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 progression-free 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 T lymphocyte 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 armamentarium in 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.