Early use of chemotherapy in metastatic prostate cancer

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Abstract

Since 2010, five new antineoplastic therapies have been FDA approved for the treatment of metastatic prostate cancer. With additional treatment options, questions arose about the optimal sequence of these agents. Until recently, chemotherapy has been deferred until later in the disease course in favor of next-generation androgen deprivation therapy. Prior to the development of abiraterone acetate and enzalutamide, clinical trials were opened investigating the combination of chemotherapy with androgen deprivation therapy in patients with metastatic hormone-sensitive disease. With the development of new oral therapies used to treat castration-resistant disease, these trials were largely forgotten or felt to be obsolete. Recently, two trials have been reported showing an overall survival benefit of the early use of chemotherapy in patients with hormone-naive prostate cancer, changing the treatment paradigm for metastatic disease. Here we review the history of chemotherapy in treating prostate cancer and the emerging evidence favoring its use as first-line therapy against metastatic hormone-sensitive disease.

Keywords

Docetaxel; Hormone sensitive; Androgen deprivation therapy

Introduction

Prostate cancer is the most common non-skin cancer in men with over 180,000 new cases expected to be diagnosed in 2016.[1] Local therapies for early-stage disease are effective leading to favorable clinical outcomes. When metastatic disease develops, patients are initially treated with androgen deprivation therapy (ADT). Although response rates to ADT are near 80%, inevitably, the cancer learns to grow in a low testosterone environment, leading to a clinical state of castration resistance. Docetaxel chemotherapy was among the first treatments to be Food and Drug Administration (FDA) approved for metastatic

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castration-resistant prostate cancer (mCRPC) based on a survival benefit. When docetaxel became the standard-of-care (SOC) treatment for mCRPC in 2004, several trials were subsequently launched to assess the effect of docetaxel in metastatic hormone-naive disease, but it would be a decade before the data matured. During the years when the trials were ongoing, preclinical research focused on mCRPC and reaffirmed that androgen receptor (AR) signaling continued to drive tumor growth upon developing castration resistance. The next generation of ADT (i.e. abiraterone acetate, enzalutamide) was then developed and shown to prolong survival in mCRPC patients. AR-targeted therapies gained favor over chemotherapy based on perceived safety profile and novelty, a trend many clinicians felt would continue. Docetaxel, and subsequently cabazitaxel, were then deferred until late-stage disease and trials involving chemotherapy in hormone-sensitive disease were all but forgotten.

Recently, these chemotherapy trials in patients with metastatic hormone-naive prostate cancer have been published. The long-awaited evidence favored the use of chemotherapy with ADT, which has changed the treatment paradigm for metastatic prostate cancer. Here we review the history of chemotherapy in prostate cancer and discuss the evidence for its use as frontline therapy in combination with ADT for metastatic disease.

History of chemotherapy in patients with mCRPC

After the pioneering work of Charles Huggins showed an inhibitory effect of testosterone suppression on prostate cancer growth, the history of treatment for metastatic prostate cancer began with surgical castration (i.e. orchiectomy).[2] In the 1960s, drug therapy evolved after the Veterans Administration Cooperative Urologic Research Group (VACURG) demonstrated that oral estrogen, in the form of diethylstilbestrol, was as effective as orchiectomy in treating prostate cancer.[3] Although orchiectomy remained the gold standard of treatment through the 1980s, the VACURG findings fostered the notion of medical castration as an alternative to orchiectomy. Flutamide, an oral, non-steroidal antiandrogen was then developed, which could inhibit AR signaling through receptor blockade. During the 1970s, flutamide showed clinical efficacy against prostate cancer.[4] Subsequently, the structure of luteinizing hormone-releasing hormone (LHRH) was identified. In 1980, intranasal buserelin was administered to the first patient with prostate cancer, which resulted in a significant decrease in serum testosterone.[5] However, a transient rise in serum androgens was noted which caused concern for possible disease flare. The combination of an antiandrogen (flutamide) with an LHRH agonist (LHRH ethylamide [HOE-766]) prevented this flare phenomenon, resulting in a decrease in prostatic acid phosphatase levels and symptomatic improvement in 9 of 10 patients.[6] In the decades that followed, several generations of antiandrogens (nilutamide, bicalutamide) and LHRH agonists (leuprolide, goserelin, triptorelin) have been used to treat prostate cancer. Androgen suppression via LHRH agonists has since remained the backbone of therapy for metastatic hormone-sensitive disease. Once progression occurs on AR targeted therapies, treatment options prior to 2004 were limited. This led several investigators to test different therapeutic approaches, including chemotherapy, in patients with mCRPC.

Clinical trials involving the use of cytotoxic chemotherapy in advanced prostate cancer began in the 1950s with alkylating agents. The response rates to chemotherapy were typically low and results were difficult to interpret due to the small number of patients and lack of meaningful endpoints.[7] This prompted many thought leaders in the field to suggest that prostate cancer was a chemotherapy-resistant disease.[7–9] Due to the perceived lack of survival benefit, chemotherapy trials were then designed to assess palliation endpoints. In 1996, mitoxantrone in combination with prednisone was the first FDA-approved chemotherapy for mCRPC based on symptomatic improvement.[10] Mitoxantrone is a topoisomerase II inhibitor given intravenously ($12 mg/m^2$) on a 3-week schedule. Side effects range from mild (nausea, alopecia) to more severe (dose-dependent cardiomyopathy). Prostate-specific antigen (PSA) responses were low and no survival benefit was shown.[10–12] Although mitoxantrone achieved palliation benefits, there was no chemotherapeutic agent that improved overall survival in prostate cancer until 2004.

Docetaxel and paclitaxel were developed in the early 1990s.[13] In prostate cancer, preclinical data suggested a potential synergistic effect of estramustine and docetaxel.[14] Several early-phase trials found the combination to be safe and clinically active against castration-resistant prostate cancer.[15–17] SWOG9916 was a randomized Phase III trial in mCRPC patients, which compared docetaxel + estramustine to mitoxantrone with both arms containing a steroid backbone. The 21-day cycle of docetaxel ($60 mg/m^2$ given on Day 2) with estramustine (280 mg three times daily on Days 1–5) significantly increased the median overall survival by 1.9 months and included improved PSA and objective responses.[18] Due to concerns about increased thromboembolic events caused by estramustine, docetaxel was studied as a single agent and shown to have activity in advanced prostate cancer.[19,20]

Tannock et al., in the pivotal Phase III TAX327 trial involving mCRPC patients, showed a 2.4-month increase in overall survival in the docetaxel (given every 3 weeks) + prednisone arm compared with mitoxantrone + prednisone.[21] Docetaxel ($75 mg/m^2$) given every 3 weeks also had a significant survival advantage over weekly docetaxel ($30 mg/m^2$). Use of docetaxel either weekly or every 3 weeks had increased adverse events (peripheral edema, neuropathy, gastrointestinal toxicities) compared with mitoxantrone, but significant reductions in pain and improved quality of life measures were noted. Although use of single-agent docetaxel was FDA approved in 2004 and most clinicians stopped using estramustine, it was not until 2008 that docetaxel was compared head-to-head with docetaxel + estramustine. One hundred and fifty men with mCRPC were randomly assigned to docetaxel ($35 mg/m^2$ on Days 2 and 9 every 21 days) and prednisone (10 mg daily) with or without estramustine (280 mg on Days 1–5 and 8–12 every 21 days), which resulted in no difference in PSA response or overall survival.[22] The combination also resulted in increased toxicities confirming the clinical practice to use docetaxel as a single agent. Both SWOG9916 and TAX327 are credited with establishing docetaxel given on a 3-week schedule as first-line chemotherapy in metastatic prostate cancer after developing disease progression on conventional hormonal therapy.

The exact mechanism of action of docetaxel in prostate cancer is unclear. Docetaxel is generally known to stabilize microtubules preventing cellular division and resulting in cell-cycle arrest. However, more recent evidence suggests that docetaxel can inhibit the

nuclear translocation of AR in prostate cancer.[23] Resistance to docetaxel may develop through several mechanisms including drug efflux, alterations in microtubule structure, activation of survival pathways, and changes in the tumor vasculature.[24–27] In an effort to overcome resistance, investigators looked at combining targeted therapies with docetaxel. Multi-tyrosine kinase inhibitors and VEGF-targeted therapies did not show significant efficacy in several trials against prostate cancer.[28–32] Although pilot studies suggested thalidomide may have added benefit when given with docetaxel, a randomized Phase III trial with lenalidomide did not increase survival.[33–35] Natural products (i.e. calcitriol, vitamin D analogues), small molecule inhibitors, and vaccination have not improved upon the survival advantage of docetaxel alone.[36–43] With no clear combination strategy evident, attempts were made to identify a second-line chemotherapy for castration-resistant prostate cancer. Several Phase II studies explored combinations of platinum agents with and without antimetabolites, but without a larger Phase III study, these treatments have not been clinically utilized.[44–46] It would not be until 2010 that a chemotherapy would become FDA approved for mCRPC following progression on docetaxel.

Cabazitaxel, a semi-synthetic member of the taxane family, was developed as a derivative of docetaxel. Two potential advantages of cabazitaxel over docetaxel are: (1) the diminished affinity for P-glycoprotein, an important drug efflux pump and (2) the ability to cross the blood–brain-barrier.[47] In the Phase III trial, TROPIC, men with mCRPC and prior exposure to a docetaxel-containing regimen were randomized to receive cabazitaxel (25 mg/m^2 every 3 weeks) or mitoxantrone (12 mg/m^2 every 3 weeks), with both groups receiving prednisone. Cabazitaxel significantly improved overall survival by 2.4 months, which was the primary endpoint of the study.[48] With additional follow-up, 2-year survival was also improved in the cabazitaxel group with similar palliation benefits observed when compared with mitoxantrone.[49] Based on the results from TROPIC, cabazitaxel became the FDA approved, second-line chemotherapy after progression on docetaxel. Mitoxantrone was relegated to third-line chemotherapy.

Despite advances in chemotherapy for castration-resistant disease, researchers continued to focus their efforts on targeting the AR pathway based on the observation that prostate cancer, following progression on conventional ADT, still continued to have an intact AR signaling axis.[50] Subsequently, therapeutic agents that attenuated AR signaling via alternative mechanisms were explored. Inhibitors of extratesticular androgen synthesis, including ketoconazole and abiraterone acetate, suppressed androgen production from the adrenal glands. Ketoconazole can inhibit adrenal androgen synthesis via its effect on multiple cytochrome p450 enzymes and was shown to decrease PSA levels in patients with prostate cancer.[51] However, the ability of ketoconazole to inhibit cytochrome P450 (CYP) – 3A may result in significant drug interactions, particularly with psychotropic medications.[52] Abiraterone acetate is an irreversible inhibitor of the CYP-17, a key enzyme in androgen biosynthesis. After initially being FDA approved for use in mCRPC patients following chemotherapy, abiraterone acetate (1000 mg by mouth daily with prednisone 5 mg twice daily) demonstrated a survival benefit versus placebo (prednisone alone) in patients without prior docetaxel exposure.[53] Side effects of abiraterone acetate include mineralocorticoid excess (i.e. fluid retention, hypokalemia, hypertension), liver function test elevation, and cardiac abnormalities such as tachycardia and atrial fibrillation. Enzalutamide

(160 mg by mouth daily), a second-generation antiandrogen, similarly received FDA approval for the treatment of mCRPC in both the pre- and post-chemotherapy setting after demonstrating an increase in overall survival.[54,55] The most common adverse event reported was fatigue in half of the patients. The enthusiasm for an orally administered drug such as abiraterone acetate and enzalutamide is offset by the cost, which is estimated to be approximately $20,000 USD per 90-day supply for each. However, the clinical development and implementation of abiraterone acetate and enzalutamide supported the notion that next-generation targeting of AR signaling would further defer the use of chemotherapy for mCRPC, particularly in an older population of prostate cancer patients.

Radiopharmaceutical treatment and immunotherapy have also been shown to prolong survival in select populations of mCRPC patients. A calcium mimic, Radium-223, is an alpha-emitting radioisotope which is readily taken up at sites of osseous metastases. In patients with bone-only disease, previously treated with docetaxel or chemotherapy ineligible, Radium-223 led to an increase in overall survival versus placebo.[56] Radium-223 is not indicated for patients with lymph node and/or visceral metastases. Sipuleucel-T is an autologous dendritic cell vaccine, which is administered following dendritic cell priming with a GM-CSF-prostatic acid phosphatase fusion protein.[57] In mCRPC patients with asymptomatic or minimally symptomatic disease, sipuleucel-T administration led to a 4.1-month increase in median survival versus placebo.[58] Whereas chemotherapy and AR-directed therapy are more broadly used in the treatment of mCRPC, both Radium-223 (bone-only) and sipuleucel-T (asymptomatic/minimally symptomatic) are only FDA approved for select mCRPC patients who meet the eligibility criteria.

Evidence for early use of chemotherapy

With the recent development of new drugs for mCRPC, a focus of clinical trials and retrospective analyses has been on the most effective sequence of therapies. To date, several retrospective studies have provided little guidance on the proper timing of chemotherapy versus next-generation ADT in patients with mCRPC.[59–63] The sequence of abiraterone acetate, enzalutamide and chemotherapy largely depends on patient characteristics, side-effect profile, as well as patient and provider preference (Fig. 1).

Until recently, ADT alone had been the gold standard of treatment for metastatic, hormone-naive prostate cancer. Given FDA approval of docetaxel in 2004 and no other known life-prolonging therapies at the time, a number of trials were launched investigating the combination of ADT with docetaxel in patients with newly metastatic disease. Following the waves of new drugs for mCRPC, these trials were easy to forget and almost rendered obsolete. The conventional wisdom was to incorporate these new agents at the time of castration resistance pushing chemotherapy further down in the lines of treatment. Chemotherapy would then be considered following the use of abiraterone acetate and/or enzalutamide. Three clinical trials (GETUG-AFU15, CHAARTED, and STAMPEDE) have challenged this paradigm looking at the effect of ADT with concurrent chemotherapy for metastatic hormone-naive disease. Investigators hypothesized that chemotherapy may be better tolerated earlier in the disease course rather than in the latter stages of disease when the performance status tends to be worse. Moreover, the cytotoxic effect of chemotherapy

may enhance ADT-mediated apoptosis resulting in synergistic cell kill. As these trials matured, the findings identified a clinical benefit of using chemotherapy in hormone-sensitive disease and forced providers to reexamine how metastatic prostate cancer is treated. We seek to describe the results of each trial and how the field of chemo-hormonal therapy has since evolved (Table 1).

In 2004, the first Phase III trial, GETAUG-AFU15, began accruing patients in an attempt to answer the question of whether chemotherapy when combined with ADT could affect survival in patients with newly metastatic prostate cancer. The trial randomized 385 men with metastatic prostate cancer to receive ADT alone or ADT + docetaxel (75 mg/m^2 every 3 weeks, up to 9 cycles) with a primary endpoint of median overall survival.[64] In 2013, the trial results showed a non-significant increase in median overall survival of 4.7 months with the addition of chemotherapy in patients with metastatic hormone-naive disease. Although progression-free survival was significantly increased with a trend towards improved overall survival in the chemotherapy group, the trial was viewed as a negative study. At the time, the lack of perceived benefit from early chemotherapy fit with conventional wisdom.

In 2014, the initial results from the randomized, Phase III CHAARTED trial were reported at the annual American Society of Clinical Oncology (ASCO) meeting, which contradicted the GETUG-AFU15 findings. Opened in 2006, CHAARTED (E3805) accrued a total of 790 men with metastatic hormone-naive disease who were randomized to ADT or ADT + docetaxel (75 mg/m^2 every 3 weeks for 6 cycles).[65] The trial was originally designed to look at men with high-volume disease only, defined as visceral metastases and/or four or more bone metastases. During accrual, an amendment was approved which allowed men with low volume disease to enroll. Median overall survival was significantly increased by 13.6 months in the group receiving docetaxel together with ADT. This survival increase was largely driven by the effect seen in the high-volume disease cohort, which represented approximately 2/3 of all patients participating in the trial. The high-volume group had a 17-month increase in overall survival with the addition of chemotherapy to conventional ADT. The median overall survival in the low-volume disease cohort was not reached in either arm of the study (Table 2). Since the high-volume cohort was accrued earlier and had poorer outcomes, the effect on survival was readily apparent at the time of analysis. Given that the survival advantage of ADT + docetaxel remained significant in all patients on study, low-volume patients are still likely to benefit from the combination. However, the magnitude of benefit is potentially less and may become significant with further follow-up. Although the findings of the CHAARTED trial were impressive, the negative results in the GETUG-AFU15 trial led investigators to critically analyze both trials in order to get clarification of the role of early chemotherapy.

The first key issue with GETUG-AFU15 is the lack of statistical power to detect a survival difference. Seven hundred and ninety patients were randomized in CHAARTED compared with only 385 in GETUG-AFU15. Had GETUG-AFU15 accrued more patients, the overall survival difference with chemo-hormonal therapy may have been significant. Irrespective of the statistical concerns, the GETUG-AFU15 trial findings hinted at a benefit of adding docetaxel to ADT, which is consistent with the CHAARTED trial. A second issue with these trials is the difference in the number of high-volume disease patients. In GETUG-AFU15,

less than half of patients randomized were considered to have high-volume disease versus nearly two thirds in CHAARTED. Since high-volume patients had the most benefit from chemo-hormonal therapy, having a larger proportion of these patients in CHAARTED increased the likelihood of achieving a survival difference. Gravis et al., did a post hoc analysis of the GETUG-AFU15 trial, subdividing patients into low- and high-volume disease to better mirror the population in the CHAARTED study (Table 2).[66] In retrospect, a non-significant improvement in overall survival was noted in the high-volume group of patients receiving chemotherapy with ADT. However, the lack of statistical power and retrospective analysis make further interpretation difficult. One minor difference between trials is that fewer patients discontinued docetaxel due to toxicity in the CHAARTED trial, which may have led to more favorable outcomes. After all issues were considered, many practitioners favored the results of the CHAARTED study over GETUG-AFU15. However, some still sought clarification before giving chemotherapy to patients with hormone-naive prostate cancer.

A third trial, STAMPEDE, was key to settling the debate about the role of early chemotherapy in metastatic hormone-naive prostate cancer. In STAMPEDE, nearly 3000 men with high-risk locally-advanced or metastatic prostate cancer were randomized to SOC (i.e. ADT), SOC + zolendronic acid, SOC + docetaxel, or SOC + docetaxel + zolendronic acid.[67] The findings were reported at the 2015 ASCO meeting and showed a 10-month increase in overall survival with the addition of chemotherapy to SOC (HR for death: 0. 78, P = 0.006) compared with SOC alone. In STAMPEDE, volume of disease was not pre-specified, supporting the CHAARTED conclusion that docetaxel will benefit patients with both high- and low-volume disease. The results of STAMPEDE favor the early use of chemotherapy in combination with ADT in metastatic prostate cancer.

Future directions

Although the use of early docetaxel in the treatment of prostate cancer is becoming more commonplace, clinical questions still remain. For instance, in the above three trials, patients were generally younger (median age < 65 years old) with an excellent performance status. In real-world practice, many patients with newly metastatic disease are older and less physically fit. These trials do not answer the question of how to treat elderly patients in this context. Older patients or those with a poorer functional status may still benefit from chemotherapy with ADT, but concerns about safety are significant and must be considered. In such patients, volume of disease may be considered since those with high-volume disease may benefit the most from chemotherapy.

With respect to volume of disease, many providers remain apprehensive about treating low-volume disease patients with docetaxel. In CHAARTED, the addition of chemotherapy to ADT prolonged survival in patients with metastatic prostate cancer, with a trend towards improved overall survival in a subgroup analysis of those patients with low-volume disease. Should this trend in improved survival remain not statistically significant with additional follow-up, we must defer to the findings of STAMPEDE which did not pre-specify volume status as an inclusion criteria and prospectively supports the use of chemohormonal therapy in all M1 patients. However, we may need to reconsider the current definition of low-

and high-volume disease to better capture those low-volume patients more likely to benefit from the addition of chemotherapy. For instance, certain oligometastatic prostate cancer may respond more favorably to local therapies such as stereotactic body radiation therapy with curative intent.[68] The remaining patients with low-volume, metastatic disease may be more effectively treated with a palliative, systemic approach (i.e. ADT + docetaxel).

The role of cabazitaxel in metastatic hormone-naive disease is yet to be determined. FIRSTANA was a Phase III trial comparing cabazitaxel to docetaxel in patients with chemotherapy-naive mCRPC. The results of FIRSTANA were recently reported at the 2016 ASCO meeting, which showed that cabazitaxel was not superior to docetaxel for overall survival.[69] However, cabazitaxel given at 25 mg/m^2 yielded a significant improvement in tumor response compared to docetaxel. Consideration may be given to testing cabazitaxel + ADT in patients with metastatic hormone-sensitive disease. Currently, cabazitaxel should not be used in this context.

Following chemohormonal therapy in hormone sensitive metastatic disease, it remains to be determined whether retreatment with docetaxel will yield clinical benefit upon developing castration resistance. A practical approach for these patients with mCRPC is to consider docetaxel retreatment following progression on second-generation ADT. However, patients should be carefully followed after each cycle and treatment could be changed to cabazitaxel at first signs of progression. Prospective data will be needed to determine whether docetaxel retreatment or use of cabazitaxel following disease progression on second generation ADT is a more favorable therapeutic strategy.

The optimal sequence of therapies for metastatic prostate cancer remains unknown. The recent trials involving docetaxel + ADT in metastatic hormone-naive prostate cancer supports its use in properly selected patients and also shows that the SOC treatment is constantly being challenged and subject to change. Several clinical trials are ongoing looking at various combinations of chemohormonal and androgen deprivation therapies (Table 3). As the data from these trials are published and the findings of CHAARTED and STAMPEDE mature, we should expect further changes in how we treat metastatic, hormone sensitive prostate cancer. Both researchers and clinicians must keep an open mind not only to the type of therapy available, but also where it may be best utilized within the treatment paradigm.

Acknowledgments

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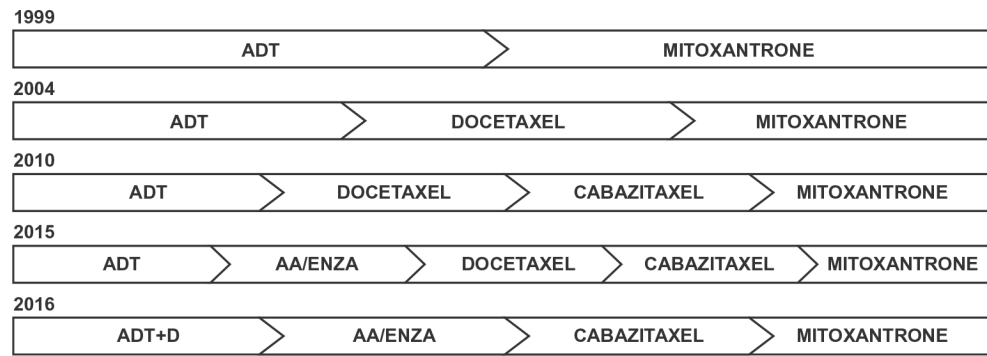
1999

ADT	MITOXANTRONE

2004

ADT	DOCETAXEL	MITOXANTRONE

2010

ADT	DOCETAXEL	CABAZITAXEL	MITOXANTRONE

2015

ADT	AA/ENZA	DOCETAXEL	CABAZITAXEL	MITOXANTRONE

2016

ADT+D	AA/ENZA	CABAZITAXEL	MITOXANTRONE

Fig. 1.

History of treatment paradigms for metastatic prostate cancer. The treatment of metastatic prostate cancer has evolved since 1999 with the development of new therapeutic agents. Recent evidence now favors the use of chemotherapy early in the course of treatment for metastatic hormone-sensitive prostate cancer. D = Docetaxel, AA = Abiraterone Acetate, Enza = Enzalutamide.

Table 1

Overall survival of patients with metastatic prostate cancer treated with chemohormonal therapy versus androgen deprivation therapy alone in three clinical trials.

Clinical trial	ADT + chemo (months)	ADT (months)	HR (95% CI)	P-value	Date published
GETUG-AFU 15	58.9	54.2	1.01 (0.75–1.36)	0.955	2013
CHAARTED	57.6	44	0.61 (0.47–0.80)	<0.001	2015
STAMPEDE	81	71	0.78 (0.66–0.93)	0.006	2015

Table 2

Overall survival of patients with low- and high-volume metastatic prostate cancer treated with chemohormonal therapy versus androgen deprivation therapy alone.

Clinical trial	Disease volume	ADT + chemo (months)	ADT (months)	HR (95% CI)	P-value	Follow-up (months)
GETUG-AFU 15	High	39.8	35.1	0.78 (0.56–1.09)	0.14	83.9
	Low	NR	83.4	1.02 (0.67–1.55)	0.9	
CHAARTED	High	49.2	32.2	0.60 (0.45–0.81)	<0.001	28.9
	Low	NR	NR	0.60 (0.32–1.13)	0.11	

Table 3

Ongoing clinical trials enrolling patients with metastatic, hormone sensitive prostate cancer.

Clinical Trials for Metastatic Hormone Sensitive Prostate Cancer
Chemotherapy
ODM-201 in Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer – NCT02799602
Docetaxel and PROSTVAC for Metastatic Castration-Sensitive Prostate Cancer – NCT02649855
A Phase III of ADT ± Docetaxel ± Local RT ± Abiraterone Acetate in Metastatic Hormone-naïve Prostate Cancer (PEACE1) – NCT01957436
AR Targeted Therapies
A Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients With Metastatic Hormone Sensitive Prostate Cancer (mHSPC) – NCT02677896
Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer (ENZAMET) – NCT02446405
Dose Finding Study of BKM 120 in Combination With LH-RH Agonists and Bicalutamide in Men With Non Castrate Metastatic Prostate Cancer (NCMPC-BKM) – NCT02487823
LHRH Analogue Therapy With Enzalutamide or Bicalutamide in Treating Patients With Metastatic Hormone Sensitive Prostate Cancer – NCT02058706
Enzalutamide Versus Standard Androgen Deprivation Therapy for the Treatment Hormone Sensitive Prostate Cancer – NCT02278185
A Study of Apalutamide (JNJ-56021927, ARN-509) Plus Androgen Deprivation Therapy (ADT) Versus ADT in Participants With mHSPC (TITAN) – NCT02489318
A Phase II Study of Androgen Deprivation Therapy With or Without Palbociclib in RB-Positive Metastatic Prostate Cancer – NCT02059213
Bicalutamide and Goserelin or Leuprolide Acetate With or Without Cixutumumab in Treating Patients With Newly Diagnosed Metastatic Prostate Cancer – NCT01120236
S1216, Phase III ADT + TAK-700 vs. ADT + Bicalutamide for Metastatic Prostate Cancer (S1216) – NCT01809691
Ipilimumab + Androgen Deprivation Therapy in Prostate Cancer – NCT01377389