoing trials of new hormonal agents
- Possibility that OS with letrozole will be greater than OS with tamoxifen
Statistical Considerations in Clinical Trial Designs for First-line Hormonal Treatment of Metastatic Breast Cancer
Outline

- Active Control
- Terminology
- Assumptions
- Non-inferiority Designs
- Sample Sizes (power = 0.8, one-sided $\alpha = 0.025$)
- Perspective Issues
- Issues for Discussion
Active Control versus Drug “X”

- Tamoxifen (T)
- Letrozole (L)
Terminology

- **Superiority**
  = Drug ‘X’ better than Active Control
- “Non-inferiority”
  = ‘X’ not much less effective than Active Control
≠ ‘Was Not Different’ or ‘Similar’
Assumptions

- ‘L’ has an effect (compared to placebo)
- Can reliably estimate ‘L’ effect size
  - ‘L’ effect size compared to ‘Placebo’
  - ‘L’ effect size compared to ‘T’
  - or ‘T’ effect size compared to ‘Placebo’
- Control (‘L’) effect in the future study population will be same as in the historical population.
Non-inferiority Trial Design Considerations

- Endpoint - Response Rate
  - Time to Progression

- Control Effect

- $\Delta \%$ Retention
Estimates of True Control Effect

Lower 95% C.L. (\( \alpha \ll 0.025 \))

Lower \( \gamma \) % C.L. (\( \alpha = 0.025 \))

Point Estimate (\( \alpha >> 0.025 \))
Endpoint: Response Rate
**Endpoint - Response Rate**

**Sample Sizes - Point Estimate of Letrozole Effect Relative to Placebo**

<table>
<thead>
<tr>
<th>Total N patients</th>
<th>Point Estimate of Response</th>
<th>Control Effect to be Retained</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>300</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>1200</td>
<td>30%</td>
<td>75%</td>
</tr>
</tbody>
</table>
### Endpoint - Response Rate

Sample Sizes - Point Estimate of Letrozole Effect Relative to Tamoxifen

<table>
<thead>
<tr>
<th>Total N patients</th>
<th>Estimate of Control Effect ('L' over 'T')</th>
<th>% Effect Retained of 'L' over 'T'</th>
</tr>
</thead>
<tbody>
<tr>
<td>587</td>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>1319</td>
<td>10%</td>
<td>50%</td>
</tr>
<tr>
<td>5275</td>
<td>10%</td>
<td>75%</td>
</tr>
</tbody>
</table>
### Endpoint - Response Rate

Sample Sizes - Lower 95% C.L. of Letrozole Effect Relative to Placebo

<table>
<thead>
<tr>
<th>Total N patients</th>
<th>Lower 95% C.L. of Response</th>
<th>Control Effect to be Retained</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>26%</td>
<td>25 %</td>
</tr>
<tr>
<td>360</td>
<td>26%</td>
<td>50 %</td>
</tr>
<tr>
<td>1430</td>
<td>26%</td>
<td>75 %</td>
</tr>
</tbody>
</table>

Fixed Margin Approach of \( \leq 10\% \), \( N = 660 \)
Endpoint: Time to Progression
Endpoint - Time to Progression
Sample Sizes - Point Estimate of Active Control Effect Relative to Tamoxifen

<table>
<thead>
<tr>
<th>N, Total # of Events</th>
<th>Hazard Ratio of T vs. L</th>
<th>Control Effect to be Retained</th>
</tr>
</thead>
<tbody>
<tr>
<td>456</td>
<td>1.4</td>
<td>25 %</td>
</tr>
<tr>
<td>944</td>
<td>1.4</td>
<td>50 %</td>
</tr>
<tr>
<td>3456</td>
<td>1.4</td>
<td>75 %</td>
</tr>
</tbody>
</table>
### Endpoint - Time to Progression
Sample Sizes - Lower 95% C.L. of Active Control Effect Relative to Tamoxifen

<table>
<thead>
<tr>
<th>Letrozole</th>
<th>Anastrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N, Total # of Events</strong></td>
<td><strong>Control Effect to be Retained</strong></td>
</tr>
<tr>
<td>1,646</td>
<td>25 %</td>
</tr>
<tr>
<td>3,542</td>
<td>50 %</td>
</tr>
<tr>
<td>13,523</td>
<td>75 %</td>
</tr>
</tbody>
</table>
**Endpoint - Time to Progression**

Sample Sizes - $\gamma \%$ Lower C.L. of Active Control Effect Relative to Tamoxifen, & preserving $\alpha = 0.025$

<table>
<thead>
<tr>
<th>N, Total # of Events</th>
<th>Control Effect to be Retained</th>
<th>$\gamma %$ Lower C.L.</th>
<th>N, Total # of Events</th>
<th>Control Effect to be Retained</th>
<th>$\gamma %$ Lower C.L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>665</td>
<td>25 %</td>
<td>53%</td>
<td>673</td>
<td>25 %</td>
<td>57%</td>
</tr>
<tr>
<td>1,427</td>
<td>50 %</td>
<td>55%</td>
<td>1,457</td>
<td>50 %</td>
<td>59%</td>
</tr>
<tr>
<td>5,465</td>
<td>75 %</td>
<td>58%</td>
<td>5,631</td>
<td>75 %</td>
<td>62%</td>
</tr>
</tbody>
</table>

Letrozole

Anastrozole
Summary: Endpoint Response Rate, 50% of Active Control Effect Retained

<table>
<thead>
<tr>
<th>Design Approach</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point Estimate (30%)</td>
<td>300</td>
</tr>
<tr>
<td>Active Control Effect Relative to Tamoxifen (10%)</td>
<td>1319</td>
</tr>
<tr>
<td>Lower 95% C.L. (26%)</td>
<td>360</td>
</tr>
<tr>
<td>Historical Approach ≤ 10%</td>
<td>660</td>
</tr>
</tbody>
</table>
Summary: Endpoint Time-to-Progression, 50% of Active Control Effect Relative to Tamoxifen Retained

<table>
<thead>
<tr>
<th>Design Approach</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point Estimate (1.4)</td>
<td>944</td>
</tr>
<tr>
<td>Lower 95% C.L.</td>
<td>3542</td>
</tr>
<tr>
<td>Lower 55% C.L., $\alpha = 0.025$</td>
<td>1427</td>
</tr>
</tbody>
</table>
Sample Size For Superiority Trial With Tamoxifen As The Comparator

Assuming: Response Rate as the Endpoint,
Tamoxifen Response Rate = 20%,
Drug ‘X’ Response Rate = 30%,
Total Sample Size = 586 patients (power = 0.8, $\alpha = 0.025$)

Assuming: Time to Progression as the Endpoint,
Median TTP for Tamoxifen = 6.0 months,
Median TTP for Drug ‘X’ = 9.4 months,
Total Sample Size = 200 events (power = 0.8, $\alpha = 0.025$)
Perspective Issues

- Effect size of Letrozole estimated from One, large, well conducted, randomized study
  - Convincing evidence of Superiority
  - Is the effect size over estimated?
  - Effect size w.r.t. TTP is L vs. T and not L vs. Placebo
- No estimated effect size of Tamoxifen w.r.t TTP
- If Non-inferiority trials - Replication mandatory
- If Non-inferiority trials - more patients
- If Non-inferiority trials and TTP endpoint - more patients
Issues for Discussion

- Superiority (compared to Tamoxifen or Letrozole)  
  versus  
  Non-inferiority (compared to Letrozole)
- % of Letrozole effect to be retained
- Endpoint: Response Rate versus Time to Progression; Survival ??
- Given the sample sizes, is it feasible to conduct a non-inferiority study?
Summary: Comparators

- Tamoxifen frequently used
- Is letrozole superior?
- Are all aromatase inhibitors superior?
  - Anastrozole superior to tam in study 030, 1st-line
  - No direct comparison of different aromatase inhibitors
Summary: Endpoints

- Traditionally, RR
- A change to TTP will require
  - Non-inferiority to letrozole or superiority to tamoxifen, because of available dataset
  - Larger sample size
Questions to the Committee