The DoD Prostate Cancer Clinical Trials Consortium

Translating novel discoveries into FDA-approved therapies involves many lengthy phases of clinical testing. The multi-institutional Prostate Cancer Clinical Trials Consortium (PCCTC) was created to help accelerate the clinical testing of novel therapies in prostate cancer that would lead to improved standards of care. This interactive timeline shows the evolution of the PCCTC since its initial funding by the DoD Prostate Cancer Research Program (PCRP), as well as the PCCTC's critical involvement in the clinical trials that led to FDA approval of two therapies that have become the standard of care for those with advanced prostate cancer: abiraterone and enzalutamide.

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The Prostate Center Clinical Trials Consortium				
2005	**PCCTC Initiated**	*The PCRP offers the first DoD Clinical Consortium Award to support clinical testing of promising prostate cancer therapeutics (Apr 2005 - Apr 2006)*	In 2005, the Prostate Cancer Research Program (PCRP) recognizes a critical need for advancing the clinical testing of novel therapeutics for prostate cancer. To address this gap, the PCRP offers its first funding opportunity aimed at supporting a multi-institutional, collaborative network of leading prostate cancer research centers. The clinical consortium, referred to as the Prostate Cancer Clinical Trials Consortium (PCCTC), not only facilitates a more rapid rate of patient accrual and trial completion, but also fosters the co-development of new clinical trials and projects between investigators, research sites, and industry partners, ultimately allowing the field of prostate cancer clinical research to advance at an accelerated pace.	• Prostate Cancer Clinical Trials Consortium (PCCTC) website (http://pcctc.org) • Fiscal Year 2005 PCRP Clinical Consortium Program Announcement (http://cdmrp.army.mil/funding/pa/05pcrpcca_pa.pdf) • PCRP Clinical Consortium Awards (http://cdmrp.army.mil/pcrp/consortia#1)
	MSKCC is Selected as the PCCTC Coordinating Center	*Memorial Sloan-Kettering Cancer Center (MSKCC) is recommended for funding as the coordinating center for the 2005 PCCTC. The PCRP charges the coordinating center with serving as the information and planning nexus of the PCCTC, as well as providing administrative, operational, and data management support services for the other participating clinical research sites (Oct 2005 - Oct 2005)*	In response to this challenge, the MSKCC coordinating center, led by Dr. Howard Scher, creates a new paradigm for collaborative drug development, an organizational structure that allows transparent project co-development between investigators, clinical sites, and research sponsors. Capitalizing on their long histories of collaboration, scientific expertise, and unique institutional resources, members of the PCCTC work together on a single mission: to design, implement, and complete hypothesis-driven Phase I and Phase II trials in prostate cancer, translating scientific discoveries to improved standards of care for patients.	• Fiscal Year 2005 PCRP Clinical Consortium Program Announcement (http://cdmrp.army.mil/funding/pa/05pcrpcca_pa.pdf) • Objectives of the MSKCC FY05 CCA award (http://cdmrp.army.mil/search.aspx? LOG_NO=PC051382)
	PCRP Funds Seven Clinical Research Sites to Establish PCCTC	*Initial DoD-funded Clinical Consortium comprises eight sites, including the coordinating center (Oct 2005)*	The DoD funds eight Clinical Consortium Awards to add seven clinical research sites to the PCCTC. As members of the Consortium, the clinical research sites are expected to work collaboratively to identify new clinical trials for implementation by the Consortium and participate in multi-institutional trials proposed and accepted as PCCTC trials. The seven funded clinical research sites (in addition to a clinical research site at Memorial Sloan-Kettering Cancer Center) are: 1. University of California at San Francisco 2. Dana Farber/Harvard Cancer Center 3. Johns Hopkins University 4. MD Anderson Cancer Center 5. University of Michigan 6. Oregon Health and Science University 7. University of Wisconsin	• Fiscal Year 2005 PCRP Clinical Consortium Program Announcement (http://cdmrp.army.mil/funding/pa/05pcrpcca_pa.pdf)
2006	**PCCTC Surpasses 200 Patient Accruals to Prostate Cancer Clinical Trials**	*Collaborative efforts result in 208 patients recruited to PCCTC trials in the first year (Nov 2006)*	In 1 year of initiating the DoD-funded PCCTC, the Consortium approves 23 proposed trials, 19 of which are open and recruiting patients, and 4 of which are using agents that are novel for prostate cancer treatment. Their rate of patient accrual to PCCTC trials is also rapidly increasing as they continue to work on standardizing procedures across the Consortium, with just over 200 patients recruited to active PCCTC trials in the first year.	
2007	**PCCTC Expanded to Ten Clinical Research Sites**	*PCRP re-offers the Clinical Consortium Award in FY06 (May 2007)*	The first year of the PCRP-funded PCCTC showed great potential for continued growth and accomplishment by the partnering institutions. To further strengthen the Consortium, the PCRP opts to consider adding a few additional clinical research sites to the currently funded PCCTC and re-offers the Clinical Consortium Award in FY06 for that purpose. Two additional institutions, Duke Comprehensive Cancer Center and the University of Washington, receive the award and are incorporated into the PCCTC, expanding the total number of clinical research sites from 8 to 10.	• Fiscal Year 2006 PCRP Clinical Consortium Program Announcement (http://cdmrp.army.mil/funding/pa/06pcrpcca_pa.pdf)
	PCCTC Finalizes First Trial Agreement with Industry Sponsor	*Agreement protects interests of Consortium investigators when dealing with an industry sponsor (Sep 2007)*	The coordinating center recognizes the need to develop a Master Clinical Trials Agreement (MCTA) to protect the rights of the investigators to any data and intellectual property generated from an industry-sponsored clinical trial. This MCTA would enable the coordinating center to help streamline agreements between the PCCTC and industry to facilitate clinical trials.	
2008	**Spreading the Word About the PCCTC**	*A multicenter mechanism for the rapid design, development and implementation of early-phase clinical trials. (Jun 2008 - Jan 2009)*	Word about the unique infrastructure established by the federally funded PCCTC is publicized to the scientific community through specific publications at the 2009 American Society of Clinical Oncology (ASCO) meeting, as well as in the *Clinical Genitourinary Cancer* journal in January 2009. These articles detail the goal of the DoD to create a Consortium that would conduct early-phase, multi-center clinical trials in prostate cancer and the group's progress to date in achieving that goal. At the time of publication, the Consortium notes that, to date, it has opened 47 trials and recruited 1,282 patients to PCCTC-led trials.	• Morris MJ, Basch EM, et al. 2009. Department of Defense Prostate Cancer Clinical Trials Consortium: A new instrument for prostate cancer clinical research. Clin Genitourin Can 7(1):51-57. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3394090/)

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	PCCTC Makes Landmark Recommendations for Clinical Trial Design	*Results from PCWG2 are published (Mar 2008)*	Leading prostate cancer researchers, including investigators that are now part of the PCCTC, recognize the need to establish universal guidelines for the design and implementation of new clinical trials for prostate cancer. The results of a collaborative initiative called the Prostate-Specific Antigen Working Group (PCWG1) were released in 1999, but the focus of these recommendations on a specific group of patients led to a challenge by the FDA in 2004 to update the eligibility and outcome measures of PCWG1. In response, investigators from the PCRP-funded PCCTC rise to the challenge by forming the Prostate Cancer Working Group 2 (PCWG2) and issue recommendations for the design of end points for prostate cancer clinical trials for patients with metastatic castration-resistant prostate cancer. The recommendations produced by PCWG2, published in the *Journal of Clinical Oncology* in early 2008, have a profound impact on clinical trial design, the evaluation of new therapies, and drug approvals.	• Scher, HI, Halabi S, et al. 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):1148-59. (https://www.ncbi.nlm.nih.gov/pubmed/18309951)
	PCCTC is Further Expanded to Thirteen Clinical Research Sites	*PCRP Recompetes the Clinical Consortium Award in FY08 (Dec 2008)*	The continued success of the DoD-funded PCCTC leads the PCRP to continue supporting a Clinical Consortium for 5 more years. The FY08 Clinical Consortium Award (CCA) is openly recompeted, and the program funds 13 clinical research sites and a coordinating center. Memorial Sloan-Kettering Cancer Center successfully competes to remain the coordinating center for the PCCTC; the other 13 clinical research sites are listed below. In addition to requiring the Consortium investigators to continue submitting novel trials for execution by the PCCTC and recruiting patients to other Consortium-led trials, the new FY08 CCA also places significant emphasis on incorporating biomarker questions into PCCTC-led trials. In an era where biomarkers seem to be the future of predictive medicine, this new element enables the PCCTC to address key questions related to biomarkers, while simultaneously testing the efficacy of new treatments for prostate cancer. The 13 clinical research sites are: 1. University of California, San Francisco 2. University of Chicago 3. Dana-Farber Cancer Institute 4. Duke University Medical Center 5. Johns Hopkins University 6. MD Anderson Cancer Center 7. Memorial Sloan-Kettering Cancer Center 8. University of Michigan 9. Oregon Health & Science University 10. State University of New Jersey at Rutgers 11. University of Washington 12. Wayne State University 13. University of Wisconsin, Madison	• Fiscal Year 2008 PCRP Clinical Consortium Program Announcement (http://cdmrp.army.mil/funding/pa/08pcrpcca_pa.pdf)
2010	**PCCTC Develops Considerable Hold on Prostate Cancer Clinical Research Landscape**	*(Jan 2010)*	The PCCTC reports to the DoD that PCCTC studies currently represent 22% of all Phase I and Phase II prostate cancer clinical trials that are open in the United States by the end of 2009. In addition, the PCCTC reports remarkable success with their studies, advancing the first eight agents studied in the Consortium to Phase III development. As of January 2010, the PCCTC has 34 trials open and enrolling patients, with another 23 pending activation and 45 that have been completed or are no longer recruiting patients. The total number of patients recruited to these Phase I and Phase II trials now exceeds 2,200.	
2011	**First Agent Tested by PCCTC Receives FDA Approval**	*Abiraterone acetate is FDA approved under brand name Zytiga™ (Mar 2011)*	The PCCTC celebrates their success in securing FDA approval for ZYTIGA™. This drug was brought through clinical testing by the PCCTC at nearly twice the traditional speed for most drugs, creating an enormous impact for men with metastatic castration-resistant prostate cancer.	• PCRP Article: The PCRP Facilitates Rapid Pace for Clinical Trials (http://cdmrp.army.mil/pubs/news/pdf/pc_newsletter_Feb2011.pdf) • Program News (http://cdmrp.army.mil/pubs/news/pdf/pc_newsletter_June2011.pdf) • FDA Report: FY 2011 Innovative Drug Approvals (https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm278358.pdf)
	Accomplishments of the PCCTC Featured at the PCRP IMPaCT Meeting	*Innovative Minds in Prostate Cancer Today (IMPaCT) (Mar 2011)*	The PCRP IMPaCT meeting was held to provide a broad overview of the latest advancements in prostate cancer research and highlight the important contributions made by PCRP-funded investigators. Educational sessions led by experts offer in-depth coverage of topics such as prostate cancer screening, treatment options of localized disease, and quality of life in late-stage disease, among others. Presentations by PCCTC investigators during the session entitled, "The Process of Basic Research to Phase III Trials," highlighted the tremendous contribution the consortium has made toward advancing new treatment options for prostate cancer patients.	• IMPaCT Plenary Session Videos featuring PCCTC Investigators Dr. Higano, Dr. Hussain, and Dr. Scher (http://cdmrp.army.mil/pubs/video/pc/impact_ps2_videos) • IMPaCT Plenary Session Videos featuring PCCTC Investigator Dr. George (http://cdmrp.army.mil/pubs/video/pc/impact_ps2_videos) • PCRP Video: Prostate Cancer Clinical Trials Consortium: Bringing the "Best of the Best" to Prostate Cancer Patients (http://cdmrp.army.mil/pubs/video/pc/IMPaCTVideo_pcctc) • IMPaCT meeting highlights in PCRP Perspectives Newsletter (http://cdmrp.army.mil/pubs/news/pdf/pc_newsletter_June2011.pdf)
	PCCTC Continues to Increase Interaction with Industry Sponsors	*(Sep 2011)*	From the first Master Clinical Trial Agreement that was established in 2007, the PCCTC continues to attract industry sponsors and, to date, has fully executed 15 PCCTC coordinating center service agreements. Industry sponsors who have utilized the clinical trial design services of the PCCTC include Medivation, Abbott, Tokai, Genentech, and Exelixis, among others.	

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2012	**Second Novel Agent Clinically Tested by PCCTC Receives FDA Approval**	*Enzalutamide is FDA approved under the brand name XTANDI™ (Sep 2012)*	First tested by the PCCTC in 2007 in a Phase I and II dose-escalation trial, the PCCTC rapidly moves enzalutamide through Phase I and II trials, leading to FDA approval in record time. "The accelerated development and approval of enzalutamide illustrates how the PCCTC's unique academic-industry co-development paradigm can bring life-prolonging drugs to patients faster. Beginning with the first-in-man trial that incorporated PCWG2 metrics developed by Consortium members to ensure drugs are not discontinued prematurely, to the rapid trial activation and expansion once clinical benefit was observed in the first patients treated, our model is built on successful partnerships to achieve shared goals," says Dr. Scher.	• PCRP Highlight: PCRP Clinical Consortium Accelerates Enzalutamide to FDA Approval (http://cdmrp.army.mil/pubs/video/pc/IMPaCTVideo_pcctc) • 2012 CDMRP Annual Report, pg. 34 (http://cdmrp.army.mil/pubs/annreports/2012annrep/2012annreport.pdf)
	PCCTC Surpasses New Patient Accrual Milestone	*Over 3,000 patients recruited to PCCTC trials (Sep 2012)*	The PCCTC continues to advance prostate cancer clinical trials, having now activated 113 trials, with an active portfolio of 34 trials currently open and enrolling, and another 10 trials pending activation. The PCCTC has recruited 3,479 patients to these 113 Phase I and Phase II clinical trials and continues to accelerate testing of novel therapies for prostate cancer.	
	PCCTC Launches the Affiliate Site Program	*Affiliate site program part of the FY13 Clinical Consortium Award recompete (May 2013)*	The PCCTC demonstrated substantial growth and achievement during the previous 5 years of funding and is on the cusp of filing to become an independent limited liability company (LLC) as part of its plan to develop financial independence. The PCRP recognizes the need to continue supporting a Clinical Consortium during this transition period and recommends re-offering the Clinical Consortium Award in FY13. The program chooses to financially support 10 sites this year, but requires the coordinating center to provide another opportunity for financial support to other sites of its choosing, called affiliate sites. The coordinating center releases a Request For Applications to the scientific community and selects three sites to become the first funded affiliate sites of the PCCTC. The DoD-funded primary and affiliate (*) sites that were funded in response to the FY13 CCA are listed below: 1. University of California, Los Angeles 2. University of California, San Francisco 3. University of Chicago * 4. Dana-Farber / Harvard Cancer Center 5. Duke University Medical Center 6. Johns Hopkins University 7. Memorial Sloan-Kettering Cancer Center 8. University of Michigan * 9. Oregon Health & Science University 10. Sidney Kimmel Cancer Center, Thomas Jefferson University * 11. University of Washington 12. Wayne State University 13. Weill Cornell Medical College 14. University of Wisconsin, Madison	• RFA: PCCTC Affiliate Clinical Research Sites (http://pcctc.org/news/rfa-pcctc_affiliate_clinical_research_sites/)
	PCCTC Surpasses New Patient Accrual Milestone	*Over 4,000 patients recruited to PCCTC trials (Dec 2013)*	The PCCTC continues to advance prostate cancer clinical trials, having now activated 127 trials, with an active portfolio of 30 trials currently open and enrolling, and another 15 trials pending activation. The PCCTC has recruited over 4,000 patients to these 113 Phase I and Phase II clinical trials and continues to accelerate testing of novel therapies for prostate cancer.	
2014	**The Clinical Consortium Legally Becomes PCCTC, LLC**	*PCCTC, LLC, offers services to ensure efficient trial selection, reporting, site management, clinical operations, and data analyses for prostate cancer clinical trials (Feb 2014)*	In response to the DoD's requirement that the Clinical Consortium work toward establishing financial independence, the coordinating center at Memorial Sloan-Kettering Cancer Center officially files papers to establish PCCTC, LLC. The establishment of an LLC positions the Consortium to independently provide support to the pharmaceutical, biotechnology, and medical device industries in the form of research services.	• 2014 CDMRP Annual Report, pg. 10 (http://cdmrp.army.mil/pubs/annreports/2014annrep/2014annreport.pdf)
	PCCTC Surpasses New Patient Accrual Milestone	*Over 4,800 patients recruited to PCCTC trials (Sep 2014)*	The PCCTC continues to advance prostate cancer clinical trials, having now activated 156 trials, with an active portfolio of 33 trials currently open and enrolling, and another 15 trials pending activation. The PCCTC has recruited 4,811 patients to these 156 Phase I and Phase II clinical trials and continues to accelerate testing of novel therapies for prostate cancer.	
	PCCTC, LCC Becomes The First Qualified Vendor of Novartis		In addition to having executed over 20 service agreements with outside industry sponsors, PCCTC, LLC, is recognized as a qualified vendor by Novartis. In subsequent years, PCCTC, LLC, continues to receive vendor qualification status for other pharmaceutical companies, including Janssen, Medivation, Zenith Pharmaceuticals, Innocrin Pharmaceuticals, and Boehringer Ingelheim.	• 2014 CDMRP Annual Report, pg. 72 (http://cdmrp.army.mil/pubs/annreports/2014annrep/2014annreport.pdf)
2015	**Streamlining Approvals for Clinical Research Protocols to Maximize Efficiency**	*The PCCTC moves to using a centralized Institutional Review Board (IRB) services company*	One of the biggest challenges when collaborating across different institutions for clinical trials is working to obtain individual protocol approvals from each institution's IRB. In an effort to maximize efficiency and further enhance the quality of its research review process, PCCTC, LLC, enters into an agreement with WIRB-Copernicus Group to serve as the sole source for review and approval of their cancer research protocols, which demonstrates a reduction in administrative delays and further accelerates new clinical trials.	• WIRB-Copernicus Group and the Prostate Cancer Clinical Trials Consortium Announce New Partnership to Improve Efficiency of Oncology Research Reviews (http://www.prnewswire.com/news-releases/wirb-copernicus-group-and-the-prostate-cancer-clinical-trials-consortium-announce-new-partnership-to-improve-efficiency-of-oncology-research-reviews-300150395.html)

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2016	**Prostate Cancer Working Group 3 Releases Updated Guidelines**	*(Apr 2016)*	When the PCWG2 recommendations were published in 2008, docetaxel was the only approved life-prolonging therapy for metastatic castration-resistant prostate cancer. Since then, five additional drugs have been approved, creating the need to update the recommendations and, in particular, to better align clinical trial questions with clinical practice. The PCWG3 formally convened eight times between June 2012 and February 2015 to develop the consensus recommendations, which included a revised disease states model, eligibility criteria, outcome criteria, and reporting methodology. The updated recommendations provide a framework for how best to use available agents in clinical practice, building on recent reports showing that metastatic castration-resistant prostate cancer consists of several distinct biologic subtypes, and thus creating the need to characterize the biology of an individual patient's tumor when a change in therapy is needed by direct biopsy of a metastatic site, circulated nucleic acid, or circulating tumor cells in blood.	• PCRP Highlight: Establishing Guidelines for Castration Resistant Prostate Cancer Clinical Trials: A Collaborative Effort Led by PCCTC Investigators (http://cdmrp.army.mil/pcrp/research_highlights/16scher_highlight) • Scher HI, Morris MJ, et al. 2016. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 34(12):1402-18. (https://www.ncbi.nlm.nih.gov/pubmed/26903579)
	FDA Fast Tracks Another Agent Developed with PCCTC, LLC	*Seviteronel (VT-464) (Jan 2016)*	Another androgen-targeting agent, seviteronel (VT-464), receives the FDA's "fast track" designation for treating patients with metastatic castration-resistant prostate cancer. PCCTC, LLC, was involved in the Innocrin-sponsored Phase I and Phase II studies.	• FDA Fast Tracks Tx for Metastatic Castrate-resistant Prostate CA (http://www.empr.com/drugs-in-the-pipeline/fda-fast-tracks-tx-for-metastatic-castrate-resistant-prostate-ca/article/464082/) • Clinical Trial NCT02445976 (https://clinicaltrials.gov/ct2/show/NCT02445976?term=vt-464&rank=1) • Clinical Trial NCT02012920 (https://clinicaltrials.gov/ct2/show/NCT02012920?term=vt-464&rank=4) • Nordquist, LT, et al. 2016. Objective response of the dual CYP17-Lyase inhibitor/androgen receptor (AR) antagonist, VT-464, in patients with CRPC. ASCO Ann Meeting Pro 34(2). (http://meetinglibrary.asco.org/content/158354-172)
2017	**PCCTC Surpasses New Patient Accrual Milestone**	*Almost 6,000 patients recruited to PCCTC trials (Mar 2017)*	The PCCTC continues to advance prostate cancer clinical trials, having now activated 215 trials, with an active portfolio of 43 trials currently open and enrolling, and another 10 trials pending activation. The PCCTC has recruited 5,966 patients to these 162 Phase I and Phase II clinical trials and continues to accelerate testing of novel therapies for prostate cancer.	
Abiraterone				
2007	**Efficacy and Safety Study Supports Further Development of Abiraterone Acetate**	*Phase II study of abiraterone acetate and prednisone in prostate cancer patients who failed androgen deprivation and docetaxel-based chemotherapy (Apr 2007 - Nov 2007)*	This Phase II study evaluates the anti-tumor efficacy and safety of abiraterone acetate in combination with prednisone in 58 patients with advanced prostate cancer. Anti-tumor efficacy is assessed by the proportion of patients achieving a prostate-specific antigen (PSA) decline of >50% (PSA response), which is part of the Prostate Specific Antigen Working Group criteria published in 2008. The study finds that abiraterone acetate is well tolerated and demonstrates anti-tumor activity, with a >50% decline in PSA confirmed in 35% of the patients. The results of this study support the need for additional development and testing of abiraterone as a potential therapy for men with advanced prostate cancer.	• Clinical Trial NCT00485303 (https://clinicaltrials.gov/ct2/show/NCT00485303?term=nct00485303&rank=1) • Danila DC, Morris MJ, et al. 2010. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. J Clin Oncol 28(9):1496-1501. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3040042/)
	Early Phase I/II Open Label Study to Determine the Maximum Tolerated Dose of Abiraterone Acetate	*Maximum tolerated dose, safety, tolerability, and activity of abiraterone acetate evaluated in hormone-refractory prostate cancer patients (May 2006 - Jul 2007)*	Sponsored by Cougar Biotechnology, Inc., the PCCTC leads an early clinical trial to establish the recommended dose for future trials to evaluate the efficacy of abiraterone acetate in prostate cancer patients. Forty-five patients are enrolled in the study, and the first results show positive clinical data for abiraterone acetate, as presented at the 2007 American Society of Clinical Oncology (ASCO) meeting. Investigators also introduce the concept of bone-flare, which was observed after treatment with abiraterone. Defining this response in patients is critical because a "flare" during bone scans could result in potential errors, causing patients to be taken off active agents too soon.	• Clinical Trial NCT00473512 (https://clinicaltrials.gov/ct2/show/NCT00473512?term=nct00473512&rank=1) • Cougar Biotechnology Announces Presentation of Positive CB7630 Clinical Data at ASCO Annual Meeting (http://www.businesswire.com/news/home/20070604005379/en/Cougar-Biotechnology-Announces-Presentation-Positive-CB7630-Clinical) • Ryan CJ, Shah S, et al. 2011. Phase II study of abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. Clin Can Res 17(14):4854-61. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3657705/)
2008	**Large Phase III Study Demonstrates Increased Survival with Abiraterone Acetate Treatment**	*Key Phase III study provides data needed to file for FDA approval (May 2008 - Oct 2012)*	PCCTC investigators lead a large Phase III trial sponsored by Cougar Biotechnology, Inc., to compare the clinical benefit of abiraterone acetate plus prednisone with placebo plus prednisone in 1,195 patients with metastatic castration-resistant prostate cancer who have failed one or two chemotherapy regimens, one of which contains docetaxel. Interim data from this Phase III trial show a statistically significant improvement in overall survival and an acceptable safety profile, leading the Independent Data Monitoring Committee to recommend that the study be unblinded and that abiraterone acetate be offered to all patients that are currently receiving the placebo, so they could benefit from the treatment. These data are also sufficient to allow Cougar Biotechnology to begin filing marketing applications in anticipation of obtaining FDA approval for abiraterone. Further analysis of the results from the Phase III study also indicate additional patient benefits from abiraterone acetate, including pain relief, delayed pain progression, and prevention of skeletal-related events.	• Clinical Trial NCT00638690 (https://clinicaltrials.gov/ct2/show/NCT00638690?term=NCT00638690&rank=1) • de Bono JS, Logothetis CJ, et al. 2011. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364(21):1995-2005. (https://www.ncbi.nlm.nih.gov/pubmed/21612468?dopt=Abstract) • Study of Investigational Agent Abiraterone Acetate for Metastatic Advanced Prostate Cancer Unblinded After Meeting Pre-Determined Criteria (http://www.investor.jnj.com/releasedetail.cfm?releaseid=506329) • Abiraterone Acetate Significantly Improved Overall Survival for Patients with Metastatic Advanced Prostate Cancer (http://www.fiercebiotech.com/biotech/abiraterone-acetate-significantly-improved-overall-survival-for-patients-metastatic) • Fizazi K, Scher HI, et al. 2012. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 13(10):983-92. (https://www.ncbi.nlm.nih.gov/pubmed/22995653?dopt=Abstract) • Logothetis CJ, Basch E, et al. 2012. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol 13(12):1210-17. (https://www.ncbi.nlm.nih.gov/pubmed/23142059?dopt=Abstract)

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	Phase III Study Demonstrates That Abiraterone Acetate Can Delay the Initiation of Chemotherapy	*Additional testing of abiraterone acetate in pre-chemotherapy patients looks to expand indication use for patients with metastatic castration-resistant prostate cancer (Apr 2009 - May 2010)*	Following on the positive results from the first Phase III trial, PCCTC investigators investigate the potential benefit of abiraterone acetate in 1,088 patients with metastatic castration-resistant prostate cancer that did not receive chemotherapy. Patients on this study showed tumor progression, but were asymptomatic or mildly symptomatic. The results demonstrate that abiraterone again shows a trend toward improved overall survival and significantly delays clinical decline and initiation of chemotherapy in patients with metastatic castration-resistant prostate cancer. (Sponsor: Janssen Research & Development, LLC.)	• Clinical Trial NCT00887198 (https://clinicaltrials.gov/ct2/show/NCT00887198?term=NCT00887198&rank=1) • Ryan CJ, Smith MR, et al. 2013. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368(2):138-48. (https://www.ncbi.nlm.nih.gov/pubmed/23228172?dopt=Abstract) • Basch E, Autio K, et al. 2013. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. Lancet Oncol 14(12):1193-99. (https://www.ncbi.nlm.nih.gov/pubmed/24075621?dopt=Abstract) • Rathkopf DE, Smith MR, et al. 2014. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy. Eur Urol 66(5):815-25. (https://www.ncbi.nlm.nih.gov/pubmed/24647231?dopt=Abstract)
2009	**Phase II Study Shows Abiraterone Enhances Androgen Suppression when Combined with Leuprolide**	*Crossover assignment study provides new insight into neoadjuvant therapy before prostatectomy (Nov 2009 - Mar 2012)*	For men with localized prostate cancer that has not yet spread to other areas outside the prostate, the two main localized treatment options are prostatectomy or radiation therapy. Previously, cure rates for men with localized, high-risk prostate cancer are suboptimal with these types of localized therapy, although there is some evidence that combining androgen-deprivation therapy (ADT) with radiation therapy can improve patient outcomes. Since this addition of ADT had not yet been studied in patients who elected to instead undergo a prostatectomy, PCCTC investigators launched a randomized, open-label Phase II study to investigate the benefits of giving patients intense ADT prior to prostatectomy. The study included combination therapy from two ADT agents - a luteinizing hormone-releasing hormone agonist called leuprolide, and the testosterone blocking agents, abiraterone acetate. The results of the study published in 2014 suggested that providing patients with more intense ADT provides a promising neoadjuvant (or first treatment) approach to more completely controlling prostate cancer for men who elect surgery as their primary form of local therapy.	• Clinical Trial NCT00924469 (https://clinicaltrials.gov/ct2/show/NCT00924469?term=nct00924469&rank=1) • Taplin ME, Montgomery B, et al. 2014. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin Oncol 32(33):3705-15. (https://www.ncbi.nlm.nih.gov/pubmed/?term=25311217) • PCCTC Study Shows Zytiga May Improve Outcomes When Taken Before Prostatectomy (http://pcctc.org/news/pcctc-study-shows-zytiga-may-improve-outcomes-when-taken-before-prostatectomy/)
	Johnson & Johnson Acquires Cougar Biotechnology, Inc., and Abiraterone Acetate	*Johnson & Johnson looks to expand their position in the global oncology market as two Phase III trials for abiraterone are ongoing (Nov 2009)*	Johnson & Johnson (J&J) acquires Cougar Biotech for $1 billion to assume their oncology portfolio, which includes the company's lead compound, abiraterone acetate. J&J continues to work with Cougar Biotech and the PCCTC to help finalize testing of abiraterone and eventually brings the agent to FDA approval.	• Johnson & Johnson Completes Acquisition of Cougar Biotechnology (http://www.investor.jnj.com/releasedetail.cfm?releaseid=395580)
2010	**Abiraterone Demonstrates Modest Clinical Efficacy for Patients Previously Treated with Ketoconazole**	*Efficacy of abiraterone is tested in metastatic castration-resistant prostate cancer patients previously treated with ketaconazole that were excluded from earlier Phase III trials (15 Sep 2010 - 04 Jan 2013)*	Due to potential overlap in mechanism and resistance between abiraterone and ketoconazole, patients who received ketoconazole were not included in earlier Phase III abiraterone trials. This study evaluates whether abiraterone would provide additional effects on circulating androgens for 39 metastatic castration-resistant prostate cancer patients who were already treated with ketoconazole. Interim study results note that a significant proportion of patients previously treated with ketoconazole demonstrate a clinical response to abiraterone therapy and provide initial evidence that DHEA (dehydroepiandrosterone) levels could be useful as a predictive biomarker for patients treated with androgen synthesis inhibitors.	• Clinical Trial NCT01199146 (https://clinicaltrials.gov/ct2/show/NCT01199146?term=nct01199146&rank=1) • Kim W, et al. 2014. Activity of abiraterone acetate in metastatic patients with castration-resistant prostate cancer (mCRPC) previously treated with ketoconazole: A prospective phase II study from the prostate cancer clinical trials consortium. ASCO Ann Meeting Proc. 32(4). (http://meetinglibrary.asco.org/content/124105-142)
2011	**FDA Approves Zytiga™**	*Approval for indication combined with prednisone to treat metastatic castration-resistant prostate cancer patients who have previously received docetaxel therapy (Apr 2011)*	On April 28th, the FDA approves abiraterone acetate (marketed as Zytiga™) in combination with prednisone to treat patients with late-stage metastatic castration-resistant prostate cancer who have received prior docetaxel (chemotherapy). This approval provides a new treatment option for men with late-stage prostate cancer who have received prior treatment and were left with very few therapeutic options to stop their prostate cancer from progressing further. The trials led by the PCCTC, in addition to funded investigators at the Royal Marsden Hospital in London, are instrumental in designing the key Phase III clinical trial that supported the FDA decision to approve the agent.	• FDA Report: FY 2011 Innovative Drug Approvals (https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm278358.pdf)
	Phase II Study Testing Combination of Abiraterone with Dutasteride	*Preliminary data suggest that dutasteride may enhance efficacy of abiraterone (Aug 2011 - Oct 2012)*	Investigators continue to investigate other possible combination therapies with abiraterone that could provide further clinical benefit for patients. This Phase II study evaluates the addition of dutasteride to abiraterone acetate and prednisone treatment. Initial results presented at the 2014 American Society of Clinical Oncology annual meeting indicate that the addition of dutasteride may enhance the efficacy of abiraterone, although final study results are not yet published.	• Clinical Trial NCT01393730 (https://clinicaltrials.gov/ct2/show/NCT01393730?term=nct01393730&rank=1) • McKay RR, Werner L, et al. 2014. Results of a phase II trial of abiraterone acetate (AA) combined with dutasteride (DUT) for men with metastatic castration resistant prostate cancer (mCRPC). ASCO Ann Meeting Proc 32(4). (http://meetinglibrary.asco.org/content/124144-142)
2012	**FDA Approves Zytiga™ for Second Indication**	*Expanded indication for metastatic castration-resistant prostate cancer patients pre-chemotherapy (Dec 2012)*	The FDA expands the indication for Zytiga™ (abiraterone acetate), approving the use of Zytiga in combination with prednisone for metastatic castration-resistant prostate cancer patients who have not previously received cytotoxic chemotherapy. Phase III trials that were critical to the FDA's decision to expand the indication were led by the PCCTC. Expanded usage quickly results in a 43% increase in Zytiga as a first-line therapy for patients with advanced prostate cancer.	• FDA Report: FY 2011 Innovative Drug Approvals (https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm278358.pdf) • Kantar Health Data Show Zytiga is Most Used First-Line Treatment in Prostate Cancer (https://www.biospace.com/article/releases/-b-kantar-health-b-data-show-zytiga-is-most-used-first-line-treatment-in-prostate-cancer-/?keywords=kantar)

Year	Title	Subtitle and Date	Description	References/Associated Links
	Fusion Stratified Study of Abiraterone and Veliparib for Metastatic Castration-Resistant Prostate Cancer Patients	*Ongoing study looking to evaluate addition of PARP-1 therapy and using ETS biomarkers (Aug 2012 - Dec 2015)*	Previous studies report that a majority of prostate cancers contain gene fusions resulting from gene rearrangements that create new gene combinations that can drive prostate cancer; the most common gene fusions involve the ETS gene. A new class of compounds, called PARP inhibitors, inhibit the DNA repair pathway and, in combination with androgen therapy, can induce further DNA damage that could enhance prostate cancer cell death. Investigators address in this Phase II study whether the addition of the PARP-1 inhibitor veliparib, plus abiraterone and prednisone, is more clinically beneficial than abiraterone and prednisone alone. Additionally, the utility of the ETS gene fusion (E-twenty-six) is evaluated as a potential predictive biomarker for response to the two treatment arms. While data are still being finalized, initial results favor the addition of veliparib to abiraterone and prednisone treatment to affect prostate-specific antigen response and limit disease progression. The study is anticipated to be complete in late 2016.	• Clinical Trial NCT01576172 (https://clinicaltrials.gov/ct2/show/study/NCT01576172?term=nct01576172&rank=1) • Hussain M, Daignault S, et al. 2016. Co-targeting androgen receptor (AR) and DNA repair: A randomized ETS gene fusion-stratified trial of abiraterone+ prednisone (Abi)+/-the PARP1 inhibitor veliparib for metastatic castration-resistant prostate cancer (mCRPC) patients (pts)(NCI9012) – A University of Chicago phase II consortium trial. ASCO Ann Meeting Proc 34(15). (http://meetinglibrary.asco.org/content/163784-176) • Kumar-Sinha C, Tomlins SA, et al. 2008. Recurrent Gene Fusions in Prostate Cancer. Nat Rev Cancer 8(7):497-511. (https://www.ncbi.nlm.nih.gov/pubmed/18563191)
	New Combination Therapy Approach Combining Abiraterone with Degarelix	*Investigators look to add a GnRH agonist to enhance the efficacy of abiraterone treatment(Date - ongoing)*	Degarelix acetate was approved by the FDA in December 2008 for the treatment of patients with advanced prostate cancer; it targets the production of testosterone by interfering with the GnRH (gonadotropin-releasing hormone) pathway. Combination therapy of degarelix and abiraterone would target androgens in prostate cancer from two different pathways and hopefully enhance androgen suppression to prevent disease progression. This ongoing Phase I/II study seeks to evaluate the benefit of adding degarelix to abiraterone treatment for men with a rising prostate-specific antigen or clinically metastatic disease after radical prostatectomy. The study is ongoing and still recruiting, and no data have been presented to date.	• Clinical Trial NCT01751451 (https://clinicaltrials.gov/ct2/show/NCT01751451?term=nct01751451&rank=1) • NDA Approval Letter: FDA Approves Drug for Patients with Advanced Prostate Cancer (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/022201s000ltr.pdf)
	Combining Immunotherapy (Ipilimumab) with Abiraterone and Prednisone	*A study combining ipilimumab with AA plus prednisone in chemotherapy and immunotherapy-naïve patients with progressive metastatic CRPC (September 2012 - September 2016)*	Ipilimumab, a humanized monoclonal antibody directed against CTLA-4, is currently FDA-approved for patients with advanced melanoma and generates a cytotoxic T-lymphocyte (CTL)-mediated immune response against cancer cells. Investigators are looking to add immunotherapies to enhanced targeted therapies, such as abiraterone. This Phase II trial investigates the clinical benefit of combining ipilimumab with abiraterone plus prednisone in chemotherapy- and immunotherapy-naive patients with progressive metastatic castration-resistant prostate cancer.	• Clinical Trial NCT01688492 (https://clinicaltrials.gov/ct2/show/NCT01688492?term=nct01688492&rank=1) • Information about ipilimumab (http://www.cancer.gov/publications/dictionaries/cancer-drug?CdrID=38447)
2013	**Phase II Trial Combining Abiraterone, Radiotherapy, and Short-Term Androgen Deprivation**	*Testing a new combination of abiraterone with radiotherapy to generate undetectable PSA (Sep 2013 - Sep 2018)*	Patients diagnosed with high-risk prostate cancer that may be spreading to other areas outside the prostate may elect to receive external beam radiation to attack the prostate-confined cancer, as well as standard androgen-deprivation therapy with a GnRH agonist to attack cells outside the prostate. This study investigates whether adding treatment with abiraterone and prednisone will increase the frequency of undetectable metastatic castration-resistant prostate cancer. The study is ongoing and still recruiting, and no data have been presented to date.	• Clinical Trial NCT01717053 (https://clinicaltrials.gov/ct2/show/NCT01717053?term=nct01717053&rank=1) • Information about ipilimumab (http://www.cancer.gov/publications/dictionaries/cancer-drug?CdrID=38447)
	Evaluating Whether Increasing the Dose of Abiraterone Provides Additional Benefit	*Investigators look to see whether increasing the dose of abiraterone to 2,000 mg daily is safe and potentially effective (Mar 2013 - Mar 2014)*	Patients taking abiraterone may find some initial clinical benefit, but their cancer may develop resistance and begin growing again in spite of treatment. This study seeks to test whether increasing the dose of abiraterone in combination with prednisone for patients whose cancer has grown while taking the standard dose is safe and effective in limiting further cancer growth. However, investigators note that results to date indicate that "pharmacokinetic failure alone is unlikely to explain resistance to standard-dose abiraterone acetate, and increasing the dose at the time of resistance may be of limited clinical utility."	• Clinical Trial NCT01637402 (https://clinicaltrials.gov/ct2/show/NCT01637402?term=nct01637402&rank=1) • Friedlander TW, Graff JN, et al. 2015. Initial results from a phase II study of increased-dose abiraterone acetate in patients with castration resistant prostate cancer (CRPC). ASCO Ann Meeting Proc 33(7). (http://meetinglibrary.asco.org/content/141641-159)
	Adding HSP90 Inhibitor to Abiraterone Acetate	*HSP90 inhibitor given to patients who no longer respond to abiraterone (Jan 2013 - Feb 2014)*	Investigators take another approach to help patients who no longer respond to abiraterone by testing treatment with the HSP90 inhibitor, AT13387, while continuing abiraterone and prednisone treatment. Investigators hope that AT13387 will provide the same clinical benefits of inhibiting prostate cancer proliferation and tumor growth similar to the results of earlier in vivo studies. This two-part study is complete and waiting to analyze its data.	• Clinical Trial NCT01685268 (https://clinicaltrials.gov/ct2/show/NCT01685268?term=nct01685268&rank=1) • Ferraldeschi R, Hedayat S, et al. 2013. In vitro and in vivo antitumor activity of the next generation HSP90 inhibitor, AT13387, in both hormone-sensitive and castration-resistant prostate cancer models. Can Res 73(8):2433. (http://cancerres.aacrjournals.org/content/73/8_Supplement/2433.short) • Ferraldeschi R, Slovin S, et al. 2014. A phase 1/2 study of AT13387, a heat shock protein 90 (HSP90) inhibitor in combination with abiraterone acetate (AA) and prednisone (P) in patients (PTS) with castration-resistant prostate cancer (MCRPC) no longer responding to AA. Ann Oncol 25 (suppl_4):iv267-iv268. (https://academic.oup.com/annonc/article/25/suppl_4/iv267/2238907/776PA-PHASE-1-2-STUDY-OF-AT13387-A-HEAT-SHOCK)
	Combination Trial Ends Due to Toxicity Issues with BEZ235	*Patients unable to tolerate BEZ235 at the lowest dose (Jan 2013 - Jun 2014)*	This Phase I/II study looks at adding BEZ235 (dactolisib), a PI3K and mTOR inhibitor, to enhance the current standard abiraterone and prednisone treatment in men with metastatic castration-resistant prostate cancer who have previously had docetaxel therapy. Unfortunately, toxicity issues at the lowest possible dose of BEZ235 lead to early termination of the trial.	• Clinical Trial NCT01717898 (https://clinicaltrials.gov/ct2/show/NCT01717898?term=nct01717898&rank=1) • Siegel A, et al. 2014. Results of a multicenter phase I/II trial of abiraterone acetate plus BEZ235 in metastatic, castration-resistant prostate cancer (mCRPC). ASCO Ann Meeting Proc 32(15). (http://meetinglibrary.asco.org/content/126976-144)
2014	**Evaluating the Need for Prednisone when Taking Abiraterone**	*First study testing the safety and effectiveness of abiraterone alone (Dec 2013 - Jun 2018)*	Prednisone has been a long-time treatment option for men with metastatic castration-resistant prostate cancer, and early studies testing the effectiveness of abiraterone included concurrent treatment with prednisone. Whether or not prednisone was required for maximum effectiveness of abiraterone has not yet been determined, and if it is determined unnecessary, that could reduce treatment costs for patients. This ongoing study compares the safety and effectiveness of abiraterone monotherapy compared to abiraterone plus prednisone. No results have been presented to date.	• Clinical Trial NCT02025010 (https://clinicaltrials.gov/ct2/show/NCT02025010?term=nct02025010&rank=1)

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	Adding Cabazitaxel to Abiraterone Acetate	*Additional incorporation of biomarker tests for predicting patient response to therapy (Aug 2014 - Aug 2017)*	Cabazitaxel is another taxane chemotherapy that is FDA-approved for metastatic castration-resistant prostate cancer. Earlier abiraterone studies evaluated the benefit of abiraterone plus prednisone treatment for men who had prior taxane therapy with docetaxel, but this trial evaluates the co-administration of the more effective taxane treatment, cabazitaxel, along with abiraterone and prednisone. In addition, investigators are evaluating the expression levels of the RB gene in tumor samples from enrolled patients to test a possible correlation between low RB levels and a stronger response to cabazitaxel. The study is ongoing and still recruiting, and no data have been presented to date.	• Clinical Trial NCT02218606 (https://clinicaltrials.gov/ct2/show/NCT02218606?term=nct02218606&rank=1) • Benefits of Cabazitaxel in Advanced Stages of Prostate Cancer (https://prostatecancernewstoday.com/2015/02/24/benefits-of-cabazitaxel-in-advanced-stages-of-prostate-cancer/)
Enzalutamide				
2007	**Early Phase I Open Label Study to Determine the Maximum Tolerated Dose of MDV3100**	*Phase I study of MDV3100 in prostate cancer patients who failed androgen deprivation therapy (Jul 2007 - Sep 2010)*	A novel androgen-receptor antagonist, MDV3100 (later renamed enzalutamide), is initially developed by Dr. Charles Sawyer and brought to the PCCTC for clinical testing. While trials evaluating abiraterone are already underway, enzalutamide blocks androgens from binding to the androgen receptor and prevents transport of androgens into the cell nucleus. This initial Phase I study evaluates the safety and maximum tolerated dose of MDV3100 in patients with metastatic castration-resistant prostate cancer, leading to further development and testing of MDV3100 for metastatic castration-resistant prostate cancer patients.	• Clinical Trial NCT00510718 (https://clinicaltrials.gov/ct2/show/NCT00510718?term=nct00510718&rank=1) • Tran C, Ouk S, et al. 2009. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 324(5928):787-90. (https://www.ncbi.nlm.nih.gov/pubmed/?term=19359544) • Scher HI, Beer TM, et al. 2010. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study. Lancet 375(9724):1437-46. (https://www.ncbi.nlm.nih.gov/pubmed/20398925)
2009	**Enzalutamide Significantly Prolongs Survival of Metastatic Castration-Resistant Prostate Cancer Patients after Chemotherapy**	*Phase III AFFIRM study shows treatment benefits (Sep 2009 - Nov 2011)*	The PCCTC participates in the Phase III AFFIRM trial that investigates the benefits of enzalutamide for patients with metastatic castration-resistant prostate cancer who have been previously treated with docetaxel-based chemotherapy. The initial results from the study of 1,199 patients presented at the 2012 Genitourinary-American Society of Clinical Oncology meeting demonstrate that MDV3100 significantly improves overall survival and reduces the risk of death by 37% compared to those patients that receive the placebo. This results in a recommendation to unblind the study so that all patients can benefit from enzalutamide treatment. Further analysis of the data collected during the Phase III study also leads investigators to conclude that enzalutamide provides further benefits by delaying pain progression and severity and providing improved well-being and everyday function for patients with metastatic castration-resistant prostate cancer. Results from this study are critical to obtaining FDA approval in 2010.	• Clinical Trial NCT00974311 (https://clinicaltrials.gov/ct2/show/NCT00974311) • Scher HI, Fizazi K, et al. 2012. Effect of MDV3100, an androgen receptor signaling inhibitor (ARSI), on overall survival in patients with prostate cancer postdocetaxel: Results from the phase III AFFIRM study. ASCO Ann Meeting Proc 30(5). (http://meetinglibrary.asco.org/content/89497-116) • Scher HI, Fizazi K, et al. 2012. Effect of MDV3100, an androgen receptor signaling inhibitor (ARSI), on overall survival in patients with prostate cancer postdocetaxel: Results from the phase III AFFIRM study. ASCO Ann Meeting Proc 30(5). (http://meetinglibrary.asco.org/content/89497-116) • Scher HI, Fizazi K, et al. 2012. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187-97. (http://www.nejm.org/doi/full/10.1056/NEJMoa1207506#t=article) • Fizazi K, Scher HI, et al. 2014. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. Lancet Oncol 15(10):1147-56. (https://www.ncbi.nlm.nih.gov/pubmed/25104109?dopt=Abstract)
2010	**Evaluation of Enzalutamide Effectiveness in Patients Prior to Chemotherapy**	*Phase III PREVAIL study shows treatment benefits pre-chemotherapy (Sep 2010 - Sep 2013)*	In contrast to the AFFIRM study, the PREVAIL Phase III trial evaluates the effectiveness of enzalutamide in metastatic castration-resistant prostate cancer patients whose disease is progressing, despite having androgen deprivation therapy, but who have not yet had chemotherapy. PCCTC investigators present results at the 2014 Genitourinary-American Society of Clinical Oncology annual meeting, describing how treatment with enzalutamide significantly improves both overall survival and radiographic progression-free survival in men who have not yet had chemotherapy.	• Clinical Trial NCT01212991 (https://clinicaltrials.gov/ct2/show/NCT01212991) • Beer TM, Armstrong AJ, et al. 2014. Enzalutamide in men with chemotherapy-naive metastatic prostate cancer (mCRPC): Results of phase III PREVAIL study. ASCO Ann Meeting Proc 32(4). (http://meetinglibrary.asco.org/content/123836-142) • Beer TM, Armstrong AJ, et al. 2014. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371(5):424-33. (https://www.ncbi.nlm.nih.gov/pubmed/24881730?dopt=Abstract) • Loriot Y, Miller K, et al. 2015. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol 16(5):509-21. (https://www.ncbi.nlm.nih.gov/pubmed/25888263?dopt=Abstract)
2012	**FDA Approves XTANDI™**	*Approval for indication to treat metastatic castration-resistant prostate cancer patients who have previously received androgen deprivation therapy (Aug 2012)*	Rapid completion of Phase I and Phase II trials by the PCCTC result in FDA approval of the latest prostate cancer therapy for metastatic castration-resistant prostate cancer patients in record time. The approval of enzalutamide offers yet another powerful drug to the growing arsenal of therapeutics targeting a deadly form of advanced prostate cancer.	• FDA Notification: FDA Approves New Treatment for a Type of Late Stage Prostate Cancer (https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm381452.htm) • PCRP Highlight: PCRP Clinical Consortium Accelerates Enzalutamide to FDA Approval (http://cdmrp.army.mil/pcrp/research_highlights/2012#7)
	Phase II Study Evaluating Enzalutamide as a Neoadjuvant Therapy	*Combination therapy of enzalutamide, dutasteride, and leuprolide (Mar 2012 - Mar 2013)*	In contrast to other anti-androgens, enzalutamide also causes significant prostate cancer cell death or apoptosis. Given the potency of this agent and the survival benefit demonstrated in the studies that resulted in FDA approval, PCCTC investigators examine the use of enzalutamide in combination with two other androgen-suppressing agents, leuprolide and dutasteride. The study is no longer recruiting patients, but data on its results have not yet been presented.	• Clinical Trial NCT01547299 (https://clinicaltrials.gov/ct2/show/NCT01547299?term=nct01547299&rank=1)

Year	Title	Subtitle and Date	Description	References/Associated Links
	Enzalutamide Outperforms Bicalutamide in Phase II STRIVE Study	*Enzalutamide versus bicalutamide evaluated in both metastatic and non-metastatic castration-resistant prostate cancer patients (Aug 2012 - Feb 2015)*	PCCTC investigators seek to answer two key questions in this Phase II study: (1) does enzalutamide provide greater benefit compared to bicalutamide and (2) is this treatment also effective in patients with non-metastatic castration-resistant prostate cancer (CRPC) disease, for which there is currently no approved therapy? Initial results presented at the 2015 American Urological Association annual meeting show that treatment with enzalutamide does significantly reduce the risk of prostate cancer progression or death, compared to bicalutamide. Furthermore, these beneficial effects are observed in both non-metastatic and metastatic CRPC patients, potentially providing a new treatment option for a group of patients with previously limited treatment choices at a critical stage in disease progression.	• Clinical Trial NCT01664923 (https://clinicaltrials.gov/ct2/show/NCT01664923?term=nct01664923&rank=1) • Penson DF, Armstrong AJ, et al. 2016. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. J Clin Oncol 34(18):2098-2106. (http://ascopubs.org/doi/abs/10.1200/jco.2015.64.9285)
2013	**Identifying Mechanisms of Resistance to Enzalutamide Therapy**	*PCCTC investigators look for answers to help patients whose disease spreads after enzalutamide treatment (Mar 2013 - Oct 2017)*	In contrast to most clinical trials where the primary objective is to determine whether a new treatment will provide patient benefit compared to standard-of-care therapy, this particular study addresses an important issue regarding how to combat prostate cancer that no longer responds to enzalutamide treatment. In order to know how to treat resistant disease, PCCTC investigators collect blood and tissue samples from patients who are receiving enzalutamide treatment, which is the key focus of this clinical trial. The study is ongoing, and no data have been presented to date.	• Clinical Trial NCT02228265 (https://clinicaltrials.gov/ct2/show/NCT02228265?term=nct02228265&rank=1)
	Addressing Enzalutamide Resistance Through Tumor Sequencing	*Incorporating analysis of circulating tumor cells as a marker of therapeutic response (Sep 2013 - Feb 2017)*	Circulating tumor cells (CTCs) are emerging as a potential solution for analyzing tumor cells without using more-invasive procedures such as a tumor biopsy. This study plans to address the question of what molecular changes occur during the course of enzalutamide treatment that might provide clues to why some patients develop resistance to enzalutamide. PCCTC investigators plan to use cutting-edge technology to analyze androgen receptor variants, gene fusions, and androgen levels in CTCs and how they correlate to prostate-specific antigen levels and radiographic progression. The study is ongoing and no data have been presented to date.	• Clinical Trial NCT01942837 (https://clinicaltrials.gov/ct2/show/NCT01942837?term=nct01942837&rank=1)
	Novel Combination Therapy Trial with Mifepristone	*Glucocorticoid receptor antagonist mifepristone targets androgens from another angle (Dec 2013 - Dec 2017)*	To prevent prostate cancer cells from developing resistance to anti-androgen therapies, such as enzalutamide, studies continue to investigate combination therapies with multiple anti-androgens that target androgens from multiple pathways. The anti-androgen mifepristone (RU-486) specifically targets the glucocorticoid receptor that has been associated with mechanisms of resistance in prostate cancer (see Aurora, et al reference). This early-phase trial, supported by a PCRP 2012 Clinical Exploration Award (PC121149), investigates whether a combination therapy of two anti-androgens, enzalutamide and mifepristone, will reduce prostate cancer progression in patients with metastatic hormone-resistant prostate cancer. The study is ongoing, and no data have been presented to date.	• Clinical Trial NCT02012296 (https://clinicaltrials.gov/ct2/show/NCT02012296?term=nct02012296&rank=1)
2014	**Examining Molecular Mechanisms Underlying Tumor Progression Despite Enzalutamide Treatment**	*Incorporating genetic and molecular indicators for assessing enzalutamide response (Feb 2014 - Aug 2017)*	Continuing on the path towards precision medicine, investigators evaluate the correlation between baseline molecular features and prostate-specific antigen (PSA) changes for patients on enzalutamide therapy to see whether the molecular markers can help improve the ability to determine which patients are responding positively to enzalutamide treatment versus patients whose disease is progressing and should consider other treatment options.	• Clinical Trial NCT02099864 (https://clinicaltrials.gov/ct2/show/NCT02099864?term=nct02099864&rank=1)
	Study Assesses Benefit of Adding Enzalutamide to LHRH and Bicalutamide	*Phase II study evaluates triple hormone deprivation therapy in hormone-sensitive prostate cancer (Mar 2014 - Feb 2016)*	The standard treatment option for men who develop metastatic prostate cancer is to begin androgen deprivation therapy to starve the cells of androgen, a key driver of prostate cancer cell growth. The agents typically used in these hormone-sensitive patients are luteinizing hormone-releasing hormone analogue plus bicalutamide. By combining these treatments with enzalutamide, PCCTC investigators are testing whether the ability of enzalutamide to target the androgen pathway from another three areas will further enhance the effects of these agents and help patients achieve prostate-specific antigen remission after 7 months. The study is ongoing, and no data have been presented to date.	• Clinical Trial NCT02058706 (https://clinicaltrials.gov/ct2/show/NCT02058706?term=nct02058706&rank=1)
	Adding Enzalutamide to ADT and Radiation Therapy	*Salvage Therapeutic Radiation with Enzalutamide and Androgen-Deprivation Therapy in Men with Recurrent Prostate Cancer (STREAM) Trial (Apr 2014 - Dec 2018)*	Patients whose prostate-specific antigen (PSA) begins to rise after they have had a prostatectomy quickly seek additional treatment to eliminate any remaining prostate cancer cells before the spread. Androgen deprivation therapy (ADT) can starve the cells of androgen, and salvage radiation therapy targets any prostate cancer cells that may not have migrated far from the prostate. But this treatment is not a guarantee that all remaining cells will be eliminated, so PCCTC investigators are investigating whether adding enzalutamide to ADT and salvage radiation therapy in men that have a rising PSA after prostatectomy will improve the time before the disease may progress. The study is ongoing, and no data have been presented to date.	• Clinical Trial NCT02057939 (https://clinicaltrials.gov/ct2/show/NCT02057939?term=nct02057939&rank=1)
	Testing the Safety and Efficacy of Therapy Combinations with GDC-0068	*Investigators look to see whether GDC-0068 enhances patient response to enzalutamide (Jul 2011 - Feb 2017)*	This dose escalation study focuses on addressing the safety, tolerability, and pharmacokinetics of a new Akt inhibitor, GDC-0068 (ipatasertib), when individually combined with other FDA-approved agents, including docetaxel, paclitaxel, fluoropyrimidine plus oxaliplatin (mFOLFOX6), and enzalutamide, for patients with metastatic castration-resistant prostate cancer. The study is ongoing, and no data have been presented to date.	• Clinical Trial NCT01362374 (https://clinicaltrials.gov/ct2/show/NCT01362374?term=nct01362374&rank=1)

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	Addition of Enzalutamide to Radiation Therapy After Prostatectomy	*Enzalutamide is the only hormone therapy used with radiation (Aug 2014 - Aug 2020)*	Similar to the STREAM study, this Phase II trial evaluates whether adding enzalutamide treatment to patients who elect to have salvage radiation therapy once their prostate-specific antigen begins to rise after prostatectomy provides added benefit over radiation therapy alone. The difference between this study and the STREAM trial is that enzalutamide is the only hormone therapy used. Investigators are also testing whether using a more potent anti-androgen (enzalutamide) will shorten the treatment time, which will ultimately minimize side effects for patients. The study is ongoing, and no data have been presented to date.	• Clinical Trial NCT02203695 (https://clinicaltrials.gov/ct2/show/NCT02203695?term=nct02203695&rank=1)
	FDA Expands Indication for Enzalutamide	*Enzalutamide can now be used as a first-line therapy (Sep 2014)*	Initial approval by the FDA included use of enzalutamide for patients as a second-line treatment, meaning that patients with metastatic castration-resistant prostate cancer would have already had to fail one treatment (docetaxel) before they could be recommended to try enzalutamide. Based on the evidence from the PCCTC Phase III PREVAIL trial, the FDA expands the indication of enzalutamide, making it available to patients who have not yet received chemotherapy.	• News Release: U.S. FDA Approves New Indication for the Use of XTANDI® (enzalutamide) Capsules for Patients with Metastatic Castration-Resistant Prostate Cancer (http://newsroom.astellas.us/news-releases?item=137065)