AD_____

Award Number: W81XWH-09-1-0146

TITLE: Prostate Cancer Clinical Trials Group: The University of Michigan Site

PRINCIPAL INVESTIGATOR: Maha Hussain

CONTRACTING ORGANIZATION: The University of Michigan
Ann Arbor, MI 48109

REPORT DATE: April 2011

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| **1. REPORT DATE** *(DD-MM-YYYY)* | **2. REPORT TYPE** | **3. DATES COVERED** *(From - To)* |
|---|---|---|
| 01-04-2011 | Annual | 1Apr 2010 - 31 Mar 2011 |

**4. TITLE AND SUBTITLE**
Prostate Cancer Clinical Trials Group: The University of Michigan Site

**5a. CONTRACT NUMBER**

**5b. GRANT NUMBER**
W81XWH-09-1-0146

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
Maha Hussain

E-Mail: mahahuss@umich.edu

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**
The University of Michigan
Ann Arbor, MI 48109

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**
Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**
Abstract on next page.

**15. SUBJECT TERMS**
prostate cancer, phase I/II, phase II, clinical consortium

| **16. SECURITY CLASSIFICATION OF:** | | | **17. LIMITATION OF ABSTRACT** | **18. NUMBER OF PAGES** | **19a. NAME OF RESPONSIBLE PERSON** |
|---|---|---|---|---|---|
| **a. REPORT** | **b. ABSTRACT** | **c. THIS PAGE** | | | USAMRMC |
| U | U | U | UU | 53 | **19b. TELEPHONE NUMBER** *(include area code)* |

**14. ABSTRACT**

**Our efforts over this reporting period (April 1, 2010 to March 31, 2011) was on proposing three new concepts and accruing to six DOD-PCCTC trials including two that stem from major contributions by our group**

c09-057 is a randomized, double-blind, placebo-controlled, multi-center Phase II trial investigating two EMD 525797 dosing regimens in asymptomatic or mildly symptomatic mCRPC subjects. Dr. Husain was heavily involved in the design of this study with the sponsor. Our site expects the protocol to be activated on May 10, 2011.

c11-080 is a multi-institutional Phase I and biomarker study of Everolimus added to combined hormonal and radiation therapy for high risk prostate cancer introduced to the PCCTC by Dr. Daniel Hamstra who wrote the protocol for this study which was based on pre-clinical work supported by a Young Investigator Award from the Prostate Cancer Foundation (PCF). The clinical trial is being supported by an ASCO Career Development Award. Three other PCCTC institutions will be participating in this study. We expect to activate this trial in late May or early June 2011.

c11-079 is the Phase II expansion cohort of the randomized discontinuation trial of XL184 in solid tumors introduced to the PCCTC by Dr. David Smith. Dr. Smith and Dr. Hussain were involved in designing the expansion phase of this study with the sponsor. Nine other PCCTC institutions are participating in this trial.

We also were the lead site for the c09-031 study which was a proof of principle pilot study looking at the combination of ABT-888 (an oral PARP inhibitor) with Temzolomide (an oral DNA methylating agent) in patients progressing on up to two prior therapies for castration-resistant disease. Dr. Hussain was involved in the trial design of this study with the sponsors. This trial completed accrual in October 2010. Six of the twenty–four patients accrued to this study were from our site.

c07-012 was a CTEP-sponsored Phase II trial evaluating AT-101 in men with new MI prostate cancer. This trial was based on an agent that was developed by a University of Michigan scientist through work funded by our Prostate Cancer SPORE. The study design of this trial was based on data published by Dr. Hussain regarding the relationship of PSA nadir after ADT with survival in new M1 patients. The trial completed accrual in 18 months and closed in September 2010 with 20/55 patients accrued from our site.

**Table of Contents**



**Meeting Abstracts**

A. **c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy.** **Maha Hussain**, Dana Rathkopf, Glenn Liu, Andrew J. Armstrong, William Kevin Kelly, Anna Ferrari, John Hainsworth, Ling Yang, Jonathan Schwartz, Hagop Youssoufian, Celestia S. Higano. **Innovative Minds in Prostate Cancer Today (IMPaCT) Meeting 2011 (Abstract PC080189-2043).**

B. **Title: The Prostate Cancer Clinical Trials Consortium: A Collaborative Multicenter Prostate Cancer Research Model**. **Presentation at the Innovative Minds in Prostate Cancer Today.** Howard I. Scher, Tomasz M. Beer, Michael A. Carducci, Paul Corn, Robert Dipaola, Daniel J. George, Andrea L. Harzstark, Elisabeth I. Heath, Celestia S. Higano, **Maha Hussain**, Michael J. Morris, Susan F. Slovin, Walter Stadler, Mary-Ellen Taplin, George Wilding. **(IMPaCT) Meeting 2011 (Abstract PC081610-1865).**

C. **c07-012- Phase II study of AT-101 to abrogate Bcl-2-mediated resistance to androgen-deprivation therapy (ADT) in patients (pts) with newly diagnosed androgen-dependent metastatic prostate cancer (ADMPC).** M.N. Stein, I. Khan, **M. Hussain**, G. Lui, G. Wilding, E.M. Posadas, W.M. Stadler, C. Jeyamohan, S. Eddy, R.S. DiPaola, Prostate Cancer Clinical Trials Consortium. **American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 137).**

D. **c09-024 – A randomized phase II study of pazopanib in castrate-sensitive prostate cancer: A University of Chicago phase II consortium/DoD Prostate Cancer Clinical Trials Consortium study.** J.E.Ward, S. Limvorask, T. Karrison, G.S. Chatta, **M. Hussain**, D. H. Shervin, R.Z. Szmulewitz, W.M. Stadler, E. M. Posadas**. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 170).**

E. **c11-079 – Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease.** **D.C. Smith**, M.R. Smith, E.J. Small, C. Sweeney, R. Kurzrock, M.S. Gordon, N.J. Vogelzang, C. Scheffold, M.D. Ballinger, **M. Hussain**. **American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 127).**

F. **c11-079 -Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease.** **D.C. Smith**, A. Spira, J. De Grève, L. Hart, S. Holbrechts, C.C. Lin, **M. Hussain**, S. Herrick, K. Houggy, N. Vogelzang. **Poster presentation at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, 2010.**

G. **c11-079- Cabozantinib (XL184) in metastatic castration resisitant prostate cancer (mCRPC): Results from a phase 2 randomized trial.** **M. Hussain,** M.R. Smith, C. Sweeney, P.G. Corn, A. Elfiky, M.S. Gordon, N. B. Haas, A.L. Harzstark, R. Kurzrock, P. Laura Jr., C. Lin, A. Sella, E.J. Small, A.I. Spira, U. N. Vaishampayan, N.J. Vogelzang, C. Scheffold, M.D. Ballinger, F. Schimmoller, **D.C. Smith**. **Oral presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting, Genitourinary Cancer Session (Prostate Cancer), 2011.**

**Publications**

H. **c05-007 - Phase II study of Cilengitide (EMD 121974, NSC 707544) in patients with non-metastatic castration resistant prostate cancer, NCI-6735. A study by the DOD/PCF prostate cancer clinical trials consortium;** **Alva, A**, Slovin S, Carducci M, Dipaola R, **Pienta K**, Agus D, **Cooney K**, Chen, A, **Smith DC**, **Hussain M**. ***Invest New Drugs*. 2010 Nov 4. [Epub ahead of print] PMID: 21049281**

I. **c05-008 – Ixabepilone, Mitoxantrone, and Prednisone for Metastatic Castration-Resistant Prostate Cancer After Docetaxel-Based Therapy. A Phase 2 Study of the Department of Defense Prostate Clinical Trials Consortium;** Harzstark AL, Rosenberg JE, Weinberg VK, Sharib J, Ryan CJ, **Smith DC**, Pagliaro LC, Beer TM, Liu G, Small EJ. ***Cancer*. 2010 Dec 29. [Epub ahead of print] PMID: 21192058**

**INTRODUCTION**
University of Michigan Comprehensive Cancer Center

The Prostate Oncology Program is an interdisciplinary group of 37 laboratory, translational and clinical researchers from 11 departments and four schools with over $13 million in annual direct research support. The Prostate Oncology Program continues its primary mission of translating basic and clinical discoveries in prostate cancer into effective medical solutions. The program includes a Prostate SPORE, a PO1 on the Biology of Prostate Cancer Bone Metastasis, a Department of Defense funded Prostate Cancer Clinical trials Consortium site (DOD-PCCTC), a prostate-focused Early Disease Research Network (EDRN) site, a NIDDK training grant in Clinical and Translational Research Training in Urology (T32) and a N01 contract with CTEP (University of Chicago – Early Therapeutics Development with Phase II emphasis group). The Program is committed to creating and sustaining a multidisciplinary environment for basic and clinical researchers studying prostate cancer. The success of this multidisciplinary environment is reflected in the number of intra- and inter-programmatic publications published by the group in the last five years (The program has over 700 publications, of which 140 publications are in high impact journals (Impact factor >7.5) [and of these 21% are intra-programmatic and 23% are inter-programmatic]. The objective of the Prostate Oncology Program is to understand the biology of prostate cancer and to use this information to develop new tools for the detection, diagnosis, prevention, and treatment of prostate cancer. This objective is being pursued through investigations addressing four over-arching aims: Aim 1: To investigate the genetic and epigenetic events that contribute to malignant transformation. Aim 2: To characterize aberrations in cellular biology and function in urological cancers. Aim 3: To translate basic scientific discoveries to develop new biomarkers and therapies in urological cancers. Aim 4: To evaluate clinical outcomes with the purpose of guiding therapy development while reducing cancer-related mortality as well as cancer and therapy-associated morbidities. The goals of the Prostate and Urological Oncology Program at the University of Michigan reverberates that of the Department of Defense's: to combine the efforts of the nation's leading investigators and scientists to test novel therapeutic interventions that will ultimately decrease the overall impact of the disease. That is, to prevent, to detect, and to cure prostate cancer and to improve the quality of life for individuals living with prostate cancer and their families.

**ANNUAL REPORT — BODY**

University of Michigan Comprehensive Cancer Center

The contributions and participation of the University of Michigan as a clinical consortium research site during the reporting period (04-01-2010 to 03-31-2011) of the DOD-PCCTC grant are summarized in this report. The focus of the University of Michigan during the period of DOD-PCCTC funding has been to continue work with the consortium investigators and outside sponsors to bring novel research to the DOD-PCCTC, to continue to actively accrue to DOD-PCCTC trials, and to expand collaboration with other nonconsortium institutions. At the end of the second year of DOD-PCCTC funding from the new 2009 Clinical Consortium Award, three studies with novel drugs were introduced to the DOD-PCCTC by the University of Michigan. Five studies have recently been completed and are undergoing final analysis of clinical and biological samples. We continue to maintain and improve the necessary infrastructure to facilitate the execution of multicenter trials; a process that includes data sharing, opening and accruing to consortium trials, disseminating initial findings from PCCTC-DOD trials to the Consortium and larger research community, as well as introducing important and novel translational clinical trials to the DOD-PCCTC for member participation.

Going forward during this new grant period, we will continue to introduce new concepts based on data generated by our scientists taking advantage of the DOD-PCCTC strengths both from an intellectual scientific perspective and accrual abilities, participate in consortium studies and complete analysis and reporting of the University of Michigan-led completed trials.

**Administrative Infrastructure**

The investigators and research personnel that are funded, in part, by the Department of Defense grant can be found in Table 1. Currently they include four medical oncologists, one radiologist, three data managers, one biostatistician, one clinical research nurse, one study coordinator and one study administrator.

***Table 1. University of Michigan Personnel***

| | |
|---|---|
| Maha Hussain, M.D, FACP, Professor, Departments of Internal Medicine and Urology | University of Michigan<br>Comprehensive Cancer Center<br>Internal Medicine, Hematology Oncology<br>7303 Cancer Center, SPC 5946<br>Ann Arbor, MI 48109-5946<br>734-936-8906<br>mahahuss@umich.edu |
| David C. Smith, M.D., FACP, Professor, Departments of Internal Medicine and Urology | University of Michigan<br>Comprehensive Cancer Center<br>Internal Medicine, Hematology Oncology<br>7302 Cancer Center, SPC 5946<br>Ann Arbor, MI 48109-5946<br>734-936-6884<br>dcsmith@umich.edu |
| Kathleen Cooney, M.D, Professor, Departments of Internal Medicine and Urology | University of Michigan<br>Comprehensive Cancer Center<br>Internal Medicine, Hematology Oncology<br>7216 Cancer Center, SPC 5948<br>Ann Arbor, MI 48109-5948<br>734 -764-2248<br>kcooney@umich.edu |
| Kenneth J. Pienta, MD, Professor, Departments of Internal Medicine and Urology | University of Michigan<br>Comprehensive Cancer Center<br>Internal Medicine, Hematology Oncology<br>7303 Cancer Center, SPC 5946<br>Ann Arbor, MI 48109-5946<br>734-647-3421<br>kpienta@umich.edu |
| Mahmoud M Al-Hawary, MD, Assistant Professor of Radiology | University of Michigan<br>Department of Radiology<br>UH B1-D502F<br>Ann Arbor, MI 48109-5030<br>734-761-2931<br>alhawary@umich.edu |
| Stephanie Daignault, MS, Biostatistician, Biostatistics Core | University of Michigan<br>Comprehensive Cancer Center<br>NI8D11 300 NIB SPC 5473<br>Ann Arbor, MI 48109-5473<br>734-647-3271<br>sfaruzzi@umich.edu |
| Charles Leister, Clinical Research Coordinator Healthcare | University of Michigan<br>North Campus Research Complex<br>Clinical Trials Office<br>2800 Plymouth Road, Building 300<br>Ann Arbor, MI 48109-2800<br>734-232-2464<br>cleister@umich.edu |
| Tamara Huebner, Clinical Nurse III | University of Michigan<br>Comprehensive Cancer Center<br>Internal Medicine, Hematology Oncology<br>B1531 Cancer Center, SPC 5903<br>Ann Arbor, MI 48109-5903<br>734-763-4992 |

| | |
|---|---|
| | thuebner@umich.edu |
| Gregory Campbell, Research Project Administrator | University of Michigan<br>Comprehensive Cancer Center<br>Internal Medicine, Hematology Oncology<br>7303 Cancer Center, SPC 5946<br>Ann Arbor, MI 48109-5946<br>734 -647-9075<br>gwcampbe@umich.edu |
| Liz Vasher, Multi-Site Coordinator | University of Michigan<br>North Campus Research Complex<br>Clinical Trials Office<br>2800 Plymouth Road, Building 300<br>Ann Arbor, MI 48109-2800<br>734-233- 0797<br>evasher@umich.edu |
| Ann Rauschl, Solid Tumor, Team Leader | University of Michigan<br>North Campus Research Complex<br>Clinical Trials Office<br>2800 Plymouth Road, Building 300<br>Ann Arbor, MI 48109-2800<br>734 -232 -0753<br>annrausc@umich.edu |
| Patricia Jo Harvey, GU Data Manager | University of Michigan<br>North Campus Research Complex<br>Clinical Trials Office<br>2800 Plymouth Road, Building 300<br>Ann Arbor, MI 48109-2800<br>734-936-2738<br>harveypj@umich.edu |
| Amie Anderson, GU Data Manager | University of Michigan<br>North Campus Research Complex<br>Clinical Trials Office<br>2800 Plymouth Road, Building 300<br>Ann Arbor, MI 48109-2800<br>734 615 1749<br>acander@umich.edu |
| Lisa Seibold, GU Data Manager | University of Michigan<br>North Campus Research Complex<br>Clinical Trials Office<br>2800 Plymouth Road, Building 300<br>Ann Arbor, MI 48109-2800<br>734-936-0467<br>lseibold@umich.edu |

A list of personnel who received any pay for the research efforts described in this report appears in Supporting Data (**Table F**).

As a consortium research site, the University of Michigan fulfilled the following tasks:

**Task #1: Conduct the clinical trials along the lines of research outlined in the proposal. Patient accrual and sample collection** (Months 1-48).

Includes patient accrual and biological samples collection for: 1. Studies that have been activated in the final quarter of the previous funding period and 2. All new studies that will be proposed for this funding period. This is for studies initiated both by the University of Michigan and other consortium sites. Outlined in the initial proposal were five research objectives relating to this first task in the statement of work

1. Introduce and accrue to new clinical trials.
2. Participate and accrue to other member's trials with the expectation that patient contribution

to trials from other sites shall constitute at least 20% of the total number of patients our site contributes to all trials.
3. Data collection and biologic sample collection.
4. Accrue a minimum of 35 patients per year to consortium trials annually with every effort made to expand this enrollment to 50 patients or more annually. At least 5% of all accrued patients, independently or in partnership with other consortium or non-consortium institutions, will be from disproportionately affected populations.
5. Present at least one clinical trial to the consortium per year with the expectation of presenting two or more clinical trials to the consortium per year.
6. We will be constantly monitoring the quality of the data collected using previously implemented Consortium standard operating procedures in addition to timely data sharing and reporting.
7. Submit and present interim or final reports on completed trials as appropriate at national meetings and symposia.
8. We will adhere to all consortium procedures and fulfill our University of Michigan IRB requirements for the conduct of clinical trials and the protection of human subjects.
9. Participate in all consortium activities and committees (Dr. Hussain is a member of the Clinical Review of Data Management committee and Dr. Smith is a member of the Clinical Research Quality Assurance committee).
10. Take an active role in helping to implement the Coordinating Center's plan for the financial self-sufficiency of the consortium by the end of the award period.
11. Prepare, submit and present where appropriate the required semi-annual briefings for the EAB and USAMRMC staff at consortium meetings; submit annual written progress reports and a final written comprehensive report to the USAMRMC .

Table 2 presents all the DOD-PCCTC trials that were open for accrual during this reporting period at the University of Michigan. From this table, it is apparent that the University of Michigan is successfully working towards accomplishing Objective 4, accruing a minimum of 35 patients a year to consortium trials. During this current reporting period we have accrued 38 patients to consortium trials. Table C and D show that we have accrued approximately 11 % of our accruals for this reporting period from disproportionately affected populations (DAP). Table E shows that our patient contribution to trials from other sites constituted 21% of the total number of patients our site contributes to all trials. During this reporting period we accrued 2 patients to our phase III biomarker trial SWOG S0421 (b09-004) (see Table 2).

Table 4 presents all the DOD-PCCTC trials that are either open for accrual or are in the process of being activated for accrual at the University of Michigan. Each trial's specific area of focus as related to Objective #1 can be found in the first column of Table 4. From this table, it is apparent that the University of Michigan is successfully working towards accomplishing Objective 1, carrying out a wide range of clinical trials to develop more effective systemic therapies for prostate cancer.

With regards to objective 10, the University of Michigan has developed and maintained successful collaborative efforts. The University of Michigan has maintained a successful membership in the University of Chicago Phase II Consortium sponsored by the Cancer Therapy Evaluation Program (CTEP), of the Division of Cancer Treatment and Diagnosis (DCTD) of the National Cancer Institute (NCI) (http://www.cancer.gov/). The major emphasis of this consortium is on Phase II studies, pilot protocols that explore promising single agent and combination therapies, and high priority studies that are pivotal for drug development and require rapid initiation, completion, and data reporting. These groups provide a valuable addition to our group's other diverse collaborative research networks including: the PCCTC, the PCF Therapy Consortium and National cooperative groups (SWOG, RTOG, ECOG) and can particularly synergize with the DOD-PCCTC. Successful collaborations we believe are the first step towards implementing the Coordinating Center's plan for the financial self-sufficiency of the consortium by the end of the award period.

**Table 2: Total and current reporting period University of Michigan Accruals to DOD-PCCTC Trials**

| DOD Number | PROTOCOL TITLE | UM PI | Total UM Accrual | UM Accrual Apr 01 2010– Mar 31 2011 |
|---|---|---|---|---|
| **c07-012** | A Phase II study of AT101, to abrogate bcl-2 mediated resistance to androgen ablation therapy in patients with newly diagnosed stage D2 prostate cancer. (NCI #8014) | **Dr. Hussain** | 20 | 6 |
| **c08-009** | A Phase II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-refractory Prostate Cancer **(Study closed by sponsor early)** | **Dr. Hussain** | 12 | 1 |
| **c09 -031** | A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temozolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease | **Dr. Hussain** | 6 | 6 |
| **c09-033** | A Randomized Phase II Clinical Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer | **Dr. Smith** | 5 | 1 |
| **c09-044** | A Phase 2 Multicenter Open-label Study Evaluating the Safety and Efficacy of TAK-700 in Patients with Nonmetastatic Castration-resistant Prostate Cancer (CRPC) and a Rising Prostate-specific Antigen (PSA) | **Dr. Hussain** | 5 | 5 |
| **c10-079** | A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors | **Dr. Smith** | 22 | 19 |
| **Totals** | | | **44** | **38** |
| **Biomarker Trials** | | | | |
| **DOD Number** | **PROTOCOL TITLE** | **UM PI** | **Total UM Accrual** | **UM Accrual Apr 01 2010– Mar 31 2011** |
| **b09-004** | S0421 - A Phase III study of Docetaxel and Atrasentan versus Docetaxel and placebo for patients with advanced hormone refractory prostate cancer | **Dr. Hussain** | 18 | 2 |

**Task #2: We will collect and analyze blood, urine and tissue samples collected on all the consortium clinical trials that are led by the University of Michigan.** (Sample Collection: Months 1-48), (Analysis: Months 48-60).

- Using the consortium-developed management plan for acquisition, delivery, and storage of biological samples to the appropriate laboratories for testing or storage

Sample collection for the correlative endpoints for the clinical trials are progressing, please see correlative studies column of Table 4 for a list of ongoing correlative research included in the DOD-PCCTC trials and Table 3 for a breakdown of the samples that have been collected for DOD-PCCTC trials thus far.

Please see the following description of the scientific correlative objectives for one of the studies introduced to the DOD-PCCTC by the University of Michigan that highlight the scope of our efforts in this area (trial is expected to activate at our site on 5-10-2011):

1. **c09-057, A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)**

•Serum concentration data and PK parameters of EMD 525797 derived from non-compartment analysis;
• Population PK of EMD 525797;
• Candidate cell type counts, proteins or metabolites circulating in the blood and/or expressed by the tumor or change in concentrations and their and their relationship to the clinical outcome and/or drug activity markers.
• Individual genetic variations in the host genome and/or in the tumor genome or between them and the clinical outcome and/or drug activity markers.
• mRNA levels or change in mRNA levels in whole blood and/or tumor samples associated to the clinical outcome and/or drug activity markers.
• Protein or metabolite concentrations or change in concentrations in urine and the clinical outcome and/or drug activity markers.
• Exploring the relationship of the count or change in count of circulating endothelial cells measured in whole blood with the clinical outcome and or drug activity markers

**Table 3: Samples collected for DOD-PCCTC correlative studies to date**

| Correlative Studies Sample Collection | | |
|---|---|---|
| DOD Number | Study Title | Samples Collected to date |
| c07-044 | A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA | 14 Whole Blood CTC Samples<br>12 Urine Sets<br>157 Serum Sets<br>92 Plasma Sets |
| c08-009 | A Phase I/II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-Refractory Prostate Cancer (Study # CA301) | 88 Serum Sets |
| c09-031 | A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temzolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease | 44 Whole Blood CTC Samples<br>6 Whole Blood Pharmacogenetic Samples<br>144 Plasma Sets<br>22 Serum Sets |
| c09-033 | A Randomized Phase II Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer | 14 Skin Biopsy Samples<br>62 Plasma Sets<br>90 Whole Blood CTC samples |
| c10-079 | A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors | 15 Sets of Archived Tumor Blocks/Slides<br>21 Whole Blood Pharmacogenetic Samples<br>209 Plasma Sets |
| b09-004 | S0421 - A Phase III study of Docetaxel and Atrasentan versus Docetaxel and placebo for patients with advanced hormone refractory prostate cancer | 84 Serum Sets<br>46 Whole Blood CTC Samples |

**Table 4. Current areas of research by stage of disease, including correlative research**

| Current University of Michigan DOD-PCCTC Prostate Cancer Clinical Trials Summary | | | | | |
|---|---|---|---|---|---|
| **Area of Focus** | **Title** | **UM PI** | **Lead Site** | **Trial Status** | **Correlative Studies** |
| **Neoadjuvant** | | | | | |
| Signal transduction | 2011.030, c09-041, A Randomized Trial of Preoperative GDC-0449 and Androgen Ablation Alone Followed by Radical Prostectomy for Select Patients with Locally Advanced Adenocarcinoma of the Prostate | Dr. Jeffrey Montgomery | MDACC | Expected to open late May 2011. | Analyze tumor specimens for changes in hedgehog and androgen signaling, proliferation, apoptosis and markers linked to progression between the two arms; collect and archive tissue from the primary tumor, bone marrow biopsy/aspirate and blood (serum, plasma) for future studies. |
| Signal transduction | c10-080, A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High Risk Prostate Cancer | Dr. Daniel Hamstra | **University of Michigan** | Expected to open late May or early June 2011. | To assess PTEN axis, the following biomarkers will be analyzed by IHC analysis; PTEN, Akt, Phos-Akt (Ser 473), Phos-Akt (Thr 308), p70S6K, Phos-p70S6K (Thr421/Ser424), 4EBP1, Phos-4EBP1, Stathmin; to evaluate putative markers of neo-angiogenesis and hypoxia, the following will be evaluated in tumor tissue before and after everolimus therapy; VEGF-A, HIF1-alpha, CD31 micro-vessel density. |
| **Prostate (Rising PSA - Androgen Dependent)** | | | | | |
| Angiogenesis and Intermittent Androgen Ablation | 2007.086, c09-024, A Randomized, Phase II Study of GW786034 (Pazopanib) in Stage D0 Relapsed Androgen Sensitive Prostate Cancer Following Limited GnRH Agonist Therapy | Dr. Maha Hussain | University of Chicago | Closed permanently 4/20/2010 due to multiple early patient discontinuations. | |
| **Prostate (Rising PSA - Androgen Independent)** | | | | | |
| Angiogenesis in tumor development and progression/bone | 2009.091, c07-044, A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA | Dr. Maha Hussain | **University of Michigan** | Open and accruing | Evaluate changes in bone turnover markers, assess archival tumor samples for candidate biomarkers including the TMRSS2/ERG fusion gene, characterize biomarkers in CTC's. |
| **Metastatic Androgen Dependent Front Line** | | | | | |
| Signal Transduction | 2008. 064 c07-012 A Phase II Study of AT101 to abrogate BCL-2 Mediated Resistance to Androgen Ablation Therapy in Patients with Newly Diagnosed Stage D2 Prostate Cancer. NCI 8014 | Dr. Maha Hussain | CINJ | Met accrual goal, closed 9-14-10. | Determine changes in Bcl-2 and BAX/BAK protein expression in peripheral blood mononuclear cells and in baseline tumor tissue. |
| **Metastatic Castrate-Resistant Front Line** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Angiogenesis and hedgehog pathway inhibitor | 2009.042, c09-033, A Randomized Phase II Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer | Dr. David Smith | JHU | Met accrual goal, closed 10-1-2010. | To investigate changes in itraconazole PK, serum testosterone, DHEA-S, ACTH, serum cortisol, aldosterone, and VEGF levels with time, changes in GLi1 mRNA expression levels and advanced MRI parameters with time. |
| Angiogenesis in tumor development and progression/bone | c09-057, A Randomized Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Asymptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC) | Dr. Maha Hussain | **University of Michigan** | Site activation May 10, 2011. | Serum PK, mRNA levels in whole blood or tumor samples, change in circulating endothelial cell count in whole blood with clinical outcome or other drug markers. |
| Signal Transduction | 2010.005, c09-048, Phase I/II Trial of Anti-IGF-IR Monoclonal Antibody IMC-A12 plus mTOR Inhibitor Temsirolimus (CCI-778) in metastatic castration-resistant prostate cancer (CRPC). NCI #8417 | Dr. Maha Hussain | MSKCC | Closed 3-4-2011 by lead site (MSK) because of toxicities. | CTC analysis, PET imaging, tumor biopsy to evaluate biomarkers. |
| Cytotoxic Therapy (taxane derivative) | c10-071, A Phase II study of single-agent tesetaxel in chemotherapy-naïve and chemotherapy-exposed patients who have progressive, castration-resistant prostate cancer | Dr. David Smith | MSKCC | Expected to open June 2011 | |
| Signal Transduction (MET and VEGFR2 inhibition) | c10-079, A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors | Dr. David Smith | **University of Michigan** | RDT- open and accruing. | MRI, CT scan, and/or bone scans; PK; pharmacodynamic biomarkers (eg, sMET, HGF, VEGF-A, PlGF, sVEGFR2); tumor samples assayed for signaling pathways; CTCs; genotyping /single nucleotide polymorphism analysis (pharmacogenomics); markers of bone turnover serum NTx, CTx, and bone alkaline phosphatase) |
| **Metastatic Castrate-Resistant After Docetaxol** | | | | | |
| Signal Transduction (MET and VEGFR2 inhibition | C10-079, A Phase II Trial of XL184 in Patients with Castrate-Resistant Cancer Metastatic to Bone | Dr. David Smith | **University of Michigan** | Phase II prostate expansion expected to open in early May2011 | MRI, CT scan, and/or bone scans; PK; pharmacodynamic biomarkers (eg, sMET, HGF, VEGF-A, PlGF, sVEGFR2); tumor samples assayed for signaling pathways; CTCs; genotyping /single nucleotide polymorphism analysis (pharmacogenomics); markers of bone turnover serum NTx, CTx, and bone alkaline phosphatase) |

| | | | | | |
|---|---|---|---|---|---|
| Signal Transduction (DNA repair) | 2009.114, c09-031, A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temzolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease | Dr. Maha Hussain | **University of Michigan** | Closed 10/22/10 met accrual goal. | Exploratory research to find biomarkers that may serve as surrogates for clinical endpoints in future ABT-888 studies or that may be predictive of ABT-888 activity will be conducted. Blood samples will be collected at designated time points throughout the study. Archived tissue samples (if available) will be collected while subjects are on study. |
| Signal Transduction (mTOR pathway inhibition) and Cytotoxic Therapy | c09-025, Phase II trial of carboplatin and RAD001 in metastatic castrate resistant prostate cancer (CRPC) pretreated with docetaxel therapy | Dr. David Smith | Wayne State | Expected to open early May 2011. | Phospho mTOR status of prostate cancer in archival tissue, PK response predictors ($p70^{s6}$/$p70^{s6}$ phosphoprotein, AKT/pAKT, PK of the 2 drugs in ~ 50% of patients. |
| Cytotoxic Therapy | 2011.016, c10-071, A Phase II study of single agent tesetaxel in chemotherapy naïve and chemotherapy exposed patients who have progressive, castration resistant prostate cancer | Dr. Maha Hussain | MSKCC | Expected to open June 2011 | |
| Cytotoxic Therapy | 2008.033, c08-009, A Phase I/II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-Refractory Prostate Cancer (Study # CA301) | Dr. Maha Hussain | MDACC | Closed 2-1-11 by Celgene. PCCTC currently in discussions to possibly re-open given promising early results. | PK samples to determine caveolin-1 levels |

**Task #3: Final Analysis and Report Writing**. A final clinical and statistical analysis of all data (clinical and correlative) on all University of Michigan led trials will be undertaken. A final report and draft manuscripts will be circulated to all co-authors and submitted to appropriate scientific journals for publication. (Months 54-60).

The results of the c08-001 trial (IMC-A12 and IMC-1121B) were reported by Dr. Hussain at the 2011 IMPaCT meeting (Appendix A). Final reporting is awaiting mature survival data. A draft manuscript for the c05-007 study (cilengitide non-met) was circulated to all co-authors and a manuscript was submitted and subsequently published in the journal *Investigational New Drugs* in November 2010 (Appendix H). For all other completed trials we are awaiting more mature survival and efficacy data before publishing the results.

***As part of their SOW, each participating site was expected to present at least 1 clinical trial each year for the consortium's consideration.***

In the second year of the new DOD-PCCTC CCA research site award, the University of Michigan presented three studies to the DOD-PCCTC. The following are the three trials that were presented by University of Michigan to the consortium. All three trials were accepted for consortium participation during the current reporting period.

**1. c09-057, A Randomized Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Asymptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC).**

This is an exploratory, randomized, double-blind, placebo-controlled, multi-center Phase II trial investigating two EMD 525797 dosing regimens in asymptomatic or mildly symptomatic mCRPC subjects. EMD 525797 is a de-immunized monoclonal IgG2 antibody antagonist directed against the alpha-v (αv) subunit of human integrin receptors. EMD 525797 binds specifically to the αv-chain, thereby inhibiting ligand binding to all αv-heterodimers (αvß1, αvß3, αvß5, αvß6, αvß8). αv-integrins are highly expressed in angiogenic, proliferating tumor blood vessels and on certain types of tumor cells. In addition, in a limited set of tumors, increased expression of αvß3 is associated with increased cell invasion and metastasis [1]. It has been demonstrated that members of the αv-integrin family play a direct role in tumor progression, tumor angiogenesis and metastasis [2]. Histochemical data [3]and *in vitro* studies on colorectal cancer (CRC) cell lines, prostate cancer cell lines, endothelial cells and osteoclasts have shown that αv-integrins are expressed on the tumor vasculature, tumor cells and osteoclasts [3-5].

The primary objective of the trial is to evaluate whether two dose levels of EMD 525797 administered as 1 hour I.V. infusion every 3 weeks is superior to standard of care (SoC) as assessed by progression free survival time (PFS) in subjects with asymptomatic or mildly symptomatic mCRPC . Secondary objectives are to evaluate the efficacy, safety profile, and pharmacokinetic (PK) profile of EMD 525797 and evaluate changes in circulating tumor and endothelial cells (CTCs).

2. **c11-079, A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors.** This is a Phase 2 study to evaluate the efficacy and safety of XL184 in subjects with selected advanced tumor types. XL184 is a small molecule which inhibits multiple receptor tyrosine kinases. Its primary targets include MET, VEGFR2 and RET which play critical roles in angiogenesis and tumor cell proliferation, invasion, and metastasis. In preclinical studies XL184 has rapid effects on endothelial cells resulting in vascular breakdown and tumor cell death within 24 hours after administration.

These changes translate into significant tumor growth inhibition or tumor regression in multiple xenograft tumor models including human lung, breast, thyroid, and brain cancer. In addition, XL184 results in a substantial reduction in tumor invasiveness and metastasis in the RIP-Tag2 mouse model of pancreatic neuroendocrine cancer. In phase I studies XL184 demonstrated good oral availability with a half-life of 80-90hours and tolerable toxicity profile. The most common adverse events were fatigue, diarrhea, anorexia, rash, and palmar-plantar erythrodysesthesia (PPE) syndrome. In terms of activity, almost 40% of patients showed stable disease greater than 3 months with several up to 6 months while on treatment.[6,7]

Based on target rationale and observed anti-tumor activity in early clinical studies, a phase III trial is ongoing in medullary thyroid cancer and phase II studies are ongoing in glioblastoma, prostate cancer, ovarian cancer, non-small cell lung cancer, and several other solid tumors. The current trial of XL184 in patients with advanced prostate cancer has shown significant effects on bone lesions in patients both pre- and post-therapy with docetaxel Subjects were enrolled into one of nine tumor type cohorts (including prostate). All cohorts will initially follow the Randomized Discontinuation Trial (RDT) design. Based on periodic review of all available data, enrollment into specific cohorts may be halted, continued within the RDT design, or closed in favor of opening open label non-randomized expansion (NRE) cohorts. Because of early promising data, the accrual was stopped and a phase II expansion cohort for prostate cancer patients was introduced to the PCCTC by Dr. Smith in December 2010.

We propose to conduct a phase II trial aiming at estimating the efficacy of XL184 in chemotherapy-naive patients with CRPC and bone metastases and characterize the effects of XL184 on prostate cancer bone lesions using novel methods to assess bone metabolism and tumor activity. The primary endpoint of the trial will be to assess the proportion of patients who do not exhibit disease progression, and thus achieve clinical benefit from the agent. Correlative studies will include assessment of several biomarkers of bone metabolism, which are present in serum and bone. At the same time, information about tumor activity in the bone will be obtained via imaging with diffusion MRI. We are currently enrolling CRPC patients at our site and four other DOD-PCCTC institutions with three additional member institutions to join in the prostate expansion cohort for this study. Dr. Smith presented preliminary data from the open label Lead-in

Stage of the ongoing adaptive design phase II randomized discontinuation trial of XL184 at the 2011 ASCO GU Cancers Symposium and the 2010 EORTC-NCI-AACR Symposium on Molecular Targets and Cancer (see Appendix E and F). It showed that 13 of the 15 patients (87%) with known bone metastases had either complete or partial remission of the lesions on bone scan. Multiple cases of complete or near complete resolution were observed in both docetaxel and docetaxel-naïve subgroups. Dr. Hussain will give an oral presentation of the final data on XL184 in these patients at the 2011 Annual ASCO meeting Prostate Cancer session (Appendix G).

3. **c11-080, A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High Risk Prostate Cancer.** Prostate cancer exhibits significant heterogeneity in genetic make-up, however, inactivation of the Phosphatase and Tensin homolog deleted on chromosome 10 (PTEN) tumor suppressor gene is one of the more common events occurring in as many as 20-25% of all prostate cancers and is more common in high-grade tumors. PTEN loss has been associated with higher Gleason grade, higher pathologic stage, increased biochemical failure, and radiation resistance. Further, tumor hypoxia, which is common in prostate cancer, is a major determinant of both radiation resistance and prostate cancer recurrence. The mammalian target of rapamycin (mTOR) is a critical player in both prostate tumor pathophysiology and neo-vascular growth. In preclinical models tumors mutant in PTEN have increased levels and activity of mTOR and are sensitive to mTOR inhibitors while inhibition of the mTOR pathway has also been demonstrated to inhibit tumor neo-angiogenesis. As a result the combination of radiation therapy and mTOR inhibition has been demonstrated to radiosensitize both PTEN null and PTEN wild-type tumors through actions directed at both tumor and vascular cells. Therefore, we are conducting a phase I trial using a time-to-event continual re-assessment model (TITE-CRM) to evaluate the safety of adding the mTOR inhibitor, everolimus (RAD001, Afinitor), to hormonal therapy and radiation therapy for high-grade or locally advanced prostate cancers. In addition, following a lead in with everolimus we will evaluate biomarkers for tumor and vascular response to ascertain the extent of inhibition achieved at the maximally tolerated dose. This treatment represents a novel targeted method to address known mechanisms of resistance to the current standard therapy and has the potential to significantly improve clinical outcomes. If this study achieves its goal of identifying an appropriate dose of Everolimus which is safe within the protocol specified definition and achieves pharmacodynamic evidence for suppression of the Akt/mTOR/PTEN signaling pathway then it will have been deemed a success and a larger confirmatory Phase 2 study could be undertaken at the identified dose level. Three other DOD-PCCTC member institutions will be participating in this study with The University of Michigan as the lead site. The pre-clinical work leading to the development of this protocol was supported by Novartis Pharmaceuticals and an ASCO Career Development award.

***DOD-PCCTC participating institutions are charged with maintaining an annual accrual rate of 35 patients to DOD-PCCTC participating trials.***

Currently, there are two DOD-PCCTC trials actively accruing, one trial pending site activation, one trial where the protocol is being re-written to address scientific review committee questions, three trials pending protocol approval and five trials closed to accrual. The University of Michigan has accrued 38 patients during the second year of this award year award period. We are confident once these new trials open we will be able to maintain an annual accrual rate of 35 patients to DOD-PCCTC participating trials. **Please refer to Table 4 for trial status information and Table 2 for the accrual numbers for the trials that accrued in this period.**

*University of Michigan* **Biomarker Trials**

- Currently we have one DOD-PCCTC biomarker trial, b09-004, SWOG S0421, A Phase III study of Docetaxel and Atrasentan versus Docetaxel and placebo for patients with advanced hormone refractory prostate cancer. Two other DOD-PCCTC institutions (Johns Hopkins University and the University of Washington) also participated in this study. This study was designed to prospectively test whether a 30% reduction in PSA and the slope of PSA from baseline to three months post randomization is a surrogate marker for survival. This study also collected serum markers of bone reabsorption. During this reporting period, we accrued two patients to this study (18 total at our site) **(see Table 2)**. This study closed to accrual on 11/09/2010.

**KEY ACCOMPLISHMENTS**

University of Michigan Comprehensive Cancer Center

As of March 31, 2011, our accomplishments during the award period are listed below.

**Infastructure**

• Collaborated with other DOD-PCCTC sites to improve the data collection process with the consortium database, to make the system more time effective and accurate.

• Have additional roles in the consortium as a member of the Clinical Review of Data Management Committee (Dr. Hussain) and as chair of the Clinical Research Quality Assurance Committee (Dr. Smith).

• Participated in all the Prostate Cancer Clinical Trials Consortium meetings, including the most recent DOD-EAB review meeting held November 18-19th, 2010 in Falls Church, Virginia and the PCCTC PI meeting in Orlando, Florida on February 16th, 2011.

• Extended collaboration between the DOD-PCCTC and the University of Chicago CTEP-sponsored Phase II Consortium and other non-consortium sites.

**Research/Protocol Development**

• Served as the lead site for the DOD-PCCTC for three protocols to date, will serve as the lead site for two other trials (one awaiting activation and the other IRB protocol approval). Two of these trials are based in part on scientific data generated by our group.

• Accrued 71 patients to DOD-PCCTC trials to date for the first two years of the new award period (105 in the previous three year award period).

• Collected 1120 samples for correlative studies of DOD-PCCTC trials.

• Presented two abstracts on DOD-PCCTC Consortium trials at the IMPaCT meeting Symposium, March 9th-12th, 2011 in Orlando, Florida **(Appendix A and B)**.

•Presented three abstracts on DOD-PCCTC Consortium trials at the ASCO Genitourinary Cancers Symposium, March 17th-19th, 2011 in Orlando, Florida **(Appendix C, D and E)**.

•Presented one poster at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, November 16th-19th, 2010 in Berlin, Germany **(Appendix F)**.

•Submitted an oral presentation for the c11-079 trial (XL184) for the 2011 ASCO Annual meeting on June 3rd-7th, 2011 in Chicago, Illinois **(Appendix G)**.

• Published one manuscript on one of the DOD-PCCTC trials, c05-007 Cilengitide (Investigational New Drugs. Published Online 04 Nov 2010) **(Appendix H)**.

• We were co-authors on one manuscript for the DOD-PCCTC trial c05-008 Ixabepilone (Cancer. 2010 Dec 29) **(Appendix I).**

**REPORTABLE OUTCOMES**

University of Michigan Comprehensive Cancer Center

During the 2nd year of this 5-year grant period, investigators at the University of Michigan have been listed as authors on a total of 5 abstracts, 1 poster presentation, 1 oral presentation and 2 manuscripts. The abstract and all manuscripts have been published. A complete listing of abstracts and publications appears in the Bibliography section, and the abstracts and manuscripts appear in the Appendix section.

In this reporting period, during our second 12 months of funding, five studies have been completed. We published one manuscript on the c05-007 study in the journal Investigational New Drugs (see **Appendix H**). Dr. Smith was a co-author on the c05-008 manuscript published in the journal Cancer (see **Appendix I)**.

c07-012 is a CTEP-sponsored Phase II trial evaluating AT-101 in men with new M1 prostate cancer. This trial was based on an agent that was developed by a University of Michigan scientist (Dr. Shaomeng Wang) through work funded by our Prostate Cancer SPORE. Pre-clinical data from our group led to moving this agent into the clinic. The study design of this trial is based on data published by Dr. Hussain regarding the relationship of PSA nadir after ADT with survival in new M1 patients. 20/55 patients accrued to this trial were from our center. This trial completed accrual in September, 2010.

During this reporting period, the following abstracts were presented at the following scientific meetings:

• c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy. Innovative Minds in Prostate Cancer Today (IMPaCT) Meeting 2011. Author: Dr. Maha Hussain. Abstract PC080189-2043). **(Appendix A)**

• The Prostate Cancer Clinical Trials Consortium: A Collaborative Multicenter Prostate Cancer Research Model. Presentation at the Innovative Minds in Prostate Cancer Today. IMPaCT Meeting 2011 (Abstract PC081610-1865). Co-author: Dr. Maha Hussain. **(Appendix B**)

•c07-012- Phase II study of AT-101 to abrogate Bcl-2-mediated resistance to androgen-deprivation therapy (ADT) in patients (pts) with newly diagnosed androgen-dependent metastatic prostate cancer (ADMPC). American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 137).Co-author: Dr. Maha Hussain. **(Appendix C)**

•c09-024 – A randomized phase II study of pazopanib in castrate-sensitive prostate cancer: A University of Chicago phase II consortium/DoD Prostate Cancer Clinical Trials Consortium study. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 170). Co-author: Dr. Maha Hussain. **(Appendix D)**

•c11-079 – Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 127). Author: David C. Smith. **(Appendix E)**

•c11-079 – Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. Poster presentation at the 22$^{nd}$ EORTC-AACR Symposium on Molecular Targets and Cancer Therapeutics. 2010. Author: David C. Smith **(Appendix F)**

•c11-079- Cabozantinib (XL184) in metastatic castration resisitant prostate cancer (mCRPC): Results from a phase 2 randomized trial. Oral presentation submitted to the American Society of Clinical Oncology (ASCO) Annual Symposium, Genitourinary Cancer Session, 2011. Author: Dr. Maha Hussain **(Appendix G)**

**CONCLUSIONS**

University of Michigan Comprehensive Cancer Center

The contributions and participation of the University of Michigan during this reporting period (04-01-2010 to 03-31-2011) of the DOD-PCCTC CCA research site award are summarized in this report.

The focus of the University of Michigan during the this period of the DOD-PCCTC has been to work with consortium investigators and outside sponsors to bring novel research to the DOD-PCCTC, to actively accrue to DOD PCCTC trials, and to expand collaboration with other non-consortium institutions.

University of Michigan research personnel have actively participated in a variety of activities to facilitate research and communication between participating institutions including teleconferences, scheduled conference calls and Investigator meetings.

The University of Michigan has presented a total of three studies to the DOD-PCCTC for member participation since April 2010. Currently, there are two DOD-PCCTC trials actively accruing at the University of Michigan with five additional studies that will be activated by the end of the third quarter 2011.

We have accrued 71 patients to DOD-PCCTC trials to date (38 during this reporting period, with 11% accrued from disproportionately affected populations).

We have completed accrual to five trials and activated several new consortium trials. Our efforts have led to several national presentations and publications.

The University of Michigan continues to believe in the importance of targeted correlatives studies to better understand the biology, mechanisms of response and progression of this disease to eventually increase therapeutic efficacy. Sample collection for the correlative endpoints is progressing. To date, we have collected approximately 1120 samples (with ~1,500 samples from the previous three year award period) for the correlative endpoints to DOD-PCCTC trials.

In the 2$^{nd}$ year of this new funding period with the DOD-PCCTC, the University of Michigan will continue accrual to active consortium trials, will introduce new concepts that will capitalize on the scientific productivity of our group coupled with the accrual and scientific strength of the DOD-PCCTC, open additional consortium trials and continue to finalize analysis and reporting of completed projects

## References
## University of Michigan Comprehensive Cancer Center


1. Felding-Habermann B, Fransvea E, O'Toole TE, et al: Involvement of tumor cell integrin alpha v beta 3 in hematogenous metastasis of human melanoma cells. Clin Exp Metastasis 19:427-36, 2002
2. Nemeth JA, Nakada MT, Trikha M, et al: Alpha-v integrins as therapeutic targets in oncology. Cancer Invest 25:632-46, 2007
3. Max R, Gerritsen RR, Nooijen PT, et al: Immunohistochemical analysis of integrin alpha vbeta3 expression on tumor-associated vessels of human carcinomas. Int J Cancer 71:320-4, 1997
4. Putz E, Witter K, Offner S, et al: Phenotypic characteristics of cell lines derived from disseminated cancer cells in bone marrow of patients with solid epithelial tumors: establishment of working models for human micrometastases. Cancer Res 59:241-8, 1999
5. Zheng DQ, Woodard AS, Fornaro M, et al: Prostatic carcinoma cell migration via alpha(v)beta3 integrin is modulated by a focal adhesion kinase pathway. Cancer Res 59:1655-64, 1999
6. Salgia R H, D.CS., Camacho, L.H., et al.: A phase I dose escalation study of the safety and pharmacokiinetics (PK) of XL184, a VEGR and MET kinase inhibitor, administered orally to patients (pts) with advanced malignancies. Journal of Clinical Oncology 2007; Abstract(25):14031.
7. Salgia R S, S., Hong, D.S., et al. : A phase I study of XL184, a RET, VEGFR2, and MET kinase inhibitor, in patients (pts) with advanced malignancies, including pts with medullary thyroid cancer (MTC)
Journal of Clinical Oncology 2008; Abstract(26):3522

**Appendices**
University of Michigan Comprehensive Cancer Center

**Abstracts:**

1. c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy. **Maha Hussain**, Dana Rathkopf, Glenn Liu, Andrew J. Armstrong, William Kevin Kelly, Anna Ferrari, John Hainsworth, Ling Yang, Jonathan Schwartz, Hagop Youssoufian, Celestia S. Higano. Innovative Minds in Prostate Cancer Today (IMPaCT) Meeting 2011 (Abstract PC080189-2043). **(Appendix A)**

2. The Prostate Cancer Clinical Trials Consortium: A Collaborative Multicenter Prostate Cancer Research Model. Howard I. Scher, Tomasz M. Beer, Michael A. Carducci, Paul Corn, Robert Dipaola, Daniel J. George, Andrea L. Harzstark, Elisabeth I. Heath, Celestia S. Higano, **Maha Hussain**, Michael J. Morris, Susan F. Slovin, Walter Stadler, Mary-Ellen Taplin, George Wilding. Innovative Minds in Prostate Cancer Today (IMPaCT) Meeting 2011 (Abstract PC081610-1865). **(Appendix B)**

3. c07-012- Phase II study of AT-101 to abrogate Bcl-2-mediated resistance to androgen-deprivation therapy (ADT) in patients (pts) with newly diagnosed androgen-dependent metastatic prostate cancer (ADMPC). M.N. Stein, I. Khan, **M. Hussain**, G. Lui, G. Wilding, E.M. Posadas, W.M. Stadler, C. Jeyamohan, S. Eddy, R.S. DiPaola, Prostate Cancer Clinical Trials Consortium. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 137).Co-author: Dr. Maha Hussain. **(Appendix C)**

4. c09-024 – A randomized phase II study of pazopanib in castrate-sensitive prostate cancer: A University of Chicago phase II consortium/DoD Prostate Cancer Clinical Trials Consortium study. J.E.Ward, S. Limvorask, T. Karrison, G.S. Chatta, **M. Hussain**, D. H. Shervin, R.Z. Szmulewitz, W.M. Stadler, E. M. Posadas**.** American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 170). **(Appendix D)**

5. c11-079 – Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. **D.C. Smith**, M.R. Smith, E.J. Small, C. Sweeney, R. Kurzrock, M.S. Gordon, N.J. Vogelzang, C. Scheffold, M.D. Ballinger, **M. Hussain**. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 127). **(Appendix E)**

6. c11-079 – Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. **D.C. Smith**, A. Spira, J. De Grève, L. Hart, S. Holbrechts, C.C. Lin, **M. Hussain**, S. Herrick, K. Houggy, N. Vogelzang. Poster presentation 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics 2010. **(Appendix F)**

7. c11-079- Cabozantinib (XL184) in metastatic castration resisitant prostate cancer (mCRPC): Results from a phase 2 randomized trial. **M. Hussain,** M.R. Smith, C. Sweeney, P.G. Corn, A. Elfiky, M.S. Gordon, N. B. Haas, A.L. Harzstark, R. Kurzrock, P. Laura Jr., C. Lin, A. Sella, E.J. Small, A.I. Spira, U. N. Vaishampayan, N.J. Vogelzang, C. Scheffold, M.D. Ballinger, F. Schimmoller, **D.C. Smith**. Oral presentation submitted to the American Society of Clinical Oncology (ASCO) Annual Symposium, Genitourinary Cancers Session (Prostate Cancer), 2011.

Manuscripts:

1. c05-007 - Phase II study of Cilengitide (EMD 121974, NSC 707544) in patients with non-metastatic castration resistant prostate cancer, NCI-6735.Alva, A, Slovin S, Carducci M, Dipaola R, Pienta K, Agus D, Cooney K, Chen, A, **Smith DC, Hussain M**. A study by the DOD/PCF prostate cancer clinical trials consortium. *Invest New Drugs*.2010 Nov 4. [Epub ahead of print]. **PMID: 21049281 (Appendix G)**
2. c05-008 – Ixabepilone, Mitoxantrone, and Prednisone for Metastatic Castration-Resistant Prostate Cancer After Docetaxel-Based Therapy. Harzstark AL, Rosenberg JE, Weinberg VK, Sharib J, Ryan CJ, **Smith DC**, Pagliaro LC, Beer TM, Liu G, Small EJ. A Phase 2 Study of the Department of Defense Prostate Clinical Trials Consortium. Cancer. 2010 Dec 29. [Epub ahead of print]. **PMID: 21192058 (Appendix H)**

**SUPPORTING DATA**
*University of Michigan*

Table A. Trials Introduced by the *University of Michigan* (as of 04/01/20010)

| LOI # | Protocol Title (Phase, Intervention, Population) | Target Accrual | Current Accrual (UM/ Other Sites) | Submitted | | PI | PCCTC-DOD Participating Sites | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | | Start Date | End Date | | | |
| c09-031 | A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temozolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease | 24 | 24(6/18) | 5/17/2010 | 10/22/10 | Dr. Maha Hussain | MSK, OHSU, UCSF, UWisc | Met accrual goal |
| c09-041 | A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA | 42 | 27(5/22) | 4/8/2010 | Open and accruing | Dr. Maha Hussain | DF-HCC, OHSU, JHU, UCSF, MDACC, UWisc,Duke | |
| c09-057 | A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC) | 225 | | UMich SIV 5/10/2011 | | Dr. Maha Hussain | MDACC, CINJ, Wayne State, UChicago | |
| c11-079 | A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors | 420 | 78(22/56) | 12/17/09<br>1/5/11 to PCCTC | Open and accruing | Dr. David Smith | MSK, DF-HCC, UCSF, MDACC, Wash, Duke, Wayne State | |
| c11-080 | A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High Risk Prostate Cancer | 40 | | Expected to open late May or early June 2011 | | Dr. Dan Hamstra | JHU, Duke, UChicago (NWestern) | |

Table B. Trials in Which the *University of Michigan* Participated (as of 04/01/2010)

| LOI # | Protocol Title (Phase, Intervention, Population) | Target Accrual | Current Accrual (UM/Other Sites) | Submitted | | University of Michigan PI | Lead Site | Other Participating Sites |
|---|---|---|---|---|---|---|---|---|
| | | | | Start Date | End Date | | | |
| c07-012 | A Phase II study of AT101, to abrogate bcl-2 mediated resistance to androgen ablation therapy in patients with newly diagnosed stage D2 prostate cancer: NCI 8014 | 55 | 55(20/35) | 11/14/2008 | 9/14/2010 | Dr. Maha Hussain | UWisc | CINJ, Univ of Chicago |
| c08-009 | A Phase II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-refractory Prostate Cancer | 35 | 28(12/16) | 1/09/2009 | 10/27/2009 | Dr. Maha Hussain | MDACC | |
| c09-024 | A Randomized, Phase II Study of GW786034 (Pazopanib) in Stage D0 Relapsed Androgen Sensitive Prostate Cancer Following Limited GnRH Agonist Therapy | 94 | 45(6/39) | 11/1/2007 | 4/20/2010 | Dr. Maha Hussain | UMich | UWisc, UChicago |
| c09-033 | A Randomized Phase II Clinical Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer | 58 | 26(5/21) | 12/1/2009 | 10/1/2010 | Dr. David Smith | JHU | Wayne State |
| c08-009 | A Phase I/II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-refractory Prostate Cancer (Re-opened) | 53 | 1(1/0) | 12/1/2010 | 2/2/2011 | Dr. Maha Hussain | MDACC | UCSF |

Table C. Quarterly Patient Accrual by the *University of Michigan* (as of 04/01/2010)

| Quarter | Accrual Per Quarter | DAP Accrual Per Quarter | Total Accrual To Date |
|---|---|---|---|
| 2Q10 | 13 | 2 | 15 |
| 3Q10 | 10 | 3 | 28 |
| 4Q10 | 7 | | 35 |
| 1Q11 | 3 | | 38 |
| 2Q11 | | | |

Table D. *University of Michigan* disproportionately affected populations (DAP) accruals by individual trials and accrual totals (as of 04/01/2010)

| DOD# | White | African-American | White Hispanic | Total |
|---|---|---|---|---|
| **c07-012** | **4** | **2** | | **6** |
| **c08-009** | **1** | | | **7** |
| **c09-031** | **5** | **1** | | **13** |
| **c09-033** | **1** | | | **14** |
| **c09-044** | **5** | | | **19** |
| **c11-079** | **17** | **1** | **1** | **38** |
| **Total** | **33**<br>**89.2%** | **3**<br>**8.1%** | **1**<br>**2.7%** | **100%** |

Table E. The *University of Michigan* patient contribution to other DOD-PCCTC member trials (as of 04/01/2010)

| UMich site led studies (Accrual #) | | UMich site accruals to other consortium site led studies (Accrual #) | |
|---|---|---|---|
| c11-079 XL184 | (19) | c09-033 Itraconazole | (1) |
| c09-044 TAK700 | (5) | c08-033 Nab-docetaxel | (1) |
| c09-031 ABT-888 | (6) | c07-012 AT-101 | (6) |
| Total | 30 | | 8 |
| **% total of accruals** | **79** | | **21%** |

Table F. Personnel Receiving Pay From the Research Effort at the *University of Michigan*

| **Role** | **Name** |
|---|---|
| Principal Investigator | Maha Hussain, MD |
| Co-Investigator | David C. Smith, MD |
| Co-Investigator | Kenneth J. Pienta, MD |
| Co-Investigator | Kathleen Cooney, MD |
| Clinical Research Coordinator - Reg | Charles Leister |
| Clinical Research Administrator | Gregory Campbell |
| Research Nurse | Tamara Huebner |
| GU Data Manager | Patricia Jo Harvey |
| GU Data Manager | Amie Anderson |
| Biostatistician | Stephanie Daignault-Newton |

## Appendix A

PC080189-2043

# A PHASE 2 RANDOMIZED STUDY OF CIXUTUMUMAB (IMC-A12) OR RAMUCIRUMAB (IMC-1121B) PLUS MITOXANTRONE AND PREDNISONE IN PATIENTS (PTS) WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (CRPC) FOLLOWING DISEASE PROGRESSION ON DOCETAXEL-BASED CHEMOTHERAPY

**Maha Hussain,1 Dana Rathkopf,2 Glenn Liu,3 Andrew J. Armstrong,4 William Kevin Kelly,5 Anna Ferrari,6 John Hainsworth,7 Ling Yang,8 Jonathan Schwartz,8 Hagop Youssoufian,8 and Celestia S. Higano9**

1University of Michigan, Ann Arbor, 2Memorial Sloan-Kettering Cancer Center, 3University of Wisconsin Carbone Cancer Center, 4Duke University Medical Center, 5Yale University, 6New York University Cancer Institute, 7Sarah Cannon Cancer Center, 8ImClone Systems, Inc., and 9Fred Hutchinson Cancer Research Center

**Background:** Vascular endothelial growth factor (VEGF)-mediated angiogenesis and insulin-like growth factor (IGF-1R)-mediated signaling contribute to prostate cancer progression. Cixutumumab (CIX; IMCA12) is a fully human IgG1 recombinant monoclonal antibody (MAb) that specifically targets the human IGF-IR and ramucirumab (RAM; IMC-1121B) is a fully human IgG1 MAb that inhibits VEGF receptor-2 (VEGFR-2) binding and signaling. We investigated the safety and efficacy of CIX or RAM in combination with mitoxantrone (M) plus prednisone (P) in castration-resistant prostate cancer (CRPC) patients (pts) that had progressive disease (PD) on docetaxel.

**Methods:** Eligible pts had metastatic CRPC with PD during/within 120 days of docetaxel (defined as PD by RECIST, at least two new bone lesions, and/or increasing prostate specific antigen [PSA]), ECOG PS 0-2, PSA ≥ 2 ng/mL, and adequate organ function. All pts received M 12 mg/m2 IV on day 1 every 3 weeks + P 5 mg PO BID and were randomized to either CIX 6 mg/kg or RAM 6 mg/kg each administered intravenously weekly for up to 12 cycles. Tumor assessments were after the first three cycles, then every 6 weeks. The primary endpoint was composite progression-free survival (cPFS, as defined by RECIST, bone scan progression, new skeletal events, and other components, including death). Other endpoints were safety, response, overall survival (OS), and pharmacokinetic/pharmacodynamic profiles. Sample size was based on a targeted 50% improvement in median cPFS from 11.1 to 16.7 weeks, based on results presented from a large trial in chemotherapy refractory CRPC in which a similar cPFS was employed (SPARC; Sternberg et al. ASCO, 2007).

**Results:** Of 139 pts randomized, 132 received study treatment. The median age for the 66 pts on CIX was 65 years and for the 66 pts on RAM 68 years. The median PSA for CIX was 118.5 ng/mL and 113.8 ng/mL for RAM. Median number of cycles was 5 for CIX and 6 for RAM. Median duration of follow-up was 6.8 months (m) for CIX and 9.1 m for RAM. Nineteen pts continue to receive RX as of 7-29-10. The most frequently observed adverse events considered at least possibly related to study drug: for CIX included fatigue 59% (15% Grade [G] ≥3), nausea 38% (2% G≥3), and anorexia 33% (0 G≥3); for RAM included fatigue 58% (5% G≥3), nausea 35% (0 G≥3), and diarrhea 30% (2% G≥3). Preliminary median cPFS is 4.1m (2.2-6.3 m 95% CI [confidence interval]) on CIX and 7.4 m (4.5-9.3 m 95% CI) on RAM. Preliminary OS is 10.2 m (6.4-15.4 m 95% CI) on CIX and 13.0 m (9.3-16.7 m 95% CI) on RAM. Preliminary PSA response is the same for both arms at 21% (11%-34% 95% CI). Preliminary radiographic response rate (CR+PR) is 9.1% (3.4%-18.7% 95% CI) on CIX and 10.6% (4.4%-20.6% 95% CI) on RAM.

**Conclusions:** Both CIX/M/P and RAM/M/P were reasonably tolerated in CRPC. Preliminary PFS and OS of RAM/M/P appear encouraging, favoring further investigation of this regimen.

**Impact:** Therapeutic options in chemotherapy refractory prostate cancer are limited. The protocol investigated two novel regimens involving targeted monoclonal antibodies in combination with an established cytotoxic chemotherapy in pts with docetaxel-refractory CRPC. The addition of an anti-VEGFR2 antibody therapy to M/P appears encouraging and may be associated with enhanced efficacy and a favorable safety profile.

*This work was supported by the U.S. Army Medical Research and Materiel Command under W81XWH-09-1-0146.*

Appendix B

PC081610-1865

# THE PROSTATE CANCER CLINICAL TRIALS CONSORTIUM: A COLLABORATIVE MULTICENTER PROSTATE CANCER RESEARCH MODEL

**Howard I. Scher,[1] Tomasz M. Beer,[2] Michael A. Carducci,[3] Paul Corn,[4] Robert Dipaola,[5] Daniel J. George,[6] Andrea L. Harzstark,[7] Elisabeth I. Heath,[8] Celestia S. Higano,[9] Maha Hussain,[10] Michael J. Morris,[1] Susan F. Slovin,[1] Walter Stadler,[11] Mary-Ellen Taplin,[12] and George Wilding[13]**

[1]Memorial Sloan-Kettering Cancer Center, [2]Oregon Health & Science University, [3]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, [4]University of Texas M. D. Anderson Cancer Center, [5]Cancer Institute of New Jersey, [6]Duke Comprehensive Cancer Center, [7]University of California, San Francisco Comprehensive Cancer Center, [8]Karmanos Cancer Institute, [9]University of Washington, [10]University of Michigan Cancer Center, [11]University of Chicago, [12]Dana-Farber Cancer Institute, and [13]University of Wisconsin Comprehensive Cancer Center

**Background and Objectives:** The Prostate Cancer Clinical Trials Consortium (PCCTC) was formed in 2006 by congressional mandate with support from the Department of Defense (DOD) Clinical Consortium Award and the Prostate Cancer Foundation (PCF) with the objective of streamlining early phase drug development, enhancing collaboration among prostate cancer research centers, and promoting clinical trial availability for patients. A novel infrastructure centered at Memorial Sloan-Kettering Cancer Center supports this consortium to design, review, prioritize, and conduct Phase I and Phase II trials. Additionally, PCCTC is spearheading an effort to develop novel biomarkers and explore new endpoints associated with its trials.

**Methodologies:** The initial PCF and DOD award funded the consortium for 3 years and was renewed in 2007 for 5 additional years. The consortium facilitates trial development between member sites, individual investigators, and research sponsors. To do so, a comprehensive suite of services and administrative, legal, and financial elements have been developed to manage and eliminate barriers to the design, activation, and completion of early-phase multicenter trials. Critical portfolio analysis centered on strategic growth has been initiated to drive the scientific agenda.

**Results to Date:** The PCCTC has expanded its membership from 8 to 13 National Cancer Institute-designated Comprehensive Cancer Centers. Unified protocol and consent language, standard endpoints (PCWG2), novel biomarkers, and the use of "Go-No Go" metrics have been developed and adopted. As of July 2010, more than 2,227 men with prostate cancer have been enrolled in consortium trials since inception. In this time, the PCCTC has reviewed 129 proposals, accepting 103 for activation, 45 of which have been completed. Principles for the analytical validation of biomarkers have been established within the PCCTC, and efforts to qualify circulating tumor cell (CTC) and imaging biomarkers have been embedded in consortium trials. The PCCTC has studied 10 agents in a succession of trials and crucially, advanced 5 therapeutic candidates to Phase III study.

**Conclusion:** The PCCTC fulfills a congressional directive to create an instrument dedicated to rapid accrual to early-phase, multicenter trials in prostate cancer. Centralized management of research activities has yielded an increased number of proposed trials and patients accrued, critical reviews of biomarkers, and notably, development in the Phase III space. With continued support from the DOD and PCF, the PCCTC is evaluating clinical and translational business models for sustainability into the future**Impact Statement:** The PCCTC is the first prostate cancer clinical consortium and has redefined the collaborative multicenter effort to develop novel therapies, endpoint, and biomarkers in prostate cancer.

*This work was supported by the U.S. Army Medical Research and Materiel Command under W81XWH-09-1-0147 and the Prostate Cancer Foundation.*

ASCO American Society of Clinical Oncology
www.asco.org

# Phase II study of AT-101 to abrogate Bcl-2-mediated resistance to androgen-deprivation therapy (ADT) in patients (pts) with newly diagnosed androgen-dependent metastatic prostate cancer (ADMPC).

**Sub-category:**
Prostate Cancer
**Category:**
Genitourinary Cancer
**Meeting:**
2011 Genitourinary Cancers Symposium
**Session Type and Session Title:**
General Poster Session B: Prostate Cancer
**Abstract No:**
137
**Citation:**
J Clin Oncol 29: 2011 (suppl 7; abstr 137)
**Author(s):**
M. N. Stein, I. Khan, M. Hussain, G. Liu, G. Wilding, E. M. Posadas, W. M. Stadler, C. Jeyamohan, S. Eddy, R. S. DiPaola, Prostate Cancer Clinical Trials Consortium; The Cancer Institute of New Jersey/University of Medicine and Dentistry of New Jersey, New Brunswick, NJ; Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, New Brunswick, NJ; University of Michigan, Ann Arbor, MI; University of Wisconsin Carbone Cancer Center, Madison, WI; The University of Chicago Medical Center, Chicago, IL; The Cancer Institute of New Jersey, New Brunswick, NJ

**Abstract:**

**Background:** Preclinical studies demonstrate that Bcl-2 is over-expressed in most pts with prostate cancer, causes drug resistance to ADT, and that modulation of Bcl-2 improves sensitivity of tumor cells. We are conducting a phase II study for men with ADMPC to test the hypothesis that AT-101, a small molecule Bcl-2 inhibitor, improves clinical results of pts initiating ADT for metastatic prostate cancer. Building on results from SWOG 9346 (Hussain JCO 2006) demonstrating that PSA nadir after 7 mo of ADT predicts survival, we are using a novel phase II trial design, in which the primary endpoint is the percentage of patients with PSA ≤ 0.2 ng/ml at 7 mo of ADT plus AT-101. **Methods:** Pts had ADMPC, PSA > 5.0 ng/ml within 12 wks prior to registration and no prior ADT for metastatic disease. ADT with LHRH agonist and bicalutamide started 6 wks prior to initiation of oral AT-101, 20 mg/day for 21 days of 28 day cycle. Pts received up to 8 cycles of ADT and AT-101. A total of 55 pts were enrolled (to obtain 48 evaluable pts) to in a two stage design with null hypothesis 48% versus alternative 68% with PSA ≤ 0.2 at 7 mo. With $\alpha = 0.1$ and $\beta = 0.9$, > 27 pts meeting this endpoint are required to recommend further study. **Results:** 55 pts were enrolled, median age 61.5 y; Gleason score (GS) 6 (5%),GS 7 (30%), GS 8 (24%), and GS 9 (41%). 3 pts had visceral mets and the remaining pts had bone or nodal metastasis. 42 pts have discontinued (9 toxicity, 9 progression, 1 withdrew) or completed (n = 23) 7 mo of treatment. In intention to treat analysis, 11 of 42 pts (26%) met the primary endpoint 10, of 42 (23%) pts had PSA > 0.2 and < 4.0 ng/ml after 7 mo. Grade 1/2 toxicities (%) included fatigue (36/9), nausea (20/9), vomiting (13/7), anorexia (15/2), AST/ALT (25/5), hypercalcemia (9/0), constipation (13/3), dry skin (9/0), anemia (18/0), sensory neuropathy (7/7), vomiting (12/7), hyperglycemia (7/4). Grade 3 toxicities were sensory neuropathy 2 pts, GI obstruction 1 pt, syncope 1 pt. **Conclusions:** Although final study results are pending the analysis of pts currently on therapy, 26% of pts achieved an undetectable PSA at 7 mo in a population with aggressive disease (66% GS ≥ 8).

Appendix D

American Society of Clinical Oncology
www.asco.org

## A randomized phase II study of pazopanib in castrate-sensitive prostate cancer: A University of Chicago phase II consortium/DoD Prostate Cancer Clinical Trials Consortium study.

**Sub-category:**
Prostate Cancer
**Category:**
Genitourinary Cancer
**Meeting:**
2011 Genitourinary Cancers Symposium
**Session Type and Session Title:**
General Poster Session B: Prostate Cancer
**Abstract No:**
170
**Citation:**
J Clin Oncol 29: 2011 (suppl 7; abstr 170)
**Author(s):**
J. E. Ward, S. Limvorasak, T. Karrison, G. S. Chatta, M. Hussain, D. H. Shevrin, R. Z. Szmulewitz, W. M. Stadler, E. M. Posadas; The University of Chicago Medical Center, Chicago, IL; University of Pittsburgh Medical Center, Pittsburgh, PA; University of Michigan, Ann Arbor, MI; NorthShore University Health System, Evanston, IL

**Abstract:**

**Background:** Intermittent androgen suppression (IAS) has been studied as a way of minimizing toxicity from long term androgen deprivation therapy (ADT). Based on previous studies with similar agents, we hypothesized that inhibition of VEGFR would result in prolonged time to PSA progression (TTPP) and allow for longer periods off ADT. **Methods:** Men with biochemically recurrent, progressive prostate cancer and no evidence of macroscopic metastases were enrolled. They received 6 months of ADT. If at the end of that time the PSA was <0.5 ng/mL (with castrate testosterone levels), they were randomized to pazopanib 800 mg/d or observation. The primary outcome was TTPP, defined as time to a PSA >4.0 ng/mL, at which time they were restarted on ADT. **Results:** 37 pts met randomization criteria. 18 were randomized to pazopanib. Only 4 pts met the endpoint criteria of TTPP, whereas 13 (72%) pts went off study for other reasons with 1 pt on treatment at study closure. Reasons for discontinuation included drug toxicity (grade 1/2, 9 pts) and patient preference (2 pts). No grade 3/4 toxicity was noted. 1 pt was removed due to pulmonary embolus, 1 pt due to MD discretion and 1 pt due to noncompliance. 19 pts were randomized to observation of which 12 were off treatment when the study was stopped. Only 5 pts met criteria for TTPP, whereas 7 of 12 (58%) dropped out for other reasons, including the frequency of protocol related blood draws and visits (3 pts) and randomization to observation (2 pts), 1 pt was removed per MD discretion and 1 pt transferred care. Due to high dropout rates in both arms, accrual was halted as the primary endpoint could not be measured robustly. **Conclusions:** Minimizing the long term toxicities of ADT is an unmet need in prostate cancer therapy. Hence clinical interventions in concert with IAS represent an attractive area for drug development. This trial has outlined several barriers that exist in studying this patient population and might help to optimize future studies. Future trial design in this arena should investigate drugs with minimal toxicity and employ a design that maximizes patient convenience while anticipating the low threshold for patient drop out.

Appendix E

American Society of Clinical Oncology
www.asco.org

# Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease.

**Sub-category:**
Prostate Cancer
**Category:**
Genitourinary Cancer
**Meeting:**
2011 Genitourinary Cancers Symposium
**Session Type and Session Title:**
General Poster Session B: Prostate Cancer
**Abstract No:**
127
**Citation:**
J Clin Oncol 29: 2011 (suppl 7; abstr 127)
**Author(s):**
D. C. Smith, M. R. Smith, E. J. Small, C. Sweeney, R. Kurzrock, M. S. Gordon, N. J. Vogelzang, C. Scheffold, M. D. Ballinger, M. Hussain; University of Michigan Cancer Center, Ann Arbor, MI; Massachusetts General Hospital Cancer Center, Boston, MA; University of California, San Francisco, San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA; University of Texas M. D. Anderson Cancer Center, Houston, TX; Pinnacle Oncology of Arizona, Scottsdale, AZ; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Exelixis, South San Francisco, CA; University of Michigan, Ann Arbor, MI

**Abstract:**

**Background:** XL184 is an oral, potent inhibitor of MET and VEGFR2. MET pathway activation promotes tumor growth, invasion and metastasis. Overexpression of MET and/or its ligand HGF are associated with prostate cancer metastasis. In preclinical studies, androgen ablation upregulates MET signaling. Preliminary data from the open label Lead-in Stage of an ongoing adaptive design phase II randomized discontinuation trial are presented. **Methods:** Eligible pts had CRPC, measurable disease with or without bone metastasis, and disease progression on ≤1 prior non-hormonal systemic treatment. XL184 was administered orally for 12 weeks (wks). Tumor (RECIST) and bone scan response (complete or partial resolution) were assessed every 6 wks. Primary endpoint is objective response rate at wk 12. Pts with SD at wk 12 will enter a placebo-controlled randomized phase. **Results:** As of 10/4/10, 72 pts have been enrolled. Median time on study was 50 days (range, 6+-350+ days). Median age was 69 yrs; 45% of pts were docetaxel-pretreated. All pts had measurable disease, including 69% with visceral metastases. To date, there are 24 response evaluable pts, defined as enrolled ≥12 wks prior to data cutoff. 5/24 (21%) pts had a partial response (≥30% reduction) in measurable disease with 3 responses confirmed at 12 wks and 2 unconfirmed responses ongoing. 6/24 (25%) had PSA declines of ≥50%. 13 of 15 (87%) pts with known bone metastases had either complete or partial resolution of lesions on bone scan. Bone scan responses were associated with investigator-reported improvement in bone pain in 11/15 (73%) with pain at baseline. Effects on osteoclast and osteoblast activity were observed: plasma C-telopeptide declined ≥50% in 8/12 (66%) pts and serum total alkaline phosphatase (tALP) declined ≥50% in 5/8 (63%) pts with bone metastases and baseline elevated tALP. The most common AEs ≥Grade 3 severity (related) were fatigue (10%), diarrhea (3%) and elevated AST (3%). **Conclusions:** XL184 results in tumor responses, partial or complete resolution of lesions on bone scan, and symptom relief in pts with metastatic CRPC, including those pretreated with docetaxel. XL184 also decreased biomarkers of both osteoblast and osteoclast activity.

**406 Phase 2 study of XL184 in a cohort of patients (pts) with castration resistant prostate cancer (CRPC) and measurable soft tissue disease**

POSTER
**D.C. Smith** A. Spira, J. De Grève, L. Hart, S. Holbrechts, C.C. Lin, M. Hussain, S. Herrick, K. Houggy, N. Vogelzang University of Michigan, Department of Medicine Ann Arbor USA; Fairfax Northern Virginia Hematology-Oncology PC, NA Fairfax USA; Universitair Ziekenhuis Brussel, Department of Medical Oncology Brussels

**Background:** XL184 is an oral potent inhibitor of MET, VEGFR2 and RET. Activation of the MET pathway promotes tumor growth, invasion, and metastasis. Overexpression of MET and/or its ligand HGF have been shown to correlate with prostate cancer metastasis to lymph nodes and bones, and disease recurrence. In addition, androgen ablation has been shown to upregulate MET signaling in preclinical studies. Targeting the MET pathway with XL184 may therefore be a promising treatment strategy. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with CRPC.

**Methods:** Eligible pts have CRPC with measurable disease and have progressed on up to 1 prior non-hormonal systemic treatment after antiandrogen withdrawal. XL184 is administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response is assessed radiologically every 6 wks. Pts with partial or complete response (PR or CR) at wk 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184. Pts with SD at wk 12 are randomized 1:1 to receive XL184 or placebo. Cross-over from placebo to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage. PSA levels will be correlated with clinical outcomes.

**Results:** A total of 16 pts have been enrolled with a median age of 69 years. The median number of prior non-hormonal systemic treatments was 1, with 7 pts receiving docetaxel. Of 9 pts who were evaluable (minimum 12 wks follow up) to date, 1 pt achieved a PR and 5 pts achieved SD for an overall disease control rate of 67% at wk 12. Two pts achieved a near complete resolution of tracer uptake on bone scan with one pt previously treated with docetaxel who attained a 41% reduction in measurable disease and a reduction of PSA > 50% at wk 12. Most frequently observed adverse events regardless of causality with CTCAE Grade ⩾3 in the Lead-in Stage were fatigue and asthenia (each n = 2).

**Conclusions**: Preliminary results suggest that XL184 is active in CRPC pts who failed prior treatment. XL184 was generally well tolerated. Updated efficacy and safety results will be presented.

**Poster Presentation at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Berlin, Germany 16-19 November, 2010.**

Appendix G

2011 ASCO Annual Meeting

Maha Hussain

Logout

HOME

MY PRESENTATION

Oral Abstract Session: Genitourinary Cancer (Prostate)
Role: Presenter

- Session Information
- Session Responsibilities
- My Abstract
- Upload/View Presentation

MY TASKS

MY PROFILE

ATTENDING MEETING

OTHER RESOURCES

My Presentation

## My Abstract

For your convenience, a copy of your submitted abstract is below.

**Abstract ID (Temp. Abst. ID): 4516(82339)**
**Title:** Cabozantinib (XL184) in metastatic castration resistant prostate cancer (mCRPC): Results from a phase 2 randomized discontinuation trial.
**Author(s):** M. Hussain, M. R. Smith, C. Sweeney, P. G. Corn, A. Elfiky, M. S. Gordon, N. B. Haas, A. L. Harzstark, R. Kurzrock, P. Lara Jr., C. Lin, A. Sella, E. J. Small, A. I. Spira, U. N. Vaishampayan, N. J. Vogelzang, C. Scheffold, M. D. Ballinger, F. Schimmoller, D. C. Smith
**Abstract:**
**Background:** Cabozantinib (Cabo) is an inhibitor of MET & VEGFR2. MET signaling promotes tumor growth, invasion & metastasis. **Methods:** mCRPC patients (pts) with progressive measurable disease (mRECIST) received Cabo at 100 mg qd PO over a 12 week (wk) Lead-in stage. Response was assessed q6 wks. Treatment ≥ wk 12 was based on response: pts with PR continued open-label Cabo, pts with SD were randomized to Cabo vs placebo, & pts with PD discontinued. Primary endpoint was objective response rate (ORR) per mRECIST in the Lead-in stage. Up to 200 pts could be enrolled to target 70 randomizations. Bone scans (b-scans) were independently reviewed. **Results:** Accrual was halted at 168 pts based on an observed high rate of clinical activity. 100 pts are currently evaluable for the Lead-in stage; median age 68, 47% with visceral disease, 78% with bone metastasis, & 47% docetaxel (D) pretreated. Median f/u was 4 months (range, 1-15); median PFS not yet reached. Most common related Grade 3/4 AEs were fatigue (11%), HTN (7%), & hand-foot syndrome (5%); no related Grade 5 AEs reported. Dose reductions for AEs occurred in 51% of pts, & discontinuations in 10%. **Bone effects**: 86% (56/65 pts evaluable by b-scan) had complete or partial resolution of lesions on b-scan as early as wk 6. Eight pts (12%) had SD & 1 pt (2%) had PD. In 28 pts receiving narcotics for bone pain, 64% had improved pain & 46% decreased or halted narcotics, per investigator. Median maximum rise in hemoglobin in anemic pts (Hb < 11 g/dL) was 2.2 g/dL (range, 0.6-3.5). Osteoclast & osteoblast effects were observed: 55% had declines of ≥50% in plasma C-Telopeptide; 56% of pts with elevated tALP had declines of ≥50%. **Soft tissue effects**: Objective tumor shrinkage occurred in 84% of pts. ORR at wk 12 was 5%; 3 additional PRs await confirmation. PSA changes were independent of clinical activity. Overall, wk 12 disease control rate (PR+SD) was 71%. Randomization was halted & pts unblinded due to high rates of b-scan resolution & pain relief.
**Conclusions:** Cabo showed clinical activity regardless of prior D in mCPRC pts, particularly in pts with bone disease, as reflected by high rates of b-scan resolution & pain relief, in addition to improvements in Hb & tumor regression.

**Upload your Presentation:**
Link to upload site will be available April 15, 2011

**Plan Your Meeting:**
ASCO's ePlanner will be available April 18, 2011

**Book Your Housing:**
Housing Reservation Deadline: Wednesday, April 20, 2011

**View ASCO Abstracts:**
Abstracts to be Released on ASCO.org May 18th at 6:00 PM EDT

Appendix H

Invest New Drugs
DOI 10.1007/s10637-010-9573-5

PHASE II STUDIES

# Phase II study of Cilengitide (EMD 121974, NSC 707544) in patients with non-metastatic castration resistant prostate cancer, NCI-6735. A study by the DOD/PCF prostate cancer clinical trials consortium

**Ajjai Alva · Susan Slovin · Stephanie Daignault · Michael Carducci · Robert DiPaola · Ken Pienta · David Agus · Kathleen Cooney · Alice Chen · David C. Smith · Maha Hussain**

Received: 22 September 2010 / Accepted: 21 October 2010


**Summary** *Background*: Integrins mediate invasion and angiogenesis in prostate cancer bone metastases. We conducted a phase II study of Cilengitide, a selective antagonist of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, in non-metastatic castration resistant prostate cancer with rising PSA. *Methods*: Patients were observed for 4 weeks with PSA monitoring, and then treated with 2,000 mg IV of cilengitide twice weekly until toxicity/progression. PSA, circulating tumor cells (CTCs) and circulating endothelial cells (CECs) were monitored each cycle with imaging performed every three cycles. Primary end point was PSA decline by ≥50%. Secondary endpoints were safety, PSA slope, time to progression (TTP), overall survival (OS), CTCs, CECs and gene expression. *Results*: 16 pts were enrolled; 13 were eligible with median age 65.5 years, baseline PSA 8.4 ng/mL and median Gleason sum 7. Median of three cycles was administered. Treatment was well tolerated with two grade three toxicities and no grade four toxicities. There were no PSA responses; 11 patients progressed by PSA after three cycles. Median TTP was 1.8 months and median OS has not been reached. Median pre- and on-treatment PSA slopes were 1.1 and 1.8 ng/mL/month. Baseline CTCs were detected in 1/9 patients. CTC increased (0 to 1; 2 pts), remained at 0 (2 pts) or decreased (23 to 0; 1 patient) at progression. Baseline median CEC was 26 (0–61) and at progression, 47 (15–148). Low cell counts precluded gene expression studies. *Conclusions*: Cilengitide was well tolerated but had no detectable clinical activity. CTCs are of questionable utility in non-metastatic prostate cancer.

**Keywords** EMD 121974 · Cilengitide · Non-metastatic castration resistant prostate cancer

This study was presented in part at the 2010 American Society of Clinical Oncology Genitourinary Symposium.

A. Alva · S. Daignault · K. Pienta · K. Cooney · D. C. Smith · M. Hussain (✉)
University of Michigan Comprehensive Cancer Center,
7314 Cancer Center, 1500 East Medical Center Drive,
Ann Arbor, MI 48109-5946, USA
e-mail: mahahuss@med.umich.edu

S. Slovin
Memorial Sloan-Kettering Cancer Center,
New York, NY, USA

M. Carducci
The Sidney Kimmel Comprehensive Cancer Center,
Johns Hopkins School of Medicine,
Baltimore, MD, USA

R. DiPaola
The Cancer Institute of New Jersey,
New Brunswick, NJ, USA

D. Agus
University of Southern California,
Los Angeles, CA, USA

A. Chen
National Cancer Institute,
Bethesda, MD, USA

*Present Address:*
A. Alva
Baylor College of Medicine,
Houston, TX, USA

Published online: 04 November 2010

## Introduction

Non-metastatic castration resistant prostate cancer (CRPC) is a distinct disease state that is characterized by rising PSA despite androgen deprivation therapy without evidence of distant metastases. This clinical state could last a few years and presents an opportunity to intervene with therapy designed to delay progression to metastatic disease [1]. Delay/prevention of clinical systemic metastasis is a clinically meaningful objective.

Formation of bone metastasis is a multi-step process that involves invasion of the vasculature by tumor cells, cell migration to and adhesion at distant bone sites, angiogenesis and tumor growth [2, 3]. Interactions between tumor and endothelial cells on one hand and the extracellular matrix (ECM) components (such as vitronectin, fibronectin and osteopontin) on the other mediate several of these steps. Interactions of the ECM with tumor cells and endothelial cells are dependent on a class of transmembrane cell surface receptors called integrins.

### The role of integrins in prostate cancer metastases

Integrins transduce signals between the ECM and the intracellular cell signaling pathways of endothelial or tumor cells in both directions[4]. Structurally, they are heterodimers consisting of an alpha and a beta subunit. At least 18 alpha and eight beta subunits have been identified with more than 24 unique integrin heterodimers recognized so far[5].

Integrins play important roles in cell migration, adhesion, invasion, proliferation, survival and angiogenesis of epithelial neoplasms [4, 6, 7] . $\alpha_v\beta_3$ is expressed in prostate cancer cells but not in normal prostate cells[8]. Prostate cancer cell lines derived from bone metastases uniformly express $\alpha_v\beta_3$[9]. Preclinical studies show that $\alpha_v\beta_3$ integrin mediates the adhesion of prostate cancer cells to ECM components of the bone such as osteopontin [10, 11]. $\alpha_v$ integrins also promote survival of prostate cancer cells in bone[12] and siRNAs directed against $\alpha_v$ integrins induce apoptosis of PC3 prostate cancer cells in bone[13]. $\alpha_v\beta_3$ also mediates osteopontin (ECM component) triggered proliferation of castration resistant prostate cancer cells in bone[14]. Bone turnover by osteoblasts and osteoclasts involves interaction of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ with osteopontin and bone sialoprotein [15, 16]. Blockade of $\alpha_v\beta_3$ reduces osteoclast recruitment and bone lysis initiated by metastatic cancer cells[17]. Thus, integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ promote metastasis of prostate cancer cells to bone in each step of the metastatic process [4, 5, 18].

Endothelial cells when activated by tumor secreted cytokines express $\alpha_v\beta_3$ [19]. A crucial role of $\alpha_v\beta_3$ in activated endothelial cells is to inhibit apoptosis by up-regulating NF-kB activity [20, 21]. Antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ block endothelial cell proliferation and differentiation induced by fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor (VEGF) in cell lines, chicken chorioallantoic membrane (CAM) and severe combined immunodeficient (SCID) mice [22]. Novel agents that target integrins have shown promising clinical activity in glioblastoma multiforme [23].

*Cilengitide* Cyclo-l-Arg-Gly-l-Asp-d-Phe-N (Me) l-Val; (Merck KGaA, Darmstadt, Germany) is a cyclic pentapeptide and RGD mimetic that selectively and competitively antagonizes ligand binding to $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in vitro. Cilengitide or EMD121974 inhibited proliferation and increased apoptosis in cell lines and caused tumor regression in cell culture [24, 25]. It blocks angiogenesis stimulated by VEGF and FGF in a 3-D gel of bovine endothelial cells [26]. Cilengitide also inhibited $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in CAM and in orthotopic models of human melanoma, medulloblastoma and glioblastoma (GBM) in nude and SCID mice [27, 28].

In a phase I clinical trial of cilengitide in advanced solid tumors, twice-weekly infusions of cilengitide were administered to 37 patients continuously at doses from 30 mg/m$^2$ up to 1600 mg/m$^2$ in 4 week cycles [29]. In another phase I trial, 20 patients were treated at two doses (600 and 1200 mg/m$^2$ on the same schedule as the above study) [30]. In both studies, no dose limiting toxicity was observed. The terminal half-life at all doses in both studies was around 4 h. $C_{max}$ concentrations achieved in plasma at 120 mg/m$^2$ were comparable to tumor inhibitory plasma levels in mice. No hematological or grade 3/4 non-hematologic toxicity were reported. In the phase I component of two NCI sponsored studies (NCT00022113 and NABTT-9911/ NCT00006093) of cilengitide given intravenously twice weekly, no dose limiting toxicity was observed at doses as high as 2400 mg/m$^2$.

Given the critical role of integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in promoting angiogenesis and bone metastasis in prostate cancer and the preclinical and clinical safety profile of cilengitide we conducted a single-arm multi-center NCI sponsored phase II study of single agent cilengitide (NCI-6735) in non-metastatic rising PSA-only castration-resistant prostate cancer. The dosing and schedule were based on earlier phase I trials of cilengitide and phase II trials in advanced melanoma (00082875 MDACC 2004) and recurrent GBM (NCT00093964).

## Patients and methods

Patients were eligible if they had a histologic or cytologic diagnosis of prostate cancer with no evidence of metastatic

disease or local progression on radiologic imaging (Bone scan, CT/MRI of abdomen and pelvis) and had three consecutive rising levels of prostate specific antigen (PSA) at a minimum of one week intervals with the last of those values ≥2 ng/mL. Patients had to have PSA progression despite androgen deprivation therapy and anti-androgen withdrawal (≥ 4 weeks off flutamide; ≥ 6 weeks off bicalutamide or nilutamide). ECOG performance status of 0–2 and adequate organ and hematologic function were required (ANC ≥1500/uL, platelets ≥100,000/uL, serum creatinine ≤1.5×upper limits of normal, normal bilirubin and LFTs ≤2.5×upper limits of normal). Patients who had not had orchiectomy were required to continue on LHRH agonist therapy with a castrate range testosterone level. Patients on stable doses of steroids or megace for longer than 1 month continued on the same doses. Patients had to be >4 weeks from major surgery and prior systemic anti-cancer therapy. No previous treatment with cilengitide was allowed. Continuing bisphosphonate use was permitted if on stable doses for >6 weeks prior to registration on protocol but was not allowed to be initiated while on the study. No concurrent herbal or food supplements (such as PC-SPES or saw palmetto) other than a daily multivitamin were allowed during the study. Patients with a second active malignancy (less than 2 years from completion of therapy or with current evidence of disease) were excluded except for superficial bladder cancer or non-melanomatous skin cancer. Men of reproductive potential had to agree to use effective contraception. All patients on the study signed an informed consent approved by the institutional review board at the respective participating institution prior to study entry. This Cancer Therapy Evaluation Program (CTEP) sponsored trial was conducted by the Department of Defense-Prostate Cancer Clinical Trials Consortium.

## Treatment plan

Patients had a lead-in observation period of 4 weeks with PSA measured at 2 weeks and 4 weeks (Fig. 1). Treatment with cilengitide began after the 4 weeks lead-in period. Cilengitide was administered at a starting dose of 2000 mg intravenously over 1 h twice weekly each week in 4 week cycles without any planned breaks between cycles. Grade 4 hematologic or grade 3 or 4 non-hematologic toxicities by NCI CTCAE version 3.0 necessitated holding the drug until resolution of toxicities to grade ≤1 and re-starting treatment at −1 dose level (1600 mg/dose). Recurrent serious toxicity triggered reduction to −2 dose level (1200 mg/dose) after resolution to ≤1 grade. Therapy was stopped for a third occurrence of toxicity of that grade. Treatment could be interrupted for a maximum of two consecutive doses or four doses in a 12-week period. Based on phase I studies of cilengitide that demonstrated no dose-toxicity relationship

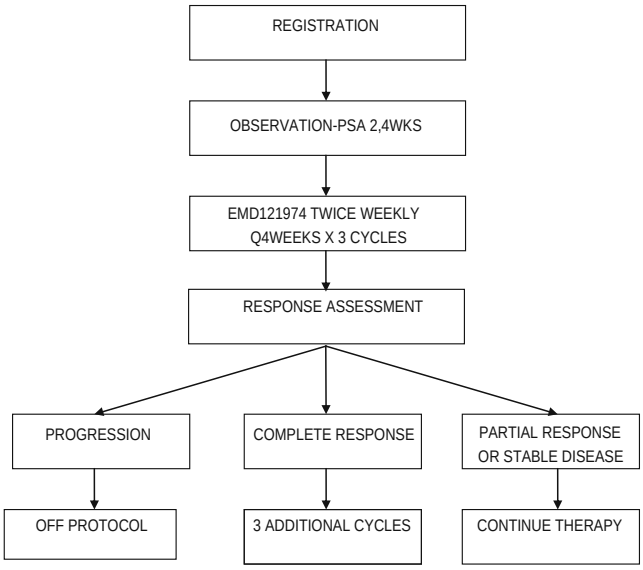


**Fig. 1** Treatment Schema

and no DLT at doses up to 2000 mg, dosing was not based on body weight or surface area [23, 29]. Cilengitide was provided by DCTD, NCI.

## Duration of therapy and monitoring

In the absence of toxicity, patients were treated on protocol for a minimum of three cycles (12 weeks) prior to response assessment in order to permit an adequate evaluation of the effect of the investigational agent. Patients were evaluated for toxicity and had PSA measured each cycle. Imaging with bone scan and CT or MRI abdomen/pelvis was performed every three cycles. Beyond the first three cycles, treatment was stopped when any one of the following occurred: clinical or PSA progression, after three additional cycles beyond complete response, recurrence of serious toxicity in spite of dose reduction to −2 dose level and maximally allowed dose interruptions, patient preference or worsening of the patient's general medical condition that precluded further treatment in the judgment of the investigator. The PSA value at the end of the 4 week lead-in period prior to the first dose was considered the baseline PSA.

## End points and statistical design

Complete response was defined as PSA <0.2 ng/mL, partial response as decline in PSA by 50% from baseline and progression as ≥25% rise in PSA over baseline or nadir whichever was lower[31]. PSA responses and progression needed confirmation by a successive PSA at least 4 weeks later. Patients not meeting criteria for either response or progression were considered to have stable disease. Patients

with partial response or stable disease by PSA criteria with no evidence of objective disease progression continued treatment with cilengitide until criteria for halting therapy were met.

The primary end-point of the study was PSA response rate (complete and partial response) in patients treated with single-agent cilengitide in non-metastatic castration-resistant prostate cancer. Secondary endpoints were safety of cilengitide, changes in PSA slope with treatment, response duration, time to progression and survival. For calculation of pre-treatment PSA slope, at least three PSA values including the lead-in observation period values on weeks 2 and 4 (baseline) were included. For on-treatment PSA slope, the baseline PSA and all PSA values in the first 6 months of treatment with cilengitide were considered. The study was designed to accrue 32 patients to provide 90% power at the 10% significance level to detect a difference between a 5% versus a 20% response rate. If four or more PSA responses were seen in this population, further study would be undertaken. To prevent against excess toxicity, if ≥3 of the first 12 patients experienced a high-grade non-hematologic toxicity (grade 3 and/or 4) excluding alopecia, nausea or vomiting, the trial would stop early. All of the eligible patients (with the exception of those who received no study medication) are included in the main analysis of the response rate. Survival and time to progression was determined by Kaplan-Meier analysis.

### Correlative biology studies

In the absence of objective disease in non-metastatic CRPC, we planned to evaluate circulating tumor and endothelial cells (CTC and CEC). Correlatives included enumeration of CTC using the CellSearch assay (Veridex, Huntington Valley, PA) and CEC using the CellTracks reagents (Veridex, formerly Immunicon Corp.). All CTC and CEC enumeration was performed at Immunicon Corp. and results were communicated to the study authors. RNA isolation was performed from CTCs and CECs from blood collected at baseline and the beginning of each cycle. Analyses included serial enumeration of CTCs and CECs in study patients, comparison of CTC/CEC numbers between patients, and microarray genotyping of CTCs/CECs.

## Results

### Baseline characteristics

Between January 2005 and May 2007, 16 patients were registered to the protocol at six centers. The protocol was closed due to lack of any PSA response coupled with slow accrual. 1 patient progressed clinically before any treatment and was not included in the toxicity or efficacy analysis. Two patients who received study drug were deemed ineligible as they did not meet entry PSA criteria of three consecutive rises in PSA but were included in the toxicity analysis. Table 1 describes the baseline demographic and clinical data of the 13 eligible patients. Median age was 65.5 years, median baseline PSA at registration was 8.4 with a range of 2.2 to 77, Gleason sum was seven in 46.2% and 8–9 in another 38.5%, and median Karnofsky performance score was 90 (range, 80–100). Six patients had undergone prior radical prostatectomy and five had undergone definitive radiation treatment. Three patients each had received salvage and adjuvant radiation therapy. Median time since hormone initiation for the 13 eligible patients was 4.7 years (range, 1–10.6 years). Median pre-treatment PSA slope was 1.1 ng/mL/month.

### Efficacy and survival

Patients were treated for a median of three cycles (range 3–8) with cilengitide. There were no PSA responses; two patients had stable disease (SD) at 12 weeks (Fig. 2) and 11 patients had progressed by PSA criteria (two by imaging also) at first assessment after three cycles. Median on-treatment PSA slope was 1.8 ng/mL/month (not significantly different from pre-treatment slope) (Fig. 2). Time to PSA progression was 1.8 months (95% CI: 0.9–2.8). All patients are off protocol therapy. With a median follow-up of 3.1 years (range, 16 months –5 years), median overall survival has not been reached for the cohort; 5 of 13 (38%) evaluable patients have died.

### Treatment related toxicity

Toxicity was evaluated by NCI-CTCAE (ver. 3) criteria in all 15 treated patients including the two ineligible patients. Therapy was tolerated very well with no grade 4 or higher adverse events reported (Table 2), There were two grade 3 (atrial fibrillation) and three grade 2 adverse events (dyspnea, lymphopenia and osteonecrosis). The patient who developed osteonecrosis was not on bisphosphonates when he was diagnosed with avascular necrosis of the femoral head. There were 22 grade 1 adverse events. Dose reduction to −1 dose level was needed in one patient (atrial fibrillation).

### Correlative analysis

In patients tested at baseline for CTCs ($n$=9), only one had any CTCs (range 0–23) reflecting the relative paucity of CTCs. For those with CTC data at progression ($n$=5), CTC increased from 0 to 1 (2 patients), remained at 0 (2 pt) and decreased

**Table 1** Baseline characteristics of eligible patients ($n$=13)

| | |
|---|---|
| Median Age (range) | 65.5 yrs (53.8–78.1) |
| Median Karnofsky Performance Score (range) | 90 (80–100) |
| Median baseline PSA (range) | 8.4 (2.2–77) |
| Gleason sum(%) 6 | 2 (15.4%) |
| 7 | 6 (46.2%) |
| 8 | 2 (15.4%) |
| 9 | 3 (23.1%) |
| Prior Radiation to prostate | 11 |
| Definitive | 5 |
| Adjuvant | 3 |
| Salvage | 3 |
| Radical Prostatectomy | 6 |
| No Local Treatment Modality | 2 |
| Median time since ADT initiation (range) | 4.7 yrs (1–10.6) |

from 23 to 0 (1 pt). In patients with baseline CEC data ($n$=10), median CEC number was 26 (range 0–61). 8 patients had serial CEC counts. At progression ($n$=7), median CEC was 47 (range 15–148). Low cell counts and RNA yield precluded correlative gene expression studies. The trend of CECs on treatment is shown in Fig. 3. The significance of the transient increase in CECs on treatment is unclear.

## Discussion

Routine PSA measurement after definitive local treatment and use of early androgen deprivation therapy have resulted in non-metastatic castration resistant prostate cancer disease state which is characterized by rising levels of PSA despite castrate levels of testosterone without other evidence of disease[32]. On the control arms of two separate randomized phase III trials evaluating atrasentan and zoledronic acid in non-metastatic CRPC patients, the median time to metastases was 25 and 30 months respectively[1, 33]. Non-metastatic CRPC offers a potential therapeutic window to decrease morbidity from CRPC by delaying or preventing systemic metastases yet few trials have been conducted in this stage due to the substantial challenges posed by the lack of measurable disease. However, the natural history of non-

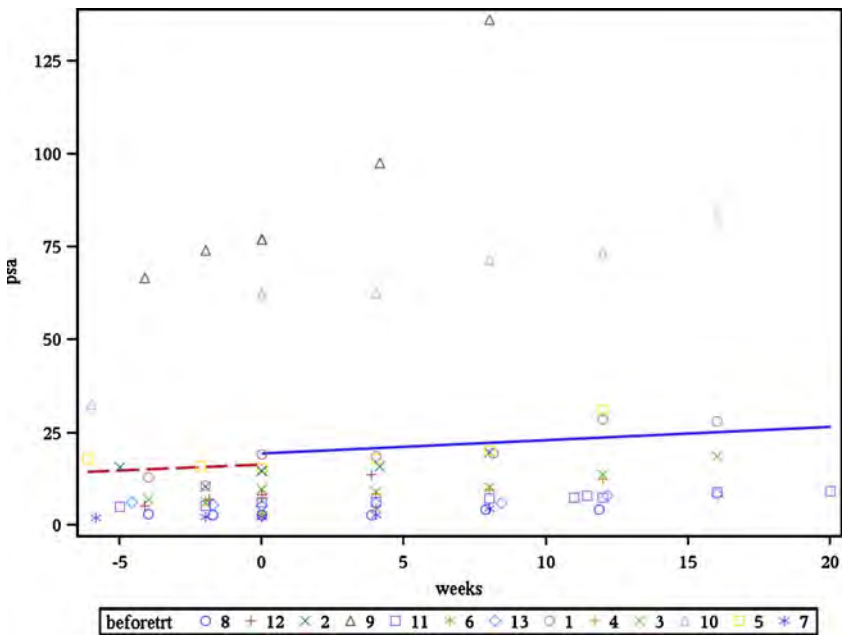


**Fig. 2** PSA velocity before and after treatment with Cilengitide in evaluable patients ($n$=13). The broken and solid lines represent median pre-treatment and post-treatment PSA velocity respectively. Treatment with Cilengitide started at week 0. Individual PSA values for all 13 eligible patients are shown as a scatter plot

**Table 2** Treatment related adverse events[a]

| Adverse Event | Grade | Number |
|---|---|---|
| Arthritis | 1 | 2 |
| Increased aspartate aminotransferase | 1 | 1 |
| Constipation | 1 | 1 |
| Diarrhea | 1 | 1 |
| Dry eye syndrome | 1 | 1 |
| Edema | 1 | 1 |
| Fatigue | 1 | 4 |
| Flushing | 1 | 1 |
| Headache | 1 | 1 |
| Decreased hemoglobin | 1 | 2 |
| Hyperglycemia NOS | 1 | 1 |
| Hyperglycemia | 1 | 1 |
| Hyponatremia | 1 | 1 |
| Memory impairment | 1 | 1 |
| Nausea | 1 | 1 |
| Rash (desquamating) | 1 | 1 |
| Toothache | 1 | 1 |
| Dyspnea | 2 | 1 |
| Lymphopenia | 2 | 1 |
| Osteonecrosis | 2 | 1 |
| Atrial fibrillation | 3 | 2 |

[a] Includes all grade 1 and above toxicities considered unknown, possible, likely or probably related to Cilengitide

metastatic CRPC is variable with greater PSA velocity and absolute PSA value predicting a more aggressive clinical course [1]. A risk adapted approach defined by such factors or other biomarkers including CTCs would certainly optimize clinical trial design in this setting.

In the absence of a control arm, a lead-in period of observation was proposed to utilize each patient as his own control by analyzing changes in PSA slope before and on treatment. We hypothesized that CTC and CEC changes could reflect disease activity and also provide a method of performing gene expression studies to verify drug activity on the intended target (the integrin pathway).

In this trial, there was no evidence of activity of Cilengitide as a single agent in this setting. There are several possible explanations for the result. It is possible that integrin mediated cell signaling was not abrogated adequately. Our ability to verify if this indeed was the case and detect drug effect on the intended target was hampered by the paucity of CTCs for the planned correlative analyses. In retrospect, CTCs (as assayed by the Veridex CellSearch test) were not ideal correlates for this trial as they are infrequently detected in the non-metastatic setting [34–36]. Though CTCs have been shown to be prognostic [37] and possibly predictive of a survival benefit with treatment in metastatic CRPC [38, 39], CTC number appears to be dependent on the tumor burden [35, 40]. CTCs are detected more frequently and at higher numbers per patient in metastatic prostate cancer. In one study, >65% patients had ≥5 CTCs/7.5 ml blood [41]. In contrast, only 14% of patients with localized epithelial cancer have ≥2

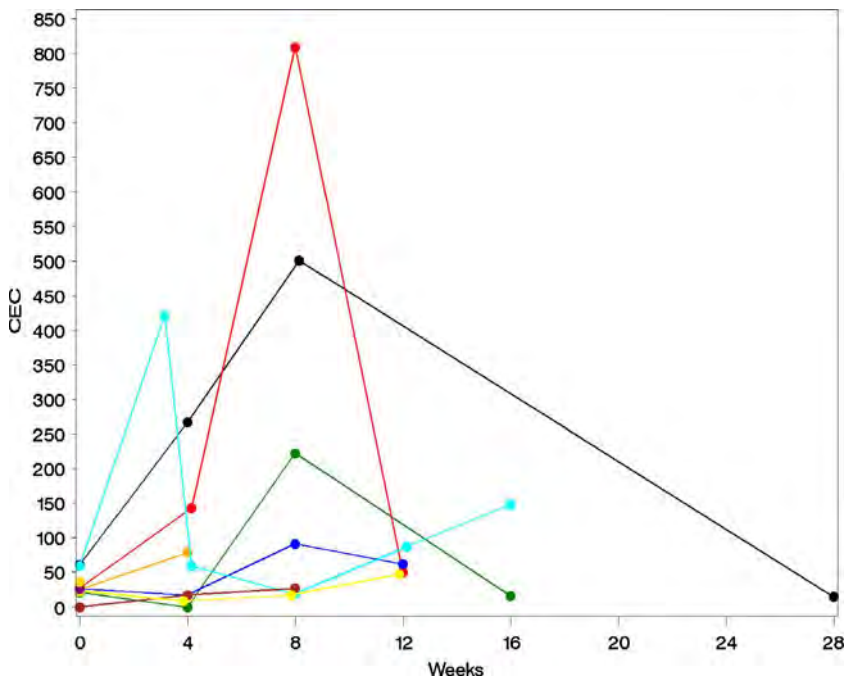


**Fig. 3** Circulating endothelial cells on treatment (0 weeks indicates start of treatment)

CTCs/7.5 ml. This difference becomes especially relevant when gene expression studies are planned on CTCs as ≥ 100 CTCs per patient were necessary in one study to perform such studies [42]. CTCs by currently approved assays are of questionable value in non-metastatic prostate cancer due to low sensitivity. Methods of enrichment for CTCs or alternative techniques of detection could prove promising in non-metastatic CRPC[43].

CECs have been investigated as surrogates for angiogenesis and as prognostic and predictive biomarkers [44, 45]. However, experience with CECs in prostate cancer is more limited than with CTCs. One study of CECs in metastatic prostate cancer treated with docetaxel found CEC declines after 2–5 weeks of treatment but not baseline CECs to be of prognostic value[39].

It is conceivable that integrin signaling was indeed blocked (suggested by the activity of Cilengitide at similar doses in GBM and modest activity in metastatic CRPC[46]) but was not adequate in and of itself in non-metastatic CRPC. The presence of multiple integrin molecules and other pro-angiogenic pathways provides significant redundancy in intracellular signaling pathways. Compensatory pathways could be triggered by inhibition of specific molecular targets (e.g. treatment with an anti-angiogenic peptide Angiotensin II (1–7) resulted in higher serum levels of pro-angiogenic factors such as placental derived growth factor [47]). A broad acting pan-integrin inhibitor may show greater clinical activity. Combination of an integrin antagonist with other therapies including conventional chemotherapy could enhance activity.

The trial suffered from a familiar problem seen in previous studies of non-metastatic castration resistant prostate cancer: poor accrual. An ECOG study of chemotherapy compared to ketoconazole (ECOG 1899) closed due to poor accrual. Novel trial designs and endpoints to assess potentially cytostatic therapies in non-metastatic CRPC are urgently needed. PSA based endpoints are likely not suitable to assess activity of cytostatic agents in non-metastatic CRPC. Change in PSA slope was designed into the trial as one possible indicator of drug activity but also relies on PSA. It is also unknown how PSA endpoints relate to clinical objectives in non-metastatic CRPC. The PCCTWG has recommended not relying solely on PSA to stop therapy [32]. In a phase II trial in metastatic CRPC, this approach demonstrated evidence of modest activity for single agent Cilengitide[46, 48]. Several investigators have pointed out the drawbacks in utilizing conventional endpoints in trials of targeted agents and have recommended time to event or progression free survival at a particular timepoint as more suitable[32, 49, 50]. A placebo controlled randomized controlled trial with a clinical end point (e.g. metastasis free survival) may be a more optimal trial design to investigate biological agents in non-metastatic CRPC. The low clinical event rate in the context of non-metastatic CRPC presents a problem in utilizing such an approach as well [1].

There was no MTD identified in the phase I trials of Cilengitide. It is unclear if higher doses of Cilengitide would exhibit increased activity in non-metastatic CRPC. In our trial with this agent in metastatic CRPC, there was a modest increase in TTP between the 500 mg and 2000 mg/dose arms which is the dose we used in the current trial [46].

Cilengitide was well tolerated but did not elicit PSA responses in this trial of non-metastatic CRPC patients. CTCs are of questionable utility in non-metastatic prostate cancer.

**Acknowledgement** Cancer Therapy Evaluation Program (CTEP), PC051382, PC051375, Prostate Cancer Foundation (PCF) N008367, Veridex (formerly Immunicon Corp.)

## References

1. Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, Wynne C, Murray R, Zinner NR, Schulman C, Linnartz R, Zheng M, Goessl C, Hei YJ, Small EJ, Cook R, Higano CS (2005) Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 23(13):2918–2925. doi:10.1200/JCO.2005.01.529
2. Ibrahim T, Flamini E, Mercatali L, Sacanna E, Serra P, Amadori D (2010) Pathogenesis of osteoblastic bone metastases from prostate cancer. Cancer 116(6):1406–1418. doi:10.1002/cncr.24896
3. Loberg RD, Logothetis CJ, Keller ET, Pienta KJ (2005) Pathogenesis and treatment of prostate cancer bone metastases: Targeting the lethal phenotype. J Clin Oncol 23(32):8232–8241. doi:10.1200/JCO.2005.03.0841
4. Felding-Habermann B (2003) Integrin adhesion receptors in tumor metastasis. Clin Exp Metastasis 20(3):203–213
5. Cooper CR, Chay CH, Pienta KJ (2002) The role of alpha(v)beta (3) in prostate cancer progression. Neoplasia 4(3):191–194. doi:10.1038/sj/neo/7900224
6. Fornaro M, Manes T, Languino LR (2001) Integrins and prostate cancer metastases. Cancer Metastasis Rev 20(3–4):321–331
7. Slack-Davis JK, Parsons JT (2004) Emerging views of integrin signaling: Implications for prostate cancer. J Cell Biochem 91 (1):41–46. doi:10.1002/jcb.10665
8. Zheng DQ, Woodard AS, Fornaro M, Tallini G, Languino LR (1999) Prostatic carcinoma cell migration via alpha(v)beta3 integrin is modulated by a focal adhesion kinase pathway. Cancer Res 59(7):1655–1664
9. Putz E, Witter K, Offner S, Stosiek P, Zippelius A, Johnson J, Zahn R, Riethmuller G, Pantel K (1999) Phenotypic characteristics of cell lines derived from disseminated cancer cells in bone marrow of patients with solid epithelial tumors: Establishment of working models for human micrometastases. Cancer Res 59 (1):241–248
10. Zheng DQ, Woodard AS, Tallini G, Languino LR (2000) Substrate specificity of alpha(v)beta(3) integrin-mediated cell migration and phosphatidylinositol 3-kinase/akt pathway activation. J Biol Chem 275(32):24565–24574. doi:10.1074/jbc.M002646200
11. McCabe NP, De S, Vasanji A, Brainard J, Byzova TV (2007) Prostate cancer specific integrin alphavbeta3 modulates bone

metastatic growth and tissue remodeling. Oncogene 26(42):6238–6243. doi:10.1038/sj.onc.1210429
12. Keller ET, Brown J (2004) Prostate cancer bone metastases promote both osteolytic and osteoblastic activity. J Cell Biochem 91(4):718–729. doi:10.1002/jcb.10662
13. Bisanz K, Yu J, Edlund M, Spohn B, Hung MC, Chung LW, Hsieh CL (2005) Targeting ecm-integrin interaction with liposome-encapsulated small interfering rnas inhibits the growth of human prostate cancer in a bone xenograft imaging model. Mol Ther 12(4):634–643. doi:10.1016/j.ymthe.2005.05.012
14. Thalmann GN, Sikes RA, Devoll RE, Kiefer JA, Markwalder R, Klima I, Farach-Carson CM, Studer UE, Chung LW (1999) Osteopontin: Possible role in prostate cancer progression. Clin Cancer Res 5(8):2271–2277
15. Ross FP, Chappel J, Alvarez JI, Sander D, Butler WT, Farach-Carson MC, Mintz KA, Robey PG, Teitelbaum SL, Cheresh DA (1993) Interactions between the bone matrix proteins osteopontin and bone sialoprotein and the osteoclast integrin alpha v beta 3 potentiate bone resorption. J Biol Chem 268(13):9901–9907
16. Cheng SL, Lai CF, Fausto A, Chellaiah M, Feng X, McHugh KP, Teitelbaum SL, Civitelli R, Hruska KA, Ross FP, Avioli LV (2000) Regulation of alphavbeta3 and alphavbeta5 integrins by dexamethasone in normal human osteoblastic cells. J Cell Biochem 77(2):265–276. doi:10.1002/(SICI)1097-4644(20000501)77:2<265::AID-JCB9>3.0.CO;2-6
17. Nemeth JA, Cher ML, Zhou Z, Mullins C, Bhagat S, Trikha M (2003) Inhibition of alpha(v)beta3 integrin reduces angiogenesis, bone turnover, and tumor cell proliferation in experimental prostate cancer bone metastases. Clin Exp Metastasis 20(5):413–420
18. Manes T, Zheng DQ, Tognin S, Woodard AS, Marchisio PC, Languino LR (2003) Alpha(v)beta3 integrin expression up-regulates cdc2, which modulates cell migration. J Cell Biol 161(4):817–826. doi:10.1083/jcb.200212172
19. Brooks PC, Clark RA, Cheresh DA (1994) Requirement of vascular integrin alpha v beta 3 for angiogenesis. Science 264(5158):569–571
20. Malyankar UM, Scatena M, Suchland KL, Yun TJ, Clark EA, Giachelli CM (2000) Osteoprotegerin is an alpha vbeta 3-induced, nf-kappa b-dependent survival factor for endothelial cells. J Biol Chem 275(28):20959–20962. doi:10.1074/jbc.C000290200
21. Scatena M, Almeida M, Chaisson ML, Fausto N, Nicosia RF, Giachelli CM (1998) Nf-kappab mediates alphavbeta3 integrin-induced endothelial cell survival. J Cell Biol 141(4):1083–1093
22. Kumar CC, Malkowski M, Yin Z, Tanghetti E, Yaremko B, Nechuta T, Varner J, Liu M, Smith EM, Neustadt B, Presta M, Armstrong L (2001) Inhibition of angiogenesis and tumor growth by sch221153, a dual alpha(v)beta3 and alpha(v)beta5 integrin receptor antagonist. Cancer Res 61(5):2232–2238
23. Nabors LB, Mikkelsen T, Rosenfeld SS, Hochberg F, Akella NS, Fisher JD, Cloud GA, Zhang Y, Carson K, Wittemer SM, Colevas AD, Grossman SA (2007) Phase i and correlative biology study of cilengitide in patients with recurrent malignant glioma. J Clin Oncol 25(13):1651–1657. doi:10.1200/JCO.2006.06.6514
24. Brooks PC, Montgomery AM, Rosenfeld M, Reisfeld RA, Hu T, Klier G, Cheresh DA (1994) Integrin alpha v beta 3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels. Cell 79(7):1157–1164.
25. Oliveira-Ferrer L, Hauschild J, Fiedler W, Bokemeyer C, Nippgen J, Celik I, Schuch G (2008) Cilengitide induces cellular detachment and apoptosis in endothelial and glioma cells mediated by inhibition of fak/src/akt pathway. J Exp Clin Cancer Res 27:86. doi:10.1186/1756-9966-27-86
26. Nisato RE, Tille JC, Jonczyk A, Goodman SL, Pepper MS (2003) Alphav beta 3 and alphav beta 5 integrin antagonists inhibit angiogenesis in vitro. Angiogenesis 6(2):105–119. doi:10.1023/B:AGEN.0000011801.98187.f2
27. MacDonald TJ, Taga T, Shimada H, Tabrizi P, Zlokovic BV, Cheresh DA, Laug WE (2001) Preferential susceptibility of brain tumors to the antiangiogenic effects of an alpha(v) integrin antagonist. Neurosurgery 48(1):151–157
28. Taga T, Suzuki A, Gonzalez-Gomez I, Gilles FH, Stins M, Shimada H, Barsky L, Weinberg KI, Laug WE (2002) Alpha v-integrin antagonist emd 121974 induces apoptosis in brain tumor cells growing on vitronectin and tenascin. Int J Cancer 98(5):690–697. doi:10.1002/ijc.10265
29. Eskens FA, Dumez H, Hoekstra R, Perschl A, Brindley C, Bottcher S, Wynendaele W, Drevs J, Verweij J, van Oosterom AT (2003) Phase i and pharmacokinetic study of continuous twice weekly intravenous administration of cilengitide (emd 121974), a novel inhibitor of the integrins alphavbeta3 and alphavbeta5 in patients with advanced solid tumours. Eur J Cancer 39(7):917–926.
30. Hariharan S, Gustafson D, Holden S, McConkey D, Davis D, Morrow M, Basche M, Gore L, Zang C, O'Bryant CL, Baron A, Gallemann D, Colevas D, Eckhardt SG (2007) Assessment of the biological and pharmacological effects of the alpha nu beta3 and alpha nu beta5 integrin receptor antagonist, cilengitide (emd 121974), in patients with advanced solid tumors. Ann Oncol 18(8):1400–1407. doi:10.1093/annonc/mdm140
31. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, Figg WD, Freidlin B, Halabi S, Hudes G, Hussain M, Kaplan R, Myers C, Oh W, Petrylak DP, Reed E, Roth B, Sartor O, Scher H, Simons J, Sinibaldi V, Small EJ, Smith MR, Trump DL, Wilding G et al (1999) Eligibility and response guidelines for phase ii clinical trials in androgen-independent prostate cancer: Recommendations from the prostate-specific antigen working group. J Clin Oncol 17(11):3461–3467
32. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, Higano C, Bubley GJ, Dreicer R, Petrylak D, Kantoff P, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A, Hussain M (2008) Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the prostate cancer clinical trials working group. J Clin Oncol 26(7):1148–1159. doi:10.1200/JCO.2007.12.4487
33. Nelson JB, Love W, Chin JL, Saad F, Schulman CC, Sleep DJ, Qian J, Steinberg J, Carducci M (2008) Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. Cancer 113(9):2478–2487. doi:10.1002/cncr.23864
34. Davis JW, Nakanishi H, Kumar VS, Bhadkamkar VA, McCormack R, Fritsche HA, Handy B, Gornet T, Babaian RJ (2008) Circulating tumor cells in peripheral blood samples from patients with increased serum prostate specific antigen: Initial results in early prostate cancer. J Urol 179 (6):2187–2191; discussion 2191. doi:10.1016/j.juro.2008.01.102
35. Helo P, Cronin AM, Danila DC, Wenske S, Gonzalez-Espinoza R, Anand A, Koscuiszka M, Vaananen RM, Pettersson K, Chun FK, Steuber T, Huland H, Guillonneau BD, Eastham JA, Scardino PT, Fleisher M, Scher HI, Lilja H (2009) Circulating prostate tumor cells detected by reverse transcription-pcr in men with localized or castration-refractory prostate cancer: Concordance with cellsearch assay and association with bone metastases and with survival. Clin Chem 55(4):765–773. doi:10.1373/clinchem.2008.117952
36. Maestro LM, Sastre J, Rafael SB, Veganzones SB, Vidaurreta M, Martin M, Olivier C, DELO VB, Garcia-Saenz JA, Alfonso R, Arroyo M, Diaz-Rubio E (2009) Circulating tumor cells in solid tumor in metastatic and localized stages. Anticancer Res 29(11):4839–4843

37. Danila DC, Heller G, Gignac GA, Gonzalez-Espinoza R, Anand A, Tanaka E, Lilja H, Schwartz L, Larson S, Fleisher M, Scher HI (2007) Circulating tumor cell number and prognosis in progressive castration-resistant prostate cancer. Clin Cancer Res 13 (23):7053–7058. doi:10.1158/1078-0432.CCR-07-1506
38. de Bono JS, Scher HI, Montgomery RB, Parker C, Miller MC, Tissing H, Doyle GV, Terstappen LW, Pienta KJ, Raghavan D (2008) Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res 14 (19):6302–6309. doi:10.1158/1078-0432.CCR-08-0872
39. Strijbos MH, Gratama JW, Schmitz PI, Rao C, Onstenk W, Doyle GV, Miller MC, de Wit R, Terstappen LW, Sleijfer S Circulating endothelial cells, circulating tumour cells, tissue factor, endothelin-1 and overall survival in prostate cancer patients treated with docetaxel. Eur J Cancer. doi:10.1016/j.ejca.2010.03.030
40. Moreno JG, O'Hara SM, Gross S, Doyle G, Fritsche H, Gomella LG, Terstappen LW (2001) Changes in circulating carcinoma cells in patients with metastatic prostate cancer correlate with disease status. Urology 58(3):386–392
41. Shaffer DR, Leversha MA, Danila DC, Lin O, Gonzalez-Espinoza R, Gu B, Anand A, Smith K, Maslak P, Doyle GV, Terstappen LW, Lilja H, Heller G, Fleisher M, Scher HI (2007) Circulating tumor cell analysis in patients with progressive castration-resistant prostate cancer. Clin Cancer Res 13(7):2023–2029. doi:10.1158/1078-0432.CCR-06-2701
42. Smirnov DA, Zweitzig DR, Foulk BW, Miller MC, Doyle GV, Pienta KJ, Meropol NJ, Weiner LM, Cohen SJ, Moreno JG, Connelly MC, Terstappen LW, O'Hara SM (2005) Global gene expression profiling of circulating tumor cells. Cancer Res 65 (12):4993–4997. doi:10.1158/0008-5472.CAN-04-4330
43. Stott SL, Lee RJ, Nagrath S, Yu M, Miyamoto DT, Ulkus L, Inserra EJ, Ulman M, Springer S, Nakamura Z, Moore AL, Tsukrov DI, Kempner ME, Dahl DM, Wu CL, Iafrate AJ, Smith MR, Tompkins RG, Sequist LV, Toner M, Haber DA, Maheswaran S Isolation and characterization of circulating tumor cells from patients with localized and metastatic prostate cancer. Sci Transl Med 2 (25):25ra23. doi:10.1126/scitranslmed.3000403
44. Georgiou HD, Namdarian B, Corcoran NM, Costello AJ, Hovens CM (2008) Circulating endothelial cells as biomarkers of prostate cancer. Nat Clin Pract Urol 5(8):445–454. doi:10.1038/ncpuro1188
45. Beerepoot LV, Mehra N, Vermaat JS, Zonnenberg BA, Gebbink MF, Voest EE (2004) Increased levels of viable circulating endothelial cells are an indicator of progressive disease in cancer patients. Ann Oncol 15(1):139–145
46. Bradley DA, Daignault S, Ryan CJ, Dipaola RS, Smith DC, Small E, Gross ME, Stein MN, Chen A, Hussain M Cilengitide (emd 121974, nsc 707544) in asymptomatic metastatic castration resistant prostate cancer patients: A randomized phase ii trial by the prostate cancer clinical trials consortium. Invest New Drugs. doi:10.1007/s10637-010-9420-8
47. Petty WJ, Miller AA, McCoy TP, Gallagher PE, Tallant EA, Torti FM (2009) Phase i and pharmacokinetic study of angiotensin-(1–7), an endogenous antiangiogenic hormone. Clin Cancer Res 15 (23):7398–7404. doi:10.1158/1078-0432.CCR-09-1957
48. Bradley DA, Daignault S, Ryan CJ, Dipaola RS, Smith DC, Small E, Gross ME, Stein MN, Chen A, Hussain M (2010) Cilengitide (emd 121974, nsc 707544) in asymptomatic metastatic castration resistant prostate cancer patients: A randomized phase ii trial by the prostate cancer clinical trials consortium. Invest New Drugs. doi:10.1007/s10637-010-9420-8
49. Adjei AA, Christian M, Ivy P (2009) Novel designs and end points for phase ii clinical trials. Clin Cancer Res 15(6):1866–1872. doi:10.1158/1078-0432.CCR-08-2035
50. Fox E, Curt GA, Balis FM (2002) Clinical trial design for target-based therapy. Oncologist 7(5):401–409

Original Article

# Ixabepilone, Mitoxantrone, and Prednisone for Metastatic Castration-Resistant Prostate Cancer After Docetaxel-Based Therapy

## A Phase 2 Study of the Department of Defense Prostate Cancer Clinical Trials Consortium

Andrea L. Harzstark, MD[1]; Jonathan E. Rosenberg, MD[2]; Vivian K. Weinberg, PhD[1]; Jeremy Sharib, BS[1]; Charles J. Ryan, MD[1]; David C. Smith, MD[3]; Lance C. Pagliaro, MD[4]; Tomasz M. Beer, MD[5]; Glenn Liu, MD[6]; and Eric J. Small, MD[1]

**BACKGROUND:** Mitoxantrone plus prednisone and ixabepilone each have modest activity as monotherapy for second-line chemotherapy in patients with docetaxel-refractory castration-resistant prostate cancer. Clinical noncross-resistance was previously observed. Phase 1 testing determined the maximum tolerated dose and dose-limiting toxicities with the combination regimen; a phase 2 study was conducted to evaluate the activity of the combination. **METHODS:** Patients with metastatic progressive castration-resistant prostate cancer during or after 3 or more cycles of taxane-based chemotherapy enrolled in a phase 2 multicenter study of ixabepilone 35 mg/m$^2$ and mitoxantrone 12 mg/m$^2$ administered on Day 1 every 21 days with pegfilgrastim support, along with prednisone 5 mg twice daily. Patients were evaluated for disease response and toxicity. **RESULTS:** Results are reported for the 56 evaluable patients. Twenty-five (45%; 95% confidence interval [CI], 31%-59%) experienced confirmed ≥50% prostate-specific antigen (PSA) declines, 33 (59%; 95% CI, 45%-72%) experienced confirmed ≥30% PSA declines, and 8 of 36 patients (22%; 95% CI, 10%-39%) with measurable disease experienced objective responses. Median time to PSA or objective progression was 4.4 months (95% CI, 3.5-5.6), and median progression-free survival was also 4.4 months (95% CI, 3.0-6.0). Median overall survival was 12.5 months (95% CI, 10.2-15.9). Thirty-two percent of patients experienced grade 3 of 4 neutropenia, and 11% experienced grade 3 or higher neutropenic infections, including 1 treatment-related death. Grade 2 and 3 neuropathy occurred in 11% and 12.5% of patients, respectively. **CONCLUSIONS:** These results suggest that the combination of ixabepilone and mitoxantrone is both feasible and active in castration-resistant prostate cancer and requires dosing with pegfilgrastim. ***Cancer* 2011;00:000–000.** *© 2010 American Cancer Society.*

**KEYWORDS:** prostate cancer, chemotherapy, metastatic, mitoxantrone, ixabepilone, docetaxel.

**Mortality** in prostate cancer is primarily related to the development of metastatic castration-resistant disease, and options after docetaxel, the first-line standard of care, remain limited.[1] Recent data have established cabazitaxel as the standard second-line therapy.[2] Mitoxantrone with prednisone, which has been demonstrated to improve quality of life as front-line therapy, has been used extensively, with 50% PSA declines reported in 20% of patients previously treated with docetaxel.[3-5] Ixabepilone, an epothilone analog, has similarly been demonstrated to have a 17% response rate in this setting. Of interest, objective responses to mitoxantrone/prednisone after second-line ixabepilone and conversely to ixabepilone after second-line mitoxantrone/prednisone were observed during a randomized phase 2 study, suggesting there is noncross-resistance with the 2 regimens.

On the basis of the nonoverlapping toxicity of these regimens and their apparent noncross-resistance, a phase 1 study combining these agents was undertaken in patients previously treated with docetaxel.[6] The combination was well

**Corresponding author:** Andrea L. Harzstark, MD, Department of Medicine, University of California, San Francisco; Helen Diller Family Comprehensive Cancer Center, 1600 Divisadero Street, Box 1711, San Francisco, CA 94143-1711; Fax: (415) 353-7779; andrea.harzstark@ucsf.edu

[1]Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, San Francisco, California; [2]Dana Farber Cancer Institute, Boston, Massachusetts; [3]University of Michigan, Ann Arbor, Michigan; [4]The University of Texas M. D. Anderson Cancer Center, Houston, Texas; [5]Oregon Health and Science University Knight Cancer Institute, Portland, Oregon; [6]University of Wisconsin Carbone Cancer Center, Madison, Wisconsin

The first 2 authors contributed equally to this article.

Presented in part at the Annual Meeting of the American Society of Clinical Oncology, Orlando, Florida, May 29-June 2, 2009.

**DOI:** 10.1002/cncr.25810, **Received:** June 23, 2010; **Revised:** September 21, 2010; **Accepted:** October 18, 2010, **Published online** in Wiley Online Library (wileyonlinelibrary.com)

tolerated. Although hematologic toxicity required treatment with pegfilgrastim, other toxicity, including neurotoxicity, was modest. The regimen recommended for phase 2 testing was mitoxantrone 12 mg/m$^2$ and ixabepilone 35 mg/m$^2$, given with prednisone 5 mg twice daily, along with pegfilgrastim 6 mg on Day 2. Responses, as defined by a $\geq$50% PSA decline, were observed in 31% of patients, with objective responses in 2 of 36 patients in the phase 1 study. When limited to the 21 patients treated with 12 mg/m$^2$ of mitoxantrone plus ixabepilone at a dose of 30 mg/m$^2$ or higher, 43% of patients experienced prostate-specific antigen (PSA) declines of $\geq$50% (95% confidence interval [CI], 22% to 66%). When compared with the response proportions reported for monotherapy with either ixabepilone or mitoxantrone of approximately 20%, these results suggested at least additive effects of the 2 agents and were sufficiently promising to warrant a phase 2 study to determine the activity of this novel regimen.

## MATERIALS AND METHODS

### *Study Design*

This study was a multicenter, single-arm, phase 2 study of ixabepilone and mitoxantrone with prednisone in castration-resistant prostate cancer patients who developed progressive disease during or after docetaxel-based chemotherapy. This study was undertaken in the Department of Defense Prostate Cancer Clinical Trials Consortium, with accrual occurring at 6 academic centers. The primary endpoint of the study was the proportion of patients achieving $\geq$50% PSA declines. Secondary endpoints included overall safety, the frequency of objective responses, time to progression, progression-free survival, and overall survival. This study was approved by the Clinical Trial Evaluation Program of the National Cancer Institute, the Prostate Cancer Clinical Trials Consortium Review Committee, and the local institutional review boards of participating institutions. All patients provided written informed consent.

### *Eligibility*

Patients were required to have histologically confirmed prostate cancer with metastatic spread and progressive disease despite castrate testosterone levels. Patients were required to have received at least 3 cycles of taxane-based chemotherapy, and only 1 prior chemotherapy regimen was permitted. For patients with measurable disease, progression was defined according to Response Evaluation Criteria in Solid Tumors (RECIST), and for patients without measurable disease, a PSA of $\geq$2 ng/mL and a bone scan consistent with metastasis were required. Patients without measurable disease were required to have either PSA progression or a bone scan demonstrating 1 or more new metastatic lesions. PSA progression was defined according to PSA Working Group 1 criteria.[7] Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and $\leq$grade 1 peripheral neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0). Patients who had not undergone prior orchiectomy were required to remain on a luteinizing hormone-releasing hormone agonist. Other hormonal therapy, with the exception of prednisone 5 mg twice daily, as given with docetaxel, was not allowed within 4 weeks of study entry. Docetaxel was not allowed within 4 weeks of enrollment. No prior mitoxantrone or ixabepilone was allowed. Radiation or radiopharmaceutical therapy must have been completed at least 4 and 8 weeks, respectively, before enrollment. Cardiac ejection fraction was required to be above the lower limit of normal for the institution. Patients with clinically significant cardiovascular disease, including New York Heart Association class III or IV heart failure, active angina, or a history of myocardial infarction within 6 months, were excluded. Laboratory requirements included testosterone $<$50 ng/dL; creatinine $\leq 1.5 \times$ upper limit of normal (ULN) or calculated creatinine clearance $\geq$40 mL/min; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $<2.5 \times$ ULN; granulocytes $\geq$2000/mm$^3$; platelets $\geq$100,000/mm$^3$; and total bilirubin $\leq 1.5 \times$ ULN. Because ixabepilone is a CYP3A4 substrate, concurrent use of moderate to strong CYP3A4 inhibitors was prohibited.

### *Study Therapy*

Patients were treated on day 1 of 21-day cycles. Premedication with oral H1- and H2-blockers was administered 1 hour before treatment to prevent hypersensitivity reactions. Patients received mitoxantrone 12 mg/m$^2$ intravenously over 30 minutes. Ixabepilone 35 mg/m$^2$ was subsequently administered as a continuous infusion over 3 hours. Patients were monitored for hypersensitivity reactions for 1 hour. If grade 2 to 4 hypersensitivity reactions developed despite antihistamine premedication, corticosteroid premedication was used for subsequent cycles. Prednisone was administered 5 mg twice daily continuously. Pegfilgrastim 6 mg was administered subcutaneously on Day 2. Patients were treated until disease

progression, unacceptable toxicity, or patient preference to discontinue therapy.

### Assessment for Response and Toxicity

Patients were assessed with chest x-ray or chest computed tomography (CT), CT of the abdomen and pelvis, and bone scan every 3 cycles. PSA, complete blood count with differential and platelets, electrolytes, blood urea nitrogen, creatinine, magnesium, lactate dehydrogenase, albumin, AST, ALT, total bilirubin, and alkaline phosphatase were obtained every cycle. Physical examination and assessment of performance status were undertaken each cycle. Echocardiogram or MUGA (Multi Gated Acquisition) Scan was performed at baseline, every 3 cycles, and as clinically indicated.

Objective response was defined by RECIST, and both 50% and 30% PSA declines were determined, with a repeat PSA required 3 weeks later for confirmation.[7,8] Disease progression was defined as new metastases outside of the bone, $\geq$1 new bone lesions confirmed on repeat imaging, a need for radiation while on therapy, unequivocal progression of nontarget lesions, progression by RECIST, or PSA progression. PSA progression was defined according to PSA Working Group 1 criteria, with a PSA increase of 25% above the nadir value, occurring at least 9 weeks (3 cycles) after initiating the study.

Toxicity was monitored by history, physical examination, and laboratory assessment before each cycle. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria version 3.0. For grade 3 or higher toxicities, both ixabepilone and mitoxantrone were held until resolution to $\leq$grade 1, then reinstituted at 5 mg/m$^2$ less of ixabepilone and 2 mg/m$^2$ less of mitoxantrone. The same process was required for recurrent toxicities, with a third recurrence resulting in removal from study therapy. For corticosteroid toxicity, prednisone doses could be modified without removing a patient from protocol therapy. For neurotoxicity secondary to ixabepilone, therapy was held for grade 2 or 3 toxicity but otherwise managed as above. Alopecia, lymphopenia, anemia, and toxicities related to androgen deprivation were excluded as dose-limiting or modifying criteria.

### Statistical Considerations

The primary endpoint of this study was the proportion of patients responding to treatment defined as observing a PSA decline of $\geq$50% (PSA response) based on PSA Working Group 1 criteria. Treatment of 58 patients allowed for the detection of a PSA response proportion of 35%, compared with a null hypothesis of 20% with a power of 0.90 and a level of significance of 0.10. Simon's MiniMax 2-stage design was used for accrual, to allow for an interim analysis for efficacy after the first 33 patients had been accrued and had been followed for 3 cycles of treatment. Had 6 or fewer of the first 33 patients enrolled demonstrated a PSA decline of $\geq$50%, accrual would have been terminated, resulting in a probability of early termination if the null hypothesis were true of 50%. Objective responses were evaluated according to RECIST for patients with measurable disease. Descriptive statistics were calculated to characterize the patient cohort, baseline disease parameters, outcome, and toxicity. The time to progression, progression-free survival, and overall survival were measured from the start of protocol therapy and evaluated using the Kaplan-Meier product limit method.

## RESULTS

### Patient Characteristics

Between November 2007 and March 2009, 58 patients were enrolled at 6 member institutions of the Department of Defense Prostate Cancer Clinical Trials Consortium. Two patients were ineligible: 1 because of pre-existing spinal cord compression and 1 because of a secondary diagnosis of colon cancer diagnosed after 2 cycles of therapy; therefore, 56 evaluable patients were included in these analyses. Four patients did not complete the minimum 3 cycles of therapy defined by the protocol to be necessary for response assessment; 2 discontinued for progressive disease and 2 withdrew because of concerns over rising PSA. These 4 patients are included in both efficacy and toxicity analyses. Patient characteristics are summarized in Table 1. The median age of patients at the start of protocol therapy was 66.7 years. Sixty-nine percent of patients had a Gleason score of 8 to 10. Sixty-six percent had an ECOG performance status of 1 to 2, and 34% had an ECOG performance status of 0. The median PSA was 171.2 (range, 2.79-3717.1), and the median alkaline phosphatase was 134 (range, 42-1094). All patients had received prior docetaxel therapy once every 3 weeks. The median number of prior chemotherapy cycles was 8 (range, 3-33). The median prior treatment duration was 6.4 months (range, 2.2-29.1), and the median time between discontinuation of docetaxel and initiation of study therapy was 53 days (range, 5-413). Fifty percent of patients (28 of 56) had experienced a PSA response to prior taxane-based therapy by PSA Working Group 1

**Table 1.** Patient Characteristics (N=56)

| | |
|---|---|
| Median age at entry (range) | 66.7 (47-83) |
| **ECOG PS at protocol entry, patients (%)** | |
| 0 | 19 (34) |
| 1-2 | 37 (66) |
| **Gleason score at diagnosis (n=54), patients (%)** | |
| 4-6 | 3 (5.5) |
| 7 | 14 (26) |
| 8-10 | 37 (68.5) |
| Median PSA, ng/mL (range) | 171.2 (2.79-3717.1) |
| **Baseline laboratory results at protocol entry** | |
| Median LDH, IU/L (range) | 290 (123-2333) |
| Median alkaline phosphatase, U/L (range) | 134 (42-1094) |
| Median hemoglobin, g/dL (range) | 11.7 (9.3-14.1) |
| **Prior chemotherapy: best response, patients (%)** | |
| PSA response/partial response | 28 (50) |
| Stable disease for patients with objective disease | 18 (32) |
| Progressive disease | 10 (18) |
| Prior 3-week chemotherapy cycles, median No. (range) | 8 (3-33) |
| Median duration, mo (range) | 6.4 (2.2-29.1) |
| Median duration from end of taxane, d (range) | 53 (5-413) |
| **Study treatment** | |
| Cycles received, median No. (range) | 5+ (1-13) |
| Still on treatment, patients | 1[a] |

ECOG indicates Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.
[a] Duration 10.4 months.

**Table 2.** Response Data

| Response | No. | % |
|---|---|---|
| ≥30% PSA decline | 33 | 59 |
| ≥30% PSA decline by 12 weeks | 31 | 55 |
| ≥50% PSA decline | 25 | 45 |
| ≥50% PSA decline by 12 weeks | 17 | 30 |
| Objective responses | 8/36 | 22 |

PSA indicates prostate-specific antigen.

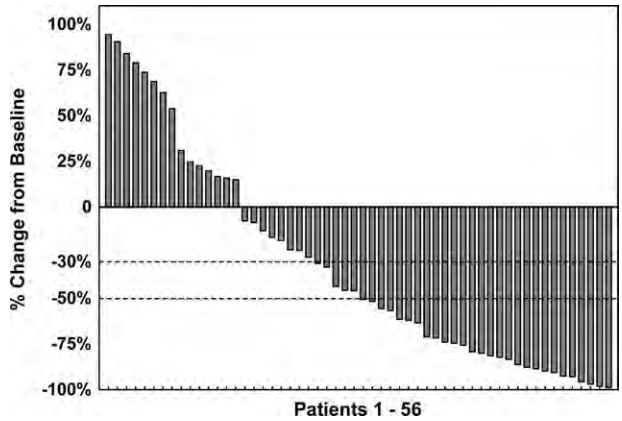


**Figure 1.** Maximum percentage change in prostate-specific antigen is shown.

criteria, whereas half of the enrolled patients never had a PSA response to docetaxel therapy. Fifty-nine percent of patients had subsequently progressed on docetaxel therapy by PSA criteria alone, 30% had radiographic progression, 9% stopped docetaxel therapy for toxicity, and 2% stopped with stable disease after completing a planned course of therapy. Thus, 89% of patients had developed docetaxel-resistant castration-resistant prostate cancer before enrolling on this trial. Twenty-five percent (14 patients) of patients received therapy after docetaxel but before beginning this study, including ketoconazole (n = 5), sunitinib (n = 3), bicalutamide (n = 2), palliative radiotherapy (N = 2), PSMA ADT (an antibody against prostate specific membrane antigen), and GVAX (a vaccine consisting of prostate cancer cells modified to secrete granulocyte-macrophage colony-stimulating factor), 1 each.

Clinical efficacy to ixabepilone and mitoxantrone with prednisone chemotherapy is reported for all 56 eligible patients (Table 2). Overall, 25 (45%) patients experienced confirmed PSA declines of ≥50% (Fig. 1; 95% CI, 31%-59%), and 33 (59%) had confirmed PSA declines of ≥30% (95% CI, 45%-72%). After 12 weeks of protocol therapy, 30% of the patients achieved PSA declines of at least 50%, indicating that the study null hypothesis of 20% can be rejected (1-sided binomial exact test: $P = .04$). Partial objective RECIST-defined responses were observed in 8 patients of 36 with measurable disease (22%; 95% CI, 10%-39%).

With a median follow-up of 9.9 months (range, 3.1-19.4) from the start of protocol therapy, the median time to progression was 4.4 months (95% CI, 3.5-5.6). The median PSA or objective progression-free survival was also 4.4 months (Fig. 2; 95% CI, 3.0-6.0), and the median overall survival was 12.5 months (Fig. 3; 95% CI, 10.2-15.9).

Patients with a prior response to docetaxel therapy were as likely to respond to ixabepilone and mitoxantrone with prednisone second-line therapy as patients with no prior response to docetaxel. Of the 28 patients who had a ≥50% PSA decline with docetaxel-based therapy, 39% had a ≥50% PSA decline with ixabepilone and mitoxantrone with prednisone. Of the 10 patients whose best

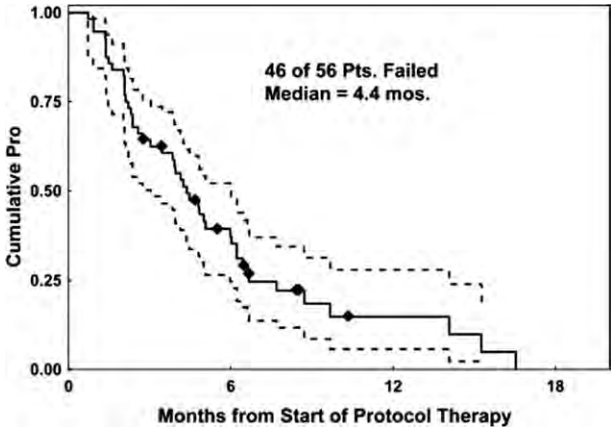


**Figure 2.** Progression-free survival with ixabepilone and mitoxantrone with prednisone is shown. Pro indicates progression; Pts., patients.

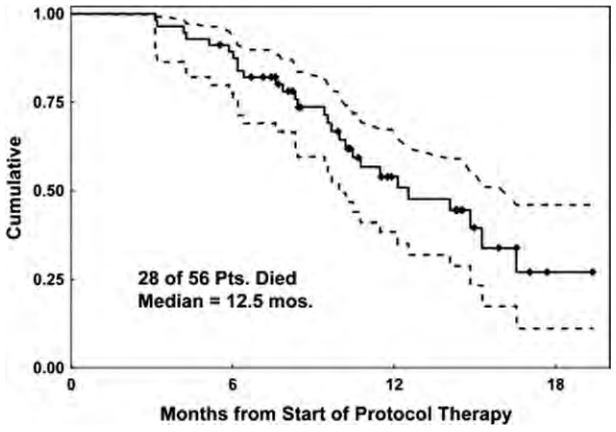


**Figure 3.** Overall survival with ixabepilone and mitoxantrone with prednisone is shown.

response to docetaxel-based therapy was progressive disease, 40% had a $\geq$50% PSA response to ixabepilone and mitoxantrone with prednisone ($P = .71$).

### *Toxicity*

Toxicity data are reported for all 56 eligible patients and are summarized in Table 3. Thirty-two percent of patients experienced grade 3 or 4 neutropenia. Eleven percent of patients had neutropenia associated with infection. Five grade 3 infections occurred in 5 patients (2 pulmonary, 1 skin, 1 *Clostridium difficile* colitis, 1 septic arthritis of the elbow), and 1 grade 4 bacteremia occurred. One treatment-associated death occurred in the 1 patient on study on verapamil, a moderate CYP3A4 inhibitor. This patient

**Table 3.** Toxicity Related to Study Therapy

| Adverse Event | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|
| **Hematologic** | | | |
| Leukopenia | 9 | 11 | |
| Lymphopenia | 17 | 3 | |
| Neutropenia | 6 | 10 | |
| Anemia | 3 | 1 | |
| Thrombocytopenia | 7 | 3 | |
| **Nonhematologic** | | | |
| Allergic reaction | 1 | | |
| AST/ALT increased | 1 | | |
| Dyspnea | 2 | | |
| Fatigue | 5 | | |
| Hyperbilirubinemia | 1 | | |
| Hypoalbuminemia | 1 | | |
| Infection | 5[a] | 1[a] | 1[b] |
| Hypocalcemia | 1 | | |
| Hypophosphatemia | 1 | | |
| Mucositis | 1 | | |
| Nausea/vomiting | 1 | | |
| Neuropathy | 7 | | |
| Vasovagal episode | | 1 | |

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.
[a] Sites of infection: skin (cellulitis), blood (methicillin-resistant *Staphylococcus aureus*, grade 4), pneumonia (2), colon (*Clostridium difficile* colitis), elbow (septic arthritis). All but septic arthritis associated with neutropenia. The *C. difficile* infection occurred in a patient with pneumonia treated with antibiotics.
[b] There was 1 treatment-related death in a patient with urosepsis and neutropenia who was on verapamil.

experienced urosepsis in association with neutropenia. Grade 3 or higher thrombocytopenia and anemia were uncommon (18% and 7%, respectively). Cardiovascular toxicity included 1 grade 4 cardiac infarct, 1 grade 3 atrial fibrillation, and 1 grade 2 decrease in ejection fraction. Grade 2 and 3 sensory neuropathy was observed in 6 and 7 patients (11% and 13%), respectively. Other toxicities of note included grade 2 fatigue in 13 patients and grade 3 fatigue in 5 patients.

### *Treatment Administered*

Patients were removed from study therapy primarily for progressive disease. Twenty-seven and 9 patients (48% and 16%) discontinued protocol treatment because of PSA and objective progression, respectively, and 4 (7%) others had both PSA and objective disease progression. Ten (18%) patients discontinued therapy for toxicity after a median of 7 cycles (range, 1-13). Two (4%) patients discontinued after completing 12 cycles, and 3 (5%) patients withdrew, 2 because of concerns over rising PSA, and 1 because of a combination of toxicity and concerns over rising PSA. One (2%) patient remains on therapy 10.6 months from the start of protocol therapy having received 8 cycles of therapy to date.

## DISCUSSION

After progression on docetaxel-based chemotherapy, chemotherapy options for patients with metastatic castration-resistant prostate cancer remain poor. Recently reported data suggest that cabazitaxel may represent an important therapeutic option for patients with progressive disease after docetaxel.[2] Mitoxantrone with prednisone is often used as second-line therapy but is associated with a PSA response rate of only 20%.[5] Ixabepilone also has a disappointing PSA response rate of 17% after docetaxel. The objective response rates associated with ixabepilone monotherapy and mitoxantrone with prednisone after docetaxel are also low at 4% and 10%, respectively. On the basis of results from a randomized phase 2 study suggesting that ixabepilone and mitoxantrone with prednisone have noncross-resistance and a phase 1 trial of the ixabepilone and mitoxantrone with prednisone combination demonstrating surprisingly high activity, the present phase 2 trial was undertaken.[5]

The ixabepilone and mitoxantrone with prednisone regimen was found to have significant activity, with a PSA response proportion of 45%, and an equally promising objective response proportion of 22%. The overall survival in this group of patients was 12.5 months. Although direct comparisons are not possible across studies, and differences in patient populations may account for results observed, it is notable that the overall survival was 10.4 months on the ixabepilone arm (with mitoxantrone on progression) and 9.8 months on the mitoxantrone arm (with ixabepilone on progression) in the randomized phase 2 study of ixabepilone or mitoxantrone after docetaxel. The time to progression of 4.4 months also appears favorable in comparison to the 2.3-month time to progression on mitoxantrone monotherapy in the randomized phase 2 study.

Data from a randomized phase 3 study comparing cabazitaxel to mitoxantrone with prednisone in patients who had progressed after docetaxel-based therapy indicated that cabazitaxel was associated with a PSA response proportion of 39%, in comparison to 18% on the mitoxantrone/prednisone arm. Although these results cannot be directly compared with the results of the current study of ixabepilone with mitoxantrone and prednisone, the response proportion of 45% in the current study suggests further study may be warranted.

Of interest, response to ixabepilone and mitoxantrone with prednisone does not appear to be dependent on prior response to docetaxel. Although definitive conclusions cannot be drawn given the small numbers of patients, these data suggest that there is no significant cross-resistance between docetaxel and ixabepilone/mitoxantrone with prednisone, and that ixabepilone and mitoxantrone with prednisone therapy may be useful in patients with progressive disease after docetaxel, regardless of docetaxel sensitivity.

The combination of these 2 agents did not appear to result in a dramatic increase in toxicity. Although comparison across studies is fraught with difficulty, toxicity with the study regimen appears to be similar to that associated with mitoxantrone/prednisone use in the second-line alone. In the randomized phase 2 study of mitoxantrone/prednisone and ixabepilone monotherapy, 10% of the 41 patients on the mitoxantrone/prednisone second-line arm experienced febrile neutropenia, and 9% of the 56 patients on this study of the combination (with pegfilgrastim support) experienced febrile neutropenia. It is important to note, however, that this margin of safety can be achieved with the ixabepilone and mitoxantrone with prednisone regimen at the doses studied only with pegfilgrastim support.

Sixteen percent of patients discontinued therapy for toxicity in this phase 2 study of the combination, a number that appears to be similar to the number of patients discontinuing docetaxel as first-line treatment for toxicity. In the randomized phase 2 study of mitoxantrone or ixabepilone, 10% of the 41 patients on mitoxantrone discontinued therapy for toxicity.[1]

Nonhematologic toxicity was minimal. Despite substantial doses of mitoxantrone (66% of patients received >6 cycles), minimal cardiac toxicity was observed. Similarly, less neuropathy was observed than expected in this taxane-pretreated population, with 11% and 12.5% of patients developing grade 2 and 3 neurotoxicity, respectively. However, these results may reflect patient selection. As with the prior second-line ixabepilone prostate cancer studies, patients with grade 2 or higher neuropathy at baseline after docetaxel were excluded. This may have selected a patient population less likely to experience neuropathy. Nevertheless, neuropathy was comparable to that seen in breast cancer studies[9-13] in which 12% to 20% of patients develop grade 3 neurotoxicity.

One potential weakness of this study is that the eligibility criteria did not require a previous history of progression while receiving docetaxel-based therapy, but rather required disease progression during or after docetaxel therapy, possibly selecting for a more chemotherapy-sensitive population. However, 89% of the patients on study had, in fact, progressed while receiving docetaxel therapy, suggesting that this study enrolled patients with

docetaxel resistance. Furthermore, there did not appear to be a difference in response proportion as a function of prior response to docetaxel, although small numbers limit this analysis.

Another potential criticism of this study is that the primary endpoint, the proportion of patients achieving a $\geq$50% decline in PSA, per PSA Working Group Criteria, is of uncertain clinical significance. However, the PSA Working Group criteria were initially established to be used specifically in this setting, as a screen for the activity of cytotoxic agents in the phase 2 setting.[7] In addition, the objective response proportion, time to progression, and overall survival observed with ixabepilone and mitoxantrone with prednisone therapy all appeared to be favorable compared with that associated with mitoxantrone monotherapy, suggesting that the high proportion of patients with an observed PSA decline may be associated with improved survival outcomes. Definitive evidence of benefit can only be established by evaluating overall survival in a phase 3 study.

In summary, the combination of ixabepilone and mitoxantrone with prednisone appears to have greater activity than either mitoxantrone or ixabepilone alone in the second-line setting for castration-resistant prostate cancer, and suggests at least additive if not synergistic activity in a disease state where improvement in outcome is needed and long overdue. The combination is well tolerated, although some hematologic toxicity is present and dosing with pegfilgrastim is required. The results of this study suggest that it is appropriate to study further the ixabepilone and mitoxantrone with prednisone regimen in patients with docetaxel-resistant castration-resistant prostate cancer.

## CONFLICT OF INTEREST DISCLOSURES

This study was supported in part by: Department of Defense Physicians Research Training Grant No. W81XWH-05-1-175 from the Cancer Therapy Evaluation Program of the National Cancer Institute, Department of Defense Prostate Cancer Clinical Trials Consortium Grant No. W81XWH-06-01-0256, and the Prostate Cancer Foundation.

## REFERENCES

1. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351:1502-1512.
2. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol*. 1999;17:2506-2513.
3. Berthold DR, Pond GR, Roessner M, de Wit R, Eisenberger M, Tannock AI. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. *Clin Cancer Res*. 2008;14:2763-2767.
4. Rosenberg JE, Weinberg VK, Kelly WK, et al. Activity of second-line chemotherapy in docetaxel-refractory hormone-refractory prostate cancer patients: randomized phase 2 study of ixabepilone or mitoxantrone and prednisone. *Cancer.* 2007;110:556-563.
5. Rosenberg JE, Ryan CJ, Weinberg VK, et al. Phase I study of ixabepilone, mitoxantrone, and prednisone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel-based therapy: a study of the department of defense prostate cancer clinical trials consortium. *J Clin Oncol.* 2009;27:2772-2778.
6. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol*. 1999; 17:3461-3467.
7. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008;26:1148-1159.
8. Sartor AO, Oudard S, Ozguroglu M, et al. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC). Paper presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium, March 5-7, 2010, San Francisco, California.
9. Low JA, Wedam SB, Lee JJ, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in metastatic and locally advanced breast cancer. *J Clin Oncol.* 2005; 23:2726-2734.
10. Thomas E, Tabernero J, Fornier M, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. *J Clin Oncol.* 2007;25:3399-3406.
11. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol.* 2007;25:3407-3414.
12. Roche H, Yelle L, Cognetti F, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. *J Clin Oncol.* 2007;25:3415-3420.
13. Denduluri N, Low JA, Lee JJ, et al. Phase II trial of ixabepilone, an epothilone B analog, in patients with metastatic breast cancer previously untreated with taxanes. *J Clin Oncol*. 2007;25:3421-3427.