Almost 21,000 papers on breast cancer were published in 2019; it remains a huge challenge worldwide, with a relatively high incidence in more developed countries, resulting in more than a quarter of a million cases every year. Eighty percent of those cases are curable. Unfortunately, the remainder are still deadly, sooner or later, and end in more than 42,000 deaths every year in the U.S. alone - five every hour, and two for every paper published on breast cancer.

A close examination of these numbers shows us that we are still not able to reduce deaths from breast cancer despite all our work. Increased screening has helped, but we are not able to know which of the cases we find are going to recur as a deadly disease, and how our response to these cases can be better tailored to reduce treatment and produce better results. A better understanding of the biology of breast cancer is fundamental to making progress with this disease.

Overall, research in breast cancer seemed to group itself around five fundamental questions:

- How do breast tumors initiate, and which early lesions will progress? Which tumors don’t require treatment?
- What dictates the breast cancer subtypes? What about heterogeneity?
- How do tumor cells evade therapy? Systemic therapy is given to prevent recurrence, but 20-30% of breast cancers recur.
- Why are certain cancers capable of metastatic growth? Which ones?
- Why can’t we cure metastatic breast cancer (yet)? Are there promising new targets?

One theme recurs in the research into all the questions: functional plasticity – a term most often used in neuroscience to describe a response to injury or other insult. The same process is apparent in cancer.

A range of research work in 2019 showed us that the cell of origin matters when it comes to tumor initiation and progression. Recent studies confirmed that the cell state can be altered during tumorigenesis with BRCA1. EM-like plasticity is a frequent early event during tumorigenesis, with immune-mediated restriction of progression through antigen presentation and Treg activity.

What dictates the breast cancer subtypes? Research in 2019 offered us many insights into breast cancer subtype. The ER cistrome is reprogrammed in ER+ tumors, perhaps based on the chromatin landscape of the cell of origin. Additionally, phosphorylation of EZH2 causes a dominant basal-like phenotype that can switch to ER+ luminal by blocking this phosphorylation, and there is evidence of a “plastic” subtype that may influence therapy response.

How, then, do tumor cells evade therapy? In 2019, research indicated that pre-existing populations can phenotype-switch when challenged with therapy, resulting in transcriptional plasticity and epigenetic regulation that may be reversible.
The potential role for rechallenge with a CDK4/6i. RB1 has Hippo signaling via CDK6, which may point towards further issue; FGFR1 is a potential mechanism of resistance, and setting. Could AKT inhibitors could be helpful? Elsewhere, resistance. This raises questions concerning the clinical that PTEN loss is a double blow for therapeutic intervention. Effective for p53 wildtype tumors; other investigations show combination of CDK4/6i and MDM2i therapy may prove to CDK4/6 inhibitors, and CDK2 is emerging as an important treatment as well: melanomas are often intrinsically resistant to CDK4/6 inhibitors, and CDK2 is emerging as an important driver of resistance. Research in 2019 indicated that a combination of CDK4/6i and MDM2i therapy may prove effective for p53 wildtype tumors; other investigations show that PTEN loss is a double blow for therapeutic intervention. PTEN loss could mediate both PI3K and CDK4/6 inhibitor resistance. This raises questions concerning the clinical implications for PI3K inhibitors in dual inhibition of CDK4/6/CDK6 setting. Could AKT inhibitors could be helpful? Elsewhere, investigations indicated that aberrant FGFR signaling is an issue. FGFR, however, and studies emphasized the importance of using matched control cDNA from white blood cells. Cancer screening through cDNA is one step closer through ‘DNA Evaluation of Fragments for early Interception’ (DEFI). There is still work to be done for its use in breast cancer, especially early stage. A more comprehensive survey of the genomic landscape of metastatic breast cancer is underway, emphasizing the need to exploit treatments early: the occurrence of HER2 and HER3 mutations.

**YEAR IN REVIEW: TRANSLATIONAL RESEARCH**

2019 was a big year for focusing on hormone receptor positive tumors and resistance to CDK 4/6i inhibitors. These are very familiar pathways, but additional research into the mechanics of ER and CDK4/6 resistance continues. Additionally, there have been advances in early detection, prediction, and discovery, especially, and work with CTCs, ctDNA, and genomics. In targeting CDK4/6, research shows that de novo or acquired resistance to CDK4/6 inhibitors is almost inevitable. Apart from ER, it is difficult to delineate patients who will most benefit from combination therapy, and dual endothelial and CDK4/6 inhibitor therapy imposes a profound G1-S arrest.

The emerging theme of resistance focuses on pleiotropic mechanisms of resistance, each numerically small in effect. Cyclin E-CDK2 provides an alternate pathway for G1-S progression; patients with high CCNE1 still benefited. CCNE1-CDK2 provides an alternate means of phosphorylating RB. There are lessons to be learned from melanoma research, indicating that a combination of CDK4/6i and MDM2i therapy may prove effective for p53 wildtype tumors; other investigations show that PTEN loss is a double blow for therapeutic intervention. PTEN loss could mediate both PI3K and CDK4/6 inhibitor resistance. This raises questions concerning the clinical implications for PI3K inhibitors in dual inhibition of CDK4/6/CDK6 setting. Could AKT inhibitors could be helpful? Elsewhere, investigations indicated that aberrant FGFR signaling is an issue. FGFR, however, and studies emphasized the importance of using matched control cDNA from white blood cells. Cancer screening through cDNA is one step closer through ‘DNA Evaluation of Fragments for early Interception’ (DEFI). There is still work to be done for its use in breast cancer, especially early stage. A more comprehensive survey of the genomic landscape of metastatic breast cancer is underway, emphasizing the need to exploit treatments early: the occurrence of HER2 and HER3 mutations.

2019 saw new and continuing investigations into early detection, prediction, and discovery: circulating tumor cells (CTCs), ctDNA, and genomics were all investigated, including work into circulating tumor cells and late resistance. Research showed that liquid-based markers may help stratify late risk for ER+ disease, and that CTCs were not predictive for ER- disease. Studies into the landscape of single vs. clusters of CTCs identified some actionable vulnerability, and showed that CTC clusters provoke more metastases. Other investigations including tumor surveilance with CTCs in patients with hormone depleted disease. ctDNA may be a marker of disease relapse/PFS and a surrogate marker of response in NAC. CTCs identified some actional vulnerability, and showed that whole-genome sequencing is a useful tool for identifying DNA alterations in small populations of CTCs. ctDNA, and genomics were all investigated, including work into circulating tumor cells and late resistance. Research showed that liquid-based markers may help stratify late risk for ER+ disease, and that CTCs were not predictive for ER- disease. Studies into the landscape of single vs. clusters of CTCs identified some actionable vulnerability, and showed that CTC clusters provoke more metastases. Other investigations including tumor surveilance with CTCs in patients with hormone depleted disease. ctDNA may be a marker of disease relapse/PFS and a surrogate marker of response in NAC.

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**EARLY BREAST CANCER**

In Saturday’s Year in Review session on early-stage breast cancer, Dr. Masakazu Toi, MD, PhD, from Kyoto University in Japan, discussed highlights from 2019 research, including escalation and de-escalation of treatment for HER2-positive disease, predictive and prognostic markers of benefit from pertuzumab and chemotherapy, and the role of immunotherapy in treatment of triple negative disease.

"DO LESS/DO MORE" APPROACH FOR TREATMENT OF HER2-POSITIVE BREAST CANCER

An updated analysis of the APHINITY trial showed a continued benefit in invasive disease, and a trend with addition of pertuzumab in patients with node-positive disease at a median of 74.1 months follow-up (87.9% vs 83.4% with placebo; hazard ratio [HR] 0.72). According to Toi, these results highlighted the importance of using matched control cDNA from white blood cells. Cancer screening through cDNA is one step closer through ‘DNA Evaluation of Fragments for early Interception’ (DEFI). There is still work to be done for its use in breast cancer, especially early stage. A more comprehensive survey of the genomic landscape of metastatic breast cancer is underway, emphasizing the need to exploit treatments early: the occurrence of HER2 and HER3 mutations.

However, he added that patients with low-risk HER2-positive disease would likely benefit from a “do less” approach for treatment. Subgroup analysis from the phase III KRISTINE trial showed that patients who achieved a pathologic complete response (pCR) had better DFS than patients with residual disease at 3-year follow-up, with no difference between neoadjuvant trastuzumab emtansine (T-DM1) vs pertuzumab and the trastuzumab, pertuzumab, and chemotherapy arms. Toi suggested that the nearly identical DFS between treatment arms may have been because patients in the T-DM1 plus pertuzumab arm received adjuvant chemotherapy if they had residual tumor >1 cm or nodal disease. This ‘rescue-type chemotherapy approach’ often results in less toxicity for patients, said Toi. In addition, the randomized phase II JATEMT trial showed the importance of 5-year DFS with T-DM1 therapy for the trastuzumab plus paclitaxel arm (97.9% vs 92.8%, p=0.001) with the not all Triple Negative Breast Cancers (TNBCs) are created equal. Some are actionable, and research this year showed that whole-genome sequencing could better inform clinical decision making. We saw equally important inquiries into the resection of 3.2% of tumors, demonstrating that in the future, panel tests could be used to identify HR deficiency.

Finally, 2019 saw a growing role for the immune system well beyond lymphocyes, which has been the target of therapy to date. Recent work in the field of TNBC and the immune microenvironment emphasized the importance of value of TAMS as a therapeutic target, confirming a strong prognostic role of stromal tumor-infiltrating lymphocytes (sTILs) in early stage TNBC and the role of tumor necrosis factor (TNF) as a predictor of benefit from most TNBC treatments. Investigations into the therapeutic targeting of CDK2/CDK13 revealed novel ways to exploit HR-competent tumors, while other research showed that tumor-associated macrophages (TAMS) could be a new therapeutic target. The S1GECI/CCLI signature is associated with poorer outcome, while cancer-specific targeting of TAMS has therapeutic potential.

2019 offered us a plethora of new mechanisms of CDK4/6 resistance, many revealing new targeting strategies. They may be small in impact individually, but they indicate many new pathways for inquiry, rather than assuming that "one size fits all". ctDNAs are showing immediate relevance and long term promise, and further genomic advances are on the way. 2019 also showed a growing emphasis on identifying and/or inducing “BRCAness” in tumors, which will make them more susceptible to conventional therapies used in the clinic. Finally, we saw many new strategies to target TNBC and to target new subclasses of immune cells, including macrophages.

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added benefit of no chemotherapy-induced cytotoxicity with the former regimen, according to Toi. “The ‘do less/do more’ approach is important to develop more individualized treatment for patients,” he said.

PREVENTIVE AND PROGNOSTIC MARKERS OF RESPONSE TO THERAPY

Dr. Toi continued with an overview of studies investigating potential genomic and clinical correlates of prognosis and response to treatment. A biomarker analysis of the APEHILL1 trial showed that activation of the PIK3CA mutation pathway, Myc overexpression, ZNF amplification, and basal phenotype were associated with unfavorable outcomes, whereas HER2 copy number ≥6 and TOP2A amplification appeared to be favorable prognostic markers. Additionally, density of tumor-infiltrating lymphocytes >75% and a T-cell signature were significant predictors of benefit from pertuzumab.

Dr. Toi also discussed a recent publication in the New England Journal of Medicine that combined clinical risk factors with a genomic-based recurrence score to predict benefit from chemotherapy in early HER2-negative breast cancer. The study showed that while clinical risk did not predict benefit from chemotherapy on its own, it could provide additional prognostic information to the genomic recurrence score. Additionally, the study found that premenopausal patients 45 to 50 years of age with a recurrence score of 16 to 25 derived the greatest absolute benefit from chemotherapy.

“I integrated risk provides greater prognostic precision and may have clinical utility, presumably superior to clinical or genomic features used individually,” said Dr. Toi.

Dr. Toi discussed a potential algorithmic approach originally presented by Joseph A. Sparano, MD, for using integrated recurrence score and clinical risk to guide treatment for women ≥50 years of age. The algorithm suggested that tamoxifen alone may be adequate for patients with low integrated risk for distant recurrence, while ovarian function suppression, an aromatase inhibitor, and chemotherapy are recommended for patients with high recurrence score (26-100) and high clinical risk. The algorithm suggested that ovarian function suppression plus aromatase inhibitor therapy may be given as an alternative to chemotherapy in patients with recurrence score 16 to 25 and high clinical risk or recurrence score 21 to 25 and low clinical risk, but Toi indicated that more research is needed to support this strategy.

NEOADJUVANT CHEMOTHERAPY PLUS IMMUNOTHERAPY

Dr. Toi discussed several trials that are investigating immunotherapy oncologists with other therapies in the neoadjuvant setting. Results of the Keynote-522 trial, which were presented at this year’s ESMO and SABCS meetings, showed a significant improvement in pCR with addition of pembrolizumab to neoadjuvant chemotherapy in patients with triple negative breast cancer (TNBC). In addition, the GeparNuevo trial showed that a “window approach,” in which neoadjuvant durvalumab was given for 2 weeks prior to durvalumab plus chemotherapy, led to a pCR of 61% in women with TNBC. By contrast, the NeoTRIP trial did not show a benefit of adding atezolizumab to carboplatin and nab-paclitaxel in the neoadjuvant setting, although Dr. Toi noted that the trial is ongoing and the outcomes following the anthracycline-based chemotherapy in the adjuvant setting may provide important information.

“We are very excited about how we can develop immunotherapy oncologists for triple negative disease, particularly in the neoadjuvant setting,” said Dr. Toi.

Dr. Toi added that the TONIC study, which investigated the effects of different types of induction therapy on the tumor microenvironment and response to nivolumab in patients with TNBC, showed that short-term exposure to cisplatin or doxorubicin prior to nivolumab improved response compared to nivolumab with no induction therapy, whereas induction therapy with cyclophosphamide or radiation therapy did not improve response to nivolumab. Additionally, an ongoing trial (CheckMate 742) is studying neoadjuvant nivolumab, anastrozole, and a CDK4/6 inhibitor (abemaciclib or palbociclib) before surgery, showing an association between resistance to CDK4/6 inhibitors and changes in the tumor microenvironment.

Dr. Toi concluded that more research is needed on the types of chemotherapy given with immunotherapy, the difference in efficacy between PD-1 or PD-L1 antibodies, the optimal window for immuno-oncology, and the selection of adjuvant chemotherapy for patients post-oncotype disease after neoadjuvant immunotherapy plus chemotherapy.

PI3K INHIBITION FOR PIK3CA-MUTATED DISEASE

Dr. Hurvitz continued her presentation with an overview of the phase III SOLAR-1 trial, which showed that addition of alpelisib to fulvestrant improved PFS in patients with pretreated HR-positive, PIK3CA-mutated metastatic breast cancer but not in patients with PIK3CA-wild type tumors. The U.S. Food and Drug Administration (FDA) approved alpelisib in combination with fulvestrant in postmenopausal women or men with PIK3CA-mutated HR-positive advanced or metastatic breast cancer after progression on endocrine therapy. However, Dr. Hurvitz noted that the toxicity profile for alpelisib is clinically significant and several unanswered questions remain, including the degree of benefit for patients previously treated with everolimus, the optimal combination of alpelisib plus chemotherapy for patients previously treated with fulvestrant, the benefit of alpelisib in patients previously treated with or in combination with a CDK4/6 inhibitor, and the degree of benefit of alpelisib for other types of breast cancer with PIK3CA alterations.

YEAR IN REVIEW: METASTATIC BREAST CANCER

In Saturday’s Year in Review session on metastatic breast cancer, Sara A. Hurvitz, MD, from the University of California, Los Angeles, presented highlights from 2019 research on CDK4/6 inhibition in HR-positive disease. PI3K inhibition in PIK3CA-mutated disease, novel targeted therapies in HER2-positive disease, and new treatment combinations in triple negative breast cancer (TNBC).

CDK4/6 INHIBITION IN HR-POSITIVE METASTATIC BREAST CANCER

Results from MONALEESA-7, the first phase III trial that investigated CDK4/6 inhibition exclusively in premenopausal patients, presented at ASCO 2019 and published in the New England Journal of Medicine, showed that more patients who received ribociclib plus endocrine therapy were alive at 42 months than those who received placebo plus endocrine therapy (70.2% vs 46.0%, p=0.00973). The MONALEESA-3 trial, which was presented at the ESMO 2019 meeting, showed that, compared to placebo plus fulvestrant, ribociclib plus fulvestrant led to significantly better progression-free survival (PFS) for patients in the first-line setting or with a disease-free interval >12 months after prior endocrine therapy (median 33.6 vs 19.2 months, hazard ratio [HR] 0.55) and patients in the second-line setting or disease relapse >2 months after starting endocrine therapy (median 14.6 vs 9.1 months, HR 0.57). Median overall survival (OS) was also significantly improved with ribociclib plus fulvestrant in the first- and second-line settings.

The MONARCH2 trial presented at the ESMO 2019 meeting also showed that palbociclib plus fulvestrant improved PFS and OS over placebo plus fulvestrant in patients with no or one line of prior endocrine therapy (median PFS 16.9 vs 9.3 months with placebo, HR 0.34; OS 46.7 months vs 37.3 months, HR 0.36). Additionally, HR values were similar in the first and second-lines, “underscoring that in the second-line setting, the use of a CDK4/6 inhibitor improves survival outcomes,” said Dr. Hurvitz.

She also noted that while the GEICAM trial presented at SABCS 2019 did not show a benefit of palbociclib plus exemestane or fulvestrant over capecitabine in terms of PFS outcomes or ORRs in patients with pretreated HR-positive metastatic breast cancer, the palbociclib-based regimen may be problematic due to its low toxicity. “Toxicity should certainly be considered when we’re choosing which therapy to deliver to our patients,” she said.

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NOVEL THERAPIES FOR METASTATIC HER2-POSITIVE BREAST CANCER

The HER2CLIMB trial investigating tucatinib, trastuzumab, and capecitabine in patients with HER2-positive metastatic breast cancer was the first to allow enrollment of patients with progressive CNS metastasis due to the CNS activity of tucatinib demonstrated in previous trials, according to Dr. Hurvitz. Nearly half of the patients in the trial had CNS metastases, and approximately 40% of those patients had CNS metastases that were untreated or treated and progressing. A significant 2.2-month improvement in PFS was demonstrated with tucatinib in the overall population and among the patients with CNS metastases. OS was significantly improved with tucatinib over placebo in the overall study population and the subgroup with CNS metastases. Diarrhea was more common in the tucatinib arm, likely due to the use of two HER2-targeted therapies along with capecitabine, according to Dr. Hurvitz.

TREATMENTS FOR TRIPLE NEGATIVE BREAST CANCER

The DESTINy-Breast01 trial showed that trastuzumab deruxtecan, a novel HER2-targeted antibody-drug conjugate, led to an overall response rate of 60.9% in patients with heavily pretreated unresectable or metastatic HER2-positive breast cancer. Dr. Hurvitz noted that patients with less than 3 prior lines of therapy had an ORR of approximately 75%, and even patients with lower levels of HER2 expression (IHC 1+ or 2+) had an ORR close to 50%. However, four cases of grade 5 interstitial lung disease were reported, and Dr. Hurvitz stressed the importance of elucidating the pathophysiology of this complication, which does not always respond to steroid treatment, in future studies.

The last section of Dr. Hurvitz’s talk focused on key studies in TNBC. The Impassion130 trial showed that first-line treatment with atezolizumab plus nab-paclitaxel significantly improved PFS and led to an improvement in OS by 7 months in patients with metastatic, PD-L1 positive TNBC. These results prompted accelerated FDA approval of atezolizumab plus nab-paclitaxel in the frontline setting for this patient population.

Additionally, a phase Ib study showed an overall response rate of 73% with ipatasertib (Akt inhibitor), atezolizumab, and paclitaxel or nab-paclitaxel in patients with treatment-naïve locally advanced or metastatic TNBC. Although Dr. Hurvitz noted that adverse events will need to be managed carefully with addition of an Akt inhibitor, she anticipated that ipatasertib will likely be used in combination with other therapies in upcoming clinical trials.

Furthermore, phase I results of a trial published in the New England Journal of Medicine showed an ORR of 33% with sacituzumab govitecan, a novel antibody-drug conjugate, in heavily pretreated patients with metastatic TNBC. These promising results have prompted the initiation of the phase III ASCENT study comparing sacituzumab govitecan with investigator’s choice of therapy in patients with pretreated metastatic TNBC.

Dr. Hurvitz concluded that while much progress has been made this year in metastatic breast cancer, “involvement of colleague patient advocates should inspire us to de-escalate [therapy] when we’re able to, target and identify targets, and help counter-resistance so we can begin to move the field forward and see vast improvements in survival.”