What Is The Role Of Targeted Therapies In Metastatic Disease?

Hyman B. Muss, MD, USA
SIOG Paris 2011
Metastatic Breast Ca 2011

- Goal: “to keep you feeling as well as possible for as long as possible”
- In 2011 all therapy is palliative
- Long term survival in 2-3%
- Median life expectancy = 28-32 months for all
- 22% 5 yr survival, 10% 10 yr survival
- Many drugs and modest progress in this setting
- Much of current survival improvement “lead time”
What is targeted therapy?

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression.

National Cancer Institute USA
Molecular mechanisms of cancer
Some targets are more important than others!
Targeted Agents MBC

• Effective targets
  ➢ Endocrine therapy
  ➢ Anti-Her-2 agents
  ➢ Evirolimus in ER+ HER2- (maybe)

• Modest so far
  ➢ Bevacizumab
  ➢ Sorafenib
  ➢ Sunitinib
Targeted Agents for ER+

• If HER-2 negative
  ➢ Single agent endocrine until clear progression
  ➢ BOLERO trial (exemestane ± evirolimus)

• If HER-2 positive
  ➢ Consider endocrine + anti-HER-2 therapy
  ➢ No survival benefit
  ➢ Cost and access issues as well as toxicity
Cross-Talk Between Signal Transduction and Endocrine Pathways

- Growth factor
- Estrogen

Plasma membrane

- EGFR / HER2

Growth factor

Estrogen

Lapatinib

trastuzumab

EGFR / HER2

SOS

RAS

RAF

MEK

m-TOR

p90RSK

MAPK

Cell survival

Akt

Cytoplasm

ER

Letrozole

evirolimus

m-TOR

p90RSK

MAPK

Cell growth

Basal transcription machinery

ERE

ER target gene transcription

Nucleus

p160 CBP

Basal transcription machinery

ER

CBP

ER

Cell survival

Adapted from Johnston S. Clin Cancer Res. 2005;11:889S-899S.
### BOLERO-2 (average age 62) ER+, HER2-, advanced BC

<table>
<thead>
<tr>
<th></th>
<th>Exemestane</th>
<th>E/Evirolimus</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (central)</td>
<td>4.1 months</td>
<td>10.6 months</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CR+PR</td>
<td>0.4%</td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td>Clinical Benefit</td>
<td>18%</td>
<td>33.4%</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>13%</td>
<td>10%</td>
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</tr>
</tbody>
</table>

N=724; Toxicity stomatitis, anemia greater with combination
Targeted Agents for HER2 +

• If ER+ consider with endocrine therapy
• If ER- neg or endocrine refractory:
  ➢ Chemotherapy + anti- HER-2
    • Single agents + trastuzumab
    • Capecitabine + lapatinib
  ➢ Anti-HER2 therapy alone
    • Single agent trastuzumab (?lapatinib)
    • Combination trastuzumab/lapatinib
  ➢ Coming: TDM-1, pertuzumab, neratinib
HER2- Added to ER+ Target

TAnDEM (Anastrozole v A+Trastuzumab)
N=207, improved PFS, not OS
Median age 56

EGF30008 (Letrozole v L+Lapatinib)
219 HER2+, improved PFS, not OS
Median age 60

Kaufman, B. et al. JCO, 2009; Johnston et al, JCO 2009
Response Rate: HER2+ Population (N=219)
EGF 30008 Johnson et al JCO

Response rates were compared using stratified Fisher’s exact test.
**First-line Letrozole With or Without Trastuzumab in Hormone Receptor–Positive/HER2\(^+\) MBC: eLEcTRA**

- **Study design:**
  - Postmenopausal HR\(^+\)/HER2\(^+\) locally advanced or metastatic breast cancer randomized to letrozole-alone or letrozole/trastuzumab (arm B)
  - Patients with HR\(^+\)/HER2\(^-\) tumors received letrozole alone (arm C).

<table>
<thead>
<tr>
<th></th>
<th>HER2(^+) Letrozole Alone (n = 31)</th>
<th>HER2(^+) Letrozole/Trastuzumab(^a) (n = 26)</th>
<th>HER2(^-) Letrozole Alone(^a) (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TTP</strong></td>
<td>3.3 months</td>
<td>14.1 months</td>
<td>15.2 months</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>13%</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td><em>P</em></td>
<td></td>
<td><em>P</em> = .3124</td>
<td><em>P</em> = 1.00</td>
</tr>
<tr>
<td><strong>CBR</strong></td>
<td>39%</td>
<td>65%</td>
<td>77%</td>
</tr>
<tr>
<td><em>P</em></td>
<td></td>
<td><em>P</em> = .0636</td>
<td><em>P</em> = .0024</td>
</tr>
</tbody>
</table>

Huober et al. SABCS 2009; abstract 4094.
The Question:
Is giving combination endocrine and anti-HER-2 better than doing sequentially?
Lapatinib ± Trastuzumab in Heavily Pretreated MBC: Updated Survival Analysis
Median Age = 51 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Lapatinib/Trastuzumab (n = 146)</th>
<th>Lapatinib (n = 145)</th>
<th>HR/OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>3 months</td>
<td>2 months</td>
<td>HR 0.73</td>
<td>.008</td>
</tr>
<tr>
<td>Median OS</td>
<td>14 months</td>
<td>9.5 months</td>
<td>HR 0.74</td>
<td>.026</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>10%</td>
<td>7%</td>
<td>OR 1.5</td>
<td>.46</td>
</tr>
<tr>
<td>Clinical Benefit Rate*</td>
<td>25%</td>
<td>12%</td>
<td>OR 2.2</td>
<td>.01</td>
</tr>
</tbody>
</table>

Updated OS adjusted for baseline covariates: HR 0.71; P = .0116
Lapatinib + Trastuzumab
HER-2 positive MBC older pts

• 60 and older
• Primary Aim: Grade 3+ non-heme toxicity
• N=40

• Eligibility
  ➢ PS 0-2
  ➢ Any number of prior therapies
  ➢ Prior lapatinib and/or trastuzumab allowed

COH 10112 Hurria PI for Cancer Aging Research Group “CARG”
What about bevacizumab? (Anti-VEGF)
**Bevacizumab first line**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>PFS (primary endpoint)</th>
<th>ORR</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E2100</strong></td>
<td>Until Progression (n=722)</td>
<td>12 vs. 6 mos (p&lt;0.001)</td>
<td>Low: 8.7 vs 8 mos (p=0.03)</td>
<td>27 vs. 25 mos (p=0.16)</td>
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<tr>
<td></td>
<td></td>
<td>High: 8.8 vs 8 mos (p=0.0099)</td>
<td>ORR: 37 vs. 21% (p&lt;0.001)</td>
<td></td>
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<tr>
<td><strong>AVADO</strong></td>
<td>Until Progression placebo (n=736)</td>
<td></td>
<td>PFS (primary endpoint)</td>
<td>Overall Survival: No sig. difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X: 8.7 vs. 5.7 mos (p=0.0002)</td>
<td>Low: 55 vs 44% (p=0.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High: 63 vs 44% (p=0.0001)</td>
<td>ORR:</td>
<td></td>
</tr>
<tr>
<td><strong>Ribbon-1</strong></td>
<td>Until Progression placebo (n=1237)</td>
<td></td>
<td>ORR: X: 35 vs 24% (p=0.0092)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>A/T: 9.2 vs. 8 mos (p&lt;0.0001)</td>
<td>High: 63 vs 44% (p=0.0001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall Survival: No sig. difference</td>
<td>Overall Survival: Not mature</td>
<td></td>
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</table>
ATHENA in ≥ 70 Years

- 2,251 pt Phase II trial of chemo + bev
- First line, any chemo (46% taxanes)
- 175 (8%) ≥ 70 yrs, 51 ≥ 75, 7 ≥ 80
- Response 42%, TTP 10.4 months
- 73% ≥ had a comorbidity (54% < 70)
- G3+ toxicity 60% vs 54% < 70
- Hypertension, proteinuria higher ≥ 70
- Mortality similar

Biganzoli Ann Oncol 2011
Bevacizumab

- Probably higher toxicity in elders but not convincingly so.
- Adds About 10-20% to response
- Adds a 2-3 months to disease control (PFS)
- No survival advantage
- High cost
- Await adjuvant data
Targeted Rx in Elders - Issues

- Most trials with median ages in 50’s
- Good performance status
- Small samples of older patients
  - Response rates, PFS likely similar
  - Uncertain about toxicities
- High costs when approved
- Access varies among nations
- Little information on older patients
Thank You!

UNC – Lineberger Comprehensive Cancer Center

UNC – North Carolina Cancer Hospital