Astellas Response to the NICE Appraisal Consultation Document (ACD)

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

Astellas welcomes the Committee's draft recommendation for the use of enzalutamide, and is generally satisfied that all of the relevant evidence has been appropriately interpreted. Many thanks for the opportunity to add some further clarifications at this stage of the appraisal.

Our response to the ACD is structured into two sections. Firstly, discussing the evidence presented in the ACD and whether any relevant information has been omitted from the evaluation. Secondly, an Appendix presents a small additional analysis to address a gap in the evidence identified by the Committee which will enable an evaluation of enzalutamide for patients who had received two or more courses of chemotherapy and for whom best supportive care would be the relevant comparator. We hope that this short addition to the evidence presented in our initial document will support a recommendation for using enzalutamide in all post-chemotherapy patients, as identified in the appraisal scope.

Section 1

- In section 3.22 the ACD confuses results from the interim and final analyses:

  "*It then fitted alternative parametric functions (exponential, Weibull, log-logistic, log-normal and gamma) to patient-level data for the placebo group in AFFIRM (representing best supportive care) and extrapolated the curves beyond the end of the trial, using the interim analysis cut-off date (25 September 2011) for overall survival, and the final cut-off date (16 December 2011) for progression-free survival*."

  This is incorrect and should state: "(...) *using the final cut-off date (16 December 2011) for overall survival, and the interim analysis cut-off date (25 September 2011) for progression-free survival*."

- The ACD mentions several times (section 3.28, 4.14 and 4.15) that no costs for hospitalisations were included in the model. This is incorrect: the model does include hospitalisation costs for adverse events (AEs) and skeletal related events (SREs). SRE costs included in the model were spinal cord compression, pathological bone fracture, radiation to the bone, and surgery to the bone. As discussed in the manufacturer submission section 7.5.7, the costs for spinal cord compression were included through HRG HC28b–Spinal Cord conditions with CC (NHS Trusts Non-Elective Inpatient Long Stay), at a cost per event of £6,047. Also the costs for pathological bone fracture (£5,042) and surgery to the bone (£3,888) were based on non-elective inpatient (long stay) HRG data. The Committee's concern that no costs for spinal cord compression were included in the model (section 4.14) is therefore not supported.

UK clinical experts indicated that hospitalisations would be mainly SRE related (with some additional hospitalisations due to AEs or end-of-life stays). As hospitalisation costs were included, the statement on a potentially increased ICER when including hospitalisation costs in section 4.15 of the ACD is incorrect.

- In section 4.8 the Committee concluded that it could not make any recommendations for enzalutamide for patients who had received two or more courses of chemotherapy and for whom best supportive care would be the relevant comparator. There is no clinical rationale why enzalutamide would work differently in patients who have received two or more courses of chemotherapy, and the exclusion of this artificial subgroup is only due to the restrictions of a previous appraisal. This subgroup was not identified during the scoping meeting with NICE, nor was it requested by the ERG during the clarification request. As mentioned in the ACD, only a very small proportion of the mCRPC population would have received two or more prior chemotherapies, and it would be an ethically appropriate decision to fund enzalutamide for these patients, with a very small budget impact. The Committee did not consider this subgroup as the submission only presented evidence for the total population. To allow the Committee an evaluation of enzalutamide in this group of patients, the appendix of this response document presents the cost-effectiveness results for this subgroup.

- In section 4.7 the ACD mentions the incidence of spinal cord compression as 8.3% of the people treated with enzalutamide and 7.3% of those who received placebo. It should be noted that these incidences do not take into account the difference in follow-up duration (total patient years, [redacted] for enzalutamide and [redacted] for placebo). The exposure adjusted incidence rate is stated in section 7.3.1.4 of the manufacturer submission as [redacted] events per patient year for enzalutamide and [redacted] events per patient year on BSC. When the exposure adjusted incidence rate for abiraterone was analysed through indirect comparison, this resulted also in [redacted] events per patient year.

- The modelling scenario preferred by the Committee is described in section 4.15 of the ACD and includes the following aspects:

  - OS for abiraterone modelled as a constant hazard ratio over time.
  - Equal 'on-treatment' utility gain for enzalutamide and abiraterone
  - The actual patient access scheme discount for abiraterone
  - Including hospitalisation costs

  As described in the previous sections, hospitalisation costs were included in the model. As none of the other modifications proposed by the Committee affect the comparison with BSC, it should be noted that the most plausible ICER for enzalutamide against BSC is the ICER presented in the manufacturer submission base case: £43,587 / QALY gained.

Appendix – additional analysis of patients who have received two or more prior courses of chemotherapy.

Following the recommendations of the Committee, a subgroup analysis was performed to represent patients who have received two or more courses of chemotherapy. In this subpopulation BSC is the only relevant comparator.

In line with the most plausible scenario described in section 4.15 of the ACD, no changes were made to the model. Also, in line with section 4.12 of the ACD, the on treatment utility gain for enzalutamide was maintained.

Methods

In line with the original model, Weibull curves were fit for placebo patients who had received two or more courses of chemotherapy. The Weibull intercept and scale were [redacted] and [redacted] resulting in [redacted] and [redacted]. This curve resulted in a median placebo OS of 12.8 months, compared to 13.0 months for the original curve based on the overall AFFIRM population.

For enzalutamide OS in the subgroup, the HR at the time of database lock was 0.656 (95% CI: [0.481; 0.895]).

Similarly, the placebo Weibull curve for TTD was derived: The Weibull intercept and scale were [redacted] and [redacted] resulting in [redacted] and [redacted]. This curve resulted in a median placebo TTD of 3.6 months, compared to 3.7 months for the original curve based on the overall AFFIRM population.

The enzalutamide TTD HR in the subgroup was [redacted].

The subgroup parameters were applied in the model using the Committees preferred assumptions.

Results

As shown in Table 1, patients in the subgroup have a lower life expectancy than the total population. In addition, as the efficacy of enzalutamide is lower in the subgroup with two or more prior chemotherapies, the difference in life years (LYs) gained is lower than in the base case, but at [redacted] discounted life years ([redacted]) still higher than 3 months.

As a result of the lower life expectancy, the time on treatment is also lower, resulting in lower technology acquisition costs for the subgroup. The incremental cost-effectiveness of enzalutamide vs. BSC in this population is £45,509, which is in line with the ICERs for other drugs accepted under the criteria for life extending drugs.

For mCRPC patients who have received two or more courses of chemotherapy, currently no treatment option is available. Enzalutamide meets all criteria to be considered by NICE under the Supplementary Advice on appraising EoL medicines for patients who received two or more courses of chemotherapy:

- **The treatment is indicated for patients with a short life expectancy, normally less than 24 months**
  As indicated by the median survival in the control arms of the COU-AA-301 study (25) and the AFFIRM study (3), patients currently treated with BSC have a short life expectancy of approximately one year. This is also confirmed by the median survival of 12.8 months in this subgroup.

- **The treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment**
  Enzalutamide showed an increase in median OS in the AFFIRM study of more than three months. In the subgroup analysis this translated into a gain of [redacted] or [redacted].

- **The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.**
  As indicated in the original MS, the potential patient population for enzalutamide in 2013 is estimated at 2,977 patients. Only a very small proportion of these patients would have received two or more prior chemotherapy regimens.

Table 1 - Cost-effectiveness results of enzalutamide vs BSC in the subgroup and the total population

	Two or more prior chemo		**Total population**	
	Enzalutamide	**BSC**	**Enzalutamide**	**BSC**
Technology acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]	[redacted]
QALYS	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]	[redacted]
ICER	**-**	**£45,509**	**-**	**£43,587**