Randomized phase 2 study of sipuleucel-T (Sip-T) with or without radium-223 (Ra-223) in men with bone-metastatic castration resistant prostate cancer

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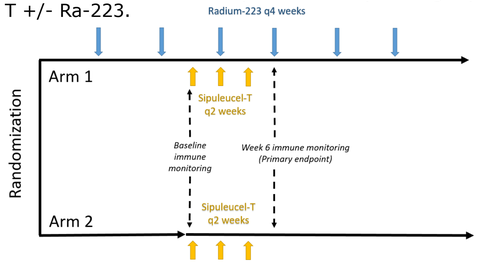
Background and Rationale

- It has been suggested that immune modulation can be enhanced by radiation therapy through a variety of mechanisms, including via enhanced display of tumor associated antigens [1]
- Radiopharmaceutical agents have been shown to upregulate tumor antigens in prostate cancer models [2]
- Radium-223 is an α-emitting radioisotope which is a bone-seeking calcium mimetic, selectively targets the area with increased bone turnover, and is FDA approved for the treatment of mCRPC with symptomatic bone mets [3]
- SipT is an autologous cell based immunotherapy, FDA approved for the treatment of minimally symptomatic mCRPC [4]

Hypothesis: We hypothesized that combined use of radium-223 and sipuleucel-T would enhance the sipuleucel-T induced immune response, which translates to better clinical outcomes

Patients and Methods

We conducted an investigator-initiated, open-label, randomized, multi-center phase II study testing Sip-T +/- Ra-223.



Key Inclusion Criteria

1. Asymptomatic or minimally-symptomatic bone-dominant mCRPC
2. Serologic or radiographic progression of disease
3. Absolute PSA ≥ 2.0 ng/ml
4. ECOG performance status of 0-1
5. Prior (not concurrent) abiraterone/enzalutamide permitted

Key Exclusion Criteria

1. Prior IV chemotherapy for mCRPC (for hormone sensitive disease was permitted)
2. Visceral (liver/lung) metastases > 1.0cm in long axis; adenopathy >3.0cm in short axis; known brain metastases
3. Prior α- or β- emitting radiopharmaceutical drugs
4. Radiation within 28 days; steroids within 2 weeks
5. Inadequate organ and bone marrow function:
   Creatinine Clearance <50 ml/min;
   Hgb <10 g/dl, ANC <1.5 x10^9/L, Plt <75 x10^9/L

Objective and Endpoints

Primary objective: To determine whether Ra-223 with Sip-T enhances immune responses to Sip-T measured by PA2024-specific T-cell proliferation compared to Sip-T alone

With 30 patients per arm, we sought to detect a 3.6-fold difference between the arms with 80% power in mean PA2024-specific T-cell proliferation 6 weeks after the first Sip-T infusion

Primary endpoint: *PA2024-specific T-cell proliferation* in peripheral blood, using a tritiated thymidine (^{3}H-thymidine) incorporation assay

Key secondary clinical endpoints:

- PSA (≥50%) response rates
- Alkaline phosphatase (≥30%) response rates
- Time to radiographic/clinical progression
- Safety/toxicity of the Sip-T/Ra-223 combination

Key secondary immune endpoints:

- PA2024-specific and PAP-specific IFNγ-ELISPOT responses in peripheral blood
- PAP-specific T-cell proliferation responses in peripheral blood
- PA2024-and PAP-specific humoral (IgM+IgG antibody) responses
- Antigen spread: humoral (IgG) responses to non-target antigens

Results

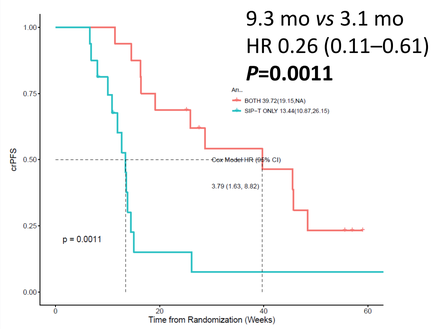
32 eligible subjects were accrued at 4 sites: Johns Hopkins, Tulane, Duke, Cedars Sinai between 5/2017 and 11/2018.

Table 1. Baseline characteristics

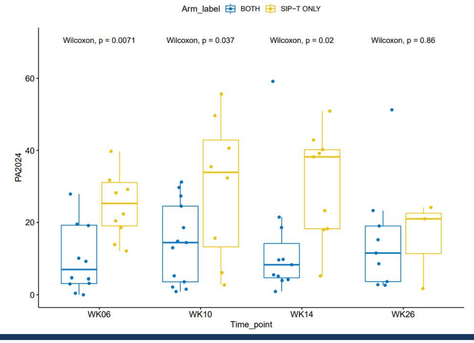
	Ra-223 + SipT N=16	SipT N=16	P-value
Age, mean (range)	71.6 (64-88)	70.3 (57-86)	0.59
Gleason sum			0.53
6	1 (6%)	1 (6%)	
7	4 (25%)	4 (25%	
>=8	11 (69%)	11 (69%)	
ECOG			0.69
0	11 (69%)	13 (81%)	
1	5 (31%)	3 (19%)	
Prior RP (% yes)	10 (63%)	6 (38%)	0.29
Prior XRT (% yes)	9 (56%)	8 (50%)	0.72
Prior abiraterone (% yes)	0 (0%)	4 (25%)	0.10
Prior enzalutamide (% yes)	6 (38%)	3 (19%)	0.43
Prior chemotherapy (% yes)	0 (0%)	4 (25%)	0.10
Baseline PSA ng/mL, median (IQR)	25 (9.2-110.1)	33 (4.6-71)	0.83
Baseline alk phos u/L, median (IQR)	89 (79-112)	92 (80-114) u/L	0.99

Results

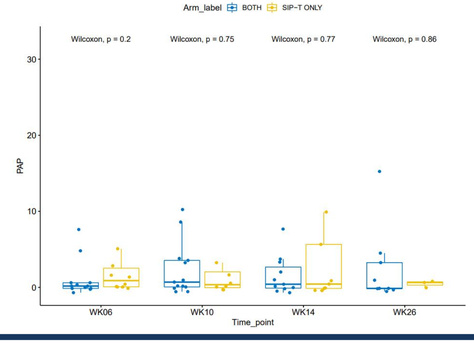
Time to radiographic/clinical progression



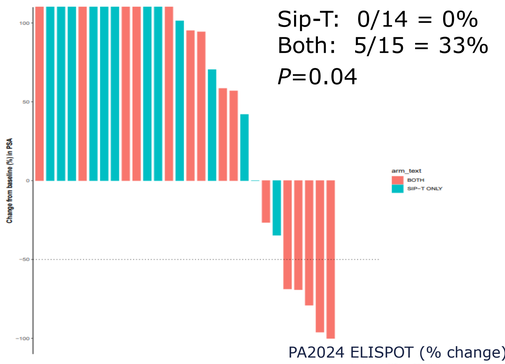
PA2024, Proliferation index (% change from baseline)



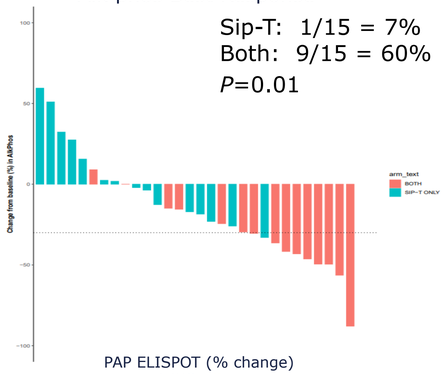
PAP, Proliferation index (% change from baseline)



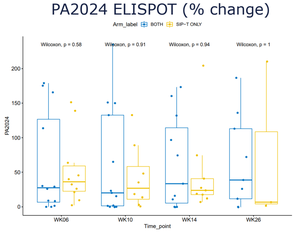
PSA Best Response



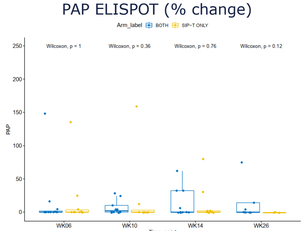
Alk phos Best Response



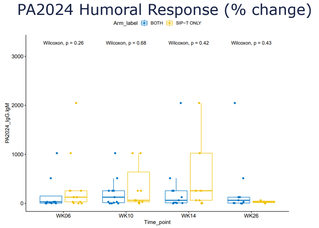
PA2024 ELISPOT (% change)



PAP ELISPOT (% change)



PA2024 Humoral Response (% change)



PAP – Humoral Response (% change)

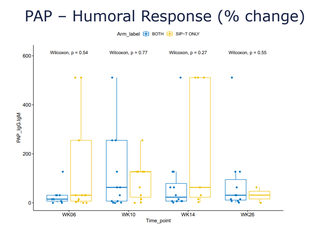


Table 3. Adverse Events if occurred in ≥ 3 people or grade 3

	Sip-T + Rad-223		Sip-T	
	Any Grade	Grade 3	Any Grade	Grade 3
Constitutional				
Pain	12 (75%)	3 (19%)	12 (75%)	-
Chills	2 (13%)	-	7 (44%)	-
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	1 (6%)	4 (25%)	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%)	-
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%)	

Conclusions

- Peripheral immune responses were lower in the SipT +Ra-223 group although with improved clinical outcomes compared to sipT alone
- These data suggest a synergistic effect of the combination, especially with respect to clinical outcomes

Acknowledgements

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[1]Shore ND, et al. Cancer Control 2013; 20(1):7-16. [2] Chakraborty M, et al. Clin Cancer Res 2008; 14(13):4241-4249. [3] Parker C, et al. NEJM; 2013; 369:213-223. [4] Kantoff PW, NEJM; 2010 363(5):411-22.