Evaluation of a novel transcriptomic tumor signature (PROSTest) as response biomarker for ^{177}Lu-PSMA therapy in advanced prostate cancer

Authors: Alin Chirindel, Mark Kidd, Cyrill Rentsch, Frank Stenner, Arnoud Templeton, Egbert Nitzsche, Damian Wild, Guillaume Nicolas and Irvin Modlin

Background:
Radionuclide therapy targeting the prostate-specific membrane antigen (PSMA) has proven to be an effective treatment in men with metastatic castration-resistant prostate cancer (mCRPCs). Despite representing a significant therapeutic breakthrough, a critical unmet need in PSMA-targeted radionuclide therapy is a response biomarker for treatment optimization. Imaging and standard biomarkers have limited value. The PROSTest is a new 27-gene algorithmic signature originally developed for prostate cancer (adenocarcinoma) diagnosis. We hypothesized that PROSTest would be elevated in mCRPCs and could have utility as a biomarker for mCRPC management.

Methods:
Prospective enrollment of 113 mCRPC for ^{177}Lu-PSMA therapy (KlbB-5338-0302021 study). Pathology, clinical, and biomarker data were available as was PSMA-PET/CT. Blood samples were collected for PROSTest prior to therapy. Target genes were isolated and amplified using qPCR. PROSTest scores (0-100) were obtained following algorithmic analysis. Scores were correlated with mCRPC diagnosis and baseline information. Scores and standard clinical measures were evaluated as prognostic factors with survival as the endpoint. Mann-Whitney U-test, Kaplan-Meier survival and Cox proportional hazards regression analysis were utilized. All data: median (IQ range).

Results:
89 (79%) patients were evaluable. Median age (range) was 75 (68-80). Disease characteristics at the time of diagnosis included Gleason scores which were predominantly 8-10 (70%) and TMM: T3-T4 tumors (67%), N1 (53%), M1 (45%). At the time of therapy, all patients were metastatic and all exhibited PSMA-positive disease.

The highest tumor SUV_{max} was 51 (28-78). PSA levels were 69ng/mL (18-305). The median PROSTest score was 89 (81-92). PROSTest scores were weakly correlated with age (r=0.33, p=0.0015) but not with baseline histopathological parameters (e.g., Gleason score, TNM) or pre-treatment imaging results (e.g., SUV_{max}). Twenty-four (27%) have perished following treatment initiation. Treatment and follow-up are ongoing: the median is 5 months (3-18). The mOS was 15 months. No factors were associated with death as an outcome except for the PROSTest score. PROSTest scores >79 were associated with significantly increased risk for mortality (HR: 2.9, 95% CI: 1.5-7.4). The mOS was 14 months in patients with pre-therapy PROSTest scores >79 compared to mOS not reached for PROSTest scores <79 (p=0.02). In the COX model, baseline PROSTest was confirmed to be significantly predictive of death despite therapy (β = 1.51, p=0.01).

Conclusions:
The PROSTest blood gene expression score is elevated in mCRPCs. Levels are not associated with baseline clinical, histopathological, or pretreatment PSA or imaging parameters. Elevated expression (>79) of this biomarker prior to treatment was associated with a lower survival and could be used to predict survival in those patients undergoing ^{177}Lu-PSMA.

About Wren Laboratories:
Founded in 2014, Branford, CT-based Wren Laboratories is a CLIA-certified and CAP-accredited liquid biopsy molecular diagnostic laboratory intent on developing unique, minimally invasive, and highly accurate fluid-based testing solutions.

A subsidiary of Clifton Life Sciences, Wren Laboratories is driven to develop liquid biopsy diagnostic and monitoring tests for various cancers including Neuroendocrine, Prostate, Lung, Melanoma, Myeloma, Colorectal, and Breast Cancer as well as Endometriosis.

688 East Main Street, Branford, CT 06405 | 1 (203) 208-3464 | wrenlaboratories.com