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TITLE: **Targeting BRCAness in Gastric Cancer**

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13. SUPPLEMENTARY NOTES

14. ABSTRACT: This application aims at improving outcomes for patients with stomach cancer, a 2015 PRCRP Congressionally Directed Topic Area. Germline as well as somatic mutations in genes involved in DNA repair by homologous recombination (HR) are common in stomach cancer. For example, BRCA1/2 mutations are found in 15% of gastric cancers and are associated with poor survival. As partnering PI Dr. Ashworth has demonstrated, the DNA repair protein PARP compensates for loss or BRCA protein in BRCA1/2 mutant cells rendering such cells exquisitely sensitive to inhibition of PARP. Furthermore, tumors characterized by genomic instability (resulting in extensive loss of heterozygosity) and susceptibility to PARP inhibitors or platinum agents in the absence of BRCA1/2 mutations have been identified, a phenomenon known as "BRCAness". We expect that 25% of advanced gastric cancers harbor mutations conferring "BRCAness". Published data suggests that the PI3 kinase pathway regulates HR repair and our own data suggest that MEK inhibitors synergize with PARP inhibitors. With this application, we aim at identifying additional mechanisms regulating HR repair that could be exploited therapeutically. In addition, due to the high mutational burden associated with BRCAness, it is to be expected that BRCA1/2 mutations or BRCAness result in susceptibility to PARP inhibitors. Studies proposed here will be carried out in context with clinical trialdesigned by us (PI: Korn) to test the PARP inhibitor talazoparib in combination with chemotherapy in patients with gastroesophageal whose tumors harbor BRCA1/2 mutations or mutations conferring BRCAness. Enrollment will begin during the first quarter of 2016. Hypothesis. We hypothesize that gastric cancers displaying BRCAness are susceptible to PARP inhibition. We further hypothesize that oncogenic signal transduction pathways regulate HR activity and that HR deficient tumors are sensitive to immunotherapy, thus providing a basis for the design of rational combinations therapies.

15. SUBJECT TERMS
Gastric cancer, BRCAness, DNA repair, DNA damage, PARP inhibitor, MEK inhibitor

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1. Introduction

Inactivating germline and somatic mutations affecting genes involved in DNA damage repair are features of upper gastrointestinal malignancies, but we do not know how common these lesions are. Genes encoding for proteins important for mismatch, base-excision, and homologous recombination (HR) repair are affected in subsets of these tumors. For example, mutations in the HR genes *BRCA1* and *BRCA2* have been found in some gastric cancers. Loss of BRCA1 protein expression has been found in 21% of gastric cancers and was associated with diffuse-type histology and poor survival. PARP1 (polyADP ribose polymerase 1) is an enzyme essential for base-excision repair, a complementary DNA repair pathway to the HR repair pathway inactivated by mutations in *BRCA1* and *BRCA2*.

The purpose of this research is to elucidate *BRCA1* and *BRCA2* mutations in gastric cancer can alter adaptive immune responses within the tumor. By using T cell receptor (TCR) sequence, we can assess the T cell repertories within patients who harbor tumors with or without pathogenically mutated *BRCA1* and/or *BRCA2*. Addressing these questions will set the stage for development of increasingly efficient treatment strategies for GI cancers involving immunotherapies.

2. Keywords.

Gastric cancer, BRCAness, T cell receptor

3. Accomplishments

- **What were the major goals of the project?**

  Specific Aim 1: Define the T cell receptor diversity of gastric cancer patients

  Major Task 1:

  · Obtain tumor and/or blood samples from gastric cancer patients
  · Perform TCR sequencing on gastric cancer patient samples.
  · Assess the clonality and convergence indices for the TCR repertoires from different patients.

  Specific Aim 2: Determine whether BRCA status associates with difference in TCR repertoire.

  Major Task 2:

  · Define BRCA status in the gastric cancer patients
  · Assess for associations between BRCA status and TCR repertoire.

  What was accomplished under these goals?

  Major Task 1.

We obtained biopsy and blood samples from patients participating in the clinical trial: A Phase 1 / 2 Study of Olaparib in Combination with Ramucirumab in Metastatic Gastric and Gastroesophageal Junction Adenocarcinoma [NCT03008278].

We have assessed the T cell repertories contained within the tumors and blood of patients from Dr. Cecchini's study (Table 1). We stratified patient into long survival (≥202days) or short survival. While we did not see a difference in the circulating T cell repertoire, we did see differences in the intratumoral T cell repertoires. Specifically, patients with long survival had lower T cell clonality and T cell convergence. Longer survival in this trial was therefore associated with a more diverse T cell repertoire within the tumors prior to treatment.

Table 1. Associations between survival and TCR repertoire

		Long Survival	Short Survival	p
Blood				
	Clonality	0.13 [0.07, 0.20]	0.11 [0.04, 0.27]	0.935
	Convergence	0.27 [0.13, 0.65]	0.27 [0.08, 0.52]	0.935
Tumor				
	Clonality	0.26 [0.20, 0.29]	0.37 [0.31, 0.42]	0.034
	Convergence	0.69 [0.69, 0.91]	0.95 [0.92, 0.97]	0.034

Major Task 2.

We assessed patients for BRCA status by whole exosome sequencing and classified patients into those who either possessed or did not possess pathogenic mutations for either *BRCA1* and/or *BRCA2*. We then assessed whether BRCA status is associated with differences in the TCR repertoire. We found that the presence of pathogenic *BRCA1*, *BRCA2*, and *BRCA1/2* mutations was not associated with differences in TCR clonality or convergence (Figure 1A, B, C, respectively).

We also assessed whether BRCA status associated with overall survival in this clinical trial. We found that the presence of pathogenic *BRCA1*, *BRCA2*, and *BRCA1/2* mutations was not associated with a difference in overall survival (Figure 2A, B, C, respectively).

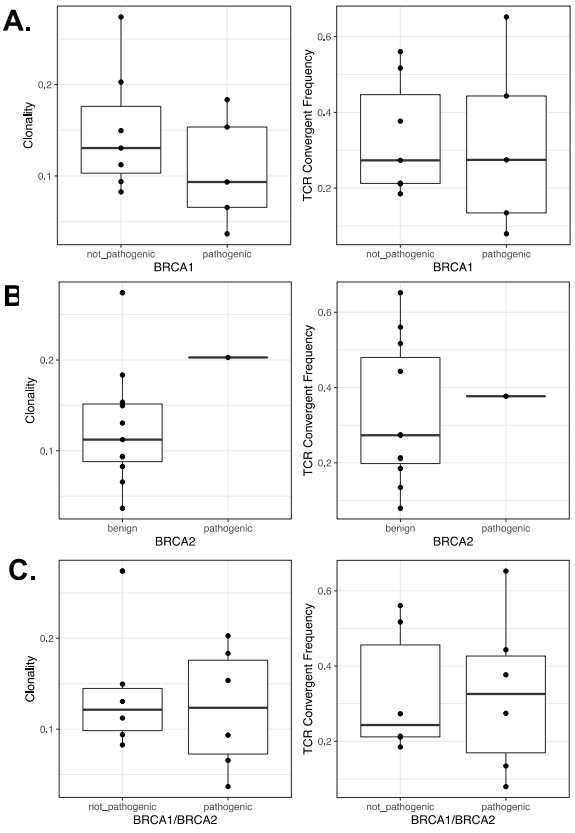

Figure 1. Associations between BRCA status and TCR repertoire. TCR clonality (left panels) and convergence (right) were assessed in samples from patients with or without pathogenic mutations in BRCA1 (A), BRCA2 (B), or for either mutation (C).

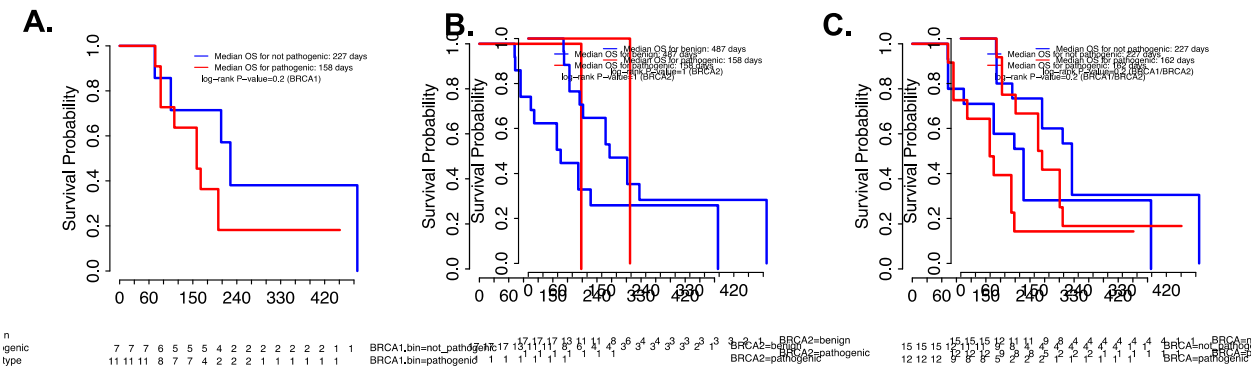

Figure 2. Associations between BRCA status and overall survival. Kaplan Meier plots for overall survival are shown for patients with or without pathogenic mutations in BRCA1 (A), BRCA2 (B), or for either mutation (C).

4. IMPACT

• What opportunities for training and professional development has the project provided?

N/A

• How were the results disseminated to communities of interest?

We have discussed these studies at the Helen Diller cancer Center and plan on submitting This study for publication in the near future.

• What do you plan to do during the next reporting period to accomplish the goals?

We plan a draft publication in 2021.

• What was the impact on technology transfer?

Nothing to report

• What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS

• Changes in approach and reasons for change

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  In the original proposal, Dr. Fong was to perform T cell receptor (TCR) sequencing on samples derived from Dr. Korn's study. Unfortunately, the drug company that Dr. Korn was working with withdrew support for the clinical trial. Dr. Collisson has secured new samples from Dr. Michael Cecchini at Yale, who provided samples from his clinical trial on which we assessed TCR sequencing and whole exosome sequencing to assess BRCA status.

- **Changes that had a significant impact on expenditures**
  N/A

• Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report

6. PRODUCTS
Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
Nothing to report

8. SPECIAL REPORTING REQUIREMENTS
Nothing to report