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
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| | Protocol Title: | 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 |
| | Principal Investigator Name/Contact Info: | Ketan K. Badani, MD/ 212-241-3919/ ketan.badani@mountsinai.org |
| | Primary Contact Name/Contact Info | Kennedy.okhawere@mountsinai.org Kennedy Okhawere |
| | Date Revised: | 7/22/2022 |
| | Study Number: | **GCO#1:** 16-**1314** |

# HRP-503 Application (Protocol Supplement)

- *This application can only be used in conjunction with a protocol. If this project does not have a protocol from the sponsor or is already included in a grant application then a comprehensive protocol should be developed. A comprehensive template and online wizard is located at: NIH Wizard.*
- *Note that, depending on the nature of your research, certain questions, directions, or entire sections below may not be applicable, or may have been fully covered in the protocol. Provide information if and when applicable. If the answer is found in the protocol please provide a page reference. If the question is not applicable to the study, mark the section "N/A". Do not delete any sections.*
- *Be sure to complete any supplement questions from one or another ancillary office that you receive during the RUTH application process. Please make certain that the protocol, this 503 application and responses to ancillary offices do not contradict each other and the information is incorporated in all documents where appropriate. Be sure to save the Ancillary office responses you provided within RedCap and upload them to Ruth.*
- *Throughout this application are references to checklists. These tools are used by the IRB to make specific regulatory findings. To allow us to do that it is the applicant's responsibility to ensure that your protocol has sufficiently addressed these additional regulatory criteria for approval, and that the applicant identifies those protocol specific findings required by the checklist. how will they do that, here or a separate form?*
- *Keep an electronic copy of this version of the document. You will need to modify this copy when making changes.*

## 1. Setting of the Human Research:

Research procedures will be performed at Mount Sinai West Hospital and Mount Sinai Main Hospital. Screening evaluations will occur at FPA Urology practice locations and the Mount Sinai West Hospital Urology office.

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# 2. Resources Available to Conduct the Human Research:

The operating surgeon's part of this study collectively perform 600 RP a year and expect to see 135 high-risk patients each year subject.

All personnel on the trial are adequately informed of the protocol and their role in all study related activities. All study personnel have completed CITI training requirements to conduct clinical research. Prior to active recruitment, the principal investigator will go through all aspects of the study with the study personnel. These aspects include the alternative standard therapy if the subjects were not part of this trial, the trial design, study rational, study related risks and benefits, the role of each personnel participating in the study, who to contact with any questions, and how to respond to situations or circumstances in which they are not accustomed to, or did not get briefed during the training session

# 3. Study Design:

A phase I single-arm open label dose-escalation study study. This trial utilizes a 3+3 dose escalation design which will evaluate the MTD and, safety of CivaSheet® with a fixed dose of adjuvant EBRT (45 Gy) during RP in men with high risk PCa.

## a) Recruitment Methods (see PPHS policy):

Source of potential subjects: Men with a diagnosis of NCCN high risk prostate cancer or NCCN intermediate-risk cancer with preoperative MRI evidence of extracapsular extension (ECE), seminal vesicle invasion (SVI) or N1 disease who are eligible to undergo RP with adjuvant EBRT as their definitive therapy.

Methods to identify potential subjects: All eligible subjects presenting to the PI or a Co-PI with a diagnosis of NCCN high-very high prostate cancer or NCCN intermediate high-risk cancer with preoperative MRI evidence of ECE, SVI or N1 disease are eligible to undergo RP with adjuvant EBRT as their definitive therapy who also meet inclusion will be consented by the PI or a Co-PI. If a potential subject then expresses interest in participating in the study, the physician/surgeon will present the potential subject with an informed consent form. All aspects of the trial will be discussed with interested subjects including the voluntary nature of their participation. Adequate time will be given to the subject to ask questions related to

the conduct of the trial. We will not advertise for this trial. Subjects will be recruited from the clinic.

## b) Inclusion and Exclusion Criteria:

- Any subject with NCCN very high or high risk adenocarcinoma of the prostate defined as ≥T3a, Gleason score ≥ 8, or PSA > 20 who is eligible for RP (open or robotic) with adjuvant EBRT as an initial treatment option.
- Any subject with NCCN Intermediate Risk adenocarcinoma of the prostate defined as T2b-T2c, Gleason score 7, or PSA 10-20 who is eligible for RP (open or robotic) with adjuvant EBRT as an initial treatment option and at least one of the following adverse features present in pre-operative imaging: SVI, ECE, N1 disease.
- Subject must have had a pre-operative MRI or must obtain a pre-operative MRI to be eligible for participation in this study.
- Ability to understand and the willingness to sign a written informed consent.

Exclusion Criteria

- Any subject who has undergone prior radiation to the pelvis.
- Subjects presenting with distant metastases.
- On any investigational drug(s), androgen deprivation therapy or therapeutic device(s) within 30 days preceding screening.
- Currently taking immunosuppressants, or with poorly controlled diabetes (HbA1c >8).
- Subjects with prior treatment for PCa including BT, RT or hormone therapy.

## c) Number of Subjects:

This is a 3+3 dose escalation design study to determine the MTD. This study will use 2 dose levels and 1-6 subjects at each dose level. The first subject enrolled at each dose level (60 and 75 Gy) will be monitored for the entire DLT window (3 months post EBRT completion) with subsequent subjects enrolled either at the same dose (if only 1 of the first 3 subsequent subjects at the given dose experiences DLT) or in the

next dose level if the preceding dose is deemed acceptable (i.e., < 33% DLT within 90 days post EBRT). If in the first subject, Grade 4-5 hematuria, fistula formation, proctitis or death occurs in the DLT window, the trial will be terminated. The total number of subjects for this single arm 3+3 trial design is therefore a minimum of 1 and a maximum of 12.

The dose escalation design utilized for the present study will proceed as follows: The first subject will be enrolled at 60 Gy. Once the entire DLT window (i.e., 90 days post EBRT) is complete for this first subject, the next 2 subjects will be enrolled at 60 Gy. If in the first subject, grade 4 or higher hematuria, proctitis, fistula formation or death occurs in the DLT window, the trial will be terminated. If 2 of the first 3 subjects experience DLT at 60 Gy, the trial will be terminated. If 0 or 1 of the first 3 subjects enrolled at 60 Gy experience a DLT after the third subject's entire DLT window is complete, an additional three subjects will be enrolled at 60 Gy. If ≥ 33 % of subjects experience DLT at 60 Gy, the trial will be terminated. If after the sixth subject's DLT window is complete and < 33% of subjects experience DLT at 60 Gy, the first subject at 75 Gy will be enrolled.Once the entire DLT window (i.e., 90 days post EBRT) is complete for this first subject at 75 Gy, the next two subjects will be enrolled at 75 Gy. If in the first subject at 75 Gy, grade 4 or higher hematuria, fistula formation, proctitis or death occurs in the DLT window, 60 Gy will be considered the MTD and no additional subjects will be enrolled at 75 Gy. If 2 of the first 3 subjects experience DLT at 75 Gy, 60 Gy will be considered the MTD and no additional subjects will be enrolled at 75 Gy. If 1 or 0 of the first 3 subjects enrolled at 75 Gy experience a DLT after the third subject's entire DLT window is complete, an additional 3 subjects will be enrolled at 75 Gy. If ≥ 33 % of subjects experience DLT at 75 Gy, no additional subjects will be enrolled at 75 Gy and 60 Gy will be considered the MTD. If after the sixth subject's DLT window is complete and < 33% of subjects experience DLT at 75 Gy, 75 Gy will be considered the MTD.

The true risk of toxicity is expected to be in the range of 10-50%. The following table shows the corresponding probabilities of dose escalation.

| True Risk of Toxicity | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
|---|---|---|---|---|---|
| Probability of Escalation | 0.96 | 0.87 | 0.69 | 0.50 | 0.31 |

A minimum of 3 and a maximum of 6 subjects within a dose level must be observed for one cycle (90 day post EBRT completion) before accrual to the next higher dose level may begin.

Three patients within a dose level must be observed for one cycle (30 days post EBRT) before accrual to the next higher dose level may begin. The treatment for this study is RP + Civasheet implant + adjuvant EBRT for patients with high-risk or intermediate (non-clinically localized) prostate cancer with adverse pathologic features including seminal vesicle invasion, extra prostatic extension or a positive surgical margin. Since the clinical guidelines recommend adjuvant EBRT post RP only for patients with adverse pathologic features at RP, patients without these adverse pathologic features at RP will be replaced with additional patients at that dose level. Since however eligibility criteria is for high risk or non-clinically localized intermediate risk prostate cancer, the anticipated number of patients without these adverse pathologic features who will not receive adjuvant EBRT is 2 or less. While toxicities among these patients will be monitored according to the protocol, toxicities among these patients will not be used in determinations of the MTD. The MTD will only be determined for patients undergoing RP + Civasheet implant + adjuvant EBRT.

If a subject is withdrawn from the study prior to completing the entire cycle of therapy or prior to completing the entire DLT window without experiencing a DLT prior to withdrawal, an additional subject may be added to that dose level. Subjects missing doses due to a DLT will not be replaced since these subjects will be considered to have experienced a dose limiting toxicity.

## d) Study Timelines:

The duration of an individual subject's participation in this study including follow-up is 5 years.

The expected duration for the investigators to complete this ranges between 1 month for a minimum of 1 subject and 44 months for a maximum of 12 subjects.

**Table 1. Time and events table for those undergoing RP + Civasheet implant + adjuvant EBRT.**

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| | Pre-study | Day 1 | Discharge (Typically Day 2) | 1 Week | 1 Month | 6 Weeks | 12 Weeks | 23 Weeks | 35 Weeks | Routinely for 4 years after Study completion |
|---|---|---|---|---|---|---|---|---|---|---|
| Assessment | X | X | X | X | X | X | X | X | X | X |
| Informed Consent, AE, Medical History/Medications, Eligibility criteria, Pre-Surgical clearance (i.e., chest, EKG, etc.). | X | | | | | | | | | |
| Toxicity/ AE/ Complications (including DLT) Evaluations | | X | X | X | X | X | X | X | X | X |
| X-Ray | X | | | | | | | | | |
| CBC | X | X | X | | | | | | | |
| Other required labs (PSA, testosterone, BMP) | X | X | X | X | | | | X | X | X |
| IIEF | X | | | X | X | | | X | X | X |
| MRI | X | | | | | | | | | |
| CT Scan | | | X | | X | | X | | X | |
| Radical Prostatectomy + Civasheet Implant | | X | | | | | | | | |
| EBRT for 5 weeks | | | | | | X | | | | |

**Table 2. Time and events table for those undergoing RP + Civasheet implant without adjuvant EBRT.**

| | Pre- | Day | Discha | 1 | 1 | Routinel |
|---|---|---|---|---|---|---|





Effective Date: 10/18/2022
End Date:10/17/2023

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| | study | 1 | rge (Typically Day 2) | Week | Month | y for 4 years after Study completion |
|---|---|---|---|---|---|---|
| Assessment | X | X | X | X | X | X |
| Informed Consent, AE, Medical History/Medications, Eligibility criteria, Pre-Surgical clearance (i.e., chest, EKG, etc.). | X | | | | | |
| Toxicity/ AE/ Complications (including DLT) Evaluations | | X | X | X | X | X |
| X-Ray | X | | | | | |
| CBC | X | X | X | | | |
| Other required labs (PSA, testosterone, BMP) | X | X | X | X | | X |
| IIEF | X | | | X | X | X |
| MRI | X | | | | | |
| CT Scan | | | X | | X | |
| Radical Prostatectomy + Civasheet Implant | | X | | | | |

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include informed consent, obtaining complete medical, surgical and infection history, demographic data, review of subject eligibility criteria, review of previous and concomitant medications, physical exam including height, weight and vital signs (temperature, pulse, respirations, blood pressure), baseline adverse event

identification, complete blood count test, serum chemistries via a comprehensive metabolic pattern (including albumin, creatinine, etc.), an MRI prior to surgery if not already obtained prior to surgery and completion of the international index of erectile function questionnaire.

Procedures During Treatment

Prior to Treatment

- Physical exam, vital signs
- Hematology
- Serum chemistries

Day 1

- Radical Prostatectomy + Civasheet implant
- X-Ray for baseline assessment of Civasheet stability

1 week after RP + Civasheet Implant

- Physical exam, vital signs
- Hematology
- Serum chemistries
- Pathology Review
- JP Drain and Catheter removal

1 Months After RP + Civasheet Implant

- CT Scan for assessment of Civasheet stability, assessment of cancer recurrence and also for EBRT planning among those with adverse pathologic features who will undergo EBRT

3 and 6 Months After RP + Civasheet Implant

- CT Scan for assessment of Civasheet stability and assessment of cancer recurrence among those with adverse pathologic features who will undergo EBRT.

6 weeks after RP+ Civasheet Implant

- EBRT given at 45 Gy in 25 fractions for 5 weeks (Monday- Friday) among those with adverse pathologic features at EBRT.

90 Days after Completion of EBRT

- Assessment of cumulative DLT's to decide whether progression to next dose or termination of study is necessary.

Follow-Up:

~~• Subjects will be followed every 6 months after completion of study treatment for 4 years or if the subject withdraws consent from participation, the subject will not be followed-up. Subjects may be followed- up by telephone or contacted by phone to schedule Mount Sinai office visits to monitor for cancer recurrence and or cancer progression in addition to late toxicity.~~

• Subjects will be followed yearly after completion of study treatment for 4 years or if the subject withdraws consent from participation, the subject will not be followed-up. Subjects may be followed- up by telephone or contacted by phone to schedule Mount Sinai office visits to monitor for cancer recurrence and or cancer progression in addition to late toxicity.

• If patients are not scheduled for their follow-up visits with Mount Sinai Health System, the study team will call the patient to schedule a visit.
  • If the patient schedules a follow-up at Mount Sinai, appropriate measures will be assessed according to the protocol and data will be recorded.
• If the patient is seeing a physician outside of Mount Sinai Health System, we will request that their labs and physician notes are sent to us.
  • A research coordinator will review and record the outside labs and contact the patients to collect any missing information that can be obtained by phone (i.e. bleeding, incontinence, etc.)
  • A symptomology follow-up form, as well as an IIEF assessment form are attached,
  • If additional information is necessary to assess DLTs or AEs, a coordinator will call the patient and request they schedule a follow up visit at Mount Sinai. If the patient is unable to come in for a follow-up visit, they will be dropped the study.
• If patients are not responsive after 2 attempts, they will be considered lost to follow up and replaced.

For those with adverse pathologic features: At 1 week post RP+ Civasheet

implant, 6 weeks after EBRT, 3 months after EBRT and 6 months after EBRT during the clinic visits, subjects will complete the IIEF to assess baseline erectile function following treatment. Subjects will undergo PSA testing for each follow-up visit. Those without adverse pathologic features not undergoing adjuvant EBRT will complete the IIEF to assess baseline erectile function following treatment and will also undergo PSA testing for each follow-up visit. Also at each follow-up visit or telephone follow up, subjects will be screened for toxicity and complications. The assessments may be done by phone when possible or lab results may be sent by the patient to our EMR if patient has followed up with an outside physician. For all patients, a CT-scan at day 0 (RP+Civasheet implant) will be done for a baseline stability assessment of the Civasheet. For all patients, a one month post-implant CT scan will be done of the pelvis for three purposes. The first purpose will be to perform a post-implant dosimetric analysis of the implanted Civasheet®. The bladder, rectum and any other identifiable structures (small bowel, large bowel of lymph nodes) will be outlined. The delivered dose will be calculated using a dose volume histogram and recorded. The second part of the CT will be to design the post-implant external beam radiation field among those who will undergo adjuvant EBRT. The third part will be to assess the stability of the Civasheet and any changes in position from initial implant. Among those who will undergo adjuvant EBRT, an additional post-implant CT scan at 90 days and 6 months will be done of the pelvis to prove stability of the device/implant method and to assess for cancer recurrence while whose not undergoing adjuvant EBRT will not receive this imaging at 90 days and 6 months.

## e) Specimen Banking for Future Uses Not Part of This Project:

NA

## f) Data Storage, Transmission and Confidentiality:

To ensure data accuracy and completeness, random checks will be done by members of the research team listed in the protocol who are not directly responsible for data collection and entry. Data irregularities and errors will be collected and reported to the . Data collected and stored for current and future research use will include age, gender, [ype here]

race, height, weight, , study information (subject study ID), medical history (allergies, other illnesses, symptoms at presentation, medications, prior surgery), physical examination information (Whole body physical exam including related to the rectal exam for prostate cancer screening) information related to prostate cancer (pathology from biopsy and surgery), any imaging data pertaining to prostate cancer (CT, MRI, ultrasound, bone scan), blood tests done as part of cancer work up (PSA, testosterone – total and free), procedural data (prostatectomy, external beam radiation therapy if necessary), and responses to all study related questionnaires (the International index of erectile function questionnaire), follow-up data including blood work, questionnaires, imaging. Subject data collected will be associated with unique study numbers and to connect each subject with their clinical data. Data excluding names, social security numbers, hospital record numbers, address [mailing and email], phone numbers, fax numbers, account numbers, health plan number will be stored on a secure computer in the PI's locked office or kept in REDCap (Research Electronic Data Capture), a secure web application. REDCap is a project creation tool to build and manage online clinical databases and to collect and manage online clinical data. REDCap provides audit capabilities to track researchers' use of the platform. Data will be stored indefinitely. All study data at Mount Sinai stored electronically will follow MSMC policies. All PHI not stored in the database will be encrypted and password protected. The key to the identification number to connect subjects with their clinical data will also be kept in REDCap and on a secured computer in the PI's locked office. The PI is responsible for receipt or transmission of the data. All research team members listed on this protocol will have access to the data with identifiers during the conduct of the trial. Data will only be used by these team members in the PI's locked office. Data will be transmitted for use only on a secured server having password protected access by only research personnel listed on this protocol.

Random checks will be done by members of the research team other than the person responsible for data collection to ensure data accuracy and completeness. Specifically, 10% of subject records will be randomly selected and comparison between electronic medical records and electronic database records will be made. If errors are more common than the acceptable quality threshold of 50 per 10,000 fields established by the Society for Clinical Data management, then a complete check of the data will be performed prior to data analysis. Any irregularity will be corrected and reported to the PI.

ISMMS Principal Monitor:

Principal Investigator Last Name:
ıdani First Name: Ketan

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Fax: 212-410-7194

E-Mail: richard.stock@mountsinai.org

The PI is directly involved with the clinical care of the subjects. He has led the prostate and kidney cancer research program at Columbia University Medical Center for the past 7 years and is currently the Director of the Comprehensive Kidney Cancer Program at Mount Sinai Health System. Dr. Badani is involved in numerous clinical trials, feasibility and safety studies of new technology, and health related quality of life outcomes

research. He serves as an editor and/or reviewer for numerous publications including Cancer, Journal of Urology, Urologic Oncology, Journal of Endourology, among others.

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator will assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. Except for an emergency situation in which proper care for the protection, safety, and

well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

The Principal Investigator at each institution or site is responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and his required final signature will verify the accuracy of the data

Adverse events, complication, toxicity and subject compliance with the protocol will be monitored. Adverse events related to surgery will be graded using the Dino-Clavien grading system. As per standard care, standard side effects of surgery including but not limited to fever, chills, nausea, vomiting, abdominal pain, constipation, incontinence will be monitored and appropriate therapy implemented. The adverse events for surgery we monitor include infection, stricture, abscess, bowel perforation, erosion into surrounding structures, bleeding, fistula, worse rates of continence and erectile function. Adverse events and toxicity associated with radiation we monitor include GI and GU toxicity, bladder and rectal adverse effects, urethral strictures, hematuria, radiation proctitis. All toxicity will be graded according to the RTOG acute and late morbidity scoring schemes. The adverse events related to the implementation of the Civasheet® include radiation to other areas due to movement of the sheet which will be monitored with a 30 day post implant CT to ensure stability of the device and implant method for all patients and additionally at 90 days and at 6 months for those undergoing EBRT. To ensure subject compliance, subjects will be counseled each visit or phone call as on the adherence to study criteria. Subject failure to follow up or comply with protocol as well as the reasons for failure to follow up or comply with protocol will be assessed and documented.

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Adverse events and toxicity will be monitored and assessed at each follow-up visit or phone call for all subjects enrolled. After the first subject's DLT window is complete at 60 Gy (90 days post-EBRT), we will make a decision to enroll additional subjects at 60 Gy only if Grade 4-5

hematuria, proctitis, or fistula are not observed. If 2 additional subjects are enrolled at 60 Gy, we will review for DLTs after completion of the 90 day DLT window and enroll 3 additional subjects at 60 Gy if DLT has been observed in 1 subject, or enroll 1 subject at 75 Gy if no DLT were observed or terminate the trial if ≥33% DLT were observed in all subjects. For the next group of subjects at 60 Gy, we will review DLT/toxicity after all three subjects have completed the 90 days DLT window after EBRT. After the first subject's DLT window is complete (90 days post-EBRT) at 75 Gy, we will make a decision to enroll additional subjects at 75 Gy only if Grade 4-5 hematuria, proctitis, or fistula are not observed. If 2 additional subjects are enrolled at 75 Gy, we will review for DLTs after completion of the 90 day DLT window and enroll 3 additional subjects at 75 Gy if DLT has been observed in 1 subject, or terminate the trial if ≥33% DLT were observed among the first three subjects at 75 Gy. For the next group of three subjects at 75 Gy, we will review DLT/toxicity after all three subjects have completed the 90 days DLT window. We will additionally describe rates of complications and toxicity (i.e., acute and late overall, GU and GI) by grade and by dose once the 6 month follow-up period is complete for all subjects. Toxicities among those not receiving EBRT will not affect the MTD determination or the decision to enroll additional patients at the same dose or at a higher dose. The DMC will review data at least once annually.

If the DMC recommends termination of the study we will terminate the study. If in the first subject at any dose Grade 4-5 hematuria, proctitis or fistula occur, we will terminate the study. If ≥ 33% of subjects experience DLT (i.e., Grade 3 hematuria, proctitis, urinary retention) within the first 90 days post EBRT, the trial will be closed.

The Clavien-dindo classification of surgical complications will be used to assess complications and the NCI-CTCAE v4.0 in addition to the RTOG acute and late morbidity scoring criteria will be used to grade adverse events and toxicity.

Should a temporary or permanent suspension of our study occur, we will report the occurrence to the IRB and CivaTech Oncology®. If terminated, we will inform the IRB and research offices of termination. If terminated, we will continue to offer the standard of care for study subjects. If study termination is due to safety concerns, we will inform subjects by phone, mail or email of the study's status. If terminate not due to safety concerns, we will inform subjects during routine clinical visits.

The study will use the DSMC of the TCI as the data monitoring committee. All unexpected adverse events will be presented to the DSMB for review. All recommendations of the DSMB will be followed and implemented. If a situation arises in which the DSMC recommends termination of the study, we will terminate the study. To ensure data accuracy and completeness, random checks will be done by members of the search team listed in the protocol who are not directly responsible for data collection



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and entry. Data irregularities and errors will be collected and reported to the PI. Should a temporary or permanent suspension of our study occur, we will report the occurrence to the IRB and MiMedx®. This study will use of the Tisch Cancer Center as the data monitoring committee. If notable safety issues are found in our interim analysis, the study will be interrupted as per DSMB recommendations. DSMB recommendations will be followed and implemented.

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

The study investigator will retain all study documentation pertaining to the conduct of a clinical trial according to government agency regulations and directives. Study documents will be kept on file until three years after the completion and final study report of this investigational study.

ADVERSE EVENTS

- Adverse Event Monitoring

  Adverse event data collection and reporting will be done to ensure the safety of subjects enrolled in this study as well as those who will enroll in future studies using similar agents. Adverse events will be reported in a routine manner at scheduled times during this trial. Additionally, certain adverse events will be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

  All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

  - the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
  - any abnormal laboratory values have returned to baseline;

- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

- Definition of Adverse Event

  An adverse event (AE) is defined as any untoward medical occurrence in a subject receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- Severity of Adverse Events

  All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html and will also rely on the radiation therapy oncology group's (RTOG) late and acute radiation morbidity criteria for assessing toxicity available at https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity_grading/RTOG

  If no CTCAE grading is available, the severity of an AE is graded as follows:

  Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

  Moderate (grade 2): the event causes discomfort that affects normal daily activities.

  Severe (grade 3): the event makes the subject unable to perform normal daily activities or significantly affects his/her clinical status.

  Life-threatening (grade 4): the subject was at risk of death at the time of the event.

  Fatal (grade 5): the event caused death.

- Serious Adverse Events

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

* Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

* Is life-threatening.

(the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

* Requires in-subject hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

* Results in persistent or significant disability or incapacity.

* Is a congenital anomaly/birth defect

* Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the subject, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse

Event".

- Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy

Attribution categories are as follows:

- Definite – The AE is clearly related to the study treatment.

- Probable – The AE is likely related to the study treatment.

- Possible – The AE may be related to the study treatment.

- Unrelated – The AE is clearly NOT related to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) will also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

• the current known adverse events listed in the Agent Information Section of this protocol;

• the drug package insert;

• the current Investigator's Brochure

- Reporting Requirements for Adverse Events

Expedited Reporting

• The Principal Investigator will be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of EBRT.

• Expedited reporting to Civatech Oncology is not required for adverse events.

• The IRB/PPHS will be notified within 5 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

- The following events meet the definition of UPR

a. Any new information that indicates a new or increased risk, or safety issue (e.g., interim analysis, safety monitoring report, publication, updated sponsor safety report), that indicates an unexpected change to the risk/benefit ratio for the research.

b. An investigator brochure, package insert, or device labeling is revised to indicate an increase or magnitude of a previously known risk, or describes a new risk.

c. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in research protocol

d. Protocol deviation or violation that harmed subjects or others or that indicated subjects or others might be at increased risk of harm.

e. Complaint of subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm

f. Any breach in confidentiality that may involve risk to the subject or others.

g. Any harm experienced by a subject or other individual that in the opinion of the investigator is unexpected and at least probably related to the research procedures.

- Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

- Stopping Rules

If the DMC recommends termination of the study we will terminate the study. If in the first subject at any dose Grade 4-5 hematuria, proctitis or fistula occur, we will terminate the study. If ≥ 33% of subjects experience DLT at any dose level (i.e., Grade 3 hematuria, proctitis, urinary retention) within the first 90 days post EBRT, the trial will be closed.

- In accordance with local IRB requirements, the following information will be reported within five (5) business days.

• Non-compliance with federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance

• Failure to follow the protocol due to the action or inaction of the investigator or research staff.

• Breach of confidentiality

• Premature suspension or termination of the research by the sponsor or investigator.

## g) Withdrawal of Subjects:

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons without the subject's consent. The reason for study removal and the date the subject was removed will be documented in the Case Report Form. The subject will be followed-up per protocol unless subject voluntarily withdraws consent from study. Reasons for discontinuation may include:

- Subject voluntarily withdraws from treatment (follow-up permitted);
- Subject withdraws consent (termination of treatment and follow-up);
- Subject is unable to comply with protocol requirements;
- Subject demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator) and hormonal therapy is required;
- Treating physician judges continuation on the study would not be in the subject's best interest;
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- Research study is stopped;
- Subject does not meet study criteria;
- Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years will be documented and approved by the Data Monitoring Committee.

If a situation arises in which the DSMC recommends termination of the study, we will terminate the study. If terminated, we will inform the IRB and research offices of termination. If terminated, we will continue to offer the standard of care for study subjects. If study termination is due to safety concerns, we will inform

them by phone, mail or email of the study's status. If terminate not due to safety concerns, we will inform subjects during routine clinical visits.

If subjects withdraw from the study, we will reach out to them as to the reason for withdrawal. In addition to an analysis of for subjects having completed the study, we will complete an intent-to-treat analysis.

## h) Data and Safety Monitoring Plan:

**For projects with a Data Safety Monitoring Board/Data Safety Committee (DMSB/DMC):**
If not included in the protocol, attach a description of the DMC/DSMB, including the number, names (if available} and area of professional expertise of the members. The responsibilities of the DSMB/DMC must be clear as well as their powers and their degree of independence. The DSMB charter must be provided to the PPHS before the study may begin. Reports of the DMC/DSMB must be made available to the local PI and the MSSM PPHS. The report need not contain specifics of the study or data, but there should be clear statement if the study can continue as is, or requires changes or termination.

## i) For other projects with greater than minimal risk a monitoring plan must be provided:

1. List the name(s) of the individual(s) at MSSM who will be responsible for data and safety monitoring of this study. For each individual, indicate their role, name, title, and department information. The Principal Investigator may be the only monitor of a study.

2. If the qualifications of an individual to serve as a monitor are not contained in the PPHS application, they must be added to the DSMP either as a narrative description or as a CV.

**MSSM Principal Monitor:**
Indicate whether this person is the PI, a Team Member, or is Independent:
Last Name:
First Name:
Academic Title:
Department:
Mailing Address:
Phone:
Fax:

E-mail:

**MSSM Additional Monitor:**
Indicate whether this person is the PI, a Team Member, or is Independent:
Last Name:
First Name:
Academic Title:
Department:
Mailing Address:
Phone:
Fax:
E-mail:

3. Justify your choice of principal monitor in terms of the assessed risk to the research subject‘s health and wellbeing. In high risk studies when the principal monitor is independent of the study staff, indicate the individual’s credentials, relationship to the PI, and the rationale for selection.
4. List the specific items that will be monitored for safety (e.g., adverse events, subject compliance with the protocol, drop outs, etc.).

5. Indicate the frequency at which ACCUMULATED safety and data information (items listed in number 3 above and interim analysis of efficacy outcomes) will be reviewed by the monitor(s) or the Data Monitoring Committee (DMC). Although this information must be reviewed at least annually, the higher the study risks, the more frequently reviews must be scheduled.

6. Where applicable, describe rules which will guide interruption or alteration of the study design.

7. Where applicable, indicate dose selection procedures that will be used to minimize toxicity.

8. List any specialized grading system that will be used to evaluate adverse events (e.g., National Cancer Institute Common Toxicity Criteria).

9. Describe procedures that will be used to assure data accuracy and completeness.

10. Should a temporary or permanent suspension of your study occur, in addition to the PPHS, indicate to whom (NIH, FDA, sponsor, IRB) will you report the occurrence.

## j) Withdrawal of Subjects:


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Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons without the subject's consent. The reason for study removal and the date the subject was removed will be documented in the Case Report Form. The subject will be followed-up per protocol unless subject voluntarily withdraws consent from study. Reasons for discontinuation may include:

- Subject voluntarily withdraws from treatment (follow-up permitted);
- Subject withdraws consent (termination of treatment and follow-up);
- Subject is unable to comply with protocol requirements;
- Subject demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator) and hormonal therapy is required;
- Treating physician judges continuation on the study would not be in the subject's best interest;
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- Research study is stopped;
- Subject does not meet study criteria;
- Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years will be documented and approved by the Data Monitoring Committee.

If a situation arises in which the DSMC recommends termination of the study, we will terminate the study. If terminated, we will inform the IRB and research offices of termination. If terminated, we will continue to offer the standard of care for study subjects. If study termination is due to safety concerns, we will inform them by phone, mail or email of the study's status. If terminate not due to safety concerns, we will inform subjects during routine clinical visits.

If subjects withdraw from the study, we will reach out to them as to the reason for withdrawal. In addition to an analysis of for subjects having completed the study, we will complete an intent-to-treat analysis.

# 4. Provisions for Research Related Harm/Injury:

In the event of physical or psychological harm to subjects, we will consult medical and psychological teams as necessary to care for the subjects. In the event of research related injury, standard care will be provided to subjects and will be billed to subject's insurance.

# 5. Recordings:

N/A

# 6. Provisions to Protect the Privacy Interests of Subjects:

PI and Co-PI's will explain the study to subjects in a private room. Throughout the study, adequate time will be given to subjects to ask questions about the study which will be answered accordingly. All procedures as well will be done in a private room. As explained in section 5h all subject clinical data will be kept confidential.

To ensure subjects feel at ease with the study, all study procedures will be explained in a private room with the subject by the PI or Co-PIs allowing adequate time for questions and answers. The subject will be allowed to ask questions to the PI or Co-PIs at any time throughout the study and will be informed of the voluntary nature of the study and the ability to withdraw at any time without penalty or changes to the subject's normal standard of care. Subjects will be given copies of the informed consent and if the subject agrees to participate, he or she will sign the form in the presence of the PI or a Co-PI. When subjects are contact, they will be informed of the details of who they are speaking with as well as the PI.

Appropriate members (i.e., Co-PI's, protocol listed research members) may contact the prospective subject about the research. Co-investigators are qualified research personnel with CITI training and sufficient understanding of the study. The research personnel are able to explain all study related procedures and aspects to subjects and answer study related questions of subjects throughout the study. PI and Co-PI's will explain the study to subjects in a private room. Throughout the study, adequate time will be given to subjects to ask questions about the study which will be answered accordingly. All procedures as well will be

done in a private room. As explained in section 5h all subject clinical data will be kept confidential.

## 7. Economic Impact on Subjects:

There are no expected costs to subjects for participation in this study. Procedure related complication and toxicity resulting from the treatment will be treated with standard of care. Standard of care treatment including care related to visits (hospital, emergency, office) and/or hospitalization will result in billing to the subject's insurance. There is no compensation for participation in this study. The cost of the Civasheet and the CT scan prior to the patient's discharge will be covered by the sponsor, Civatech Oncology. All other costs associated with the subject's standard of care must be paid by the subject/ insurance.

## 8. Payments/Reimbursements to Subjects:

There is no compensation for participation in this study.

## 9. Consent Process:

The IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB will approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator will comply with the applicable regulatory requirement(s), and will adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form includes all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject

understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a subject's participation in the trial, the written informed consent form will be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

All study procedures will be explained in a private room with the subject by the PI or Co-PIs with adequate time to ask questions and have them answered by the research personnel. Subjects will be informed of the voluntary nature of the study and the ability to withdraw at any time without penalty or changes to the subject's normal standard of care.

Subjects will be given copies of the informed consent and if the subject agrees to participate, he or she will sign the form in the presence of the PI or a Co-PI. Subjects will be allowed to ask questions before and after signing the consent form and will have them addressed accordingly.

## 10. Process to Document Consent in Writing:

A PI or Co-PI will discuss the study with subject allowing adequate opportunity for questions. The individual explaining the study will go line by line with the subject on each of the following informed consent elements: title, principal Investigator, Purpose of Research Study, Description of What's Involved, Responsibilities, Risks, Benefits. Subject will be given the opportunity to sign and date the PPHS approved informed consent with co-PI or PI's signature and date as well .A copy of the signed consent and give to subject and a copy of the signed consent form will be scanned into the subjects electronic medical record in EPIC (Mount Sinai's electronic medical records system). Also the entire consent process will be documented in the subject's chart. The original signed consent form will be put into the regulatory binder.

## 11. Vulnerable Populations:

| *Include* | *Exclude* | *Vulnerable Population Type* |
|---|---|---|
| | | *Adults unable to consent* |

| | | |
|---|---|---|
| | | *Individuals who are not yet adults (e.g. infants, children, teenagers)* |
| | | *Wards of the State (e.g. foster children)* |
| | | *Pregnant women* |
| | | *Prisoners* |

## 12. Multi-Site Human Research:

This is a single site study.

## 13. Community-Based Participatory Research

**N/A**

## 14. Sharing of individual and study Results with Subjects:

The results of this study will not be shared with the subjects.

## 15. External IRB Review History

N/A

## 16. Control of Drugs, Biologics, or Devices:

Civasheet®, a membrane like brachytherapy device, is a biodegradable low dose radiation sheet with a series of small radioactive 103 palladium (Pd-103) capsules on one side of the sheet. Civasheet® can be custom cut and permanently implanted to offer unidirectional, localized radiation directly to cancerous tissue while gold shielding health surrounding tissue due to the unidirectional radiation the sheet offers.

103 Pd used in Civasheet® is often used for brachytherapy seed implantation used in a unimodal or multimodal fashion with EBRT+HT or with EBRT alone in the treatment of local and locally advanced prostate cancer.

Civasheet will implanted during radical prostatectomy on areas at suspicious for local advancement or positive surgical margins. Civasheet has Pd-103 capsules on one side of the sheet to provide local unidirectional radiation to areas suspicious for local advancement and positive surgical margins while gold shielding nearby organs including the bladder and rectum from radiation

Civasheet® is the first commercially available polymer encapsulated bioabsorbable brachytherapy device that has integrated radiation shielding available. Civasheet® is designated as a medical device by the U.S. Food and Drug Administration and is the only FDA 510K cleared sheet device on the market. It is produced in accordance with the FDA regulations for Current Good Manufacturing Practice (cGMP). Civasheet is a Class 2 FDA 510K cleared sheet device on the market which is commercially available and provided free of charge for the study. Forceps will be used when handling the Civasheet with the gold shielded side of the Civasheet towards the surgeon's body. Shielded radiation gloves will be used to reduce the dose to hands.

After reviewing the MRI of subjects enrolled in the study, Civasheet® will be order by the Department of Radiation Oncology. The sheet will be delivered to the Department of Radiation Oncology similar to how all of the radioisotopes ordered to the Department are delivered. The sheet will be stored in the Department of Radiation Oncology's hot lab. The size and dimensions of the Civasheet® will be determined by the radiation oncologist and physicist based on the subject' and will be pre-cut in the radiation oncology hot lab and then given to the operating surgeon in the operating room. Regardless of the subject, the Civasheet will be handled by the operating surgeon with instruments following the same protocol for the handling of brachytherapy seed implants. The department will bring the material to the operating room when it is time to implant it. Un-implanted portions of the sheet will be returned to the Department of Radiation Oncology's hot lab. It is Mount Sinai Medical Center's responsibility to maintain records to trace Civasheet® following the implantation of the device including the amount implanted or discarded. If study

material is left over it will be stored in the Department of Radiation Oncology's hot lab and then CivaTech Oncology will issue a customer goods return number and for the remaining product to be returned.

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