



Ovarian Cancer
Research Fund Alliance



**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 Niraprib 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.



Ovarian Cancer
Research Fund Alliance



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 breast feeding 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.



Ovarian Cancer
Research Fund Alliance



Status update

6 Months:

In the first 6 months of this grant, the team has made considerable progress in all aspects of the project.

- The Team has rapidly established a strong collaborative infrastructure between the groups who will work on the different Aims. They are working to establish standardized review of tumor material by the Team's pathologists so that they optimize the use of information from different trial sites.
- The Team has started analyzing DNA sequencing data from ovarian tumor biopsies from patients enrolled in an ongoing PARP inhibitor clinical trial. They are finding clues as to the genetic changes that associate with sensitivity to the PARP inhibitor rucaparib in women without BRCA mutations. This approach may allow them to predict who will respond to these drugs. Dr. Swisher, the Dream Team Co-leader, presented these preliminary results at the AACR Ovarian Cancer Symposium in October 2015.
- The Dream Team has started laboratory studies and analyses of clinical trial samples to understand the biology of why some patients may not respond to certain therapies.
- Two clinical trials are actively recruiting ovarian cancer patients to evaluate new drug combinations. Additional trials are pending activation.
- They acted quickly on the suggestions of the Joint Scientific Advisory Committee to incorporate an immunotherapy focus to their work. In collaboration with Merck/Tesaro, they are planning a new clinical trial to test an immunotherapy drug pembrolizumab (Keytruda®), currently approved for use in metastatic melanoma and a type of lung cancer, in combination with a PARP inhibitor niraparib.
- Development of the Dream Team's genetic testing trial, now named MAGENTA (MAKing GENetic Testing more Accessible), and their prevention trial WISDOM (Women choosing Interval Salpingectomy with Delayed Oophorectomy to postpone Menopause) continues. The MAGENTA trial seeks to increase access to genetic testing for ovarian cancer risk in the community by using online genetic counseling. Based on the growing understanding that ovarian cancer may start in the fallopian tubes, the WISDOM trial will offer women at high risk of ovarian cancer the option to remove their fallopian tubes as an approach to reduce their risk while avoiding forced menopause by preserving their ovaries.



Ovarian Cancer
Research Fund Alliance



12 Months:

In the 7-12 month period of this grant, this Dream Team continues to make significant progress in all research areas.

- The Team has identified two ways by which patients may be resistant to PARP inhibitor treatment. Understanding why some patients stop responding to PARP inhibitors will provide insight into potential drug combinations to overcome resistance.
- The Team has identified a potential “biomarker” or biological signal that may be used to predict how well a patient’s tumor will respond to treatment with a PARP inhibitor. The Team has identified the best dose strategies to use in two different combination clinical trials (veliparib and dinaciclib in patients with solid tumors, *ClinicalTrials.gov* Identifier: NCT01434316; oral PI3kinase inhibitor BKM120 or BYL719 and the oral PARP inhibitor olaparib in patients with recurrent triple negative breast cancer or high grade serous ovarian cancer, *ClinicalTrials.gov* Identifier: NCT01623349) and is analyzing tumors from patients with or without the combination treatment.
- The genetic testing clinical trial, MAGENTA, has been revised and is not yet open. The Dream Team aims to enroll 3,000 patients by December 2018.
- The surgical prevention clinical trial was renamed to WISP (Women choosing Surgical Prevention). The MDACC protocol was approved in May, 2016. The enrollment target is 230 of which 3 patients have been enrolled.
- The Team has published two reviews (Nat Rev Mol Cell Biol. 2016; 17:337 and Mol Cell. 2016;62:777) and two research articles (Oncotarget. 2016;7:13587 and JAMA Oncol. 2016;2:370).
- The Team plans to launch the Merck Supplement/Tesaro Project (with funding from the SU2C Catalyst™), which provides an additional \$1 million to complete a trial of niraparib/pembrolizumab. They are working on the approval of IRBs at all six cooperating institutions.
- Eliezer M. Van Allen from Dana-Farber Cancer Institute is the Young Investigator of this Dream Team, as well as a member of the Prostate Cancer Dream Team. Dr. van Allen received a Philip A. Sharp Innovation in Collaboration Award with Principal, Maria Jasin to study the use of genetic information from ovarian and prostate cancer patients to design new tests and a computational approach to analyze DNA repair pathways allowing better prediction of which patients will respond to PARP inhibitors.



Ovarian Cancer
Research Fund Alliance



18 Months:

The team continues to make significant progress toward their specific aims. Highlights are listed below.

- They have demonstrated that some OC with no mutations in BRCA1/2 respond to a combination of PI3K inhibitor plus olaparib.
- They have launched the MAGENTA trial website.
- The Team has opened the surgical WISP trial and enrolled women at risk of OC.
- Preclinical studies continue testing novel drug combinations extending the use of PARPi.
- The Team continues to develop functional assays in the laboratory to determine mutations in DNA repair genes.

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.
- The team has published one review (Chem. Med. Chem. 2016; 59:4511-4525) and three research articles (Cancer Discov. 2017 Jun 6. pii: CD-17-0419; J Clin. Oncol. 2017 May 4:JCO2016721340.; and Clin Can Res, 2017 (Epub ahead of print, PMC)), and has additional manuscripts in preparation.