Understanding Today’s Hormonal & Targeted Therapies

Sara A Hurvitz, MD, FACP
Associate Professor of Medicine
Director, Breast Oncology Program, UCLA
Overview

• Breast Cancer Molecular Subtypes: Evolution in our understanding and treatment of the disease
• Hormonally targeted therapies
  – Tamoxifen, AI’s, AI’s in premenopausal women
  – Bisphosphonates to reduce risk of recurrence
  – Future possible therapy: CDK4/6i (e.g. palbociclib)
• HER2-targeted approaches
  – Trastuzumab story
  – Pertuzumab
  – Future possible therapy: T-DM1, neratinib
Contiguous Cancer Growth Theory:
Halsted Radical Mastectomy 1882-1970s

THEORY: CANCER SPREADS FROM ONE SOURCE
Tumors spread in orderly fashion from breast to lymph nodes to distant parts of body. Hence, the more aggressive the surgery, the better the chance of cure.
Classification: Histologic vs. Biologic Subtypes

Rudolf Ludwig Karl Virchow (1821-1902)

Die Krankhaften Geschwülste 1863
## Pathology of Invasive Breast Carcinomas

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Frequency</th>
<th>Associated features</th>
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</thead>
<tbody>
<tr>
<td>Infiltrating Ductal</td>
<td>70-80%</td>
<td>When DCIS is associated, goal is to obtain surgical margins clear of both invasive tumor and DCIS to reduce risk of recurrence</td>
</tr>
<tr>
<td>Invasive Lobular</td>
<td>5-10%</td>
<td>LCIS or DCIS; higher freq bilateral &amp; multicentric, spread to unusual locations (meninges, peritoneum, GI)</td>
</tr>
<tr>
<td>Mucinous/Colloid</td>
<td>2.4%</td>
<td>Well circumscribed, tumor cells dispersed in large pools of extracellular mucus; uniform, low grade nuclei, prognostically favorable variant of invasive breast carcinoma.</td>
</tr>
<tr>
<td>Metaplastic</td>
<td>&lt;5%</td>
<td>Poorly differentiated ductal carcinoma combined with squamous cell carcinoma and/or various forms of sarcomatous differentiation; tends to be resistant to chemotherapy</td>
</tr>
<tr>
<td>Tubular</td>
<td>&lt;5%</td>
<td>Well differentiated, low-grade, unusual pre-mmg era, now more common, indolent and rarely metastasizes</td>
</tr>
<tr>
<td>Medullary</td>
<td>&lt;5%</td>
<td>Poorly differentiated, lymphoplasmacytic infiltrate, prognosis more favorable despite aggressive histologic features, associated with BRCA1, usually ER-PR-</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>&lt;5%</td>
<td>Aggressive with lymph node metastases even when small</td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td>&lt;5%</td>
<td>Rare, morphologically identical to that of salivary glands, tends to be favorable prognosis,</td>
</tr>
</tbody>
</table>

**Systemic Cancer Theory:**

**Modified Radical Mastectomy & Lumpectomy:**  
1960s - present

**THEORY:** Breast cancer is a systemic disease, even in its early stages. Thus, variations in local/regional treatment are unlikely to affect survival. Showed through multiple clinical trials that less surgery has same survival and recurrence rates as more surgery.

Bernard Fisher, MD

Former Treatment Approach to Early Breast Cancer

Local-Regional Treatment

Surgery (MRM or BCT)
Radiation (if BCT or if MRM and ≥ 4+ LN)

Goal: Prevent disease from coming back in breast/surrounding tissues. Some impact on survival.

**WHY WOULD ANY MEDICINE BE NEEDED IF MARGINS CLEAR AND LYMPH NODES CLEAN?**
The Beginning of Systemic Therapy for Breast Cancer

- If tumors are systemic (already spread to other organs before detected) would chemo around time of surgery help improve cure rates?
- NSABP B01-Perioperative Chemotherapy (1958)
  - 826 patients Thiotepa vs. Placebo
  - Benefit seen for premenopausal women + >3 LNs
  - Considered negative trial
- Several subsequent studies confirmed systemic therapy SAVES LIVES by preventing stage IV recurrences (even in LN negative!)

Bernard Fisher, MD
From Heretic to Hero
Breast Cancer is Not All One Disease
A major shift in how we classify and treat cancers

<table>
<thead>
<tr>
<th></th>
<th>Classification</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional</td>
<td>Tumors classified by how they look under the microscope and their organ of origin</td>
<td>Tumors treated with chemotherapy that kills all rapidly dividing cells</td>
</tr>
<tr>
<td>Present &amp; Future</td>
<td>Tumors classified by the molecular problems that cause them to behave like cancer</td>
<td>Tumors treated with therapy that is rationally targeted toward the molecular defect in tumor cells, thus leaving normal cells alone</td>
</tr>
</tbody>
</table>
“Targeted” Therapy

• Specifically target/kill tumor cells, leaving normal cells alone

• Requires
  – an understanding of the underlying biological reasons that cells became malignant, thus allowing subcategorization of tumors based on molecular abnormality
  – a knowledge of how cancerous cells are different from normal cells

• Goal: Less toxic, more effective treatments
Endocrine Therapy

Targeting cancer cells that express estrogen/progesterone receptors
Endocrine Therapy

• (Anti)Hormonal Therapy - first kind of targeted therapy
• First recognized in the 1890s, by a Scottish surgeon George Beatson. Learned from Scottish farmers that the removal of ovaries from cows alters their ability to lactate.
• Removed ovaries from 3 women with breast cancer - the breast tumors shrank dramatically, however when repeated on a larger scale in London - only 2/3 of the patients responded.
• Estrogen discovered by Doisy in 1920
• Estrogen receptor discovered by Elwood Jensen in 1968
Hormonally Driven Cancers

• ~60-75% breast cancer ER+
• Tamoxifen blocks the estrogen receptor
• Aromatase inhibitors (AI’s) interfere with the peripheral production of estradiol
ESTROGEN BLOCKADE: TAMOXIFEN

- **Tamoxifen** is a Selective Estrogen Receptor Modulator-discovered in 1962
  - Blocks the effects of estrogen/competes with estrogen for the receptor binding
  - Has anti-estrogenic effects in the breast
  - Pro-estrogenic effect in the bone
  - Pro-estrogenic effect in the uterus
- Used in both pre/post menopausal women
- Standard of care in premenopausal women (5 years), who make most estrogen in the ovaries
5 years of tamoxifen versus no tamoxifen*

**RECURRENT**

ER+

Control 46.1%

33.0% ≈ 5 years tamoxifen

15-y gain 13.0% (SE 1.1)

Logrank 2p < 0.0001

**BREAST CANCER MORTALITY**

ER+

Control 32.7%

23.6% ≈ 5 years tamoxifen

15-y gain 9.1% (SE 1.0)

Logrank 2p < 0.0001

*EBCTCG, Lancet 2011; 378: 771–84
## Side effects and therapeutic effects of 10 years of tamoxifen on 15-year mortality in meta-analysis & ATLAS

<table>
<thead>
<tr>
<th></th>
<th>Tam 5 vs 0 Meta-analysis (n=10,645)</th>
<th>Tam 10 vs 5 ATLAS (n=6846)</th>
<th>Tam 10 vs 0 (estimated as product of RRss)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer and PE mortality</td>
<td>0.2% loss</td>
<td>0.2% loss</td>
<td>0.4% loss</td>
</tr>
<tr>
<td>Breast cancer mortality</td>
<td>9% gain</td>
<td>3% gain</td>
<td>12% gain</td>
</tr>
</tbody>
</table>

Estimated effects of 10 years tamoxifen compared to 0 on 15 year mortality: absolute gain is approx 30 times the absolute loss
Adjuvant Endocrine Trials: Efficacy

• Aromatase Inhibitors Began testing in 1990s
  • Anastrozole (Arimidex)
  • Letrozole (Femara)
  • Exemestane (Aromasin)

• Appropriate only for post-menopausal women with ER+ and/or PR+ tumors

• Multiple randomized phase III clinical trials have been performed, all of which show a 2-6% reduction in the risk of breast cancer recurrence compared to tamoxifen

• Current standard is 5 years (awaiting results vs. 10 yrs)
Als versus tamoxifen: benefit/risk

- ↓ Osteoporosis risk
- ↓ Musculoskeletal syndrome
- ↓ Cost

Tamoxifen

Patient history

AI

↓ Neurocognition
↓ Sexual function
↓ Hyperlipaemia
↓ Cardiovascular disease
↓ DVT
↓ Stroke
↓ Endometrial cancer
↓ Hot flashes

What we know: ER+ breast cancer

- For hormone receptor positive breast cancer, hormones are part of the driving force of cancer.
- Hormonally-targeted therapy SAVES lives and PREVENTS stage IV incurable cancer.
  - Tamoxifen x 5-10 years for premenopausal women
  - Aromatase inhibitors x 5 years (maybe 10?) for postmenopausal women
SOFT Trial: Study Design

- Primary analysis (n = 2033)
- Median follow-up 5.6 years

3,047 patients randomized in ITT

Two patient cohorts:
No chemotherapy (47%)
premenopausal, within 12 weeks of surgery (median time since surgery = 1.8 months)

Prior chemotherapy (53%)
premenopausal* after chemotherapy:
Randomize within 8 months of completion (median time since surgery = 8.0 months)

Primary endpoint: DFS

*According to locally-determined estrogen level in premenopausal range

Only 11.6% of patients in study had HER2+ disease (17% of whom did NOT receive chemotherapy)
SOFT Trial: Primary and Secondary Analysis

- DFS in overall population was similar among treatment groups

- T + OFS vs T: 19% reduction in breast cancer recurrence ($P = .09$)
- E + OFS vs T: 36% reduction in breast cancer recurrence

The lower-risk, chemotherapy-naïve cohort: No difference among treatment groups

In the chemotherapy cohort, T + OFS reduced recurrence by 22%

In the chemotherapy cohort, E + OFS reduced recurrence by 35%

What may be coming soon for early ER+ breast cancer?

A look at new insights from metastatic ER+ breast cancer: CDK4/6 inhibitors
Rb as Master-Regulator of the R-point
<table>
<thead>
<tr>
<th>Rank</th>
<th>Sample Name</th>
<th>IC50 nM</th>
<th>IC50g SE</th>
<th>Response</th>
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<tr>
<td>1</td>
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</tbody>
</table>
Phase 2 Design

Part 1

- ER+, HER2– BC
- Randomization: 1:1
- Treatment: PD 0332991 125 mg QD\(^a\) + Letrozole 2.5 mg QD
- Letrozole 2.5 mg QD

Part 2

- ER+, HER2– BC with CCND1 amp and/or loss of p16
- Randomization: 1:1
- Treatment: PD 0332991 125 mg QD\(^a\) + Letrozole 2.5 mg QD
- Letrozole 2.5 mg QD

Primary Endpoint: PFS
Stratification Factors:
- Disease Site (Visceral vs Bone only vs Other)
- Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)
Progression-Free Survival (ITT)

FDA Approved for metastatic BC 2/2015

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=84)</th>
<th>LET (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>20.2 (13.8, 27.5)</td>
<td>10.2 (5.7, 12.6)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.488 (0.319, 0.748)</td>
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</tr>
<tr>
<td>p-value</td>
<td>0.0004</td>
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</table>
PALOMA3 Study Design

- HR+, HER2- ABC
- Pre-/peri-* or post-menopausal
- Progressed on prior endocrine therapy:
  - On or within 12 mo adjuvant
  - On therapy for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

2:1 Randomization
N=521

Stratification:
- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-/peri- vs Post-menopausal

Palbociclib (125 mg QD; 3 wks on/1 wk off) + Fulvestrant† (500 mg IM q4w)
n=347

Placebo (3 wks on/1 wk off) + Fulvestrant† (500 mg IM q4w)
n=174

*All received goserelin.

Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.

†administered on Days 1 and 15 of Cycle 1.
Progression-free Survival

A Assessment by Investigators

Hazard ratio, 0.42 (95% CI, 0.32–0.56)
P<0.001

Palbociclib–fulvestrant (N=347)
Median progression-free survival, 9.2 mo (95% CI, 7.5–NE)

Placebo–fulvestrant (N=174)
Median progression-free survival, 3.8 mo (95% CI, 3.5–5.5)
Do Bone Modifying Agents Reduce Risk of Recurrence or Death from Early Stage Breast Cancer?
Distant Recurrence Rate
10 year outcome, 18,766 patients

Lancet 2015
Distant Recurrence in Bone
10 year outcome, 18,766 patients

RR 0.83 (95% CI 0.73–0.94)
Log-rank 2p = 0.004
10-year gain 1.1% (95% CI –0.1 to 2.3)

Lancet 2015
9% Relative Reduction in Mortality

Breast cancer mortality (%)

RR 0.91 (95% CI 0.83–0.99)
Log-rank 2p = 0.04
10-year gain 1.7% (95% CI 0.0 to 3.5)

Control 18.4%
Bisphosphonate 16.6%

Death rates (%/year: total rate minus rate in women without recurrences) and log-rank statistics

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Years 0–4</th>
<th>Years 5–9</th>
<th>Years ≥10</th>
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</thead>
<tbody>
<tr>
<td>Bisphosphonate</td>
<td>1.83 (1.70–1.97)</td>
<td>1.81 (1.59–2.03)</td>
<td>1.21 (0.72–1.69)</td>
</tr>
<tr>
<td>Control</td>
<td>1.98 (1.84–2.12)</td>
<td>1.97 (1.75–2.20)</td>
<td>1.69 (1.12–2.25)</td>
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<tr>
<td>Rate ratio (95% CI)</td>
<td>0.91 (0.81–1.01)</td>
<td>0.92 (0.75–1.10)</td>
<td>0.66 (0.18–1.15)</td>
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<tr>
<td>from (O−E)/V</td>
<td>−30.5/321.7</td>
<td>−9.5/121.0</td>
<td>−4.5/10.9</td>
</tr>
</tbody>
</table>

Lancet 2015
Reduction in Mortality Restricted to Post-Menopausal Women

**Diagram E**
- 6171 women
- RR 1.00 (95% CI 0.86–1.15)
- Log-rank 2p = 0.96
- 10-year gain 0.1% (95% CI –2.9 to 3.0)
- Control 20.7%
- Bisphosphonate 20.6%

**Diagram F**
- 11767 women
- RR 0.82 (95% CI 0.73–0.93)
- Log-rank 2p = 0.002
- 10-year gain 3.3% (95% CI 0.8 to 5.7)
- Control 18.0%
- Bisphosphonate 14.7%
## Similar Effects on Bone Recurrence Irrespective of Type of Bisphosphonate

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women Allocated Bisph</th>
<th>Allocated Not</th>
<th>Bisph events Logrank Variance O-E of O-E</th>
<th>Ratio of annual event rates Bisph : Not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate</td>
<td>139/2514 (5.5%)</td>
<td>165/2539 (6.5%)</td>
<td>-16.7</td>
<td>67.5</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>200/4642 (4.3%)</td>
<td>250/4648 (5.4%)</td>
<td>-24.1</td>
<td>108.7</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>80/460 (17.4%)</td>
<td>76/493 (15.4%)</td>
<td>5.1</td>
<td>33.1</td>
</tr>
<tr>
<td>Risedronate</td>
<td>0/200 (0.0%)</td>
<td>2/198 (1.0%)</td>
<td>-0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>78/2040 (3.8%)</td>
<td>49/1032 (4.7%)</td>
<td>-8.0</td>
<td>27.3</td>
</tr>
<tr>
<td>Alendronate</td>
<td>(no data)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(f) subtotal</td>
<td>497/9856 (5.0%)</td>
<td>542/8910 (6.1%)</td>
<td>-4.6</td>
<td>237.1</td>
</tr>
</tbody>
</table>

Heterogeneity between 5 categories: $\chi^2 = 5.9; p > 0.1; NS$

---

EBCTCG, Lancet June 2015, in press

Presented By Robert Coleman at 2015 ASCO Annual Meeting
SWOG 0307: Bisphosphononates and DFS

S0307: Study Design

- **Arm 1**: 3 years of zoledronic acid (ZA) (4 mg IV monthly × 6, then q3 months × 2.5 years)  
  - N = 2262

- **Arm 2**: 3 years of clodronate (CLOD) (1600 mg po daily)  
  - N = 2268

- **Arm 3**: 3 years of ibandronate (IBAN) (50 mg po daily)  
  - N = 1567
S0307 Primary Endpoint: Disease-Free Survival

Median Follow-up 5.4 years
No differences in DDFS or OS
No differences by ER, Her2
No differences in >60 years

Gralow J et al. ASCO 2015, abs 503
Targeting HER2
HER2-Driven Cancers

Normal:
~20,000-50,000 HER2 receptors

Overexpressed HER2
(~20% breast ca HER2+)
Up to ~2,000,000 HER2 receptors
Significance of HER-2/neu

Median Survival:
Her2/neu Negative: 6-7 yrs
Her2/neu Positive: 3 yrs
## Trastuzumab in Metastatic Breast Cancer
### The Pivotal Trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate</th>
<th>Time to Progression</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>32%</td>
<td>4.6 mos</td>
<td>20.3 mos</td>
</tr>
<tr>
<td>Chemo + Trastuzumab</td>
<td>50%</td>
<td>7.4 mos</td>
<td>25.1 mos</td>
</tr>
</tbody>
</table>

*Salamon, NEJM, 2001; 344: 783*
Trastuzumab Has Changed the Natural History of HER2+ Metastatic Breast Cancer

- Patients with HER2-positive metastatic breast cancer (MBC) now have comparable outcomes with HER2-negative MBC
# Trastuzumab for Early Breast Cancer

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>ARMS</th>
<th># Pts</th>
<th>DFS</th>
<th>OS</th>
<th>HR</th>
<th>F/U</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Int N9831 + NSABP B31</strong>&lt;br&gt;Romond NEJM 2005; 353: 1673</td>
<td>AC→Taxol®(T)&lt;br&gt;AC→TH&lt;br&gt;AC→T→H</td>
<td>3351</td>
<td>4-yr DFS: 85% AC-TH&lt;br&gt;67% AC-T&lt;br&gt;P&lt;0.0001</td>
<td>4-yr OS: 91% AC-TH&lt;br&gt;87% AC-T&lt;br&gt;P=0.015</td>
<td>OS 0.67&lt;br&gt;DFS 0.48</td>
<td>4 yr</td>
<td>H qwk</td>
</tr>
<tr>
<td><strong>HERA</strong>&lt;br&gt;Smith ASCO 2006 Scientific Special Session</td>
<td>Std chemo then:&lt;br&gt;Observ vs.&lt;br&gt;H x 1 yr vs.&lt;br&gt;H x 2 yr</td>
<td>5090</td>
<td>3-yr DFS: 81% H 1 yr&lt;br&gt;74% no H&lt;br&gt;P&lt;0.0001</td>
<td>3-yr OS: 92.4%&lt;br&gt;89.7% no H&lt;br&gt;P=0.0115</td>
<td>OS 0.66&lt;br&gt;DFS 0.64</td>
<td>2 yr</td>
<td>1/3 pts LN neg, H qw3wk, 1/4 prior taxane, x-over allowed</td>
</tr>
<tr>
<td><strong>BCIRG 006</strong>&lt;br&gt;Slamon NEJM 2011</td>
<td>AC→Taxotere® (T)&lt;br&gt;AC→TH&lt;br&gt;T/Carboplatin/H</td>
<td>3222</td>
<td>84% AC-TH&lt;br&gt;81% TCH&lt;br&gt;75% AC-T</td>
<td>92% AC-TH&lt;br&gt;91% TCH&lt;br&gt;87% AC-T</td>
<td>OS: 0.63&lt;br&gt;ACTH 0.77&lt;br&gt;TCH</td>
<td>65 mo</td>
<td>After chemo, H given q3wk</td>
</tr>
</tbody>
</table>
Overall Survival Early Breast Cancer
Impact of adjuvant trastuzumab

• 1458 patients with operable, non-metastatic breast cancer from Italy (Registry)
• 1210 (83%) HER2 negative (blue line)
• 219 (15%) HER2+
  – 53 received trastuzumab (green line)
  – 161 did not receive trastuzumab (red line)

Musolino, et al. Cancer 2010
Extenet: Phase III RCT
2 year analysis

• Approximately 25% of patients have disease recurrence after adjuvant trastuzumab-based therapy

• HERA showed no benefit with extended use of trastuzumab (2 years) compared to 1 year

• Question: Will use of 1 year of irreversible HER1/HER2 TKI after 1 year trastuzumab improve outcomes?
Study Design

- HER2+ breast cancer (local)
- Prior adjuvant trastuzumab & chemotherapy
- Lymph node +/- or residual invasive disease after neoadjuvant therapy
- ER/PR + or -

1:1 randomization

Neratinib x 1 year
240mg/day
N=2840

Placebo x 1 year

Part A
2-year follow-up for iDFS

Part B
5-year follow-up for iDFS

Part C
5+ year survival

- Primary endpoint: invasive disease-free survival (iDFS)
- Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- Other analyses: biomarkers, health outcome assessment (FACT-B, EQ-5d)
- Stratified by: nodes 0, 1–3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab
Primary Endpoint: Invasive DFS (ITT)

P-value = 0.009
HR (95% CI) = 0.67 (0.50–0.91)

No. at risk
Neratinib: 1420 1291 1260 1229 1189 1150 1108 1033 662
Placebo: 1420 1367 1324 1292 1243 1209 1163 1090 704

Months after randomization

Disease-free survival (%)
**iDFS by Hormone Receptor**

HR-positive (n=1631)

- HR = 0.51 (95% CI 0.33–0.77)
- p = 0.001

HR-negative (n=1209)

- HR = 0.93 (95% CI 0.60–1.43)
- p = 0.735

---

**Graphs:**

- Disease-free survival over months after randomization for Neratinib and Placebo groups.
- Comparison between HR-positive and HR-negative hormone receptor status.

---

**Additional notes:**

- No. at risk:
  - HR-positive: 816, 737, 721, 698, 677, 653, 629, 591, 538, 380
  - HR-negative: 604, 554, 533, 531, 512, 497, 473, 442, 282

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**Acknowledgments:**

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT: ASCO Annual Meeting

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**Institutional Logos:**

- UCLA Health System
- David Geffen School of Medicine
Summary: Extenet

- Use of neratinib for 1 year after 1 year of adjuvant trastuzumab improved iDFS by 2.3% at 2 years
- Possibly greater impact on HR+ disease
- Diarrhea most common toxicity
  - Dose limiting
  - Requires intensive loperamide upfront
- Not yet FDA approved
Neoadjuvant HER2+
Why Neoadjuvant Systemic Therapy?

• Similar to adjuvant therapy, improves disease-free and overall survival
• Increases breast-conserving surgery rates with operable locally advanced BC\(^1,2\)
• Neoadjuvant trial design allows \textit{in vivo} analyses
• Monitor response and adjustment systemic therapy
• Residual cancer after neoadjuvant systemic therapy: prognostic?\(^3,4\)

pCR rates by tumor subtypes

Cortazar, et al. Lancet. 2014 Jul 12;384(9938):164-72
Association of pCR on EFS in HER2+

pCR=ypT0/is ypN0

Cortazar, et al. Lancet. 2014 Jul 12;384(9938):164-72
Effects of ligand binding to the HER3 receptor

Ligand binds
Conformational change from “closed” to “open” state
Exposes the dimerization domain and allows the formation of dimers
Triggers intracellular signaling pathways through transphosphorylation
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- Conformational change from “closed” to “open” state
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- Triggers intracellular signaling pathways through transphosphorylation

HER2

HER3

Ligand binds

Conformational change from “closed” to “open” state

Exposes the dimerization domain and allows the formation of dimers

Triggers intracellular signaling pathways through transphosphorylation

P13K

AKT

PDK1

NFκB

GSK3β

mTOR

Cyclin D1

p27

BAD

survival

↓ apoptosis

angiogenesis

proliferation

cell cycle control
CLEOPATRA: First-line HER2+ BC

- CLEOPATRA – basis of FDA approval for pertuzumab

 Patients with HER2+ metastatic BC centrally confirmed (N = 808)

\[ \text{n = 406} \]

Placebo + trastuzumab

\[ \text{n = 402} \]

Pertuzumab + trastuzumab

\[ \text{PD} \]

Docetaxel*

\[ \geq 6 \text{ cycles recommended} \]

\[ \text{PD} \]

\[ \text{Docetaxel}* \]

\[ \geq 6 \text{ cycles recommended} \]

- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m², escalating to 100 mg/m² if tolerated

- 1 prior line of hormonal therapy allowed for pts with ER+/PgR+ BC
- Only ~10% of pts had prior TRAS as neo/adjuvant therapy
- <50% of pts had prior chemotherapy
- No crossover allowed
- Study powered at 80% to detect a 33%↑ in OS

Abbreviations: BC, breast cancer; ER, estrogen receptor; PgR, progesterone receptor; pts, patients.

*< 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion.

CLEOPATRA Overall Survival

ESMO 2014 update on OS at 50 months median follow-up

<table>
<thead>
<tr>
<th>PTZ + TRAS + DOC</th>
<th>Placebo + TRAS + DOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>56.5 months</td>
<td>40.8 months</td>
</tr>
<tr>
<td>HR = 0.68, P = .0002</td>
<td></td>
</tr>
</tbody>
</table>

- 48 patients crossed over from placebo to PTZ arm after previous report of OS benefit
- Long-term cardiac safety profile maintained

Patients with operable or locally advanced/inflammatory HER2-positive breast cancer

- **Chemonaive and primary tumors >2 cm (N = 417)**
  - **TH (n = 107)** Docetaxel + Trastuzumab
  - **THP (n = 107)** Docetaxel + Trastuzumab + Pertuzumab
  - **HP (n = 107)** Trastuzumab + Pertuzumab
  - **TP (n = 96)** Docetaxel + Pertuzumab

Study dosing q3wk x 3

- FEC q3wk x 3
  - Trastuzumab q3wk, cycles 5-17
- FEC q3wk x 3
  - Trastuzumab q3wk, cycles 5-17
- Docetaxel q3wk x 4→
  - FEC q3wk x 3
  - Trastuzumab q3wk, cycles 5-17
- FEC q3wk x 3
  - Trastuzumab q3wk, cycles 5-21

**FEC** = 5-fluorouracil, epirubicin, and cyclophosphamide.

Locally advanced = T2-3, N2-3, M0, or T4a-C, any N, M0; operable = T2-3, N0-1; inflammatory = T4d, any N, M0.

# NeoSphere Study: pCR for Neoadjuvant Pertuzumab, Trastuzumab, Docetaxel

<table>
<thead>
<tr>
<th>Pts with pCR, n (%)</th>
<th>Trastuzumab, Docetaxel (n = 107)</th>
<th>Pertuzumab, Trastuzumab, Docetaxel (n = 107)</th>
<th>Pertuzumab, Trastuzumab (n = 107)</th>
<th>Pertuzumab, Docetaxel (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>31 (29.0)</td>
<td>49 (45.8)</td>
<td>18 (16.8)</td>
<td>23 (24.0)</td>
</tr>
<tr>
<td>N– at surgery</td>
<td>23 (21.5)</td>
<td>42 (39.3)</td>
<td>12 (11.2)</td>
<td>17 (17.7)</td>
</tr>
<tr>
<td>N+ at surgery</td>
<td>8 (7.5)</td>
<td>7 (6.5)</td>
<td>6 (5.6)</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>ER and/or PR positive</td>
<td>10/50 (20.0)</td>
<td>13/50 (26.0)</td>
<td>3/51 (5.9)</td>
<td>8/46 (17.4)</td>
</tr>
<tr>
<td>ER and PR negative</td>
<td>21/57 (36.8)</td>
<td>36/57 (63.2)</td>
<td>15/55 (27.3)</td>
<td>15/50 (30.0)</td>
</tr>
</tbody>
</table>

PFS: all arms of therapy, ITT population

Kaplan-Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up.

Three late events occurred with PTD: two cases of progressive disease (PD) at 63 and 71 months, and one death due to an unrelated cerebrovascular accident without PD at 76 months.
Summary NeoSphere

- DFS/PFS tends to be better with THP (results descriptive)
- Patients with total pCR had better PFS/DFS
- Results support use of pCR as endpoint in studies as appears to be early indicator of benefit
**TRYPHAENA Cardiac Safety Study of Dual HER2 Targeting ± Anthracycline Tx: Results**

<table>
<thead>
<tr>
<th>pCR rate, %</th>
<th>Arm A FEC+HP→THP (n = 73)</th>
<th>Arm B FEC→THP (n = 75)</th>
<th>Arm C TCHP (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ypT0/is[^1]</td>
<td>61.6</td>
<td>57.3</td>
<td>66.2</td>
</tr>
<tr>
<td>ypT0ypN0[^1]</td>
<td>50.7</td>
<td>45.3</td>
<td>51.9</td>
</tr>
<tr>
<td>ER/PR negative[^2] (ypT0/is)</td>
<td>79.4</td>
<td>65.0</td>
<td>83.8</td>
</tr>
<tr>
<td>ER and/or PR+[^2] (ypT0/is)</td>
<td>46.2</td>
<td>48.6</td>
<td>50.0</td>
</tr>
</tbody>
</table>

- No new or unexpected cardiac adverse events observed

Sept 30, 2013: FDA Approval of First Neoadjuvant Regimen in Breast Cancer

Roche’s Perjeta Wins Approval for Early Breast Cancer
By Anna Edney - Sep 30, 2013

Roche Holding AG (ROG)’s Perjeta won expanded U.S. approval as the first pre-surgical therapy in breast cancer, increasing the odds the disease may be stopped in those diagnosed with early stage HER2-positive tumors.

3 approved regimens (pertuzumab not indicated post-op):
1. Docetaxel/trastuzumab/pertuzumab (THP) x 4 (then FEC x 3 post-op)
2. FEC x 3 → THP x 3, followed by surgery
3. Docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP) x 6; followed by surgery
T-DM1: Mechanism of Action

Adapted from LoRusso PM et al. Clin Cancer Res. 2011;17:6437-6447.
EMILIA: TDM-1 Phase 3 Trial Design

Key endpoints

**Primary:** Progression-free survival (PFS, central assessment), safety, overall survival

**Secondary:** Objective response, duration of objective response, PFS (investigator review)

**Stratification factors:** World region, number of prior chemo regimens for ABC or unresectable LABC, presence of visceral disease

---

EMILIA

N = 978

- Postmenopausal
- ABC
- Prior taxane and progression on TRAS
- Cardiac ejection fraction ≥50%
- ECOG PS ≤ 1

---

T-DM1

(3.6 mg/kg IV q3w)

---

Lapatinib + Capecitabine

(L: 1250 mg/d PO)

(C: 1000 mg/m² PO bid, days 1-14q3w)

---

EMILIA: Overall Survival

**Overall Survival, %**

- **LAP + CAP**
  - Median No. of Months: 25.1
  - No. of Events: 182
  - Stratified hazard ratio: 0.68 (95% CI, 0.55-0.85) \( P < .001 \)
  - Efficacy stopping boundary: \( P = .0037 \) or hazard ratio, 0.73

- **T-DM1**
  - Median No. of Months: 30.9
  - No. of Events: 149
  - Stratified hazard ratio: 0.69 (95% CI, 0.56-0.85) \( P < .001 \)
  - Efficacy stopping boundary: \( P = .0037 \) or hazard ratio, 0.73

**Median No. of Months and No. of Events**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median No. of Months</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAP + CAP</td>
<td>25.1</td>
<td>182</td>
</tr>
<tr>
<td>T-DM1</td>
<td>30.9</td>
<td>149</td>
</tr>
</tbody>
</table>

---

No. at risk:

- **LAP + CAP**
  - No. at risk: 496, 471, 453, 435, 403, 368, 297, 240, 204, 159, 133, 110, 86, 63, 45, 27, 17, 7, 4

- **T-DM1**
  - No. at risk: 495, 485, 474, 457, 439, 418, 349, 293, 242, 197, 164, 136, 111, 86, 62, 38, 28, 13, 5

**CAP, capecitabine; LAP, lapatinib**

T-DM1 (Kadcyla) FDA Approved
February 2013

New standard second-line therapy for HER2+ MBC
ADAPT HER2+/HR+: Trial Design

*Standard chemotherapy recommended after surgery; trastuzumab to be completed, for total of one year.*
ADAPT HER2+/HR+: pCR (no invasive tumor in breast and nodes)

- pCR rates substantially higher in T-DM1 containing arms ($p<0.001$ A or B vs. C)
KRISTINE – BO28408/ TRIO 021

Study schema

Patients with HER2-positive, operable, locally advanced or inflammatory breast cancer (tumor >2cm) n=432; 216/arm

Stratification factors:
- HR status: ER and/or PgR positive vs. both negative
- Geographic location: NA vs. Europe vs. Rest of World
- Stage at presentation: II-IIIA vs. IIIB-IIIC

- HER2-directed therapy may continue until disease recurrence, unacceptable toxicity, or study termination by the Sponsor for a maximum of 18 cycles
- Patients in Arm B should be considered to receive adjuvant chemotherapy per clinician discretion. Four cycles of anthracycline-based chemotherapy is recommended.
- Radiotherapy as per local clinical standards
- Patients whose tumors were ER and/or PgR positive will receive adjuvant hormonal therapy (i.e., tamoxifen or aromatase inhibitor) as per local clinical standards
Summary: Individualized Treatment Options Available

- **ER+ breast cancer**
  - Aromatase inhibitors
    - Preferred agents for post-menopausal
    - Becoming preferred for high risk pre-menopausal (plus ovarian suppression!)
  - Tamoxifen
  - Investigational: palbociclib

- **HER2-driven breast cancer**
  - Early disease
    - Trastuzumab (plus pertuzumab) plus chemotherapy
    - Possible use of neratinib in some patients?
    - Under investigation: T-DM1
Treatment Approach to Early Breast Cancer

**Local-Regional Treatment**
- Surgery (MRM or BCT)
- Radiation (if BCT or if MRM and ≥ 4+ LN)

**Systemic Treatment**
- Tamoxifen
- Aromatase Inhibitors (if ER+)
- Cytotoxic Chemotherapy (if ER/PR neg or large tumor or LN positive)

**Targeted/Biologics**
- Trastuzumab
- Pertuzumab
- Bisphosphonates?
- Palbociclib maybe?

**Goal:** Prevent disease from coming back in breast/surrounding tissues. Some impact on survival.