What Predicts Minimal Response to Abiraterone in Metastatic Castrate-resistant Prostate Cancer?

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Abstract. *Background: Several treatments have been shown to prolong survival in metastatic castrate-resistant prostate cancer (mCRPC); the optimum sequencing of these is not established. We investigated methods of identifying patients with mCRPC unlikely to respond to abiraterone. Patients and Methods: A retrospective analysis was carried-out in 47 consecutive patients with mCRPC treated sequentially with androgen deprivation (LHRHa), bicalutamide, docetaxel then abiraterone. Results: The median progression-free survival in patients treated with abiraterone was shorter in those with ≤18 months' response to LHRHa (118 vs. 279 days; p=0.018), bicalutamide non-responders (91 vs. 196 days; p=0.003) and patients with ≤6 months' response to docetaxel (102 vs. 294 days; p<0.001). The median overall survival was also shorter (348 vs. 815 days, p=0.016; 413 vs. 752 days, p=0.009; and 325 vs. 727 days, p<0.04, respectively). Conclusion: A response of ≤18 months' to LHRHa, non-response to bicalutamide and ≤6 months' response to docetaxel predicted poor response to abiraterone.*

In Europe, prostate cancer is the most common cancer among men, with 382,000 new cases and 89,000 deaths annually (1). For metastatic prostate cancer, androgen deprivation therapy (ADT), usually involving orchidectomy or luteinising hormone-releasing hormone agonists (LHRHa), is the mainstay of treatment. ADT will only be effective for a finite period of time, and most men will eventually develop metastatic castrate-resistant prostate cancer (mCRPC) (2). In 2004, the TAX327 study changed the prostate cancer treatment paradigm, showing a survival benefit for docetaxel-plus-prednisolone compared to mitoxantrone-plus-prednisolone in patients with mCRPC (3, 4). Since 2010, several new agents have been shown to prolong overall survival in men with mCRPC after docetaxel treatment (Table I) (5-8). These new agents have significantly improved the outcomes of men with mCRPC, however, there are a proportion of patients who do not respond to a particular therapy. For example, in the Cou-301 trial, only 38% of patients in the abiraterone arm had a PSA and/or radiological response (5). It is reasonable to assume there are a significant number of patients on abiraterone who do not respond to treatment, develop worsening disease-related symptoms, suffer a fall in performance status and as a consequence are not fit enough for other potentially disease-modifying therapy. A pragmatic method of identifying patients unlikely to benefit from a particular treatment would have meaningful clinical application.

A small number of studies have reported potential laboratory and clinical predictors of response to abiraterone. A pre-treatment neutrophil to lymphocyte ratio (NLR) >5 and lactate dehydrogenase level (LDH) >220 U/l may be associated with a lack of response to abiraterone (9-11). There is evidence that androgen receptor isoform encoded by splice variant 7 (AR-V7) lacks the ligand-binding domain and remains constitutively active as a transcription factor; detection of AR-V7 in circulating tumor cells from patients with mCRPC may be associated with resistance to abiraterone (12). These findings require large-scale prospective validation, and the use of genetic predictors of response to treatment in mCRPC is likely to be some way off in routine clinical practice. Therefore, there is a need for a practical method of identifying patients who are unlikely to respond to a particular treatment so that a more appropriate therapy can be used.

Bicalutamide is an oral anti-androgen that works by preventing the binding of testosterone to the AR (13). Abiraterone is an inhibitor of cytochrome *P450 17A1* (CYP17A1) that impairs AR signaling by depleting adrenal and intra-tumoral androgens (14, 15). Both bicalutamide and abiraterone act *via* the AR, albeit in different ways.

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Table I. *Key trials in metastatic castration-resistant prostate cancer (mCRPC).*

Trial (ref)	Drug	Setting	HR	OS (months)
TAX 327 (8)	3-Weekly docetaxel	mCRPC	0.79	19.2
	Mitoxantrone			16.3
TROPIC (8)	Cabazitaxel	Post-docetaxel	0.70	15.1
	Mitoxantrone			12.7
COU-301 (5)	Abiraterone/prednisolone	Post-docetaxel	0.74	14.8
	Prednisolone			10.9
AFFIRM (6)	Enzalutamide	Post-docetaxel	0.63	18.4
	Placebo			13.6
IMPACT (7)	Sipuleucel-T	Post-docetaxel	0.78	25.8
	Control			21.7
ALSYMPCA (36)	Radium 223	Post-docetaxel	0.70	14.1
	Placebo			11.3
COU-302 (26, 27)	Abiraterone/prednisolone	mCRPC (pre-docetaxel)	0.81	34.7
	Prednisolone			30.3
PREVAIL (37)	Enzalutamide	mCRPC (pre-docetaxel)	0.70	32.4
	Placebo			30.4

Therefore, we hypothesized that i) response to bicalutamide may predict response to abiraterone; and ii) response to any line of previous treatment may predict response to abiraterone.

We performed a detailed analysis of patients with mCRPC receiving multiple lines of therapy in order to attempt to identify those who have limited benefit from abiraterone.

Patients and Methods

A retrospective analysis of 47 consecutive eligible patients with mCRPC treated in a single cancer Centre was conducted. Patients were eligible to participate in the study if they had metastatic disease, histologically-confirmed prostate cancer (or a PSA >50 ng/ml and a malignant-feeling prostate). All patients included were treated sequentially with androgen deprivation, bicalutamide (and bicalutamide withdrawal), docetaxel plus prednisolone, and then abiraterone. All patients were treated with LHRHa to achieve castration levels of testosterone (<0.7 nmol/l). Data were collected on patient and disease demographics, treatment received and response.

PSA response was defined as any decrease in the PSA concentration from the pretreatment baseline PSA value, confirmed with a second value a minimum of 3 weeks later. Disease progression was defined as two consecutive increases in the PSA concentration over the nadir with a minimum rise of 5 ng/ml, or radiographic evidence of disease progression without PSA progression and a serum testosterone level of <0.7 nmol/l.

In the absence of a standardised definition of 'short' or 'long' duration of response to a line of therapy, we divided the patients into two groups based on our clinical experience. Response to androgen deprivation was categorized into those who responded for >18 months, and those who responded for ≤18 months. Docetaxel response was categorized into those who responded for >6 months and those who responded for ≤6 months. Bicalutamide responders were defined as achieving any decrease in the PSA concentration from the pre-treatment baseline PSA value, confirmed with a second value a minimum of 3 weeks later. Bicalutamide non-responders were defined as all other patients not falling into the 'responder' category.

Kaplan–Meier estimation of median progression-free survival (PFS) and overall survival (OS), and comparison of the sub-groups (defined above) using log-rank analysis was performed using SPSS Statistics (IBM, Armonk, New York, USA).

Results

The demographics of the patients included in the study are shown in Table II. At the time of the analysis, 38 patients had died. The median follow-up was 58.8 months (range=21.5-164.0 months). Patients whose line of therapy was stopped due to reasons other than progression were excluded from subgroup analysis. Reasons for switching to the next line of therapy prior to relapse were: neutropenic sepsis, intolerance to therapy, chemotherapy reaction, patient choice and orchidectomy.

Progression-free survival (Figure 1). The median PFS considering the whole cohort from commencement of abiraterone was 162 days (5.3 months). Men who responded to LHRHa for >18 months had a significantly longer PFS than men who responded for ≤18 months (279 days *vs.* 118 days, $p=0.018$). A similar effect was seen for bicalutamide responders compared to non-responders (196 days *vs.* 91 days, $p=0.003$), and in the >6-month docetaxel responders compared to the ≤6-month docetaxel responders (294 days *vs.* 102 days, $p<0.001$).

Overall survival (Figure 1). The median OS for the whole cohort from commencement of abiraterone was 637 days (21.0 months) Men who responded to LHRHa for >18 months had a significantly longer OS than men who

Table II. *Patients' demographics*.

Characteristic	Median	Range
Age at diagnosis of metastatic disease	67.6 years	51.2-81.1 years
PSA at presentation	52 ng/ml	6.5-2937 ng/ml
Gleason score	n	%
6	1	2.1
7	15	31.9
8	9	19.1
9	11	23.4
10	2	4.3
No histology	9	19.1
Duration of LHRHa response	15.4 months	2.7-126.6 months
Duration of bicalutamide response	4.7 months	0-49.1 months
Cycles of docetaxel	6 cycles	1-14 cycles
Time to PSA progression post docetaxel	7.45 months	0-19.2 months

PSA: Prostate-specific antigen; LHRHa: luteinising hormone-releasing hormone agonist.

Table III. *Median progression-free survival (PFS) and median overall survival (OS) from commencement of abiraterone therapy according to response to: luteinizing hormone-releasing hormone agonists (LHRHa); bicalutamide and docetaxel*.

Factor		Number of patients	Median PFS (days)	Log-rank *p*-value	Median OS (days)	Log-rank *p*-Value
LHRHa response	≤18 Months	29	118	$p=0.018$	348	$p=0.016$
	>18 Months	18	279		815	
Bicalutamide	Non-responders	16	91	$p=0.003$	413	$p=0.009$
	Responders	27	196		752	
Docetaxel response	≤6 Months	20	102	$p<0.001$	325	$p=0.04$
	>6 Months	25	294		727	

responded for ≤18 months (814 days *vs*. 348 days, $p=0.016$). The >6-month docetaxel responders had a significantly longer OS compared to ≤6-month responders (727 days *vs*. 325 days, $p=0.04$). The most significant difference in OS was seen in bicalutamide responders compared to non-responders (752 days *vs*. 413 days, $p=0.009$).

Discussion

Patients were treated sequentially with LHRHa, bicalutamide, bicalutamide withdrawal, docetaxel and then abiraterone. This retrospective study shows patients with shorter response duration to prior treatments, and in particular non-responders to bicalutamide, have minimal response to abiraterone treatment.

Anti-androgens first developed to treat prostate cancer, such as bicalutamide, work by targeting the AR. The precise mechanism of action is not known, but there is evidence to suggest bicalutamide antagonises the AR by accessing an additional binding pocket adjacent to the hormone-binding domain (HBD). This distorts the HBD, disrupting ligand binding (16). The AR plays a pivotal role in mCRPC. The AR is a nuclear receptor, which responds to the hormones testosterone and dihydrotestosterone by modulating gene expression in a variety of cells, including prostate tissue (16). Studies have suggested that progressive disease as evidenced by rising serum PSA during ADT reflects activation of AR transcriptional activity (17). There are several mechanisms that result in post-castration activation of the AR (18). These include incomplete blockade of AR-ligand signaling, *AR* mutations, *AR* amplifications, aberrant AR co-regulator activities and development of *AR* splice-variants (17, 18). In addition, evidence suggests that intratumoral levels of testosterone and dihydrotestosterone in patients with mCRPC are higher than serum levels, and similar to levels found pre-castration (19). There is also evidence to show that prostate cancer may become androgen-independent through inhibition of specific genes (20), resulting in transactivation of AR signalling.

Mechanisms of resistance to bicalutamide include changes in the structure of the HBD of the AR (21), and *AR* gene amplification (22). There is evidence that *AR* gene

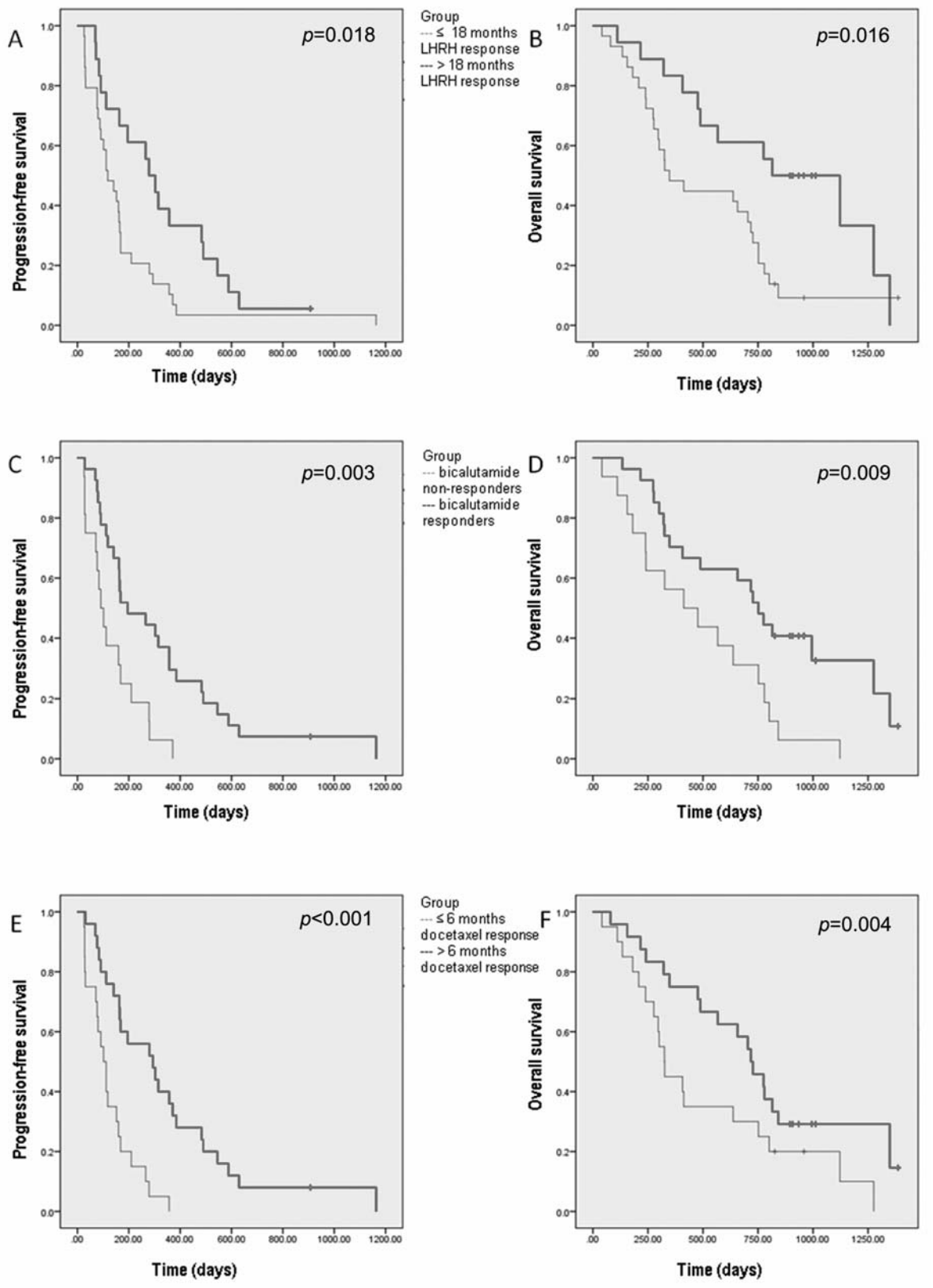

Figure 1. *Kaplan–Meier estimation of progression-free survival (A, C, E) and overall survival (B, D, F) by response to luteinizing hormone-releasing hormone agonists (LHRHa) (A, B), bicalutamide (C,D), and docetaxel (E,F).*

amplification is associated with greatly elevated serum PSA concentrations due to up-regulation of the *PSA* gene (23). Clinically, distinction between the two resistance mechanisms might be made by analyzing PSA and LDH levels. A high level of LDH is associated with a high tumor burden (24), and likely with high serum PSA levels. Therefore, a highly elevated level of serum PSA in the setting of a normal or only slightly elevated level of LDH might indicate *AR* gene amplification as the likely mechanism of bicalutamide resistance, rather than HBD structural change. Increasing the dose of bicalutamide may overcome resistance due to *AR* amplification, but this is likely to be associated with excessive drug-related toxicity, and therefore is not routine in clinical practice.

The second drug included in the treatment paradigm for patients in this study was docetaxel. This is a taxane chemotherapy, which acts by reversibly binding to microtubules, resulting in a decrease in cell-free tubulin and thus inhibition of mitotic cell division and initiation of apoptosis. Resistance to docetaxel is multi-factorial, and it is well-known that a dominant mechanism of resistance is *via* the drug efflux pump p-glycoprotein (25).

Abiraterone is a licensed oral hormonal therapy for the treatment of mCRPC. It is a specific inhibitor of CYP17A1 (19), which is a rate-limiting enzyme in androgen biosynthesis. Abiraterone suppresses androgen production in all tissues, including the adrenal gland and testes (19). In men with mCRPC, abiraterone has been shown to be beneficial in the pre- (26, 27) and post-docetaxel (5) setting. However, a proportion of men do not benefit from abiraterone. There are likely to be several mechanisms of resistance to abiraterone, including an increase in intra-tumoral androgen synthesis (28), and increased expression of *AR* variants (29). In addition, overexpression of CYP17A1 leading to increased synthesis of androgens has been shown to occur in patients receiving abiraterone (29). Expression of androgen-regulated genes may be driven by alternative steroid receptors such as the glucocorticoid receptor (30, 31).

Routine clinical application of a molecular-based test to predict response to abiraterone is not yet on the horizon. Antonarakis *et al*. have reported that the detection of the splice variant AR-V7 in circulating tumor cells from patients with mCRPC may be associated with resistance to abiraterone (12). However, these findings require large-scale prospective validation. Afshar *et al*. conducted an analysis of 61 patients treated with abiraterone to identify predictors of response (32). Three independent predictors of OS were identified: duration of response to ADT, performance status and baseline haemoglobin level (32). Other investigators have reported that a pre-treatment NLR >5 and LDH >220 U/l may be associated with a lack of response to abiraterone (9-11). It may be that using pre-treatment LDH in combination with response to prior therapy may allow a more robust predictive model of abiraterone response to be developed, however, in our retrospective study, LDH was not routinely measured for any patient, and we were unable to test this hypothesis.

In the absence of any validated predictors of response to abiraterone, we set out to look for pragmatic clinical predictors that could easily be applied in the clinic to guide us in deciding the most appropriate treatment. These predictors might facilitate selection of alternative therapies, such as second-line chemotherapy, immunotherapy, enzalutamide or radium-223, for patients with a low chance of response to abiraterone. In our experience, pragmatic clinical predictors of minimal response to abiraterone were: <18-month response to LHRHa, <6-month response to docetaxel chemotherapy, and non-response to bicalutamide.

All three of these predictors were associated with a statistically significant shorter PFS and OS on abiraterone. The most significant predictor of poorer survival with abiraterone was a lack of response to bicalutamide. Both bicalutamide and abiraterone act *via* the AR, making this observation biologically plausible. It is less obvious why a limited response to docetaxel predicts a poor response to abiraterone. Seemingly, these drugs have difference mechanisms of action and different resistance mechanisms. There are, however, pre-clinical data to suggest cross-resistance between docetaxel and abiraterone (33). In addition, phase II data from clinical trials show greater activity of abiraterone when used before chemotherapy compared to its use after chemotherapy (34), which suggests there may be a common mechanism of action.

Enzalutamide is an AR signaling inhibitor licensed for use in mCRPC. Our observed predictors of response to abiraterone might be applicable to enzalutamide. Enzalutamide exerts its activity by binding avidly to the ligand-binding domain of the AR, competing with and displacing testosterone and dihydrotestosterone, while also inhibiting translocation of the AR into the nucleus and impairing transcriptional activation of androgen-responsive target genes (6, 35). Studies have already shown that overexpression of CYP17A1 (or other steroidogenic enzyme) occurs both in patients receiving abiraterone and those receiving enzalutamide (12). In addition, the detection of the AR-V7 splice variant in circulating tumor cells from patients with mCRPC has been associated with resistance to both abiraterone and enzalumatide (12).

Our findings suggest there may be relatively simple clinical predictors of response that can be used to select treatment for patients with mCRPC. We report that no response to bicalutamide may be a good predictor of poor outcome in terms of OS with use of abiraterone in the post-chemotherapy setting. It will be interesting to see whether this finding is replicated when abiraterone is given before chemotherapy in mCRPC. These findings need validation

in larger studies, and we are currently looking at whether similar clinical predictors can be used to predict response to enzalutamide after docetaxel treatment in men with mCRPC.

In conclusion, this study identified pragmatic clinical parameters that predict minimal response to abiraterone, in particular a significantly worse OS in previous non-responders to bicalutamide.

Conflicts of Interest

RSD received an educational grant from Astellas and Sanofi-Aventis. CS received a grant to support data collection for other projects from Atsellas, and honoraria (advisory board) from Pfizer. JT received honoraria (advisory board) from Astellas, Bayer, Jansen, and honoraria (educational meetings) from Jansen, Astellas and Otsuka. MB received honoraria (educational meetings) from Leo, GSK. JS received an educational grant from Janssen, and honoraria from Janssen and Astellas. JFL received honoraria (advisory board) from Astellas, Sanofi-Aventis, Janssen, and honoraria (educational meetings) from Astellas and Sanofi-Aventis.

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