Mechanisms of Resistance to Hormonal Therapy

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Antagonizing Estrogen Dependent Growth

Premenopausal

Ovaries

Pre- and Postmenopausal

Peripheral

**FAT:** including breast fat

**FIBROBLASTS:** around primary and metastases

**OFS**

GnRH inhibitors or OVX

**Exogenous Estrogens**

- Environmental
- Pharmacologic (vaginal)

**Aromatase Inhibitors**

- Tamoxifen
- Fulvestrant

**Cancer Cell**

**Estrogen**

**ER**

**ER**

**Environmental**

**Pharmacologic (vaginal)**
Hormone Receptor-Positive Breast Cancer Is Heterogeneous in Biology and Behavior

Luminal A

Luminal B

10% of ER+ are nonluminal

Courtesy C. Perou
Adjuvant Endocrine Options

- **Postmenopausal**
  - Tamoxifen
  - Aromatase inhibitors

- **Premenopausal**
  - Tamoxifen
  - +/- ovarian suppression

*Singly or in sequence*
Adjuvant Endocrine Strategies in Postmenopausal Women

Three Strategies

- **Als as Initial Therapy**
  - TAM X 5 Yrs
  - AI X 5 Yrs

- **Als After 2-3 Yrs of TAM**
  - TAM X 5 Yrs
  - TAM X 2-3
  - AI X 2-3

- **Als After 5 Years of TAM**
  - TAM X 5 Yrs
  - AI X 5 Yrs
  - PLAC X 5 Yrs

Letrozole
Anastrozole
Exemestane

**MA.27: Efficacy Exemestane = Anastrozole**
Goss et al, SABCS 2010
Tamoxifen Resistance By Inadequate Metabolism?

Tamoxifen metabolized by CYP2D6 to more active endoxifen

Preclinical and several clinical studies – 2D6 activity = tam efficacy

NCCTG Adjuvant Trial 89-30-52

Goetz et al, JCO 2005
Pharmacogenetics-Based Decision-Making?

If mutant CYP2D6 ↑ risk of recurrence 86%, then...

in known normal 2D6, tamoxifen = AI

Punglia et al. JNCI 2008
Tailoring Endocrine Rx by 2D6 in 2011

Prospective randomized trials
Postmenopausal
*CYP2D6 genotyping should not be used in routine patient management

ATAC, Rae et al, SABCS’10

BIG 1-98, Leyland-Jones et al, SABCS’10
Ovarian Estrogens and Tamoxifen Resistance

**Recurrence**
- **Tamoxifen**
- **LHRH + tamoxifen**

HR = 0.85, 95% CI = [0.67-1.09], P = 0.20

**Death after recurrence**
- **Tamoxifen**
- **LHRH + tamoxifen**

HR = 0.84, 95% CI = [0.59-1.19], P = 0.33

22.8% vs. 18.2%
4.6% reduction

8.8% vs. 7.3%
1.5% reduction

Cuzick Lancet 2007
Stockholm Subset of ZIPP Trial

N=925 @12y

PREMENOPAUSAL

pT ≥ 10 mm
pN 0
N = 466

pN 1-3+
N = 323

CMF x 6

CMF x 6 +
locoreg. RT

RANDOMIZE
N= 925

Control
N = 234

Tamoxifen
N = 231

Tam+ Goserelin
N = 229

Goserelin
N = 231

~20% ER-negative

Sverisdottir et al, SABCS 2010
Tamoxifen, Goserelein or Both: Results

• Tamoxifen and ovarian suppression both reduce relapse

• No obvious benefit to combination

• Goserelein efficacy depended on ER level, tam not.

Sverisdottir et al, SABCS 2010
Overcoming Endocrine Insensitivity by Adding Chemotherapy – How to Choose?

- Oncotype Dx Recurrence Score
- 70-gene Mammaprint
- Genomic grade index
- Intrinsic subtype

All are prognostic, more limited validation regarding adding chemotherapy, none can pick drugs
Recurrence Score – Endocrine Insensitivity but Chemosensitivity

- TAMOXIFEN
- TAMOXIFEN + (C)MF

10-Year Risk BC Death

- RS <18
- RS 18-30
- RS ≥31

Chemotherapy benefit


- Similar findings with other profiles
- True across clinical subsets (N0/N+, T) – however underlying risk varies
- Profiles for endocrine and chemo sensitivities often inverse
Late Recurrence and Aromatase Inhibition (total 10 years adjuvant therapy)

Goss et al NEJM 2003

<table>
<thead>
<tr>
<th>Variable</th>
<th>Letrozole Group (N=2575)</th>
<th>Placebo Group (N=2582)</th>
<th>Absolute Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yr 1</td>
<td>98.6</td>
<td>97.8</td>
<td>0.8 (0.0 to 1.5)</td>
</tr>
<tr>
<td>Yr 2</td>
<td>96.7</td>
<td>94.8</td>
<td>1.9 (0.6 to 3.3)</td>
</tr>
<tr>
<td>Yr 3</td>
<td>95.2</td>
<td>90.2</td>
<td>5.0 (2.7 to 7.3)</td>
</tr>
<tr>
<td>Yr 4</td>
<td>92.8</td>
<td>86.8</td>
<td>6.0 (2.0 to 10.1)</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yr 1</td>
<td>99.8</td>
<td>99.7</td>
<td>0.1 (−0.2 to 0.4)</td>
</tr>
<tr>
<td>Yr 2</td>
<td>98.9</td>
<td>98.6</td>
<td>0.3 (−0.5 to 1.1)</td>
</tr>
<tr>
<td>Yr 3</td>
<td>97.7</td>
<td>96.9</td>
<td>0.8 (−0.8 to 2.3)</td>
</tr>
<tr>
<td>Yr 4</td>
<td>96.0</td>
<td>93.6</td>
<td>2.4 (−0.9 to 5.6)</td>
</tr>
</tbody>
</table>

Adjuvant therapy impact seen in each year
Who is appropriate for extended adjuvant therapy?
Risk Factors for Late Recurrence

Risk after 5 years is still relatively high and poorly understood

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER (- referent)</td>
<td>Positive, endocrine Rx</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>Positive, no endocrine Rx</td>
<td>1.87</td>
</tr>
<tr>
<td>Stage (I referent)</td>
<td>II</td>
<td>2.13</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>2.49</td>
</tr>
<tr>
<td>Grade (1 referent)</td>
<td>2</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Brewster et al, JNCI 2008
The Way Forward – Profiling Endocrine Response

**Genomic Index of Sensitivity to Endocrine Therapy for Breast Cancer**

W. Fraser Symmans, Christos Hatzis, Christos Sotiriou, Fabrice Andre, Florentia Peintinger, Peter Regimbald, Guenter Daxenbichler, Christine Desmedt, Julien Demont, Christian Marth, Suzette Delaloge, Thomas Bauernhofer, Vicente Valero, Daniel J. Booser, Gabriel N. Hortobagyi, and Lajos Pusztai

Gene sets to predict hormonal sensitivity, validation pending

**Outcome Prediction for Estrogen Receptor–Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics**


**A Comparison of PAM50 Intrinsic Subtyping with Immunohistochemistry and Clinical Prognostic Factors in Tamoxifen-Treated Estrogen Receptor–Positive Breast Cancer**

Torsten O. Nielsen, Joel S. Parker, Samuel Leung, David Voduc, Mark Ebbert, Tammi Vickery, Sherri R. Davies, Jacqueline Snider, Inge J. Stijlemans, Jerry Reed, Maggie C.U. Cheang, Elaine R. Marcis, Charles M. Perou, Philip S. Bernard, and Matthew J. Ellis
Comparison of Methods
Determining Endocrine Sensitivity

Association with outcome in tam-treated cohort

Nielsen et al., CCR 2010
ER and Signal Transduction Pathway Crosstalk

Adapted from Steve Johnston and Paul Goss
HER1-3 and AI Benefit: TEAM Trial

- Correlative substudy HER1-3
  Hypothesized that AI benefit mostly in HER1-3+

- Looked good at 2.75 years... However at 5 years effect gone

**Bartlett et al, SABCS 2010**
Overcoming Endocrine Resistance: Mode of Action in HER2+/HR+ Breast Cancer

- Aromatase inhibitor
- Androgens
- Oestrogen
- ErbB heterodimer signalling Ligands
- EGFR (or other ErbB)
- Antibodies
- Gene transcription Nuclear genomic ER-mediated response
- PI3K/Akt
- MAPK pathway

Adapted from Prat. Nat Clin Pract Oncol 2008
Phase III Trial Letrozole vs Letrozole + Lapatinib: ER+/HER2+ Cohort

N=219

<table>
<thead>
<tr>
<th></th>
<th>Letrozole + placebo (N=108)</th>
<th>Letrozole + lapatinib (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressed or died</td>
<td>89 (82%)</td>
<td>88 (79%)</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>3.0</td>
<td>8.2</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.71 (0.53, 0.96)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.019</td>
<td></td>
</tr>
</tbody>
</table>

No significant impact seen in HER2- cohort

CALGB 40302: Fulvestrant vs Fulvestrant + Lapatinib

Co-targeting ER and EGFR/HER2 only appears to be effective in HER2+
Similar findings in TANDEM (AI +/- Trastuzumab)
Role of EGFR unclear
Overcoming Endocrine Resistance

- Aromatase inhibitor
- Oestrogens
- Androgens
- ErbB heterodimer signalling
- Ligands
- EGFR (or other ErbB)
- ErbB2

Non-genomic ER-mediated response

Cytoplasm

Nuclear genomic ER-mediated response

Gene transcription

Adapted from Prat. Nat Clin Pract Oncol 2008
Downstream inhibition of mTOR has potential for:

- Enhancement of the effects of chemo- and endocrine therapy
- Angiogenesis inhibition

Downstream of PI3K and PTEN
- Controls growth and proliferation

mTOR signaling often deregulated in cancer
- mTOR has potential for:
  - Antiproliferative effects on tumor cells
  - Angiogenesis inhibition
  - Enhancement of the effects of chemo- and endocrine therapy
Dual Approaches to Signaling Pathways: Targeting mTOR Along With ER

- 270 ER+ postmenopausal breast cancer patients, no prior Rx.
  - Increased RR with mTOR inhibitor everolimus

- Change in Ki67-antiproliferative effect ↑ with RAD001 across PI3KCA WT or mutant
  - Especially mutant

- Selection may be key

<table>
<thead>
<tr>
<th>Neoadjuvant regimen:</th>
<th>Everolimus + letrozole</th>
<th>letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>138</td>
<td>132</td>
</tr>
<tr>
<td>Radiographic response rate</td>
<td>80 (58%)</td>
<td>62 (47%)</td>
</tr>
<tr>
<td>P</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

Baselga J et al, JCO 2009
Targeting mTOR: TAMRAD

- Randomized, controlled phase II trial
  - Primary endpoint: CBR at 6 mos (CR + PR + SD)

Stratified by primary vs secondary hormone resistance*

Hormone receptor + HER2-negative, MBC with previous AI exposure
(N = 111)

Everolimus 10 mg/day + Tamoxifen 20 mg/day
(n = 54)

Tamoxifen 20 mg/day
(n = 57)

Bachelot T, et al. SABCS 2010
TAMRAD: Increase in Clinical Benefit With TAM + RAD vs TAM Alone

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>TAM + RAD (n = 54)</th>
<th>TAM (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>61.1</td>
<td></td>
<td>42.1</td>
</tr>
</tbody>
</table>

\[ P = .045^* \]

Side effects significantly worse:
- Stomatitis
- Diarrhea
- Rash
- Fatigue
- Anorexia

*Exploratory analysis.

Bachelot T, et al. SABCS 2010
## TAMRAD: TTP/OS in Primary and Secondary Resistance

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>TAM Alone (n = 57)</th>
<th>TAM + RAD (n = 54)</th>
<th>HR (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP, mos</td>
<td>4.5</td>
<td>8.6</td>
<td>0.53 (0.35-0.81)</td>
<td>.0026</td>
</tr>
<tr>
<td>▪ Primary hormone resistance</td>
<td>3.9</td>
<td>5.4</td>
<td>0.74 (0.42-1.30)</td>
<td>NR</td>
</tr>
<tr>
<td>▪ Secondary hormone resistance</td>
<td>5.0</td>
<td>17.4</td>
<td>0.38 (0.21-0.71)</td>
<td>NR</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>~ 24†</td>
<td>Not reached</td>
<td>0.32 (0.15-0.68)</td>
<td>.0019</td>
</tr>
</tbody>
</table>

*Exploratory log rank test.
†Estimate based on Kaplan-Meier curve.

IGF1R – downstream activation of PI3K / Akt signaling and MAP pathways

Implicated in endocrine resistance

AMG 479 = humanized monoclonal Ab against IGF1R

Musgrove, NatRevCancer2009
Randomized Placebo-Controlled Phase II Trial of AI + AMG 479

- AMG 479 -
- Randomized, placebo-controlled, double-blind phase II trial
  - Primary endpoint: PFS

Randomized 2:1; stratified by exemestane vs fulvestrant and disease extent

Postmenopausal HR+ MBC 2nd line endocrine (n=156)

AMG 479 12 mg/kg IV every 2 wks + Exemestane or Fulvestrant* (n = 106)

Placebo IV every 2 wks + Exemestane or Fulvestrant* (n = 50)

Until disease progression

* Investigator discretion.

Kaufman PA, et al. SABCS 2010
AMG 479: No Significant Effect on PFS

<table>
<thead>
<tr>
<th>Outcome, Mos</th>
<th>AMG 479 (n = 106)</th>
<th>Placebo (n = 50)</th>
<th>HR* (80% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>3.9</td>
<td>5.7</td>
<td>1.17 (0.91-1.50)</td>
<td>.435</td>
</tr>
</tbody>
</table>

Targeting PI3K/mTOR pathway looks promising but not easy, and not without toxicity

Does it work in de novo and acquired resistance?
Summary

• Treatment decisions in ER+ are still guided by clinical variables with emerging genomics:
  – Prognosis and chemotherapy benefit
  – Pharmacogenomics – NOT PROVEN

• Resistance to endocrine therapy –
  – HER2 crosstalk – YES
  – EGFR crosstalk – NOT PROVEN
  – Other signaling pathways – MAYBE

• Endocrine sensitivity profiles are coming, how will we use them?
Thanks!