Chemotherapy Insights from the 2012 San Antonio Breast Cancer Symposium

Kathy S. Albain, MD, FACP
Professor of Medicine
Loyola University Chicago Stritch School of Medicine
Cardinal Bernardin Cancer Center
kalbain@lumc.edu

SABCS 2012 Chemotherapy Insights

- Metastatic disease
- “Adjuvant” systemic therapy for local/regional recurrence
- Adjuvant chemotherapy - mature outcomes from 3 older trials, and 1 newly reporting study
- Neoadjuvant chemotherapy - annual McGuire lecture, meta-analyses, novel agents, residual disease
- Treatment-related AML/MDS - new NCCN analysis
- Clinical Science Forum “Treatment on the Edges – Discordance Between Stage and Biology”

Thanks to colleagues who shared slides, and to Susan Peck, PhD for assistance in gathering and summarizing data
SABCS 2012 Chemotherapy Insights

**METASTATIC DISEASE**

Phase III Eribulin vs Capecitabine
Plenary Lecture 4 on ABC1

Global Open-label Phase III Trial (Study 301)

Patients (n = 1102)
Locally advanced or MBC
- ≤3 prior chemotherapy regimens (≥2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Eribulin megluime 1.4 mg/m² 2- to 5-min IV Day 1 & 8 q21 days
Randomization 1:1

Capecitabine 1250 mg/m² BID orally Days 1-14, q21 days

Co-primary endpoint
- OS and PFS

Secondary endpoints
- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

Progression-Free Survival

<table>
<thead>
<tr>
<th>Independent Review</th>
<th>Median (mos)</th>
<th>Eribulin (n=554)</th>
<th>4.1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Capecitabine (n=548)</td>
<td>4.2</td>
</tr>
</tbody>
</table>

HR† 1.079 (95% CI 0.932, 1.250)  p value‡=0.305

<table>
<thead>
<tr>
<th>Investigator Review</th>
<th>Median (mos)</th>
<th>Eribulin (n=554)</th>
<th>4.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Capecitabine (n=548)</td>
<td>4.1</td>
</tr>
</tbody>
</table>

HR† 0.977 (95% CI 0.857, 1.114)  p value‡=0.736

Kaufman et al. PSABCS 2012
Overall Survival

Median OS (months)

Eribulin (n=554) 15.9
Capecitabine (n=548) 14.5

HR† 0.879 (95% CI 0.770, 1.003)
p value‡ =0.056

Prespecified Subset Analyses for OS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Eribulin Median (months)</th>
<th>Capecitabine Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.879 (0.770, 1.003)</td>
<td>15.9</td>
<td>14.5</td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.965 (0.688, 1.356)</td>
<td>14.3</td>
<td>17.1</td>
</tr>
<tr>
<td>Negative</td>
<td>0.838 (0.715, 0.983)</td>
<td>15.9</td>
<td>13.5</td>
</tr>
<tr>
<td>ER status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.897 (0.737, 1.093)</td>
<td>18.2</td>
<td>16.8</td>
</tr>
<tr>
<td>Negative</td>
<td>0.779 (0.635, 0.955)</td>
<td>14.4</td>
<td>10.5</td>
</tr>
<tr>
<td>Triple negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.702 (0.546, 0.909)</td>
<td>14.4</td>
<td>9.4</td>
</tr>
<tr>
<td>No</td>
<td>0.927 (0.795, 1.081)</td>
<td>17.5</td>
<td>16.6</td>
</tr>
</tbody>
</table>

I Agree with the Authors’ Conclusions

- No significant superiority (OS, PFS) of eribulin vs capecitabine in MBC and 1-3 lines of prior therapy
- Toxicity of both agents consistent with previously reports
- Pre-specified exploratory subgroup analyses suggest greater therapeutic benefit with eribulin in ER-, HER2- and triple negative disease, supporting further study
MBC SURVIVAL OVER TIME

- Median survival improved during past decade (14 months in 1991, 22 months in 2001) BUT advances in MBC are measured in days/months and median survival is still 2-3 yrs!
- This is NOT a "chronic disease!"

ADVANCES HAVE BEEN DIFFERENT IN VARIOUS MBC SUBTYPES

- HER2+ BC: major advances
- TNBC: less advances
- ER+ BC: advances until the 90's and then stalled...

INTERNATIONAL CONSENSUS GUIDELINES NOW EXIST
"Adjuvant" Systemic Therapy for Locoregional Recurrence

Phase III CALOR Trial

No prospective randomized trial of 'adjuvant' chemotherapy for ILRR published in past 30 years! Aebi et al. PSABCS 2012

Planned n = 977, HR 0.74; modified n=265, HR 0.6; very slow accrual, closed 1/2010, no interim analysis; planned analysis at median f/up 4 years (this report)

CALOR International Collaboration

Planned n = 977. HR 0.74; modified n = 265. HR 0.6; very slow accrual, closed 1/2010, no interim analysis; planned analysis at median f/up 4 years (this report)

Participants

| BSG | 89 |
| IBCSG | 57 |
| Individual Centers (Hungary, South Africa, Peru) | 29 |
| IAC (Switzerland) | 14 |
| ANZ ESP (Australia) | 2 |
| GEICAM (Spain) | 20 |
| BOOG (The Netherlands) | 12 |
| NSABP | 73 |

TOTAL PARTICIPATION: 162
Adjuvant chemotherapy reduced the risk of:
- DFS events by 41% (ER+ 6%; ER- 68%)
- Death by 59% (ER+ 60%; ER- 57%)

Adjuvant chemotherapy should be recommended for patients with completely resected isolated local or regional recurrence who have definitive RT and adequate hormonal therapy.

The data are strongest for patients with ER-negative recurrences; longer follow-up intended to assess ER+.

The CALOR Trial Results of Aebi et al Inform Standard of Care for Patients with ILRR

There will never be another randomized trial on this question!
(with international collaboration, did not meet accrual goals)
SABCS 2012 Chemotherapy Insights

ADJUVANT CHEMOTHERAPY Phase III

MA21, TACT2, AGO - mature survival
BEATRICE – first report

NCIC CTG Phase III MA.21

Stratification: Number of nodes 4+ve (0-1-3, 4-10, >10);
Surgery (partial vs. mastectomy);
ER (+ive vs. -ive)

MA.21 Mature Toxicity Data

<table>
<thead>
<tr>
<th></th>
<th>CEF %</th>
<th>ECF %</th>
<th>AT %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>23</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Infection with Bacterial Neutropenia</td>
<td>9</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Sensory Neumopathy</td>
<td>88</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>Motor Neumopathy</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Treatment adverse events</td>
<td>7.6</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CEF %</th>
<th>ECF %</th>
<th>AT %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac - LVEF</td>
<td>94</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>94</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Leukocytosis/MDS</td>
<td>1.3</td>
<td>1.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>
MA.21 Mature Results for RFS/OS

TACT2 trial design

TACT2, a phase III trial with 2 x 2 factorial design, E-CMF as control, tests two hypotheses:
A) crossing anthracycline chemotherapy offers greater efficacy
B) oral SFU prodrug capecitabine gives similar efficacy but better toxicity profile to CMF

RANDOMISATION

Randomisation schedule (2): 4 cycles, 3-weekly, 100mg/m², followed by:
- 4 cycles, 3-weekly, 100mg/m² + Pegfilgrastim 5mg day 2

RANDOMisation schedule (2): 4 cycles, 3-weekly, 100mg/m² + Pegfilgrastim 5mg day 2

CMF 4 cycles
- 60/40/600mg/m²
- 50/40/600mg/m²
- 100/40/600mg/m²
- PO: days 1-14

Capecitabine (Q): 4 cycles, 2500mg/m²
- Oral: days 1-14

Capecitabine (Q): 4 cycles, 2500mg/m²
- Oral: days 1-14

TTR – Univariate analyses

Univariate hazard ratio = 0.96 (95% CI: 0.91 – 1.03)
Logrank p-value = 0.06

Number of events (years)
- E: 59
- aE: 56
- E: 19
- aE: 21
- aE: 21
- aE: 21
- aE: 21
- aE: 21
- aE: 21
- aE: 21

The presentation of the individual properties of the author is not an endorsement by the authors or the organization of the presentation.
What Have We Learned from These 3 Updates (and prior studies)?

- AC/EC then taxane q 3 weeks not superior to second generation non-taxane regimens CEF/CAF (with oral C).
- Don’t forget this regimen to spare patients of taxane neuropathy when level of risk justifies the less intense approaches.
- More intense/dense third generation regimens are superior (when the paclitaxel is given weekly or every 2 weeks).
- Unclear if necessary to give the AC/EC component q 2 weeks if T is given weekly or q 2 weeks (scheduling of the taxane seems more critical).
- Whether “intense plus dense” regimens are superior to “dense” is unstudied.
- Leukemia risk low but real (informed consent!)
BEATRICE Trial
Conclusions/Critique

- First report of phase III adjuvant trial solely in TNBC
- DFS at 3 years better than projected in both arms
- No new adverse event signal, similar to MBC studies
- While no statistically significant improvement, HR 0.87 (95% CI 0.72-1.07)
- Await OS analysis when mature, as well as ECOG adjuvant bevacizumab trial
- Still lack robust predictive biomarker(s) to select patients for bevacizumab-based therapy

SABCS 2012 Chemotherapy Insights

NEoadjuvant CHEMOTHERAPY

McGuire Memorial Lecture
2 Meta-analyses
I-SPY 2 (new agents)
Residual Disease (new agents)

Neoadjuvant Systemic Therapy: Promising Experimental Model or Improved Standard of Care?

- Historical background
- Preclinical studies
- Randomized trials
- pCR as intermediate endpoint
- Breast-conserving therapy after NAST
- Predictive factors for pCR
- Is NAST optimal for all patients?
Is Neoadjuvant Systemic Therapy Optimal for All Patients?

• Yes, if patients are otherwise candidates for systemic therapy
• If indication for systemic therapy is uncertain, surgical removal is preferable.
• NAST should be tailored to the biological profile of the primary tumor.
• Primary and/or nodes must be measurable and monitored
• Multidisciplinary team must be available

Future Application of Neoadjuvant Systemic Therapy

• Definitive treatment without surgery
  – Several French series
  – Inflammatory breast cancer
  – Highest pCR rate in small tumors
• New drug development
• Monitoring biological endpoints
• Randomized neoadjuvant trials to justify or avoid randomized adjuvant trials.

AGO-B/GBG Very Young Age Neoadjuvant Metaanalysis - Objectives

• Three age groups:
  – ≤35 (n=704)
  – 36-50 (n=4167)
  – ≥51 (n=4078)
• Compare:
  – pCR rate
  – disease free survival (DFS)
  – local recurrence free survival (LRFS)
  – overall survival (OS)

Loibl et al. PSABC 2012
Breast Cancer Subtypes According to Age

Loibl et al. PSABC 2012

pCR Rates Overall and in Subgroups

Adjusted for age, tumor size, nodal status, histological type, grading, and race. Very young age significant independent predictor in TNBC and HR+ HER2-.

AGO-B/GBG Young Age Metaanalysis
Main Outcome Results

- Confirms prior studies that biology is different in very young; therapy should be directed to biology, not age per se
- DFS worse for very young
  \( \leq 35 \text{ vs. } \geq 36-50: HR 0.83 \ [95\%CI 0.70-0.98] \ p=0.031 \)
- LRFS worse for very young
  \( \leq 35 \text{ vs. } \geq 36-50: HR 0.74 \ [95\%CI 0.58-0.95] \ p=0.018 \)
- Study does not account for BRCA status
DFS in Different Subtypes by pCR and Age

Loibl et al. PSABCS 2012

Before FDA opens a regulatory path for neoadjuvant trials it is essential to have better knowledge of neoadjuvant endpoints needed to support regulatory approval for neoadjuvant breast cancer

Meta-analysis of the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC)

CTNeoBC Selected Trials

- 12 neoadjuvant randomized controlled trials
- pCR clearly defined with all necessary data collected
- Long-term follow-up EFS and OS data collected

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBG/AGO</td>
<td>7</td>
</tr>
<tr>
<td>NSABP</td>
<td>2</td>
</tr>
<tr>
<td>EORTC/BIG</td>
<td>1</td>
</tr>
<tr>
<td>IIA</td>
<td>2</td>
</tr>
<tr>
<td>Total # patients</td>
<td></td>
</tr>
</tbody>
</table>

Cortazar et al. PSABCS 2012
CTNeoBC Four Questions Summary

1. Is pCR associated with long term outcomes (EFS and OS)?
   - Individual patients who attain a pCR have a more favorable long-term outcome (nothing new).

2. Which pCR definition is best associated with long term outcome?
   - Comparable EFS or OS regardless of presence or absence of DCIS.
   - For consistency, a standard pCR definition (ypT0ypN0 or ypT0/isypN0) should be used in future trials.

3. In which breast cancer subtypes does pCR correlate with long term outcome?
   - Triple negative (HR=0.24)
   - HER2+/ HR- (HR=0.25)
   - HR+ high grade (HR=0.27)
   - HER2+/ HR+ (HR=0.58)

4. What magnitude of pCR improvement in a randomized trial will predict long term clinical benefit (EFS and OS improvement)?
   - Could not be established, possibly due to:
     - low pCR rates
     - heterogeneous population
     - lack of targeted therapy except NOAH trial
   - The absolute magnitude of improvement in pCR rate needed to impact long-term outcome may be greater than observed in these trials and may vary according to breast cancer subtype.
Proposal to Accelerate FDA Approval through Neoadjuvant Trials using pCR as Surrogate (Draft FDA Guidance)

Achieve surrogate endpoint predicting clinical outcome

Promising drug candidate and associated biomarker

Replicate effect of drug/biomarker pair on surrogate

Achieve clinical outcome (regulatory standard for FDA approval)

Accelerated drug approval

Approval of biomarker

Full drug approval


Summary of I-SPY2 Study Plan for Patients with Tumor Size at least 2.5 cm

MRI

Blood Draw

Consent #1 Screening Consent

Biopsy for 70 gene expression profile

Consent #2 Treatment Consent

Consent #3 Screening Consent

Paclitaxel* + Investigational Agent A (12 weekly cycles)

AC (4 cycles)

Paclitaxel* + Investigational Agent B (12 weekly cycles)

AC (4 cycles)

Paclitaxel* + Investigational Agent B (12 weekly cycles)

AC (4 cycles)

AC (4 cycles)

MRI

Blood Draw

MRI

Blood Draw

MRI

Biopsy

Blood Draw

MRI

Blood Draw

MRI

Blood Draw

AC

AC

AC

AC

5 drug companies

3 device companies

1st drug/biomarker "graduating"

New pipeline drugs

Funding: Public/Private Partnerships
I-SPY 2 Biomarker Profile Drives Randomization Assignment to Experimental Arms

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>HER2+</th>
<th>HER2-</th>
<th>HER2+</th>
<th>HER2-</th>
</tr>
</thead>
<tbody>
<tr>
<td>neratinib</td>
<td>Pan ErbB</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABB-88**</td>
<td>PARP inhibitor</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AMG 386</td>
<td>Arginase</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMG 479</td>
<td>KDR inhibitor</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>M3-2206</td>
<td>AKT inhibitor</td>
<td>Yes***</td>
<td>Yes***</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Neratinib is delivered in place of trastuzumab in HER2+ patients
** ABB-88 is delivered in combination with both paclitaxel and carboplatin in HER2 negative patients
*** M3-2206 is delivered in combination with trastuzumab in HER2+ patients

---

SABCS 2012 Chemotherapy Insights

**t-AML/MDS after Chemotherapy for Early Breast Cancer**

New NCCN Data Base Analysis

---

Two Typical Patterns of t-AML/MDS

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Latency</th>
<th>Onset</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>1 – 3 years (range 0.5 – 4.5)</td>
<td>No prodrome</td>
<td>M4, M5 common (M3 with mitoxantrone)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4 – 6 years (range 1 – 20)</td>
<td>Preceded by MDS</td>
<td>M6, M7</td>
</tr>
</tbody>
</table>
Characteristics of NCCN Leukemia Cohort (n = 51/20,482; 0.25%)

<table>
<thead>
<tr>
<th>Event</th>
<th>n</th>
<th>Median Time to Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>51*</td>
<td>3.3 years</td>
</tr>
<tr>
<td>Myeloid Leukemia</td>
<td>40 with cytogenetics</td>
<td>3.5 years</td>
</tr>
<tr>
<td>- “translocation”</td>
<td>16 (8 with MLL translocation)</td>
<td>1.9 (1.1 – 5 years)</td>
</tr>
<tr>
<td>- “adverse/MDS-like”</td>
<td>12 (10 complex)</td>
<td>4.9 (1.7 – 8 years)</td>
</tr>
<tr>
<td>Lymphoid Leukemia</td>
<td>7</td>
<td>2.0 years</td>
</tr>
<tr>
<td>- CLL</td>
<td>4</td>
<td>2.3 (0.7 – 3.7 years)</td>
</tr>
<tr>
<td>- ALL</td>
<td>3</td>
<td>1.9 (1.1 – 4.8 years)</td>
</tr>
</tbody>
</table>

*One third of leukemia patients had a family history of breast or ovarian cancer

Karp et al. PSABCS 2012

NCCN Cumulative Incidence t-AML/MDS

Adjuvant chemotherapy had cumulative 10-year incidence of leukemia of ~ 0.5%. This is higher than previously reported

Almost half of the events occurred beyond year 5, so education of PCPs of survivors needed

Radiation alone appears to be a risk factor, but may not add significant risk if already treated with chemotherapy

Leukemia risk was not limited to MDS/AML, since high risk lymphoid leukemias were also observed

Rates for commonly used TC regimen not yet known

Karp et al. PSABCS 2012

NCCN t-AML/MDS Conclusions

Adjuvant chemotherapy had cumulative 10-year incidence of leukemia of ~ 0.5%. This is higher than previously reported

Almost half of the events occurred beyond year 5, so education of PCPs of survivors needed

Radiation alone appears to be a risk factor, but may not add significant risk if already treated with chemotherapy

Leukemia risk was not limited to MDS/AML, since high risk lymphoid leukemias were also observed

Rates for commonly used TC regimen not yet known

Karp et al. PSABCS 2012
SABCS 2012 Chemotherapy Insights

CLINICAL SCIENCE FORUM
Treatment on the Edges – Discordance Between Stage and Biology

Bad Stage... but Good Biology
Low Stage... but Adverse Biology

Albain KS and Piccart M. PSABCS 2012; www.SABCS.org/

On one edge...
Bad stage/risk... but
"Good"/indolent biology

On the other edge:
Low stage/risk... but
"Bad"/adverse biology

Adjuvant Treatment on the Edges – Vexing Clinical Dilemmas!

Kathy S. Albain, MD, FACP
Martine J. Piccart, MD, PhD

Concordant Stage/Risk and Biology

What Should Drive Treatment Decisions when Bad Stage (Predicting High Recurrence Risk) Coexists with Favorable Biologic Features - I

• We cannot reliably identify those cured by surgery alone despite high risk/bad stage
• Modern adjuvant/neoadjuvant chemotherapy benefits patients with luminal breast cancer in general (2011 Oxford Overview)
• Yet this standard approach over-treats many
• In high risk settings, biologic subtypes of ER+ disease differ in 1) degree of sensitivity to chemotherapy (predicted best by a combination of factors/genes) as well as in 2) degree of endocrine responsiveness
What Should Drive Treatment Decisions when Bad Stage (Predicting High Recurrence Risk) Coexists with Favorable Biologic Features - II

- Avoidance of standard chemotherapy due to relative resistance may be justified in higher risk, HER2 non-enriched subgroups that are endocrine responsive with low proliferation (variably defined by low 21 gene RS, luminal A, low risk 70 gene signature)
- The highest risk scenarios that also present with this biologic profile require alternate strategies to increase cure rates

S1007 RxPONDER Schema

- Patients consent to study enrollment, ECOG, discussion of personal risk, HER2 status, metastatic disease and biologic tumor characteristics
- RS already available
- Physician and patient discuss randomization knowing the RS
- Patients consent to study-sponsored RS testing, discussion of potential trials, tumor tissue submission and linkage to cancer registry data

STEP 1 REGISTRATION
- Tumor tissue submission for RS

STEP 2 REGISTRATION RANDOMIZATION
- RECURRENCE SCORE
- N=33,800
- Discuss alternative trials
- N=5,600
- Physician and patients discuss randomization knowing the RS
- N=1,600
- Record chosen therapy and followed for vital status through cancer registry

STEP 2 REGISTRATION RANDOMIZATION
- N=4,000
- Randomization stratified by
  1. RS
     a. RS ≤ 13 vs. 14 vs. 15 vs. 16
     b. Menopausal status
     c. Axillary node dissection vs. sentinel node biopsy
  2. RS > 25
     a. Accept
     b. Refuse

Medical Oncology Investigators:
Gonzalez-Angulo A-M, PI; Hortobagyi G; Albain K

Accrual as of 1/25/13
- Registration 1 (goal 9400)
  - 2050
- Registration 2 (goal 4000)
  - 466 Chemotherapy + endocrine therapy
  - 467 Endocrine therapy alone
SWOG 1207 Phase III adjuvant endocrine therapy + everolimus/placebo in high-risk, node-positive, hormone receptor-positive, HER2-neu normal breast cancer

Number of positive nodes?
3 positive
4+ positive
RS > 25

SWOG SWOG 1207 Phase III adjuvant endocrine therapy + everolimus/placebo in high-risk, node-positive, hormone receptor-positive, HER2-neu normal breast cancer

Low risk
3 positive nodes and RS ≤ 25

RS 25

CURRENT RX
Chemotherapy; endocrine therapy
No Chemotherapy; endocrine therapy

RANDOMIZATION
Chemotherapy vs. No Chemotherapy
Adjuvant or neoadjuvant chemotherapy
Post-chemotherapy (stratification by number of lymph nodes and timing of chemotherapy)

EVEROLIMUS vs. Placebo

CURRENT RX
PONDER trial S1007
New adjuvant trial S1207

Low risk
3 positive nodes and RS ≤ 25
RS > 25 or 4+ positive

RS > 25

Highlights of early TCGA findings using 500 tumors

1. Basal-like tumors form a distinct subtype by gene expression, DNA methylation, protein patterns, and by microRNA expression profiling (75% of Triple-negative breast cancers are of the Basal-like subtype)

2. The 10 most frequently mutated genes in ER+/HER2- tumors occur within a diversity of pathways and includes PIK3CA(48%), TP53(20%), MAP3K1(18%), GATA3(14%), CDH1(9%), MLL3(8%), MAP2K4(6%), PTEN(5%), RUNX1(4%) and AKT1(3%).

3. DNA methylation analysis identifies Basal-like tumors as showing a hypo-methylation phenotype and a subset of tumors are cases having frequent promoter CpG island hyper-methylation phenotype.

4. Integrated pathway analyses identifies distinct mechanisms of PIK3CA pathway activation by subtype

5. Complex and numerous DNA copy number changes are associated with the Basal-like, HER2-enriched, and LumB subtypes, and are independent predictors of poor outcomes

6. HER2+ tumors are molecularly heterogeneous and tumors that are clinical HER2+ AND HER2-enriched subtype appear to show activation of HER2 and HER1 signaling

Low Stage – Adverse Biology: When They Collide

Plan of presentation

- The natural history of T1a,bN0M0 breast cancer
- Consensus about a non endocrine therapy threshold
- The learning curve about what constitutes “adverse biology”
- To treat or not to treat
- Take-home messages
**T_{1a,b}N_{0}M_{0}: Take-home messages**

- **Literature:** Few large population-based studies, many small single institutional studies subject to bias; all studies are retrospective; few have truly mature follow-up.
- **Clinical trials:** Mostly not open to T_{1a,b}N_{0}M_{0}; we need more initiatives like the ones of the Dana Farber Institute.

**TO TREAT?**
- Age ≤ 35y
- Vascular invasion
- HER2 positivity
- Luminal subtype with High Risk Genomic Profile

**NOT TO TREAT?**
- Comorbidities

---

**SABCS 2012 Chemotherapy Insights**

**SUMMARY – IMPACT ON CLINICAL PRACTICE?**

- **Metastatic disease** – not this year, but ABC1 of international importance.
- “Adjuvant” systemic therapy for local/regional recurrence - yes.
- Adjuvant chemotherapy - mature outcomes from 3 older trials, and 1 newly reporting study - yes.
- Neoadjuvant chemotherapy - annual McGuire lecture, meta-analyses, novel agents, residual disease - yes.
- Treatment-related AML/MDS - new NCCN analysis - yes.
- Clinical Science Forum “Treatment on the Edges – Discordance between Stage and Biology” - yes.