Research Round-up: An AACR Special Conference "Addressing Critical Questions in Ovarian Cancer Research and Treatment" October 1-4, 2017 in Pittsburgh, Pennsylvania

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Every other year, the American Association for Cancer Research (AACR) brings together ovarian cancer researchers from around the world to share knowledge and encourage multi-disciplinary collaboration. This year's focus on critical questions led to energetic discussions about ways to take information from basic laboratory science into directions needed to make meaningful impact to patients. Each session was chaired by experts in that particular field and included research presentations with the potential to uncover deeper insights needed to overcome existing challenges. As many of the presentations involved preclinical findings that are not yet published or actionable, this report will provide only a brief overview.

CHALLENGES IN OVARIAN CANCER

The conference kicked off with a comprehensive summary of research efforts and challenges in prevention, early detection, biology, heterogeneity, and immunology by Anil Sood and Robert Bast of MD Anderson and Kunle Odunsi of Roswell Park Cancer Institute, as well as an overview of ovarian cancer treatments by Ursula Matulonis from Dana-Farber and Robert Edwards from the University of Pittsburgh. Joan S. Brugge from Harvard elegantly summarized the complexities of ovarian cancer and future directions of research.

- Research is critical because the death-to-incidence ratio remains high.
- Key conclusions of the 2016 IOM/NAS report on ovarian cancer were reviewed. For more information see: http://nationalacademies.org/HMD/reports/2016/state-of-ovarian-cancer
- Heterogeneity is a key feature of high grade serous ovarian cancer.
  (Heterogeneity in a nutshell: The cellular components of ovarian cancer are very different from patient to patient. Also, heterogeneity often exists in multiple sites of cancer within the same patient and even within a single tumor [intra-tumor heterogeneity]. This may explain in part why some patients who initially respond well to a cancer drug eventually relapse.)
- There is a need for more basic scientific work in ovarian cancer and multi-disciplinary collaborations are needed to integrate data into meaningful information.

BASIC SCIENCE

The work to understand the complexities of ovarian cancer, including heterogeneity, acquired resistance and metastasis, starts with data screens and continues in cells and animal models in order to identify vulnerabilities and develop novel strategies to bring to patients. Sessions included:

- Tumor Microenvironment chaired by Anil Sood of MD Anderson and Frances Balkwill of the Barts Cancer Institute in London.
- Metabolic Changes in Ovarian Cancer chaired by Ernst Lengyel of the University of Chicago and Ahmed Ahmed from the University of Oxford.
- Genetics and Molecular Drivers chaired by Anil Sood of MD Anderson and Robert Rottapel of Princess Margaret Cancer Centre in Toronto.

PREVENTION AND EARLY DETECTION

Robert Bast from MD Anderson described the reduction in mortality an early detection tool would bring as well as outlining the difficulties encountered thus far. This session also included presentations of ongoing, early work using blood tests to detect circulating tumor DNA (ctDNA) and microRNA (miRNA).

- More genetic counseling and testing is needed to identify those at higher risk for ovarian cancer to provide access to currently available risk-reducing/prevention strategies.
  NOTE: For more information on genetic testing, see: https://ocrfa.org/patients/about-ovarian-cancer/risk-factors/genetic-testing/. Women at high risk for ovarian cancer may be eligible for free genetic testing through the MAGENTA trial; more information available here: https://magenta.mdanderson.org/

- Strict requirements for general/healthy population-based screening (which is different from high-risk surveillance). Screening tool needs high sensitivity (≥75%) AND very high specificity (99.6%).
  Sensitivity is the ability of a test to correctly identify those with the disease (true positive)
  Specificity is the ability of a test to correctly identify those without the disease (true negative)
  NOTE: For more information on the basics of general population screening, see: http://wiki.cancer.org.au/policy/Principles_of_screening
- Francesmary Modugno of the University of Pittsburgh presented the results of the HOPE Study conducted in western Pennsylvania which indicates that breastfeeding protects against epithelial ovarian cancer. More work is needed before guidelines can be implemented.

DNA DAMAGE AND REPAIR

Ursula A. Matulonis from Dana Farber and Roger Greenberg from the University of Pennsylvania chaired this session and reviewed the mechanics of DNA damage and repair along with the clinical trials that led to recent FDA approvals of PARP inhibitors. Click here for an overview of PARP inhibitors: https://www.curetoday.com/conferences/20th-ovarian-national-conference/parp-inhibitors-changing-the-landscape-of-ovarian-cancer-treatment

- PARP inhibitors, drugs that interfere with a cancer cell's ability to repair its own DNA, are an exciting new class of drugs for ovarian cancer. Acquired resistance to PARP inhibitors needs to be addressed.
- Combining PARP inhibitors with other therapeutic agents (including immunotherapy) may be needed to increase efficacy and experts from multiple fields will need to work together to carry out combination studies.
- Several PARP inhibitor combination clinical trials are in development and open for enrollment. For more information about finding a PARP inhibitor clinical trial: https://ocrfa.org/patients/clinical-trials/look-clinical-trial/

IMMUNOTHERAPY

This session was chaired by Kunle Odunsi of Roswell Park Cancer Institute and David Spriggs of Memorial Sloan Kettering. Except for a few individual robust responses, overall ovarian cancer response rates for protein vaccines and checkpoint inhibitors has been moderate. Research is needed to explore blocking multiple pathways by combining complementary inhibitors to increase response. Presentations included:

- Brad Nelson of the British Columbia Cancer Agency in Canada addressed how the immune system contends with intratumoral heterogeneity.
- Daniel J. Powell from the University of Pennsylvania presented work on fundamental immunobiology and adoptive T cell therapy.
- Li Shen of Roswell Park Cancer Institute discussed work regarding adoptive transfer of engineered T cells and effect on the tumor microenvironment.
- Several immunotherapy trials are in development or open for enrollment. For more information about finding an immunotherapy clinical trial: https://ocrfa.org/patients/clinical-trials/look-clinical-trial/

DRUG RESPONSE AND RESISTANCE TO THERAPY

A particularly frustrating problem in ovarian cancer is that even with relatively high initial response rates, resistance to therapy frequently develops. Researchers from institutions around the world are working to address this problem. Presentations included:

- Session co-chair David D. L. Bowtell from the Peter MacCallum Cancer Centre in Australia presented work identifying ABCB1 fusions role in acquired chemotherapy resistance in high-grade serous ovarian cancer.
- Session co-chair Gordon B. Mills of MD Anderson spoke about a systems approach to drug development and work to create a real-time assay to reveal how tumors acquire resistance to therapy.
- Christopher Lord from the Cancer Research UK London Research Institute presented work exploiting synthetic lethality to overcome resistance.
- Anniina Färkkilä of Dana-Farber/University of Helsinki, in Finland presented findings measuring ctDNA samples over time to reveal actionable mutations.

RARE TUMORS

David Gershenson of MD Anderson and David Huntsman of the University of British Columbia in Vancouver chaired a session on rare tumors, many of which occur in younger women and are very aggressive. The small numbers of patients make studying rare tumors difficult and requires multi-institutional collaboration. Although most of the presentations in this session (and other sessions of the conference) include work in progress that is not yet actionable, this listing is provided to highlight that important efforts to understand rare ovarian cancer tumors is happening around the world.

- Progress and future directions in the management of **low-grade serous** cancer of the ovary, David M. Gershenson, The University of Texas MD Anderson Cancer Center, Houston, TX
- **Granulosa cell** and other rare ovarian cancers: Genomic-derived diagnostics and emergent management strategies, David Huntsman, University of British Columbia, Vancouver, BC, Canada
- Therapeutic targeting of ARID1A mutation in ovarian cancer, Rugang Zhang, The Wistar Institute, Philadelphia, PA (**clear cell**)
- **Small cell carcinomas** of the ovary: Strengths and weaknesses, Douglas A. Levine, New York University, New York, NY (SCCOHT appears to respond to checkpoint blockade)
- The driver mutational landscape of ovarian **squamous cell carcinomas** arising in mature cystic teratoma, Darren Ennis, Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom
- TERT is frequently mutated in adult-type **granulosa cell** tumors of the ovary compared to other malignant sex cord-stromal tumors* Jessica A. Pilsworth, University of British Columbia, Vancouver, BC, Canada
- Arginine deprivation as a potential targeted therapy for **clear cell** ovarian carcinoma, Jennifer Xiao Ye Ji, University of British Columbia, Vancouver, BC, Canada
- For more information about finding a clinical trial for rare ovarian cancers: https://ocrfa.org/patients/clinical-trials/look-clinical-trial/

For more information on rare ovarian cancer tumors, please see David Gershenson's recent webinar for OCRFA here: https://ocrfa.org/patients/resources/webinars/

PANEL DISCUSSION: INNOVATIVE TRIAL DESIGN

This session was chaired by Elise Kohn of NCI chaired and included panelists Michael J. Birrer, University of Alabama at Birmingham who discussed the drop in gynecologic cancer clinical trial participants, and Robert Coleman from MD Anderson who discussed lessons learned from a recent phase III randomized trial.

- Ovarian cancer clinical trials need to be scientifically justified, clinically meaningful and feasible.
- Smaller, smarter trials that incorporate biomarkers require fewer participants.
- Biomarkers need to be identified and validated.
- Major types of biomarkers:
  Predicative biomarkers indicate potential response to therapy.
  Prognostic biomarkers relate to outcome independent of intervention.
  Pharmacodynamic markers address drug activity.
  Pharmacokinetic behavior is important in combinations and for new drugs/populations.

During the Q&A session, a researcher asked if patient advocates were involved in the clinical trial review process. Advocates and survivors are actively involved in all areas of the drug development process: at funding and regulatory agencies and institutes, cooperative groups, and even participate as members of research teams, including large consortia and the Stand Up to Cancer Ovarian Cancer Dream Team. Involvement of research advocates is crucial to ensure that trials are relevant to those living with disease and to protect our most precious resource—clinical trial participants.

For information about research advocacy and to get involved, please see: https://ocrfa.org/advocacy/research-advocacy/

To see a list of all speakers and presentations: http://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=126#.Wdi9x43rvoo

For more information about finding a clinical trial: https://ocrfa.org/patients/clinical-trials/look-clinical-trial/