CHEMOTHERAPY AND NEW DRUGS IN PROSTATE CANCER

***Nicolas Mottet**

Department of Urology, University Hospital, Hôpital Nord, St Etienne, France
**Correspondence to Nicolas.mottet@chu-st-etienne.fr*

Disclosure: N.M. has received grants or research support from Takeda/Millenium, Astellas, Pierre Fabre, Sanofi, and Pasteur; and honoraria or consultation fees from Takeda/Millenium, Jansen, Astellas, BMS, Bayer, IPSEN, Ferring, Novartis, Nuclétron, Pierre Fabre, Sanofi, and AstraZeneca.
Received: 17.12.14 **Accepted:** 13.02.15
Citation: EMJ Urol. 2015;3[2]:103-110.

INTRODUCTION

Prostate cancer (PrC) is the fourth most common cancer (for both sexes combined) and the second most common cancer in men (accounting for 15% of all new male cancer cases), with a worldwide incidence of approximately 1,111,200, a 5-year prevalence of 3,924,000, and a mortality incidence of 307,000 for the year 2012.[1] Since the 1990s, the increasing use of prostate-specific antigen (PSA) testing has had a significant influence on incidence rates, much more so than on mortality rates.[1] As diagnosis can be established very early in the disease, most cases of PrC are treated at a localised stage with very good 10-year relative survival and progression-free survival (PFS) rates.

However, some men might develop advanced or metastatic disease at diagnosis or following initial treatment, requiring the use of systemic therapy including chemotherapy in some cases. According to the Surveillance, Epidemiology, and End Results Program (SEER) database for the period 2004-2010, 81% of PrC patients in the USA were diagnosed with local disease, and only 12% and 4% presented with regional and metastatic disease at diagnosis, respectively.[2] Advances in clinical research have led to the development of several strategies to manage advanced PrC. This review aims to summarise the current standard of care (SoC) for chemotherapy use in castration-resistant prostate cancer (CRPC) or hormone-sensitive prostate cancer, in light of the available new hormonal treatments.

CLINICAL SETTINGS REQUIRING CHEMOTHERAPY USE IN PROSTATE CANCER

As opposed to many other malignancies, cytotoxic chemotherapy (CC) in PrC has no place as a neoadjuvant treatment modality in 2015. However, within the last two decades, taxane-based combination regimens have emerged as significant therapeutic options in metastatic CRPC (mCRPC). Chemotherapy in PrC primarily includes docetaxel and cabazitaxel, both taxanes. In 2015, during the last European Association of Urology (EAU) meeting in Madrid, the EAU published the latest version of their guidelines for the management of PrC, based on a systematic review of all the available clinical evidence to date.[3] The current guidelines mainly reserve the use of docetaxel chemotherapy for patients with mCRPC, as first-line and second-line treatment modalities. The American Urology Association (AUA) also only recommended docetaxel-based chemotherapy but mainly in symptomatic mCRPC.[4,5] Mitoxantrone was recommended by the AUA in mCRPC patients with good performance status and who were not eligible for docetaxel therapy, but mitoxantrone only confers a quality of life (QoL) benefit and no survival benefit.

HIGH-RISK/LOCALLY ADVANCED PROSTATE CANCER

While androgen deprivation therapy (ADT) combined with radiotherapy provides significant and sustained positive clinical outcomes in men with advanced disease, most patients will develop resistances to hormone therapy over time, as is the case with most hormone-dependant malignancies.

To date, only two studies have evaluated the use of chemotherapy as an adjuvant modality to radiation therapy, but current evidence shows that this therapeutic strategy only generated inconclusive findings in terms of clinical outcomes and additional toxicity. In the GETUG12 trial,[6] which included 413 patients with high-risk local disease, radiation therapy was combined with either ADT plus a combination regimen of docetaxel, estramustine, and prednisone, or ADT alone. No significant difference in the overall survival (OS) rate (median follow-up of 7.6 years) was observed.

Another clinical study (the RTOG 99-02 clinical trial)[7] evaluated the added benefit of the combination of paclitaxel, etoposidel, and estramustine to long-term ADT plus radiation therapy, versus ADT plus radiation therapy alone in 397 patients with high-risk localised PrC. The study was terminated early due to toxicity in the form of accrued thromboembolic toxicity, as well as haematological and gastrointestinal toxicity. In non-metastatic CRPC, chemotherapy has no place and should only be considered in experimental clinical trials in locally advanced situations, as advised by AUA and EAU guidelines.[4,5,8]

CHEMOTHERAPY IN METASTATIC PROSTATE CANCER

Metastatic Castration-Sensitive Prostate Cancer

In a small proportion of patients, most presenting with high-grade disease, PrC can progress to metastatic PrC (mPrC). While localised and regional PrC are associated with a nearly 100% rate of 5-year relative survival, OS drops to 72% at 2 years and 28% at 5 years in mPrC.[2,9,10] In newly diagnosed mPrC, the first-line treatment modality is ADT, as the disease is generally castration-sensitive. However, in high-volume metastases, additional OS benefit could be obtained with a taxane, docetaxel, combined with prednisone and used as an adjuvant therapy, as suggested by the CHAARTED trial.[11]

In the CHAARTED trial, conducted by the Eastern Cooperative Oncology Group (ECOG),[11] 790 men with treatment-naïve, castration-sensitive mPrC, of which 65% had high-volume metastases (mPrC with visceral metastases or more than four bone metastases and at least one bone metastasis beyond the pelvis and vertebral column), were assigned to either combination therapy with ADT and docetaxel (six cycles of docetaxel 75 mg/m^2 every 3 weeks) or to ADT alone. After a median follow-up of 29 months, early results indicate that the combination arm demonstrated a significant OS advantage over ADT alone (median: 57.6 versus 44.0 months; hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.47-0.80). Between high-volume and low-volume patients, the HRs were comparable (0.60 versus 0.63, respectively) but no statistical significance was reached in low-volume disease patients. However, a full publication is awaited in order to fully interpret the results.

The GETUG15 trial is a randomised, open-label Phase III study attempting to address the same question as the CHAARTED trial. A total of 375 castration-sensitive mPrC patients were randomly assigned to receive ADT or ADT plus docetaxel (nine cycles of docetaxel 75 mg/m^2 every 3 weeks). The difference in median survival between both arms was not statistically significant (46.5 versus 60.9 months, respectively; HR: 0.9; 95% CI: 0.7-1.2) after a median follow-up of 82.9 months.[12,13] The updated data from GETUG15 now uses the same definition of disease extent as in CHAARTED. After a median follow-up of 82.9 months, there was no statistical difference in median OS for the high-volume disease group (35.1 versus 39.0 months; HR: 0.8; 95% CI: 0.6-1.2). This difference between the two trials might partly be explained by the differences in subsequent treatment. It is still unclear whether docetaxel should be systematically used with ADT in a subgroup of castration-sensitive mPrC patients. This should at least be discussed in the high-volume situations. Further clinical data such as the expected STAMPEDE trial, the full paper from CHAARTED, and possibly a formal meta-analysis will be needed to fully interpret the results and the role of chemo-hormonal therapy in this clinical setting.

Metastatic Castration-Resistant Prostate Cancer

In the last decade, multiple therapeutic options were developed to address mCRPC, in the form of agents targeting the androgen pathway (abiraterone[14,15] and enzalutamide),[16] radium-223,[17] vaccine (sipuleucel-T),[18] and taxane-based chemotherapy (Table 1). All of the above-cited approaches except sipuleucel-T have demonstrated improved outcomes in terms of radiographic PFS. All including sipuleucel-T demonstrated a significantly prolonged OS, highlighting the weak link between PFS and survival. However, there

is no evidence of superiority of one therapeutic modality over the others as no formal head-to-head comparison is available. Furthermore, the inclusion criteria are different across the trials. In all cases, the EAU and AUA guidelines endorse multidisciplinary team management.[4,5,8]

The choice of therapy for mCRPC is not clearly defined and depends on the metastatic disease presentation, namely metastasis extent (especially the visceral locations), symptoms, localisation and rate of progression, possibly also the speed of progression, as well as the toxicity profile of each approach relative to the side-effects-associated burden already experienced by the patient, associated comorbidities, performance status, and patient preference. Abiraterone and enzalutamide were both evaluated in chemotherapy-naïve patients[19,20] and patients failing chemotherapy with docetaxel,[14,16] and demonstrated activity in both clinical settings. Radium-223 therapy is reserved for patients with extensive symptomatic bone metastases but no known visceral metastases.[4,5,21,22]

Docetaxel in chemotherapy-naïve metastatic castration-resistant prostate cancer

In chemotherapy-naïve mCRPC, the SoC was initially mitoxantrone therapy at first, following two randomised trials that demonstrated a palliative benefit in symptomatic mCRPC without any survival improvement.[23,24] Nowadays, mitoxantrone's role is minimal, if present at all. Docetaxel (75 mg/m^2 every 3 weeks) plus daily oral prednisone (5 mg twice per day) is now considered the SoC for mCRPC requiring chemotherapy-based approaches in chemotherapy-naïve patients.[8,25,26] This was established following the pivotal findings from a randomised clinical trial, the TAX-327 trial, in 1,006 men with mCRPC. Two docetaxel regimens (75 mg/m^2 every 3 weeks or 30 mg/m^2 weekly) were compared with mitoxantrone (12 mg/m^2 every 3 weeks).[27] Both treatment arms also included prednisone therapy. The first schedule of docetaxel showed significant superiority over the second docetaxel schedule and mitoxantrone in terms of OS (19.2, 17.8, and 16.3 months, respectively) and 3-year survival rates, over a wide range of patients. PSA response was higher in the docetaxel treatment groups than in the mitoxantrone group, as was the QoL benefit.[28]

However, in this study, the 3-weekly docetaxel regimen was associated with higher occurrences of Grade 3 or 4 neutropaenia. In patients who do not tolerate a docetaxel regimen of 75 mg/m^2 every 3 weeks, docetaxel can be administered more frequently, as demonstrated by a randomised Phase III trial (NCT00255606) in 361 chemotherapy-naïve patients with mCRPC.[29] Patients were randomly assigned to a schedule of 75 mg/m^2 every 3 weeks, or 50 mg/m^2 every 2 weeks. This regimen was associated with longer time to treatment failure and lower toxicity, namely Grade 3-4 events and neutropaenic infections. However, the size of the trial precludes this schedule to be considered the SoC.

In the elderly, the use of docetaxel either as a standard regimen (performance status 0 or 1) or an adapted regimen (performance status >2) was also explored. In 175 patients (aged 75 and older) docetaxel demonstrated additional benefits with an OS of 15 months and a median PFS of 7.4 months.[30] Nevertheless, the recent recommendations from the International Society of Geriatric Oncology highlight the need to manage PrC according to each patient's individual health status, not according to age.[31]

The SoC also changed from mitoxantrone plus prednisone to docetaxel therapy after the SWOG 99-16 study, in which docetaxel plus estramustine improved the median survival by 2 months when compared with mitoxantrone plus prednisone.[32] In this Phase III trial, the former combination improved OS (17.5 months versus 15.6 months, p=0.02) with a corresponding HR for death of 0.80 (95% CI: 0.67-0.97). However, docetaxel plus estramustine was associated with substantial toxicity leading to estramustine no longer being used in combination with docetaxel. A number of clinical trials have evaluated the use of other agents as a combination therapy with docetaxel and prednisone, such as dasatinib,[33] bevacizumab,[34] or aflibercept,[35] but all these combinations failed. Based on the difference between these two available taxanes, a Phase III clinical trial (the FIRSTANA study) is currently ongoing to evaluate and compare docetaxel with two doses of cabazitaxel as a first-line treatment in patients with mCRPC. This randomised, open-label, multi-centre study (NCT01308567) aims to evaluate both compounds in terms of efficacy (OS, PFS), QoL, and safety.[36]

In second-line chemotherapy for mCRPC, the EAU does not suggest a definitive treatment strategy but highlights that cabazitaxel, abiraterone, enzalutamide, and radium-223 are effective in the

post-docetaxel setting. Docetaxel re-challenging could be suggested in the second-line setting following first-line docetaxel in well-responding patients with a relapse at least 3 months after stopping first-line docetaxel. It is unclear whether docetaxel still has a place given the availability of new compounds.[37]

Cabazitaxel as a second-line chemotherapy agent

Cabazitaxel is a novel microtubule-targeted, taxane-derived agent that has demonstrated important clinical anti-tumoural activity following docetaxel failure. As a consequence, cabazitaxel was approved as a second-line modality for CRPC requiring the use of chemotherapy in combination with prednisone in chemotherapy-experienced patients.[38] Current EAU, AUA, and American Society of Clinical Oncology guidelines recommend cabazitaxel in relapsing patients with prior docetaxel therapy and good performance status.[4,5,39] The TROPIC trial[40,41] was the study supporting this treatment strategy, and which compared mitoxantrone plus prednisone with cabazitaxel plus prednisone in 755 men with CRPC progressing on docetaxel therapy. OS was improved in the cabazitaxel group (median survival of 15.1 and 12.7 months, respectively), as well as the PFS (2.8 and 1.4 months, respectively) and the 2-year OS rate (27% and 16%, respectively).

Nevertheless, cabazitaxel is associated with non-negligible toxicity, with 82% of patients experiencing Grade 3 or higher neutropaenia and 47% of patients experiencing diarrhoea (6% Grade 3 or higher). These adverse events can be effectively managed and even prevented if the patient is surrounded by an experienced team, as demonstrated by the real-life data published by Heidenreich et al.[42] This is especially true for Grade 3-4 neutropaenia and diarrhoea.

An ongoing Phase III clinical trial (PROSELICA trial, NCT01308580) will certainly provide further efficacy, dosing, and safety data on the use of cabazitaxel plus prednisone in mCRPC patients previously treated with docetaxel.[43] This randomised, open-label, multi-centre study will evaluate cabazitaxel 20 mg/m^2 versus cabazitaxel 25 mg/m^2 not only to determine the non-inferiority of cabazitaxel 20 mg/m^2 in terms of OS, but also to evaluate the safety profile, particularly the myelotoxicity, of both cabazitaxel regimens.

Table 1: Key Phase III clinical trials in metastatic castration-resistant prostate cancer.

Study	Agents	n	Indication	Inclusion criteria	HR	Δ OS (months)
TAX-327[27]	Docetaxel/prednisone vs. mitoxantrone/prednisone	1,006	mCRPC	-	0.76	+2.9
IMPACT[18]	Sipuleucel-T vs. placebo	512	mCRPC (pre-docetaxel)	Asymptomatic	0.78	+4.1
COU-AA-302[46]	Abiraterone/prednisone vs. prednisone	1,088	mCRPC (pre-docetaxel)	Asymptomatic/no visceral metastases	0.81	+4.4
COU-AA-301[14]	Abiraterone/prednisone vs. prednisone	1,195	mCRPC (post-docetaxel)	-	0.74	+4.6
PREVAIL[49]	Enzalutamide vs. placebo	171	mCRPC (pre-docetaxel)	Asymptomatic/ visceral metastases allowed (11%)	0.76	+4 (estimated)
AFFIRM[16]	Enzalutamide vs. placebo	1,199	mCRPC (post-docetaxel)	-	0.63	+4.8
TROPIC[40]	Cabazitaxel/prednisone vs. mitoxantrone/prednisone	755	mCRPC (post-docetaxel)	-	0.70	+2.4
ALSYMPCA[21,22]	Radium-223 vs. placebo	921	mCRPC	No visceral metastases	0.70	+2.8

mCRPC: metastatic castration-resistant prostate cancer; HR: hazard ratio; OS: overall survival.

Salvage hormonal therapy with novel agents

Abiraterone

Abiraterone acetate is a CYP17A1 inhibitor that inhibits the synthesis of testosterone at the adrenal level and plays a major role at the intracrine level by suppressing androgen synthesis in intraprostatic cells. It has to be used in conjunction with prednisone 10 mg daily. It has demonstrated significant benefits in OS in key Phase III trials, in both docetaxel-naïve and docetaxel-experienced mCRPC patients.[14,20,44] In 1,195 mCRPC docetaxel-experienced patients,[14,44,45] abiraterone plus prednisone significantly improved OS over placebo plus prednisone (median: 15.8 versus 11.2 months; HR: 0.74; 95% CI: 0.64-0.86), as well as time to PSA progression and radiographic PFS. Comparable results were observed in a Phase III trial in 1,088 chemotherapy-naïve patients who were randomised to either abiraterone plus prednisone or placebo plus prednisone.[15,20,46] After a median follow-up of 49.2 months, abiraterone demonstrated significant and meaningful prolonged OS (median: 34.7 versus 30.3 months; HR: 0.81; 95% CI: 0.70-0.93).[46]

Enzalutamide

Enzalutamide is an androgen receptor antagonist that demonstrated important clinical activity in CRPC. Its affinity for the androgen receptor is higher compared with the previously available antagonists, and it has a specific mode of action with the inhibition of receptor trafficking from the cytoplasm to the nucleus. In the AFFIRM trial, 1,199 docetaxel-experienced patients were randomised to receive enzalutamide or placebo.[16,47] After a median follow-up of 14.4 months, improved median survival was observed in the enzalutamide group versus placebo (18.4 months versus 13.6 months), as well as improved PSA response, radiographic PFS, and QoL.

The Phase III PREVAIL study[19] aimed to evaluate the efficacy and safety of enzalutamide in 1,717 mCRPC patients who were chemotherapy-naïve. Median OS (risk of death, HR: 0.71; p<0.0001) was significantly higher in the enzalutamide arm compared with placebo. This trial led to an EMA indication extension for chemotherapy-naïve patients in October 2014.[48] Updated results were presented at EAU 2015[49] based on 784 deaths. The overall results were confirmed (OS: HR: 0.77; 95% CI: 0.67-0.88; p=0.0002) and a 4-month improvement in median survival with enzalutamide (35.3 months [95% CI: 32.2 - not yet reached]) versus placebo (31.3 months [95% CI: 28.8-34.2]). After a median follow-up of 31 months, 52% of enzalutamide and 81% of placebo patients received ≥1 subsequent life-extending PrC therapies.

Other chemotherapy strategies beyond first and second-line

Given the lack of Phase III trial data, there is no current SoC for patients progressing on cabazitaxel therapy, and treatment modalities following taxane failure are limited, mostly based on limited Phase II cohorts at best. Third-line salvage strategies for taxane-refractory mCRPC include platinum-based regimens such as carboplatin, either in combination with docetaxel[50] or paclitaxel.[51] In Phase II clinical studies both regimens yielded further additional benefits, although modest, with median OS of 12.4 and 9.9 months, respectively. However, the available experience has been obtained before the availability of abiraterone, enzalutamide, or radium-223.

Oxaliplatin was also evaluated in three Phase II studies in heavily pre-treated CRPC patients, in combination with 5-fluorouracil,[52] capecitabine,[53] or pemetrexed.[54] Median OS was 11.4, 5.5, and 11.9 months, respectively, with manageable toxicities. Cisplatin was also evaluated in combination with prednisone in 25 men who were refractive to docetaxel; 23% of patients with measurable disease displayed a partial response (median PFS: 6 months; OS: 55 weeks).[48]

Emerging new agents in ongoing clinical trials

Emerging non-hormonal therapies that are currently being evaluated include novel immunotherapies such as sipuleucel-T - an autologous-registered and FDA-approved prostatic acid phosphatase,[18,55] ProstVac-VF - a PSA-targeted poxviral-based vaccine,[56] and nivolumab - an anti-PD1 antibody.[57] Small molecule inhibitors such as custirsen[58-60] are also currently being investigated in order to expand the therapeutic armamentarium for the remaining unmet needs in advanced PrC. Considering the lack of survival benefit, the development of tasquinimod was stopped, according to a press release April 16, 2015.

CONCLUSION

Contrary to many other malignancies, CC is still reserved for few clinical settings within PrC. These settings have been the subject of major clinical

research in past decades, since they represent important unmet needs. While abiraterone and enzalutamide were first evaluated in patients following failure of docetaxel, recent clinical data demonstrate improved OS and good safety profiles in chemotherapy-naïve mCRPC for both new agents. Additionally, the indications for CC could be extended to selected ADT-naïve mPrC patients following the promising results of the CHAARTED trial on docetaxel combination therapy with ADT, which could very well challenge the current paradigm. However, uncertainty remains regarding the optimal target population, based on the conflicting results available. Long-term results from both these studies and ongoing trials will help further ascertain the role of chemotherapy in PrC, and will help refine the most appropriate treatment strategies for mPrC.

Acknowledgements

Medical writing assistance was provided by Dr Caroline Charles (Scilink Medical Writing), supported by Sanofi.

REFERENCES

1. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. 2013. http://globocan.iarc.fr. 10 April 2015.

2. National Cancer Institute, Surveillance, Epidemiology, and End Results Program. SEER stat fact sheets: prostate cancer. http://seer.cancer.gov/. 10 April 2015.

3. Mottet N et al. EAU Guidelines on Prostate Cancer. 2015. http://uroweb.org/guideline/prostate-cancer/. 19 April 2015.

4. Cookson MS et al. Castration-resistant prostate cancer: AUA Guideline. J Urol. 2013;190(2):429-38.

5. Cookson MS et al. Castration-resistant prostate cancer: AUA guideline amendment. J Urol. 2015;193(2):491-9.

6. Fizazi K et al. Docetaxel-estramustine in localized high-risk prostate cancer: results of the French Genitourinary Tumor Group GETUG 12 phase III trial. J Clin Oncol. 2014;32:5s(suppl; abstr 5005).

7. Rosenthal SA et al. Phase III multi-institutional trial of adjuvant chemotherapy with paclitaxel, estramustine, and oral etoposide combined with long-term androgen suppression therapy and radiotherapy versus long-term androgen suppression plus radiotherapy alone for high-risk prostate cancer: preliminary toxicity analysis of RTOG 99-02. Int J Radiat Oncol Biol Phys. 2009;73(3):672-8.

8. Heidenreich A et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65(2):467-79.

9. Attard G et al. Combining enzalutamide with abiraterone, prednisone, and androgen deprivation therapy in the STAMPEDE trial. Eur Urol. 2014;66(5): 799-802.

10. James ND et al. Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). Eur Urol. 2014;doi: 10.1016/j.eururo.2014.09.032. [Epub ahead of print].

11. Sweeney C et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial. J Clin Oncol. 2014;32:5s(suppl; abstr LBA2).

12. Gravis G et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(2):149-58.

13. Gravis G et al. Androgen deprivation therapy (ADT) plus docetaxel (D) versus ADT alone for hormone-naïve metastatic prostate cancer (PCa): Long-term analysis of the GETUG-AFU 15 phase III trial. J Clin Oncol. 2015;33:(suppl 7; abstr 140).

14. Fizazi K et al. 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. 2012;13(10):983-92.

15. Rathkopf DE et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol. 2014;66(5): 815-25.

16. Scher HI et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. New Engl J Med. 2012;367(13):1187-97.

17. Parker C et al. Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA). J Clin Oncol. 2012;30:(suppl; abstr LBA4512).

18. Kantoff PW et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411-22.

19. Beer TM et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(5):424-33.

20. Ryan CJ et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138-48.

21. Parker C et al. Overall Survival Benefit of Radium-223 Chloride (Alpharadin™) in the Treatment of Patients with Symptomatic Bone Metastases in Castration-resistant Prostate Cancer (CRPC): a Phase III Randomized Trial (ALSYMPCA). Eur J Cancer. 2011;47(suppl 2):3.

22. Parker C et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-23.

23. Tannock IF et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol. 1996;14(6): 1756-64.

24. Kantoff PW et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. J Clin Oncol. 1999;17(8): 2506-13.

25. Basch EM et al. American Society

of Clinical Oncology endorsement of the Cancer Care Ontario Practice Guideline on nonhormonal therapy for men with metastatic hormone-refractory (castration-resistant) prostate cancer. J Clin Oncol. 2007;25(33):5313-8.

26. National Institute for Health and Care Excellence. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer. 2006. https://www.nice.org.uk/guidance/ta101. 10 April 2015.

27. Tannock IF et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12.

28. Berthold DR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol. 2008;26(2):242-5.

29. Kellokumpu-Lehtinen PL et al. 2-Weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. Lancet Oncol. 2013;14(2):117-24.

30. Italiano A et al. Docetaxel-based chemotherapy in elderly patients (age 75 and older) with castration-resistant prostate cancer. Eur Urol. 2009;55(6):1368-75.

31. Droz JP et al. Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. Lancet Oncol. 2014;15(9): e404-14.

32. Petrylak DP et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351(15):1513-20.

33. Araujo JC et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. Lancet Oncol. 2013;14(13):1307-16.

34. Kelly WK et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. J Clin Oncol. 2012;30(13):1534-40.

35. Tannock IF et al. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. Lancet Oncol. 2013;14(8):760-8.

36. Sanofi. Cabazitaxel versus docetaxel both with prednisone in patients with metastatic castration resistant prostate cancer (FIRSTANA). Clinical trial: NCT01308567. 2015. http://www.clinicaltrials.gov/ct2/show/NCT01308567?term=NCT01308567&rank=1. 3 December 2014.

37. Ansari J et al. Role of second-line systemic treatment post-docetaxel in metastatic castrate resistant prostate cancer- current strategies and future directions. Anticancer Agents Med Chem. 2011;11(3):296-306.

38. Sanofi. JEVTANA (cabazitaxel) package insert. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/201023lbl.pdf. 10 April 2015.

39. Basch E et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2014;32(30):3436-48.

40. de Bono JS et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-54.

41. Bahl A et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol. 2013;24(9):2402-8.

42. Heidenreich A et al. Safety of cabazitaxel in senior adults with metastatic castration-resistant prostate cancer: results of the European compassionate-use programme. Eur J Cancer. 2014;50(6):1090-9.

43. Sanofi. Cabazitaxel at 20 mg/m^2 compared to 25 mg/m^2 with prednisone for the treatment of metastatic castration resistant prostate cancer (PROSELICA). Clinical trial: NCT01308580. 2015. http://www.clinicaltrials.gov/ct2/show/NCT01308580?term=NCT01308580&rank=1. 6 December 2014.

44. de Bono JS et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21): 1995-2005.

45. Logothetis CJ et al. 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. 2012;13(12):1210-7.

46. Ryan CJ et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152-60.

47. Fizazi K et al. 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. 2014;15(10):1147-56.

48. Buonerba C et al. Phase II trial of cisplatin plus prednisone in docetaxel-refractory castration-resistant prostate cancer patients. Cancer Chemother Pharmacol. 2011;67(6):1455-61.

49. Tombal B. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC): Final overall survival analysis of the phase 3 PREVAIL study. 2015. Presented at the 2015 EAU Congress, Madrid, Spain. 28 April 2015.

50. Ross RW et al. A phase 2 study of carboplatin plus docetaxel in men with metastatic hormone-refractory prostate cancer who are refractory to docetaxel. Cancer. 2008;112(3):521-6.

51. Kentepozidis N et al. Paclitaxel in combination with carboplatin as salvage treatment in patients with castration-resistant prostate cancer: a Hellenic oncology research group multicenter phase II study. Cancer Chemother Pharmacol. 2012;70(1):161-8.

52. Droz JP et al. Phase II study of oxaliplatin versus oxaliplatin combined with infusional 5-fluorouracil in hormone refractory metastatic prostate cancer patients. Ann Oncol. 2003;14(8):1291-8.

53. Gasent Blesa JM et al. Phase II trial of oxaliplatin and capecitabine after progression to first-line chemotherapy in androgen-independent prostate cancer patients. Am J Clin Oncol. 2011;34(2): 155-9.

54. Dorff TB et al. Efficacy of oxaliplatin plus pemetrexed in chemotherapy pretreated metastatic castration-resistant prostate cancer. Clin Genitourin Cancer. 2013;11(4):416-22.

55. Antonarakis ES et al. A randomized phase II study evaluating the optimal sequencing of sipuleucel-T and androgen deprivation therapy (ADT) in biochemically recurrent prostate cancer (BRPC): immune results. J Clin Oncol. 2013;31:(suppl; abstr 5016).

56. Kantoff PW et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol. 2010;28(7):1099-105.

57. Topalian SL et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26): 2443-54.

58. Chi KN et al. Randomized phase II study of docetaxel and prednisone with or without OGX-011 in patients with metastatic castration-resistant prostate cancer. J Clin Oncol. 2010;28(27): 4247-54.

59. Teva Pharmaceutical Industries. Comparison of docetaxel/prednisone to docetaxel/prednisone in combination with OGX-011 in men with prostate cancer (SYNERGY). Clinical trial: NCT01188187. 2015. https://clinicaltrials.gov/ct2/show/NCT01188187. 28 April 2015.

60. OncoGenex Technologies. Comparison of cabazitaxel/prednisone alone or in combination with custirsen for 2nd line chemotherapy in prostate cancer (AFFINITY). Clinical trial: NCT01578655. 2015. https://clinicaltrials.gov/ct2/show/NCT01578655. 28 April 2015.