

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

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# 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  $\leq 10\%$
- “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<sup>®</sup>

## 1<sup>st</sup> line Metastatic Breast Cancer

- Approved: October 1995
- Trials: 3 randomized Phase 3
- Comparator: Tamoxifen
- Sample size: 1526 patients in all trials
- 1<sup>o</sup> 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 1<sup>st</sup> line MBC

## Efficacy Results

	U.S.		Nordic		East Europe	
	Tor	Tam	Tor	Tam	Tor	Tam
Dose (mg)	60	20	60	40	60	18
RR (%)	21	19	31	37	20	21
95% C.I.	(-5.8, 10)		(-15, 3.1)		(-9.5, 8.6)	
TTP median months	5.6	5.8	7.3	10	5.0	5.1
Hazard Ratio 95% C.I.	1.007 (0.805, 1.259)		0.801 (0.643, 0.998)		1.015 (0.787, 1.311)	

# 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<sup>®</sup>

## 1<sup>st</sup> line Metastatic Breast Cancer

- Approved: September, 2000
- Trials: 2 randomized Phase 3
- Comparator: Tamoxifen
- Sample size: 1021 patients in all trials
- 1<sup>o</sup> 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 1<sup>st</sup> line MBC

## Efficacy Results

	Trial 0030		Trial 0027	
	A	T	A	T
Dose (mg)	1	20	1	20
Response Rate (%)	21	17	33	33
Odds Ratio	1.30		1.01	
Diff. (A-T)	4.01		0.32	
95% C.I.	(- 4.74, 12.78)		(- 7.10, 7.74)	
TTP median months	11	5.6	8.2	8.3
Hazard Ratio , 95% C.I.	1.42 (1.11, 1.82)		1.01 (0.85, 1.20)	
<i>P</i> - value	<i>P</i> = 0.006		<i>P</i> = 0.920	

# Letrozole: Femara<sup>®</sup>

## 1<sup>st</sup> line Metastatic Breast Cancer

- Approved: December, 2000
- Trial: 1 randomized Phase 3
- Comparator: Tamoxifen
- Sample size: 916 patients
- 1<sup>o</sup> Endpoint: TTP
- Designed to show superiority

# Letrozole 1<sup>st</sup> line MBC

## Efficacy Results

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

# 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

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# 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'

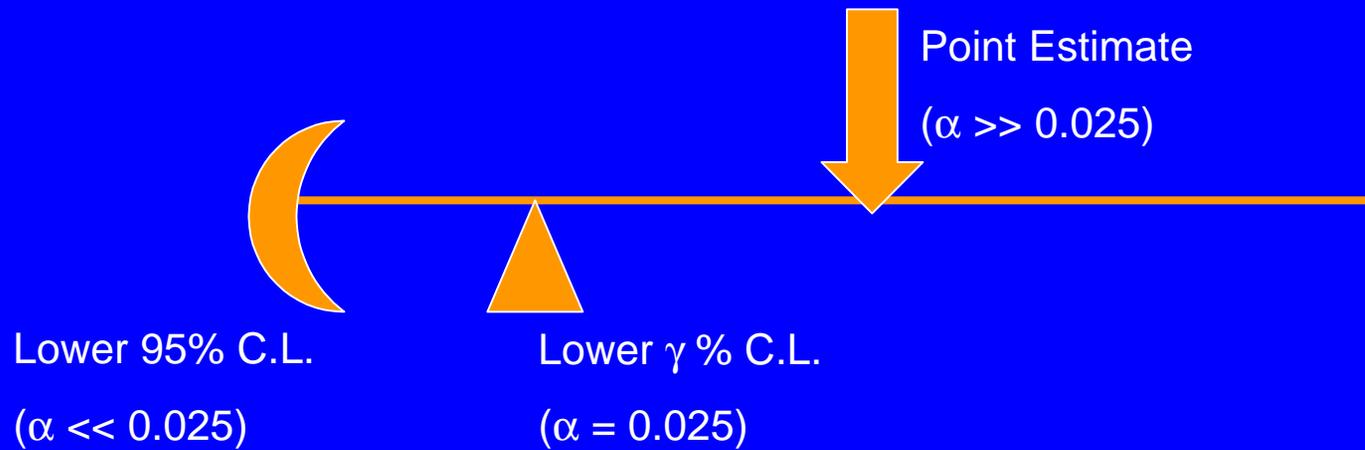
# Assumptions

- '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



Endpoint: Response Rate

Endpoint - Response Rate  
Sample Sizes - Point Estimate of Letrozole  
Effect Relative to Placebo

<b>Total N patients</b>	<b>Point Estimate of Response</b>	<b>Control Effect to be Retained</b>
<b>140</b>	<b>30%</b>	<b>25 %</b>
<b>300</b>	<b>30%</b>	<b>50 %</b>
<b>1200</b>	<b>30%</b>	<b>75 %</b>

**Endpoint - Response Rate**  
**Sample Sizes - Point Estimate of Letrozole**  
**Effect Relative to Tamoxifen**

<b>Total N patients</b>	<b>Estimate of Control Effect ('L' over 'T')</b>	<b>% Effect Retained of 'L' over 'T'</b>
<i>587</i>	<i>10%</i>	<i>25%</i>
<i>1319</i>	<i>10%</i>	<i>50%</i>
<i>5275</i>	<i>10%</i>	<i>75%</i>

**Endpoint - Response Rate**  
**Sample Sizes - Lower 95% C.L. of Letrozole**  
**Effect Relative to Placebo**

<b>Total N patients</b>	<b>Lower 95% C.L. of Response</b>	<b>Control Effect to be Retained</b>
<b>120</b>	<b>26%</b>	<b>25 %</b>
<b>360</b>	<b>26%</b>	<b>50 %</b>
<b>1430</b>	<b>26%</b>	<b>75 %</b>

**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**

<b>N, Total # of Events</b>	<b>Hazard Ratio of T vs. L</b>	<b>Control Effect to be Retained</b>
<b>456</b>	<b>1.4</b>	<b>25 %</b>
<b>944</b>	<b>1.4</b>	<b>50 %</b>
<b>3456</b>	<b>1.4</b>	<b>75 %</b>

**Endpoint - Time to Progression**  
**Sample Sizes - Lower 95% C.L. of Active**  
**Control Effect Relative to Tamoxifen**

**Letrozole**

<b>N, Total # of Events</b>	<b>Control Effect to be Retained</b>
<b>1,646</b>	<b>25 %</b>
<b>3,542</b>	<b>50 %</b>
<b>13,523</b>	<b>75 %</b>

**Anastrozole**

<b>N, Total # of Events</b>	<b>Control Effect to be Retained</b>
<b>1,786</b>	<b>25 %</b>
<b>3,849</b>	<b>50 %</b>
<b>14,723</b>	<b>75 %</b>

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

**Letrozole**

**Anastrozole**

<b>N, Total # of Events</b>	<b>Control Effect to be Retained</b>	<b><math>\gamma</math> % Lower C.L.</b>
<b>665</b>	<b>25 %</b>	<b>53%</b>
<b>1,427</b>	<b>50 %</b>	<b>55%</b>
<b>5,465</b>	<b>75 %</b>	<b>58%</b>

<b>N, Total # of Events</b>	<b>Control Effect to be Retained</b>	<b><math>\gamma</math> % Lower C.L.</b>
<b>673</b>	<b>25 %</b>	<b>57%</b>
<b>1,457</b>	<b>50 %</b>	<b>59%</b>
<b>5,631</b>	<b>75 %</b>	<b>62%</b>

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

<b>Design Approach</b>	<b>N</b>
Point Estimate (30%)	300
Active Control Effect Relative to Tamoxifen (10%)	1319
Lower 95% C.L. (26%)	360
Historical Approach $\leq$ 10%	660

Summary: Endpoint Time-to-Progression,  
50% of Active Control Effect Relative to  
Tamoxifen Retained

<b>Design Approach</b>	<b>N</b>
Point Estimate (1.4)	944
Lower 95% C.L.	3542
Lower 55% C.L., $\alpha = 0.025$	1427

# 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

