Navigating Breast Cancer Therapeutics: Early and Late Stage Disease

Scott Christensen, MD
Professor, Hematology/Oncology
UC Davis Comprehensive Cancer Center

Outline

• SABCS 2013 Highlights
  • Biomarkers
  • Prevention/Supportive Care
  • Early Stage Breast Cancer
  • Her 2+ Breast Cancer
  • Metastatic Breast Cancer
• ASCO 2014 Highlights
  • Early Stage Breast Cancer
  • Her 2+ Breast Cancer
  • Metastatic Breast Cancer
• Prognostication & Prevention
• Best Clinical Practice

San Antonio Breast Cancer Symposium 2013

Genetic Landscape of MBC

• Exome sequencing of 100 pairs of MBC and normal breast tissue DNA (Integragen Inc, Hiseq platform)
• Targeted sequencing of 100 genes in 240 MBC biopsies
• PIK3CA 26%, AKT1 4%, PTEN 4%, ERBB 2%, K-Ras 1%, ATM 1%, CDH1 2%, GATA3 2%. PTPN11 1%, PTPRD 1%, ROS1 1%
• Many of them are drugable and involved in metastatic process and drug resistance

Bachelot et al, #S6-07, SABCS 2013

Biomarkers
56.07
S4-04
P04-1
56.06
Exome Sequencing To Identify Actionable Mutations In mTNBC

- 38 pts with mTNBC and matched specimens of germ-line DNA, primary and metastatic tumors
- Whole-exome sequencing by Agilent solution-based system of exon capture with 10 GB of sequencing data
- Striking genetic heterogeneity between primary and metastatic tumors
- No single driver mutation that was common to metastatic tumors, indicating diverse genetic pathways contributing to metastasis
- Mutations in APC and mTOR more frequent in metastatic than primary tumors
- Nonsense mutations of ER in primary and metastatic tumors but not in germ-line DNA
- EGFR and HER2 mutations not detected

O'Shaughnessy et al, #PD4-1, SABCS 2013

Gene Mutations And Protein Expression in TNBC vs non-TNBC

- 5500 pts evaluated for mutation (Sanger or Illumina Truseq), protein expression (IHC) and/or amplification/rearrangement (FISH or CISH), 16% with TNBC
- Mutation: TNBC has higher p53 mutation (60% vs 30%), lower PIK3CA (12% vs 31%)
- Amplification: TNBC has higher amplification of EGFR (24% vs 13%), lower HER2, PIK3CA, cMYC and TOP2A
- IHC: TNBC has higher AR (56% vs 15%)

O'Shaughnessy et al, #PD4-1, SABCS 2013

Heterogeneity Between Primary And Metastases Prior To Treatment

- High-depth whole exome sequencing and SNP6 copy number profiling of primary and met biopsies from 7 pts with de novo MBC prior to systemic therapy
- Significant genomic differences between primary and met tumors
- Median 105 of single nucleotide variants (SNVs) and 54 insertions/deletions (indels) identified, of which 36 and 11 were shared between the primary and secondary tumors
- 50% driver SNVs and 70% pathogenic indels were restricted to either primary or met tumors, including the epithelial-to-mesenchymal transition (EMT)-related genes TGFB1, SMAD4 and TCF7L2

Bidard et al, #S6-06, SABCS 2013

Prevention/Supportive Care

IBIS II HOPE

IBIS-II Chemo-prevention In High Risk Postmenopausal Women

- Randomized phase III UK trial
- 3864 women with high risks of BC, median f/u 5.03 yrs
- Primary end point: incidence of BC, including DCIS
- Anastrozole vs placebo for 5 years

Cuzick et al, #S3-01, SABCS 2013
Early Stage Breast Cancer

CALGB 40603
Phase II Study of TH In HER2+, Node- EBC

- 410 pts, HER2+ EBC
- T1mi 3%; T1a 27%, T1b 20%, T1C 41%, T2 <3 cm 9%
- Weekly paclitaxel x12 with trastuzumab for 1 year
- Null hypothesis: 3-year failure rate of 9.2% (failure)
- Alternative hypothesis: 3-year failure rate of 5% (success)
- Due to limited number of events, DMSB approved data release with 1316 PYFU and median f/u of 3.2 years

Tolaney, S et al, #S1-04, SABCS 2013
Metastatic Breast Cancer

S0500

SWOG S0500: CTC's In Guiding MBC Chemotherapy

(CTC found in 75% MBC, half >5 CTC/7.5 ml whole blood)

Smerage et al, #S5-07, SABCS 2013
SWOG S0500
CTC’s in Guiding CT in MBC

• Conclusion:
  • CTC prognostic in MBC at baseline and after first chemo
  • Changing chemo based on CTC after first chemo does not affect OS or PFS

ASCO 2014

Smerage et al, #S5-07, SABCS 2013

Early Stage Breast Cancer
LBA1 SOFT/TEXT Combined Analysis
LBA505 SO230 POEMS

TEXT/SOFT Trial Designs

Enrolled: Nov03-Apr11
• Premenopausal
• ≤12 wks after surgery
• Planned OFS
• No planned chemo
• OR
tamoxifen
• ≤8 mos after chemo

TEXT (N=2672)
• Tamoxifen+OFS x 5y
• Exemestane+OFS x 5y

Joint Analysis
(N=4690)
• Tamoxifen+OFS x 5y
• Exemestane+OFS x 5y

Median follow-up 5.7 years

Enrolled: Feb05-Feb08
• Premenopausal
• ≤12 wks after surgery
• No prep
• OR
• ≤8 mos after chemo

TEXT (N=2672)
• Tamoxifen+OFS x 5y
• Exemestane+OFS x 5y

SOFT (N=3066)
• Tamoxifen x 5y
• Exemestane+OFS x 5y

TEXT/SOFT: Exemestane+OFS Improved DFS

Difference 3.8% at 5 years

5.7 years median follow-up

TEXT/SOFT Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No chemo TEXT (N=1053)</th>
<th>No chemo SOFT (N=943)</th>
<th>Chemo TEXT (N=1807)</th>
<th>Chemo SOFT (N=1807)</th>
<th>Overall (N=4690)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;40 yr</td>
<td>16%</td>
<td>9%</td>
<td>30%</td>
<td>49%</td>
<td>27%</td>
</tr>
<tr>
<td>LN +</td>
<td>21%</td>
<td>8%</td>
<td>66%</td>
<td>57%</td>
<td>42%</td>
</tr>
<tr>
<td>T-size &gt;2cm</td>
<td>19%</td>
<td>15%</td>
<td>53%</td>
<td>47%</td>
<td>36%</td>
</tr>
<tr>
<td>HER2 +</td>
<td>5%</td>
<td>3%</td>
<td>17%</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>Surgery to random (median)</td>
<td>1.5 mo</td>
<td>1.8 mo</td>
<td>1.2 mo</td>
<td>8.0 mo</td>
<td>1.6 mo</td>
</tr>
</tbody>
</table>
TEXT/SOFT: Exemestane+OFS Reduced Recurrence

Exemestane+OFS, as compared with tamoxifen+OFS, significantly improves DFS, BCFI and DFI and is a new treatment option for premenopausal women with HR+ early breast cancer

No significant difference in overall survival, conclusions premature at this early point in follow-up of HR+ breast cancer

Side effect profile of exemestane+OFS mirrors that seen with AIs in postmenopausal women

Some premenopausal women diagnosed with HR+ breast cancer have an excellent prognosis with highly-effective endocrine therapy alone

Long-term follow-up needed

Prevention Of Early Menopause Study: POEMS

POEMS Trial Design

n=118

Primary endpoint: Ovarian failure at 2 years

Secondary endpoint: Pregnancy outcome (ovarian dysfunction 1.2 yrs)

Exploratory: DFS/OFS

SO230: POEMS

• Premature ovarian failure is a common toxicity of chemotherapy administration in premenopausal women with breast cancer.

• SWOG-coordinated randomized Phase III study evaluating the impact of LHRH analog administration with chemotherapy for early stage ER/PBR- breast cancer on incidence of premature ovarian failure.

• Study accrual 2/04—5/11: 257 patients, 218 evaluable; stages I-III

• 62% study population had complete primary endpoint data

Prevention Of Early Menopause Study: POEMS
POEMS Conclusions

- LHRH analog (goserelin) administration with chemotherapy for ER+ early stage breast cancer was associated with less premature ovarian failure and more subsequent pregnancies.
- Premenopausal ER+ breast cancer patients should consider this new treatment strategy to prevent premature ovarian failure.
- There is no direct evidence evaluating this approach in ER+ breast cancer patients.
- Theoretical concerns exist concerning OFS reducing chemotherapy efficacy in ER+ breast cancer.
- In an exploratory analysis, monthly goserelin administration was associated with improved DFS and OS in premenopausal ER+ breast cancer.

Her2+ Breast Cancer

ALTTO Trial

- Phase III randomized, multicenter international trial enrolling over 8000 women.
- Study hypothesized dual Her2 blockade would result in improvements in breast cancer recurrence and death compared to anti-Her2 monotherapy.
- NeoALTTO trial documented higher pathologic CR rate at time of definitive surgery with usage of dual Her2 blockade.
- Anticipated that ALTTO would confirm neoadjuvant results in the adjuvant setting.

ALTTO Trial: Adjuvant Double Her2 Blockade

- Sequential or concurrent chemotherapy.

Statistical Considerations

- Target enrollment of at least 6,000 patients.
- Timing of primary analysis: 180 DFS events are required for the comparison of T vs. T (90% power using a 2 sided alpha error = 0.0087), OR
- 4.5 year median follow-up, whichever comes first.
- Event rate lower than anticipated: the current analysis is based on 535 DFS events at a median follow-up of 4.45 years (range: 3.5 to 6.40 years).
- First interim efficacy analysis (OSMC on 18th August 2011): comparison of Lapatinib alone versus Trastuzumab alone or crossover to Trastuzumab. Lapatinib-alone arms not reported here.
**ALTTO Trial: DFS**

**OPTIMIZE 2**

- Phase III randomized trial enrolling 403 women with metastatic breast cancer involving bone
- Previous studies have demonstrated reductions in SREs with monthly administration of zoledronic acid
- Concerns exist over observed toxicities (ONJ, Renal Insufficiency, Atypical Fractures) associated with prolonged monthly administration of zoledronic acid
- Study evaluated safety and efficacy of a less frequent dosing schedule of zoledronic acid compared to current standard

**ALTTO Trial: OS**

**Results**

- Primary endpoint: not met
- 20-40% of pts in the lapatinib arms did not reach 85% of the planned lapatinib dose
- Neoadjuvant results of the NeoALTTO trial did not translate into improved survival in the adjuvant setting
- Excellent performance of the control arm in a population “closer” to real world patients
- Results will fuel continuing debate

**ALTTO Trial Conclusions**

- Primary endpoint: not met
- 20-40% of pts in the lapatinib arms did not reach 85% of the planned lapatinib dose
- Neoadjuvant results of the NeoALTTO trial did not translate into improved survival in the adjuvant setting
- Excellent performance of the control arm in a population “closer” to real world patients
- Results will fuel continuing debate

**OPTIMIZE 2**

- Phase III randomized trial enrolling 403 women with metastatic breast cancer involving bone
- Previous studies have demonstrated reductions in SREs with monthly administration of zoledronic acid
- Concerns exist over observed toxicities (ONJ, Renal Insufficiency, Atypical Fractures) associated with prolonged monthly administration of zoledronic acid
- Study evaluated safety and efficacy of a less frequent dosing schedule of zoledronic acid compared to current standard

**ALTTO Trial: Selected AEs Per Arm**

- No cardiac toxicity concerns

**Metastatic Breast Cancer**

**LBA9500**

**OPTIMIZE 2**
OPTIMIZE 2

- Non-inferiority study
- All patients received monthly IV bisphosphonate (zoledronate or pamidronate) for 1 year prior to randomization to either continued monthly treatment with zoledronic acid or every 3 months at the current FDA-approved dose (4 mg)
- Median follow-up: 11.9 months
- At 2 years, incidence of SREs was similar (22% vs. 23%, p=0.724) in the two arms indicating non-inferiority
- No statistically significant differences in toxicities were observed

Hortobagyi, LBA9500, ASCO 2014

OPTIMIZE 2 Conclusions

- Women with metastatic breast cancer and bony metastases can safely and effectively switch to a less frequent dosing schedule of bisphosphonate therapy after 1 year of monthly treatment.
- Less frequent dosing schedule is safe and effective
- Less frequent dosing schedule was associated with numerically fewer toxicities, but the difference was not statistically significant
- Results should be interpreted cautiously given the modest sample size and somewhat limited follow-up time

Prognostications & Predictions

Breast Cancer index
Pam 50

Extended Endocrine Therapy Trials

- Extended endocrine therapy trials have demonstrated significant benefit; however, without further patient selection, the absolute benefit is modest

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment</th>
<th>Trial Size</th>
<th>Median Follow-up</th>
<th>HR (DFS)</th>
<th>HR (OS)</th>
<th>Absolute Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA.17</td>
<td>Pre-menopausal</td>
<td>Letrozole (5y) vs PBO</td>
<td>5187</td>
<td>30 m</td>
<td>0.58 (0.45-0.76)</td>
<td>0.82 (0.57-1.19)</td>
<td>4% vs 4%</td>
</tr>
<tr>
<td>ABCSG 6a</td>
<td>Pre-menopausal</td>
<td>Anastrozole (3y) vs no treatment</td>
<td>856</td>
<td>62.3 m</td>
<td>0.62 (0.40-0.96)</td>
<td>0.89 (0.59-1.34)</td>
<td>7.8% vs 12.2%</td>
</tr>
<tr>
<td>ATLAS</td>
<td>Pre-menopausal</td>
<td>Tamoxifen (5y) vs no treatment</td>
<td>6,846</td>
<td>10+ y</td>
<td>0.84 (0.76-0.94)</td>
<td>0.87 (0.78-0.97)</td>
<td>21.4% vs 25.1%</td>
</tr>
<tr>
<td>aTTom</td>
<td>Pre- and post-menopausal</td>
<td>Tamoxifen (5y) vs no treatment</td>
<td>6,953 (~80% ER+)</td>
<td>8.6 y</td>
<td>0.85 (0.76-0.95)</td>
<td>0.94 (0.86-1.03)</td>
<td>28% vs 32%</td>
</tr>
</tbody>
</table>

5 Gray et al., J Clin Oncol 31, 2013 (suppl; abstr 5).

- Likelihood of benefit from extended endocrine therapy
- Binary result: High/Low

BCI Reports Two Biomarkers

Prognostic (BCI Score)
- Algorithmic combination of MGI (Proliferation Pathway) and H/I (Estrogen Signaling Pathway)
- Individualized risk of late recurrence (years 5-10)

Predictive (H/I ratio)
- Likelihood of benefit from extended endocrine therapy
- Binary result: High/Low

Three Prognostic Validation Cohorts

Stockholm RCT | Multi-Institutional | TransATAC RCT
---|---|---
Validation in Prospective RCT | Validation in Multi-Institutional Cohort of Consecutive Cases | Validation in Prospective RCT & Head to Head with Oncotype Dx
317 Patients | 1,340 Patients | 645 Patients
Post-menopausal | Pre- and post-menopausal | Post-menopausal
ER +, LN - | ER +, LN - | ER +, LN -
5y TAM | 5y TAM | 5y TAM or Ax
BCI was a highly significant predictor of 10-year risk of recurrence

Summary of BCI Score Validation Studies

- Patient Population: ER+, LN- early stage breast cancer
- 1340 patients studied across the three cohorts
- Two prospective/re-trospective studies
- Large proportion of patients (55%–64%) in all 3 cohorts classified as low risk
  - These patients continued to be low-risk beyond 5 years (<3.5% ROR)

<table>
<thead>
<tr>
<th></th>
<th>TransATAC (N=665)</th>
<th>Stockholm (N=317)</th>
<th>Multi-institutional (N=358)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Post-menopausal</td>
<td>ER+, N0, 10% HER2+</td>
<td>5y AI or TAM</td>
</tr>
<tr>
<td></td>
<td>Post-menopausal</td>
<td>ER+, N0, 7% HER2+</td>
<td>2–5y TAM</td>
</tr>
<tr>
<td></td>
<td>Pre and Post-menopausal</td>
<td>ER+, N0, 12% HER2+</td>
<td>5y TAM</td>
</tr>
<tr>
<td></td>
<td>32% adjuvant chemo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10 Yrs</td>
<td>Low 59%</td>
<td>Intermediate 25%</td>
<td>High 16%</td>
</tr>
<tr>
<td></td>
<td>3.5% (2.0–6.1%)</td>
<td>13.4% (8.5–20.5%)</td>
<td>13.3% (7.4–23.4%)</td>
</tr>
<tr>
<td></td>
<td>Inter 64%</td>
<td>Low 20%</td>
<td>Intermediate 25%</td>
</tr>
<tr>
<td></td>
<td>2.8% (0.3–5.2%)</td>
<td>7.2% (0.1–13.8%)</td>
<td>10.1% (0.1–19.1%)</td>
</tr>
<tr>
<td></td>
<td>High 15%</td>
<td>Intermediate 16%</td>
<td>High 23%</td>
</tr>
<tr>
<td></td>
<td>2.5% (0–5.0%)</td>
<td>16.9% (6.5–26.2%)</td>
<td>15.0% (5.5–23.6%)</td>
</tr>
</tbody>
</table>

H/I Endocrine Response Biomarker

- The H/I ratio (HoxB13/IL17BR), which is part of the BCI Score, is also reported separately because of its distinct clinical utility
  - Endocrine response biomarker
- Previous studies have consistently demonstrated that H/I is predictive of response to endocrine therapy\(^1,2\)


Background

- The MA.17 landmark trial demonstrated, for the first time, the clinical benefit of extended endocrine therapy

<table>
<thead>
<tr>
<th>Patient Trial Design</th>
<th>Patient Trial Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goss PE et al., N Engl J Med 2003;349</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Benefit Analyses: Unadjusted and Adjusted

- High H/I was associated with a 67% reduction in the risk of recurrence (p=0.006) in patients treated with extended endocrine therapy
- Patients with Low H/I had no significant benefit from extended therapy
- Significant interaction between treatment and H/I: p=0.03
Patients with High H/I had a 5yr absolute benefit of 16.5% from extended endocrine therapy with letrozole (p=0.007)

Patients with Low H/I had no significant benefit from extended endocrine therapy with letrozole (p = 0.35)


Across studies, approximately 55-60% of patients are Low H/I

### Best Clinical Practice

- Genetic alteration is common in primary and metastatic tumors and in tumors undergoing treatment
- Identification of biomarkers and mutations by genome sequencing will not only unravel mechanisms of drug resistance but help to advance tailored targeted therapy
- AIs have been established as preventative agents
- Pts with stage I HER2+ tumors may be offered TH chemotherapy
- Anti-angiogenesis agents are unlikely to be effective in unselected patients; additional biomarker studies are urgently needed
- Carboplatin added to a taxane backbone increases pCR in TNBC

### PAM50 Predicting Late Relapse in EBC

- 2485 pts from ABCSG-8 and transATAC trials who did not relapse in 0-5 yrs
- Clinical treatment score (CTS, from transATAC) is the strongest prognostic score for late relapse
- PAM50 risk of recurrence (ROR) score adds significant prognostic value for late relapse
- Risk of distant relapse at 10 yrs for low risk group is 5.7%, intermediate risk 14.6% and high risk 29.3%
- Pts with luminal A subtype had a 70% lower risk of distant relapse than luminal B (HR 0.03, p<0.0001)

Sestak et al, #S6-04, SABCS 2013

### Clinical Practice Changes

- AIs now have level 1 evidence supporting usage in the premenopausal setting in association with OFS and demonstrate similar improvements in DFS observed in the postmenopausal setting compared to tamoxifen
- Less premature ovarian failure and improved fertility preservation is observed with OFS during chemotherapy administration in ER+ breast cancer and is associated with improvements in DFS and OS
- Dual anti-Her2 blockade with trastuzumab/lapatinib did not improve DFS or OS and was associated with increased toxicity in the adjuvant setting
- Less frequent bisphosphonate administration after 1 year of monthly treatment is safe and non-inferior to continued monthly treatment in metastatic breast cancer with bony metastases
- Predictive/prognostic biomarkers may help select patients most likely to benefit from a particular therapeutic strategy

Thank You