

A DNA vaccine encoding the androgen receptor ligand binding domain enhances antigen-specific immune responses in prostate cancer patients

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Background: While the androgen receptor has been the central pharmacological target for advanced prostate cancer for more than 60 years, we have shown that it is also an immunological target antigen. Some prostate cancer patients have AR-specific immune responses, including cytolytic CD8+ T cells that can recognize and lyse prostate tumor cells. Additionally, a DNA vaccine encoding the AR ligand-binding domain (LBD) has been shown to augment ARLBD-specific immune responses, decrease tumor development, and increase overall survival in multiple pre-clinical models. We have also shown that androgen deprivation therapy (ADT) increases AR expression in tumor cells, which makes them more susceptible to lysis by ARLBD-specific T cells, suggesting combining this vaccine with ADT would be a rationale clinical approach. We report here an interim analysis from a phase I clinical trial evaluating this vaccine in patients with metastatic prostate cancer recently initiated on androgen deprivation therapy.

Methods: Patients with metastatic prostate cancer recently enrolled on ADT were immunized following either a biweekly or staggered immunization schedule with a plasmid DNA vaccine encoding the ARLBD (pTVG-AR) alone or in combination with GM-CSF. The primary endpoints of the trial are safety and immunological response, with secondary objectives evaluating the effects of schedule and GM-CSF on the generation of immune responses, as well as PSA progression and 18-month PSA progression free survival. Immunological responses were measured using IFN γ and granzyme B ELISPOT, as well as CD4+ and CD8+ T cell proliferation.

Results: To date, thirteen patients have been enrolled on trial and received at least two immunizations. No serious adverse events have been observed, and no events greater than grade 2 have been identified. At least 5/11 patients developed enhanced ARLBD-specific immune responses following immunization. Additionally, antigen-spread to the AR amino-terminal domain was observed in 1/11 patients, as well as to PAP in 3/11 patients and PSA in 3/11 patients. To date, 2/13 patients have experienced PSA progression within 18 months.

Conclusions: Intradermal immunization of metastatic prostate cancer patients with pTVG-AR resulted in no significant adverse events, regardless of the schedule of administration or inclusion of GM-CSF, while enhancing antigen-specific immune responses. Continued accrual will shed light onto differences between schedule and co-administration of adjuvant, as well as effects on time to PSA progression.

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