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

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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. Studies utilizing J591 radiolabeled with Lutetium-177 (^{177}Lu) have demonstrated safety, efficacy, and accurate, selective tumor targeting in the metastatic castration-resistant prostate cancer (CRPC) setting. The physical properties of ^{177}Lu are best suited for 1-3 mm tumors (those not seen on standard imaging modalities). 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 ≥ 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

As part of the initial tasks, appropriate language incorporating the USAMRMC, ORP, and HRPO elements to the protocol was inserted and subsequently approved by the WCMC IRB and CTSC, the FDA, and ORP, delaying start of the study. Following initiation at WCMC, completion of the study has been delayed for a number of reasons which are continuing to be addressed.

Accrual to the study has been much slower than anticipated. The study was designed to target a subset of a large patient population. Though as many as 50,000 men in the U.S. per year suffer from biochemical recurrence after surgery and/or radiation, only a fraction of them meet the high risk criteria as written into the study. Based upon the science of

the treatment combined with the statistical design and the fact that several large phase III studies have recently been completed with nearly identical inclusion criteria, we believe that the basic study design should not be changed at this point. However, it is quite clear that multiple sites are required to complete the study in a timely manner. This was recognized from the start, but the length of time required to initiate additional sites has been significantly longer than expected. Despite fairly universal scientific interest in the study and initial verbal and written agreements, several sites have stalled or withdrawn due to a number of reasons. Therefore we have taken several steps to address this issue.

Based upon feedback obtained from each site that chose not to participate in the study after the start-up process had already begun, one of the main concerns has been financial worry from the institution. Sub-site investigators have generally agreed to participate based upon their enthusiasm for the study drug and the belief that they could participate in the study with better reimbursement than a NCI cooperative group study; however, many of their institutions have disagreed. The funds from the PCRP Clinical Trial Award cover only preparation of the study drug, personnel expenses at WCMC, and a fraction of the built-in correlative studies. We have been able to enhance this by 1) leveraging the award to obtain additional grant support from the Prostate Cancer Foundation, NIH (via the CTSA), additional DOD funds (via the PCCTC), and 2) by increasing philanthropic support, which is funding the additional sites. In addition, the previous Clinical Research Organization (CRO), Genexion, has been dismissed and a new CRO (Pharmatech) has been contracted and is facilitating site start-up with the initial promise of 25 subjects within 12 months at 5 sites. This process has taken longer than anticipated, but their contract is being renewed for another year as the start-up process has started or continues at several sites. Should this relationship prove fruitful, it is anticipated that we will expand the contract to increase sites and subject numbers. It should be noted that WCMC and the PI have been able to leverage DOD funds via the PCMRP Clinical Trial Award with DOD funds via the PCCTC in combination with funds from the Prostate Cancer Foundation, NIH funds via the CTSA, and philanthropic funds to initiate and continue this study.. Based upon this additional support, we have essentially been able to double the amount of per-subject reimbursement for other sites, significantly increasing interest in participation. One interesting secondary endpoint has been the ability of radiolabeled J591 to image sites of disease that were previously not apparent on standard imaging. However, because of the study design with at least a month of hormonal therapy prior to treatment/imaging and the advent of improved imaging (immuno-PET) this has become less important. As most sites are using a significant amount of their per-subject budget on this study procedure, it is important to re-consider this approach. In fact, some sites declined the study because of the cost of this scan. We have conducted an interim futility analysis and have determined that more images should be performed with the plan to repeat an interim analysis in the future. Should it be determined by our statistical team that this secondary endpoint is futile, an amendment will be submitted to drop this scan. We have 5 actively accruing outside sites for this secondary endpoint.

The WCMC study team has met with the study statistician and discussed with several site PI's about the possibility of an amendment to increase accrual and speed to study

completion. A teleconference including the PI from each site is being scheduled for October, 2015. It is anticipated that a modification to entry criteria removing the requirement for prior prostatectomy or prostate radiation (providing that there is no evidence of significant prostatic disease on digital rectal exam and multiparametric MRI). In addition, a statistical re-design is anticipated to decrease the total “n” for the study while keeping the endpoints objective and clinically meaningful.

Overview of study sites:

- Weill Cornell Medical College: Approximately 30 pre-screen failures, 2 screen failures, 6 subjects randomized
- University of Iowa: 1 screen failure, 5 subjects randomized
- Indiana University: 1 screen failure, 13 subjects randomized
- University of Southern California: 2 screen failures, 3 subjects randomized
- Emory University – 0 screen failures, 0 subjects treated
- Cedars Sinai Medical Center – 1 screen failure, 0 subjects treated
- University of Utah – 1 screen failure, 3 subjects randomized
- University of Kansas Medical Center – 2 screen failures, 3 subjects randomized
- Georgetown University – 1 screen failures, 1 subject randomized
- University of Arizona – 1 pre-screen failure; 0 subjects treated
- UF Health (Orlando) – 1 subject randomized
- University of Pittsburgh Medical Center – 0 subjects randomized, 1 in screening

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

IRB Approved:

- Weill Cornell Medical College
- University of Iowa
- Indiana University
- University of Southern California
- Emory University
- Cedars Sinai Medical Center
- University of Utah
- Kansas University Medical Center
- Georgetown University
- University of Arizona
- UF Health - Orlando
- University of Pittsburgh Medical Center
- North Shore Hematology (not open to accrual, pending lutetium license)

Sites pending regulatory review:

- Cookeville Regional Medical Center – contract finalized, pending reviews
- University of Hawaii Cancer Center – contract in progress
- Durham VA – budget and contract process in progress
- Queens Medical Center – start up in progress
- Puerto Rico site pending review by radiation safety officer assessing feasibility of shipping study drug

The study was initially primarily offered via the CTSA and PCCTC groups, has now expanded to additional sites and the Pharmatech network.

SOW Task **1a,b,c**: Amendments have been approved by ORP and WCMC IRB

Task **2a,b**: See above

Task **3a,b,c**: Safety lead-in phase completed, reported, reviewed by DSMB

Task **4a**: see above

Task **4b**: Weekly email communication with sites, phone/teleconferences on a regular basis.

Task **4c**: Ongoing IRB and FDA updates; last full DSMB submission July 2014.

Additional plans for recruitment: One of the most common reasons for ineligibility is the requirement to fall into the high-risk group based upon PSA kinetics or high absolute value. Many potential subjects may not be eligible at initial evaluation, but could become eligible at future time points. We have been in discussion with several of the lower accruing sites. In addition to obtaining a HIPAA waiver for pre-screening and establishing a “pre-screening log” designed to allow potential subjects to be followed, we will also be able to analyze data on pre-screen “failures”. The PI has plans to travel to lower accruing sites to additionally identify reasons for low accrual, meet with study team members to discuss strategies to increase accrual, and to deliver a scientific lecture to members of institution at a forum such as grand rounds or tumor board which will highlight the study and increase referrals. Organizations such as the PCF have recognized the merit of our approach and have highlighted this study.

III. Key Research Accomplishments

Recurrent prostate cancer is a significant problem and the development of metastatic disease is associated with morbidity and mortality. Prostate specific membrane antigen is the single most well-established, highly specific prostate epithelial cell membrane antigen known. It is highly over-expressed in the castrate state, and is accurately targeted by J591. Systemic radionuclide therapy has recently been approved for men with symptomatic metastatic CRPC to bone (Rad223, Xofigo ®) leading to excitement within the field. A more tumor-targeted approach utilizing J591 is of increased importance. The recent publication of our prior multicenter phase II study of ¹⁷⁷Lu-J591 in men with metastatic CRPC in *Clinical Cancer Research* (attached) has generated renewed scientific and clinical interest. In addition, recent studies utilizing J591-based immuno-PET imaging providing additional evidence that micrometastatic sites of disease can be identified by J591 have reinforced our hypothesis. One potential drawback of this approach is the theoretical long-term toxicity due to radiation to bone marrow. Our

recent publication which evaluated long-term follow up after anti-PSMA radioimmunotherapy with radiolabeled J591 provides additional safety data (attached).

- The protocol has been approved by the WCMC IRB and CTSC as well as ORP, 11 investigational sites activated as of September 2014
- WCMC has contracted Pharmatech to assist with identification of additional sites and facilitate regulatory start-up and patient enrollment (committed to patient enrollment of 25 per year).
- A subject recruitment advertisement has been approved by the WCMC IRB and have received assistance from the Prostate Cancer Foundation, with success via increase in exposure and referrals following a press release in December, 2013. Plans are to utilize these approved “ads” in collaboration with personnel at each active site. The Study Chair will be visiting slow enrolling sites to increase enrollment.

IV. Reportable Outcomes

None since October 2014

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 included with this report.

VII. Appendices

Attachment 1: Approval documents: (a) Most recent WCMC IRB approval document



Weill Cornell Medical College

Institutional Review Board
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November 5, 2014

Scott T. Tagawa, M.D.

Submission Type:	Continuing Review with Amendment
Protocol Number:	0810010067R006
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
Status of IRB Protocol:	Open
Risk Level:	Greater than Minimal Risk
Amendment Summary:	The following individuals are being added as co-investigators on the protocol and will be involved in study-related procedures: Ana Molina, MD and Meghan Moran, NP.

Dear Dr. Tagawa,

The renewal for the abovementioned protocol was reviewed at the **November 5, 2014** meeting of the Institutional Review Board IRB Cancer #2.

The protocol and its relevant documents stand approved for the following period:

- Consent Form
- HIPAA Authorization Form
- Subject Materials: FACT-P Questionnaire, Brochure, Information Sheet, and Medication Diary
- Adverse Event & IND Safety Reporting Cumulative Table
- Deviation Log

Approved: November 5, 2014

Expires: November 4, 2015

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 Kracmer, 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.
- **Immediate Reporting:** Investigators must follow the Immediate Reporting Policy at http://weill.cornell.edu/research/research_integrity/institutional_review_board/irb_adv.html

- Failure to comply with IRB directives within specified time frames may result in federally mandated penalties, up to and including suspension or termination of IRB approval and mandatory reporting to the Federal government.
- **Human Gene Transfer:** If this is a human gene transfer protocol, it is a term and condition of IRB approval that the principal investigator obtains Institutional Biosafety Committee (IBC) approval of all amendments prior to initiation, reportable adverse events as per WCMC policy, and annual reports as per M-I-C-3 of the NIH Guidelines for Research Involving Recombinant DNA Molecules. View the IBC website at http://weill.cornell.edu/research/research_integrity/ibc.html or contact ibc@med.cornell.edu if you require assistance in complying with these requirements.
- **Other reporting:** The reporting requirements of various regulatory bodies may differ with regard to both what must be reported and when. You are responsible for acquainting yourself with and abiding by all applicable federal and state regulatory reporting requirements.
- **Changes to this protocol:** If you want to change this research in any way or if any unanticipated hazardous conditions emerge affecting the rights or welfare of the human subjects involved in it, you must submit an amendment detailing these changes to the IRB for review and approval prior to implementing those changes. If the CTSC is used, the changes must also be submitted to the Translational Research Advisory Committee (TRAC). It is your responsibility to obtain approval for any such changes prior to initiating them.
- **Continuing approval:** You will receive a reminder via email for continuing review of this protocol in advance of the expiration date. The continuing review forms must be filed with the IRB sufficiently early to permit timely review and approval if the project is to continue beyond the period for which it was approved. Please note, no study related activities can continue beyond the WCMC IRB expiration date, including subject recruitment, enrollment, intervention and data analysis.
- **If your research study involves human tissues:** In addition to IRB approval, Section 4.4 of the hospital By-Laws "Specimens Removed During Resective Surgery" requires that all specimens removed during surgical diagnostic procedures that will be used for research must be approved by Pathology Service. Information about Pathology review can be found online at http://www.med.cornell.edu/research/for_pol/forms/Pathology_Review_Instructions.pdf
- **If the IRB is requiring that you obtain informed consent from subjects:** The signed IRB approved consent forms must be kept in the subject's hospital chart. If the subject has no New York Presbyterian Hospital chart, you are responsible for retaining such signed forms in your research files.
- **Information about the WCMC IRBs:** The Weill Cornell Medical College (WCMC) Institutional Review Board (IRB) is 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. The WCMC IRB is registered on that FWA. The registration number for the IRB is: General IRB #1 IRB00009417, General IRB #2 IRB00009418, Cancer IRB#1 IRB00009420, Cancer IRB#2 IRB00009421 and Expedited IRB IRB00009419. Should you need additional information about the terms of the WCMC FWA or the WCMC IRBs, please refer to http://weill.cornell.edu/research/research_integrity/institutional_review_board/index.html.
- Note that new federal legislation took effect April 7, 2008, (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html>), requiring that all peer-reviewed journal articles resulting from NIH supported research be deposited in PubMed Central, the NIH free digital archive of biomedical and life sciences journal literature, and be made publicly available within twelve months of publication. The Library and RASP have prepared general information which you can see at: <http://library.med.cornell.edu/FacPub/nihpolicy.html>
- The International Committee of Medical Journal Editors (ICMJE) has established a requirement that all clinical trials be entered in a public registry before the onset of patient enrollment as a condition of consideration for publication. Additional information may be found at <http://clinicaltrials.gov/> and at http://www.icmje.org/clin_trialup.htm Please contact the Protocol Registration System ("PRS") administrator by e-mail at octa@med.cornell.edu to set up a PRS user account to register new and ongoing investigator-initiated clinical trials. The e-mail should contain the PIs full name, department, phone number and e-mail address.