A Phase I Single-Arm Open Label Dose-Escalation Study of CivaSheet With Radical Prostatectomy With or Without Adjuvant External Beam Radiation Therapy in Patients With High Risk Prostate Cancer
Dr. Ketan Badani
NCT03657108
Document Date: 10-18-2022

Primary Outcome: We will determine the MTD for Civasheet when administered with RP and adjuvant EBRT. MTD is defined as the highest dose of the Civasheet® not yielding unacceptable toxicity. Specifically if > 33 % of subjects experience DLT at any dose level, the dose level below that level will be considered the MTD. Or if the highest level (75 Gy) has been reached and < 33% of subjects have experienced DLT, 75 Gy will be considered the MTD.. The present study defines dose limiting toxicity as the development of Grade 3 or higher (According to the NCI'S CTCAE v 4.0) urinary retention, hematuria or rectal bleeding/radiation proctitis within 90 days post EBRT which is given 6 weeks after RP + Civasheet implant for 5 weeks. Toxicities experienced among those not receiving adjuvant EBRT will not be used in the determination of the MTD. Binary or categorical outcomes will be described with proportion and 95% confidence intervals and continuous measures will be summarized with mean (SD) or median (IQR), as appropriate.

While all genitourinary and gastrointestinal toxicities according to the NCI-CTCAE will be documented and evaluated every time a subject is seen Grade 3-5 hematuria, urinary retention and rectal bleeding/radiation proctitis are the specific toxicities used for dose escalation procedures. This study defines DLT as the development of NCI-CTCAE Grade >3 urinary retention, Grade 3 hematuria or Grade 3 rectal bleeding/radiation proctitis within 90 days post EBRT which is given 6 weeks after RP + Civasheet implant for 5 weeks. Grade 3 hematuria according to the NCI-CTCAE is defined as gross hematuria with indications including transfusion, IV medications, hospitalization, elective endoscopic, radiologic or operative intervention and limiting self-care activities for daily living. Grade 3 urinary retention is defined as an incomplete ability to empty the bladder with indications including elective operation or radiologic intervention, substantial loss of affected kidney function or development of mass. Grade 3 rectal bleeding/proctitis is defined as severe symptoms; fecal urgency or stool incontinence and limiting self-care activities for daily living. If > 33% of subjects experience these DLT at any dose, the dose level below that level will be considered the MTD. If ≥ 33% subjects experience a DLT at 60 Gy, the trial will be closed and no additional subjects will be enrolled. Also, if the first subject enrolled at 60 Gy experiences NCI-CTCAE Grade 4 or higher hematuria, fistula formation or proctitis, no additional subjects will be enrolled and the trial will be closed. If the first subject enrolled at 75 Gy experiences Grade 4 or higher hematuria, fistula formation or proctitis, no additional subjects will be enrolled at 75 Gy and 60 Gy will be considered the MTD. Grade 4 hematuria is defined as hematuria with life-threatening consequences and urgent radiologic or operative intervention indicated. Grade 4 or higher fistula (anal or urinary) formation is defined as a fistula with life-threatening consequences with urgent radiologic or operative intervention indicated. Grade 4 or higher proctitis is defined as proctitis with life-threatening consequences and urgent intervention indicated. The time frame for DLT evaluation is the first 90 days after EBRT. EBRT is given 6 weeks after RP+ Civasheet implant at 45 Gy in 25 fractions (Monday-Friday for 5 weeks). If > 33 % of subjects experience DLT at any dose level, the dose level below that level will be

considered the MTD. Or if the highest level (75 Gy) has been reached and < 33% of subjects have experienced DLT, 75 Gy will be considered the MTD. If in the first subject treated at 75 Gy, NCI-CTCAE Grade 4 or higher hematuria, prostatitis or fistula formation occur, no additional subjects will be enrolled at 75 Gy and 60 Gy will be considered the MTD.

Secondary: We will describe the adverse events, toxicity and complication profile associated with Civasheet overall and at each dose when administered with RP and EBRT and also separately for those not receiving EBRT. Overall and for 60 and 75 Gy, the toxicity and complication profile associated with the Civasheet® will be assessed. Rates for surgical complications and adverse events, acute (< 90 days) and late (18 months days) GU and GI toxicity and adverse events using the NCI-CTCAE v4.0, RTOG Acute Toxicity Scale and Late Radiation Morbidity scales will be assessed. Erectile preservation and total urinary incontinence will be assessed overall and for each dose group once all subjects have completed the 6 month follow-up after EBRT. Peri- and post-operative complications associated with surgery will be assessed and graded using the Clavien-Dindo classification of surgical complications. Erectile preservation rates [IIEF score (erectile component) > 18] will be assessed, continence defined as the use of no pads will also be assessed. Binary or categorical outcomes will be described with proportion and 95% confidence intervals and continuous measures will be summarized with mean (SD) or median (IQR), as appropriate.

BCR defined as a post-prostatectomy serum PSA > 0.2 ng/ml will also be assessed for each subject. To evaluate cancer control, the Kaplan Meier-Method will be used to estimate BCR overall and for each dose group and separately for those receiving vs. not receiving EBRT once all subjects have completed the 6 months follow-up after EBRT or 6 months follow-up after Civasheet implant if no EBRT is given.