

AD_____

AWARD NUMBER: W81XWH-04-1-0884

TITLE: Radioimmunotherapy (RIT) Dose-Escalation Studies in Prostate Cancer Using Anti-PSMA Antibody 177Lu-J591: RIT Alone and RIT in Combination with Docetaxel

PRINCIPAL INVESTIGATOR: Shankar Vallabhajosula, Ph.D.

CONTRACTING ORGANIZATION: Cornell University
New York, NY 10021

REPORT DATE: October 2009

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE 12/14/2009		2. REPORT TYPE Technical (Annual) Report		3. DATES COVERED September 15 2008 – September 14 2009	
4. TITLE AND SUBTITLE Radioimmunotherapy (RIT) Dose-Escalation Studies in Prostate Cancer Using Anti-PSMA Antibody ¹⁷⁷ Lu-J591: RIT Alone and RIT in Combination with Docetaxel.				5a. CONTRACT NUMBER W81XWH-04-1-0884	
				5b. GRANT NUMBER PC040566	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Shankar Vallabhajosula, Ph.D.				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Weill Medical College of Cornell University 1300 York Avenue New York, NY 10021-4870				8. PERFORMING ORGANIZATION REPORT	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT In the fall of 2007, we started the phase I dose escalation studies with ¹⁷⁷ Lu-DOTA-huJ591 monoclonal antibodies (mAb) using dose fractionation regimen. In patients with PCa and who have recurrent and/or metastatic disease, ¹⁷⁷ Lu dose (20-40 mCi/m ²) was escalated in 5 different dose levels (3-6 patients at each dose level). At each dose level, the patients received <u>two doses</u> of ¹⁷⁷ Lu-J591 mab (20 mg/dose), 2 weeks apart. A total of 22 patients have been treated and the MTD with the dose fractionation is regarded as 40 mCi/m ² dose given twice two weeks apart. The results of this study clearly demonstrate that administration of ¹⁷⁷ Lu-J591 treatment dose in a fractionated dose regimen is relatively safe with reduced hematologic toxicity than a single dose treatment. Building upon this data, a <u>phase I fractionated-dose ¹⁷⁷Lu-J591 plus docetaxel</u> , has begun enrollment. This protocol represents the intent of the SOW-4 in the original grant application. Patients will receive docetaxel, 75 mg/m ² every 21 days As of July 2009, two patients were recruited in group 1 (20 mCi/m ²). Due to protocol amendments, the revised protocol was resubmitted to HSRRB for review. We plan to complete recruitment in this trial before September 2010.					
15. SUBJECT TERMS Radioimmunotherapy, Prostate cancer, ¹⁷⁷ Lu-DOTA-J591 antibody, Dose-Fractionation					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT Unlimited	b. ABSTRACT Unlimited	c. THIS PAGE Unlimited			19b. TELEPHONE NUMBER (include area code) 212-746-5694

Table of Contents

	<u>Page</u>
Introduction	1
Body.....	2
Key Research Accomplishments.....	3
Reportable Outcomes.....	5
Conclusion.....	6
References.....	None
Appendices.....	None

Introduction

We still lack a systemic treatment that clearly demonstrates improved survival in patients with disseminated hormone resistant prostate cancer (PC). Targeted radioimmunotherapy (RIT) utilizing radiolabeled monoclonal antibodies (mAbs) directed to cancer-related cell surface antigens has been clinically validated with the FDA approval of ^{90}Y and ^{131}I labeled anti-CD20 mAbs (Zevalin and Bexxar) for the treatment of lymphoma. Metastatic PC is a rational candidate for RIT since PC is radioresponsive, and typically develops as small-volume micro-metastatic sites of disease in marrow and lymph nodes that receive high levels of mAb. In PC, the most well established, prostate-restricted, cell surface antigen yet identified is prostate specific membrane antigen (PSMA). It is an ideal target for developing therapeutic agents as it is expressed by all the PCs and the expression levels progressively increase in more poorly differentiated, metastatic and hormone-refractory prostate cancers (HRPC).

J591 is a de-immunized mAb that binds with a very high affinity to the extracellular domain of PSMA on the viable tumor cells. In addition, the PSMA-J591 antibody complex is internalized, thereby delivering any antibody payload (radioisotope or drug) to the interior of the targeted cells. We have demonstrated radiolabeled J591 sensitively and specifically targets sites of metastatic PC in both bone and soft tissue. In a Phase I studies, we have determined that ^{90}Y -J591 (17.5 mCi/m²) and ^{177}Lu -J591 (70 mCi/m²) mAbs either decrease or stabilize serum PSA levels. We have selected ^{177}Lu -J591 as an agent of choice for further studies. ^{90}Y may be appropriate for larger tumors while ^{131}I may be more cytotoxic for smaller, micro-metastatic lesions typically seen in HRPC. ^{177}Lu behaves chemically like ^{90}Y and is stable in vivo. ^{177}Lu has low energy β - particles and suitable γ photons for dosimetric studies. Thus it has advantages of both ^{90}Y and ^{131}I , but none of their disadvantages. Therefore **^{177}Lu -J591 may be an ideal agent for RIT studies of PC.** The degree of anti-tumor response following RIT depends on several variables, especially total (cumulative) radiation dose to the tumor, dose-rate and tumor radiosensitivity. Also, myelotoxicity is the dose-limiting factor in RIT. Therefore strategies are needed to optimize dosimetry to the bone marrow and tumor. Dose-fractionation is a practical strategy to decrease the dose to bone marrow while increasing the cumulative radiation dose to the tumor at an optimal dose-rate. Preclinical studies strongly support this strategy. Combined modality radioimmunotherapy (CMRIT) is another strategy designed to enhance the cascade of molecular events required for apoptotic tumor cell death resulting from the continuous low dose-rate radiation. FDA approved anti-neoplastic agent Docetaxel can cause microtubular dysfunction and as a result cells are blocked in the G2/M phase of the cell cycle, thus increasing sensitivity of cells to radiation.

Therefore, we proposed to perform two independent phase I dose-escalation studies in patients with HRPC. The first protocol was designed to determine the cumulative MTD of ^{177}Lu -J591, in a fractionated dose regimen of 2 low dose treatments given 2 weeks apart. A follow up protocol was designed to determine docetaxel (75 mg/m² ever 21 days) to be given in combination with a fractionated dose regimen of ^{177}Lu -J591 (20-40 mCi/m²). This research proposal thus combines several important strategies for successful RIT of PC; a very specific and high affinity anti-PSMA mAb J591, an ideal radionuclide ^{177}Lu with useful γ and β - energies for imaging and therapy, **dose fractionation and CMRIT strategies (with docetaxel) to reduce myelotoxicity and to augment the anti-tumor response of RIT.** In SOW, we have identified 4 major tasks and have successfully completed the first 3 tasks as of September 2009.

Body of Text based on SOW

REVISED STATEMENT OF WORK (SOW) July 20, 2009

Task 1: Preparation of ^{177}Lu -DOTA-J591 mAB for clinical studies.

Under GMP conditions, monoclonal antibody HuJ591-GS Antibody was DOTA conjugated, vialled and labeled by Immunomedics Inc. which is the current manufacturer of record for the vialled DOTA-HuJ591 antibody drug product. The manufacturer's address and telephone number are:

Immunomedics Inc., 300 Americasn Road, Morris Plains, NJ 07950

Phone: 973-605-8200

The drug product consists of DOTA-HuJ591 antibody in 0.3 M ammonium acetate, pH 7.2, in 2 mL thermoplastic vials with gray butyl rubber stoppers and blue flip-off crimp seal closures. The nominal concentration is 8.0 mg/mL and the nominal fill volume is 1.3 mL. There are no other excipients added.

^{177}Lu -Labeling of DOTA-J591: 3 batches of the above lot of DOTA-J591 were labeled with ^{177}Lu to a specific activity of 10-20 mCi/mg. All the QC tests indicated that the material is suitable for clinical studies.

The above process was started around October and final tests were completed by March 2007.

Task 2: Obtain IRB approval of the Phase I dose escalation protocol using ^{177}Lu -J591 in a fractionated dose regimen

- After 16 months of interaction with HSRRB at DOD, the protocol was finally approved in May 2006. Subsequently, the protocol (modified by Cornell IRB and DOD HSRRB) was submitted to FDA for permission to start the clinical trial under an IND.
- In August 2006, the physician who is responsible for recruiting the patients and who is the PI on the institutional protocol left Cornell medical center. We subsequently replaced the physician and resubmitted the protocol for IRB approval and FDA approval.
- Finally in January 2007, we received the approval from FDA following minor modifications to the protocol as suggested by FDA.
- The revised protocol was resubmitted to Cornell IRB and then finally to HSRRB at DOD (in January 2007)
- After several communications, we were just informed that the protocol is finally approved. We are still waiting for the formal letter of approval from DOD.
- **The protocol was finally approved by HSRRB in July 2007 and clinical studies started**

Task 3: Phase I clinical trial with ^{177}Lu -J591 Dose fractionation regimen

- The Task 3 was started in the fall of 2007.
- A total of 22 patients have been treated and the MTD with the dose fractionation is regarded as 40 mCi/m² dose given twice two weeks apart. The results of this study as originally proposed in the grant application clearly demonstrates that the original intent of the SOW-3 has been met and can be considered completed.
- We formally wish to close out the HRPO protocol Log Number A-13087.1.
- Preliminary data from this trial was presented at the Genitourinary Cancer symposium in 2009.

Task 4: Phase 1 Clinical trial with Combination Therapy (^{177}Lu -J591 and Docetaxel)

- The design of Phase 1 protocol of combination therapy was finalized. The protocol was formally approved by IRBs at both Cornell and DOD (HSRRB)
- Each patient would receive Docetaxel (75 mg/m², given every 21 days) and will be assigned to one of the 5 dose levels of ^{177}Lu -J591 (20-40 mCi/m²).
- The goal is to study 5 groups starting with 20 mCi/m². The patient would first receive 4 weeks of Docetaxel and on week 5 and 7 would also receive ^{177}Lu -J591 dose. The plan is to recruit 3 patients in each group every 3 months.
- As of July 09, two patients were recruited into the trial and received the treatment dose.
- We hope to complete the recruitment before September 2010. The final data analysis will be completed after the patient recruitment is finished.

Key Research Accomplishments

A. Phase 1 dose-escalation studies with ^{177}Lu -DOTA-J591: Dose fractionation regimen (SOW Task-3)

Protocol: "Radioimmunotherapy Phase I Dose-Escalation Studies in Prostate Cancer Using ^{177}Lu -J591 Antibody: Dose Fractionation Regimen"

HRPO Log Number A-13087.1, submitted by Scott Tagawa, M.D.

Protocol summary: A phase I clinical protocol was designed to study the safety of fractionated dose administration of ^{177}Lu -J591 monoclonal antibody (mAb) to patients with progressive metastatic prostate cancer. Each patient would receive 2 doses given two weeks apart. Cohort 1 would receive 20 mCi/m² and 2 doses. Subsequently, the dose is escalated in 5 mCi/m² per cohort (3-6 subjects) up to 40 mCi/m² x 2 doses. Each patient is **followed for 14 weeks** following the administration of the second dose to determine hematological toxicity. The primary endpoint is to determine the dose limiting toxicity (DLT) and the cumulative maximum tolerated dose (MTD) of fractionated ^{177}Lu -J591 and the secondary endpoint is preliminary efficacy.

Results: A total of 22 patients have been treated (see table below), with the completion of Cohort 5 (40 mCi/m² x2). Median age is 71 (range 57-86), median baseline PSA 48.6 (5.1 – 517.3). 90% had bone mets and 43% extra-osseous visceral mets (lung, liver). Targeting of known sites of PC metastases was seen in the majority of patients.

All the enrolled subjects completed 14 week follow-up to determine hematologic toxicity. Despite achieving cumulative doses exceeding the single-dose maximum tolerated dose (70 mCi/m², a dose at which 40% require platelet transfusions), only 1 pt experienced reversible Gr-4 neutropenia and thrombocytopenia and one additional pt experienced reversible Gr-4 thrombocytopenia; no growth factors or transfusions have been needed. There was no Gr >1 non-hematologic toxicity. The MTD with the dose fractionation is regarded as 40 mCi/m² dose given twice two weeks apart.

Cohort	Dose mCi/m ²	No. of subjects	14 week Follow-up
1	20	3	Completed
2	25	3	Completed
3	30	4	Completed
4	35	6	Completed
5	40	6	Completed

Conclusions: Fractionated dose ^{177}Lu -J591 is well tolerated, with reversible myelosuppression. With dose-fractionation, subjects are able to tolerate higher cumulative doses than with single-dose ^{177}Lu -J591. The results of this Phase 1 dose escalation and dose fractionation study as originally proposed in the grant application (**Statement of Work 3**) clearly demonstrates that the original intent of the SOW-3 has been met and can be considered completed.

No additional patients will be recruited under this protocol.

We formally wish to close out the HRPO protocol Log Number A-13087.1.

B. Phase 1 Clinical trial with Combination Therapy (^{177}Lu -J591 and Docetaxel) (SOW, Task-4)

Protocol: "A phase I trial of docetaxel/prednisone plus fractionated ^{177}Lu -J591 anti-prostate-specific membrane antigen monoclonal antibody in patients with metastatic, castrate-resistant prostate cancer" **WCMC IRB#: 0812010139**

The design of Phase 1 protocol of combination therapy was finalized. The protocol was formally approved by IRBs at both Cornell and DOD (HSSRB). Each patient would receive Docetaxel (75 mg/m², given every 21 days) and will be assigned to one of the 5 dose levels of ^{177}Lu -J591 (20-40 mCi/m²). The goal is to study 5 groups starting with 20 mCi/m². The patient would first receive 4 weeks of Docetaxel and on week 5 and 7 would also receive ^{177}Lu -J591 dose. The plan is to recruit 3 patients in each group every 3 months.

Primary objective

- To determine the maximum tolerated dose of fractionated ^{177}Lu -DOTA-J591 administered concurrently with three weekly docetaxel for the treatment of patients with metastatic, castrate-resistant prostate cancer.

Secondary objectives

- To determine the toxicity profile of docetaxel with fractionated ^{177}Lu -DOTA-J591.
- To determine the tumor response rate.
- To define the PSA response rate across all dose levels.
- To define the duration of PSA response.
- To assess the overall and prostate cancer specific survival rate of patients following this combination treatment.

Key inclusion criteria:

- Histologic diagnosis of prostate adenocarcinoma.
- Patient must have progressive metastatic prostate cancer despite adequate medical or surgical castration therapy

Patient accrual:

Patients will receive docetaxel, 75 mg/m² every 21 days. In addition, patients will be assigned to one of five dose levels of ^{177}Lu -DOTA-J591 (Table 1). Patients will receive two infusions of ^{177}Lu -DOTA-J591 two weeks apart starting on 2-3 days prior to cycle 3 of docetaxel. Cycle 4 of docetaxel will be delayed until recovery from ^{177}Lu -DOTA-J591-associated hematologic toxicity. Patients will be followed for toxicity (Table 2).

Table 1: Dose Levels

^{177}Lu Dose level	Dose/Schedule
<u>1</u>	20 mCi/m ² /dose
<u>2</u>	25 mCi/m ² /dose
<u>3</u>	30 mCi/m ² /dose
<u>4</u>	35 mCi/m ² /dose
<u>5</u>	40 mCi/m ² /dose

Table 2: Dose Escalation Schedule

#DLT/#Patients	Decision
0/3	Escalate to the next higher dose
1/3	Add 3 patients at the same dose
1/6	Escalate to the next higher dose/Trial ends
> 2/3 or >2/6	Decrease dose for the next group of pts

These patients will be recruited from the patient population at Weill Cornell Medical College (WCMC)-New York Presbyterian Hospital (NYPH) Urology or Medical Oncology Clinics and Clinical and Translational Science Center (CTSC) as well as other participating centers. Drs. Tagawa and Nanus will see patients twice a week in the clinic. It is expected that 6-8 patients/month may be eligible to participate in the trial and 2-3 patients each month can be enrolled in this trial. Patients can only be recruited in the successive dose levels, only after follow-up to assess toxicity. Since a minimum of 15 and a maximum of 30 are planned for enrollment, we expect that the enrollment may be completed <18 months.

As of July 09, two patients were recruited into the trial and received the treatment dose.

We hope to complete the recruitment before September 2010. The final data analysis will be completed after the patient recruitment is finished.

Future plans:

We plan to continue the ^{177}Lu -J591 Phase I dose-fractionation protocol in order to expand the MTD cohort so that statistically meaningful efficacy data can be generated. We do, however, understand that efficacy assessment was not part of the original intent of the tasks described in the grant application. We will revise the current Cornell IRB and HRPO approved protocol (A-13087.1) to remove any reference to DOD and obtain the approval of Cornell IRB prior to recruitment of subjects. We also wish to assure that any future studies involving the ^{177}Lu -J591 dose-fractionation regimen will be conducted without the DOD funds.

Reportable Outcomes

Phase I trial of fractionated-dose ^{177}Lu -J591 radiolabeled antiprostata-specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu -J591) in patients (pts) with metastatic castrate-resistant prostate cancer (metCRPC).

Sub-category:

Early/Localized disease, Locally Advanced/Recurrent/Advanced disease, and Biology

Category:

Genitourinary Cancers

Meeting:

2009 Genitourinary Cancers Symposium

Abstract No:

172

Author(s):

Tagawa ST, Vallabhajosula S, Goldsmith SJ, Petrillo K, Matulich D, Kaplan J, Bander NH, Nanus DM; Weill Cornell Medical College, New York, NY

Abstract:

Introduction: A phase II trial of single-dose ^{177}Lu -J591 radioimmunotherapy (RIT) in pts with metCRPC confirmed previously described anti-tumor activity, excellent targeting of met sites, and acceptable toxicity with an apparent dose-response relationship [Tagawa et al, ASCO 2008]. Dose fractionation of RIT may decrease toxicity (myelosuppression) while maintaining or increasing efficacy [DeNardo et al, 2002].

Methods: In this phase I study, cohorts of 3-6 pts with progressive metCRPC receive 2 fractionated doses of ^{177}Lu -J591 2 weeks apart: Cohort 1 (20 mCi/m² x2), dose escalation 5 mCi/m² per dose per cohort. The primary endpoint is to determine dose limiting toxicity (DLT) and the cumulative maximum tolerated dose (MTD) of fractionated ^{177}Lu -J591 RIT with pharmacokinetics and dosimetry and secondary endpoints of efficacy. DLT was defined as Gr >3 hematologic toxicity or Gr >2 non-hematologic toxicity.

Results: Median age of the 11 treated pts is 78 (range 63-86), median baseline PSA 49.5 (23.7-265.9), 91% with ECOG PS 1, 9% ECOG 2. 82% had bone mets, 45% lymph node mets, and 36% extra-osseous visceral mets (lung). All pts had progressed after 1-3 hormonal therapies and 36% progressed on 1-4 lines of chemotherapy including docetaxel. No DLT's have been seen. 2 pts experienced reversible Gr 3 neutropenia and 1 Gr 3 thrombocytopenia; no growth factors or transfusions were needed. There was no Gr >1 non-hematologic toxicity. Overall, 5 of 11 pts experienced a PSA decline. Excluding the lowest dose-level, 63% experienced a PSA decline (with median time to progression of 20 weeks), 2 with >30% decline, 1 with >50% decline. Excellent targeting of known sites of PC metastases was seen in the majority of pts.

Conclusions: Fractionated dose ^{177}Lu -J591 is well tolerated, with reversible myelosuppression, demonstrating anti-tumor activity in pts with progressive metCRPC. The MTD has not yet been reached and enrollment continues on cohort 4 (35 mCi/m² x2) with plans to proceed to combination therapy with docetaxel.

Conclusions

- Fractionated dose ¹⁷⁷Lu-J591 is well tolerated, with reversible myelosuppression. With dose- fractionation, subjects are able to tolerate higher cumulative doses than with a single-dose ¹⁷⁷Lu-J591. The results of this Phase 1 dose escalation and dose fractionation study as originally proposed in the grant application (**Statement of Work 3**) clearly demonstrates that the original intent of the SOW-3 has been met and can be considered completed. We formally wish to close out the HRPO protocol Log Number A-13087.1.
- As of September 2009, two patients were recruited into a combination therapy (RIT + Docetaxel) phase I clinical trial and received the treatment dose. We hope to complete the recruitment in this study before September 2010. The final data analysis will be completed after the patient recruitment is finished.