A summary report containing selected proceedings from the San Antonio Breast Cancer Symposium on December 8-12, 2015

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Dear Colleagues,

The 38th annual San Antonio Breast Cancer Symposium continued the tradition of exciting advances in the world of breast cancer research and treatment. This year, we welcomed more than 7,500 attendees from 90 countries. All total, 1154 posters, 55 poster discussions, 88 ongoing trial posters, and 46 podium presentations were held over the 5 days.

The career development forum remained a very popular event for young oncologists and researchers in training. New this year to the meeting was a special session on breast cancer management in low and middle income countries. This session was well attended, generated lively discussions, and will continue as a special session again at the 2016 meeting. Also new this year was a very special session on advancing your career with advocates. The aim of this session was to bring together advocates and clinicians to learn more about the benefits of involving patient advocates in clinical research.

Every year, exciting themes emerge from the conference, and this report will help provide some of the highlights from the meeting. Included in the report are the following sections:

- Advances in Biomarkers and Preclinical Research
- Local Therapies
- Imaging
- Topics in Systemic Therapies
- Early Clinical Trials

On behalf of the executive committee, we hope you enjoyed your week in San Antonio and hope to see you next December for the 39th annual Symposium.

Sincerely,

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Preclinical: Advances in Biomarkers and Preclinical Research

Preclinical investigations into potential targets for therapy, resistance to therapy, and biomarkers for surveillance, prognosis, and treatment were well represented at the 38th Annual SABCS Symposium. Here we highlight the findings of seven such studies.

[S2-03] Dr. Janni presented data from the German Success A trial, that looked at the prognostic significance of circulating tumor cells (CTC) in high-risk early breast cancer. These can be detected in approximately 20% of patients with early breast cancer and 60% of patients with advanced breast cancer. The presented data are from 1087 patients whose CTC status was determined before the beginning of therapy and again 2 years after adjuvant chemotherapy (CTX). These patients had a median age of 53 years and two-thirds of them had positive lymph nodes. Two years after adjuvant CTX, at least one CTC was detected in 21 mL of blood in 18.2% of this population. The presence of CTC was not associated with patient or tumor characteristics or with treatment modality used. Dr. Janni concluded that CTC 2 years after adjuvant CTX is a significant independent prognostic factor for poor OS and DFS. The worst survival outcomes were seen in patients who had CTC prior to treatment and 2 years after treatment. There was evidence that the prognostic value of CTC 2 years after adjuvant chemotherapy might not apply to HER2-positive tumors. Dr. Janni suggested that monitoring of minimal residual disease during follow up might be useful as a surveillance marker to identify which patients are at high risk for relapse and might benefit from closer follow up or secondary treatment.

[S2-07] Dr. Chandarlapaty presented data from his study of ESR1 mutations, looking for evidence that the presence of these mutations could be used to select patients for endocrine-based therapies. This study determined the presence of ESR1 mutations using baseline plasma and archival tissue from 521 patients from the BOLERO-2 study. These patients had estrogen receptor (ER)-positive metastatic breast cancer and received aromatase inhibitors (AI) in the adjuvant or metastatic setting. Droplet digital polymerase chain reaction was used to analyze plasma DNA for the presence of the two most common ER mutations: aspartate 528 to glycine (D538G) and tyrosine 537 to serine (Y537S). These mutations result in an active ER independent of the presence of estrogen. The plasma DNA had a high rate of mutations, with a mutation detected in 29% of the patients. Next-generation sequencing of archival tumor DNA revealed a considerably lower rate of mutations, with only 1.3% of archival tumor samples containing a mutation. Interestingly, ESR1 mutations were more frequent in patients who received AI in the metastatic setting compared to those who received it in the adjuvant setting. Median OS was decreased in patients who had either mutation (D538G or Y537S) compared to wild type. Response to treatment varied depending on which mutation was present. In those patients with D538G mutation, the progression-free survival (PFS) with exemestane treatment was shorter than with wild type, and both the D538G and wild-type groups benefited from addition of everolimus to exemestane. The Y537S group did not derive a PFS benefit from addition of everolimus to exemestane. This study showed the feasibility of using archival plasma frozen at -70°C for detection of mutations. It also showed that ESR1 mutations are common and are associated with poorer outcomes. This study suggested that individual mutations have a differential impact on the biology of the tumor and may affect response to treatment; this will need to be validated biologically and clinically.
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[S3-02] Dr. Albain presented data from a study that also gave insight into prognostic information and treatment selection. This study used archival material from the Southwest Oncology Group (SWOG) S8814 trial material. Material was from patients with ER-positive, lymph-node positive breast cancers who had been treated with either tamoxifen alone or cyclophosphamide, doxorubicin (Adriamycin), and fluorouracil (CAF), followed by tamoxifen. SWOG S8814 had shown that cancers with a low 21-gene recurrence score (RS) had a good prognosis and did not benefit from CAF, whereas cancers with a high RS received significant benefit from CAF. The current study used RNA sequencing to find other genes and networks that are associated with prognosis and response to treatment. The analysis of prognosis for residual risk after CAF followed by tamoxifen was uninformative. Prognosis analysis of the tamoxifen arm however showed a 5-metagene signature associated with DFS: immune, extracellular matrix stroma, chromatin, transforming growth factor (TGF) β, and ESR1. Using this model, patients were divided into high and low 10-year risk groups. The investigators found the optimal prediction of chemotherapy benefit was based on three metagenes: proliferation, TGF β, and ESR1. Patients in the low 10-year risk group, received much more benefit from tamoxifen alone compared to CAF followed by tamoxifen. Patients in the high 10-year risk group received more benefit from CAF followed by tamoxifen. [figure] Though validation is required, these signatures possibly may be used to identify patients who would have excellent outcomes with endocrine therapy alone despite positive lymph nodes, and those patients who would require chemotherapy and/ or biologics.

[S4-07] Dr. Harris presented the findings of work on APOBECs, enzymes that are part of overall innate immunity response against DNA viruses and also contribute to mutation signatures in cancer. The most relevant APOBEC for cancer mutagenesis is 3B (A3B). Overexpression of A3B has been shown to lead to increased mutation rates. A3B, which is overexpressed in approximately 50%...
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of all breast cancers, was shown to be associated with poorer DFS and OS when present in high levels in ER-positive breast cancer, including during tamoxifen treatment. The median PFS seen in the A3B high group was 7.5 months, and the median PFS seen in the A3B low group was 13.3 months. Animal studies showed that endogenous A3B knockdown slows tamoxifen resistance. [figure]

Dr. Harris emphasized the point that A3B is a gain-of-function mutator that is a possible target for therapeutic inhibition.

[S3-04] ESR1 is positive in approximately 70% of all breast cancers, most of which have good initial response to antiestrogens and AI, yet many develop resistance to these treatments. One mechanism of resistance is mutations of ESR1, that lead to constitutive interaction between the receptor and its coregulators. Dr. Vadlamudi reported on work that looked at endocrine coregulator binding inhibitors (ECBI), that might block estrogen-mediated proliferation from both ligand-dependent and ligand-independent mechanisms. ECBI-11 was shown to inhibit growth of ER-positive breast cancer cells, including those that were resistant to endocrine therapy with tamoxifen or letrozole; it did not, however, inhibit growth of triple-negative breast cancer cells. ECBI-11 was shown to bind to both mutant and wild-type ESR1. Animal studies showed that it is orally bioavailable, well-tolerated, and inhibited growth in ESR1-positive xenograft models and ex vivo models [figures]. The investigators concluded that ECBI is active against some endocrine-resistant breast cancers. Preclinical models showed efficacy as a treatment of these tumors, which may delay treatment with chemotherapy.
Dr. Baselga presented data from the phase III, randomized BELLE-2 trial. This trial looked at buparlisib, a pan-PI3K inhibitor, plus fulvestrant in endocrine-resistant hormone-receptor positive advanced breast cancer in 1147 postmenopausal women. The combination treatment was shown to be beneficial in these patients, with a PFS in the buparlisib arm of 6.9 months compared to 5.0 months in the placebo-plus-fulvestrant arm. Adverse events, however, caused 13.2% of patients in the combination arm to discontinue treatment. These adverse events included transaminitis, hyperglycemia, rash, anxiety, and depression. The investigators also analyzed the group of patients whose primary tumor was PI3K-activated and found that the slight improvement was not statistically significant. Interestingly, patients with PIK3CA mutations in circulating tumor DNA had a statistically significant improvement in PFS compared to the placebo arm, 7.0 months versus 3.2 months respectively. This benefit was not seen in wild-type circulating tumor DNA. Additionally, patients in the placebo group who had the mutations had worse outcome than the patients with wild-type [figure]. Selection of patients for buparlisib plus fulvestrant treatment may be improved with assessment of PIK3CA mutations in ctDNA.
Local Therapies

[S2-01] Dr. Bodilsen presented data from the Danish Breast Cancer Cooperative Group study that evaluated the importance of margin width and re-excision in breast-conserving treatment of early breast cancer. The data included 11,900 patients diagnosed with invasive, unilateral breast cancer. All patients had undergone breast-conserving surgery, and all were younger than 75 years of age.

The overall risk for local recurrence was 2.4% at 5 years and 5.9% at 9 years. In an adjusted analysis, risk for local recurrence was lower in patients with a negative final margin (<1 mm) compared to patients with a positive final margin. [figure] No difference in risk for recurrence was seen in patients with narrow negative margins versus those with wider negative margins.

Features other than margins that increased the risk for local recurrence included age younger than 50 years, histologic grade >2, tumors that required re-excision, and greater than four positive lymph nodes. A lower risk for recurrence was seen in patients who received chemotherapy or boost and in patients whose tumors were ER positive.

The investigators looked at data regarding repeat surgery as well. They showed that the number of patients undergoing repeat surgery decreased from 27% of patients in 2000 to 16% in 2009. Additionally, the presence of residual disease at repeat surgery, invasive or in situ, was found to increase the risk for local recurrence, but did not affect overall survival (OS).

[S3-05] Dr. van Maaren presented data concerning the effect of breast-conserving surgery and mastectomy on 10-year OS. Prior randomized controlled trials from the 1980s showed that survival was equal between patients with early-stage breast cancer who underwent breast-conserving surgery with adjuvant radiation therapy and patients who underwent mastectomy. Recent observational studies, however, have indicated that breast-conserving therapy is associated with better survival, yet these studies have rather short follow-up of only 5 years.

This observational study had a median follow-up of 11.3 years. It looked at data from 37,207 women diagnosed with early-stage breast cancer in the Netherlands who had been treated either with breast-conserving therapy and adjuvant radiation therapy or with mastectomy. The investigators wanted to compare the 10-year OS and distant-metastasis-free survival rates in patients who received breast-conserving therapy and those who received mastectomy. The breast-conserving group was younger and had smaller, well-differentiated tumors; fewer of the breast-conserving group had received hormonal therapy or axillary lymph node dissections.

After correcting for confounding variables, the data showed that the patients who received breast-conserving therapy had approximately a 20% increase in OS compared to patients treated with mastectomy. [figure] In fact, breast-conserving therapy was found to have a better 10-year OS in all T and N stages. However, the 10-year distant-metastasis-free survival was better in only one group of the breast-conserving therapy patients, those with T1N0 disease.

The authors believe that radiotherapy may account for some of the difference in survival between breast-conserving therapy and mastectomy, especially in the T1N0-staged patients. Though the authors attempted to correct for confounding factors, e.g., younger patients in the breast-conserving therapy group, indications for surgery, and lack of information on HER2 status, they acknowledge that it was not possible to completely eliminate the confounders.

To hear content from the Question and Answer section of the presentation S2-01, click here.

To hear content from the Question and Answer section of the presentation S3-05, click here.
In recent years, there has been an increase in mastectomies over breast-conservation surgeries as a local treatment option for breast cancer. While there are medical indications for mastectomy instead of lumpectomy, misconceptions and fears on the part of the patient also drive this treatment decision. Value of the different treatment options is not considered by most patients when making the decision about which treatment to receive.

Dr. Smith presented a study that investigated the relative value of local treatment options. This study compared complication burden, total payer's cost, complication-related cost, and non-complication cost of breast cancer treatment modalities. Data were obtained from two cohorts: the MarketScan Commercial Claims and Encounters database, that included younger patients with private insurance, and the Surveillance, Epidemiology, and End Results (SEER) program database, that included older patients with Medicare coverage. Patient data were excluded if the patient had received neoadjuvant chemotherapy or post-mastectomy radiation therapy, both of which indicated advanced cancer. The MarketScan cohort included 44,344 patients whose median age was 53 years, and the SEER cohort included 60,867 patients whose median age was 75 years.

In both cohorts, the most common treatment received was lumpectomy plus whole-breast irradiation. Mastectomy plus reconstruction, in either cohort, had twice the complication burden of lumpectomy plus irradiation. The lowest risk for complications was seen with mastectomy (in the MarketScan cohort) and with lumpectomy alone (in the SEER cohort). The authors concluded that mastectomy plus reconstruction had a two-fold higher risk for complications than lumpectomy plus whole-breast irradiation.

The highest cost of complications was seen with mastectomy plus reconstruction in both cohorts. Furthermore, they concluded that the risk for complications and total cost are lowest in younger women with mastectomy alone and in older women with lumpectomy alone.

The authors found that high-value treatments for women wishing to conserve their breasts are lumpectomy plus whole-breast irradiation (for younger women) and lumpectomy plus whole-breast irradiation or lumpectomy alone (for older women). Additionally, hypofractionated whole-breast irradiation would improve the value of lumpectomy plus whole-breast irradiation.

The authors acknowledged that the study is limited by the fact that all patients included in the data would not have been eligible for all local treatment modalities, complications were assessed using claims codes, and late events were not captured. They caution that the findings are most useful when making decisions about initial management. Also, reconstruction is considered of high value after mastectomy has been performed.

To determine the risk from radiation therapy, data were collated from 75 worldwide trials. These trials randomized more than 40,000 women to radiation therapy versus no radiation therapy, with the median date of entry being 1983. The investigators accounted for the change in radiation doses since these studies were performed; the average lung dose has decreased from 10 Gy to 5 Gy, and the average cardiac dose has decreased from 6 Gy to 4 Gy.

Analysis of the data showed that the excess rate ratio of lung cancers in women treated with radiation therapy versus those who...
Local Therapies

did not receive radiation therapy was 12% per Gy. The excess rate ratio for cardiac mortality was 4% per Gy.

Using these excess rate ratios, modern radiotherapy doses, and modern population-based data, the investigators estimated the 30-year risk for lung cancer and cardiac mortality. They found that the combined risk from radiotherapy is less than 1% in nonsmokers. In long-term smokers, however, the predicted risk is increased; the risk for ischemic heart disease increases from 8.0% to 8.6% and the risk for lung cancer increases from 9.4% to 11.3%. Importantly, the risk for lung cancer in long-term, current smokers increases from 9.4% to 13.8% with radiation therapy. [figure]

The authors concluded that net long-term effect on mortality from radiotherapy can be determined by a patient’s smoking status. Additionally, since most of the risk for lung cancer begins 10 years after radiotherapy, much of the lung cancer risk may be avoided if a patient stops smoking at the time of radiation therapy.

To hear content from the Question and Answer section of the presentation S5-08, click here.
Imaging

Dr. Holt presented the data from a comparison of the diagnostic performance of 2-dimensional (2D) synthetic mammography versus digital breast tomosynthesis in 2500 patients. In his opening remarks, he questions why 3D mammography is not already being widely used based on published trials. A previous study by Skanne et al published in 2013 examined the benefit of performing 2D plus 3D combination in 12,631 women. This study found a 40% increase in the detection of invasive breast cancers, a 27% increase in detection of all cancers (invasive and in situ cancers combined), and a 15% decrease in false-positive rates. Italian investigators found similar results in the STORM trial (7294 patients), published in Lancet Oncology in 2013. Dr. Holt outlined the potential limitations of 3D mammography, that include increased cost for equipment and radiologist time, increased patient time, about double the dose of radiation, and the need for training. Synthetic 2D mammography is a 2D image derived entirely from the 3D data. It reduces the exposure of radiation by half compared to the 2D plus 3D combination; it requires less compression force than standard 2D mammography; it is easier to compare to prior 2D films; and retains much of the information from key 3D slices.

The question put forth by Dr. Holt is whether reading the 2D synthetic mammograms, with selective reading of the 3D images, is a possible solution to bridging the benefit of increased cancer detection rate achieved from 3D mammography, while overcoming the limitations of 3D mammography. To answer this question, 3D mammograms were performed on 2500 unselected patients in a symptomatic and follow-up setting (4589 images). One expert radiologist assigned Breast Imaging Reporting and Data System M1 through M5 ratings to the 2D synthetic and 3D films. The results showed a close correlation between the 2D and 3D images, with a few significant outliers.

If the radiologist had been required to read the 3D films only if the 2D films were reported as suspicious for malignancy or possibly malignant, ie, M3 or greater, only 280 additional 3D films would have been required to be viewed. This would have saved 3.5 hours of radiologist interpretation time. There were, however, 11 patients who had benign results with the 2D images and abnormal results with the 3D images. Ultimately, 10 of these abnormalities were found to be benign. Interestingly, breast density did not select for patients who had occult cancers with interpretation of 2D films.

It is important to stress that these studies were completed in symptomatic patients and not in a screening population. Additionally, all films were read by one radiologist who has experience in reading 2D and 3D films. A larger screening trial will be needed to confirm the findings of this study.
NEOADJUVANT THERAPY

ESTROGEN-RECEPTOR POSITIVE, HER2-NEGATIVE BREAST CANCER

[C6-05] Cyclin-dependent kinases 4 and 6 promote cell-cycle phase progression and activate downstream target genes. These kinases are activated in estrogen-receptor positive breast cancer. Palbociclib, an inhibitor of these kinases, has been shown to be effective against metastatic breast cancer when used in combination with fulvestrant or AI.

Dr. Ma presented data from a single-arm phase II study in which 45 patients with stage II or stage III estrogen-receptor positive HER2-negative breast cancer were treated with anastrozole alone, followed by anastrozole plus palbociclib. Thirty-nine patients completed the study. Patients underwent serial biopsies throughout treatment and surgical excision at the end of treatment. The investigators were testing their hypothesis that the addition of palbociclib to aromatase inhibitors would result in 50% improvement in complete cell-cycle arrest, which they defined as Ki67 no greater than 2.7% at cycle 1 day 15.

Neutropenia was the most common side effect experienced, occurring in 56% of patients, including 22% grade 3 and 4% grade 4. Overall, grade-3 adverse events were rare. Dose reductions were required in two patients because of elevated liver enzymes, in four patients because of grade-3 or grade-4 neutropenia, and in one patient because of a grade-2 rash.

The overall response rate was 67%. A complete response was seen in 24%, and a partial response was seen in 43%. No pCRs were seen.

Complete cell-cycle arrest was seen in 87% of all patients, in 79% of patients with wild-type PIK3CA, and in 100% of patients with mutant PIK3CA. Anastrozole alone resulted in complete cell-cycle control in 26% of patients. Addition of palbociclib resulted in complete cell-cycle control in 60% of patients. [figure]

Significant Ki67 reduction was seen with anastrozole alone, and this was enhanced with the addition of palbociclib, regardless of PIK3CA status or luminal A or luminal B subtype. The tissue obtained at surgery at the end of the trial showed an increase in Ki67 compared to the Ki67 seen in the biopsy taken at cycle 1 day 15. This was thought to be caused by the discontinuation of palbociclib four weeks prior to surgery to allow for recovery of neutropenia. Subsequently, patients were given palbociclib 10 days to 12 days immediately prior to surgery, and a smaller increase in Ki67 was seen.

The authors concluded that cell-cycle control is enhanced with the addition of palbociclib to anastrozole, regardless of PIK3CA or luminal A or luminal B status. The rebound of Ki67 seen after four weeks off palbociclib suggests that palbociclib should be considered a maintenance treatment, like endocrine therapy.

HORMONE-RECEPTOR POSITIVE, HER2-POSITIVE BREAST CANCER

[C6-03] The Adjuvant Dynamic marker-Adjusted Personalized Therapy (ADAPT) trial is looking at early response to treatment with subtype-specific short-term therapy for three weeks followed by biopsy or surgery. Dr. Harbeck presented data from the HER2-positive subtype.

In this subtrial, 375 patients with HER2-positive and hormone-receptor positive breast cancer were randomized to one of three 12-week neoadjuvant treatment arms: trastuzumab plus endocrine therapy (control arm), TDM1 with endocrine therapy, or TDM1 without endocrine therapy. Patients underwent biopsy at three weeks to assess response. Patient characteristics included a median age of approximately 50 years, approximately 50% of patients had tumors greater than 2 cm, and approximately one-third had clinically positive lymph nodes. More than 80% of tumors were stage 3, and median Ki67 was 40%.

Side effects of all grades were more common in the TDM1 arms, and included thrombocytopenia, elevated liver enzymes, fatigue, and nausea. Elevated liver enzymes, however, was the only high-grade adverse event seen more frequently in the TDM1 arms (4.1% versus 0%).
The pCR rate was similar in the TDM1 without endocrine therapy arm and the TDM1 with endocrine therapy arm (41% and 41.5%, respectively). The pCR rate in the trastuzumab arm was only 15.1%. No significant difference was seen in the pCR rate based on menopausal status.

Early response was determined from the biopsy performed at three weeks. Patients were considered to have an early response if their biopsies showed low cellularity (fewer than 500 tumor cells) or at least a 30% decrease in Ki67. Patients with this early-response biomarker had a higher pCR rate than those who did not have the early-response biomarker (40% versus 19.8%). The early-response biomarker was associated with a higher pCR rate in both TDM1 arms than in the trastuzumab arm.

The authors concluded that four cycles of neoadjuvant TDM1, without systemic chemotherapy, in early HER2-positive, hormone-receptor positive breast cancer led to a 40% pCR rate. The addition of endocrine therapy, however, did not increase the rate of pCR. Dr. Harbeck stressed that the overall toxicity of the four cycles of TDM1 was very low. She believes that de-escalation of therapy in HER2-positive, hormone-receptor positive breast cancer is possible and that single-agent TDM1 should be further evaluated.

TRIPLE-NEGATIVE BREAST CANCER

Dr. Gluz also reported data from the ADAPT trial. His presentation focused on the triple-negative subgroup. The study investigated the efficacy of nab-paclitaxel plus carboplatin in these patients. In addition, this study looked at the correlation between the response after three weeks of therapy and complete pathological response.

This study randomized 336 patients with triple-negative breast cancer to receive either 12 weeks of nab-paclitaxel plus carboplatin or 12 weeks of nab-paclitaxel plus gemcitabine. Patients underwent biopsy at three weeks to assess response to treatment. The 12-week treatment was followed by either biopsy or surgery. The median age of the patients was approximately 50 years. Two-thirds of patients had tumors greater than 2 cm, and more than 90% had grade-3 disease.

Dose reductions were required more often in the gemcitabine arm than in the carboplatin arm (20.6% versus 11.9%). Adverse events were more common with gemcitabine (17.2%) than with carboplatin (10.6%). In both treatment arms, grade-3 or grade-4 neutropenia occurred in approximately 15% of patients, with just one patient experiencing febrile neutropenia (carboplatin arm).

There was a significantly higher rate of pCR in patients receiving carboplatin (45.9% versus 28.7%). The pCR rate was compared to the presence of the early-response biomarker on the three-week biopsy. As previously stated, the early-response biomarker was defined as the presence of fewer than 500 invasive tumor cells and a greater than 30% decrease in Ki67. In both treatment arms, patients who had the early-response biomarker had a higher rate of pCR. The carboplatin arm was found to be superior to the gemcitabine arm in almost all patient groups.

The authors concluded that nab-paclitaxel plus carboplatin resulted in a superior pCR rate compared to nab-paclitaxel plus gemcitabine. Furthermore, the carboplatin-containing therapy was associated with less toxicity. They also found that morphological changes seen early in treatment appear to predict pCR regardless of treatment. Ongoing correlative analyses are looking for factors that might be predictive of the efficacy of carboplatin. Results of this trial should be validated in larger studies.

Dr. Gluz emphasized that the efficacy seen with this regimen appears comparable to longer, less tolerable anthracycline/taxane-containing regimens. Further investigation is needed to look at therapy de-escalation and at this combination therapy plus targeted therapies. Further investigation is also required regarding the length of treatment.
TRIPLE-NEGATIVE AND HER2-POSITIVE BREAST CANCER

[**S2-04**] The addition of carboplatin to anthracycline/taxane-based neoadjuvant therapy was shown to increase the pCR rate by 17% in patients with triple-negative breast cancer (GeparSixto and CALGB 40603). Dr. von Minckwitz reported on the disease-free survival (DFS) in the GeparSixto study after 35 months of observation.

In this study, 595 patients with triple-negative breast cancer or HER2-positive breast cancer were randomized to receive 18 weeks of preoperative neoadjuvant paclitaxel and non-pegylated liposomal doxorubicin, with or without carboplatin. Patients with HER2-positive disease also were treated concurrently with trastuzumab and lapatinib. Patients with triple-negative disease received concurrent bevacizumab every three weeks.

Overall, the addition of carboplatin was associated with a significantly higher pCR rate (43.7% versus 36.9%). In the triple-negative group, the rate was approximately 16% higher in the carboplatin arm (53.2% versus 36.9%, odds ratio 1.94). The HER2-positive group, however, had a lower pCR rate in the carboplatin arm, 32.8% versus 36.8%.

Likewise, DFS was different between the two treatment arms. For the patients with HER2-positive disease, the survival curve in the carboplatin arm was slightly lower than in the control arm. Patients with triple-negative disease, however, showed a 10% improvement in three-year DFS in the carboplatin arm compared to the control arm (85.8% versus 76.1%). [figure]

BRCA status also was shown to affect response and survival. Pathological complete response in patients with wild-type BRCA was approximately 17% higher in the carboplatin arm (50.8% versus 33.1%), which was statistically significant. The improvement seen in patients with BRCA mutations was smaller and not statistically significant (61.5% versus 50.5%), although only 50 patients with BRCA mutations were included in the study. Improvement in DFS was seen in the carboplatin arm in patients with wild-type BRCA, but not in patients with mutated BRCA.

Additionally, the prognostic significance of pCR was shown to be independent of BRCA status. Patients who achieved pathological complete response, regardless of BRCA status, had a favorable prognosis.

The authors concluded that these results support the use of carboplatin in the neoadjuvant treatment of patients with triple-negative breast cancer.

BRCA MUTATIONS IN BREAST CANCER

[**S5-06**] Dr. Fasching reported on results of the triple-negative subgroup of the GeparQuinto prospective study. This study looked at the efficacy of using BRCA1/2 mutation status to predict therapeutic response, and the use of pCR and BRCA1/2 mutation status as prognostic indicators after surgery.

This study included 678 patients with triple-negative breast cancer. All patients received four cycles of epirubicin and cyclophosphamide...
followed by four cycles of docetaxel. Patients were then randomized to receive either open-label bevacizumab or no bevacizumab. Patients underwent surgery at the end of this treatment.

The subprotocol presented here included 461 patients with triple-negative breast cancer who were genotyped for BRCA1/2 mutations: 69 had germline mutations of BRCA1, and 13 had germline mutations of BRCA2. The bevacizumab arm contained 35 patients with BRCA1/2 mutations, and the no-bevacizumab arm contained 47 patients with BRCA1/2 mutations.

Regardless of treatment, the pCR rate was higher in patients with BRCA1/2 mutations compared to patients with wild-type BRCA (50% versus 30.8%). Similarly, DFS rates were better in patients with BRCA1/2 mutations than in patients with wild-type BRCA. It also was shown that pCR had more prognostic significance in patients with wild-type BRCA1/2.

With the addition of bevacizumab, patients with wild-type BRCA had a higher pCR rate than those with mutated BRCA1/2 (35.8% versus 26.2%). The benefit of bevacizumab was also seen in patients with mutated BRCA1/2 (65.7% versus 38.3%). This increase in pCR, however, did not lead to improved survival. [figure]

The authors concluded that carriers of BRCA1/2 mutations had a better prognosis. The addition of bevacizumab to neoadjuvant chemotherapy in these patients led to significantly higher pCR rates. The highest pCR rate was seen in carriers of BRCA1/2 mutations who received bevacizumab; however, increased survival was not seen in these patients. Pathological complete response as a prognostic indicator appeared less strong in patients with BRCA1/2 mutations than in patients with wild-type BRCA1/2, although the test for interaction was not significant.

ADJUVANT THERAPY

In this section of the SABCS 2015 Monograph, we highlight some important new information in regards to adjuvant therapies in breast cancer. For some breast cancer subtypes, more therapy may improve outcomes. Examples include the addition of capecitabine for residual disease following neoadjuvant chemotherapy, more aggressive systemic treatment for early-stage HER2-positive breast cancers, the addition of neratinib following adjuvant trastuzumab, and the addition of adjuvant denosumab to standard therapy. However, in the luminal A subgroup of breast cancer, a different trend has emerged. Even high-risk patients with node-positive disease and large primary tumor size showed little or no benefit in disease recurrence with adjuvant chemotherapy. It is critical to weigh the addition of more therapy against the added toxicities. Ways to possibly decrease cardiac toxicities from HER2-directed therapies, and patient-reported side effects from hormonal therapy, are also important areas of discussion. These selected abstracts from the SABCS 2015 meeting demonstrate the complexity of adjuvant therapy selection within the growing diversity of breast cancer subtypes.

[S1-07] Dr. Toi presented the data from a phase III, multicenter trial of adjuvant capecitabine in breast cancer patients with HER2–negative subtype and pathological residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04). Given that patients with pathological residual invasive disease after neoadjuvant chemotherapy have a higher risk for relapse, this study sought to evaluate whether additional chemotherapy with open-label capecitabine, given at a dose of 2500 mg/m2 /day daily for 14 days of a 21-day cycle for a total of 8 cycles, could decrease the risk for recurrence. The control group was assigned to standard therapy. Both groups received adjuvant hormonal therapy, and radiation therapy was completed if indicated. The primary endpoint was DFS, and secondary endpoints included OS, period of time from initiation of neoadjuvant chemotherapy to recurrence or death, safety, and cost-effectiveness.

The trial randomized 910 patients, 455 to capecitabine and 455 to the control group. In each group, approximately 40% had stage III disease. A local guideline from the Japanese Breast Cancer Society was used to assess the histological-effect grading by neoadjuvant chemotherapy on a scale of 0-3. Using this scale, approximately 56% of the patients in the capecitabine arm had a poor response to neoadjuvant chemotherapy and 53% of the patients randomized to the control arm had a poor response. Eighty percent of the patients received an anthracycline and taxane-containing regimen. In patients...
**Topics in Systemic Therapies**

assigned to receive six cycles of adjuvant capecitabine, the relative
dose intensity was 87.9%, with 24% requiring dose reductions.
In the group planned for eight cycles of adjuvant capecitabine,
the relative dose intensity was 79.1%, with 37% requiring dose
reduction.

Discontinuation of therapy occurred in 18% of patients in the
six-cycle group and in 25% of patients in the eight-cycle group.
Neutropenia and diarrhea greater than grade 3 were more common
in the capecitabine arm, and any grade of hand-foot syndrome
was recorded in 72% of patients. Five-year DFS was 82.8% in
the capecitabine group, compared to 67.7% in the control group.
Overall survival was 94% in the treatment arm and 89% in the
control group. On subgroup analysis, all groups favored treatment
with capecitabine as well.

**STAGE I, HER2-POSITIVE BREAST CANCER**

[S6-06] The addition of trastuzumab to chemotherapy has been
shown to increase OS and DFS in stage II and stage III HER2-
positive breast cancers. The use of systemic therapy for early
stage HER2-positive breast cancer has increased despite the small
numbers of patients with stage I disease treated on randomized
trastuzumab trials.

Dr. van Ramshorst presented data from an observational study
of the Netherlands Cancer Registry that addresses the use of
trastuzumab-based chemotherapy in stage I, HER2-positive breast
cancer. The primary endpoints were OS and breast-cancer–specific
survival with subgroup analyses based on tumor sizes. The study
included 3,512 patients; 45% received chemotherapy and/or
trastuzumab and 55% received no chemotherapy or trastuzumab.
In the treated group, 92% received both chemotherapy and
trastuzumab, 5% received chemotherapy alone, and 3% received
trastuzumab alone. The lack of consensus and guidelines regarding
the treatment of stage I disease accounts for the variation in the
treatments received. Analysis of the two groups revealed that
younger patients were more likely to receive systemic therapy, as
were patients with higher pathological stage (tumor and nodal),
higher grade, and negative hormone-receptor status. In addition,
patients who received systemic therapy were more likely to receive
endocrine therapy.

After a median followup of 61 months, patients in the treatment
group had improved survival compared to the non-treated group.
The 8-year overall survival in the treated group was 95%, versus
84% in the non-treated group. On subgroup analysis, this held true
for T1a, T1b, and T1c tumors. The difference in the survival curves in
the T1a group, however, was not statistically significant. This could
be explained by the lack of events in the treatment group. [figure]
Breast-cancer–specific survival curves also showed improved
survival in the treatment group.

Dr. van Ramshorst emphasized that the absolute benefit of the
treatment might be modest if the baseline risk is low. Risks and
benefits must be discussed with individual patients to determine
which treatment is best for them.

**PREMENOPAUSAL LUMINAL A BREAST CANCER**

[S1-08] Dr. Nielsen presented the analysis of high-risk premenopausal
luminal A breast cancer patients in the DBCG77B study. This trial
included 1146 premenopausal women with tumor size greater than
5 cm or with lymph node involvement. The hormone-receptor status
and HER2 status were mixed. The patients had received local
therapy with mastectomy, axillary dissection, and regional radiation
None of the patients received adjuvant hormonal therapy. Patients were randomized to four different treatment groups: CMF, cyclophosphamide monotherapy, levamisole, and control. The original endpoint for this trial was 10-year DFS, which favored both the chemotherapy arms over the control and levamisole arms. Intrinsic subtyping by immunohistochemistry was performed on tissue microarrays. The two chemotherapy arms were combined to maximize the power of the study. The four tumor subtypes included Luminal A (estrogen- and progesterone-receptor positive, HER2-negative, and Ki67 less than 13%), Luminal B, HER2-enriched, and basal-like. Tissue arrays and immunohistochemistry informative for subtype were available in 633 of the samples. Of the informative samples, 165 were luminal A and 468 comprised the other three subtypes. The clinical characteristics of these samples were similar to the original trial.

Compared to the levamisole and control arms, patients with non-luminal A subtypes who received chemotherapy had an increased DFS; however, no improvement in DFS was seen in patients with luminal A subtypes. This study suggests that even in a potentially higher-risk group of patients, i.e., premenopausal, node positive, and tumor size greater than 5 cm, those with luminal A breast cancer subtypes derive no benefit from adjuvant chemotherapy. The obvious limitations of this trial are that the patients did not receive an anthracycline/taxane-based regimen and did not receive adjuvant hormonal therapies.

TRASTUZUMAB TOXICITY

With the use of more combined HER2-directed therapies in the neoadjuvant and adjuvant settings, it is prudent to balance the toxicities with the clinical benefits. Dr. Pituskin discussed the primary results of the MANTICORE trial, a Canadian study designed to determine whether angiotensin-converting enzyme (ACE) inhibitors and beta blockers can prevent decreases in cardiac ejection fraction and the left ventricular remodeling seen in patients with early-stage breast cancer receiving trastuzumab. This was a relatively small randomized trial of 99 patients who were assigned to one of three arms: ACE inhibitor, beta blocker, or placebo. The study found that the addition of an ACE inhibitor or a beta blocker to the care of patients on adjuvant trastuzumab was both safe and tolerable. The data also suggest that the addition of a beta blocker or ACE inhibitor safely prevents decline in left ventricular ejection fraction, but they were not able to correlate a decrease in left ventricular remodeling.

DENOSUMAB IN POSTMENOPAUSAL BREAST CANCER

Dr. Gnant presented data from the ABCSG-18 trial that looked at the impact of adjuvant denosumab on DFS. There have been conflicting results regarding the utility of bone-targeting therapy in the prevention of breast cancer recurrence. A recent meta-analysis of adjuvant bisphosphonates in postmenopausal breast cancer was completed by the EBCTCG and published in the Lancet in October 2015. This meta-analysis found that adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival in the postmenopausal setting. At the 2015 annual ASCO meeting, Dr. Gnant presented data from the ABCSG-18 trial that showed that adjuvant denosumab at 60 mg twice yearly reduces clinical fractures and can be administered without significant toxicity. This study looked at whether improved outcomes similar to those seen with bisphosphonate treatment are seen with RANK-ligand inhibitor treatment. This prospective, phase III trial randomized 3425 postmenopausal patients to placebo, denosumab 200 mg twice yearly, or denosumab 60 mg twice yearly and found a significant reduction in clinical fractures with denosumab treatment.

To hear content from the Question and Answer section of the presentation S1-08, click here.
women with breast cancer who were receiving AI to receive denosumab, 60 mg SC every 6 months, versus placebo. The primary endpoint was time to first clinical fracture and was reported at the American Society of Clinical Oncologists (ASCO) annual meeting in 2015. Secondary endpoints included other bone-related outcomes, DFS, and OS. Side effects seen were mostly associated with the AI treatment, such as hot flushes, arthralgia, and bone pain. Importantly, there were no cases of osteonecrosis of the jaw.

In the placebo group, 203 events occurred, compared to 167 in the denosumab group, resulting in a hazard ratio of 0.816 (p = 0.0510), which was borderline statistically significant. Although completely exploratory at this point, a subgroup analysis suggested that giving denosumab early may result in more benefit. Additionally, patients with at least T2 tumors who have ductal histology and are estrogen-receptor positive may derive more benefit from denosumab therapy. The authors concluded that results of this time-driven analysis indicate that denosumab increases DFS in patients with postmenopausal breast cancer. The benefit seen is similar to the benefit seen in the EBCTCG bisphosphonate meta-analysis.

HER2-POSITIVE BREAST CANCER

It is known that, following adjuvant trastuzumab, relapse of breast cancer may occur in up to 26.3% of patients at 8.4 years. Neratinib, a tyrosine kinase inhibitor with pan-HER activity, has been shown to be effective in both trastuzumab-naive and trastuzumab-treated metastatic breast cancers.

Dr. Chan reported data from the ExteNET trial regarding use of neratinib after trastuzumab-based adjuvant therapy. The results of the primary analysis, presented at the ASCO annual meeting in 2015, showed that patients who received neratinib had an absolute benefit in DFS of 2.3% at 2 years.

Although the 3-year invasive DFS data are exploratory, they support the findings of the 2-year primary analysis. These data show a consistent benefit with neratinib for up to 48 months. Although this benefit was greatest in patients with centrally-confirmed HER2-positive disease or hormone-receptor positive disease, or those who completed trastuzumab within the last 12 months. The grade-3 diarrhea that occurred in 40% of patients in the first 30 days of neratinib therapy abated, and those patients had the same quality-of-life score as the placebo arm at 3 months of therapy. A recent study has shown that premedication with loperamide can decrease the incidence of grade-3 diarrhea to between 0% and 17%.

DUCTAL CARCINOMA IN SITU

Dr. Ganz presented the patient-reported outcomes from the NRG Oncology/NSABP B-35 trial that looked at anastrozole versus tamoxifen in postmenopausal patients with ductal carcinoma in situ. All patients had hormone-receptor–positive disease and were treated with lumpectomy followed by whole breast irradiation. Patients were randomized to receive tamoxifen and placebo for 5 years or anastrozole and placebo for 5 years. Breast cancer–free interval was the primary aim, and quality of life and symptoms was a secondary aim. The breast cancer–free interval data were previously...
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presented at the 2015 ASCO annual meeting and showed the breast cancer-free interval with anastrozole was 93.5% versus 89.2% with tamoxifen at 10 years for patients 60 years old and older. Importantly, the difference between the two treatment arms was not evident until 8 years after randomization.

This study was stratified by age: greater than 60 years and less than 60 years. Multiple patient-reported outcomes instruments were used to determine symptoms and quality of life. The trial obtained quality-of-life data on 1193 patients. Both anastrozole and tamoxifen were shown to be well tolerated. No differences in physical or mental health–related quality-of-life indicators were seen between the two treatments. Neither treatment increased fatigue, depressive symptoms, cognitive problems, or weight gain. The severity of vasomotor symptoms, bladder control, and gynecological symptoms was higher in the tamoxifen group than in the anastrozole group. No difference in sexual functioning score was seen between the two groups. The severity of musculoskeletal and vaginal symptoms was higher in the anastrozole group than in the tamoxifen group. (figure) In both groups, vasomotor and vaginal symptoms, weight gain, and gynecological symptoms were worse in women younger than 60 years.

Combining the data from the patient-reported outcomes with the breast cancer–free interval will help patients and physicians make more personalized treatment decisions.

To hear content from the Question and Answer section of the presentation S6-04, click here.
Early Clinical Trials

[S5-07] Pembrolizumab, an anti-PD-1 antibody, has been approved for use in metastatic melanoma and non-small-cell lung cancer and has been shown to be active against PD-L1-positive triple-negative breast cancer. Dr. Rugo presented results of the estrogen-receptor positive, HER2-negative cohort of a trial of pembrolizumab in PD-L1-positive advanced solid tumors (KEYNOTE-028). Twenty-five patients were treated with pembrolizumab, 10 mg/kg every 2 weeks. The primary endpoint was overall response rate. Most adverse events that occurred were grade 1 or grade 2. Immune-related adverse events included grade-3 autoimmune hepatitis (4%), grade-2 hyperthyroidism (4%), grade-2 hypothyroidism (12%), and grade-1 pneumonitis (4%). Overall response rate was 12%, with three partial responses and four with stable disease. The overall response rate was increased to 14% in the 22 patients who underwent at least one scan after baseline. [figure] Median time to response was 8.0 weeks, and the median duration of response has not been reached.

Dr. Rugo discussed the differences seen in the JAVELIN study of PD-L1 inhibitor avelumab (see below). She posited that different immunohistochemical assays may have led to differences in reported PD-L1 positivity, the inclusion criteria of the avelumab trial may have influenced results, and differences may exist between the immune checkpoint inhibitors.

The authors concluded that pembrolizumab is safe and led to durable responses in this patient population. Immune therapy should be further investigated in these patients.

[S1-04] Dr. Dirix presented the initial results for the JAVELIN clinical trial, that evaluated the use of avelumab, a human anti-PD-L1 antibody, in patients with locally-advanced breast cancer. This trial enrolled 168 patients from different breast cancer subgroups: 58 triple-negative, 72 hormone-receptor positive and HER2 negative, and 26 HER2 positive. Patients were not selected for PD-L1 expression. The endpoints of this phase Ib study were safety and tolerability.

Avelumab was found to have an acceptable safety profile. Potentially immune-related toxicities occurred in approximately 10% of patients, including hypothyroidism, pneumonitis, thrombocytopenia, and autoimmune hepatitis, four of which were grade 3 or grade 4. Treatment-related death occurred in two patients. The overall response rate was low, at 4.8%; one patient had a complete response, and seven patients had a partial response. Five of the eight responders were in the triple-negative subgroup (overall response rate of 8.6%), although responses occurred in all subtypes. Tumor shrinkage of at least 30% was seen in 9.5% and in 17.2% of the patients with triple-negative subtype. [figure] Response rate was also higher in patients who had PD-L1 expression by immune cells within the tumor compared to those without expression (33.3% vs. 2.4%). Median time to response was 11.4 weeks, and median duration of response was 28.7 weeks. Among the five TN responders, four had PD-L1-positive immune cells. At the time of data cut off for this presentation, response was ongoing for five of the eight patients. Thus, selecting for triple-negative patients with PD-L1-positive immune cells in future studies may improve the therapeutic benefit of avelumab.