Phase II study of pembrolizumab plus androgen deprivation therapy in combination with radiotherapy for high-risk localized prostate cancer

Mark Garzotto[1,2,5], Amy E. Moran[3], Ryan Kopp[1,5], Wesley Stoller[5], Tomasz M. Beer[4], Julie Graff[4,5], Alexandra O. Sokolova[4], Arthur Hung[2]

Affiliations: Department of Urology[1], Department of Radiation Medicine[2], Cell, Development & Cancer Biology[3], Department of Hematology Medical Oncology, Knight Cancer Institute[4], Oregon Health & Science University; Department of Veterans Affairs[5].

Background: Androgen deprivation has been shown to act synergistically with both radiotherapy and immune checkpoint inhibitors (ICIs) in clinical and experimental systems (Guan *et al.* Nature, 2022). Androgen deprivation (ADT) results in activation and mobilization of CD8 T-cells into the prostate and expression of tumor antigens (i.e. cross-priming). Furthermore, ADT may delay the development of an immunologically "exhausted" phenotype. Whereas, RT may increase antigen expression and thus sensitize prostate cancer cells to ICIs. Thus, the addition of ICI to standard of care RT + ADT may work synergistically through multiple pathways. We hypothesized that ICI at time of ADT initiation would synergistically activate a robust immunologic response in subjects with clinically localized, high-risk prostate cancer being treated with primary RT.

Methods: This is a single-arm, single-stage Phase II trial to evaluate efficacy and safety of pembrolizumab and AR targeting in combination with RT in subjects with high-risk localized prostate cancer. Inclusion criteria include any of the following: 1) Gleason ≥ 8, PSA ≥ 20 ng/mL, or clinical cT3a-b disease. The primary endpoints include post-irradiation biopsy complete response rate at 6 months and safety. Secondary endpoints include: post-radiation biopsy rate by pre-treatment PD-L1 expression, irAEs, BCR, and HRQOL. Planned treatment with RT includes pembrolizumab (200 mg Q 3W for 12 months) plus bicalutamide (50 mg/d, for six months) and LHRH agonist (continuous for 24 mo.). A sample size of 32 patients (accommodate 10% drop out) is required to test the null hypothesis of 35% vs. an alternative hypothesis of 60% (one-sided α=4.8%).

Clinical Trial Registry: NCT06528210

Funding: Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Conflict of Interest: Trial Support from Merck (MISP) to M. Garzotto.