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: Previous studies have shown that 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. Further evidence suggest that removal of the primary may improve outcomes by reducing the risk of tumor self-seeding. 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 these lesions using new microscale technologies to extract tumor, stromal and immune cells for molecular and functional analysis. Here we present the preliminary results of the first 10 patients in a pilot trial of neoadjuvant chemohormonal theray to test these hypotheses. **Methods:** This is an open-label, single-arm, trial designed to examine whether multimodal treatment with chemohormonal therapy followed by prostatectomy can be beneficial for a subset of men with newly diagnosed prostate cancer. Thirty patients with locally advanced or oligometastatic disease will be treated with ADT and docetaxel for three cycles followed by prostatectomy. The primary endpoint is pathologic complete response rates. Secondary clinical objectives are percentage of change in PSA from baseline to week 4 after prostatectomy, maximum decline in PSA that occurs at any point, rate of patients with PSA recurrence at month 12 after surgery as well as safety and tolerability. Exploratory interventions include PSMA PET/MRI imaging as a method for determining treatment response and response heterogeneity in primary prostate cancer and metastatic lesions as well as evaluation of genomic and gene expression signatures in cancer cells, prostate stroma, bone marrow microenvironment and circulating tumor cells. **Results:** All patients had multi-focal prostate cancer detected on PSMA PET/MRI. A decrease in PSMA PET activity was observed in all patients with differential response in multi-focal lesions. One patient had an increase in PSMA PET activity while on study in one lesion. No patients achieved a complete pathologic response, however all patient had an undetectable PSA on week 4 after surgery. No surgical complications were observed and 9/10 patients had a significant decrease in prostate size. Dissection of the prostate based on PSMA signal identified heterogeneous immune infiltrates across multi-focal lesions with 4/10 patients showing an increase in M2 macrophage infiltration. Similarly, 4/10 patients also exhibited loss of MHC class 1 expression. **Conclusion:** The treatment was well tolerated with side effects similar to previously described with chemohormonal therapy. Our initial results identify significant heterogeneity in multi-focal primary prostate cancer with altered 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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