OPTIMIZING THE SEQUENCE OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER TREATMENT OPTIONS

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“A mind all logic is like a knife all blade. It makes the hand bleed that uses it.”

- Rabindranath Tagore

For my grandparents: Soekhradj, Bhoedanie, Jan and Silvie

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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]

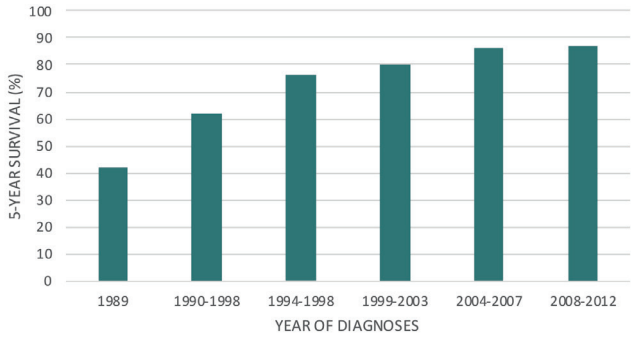

Figure 1. Relative five-years survival of patients with prostate cancer in the Netherlands from 1989 – 2012

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.

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ENZALUTAMIDE

Chapter 2

Clinical activity and Tolerability of Enzalutamide (MDV3100) in Metastatic Castration Resistant Prostate Cancer Patients progressing after Docetaxel and Abiraterone Treatment

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ABSTRACT

Background

Both Enzalutamide (Enz) and Abiraterone acetate (AA) are hormonal treatments, which have shown survival advantage in patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with docetaxel (Doc). Recently limited activity of AA after Enz treatment was shown, however, there are no clinical data on the activity of Enz in patients progressing after AA and Doc treatment.

Methods:

The efficacy and tolerability of Enz in men with progressive metastatic castrate resistant prostate cancer previously treated with Doc and AA was investigated. Toxicity and progression free survival (PFS), time to PSA progression (TTPP) and overall survival (OS), were retrospectively evaluated.

Results

Sixty-one patients were included in the analysis. The median age was 69 years (IQR 64-74), 57 patients (93%) had an ECOG performance status 0-2, 48 patients (79%) had bone metastases, 33 patients (54%) had lymph-node metastases and 13 (21%) visceral metastases. Median duration of Enz treatment was 14.9 weeks (IQR 11.1 – 20.0) and 13 patients (21%) had a maximum PSA decline of ≥50%. The median PFS was 12.0 weeks (95% CI 11.1 – 16.0), the median TTPP 17.4 weeks (95% CI: >16.0) and median OS 31.6 weeks (95% CI: > 28.7). Enz was well tolerated, with fatigue and muscoskeletal pain as the most frequent ≥grade 2 adverse events. PSA response on Doc and AA did not predict for PSA response on Enz.

Conclusions

Enz has modest clinical activity in mCRPC patients previously treated with Doc and AA.

INTRODUCTION

Prostate cancer is the most prevalent cancer among men in the western world and the second leading cause of male cancer death [1, 2]. After an initial response to medical or surgical castration, the disease will progress into castration resistant prostate cancer (CRPC)[3]. CRPC, however, is still driven by androgen-receptor signaling, requiring lower than castration testosterone levels as a result of androgen receptor modulations [4-6]. Therefore, new drugs have been developed that more effectively inhibit androgen receptor signaling. Enzalutamide (Enz, MDV3100, Xtandi®), a novel nonsteroidal androgen-receptor (AR) signaling inhibitor, has shown survival advantage in metastasized CRPC (mCRPC) patients previously treated with Docetaxel (Doc) in combination with prednisone [7]. However, earlier, Abiraterone Acetate (AA, Zytiga®), an inhibitor of testosterone synthesis, has shown a comparable survival advantage in combination with prednisone in the same patient population [8]. It is suggested that Enz and AA actions are non-overlapping and therefore potentially synergistic [9]. However, only limited activity of AA was described in two cohort studies of patients previously treated with Enz [10, 11]. Reversely, there is no data on the antitumor activity of Enz following AA treatment in mCRPC patients. Knowledge of the clinical cross-resistance in both sequences of these anti-hormonal treatments is of value for future trial design.

Pending final registration of Enz in The Netherlands, Astellas Pharma Europe Ltd. established an Expanded Access Program (EAP) for patients with progressive disease and no satisfactory alternative treatments available. Therefore, Enz treatment was positioned after Doc and AA treatment. Here we report tolerability and efficacy of Enz in a cohort of mCRPC patients previously treated with Doc and AA.

PATIENTS AND METHODS

Patients and treatment

In this multicenter, observational study, we included patients with progressive mCRPC enrolled in the Dutch EAP for ENZ, treated earlier with Doc and AA. Patients all progressed on or did not tolerate AA treatment and consented to join the program. Inclusion criteria for the EAP included: effective surgical or medical castration, progressive disease, ECOG performance 0-2 and no satisfactory alternative treatment at the physician's discretion. The exclusion criteria of the EAP included: earlier treatment with- or participation in a clinical trial with ENZ, severe concurrent disease, inadequate bone marrow, liver, vascular, hart and kidney functions and prior chemotherapy, biologic therapy or radiation therapy within 3 weeks prior to treatment and radionucleotides treatment 8 weeks prior to treatment.

Enz was given as a once daily dose of 160 mg. All patients received at least one dose of Enz. Treatment was continued until clinical deterioration, disease progression and/or unacceptable adverse effects, all to physician discretion, or death.

Study procedures and data collection

Patient baseline characteristics were documented including age, ECOG performance status, disease characteristics (including Gleason score, involved metastatic sites, number of metastatic sites), blood test results (including hemoglobin concentration, liver chemistry tests, creatinine, testosterone and PSA), clinical signs of disease progression, previous anti-hormonal and chemotherapy treatments (including duration of Doc and AA treatment, best PSA response to Doc and AA treatment and reason for AA discontinuation) and use of concomitant medication with known interaction with Enz (macrolide antibiotics, benzodiazepines, immune modulators, anti-epileptics, coumarins, colchicine, digoxin).

Clinical and biochemical activity and toxicity, was assessed at Enz treatment initiation and every month according to the EAP protocol, including ECOG performance and toxicity recording using Common Toxicity Criteria (CTC v 4.0). Imaging studies were performed at the discretion of the physician. Prostate cancer progression and survival were followed up until April 2013.

PSA response was evaluated using the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendations [12]. Progression Free Survival (PFS) was defined as the time of treatment start to the first date of confirmed progression or the date of last follow-up. Progression was defined as PSA progression and/or radiographic progression and/or clinical progression. As recommended by the PCWG2, PSA response was defined as ≥ 50% decline from baseline and PSA progression as a 25% increase and a minimum of 2 ng/ml, confirmed with a second PSA reading a minimum of 3 weeks later. Where no decline from baseline was documented, PSA progression was defined as a 25% increase from baseline value along an increase in absolute value of at least 2 ng/ml after 12 weeks of treatment. PSA declines of < 30%, <50% and <90% from baseline after 12 weeks with or without conformation were also evaluated. Objective responses were measured according to RECIST [13]. Bone progression based on bone scans was assessed according to the PCWG2 criteria. Overall survival (OS) was calculated from the date of start of Enz treatment to the date of death or date of last follow-up. Informed consent was obtained from all patients prior to enrolment into the EAP and patient's outcomes were analyzed with ethics committee approval.

Statistical analysis

In line with PCWG2 criteria, waterfall plots with maximum PSA decline from baseline and PSA after 12 weeks of treatment were constructed. Survival and progression were evaluated using Kaplan-Meier (KM) estimates. Patients who did not achieve a 50% fall in PSA on Doc or AA were designated Doc or AA non-sensitive, respectively, and patients with a ≥50% decline in PSA on Doc or AA treatment were designated Doc or AA-sensitive, respectively. Best PSA responses on Enz were compared between subpopulations of patients according to Doc and AA sensitivities using a two sample t-test. Predictive power of best Doc and AA response and their interaction for maximum PSA decline on Enzalutamide was evaluated by means of linear regression using a log link. Statistical analyses were conducted using Statistical Analysis System (SAS) statistical software and R.[14]

RESULTS

Patients

Starting in June 2012, a EAP for Enz was established in the Netherlands. At the time of closing of the program in March 2013, 61 patients in 9 hospitals, previously treated with both Doc and AA, were evaluable for treatment outcome and tolerability. Patient characteristics at the time of Enz treatment initiation are summarized in Table 1. The median age before starting Enz treatment was 69 years (IQR 64 – 74), ECOG performance was 0-1 in 57% and 2 in 36% of patients, 79% of patients had bone metastases and 54% lymph node metastases and the majority (93%) had more than one metastatic site. With respect to laboratory results, the median hemoglobin concentration was 11.0 g/dL (IQR 9.9 – 12.5), Alkaline Phosphatase (ALP) 191 U/L (IQR 100 – 288) and Lactate Dehydrogenase (LDH) 241 U/L (IQR 191 – 385) at the time of Enz treatment initiation. Disease progression at the time of Enz treatment initiation presented in 95% as a PSA progression and in 87% of patients as clinical progression and could be confirmed in 57% by a bone scan and in 30% of patients as progression of measurable lesions.

Ninety percent of patients had one course of Doc treatment, while 10% had two or more courses. The median number of cycles of Doc in all courses combined was 8 (IQR 6 – 10). Thirty % of patients had at least one course of Cabazitaxel in combination with prednisone. The median duration of AA treatment was 26 weeks (IQR 13 – 37) and the reason for AA discontinuation was disease progression after initial response in 54% and no initial activity in 38% of patients. All patients were treated with an LHRH antagonist/agonist or had an orchidectomy, while 18% used steroid drugs as mono therapy at the time of Enz treatment initiation. Twenty % of patients used drugs with a known interaction with Enz.

Table 1. Patient and treatment characteristics

Patient demographics	**Number of patients (%), median values (IQR)**	
Age	*Median*	*IQR*
	69	64-74
ECOG performance status	*n*	%
0-1	35	(57%)
2	22	(36%)
3	4	(7%)
Gleason score		
≤6	10	(17%)
7	14	(23%)
≥8	26	(43%)
Not available	11	(18%)
Metastatic sites		
Bone	48	(79%)
Lymph nodes	33	(54%)
Visceral metastases	13	(21%)
Number of metastatic sites		
0	0	(0%)
1	1	(2%)
≥2	57	(93%)
Unknown	3	(5%)
Laboratory	*Median*	*IQR*
PSA (μg/L)	267	(79 – 687)
Haemoglobin (g/dL)	11.0	(9.9 – 12.5)
ALP (U/L)	191	(100 – 288)
LDH (U/L)	241	(191 – 385)
ALAT (U/L)	18	(14 – 26)
Creatinine (μmol/L)	74	(64 – 87)
Testosterone (nmol/L)	<0.5	(<0.2 – <0.7)
Disease progression	*n*	%
PSA increase	58	(95%)
Progression on bone scan	35	(57%)
Progression: Clinical progression	53	(87%)
Progression: Measurable lesions	18	(30%)
Docetaxel treatment	*Median*	*IQR*
Number of cycles (all courses)	8	(6 – 10)
Number of courses	*n*	%
One course	55	(90%)
Two courses	5	(8%)
Three courses	1	(2%)

Previous chemotherapy (other than docetaxel)		
Mitoxantrone	2	(3%)
Cabazitaxel	18	(30%)
Abiraterone treatment	*Median*	*IQR*
Duration of treatment (weeks)	26	(13 – 37)
Reason for discontinuation:	*n*	%
Intolerance	4	(7%)
Progression	33	(54%)
No activity	23	(38%)
Unknown	1	(2%)
Antihormonal treatment while on Enzalutamide		
LHRH antagonist/agonist	59	(97%)
Orchidectomy	2	(3%)
Dexamethasone/prednisone mono therapy	11	(18%)
Previous antihormonal treatment (other than Abiraterone)		
Ketoconazol	0	(0%)
Diethylstilbestrol	0	(0%)
Concomitant medication with known interaction with Enzalutamide	13	(22%)

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen; ALP: serum Alkaline Phosphatase; LDH: Lactate dehydrogenase; ALAT, Alanine-aminotransferase

Antitumor effects

Patients started Enz treatment a median of 60.7 weeks (IQR 36.6 – 78.2) after Doc discontinuation and 8.9 weeks (IQR 4.3 – 28.9) weeks after AA discontinuation (Table 2). The median duration of Enz treatment was 14.9 weeks (IQR 11.1 – 20.0) and median follow-up was 16.3 weeks (IQR 13.7 – 21.1). A ≥ 30% maximum PSA decline was observed in 28 patients (46%), a ≥50% PSA decline in 13 patients (21%) and a ≥90% PSA decline in 2 patients (3%)(Figure 1). The maximum PSA decline was reached after a median of 5.0 weeks (IQR 4.0 – 8.6). Eighteen patients (30%) had no PSA response at any time. For each patient we collected the PSA measurement at the time point closest to 12 weeks after Enz treatment initiation (median 12 weeks, IQR 10.7 – 13.6). A ≥ 30% PSA decline was observed in 17 patients (28%), a ≥50% PSA decline in 9 patients (15%) and a ≥90% PSA decline in 1 patient (2%). Reasons for Enz treatment discontinuation included no initial activity in 16 patients (26%), progressive disease in 22 patients (36%) and death in 2 patients (3%). One patient died of a hemorrhagic stroke and one patient died of disease progression while on Enz reatment. One (2%) patient was intolerant for Enz and experienced severe nausea and fatigue (Table 2). At the time of analysis, 19 patients (31%) were still on Enz treatment. PFS is depicted in Figure 2. The KM estimate for the median PFS is 12.0 weeks (95% C.I.:11.1 – 16.0) (Table 2), the estimated median Time To PSA Progression (TTPP) 17.4 weeks (95% confidence > 16.0)(Table 2) and median OS 31.6 weeks (95% confidence > 28.7)(Table 2; Figure 2). Of the eleven (18%) patients on steroid therapy at Enz initiation, 4 (36%) had a maximum PSA response

≥30%, 2 (18%) a maximum PSA response ≥50% and 1 (9%) patient had a PSA response ≥90%. Median time to maximum PSA response was 6.9 weeks (IQR 3.6– 10.5) in these patients.

Tolerability

No unexpected toxicity of Enz was reported. Of the 382 Adverse Events (AE) collected, the majority (247; 65%) was grade 1 (Table 2). Grade 2 (101; 26%) and grade 3 (34; 9%) AEs were less frequent. Hot flushes were all grade 1. Fatigue was the most frequent grade 2 and 3 AE, 60 (59%) and 16 (47%), followed by musculoskeletal pain 27 (27%) and 7 (20%), respectively.

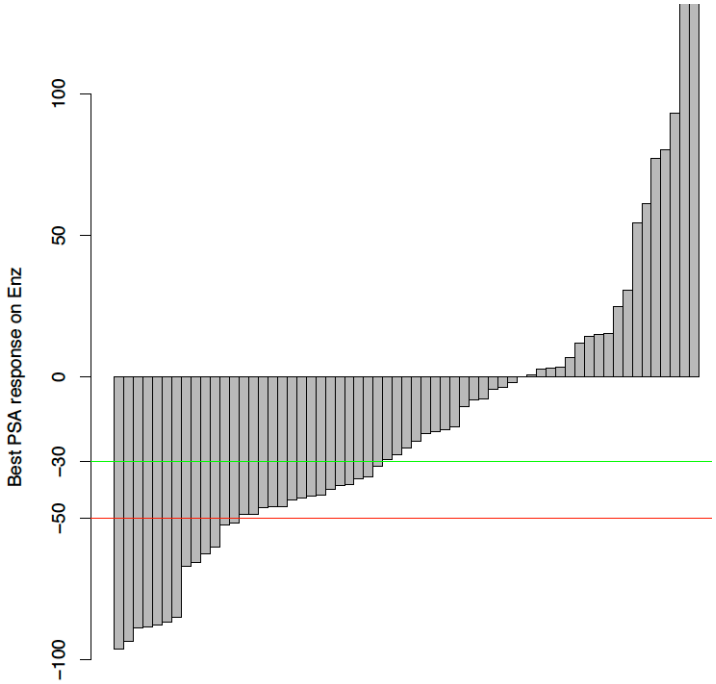

Figure 1. The best prostate-specific antigen (PSA) responses to Enzalutamide (Enz) are illustrated.

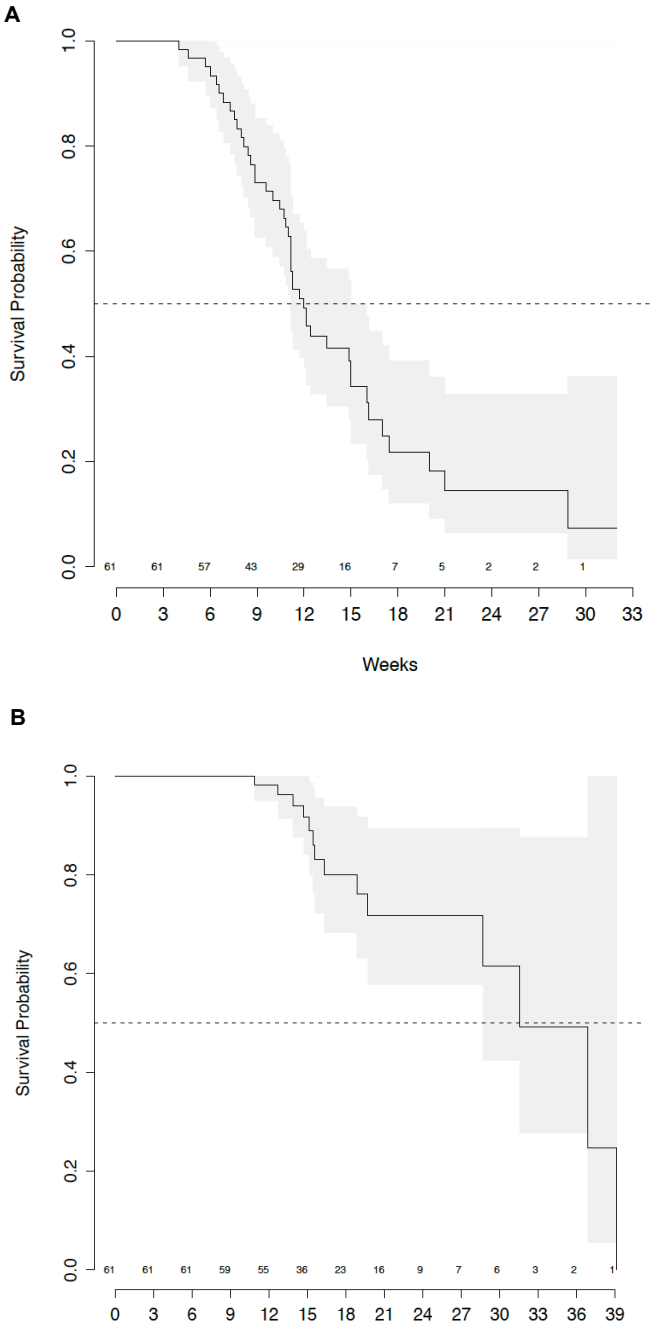

Figure 2. (Top) Progression-free survival and (Bottom) overall survival are illustrated.

Table 2. Outcomes of Enzalutamide Treatment After Abiraterone Treatment

Outcome Variable	Median [IQR] or No. of Patients (%)
Time after docetaxel discontinuation, wk	60.7 [36.6-78.2]
Time after Abiraterone discontinuation, wk	8.9 [4.3-28.9]
Duration of Enzalutamide treatment, wk	14.9 [11.1-20.0]
Follow-up, wk	16.3 [13.7-21.1
Time to maximum PSA decline, wk	5.0 [4.0-8.6]
PSA decline	
>30%	28 (46)
>50%	13 (21)
>90%	2 (3)
Reason for Enzalutamide discontinuation	
No initial activity	16 (26)
Progressive disease	22 (36)
Death	2 (3)
Intolerance	1 (2)
Reason unknown	1 (2)
Treatment ongoing on date of data collection	19 (31)
Survival	
PFS: Median/95% CI, wk	12.0/11.1-16.0
Time to PSA progression: Median/95% CI, wk	17.4/>16.0
OS: Median/95% CI, wk	31.6/>28.7
Adverse events	
Grade 1	247
Grade 2	101
Grade 3	34

Abbreviations Wk, weeks; PSA, prostate specific antigen; CI, Confidence interval; PFS, progression-free survival; OS Overall survival

Relation between Doc and AA response and response to Enz

Table 3 summarizes characteristics of patients that did not reach a ≥50% PSA response on Doc or AA treatment and were considered Doc or AA non-sensitive, respectively, and patients that reached a ≥50% PSA response on these treatments and were considered Doc or AA sensitive, respectively, and the entire population. The 24 patients considered Doc non-sensitive, received less cycles of Doc and had a lower median best PSA response to Doc treatment, compared to the 29 patients who were considered Doc sensitive and the entire population (6, 10, 8 cycles and -20.1%, -78.3%, -59.7%, respectively)(Table 3). Duration of AA treatment was not different between Doc non-sensitive and sensitive patients and the entire population (26.1, 21.9 and 25,9

weeks, respectively). Although not statistically significant, the median maximum response on AA treatment was better in the Doc non-sensitive then in the Doc sensitive population (-27.7% and -9.2%, respectively). Five (21%) Doc non-sensitive and 5 (18%) Doc sensitive patients had a ≥50% PSA response on AA treatment. However, there was no difference in maximum PSA response to Enz treatment (median -28.4%, -22.8% and -25.2%, respectively)(Table 3) and duration of Enz treatment (median 14.6, 14.9 and 14.9 weeks, respectively) between Doc non-sensitive and sensitive patients and the entire population. The 43 patients who were considered AA non-sensitive received AA treatment for a shorter period than patients considered AA sensitive (21.6 and 39.1 weeks, respectively). There was no difference in median maximum PSA response to Enz treatment (-31% and -20%, respectively)(Table 3) and duration of Enz treatment (median 15 and 17.4 weeks, respectively) between AA non-sensitive and sensitive patients. Best response on AA and Doc were not found to be predictive for response on Enz.

DISCUSSION

The response rates on Enz in men with mCRPC previously treated with Doc and AA and survival outcomes suggest a modest activity in this cohort of patients. Fourty-six % of patients had a PSA decline ≥30% on Enz, however, only 21% had a PSA decline ≥50%. These PSA response rates are comparable to PSA response rates reported in a smaller cohort of 35 mCRPC patients treated with Enz after previous AA treatment [15] Median TTPP on Enz, as estimated by the KM-method, was 17.4 weeks and median OS 31.6 weeks. These outcomes compare unfavorably with the outcomes of the AFFIRM study of Enz in the post-docetaxel setting, where 54% of patients were reported to have a ≥50% PSA response, median TTPP was 36.1 weeks and median OS 80 weeks. However, comparison is hampered by the more advanced stage of the disease of patients in the current analysis than patients in the AFFIRM study, which is reflected by a poorer performance score, lower hemoglobin concentration and a higher PSA at baseline [7]. A post-hoc analysis of the AFFIRM data, suggested a worse outcome of patients using corticosteroid while on Enz treatment [16]. Eighteen % of patients in the present cohort were using corticosteroids, however, maximum PSA response and time to maximum PSA response seemed not different from the total population. Enz treatment was well tolerated in these extensively pretreated patients with advanced disease and no unexpected AEs were reported. As in the AFFIRM study fatigue was the most frequent AE and hot flushes were all grade 1 [7]. However, in contrast, diarrhea was a non-frequent AE in the current study and musculoskeletal pain was more common than in the AFFIRM study.

Recently, Loriot *et al* and Noonan *et al* reported modest response rates and survival outcomes of AA treatment in cohorts of 38 and 30 patients, respectively, who progressed on Enz treatment [10, 11]. In these studies PSA response rates of ≥50% were reported in 8% and 4% of patients,

Table 3. Response on AA and Enz treatment in relation to Doc sensitivity and response on Enz treatment in relation to AA sensitivity

Doc treatment [a]	**Median (IQR)**		
	Doc non-sensitive (n=24)	**Doc sensitive (n= 29)**	**Entire population (n=61)**
Number of docetaxel cycles.[b]	6 (4 - 7.25)	10 (8-10)	8 (6 – 10)
Maximum PSA response (%) on Doc treatment. [c]	-20.1% (-43.3% – -5.1%)	-78.3% (-94.7% – -70.2%)	-59.7% (-78.9% – -39.8%)
Duration (weeks) of AA treatment.	26.1 (12.6 – 38.6)	21.9 (13.1 – 34.6)	25.9 (13.1 – 37.3)
Maximum PSA response (%) on AA treatment. [c]	-27.7% (-43% – 0.0%)	-9.2% (-38.9% – 0.0%)	-22.3% (-43.4% – 0.0%)
Duration (weeks) of Enz treatment.	14.6 (11.6 – 22)	14.9 (10.9 – 17.4)	14.9 (11.1 – 20)
Maximum PSA response (%) on Enz treatment. [c]	-28.4% (-44.0% – +1.1%)	-22.8% (-62.7% – +7.0%)	-25.2% (-46.4% – +3.0%)
AA treatment [a]	**Median (IQR)**		
	AA non-sensitive (n=43)	**AA sensitive (n= 13)**	**Entire population (n=61)**
Duration (weeks) of AA treatment	21.6 (13.1 – 30.4)	39.1 (30.4 – 43.7)	25.9 (13.1 – 37.3)
Maximum PSA response (%) on AA treatment. [c]	0.0% -28.1% - 0.0%	-87.4 (-98.6% – -80.0%)	-22.3% (-43% – 0.0%)
Duration (weeks) of Enz treatment.	15 (11.2 – 20.5)	17.4 (12.7 – 21.3)	14.9 (11.1 – 20.0)
Maximum PSA response (%) to Enz treatment. [c]	-31% (-56% – +5.1%)	-20% (-38.3 – -7.7)	-25.2% (-46.4% – +3.0%)

Abbreviations: AA, Abiraterone acetate in combination with prednisone; Doc, docetaxel in combination with prednisone; Enz, Enzalutamide; IQR, interquartile range; PSA, prostate-specific antigen.

[a] Patients were stratified according to their maximum PSA response, <50% or ≥50%, on Doc or AA treatment. The Doc response was not known in 8 patients, and the AA response was not known in 5 patients.

[b] This included only the first course of Doc treatment.

[c] The maximum PSA response is indicated as the percentage of the baseline value. A negative value reflects a PSA decrease.Doc and AA non-sensitive is defined as a maximum PSA response <50% and Doc and AA sensitive as a maximum PSA response ≥50%.

respectively, which is lower than the 21% of patients in the current cohort. However, the median PFS reported by Loriot *et al* and Noonan *et al* were in the same range as the median PFS of the current cohort, 11.7 weeks, 15.4 weeks and 12.0 weeks, respectively, as were the reported median OS of the three studies, 31.3 weeks, 50.1 weeks and 31.6 weeks, respectively.

Enz inhibits androgen-receptor signaling by competitively inhibiting the binding of androgens, inhibiting the translocation of ligand bound receptor to the nucleus and binding to its response elements in the DNA [17]. In contrast, AA inhibits CYP17A, which is crucial for testosterone synthesis, with potent suppression of extragonadal androgen production as a result [18]. Although by different means, both drugs target persistent AR signaling. Despite the differences in patient populations between the AFFIRM study and the studies into the sequence of AA and Enz, data from these studies suggest the possibility of cross-resistance. However, in the current study PSA response on AA treatment did not predict for PSA response on Enz treatment, which is in line with the non-statistically significant relation between PSA response on Enz and PSA response on AA in the study of Loriot *et al* [10].

There is limited data on the mechanism of resistance against AA and Enz. Since AA and Enz both target AR signaling, the mechanism of cross-resistance might be at the AR level, including AR modifications, complex interactions of AR with coactivators or correpressors and mutual regulation of miRNA and AR [19]. In xenografts of human mCRPC treated with AA, induction of AR expression and AR splice variants was demonstrated [20, 21], while in another study AR splice variants were identified as key mediators of persistent AR signaling and resistance to Enz [22]. Increased steroidogenesis activation might also mediate cross-resistance between AA and Enz [19]. Testosterone levels in blood and bone marrow of patients treated with AA were undetectable on treatment discontinuation [23], however, Enz treatment increased the testosterone levels in bone marrow of patients and decreased nuclear AR expression [24]. In a mouse model of human prostate cancer, the oncogenic AKt pathway was activated when the AR was inhibited [25]. This reciprocal activation of oncogenic pathways upon AR inhibition might represent a mechanism of resistance to AR receptor antagonists [19].

Combination treatment of Enz and AA might reverse some mechanisms of drug resistance. A study in human prostate cancer cell lines provided evidence that the glucocorticoid drugs administered with AA, to prevent side effects, and mineralocorticoid receptor antagonists could activate mutant AR, which was inhibited by Enz [26]. These findings provide a rationale for combination treatment. Currently a Phase II trial into the safety and tolerability of Enz in combination with AA is enrolling (NCT01650194).

In conclusion, patients in the current study who previously progressed on AA had a modest PSA response rate and limited survival on subsequent Enz treatment. PSA response on AA

treatment did not seem to predict for Enz treatment outcome. Although a higher PSA response rate was found in patients treated with Enz after progression on AA treatment, PFS and OS were in the same range as those described in two cohorts of men with mCRPC treated with AA after progression on Enz. Data from these three studies suggest limited activity and no preference for either sequence of treatments. However, recommendation on the sequencing of Enz and AA in the post-docetaxel setting cannot be concluded, since these data are only hypothesis generating. Further studies are needed to establish the sequence of treatments with these new drugs.

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Drs. van Oort, van den Berg, and Bergman report personal fees from Astellas Pharma and Jansen Pharma outside the submitted work. Drs. Hamberg and de Jong report personal fees from Jansen Pharma outside the submitted work. Dr. van den Eertwegh reports personal fees from Astellas Pharma outside the submitted work.

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ENZALUTAMIDE

Chapter 3

Prognostic Parameters for Response to Enzalutamide after Docetaxel and Abiraterone Treatment in Metastatic Castration-Resistant Prostate Cancer Patients; a Possible Time Relation

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ABSTRACT

Background

Abiraterone Acetate (AA) and Enzalutamide (Enz) are effective hormonal treatments in mCRPC patients. Retrospective studies suggested clinical cross-resistance between Enz and AA. However, 12.8-39.1% of patients previously treated with docetaxel (Doc) and AA do respond to Enz. These responders have not been characterized.

Methods

102 Enz treated mCRPC patients after AA and Doc treatment were included in this study. Differences in patient characteristics and previous treatment outcomes between PSA responders and non-responders on Enz were evaluated.

Results

Median Progression-Free Survival was 12.2 weeks (95%CI 11.7-14.3) and Overall Survival 43.5 weeks (95%CI 37.4-61.2). There were 26 (25%) Enz-responders and 76 (75%) non-responders. Significant higher percentages of Gleason scores ≥8 and PSA doubling times (PSA-DT) <3 months were found in Enz responders than in non-responders. The interval between end of AA and start of Enz treatment (IAE) for responders was 24.6 weeks (IQR 4.0-48.1) and 8.9 weeks for non-responders (IQR 3.7-25.9) ($p=0.08$). In an IAE <40 days subgroup (34 patients), Enz responses were related to AA non-responsiveness, while univariate and logistic regression analysis of baseline criteria of a subgroup of patients with an IAE≥40 (68 patients) revealed significant differences in baseline PSA levels, PSA-DT <3 months, Gleason scores ≥8 and IAE's between Enz responders and non-responders.

Conclusions

PSA response to Enz after previous AA and Doc treatment was associated with a longer IAE, a higher Gleason score and a PSA-DT <3 months. Identification of these patients might be of value for sequencing of treatment options.

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) is a prevalent and incurable disease, associated with high morbidity and mortality[1]. In recent years multiple drugs have become available that showed an increased quality of life and overall survival (OS) of mCRPC patients. Abiraterone acetate in combination with prednisone (AA) and Enzalutamide (Enz) both target the androgen receptor and both have proven efficacy in patients with mCRPC[2–5]. Enz inhibits Androgen-Receptor (AR) signaling through inhibition of androgen binding to the AR, reducing the efficiency of the AR complex nuclear translocation, preventing the AR complex from binding to response elements in the DNA and recruitment of its coactivators[3], while AA inhibits the synthesis of testosterone[6]. Several retrospective studies evaluated the efficacy of Enz in mCRPC patients previously treated with Docetaxel (Doc) and AA. The rate of PSA responses (≥50% PSA decline) varied between 12.8% and 39.1%[7–13], OS and Progression Free Survival (PFS) varied between 4.8 – 8.5 months[7, 9, 11] and between 2.9 – 4.0 months[7–9, 12], respectively. The reported PSA response rates, OS and PFS of Enz after Doc and AA treatment were all lower than the 54%, 18.4 months and 8.3 months, respectively, reported in mCRPC patients previously treated with Doc only[3]. These results suggest a significant clinical cross-resistance, however, a proportion of patients treated with Enz previously treated with Doc and AA did have a PSA response. Here we report the characteristics of these patients. This information might be of value for optimal sequencing of treatment options for mCRPC patients.

PATIENTS AND METHODS

Patients, study procedures and data collection

Recently, we reported on the efficacy of Enz in 61 mCRPC patients previously treated with Doc and AA in a retrospective multicenter study[7]. These patients were included in the Dutch Expanded Access Program (EAP) for Enz. For the current analysis, all 36 Dutch Uro-Oncology Study group (DUOS) hospitals were approached for updated records of patients included in the EAP and for new patients treated with the drug sequence of interest. Data from 9 hospitals on all 61 patients in the EAP could be updated and 14 hospitals indicated to hold records of 41 additional patients treated with Enz after previous Doc and AA not in the EAP.

Institutional Review Board (IRB) approval for retrospective collection and analysis of patient data was obtained from the Netherlands Cancer Institute, which covered all participating hospitals. Personal data were encoded and no informed consent was required.

Prior to Enz treatment (160mg orally daily) baseline characteristics were documented. Patients were assessed every 4-6 weeks during Enz treatment. Radiologic assessment was at the

discretion of the physician. Progression Free Survival and Overall Survival were followed up until May 2014 and assessed according to PCWG2 criteria[14]. PSA response was defined as a PSA decline of ≥50% from baseline, PSA doubling time (PSA-DT) was calculated for patients with at least three PSA measurements within the three months prior to Enz treatment according to PCWG2 criteria[14]. Duration of Enz response (DER) was defined as time from first PSA response (≥50% PSA decline) on Enz until PSA progression as defined by PCWG2[14]. Only patients who had an PSA response were included into the calculation. Patients with no PSA progression were censored at last follow-up. Radiologic responses were assessed according to RECIST[15] and PCWG2 criteria[14]. Interval between AA and Enz treatment (IAE), Interval between Doc and Enz (IDE) and Interval between last treatment and Enz (ILTE) were defined as time between last dose of AA, last dose of Doc treatment and end of last systemic therapy and start of Enz, respectively. Duration of Enz treatment (Enzdur) was defined as start of Enz through last day of treatment.

Patients were designated Doc or AA sensitive if they had a PSA decline of at least 50%. Those patients who did not achieve a 50% PSA decline were designated Doc or AA non-sensitive.

Statistical analysis

Follow-up time, OS , PFS and DER were evaluated using Kaplan-Meier (KM) estimates. Univariate comparisons of patient and treatment characteristics between Enz-responders and non-responders were assessed using a t-test or Wilcoxon-Mann-Witney test for continuous variables and by Fisher's exact test for categorical variables. Effect of IAE on response was evaluated graphically, as well by means of logistic regression. Effects of other patient and treatment characteristics on Enz-response were subsequently evaluated in bivariate logistic regressions using IAE as a covariate. The univariate comparisons above were repeated for the subgroup of patients with IAE$<$40 and the IAE≥40. For response to AA we tested for a statistical interaction with IAE as a predictor of Enz-response – both in the continuous setting (logistic regression) as in the dichotomized setting (using 40 days as cut off point). Aike's Information Criterion was used to decide whether or not to include a quadratic term (of the IAE) in the logistic regressions. Based on this it was decided to do so only for the subpopulation of patients with IAE≥40. All analyses were repeated for the subpopulation of patients receiving AA for at least 12 weeks. All p-values were two-sided and considered significant if $p<0.05$. No correction was made for multiple significance testing. Statistical Analysis System (SAS) statistical software and R were used for statistical analysis[16].

RESULTS

Patients

A total of 102 patients were included from 14 medical centers located in the Netherlands. All patients treated with Enz after AA and Doc in the participating centers have been included. Patient and tumor specific characteristics and previous treatments are listed in table 1 and supplementary table 1. For 6 patients (6%) the Enz dose was reduced as a result of adverse events (data not shown). Ninety patients (88%) had one course of Doc treatment prior to Enz treatment, while 12% had more than one course. Sixty-four % of the patients were considered Doc sensitive (≥50% PSA decline). The median AA treatment duration was 26 weeks (IQR 14 – 38). Twenty-eight % of the patients were considered AA-sensitive (≥50% PSA decline).

PSA response on Enz treatment and survival

Enz treatment was initiated a median of 60.6 weeks (IQR 40.9 – 87.9) and 9.7 weeks (IQR 3.7 – 31.4) after Doc (IDE) and AA discontinuation (IAE), respectively (Table 1). Twenty-six patients (25%) had a PSA response on Enz treatment (Table 1). The Kaplan-Meier estimate for the median Progression free survival (PFS) was 12.2 weeks (95% C.I.:11.7 – 14.3), the median overall survival (OS) was 43.5 weeks (95% CI 37.4 – 61.2) (Table 1) and median DER was 26.0 weeks (95% C.I.: >10.4) (Table 2). Two patients were excluded from the OS and PFS analysis due to lack of follow-up. Enz response, PFS and OS did not change when analysis was limited to patients treated with AA for a minimum of 12 weeks (86 patients), as advised by the PCWG2[14].

Clinical variables associated with PSA response

In Table 2 the characteristics of 26 Enz-responders and 76 non-responders are compared. Enz-responders had a significant longer median OS and PFS compared to non-responders (64.3 and 37.4 weeks; p=0.014 and 22.2 and 11.7 weeks; p=<0.0001, respectively). Eighty-six percent of the responders had a Gleason score ≥8 compared to 46% of the non-responders (p=0.006). Enz-responders had a significantly shorter PSA-DT (<3 months) compared to non-responders (44% and 16%, respectively; *p*=0.037).

The median IAE in the Enz responders and non-responders group were 24.6 weeks (IQR 4.0 - 48.1) and 8.9 weeks (IQR 3.7 – 25.9), respectively (p=0.08). Although the IAE did not differ significantly between responders and non-responders, the shape of the graph representing the relation between PSA response and IAE prompted more detailed investigation of this relation (Figure 1).

Table 1. Patient characteristics and treatment outcomes

Survival	*Median*	*95% C.I.*
Median PFS (weeks)	12.2	(11.7 – 14.3)
Median OS (weeks)	43.5	(37.4 – 61.2)
ECOG performance status	*n*	
0-1	61	(60%)
2	31	(30%)
3	4	(4%)
Not available	6	(6%)
Gleason score	*n*	%
≤6	15	(17%)
7	24	(27%)
≥8	49	(56%)
Not available	11	(18%)
Metastatic sites	*n*	
Bone metastases/ bone only	80 / 22	(78%) / (22%)
Lymph node involvement/ lymph node only	62 / 4	(61%) / (4%)
Bone and lymph nodes only	56	(55%)
Visceral	20	(20%)
PSA doubling time (n=66)	*n*	%
< 3 months	15	(23%)
≥ 3 months	51	(77%)
Disease progression	*n*	
PSA increase	97	(95%)
Progression on bone scan	60	(59%)
Progression: Clinical progression	90	(88%)
Progression: Measurable lesions	32	(31%)
Docetaxel treatment	*Median*	*IQR*
Number of cycles (all courses)	9	(6 – 10)
Cabazitaxel treatment	*n*	
Patients treated	36	(35%)
Number of cycles (all courses)	6	(4 – 8)
Abiraterone treatment	*Median*	*IQR*
Duration of treatment (weeks)	26	(14.3 – 38.1)
IDE (Weeks)	60.6	(40.9 – 87.9)
IAE (Weeks)	9.7	(3.7 – 31.4)
Enzdur (weeks)	14.3	(9.7 – 20.6)
Follow-up (weeks)	15.0	(11.7 – 15.7)

Time to maximum PSA decline (weeks)	6.5	(4.0 – 11.9)
Maximum PSA decline	*n*	
≥30%	44	(43%)
≥50%	26	(25%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PSA, prostate-specific antigen. C.I.: Confidence interval; IDE, time interval between discontinuation of Doc and start of Enz; IAE, time interval between discontinuation of AA and start of Enz; Enzdur, duration of Enzalutamide treatment; PFS, Progression free survival; OS, Overall survival

PSA response on Enz treatment as a function of time between AA and Enz treatment

Two distinct peaks in percentage of Enz-responders can be identified: a smaller group within an IAE<40 days (IAE<40) and a larger group with a linear relation between Enz response and IAE (IAE≥40) (Figure 1). In Figure 2 Swimmer plots are constructed of patients with an IAE≥40 (Upper panel) and IAE<40 (lower panel). Swimmer plots represent survival from first treatment of castration resistant disease and response on Enzalutamide in relation to response on other life-prolonging treatments on an individual basis.

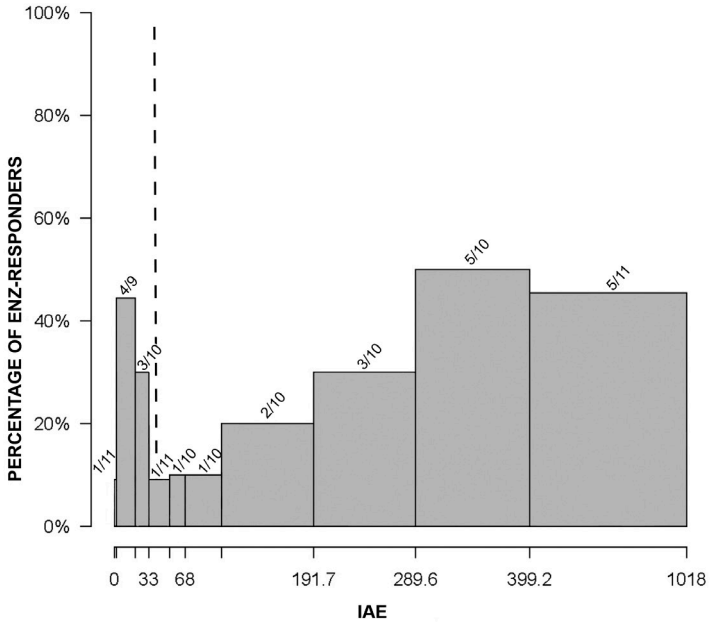

Figure 1. Percentage of Enz responders as a function of the interval between end of AA treatment and start of Enz treatment (IAE). The heights of the boxes represent the percentage of Enz-responders in that interval. Each box contains roughly 10% of all patients. The width of the box corresponds with the IAE. Two peaks of Enz-responders can be distinguished (separated by a vertical dotted line at 40 days).

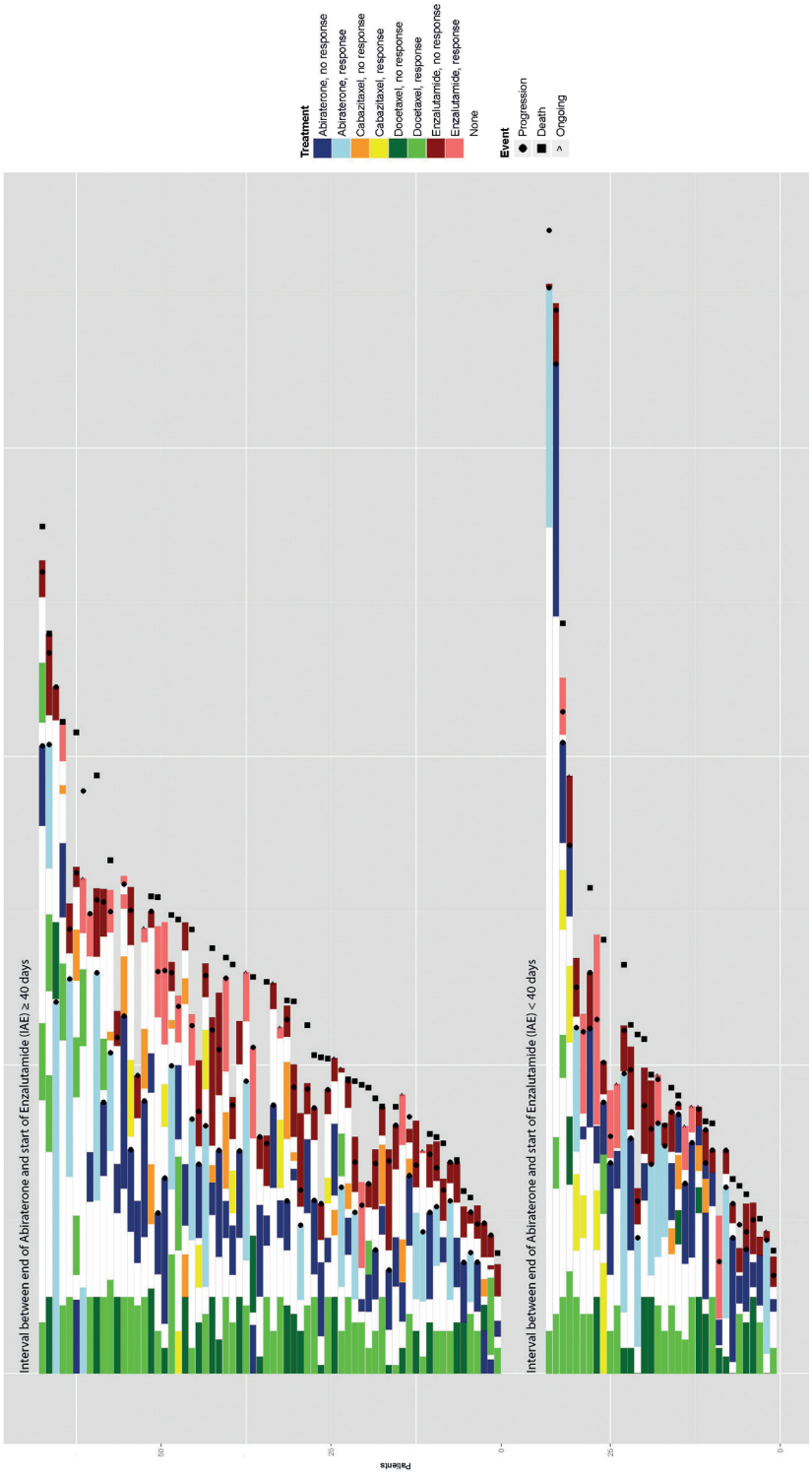

Figure 2. Swimmer plot of patients with an interval of at least 40 days between end of AA treatment and start of Enz treatment (IAE≥40)(Upper panel) and less than 40 days between end of AA treatment and start of Enz treatment (IAE<40)(Lower panel). Length of each bar represents survival of one patient. Bars are ordered by duration of follow-up, starting from first treatment of castration resistant cancer. The colors indicate duration of treatment and response on life-prolonging treatments. Progression was defined as either radiological, clinical of biochemical.

Baseline characteristics and univariate analysis of these two groups are listed in table 2 and supplementary table 2. Univariate analysis of all baseline characteristics of the IAE<40 days group of 34 patients revealed significant differences in neutrophil granulocytes levels and duration of Enz treatment between Enz responders and Enz non-responders. Baseline characteristics of the IAE≥40 group of 68 patients, showed significant differences in PSA levels, Gleason score, bone only metastases, PSA-DT <3 months, IDE, IAE and ILTE between Enz responders and Enz non-responders (table 2).

In the IAE≥40 group PSA responses on AA for Enz responders and non-responders were 29% and 28%, respectively, while, in the IAE<40 subgroup all but one (11%) of the Enz-responders were AA-non-responsive. However, the difference in AA response between the IAE<40 and IAE≥40 subgroups was not significantly different.

Logistic regression analysis

Logistic regression analysis of the probability of PSA response on Enz treatment was performed using IAE as the independent variable as well as using various disease and patient characteristics as the independent variable with IAE as a covariate. Analysis was performed for the entire cohort and for the IAE≥40 group, the adjusted p–values are displayed in table 3.

In the entire cohort (n=102), the logistic model of the influence of IAE on the rate of Enz-responders seemed to be more accurate than a model suggesting that IAE had no influence on the rate of Enz-responders, however was not statistically significant better (p=0.058 in a likelihood ratio test). In the bivariate logistic models, the predictors for Enz-response in the entire population compensating for IAE were PSA-DT <3 months (adj. p=0.037) and duration of Enz treatment (adj. p=0.003).

For the IAE≥40 subpopulation, IAE was a predictor of Enz-response in the univariate logistic model (p=0.007). The predictors for this subpopulation in the bivariate logistic models were PSA-DT <3 months (adj. p=0.019), involvement of lymph nodes (adj. p=0.017) and having only bone metastases (adj. p=0.005).

Table 2. Univariate analysis of baselines variables for sub-populations

	Entire Cohort			IAE<40			IAE ≥ 40		
	Number of patients (%), median values (IQR)			*Number of patients (%), median values (IQR)*			*Number of patients (%), median values (IQR)*		
	Responders n=26 (25%)	**Non-responders n=76 (75%)**	**p- value**	**Responders n=9 (26%)**	**Non-responders n=25 (74%)**	**p- value**	**Responders n=17 (25%)**	**Non-responders n=51 (75 %)**	**p-value**
Survival*									
Median OS (weeks)	64.3 (>47.8)	37.4 (28.7-54.3)	0.014						
Median PFS (weeks)	22.2 (14.8-36.9)	11.7 (10.0-12.2)	<0.0001						
Median DER (weeks)	26.0 (>10.4)	N/A	N/A						
Gleason score*			*0.006*			*0.17*			*0.024*
≤6	1 (5%)	14 (21%)		1 (14%)	4 (19%)		0 (0%)	10 (22%)	
7	2 (10%)	22 (33%)		0 (0%)	7 (33%)		2 (14%)	15 (33%)	
≥8	18 (86%)	31 (46%)		6 (86%)	10 (48%)		12 (86%)	21 (46%)	
Metastatic sites									
Bone only*	9 (35%)	13 (17%)	*0.09*	1 (11%)	6 (24%)	*0.64*	8 (47%)	7 (14%)	*0.007*
Baseline laboratory values*									
Neutrophil granulocytes (x10^9/L)*	4.9 (3.6-7.9)	5.5 (4.6-7.5)	*0.41*	4.1 (3.6-4.4)	6.0 (4.6-8.0)	*0.015*	6.6 (3.6-8.2)	5.2 (4.2-7.1)	*0.91*
PSA (μg/L)*	404 (138-1380)	311 (86-709)	0.09	112 (47-345)	311 (96-700)	0.5	656 (262-2554)	318 (84-727)	0.01

PSA doubling time *			*0.037*			*1*			*0.016*
< 3 months	7 (44%)	8 (16%)		1 (20%	3 (18%)		6 (55%)	5 (15%)	
≥ 3 months	9 (56%)	42 (84%)		4 (80%)	14 (82%)		5 (45%)	28 (85%)	
Previous systemic therapies*									
Duration of AA treatment (weeks)	26.1 (13.3-40.1)	26.0 (16.9-35.6)	0.81	28.3 (13.0-39.3)	34.9 (13.4-43.7)	*0.23*	26.1 (17.1-42.6)	25.1 (17.3-30.4)	*0.58*
AA-sensitivity	6 (23%)	21 (30%)	0.61	1 (11%)	8 (35%)	*0.38*	5 (29%)	13 (28%)	
Time between treatments									
IDE (weeks)*	71.4 (58.4-04.4)	53.1 (39.1-76.3)	0.26	60.7 (58.0-64.1)	52.6 (25.7-77.0)	*0.50*	91.1 (71.3-114.6)	56.9 (41.4-73.6)	*0.043*
IAE (weeks)*	24.6 (4.0-48.1)	8.9 (3.7-25.9)	0.08	1.9 (0.6-3.7)	0.9 (0-3.3)	0.55	45.7 (14.0-33.3)	15.0 (8.1-24.7)	0.023
ILTE (weeks)*	13.4 (4.0-28.6)	7.9 (3.1-12.6)	0.09	1.9 (0.6-3.7)	0.9 (0-3.3)	0.55	21.2 (14.0-33.3)	10.3 (7.9-21.4)	0.036
Enzdur (weeks)	17.9 (14.9-31.6)	12.1 (9.0-18.3)	0.017	22.6 (17.0-35.1)	11.7 (7.9-19.7)	0.048	17.3 (13.9-30.1)	12.3 (10.1-17.4)	0.18

Abbreviations: IQR, interquartile range; OS, Overall survival; PFS, Progression Free Survival; DER, Duration of Enz Response; N/A, Not Applicable; LN, lymph node; PSA, prostate-specific antigen; AA, Abiraterone acetate; AA-sensitivity was defined as ≥50% PSA decline from baseline; IDE, interval between discontinuation of Docetaxel and start Enzalutamide; IAE, Interval between discontinuation Abiraterone and start Enzalutamide; ILTE, Interval between discontinuation of last systemic treatment and start of Enzalutamide; Enzdur, Duration of Enz treatment; * Percentages are based on number of patients with available data.

Table 3. Multivariable analysis using IAE as independent variable

	Entire cohort (n=102)	**IAE ≥ 40 days sub-group**
Likelihood ratio test	26/102; *p= 0.058*	17/68; *p=0.0065*
Dependent variables	Adjusted *p*-value	Adjusted *p*-value
Metastatic sites		
Bone metastases	*0.7*	*0.39*
Lymph node involvement	*0.17*	*0.017*
Visceral	*0.56*	*0.75*
Bone only	*0.06*	*0.0049*
Lymph nodes only	*0.9*	*0.99*
Bone and lymph nodes only	*0.2*	*0.07*
Time between treatments		
IDE	*0.42*	*0.27*
ILTE	*0.29*	*0.65*
PSA-DT < 3 months	*0.037*	*0.019*
Enzdur	*0.0033*	*0.07*

Abbreviations: IAE, Interval between discontinuation Abiraterone and start Enzalutamide; IDE, interval between discontinuation of Docetaxel and start Enzalutamide; ILTE, Interval between discontinuation of last systemic treatment and start of Enzalutamide; Enzdur, Duration of Enz treatment

DISCUSSION

In this retrospective analysis of 102 mCRPC patients treated with Enz after Doc and AA, we describe the characteristics of patients with a ≥50% PSA response. The PSA response rates, median OS and PFS on Enz treatment of mCRPC patients pretreated with Doc and AA were comparable to our previous report and other retrospective studies[7–13]. Enz-responders had a significant longer OS and PFS compared to non-responders, which were in the same range as reported by Brasso et al [12]. The ≥50% PSA response rate on Enz in the current patient cohort is much lower than the 54% in AA-naïve patients as reported in the AFFIRM trial[3].

Several retrospective cohort studies suggest a significant clinical cross-resistance between Enz and AA[7–13, 17], which might be explained by the common molecular target of both drugs. However, preclinical evidence for cross-resistance is scarce. Higher Gleason scores (≥8) have been associated with higher recurrence rates and mortality. However, in the current cohort a relation was found between Gleason score ≥8 and a higher rate of PSA response. In the AFFIRM trial, Gleason ≥8 patients had a non-significant favorable hazard ratio over Gleason ≤7 patients with respect to OS (0.60 and 0.67, respectively)[18]. PSA-DT is a valuable tool in the pre-Docetaxel setting for predicting survival and risk for metastatic disease. However, it has not been evaluated for prediction of response to therapy[19–22]. Our observation, that patients with a PSA-DT <3

months were more likely to respond to Enz, was validated both univariately and related to IAE. The relation was stronger in the IAE≥40 group. The relation between PSA baseline level, Gleason ≥8 and PSA-DT <3 months and Enz response might be related to the rate of cell cycle passage and dependence on AR signaling.

Even though there was no statistical significant difference in IAE between PSA responders and non-responders for the whole population, analysis of Enz-responders as a function of IAE revealed two groups of patients responding to Enz, IAE<40 days and IAE≥40 days. An interesting difference between the groups was that only 1 (11%) Enz responder in the IAE<40 group was AA-sensitive, while 8 (35%) Enz responders in the IAE≥40 group were AA-sensitive. The low PSA response rates on AA and high response rates on Enz in the IAE<40 group, suggests a mechanism of AA resistance not shared with Enz resistance. This exclusive mechanism of AA resistance could be related to differences in the mode of action between the AR targeting drugs. However, the difference in AA response between the IAE<40 and IAE≥40 Enz response subgroups was not statistically significant, likely due to the low number of Enz responders.

In the IAE≥40 subgroup, IAE showed a linear relation with Enz response. The PSA response rates of 50% after an IAE of 390 days was comparable to AA-untreated patients as reported in the AFFIRM trial[3]. This time relation and reversibility of acquired cross-resistance suggests plasticity of the cells' behavioral repertoire to adapt to changes in their microenvironment[23]. Carver et al. reported that the androgen receptor pathway activates reciprocal negative feedback of the PI3K-pathway. Inhibition of the androgen receptor could promote activity of PI3K signaling, which results in androgen independent proliferation[24]. Possibly, these changes are energetically unfavorable and cells might reverse to testosterone dependence upon cessation of AR targeted therapy, which might explain the time relation between AA and Enz treatment.

Reversibility of sensitivity to AR targeted drugs might have consequences for sequencing of treatment options. Our data suggests that, when an interval between AA and Enz treatment is introduced, both treatment options can be deployed. Both AA and Enz have shown survival benefit in patients not treated with Doc[4, 5]. Therefore treatment with Doc and second line options Cabazitaxel and/or Radium-223 between AA and Enz treatment might be an optimal sequence. However, there is no data suggesting a relation between interval between AA and previous Enz treatment and response to AA.

In conclusion, in this retrospective study we identified 3 possible characteristics of Enz-responders after previous Doc and AA treatment: IAE, PSA-DT <3 months and Gleason ≥8. Our data suggests that PSA responses on both AA and Enz can be achieved, however with a long interval between the treatments. This is a retrospective study and as such more prone to bias and confounding. Therefore, recommendation on the timing and sequencing of Enz and

AA in the post-Docetaxel setting cannot be made. We also note that our analysis is largely data driven and exploratory: conclusions are only hypothesis generating and need to be validated prospectively.

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DISCLOSURES:

Conflict of Interest: Drs. van Oort, van den Berg, Hamberg, van Eertwegh and Bergman are on Advisory Boards of Janssen Pharma and Astellas. Dr. Hamberg, van Eertwegh and Bergman received speakers fee from Astellas, Jansen Pharma. Dr. Bergman has received a research grant from Astellas, not related to this study. All remaining authors have declared no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary table 1. Patient characteristics and treatment outcomes

Age	*Median*	*IQR*
	72	64-77
Number of metastatic sites	*N*	%
0	0	(0%)
1	1	(1%)
≥2	99	(97%)
Unknown	2	(2%)
Laboratory values at start of Enz treatment (entire cohort; n=102)	*Median*	*IQR*
PSA (μg/L)	335	(95 – 723)
Haemoglobin (mmol/L)	7.1	(5.7 – 7.9)
Leucocytes (x10^9/L)	7.5	(6.3 – 9.3)
Neutrophil granulocytes (x10^9/L)	5.2	(4.1 – 7.5)
Thrombocytes (x10^9/L)	272	(218 – 340)
ALP (U/L)	170	(94 – 285)
Albumin (U/L)	39	(35 – 42)
Bilirubin (μmol/L)	7	(5 – 8)
LDH (U/L)	244	(192 – 390)
EGFR (ml/min/1.73m^2/L)	62	(60 – 90)
Mitoxantrone treatment	*N*	%
Patients treated	3	(3%)
Antihormonal treatment while on Enzalutamide		
LHRH antagonist/agonist	98	(96%)
Orchidectomy	4	(4%)
Dexamethasone/prednisone mono therapy	12	(12%)
Previous antihormonal treatment (other than Abiraterone)	*N*	%
Ketoconazol	0	(0%)
Diethylstilbestrol	0	(0%)
Abiraterone treatment	*Median*	*IQR*
Reason for discontinuation:	*N*	%
Intolerance	6	(6%)
Relapse	57	(56%)
No response	38	(37%)
Unknown	1	(1%)

ALP, alkaline phosphatase; IQR, interquartile range; LDH, lactate dehydrogenase; EGFR, Estimated glomerular filtration rate; PSA, prostate-specific antigen.

Supplementary table 2. Univariate analysis of baselines variables for sub-populations

	Entire Cohort			IEA<40			IEA ≥ 40		
	Number of patients (%), median values (IQR)			*Number of patients (%) median values (IQR)*			*Number of patients (%), median values (IQR)*		
	Responders n=26 (25%)	**Non-responders n=76 (75%)**	**p- value**	**Responders n=9 (26%)**	**Non-responders n=25 (74%)**	**p- value**	**Responders n=17 (25%)**	**Non-responders n=51 (75 %)**	**p-value**
Age (years)	72 (64 – 76)	72 (64 – 77)	0.8	73 (69 - 78)	71 (63 - 77)	0.45	70 (63 – 75)	72 (64 – 76)	0.45
Metastatic sites									
Bone metastases	21 (81%)	59 (78%)	*1*	6 (67%)	19 (76%)	*0.67*	15 (88%)	40 (78%)	*0.49*
LN involvement	13 (50%)	49 (64%)	*0.25*	6 (67%)	14 (56%)	*0.7*	7 (41%)	35 (69%)	*0.08*
LN only	1 (4%)	3(4%)	*1*	1 (11%)	1 (4%)	*0.47*	0 (0%)	2 (4%)	*1*
Bone + LNs only	12 (46%)	46 (61%)	*0.25*	5 (56%)	13 (52%)	*1*	7 (41%)	33 (65%)	*0.1*
Visceral	4 (16%)	16 (22%)	*0.77*	2 (22%)	6 (24%)	*1*	2 (12%)	10 (20%)	*0.71*
Laboratory values at Enzalutamide initiation									
Haemoglobin (mmol/L)	7.0 (6.5-7.9)	7.1 (6.8-8.0)	0.64	7.7 (6.9-8.0)	7.40 (6.9-8.2)	0.57	6.8 (6.2-7.6)	6.9 (6.3-7.7)	0.4
ALP (U/L)	176 (137-292)	162 (88-282)	0.54	225 (135-240)	142 (103-308)	0.34	175 (143-341)	164 (83-280)	0.89
Albumin (U/L)	36 (30-40)	39 (36-43)	0.09	40 (38-42)	42 (38-44)	0.44	31 (30-37)	38 (36-41)	0.08
Bilirubin (μmol/L)	6.5 (5-8)	7 (5-8)	0.47	7 (6.0-8.0)	8 (4.9-10.0)	0.65	5.3 (4.8-7.0)	7.0 (5.0-8.0)	0.51
LDH (U/L)	233 (198- 433)	246 (191-381)	0.72	218 (192-259)	241 (207-531)	0.027	364 (205-552)	248 (190-340)	0.33
Previous systemic therapies*									
Number of Doc courses	9.5 (6 – 10)	8 (6 – 10)	0.88	9 (6 - 10)	8 (4 - 10)	0.66	10 (6 – 10)	9 (6 – 10)	0.92
Doc-sensitivity	21 (81%)	39 (57%)	0.05	7 (78%)	12 (52%)	0.25	14 (82%)	27 (60%)	0.14
Number of Cab courses	8 (6 – 8)	5.5 (4 – 8)	0.59	8 (7.0 - 8.0)	5 (4.5 - 10.0)	0.95	7 (5.0 – 8.2)	6 (3.0 – 8.0)	0.51

Abbreviations: IQR, interquartile range; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; AA, Doc-sensitivity was defined as ≥50% PSA decline from baseline; Doc, Docetaxel; Cab, Cabazitaxel;

* Percentages are based on number of patients with available data.


ENZALUTAMIDE

Chapter 4

Enzalutamide as a fourth- or fifth-line treatment option for metastatic castration resistant prostate cancer

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ABSTRACT

Objective

To evaluate the efficacy of Enzalutamide (Enz) as fourth or fifth-line treatment in men with metastasized castration resistant prostate cancer (mCRPC), by analyzing a retrospective cohort of heavily pretreated patients.

Methods

We evaluated toxicity, overall survival (OS), Progression-Free Survival (PFS) and Time To PSA Progression (TTPP) data from 47 CRPC patients treated with fourth or fifth-line Enz.

Results

All patients were treated with Docetaxel (Doc) and Abiraterone acetate (AA) and 42 patients (89%) with Cabazitaxel (Cab). The median age of the patients was 69 years (IQR, 63-73.5), 79% had bone metastases, 55% had lymph-node metastases, and 17% had visceral metastases. The median duration of Enz treatment was 12.0 weeks (IQR, 8.3-20.4), 11 patients (23%) responded to Enz (maximum PSA decline ≥50%). In general, Enz was well tolerated, with the most frequent reported adverse events being fatigue and nausea. The median OS was 40.1 weeks (95%CI, 25.4-61.4), the median PFS was 12.1 weeks (95%CI, 9.9–14.0) and the median TTPP was 15.7 weeks (95%CI, 14.0–28.7).

Conclusions

Analysis of this retrospective cohort suggests Enz is well tolerated and that there is a 23% response rate in heavily pretreated CRPC patients, which is comparable with third line treatment outcomes.

INTRODUCTION

Prostate cancer is the most frequent cancer amongst men in the Western world[1]. Metastasized castration resistant disease is the advanced stage of prostate cancer (mCRPC) with high morbidity and mortality as hallmarks[2]. Docetaxel (Doc) was the first treatment to improve overall survival of mCRPC patients[3]. In recent years four new drugs have been developed simultaneously, all increasing overall survival (OS) of mCRPC patients previously treated with docetaxel[4–7].

Enzalutamide (Enz) and Abiraterone (AA) are both hormonal treatments. AA inhibits androgen synthesis by inhibiting cytochrome P-450 17A1 (CYP17A1)[5]. Enz inhibits androgen receptor (AR) signaling by inhibition of ligand binding, nuclear translocation of the AR, DNA binding and coactivator recruitment[4]. Cabazitaxel (Cab) is a second-generation semisynthetic taxane. Like docetaxel (Doc), Cab disrupts microtubule function, leading to mitotic block and apoptosis[7, 8]. Radium-223 (RAD) is an alpha-emitting radionuclide, which targets bone metastases where it emits high-energy alpha-particles and causes double-strand DNA breaks[6].

Little data is available on the optimal sequencing of these new second line options[9–14]. There is evidence that there is clinical cross-resistance between AA and Enz and also between the hormonal drugs and the taxanes[9–16]. Post hoc studies suggest that patients with primary tumor Gleason scores between 7 and 10 might derive survival benefit from first-line docetaxel, while Gleason scores <7 do not[17]. These data suggest that the optimal sequence of treatment options is individual. Relatively small retrospective studies reported on the activity of Enz as a third-line treatment after Doc and Cab or AA[9–14, 18]. However, there is limited data on the efficacy of Enz as a fourth-or fifth-line treatment. Here we report the efficacy and tolerability of Enz treatment, after previous treatments with Doc, AA, Cabazitaxel and RAD.

PATIENTS AND METHODS

In this multicenter, retrospective study, we included patients with progressive mCRPC treated with at least 3 lines of systemic life-prolonging therapy after castration resistance and prior to Enz treatment. The systemic therapies included were Doc, AA, Cab and RAD. All 36 Dutch Uro-Oncology Study Group (DUOS) hospitals were approached for retrospective data from patients treated with Enz. Most of these patients participated in the Dutch Expanded Access Program (EAP) for Enz. In total 109 patients were included in a database. Forty-seven of the patients from 13 hospitals were treated with Enz after at least three previous lines of systemic therapy. In all patients the starting dose of Enz was 160 mg once daily and all patients received at least one dose of Doc, AA, and Enz. Treatment was continued until disease progression (either clinical, radiological or biochemical), clinical deterioration and/or unacceptable adverse effects, all to

physician's discretion, or death. Approval for retrospective collection and analysis of patient data was obtained from the Institutional Review Board (IRB) of the Netherlands Cancer Institute. Personal data were encoded and no informed consent was required.

Study procedures and data collection

Baseline characteristics prior to Enz treatment were documented. The patient baseline characteristics included age, disease characteristics, laboratory results, and previous anti-hormonal and chemotherapy treatments. During Enz-treatment, patients were assessed every 4-6 weeks. Adverse events and toxicity of Enz treatment were recorded using Common Terminology Criteria for Adverse Events (CTCAE v 4.0). Radiologic evaluations were performed at the physician's discretion. Patient follow-up and survival were registered and last updated in July 2015.

The Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendations were used to evaluate PSA response[19]. A PSA decline from baseline of at least 50% was considered a PSA response. An increase of 25%, with a minimum of 2 ng/ml, confirmed with a second PSA measurement at least 3 weeks later was considered PSA progression. If no PSA-decline from baseline was documented, PSA progression was defined as a 25% increase from baseline value along with an increase in absolute value of at least 2 ng/ml after 12 weeks of treatment. PSA declines at 12 weeks after start of ENZ were categorized and evaluated in three groups: $<$ 30%, $<$50% and $<$90% from baseline with or without conformation. Progression Free Survival (PFS) was defined as start date of Enz to the first date of confirmed progression. Progression was defined as PSA, radiological or clinical progression or a combination of the three. Overall survival (OS) was defined as the first day of Enz treatment until death or last follow-up.

Statistical analysis

In line with PCWG2 criteria, Kaplan-Meier estimates were used to evaluate survival and progression. Doc, AA or Cab sensitivity was defined as a PSA decline of at least 50%. Patients who did not achieve a 50% PSA decline were considered Doc, AA or Cab non-sensitive. Statistical analyses were conducted using Statistical Analysis System (SAS) statistical software (SAS Institute Inc., Chicago, Ill) and R (R Foundation for Statistical Computing, Vienna, Austria).[20]

RESULTS

Patients

Forty-seven patients were included from 13 Dutch medical centers. Prior to Enz treatment, all patients had at least 3 life-prolonging systemic therapies since castration resistance. Patient and disease characteristics are listed in table 1. The median age at baseline was 69 years (IQR 63-73.5 years); ECOG-scores of 0-1, 2 or 3 were reported in 68%, 27% and 5% of the patients, respectively. Forty-nine % of patients had prostate cancer of a Gleason score ≥ 8. Seventy-nine % of patients had bone metastases, 55% had lymph node metastases and 17% had visceral metastases.

All patients had ≥2 metastases and median PSA was 463 (IQR 98.9-904) μg/L, Alkaline Phosphatase 178 (IQR 95.0-290) U/L and lactate dehydrogenase (LDH) 299 (IQR 199.0-451.5) U/L. All these base line characteristics are in line with advanced disease. Disease progression at the time of baseline presented in 98% of patients as a rise in PSA, in 87% of patients as clinical progression and in 55% of patients as progression of bone lesions assessed by a bone scan and in 34% of patients as progression of measurable lesions.

Thirty-seven patients (79%) were treated with Enz as a fourth-line therapy and 10 (21%) were treated as a fifth-line therapy. Sequencing of the treatments is presented in table 2 and figure 1. All patients were treated with Doc and AA, 22 patients (46%) were treated with Doc first, AA second and Cab third-line, before receiving Enz. Seven patients (15%) were treated with Doc first, Cab second and AA third-line before receiving Enz. Two patients were treated with RAD prior to Enz treatment. Characteristics of previous treatments are listed in table 3. Seventy-four percent of the patients received 1 series of Doc- cycles, 23% received a second series. 72% of the patients were Doc sensitive. All Doc series combined, patients received a median of 10 cycles (IQR 8-12 cycles). Eighty-nine percent of the patients received at least one series of Cab, while 21% of the patients were Cab-sensitive. One patient received a second series of Cab. The median number of cycles of Cab was 6 (IQR 4-8 cycles). All patients received AA, the median duration of treatment was 25 weeks (IQR 13.0-34.8 weeks), while 21% of the patients treated with AA were considered sensitive. Two patients were treated with RAD, prior to Enz treatment. One patient received 4 injections and the other received 5. All patients were either surgically castrated or chemically castrated. Nine percent of the patients received steroid drug monotherapy during Enz treatment.

Table 1. Patient demographics

	Median [IQR] or No. of patients (%)
Age	69 [63 - 73.5]
ECOG performance score	
0-1	30 (64%)
2	12 (26%)
3	2 (4%)
unknown	3 (6%)
Gleason Score	
≤ 6	8 (17%)
7	11 (23%)
≥ 8	23 (49%)
unknown	5 (11%)
Metastatic sites	
Bone involvement / Bone only	37 (79%) / 13 (28%)
Lymph nodes involvement / Lymph node only	26 (55%) / 2 (4%)
Bone and lymph nodes only	24 (51%)
Visceral	8 (17%)
No. of metastatic sites	
≥ 2	47 (100%)
Laboratory values*	
PSA (μg/L)	463 [98.9 - 904]
Haemoglobin (g/dL)	10.8 [10.0 - 12.1]
Leucocytes ($x10^9$/L)	8.0 [6.4 - 10.4]
Neutrophil granulocytes ($x10^9$/L)	6.7 [4.2 - 8.2]
Thrombocytes	299 [216 – 360]
Alkaline phosphatase (U/L)	178 [95.0 - 290]
Albumine (U/L)	38.1 [32.8 - 41.3]
Bilirubin (μmol/L)	5.4 [4.0 - 8.0]
LDH value (U/L)	299 [199.0 - 451.5]
Disease progression based on:	
Increased PSA	46 (98%)
Clinical progression	41 (87%)
Bone scan	26 (55%)
Measurable lesions	16 (34%)

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen; * Percentages are based on number of patients with available data.

Table 2. Sequencing of treatments

First line	*n*	Second line	*n*	Third line	*n*	Fourth line	n	Fifth line	*n*
Doc	43	AA/P	26	Cab	23	Rad	1	Enz	1
						Enz	22		
				Doc	3	Enz	3		
		Cab	10	AA/P	10	Cab	1	Enz	1
						Doc	1	Enz	1
						Rad	1	Enz	1
						Enz	7		
		Doc	7	Cab	4	AA/P	4	Enz	4
				AA/P	3	Cab	1	Enz	1
						Enz	2		
Cab	2	Doc	2	AA/P*	2	Enz	2		
AA/P	2	Doc	2	Doc	1	Cab	1	Enz	1
				Cab	1	Enz	1		

Abbreviations: Doc, Docetaxel ; AA/P, Abiraterone acetate/Prednisone; Cab, Cabazitaxel; Enz, Enzalutamide; Rad, Radium-223

*One patient was treated with Doc and AA/P simultaneously.

Antitumor effects

The median time to maximum PSA decline was 5.14 weeks (IQR 4-8.79 weeks). Eighteen patients (38%) had a maximum PSA decline ≥30%, 11 patients (23%) had a max PSA response of ≥50% and 1 patient (2%) had a max PSA response of ≥90%. Seventeen patients (37%) had no PSA decline at any time. Enz treatment was discontinued in 33% of the patients as a result of no clinical activity or PSA response, in 25% because of progressive disease and in 13% because of death.

The Kaplan-Meier estimate of PFS was 12.1 weeks (95% Confidence Interval [CI], 9.9-14 weeks) (Table 4; Figure 2, top). The median OS was 40.1 weeks (95%CI, 25.4-61.4 weeks)(figure 2, bottom), the estimated time to PSA progression was 15.7 weeks (95% CI, 14.0 – 28.71 weeks) (table 2). The median time between Doc and Enz (IDE) was 66.7 weeks (IQR 50.5-95.14 weeks), the median time between end of AA and start of Enz (IAE) was 26.29 weeks (IQR 7.21-45.57 weeks) (table 4). The median duration of Enz treatment was 12 weeks (IQR 8.29-20.43 weeks).

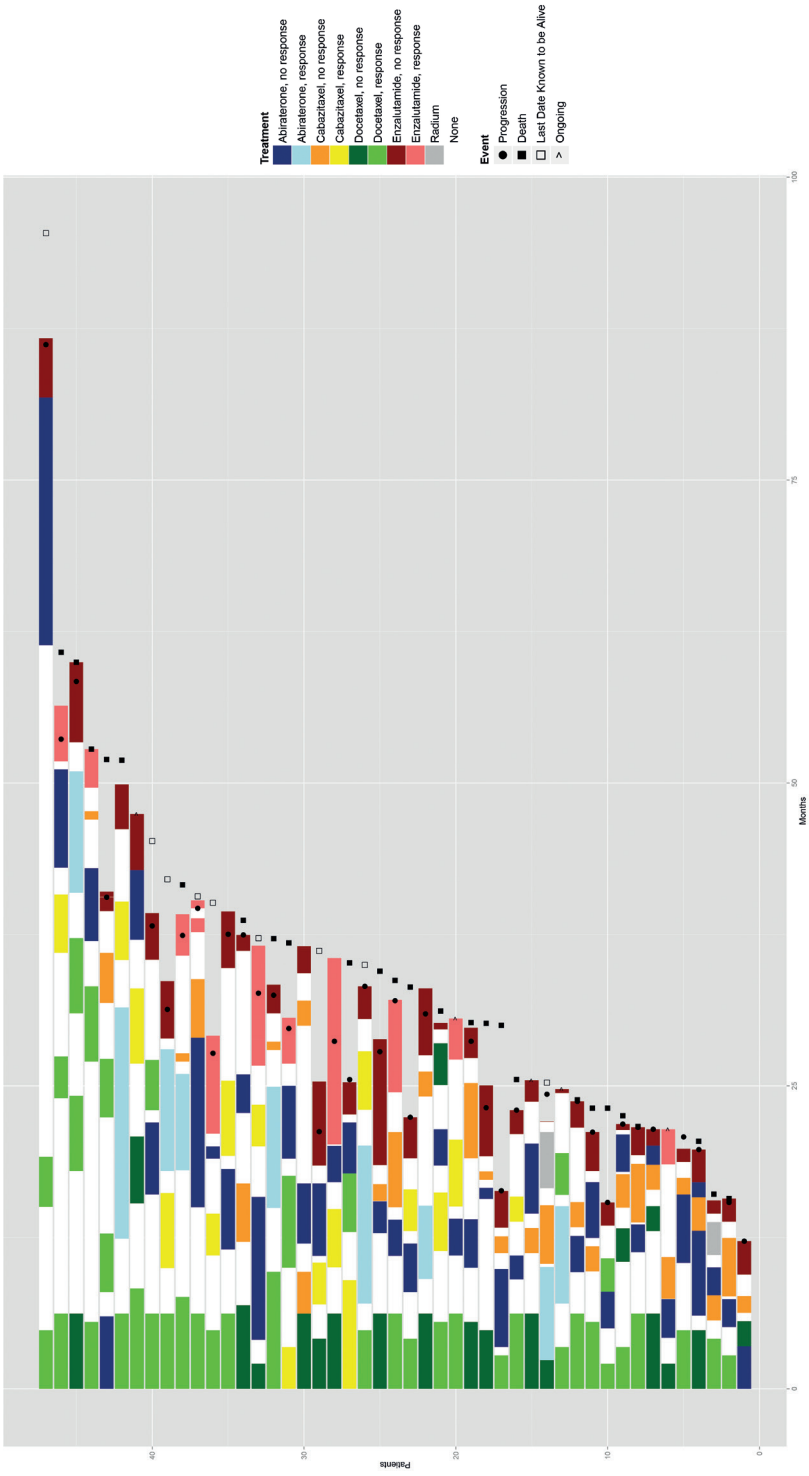

Figure 1. Swimmer plot of patients treated with Enz as fourth or fifth-line. Length of each bar represents survival of one patient. Bars are ordered by duration of survival, patients with the longest survival are displayed at the top. Each bar starts with the first treatment after castration resistant prostate cancer. The colors indicate duration of treatment and response on Doc, AA/P, Cab, Rad and Enz. Progression was defined as either radiological, clinical of biochemical.

Table 3. Previous treatments characteristics

	Median [IQR] or No. of patients (%)
Mitoxantrone	2 (4%)
Docetaxel treatment	47 (100%)
No. of cycles in all series	10 (8 - 12)
Number of series	
1	35 (74%)
2	11 (23%)
3	1 (2%)
Docetaxel (first series) non-sensitive*	12 (28%)
Docetaxel (first series) sensitive*	31 (72%)
Cabazitaxel treatment	42 (89%)
No. of cycles in all series	6 [4 - 8]
Number of series	
1	41
2	1
Cabazitaxel (first series) non-sensitive*	33 (79%)
Cabazitaxel (first series) sensitive*	9 (21%)
Abiraterone treatment	47 (100%)
Duration of treatment (weeks)	25 [13.1 - 34.8]
AA/P non-sensitive*	33 (79%)
AA/P sensitive*	9 (21%)
Radium-223 treatment	2 (4%)
No. of injections	4.5 [4 – 5]
Antihormonal treatment while on Enzalutamide	
LHRH-agonists/antagonists	43 (91%)
Orchidectomy	3 (6%)
Dexamethason/Prednisone	4 (9%)
Previous antihormonal treatments (other than Abiraterone)	
Ketoconazol	0
Diethylstilbestrol	0

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen; AA/P, Abiraterone acetate/Prednisone; *Sensitivity was defined as ≥50% PSA decline from baseline;

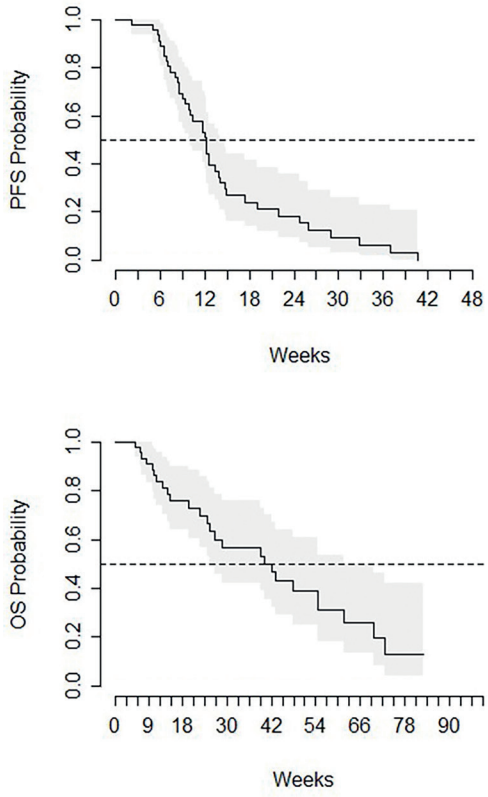

Figure 2. (Top) Progression-free survival and (Bottom) overall survival are illustrated of mCRPC patients treated with Enz as a fourth- of fifth-line treatment.

Tolerability

In total 269 adverse events (AEs) were collected. Most AE's were grade 1 (77%) and grade 2 (20%), while grade 3 (3%) AE's were reported less frequent (table 4). Fatigue was the most reported grade 2 and 3 AE and was observed in 16 patients (35%) and 4 patients (9%), respectively. The second and third most reported grade 2 and 3 AEs were nausea (6 patients [13%] and 3 patients [7%], respectively) and muscoskeletal pain (7 patients [15%] and 1 patient [2%], respectively).

Table 4. Outcomes of Enzalutamide treatment

	Median [IQR] or number of patients (%)
Follow-up (weeks)	57.1 [>42.6]
Duration of Enzalutamide treatment (weeks)	12.0 [8.3-20.4]
Enzalutamide dosage adjustment	5 (11%)
Time to lowest PSA value (weeks)	5.1 [4-8.8]
PSA decline	
≥ 30%	18 (38%)
≥ 50%	11 (23%)
≥ 90%	1 (2%)
Reason for Enzalutamide discontinuation	
Intolerance	4 (9%)
No activity	18 (38%)
Relapse	13 (28%)
Death	6 (13%)
Treatment ongoing on date of collection	6 (13%)
Survival	*median (95% CI)*
Progression Free Survival (weeks)	12.1 (9.9 – 14.0)
Overall Survival (weeks)	40.1 (25.4 - 61.4)
Time To PSA Progression (weeks)	15.7 (14.0 – 28.7)
Time between treatments	
IDE (weeks)	66.7 [50.5 - 95.1]
ICE (weeks)	16.9 [8.43 - 33.3]
IAE (weeks)	26.3 [7.2 - 45.6]
Total number of adverse events by grade	
Grade 1	206
Grade 2	54
Grade 3	9

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen; IDE, interval between discontinuation of Docetaxel and start Enzalutamide; IDE, interval between discontinuation of Cabazitaxel and start Enzalutamide; IAE, Interval between discontinuation Abiraterone and start Enzalutamide

DISCUSSION

The rate of PSA responses to Enz (≥50% PSA decline) as a fourth- or fifth-line therapy is similar to the 12.8% and 39.1% response rates reported in patients treated with Enz as a third-line therapy,[9–14, 18]. These rates are significantly lower than the 54% response rate reported in the AFFIRM trial, where patients were treated with Enz after progressing on Doc[4]. The 40.1 weeks

OS of patients treated with Enz in fourth- of fifth-line was significantly lower than the 80 weeks reported in the AFFIRM trial, most likely because patients in this cohort are in a more advanced stage of their disease. Advanced disease was reflected in high base line serum levels of PSA and Alkaline phosphatase. Surprisingly the median OS in our cohort is longer compared to reports on third-line Enz therapy in Doc and AA pretreated patients. The OS in these reports vary between 20.9 and 36.9 weeks. This might be explained by selection of patients with a more protracted course of the disease who are eligible for fourth- or fifth-line Enz treatment. Moreover, a longer time interval between AA and Enz (IAE) might also contribute to a longer survival. In our previous report we presented the characteristics of Enz-responders after previous Doc and AA treatment[21]. Median OS of the Enz responders was 64.3 weeks. A longer IAE was associated with ≥50% PSA-response[21]. Of the 47 patients in the present cohort, 32 (68%) had at least one other life-prolonging treatment between AA and Enz, resulting in a IAE of 26.3 weeks. Although other reports on the efficacy of Enz after Doc and AA treatment do not report IAE, it can be assumed that this will be significantly shorter, because most patients were treated with Doc, followed by AA and subsequent Enz.

The response rates on Cab and AA in this cohort are lower than reported in the phase-three trials (39.2% and 38.0%, respectively)[5, 7] into second-line efficacy. In our cohort, 63% of the patients treated with Cab received Cab as a third- or fourth line therapy. Fifty percent of the patients received AA as a third or fourth-line therapy. The lower response rates for Cab and AA in our cohort can probably be contributed to their position in the treatment-sequence. Only 2 patients in this cohort were treated with Radium-223, because Radium-233 was not widely available when patients in this cohort were treated.

The number of reports on fourth-line therapies in mCRPC is limited, based on small cohorts and all are retrospective[18, 22, 23]. One study reports of 38 patients treated with miscellaneous fourth-line treatments with an OS of 20 weeks[18]. Fifteen of these patients received Enz as a fourth line therapy and the response rate, based on ≥50% PSA decline was only 7%. Five of the 15 patients received Enz immediately after AA, however, no response rates were presented for these 5 patients. Another study reported on 36 patients treated with AA as a fourth-line or fifth-line treatment[22]. The OS in this group was 68 weeks, however, these patients were not pretreated with Enz or AA, but were treated with three lines of chemotherapy (Doc and Cab). A third study reports on 5 patients treated with Doc, AA and Enz before being treated with Cab[23]. Three of these patients had ≥50% PSA decline while receiving Cab, none of these three patients had a ≥50% PSA decline to Enz or AA. Data on the patients treated in this sequence was not separately analyzed and no OS data was reported.

Enz as a fourth and fifth-line therapy was overall well tolerated. The frequency and type of AE's were similar to those reported in the AFFIRM and Prevail trial[4, 24], with fatigue being the most

common AE. The reported AE's in the current cohort are also in line with our previous reports on efficacy and safety of Enz after previous Doc and AA treatment[9]. These results suggest that the toxicity of Enz is independent of its position in treatment-sequence.

Although this data is retrospective and hypothesis-generating, treatment with Enz as a fourth- or fifth-line treatment might not be without merit, even when considering the considerable costs when given on empirical basis.

FUNDING SUPPORT

No specific funding was requested for this project.

CONFLICT OF INTEREST

Drs. van Oort, van den Berg, Hamberg, van Eertwegh and Bergman are on Advisory Boards of Janssen Pharma and Astellas. Dr. Hamberg, van Oort, van Eertwegh and Bergman received speakers fee from Astellas and Jansen Pharma. Drs. Van Oort was on the Advisory boards of Bayer and Sanofi and received a speaking fee from Sanofi.
Dr. Bergman and van Oort received a research grant from Astellas, not related to this study.
Drs van Oort received a research grant from Janssen, not related to this study.
All remaining authors have declared no conflicts of interest.

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Radium-223

Chapter 5

A Prospective Observational Registry Evaluating Clinical Outcomes of Radium-223 Treatment in a Non-study Population

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ABSTRACT

Introduction

The ALSYMPCA study established a 3.6 month Overall Survival (OS) benefit in metastatic Castration Resistant Prostate Cancer (mCRPC) patients treated with Radium-223 dichloride (Ra-223) over placebo. Here we report clinical outcomes of Ra-223 treatment in a non-study population.

Methods

In this prospective registry, patients from 20 Dutch hospitals were included prior to Ra-223 treatment. Clinical parameters collected included previous treatments and Adverse Events. Primary outcome was 6 months Symptomatic Skeletal Event (SSE) free survival, while secondary outcomes included Progression-Free Survival (PFS) and Overall Survival (OS).

Results

Of the 305 patients included, 300 were evaluable. The mean age was 73.6 years, 90% had ≥6 bone metastases and 74.1% were pretreated with Docetaxel, 19.5% with Cabazitaxel and 80.5% with Abiraterone and/or Enzalutamide. Of all patients, 96.7% were treated with Ra-223 and received a median of 5 cycles. After a median follow-up of 13.2 months, 6 months SSE-free survival rate was 83%, median PFS was 5.1 months and median OS was 15.2 months. 6 months SSE-free survival rate and OS were comparable with those reported in ALSYMPCA. 'Previous Cabazitaxel treatment' and 'bone-only metastases' were independent predictors of a shorter and longer PFS, respectively, while above median LDH and 'bone-only metastases' were independent predictors of shorter and longer OS, respectively. Toxicity was similar as reported in the ALSYMPCA trial.

Conclusion

These results suggest that in a non-study population, Ra-223 treatment is well-tolerated, equally effective as in the ALSYMPCA population and that patients not previously treated with Cabazitaxel benefit most from Ra-223.

INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide, with over 1 million newly diagnosed cases each year.[1] At presentation, approximately 11% of patients have bone metastases[2], while approximately 70% of metastatic prostate cancer patients develop bone metastases during the course of their disease.[3] Bone metastases have a detrimental impact on quality of life.[4] These metastases are the most common cause of cancer-related pain, pathological fractures, compression of the spinal cord, vertebral instability and hypercalcemia.[5]

Until 2013, bone directed treatment of symptomatic metastases was limited to beta-emitting radionuclides, external beam-radiation therapy (EBRT), bisphosphonates, denosumab and surgery.[6] Although these therapies are effective for pain palliation and prevention, no Overall Survival (OS) benefit was established.[7, 8] This changed with the introduction of Radium-223 dichloride (*Xofigo*®; Ra-223), a targeted alpha therapy that selectively binds to areas of increased bone turnover. In 2013, the ALSYMPCA phase III trial reported a survival benefit of 3.6 months in metastatic Castration-Resistant Prostate Cancer (mCRPC) patients treated with Ra-223 compared to placebo, rendering Ra-223 the only radionuclide treatment with a survival benefit.[6]

Over recent years, the treatment options for mCRPC patients have expanded.[9] Although, patients previously treated with Docetaxel (Doc) as well as patients not-treated with Doc were included in ALSYMPCA, none of these patients had been treated with the newer life-prolonging agents Abiraterone (Abi), Enzalutamide (Enz) and Cabazitaxel (Cab). These newer generation drugs became available after accrual of the ALSYMPCA trial was completed.[10–13] This raises the question whether the results of ALSYMPCA are representative for present patients treated with Ra-223. Therefore, we conducted a prospective registry of Ra-223 treated mCRPC patients in the Netherlands. The primary goal of this registry was to assess the 6 months symptomatic skeletal event (SSE) free survival rate in a non-study population, while OS, progression-free survival (PFS), and safety were secondary outcomes.

PATIENTS AND METHODS

Study design and patients

In this non-interventional, multicenter, prospective, observational registry, patients aged 18 years or older with progressive mCRPC and scheduled for Ra-223 treatment were included in 20 hospitals in the Netherlands. This registry was approved by local medical ethics committees. Obtaining signed Informed Consent was not required, but patients had to provide oral consent and written approval for the documentation and use of their identifiers. Patients received Ra-223

at the treating physician's discretion. There were no other in- and exclusion criteria or stopping rules. During Ra-223 treatment, patients were evaluated at the outpatient clinic every 4 weeks during treatment, where ECOG performance, adverse events (AE) and clinical lab assessments were documented. Radiological evaluation during and after Ra-223 treatment and frequency of follow-up visits was at the physician's discretion. All patients scheduled to be treated with Ra-223 were included in our analysis. Clinical data was collected from the medical records after completion of Ra-223 treatment.

Procedures and data

Using an electronic case-report form, we recorded multiple baseline characteristics, efficacy assessments, AE (graded according to Common Terminology Criteria for Adverse Events v. 4.0[14]) and SSE during Ra-223 treatment (defined as the time from inclusion to first need for EBRT to relieve skeletal symptoms, new pathological fractures, spinal cord compression, or tumor-related orthopedic surgical intervention). Patients were considered symptomatic when they used analgesics regularly or were treated with EBRT for cancer-related bone pain in the previous 12 weeks, which is the same definition as used in ALSYMPCA. [15]

Progression Free Survival (PFS) was calculated from the date of first Ra-223 treatment to the date of confirmed progression. Patients were considered progressive in case of clinical progression (defined as clinical signs of progression), radiological progression (according to RECIST v. 1.1)[16], started with subsequent treatment or death, all in line with PCWG3 reccomendations.[17] OS was calculated from the date of the first Ra-223 cycle to the date of death or censored at last follow-up. PSA and Alkaline Phosphatase (ALP) declines from baseline during Ra-223 treatment of ≥30%, ≥50%, and ≥90% were evaluated as best response. Time to ALP progression was defined as an increase of ≥25% from baseline at ≥12 weeks, in patients with no decrease from baseline, or as an increase of ≥25% above the nadir in patients with an initial decrease from baseline. Time to subsequent treatment was defined as time from last cycle of Ra-223 until start of any systemic life-prolonging anti-prostate cancer treatment. The treating physician provided reasons for discontinuation of Ra-223.

Sample size and statistical analysis

The dual endpoints of the study are 6 months SSE-free survival and reduction of pain as measured by the Brief Pain Inventory (BPI). ALSYMPCA reported an SSE-free survival rate at 6 months of 78%. We calculated that if the SSE-free 6 months survival rate in our population is similar to that in the ALSYMPCA population, with 300 patients we can estimate it with a .95-confidence interval of 5 percentage points above and below. In particularly we expect to have over 95% power to show that the 6 months SSE-free survival rate on Ra-223 lies statistically significantly above 70%. In parallel to these considerations we looked at the power to detect a decrease in pain score when comparing patient reported outcomes (PRO) while on radium treatment with baseline. Of

each of the 300 patients we expected an average of 4.5 measurements, bringing the expected number of measurements to 1350. However, for the sake of the power calculation we restricted ourselves to a very basic comparison of only two measurements per patients: pain after six months and pain at baseline. For this comparison, simulations show that under a wide range of assumptions concerning the initial distribution of pain scores over the patients, with 300 patients we have more than 95% power to detect (in a paired t-test) an average decrease in pain as small as one point on BPI pain scale. The pain response on Ra-223 therapy will be presented in a separate publication, along with other PROs.

In line with PCWG3 recommendations[17], survival and progression were evaluated using Kaplan-Meier (KM) estimates. The log-rank test was used in univariate survival analysis to identify variables that could predict OS and PFS. Factors with P values ≤0.10 were included in a multivariate model for survival rate by Cox proportional-hazard analysis. Statistical analyses were conducted using Statistical Analysis System (SAS) statistical software (SAS Institute Inc., Chicago, Ill., USA) and R (R Foundation for Statistical Computing, Vienna, Austria)[18].

RESULTS

Patient Characteristics

Between February 2015 and March 2018, 305 patients from 20 Dutch hospitals were enrolled in the ROTOR. The median follow-up was 13.2 months (95% confidence interval [CI] 12.1-14.4 months). Five patients were excluded because written approval to use identifiers was not obtained or not properly stored according to guidelines. Therefore, 300 patients were evaluable (Figure 1). Out of these 300 patients, 10 had no baseline data available and from 10 no AE data were collected. Baseline patient characteristics are summarized in Table 1. Practically all patients had an ECOG performance score of 0-1, all patients had two or more bone metastases and 19.6% of the patients were asymptomatic prior to RA-223 treatment.

Previous, concomitant and RA-223 treatment

For 11.3% of the patients, Ra-223 was the first treatment line, 34.7% received 1 line of systemic treatment prior to Ra-223, while 54% of the patients received 2 or more lines prior to Ra-223 (Table 1). Of the patients treated with life-prolonging therapy prior to Ra-223, 80.5% were treated with Abi and/or Enz, 74.1% were treated with Doc and 19.5 % were treated with Cab. All patients treated with Cab had previously been treated with Doc. EBRT within 12 weeks prior to Ra-223 was received by 8.7% of patients. Forty-one percent of the patients were treated with bisphosphates or denosumab. Of the 300 evaluable patients, 290 received at least one cycle of Ra-223, while the median number of cycles was 5 and 54.7% of patients received at least 5 Ra-223 cycles (Table 2). Reported reasons for Ra-223 treatment discontinuation included, six cycles

completed (46.3%), symptomatic progression (35%), no PSA response (20.7%) and radiological progression (16%)(Table 2).

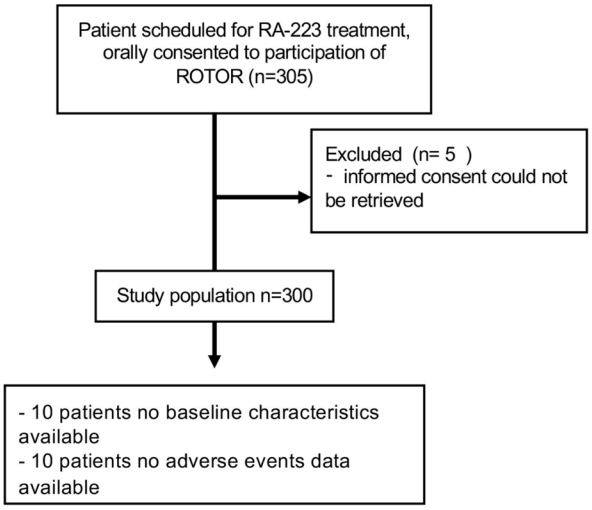

Figure 1. Consort diagram

Table 1. Patient and Treatment Characteristics

Patient Demographics	**Median [IQR], Number of Patients (%) or value**
Age, years	73.6 [46.3-91.5]
ECOG performance status	*(n=279)*
0-1	264 (94.6)
2	15 (5.3)
≥3	0
Symptomatic patients	131(80.4)
Asymptomatic patients	32 (19.6)
Gleason	(n=251)
≤7	87 (34.9)
8	67 (26.9)
≥9	95 (38.2)
Metastatic sites	*(n=290)*
Bone	287 (99.0)
Lymph nodes	84 (29.0)
Visceral organs	0 (0)

No. of bone metastases	*(n=272)*
0-1	0
2-6	21 (7.7)
>6	246 (90.4)
Super scan	5 (1.8)
Laboratory values	
PSA, mg/L	72.3 [25.0-175.0]
Hemoglobin, g/dL	12,6 [11.3-13.4]
ALP, U/L	138 [85-248]
ALP ³220 U/L	81 (27.9)
LDH, U/L	225.0 [192-296]
Albumin, g/L	42 [38-44]
Calcium, mmol/ml	2.35 [2.26-2.43]
Testosterone, nmol/l	0.5 [0.45-0.50]
Previous lines of systemic life prolonging treatments	*(n=300)*
0	34 (11.3)
1	104 (34.7)
2	96 (32.0)
3	50 (16.7)
4	13 (4.3)
5	3 (1.0)
Specific previous treatments	*(n=266)*
Abiraterone and or Enzalutamide	214 (80.5)
Docetaxel	197 (74.1)
Cabazitaxel	52 (19,5)
Radiotherapy 12 weeks prior to treatment	26 (8.7)
Concomitant medication	*(n=294)*
Bisphosphonates	49 (16.7)
Denosumab	63 (24.4)

Abbreviations: n:patients evaluable; ECOG: Eastern Cooperative Oncology Group; ALP: serum Alkaline Phosphatase; LDH: Lactate dehydrogenase; PSA: serum Prostate Specific Antigen;

Clinical outcomes

The primary outcome of this study, 6 months SSE free survival was 83%, which is 5% higher than the 78% reported in ALSYMPCA (Figure 2a). During Ra-223 treatment, 58 patients (19.3%) experienced an SSE (Table 2); 2.3% of these SSE were pathological fractures, 5.7% spinal cord compressions, 11% EBRTs and 0.3% tumor-related orthopedic surgical intervention. After a median follow-up of 13.2 months (95%CI 12.1-14.4), PFS was 5.1 months (Figure 2b) and OS was 15.2 months (Figure 2c; Table 2). PSA and ALP declines of ≥50% were observed in 4.3% and 22.0% of patients, respectively (Table 2). Patients with a PSA decline >30% had median PFS

and OS of 10.4 and 21.0 months, respectively. Patients with ALP declines >30% had median PFS and OS of 6.2 and 19.1 months, respectively (Table 2). Both PSA and ALP responses were related with longer then median PFS and OS, while ALP responses were more frequent. Time to ALP progression was 6.3 months (95%CI 6.0-6.6) (Table 2). Although asymptomatic patients were infrequent, these patients had better PFS compared to symptomatic patients, 5.9 and 4.3 months, respectively (Table 2). Symptomatic patients had an OS of 13, 4 months, while there were not enough events to calculate OS in asymptomatic patients. (Supplementary figure 1a; Table 2). PFS in patients previously treated with Cab was 4.2 month, while Cab naïve patients had a PFS of 5.2 months (Table 2; Supplementary figure 2d). During Ra-223 treatment 28.1% of the patients were hospitalized and median time from first Ra-223 treatment until start of subsequent treatment was 5.9 months (95%CI 4.1-7.7) (Table 2).

Table 2. Outcomes of Radium-223 treatment

Outcome variables	Median [IQR], No. of Patients (%) or 95% CI
No. of Radium-223 cycles	
Median number of cycles	5.0 [3-6]
0	10 (3.3)
1-2	40 (13.3)
3-4	86 (28.7)
5-6	161 (53.7)
>6	3 (1.0)
ALP decline	*(n=255)*
³30%	122 (47.8)
³50%	56 (22.0)
³90%	1 (0.4)
Time to ALP progression, Months	6.3 (6.0-6.6)
PSA decline	*(n=256)*
³30%	16 (6.3)
³50%	11 (4.3)
³90%	3 (1.2)
Reason for Radium-223 discontinuation	
Six cycles completed	139 (46.3)
Symptomatic progression	105 (35.0)
No PSA response	62 (20.7)
Radiological progression	48 (16.0)
Intolerance	44 (14.7)
Death	8 (2.7)
Other/Reason unknown	9 (3.0)

Symptomatic skeletal event during Radium-223 treatment	
Total SSE	58 (19,3)
Pathological fractures	7 (2.3)
Radiotherapy	33 (11.0)
Spinal cord compression	17 (5.7)
Bone surgery	1 (0.3)
Time to first SSE, Months	*Median not reached*
Progression free survival (Months)	
Whole population	5.1 (4.5-5.8)
Patients >30% PSA decline	10.4 (6.6-14.2)
Patients >30% ALP decline	6.2 (5.1-7.3)
Patients with bone-only metastases	5.5 (4.9-6.0)
Symptomatic patients	4.3 (3.3-5.3)
Asymptomatic patients	5.9 (4.9-6.9)
Patients not treated with Cabazitaxel	5.2 (4.5-5.9)
Patients treated with Cabazitaxel	4.2 (3.5-4.8)
Overall Survival (Months)	
Whole population	15.2 (12.8-17.6)
Patients >30% PSA decline	21.0 [14.7-27.2)
Patients >30% ALP decline	19.1 (13.5-24.6)
Symptomatic patients	13.4 (9.5-17.3)
Asymptomatic patients	*Median not reached*
Time to subsequent treatment, Months	5.9 (4.1-7.7)
Hospital admission during Radium-223 treatment	82 (28.1)

Abbreviations: ALP: serum Alkaline Phosphatase; PSA: serum Prostate Specific Antigen; SSE: Symptomatic Skeletal Event

Univariate and multivariate analysis affecting PFS and OS

Univariate and multivariate analysis of factors associated with PFS and OS are summarized in Table 3. According to univariate analysis, previous Doc, previous Cab, elevated ALP, elevated LDH and higher Gleason score, were associated with shorter PFS, while higher serum calcium levels, higher hemoglobin, bone-only metastases, >30% ALP decline and >30% PSA decline and number of Ra-223 cycles were associated with longer PFS. However, multivariate analysis only confirmed previous use of Cab and bone-only metastases as independent predictors of a shorter and longer PFS, respectively.

Univariate analysis suggested an association between shorter OS and line of treatment, previous Cab, elevated ALP and elevated LDH, while higher serum calcium, bone-only metastases, >30% ALP decline, number of Ra-223 cycles and >30% PSA decline were associated with a longer

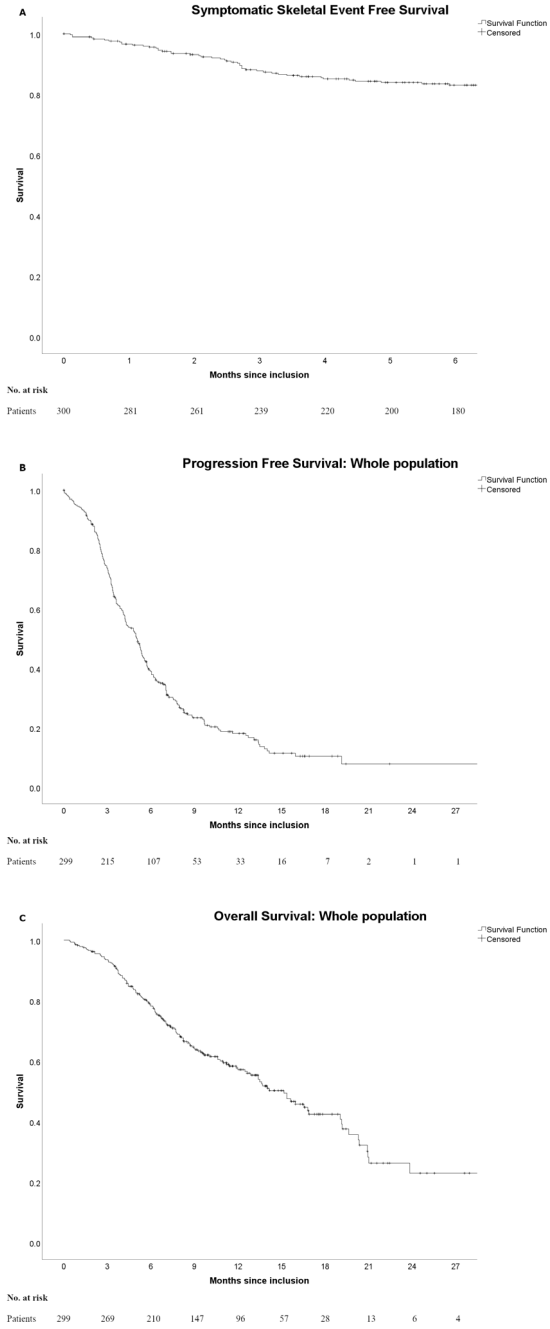

Figure 2.

A: Kaplan-Meier curves of Symptomatic Skeletal Event Free Survival. **B:** Kaplan-Meier curves of Progression Free Survival of the whole population. **C:** Kaplan-Meier curves of Overall Survival of the whole population

OS. Only elevated LDH and bone-only metastases were independent predictors in a multivariate Cox model of shorter and longer OS, respectively.

Tolerability

Adverse event (AE) were collected from 290 patients (Supplementary table 1). Grade 3 anemia was observed in 18.6% of the patients, but no grade 4. Grade 3 thrombocytopenia was observed in 3.1% of the patients and grade 4 in 1%. Grade 3 neutropenia was observed in 2.4% and grade 4 in 0.3%. The most common reported non-hematologic AE was fatigue (61.4%). The majority of these patients had grade 1-2 fatigue (55.5%). Other common non-hematologic AEs (all grades) were nausea (31%) and diarrhea (28.6%).

DISCUSSION

When ALSYMPCA was conducted, no life-prolonging treatments apart from Doc were available. Patients not fit for, or refusing chemotherapy had no other treatment options than participation in the ALSYMPCA trial, while nowadays these patients are treated with less toxic second-generation androgen receptor-antagonists.[19, 20] As a result, only 11% of patients received Ra-223 as a first-line treatment in the present cohort, while 80.5% of patients were treated with Abi or Enz prior to Ra-223. Moreover, 54% of patients received two or more lines of treatment prior to Ra-223 treatment. This suggests that with the introduction of new life-prolonging treatment options, Ra-223 is now used in more pre-treated patients then in ALSYMPCA.

Although patients in the registry were predominantly treated with Ra-223 in second and later lines, and patients in the ALYMPCA population were treated in first or second line, OS in the registry is comparable to OS in the treatment arm of ALSYMPCA (15.2 months and 14.9, respectively).[6] The comparable OS might be attributed to strict patient selection for Ra-223 treatment in real-life, but also to effective subsequent treatments. Better patient selection is reflected by a lower frequency of ECOG ≥2 scores (5% and 13%, respectively), lower baseline PSA levels (PSA 72.3mg/L and 146 mg/L, respectively) and lower baseline ALP levels (ALP 128 U/L and 211 U/L, respectively) in the non-study cohort when compared to the ALSYMPCA population. Univariate regression analysis in our cohort suggests that higher PSA and higher ALP are associated with shorter OS, confirming reports from previous studies.[21, 22]

The rate of ≥30% ALP declines in our cohort was similar to what was reported in ALSYMPCA (47.8% and 46.8%, respectively). In the present cohort, a >30% decrease of ALP from baseline was associated with a longer median PFS and OS when compared to the entire cohort. This favorable outcome was also reflected in univariate analysis of PFS and OS. This is in agreement with the results of a post-hoc analysis of ALSYMPCA, where a significant decline in risk of death

Table 3. Univariate and multivariate analysis of factors affecting Progression Free Survival (PFS) and Overall Survival (OS)

Variable	PFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	P	HR	95%	p	HR	95% CI	P	HR	95%	p
Age + 1y	0.98	0.97-1.0	0.010	1.01	0.98-1.04	0.628	1.00	0.98-1.02	0.750			
ECOG +1	1.10	0.84-1.42	0.47				1.31	0.94-1.85	0.114			
Calcium	0.41	0.14-1.18	0.098	1.50	0.25-9.14	0.658	0.36	0.14-0.89	0.027	0.61	0.06-6.51	0.680
Log ALP	1.29	1.15-1.46	<0.001	1.22	0.96-1.55	0.106	1.51	1.31-1.73	<0.001	1.25	0.94-1.65	0.124
>30% ALP decline	0.58	0.45-0.75	<0.001				0.68	0.48-0.97	0.028			
Log PSA	1.05	0.99-1.12	0.081	0.98	0.89-1.08	0.663	1.19	1.09-1.29	<0.001	1.07	0.94-1.22	0.301
>30% PSA decline	0.36	0.21-0.61	<0.001				0.39	0.18-0.83	0.005			
Log LDH	1.84	1.50-2.26	<0.001	1.28	0.82-1.00	0.284	3.09	2.43-3.93	<0.001	2.99	1.85-4.84	<0.001
Hb +1	0.89	0.82-0.96	0.004	0.98	0.84-1.14	0.779	0.76	0.69-0.85	<0.001	0.94	0.77-1.15	0.534
Gleason + 1	1.27	1.12-1.44	<0.001	1.05	0.87-1.26	0.62	1.16	0.99-1.36	0.071	0.92	0.75-1.14	0.451
No of metastases	1.01	1.00-1.01	0.03	1.02	1.01-1.03	0.003	1.18	0.91-1.51	0.211			
Only bone metastases	0.57	0.43-0.75	<0.001	0.31	0.19-0.49	<0.001	0.49	0.35-0.69	<0.001	0.21	0.13-0.46	<0.001
Line nr	1.04	0.91-1.19	0.59				1.22	1.03-1.45	0.023	1.38	0.89-2.13	0.148
Abi and/or Enz	0.78	0.56-1.08	0.128				1.26	0.80-1.98	0.314			
Docetaxel	1.41	1.03-1.94	0.031	1.33	0.81-2.22	0.248	1.40	0.92-2.13	0.113			
Cabazitaxel	1.44	1.04-1.99	0.026	1.89	1.01-3.51	0.046	2.31	1.58-3.38	<0.001	1.46	0.64-3.34	0.371
Denosumab	0.99	0.67-1.27	0.605				0.69	0.44-1.08	0.105			
Bisphosphonates	0.95	0.68-1.34	0.767				1.15	0.76-1.76	0.505			
Symptomatic	1.29	0.72-2.34	0.394				1.15	0.74-1.80	0.535			
No of Ra223 cycles	0.63	0.58-0.69	<0.001				0.60	0.56-0.64	<0.001			

All values are at baseline. Age+1Y:HR per year age difference; ECOG +1: HR per every ECOG-point increase; Line nr: HR per every additional treatment-line. Calcium: HR per 1.0 mmol/L increase of calcium; Log ALP: HR per every doubling of Alkaline phosphatase; >30% ALP decline: >30% ALP decline during treatment from baseline; Log PSA: HR per every doubling of PSA; >30% PSA decline: >30% PSA decline during treatment from baseline; Log LDH: HR per every doubling of Lactate dehydrogenase; Hb+1: HR per every point (g/dL) of hemoglobin increase; Gleason+1: HR per every point of Gleason score increase; No of metastases: HR per increase of number of metastases ranging from 0-1. 2-6. >6 or superscan. Symptomatic: Patients were considered symptomatic when they used analgesics regularly or were treated with EBRT for cancer-related bone pain in the previous 12 weeks; No of Ra223 cycles: every additional cycle after the first Ra-223 cycle.

in patients with a ALP decline after 12 weeks was reported.[6, 23] A >30% PSA decline from baseline was associated with an even more favorable PFS and OS in univariate analysis when compared to the entire cohort. In contrast to our findings, a post-hoc analysis of ALSYMPCA reported no correlation between PSA response and OS.[23]

Compared to ALSYMPCA, patients in the present cohort had more Grade 3 anemia (18% and 11%, respectively). Other hematological AEs were similarly frequent as in ALSYMPCA. The most common non-hematological AEs in the present cohort and in ALSYMPCA were nausea (27% and 36%, respectively), diarrhea (27.7% and 25%, respectively) and fatigue (61.4% and 26%, respectively). The cause of the significant difference in fatigue between the studies is unclear, since there are no major differences between baseline ECOG-performance score and baseline hemoglobin between our cohort and ALSYMPCA. The more advanced and pre-treated stage of non-study mCRPC patients treated with Ra-223 might account for the differences found. However, the differences are mainly in the occurrence of grade 0-2 fatigue (55% and 22%, respectively), while grade 3 (5.9% and 4%, respectively) and grade 4 fatigue (0% and 1%, respectively) are comparable.

An update of safety in ALSYMPCA, 3 years after first injection revealed no new long-term complications or safety concerns.[6, 24] Also, the present cohort raises no new short-term safety concerns, apart from those already reported in ALSYMPCA. However, the Pharmacovigilance Risk Assessment Committee (PRAC) from the European Medicines Agency (EMA) recently advised to restrict the use of Ra-223 to third line treatment or to patients with no other treatment options. [25, 26] This recommendation was based on higher mortality and fracture rates in patients treated with Abi and Ra-223 in the ERA-223 trial.[27] It was concluded that the mortality was not the result of the interaction between Ra-223 and Abi, but due to Ra-223 treatment alone. In our real-life population, the majority of patients were treated with Ra-223 in second or third line, while the rate of SSE was comparable to ALSYMPCA, where patients were treated in first or second line. This could not be attributed to differences in use of denosumab or bisphosphonates, which was approximately 40% in both studies. Therefore, this study does not support the advice to treat patients in later line with Ra-223 for safety reasons.

In univariate analysis of our cohort, more systemic anti-cancer treatment prior to Ra-223 did not affect PFS. However, line of Ra-223 treatment was associated with OS, which is obviously the consequence of more advanced disease in later lines of treatment. There was no association between prior Abi or Enz treatment and PFS or OS, but both in univariate and multivariate cox-regression analysis, previous Cabazitaxel treatment was associated with a less favorable PFS and OS. The association between prior chemotherapy and shorter survival has been reported in retrospective studies, while Alva et al. reported that prior treatment with Abi or Enz had no negative effect on OS, which agrees with our findings. [28, 29] Bone-only metastases was associated with favorable PFS and OS in both univariate and multivariate cox-regression analysis. However, in

ALSYMPCA, patients with a single lymphadenopathy of less than 3 cm in the short-axis diameter were included.[6] In the current study, no data was collected on the extension of extra osseous metastases. Consequently, no new cutoff for the maximum number of lymph nodes involved, in order to benefit from Ra-223 can be suggested.

The main limitation of this study was its non-randomized nature. Moreover, dates of radiological assessments prior, during and after Ra-223 treatment were not prescribed but at the discretion of the treating physician. Another limitation of this study was that there are likely different criteria between the participating centers to select patients for Ra-223 treatment. This might be the result of the absence of reliable data to base selection on. However, these differences in patient selection reflect the non-study nature of the population.
In conclusion, this prospective registry of Ra-223 treatment in a non-study mCRPC population, suggests that Ra-223 is safe and effective. Moreover, efficacy in the non-study population seems comparable with the less treated ALSYMPCA population. Moreover, the data of this non-study cohort suggests that patients not previously treated with Cab, have a favorable outcome. These findings need confirmation.

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DISCLOSURE STATEMENT

Bergman participated in Advisory Boards of Janssen Pharma, Bayer, Sanofi and Astellas, received speaking fees from Astellas, Bayer, Jansen Pharma and Astellas and received a research grants from Sanofi and Astellas, not related to this study. Zwart participated in Advisory Boards of Astellas and received research grants of Astellas and AstraZeneca. Haanen has provided consultation, attended advisory boards, and/or provided lectures for: AIMM, Amgen, AZ/Medimmune, Bayer, BMS, GSK, Ipsen, Merck Serono, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics for which NKI received honoraria. He also received grant support from Bayer, BMS, MSD, Novartis, Neon Therapeutics, and Pfizer. All remaining authors have declared no conflicts of interest.

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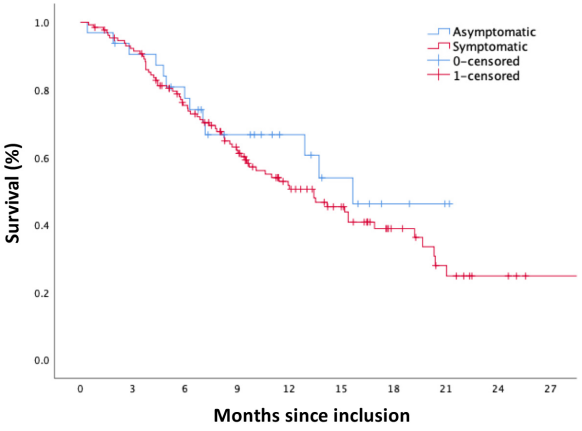
SUPPLEMENTARY MATERIAL

Supplementary Table 1. Adverse events

	Present at baseline	During treatment
	No. of Patients (%)	No. of Patients (%)
Most common hematologic		
Anemia		
Grade 3	51 (17.6)	54 (18.6)
Grade 4	0 (0)	0 (0)
Thrombocytopenia		
Grade 3	3 (1.0)	9 (3.1)
Grade 4	1 (0.3)	3 (1.0)
Neutropenia		
Grade 3	2 (0.3)	7 (2.4)
Grade 4	0 (0)	1 (0.3)
Most common non-hematologic		
Nausea (all grades)	7 (2.4)	90 (31.0)
Diarrhea (all grades)	1 (0.3)	83 (28.6)
Fatigue (all grades)	47 (16.2)	178 (61.4)
Grade 1-2	40 (13.8)	161 (55.5)
Grade 3	7 (2.4)	17 (5.9)
Grade 4	0 (0)	0 (0)

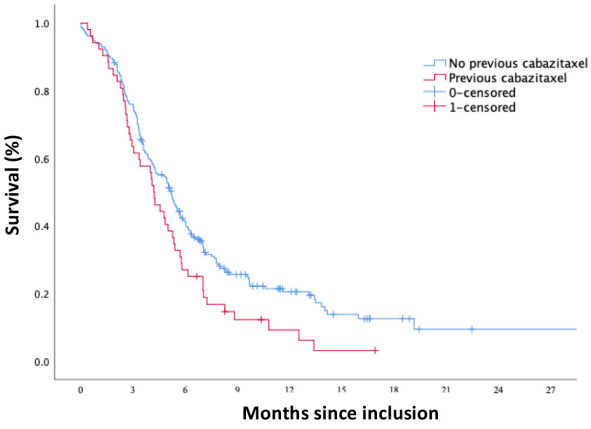
A **Overall Survival: symptomatic patients**



No. at Risk

Not Sympt.	32	27	22	15	10	6	2	0	0	0
Sympt.	131	117	88	65	43	30	15	8	3	0

B **Progression Free survival: previous cabazitaxel treatment**



No. at Risk

No CAB	213	160	79	38	22	10	5	1	1	1
CAB	52	32	13	4	2	0	0	0	0	0

Supplementary Figure 1.

A: Kaplan-Meier curves of Overall survival in symptomatic and asymptomatic patients. **B:** Kaplan-Meier curves of progression Free survival in patients previously treated with Cabazitaxel


Radium-223

Chapter 6

Integrated Analysis of Pain, Health-Related Quality of Life and Analgesic use in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Radium-223

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#These authors contributed equally

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ABSTRACT

Background

First line- or post docetaxel Radium-223 (Ra-223), an alpha-emitting radiopharmaceutical, treatment established an improved overall survival and Health-Related Quality of Life (HRQoL) in symptomatic metastatic castration-resistant prostate cancer (mCRPC) patients. However, effects on pain were not specifically evaluated. Here we assess integrated HRQoL, pain and opioid use in a contemporary, more extensively pretreated, symptomatic and asymptomatic mCRPC population.

Patients and methods

mCRPC patients scheduled for Ra-223 treatment were included in a real-life cohort and analyzed for HRQoL, pain and opioid use, using FACT-P and BPI-SF questionnaires and recording of opioid use and dosage, respectively. Primary outcome measure was the percentage of patients experiencing a complete pain response, while a complete- or partial pain response (better BPI-SF score and decrease of opioid use) and a better- or no change in HRQoL was evaluated as an integrated overall clinical response (IOCR)

Results

This registry included 300 patients, of whom 105 (35%) were evaluable for FACT-P and BPI-SF during Ra-223 treatment. Forty-five (43%) patients had PAB (BPI-SF worst pain score 5-10 points) and 60 (57%) had no-PAB (BPI-SF worst pain score 0-4 points). Complete pain response was achieved in 31.4% of the patients, while 58% had an IOCR. The median time to pain progression was 5.6 months, and the median time to deterioration of FACT-P scores was 5.7 months, the difference between PAB and no-PAB patients was not significant.

Conclusions

In contemporary, extensively pretreated mCRPC patients, Ra-223 treatment induced complete pain responses while Integrated analysis of HRQoL, pain response and opioid use, demonstrated that the majority of patients derive clinical benefit.

INTRODUCTION

Each year, over 1.2 million men are diagnosed with prostate cancer worldwide and approximately 350.000 patients succumb to the consequences of this disease, rendering it the most common non-cutaneous cancer in males and the second-largest cause of cancer-related death in men.[1] Metastatic castration-resistant prostate cancer (mCRPC) is the end stage of this disease with high morbidity and mortality as hallmarks.[2] Up to 90% of mCRPC patients develop bone metastases, which are not only associated with a shorter life expectancy, but also with cancer-related pain and skeletal-related events, including pathological fractures, compression of the spinal cord, vertebral instability and hypercalcemia, which all affect Health-Related Quality of Life (HRQoL).[3] Symptoms and complications of bone metastases can be treated with analgesics, external beam-radiation therapy (EBRT), bisphosphonates, RANK-ligand inhibitors, surgery and radiopharmaceuticals.[4]

In the ALSYMPCA study, the alpha-emitter Radium-223 dichloride (Ra-223) showed a 3.6 month overall survival (OS) benefit and a favorable HRQoL in symptomatic mCRPC patients.[4] However, the effect of Ra-223 on pain was not evaluated using pain-specific questionnaires, and changes in the dosages of analgesics were not considered in the evaluation of pain.[5] Another study showed that asymptomatic mCRPC patients treated with Ra-223 had better treatment outcomes than symptomatic patients, but HRQoL and pain were not assessed.[6] Since the introduction of Ra-223 into the clinic in 2013, the number of treatment options for mCRPC patients has expanded significantly.[7] Consequently, contemporary patients treated with Ra-223 are more extensively pretreated, questioning the present relevance of HRQoL results from the ALSYMPCA study.[8] Given the paucity of knowledge on the effect of Ra-223 on pain and HRQoL in contemporary symptomatic and asymptomatic mCRPC patients, there is a need for a reevaluation.[8] In this observational study we evaluated and integrated the effect of Ra-223 on patient-reported pain, analgesic use and HRQoL in a real-life cohort. Patients with pain at baseline (PAB) and no pain at baseline (no-PAB) were assessed separately.

METHODS

Study population and design

A non-interventional, multicenter, prospective observational registry was initiated to evaluate clinical outcomes, HRQoL, pain and analgesic use in a real-life mCRPC population treated with Ra-223. The study design is fully described elsewhere.[8] In short, patients aged 18 years or older with progressive mCRPC and scheduled for Ra-223 treatment were included prospectively in 20 hospitals in the Netherlands (intention-to-treat population). There were no other in- and exclusion criteria or stopping rules. Paper questionnaires were sent to the patients one week before each

treatment and monthly in follow-up, which were returned by mail to the data management office. Clinical data was collected from the medical records after completion of Ra-223 treatment. This registry was approved by local medical ethics committees. Obtaining signed informed consent for the study was not required, but patients had to provide oral consent and written approval for registration and use of their identifiers.

Procedures

Patients were treated with Ra-223 at 4 week intervals, according to the manufacturer's guidelines. Number of treatments was at the physician's discretion, who provided the motivation for discontinuation. Patients were evaluated at the outpatient clinic prior to each treatment, where Eastern Cooperative Oncology Group performance and clinical lab assessments were documented. Radiological evaluation during and after Ra-223 treatment and frequency of follow-up visits were at the physician's discretion. Patients' baseline characteristics within 14 days prior to the first Ra-223 treatment were recorded. Baseline characteristics, efficacy assessments and patient reported outcome measures (PROMs) were stored in an electronic case-report form. Follow-up was continued until start of subsequent treatment or death.

Patient reported outcomes measures

HRQoL and pain were assessed using the validated patient self-reported measures Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory-Short Form (BPI-SF), respectively. [9–11] Furthermore, patients were asked to list all analgesic drugs (free text: name, dose, frequency and period of use) used in the previous 4 weeks. Patients were requested to complete all questionnaires at baseline and every 4 weeks during and after Ra-223 treatment until start of subsequent treatment or death. Patients were considered evaluable for pain, opioid use and HRQoL analysis when baseline questionnaires and at least one set of questionnaires during treatment were returned. According to published algorithms, scale scores were calculated when at least 50% of the items in that scale had been completed.[9–11]. An overview of the questionnaires and their use and interpretation is provided in Supplementary Table 1.

Brief Pain Inventory-Short Form

The BPI-SF contains 4 items on pain severity (worst pain, least pain, Average pain and pain now) and 7 items on pain interference (*e.g.:* during sleep, walking, daily activities).[9] Every question is scored from 0 to 10, where 0 is no pain/interference and 10 is the worst imaginable pain/interference (Supplementary Table 1). The clinically meaningful change of BPI-SF score (CMC-BPI) was defined as a change of score of at least 30% from baseline score, with a minimum of 2 points.[9, 10] Two groups in the cohort were separately analyzed; no-PAB patients were defined as a Worst Pain score at baseline between 0 and 4 points, and PAB patients were defined as a Worst Pain score between 5-10. This division is in line with the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommendations.[12]

Functional Assessment of Cancer Therapy-Prostate

The FACT-P is a validated 39-item questionnaire, including the FACT-General original subscales: Physical Well-being (PWB), Social/Family Well-being (SWB), Emotional Well-being (EWB), and Functional Well-being (FWB), and a prostate cancer subscale (PCS).[11] Items are rated on a five-point scale ranging from 0 (not at all) to 4 (very much). Subscales as well as the total score can be calculated by the sum of the items. When not all subscales are evaluable, the total score cannot be calculated. The range of these scores is (0–156) for the FACT-P total score, (0–28) for the PWB, SWB, and FWB, (0–24) for EWB, and (0–48) for PCS. (Supplementary Table 1). The clinically meaningful change of FACT-P (CMC-FACT) was defined as a minimal change of 10 points from baseline for the Total FACT-P score, 3 points from baseline for the subscales and 2 points from baseline for pain. A higher score indicates a better HRQoL.[13]

Analgesic use

Patients were asked to fill out a list of all analgesics, dosages and frequencies used in the past 4 weeks (Supplementary Table 1). Dosages of the various opioid drugs and formulations were converted to oral morphine equivalents in mg per day (Supplementary Table 2). Non-opioids and on-demand opioids were not included in our analysis.

Endpoints and statistical analyses

The primary endpoint of the study was the percentage of patients experiencing a complete pain response. The International Bone Metastases Consensus Working Party (IBMCWP) has defined criteria for evaluating results of these types of studies.[14] In this classification, the use of opioid drugs was integrated into the PROMs as follows: A complete pain response was defined as a score of 0 on the BPI-SF Worst pain item and no increase in daily use of analgesics; a partial response was defined as a pain reduction of at least 2 points on the BPI-SF Worst pain item or a reduction of at least 25% of daily use of analgesics; pain progression was defined as an increase in pain of at least 2 points on the BPI-SF Worst pain item or an increase of at least 25% of daily analgesic use. Indeterminate response was defined as all pain decreases, not captured by complete response or partial response. Patients were categorized according to their best response.[14] Secondary endpoints included the percentage of patients experiencing a partial and an indeterminate pain response. Moreover, patients were categorized by their Total FACT-P response, which was “improved HRQol” (better score meeting CMC-FACT), “no change in HRQoL” (no change or changes not meeting CMC-FACT), or “worse HrQoL” (deteriorated score meeting CMC-FACT). A complete or partial pain response and an improved HRQoL or no change in HRQoL were evaluated as an Integrated Overall Clinical Response (IOCR).

Moreover, secondary outcomes included Time to Total FACT-P Deterioration (TTFD), Time to Pain Progression (TPP), Progression Free Survival (PFS) and OS. Definitions of the secondary endpoints are listed In Supplementary Table 3,. All time-to-event endpoints were estimated using the Kaplan-

Meier product limit method. Patients who did not experience an event of interest were censored at their last day of follow-up for OS and PFS and at the time of their last questionnaire for TTFD or TPP.

Sample size calculation

The sample size was chosen to ensure enough power to detect a meaningful increase (compared to historical placebo) of the number of Ra-223 treated patients with a complete pain response. From the placebo arm of the ALSYMPCA trial we estimated that, without treatment, up to 20% of patient will have a complete or partial pain response.[4] Our interest is in the power to find a one-sided 95% confidence interval around our observed pain response rate that lies entirely above the 'placebo rate' of 20%, under the assumption of a true pain response rate of 30% or more. We computed this power under various assumptions on the percentage of patients returning at least two PROMs forms. Of the scenarios presented in the Supplementary Table 4, we considered the number of 120 evaluable patients the most realistic. We estimated a 40% response rate based on the reported 10-70% response rates in previous studies on self-reported outcome measures in real-life populations .[15–17] As shown in Supplementary Table 4, the power at this percentage of evaluable patients is 81%.

Software

TENALEA, an online service, was used to collect data. IBM SPSS statistics for iOS, version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for iOS, Version 25.0. Armonk, NY: IBM Corp.) and Statistical Analysis System (SAS) statistical software were used for statistical analysis and for conducting graphs. Additional graphs and analyses were made and performed using GraphPad Prism version 8.00 for Mac OS X, GraphPad Software, La Jolla California USA, www.graphpad.com.

RESULTS

Baseline characteristics and survival

Between April 2015 and March 2018, 305 mCRPC patients from 20 Dutch hospitals, scheduled for Ra-223 treatment were included. Five patients were excluded because written approval to use identifiers (name, address, residence) could not be retrieved or was not stored according to guidelines (Figure 1). This registry included 300 patients (registry sample), of whom 121 (40%) completed the baseline questionnaires, and 105 (35%) completed a baseline and at least one follow-up BPI-SF and FACT-P questionnaire and were therefore evaluable for the individual questionnaires (evaluable sample). One hundred and three patients were evaluable for pain response analysis, because 2 patients provided insufficient data on analgesics use.

The registry sample and the evaluable sample were comparable on most baseline and survival characteristics and treatment outcomes (Table 1, Supplementary table 5). However, patients in the

evaluable sample used calcium/vitamin D suppletion more often (52% and 41.0%, respectively, p=0.02), and bisphosphonates less often (10% and 16.7%, respectively, p=0.03) than patients in the registry sample. Moreover, evaluable patients less often received EBRT in the 12 weeks prior to Ra-223 (2% and 8%, respectively, p=0.01). Although there was no significant difference in PFS, OS was significantly shorter in the registry sample than in the evaluable sample (15.2 and 19.6 months, respectively, p=0.04).

Of the 105 evaluable patients, 45 had pain at baseline (PAB) and 60 had no pain at baseline (no-PAB) (Figure 1, Table 1). The baseline characteristics of the two groups were comparable, however, as expected, more PAB patients used opioids (51.2% and 16.7%. respectively, p<0,001). After a median follow-up of the evaluable sample of 13.2 months, PAB patients had a significantly shorter OS than no-PAB patients (13.5 and 20.3 months, respectively, p=0.05) (Table 2, Supplementary Figure 1A).

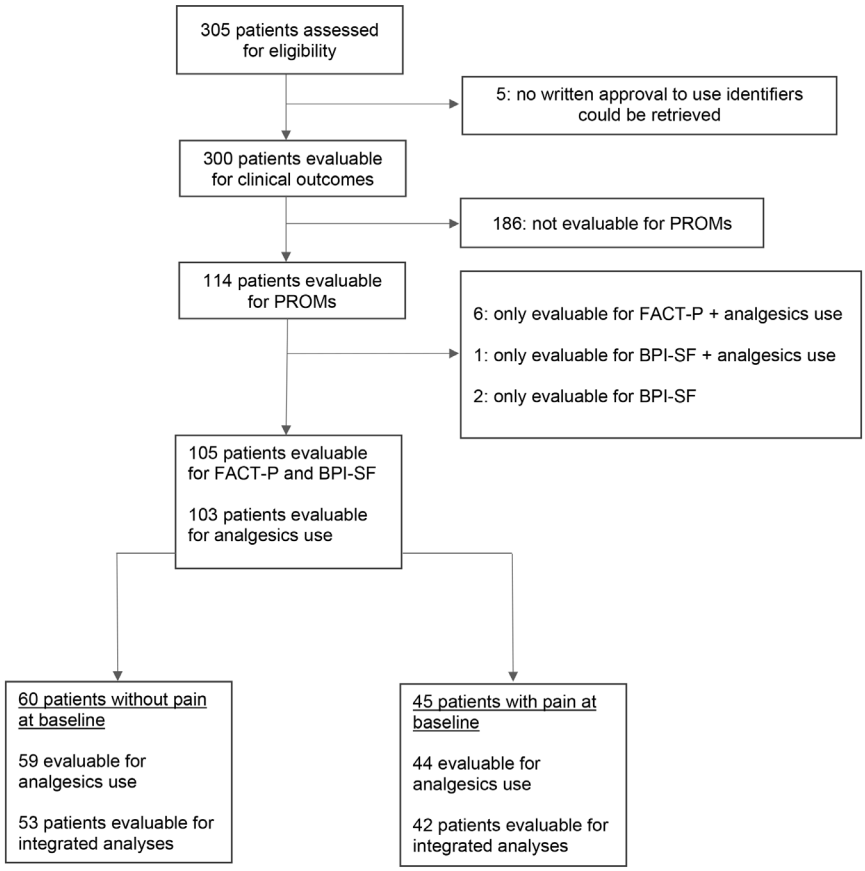

Figure 1. Consort diagram.

Health-related Quality of Life

Questionnaires completion rates per time point are listed in Supplementary Table 6.

BPI-SF

BPI-SF baseline values are reported in Supplementary table 7. PAB patients scored significantly higher on all baseline BPI-SF subscales compared to no-PAB patients ($p<0.001$), while the Worst pain subscale was used to define PAB and no-PAB patients. Median and mean times to deterioration of the BPI-SF subscales are reported in Table 3. The median TPP was 5.6 months in the evaluable sample (Table 3, Figure 2A). PAB patients had a significantly longer median time to deterioration of the BPI-SF subscale Average pain than no-PAB patients (12.6 and 5.5 months, respectively, $p=0.03$). (Table 3, Supplementary Figure 2). PAB patients also had a longer TPP than no-PAB patients (11.1 and 4.1 months, respectively; $p=0.001$)(Figure 2A). Changes in time of the BPI-SF Worst pain and Average pain subscales are displayed in Figure 2A and B, respectively, and the other BPI-SF subscales in Supplementary Figure 3. During treatment, 49.5% of the evaluable sample had a clinically meaningful improvement of the BPI-SF Worst pain subscale (Table 3; Figure 2B).

Table 1. Baseline characteristics of the registry sample and symptomatic and asymptomatic evaluable patients

Patient demographics	**Median or value [IQR], Number of Patients (%)**					
	Registry sample (*n*=300)	**Evaluable sample (*n*=105)**	***p***	**Pain at Baseline (*n=45*)**	**No Pain at Baseline (*n=60*)**	***p***
Age, years	73 [67-78]	73 [68–77]	ns	73 [68-77]	72 [66-78]	ns
ECOG performance status, no. of patients (%)			ns			ns
0-1	264 (88.0)	94 (90)		39 (87)	55 (92)	
2	15 (5.0)	3(3)		2 (4)	1 (2)	
≥3	0	0		0	0	
Missing data	21 (7.0)	8 (8)		4 (9)	4 (7)	
Gleason score, no. of patients (%)			ns			ns
≤7	87 (29.0)	27 (26)		10 (22)	17 (28)	
8	67 (22.3)	32 (30)		12 (27)	20 (33)	
≥9	95 (31.7)	27 (26)		14 (31)	13 (22)	
Missing data	51 (17.0)	19 (18)		9 (20)	10 (17)	
Metastatic sites, no. of patients (%)						
Bone	297 (99.0)	100 (95)	ns	44 (98)	56 (93)	ns
Lymph nodes	84 (29.0)	22 (21)	ns	10 (22)	12 (20)	ns
Visceral organs	0	1 (1)	ns	0	1 (2)	ns
Missing data	3 (1)	3 (3)		0	3 (5)	

No. of bone metastases, no. of patients (%)			ns			ns
0-1	0	2 (2)		1 (2)	1 (2)	
2-6	21 (7.0)	12 (11)		5 (11)	7 (2)	
>6	246 (82.0)	87 (83)		37 (82)	50 (80)	
Super scan	5 (1.7)	2 (2)		0	2 (3.1)	
Missing data	28 (9.3)	6 (6)		3 (7)	3 (5)	
Laboratory values						
PSA, mg/l	72.3 [25.0-175.0]	72 [22-179]	ns	73 [16-225]	72.0 [23-172]	ns
Hemoglobin, mmol/l	12.6 [11.3-13.4]	12.6 [11.6-13.4]	ns	12.3 [11.6-13.4]	12.7[11.6-13.4]	ns
ALP, U/l	138 [85-248]	118 [75-242]	ns	136 [85-330]	102 [73-186]	ns
ALP ^{3}220 U/l, *n (%)*	81 (27.0)	28 (27)	ns	15 (33)	13 (22)	ns
LDH, U/l	225.0 [192-296]	213 [183-280]	ns	237 [190-298]	206 [179-237]	0.07
Albumin, g/l	42 [38-44]	42 [40-44]	ns	42 [39-44]	42 [40-44]	ns
Calcium, mmol/l	2.4 [2.3-2.4]	2.4 [2.3-2.4]	ns	2.3 [2.2-2.4]	2.4 [2.3-2.4]	0.06
Testosterone, nmol/l	0.5 [0.45-0.50]	0.5 [0.5-0.5]	ns	0.5 [0.5-0.5]	0.5 [0.3-0.5]	ns
Previous lines of systemic treatments (%)			ns			ns
0	34 (11.3)	10 (10)		5 (11)	5 (8)	
1	104 (34.7)	34 (32)		10 (22)	24 (40)	
2	96 (32.0)	35 (33)		21 (47)	14 (23)	
3	50 (16.7)	19 (18)		4 (9)	15 (25)	
4	13 (4.3)	5 (5)		4 (9)	1 (2)	
5	3 (1.0)	1 (1)		1 (2)	0	
Missing data	0	1 (1)		0	1 (2)	
Specific previous treatments, no. of patients (%)						
Abiraterone and or Enzalutamide	214 (71.3)	75 (71)	ns	31 (69)	44 (73)	ns
Docetaxel	197 (65.7)	73 (71)	ns	35 (78)	38 (63)	ns
Cabazitaxel	52 (17.3)	18 (17)	ns	10 (22)	8 (13)	ns
Radiotherapy 12 weeks prior to treatment	23 (8)	2 (2)	0.01	2 (4)	0	ns
Concomitant medication, no. of patients (%)						
Bisphosphonates	49 (16.7)	11 (10)	0.03	3 (7)	8 (13)	ns
Denosumab	63 (24.4)	25 (24)	ns	14 (31)	11 (18)	ns
Calcium/Vitamin D	123 (41.0)	55 (52)	0.02	25 (56)	30 (50)	ns
Analgesics use		*n=103*		*n=44*	*n=59*	
Non-opioids	NA	3 (2.9)		0 (0)	3 (6.7)	
Opioids	NA	38 (36)		25 (56)	13 (22)	<0.001
Dose (mg/day) *	NA	44.4 [18.8-111.6]		60 [15-118.8]	30 [30-75]	ns

Data are n (%), median or value [IQR]. Abbreviations: ECOG Eastern Cooperative Oncology Group; PSA serum Prostate Specific Antigen; ALP serum Alkaline Phosphatase; LDH Lactate Dehydrogenase; mg milligram; *oral morphine equivalent; ns, not significant; NA, not available.

Table 2. Clinical outcomes of Radium-223 treatment

Outcome variables		**Median [IQR or 95% CI], No. of Patients (%)**			***p* ***
		Evaluable sample (*n*=105)	**Pain at baseline (*n*=45)**	**No-Pain at baseline (*n*=60)**	
Follow-up, months		13.2 (11.4-15)	13.4 (10.1-17.5)	13.2 (11.3-16.3)	ns
No. of Radium-223 cycles, median		5 [4-6]	5 [3-6]	6 [4-6]	0.003
ALP decline, no. of patients (%)					
³30%		39 (37)	17 (38)	22 (37)	ns
³50%		18 (17)	11 (24)	7 (12)	ns
³90%		1 (1)	1 (2)	0 (0)	ns
Missing		3 (3)	2 (4)	1 (2)	ns
Time to ALP progression, months					ns
	Median	6.8 (6.2-NR)	7.4 (6.0-NR)	6.6 (6.2-NR)	
	Mean	8.0 (6.7-9.2)	7.7(5.9 – 9.5)	7.5 (6.3 – 8.7)	
PSA decline , no. of patients (%)					
³30%		7 (7)	2 (4)	5 (8)	ns
³50%		2 (2)	0 (0)	2 (3)	ns
³90%		2 (1.8)	0	2 (3.1)	ns
Missing		3 (3)	2 (4)	1 (2)	ns
Reason for Radium-223 discontinuation, no. of patients (%)					
Six cycles completed		55 (52)	16 (36)	39 (65)	0.003
Symptomatic progression		32 (30)	19 (42)	13 (22)	0.03
PSA progression		27 (26)	15 (33)	12 (20)	ns
Radiological progression		14 (13)	7 (16)	7 (12)	ns
Intolerance		12 (11)	6 (13)	6 (10)	ns
Death		3 (3)	3 (7)	0	ns
Other		1 (1)	1 (2)	0	ns
Time to first SSE, months					ns
	Median	6.8 (6.2-NR)	NR	NR	
	Mean	23.7 (21.9-25.4)	19.5 (16.6-22.3)	22.4 (20.7-24.1)	
Progression free survival, months		5.2 (4.8-6)	4.8 (3.6-5.5)	5.7 (4.9-7)	ns
Overall Survival, months		19.6 (16.6-NR)	13.5 (9.5-NR)	20.3 (19.2-NR)	0.05
Time to subsequent treatment, months					ns
	Median	3.7 (2.7-8.8)	3.1 (2.1-NR)	4.1 (3.2-NR)	
	Mean	6.5 (5.2-7.8)	5.9 (3.9-7.9)	6.8 (5.2-8.4)	
Hospital admission during Radium-223 treatment, no. of patients (%)		24 (23)	13 (29)	11 (18)	ns

* Pain at baseline *vs* No-pain at baseline

Abbreviations: 95% CI: 95% confidence interval; PAB: Pain at Baseline, No-PAB: No Pain At Baseline, ALP: alkaline phosphatase, PSA: serum Prostate Specific Antigen, SSE: Symptomatic Skeletal Event, NR: Not reached; ns: Not significant.

The percentage of patients in the evaluable sample experiencing a complete pain response for the duration of Ra-233 treatment, as defined by IBMCWP was 31.4% (Table 3).

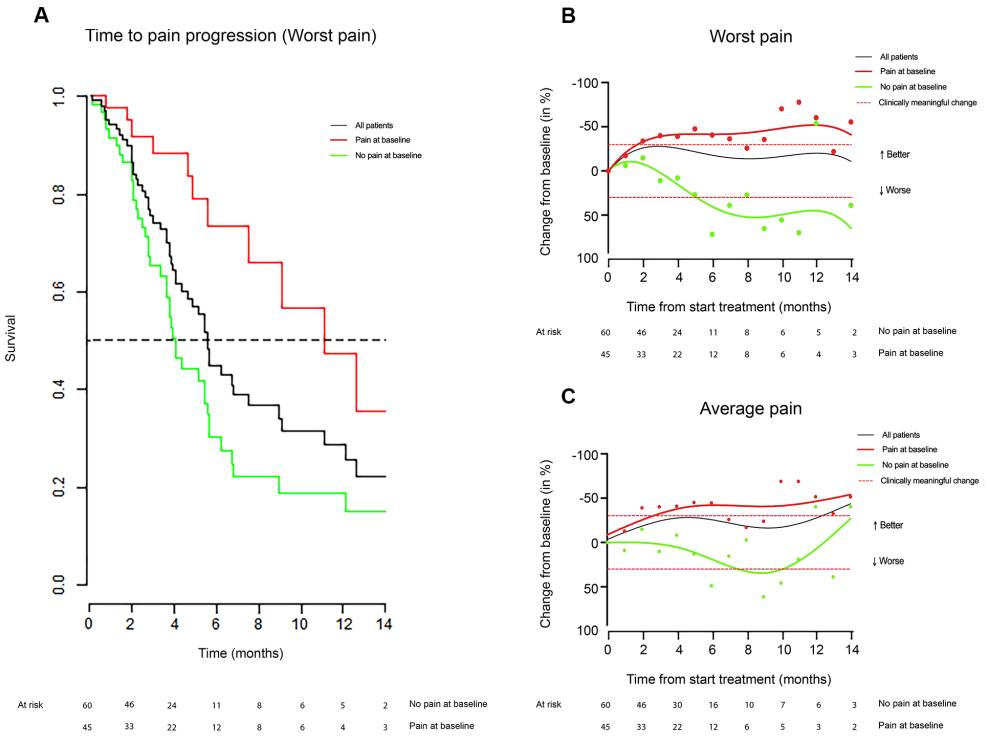

Figure 2. Brief Pain Inventory (BPI).

A: Kaplan-Meier estimates of time to clinically meaningful BPI– Worst pain subscale score deterioration for the evaluable sample (black line), patients with pain at baseline (red line) and patients without pain at baseline (green line). The horizontal dotted line represents 50% events. **B:** Change in Brief Pain Inventory (BPI) – Worst pain and **C:** Average pain subscales scores over time in the evaluable sample (black line), patients with pain at baseline (red line) and patients without pain at baseline (green line). Data points show average scores at time points, while the lines are made to fit the trend of change of score in time. The horizontal dotted lines represent the threshold for clinically meaningful change from baseline.

FACT-P

FACT-P baseline values are reported in Supplementary Table 7. PAB patients had a significantly lower baseline total FACT-P score than no-PAB patients (95.2 and 107.6, respectively, $p<0.001$), suggesting a worse HRQoL. Moreover, PAB patients had significantly lower baseline FACT-P subscale scores, suggesting a poorer performance on PCS (26.2 and 31.6, respectively, $p<0.001$), PWB (19.8 and 22, respectively, $p<0.001$), EWB (12.5 and 14.1, respectively,

p=0.031), FWB (16.5 and 18.2, respectively, p=0.039) and pain (5.9 and 11.5, respectively, p<0.001) than no-PAB patients.

Median and mean TTFD and other deteriorations of FACT-P subscales are reported in Table 3. The median TTFD was 5.7 months in the evaluable sample, while there was no significant difference between PAB and no-PAB patients (Table 3; Figure 3A). There were also no significant differences in all other time to FACT-P subscale deteriorations between PAB and no-PAB patients (Table 3; Supplementary Figure 4). During treatment, 31.4% of the evaluable sample had a clinically meaningful improvement of Total FACT-P, with no significant difference between PAB and no-PAB patients (Table 3; Figure 3B). Changes in time of the FACT-P subscales are displayed in Supplementary Figure 5.

Table 3. Patient-reported outcomes: Median time to BPI-SF and FACT-P deterioration and pain response

Outcome variables		**Median [IQR], No. of Patients (%) [IQR or 95% CI]**			***p* ***
		Evaluable sample (*n*=105)	**Pain at baseline (*n*=45)**	**No pain at baseline (*n*=60)**	
Time to BPI-SF deterioration, months					
Worst pain					0.001
	Median	5.6 (4.7-9)	11.1 (7.6-NR)	4.1 (3.6-5.7)	
	Mean	7.9 (6.4-9.4)	11.2 (8.5-13.8)	6.1 (4.6-7.7)	
Least pain					ns
	Median	7.1 (6.2-NR)	14.1 (6.9-NR)	6.5 (5.8-NR)	
	Mean	10.7 (8.5-12.9)	11.5 (8.3-14.7)	9.6 (7.3-11.9)	
Average pain					0.03
	Median	6.1 (5.5-NR)	12.6 (6.2-NR)	5.5 (4.1-6.8)	
	Mean	9.4 (7.8-11)	11.5 (8.8-14.2)	8 (6.1-9.8)	
Pain now					ns
	Median	6.2 (4.7-NR)	NR (10-NR)	5.7 (4.1-7.2)	
	Mean	9 (7.3-10.6)	11.9 (9.1-14.6)	7.7 (5.8-9.6)	
Overall pain interference					ns
	Median	8.3 (6.5-13.5)	10.6 (7.2-NR)	6.7 (5.7-NR)	
	Mean	10.4 (8.2-12.5)	9.9 (7.1-12.8)	9.8 (7.5-12.1)	
Clinically meaningful improvement of BPI-Worst Pain during treatment, No of patients (%)		52 (49.5)	35 (77.7)	17 (28.3)	< 0.0001
Pain response, no. of patients (%)					0.004
Complete		33 (31.4)	9 (20.0)	24 (40.0)	0.03
Partial		28 (26.7)	21 (46.7)	7 (11.7)	0.0001
Indeterminate		35 (33.3)	11 (24.4)	24 (40.0)	ns
Progressive pain		6 (5.7)	3 (6.7)	3 (5.0)	ns
Not evaluable		3 (2.8)	1 (2.2)	2 (1.7)	

Time to FACT-P deterioration, months					
Total					ns
	Median	5.7 (3.3-NR)	13.7 (2.5-NR)	5.5 (3.1-NR)	
	Mean	7.8 (6.2-9.3)	8.4 (6.4-10.5)	7 (5.4-8.6)	
Prostate cancer subscale					ns
	Median	9.8 (7-NR)	NR (6.4-NR)	9.8 (7-NR)	
	Mean	11.1 (8.9-13.2)	12.4 (9.6-15.2)	9.9 (7.5-12.3)	
Physical well-being					ns
	Median	NR (7.2-NR)	12.6 (6.4-NR)	NR (NR-NR)	
	Mean	12.4 (10.4-14.4)	10.2 (7-13.5)	12.8 (10.7-14.9)	
Social well-being					ns
	Median	13.2 (11.2-NR)	NR (NR-NR)	13.2 (10.4-NR)	
	Mean	13.2 (11.1-15.3)	14.6 (12.3-17)	12.3 (10-14.6)	
Emotional well-being					ns
	Median	NR (NR-NR)	NR (12.6-NR)	NR (NR-NR)	
	Mean	13.6 (12.1-15.2)	14.4 (12-16.8)	13.1 (11.2-15)	
Functional well-being					ns
	Median	NR (12.7-NR)	12.7 (7.6-NR)	NR (NR-NR)	
	Mean	13.9 (12-15.9)	12.4 (9.2-15.6)	14.2 (12.2-16.2)	
Pain					ns
	Median	10.7 (9-NR)	12.6 (12.6-NR)	9 (5.8-NR)	
	Mean	9.6 (7.9-11.3)	11 (8.9-13.1)	8.3 (6.9-9.7)	
Clinically meaningful improvement of Total FACT-P during treatment, No of patients (%)		33 (31.4)	17 (37.7)	16(26.7)	ns

* Pain at baseline *vs* No-pain at baseline.

Abbreviations: BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; NR: Not reached. ns: Not significant. Clinically meaningful improvement of total Fact-P was defined as a minimal change of 10 points from baseline for the Total FACT-P score, 3 points from baseline for the subscales and 2 points from baseline for pain. ; The Clinically Meaningful improvement of BPI-SF score (CMC-BPI) was defined as a change of score of at least 30% from baseline score, with a minimum of 2 points.

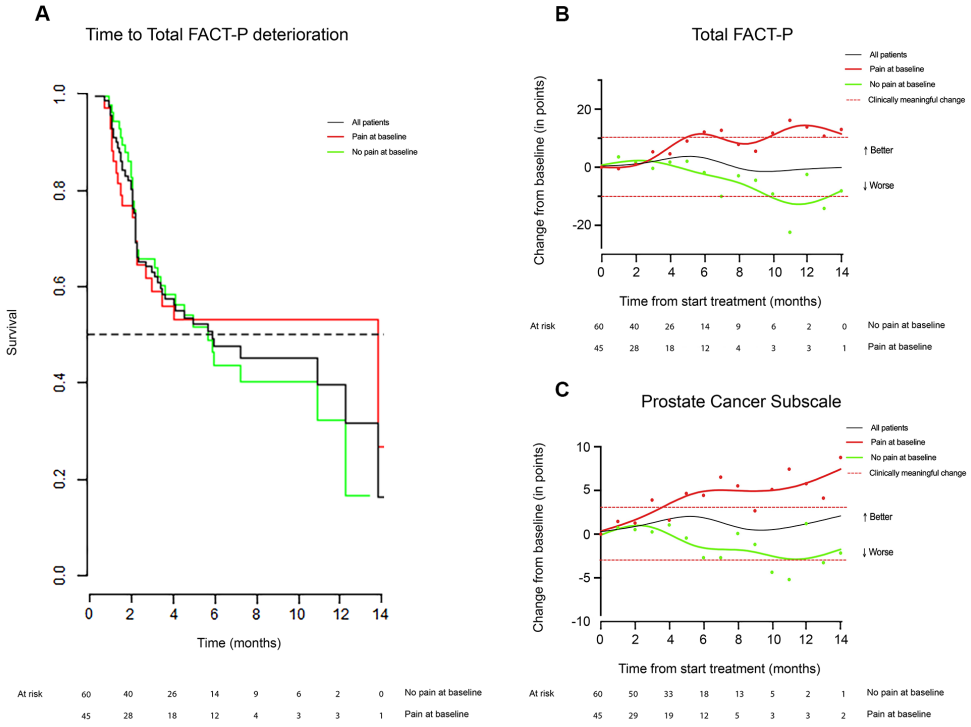

Figure 3. Functional Assessment of Cancer Therapy–Prostate (FACT-P)

A: Kaplan-Meier estimates of time to clinically meaningful Total Functional Assessment of Cancer Therapy–Prostate (FACT-P) score deterioration for the evaluable sample (black line), patients with pain at baseline (red line) and patients without pain at baseline (green line). The horizontal dotted line represents 50% events. **B:** Change in Total FACT-P and **C:** Prostate cancer subscale scores in time for the evaluable sample (black line), patients with pain at baseline (red line) and patients without pain at baseline (green line). Data points show average score at time points, while the lines are made to fit the trend of change of score in time. The horizontal dotted lines represent the threshold for clinically meaningful change from baseline.

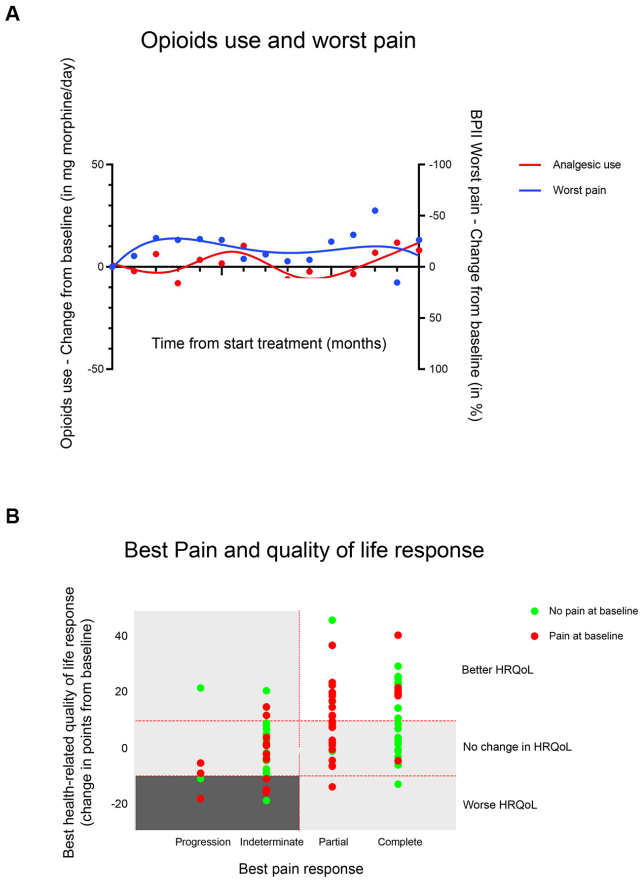

Figure 4. Integrated pain and Health related quality of life response.

A: Percentage change in Brief Pain Inventory (BPI) – Worst pain subscale scores from baseline in time (blue line) and change in average analgesics use from baseline in mg morphine equivalents per day (red line). **B:** Patients were categorized for their best pain response (Worst pain subscale) integrated with opioid drugs use according to IBMCWP recommendations (Horizontal axis: Progression, Indeterminate, Partial and Complete response) and for their best health-related quality of life response (Vertical axis: Total FACT-P clinically meaningful better or worse or not meeting these criteria and therefore considered as No change). The red, horizontal dotted lines represent the threshold for clinically meaningful Total FACT-P change (10 points), while the vertical dotted line separates progression and indeterminate pain responses from partial and complete pain responses. Red dots represent Pain at baseline patients and green dots no-Pain at baseline patients.

Analgesics use and integration of PROMs results

Use of analgesics in the evaluable sample decreased during Ra-223 treatment and remained low during follow-up (Figure 4A; Supplementary Figure 6). The score of the BPI-SF subscale Worst pain did not clinically meaningfully change during Ra-223 treatment and in follow-up. Ninety-five patients had sufficient data to be categorized for best pain response and total-FACT-P response. Fifty-five (57.9%) had an IOCR, of whom 27 (49.1%) were PAB and 28 (50.9%) were no-PAB patients (Figure 4B).

DISCUSSION

In this prospective study, 31.4% of mCRPC patients treated with Ra-223 had a complete pain response, which was the primary outcome. In the ALSYMPCA study, pain was evaluated using the non-pain-specific questionnaires FACT-P and EQ-5D.[5] Evaluation of opioids use was limited to baseline opioid use and 3 monthly assessment of opioid use in patients without baseline use. A non-significant reduction in pain was found between Ra-223 and placebo treated patients at 16 and 24 weeks of treatment.[4, 5] The percentages of patients experiencing a clinically meaningful improvement of total FACT-P in our cohort was comparable with ALSYMPCA (31.4% and 24.6%, respectively).[5] However, there are critical differences between the ALSYMPCA population and the population in the current cohort. The ALSYMPCA trial was conducted in a time when there was no other treatment for mCRPC patients then docetaxel. Consequently, in ALSYMPCA, patients received Ra-223 after docetaxel or as a first line mCRPC treatment. Contemporary mCRPC patients have multiple treatment options. In this study more than half of the patients received at least 2 treatments prior to Ra-223 treatment. It can be assumed that the extensively pretreated patients in this study are prone to poorer performance, while strict patient selection might compensate for that. Moreover, in ALSYMPCA patients were symptomatic, while in this study the majority of patients had no pain at baseline. Unfortunately, baseline Total FACT-P scores of patients included in ALSYMPCA have not been made available.[5, 18]

In this study, outcomes of the different PROMs were integrated into an IOCR, which was established in 58% of patients. Cancer related pain and HRQoL are not mutually exclusive, as was reported previously.[19, 20] However, some patients had more pain but a better HRQoL, while others experienced less pain and a worse HRQoL. In part this can be explained by inclusion of the best pain response and best HRQoL change for establishing the IOCR. Moreover, HRQoL can also be affected by other domains than pain, including fatigue, psychological distress, financial problems or social problems.[21] Another possible explanation is that this is caused by response shift, where patients accommodate to their pain by cognitive reframing and re-prioritizing of previously held values, internal standards and expectations to help cope with high levels of pain. [22]

The strength of this study lies in the inclusion of a contemporary real-world population, pretreated with multiple mCRPC treatment options. Moreover, both symptomatic and asymptomatic patients were included, as this inclusion criterium of the ALSYMPCA study is generally not considered in daily practice. This makes the results of this study directly applicable to current prostate cancer patients' treatment.

Limitations of this study include its non-randomized nature and the likelihood of survival and selection bias. Another limitation is the lower than expected questionnaires completion rates. The percentage of patients evaluable was within the previously reported 10-70% range of response rates in studies on self-reported outcome measures in real-life populations[15–17], but lower than the 40% we assumed for the power calculation. It was previously reported that a higher frailty score was a strong predictor for non-completion. [23] The older age and more advanced disease and with that a presumably higher frailty score of patients in our cohort compared with similar studies in patients with other cancers, might explain the lower than expected completion rates. Despite the above, the evaluable sample seemed to be representative for the registry sample since there were no major differences in baseline characteristics.

In conclusion, our study shows that a significant proportion of Ra-223 treated symptomatic and asymptomatic, extensively pretreated mCRPC patients experience an improved HRQoL and a pain response. These results suggest that the majority of contemporary mCRPC patients derives clinical benefit from Ra-223 treatment.

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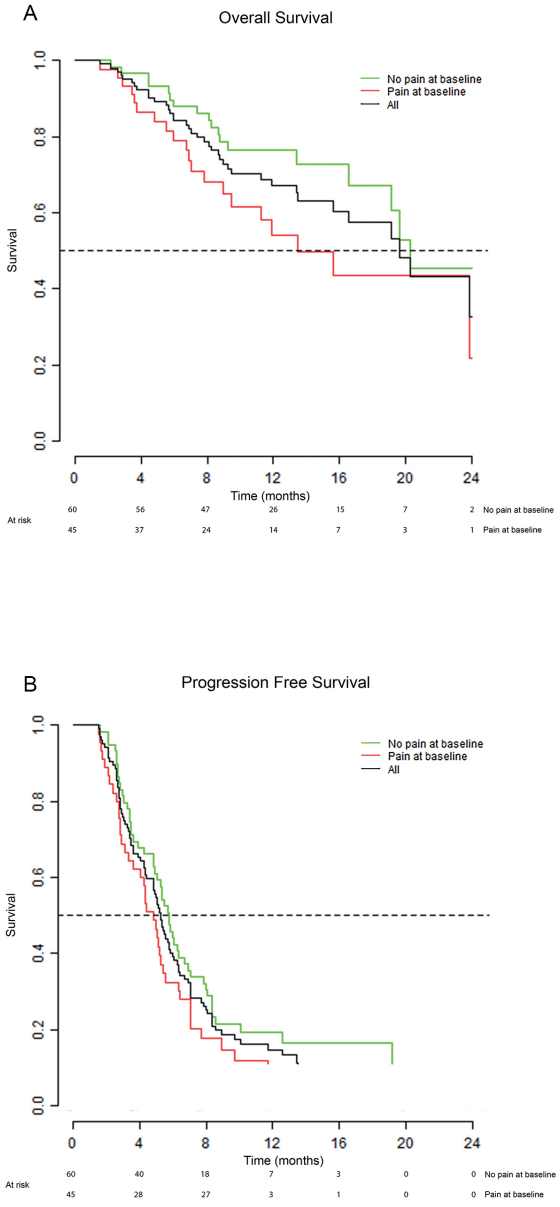
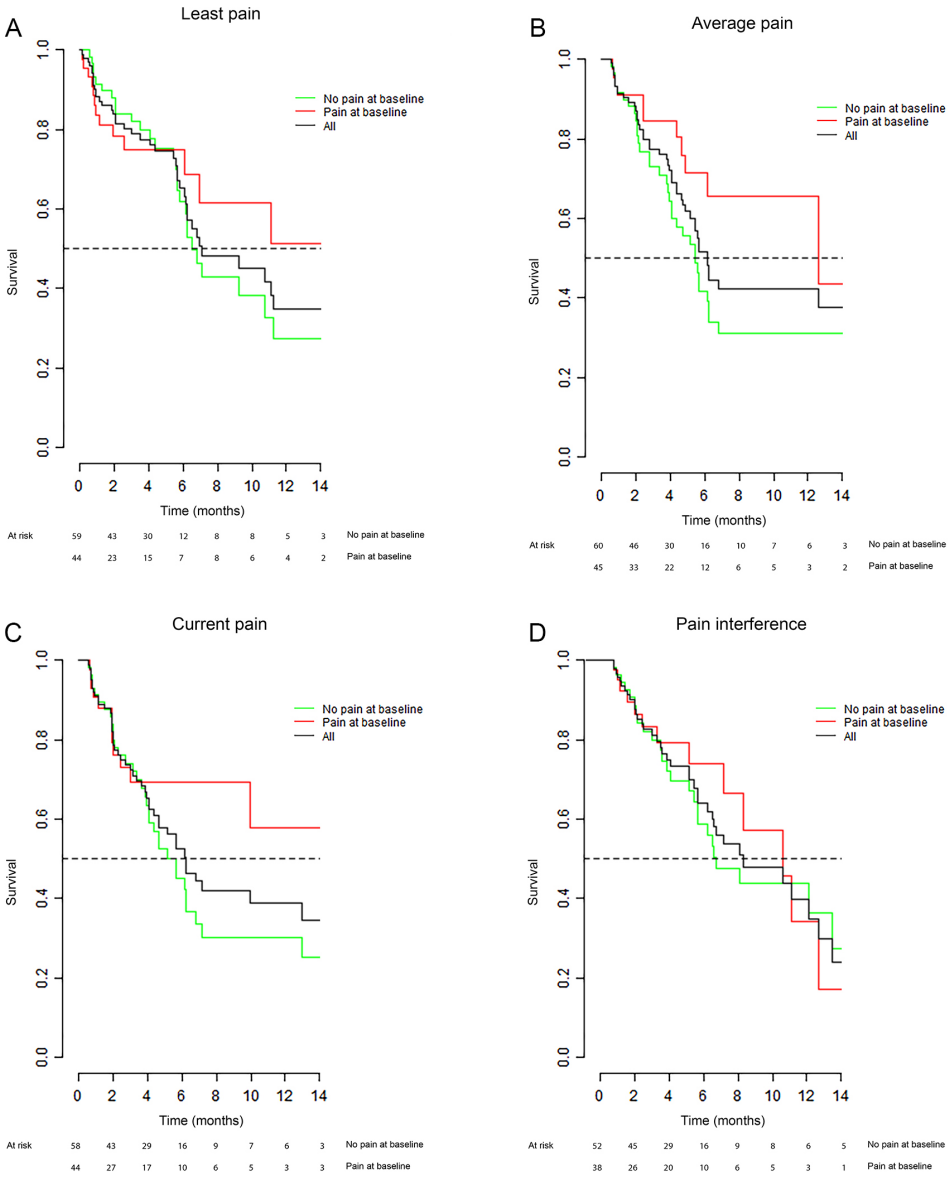
SUPPLEMENTARY MATERIALS



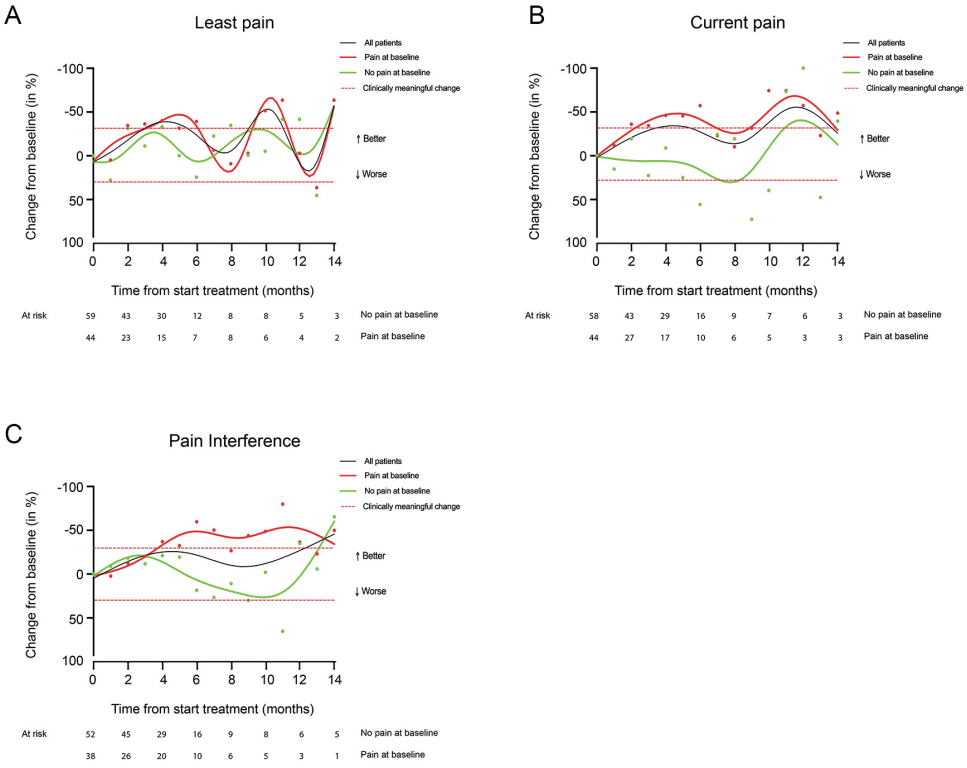
Supplementary Figure 1. Kaplan-Meier estimates of survival in the evaluable sample.

A. Overall survival, **B.** Progression free survival. Black lines represent the evaluable sample, red lines patients with pain at baseline and green lines patients without pain at baseline. The horizontal dotted lines represent 50% events.



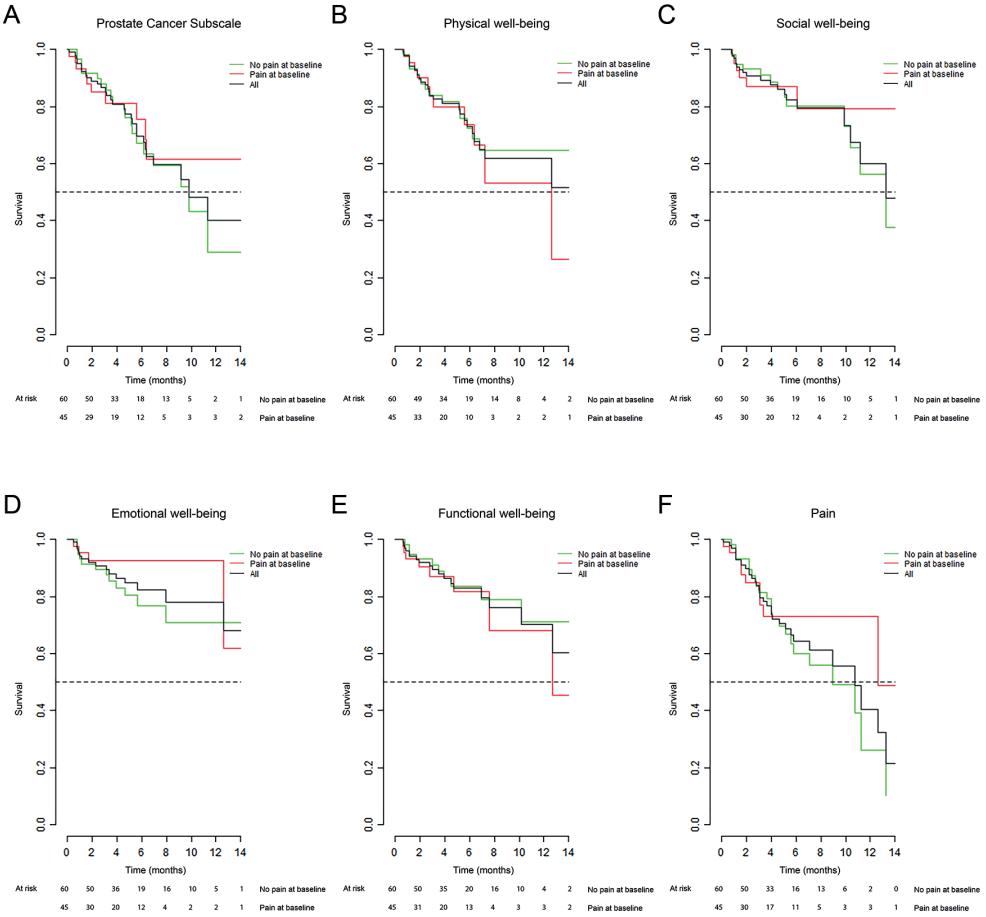
Supplementary Figure 2. Kaplan-Meier estimates of time to clinically meaningful Brief Pain Inventory (BPI) subscales score deteriorations.

A: BPI - Least pain subscale, **B:** BPI – Average pain subscale, **C:** BPI – Current pain subscale, **D:** BPI – Pain interference subscale. Black lines represent the evaluable sample, red lines patients with pain at baseline and green lines patients without pain at baseline. The horizontal dotted lines represent 50% events.



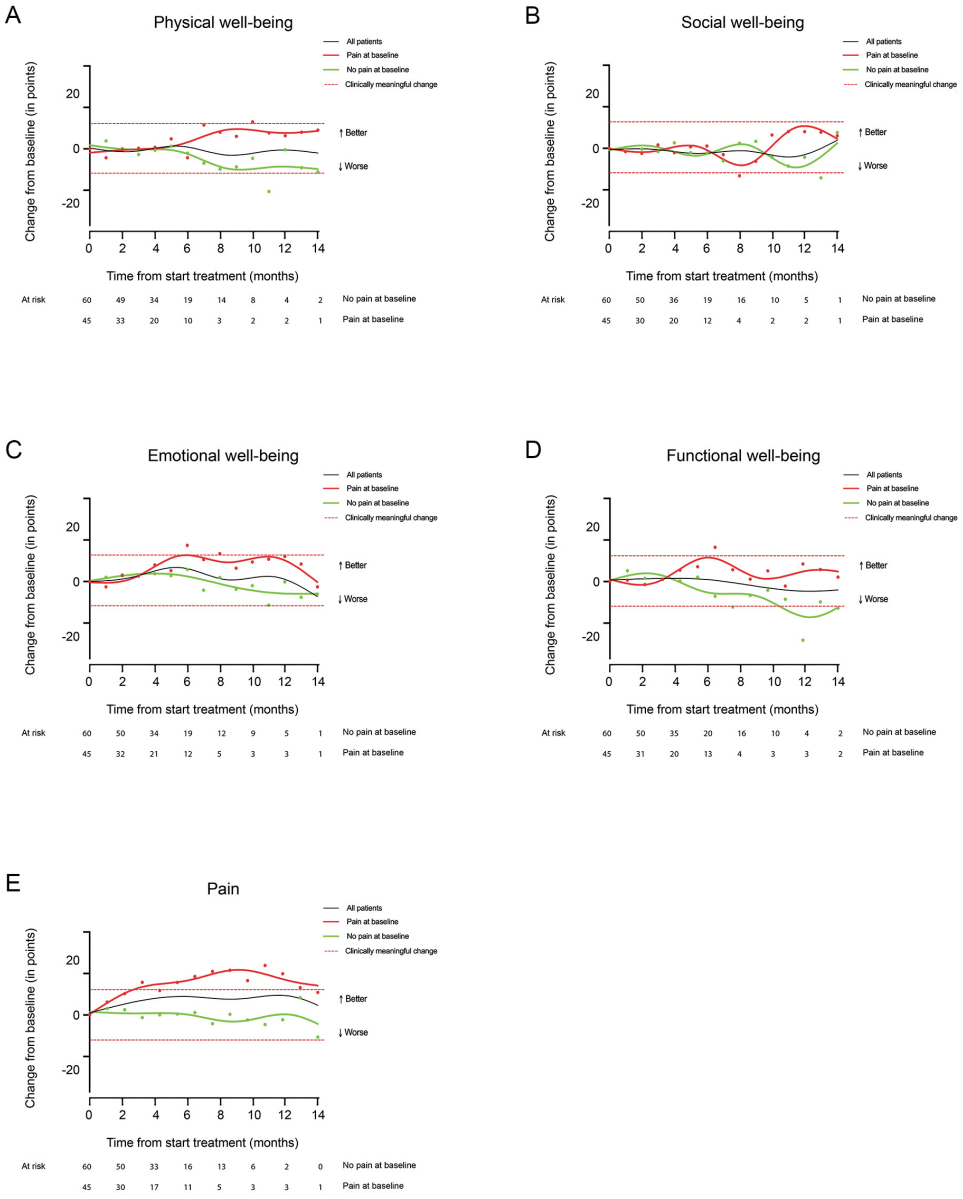
Supplementary Figure 3. Change of Brief Pain Inventory (BPI) subscale scores in time.

A: BPI – Least pain subscale, **B:** BPI – Current pain subscale, **C:** BPI - Pain interference subscale. Data points show average scores at time points, while the lines are made to fit the trend of change of score in time. The black lines represent the evaluable sample, the red line patients with pain at baseline and the green line patients without pain at baseline. The horizontal dotted lines represent the threshold for clinically meaningful change from baseline for BPI.



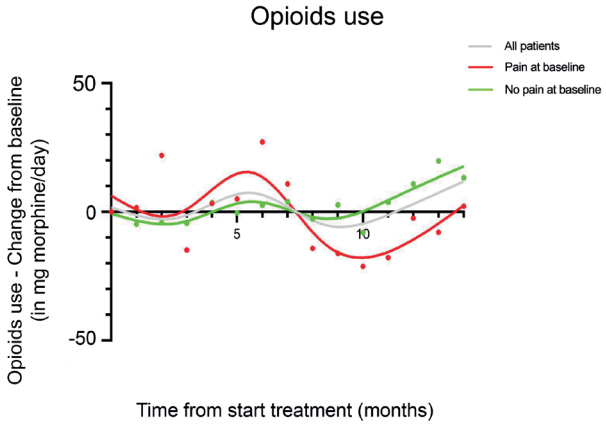
Supplementary Figure 4. Kaplan-Meier estimates of time to clinically meaningful Functional Assessment of Cancer Therapy–Prostate (FACT-P) subscales score deteriorations.

A: FACT-P – Prostate cancer subscale, **B:** FACT-P – Physical well-being subscale, **C:** FACT-P – Social well-being subscale, **D:** FACT-P –Emotional well-being subscale, **E:** FACT-P – Functional well-being subscale, **F:** FACT-P – Pain subscale. Black lines represent the evaluable sample, red lines patients with pain at baseline and green lines patients without pain at baseline. The horizontal dotted lines represent 50% events.



Supplementary Figure 5. Change of Functional Assessment of Cancer Therapy–Prostate (FACT-P) subscale scores in time.

A: FACT-P – Physical well-being subscale, **B:** FACT-P – Social well-being subscale, **C:** FACT-P –Emotional well-being subscale, **D:** FACT-P – Functional well-being subscale, **E:** FACT-P – Pain subscale. Data points show average scores at time points, while the lines are made to fit the trend of change of score in time. The black lines represent the evaluable sample, the red lines patients with pain at baseline and the green lines patients without pain at baseline. The horizontal dotted lines represent the threshold for clinically meaningful change from baseline for FACT-P.



Supplementary Figure 6. Average change in opioids use from baseline in mg morphine equivalents per day. The grey line represents the evaluable sample, the red line patients with pain at baseline and the green line patients without pain at baseline.

Supplementary Table 1. Questionnaires used to assess health-related quality of life, pain and analgesics use.

	Number of items	Score range	Clinically meaningful change	Description	Completion dates
Functional Assessment of Cancer Therapy-Prostate (FACT-P)				A validated questionnaire used to evaluate HRQol in mCRPC patients. A higher FACT-P total score represents better HRQoL	Baseline, once every 4 weeks until start of subsequent treatment or death
Total score	39	0-156	10 points from baseline		
Prostate cancer subscale	12	0-48	3 points from baseline		
Physical well-being	7	0-28	3 points from baseline		
Functional well-being	7	0-28	3 points from baseline		
Emotional well-being	6	0-24	3 points from baseline		
Social well-being	7	0-28	3 points from baseline		
Pain	4	0-16	2 points from baseline		
Brief Pain Inventory-Short Form (BPI-SF)				A commonly used validated questionnaire used to evaluate pain in cancer trials. This questionnaire assesses several aspects of pain. Each aspect is assessed with an individual score on a scale of 0-10, with higher scores representing more pain.	Baseline, once every 4 weeks until start of subsequent treatment or death
Worst pain	1	0-10	Increase ≥ 30% and ≥ 2 point from baseline		
Least Pain	1	0-10	Increase ≥ 30% and ≥ 2 point from baseline		
Average pain	1	0-10	Increase ≥ 30% and ≥ 2 point from baseline		
Current Pain	1	0-10	Increase ≥ 30% and ≥ 2 point from baseline		
Pain interference	7	0-10	Increase ≥ 30% and ≥ 2 point from baseline	Described as pain during daily activities (*e.g.:* sleep, mood)	
List of opioid drugs used				Free text list of all opioid drugs used in the previous 4 weeks	Baseline, once every 4 weeks until start of subsequent treatment or death

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; HRQoL, health-related quality of life;

Supplementary Table 2. Conversion of opioid drugs to oral morphine

Morphine		**Fentanyl**	**Oxycodon**		**Hydromorphine**		**Tramadol**	**Buprenophine**	**Tapentadol**
Oral	S.C./I.V	Patch	Oral	S.C./I.V.	Oral	S.C/I.V.	Oral	Patch	Oral
mg/24h	mg/24h	μg/h	mg/24h	mg/24h	mg/24h	mg/24h	mg/24h	μg/h	mg/24h
30	10	12	20	10	8	2	150	-	75-100
60	20	25	40	20	12	4	300	-	150
120	40	50	80	40	24	8	-	52.2	300
180	60	75	120	60	36	12	-	-	450
240	80	100	160	80	48	16	-	105	-
360	120	150	240	120	72	24	-	-	-
480	160	200	320	160	96	32	-	-	-

Abbreviations: S.C., subcutaneously; I.V., intravenously; mg/h, milligrams per hour; μg/h, microgram per hour;

Supplementary Table 3. Definitions of time-to-event secondary endpoints

Endpoint	Definition
Time to Total FACT-P Deterioration (TTFD)	Time from the date of first Ra-223 course to the first moment of a decrease in Total FACT-P score of at least 10 points from baseline
Time to Pain Progression (TPP)	Time from the date of first Ra-223 treatment to the moment of an increase in worst pain score fulfilling the CMC-FACT criteria*
Progression Free Survival (PFS)	Date of first Ra-223 treatment to the date of confirmed disease progression. Progression was defined as, clinical progression (defined as clinical signs of progression), radiological progression (according to RECIST v. 1.1)†, onset of a subsequent treatment or death, all in line with PCWG3 recommendations††.
Overall Survival (OS)	Date of the first Ra-223 cycle to the date of death

Abbreviations: CMC-FACT-P, clinically meaningful change of Functional Assessment of Cancer Therapy–Prostate. Defined as a minimal change of 10 points from baseline for the Total FACT-P score, 3 points from baseline for the subscales and 2 points from baseline for pain

†Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur. J. Cancer 2009; 45(2):228–247.

††Scher HI, Morris MJ, Stadler WM et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J. Clin. Oncol. 2016; 34(12):1402–18.

Supplementary Table 4. Power calculations

Number of evaluable patients (out of 300)	300	200	150	120	100	50
Power to find significant increase in proportion of pain responses compared to 20%	99%	95%	88%	81%	70%	43%

Supplementary Table 5. Comparison of treatment outcomes of the registry sample and the evaluable sample for pain and quality of life

	Median [IQR], Number of Patients (%) or value (n=patients evaluable)		
	Registry sample (*n=300*)*	**Evaluable sample (*n=105*)**	***P***
Treatment outcomes			
Follow-up, months	13.2 (12.1-14.4)	13.2 (11.4-15)	Ns
No. of Radium-223 cycles			Ns
Median no. of cycles	5.0 [3.0-6.0]	5 [4-6]	
ALP decline	*(n=255)*	*(n=102)*	
≥30%	122 (47.8)	39 (37%)	Ns
≥50%	56 (22.0)	18 (17%)	Ns
≥90%	1 (0.4)	1 (1%)	Ns
Time to ALP progression, months			Ns
Median	6.7 (6.4 – 7.4)	6.8 (6.2-NR)	
Mean	7.9 (6.7 – 9.2))	8.0 (6.7-9.2)	
PSA decline	*n=256*	*n=103*	
≥30%	16 (6.3)	7 (7%)	Ns
≥50%	11 (4.3)	2 (2%)	Ns
≥90%	3 (1.2)	2 (1.8%)	Ns
Time to first SSE, months	Median not reached	Median not reached	
Progression free survival, months	5.1 (4.5-5.8)	5.2 (4.8-6)	Ns
Overall Survival, months	15.2 (12.8-17.6)	19.6 (16.6-NR)	0.04
Time to subsequent treatment, months	5.9 (4.1-7.7)	3.7 (2.7-8.8)	Ns
Hospital admission during Radium-223 treatment	82 (28.1)	24 (23%)	Ns

Abbreviations: ECOG: Eastern Cooperative Oncology Group; PSA: serum Prostate Specific Antigen; ALP: serum Alkaline Phosphatase; LDH: Lactate Dehydrogenase; SSE: Symptomatic Skeletal Event. Ns:Not significant; Base-line characteristics of the whole population was previously described (Badrising *et al*, Int. J Cancer 2020).

Supplementary Table 6. Completion rates for questionnaires

Radium cycle	Number of patients	At least one completed questionnaire (%)	All three questionnaires completed (%)	All three questionnaires completed including baseline (%)
Baseline	300	126 (42)	121 (40)	121 (40)
Cycle 1	290	184 (63)	181 (62)	66 (23)
Cycle 2	272	182 (67)	181 (67)	80 (29)
Cycle 3	250	170 (68)	168 (67)	74 (30)
Cycle 4	210	130 (62)	130 (62)	58 (28)
Cycle 5	164	110 (67)	109 (67)	55 (34)
Cycle 6	140	108 (77)	108 (77)	46 (33)

Supplementary Table 7. Baseline scores of Patient Reported Outcomes

Outcome variables	Mean (SD)			
	Evaluable sample (*n*=105)	Pain at baseline (*n*=45)	No pain at baseline (*n*=60)	*p**
BPI-SF				
Worst pain	4.2 (2.8)	7.0 (1.1)	2.1 (1.4)	
Least pain	1.8 (1.7)	2.8(1.8)	1.1 (1.1)	<0.001
Average pain	3.1 (2.1)	5.0 (1.5)	1.6 (1.2)	<0.001
Pain now	2.4 (2.3)	4.0 (2.4)	1.2 (1.3)	<0.001
Overall pain interference	3.0 (2.2)	4.1 (1.9)	2.2 (2.0)	<0.001
FACT-P				
Total score	102.0 (17.4)	95.2 (13.0)	107.6 (18.6)	<0.001
Prostate cancer subscale	29.2 (6.6)	26.2 (4.5)	31.6 (6.9)	<0.001
Physical well- being	21.1 (4.3)	19.8 (3.3)	22.0 (4.7)	<0.001
Social well-being	21.0 (4.4)	20.5 (4.5)	21.5 (4.3)	0.59
Emotional well-being	13.4 (3.5)	12.5 (3.5)	14.1 (3.4)	0.031
Functional well-being	17.5 (5.2)	16.5 (4.1)	18.2 (5.8)	0.039
Pain	9.1 (4.1)	5.9 (2.7)	11.5 (3.3)	<0.001

*Pain at baseline vs no pain at baseline

Abbreviations: SD: Standard deviation ; BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate;

Chapter 7

Summarizing discussion and future perspectives

SUMMARIZING DISCUSSION

Until 2012 Docetaxel was the only treatment with a proven survival benefit for patients with metastatic castration-resistant prostate cancer (mCRPC). After 2012, multiple new agents were introduced, all in patients primarily treated with Docetaxel. Abiraterone Acetate (hereafter referred to as Abiraterone) and Enzalutamide are both androgen-signalling-targeted inhibitors.[1] Cabazitaxel is a second generation taxane and Radium-223 dichloride (hereafter referred to as Radium-223) is a targeted alpha therapy that selectively binds to areas of increased bone turnover. [2, 3] Since the new second line treatment options were developed simultaneously, at the time of approval there was no information available whether mCRPC patients would benefit more from one new agent over another. To date, still no head to head comparisons between treatment options for patients who progressed during or after docetaxel treatment are available, and therefore it is not clear which sequence of treatments would be optimal.

In **Chapter 2** we retrospectively evaluated the efficacy and tolerability of Enzalutamide in patients pre-treated with at least Docetaxel and Abiraterone. We concluded that Enzalutamide was well tolerated in this population, and that the adverse-events were similar to those reported in the AFFIRM trial, where Enzalutamide was evaluated as a treatment of mCRPC patients previously treated with docetaxel. However, patients had lower PSA response rates when compared to patients included in the AFFIRM trial (21% and 54% had a serum PSA decrease of ≥50% from the value at start of treatment, respectively) and a shorter progression free survival (PFS) (PFS survival rates were 12.0 and 36.1 weeks, respectively).[4] The CARD-trial, a multicenter, open-label, randomized trial evaluated efficacy of androgen-signalling-targeted inhibitors (Abiraterone/Enzalutamide) in patients previously treated with Docetaxel followed by cross-over to the other androgen-signalling-targeted inhibitor. It was reported that Cabazitaxel was superior to the androgen-signalling-targeted inhibitor in terms of imaging-based PFS and Overall Survival (OS). A post-hoc analysis showed that patients treated with Enzalutamide after prior Docetaxel and Abiraterone had better imaging-based PFS when compared to patients treated with Abiraterone after prior Docetaxel and Enzalutamide naïve-patients treated with Abiraterone. No OS was reported for these post-hoc analyses. [5] Results from the CARD-trial and several other prospective and retrospective trials, including our study, suggest cross-resistance between Abiraterone and Enzalutamide. [1, 4–9]

There are multiple mechanisms of resistance to androgen-signalling-targeted inhibitors described.[10] Several of these proposed mechanisms are, both systemic and intratumoral upregulation of androgens, androgen receptor (AR) overexpression, amplifications, mutations and splice variants, alteration of pathways involved in cross-talk with AR signaling, neuroendocrine transformation and immune system deregulation.

In recent years, much research attention was drawn to aberrant AR signalling caused by AR splice variants. In these splice variants, the AR protein has a transactivating N-terminal but is missing the C-terminal ligand binding domain. Even though there is no binding domain, the AR receptor is still capable of activating target genes without being activated by androgens.[11–13] AR splice variant 7 (AR-V7) is found to be one of the most commonly expressed AR splice variants in both clinical and preclinical studies.[10] Multiple studies have shown that the presence of AR-V7 is a predictor of poor response to androgen-signalling-targeted inhibitors, but is not a predictor for response to taxane chemotherapy.[12] Antonarakis et al reported that AR-V7 could be present prior to the start of androgen-signalling-targeted inhibitor, but also that some patient converted from AR-V7-negative to AR-V7-positive during treatment. It is likely that this conversion is an important survival mechanism of prostate cancer cells to androgen-signalling-targeted inhibitors, which explains resistance and cross-resistance to androgen-signalling-targeted inhibitor.

In **Chapter 3**, we retrospectively identified parameters predicting response to Enzalutamide in patients previously treated with Abiraterone and docetaxel. In this study, a response was defined as a serum PSA decrease of ≥50% from the value at start of treatment We found that higher Gleason-scores, shorter PSA-doubling time and a longer time interval between ending Abiraterone and starting Enzalutamide were associated with response to Enzalutamide treatment. When the time interval between end of Abiraterone and start of Enzalutamide treatment was more specifically evaluated, we could identify two groups with a relatively high percentage of PSA responses to Enzalutamide treatment. One group with a short time interval (< 40 days) and one group with longer time interval (≥40 days) between the two agents. With the exception of one patient, none of the Enzalutamide responders in the <40 days group had a PSA response on the prior Abiraterone treatment, while in the ≥40 days group, 29% of the Enzalutamide responders responded to the prior Abiraterone treatment. Moreover, in the ≥40 days subgroup a linear relation could be identified between time interval between end of Abiraterone and start of Enzalutamide and PSA response to Enzalutamide. The PSA response rates of mCRPC patients on Enzalutamide with an interval of >390 days was comparable to Abiraterone-naive patients as reported in the AFFIRM trial.[7, 14] These results are suggestive of different cross-resistance patterns and with that possible differences in molecular mechanisms of resistance. Patients might be resistant to Abiraterone, but not to Enzalutamide, patients might be resistant to both agents and patients with an acquired cross-resistance to Enzalutamide might regain sensitivity in time. In the CARD trial patients who were treated with androgen-signalling-targeted inhibitors before Docetaxel had a lower chance of progression on third line androgen-signalling-targeted inhibitor treatment when compared to patients who received Enzalutamide/Abiraterone after Docetaxel and directly crossed-over to third line Enzalutamide/Abiraterone.[5] These results of the CARD trial might supports our finding and hypothesis that in time, cross-resistance between the androgen-signalling-targeted inhibitors is reversible. We hypothesize that the acquired cross-

resistance is an energetically unfavorable state and prostate cancer cells might reverse to a higher level of testosterone dependence upon cessation of AR targeted therapy in time. [7]

In **Chapter 4** we evaluated whether Enzalutamide was viable as a fourth- or fifth- line treatment option for men with castration resistant prostate cancer. Patients in our cohort were all treated with Docetaxel and Abiraterone, and at least a third-line treatment option. Third- and fourth-line treatments were Cabazitaxel in most cases, while a few patients were treated with Ra-223. We found that while the PSA response rates were much lower than those reported in the AFFIRM trial (23% and 54%, respectively), they were similar to response rates of other studies evaluating third-line Enzalutamide.[6, 15–17] Surprisingly, the median OS in our cohort (40.1 weeks) was longer compared to other reports of third-line Enzalutamide therapy in Docetaxel and Abiraterone-native patients (21.7 and 32.6 weeks)[6, 15–17]. This might be explained by survival bias, caused by the selection of patients for fourth- or fifth-line Enzalutamide treatment, who probably have a more protracted course of the disease.[17]

Radium-223

In 2013, the ALSYMPCA phase III trial reported a survival benefit, longer time to symptomatic skeletal Events (SSE) and better quality of life in mCRPC patients treated with Ra-223 compared to placebo, rendering Ra-223 the only radionuclide treatment with a survival benefit in mCRPC patients.[18] Although, patients previously treated with Docetaxel (Doc) as well as patients not-treated with Doc were included in ALSYMPCA, none of these patients had been treated with androgen-signalling-targeted inhibitors or Cabazitaxel. These newer generation drugs became available after accrual of the ALSYMPCA trial was completed.[14, 19–21] This raised the question whether the results of ALSYMPCA were representative for present patients treated with Ra-223.

In **Chapter 5**, we report the results of ROTOR, a prospective registry of Ra-223 treated mCRPC patients in the Netherlands. Even tough patients in our cohort were more heavily pretreated, the OS was comparable to the patients in the treatment arm of the ALSYMPCA trial (15.2 months and 14.9, respectively). A likely explanation is that in the Netherlands mostly patients with good performance scores were selected for Ra-223 treatment. This is reflected by the lower frequency of Eastern Cooperative Oncology Group (ECOG) ≥2 performance scores and lower baseline serum Prostate Specific Antigen (PSA) and alkaline phosphatase (ALP) levels when compared to the ALSYMPCA cohort. Toxicity was similar as reported in the ALSYMPCA trial.

There was no association between prior Abiraterone or Enzalutamide treatment and PFS or OS, but both in univariate and multivariate cox-regression analysis, previous Cabazitaxel treatment was associated with a less favorable PFS and OS. The association between prior chemotherapy and shorter survival has previously been reported in two retrospective studies. [22, 23] Moreover, a retrospective trial, assessing clinical correlates associated with response, confirmed our

finding that prior treatment with Abiraterone or Enzalutamide had no negative effect on OS.[22] These results suggest that in a non-study population, Ra-223 treatment is well-tolerated, equally effective as in the ALSYMPCA population and that patients not previously treated with Cabazitaxel benefit most from Ra-223.

Radionuclides in prostate cancer treatment were historically indicated for painful bone metastases, but an OS benefit of these beta-emitters was not established.[24] The ALSYMPCA trial evaluated patient-reported quality of life. Pain was not assessed with a questionnaire validated to assess pain, but with the pain related sub-questions of the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaires. Moreover, use of analgesics were not used in the pain evaluation, even though this is recommended by the International Bone Metastases Consensus Working Party (IBMCWP).[25, 26] In **Chapter 6** we report outcomes of integrated Health- Related Quality of Life (FACT-P questionnaire), Pain (BPI-SF questionnaire) and opioid use (free text) in a non-Study Cohort of mCRPC patients treated with Ra-223. Hundred and five patients were evaluable for patient reported outcomes. The percentage of evaluable patients experiencing a complete pain response, partial response, indeterminate response or experienced progressive pain during Ra-233 treatment were 31.4%, 26.7%, 33.3% and 5.7%, respectively. Integrated analysis of analgesics questionnaires, FACT-P and BPI showed that 55 patients (57.9%) had a complete pain response or partial pain response and a better HRQoL a better HRQoL or no change in HRQoL. Multivariate analyses suggested that pain at baseline (PAB) and more Ra-223 treatments were significantly associated with a higher probability of a pain response and a better or no change in HRQoL. These results suggest that Ra-223 affects HRQoL and pain in a contemporary mCRPC population. Moreover, our results suggest that patients with pain benefit more from Ra-223 than patients without, but this has to be evaluated in a placebo-controlled trial benefit.

Because Ra-223 is well tolerated it is attractive to explore combinations with another systemic anti-cancer treatment which is not limited to bone metastases. Several studies combining Ra-223 with other agents have been conducted and are being conducted.[27] The ERA-223 trial, was prematurely terminated because of higher mortality and fracture rates in the Ra-223 arm in combination with Abiraterone.[28] This resulted in an advice from the Pharmacovigilance Risk Assessment Committee (PRAC) and the European Medicines Agency (EMA) to restrict the use of Ra-223 to third line treatment or to patients with no other treatment options. They concluded that the mortality was not because of the interaction between Ra-223 and Abiraterone, but probably caused by Ra-223 alone. They also raised concerns about Ra-223 promoting lymph node and visceral metastases.[29, 30] The number of patients in ALSYMPCA and ERA-223 with lymph node metastases have not been made public and therefore a post-hoc analysis of this subgroup could not be performed. Our results do not support the advice given by the PRAC and EMA, since prior treatment with Cabazitaxel was associated with a shorter PFS (chapter 5), while no such

associations were found for prior treatment with Abiraterone or Enzalutamide. The association with chemotherapy and shorter survival has also been reported in several retrospective studies.[22, 23] Alva et al, report that patients in their cohort had a shorter survival when they had prior chemotherapy, but prior treatment with Abiraterone or Enzalutamide had no negative effect on OS.[22] More research is needed to confirm these findings. When confirmed, they would contradict the advice of the EMA to give RA-223 to patients as a third-line treatment or later, as Doc will be a first- or second line treatment for most patients.

FUTURE PERSPECTIVES

In recent years many advances have been made in the treatment of metastasized prostate cancer. These advances include new drugs, like treatment with immunotherapy and Poly ADP-ribose polymerase (PARP) inhibitors. Also new combinations of frequently used drugs are being evaluated. Currently, there are several ongoing studies evaluating the efficacy of newer androgen-signalling-targeted inhibitors and targeted therapies. Here we will discuss recent advances in combination of systemic therapies, immunotherapy and PARP-inhibitors in men with mCRPC.

Combination studies

The efficacy of suppressing serum testosterone in men with advanced prostate cancer was first reported in 1941.[31] Until 2015, treatment of patients with metastasized prostate cancer consisted of ADT until the prostate cancer became castration resistant, after which patients were treated with Docetaxel. In 2015, the CHAARTED trial reported a significant improvement of overall survival by combining Docetaxel with ADT in men with metastatic prostate cancer.[32] These results were confirmed in the STAMPEDE trial in 2016.[33] These spectacular results made many physicians and researchers curious to the efficacy of other combinations with ADT. Several trials have been published evaluating the efficacy of Enzalutamide plus ADT and also Abiraterone plus ADT in metastatic hormone sensitive prostate cancer. These trials show similar results, however to date no prospective study has made a direct comparison of ADT plus Docetaxel, Abiraterone or Enzalutamide. [34–36]

In the metastatic castration-resistant setting, there have been several trials evaluating combination of systemic agents.

A recently published phase 2 trial evaluating tolerability of the combination of Abiraterone and Enzalutamide reported manageable safety profiles. However, PSA-decline rates were similar to those reported in COU-AA-302 (Abiraterone/prednisone monotherapy) and PREVAIL (Enzalutamide monotherapy, but time to progression was shorter in the phase-2 trial.[37] The efficacy of this combination is being evaluated in a phase III trial (NCT01949337).

Preliminary results of two phase 2 trials evaluating the combination of Docetaxel and Enzalutamide and Cabazitaxel and Enzalutamide show promising results. The definitive results of both trials have not been published yet. [38, 39]

A trial similar to ERA-223 is being performed with Enzalutamide instead of Abiraterone. An interim analysis reported there to be no increased fracture and mortality rate in patients treated with the combination.[40] A major difference between ERA-223 and this trial is that patients in this trial were required to use bone health agents, like Denosumab and bisphosphonates. A clinical trial evaluating the combination of Ra-223 and Docetaxel is also being performed, results are also pending.

Immunotherapy

Treatment with Sipuleucel-T, an autologous dendritic cell vaccine, did result in longer OS when compared to placebo, but had no significant effect on PFS.[41] Sipuleucel-T has not been available in Europe since 2015, but is still available in the United States of America.

In several other malignancies, treatment with immunotherapy has yielded significant responses.[42] These treatments were also evaluated in patients with prostate cancer. However, most of the results were disappointing. In 2014, results of treatment with Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4 (CTLA4), in patients with mCRPC progressing after Docetaxel was published (Ipi 043 trial). The authors reported an increased PFS, but failed to show a significant OS benefit.[43] Another trial evaluating efficacy of Ipilimumab in Docetaxel naïve-mCRPC patients also failed to show a significant OS benefit (Ipi 095 trial).[44] A recently published long-term survival update of the Ipi 045 trial did report a significant survival benefit after 2 years follow-up, however only a select group of patients seemed to benefit from Ipilimumab. Definitive biomarkers to select these patients have not yet been identified.[45]

Keynote-199 was a phase-2 trial evaluating Pembrolizumab, a checkpoint inhibitor which targets programmed cell death protein 1 (PD-1), in mCRPC patients. Preliminary results were disappointing, with only a small fraction of the patients having a response (5% of the patients had a complete or partial response). [46, 47] The Check-mate 650-trial is a phase-2 trial evaluating nivolumab , a programmed cell death ligand (PDL-1) inhibitor, and ipilimumab, results are yet to be published. However, preliminary data of this study suggested that Docetaxel naïve patients have a better response than Docetaxel pre-treated patients (25% and 10% of the patients had a complete or partial response, respectively). These results are underwhelming when compared to results from other malignancies with the same treatment regiment, while grade 3-4 toxicity was common.[46, 48] The reason why prostate cancers responds poorly to immunotherapy is not fully understood. In other cancer types, microsatellite instability-high (MSI-H) and deficient mismatch repair pathway (dMMR) have proven to be biomarkers predicting response to immune checkpoint

blockade, like Pembrolizumab and Nivolumab.[49] The prevalence of MSI-H and dMMR is low in prostate cancer, this could explain the disappointing results of immune checkpoint inhibitors in patients with mCRPC.

PARP inhibitors

In prostate cancer, the relevance of genes involved in DNA damage repair (DDR) pathways, notably BRCA1/2, ATM and CDK12 genes, have only recently been recognized. These mutations are present in 10% of the primary tumours and 25% of metastases, with BRCA2 being the most common.[50] In other tumours with DDR defects, Poly ADP-ribose polymerase (PARP) inhibitors and platinum-based chemotherapy have proven to be effective. There is anecdotal evidence that mCRPC patients with BRCA2 germline mutations respond well to platinum based chemotherapy.[50] To date several phase 1 and phase 2 studies have been published of Olaparib and Veliparib, both PARP-inhibitors. Results of a phase 2 trial evaluating the PSA-response in mCRPC patients treated with the combination of Veliparib and Abiraterone/prednisone, compared to Abiraterone/prednisone monotherapy were published. This trial failed to show superiority of the combination when compared to Abiraterone monotherapy in the entire population. [51, 52]

There are a few phase 2 and one phase 3 trials evaluating efficacy of Olaparib. The TOPARP-A study, a phase 2 trial evaluating Opalarib monotherapy in heavily pretreated mCRPC patients, whom had not undergone genetic testing. The authors reported a 33% response rate in the entire population. Subgroup analysis revealed high response rates (88%) in patients with DDR. The TOPARP-B study, evaluated two different dosages of Olaparib monotherapy in mCRPC patients with pathogenic DDR alterations. They reported response rates of 54% and 39% in the high and low dose groups, respectively. Subgroup analyses revealed response rates of 83% for patients with BRCA1/2 mutations. [51, 53, 54]

The PROfound trial, a phase 3 trial evaluating Olaparib in mCRPC patients with a wide array of mutations in genes involved in homologous recombination DNA repair, pretreated with an androgen-signalling-targeted inhibitor and comparing it with androgen-signalling-targeted inhibitor after prior treatment with an androgen-signalling-targeted inhibitor. Response rates of 22% and 4% were reported in the Olaparib and control group, respectively. Patients treated with Olaparib also had longer overall survival rates (17.3 and 14.0 months, respectively). Toxicity was more prevalent in the Olaparib group when compared to the control group. Twenty-three percent of the patients in the Olaparib group required dose reductions, 20% discontinued due to an adverse event and in 4% of the patients treatment was interrupted because of an adverse event.[55, 56] With that, approval of Olaparib as the first targeted therapy for the treatment of mCRPC patients is expected in the near future.

CONCLUSION

Unlike a decade ago, when there was just one life prolonging treatment for mCRPC, we now have an arsenal of treatment options available. Before writing this thesis, there was much uncertainty with regards to sequencing of treatment options for mCRPC patients. Throughout this thesis some of these uncertainties have been addressed, while many still remain. New sequencing studies, new indications and new agents have provided us with new questions on the optimal treatment sequences. I believe that there is no "one size fits all" drug sequence and that the future lies in personalized cancer treatment, where the optimal treatment sequence will dependent on patient, disease and genetic characteristics.

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Appendices

ENGLISH SUMMARY

Prostate cancer is the second most common cancer in men worldwide, with over 1 million newly diagnosed cases each year. Until 2012 Docetaxel was the only treatment with a proven survival benefit for patients with metastatic castration-resistant prostate cancer (mCRPC). Over recent years, multiple new anti-cancer agents were introduced for patients with mCRPC. The phase-3 studies evaluating these agents were mostly performed in patients primarily treated with Docetaxel. Many of these agents were developed and evaluated in parallel to each other. Abiraterone and Enzalutamide were two of these drugs, both targeting the androgen receptor (AR). It was unclear what the efficacy and safety was of treating patients who already were treated with one of these two agents, with the other agent. In Chapter 2 we retrospectively evaluated the efficacy and tolerability of Enzalutamide in patients pre-treated with at least Docetaxel and Abiraterone. We concluded that Enzalutamide was well tolerated in this population, and that the adverse-events were similar to those reported in the AFFIRM trial. The AFFIRM trial was a phase III trial evaluating the efficacy and safety of Enzalutamide in mCRPC patients previously treated with Docetaxel. However, the efficacy of Enzalutamide in our cohort was worse than those of patients in the AFFIRM trial. Patients had lower Prostate-Specific Antigen (PSA) response rates compared to those in the AFFIRM trial (21% and 54%, respectively) and a shorter progression free survival (PFS) (PFS rates were 12.0 and 36.1 weeks, respectively). Our findings were suggestive of cross-resistance between Abiraterone and Enzalutamide.

Because of the lower response rates and PFS rates, we tried to identify parameters predicting response. In Chapter 3 we report that higher Gleason-scores, shorter PSA-doubling time and a longer time interval between ending Abiraterone and starting Enzalutamide were associated with response to Enzalutamide treatment. We could distinguish two groups with a relatively high percentage of PSA responses to Enzalutamide treatment. One group with a short time interval between ending Abiraterone and starting Enzalutamide (IAE $<$ 40 days) and one group with longer time interval (IAE ≥40 days). In the IAE $<$40 days subgroup, all but one of the Enzalutamide-responders had no response to Abiraterone, while in the IAE ≥40 days subgroup, 29% of the Enzalutamide-responders responded to the prior Abiraterone treatment. Moreover, in the ≥40 days subgroup, a linear relation could be identified between time interval between end of Abiraterone and start of Enzalutamide and PSA response to Enzalutamide. The PSA response rates of patients treated with Enzalutamide with an IAE of $>$390 days was comparable to Abiraterone-naive patients, as reported in the AFFIRM trial. These results suggest that some patients might be resistant to Abiraterone, but not to Enzalutamide; that some patients might be resistant to both agents and that patients some with an acquired cross-resistance to Enzalutamide might regain sensitivity in time. These findings are hypothetical and need to be evaluated prospectively.

Because efficacy of Enzalutamide in the AFFIRM trial was evaluated as second-line therapy, not many much was known of the tolerability of Enzalutamide in heavily pre-treated patients. In Chapter 4 we retrospectively analyzed patients from our cohort whom received Enzalutamide as fourth- or fifth-line therapy after castration resistance. Enzalutamide was well tolerated and the frequency of adverse events was similar to those reported in the AFFIRM trial. The response rate was 23%, which was comparable to retrospective reports of third-line Enzalutamide. This data was retrospective and hypothesis generating, but did suggest that fourth- or fifth-line treatment was a possible treatment option, even when considering the considerable costs when given on empirical basis.

Almost 70% of the patients with mCRPC develop bone metastases during the course of their disease. Bone metastases and especially the pain associated with them, have a significant impact on quality of life. Symptomatic bone metastases can be treated with bone directed treatment and until 2013 the treatment options were limited to beta-emitting radionuclides, external beam-radiation therapy, bisphosphonates, RANKL inhibitor and surgery. In 2013, results of the ALSYMPCA trial were published, a phase 3 trial evaluating the efficacy of Radium-223 (Ra-223) in men with mCRPC and symptomatic bone metastases without visceral metastases. Ra-223 is a targeted alpha-emitting radionuclide that selectively binds to areas of increased bone turnover. The patients included in the ALSYMPCA trial were either pretreated with Docetaxel or had not received any systemic anticancer therapy after castration resistance. Other agents, like Enzalutamide, Abiraterone and Cabazitaxel were not available during the accrual of the ALSYMPCA. This raised the question whether the results of ALSYMPCA were representative for patients with mCRPC previously treated with systemic anti-cancer agents, other than Docetaxel. In Chapter 5 we report the results of the ROTOR trial, a prospective observational multicenter trial evaluating the efficacy and tolerability of Ra-223 in a non-study population. In 11.3% of the 300 evaluable patients, Ra-223 was the first treatment after castration resistance. Of the pretreated patients, 80.5% was pretreated with Abiraterone or Enzalutamide, while 74% was pretreated with Docetaxel. The 6 months symptomatic skeletal event (SSE) free survival rate was 83%, median PFS was 5.1 months and median Overall Survival (OS) was 15.2 months. Toxicity, 6 months SSE-free survival rate and OS were comparable to those reported in ALSYMPCA. Previous Cabazitaxel treatment' and 'bone-only metastases' were independent predictors of a shorter and longer PFS, respectively, while above median serum lactate dehydrogenase and 'bone-only metastases' were independent predictors of shorter and longer OS, respectively.

These results suggest that in a non-study population Ra-223 treatment: is well-tolerated, is equally effective as in the ALSYMPCA population and that patients not previously treated with Cabazitaxel benefit most from Ra-223.

In the ALSYMPCA trial, health-related quality of life (HRQoL) was also assessed, and patients treated with Ra-223 had a HRQoL benefit over patients treated with placebo. Even though radionuclides are usually given to patients as a treatment for painful bone metastases, effect of Ra-223 on pain and opioid use were not systematically evaluated. Moreover, contemporary patients have significantly more treatment options and are therefore more extensively pretreated, which raises the question if Ra-223 still has a positive effect on HRQoL. The uncertainty of the clinical benefit and effect on pain of Ra-223 causes much uncertainty for both patients and their treating physicians. In Chapter 6 we report results of an integrated analyses on pain, HRQoL and analgesics use in mCRPC patients treated with Ra-223. Of the 300 included patients, 105 were evaluable for both Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory-Short Form (BPI-SF) questionnaires. Forty-five (43%) patients had pain at baseline (PAB; BPI-SF score 5-10 points) and 60 (57%) had no pain at baseline (no-PAB; BPI-SF score 0-4 points), and 78% of PAB patients had an improvement of the BPI-Worst pain subscale during treatment. Ninety-three out of the 300 patients were also evaluable for opioid use, of whom 33 (31,4%) experienced a complete pain response and 55 (58%) experienced an integrated overall clinical response.

Our study showed that a significant proportion of Ra-223 treated symptomatic and asymptomatic, extensively pretreated mCRPC patients experienced an improved HRQoL and a pain response. These results suggest that the majority of contemporary mCRPC patients derives clinical benefit from Ra-223 treatment.

Finally in Chapter 7 we discuss the results presented in this thesis and discuss current and future perspectives.

NEDERLANDSE SAMENVATTING

Prostaatkanker is de op één na meest voorkomende kanker bij mannen wereldwijd, met meer dan 1 miljoen nieuw gediagnosticeerde gevallen per jaar. Docetaxel was tot 2012 de enige behandeling met een bewezen overlevingsvoordeel voor patiënten met gemetastaseerd castratieresistent prostaatkanker (mCRPC). In de afgelopen jaren zijn er meerdere nieuwe geneesmiddelen geïntroduceerd voor patiënten met mCRPC. De fase-3 studies die de overlevingswinst van deze nieuwe middelen aantoonden zijn voornamelijk verricht op mCRPC patiënten die eerder met Docetaxel waren behandeld. Veel van deze nieuwe geneesmiddelen zijn parallel aan elkaar ontwikkeld en geëvalueerd. Abiraterone en Enzalutamide waren twee van deze geneesmiddelen, beide gericht op de androgeenreceptor (AR). Het was nog niet bekend wat het effect op de werkzaamheid en veiligheid van deze twee nieuwe middelen was, wanneer patiënten die al eerder met één van deze twee geneesmiddelen behandeld waren, behandeld zouden worden met de ander. In Hoofdstuk 2 hebben we retrospectief de effectiviteit en veiligheid van Enzalutamide geëvalueerd bij patiënten die eerder behandeld waren met ten minste Docetaxel en Abiraterone. De AFFIRM studie is een fase III-studie die de werkzaamheid en veiligheid van Enzalutamide onderzocht in mannen met mCRPC die eerder met docetaxel waren behandeld. We concludeerden dat Enzalutamide goed werd verdragen door deze populatie en dat de bijwerkingen vergelijkbaar waren met die gerapporteerd in de AFFIRM-studie. De werkzaamheid van Enzalutamide in ons cohort was echter slechter dan die van patiënten in de AFFIRM-studie. Patiënten hadden lagere prostaat-specifieke antigeen (PSA) responspercentages vergeleken met die in het AFFIRM-onderzoek (respectievelijk 21% en 54%) en een kortere progressievrije overleving (PFS) (PFS-percentages waren respectievelijk 12,0 en 36,1 weken). Onze bevindingen waren suggestief voor kruisresistentie tussen Abiraterone en Enzalutamide.

Vanwege de lagere respons- en PFS-percentages hebben we geprobeerd parameters te identificeren die de response kunnen voorspellen. In Hoofdstuk 3 rapporteren we dat hogere Gleason-scores, kortere PSA-verdubbelingstijd en een langer tijdsinterval tussen het beëindigen van Abiraterone en het starten van Enzalutamide geassocieerd waren met respons op behandeling met Enzalutamide. We konden twee groepen onderscheiden met een relatief hoog percentage PSA-daling na behandeling met Enzalutamide: Een groep met een kort tijdsinterval tussen het beëindigen van Abiraterone en het starten van Enzalutamide (IAE $<$40 dagen) en een groep met een langer tijdsinterval (IAE ≥40 dagen). In de groep met korte intervallen hadden alle Enzalutamide-responders, op één na, geen respons op Abiraterone. Terwijl in de IAE ≥40 dagen subgroep, 29% van de Enzalutamide-responders reageerden op de eerdere behandeling met Abiraterone. Bovendien werd in de IAE ≥40 dagen subgroep een lineair verband gezien tussen enerzijds het tijdsinterval tussen het staken van Abiraterone en het starten van Enzalutamide (IAE) en anderzijds PSA-respons op Enzalutamide. De PSA-responspercentages van patiënten

behandeld met Enzalutamide met een IAE van> 390 dagen waren vergelijkbaar met patiënten die nooit met Abiraterone behandeld waren, zoals gerapporteerd in de AFFIRM studie. Deze resultaten suggereren dat sommige patiënten mogelijk resistent zijn tegen Abiraterone, maar niet tegen Enzalutamide; dat sommige patiënten mogelijk resistent zijn tegen beide middelen en dat patiënten met een verworven kruisresistentie tegen Enzalutamide na verloop van tijd weer gevoelig kunnen worden. Deze bevindingen zijn hypothetisch en moeten prospectief worden onderzocht.

Omdat de werkzaamheid van Enzalutamide in de AFFIRM studie werd geëvalueerd als tweedelijnsbehandeling, was er niet veel bekend over de verdraagbaarheid van Enzalutamide bij patiënten die meerdere andere anti-kanker behandelingen hadden gehad na castratieresistentie. In Hoofdstuk 4 hebben we retrospectief patiënten geanalyseerd uit ons cohort die Enzalutamide kregen als vierde- of vijfde lijn therapie na castratieresistentie. Enzalutamide werd goed verdragen en het bijwerkingsprofiel was vergelijkbaar met die van de AFFIRM studie. Het responspercentage was 23%, vergelijkbaar met retrospectieve effectiviteitsevaluaties van derdelijns Enzalutamide. Deze gegevens waren retrospectief en hypothese-genererend, maar suggereerden wel dat behandeling in de vierde of vijfde lijn een behandelingsoptie was, zelfs als we de aanzienlijke kosten op empirische basis in overweging nemen.

Bijna 70% van de patiënten met mCRPC ontwikkelt botmetastasen in de loop van hun ziekte. Botmetastasen en vooral de pijn die ermee gepaard gaan, hebben een grote invloed op de kwaliteit van leven. Symptomatische botmetastasen kunnen worden behandeld met botgerichte behandeling en tot 2013 waren de behandelingsopties beperkt tot bètastralende radionucliden, radiotherapie, bisfosfonaten, RANKL-remmer en chirurgie. In 2013 werden de resultaten van de ALSYMPCA-studie gepubliceerd, een fase 3-studie die de werkzaamheid van Radium-223 (Ra-223) evalueert bij mannen met mCRPC en symptomatische botmetastasen zonder viscerale metastasen. Ra-223 is een gerichte alfastralende radionuclide die selectief bindt aan gebieden met een verhoogde botomzetting. De patiënten die in de ALSYMPCA-studie waren opgenomen, waren ofwel eerder behandeld met Docetaxel of hadden geen systemische antikankertherapie gekregen na castratieresistentie. Andere middelen, zoals Enzalutamide, Abiraterone en Cabazitaxel, waren niet beschikbaar tijdens de inclusie van ALSYMPCA. Hierdoor kwam de vraag of de resultaten van de ALSYMPCA studie wel representatief waren voor patiënten met mCRPC die eerder waren behandeld met systemische antikankermiddelen anders dan (alleen) Docetaxel. In Hoofdstuk 5 beschrijven we de resultaten van de ROTOR trial, een prospectieve observationele multicenter studie die de effectiviteit en verdraagbaarheid van Ra-223 evalueert in een niet-studiepopulatie. Bij 11,3% van de 300 patiënten was Ra-223 de eerste behandeling na castratieresistentie. Van de patienten die reeds andere behandelingen hadden gekregen vóór Ra-223 was 80,5% eerder behandeld met Abiraterone of Enzalutamide, 74% behandeld met Docetaxel en 20% met Cabazitaxel. De 6 maanden symptomatische skelet-gerelateerde gebeurtenis (SSE) vrije overleving was 83%, de mediane PFS was 5,1 maanden en de mediane totale overleving (OS) was

15,2 maanden. Toxiciteit, 6 maanden SSE-vrije overleving en OS waren vergelijkbaar met wat er in de ALSYMPCA studie gerapporteerd werd. Vervolgens is gekeken naar de voorspellende waarde van verschillende parameters op PFS en OS. Eerdere behandeling met Cabazitaxel en het hebben van 'alleen botmetastasen' waren onafhankelijke voorspellers van respectievelijk een kortere en langere PFS, terwijl boven gemiddelde serum lactaatdehydrogenase en het hebben van 'alleen botmetastasen' onafhankelijke voorspellers waren van respectievelijk kortere en langere OS.

Deze resultaten suggereren dat in een niet-studie populatie de behandeling met Ra-223 goed wordt verdragen, even effectief is als in de ALSYMPCA-populatie en dat patiënten die niet eerder met Cabazitaxel zijn behandeld het meeste baat hebben bij Ra-223.

In de ALSYMPCA-studie werd ook de gezondheid gerelateerde kwaliteit van leven (HRQoL) beoordeeld, hieruit bleek dat patiënten die werden behandeld met Ra-223 een HRQoL voordeel hadden ten opzichte van patiënten die werden behandeld met placebo. Hoewel radionucliden normaliter aan patiënten worden gegeven als behandeling voor pijnlijke botmetastasen, werd het effect van Ra-223 op pijn en opioïdengebruik niet systematisch geëvalueerd. Bovendien hebben hedendaagse patiënten significant meer behandelingsopties en zijn daarom vaak uitgebreider voorbehandeld. Dit doet de vraag doet rijzen of Ra-223 nog wel een positief effect heeft op HRQoL in deze vaak uitgebreidere voorbehandelde populatie. De onzekerheid over het effect van Ra-223 op pijn en HRQoL veroorzaakt veel onzekerheid voor zowel patiënten als hun behandelende artsen. In Hoofdstuk 6 rapporteren we de resultaten van een geïntegreerde analyse van pijn, HRQoL en analgetica gebruik bij een hedendaagse mCRPC patiëntenpopulatie behandeld met Ra-223. HRQol werd geëvalueerd door gebruik te maken van een voor prostaatkanker gevalideerde vragenlijst, de Functional Assessment of Cancer Therapy-Prostate (FACT-P). Voor pijn werd gebruik gemaakt voor een gevalideerde vragenlijst gericht op het evalueren van pijn, de Brief Pain Inventory-Short Form (BPI-SF). De analgetica vragenlijst was een lijst waar patiënten zelf opschreven wat ze aan pijnstilling gebruikten. Van de 300 geïncludeerde patiënten waren 105 evalueerbaar voor zowel de FACT-P als BPI-SF vragenlijsten. Vijfenveertig (43%) patiënten hadden pijn op baseline (PAB; BPI-SF-score 5-10 punten) en 60 (57%) hadden geen pijn op baseline (no-PAB; BPI-SF-score 0-4 punten). Achtenzeventig procent van de PAB-patiënten had tijdens de behandeling een verbetering van de BPI-SF 'ergste pijn' subschaal. Vijfennegentig van de 300 patiënten waren ook evalueerbaar voor het gebruik van opiaten, van wie 33 (31,4%) een volledige pijnresponse had. Geïntegreerde analyse van de analgetica vragenlijsten, FACT-P en BPI toonden aan dat 58% van de patiënten een complete of partiele pijn response hadden, gecombineerd met verbetering of stabiel blijven dan de HRQoL.

Onze studie toonde aan dat een significant deel van de met Ra-223 behandelde symptomatische en asymptomatische, uitgebreid voorbehandelde mCRPC-patiënten een verbeterde HRQoL en

pijnrespons ervoeren. Deze resultaten suggereren dat de meerderheid van de hedendaagse mCRPC-patiënten klinisch voordeel haalt uit de behandeling met Ra-223.

Ten slotte bespreken we in Hoofdstuk 7 de resultaten die in dit proefschrift worden gepresenteerd en bespreken we huidige ontwikkelingen en toekomstige perspectieven.

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CURRICULUM VITAE

Sushil Koewarsingh Badrising was born in Amsterdam, the Netherlands on September 2nd, 1982. He grew up in Purmerend, but moved to Paramaribo, Suriname, at the age of 12. He attended and graduated from the Arthur A. Hoogendoorn Atheneum. In 2002 he moved back to the Netherlands and started medical training at the Academic Medical Center (University of Amsterdam). He did an internship at the Netherlands institute for Neuroscience (NIN) under the supervision of dr. Tom J. van den Berg. After obtaining his medical degree, he started working at the department of internal medicine at the Tergooi hospitals in Hilversum and Blaricum under supervision of dr. Peter J. de Vries, internist. While working as a resident he collaborated in a study supervised by dr. Andries M. Bergman. This study led to his first publication and led to the start of his PhD research at the Netherlands Cancer Institute at the Medical Oncology department, supervised by dr. Andries M. Bergman and prof. John B.A.G. Haaanen. He performed research on optimizing the treatment sequences in patients with metastatic castration-resistant prostate cancer. In 2016 he started his residency training in pulmonary medicine at the Radboud University Medical Center in Nijmegen under the supervision of dr. Monique H.E. Reijers and prof. Michel M. van der Heuvel. In 2021 he completed his residency with a special interest in the field of thoracic oncology, while finishing his PhD research in his spare time. His goal is to treat patients with thoracic malignancies and continue doing research.