HIGHLIGHTS FROM THE 39TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM

A summary report containing selected proceedings from the San Antonio Breast Cancer Symposium on December 6-10, 2016

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Dear Colleagues,

Thank you for submitting your work and for participating in the 39th annual San Antonio Breast Cancer Symposium. This year, we moved into a new meeting space and hopefully all attending enjoyed the new accommodations for the display of 1291 posters and more than 50 oral presentations outlining the most recent advancements in breast cancer. New to this year’s conference was the Friday night session, View from the Trenches: What Will You Do On Monday Morning. This session was very well attended and generated dynamic discussions on the practical application of information presented during the week.

We are now on the eve of celebrating the 40th symposium and are looking forward to a wonderful conference next December. We hope to continue to innovate and adjust along with this dynamic field of cancer research and treatment. This report highlights some of the research and trials presented this year with audio and video links. Also included in this summary is a section on special patient populations including BRCA related breast cancers, pregnancy associated breast cancer and racial differences and disparities in breast cancer care. We hope you find this a useful reference when reviewing the major presentations of the conference.

Included in the report are the following sections:

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

On behalf of the executive committee, we hope you enjoyed your week in San Antonio and look forward to seeing you next December when we celebrate the 40th anniversary of the San Antonio Breast Cancer Symposium.

Sincerely,

Kent Osborne, MD
Carlos Arteaga, MD
Virginia Kaklamani, MD
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Advances in Biomarkers and Preclinical Research

PREDICTION MODELS

[PD7-03] The Anne Arundel Medical Center (AAMC) risk model predicts 5 year risk of distant metastatic disease using standard pathological data. In this model, low-risk disease is defined as grade 1 and progesterone-receptor positive; high-risk disease is defined as grade 3 or <20% positive for estrogen receptors. This model has been shown to correlate with risk groups as assigned by the OncotypeDX recurrence score, but the prognostic value had not been studied. Dr. Jackson reported on a study that compared the ability of the AAMC model to predict metastatic recurrent risk compared to the recurrence risk as defined by the TAILORx trial and the OncotypeDX assay. This study utilized a prospective registry of invasive breast cancers treated at MD Anderson between 2005 and 2015. The investigators selected estrogen receptor positive, node negative, cases with available OncotypeDX recurrence scores. Each case was assigned to a risk group using the three different methodologies: the AAMC definition and the recurrence scores based on definitions use in TAILORx and OncotypeDX. Mean follow-up was 3.6 years, and 25% of patients had ≥5 years of follow-up.

The AAMC low-risk group had a 5-year distant recurrence rate of 2.7%, similar to the TAILORx and OncotypeDX low-risk groups. The AAMC high-risk group had a 5-year distant recurrence rate of 22.8%, also similar to the TAILORx and OncotypeDX high-risk groups. The number of cases categorized as AAMC high-risk was 230, similar to the number of cases in the TAILORx high-risk group. The lengths of the intervals without distant metastases in the AAMC risk groups were similar to the corresponding TAILORx risk groups. The investigators found that the Oncotype RS underestimated the risk for some grade-3 tumors in the TAILORx trial. They also found that a low percentage of staining of progesterone receptors (<3%) was strongly associated with recurrence and poor prognosis, regardless of the Oncotype score. The authors concluded that categorizing low risk and high risk patients based on the AAMC model, can easily and reliably identify a large number of patients unlikely to benefit from Oncotype testing.

[PD7-05] Dr. Peethambaram presented key findings from a study of the 21-gene recurrence score (RS) assay. While this assay is routinely used in node negative, estrogen-receptor positive, HER2 negative breast cancers, guidelines from the National Comprehensive Cancer Network and American Society of Clinical Oncologists do not concur regarding the use of RS in node-positive disease. This study aimed to investigate the current use of RS in node-positive disease.

Data were obtained from 72,897 patients with estrogen-receptor positive, HER2-negative breast cancer from a large, national cancer database. Patients with pathological stage T1-4c and positive lymph nodes were included, and those who had received neoadjuvant therapy were excluded. The RS had been performed in 15,028 patients, with an increase in the use of RS between 2010 (15%) and 2013 (25%). Testing was more likely to occur in patients aged 50 years to 79 years and those who had lower T stage, N stage, and grade. Testing was less likely to occur in patients who were black, those who had Medicaid or no insurance, and those who received treatment in community cancer programs.

Chemotherapy was recommended in 81% of patients who did not undergo RS and in only 50% of patients who did undergo RS. Chemotherapy was recommended in a majority of patients with high-risk scores, regardless of nodal stage. Recommendations for chemotherapy in patients with low-risk scores increased with increasing nodal stage. Similarly, there was a tendency for the recommendation for chemotherapy to increase with increasing nodal stage in patients with lower intermediate scores (18 to 25). As in the high-risk group, the majority of patients with higher intermediate scores (26 to 30) were recommended to receive chemotherapy. Chemotherapy was recommended for patients with N2- and N3-disease, regardless of the RS. Ongoing prospective trials will
determine how well the RS predicts the benefit of chemotherapy in node-positive breast cancer.

A 2010 overview of randomized trials showed that the addition of radiation therapy to lumpectomy for patients with DCIS results in a 15% reduction in local failure, with no increase in survival. Importantly, however, 72% of patients had good outcomes without radiation therapy. Dr. Whitworth discussed the first of three planned validation studies of a new biological risk profile to be used to predict recurrence in patients treated for DCIS with breast conservation surgery. The aim is to use this risk score to help identify those patients who will receive benefit from radiation therapy. The risk signature integrates immunohistochemical biomarkers and clinicopathological factors to result in a risk score ranging from 0 to 10. The study included 455 patients with DCIS who had been treated with breast conservation surgery; 377 had received radiation therapy and 78 had not. In patients who did not receive radiation therapy, a biological risk score ≤3 was associated with a 10% risk for local failure at 10 years, and a risk score >3 was associated with a 30% risk for local failure at 10 years. Those patients with a risk score >3 who did receive radiation therapy, however, had a local recurrence rate of 10%. The investigators concluded that this assay appears to identify those patients with a low risk for recurrence who are less likely to benefit from radiation therapy and those with a higher risk for recurrence who are more likely to benefit from radiation therapy. A report from the next planned study, more heavily weighted to patients who did not receive radiation therapy, is expected in January 2017. The Swedish DCIS study with 20 years of follow-up is expected to be completed in March 2017.

KPNW Biologic Risk Groups by Treatment

Data from node-negative disease in the first 10 years showed that all six signatures provided both significant prognostic information for distant recurrence and additional prognostic information beyond clinical variables. The BCI and ROR were the strongest predictors in this group. Only the CTS and EPclin provided significant prognostic information for distant recurrence in this timeframe for node-positive disease, although all signatures provided a small amount of useful additional prognostic information. EPclin was the strongest predictor and provided the most independent information beyond clinical variables in this group.

In the first 10 years, all commercial signatures provided good stratification of risk for node-negative disease and identified the majority of these patients as low risk (<10%) for distant recurrence. Only the ROR and EPclin provided good discrimination of risk in node-positive disease in this time period.

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[S6-05] Multigene expression profiles have been shown to add useful information regarding the prognosis of hormone-receptor positive breast cancer. Dr. Sestak’s presentation of the TransATAC study reviewed the results of a comprehensive comparison of the accuracy of six prognostic signatures in the prediction of late recurrence in node-negative disease and node-positive disease. This study included 818 postmenopausal women with estrogen-receptor positive, HER2-negative disease. The women were randomized to receive either tamoxifen or anastrozole for 5 years with no participants receiving chemotherapy as initial treatment. Median follow-up was 10 years. The six signatures investigated were the Breast Cancer Index (BCI), the Risk of Recurrence (ROR) score, the Oncotype Recurrence Score (RS), the EndoPredict (EPclin), Clinical Treatment Score (CTS), and four immunohistochemical stains (IHC4). The BCI, ROR, ENclin, and RS are commercial signatures validated by the investigators, and the CTS and IHC4 were developed by the investigators.

In the first 10 years, all commercial signatures provided good stratification of risk for node-negative disease and identified the majority of these patients as low risk (<10%) for distant recurrence. Only the ROR and EPclin provided good discrimination of risk in node-positive disease in this time period.
The data from years 5 to 10 showed that the prediction of distant recurrence was less clear. In node-negative disease, the BCI, ROR, and EPclin provided significant prognostic information for late distant recurrences, while the IHC4 and RS did not. The strongest independent predictor in this group was the ROR. In node-positive disease, only CTS and EPclin provided substantial prognostic information, although the ROR and EPclin provided a small amount of useful additional prognostic information in addition to clinical variables.

In years 5 to 10, only the ROR provided good discrimination of risk in node-negative disease, although all of the commercial signatures identified the majority of these patients as low risk for 10-year distant recurrence. The ROR and EPclin also identified a good proportion of women with node-positive disease who had low risk for 10-year distant recurrence. The BCI and RS did not provide clear risk stratification in this group.

The investigators concluded that the value of chemotherapy is limited in node-negative disease characterized as low risk of distant recurrence in the first 10 years by any of these signatures. The same is true of node-positive disease characterized as low risk for distant recurrence in the 5-year to 10-year timeframe by any of the signatures or in node-positive disease characterized as low risk for distant recurrence in this timeframe by ROR or EPclin.

The investigators concluded that the value of chemotherapy is limited in node-negative disease characterized as low risk of distant recurrence in the first 10 years by any of these signatures. The same is true of node-positive disease characterized as low risk for distant recurrence in the 5-year to 10-year timeframe by any of the signatures or in node-positive disease characterized as low risk for distant recurrence in this timeframe by ROR or EPclin.

**Conclusions**

- Unique cohort with well annotated samples, mature clinical outcome, and prognostic information for six signatures

**Prediction of recurrence in years 0-10**:

- **Node-negative**:
  - Good predictors and identify patients with a low DR risk → value of chemotherapy limited

- **Node-positive**:
  - ROR/EPclin identify patients with low DR risk → value of chemotherapy limited

**Conclusions II**

**Prediction of recurrence in years 5-10**:

- **Node-negative**:
  - BCI, ROR and EPclin good predictors for late DR (above and beyond CTS)
  - All signatures identify patients with low risk of late DR → extended endocrine therapy not justified

- **Node-positive**:
  - ROR/EPclin identify patients at low risk of late DR → extended endocrine therapy not justified

- **Limitation**:
  - CTS/IHC4 trained and ROR cut-off points estimated in transATAC

- Incorporation of certain clinical variables important

**GENOMICS**

[PD1-02] Dr. Rossi discussed a retrospective study of 91 patients with locally-advanced or metastatic breast cancer who underwent longitudinal assessment of their disease by circulating tumor-cell analysis. Serial samples were obtained from 65% of the patients. The most frequently altered genes were TP53, PI3K, and HER2. A statistically significant difference in progression-free survival was found between patients whose circulating tumor DNA at baseline was <0.5% and those whose circulating tumor DNA at baseline was ≥0.5%. Likewise, a statistically significant difference in overall survival was seen between patients who had <2 alterations at baseline and those who had ≥2 alterations at baseline. Additionally, higher percentages of circulating tumor DNA occurred in patients with higher number of alterations. The investigators concluded that liquid biopsy represents an effective tool in the management of patients with metastatic breast cancer. It can be used to assess tumor burden, to evaluate heterogeneity of the disease, and to predict patient outcome.

**3. Results**

- Patients: 91 total, 78 (94%) progressions, 36 (40%) deaths
  - Median PFS: 5.2 months
  - Median OS: 21.9 months
- **Genomic signatures**:
  - 27 (33) with alterations; 65% of the pts had serial samples
  - Average % cDNA: 4.5 (0.5-29.2)
  - Average number of alterations: 3.9 (1-7)
  - Altered genes: TP53 (21%), PIK3CA (7%), ERBB2 (20%)
- % cDNA ≥ 0.5 and number of alterations ≥ 2 are associated with a worse prognosis
- Higher values of % cDNA occur with higher number of alterations
- Alterations ≥ 2 and % cDNA ≥ 0.5 or alterations ≥ 2 and % cDNA ≥ 6.0% (p = 0.001)

**4. Conclusions**

- Quantitative and qualitative measurement of cDNA at baseline, along with the possibility of longitudinal monitoring, provides an invaluable tool in the management of patients with MBC

[PD1-03] Dr. Hoadley presented results from a correlative analysis of data from the CALGB 40603 (Alliance) trial; which was a neoadjuvant trial in women with triple negative breast cancer stage II-III. This trial had four treatment arms with patients randomized to paclitaxel, paclitaxel + bevacizumab, paclitaxel + carboplatin or paclitaxel + bevacizumab + carboplatin, all followed by dose dense Adriamycin and cyclophosphamide. All patients had a research biopsy prior to the start of neoadjuvant chemotherapy for RNA and DNA sequencing. The goal of this analysis was to develop models to predict pathological complete response.

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As previously reported, this cohort had a high rate of basal-like disease (88%). Benefit from carboplatin was experienced by all patients; however, benefit from bevacizumab was seen only in the basal-like subset. RNA sequencing data and analysis of pathological complete response were available for 389 patients. Gene-expression signatures were calculated for previously published signatures (≈500). Pathological complete response was predicted by 17 signatures, plus treatment with carboplatin and bevacizumab. Resistance was associated with six signatures. The ability to predict pathological complete response was moderate, with sensitivity 68% and specificity 64%.

Dr. Gonçalves presented the initial molecular results of the randomized phase II SAFIR 02 study, which is evaluating the feasibility of choosing individual treatment based on high throughput genomic analysis. This clinical trial design was based on the SAFIR01/UNICANCER study which showed a high number of patients (65%) harboring targetable molecular alterations. The SAFIR 02 study will enroll 1460 patients with HER 2 negative, endocrine resistant or triple negative metastatic breast cancer who are initiating first line chemotherapy. Patients undergo a biopsy of a metastatic site for next-generation sequencing and comparative genomic hybridization. At the end of a predetermined course of chemotherapy, patients with stable or responsive disease and a targetable molecular alteration are randomized to continue on the same chemotherapy as maintenance therapy or to switch to targeted therapy. The primary endpoint is progression free survival.

Early results from the 457 enrolled patients show that biopsy failure and failure of molecular analysis because of low cellularity occurred uncommonly (10% and 14%, respectively). Targetable genomic alterations were found in 67% patients, most in the PI3K-AKT-MTOR pathway. Unexpectedly, there was a higher rate of targetable molecular alterations in hormone-receptor positive, HER2-negative disease than in triple-negative disease. Additionally, a significant level of randomization failure has occurred, predominantly because of progressive disease during the chemotherapy induction phase.

Dr. Loi presented the results of a study that evaluated the ability of next-generation sequencing of tumor DNA to offer prognostic and predictive information for breast cancer in postmenopausal women. Archival tumor DNA was obtained from estrogen-receptor positive and HER2-negative tumors from 538 women who received either letrozole or tamoxifen as part of the BIG 1-98 trial. Sequencing of the DNA showed 19 genes with >5% frequency. Mutation of phosphoinositide 3-kinase (PI3K) was the most common somatic alteration, and was seen in 49% of the population. Mutation of p53 and amplification of cyclin D1 also were common. Mutation of PI3K was significantly mutually exclusive, with mutations of AKT1 and PTEN, and with a number of gene amplifications. In contrast, gene amplifications commonly occurred together. Mutations of p53 commonly occurred with gene amplifications, which suggests that these drive genomic instability. Mutations of CDH1 and PTEN were significantly associated with larger size of tumor. Mutations of PI3K and mitogen-activated protein kinase 3 were significantly associated with lower Ki67 levels, suggesting that these mutations drive the luminal-A phenotype. Mutation of p53 and amplification of cyclin D1, fibroblast growth factor receptor 1, and MYC were associated with high levels of Ki67, suggesting that these alterations drive the luminal-B phenotype.

Univariate analysis showed that mutation of PI3K was significantly associated with lower rates of distant recurrence. Higher rates of distant recurrence, however, were significantly associated with mutation of p53, amplification of 11q13, amplification of 8p11, and increasing number of total alterations.

Amplification of 11q13, amplification of 8p11, and total number of alterations were again significantly associated with higher rates of distant recurrence, with multivariate analysis that adjusted for age, tumor size, tumor grade, and nodal status. Poorer rates of survival were seen in patients with amplification of 11q13 and 8p11.
The majority of PI3K mutations (76%) coexist with other driver alterations, most commonly amplification of 11q13, and the coexistence of alterations was shown to influence the PI3K phenotype. Patients with mutation of PI3K without amplification of 11q13 had a 5-year distant-recurrence-free survival rate of 96%. However, in those with amplification of 11q13, the 5-year distant-recurrence-free survival rate decreased to 85%.

Patients with mutation of PI3K had a 5-year distant-recurrence-free survival rate of 98% when treated with letrozole monotherapy. Patients with PI3K mutation without amplification of 11q13 had a 5-year distant-recurrence-free survival rate of 99%. This suggests that use of the genotype of PI3K and status of 11q amplification can identify patients who may derive a greater benefit from letrozole monotherapy.

Genomic data was obtained from patients with breast cancer of 38,326 Caucasian women. The tumors were tested with panels that evaluated 21 known and candidate breast-cancer predisposition genes, excluding BRCA. The control population was taken from the Exome Aggregation Consortium.

The frequency of pathogenic mutations was 6%. The most common pathogenic mutations were ATM, CHEK2, and PALB2. Comparison of the patient population and the control population showed that ATM and CHEK2 were associated with moderate risk and PALB2 was associated with high risk. BRIP1, now recognized as an ovarian cancer gene, was found to be a low-risk or no-risk breast cancer gene. The data established BARD1 and RAD51D as moderate-risk genes. MSH6 was found to be nearing clinical relevancy as a predictor of breast cancer and will require more studies. Genes found by this study not to predict breast cancer include MRE11A, NBN, RAD50, and RAD51C (ovarian cancer gene).

Syndromic breast cancer genes, p52 and CDH1, were confirmed to be associated with increased risk for breast cancer.

The study confirmed that PALB2 is a high-risk gene and verified that MRI should be considered or recommended in patients with ATM, CHEK2, or PALB2. The data support the consideration of risk-reducing mastectomy in patients with ATM or PALB2. Based on the findings of this study, consideration of MRI might be given to women with BARD1, RAD51, or MSH6.

**Associations of pathogenic variants with breast cancer**

**Caucasian Cases vs. ExAC NFE-non-TCGA**

<table>
<thead>
<tr>
<th>Gene</th>
<th>CaseAC</th>
<th>CaseAN</th>
<th>ControlAC</th>
<th>ControlAN</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
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<tr>
<td>ATM</td>
<td>15</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>1.5</td>
<td>0.84-2.76</td>
<td>0.15</td>
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<tr>
<td>CHEK2</td>
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<td>15</td>
<td>5</td>
<td>10</td>
<td>2.0</td>
<td>1.1-3.77</td>
<td>0.02</td>
</tr>
<tr>
<td>PALB2</td>
<td>12</td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>2.4</td>
<td>1.4-4.42</td>
<td>0.002</td>
</tr>
<tr>
<td>MRE11A</td>
<td>8</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>0.8</td>
<td>0.4-1.82</td>
<td>0.65</td>
</tr>
<tr>
<td>NBN</td>
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<td>10</td>
<td>5</td>
<td>10</td>
<td>0.8</td>
<td>0.4-1.82</td>
<td>0.65</td>
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<tr>
<td>RAD50</td>
<td>12</td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>2.4</td>
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<tr>
<td>RAD51C</td>
<td>12</td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>2.4</td>
<td>1.4-4.42</td>
<td>0.002</td>
</tr>
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</table>

Dr. Tanioka presented the integrated analysis of multidimensional genomic data from the CALGB 40601 trial, which was a randomized neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib in women with HER2-positive breast cancer. This part of the study integrates RNA data and DNA data to predict pathological complete response rates. Pretreatment research biopsy was utilized for RNA sequencing and DNA exome sequencing. Assessments of both RNA and DNA were performed on 161 patients treated with trastuzumab and paclitaxel with the goal to discover a biologic basis for responsiveness to trastuzumab-based regimens.

Analysis was performed to identify functional genetic drivers using both DNA and RNA expression data. Genes at chromosome 6p, predominantly amplifications, were ranked high in samples that had undergone pathological complete response and low in those that had not, indicating that these tumors had increased sensitivity to this treatment regimen. Genes at 22q or 11q, predominantly deletions, were ranked high in samples that had undergone non-pathological complete response and low in samples that had not, indicating these tumors had increased resistance to this treatment regimen.

Amplification of HER2 was seen in both pathological complete responses and non-pathological complete responses. Gain of 6p was seen in samples that had undergone pathological complete response, indicating these tumors had increased sensitivity to this treatment regimen. Loss
of 11q and 22q was seen in samples that had not undergone pathological complete response, indicating these tumors had increased resistance to this treatment regimen.

Computational analysis found 15 overlap genes, but a correlation between copy number and RNA gene expression values was found only with MAPK14 at 6p and CBL at 11q. The investigators hypothesized that MAPK14 leads to apoptosis of cancer cells with anti-HER2 therapy. Further, they hypothesized that deletion of CBL leads to HER2 persistence with anti-HER2 therapy.

Gene expression signatures and changes in DNA copy number were the features found to be most predictive of pathological complete response. The tumor subtype, tumor genetics, and microenvironment each were independent predictors of response.

**Take Home Messages**

- **Axillary nodes initially involved before NAC**
  - After NAC
    - risk of a false negative rate > 20%, not controllable
    - Clinical risk of a FN case after NAC remains unknown
    - SLNB is not proved to be a safe procedure outside trials
While the benefits of both radiation therapy for nodal disease and reconstruction after mastectomy have been established, there are limited data regarding the integration of the two. Results of a prospective study presented by Dr. Jagsi have added to these limited data. This study compared the rate of complications and patient satisfaction experienced by 2014 women who had undergone reconstruction, 553 of whom also received radiation therapy.

In 2 years of follow-up, more patients in the radiation group (one-third) experienced at least one complication (e.g., wound infection, hematoma) than in the no-radiation group (one-quarter). The highest rate of complications was experienced by women who received radiation therapy and implant reconstruction (39%), compared to women who received radiation therapy and autologous reconstruction (26%), and women who did not receive radiation therapy (implant reconstruction 22%, autologous reconstruction 28%).

Multivariate analysis showed that treatment of both breasts and a higher body-mass index were predictors of complications. Additionally, the odds of a complication occurring by 2 years in women who received radiation therapy was increased by 2.64 times in women who received implants, yet no significant difference was seen in women who underwent autologous reconstruction. Failure of reconstruction by 2 years occurred more frequently in the radiation-therapy group (11.4%) than in the no-radiation-therapy group (3.4%).

Questionnaires that evaluated patient-reported outcomes showed that patients who received radiation therapy plus implant reconstruction had significantly lower satisfaction with their breasts. Similar patterns of satisfaction were seen when patients were questioned about treatment outcome, psychosocial well-being, and physical well-being.

The investigators concluded that radiation therapy appears to compromise the outcomes of implant reconstruction. In women who receive radiation therapy, autologous reconstruction appears to result in superior patient-reported outcomes and a lower risk for complication than reconstruction with implants.

**Reconstruction Failure**

- By two years, reconstructive failure occurred in 11.4% of radiated pts and 3.4% of non-radiated pts

**[S3-08] Dr. Langhans presented data from a randomized, controlled trial that compared wire-guided localization of non-palpable breast lesions to localization by placement of a seed of titanium with 125Iodine. The data are from 378 patients with non-palpable invasive breast cancer or DCIS, visible on ultrasonography.**

No significant difference in the number of positive margins was seen between the seed group (23) and the wire-guided group (26). Likewise, no significant difference in the number of positive margins was detected in a subanalysis of patients with invasive cancer. Both groups had similar amounts of tissue removed and similar durations of procedures. No difference was detected in pain perception between the groups, regardless of the use of local anesthesia. Complication rates were similar between the groups, as were the identification rates of sentinel lymph nodes. All seeds were identified by the pathologist, and the seeds did not increase the difficulty of microscopic examination. The major advantage of radioactive-seed localization is the flexibility it permits as the long half-life of 125Iodine allows placement of the seed several days before surgery.

The results of this trial support results from previous trials. Dr. Langhans questions whether the evidence is now sufficient to consider radioactive-seed localization the standard for localization of non-palpable breast lesions.

**Margin status**

<table>
<thead>
<tr>
<th></th>
<th>RSL (%)</th>
<th>WSL (%)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Intention-to-treat</td>
<td></td>
<td></td>
<td>0.66</td>
<td>1.15 (0.83-2.10)</td>
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<td>172 (55.2%)</td>
<td>169 (55.7%)</td>
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</tr>
<tr>
<td>Positive</td>
<td>25 (11.8%)</td>
<td>26 (13.3%)</td>
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<td></td>
</tr>
<tr>
<td>Per-protocol</td>
<td></td>
<td></td>
<td>0.62</td>
<td>1.17 (0.84-2.14)</td>
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<td>164 (50.2%)</td>
<td>164 (50.5%)</td>
<td></td>
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<tr>
<td>Positive</td>
<td>22 (11.8%)</td>
<td>26 (13.5%)</td>
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<tr>
<td>DCIS</td>
<td></td>
<td></td>
<td>0.997</td>
<td>1.0 (0.52-1.99)</td>
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<td>Negative</td>
<td>172 (55.2%)</td>
<td>164 (50.5%)</td>
<td></td>
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<tr>
<td>Positive</td>
<td>22 (11.3%)</td>
<td>26 (13.4%)</td>
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The imaging of breast cancer is continuing to evolve. Here we highlight three presentations that discussed very different aspects of imaging: the use of a probe for intraoperative visualization of tumor, the importance of later PET imaging for prediction of response to treatment and prognosis, and methods for optimal measurement of functional tumor volume.

**[PD3-02]** Dr. Unkart discussed a phase I trial that investigated the use of a probe that allows intraoperative visualization of a tumor. Twenty-seven patients in five different dose cohorts received intravenous AVB-620 between 2 and 24 hours prior to surgery. In patients with invasive tumors, the probe was cleaved by upregulated proteases in the tumors resulting in increased intensity of the dye Cy5 and decreased intensity of the dye Cy7. These intensity changes were more apparent in patients who received higher doses of AVB-620. Fluorescence-intensity signals of the dyes were measured, and software calculated an intensity ratio within 1 sec. This ratio was used to determine whether the surgical margin was positive for a resected tumor. Ongoing research is determining the appropriate threshold of the intensity ratio. No adverse events were experienced by the study participants. The utility of AVD-620 in ductal carcinoma in situ (DCIS) has not yet been determined.

**[PD3-03]** Dr. Muñoz-Sanchez discussed the results of a prospective, multicenter study of 132 patients with newly-diagnosed locally-advanced breast cancer. The study investigated the efficacy of positron emission tomography/computed tomography (PET/CT) as a predictor of response to neoadjuvant chemotherapy (NAC) and as a predictor of prognosis. All patients underwent PET/CT at baseline (PET-1), after a second cycle of NAC (PET-2), and after the last cycle of NAC (PET-3). The median follow-up was 32 months. The results of PET-3 were found to be a significant predictor of the response seen in tumors in both breast and lymph nodes and for patient prognosis. Binary analysis showed that only PET-3 was able to predict pathological response in lymph nodes. Sensitivity and specificity of prediction of response was best when a cutoff value of 62% was used for the difference between the standardized uptake value (SUV) 1 and SUV2, and a cut-off value of 84% was used for the difference between SUV1 and SUV3. A difference of at least 70% between SUV1 and SUV3 was a predictor of disease-free survival. Binary lymph node assessment of PET-3 was related to overall survival and disease-free survival. While differences in SUV were not related to DFS or overall survival of low-risk breast cancer, ie, luminal A subtype, differences in SUV were related to disease-free survival and overall survival in high-risk breast cancer, ie, triple-negative and HER2-positive subtypes. Previous literature has used results of early PET, ie, after a second or third cycle of NAC, to decide whether a patient is responding; however, this current study suggests that results of PET-2 are not the ideal predictor of response.

**[PD3-05]** Dr. Li discussed the effect of MR imaging contrast kinetic thresholds for prediction of neoadjuvant chemotherapy response in breast cancer subtypes using data from the ACRIN 6657 and I-SPY 1 clinical trials. The focus of this study was to determine if adjusting the enhancement thresholds for different breast cancer subtypes improved the ability of functional tumor volume (FTV) to predict pathologic response to neoadjuvant therapy. Data were available from 116 patients undergoing NAC. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was used to measure functional tumor volume. A range of thresholds was set to assess the optimal threshold parameters of the DCE-MRI. Thresholds for enhancement percentage were set from...
Conclusion

The FTV prediction of pCR was affected by varying the contrast kinetic thresholds and the effect was observed to be different among breast cancer subtypes.

- This study is limited by small sample size (n=116)
- Results are specific to the DCE-MRI image acquisition technique used in the ACRIN 6657 study
- Cross-validation and prospective studies are needed to test the optimized thresholds

SYSTEMIC THERAPIES

[S6-03] Dr. Ejlertsen presented the 5-year data from the DBCG 07-READ trial of 2012 patients with early, invasive breast cancer. These cancers were considered high risk (eg, node positive, young age, high grade) and determined by fluorescent in-situ hybridization to have normal TOP2A status. Patients were randomized to receive either three cycles of epirubicin plus cyclophosphamide followed by three cycles of docetaxel vs six cycles of docetaxel plus cyclophosphamide.

There was no difference in disease-free survival or overall survival seen between the two treatment groups. Subgroup analysis, however, showed that patients with grade-3 tumors in the group that received docetaxel plus cyclophosphamide had a 30% reduction in risk for recurrence. In contrast, patients with grade-1 and grade-2 tumors who received epirubicin, cyclophosphamide, and docetaxel had significantly better disease-free survival and overall survival. Superior disease-free survival was demonstrated in premenopausal patients treated with doxorubicin plus cyclophosphamide, whereas superior disease-free survival was seen in postmenopausal patients treated with epirubicin, cyclophosphamide, and docetaxel.

The group receiving epirubicin, cyclophosphamide, and docetaxel reported a higher frequency of grade-3 and grade-4 adverse events, ie, mucositis, myalgia, peripheral neuropathy, vomiting, nausea, fatigue, and peripheral edema.

[51-02] Dr. Kornblum discussed the PrECOG 0102 trial that investigated the addition of everolimus to fulvestrant in the treatment of breast cancer resistant to therapy with aromatase inhibitors. This trial included 131 postmenopausal women with hormone receptor positive and HER2 negative breast cancer. Patients were randomized to receive fulvestrant with either everolimus or placebo. A continuation phase after 12 cycles of treatment allowed patients without progression of disease or unacceptable toxicity to continue on fulvestrant therapy.

The combination of fulvestrant and everolimus was associated with more toxicity than fulvestrant with placebo, including a higher rate of grade-3 adverse events (48% vs 14%). The most commonly occurring adverse events were stomatitis, pneumonitis, fatigue, hyperglycemia, and anemia. Although corticosteroid mouthwash was not used in this study, it has been shown to reduce the risk for grade-1 and grade-2 stomatitis (65% vs 25%).

The addition of everolimus was associated with an increase in median progression-free survival from 5.1 months to 10.4 months. Median overall survival was not different between the groups at median follow up of 25 months. Data regarding the implications of body-mass index on treatment outcomes are not yet available and will be reported at a later date. The authors concluded that the addition of everolimus to anti-estrogen therapy in AI resistant breast cancer can improve clinical outcomes.

[51-02] Dr. Ejlertsen presented the 5-year data from the DBCG 07-READ trial of 2012 patients with early, invasive breast cancer. These cancers were considered high risk (eg, node positive, young age, high grade) and determined by fluorescent in-situ hybridization to have normal TOP2A status. Patients were randomized to receive either three cycles of epirubicin plus cyclophosphamide followed by three cycles of docetaxel vs six cycles of docetaxel plus cyclophosphamide.

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The group receiving epirubicin, cyclophosphamide, and docetaxel reported a higher frequency of grade-3 and grade-4 adverse events, ie, mucositis, myalgia, peripheral neuropathy, vomiting, nausea, fatigue, and peripheral edema.
[S1-03] Dr. Tjan-Heijnen presented the first results of the Dutch phase III DATA trial of 1912 postmenopausal women. This trial randomized patients with non-metastatic hormone receptor positive breast cancer to receive anastrozole for either 3 years or 6 years after completing 2 to 3 years of adjuvant tamoxifen therapy. The primary endpoint of the study was adapted disease free survival (aDFS) which was defined as DFS as of three years after randomization. DFS analysis included local or distant breast cancer recurrence, secondary non-invasive breast cancer, contralateral breast cancer, and all-cause mortality. Secondary endpoints included adapted overall survival and adverse events.

There was no significant difference in the adapted disease-free survival between the treatment groups (83.1% in the 6 year group and 79.4% in the 3 year group). However, subgroup analysis of tumor size, nodal status, receptor status and prior chemotherapy reveal groups of patients that may benefit from extended endocrine therapy. Patients with tumor sizes greater than 2cm, positive axillary lymph nodes, both estrogen and progesterone receptor positive and Her2 negative all favored 6 years of endocrine therapy. Patients who received chemotherapy as part of their breast cancer treatment also benefited from longer duration of endocrine therapy. An unplanned analysis of patients that exhibited all of these parameters (T2 tumors, ER and PR positive, HER2 negative, positive lymph node involvement and prior chemotherapy) showed a 10% difference in aDFS between the two treatment arms in favor of 6 years of hormonal therapy. There was no difference in the secondary endpoint of aOS between the two groups (90.8 in the 6 year group and 90.4 in the 3 year group) with median follow up of only 4.1 years.

Reports of adverse events were slightly more common in the 6-year group. Moreover, more patients terminated treatment early because of adverse events in this group. This was an intent to treat analysis and data from patients that stopped therapy earlier were included in the final analysis.

The investigators plan to perform multivariate analyses and interaction analyses to help validate the data from the subgroups.

[S1-04] Dr. Blok presented the results of the phase III, IDEAL trial. This trial investigated 1824 postmenopausal women with hormone receptor positive breast cancer who had completed 5 years of adjuvant hormone therapy. Patients were randomized to receive extended therapy with letrozole for either 2.5 years or 5 years. The median follow-up was 6.5 years.

No difference was detected between the groups in terms of disease-free survival (~88% in both groups) or overall survival (~93% in both groups).
Likewise, a pre-planned subgroup analysis did not show improved disease-free survival in the group with longer extended treatment. There also was no significant difference in the distant-metastasis-free interval between the groups. There was, however, a small absolute risk reduction (1%) of second primary breast cancers detected at 5 years in the patients who received 5 years of extended treatment.

The authors concluded that patients gain no benefit from adjuvant aromatase inhibitor therapy beyond 2.5 years.

**Results - DFS**

Looking at the secondary end point of cumulative incidence of breast cancer free interval, the letrozole group had a statistically significant reduction compared to the placebo group (6.7% vs 10.0%). Cumulative incidence of distant recurrence was also lower in the letrozole group with a 28% reduction. Letrozole was associated with a lower 7-year cumulative incidence of distant recurrence (3.9% vs 5.8%), although this benefit did not occur until after 4.1 years of treatment.

Dr. Mamounas presented the results of the NSABP B-42 trial which was a randomized placebo controlled clinical trial of extended adjuvant endocrine therapy with letrozole in postmenopausal women with hormone receptor positive breast cancer who had completed previous adjuvant treatment with an aromatase inhibitor. The aim of this trial was to determine if five years of letrozole compared to placebo improved disease free survival (DFS) in patients who had already completed five years of hormonal therapy with either an aromatase inhibitor or tamoxifen.

Patients were eligible for the trial if they had estrogen and/or progesterone receptor positive stage I-IIa invasive breast cancer and were disease free after five years of endocrine therapy. Patients were randomized to receive 5 years of treatment with either letrozole or placebo. The primary endpoint was DFS as defined by local, regional, distant recurrence, contralateral breast cancer and all-cause mortality. Secondary endpoints included overall survival, breast cancer free interval, osteoporotic fractures and arterial thrombotic events.

Results include data from 3923 patients over a median follow-up of 6.9 months. There was no significant difference in 7-year disease-free survival detected between the groups (letrozole 84.7%, placebo 81.3%). A subgroup analysis based on nodal status, prior tamoxifen treatment, bone density, and age less than or older than 60 years was completed and showed no difference in DFS between the treatment and control groups. When analyzing the individual components of DFS, most of the benefit came from reduction in distant recurrence with 4.4% distant recurrence in the placebo group vs. 3.1 in the treatment group. There was also a difference in second primary breast cancers (30 in the treatment group vs 59 in the placebo group).

**[S1-05]** Dr. Mamounas presented the results of the NSABP B-42 trial which was a randomized placebo controlled clinical trial of extended adjuvant endocrine therapy with letrozole in postmenopausal women with hormone receptor positive breast cancer who had completed previous adjuvant treatment with an aromatase inhibitor. The aim of this trial was to determine if five years of letrozole compared to placebo improved disease free survival (DFS) in patients who had already completed five years of hormonal therapy with either an aromatase inhibitor or tamoxifen.

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No significant difference between the groups was seen in overall survival or osteoporotic fractures. While the cumulative incidence of arterial thrombotic events was not different between the groups, non-proportionality of hazards for arterial thrombotic events showed that patients received a benefit from <2.5 years of treatment with letrozole and a detriment with >2.5 years of treatment.

Clinical and pre-clinical studies have shown that mTORC1 inhibition can promote AKT phosphorylation via activation of a feedback pathway, and that phosphorylation of AKT may contribute to mTOR inhibitor resistance. PIK3 inhibitors may attenuate this phosphorylation of AKT, and in so doing, demonstrate a clinical benefit in patients who have progressed on an mTOR inhibitor. This was the scientific basis for the BELLE3 trial presented by Dr. Di Leo. BELLE-3 is a phase III randomized study of buparlisib and fulvestrant in hormonal receptor positive, HER2 negative locally advanced or metastatic postmenopausal women who were previously treated with an aromatase inhibitor and who have progressed after an mTOR inhibitor therapy. Patients (n=432) were randomized to receive either fulvestrant plus buparlisib or fulvestrant plus placebo. The primary endpoint was progression free survival (PFS) and secondary endpoints included overall survival (OS), PFS and OS by PIK3CA status, overall response rate and safety.

Most patients (≈90%) had discontinued treatment at the time of data cutoff. Patients who received buparlisib had an increased rate of dose interruptions, dose reductions, and discontinuation of treatment because...
of adverse events. Both groups had two deaths suspected to be related to study treatment.

The buparlisib arm had a longer progression-free survival (3.9 months vs 1.8 months) and the objective response rate was higher in the buparlisib arm. Subgroup analysis showed that combination treatment was associated with a higher progression-free survival in all the subgroups evaluated. Patients with mutation of PIK3CA, detected in the primary tumor or in circulating tumor DNA, had superior progression-free survival. Most of the benefit from the combination therapy was seen in patients who had visceral disease at the beginning of the study. No correlation was found between PIK3CA status and visceral disease status.

Grade-3 or grade-4 elevation of transaminases was seen in 20% of the combination group. Mood disorders were experienced by 20% of the combination group, including three suicide attempts.

The authors concluded that the addition of buparlisib to fulvestrant improved progression-free survival in this population. Patients with mutations of PIK3CA or visceral disease appeared to receive the most benefit from the combination. Concerns with toxicity, however, may pose a challenge to this combination.

At the time of this analysis, the median follow-up was 4.6 years. There was no statistical difference in disease free survival between the two groups (94.3% in the ibandronate group vs 90.8%). In regards to time to bone metastases as the first event, the ibandronate group was 1.2% vs 3.1% in the hormonal therapy alone group. This difference was not statistically significant.

Upper gastrointestinal events were the most common adverse events seen in the ibandronate group. Most adverse events were mild; however, the adherence to ibandronate was 67%. Osteonecrosis of the jaw occurred in four patients (0.7%) in the ibandronate arm. Monitoring of renal function during treatment with ibandronate showed that creatinine levels remained stable, although five patients (0.9%) discontinued treatment because of increased creatinine, and two patients developed renal failure (most likely not related to ibandronate).

The authors concluded that a non-statistically significant trend toward benefit was seen with the addition of ibandronate to adjuvant endocrine therapy in this population of patients. While ibandronate appears safe, 20% of patients discontinued treatment because of side effects. Dr. Vliek questioned whether the analysis was performed too early and whether the study was underpowered due to necessary protocol changes made secondary to slow accrual.

**FIRST RESULTS**

**TIME TO BONE METASTASES AS FIRST EVENT**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
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<th>HR (CI)</th>
</tr>
</thead>
<tbody>
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<td>6</td>
<td>1.2%</td>
<td>0.59 (0.30-1.14)</td>
</tr>
<tr>
<td>HTx only</td>
<td>15</td>
<td>3.1%</td>
<td></td>
</tr>
</tbody>
</table>
HER 2 POSITIVE

[S3-03] Dr. Prat presented the first results of the PAMELA trial that evaluated the use of intrinsic subtypes to predict pathological response with dual-HER2 blockade in the absence of chemotherapy. Given that HER2 positive breast cancer is both clinically and biologically diverse, the investigators sought to evaluate the ability of HER2 enriched subtype to predict pathological complete response with dual HER2 blockade and to explore the association of baseline subtype with rate of pathological complete response. The PAM50 index was used to classify tumors at baseline into five subtypes: Luminal A, Luminal B, HER2 Enriched, Basal-like and Normal-like.

This phase II trial included 151 patients with stage I-IIIa breast cancer, centrally confirmed HER2 positive, and tumor size 1 cm or greater. The patients received neoadjuvant trastuzumab plus lapatinib, and endocrine therapy based on their menopausal status. Intrinsic subtyping with the PAM50 assay was performed at baseline and after week two of treatment with a repeat breast biopsy.

The most common intrinsic subtype at baseline was HER2 enriched (66.9%), followed by luminal A (14.6%), luminal B (10.6%), basal (5.9%), and normal (2%). Nearly half of the tumors positive for hormone receptors were also HER2 enriched (49.3%). The intrinsic subtype was determined at baseline and then compared to the subtype of the same tumor after two weeks of treatment. Interestingly, there was an increase in the percentage of normal-like subtypes (2.1% vs 48.6%) and luminal A subtypes (15.3% vs 25%). Also observed was a decrease in the percentage of HER2-enriched subtypes (66.7% vs 18%) and luminal B subtypes (10.4% vs 2.8%). The percentage of basal-like subtype was unchanged (5.6%).

The rate of pathological complete response in the breast was higher in the HER2-enriched subtype than in the non-HER2-enriched subtype (40.6% vs 10.0%). Similarly, the rate of pathological complete response in both breast and axilla was higher in the HER2-enriched subtype (34.7% vs 10.0%). In the non-HER2-enriched subtype, pathological complete response rate in the breast was highest in normal-like disease (66.7%), followed by the luminal B group (12.5%), the basal-like group (11.1%), and the luminal A group (0.0%). The rate of pathological complete response in the breast was higher in disease negative for hormone receptors than in disease positive for hormone receptors (43.2% vs 18.2%). Univariate analysis showed that status of hormone receptors and intrinsic subtype were significantly associated with pathological complete response.

More tumors with normal-like subtype at week two achieved pathological complete response than those with non-normal subtype at week two (48.6% vs 13.5%). Mean tumor cellularity of the normal-like subtype at week two was also lower than non-normal (7.1% vs 37.0%).

The authors concluded the HER2-enriched subtype is a strong predictor of sensitivity to dual blockade of HER2 in breast cancer positive for HER2 in the absence of chemotherapy. Determination of intrinsic subtype at baseline and week two can potentially aid in identifying patients who will achieve a pathological complete response. The authors of this study concluded that studies evaluating the long-term survival outcomes of chemotherapy-free dual HER2 blockade are justified after selecting patients based on variables such as intrinsic subtyping. Further validation of these findings is ongoing.

Intrinsic subtype at week 2 vs. pCR in the breast

Week 2 samples (N=144)

[S3-04] Dr. Arpino presented results from the primary analysis of the phase II PERTAIN trial. This study assessed the efficacy and safety of the addition of pertuzumab to trastuzumab plus an aromatase inhibitor in 258 postmenopausal women with advanced hormone receptor and Her2 positive breast cancer. Patients were randomized to receive either the combination of pertuzumab, trastuzumab, and an aromatase inhibitor or trastuzumab plus an aromatase inhibitor. Induction chemotherapy with doctaxel or paclitaxel was received by ≈55% of patients and was given at the discretion of their treating physicians. The decision to give chemotherapy had to be made prior to randomization.

The primary endpoint of this clinical trial was progression-free survival and was reported with a median of 31 months of follow up. Progression free survival was significantly longer in the pertuzumab arm than in the control arm (18.9 months vs 15.8 months). Subgroup analysis showed that this advantage was present also in patients who did not receive induction chemotherapy (21.72 months vs 12.45 months). Of the patients who had measureable disease at baseline (109 in pertuzumab arm; 106 in control arm), there was a non-significantly higher overall response rate in the pertuzumab arm (63.3% vs 55.7%). Unstratified analysis showed a longer duration of response in the pertuzumab arm (27.1 months vs 15.1 months).

In regards to toxicity, the pertuzumab arm had a higher incidence of grade-3 and grade-4 adverse events with diarrhea being the most frequent and severe side effect in patients receiving pertuzumab. Adverse events caused the discontinuation of pertuzumab in 10.2% and the interruption of pertuzumab in 26.8%. The incidence of all adverse events, except
alopecia, was higher in the pertuzumab arm. Left-ventricular ejection fraction remained >45% in ≈ 90% of patients in the study. The authors concluded combination treatment with pertuzumab, trastuzumab, and an aromatase inhibitor was superior to trastuzumab plus aromatase inhibitor in this subset of patients. The trend toward improved overall response rate and duration of response with pertuzumab support the primary progression-free survival analysis.

**Primary Progression-Free Survival Analysis (Stratified, ITT Population)**

![Graph showing survival analysis](image)

**[S3-06]** Dr. Rimawi presented the primary analysis of the NSABP B-52 trial which evaluated the addition of hormonal therapy to standard of care neoadjuvant therapy in patients with at least stage 2 hormone receptor and HER2 positive breast cancer. This study randomized 315 patients with breast cancer positive for estrogen and/or progesterone receptors, and positive for HER2, to receive combination docetaxel, carboplatin, trastuzumab, and pertuzumab or this combination plus hormonal therapy. Postmenopausal patients received estrogen deprivation with an aromatase inhibitor, and premenopausal patients were treated with ovarian suppression plus an aromatase inhibitor. The primary outcome was pathologic complete response in the breast and lymph nodes and secondary endpoints were pathologic complete response in the breast and safety and tolerability. Recurrence-free interval and overall survival will also be reported once this data matures.

Toxicity was similar in both groups and consistent with the expected toxicities of the TCHP regimen. Diarrhea, nausea, vomiting, dehydration, anemia, and hypokalemia were common, and occurred with similar frequency in both arms. Febrile neutropenia occurred in ~6% of the control arm and 8% of the estrogen-deprivation arm. However, rates of completion of treatment were high in both arms (TCHP ~90%; aromatase inhibitor ~80%; ovarian suppression 90%). The addition of hormonal suppression did not appear to increase toxicities.

This study found no statistical difference in the rate of pathological complete response in the breast and axilla in the estrogen-deprivation arm vs. the standard of care arm (46% vs 41%). This finding persisted when the groups were analyzed by menopausal status. There was no statistical change in pathological complete response rates in premenopausal women in the estrogen-deprivation arm (46% vs 44%) and in postmenopausal women in the estrogen-deprivation arm (45% vs 38%). In regards to the secondary endpoint of pathologic complete response in the breast alone, there was no statistically significant difference between the endocrine deprivation group compared to the standard of care group with a rate of response of 47% vs 44% respectively.

The authors concluded that the addition of estrogen deprivation to neoadjuvant chemotherapy and anti-HER2 therapy was not antagonistic and did not increase toxicity. There was no statistically significant increase in pathological complete response rates with the addition of endocrine deprivation to standard of care neoadjuvant therapy in hormone receptor positive and HER2 positive breast cancer. This study collected tumor samples from baseline, 2 weeks after the start of treatment, and at the time of surgical resection. Molecular analysis of these tumor samples may elucidate a patient population that could potentially benefit from the addition of endocrine therapy.

**MECHANISMS OF RESISTANCE**

**[S4-02]** Dr. Fuqua discussed the role of mutations of Y537S ESR1 in the transcription of genes, growth of metastatic breast cancer, and hormone resistance. These mutations are acquired during the treatment of metastatic breast cancer with aromatase inhibitors, and are present in 20% to 40% of metastatic breast cancer. Metastatic breast cancers with mutation of ESR1 have been treated effectively with fulvestrant; however, monotherapy with aromatase inhibitors may be counter-indicated.

Their research group used CRISPR technology to create a complete knock-in Y537S ESR1 mutation cell line which had constitutively high transcription of estrogen receptor, and constitutive activation of genes that are classically regulated by estrogen (ie, progesterone receptor, c-MYC, and cyclin D1). Growth assays performed in these cells were resistant to tamoxifen and responsive to fulvestrant. In addition, there was pronounced synergy to fulvestrant when combined with either everolimus (mTOR inhibitor), palbociclib (CD4/6 inhibitor), or pictilisib (PI3K inhibitor). No synergy, however, was seen with fulvestrant plus trametinib (MEK inhibitor). Complete knock-in cells also were noted to induce epithelial-to-mesenchymal transition that allows epithelial cells to gain migratory and invasive properties. Tamoxifen inhibited this transition in both wild-type and mutant cells.
Based on the above work, a mouse preclinical study was performed in wildtype and knock-in Y537S ESR1 mutant cells. Animal studies showed that tamoxifen was effective in the halving of primary tumors with wild-type cells, and the wild-type cells were sensitive to withdrawal of estrogen; however, tumors with mutant cells continued to grow in the estrogen-control arm, the estrogen-withdrawal arm, and the arm with tamoxifen plus withdrawal of estrogen. The frequency of macro-metastases was similar in the wild-type estrogen-control arm and the mutant estrogen-control arm. Mutant cells in the estrogen-withdrawal arm had an increased frequency of macro-metastases; however, macro-metastases were inhibited by tamoxifen. Tamoxifen also blocked micro-metastases to lung in tumors with mutant ESR1. Distant macro-metastases maintained the epithelial-to-mesenchymal transition phenotype.

Mixing experiments showed that primary tumor growth, the frequency of macro-metastases, and the frequency of micro-metastases to lung increase with increases in the proportion of mutant cells. Additionally, mutant cells became the dominant cell type.

Disease-free survival of tumors positive for estrogen receptors could be predicted with a signature of mutant cells. This signature also was predictive of metastases to lung, but not to bone or brain.

The authors concluded that ESR1 mutations are a mechanism of acquired hormone resistance that enhances tumor progression and metastatic behavior. Dr. Fuqua stressed the critical need for agents that block epithelial-to-mesenchymal transition as a potential method to decrease development of metastasis.

**Synergistic Response with Fulvestrant + Targeted Agents**

MetaSite scores were significantly lower in tumors that were positive for hormone receptors and negative for HER2. Also in this group, the distant-recurrence-free interval was associated with MetaSite scores during years 0 to 5, but not years 5 to 10. A significant association was seen between MetaSite score and distant and overall recurrences.

Poor correlation was found between MetaSite score and Recurrence Score (RS). Comparison of the two scores, however, showed higher risk for distant recurrence in patients with RS <18 (classical cutpoints) who had upper-tertile MetaSite scores (>10-fold increase) and mid-tertile MetaSite scores (>5-fold increase). Patients with RS 11 to 25 (TAILORx cutpoints) had higher risk for distant recurrence with upper-tertile MetaSite scores (>4-fold increase) and mid-tertile MetaSite scores (2-fold increase). MetaSite score and clinicopathological covariates (ie, nodal status, tumor size, grade) were significantly associated with recurrence.

The authors concluded that MetaSite score provides prognostic information for early recurrence in hormone receptor positive, Her2 negative breast cancer. This prognostic information is independent of tumor size, grade, nodal status, and RS. The score complements the prognostic information obtained in low- to mid-range RS.

Tumor micro-environments of metastasis (TMEM) are microanatomic structures found in human breast cancer that are sites of tumor cell intravasation and dissemination from primary tumor to distant organs, and from distant organs to other distant organs. TMEM score is based on a triple immunostain and has no correlation with IHC4, nodal status, or tumor size. It has been shown to be prognostic for distant recurrence in breast cancer positive for estrogen receptors and negative for HER2.

Dr. Sparano discussed a study that evaluated the association of TMEM score and recurrence in a clinical trial population of 600 women with stage I-III breast cancer and ≤3 positive axillary lymph nodes. The median follow-up was 15 years. The triple immunostain was performed on whole-sections of tumor to determine the MetaSite score (ie, the sum of the top 3 areas of highest density of staining).

**Highlights from the 39th Annual San Antonio Breast Cancer Symposium**
SURVIVORSHIP

[PD4-01] Dr. Lu presented results of a clinical trial of acupuncture as a treatment for peripheral neuropathy induced by chemotherapy. This study randomized 40 patients to receive either acupuncture for 8 weeks or usual care. After 8 weeks of intervention, the control group received low-dose acupuncture for 8 weeks. The patients in the acupuncture arm reported significant reduction and improvement in symptoms after 8 weeks of treatment compared to the control arm. The authors suggest that acupuncture might be an effective treatment for these patients.

[PD6-04] Dr. Pagani presented results from the HOHO study that compared attitudes of young women in Europe and the United States regarding breast cancer and fertility. The study enrolled 300 young women (18 years to 40 years of age) with breast cancer in Italy and Switzerland. The participants were given questionnaires every 6 months for 3 years, then yearly for 7 years. A qualitative comparison was performed between the European baseline data and published data from the United States.

Both cohorts had a high rate of discussion at time of diagnosis between patient and physician regarding future fertility (70%). The European cohort was more likely to have fertility concerns, have desire for future pregnancy, and take steps to reduce infertility. European women also were more concerned about fertility when making decisions about treatment and about caring for children in case of breast cancer recurrence.

The authors concluded that many young women with breast cancer have concerns about fertility that potentially affect their treatment decisions. Concerns about relapse could explain the decrease in pregnancy desire after diagnosis. There appear to be differences in concerns about fertility between women in Europe and women in the United States, and further collection of data is required to determine whether these differences persist in larger cohorts.

RESULTS

- Almost 70% of women in both cohorts discussed future fertility with their doctors at diagnosis.
- Fertility concerns, desire for future pregnancy and steps to reduce infertility more common in the European cohort.
- European women more concerned about fertility at treatment decision-making and about caring for children in case of breast cancer recurrence.

CONCLUSIONS

- Many young women with breast cancer are concerned about fertility, potentially affecting their treatment decisions.
- Concerns about relapse could explain the decrease in pregnancy desire after diagnosis.
- Differences between European and US women seem to emerge: continued data collection will determine if they persist over time.
- The POSITIVE trial (BIG52-14/ALLIANCE 221405) is addressing safety and outcome of pregnancy after breast cancer.

[PD6-04] Devices that cool the scalp to 64°F have been shown to increase retention of hair in patients receiving chemotherapy by reducing blood flow and exposure of hair follicles to chemotherapy. Dr. Nangia presented results of the Scalp Cooling Alopecia Prevention trial, the first randomized trial to evaluate scalp cooling effect on alopecia. This study included 182 women with stage I-II breast cancer and planned chemotherapy with taxane and/or anthracycline. Participants were randomized to the control group (no scalp cooling) or to the scalp-cooling group (cooling cap worn 30 minutes prior to chemotherapy, during chemotherapy, and 90 minutes after chemotherapy). Accrual of patients was stopped early because of the superior retention of hair experienced by the scalp-cooling group.

Interim analysis showed that more patients in the scalp-cooling group (50%) retained hair than in the control group (0%). The most common grade 1 and 2 adverse events were headache, nausea, and dizziness. Most participants rated the devise as reasonably comfortable. Quality-of-life assessments showed no significant differences between the treatment groups, or between the group that experienced retention of hair and the group that developed alopecia. As expected, a higher rate of hair retention was observed in the participants who received taxane based chemotherapy (65%) compared to patients who received an anthracycline (22%).

Studies of scalp cooling also have been performed in other countries. Metastasis of breast cancer to the scalp, which has been a concern since initiation of scalp cooling therapy, was rare and was not increased with scalp cooling. Similarly, there is no adverse impact on overall survival in patients who undergo scalp cooling. The authors concluded that devices that cool the scalp are highly effective for maintaining hair during chemotherapy.
Multiple large, randomized clinical trials have shown that treatment with selective estrogen-receptor modulators (SERMs) in women with increased risk for breast cancer can decrease breast cancer incidence by more than 30%. However, these medications have many potential side effects including increased risk for thromboembolic events, endometrial cancer, and menopausal symptoms. Dr. Smith reported the results of the International Breast Cancer Intervention study that investigated the relationship between menopausal symptoms and adherence to tamoxifen. This study randomized 3987 women with an increased risk for breast cancer to receive either placebo or tamoxifen. This study found adherence to placebo was significantly higher than adherence to tamoxifen (71.5% vs 62.1%). Similarly, participants in the placebo arm stayed on the study significantly longer (4.3 years vs 3.9 years). The highest rates of drop-out from the study occurred in the first 12 months of therapy, and were higher in the tamoxifen arm.

This study found adherence to placebo was significantly higher than adherence to tamoxifen (71.5% vs 62.1%). Similarly, participants in the placebo arm stayed on the study significantly longer (4.3 years vs 3.9 years). The highest rates of drop-out from the study occurred in the first 12 months of therapy, and were higher in the tamoxifen arm.

Overall, side effects were reported as mild in the majority of the participants, and included nausea/vomiting (5%), headaches (7%), hot flashes (31%), and gynecologic symptoms (20.9%). There was an association between adherence and both nausea/vomiting and headaches, although not between adherence and either hot flashes or gynecologic symptoms. The difference in adherence between the two arms based on the presence of menopausal symptoms was not statistically significant. In contrast, there was a significant direct relationship between adherence and the severity of the symptoms experienced.

The authors concluded that two-thirds of women were adherent to treatment for 4.5 years, and the drop-out rates were highest in the first 12 months of therapy. Similar rates of adherence were observed in women with menopausal symptoms in both arms, suggesting that naturally-occurring symptoms may be ascribed to the treatment with SERMs. Interventions to manage menopausal symptoms, particularly during the first year of treatment, may increase compliance and duration of therapy.

Dr. Chlebowski presented results of a Women’s Health Initiative trial that investigated the effects of modifications of diet on prevention of breast cancer. This study included 48,835 postmenopausal women whose intake of fat was >32% of their daily caloric intake. The participants were randomized to a control group that received a dietary guideline report or to a dietary-intervention group that received 18 group sessions with trained dieticians who emphasized daily dietary targets, ie, limiting calories from fat to 20%, five daily servings of fruits and vegetables, and six daily servings of whole grains.

The intervention group reduced the percentage of fat calories by 40% at year 1 (maintained throughout the intervention), and had an average weight loss of 2.2 kg. At 8.5 years, the intervention group had a non-statistically significant lower rate of breast cancer. While there was no significant difference in the number of deaths attributable to breast cancer between the groups after median follow-up of 8.5 years and 16.1 years, the intervention group had significantly fewer deaths from any cause after breast cancer in both of these follow-up time periods.

Subgroup analysis of the deaths from any cause after breast cancer showed that the greatest benefit from dietary interaction was observed in women with a waist circumference >88 cm at baseline and in women who had the highest quartile of energy from fat at baseline. Women with baseline energy from fat <27.9% received no benefit from dietary interaction, suggesting that benefit occurs with only a modest reduction of fat intake.
Characteristics of the 3034 breast cancers that occurred were similar between both groups, except that the intervention group had fewer estrogen receptor positive and progesterone receptor negative cancers. The authors concluded that the differential effect of diet on progesterone receptors accounted for 27% of the differences in deaths after breast cancers. Weight loss, however, did not account for any of the benefit.

Women with a low-fat dietary pattern had a non-significantly reduced risk for death from breast cancer and a significantly reduced risk for death from any cause after breast cancer. Benefits from these changes in diet were more likely in women who at baseline received >37% energy from fat, and women with waist circumference >88 cm.

Subgroup Analysis/Deaths After Breast Cancer: Cumulative Follow-up

Greater dietary effect in women with waist circumference ≥88cm

[S5-06] Joint and muscle pain are commonly experienced side effects for patient on treatment with aromatase inhibitors. Dr. Henry presented the results of this SWOG 1202 trial that evaluated the use of duloxetine for treatment of musculoskeletal syndrome associated with aromatase inhibitors. This study enrolled 229 postmenopausal women with stage I-III breast cancer who had worsening musculoskeletal pain after starting treatment with an aromatase inhibitor with a primary objective to assess whether 12 weeks of duloxetine decreases average joint pain as assessed with a brief pain index. Duloxetine is a serotonin norepinephrine reuptake inhibitor which is used for the treatment of depression and more recently was also FDA-approved for the treatment of multiple chronic pain disorders. Patients on this trial were randomized to receive duloxetine or matching placebo for 13 weeks. Duloxetine was given at a dose of 60mg daily with a 30mg one week taper at the beginning and end of treatment.

A 2 point improvement in pain on a 10 point scale is considered clinically meaningful for an individual patient. Average joint pain in the duloxetine group was improved by 0.82 points compared to the placebo group. This difference was appreciable after 2 weeks of therapy. More patients in the duloxetine group reported a 2-point improvement in joint pain after 2 weeks of treatment (54% vs 44%), 6 weeks of treatment (69% vs 49%), and 12 weeks of treatment (69% vs 60%). This difference was not maintained at 12 weeks after completion of treatment (duloxetine 60% vs placebo 59%).

Duloxetine was relatively well tolerated and side effects were consistent with primary duloxetine clinical trials. Grade-3 adverse events were reported by 12 patients in the duloxetine arm and five patients in the placebo arm. The most common grade-3 adverse event was insomnia, present in four patients in the duloxetine group and one in the placebo group. Adverse events occurred more frequently in the duloxetine group (78% vs 50%). Adverse events resulted in discontinuation of treatment in 21 patients in the duloxetine arm and 19 patients in the placebo arm. Gastrointestinal symptoms, dizziness, dry mouth, fatigue, and insomnia were the most common side effects experienced by patients in the duloxetine arm.

In regards to the secondary endpoints of this trial, there was a statistically significant improvement in worst joint pain, interference of pain with daily activities, pain in the knees and hips, pain of the hands, and quality-of-life assessment in the duloxetine arm. There was no difference in the rates of depression between the arms. Patients in the duloxetine arm also reported a statistically significant improvement in pain and stiffness.

The authors concluded that treatment with duloxetine resulted in decreased average joint pain in women with musculoskeletal syndrome associated with treatment with aromatase inhibitors. The results observed with duloxetine were superior to those observed with placebo, although improvement in joint pain was seen in both study arms. Duloxetine was associated with modest improvements in quality of life.
While the use of aromatase inhibitors in women with breast cancer positive for estrogen receptors has been shown to decrease breast cancer related mortality, concerns have been raised regarding the cardiovascular implications of long-term therapy. Studies of the effect of aromatase inhibitors on cardiovascular disease were discussed by Dr. Baes and Dr. Kamaraju.

[S5-07] Dr. Baes reported on the effect of aromatase inhibitors on endothelial function in a cross-sectional study of 25 healthy postmenopausal women and 36 postmenopausal women receiving an aromatase inhibitor for treatment of locally-advanced breast cancer. The breast-cancer group showed a trend toward decreased large-artery elasticity and small-artery elasticity, and had significantly reduced measurements of arterial elasticity. These changes persisted after controlling for differences in systolic blood pressure. No association was observed between endothelial function and the duration of treatment with an aromatase inhibitor. The authors concluded that treatment with aromatase inhibitors was associated with reductions in endothelial function, which is a predictor of cardiovascular disease.

[PD4-07] Dr. Kamaraju presented a Medicare analysis that evaluated the risk for cardiovascular disease associated with aromatase inhibitors. This population-based cohort study had 5 years of follow-up of women who were ≥67 years of age and on treatment with an aromatase inhibitor or tamoxifen. While more myocardial infarctions occurred in the aromatase-inhibitor group (209 vs 42), that difference was not retained after controlling for preexisting co-morbidities. The authors concluded that while the incidence of myocardial infarction was higher in this study than other randomized clinical trials, the rate was <2%. Furthermore, the patients in this study were older and had more comorbidities than those included in other random clinical trials.

NEW THERAPEUTIC APPROACHES

[PD2-08] Dr. Hyman presented a preliminary analysis of the SUMMIT trial. This analysis included data from patients with ERBB2-mutant ER positive and Her2 negative metastatic breast cancer receiving combination of neratinib plus fulvestrant compared to neratinib monotherapy. Neratinib monotherapy data was also presented at this conference last year and updated data in the treatment group was presented this year. The monotherapy group included 25 patients and 17 patients were enrolled in the combination group with neratinib plus fulvestrant. The majority of patients in both cohorts had visceral metastases and had received prior treatments, including endocrine therapy.

The overall response rate in the neratinib monotherapy cohort was 33%, 25% with confirmed response. The combination-therapy cohort had an overall response rate of 58%, 25% with confirmed response. While the patterns of co-mutation are not complete, early data suggests non-responders in the monotherapy cohort had a clustering of PI3K-hotspot mutations and p53 mutations. Co-mutation data are not yet available for the combination cohort.

Prophylaxis with loperamide was used in this study to prevent treatment-associated diarrhea. Grade-3 diarrhea, experienced by 11% of the combination group and 24% of the monotherapy group, had a median duration of 1 day, and was not a cause for discontinuation of therapy.

The authors concluded that neratinib has clinical activity as a single agent in patients with breast cancer with mutation of HER2 and heavy pretreatment. The determination of the incremental clinical benefit of neratinib plus fulvestrant requires additional enrollment and longer follow-up. Treatment was not limited by diarrhea when appropriate prophylaxis was given and no additional safety concerns arose with combining neratinib plus fulvestrant.
Dr. De Angelis discussed a study of GS-6510, a novel inhibitor of the BRD4 protein. BRD4 is a member of the BET (bromo and extraterminal domain) protein family which acts as an epigenetic reader that binds acetylated lysines on histones. This process facilitates the recruitment of epigenetic and transcription factors required for gene transcription. Dr. De Angelis’ group has previously shown that BRD4 inhibition reduces ESR1 gene expression and decreases mRNA expression and protein levels of ER in preclinical studies. The aim of this study was to assess the activity of the new BRD4 inhibitor GS-6510 in estrogen receptor positive endocrine sensitive and resistant breast cancer models as both monotherapy and in combination with fulvestrant.

In this study, they used a panel of three endocrine sensitive breast cancer cell lines (MCF7, T47D, ZR75-1) as well as their endocrine resistant derivatives to evaluate the effect of GS-6510 on tumor cell growth. On endocrine sensitive cell lines, GS-6510 was effective in decreasing cell growth, and GS-6510 also enhanced the activity of endocrine therapies when combined with tamoxifen and fulvestrant. Next, the group evaluated the effect of GS-6510 activity alone and in combination with fulvestrant in a HBCx34 PDX model. Mice were randomized to receive placebo, fulvestrant, GS-6510, or fulvestrant plus GS-6510. Monotherapy with either fulvestrant or GS-6510 slowed tumor growth significantly in this model compared to vehicle alone. While monotherapy with fulvestrant or GS-6510 did not result in tumor regression, the combination of GS-6510 and fulvestrant resulted in decrease in tumor size.

To better understand the mechanism of activity of GS-6510, gene expression analysis was completed. GS-6510 alone or in combination with fulvestrant inhibited expression of genes associated with estrogen-receptor signaling and cell cycle regulation. Monotherapy with GS-6510 also inhibited expression of genes that are insensitive to fulvestrant (eg, BCL2, CDK6). Monotherapy with GS-6510 resulted in marked inhibition of cell growth and a reduced level of estrogen-receptor protein in cell lines with estrogen-receptor deprivation or tamoxifen resistance. In both cell lines, the combination of GS-6510 plus fulvestrant was associated with a significantly greater inhibition of cell growth and better suppression of levels of estrogen receptor, c-MYC, and phospho-RB. GS-6510 remained effective in endocrine-resistant cells that had lost expression of estrogen receptor and exhibited growth independent of estrogen receptor.

The authors concluded that the epigenetic regulator BRD4 is a suitable target for therapeutic intervention in estrogen receptor positive breast cancer and the anti-tumor efficacy of GS-6510 in this patient population should be further explored. Also, epigenetic targets such at the BRD4 may have a role in overcoming endocrine resistance.

Dr. Flanagan discussed proteolysis-targeting chimera (PROTAC) that recruit E3 ligases and promote degradation of estrogen receptor-α (ERα) at the intracellular level.

Incubation of T47D cells with PROTAC for 72 hours resulted in reductions of levels of ERα in both the nuclear soluble and nuclear pellet fractions of the cells. The anti-proliferation effects of fulvestrant and PROTAC were greater than those of selective estrogen-receptor downregulators (SERD). Cellular expression proteomic studies showed that levels of receptor are selectively reduced by active PROTAC, but not inactive PROTAC.

Subcutaneous PROTAC was well tolerated in mouse models and resulted in 70% tumor reduction, despite high levels of estradiol. ERα levels were reduced by 60% in these animals. Oral PROTAC was shown to decrease levels of ERα by 60%, slightly better than fulvestrant (50% reduction).
The authors concluded that PROTAC reduced ERα using a different mechanism than fulvestrant and current clinical SERDs. Levels of ERα were reduced by either subcutaneous or oral PROTACs in all cell lines tested.

The most common adverse event that occurred with abemaciclib was diarrhea. The rate of grade-3 diarrhea with prophylactic loperamide was 4%. The rate of grade-3 and grade-4 neutropenia was 8.2%.

The authors concluded that 2 weeks of treatment with abemaciclib, with or without anastrozole, significantly reduced Ki67 compared to anastrozole alone. Changes in histology induced by treatment suggested that suppression of the cell cycle is associated with tumor differentiation. Abemaciclib plus anastrozole may also induce infiltration of cytotoxic and suppressor T cells. Objective response was seen in the majority of patients who received abemaciclib and anastrozole.

**[S4-06]** Estrogen stimulates D-type cyclins in breast cancer positive for hormone receptors, resulting in the activation of CDK4 and CDK6, release of E2F transcription factor, and progression of the cell cycle. Dr. Hurvitz discussed the phase II neoMONARCH study that evaluated the use of abemaciclib, a CDK4/6 inhibitor, in postmenopausal women with hormone receptor positive and HER 2 negative breast cancer. Patients were randomized 1:1:1 to either anastrozole, anastrozole plus abemaciclib, or abemaciclib for 2 weeks followed by 14 weeks of abemaciclib plus anastrozole. Patients underwent core biopsies at baseline, 2 weeks, and 16 weeks. Loperamide was given as primary prophylaxis against diarrhea caused by abemaciclib during the first month of therapy. Data include results of 161 patients. The treatment arms had similar baseline values of Ki67.

The arms containing abemaciclib had significantly higher reductions of Ki67 at week 2 than the anastrozole arm. Similarly, complete cell-cycle arrest (Ki67 <2.7% at day 15) was achieved in more patients who received abemaciclib. Core biopsies obtained from 59 patients after 16 weeks of therapy showed that all but 4 had decreased Ki67. The radiological objective response rate was 54.7% and the caliper objective response rate was 56.6%. Pathological complete response was seen in 3 of 95 patients who underwent surgery after treatment.

Formation of tubules was seen in the histology of biopsies obtained after 2 weeks of abemaciclib monotherapy. This histologic change was preserved and increased at day 28 with combination therapy, and was associated with a reduction of Ki67. Infiltration by T cells was not present at baseline or at cycle 1 day 15 (abemaciclib monotherapy); however, there was a profound infiltration of CD-3 positive and CD-8 positive T cells by cycle 5 day 28 (combination treatment).

**[S6-04]** PIK3CA is frequently mutated in cancer cells and is a potentially therapeutic target in breast cancer. Dr. Friedman from Genentech presented preclinical data regarding taselisib, which is a new inhibitor of PI3K. Compared to other PI3K inhibitors, taselisib had increased potency in mutant PIK3CA cell lines because of its unique ability to block overactivation of compensatory pathways to lead to resistance. The anti-tumor activity of most inhibitors of the PI3K pathway is attenuated because of induction of negative feedback that activates the pathway at the level of the receptor tyrosine kinases. Taselisib, however, is able to suppress this pathway better than the other inhibitors of PI3K.

Cell lines that contain mutated EGFR and wild-type PI3K were engineered to have PI3Kα mutations. Taselisib showed increased potency in the cells with mutant PI3Kα, while potency was not shifted with the other PI3K inhibitors. This implies that taselisib has a unique mechanism of action on the mutant cells. Further investigation showed that taselisib resulted in selective depletion of p110α protein in cells with mutant PIK3CA, but not in wild-type cells. In assays of cell death, apoptosis was induced by PI3K inhibitors in mutant cells, but not wild-type cells; the strongest induction of apoptosis was seen with taselisib. Furthermore, taselisib was associated with regression of PIK3CA-mutant tumors in mice, whereas stasis was observed with other inhibitors.
The authors concluded that taselisib strongly suppresses the PI3K pathway via a unique mechanism of action that leads to the depletion of mutant p110α protein. This unique mechanism of action results in increased suppression of cell growth, longer duration of response per dose, and decrease in the negative feedback loop that can result in drug resistance.

**Special Populations**

**BRCA RELATED BREAST CANCER**

[S2-02] BRCA1 and BRCA2 are important genes in homologous recombination, an error-free mechanism that repairs breaks in double-stranded DNA. In cells that lack either BRCA1 or BRCA2, these breaks are repaired by mechanisms that are prone to error. Deficiency of homologous recombination requires complete inactivation of BRCA1 or BRCA2 by germline mutation and loss of heterozygosity or a second somatic mutation.

The first aim of this study was to define the somatic genetic alterations of BRCA1 and BRCA2 breast cancers. The study’s second aim was to determine loss of heterozygosity of BRCA1/2 wildtype alleles or mutations affecting additional tumor suppressor genes that would be present and clonal in these cancers. Clonal expression was defined as being present in virtually all tumor cells. Dr FC Geyer and his research group sequenced the genes of 29 BRCA1 breast cancers and 10 BRCA2 breast cancers.

The only gene that was recurrently mutated in the majority of BRCA1 tumors was TP53 (76%). These mutations always were coupled with loss of heterozygosity and were mostly clonal. Clonal mutations of TP53 were also significantly associated with estrogen receptor negativity. Mutations in NF1, PTEN, and RB1 were found in 7-10% of the tumor samples.

In regards to the second hit affecting the wild type BRCA1, bi-allelic BRCA1 inactivation was seen in all but one tumor. Clonal BRCA1 loss of heterozygosity of the wild-type allele was found in 72% of the tumors. Subclonal BRCA1 loss of heterozygosity was found in 21% of tumors, suggesting that complete inactivation of BRCA1 was not the first somatic genetic event. Two-thirds of the tumors with clonal BRCA1 had high large-scale transition (LST) scores (predictor of deficiency of homologous recombination), while only 2 of 6 cases with subclonal BRCA1 loss of heterozygosity had high LST scores. There were no differences seen in the frequency of bi-allelic BRCA1 inactivation between tumors with negative estrogen receptors and those with positive estrogen receptors. This suggests that BRCA1 tumors positive for estrogen receptors lack the ability to perform homologous recombination.

No genes were found to be recurrently mutated in a majority of the BRCA2 tumors. Clonal loss of heterozygosity of the BRCA2 wild-type allele was found in all tumors, although only 50% had high LST scores.

The authors concluded that BRCA1 breast cancers frequently have recurrent mutations of TP53. The second-hit effect in wild-type BRCA1 is present in most tumors, and is clonal in the majority of cases. Chronology of somatic events is heterogeneous; however, mutations affecting TP53, or other tumor suppressor genes, are likely to precede BRCA1 loss of heterozygosity in a subset of cases. BRCA2 tumors are genetically heterogeneous, without a highly-recurrent altered gene. They harbor mutations of PIK3CA less frequently than sporadic breast cancers positive for estrogen receptors. All tumors in this study had clonal loss of heterozygosity of the wild-type BRCA2 allele. This suggests complete inactivation of BRCA2 was an early somatic genetic event.
Dr. Eccles presented results of the Prospective Study of Outcomes for Sporadic vs Hereditary breast cancer (POSH) study. This study set out to evaluate BRCA mutations as an independent prognostic factor in a prospective study. Previous retrospective studies resulted in conflicting data and thus a prospective study is of value. This study included 2759 women ≤40 years of age with invasive breast cancer. Mutations of BRCA were found in ≈14%, BRCA1 more commonly than BRCA2 (212 vs 170). BRCA1 mutation carriers were younger, had smaller tumors, and were more likely to have triple-negative tumors. Carriers of BRCA2 mutations were more likely to have node-positive disease and be estrogen receptor positive.

Over 8.2 years of median follow-up, no statistical differences were observed in outcomes between those who carried the mutations and those who did not. In the patients who had triple-negative breast cancer (19%), carriers had an 11% survival advantage at 10 years, although the maximum benefit of survival was observed in the first few years.

Breast cancer treatments were similar between groups, although more carriers underwent bilateral mastectomy (15% vs 3%). Patients who did not undergo bilateral mastectomy had a 2% survival advantage at 5 years and 10 years.

The authors concluded there was no significant difference in outcomes between BRCA mutation carriers and non-carriers, except that carriers with triple-negative breast cancer have a survival benefit over non-carriers with triple-negative breast cancer. No survival advantage was seen with bilateral mastectomies during the follow up period.

Dr. Lindeman reported on work that investigated RANK ligand as a target for prevention of BRCA1 associated breast cancers. As part of his presentation, he outlined the emerging role of progesterone signaling in BRCA1 mutated breast cancer. RANKL is also being recognized for its key effects on progesterone signaling in mice. When progesterone binds to ductal cells in BRCA1 mutated mouse models, RANKL is increased and results in a positive feedback to stem cells resulting in mammary cell expansion. Thus, Dr. Lindeman’s group sought to further investigate the relevance of the progesterone/RANKL/RANK signaling pathway in tissue samples from patients with BRCA1 mutations.

First, he and his research group showed that premenopausal BRCA1 mutation carriers have twice the percentage of luminal progenitor cells positive for RANK compared to non-carriers. Additionally, breast tissue from BRCA1 mutation carriers had markedly increased proliferation genes and deficient mechanisms for repair of DNA. Tumors with mutations of BRCA1 also had higher expression of RANK.

Increased proliferation, shown by increased Ki67, was found in organoid models of tumors with mutations of BRCA1, and exposure to progesterone resulted in further increases. This progesterone-induced proliferation was curtailed by co-treatment with denosumab, an inhibitor of RANK ligand. Based on these findings, a pilot clinical trial “BRCA-D” was developed. This is a pre-operative window study evaluating the biological effects of denosumab on normal breast tissue from BRCA1/2 mutation carriers and high-risk women. A luteal phase breast biopsy is taken at baseline and then patients receive three doses of monthly denosumab prior to planned surgical resection. Early data from this pilot study in women with BRCA1 show a profound reduction in Ki67 after three doses of denosumab.

Dr. Lindeman also presented supporting data that RANKL inhibition delays tumor development in a BRCA1 mouse mammary tumor model. In this model, 65% of the mice remained free of tumor, and hyperplasia was reduced in mice who received RANKL inhibition. While oophorectomy has been shown also to delay tumors in BRCA1 mouse models, the RANK-ligand inhibitor appeared to be at least as effective.

Dr. Lindeman concluded that inhibition of RANK ligand might switch off the hyperproliferative process that occurs with mutations of BRCA1. The BRCA-P trial, a phase III international trial, is planned to compare the efficacy of denosumab in the prevention of breast cancer in carriers of mutations of BRCA1 and BRCA2.
Veliparib is an oral selective inhibitor of PARP-1 and PARP-2, and antitumor activity with veliparib as single agent therapy has been seen in early clinical trials in patients with BRCA positive breast cancer. A phase 1 clinical trial of veliparib in combination with carboplatin and paclitaxel has been conducted with acceptable toxicity.

Dr. Han presented the safety and efficacy results of the first randomized phase II trial of combination carboplatin and paclitaxel plus either placebo or veliparib. The BROCADE trial randomized 290 patients with locally-recurrent or metastatic BRCA mutation positive breast cancer in a 1:1:1 fashion to receive treatment with veliparib/carboplatin/paclitaxel or placebo/carboplatin/paclitaxel or veliparib/TMZ. The veliparib/TMZ data was presented separately. Patients were stratified based on hormone receptor status, prior cytotoxic chemotherapy, and performance status. Primary endpoint of the study was progression free survival and secondary endpoints included overall survival and overall response rate.

The median progression-free survival in the veliparib arm was 14.1 months vs 12.3 months in the placebo group. This difference of 1.8 months was not statistically significant. Early analysis of overall survival was also not statistically significant with overall survival in the veliparib arm of 28.3 months vs 25.9 months in the placebo group. However, the prespecified number of events had not yet occurred at the time of this analysis. Additionally, clinical benefit rate and median duration of response were both similar between the veliparib and placebo groups. The overall response rate was high in both arms, and was significantly higher in the veliparib group (77.8% vs 61.6%). No significant increase in adverse events was seen in the veliparib arm compared to the placebo arm. The rates of drug interruption, dose reduction, and discontinuation of treatment were similar between the arms.

The authors concluded that the addition of veliparib to carboplatin plus paclitaxel resulted in a non-statistically significant trend towards improved progression-free survival and overall survival, and a significant increase in overall response rate. The safety profile of carboplatin plus paclitaxel was comparable to that combination plus veliparib. Further evaluation of this combination is ongoing in the phase III randomized trial BROCADE3.

Dr. Wolf presented data on the veliparib plus carboplatin combination arm in patients with triple negative breast cancer. Five biomarkers were evaluated as specific predictors of response to veliparib and carboplatin and included BRCA1/3 germline mutation, PARP1 protein, and three gene expression signatures that relate to deficiency of repair of DNA damage. The primary endpoint of the trail is pathologic complete response.

Evaluation of the concordance of these biomarkers showed that they did not identify the same patients. Prediction of sensitivity to treatment was improved in patients who had multiple biomarkers that predict sensitivity. Nearly all of the specific sensitivity to veliparib/carboplatin was seen in the 40% of patients with triple-negative breast cancers who had both Mammaprint 2 and high PARPi-7. In the subset positive for hormone receptors and negative for HER2, those patients with Mammaprint 2 and...
high PARPi-7 also had higher rates of pathological complete response with veliparib/carboplatin (49% vs 15%), but only 9% of the patients were in this category.

The authors concluded that PARPi-7, BRCAAness, and Mammaprint 1/2 specifically predict response to veliparib/carboplatin. Tumors that were characterized as Mammaprint 2 and PARPi-7 high were more sensitive to veliparib/carboplatin than tumors with only one of those markers. Dr. Wolf cautions that the sample size in this trial is small and trials with larger patient cohorts are needed.

[PD6-05] Dr. Jerzak presented results from the phase III TNT trial of 376 women with advanced, metastatic triple-negative or BRCA-mutated breast cancer. This study investigated differential sensitivity to platinum vs docetaxel. The overall trial results showed similar performance of carboplatin and docetaxel. In contrast, in the pre-specified subgroup with germline mutation of BRCA1, a significantly higher response rate was observed with carboplatin (68% vs 33%). The performance of the drugs was similar in the subgroup with wild-type BRCA1 and BRCA2.

Aberrant methylation of cytosines in the context of CpG dinucleotides in the regulatory region of BRCA1 results in epigenetic silencing of the gene in 10% to 40% of triple-negative breast cancers. BRCA1 methylation was found in 18% of 224 tumors. Patients with methylation of BRCA1 did not have a significantly higher response to docetaxel. Patients with germline mutation of BRCA1, on the other hand, had a significantly higher rate of response to carboplatin than to docetaxel.

The status of BRCA1 mRNA was assessed in 191 samples, 16% of which were silenced. Of the tumors that were methylated, 66% were silenced. The BRCA1-silenced population again did not have a higher response rate to docetaxel. There was a significant relationship between germline mutation and progression-free survival in patients treated with carboplatin, but not docetaxel. Methylation of BRCA1 had no significant effect on progression-free survival following either drug. The level of deficiency of homologous recombination had no predictive value for carboplatin benefit. In ovarian cancer, mutations of BRCA1 and BRCA2 are associated with improved survival after platinum-based therapy compared to wild-type, but methylation of BRCA1 is not.

The authors concluded that response and progression-free survival following carboplatin in metastatic breast cancer is significantly associated with germline mutation of BRCA1 and BRCA2, but not with epigenetic silencing by methylation of BRCA1. It is likely that epigenetic silencing is both heterogeneous and reversible under the selective pressure of standard-of-care adjuvant chemotherapy that damages DNA. The results of this trial support rapid testing for germline mutation of BRCA1 and BRCA2 to guide treatment in metastatic triple-negative breast cancer, but not testing for methylation of BRCA1 or silencing of mRNA.

PREGNANCY ASSOCIATED BREAST CANCER

[PD6-05] Dr. Jerzak presented results of a prospective evaluation of clinical outcomes in women with pregnancy associated breast cancer (PABC). Pregnancy associated breast cancer was defined as breast cancer diagnosed during pregnancy or within 12 months postpartum. It is estimated that PABC occurs in about 10% of women who are diagnosed with breast cancer before the age of 40 years and may be associated with a worse prognosis. It is not clear if this worse prognosis is secondary to delays in diagnosis or a difference in tumor biology. Thus the objective of this study was to compare disease free survival, overall survival, and tumor pathology between women with PABC vs non-PABC in a prospective database.
This prospective cohort included 224 women ≤40 years of age with stage I-III breast cancer diagnosed between 2008 and 2015 at a single treatment center in Canada. The cohort of women with PABC were younger, ≈2 times more likely to have locally-advanced disease, and more likely to be hormone receptor negative.

The 3-year disease-free survival rate was lower in women with PABC (79% vs 90%), but the difference was not significantly significant. There was also a higher rate of involvement of axillary nodes in women with PABC who underwent primary surgery, although this too was not found to be significant when corrected for age and tumor size.

The authors concluded that PABC appears to be associated with decrease in expression of estrogen and progesterone and a trend towards greater nodal involvement. This suggests a more aggressive biology in comparison to women without PABC. While the decrease in DFS is not statistically significant, this may be secondary to a low event rate with a median follow up of only 3.5 years.

**Results contd**

Kaplan-Meier estimate for DFS

- Among 166 women without locally advanced disease, PABC was associated with + nodal involvement
- OR 2.8 (95% CI 1.0 - 8.7), p=0.06 after adjustment for age and tumor size

**Conclusions**

- Lower ER/PR expression & trend toward greater nodal involvement in PABC suggests a more aggressive disease biology.
- Adverse 3-year DFS & OS cannot be excluded due to low event rates at this time.

**Oncologic outcome of pregnancy associated breast cancer: a case-control study**

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<thead>
<tr>
<th>Characteristics</th>
<th>PABC</th>
<th>Control</th>
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<tr>
<td>Age (Median)</td>
<td>36.1</td>
<td>36.2</td>
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<tr>
<td>Breast Conservation Surgery</td>
<td>22%</td>
<td>38%</td>
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<td>AJCC Stage</td>
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</tr>
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<td>Node +ve</td>
<td>32%</td>
<td>48%</td>
</tr>
<tr>
<td>Subtype ER+HER2+</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>HER2+</td>
<td>24%</td>
<td>20%</td>
</tr>
<tr>
<td>Triple negative</td>
<td>39%</td>
<td>29%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Adjuvant</td>
<td>82%</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>18%</td>
<td>14%</td>
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</table>

**Overall Survival**

- 5 year OS: PABC 87.0% vs Control 95.3%
- 10 year OS: PABC 80.6% vs Control 87.3%

**[PD6-06]** The purpose of this study was to access the long term outcomes in women diagnosed with pregnancy associated breast cancer (PABC) in comparison to a matched cohort with non-PABC. Dr. Damian McCartan presented the outcome data on 188 women with PABC treated at Memorial Sloan Kettering Cancer Center between 1992 and 2015 in comparison to 188 matched controls based on age and year of diagnosis.

This study found that women with PABC were more likely to have stage III disease (33% vs 21%), grade III tumors (88% vs 70%), lymphovascular invasion (57% vs 47%), and triple negative disease (33% vs 23%). More women in the PABC group received adjuvant therapy (82% vs 71%) and neoadjuvant therapy (18% vs 14%).

The overall survival at the 5-year and 10-year endpoints was not significantly different between the two groups. The 5-year overall survival for PABC was 87% compared to 95% in the non-PABC group. The 10-year overall survival was 80% in the PABC and 87% in the non-PABC. The authors concluded that the PABC group likely had a lower 5 year overall survival secondary to an increase in the higher stage at presentation, higher grade, and increased incidence of triple negative subtype in this group. There was also no statistically significant increase in the rate of HER2 positivity in the PABC cohort, and some of these women were diagnosed and treated in the era prior to trastuzumab.

**[PD6-07]** Previous studies have shown that Tumor Infiltrating Lymphocytes (TILs) may be more common in women with pregnancy associated breast cancer (PABC). It has also been shown in previous studies that TILs are more common in triple negative breast cancers, and that women with PABC are more likely to have triple negative breast cancer in comparison to matched controls without PABC. Therefore, Dr. Blanco and her research group evaluated the expression of PD-1 and PD-L1 in patient with PABC and compared them to a group of nulliparous women matched for age, stage, and grade at diagnosis. For this study, pregnancy associated breast cancer (PABC) was defined as diagnosis of breast cancer within two years of pregnancy.

A total of 21 tumor samples were evaluated from women with PABC and these were compared to 15 matched controls. Strong expression of PD-L1 was observed in 42.9% of tumors in the pregnancy-associated group and in none of the tumors in the control group. The expression of PD1 was similar in both groups. The authors therefore concluded that TILs in women with PABC strongly express PD-L1 in comparison to TILs in women without PABC. This higher PD-L1 expression did not correlate with any of the tumor characteristics evaluated in this study. The expression of PD-1 was similar in both groups. There appears to be a complex interaction between tumor cells and the local immune system.
RACIAL DIFFERENCES AND DISPARITIES

[PD8-03] Dr. Ademuyiwa discussed racial differences in the mutational landscape of triple-negative breast cancer. It has been established that black women have poorer breast cancer specific outcomes than white women, despite having a lower incidence of breast cancer. Triple-negative disease, which has an overall worse prognosis, is more common in black women than in white women; it is unclear whether there are racial differences in the outcomes associated with triple negative breast cancer. This study used data from The Cancer Genome Atlas from 1104 patients with primary breast cancer, 178 of whom had triple-negative disease. Overall, tumors in black women were more often basal (34.5% vs 16.1%), and had higher median numbers of somatic mutations (39.5 mutations vs 34 mutations), although these characteristics did not have racial differences in the triple-negative cohort. Recurrently mutated genes that were present in high prevalence and showed racial differences included TP53 (black 46%; 27% white), PIK3CA (black 23%; white 34%), and MLL3 (black 12%; white 6%), although no racial differences in these genes were found in the triple-negative tumors. Black women had a shorter time to progression and lower disease-free survival; however, again no racial differences were seen in these outcomes for TNBC.

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The authors concluded that the mutational landscape of breast cancer has racial differences, including mutations of PIK3CA, expression of androgen receptors, and copy-number variation. Dr. Lynce cautioned that sample size was small in this study and larger studies would be needed to confirm these findings.

[PD8-04] Dr. Lynce presented results of a retrospective study of biomarker data obtained from 565 samples of breast cancer with the aim to determine if potentially targetable mutations vary based on ethnic background. Breast cancer of black women represented ≈20% of the samples. Triple-negative disease occurred more commonly in black patients than in white patients (32.2% vs 17.0%). Overall, immunohistochemical stains showed white patients had higher expression of androgen receptors; there was a non-significant trend toward higher expression of androgen receptors in triple-negative disease of white women. The most frequently mutated genes in all cases were TP53 and PIK3CA. The frequency of mutation of PIK3CA was statistically significantly higher in tumors of white women, and the locations of these mutations were different based on race. Analysis of copy-number variation showed tumors of black patients had an excess of copies of CCND1, FGF4, and FGF19, genes that are part of the amplicon for cyclin D1 core on 11q13.

The authors concluded that the molecular landscape of breast cancer has racial differences, including mutations of PIK3CA, expression of androgen receptors, and copy-number variation. Dr. Lynce cautioned that sample size was small in this study and larger studies would be needed to confirm these findings.
A comparative analysis of the genomic landscape of breast cancers from women of African and European ancestry was presented in a poster discussion by Dr. Olopade. Worldwide, the ratio of mortality of breast cancer to incidence of breast cancer is lowest in the United States, whereas Africa has the highest ratio. Additionally, the majority of the genomic data being used to develop new drugs for breast cancer come from women of European ancestry.

In this study, whole-exome sequencing (147 cases) and whole-genome sequencing (40 cases) were performed on tumor-normal pairs from patients in Africa. The aim of the study was to develop an analytic platform for African genomes. Genomic data from the African tumors were compared to data from tumors of black women in the United States and women of European ancestry (The Cancer Genome Atlas database).

Patients in Nigeria were, on average, ≥10 years younger than both black patients and white patients in the United States. Mutation of TP53 was present in the majority of tumors of women in Nigeria. Black women in the United States also had a high rate of this mutation, while women of European ancestry had a much lower rate. Overexpression of HER2 was highest in Nigerian women, second highest in black women in the United States, and lowest in white women. The African cohort had a much higher rate of APOBEC signature than the other cohorts.

The authors concluded global disparities in the research and care of breast cancer are fueled by inadequate allocation of resources. Collaborative research and inclusion of more diverse patient populations can potentially help address disparities in breast cancer outcomes.

Dr. Caswell-Jin reported on the racial differences associated with multiple-gene panels that assess risk for hereditary cancer. The cohort in this study had a higher percentage of Asian and Hispanic patients than other studies that have investigated racial differences which have been more predominately comprised of white patients. Asians and Hispanics were tested at younger ages and with less family history of cancer than patients who identified as white or Ashkenazi Jewish.

The possibility of a pathogenic result (detection of ≥1 pathogenic gene variant) or an uncertain result (detection of a variant of undetermined significance) increases as the number of genes on a panel increases. Regardless of the size of the panel, however, the probability of a pathogenic result is similar for white and non-white patients, and the chance of an uncertain result is higher for non-white patients. Racial differences were seen also in the frequency of mutations of pathogenic genes, eg, mutations of CHEK2 were found in significantly more white patients than black patients (3.8% vs 1.0%).
The authors concluded Asian and Hispanic patients present for hereditary cancer testing at younger ages and with less family history of cancer than white patients. Uncertain results were more common in non-white patients than in white patients. Given that there is racial diversity in the frequency of gene mutations, it is important to consider racial diversity in clinical trials and in analysis of banked samples to ensure patients from varied ethnic groups can benefit from molecularly targeted therapies.

Different spectrum of pathogenic mutations between ethnicities

- **CHEK2**: 3.8% of Whites, 1.0% of non-Whites ($P = 0.002; \text{ FDR} = 0.02$)
- **PALB2**: 0.3% of Whites, 1.5% of non-Whites ($P = 0.02; \text{ FDR} = 0.08$)