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Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen

Critique of additional information submitted by Astellas

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

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ERG Critique

The Evidence Review Group (ERG) was requested by NICE to provide a critique of the additional information submitted by Astellas.

The additional information consists of 12 retrospective single arm studies, presented as four full papers and eight abstracts (one of the abstracts also included a conference poster). The studies looked at sequential use of enzalutamide following abiraterone.

Looking at the four full papers only, the general conclusion seems to be that evidence on the effectiveness of enzalutamide following abiraterone is limited:

- Schrader et al. 2013: Treatment with enzalutamide was associated with a low response rate in patients progressing after abiraterone treatment. Various experimental findings suggest that the expression of AR-LBD mutants or ARDLBD in CRPC might be responsible for the failure of both abiraterone and enzalutamide. Although cross-resistance between abiraterone and enzalutamide is a common phenomenon, it is not inevitable, and a small but significant number of patients can benefit from sequential treatment. Therefore, a more detailed and integrated analysis of AR signaling is necessary.

- Bianchini et al. 2013: In conclusion, enzalutamide has modest antitumour activity in advanced-stage CRPC patients when used after docetaxel and abiraterone. Larger prospective studies are now needed to provide further data regarding optimal treatment sequencing and the potential benefits of combing abiraterone and enzalutamide.

- Badrising 2013: In conclusion, patients in the current study who previously progressed on AA had a modest PSA response rate and limited survival on subsequent Enz treatment. PSA response on AA treatment did not seem to predict for Enz treatment outcome. PFS and OS were in the same range as those described in 2 cohorts of men with mCRPC who received AA after progressing on Enz. Data from these 3 studies suggest limited activity and no preference for either sequence of treatments. However, a recommendation on the sequencing of Enz and AA in the postdocetaxel setting cannot be made, because these data are only hypothesis generating. Further studies are needed to establish the sequence of treatments with these new drugs.

- Schmid et al. 2013: In this prospective analysis, the efficacy of enzalutamide therapy after taxane chemotherapy and abiraterone (DAE) was moderate in comparison to its use in earlier tumor stages. The median overall survival time was 7.5 months. These preclinical results do not support the consecutive use of abiraterone and enzalutamide (and vice versa), in our opinion. Therefore, a reasonable therapeutic strategy might be the alternating use of chemotherapy and antihormonal drugs.

Finally, the largest study was performed in 195 patients with mCRPC, 150 of whom had previously been treated with abiraterone (Cheng et al. 2014). This study provided a comparison of prior abiraterone treated patients and abiraterone-naive patients. Although, this comparison was not based on randomised groups and differences in results may be dependent on underlying differences in groups. The authors found:

> "Overall, 42% (76 of 183) of Enza-treated patients achieved a 30% or greater PSA decline, with 39% (58 of 150) response among prior Abi-treated patients and 55% (18 of 33) response among Abi-naïve patients. Of 79 patients who lacked significant response to prior Abi, 30% (25 of 79) achieved a 30% or greater PSA decline and 19% (15 of 79) achieved a 50% or greater PSA decline with subsequent Enza. Odds of achieving a 30% or greater PSA response on Enza was 2.3 times higher for Abi-naïve patients versus prior Abi-treated patients (95% CI 1.0–5.5, P=0.06) and 1.9 times higher for Abi-responders vs Abi-non-responders (95% CI 1.0–3.7, P=0.06) after adjusting for prior docetaxel and concurrent steroid use."

The authors' conclusion was: "In this multi-center retrospective study, 39% of patients achieved a 30% or greater PSA decline with Enza after prior Abi treatment. While the activity of Enza appears to be blunted in the post-Abi setting, PSA declines still occur in a meaningful proportion of patients. Notably, 30% of patients without significant response to prior Abi responded to subsequent treatment with Enza, suggesting a subset of men with distinct biological resistance pathways."

However, all studies are retrospective, have small patient numbers (11 studies with 23 to 75 patients and one study with 150 patients previously treated with abiraterone), have no control arm, short periods of follow-up and very little data on progression-free survival and/or overall survival. As such, these studies are not suitable for a proper analysis of the question under consideration: "Is there a difference in the effectiveness of enzalutamide in patients who have been treated with abiraterone compared to patients who have not previously been treated with abiraterone".

Overall, the ERG is of the opinion that there is insufficient evidence to say whether the effectiveness of enzalutamide is different following treatment with abiraterone. Although, preliminary evidence seems to suggest that this is possibly the case. Furthermore, it is unclear how any differences in clinical effectiveness of enzalutamide following abiraterone will affect the cost-effectiveness of enzalutamide.