Published in final edited form as:

Prostate Cancer Prostatic Dis. 2016 December ; 19(4): 398–405. doi:10.1038/pcan.2016.31.

Predictors of duration of abiraterone acetate in men with castration resistant prostate cancer

Rana R. McKay, MD¹, Lillian Werner, MS¹, Matthew Fiorillo, BA¹, Mari Nakabayashi, MD, PhD¹, Philip W. Kantoff, MD^{1,2}, and Mary-Ellen Taplin, MD¹

¹Dana-Farber Cancer Institute, Boston, MA

²Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Background—Androgen receptor signaling remains important in castration resistant prostate cancer (CRPC) as demonstrated by the efficacy of abiraterone acetate (henceforth abiraterone) in phase III trials. Given that heterogeneous patient responses are observed, we sought to determine clinical factors associated with duration of abiraterone.

Methods—We retrospectively identified patients with CRPC treated with abiraterone in our database. Patient characteristics and types and duration of prostate cancer therapies were analyzed. These parameters were analyzed with duration of abiraterone in univariate and multivariable analyses.

Results—We identified 161 patients who had received abiraterone. All had received primary androgen deprivation therapy (ADT), 86% prior secondary hormone therapy, and 33% prior chemotherapy. The median duration of primary ADT was 23 months, duration of secondary hormone therapy (excluding abiraterone) was 17 months, and duration of chemotherapy was 8 months. We demonstrated that lower prostate specific antigen (PSA) at abiraterone initiation, longer primary ADT duration, no prior ketoconazole, no prior chemotherapy and longer chemotherapy duration were associated with a longer duration on abiraterone in univariate analysis. In multivariable analysis, duration of primary ADT (duration of abiraterone 9 versus 13 months for ≤ 12 versus >12 months, $p=0.03$) and no use of prior chemotherapy (duration of abiraterone 16 versus 7 months for no versus yes prior chemotherapy, $p<0.01$) were associated with duration of abiraterone.

Conclusions—Several clinical parameters including type and duration of prior therapy are predictive of responsiveness to abiraterone. These parameters are logical and correlate with smaller disease burden or less exposure to prostate cancer therapies. This information can help physicians counsel patients about the potential durability of efficacy of abiraterone. Identifying predictive biomarkers that inform patient selection for therapy is critical to optimizing treatment outcomes.

Corresponding Author: Rana R. McKay, MD, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02115, Telephone: 617-632-3237, Fax: 617-632-2165, rmckay5@partners.org.

Conflicts of Interests: MET receives research funding and advisory board honorarium from Janssen. PWK is a paid advisor to Janssen. The remaining authors have no disclosures.

Introduction

Since the pioneering work of Huggins and Hodges, the principle treatment for PC is androgen deprivation therapy (ADT) (1). For most men, ADT controls symptoms by inducing clinical responses and a decline in prostate specific antigen (PSA). This tumor regression can lead to a prolonged period of disease control. The duration of primary ADT is variable, and most patients with metastatic disease develop metastatic castration-resistant prostate cancer (mCRPC) within a 1–2 years of starting ADT (2, 3).

Treatment of mCRPC is rapidly evolving, and additional medications have been Food and Drug Administration (FDA) approved to combat disease progression. The importance of androgen receptor (AR) signaling following castration is made evident by the success of next generation hormone therapies including abiraterone acetate (abiraterone henceforth) and enzalutamide (4–7). Abiraterone is a potent inhibitor of CYP17 which inhibits 17 alpha-hydroxylase and 17, 20-lyase resulting in suppression of androgen synthesis in the testes, adrenal gland, and PC cells (5).

The effectiveness of abiraterone was established in two phase III trials. In these studies, abiraterone was found to increase survival and delay radiographic progression: median radiographic progression-free survival (PFS) 5.6 months post-chemotherapy (COU-AA-301) and 16.5 months pre-chemotherapy (COU-AA-302) (5, 6). Despite a demonstrable benefit of abiraterone, amongst responders, the degree of clinical effectiveness varies greatly.

For these reasons, identification of clinical biomarkers is necessary to optimize patient selection for therapy and better counsel patients regarding expectations of therapy. Prognostic factors, including age, PSA, metastasis location, and prior PC therapies, are important considerations in disease management. A more thorough understanding of the prognostic characteristics prior to abiraterone would help physicians identify men most likely to benefit from treatment and better counsel patients.

We previously demonstrated that duration of secondary hormone therapy (SHT) correlates with the duration of prior primary ADT (8). Patients who received ADT for ≥ 24 months received SHT for a median duration of 40.0 months compared to 18.4 months for patients receiving <24 months of primary ADT (5). These data highlight that a subset of PCs are biologically more responsive to AR pathway manipulations, and will exhibit a superior response to AR targeted therapies such as abiraterone. Additionally, several prior have investigated clinical parameters, including primary ADT duration, associated with PFS and overall survival (OS) in patients with mCRPC treated with abiraterone (9–16). We sought to confirm the impact of baseline clinical characteristics on abiraterone duration and specifically evaluate duration of prior therapies including primary ADT, SHT, and chemotherapy on abiraterone duration.

Patients and Methods

Database

This cohort was generated from the Prostate Clinical Research Information System (CRIS) at the Dana-Farber Cancer Institute (DFCI) (17). The CRIS database utilizes data-entry software to generate a central repository of comprehensive patient data. All patients seen at DFCI and Brigham and Women's Hospital with a diagnosis of PC are eligible for participation and the consent rate is 86%. This study was approved by the Institutional Review Board at the Dana-Farber/Harvard Cancer Center. Informed consent was obtained from all subjects in this study. Data is maintained in an Oracle relational database (Oracle, Redwood Shores, CA). Additional information was collected from within the longitudinal medical record.

Patient Selection and Quality Control

We identified 178 CRPC patients treated with abiraterone. For quality-control, a research physician (RM) reviewed the medical records of a subset of patients. A total of 17 patients were excluded for receipt of abiraterone for localized disease, concurrent medical illness necessitating long-term ketoconazole use, or incomplete history or follow-up data. All patients were diagnosed with PC between 1987–2012, and received abiraterone between 3/2009–9/2013. The final cohort consisted of 161 patients.

Statistical Analysis

Clinical and disease characteristics at the time of diagnosis and duration of primary ADT, SHT and chemotherapy were summarized as median and inter-quartiles range for continuous variables, and as number and percentage for categorical variables. Duration of primary ADT was defined as the time between the date of the first luteinizing hormone-releasing hormone (LHRH) agonist/antagonist or orchiectomy and start of next-line PC therapy. An anti-androgen starting within six months of an LHRH agonist/antagonist was classified as primary ADT. Duration of SHT was defined as the sum of durations of each secondary hormone agent. Patients may have received other PC directed therapies between courses of SHT. Anti-androgen withdrawal was not captured as SHT. Duration of chemotherapy was defined as the sum of the durations of each chemotherapy agent given. Patients may have received non-chemotherapy (such as hormonal therapy or immunotherapy) in between courses of chemotherapy.

The primary analysis was to evaluate whether baseline clinical parameters and type and duration of prior therapy were associated with abiraterone duration. Abiraterone duration was defined as the time between start of abiraterone to the initiation of next-line therapy or censored for patients still on therapy. The log-rank test was used to correlate variables with abiraterone duration in univariate analysis. Variables, including PSA and duration of prior therapy, were dichotomized at median or clinically meaningful cutoff points. Multivariable analysis was performed using the Cox proportional hazard regression. Thresholds for statistical significance was $p=0.05$. The Kaplan-Meier method was used to estimate abiraterone duration.

Results

Patient and Disease Characteristics

The median age at diagnosis was 60 years (interquartile: 55, 64), and 45% of patients had a Gleason score ≥ 8 at diagnosis (Table 1). The majority of patients (73%) received primary local therapy. At abiraterone initiation, median PSA was 20.3 ng/mL and most patients had bone (75%) and/or lymph node metastases (54%).

Practice Patterns of Abiraterone Administration

Utilization of abiraterone increased over time consistent with FDA approval for mCRPC in 2011: 2% received abiraterone prior to 2011, 26% in 2011, and 52% in 2012. Additionally, a higher percentage received abiraterone without prior chemotherapy in 2012 (53%) and 2013 (28%) than in 2009–2010 (3%).

Type and Duration of Prior Therapy

All patients received primary ADT, and the median duration of treatment was 23 months (interquartile: 12, 42). The majority of patients also received prior SHT (n=139, 86%) of which 99% (n=137) received an anti-androgen, 38% (n=53) received ketoconazole, and 5% (n=7) received enzalutamide. The median duration of prior SHT was 17 months (interquartile: 6, 46). Additionally, 33% of patients (n=53) received prior chemotherapy at a median duration of 8 months (interquartile 5, 14). Chemotherapeutic agents included docetaxel (n=51), cabazitaxel (n=26), and other (n=14). Thirty-two patients (20%) received more than two types of prior chemotherapy agents. Patients receiving chemotherapy had a shorter time on primary and secondary ADT compared to individuals who did not receive prior chemotherapy (Table 1). The median duration of abiraterone use for the entire cohort was 12 months and 87 patients had discontinued treatment at the time of analysis. The median duration of primary ADT and secondary ADT increased over the following years: 2009–2011, 2012, and 2013; while, the median duration of chemotherapy decreased during these time periods (Table 2).

Association of Clinical Parameters and Prior Treatment Duration with Duration of Abiraterone

PSA at initiation of abiraterone therapy correlated with duration of abiraterone in univariate analysis. Patients with a lower PSA at initiation of abiraterone were more likely to remain on therapy for a longer period of time compared to patients with a higher PSA (duration of abiraterone 16 versus 10 months PSA ≤ 20.3 ng/mL or > 20.3 ng/mL, $p=0.01$) (Table 3, Figure 1A). The duration of abiraterone was not associated with baseline Gleason score, PSA at PC diagnosis, PSA at primary ADT initiation, or sites of metastasis at initiation of abiraterone (Table 3).

Longer duration of primary ADT, no prior ketoconazole, no prior chemotherapy, and longer duration of chemotherapy correlated with longer duration of abiraterone in univariate analysis (Table 3, Figure 1B–E). Patients receiving >12 months of primary ADT were more likely to have a longer duration on abiraterone compared to patients receiving ≤ 12 months (duration of abiraterone 13 versus 9 months for primary ADT duration >12 or ≤ 12 months,

p=0.03). Patients receiving prior ketoconazole had a shorter duration on abiraterone therapy compared to those never receiving ketoconazole (median duration of abiraterone 10 versus 13 months for patients with and without prior ketoconazole, p=0.02). Similarly, use of chemotherapy prior to abiraterone was associated with a shorter duration on abiraterone compared to those who did not receive prior chemotherapy (median duration of abiraterone 16 versus 7 months for patients with and without prior chemotherapy, p<0.01). Receipt of >8 months of chemotherapy was associated with longer duration on abiraterone compared to receipt of ≤8 months of chemotherapy (duration of abiraterone 11 versus 6 months for chemotherapy >8 months or ≤8 months, p=0.04). Duration of SHT and anti-androgen use was not associated with duration of abiraterone.

In multivariable analysis, longer duration of primary ADT and no prior chemotherapy were associated with longer duration of abiraterone (Table 4). Given that 66% of patients had not received prior chemotherapy, duration of chemotherapy was not included in the multivariable analysis.

Prior Enzalutamide and Duration of Abiraterone

Seven patients received enzalutamide prior to abiraterone. The median duration of primary ADT and SHT for these patients was 29 and 26 months, respectively. The median duration of abiraterone was 8 months (range 3–13 months).

Discussion

As the treatment landscape for mCRPC continues to expand, patient selection for therapy and thoughtful sequencing of agents is paramount. Data from prospective studies evaluating the optimal succession of currently approved therapies is lacking but several trials seeking to answer this question are ongoing. We sought to validate previously identified factors associated with abiraterone duration in our clinical database. Our analysis demonstrates that longer duration of primary ADT and no prior chemotherapy were associated with longer abiraterone duration.

We previously demonstrated that longer primary ADT duration was associated with a longer SHT duration, suggesting that AR signaling remains a vital target in CRPC (8). In our prior work, the duration of primary ADT was 24 months, similar to this study (23 months), however duration of SHT was 30.3 months, longer compared to our current study (17 months). This is likely a reflection of the limited mCRPC treatments and increased ketoconazole use in our prior cohort or men treated from 1993–2008. Furthermore, several studies have demonstrated that time to castration-resistance is a predictor of sensitivity to next-generation AR targeting agents (15, 18). In a retrospective analysis of 173 patients, a short time to CRPC (<12 months) was predictive of shorter PFS and OS and lower PSA response rate (15). Additionally, a post-hoc analysis from COU-AA-301 and COU-AA-302 demonstrated that though median time-to-event measures were shorter for patients receiving a shorter duration of LHRH agonist/antagonist or AR antagonist (excluding enzalutamide), the clinical benefit from abiraterone was observed for OS, PFS, and PSA response for nearly all durations of prior endocrine therapy (9).

Chi and colleagues developed a prognostic model for OS in mCRPC patients receiving abiraterone after chemotherapy derived from the COU-AA-301 phase III trial (10). The model, which was externally validated, included time from ADT initiation to abiraterone treatment 36 months (16). This time variable, which is different than the time variables used in our analysis and includes the duration of primary ADT and SHT, was prognostic in determining outcomes to abiraterone. Additional variables included in the model were performance status, liver metastases, low albumin, high alkaline phosphatase, and high lactate dehydrogenase (16). In our cohort, which included only three patients with liver metastases at initiation of abiraterone therapy, metastatic sites were not predictive of abiraterone duration.

Though prognostic models in mCRPC have included PSA in addition to other clinical parameters, several series evaluating variables associated with survival post-abiraterone have not found PSA to be prognostic in multivariable analysis (10, 13, 15, 19). Furthermore, results from COU-AA-301 demonstrate that the benefit of abiraterone was seen in subgroups with baseline PSA > and median (20). In a post-hoc analysis of the phase III study of enzalutamide versus placebo in mCRPC post-chemotherapy, baseline PSA was a marker of disease burden (21). Though patients with a higher PSA had increased burden of disease and shorter median time-to-event measures, the benefit of enzalutamide compared to placebo on OS, PFS, and time-to-PSA progression was demonstrated across all PSA quartiles. In our cohort, though baseline PSA was prognostic in univariate analysis, it did not reach statistical significance in multivariable analysis.

In our cohort, 89% of patients received SHT, including 33% patients who received prior ketoconazole and 4% prior enzalutamide. We demonstrate that duration of prior SHT did not correlate with duration of abiraterone. In univariate analysis, use of ketoconazole was associated with decreased duration of abiraterone, likely related to overlapping mechanisms of action and resistance between these agents, though this was not significant in multivariable analysis. Though phase III trials of abiraterone excluded prior ketoconazole, our data are consistent with phase II studies, which demonstrate modest clinical activity of sequential use of androgen synthesis inhibitors ketoconazole and abiraterone (12, 22). Kim and colleagues showed that baseline androgen levels, specifically dehydroepiandrosteronedione, were predictive of response to abiraterone in patients previously treated with ketoconazole.(12) In our dataset, though numbers are small, the median duration of abiraterone of patients receiving prior enzalutamide was 8 months, which was shorter than the median duration of abiraterone for the entire cohort (12 months).

Retrospective analyses have demonstrated cross-resistance with AR-targeted therapies. Lortiot and colleagues initially described the antitumor activity of abiraterone following docetaxel and enzalutamide (14). In 38 patients progressing on docetaxel and enzalutamide, abiraterone resulted in 50% PSA decline in only three patients (14). Noonan and colleagues demonstrated similar results in patients pretreated with docetaxel and enzalutamide (23). In a cohort of 30 patients, while 70% had a 30% decline in PSA on enzalutamide, only 11% had a 30% decline in PSA on sequential abiraterone (23). Furthermore, several studies report modest clinical activity to enzalutamide following docetaxel and/or abiraterone (24–27). While abiraterone and enzalutamide, a potent-anti-

androgen, have differing mechanisms of actions, acquired resistance develops in nearly all patients and some individuals experience primary resistance to therapy. Several mechanisms of resistance have been reported including systemic and intratumoral androgen biosynthesis, AR mutations and amplifications, AR splice variants, glucocorticoid receptor over-expression, and activation of alternate pathways (28).

In our analysis, we demonstrate that use of prior chemotherapy was associated with a shorter duration of abiraterone. Based on results from COU-AA-301 and COU-AA-302, PSA response rate (50% decline in PSA from baseline) was 29% for COU-AA-301 compared to 62% for COU-AA-302 (5, 6). Additionally, PFS was 5.6 months compared to 16.5 months for COU-AA-301 and COU-AA-302 (5, 6). Additionally, several studies report modest activity of docetaxel following abiraterone (29, 30). Although these results may suggest some degree of cross-resistance between chemotherapy and abiraterone, men receiving prior chemotherapy may be farther along in the disease course with greater tumor burden and more diverse non-AR pathway growth. The principal mechanism of action of taxane agents includes disruption of microtubules with cell division arrest and recent studies suggest that at physiologic concentrations taxanes do not act through the AR as previously suspected (31). Interestingly, we demonstrate that longer duration of chemotherapy predicts for longer duration of abiraterone in univariate analysis, however given the limited sample size, this parameter was excluded from multivariable analysis. Several hypotheses might explain this observation including potentially improved performance status of patients able to remain on therapy for a longer duration and differing underlying tumor biology in patients more responsive to standard therapies. Limited studies have evaluated whether duration of chemotherapy impacts abiraterone duration. These results are hypothesis-generating and need to be validated in larger studies. Additionally, the impact of docetaxel for hormone-sensitive disease on abiraterone outcomes needs to be further explored (3).

The variable responsiveness to abiraterone in CRPC creates a compelling need to develop biomarkers to personalize therapy. Biomarkers under analysis include serum hormone levels and AR amplification (32). Recently, Antonarakis and colleagues demonstrated that AR splice variant 7 (AR-V7) was associated with primary resistance to abiraterone and enzalutamide (33). Additionally, precision medicine platforms have been undertaken with the goal of identifying molecular drivers of disease for the application of personalized approaches for cancer therapeutics (34). The development of novel agents including new AR inhibitors, androgen synthesis inhibitors, tyrosine kinase inhibitors, and immunotherapies are currently in testing. Galeterone, a CYP17 inhibitor which induces AR degradation potentially conferring activity in the presence of AR splice variants, is currently under investigation in a phase III biomarker trial (35). In addition to targeting the AR pathway, alternative pathways, including the DNA-repair pathway, have emerged as potential targets in CRPC (34, 36). Based on a phase II study of olaparib in mCRPC, 88% of patients with DNA-repair gene aberrations had a response to treatment (36). Along with new drug development, combinatorial strategies are being explored. The goal of combinatorial treatment is to achieve maximal and durable tumor responses by blocking several targets simultaneously. Several examples include the combination of abiraterone with docetaxel, cabazitaxel, and also ARN-509, a new generation anti-androgen.

Several limitations exist in our study. We use the metric “duration of treatment” rather than actual “response duration.” Duration of treatment reflects “real-world” practice patterns, as the determination to discontinue treatment is based on the physician’s clinical judgment of patient benefit. Additionally, median primary ADT duration in this cohort (23 months) is similar to the median time-to-progression on ADT in our previous cohort of 553 patients with hormone-sensitive PC (23.7 months) supporting duration of treatment as a surrogate for time-to-progression (37). Furthermore, given limited sample size, analyses were not conducted in pre- and post-chemotherapy patients separately. Despite quality control efforts, our study is limited by its retrospective design, potential for selection bias, and incomplete or variable assessments.

In summary, in this large cohort we describe predictors of responsiveness to abiraterone. Given the heterogeneity of response to abiraterone, several clinical predictors including type and duration of prior therapy, can help physicians counsel patients on the potential efficacy of abiraterone. We confirm that longer primary ADT duration and no prior chemotherapy are associated with longer duration of abiraterone exposure. Additionally, our work highlights the importance of identifying predictive biomarkers to inform patient selection for developing sequential and combinatorial treatment strategies in mCRPC.

Acknowledgments

This project was support in part by the Fairweather Family Fund at the Dana-Farber Cancer Institute (MET).

References

1. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *CA Cancer J Clin.* 1972; 22(4):232–40. [PubMed: 4625049]
2. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet.* 2015
3. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med.* 2015; 373(8):737–46. [PubMed: 26244877]
4. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med.* 2014; 371(5):424–33. [PubMed: 24881730]
5. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011; 364(21):1995–2005. [PubMed: 21612468]
6. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med.* 2013; 368(2):138–48. [PubMed: 23228172]
7. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med.* 2012; 367(13):1187–97. [PubMed: 22894553]
8. Nakabayashi M, Werner L, Oh WK, Regan MM, Kantoff PW, Taplin ME. Secondary hormonal therapy in men with castration-resistant prostate cancer. *Clinical genitourinary cancer.* 2011; 9(2): 95–103. [PubMed: 21958520]

9. Bellmunt J, Kheoh T, Yu MK, Smith MR, Small EJ, Mulders PF, et al. Prior Endocrine Therapy Impact on Abiraterone Acetate Clinical Efficacy in Metastatic Castration-resistant Prostate Cancer: Post-hoc Analysis of Randomised Phase 3 Studies. *European urology*. 2015
10. Chi KN, Kheoh TS, Ryan CJ, Molina A, Bellmunt J, Vogelzang NJ, et al. A prognostic model for predicting overall survival (OS) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate (AA) after docetaxel. *ASCO Meeting Abstracts*. 2013; 31(15_suppl):5013.
11. Fizazi K, Flaig TW, Stockle M, Scher HI, de Bono JS, Rathkopf DE, et al. Does Gleason score at initial diagnosis predict efficacy of abiraterone acetate therapy in patients with metastatic castration-resistant prostate cancer? An analysis of abiraterone acetate phase III trials. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2016; 27(4): 699–705.
12. Kim W, Zhang L, Wilton JH, Fetterly G, Mohler JL, Weinberg V, et al. Sequential use of the androgen synthesis inhibitors ketoconazole and abiraterone acetate in castration-resistant prostate cancer and the predictive value of circulating androgens. *Clin Cancer Res*. 2014; 20(24):6269–76. [PubMed: 25336698]
13. Leibowitz-Amit R, Templeton AJ, Omlin A, Pezaro C, Atenafu EG, Keizman D, et al. Clinical variables associated with PSA response to abiraterone acetate in patients with metastatic castration-resistant prostate cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2014; 25(3):657–62.
14. Llori Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2013; 24(7):1807–12.
15. Llori Y, Eymard JC, Patrikidou A, Ileana E, Massard C, Albiges L, et al. Prior long response to androgen deprivation predicts response to next-generation androgen receptor axis targeted drugs in castration resistant prostate cancer. *Eur J Cancer*. 2015; 51(14):1946–52. [PubMed: 26208462]
16. Ravi P, Mateo J, Lorente D, Zafeiriou Z, Altavilla A, Ferraldeschi R, et al. External validation of a prognostic model predicting overall survival in metastatic castrate-resistant prostate cancer patients treated with abiraterone. *European urology*. 2014; 66(1):8–11. [PubMed: 24685433]
17. Oh WK, Hayes J, Evan C, Manola J, George DJ, Waldron H, et al. Development of an integrated prostate cancer research information system. *Clin Genitourin Cancer*. 2006; 5(1):61–6. [PubMed: 16859581]
18. Nadal R, Tsai HL, Sinibaldi VJ, Paller CJ, Antonarakis ES, Denmeade SR, et al. Prognostic factors for clinical outcomes in patients with metastatic castration resistant prostate cancer treated with sequential novel androgen receptor-directed therapies. *Prostate*. 2016; 76(5):512–20. [PubMed: 26689606]
19. Halabi S, Small EJ, Kantoff PW, Kattan MW, Kaplan EB, Dawson NA, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol*. 2003; 21(7):1232–7. [PubMed: 12663709]
20. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. 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(10):983–92. [PubMed: 22995653]
21. Saad F, de Bono J, Shore N, Fizazi K, Llori Y, Hirmand M, et al. Efficacy outcomes by baseline prostate-specific antigen quartile in the AFFIRM trial. *European urology*. 2015; 67(2):223–30. [PubMed: 25171902]
22. Danila DC, Morris MJ, de Bono JS, Ryan CJ, Denmeade SR, Smith MR, et al. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. *J Clin Oncol*. 2010; 28(9):1496–501. [PubMed: 20159814]
23. 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. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2013; 24(7):1802–7.

24. Badrising S, van der Noort V, van Oort IM, van den Berg HP, Los M, Hamberg P, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer*. 2014; 120(7):968–75. [PubMed: 24382803]
25. Cheng HH, Gulati R, Azad A, Nadal R, Twardowski P, Vaishampayan UN, 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(2):122–7. [PubMed: 25600186]
26. Nadal R, Zhang Z, Rahman H, Schweizer MT, Denmeade SR, Paller CJ, et al. Clinical activity of enzalutamide in Docetaxel-naïve and Docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. *Prostate*. 2014; 74(15):1560–8. [PubMed: 25176007]
27. Schrader AJ, Boegemann M, Ohlmann CH, Schnoeller TJ, Krabbe LM, Hajili T, et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *European urology*. 2014; 65(1):30–6. [PubMed: 23849416]
28. Buttigliero C, Tucci M, Bertaglia V, Vignani F, Bironzo P, Di Maio M, et al. Understanding and overcoming the mechanisms of primary and acquired resistance to abiraterone and enzalutamide in castration resistant prostate cancer. *Cancer Treat Rev*. 2015
29. Mezynski J, Pezaro C, Bianchini D, Zivi A, Sandhu S, Thompson E, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2012; 23(11):2943–7.
30. Schweizer MT, Zhou XC, Wang H, Bassi S, Carducci MA, Eisenberger MA, et al. The Influence of Prior Abiraterone Treatment on the Clinical Activity of Docetaxel in Men with Metastatic Castration-resistant Prostate Cancer. *European urology*. 4
31. de Leeuw R, Berman-Booty LD, Schiewer MJ, Ciment SJ, Den RB, Dicker AP, et al. Novel actions of next-generation taxanes benefit advanced stages of prostate cancer. *Clin Cancer Res*. 2015; 21(4):795–807. [PubMed: 25691773]
32. Ryan CJ, Molina A, Li J, Kheoh T, Small EJ, Haqq CM, et al. Serum androgens as prognostic biomarkers in castration-resistant prostate cancer: results from an analysis of a randomized phase III trial. *J Clin Oncol*. 2013; 31(22):2791–8. [PubMed: 23816964]
33. Antonarakis ES, Lu C, Wang H, Lubner B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med*. 2014; 371(11):1028–38. [PubMed: 25184630]
34. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell*. 2015; 161(5):1215–28. [PubMed: 26000489]
35. Njar VC, Brodie AM. Discovery and development of Galeterone (TOK-001 or VN/124-1) for the treatment of all stages of prostate cancer. *J Med Chem*. 2015; 58(5):2077–87. [PubMed: 25591066]
36. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med*. 2015; 373(18):1697–708. [PubMed: 26510020]
37. Ross RW, Xie W, Regan MM, Pomerantz M, Nakabayashi M, Daskivich TJ, et al. Efficacy of androgen deprivation therapy (ADT) in patients with advanced prostate cancer: association between Gleason score, prostate-specific antigen level, and prior ADT exposure with duration of ADT effect. *Cancer*. 2008; 112(6):1247–53. [PubMed: 18293426]

Figure 1.

Association of duration of abiraterone therapy with A) PSA at initiation of abiraterone, B) duration of primary androgen deprivation therapy, C) use of prior ketoconazole, D) use of chemotherapy, and E) duration of chemotherapy.

Table 1

Patient and disease characteristics.

	Total N=161		Prior Chemotherapy N=53		No Prior Chemotherapy N=108	
	N	Median (q1, q3)	N	Median (q1, q3)	N	Median (q1, q3)
At Diagnosis						
Age	156	60 (55, 64)	50	59 (54, 64)	106	60 (56, 65)
PSA (ng/mL)	150	9.5 (5.4, 33.4)	46	9.6 (6.1, 33.4)	104	9.5 (5.3, 34.1)
Gleason score						
6	28	17%	9	17%	19	18%
7	51	32%	11	21%	40	37%
8	73	45%	28	53%	45	42%
Unknown	9	6%	5	9%	4	4%
T stage						
T1	100	62%	36	68%	64	59%
T2	34	21%	8	15%	26	24%
T3/T4	6	4%	0	0%	6	6%
Unknown	21	13%	9	17%	12	11%
N stage						
N0	63	39%	16	30%	47	44%
N1	13	8%	2	4%	11	10%
Unknown	85	53%	35	66%	50	46%
M stage						
M0	67	42%	16	30%	51	47%
M1	28	17%	12	23%	16	15%
Unknown	66	41%	25	47%	41	38%
Prior Therapy						

	Total N=161		Prior Chemotherapy N=53		No Prior Chemotherapy N=108	
	N	Median (q1, q3)	N	Median (q1, q3)	N	Median (q1, q3)
Primary local treatment						
RP	70	43%	20	38%	50	46%
RT	4	30%	15	28%	33	31%
None	43	27%	18	34%	25	23%
Receipt of ADT during local treatment						
No	122	76%	41	77%	81	75%
Yes	39	24%	12	23%	27	25%
PSA at initiation of primary ADT (ng/mL)	135	10.9 (9.3, 45.8)	39	9.1 (4.7, 45.1)	96	12.8 (3.1, 47.9)
Duration of primary ADT	161	23 (12, 42)	53	13 (10, 31)	108	28 (15, 49)
Duration of secondary ADT						
Bicalutamide	139	17 (6, 46)	44	15 (6, 42)	95	19 (7, 49)
Nilutamide	152	94%	48	91%	104	96%
Flutamide	84	52%	29	55%	55	51%
Ketoconazole	14	9%	7	13%	7	6%
Enzalutamide	53	33%	2	49%	27	25%
	7	4%	0	0%	7	6%
Duration of chemotherapy	53	8 (5, 14)	53	(5, 14)		
Docetaxel	51	96%	51	96%		
Cabazitaxel	49	49%	49	49%		
At abiraterone initiation						
PSA (ng/mL)	155	20.3 (6.2, 66.5)	48	63.4 (15.4, 151.2)	107	13.0 (4.5, 40.0)
Presence of metastases						
No	11	7%	0	0%	11	10%
Yes	150	93%	53	100%	97	90%
Sites of metastasis						

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	Total N=161		Prior Chemotherapy N=53		No Prior Chemotherapy N=108	
	N	Median (q1, q3)	N	Median (q1, q3)	N	Median (q1, q3)
Bone	120	75%	49	92%	71	66%
Lymph node	87	54%	32	60%	55	51%
Lung	17	11%	10	19%	7	6%
Liver	3	2%	2	4%	1	1%
Other	11	7%	2	4%	9	8%
Year of initiation						
2009–2010	4	2%	1	2%	3	3%
2011	42	26%	24	45%	18	17%
2012	84	52%	27	51%	57	53%
2013	31	19%	1	2%	30	28%

PSA=prostate specific antigen, RP=radical prostatectomy, RT=radiotherapy, ADT=androgen deprivation therapy.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Duration of prior therapy by year of abiraterone initiation.

Year of Abiraterone Initiation	2009–2011		2012		2013	
	N	Median (q1, q3)	N	Median (q1, q3)	N	Median (q1, q3)
Duration of ADT	46	21 (12, 41)	84	22 (11, 40)	31	28 (15, 52)
Duration of secondary hormone therapy	39	14 (8, 49)	74	15 (6, 39)	26	25 (6, 52)
Duration of chemotherapy	25	9 (4, 15)	27	7 (6, 8)	1	

ADT=androgen deprivation therapy.

Table 3

Univariate analysis of the association of clinical parameters and prior treatment duration with duration of abiraterone (months).

Clinical Parameter	N	Number of Patients Discontinued Abiraterone	Median Duration of Abiraterone (months)	P-value
Gleason score				0.17
6	28	16	10	
7	51	21	20	
8	73	43	11	
PSA at diagnosis				0.72
9.5 ng/mL	75	39	12	
>9.5 ng/mL	75	42	12	
PSA at initiation of primary ADT				0.27
10.9 ng/mL	67	36	15	
>10.9 ng/mL	68	35	10	
PSA at initiation of abiraterone				0.01
20.3 ng/mL	78	35	16	
>20.3 ng/mL	77	48	10	
Metastases at initiation of abiraterone				0.33
None	11	3	24	
Bone and/or lymph node	119	64	11	
Visceral	30	19	14	
Duration of primary ADT				0.03
12 months	40	30	9	
>12 months	121	57	13	
Duration of secondary ADT				0.80
12 months	54	32	11	
>12 months	85	45	13	
Use of bicalutamide				0.14
No	9	6	5	
Yes	152	81	12	
Use of nilutamide				0.93
No	77	38	13	
Yes	84	49	12	
Use of flutamide				0.55
No	147	78	13	
Yes	14	9	8	

Clinical Parameter	N	Number of Patients Discontinued Abiraterone	Median Duration of Abiraterone (months)	P-value
Use of ketoconazole				0.02
No	108	49	13	
Yes	53	38	10	
Use of chemotherapy				<0.01
No	108	41	16	
Yes	53	46	7	
Duration of chemotherapy				0.04
8 months	32	29	6	
>8 months	21	17	11	

PSA=prostate specific antigen, ADT=androgen deprivation therapy.

Bolded p-values are statistically significant.

Table 4

Multivariable analysis of the association of clinical parameters and prior treatment duration with duration of abiraterone (months).

Clinical Parameter	Hazard Ratio (95% Confidence Interval)	P-value
PSA at initiation of abiraterone		0.06
20.3 ng/mL	0.63 (0.40, 1.01)	
>20.3 ng/mL	1 (reference)	
Duration of primary ADT		0.01
>12 months	0.54 (0.34, 0.86)	
12 months	1 (reference)	
Use of ketoconazole		0.25
No	0.76 (0.48, 1.21)	
Yes	1 (reference)	
Use of chemotherapy		<0.01
No	0.44 (0.28, 0.70)	
Yes	1 (reference)	

PSA=prostate specific antigen, ADT=androgen deprivation therapy.

Bolded p-values are statistically significant.