Novel Strategies in Systemic Therapies: Overcoming Endocrine Therapy Resistance

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Geffen School of Medicine at UCLA
Goals for Today

- Understand ER signaling
- Understand proposed mechanisms of resistance to ER directed therapy
- Appreciate new approaches in development to target ER+ breast cancer
<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Event/Description</th>
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<tbody>
<tr>
<td>1895</td>
<td>Beatson</td>
<td>Ovariectomy and tumor regression</td>
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<td>1958</td>
<td>Lerner et al.</td>
<td>Non-steroidal antiestrogen MER-25</td>
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<td>1971</td>
<td>Cole et al.</td>
<td>Tamoxifen clinical trials</td>
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<td>1978</td>
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<td>FDA approves tamoxifen</td>
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<td>1982</td>
<td>Klijn et al.</td>
<td>LHRH agonist</td>
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<td>1988</td>
<td>Buzdar et al.</td>
<td>Raloxifene and SERM’s</td>
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<td>1990</td>
<td>Powles et al.</td>
<td>Tamoxifen for prevention of BC</td>
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<td></td>
<td>Wakeling et al.</td>
<td>SERD’s (ER down-regulators)</td>
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<td>1993</td>
<td>Iveson et al.</td>
<td>New generation aromatase inhibitors</td>
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<tr>
<td>2003</td>
<td>Jakesz et al.</td>
<td>Endocrine blockade superior chemotx</td>
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Antiestrogen (AE) Resistance

De novo
Absence of ER/PR

Failed response to AE in HR+ tumors:
- ER+/PR+ (25%)
- ER+/PR- (66%)
- ER-/PR+ (55%)

Acquired
Loss of AE response by tumor initially responsive (most retain ER expression)

Most responsive tumors eventually develop resistance
Estrogen Receptor Action: New Concepts

**Ligand-dependent receptor activation**
- 17β-Estradiol
- Nuclear estrogen receptor
- Nuclear actions

**Ligand-independent receptor activation**
- Growth factor
- Increased protein kinases
- Decreased protein phosphatases
- Activation of estrogen receptors
- Nuclear actions

**Nonnuclear action through cell-surface receptors**
- Estrogen receptor
- Caveola
- Mitogen-activated protein kinase
- Nonnuclear actions

HER Family and ER resistance
ER and HER-2 receptor interactions

1986  • Tyrosine phosphorylation of ER
1989  • HER-2 overexpression correlates ER- / PR- phenotype
1990  • Estrogen downregulates HER-2 receptor levels in tumors
1992  • Tyrosine kinase inhibitors block E2-dpndt cancer growth
1993  • Tamoxifen resistance with overexpressed HER-2 in vitro
1994  • HER-2-overexpressing cancers have tamoxifen-resistance
1995  • HER-2-induced phosphorylation and activation of ER
      • HER-2 / ER cross-talk : HER-2 downregulates ER
2001  • Interaction between steroid receptor coactivator and HER-2
2003  • ER and HER-2 co-localize to caveolae-like membrane domains in breast cancer cells
HER-2 Overexpression and ER in the Clinic

Konecny et al. JNCI (2003)
Trastuzumab Plus Anastrozole versus Anastrozole Alone for the Treatment of Postmenopausal Women With Human Epidermal Growth Factor Receptor 2–Positive, Hormone Receptor–Positive Metastatic Breast Cancer: Results From the Randomized Phase III TAnDEM Study

Bella Kaufman, John R. Mackey, Michael R. Clemens, Poonamalle P. Bapsy, Ashok Vaid, Andrew Wardley, Sergei Tjulandin, Michaela Jahn, Michaela Lehle, Andrea Peyereislova, Cédric Révil, and Alison Jones

A

B

<table>
<thead>
<tr>
<th>Events</th>
<th>Median PFS</th>
<th>95% CI</th>
<th>Hazard ratio</th>
<th>P</th>
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<tr>
<td>87</td>
<td>4.8 months</td>
<td>3.7 to 7.0</td>
<td>0.65</td>
<td>.0016</td>
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<td>99</td>
<td>2.4 months</td>
<td>2.0 to 4.6</td>
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<th>Events</th>
<th>Median PFS</th>
<th>95% CI</th>
<th>Hazard ratio</th>
<th>P</th>
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<td>63</td>
<td>5.6 months</td>
<td>3.6 to 8.3</td>
<td>0.62</td>
<td>.006</td>
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<tr>
<td>69</td>
<td>2.8 months</td>
<td>2.0 to 6.3</td>
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Patients and Methods

EGF30008 Phase III Study Design

Stratification:
- Locally tested ER+ and/or PgR+
- Postmenopausal
- HER2+, HER2-, HER2 unknown
- Stage IIIb/IIIc, IV
- No prior treatment for MBC

Primary endpoint: Investigator assessed PFS

N = 1286 of which 219 were Her2+

Johnston JCO 2009
Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer

**PFS: HER2-ve Patients (N=952)**

**≥ 6 Mo Since D/C of Tam (33%) or No Tam (67%)**
- Median tam duration 5 y
- Median time since d/c 3.5 y

<table>
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<th>Treatment</th>
<th>Median PFS, mo</th>
<th>Hazard ratio (95% CI), p-value</th>
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<td>Let</td>
<td>15.0</td>
<td>0.94 (0.79, 1.13); p=0.522</td>
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<td>Let + Lap</td>
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<table>
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<th>Treatment</th>
<th>Median PFS, mo</th>
<th>Hazard ratio (95% CI), p-value</th>
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</thead>
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<tr>
<td>Let</td>
<td>3.1</td>
<td>0.78 (0.57, 1.07); p=0.117</td>
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<tr>
<td>Let + Lap</td>
<td>8.3</td>
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**< 6 Mo Since D/C of Tam**
- Median tam duration 2.8 y
- Median time since d/c 1 mo

Johnston JCO 2009
Available Data

1286 patients randomized

219 (17%) HER2+ (3+ or FISH-positive by reference laboratory)

952 (74%) HER2-negative

Less 19 patients ER-negative in central review

821/952 (86%) Material available for this quantitative ER, PR analysis (USC lab M Press)
Calculation of H-Score

H-Score = (% staining 1+ x 1) + (% staining 2+ x 2) + (% staining 3+ x 3)

Maximum H-Score = 100% 3+ x 3 = 300
ER and PR Subgroups Were Analyzed in Quartiles

**ER**
- ER Quartile 1: H-Score <160
- ER Quartiles 2 and 3: ≥160 & <250
- ER Quartile 4: ≥250
- Median = 218

**PR**
- PR Quartile 1: H-Score <40
- PR Quartiles 2 & 3: ≥40 and <220
- PR Quartile 4: ≥220
- Median = 141
• Figures 4A, 4B, and 4C. PFS by treatment arm: grouped by ER quartile

• Patients treated with letrozole + lapatinib with low ER expression had a significant benefit from the addition of lapatinib vs placebo:

• Median PFS was 13.6 months with letrozole + lapatinib vs 6.6 months letrozole + placebo (HR [95% CI] = 0.65 [0.47, 0.9], $P$<.05)
5A. PR Quartile 1: H-Score <40

5B. PR Quartiles 2 and 3: H-Score ≥40 and <220

5C. PR Quartile 4: H-Score ≥220

- Figures 5A, 5B, and 5C. PFS by treatment arm: grouped by PR quartile
- Unlike ER, strength of PR expression did not correlate with outcome from the addition of lapatinib to letrozole
Conclusions: HER –family and ER

- There is a statistically significant benefit in PFS for HER2-negative patients treated with lapatinib for the subset of patients with ER H-score in the lowest quartile, (ER H-score <160)
  - ER Q1: N=207
  - Median PFS 13.6 months letrozole + lapatinib vs 6.6 months letrozole + placebo
  - HR (95% CI) = 0.65 (0.47,0.9); P<.05

- Within that group, there appears to be a relationship between quantitative hormone receptor measurements and peptide growth factor dependence

- A prospective study evaluating this hypothesis is planned
PI3-kinase and ER resistance
PI3-kinase and Endocrine Therapy

- Key signaling pathway modulating effects of ER and RTK signaling
- Increased AKT/PI3-kinase activity mediates endocrine resistance
- Pre-clinical data suggests that inhibiting mTOR reverses endocrine resistance
  - Synergy with letrozole
  - Neoadjuvant study comparing letrozole to letrozole and everolimus showed increased response rate with the combination (68% vs 59%)\(^1\)
    - Decreased Ki67 with combination (57% vs 30%)
  - Randomized Phase II everolimus + tam vs tam alone after prior AI
    - TTP 8.6 mos combo, vs 4.5 mos tam alone \(^2\)

\(^1\) Baselga et al JCO 2009 \(^2\) Bachelot et al. SABCS 2010
Everolimus Counters the Effects of Molecular Changes in Signaling Pathways Conferring Estrogen Resistance

Patients and Methods

BOLERO 2 Phase III Study Design

- Locally tested ER+
- Postmenopausal
- HER2-
- Stage IIIb/IIlc, IV
- Disease refractory to nonsteroidal aromatase inhibitors

N = 705

Randomize

Exemestane 25mg daily + Everolimus 10 mg daily

Exemestane 25 mg daily + Placebo

Primary endpoint: PFS
Patients and Methods

BOLERO 2 Phase III Study Design

- Locally tested ER+
- Postmenopausal
- HER2-
- Stage IIIb/IIIc, IV
- Disease refractory to nonsteroidal aromatase inhibitors

Randomize

Exemestane 25mg daily + Everolimus 10 mg daily

Exemestane 25 mg daily + Placebo

Primary endpoint: PFS

N = 705

June 2011: Press release: has met primary endpoint
Targeting the cell cycle in ER+-breast cancer
Cyclin D Kinases and Cancer

- CDKs are a subgroup of serine/threonine kinases
  - In general very small proteins (34-40 kDa)
  - Bind to activating proteins: cyclins
  - Without cyclins, CDKs have little kinase activity

- Play a key role in regulating cell cycle progression through all phases of the cell cycle
  - Various cyclin/CDK complexes act at different parts of the cell cycle
  - Temporal and quantitative regulation

- Negative regulation by Cyclin dependent kinase inhibitors (CKI)
  - INK 4 family (p15, p16, 18, p19)
  - Cip/Kip family (p21, p27, p57)

- Alterations in CDKs are uncommon, compared with cyclin dysregulation
  - Altered regulation/ expression in many malignancies

- Cyclin D1 amplification has been described in various malignancies, including breast cancer, with variable prognostic significance
  - t(11;14) mantle cell lymphoma

- Rb loss, a well known oncogenic event
Rb as Master-Regulator of the R-point

Modified from Figure 8.19  *The Biology of Cancer* (© Garland Science 2007)
PD 0332991 Background

The Compound
- Potent, selective, reversible inhibitor of CDK4,6
- Small molecule
- Oral agent

The Opportunity
- Potential First-in-Class
- Potential impact on hematopoietic and solid tumors
- Potential use in pediatric indications
- Single agent and combination approaches under investigation
Rb as Master-Regulator of the R-point

Modified from Figure 8.19  *The Biology of Cancer* (© Garland Science 2007)
PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro

Richard S Finn¹, Judy Derin², Dylan Conklin¹, Ondrej Kalous¹, David J Cohen¹, Amrita J Desai¹, Charles Ginther¹, Mohammad Atefi¹, Isan Chen², Camilla Fowst³, Gerret Los² and Dennis J Slamon¹

Figure 1

Inhibitory concentration and cell type. Bar graph of IC₅₀ values (nM) and cell type. Cell lines are color coded by subtype: light blue, luminal; dark blue bars or stripes, HER2 amplified; yellow, nonluminal/undergone an epithelial-to-mesenchymal transition; red, nonluminal; turquoise, immortalized.
PD-0332991: Cell Cycle Analysis

Sensitive lines

Resistant lines
A. Total pRb

B. Phospho-Rb (serine 780)

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Sensitive

Resistant
Hypothesis – Patient Selection in Breast Cancer Population

Differentially expressed genes between sensitive and resistant cell lines. Results of analysis of variance (ANOVA) identifying 450 differentially expressed genes between sensitive cell lines ($IC_{50} < 150$ nM) and resistant cell lines ($IC_{50} > 1,000$ nM). Retinoblastoma and cyclin D1 expression were higher in, and CDKN2A (p16) was lower in, sensitive cell lines. Full results of the ANOVA are available in the Additional data files.
Hypothesis – Patient Selection in Breast Cancer Population

Elevated Cyclin D1 RB

Decreased p16
Abrogated Response to Cellular Stress Identifies DCIS Associated with Subsequent Tumor Events and Defines Basal-like Breast Tumors

Mona L. Gauthier,1,4,7 Hal K. Berman,1,3,7,8 Caroline Miller,1 Krystyna Kozakiewicz,1 Karen Chew,2 Dan Morris,9,4 Joseph Rabban,1 Yunn Yi Chen,1 Karla Kerkikowska,5,6 and Thea D. Tlsty1,2,4
MCF7

% Inhibition

Concentration (nM)

Tamoxifen

PD-2991

Combo

EFM19

% Inhibition

Concentration (nM)

T47D

% Inhibition

Concentration (nM)
TRIO 18/ A5481003: Phase I/II Study of Letrozole in combinations with PD-0332991 in Post-menopausal ER+ Advanced Breast cancer

- Phase I complete
- Randomized Phase II accruing
TRIO 18: Phase 1 Patient Summary

<table>
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<tr>
<th>Pt. ID</th>
<th>Age</th>
<th>Prior Systemic Tx</th>
<th>Prior XRT</th>
<th>DLT</th>
<th>Best Response</th>
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<tr>
<td>1001-1002</td>
<td>66</td>
<td>TC (2005); Anastrozole (2005-8)</td>
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<td>PR</td>
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<td>1001-1003</td>
<td>43</td>
<td>FEC → T (2005); Tamoxifen (2005-8)</td>
<td>2006</td>
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<td>SD (bone only)</td>
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<tr>
<td>1001-1004</td>
<td>59</td>
<td>AC→ T (2004); Anastrozole (2004)</td>
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<td>−</td>
<td>SD</td>
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<td>1001-1005</td>
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<td>Tamoxifen (2005-9)</td>
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<td>1001-1006</td>
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<td>None</td>
<td>−</td>
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<td>Fluoxymesterone (1997); Anastrozole (1997-2001)</td>
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<td>AC → T (2003); Anastrozole (2003-8)</td>
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<td>AC → Paclitaxel (2002)</td>
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<td>CMF (1988)</td>
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- **Duration of Treatment (months)**
  - **PR**
  - **Active patients**
## TRIO 18: Most Common AEs (N=12)

<table>
<thead>
<tr>
<th>PT</th>
<th>Grade 1 (n)</th>
<th>Grade 2 (n)</th>
<th>Grade 3 (n)</th>
<th>Grade 4 (n)</th>
<th>Total (n)</th>
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<td>7</td>
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<td>Fatigue</td>
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<td>6</td>
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<td>Nausea</td>
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<td>Decreased appetite</td>
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<td>0</td>
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<td>2</td>
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TRIO 18: Phase 1 Summary

- Phase 1 (N=12)
  - MTD: PD 0332991 125 mg QD (Schedule 3/1) in combination with letrozole 2.5 mg QD
  - 3 DLTs:
    - 2 pts with grade 4 neutropenia
    - 1 pt with 5 doses held d/t elevated creatinine deemed treatment-related
  - No treatment-related SAEs
  - No discontinuations due to AEs
    - Common treatment-related AEs: neutropenia, leukopenia, fatigue
  - No febrile neutropenia
  - No drug-drug interaction
  - Efficacy: 3 PRs and 9 SDs (PR=33%; CBR=67%)
  - Median duration of treatment: 12 months (range: 2 – 21+)
  - Currently 6 patients active
Phase 2 Study Design (Part I, completed)

**ER+, HER2 neg BC**

**Stratification Factors:**
- Disease site
  - Visceral vs. bone-only vs. other
- Disease-free interval
  - >12 vs. ≤12 months

**Randomization**

**Arm A**
- PD 0332991 125 mg/day (Schedule 3/1)
- + Letrozole 2.5 mg/day

**Arm B**
- Letrozole 2.5 mg/day

N=60

Primary Endpoint: Progression-free Survival (PFS)
Phase 2 Study Design (Part II, ongoing)

Primary Endpoint: Progression-free Survival (PFS)

Arm A
PD 032991 125 mg/day (Schedule 3/1)

Arm B
Letrozole 2.5 mg/day

N=150

Biomarker Selection
- ER+, HER2- BC
- CCND1 amp
- and/or loss of p16
Conclusions:

- Anti-estrogen therapy has made a significant impact in the treatment of breast cancer
- Still there are women that relapse and die of their disease
- Several mechanisms of resistance have been suggested
  - Peptide growth factor signaling
  - Activation of alternative signaling pathways
- Studies integrating new biologics into this area are showing promise
- Ultimately, understanding biology of an individual patients tumor will allow for optimal selection for new therapies
  - “Personalized medicine”