Pilot trial of neoadjuvant combination androgen deprivation, AR-targeted vaccination, and PD-1 blockade in patients with newly diagnosed prostate cancer

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Background: Even though androgen deprivation therapy (ADT) remains the mainstay of treatment for metastatic prostate cancer (PC), in the neoadjuvant setting it has not been shown to affect long-term outcomes [1-5]. ADT combined with newer androgen receptor (AR) pathway inhibitors in the neoadjuvant setting have shown higher response rates compared to historic data [6]. The primary mechanism of resistance following ADT is overexpression of the AR, suggesting that immunological targeting of the AR might be advantageously combined with ADT. An ongoing phase I trial combining ADT with a DNA vaccine targeting the AR ligand-binding domain (pTVG-AR) with or without GM-CSF in patients with newly diagnosed metastatic disease is currently in progress (NCT02411786). In another ongoing study by our group (NCT02499835), we have found that the anti-tumor efficacy of a DNA vaccine (in this case targeting prostatic acid phosphatase [pTVG-HP]) can be increased when used in combination with PD-1 blockade. **Methods:** This is a proposal for an open-label, multicenter pilot trial designed to examine whether combination AR-targeted therapy, using multi-targeted AR pathway inhibitors in combination with a DNA vaccine targeting the AR, pTVG-AR, and with or without PD-1 blockade, can induce and/or augment therapeutic T-cells specific for the AR in patients with newly diagnosed PC undergoing prostatectomy. Patients will be randomized to 3 arms, with arm A receiving ADT in combination with abiraterone and apalutamide (AAA), arm B receiving AAA in combination with pTVG-AR and arm C receiving AAA in combination with pTVG-AR and nivolumab. Primary endpoints are safety and efficacy as measured by pathological complete response rates at the time of prostatectomy. Secondary objectives are to determine 1 year PSA progression-free survival rates, whether treatment with pTVG-AR, with or without nivolumab, elicits persistent systemic AR-specific Th1-biased T-cell responses as well as whether treatment with pTVG-AR, with or without nivolumab, elicits increased prostate tissue-infiltrating CD8+ T cells. Key inclusion criteria are localized intermediate to high-risk prostate adenocarcinoma with no evidence of distant metastases and eligibility for radical prostatectomy. Key exclusion criteria include prior hormonal therapy and radiation to the prostate. After establishing safety and efficacy, future confirmatory clinical trials with the optimum treatment schedule will be planned.

Conflicts of Interest: G. Liu is co-founder and CMO of AIQ Services. D.G. McNeel reports receiving a commercial research grant from, has ownership interest in, and is a consultant for Madison Vaccines Inc. C. Kyriakopoulos has no conflict of interest to disclose.

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