KSR Critique of Astellas Response to the NICE Appraisal Consultation Document (ACD)

In response to the points raised by Astellas, we would like to add the following information:

Section 1

1. Section 4.3.2 (page 80) of the ERG report states:
   "The data cut-off used for the AFFIRM study is the IA analysis (25 September 2011) for all outcome measures [Scher 2012] with the exception of OS, where the database lock was used (16 December 2011)."

   However, the ACD (section 3.22) states:
   "(…) 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."

   Response:
   The ERG agrees with the correction proposed by the Manufacturer for section 3.22 of the ACD. The section: should be replaced with : *"(…) using the final cut-off date (16 December 2011) for overall survival, and the interim analysis final cut-off date (25 September 2011) for progression-free survival."*

2. Section 5.2.8 (page 118) of the ERG reports states:
   "No costs for hospitalisations were included in the base case. UK clinical experts confirmed that all hospitalisations would have been captured by AEs, SREs and terminal treatment costs."

   However, the ACD (section 3.28) states:
   "*No costs for hospitalisation were assumed in the model."*

   Response:
   The ERG agrees that hospitalisation costs are not separately included in the economic model but they are instead integrated through the costs of adverse events (AEs) and skeletal related events (SREs). This seems a reasonable approach.

3. Additional subgroup analysis for patients who had received two or more courses of chemotherapy.

   Response:
   The ERG has checked the additional subgroup analysis using the Manufacturer's base case model and Weibull parameters provided in the appendix of the Manufacturer's Response to the NICE ACD. The ERG has compared the deterministic results of the model with (deterministic) results provided by the manufacturer. The ERG notes that all results were the same, except for the fact

that the median placebo OS should be 12.3 months (instead of 12.8 months as written in the 'Methods' section of the Manufacturer's response to the ACD).

In addition, it should be made clear that the presented gain of 0.32 LY or 3.8 months provided by the Manufacturer (in the 'Results' section) is the discounted mean estimate for Enzalutamide versus placebo. The (undiscounted) median gain for this subgroup is 0.30 LY or 3.6 months. Table 1 presents the undiscounted/discounted mean and table 2 presents the undiscounted median overall survival based on Manufacturer's base case scenario for both the total population and the subgroup of patients who had received two or more courses of chemotherapy.

Table 1 - Mean overall survival in months as for the Manufacturer's base case scenario (undiscounted and discounted deterministic results)

	Total population			**Two or more prior chemo subgroup**		
	Enzalutamide	BSC	Abiraterone	Enzalutamide	BSC	Abiraterone
Mean OS (undiscounted)	[redacted]	[redacted]	[redacted]	17.7	13.7	15.1
Difference*		[redacted]	[redacted]		4.0	2.7
Mean OS (discounted)	[redacted]	[redacted]	[redacted]	17.1	13.4	14.7
Difference*		[redacted]	[redacted]		3.8	2.5

*Compared with Enzalutamide. Abbreviations: BSC: best supportive care.

Table 2 - Median overall survival in months as for the Manufacturer's base case scenario (undiscounted deterministic results)

	Total population			**Two or more prior chemo subgroup**		
	Enzalutamide	BSC	Abiraterone	Enzalutamide	BSC	Abiraterone
Median OS (undiscounted)	17.5	13.0	15.2	15.9	12.3	14.5
Difference*		4.5	2.3		3.6	1.4

*Compared with Enzalutamide. Abbreviations: BSC: best supportive care.

4. The percentages of spinal cord compression for patients treated with Enzalutamide and placebo mentioned in the ACD (section 4.7) correspond with the percentages in Table 15 of the MS (page 64) and Table 4.9 (page 580 of the ERG report).

<u>Response:</u>

Although it is not a factual error, the ERG agrees with Manufacturer's comment that it is better to compare incidence rates instead of percentages based on number of events unadjusted for follow-up duration. The economic model uses the incidence rates for skeletal related events (SREs) which are described by the Manufacturer in Table 51 of the MS (page 134) and in the response to the NICE ACD. The ERG's summary on the subject and the comment on the usage of such incidence rates for AEs and SREs can be found in section 5.2.6 (page 111) of the ERG report.

5. In the response to the ACD the Manufacturer states:
"(…) 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."

Response:
In section 4.15 of the ACD it is stated that:
"The Committee (…) agreed that modelling overall survival for abiraterone should assume a constant hazard ratio over time; and that the analysis should incorporate equal 'on-treatment' utility increases for enzalutamide and abiraterone, the actual patient access scheme discount for abiraterone, and hospitalisation costs. The Committee was aware that none of the analyses presented by the manufacturer or the ERG applied these assumptions and model inputs simultaneously."

The Manufacturer's base case scenario is not in concordance with the Committee's preferred modelling scenario (ACD section 4.15). The ERG base case was more in line with the Committee's preferred modelling scenario as equal 'on-treatment' utility increases for enzalutamide and abiraterone were assumed (in contrast with the manufacturer's base case assuming non-equal 'on-treatment' utility increases). In the light of the Committee preferred modelling scenario the ERG has modified the manufacturer's base case model to incorporate the following:

- Assuming a constant hazard ratio over time for abiraterone (overall survival)
- Incorporating equal 'on-treatment' utility increases for enzalutamide and abiraterone. The 'on-treatment' utility gain for abiraterone (0.04) was applied for both treatments as this was considered more conservative and entails a lower risk of double counting than applying the 'on-treatment' utility gain for enzalutamide ([redacted]).
- As the ERG is kept unaware of the actual patient access scheme (PAS) discount for abiraterone, the ERG is unable to exactly incorporate the modifications proposed by the Committee.
  [redacted].

Table 3 below presents (deterministic and probabilistic) results for total population and Table 4 presents (deterministic and probabilistic) results for the subgroup of patients who had received two or more courses of chemotherapy.

Table 3 –Cost-effectiveness results for the total population as for the Committee's preferred scenario

Treatment	Expected outcomes		Enzalutamide compared to		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Committee preferred scenario for the total population (deterministic results)					
Enzalutamide	[redacted]	[redacted]			
Abiraterone*	[redacted]	[redacted]	[redacted]	[redacted]	£22,604**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£45,898
Committee preferred scenario for the total population (probabilistic results)					
Enzalutamide	[redacted]	[redacted]			
Abiraterone*	[redacted]	[redacted]	[redacted]	[redacted]	£22,302**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£45,764

Abbreviations: BSC: best supportive care. * In section 4.3 of the ACD Abiraterone was not considered as a comparator for the subgroup of patients who have received 2 or more chemotherapy regimens. **Extendedly dominated.

Table 4 –Cost-effectiveness results for the subgroup of patients who had received two or more courses of chemotherapy as for the Committee's preferred scenario

Treatment	Expected outcomes		Enzalutamide compared to		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Committee preferred scenario for the subgroup population (deterministic results)					
Enzalutamide	[redacted]	[redacted]			
Abiraterone*	[redacted]	[redacted]	[redacted]	[redacted]	£22,866**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£48,020
Committee preferred scenario for the subgroup population (probabilistic results)					
Enzalutamide	[redacted]	[redacted]			
Abiraterone*	[redacted]	[redacted]	[redacted]	[redacted]	£22,100**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£47,321

Abbreviations: BSC: best supportive care. * In section 4.3 of the ACD Abiraterone was not considered as a comparator for the subgroup of patients who have received 2 or more chemotherapy regimens. **Extendedly dominated.