Multidisciplinary treatment of metastatic prostate cancer

Bouman, E.W.

2020

document version
Publisher's PDF, also known as Version of record

5

A phase I trial of cabazitaxel combined with rhenium-188-HEDP in patients with metastatic castration-resistant prostate cancer who progressed on or after a docetaxel containing treatment: the ReCab trial.

This chapter is published in Clinical Nuclear Medicine, 2017

Abstract

Background

In patients with metastatic castration resistant prostate cancer (mCRPC), bone-seeking radiopharmaceuticals such as rhenium-188-HEDP (Re-188 HEDP), are effective for pain palliation and have a marked anti-tumor effect. Cabazitaxel is the standard second-line chemotherapy for mCRPC patients. We performed a phase I study investigating the safety and feasibility of the combined treatment with Re-188 HEDP and cabazitaxel in mCRPC patients.

Patients and methods

Patients with mCRPC and documented disease progression on or after docetaxel were eligible for inclusion.

In both dose levels, cabazitaxel (4 cycles of cabazitaxel 25 mg/m^2 + 2 cycles of cabazitaxel 20mg/m^2 in level one, and six cycles of cabazitaxel 25mg/m^2 in level two) were combined with two cycles of Re-188 HEDP 40 MBq/kg (1.1 mCi/kg) (after the second and fourth cabazitaxel cycle).

Three patients were planned for each dose level, expanding to 6 patients in case of a dose limiting toxicity (DLT). A DLT is defined as any grade 4 toxicity, or grade 3 toxicity delaying the next treatment cycle.

Results

Twelve patients were included, of whom 3 had progressive disease before the 3th cycle of cabazitaxel. In total, 1 DLT occurred (dose level 1), after treatment cycle 6 (Re-188 HEDP) (thrombopenia grade 3 delaying the next treatment cycle). The cohort was expanded to 6 patients, with no further DLTs. No DLT occurred in dose level 2. The most important adverse events were of hematological origin, followed by mild fatigue and diarrhea.

Conclusion

Combination therapy with cabazitaxel and Re-188 HEDP is feasible and generally well tolerated with similar hematological toxicity compared to cabazitaxel monotherapy.

Introduction

The therapeutic field of prostate cancer is rapidly evolving. Many therapeutic strategies have been studied for metastatic castration-resistant prostate carcinoma (mCRPC) including immunotherapy, additional hormonal treatments, anti-bone resorptive agents and chemotherapy[1]. Docetaxel is standard first-line chemotherapy for patients with mCRPC. Since publication of the TROPIC trial in 2010, cabazitaxel is registered as second-line chemotherapy for patients with progressive disease during or after docetaxel-based therapy[2]. Cabazitaxel is a tubulin-binding taxane drug that has proven antitumor activity in taxane-resistant tumors. In the registration trial (TROPIC), compared to chemotherapy with mitoxantrone plus prednisone, cabazitaxel plus prednisone provided a median overall survival benefit of 2.4 months (15.1 versus 12.7 months)[2]. Although this was a significant improvement, the benefit is still moderate and further studies are warranted.

As bone is the predominant site of metastases in mCRPC, bone-seeking radiopharmaceuticals are frequently used for palliation of bone-pain[3]. Radiopharmaceuticals, such as strontium-89, samarium-153-EDTMP and rhenium-188 hydroxyethylidene diphosphonate (Re-188 HEDP) have high affinity for bone metastases and deliver local high-energy beta radiation[4]. Several studies suggest that besides a palliative effect, these radionuclides also have an anti-tumor effect. Tu and colleagues were the first to report a significant survival benefit achieved by radionuclide-therapy[5]. They randomized 72 patients with mCRPC, who were clinically stable or responding following induction chemotherapy, to receive doxorubicin with or without strontium-89. Median overall survival was significantly longer with the combination therapy (27.7 months versus 16.8 months). However, this was a small study with important imbalances in the study arms and the chemotherapeutic regimen used was not the current standard of care. Further evidence of the potential anti-tumor effect of beta-emitting radionuclides was suggested by a study group from Bonn[6]. Sixty-four patients with progressive mCRPC and bone pain were randomly assigned to receive either a single injection of Re-188 HEDP or a further injection 8 weeks later. Pain palliation was better in the group receiving repeated treatment. Furthermore, median survival was longer in the group receiving two injections of Re-188 HEDP as compared to the single-treatment group (12.7 months versus 7.0 months; p=0.043).

Docetaxel has previously been combined with samarium-153-EDTMP and rhenium-186-HEDP both in phase I as well as in phase II trials[5, 7-10] Combination therapy of docetaxel with these beta-emitting radiopharmaceuticals was found to be feasible and well tolerated.

Thus far, beta-emitting radiopharmaceuticals have not been combined with cabazitaxel in patients with bone-metastatic CRPC who progressed during or after docetaxel. We conducted this phase I trial to investigate whether the combination of cabazitaxel/prednisone with repeated Re-188 HEDP is feasible and to determine the dosing schedule for a subsequent phase II trial.

Materials and methods

Patients

Men with histological confirmed prostate carcinoma were eligible if they had bone metastatic disease and evidence of disease progression despite serum testosterone <50 ng/dl. Minimum evidence of PSA progression was defined as a 25% increase of PSA over a reference value of PSA, provided that the increase was more than 2 ng/ml. Radiological progression was assessed using the RECIST 1.1 criteria. Bone metastases had to show uptake of ^{99m}Tc-hydroxy-methylene diphosphonate (HDP) at bone scintigraphy. All patients were pre-treated with docetaxel. Previous exposure to Re-188 HEDP or radium-223-chloride was not allowed within two months prior to inclusion. Other inclusion criteria were: WHO performance status 0 or 1, age >18 years, and life expectancy of at least three months. Patients were required to have an ANC ≥1.5 x 10^9/l, a platelet count ≥100 x 10^9/l, a hemoglobin ≥9.0 g/dl and adequate renal and liver function.
Patients receiving LHRH agonists were mandated to continue this treatment during the study. This study was approved by the institutional review board and medical ethics committee for both sites. Informed consent was obtained from all individual participants included in the study.

Study design and treatment plan

The design of this dose escalation study is shown in Table 1. Six cycles of 3-weekly cabazitaxel were administered at increasing dosages, either cabazitaxel 20 or 25mg/m^2. Re-188 HEDP 40 MBq/kg (1.1 mCi/kg) was administered after the second and after the fourth cycle of cabazitaxel. The injection of Re-188 HEDP was followed by a 4-week interval before the next cycle of cabazitaxel was administered. Inclusion started in dose level one, dose level -1 was only to be used if dose level 1 was not tolerated.

Table 1 Dose escalation schedule

Dose level	Trial Cycle 1	Trial Cycle 2	Trial Cycle 3	Trial Cycle 4	Trial Cycle 5	Trial Cycle 6	Trial Cycle 7	Trial Cycle 8
-1*	CBZ 20mg/m^2	CBZ 20mg/m^2	Re-188 40MBq/kg	CBZ 20mg/m^2	CBZ 20 mg/m^2	Re-188 40MBq/kg	CBZ 20mg/m^2	CBZ 20 mg/m^2
1	CBZ 25mg/m^2	CBZ 25mg/m^2	Re-188 40MBq/kg	CBZ 25mg/m^2	CBZ 25mg/m^2	Re-188 40MBq/kg	CBZ 20mg/m^2	CBZ 20mg/m^2
2	CBZ 25mg/m^2	CBZ 25mg/m^2	Re-188 40MBq/kg	CBZ 25mg/m^2	CBZ 25mg/m^2	Re-188 40MBq/kg	CBZ 25mg/m^2	CBZ 25mg/m^2

CBZ = Cabazitaxel; Re-188 = Rhenium-188 HEDP; 40 MBq/kg = 1.08 mCi/kg

*Dose level -1 was only to be used if dose level 1 was not tolerated.

All patients received prednisone 10 mg orally during the whole treatment period. After completing this dose escalation schedule, patients were scheduled to continue treatment with cabazitaxel to a maximum of 10 cycles of chemotherapy. Adverse events were graded using the NCI Common Terminology Criteria version 4.0.

Re-188 HEDP was produced as described in literature[11]. Three patients were assigned to each dose level. If a dose limiting toxicity (DLT) occurred in one of three patients in a particular dose level, the group was expanded to six patients. The first seven weeks after administration of Re-188 HEDP were defined as the DLT period. Full blood count, renal and liver function tests were performed weekly during the DLT-period. When none of the three patients (or ≤1 of 6) in a dose level experienced a DLT in this period, the next patients could be included in the next dose level. A DLT could be hematological or non-hematological. Unacceptable hematological toxicity was defined as neutropenia grade 4 lasting more than 7 days or grade 3 when there was failure of count recovery to allow for the next treatment cycle on time. Dose limiting thrombocytopenia was defined as any grade 4 thrombocytopenia or a grade 3 thrombocytopenia when failure of count recovery to allow for the next treatment cycle on time. In addition, anemia grade 4 was defined as DLT. All grade 4 non-hematological toxicities were defined as dose limiting. Grade 3 non-hematological toxicity was also unacceptable, except for nausea, vomiting or diarrhea unless not recovered to allow for next cycle on time. The next cycle of treatment could be given if the absolute neutrophil count (ANC) was at least 1.5 x 10^9/l, the platelet count was more than 75 x 10^9/l and non-hematological toxicities (except alopecia) were recovered to baseline. Usage of granulocyte-colony stimulating factor was allowed and could be considered as primary prophylaxis in high-risk patients. A dose reduction for

cabazitaxel (25 mg/m^2 to 20 mg/m^2) was given when a patient experienced a DLT. No more than one dose reduction was allowed.

Statistical analysis

The primary endpoint of this study was to establish a safe and feasible dosing schedule for the combination of cabazitaxel and repeated Re-188 HEDP. A standard phase I dose escalation study design was used with three to six patients in each dose level. The results are reported as descriptive statistics.

Results

This study enrolled 12 patients between September 2012 and July 2015. Three additional patients were necessary because three patients could not fulfil the study protocol due to progressive disease early in the treatment schedule (1 patient after the second cycle of cabazitaxel and 2 patients directly after the first cycle of Re-188 HEDP).

The last patient finished the final DLT period on January 11, 2016. Patients were included at the Meander Medical Center Amersfoort and the VU University Medical Center Amsterdam; both centers included 6 patients. The baseline characteristics are shown in Table 2.

The 12 included patients received 96 treatment cycles in total (76 cycles of cabazitaxel), with a median of 7 cycles cabazitaxel per patient (range 2-10). Twenty cycles of Re-188 HEDP were given with a median dose of 3.2 GBq (86.5 mCi) per cycle. Three patients stopped study treatment because of early progressive disease; they all had received two cycles of cabazitaxel and two of the three patients also received one cycle of Re-188 HEDP. During the whole study, no dose reductions were necessary. There were 3 treatment delays of one week each; cycle 7 had to be delayed twice due to a thrombocytopenia grade 2 (no DLT, because a DLT was defined as a grade 3 thrombopenia), and cycle 8 was delayed once at request of the patient. In total, 6 patients received G-CSF, which is specified in Table 2.

One DLT occurred in dose level 1, after the second cycle of Re-188 HEDP (treatment cycle 6). This patient developed a thrombocytopenia grade 3, which did not recover in time for the next cycle of cabazitaxel. After recovery of the thrombocytopenia, he was treated off protocol. Three extra patients were included in dose level 1 because of this DLT. No further DLT's occurred in the expansion cohort of dose level 1, neither in dose level 2.

Table 2 Baseline characteristics

Baseline characteristics n = 12	
Age, years	
Median (range)	67.4 (60.5-75.3)
Time since metastatic disease, years	
Median (range)	4.7 (2.5-11.3)
Gleason score	
<7	3
7	4
>7	5
Assigned dose level	
1	8*
2	4#
Previous therapy	
Docetaxel (median number of cycles)	10
Bicalutamide (n)	8
Abiraterone (n)	4
Enzalutamide (n)	1
EBRT (n)	5
Radiopharmaceuticals (n)	4∞
Baseline lab results (median; range)	
PSA (ng/ml)	272 (51-902)
Hb (mmol/L)	7.9 (5.9-10.1)
ALP (U/L)	256 (59-918)
LD (U/L)	261 (191-1231)
Use of G-CSF	5 pts in cycle 1,
Start in cycle	1 pt in cycle 5
VAS score (median, range)	3 (0-5)

*drop out of two patients due to progressive disease; #drop out of one patient due to progressive disease
∞2patients samarium, 2 patients rhenium-188 HEDP; PSA; prostate specific antigen, Hb; haemoglobin, AF; alkaline phosphatase , LD; lactate dehydrogenase G-CSF; Granulocyte Colony Stimulating Factor, VAS; Visual Analogue Scale

The most common side effects were of hematological origin; all patients developed grade 1 or 2 anemia during the treatment. In addition, 41.6% of the treatment cycles resulted in a thrombocytopenia, mostly grade 1 (29.1% of treatment cycles). Neutropenic fever occurred once (grade 3, after treatment cycle 7), whereas in 32.3% of the treatment cycles patients developed some degree of neutropenia. Most important non-hematological adverse events were fatigue, skeletal pain nausea, altered taste and diarrhea.

Three SAE's occurred within the DLT period. One patient was admitted because of neutropenic fever 11 days after the 5th cycle of cabazitaxel (7th cycle in trial); he was

treated with ceftriaxone and recovered in time for the next dose of cabazitaxel. Another patient, who was excluded later because of progressive disease, was admitted after the 2nd treatment cycle for drainage of an abscess in the left buttock, which was already present before start of treatment. The third SAE was an admission because of an increase in bone pain 3 weeks after the first cycle of Re-188 HEDP, which appeared to be due to progressive disease. In addition, 1 patient was admitted 3 weeks after the DLT period (3 weeks after the 8th treatment cycle) because of constipation, probably due to morphine use.

An overview of the adverse events in 96 treatment cycles is presented in Table 3, with a specification of hematological adverse events in Table 4. In Table 5, we compare the incidence of hematological side effects per patient of the investigated combination of cabazitaxel plus Re-188 HEDP with cabazitaxel alone (the Tropic trial2), docetaxel plus Re-186 HEDP (Taxium I9) and docetaxel plus Re-188 HEDP (Taxium II12).

A decline in PSA-value of ≥25% from baseline was seen in 9 out of 12 patients (with a decline of ≥ 50% in 4 of these patients), as shown in Figure 1 (PSA change between baseline PSA and nadir, and change between baseline PSA and end of study treatment). Two patients with an initial decline in PSA showed an increase during the trial (6.3 and 4.6 months after the first treatment cycle). Three patients suffered from disease progression early in the treatment schedule; they all had increasing PSA levels from the start of treatment. A PSA flare due to the treatment was very unlikely because all PSA rises were confirmed by later samples.

There were no significant changes in quality of life or pain between baseline and the end of treatment, as measured with the QLQ-30 questionnaires and a visual analogue scale.

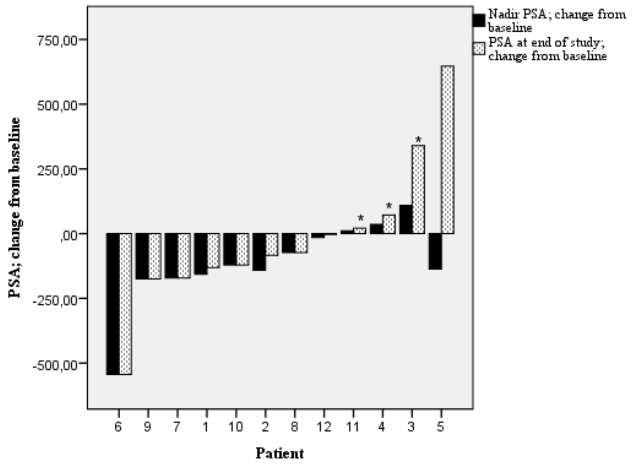

*Figure 1 Prostate-specific antigen change from baseline (baseline to nadir and baseline to PSA at end of study treatment). *Withdrawn because of progressive disease.*

Table 3 Adverse events in 96 cycles of treatment (12 patients); Grade 1 and 2 AE's are only displayed if present in at least two treatment cycles

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Haematological				
Anaemia	64 (66.7%)	30 (31.3%)	2 (2.1%)	0
Thrombocytopenia	28 (29.1%)	9 (9.4%)	3 (3.1%)*	0
Neutropenia	0	7 (7.3%)	8 (8.3%)	16 (16.7%)
Neutropenic fever	0	0	1 (1.0%)	0
Gastro-intestinal				
Constipation	2 (2.1%)	1 (1.0%)	1 (1.0%)	0
Diarrhea	4 (4.2%)	5 (5.2%)	0	0
Nausea	6 (6.3%)	3 (3.1%)	0	0
Vomiting	2 (2.1%)	0	0	0
Pyrosis	0	3 (3.1%)	0	0
Mucositis	2 (2.1%)	0	0	0
Altered taste	8 (8.3%)	0	0	0
Other				
Fever	3 (3.1 %)	1 (1.0%)	0	0
Skeletal pain	8 (8.3%)	3 (3.1%)	1 (1.0%)	0
Fatigue	28 (29.1 %)	12 (12.5%)	0	0
Neuropathy	5 (5.2%)	0	0	0
Dry eyes	1 (1.0%)	1 (1.0%)	0	0
Dyspnoea d'effort	2 (2.1%)	0	0	0
Abscess	0	0	1 (1.0%)	0

* Of which 1 dose limiting toxicity, due to failure of recovery in time for the next cycle of treatment

Table 4 Nadir blood values (occurring after cycle number)

Patient	Initial Hb (mmol/L)	Maximum nadir Hb ($x10^9$/l)	Initial ANC ($x10^9$/l)	Maximum nadir ANC ($x10^9$/l)	Initial platelet count ($x10^9$/l)	Maximum nadir platelet count ($x10^9$/l)
1	5.9	5.3 (5)	6.4	0.2 (5)	336	94 (5&6)
2	6.6	5.6 (8)	2.7	0.4 (1&2)+	241	54 (6)
3	7.9	5.1 (2)	6.6	6.8 (1)+	369	201 (1)
4∞	6.6	4.9 (3)	2.95	4.2 (1)	200	148 (3)
5	7.4	6.1 (5)	3.87	0.6 (4)+	306	49 (6)
6	7.1	5.3 (4)	4.7	<0.1 (4)	238	69 (7)
7	8.3	7.2 (5)	4	0.4 (7)	262	159 (7)
8	7.9	6.1 (7)	8.04	1.3 (4)+	322	42 (7)
9	8.1	6.2 (8)	5.4	<0.1 (3)	209	72 (7)
10	10.1	6.3 (7)	3.9	0.1 (4)	247	39 (7)
11∞	9.0	7.4 (1)	3.3	4.9 (1)+	283	280 (3)
12	8.6	7.1 (7)	4.24	1.6 (2)+	194	60 (7)

ANC= absolute neutrophil count, Hb=haemoglobin

*Discontinuation of treatment due to progressive disease after cycle 2

∞Discontinuation of treatment due to progressive disease after cycle 3

+ Granulocyte Colony Stimulating Factor (G-CSF) prophylaxis

Hb; haemoglobin, ANC; absolute neutrophil count

Table 5 Comparison of the incidence of adverse events; number of patients (%)

Adverse event	ReCab I[1] N=12	Tropic trial[2] N=371	Taxium I[3] N=14	Taxium II[4] Docetaxel N=42	Taxium II[5] Combination N=44
Anemia					
All grades	12 (100%)	360 (97%)	9 (64%)	12 (29%)	13 (30%)
≥grade 3	1 (8%)	41 (11%)	0	0	1 (2%)
Thrombocytopenia					
All grades	10 (82%)	174 (47%)	10 (71%)	0	11 (25%)
≥grade 3	3 (25%)	15 (4%)	2 (14%)	0	0
Neutropenia					
All grades	8 (67%)	349 (94%)	14 (100%)	3 (7%)	8 (18%)
≥grade 3	7 (58%)	304 (82%)	13 (93%)	2 (5%)	7 (16%)
Febrile neutropenia	1 (8%)	30 (8%)	2 (14%)	6 (14%)	6 (14%)

1 Cabazitaxel+rhenium 188 HEDP; 2 Cabazitaxel+prednisone; 3 Docetaxel+prednisone+rhenium-186 HEDP; 4 Docetaxel+prednisone; 5 Docetaxel+prednisone+ rhenium-188 HEDP

Discussion

This dose finding trial demonstrates that the combination of cabazitaxel with Re-188 HEDP is feasible and generally well tolerated by patients with mCRPC and bone metastases. Thrombocytopenia was the most relevant hematological side effect, which is well known for Re-188 HEDP[6, 13-15]. This occurred in 41.6% of the treatment cycles, and in 82% of the included patients. The only dose limiting toxicity was a thrombocytopenia grade 3 after the second cycle of Re-188 HEDP, which caused delay of the next treatment cycle. Another 2 patients developed a thrombocytopenia grade 3 but recovered in time for the next treatment cycle and therefore did not fulfil the criteria for a DLT. In addition, 2 patients had 1 week treatment delay of a scheduled cycle of cabazitaxel because of a thrombocytopenia grade 2. The lowest values of thrombocytes were mainly seen after cycle 6 and 7. No problems other than treatment delay occurred; no bleeding complications were seen.

As known from previous studies the lowest value of thrombocytes is expected four weeks after administration of Re-188 HEDP[6, 13, 14]. Therefore, an interval of 4 weeks after the Re-188 HEDP injection was planned before continuing with cabazitaxel. In the study of Chang et al. the incidence of thrombocytopenia was significantly higher in patients with a low baseline thrombocyte count ($<200 \times 10^9/L$)[14]. We did not find this correlation in our study, which might be due to the small study population.

Neutropenia (any grade) occurred in 67% of included patients (in 32.2% of the treatment cycles) and 58% of the patients had a grade 3 or 4 neutropenia (occurring in 25% of treatment cycles). Neutropenia is a common side effect of cabazitaxel. In the TROPIC-trial 378 patients were treated with cabazitaxel 25 mg/m2 three weekly (prophylactic G-CSF was not allowed at cycle 1). Neutropenia was reported in 94% of patients and 82% of the patients had one or more episode of grade 3 or 4 neutropenia[2]. In our study only two episodes of neutropenia (both grade 2) occurred after Re-188 HEDP injection, whereas all other cases of neutropenia (n= 29) occurred after a cycle of cabazitaxel. However, this resulted just once (1/12 = 8.3% of the patients) in an episode of neutropenic fever, which resolved without complications after intravenous administration of antibiotics. This incidence of neutropenia appears lower than in the TROPIC trial; this may be attributed to the fact that the Recab trial allowed prophylactic G-CSF since cycle 1, according to the international guidelines.

Since neutropenia and neutropenic fever can result in major and life threatening complications, primary prophylaxis with G-CSF must be considered, especially in patients

with higher risk of severe complications from neutropenia (for example age >65 years, extensive bone metastases or previous episodes or febrile neutropenia with other chemotherapy)[16].

All patients suffered from anemia. However, 75% of the patients already had an anemia at baseline. In 14 treatment cycles, we registered an increase of at least one grade of anemia.

In a previous phase I trial, the TAXIUM study, docetaxel was combined with Re-186 HEDP instead of Re-188 HEDP[9]. The main difference between these two beta-emitters concerns the dose; due to the shorter half-life of Re-188 HEDP, a higher dose can be given, which results in more activity in the tumor and makes Re-188 HEDP the most powerful beta-emitter. When we compare the side effects per patient in this study with the TAXIUM trial, the incidence of anemia and thrombocytopenia was higher in this phase I trial (anemia in 100% versus 64% of the patients and thrombocytopenia in 82% versus 71% of the patients). This was not unexpected. In the first place, the mean dosage of Re-188 HEDP in this trial was higher than in the TAXIUM trial (respectively cumulative 6.4 GBq (173.0 mCi) versus 2.5, 3.75 and 5,0 GBq (67.6, 101.4 and 135.1 mCi)).

In addition, the TAXIUM study included patients who were eligible for first-line chemotherapy with docetaxel, whereas in our study patients had more advanced disease and were previously treated with docetaxel, probably resulting in less bone marrow reserve.

As expected, the most reported non-hematological side effects were fatigue, skeletal pain and diarrhea. Those side effects did not cause major problems, other than discomfort for the patient. The incidence and grade of non-hematological side effects were comparable to the results of the earlier mentioned TROPIC trial[2].

Although this trial was not designed to assess efficacy, some results concerning PSA response are available. Four patients (33%) showed a PSA response ≥ 50% from baseline, which lasted until the last measured PSA in the trial. In addition, 3 other patients showed a consistent PSA response of ≥ 25%. This is comparable to the results of the TROPIC trial in which 39.2% of the patients experienced a decline in PSA ≥50%[2].

A randomized phase II trial comparing standard second line cabazitaxel/prednisone with combination treatment of cabazitaxel/prednisone and Re-188 HEDP started in April 2016.

Conclusion

Combined therapy with cabazitaxel 25 mg/m^2 and Re-188 HEDP 40 MBq/kg (1.1 mCi/kg) is feasible and generally well tolerated in patients with mCRPC progressive during or after first-line docetaxel. We will continue with a phase II trial, in which patients will be randomized between cabazitaxel 25 mg/m^2 plus prednisone 10 mg daily or cabazitaxel/prednisone plus 2 cycles of Re-188 HEDP 40 MBq/kg (1.1 mCi/kg).

References

1. van Dodewaard-de Jong JM, Verheul HMW, Bloemendal HJ, de Klerk JMH, Carducci MA, van den Eertwegh AJM. New Treatment Options for Patients With Metastatic Prostate Cancer: What Is The Optimal Sequence? *Clinical genitourinary cancer.* 2015;13:271-279.

2. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet (London, England).* 2010;376:1147-1154.

3. Vogelzang NJ, Crawford ED, Zietman A. Current clinical trial design issues in hormone-refractory prostate carcinoma. Consensus Panel. *Cancer.* 1998;82:2093-2101.

4. Lam MG, de Klerk JM, van Rijk PP, Zonnenberg BA. Bone seeking radiopharmaceuticals for palliation of pain in cancer patients with osseous metastases. *Anti-cancer agents in medicinal chemistry.* 2007;7:381-397.

5. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet (London, England).* 2001;357:336-341.

6. Palmedo H, Manka-Waluch A, Albers P, et al. Repeated bone-targeted therapy for hormone-refractory prostate carcinoma: tandomized phase II trial with the new, high-energy radiopharmaceutical rhenium-188 hydroxyethylidenediphosphonate. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2003;21:2869-2875.

7. Morris MJ, Pandit-Taskar N, Carrasquillo J, et al. Phase I study of samarium-153 lexidronam with docetaxel in castration-resistant metastatic prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27:2436-2442.

8. Fizazi K, Beuzeboc P, Lumbroso J, et al. Phase II trial of consolidation docetaxel and samarium-153 in patients with bone metastases from castration-resistant prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27:2429-2435.

9. van Dodewaard-de Jong JM, de Klerk JM, Bloemendal HJ, et al. A phase I study of combined docetaxel and repeated high activity 186Re-HEDP in castration-resistant prostate cancer (CRPC) metastatic to bone (the TAXIUM trial). *European journal of nuclear medicine and molecular imaging.* 2011;38:1990-1998.

10. Tu SM, Mathew P, Wong FC, Jones D, Johnson MM, Logothetis CJ. Phase I study of concurrent weekly docetaxel and repeated samarium-153 lexidronam in patients with castration-resistant metastatic prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27:3319-3324.

11. ter Heine R, Lange R, Breukels OB, et al. Bench to bedside development of GMP grade Rhenium-188-HEDP, a radiopharmaceutical for targeted treatment of painful bone metastases. *International journal of pharmaceutics.* 2014;465:317-324.

12. van Dodewaard-de Jong JM, de Klerk JMH, Bloemendal HJ, et al. A randomised, phase II study of repeated rhenium-188-HEDP combined with docetaxel and prednisone versus docetaxel and prednisone alone in castration-resistant prostate cancer (CRPC) metastatic to bone; the Taxium II trial. *European journal of nuclear medicine and molecular imaging.* 2017;44:1319-1327.

13. De Klerk JM, Zonnenberg BA, Blijham GH, et al. Treatment of metastatic bone pain using the bone seeking radiopharmaceutical Re-186-HEDP. *Anticancer research.* 1997;17:1773-1777.

14. de Klerk JM, van het Schip AD, Zonnenberg BA, et al. Evaluation of thrombocytopenia in patients treated with rhenium-186-HEDP: guidelines for individual dosage recommendations. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine.* 1994;35:1423-1428.

15. Cheng A, Chen S, Zhang Y, Yin D, Dong M. The tolerance and therapeutic efficacy of rhenium-188 hydroxyethylidene diphosphonate in advanced cancer patients with painful osseous metastases. *Cancer biotherapy & radiopharmaceuticals.* 2011;26:237-244.

16. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015;33:3199-3212.