PHASE III RANDOMIZED TRIAL COMPARING SHORT COURSE ANDROGEN DEPRIVATION THERAPY AND ULTRA-HYPOFRACTIONATED SBRT VERSUS ULTRA-HYPOFRACTIONATED SBRT ALONE FOR INTERMEDIATE PROSTATE CANCER

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Michael J. Zelefsky, MD	Radiation Oncology
Co-Principal Investigator(s)/Department:	Sean McBride, MD	Radiation Oncology
	Marisa Kollmeier, MD	Radiation Oncology
Investigator(s)/Department:	Annemarie Shepherd, MD	Radiation Oncology
	C. Jillian Tsai, MD	Radiation Oncology
	Daphna Gelblum, MD	Radiation Oncology
	Melissa Zinovoy, MD	RadiationOncology
	Richard Gewanter, MD	Radiation Oncology
	Boris Mueller, MD	Radiation Oncology
	Borys Mychalczak, MD	Radiation Oncology
	Laura Happersett, MA	Medical Physics
	Behfar Ehdaie, MD	Surgery
	Samson Fine, MD	Pathology
	Zhigang, Zhang, PhD	Biostatistics
	John Cuaron, MD	Radiation Oncology
	Marsha Reyngold, MD	Radiation Oncology
	Lior Braunstein, MD	Radiation Oncology
	Nancy Lee, MD	Radiation Oncology
	Beryl McCormick, MD	Radiation Oncology
	Oren Cahlon, MD	Radiation Oncology
	Atif Khan, MD	Radiation Oncology
	Danielle Max, PA	Radiation Oncology
	Daniel Gorovets, MD	Radiation Oncology
	Daniel Shasha, MD	Radiation Oncology
	Quincey LaPlant, MD	Radiation Oncology
	Christopher Barker, MD	Radiation Oncology
	Janice Terlizzi, APN	Nursing
	Lauren Cutrone, NP	Nursing
	Carol Ann Milazzo, NP	Nursing
	Erin Gillespie, MD	Radiation Oncology
	Lior Braunstein, MD	Radiation Oncology
	Michael Bernstein, MD	Radiation Oncology
	Jung Kang, MD	Radiation Oncology
	Ariel Marciscano, MD	Radiation Oncology
	Justin Mann, MD	Radiation Oncology
	Narek Shaverdian, MD	Radiation Oncology
	Linda Chen, MD	Radiation Oncology
	Dhwani Parikh, MD	Radiation Oncology

	Carla Hajj, MD	Radiation Oncology
	Yao Yu, MD	Radiation Oncology
	David Guttman, MD	Radiation Oncology
	Eileen Jackson, NP	Nursing
	Ilana Genin, NP	Nursing
	Janine Davis (Cleary), APN	Nursing
	Janet Cogswell, RN	Nursing
	Jennifer Howgate-Klingaman, RN	Nursing
	Lisa Sarmasti, RN	Nursing
	Geri Arnell, RN	Nursing
	Megan Stasi, RN	Nursing
	Ofer Maimran, RN	Nursing
	Nicole Heinz, RN	Nursing
	Raylene Langish, RN	Nursing
	Jessica Marchisotto, RN	Nursing
	Irene Kelly, RN	Nursing
	Gloria Wasilewski, RN	Nursing
	Sherie Mar-Chaim, RN	Nursing
	Maureen Kennedy, RN	Nursing
Consenting Professional(s)/Department:	Michael J. Zelefsky, MD	Radiation Oncology
	Sean McBride, MD	Radiation Oncology
	Marisa Kollmeier, MD	Radiation Oncology
	Annemarie Shepherd, MD	Radiation Oncology
	C. Jillian Tsai, MD	Radiation Oncology
	Daphna Gelblum, MD	Radiation Oncology
	Melissa Zinovoy, MD	Radiation Oncology
	Richard Gewanter, MD	Radiation Oncology
	Boris Mueller, MD	Radiation Oncology
	Borys Mychalczak, MD	Radiation Oncology
	Behfar Ehdaie, MD	Surgery
	John Cuaron, MD	Radiation Oncology
	Marsha Reyngold, MD	Radiation Oncology
	Lior Braunstein, MD	Radiation Oncology
	Nancy Lee, MD	Radiation Oncology
	Beryl McCormick, MD	Radiation Oncology
	Oren Cahlon, MD	Radiation Oncology
	Atif Khan. MD	Radiation Oncology
	Daniel Gorovets, MD	Radiation Oncology
	Daniel Shasha, MD	Radiation Oncology
	Christopher Barker, MD	Radiation Oncology
	Erin Gillespie, MD	Radiation Oncology
	Lior Braunstein, MD	Radiation Oncology
	Michael Bernstein, MD	Radiation Oncology
	Jung Kang, MD	Radiation Oncology
	Ariel Marciscano, MD	Radiation Oncology
	Quincey LaPlant, MD	Radiation Oncology

	Justin Mann, MD Narek Shaverdian, MD Linda Chen, MD Dhwani Parikh, MD Carla Hajj, MD Yao Yu, MD David Guttman, MD	Radiation Oncology Radiation Oncology Radiation Oncology Radiation Oncology Radiation Oncology Radiation Oncology Radiation Oncology

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Basking Ridge	All Protocol Activities
Bergen	All Protocol Activities
Commack	All Protocol Activities
Monmouth	All Protocol Activities
Rockville Centre	All Protocol Activities
Westchester	All Protocol Activities
Nassau	All Protocol Activities

MSK Alliance Clinical Trials Sites	**PI's Name**	**Site's Role**
Baptist Alliance MCI	Marcio Fagundes, MD	Data Collection
Lehigh Valley Health Network	Dennis Sopka, MD	Data Collection

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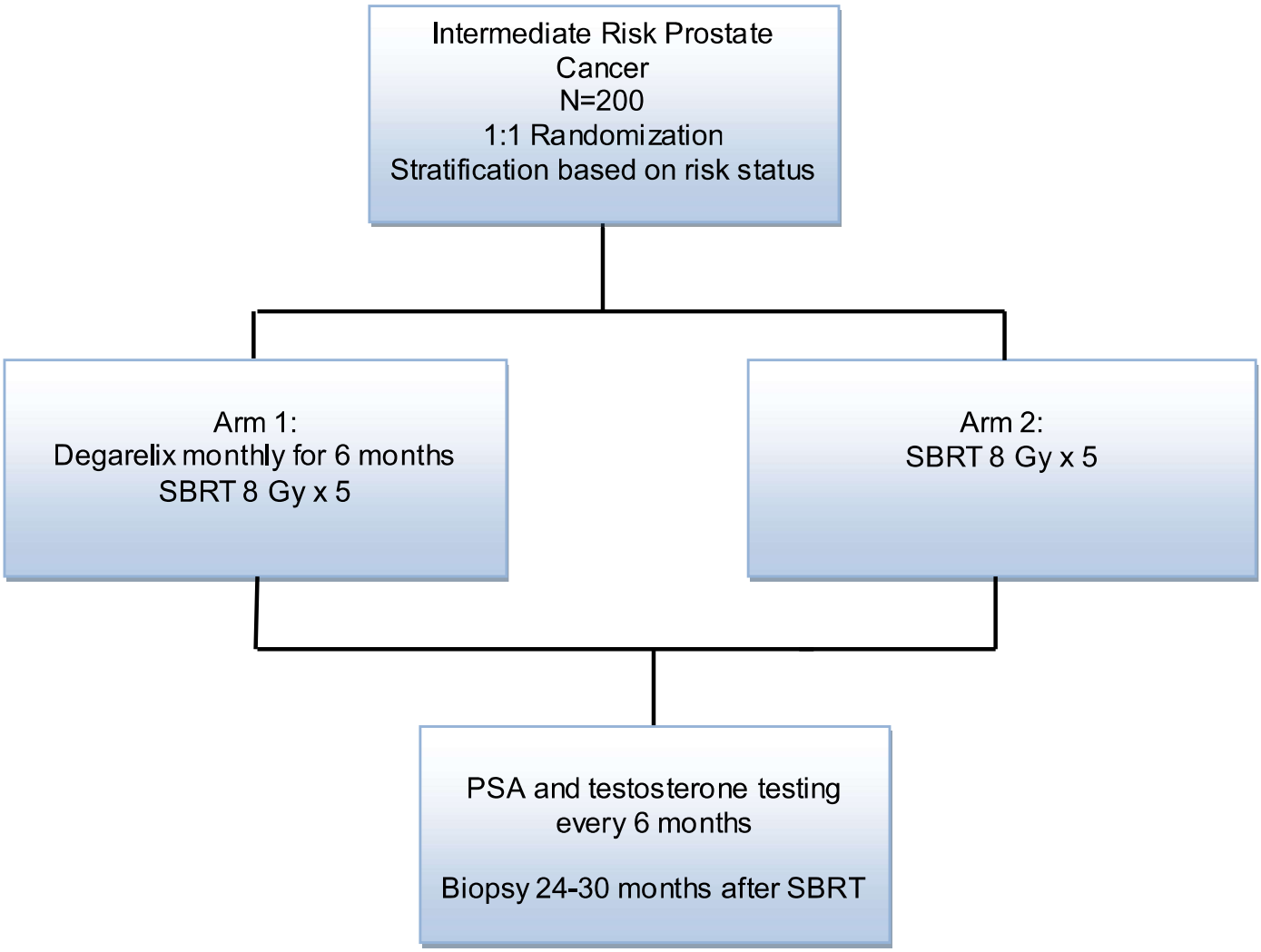
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

For this proposed Phase III study, intermediate risk prostate cancer patients will be randomized to receive 6 months of Androgen Deprivation Therapy (ADT) in conjunction with stereotactic body radiosurgery (SBRT) directed to the prostate versus SBRT alone. The patient population eligible will include patients with NCCN defined intermediate risk disease. ADT will be administered with Degarelix monthly injections. SBRT will be delivered with a prescription dose of 8 Gy x 5 to the planning target volume. Inter-fraction motion targeting and target position corrections will be utilized for each of the 5 treatment fractions. All patients will be followed every 6 months for 2 years and will undergo routine 24-30 months post-SBRT prostate biopsies to assess for local tumor control.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives

- To compare 24-30 month post-SBRT prostate 12 core biopsy outcomes between intermediate risk patients treated with SBRT and short course ADT versus SBRT alone.

Secondary Objectives

- To assess whether the addition of 6 months of ADT with high dose SBRT decreases incident rates of biochemical failure and distant failure, or improves survival rate for intermediate risk prostate cancer patients compared to SBRT alone.

- To assess the differences in short-term and long-term quality of life outcomes by comparing EPIC-26, IPSS, and SF-12 survey results between intermediate risk prostate cancer patients treated with SBRT + short course ADT versus SBRT alone.

3.0 BACKGROUND AND RATIONALE

3.1 Improved Outcomes with ADT and Conventionally Fractionated EBRT for Intermediate Risk Disease

Data from two randomized trials have demonstrated survival advantages when using short course ADT in conjunction with low dose (70 Gy) conventionally fractionated radiotherapy for patients with intermediate risk disease (1, 2). While these studies have not confirmed the need for ADT in the era of dose escalation in the ranges of 78-80 Gy it is assumed that ADT would be advantageous as well even when higher radiation dose levels are employed. Retrospective data from Memorial Sloan-Kettering Cancer Center have demonstrated that improved distant metastases-free survival and prostate cancer mortality survival outcomes are observed with the addition of short course ADT to high-dose ($\geq$ 81 Gy) conventionally fractionated radiotherapy among patients with intermediate risk disease (3). Between 1992 and 2007, 1024 patients with NCCN intermediate risk prostate cancer were treated at Memorial Sloan Kettering Cancer Center and its regional facilities with definitive external beam radiation with doses of ≥ 81 Gy. Unfavorable intermediate risk factors were defined as primary Gleason score (GS) of 4, percentage of positive biopsy cores (PPBC) ≥ 50%, and more than one intermediate risk factors (IRF). Unfavorable intermediate risk patients had at least one of these factors, whereas favorable intermediate risk patients had none, with a median follow-up was 6 years. 51% of patients received short-course androgen deprivation therapy (ADT). In that study we noted that ADT was associated with an improvement in all outcomes in our multivariate models. Patients with unfavorable intermediate risk disease had inferior rates of PSA-RFS (HR = 2.37, 95% CI: 1.68-3.36, P <0.0001), DM (HR=4.34, 95% CI: 1.95-9.67, P=0.0003), and PCSM (HR=7.39, 95% CI: 1.75-31.31, P = 0.007) compared to those with favorable intermediate risk disease. Patients with multiple unfavorable risk factors had particularly poor prognosis, with 8 year rates of PSA-RFS, DM, and PCSM of 60%, 23%, and 12%, respectively. Benefits of using ADT were most noted among patients with intermediate risk features with unfavorable characteristics. In a prior publication we also noted improved post-treatment biopsy outcomes among patients who were treated with external beam radiotherapy (EBRT) with the addition of a short-course of ADT compared to external radiotherapy alone short course NAAD had a significant impact on the posttreatment biopsy outcome. Of patients who did not receive ADT 86 of 206 (42%) had a positive biopsy compared to 21 of 133 (16%) who received ADT (p <0.0001). Zelefsky MJ, Reuter VE, Fuks

Z, et al Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer J Urol. 2008 Apr;179(4):1368-73. In a recent update among intermediate risk patients who underwent post-treatment biopsies the incidence of a positive biopsy among those who received short course ADT with EBRT was 15% compared to 35% among those treated with EBRT alone (p< 0.001)[unpublished data]

3.2 Clinical Outcomes with SBRT for Prostate Cancer

Stereotactic hypofractionated radiotherapy is commonly utilized as a form of definitive therapy for patients with favorable and intermediate risk prostate cancer. There have been multiple retrospective studies indicating excellent PSA relapse-free survival outcomes at 5 years and low rates (<2%) of grade 3 or higher urinary or rectal toxicities (4-9). In 2009 we initiated a Phase I-II dose escalation study where favorable and intermediate risk prostate cancer patients were treated with SBRT to the prostate. The initial dose level was 32.5 Gy in 5 fractions. After 30 patients were accrued the next dose level was initiated at 35 Gy in 5 fractions for the subsequent 30 patients. Escalation of dose continued in this fashion to 37.5 Gy in 5 fractions and finally 40 Gy in 5 fractions. Accrual to the study completed 6 months ago and to date no grade 4 toxicities have been observed at any of the dose levels and the incidence of grade 3 rectal or urinary toxicities has been < 2%. The current prescription dose used at MSKCC for SBRT is 40 Gy in 5 fractions and the excellent tolerance associated with treatment can be attributed to several factors including: the use of tight margins of 5 mm around the circumference of the clinical target volume and 3 mm at its posterior aspect, and the use of image guidance with inter-fraction and intra-fraction motion correction for enhanced accuracy. Because of the short duration of therapy compared to conventionally fractionated IMRT which spans for 10 weeks, SBRT to 40 Gy in 5 fractions has become the most common mode of external beam radiotherapy at Memorial Sloan Kettering Cancer Center. While the median follow up in this experience is 24 months, the PSA relapse rates have been <15% at 3 years. Currently RTOG 0938 is in the midst of a randomized Phase II trial which compares 36.25 Gy in 5 fractions using 7.25 Gy compared to 51.6 Gy in 12 fractions of 4.3 Gy. In the study the eligibility criteria include favorable risk patients and the primary endpoint in that study is 12 month health related quality of life outcomes for treated patients.

3.3 Study Rationale

To date there have been no studies exploring the impact of short course ADT for intermediate risk patients who are treated with SBRT. On the one hand the use of high dose SBRT with its greater radiobiological dose delivery may obviate the need for short course ADT and potentially reduce the deleterious impact this therapy would have on the quality of life of the individual patient. On the other hand, the addition of short course ADT even in the setting of high dose SBRT may further improve survival outcomes especially among the cohort of intermediate risk patients with more unfavorable disease characteristics as has been demonstrated in published Phase III trials when conventionally fractionated radiotherapy was used (1, 2). With the increasing number of patients being treated with SBRT at our institution and in the United States, this issue is of significant clinical importance. This study will evaluate the tumor control outcomes in each group and as the primary objective of this study we will evaluate local tumor control with a 2- year post treatment biopsy considered to represent an excellent surrogate endpoint for local disease control and more reflective of this endpoint than PSA-relapse-free survival. This biopsy endpoint has been successfully used in our Phase I dose escalation study (IRB- 09-035) evaluating local control in SBRT treatment patients. However, in addition to 2 year biopsy outcomes, biochemical control and distant metastases-free survival will also be evaluated.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

For this proposed Phase III study, intermediate risk patients will be randomized to received 6 months of ADT which would be given 3 months prior to planned SBRT to the prostate and 3 months during/following SBRT. ADT will be administered via Degarelix monthly injections. SBRT will be delivered with a prescription dose of 8 Gy x 5 prescribed to the planning target volume. Inter-fraction motion targeting and target position correction will be utilized as is routine in our department during the treatment SBRT.

The primary end-point of this study is the proportion of patients who have positive 2-year post-treatment prostate biopsies. Based on our previous published experience, we expect that the 2-year rate of a positive biopsy using ADT with ultra-hypofractionated SBRT for intermediate risk features would be 15% compared to 35% for those patients treated with SBRT alone. We anticipate we would require powering the study with 100 patients in each arm. Randomization will be stratified by favorable-intermediate and unfavorable-intermediate risk status (unfavorable-intermediate risk will be defined as patients having Gleason 4+3, >50% positive biopsy cores or 2 intermediate risk factors combined such as Gleason 7 and PSA> 10 ng/ml).

The primary endpoint is the 2-year biopsy which is generally scheduled at the end of the second year. However, we have provided some flexibility as to prevent prospective and retrospective deviations. Therefore, we have chosen to allow the primary endpoint biopsy to occur between 24-30 months which we believe is reasonable based on our clinical experience.

4.2 Intervention

Eligible patients with intermediate risk disease will be randomized to ADT with SBRT versus SBRT alone. The ADT patients will be treated with monthly degarelix injections. After three months (+/- 1 month) have elapsed, these patients as per routine would undergo fiducial marker placement followed by simulation and SBRT to follow. For this cohort ADT will continue until 6 months of Degarelix is administered. If a patient develops an allergic reaction to the Degarelix injection, he may be switched to Leuprolide acetate monthly injections in its place.

For patients treated with SBRT alone referral will be made for fiducial marker placement with simulation and SBRT to follow. Patients will then be followed at 6 month intervals with routine serum PSA and testosterone testing. All patients will undergo a post-SBRT standard 12 core prostate biopsy at 24-30 months after completion of SBRT to evaluate local tumor control status.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Degarelix Drug Product

This is a commercially available, injectable, long acting analog of the native LHRH peptide. It is administered via subcutaneous injection to the abdominal region only. The manufacturer's instructions should be followed. Degarelix wil be provided by Ferring Pharmaceuticals as Firmagon.

Radiation Therapy

Stereotactic, ultra-fractionated radiotherapy will be administered every other day for five total treatments using an intensity modulated treatment plan directing its dose of 8.0 Gy to the prostate and seminal vesicles. At least 3 days prior to CT simulation, 3 fiducial markers will be placed transrectally or transperineally within the prostate gland to be used for target localization on a daily basis for image-guided therapy. Treatment planning dose constraints will be optimized per criteria outlined in Section 9.0

Health-related Quality of Life Metrics

The Expanded Prostate Cancer Index Composite (EPIC) was developed at the University of Michigan and the University of California-Los Angeles. It was designed to assay health related quality of life among men with prostate cancer. EPIC has been validated in men with localized prostate cancer who underwent surgery, external beam radiation, or brachytherapy with or without adjuvant hormones. EPIC is both sensitive and specific to HR-QOL effects of these therapies and to HR-QOL effects of cancer progression. EPIC-26 was developed as a short-form version of the full EPIC and contains 26 items and the same 5 domains as the complete EPIC version (Urinary Incontinence, Urinary Irritative/Obstructive, Bowel, Sexual, and Hormonal). Information regarding the statistical validation of EPIC can be found at: https://medicine.umich.edu/sites/default/files/content/downloads/Development%20and%20Validation%20of....pdf

The Medical Outcomes Study SF-12 is a validated measure of General Health Function developed by RAND. It is intended to be used to derive 2 summary scores (physical and mental component summaries) relevant to general HR-QOL status. It provides a context for EPIC score results. The SF-12 items themselves are not included in the calculation of any EPIC domain scores.

The International Prostate Symptom Score (IPSS) index is a validated and widely used instrument that is currently administered as part of routine patient evaluation in our clinics. The IPSS index yields a single index score and represents is a seven item questionnaire designed to assess urinary functioning, specifically urinary frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency. Questions are rated on a six point Likert scale with higher scores indicating more difficulty in urinary functioning. This measure demonstrated a high internal consistency (Cronbach's alpha = 0.84) with excellent test-retest reliability (r = 0.92). The IPSS index also demonstrated good validity with strong associations with other measures of urinary difficulties. The IPSS index also showed appropriate sensitivity to change. This measure has been widely used in clinical practice and research protocols. We will be using the information obtained as a part of the standard of care visit for this research study.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Biopsy proven intermediate risk prostate cancer, which includes patients with any one of the following variables:
    - Gleason 7 disease
    - PSA 10-20 ng/ml
    - Clinical T2b-T2c disease

Note: Patients who only have radiographic evidence of T3 disease (i.e. extracapsular extension, or seminal vesical invasion radiographically) will not be excluded.

- Serum testosterone ≥ 240 ng/dL determined within 2 months prior to enrollment
- At least 4 weeks must have elapsed from major surgery
- KPS ≥ 80%
- Prostate size as determined on MRI to be < 90 cc. Prostate size can be determined on CT scan if MRI is not available.
- 18 years of age or older
- IPSS ≤ 20
- Patient must be available for follow-up. After 2 years of follow-up following post-treatment biopsy, telephone-based follow-up will be acceptable
- Laboratory test findings within 8 weeks of randomization:
  - Adequate hepatic function with serum bilirubin ≤ 1.5 times the upper institutional limits of normal (ULN), ALT and AST ≤ 2.5 x ULN. Patients with a history of Gilbert's syndrome may be enrolled if the total bilirubin is < 3 mg/dL with a predominance of indirect bilirubin
  - Adequate renal function with serum creatinine ≤ 1.5 x ULN
  - Adequate hematologic function with absolute neutrophil counts ≥ 1,500 cell/mm^3 and platelets ≥ 100,000 cells/mm^3 and hemoglobin value ≥ 9 g/dL (Note: patients whose anemia has been corrected to a hemoglobin value ≥ 9 g/dL with blood transfusions are allowed)

6.2 Subject Exclusion Criteria

- CT or MRI evidence of metastatic disease to the bone.
- Patients with one or more positive lymph nodes considered suspicious as determined by clinical assessment on MRI or CT
- Prior treatment for prostate cancer, including history of chemotherapy, hormonal therapy within 30 days of enrollment or surgery for prostate cancer (except for prior TURP or greenlight PVP which would be allowed)
- History of another malignancy within the previous 3 years except for the following: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, currently in complete remission, or any other cancer that has been in complete remission for at least 3 years
- Patients with Crohn's disease or ulcerative colitis

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or the research team at Memorial Sloan-Kettering Cancer Center (MSK). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

In regards to accrual numbers, MSK plans to enroll 50 patients per year at Main Campus, and 50 patients per year between all regional sites.

This limited waiver will apply only to MSKCC.

8.0 PRETREATMENT EVALUATION

The following must be completed prior to randomization:

- MSKCC pathology review confirming cancer
- The following screening tests and assessments should be performed within 8 weeks prior to randomization to confirm eligibility:
    - Full medical history and physical exam, including DRE and performance status
    - MRI of the prostate and pelvis within 6 months of randomization. (CT of the pelvis with contrast may be performed if MRI is contraindicated)
    - Radionuclide bone scan if there is suspicion of bone metastases within 6 months of randomization.
    - Lab tests:
        - PSA
        - Baseline CBC, CMP (Na, K, Cl, CO2, Ca, T. Protein, Albumen, Creatinine, Glucose, BUN, Alk Phos, ALT, AST, T. Bili), Conj. Bili,

        - Testosterone level
    - Questionnaires:
        - IPSS documenting score < 20
        - EPIC
        - SF-12

Once eligibility is confirmed, the patient should undergo randomization.

9.0 TREATMENT/INTERVENTION PLAN

Androgen Deprivation Therapy Arm: Within two weeks prior to the first injection, patients will obtain routine blood tests including CBC and liver function tests and testosterone levels. Degarelix injections will be administered in the radiation oncology clinics monthly. The first injection is administered as a boost, 240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/mL which is then followed by 80 mg given as one subcutaneous injection at a concentration of 20 mg/mL every 28 days (+/- 7days). In 10% of patients a skin rash could develop at the injection site. If this is noted and symptomatic for the patient the injection could be switched to monthly Lupron intramuscular injections (7.5.mg).

Study treatment: Stereotactic, Ultra-Fractionated Radiotherapy (same for each arm)

Intensity-modulated, image-guided, ultra-hypofractionated external beam radiotherapy will incorporate prostate and seminal vesicles and this planning target volume will receive 8 Gy x 5 fractions. As per routine for intermediate risk patients, the lymph nodes will not be included within the treatment portal.

9.1 Prior to Simulation

Fiducial markers as per routine will be placed into the prostate to be used for image guidance and this will be performed a minimum of 3 days prior to simulation.

9.2 Simulation

- Patients will perform a bowel preparation the night before simulation.
- Patients will be supine and positioned in a thermoplastic mold with Aquaplast immobilizations routinely done.
- Oral contrast may be administered for simulation.
- A Foley catheter will be placed for simulation only.
- A rectal catheter will be placed for simulation only.
- CT images will be obtained as per existing department protocols and sent to the treatment planning system
- If MR images will be obtained as per existing department protocols they will be sent to the treatment planning system as well.

Participating sites may follow institutional simulation guidelines as long as the simulation guidelines have been reviewed and approved by the PI.

9.3 Treatment Planning

- CTV will include the prostate, seminal vesicles, and any areas at risk of extra-capsular extension.

- PTV will include a 5 mm expansions on CTV in all directions save for posterior; the posterior expansion will be 3 mm.
- The following normal tissue should be contoured:, bladder, , rectum(The rectum should be contoured from the anus to the rectosigmoid flexure), urethra, penile bulb,bilateral femoral heads and necks, large bowel, small bowel, external body contour. For PTV, the D95% should be >= 90% of the prescribed dose of 8 Gy per fraction.

Constraints to Normal Tissue

Rectum:
1) Maximum dose <=41.2Gy
2) Dose to 1cc < =38.5 Gy (D1cc<= 38.5 Gy)
3) V24Gy <= 25%
4) Mean dose <= 16.4Gy
5) V30.15Gy <= 8CC

Urethra:
1) Maximum dose <= 42 Gy
2) Dose to 1cc <=40 Gy (D1cc<=40 Gy)

Bladder:
1) Maximum dose <= 42Gy
2) V36Gy <= 10%
3) V20Gy <= 50%

Large Bowel:
1) Maximum dose <= 29 Gy

Small Bowel:
1) Maximum dose <=25 Gy

Femoral Heads:
1) Maximum dose <= 31 Gy
2) V21.6Gy <= 10 CC

Penile Bulb
1) Maximum dose <= 40Gy
2) D 3CC <= 21.6Gy

- Beam arrangements, optimization structures and optimization parameters will be defined at the discretion of the treatment planner using routine departmental procedures.
- The treatment plan will be approved and reviewed by the attending physician.
- The treatment plan will go through quality assurance procedures per departmental guidelines.
- Treatment should be initiated approximately 14 days after simulation (+/-7 days).

9.4 SBRT Delivery

- Patients will be treated every other day.
- Metamucil 1 teaspoon in 8 ounces of water should be taken prior to simulation and continued on a daily basis and continue until completion of radiation treatment. In addition a fleets enema 1-3 hours before simulation and each treatment will also be advised for the patient to take.

- Patients will be encouraged to evacuate their bowels approximately 1 hour prior to treatment.
- Patients will be immobilized as in simulation and aligned using lasers and skin tattoos/marks in treatment room.
- Any necessary translational shifts in patient position will be made once based on position of fiducial markers have been spatially reconciled with the simulation reference data set.
- Any deviation of ≥ 2mm from the planned position will require treatment interruption and positional correction.
- Participating sites may follow institutional guidelines for treatment targeting, as long as treatment targeting methods have been reviewed and approved by the PI.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Evaluation during Treatment

- Patient completion of study specific PRO assessments
  - EPIC-26
  - SF-12
  - IPSS

10.2 Evaluation during Follow-Up

- Physical exam
- Performance status
- Clinical evaluation for late urinary, rectal toxicity and sexual dysfunction per standard CTCAE assessments and grading.
- PSA
- Serum Testosterone
- EPIC – 26
- SF-12
- IPSS
- Prostate biopsy, 24-30 months post SBRT

Table 1. Schedule of assessments

	Pre-Treatment		During Radiation Therapy	Follow up
	Within 8 weeks prior to study randomization	Within 2 week prior to the initiation of Degarelix[1]		Every 6 months for 2 years
Informed consent	X			
Medical history	X			
Physical exam	X			X
Digital rectal exam	X			
Performance status	X			X
Histologic or pathologic confirmation of disease	X[2]			
MRI prostate/pelvis within 6 months of randomization	X[3]			
Bone scan within 6 months of randomization if determined necessary	X			
EPIC-26	X		X[4]	X
SF-12	X		X[4]	X
IPSS	X		X[4]	X
PSA	X	X		X
CBC	X	X		
Comp	X	X		
Liver function tests	X	X		
Serum testosterone	X	X		X
Toxicity assessment				X
Degarelix			X[5]	
Fiducial marker placement			X[6]	
Radiation therapy			X[7]	
Biopsy				X[8]

1. For patients randomized to the ADT + SBRT arm
2. Histologic or pathologic confirmation of disease can be done anytime prior to randomization.
3. CT of the pelvis with contrast may be performed if MRI is contraindicated.
4. To be completed during treatment, at the 3rd of 5th fraction of later
5. Degarelix will be given monthly (+/- 7 days), 3 months before and 3 months after radiation therapy.
6. Fiducial markers will be placed 3 days before simulation.
7. Radiation therapy will be given every other day.
8. Prostate post-treatment biopsy will be performed once at 24-30 months post SBRT.

11.0 TOXICITIES/SIDE EFFECTS

In each arm standard SBRT will be used delivering 40 Gy in 5 fractions to the prostate and seminal vesicles and patients will be randomized to receive 6 months of ADT using Degarelix monthly injections or SBRT alone without ADT. ADT administration is routine and its side effect profile well recognized and established. Side effects of ADT (Degarelix) include hot flashes, fatigue, weight gain, loss of libido, muscle tone decrease and gynecomastia. These side effects generally reverse 6-12 months after cessation of ADT. Any urinary or rectal toxicity that is grade 3 or higher will be considered an adverse event.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the primary endpoint of this study, post-SBRT prostate biopsies will be performed to assess local tumor control for each of the treatment arms. While post-SBRT biopsies performed outside of MSKCC are permitted for the study, the central pathology review will be performed by the MSKCC pathology department. For the central pathology review, please send the study patients' post-SBRT prostate biopsy slides the address listed in the laboratory manual in appendix IV.

As has been well established criteria for the assessment of post-radiation biopsies (10), post-treatment biopsies will be categorized as negative if there is no evidence of adenocarcinoma, positive if there is evidence of adenocarcinoma (which could be assigned a Gleason score), or treatment effect ,where adenocarcinoma is noted displaying severe treatment effect precluding the assignment of a Gleason score. In our experience this latter classification is associated with a clinical behavior more consistent with a negative biopsy.

Biochemical recurrence will be determined according to the established Phoenix criteria of 2 ng/nl elevation of the PSA nadir level (nadir + 2 definition). Distant metastases will be defined as patients with imaging evidence or biopsy-proven metastatic disease in distant sites outside of the prostate most commonly in bone. Therefore the cumulative incidence of biochemical failure and distant failure will be computed by setting the starting time as the beginning date of the treatment until the event of interest, with death without the event of interest as the competing risk. Overall survival is defined from the beginning date of the treatment until death.

13.0 CRITERIA FOR REMOVAL FROM STUDY

- Patient decides to withdraw from the study.
- Intercurrent illness that prevents treatment and/or follow-up imaging.
- Unacceptable adverse event that may be directly related to the protocol intervention.
- General or specific changes in the patient's condition that renders the patient unacceptable for further treatment, in the judgment of the investigator.
- Initiation of non-study therapy for prostate cancer.
- Does not meet inclusion/exclusion criteria.

14.0 BIOSTATISTICS

The primary objective of this phase III trial is to compare 2-year biopsy positivity rate of intermediate risk prostate cancer patients treated with SBRT + short course ADT versus SBRT alone. The 2-year biopsy positivity rate will be calculated in each arm as a proportion of patients whose 2-year (from the end of SBRT) biopsy result is positive over patients who have 2-year biopsy results examined or whose 2-year biopsy results are regarded as positive (see the replacement rule below). We plan to analyze an evaluable sample of 200 patients, randomized in a 1:1 ratio to the two arms. This sample size has a power greater than 0.90 and type 1 error rate of 0.05 if the true 2-year biopsy positivity rates are 35% and 15% respectively, for the two arms using a two-sided, two-sample proportion test. This test will also be adjusted for the randomization stratification variables. Patients who died due to disease within 2 years from the end of SBRT will be regarded as having a positive biopsy. Patients who died not due to disease or are lost to follow-up within 2 years from the end of SBRT without any sign of progression will be replaced. To this end we will enroll an additional 10% patients upfront so the totally sample size is 223. However, only the first 200evaluable patients will be counted towards the primary endpoint. One interim analyses and one final analysis are planned (using equal spacing of looks) and the null hypothesis that the two arms have the same 2-year biopsy positivity rates will be rejected at these two looks if the p-values are <0.003 and <0.049, respectively, based on the Lan-DeMets alpha spending function approach. We expect that 100 patients will be enrolled each year, 50 from MSK and 50 between all regional sites. Therefore we anticipate to complete the enrollment in 2-3 years, plus an additional 2-year mandatory follow-up.

For the secondary objectives, the cumulative incidence rates of biochemical failure and distant failure will be evaluated by the competing risks method and Gray's test will be used to compare the two arms. Overall survival rates will be estimated by Kaplan-Meier method and compared by log-rank tests. QOL outcomes will be summarized and tabulated. Results from the two arms will be compared by Wilcoxon rank sum tests at time points when these surveys are conducted. All patients will be analyzed for the secondary objectives.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Patients will be randomized to receive ADT+SBRT, or SBRT alone. Immediately after consent is obtained, the RSA at MSKCC will register participants in the Clinical Trials Managmenet System (CTMS). Once the participant's eligibility is established the registration will be finalized and the participants will be randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, and will be stratified by favorable vs unfavorable intermediate risk. After the treatment

arm is determined by randomization, the RSA will notify physicians at MSKCC of the treatment arm and participant ID via email within 24 hours of randomization.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into Medidata RAVE. Source documentation will be available to support the computerized patient record. All research material from this study will be handled with the same confidentiality as patient's other medical data. Data collected will include participant demographics, PRO outcomes data, PSA and testosterone values, and biopsy results.

16.1 Quality Assurance

Eligibility of patients will be verified with the corresponding investigator. Only the designated investigators can obtain informed consent.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. Institutional processes are in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, and two institutional committees are responsible for monitoring the activities of our clinical trials programs. The committees, *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board (see section 16.2).

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at MSK were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials," which can be found at:
http://cancertrials.nci.nih.gov/researchers/dsm/index.html.

The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf.

17.0 PROTECTION OF HUMAN SUBJECTS

Patient Confidentiality: Patient/subject privacy and confidentiality will be maintained according to MSK guidelines and all data derived from this study will be kept in a secure database. All data and results will be anonymously reported with regard to individual subjects.

Voluntary nature of the study: Subjects will be made aware of the voluntary nature of the study as part of the informed consent process. They will be allowed to withdraw participation at any time without the risk of alteration in the quality of their medical care.

The subjects will be responsible for all charges associated with the items that are part of the routine clinical care, including the post treatment 12 core biopsy and the follow up PSA measurements. Subjects will not be compensated for their participation. If the patient is injured as a result of being in this study, emergency care, hospitalization, and outpatient care will be made available by the hospital and billed to the patient and his insurance company as standard of care.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report is submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to

withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Appendix I: EPIC-26

Appendix II: SF-12

Appendix III: IPSS

Appendix IV: Laboratory Manual