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First Report of NRG Oncology/Radiation Therapy Oncology Group 0622: A Phase 2 Trial of Samarium-153 Followed by Salvage Prostatic Fossa Irradiation in High-Risk Clinically Nonmetastatic Prostate Cancer After Radical Prostatectomy.

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First Report of NRG Oncology RTOG 0622: A Phase II Trial of Samarium-153 Followed by Salvage Prostatic Fossa Irradiation in High-Risk, Clinically Non-Metastatic Prostate Cancer after Radical Prostatectomy

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Abstract

Purpose: There is limited information regarding the utility of Samarium-153 lexidronam (Quadramet) in the setting of men with prostate cancer status post radical prostatectomy (RP), who develop biochemical failure with no clinical evidence of osseous metastases.

Methods and Materials: Trial NRG Oncology RTOG 0622 is a single-arm Phase II trial that enrolled men with pT2-T4, N0–1, M0 prostate cancer status post RP, who meet at least one of these biochemical failure criteria: (1) PSA >1.0ng/ml; (2) PSA >0.2ng/ml if Gleason score of 9–10; or (3) PSA >0.2ng/ml if N1. Patients received Samarium-153 (2.0mCi/kg IV x 1) followed by salvage external beam radiation therapy (EBRT) to the prostatic fossa (64.8–70.2Gy in 1.8Gy

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daily fractions). No ADT was allowed. The primary objective was PSA response within 12 weeks of receiving Samarium-153. The secondary objectives were to (1) assess the completion rate for the regimen of Samarium-153 and EBRT, (2) evaluate the hematological toxicity and other adverse events (AE) at 12 and 24 weeks, and (3) freedom from progression (FFP) rate at 2 years.

Results: A total of 60 enrolled eligible patients were included in this analysis. Median follow up was 3.97 years. PSA response was achieved in 7/52 (13.5%) evaluable patients compared to the 25% hypothesized. The 2-year FFP was 25.5% (95% CI: 14.4–36.7%), and biochemical failure rate was 64.4% (95% CI: 50.5–75.2%). Samarium-153 was well tolerated, with 16/60 Grade 3–4 hematologic AEs and no Grade 5 hematologic AEs. RT was also well tolerated, with no Grade 3–5 acute RT-related AEs, and 1 Grade 3–4 and no Grade 5 late RT-related AEs.

Conclusion: Trial NRG Oncology RTOG 0622 did not meet its primary endpoint of PSA response, although the regimen of Samarium-153 and salvage EBRT was well tolerated. Although the toxicity profile supports study of Samarium-153 in high-risk disease, it may not be beneficial in men receiving EBRT.

Summary

Trial NRG Oncology RTOG 0622 is a single-arm Phase II trial of men with high-risk prostate cancer after radical prostatectomy, enrolled at PSA failure but without clinical evidence of osseous metastases, who received Samarium-153 followed by salvage prostatic fossa radiation. Although this trial did not meet its primary endpoint of PSA response, it demonstrated the safety and tolerability of this regimen. The latter finding may support further use of Samarium-153 in high-risk, non-metastatic cases after radical prostatectomy.

Keywords

Prostate cancer; radical prostatectomy; Samarium-153; salvage radiation; PSA failure

Introduction

Men with prostate cancer who undergo radical prostatectomy (RP) continue to represent a challenging cohort for oncologic management, as one-third will eventually develop biochemical failure.[1] A significant proportion of biochemical recurrences lead to clinically-evident distant metastases at a median of 8 years after PSA failure, followed by death from prostate cancer at a median of 5 years after the onset of distant metastases.[2] Thus, there has been significant interest in expanding the repertoire of treatment options for high-risk but not yet metastatic men after RP, with the rationale that aggressive treatment of this cohort may reduce the proportion of men who will eventually develop metastases and die of prostate cancer.

When metastatic disease does develop in prostate cancer, it is known that the vast majority involve bony metastases, and many men who die of metastatic prostate cancer have bone-only metastases. The extent of disease based on bone scans has been shown to correlate with clinical outcomes.[3,4] Thus, aggressive control of bony metastases represents an important goal for metastatic prostate cancer.

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Over the years, multiple radionuclide conjugates have been tested and shown to be efficacious in the palliation of bone metastases.[5] These include the beta emitters strontium-89 chloride[6] and samarium-153 lexidronam,[7] and more recently the alpha emitter radium-223 dichloride.[8] Samarium-153 (Sm-153) is a beta emitter with an average beta particle energy of 233keV and a physical half-life of 46.3 hours. This radionuclide is chelated to lexidronam, also known as ethylene diamine tetramethylene phosphonate (EDTMP), and is marketed as Quadramet. Sm-153 has been shown to have an affinity for bone, specifically in regions of bone turnover in association with hydroxyapatite. In the setting of metastatic disease, Sm-153 has been shown to preferentially accumulate in blastic lesions compared to normal bone by a 5-fold ratio.

Trial NRG Oncology RTOG 0622 was designed to test the hypothesis that administration of Quadramet in the post-RP setting with documented PSA failure, but clinically and radiographically without evidence of non-nodal metastatic involvement, may help to target occult micrometastatic osseous disease, thus conferring an advantage in prostate cancer control compared with standard-of-care salvage radiation therapy alone. Here, we report the key findings in the first published report of this trial.

Patients and Methods

Trial Overview and Key Enrollment Criteria

Trial NRG Oncology RTOG 0622 is a single-arm phase II clinical trial that enrolled men with histologically-confirmed prostate cancer who underwent RP with pT2-T4, N0–1, M0 disease and had an elevated post-RP PSA, to receive Sm-153 (Quadramet; Cytogen Corporation) followed by salvage external beam radiation therapy (EBRT) to the prostatic fossa. Postoperative PSA obtained within 4 weeks of study registration was required to meet at least one of the following criteria: (1) PSA >1.0ng/mL (2) PSA >0.2ng/ml if Gleason score of 9–10; or (3) PSA >0.2ng/ml if N1. All patients were required to have a whole body bone scan that was negative for osseous metastases within 4 months of study registration, as well as abdominal imaging negative for metastases within 6 months of registration. Patients with prior pelvic radiotherapy for any indication and/or prior chemotherapy for prostate cancer were excluded. In addition, patients who received androgen-deprivation therapy (ADT) within the preceding 3 months were excluded.

Signed informed consents were obtained from all patients at the time of study enrollment. The use of drugs in this protocol met the criteria for IND exemption under Title 21 CFR 312.2(b). This trial was approved by institutional review boards at the respective study sites.

Protocol Treatment

Within two weeks of registration, patients received Sm-153 as a single intravenous infusion at a dose of 2.0mCi/kg. This dose was calculated to deliver an effective bone surface radiation dose of 50.0Gy, which was the maximum tolerated dose (MTD) on a prior phase I trial.[9]

Twelve weeks following Samarium-153 administration, all patients then proceeded to receive salvage EBRT to the prostatic fossa. For the EBRT component, all patients were

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required to undergo CT simulation and were treated with either three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) technique. Clinical target volume (CTV) was defined to include the prostatic fossa, extending from the seminal vesicle stump to the urethral-vesicular junction and limited laterally by the body of the ischium and pelvic musculature. Pelvic nodal irradiation was not offered on this trial. The CTV was expanded by 4–10mm to define the planning target volume (PTV). EBRT dose was prescribed to 64.8–70.2Gy (36–39 daily fractions of 1.8Gy, delivered 5 days per week over 7–8 weeks). ADT was not allowed on this trial.

Patients who did not respond to therapy were initiated on salvage ADT, consisting of gonadotropin-releasing hormone (GnRH) receptor agonist (Zoladex (goserelin) or Lupron (leuprolide)) with or without an antiandrogen (Casodex (bicalutamide) or Eulexin (flutamide)).

Statistical Analysis

The primary objective of this study was to assess the PSA response following Sm-153 administration, where the PSA response was defined as a 30% decline within 12 weeks compared to baseline. It was expected that ≤10% of patients not treated with Sm-153 would have a PSA response and therefore hypothesized that Sm-153 would improve the proportion of patients with a PSA response to ≥25%. Using Fleming's Multiple Testing procedure[10] with a significance level of 0.019, 69 patients are required for 91% statistical power.

The secondary objectives were to (1) assess the completion rate for the regimen of Sm-153 and EBRT, (2) evaluate the hematological toxicity and other adverse events (AE) at 12 and 24 weeks, and (3) freedom from progression (FFP) rate at 2 years. The completion of protocol treatment, defined as receiving at least 64.8 Gy radiation after the Sm-153 injection will be tested using an exact test for a binomial proportion against a rate of ≤50%. The null hypothesis is that the proportion of patients who complete protocol treatment is ≤50% and the alternative is that it is 80%.

All patients were evaluated for toxicity and PSA response at 12 and 24 weeks from the injection of Sm-153. AEs were evaluated by the NCI Common Terminology Criteria for Adverse Event (CTCAE) version 3.0. The treatment-related attribution included definitely, probably, or possibly related to treatment. The Sm-153-related AEs were defined as (1) Hematologic AEs: Platelet grade 3–5, WBC grade 3–5, hemoglobin grade 3–5, and/or any secondary leukemia; (2) Hemorrhage/bleeding AEs: GI bleeding (anus, rectum) grade 3–5, and/or GU bleeding (bladder, prostate, urethra) grade 3–5; and (3) Sm-153-related grade 5 AE prior to radiation treatment (RT). Sm-153-related AEs were defined as those occurring within 12 weeks of the injection and prior to the start of RT. Acute RT-related AEs were defined as those occurring <90 days from the end of RT, and late RT-related AEs were defined as those occurring ≥90 days from the end of RT. Multivariate logistic regression was used to model the distribution of treatment-related AEs. Clinical T-stage, baseline PSA, Gleason score, and age were identified as predictor variables for statistical analyses. Both unadjusted and adjusted odds ratios and the respective 95% confidence intervals were computed.

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Progression was defined as biochemical (PSA) failure at any time for 2 years after prostatic fossa RT, initiation of systemic therapy, or clinical failure. PSA failure was defined as a rise of ≥0.2ng/ml above the nadir PSA after completion of salvage RT followed by another higher value or a continued rise in the serum PSA despite RT. Local failure was defined as the development of a new palpable abnormality in the prostate bed after enrollment in the protocol. Regional failure was defined as radiographic evidence (CT or MRI) of lymphadenopathy (lymph node size ≥ 1.5 cm) in a patient without the diagnosis of a hematologic/lymphomatous disorder associated with adenopathy. Distant metastasis was defined as evidence of hematogenous spread documented by imaging (e.g., bone scan, CT, MRI). Freedom from progression (FFP) was measured from the date of registration to date of progression, including death from any cause, or last known follow-up date. FFP was estimated using the Kaplan-Meier method.[11] Time to progression was measured from the date of registration to date of progression or last known follow-up. Patients who died without progression were treated as a competing risk. Time to local, regional, and distant failure was measured from the date of registration to the date of failure or last known follow-up. Patients who died without a failure were treated as a competing risk. The cumulative incidence approach was used to estimate the median time to progression, time to local failure, time to regional failure, and time to distant failure to account for the competing risk of death.[12]

Results

Patient demographics and trial compliance

This study enrolled 67 patients, of whom 5 were ineligible. The reasons for ineligibility included absolute neutrophil count and platelets not within protocol criteria (n=1), bone scan not done within protocol criteria (n=3), and no abdominal imaging done prior to registration (n=1). Among the 62 eligible patients, 2 withdrew consent early in the study, and AE information was available for the remaining 60 patients. Patient demographics are shown in Table 1. The median age of enrolled patients was 65 (interquartile range 60–69). Most patients were white (83.9%) and were not Hispanic or Latino (88.7%). The majority of enrolled patients had Zubrod performance status of 0 (83.9%). Most cases had a T stage of pT3 (75.8%) and an N stage of pN0 (87.1%). Most patients had a post-operative PSA >1ng/ml (56.5%), and the majority had Gleason scores of 8–10 (56.5%). The median post-operative PSA was 1.99.

Most of the patients received treatment per protocol, or with an acceptable variation for tumor volume contouring score (90.0%), organ at risk contouring score (90%), and tumor volume dose volume analysis score (81.7%). Most patients (57/60; 95.0%) received Sm-153 and at least 64.8Gy of RT. This was significantly more than the hypothesized 50% ($p<0.0001$).

Tolerability and toxicity of regimen

Overall toxicity information is presented in Table 2A and Supplemental Table 1. There was only one grade 5 AE (non-hematologic) that occurred 49 days from the Sm-153 injection, but was not considered to be related to treatment.

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Sm-153-related AEs are presented in Table 3. There were 16/60 patients (26.7%) that experienced grade 3–5 Sm-153-related AEs. Among hematologic AEs, 15 patients experienced at least one Grade 3 AE (8 Grade 3 leukopenia and 10 Grade 3 thrombocytopenia) and 1 patient experienced Grade 4 thrombocytopenia. No Grade 5 hematologic AEs were noted. In addition, there were no observed hemorrhage/bleeding AEs. None of the pre-specified variables (age, baseline PSA, clinical T-stage, or Gleason score) were significantly associated with occurrence of Sm-153-related AEs (Table 4A). There were 4 patients who experienced Grade 4 hematologic events with any relationship to protocol treatment. One patient experienced both Grade 4 neutropenia and Grade 4 thrombocytopenia.

There were 36 patients with acute RT-related AEs (Table 2B, Supplemental Table 2). Only one Grade 3 AE (non-hematologic) unlikely related to the treatment was noted during the acute RT period, and there were no Grade 4–5 AEs during this period. Based on logistic regression models, none of the predictor variables specified in the protocol (age, baseline PSA, clinical T-stage, or Gleason score) were significantly associated with acute RT-related toxicity (Table 4B). There were 35 patients who experienced AEs during the late RT period, although only one (2.9%) Grade 3 AEs and no Grade 4–5 late RT-related AEs noted (Table 2C, Supplemental Table 3).

PSA response

All PSA values within 12 weeks from the injection that were also prior to the start of RT were considered. Of the 60 evaluable patients, only 52 had PSA values in the appropriate time frame, with 5 having only having values after the start of RT, 3 had values only after 12 weeks from the injection. With the reduced sample size of 52 evaluable patients, this study had only 78% power. Using this reduced power and sample size, at least 11 patients with ≥30% decline would be required to reject the null hypothesis. Seven of 52 patients (13.5%) achieved ≥30% decline in PSA values from their respective pre-treatment baseline values. However, most patients experienced a PSA increase over time (mean increase of 0.177, standard deviation=0.479). Out of the 30 patients with a post-operative PSA > 1.0ng/mL, 4 (13.3%) achieved ≥30% decline in PSA. For the 22 patients with a post-operative PSA > 0.2ng/mL and nodal disease or a Gleason score of 9 or 10, 3 achieved ≥30% decline in PSA (13.6%). By logistic regression, none of the specified predictor variables of age, baseline PSA, clinical T-stage, or Gleason score were significantly associated with PSA response (Table 4C).

Biochemical and radiographic failure events

The median follow-up was 4.0 years for all patients (n=60), and 4.0 years for all living patients (n=50). There were 44 failure events, among which 38 were biochemical failures, 2 were local failures, 2 were regional failures, and 13 were distant failures (Table 5). The 2-year estimate for FFP was 25% (95% confidence interval [CI]: 14–37%). Time to progression showed a rate of 74.5% (95% CI: 60.9–83.9%) at 2 years. Biochemical failure showed a rate of 64.4% (95% CI: 50.5–75.2%) at 2 years.

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Discussion

Here we report the results of Trial NRG Oncology RTOG 0622 at a median follow up of 4.0 years. This trial was designed to test the hypothesis that administration of Sm-153 lexidronam in prostate cancer patients with documented PSA failure after RP, but without evidence of non-nodal metastatic involvement, may confer an advantage in prostate cancer control compared with standard-of-care salvage RT alone. As noted above, the study unfortunately did not meet its primary endpoint of PSA control. Among the 52 analyzable patients, only 7 (13.5%) achieved a PSA response after Sm-153. However, it should be noted that the regimen of Sm-153 and prostatic fossa RT was well tolerated: 15/60 patients experienced Grade 3 hematologic AEs, 1/60 patients experienced Grade 4 hematologic AE (thrombocytopenia), and no patients experienced Grade 5 hematologic AEs. The single Grade 5 AE (non-hematologic) occurring 49 days after Sm-153 injection was not considered to be treatment-related. RT was also well tolerated, with no Grade 3–5 acute RT-related AEs, and one Grade 3 no Grade 4–5 late RT-related AEs.

Given the limited PSA response on this trial, the current evidence does not support the use of Sm-153 with salvage RT in this particular high-risk post-RP cohort, prior to the development of radiographically-evident osseous metastases. The most likely explanation for the results is that Sm-153 is not effective in treating micrometastatic osseous lesions. It is possible that there was insufficient bone turnover at micrometastatic sites to allow sufficient localization of the radionuclide. Even if Sm-153 could localize appropriately to these sites, early prostate cancer metastases may somehow be relatively radioresistant, thus not allowing as much of a therapeutic benefit as would be expected given the relatively low disease burden. Future trials are likely to use Rm-223 rather than Sm-153 and in retrospect may have been the preferred agent for this trial. It should be noted that 13/60 patients did eventually develop distant failures in follow up (estimated 2-year distant failure rate of 22.0%, with 95% CI of 12.4–33.3%). Although we do not have detailed information regarding the sites of distant failure, it is almost certainly the case that most of these events were osseous metastases. Altogether, the data suggest that these patients do have a significant risk of distant failure, but the timing of treatment is critical as their risk of disease progression could not be mitigated by the current strategy. While effective in treating clinically evident osseous metastases, Sm-153 appears to be ineffective at earlier time points and unlike Ra-223 it has never been demonstrated to improve survival in men with advanced metastatic prostate cancer. It should be noted that this study was designed as a single-arm Phase II trial without ADT, with a relatively high pre-treatment PSA of >2ng/ml in the majority of men. In this regard, it is not clear which contemporary post-RP series would offer the most appropriate comparison of biochemical and clinical control outcomes.

In patients with PSA failure after RP, the benefits of salvage radiation to the prostatic fossa have already been well documented from prospective trials with long-term follow up, as well as multiple retrospective series. The three randomized trials of post-RP radiation in patients with one or more high-risk features (extracapsular extension, seminal vesicle involvement, and/or positive margins) have demonstrated significant improvements in clinical endpoints including biochemical control,[13–15] progression-free survival,[14,15] metastasis-free survival,[13] and overall survival.[13] In the setting of early biochemical failure as defined by a rising

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PSA, retrospective evidence has supported the benefit of salvage radiation in improving prostate cancer-specific survival.[16]

Of note, ADT was not included as part of the initial management of patients on Trial NRG Oncology RTOG 0622. However, there has been mounting evidence of the importance of ADT in the management of post-RP biochemical failure. NRG Oncology RTOG 9601 (NCT00002874) showed improved overall survival and freedom from subsequent biochemical failure with the inclusion of ADT to salvage EBRT in a similar high-risk post-RP cohort.[17] The recently published Groupe d'Etudes des Tumeurs Uro-Génitales (GETUG)-16 trial (NCT00423475) showed that inclusion of short-term Goserelin to salvage RT conferred an improvement in progression-free survival, although no significant overall survival benefit was found.[18] Regarding the subset of post-RP patients who are found to be node-positive (8/62 of the patients enrolled on Trial NRG Oncology RTOG 0622), randomized evidence from ECOG 3886 has convincingly demonstrated a significant OS benefit with the utilization of immediate ADT,[19] so it is likely that this cohort of patients would be offered ADT in the early post-RP period.

The timing of further intervention after RP is a topic of multiple ongoing trials, although there are multiple lines of retrospective evidence supporting improved clinical outcomes with earlier intervention.[20,21] Early vs. deferred salvage radiation is currently the subject of several ongoing trials, including Trans-Tasman Radiation Oncology Group (TROG) Radiotherapy – Adjuvant Versus Early Salvage (RAVES) 08.03 (NCT00860652), GETUG-17 (NCT00667069), and Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS; Medical Research Council PR10; NCT00541047). The results of these studies are eagerly awaited as they will help to guide future practice in the setting of high-risk prostate cancer patients after RP, including those who might have not yet experienced biochemical failure.

In summary, the results of Trial NRG Oncology RTOG 0622 demonstrate that Sm-153 does not confer a significant PSA benefit when given with salvage prostatic fossa radiation in the setting of high-risk post-RP patients with biochemical failure, but no clinically evident osseous metastases. While a negative finding, the relatively good toxicity profile of this agent does leave open the possibility of other approaches that may be able to take advantage of its utility in treating osseous metastases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Pretreatment Characteristics (n=62)

Age(years)	
Median	65
Min - Max	49 - 83
Q1 - Q3	60 - 69
Race	
Asian	3 (4.8%)
Black or African American	7 (11.3%)
White	52 (83.9%)
Ethnicity	
Hispanic or Latino	3 (4.8%)
Not Hispanic or Latino	55 (88.7%)
Unknown	4 (6.5%)
Zubrod Performance Status	
0	52 (83.9%)
1	10 (16.1%)
T Stage	
pT2	15 (24.2%)
pT3	47 (75.8%)
N Stage	
pN0	54 (87.1%)
pN1	8 (12.9%)
Post-Operative PSA	
Post-operative PSA > 1.0	35 (56.5%)
Post-operative PSA > 0.2 and with a surgical tumor Gleason of 9 or 10	25 (40.3%)
Post-operative PSA rising > 0.2 with nodal disease	2 (3.2%)
Gleason	
2–6	4 (6.5%)
7	23 (37.1%)
8–10	35 (56.5%)

Q1 = first quartile; Q3 = third quartile.

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Table 2.

Number of Patients with an Adverse Event by Category and Grade Definitely, Probably, or Possibly Related to Treatment (n=60)

	Grade				
Category	**1**	**2**	**3**	**4**	**5**
A. Overall Treatment Toxicity					
Blood/bone marrow	10	17	17	5	0
Coagulation	0	1	0	0	0
Constitutional symptoms	22	8	0	0	0
Dermatology/skin	4	1	0	0	0
Endocrine	8	1	0	0	0
Gastrointestinal	20	5	1	0	0
Hemorrhage/bleeding	4	0	0	0	0
Infection	0	1	0	0	0
Metabolic/laboratory	7	0	0	0	0
Musculoskeletal/soft tissue	1	1	0	0	0
Neurology	0	2	0	0	0
Pain	7	2	0	0	0
Renal/genitourinary	24	12	0	0	0
Sexual/reproductive function	2	6	0	0	0
B. Acute Radiotherapy Toxicity					
Blood/bone marrow	7	5	0	0	0
Constitutional symptoms	15	4	0	0	0
Dermatology/skin	3	1	0	0	0
Endocrine	1	1	0	0	0
Gastrointestinal	11	5	0	0	0
Hemorrhage/bleeding	1	0	0	0	0
Infection	0	1	0	0	0
Metabolic/laboratory	2	0	0	0	0
Musculoskeletal/soft tissue	1	0	0	0	0
Neurology	1	1	0	0	0
Pain	6	0	0	0	0
Renal/genitourinary	21	4	0	0	0
Sexual/reproductive function	1	1	0	0	0
C. Late Radiotherapy Toxicity					
Blood/bone marrow	3	1	0	1	0
Constitutional symptoms	8	1	0	0	0
Dermatology/skin	2	0	0	0	0
Endocrine	6	1	0	0	0
Gastrointestinal	9	2	0	0	0
Hemorrhage/bleeding	2	0	0	0	0

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	Grade				
Category	**1**	**2**	**3**	**4**	**5**
Musculoskeletal/soft tissue	0	1	0	0	0
Neurology	0	1	0	0	0
Pain	1	1	0	0	0
Renal/genitourinary	13	7	0	0	0
Sexual/reproductive function	1	4	0	0	0

Includes adverse events where relationship to protocol treatment is missing.

Adverse events were graded with CTCAE version 3.0.

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Table 3.

Number of Patients with an Adverse Event by Category, Term, and Grade Samarium 153 Toxicity at 12 weeks Definitely, Probably, or Possibly Related to Treatment (n=16)

Category Term	Grade				
	1	2	3	4	5
BLOOD/BONE MARROW	13	17	15	1	0
Hemoglobin decreased	25	0	0	0	0
Leukopenia	12	17	8	0	0
Platelet count decreased	19	15	10	1	0
HEMORRHAGE/BLEEDING	0	0	0	0	0
TREATMENT -RELATED GRADE 5 AE	N/A	N/A	N/A	N/A	0

Includes adverse events where relationship to protocol treatment is missing.

Adverse events were graded with CTCAE version 3.0.

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Table 4.

Logistic Regression Estimates

Variable	Estimate	Standard Error	p-value	Odds Ratio Estimate	95% Wald Confidence Limits	
A. Samarium-153 Related AEs at 12 weeks *[1]*						
Age	0.03	0.05	0.50	1.03	0.94	1.13
Baseline PSA	−0.16	0.14	0.26	0.85	0.64	1.13
Clinical T-stage (pT2 vs. pT3)	0.31	0.36	0.39	1.85	0.46	7.53
Gleason score (<8 vs. 8–10)	−0.19	0.34	0.58	0.69	0.18	2.62
B. Acute RT related AEs *[3]*						
Age	−0.02	0.04	0.54	0.98	0.90	1.06
Baseline PSA	0.02	0.07	0.82	1.02	0.88	1.17
Clinical T-stage (pT2 vs. pT3)	0.11	0.33	0.74	1.25	0.35	4.52
Gleason score (<8 vs. 8–10)	−0.27	0.29	0.35	0.59	0.19	1.81
C. PSA Response *[3]*						
Age	0.09	0.06	0.15	1.09	0.97	1.24
Baseline PSA	0.09	0.08	0.26	1.09	0.94	1.27
Clinical T-stage (pT2 vs. pT3)	−0.23	0.63	0.72	0.63	0.05	7.53
Gleason score (<8 vs. 8–10)	−0.33	0.50	0.51	0.52	0.07	3.70

*[1]*Outcome variable: Samarium-153 Related AE (Yes/No)

*[2]*Outcome variable: Acute RT related AE (Yes/No)

*[3]*Outcome variable: PSA response (>30% change,<=30% change)

Bolded levels are reference levels

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Table 5.

2 Year Estimates (n=60)

	Estimate (%)	95% CI (%)	Number of Failures
Freedom From Progression *	25.5	(14.4, 36.7)	44
Time to Progression§	74.5	(60.9, 83.9)	44
Biochemical Failure§	64.4	(50.5, 75.2)	38
Distant Failures§	22.0	(12.4, 33.3)	13
Regional Failure§	3.4	(0.6, 10.4)	2
Local Failures§	3.4	(0.6, 10.5)	2

*Estimated using Kapan Meier method

§Estimated using cumulative incidence method