Sequential Treatment with Abiraterone and Enzalutamide in Swedish Patients with Metastatic Castration-Resistant Prostate Cancer

Fridlund M*, Johansson S, Laurell A, Emanuelsson M and Enblad G
Department of Immunology, Genetics and Pathology, Experimental and Clinical Oncology, Uppsala University, Sweden

*Corresponding author:
Markus Fridlund,
Department of Immunology, Genetics and Pathology,
Experimental and Clinical Oncology,
Uppsala University, Akademiska sjukhuset,
Uppsala 751 85, Sweden.

Received: 16 Nov 2020
Accepted: 04 Dec 2020
Published: 10 Dec 2020

Copyright:
©2020 Fridlund M et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Citation:
Fridlund M (2020) Sequential Treatment with Abiraterone and Enzalutamide in Swedish Patients with Metastatic Castration-Resistant Prostate Cancer. Universal Journal of Oncology. Vol (2): Issue (1): 1-8

Keywords:
Abiraterone; Enzalutamide; Metastatic castration-resistant prostate cancer; Sequential treatment

Abbreviations:
AA: Abiraterone Acetate; CI: Confidential Interval; ECOG: Eastern Cooperative Oncology Group; ENZ: Enzalutamide; mCRPC: Metastatic Castration-Resistant Prostate Cancer; PFS: Progression Free Survival; PPC: Patient-Overview Prostate Cancer; PS: Performance Status; PSA: Prostate-Specific Antigen; PSA-PFS: Prostate-Specific Antigen Progression Free Survival

1. Abstract

1.1. Background: Sequential treatment with abiraterone followed by enzalutamide or vice versa in patients with metastatic castration-resistant prostate cancer (mCRPC) is not generally recommended in Sweden. However, selected patients, with few treatment options, have received both treatments with promising results.

1.2. Objective: To determine whether patients with mCRPC could benefit from receiving abiraterone or enzalutamide as second-line therapy and if the sequencing order has any significance.

1.3. Design, setting, and participants: This retrospective register study enrolled 66 patients with mCRPC treated with abiraterone followed by enzalutamide or vice versa at Uppsala University Hospital between the years of 2012 and 2019. The median follow-up was 28.8 months.

1.4. Outcome measurements and statistical analysis: Prostate-specific antigen (PSA) response rates, progression-free survival (PFS) of the first- and second-line treatment, combined PFS and overall survival were compared between the two study groups and between responders and non-responders to both treatments using log-rank analysis and multivariate Cox regression.

1.5. Results and limitations: Thirty patients (47%) responded with a PSA decline to both treatments, resulting in a significantly longer combined PFS compared to non-responders (Responders, 19.0 months vs. Non-responders, 12.9 months; P = 0.039). The PSA response rate to second-line treatment with enzalutamide was 68% and to second-line treatment with abiraterone 33% (P = 0.023). No significant differences were found in overall survival between non-responders and responders. Limitations include the retrospective design, the few numbers of patients and the short follow-up.

1.6. Conclusions: A substantial PSA response was obtained by adding a second-line anti-androgen to patients with mCRPC. Treating with abiraterone followed by enzalutamide was more effective than the reverse order.
2. Introduction

2.1. Background

As the second most commonly diagnosed malignancy and the sixth leading cause of cancer mortality in men worldwide, prostate cancer is a major health concern [1]. Metastatic castration-resistant prostate cancer (mCRPC) is a late stage of the disease, at which the tumour cells have acquired the ability to progress despite castrate levels of testosterone by androgen deprivation therapy [2]. After developing mCRPC there are several life prolonging treatment options such as chemotherapy with docetaxel and cabazitaxel and two oral anti-androgens, abiraterone (AA) and enzalutamide (ENZ). It was recently suggested that cabazitaxel improves a number of clinical outcomes, as compared with abiraterone and enzalutamide, in patients who has been previously treated with docetaxel and the alternative anti-androgen drug [3].

Abiraterone is a potent and selective inhibitor of the enzyme CYP17A1, playing an important role in the androgen synthesis [4], while enzalutamide more specifically inhibits the androgen receptor itself [5]. In previous trials, both abiraterone and enzalutamide showed an improved prostate-specific antigen (PSA) progression-free survival (PFS) and overall survival, both in chemotherapy-naïve patients [6, 7] and in those previously treated with chemotherapy [8, 9].

The optimal way of using abiraterone and enzalutamide is of great importance to the clinic. Cross-resistance exists between these two drugs, resulting in expected low efficiency of using a second-line anti-androgen therapy [4, 10-12]. The clinical experience however, is that some patients do respond to a second-line treatment [11-14].

In several studies the impact of the sequencing order of abiraterone and enzalutamide treatment was investigated. Small differences were shown for PSA response rates and PFS, favouring treatment with abiraterone followed by enzalutamide rather than enzalutamide followed by abiraterone [15-19]. This was recently confirmed in a randomized study [20]. Only one study claimed the opposite [21]. In Sweden, sequencing strategy with abiraterone and enzalutamide has not yet been recommended [22]. However, selected patients, with few treatment options, have received second-line therapy with promising results.

2.2. Objectives

We want to elucidate the efficacy of both a first-line and a second-line anti-androgen treatment and if the order does matter, by a retrospective, register study, on patients with mCRPC managed at the department of Oncology in the Uppsala University Hospital. The outcome measures chosen are PSA response rates, PSA-PFS, PFS and overall survival.

3. Patients and Methods

3.1. Patients and Study Design

We analysed data from patients with mCRPC treated at Uppsala University Hospital in Sweden between the years of 2012 and 2019. The study population was extracted from the Patient-Overview Prostate Cancer (PPC), which is part of the National Prostate Cancer Register. The patients were defined according to the evidence of disease progression, either by PSA elevation or by clinical or radiographic progression, despite receiving continuous androgen deprivation therapy. Only patients treated with both abiraterone and enzalutamide sequentially, regardless of other treatments given prior to and in between these two drugs, were included, and divided into two study groups: patients receiving abiraterone followed by enzalutamide (AA-ENZ) and patients receiving enzalutamide followed by abiraterone (ENZ-AA). No further exclusion criteria were applied.

Through PPC and medical records we retrieved information about prognostic factors such as age, Gleason score, Eastern Cooperative Oncology Group (ECOG) performance status (PS) [23], number and sites of metastasis according to imaging and serum PSA at diagnosis and at initiation of each treatment. We also collected information about all treatments given prior to and in between abiraterone and enzalutamide, and the treatment duration of each of the two, the PSA kinetics during the treatments, reasons of discontinuation of each therapy and survival status. Serum PSA was measured frequently, and imaging and clinical examinations were performed continuously, throughout the study time.

In order to conduct this study, we obtained ethical approval from the Research Ethics Board at Uppsala University Hospital (dnr 2016-239 PCBaSe 4.0).

3.2. Endpoints

Our primary endpoint was to measure individual PSA kinetics for each study patient in order to compare how many responded with a PSA decline in each study group and in total. Secondary endpoints included the measuring of PFS of first-line and second-line treatment, combined PFS and overall survival. PFS was defined as the time from initiation of each treatment to the time of disease progression, evaluated by a physician based on clinical or radiographic progression, or based on only PSA progression independently, then expressed as PSA-PFS. PSA progression was defined as a 25 % increase from baseline or nadir. Combined PFS was measured by simply adding the time of PFS from first with second treatment. In the estimation of PFS, patients who discontinued treatment based on any adverse effect, at their own choice or who were still on treatment with their second-line drug when collecting data to this study, were censored in the analysis. Overall survival was calculated from the initiation date of the first-line treatment to the date of death of any cause or censoring on February 12, 2019. Finally, a multivariate analysis was carried out in order to search for independent clinical factors that could predict for longer survival.
3.3. Statistical Analyses
Patient characteristics were compared using the Mann-Whitney U-test for continuous variables and Fisher’s Exact Test (n = 2) or Pearson Chi-Square (n ≥ 3) for categorical variables, depending on the number of alternatives (indicated by the parenthesis) to the categorical variable. Comparing the treatment response of first and second treatment in total, Wilcoxon Signed-Rank Test was used for continuous variables and McNemar’s Test for categorical variables. Survival distributions were estimated using the Kaplan-Meier method for PFS and overall survival and the log-rank test was performed in order to compare survival time between the groups in the analysis. The Cox proportional hazard regression model was performed for the estimations in the multivariate analysis. All tests were 2-sided and considered significant at P < 0.05. All statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 24.0.

4. Results

4.1. Patient Characteristics
Out of 338 men treated at Uppsala University Hospital and registered in the PPC between the years of 2012 and 2019, 66 (20%) were treated with both abiraterone and enzalutamide and were included in this study. Forty-eight (73%) were enrolled in the AA-ENZ study group and 18 (27%) in the ENZ-AA group. The median follow-up, from initiation of the first-line treatment to the date of death of any cause or censoring on February 12, 2019, was 28.8 months (Range, 2.0 - 68.0; Mean, 30.4). Patient characteristics at initiation of the first-line and second-line treatment are shown in (Table 1 and 2), respectively. No significant differences were found in any of the prognostic factors such as age, the time from castration-resistant prostate cancer diagnosis to the initiation of first-line treatment and the time between the two study drugs, ECOG PS, the presence of bone, lymph node or visceral metastasis according to imaging and PSA. The number of patients who received any treatment prior to first-line therapy with abiraterone or enzalutamide, was 52% and 50%, respectively, with no significant difference (P = 1.000). In both study groups, the most commonly used prior treatment drug was docetaxel. The number of patients who received one or two treatments in between the study drugs and prior to second-line therapy with enzalutamide and abiraterone was 44% and 50%, respectively, with no significant difference (P = 0.783). The most commonly used drug in between was cabazitaxel and radium-223, respectively; the difference was not significant (P = 0.302).

| Table 1 | Patient characteristics at the time first-line treatment was initiated |
|---------|---------------------------------------------------------------|
|         | AA-ENZ (n = 48) | ENZ-AA (n = 18) | P value |
| Median age, years (range) | 71.8 (56.7 - 84.1) | 73.3 (63.5 - 83.4) | 0.21 |
| Median time from CRPC to AA/ENZ, months (range) | 8.1 (0 - 139.4) | 8.8 (0 - 62.6) | 0.908 |
| Patients who received prior treatment lines | n = 25 (52 %) | n = 9 (50 %) | 1 |
| Number of prior treatment lines | 0.591 |
| 1 | n = 22 (88 %) | n = 7 (78 %) |
| 2 | n = 3 (12 %) | n = 2 (22 %) |
| Name of prior treatments | 0.525 |
| Docetaxel | n = 21 (84 %) | n = 6 (67 %) |
| Radium-223 | n = 1 (4 %) | n = 1 (11 %) |
| Docetaxel + Radium-223 | n = 3 (12 %) | n = 2 (22 %) |
| ECOG PS | 1 |
| 0-1 | n = 47 (98 %) | n = 17 (94 %) |
| > 2 | n = 1 (2 %) | - |
| Unknown | - | n = 1 (6 %) |
| Bone metastasis present* | n = 37 (77 %) | n = 15 (83 %) | 0.609 |
| Lymph node metastasis present* | n = 15 (31 %) | n = 6 (33 %) | 1 |
| Visceral metastasis present* | n = 5 (10 %) | n = 2 (11 %) | 1 |
| Median PSA, µg/L (range) | 43.5 (4.2 - 1726) | 43.0 (2.6 - 1656) | 0.97 |

Abbreviations: AA = abiraterone acetate; CRPC = castration-resistant prostate cancer; ECOG = eastern cooperative oncology group; ENZ = enzalutamide; n = number; PS = performance status; PSA = prostate-specific antigen; * = according to imaging
4.2. Prostate-Specific Antigen Response Rates

Individual PSA kinetics for each study patient are presented in (Figure 1A-D). Out of 48 patients treated with abiraterone as first-line therapy, 35 (73%) responded with a PSA decline. The median decline rate compared to PSA baseline at treatment initiation was -71.0% (Range, -99.7 - +248.1; Mean, -34.5). Out of 17 patients treated with enzalutamide as first-line therapy (one patient was missing), 16 (94%) responded with a PSA decline. The median decline rate compared to PSA baseline at treatment initiation was -94.4% (Range, -99.9 - +8.3; Mean, -76.1). The difference in PSA response rate between abiraterone and enzalutamide as first-line treatment was not significant (P = 0.090).

Out of 47 patients treated with enzalutamide as second-line therapy (one patient was missing), 32 (68%) responded with a PSA decline. The median decline rate compared to PSA baseline at treatment initiation was -25.8% (Range, -99.9 - +536.8; Mean, -5.6). Out of 18 patients treated with abiraterone as second-line therapy, 65 (33%) responded with a PSA decline. The median decline rate compared to PSA baseline at treatment initiation was +41.0% (Range, -90.6 - +221.1; Mean, +46.9). The difference in PSA response rate between abiraterone and enzalutamide as second-line treatment was significant (P = 0.023).

Comparing the first-line treatment with the second-line treatment for all patients, a significant lower PSA response rate to the second-line treatment was observed. Fifty patients out of 65 (77%) responded with a PSA decline to the first-line treatment and only 38 patients out of 65 (58%) responded to the second-line therapy, with one missing at each measurement (P = 0.045).

The median time of PSA-PFS of the first-line treatment with abiraterone was 7.8 months (Range, 0.8 - 19.8; Mean, 8.4) and with enzalutamide 4.9 months (Range, 2.8 - 12.6; Mean, 7.6); the difference was not significant (P = 0.659). The median time of PSA-PFS of the second-line treatment with enzalutamide was 4.4 months (Range, 0.6 - 25.2; Mean, 7.0) and with abiraterone 2.7 months (Range, 0.8 - 7.7; Mean, 3.4); the difference was not significant (P = 0.072). The median time of combined PSA-PFS in the AA-ENZ study group was 13.6 months (Range, 2.0 - 23.8; Mean, 15.7) and in the ENZ-AA study group 9.6 months (Range, 4.3 - 16.1; Mean, 11.1); the difference was not significant (P = 0.105).

Table 2  Patient characteristics at the time second-line treatment was initiated

|                                | AA-ENZ (n = 48) | ENZ-AA (n = 18) | P value |
|--------------------------------|-----------------|----------------|---------|
| Median age, years (range)      | 73.3 (58.2 - 85.6) | 73.9 (64.0 - 85.1) | 0.216   |
| Median time between treatments, months (range) | 3.6 (0 - 23.2) | 1.6 (0 - 19.8) | 0.813 |
| Patients who received other treatment lines in between | n = 21 (44 %) | n = 9 (50 %) | 0.783 |
| Number of treatment lines in between |               |               | 0.287 |
| 1                               | n = 17 (81 %) | n = 9 (100 %) |         |
| 2                               | n = 4 (19 %) | -             | 0.302  |
| Name of treatments in between   |                 |                 |         |
| Docetaxel                       | n = 3 (14 %) | n = 1 (11 %) |         |
| Cabazitaxel                     | n = 10 (48 %) | n = 3 (33 %) |         |
| Radium-223                      | n = 4 (19 %) | n = 5 (56 %) |         |
| Docetaxel + Radium-223          | n = 1 (5 %) | -             |         |
| Cabazitaxel + Radium-223        | n = 3 (14 %) | -             |         |
| ECOG PS                         |                 |                 | 1       |
| 0-1                             | n = 43 (90 %) | n = 16 (89 %) |         |
| ≥ 2                             | n = 5 (10 %)  | n = 2 (11 %)  |         |
| Bone metastasis present*        | n = 39 (81 %) | n = 16 (89 %) | 0.43    |
| Lymph node metastasis present*  | n = 19 (40 %) | n = 7 (39 %)  | 1       |
| Visceral metastasis present*    | n = 10 (21 %) | n = 5 (28 %)  | 0.523   |
| Median PSA, µg/L (range)        | 115.5 (0.1 - 2953) | 86.5 (5.7 - 8089) | 0.599 |

Abbreviations: AA = abiraterone acetate; ECOG = eastern cooperative oncology group; ENZ = enzalutamide; n = number; PS = performance status; PSA = prostate-specific antigen; * = according to imaging

UA Publications  Volume (2)- Issue (1): 1-8
4.3. Progression-Free Survival

(Figure 2A-B) shows Kaplan-Meier estimates for PFS calculated from the start of each treatment. The median time of PFS of the first-line treatment with abiraterone was 8.9 months (Range, 0.9 - 23.0; Mean, 9.2) and with enzalutamide 12.1 months (Range, 3.2 - 23.7; Mean, 12.3); the difference was not significant (P = 0.109). The median time of PFS of the second-line treatment with enzalutamide was 4.6 months (Range, 0.4 - 30.7; Mean, 8.0) and with abiraterone 2.2 months (Range, 0.9 - 13.0; Mean, 4.4); the difference was not significant (P = 0.143). The median time of combined PFS in the AA-ENZ study group was 15.0 months (Range, 2.3 - 27.1; Mean, 17.5) and in the ENZ-AA study group 15.4 months (Range, 4.1 - 27.3; Mean, 16.0); the difference was not significant (P = 0.881), (Figure 2C).

Abbreviations: AA = abiraterone acetate; ENZ = enzalutamide; n = number; PSA = prostate-specific antigen; CI = confidence interval; OS = overall survival; PFS = progression-free survival.
4.4. Overall Survival
At the time of censoring, 30 patients out of 66 (45%) had died. (Figure 2D) shows Kaplan-Meier estimates for overall survival calculated from start of the first-line treatment according to each study group. The median overall survival in the AA-ENZ study group was 43.0 months (Range, 9.0 - 59.3; Mean, 42.6) and in the ENZAA study group 40.8 months (Range, 9.2 - 44.2; Mean, 36.9); the difference was not significant (P = 0.779).

4.5. Responders to Both Treatments
Thirty patients out of 64 (47%) responded with a PSA decline to both treatments, with one missing in each treatment comparison. The Kaplan-Meier estimates for combined PFS showed an improvement for responders compared to non-responders (P = 0.039), (Figure 3A). The combined PFS of the responders was 19.0 months (Range, 5.5 - 27.3; Mean, 20.4) and of the non-responders 12.9 months (Range, 2.3 - 24.4; Mean, 14.1). Responders had a somewhat longer overall survival than non-responders, (Figure 3B). The median overall survival of responders was 48.2 months (Range, 19.1 - 59.3; Mean, 46.8), and of non-responders 36.9 months (Range, 9.0 - 56.2; Mean, 38.2); the difference was not significant (P = 0.101).

4.6. Multivariate Analysis
The multivariate analysis for combined PFS and overall survival, presented in (Table 3), identifies that the sequencing order of abiraterone and enzalutamide, visceral metastasis present at the time of initiation of first-line treatment according to imaging and treatment(s) in between the study drugs are not independent predictors for neither combined PFS nor overall survival. However, it indicates that there is a significantly higher risk of discontinuation to abiraterone or enzalutamide if prior treatment(s) is applied, with a risk elevation of 2.18 (95% CI, 1.07 - 4.43; P = 0.031) for combined PFS. Prior treatment(s) is however not an independent predictor for overall survival. The model also illustrates that PSA response to both treatments is an independent predictor for both combined PFS and overall survival, estimating a risk reduction of discontinuation to abiraterone or enzalutamide due to tumour progression of 0.43 (95% CI, 0.21 - 0.88; P = 0.021) for combined PFS and a risk reduction of death of 0.34 (95% CI, 0.12 - 0.94; P = 0.037) for overall survival.

| Table 3 | Multivariate Analysis for Combined PFS and OS |
|---------|---------------------------------------------|
|         | Combined PFS | OS |
|         | Hazard Ratio (95 % CI) | P value | Hazard Ratio (95 % CI) | P value |
| Sequence group | | | | |
| ENZ-AA (n = 18) | 1.0 | 0.408 | 1.0 | 0.527 |
| AA-ENZ (n = 48) | 1.37 (0.65 - 2.91) | 0.724 | 1.44 (0.47 - 4.41) | 0.061 |
| Visceral metastasis before first treatment | | | | |
| Absent* (n = 59) | 1.0 | | 1.0 | |
| Present* (n = 7) | 0.82 (0.28 - 2.43) | 0.031 | 3.08 (0.95 - 9.94) | 0.455 |
| Prior treatment(s) | | | | |
| Not applied (n = 32) | 1.0 | | 1.0 | |
| Applied (n = 34) | 2.18 (1.07 - 4.43) | 0.361 | 1.42 (0.57 - 3.51) | 0.678 |
| Treatment(s) in between | | | | |
| Not applied (n = 36) | 1.0 | | 1.0 | |
| Applied (n = 30) | 1.38 (0.69 - 2.74) | 0.361 | 0.83 (0.35 - 1.97) | 0.037 |
| PSA-response to both treatments | | | | |
| Not achieved (n = 34) | 1.0 | | 1.0 | |
| Achieved (n = 30) | 0.43 (0.21 - 0.88) | 0.021 | 0.34 (0.12 - 0.94) | 0.037 |

Abbreviations: AA = abiraterone acetate; CI = confidence interval; ENZ = enzalutamide; n = number; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; * = according to imaging
5. Discussion
In this retrospective register study, we show that a substantial PSA response was obtained by adding a second line anti-androgen to patients with mCRPC. This resulted in a significantly longer combined PFS compared to patients not responding to second-line treatment. Consistently, the multivariate analysis illustrates that response to both treatments is an independent predictor for combined PFS and overall survival, suggesting that such a treatment regime is advantageous. However, with only 66 patients included and a short follow-up of 28.8 months, we cannot conclude that sequential treatment brings a longer survival compared to using only one of the two anti-androgen drugs. The provision of a second-line anti-androgen treatment was dependent on the decision of different physicians. This might have created a selection bias, favoring the inclusion of patients who were more likely to respond to both treatments, based on characteristics invisible for this study. Consequently, the probability of responding to both treatments might have been superior in this particular study population than in the group in general. Nevertheless, our findings emphasize what already is suggested, that a substantial PSA response can be obtained by adding a second-line anti-androgen to patients with mCRPC.

Our results also suggest that resistance mechanisms exist. The PSA response rates of the second-line treatment was significantly inferior compared to the first-line treatment. The multivariate analysis also shows that prior treatment(s) is associated with a significant risk elevation of discontinuation to abiraterone or enzalutamide due to tumour progression, indicating that resistance mechanisms are connected to sequential treatment strategy. However, if used in sequential regime, our results are in accordance with previous studies, showing a greater PSA response rate to a second-line treatment with enzalutamide compared to abiraterone. Why enzalutamide seems to retain higher clinical activity after first-line treatment with abiraterone and not vice versa is an intriguing observation. One theory is that the expression of the androgen receptor increase during the treatment of abiraterone and not by enzalutamide, which was suggested by two previously studies [24, 25].

There are several limitations associated to this study. Firstly, and most importantly, the follow-up is short, why no conclusions in terms of potential differences in survival can be drawn. Secondly, the inclusion of both chemotherapy-naïve and post-chemotherapy patients in the same study group may have confound the results, despite no significant differences were found in patient characteristics. Thirdly, having small groups and being retrospective in design makes the study potentially underpowered to detect true differences. Other limitations include the uneven number of patients in the two study groups and that the definition of disease progression was not determined but dependent on individual physicians. Accordingly, these results might not establish any recommendations in this matter, but function as a useful retrospective finding that can operate as a hypothesis for future prospective studies.

6. Conclusions
This study provides preliminary evidence that a substantial PSA response is obtained by adding a second-line anti-androgen drug to patients with mCRPC, suggesting that sequential treatment, in contrast to Swedish recommendations, might be beneficial. Treating with abiraterone followed by enzalutamide was more effective than the reverse order. We propose that a multi-center study including more patients, especially those receiving only one of the two anti-androgen drugs as a control group, should be conducted in order to definitely answer whether sequential treatment with abiraterone and enzalutamide is to prefer or not.
References

1. World Health Organisation. “Cancer Today. Estimated Incidence, Mortality and Prevalence Worldwide in 2018”. 2019.
2. A. Heidenreich, Bastian JP, Bellmum J, Bolla M, Joniau S, et al. “EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer”. Eur. Urol. 2014; 65: 467–79.
3. Wit RD, Bono JD, Sternberg CN, Fizazi K, Tombal B, et al. “Cabanitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer”. N Engl J Med. 2019; 381: 2506–18.
4. Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, et al. “Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100)”. Ann. Oncol. 2013; 24: 1807–12.
5. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, et al. “Development of a second-generation antiandrogen for treatment of advanced prostate cancer”. Science. 2009; 324: 787–90.
6. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PFA, et al. “Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study”. Lancet Oncol. 2015; 16: 152–60.
7. Beer TM, Armstrong AJ, Rathkopf D, Lorot Y, Sternberg CN, et al. “Enzalutamide in metastatic prostate cancer before chemotherapy”. N. Engl. J. Med. 2014; 371: 424–33.
8. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, et al. “Abiraterone and increased survival in metastatic prostate cancer”. N. Engl. J. Med. 2011; 364: 1995–2005.
9. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, et al. “Increased survival with enzalutamide in prostate cancer after chemotherapy”. N. Engl. J. Med. 2012; 367: 1187–97.
10. Cheng H, Gulati R, Azad A, Nadal R, Twardowski P, et al. “Activity of enzalutamide in men with metastatic castration-resistant prostate cancer is affected by prior treatment with abiraterone and/ or docetaxel”. Prostate Cancer Prostatic Dis. 2015; 18: 122–7.
11. Schrader AJ, Boegemann M, Ohlmann CH, Schnoeller TJ, Krabbe LM, et al. “Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone”. Eur. Urol. 2014; 65: 30–36.
12. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, et al. “Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide”. Ann. Oncol. 2013; 24: 1802–07.
13. Yamada Y, Mastubara N, Tabata KI, Satoshi T, Kamiya N, et al. “Abiraterone acetate after progression with enzalutamide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: a multi-center retrospective analysis”. BMC Res. Notes. 2016; 9: 471.
14. Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, and Chi KN. “Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients”. Eur. Urol. 2015; 67: 23–29.
15. Matsubara N, Yamada Y, Tabata KI, Satoshi T, Kamiya N, Suzuki H, et al. “Abiraterone Followed by Enzalutamide Versus Enzalutamide Followed by Abiraterone in Chemotherapy-naive Patients With Metastatic Castration-resistant Prostate Cancer”. Clin Genitourin Cancer. 2018; 16: 142–8.
16. Miyake H, Haru T, Tamura K, Sugiyama T, Furuse H, Ozono S, Fujisawa M. “Comparative Assessment of Efficacies Between 2 Alternative Therapeutic Sequences With Novel Androgen Receptor-Axis-Targeted Agents in Patients With Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer”. Clin Genitourin Cancer. 2017; 15: 591–7.
17. Maughan BL, Luber B, Nadal R, and Antonarakis ES. “Comparing Sequencing of Abiraterone and Enzalutamide in Men With Metastatic Castration-Resistant Prostate Cancer: A Retrospective Study”. Prostate. 2017; 77: 33–40.
18. Terada N, Maughan BL, Akamatsu S, Kobayashi T, Yamasaki T, Inoue T, et al. “Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naive castration-resistant prostate cancer: The Kyoto-Baltimore collaboration”. Int. J. Urol. 2017; 24: 441–8.
19. Zhang W, Wu TY, Chen Q, Shi XL, Xiao GA, Zhao L, et al. “Indirect comparison between abiraterone acetate and enzalutamide for the treatment of metastatic castration-resistant prostate cancer: a systematic review”. Asian J. Androl. 2017; 19: 196–202.
20. Khalaf DJ, Annala M, Taavitsainen A, Finch DL, Oja C, Vergidis J, et al. “Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial”. The Lancet Oncology. 2019; 20: 1730–9.
21. Maines F, Caffio O, Veccia A, Trentin C, TORTora G, Galligioni E, et al. “Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer”. Crit. Rev. Oncol. Hematol. 2015; 96: 498–506.
22. Regionala cancercentrum i samverkan, “Nationellt vårdprogram för prostatatcancer”. 2019.
23. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. “Toxicity and response criteria of the Eastern Cooperative Oncology Group”. Am. J. Clin. Oncol. 1982; 5: 649–55.
24. Emamekhoo H, Barata PC, Edwin NC, Woo KM, Grivas P, and Garcia JA. “Evaluation of Response to Enzalutamide Consecutively in Prostatic Cary. 2016; 7: 26259–26274.