

# Toxicity, Adverse Events, and Quality of Life Associated with the Treatment of Metastatic Castration-Resistant Prostate Cancer

Senol Tonyali<sup>a</sup> Hakan Bahadir Haberal<sup>b</sup> Emrullah Sogutdelen<sup>b</sup>

<sup>a</sup>Department of Urology, Turkiye Yuksek Ihtisas Training and Research Hospital; <sup>b</sup>Department of Urology, Hacettepe University School of Medicine, Ankara, Turkey

## Key Words

Castration resistant prostate cancer • Docetaxel • Cabazitaxel • Enzalutamide • Abiraterone acetate • Quality of life

## Abstract

**Objectives:** Among males, prostate cancer (PCa) is the most common cancer in Europe and the second most common cancer worldwide, especially in those aged > 70 years. With the advent of novel alternative treatments, survival in patients with advanced PCa has increased. PCa is now considered a chronic disease. Survival is an important endpoint in advanced PCa, as is quality of life (QoL). The effects of the disease and its treatment on patient health-related QoL must be taken into account when selecting the most appropriate treatment options. The present literature review aimed to provide an overview of metastatic castration-resistant prostate cancer treatment modalities, with an emphasis on side effect profiles and general health-related QoL. **Methods:** PubMed was searched using the keywords metastatic castration-resistant prostate cancer, docetaxel, cabazitaxel, enzalutamide, abiraterone acetate, and QoL. **Conclusion:** Based on the studies reviewed herein, abiraterone acetate and enzalutamide provide favorable outcomes, in terms of hematological adverse events. As enzalutamide and abiraterone acetate can be taken orally, they might have a positive effect on patient QoL.

Copyright © 2016 S. Karger AG, Basel

## Introduction

Among males, prostate cancer (PCa) is the most common cancer in Europe [1] and the second most common cancer worldwide, especially in those aged > 70 years [2]. Docetaxel was the sole chemotherapeutic agent approved by the United States Food and Drug Administration for the treatment of metastatic castration-resistant prostate cancer (mCRPC) until 2004. Since then, many alternative treatments have emerged, the most remarkable of which are enzalutamide, cabazitaxel, and abiraterone acetate (AA) [3, 4]. With the advent of novel alternative treatments survival in patients with advanced PCa has increased. PCa is now considered a chronic disease [5].

Survival is an important endpoint in advanced PCa, as is quality of life (QoL). The effects of the disease and its treatment on patient health-related QoL (HRQoL) must be taken into account when selecting the most appropriate treatment options [6].

Improvement in QoL is an important objective in the treatment of patients with mCRPC. Relevant validated questionnaires include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (QLQ-C30) [7], the Prostate Cancer Module for the QLQ-C30 (including physical functioning and overall perception of well-being) [8, 9], and the McGill Pain Questionnaire-Short Form (including pain words, pain degree, and pain intensity) [10]. In addition, the Functional Assessment of Cancer Therapy-Prostate Questionnaire (FACT-P) is a reliable self-administrated

**Table 1.** Most commonly seen adverse events related to mCRPC treatment

Side effect	Abirateron acetate		Enzalutamide		Cabazitaxel		Docetaxel <sup>#</sup>
	COU-AA-302	COU-AA-301	AFFIRM	PREVAIL	TROPIC	UK-EAP	TAX 327
Neutropenia	–	1%	–	–	94%	12.5%	32%
Febrile neutropenia	–	0	–	–	8% (Gr ≥ 3)	1.8%	3% <sup>^</sup>
Anemia	–	23%	–	–	97%	–	5%
Thrombocytopenia	–	4%	–	–	47%	–	1% <sup>^</sup>
Fatigue	–	44%	34%	36%	37%	54.5%	53% <sup>^</sup>
Vomiting	–	21%	–	–	23%	–	42% <sup>*</sup>
Diarrhea	–	18%	21%	16%	47%	64.3%	32%
Constipation	–	26%	–	22%	20%	–	–
Asthenia	–	13%	–	13%	20%	–	–
Sensory neuropathy	–	–	–	–	–	–	30%
Back pain	–	30%	–	27%	16%	–	–
Peripheral edema	31% (fluid retention and edema)	31% (fluid retention and edema)	–	11%	–	–	19%
Dyspnea	–	13%	–	–	12%	–	15%
Stomatitis	–	–	–	–	–	–	20%
Hot flushes	–	9% (pyrexia)	20%	18%	12% (pyrexia)	–	–
Arthralgia	–	27%	–	20%	11%	–	–
Headache	–	–	12%	10%	–	–	–
Hypertension	24%	10%	–	13%	–	–	–
Cardiac events	23%	13%	6%	10%	–	0.9%	–
Increase in LFT levels	13% ALT, 12% AST	10% (LFT abnormality)	1% (LFT abnormality)	1% (ALT only)	–	–	–
Nausea	–	30%	–	–	34%	46.4%	–
Musculoskeletal pain/myalgia	–	17–25% (pain in arm or leg- bone pain)	14%	–	5% (bone pain)	–	14%
Asthenia	–	13%	–	13%	20%	–	–
Seizure	–	–	< 1%	< 1%	–	–	–
Death	4%	13%	3%	4%	5%	3.6%	0.3%

UK-EAP= United Kingdom Early Access Programme; LFT = liver function test; ALT = alanine aminotransferase; AST = aspartate aminotransferase. \*nausea or vomiting or both<sup>†</sup>; <sup>#</sup>every 3 week; <sup>^</sup>Grade 3 or 4.

scale used to assess HRQoL in patients with PCa [11]. Comprehensive assessment of patient QoL can be performed using these questionnaires.

The present literature review aimed to provide an overview of mCRPC treatment modalities, with an emphasis on side effect profiles and general HRQoL — including well-being, vitality, fatigue, pain, and general health status, and PCa-specific HRQoL — including urinary, bowel, and sexual functioning.

## Materials and Methods

PubMed was searched using the keywords mCRPC, docetaxel, cabazitaxel, enzalutamide, AA, and QoL, without any restrictions concerning date of publication. All studies that consisted of a relatively adequate number of patients with CRPC and fulfilled the inclusion criteria — analysis of QoL and adverse events in patients treated for mCRPC — were included in the review.

## Results

### Docetaxel

Docetaxel is one of the most commonly used chemotherapeutic agents for solid neoplasms and it has various side effects that impairs patient's QoL [12].

A multicenter randomized phase II trial on the effect of docetaxel — with and without estramustine — on QoL and pain used the QLQ-C30 to evaluate QoL and the Brief Pain Inventory to evaluate pain. In response to the treatment a decrease in QoL was observed based on the QLQ-C30 global QoL subscale score (25.4%) and fatigue subscale score (32.2%) [13].

In the TAX 327 phase III, non-blinded, randomized trial [14], docetaxel plus prednisone [docetaxel every 3 weeks (n = 332) and weekly (n = 330)] was compared to mitoxantrone plus prednisone (MP) (n = 335). Patient QoL was assessed using the FACT-P questionnaire. It was

observed that  $\geq 1$  serious adverse events occurred in 26% of the patients that received docetaxel every 3 weeks and in 20% of those that received mitoxantrone. There were 2 treatment-related deaths in the docetaxel group. Serious and low-grade adverse events that occurred are shown in table 1. The percentage of patients with improvement in QoL was significantly higher in the docetaxel group [docetaxel every 3 weeks (22%) and weekly docetaxel (23%)] than in the mitoxantrone group (13%) ( $p = 0.009$  and  $p = 0.005$ , respectively).

Another large ( $n = 1,050$ ), randomized, placebo-controlled, phase III trial (CALGB 90401) was conducted to compare docetaxel plus prednisone, with and without bevacizumab [15]. The overall adverse events in the docetaxel plus prednisone group included grade 3 events (31%), grade 4 events (24%), and lethal adverse events (1%) [15]. Kornblith et al. [16] studied the effect of docetaxel, estramustine, and low-dose (40 mg daily) hydrocortisone on QoL in men diagnosed with hormone refractory PCa ( $n = 44$ ). Patient QoL was measured via FACT-P, the Mental Health Inventory-17, and the Brief Pain Inventory. Significant improvement in QoL was observed based on the FACT-P Emotional Well-Being and Prostate Cancer-Specific subscale scores ( $p = 0.014$  and  $p = 0.018$ , respectively). However, there was not a significant improvement in the Brief Pain Inventory scores over the course of 6 months.

The Southwest Oncology Group [17] studied the effects of docetaxel plus estramustine (DE) and MP on QoL and pain in patients with advanced PCa. The study included 674 patients, of which 338 received DE and 336 received MP. QoL was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 and McGill Pain Questionnaire-Short Form. A pain response (decrease) was reported in 68 (21%) of the patients in the DE group and in 75 (24%) of the patients in the MP group, with the difference between groups not being significant ( $p = 0.12$ ). In addition, there was not a significant difference in global QoL change between the 2 groups. However, nausea was significantly more severe in the DE group at 10 weeks and 6 months.

### *Enzalutamide*

Enzalutamide is an oral irreversible antagonist of androgen receptors, which also affects intracellular androgen receptor trafficking and signaling [18].

A phase III placebo-controlled study by the AFFIRM group [19] randomly assigned 1,199 CRPC patients to receive enzalutamide ( $n = 800$ ) or a placebo ( $n = 399$ ). The adverse event rate was 98% in both groups. How-

ever, the incidence of grade  $\geq 3$  adverse events was lower in the enzalutamide group (45.3%) than in the placebo group (53.1%). In the enzalutamide group, adverse events of any grade included fatigue (34%), diarrhea (21%), hot flashes (20%), musculoskeletal pain (14%), headache (12%), cardiac disorder (6%), seizure ( $< 1\%$ ), and myocardial infarction ( $< 1\%$ ). Adverse events leading to death occurred in 23 (3%) of the patients in the enzalutamide group. Enzalutamide was noted to be superior to a placebo in terms of QoL response, for instance, the FACT-P QoL response was 43% in the enzalutamide group, versus 18% in placebo arm ( $p < 0.001$ ) [19]. Their findings showed that enzalutamide has a favorable toxicity profile and an adverse event rate identical to that of a placebo (table 1).

A multinational phase III double-blind study (PREVAILE) randomly assigned 1,717 patients to receive enzalutamide or a placebo. Grade  $\geq 3$  adverse events occurred in 43% of the patients in the enzalutamide group, versus 37% of those in the placebo group. The most common adverse event in the enzalutamide group was fatigue (36%), followed by back pain (27%), and constipation (22%). Only 1 patient in each group had a seizure. Adverse events leading to death occurred in 4% of the patients in each group (table 1) [20].

### *Cabazitaxel*

Cabazitaxel is a tubulin-binding taxane that acts by blocking mitosis in tumor cells and preventing the nuclear translocation of androgen receptors. It is administered intravenously [21].

The primary study that supported the approval of cabazitaxel was the TROPIC EFC6193 trial [4], a large-scale randomized phase III study that compared cabazitaxel plus prednisone ( $n = 371$ ) and MP ( $n = 371$ ). The most common adverse events in the cabazitaxel arm were hematological, including neutropenia, leukopenia, anemia, and thrombocytopenia, with grade  $\geq 3$  rates of 82, 68, 11, and 4%, respectively. The most common non-hematological adverse event was diarrhea, with a rate of 47% for all grades. Febrile neutropenia grade  $\geq 3$  was observed in 8 and 1% of patients in the cabazitaxel and mitoxantrone groups, respectively. In total, 18 (5%) patients in the cabazitaxel group died due to adverse events (table 1).

Due to the lack of quality QoL data, and the high rate of neutropenia and diarrhea in the TROPIC trial, another study was conducted to determine the safety of cabazitaxel and measure patient QoL. QoL was assessed using the Euro QoL-5D 3 Level version questionnaire and pain

was assessed using a visual analogue scale. The most common adverse event (all grades) was diarrhea (64.3%), followed by fatigue (54.5%), nausea (46.4%), and neutropenia (12.5%). The rate of grade 3–4 neutropenia was 9.8% in that study, as compared to 82% in the TROPIC study. Additionally, QoL and pain improved as the number of cabazitaxel treatment cycles increased. The mean improvement in the Euro Qol-5D 3 Level score after the tenth cycle of cabazitaxel was +0.065, which was not statistically significant. Furthermore, 57.1% of the patients reported that they had no pain or discomfort after the tenth cycle, versus 22.3% at the baseline [5].

#### *Abiraterone Acetate*

AA is an orally administered drug that affects the synthesis of androgen from precursors by inhibiting the enzyme CYP17A1 [22].

A recent multinational placebo-controlled, randomized, double-blind phase III (COU-AA-301) trial compared AA plus prednisolone (n = 791) and a placebo plus prednisolone (n = 394). Fatigue was the most common adverse event in both groups (AA plus prednisolone: 44%, placebo plus prednisolone: 43%). Other common adverse events in both groups were back pain, nausea, constipation, bone pain, and arthralgia, which all occurred at similar rates (table 1) [23]. As expected, mineralocorticoid-related adverse events associated with AA, such as fluid retention/edema, and hypokalemia, were more common in the abiraterone group (31 and 17%) than in the placebo group (22 and 8%). Finally, the incidence of global treatment-related adverse events and mortality was similar in both groups (abiraterone group: 77 and 13%, respectively, placebo group: 77 and 16%, respectively) [24].

In the COU-AA-302 trial, conducted with 1,088 chemotherapy-naïve patients with mCRPC, the reported rate of any serious adverse events and grade 3 or 4 adverse events were 38 and 54%, respectively [25]. The most common adverse events were fluid retention/edema, hypokalemia, hypertension, cardiac disorders, atrial fibrillation, and an increase in liver enzymes (table 1). Adverse events led to death in 4% of the patients in the AA group and in 3% in the placebo group.

#### **Conclusion**

The life expectancy of patients with mCRPC is increasing with time. Currently, patient comfort and QoL are at the center of mCRPC patient management. Although, there are numerous treatment alternatives for mCRPC, due to variation in study design, reported adverse events, and treatment procedures (during and post docetaxel, and single or combined regimens), comparison of treatment-related adverse events and patient QoL during and post treatment is not possible. Docetaxel and cabazitaxel are both taxane group chemotherapeutics administered intravenously with similar hematological side effect profiles. AA and enzalutamide are new agents using novel ways to suppress androgens. AA and enzalutamide have been proven to be efficacious before and after chemotherapy in mCRPC [26].

Based on the studies reviewed, AA and enzalutamide provide favorable outcomes, in terms of hematological adverse events. As enzalutamide and AA can be taken orally, they might have a positive effect on patient QoL. Thus, they might be the first choice of treatment in mCRPC.

#### **References**

- 1 Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, Mottet N: EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol* 2014;65:124–137.
- 2 James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, Hetherington J, Hoskin PJ, Jones RJ, Laing R, Lester JF, McLaren D, Parker CC, Parmar MK, Ritchie AW, Russell JM, Strelbel RT, Thalmann GN, Mason MD, Sydes MR: Survival with newly diagnosed metastatic prostate cancer in the “docetaxel era”: data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). *Eur Urol* 2015;67:1028–1038.
- 3 Nakazawa M, Antonarakis ES, Luo J: Androgen receptor splice variants in the era of enzalutamide and abiraterone. *Horm Cancer* 2014;5:265–273.
- 4 de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147–1154.

- 5 Bahl A, Masson S, Malik Z, Birtle AJ, Sundar S, Jones RJ, James ND, Mason MD, Kumar S, Bottomley D, Lydon A, Chowdhury S, Wylie J, de Bono JS: Final quality of life and safety data for patients with metastatic castration-resistant prostate cancer treated with cabazitaxel in the UK Early Access Programme (EAP) (NCT01254279). *BJU Int* 2015;116:880–887.
- 6 van Andel G, Bottomley A, Fossa SD, Efficace F, Coens C, Guerif S, Kynaston H, Gontero P, Thalmann G, Akdas A, D'Haese S, Aaronson NK: An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. *Eur J Cancer* 2008;44:2418–2424.
- 7 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–376.
- 8 King MT, Costa DS, Aaronson NK, Brazier JE, Cella DF, Fayers PM, Grimison P, Janda M, Kemmler G, Norman R, Pickard AS, Rowen D, Velikova G, Young TA, Viney R: QLU-C10D: a health state classification system for a multi-attribute utility measure based on the EORTC QLQ-C30. *Qual Life Res* 2016;25:625–636.
- 9 Blazeby JM, Hall E, Aaronson NK, Lloyd L, Waters R, Kelly JD, Fayers P: Validation and reliability testing of the EORTC QLQ-N-MIBC24 questionnaire module to assess patient-reported outcomes in non-muscle-invasive bladder cancer. *Eur Urol* 2014;66:1148–1156.
- 10 Melzack R: The short-form McGill Pain Questionnaire. *Pain* 1987;30:191–197.
- 11 Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ: Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology* 1997;50:920–928.
- 12 Al-Batran SE, Hozael W, Tauchert FK, Hofheinz RD, Hinke A, Windemuth-Kieselbach C, Hubner A, Burmester M, Koenigsmann M, Wiegand J, Zur Hausen G, Linsse B, Kuhl R, Pauligk C: The impact of docetaxel-related toxicities on health-related quality of life in patients with metastatic cancer (QoliTax). *Ann Oncol* 2015;26:1244–1248.
- 13 Caffo O, Sava T, Comploj E, Fariello A, Zustovich F, Segati R, Sacco C, Veccia A, Galligioni E: Impact of docetaxel-based chemotherapy on quality of life of patients with castration-resistant prostate cancer: results from a prospective phase II randomized trial. *BJU Int* 2011;108:1825–1832.
- 14 Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Theodore C, James ND, Tureson I, Rosenthal MA, Eisenberger MA: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502–1512.
- 15 Kelly WK, Halabi S, Carducci M, George D, Mahoney JF, Stadler WM, Morris M, Kantoff P, Monk JP, Kaplan E, Vogelzang NJ, Small EJ: Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol* 2012;30:1534–1540.
- 16 Kornblith AB, Herndon JE, 2nd, Zuckerman E, Godley PA, Savarese D, Vogelzang NJ: The impact of docetaxel, estramustine, and low dose hydrocortisone on the quality of life of men with hormone refractory prostate cancer and their partners: a feasibility study. *Ann Oncol* 2001;12:633–641.
- 17 Berry DL, Moynour CM, Jiang CS, Ankerst DP, Petrylak DP, Vinson LV, Lara PN, Jones S, Taplin ME, Burch PA, Hussain MH, Crawford ED: Quality of life and pain in advanced stage prostate cancer: results of a Southwest Oncology Group randomized trial comparing docetaxel and estramustine to mitoxantrone and prednisone. *J Clin Oncol* 2006;24:2828–2835.
- 18 Cheng HH, Gulati R, Azad A, Nadal R, Twardowski P, Vaishampayan UN, Agarwal N, Heath EI, Pal SK, Rehman HT, Leiter A, Batten JA, Montgomery RB, Galsky MD, Antonarakis ES, Chi KN, Yu EY: 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;18:122–127.
- 19 Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Flechon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS: Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187–1197.
- 20 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, Tombal B: Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424–433.
- 21 Castellano D, Anton Aparicio LM, Esteban E, Sanchez-Hernandez A, Germa JR, Batista N, Maroto P, Perez-Valderrama B, Luque R, Mendez-Vidal MJ: Cabazitaxel for metastatic castration-resistant prostate cancer: safety data from the Spanish expanded access program. *Expert Opin Drug Saf* 2014;13:1165–1173.
- 22 Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN: Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol* 2013;24:1802–1807.
- 23 de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB, Jr., Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Flechon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI: Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.
- 24 Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, Staffurth JN, North S, Vogelzang NJ, Saad F, Mainwaring P, Harland S, Goodman OB Jr, Sternberg CN, Li JH, Kheoh T, Haqq CM, de Bono JS: Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012;13:983–992.
- 25 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, Rathkopf DE: Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve 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;16:152–160.
- 26 Zhang T, Dhawan MS, Healy P, George DJ, Harrison MR, Oldan J, Chin B, Armstrong AJ: Exploring the clinical benefit of docetaxel or enzalutamide after disease progression during abiraterone acetate and prednisone treatment in men with metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer* 2015;13:392–399.