This was the second year of this clinically oriented session, chaired by Lisa Carey, in which the most potentially practice changing or controversial presentations are reviewed and discussed by an expert panel. Matthew Ellis discussed endocrine therapy, starting with the long-term follow-up (FU) of the TEXT and SOFT trials (Francis and Fleming et al). The panel concluded that premenopausal women with higher risk disease, and those who have received chemotherapy, should receive OFS as a component of adjuvant endocrine therapy, and that the combination of OFS plus aromatase inhibitor (AI) or OFS plus tamoxifen are both reasonable options with a small preference for the AI combination for high risk disease. Even with almost 10 years of FU, longer-term data are important to capture late events that particularly affect this clinical subset. Patty Spears, a patient advocate on the panel, commented that it is important to balance risk versus benefit, and to evaluate long-term risks of early menopause as well.

The discussion then turned to duration of adjuvant endocrine therapy, with a summary of the ABCSG-16 trial (Gnant et al), which evaluated an additional 2 versus 5 years of AI therapy in women who completed 5 years of any endocrine therapy. At a median FU of almost 9 years, there was no difference in either disease free or OS, but there was an increase in the risk of fractures from 4.6 to 6.2% (p=0.053). Dr. Ellis noted that extending tamoxifen from 5 to 10 years in the ATLAS trial reduced both recurrence and breast cancer mortality and that it is not yet certain that extended AI therapy will be as beneficial – but a future meta-analysis might help.

Genomic tests have been studied to understand which patients have a continued risk of recurrence after 5 years and could potentially benefit from extended endocrine therapy. The panel discussed the potential value of the CTS5 algorithm. This algorithm, presented by Ivana Sestak, was developed from the ATAC dataset and validated using data from BIG 1-98. This is an inexpensive method, based on existing clinical variables, to determine who might be at very low risk of late recurrence and consequently would not need extended endocrine therapy. The next step might be to see if genomic tests add meaningful information to this simple approach. The idea of monitoring blood markers was also addressed based on a study from ECOG presented by Joe Sparano, which found an association with circulating tumor cells (CTCs) in blood about 5 years after diagnosis and risk of distant recurrence within the next 2 years in women with HR+ breast cancer. The panel noted that there was only a small number of patients with CTCs and while this method may identify relapse earlier than other approaches it is not clear that this or other similar approaches will improve outcome for those with early stage disease.

Adjuvant bisphosphonates have been shown to result in a <2% decrease in bone metastases and breast cancer death in post-menopausal women in a large meta-analysis. Dr. Ellis discussed the SUCCESS A trial (Janni et al), showing no
additional benefit from extending zoledronate from 2 to 5 years in patients with bone metastases. However, this study had a 2-year follow-up compared to close to 19,000 in the meta-analysis, and having only 3 years of FU. For these reasons, the panel considered this a small study with uncertain benefit, and that there still remains some controversy about timing and routine use of these drugs.

Dr. Ellis then discussed the MONALEESA 7 trial (Tripathy et al), the first study evaluating hormone therapy with a targeted agent, fulvestrant, in premenopausal women, and that the similarity in PFS benefit seen with ribociclib and either AIs or tamoxifen is encouraging. This is the only study dedicated to premenopausal women, although premenopausal women made medically postmenopausal were included in PALOMA3 and MONARCH3. The panel noted that there are no data of CDK4/6 inhibitors in breast cancer with local-regional recurrence.

Next, Steven Vogel discussed several studies focusing on symptom management and new therapies for hormone receptor positive disease. A pooled analysis of fertility preservation (Lambertini et al) was to provide additional support for the concept that OS with LHRH agonists during chemotherapy improves preservation of ovarian function. Interestingly, there was a mix of HR+ and HR- patients in these studies and no evidence of detriment in breast cancer outcomes was seen in either group. This is a difficult area to study. More women who received OVS had pregnancies but the numbers remain small (10% versus 5%) and may not be as successful as other options such as oocyte/embryo cryopreservation. Decisions to use OSV during chemotherapy for fertility preservation should be individualized, but it is safe and a reasonable option.

A pooled analysis of the MONARCH 2 and 3 trials (Goetz et al) that combined abemaciclib and hormone therapy in first or later line therapy was reviewed in terms of its implications on current practice. The investigators found that some subgroups (bone, low grade, long relapse-free interval) had reasonably good PFS, with Monetary value of 12 months of abemaciclib versus concurrent chemotherapy, demonstrating improvement in risk of recurrence and breast cancer mortality, with no difference based on HR status. Dr. Winer noted that this supports what has become common use especially with aromatase-inhibitor based regimens and should be continued, although growth factors are required.

The GeparSepto trial (Shrieve et al) evaluated iso-125 mg/mL of nab-paclitaxel for 12 weeks followed by 4 weeks of anthracycline, compared to standard paclitaxel-based chemotherapy. Disease-free survival was superior in the patients who received nab-paclitaxel, regardless of HR status with a 7.3% difference at 4 years, but without an impact on OS. Peripheral neurotoxicity was significantly higher. Longer-term FU of CALGB 40502 (Ruge et al), which compared nab-paclitaxel to paclitaxel as first line therapy for metastatic breast cancer, demonstrated consistent results. He reasoned that with nab-paclitaxel and similar outcomes with nab paclitaxel and paclitaxel. Unlike the GeparSepto trial, in the post-hoc subset analysis there is no sign of benefit with nab-paclitaxel and OS favoring nab-paclitaxel in the triple negative disease subset, although toxicity, dose reductions and discontinuations were higher. The panel noted that they would use nab-paclitaxel over paclitaxel in patients with diabetes, or in those with allergic reactions to paclitaxel. The dose of nab-paclitaxel and the toxicity with the higher doses used in these trials remain an issue, as well as the inconsistencies of results and absence of a biologic rationale for the interaction. In the metastatic setting the toxicity makes this less appealing, but in the (neo)adjuvant setting nab-paclitaxel is a reasonable option. A larger validation study would be helpful, but is likely not practical. Sue Heiselemb suggested that similar or pooled analyses for the phase II palbociclib and ribociclib trials might be useful.

Dr. Vogel also reviewed an interesting randomized placebo-controlled study presented by Dawn Hermans showing that acupuncture could reduce (but not eliminate) pain associated with aromatase inhibitors. The panel commented that cost could be an issue that might limit access ($1250 for 12 weeks) as well as the dangers of unplanned subset analyses. However this type of analysis might help identify those who could wait to start CDK4/6 inhibitors until after chemotherapy. This large study is a definitive answer to this question.

The Manta trial (Schmid et al) showed no benefit from a novel TORC1/2 inhibitor added to fulvestrant, but showed a large PFS of 12.3 months in the fulvestrant plus exemestane control arm with expected toxicity, supporting significant activity with this combination; endometrius has also demonstrated improved PFS compared to duarte duarte duarte in breast cancer. Considering this combination following CDK4/6 inhibitor therapy but prior to treatment with a CDK4/6 inhibitor has added to exemestrangein (Krop et al) was stated in women with metastatic HR+ breast cancer with some evidence of activity and a potential role for complete response. Sues panel commented not to recommend use of this agent in HR+ breast cancer without further data.

Eric Winer then prevented data from studies focusing on chemotherapy and HER2 targeted treatment. The EBC1CG (Gray et al) was reviewed in terms of a non-meta-analysis of the use of trastuzumab versus concurrent chemotherapy, demonstrating improvement in risk of recurrence and breast cancer mortality, with no difference based on HR status. The panel commented that cost might be an issue that might limit access ($1250 for 12 weeks).

Lastly, Dr. Winer discussed the EMBRACA trial (Litton et al), which demonstrated superiority in PFS and response for the PAKK receptor inhibitor talazoparib compared to physicians choice chemotherapy in patients with metastatic breast cancer associated with a germline mutation in BRCA1 or 2. Too early for assessment of OS, but very active, reasonably well tolerated, with improved quality of life compared to chemotherapy. The panel noted they were looking forward to adjuvant data and that ongoing studies of combinations are intriguing (with immunotherapy, and others).

Mike Dixon then discussed locoregional management of breast cancer, reviewing a meta-analysis of breast conservation margins (Vicini et al), primary endocrine therapy for DCIS (Hwang et al), a prediction tool for estimating benefit of radiation for DCIS (Wamborg et al) and a presentation evaluating arm morbidity in young women (Kujer et al). He noted that this is the third meta-analysis about margin width. Dr. Dixon’s conclusions were that a 1-cm margin is optimal (the current recommendations work), clear margins need individual multidisciplinary management, and a 1-cm margin with a 2-cm margin for a harmonization for invasive and in situ cancer recommendations with an international consensus.

Neoadjuvant hormone therapy for ER-rich DCIS can be used to convert tumor to ER-negative for breast conservation. Patients with those with extensive calcifications and is safe. Dixon noted. MRI might be useful to evaluate response, but not at all DCIS is visible on MRI. The ongoing studies of combinations will likely be more promising. The panel noted that there were limitations to meta-analysis of breast conservation, such as those in the JAK2-STAT or SWI/SNF pathways that may drive cancer.

Another important finding that was highlighted was the impact of HER2 negativity on outcomes for breast cancer, research that was presented in a publication in Science, Ereda Toska and her team from Memorial Sloan Kettering Cancer Center used assays to investigate the epigenetic characteristics of breast cancer cells from patients who received treatment with PI3K inhibitors. The investigators found that inhibition of the PI3K pathway activates estrogen receptor (ER)-dependent transcription through the histone methyltransferase KMT2D, an epigenetic regulator. This important discovery can epigenetically inform treatment decisions, such as whether the combination of PI3K inhibitors and anti-ER therapies may be beneficial in this type of breast cancer.

Dr. Parsons concluded with a discussion of a study (Pappas et al) that investigated the activity of pS3 under low-stress conditions. Research found that investigation of a stress test for the identification of important tumor suppressor genes, such as PTEN and FOXO1, through consensus binding sites in enhancers and promoters, which could contribute to pS3-mediated tumor suppression.
Year In Review: Translational Research

Nicholas C. Turner, MD/PhD, from the Institute of Cancer Research in London, highlighted developments in translational research over the past year.

Dr. Turner began his discussion by focusing on the importance of reducing overtreatment in early breast cancer. The study analyzed suppression of Ki67, a protein in cells that increases as treatment is administered. There was no evidence that interventions based on the results of the assays improve patient outcomes. He also stated that patients who had not declined to below 10% predicted poor prognosis for these patients.

Conversely, ACOSOG Z1031, a randomized, phase II trial comparing neoadjuvant exemestane, letrozole, and anastrozole found that postmenopausal women with estrogen receptor (ER)-positive breast cancer may have better prognosis after receiving neoadjuvant therapy. The completion of neoadjuvant therapy and surgery, a significant number of patients were found to achieve pathologic complete response (pCR), which is a robust biomarker to estimate residual risk. These studies also encourage the validation of the potential clinical utility of the methodology, incorporating information from gene expression profiling or molecular markers should not be perceived as mandatory. Kim et al concluded in their study that integrating histopathologic and molecular information into the decision-making process allows refocusing of the use of new molecular tools to cases with uncertain risk.

Questions on quality of life were also asked this past year. Hershman presented a talk on the role of acupuncture over sham acupuncture over controls (wait-listed for acupuncture) in the impacts on AI musculoskeletal toxicity. Data on duoduline revealed an impact of 12 weeks. The ART trial observed that letrozole is associated with greater inhibition of Ki67 in women with breast cancer.

Overview Committee of the 20-year risks of breast cancer recurrence after stopping endocrine therapy at 5 years showed that, despite attempts to identify the optimal proliferation genomic profiling, the old, high quality pathology/tumor size/node status remains powerful for new assays. Data confirmed that in the adjuvant setting, trastuzumab does not benefit HER2-targeted therapy, data increasingly show that shorter is not better. Data on duoduline revealed an impact of 12 weeks. The ART trial observed that letrozole is associated with greater inhibition of Ki67 in women with breast cancer.

Dr. Turner concluded this section by saying that the significance of the gut microbiome to breast cancer remains unknown, and efforts to investigate are essential.

Year End Review: Early Breast Cancer in Review

Highlighting several key papers in early breast cancer since last year’s Symposium, Dr. Antonio C. Wolff began his Year in Review covering access to care, risk factors, and risk reduction. “The global burden of women’s cancers: a grand challenge in global health” by Ginsburg et al highlighted the disparities in cancer care, especially in low- and middle-income countries. Additionally, excessive weight gain and obesity are also becoming global health threats to risk of cancer and not just in low- and middle-income countries. There is growing evidence of the importance of weight loss, especially in older cancer survivors.

Transferring into individual patient discussion, Dr. Wolff presented Kuriyan et al’s paper on the genetic counseling of newly diagnosed breast cancer patients. The fraction of patients who wanted testing and were given the opportunity was only half, while 20% of lower risk patients were provided counseling. Kuriyan et al’s paper found cumulative breast and ovarian cancer risk in carriers of BRCA1/2 mutations who are important for counseling on preventive strategies and for family.

De-escalation of local therapy was also a common theme predict breast cancer recurrence. Dr. Turner noted that these approaches add to a small set of proof-of-principle studies that explore the potential to reduce overtreatment in early breast cancer studies, and no evidence that interventions based on the results of the assays improve patient outcomes. He also stated that therapies that may predict high risk for relapse, a negative result can imply either that there is no cancer present, or that the assay has failed to detect the presence of cancer.

Dr. Turner discussed developments in noninvasive breast cancer testing. He discussed liquid assays, such as the measurement of circulating tumor cells, which can potentially feature include:

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Ending this year’s Symposium, Dr. Nancy Lin presented a talk highlighting advancement on advanced and metastatic breast cancer in 2017.

She began her review with CDK4/6 inhibitors. PALOMA-1, PALOMA-2, MONALEESA-2, and MONARCH-3 trials all saw similar results in hazard ratio, progression-free survival, and objective response rate. The data suggest leaning away from chemotherapy in ER+ patients and towards endocrine therapy. MONALEESA-7 compared ribociclib vs placebo in pre- or perimenopausal women who had not received prior endocrine therapy in the advanced disease setting. Substantial improvement in progression-free survival was observed in favor of the ribociclib arm, as well as a sustained improvement in quality of life. She summarized that for pre- and postmenopausal women who have ER+, HER2-negative metastatic breast cancer, CDK4/6 inhibitors are one standard option in the first line setting. No conclusions can be made yet on whether one CDK4/6 inhibitor is superior to another. Goel et al showed that the combination of CDK4/6 inhibitor and an immune checkpoint inhibitor could have clinical efficacy, while the PACE trial asked whether there’s value in continuing CDK4/6 inhibitor beyond progression and whether there’s value in the addition of a checkpoint inhibitor. The PATINA trials looked into the role of CDK4/6 inhibitors in the treatment of HER2+ breast cancer.

PARP inhibitors were also an important topic this year in advanced and metastatic breast cancer. OlympiAD compared olaparib vs chemotherapy (vinorelbine, capecitabine, or eribulin) in BRCA-associated breast cancer. Olaparib is currently under FDA priority review in the setting of gBRCA 1/2 mutated metastatic breast cancer. EMBRACA, presented at this meeting by Dr. Litton, presented a significant prolongation of progression-free survival in favor of talazoparib, with results similar to OlympiAD’s. There are currently several ongoing studies looking at leveraging the value of PARP inhibitors in the setting of gBRCA 1/2 metastatic disease.

Dr. Lin then moved onto antibody conjugates, beginning with IMMU-132 (anti-Trop-2 plus the irinotecan derivative SN-38), for which Bardia et al reported a response rate of 30% in heavily pretreated metastatic triple negative breast cancer. SGN-LIV1A is another antibody drug conjugate that recognizes LIV1, a transmembrane protein present in nearly all breast cancer subtypes, and carries the microtubule-targeting monomethyl auristatin. Modi et al presented here results with this compound in patients with refractory triple negative breast cancer, with an overall response rate of 25%. Data on DS-8201a (trastuzumab deruxtcan) was also presented by Modi et al.

HER2-targeted kinase inhibitors in development to note are neratinib, an oral, irreversible inhibitor, tucatinib, a selective HER2 inhibitor, and pyrotinib, a pan-HER inhibitor. Freedman et al looked at the combination of neratinib and capecitabine in patients with HER2+ breast cancer brain metastases, which occur in over half of patients over time, and reported an intracranial response rate of 50%. A 2016 phase 1 study by Hamilton et al. had reported a 42% ORR in CNS metastases with tucatinib added to trastuzumab and capecitabine. Ma et al, in their phase 1 pyrotinib trial, observed an overall response rate of 83.3% in trastuzumab-naive metastatic breast cancer patients and 33.3% in trastuzumab-treated patients. This meeting’s audience also learned from Xu et al about a randomized phase 2 pyrotinib/capecitabine vs lapatinib/capecitabine trial, with improvements in the objective response rate and median progression-free survival at the cost of higher toxicities in the pyrotinib/capecitabine arm.

In 2017, several studies, such as KEYNOTE-110, IMPassion-130, I-SPY2, and PANACEA, looked into immunotherapy. The PANACEA study showed that stromal TILs ≥ 5% could be a potential predictive marker in PD-L1 positive patients. Moving forward into 2018, Dr. Lin points out, IO combinations will be a main focus. Kohrt et al looked into CD137 and a mechanism of trastuzumab cell killing mediated via ADCC. Data suggest that specificity to particular tumor cells can be created using a systemic administration of a CD137 agonist. This concept is further being investigated in the AVIATOR trial.

To cap off her review, Dr. Lin highlighted potential topics and advancements in 2018. For CDK4/6 inhibitors, their role in HER2+ metastatic disease and continuation of post-progression in combinations will be hot topics. For PARP inhibitors, the key will be the exploration of their role in other germline/somatic alterations. For antibody drug conjugates, there are a few agents to watch for. For HER2-targeted kinase inhibitors, NALA results and accrual to randomized trials are to be expected. Finally, for immunotherapy, the field will continue to explore agents in other subtypes.