INTRODUCTION

The CARE (Community. Academic. Research. Education.) Breast Cancer Faculty is a national group of specialists from across Canada who gather, discuss and address gaps in knowledge, with education outputs framing news from a Canadian perspective. The mission of the CARE Breast Cancer Faculty is to enhance medical education with the explicit goal of improving patient outcomes.

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CARE — CONFERENCE HIGHLIGHTS FROM SABCS 2013

The treatment of breast cancer is rapidly evolving with an increased appreciation of tumor biology and development of targeted drugs. “Canadian Perspectives” shares news and developments in breast cancer as covered at the SABCS meeting, framed from a Canadian perspective.

Commentary and perspectives have been provided by the CARE Breast Cancer working group faculty

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For additional information or to join CARE, please visit us at careeducation.ca or contact us at carefaculty@careeducation.ca
Adjuvant Bisphosphonate (BP) Therapy

BPs are traditionally given to women with bone loss, and have demonstrated anti-cancer activity preclinically and in clinical trials during adjuvant breast cancer therapy. The metastasis-preventing effect of bisphosphonates has been explained by their putative effects on the bone marrow microenvironment, which provides a site for cancer cells to evade immune surveillance and adjuvant systemic anti-cancer therapy.

Table 1 below provides an overview of trials and data supporting the use of BP therapy for breast cancer patients.

Table 1: Observational Studies of BP Therapy

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Study Design</th>
<th>Patient Cases (% BP)</th>
<th>Control Subjects (% BP)</th>
<th>Correction for BMD differences</th>
<th>Breast Cancer Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rennert</td>
<td>Case-control oral BP</td>
<td>1822 (10.5%)</td>
<td>2207 (14.8%)</td>
<td>NONE</td>
<td>OR 0.72 (0.57–0.90)</td>
</tr>
<tr>
<td>Newcomb</td>
<td>Case-control</td>
<td>2336 (4.4%)</td>
<td>2975 (6.2%)</td>
<td>Limited adjustment</td>
<td>OR 0.67 (0.51–0.89)</td>
</tr>
<tr>
<td>Vestergaard</td>
<td>Cohort alen/etid</td>
<td>87,104</td>
<td>3 age matched controls not on BP</td>
<td>NONE</td>
<td>Alen HR 0.53</td>
</tr>
<tr>
<td>Chlebowski</td>
<td>Cohort 154,768 WHI</td>
<td>9748 with BMD info; 5092 BC cases</td>
<td>2816 (18%) BP users</td>
<td>Hip fracture prediction score</td>
<td>HR 0.68 (0.52–0.88); strong data in HR+; trend in HR-</td>
</tr>
</tbody>
</table>

CARE Faculty Perspective:
The findings in these trials on the incidence of contralateral (new BC) tumours provide the strongest evidence of a direct effect on BP on BC development. The Chlebowski Cohort trial drew from the Women’s Health Initiative cohort of 154,768 women. The “hip fracture prediction score” is a validated score to adjust for potential differences in BMD between BP users and non-users. Adjustments were also made for menopausal hormone therapy use, and other breast cancer risk factors.

ABCSG12 AND AZURE TRIALS

Two important trials studying adjuvant zoledronic acid are the ABCSG12 trial, presented at ASCO 2008, and the AZURE trial, published in the NEJM in 2011. These trials, anticipated to be similar, showed very different results from one another. This has generated a lot of discussion regarding why this was seen. A head-to-head comparison summarizing the results of these two trials can be found in Table 2 below.

Table 2: Results of the ABCSG12 and AZURE Trials

<table>
<thead>
<tr>
<th></th>
<th>ABCSG 12</th>
<th>AZURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size, stage</td>
<td>N = 1803, I and II</td>
<td>N = 3360, II and III</td>
</tr>
<tr>
<td>Median age</td>
<td>45</td>
<td>Not in Table 1</td>
</tr>
<tr>
<td>Node positive</td>
<td>30%</td>
<td>98%</td>
</tr>
<tr>
<td>preMP</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>ER and/or PR pos</td>
<td>100%</td>
<td>78.5%</td>
</tr>
<tr>
<td>Received chemotherapy</td>
<td>5% NAT</td>
<td>95.5%</td>
</tr>
<tr>
<td>ZOL administration</td>
<td>Less intense, 3 years</td>
<td>More intense, 5 years</td>
</tr>
<tr>
<td>DFS events</td>
<td>137 (47.8 mo)</td>
<td>752</td>
</tr>
<tr>
<td>Control arm BP use</td>
<td>??</td>
<td>8.7%</td>
</tr>
<tr>
<td>“Low estrogen state” benefits</td>
<td>N = 1390 (77%), better DFS/OS, less contral/bone mets/locoregional/distant mets (not nonBMFS)</td>
<td>N = 1041 (31%), better DFS/OS, less visceral/locoreg mets (not distant skeletal mets)</td>
</tr>
</tbody>
</table>

CARE Faculty Perspective:
There are two camps of thinking on this subject created by the differences seen in these trials. The decision as to which trial has the most impact on practice strongly rests with individual opinion/interpretation.
**SABCS 2013 CONTENT OF INTEREST**

**SABCS 2013 Session S4-07: Effects of BP Treatment on Recurrence and Cause-Specific Mortality in Women With Early Breast Cancer: A Meta-Analysis of Individual Patient Data From Randomised Trials.**

*Coleman et al.*

**Background:** Disseminated tumour cells can remain dormant in the bone marrow for years prior to subsequent activation and the development of overt metastases. Bisphosphonates have profound effects on bone physiology and could potentially modify the metastatic disease process. Variable outcomes in terms of disease recurrence have been reported, with efficacy apparently influenced by menopausal status.

**Conclusion:** Adjuvant bisphosphonates reduce bone recurrences and improve breast cancer survival in postmenopausal but not premenopausal women.

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**CARE Faculty Perspective:**

The benefits reported in this adjuvant bisphosphonate meta-analysis are robust and the results are expected to be practice changing. At minimum, the results are worthy of a discussion with each of our adjuvant postmenopausal breast cancer patients (most of whom will already be at risk for bone loss due to age alone and/or adjuvant aromatase inhibitor (AI) therapy). The question of which bisphosphonate and schedule to choose is left up to the treating oncologist and their patient to decide. Drug side effect profile, out of pocket cost, and patient convenience need to be kept in mind.

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**Aromatase Inhibitor-Induced (AIA)**

There is a lot of ambiguity surrounding this syndrome as most studies define it differently. AIA is a common reason for discontinuation/nonadherence. This creates major QoL concerns and altered recurrence risk with adherence issues often starting after year 2 of therapy.

**IMPACT ON DISCONTINUATION**

Table 3 below outlines key trials that investigated incidence of AIA and discontinuation rate.

**Table 3: AIA Incidence and Discontinuation**

<table>
<thead>
<tr>
<th>Arthralgia Incidence</th>
<th>Incidence of Severe AIA</th>
<th>Discontinuation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large adjuvant trials</td>
<td>5%–36%*</td>
<td>&lt; 10%*</td>
</tr>
<tr>
<td>ATAC</td>
<td>36% (29% TAM)</td>
<td>TAM 14.3% vs. ANA 11.1%, p = .0002</td>
</tr>
<tr>
<td>MA-17</td>
<td>25% (15% placebo)</td>
<td>LET 4.9% vs. placebo (3.6%), p = .019</td>
</tr>
<tr>
<td>IES</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Community trial, n = 200, Crew et al.***</td>
<td>47%</td>
<td>Half new, half worse</td>
</tr>
<tr>
<td>Pharmacy records, n = 12,000 ANA pts, Partridge et al.^</td>
<td>50%–68% adherence at 3 yrs</td>
<td></td>
</tr>
</tbody>
</table>

*Hershman J of Clin Oncol Vol 26, 19 July 2008

**CARE Faculty Perspective:**

A better understanding of the natural history of this syndrome is important in order to identify patients who have the highest risk for severe toxicity while on AIs. Increased awareness of AI-induced AIA will allow for proactive management/preparation to motivate patients to improve adherence. Possible interventions include:

- NSAIDs/coxibs/analgesics
- glucosamine plus chondroitin
- sleep aids
- topical capsaicin
- hot packs
- TENS
- footwear changes
- massage
- hypnosis
- yoga

**References:**

**SABCS 2013 CONTENT OF INTEREST**

**SABCS 2013 Session S3-02:** Associations Between Baseline Patient-Reported Symptoms and Discontinuation of Adjuvant Aromatase Inhibitor (AI) Therapy.  
*Henry et al.*

**Background:** Non-adherence and non-persistence with AI therapy are common and have been associated with increased mortality. A major reason for premature discontinuation of therapy is toxicity of AI therapy. We performed an exploratory analysis to investigate associations between patient-reported symptoms at the time of AI initiation and discontinuation of AI therapy due to toxicity.

**Conclusions:** Patient-reported symptoms present prior to initiation of AI therapy may predispose patients to early discontinuation of treatment. Pre-emptive management of these symptoms, rather than treatment of AI toxicity after its development, may improve adherence to and persistence with therapy.

**SABCS 2013 CONTENT OF INTEREST**

**SABCS 2013 Session S3-03:** Randomized Trial of Exercise vs. Usual Care on Aromatase Inhibitor-Associated Arthralgias in Women With Breast Cancer: The Hormones and Physical Exercise (HOPE) Study.  
*Irwin et al.*

**Purpose:** Arthralgias occur in up to 50% of women with breast cancer treated with adjuvant aromatase inhibitors, and are one of the most common reasons for poor adherence to therapy. We examined whether a year-long exercise program improves arthralgias in breast cancer survivors taking AIs.

**Conclusion:** We found that participating in an exercise intervention led to clinically meaningful improvements in AI-induced arthralgias in breast cancer survivors experiencing moderate joint pain. The intervention also induced favorable changes in body weight and cardiorespiratory fitness, factors that may be linked to incidence and severity of AI-induced arthralgias. Further work is needed to determine whether exercise leads to increased AI adherence and possibly better outcomes in women with breast cancer.
Cyclin-Dependent Kinase Inhibitors

Palbociclib is an investigational, oral and selective inhibitor of cyclin dependent kinases (CDK) 4 and 6. Inhibition of CDK 4 and 6 has been shown to prevent the deactivation of retinoblastoma susceptibility gene protein, a tumour suppressor protein, and interfere with tumour cell progression.

A randomized phase 2 study of palbociclib in combination with letrozole (TRIO-18) presented at SABCS 2012 (abstract S1-6) showed statistically and clinically significant improvement in median PFS with the addition of palbociclib. As a result, in April 2013 the U.S. FDA granted palbociclib a “breakthrough therapy” designation allowing for expedited drug development/approval.

Breast Cancer Prevention

Currently tamoxifen and raloxifene are the only two FDA-approved agents for breast cancer chemoprevention. Patients potentially eligible for breast cancer chemoprevention (according to ASCO/NCCN/USPTF) include:

▶ Age over 60 years.
▶ Age over 35 years with a history of LCIS, DCIS, or ADH/ALH.
▶ Women between 35–59 years with a Gail model risk of breast cancer ≥ 1.66% over 5 years.
▶ Women with known BRCA1 or BRCA2 mutations who do not undergo prophylactic mastectomy (> 50% lifetime risk).

Another agent being investigated for BC prevention is exemestane. Figure 1 below shows the preventative potential of various agents in terms of the number of patients at year 5 that needed to be treated (NNT) for BC including tamoxifen, raloxifene, and exemestane.

Figure 1: AIA Incidence and Discontinuation

Exemestane MAP 3 (31) 67 71
Tamoxifen death (37) 22 25 25
Rosuvastatin CVD JUPITER (38) 8 22 25 27
Tamoxifen recurrence (37) 8
Tamoxifen P=1 BC (36) 67
Raloxifene CORE IBC (36) 71
5-Year NNT vs. Placebo

ER-POSITIVE BREAST CANCER

The report content and visuals that follow are drawn from the presentation by Dr. Anil Abraham Joy during CORE @ SABCS 2013 and are augmented with session and abstract content from SABCS 2013.

Topics covered in this section include:

► Cyclin-Dependent Kinase Inhibitors
► Breast Cancer Prevention
► Improvements in Metastatic Breast Cancer

SABCS 2013 CONTENT OF INTEREST


Background: Third generation aromatase inhibitors are the most effective endocrine treatment for hormone receptor positive breast cancer in postmenopausal women. Here, we assess the efficacy of anastrozole in postmenopausal women who do not have breast cancer, but are at high risk of developing the disease.

Conclusions: Anastrozole is an effective agent for reducing breast cancer incidence in postmenopausal women at high risk. Anastrozole was well tolerated and side effects associated with oestrogen deprivation were only slightly higher than for placebo.

Improvements in Metastatic Breast Cancer

SABCS 2013 CONTENT OF INTEREST

SABCS 2013 Abstract S3-07: Letrozole Plus Dasatinib Improves PFS in HR+, HER2- Postmenopausal MBC Receiving First-Line AI Therapy. Vukelja et al.

Introduction: Dasatinib inhibits the protein tyrosine kinase, SRC, which can support the development of bone metastases in patients with ER+ breast cancer. The primary objective of this study is to determine if letrozole plus dasatinib increases the clinical benefit rate (CBR) (CR + PR + SD ≥ 6 mos) in first-line MBC patients compared with letrozole alone. Secondary objectives include overall response, progression-free survival, time to treatment failure (TTF), and toxicity.

Conclusion: The addition of dasatinib to letrozole in MBC patients receiving their first AI therapy for metastatic disease did not improve CBR compared with letrozole alone. Median PFS improved from 11 to 22 months (p = .05) with the addition of dasatinib, suggesting dasatinib improved duration of disease control combined with letrozole. Most patients tolerated full dose dasatinib until PD. 25% of patients remain on study therapy.
**Evolving Story that Holds Interest:**

**mTOR Pathway**

The mTOR pathway is active in breast cancer. Genetic alterations result in activation of the PI3K/AKT/mTOR pathway in breast cancer. These genetic alterations include loss of PTEN protein (~30% to 48%); PTEN mutation (< 5%); PIK3CA mutation (~21% to 33%), with approximately 30% to 40% of breast cancer cells exhibiting AKT activation. Over expression/mutation of receptor tyrosine-kinases (e.g., HER2, EGFR) may also activate the PI3K/AKT/mTOR pathway.

Everolimus is an oral mTOR inhibitor given daily. It binds to FKBP12, forming a complex that inhibits activity and downstream effects.

Faculty began discussion of everolimus and the mTOR pathway in breast cancer starting at ESMO 2011 with the presentation of the BOLERO-2 phase 3 trial (J. Baselga). At this time, the mTOR pathway was very little understood and there was an unmet clinical therapeutic need in endocrine resistant ER-positive and HER2- normal advanced breast cancer patients. BOLERO-2 was the first large phase 2 study of a targeted agent when added to endocrine therapy to significantly improve PFS, response rate, while keeping a manageable safety profile.

Discussion continued at SABCS 2011 with updated results on this trial. Again, although showing more toxicity associated with everolimus use, faculty reported a manageable side effect profile and emphasized educating patients and health care staff about the potential for toxicity and effective management strategies. This presentation prompted the faculty to raise the question of which patient population will most benefit from this therapeutic strategy, as well as addressed potential barriers for funding/access of targeted therapies.

Since then, the use of everolimus in combination with exemestane has continued to be a key topic, with further results presented and discussed at SABCS 2012, ASCO 2013 as well as numerous abstracts presented at SABCS 2013.

The significant benefit shown throughout these studies has made the combination of everolimus and exemestane a standard for the treatment of medically fit post-menopausal women with ER+ MBC post progression on a non-steroidal AI.

More data on everolimus in combination with exemestane, is anticipated with the 4EVER trial. This study will look to further evaluate the combination of EVE + EXE in a broader population to obtain greater insights and presents an extensive exploratory translational research program.
HER2-POSITIVE BREAST CANCER

The report content and visuals that follow are drawn from the presentation by Dr. Sunil Verma during CORE @ SABCS 2013 and are augmented with session and abstract content from SABCS 2013.

Topics covered in this section include:
- Neoadjuvant Therapy for HER2-Positive Disease
  - pCR as a Relevant Surrogate Endpoint
  - Benefit of Dual Targeted Anti-HER2 Therapy in the Neoadjuvant Setting
  - Implications of Recent FDA Approval of Pertuzumab
- Adjuvant Therapy for HER2-Positive Disease
  - Non-Anthracycline-Based anti-HER2 Adjuvant Therapy

Neoadjuvant Therapy for HER2-Positive Disease

**pCR AS A RELEVANT SURROGATE ENDPOINT**

Figure 2 below outlines key trials that show the impact on pCR rates from the addition of trastuzumab to neoadjuvant chemotherapy in patients with HER2-positive EBC.

The graphs in Figure 3 below show the pCR correlation for HER2-positive in neoadjuvant breast cancer meta-analysis.

**Figure 2: Key Trials**

- **MD Anderson**
  - HER2+ HR+ HER2+ HR-
  - n = 465
  - p = not reported
- **NSABP**
  - HER2+ HR+ HER2+ HR-
  - n = 117
  - p < 0.001
- **GeparQuattro**
  - HER2+ HR+ HER2+ HR-
  - n = 446
  - p = not reported
- **German trials meta-analysis**
  - HER2+ HR+ HER2+ HR-
  - n = 402
  - p = not reported
- **CTNeoBC meta-analysis**
  - HER2+ HR+ HER2+ HR-
  - n = 471
  - p = not reported

**Figure 3: pCR Correlation for HER2-Positive FDA Collaborative Trials**

- **HER2+ HR+**
  - p = 0.031
  - p = 0.001

**CARE Faculty Perspective:**

The graphs above show correlation between pCR and EFS. This supports pCR as an effective surrogate for event-free survival for patients receiving neoadjuvant trastuzumab.

SABCS 2013 CONTENT OF INTEREST

**SABCS 2013 Session S1-01: The Association Between Event-Free Survival and Pathologic Complete Response to Neoadjuvant Lapatinib, Trastuzumab or Their Combination in HER2-Positive Breast Cancer. Survival Follow Up Analysis of the NeoALTTO Study (BIG 1-06). Piccart-Gebhart et al.**

**Background:** The NeoALTTO study demonstrated a significantly higher breast pCR rate (NSABP definition – ypT0/is) with dual HER2 blockade using lapatinib and trastuzumab compared with single HER2 blockade using either lapatinib or trastuzumab (51.3% vs. 24.7% vs. 29.5%, respectively; p < .01 for both) in HER2-positive primary breast cancer. A similar pattern was seen for locoregional pCR (ypT0/is ypN0) (Baselga J et al. Lancet 2012).

**BENEFIT OF DUAL TARGETED ANTI-HER2 THERAPY IN THE ADJUVANT SETTING**

Despite differences in the design of dual anti-HER2 neoadjuvant trials, data suggests that there is a benefit shown with an improvement in pCR.

The combination of chemo with dual targeted therapies is superior to chemo and single agent anti-HER2 agent (pCR), however questions remain. These include:

- How does vertical blockade (lapatinib and trastuzumab) compare with horizontal blockade (pertuzumab and lapatinib)?
- Do the same patients benefit from dual blockade strategy? If not, how can we identify the patient more likely to benefit from additional anti-HER2 agents?
- Which patients are likely to achieve pCR with:
  - Chemo and trastuzumab?
  - Chemo and trastuzumab with another anti-HER2 agent?
  - Dual HER2 blockade with no chemo?
- Will pCR correlate with long-term survival for patients not receiving chemotherapy?
IMPLICATIONS OF RECENT FDA APPROVAL OF PERTUZUMAB

NeoSphere was the first clinical trial to investigate pertuzumab in the neoadjuvant setting. This trial showed that pertuzumab and trastuzumab plus docetaxel significantly increased the pCR rate versus other arms. (Figure 4)

Figure 4: Increased pCR Rate With Pertuzumab and Trastuzumab

On September 30, 2013, the FDA published a news release on the approval of pertuzumab for neoadjuvant breast cancer treatment based on the NeoSphere trial. This is the first drug approved for use in preoperative breast cancer. The FDA’s recommendation for pertuzumab neoadjuvant treatment is as follows:

According to the FDA Pertuzumab should be administered every 3 weeks for three to six cycles as part of one of the following treatment regimens for early breast cancer:

- Four preoperative cycles of pertuzumab in combination with trastuzumab and docetaxel followed by three postoperative cycles of FEC;
- Three preoperative cycles of FEC alone followed by three preoperative cycles of pertuzumab in combination with docetaxel and trastuzumab; or
- Six preoperative cycles of pertuzumab in combination with docetaxel, carboplatin and trastuzumab.

There was uncertainty noted by FDA on whether an improvement in pathologic complete response rate would translate into long-term clinical benefit, the appropriate chemotherapy regimen to use with this targeted therapy, the appropriate duration of pertuzumab treatment, and the sequencing of chemotherapy.

Additional concerns included an increased rate of toxicity with pertuzumab, the small size of the NeoSphere trial, the lack of patients from the United States, the lack of blinded pathology review, and the lack of prespecified pathology guideline.

Adjuvant Therapy for HER2-Positive Disease

NON-ANTHRACYLINE-BASED ANTI-HER2 ADJUVANT THERAPY

DFS and OS benefits were demonstrated during long-term follow up in the four pivotal clinical trials of trastuzumab for 1 year. Table 4 below shows an overview of the key trials for non anthracycline-based therapy.

Table 4: Key Trials for Non-Anthracycline-Based Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow Up (years)</th>
<th>N</th>
<th>DFS HR</th>
<th>DFS p-value</th>
<th>OS HR</th>
<th>OS p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA1-4</td>
<td>CT+/−RTH</td>
<td>1</td>
<td>0.54</td>
<td>&lt;.0001</td>
<td>0.76</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>vs. CT+/−RT</td>
<td>2</td>
<td>0.64</td>
<td>&lt;.0001</td>
<td>0.66</td>
<td>0.0115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.76</td>
<td>&lt;.0001</td>
<td>0.85</td>
<td>1.087</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>0.76</td>
<td>&lt;.0001</td>
<td>0.76</td>
<td>0.005</td>
</tr>
<tr>
<td>NCCTG N9831/</td>
<td></td>
<td>2</td>
<td>0.48</td>
<td>&lt;.0001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NSABP B-311-7</td>
<td></td>
<td>4</td>
<td>0.52</td>
<td>&lt;.001</td>
<td>0.61</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AC+TH vs. AC+T</td>
<td>8.4</td>
<td>4046</td>
<td>0.60</td>
<td>&lt;.0001</td>
<td>0.63</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>NCCTG N9831/</td>
<td></td>
<td>5.5</td>
<td>0.64</td>
<td>&lt;.001</td>
<td>0.63</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>322</td>
<td>0.75</td>
<td>&lt;.04</td>
<td>0.77</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CT: chemotherapy; DFS: disease-free survival; H: trastuzumab; HR: hazard ratio; OS: overall survival; RT: radiotherapy; T: taxane.


Data from these, as well as other studies, suggest that we should consider a non-anthracycline-based anti-HER2 alternative option for those patients with cardiac risk factors or underlying cardiac disease, patients where the absolute benefit of adjuvant therapy may be low (T1a, T1b tumours), and older patients (? > 70 years of age).
SABCS 2013 Abstract S1-03: Primary Results From BETH, a Phase 3 Controlled Study of Adjuvant Chemotherapy and Trastuzumab ± Bevacizumab in Patients With HER2-Positive, Node-Positive or High-Risk Node-Negative Breast Cancer.

Slamon et al.

**Background:** The humanized monoclonal antibody (mAb) trastuzumab (H) + chemotherapy prolongs disease-free survival (DFS) in patients with HER2-positive breast cancer in the adjuvant setting. Vascular endothelial growth factor (VEGF-A), one central regulator of angiogenesis, is a downstream target of HER2. Tumors overexpressing HER2 also overexpress VEGF-A and exhibit increased angiogenic potential. Combining H with the anti-VEGF-A mAb bevacizumab (B) significantly decreased tumor volume vs. B or H alone in HER2-positive xenograft models and demonstrated efficacy in phase 2 studies. In the phase 3 AVEREL study in pts with HER2-positive metastatic BC, adding B to H + docetaxel (T) led to a non-significant increase in a duration of PFS and objective response rates. Chemo plus H+B is now explored in this large phase 3 trial to assess the impact of VEGF-A blockade on residual or micrometastatic disease in the adjuvant setting.

SABCS 2013 Abstract S1-04: A Phase 2 Study of Adjuvant Paclitaxel (T) and Trastuzumab (H) (APT Trial) for Node-Negative, HER2-Positive Breast Cancer (BC).

Tolaney et al.

**Background:** Four large randomized phase 3 trials have reported significant improvements in disease-free and overall survival for H administered with adjuvant polychemotherapy for HER2-positive high-risk BC. With the success of HER2-targeting, limiting chemotherapy is both reasonable and feasible, particularly for smaller, node-negative tumors. However data are limited.

**Conclusion:** This represents the first report of TH as adjuvant therapy for node-negative HER2-positive BC. The regimen appears well tolerated and few recurrences have been observed in the study population to date. An updated analysis of efficacy, including estimates of 3-year DFS, will be presented in December when a total of 1520 PYFU in this cohort is anticipated. Based on these early data, the TH regimen may be an acceptable treatment approach for low risk HER2-positive breast cancer.

**CARE Faculty Perspective:**

*Moving forward, we need industry to work together to answer the question of horizontal vs. vertical blockade (tumour biology should be directing the biologic questions). We also need a coordinated effort to search for biomarkers to help maximize treatment benefit and for a more cost-effective and individualized treatment approach.*
Intrinsic Subtypes Within TNBC

Triple-negative breast cancer is a definition of convenience — not of biology. It is **not a single disease** (Figure 5 illustrates intrinsic subtypes in TNBC).

**Figure 5: Intrinsic Subtypes in TNBC**

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**SABCS 2013 CONTENT OF INTEREST**

**SABCS 2013 Session S1-06: Increased Tumor Associated Lymphocytes Predict Benefit From Addition of Carboplatin to Neoadjuvant Therapy for Triple-Negative and HER2-Positive Early Breast Cancer in the GeparSixto Trial (GBG 66).**

Denkert et al.

**Background:** We have recently described a significantly increased pCR rate in triple-negative breast cancer with addition of carboplatin to a non-pegylated liposomal doxorubicin/taxane (MC) combination in the neoadjuvant GeparSixto study (*von Minckwitz et al, ASCO, 2013*). Here we report the results of prospective biomarker analyses performed in GeparSixto.

**Conclusion:** Our results show that the interaction with host immune response is relevant for response to chemotherapy, this effect is particularly strong with the addition of carboplatin. Tumor-associated lymphocytes as a continuous parameter as well as LPBC as a tumor subgroup are predictive for response to neoadjuvant chemotherapy. In particular with regard to the relevant toxicity of the MC + carboplatin combination, the integration of immunological biomarkers would be helpful to identify the patients with the highest benefit from the addition of carboplatin.

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**SABCS 2013 Session S4-03: Exome Sequencing Reveals Clinically Actionable Mutations in the Pathogenesis and Metastasis of Triple-Negative Breast Cancer.**

Blackwell et al.

**Background:** Triple-negative breast cancer represents a particularly aggressive and difficult to treat form of breast cancer. No specific genetic alterations have been described as characteristic of the disease, with the exception of association with BRCA1/2, EGFR, and KRAS mutations. In this study, we sought to define clinically actionable mutations in untreated metastatic tumors as well as compare the mutational status of metastatic samples with germ-line and primary tumors using whole exome sequencing.

**Conclusions:** This data provides the most comprehensive genetic portrait of metastatic and primary TNBC to date, and represents a significant first step in identifying the genetic causes of the disease, drivers of recurrence, and potential therapeutic targets. Full results, including the primary versus metastatic tumor mutational analysis will be presented.
Neoadjuvant and Adjuvant Therapy Update

Sikov et al.

Background: Anthracycline- and taxane-based neoadjuvant chemotherapy (NAC) results in a pCR in 30–35% of TNBC patients, which is associated with improved recurrence-free and overall survival (RFS/OS). Thus, pCR rates may be useful in evaluating novel regimens in TNBC. In advanced TNBC, platinum analogues like Cb are active and addition of B to chemotherapy increases response rates and time to progression. CALGB 40603 is a 2 x 2 randomized phase 2 study designed to determine if the addition of either Cb or B to standard NAC significantly increases pCR rates in TNBC.

Conclusions: Preliminary results suggest that adding Cb or B to standard NAC significantly increases pCR rates in stage II–III TNBC. These increases are additive, with pCR (breast) in 60.6% and pCR (breast/axilla) in 50% of pts who received both. Complete and confirmed results will be reported, including pCR rates for basal-like tumors vs. not. Pts will be followed for RFS/OS to assess the impact of pCR on these endpoints.

CARE Faculty Perspective:
pCR (breast and axilla) is a validated and regulatory recognized surrogate end-point of long-term clinical outcomes following neoadjuvant systemic therapy, with the strongest correlations in the ER-/PR-/HER2- and ER-/PR-/HER2+ cohorts.

Carboplatin, when added to a weekly paclitaxel backbone, increased the pCR rate in TNBC in two randomized phase 2 trials (CALGB 40603 and GeparSixto). The addition of carboplatin to a weekly paclitaxel backbone however also increased toxicity — in particular neutropenia, febrile neutropenia, thrombocytopenia and ultimately led to greater dose reductions and/or discontinuations of treatment due to toxicity.

As TNBC is a heterogeneous disease, there are likely subtypes within TNBC that may be predictive of greater efficacy to both a taxane and platinum regimen. At present, it is not likely that carboplatin will be broadly integrated as a standard of care to the current backbone of neoadjuvant regimens, however may be worth considering in high risk inoperable triple negative LABC.

Rugo et al.

Background: I-SPY 2 is a multicenter, phase 2 screening trial using adaptive randomization within biomarker subtypes to evaluate a series of novel agents/combinations when added to standard neoadjuvant therapy (paclitaxel q wk x 12, doxorubicin & cyclophosphamide q 2–3 wk x 4, T/AC) vs. T/AC (control arm) for women with high-risk stage II/III breast cancer. The primary endpoint is pathologic complete response at surgery. Our goal is to identify/graduate regimens that have ≥ 85% Bayesian predictive probability of success (statistical significance) in a 300-patient biomarker-linked phase 3 neoadjuvant trial. Experimental regimens can “graduate” in at least 1 of 10 possible signatures defined by hormone-receptor (HR) & HER2 status & MammaPrint, with a maximum number of 120 total patients enrolled. We report final efficacy results of the oral PARP inhibitor veliparib (V, ABT-888) in combination with carboplatin (carbo), 1 of 7 experimental regimens evaluated in the trial to date.

Conclusions: Adaptive randomization successfully identified a biomarker signature for V + carbo on the basis of a modest number of patients. V + carbo has graduated with a triple-negative breast cancer signature, and is the subset recommended for this regimen’s subsequent development. There is a suggestion that HR+/HER2- tumors benefit little from this regimen and inclusion of tumors in this subset would therefore dilute its effect in a subsequent trial. Analyses are currently underway to define additional biomarkers that may be predictive of response. The I-SPY 2 standing trial mechanism efficiently evaluates agents/combinations in biomarker-defined patient subsets, with future agents/combinations reported as available.

CARE Faculty Perspective:
The I-SPY 2 standing trial mechanism efficiently evaluates agents/combinations in biomarker-defined patient subsets as a means to accelerate drug development in early-stage breast cancer. The combination of a PARP inhibitor (veliparib) and carboplatin on a backbone of a standard taxane/anthracycline regimen shows promising activity in TNBC.

A phase 3 trial will need to be performed to dissect out the differential activity of the PARP inhibitor from that of carboplatin in TNBC. Future translation work from the collected biospecimens and serial MRIs may further refine a subset within TNBC to enrich for in the confirmatory phase 3 trial.
SABCS 2013 Session S5-04: Primary Results of ROSE/TRIO-12, a Randomized Placebo Controlled Phase 3 Trial Evaluating the Addition of Ramucirumab (IMC 112b) to First-Line Docetaxel Chemotherapy in MBC.
Mackey et al.

Background: To date, anti-angiogenic strategies in metastatic breast cancer have demonstrated benefits confined to modest improvements in progression-free survival, warranting evaluation of new agents in a placebo-controlled setting. Ramucirumab, an anti-VEGF receptor 2 antibody, is a human IgG1 antibody that specifically binds VEGF receptor 2 and blocks ligand stimulated activation. Early phase studies suggested anticancer effects in several solid tumors, and a phase 3 study demonstrated survival improvements in gastric cancer. The ROSE trial was designed to evaluate ramucirumab in the setting of HER2 negative, unresectable locally recurrent or metastatic breast cancer.

Results: Between August 2008 and December 2011, 1,144 patients were randomized. At data cut-off (March 31, 2013), median follow-up was 16.2 months. Safety, final PFS and interim OS results will be presented. Anticipated data availability is early November 2013.

SABCS 2013 Abstract P3-13-03: A Phase 3, Open-Label, Randomized Study of Eribulin Versus Capecitabine in Patients (pts) With Metastatic Breast Cancer (MBC): Effect of Post-Progression Anti-Cancer Treatments (PPT) and Metastatic Progression Events on Overall Survival.
Awada et al.

Background: A phase 3 trial (Study 301; NCT00337103) in MBC comparing eribulin (E) with capecitabine (C) showed a trend for improved overall survival (HR 0.88; 95% CI 0.77, 1.00; p = .056) but not progression-free survival (HR 1.08; 95% CI 0.93, 1.25; p = .30) with E. In order to investigate this apparent discordance, post-hoc analyses assessed the effect of PPT and events defining disease progression on OS.

Conclusion: Treatment with C or any other PPT after progression on E did not account for the trend in OS benefit with E observed in the primary analysis. Pts who progressed with NM had a worse prognosis than those with IPEL. The appearance of NM was highly correlated with OS, and the apparent discordance between PFS and OS seems to be related to these different progression events.

CARE Faculty Perspective:
There continues to be new developments in triple negative breast cancer, however, we need to consider standard chemotherapy agents. Weekly Taxol, platinum doublets, eribulin and capecitabine have all shown efficacy and are reasonable options depending on prior therapy. It is important to consider these agents for patients that have progressed on therapy, as they can offer a survival benefit. The abstract that follows covers eribulin, a microtubule dynamics inhibitor, in the 3rd line treatment of metastatic breast cancer patients.
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