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

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**ABSTRACT**

Clinical trial has received WCMC IRB and CTSC approval with enrollment of initial 5 subjects at WCMC. An additional 33 subjects enrolled (28 treated) at participating sub-sites. Reports submitted to WCMC DSMB in July 2014 with approval to proceed without modifications.
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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 (\(^{177}\text{Lu}\)) have demonstrated safety, efficacy, and accurate, selective tumor targeting in the metastatic castration-resistant prostate cancer (CRPC) setting. The physical properties of \(^{177}\text{Lu}\) are best suited for 1-3 mm tumors (those not seen on standard imaging modalities). The hypothesis is that the addition of \(^{177}\text{Lu}\)-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 \(^{177}\text{Lu}\)-J591 vs ketoconazole plus trace-labeled \(^{111}\text{In}\)-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

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. 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. It is anticipated that a limited number of sites in Europe (to be funded by a separate mechanism) will be initiated in 2015 to assist with accrual. 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 are in the process of collecting all scans performed to date for an interim futility analysis. Should it be determined by our statistical team that this secondary endpoint is futile, an amendment will be submitted to drop this scan. We now have 10 active outside sites.

Overview of study sites:
- Weill Cornell Medical College: Approximately 30 pre-screen failures, 2 screen failures, 5 subjects randomized
- University of Iowa: 1 screen failure, 4 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, 2 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 Pittsburg Medical Center – completing contract

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 (contract in progress)
- Cedars Sinai Medical Center
- University of Utah
- University of Kansas Medical Center
- Georgetown University
- University of Arizona
- UF Health - Orlando
- University of Pittsburgh Medical Center (contract in progress)

IRB Approval in progress:
- Vanguard Urology, Houston, TX – budget/contract approval in process; IRB review pending

The study is currently being primarily offered via the CTSA and PCCTC groups

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. At WCMC, a new protocol is being submitted to the Clinical Study Evaluation Committee with the plan to submit to the IRB upon approval. This study will help us track patients with castration-resistant, biochemically recurrent prostate cancer on a prospective basis. We expect that this prospective registry will “feed” our $^{177}$Lu-J591 randomized study. 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 are highlighting this study (see attachment).

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 $^{177}$Lu-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


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

Attached

VII. Appendices


Attachment 2: Kaur et al, Plenary Session 2, 7th International Conference on Thrombosis and Hemostasis Issues in Cancer, Bergamo, IT, May 2014

Attachment 3: Tagawa et al, J Clin Oncol 32:5s, 2014 (suppl; abstr 5064)
Attachment 4: Tagawa et al, Poster Presentation ASCO 2014 Annual Meeting

Attachment 5: PCF research highlight, March 2014

Attachment 6: Approval documents: (a) Most recent WCMC IRB approval document
multivariate analyses were performed to identify independent VTE predictors.

**Results:** From June 2010 to June 2013, 1,322 ambulatory patients were evaluated for a new diagnosis of cancer; 13 on oral anticoagulation at the moment of enrollment were excluded from the analysis leaving 1,309 patients for evaluation. Complete follow up was available for the whole population. The mean age of the study population was 62.3 years, and 63% of patients were men; 897 patients (68.5%) were on chemotherapy. At the end of follow up, 66 patients (5.04%) had a VTE. At the univariate analysis among the traditional cardiovascular risk factor smoking and hypertension were significantly associated with an increased risk of VTE (OR 2.45, 95% CI 1.31, 4.59 and 1.63, 95% CI 1.00, 2.66 respectively) whereas DM, obesity and dyslipidemia were not. Furthermore, age, previous VTE, very high risk cancer type (stomach and pancreas) and presence of metastasis were significantly or marginally significant associated with an increased risk of VTE (p < 0.10). At the multivariate analysis only previous VTE and very high risk cancer type remained significantly associated with an increased risk of VTE (OR 13.77, 95% CI 6.94, 27.34 and 2.31, 95% CI 1.29, 4.13 respectively) whereas association with all the other variables including smoking and hypertension disappeared. Results of subgroup analyses including only patients undergoing chemotherapy during follow up period gave similar results (data not shown).

**Conclusions:** The role of traditional cardiovascular risk factors in the pathogenesis of cancer related VTE appeared limited. Other studies are necessary to confirm our preliminary findings.
Conclusions: Activation of the hemostatic and fibrinolytic systems and angiogenesis is common in cancer and generally increases with more advanced stages of prostate cancer and in advanced solid tumors. Increased hemostatic activation, fibrinolysis, and angiogenesis can be measured in peripheral blood and is prognostic for overall survival.

Table 1

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Plenary Session 3: Bleeding complications, microangiopathies and thrombocytopenias

OC-05
Clinical evidence for a link between microparticle-associated tissue factor activity and overt disseminated intravascular coagulation in patients with acute myelocytic leukemia

J. Thaler, I. Pabinger, C. Ay
Medical University of Vienna, Austria

Introduction: Recently, Gheldof and colleagues found that highly procoagulant microparticles (MPs) are released from the NB4 acute promyelocytic cell line. A large part of these MPs expressed tissue factor (TF) in addition to phosphatidylserine on the surface [1].

Aim: We determined MP-TF activity levels in AML patients with- or without overt disseminated intravascular coagulation (DIC) or acute venous thromboembolism (VTE) to investigate the role of TF-bearing MPs in AML-related coagulation disorders.

Methods: MP-TF activity was measured according to a standardized protocol for a chromogenic MP-TF-dependent factor Xa generation assay. Seven patients with AML were included: 2 patients had overt DIC, 3 patients had acute VTE and 2 patients neither had DIC nor VTE.

Results: We detected highly elevated MP-TF activity (4.43 pg/mL and 3.16 pg/mL, respectively) in the 2 AML patients with overt DIC, which decreased to 0.1 pg/mL and 0.0 pg/mL, after cessation of DIC. In the other AML patients MP-TF activity was low. D-dimer levels were highly elevated in the two AML patients with overt DIC (D-dimer: 57.71 μg/mL and 51.63 μg/mL, respectively) and 19-fold increased compared to the other patients. Only in these two AML patients the percentage of blast cells in the peripheral blood smear was high (20% and 32%, respectively). MP-TF activity, D-dimer, thrombocyte count and fibrinogen levels during the course of DIC are shown for the two patients with overt DIC (Figure 1A and 1B).

Conclusions: In this study we demonstrate that MP-TF activity is highly elevated during AML-related overt DIC and low after cessation. To our surprise MP-TF activity was low in AML patients with acute VTE.

Reference:

OC-06
Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism receiving anticoagulation


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Introduction: Guidelines recommend similar antithrombotic therapy for cancer patients with pulmonary embolism (PE) or deep vein thrombosis (DVT), even though their natural history has not been thoroughly studied.

Our clinical data strongly supports the experimental data by Gheldof and colleagues. Taken together, these two studies provide strong evidence for a determining role of TF-bearing MPs in the pathogenesis of overt DIC in patients with AML.
Plasma markers of hemostatic activation, fibrinolysis, and angiogenesis in prostate cancer and advanced solid tumors: Relationship to stage and prognosis

Gurveen Kaur, Adam Ireland, Paul Christos, Marina Mikhail, John Chapin, David M. Nanus, Scott T. Tagawa
Division of Hematology & Medical Oncology
Weill Cornell Medical College

Disclosures for
Scott T. Tagawa, MD, MS

In compliance with CME policies, 7th ICTHIC requires the following disclosures, related to the speaker's presentation, to the session audience:

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Background

- Carcinoma has long been associated with thrombotic and hemostatic complications
- Cancer + VTE is associated with poorer overall survival
- Even in the absence of overt thrombosis, many patients with cancer have elevated plasma markers of hemostatic activation and fibrinolysis
- Inflammatory and angiogenic systems are closely linked to hemostasis/fibrinolysis

Hypothesis

- Subjects with cancer will have detectable, often elevated plasma markers of hemostatic activation, fibrinolysis, and angiogenesis
- Levels of markers are associated with malignant disease stage
- Levels of markers are associated with prognosis

References:

Bouillaud, Arch Gen Med 1823
Prandoni, Blood 2002

Trousseau, Clin Med Paris 1865

Blom, JAMA 2005
Rickles, Cancer Metastasis Rev 1992

Chew, Arch Intern Med 2006
Rickles, Pathophysiol Haemost Thromb 2003

Levitan, Medicine 1999
Donati, Pathophysiol Haemost Thromb 2003
Methods: Entry Criteria

- No history of VTE, no current anticoagulation
- One of 5 cohorts prior to treatment:
  - Clinically localized prostate cancer (PC) prior to prostatectomy
  - Biochemically recurrent, non-metastatic PC prior to hormonal therapy (BRPC)
  - Castration-resistant, non-metastatic PC (M0 CRPC)
  - Advanced PC prior to hormonal therapy (APC)
  - Metastatic, refractory non-prostate solid tumors (AST)

---

1 Tagawa et al, ICTHIC 2007 & BJUI 2008
2 Arnason et al, ICTHIC 2012
3 clinicaltrials.gov NCT00859781
4 clinicaltrials.gov NCT00997677; Pail et al AACR 2014

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Adapted from Scher et al.

**“Clinical States”**

- Clinically Localized Disease
- Rising PSA
- Clinical Metastases Non-Castrate
- Castrate Metastatic Disease
- Death from other causes

---

Adapted from Scher et al.
Methods: Entry Criteria

- No history of VTE, no current anticoagulation
- One of 5 cohorts prior to treatment:
  - Clinically localized prostate cancer (PC) prior to prostatectomy\(^1\)
  - Biochemically recurrent, non-metastatic PC prior to hormonal therapy (BRPC)\(^2\)
  - Castration-resistant, non-metastatic PC (M0 CRPC)\(^3\)
  - Advanced PC prior to hormonal therapy (APC)\(^2\)
  - Metastatic, refractory non-prostate solid tumors (AST)\(^4\)

Methods (cont)

- Platelet-poor plasma collected via non-traumatic peripheral venipuncture in 2.3% sodium citrate\(^1\)
- Analyzed by ELISA for:
  - D-dimer (DD)
  - Thrombin-antithrombin complex (TAT)
  - Interleukin 6 (IL-6)
  - Interleukin 8 (IL-8)
  - Tissue factor (TF)\(^2\)
  - Vascular endothelial growth factor (VEGF)

---

2. Arnason et al, ICTHIC 2012
3. clinicaltrials.gov NCT00859781
4. clinicaltrials.gov NCT00967577; Pail et al AACR 2014

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1 – some assays in PC group with additional aprotinin, benzamidine, EDTA
2 – not analyzed in PC group
Methods (cont)

• Wilcoxon rank-sum test used to compare median baseline values across cohorts
• Median overall survival (OS) for each cohort estimated using Kaplan-Meier
• Hazard ratios for OS analyzed using log-rank (both continuous and median values used)
  – Analysis for metastatic cohorts

Results: Demographics

• N = 217
• 208 (95.9%) men; 9 women

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• AST Cohort: 5 men, 9 women
  – Lung (adenocarcinoma or mixed = 5), pancreatic (2), urothelial (2), 1 each: colon, GE Jxn, ovarian, renal cell, mucosal melanoma
## Results: Marker values

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## Results: Cohort comparison (1)

- Compared to PC (reference group)
- **D-dimer**
  - Prostate cancer: Increased with castration-resistance (p=0.07; n=5) and advanced disease (p<0.0001)
  - Higher in AST (p=0.001)
- **TAT**
  - Higher in all cohorts (p<0.0001)
Results: Cohort comparison (2)

- Compared to PC (reference group)
- **IL-6**
  - Increased with BRPC (p<0.0001) and advanced disease (p<0.0001)
  - Higher in AST (p<0.0001)
- **IL-8**
  - Higher in AST (p<0.0001)
- **VEGF**
  - Higher in AST (P=0.004)

Results: Cohort comparison (3)

- Compared to all prostate cancer cohorts (including the advanced prostate group), very late stage disease (AST) had higher levels of:
  - D-dimer (p=0.037)
  - TAT (p=0.013)
  - **IL-6** (p=0.034)
  - **IL-8** (p<0.0001)
Results: Prognosis (1)

• In univariate analysis including all subjects, as continuous variables, markers were prognostic for OS:
  – D-dimer: HR 1.001 (p<0.0001)
  – IL-6: HR 1.036 (p<0.0001)
  – IL-8: HR 1.007 (p<0.0001)
  – VEGF: HR 1.009 (p<0.0001)

Results: Prognosis (2)

• Death events driven by advanced stage pts (only 2 deaths in non-metastatic disease)
• In analysis of metastatic pts only (i.e. controlling for stage), as continuous variables, markers were prognostic for OS:
  – D-dimer: HR 1.001 (p=0.007)
  – IL-6: HR 1.022 (p=0.007)
  – IL-8: HR 1.005 (p=0.004)
  – VEGF: HR 1.020 (p<0.0001)
  – TAT: HR 1.091 (p=0.003)
Results: Prognosis (3)

• Prognostic value in metastatic pts dichotomized at median marker values:
  – D-dimer: HR 4.55 (p=0.01)
  – IL-6: HR 7.85 (p<0.001)
  – IL-8: HR 33.10 (p<0.0001)
  – VEGF: HR 3.23 (p=0.02)
  – TAT: HR 7.38 (p<0.001)

HR = 4.55
95% CI = 1.4, 14.8
p=0.01
HR = 7.85
95% CI = 2.2, 27.8
P<0.0001

HR = 33.10
95% CI = 6.4, 171.8
P<0.0001
Overall Survival by VEGF (dichotomized at median value)

HR = 3.23
95% CI = 1.1, 9.2
P=0.02

Overall Survival by TAT (dichotomized at median value)

HR = 7.38
95% CI = 2.0, 26.9
P<0.0001
Conclusions

• Consistent with hypothesis (and previous results), plasma markers of hemostatic activation, fibrinolysis, and angiogenesis are detectable in patients with cancer
• Levels of markers are associated with stage
• Levels of markers are strongly associated with prognosis, even when controlling for stage

ACKNOWLEDGEMENTS

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Michael Smith

Biostatistics & Epidemiology
Madhu Mazumdar
Paul Christos

PATIENTS AND THEIR FAMILIES

Weill Cornell Medical College
Why prostate cancer?

- I am a GU oncologist
- PC is the most common cancer in U.S. men, 2nd leading cause of cancer deaths
- Medicare claims: PC 3rd most common cancer associated with VTE, also associated with clinical fibrinolysis
- Subclinical activation of hemostasis and fibrinolysis previously demonstrated with PC
  - Higher than age-matched controls
  - Associated with surgical bleeding

Levitan, Medicine 1999  Tagnon, Cancer 1953
Kohli, Semin Thromb Hemost 2003  Tagawa BJU Int 2008
Kohli, Blood Coagul Fibrinolysis 2002
Phase I trial of docetaxel/prednisone plus fractionated dose radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody $^{177}$Lu-J591 in patients with metastatic, castration-resistant prostate cancer (mCRPC).


Weill Cornell Medical College, University of North Carolina Chapel Hill

Background- Docetaxel remains a standard agent for mCRPC and has radiosensitizing properties. $^{177}$Lu-J591 delivered with fractionated dosing leads to less myelosuppression while maintaining efficacy in mCRPC. This study was designed to determine the safety, dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of fractionated $^{177}$Lu-J591 administered concurrently with standard docetaxel.

Methods- Men with progressive mCRPC received docetaxel 75 mg/m$^2$ every 3 weeks with escalating 2 fractionated doses of $^{177}$Lu-J591 (initial dose 20 mCi/m$^2$ x2 up to max of 40 mCi/m$^2$ x2) with cycle 3. Cycle 4 of docetaxel was planned 6 weeks after cycle 3 to allow for recovery from $^{177}$Lu-J591-associated hematologic toxicity. DLT was defined as delay in docetaxel >3 weeks, prolonged myelosuppression or need for >2 platelet (plt) transfusions, febrile neutropenia, or grade >2 non-heme toxicity following $^{177}$Lu-J591. PSA was assessed prior to each cycle and CTC count (CellSearch) was assessed at baseline and after $^{177}$Lu-J591.

Results- 15 men with median age 67.3 (range 49.2-80.8), PSA 84.3 (17-776), 73.3% with elevated LDH, 71.4% unfavorable CTC counts received up to the highest anticipated dose (40 mCi/m$^2$ x2). No DLT was seen at any dose level. Significant toxicity was limited to reversible myelosuppression. Gr 4 ANC without fever occurred in 3 (20%) and Gr 4 pltts in 2 (13.3%), with 2 receiving prophylactic plt transfusion. No Gr >2 non-heme toxicity was reported. 13 had PSA decline, with 11 (73.3%) and 12 (80%) having >50% and >30% PSA decline respectively. All 14 evaluable men had decline (85.7%) or persistently undetectable (14.3%) CTC counts, with 78.6% having CTC counts decline by >50% and 78.6% having favorable counts after $^{177}$Lu-J591. Of 10 analyzed to date, all had targeting of known sites of disease by planar $^{177}$Lu-J591 imaging.

Conclusion- The combination of fractionated dose $^{177}$Lu-J591 and docetaxel/prednisone is well tolerated in patients with mCRPC. Without pre-selection, accurate targeting of known sites of disease and a strong preliminary efficacy signal was observed.
**Phase I trial of docetaxel/prednisone plus fractionated dose radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody 177Lu-J591 in patients with metastatic, castration-resistant prostate cancer (mCRPC)**


Weill Cornell Medical College, New York, NY and University of North Carolina, Chapel Hill, NC

**BACKGROUND**

- J591 is a deimmunized anti-PSMA monoclonal antibody that binds to the extra-cellular domain of PSMA+ cells with rapid internalization (Lu et al, Cancer Res 1998; Lu et al, Cancer Res 1999).
- 177Lu is a low energy β particle along with a gamma emission which allows imaging. The short range of its β emission is ideal for 1-3 mm tumor masses (although it may be suboptimal for bulky tumors)
- Lu-J591 is a deimmunized anti-PSMA monoclonal antibody that binds to the extra-cellular domain of PSMA+ cells with rapid internalization (Lu et al, Cancer Res 1998; Lu et al, Cancer Res 1999).
- 177Lu-J591 confirmed the hypothesis that fractionation has less myelosuppression, with higher cumulative doses achieved with less toxicity while maintaining efficacy
- Escalate to the next higher dose / Trial ends
- Decision

**METHODS**

**Enrollment, Baseline Characteristics**

- 15 subjects enrolled May 2009 – Sep 2013 at two institutions (3 pts in Cohort 1: 20 mCi/m^2, 4 pts in Cohort 2: 30 mCi/m^2, 4 pts in Cohort 3: 35 mCi/m^2, 4 pts in Cohort 4: 40 mCi/m^2)
- Baseline characteristics listed in Table 1 below (similar between cohorts)

**RESULTS**

- 10 (71.4%) with unfavorable counts
- 14 of 14 evaluable men had decline or persistently favorable CTC counts
- For the entire study, 11 (73.3%) with > 50% PSA decline, 13 (86.7%) any decline
- Subjects at the highest anticipated dose level were able to receive 75 mg/m2 of docetaxel q3 weeks (with a 3-wk pause for radioimmunotherapy)
- Without pre-selection for PSMA expression, accurate targeting of known sites of disease and a strong preliminary efficacy signal for the combo was observed

**CONCLUSIONS**

- The combination of fractionated dose 177Lu-J591 and docetaxel/prednisone was well tolerated with metastatic castrate-resistant prostate cancer
- Subjects at the highest anticipated dose level were able to receive 75 mg/m2 of docetaxel q3 weeks (with a 3-wk pause for radioimmunotherapy)
VISION: Conquer prostate cancer.
MISSION: Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of men experiencing the impact of the disease.

PCRP Commitment to Imaging Research

In 2014, more than 233,000 new cases of prostate cancer are estimated to be diagnosed and nearly 30,000 lives will be lost due to the disease. Although prostate cancer is a very serious, potentially lethal disease in its more aggressive forms, most men diagnosed with the disease do not die from it. The prostate cancer community recognizes that overdiagnosis and overtreatment of men with non-life-threatening prostate cancer is highly problematic and that there is a critical need to develop better tools to detect and diagnose only clinically significant prostate cancer. Between 2009 and 2012, the PCRP Integration Panel (IP), consisting of patient advocates, physician scientists, and laboratory researchers, bringing together their dedication to conquering prostate cancer, developed a strategy to more specifically address the critical needs of prostate cancer patients. To that end, the IP initiated the PCRP Overarching Challenges to encourage applicants for PCRP funding to (1) develop better tools to detect clinically relevant disease in asymptomatic men, (2) distinguish aggressive from indolent disease in men newly diagnosed with prostate cancer, and (3) develop effective treatments and address mechanisms of resistance for men with high-risk or metastatic prostate cancer. In addition, to maintain a broad portfolio of research that seeks to better understand and treat prostate cancer using a diversity of approaches, all PCRP-funded research must address at least one of seven PCRP focus areas. Two key focus areas with the ultimate goal

» continued, SEE COMMITMENT, PG. 4

PCRP-Funded Investigators in Imaging Research Work toward Improving Prostate Cancer Detection, Diagnosis, and Treatment

In prostate cancer, a recognized need persists to develop an accurate, noninvasive test that can discriminate clinically significant, life-threatening (aggressive) disease from that which is indolent and non-life-threatening. Existing methods of detection, such as elevated blood prostate-specific antigen (PSA) as a marker for prostate cancer, have contributed to overdiagnosis and overtreatment of men with non-life-threatening prostate cancer. In addition, conventional prostate biopsy after detection of elevated PSA may miss as much as 30% of the aggressive forms of prostate cancer. As a result, more-precise imaging procedures are needed to guide prostate biopsies to the most dangerous areas of the tumor and to detect metastatic spread of cancer cells. Moreover, new imaging procedures will assist with better treatment planning for patients with early-stage disease and those with more aggressive prostate cancer, as well as assessing their response to therapy. To that end, the PCRP has funded
During the 1990s, radiation therapy was proven to be curative for most patients with early-stage, localized prostate cancer. However, for some patients, curative doses were not proven to be curative for most patients. Research to the uncertain position of the prostate.

Contributions to improving prostate cancer outcomes resulted from the innovation of radiation therapy delivery technologies. One such example is prostate cancer bone metastases. Another promising approach targeting PSMA, developed by Dr. Martin Pomper of Johns Hopkins University, a FY05 PCRP awardee, uses a small-molecule PSMA binding agent that is attached to a radioactive positron emitting atom (fluorine-18) that can be visualized using a positron emission tomography (PET) scanner. Dr. Pomper demonstrated that this small-molecule PSMA probe originally described by Kozlowski and coworkers could be used to image prostate tumors in animals. Following its success, this technology was patented and then licensed to a pharmaceutical company that went on to develop closely related derivatives, which are currently in Phase II clinical trials to evaluate their utility in imaging prostate cancer metastases in patients.

Another molecular imaging approach for cancer, called metabolic imaging, takes advantage of differences in metabolism between cancer and normal cells. Choline is an essential dietary nutrient that is used to fuel the metabolism of cancer cells to metastatic sites in lymph nodes and bone. Referring to 18F-choline PET, Dr. Kwee notes, “One of the most exciting potential applications still being investigated is its use in individualizing cancer treatment, whereby images obtained with PET are used to help plan treatment at the earlier stages and select molecularly targeted therapy at more advanced stages.”

Along this same line of harnessing differences in cancer metabolism to select the most appropriate treatment for a patient, the PCRP has funded several investigators who are using alternative advanced magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS) methods to identify metabolites as biomarkers (e.g., citrate, spermine, choline, creatine) for distinguishing aggressive from indolent prostate cancer. Dr. Leo Cheng of the Massachusetts General Hospital, with funding from a FY03 PCRP award, used a specialized diagnostic technique called high-resolution magic-angle spinning MRS to study prostatectomy.
Taking Prostate Cancer Personally

Craig Pynn
Author of “One Man’s Life-Changing Diagnosis: Navigating the Realities of Prostate Cancer” (Demos Health, 2012)
PCRP Consumer Reviewer

“I knew something was really wrong when I looked down and saw all that blood in the urinal.”

So began Craig’s journey with high-risk, locally advanced prostate cancer. Shortly after he was diagnosed in January 2009, his urologist told him it was a “nasty, out of the box” cancer. Subsequent tests confirmed that the blood he saw was a direct result of prostate cancer.

“When I was diagnosed, about the only thing I knew about this cancer was that it was pronounced prostate and not prostrate.” The reality of hearing those words no guy ever wants to hear—you have prostate cancer—was the same as for every other man: a life-changing diagnosis with a very steep learning curve.

“My journey with this cancer has distinct dimensions—a three-stranded cord, if you will.”

First, there’s the clinical strand. Since the cancer had already escaped his prostate and invaded his urethra, surgery wasn’t an option. “My doctors recommended an aggressive course of treatment, and I’m sure glad they did.”

Forty-two sessions of radiotherapy and three years on hormone therapy have resulted in Craig having an undetectable prostate-specific antigen for more than four years.

“But since it escaped my prostate before I was diagnosed, I wake up each morning knowing that one of these days the cancer could come roaring back.”

Then, there’s what Craig calls the emotional/relational strand. Prostate cancer is rightly called a “couple’s disease,” and Craig’s wife, Susan, has been a loving and supportive partner, knowing too well how hormone therapy affects an intimate relationship. Complicating matters is Susan’s own chronic disease, multiple sclerosis.

“We had always assumed that I would be the healthy caregiver,” Craig says. “We have learned to love each other more deeply and take it slowly, one day at a time. We give thanks for each new day that we are together.”

The third strand is the spiritual dimension. “There is no more effective reminder of your mortality than hearing you have cancer,” Craig notes. “I always had a faith in God, but it’s not until a serious crisis comes along, and you have to deal with the Why me? and It’s so unfair questions, that you come to know what you really believe.”

“When I was diagnosed, I felt really alone. I wanted to know how other men felt. And what they feared.”

Craig discovered it wasn’t difficult to find men who had been diagnosed and treated for prostate cancer. But they were often unwilling to talk openly about their experience—especially their feelings and their fears. They’d say, “Yes, I had prostate cancer, but I’ve had surgery and I’ve moved on. Cancer is in my past.”

“So, I went looking for a book written by a man who had prostate cancer that dealt with cancer’s psychological and spiritual impact.” He found books written by women who had breast cancer that described their emotional battles and spiritual journeys. “I guess few men want to write about how they feel, or what they feared,” Craig observes.

“As an engineer, I’m pretty data-driven, so I started scouring the Internet—not just for clinical information but also for men’s personal stories. Happily, I found quite a few. And that helped.”

Wanting to record his own story, Craig started a journal. “I especially wanted to record my own feelings and fears as I underwent treatment. Eventually, writing became my daily personal therapy.”

Craig’s journal grew longer as he explored more and more of his own chronic disease, multiple sclerosis.

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Craig’s journal grew longer as he explored not just his own treatment experience and...
feelings, but also widened his research to the demographics, economics, medical controversies, and advocacy issues surrounding prostate cancer.


“My passion has become helping guys like me (as the book’s title says) navigate the realities of prostate cancer.” In addition to counseling newly diagnosed men one-on-one, Craig is active in prostate cancer advocacy, including participating with the advocacy organizations Us Too International, Malecare, and ZERO: The End of Prostate Cancer, the latter of which conducts an annual summit where participants gather in Washington, DC, to advocate for prostate cancer research funding, particularly for the innovation- and impact-based Department of Defense Prostate Cancer Research Program (PCRP), with their own senators and congresspersons.

“My passion is talking with newly diagnosed men and their spouses, and helping them make those decisions I had to make alone,” Craig emphasizes. “But equally rewarding has been my privilege to be a Consumer Reviewer for the PCRP. My four years (so far) helping to identify the best research or make a positive difference for men like me have been a fabulous learning experience as I’ve learned just how enormously complex prostate cancer is, and why it is such a challenge to eradicate this scourge.

But perhaps the most outstanding aspect of being a Consumer Reviewer has been to meet and work with the dedicated scientists and PCRP staff who are just as passionate about conquering this cancer as we guys who actually have the disease. It is difficult to imagine a more fulfilling way of giving back and helping ensure that the thousands of men who follow me will not only benefit from the terrific work being accomplished by PCRP-funded scientists, but that they will never have to experience those dark fears of feeling so alone when they hear those four awful words, you have prostate cancer.”

of developing better treatment planning for patients with early-stage or aggressive prostate cancers are biomarkers and imaging. In 2013, encouraged by Congress’s recognition of the lack of reliable diagnostic tools for guiding early detection and treating prostate cancer, the PCRP resolved to increase the focus on research with near-term clinical impact, with emphasis on the advancement of prostate cancer imaging technologies.

The PCRP has had a longstanding commitment to improving the detection and diagnosis of prostate cancer through imaging technologies, as evidenced by investments in imaging studies dating back to 1997 and representing 210 studies totaling over $80.2 million (M) in PCRP funding. These projects range from exploratory studies aimed at generating highly innovative and cutting-edge new imaging technologies and contrast agents to clinical imaging studies that have the potential to transform prostate cancer clinical care. The following innovation-based award mechanisms have proven to be a successful avenue for supporting imaging advances: Idea Development Award (91), New Investigator Award (42), Exploration - Hypothesis Development Award (16), Synergistic Idea Development Award (10), and Training Awards (43). The accompanying articles—“Featured Opinion,” by fiscal year 2013 (FY13) IP member Dr. Robert Gillies, and “PCRP-Funded Investigators in Imaging Research Work Toward Improving Prostate Cancer Detection, Diagnosis, and Treatment,” describe imaging projects funded by the PCRP that have led to major advancements for prostate cancer patients, with many ongoing studies in development or in early stages of clinical application.

Since the introduction of the PCRP overarching challenges and focus areas in FY09, the program has supported 49 awards in prostate cancer imaging research representing an investment of more than $19M. These awards have been made to 28 institutions across 19 states. In addition, the PCRP has developed new award mechanisms that focus on clinically relevant near-term investigations with an eye on impacting patient care and addressing the overarching challenge to develop better tools, including those relevant to imaging, for the detection and diagnosis of prostate cancer. The PCRP Biomarker Development Award was introduced in 2012 to fund studies that will advance prostate cancer biomarkers, including those that can be assessed using noninvasive or minimally invasive new imaging technologies or in biofluids (e.g., blood, urine), into the clinical setting. Specifically, this award supports high-impact research aimed at multi-institutional validation and/or qualification of prostate cancer biomarkers for crucial decision-making in prostate cancer management. Also introduced in 2012, the PCRP Transformative Impact Award supports multi-institutional research with near-term clinical relevance such as translational research, clinical research, and/or clinical trials that may include imaging studies, provided they have the potential to make a revolutionary impact on the clinical management of prostate cancer. For these new mechanisms, as with all PCRP awards, researchers must clearly demonstrate the potential of the study to contribute significantly to the elimination of death from prostate cancer and/or enhance the well-being of men experiencing the impact of the disease.

Since its inception in 1997 and over its 17-year history of congressional support, the PCRP has funded a large number of basic, translational, and clinical research studies using medical imaging technologies. The PCRP continues to encourage such applications that take advantage of revolutionary advances in prostate cancer imaging, and it especially seeks applications that address the critical needs of prostate cancer patients.
In April 2013, the PCRP established Brief details for the anticipated FY14 Since 2009, the PCRP-funded Prostate Important information for FY14 PCRP showing a drop in the intensity of hyperpolarized lactate a mouse prior to and following 2 days of imatinib treatment Metabolic imaging of a prostate cancer bone metastasis in tumors in the bone and decreases in the metabolic conversion of pyruvate into lactate in response to a conventional cytotoxic drug (paclitaxel) and molecular therapy targeting the tumor vasculature (imatinib), respectively. These methods are currently being used in ongoing clinical trials to determine if prostate cancer patients are responding to treatment. Another imaging approach that holds promise for detection of aggressive prostate cancer is ultrasound. Dr. Ethan Halpern of Thomas Jefferson University was funded by the PCRP between FY00 and FY05 to study intermittent ultrasound using a micro-bubble contrast agent in patients in hopes of improving the detection of prostate cancer during prostate biopsies. He showed that contrast-enhanced ultrasound provided a significant improvement in discriminating between benign and malignant areas within the prostate. This technique improves a clinician’s ability to detect malignant areas of the prostate, thereby reducing the need for repeated biopsies and providing a more accurate assessment of the aggressiveness of the disease. In a subsequent study, Dr. Halpern went on to show that contrast-enhanced ultrasound-guided biopsy significantly improves detection of high-grade prostate cancer (Gleason score 7 or greater). He notes, “Although these contrast-enhanced ultrasound techniques are not perfect, they provide the best available real-time technique for discriminating patients with clinically significant prostate cancer and can provide an additional level of reassurance that their prostate might be safely followed with active surveillance.” As these medical imaging studies show, scientists and clinicians funded by the PCRP are developing and testing more precise imaging technologies that have already led to major contributions to the care of prostate cancer patients and are likely to continue to improve the detection, diagnosis, and treatment of men with prostate cancer.


Dr. Ethan Halpern

Dr. Sabrina Ronen
of therapy. Positron emission tomography (PET) commonly employs a radioactive sugar analog called 18-F deoxyglucose (FDG) to visualize a number of cancers in the human body. For various reasons, FDG does not work well in prostate cancer, so there has been a concerted effort, funded by the PCRP, to develop newer tracers that have high sensitivity and specificity for prostate cancer. These have included radiolabeled choline, which is more rapidly taken up and metabolized by aggressive prostate cancers. Even more specificity can be found with tracers that are targeted to cell surface receptors expressed in prostate cancers and not normal tissues, such as prostate-specific membrane antigen. These tracers can be used to detect cancer in the prostate gland and metastases, which is critical to the evaluation of therapy against advanced disease.

MRI is a nonradioactive technique with exquisite sensitivity to image multiple components of cancers in the same session. Hence, multimodal MRI (mp-MRI) is commonly used to initially diagnose as well as monitor men who are on active surveillance or active treatment. The PCRP has funded researchers to expand the number of parameters available to mp-MRI scans, including multiple metabolic intermediates such as choline, citric acid, and certain lipids that are powerful biomarkers for aggressive disease. More recently, with support from the PCRP, a new MRI technique called hyperpolarized MRI is being developed that uses metabolic substrates, such as pyruvic acid, that are hyperpolarized, which increases their detectability greater than 10,000-fold. Pyruvic acid is converted rapidly to lactic acid in aggressive prostate cancers, and this conversion can be measured noninvasively. The most common imaging technique performed in prostate cancer surveillance is ultrasound; over the past few years, the PCRP has promoted the development of photoacoustic tomography, a new technique using a pulse of light to stimulate specific dyes, which then heat up slightly to generate a signal that can be detected by an ultrasound machine. This is a very powerful approach because, as with PET and MRI, these dyes can be specifically targeted to prostate cancers where they can be readily detected.

In all, the PCRP, through its strategic vision, is contributing greatly to the revolution in prostate cancer imaging, and these advancements will greatly impact and improve the management of this disease.

Summary of FY12 and FY13 Awards

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*To be determined

Visit the PCRP Webpage for Up-to-Date Program Information

The DoD PCRP supports innovative ideas and technologies to accelerate our vision to conquer prostate cancer through individual, multidisciplinary, and collaborative research. These efforts are focused toward basic research discoveries and translating discoveries into clinical practice to improve the quality of care and life of men with prostate cancer. For more information on PCRP initiatives, highlights of funded research, and consumer profiles, please visit http://cdmrp.army.mil/pcrp/default.shtml

To subscribe to this free newsletter, please contact the editor at perspectives@cdmrp.org.
November 25, 2013
Scott T. Tagawa, MD

Submission Type: Continuing Review with Amendment
Protocol Number: 0810010067 R005
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
Nature of Amendment: Submission of Sponsor Protocol, version 7 dated October 31, 2013
Removal of co-investigator: Lilja Solnes
Addition of co-investigators: David Mozley & Yuliya Jhanwar

Dear Dr. Tagawa:

The renewal for the abovementioned protocol was reviewed at the November 20, 2013 meeting of the Institutional Review Board (Cancer IRB 2).

The protocol and its relevant documents stand approved for the following period:
• Revised Informed Consent Form, version date October 31, 2013
• Sponsor’s Protocol, version 7 dated October 31, 2013
• FACT-P Questionnaire
• Subject Brochure
• Subject Information Sheet
• Cumulative deviation log
• Cumulative IND/SAE safety table
• Publication from Frontiers in Oncology, dated 08.26.13
• DSMB outcome letter for periodic review, dated 09.20.13
• FDA Annual Report, submitted to the FDA on 10.24.12

Approved: November 20, 2013 Expires: November 19, 2014

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

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.

- **Immediate Reporting:** Investigators must follow the Immediate Reporting Policy at http://weill.cornell.edu/research/researchreports/IRB/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.

- **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 Transnational 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/researchcepts/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 FWA0000093. The WCMC IRB is registered on that FWA. The registration number for the IRB is: General IRB #1 IRA00009417, General IRB #2 IRA00009418, Cancer IRB#1 IRA00009420, Cancer IRB#2 IRA00009421 and Expedited IRB IRA00009419. 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://library2.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 PI's full name, department, phone number and e-mail address.