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ISSUE 5

YEAR IN REVIEW: BASIC SCIENCE DISCOVERIES

Dedicating his talk to John Glenn for “inspiring generations of scientists and promoting science education and funding,” Dr. Mohamed Bentires-Alj opened this year’s Year in Review with an update on basic science discoveries.

His talk began with a review of advances in research on normal and neoplastic stem cells. Research this year helped define controls that need to be used to accurately interpret results of lineage tracing. Studies essentially reopened the debate on the absence or presence of multipotent stem cells within adult mammary glands. Findings by Nolan et al and Sau et al would suggest that the inhibition of RANKL can block the initiating signal and inhibition of NF- κ B may halt the proliferation. Robert A. Weinberg’s lab discovered that the activation of PKA induces mesenchymal-to-epithelial transition and the loss of tumor-initiating cells.

The talk continued with the genomic/proteomic landscape of BC and novel targets. Benjamin G. Neel’s group investigated the functional genomic landscape of human BC drivers, vulnerabilities, and resistance. Another study showed that JQ1-resistant cells remained dependent on BRD4 but not on its bromodomain, raising the possibility of bromodomain-independent recruitment of BRD4 in enhancing the growth of resistant triple-negative BC (TNBC) cells. Studies also looked into ways to target MYC+ cells, which has proven difficult until now.

On the topic of metastasis, Dr. Bentires-Alj discussed cell autonomous and non-cell autonomous mechanisms. Two tRNAs were discovered to be overexpressed in metastatic lines vs. parental lines. Latency competent cancer cells (LCCs) were shown to proliferate after infiltrating distant organs, while natural killer (NK) cells prevent the accumulation of their progeny and spare the LCCs, with the conclusion that LCCs are competent to initiate metastasis if NK surveillance stops. Neutrophils were also reported to support lung colonization of metastasis-initiating BC cells and suppress intraluminal NK cell-mediated tumor cell clearance. Finally, carcinoma-astrocyte gap junctions were discovered to promote brain metastasis by cGAMP transfer.

With that, Dr. Bentires-Alj concluded his whirlwind tour of 2016 discoveries.

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YEAR IN REVIEW: TRANSLATIONAL RESEARCH

Dr. Sherene Loi then followed up with a review on translational research. 2016 having been a big year in genomics for the community, the bottom line is now “how does this help us manage patients and develop new drugs?”

“Landscape of somatic mutations in 560 BC whole-genome sequences” from the ICGC Breast Cancer Working Group concluded that non-coding regions do not contain driver mutations, which, although a disappointment, continues to help us understand what causes BC and drives resistance to therapy. Research from the Carlos Caldas lab at Cambridge also analyzed the relationship between heterogeneity and outcome from Metabric and BIG 1-98. The Caldas lab further researched the best treatments to target 11q amplification by creating a biobank of 83 BC patient-tumor derived xenografts (PDXs). Although PDXs are promising, they are high in cost and currently overlook the impact of the immune system on the effects of therapy and tumor growth. A Nature paper from Mertins et al. on proteogenomics further underscored 11q and suggested that the PAK1 kinase needs to be targeted.

Dr. Loi also covered the impact of treatment on BC clonal populations. Gellert et al reported that a majority of tumors were clonally heterogeneous (>80%) and that treatment is changing the subclonal composition of patients. Looking into the phase III clinical trials SOFEA and Paloma3, Nicholas Turner’s group hypothesized that tumors with ESR1 mutations would do better on

fulvestrant vs aromatase inhibitor, a study that turned out positive. It concluded that the detection of ESR1 mutations will influence the next choice of endocrine therapy. Continuing on the theme of evolution under treatment, a study with Charles Swanton as senior author identified HER2+ inflammatory BC as having higher mutational load and possibly being particularly amenable to checkpoint blockade.

Key messages from the genomic studies, Dr. Loi says, include that ESR1 mutations will influence the next choice of hormonal therapy, that somatic alterations have been identified that seem to drive prognosis in ER+ diseases (11q, 8p, PIK3CA), and that new technology and findings will help to better select and stratify patients for future clinical trials.

In the immunology of cancer, Ton N. Schumacher’s group found that many tumor mutations are present, but only a minority of the resulting neoantigens are recognized by patient T cells. However, donor T cell receptors may recognize such neoantigens and be able to direct patient response via gene transfer, thus “outsourcing” the response. Other pre-clinical studies have shown that gut bacteria play a role in tumor formation, and optimal microbiota diversity may be important in response to not only chemotherapy but also cancer immunotherapies. Finally, variable cancer risk in different tissues seems to be dictated at least in part by Prom1+ cells with long-lived generative capacity, which may identify new targets for prevention.

Year in Review: Developments in Early Breast Cancer

The SABCS 2016 Year in Review session continued with a round-up of developments in early BC, presented by Dr. Virginia Kaklamani.

Dr. Kaklamani opened by highlighting findings in BC screening. A paper that looked at >72,000 Japanese women found that ultrasonography detected a greater number of early (stage 0 and 1) BC than mammography. A second paper that looked at findings on 3D mammography and ultrasonography in women with dense breasts and no lesions on previous mammography showed that the cancer detection rate was higher with ultrasonography than with 3D mammography (7.1 per 1000 patients vs 4 per 1000 patients). “Probably what we should be doing in clinic is really not a cookie-cutter approach. We should be talking to individuals based on risk and preferences, and explain the limitations of the data,” Dr. Kaklamani said.

A consensus statement made by the Society of Surgical Oncology, American Society for Radiation Oncology, and American Society of Clinical Oncology was also discussed. The statement suggested that 2-mm margins for ductal carcinoma in situ (DCIS) should be standard. The committee was clear in saying that other factors, such as residual calcifications on mammography, the extent of DCIS on the margin, and age expectancy should be considered in patients who were not able to achieve 2-mm margins.

Another study showed that not all patients with DCIS should be treated with radiation therapy. A study looking at a patient’s age, lesion size, and grade gave patients a simple prognostic score ranging from 0 to 6. Investigators found that patients who scored 0 or 1 did not receive any benefit from radiation therapy, whereas patients with a



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score of ≥ 2 did benefit. Another study that gave DCIS patients a clinical pathologic score based on an assay showed that a low score was associated with lower risk for ipsilateral breast events, and higher scores were associated with higher risk for those events. Dr. Kaklamani pointed out that the addition of radiation therapy decreased risk in both groups, but the absolute decrease was much less in the low-risk group than in the high-risk group.

Dr. Kaklamani touched on neoadjuvant approaches with an update on the I-SPY2 trial, which looked at weekly paclitaxel plus or minus addition of targeted therapies, followed by doxorubicin and cyclophosphamide, before surgery. For triple-negative breast cancer in this phase-III trial, addition of veliparib and carboplatin substantially increased the pathologic complete response (pCR) rate, though there was concern about an imbalance of BRCA+ in the two arms. For HER2+/HR- breast cancer, neratinib was superior to trastuzumab.

She then looked at a comparison of clinical risk (Adjuvant Online!) and genomic risk (70-gene signature or MammaPrint) in the MINDACT trial, in which some groups of patients included no chemotherapy in their treatment. Putting the MINDACT findings into context with TAILORx, a trial assigning individualized treatment options based on OncotypeDX, Dr. Kaklamani concluded that genomic assays can be used to identify low-risk groups prognostically, and that the risk for distant metastasis-free events was so low in these low-risk groups that chemotherapy may not be beneficial.

The International Breast Cancer Study Group trials I-V showed a substantial incidence of BC recurrences after ending the traditional 5 years of adjuvant endocrine therapy. This finding led to the MA.17R trial, a randomized trial of extending adjuvant letrozole for 5 years after completing an initial 5 years of either aromatase inhibitor (AI) therapy alone or tamoxifen followed by an AI, in postmenopausal women with early-stage

breast cancer. The trial met its primary endpoint of DFS with a modest absolute improvement of 4%, favoring the letrozole arm. NSABP's B-42 trial yielded comparable results. Dr. Kaklamani pointed out that the downside of extending AI endocrine therapy includes increased bone fractures, new-onset osteoporosis, and bone pain, but also suggested certain subgroups who could still have a net benefit from extended adjuvant AIs.

The review on early BC concluded with a list of ongoing trials, including upcoming studies to watch for next year at SABCS 2017, such as the APHINITY trial of chemotherapy plus trastuzumab and pertuzumab in HER2+ BC.

Year in Review: Advanced Breast Cancer

Following Dr. Kaklamani's review on early BC, Dr. Matthew P. Goetz presented recent findings in advanced BC.

Dr. Goetz began his review of 2016 ("the year of the CDK 4/6 inhibitor") with findings from PALOMA-2, a phase-III trial looking at postmenopausal patients with advanced ER+/HER2- BC randomized to palbociclib and letrozole or to letrozole and placebo. Because this trial showed that the addition of palbociclib improved median progression-free survival (PFS) from 14.5 mo to 24.8 mo, Dr. Goetz agreed with earlier comments made by this year's symposium plenary speaker, Dr. Stephen Johnston, that "this means we can delay chemotherapy for some patients."

Discussion of CDK 4/6 inhibitors continued with a glimpse at MONALEESA-2, a study that looked at the use of first-line ribociclib and letrozole for postmenopausal women with HR+/HER2- advanced BC, as well as another study (MONARCH 1) that looked at abemaciclib as a single agent in HR+/HER2- BC. It was concluded that CDK 4/6 inhibitors are a new standard of care for treatment of metastatic ER+ BC, and that studies showed a consistent benefit and antitumor activity in both highly endocrine-resistant and endocrine-sensitive BC.

In metastatic ER+ BC, fulvestrant can be considered a new standard for first-line ER+ BC. FALCON, a phase-III randomized trial of fulvestrant vs anastrozole in HR+ advanced BC, showed an improvement in PFS from 13.8 mo to 16.6 mo. Dr. Goetz pointed out that this trial enrolled patients who were naïve to endocrine therapy, and that a subset analysis showed patients without visceral disease had substantial improvement in PFS, which extended

out to over 22 mo. There was no difference between the drugs in patients with visceral disease.

Moving on to the targeting of the PI3K/AKT pathway, Dr. Goetz presented data from PrECOG 0102, a trial that looked at fulvestrant plus everolimus, and BELLE-3, a trial that looked at buparlisib and fulvestrant. As both trials showed improvement in median PFS, Dr. Goetz stated, "We can potentially select patients for response by using PIK3CA status."

Considering findings from the PERTAIN trial that used pertuzumab and trastuzumab plus an aromatase inhibitor (AI) in first-line patients with HR+/HER2+ metastatic or locally advanced BC, it is now understood that chemotherapy could be omitted in some patients being considered for trastuzumab/pertuzumab and hormonal therapy. In this trial, PFS improved from 15 mo to nearly 19 mo, and there was clear evidence for benefit in patients not receiving induction chemotherapy (~45% reduction in risk for disease progression.)

Dr. Goetz's talk concluded with an update on KEYNOTE-012, a trial using pembrolizumab in advanced TNBC. He pointed out that ~58% of patients in this trial were positive for PD-L1, and though pembrolizumab resulted in a low response rate (18.5%) in heavily pretreated women, the responses were prolonged (median duration of response not reached.) "We expect a lot of immunotherapy studies to read out in 2017," Dr. Goetz concluded.