SU2C - Ovarian Cancer Research Fund Alliance-National Ovarian Cancer Coalition Dream Team Translational Research Grant:
“DNA Repair Therapies for Ovarian Cancer”

AND

SU2C Catalyst® Merck-Supported Supplemental Funding Project:
“Phase 1/2 trial of Niraparib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Triple-Negative Breast Cancer and in Patients with Recurrent Ovarian Cancer”

Progress Update – June 2017 Lay Summary

Funding: $6,000,000 Grant Funded: July 2015

Dream Team Members

Dream Team Leader:
- Alan D. D’Andrea, MD, Dana-Farber Cancer Institute

Dream Team Co-leader:
- Elizabeth M. Swisher, MD, University of Washington

Principals:
- Gini F. Fleming, MD, The University of Chicago
- Scott H. Kaufmann, MD, PhD, Mayo Clinic
- Maria Jasin, PhD, Memorial Sloan Kettering Cancer Center
- Karen H. Lu, MD, UT MD Anderson Cancer Center

Advocates:
- Jamie Crase, ovarian cancer survivor and advocate
- Kathleen A. Gavin, Minnesota Ovarian Cancer Alliance; Member, NRG Oncology Committees
- Sue Friedman, Executive Director, FORCE (Facing Our Risk of Cancer Empowered)

Fast Facts on Ovarian Cancer

☐ Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system.
☐ Less than half of women diagnosed with ovarian cancer survive to five years or more.
☐ Ovarian cancer develops mainly in older women and is more common in white women than African-American women.
**Fast Facts on Ovarian Cancer Prevention**

- Ovarian cancer can be inherited. Talk to your doctor about reducing your risk if there is a history of ovarian cancer in the women in your family.
- Hormonal contraceptives, first full-term pregnancy before age 26, and breastfeeding may lower the risk of ovarian cancer.
- Maintain a healthy diet and avoid obesity

**Summary**

Ovarian cancer is usually diagnosed at an advanced stage and, despite good initial responses to treatment, recurrence is very common. Because of this, cure is unlikely, and the death rate is high. Progress toward new treatments has been slow. However, new information from genetic sequencing of high-grade serous ovarian cancers has revealed a common weakness - mutations that cause defects in biological pathways that repair damaged DNA. Cancers with certain types of DNA repair defects are responsive to specific targeted therapies, such as drugs called PARP inhibitors, one of which was recently approved by the Food and Drug Administration to treat ovarian cancers associated with mutations in the BRCA1 and BRCA2 DNA repair genes.

SU2C-Ovarian Cancer Research Fund Alliance-National Ovarian Cancer Coalition Dream Team aims to develop new therapies that target DNA repair, and to expand PARP inhibitor use to a much larger group of women, beyond those with BRCA1 and BRCA2 mutations. In addition, by screening for inherited mutations in DNA repair genes, the Dream Team hopes to identify women at high risk for ovarian cancer for whom preventative measures may be life-saving.

The Dream Team brings together existing expertise from DNA repair experts, translational investigators, and clinicians, across six institutions, to create new programs in discovery, translation, and clinical application, while cross-fertilizing and educating researchers at all levels to enhance collaboration and catalyze translational science. Their three-pronged approach will 1) apply cutting edge DNA repair science to identify ovarian cancers most likely to respond to DNA repair therapies; 2) evaluate, in three clinical trials, novel drug combinations that will sensitize ovarian tumors to PARP inhibitors thereby expanding the use of these drugs to more women; and 3) develop web-based genetic testing and counselling strategies for ovarian cancer risk, providing access to more women in the community, and test fallopian tube removal as a surgical approach to reduce risk that will avoid forced menopause by preserving a woman's ovaries.

With a combined focus on developing and expanding treatment options, as well as developing platforms for the identification of women at high risk for ovarian cancer and preventing their disease, this program is poised to quickly deliver near-term ovarian cancer patient benefit.
Status update

24 Months:

In the 19-24 month period of this grant, this Dream Team continues to make significant progress in all research areas. Highlights are listed below.

- The Team has identified a novel mechanism by which Ovarian Cancer (OC) tumor cells can become resistant to PARP inhibitors (PARPi). Understanding all of the mechanisms of drug resistance will allow this team to subset OC patients to new drug trials.
- They have completed a Phase I trial, combining a PI3 kinase inhibitor (BYL719) with a PARPi (olaparib) and demonstrated a highly significant response rate (30%) among OC patients who are non-BRCA1/2 carriers.
- They have received final IRB approval and opened the MAGENTA trial. They have enrolled their first patients and contracted with Color Genomics for all genetic counseling services.
- They have significantly increased the enrollment of women at risk of OC into their WISP (Women Choosing Surgical Intervention) prevention trial.
- The Catalyst Program has made considerable progress in the Niraparib/Pembrolizumab trial, launched as a collaboration among Tesaro, Merck, and the Dream Team laboratories. The following work was presented at the ASCO meeting in June. Importantly, this study established the feasibility of a Niraparib/Pembrolizumab combination for the treatment of heavily pretreated platinum-resistant OC (chemotherapy), and no significant overlapping toxicities were observed. The Phase II study is rapidly enrolling new patients.
- The Team has also continued to develop functional assays (Homologous Recombination- HR repair), and recently has generated new methods for the rapid organoid culture of tumor cells derived from fresh ovarian tumor biopsies. These organoids grow out in only 7-10 days and appear to be an excellent physiological match to the tumor from which they are derived. These organoids will be a very useful tool for basic research and for diagnosis and prediction of clinical drug responses.