Saturday morning’s Year in Review session began with a talk by Dr. Myles A. Brown, from the Dana-Farber Cancer Institute in Boston, MA. Dr. Brown highlighted several studies showing important scientific discoveries that continue to advance the understanding of breast cancer (BC) development and the role of targeted therapies.

One major area of interest was the identification of BC stem cells and cancer cells of origin. Some of the questions raised were whether there is a bipotential progenitor/stem cell that gives rise to both the luminal and basal compartments, and which cells of origin give rise to the various BC subtypes.

Dr. Brown discussed papers by the group working with Geoffrey Lindeman and Jane Visvader, using lineage tracing to identify bipotential stem cells in normal mouse mammary glands. Dr. Brown also acknowledged work by Mohamed Bentires-Alj and his group, which addressed the issue of whether PIK3CA mutations alter the committed nature of progenitors.

Investigators showed luminal progenitors marked by keratin 8, and basal progenitors marked by Lgr5. The mutant PIK3CA allele was expressed in one or the other to determine the contribution of the basal or luminal progenitor to the compartments. Without PIK3CA, lineage tracing showed that K8 luminal progenitors only gave rise to luminal cells and Lgr5+ basal progenitors only gave rise to basal cells (these findings were in contrast to those by Visvader et al). The group then found that when the oncogene was expressed, lineage switching occurred. In the presence of oncogene in Lgr5 cells, progenitors led to only basal tumor types, which were not like basal-like BCs, but tumors similar to nonmalignant myeloepitheliomas. On other hand, when keratin 8 was expressed, the group saw real luminal BCs as well as switching of the mark (ie, these cells could give rise to basal cells and vice versa), “so it looks like things can get mixed up when you express the oncogene.”

Next, Dr. Brown focused on findings of somatic genetic changes that drive heterogeneity and resistance to therapy. He discussed work by Kornelia Polyak and how she and her group developed a technology called Specific To Allele PCR-Fluorescent In Situ Hybridization (STAR-FISH), a method linked to allele-specific PCR which allows one to ascertain the in situ clonal architecture of a clinical tumor sample on a single-cell level.

Dr. Brown then discussed work presented by Dr. Samuel Aparicio, which looked at clonal architecture of tumors in primary patient-derived xenografts of mouse models. Dr. Brown cautioned that since Dr. Aparicio’s group saw multiple results, a patient-derived xenograft does not always represent the patient’s clonal architecture. And for those hoping to use mouse avatars to direct therapy, he warned, “if it’s polyclonal to begin with, what actually grows in the mouse might be quite different from what was present in the patient.”
Finally, Dr. Brown focused on advances in transcriptional targets in cancer. One of the papers he discussed was that from the laboratory group working with Charles Perou. This group worked on molecular portraits of invasive lobular BC, and compared them to those seen in ductal carcinoma. The phenotype of the lobular subtype is primarily driven by specific genetic mutation, and the FOXA1 mutations were found to be extremely frequent in the lobular subset, compared to the ductal subset. Dr. Brown pointed out that this finding was particularly interesting because other laboratories have identified FOXA1 as a critical profractor for the estrogen receptor.

**Update on Translational Research**

In his talk on translational research, one interesting notion raised by Dr. Matthew J. Ellis was the hypothesis that chemotherapy works by a mechanism similar to the vaccination of tumors. For example, it was hypothesized that when chemotherapy agents target cancer cells, the dying cells release antigens, which in turn vaccinate the patient.

Dr. Ellis shared a paper by Erika Vacchelli et al, which described polymorphisms in immune response that influence chemotherapy responses. The group identified a mutation in the fluoropyrimidine receptor 1, a dendritic cell activator that is rendered inactive in its mutant form, thus leading to poor overall survival in patients with the mutation. Further genetic experiments identified that the presence of the FPR1 receptor and ligand annexin 1 was required to induce the immune response. Patients who were found to have a null allele for the receptor for annexin 1 could not hone to chemotherapy-exposed cells.

Thus, Dr. Ellis concluded that this work demonstrated that chemotherapy might need to be redesigned from the perspective of maximizing the tumor vaccination effect, and that patients with null alleles for the FPR1 receptor might have more difficulty mounting an immune response.

Dr. Ellis also shared a paper by a group working with Thomas Cox. This group used mass spectrometry to identify a new player in the role of bone metastasis. Lysyl oxidase (LOX), which could predict bone metastasis, was found to be released from hypoxic EP cells. This release of LOX appears to lead to the activation of osteoclasts in preparation of the bone for the arrival of tumor cells. Dr. Ellis acknowledged that the group showed that the LOX antibody could suppress bone metastasis in this particular model, possibly advancing treatment or prevention of bone metastasis.

**Update on Early Breast Cancer**

In her update on early BC, Dr. Ruth M. O'Regan, from the University of Wisconsin, Madison, discussed ER+ BC. She touched on the TAILORX trial and how findings in low-risk groups confirm original data that many ER+ cancers do not benefit from chemotherapy. Further, molecular assays, such as the Breast Cancer Index, appear to identify a group of ER+ patients who can stop adjuvant therapy at 5 years, though she points out that this “may not be quite ready for prime time.” She also presented data from the ABCSG-26 trial showing that bone-directed therapies such as denosumab can decrease fracture rate and improve outcome in patients taking aromatase inhibitors.

Dr. O’Regan then focused on findings in HER2+ BC, and the desire to use less therapy in these patients. She showed that in a trial of 3,900 patients with small cancers (T1a-c), chemotherapy and trastuzumab were beneficial in terms of overall survival, though the findings reached statistical significance only in the T1c group. A benefit in BC-specific survival was also seen with this regimen. Hence, these findings are in accordance to National Comprehensive Cancer Network guidelines that recommend treatment for cancers >1 cm, and discussion about treatment options for cancers 5 mm to 1 cm in size. Very small cancers can potentially go without adjuvant treatment, though Dr. O’Regan did point out that data show that adding trastuzumab to chemotherapy in the adjuvant treatment of small cancers “does make sense as well.”

Information from the ADAPT trial, a multi-arm study, was also presented. This study looked at women with HER2+HR+ cancers, most of which were triple-positive. Patients received 4 cycles of trastuzumab and endocrine therapy, trastuzumab linked to a chemotherapy agent (TDM-1) alone, or TDM-1 plus endocrine therapy. Unfortunately, results showed that women who did not receive chemotherapy had low (15%) pathologic complete response (pCR), but women who received TDM-1 either alone or with endocrine therapy had pCR rates up to 40%.

But Dr. O’Regan went on to point out that the cancers within this group are very heterogeneous. According to intrinsic subtyping of these cancers, surprisingly, one-third of these cancers actually have luminal A phenotype. The rest are luminal B or HER2+ subtypes. None of the studies that have been done to look at less treatment for HR+/HER2- cancers have stratified patients based on subtyping, and maybe it is possible that these luminal A cancers may be ones that can get away with less treatment, she commented.

She concluded her talk by reviewing papers on the treatment of triple-negative BC. She wrapped up by saying, “I don’t think we’ve addressed that novel approaches are needed for post-neoadjuvant chemotherapy, and added, “I don’t really think more chemotherapy makes a lot of sense in these patients.”

**Update on Metastatic Disease**

Dr. Sibylle Loibl from the German Breast Group in Neu-Isenburg, Germany, concluded the Year in Review session with an update on metastatic disease.

She gave an overview of recent advances in endocrine therapy, where she touched on findings looking at the potency of fulvestrant (500 mg) as monotherapy. She concluded that results from the phase II FALCON trial, which compares fulvestrant to anastrozole, will add more to the story. She also noted that further investigation is needed to determine which patients should be treated with CDK4/6 inhibition plus endocrine treatment.

In regards to advances in triple-negative BC, Dr. Loibl suggested that platinum monotherapy should be considered for patients with mutant guanine BRCA status metastatic BC. Also, the androgen receptor inhibitor, enzalutamide has been proven in a population selected by androgen gene array, but “it’s not yet prime time for every day clinical practice.”

Reviewing advances in HER2+ disease, Dr. Loibl brought up the CLEOPATRA trial that showed that overall survival can be improved by nearly 16 mo with dual blockade using trastuzumab and pertuzumab, compared to using taxane alone. And in advanced HER2+ disease, dual blockade was shown to lead to a doubling in overall survival. With the addition of T-DM1, as second-line treatment, overall survival of 31 mo can be achieved.

Looking beyond the subtypes, Dr. Loibl discussed brain metastasis in the LUX-3 study. This study treated patients with ataxinib alone, ataxinib plus vinorelbine, or a treatment of the physician’s choice. There was no difference in terms of progression-free survival and overall survival, and patients who received ataxinib alone arm did slightly worse. Unfortunately, brain progression could not be effectively prevented by these strategies. Dr. Loibl pointed out that 40% of this cohort had extra-brain metastases, and most only had brain metastasis (a majority was already irradiated, and 80% received prior treatment for metastatic BC). In the HER2+ setting, because anti-HER2 treatment was used, an overall survival benefit was achieved even in patients with brain metastasis of 1 yr.

Dr. Loibl then turned to a study that investigated whether giving zoledronic acid every 3 mo might be as effective as giving it every 4 wk. The study randomized patients to either the longer or shorter treatment interval, and saw no difference in skeletal-related events between the two groups. “I think this is something we should consider when we treat our patients—that sometimes we can do more if we give less,” she concluded.
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