Optimizing the sequence of metastatic castration-resistant prostate cancer treatment options

Badrising, S.K.

Chapter 1

General introduction

Prostate cancer is the second most common cancer in males in the world and the most prevalent cancer in Dutch men.[1, 2] In 2019 almost 13.600 men in the Netherlands were diagnosed with prostate cancer, resulting in 79.200 prostate cancer patients in the Netherlands.[3] Improvements in early detection and effective treatment options have contributed to the increased five-year survival over the last two decades in the Netherlands (figure 1). The 5-year survival increased from close to 80% in 1999 to almost 90% in 2012.[4] With the availability of new drugs and increased survival, the costs of care for prostate cancer patients increased from 0.3% of the total Dutch healthcare costs in 2011 to 0.44% in 2017.[5]

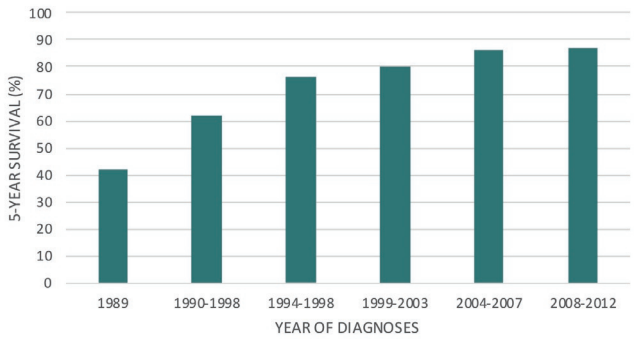

Figure 1. Relative five-years survival of patients with prostate cancer in the Netherlands from 1989 – 2012

After diagnosis of localized prostate cancer, patients may undergo surgery and/or radiotherapy, with a curative intention. However, metastatic disease cannot be cured. Until 2010, treatment of patients with metastases at presentation or after previous local therapy only consisted of lowering serum testosterone to castration levels. Low serum testosterone levels can be achieved by orchiectomy or treatment with Luteinizing hormone-releasing hormone analogues or antagonists (androgen deprivation therapy; ADT). However, despite serum testosterone at castration levels, the disease will invariably progress to metastatic castration resistant prostate cancer (mCRPC), which has high morbidity and mortality as hallmarks. Docetaxel was the first treatment that showed an overall survival benefit in mCRPC patients.[6] For a decade, docetaxel was the only treatment option for mCRPC patients. In recent years, multiple treatment options for mCRPC showed an overall survival benefit and improved quality of life. These new treatment options include the chemotherapeutic agent Cabazitaxel, androgen-signalling-targeted inhibitors Abiraterone and Enzalutamide and the alpha-emitting radionuclide Radium-223. In this review we will discuss the currently available treatment options for metastatic castration resistant prostate cancer.

CHEMOTHERAPY

Microtubules are a principal component of the cytoskeleton and are involved in many essential tasks of the cell, including cell movement, mitosis and shape. Moreover, translocation of the androgen receptor to the nucleus following testosterone binding and dimerization of the receptor, is guided by microtubles.[7] Microtubules are continually in a form of dynamic instability, which is necessary for cell division. Taxanes bind to β-tubulin heterodimers, stabilizing the microtubule and ultimately causing cell-death.[8]

Docetaxel

Docetaxel is a second generation semi-synthetic taxane, first approved for medical use in 1995. In 2004, it was registered as a treatment for mCRPC in combination with prednisone after publication of the TAX327 study. This study showed that Docetaxel was the first treatment for mCRPC-patients which improved overall survival (OS).[6] Until 2013 Docetaxel monotherapy was the first choice of treatment after patients became castration resistant.

In 2015 the CHAARTED study reported a survival benefit when Docetaxel was combined with ADT as first systemic treatment after diagnosis of high volume metastatic prostate cancer, compared with patients treated with ADT only.[9] In CHAARTED, 70% of patients were diagnosed with metastases at time of diagnosis of prostate cancer. The STAMPEDE study confirmed these results in 2016, however in this study, also patients with a locally advanced disease and patients who were previously treated for localized disease were included.[10] Docetaxel in hormone sensitive metastatic disease, resulted in a survival benefit of 10-17 months compared to ADT alone. Subgroup analysis from the STAMPEDE study showed that patients with distant metastatic disease (M1) seemed to benefit most from the addition of docetaxel in terms of overall survival, however there was no distinction made between high- and low volume metastatic patients. As a result of differences in characteristics of patients included in CHAARTED and STAMPEDE, it is unclear if all patients with hormone sensitive metastatic disease should be treated with both Docetaxel and ADT, or only patients with high-volume disease. In the Netherlands, patients with high-volume disease at diagnosis are usually treated with Docetaxel and ADT, in line with the CHAARTED inclusion criteria.[11]

Cabazitaxel (Jetvana®)

Cabazitaxel is like Docetaxel a second generation semi-synthetic taxane. In 2010, the TROPIC study compared Cabazitaxel with Mitoxantrone, both combined with prednisone, in mCRPC patients pretreated with Docetaxel. The results favoured Cabazitaxel with a 2.4 month survival benefit, compared to Mitoxantrone [12]. The FIRSTANA study compared Docetaxel with Cabazitaxel in chemotherapy-naïve mCRPC patients. The trial demonstrated no significant difference in overall survival (OS).[13] Since, Cabazitaxel had shown activity in Docetaxel treated patients,

Cabazitaxel remained a second line treatment option, while Docetaxel remained a first line treatment option. Cabazitaxel, Enzalutamide, Abiraterone and Radium-223 were all developed and evaluated in parallel as a second line therapy in patients who progressed on Docetaxel. This resulted in uncertainty with regards to optimal sequencing of the treatment options for mCRPC patients previously treated with docetaxel.

In 2019 the CARD study compared Cabazitaxel with androgen-signalling-targeted inhibitors as a third line treatment option in patients already treated with Docetaxel and androgen-signalling-targeted inhibitors. This study reported Cabazitaxel to be superior to third line androgen-signalling-targeted inhibitors directly following another androgen-signalling-targeted inhibitor (*e.g.:* Abiraterone treatment following failure on Enzalutamide), with a 2.6 months overall survival benefit and 4.3 months imaging-based progression-free survival benefit. [14]

ANDROGEN-SIGNALLING-TARGETED INHIBITORS

The vast majority of prostate cancer cells are androgen dependent for growth and proliferation. During ADT treatment, the prostate cancer cells adapt to very low concentrations of androgens through multiple mechanism, including amplification of the androgen receptors (AR) and changes in expression of AR co-regulatory proteins. Moreover, constitutively active AR splice variants arise that drive testosterone independent prostate cancer progression. The androgen receptor splice-variant 7 (ARV7) is the most extensively studied splice variant and holds promise as a drug target and a biomarker. The presence of ARV7 causes continuous AR signalling in a ligand independent fashion, resulting in a castration resistant state.[15]

Abiraterone Acetate (Zytiga®)

Cytochrome P450 c17 (CYP17) is an essential enzyme for both androgen and cortisol synthesis. Abiraterone Acetate is a second-generation oral androgen receptor inhibitor which inhibits CYP17 both intra- and extratumorally. In 2011, the COU-AA-301 study reported a survival benefit of 4.6 months in patients treated with Abiraterone in combination with prednisone compared to prednisone monotherapy in patients pretreated with Docetaxel.[16] The COU-AA-302 study evaluated Abiraterone in Docetaxel-naïve patients. Compared to the placebo-arm, patients treated with Abiraterone had a 4.4 month survival benefit.[17]

In 2017 the LATITUDE and the STAMPEDE showed improved survival of metastatic hormone sensitive prostate cancer patients when Abiraterone was added to ADT compared to ADT alone. While the LATITUDE study included only newly diagnosed metastatic patients with high-risk features for therapy failure, the STAMPEDE study included a broad population, ranging from locally advanced to metastatic hormone-sensitive prostate cancer patients.[18, 19] No direct

comparison can be made with Docetaxel in this stage of the disease, because there is no head-to-head comparison and there are major differences between LATITUDE and STAMPEDE exploring efficacy of Abiraterone and the CHAARTED and STAMPEDE trials. However, the results appear to be comparable.

As mentioned earlier, in the Netherlands, Docetaxel with ADT as first-line treatment in patients with metastatic hormone sensitive prostate cancer is preferred over Abiraterone. This is based on several factors, including the short duration of docetaxel treatment, the long duration of Abiraterone treatment and insecurity over the impact of long term effects of extreme androgen deprivation on bone density and mental health, but also the lower costs of Docetaxel compared with Abiraterone.[11]

Enzalutamide (Xtandi®)

Like Abiraterone, Enzalutamide is a second-generation orally administered androgen receptor inhibitor. Enzalutamide inhibits nuclear translocation of the AR-receptor, DNA-binding and also coactivator recruitment. [20] In 2012, the AFFIRM trial reported a survival benefit of 4.8 months in men with mCRPC pretreated with Docetaxel compared to placebo. In the PREVAIL study, the efficacy of Enzalutamide was studied in a pre-docetaxel-setting. The overall survival benefit was 2.2 months, which was comparable to Abiraterone-reported in the same setting.[21] More recently, efficacy of Enzalutamide as a treatment for metastatic hormone-sensitive prostate cancer patients was recently established in the ENZAMET trial.[22] Overall survival benefit in this patient population treated with Enzalutamide was comparable to patients treated with Docetaxel or Abiraterone. This new indication for Enzalutamide treatment awaits approval by the European Medical Association. Moreover, Enzalutamide has shown to postpone the moment of detection of metastatic disease in patients with the rare entity 'non-metastatic castration resistant prostate cancer' as was established in the PROSPER trial.[23]

Preference for Enzalutamide or Abiraterone

The phase-III studies into efficacy of Abiraterone and Enzalutamide in mCRPC patients were published shortly after one-another.[16, 20] The populations of both studies were slightly different, making a direct comparison difficult. To date, no randomized controlled trials directly comparing the efficacy of both agents have been published. However, retrospective studies found no significant difference in efficacy between the two agents.[24] A recently published meta-analysis, comparing Abiraterone and Enzalutamide trials, concluded that that Enzalutamide outperformed Abiraterone with respect to biochemical and radiological progression free survival and also PSA response rate. However, there was no significant difference with regard to overall survival.[25]

Abiraterone might have an advantage over Enzalutamide with regards to quality of life. Two recent studies, evaluating patient-reported quality of life, both reported patients treated with Abiraterone

to have better quality of life than patients treated with Enzalutamide. One of those studies found this difference only in elderly patients, while the other found it in the entire population.[26, 27] at the moment, there is no consensus in the Netherlands on which agent should have priority in patients with castration resistant prostate cancer.

Novel androgen-signalling-targeted inhibitors

In recent years there has been intense study activity into efficacy of Enzalutamide and Abiraterone for novel indications, while also two new androgen-signalling-targeted inhibitors were introduced. Apalutamide has a similar mechanism of action as Enzalutamide, but *in vitro* studies suggest that Apalutamides androgen receptor inhibition is more potent. In the Titan study, Apalutamide in combination with ADT treated metastatic hormone sensitive prostate cancer patients showed a significant longer overall survival then patients treated with ADT only.[28] Consequently, Docetaxel and three androgen-signalling-targeted inhibitors are available as treatment options for these patients, while there are no head to head comparisons to substantiate a preference. Moreover, Apalutamide has shown to postpone the moment of detection of metastatic disease in patients with non-metastatic castration resistant prostate cancer as was established in the SPARTAN trial.[29] Darolutamide, is the newest androgen-signalling-targeted inhibitor with a unique mechanism of action. As Enzalutamide and Apalutamide, Darolutamide has shown in the ARAMIS trial to postpone the moment of detection of metastatic disease in patients with non-metastatic castration resistant prostate cancer.[30]

Cross-resistance and sequencing

Because Enzalutamide and Abiraterone target the same pathway, there is a significant chance of clinical cross-resistance between the two agents, especially when used subsequently. There is also preclinical evidence of cross-resistance between Taxanes and androgen-signalling-targeted inhibitors.[31] Efficacy of Enzalutamide after Abiraterone and Abiraterone after Enzalutamide in patients with mCRPC was evaluated in a recently published phase 2 trial. The authors reported that patients treated with Enzalutamide followed by Abiraterone had a significantly lower chance to have a PSA response than patients treated with Abiraterone followed by Enzalutamide. In this trial, response rates of both androgen-signalling-targeted inhibitors given after treatment with another androgen-signalling-targeted inhibitor were lower than the response rates reported in the respective androgen-signalling-targeted inhibitor phase-3 studies in patients only pretreated with Docetaxel. [32]

In this thesis we will retrospectively focus on the efficacy of Enzalutamide in mCRPC patients previously treated with at least Docetaxel and Abiraterone (**chapter 2**).

The efficacy (defined by ≥50% PSA decline from baseline) of Enzalutamide in patients pretreated with Abiraterone and Docetaxel is between 13% and 39%.[33] Which means that more than half of

the patients receiving Enzalutamide will have no response. Being able to predict which patients respond to Enzalutamide in this setting would help much in deciding whichh agent to choose. In **chapter 3** we explore the characteristics of the responders.

While most retrospective studies explored the efficacy of Enzalutamide as a second or third-line therapy, data on efficacy in fourth or fifth line is scarce. In **chapter 4** we retrospectively assess the efficacy of Enzalutamide in this setting.

RADIOPHARMACEUTICALS

Up to 90% of patients with metastatic prostate cancer develop bone metastases.[34] Bone metastases interfere with bone formation and resorption, which can lead to deterioration of the structural integrity of the bone. This can lead to pathological fractures, increased pain, poor quality of life and reduced survival.[35]

Radiopharmaceuticals are radioactive isotopes (radionuclides) which are able to emit radiation. The range of the radiation is dependent on the type of radiation. Available radioactive isotopes for the treatment of bone-metastatic prostate cancer are alpha-emitters and beta-emitters. Alpha-emitters have the shorter range and beta-emitters the longer range. To maximize the damage to the malignant cells and minimize damage to the healthy cells, the radioactive isotopes must bind as close as possible to the malignant cells. For the treatment of bone metastases this is achieved by either using calcium mimetics which are incorporated in the bone by osteoblasts. Common side effects are changes in blood counts, as a result of damage to healthy bone marrow caused by the radiation to the progenitor cells.[35]

Until 2012, the indication for the use of radiopharmaceuticals, predominantly beta emitters, in prostate cancer were treatment of pain and improvement of Quality of Life (QoL). Radiopharmaceuticals had either no effect on OS or an OS benefit was not assessed for these agents.[36] In 2013 results were published of the ALSYMPCA study, evaluating the efficacy of the alpha emitter Radium-223 in mCRPC patients, which showed a survival benefit compared to placebo (see below).[37] This added another indication to the use of radioactive isotopes.

Radium-223 (Xofigo®)

Radium-223 (Ra-223) is an alpha-emitting calcium mimetic, which selectively binds to areas of increased bone-turnover, such as bone metastases. Unlike beta-emitters (like samarium and rhenium), alpha-emitters have a very short range. The short range causes limited damage to healthy cells, especially the blood progenitor cells in the bone marrow.[37] Because Ra-223 only binds in areas of high bone-turn over, it has no effect on visceral or lymph node metastases. This

is the reason why Ra-223 is only indicated for patients with limited lymph node-metastases and no visceral metastases.

In 2013 the ALSYMPCA study showed a survival benefit of 3.6 months as well as a longer time to first symptomatic skeletal event, when compared to placebo.[37] Patients treated with Ra-223 also had improved quality of life, compared to placebo. [38]

The population of ALSYMPCA differs from the current real-world population. Patients in the trial were minimally symptomatic and were, or previously treated with docetaxel or had no previous mCRPC treatment. None of the patients in ALSYMPCA were treated with Cabazitaxel or androgen-signalling-targeted inhibitors, because those drugs were not available during accrual of ALSYMPCA. This raises the question what the efficacy and optimal positioning is of Ra-223 in the changed landscape of treatment possibilities for mCRPC patients with predominantly bone metastases. In **chapter 5** we prospectively assess the efficacy of RA-223 in a non-study population. [39]

Because adverse events of Ra-223 are mild and Ra-223 only affects bone metastases, combination with other systemic anti-cancer agents seems a logical next step. The ERA223 phase III study evaluating the combination of Ra-223 and Abiraterone was unblinded prematurely because there were more deaths and bone fractures in the combination arm than in the placebo-arm.[40] This resulted in new recommendations for the use of Ra-223, including the use of the drug in Docetaxel pretreated patients. A trial evaluating the combination of Ra-223 and Enzalutamide is currently recruiting patients. The use of bone protective agents, including bisphosphonates or denosumab is mandatory in this trial. A recent phase 1/2a trial evaluating the efficacy of Docetaxel combined with Ra-223 reported enhanced antitumor effect in patients in the combination arm when compared to Docetaxel monotherapy.[41] This combination is currently explored in a phase III trial.

Although other radionuclides are primarily given to reduce pain, this was not directly assessed in the ALSYMPCA trial. Based on non-symptom-specific questionnaires, it was suggested that Ra-223 had a positive effect on pain, which was only measured every 12 weeks, without considering the use of analgesics.[42] In **chapter 6** we assess the effect of Ra-223 on pain, patient-reported QoL, and opioid use.

REFERENCES

1. Steward BW, Wild CP. World Cancer Report 2014, 2014. doi:9283204298.
2. Mortality rate of cancers in met in the Netherlands. [in Dutch]. [http://www.cijfersoverkanker.nl/selecties/sterfte_prostaat/img568baa08eae1b].
3. Prevalence of prostate cancer in the Netherlands [in Dutch]. [https://www.volksgezondheidenzorg.info/onderwerp/prostaatkanker/cijfers-context/huidige-situatie#!node-prevalentie-prostaatkanker].
4. Prostate cancer suvival. [in Dutch]. [https://www.kanker.nl/bibliotheek/prostaatkanker/wat-is/1095-overleving-prostaatkanker].
5. Costs of prostate cancer in the Netherlands [in Dutch]. [https://www.volksgezondheidenzorg.info/onderwerp/prostaatkanker/kosten/zorguitgaven].
6. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. N. Engl. J. Med. 2004; 351(15):1502–1512.
7. Chiu C-L, Patsch K, Cutrale F et al. Intracellular kinetics of the androgen receptor shown by multimodal Image Correlation Spectroscopy (mICS). Sci. Rep. 2016. doi:10.1038/SREP22435.
8. Oshiro C, Marsh S, Mcleod H et al. Taxane Pathway. . doi:10.1097/FPC.0b013e3283335277.
9. Sweeney CJ, Chen Y-H, Carducci M et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N. Engl. J. Med. 2015; 373(8):737–746.
10. James ND, Sydes MR, Clarke NW et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016; 387(10024):1163–1177.
11. Leyten GHJM, van Oort IM, Bergman AM. Op metastasen gerichte behandeling van prostaatcarcinoom. Tijdschr. voor Urol. 2019; 9(6–7):108–116.
12. de Bono JS, Oudard S, Ozguroglu M 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):1147–1154.
13. Oudard S, Fizazi K, Sengeløv L et al. Cabazitaxel Versus Docetaxel As First-Line Therapy for Patients With Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase III Trial-FIRSTANA. J. Clin. Oncol. 2017; 35(28):3189–3197.
14. de Wit R, de Bono J, Sternberg CN et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N. Engl. J. Med. 2019; 381(26):2506–2518.
15. Taplin M-E, Balk SP. Androgen receptor: A key molecule in the progression of prostate cancer to hormone independence. J. Cell. Biochem. 2004; 91(3):483–190.
16. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N. Engl. J. Med. 2011; 364(21):1995–2005.
17. Ryan CJ, Smith MR, de Bono JS et al. Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy. N. Engl. J. Med. 2013; 368(2):138–148.

18. James ND, de Bono JS, Spears MR et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N. Engl. J. Med. 2017; 377(4):338–351.

19. Fizazi K, Tran N, Fein L et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N. Engl. J. Med. 2017; 377(4):352–360.

20. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N. Engl. J. Med. 2012; 367(13):1187–1197.

21. Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. N. Engl. J. Med. 2014; 371(5):424–33.

22. Davis ID, Martin AJ, Stockler MR et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. https://doi.org/10.1056/NEJMoa1903835 2019. doi:10.1056/NEJMOA1903835.

23. Hussain M, Fizazi K, Saad F et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N. Engl. J. Med. 2018; 378(26):2465–2474.

24. Maughan BL, Luber B, Nadal R, Antonarakis ES. Comparing Sequencing of Abiraterone and Enzalutamide in Men With Metastatic Castration-Resistant Prostate Cancer: A Retrospective Study. Prostate 2017; 77(1):33–40.

25. Zheng X, Zhao X, Xu H et al. Efficacy and safety of abiraterone and enzalutamide for castration-resistant prostate cancer. Medicine (Baltimore). 2019; 98(44):e17748.

26. Khalaf DJ, Sunderland K, Eigl BJ et al. Health-related Quality of Life for Abiraterone Plus Prednisone Versus Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer: Results from a Phase II Randomized Trial. Eur. Urol. 2019; 75(6):940–947.

27. Thiery-Vuillemin A, Poulsen MH, Lagneau E et al. Impact of Abiraterone Acetate plus Prednisone or Enzalutamide on Patient-reported Outcomes in Patients with Metastatic Castration-resistant Prostate Cancer: Final 12-mo Analysis from the Observational AQUARiUS Study. Eur. Urol. 2020; 77(3):380–387.

28. Chi KN, Agarwal N, Bjartell A et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N. Engl. J. Med. 2019; 381(1):13–24.

29. Smith MR, Saad F, Chowdhury S et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N. Engl. J. Med. 2018; 378(15):1408–1418.

30. Fizazi K, Shore N, Tammela TL et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N. Engl. J. Med. 2019. doi:10.1056/nejmoa1815671.

31. van Soest RJ, van Royen ME, de Morrée ES et al. Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide may affect drug sequence choices in metastatic castration-resistant prostate cancer. Eur. J. Cancer 2013; 49(18):3821–30.

32. Khalaf DJ, Annala M, Taavitsainen S et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol. 2019; 20(12):1730–1739.

33. Caffo O, De Giorgi U, Fratino L et al. Clinical Outcomes of Castration-resistant Prostate Cancer Treatments Administered as Third or Fourth Line Following Failure of Docetaxel and Other Second-line Treatment: Results of

an Italian Multicentre Study. Eur. Urol. 2015; 68(1):147–53.

34. Bubendorf L, Schöpfer A, Wagner U et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum. Pathol. 2000; 31(5):578–83.

35. Nilsson S. Radionuclide Therapies in Prostate Cancer: Integrating Radium-223 in the Treatment of Patients With Metastatic Castration-Resistant Prostate Cancer. 2016. doi:10.1007/s11912-015-0495-4.

36. Sartor O, Hoskin P, Bruland ØS. Targeted radionuclide therapy of skeletal metastases. Cancer Treat. Rev. 2013; 39(1):18–26.

37. Parker C, Nilsson S, Heinrich D et al. Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. N. Engl. J. Med. 2013; 369(3):213–223.

38. Nilsson S, Cislo P, Sartor O et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. Ann. Oncol. 2016; 27(5):868–874.

39. Badrising SK, Louhanepessy RD, vd Noort V et al. A Prospective Observational Registry Evaluating Clinical Outcomes of Radium-223 Treatment in a Non-study Population. Int. J. Cancer 2019:ijc.32851.

40. Smith M, Parker C, Saad F et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019; 20(3):408–419.

41. Morris MJ, Loriot Y, Sweeney CJ et al. Radium-223 in combination with docetaxel in patients with castration-resistant prostate cancer and bone metastases: a phase 1 dose escalation/randomised phase 2a trial. Eur. J. Cancer 2019; 114:107–116.

42. Nilsson S, Sartor AO, Bruland OS et al. Pain analysis from the phase III randomized ALSYMPCA study with radium-223 dichloride (Ra-223) in patients with castration-resistant prostate cancer (CRPC) with bone metastases


ENZALUTAMIDE