ChemoImmunotherapy for the Treatment of Metastatic Prostate Cancer

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Background: Immunotherapy strategies in prostate cancer have not had broad clinical impact since the FDA approval of Sipuleucel-T in 2010. While immune checkpoint inhibitors may benefit small subsets of populations (e.g. MSI-high, CDK-12 inactivation) large scale studies have not been successful. One emerging immunotherapy strategy yet to be largely explored in prostate cancer is the use of immunocytokines. Immunocytokines are different than immune checkpoint inhibitors as the may impact the boarder pleiotropic immune microenvironment of prostate cancer, with the potential to convert immune suppressive components, giving them anti-tumor capabilities. NHS-IL12 is an immunocytokine that binds to exposed histones in necrotic tumor tissue and delivers immune stimulating IL-12 at low doses to the tumor microenvironment. (Strauss J et al., Clin Cancer Res 2019). M7824 is a bifunctional antibody that is capable of both inhibiting PDL1 and scavenging immune suppressive TGF-beta from the tumor microenvironment. (Strauss J et al., Clin Cancer Res 2018) **Methods:** NHS-IL12 has been evaluated preclinically in combination with anti-PDL1 based therapy in BALB/c mice EMT-6 and MC38 tumors. **Results:** Preclinical studies of NHS-IL12 with anti-PDL1 demonstrated enhanced efficacy with the combination of the two agents compared to each agent individually. The combination demonstrated favorable changes in peripheral immune cells, increased immune cell infiltration, and improved survival. (Xu C et al. Clin Cancer Res, 2017) **Conclusions:** Previous work done at the NCI with our collaborators have demonstrated potential synergy with docetaxel and immunotherapy. (Hodge JW, Int J Cancer, 2013). Furthermore, in the context of NHS-IL12, preclinical data suggest that chemotherapy-induced necrosis can enhance NHS-IL12 delivery to the tumor. Based on this preclinical rationale we will conduct a two-cohort clinical trial. The first cohort will evaluate docetaxel, NHS-IL12 and M7824 in high volume metastatic castration resistant prostate cancer with primary goal of enhancing patients with less than 0.2 PSA at 7 months, an established metric in this population. A second cohort (metastatic castration resistant prostate cancer) will be treated with docetaxel, NHS-IL12 and M7824 with the primary endpoint of improving progression free survival. Immune analysis will also be done on both cohorts. We plan to initiate this trial in early 2020 at the National Cancer Institute.

Conflicts of Interest: none

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