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Award Number:

W81XWH-09-1-0596

TITLE: 'A Randomized Phase 2 Trial of 177Lu Radiolabeled Anti-PSMA Monoclonal Antibody J591 in Patients With High-Risk Castrate, Biochemically Relapsed Prostate Cancer'

PRINCIPAL INVESTIGATOR:

Scott T. Tagawa, MD

CONTRACTING ORGANIZATION:

Cornell University, Inc.
New York, NY 10021-4805

REPORT DATE:

SEPTEMBER 2010

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Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES					
14. ABSTRACT Clinical trial has received WCMC IRB and CTSC approval with enrollment of initial 3 subjects. Initial report submitted to WCMC DSMB with recommendation to proceed with enrollment.					
15. SUBJECT TERMS Prostate cancer, PSA, PSMA, monoclonal antibody, radioimmunotherapy					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 19	19a. NAME OF RESPONSIBLE PERSON USARMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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I. Introduction

Men with biochemically progressive (PSA only) prostate cancer have non-radiographically apparent micrometastases that may be targeted with radioimmunotherapy. Prostate specific membrane antigen (PSMA) is the single, most well-established, highly restricted prostate epithelial cell membrane antigen known and is expressed by virtually all prostate cancers. Investigators at WCMC have generated a high-affinity antibody (J591) against the external portion of PSMA that binds to viable PSMA-expressing cells and is internalized. The hypothesis is that the addition of ¹⁷⁷Lu-J591 to ketoconazole will improve time to radiographically apparent metastases in men with biochemically progressive non-metastatic CRPC.

In this multi-center, double-blind, randomized phase II trial involving men with relapsed prostate cancer and biochemical only (PSA) progression (no radiographic evidence of metastases) despite castration at high risk of early development of metastases. The primary endpoint will be to compare the percentage of men with metastases at 18 months receiving ketoconazole plus ¹⁷⁷Lu-J591 vs ketoconazole plus trace-labeled ¹¹¹In-J591 (i.e. placebo). Secondary endpoints include PSA response, toxicity, progression-free survival, overall survival, the ability of radiolabeled J591 to image otherwise non-radiographically apparent metastatic sites, the prognostic and predictive capability of circulating tumor cells, baseline adrenal androgen levels, and circulating markers of hemostatic activation, fibrinolysis, and angiogenesis. With a sample size of 127 (2:1 randomization), the study will have a ≥ 0.80 power with a pre-set alpha of 5% to determine an absolute difference in 18-month metastasis free survival. An interim analysis after 12 months of follow-up will be performed and reviewed by the external DSMB (necessitating increase in sample size by 10% to 140). Stopping limits will be imposed such that a significant observed difference in the metastasis-free proportion will be grounds for the consideration of early termination of the study using an adjusted significance level corresponding to the O'Brien-Fleming group sequential rule.

II. Body

Overview: The clinical trial has received WCMC IRB and CTSC approval and the initial subjects in the run-in safety phase have been enrolled and treated.

SOW Task 1a, 1b: PARTIALLY COMPLETED. Additional sites are in various stages of regulatory approval:

Scientific committee, radiation safety committee, IRB approved, site activated:

- University of Iowa
- Indiana University

Note: Site initiation visits performed with each site above and each site has been activated to begin enrollment as of August, 2010.

IRB Approval in progress:

- Jefferson Kimmel Cancer Center Thomas Jefferson University – scientific review in progress

- Emory University –scientific review approved, IRB and contract in progress
- University of Southern California – scientific committee approval, IRB reviewed, response to issues in process

Other sites

- University of Pennsylvania – scientific review in process
- Stanford University – scientific review on hold pending additional funding
- University of Utah - scientific review on hold pending additional funding
- University of Medicine and Dentistry, New Jersey – scientific review
- Nevada Cancer Institute – scientific review to begin
- University of Pittsburgh Medical Center - scientific review on hold pending additional funding
- University of Chicago – scientific re-review to begin
- University of Washington - scientific review on hold pending additional funding

Problem areas / solutions:

- a. Lengthy time for review/approval at additional sites – WCMC personnel continue to work with additional sites to aide in submission/approval process. The Study Chair (grant PI) and regulatory coordinator have increased communication with each site PI and regulatory personnel to assess and assist in the process. Since the last technical report, 2 sites have been activated. In communications with other sites, one common factor is financial. Although each site PI has completed an agreement to conduct the study with the current budget, we have discovered that others within the institution have assigned a lower priority to the protocol, as they may lose money in the conduct of the study. We are in the process of additional fundraising and anticipate the ability to increase per-subject reimbursement to sites by the next performance period.
- b. Longer time to gain additional site approval may lead to increased clinical trial performance time (and therefore delayed time to analysis of results) – In addition to corrective action above, WCMC is also considering adding additional sites and is currently fundraising in anticipation of this strategy (see above).
- c. High-risk patient population – WCMC has screened/pre-screened approx 12 patients for the 3 that have been enrolled/treated. Although there is a large (approx 700,000) number of patients with biochemical relapse in the U.S., based upon our strict enrollment criteria, there may only be approximately 50,000 men in the country meeting criteria for our study. Although we would prefer to keep this population pure in order to meet our endpoint in a timely manner (presence or absence of metastatic disease on scans at 18 months), we will consider an amendment in the future. We have recently received WCMC IRB approval for advertisements to increase referrals for enrollment and have obtained assistance from the Prostate Cancer Foundation. In addition, the study was presented at the 2010 ASCO annual scientific meeting where we had the opportunity to discuss with investigators and referring physicians.

In addition, we are currently in discussion with the Prostate Cancer Clinical Trials Consortium to open study via this mechanism

Task 1c: COMPLETED. Amendments have been approved by ORP and WCMC IRB

SOW Task 2a: See 1a/b above

Task 2b: Currently in safety lead-in phase

Task 2c: Weekly email communication with sites, phone/teleconferences when necessary; monthly teleconferences to start upon initiation of >1 additional site

Task 2d: Ongoing IRB and FDA updates; last DSMB review May, 2010.

SOW Tasks 3-5: Pending completion of Tasks 1-2

III. Key Research Accomplishments

- The protocol has been approved by the WCMC IRB and CTSC as well as ORP
- The study was presented as a poster presentation at the 2010 annual scientific meeting of the American Society of Clinical Oncologists (abstract and poster attached)

IV. Reportable Outcomes

Abstract: S.T. Tagawa, J. Osborne J, P. J. Christos, S. Vallabhajosula, K. Petrillo, K. Nadeau, L. Tyrell, H. Beltran, S. J. Goldsmith, D. M. Nanus. A randomized phase II trial of ¹⁷⁷Lu radiolabeled monoclonal antibody J591 (¹⁷⁷Lu-J591) and ketoconazole in patients (pts) with high-risk castrate biochemically relapsed prostate cancer (PC) after local therapy. J Clin Oncol 28: 15s, 2010 (suppl; Abstr TPS248)

Presentation: Poster presentation, 2010 ASCO Annual Meeting

V. Conclusions

Biochemical relapse is common after local therapy for prostate cancer. Based on the physical properties of ¹⁷⁷Lu and the disease targeting ability of J591, ¹⁷⁷Lu-J591 is ideally suited to make a significant impact on this state of disease. The protocol has been approved and activated at the initial sites and progress continues at additional sites.

VI. References

None used

VII. Appendices

Attachment 1: Tagawa et al. abstract, J Clin Oncol 28: 15s, 2010 (suppl; Abstr TPS248)

Attachment 2: Poster presentation

Attachment 3: Approval documents: (a) Most recent WCMC IRB approval document, (b) Most recent WCMC CTSC Approval, (c) Most Recent ORP Approval, and (d) Iowa IRB approval, (e) Indiana IRB approval

Abstract #50838

A randomized phase II trial of ^{177}Lu radiolabeled monoclonal antibody J591 (^{177}Lu -J591) and ketoconazole in patients (pts) with high-risk castrate biochemically relapsed prostate cancer (PC) after local therapy.

S. T. Tagawa, J. Osborne, P. J. Christos, S. Vallabhajosula, K. Petrillo, K. Nadeau, L. Tyrell, H. Beltran, S. J. Goldsmith, D. M. Nanus; Weill Cornell Medical College, New York, NY

Abstract Text:

Background: Biochemical recurrence without evidence of PC on standard CT/MRI and bone scans after local therapy is common. Salvage radiotherapy affords a cure to a proportion of pts with biochemical relapse, but most suffer disease progression because of micrometastatic PC outside of the radiation field. J591 is a monoclonal antibody that targets the extracellular domain of prostate specific membrane antigen (PSMA). A phase II trial of single-dose ^{177}Lu -J591 radioimmunotherapy (RIT) in pts with progressive, metastatic castration-resistant prostate cancer (CRPC) demonstrated excellent targeting of metastatic sites, efficacy, and acceptable toxicity [Tagawa et al, ASCO 2008]. In general, RIT appears to have its greatest impact in the setting of minimal disease [Kaminski NEJM 2005; Leonard JCO2005; Press JCO 2006] and the beta emission of ^{177}Lu is best suited for lesions 1-3 mm in diameter [O'Donoghue J Nuc Med 1995] (i.e. micrometastatic disease). **Methods:** Men with high-risk CRPC (PSA doubling time < 8 months and/or PSA > 20 [Smith JCO 2005]) and no evidence of disease on CT/MRI and bone scans are randomized in a 2:1 fashion to receive double-blinded ^{177}Lu -J591 vs ^{111}In -J591 (control) and will undergo planar gamma camera imaging with SPECT following infusion. All pts receive ketoconazole plus hydrocortisone. The primary endpoint of the study is 18-month metastasis-free survival. 140 pts will be treated to allow 80% power with a 2-sided alpha of 5% to detect a 25% absolute difference (50% vs 75% metastasis free) in radiographically apparent metastasis at 18 months (with interim analysis after 50% of pts have at least 12 months follow up). Secondary/exploratory endpoints include evaluation of radiolabeled J591 imaging to detect sites of metastases not apparent on standard CT/MRI and bone scan, validation of adrenal androgen levels as biomarkers for ketoconazole [Ryan Clin Cancer Res 2007], analysis of circulating tumor cells for PSMA expression and to predict the appearance of radiographic metastases, and exploration of plasma markers of hemostasis, fibrinolysis, and angiogenesis as biomarkers.

Title:

A randomized phase II trial of ^{177}Lu radiolabeled monoclonal antibody J591 (^{177}Lu -J591) and ketoconazole in patients (pts) with high-risk castrate biochemically relapsed prostate cancer (PC) after local therapy.

Submitter's E-mail Address:

stt2007@med.cornell.edu

Is this abstract a clinical trial?

Yes

Is this clinical trial registered?

Yes

Registry Name:

Clinicaltrials.gov

Registration Number:

NCT00859781

Research Funding Source:

Other

Research Funding Source Name:

DOD PCRP W81XWH-09-1-0596; PCF Young Investigator Award; 1-KL2-RR024997-

01; UL1-RR024996

Did the trial accrue its first patient before or after April 29, 2004?

After

Trial Type:

Phase II

Research Category:

Clinical

Received Grant funding:

No

All participants were over the age of 65:

No

Sponsor: Scott T. Tagawa, MD

Topic Selection:

Genitourinary Cancer: Prostate Cancer

First Author

Presenting Author

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[Click to view Conflict of Interest Disclosure](#)



A RANDOMIZED PHASE II TRIAL OF ^{177}Lu RADIOLABELED MONOCLONAL ANTIBODY J591 (^{177}Lu -J591) AND KETOCONAZOLE IN PATIENTS WITH HIGH-RISK CASTRATE BIOCHEMICALLY RELAPSED PROSTATE CANCER AFTER LOCAL THERAPY

Scott T. Tagawa, Joseph Osborne, Paul J. Christos, Shankar Vallabhajosula, Kristen Petrillo, Koty Nadeau, Lauren Tyrell, Himisha Beltran, Stanley J. Goldsmith, David M. Nanus
Weill Cornell Medical College, New York, NY

BACKGROUND

Radiolabeled J591

- J591 is a deimmunized anti-PSMA monoclonal antibody that binds to the extracellular domain of viable PSMA+ cells with rapid internalization [Liu et al. Cancer Res 1997; Liu et al. Cancer Res 1998]
- Phase I trials of radiolabeled J591 demonstrated safety, sensitive and specific tumor targeting, and preliminary evidence of activity [Mitrowsky et al. JCO 2004; Bander et al. JCO 2005]
- The MTD of ^{177}Lu -J591 was 70 mCi/m², with reversible myelosuppression
- Phase II single-dose ^{177}Lu -J591 Radioimmunotherapy (RIT) for metCRPC**
- Two successive cohorts of pts with progressive metCRPC received one dose of ^{177}Lu -J591: Cohort 1 (65mCi/m²), 15 pts; Cohort 2: (70mCi/m², phase I MTD), 17 pts. The 1st endpoint was PSA and/or measurable disease response with 2nd endpoint of toxicity. A ^{177}Lu -J591 imaging study was performed to confirm tumor targeting.
- Median age was 71 (range 51-88), median baseline PSA 81.6 (3.3 – 2184.6), 3 with ECOG PS 0, 27 PS 1, 2 PS 2; 97% had bone mets, 25% extra-osseous visceral mets (2 liver, 5 lung, 1 adrenal). The majority (18 pts, 56%) progressed on at least docetaxel.
- Overall, 3 (10%) experienced > 50% PSA decline and 10 (31%) experienced at least 30% PSA decline. Targeting of known sites of PC metastases was seen in 30 of 32 (94%) pts [Fig 1].
- More pts treated at the phase I MTD (70 mCi/m²) experienced PSA declines (71%) than those treated with 65mCi/m² (46%) [Fig 2].
- 9 pts received 1-4 platelet transfusions (median 2); no significant hemorrhagic complications occurred. Of 32 evaluable pts, 29 had return to normal platelet counts; the remaining 3 had progressive disease with marrow involvement on RM biopsy. 27% experienced transient Gr 4 neutropenia without fevers. No serious attributable non-heme toxicity occurred.
- Current/Future aims in metastatic CRPC**
- To develop biomarkers to optimally select pts (imaging may predict response, exploration of PSMA expression in CTCs), improve therapeutic profile with dose fractionation [Tagawa et al. ASCO 2010], and combine with chemo, utilizing improved tolerability of fractionated dose RIT + the radiosensitizing and debulking properties of docetaxel [Beltran et al. ASCO 2010].
- The optimal setting for anti-PSMA RIT may be micro-metastatic disease.

Supported by:

Department of Defense PC081664
NIH 1-K12-RR024997-01, P18P5405; UL1 RR024996 (WCMC CTSC)
Prostate Cancer Foundation
Clinicaltrials.gov NCT00859781

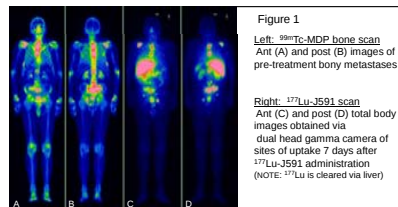


Figure 2



B Emitting Radionuclides: Rationale for ^{177}Lu -J591

	^{131}I	^{90}Y	^{177}Lu
Physical Half Life (days)	8.05	2.67	6.7
Beta Particles (mEV)	Maximum 0.61 Average 0.20	Maximum 2.280 Average 0.935	0.497 0.149
Range in Tissue (mm)	Maximum 2.4 Average 0.4	Maximum 12.0 Average 2.7	2.20 0.25
Gamma Emission (mEV)	0.364 (81%)	none	0.113-0.208 (7-13%)

^{177}Lu Lutetium

- Low energy particle with short range
- Allow higher doses with less marrow toxicity
- Gamma emission allows imaging
- May be suboptimal for bulky tumors (i.e. suboptimal for disease state tested to date: metastatic CRPC)
- Physical properties more optimal for curability in small tumors (1-3 mm) [O'Donoghue et al. J Nuc Med 2005]

Salvage Anti-PSMA Radioimmunotherapy

- Biochemical only relapse is common, affecting approximately 50,000 new men per year in the U.S. alone
- PC is radiosensitive; salvage radiotherapy is an effective salvage therapy for selected pts, but most eventually suffer distant relapse/progression because of micrometastatic disease outside of the RT field [Ward J Urol 2004; Freedland J Urol 2007; Pazzona J Urol 2005; Buskirk J Urol 2006; Stephenson JAMA 2004; JCO 2007]

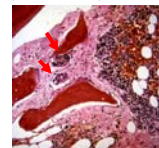


Figure 3

- Radioimmunotherapy may have greatest effect in setting of minimal disease [Kaminski Blood 2002; JCO 2005; NEJM 2005; Press Blood 2003; JCO 2006; Leonard JCO 2005]
- Nearly all prostate cancer cells express PSMA [Israeli Cancer Res 1994; Silver Clin Cancer Res 1997; Bostwick Cancer 1998; Wright Urol Oncol 1995; Wright Urology 1996]
- J591 targets known sites of disease with efficacy in the advanced setting
- ^{177}Lu is optimal for 1-2 mm lesions, i.e. micrometastatic (small volume) disease not apparent on standard scans (CT/MRI, bone scan)
- "Targeted radiotherapy" with ^{177}Lu -J591 may be able to eliminate sites of micrometastatic disease in the biochemically relapsed setting [O'Donoghue et al. J Nuc Med 2005]

Study Design

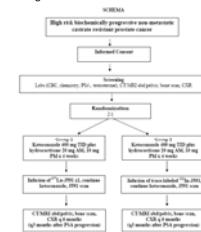
ENTRY CRITERIA (summary)

- Biochemical relapse after primary local therapy
- High risk castrate-resistant PSA progression
 - rising PSA despite medical/surgical castration and testosterone < 50 ng/mL [Smith et al. J Clin Oncol 2005]
 - absolute PSA > 20 and/or PSA DT < 8 mo
- CT/MRI and bone scan without evidence of metastatic disease
- Intact hematologic and organ function
- ECOG PS ≤ 2

RANDOMIZED Ph II: Lu-J591 in NONMETASTATIC CRPC

TREATMENT

- All pts: ketoconazole 400 mg TID + hydrocortisone 20 AM, 10 PM
- 2:1 randomization: single infusion of ^{177}Lu -J591 vs ^{111}In -J591 (mAb control)



- 1st endpoint: metastasis-free survival at 18 months
Based upon entry criteria, 50% expected to have mets at 18 months. With a sample size of 127 (2:1 randomization), ≥ 0.80 power with alpha of 5% to determine difference in 18-month metastasis free survival (75% vs 50%). Interim analysis after 50% of 18-month MFS events required for final analysis with futility analysis performed (increasing sample size to 140)
- 2nd endpoints: ability of radiolabeled J591 to image micrometastatic disease, PFS, adrenal hormone levels, hemostatic/fibrinolytic markers

SUMMARY

- Based upon the recurrence pattern of PC, J591's known ability to target sites of metastatic disease, and the physical properties of ^{177}Lu , anti-PSMA-based salvage RIT has the possibility of significantly impacting the natural course of relapsed prostate cancer

STATUS

- The study is open at WCMC and the initial subjects are accruing
- The study will open at sites throughout the United States



Weill Cornell Medical College

Rosemary Kraemer, Ph.D.
Director, Human Research Protections Programs
Division of Research Integrity
Research and Sponsored Programs
407 East 61st Street, RR-110
New York, New York 10065

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Fax: 646-962-0533
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June 10, 2010

Scott T. Tagawa, MD
Assistant Professor

Submission Type: Amendment

Protocol Number: 0810010067

Protocol Title: A Randomized Phase 2 Trial of Lu Radiolabeled Monoclonal Antibody HuJ591 (Lu-J591) and ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer after Local Therapy.

Nature of Amendment:

- Revised Investigator Initiated Protocol, Version 4 dated May 25, 2010
- Revised Informed Consent Form, Version 4 dated May 25, 2010

IRB Approval Date: June 10, 2010

Dear Dr. Tagawa:

The Institutional Review Board (IRB) has conducted an expedited review and approved the amendment to the abovementioned protocol.

Please do not hesitate to contact the IRB office staff if you have any questions or need assistance in complying with the terms of this approval.

Sincerely,

A handwritten signature in cursive script that reads "Rosemary Kraemer".

Rosemary Kraemer, Ph.D.
Director, Human Research Protections Program

Please note the following important information about this approval:

- Billing Compliance: This approval is contingent upon continued adherence with institutional billing compliance policies.

- Information about the WCMC-NYP IRBs: The Weill Cornell Medical College (WCMC)-New York Presbyterian (NYP) Institutional Review Boards (IRBs) are constituted as required by the Federal Office for Human Research Protections (OHRP). WCMC holds a Federalwide Assurance (FWA) with OHRP. The FWA number is FWA00000093. Both of the WCMC-NYP IRBs are registered on that FWA. The registration numbers for the IRBs are: IRB #1 IRB00000952; and IRB #2 IRB00004327. Should you need additional information about the terms of the WCMC FWA or the WCMC IRBs, please contact irb@med.cornell.edu.

Koty Nadeau

From: Kaarel T. Laev [ktl2001@med.cornell.edu]
Sent: Tuesday, August 24, 2010 12:47 PM
To: ktl2001@med.cornell.edu; kln2002@med.cornell.edu; stt2007@med.cornell.edu
Cc: yvh2001@med.cornell.edu
Subject: Review of 'Lu-J591 and ketoconazole for high-risk castrate non-metastatic prostate cancer'

Dear Dr. Tagawa:

Your application has been reviewed. Please see review below. To respond to any issues noted, you can log in to your protocol by opening your browser and copying the following URL into the address field:

<https://ctscweb7.ctsc.med.cornell.edu/WebCAMP/SourceCode/Login.cfm>

Review Details

Proposal Title: *Lu-J591 and ketoconazole for high-risk castrate non-metastatic prostate cancer*

Principal Investigator: *Scott T Tagawa, MD*

Date(s) of Review:

Outcome of Review: *Approved*

Comments

Versions 2,3 and 4 of the above Externally Reviewed and Approved Protocol were reviewed by the

CTSC via expedited review. You have uploaded into ePAR the IRB approval letter for these amendments, as well as the most recent IRB-stamped copies of all documents added and/or modified as the result of these amendments. Your protocol stands approved by the CTSC as amended as of August 24th, 2010. Formal approval letter to follow.



REPLY TO
ATTENTION OF

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MD 21702-5012

MCMR-RP

31 January 2010

MEMORANDUM FOR THE RECORD

SUBJECT: Initial Approval for the Protocol, "A Randomized Phase 2 Trial of ¹⁷⁷Lu Radiolabeled Monoclonal Antibody HuJ591 (¹⁷⁷Lu-J591) and Ketoconazole in Patients With High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy," Submitted by Scott T. Tagawa, MD, Weill Cornell Medical College, New York, New York, in Support of the Proposal, "A Randomized Phase 2 Trial of ¹⁷⁷Lu Radiolabeled Anti-PSMA Monoclonal Antibody J591 in Patients With High-Risk Castrate Biochemically Relapsed Prostate Cancer," Proposal Log Number PC081664, Award Number W81XWH-09-1-0596, IND # 11,613, IRB # 0810010067, HRPO Log Number A-15378.a

1. The subject protocol (version 2, dated 10/28/09; consent form revised 1/15/2010) was approved by the Weill Cornell Medical College Institutional Review Board (WCMC IRB) on 15 January 2010. This protocol was reviewed by the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) and found to comply with applicable DOD, U.S. Army, and USAMRMC human subjects protection requirements.
2. This greater than minimal risk study is approved for the enrollment of 25 subjects at the New York Presbyterian Hospital - Weill Cornell Medical College.
3. Please note the following reporting obligations. Failure to comply could result in suspension of funding.
 - a. Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the USAMRMC ORP HRPO for approval prior to implementation. Major modifications include changes in study design, a change in Principal Investigator, change or addition of an institution, change in age range, change in/addition to the study population, or a change that could potentially increase risks to subjects. All other amendments must be submitted with the continuing review report to the HRPO for acceptance.

MCMR-RP

SUBJECT: Initial Approval for the Protocol, "A Randomized Phase 2 Trial of ¹⁷⁷Lu Radiolabeled Monoclonal Antibody HuJ591 (¹⁷⁷Lu-J591) and Ketoconazole in Patients With High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy," Submitted by Scott T. Tagawa, MD, Weill Cornell Medical College, New York, New York, in Support of the Proposal, "A Randomized Phase 2 Trial of ¹⁷⁷Lu Radiolabeled Anti-PSMA Monoclonal Antibody J591 in Patients With High-Risk Castrate Biochemically Relapsed Prostate Cancer," Proposal Log Number PC081664, Award Number W81XWH-09-1-0596, IND # 11,613, IRB # 0810010067, HRPO Log Number A-15378.a

b. All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and related subject deaths must be promptly reported by phone (301-619-2165), by email (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

c. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

d. Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study must be reported to the HRPO as soon as the deviation is identified.

e. A copy of the continuing review report and the re-approval notification by the WCMC IRB must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the current approval by the WCMC IRB expires on 10 January 2011. Please note that the HRPO also conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

f. The final study report submitted to the WCMC IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

g. The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this research; the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any regulatory agencies including legal or medical actions; and any instances of serious or continuing noncompliance with the regulations or requirements must be reported immediately to the HRPO.

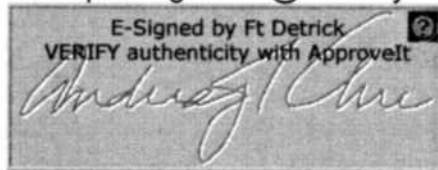
MCMR-RP

SUBJECT: Initial Approval for the Protocol, "A Randomized Phase 2 Trial of ¹⁷⁷Lu Radiolabeled Monoclonal Antibody HuJ591 (¹⁷⁷Lu-J591) and Ketoconazole in Patients With High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy," Submitted by Scott T. Tagawa, MD, Weill Cornell Medical College, New York, New York, in Support of the Proposal, "A Randomized Phase 2 Trial of ¹⁷⁷Lu Radiolabeled Anti-PSMA Monoclonal Antibody J591 in Patients With High-Risk Castrate Biochemically Relapsed Prostate Cancer," Proposal Log Number PC081664, Award Number W81XWH-09-1-0596, IND # 11,613, IRB # 0810010067, HRPO Log Number A-15378.a

4. Please Note: The USAMRMC ORP HRPO conducts random site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

5. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer or Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

6. The HRPO point of contact for this study is Paula Glauber, MS, RN, OCN, Human Subjects Protection Scientist, at 301-619-9267 or paula.glauber@us.army.mil.

An e-signature block from Ft Detrick. It includes the text "E-Signed by Ft Detrick" and "VERIFY authenticity with ApproveIt" above a stylized signature of Andrea J. Kline.

ANDREA J. KLINE, MS, CIP
Chief, Research Administrative Support
Human Research Protection Office
Office of Research Protections

INTERDEPARTMENTAL COMMUNICATION
Research Compliance Administration (RCA)
Indiana University - Purdue University Indianapolis

DATE: June 29, 2010

TO: Noah Hahn
Hematology/Oncology
RT 380
IUPUI

FROM: Sherri Ream
Research Compliance Administration

SUBJECT: Final Approval

Study Number: 1004-12

Study Title: A Randomized Phase 2 Trial of 177Lu Radiolabeled Monoclonal Antibody HuJ591 (177Lu-J591) and Ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer after Local Therapy

The study listed above has received final approval from the Institutional Review Board (IRB-02). Please note that subjects must be provided with and sign a current informed consent document containing the IRB approval stamp.

Special requirements for the inclusion of prisoners: Please note that unless your study has received approval for the inclusion of prisoners, you may not enroll and/or otherwise involve a prisoner in your study. Special requirements apply if an individual enrolled on the study either is a prisoner or has become a prisoner during the course of his/her study participation (and the study has not been previously granted approval for the enrollment of prisoners as a subject population). If the investigator becomes aware that a subject is a prisoner, all research interactions and interventions with the prisoner-participant must cease. If the investigator wishes to have the prisoner-participant continue to participate in the research, Research Compliance Administration (RCA) must be notified immediately (317-274-8289). In most cases, the IRB will be required to re-review the protocol at a convened meeting before any further research interaction or intervention may continue with the prisoner-participant. Refer to the IUPUI/Clarian Standard Operating Procedure (SOP) on *Vulnerable Populations* for further information. The SOP is available at http://researchadmin.iu.edu/Forms/human_subjects/hs_iupui/Standard_Operating_Procedures%2003%2008.pdf.

As the principal investigator of this study, you assume the responsibilities as outlined in the SOP on *Responsibilities of Principal Investigators*, some of which include (but are not limited to):

1. **CONTINUING REVIEW** - A status report must be filed with the IRB at least annually. The RCA staff will generate these reports for your completion. This study is approved from June 22, 2010 to April 20, 2011. If your study is not re-approved by this date, the study will automatically expire, which means that all research activities, including enrollment of new subjects, interaction and intervention with current participants, and analysis of identified data, must cease.
2. **STUDY AMENDMENTS** - You are required to receive prospective approval from the IRB for ANY changes to the research study, including changes to protocol design, dosages, timing or type of test performed, population of the study, and informed consent statement, prior to implementation. This request is made via an amendment form, which can be obtained at: http://researchadmin.iu.edu/HumanSubjects/IUPUI/hs_forms.html.
3. **UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS AND NONCOMPLIANCE** - You must promptly report to the IRB any event that appears on the **List of Events that Require Prompt Reporting to the IRB**. Refer to the SOP on *Unanticipated Problems Involving Risks to Subjects or Others and Noncompliance* for more information and other reporting requirements. The SOP can be found at: http://researchadmin.iu.edu/Forms/human_subjects/hs_iupui/Standard_Operating_Procedures%2003%2008.pdf. NOTE: If the study involves gene therapy and an event occurs which requires prompt reporting to the IRB, it must also be reported to the Institutional Biosafety Committee (IBC).
4. **UPDATED INVESTIGATIONAL BROCHURES, PROGRESS REPORTS and FINAL REPORTS** - If this is an investigational drug or device study, updated clinical investigational brochures must be submitted as they occur. These are submitted with an amendment form. Progress or final reports must be provided to the IRB with your written assessment of the report, briefly summarizing any changes and their significance to the study.
5. **ADVERTISEMENTS** - You can only use IRB-approved advertisements to recruit participants for your study. If you will be advertising to recruit study participants and the advertisement was not submitted to the IRB at the time your study was reviewed and approved, a copy of the information contained in the advertisement and the mode of its communication must be submitted to the IRB as an amendment to the study. These advertisements must be reviewed and approved by the IRB PRIOR to their use.
6. **STUDY COMPLETION** - You are responsible for promptly notifying the IRB when the study has been completed (i.e. there is no further subject enrollment, not further interaction or intervention with current participants, including follow-up, and no further analysis of identified data). To notify the IRB of study completion, please obtain a Continuing Review - Closeout Report form at http://researchadmin.iu.edu/HumanSubjects/IUPUI/hs_forms.html and submit it to the RCA office.
7. **LEAVING THE INSTITUTION** - If the principal investigator leaves the Institution, the IRB must be notified as to the disposition of EACH study.

PLEASE REFER TO THE ASSIGNED STUDY NUMBER AND THE EXACT TITLE IN ANY FUTURE CORRESPONDENCE WITH OUR OFFICE. In addition, SOPs exist which cover a variety of topics that may be relevant to the conduct of your research. Please visit http://researchadmin.iu.edu/Forms/human_subjects/hs_iupui/Standard_Operating_Procedures%2003%2008.pdf for a current copy of the IUPUI SOPs for Research Involving Human Subjects. All documentation related to this study must be neatly typed and must also be maintained in your files for audit purposes for at least three years after closure of the research; however, please note that research studies subject to HIPAA may have different requirements regarding file storage after closure. If you have any questions, please call Research Compliance Administration at 317/274-8289.

Please see the IRB approval email attached to this document, as well as the Documentation of Review and Approval, for a list of all documents approved with this submission.



**Human Subjects Office/
Institutional Review Board (IRB)**

105 Hardin Library for the Health Sciences
600 Newton Road
Iowa City, Iowa 52242-1098
319-335-6564 Fax 319-335-7310
irb@uiowa.edu
<http://research.uiowa.edu/hso>

IRB ID #: 200910726

To: Daniel Vaena

From: IRB-01 DHHS Registration # IRB00000099,
Univ of Iowa, DHHS Federalwide Assurance # FWA00003007

Re: A Randomized Phase 2 Trial of 177Lu Radiolabeled Monoclonal Antibody HuJ591 (177Lu-J591) with Ketoconazole in Patients with High Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy

Protocol Number:
Protocol Version: 4
Protocol Date: May 25, 2010
Amendment Number/Date(s): 1 - 10/28/2009
2 - 01/15/2010
3 - 05/25/2010

Approval Date: 09/04/10

**Next IRB Approval
Due Before:** 06/24/11

Type of Application:

- ☐ New Project
☐ Continuing Review
☒ Modification

Type of Application Review:

- ☐ Full Board:
Meeting Date:
☒ Expedited

☐ Exempt

Approved for Populations:

- ☐ Children
☐ Prisoners
☐ Pregnant Women, Fetuses, Neonates

Source of Support: Weill Cornell Medical College (WCMC)

Investigational New Drug/Biologic Name: (177)Lu-DOTA-HuJ591-GS Antibody
Investigational New Drug/Biologic Number: 11,613
Name of Sponsor who holds IND: Matthew I. Milowsky, MD

Investigational Device Name:
Investigational Device Number:
Sponsor who holds IDE:

This approval has been electronically signed by IRB Chair:
J. Andrew Bertolatus, BA, MD
09/04/10 2234

OFFICE OF THE VICE PRESIDENT
FOR RESEARCH

IRB Approval: IRB approval indicates that this project meets the regulatory requirements for the protection of human subjects. IRB approval does not absolve the principal investigator from complying with other institutional, collegiate, or departmental policies or procedures.

Agency Notification: If this is a New Project or Continuing Review application and the project is funded by an external government or non-profit agency, the original HHS 310 form, "Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption," has been forwarded to the UI Division of Sponsored Programs, 100 Gilmore Hall, for appropriate action. You will receive a signed copy from Sponsored Programs.

Recruitment/Consent: Your IRB application has been approved for recruitment of subjects not to exceed the number indicated on your application form. If you are using written informed consent, the IRB-approved and stamped Informed Consent Document(s) are attached. Please make copies from the attached "masters" for subjects to sign when agreeing to participate. The original signed Informed Consent Document should be placed in your research files. A copy of the Informed Consent Document should be given to the subject. (A copy of the *signed* Informed Consent Document should be given to the subject if your Consent contains a HIPAA authorization section.) If hospital/clinic patients are being enrolled, a copy of the signed Informed Consent Document should be placed in the subject's chart, unless a Record of Consent form was approved by the IRB.

Continuing Review: Federal regulations require that the IRB re-approve research projects at intervals appropriate to the degree of risk, but no less than once per year. This process is called "continuing review." Continuing review for non-exempt research is required to occur as long as the research remains active for long-term follow-up of research subjects, even when the research is permanently closed to enrollment of new subjects and all subjects have completed all research-related interventions and to occur when the remaining research activities are limited to collection of private identifiable information. Your project "expires" at 12:01 AM on the date indicated on the preceding page ("Next IRB Approval Due on or Before"). You must obtain your next IRB approval of this project on or before that expiration date. You are responsible for submitting a Continuing Review application in sufficient time for approval before the expiration date, however the HSO will send a reminder notice approximately 60 and 30 days prior to the expiration date.

Modifications: Any change in this research project or materials must be submitted on a Modification application to the IRB for prior review and approval, except when a change is necessary to eliminate apparent immediate hazards to subjects. The investigator is required to promptly notify the IRB of any changes made without IRB approval to eliminate apparent immediate hazards to subjects using the Modification/Update Form. Modifications requiring the prior review and approval of the IRB include but are not limited to: changing the protocol or study procedures, changing investigators or funding sources, changing the Informed Consent Document, increasing the anticipated total number of subjects from what was originally approved, or adding any new materials (e.g., letters to subjects, ads, questionnaires).

Unanticipated Problems Involving Risks: You must promptly report to the IRB any serious and/or unexpected adverse experience, as defined in the UI Investigator's Guide, and any other unanticipated problems involving risks to subjects or others. The Reportable Events Form (REF) should be used for reporting to the IRB.

Audits/Record-Keeping: Your research records may be audited at any time during or after the implementation of your project. Federal and University policies require that all research records be maintained for a period of three (3) years following the close of the research project. For research that involves drugs or devices seeking FDA approval, the research records must be kept for a period of three years after the FDA has taken final action on the marketing application.

Additional Information: Complete information regarding research involving human subjects at The University of Iowa is available in the "Investigator's Guide to Human Subjects Research." Research investigators are expected to comply with these policies and procedures, and to be familiar with the University's Federalwide Assurance, the Belmont Report, 45CFR46, and other applicable regulations prior to conducting the research. These documents and IRB application and related forms are available on the Human Subjects Office website or are available by calling 335-6564.