4.7 Studies of Quality

Feasibility of Clinical Trial Implementation Genetically Eligible Prostate Cancer Patients

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Study Name	**Feasibility of Patient Population for proposed Prostate Cancer Clinical Trial**		
Project Manager	Cathryn Garvey		
Status	Initial Study- Complete		
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Background:

Metastatic, castration-resistant prostate cancer (mCRPC) can have genomic alterations that interfere with DNA repair. Some of these genomic aberrations can increase sensitivity to poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors, such as, olaparib. Multiple mutations in several DNA repair genes were identified through the use of next-generation sequencing . These genes included BRCA1, BRCA2, ATM, PALB2, CHEK2, FANCA, and HDAC2, which are all associated with PARP inhibitor sensitivity (Mateo et.al. *N Engl J Med*. Vol 373;18. 1697-1708. 2015). In another study, germline alterations in some of the same DNA repair genes were found in 8% mCRPC patients (Robinson et.al. *Cell*. Vol 161. 1215-1228. 2015). The most common gene aberration in both studies was BRCA2. Germline BRCA2 mutations and loss of BRCA2 function is well documented in prostate cancer and is associated with poor survival outcomes for patients with prostate cancer (Mateo et.al. *N Engl J Med*. Vol 373;18. 1697-1708. 2015; Robinson et.al. *Cell.* Vol 161. 1215-1228. 2015). Mateo et.al. reported deleterious germline mutations in BRCA2 in 6% of their cohort. Additionally, germline ATM truncations usually affecting the kinase catalytic domain was also reported in 6% of the cohort. Germline mutations in the other DNA repair genes were found at a lower prevalence. Response to treatment with olaparib in this cohort was shown by declining prostate specific antigen (PSA) levels, reduction in circulating tumor cells, and regression of bone disease in this cohort shows a (Mateo et.al. *N Engl J Med*. Vol. 373;18. 1697-1708. 2015).

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Study Question:

Would TCCC have a population of prostate cancer patients that would benefit from clinical trial of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors.

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Criteria and Population Studied:

Prostate cancer patients with personal or family history of NCCN identified disease processes. Based on the National Comprehensive Cancer Network (NCCN) guidelines, patients that have a personal diagnosis or a family history of 3 or more of the following: breast cancer, ovarian cancer, pancreatic cancer, prostate cancer (Gleason 7 or higher); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer; thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of the gastrointestinal tract, or diffuse gastric qualifies for genetic testing. Therefore, all patients are given a questionnaire as a pre-screen for genetic testing.

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Study Findings

A custom designed genetic testing panel was through Invitae and consists of 25 genes associated with hereditary cancer. So far, 48 patients have met the criteria for genetic testing and proceeded. Of those 48 people, we have had 7 positive pathogenic test results.

Positive Pathogenic Genes	**Number of People**
BRCA2	3
BRCA1	2
MUTYH	1
PSM2	1

The positive results help make informed clinical decisions regarding treatment options. In addition, positive results provide the knowledge and opportunity for genetic testing to extended family members. Since genetic testing is relatively new with regards to prostate cancer, the variant of unknown significance (VUS) rate has been found to be 23% in our case. This VUS rate is comparable to early genetic testing in BRCA1/2 for breast cancer; for breast cancer the VUS rate has decreased significantly as testing has become more prevalent (Calò et al. *Cancers*. Vol 2. 1644-1660. 2010). Therefore, increase genetic testing for prostate cancer provides opportunity for further elucidation for the implications of variants of unknown significance as well as potential characterization of clinically actionable targets.

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Action taken:

Clinical trial implementation- poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors for eligible prostate cancer patients.

Benchmark Reference: NCCN Guidelines for Hereditary and Familial High Risk Breast and Ovarian Cancer

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