

A pilot trial of neoadjuvant chemohormonal therapy with PSMA PET directed dissection of prostatectomy specimens for analysis of the tumor microenvironment

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Background: Men at greatest risk of progressing to castration resistance prostate cancer (CRPC) and death are those that present with high grade, high volume, locally advanced or disease with distant metastases. Previous studies have shown that the addition of docetaxel to standard androgen deprivation therapy (ADT) significantly improves progression-free survival (PFS) and overall survival (OS) compared to standard ADT alone in men with metastatic hormone-sensitive prostate cancer. There is further evidence to suggest that removal of the primary may improve clinical outcomes by reducing the risk of tumor self-seeding. However, it is unknown which patients receive the most benefit from multi-modal interventions. To understand the molecular drivers of response and resistance to chemohormonal therapy, we utilize advanced PET/MRI imaging to identify sites of multi-focal prostate cancer and guide dissection of the prostate using 3D tissue molds to extract cancer lesions that respond and progress on chemohormonal therapy. We then disaggregate and isolate these lesions using new microscale technologies to extract tumor, stromal and immune cells for molecular and functional analysis. A pilot trial of neoadjuvant chemohormonal therapy is now open to test these hypotheses. **Methods:** This is an open-label, single-arm, pilot trial designed to examine whether early, aggressive, multimodal treatment with chemohormonal therapy followed by prostatectomy can be clinically beneficial for a subset of men with newly diagnosed prostate cancer. We aim to enroll 30 patients with locally advanced and oligometastatic disease that will be treated with ADT in combination with docetaxel for three cycles followed by prostatectomy. The primary endpoint is pathologic complete response rates at the time of prostatectomy. Secondary clinical objectives are to evaluate the percentage of change in PSA from baseline to week 4 after prostatectomy, the maximum decline in PSA that occurs at any point during treatment, the rate of patients with PSA recurrence at month 12 after surgery as well as safety and tolerability of therapy. Exploratory interventions include PSMA PET/MRI imaging as a method for determining treatment response and response heterogeneity in primary prostate cancer and metastatic lesions after treatment as well as evaluation of genomic and gene expression signatures in prostate cancer cells, prostate stroma, bone marrow microenvironment and circulating tumor cells. Key inclusion criteria are treatment-naïve high risk locally advanced or oligometastatic prostate adenocarcinoma and eligibility for treatment with docetaxel followed by prostatectomy. Key exclusion criteria include prior hormonal therapy and radiation to the prostate. **Results:** We have successfully integrated PSMA PET/MRI scan results to form 3D molds for dissection of prostatectomy specimens in patients with high risk/oligometastatic prostate cancer. The microscale technologies enable sequential extraction of live tumor, stromal and immune cells. Our initial studies identify significant heterogeneity in multi-focal primary prostate cancer with rare infiltrating immune cells and stromal cells with differential secretion of paracrine factors that may promote treatment resistance.

Conflicts of Interest: DJB and JML have equity in Salus Discovery, LLC which has licensed technology in this poster. DJB also holds equity in Bellbrook Labs LLC, Tasso Inc., Stacks to the Future LLC, Lynx Biosciences LLC, and Onexion Biosystems LLC.

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