Third-line Enzalutamide Following Docetaxel and Abiraterone in Metastatic Castrate-resistant Prostate Cancer

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Abstract. *Background: There are no published randomised trials on the efficacy of enzalutamide against metastatic castrate-resistant prostate cancer (mCRPC) after docetaxel and abiraterone. We evaluated the activity of third-line enzalutamide in men with mCRPC after docetaxel and abiraterone. Patients and Methods: Progression-free (PFS) and overall (OS) survival from the start of enzalutamide were compared according to response to abiraterone in men with mCRPC treated at a single cancer centre. Results: Median PFS and OS for the whole 34-patient cohort from starting enzalutamide were 2.7 months (95% confidence interval=1.4-4.0 months) and 10.4 months (95% confidence interval=9.0-11.7 months). There was no significant difference in PFS and OS in patients according to prostate-specific antigen response to abiraterone (≥50% vs. <50%, ≤ or >6 months). Conclusion: In mCRPC, enzalutamide has modest activity after docetaxel and abiraterone. Response to previous abiraterone is not predictive of subsequent enzalutamide response.*

The publication of the TAX 327 trial led to docetaxel plus prednisone becoming the first-line standard-of-care in patients with metastatic castrate-resistant prostate cancer (mCRPC) (1). Subsequently there have been several newer agents that have been shown to prolong overall survival (OS) in men with mCRPC who have previously received docetaxel (2-6). It is not clear how best to sequence these treatments. In addition, it is unknown whether the survival benefits seen with these newer therapies are cumulative.

Abiraterone is an oral inhibitor of cytochrome *P450* 17A1 enzyme, which inhibits production of androgens. The COU-301 trial showed a 3.9-month improvement in median OS in patients with mCRPC treated with abiraterone plus prednisolone compared to those treated with prednisolone alone in the post-docetaxel setting (2).

Enzalutamide is an oral androgen receptor signaling inhibitor. In the AFFIRM trial, patients with mCRPC receiving enzalutamide in the post-docetaxel setting had a 4.8-month improvement in median OS compared to patients randomised to receive placebo (6).

There are no published randomised trials looking at the efficacy of enzalutamide after progression on abiraterone in men with mCRPC who have previously received docetaxel. We carried out a retrospective review of men with mCRPC who had been treated with docetaxel then abiraterone followed by enzalutamide to evaluate response.

Patients and Methods

A retrospective analysis of consecutive patients with mCRPC treated at a single cancer centre was conducted. Patients were deemed eligible to be included in the study if they had metastatic disease, histologically confirmed prostate cancer (or a prostate-specific antigen (PSA) >50 ng/ml and a clinically malignant prostate). Patients had to be treated sequentially with androgen deprivation, bicalutamide initiation (and withdrawal if previous response), docetaxel plus prednisolone, abiraterone then enzalutamide. All patients were castrated either surgically or chemically with luteinising hormone-releasing hormone agonists (LHRHa) to achieve castrate levels of testosterone (<0.7 nmol/l). The following data were collected: patient and disease demographics, treatment received, progression-free (PFS) and overall (OS) survival from the start of enzalutamide treatment.

PSA response was defined as any decrease in the PSA concentration from the pre-treatment 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 (7).

Kaplan-Meier estimation of median PFS and OS was carried out using SPSS Statistics (IBM Armonk, NY, USA). PFS and OS were compared according to the response to abiraterone using log-rank analysis. In the absence of a standardised definition of a long or short duration of response, patients were grouped according to whether they had a response to abiraterone of ≤6 months or >6 months. They were also grouped according to magnitude of PSA

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Table I. *Patients' characteristics*.

Characteristic	Finding	
Median (range) age at diagnosis of metastatic disease, years	69 (50-78)	
PSA at presentation (median, range)	52 (9.5-3500)	
Gleason score	n	%
6	2	5.9
7	7	20.6
8	4	11.8
9	13	38.2
10	1	2.9
No histology	7	20.6
Median (range) cycles of docetaxel, n	6 (1-12)	
Median (range) duration of abiraterone, months	5.9 (1.0-18.4)	

response to abiraterone: <50% or ≥50%. The level of significance was set at $p \leq 0.05$ for hypothesis testing.

Results

In total, 34 patients fulfilled the inclusion criteria and were included in this study. Patient demographics are shown in Table I. At the time of analysis, 14/34 (41.2%) patients were alive. The median follow-up was 11.6 months (range=7.2-33.1 months).

Median OS from start of enzalutamide. The median OS for the whole 34-patient cohort from starting enzalutamide was 10.4 months [95% confidence interval (CI)=9.0 -11.7 months).

In the 18/34 (53%) men who had ≤6-month response to previous treatment with abiraterone, the median OS was 10.6 months (95% CI=8.6-12.5 months). In the 16/34 (47%) men who had >6-month response to abiraterone, the median OS was 7.3 months (95% CI=1.8-12.8 months). There was no significant difference in the median OS between the two groups (p=0.499) (Figure 1A).

In the 18/34 (53%) men who previously had ≥50% PSA response to abiraterone, the median OS was 9.6 months (95% CI=6.5-12.8 months). In the 16/34 (47%) men who had a <50% PSA response to abiraterone, the median OS was 10.6 months (95% CI=7.1-14.0 months). There was no significant difference in median OS between the two groups (p=0.311) (Figure 1B).

Median PFS from start of enzalutamide. The median PFS for the whole 34-patient cohort from starting enzalutamide was 2.7 months (95% CI=1.4-4.0 months).

In the 18/34 (53%) men who had ≤6-month response to previous treatment with abiraterone, the median PFS was 2.7 months (95% CI=2.3-3.1 months). In the 16/34 (47%) men who had >6-month response to abiraterone, the median PFS was 2.3 months (95% CI=0-4.8 months). There was no significant difference in median PFS between the two groups (p=0.397) (Figure 2A).

In the 18/34 (53%) men who previously had ≥50% PSA response to abiraterone, the median PFS was 2.6 months (95% CI=0.4-4.8 months). In the 16/34 (47%) men who had a <50% PSA response to abiraterone, the median PFS was 2.7 months (95% CI=1.6-3.8 months). There was no significant difference in the median PFS between the two groups (p=0.738) (Figure 2B).

Discussion

Both enzalutamide and abiraterone have been shown to prolong PFS and OS in the second-line setting in men with mCRPC whose has progressed after docetaxel chemotherapy (2, 6). The magnitude of benefit from using enzalutamide as third-line treatment after first-line docetaxel then second-line abiraterone has not been established in randomised trials, and the published data are limited to a relatively few number of non-randomised patient series. Our study adds to the cumulative knowledge on the activity of third-line enzalutamide, and is instructive as none of the patients included went on to receive cabazitaxel, radium-223 or sipuleucel-T, the other therapeutic interventions which have been shown to prolong survival in mCRPC (3-5). It is unlikely then that subsequent treatment after progression on enzalutamide in our cohort significantly affected OS.

In our cohort of 34 men with mCRPC previously treated with docetaxel and abiraterone, the median PFS from the start of third-line enzalutamide treatment was 2.7 months and the median OS 10.4 months. We found that neither PSA response to abiraterone nor duration of response to abiraterone were useful predictors of outcome with enzalutamide. There exist several retrospective case series that have reported on a similar treatment paradigm to ours, and it is useful to look at these in the context of our findings. Caffo *et al*. had the largest published cohort, and reported on 260 patients who

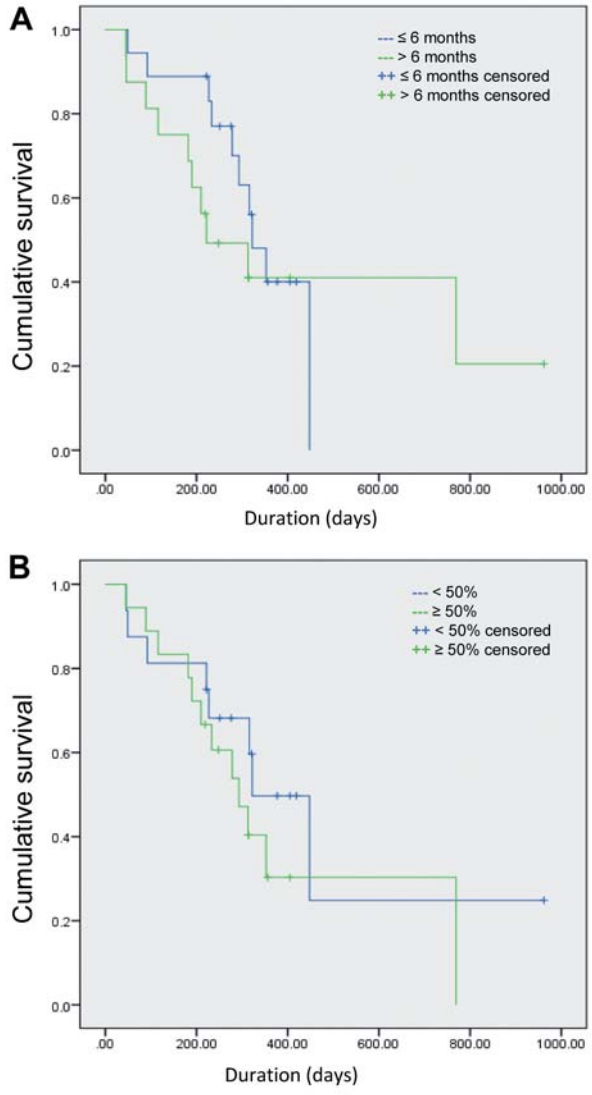

Figure 1. *Overall survival from start of enzalutamide, grouped according to duration of previous abiraterone response (A) and magnitude of previous abiraterone response (B)*

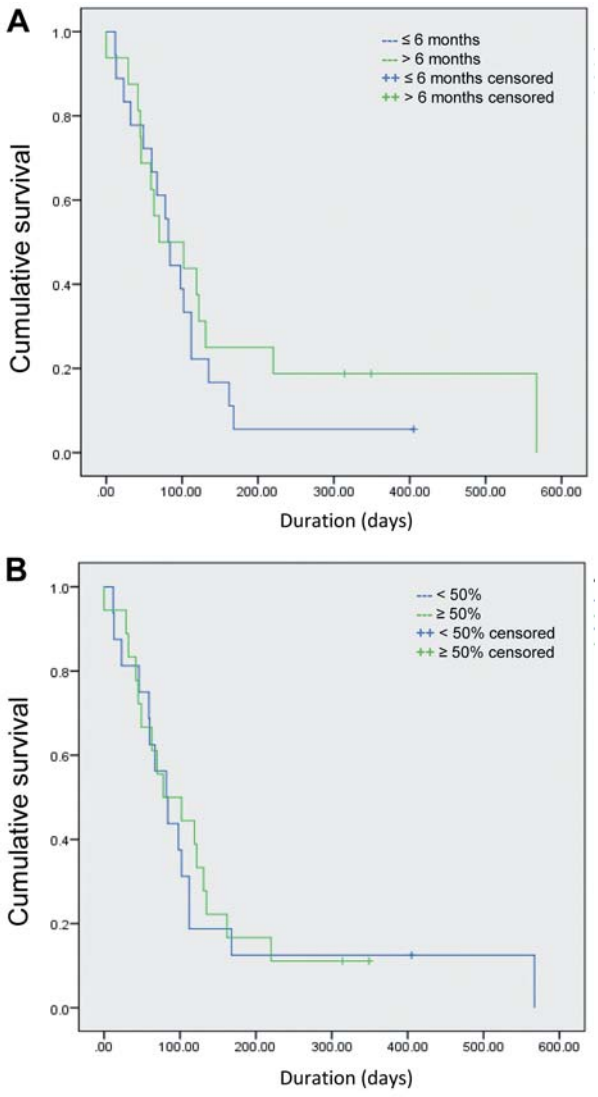

Figure 2. *Progression-free survival from start of enzalutamide, grouped according to duration of previous abiraterone response (A) and magnitude of previous abiraterone response (B).*

received docetaxel followed by various combinations of second-, third- and fourth-line treatment. Those patients receiving abiraterone then enzalutamide, or enzalutamide then abiraterone as second- and third-line treatment had a median PFS of 4 months, and median OS of 11 months, which are very similar to our findings. The authors reported no significant difference in outcomes whether enzalutamide or abiraterone was used first (8). There are five other retrospective studies where patients had similar treatment regimen to our cohort. Schrader *et al*. reported on 35 patients, and the median OS from the start of enzalutamide was 7.1 months (9). In the retrospective series of 39 patients reported by Bianchini *et al*., 5/39 (12.8%) patients had a PSA decline of ≥50% on enzalutamide, and the median duration of treatment was 2.9 months. The median OS was not reported. Of the 39 patients, 37 had evaluable PSA results when on abiraterone. In total, 15/37 had at least a 50% PSA decline on abiraterone. Of these 15 patients, 7/15 (46.7%) patients achieved a ≥30% PSA decline on enzalutamide, whilst 2/15 (13.3%) patients achieved a ≥50% PSA decline on enzalutamide. Of the 22/37 patients with a PSA decline of <50% on abiraterone, 8/22 (36.4%) had a ≥30% reduction in PSA on enzalutamide, and 2/22 (9.1%) had a ≥50% PSA decline. The authors concluded there was no significant

association between previous response to abiraterone and subsequent response to enzalutamide, which our findings support (10). Cheng *et al*. reported on a large retrospective study of 310 patients with mCRPC who had received enzalutamide. Of these, 165 patients received abiraterone and docetaxel prior to enzalutamide. It is unclear from the article whether patients received abiraterone then docetaxel, or *vice versa*. The authors reported that 24% of patients had a ≥30% PSA response to enzalutamide, and 17% had a ≥50% PSA response to enzalutamide. Their conclusion is corroborated by our findings and the Bianchini series; response to abiraterone was not robustly associated with response to subsequent enzalutamide (11). Two further retrospective series have reported similar results to our study: Zhang *et al*. reported on 19 patients with mCRPC who received treatment as per our paradigm. The median PFS in those 19 patients after starting enzalutamide was 2.8 months and the median OS was 9.6 months (12). Brasso *et al*. reported on data from 137 patients who accessed enzalutamide *via* a compassionate-use programme. The median duration of enzalutamide treatment was 3.2 months, and the median OS from the start of enzalutamide was 8.3 months (13).

Our findings are broadly in keeping with the results from other published retrospective series in which the median PFS from the start of enzalutamide ranged between 2.8 months and 4 months (2.7 months in our series), and the OS from the start of enzalutamide ranged from 7.1 months to 9.6 months (10.4 months in our series). Two series looked in detail at whether previous response to abiraterone predicted subsequent response to enzalutamide, and concluded, as we did, there was no significant association (10, 11). Our study is limited by its retrospective nature and small numbers of patients, but broadly supports the findings of similar published studies. In addition, compared to the AFFIRM trial results, which reported a 8.3 months PFS in patients with mCRPC treated with enzalutamide after docetaxel, clinical studies to date suggest more modest enzalutamide activity in patients with mCRPC previously treated with both docetaxel and abiraterone (6).

In summary, enzalutamide appears to have modest activity when used third-line in patients with mCRPC previously treated with docetaxel and abiraterone. Previous response to abiraterone does not seem to be a robust predictor of outcome with subsequent enzalutamide treatment. Larger prospective studies are now needed to inform optimal treatment sequencing in men with mCRPC.

Conflicts of Interest

Mr. Christian Smith received a grant from Astellas to support the data collection, and has received educational grants from Astellas and Sanofi-Aventis.

Dr. Rhian Davies has received educational grants from Astellas and Sanofi-Aventis.

Dr. Jason Lester has received educational grants and honoraria from Astellas, Sanofi-Aventis and Janssen.

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