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# Abiraterone acetate + prednisolone treatment beyond prostate specific antigen and radiographic progression in metastatic castration-resistant prostate cancer patients

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**Abstract**

**Objectives:** To investigate the overall survival (OS) of chemotherapy refractory patients with metastatic castration-resistant prostate cancer who were treated with abiraterone acetate + prednisolone (AA + P) beyond prostate specific antigen (PSA) and radiographic progression (PRP) until clinical progression in comparison to patients treated until PRP.

**Methods:** At our institute the AA + P treatment started in 2011 in an early-access protocol trial. In October 2012 AA became generally available. From April 2011 to November 2014, 116 patients received AA + P. The clinical trial patients (T; $n = 56$) were treated beyond PRP until clinical progression. In the nonclinical trial group (NT; $n = 57$) the treatment was covered until PRP. Three patients are still under treatment. The 2 groups were statistically homogeneous, except AA + P treatment duration. The primary objective was the OS and the secondary the PSA progression-free and radiographic progression-free survivals.

**Results:** The median OS was significantly longer ($P < 0.0001$) in the T group compared to the NT group: 21.9 (95% CI: 16.9–25) vs. 12.5 (9.3–14.1) months, respectively. In univariate analysis there were 11 parameters, which significantly affected OS, but in multivariate Cox analysis only alkaline phosphatase (AP) level at the start of treatment, systemic therapy after AA + P and cohort type (T or NT) proved to independently influence the OS. The progression-free survival curves of T and NT groups did not differ significantly.

**Conclusions:** In our retrospective analysis low levels of AP at the start of treatment, systemic therapy applied after AA + P and treatment beyond PRP proved to be independent factors of longer OS in metastatic castration-resistant prostate cancer. 

*Keywords:* Alkaline phosphatase; Clinical progression; Further systemic therapy; Overall survival; Progression-free survival

## 1. Introduction

Prostate cancer (PC) is one of the most commonly diagnosed solid organ malignancies in the developing world [1]. In Hungary it is the third most common cancer diagnosed and the fourth most common cause of cancer death among males (~1,200 cases/year) [2]. For almost all men who die of PC, castration-resistant disease will be the cause of death. In 2004, 2 pivotal trials, TAX-327 and SWOG 9916, supported the approval of docetaxel as the first metastatic castration-resistant PC (mCRPC) treatment, in combination with prednisone. Docetaxel was found to prolong median overall survival (OS) by approximately 3 months when compared with the combination of mitoxantrone and prednisone [3,4]. Consequently docetaxel became the standard first-line regimen in patients with (mCRPC). A variety of chemotherapies, targeted therapies, and immunotherapies since have been developed and approved for use in mCRPC, with the goal of improved efficacy outcomes. Abiraterone [5], cabazitaxel [6], enzalutamide [7], and $^{223}$Ra dichloride [8] were recently approved (2010–2013) by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Abiaraterone acetate (AA) is a novel, potent inhibitor of CYP17A1. It decreases production of testosterone by inhibiting CYP17A1, an enzyme that is expressed in testicular,

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adrenal, and prostate tumor tissues and is needed for androgen biosynthesis. AA + prednisone was shown to improve (OS) and progression-free survival (PFS) after treatment with docetaxel in the COU-AA-301 trial. OS was improved in the AA + prednisone group (14.8 vs. 10.9 months; hazard ratio = 0.65; 95% CI: 0.54–0.77; $P < 0.001$). PFS and prostate specific antigen (PSA) response rates were also superior in the AA + prednisone arm. The significant side effects of this medication are due to mineralocorticoid excess (hypertension, edema-fluid retention, and hypokalemia). This study led to the approval of the drug as second-line therapy after docetaxel [5]. AA and the other new agents have significantly improved the outcomes of men with mCRPC, however, there are a proportion of patients who do not respond to a particular therapy. Some studies investigated the predictive factors for OS in case of AA treatment [9–11].

The aim of this study was to investigate the OS of chemotherapy (CT) refractory mCRPC patients who were treated with AA + P beyond PSA and radiographic progression (PRP) until clinical progression (PRP) in comparison to patients treated only until PRP. Another aim of this study was to identify patients who will most likely benefit from the AA + P treatment, and help clinicians to choose from the persistently growing options.

## 2. Patients and methods

Unselected cohorts of mCRPC patients treated at the National Institute of Oncology (Budapest, Hungary) were investigated. The first AA + P treatment started on April 21, 2011 in an early-access protocol trial (NCT01217697). Every consecutive patient was treated in the clinical trial. After October 8, 2012 AA became generally available in Hungary. It has been reimbursed based on special request on an individual basis for all consecutive patients. From April 21, 2011 to November 05, 2014 116 patient received AA + P. All patients progressed during or after docetaxel treatment. AA+P was administered according to the treatment protocol including 1,000 mg AA and 10 mg prednisolone daily. All patients had ECOG 0 or 1 performance status. The clinical trial patients (T) ($n = 56$) were treated beyond PRP until clinical progression. Definition of clinical progression at the early-access protocol (EAP) [12] program was either pain progression (e.g., an opiate was needed for >2 weeks), development of a skeletal-related event (e.g., pathological fracture, spinal-cord compression, or surgery to bone); any increase in dose of prednisolone or a change to a more potent glucocorticoid for PC-related signs and symptoms; or initiation of new systemic anticancer treatment. In the nonclinical trial group (NT) ($n = 57$) the treatment was covered only until PRP. During the follow-up 3 patients remained PRP-free, thus were excluded from further analyses. The 2 groups were statistically homogeneous in every aspect, except for the definition of progression and subsequently the duration of AA + P treatment (Table 1).

Laboratory parameters and side effects were assessed every 4 weeks, efficacy (CT, bone scan, and PSA) at 3-month intervals. Treatment outcomes and adverse events were retrospectively evaluated from patient's charts.

The study was approved by the Medical Research Council and the Ethical Committee of the Institute.

### 2.1. Statistical analysis

OS, as primary objective of this study, was evaluated by the Kaplan-Meier method and log-rank test was performed. The secondary objective was PRP-free survival. The median or mean levels were compared by *t*-test or Mann-Whitney nonparametric test as required. The difference in distribution of parameters was tested by chi squared or exact test. Multivariate logistic regression was also performed. To find independent markers of survival the multivariate Cox regression analysis was used. $P < 0.05$ was considered as statistically significant. The NCSS software (Kaysville, UT) was used for all statistical analyses.

## 3. Results

Clinicopathological parameters of patients in the NT and T groups are presented in Table 1. None of the parameters, but the length of AA + P treatment showed statistical significant difference. In multivariate analysis (logistic regression) none of the parameters was statistically significant for the cohort type (NT or T).

After a median follow-up of 39.7 (95% CI: 37.4–59.8) months the median OS was significantly longer ($P = 8 \times 10^{-7}$) in the T group compared to the NT group: 21.9 (95% CI: 16.9–25) vs. 12.5 (9.3–14.1) months, respectively (Fig. 1).

To exclude an accidental effect of different tumor burden supposedly reflected by the nonsignificant, but slightly lower levels of starting PSA levels in the T group, the OS of patients from the T group with starting PSA level >median ($n = 24$) were compared with the OS of patients from the NT group with starting PSA level <median ($n = 22$). The log-rank test resulted in a $P = 0.028$ for the 17.6 (95% CI: 13.4–25.5 month) mOS in the T group and 13.6 (9.3–17.1) months in the NT group. Similar results were observed in case of other known parameters associated with tumor burden: alkaline phosphatase (AP), lactate dehydrogenase (LDH), and hemoglobin (data not shown), thus the effect of different tumor burden in case of the 2 groups can be excluded.

The difference in case of PRP-free survival curves did not reach the level of significance (Fig. 2).

Median PSA progression-free survivals (PFS) were 4.1 (2.8–7.6) and 4.6 (2.7–5.7) months ($P = 0.90$) in group NT and T, respectively. The median radiographic PFS were 5.1 (3–7) and 5.7 (4.9–7.8) months ($P = 0.29$) in group NT and T, respectively.

Table 1
Clinicopathologic characteristics of patients with castration-resistant prostate cancer treated with abiraterone acetate + prednisolone (AA + P)

| Parameters | All patients<br>*N* | Group NT<br>*N* (%) | Group T<br>*N* (%) | *P* |
|---|---|---|---|---|
| *N* | 113 | 57 | 56 | |
| Age, y; median (range) | 70 (49–90) | 70 (49–88) | 70.6 (49–90) | 0.984 |
| Metastasis at diagnosis | 54 | 25 (44) | 29 (52) | 0.399 |
| Multiple metastases at the start of AA + P | 81 | 39 (68) | 42 (75) | 0.438 |
| Metastasis | | | | |
| Bone | 103 | 49 (86) | 54 (96) | 0.094 |
| Lymph node | 44 | 20 (35) | 24 (43) | 0.397 |
| Visceral | 64 | 33 (58) | 31 (55) | 0.786 |
| Liver | 14 | 8 (14) | 6 (11) | 0.592 |
| Lung | 15 | 9 (16) | 6 (11) | 0.427 |
| Gleason score median (range) | 7.8 (3–10) | 8 (4–10) | 7.7 (3–10) | 0.467 |
| ≥7 | 81 | 42 (84) | 39 (80) | 0.570 |
| <7 | 18 | 8 (16) | 10 (20) | |
| Surgery | 18 | 12 (21) | 6 (11) | 0.133 |
| Irradiation | 30 | 15 (26) | 15 (27) | 0.955 |
| Only docetaxel | 72 | 34 (60) | 38 (68) | 0.364 |
| Docetaxel + other systemic therapy | 41 | 23 (40) | 18 (32) | |
| Systemic therapy after AA + P | 59 | 28 (49) | 31 (55) | 0.507 |
| Taxoid (docetaxel, cabazitaxel) | 27 (12, 15) | 12 (6, 6) | 15 (9, 6) | 0.931 |
| Mitoxantron | 27 | 14 | 13 | |
| Other ($^{223}$Ra, custirsen) | 5 (3, 2) | 2 (1, 1) | 3 (2, 1) | |
| Hemoglobin, g/dl; median (range) | 11.8 (8.4–15.1) | 11.7 (8.8–13.7) | 12 (8.4–15.1) | 0.057 |
| ≥14[a] | 2 | 0 | 2 (4) | 0.234 |
| <14 | 107 | 56 (100) | 51 (96) | |
| Neutrophil count, G/l; median (range) | 5.0 (1–16.9) | 4.9 (1–10.8) | 5.3 (2.4–16.9) | 0.961 |
| >7[b] | 22 | 14 (27) | 8 (16) | 0.149 |
| ≤7 | 80 | 37 (73) | 43 (84) | |
| Lymphocyte count, G/l; median (range) | 1.5 (0.5–3.4) | 1.4 (0.6–3.4) | 1.6 (0.5–3.3) | 0.275 |
| ≥1[b] | 58 | 36 (75) | 35 (78) | 0.753 |
| <1 | 35 | 12 (25) | 10 (22) | |
| NLR median (range) | 3.6 (0.5–12.6) | 3.7 (0.5–12.3) | 3.0 (1.3–12.6) | 0.422 |
| ≥3.6 | 45 | 25 (52) | 20 (44) | 0.461 |
| <3.6 | 48 | 23 (48) | 25 (56) | |
| Alkaline phosphatase, U/l; median (range) | | | | |
| At the start of therapy | 347 (138–7181) | 399 (146–7181) | 304 (138–4562) | 0.113 |
| ≥290[a] | 66 | 37 (66) | 29 (56) | 0.272 |
| <290 | 42 | 19 (34) | 23 (44) | |
| After 1 mo | 473 (113–4534) | 579 (150–4534) | 450 (113–4157) | 0.066 |
| ≥290 | 78 | 41 (75) | 37 (66) | 0.329 |
| <290 | 33 | 14 (25) | 19 (34) | |
| ≥25% decrease vs. start | 3/106 | 2/54 (4) | 1/52 (2) | 1.000 |
| ≥25% increase vs. start | 55/106 | 27/54 (50) | 28/52 (54) | 0.692 |
| After 3 mos | 427 (99–4,352) | 427 (153–4,352) | 455 (99–2,827) | 0.533 |
| ≥290 | 63 | 29 (63) | 34 (64) | 0.909 |
| <290 | 36 | 17 (37) | 19 (36) | |
| ≥25% decrease vs. start | 14/95 | 8/45 (18) | 6/50 (12) | 0.428 |
| ≥25% increase vs. start | 38/95 | 16/45 (36) | 22/50 (44) | 0.402 |
| ≥25% decrease vs. 1 mo | 28/98 | 14/45 (31) | 14/53 (26) | 0.559 |
| ≥25% increase vs. 1 mo | 20/98 | 12/45 (27) | 8/53 (15) | 0.157 |
| Lactate dehydrogenase, U/l; median (range) | | | | |
| At the start of therapy | 482 (236–2487) | 526 (247–2363) | 459 (236–2487) | 0.108 |
| >451[a] | 67 | 37 (66) | 30 (59) | 0.440 |
| ≤451 | 40 | 19 (34) | 11 (41) | |
| After 1 mo | 470 (226–1960) | 509 (290–1960) | 445 (226–1068) | 0.058 |
| >451 | 64 | 37 (67) | 27 (49) | 0.053 |
| ≤451 | 46 | 18 (33) | 28 (51) | |
| After 3 mos | 469 (262–3603) | 493 (283–3603) | 458 (262–976) | 0.188 |
| >451 | 59 | 30 (65) | 29 (56) | 0.340 |
| ≤451 | 39 | 16 (35) | 23 (44) | |
| PSA, ng/ml; median (range) | | | | |
| At the start of therapy | 161 (1.2–1990) | 191 (7.7–1990) | 131 (1.2–1335) | 0.057 |

Table 1
Continued

| Parameters | All patients<br>*N* | Group NT<br>*N* (%) | Group T<br>*N* (%) | *P* |
|---|---|---|---|---|
| >161 | 53 | 29 (57) | 24 (44) | 0.852 |
| ≤161 | 53 | 22 (43) | 31 (56) | |
| After 1 mo | 104 (0.8–5804) | 114 (2.6–5804) | 101 (0.8–1735) | 0.409 |
| >161 | 35 | 19 (46) | 16 (36) | 0.309 |
| ≤161 | 51 | 22 (54) | 29 (64) | |
| ≥25% decrease vs. start | 35/81 | 20/37 (54) | 15/44 (34) | 0.071 |
| ≥25% increase vs. start | 27/81 | 9/37 (24) | 18/44 (41) | 0.115 |
| After 3 mos | 111 (0.8–6303) | 126 (1.4–6303) | 105 (0.8–1467) | 0.759 |
| >161 | 38 | 17 (38) | 21 (40) | 0.852 |
| ≤161 | 60 | 28 (62) | 32 (60) | |
| ≥25% decrease vs. start | 38/89 | 16/37 (43) | 22/52 (42) | 0.930 |
| ≥25% increase vs. start | 36/89 | 15/37 (41) | 21/52 (40) | 0.988 |
| ≥25% decrease vs. 1 mo | 23/74 | 9/31 (29) | 14/43 (33) | 0.746 |
| ≥25% increase vs. 1 mo | 30/74 | 14/31 (45) | 16/43 (37) | 0.492 |
| From diagnose to HT, mos; mean (range) | 0.5 (0–8.8) | 0.7 (0–8.8) | 0.4 (0–8.4) | 0.424 |
| >0.5 | 13 | 8 (14) | 5 (9) | 0.395 |
| ≤0.5 | 100 | 49 (86) | 51 (81) | |
| HT duration, mos; median (range) | 19.1 (1–130) | 19 (1–107) | 21 (3–130) | 0.959 |
| >19.1 | 54 | 27 (47) | 27 (45) | 0.928 |
| ≤19.1 | 59 | 30 (53) | 29 (55) | |
| From HT to AA + P, mos; median (range) | 2.4 (0.7–10.7) | 2.2 (0.7–7.8) | 2.7 (0.7–10.7) | 0.198 |
| >2.4 | 51 | 25 (37) | 26 (46) | 0.784 |
| ≤2.4 | 62 | 32 (63) | 30 (54) | |
| From CT to AA + P, mos; median (range) | 0.5 (0–3.8) | 0.5 (0.1–3.8) | 0.6 (0–2.8) | 0.771 |
| >0.5 | 55 | 29 (51) | 26 (46) | 0.636 |
| ≤0.5 | 58 | 28 (49) | 30 (54) | |
| AA + P duration, mos; median (range) | 6.4 (1–32.2) | 4.1 (1–32.2) | 8.7 (2–31) | <0.001 |
| >6.4 | 57 | 21 (37) | 35 (63) | 0.006 |
| ≤6.4 | 56 | 36 (73) | 21 (37) | |

Group NT = patients at AA + P treatment until PSA and radiographic progression (PRP); Group T = patients at AA + P treatment beyond PRP until clinical progression; HT = hormone therapy; NLR = neutrophil to lymphocyte ratio.
[a]Lower normal limit.
[b]Upper normal limit.

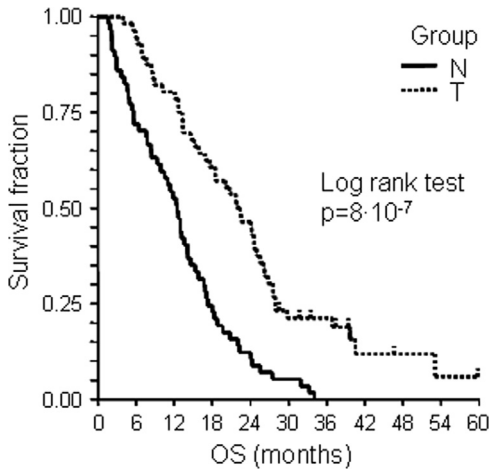


Fig. 1. Overall survival (OS) of metastatic castration-resistant prostate cancer patients treated with abiraterone acetate + prednisolone until PSA and radiographic progression (PRP) (group NT, solid line) or beyond PRP until clinical progression (group T, dashed line).

The OS in univariate analysis was significantly influenced by the presence of systemic therapy besides of docetaxel, count of white blood cells, neutrophils and lymphocytes, neutrophil to lymphocyte ratio, starting level of AP and LDH, systemic therapy after AA + P and cohort type (NT or T) (data not shown). These (significant) variables were included in the multivariate Cox regression analysis of OS. Besides of cohort type the AP level at the start of therapy and systemic therapy after AA + P proved to be independent predictors of OS (Table 2).

The PSA PFS in univariate analysis was significantly influenced by 11 parameters, but out of them only 3 was significant in Cox multivariate regression: ≥25% increase in PSA level after 3 months compared to the start or to the first month and LDH level after 1 month compared to the first month (data not shown). The radiographic PFS in univariate survival analysis was significantly influenced by 14 variables and out of them only the ≥25% increase in AP level after 3 months and that of PSA level after 1 month compared to the start proved to be independent factors in Cox multivariate analysis (data not shown).

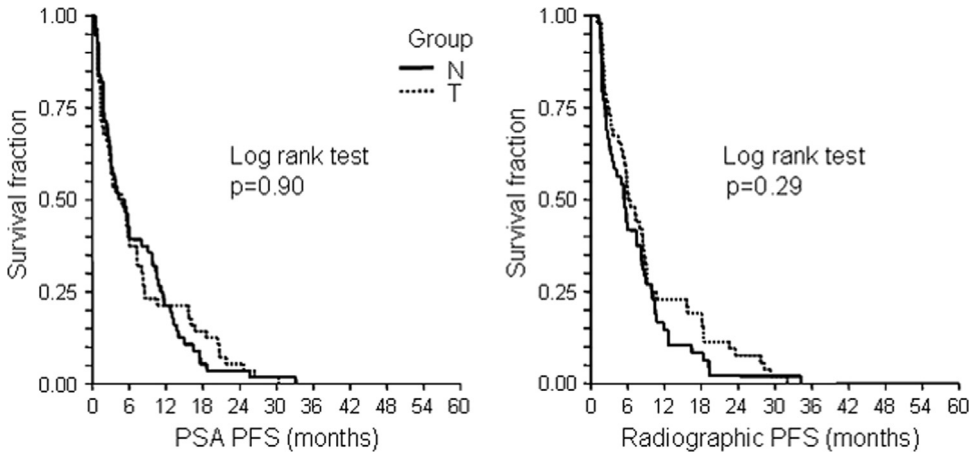


Fig. 2. Progression-free survival (PFS) according to PSA and radiographic progression of metastatic castration-resistant prostate cancer patients treated with abiraterone acetate + prednisolone until PSA and radiographic progression (PRP) (group NT, solid line) or beyond PRP until clinical progression (group T, dashed line).

The treatment was well tolerated. In contrast to other studies [5,12] no drug related adverse events of grade 3 to 4 were detected among our patient.

## 4. Discussion

In this retrospective study the treatment with AA + P beyond PSA and radiographic progression significantly improves survival. To our knowledge this phenomenon connected to AA + P treatment is new in the literature. The dissimilarity between the 2 subgroups was only the definition of progression, otherwise they were homogeneous. In this analysis predictive factors of OS were also investigated, therefore, all variables, which significantly influenced OS in the univariate analysis, were included in the multivariate Cox regression analysis. Besides of cohort type (T or NT) the AP level at the start of therapy and systemic treatment after AA + P proved to be independent predictors of OS. The AP level were already proved to be independent prognostic factor in an earlier study [11] and another study provided evidence of clinical benefit for subsequent CT in men with advanced PC whose disease progressed after treatment with AA [13].

Table 2
Independent predictors of overall survival in patients with castration-resistant prostate cancer treated with AA + P

| Parameter | HR | 95% CI | *P* |
|---|---|---|---|
| Alkaline phosphatase (U/l) at the start of therapy | | | |
| ≥290 | 1 | Reference | |
| <290 | 0.6 | 0.3–0.9 | 0.020 |
| Systemic therapy after AA + P | | | |
| Yes | 1 | Reference | |
| No | 1.7 | 1.1–2.8 | 0.029 |
| Study cohort | | | |
| Group NT | 1 | Reference | |
| Group T | 0.3 | 0.2–0.5 | <0.001 |

HR = hazard ratio of multivariate Cox regression analysis.

During the CT era the treatment of patients just until progression was a fundamental postulate. It seems that with novel treatment options the situation is changing. Some evidence suggests that, in certain circumstances, continuing a therapy beyond disease progression can be successful, and several articles address this topic. Treatment of renal cell cancer beyond progression with nivolumab [14], breast cancer with bevacizumab [15] or with trastuzumab [16], colorectal cancer with bevacuzimab [17] or with irinotecan [18] resulted in unexpected beneficial results. In mCRPC androgen deprivation therapy is a life-long treatment irrespectively of disease progression. This is based on the hypothesis that cessation of androgen suppression, with the recovery of androgen production, might allow accelerated tumor growth [19,20].

Progression during AA + P treatment or resistance may be explained by the generation of constitutively active androgen receptor splice variants [21]. Only by the presence of androgen receptor splice variants the antitumor effect of AA beyond progression can not be explained. It can be rather supposed that besides of AA-sensitive cancer cells during AA treatment enhanced proliferation of AA-resistant subclones is favored and subsequently progression is manifested. At this stage withdrawal of AA may lead to uncontrolled proliferation of both clones (AA resistant and AA sensitive), while the continuous AA treatment let only the AA-resistant subclone to proliferate.

The growing number of malignancies and drugs that challenge the custom of terminating treatment at progression warrants an in-depth examination of the definitions of disease progression. Measuring the change in tumor burden is crucial in the clinical evaluation of cancer therapeutics. The definition of regression or progression is based on anatomical bidimensional measurement of tumor size and clinical trial endpoints and therapy decisions depend on

these results. However endpoints like objective response and time to disease progression are useful only if these criteria are based on widely accepted and readily applied standard criteria. The first tumor response criteria were published by the WHO in 1981 [22]. In 2000 response evaluation criteria in solid tumors (RECIST) [23], in 2009 RECIST 1.1 was published [24]. All these criteria were not appropriate for PC patients, since 70% to 80% of patients with mCRPC do not have bidimensionally measurable disease. To address this problem the first prostate specific eligibility and response guideline for androgen independent PC was published in 1999 [25], which was followed in 2008 (in the docetaxel era) by the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendation [26]. The changing therapeutic landscape called for new trial endpoints. Both in the COU-AA-3015 [5] and in the AA EAP trials [12] patients were treated until PSA, radiographic and clinical progression. In 2016 PCWG3 introduced the concept of no longer clinically benefiting to emphasize the distinction between first evidence of progression and the clinical need to terminate or change treatment. Our result, which showed that treating mCRPC patients with AA + P beyond PRP significantly improves survival, underscores the importance of this distinction. Based on our result we can hypothesize that longer treatment with AA + P—at least until clinical progression—results in better survival. It is important to note that the whole clinical picture—and not just response criteria—should be taken into account when deciding which patients to treat beyond first progression.

There are some limitations of this analysis, which should be taken into consideration. The current retrospective analysis comprised a relatively small number of patients treated beyond RECIST-defined first progression. The ideal starting point and length of AA + P treatment can only be defined with prospective randomized trials.

One can suppose that the socioeconomic status, family support and involvement with care might be hidden differences between the 2 groups, however, Hungary provides full medical coverage for all residents, irrespective of their socioeconomic status, moreover, the best supportive care is provided for all patients beyond clinical oncologic treatments.

## 5. Conclusion

In this retrospective analysis of mCRPC patients treated with AA + P 3 independent factors influencing survival was found. Besides AP level at the start of therapy and systemic treatment after AA + P the present study demonstrated that treating patients beyond PSA and radiographic progression can result in longer OS. However further prospective investigations should strengthen our findings, the practice that AA + P is reimbursed only until RECIST-defined progression is not justifiable.

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