Highlights: 12th Annual Ovarian Cancer Research Symposium
The Rivkin Center for Ovarian Cancer and the American Association for Cancer Research
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Seattle, Washington

Submitted by Susan Leighton, OCRFA Research Advocate, and survivor

In its 24th year, the Symposium is the longest-running scientific meeting in the United States focused exclusively on ovarian cancer. The goal of the Symposium is to bring together clinicians and researchers from across the globe to encourage collaborations toward advancing the field of ovarian cancer research.

INTRODUCTORY SESSION:

Dr. Doug Levine from New York University Langone provided an overview of ovarian cancer and the current landscape of research and treatment. Dr. Brad Nelson, British Columbia Cancer Agency (Canada), presented "Tumor Microenvironment and Immunology of Ovarian Cancer." Understanding the microenvironment and the interaction of immune cells with the tumor is critical to understanding the application of immunotherapy.

Dr. Elizabeth Swisher, University of Washington, provided an update of clinical management of ovarian cancer. Much research is being done around the usefulness of maintenance therapy and which type of maintenance to use - continuous maintenance in which a patient receives chemotherapy combined with a maintenance agent (ex., bevacizumab) or switch maintenance in which a patient receives chemotherapy followed by the maintenance agent (ex., PARPi). Numerous trials have been and are being done to help stratify which approach works better for which patients. It appears likely that olaparib maintenance for patients with either a germ line or somatic mutation will become standard of care.

KEYNOTE SPEAKER: Dr. Mary-Claire King, University of Washington, discussed BRCA1 and BRCA2 gene mutations, both germ line and somatic, and the impact of those mutations on both prevention and treatments. She is a strong advocate for population screening for all women at age 30 and especially for those women with a family history of breast and ovarian cancers. Dr. King emphasized the importance of genetic counseling for those women found to be mutation carriers both for prevention and family member testing. Additionally those who test negative for the mutation should receive information about risk of developing these cancers at the same rate as the general population. She noted that many genetic results may include "variants of unknown significance." These are mutations which have not been clinically correlated to an increased risk and she feels strongly that as they are not actionable, they should not be reported to the patient.

DETECTION AND PREVENTION OF OVARIAN CANCER

Dr. Ranjit Mancanda, Barts Cancer Institute, United Kingdom, "Population Testing for Ovarian Cancer Gene Murations for Primary Prevention." It is predicted that in the United States the incidence rate of ovarian cancer will increase by 39% by the year 2035. Increase in survival statistics remains statistically

small. The importance of prevention cannot be overstated in trying to decrease the incidence. Current guidelines recommend testing for any woman who has a personal history of ovarian cancer or has a significant family history of ovarian and breast cancer; however, only 1 in 5 women who qualify for testing are actually tested. In a study of 1034 women in the UK, population testing was shown to have clinical utility, clinical validity, and analytic validity. Further population studies have shown the testing to be cost effective, to generate positive impact leading to risk-reducing salpingo-oophortectomy and some positive changes in lifestyle, and no demonstrable negative impact of testing. Dr. Mancanda concluded that population testing could help reduce the incidence of ovarian cancer when done over time.

Dr. Rosana Riques, University of Washington, "Ovarian Cancer Detection Using Ultra-Sensitive Sequencing: Challenges and Opportunities." In a quest for an early diagnostic screening test, researchers have been investigating the possibility of detecting mutant DNA in the female genital tract. A technique similar to a Pap smear was shown to be 41% sensitive at detecting the mutant DNA. A second technique of collecting the samples on tampons yielded 60% sensitivity. Trying to improve the sensitivity and believing that the sample from the cervix is too distant from the fallopian tubes, another technique called uterine lavage was designed. Fluid is injected into the uterus and retrieved via specially designed catheter; this technique proved to be 80% sensitive. Another technique under development include the PapSeek test done with an intrauterine brush or a Tao brush which have yielded approximately 60% sensitivity. These sampling methods combined with ultra-sensitive sequencing are laying ground for detection; however, much work remains to achieve consistent specificity and sensitivity.

Dr. Thing Rinda Soong, University of Washington, presented work on early tubal serous proliferations (ESP) in the absence of STICs. This study for the first time indicates lineage identity between ESPs in the distal tube and some metastatic high-grade serous carcinoma (HGCS) via a shared site-specific TP53 mutation. This underscores the likelihood that multiple precursor types in the tubes could ultimately contribute to the development of serous cancer.

Dr. Joanna Burdette, University of Illinois, discussed a study to define factors that contribute to ovarian specific metastases of fallopian tube HGSC. Human fallopian tube epithelial HGSC repeatedly induced a signal from the ovary that was identified as norepinephrine. The method developed could lead to identification of targets for therapeutic intervention to block ovarian metastasis of fallopian tube HGSC.

Dr. Kara Bernstein, University of Pittsburgh, presented research to characterize the impact of cancer-associated mutations in the RAD51 paralogs on homologous recombination. Further aim is to develop more effective predictive models for therapeutic sensitivity and resistance in patients who harbor similar mutations in these essential genes.

Dr. Kara Michels, NCI, presented research on relationship between metabolic syndrome and the risk of ovarian cancer in the United States. Data suggests that individual components of metabolic syndrome rather than the syndrome itself are associated with ovarian cancer. For serous cancers, there was an association only of elevated triglycerides and fasting glucose. It was concluded that evaluating metabolic syndrome as a composite outcome could be misleading and uninformative in ovarian cancer studies.

Dr. Jennifer Barton, University of Arizona. Utilizing a 3 serum protein biomarker panel (FBG, PF4 and CA125) researchers have been able to classify HGSC with high sensitivity and specificity with 18-84 months lead time indicating potential usefulness of the panel as screening biomarkers. Work continues

to refine the panel so it can be used to identify those patients who may have a STIC lesion before metastasis occurs.

GENOMICS AND MOLECULAR MECHANISMS OF OVARIAN CANCER

Dr. James Brenton, University of Cambridge, discussed a study with results suggesting that early TP53 mutation may permit multiple mutational processes to co-evolve and that additional signature exposures may alter the risk of developing therapeutic platinum resistance.

Dr. Rosario Corona, Cedars Sinai, described a powerful way to distinguish important noncoding somatic drivers from a much larger number of passenger mutations that accumulate during tumor development.

Dr. Nicole Heinzl, Medical University of Vienna, demonstrated the high potential of p53 aggregation as a biomarker for patients' survival, suggesting that classification of patients based on the amount of aggregated p53 could allow for better therapy decisions.

Dr. Rong Wu, University of Michigan Medical School, present study results that showed that CRISPR/Cos9-sgRNA system genome editing can be used to model gynecological cancers in mice, significantly reducing the time required to develop these models than using existing methods.

TUMOR MICROENVIRONMENT AND IMMUNOLOGY OF OVARIAN CANCER

Dr. Laurie Ailles, University Health Network, Canada, discussed how cancer associated fibroblasts (CAF) have been shown to play a role in the promotion of cancer cell proliferation and chemotherapy resistance. Stratification of patients into classes based on expression of Fibroblast Activation Protein (FAP) demonstrated that those with FAP-high (FH) CAF have significantly shorter disease-free interval and overall survival. These patients may benefit from agents that reprogram FH CAF to an FL state yielding longer disease free interval and overall survival.

Dr. Zanivan, Beatson Institute investigated the role of CLIC3 in pro-invasive tumor-stroma interactions unraveling a mechanism of cell invasion to be explored for targeting in ovarian cancer. CLIC3 is secreted by cancer cells and is abundant in stromal and tumor compartments of aggressive ovarian cancer and levels of CLIC3 in primary tumors and omental metastases correlate the poor clinical outcomes.

Dr. Yunfei Wen, MD Anderson Cancer Center, discussed research that provides new knowledge regarding the role of vascular p130cas in tumor-associated endothelial vasculature, and the pre-clinical evidence for applying the RGD-CCPM-p130cas antagonist as a therapeutic for treatment of ovarian cancer.

Dr. Kaitlin Fogg, University of Wisconsin presented data that showed that inhibiting singular soluble factors will not inhibit alternatively activated macrophage-induced effects across a group of patients and that downstream pathways should instead be evaluated as potential therapeutic targets to slow metastasis.

NOVEL THERAPEUTICS: RESPONSE AND RESISTANCE OF OVARIAN CANCER

KEYNOTE SPEAKERS: Dr. Ursula Matalonis of Dana Farber Cancer Institute spoke on novel combination strategies for recurrent ovarian cancer. Dr. Jun-Min Lee of NCI discussed cell cycle checkpoints as therapeutic targets.

Dr. Karen Levy, Stanford University, presented comparison research of total abdominal ultra-rapid FLASH irradiation to conventional total abdominal irradiation in mice. Data demonstrated that FLASH is a safe strategy to deliver effective doses of total abdominal radiation and potentially identifies a new opportunity to utilize total abdominal irradiation-FLASH for treatment of ovarian peritoneal metastases.

Dr. Nuzhat Ahmed, Fiona Elsey Cancer Research Institute, discussed how proteomic profiling of chemonaive (CN) and after chemotherapy (CR) tumor cells showed significant differences in proteins encoding for cancer stem cells. The findings unraveled some of the molecular mechanisms by which chemoresistance and relapse occur in ovarian cancer patients post-chemotherapy treatment, and may be important in designing novel options for advanced stage disease.

Dr. Dmitriy Zamarin, Memorial Sloan Kettering Cancer Center, presented that TPIV200/huFR-1 and durvalumab can be safely combined in heavily pretreated patients with platinum-resistant ovarian cancer. A subset of the patients exhibited durable disease stabilization. Post-immunotherapy follow up was suggestive of improved clinical benefit from standard therapies, creating a rationale for exploration of these agents in combination with chemotherapy.

Dr. Neil Johnson, Fox Chase Cancer Center, discussed a study which revealed that BRCA1 intron translation generates new stop codons resulting in loss of the entire BRCT domain. BRCTless proteins avoid mutant protein folding problems and promote residual DNA repair and chemotherapy resistance.

Dr. Erin George, University of Pennsylvania, suggested that treatment resistant cells are more dependent on ATR/CHK1 pathway and ATR is promising target for augmenting PARPi and platinum response in treatment resistant high grade serous ovarian cancers.