Overcoming resistance to endocrine or HER2-directed therapy

Jane Lowe Meisel, MD
Assistant Professor of Hematology and Medical Oncology
Winship Cancer Institute at Emory University
Background

- While most patients with ER+ breast cancer will do well on endocrine therapy for some time, eventually almost all acquire resistance and require chemotherapy to maintain disease control.

- The same is true for HER2+ breast cancer.
Background

• Some important questions we’ll address:

  • Why do some tumors never respond to a particular treatment?

  • Why do most eventually develop resistance to a particular treatment, even after responding well?

  • How do we overcome resistance to endocrine and HER2-directed therapy?
Overview

• Endocrine therapy
  • Mechanisms of resistance
  • Established strategies for overcoming this
    • CDK inhibition, PI3K inhibition
  • Sequencing current therapies
  • Ongoing trials and future directions

• HER2-directed therapy
  • Currently approved anti-HER2 therapy
  • Newer agents and combinations
  • Ongoing trials and future directions
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Mechanisms of resistance to endocrine therapy

• An endocrine sensitive cell depends on the estrogen receptor

• In the setting of endocrine resistance, other pathways are activated

• Dual targeting may be important to preventing cancer cell proliferation in this setting
Mechanisms of resistance: cyclin-dependent kinase (CDK 4/6 inhibition)

- In ER+ breast cancer, growth may be due to overactive CDK 4/6
- CDK 4/6 inhibition: puts the brakes on cell growth and promotes apoptosis
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The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

Richard S Finn, John P Crown, Istvan Lang, Katalin Boer, Igor M Bondarenko, Sergey O Kulyk, Johannes Ettl, Ravindranath Patel, Tamás Pinter, Marcus Schmidt, Yaroslav Shparyk, Anu R Thummala, Nataliya L Voytko, Camilla Fowst, Xin Huang, Sindy T Kim, Sophia Randolph, Dennis J Slamon

PALOMA 1

- The first randomized trial of CDK 4/6 inhibition in breast cancer

Metastatic breast cancer
ER+/HER2-
First line therapy

Letrozole alone

Letrozole + Palbociclib

PALOMA 1

PFS=20.2 vs 10.2 months (HR 0.488, p=0.0004)
PALOMA 3

- Phase III trial in women whose cancer
  - a) progressed on endocrine therapy or
  - b) metastasized ≤ 12 months after completion of adjuvant endocrine therapy

Metastatic breast cancer
ER+/HER2-
AI-resistant

Fulvestrant alone

Fulvestrant + Palbociclib

PALOMA 3

PFS 9.2 months vs 3.8 months
HR 0.422, p<0.000001

MONALEESA-2

- Ribociclib + letrozole in the first line metastatic setting

PFS (Investigator Assessment)

<table>
<thead>
<tr>
<th></th>
<th>Ribociclib + Let</th>
<th>Placebo + Let</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>334</td>
<td>334</td>
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<tr>
<td>Number of events, n (%)</td>
<td>93 (28)</td>
<td>150 (45)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (19.3–NR)</td>
<td>14.7 (13.0–16.5)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.556 (0.429–0.720)</td>
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<tr>
<td>One-sided p value</td>
<td>0.00000329</td>
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MONARCH 2

• Double blind, phase III trial of abemaciclib + fulvestrant vs. placebo + fulvestrant
• Abemaciclib – continuous dosing
• Randomized 2:1 to abemaciclib 150mg PO q12hrs vs placebo
• Results (ASCO 2017)
  • ORR 48.1% vs 21.3%
  • PFS 16.4 vs 9.3 months
  • Diarrhea 86.4% and neutropenia 46% with abemaciclib
Fig 2. Kaplan-Meier plots of progression-free survival. (A) Investigator-assessed and (B) independent central review of intent-to-treat population. HR, hazard ratio.
Mechanisms of resistance: mTOR inhibition

- mTOR activates ER in a ligand-independent fashion
- Hyperactivation of the PI3K/mTOR pathway is observed in endocrine-resistant breast cancer cells
- mTOR is a rational target to enhance the efficacy of hormonal therapy

Adapted from DiCosimo & Bassiga, Nature Clin Pract Oncol. 2009
BOLERO 2

- ER+HER2- patients with disease refractory to letrozole or anastrozole
- Other previous endocrine therapies and one prior chemotherapy in the advanced setting allowed (generally sicker patients than the CDK trials)
- 2:1 randomization to exemestane + everolimus vs exemestane + placebo

Hazard ratio, 0.36 (95% CI, 0.27–0.47)  
P<0.001 by log-rank test
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Sequencing therapies

• PALOMA-1 overall survival data presented at ASCO 2017
  • 37.5 vs 34.5 months (non-statistically significant)

• Awaiting survival data from PALOMA-2 and MONALEESA-2 to see whether using palbociclib upfront makes a survival difference

• Until then, possible options include:
  1) AI → fulvestrant + CDK → AI + everolimus → chemo*
  2) AI+ CDK → AI + everolimus → fulvestrant → chemo*
  3) fulvestrant → AI + CDK → AI + everolimus → chemo*

*clinical trials=appropriate to consider at any point
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** Areas of current investigation **

** Exemestane + entinostat (phase III) **

- Endocrine therapy plus AR blockade
  - Phase II of exemestane +/- enzalutamide in progress

- AI + mTOR inhibition + PI3K inhibition
  - Trials under design and beginning enrollment

- Trials based on tumor genomics (PIK3CA, ESR1 mutations) ongoing
  - No approvals based on these to date
Entinostat

• A small molecule inhibitor of class I histone deacetylases (proteins required for control of gene expression)

• Thought to prevent the emergence of drug tolerant clones and sensitize cells to anti-cancer therapies

• Phase II RCT (130 women): Entinostat+exemestane prolonged PFS compared with exemestane alone (4.3 vs 2.3 months) and extended OS (26.9 vs 19.8 months)

Yardley et al, JCO 31 (17) June 2013.
### Study Schema

**Stratification:**
- Setting in which patient developed resistance to prior nonsteroidal AI treatment: adjuvant vs metastatic
- Geographic region: USA vs other
- Visceral disease: yes vs no

**Randomization:**

**Arm A**
- Exemestane
  - 25 mg PO, d 1-28
  - Entinostat
  - 5 mg PO, d 1, 8, 15, and 22

**Arm B**
- Exemestane
  - 25 mg PO, d 1-28
  - Placebo
  - 5 mg PO, d 1, 8, 15, and 22

**Treatment continued until progressive disease or unacceptable toxicity**

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Accrual goal = 600 patients.
Cycle = 28 days.
The stratification factor visceral disease refers to liver and/or lung involvement.
*Treatment is blinded. Confirmation of randomization will indicate that patient is on arm X.
*Male patients will receive goserelin 3.6 mg SC injection on day 1.
*Repeat cycles every 28 days until development of disease progression or unacceptable toxicity.
*Entinostat/placebo should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal/snack. Missed doses should not be made up later.
Al = aromatase inhibitor; PO = orally; SC = subcutaneous.
Exemestane +/- enzalutamide

- Clinical question: Will inhibiting androgen signaling along with inhibiting estrogen signaling will provide benefit in patients with advanced breast cancer?

- Metastatic breast cancer
- ER+/HER2-
- Up to one prior endocrine and one prior chemo allowed in advanced setting

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Exemestane

Exemestane + enzalutamide

https://clinicaltrials.gov/ct2/show/NCT02007512
Triplet therapy

• TRINITI-1: Ribociclib + everolimus + exemestane
  • Goal: to determine if ribociclib, exemestane, and everolimus is effective following treatment with a CDK 4/6 inhibitor (aka palbociclib)

• Palbociclib + everolimus + exemestane
  • Also after progression on CDK 4/6 inhibition; can have received up to one prior chemo and can have received investigational drugs

ESR1 mutations

Image courtesy of Dana Farber Cancer Institute
Plasma ESR1 mutations and treatment of ER+ Advanced Breast Cancer

A

B

Fribbens et al, JCO 34 (25), September 2016, 2961-2968.
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A history of HER2-directed therapy

9/2013: Pertuzumab approved for neoadjuvant therapy of HER2+ breast cancer (stage II-III)

7/2017: Neratinib approved for extended adjuvant therapy for HER2+ breast cancer

Many new agents in trials!
HER2-directed therapy

**A**
- **Trastuzumab** targets HER2.
- **Extracellular** domain.
- **Intracellular** domain.
- **Subdomain IV of HER2**.

**B**
- **HER1/EGFR**.
- **HER2**.
- **HER3**.
- **HER4**.
- **Lapatinib** inhibits HER1/EGFR and HER2.
- **Inter-cellular domain**.

**C**
- **Extracellular**.
- **Pertuzumab** targets HER2.
- **Plasma membrane**.
- **Dimerization domain of HER2**.

**D**
- **HER1/EGFR**.
- **HER2**.
- **HER3**.
- **HER4**.
- **Neratinib** inhibits HER2.
- **Inter-cellular domain**.

**Inhibits HER2 forming dimer pairs**
**Suppresses multiple HER signaling pathways, leading to a more comprehensive blockade of HER signaling**
**Flags cells for destruction by the immune system**
Docetaxel +/- trastuzumab as first-line therapy for HER2-positive metastatic breast cancer: 2005

Progression-free survival
31.2 vs 22.7 mo
p = 0.0325
HER2-directed therapy

Inhibits HER2 forming dimer pairs
Suppresses multiple HER signaling pathways, leading to a more comprehensive blockade of HER signaling
Flags cells for destruction by the immune system
Patients with HER2-positive MBC centrally confirmed (N=808)

Randomization was stratified by geographic region and whether or not patients had received neoadjuvant or adjuvant chemotherapy

Baselga et al, NEJM 2012
# CLEOPATRA

## Progression-free survival

![Graph showing progression-free survival](image)

### A Independently Assessed Progression-free Survival

<table>
<thead>
<tr>
<th>Months</th>
<th>Progression-free Survival (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
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<tr>
<td>5</td>
<td>90</td>
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<tr>
<td>10</td>
<td>80</td>
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<td>15</td>
<td>70</td>
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<td>20</td>
<td>60</td>
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<td>30</td>
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<tr>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

- **Pertuzumab (median, 18.5 mo)**
- **Control (median, 12.4 mo)**

**Hazard ratio, 0.62**

(95% CI, 0.51–0.75)

**P < 0.001**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Pertuzumab</th>
<th>Control</th>
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<tbody>
<tr>
<td>402</td>
<td>345</td>
<td>267</td>
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<tr>
<td>139</td>
<td>83</td>
<td>32</td>
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<td>7</td>
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</table>

*Baselga et al, NEJM 2012*
CLEOPATRA
Overall Survival

Dual antibody therapy: First-line treatment for HER2+ MBC

• Combined HER2 blockade with pertuzumab plus trastuzumab plus a taxane is the standard of care for patients with HER2+ MBC in the first-line setting

• After achieving best response to treatment, can discontinue chemotherapy and continue trastuzumab/pertuzumab until progression
## Anti-HER2 Rx Beyond Progression

<table>
<thead>
<tr>
<th>Prior Rx</th>
<th>Agents</th>
<th>N</th>
<th>TTP</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taxane/Trastuzumab (Von Minckwitz)</strong></td>
<td>Capecitabine + trastuzumab vs capecitabine</td>
<td>156</td>
<td>8.2 months vs 5.6 months, ( P = 0.03 )</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td><strong>Heavily Pretreated (Blackwell)</strong></td>
<td>Lapatinib + trastuzumab vs lapatinib</td>
<td>296</td>
<td>NR</td>
<td>12 weeks vs 8.1 weeks, ( P = 0.008 )</td>
<td>14 months vs 9.5 months, ( P = 0.026 )</td>
</tr>
<tr>
<td><strong>Anthracycline, Taxane, Trastuzumab (Geyer)</strong></td>
<td>Capecitabine + lapatinib vs capecitabine</td>
<td>324</td>
<td>8.4 months vs 4.4 months, ( P &lt; 0.001 )</td>
<td>8.4 months vs 4.1 months, ( P &lt; 0.001 )</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

Blackwell et al., JCO 2010; Geyer et al., NEJM 2006; Von Minckwitz et al., JCO 2009. Slide courtesy of Chau Dang, MD.
T-DM1: Mechanism of Action

EMILIA Study Design

HER2+ LABC or MBC (N=980)
- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 mos of adjuvant tx

1:1

T-DM1
3.6 mg/kg q3w IV

Capecitabine
1000 mg/m² orally bid, days 1–14, q3w +
Lapatinib
1250 mg/day orally qd

- Stratified by world region, number of prior chemo regimens, presence/absence of visceral disease
- Primary endpoints
  - PFS by independent review
  - OS
  - Safety

Verma et al, NEJM 2012. Slide courtesy of Chau Dang, MD.
Progression-Free Survival by Independent Review

<table>
<thead>
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<th></th>
<th>Median (mos)</th>
<th>No. events</th>
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<tbody>
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<td><strong>Cap + Lap</strong></td>
<td>6.4</td>
<td>304</td>
</tr>
<tr>
<td><strong>T-DM1</strong></td>
<td>9.6</td>
<td>265</td>
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</table>

Stratified HR = 0.650 (95% CI, 0.55, 0.77)  
*P* < 0.001

No. at risk by independent review:

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<tr>
<th></th>
<th>Cap + Lap</th>
<th>T-DM1</th>
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Verma et al, NEJM 2012. Slide courtesy of Chau Dang, MD.
Overall Survival

Verma et al, NEJM 2012. Slide courtesy of Chau Dang, MD.
Overview: Stage IV HER2+ Disease

**HER2 (+)ER/PR (-)**

- **Pertuzumab + trastuzumab + taxane***
  - No previous adjuvant trastuzumab
  - Progression during or within 6 months of adjuvant trastuzumab

- **Previously received adjuvant trastuzumab**
  - Progression > 6 months after completion of adjuvant trastuzumab
  - Progression during or within 6 months of adjuvant trastuzumab

- **Trastuzumab+taxane***
  - TDM-1**
    - Capecitabine+trastuzumab
    - Capecitabine+lapatinib
    - Trastuzumab+lapatinib
    - Other cytotoxic chemotherapy + trastuzumab

- **Trastuzumab+pertuzumab**
  - CLINICAL TRIALS

- **Lapatinib-containing regimen**
  - CLINICAL TRIALS

*If pertuzumab is unaffordable/unavailable, trastuzumab + single-agent taxane is the preferred alternative.

**Preferred second-line option if available/affordable**
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Neratinib

- Potent, low-molecular weight, irreversible pan-TKI with activity against HER1, HER2 and HER4
- Binds to intracellular tyrosine kinase domain to inhibit auto-phosphorylation and downstream signaling
- May be more potent than lapatinib
- Most common adverse effects: diarrhea, nausea, fatigue, vomiting
Neratinib

• Now approved for extended adjuvant therapy (ExteNET - July 2017!); role in metastatic disease is still being determined

• TBCRC 022: neratinib + capecitabine in patients with measurable brain metastases who had not received either agent
  • > 50% reduction in volumetric sum of target CNS lesions in 49% of patients
  • 12 month survival 63%

• NALA: neratinib + capecitabine vs lapatinib + capecitabine in patients who have received 2 or more prior regimens in the metastatic setting (phase III, ongoing)

• Other studies ongoing: TDM-1 + neratinib; neratinib in elderly populations specifically; diarrhea prophylaxis studies

JCO 35; 2017 (suppl; abstract 1005)
https://clinicaltrials.gov/ct2/show/NCT01808573
Tucatinib

- An orally bioavailable potent TKI that is highly selective for HER2 without significant inhibition of EGFR

- Activity has been seen both systemically and in brain metastases

- Granted fast-track designation by the FDA given these successes

- Granted orphan drug designation by the FDA in 6/2017 for patients with brain metastases in breast cancer
Tucatinib

- HER2CLIMB: phase II study of tucatinib vs. placebo in combination with capecitabine and trastuzumab
  - Patients must have received trastuzumab, pertuzumab, taxane and TDM1
  - Randomization is 2:1 to tucatinib arm
  - Can have brain metastases that are treated OR untreated
  - Primary endpoint = PFS based on independent radiologic review

- Currently enrolling at Emory
“Triple positive” cancers

• A distinct biological subtype
• Lower pCR rates to neoadjuvant HER2-based chemotherapy in the upfront setting
• Crosstalk between HER2 and ER signaling may play a role in tumor resistance
• Dual anti-HER2 therapy + endocrine therapy may be superior to single-agent anti-HER2 therapy + endocrine therapy (ALTERNATIVE) and may be reasonable to pursue in patients who do not wish to have chemotherapy
• The role of CDK 4/6 inhibition and mTOR inhibition in this population is still being defined
PATINA

- Looking at the ability of CDK 4/6 inhibition to extend the amount of time spent on first line therapy for ER+HER2+ MBC

**HER2+HR+ Metastatic Breast Cancer (N=496)**
- No prior treatment in the advanced setting beyond induction treatment
- Induction treatment: Anti-HER2 based chemotherapy given prior to study randomization
- Screening procedures (before during or after induction treatment):
  - Screening consent
  - Biopsy of metastatic disease strongly recommended (not mandatory)
  - Baseline clinico-pathologic characteristics

**Randomization**

1:1

**ARM A**
Palbociclib 125mg PO daily (D1 to D21 followed by 7 days off) + Anti-HER2 Therapy * (every 3 weeks) + Endocrine Therapy ** until disease progression ***

**ARM B**
Anti-HER2 Therapy * (every 3 weeks) + Endocrine Therapy ** until disease progression ***

**Clinical Follow-up**
(for pts who discontinue treat prior to disease progression): q12 weeks until tumor progression

**Survival Follow-up:** Every 6 months until 5 years from randomization
MonarcHER

- Looking at the value of CDK 4/6 inhibition in third-line or later therapy for ER+HER2+ metastatic disease
Conclusions

- Many pathways of resistance to endocrine and HER2-directed therapy have been elucidated, and many drugs developed, to overcome resistance to endocrine and HER2-directed therapy.

- These new discoveries have made a huge difference in the quality of life and length of life of our patients.

- There are many new agents rapidly making their way from bench to bedside.
Thank you!