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Randomized phase II trial of sipuleucel-T with or without radium-223 in men with bone-metastatic castration-resistant prostate cancer

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Abstract

Purpose: To investigate if radium-223 increases peripheral immune responses to sipuleucel-T in men with bone-predominant, minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC).

Methods: 32 patients were randomized 1:1 in this open label, phase 2 multicenter trial. Patients in the control arm received 3 sipuleucel-T treatments, 2 weeks apart. Those in the combination arm received 6 doses of radium-223 monthly, with sipuleucel-T intercalated between the second and fourth doses of radium-223. The primary endpoint was a comparison of peripheral antigen PA2024-specific T cell responses (measured by proliferation index). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and PSA responses.

Results: We enrolled 32 patients, followed for a median of 1.6 years. Six weeks after the first sipuleucel-T dose, participants in the control arm had a 3.2-fold greater change in PA2024-specific T cell responses compared to those who received combination treatment (p=0.036). Patients in the combination arm were more likely to have a >50% PSA decline (5 (31%) versus 0 patients; *P*=0.04), and also demonstrated longer PFS (39 vs 12 weeks; HR 0.32; 95% CI 0.14–0.76) and OS (not-reached vs 2.6 years; HR 0.32; 95% CI 0.08–1.23).

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Disclosures: All are up to date at aacr.org for all authors

Conclusion: Our data raise the possibility of greater clinical activity with the combination of sipuleucel-T and radium-223 in men with asymptomatic bone mCRPC, despite the paradoxically lower immune responses observed. Additional study to confirm these findings in a larger trial is warranted.

Keywords

sipuleucel-T; radium-223; metastatic castration resistant prostate cancer; immunotherapy; prostate cancer

Introduction:

Sipuleucel-T is an FDA-approved autologous cell-based immunotherapy for use in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC).(1-3) While the seminal study of sipuleucel-T demonstrated an overall survival (OS) benefit of 4.1 months compared to placebo, prostate-specific antigen (PSA) responses were observed in only 2.6% of patients and there was no difference in progression-free survival compared to placebo.(1) African-American patients and those with low baseline PSA values seem to be more likely to benefit from sipuleucel-T.(4,5) Antigen-specific humoral and T-cell responses also correlate with a survival benefit to sipuleucel-T, suggesting that a stronger anti-tumor immune response may lead to better clinical outcomes.(1,6)

Radiation therapy is known to augment the activity of the immune system.(7) Radiation-induced cell death stimulates tumor-specific immune responses by enhanced display of tumor-associated antigens and upregulation of tumor-suppressive proteins and inflammatory cytokines.(8) Radium-223 is an alpha-emitting radioisotope and bone-seeking calcium mimetic which selectively targets areas with increased bone turnover.(9) It is FDA-approved for the treatment of men with mCRPC with symptomatic bone metastases, without visceral disease or bulky nodal disease, based on the pivotal phase III trial demonstrating a survival benefit.(10) Similar to sipuleucel-T, treatment with radium-223 rarely results in a PSA response.

Based on the potential immunomodulatory effects of radiotherapy, we hypothesized that the combined use of radium-223 and sipuleucel-T would enhance sipuleucel-T-induced immune responses and improve clinical outcomes in men with minimally symptomatic, bone-predominant mCRPC.

Methods

Study Design and Patients

This was an open-label, randomized phase II, investigator-initiated study conducted at four sites in the United States (NCT02463799). All patients provided written informed consent. Key eligibility criteria included: age ≥18 years with histologically documented prostatic adenocarcinoma, PSA level of ≥ 2.0ng/mL, at least one sclerotic bone metastasis, and progressive castration-resistant prostate cancer as demonstrated by two consecutive rises in PSA or new lesions on bone or CT scan. Patients were required to have asymptomatic or

minimally symptomatic disease, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, adequate bone marrow and hepatorenal function, and no narcotics for cancer related pain. Prior abiraterone and enzalutamide were permitted but not required. Concurrent osteoclast-inhibitory therapies were permitted, but not required. Patients were excluded if they had any lung or liver metastases >1 cm in long-axis diameter, lymphadenopathy > 3 cm in short-axis diameter, known brain metastasis, previous chemotherapy for mCRPC, were on steroids within 2 weeks of randomization or received prior α- or β-emitting radiopharmaceutical drugs. Detailed inclusion and exclusion criteria are available in the full protocol (supplement). This study was approved by the Institutional Review Board at each participating center, and was conducted in accordance with the Declaration of Helsinki; patients at all sites provided written informed consent before enrolment.

Treatment

Eligible patients were randomized (1:1) to receive sipuleucel-T alone or sipuleucel-T with radium-223. In the sipuleucel-T alone arm, patients received 3 infusions of commercial sipuleucel-T, separated by 2 weeks, according to the standard administration. In the combination arm, patients received 6 doses of radium-223, each 4 weeks apart, according to standard dose and schedule. Intercalated between the second and third doses of radium-223, sipuleucel-T was initiated and given every 2 weeks for three doses. Thus, the first dose of sipuleucel-T was administered in between the second and third doses of radium-223, the second dose of sipuleucel-T was given concurrently with the third dose of radium-223, and the third dose of sipuleucel-T was given in between the third and fourth doses of radium-223 (see trial schema; Figure 1). The start of the next systemic therapy was not prespecified and could begin any time after the completion of clinical trial therapy. Participants were censored at the start of the next therapy if they did not reach a progression event by that time.

Endpoints

It has previously been shown that sipuleucel-T generates PA2024- and PAP-specific immune responses in most patients, and these generally peak at 6 weeks after treatment initiation.(6) PA2024 is the target antigen of sipuleucel-T and represents a recombinant fusion protein of PAP and GM-CSF. The primary endpoint of the trial was to compare peripheral PA2024-specific T-cell proliferation responses using a ^{3}H-thymidine incorporation assay. Baseline was considered just prior to the first dose of sipuleucel-T. The fold change in proliferation was compared at week 6 after the first sipuleucel-T infusion. This was reported as the stimulation index (SI), defined as ^{3}H-thymidine incorporation in the presence of PA2024 antigen divided by ^{3}H-thymidine incorporation with media alone.(6) Secondary immune endpoints include peripheral PA2024- and PAP-specific T-cell proliferation responses at 10, 14, and 26 weeks after the first infusion of sipuleucel-T; PA2024 and PAP-specific antibody response to sipuleucel-T, which are the most strongly correlated with overall survival;(6) and sipuleucel-T induced antigen spread (*i.e.* humoral responses to non-target antigens).(11)

Key secondary clinical endpoints included progression-free survival (PFS, defined as the time from sipuleucel-T initiation to clinical or radiographic progression or death), and

overall survival (OS, defined as the interval from randomization to death from any cause). PSA 50% response rates (PSA_{50}) were also explored. To compare PFS outcomes in the two arms, baseline was considered to be the first dose of sipuleucel-T (which was administered 6 weeks after the start of radium-223 in the combination arm). A sensitivity analysis was done using date of randomization as the baseline. Radiologic assessment was investigator assessed, with progression being defined based on CT and bone scans according to PCWG2 criteria.(12,13)

Statistical Analysis

The study was designed to test the null hypothesis of no difference in immune response to sipuleucel-T based on PA2024-stimulated T cell proliferation at 6 weeks, comparing sipuleucel-T alone and sipuleucel-T plus radium-223. T-cell proliferation was compared between groups using Wilcoxon test. We sought to detect a 3.6-fold difference between the arms with 80% power in mean SI of PA2024-specific ^{3}H-thymidine uptake at week 6 after the first infusion of sipuleucel-T using a one-sided test at the 0.05 level, yielding a sample size of at least 30 total patients (*i.e.* at least 15 patients per arm). The immune response population was defined as subjects who received at least 1 infusion of sipuleucel-T and at least 2 infusions of radium-223, in the combination arm. Additional immune response parameters comparing fold change from baseline and absolute differences were compared using Wilcoxon tests.

PSA_{50} response rates between the groups were compared using Fisher's exact test. PFS and OS estimates were calculated using the Kaplan-Meier method, and were compared using the log-rank test. Univariate Cox proportional-hazards models were used to estimate hazard ratios and 95% confidence intervals (CI). These statistical tests were two-sided, and statistical significance was set at $P \leq 0.05$, unless otherwise specified.

Results

Patients

A total of 32 participants were enrolled and randomized from May 2017 through November 2018. The consort diagram is shown in Figure 2. Sixteen patients were randomized to receive sipuleucel-T alone and 16 were randomized to sipuleucel-T plus radium-223. Baseline demographic and clinical characteristics are presented in Table 1. Median age of study participants was 71.6 and 70.3 years, respectively. Race, Gleason score, baseline laboratory studies, and ECOG functional status were balanced between the arms. Four participants (25%) in each group were African American. The median PSA at study entry was 33 and 25 ng/mL, and the median alkaline phosphatase was 89 and 92 u/L, respectively. No participant in the combination arm and 4 participants (25%) in the sipuleucel-T arm received prior chemotherapy for metastatic hormone-sensitive prostate cancer. Six participants (38%) in the combination arm and 7 participants (44%) in the sipuleucel-T arm received prior abiraterone or enzalutamide. Ten participants (63%) in the combination arm and 11 participants (69%) in the sipuleucel-T arm were on bone-protective agents at baseline. All patients completed the full treatment course, except for one patient in the sipuleucel-T arm who only received 2 of the 3 doses, and two patients in the combination

arm who received all sipuleucel-T infusions but only received 3 and 4 doses of radium-223, respectively. There was no difference between the groups with regards to the cumulative CD54 upregulation of the final product parameters or the cumulative total nucleated cell count in the final product parameters.

Immune responses

Cellular responses—Our primary endpoint was not met. At week 6, the fold change in PA2024-specific proliferation index was 3.2-fold higher in the sipuleucel-T arm compared to the combination arm (median 22.4, IQR 14.2 versus 7.0, IQR 16.1; P=0.036; Figure 2A), an unexpected result for our primary endpoint. The fold change in PA2024-specific proliferation was generally higher in the sipuleucel-T alone arm through week 26 when compared to the combination arm (Figure 3A). The 6-week change in PAP-specific proliferation was numerically 2-fold higher in the sipuleucel-T alone arm compared to the combination arm but this was not statistically significant between arms (0.4, IQR 2.2 versus 0.2, IQR 0.7; P= 0.27; Figure 3B);there was little difference between the arms at later time points with respect to this parameter (Figure 3B). There were no significant differences in the fold-change of antigen-specific T cells, detected by IFN-gamma ELISPOT assays, against PA2024 or PAP at week 6 or later (Figure 3C and 3D). Individual changes in each of these over time is shown in the supplement.

Humoral responses—While there was an increase in the absolute antibody responses to PA2024 and PAP in both arms, there was no significant difference between the arms when comparing absolute antibody levels and no significant difference in the change in humoral responses (relative to baseline) to PAP or PA2024 between the arms (supplement). There was no indication of broad differential antigen spread responses between the groups. More specifically, there was no difference in the fold change of antibody response to the non-target antigens: PSA, KRAS, ERAS or KLK2. Of note, the sipuleucel-T group had a significantly higher change in antibody response to LGALS3 at week 6, week 10, and week 14 compared to the baseline (supplement).

Cytokine Analyses—There were no significant differences in the percentage change in IFN-gamma, IL-6, or TNF-α at any of the time points examined (supplement). Of the other cytokines tested (IL-10, IL-12p70, IL-13, IL-1β, IL-2, IL-4, and IL-8), the relative changes compared to baseline were not different between the arms. With regards to absolute levels, the sipuleucel-T group had higher IL-13 levels at week 10 (3,936 pg/mL in sipuleucel-T arm, IQR 5,094 compared to 1,388 pg/mL in the combination arm, IQR 2,960; p=0.019) and week 26 (33,488 pg/mL in sipuleucel-T arm, IQR 16,078 compared to 675 pg/mL in combination arm, IQR 2,381; p=0.036). There was no difference between the absolute levels of any of the other cytokines when comparing the two arms.

Clinical Outcomes

There were 29 patients that were evaluable for PSA response (3 subjects never had post-treatment PSA checks before coming off study). Five patients in the combination arm had a PSA decline of at least 50% (PSA_{50}), of which 4 were confirmed with a repeat PSA value 4

weeks later (Figure 4); there were no PSA_{50} responses in the monotherapy arm (5/15 [33%] vs 0/14 [0%]; P=0.04).

After a median of 1.6 years of follow-up, there were 24 radiographic progression events and one clinical progression event. The median PFS was 39 weeks in the combination arm compared to 12 weeks in the sipuleucel-T alone arm (HR 0.32, 95%CI 0.14–0.76; P<0.01; Figure 5A). In the sensitivity analysis, using the date of registration as the baseline, the median PFS was 44 weeks in the combination versus 12 weeks in the sipuleucel-T alone arm (HR 0.24, 95% CI 0.10-0.56). There was also a trend toward improved OS in the combination arm, with a median survival of 2.6 years in the sipuleucel-T alone arm whereas the median survival was not reached in the combination arm (HR 0.32, 95%CI 0.08–1.23; P=0.08; Figure 5B). Subsequent therapies used for treatment are shown in the supplement.

Safety

The treatment-emergent adverse events observed in this trial are consistent with the known side effects of each of the therapies, and there did not appear to be any additive toxicities (Table 2). Pain was the most common symptom reported. Chills, dizziness, and lightheadedness were more common in the sipuleucel-T arm. These were related to infusion of the immunotherapy product and were transient as expected. Nausea, diarrhea, and marrow suppression (thrombocytopenia and leukopenia) were more common in the combination arm and are likely attributed to radium-223 as anticipated. There were two skeletal-related events in the combination arm, and one in the sipuleucel-T arm – all pathologic fractures. No grade 4/5 events were observed.

Discussion

In this randomized phase II trial, we found (unexpectedly) that participants in the sipuleucel-T alone arm had an increased antigen-specific peripheral immune response compared to the combination arm, with a higher change in the T-cell proliferation index against the sipuleucel-T target antigen PA2024. There were no significant differences in the other secondary immune parameters including antibody response to PA2024 or PAP, and antigen spread to secondary non-target antigens that have been associated with improved outcomes in sipuleucel-T in prior studies.(11) LGALS8 was higher in the sipuleucel-T group in our study; however, it has not previously been associated with differences in outcomes in patients treated with sipuleucel-T.(11,14) We also observed an increase in IL-13 levels in the sipuleucel-T alone arm compared to the combination arm; the significance of this finding is not clear. Radium-223 has not been associated with any change in T-cells producing cytokines such as IFN-$^{\gamma}$, TNF-α, or IL-13.(15) Overall, we did not detect a signal of improved immunologic activity using radium-223 plus sipuleucel-T over sipuleucel-T alone. Further, we did not examine long-term immune consequences beyond approximately 26 weeks.

Despite the lack of augmented peripheral cellular and humoral responses in the combination-therapy arm, significant clinical activity was observed for those treated with sipuleucel-T plus radium-223. Five patients (33%) in the combination arm achieved a PSA_{50} response, compared to none in the sipuleucel-T alone arm. This clinical signal is

encouraging, as PSA responses are only seen in approximately 10-15% of patients treated with radium-223 and approximately 2% of patients treated with sipuleucel-T, although this could be within what is expected from radium-223 alone.(1,10,16,17) Additionally, the median PFS was significantly longer in the combination-therapy arm, with a trend towards an improvement in OS as well in the combination arm, which might not be surprising given that both agents are approved based on their individual clinical benefits. This suggests possible additive clinical effects with the use of combination radio-immunotherapy, but does not prove synergy.

Previous research has shown that antigen spread, evident by humoral responses to PSA and LGALS2, has been associated with improved OS in patients treated with sipuleucel-T in prospective trials.(11) This was not evident in our study. One hypothesis is that the radio-immunotherapy combination may have increased the number of tumor-infiltrating CD8+ lymphocytes while subsequently resulting in a compensatory decrease in circulating antigen-specific T lymphocytes, although this notion is speculative. It is also possible that radium-223 may inhibit B- and T-cell proliferation and function. While a prior small study did not show a negative impact of radium-223 on lymphocyte function (18), that study used different time points to assess immune parameters and did not examine longer term T-cell effects. Thus, radium-223 could have been myelosuppressive, leading to dampened immune responses overall; however, there was no evidence of this detected within the product parameters for sipuleucel-T. Another hypothesis is that genomic alterations could be playing a role, especially if these were not balanced across arms. It has been previously reported that patients with DNA damage repair mutations may have better responses to radium-223, which could theoretically contribute to these results.(19) In addition, anecdotal reports have suggested striking clinical responses to sipuleucel-T in some patients with mismatch-repair gene mutations and microsatellite instability.(20) Our study was conducted at a time when most patients were not undergoing tumoral DNA sequencing, and hence somatic (and germline) genomic analysis were not part of the trial.

The notion that radiotherapy may enhance the clinical effects of sipuleucel-T is supported by a recently-published randomized trial.(21) In that study, patients with asymptomatic mCRPC were randomized to receive either sipuleucel-T (n=24) alone or sipuleucel-T one week after receiving external-beam radiotherapy to a metastatic site (n=25). To this end, the median progression-free survival in subjects receiving the combined-modality approach versus those getting sipuleucel-T alone was modestly enhanced (3.7 vs 2.5 months; P=0.06). Interestingly, and broadly consistent with our findings, T-cell responses to PA2024 (measured by IFN-gamma ELISPOT assays) were observed in both arms, but were more robust in the monotherapy compared to the combination arm (P=0.03); other humoral and cellular responses were similar across arms. However, the long-term effects of this difference in immune response on patient outcomes is unknown. Additionally, not part of this study, but also to be considered, is how the timing of the two agents would affect outcomes and if concurrent versus sequential treatment of these two agents would result in different outcomes.

In our study, there were no adverse safety signals in the group of patients treated with the combination of sipuleucel-T plus radium-223. The main toxicities observed in the

combination arm were consistent with the known individual side effects of each agent, and their prevalence or intensity did not appear to be augmented compared to prior published studies of each monotherapy.

There are several limitations to our study. First, this study was focused on immune-related endpoints associated with sipuleucel-T and these immunological correlates were not specific to radium-223 treatment. To this end, the immune effects of radium-223 are understudied and incompletely understood, and might possibly be lymphodepleting. One small study of patients treated with radium-223 showed that after a single dose, treated patients had a decrease in PD-1–expressing memory CD8+ T-cells.(15) However, that study was not powered for clinical endpoints. Further, due to the small sample size of our study, all conclusions with respect to clinical efficacy should be interpreted with caution and require prospective validation. Importantly, the synergy of this combination could not be proven here. In addition, the use of the first sipuleucel-T treatment as the baseline time point for PFS estimates is unconventional and represents a departure from the norm (*i.e.* rather than time of randomization as the baseline, as was done here for OS estimates); the reason for doing this relates to the fact that imaging assessments would not have been concordant in the two arms (and would have been off by 6 weeks) had we used randomization as the baseline time point for PFS analysis. However, the supplemental sensitivity analysis yielded similar results. Additionally, progression events were determined by the investigators and we cannot rule out unconscious bias on the part of the investigators in determining events. The therapies received prior to and after the study also differed; notably, more patients in the sipuleucel-T arm received prior docetaxel. The number of participants who received subsequent abiraterone or enzalutamide after study completion was also numerically higher for the combination arm, and these differences may be contributing to the difference in overall survival seen. Further, the lack of germline and somatic mutational data limit conclusions about the potential role of DNA damage response alterations and outcomes, and there may have been imbalances in DNA repairome abnormalities across the two arms.

In conclusion, this hypothesis-generating randomized trial raises the possibility of an additive clinical effect of the combination of sipuleucel-T and radium-223, while peripheral antigen-specific immune responses were paradoxically greater in the sipuleucel-T alone arm than the combination arm. The radio-immunotherapy combination was feasible to execute, and there were no unexpected safety signals implying synergistic toxicity. A larger randomized study testing this combination, with a focus on long-term clinical outcomes, is being planned to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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Statement of translational relevance:

Radiation therapy, such as radium-223, is thought to augment the activity of the immune system and may have an impact on the response to immune therapies, such as sipuleucel-T. In this study, we report the results of a randomized phase II trial that evaluated sipuleucel-T with or without radium-223 for men with metastatic castration resistant prostate cancer. This trial demonstrated that radium-223 in combination with sipuleucel-T was associated with paradoxically lower peripheral T-cell immune responses to the target antigen, PA2024, compared to patients who received sipuleucel-T alone. Other T-cell markers of immune response were not different between the arms. Interestingly, there seemed to be a clinical benefit to the combination with an improvement in the progression free survival. On the basis of these findings, a larger trial is being planned.

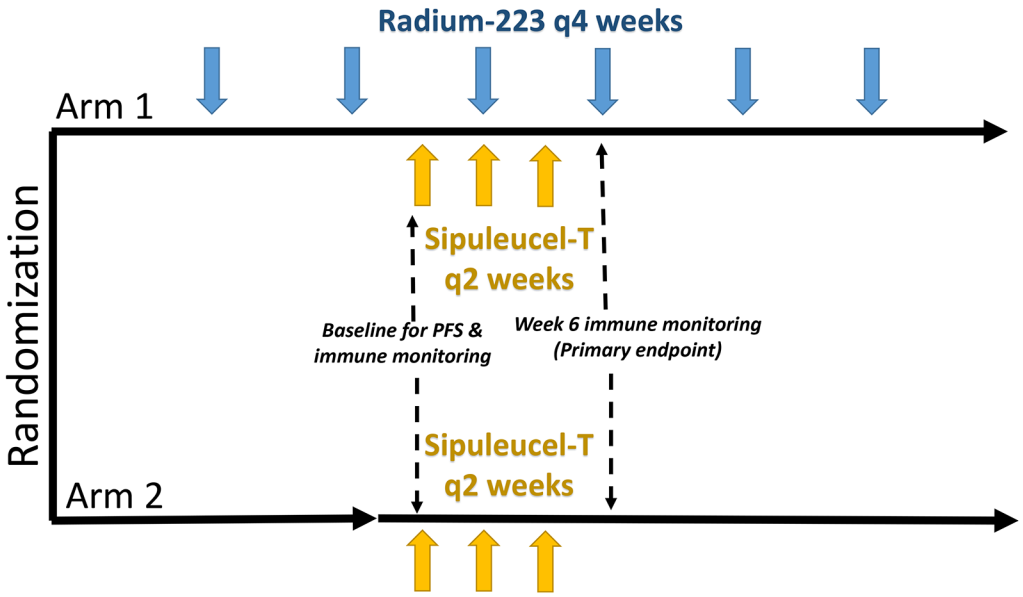

Figure 1.
Clinical trial schema

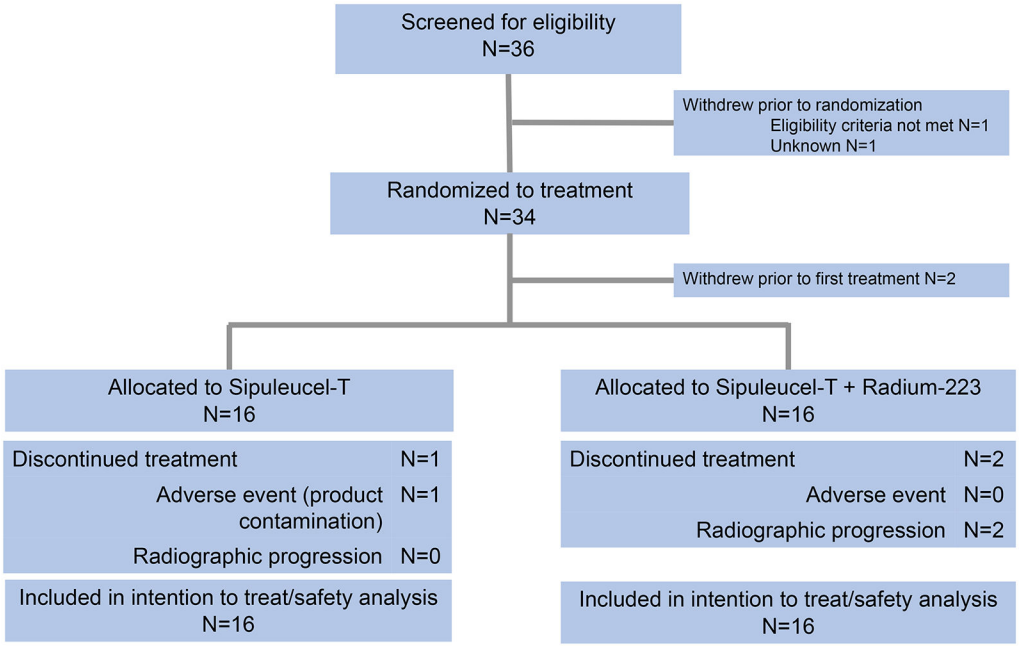

Figure 2.
Consort diagram

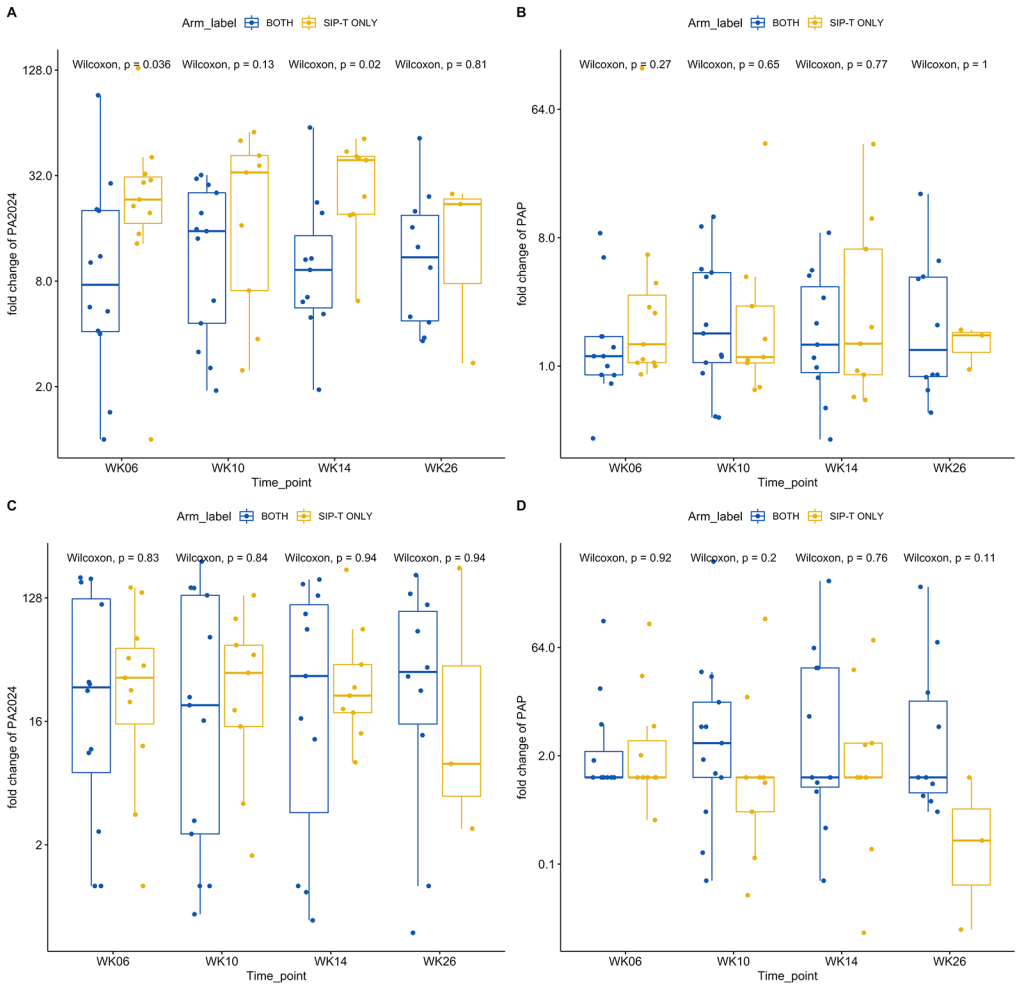

Figure 3.

Immunologic endpoints (at week 6, N = 12 in combination arm with paired data, and N=11 in sipuleucel-T alone arm with paired data).

3A. Fold change in PA2024 proliferation index compared to baseline

3B. Fold change in PAP proliferation index compared to baseline

3C. Fold change in PA2024-specific T cells by ELISPOT

3D. Fold change in PAP-specific T cells by ELISPOT

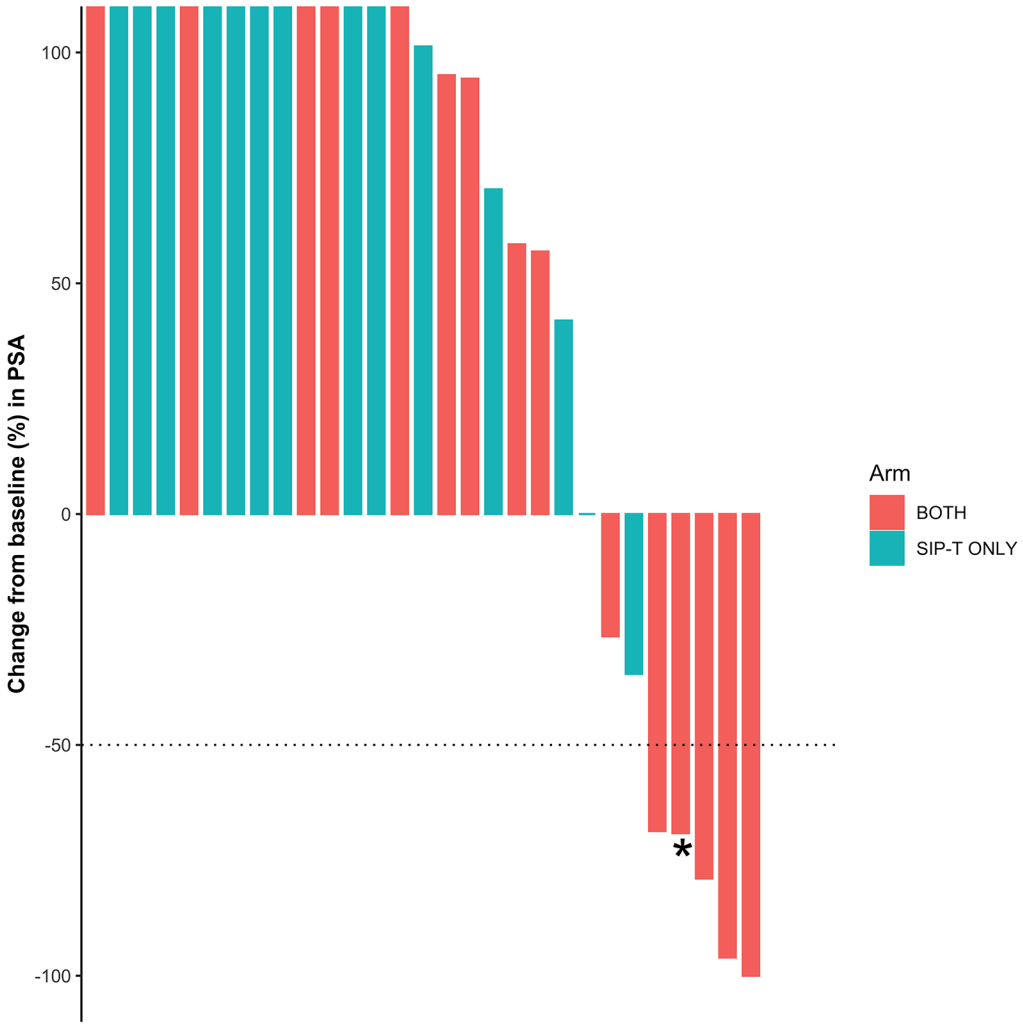

Figure 4.
Waterfall plot showing best PSA response rate

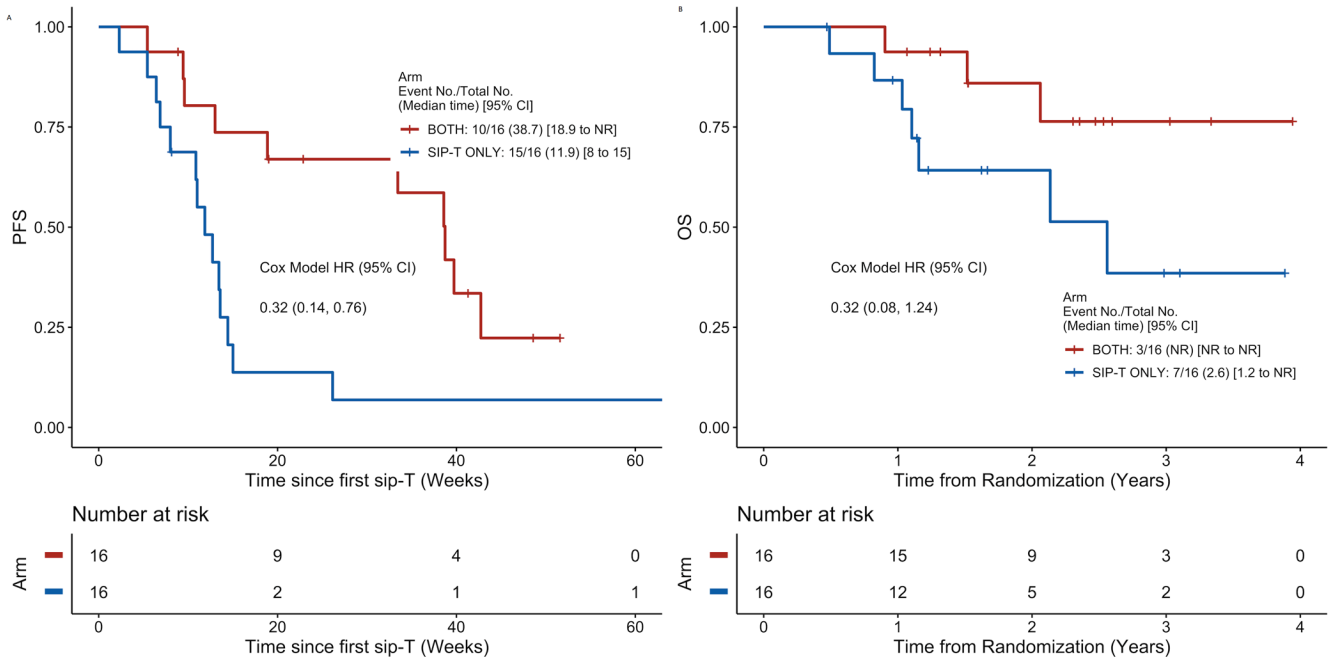

Figure 5.

Clinical endpoints

5A. Progression-free survival of the radium-223 + sipuleucel-T (red) arm compared to sipuleucel-T alone (teal).

5B. Overall survival comparing the two arms

Table 1.

Baseline characteristics of patients.

	Arm 1 Ra-223 + Sipuleucel-T (N=16)	**Arm 2 Sipuleucel-T (N=16)**
Age, mean (range)	71.6 (64-88)	70.3 (57-86)
Gleason sum		
6	1 (6%)	1 (6%)
7	4 (25%)	4 (25%
8-10	11 (69%)	11 (69%)
Race		
White	11 (69%)	10 (63%)
African American	4 (25%)	4 (25%)
Other	1 (6%)	2 (12%)
Ethnicity		
Hispanic (% yes)	0 (0%)	1 (7%)
ECOG performance status		
0	11 (69%)	13 (81%)
1	5 (31%)	3 (19%)
Prior Treatment		
Prior RP (% yes)	10 (63%)	6 (38%)
Prior RT (% yes)	9 (56%)	8 (50%)
Prior abiraterone (% yes)	0 (0%)	4 (25%)
Prior enzalutamide (% yes)	6 (38%)	3 (19%)
Prior docetaxel chemotherapy for mHSPC (% yes)	0 (0%)	4 (25%)
Baseline PSA ng/mL, median (IQR)	25 (9.2-110.1)	33 (4.6-71)
Baseline alkaline phosphatase u/L, median (IQR)	89 (79-112)	92 (80-114)
On bone protective agent (% yes)	10 (63%)	11 (69%)

mHSPC = metastatic hormone sensitive prostate cancer. RP = radical prostatectomy. RT = radiation PSA = prostate specific antigen. IQR = interquartile range.

Table 2.

Adverse Events if they occurred in ≥ 3 patients or were grade 3. There were no grade-4/5 events.

	Sip-T + Rad-223		Sip-T	
	Any Grade	**Grade 3**	**Any Grade**	**Grade 3**
Constitutional				
Pain	10 (63%)	2 (13%)	12 (75%)	-
Chills	2 (13%)	-	6 (38%)	-
Fatigue	5 (31%)	-	3 (19%)	-
Flu like symptoms	4 (25%)	-	3 (19%)	-
Fever	2 (13%)	-	1 (6%)	-
Dizziness/lightheaded	1 (6%)	-	3 (19%)	-
Fall	1 (6%)	-	2 (13%)	-
Hematologic				
Leukopenia	2 (13%)	-	-	-
Anemia	5 (31%)	1 (6%)	5 (31%)	1 (6%)
Thrombocytopenia	1 (6%)	-	-	-
Gastrointestinal				
Nausea	5 (31%)	1 (6%)	4 (25%)	-
Diarrhea	7 (44%)	1 (6%)	-	-
Constipation	2 (13%)	-	5 (31%)	-
Vomiting	2 (13%)	-	2 (13%)	-
Abdominal Pain	1 (6%)	1 (6%)	2 (13%)	-
Cardiac				
Hypertension	2 (13%)	1 (6%)	-	-
Other				
Headache	3 (19%)	-	-	-
Edema	1 (6%)	-	2 (13%)	-
Insomnia	2 (13%)	-	1 (6%)	-
Catheter related infection	-	-	1 (6%)	1 (6%)
Urinary retention	-	-	1 (6%)	1 (6%)
Skeletal related event	2 (13%)		1 (6%)	