FDA Approval of Pertuzumab (Perjeta) for Early-Stage HER2+ Breast Cancer: Accelerating the Process of Finding the Right Drug for the Right Patient Through Neoadjuvant Therapy

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Topics for Discussion

- The problem: current drug development strategies are very slow!
- What do we know about neoadjuvant therapy?
  - Some terminology
    - Neoadjuvant – treatment given before surgery
    - pCR – pathologic complete remission
      - No invasive cancer in breast (and lymph nodes) at time of surgery
- New agents to treat HER2+ breast cancer
- What does this all mean to treatment today?
Current Approach:
10-20 years for Adjuvant Drug Approval
$1-2 Billion per drug

A. Current Development Pathway

**Metastatic Setting**

| Phase 1 & 1B | Phase 2 | Phase 3 |

**Adjuvant Setting**

Surgery
Chemo
Accrual

Years
0  2  4  6  8  10  12  14  16

What conditions could enable dramatic improvements in knowledge turns?
*And take real time off the clock*
Association of pCR on Recurrence and Survival

HR = 0.48, P* < 0.001
HR = 0.36, P* < 0.001

Taken from Cortazar et al, SABCS 2012

Biggest impact in HER2+ and triple negative disease
Examples of Response to Neoadjuvant Therapy

**Pre Treatment**

- Complete response
- Partial response
- Progressive disease

**Post Treatment**
pCR Rates by Tumor Subtypes

Taken from Cortazar et al, SABCS 2012
Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity

- Trastuzumab continually suppresses HER2 activity
- Flags cells for destruction by the immune system
  - Activates ADCC
- Pertuzumab inhibits HER2 forming dimer pairs
- Suppresses multiple HER signaling pathways
- Flags cells for destruction by the immune system
  - Activates ADCC

**HER2 receptor**

**Subdomain IV of HER2**

**Dimerization domain of HER2**
Cleopatra: Study Design and Patients

- Double-blind, placebo controlled phase III trial
  - Docetaxel 75 mg/m² every 3 weeks x about 6
  - Trastuzumab and pertuzumab/placebo q 3 weeks
- Primary endpoint
  - Independently assessed progression free survival
- 808 patients with HER2+ metastatic breast cancer
  - No prior treatment for metastatic disease

Baselga et al, SABCS 2011 and NEJM, 2011
CLEOPATRA: Confirmatory Overall Survival Analysis

## CLEOPATRA (≥Grade 3 Adverse Events)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo, Trastuzumab, Docetaxel (N = 397)</th>
<th>Pertuzumab, Trastuzumab, Docetaxel (N = 407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>45.8%</td>
<td>48.9%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7.6%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14.6%</td>
<td>12.3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.0%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1.8%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>2.3%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td>2.8%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Rash (all grades)</td>
<td>24.2%</td>
<td>33.7%</td>
</tr>
</tbody>
</table>

Patients with operable or locally advanced/inflammatory* HER2-positive BC

Chemo-naïve & primary tumors >2cm (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: q3w x 4

FEC q3w x 3
trastuzumab q3w cycles 5–17

FEC q3w x 3
docetaxel q3w x 4 → FEC q3w x 3
trastuzumab q3w cycles 5–17

FEC q3w x 3
trastuzumab q3w cycles 5–21

BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide

*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0

H, trastuzumab; P, pertuzumab; T, docetaxel
NEOSPHERE: Neoadjuvant Therapy in HER2+ BC
pCR Rate, n=417 patients

New Mechanism of Drug Approval –
FDA approved 9/30/13!

APHINITY ADJUVANT TRIAL
N=3806

Central Confirmation of HER2 Status

Randomization within 7 weeks of surgery

Start treatment within 1 week

Arm 1
A
T

Arm 2
A
T

3-4 cycles 3-4 cycles

TCa x 6

3-4 cycles 3-4 cycles

TCa x 6

Trastuzumab* 6mg/kg 3-weekly

Pertuzumab** 420mg IV 3-weekly#

Trastuzumab* 6mg/kg 3-weekly

Placebo IV 3-weekly#

Anti-HER2 therapy for a total of 1 year (52 weeks)

Radiotherapy and/or endocrine therapy may be started after the end of adjuvant chemotherapy and in accordance with the protocol recommendations.

KEY

A 3-4 cycles of anthracycline containing chemotherapy

T 3-4 cycles of taxane containing chemotherapy

Trastuzumab

Placebo

Pertuzumab

TCa = 6 cycles of docetaxel and carboplatin

* Trastuzumab must be given at a 8mg/kg loading dose at the first trastuzumab cycle.
** Pertuzumab must be given at a 840mg/kg loading dose at the first pertuzumab cycle.

#All site, study and sponsor personnel will be blinded as to treatment assignment.
Cost and Implications

• Approved as neoadjuvant therapy only
  – Based on response, not outcome
  – Combined data from Neosphere and Tryphaena

• Acclerated approved requires confirmation
  – Data from Aphinity trial – due in 2016

• Roche estimates that using trastuzumab (Herceptin) and pertuzumab (Perjeta) for 9 to 18 weeks before surgery will cost $27,000 to $49,000
I-SPY 2 Adaptive Trial Design Model

* HER2 positive participants will also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.
What conditions could enable dramatic improvements in knowledge turns?

*Take real time off the clock*

A. Current Development Pathway

**METASTATIC SETTING**

<table>
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<tr>
<th>PHASE 1 &amp; 1B</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
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**ADJUVANT SETTING**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Chemotherapy</th>
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**SIGNAL**

Years

0 2 4 6 8 10 12 14 16

B. Development Pathway

**METASTATIC SETTING**

<table>
<thead>
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<th>PHASE 1 &amp; 1B</th>
<th>Chemo</th>
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**NEOADJUVANT SETTING**

In high-risk adjuvant setting

**EARLY SIGNAL**

**FOLLOW-UP**

**SIGNAL**

**ACCELERATED APPROVAL**