



## Team Progress Updates

### SU2C-Ovarian Cancer Research Fund Alliance-National Ovarian Cancer Coalition Ovarian Cancer Dream Team:

#### “DNA Repair Therapies for Ovarian Cancer”



Ovarian cancer is usually diagnosed at an advanced stage, when it is hard to treat and death rates are high. Cancers with certain types of DNA repair defects are responsive to targeted therapies, such as drugs called PARP inhibitors. These drugs help prevent cancer cells from repairing their own damaged DNA, thereby hastening the cancer cells' death.

The Dream Team brought together internationally renowned experts to focus on developing new therapies that target DNA repair and expanding the use of PARP inhibitors to a much larger group of women. In addition, by screening for inherited mutations in genes linked to DNA repair, the team worked to find ways to identify women at higher risk for ovarian cancer.

The team took a three-pronged approach to its goals:

1. Identify ovarian cancers that are likely to respond to DNA repair therapies.
2. Evaluate, in three clinical trials, new drug combinations that may sensitize ovarian tumors to PARP inhibitors.
3. Develop web-based genetic testing and counseling strategies and test surgical prevention models.

Among other achievements, the team has:

#### January 2019

- The team made significant progress towards enrollment of the MAGENTA genetic testing prevention trial and WISP surgical prevention trial. The results of these trials should improve population-scale gene testing for ovarian cancer risk.
  - They have nearly completed enrollment with almost 3,500 patients on their MAGENTA trial, with participation spanning all 50 states.
  - They have enrolled 189 patients on their WISP trial, with more than 70% of the planned patients enrolled.
- They have successfully developed the protocol of culturing organoids from fresh ovarian tumor biopsies.





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### June 2018

- The team has identified new biomarkers that can help distinguish PARP inhibitor-resistant from PARP inhibitor-sensitive tumors. These biomarkers are especially important, given that three PARP inhibitors (olaparib, rucaparib, and niraparib) have achieved FDA approval.
- The team has made tremendous progress in culturing ovarian tumor organoids from newly diagnosed cancer patients, with a 90% success rate. These organoids can subsequently be used to test possible treatments for ovarian cancers.
- The team has demonstrated promising efficacy of drug combinations that may extend the use of PARP inhibitors and is evaluating new PARP inhibitor combination therapies.
- The team also has made significant progress toward enrollment of the MAGENTA prevention trial and WISP surgical prevention trial.

### December 2017

- Identified new biomarkers which can help distinguish PARPi-resistant from PARPi-sensitive tumors
- Achieved 90 percent success rate in culturing ovarian tumor organoids from newly-diagnosed cancer patients. These short-term ovarian cancer organoids can be used to help determine the most effective drug treatment.
- Demonstrated promising efficacy of drug combinations, which may extend the use of PARP inhibitors:
  - From the Phase I trial combining a PI3 kinase inhibitor (BYL719) with a PARPi (olaparib), the Team showed that this combination is feasible, with comparable anti-cancer activity observed in patients with or without germline BRCA1/2 mutations.
  - A Phase I trial of the veliparib/dinaciclib combination continues, testing if this combination re-sensitizes cells to PARP inhibition.
- Evaluated new PARP inhibitor combinations, including the PARP inhibitor veliparib and the topoisomerase I (TOP1) inhibitor topotecan.
- Enrolled women in in MAGENTA genetic testing prevention trial and WISP surgical prevention trial:
  - MAGENTA (Making Genetic Testing More Accessible):
    - Enrolled nearly 600 patients on the MAGENTA trial;
    - Engaged advocates and SU2C in assisting with social media campaign to spread awareness of the trial;



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- Started the first Facebook page for MAGENTA and rolled their first set of paid Facebook ads;
- WISP (Women Choosing Surgical Prevention):
  - Enrolled more than 90 patients on WISP

### **June 2017**

- Identified a new 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.
- Completed a Phase I trial combining a PI3 kinase inhibitor (BYL719) with a PARP inhibitor (olaparib); demonstrated a highly significant response rate (30%) among ovarian cancer patients who are non-BRCA1/2 carriers.
- Developed functional assays and 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.

### **December 2016**

- Demonstrated that some cases of ovarian cancer with no mutations in BRCA1/2 respond to a combination of PI3K inhibitor plus olaparib.
- Tested new drug combinations extending the use of PARP inhibitors.
- Launched the MAGENTA trial website and opened the surgical WISP trial.

### **June 2016**

- Identified a potential "biomarker," or biological signal, that may be used to predict how well a patient's tumor will response to treatment with a PARP inhibitor.
- Continued to plan the MAGENTA and WISP trials.

### **December 2015**

- Started analyzing DNA sequencing data from ovarian tumor biopsies from patients enrolled in an ongoing PARP inhibitor clinical trial to find clues as to the genetic changes that associate



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with sensitivity to the PARP inhibitor rucaparib in women without BRCA mutations, which may allow researchers to predict who will respond to these drugs.

- Launched laboratory studies and analyses of clinical trial samples to understand the biology of why some patients may not respond to certain therapies.
- Began recruiting patients to clinical trials to evaluate new drug combinations.
- Continued development of the Dream Team's genetic testing trial, now named MAGENTA (Making GENetic Iesting more Accessible), and a prevention trial, WISP (Women Choosing Surgical Prevention).

