ANTICANCER RESEARCH *40*: 1101-1106 (2020)
doi:10.21873/anticanres.14049

Assessment of Factors Predicting Disease Progression in Japanese Patients With Non-Metastatic Castration-resistant Prostate Cancer

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Abstract. *Background/Aim: Despite recent introduction of several novel agents, limited data exist regarding parameters that help predict the progression of non-metastatic castration-resistant prostate cancer (nmCRPC). The objective of this study was to identify prognostic predictors in nmCRPC patients. Patients and Methods: This study included 127 consecutive Japanese nmCRPC patients treated in routine clinical practice. Prognostic outcomes in these patients were analyzed to evaluate the impact of several parameters on prostate-specific antigen progression-free survival (PSA PFS) and metastasis-free survival (MFS). Results: When the 127 patients were diagnosed with nmCRPC, the PSA and PSA doubling time (PSADT) were 13.5 ng/ml and 17.9 months, respectively. Of these, 77 (60.6%) and 50 (39.4%) were treated with first-generation anti-androgen (FGA) and novel androgen-receptor-axis-targeted agent (ARATA), respectively, as first-line therapy for nmCRPC. The median PSA PFS and MFS after the diagnosis of nmCRPC in these patients were 29.5 months and not reached, respectively. Multivariate analyses identified the following independent prognostic factors: PSA at nmCRPC, PSADT and first-line therapy for nmCRPC for PSA PFS, and PSA at nmCRPC and PSADT for MFS. Conclusion: nmCRPC patients with higher PSA and/or shorter PSADT should be treated with ARATA rather than FGA.*

Since the discovery of the androgen-dependent nature of prostate cancer (PC) by Huggins and Hodges in the 1940s, androgen deprivation therapy (ADT) has been the mainstay of treatment for advanced PC patients (1). ADT is also an important part of treatment for patients with progressive disease following definitive local therapies with a curative intent, including surgery and radiation therapy (2). Despite being initially effective in the majority of PC patients, ADT is not curative, and castration-resistant prostate cancer (CRPC) eventually develops in almost all PC patients receiving ADT (1). If the disease progresses to metastatic CRPC (mCRPC), the prognosis of patients in this stage has been reported to be extremely poor, with a median survival of approximately 3 years (3). Furthermore, metastatic disease spread is associated with several severe symptoms, such as pain and pathological fractures, which may have an unfavorable prognostic impact (4). These findings suggest that it is an important issue to delay the time to metastases in PC patients, particularly those with CRPC, in order to maintain favorable conditions without metastases-related complications and prolong survival.

If imaging studies, typically computed tomography (CT) and radionuclide bone scans, show negative findings for metastatic diseases in CRPC patients, this disease state is recognized as non-mCRPC (nmCRPC) (4). Accumulated data suggest a marked heterogeneity in nmCRPC; that is, some patients have highly aggressive diseases that rapidly metastasize and show lethal progression, while others experience a comparatively indolent clinical course (3, 4). Although measurements of prostate-specific antigen (PSA), including an elevated absolute PSA value, as well as a short PSA doubling time (PSADT), have been shown to be correlated with adverse clinical outcomes in patients with nmCRPC (3-6), limited information is available with respect to parameters that help stratify the prognosis of these patients.

Different from Western countries, the public health care system permitted the introduction of novel androgen receptor-axis-targeted agents (ARATAs), abiraterone acetate (AA) and enzalutamide (Enz), for not only mCRPC patients, but also nmCRPC patients, and vintage hormonal therapy, such as alternative antiandrogen therapy with first-generation

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Key Words: Non-metastatic, castration-resistant prostate cancer, disease progression.

antiandrogens (FGAs), bicalutamide and flutamide, is still commonly conducted after the failure of primary ADT in Japan (7, 8). Moreover, two agents, apalutamide and enzalutamide, were demonstrated to significantly improve metastasis-free survival (MFS) of high-risk nmCRPC patients in placebo-controlled phase III trials (9, 10), and have become available in Japan as well, resulting in marked changes in the treatment of nmCRPC patients. Considering the current therapeutic strategy against nmCRPC, we assessed prognostic outcomes of nmCRPC patients treated in routine clinical practice in Japan in order to identify prognostic parameters that help determine the optimal treatment option for patients with nmCRPC.

Patients and Methods

Patients. The Research Ethics Committee of our institution approved the design of this study, and it was judged to be unnecessary to obtain informed consent for involvement in this study from all patients due to its retrospective design. This study included a total of 127 consecutive Japanese patients who were diagnosed with nmCRPC between April 2013 and December 2018, and then received either FGA or ARATA as a first-line agent after the failure of primary ADT in a routine clinical setting. In this study, the selection of agents during sequential therapy was basically conducted based on the preference of each physician without strict criteria, and PSA progression against either line of therapy was defined according to the Prostate Cancer Working Group 2 (PCWG2) criteria (11).

Treatment. All patients included in this study had been diagnosed with adenocarcinoma of the prostate by histopathological examinations. ADT either by castration alone or combined androgen blockade (CAB) comprising of castration plus bicalutamide was initially performed for all these patients. Following the failure of primary ADT, imaging studies, including at least chest and abdominal CTs and radionuclide bone scans, were conducted to confirm the absence of metastasis. As first-line therapy for CRPC, either FGA or ARATA was subsequently administered. In the FGA group, bicaltamide was introduced in patients undergoing castration therapy alone, while flutamide was used as an alternative antiandrogen therapy in those receiving CAB (12). In the ARATA group, treatment with either AA or Enz was performed based on the standard dosing schedule as previously described (13, 14), and it was permitted to modify the dose of either agent according to the severity of adverse events (AEs) in each patient. Until the occurrence of disease progression or uncontrollable AEs, first-line treatment for CRPC was continued.

Evaluation. Clinicopathological data analyzed in this study were retrospectively obtained from the medical records of each patient. After initiating treatment for CRPC, the serum PSA level in addition to renal, liver and bone marrow functions were assessed every 6-12 weeks, and imaging studies by chest and abdominal CTs and radionuclide bone scans were conducted at least every 6 months in all patients. In this series, the PSA progression-free survival (PFS) and MFS were defined as the time from the initiation of first-line therapy for CRPC to PSA progression or death and that to the detection of metastatic disease spread by radiological examinations, respectively.

Table I. *Characteristics of 127 patients with nmCRPC*.

Clinical stage at diagnosis (%)	
T2	44 (34.0)
T3	65 (51.1)
T4	18 (14.9)
Median PSA at diagnosis (ng/ml, range)	19.4 (4.4-170.7)
Gleason score at diagnosis (%)	
≤7	23 (19.1)
≥8	104 (80.9)
Definitive local therapy (%)	
Prostatectomy	22 (19.1)
Radiotherapy	16 (12.8)
Type of primary ADT (%)	
Castration alone	33 (25.5)
Combined androgen blockade	94 (74.5)
Median duration of primary ADT (months, range)	15.3 (2-185)
Median age at diagnosis of nmCRPC (years, range)	71.4 (52-88)
ECOG performance status at diagnosis of nmCRPC (%)	
0 or 1	117 (93.6)
≥2	10 (6.4)
Symptom at diagnosis of nmCRPC (%)	
Negative	116 (93.6)
Positive	11 (6.4)
Median PSA at diagnosis of nmCRPC (ng/ml, range)	13.5 (1.4-122.7)
Mean PSADT at diagnosis of nmCRPC (months, range)	17.9 (4.7-62.2)
First-line therapy for nmCRPC (%)	
First-generation antiandrogen	50 (39.4)
Androgen-receptor-axis-targeted agent	77 (60.6)

ADT: Androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; nmCRPC: non-metastatic castration-resistant prostate cancer; PSA: prostate-specific antigen; PSADT: PSA doubling time.

Statistical analysis. Statview 5.0 software (Abacus Concepts, Inc., Berkley, CA, USA) was used in all statistical analyses, and $p<0.05$ was considered significant. PSA PFS and MFS rates were calculated using the Kaplan–Meier method, and differences were evaluated by the log-rank test. The prognostic significance of certain parameters was evaluated employing the Cox proportional hazards regression model.

Results

Patient characteristics. Characteristics of the 127 nmCRPC patients included in this study are summarized in Table I. Of these 127, 50 (39.4%) and 77 (60.6%) received FGA and novel ARATA, respectively, as first-line systemic therapy for nmCRPC. There were no significant differences in the major clinicopathological parameters between patients treated with FGA and those with ARATA (data not shown).

Therapeutic profile. In this study, 68 of the 127 patients (53.5%) discontinued first-line therapy due to either disease progression or intolerable AEs. Of these, 59 (86.8%) subsequently received

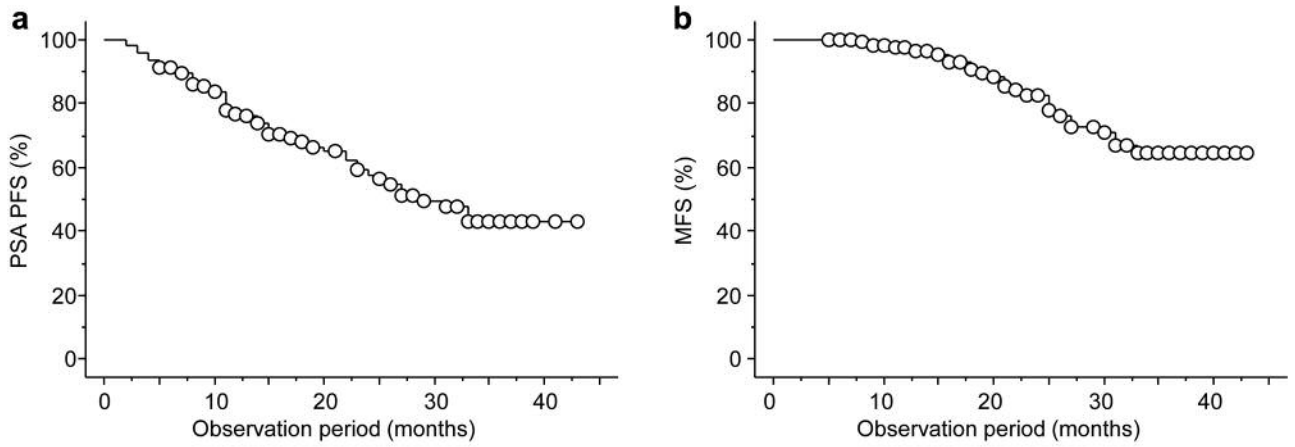

Figure 1. *(a): Prostate-specific antigen progression-free survival (PSA PFS) of 127 non-metastatic castration-resistant prostate cancer (nmCRPC) patients. (b): Metastasis-free survival (MFS) of 127 nmCRPC patients.*

Table II. *Uni- and multivariate analyses of associations between various parameters with PSA progression- and metastasis-free survival*

	PSA progression-free survival				Metastasis-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	Hazard ratio	*p*-Value	Hazard ratio	*p*-Value	Hazard ratio	*p*-Value	Hazard ratio	*p*-Value
Clinical stage at diagnosis (T2 *versus* T3 or T4)	0.73	0.62	–	–	0.66	0.43	–	–
PSA at diagnosis (ng/mL) (<20 *versus* ≥20)	0.59	0.21	–	–	0.74	0.62	–	–
Gleason score at diagnosis (≤7 *versus* ≥8)	0.32	0.039	0.53	0.2	0.41	0.11	–	–
Definitive local therapy (yes *versus* no)	0.93	0.77	–	–	0.97	0.78	–	–
Primary ADT (castration alone *versus* CAB)	1.09	0.62	–	–	1.04	0.68	–	–
Duration of primary ADT (months) (<15 *versus* ≥15)	1.42	0.13	–	–	1.37	0.23	–	–
Age at diagnosis of CRPC (years) (<70 *versus* ≥70)	0.32	0.042	0.72	0.43	0.57	0.2	–	–
ECOG PS at diagnosis of CRPC (≤1 *versus* ≥2)	0.58	0.18	–	–	0.59	0.28	–	–
Symptom at diagnosis of CRPC (yes *versus* no)	0.53	0.25	–	–	0.57	0.26	–	–
PSA at diagnosis of CRPC (ng/mL) (<10 *versus* ≥10)	0.29	0.012	0.33	0.04	0.31	0.033	0.35	0.04
PSADT at diagnosis of CRPC (months) (<10 *versus* ≥10)	0.27	0.0082	0.29	0.023	0.28	0.0097	0.31	0.028
First-line therapy for CRPC (FGA *versus* ARAT)	0.3	0.029	0.34	0.045	0.34	0.042	0.47	0.13

ADT: Androgen deprivation therapy; ARAT: androgen-receptor-axis-targeted agent; CRPC: castration-resistant prostate cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; FGA: first-generation antiandrogen; PSA: prostate-specific antigen; PSADT: PSA doubling time.

approved agents against CRPC as second-line systemic therapy, including AA, Enz and docetaxel for 19 (32.2%), 17 (28.8%) and 23 (39.0%) patients, respectively.

Prognostic outcomes. During the observation period of this study, 50 (39.4%) and 25 (19.7%) patients were judged to have developed PSA progression and metastatic diseases, respectively, and the median PSA PFS and MFS after the diagnosis with nmCRPC in the 127 patients were 29.5 months and not reached, respectively. In these 127 patients, 1-, 2- and 3-year PSA PFS rates were 77.0, 57.8 and 43.1%, respectively (Figure 1A), while 1-, 2- and 3-year MFS rates were 97.4, 82.8 and 64.4%, respectively (Figure 1B).

Prognostic predictors. As shown in Table II, uni- and multivariate analyses of several parameters were performed to identify prognostic predictors associated with PSA PFS and MFS, respectively. Univariate analyses detected significant prognostic predictors as follows: Gleason score, age at nmCRPC, PSA at nmCRPC, PSADT and first-line therapy for nmCRPC for PSA PFS, and PSA at nmCRPC, PSADT and first-line therapy for nmCRPC for MFS.

Moreover, by the multivariate analyses of these significant factors, the following parameters had independent prognostic impacts: PSA at nmCRPC, PSADT and first-line therapy for nmCRPC for PSA PFS, and PSA at nmCRPC and PSADT for MFS.

Discussion

To date, nmCRPC has been shown to have a highly heterogeneous potential with respect to the risk of developing metastatic disease spread. In previous RCTs enrolling nmCRPC patients into placebo groups, the median bone MFS (BMFS) in these patients was approximately 2 years, while several studies reported a markedly shorter BMFS in nmCRPC patients positive for unfavorable characteristics, such as a high base-line PSA and short PSADT (3, 4, 15). Although two agents, apalutamide and Enz, were recently demonstrated to significantly prolong PFS as well as MFS in nmCRPC patients with PSADT ≤10 months compared with a placebo in pivotal RCTs (9, 10), the optimal therapeutic strategy for nmCRPC patients remains to be elucidated. This situation is particularly true for Japanese nmCRPC patients, since vintage hormonal therapies using FGAs are still commonly conducted even after the approval of novel ARATAs in routine clinical practice, and the public health care system covers the treatment of CRPC patients with ARATAs irrespective of the metastatic status in Japan (7, 8). Considering these findings, it is very important to precisely analyze prognostic outcomes based on data from nmCRPC patients who received a wide variety of treatments; accordingly, in this study, we retrospectively analyzed the data from a total of 127 consecutive Japanese nmCRPC patients treated with either FGA or ARATA as first-line systemic therapy for CRPC after the failure of primary ADT in order to identify parameters that could be useful for the selection of therapeutic options for nmCRPC patients.

The 127 patients included in the study could be regarded as having a heterogeneous therapeutic history after the failure of primary ADT. Two options, treatment with either FGAs or ARATAs, are fundamentally different therapeutic approaches (16); however, no significant differences in the major clinicopathological characteristics were noted between the FGA and ARATA groups. In this cohort, thus, the introduction of ARATA for low-risk nmCRPC patients and FGA for high-risk patients could be frequent. In addition, approximately 80% of the included patients received subsequent treatments with approved agents against CRPC after the discontinuation of first-line therapy, irrespective of the type of first-line agent. Collectively, these findings suggest that the present cohort consisting of the 127 nmCRPC patients may be suitable to comprehensively assess the efficacy of heterogeneous treatment for nmCRPC patients and to identify prognostic predictors in these patients.

Despite the short observation period, the median PSA PFS and MFS following diagnosis with nmCRPC in these 127 patients were 29.5 months and not reached, respectively. However, several clinical trials targeting high-risk nmCRPC patients treated with novel ARATs reported similar or even superior prognostic outcomes to those in this study (9, 10). For example, the median time to PSA progression and that to metastasis in high-risk nmCRPC patients receiving apalutamide in the SPARTAN trial were not reached and 40.5 months, respectively (9). Similarly, the median time to PSA progression and that to metastasis were 37.2 and 36.6 months respectively in high-risk nmCRPC patients treated with enzalutamide in the POSPER trial (10). Considering these findings, the introduction of novel ARATAs for nmCRPC patients may result in effective disease control compared with that of vintage hormonal agents. In fact, our previous study also showed more favorable PSA PFS as well as MFS in nmCRPC patients receiving ARATAs than those receiving FGA after the failure of primary ADT (8).

It is of interest to evaluate the significance of parameters as predictive factors of disease progression in nmCRPC patients. In this series, multivariate analyses of several clinicopathological factors identified the following independent predictive factors: PSA at nmCRPC, PSADT and first-line therapy for nmCRPC for PSA PFS, and PSA at nmCRPC and PSADT for MFS. To date, limited information remains available regarding the prognostic prediction in patients with nmCRPC. For example, Ryan *et al*. conducted the IMAAGEN study evaluating the efficacy of abiraterone for high-risk nmCRPC patients, and reported that baseline testosterone ≥12.5 ng/dl and PSA reduction ≥90% at cycle 3 were significantly correlated with a longer time to PSA progression and radiographic evidence of disease progression (17), while Morelia *et al*. retrospectively identified a Gleason score 8-10, receiving primary localized therapy, higher PSA levels at CRPC and PSADT ≤6 months as independent predictors of a shorter time to metastasis on multivariate analysis in a total of 458 nmCRPC patients (6). Due to heterogeneous backgrounds, particularly patients' risk and provided treatments, among these studies, it would be difficult to directly compare these outcomes. However, at least based on the findings of the present study, it is strongly suggested that high-risk nmCRPC patients characterized by a higher PSA value at CRPC, as well as shorter PSADT should be intensively treated with ARATA rather than vintage hormonal therapy.

Herein, several limitations of this study should be described. Firstly, this was a retrospective study consisting of a relatively small number of patients, and the observation period was also insufficient. Therefore, it might be difficult to draw definitive conclusions based on the outcomes of this study. Secondly, as mentioned above, significant heterogeneity was noted among patients included in this study. In particular,

following the diagnosis of PC, a wide variety of treatments were performed without strict selection criteria. Thirdly, despite being repeated every 16 weeks in the two recently completed RCTs (9, 10), radiological examinations were not performed under an intensive schedule, which makes it difficult to extract a definitive finding regarding MFS. Therefore, it is important to interpret the findings presented in this study considering these limitations, and confirm the reliability of these findings by conducting a prospective study with a larger sample size.

Conclusion

This study retrospectively assessed the prognostic outcomes in a total of 127 nmCRPC Japanese patients, and reported that the median PSA PFS and MFS after the diagnosis with nmCRPC in these patients were 29.5 months and not reached, respectively. Furthermore, several parameters, including PSA at nmCRPC, PSADT and first-line therapy for nmCRPC, were shown to be independently associated with the disease progression in these patients. Collectively, these findings suggest that considering these potential risk factors, intensive treatment with ARATs should be given to selected patients with nmCRPC.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

The types of contribution by each author are as follows: Study conception and design, Hideaki Miyake; Acquisition of data, Kyohei Watanabe, Yuto Matsushita, Hiromitsu Watanabe, Keita Tamura, Daisuke Motoyama, Toshiki Ito, Takayuki Sugiyama, Atsushi Otsuka; Analysis and interpretation of data, Hideaki Miyake; Drafting of manuscript, Hideaki Miyake.

Acknowledgements

No funding or sponsorship was received for this study or publication of this article.

References

1 Donkena KV, Yuan H and Young CY: Recent advances in understanding hormonal therapy resistant prostate cancer. Curr Cancer Drug Targets *10(4)*: 402-410, 2010. PMID: 20464780. DOI: 10.2174/156800910791208544

2 Sharifi N, Gulley JL and Dahut WL: An update on androgen deprivation therapy for prostate cancer. Endocr Relat Cancer *17(4)*: R305-R315, 2010. PMID: 20861285. DOI: 10.1677/ERC-10-0187

3 Miyake H, Matsushita Y, Watanabe H, Tamura K, Motoyama D, Ito T, Sugiyama T and Otsuka A: Prognostic significance of time to castration resistance in patients with metastatic castration-sensitive prostate cancer. Anticancer Res *39(3)*: 1391-1396, 2019. PMID: 30842173. DOI: 10.21873/anticanres.13253

4 Rozet F, Roumeguère T, Spahn M, Beyersdorff D and Hammerer P: Non-metastatic castrate-resistant prostate cancer: a call for improved guidance on clinical management. World J Urol *34(11)*: 1505-1513, 2016. PMID: 26988552. DOI: 10.1007/s00345-016-1803-9

5 Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, Tombal B, Damiao R, Marx G, Miller K, Van Veldhuizen P, Morote J, Ye Z, Dansey R and Goessl C: Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol *31(30)*: 3800-3806, 2013. PMID: 24043751. DOI: 10.1200/JCO.2012.44.6716

6 Moreira DM, Howard LE, Sourbeer KN, Amarasekara HS, Chow LC, Cockrell DC, Hanyok BT, Aronson WJ, Kane CJ, Terris MK, Amling CL, Cooperberg MR, Liede A and Freedland SJ: Predictors of time to metastasis in castration-resistant prostate cancer. Urology *96*: 171-176, 2016. PMID: 27318265. DOI: 10.1016/j.urology.2016.06.011

7 Yamaguchi N, Morizane S, Yumioka T, Iwamoto H, Hikita K, Sejima T, Honda M and Takenaka A : Flutamide as an alternative anti-androgen agent and predictor of the efficacy of novel androgen receptor-targeted agents. Anticancer Res *39(7)*: 3879-3885, 2019. PMID: 31262916. DOI: 10.21873/anticanres.13538

8 Miyake H, Matsushita Y, Watanabe H, Tamura K, Motoyama D, Ito T, Sugiyama T and Otsuka A: Comparative assessment of prognostic outcomes between first-generation antiandrogens and novel androgen-receptor-axis-targeted agents in patients with non-metastatic castration-resistant prostate cancer. Int J Clin Oncol *24(7)*: 842-847, 2019. PMID: 30739263. DOI: 10.1007/s10147-019-01412-2

9 Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, Olmos D, Mainwaring PN, Lee JY, Uemura H, Lopez-Gitlitz A, Trudel GC, Espina BM, Shu Y, Park YC, Rackoff WR, Yu MK and Small EJ: Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med *378(15)*: 1408-1418, 2018. PMID: 29420164. DOI: 10.1056/NEJMoa1715546

10 Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, Ivashchenko P, Demirhan E, Modelska K, Phung, Krivoshik A and Sternberg CN: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med *378(26)*: 2465-2474, 2018. PMID: 29949494. DOI: 10.1056/NEJMoa1800536

11 Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, Higano C, Bubley GJ, Dreicer R, Petrylak D, Kantoff P, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A and Hussain M: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol *26(7)*: 1148-1159, 2008. PMID: 18309951. DOI: 10.1200/JCO.2007.12.4487

12 Momozono H, Miyake H, Tei H, Harada KI and Fujisawa M: Clinical outcomes of anti-androgen withdrawal and subsequent alternative anti-androgen therapy for advanced prostate cancer following failure of initial maximum androgen blockade. Mol Clin Oncol *4(5)*: 839-844, 2016. PMID: 27123292. DOI: 10.3892/mco.2016.817

13 Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, Carles J,

Flaig TW, Taplin ME, Higano CS, de Souza P, de Bono JS, Griffin TW, De Porre P, Yu MK, Park YC, Li J, Kheoh T, Naini V, Molina A and Rathkopf DE: 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 *16(2)*: 152-160, 2015. PMID: 25601341. DOI: 10.1016/S1470-2045(14)71205-7

14 Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim CS, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM and Tombal B: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med *371(5)*: 424-433, 2014. PMID: 24881730. DOI: 10.1056/NEJMoa1405095

15 Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, Tombal B, Damiao R, Marx G, Miller K, Van Veldhuizen P, Morote J, Ye Z, Dansey R and Goessl C: Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol *31(30)*: 3800-3806, 2013. PMID: 24043751. DOI: 10.1200/JCO.2012.44.6716

16 Davies RS, Smith C, Button MR, Tanguay J, Barber J, Palaniappan N, Staffurth J and Lester JF: What predicts minimal response to abiraterone in metastatic castrate-resistant prostate cancer? Anticancer Res *35(10)*: 5615-5621, 2015. PMID: 26408734.

17 Ryan CJ, Crawford ED, Shore ND, Underwood W 3rd, Taplin ME, Londhe A, Francis PSJ, Phillips J, McGowan T and Kantoff PW: The IMAAGEN Study: Effect of abiraterone acetate and prednisone on prostate specific antigen and radiographic disease progression in patients with nonmetastatic castration resistant prostate cancer. J Urol *200(2)*: 344-352, 2018. PMID: 29630978. DOI: 10.1016/j.juro.2018.03.125

Received December 15, 2019
Revised January 8, 2020
Accepted January 13, 2020