Published in final edited form as:
Clin Genitourin Cancer. 2009 January ; 7(1): 51–57. doi:10.3816/CGC.2009.n.009.

Department of Defense Prostate Cancer Clinical Trials Consortium: A New Instrument for Prostate Cancer Clinical Research

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Abstract

Background—In 2005, the US Department of Defense, through the US Army Medical Research and Materiel Command, Office of the Congressionally Directed Medical Research Programs, created a funding mechanism to form a clinical trials consortium to conduct phase I and II studies in prostate cancer. This is the first report of the Prostate Cancer Clinical Trials Consortium (PCCTC).

Patients and Methods—The Department of Defense award supports a consortium of 10 prostate cancer research centers. Memorial Sloan-Kettering Cancer Center was awarded the Coordinating Center grant for the consortium and charged with creating an infrastructure to conduct early-phase multicenter clinical trials. Each participating center was required to introduce ≥ 1 clinical trial per year and maintain accrual of a minimum of 35 patients per year.

Results—The PCCTC was launched in 2006 and now encompasses 10 leading prostate cancer research centers. Fifty-one trials have been opened, and 1386 patients have been accrued at member sites. Members share an online clinical trial management system for protocol tracking, electronic data capture, and data storage. A legal framework has been instituted, and standard operating procedures, an administrative structure, editorial support, centralized budgeting, and mechanisms for scientific review are established.

Conclusion—The PCCTC fulfills a congressional directive to create a clinical trials instrument dedicated to early-phase prostate cancer studies. The member institutions have built an

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administrative, informatics, legal, financial, statistical, and scientific infrastructure to support this endeavor. Clinical trials are open and accruing in excess of federally mandated goals.

Keywords

Clinical consortium; Collaborative; Infrastructure; Phase I/II trial

Introduction

Development of new therapies for prostate cancer has traditionally been performed by individual centers of excellence independently pursuing their own investigations, exploiting their own academic strengths, resources, and interests. This has been particularly true of early phase I and II studies, which are small, involve correlative studies that are difficult to conduct among multiple institutions, and require a high ratio of investigator effort to patient accruals.

In order to enhance intercenter collaboration, encourage pooling of expertise and intellectual resources, streamline and accelerate the development of new therapies, and enhance patient access to new drugs, prostate cancer research centers and advocacy groups have long sought to form a consortium focused on early-phase clinical trials. This endeavor would require funding to build an infrastructure for the fundamental aspects of collaborative clinical investigations, such as coordinating patient registrations, reporting adverse events, collecting response data, and organizing the exchange of blood and tissue specimens.

Congress allocated funds for such a consortium to the Department of Defense (DOD), creating the Prostate Cancer Clinical Trials Consortium (PCCTC). Additional funding was secured through the Prostate Cancer Foundation. Participants were selected through a competitive, peer-reviewed grant application process. The federal mandate included building the administrative, legal, informatics, and clinical infrastructure to support these studies, while meeting baseline goals for opening new studies and accruing patients. Such a consortium would need to seamlessly integrate its activities into each member institution's own procedures, routines, and methodologies. This is the first report of the activities of the PCCTC, encompassing the initial 21 months of operation.

Patients and Methods

Prostate Cancer Clinical Trials Consortium Structure

In 2005, the DOD, through the US Army Medical Research and Materiel Command, Office of the Congressionally Directed Medical Research Programs, issued a funding announcement for a clinical consortium award to facilitate the rapid completion of collaborative phase II and phase I/II clinical trials of promising new therapeutic agents and approaches for the management or treatment of prostate cancer. The total award was to be allocated over 3 years and would support 8 to 10 clinical research sites, one of which would serve as a Coordinating Center charged with developing administrative, operational, and data management support services for the participating clinical research sites.

Consortium Aims

Four aims were identified to guide the consortium's organization and scope of work: (1) develop an overall structure, including committee configurations; standard daily operating procedures; and processes for negotiating contracts, intellectual property, and budgets; (2) create a plan for coordinating protocol development and implementation; (3) harness advanced information systems that facilitate secure real-time communications, enhance quality assurance measures, and centrally manage specimens; and (4) accelerate analysis and

publication of data while ensuring equitable investigator attribution. To serve these aims and the consortium's mission, the following infrastructure and clinical elements were required:

Clinical Activity—The DOD mandated that the consortium open a minimum of 10 studies each year and maintain that level of clinical activity throughout the funding period. Each participating site was expected to present ≥ 1 clinical trial each year and accrue a minimum of 35 patients per year. To qualify as a consortium trial, a study was to be open at ≥ 2 participating centers.

Data Management—The consortium was to develop a centralized information technology infrastructure, including a clinical trial management system, an electronic data capture platform, and a common data repository. The model envisioned would allow each participating center to access and exchange clinical information while protecting each institution's and sponsor's intellectual property. Compliance with regulatory requirements, stringent security and privacy precautions, and the use of common data elements (CDEs) compatible with national and international vocabularies were design priorities. All adopted systems were to be harmonized with national standardization initiatives including the Cancer Biomedical Informatics Grid (caBIG) and the Clinical Data Interchange Standards Consortium (CDISC) of the National Cancer Institute (NCI).

Protocol Development—The consortium was to create a common protocol template, furnish editorial resources, and supply statistical support. In addition, a centralized means of contracting, budgeting, and tracking protocols through the approval process was to be developed.

Administrative Structure—A common contract would define the relationship of all participating centers. This contract would clarify the legal obligations of each center to the consortium and distinguish the intellectual property rights of the consortium from those of each center.

Communication—The consortium would require formal methods of communication and decision-making, including regular discussions among the principal investigators of each site and data coordinators and between the consortium and the DOD.

Scientific Review—The consortium would serve to ensure that the clinical trials conducted under its purview were scientifically rigorous and that trial design was innovative and consistent, with an emphasis on novel therapeutics with biomarkers and tissue collection as correlative outcome measures.

Results

Prostate Cancer Clinical Trials Consortium Structure Composition and Administrative Structure

In January 2006, the DOD granted funds to form the PCCTC to 8 institutions: Dana Farber/ Harvard Cancer Center, Johns Hopkins University, M. D. Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, Oregon Health and Science University Cancer Institute, University of California San Francisco, University of Michigan, and University of Wisconsin. In October 2006, Duke University Cancer Center and University of Washington joined the PCCTC, completing the core 10 centers. Seven of these 10 sites were also recipients of prostate cancer Specialized Programs of Research Excellence grants, as shown in Table 1. Memorial Sloan-Kettering Cancer Center was designated the Coordinating Center.

The PCCTC formed an Executive Committee to coordinate and prioritize clinical trials among its members; oversee data management; coordinate contractual, regulatory, and intellectual property issues; and supervise other work according its operating procedures (Figure 1). The Coordinating Center and Executive Committee developed standard operating procedures (SOPs) for the PCCTC and standardized processes for letters of intent (LOIs), Institutional Review Board (IRB) procedures, and budgeting.

Clinical Activity

As of third quarter 2007, 51 LOIs have been submitted and 38 accepted in the PCCTC. These are described in Tables 2A and 2B, which also show the timeline for each study's opening and closure. A representative timeline for a PCCTC phase II study is exemplified by the trial shown in Table 2A of 2-methoxyestradiol: the letter of intent was submitted on March 21, 2006; the lead site secured IRB approval on July 24, 2006; the second and third sites were IRB approved on October 26, 2006, and February 9, 2007, respectively; and the study closed to accrual on October 3, 2007, with 21 participants enrolled.

The median number of centers participating in each study is 3 (range, 2–6 sites). Ten studies also include sites outside of the PCCTC. Although some protocols involve combination studies and some agents have multiple mechanisms of action, in broad terms, 17 studies use biologic agents, 8 use cytotoxic agents, 4 use immunomodulators or other immunotherapy, and 8 use hormonal treatments.

Eleven studies are investigator-initiated, 21 are industry-sponsored, and 6 are sponsored by the Cancer Therapy Evaluation Program (CTEP). Seven studies are first use in humans, and 22 are first use in prostate cancer. A total of 657 patients have been treated in PCCTC studies to date. Nine percent of the patients in PCCTC studies represent minority populations, which is in excess of the target goal of 5% set by the DOD. Four studies are completed, 31 are open and accruing, and 3 are pending IRB approval. Five studies have been reported at meetings[1–5]; 1 study is in press. One study has proceeded to phase III, and 2 additional studies have advanced from phase I to phase II.

Since the writing of this manuscript, the PCCTC has received the competitive continuation award from the DOD, extending support for 5 additional years. During the initial 3-year performance period ending December 2008, 51 trials have opened, and 24 have completed. Between October 2005 and December 2008, the comprehensive total of patients accrued to consortium trials equaled 1386.

Data Management

The PCCTC contracted with a single software vendor to maintain an online clinical trial management system (CTMS), electronic data capture (EDC) platform, and secure central data repository (CDR). The CTMS allows investigators to create online LOIs that are automatically sent by e-mail to the principal investigators at all sites and provides feedback and priority ranking. The EDC system provides Web-based case report forms for manual data entry and is linked via interface to local institutional databases at multiple PCCTC sites, allowing for direct transmission of demographics and laboratory values to the CDR.

Harmonization with national efforts to standardize data capture and transmission has been a priority in the design and continuous review of PCCTC data management. Close ties with the NCI's caBIG and CDISC initiatives are maintained. Recommendations from the US Food and Drug Administration's (FDA) *Guidance for Industry: Computerized Systems Used in Clinical Investigations* have been followed closely for implementation of SOPs, automated audit trails, date/time stamps, internal and external security safeguards, and techniques for source documentation and copy certification.[6,7]

The data-flow model upon which the PCCTC is built permits data to be hand-entered or directly transferred from local institutional databases as standardized data elements (Figure 2). Data move through the EDC system into the CDR, where they are stored for ongoing trial management and subsequent reporting, analysis, data mining, or regulatory purposes.

Data from investigator-sponsored studies are routinely reviewed at the Coordinating Center and identified discrepancies are rectified. All case report forms used in the common data repository are reviewed by the PCCTC's Quality Assurance Committee including common data elements. At present, the Coordinating Center does not perform data verification, as the PCCTC does not function as a study sponsor, and the regulatory responsibilities of auditing are fulfilled by each trial's sponsor, be it academic or industrial.

The PCCTC is involved with national efforts to develop biospecimen tracking systems and is actively working to integrate an electronic tissue tracking system into our existing platform. Efforts are under way to identify a set of relevant, prostate cancer clinical CDEs that are harmonized with other national and international CDE vocabularies. An electronic platform for capturing patient-reported outcomes has been developed at the Coordinating Center and will be implemented in an upcoming phase II trial at multiple consortium sites.[8]

Protocol Development

In its first 9 months, the PCCTC drafted, edited, and adopted a template for protocol design, which adheres to CTEP requirements and uses PCCTC-specific, uniform reporting requirements and regulatory language. A separate template for tissue acquisition and correlative science protocols is now being developed.

The PCCTC employs a central biostatistician to provide statistical support for consortium trials, and recruited a budget director who developed a budget template and reviews protocol budgets from participating centers.

Legal Framework

The counsel of the PCCTC created a common legal framework for the participating institutions and delineated the relationship of the PCCTC to its participant organizations, the DOD, and the sponsors, allowing the PCCTC to negotiate contracts, budgets, and intellectual property as a single body. In addition, it incorporates agreed-upon terms regarding the handling of confidential information, compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), data and results, and discoveries and inventions. The PCCTC also constructed a Master Clinical Trials Agreement to be used as a template when negotiating with commercial sponsors.

Communication

Before the creation of the Consortium, the 10 institutions involved in the PCCTC rarely reviewed common scientific objectives, trial designs, or ongoing studies. The principal investigators and PCCTC Executive Committee now have monthly conference calls to plan and coordinate consortium activities, establish scientific priorities, review ongoing studies, define future objectives, and discuss operational issues. The principal investigators convene to define the scientific objectives and discuss the future direction of the Consortium. In addition, the PCCTC reports to the DOD External Advisory Board (EAB) every 6 months. The EAB in turn critiques the Consortium's performance in regard to meeting DOD-mandated aims such as trial initiation, data capture, scientific rigor, minority accrual, and others. For key issues regarding Consortium management, the Executive Committee turns to the Internal Advisory Board, which advises on legal matters, contract creation, intellectual property, and patient safety, and furnishes senior institutional oversight.

Scientific Review

Initially, each LOI is evaluated by 3 reviewers equipped with a standardized method of rating scientific value, clinical importance, and importance to the PCCTC as a whole before it is submitted for consortium consideration. Principal investigators meet monthly to review all proposed protocols for scientific rigor. In the first 21 months, 7 trials have been rejected because of lack of interest of participating members, 3 were withdrawn, and 2 are pending IRB approval, in addition to the 38 that have already been accepted. The PCCTC has been called on by industry to advise on drug development—specifically to help determine the appropriate time to advance a drug from preclinical to clinical trials, from phase I to phase II and from phase II to phase III.

Discussion

The PCCTC is the first clinical consortium created for the specific purpose of early drug development in a genitourinary malignancy. Over the past 3 years, the 10 participating sites have opened 51 studies through the Consortium—7 of which are first use in humans, and 22 of which are first use in prostate cancer. To date, 1386 patients have been enrolled. The focus of the PCCTC is specifically early-stage trials, which typically are complex and involve numerous scientific or correlative endpoints but are small in size. Such trials might require only a small number of collaborating centers to contribute patients, but these centers must closely coordinate to share registration information, adverse event reporting, and specimen tracking.

The PCCTC has developed the fundamental infrastructure needed to support early-phase, collaborative, interinstitutional studies. It has developed informatics systems to track clinical trial registration and accrual, capture electronic data in line with caBIG, CDISC, and FDA requirements, and track biospecimens. Further, it has defined CDEs, developed a shared protocol template, centralized protocol budgeting, formulated a legal framework to manage intellectual property, implemented a system of scientific review and prioritization, and developed administrative systems to allow for interinstitutional protocol development and scientific exchange.

For prostate cancer, the need for a consortium has been particularly pressing. Unlike clinical studies in other cancers, prostate cancer clinical trials have suffered from intrinsic difficulties in design that have delayed drug development. The disease has a uniquely diverse natural history, a distribution of disease that is singularly difficult to measure, and a highly variable underlying biology. The urgency to build a consortium has been amplified by the availability of an unprecedented number of drugs now available for testing. As a consortium, we have pooled resources for selecting the most promising drug candidates, designed and executed early-phase trials, and decided which drugs deserve to advance to larger phase III trials.

Lastly, clinical trial design for prostate cancer has evolved to the point of requiring formal coordination. Because the disease is bone-tropic and not amenable to standard response criteria, early readouts on clinical activity are difficult to identify.[9–12] As a result, consensus criteria have been designed by leaders in the field,[12–14] and these same leaders have collaborated through the PCCTC to update these criteria, implement unique study designs and develop and validate meaningful clinical endpoints.[15] The PCCTC is, on a national level, standardizing clinical trial design, developing novel targets and measures of treatment effect, and prioritizing therapeutic approaches.

Although prostate cancer has several SPORE programs, the primary, though not exclusive, focus of these programs is scientific development rather than clinical trials. At the other end

of the spectrum, the focus of the cooperative groups is on phase III trials rather than early drug development. The PCCTC fills, therefore, an important need, bridging the gap between basic science and large randomized clinical trials.

The idea of creating a disease-specific clinical consortium is not novel. Such consortia exist for relatively uncommon diseases, such as sarcoma (Sarcoma Alliance for Research through Collaboration), myeloma (Multiple Myeloma Research Consortium), and central nervous system (CNS) tumors (the New Approaches to Brain Tumor Therapy CNS Consortium and the Pediatric Brain Tumor Consortium), as well as common solid tumors such as lung cancer (International Lung Cancer Consortium) and breast cancer (Breast Cancer Surveillance Consortium).

The future direction of the PCCTC will, by necessity, be different from its past. The consortium was established by a granting mechanism from the DOD with additional funding from the Prostate Cancer Foundation. Future viability will rely on developing a financial plan in which the PCCTC is not reliant on a single set of funds. In the process, the PCCTC will have an opportunity to redefine its measures of success. As the PCCTC matures, its focus will shift toward enhancing a common clinical trial database, tissue collection and analysis, designing clinical trials around scientific themes, and building an auditing mechanism for data verification of investigator-sponsored studies. We will focus increasingly on accruing patients from underserved communities, and plan to expand patient access to our studies beyond the present 10 research centers.

Conclusion

In summary, the PCCTC has been formed to fulfill a congressional directive to create a clinical trials consortium dedicated to early prostate cancer studies. The PCCTC's activities are designed to accelerate progress against prostate cancer by shortening the time to the completion of critical phase I/II clinical trials, and, as importantly, by ensuring that trial designs are informative so that trial results support confident decisions about further development. Since its creation, the member institutions have built an administrative, informatics, legal, financial, statistical, and scientific infrastructure to support this endeavor, and clinical trials are open and accruing in excess of federally mandated goals.

Acknowledgments

This study is supported by the US Department of Defense Prostate Cancer Research Program and the Prostate Cancer Foundation. The authors wish to thank Mary Warren, MSW; Jake Vinson, MHA; Moshe Kelsen; Elizabeth Brand; and Hope J. Lafferty, MA, ELS, of the PCCTC for their assistance in preparing this manuscript.

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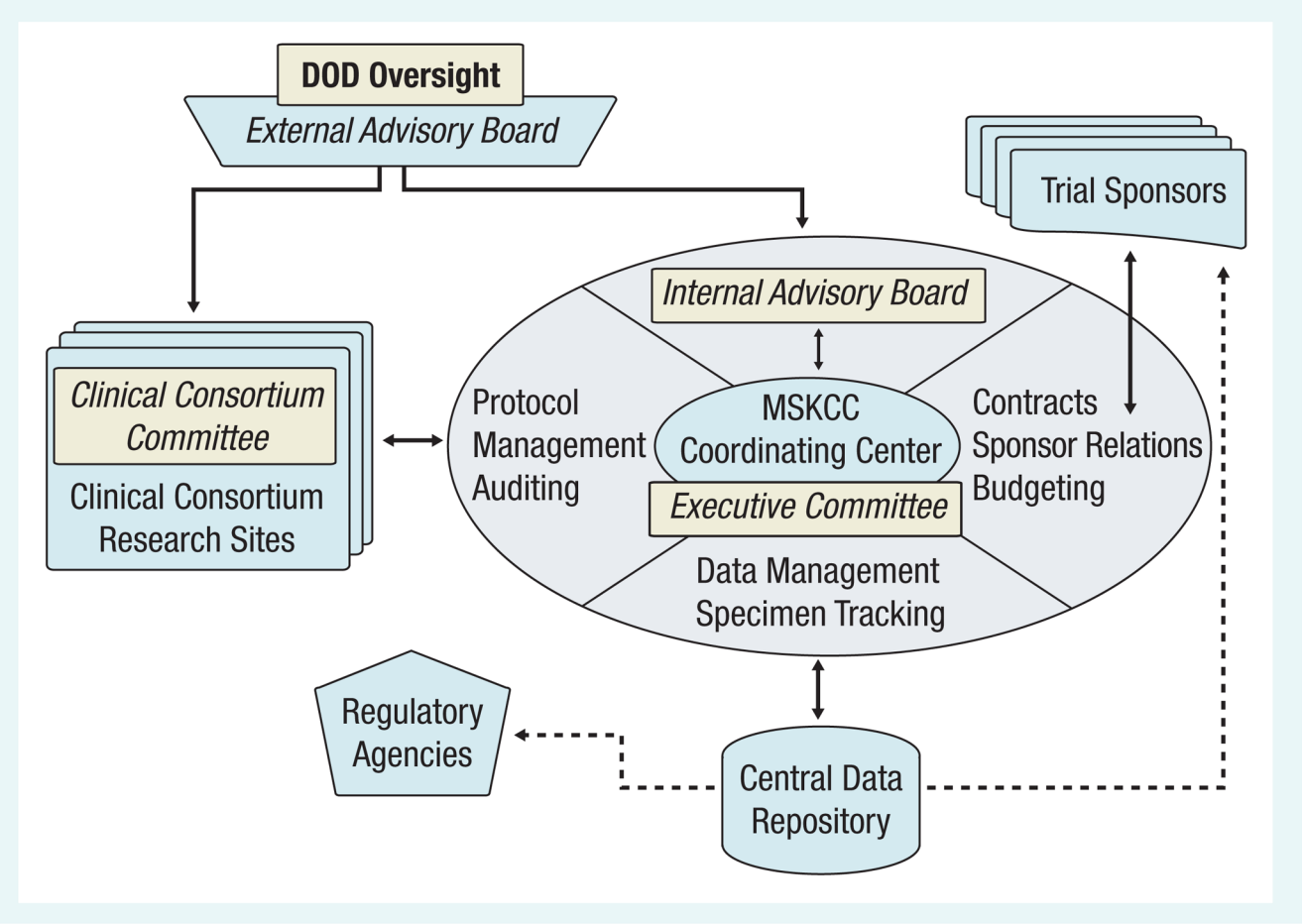

Figure 1.
Administrative Structure of the Prostate Cancer Clinical Trials Consortium
Abbreviations: DOD = Department of Defense; MSKCC = Memorial Sloan-Kettering Cancer Center

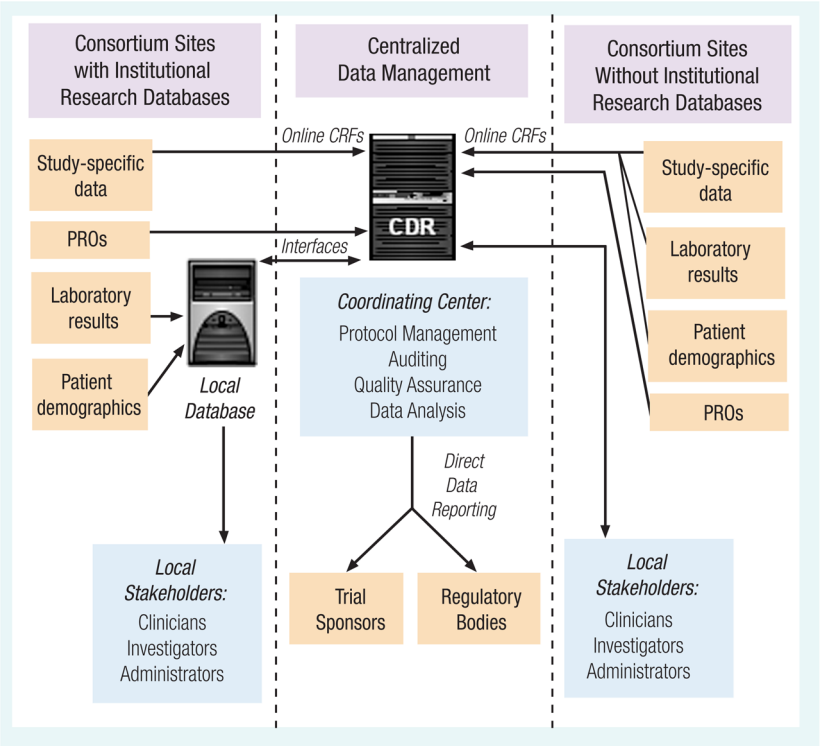

Figure 2.

Data Management in the Prostate Cancer Clinical Trials Consortium

Abbreviations: CDR = central data repository; CRF = case report form; PRO = patient-reported outcome

Table 1

Department of Defense Prostate Cancer Clinical Trials Consortium and Specialized Programs of Research Excellence Recipients

Medical Center	Principal Investigator	SPORE Grant	SPORE Principal Investigator
Dana Farber	Dr. Philip Kantoff	X	X
Johns Hopkins	Dr. Michael Carducci	X	
M. D. Anderson	Dr. Paul Mathew	X	X
University of Michigan	Dr. Maha Hussain	X	
Memorial Sloan-Kettering Cancer Center	Dr. Howard Scher	X	
Oregon Health and Science University	Dr. Tomasz Beer		
University of California/San Francisco	Dr. Eric Small	X	
University of Wisconsin Carbone Comprehensive Cancer Center	Dr. George Wilding		
Duke University	Dr. Daniel George		
University of Washington	Dr. Celestia Higano		

Abbreviation: SPORE = Specialized Programs of Research Excellence

Table 2A

Prostate Cancer Clinical Trials Consortium Studies*

Drug/Agent	Clinical State[12]	Number of Centers	Mechanism	First in Human	First in Prostate	IRB Approval	First Patient Enrolled	Closed to Accrual
2-Methoxyestradiol (2ME2, Nanocrystal Colloidal Dispersion)	Castrate metastatic	3	Metabolite of estradiol	No	No	7/24/2006	9/11/2006	10/3/2007
Abiraterone Acetate plus Prednisone	Castrate metastatic	3	Hormonal	No	No	6/1/2007	6/11/2007	4/2/2008
Abiraterone Acetate	Rising PSA castrate	2	Hormonal	No	No	5/5/2006	7/1/2006	NA
Abiraterone Acetate	Castrate metastatic	2	Hormonal	No	No	4/13/2007	5/7/2007	11/13/2007
AGS-PSCA	Castrate metastatic	2	Antibody	Yes	Yes	10/11/2005	10/25/2005	3/20/2008
AT-101	Rising PSA castrate	2	Bcl-2 antagonist	No	Yes	1/18/2006	2/13/2006	7/6/2006
AT-101/ADT	Non-castrate metastatic	2	Bcl-2 antagonist	No	No	Pending	Pending	NA
ATN-224	Rising PSA non-castrate	6	Copper superoxide dismutase inhibitor	No	Yes	9/5/2006	11/16/2006	1/8/2008
Bevacizumab	Rising PSA non-castrate	4	Anti-VEGF	No	No	Pending	Pending	NA
Bevacizumab plus Docetaxel	Localized disease	2	Cytotoxic/angiogenesis inhibition	No	No	3/7/2006	6/7/2006	NA
BMS-641988	Castrate metastatic	3	Anti-androgen	Yes	Yes	3/28/2006	4/25/2006	NA
Carboplatin plus Docetaxel for Anaplastic Disease	Castrate metastatic	2	Cytotoxic	No	No	3/15/2006	5/10/2006	NA
Lenalidomide	Rising PSA non-castrate	3	Anti-angiogenic/immunomodulator	No	No	5/30/2006	6/30/2006	NA
CGC-11047	Castrate metastatic	3	Polyamine analogue	No	Yes	4/26/2006	6/19/2006	11/29/2007
Dasatinib	Castrate metastatic	4	Bcr-Abl and SRC inhibitor	No	Yes	11/21/2006	1/8/2007	NA
Docetaxel plus Carboplatin	Castrate metastatic	2	Cytotoxic	No	No	11/11/2003	1/20/2004	NA
Docetaxel/Everolimus	Castrate metastatic	2	Chemotherapy mTOR inhibitor	Yes	Yes	9/13/2005	11/29/2005	NA
Dutasteride	Rising PSA non-castrate	2	5-α-Reductase inhibitor	No	No	5/11/2007	5/11/2007	NA
Early-Use Docetaxel	Rising PSA non-castrate	2	Cytotoxic	No	No	11/22/2006	5/1/2007	NA
Cilengitide	Castrate metastatic	3	Selective αvβ3 and αvβ5 integrin antagonist	No	Yes	8/12/2004	8/12/2004	10/15/2007

*Table reflects active trials during the first 21 months of operation.

Abbreviations: IRB = Institutional Review Board; NA = not applicable; mTOR = mammalian target of rapamycin; PSA = prostate-specific antigen; VEGF = vascular endothelial growth factor

Table 2B

Prostate Cancer Clinical Trials Consortium Studies*

Drug/Agent	Clinical State[12]	Number of Centers	Mechanism	First in Human	First in Prostate	IRB Approval	First Patient Enrolled	Closed to Accrual
Cilengitide	Rising PSA castrate	3	As above	No	Yes	10/7/2004	10/7/2004	2/1/2008
Enzastaurin	Rising PSA castrate	2	PKC-β inhibitor	No	Yes	3/28/2007	5/7/2007	NA
GM-CSF and Docetaxel	Castrate metastatic	2	Cytotoxic/growth factor	No	No	10/3/2006	4/1/2007	NA
Cixutumumab	Rising PSA castrate	3	Anti–IGF-IR receptor antibody	No	Yes	7/11/2007	8/11/2007	NA
Ixabepilone	Castrate metastatic	4	Anti-androgen	No	No	3/2/2006	4/11/2006	NA
Ketoconazole, Hydrocortisone, Dutasteride	Rising PSA non-castrate	4	Hormonal	Yes	Yes	5/30/2006	6/30/2006	NA
Panobinostat	Castrate metastatic	4	Histone deacetylase inhibitor	No	Yes	3/28/2006	4/26/2006	10/23/2007
MDV3100	Castrate metastatic	3	Anti-androgen	Yes	Yes	6/29/2007	7/13/2007	
Ipilimumab	Castrate metastatic	3	Anti-CTLA4 inhibitor	No	Yes	8/11/2005	1/10/2006	NA
MK-4721	Castrate metastatic	2	Anti-PSCA antibody	Yes	Yes	8/21/2007	10/3/2007	NA
Oligonucleotide	Castrate metastatic	2	Antisense HSP-27 oligonucleotide	Yes	Yes	6/6/2007	6/24/2007	NA
Paclitaxel Poliglumex and Transdermal Estradiol	Castrate metastatic	2	Chemohormonal	No	Yes	11/2/2006	2/28/2007	NA
Plitidepsin	Rising PSA castrate	2	Depsipeptide	No	Yes	3/3/2006	3/3/2006	NA
Rapamycin	Localized disease	3	Immunosuppressant	No	No	10/26/2005	8/15/2006	NA
Sunitinib Malate	Castrate metastatic	4	Multitargeted receptor kinase inhibitor	No	Yes	8/3/2005	10/10/2005	NA
Suberoylanilide Hydroxamic Acid (SAHA)	Castrate metastatic	4	Histone deacetylase inhibitor	No	Yes	3/2/2006	11/11/2006	NA
Vorinostat	Localized disease	2	Histone deacetylase inhibitor	No	No	11/29/2007	3/3/2008	NA
Sagopilone (ZK-Epo)	Castrate metastatic	3	Cytotoxic	No	Yes	10/6/2006	1/17/2006	NA

* Table reflects active trials during the first 21 months of operation.

Abbreviations: GM-CSF = granulocyte-macrophage colony-stimulating factor; IGF-IR = type 1 insulin-like growth factor receptor; IRB = Institutional Review Board; mTOR = mammalian target of rapamycin; NA = not applicable; PKC = protein kinase C; PSA = prostate-specific antigen; PSCA = postrate stem cell antigen