Tumor heterogeneity was the focus of some of the most exciting basic science research in 2018, Robert Benezra, PhD, said on Saturday. Single-cell sequencing studies have allowed researchers to observe that tumor cell clones were present in tissue ducts before invading invasive parenchymal tissue. The basic theme of the findings, said Dr. Benezra, of Memorial-Sloan Kettering Cancer Institute in New York City, was that “changes take place within the duct prior to extravasation.” It also has been shown that in some patients, clones of certain mutated cells were “extinguished” following treatment, and that this finding is associated with a good therapeutic outcome. Mutations that persist even after treatment are thought to have adapted to the chemotherapy. Other tumor cells may develop acquired resistance to the chemotherapy through transcriptional reprogramming. The investigators postulated that harsher, more mutagenic chemotherapy regimens may promote even more acquired resistance in certain tumor cell types.

In other research, single-cell RNA sequencing of triple negative breast cancer (TNBC) cells has shown that up-regulation of the glycosphingolipid pathway in those cells is associated with poorer therapeutic outcomes, at least in part because that mutation also was associated with an increase in innate immune cells, which may have protected pro-invasive or tumorigenic lymphocytes within that cell population.

Heterogeneity also characterizes the tumor microenvironment (TME), Dr. Benezra continued. In what he termed a “rather lovely study,” Fatima Mechta-Grigoriou and colleagues have found that subsets of TNBC cancer-associated fibroblasts (CAFs) have different genetic signatures that vary across breast cancer subtypes. One of these CAFs (CAF-S1) is associated with immunosuppression. These findings give rise to more questions, such as: “Can one CAF subtype be converted to another, or are these fixed states?” and “How do CAF subtypes compare between primary and metastatic tumors?”

Another feature of the TME is that it may influence tumor response to chemotherapy. TW Miller and colleagues have found that stromal cells may secrete fibroblast growth factor (FGF) 2, which can engage tumor FGF receptors and confer drug resistance on ER+ breast cancer cells. One question to address moving forward, said Dr. Benezra, is whether or not the FGF2 is secreted in response to tumor cell signals, “and if so, what are those...signals that are conferring that ability to resist these therapies?”

In the realm of tumor metabolism, Dr. Benezra described a “very nice” study by Gregory J. Hannon and colleagues showing that asparagine synthesis is crucial to metastatic progression.

In a particularly intriguing finding, reducing dietary asparagine in mouse models was associated with a reduction in lung metastases. Other investigators have found that increasing reactive oxygen species in the tumor environment may
promote the transition of mesenchymal to epithelial cells. Scavenging the reactive oxygen through the addition of n-acetyl cysteine had the opposite effect. Adding drugs such as n-acetyl cysteine to xenograft tumors of women with high p53 levels may have therapeutic value by hastening cell death.

The year also saw some interesting research in the area of metastatic progression. Dr. Benezra said. "In an exploration of the well-established observation that metastatic potential is related to chromosomal instability, Samuel F. Bakhoum and colleagues showed that misregulation of chromosomes can elicit a pro-inflammatory response within the tumor environment, induce epithelial-to-mesenchymal transition, and ultimately result in a higher metastatic burden within laboratory animals. Other studies examined the phenomenon of tumor dormancy and the genetics of brain metastases."

"Single-cell sequencing analysis allows for detailed analysis of tumor heterogeneity and tumor evolution, which may inform clinical decisions," Dr. Benezra concluded. "The interplay between the tumor and the microenvironment continues to reveal new basic mechanisms of tumor evolution and diversification, which may provide new targets for intervention."

Additionally, "chromosome instability may fuel tumor metastasis by inducing a pro-inflammatory response to cytoplasmic DNA." Finally, he said, "amino acid deprivation is associated with chromosomal instability, Samuel F. Bakhoum and colleagues showed that misregulation of chromosomes can elicit a pro-inflammatory response within the tumor environment, induce epithelial-to-mesenchymal transition, and ultimately result in a higher metastatic burden within laboratory animals. Other studies examined the phenomenon of tumor dormancy and the genetics of brain metastases."

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"Such an analysis has shown enormous diversity in the "guest list" and is the population of T cells relative to B cells within the TME. Dr. Tutt explained. This suggests a diversity of checkpoint receptor expression. For example, there appears to be a much higher volume of T cells and NK cells within the TME compared with normal breast tissue environment, which presents a possible target for therapies that are currently available. Understanding the TME also may be important for designing trials of treatments against the different types of cells. Other research has shown that high levels of the CD8+ class of tumor resident memory cells is associated with higher survival times, compared with patients who have fewer of these cells."

Defining "who wears what and who dances with whom" - that is, what markers are present on the immune cells and what they do - is also an important focus of research. Dr. Tutt said, "This gets us beyond a guest list to who sat with who, who danced with who, and as we all know, at any good party, learning about who came with one person and left with another might give you particularly good information along the course of treatment."

The role of tissue-infiltrating lymphocytes (TILs) also has come under close scrutiny. Much has been learned about their type, location, and genetic expression. Dr. Tutt pointed out. Variability in the 3-dimensional organization of cells and drug targets in tumors and lymphoid tissue with different types of TILs may have significant prognostic implications and "may help inform precision of drug benefit" in future clinical trials, as well as offering new biomarkers for correlative biology. He cited the example of neoadjuvant chemotherapy in the treatment of triple-negative breast cancer: a "cold" tumor with few TILs portends a poorer response to NACT and a less favorable prognosis overall.

Building on this knowledge, neoadjuvant oncolytic virotherapy prior to surgery presents another promising avenue of clinical research in mouse models. It has been shown to sensitize triple-negative breast cancer (TNBC) cells to oncolytic viruses, which infect and replicate within the breast cancer cells, leading to immunogenic cell death. The investigators concluded that pre-surgical exposure of "cold" tumors to a viral stimulus might lead to a better response to checkpoint inhibitors.

In the realm of genomics and epigenetics, particularly with respect to metastatic tumors, mutations in genes ESRR1, ERBB2, and NF1 were associated with greater resistance to endocrine therapy, compared with tumors that did not have those mutations. Dr. Tutt added. Such alterations were shown to occur in 22% of tumors, and were associated with a shorter duration of therapeutic response. All in all, SABCBS featured a "tsunami" of data on the identification of mutations and the use of therapeutic agents targeted to these mutations. Most of the differences were seen in ER-positive tumor cells, with metastatic lesions showing an even higher concentration of mutations than the primary tumors.

Current research is confirming that the "genomic landscape of metastatic breast cancer is different than that of early-stage breast cancer," although these are not the only factors that determine response or resistance to treatment. The epigenetic landscape also is important, Dr. Tutt noted.

The clinical utility of these findings has been studied in a series of "basket" trials, which group together tumors that come from different organs but have similar mutations. In a study of tumors with HER2 and HER3 mutations, a tyrosine kinase inhibitor (neratinib) elicited "meaningful" responses from breast cancer patients with missense mutations in the kinase domains.

For clinicians and patients alike, the stress of a breast cancer diagnosis may be increased by a BRCA genetic report that comes under close scrutiny. Much has been learned about their type, location, and genetic expression. Dr. Tutt pointed out. Variability in the 3-dimensional organization of cells and drug targets in tumors and lymphoid tissue with different types of TILs may have significant prognostic implications and "may help inform precision of drug benefit" in future clinical trials, as well as offering new biomarkers for correlative biology. He cited the example of neoadjuvant chemotherapy in the treatment of triple-negative breast cancer: a "cold" tumor with few TILs portends a poorer response to NACT and a less favorable prognosis overall.

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EXTENDED AROMATASE INHIBITOR THERAPY

"Data on efficacy of extended aromatase inhibitor therapy, beyond 5 years in unselected patients are not convincing," Dr. Sharma stated, in reference to the Early Breast Cancer Trials' Collaborative Group meta-analysis of over 22,000 women and 11 clinical trials. Women who received aromatase inhibitor therapy after 5 years of tamoxifen had a 3.6% 5-year gain in any recurrence, and 1.5% gain in distant recurrence. Women who received extended aromatase inhibitor therapy after 5 to 10 years of tamoxifen and aromatase inhibitor therapy had a lower gain in any recurrence (2%) and only 10% gain in distant recurrence. For women who received extended aromatase inhibitor therapy after 5 years of initial aromatase inhibitor therapy, there was a very small gain in any recurrence with negligible gain in distant recurrence.

Dr. Sharma acknowledged that the benefit of extending endocrine therapy was much larger in patients with node-positive disease, with quite significant benefits in patients with 1+ or 2+ positive nodal disease.

"Patient tolerance and long-term side effects, such as bone loss, should be kept in mind," she added.

NOVEL AGENTS IN TRIPLE-NEGATIVE BREAST CANCER

Finally, Dr. Sharma reviewed new approaches for treatment of triple-negative breast cancer. She presented data on GeparNuevo, a randomized phase II trial evaluating the addition of durvalumab (an anti-PDL1 antibody) to an anthracycline- and taxane-based chemotherapy regimen in triple-negative breast cancer. In this trial, patients who were assigned to durvalumab had a pathologic complete response rate of 53.4%, compared to 44.2% in the placebo arm, which was not statistically significant.

"We need better tools to identify the risk-benefit ratio of any function suppression in women who do not need chemotherapy," Dr. Sharma said.

PI3K INHIBITOR TRIALS

The Sandipani trial divided patients with prior progression on aromatase inhibitors according to whether they had PIK3CA-mutant tumors. Patients were then randomized to taselisib (a PI3K inhibitor) plus fulvestrant vs placebo plus fulvestrant. The primary endpoint of the study was progression-free survival in the PIK3CA-mutant group. The study indicated a statistically significant 2-month advantage in progression-free survival in the mutant cohort. "But eventually, this was felt to be not clinically meaningful, and due to the toxicity of the agent, it was decided not to move forward," Dr. Connolly said.

However, results from the SOLARI trial, which looked at a similar patient population, were statistically significant. In this study, patients with prior progression on aromatase inhibitor therapy treated in the first- or second-line setting were randomized to alpelisib plus fulvestrant vs placebo plus fulvestrant.

The primary endpoint was locally assessed progression-free survival in the PIK3CA-mutant cohort. There was a statistically significant difference of 3 months between the arms.

"There are multiple other studies ongoing, including those testing this combination after CDK inhibition and in combination with CDK inhibition," Dr. Connolly said.

NOVEL HER2 AGENTS

This year there were updates in regards to tucatinib (a selective and reversible HER2 tyrosine kinase inhibitor) in combination with T-DM1 in the phase Ib setting, and also in combination with capecitabine or trastuzumab. According to Dr. Connolly, the studies suggest that the combinations are felt to be well tolerated, and "we now have an ongoing phase III study investigating a tucatinib, capecitabine, and trastuzumab combination."

Dr. Connolly briefly highlighted agents that may be helpful to patients with central nervous system disease, which she called an area of unmet need. "Agents such as neratinib in combination with T-DM1 are being investigated in the TBCRC022 trial."

A secondary prevention trial looking at patients with newly diagnosed low-volume HER2+ breast cancer treated with local therapy is trying to determine whether T-DM1 alone or T-DM1 plus temozolomide has a role in preventing development of brain metastases in HER2+ breast cancer.

IMPASSION130: ADVANCES IN TRIPLE-NEGATIVE BREAST CANCER

"It appears that immune checkpoint agents in combination with chemotherapy have the most promise in PDL1+ triple-negative breast cancer, which accounts for approximately 40% of the population studied in IMPASSION103," Dr. Connolly said.

The IMPASSION130 trial enrolled patients with metastatic or advanced PIK3CA-negative breast cancer who had treatment-free interval of ≥2 months and an excellent score on the ECOG Scale of Performance Status. Patients were randomized to trastuzumab with Nab-paclitaxel vs placebo with Nab-paclitaxel.

Among patients in the PDL1+ cohort, the median progression-free survival advantage for the combination was 2.5 months, which was statistically significant. The median overall survival advantage in an interim analysis was >10 months (not yet statistically significant at the time of analysis).

"I feel that these results will be clinically meaningful if they are confirmed with longer follow-up and statistical significance," Dr. Connolly said.

CAN TUMOR PROFILING GUIDE USE OF TARGETED THERAPY?

"It appears that the mutations that we find in metastatic breast cancer can evolve over time, and can be subtype-specific. The question is, can we target them?"

One trial Dr. Connolly highlighted was the SAFIR-01 trial, which found targetable mutations in 46% of breast cancer patients. Ultimately, 13% of those patients matched a clinical trial. And the response rate to targeted therapy within that group was 9%.

In the SHIVA trial, patients with solid tumors (not limited to breast cancer) carrying targetable molecular alterations were randomized to the indicated targeted therapy vs chemotherapy. Disappointingly, the median progression-free survival was around 2 months, and not significantly different between the arms. "There was actually less toxicity in the chemotherapy arm," Dr. Connolly pointed out.

"We still have many ongoing trials to answer these questions, including the NCI MATCH and TAPUR trials," concluded Dr. Connolly.