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# Management of patients with metastatic castration-resistant prostate cancer — second-line treatment options according to the Polish National Health Fund therapeutic program

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## ABSTRACT

Prostate cancer is one of the most common malignancies among men worldwide. According to ESMO recommendations, systemic treatment of castrate-resistant prostate cancer (CRPC) patients includes hormonal treatment, radionuclides, and immunotherapy, and the choice of appropriate method depends, among others, on clinical symptoms of disease and possible presence of distant metastases. Polish recommendations regarding systemic treatment of CRPC are different, mainly due to distinct reimbursement conditions for individual drugs. The purpose of the two subsequent publications is to present the options of systemic treatment for CRPC patients within the Polish National Health Fund drug program. The first of the articles presents second-line treatment.

**Key words:** prostate cancer, castration-resistant prostate cancer, systemic treatment, second-line setting

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## Introduction

Prostate cancer is recognised as one of the most frequent cancers in men globally and one of the most frequent causes of cancer death [1–5]. Prostate cancer is a hormone-dependent tumour. As a consequence, castration is a major aim of treatment (surgical or pharmacological/medical) — maintaining the testosterone serum level lower than 50 ng/dl ( $< 1.7$  nmol/l), which is recognised as the castration threshold. Medical castration can be achieved by use of agonists or antagonists of gonadoliberin (LHRH, luteinising hormone releasing hormone) [1, 4–8]. Such a strategy enables disease control in the majority of patients ( $> 90\%$ ) with advanced prostate cancer. However, most men suffering from the disease develop castration-resistant prostate cancer (CRPC), with a median time to occurrence of 18–24 months [6].

The combined treatment with docetaxel and pharmacological castration is a standard of care in primarily

metastatic prostate cancer patients. Docetaxel has been used in this indication for several years, i.e. from time when the data of the TAX327 phase III prospective randomised clinical trial was published. In this trial docetaxel was proved to decrease the relative risk of death by 21% when compared to mitoxantron [1, 5]. In patients with disease progression after chemotherapy based on docetaxel several options of treatment are available. These are: second-line chemotherapy based on taxoids (cabazitaxel or docetaxel re-challenge), novel hormone therapy (abiraterone acetate and/or enzalutamide), and immunotherapy [the autologous vaccine derived from dendritic cells modified *ex vivo* (Sipuleucel-T)] [1, 4, 5, 7].

Enzalutamide is available in Poland, and, according to the announcement of the Polish Ministry of Health from October 25<sup>th</sup> 2017 referring to the list of reimbursed drugs, food products, and means of special use and medical products (Dz. Urz. Min. Zdr. 2017.105, zał. B.56) [8], it is recognised as therapeutic option in

a reimbursement procedure called the Therapeutic Program financed by the NFZ (Polish National Health Fund) since November 2017.

The aim of the publication is to describe options for the second-line of systemic treatment in men suffering from castration-resistant prostate cancer, who failed to benefit from docetaxel-based chemotherapy.

## Second-line systemic treatment

The strategy of second-line treatment in CRPC patients depends primarily on the choice of agents used previously. In men treated with docetaxel as their first line, another cytotoxic agent of taxanes — cabozantinib may be active as a therapy of the second-line. In the prospective randomised phase III clinical trial TROPIC the overall survival advantage has been proven with cabozantinib when compared with mitoxantrone (15 months vs. 13 months; 30% reduction of relative risk of death), with neutropaenia as the most frequent adverse event that significantly affected the use of the treatment — especially in patients previously treated with chemotherapy [1, 9].

Abiraterone acetate is a selective inhibitor of cytochrome P450 c17 (CYP17), an enzyme that is crucial for synthesis of androgens in testes, adrenal glands, and tumour cells of prostate cancer. First the efficacy of abiraterone acetate was assessed in patients with castration-resistant prostate cancer who failed to benefit from chemotherapy. There were 1195 men with CRPC (biochemical and/or radiographic progression despite treatment with docetaxel) enrolled to the COU-AA-301 trial. Patients were randomly assigned in a 2:1 ratio to receive either abiraterone with prednisone (1000 mg per day and 10 mg per day, respectively) or placebo and prednisone. The findings in the abiraterone were arm as follow:

- reduction of relative risk of death by 26% [hazard ratio (HR) 0.74; 95% confidence interval (CI): 0.64–0.86] and improved median OS from 11.2 months to 15.8 months;
- reduction of relative risk of biochemical progression by 42% ( $p < 0.001$ ) and radiographic progression by 33% ( $p < 0.001$ );
- increase of radiographic response rate (14% vs. 3%, respectively) and biochemical response rate (29% vs. 6%, respectively);
- improved quality of life in terms of improvement of QoL parameters when compared to baseline, and delay in deterioration of QoL in time [4].

According to the Summary of Product Characteristics, abiraterone acetate with prednisone or prednisolone is indicated in the treatment of metastatic castration-resistant prostate cancer adult patients with

progression of the disease despite previous treatment with chemotherapy based on docetaxel [10]. The same indication is defined in the NFZ therapeutic program [11, 12]. The drug is administered in a standard daily dose of 1000 mg (four tablets per 250 mg taken once a day).

Enzalutamide is a strong irreversible inhibitor of androgen receptor with no agonistic activity. The drug completely halts cell proliferation and induces apoptosis of prostate cancer tumour cells, stops translocation of androgen receptor to cell nuclei to formate transcription complexes responsible for expression of certain genes, and it inhibits binding of the receptor to DNA strands [1, 5, 11]. The efficacy and safety of enzalutamide were assessed in the phase III clinical trial AFFIRM, which enrolled almost 1200 patients with castration-resistant prostate cancer previously treated with at least one chemotherapy regimen. Patients were randomly assigned (in 2:1 ratio) to receive either enzalutamide or matching placebo in a blinded manner [5]. Enzalutamide was administered orally in a daily dose of 160 mg. The drug was administered with gonadotropin-releasing hormone (GnRH). The concomitant use of prednisone was allowed but not required. The study demonstrated statistically significant improvement of median overall survival [from 13.6 months (95% CI: 11.3–15.8 months) to 18.4 months (95% CI: 17.3 months–not reached), which reflected a 37% reduction of relative risk of death (HR 0.63; 95% CI: 0.53–0.75). For this reason, the study was unblinded and patients randomised to the control arm and receiving placebo were offered treatment with enzalutamide. The statistically significant advantage of enzalutamide over placebo in treatment of patients with CRPC has also been proven in terms of all predefined secondary end-points:

- improvement of median progression-free survival in the investigators' assessment according to RECIST (Response Evaluation Criteria In Solid Tumours) criteria from 2.9 months to 8.3 months (HR 0.404, 95% CI: 0.350–0.466;  $p < 0.0001$ );
- improved biochemical (PSA) response — 54% vs. 2%;
- improved response in soft tissues — 29% vs. 4%;
- improved parameters of quality of life — 43% vs. 18%;
- reduction of relative risk of biochemical progression by 75%, radiographic progression by 60%, relative risk of skeletal events by 31%;
- incidence of grade  $\geq 3$  adverse events according to CTCAE (Common Terminology Criteria for Adverse Events) — 45.3% vs. 53.1%.

According to the Summary of Medical Product Characteristics and the letter of the therapeutic program, enzalutamide is indicated in the treatment of adult men with metastatic castration-resistant prostate cancer in

whom progression of the disease occurred during or after chemotherapy with docetaxel [11–13].

The recommended dose of enzalutamide is 160 mg (four capsules each per 40 mg) taken once daily. In patients who did not undergo orchiectomy the treatment maintaining castration status should be continued.

Therapeutic program castration-resistant prostate cancer enables use of radium dichloride Ra-223 (alpharadin) in this population of patients as well. In the prospective multicentre randomised phase III clinical trial ALSYMPCA [14] radionuclide was compared to placebo in CRPC patients with metastatic spread limited to the skeleton, and it showed a statistically significant improvement of overall survival (median OS 14.9 months vs. 11.3 months; HR: 0.70; 95% CI: 0.58–0.83;  $p < 0.001$ ) and documented the advantage in terms of all secondary end-points (i.e. increases time to first skeletal related event (SRE) and time to biochemical (PSA) progression in a statistically significant manner.

Treatment with Ra-223 involves delivery of activity of 55 kBq per kilogram of body mass every four weeks for a total of six times. There are no data regarding the safety of treatment longer than six cycles.

The therapeutic program provides the possibility to use Ra-223 in second-line treatment of CRPC (beyond the chemotherapy with docetaxel) if metastatic spread limited to bones is documented (with exclusion of lymph nodes smaller than 2 cm in the pelvis, which are not a contraindication for introduction of the procedure).

The problem referred to use of the radiopharmaceutical in the aforementioned therapeutic program is the formal complexity, than secondary law and logistic issues as well. From the perspective of the procedure medical oncologist is its performer and contractor being responsible for enrolment, conduction, safety, and reporting via SMPT (System Monitorowania Programów Terapeutycznych; System for Monitoring of Therapeutic Programs) a course of treatment. Moreover, radionuclide may be administered by trained and qualified staff only in the adequately equipped workplace of nuclear medicine departments under supervision of specialist in nuclear medicine.

Inclusion/exclusion criteria of the therapeutic program for treatment with abiraterone acetate, enzalutamide, and alpharadin in patients who failed to benefit from docetaxel-based chemotherapy as well as tests required at baseline and during a treatment are presented in Table 1.

It should be emphasised that in the case of patients receiving chemotherapy as their second-line

of systemic treatment for CRPC there is a risk of neuroendocrine undifferentiation/transformation. This phenomenon is observed more frequently in the era of new generation hormonal agents. It should be suspected if new metastatic lesions in visceral organs develop, there is a change of skeletal lesion type from osteosclerotic to osteolytic, no change or minor increase in PSA level is observed with signs and/or symptoms of clear radiographic and/or clinical progression of the disease, or an increase of carcinoembryonic antigen (CEA) level [4]. In such cases platinum-based chemotherapy should be considered (i.e. docetaxel + carboplatin).

## Conclusions

The introduction of new agents into the system of reimbursement in Poland has significantly broadened the spectrum of therapeutic options for the treatment of patients with castration-resistant prostate cancer after failure of chemotherapy based on docetaxel. However, for example, cabazitaxel — a cytostatic agent that in the prospective multicentre randomised phase III clinical trial TROPIC [15] proved its superiority over mitoxantrone in terms of improved patients' overall survival [15.1 months (95% CI: 14.1–16.3)] vs. 12.7 months (95% CI: 11.6–13.7), respectively; HR 0.70 (95% CI: 0.59–0.83,  $p < 0.0001$ ) and progression-free survival [2.8 months (95% CI: 2.4–3.0) vs. 1.4 months (95% CI: 1.4–1.7), respectively; HR 0.74 (95% CI: 0.64–0.86,  $p < 0.0001$ )] is still unavailable in Poland.

The possibility of using only one out of three drugs is the major restriction of the therapeutic program in force. Castration-resistant prostate cancer is beginning to create a serious clinical problem because of the increasing number of patients at this stage of evolution of the disease. More efficient treatment significantly improves the survival of men with CRPC. A substantial proportion of patients are still in very good or good performance status after failure of the first and the second line of systemic treatment, which enables the subsequent causal therapy. Agents registered for treatment of CRPC are administered in a sequential manner due to their diverse mechanism of action, but the optimal sequence is still under investigation. For these reasons the therapeutic program does not keep up with Leeds of clinical practice and makes the systemic treatment of CRPC in Poland suboptimal.

**Table 1. Inclusion/exclusion criteria of therapeutic program for second-line treatment with abiraterone acetate, enzalutamide, and alpharadin in patients with castration-resistant prostate cancer (after failure of chemotherapy based on docetaxel) as well as tests required at baseline and during the treatment — according to the NFZ Therapeutic Program**

Inclusion and exclusion criteria	Withdrawal criteria for therapeutic program	Test results required at enrolment to therapeutic program	Monitoring of the treatment
<b>Abiraterone acetate</b>			
<b>All inclusion criteria must be fulfilled:</b>			
<p>Patients with prostate cancer can be enrolled to be treated with abiraterone acetate under conditions as follow:</p> <p>Histological confirmation of adenocarcinoma of the prostate (fine needle biopsy is acceptable in patients diagnosed in the past when core biopsy was not the standard diagnostics procedure)</p>	<p>Occurrence of hypersensitivity to active substance or any of excipient/vehicle substance</p> <p>Progression of the disease during the course of the treatment defined by following criteria:</p> <p>a) occurrence of at least two out of three types of progression:</p> <ul style="list-style-type: none"> <li>• clinical progression:               <ul style="list-style-type: none"> <li>— progression of pain defined as need for introduction of new opioid for period of time longer then 2 weeks (except for cases when the aforementioned introduction of opioid referred to treatment of side effects caused by previously used drug) or</li> <li>— occurrence of skeletal related event (SRE) or</li> <li>— deterioration of performance status score to at least 2 (according to WHO score system) for longer than two weeks)</li> </ul> </li> <li>b) PSA progression defined as 3 consecutive rises of serum PSA level in tests performed at least 1 week apart with proven 2 rises by 50% from baseline value (nadir), with nominal value of PSA level &gt; 2 ng/ml</li> </ul>	<p>Histological or cytological confirmation of adenocarcinoma of the prostate</p> <p>Aminotransferases serum activity assessment and tests required to define liver insufficiency score according to Child-Pugh score system</p> <p>Bone scan (if previously not performed)</p> <p>Radiographic assessment (X-ray or computed tomography or tomography of magnetic resonance) based on clinical indications</p>	<p>Always if clinically indicated: PSA serum level every 3 months</p> <p>Radiographic assessment depending on examinations performed at baseline</p> <p>Aminotransferases serum activity assessment every 2 weeks for the first 3 months of the treatment, then once every month</p> <p>Other tests depending on clinical indications</p> <p>Bone scan 6 months after beginning of the treatment in therapeutic program or upon signs of clinical progression according to defined criteria for progression</p>
<p>Castration-resistance status confirmed based on serum testosterone level of less than 50 ng/dl (1.7 nmol/l or less) in patients with disease progression according to criteria listed in section 1.3 of therapeutic program</p> <p>Disease progression based on: three consecutive rises of serum PSA level in tests performed at least 2 weeks apart with proved 2 rises by 50% from baseline value (nadir), with nominal value of PSA level &gt; 2 ng/ml or occurrence of radiographic disease progression (skeleton, visceral organs, soft tissue)</p> <p>Performance status 0–1 according to WHO classification</p> <p>Age of 18 years or older</p> <p>Patients previously treated with abiraterone acetate in so-called “non-standard chemotherapy” procedure can be enrolled to therapeutic program as well if their treatment in “non-standard chemotherapy” procedure had been started before January the 1st 2014 and upon enrolment they had no exclusion criteria according to letter of therapeutic program</p>	<p>to treatment of side effects caused by previously used drug) or</p> <p>— occurrence of skeletal related event (SRE) or</p> <p>— deterioration of performance status score to at least 2 (according to WHO score system) for longer than two weeks)</p> <p>b) PSA progression defined as 3 consecutive rises of serum PSA level in tests performed at least 1 week apart with proven 2 rises by 50% from baseline value (nadir), with nominal value of PSA level &gt; 2 ng/ml</p> <ul style="list-style-type: none"> <li>• radiographic progression defined as occurrence of at least two new metastatic lesions confirmed by radiographic assessment;</li> <li>or</li> <li>c) disease progression according to RECIST criteria</li> </ul> <p>Occurrence of adverse events precluding the patient from continuing treatment according to recommendations enclosed in Summary of Medical Product Characteristics</p> <p>informed consent withdrawal</p>	<p>Bone scan (if previously not performed)</p> <p>Radiographic assessment (X-ray or computed tomography or tomography of magnetic resonance) based on clinical indications</p>	<p>Other tests depending on clinical indications</p> <p>Bone scan 6 months after beginning of the treatment in therapeutic program or upon signs of clinical progression according to defined criteria for progression</p>
<b>Exclusion criteria:</b>			
<p>Hypersensitivity to active substance or any of excipient/vehicle substance</p> <p>Mild or severe liver function disorders (class B or C according to Child-Pugh criteria)</p> <p>Aminotransferases activity equal or higher than 2.5-fold upper of normal limit</p> <p>History of ketoconazole use in treatment of prostate cancer</p> <p>Uncontrolled heart disease or circulatory system disease</p> <p>Previous treatment with enzalutamide or abiraterone acetate</p>	<p>to treatment of side effects caused by previously used drug) or</p> <p>— occurrence of skeletal related event (SRE) or</p> <p>— deterioration of performance status score to at least 2 (according to WHO score system) for longer than two weeks)</p> <p>b) PSA progression defined as 3 consecutive rises of serum PSA level in tests performed at least 1 week apart with proven 2 rises by 50% from baseline value (nadir), with nominal value of PSA level &gt; 2 ng/ml</p> <ul style="list-style-type: none"> <li>• radiographic progression defined as occurrence of at least two new metastatic lesions confirmed by radiographic assessment;</li> <li>or</li> <li>c) disease progression according to RECIST criteria</li> </ul> <p>Occurrence of adverse events precluding the patient from continuing treatment according to recommendations enclosed in Summary of Medical Product Characteristics</p> <p>informed consent withdrawal</p>	<p>Bone scan (if previously not performed)</p> <p>Radiographic assessment (X-ray or computed tomography or tomography of magnetic resonance) based on clinical indications</p>	<p>Other tests depending on clinical indications</p> <p>Bone scan 6 months after beginning of the treatment in therapeutic program or upon signs of clinical progression according to defined criteria for progression</p>

**Table 1 cont. Inclusion/exclusion criteria of therapeutic program for second-line treatment with abiraterone acetate, enzalutamide, and alphaaradin in patients with castration-resistant prostate cancer (after failure of chemotherapy based on docetaxel) as well as tests required at baseline and during the treatment — according to the NFZ Therapeutic Program**

Inclusion and exclusion criteria	Withdrawal criteria for therapeutic program	Test results required at enrolment to therapeutic program	Monitoring of the treatment
<b>Enzalutamide</b>			
<b>All inclusion criteria must be fulfilled:</b>			
Age of 18 years or older	Progression of the disease during the course of the treatment with enzalutamide defined as occurrence of at least one out of three of following criteria listed in points a–c:	Histological confirmation of adenocarcinoma of the prostate	Clinical assessment
Histological confirmation of adenocarcinoma of the prostate	a) three consecutive rises of serum PSA level in tests performed at least 1 week apart. Minimal PSA level rise by 50% from baseline value with nominal value of PSA level > 5 ng/ml	Serum	Testosterone serum level every 3 months
Castration-resistance status confirmed based on serum testosterone level of less than 50 ng/dl (1.7 nmol/l or less)	b) signs of radiographic progression in soft tissue according to RECIST criteria	Serum aminotransferases activity, bilirubin level, albumin level, INR	PSA serum level every 3 months, in the case of PSA level rising, subsequent PSA level assessments should be performed every 28–30 days
ECOG performance status 0–1	c) progression of bone metastatic lesions defined as appearance of at least 2 new lesions in bone radiographic assessment according to Prostate Cancer Working Group 2 (occurrence of at least two new skeletal lesions in bone scan)	assessment and calcium to rule out biochemical (PSA) progression	Bone scan at least every 6 months or upon clinical indications (if progression with occurrence of new metastatic lesions is suspected during the treatment there is a requirement to confirm findings from the first assessment with subsequent assessment performed after next ≥ 6 weeks)
Disease progression on or after treatment with docetaxel defined as appearance of at least one out of three of following criteria described in lit. a–c:	any of excipient/vehicle substance	Creatinine serum level	Other test with choice depending on clinical situation and localisation of metastatic lesions at baseline, radiographic assessment enabling evaluation of response to the treatment according to RECIST (except for bone scan) should be performed at least every 3 months
a) three consecutive rises of serum PSA level in tests performed at least 1 week apart. Minimal PSA level rise by 50% from baseline value with nominal value of PSA level > 2 ng/ml	Occurrence of hypersensitivity to enzalutamide or any of excipient/vehicle substance	Testosterone serum level	
b) progression of bone metastatic lesions defined as appearance of at least 2 new lesions in bone radiographic assessment according to Prostate Cancer Working Group 2 (occurrence of at least two new skeletal lesions in bone scan)	Occurrence of adverse events precluding the patient from continuing treatment according to recommendations enclosed in Summary of Medical Product Characteristic	PSA serum level	
c) progression of bone metastatic lesions defined as appearance of at least 2 new lesions in bone radiographic assessment according to Prostate Cancer Working Group 2 (occurrence of at least two new skeletal lesions in bone scan)	Informed consent withdrawal	Bone scan (if not performed within last 6 months)	
Patients with castration-resistant prostate cancer previously treated with enzalutamide after failure of treatment with docetaxel and financed in a different way can still be enrolled to a therapeutic program to maintain treatment continuum		Radiographic assessment (X-ray or computed tomography or tomography of magnetic resonance) of the chest, abdomen and pelvis	
<b>Exclusion criteria:</b>		assessment with subsequent assessment performed after next ≥ 6 weeks)	
Hypersensitivity to enzalutamide or any of excipient/vehicle substance		assessment (X-ray or computed tomography or tomography of magnetic resonance) of the chest, abdomen and pelvis	
Severe renal insufficiency, severe liver insufficiency (class C according to Child-Pugh score system)		assessment with subsequent assessment performed after next ≥ 6 weeks)	
Cardio-vascular impairment: myocardial infarction within last 6 months or unstable angina pectoris (within last 3 months) or congestive heart failure NYHA class III or IV or significant and uncontrolled arrhythmia or conduction disorders (i.e. prolongation QTcF interval to > 470 ms), hypertension either untreated or uncontrolled with adequate treatment		assessment with subsequent assessment performed after next ≥ 6 weeks)	
Hereditary intolerance to fructose		assessment with subsequent assessment performed after next ≥ 6 weeks)	
Previous treatment with enzalutamide or abiraterone acetate		assessment with subsequent assessment performed after next ≥ 6 weeks)	
History of seizures or history of other factors predisposing to seizures		assessment with subsequent assessment performed after next ≥ 6 weeks)	



**Table 1 cont. Inclusion/exclusion criteria of therapeutic program for second-line treatment with abiraterone acetate, enzalutamide, and alpharadin in patients with castration-resistant prostate cancer (after failure of chemotherapy based on docetaxel) as well as tests required at baseline and during the treatment — according to the NFZ Therapeutic Program**

Inclusion and exclusion criteria	Withdrawal criteria for therapeutic program	Test results required at enrolment to therapeutic program	Monitoring of the treatment
<b>Radium dichloride Ra-223</b>			
<b>Including criteria:</b>			
<p>Histological or cytological confirmation of adenocarcinoma of the prostate</p> <p>Castration-resistance status confirmed based on serum testosterone level of less than 50 ng/dl (1.7 nmol/l) or less regardless of medical castration (pharmacologic castration should be continued) or surgical castration</p> <p>Progression of prostate cancer defined as:</p> <ul style="list-style-type: none"> <li>a) three consecutive rises of serum PSA level in tests performed at least 1 week apart, with proved 2 rises by 50% from baseline value (nadir), with nominal value of PSA level &gt; 5 ng/ml or</li> <li>b) signs of radiographic progression</li> </ul> <p>At least 6 metastatic skeletal lesions confirmed on bone scan</p> <p>Pain related to skeletal metastatic lesions requiring continuous treatment with analgesics or palliative radiotherapy within period not longer than 12 weeks before beginning of the treatment</p> <p>No visceral metastases except for involvement of pelvic lymph nodes with diameter in short axis equal or lower than 2 cm</p> <p>Treatment with docetaxel completed at least 4 weeks before beginning of the treatment with radium 223 or documented contraindications for docetaxel</p> <p>ECOG performance status 0–2</p> <p>Age of 18 years or older</p> <p>Peripheral blood test results:</p> <ul style="list-style-type: none"> <li>a) platelets higher or equal to <math>1.0 \times 10^5/\text{mm}^3</math></li> <li>b) absolute neutrophil count higher or equal to 1500/mm<sup>3</sup></li> <li>c) haemoglobin level higher or equal to 10.0 g/dl</li> </ul> <p>Serum total bilirubin level lower or equal to <math>1.5 \times \text{ULN}</math></p> <p>Serum activity of AspAT and AlAT lower or equal to <math>2.5 \times \text{ULN}</math></p> <p>Serum creatinine level lower or equal to <math>1.5 \times \text{ULN}</math></p> <p>Life expectancy longer than 6 months</p> <p>According to letter of the therapeutic program treatment reimbursement refers to 6 drug injections each 4 weeks apart unless decision for withdrawal is made according to point 4.4 of therapeutic program procedure</p>	<p>Occurrence of unacceptable hematologic toxicity i.e. grade 3 or 4 neutropenia or thrombocytopenia according to NCI — CTC criteria lasting longer than 14 days irrespectively to adequate supportive treatment or another grade 4 toxicity according to NCI-CTC persisting irrespectively to supportive treatment for longer than 7 days</p> <p>Start of subsequent treatment with another radionuclide — with exception for palliative radiotherapy as treatment of solitary metastatic lesion</p> <p>Deterioration of performance status score to at least 2 according to WHO score system when compared to baseline assessment</p> <p>PSA progression defined as three consecutive rises of serum PSA level in tests performed at least 1 week apart. Minimal PSA level rise by 50% from baseline value with nominal value of PSA level &gt; 5 ng/ml</p> <p>Uncontrolled stool incontinence</p> <p>Spinal cord compression confirmed with clinical assessment or with tomography of magnetic resonance that either cannot be treated with local measures or its treatment would require subsequent Ra-223 dose delay by more than 4 weeks</p> <p>Any other disorders or conditions that in opinion of clinician may preclude the patient from continuing treatment with radium dichloride Ra-223</p>	<p>Laboratory tests performed within 2 weeks before enrolment to the treatment in therapeutic program, radiographic assessment (except for bone scan) within 2 months before enrolment to the treatment in therapeutic program, bone scan should be performed within no more than 3 months before enrolment to the treatment in therapeutic program.</p> <p>Tests to be performed at enrolment to treatment in the therapeutic program:</p> <ul style="list-style-type: none"> <li>a) total blood count</li> <li>b) serum PSA level</li> <li>c) serum tests: bilirubin level, creatinine level, alkaline phosphatase activity, testosterone level</li> <li>d) serum activity assessment of transaminases (AspAT, AlAT)</li> <li>e) bone scan</li> <li>f) computer tomography of abdomen and pelvis</li> <li>g) chest X-ray or computed tomography</li> </ul>	<p>Before each dose administered during treatment in therapeutic program following test should be performed as safety monitoring:</p> <ul style="list-style-type: none"> <li>a) total blood count</li> <li>b) serum bilirubin level</li> <li>c) creatinine level</li> <li>d) alkaline phosphatase activity</li> <li>e) serum activity of aminotransferases (AspAT, AlAT)</li> <li>f) serum PSA level</li> </ul> <p>4–8 weeks after completion of treatment in the therapeutic program tests described in point 1 should be performed (once)</p> <p>Other tests should be performed based on clinical judgement and discretion of the physician</p>

**Table 1 cont. Inclusion/exclusion criteria of therapeutic program for second-line treatment with abiraterone acetate, enzalutamide, and apalutamide in patients with castration-resistant prostate cancer (after failure of chemotherapy based on docetaxel) as well as tests required at baseline and during the treatment — according to the NFZ Therapeutic Program**

Inclusion and exclusion criteria	Withdrawal criteria for therapeutic program	Test results required at enrolment to therapeutic program	Monitoring of the treatment
<b>Radium dichloride Ra-223</b>			
<b>Exclusion criteria:</b>			
Active concomitant malignancy (except for basal cell carcinoma of the skin) or history of other malignancy unless its treatment was not curative or had been undertaken with intention for cure yet had not reached its endpoint			
Significant side effects of chemotherapy not recovering within 4 weeks after completion of the treatment (except for persistent neuropathy)			
Previous treatment with strontium-89, samarium-53, radium-223 or radium-226 within 24 weeks before enrolment to treatment in the therapeutic program			
Spinal cord compression confirmed with clinical assessment or with tomography of magnetic resonance that requires either local intervention or radiotherapy (treatment with radium dichloride Ra-223 may be introduced after effective completion of local treatment)			
Metastatic lesions to central nervous system uncontrolled with local treatment			
Presence of at least one out of the following concomitant disorders:			
a) uncontrolled infection			
b) heart failure of NYHA III or IV			
c) Crohn's disease or colitis ulcerosa			
d) bone marrow myelodysplasia			
Uncontrolled stool incontinence			
Any other disorders or conditions that in opinion of clinician may constitute contraindication for administration of radium dichloride Ra-223			

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