MCC Clinical Trial Padres Pedal the Cause Fall 2018

Investigating the Efficacy of radium-223 with Olaparib in Men with Metastatic Castration-resistant Prostate Cancer

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Scientific Abstract:

Radium-223 Is an alpha-emitting radiopharmaceutical with bone-seeking proclivity. Though it has prolonged survival in metastatic castration-resistant prostate cancer (mCRPC), resistance develops in nearly all individuals. Cell survival following radiation is largely dependent on tumor cell ability to efficiently and faithfully repair DNA. Poly(ADP-ribose) polymerase 1 (PARP1), which can be inhibited by olaparib, is critical to the DNA repair process. In preclinical models, radiation with PARP inhibition leads to enhanced cell death and delay in tumor growth. Additionally, emerging genomics data demonstrate that 25% of mCRPC patients harbor alterations in homologous recombination (HR) genes, sensitizing individuals to PARP inhibition. We hypothesize that radium-223 and olaparib will result In improved outcomes (radiographic progressionfree survival) in mCRPC patients. We will investigate this hypothesis in the context of a National Cancer Institute (NCI) phase 1/11 randomized clinical trial of radium-223 with or without olaparib. To ascertain the spectrum of molecular aberrations in DNA repair pathways, correlate HR deficiency status with outcomes, and investigate mechanism of resistance, patients will undergo a mandatory baseline and optional progression biopsy for Oncopanel panel sequencing, whole exome sequencing, and whole transcriptome sequencing. Given that radium-223 and the DNA damage response induce immunogenic modulation and enhance cytotoxic Tlymphocyte tumor lysis in vitro, patients will undergo immunoprofiling via peripheral blood mononuclear cell (PBMC) phenotyping, T-cell receptor sequencing (TCR), and evaluation of tumor infiltrating lymphocytes in tumor tissue to investigate the rationale for therapy with checkpoint inhibition. This work has the potential to improve survival and expand the treatment arrnamentarlum in mCRPC.

Lay Abstract:

Metastatic castration-resistant prostate cancer heralds a lethal disease and represents a major unmet need in clinical practice. Despite the confirmed efficacy of approved agents for men with mCRPC, resistance to treatment is universal. Novel treatments and combinations are imperative to improve outcomes for patients. Radium-223, an alpha emitting radioisotope, has been shown to prolong overall survival in mCRPC2. Studies have demonstrated that enhanced DNA repair is a potential resistance mechanism to radiation and impairment of this process, via PARP inhibitors such as olaparib, can promote cell death and delay tumor growth. We hypothesize that the addition of olaparib to radium-223 will improve survival for patients and outcomes may be dependent on tumor DNA repair status which may serve as predictive biomarker of response. To test this hypothesize, we have designed a phase 1/11 open-label randomized clinical trial of standard of care radium-223 with or without olaparib. To investigate molecular mechanisms of response and resistance to treatment and interrogate molecular aberrations in the DNA repair pathway, patients will undergo a mandatory baseline and optional progression tumor biopsy. Additionally, lmmunoprofiling of blood and tissue specimens will be performed on a subset of patients to investigate the rationale for combinatorial immunotherapy to radium-223 with or without olaparib. This study has the potential to improve the efficacy of existing treatment options for mCRPC

patients. By harnessing vast advances in technology, genetics, and biomedical research, molecular tumor profiling has the potential to better inform patient selection for a given treatment and transform clinical decision making.