Strategies for Metastatic Disease and What's in the Pipeline

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Dr. Rugo has financial relationships with commercial interests that produce healthcare-related products or services relevant to the content I am planning, developing, presenting with Genomic Health, GlaxoSmithKline, Genentech/Roche, Plexxikon, Novartis, Eisai, Merck, Pfizer, and Amgen.
SABCS 2013:
Advanced Disease and Bisphosphonates for Early Stage Breast Cancer

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Topics

• Should primary tumor surgery be standard treatment for patients with de novo metastatic breast cancer?
• Can we use CTCs as a surrogate marker of response to change outcome?
• Novel agents in the pipeline
• Should we use bisphosphonates to reduce recurrence in patients with early stage disease?
Resection of the intact primary tumor in women with Stage IV breast cancer is associated with longer survival.

Overall hazard ratio 0.69 (95% CI 0.63, 0.77)

Randomized trials: Impact of Local Therapy

<table>
<thead>
<tr>
<th>Country</th>
<th>Accrual Period</th>
<th>N</th>
<th>Initial Therapy</th>
<th>Radiotherapy</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>2005-12</td>
<td>350</td>
<td>CAF±T</td>
<td>If indicated</td>
<td>Time to progression</td>
</tr>
<tr>
<td>Japan JCOG 1017</td>
<td>2011-16</td>
<td>410</td>
<td>Systemic therapy</td>
<td>Not addressed</td>
<td>Survival</td>
</tr>
<tr>
<td>USA and Canada</td>
<td>2011-16</td>
<td>368</td>
<td>Systemic therapy</td>
<td>Per standards for stage I-III</td>
<td>Survival</td>
</tr>
<tr>
<td>Turkey</td>
<td>2008-12</td>
<td>281</td>
<td>Surgery</td>
<td>For breast conservation</td>
<td>Survival</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2011-16</td>
<td>516</td>
<td>Surgery</td>
<td>For positive margins or palliation</td>
<td>2-year survival</td>
</tr>
<tr>
<td>Austria</td>
<td>2010-19</td>
<td>254</td>
<td>Surgery</td>
<td>Per standards for stage I-III</td>
<td>Survival</td>
</tr>
</tbody>
</table>
Two Completed Randomized Trials

<table>
<thead>
<tr>
<th></th>
<th>Tata Memorial</th>
<th>Turkey MF 07-01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>350 (2005-12)</td>
<td>271 (2008-12)</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Overall survival</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Projected benefit</td>
<td>Median survival Increase from 18 to 24 months</td>
<td>3-year survival improves from 17% to 35%</td>
</tr>
<tr>
<td>Initial therapy in experimental arm</td>
<td>CAF±T</td>
<td>Primary site local therapy</td>
</tr>
<tr>
<td>Stratification</td>
<td>Number and type of metastases, ER status, age, menopause</td>
<td>None described</td>
</tr>
<tr>
<td>Inclusion of radiotherapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Subset analyses (Pre-planned?)</td>
<td>Age, ER status, HER2 status, Number and type of metastases</td>
<td>Age, ER/HER2/triple negative; one organ site; bone only; all other; solitary bone lesion; multiple bone lesion</td>
</tr>
</tbody>
</table>

Indian Trial

Badwe et al, SABCS 2014

MBC ➔ Anthracyclines +/- Taxanes (CR/PR) ➔ Loco-Regional Rx

Stratification

- Site of metastases
  - Visceral
  - Bone
  - Visceral + Bone
- No of Metastases
  - ≤ 3
  - > 3
- ER/PgR:
  - Positive
  - Negative
Results

• 350 enrolled
  – 60% ER+
  – More premenopausal in the no surgery arm
  – 74% had > 3 metastatic sites
  – 10% of those randomized to no local therapy had palliative mastectomy

• Efficacy
  – Overall survival identical between the two arms
  – Subgroup analysis did not find an isolated group with benefit
  – Improved distant DFS and local PFS

Distant Progression-free Survival

![Graph showing Distant Progression-free Survival](image)
Demographics and Results

- 293 of recruited patients eligible
  - 278 evaluable
    - 86 vs 72% HR+ disease
    - 30% HER2+
    - 25% BCS, 90% ALND
- Median OS
  - 46 vs 42 months
  - 16 vs 24 months in TNBC (NS)
Subgroup Analyses

- Multiple subgroups analyzed
  - Not prospectively defined
  - Trends described:
    - Worse OS with surgery upfront
      - Multiple liver and lung mets
      - TNBC
    - Better OS with surgery upfront
      - Solitary bone mets
      - Bone only mets
      - Age < 55

Survival outcomes

<table>
<thead>
<tr>
<th>Primary endpoint survival</th>
<th>Tata Memorial</th>
<th>Turkey MF 07-01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio</td>
<td>1.04 (95% CI 0.8-1.3), p=.79</td>
<td>0.76 (95% CI 0.49-1.16), p=0.2</td>
</tr>
<tr>
<td>Survival duration/rate</td>
<td>21 months vs. 19 months, p=0.60</td>
<td>Fraction alive 35% in surgical group and 31% in non-surgical group (median f/u 21 months)</td>
</tr>
</tbody>
</table>

Secondary endpoints

| Local control | HR 0.16, 95% CI 0.10-0.26 | Not calculated (too few events) |
| Quality of life | Planned | Planned |
| Morbidity     | Planned | Planned |
ECOG 2108: opened Feb 2011

880 368 Women with intact primary tumors
Metastatic disease at any site
(exclude sites with very poor prognosis)

Optimal systemic therapy
(eg NCCN guidelines)
Planned drop-out rate 30%, actual 17%

Randomize 660 258 women with response or stable disease
Stratified by type of initial therapy (endocrine/cytotoxic/combination)

330 129 Early local therapy once
response/stable
documented (surgery plus XRT)

330 129 Delayed local therapy.
Planned cross-over rate 15%, actual 12.5%

Conclusions

• Questions
  – Effect of subsets/tumor biology requires prospective
    identification of subgroups
    • May help to identify smaller effects
  – Treatment post progression may be important

• What is the bottom line?
  – It is unlikely that surgery of the primary site for de
    novo metastatic breast cancer will have a large effect
    on outcome
  – Surgery should not be offered to patients across the
    board
  – Local control may be improved
    • What subset of disease?
  – Decisions must be individualized with careful
    assessment of quality of life

Pl: Khan
CTCs as a Surrogate Marker of Effective Treatment

- **SWOG 0500**
  - Will changing therapy based on poor response evidence by elevated CTCs improve outcome?
- **CTCs measured using the Cell Search System**
  - Automated detection of EpCAM enriched, keratin and CD45 positive cells
- **Prior studies** (Cristofanilli, 2004; Hayes 2007, Liu 2011)
  - CTC > 5 at baseline associated with significantly worse PFS and OS
  - CTC > 5 at first follow-up associated with greatest difference in PFS and OS

**Schema: S0500**

- **CTCs drawn at baseline prior to 1st-line chemotherapy**
  - CTC < 5
  - CTC ≥ 5
- **CTCs drawn 3 weeks after 1st dose of chemotherapy**
  - CTC < 5
  - CTC ≥ 5

- **Arm A**
  - Monitor for PFS & OS
  - CTC < 5
  - CTC ≥ 5
- **Arm B**
  - Maintain 1st-line chemotherapy until progression
  - 163 (57%)
- **Arm C1**
  - Maintain 1st-line chemotherapy
  - 123 (43%)
- **Arm C2**
  - Switch to alternate therapy

- **Randomized 1st endpoint OS**
- **Primary endpoint OS**
- **120 patients randomized**
  - 83% power to detect a 70% improvement in OS
S0500 – Overall Survival

Subset Analyses
- No difference based on:
  - Age
  - Tumor subtype
  - HER2 status
  - HR status
- No difference in PFS
  - 3.5 vs 4.6 months
- Persistent elevation of CTCs predicted worse outcome regardless of therapy

Overall Survival by Randomized Arm

<table>
<thead>
<tr>
<th>Eligible Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm C1: Maintain therapy (n=64; 50 deaths)</td>
</tr>
<tr>
<td>Arm C2: Change therapy (n=59; 48 deaths)</td>
</tr>
</tbody>
</table>

Median Arm C1: 12 months
Median Arm C2: 12 months
HR (C2 vs. C1) = 1.01
Log-rank p = 0.83

Overall Survival by Arm

<table>
<thead>
<tr>
<th>Eligible Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A (n=276; 146 deaths)</td>
</tr>
<tr>
<td>Arm B (n=163; 107 deaths)</td>
</tr>
<tr>
<td>Arms C1/C2 (n=123; 98 deaths)</td>
</tr>
</tbody>
</table>

Median Arm A: 35 months
Median Arm B: 23 months
Median Arm C1/C2: 13 months
Log-rank p < 0.0001

Enumerated CTCs are highly prognostic in the setting of metastatic breast cancer

Progression-Free Survival by Arm

<table>
<thead>
<tr>
<th>Eligible Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A (n=276; 232 events)</td>
</tr>
<tr>
<td>Arm B (n=163; 150 events)</td>
</tr>
<tr>
<td>Arm C1/C2 (n=123; 121 events)</td>
</tr>
</tbody>
</table>

Median Arm A: 11.1 months
Median Arm B: 8.9 months
Median Arm C1/C2: 4.9 months
Log-rank p < 0.0001

CTCs are being investigated on a molecular level
- Molecular analysis of CTCs may provide predictive information
- Identify targets of interest
ROSE Phase III Trial

- Ramucirumab
  - Recombinant monoclonal antibody
  - Binds to the extracellular domain of VEGFR2 to block ligand binding
- First line chemotherapy for HER2 negative disease
  - 1144 patients randomized 2:1 with PFS endpoint
    - 22-25% triple negative
  - Docetaxel + ramucirumab/placebo
- Results
  - PFS (investigator): 9.5 vs 8.2 mos, HR 0.88 (p=.077)
  - PFS (independent): 11.1 vs 8.5 mos, HR 0.79 (p=.008)
  - OS 27 months in both arms
    - ORR, TTP significantly greater in experimental arm
  - More toxicity in the exp arm (Htn, PPE, epistaxis, lacrimation, FN, stomatitis)

Dasatinib and c-Src

- Dasatinib is an oral inhibitor of c-Src, BCR-ABL, etc
  - Approved for CML
- ER complexes with c-SRC and PI3K to drive endocrine resistance and cell growth
  - Synergy demonstrated between inhibition of aromatase and c-Src
  - c-Src regulates osteoclast mediated bone turnover
- Phase II, non-comparative trial
- Letrozole +/- dasatinib as first AI for MBC
  - Primary endpoint: clinical benefit rate
  - Optional crossover on progression
  - 120 patients
    - L/D: 56 and D: 61
Results

• 42 vs 32% de novo stage IV disease
• 26% required dasatinib dose reduction
  – Toxicities: rash, edema, fatigue, nausea, neutropenia, pleural effusions
• Efficacy
  – CBR
    • L/D: 71% and L: 66% (no difference)
    • 35 pts crossed over
      – CBR 23% (8/35)
  – PFS
    • L/D: 20.1 mos and L: 9.9 mos
• Prior studies showed no difference in PFS when dasatinib was added to fulvestrant or exemestane
  – Role of line of therapy?
  – Lots of competitors in this treatment setting
    • CDK 4/6 inhibitors
    • PI3K inhibitors

Hsp90 inhibitors prevent the stabilization and activation of client proteins critical to malignant growth

Client proteins, including:
- ALK, AKT, BCR-ABL,
- BRAF, CDK4, CHK1,
- EGFR, FLT3, HER2,
- HIF1a, KIT, MET,
- PDGFRα, CRAF, SRC,
- VEGFR, AR, ER …

Proper folding

Activated client; cell survival, proliferation

Ganetespib prevents Hsp90 binding to client (competitively binds the ATP pocket of hsp90)

Inactive client, degraded through proteasome
Single target, simultaneous inhibition of multiple oncogenic pathways

Ganetespib

HSP90

Ganetespib (nM)

Ganetespib

HSP90 inhibitor

Enchant-1 phase 2 trial

15 patients in single arm trial

CR/PR in 3 of 4 with HER2+ disease

CR/PR in 2 of 11 with TNBC

Metabolic response correlated with objective response

Well tolerated with ~20% grade 3 diarrhea

Additional trials ongoing or planned

Potentiates chemotherapy activity

Combination with hormone therapy
LCL 161

- Oral antagonist of inhibitor of apoptosis proteins
  - 17 patients, oral weekly dose with paclitaxel IV
  - 61% TNBC
  - 78% prior taxane
  - Well tolerated (5% FN, no cytokine release)
  - 47% PR, 35% SD
- Ongoing trial
  - Phase II neoadjuvant trial of paclitaxel and LCL 161 in patients with TNBC stratified by gene expression signature (n=200, NCT01617668).

In vitro Antitumor Activity of N-BIS

- Inhibition of cancer cell adhesion to extracellular matrix proteins
  (Pluijm et al., J Clin Invest, 1996; Boissier et al., Cancer Res, 1997; and others ....)
- Inhibition of cancer cell proliferation and induction of apoptosis
  (Shipman et al., Br J Haematol, 1997; and others ....)
- Inhibition of cancer cell migration and invasion
  (Boissier et al., Cancer Res, 2000; and others ....)
- Inhibition of angiogenesis
  (Fournier et al., Cancer Res, 2002; Wood et al., JPET, 2002; and others ....)
- Stimulation of the expansion of human γδT cells
  (Kunzmann et al., Blood, 2000; and others ....)
Bisphosphonates Embed In Bone And Interrupt The Vicious Cycle


Zoledronic Acid Inhibits Bone, Liver and Lung Metastases in the Murine 4T1/luc Orthotopic Breast Cancer Model

Hiraga et al., Clin Cancer Res, 2004
NATAN Study (AGO-B/GBG)

Stratification factors
- Center
- Hormone receptor status (<10 or ≥ 10 % ER or PgR)
- Age (<50 / ≥50 years)
- Time since surgery (within 3 months, 1 year, 2 years, or 3 years)
- ypT1-4 and/or ypN1-3 after at least 4 cycles of chemotherapy with an anthracycline and taxane

Prior and/or simultaneous endocrine/trastuzumab treatment or radiotherapy

Statistical assumptions: increase DFS from 58% to 67.2% (OR .73)

Zoledronate 4 mg iv.
- Every 4 weeks for the first 6 doses (year 0-0.5)
- Every 3 months for 8 doses (year 0.5-2.5)
- Every 6 months for 5 doses (year 2.5-5.0)

Results
- 693 enrolled
  - 79% HR+, 17% HER2+
  - 17% > 1 year after axillary surgery
- Observed event rate 50% of expected
  - Met futility endpoint
Treatment effect in subgroups

Non-significant trend favoring zoledronate in patients >55 years is in concordance with EBCTCG meta-analysis (Coleman et al)

Ongoing Post-Neoadjuvant Trials

- Rucaparib/cisplatin vs cisplatin in TNBC (accrual completed)
- Trastuzumab emtansine in HER2+ (Katherine)
- Palbociclib in HR+/HER2- high risk disease (Penelope)
  - 800 patients internationally
  - Randomized with hormone therapy to receive palbociclib vs placebo for 13 cycles (28 d cycles)
  - High risk by CPS-EG staging system (Mittendorf et al, JCO 2011)
    - Clinical stage
    - Pathologic stage
    - Histologic marker (ER neg, nuclear grade 3)
Effect of Bisphosphonates on Recurrence and Cause-specific Mortality in Women with ESBC: Meta-analysis of Randomized Trials

- Data received on 22 out of 36 trials with clodronate and aminobisphosphonates
  - 17,791 patients (77% of the total available patients)
- Evaluate recurrence
  - Bone vs non-bone sites
  - Pre- and post-menopausal women

Breast Cancer Recurrence: All women
Breast Cancer Recurrence: Postmenopausal Women*

Distant Recurrence

Bone Recurrence

Non Bone Recurrence

Significantly Greater Effect on Bone than Other Distant Recurrence

* Includes induced menopause and women aged >55 if unknown

Bone Recurrence By Menopausal Status

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women Allocated</th>
<th>Biphosphatemia</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10-y gain</td>
<td>10-y gain</td>
<td>Logrank</td>
</tr>
<tr>
<td></td>
<td>Not</td>
<td>gain 3.5% (SE 1.2)</td>
<td>gain 0.9% (SE 0.0)</td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>170/3314</td>
<td>163/2711</td>
<td>-5.3</td>
</tr>
<tr>
<td>Peri-menopausal</td>
<td>28/461</td>
<td>19/367</td>
<td>2.0</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>222/5737</td>
<td>286/5299</td>
<td>-47.6</td>
</tr>
<tr>
<td>Total</td>
<td>420/9332</td>
<td>468/8377</td>
<td>-51.1</td>
</tr>
</tbody>
</table>

99% or 95% confidence intervals

Heterogeneity between 3 categories: $\chi^2 = 7.5; p = 0.02$

† Includes women aged < 45 if unknown

‡ Includes women aged 45-55 if menopausal status unknown

Significantly Reduced Bone Recurrence in Postmenopausal Women
Distant Recurrence At Sites Other Than Bone By Menopausal Status

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women Allocated</th>
<th>Bisph</th>
<th>Allocated Not</th>
<th>Logrank Variance</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-menopausal</td>
<td>435/3134 (13.9%)</td>
<td>387/2711 (14.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peri-menopausal</td>
<td>38/461 (8.2%)</td>
<td>31/367 (8.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>523/5737 (9.1%)</td>
<td>533/5299 (10.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>996/9332 (10.7%)</strong></td>
<td><strong>951/6377 (11.4%)</strong></td>
<td><strong>8 8410.4</strong></td>
<td><strong>0.979 (SE 0.049)</strong></td>
<td></td>
</tr>
</tbody>
</table>

99% or - - - 95% confidence intervals

Heterogeneity between 3 categories: \( \chi^2 = 1.7; p > 0.1; \text{NS} \)

May be an underestimate due to different competing risks

No Difference in Non-bone Recurrence in Postmenopausal Women

Mortality – All Women

Breast cancer mortality

17709 women

10-y gain 1.7% (SE 0.9)
Logrank 2p = 0.04

Non-breast cancer mortality

17709 women

10-y loss 0.1% (SE 0.6)
Logrank 2p = 0.96
Mortality In Post-menopausal Women

Conclusions

- Adjuvant bisphosphonates reduce bone metastases and improve survival in post-menopausal women.
  - 34% reduction in risk of bone recurrence (p=0.00001).
  - 17% reduction in risk of breast cancer death (p=0.004).
  - No significant reduction in first distant recurrence outside bone
  - Risk reductions similar irrespective of ER, node status, use/non use of chemotherapy.
  - Benefits similar for aminobisphosphonates and clodronate.

- No effects apparent on disease outcomes in pre-menopausal women.

- No significant effects on non breast cancer deaths, contralateral breast cancer or loco-regional recurrence.
Implications for Clinical Practice

• For post-menopausal women taking aromatase inhibitors for early stage breast cancer
  – Use of bisphosphonates should be considered
  – This is particularly straightforward in those with at least osteopenia
  – Zoledronate IV every 6 months, or other aminobisphosphonates
  – Dental education!

Thank you!