"An **international scientific symposium** for interaction and exchange among basic scientists and clinicians in breast cancer."

HIGHLIGHTS FROM SAN ANTONIO BREAST CANCER SYMPOSIUM®

2018 | DECEMBER 4-8

HENRY B. GONZALEZ CONVENTION CENTER, SAN ANTONIO, TEXAS, USA

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SAN ANTONIO BREAST CANCER SYMPOSIUM®

Dear Colleagues,

Thank you for submitting your work and for participating in the 41th annual San Antonio Breast Cancer Symposium. In this overview, you will find a summary of a selection of oral presentations from this year. Additional resources are available on line through sabcs.org to assist in your learning activities. The executive committee hopes that these resources help highlight the remarkable research that was presented this year at the San Antonio Breast Cancer Symposium.

On behalf of the executive committee, we hope you enjoyed your week in San Antonio and look forward to seeing you next December for the 42nd annual San Antonio Breast Cancer Symposium.

Sincerely,

Kent Osborne, MD
Carlos Arteaga, MD
Virginia Kaklamani, MD

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REPORT CONTENT

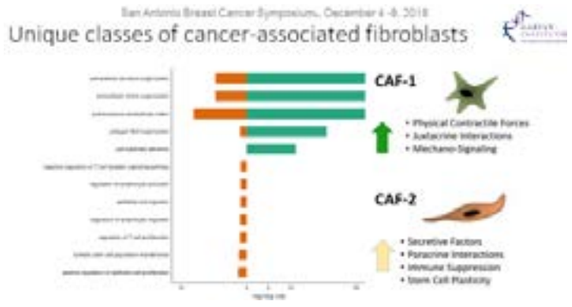
Basic Science and Preclinical

[GS1-01] Dr. Swarbrick started his presentation with the reminder that breast cancer, like all solid tumors, are really complex cellular ecosystems and the interactions among these different subtypes are key in determining the etiology of the cancer and predicting its response to therapy. The tumor microenvironment holds promise for new therapeutic options, but first a deep understanding of the complex interactions in the tumor microenvironment is needed. His lab has thus undertaken the task of developing a breast cancer cell atlas. Patient samples are collected and undergo parallel single-cell RNA-sequencing and a new technique developed by this lab called RAGE-sequencing that results in targeted long read sequencing. CITE-seq is also being completed to collect proteomic data in parallel to the RNA data. CITE-seq uses an antibody barcode method and this analysis utilized a library of more than 125 barcoded antibodies against a variety of stromal, epithelial and immune targets as part of the cell phenotyping efforts. The current breast cancer cell atlas includes over 125,000 cells from 25 distinct tissue types. The overall goal is to correlate the frequency of cell type and molecular features to each other and eventually to clinical pathological features of these patients.

As an example of the subtyping on a molecular level, two unique classes of cancer-associated fibroblasts were identified: CAF-1 and CAF-2. The CAF-2 population was distinctly different compared to the CAF-1 population in that they have increased secretory factors, more immune suppression and increased stem cell plasticity. New markers for identifying the subset of cancer associated fibroblasts were also established with CAF-1 cells expressing ACTC2 and CAF-2 cells expressing CD34. Knowing the expression pattern of the different cancer associated fibroblasts enables these cells to be more easily identified in a tissue sample, appropriately isolated, and selected for additional study.

This work has also been applied to the study of the breast cancer immune milleu with a more detailed evaluation of the tumor associated T-cells. CITE-Seq analysis of 98 cell-surface markers was completed and resulted in very detailed mapping of the different immune cell types residing in a single tissue sample to include subsets such as CD45 memory T-cell, CD69 activated T-cells, and CD56 NK T-cells. The authors hope that the building of this multi-omic breast cancer cell atlas will help to drive new discoveries in breast cancer directed therapeutics.

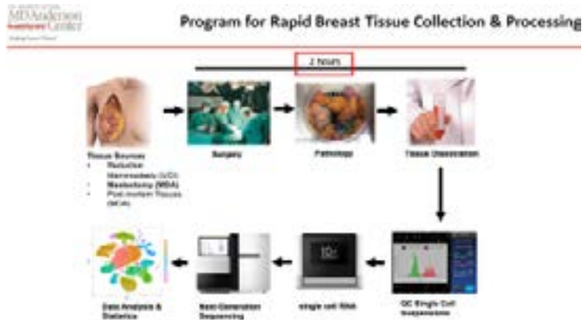
To Hear Content from the Question and Answer Section of the Presentation **GS1-01**
CLICK HERE



[GS1-03] Breast cancer often metastasis to the bone, and the bone microenvironment can be changed by the metastatic cancer cells to produce a more favorable environment for continued metastatic cancer cell growth and spread. The author purpose in this presentation that there is an interplay between the osteoblasts and the disseminated breast cancer cells which creates a modified osteoblasts referred to as an "educated osteoblast" (EO). These EO cells in turn interact via exosomes and proteins with the disseminated cancer cells and result in decreased proliferation of metastatic breast cancer cells in the bone. This process many have implications in metastatic latency. Thus, the object of this study was to analyze crosstalk between osteoblasts and breast cancer cells and its effect ono breast cancer cell proliferation.

Through a series of mouse models and human bone tissue from a biorepository of patients with metastatic breast cancer, a signature for the EO cell was determined. Osteoblasts that were exposed to breast cancer cells expressed protein alterations that include decreased in IL6 and a decrease in Alpha-SMA expression. The authors then evaluated the effect of EO on the growth of cancer cells and found that breast cancer cell growth was reduced with exposure to EO conditioned medium. This effect was observed in both hormonal receptor sensitive and triple negative cell lines. Then, the EO medium was further evaluated to determine the factors responsible for this decrease in breast cancer cell proliferation. A cytokine array of more than 400 different cytokines was completed and two cytokines were found to be one particular interest. One is Decorin, which is an antitumor molecule, and the second was NOV. Additional experiments were completed to verify that Decorin and NOV had a part to play in the decrease in breast cancer cell proliferation, and there was the expected responses on cell growth supporting their roles as key cytokines.

Next, the researcher focused on the role exosomes were playing in this bone microenvironment. Exosomes were isolated from EO and characterized them for specific lineage markers including Calnexin, CVD63, TSG101, CD9, GM130. Breast cancer cells were then cultured with EO-derived exosomes and cancer cell proliferation was decreased with increasing concentration of EO-derived exosomes. Exposure to EO-derived exosomes also resulted in a change in breast cancer cell morphology and decrease in Ki-67 expression. The cancer cells were showed to be taking up the EO-derived exosomes by staining EO-derived exomes with CD63-RFP staining and visualization with in the cancer cells. The authors concluded that a subpopulation of osteoblasts become "educated" by exposure to breast cancer tumor cells and these educated osteoblasts then suppress cancer growth by changing the microenvironment through altered protein and exosome expression. This ongoing suppression may be a contributing factor to the development of latent breast cancer recurrence.



[GS1-05] Triple negative breast cancer is very heterogeneous with multiple different subtypes and these tumors are often stratified based on the presence or absence of immune cells features. Different cells lines can be consider immune high or cold and differ in their expression of immune check point gene expression. This lab used varying triple negative mouse models and evaluated their response to immune check point inhibitors. The goal was to use sensitive and resistant mouse models to identify unique biomarkers that could potentially be used as predictors of response to therapy. A drug combination of an anti-PD1 and Anti-CTLA4 was utilized. The major of the models were resistant to the immune check point inhibitors. One model, named KPB25L, demonstrated weak responsiveness to immune check point inhibitors. Given the abundance of resistant mouse models, additional focus was directed towards the mutation burden in these models. The mouse models had a lower burden of mutations when compared to human triple negative tumors and in human tumors where immune check points have been successful therapies.

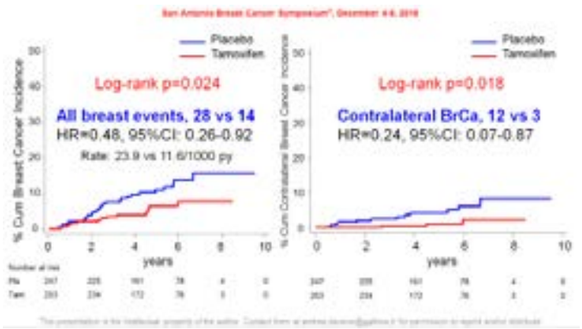
In human breast cancer, mutagenesis and elevated tumor burden is related to Apobec3 activity. Thus ectopic Apobec3 expression in the mouse models was used to increase the mutation burden. The newly developed mouse models showed an increase in response to immune check point inhibitors, and the addition of Apobec3 expression essentially converted resistant models to those sensitive to check point inhibitors. Genomic features were then evaluated in the sensitive models. Activated CD4 T-cells, CD8 T-cells and B-cell clusters were all associated with sensitive tumors. In sensitive models, the expression of these immune cells increased after one week of therapy with immune check point inhibitors. Finally, a supervised analysis of sensitive and resistant models at pretreatment was performed with identification of significant gene expression changes after treatment. A new B-cell and T-cell Co-cluster was identified and then tested across multiple datasets and other cells lines. This new B-cell and T-cell Co-cluster predicted response to immune checkpoint therapy, chemotherapy and trastuzumab based therapy in breast cancer cell lines.

Local Therapies/Prevention

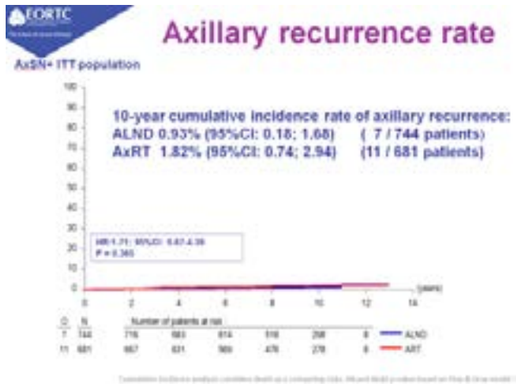
[GS3-01] In the modern era of breast cancer screening, intraepithelial neoplasms that include ADH, DCIS and LCIS, account for about 20% of all new breast neoplasms. The current standard therapy of hormonal therapy for 5 years and radiation does not change breast cancer related mortality and there are well established side effects from treatment. The most common side effects of tamoxifen include increased risk of endometrial cancer, venous thrombosis and menopausal symptoms. Tamoxifen was developed more than 50 years ago and the minimal active dose of tamoxifen is not well established. Thus, this study sought to evaluate if a decreased dose of tamoxifen at 5mg per day and a shorter duration of 3 years was as effective and less toxic than the standard dosing of 20mg per day for five years. A previous neoadjuvant window trial of lower tamoxifen showed that doses of 1 mg and 5 mg were non-inferior compared to 20 mg dosing in reduction of Ki-67.

This trial enrolled women less than 75 years with ADH, LCIS or estrogen receptor positive DCIS and randomized them to tamoxifen 5mg/day or placebo for three years and 2 years of follow up. The primary endpoint of the study was incidence of invasive breast cancer or DCIS. Five hundred women were randomized in 14 centers in Italy and QOL questionnaires were also completed. The median follow up at the time of this presentation was about 5.1 months. There was a 52% reduction in the risk of recurrence in the treatment arm compared to the placebo arm, and a 75% reduced risk of developing breast cancer in the contralateral breast in women on tamoxifen. The rate of endometrial cancer and venous thrombotic events were not different between the tamoxifen group and the placebo group. The patient reported outcomes included assessment of hot flashes, vaginal dryness and musculoskeletal complaints and suggested a small increase in hot flashes on the tamoxifen arm versus the placebo arm. The authors concluded that tamoxifen at 5mg per day for three years halves the

recurrence risk of intraepithelial neoplasms which is similar to the risk reduction with the higher dose of 20mg per day. The rates of endometrial cancer and thrombotic events are not different from placebo and less than the rate seen with higher tamoxifen dosing. The decrease in contralateral breast cancer rates is suggestive of a preventative benefit with the lower dose tamoxifen as well.



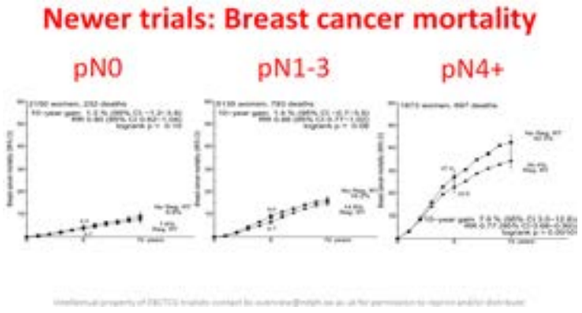
[GS4-01] Dr. Rutgers presented the ten year results from the EORTC AMAROS clinical trial evaluating radiotherapy or surgery of the axilla after a positive sentinel node. The AMAROS trial included patients with clinical stage T1-2, node negative breast cancer who were randomized to receive axillary radiation or an axillary dissection. Randomization was completed prior to surgery and no neoadjuvant chemotherapy was allowed. Patients who were found to have 4 or more positive nodes were allowed to proceed with radiotherapy regardless of their randomization. The first primary analysis was presented in 2013 after 6 years of follow up with a very low rate of axillary recurrence in both arms: 4 of 744 patients in the axillary lymph node dissection group and 7 or 681 patients in the axillary radiation group. The ten year results were presented as an ITT analysis with no significant difference in the axillary recurrence rate, disease-free survival, distant metastasis free survival, breast cancer survival and overall survival. Lymphedema, shoulder function and quality of life were also evaluated. The rate of lymphedema was about double in the group with an axillary clearance compared to axillary radiation. Shoulder function was not significantly impacted in either group. The authors concluded that both axillary lymph node dissection and axillary radiotherapy provide good and comparable locoregional control in patients with a positive sentinel lymph node with no difference in disease free survival or overall survival, and that axillary radiotherapy can be considered the standard of care for patients who meet AMAROS eligibility criteria.



[GS4-02] The purpose of the study was to evaluate the impact of extended regional nodal radiation therapy which includes radiation of the axilla, supraclavicular and internal mammary nodes, in comparison to radiation therapy to the breast alone. Fourteen trials were identified, nine of which included all three of the nodal regions, and in total included 13,404 individual patients. Two analyses were performed. The first included all the trials and the second separated the older trials from the newer trials based on the improvement in target cover and lower heart dose in the newer set of trials. The older trials were performed between 1961 and 1978 and the newer trials began after 1989 and included about 11,000 women. Follow up in the new trials is, as expected, shorter in the older trials.

With all trials combined, regional nodal radiation therapy decreased risk of recurrence by about 3% and breast cancer mortality by about 4%. The impact on decreased recurrence and mortality appears mainly from the newer trials with no benefit seen in the older trials. The older trails actually showed an increased risk of non-breast cancer mortality in patients who received nodal radiation, but there was no difference in non-breast cancer mortality in the newer trials. This increased non-cancer mortality in the older trials is presumed to be from the increased cardiac and pulmonary toxicity incurred from extended nodal radiation.

The newer trials were analyzed based on nodal status, and regional nodal therapy had no significant impact on breast cancer mortality in patients with 0-3 positive axillary nodes. However, patients with 4 or more positive nodes had about an 8% decreased risk of breast cancer mortality if they received nodal radiation therapy. The authors concluded that the older clinical trials of regional nodal radiation did not significantly affect breast cancer mortality and actually increased the risk of overall mortality. However, analysis of the newer radiotherapy trials with more modern radiotherapy techniques show a significantly reduced risk of breast cancer mortality and overall morality, especial in patients with four or more involved axillary lymph nodes.



To Hear Content from the Question and Answer Section of the Presentation **GS4-02**
CLICK HERE

[GS4-03] This presentation focused on the benefits of using accelerated partial breast irradiation (APBI) in comparison to whole breast irradiation (WBI). Whole breast irradiation is a standard of care therapy following breast conserving surgery that reduces the risk of local recurrence. This radiation therapy is administered in daily fractions of about 2-2.7 Gy over 3-6 weeks. The rational for using APBI is that most local recurrence arise at the primary site. This radiation is given to the surgical cavity and the surround margin of normal breast tissue. 3D conformal RT (3D-CRT) or Intensity modulated RT (IMRT) are two non-invasive methods to deliver APBI.

The primary objective of the RAPID trial was to determine if APBI using 3D-CRT was non-inferior to WBI following breast conserving surgery. Secondary objectives included disease free survival, event free survival, overall survival, radiation toxicity and cosmetic outcome. Patients included on this trial had invasive breast cancer or DCIS of less than 3 cm with negative margins of resection and were node negative. Age less than 40, mutli-centric disease and lobular histology were all exclusion criteria. More than 2,000 patients were randomized 1:1 to WBI or APBI. APBI was administered in 3-5 non-coplanar fields using 3D-CRT or IMRT. The surgical cavity was treated with 1 cm margin of surrounding tissue. The dose was 38.5 Gy in 10 fractions given twice a day at least 6 hours apart. Whole breast irradiation was delivered using standard fields with a dose of 50Gy in 25 fractions of 42.5 Gy in 16 fractions. A boost was given in moderate to high risk cases as per local center criteria.

After a median follow up of 8.6 years, in-breast recurrence risk between the two treatment arms was not significantly different, and thus the criteria for non-inferiority was for APBI was meet. There was also no significant difference between the two groups in regards to disease free recurrence, event free survival and mortality. In regards to acute toxicities, there was less acute toxicity in the APBI group, but there was higher late radiation toxicity in the APBI group. The cosmetic outcomes did show an important difference. In the WBI, poor cosmetic rating was noted at about 18% at baseline and this rate stayed steady throughout the duration of the study. In the APBI group, the poor cosmetic rating was only 19% at baseline, but slowly increased over the years, and at year 7, 36% of patients were considered to have a poor cosmetic result. The results of the cosmetic rates were similar in both the nurse assessment and the patient assessment. The authors concluded that APBI was non-inferior to WBI in preventing local recurrence. APBI had less acute toxicity, but had worse cosmetic outcomes with long term follow up. Thus, the study authors were unable to recommend for twice a day dosing and once a day dosing is currently being evaluated.

[GS4-04] Dr. Vicini presented the results from the NSABP B-39/RTOG 0413 clinical trial that evaluated whole breast irradiation after adjuvant chemotherapy compared to partial breast irradiation prior to adjuvant chemotherapy. The whole breast irradiation (WBI) included 50 Gy in 2.0 Gy per fraction or 50.4 Gy in 1.8 Gy per fraction followed by an optimal boost to at least 60 Gy. The partial breast irradiation (PBI) was administered as 34 Gy in 3.4 Gy fractions interstitial brachytherapy or mammosite balloon catheter or 38.5 Gy in 3.85 fractions given as 3D conformal external beam radiation. Over 4,000 patients were randomized 1:1 to the two study arms. The primary endpoint of the trial was ipsilateral breast tumor recurrence (IBTR), both invasive and DCIS. The secondary endpoints included distant disease free interval, recurrence free interval and overall survival.

PBI did not meet the criteria for equivalence to WBI in controlling for IBTR as the absolute difference in the 10 year cumulative incidence of IBTR between PBI and WBI was only 0.7%. PBI patients had more recurrence outside of the tumor bed region. The ten year recurrence free interval was 93.4 % in the WBI group and 91.8% in the PBI group which

was statistically significant with a p value of 0.02. There were no significant differences in the distant disease-free interval, overall survival, and disease-free survival. The rate of grade 3 and grade 4 toxicities were similar in both groups. This trial data does not support that WBI and PBI are equivalent, however, the absolute difference in the 10 year cumulative incidence of IBTR in the PBI group was small at 0.7%. Grade 3-5 toxicities were low and similar in both arms. Because the difference between the two groups was small, the authors suggest that PBI may be an acceptable alternative to WBI for some women after breast conserving surgery.

Ipsilateral Breast Tumor Recurrence (IBTR)

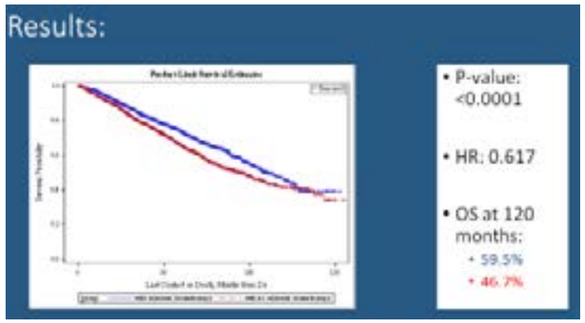
- Per protocol-defined margin, to declare PBI and WBI equivalent regarding IBTR risk, the 90%CI for the observed HR had to lie entirely between 0.667 and 1.5
- We observed 161 IBTRs as first events
  - 90 PBI *v* 71 WBI (HR 1.22; 90%CI 0.94-1.58)
- PBI did not meet the criteria for equivalence to WBI in controlling IBTR based on the upper limit of the HR CI
- Absolute difference in 10-yr cumulative incidence of IBTR between PBI and WBI was only 0.7% (4.6% *v* 3.9%)

Systemic Therapies
General Topics

[GS2-02] Utilizing the Nation Cancer Database, Dr. Shreya Sinha presented an analysis of efficacy and utilization of adjuvant chemotherapy in elderly patients with early stage breast cancer. The data regarding efficacy of commonly used breast cancer treatments is limited in the elderly population in part to their exclusion from clinical trials. The current NCCN guidelines underscore this in a notation that there are limited data to make chemotherapy recommendations for patients greater than 70 years of age. The two objectives of this study were to identify factors associated with the use of adjuvant chemotherapy in elderly women (defined as at least 65 years of age) with early stage breast cancer, and to analyze if adjuvant chemotherapy influence overall survival in this group. Data was collected from the National Cancer Database which is a hospital registry dataset from more than 1,500 Commission on Cancer accredited facilities in the United States. The selected patients were diagnosed between 2004 -2015, were greater than 65 years, and had stage I, II or III breast cancers. All histologic subtypes were included. Of notes, HER-2 status data was not available prior to 2010 and thus not included in the analysis. Applying these limits, 160,676 patients were identified for the analysis of which 60% (97,128) had treatment with adjuvant therapy and 40% (63,548) did not. The statistical method utilized an adjusted odds ratio and was adjusted for histology, stage, grade, age, comorbidity index, race and hormonal status.

The factors associated with receiving adjuvant chemotherapy included: higher grade tumors, hormonal receptor negative histology, higher stage, age less than 80, having private insurance, and being treated in a community setting. Having a total mastectomy versus lumpectomy and having adjuvant radiation therapy also increased to likelihood of receiving adjuvant chemotherapy. Women with higher morbidity scores were less likely to receive adjuvant chemotherapy. Race was not a significant factor. Women who received chemotherapy had an increase in overall survival in all stages and all histologic subtypes. The benefit of adjuvant chemotherapy increased with increasing stage with a HR of 0.66 in stage III breast cancer in favor of women who received adjuvant chemotherapy. Triple negative breast cancer subtypes also had the most profound effect from adjuvant chemotherapy with a HR of 0.547 in favor of women receiving adjuvant chemotherapy.

The authors concluded that receiving chemotherapy is associated with an increased in overall survival in patients with all stages and histology types for patients greater than age 65 years. Patients with more advanced stage and triple negative breast cancers had a greater benefit than patients with hormonal therapy positive or earlier stage breast cancer. Including validated geriatric assessments, such as the CARG score, can further help predict patients with increased risks from receiving chemotherapy.



[GS2-03] Dr. Laura Spring presented the results of pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) and the impact on breast cancer recurrence and mortality in an individual patient-level meta-analyses of over 27,000 patients stratified by breast cancer subtype and treatment. A previous study by Cortazar et al based on pooled analysis of 12 clinical trials showed that a pCR after NAC was significantly associated with improved event-free survival (EFS) and overall survival (OF). However, there remains a gap in our knowledge in regards to using pCR to tailor adjuvant therapy and the effect of the magnitude of pCR change in regards to event-free survival. Thus this study sought to close this knowledge gap.

The objectives of this study were threefold: to evaluate the association between pCR and EFS and OS by breast cancer

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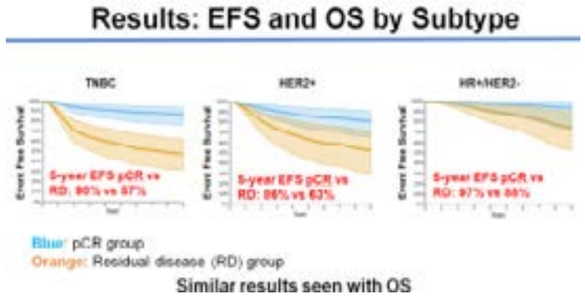
subtype, to determine the impact of adjuvant chemotherapy on association between pCR and clinical outcomes, and asses the relationship between the magnitude of change in pCR and event-free survival. The meta-analyses included 52 studies with 27,895 patients, ranged from 1999-2016, and included a global population. About half the studies were randomized clinical trials and 42% were retrospective studies. The median follow up time was 48 months for recurrence and 50 months for survival.

The analysis found that patients who achieve a pCR had both a better event-free survival (HR 0.39) at 88% vs 67% and overall survival (HR 0.22) at 94% vs 75%. This was true for all breast cancer subtypes, but the greatest difference was seen in the triple negative subtype with an event-free survival of 90% in the pCR group compared to 57% on the non pCR group. Giving additional adjuvant chemotherapy after achieving pCR did not have a significant effect on EFS or OS. The magnitude of change in pCR did predict treatment effect on event-free survival, but with some uncertainty in the model. The authors concluded that achieving a pCR following NAC is associated with significant improved EFS, particularly for triple negative and HER2 positive breast cancer. The similar EFS in patients that received adjuvant chemotherapy after a pCR supports the potential de-escalation of therapy for this group of patient in omission of adjuvant chemotherapy. They suggest additional research is needed to evaluate the clinical utility of escalation and de-escalation strategies in the adjuvant setting after based on degree of pathologic response from neoadjuvant chemotherapy.



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[GS6-04] Dr. Magnuson presented the work of the Cancer and Aging Research Group in their efforts to development and validate a chemotherapy toxicity risk score specific for elderly patient with breast cancer receiving chemotherapy. The need for accurate assessment tools in this population is in part due to the lack elderly patients enrolled in clinical trials, and because age is one of the leading risk factors for developing breast cancer. There are relatively few tools to help weight risks and benefits of chemotherapy in the elderly breast population. Thus, this study sought to build upon the CARG toxicity tool, a fully developed and validated prediction tool for elderly patients with any solid tumor, and make it more applicable to the elderly breast cancer population. The two objectives of this study were to develop and validate the CARG-BC (breast cancer) toxicity score and then evaluate the CARG-BC's association with dose modifications, dose intensity and hospitalizations.

The conceptual model included the CARG score in addition to lab data, sociodemographic factors, a geriatric assessment, and tumor and treatment specific information. Patients were enrolled across 16 sites and eligible patients were those at least 65 years of age with stage I-III breast cancer who were anticipated to receive neoadjuvant or adjuvant chemotherapy. They all had pre and post treatment geriatric assessments and data was collect to include: drugs, doses, schedule, duration, toxicity grading, hospitalization, and dose modifications. The median age was 70 with a range of 65 to 85 years. The majority of the patients were hormone receptor (HR) positive and HER2 negative (48%), although 24% were triple negative and 27% HER2 positive. Stage 1 patients represented 39%, stage II 41% and stage III 20% of the total study group. In this patient cohort, 82% received adjuvant chemotherapy or which 90% was multi-agent chemotherapy and 38% received an anthracycline based regimen.

As expected, toxicity was high in the group of patients. Grade 3-5 toxicity was recorded in 43% of the patients. Fatigue, infection with normal neutrophil count and dehydration were the most common severe side effects experience in the group. Hospitalization rates were 23% and 24% of patients discontinued therapy. Dose reductions during chemotherapy were required for 24% of patients.

Elements of the final CARG-BC score added to the CARG included use of an anthracycline, stage, duration of chemotherapy, liver function, ability to walk a mile and social support. The CARG-BC was able to predict increasing risk of having a grade 3-5 toxicity and outperformed the existing CARB toxicity score. The CARG-BC was then compared to physician assigned Karnofsky performance status score, which is the most commonly used performance assessment, and the CARB-BC was more robust in predicting grade 3-5 toxicity. The model was also able to predict increasing risk for dose delays, dose reductions, hospitalizations and reduced relative dose intensity.

CARG-BC Risk Score		
Risk factors for Gr. 3-5 Toxicity	**OR (95% CI)**	**Score**
CARG Score: Medium Risk High Risk	2.47 (1.35-4.51) 2.26 (0.70-7.35)	3
Anthracycline	1.37 (0.65-2.85)	1
Stage II/III	1.79 (1.00-3.23)	2
Duration of tx > 3 months	2.98 (1.46-6.09)	4
Abnormal liver function	2.21 (0.90-5.47)	3
Limited in walking a mile	2.22 (1.21-4.05)	3
Lack of someone to provide advice	2.34 (0.99-5.58)	3

To Hear Content from the Question and Answer Section of the Presentation **GS6-04**
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Hormone Receptor Positive

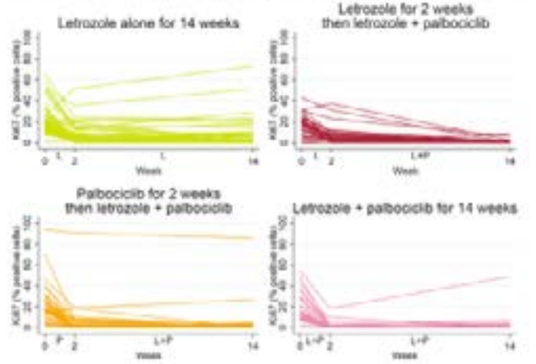
[GS3-02] Dr. Dowsett presented the results of the PALLET trial, a collaboration between the UK and NSABP cooperative group. He reported that palbociclib has now been used in more than 100,000 women with advanced disease, but this is the largest clinical trial to date in early breast cancer of endocrine therapy versus the combination of endocrine therapy and palbociclib. The efficacy of the combination of palbociclib and endocrine therapy has been consistently demonstrated in the series of PALOMA trials in patients with metastatic breast cancer. Clinical trials evaluating the benefit of palbociclib in combination with hormonal therapy in the adjuvant setting are ongoing, but at the current time there are no established biomarkers to predict which patients benefit from the addition of a CDK 4/6 inhibitor like palbociclib.

PALLET is a phase two randomized trial with parallel protocols in United Kingdom and North America. Patients included postmenopausal women with estrogen receptor positive, Her2 negative breast early invasive breast cancer with tumor size at least 2 cm by ultrasound. Patients were enrolled into four treatment arms in a 3:2:2:2 ratio to the follow arms: letrozole for 14 weeks, letrozole for 2 weeks followed by letrozole and palbociclib for 14 weeks, palbociclib for two weeks followed by palbociclib and letrozole for 14 weeks, or letrozole and palbociclib for 14 weeks. Core needle biopsies were performed at baselines, at two weeks for the groups that had a run in of monotherapy, and at conclusion of the 14 weeks of combined therapy. Both drugs were given at standard doses as letrozole 2.5mg daily and palbociclib 125mg daily for days 1-21 of a 28 day cycle. Letrozole was continued until surgery. Primary endpoints were change in Ki67 and clinical response by ultrasound after 14 weeks of therapy. The secondary endpoints included the added effect on Ki-67 when either palbociclib or letrozole was added to first therapy. A total of 307 patients were recruited over three years, and of those patients, 90.8% had clinical response data available and 62% had paired samples for Ki67 analysis. All four groups were well balanced.

The clinical response data was similar across all groups with no significant difference in objective response rates in the letrozole alone arm A (49.5%) compared to the letrozole + palbociclib arm D (54.4%). When the letrozole alone arm (A) is compared to the other three arms that included combination therapy at some point, the percentage change in Ki67 was 88.5% with letrozole alone and 97.4% in the combination arms. Interestingly, the treatment arms that included palbociclib had a combined complete cell cycle arrest, as defined by a Ki67 of 2.7 or less, of 90% by week 14 as compared to only 59% in the letrozole alone arm. The palbociclib arms had a greater decrease in c-PARP which is a marker of apoptosis. This drop in c-PARP is consistent with the notation that withdrawing a proliferation signal will subsequently result in a decrease in apoptosis. Importantly, there were no new safety signals in the study. Neutropenia and fatigue remains high. The rate of hot flashes was actually lower in the combination arms than in the letrozole alone arm.

The authors concluded that the combination of letrozole and palbociclib enhances the suppression of malignant cell proliferation as assessed by ki-67, enhanced the proportion of patients that achieve a complete cell cycle arrest, but did not substantially increase the clinical response rate. The later may be due less apoptosis as measured by c-PARP. Additional secondary biomarker analyses are ongoing.

Co-primary endpoints:
Individual trajectories of Ki67 by randomized treatment grc



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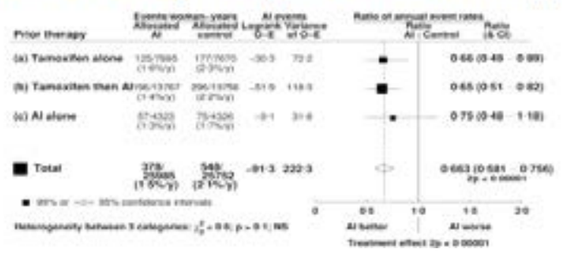
[GS3-03] The ideal duration of hormonal therapy for women with hormone receptor positive breast cancer beyond 5 years was evaluated by this analysis. Previous trials of extended therapy with an third generation aromatase inhibitor (AI) varied and included therapy with an AI after 5 years of tamoxifen, after 5-10 years of tamoxifen then an AI, and after 5 years of an AI without previous tamoxifen treatment. This meta-analysis included 7,483 of tamoxifen only, 12,304 with tamoxifen and AI, and 4,764 patients with AI alone. Median follow up was less than seven years. In the trials of tamoxifen alone, the addition of an AI resulted in a one-third reduction in recurrence over the five year follow up period. The analysis found that the greatest benefit of extending AI therapy was in the group that only received prior tamoxifen therapy. This group of patients had an earlier drop in recurrence compared to the placebo group and a greater absolute benefit with a RR of 0.67 favoring the AI group. Patients that had received prior tamoxifen and an AI, still had a benefit from extended AI therapy with a RR of 0.81, but the benefit was smaller and not as immediate. Given the average follow up is less than 7 years, the full benefit of extended AI therapy in the groups previously treatment with an AI may not yet be fully mature. While all sites of recurrence were decreased, the greatest effect was in the development of contralateral breast cancer. The nodal status was also examined and the benefit of extended AI therapy increased with the increasing nodal burden. In node negative patients, the decrease in recurrence was 1.1% with extended AI therapy compared to 3.8% in patients with 1-3 positive nodes and 7.7% in patient with four or more positive nodes. Regarding toxicities, women on extended AI therapy had a 1.8% increased risk of bone fractures, but no difference in death without evidence of breast cancer recurrence.

The authors concluded that there is about a 35% proportional reduction in recurrence for women who have received 5 years of tamoxifen and about a 20% proportional reduction in risk of recurrence in women receiving an AI who were treatment with an AI in the past. Risk reduction appears in the first two years following tamoxifen, but is delayed to at least three years in women previously treated with an AI. The benefit of extended therapy increased with nodal burden and risks included increased fracture risk by about 25%. Long term follow up is needed for evaluation of effect on mortality

Effect on recurrence in in years 2-4 after treatment divergence by prior endocrine therapy



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[GS3-08] The PI3K pathway is frequently altered in hormone receptor positive breast cancer and has been associated with resistance to endocrine therapies. Alpelisib is a selective PI3K-alpha inhibitor and has been evaluated in a phase 1b trial in combination with fulvestrant. In this trial, the median progression free survival was 9.1 months in heavily pretreated, hormone receptor positive advanced breast cancer with PI3K mutations.

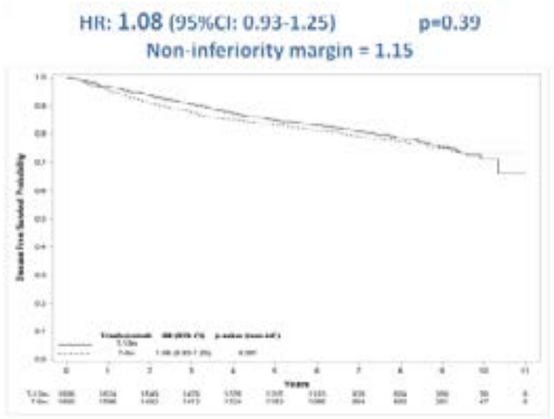
The SOLAR-1 trial was a phase 3 randomized, double-blinded, placebo-controlled trial of patients with advanced breast cancer with recurrence or progression after prior aromatase inhibitor therapy. The PI3K mutation status was evaluated and patients were placed into two arms: alpelisib and fulvestrant versus fulvestrant and placebo. The primary endpoint was progression free survival (PFS) in the PIK3CA- mutant cohort. In the PIK3CA-mutant cohort, there was an 11.0 month median PFS in the alpelisib and fulvestrant arm compared to 5.7 months in the fulvestrant and placebo group, and this was statistically significant. The majority of patients on this trial were clinically endocrine therapy resistant and there was benefit to alpelisib regardless of line of therapy or prior CDK 4/6 inhibitor treatment. The overall survival (OS) data remains immature at the time of this presentation as the median OS in the alpelisib arm has not yet been reached. The most common toxicity is hyperglycemia which is an on target adverse event. It most commonly occurs within the first two weeks and can be effectively managed with oral anti-diabetic medications. Progression free survival was significantly prolonged in patients whose PIK3CA mutational status was determined by ctDNA anaylsis. Thus mutational status

as determined by ctDNA can be considered for selecting patients for treatment with PI3Kinase inhibitors.

HER2 Positive

[GS2-07] Dr. Pivot reported the final results of the PHARE study which was a clinical trial with the primary objective to compare the effect of 6 months versus 12 months of treatment with trastuzumab in HER2 positive early stage breast cancer. The primary endpoint was disease free survival (DFS) in the non-inferiority study. All patients with HER2 positive breast cancer with normal cardiac function who were to receive trastuzumab were eligible for the trial. Stratification was by estrogen receptor status and if chemotherapy was to be concurrent or sequential with trastuzumab. The study starting in May 2006, and 3,384 were enrolled which represented about 20% of the patients in France with HER2 positive breast cancer.

This final analysis was after an average of 7.5 years of follow up. The disease free survival HR was 1.08 with a 95% confidence interval which included the margin of non-inferiority. Thus, the study failed to demonstrate that 6 months was not inferior to 12 months of trastuzumab therapy. A subgroup analysis did not demonstrate a group where 6 months was non inferior to 12 months of treatment. The authors mention that the PHARE study and PERSEPHONE study were very similar trials but reached opposite conclusions based on the variation in the determining the appropriate difference between the two arms to reach the decided level of non-inferiority between two therapeutic options.



[GS1-10] It has been shown that patients with residual disease after neoadjuvant HER2-targeted therapies in combination with chemotherapy are at increased risk for recurrence and breast cancer related death. T-DM1 is known to be against HER2 positive breast cancer after progression on taxanes and her2 directed therapies. Thus, KATHERINE was designed to evaluate the benefits of substituting T-DM1 for trastuzumab in patients with residual invasive cancer after neoadjuvant chemotherapy (NAC).

The study included patients with centrally confirmed HER2 positive breast cancer with at least clinical stage T1-2/N0-3/M0 (cT1a-n/N0 were excluded) who were treated with a minimum of 9 weeks of a taxane and 9 weeks of trastuzumab with residual invasive tumor in the breast or axillary nodes. Anthracyclines, alkylating agents and additional HER2-targeted agents were also allowed. Patients were stratified based on stage, hormone receptor status, type of neoadjuvant HER2 therapies received, and pathologic nodal status at the time of surgery. A total of 1,486 patients were randomized on a one to one fashion to T-DM1 3.6 mg IV every 3 weeks for 14 cycles or trastuzumab 6 mg/kg IV every three weeks for 14 cycles. Radiation and endocrine therapies were administered by local protocols concurrently with the HER2 directed therapies. The primary endpoint for the study was invasive disease free survival (IDFS).

The three year invasive disease free survival in the T-DM1 was 88.3% versus 77.0 % in the trastuzumab arm which was a statistically significant difference (p less than 0.0001) with a HR 0.50 (95% CI 0.39-0.64). In the subgroup analysis, most the major and key subgroups all favorited the T-DM1 group including hormonal receptor status, clinical stage at presentation and pathologic nodal status after preoperative therapy. Benefit was also present in the T-DM1 groups regardless of the burden of residual disease. There was a small population on the study who were HER2 negative (IHC

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scores of 0-2+) by central testing and these patients did not show benefit from treatment with T-DM1. Development of distant recurrence also favored the T-DM1 group with 83% event free rate in the trastuzumab arm versus 89.7% in the T-DM1 arm (HR 0.60 95% CI 0.45-0.79). T-DM1 had an overall increase in all grade adverse events compared to trastuzumab, most being grade one and grade two. Toxicities that were at least a grade three were most likely to included fatigue, nausea, thrombocytopenia, increase in liver function tests and sensory neuropathy.

The authors concluded that adjuvant T-DM1 will likely become a standard of care option for patients with residual disease after neoadjuvant therapy as it demonstrated improvement in invasive disease free survival compared to adjuvant trastuzumab. This benefit was consistent across key subgroups to include hormone receptor status, extent of residual disease and previous treatment with single or dual HER2 directed therapies. While the T-DM1 group experienced more grade three toxicities compared to the trastuzumab arm, no new safety signals were identified. The overall survival data is not yet mature and will be analyzed after longer term follow up has been achieved.

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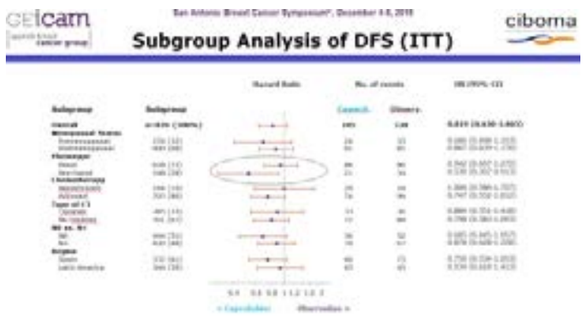
Triple Negative Breast Cancer

[GS2-04] The standard of care for early stage triple negative breast cancer (TNBC) is chemotherapy. Despite conventional polychemotherapy, a large number of patients will relapse. Thus, additional adjuvant therapies are needed to help decrease the risk of recurrence in this subgroup of patients with triple negative breast cancer. The Create-X trial, which was previous presented at SABCS and subsequently published in the New England Journal, reported an improvement in progression free survival (PFS) and overall survival by adding capecitabine for 6 to 8 cycles in patients with TNBC and residual disease after neoadjuvant chemotherapy. Capecitabine was chosen in part as its mechanism of action is partially non-resistant with anthracyclines and taxanes which are the most common components of polychemotherapy regimens for TNBC.

This study was an international randomized phase III trial that included 876 patients with TNBC that was at least a stage T1c with any nodal status who received treatment with an anthracycline +/- taxanes in the adjuvant or neoadjuvant setting. Patient were randomized to capecitabine 1000mg/m2 twice daily for 14 days of a 21 day cycle for eight total cycles or to an observation arm only. The primary endpoint was disease free survival (DFS) and secondary endpoints included overall survival (OS), subgroup analyses, safety, and biomarker studies. The study enrolled between 2006 and 2011 and start of enrollment was prior to the Create-X trial reporting initial results. The capecitabine dose intensity was about 87% and no new safety signals were identified.

After a median follow up of 7.4 years, 105 DFS events were observed in the capecitabine arm versus 120 in the observation arm which was not statistically significant with a HR of 0.82 (95% CI 0.63-1.06) and a p value of 0.136. The overall survival was also not statistically significant between the two arms with a HR of 0.92 (95% CI 0.66-1.28) with 71 deaths in the capecitabine arm and 73 deaths in the observation arm. In the subgroup analysis, only the non-basal subgroup had a significant improvement in DFS and OS with capecitabine versus observation. The non-basal group was defined as EGFR negative and CK 5/6 negative. The authors conclude that this study failed to show a DFS or OS benefit with the addition of capecitabine to standard polychemotherapy regimens for patients with TNBC, but the

sub group of patients with non-basal like phenotype did have an increase in DFS and OS with adjuvant capecitabine.



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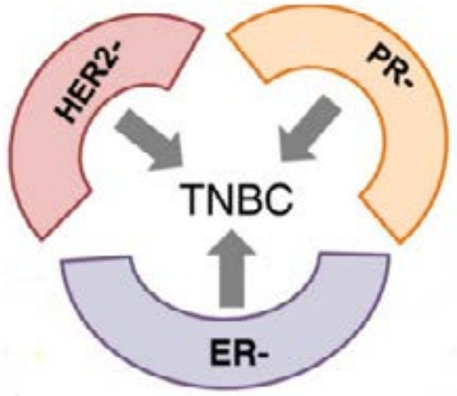
[GS2-05] Dr. Morante discussed the results of a retrospective study evaluating the impact of time to initiation of chemotherapy in patients with Triple Negative Breast Cancer (TNBC) in Peru. Previous studies have suggested that delays in initiation of chemotherapy after surgery is particularly harmful in patients with TNBC as it results in worse overall survival and breast cancer specific mortality. This study included 687 patients with upfront surgery for TNBC who completed adjuvant chemotherapy. Patients with inflammatory breast cancer or who received neoadjuvant chemotherapy were not included in the analysis. The majority of patients started adjuvant chemotherapy between 31-60 days after surgery (47.9%), but 16.7% started after 61 days from surgery and 7.9% were delayed at least 91 days. The study found that patients who received chemotherapy within 30 days of surgery had an 82% overall survival (OS) compared to 65.1% OS in patient with delays of at least 91 days. Furthermore, time to initiation of chemotherapy was found to be an independent prognostic factor for overall survival in this patient population. The authors concluded to initiation of chemotherapy earlier may represent a feasible and readily available means to improve outcomes in patients with TNBC.



Gajulapalli VNR, et al. Biosci Rep. 2016 Dec 23;36(6).

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[GS5-06] The predictive and prognostic marker data in the Women's Health Group WSG-ADAPT-TN trial was presented by Dr. Gluz. This trial evaluated patients with triple negative breast cancer randomized to two treatment arms: one arm received nab-paclitaxel + gemcitabine and the other arm received nab-paclitaxel + carboplatin. After 12 weeks for treatment, all patients proceeded to surgery and adjuvant Adriamycin was recommended but not required. The primary endpoint was pathologic complete response (pCR) rate after the 12 weeks of neoadjuvant chemotherapy and this data was previously presented at SABCS in 2015. Patients on the nab-paclitaxel + carboplatin arm had an increase in pCR compared to the gemcitabine arm and patient who achieved a pCR had an increased event free survival.

This presentation focused on translational results of this trial and the predictive markers for pCR. There were markers that were predictive of response to either gemcitabine or the carboplatin arm, and there were four markers that were shared among both arms, but there were no biomarkers that were predictive for EFS benefit for carboplatin versus gemcitabine containing regimens. Patients with high baseline PD1 as measured by mRNA appeared to be the best candidates for potential de-escalated therapy as they had the best EFS when a pCR was obtained regardless of the treatment arm. In patients that did not achieve a pCR, clinical

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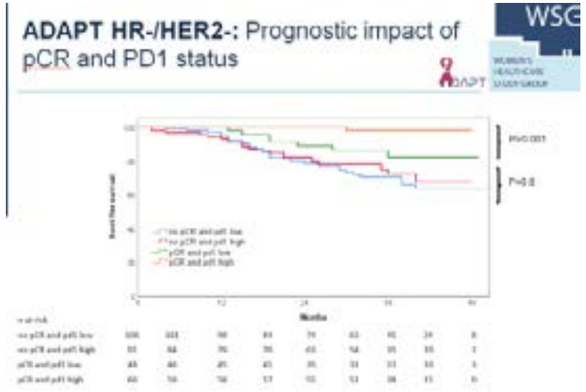
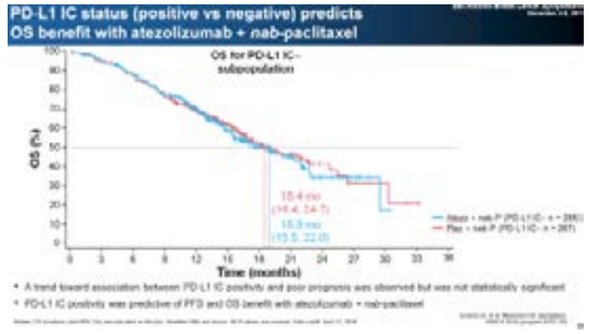
factors such as Ki-67 and clinical node negative status are strong prognostic factors and thus can be considered for further risk stratification.



[GS1-04] The biomarker update of the IMprassion130 was presented by Dr. Emens. IMprassion130 is a randomized phase III international trial of atezolizumab or placebo + nab-paclitaxel in treatment naïve metastatic triple negative breast cancer. The main trial results has already been presented and showed statistically significant improved progression free survival and overall survival in patients with PD-L1 expression. The median overall survival improvement was from 15.5 months to 25.0 months in patients with PD-L1 positivity.

This presentation focused on the whether immune biology and BRCA1/2 mutation status were associated with clinical benefit from atezolizumab and nab-paclitaxel. The biomarker analysis included PD-L1 on immune cells and tumor cells, the presence of intratumoral CD8+ T cells by IHC, and stromal TILs by H&E. BRCA 1/2 mutation status was determined by the FoundationOne assay. Patients who are PD-L1 immune cell negative had no benefit from atezolizumab. Importantly, patients who were PD-L1 positive but treatmented on the placebo arm had significantly decreased progression free survival by about 10 months compared to the group that received treatment with atezolizumab. Thus, the authors concluded that PD-L1 expression on immune cells is predictive of improved PFS and OS favoring treatment with atezolizumab. PD-L1 expression of at least 1% on the immune cells was the apparent level to reach this benefit. Furthermore, patients with CD8 positive T cells only derived benefit if they were also PD-L1 positive. Having CD8 positive T cell expression in the absence of PD-L1 expression did not predict benefit from atezolizumab. This was the same for stromal TILs. Patients with stromal TILs only achieved a benefit if they were also PD-L1 positive. The BRCA mutation status also did not provide a benefit in the PD-L1 negative setting.

This biomarker focused presentation provided important data in regards to who benefits from the additional of atezolizumab to chemotherapy. PD-L 1 expression was the only biomarker that was predictive of benefit, and expression of 1% or more on immune cells was enough to reach this benefit. PD-L1 immune cell expression was the best predictor as none of the other biomarkers predicted response in the absence of PD-L1 expression. This benefit was seen regardless of BRCA mutation status. This data supports the testing of PD-L1 expression on immune cells in patients with newly diagnosed advanced triple negative breast cancer to evaluate for potential immunotherapy benefit.



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Survivorship/ Treatment Toxicity

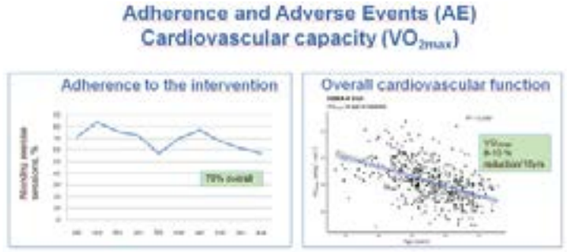
[GS5-01] Relatively small studies have evaluated the prophylactic use of angiotension converting enzyme (ACE) inhibitors and beta blockers (BB) in cardiotoxicity from trastuzumab treatment. This trial set out to evaluate the benefits of either carvedilol or lisinopril in a randomized, blinded and placebo controlled multicenter community-based setting. Patients with HER2 positive breast cancer with planned treatment with trastuzumab for one year were randomized to receive carvedilol, lisinopril or placebo from the start of trastuzumab through 52 weeks of therapy. Cardiotoxicity for the propose of this trial was defined as an absolute decrease in left ventricular ejection fraction (LVEF) of 10% or at least 5% decrease if the baseline LVEF was less than 50%. The primary endpoint was cardiotoxicity during the 52 weeks of trastuzumab therapy and within the year of completing trastuzumab. Secondary endpoints included toxicity, tolerability, quality of life, and lab values such as BNP

and troponins. Patients were stratified based on exposure to anthracycline chemotherapy.

The trial randomized 468 patients to placebo, lisinopril 10mg daily or carvedilol 10mg daily for 52 weeks. Left ventricular function and quality of life assessments were completed every 6 months. Only 250 patients completed the 52 weeks treatment period and the most common reasons for coming off treatment were cardiotoxicities and side effects to the intervention. This was an overall negative study with cardiotoxicity similar in all three cohorts. The cardiac toxicity was 32% in the placebo cohort, 29% in the carvedilol cohort and 30% in the lisinopril cohort. Cardiotoxicity free survival was also comparable between the three groups. However, there is a significant benefit to both carvedilol and lisinopril over placebo in patients previously treated with an anthracycline. In regard to side effects, more patients reported fatigue, dizziness, cough and hypotension in the lisinopril cohort compared to the carvedilol cohort. The authors concluded that patients with previous anthracycline use may benefit from the addition of a beta blocker or ACE inhibitor during trastuzumab to prevent cardiotoxicity.

[GS5-02] Women with breast cancer have a higher risk of cardiovascular complications than women without a history of breast cancer, and heart failure that develops as a complication of cancer therapy has a worse long-term prognosis compared to heart failure not related to cancer therapy. The EBBA-II trial sought to evaluate whether a 12 month exercise program during adjuvant therapy influenced cardiopulmonary function. The trial also evaluated the efficacy and safety profile of a tailored exercise program, and explored the optimal duration and intensity of the exercise program. Patients with early stage breast cancer or DCIS/LCIS were enrolled in either a 12 month exercise program tailored based on baseline cardiovascular function or to a standard of care group that were counseled based on local guidelines. The primary outcome was change in VO_2 max from baseline.

Adherence to intervention was high at 70% overall completion of the exercise sessions. Patients in the exercise group had a slight increase in VO_2 max by 0.3% whereas the control group had a decrease in VO_2 max by 8.9% at the 12 month assessment. In the subgroup analysis of patients that received chemotherapy, patients in the exercise group had an overall 0.8% decrease in VO_2 max while the control group had a 6.4% decrease in VO_2 max at the 12 month assessment. This effect was even greater for patient who received a taxane as part of their adjuvant therapy. The authors concluded that all subgroups benefited from exercise during breast cancer treatment, particularly patients receiving adjuvant chemotherapy, and tailored exercise programs should be incorporated into breast cancer treatment guidelines.



[GS5-03] Obesity and low physical activity has been associated with increased risk of developing malignancies such as breast cancer, and obese patients with breast cancer have increased risk of recurrence and reduced survival. The SUCCESS C study was a large randomized phase III trial of HER2 negative patients who were treatment with either six cycles of Docetaxel/Cyclophosphamide or three cycles of FEC followed by three cycles of Docetaxel. The trial then had a second randomization to either a lifestyle intervention arm or to a non-lifestyle intervention control arm. The lifestyle intervention included a two year standardized and structured telephone and mail-based lifestyle intervention program with a goal of weight loss through diet and exercise. The control group received general recommendations for a healthy lifestyle through mailings after chemotherapy and again after one year. Patients qualified for the lifestyle intervention part of the SUCCESS trial if they had a BMI between 24.0 and 40.0 kg/m^2 and this included 1146 patients in each lifestyle intervention arm. Both arms were well balanced, and the average BMI in each group was about 28 kg/m^2.

The intensified lifestyle intervention group lost and average of 1.0 kg whereas the control group gained 0.95 kg. The two treatment arms showed no difference in disease free survivial (DFS) or overall survival (OS). Only about 64% of patients completed the lifestyle invention, so the study authors completed an unplanned explorative subgroup analysis on patients in both groups who that completed the planned intervention. Patients that completed the intensified lifestyle intervention lost an average of 3.6 kg. When only patients that completed the interventions were analyzed, there was a significant difference in DFS between the

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two groups. The authors note limitations to this subgroup anaylsis to include low adherence to the intensified lifestyle intervention program and this analysis was explorative and not planned. Due to low compliance, the number of events in the subset analysis is relatively low, and potential bias may be unaccounted for in a "healthy participant effect" influencing which patients are able to complete all the lifestyle intervention arm requirements.

[GS4-07] Black race has been associated with worse outcomes in both population-based and clinical trial cohorts, and this disparity persists after adjusting for treatment delivery variables. The TAILORx trial enrolled 9,719 women with hormone receptor positive, HER2 negative, node negative breast cancer and they were randomized to four different arms based on the 21 gene recurrence score (RS). Patients with a RS between 0-10 (Arm A) received adjuvant endocrine therapy alone, and patients with a score of greater than 26 (Arm D) all received adjuvant chemotherapy followed by endocrine therapy. Patients with an intermediate score of 11-25 were randomized equally to either endocrine therapy alone (arm B) or to chemotherapy and endocrine therapy (arm C). The primary endpoint was non inferiority in arm B to arm C in regards to invasive disease free survival, and this primary endpoint was achieved and this data was presented at ASCO in 2018.

This presentation focused on the analysis of clinical outcomes in all arms combined and in the randomized arms (arm B and C) to determine if the lack of chemotherapy benefit is also true in race and ethnicity subsets. This was a planned analysis examining the association between clinical outcomes with race or ethnicity. Race was separated into four groups: white, black, Asian and other/unknown. Ethnicity was Hispanic or non- Hispanic. The four outcome endpoints were invasive disease free survival (iDFS), relapse-free survival, distant relapse free survival (DRFS) and overall survival. In regards to ethnicity, only 9% were Hispanic. The majority of patients were white at 84%, black race was 7%, Asian race 4%, and other or unknown was 4%.

Women of black race had significantly worse outcomes compared with women of white race in the study population overall and in the two randomized arms. This was independent of other factors in a proportional hazards model. An analysis was then completed for arm A and arm D only. The arm A patients had favorable risk scores (10 or less) and received endocrine therapy alone. In this group, there was no significant difference in iDFS or DRFS between blacks and whites. This was also true when the same analysis was completed in the high risk arm D where all patients received chemotherapy and endocrine therapy. This lack of difference in arms A and D may explain why the disparity outcomes are less pronounced in the overall population compared to the randomized cohorts (arms B&C). Furthermore, the relative benefit from endocrine therapy is greater in the intermediate RS group and thus racial difference in the actual adherence, sensitivity to antiestrogen therapies or both may contribute to a more pronounced difference by race in arms B and C. In addition, tumor biology and proliferation genes may differ by race and future analysis of single gene and gene groups by racial group are planned.

The authors concluded that the main conclusion of TAILORx – that chemotherapy can be safely avoided in hormone receptor positive, HER2 negative, node negative patients with recurrent scores of less than 26 – is true for all races and ethnicities analyzed in this study. However, there were higher recurrence rates and overall mortality for women of black race compared to other races. This was despite being enrolled in the same trial and receiving standard cancer care. This disparity was not accounted for by RS, reported endocrine therapy duration, type of adjuvant chemotherapy or clinicopathologic factors. This data supports emerging evidence that biologic basis may be contributing to racial disparities observed in breast cancer outcomes.