Susan G. Komen

Research Grants – Fiscal Year 2015

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PARP inhibition in homologous recombination-deficient breast cancer

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Public Abstract:

Poly ADP ribose polymerases (PARPs) play an important role in DNA repair in the human body. Inhibitors of PARP have been shown to lead to disease improvement in breast cancer patients, who carry an inherited BRCA mutation. The theory is that tumors arising in BRCA mutation carriers have damaged DNA repair mechanisms making them susceptible to additional DNA damage by PARP inhibitors. It has been hypothesized that PARP inhibitors may also have a role in the treatment of triple-negative (estrogen receptor-, progesterone receptor-negative and HER2 receptor normal) breast cancer patients, who do not have an inherited risk, but whose tumors have similar DNA repair defects and thus act "BRCA-like." Furthermore, there has been increased awareness of other hereditary breast cancer syndromes, such as PALB2, that are also implicated in the same DNA repair pathway as BRCA. In addition, as researchers conduct more testing on the tumor tissue itself, we are identifying patients with similar gene mutations, who may also benefit from PARP inhibitor therapy. The role of PARP inhibitors in these breast cancer patient populations remains undefined. The question is important as treatment in the advanced setting is often limited to chemotherapy, which can be associated with toxic side effects and short-term tumor responses.

In this clinical trial, we aim to evaluate if an oral PARP inhibitor can shrink tumors in patients with advanced breast cancer, who carry faulty DNA repair mechanisms, either due to a triple-negative "BRCA-like" breast cancer or due to a hereditary or tumor-tissue breast cancer gene mutation in the same pathway as BRCA. Patients with triple-negative breast cancer, whose tumors are "BRCA-like" based on a novel assay by Myriad Genetics, will be enrolled in Cohort A of our trial. Patients with a hereditary

breast cancer similar in its origin to BRCA, or whose tumors have been evaluated and found to have a mutation in the same DNA repair pathway, will be eligible to enroll in Cohort B. All patients will be given daily BMN 673, a potent, oral PARP inhibitor. We will assess for tumor response every 8 weeks with imaging. Our hypothesis is that this powerful class of drugs, which is often better tolerated compared to standard chemotherapy, can lead to sustained anti-cancer activity in breast cancer patients beyond those who carry a harmful BRCA mutation. Notably only about 5-10% of breast cancer patients carry a BRCA mutation, and those patients, who do not have this inherited risk, are not eligible for current PARP inhibitor trials.

This work is important because women with advanced breast cancer are often left with chemotherapy as the only drug option. If our hypothesis is true, and our trial shows clinical activity in these high-risk breast cancer patients, it will provide an effective, targeted drug option. Furthermore, this trial will accelerate research in early-stage breast cancer, where it has the greatest potential to impact mortality.