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

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

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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.
**4. TITLE AND SUBTITLE**

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

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

Cornell University, Inc
New York, NY 10021

**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

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**16. SECURITY CLASSIFICATION OF:**

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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 $^{177}$Lu-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 $^{177}$Lu-J591 vs ketoconazole plus trace-labeled $^{111}$In-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 $\geq 0.80$ 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


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 $^{177}$Lu and the disease targeting ability of J591, $^{177}$Lu-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
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.


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-J951 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 where over the age of 65:
No
Sponsor: Scott T. Tagawa, MD
Topic Selection:
Genitourinary Cancer: Prostate Cancer
First Author
Presenting Author
Scott T. Tagawa, MD
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Click to view Conflict of Interest Disclosure
A RANDOMIZED PHASE II TRIAL OF 177Lu RADIOLABELED MONOCLONAL ANTIBODY J591 (177Lu-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 Pettrillo, Kota Nadeau, Lauren Tyrell, Himisha Beltran, Stanley J. Goldsmith, David M. Nanus
Well Cornell Medical College, New York, NY

BACKGROUND

Salvage Anti-PSMA Radioluminotherapy
• J591 is a dimerized anti-PSMA monoclonal antibody that binds to the extracellular domain of viable PSMA+ cells with rapid internalization
• Phase I trials of radionuclide-labeled J591 demonstrated safety, sensitive and specific tumor targeting, and preliminary evidence of activity

Salvage Anti-PSMA Radioluminotherapy endpoints: ability of radiolabeled J591 to image micrometastatic disease

Radioemitting Radionuclides: Rationale for 177Lu-J591

177Lu-J591 Imaging Study

Figure 1

177Lu vs 111In-J591 (mAb control)

Figure 2

B Emission Radionuclides: Rationale for 177Lu-J591

Figure 3

Salvage Anti-PSMA Radioluminotherapy Study Design

SUMMARY

TREATMENT

• All pts: ketoconazole 400 mg TID + hydrocortisone 20 AM, 10 PM
• 2:1 randomization: single infusion of 177Lu-J591 vs 1nJ591 (ratio control)

ENTRY CRITERIA (summary)

• Biochemical relapse after primary local therapy
• High-risk castrate-resistant PSA progression

Physical properties more optimal for small (1-3 mm) disease

Beta Particles (mEv)

Average

Minimum

Maximum

177Lu

0.20

0.149

0.935

131I

0.61

0.61

0.61

90Y

Not available

Not available

Not available

Beta Particle Range in Tissue (mm)    Average

Minimum

Maximum

177Lu

2.280

2.280

2.280

131I

1.3

1.3

1.3

90Y

4.0

4.0

4.0

Status

• 1 endpoint: metastasis-free survival at 18 months

Based upon entry criteria, 50% expected to have mets at 18 months. With a sample size of 137 (2:1 randomization), a 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)

• 2 endpoints: ability of radiolabeled J591 to image micrometastatic disease, PFS, adrenal hormone levels, hemostatic/fibrinolytic markers

177Lu vs 111In-J591

Figure 3

B Emission Radionuclides: Rationale for 177Lu-J591

Figure 2

B Emission Radionuclides: Rationale for 177Lu-J591

Figure 1

177Lu vs 111In-J591 (mAb control)
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,

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 FWA0000093. 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.
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.ctse.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.
MEMORANDUM FOR THE RECORD

31 January 2010

SUBJECT: Initial Approval for the Protocol, “A Randomized Phase 2 Trial of $^{177}$Lu Radiolabeled Monoclonal Antibody HuJ591 ($^{177}$Lu-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 $^{177}$Lu 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 $^{177}$Lu Radiolabeled Monoclonal Antibody HuJ591 ($^{177}$Lu-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 $^{177}$Lu 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 $^{177}$Lu Radiolabeled Monoclonal Antibody HuJ591 ($^{177}$Lu-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 $^{177}$Lu 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.

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 Hud591 (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_iupui/standard_operating_procedures%20.03%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/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_iupui/standard_operating_procedures%20.03%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, no 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/human_subjects_iupui/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_iupui/standard_operating_procedures%20.03%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.
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: Modification

Type of Application Review: 
Full Board: 
Meeting Date: 
Expedited

Approved for Populations: 
Children
Prisoners
Pregnant Women, Fetuses, Neonates
Exempt

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
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.