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in collaboration with:

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ADDENDUM TO
Abiraterone for the treatment of chemotherapy naïve metastatic castration-resistant prostate cancer

Addendum by the ERG in response to comments raised during ACD consultation on the benefit of delaying chemotherapy

(exploratory analyses requested by Committee Chair)

1). We recall an issue raised at the first ACM that in the model people spent longer in the treatment phase where they had stopped abiraterone but had not yet started docetaxel than would be expected in clinical practice.

a) Were people experiencing the lower utility associated with being symptomatic before receiving docetaxel for the entire 6 months?

In the model, patients indeed experience a lower utility of [redacted] during the BSC (pre-docetaxel) phase (between 1st line active treatment end and docetaxel start) compared to the utility during 1st line active treatment ([redacted]) and docetaxel treatment ([redacted]) (MS Table 66).

b) Could this affect whether the model captures the benefits of delaying chemotherapy?

If patients reach the 'BSC (pre-docetaxel)' phase (time between end of 1st line active treatment and docetaxel start) in the model, they spend on average [redacted] months in this phase (see Table 1; [redacted] year ([redacted] months) for AAP and [redacted] year ([redacted] months) for BSC). Clinical experts mentioned, during the first ACM meeting, this is most likely to be approximately one week in practice. Although this decreases face validity, it does not impact the ICER very much as the mean survival in the 'BSC (pre-docetaxel)' phase is almost equal for both comparators ([redacted] for AAP and [redacted] for BSC; calculated based on Table 1).

Table 1: Summary of proportion of patients in and respective duration in each treatment phase (MS Table 68)

Treatment phase	**AAP % in each treatment phase[a]**	**AAP Mean duration (undiscounted)**	**BSC % in each treatment phase[a]**	**BSC Mean duration (undiscounted)**
Pre-docetaxel				
1st line active treatment	[redacted]	[redacted]	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
On-docetaxel				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
BSC (post-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
Post-docetaxel				
Post-docetaxel active treatment	[redacted]	[redacted]	[redacted]	[redacted]

BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Percentage (among the total starting population) who reach each 'state' in the treatment pathway.

2) Explain the extent to which the model already captures benefits of delaying chemotherapy

Patients spent a total of [redacted] and [redacted] years (undiscounted; see Table 2) in the pre-docetaxel phase for AAP and BSC respectively (difference of 11.9 months). During this phase AAP gains more QALYs compared to BSC, while in the two later phases (on-docetaxel and post-docetaxel) BSC gains more QALYs compared to AAP (see MS Table 70). The QALY gain (of 0.71; discounted) in the pre-docetaxel phase for AAP is partly due to the 'AAP on-treatment utility increment'. However, when removing this utility increment, most of the QALY gain in the pre-docetaxel phase is maintained ([redacted]; calculated from the model). The pre-docetaxel QALY gain for AAP versus BSC is thus mainly due to the differences in time spent in that phase (and the accompanying differences in utility scores between the phases). Moreover, the main difference in the pre-docetaxel phase between AAP and BSC (in terms of mean time spent in a phase) is due to the difference in time on 1st line active treatment ([redacted] months (out of 11.9 months); undiscounted see Table 1). As patients in the AAP arm spend more time in the 1st line active treatment phase (benefiting from a higher utility), the benefit of delaying docetaxel is incorporated and probably one of the main drivers behind the QALY gain for AAP (given that the total QALY gain is [redacted]; see MS Table 70).

Table 2: Summary of proportion of patients and respective duration in each treatment phase (ERG report Table 5.11)

Survival (years)	**Mean survival of those who entered the phase**		**% entered this phase**	**Mean survival**	
	Undiscounted	**Discounted**		**Undiscounted**	**Discounted**
AAP					
Pre-docetaxel survival[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-docetaxel survival[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-docetaxel survival[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival (total LYs)				[redacted]	[redacted]
BSC (PP)					
Pre-docetaxel survival[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-docetaxel survival[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-docetaxel survival[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival (total LYs)				[redacted]	[redacted]
Incremental (AAP - BSC (PP))					
Pre-docetaxel survival[a]	0.99	0.83	0%	0.99	0.83
On-docetaxel survival[b]	-0.18	-0.18	-6%	-0.17	-0.16
Post-docetaxel survival[c]	-0.04	-0.05	-4%	-0.05	-0.05
Overall survival (total LYs)				**0.77**	**0.62**

Source: MS[1] Table 69 and DES model

AAP, abiraterone acetate plus prednisolone; LY, life year; BSC, best supportive care; PP, placebo plus prednisolone.

[a] Includes pre-docetaxel treatment and BSC before docetaxel treatment start

[b] Includes time between docetaxel treatment end and post-docetaxel active treatment start or death before post-docetaxel active treatment start

[c] Includes time after post-docetaxel active treatment start

3) Explain how your proposed threshold analysis works, the results and any limitations

The benefits of delaying docetaxel are reflected in the model as the contrast between the quality of life during the pre-docetaxel and on-docetaxel phases. In the analyses described below, the utility values for these phases are varied to extreme values to assess the impact of increasing the benefits of delaying docetaxel.

In the first analysis the 'Post-ADT baseline' utility of [redacted] is increased to [redacted], resulting in a utility of 1.0 for AAP (by adding the 'AAP on-treatment utility increment') and [redacted] for BSC while on 1st line active treatment. In this analysis, the QALY gain for AAP in the pre-docetaxel phase would increase to [redacted] and the deterministic ICER would decrease to £38,851 (Table 3). Additionally, in case the BSC (pre-docetaxel) utility of [redacted] would be increased to 1.0 (next to a 'Post-ADT baseline' utility [redacted]), this would result in a similar ICER (£38,950).

In the second analysis, the 'on-docetaxel' utility of [redacted] is decreased to 0.0. In this analysis, the on docetaxel QALY gain of -0.10 in the base case (for AAP versus BSC) would increase to [redacted] resulting in an ICER of £44,466.

Thirdly, if both the 'Post-ADT baseline' utility would be increased to [redacted] and the 'on-docetaxel' utility would be decreased to 0.0, this resulted in an ICER of £37,257.

In conclusion, the pre-docetaxel and on-docetaxel health state utility values should be increased/decreased to implausible values (i.e. larger than 1.0 and/or lower than 0.0) in order for AAP to be cost-effective.

When interpreting these additional analyses (and response to question 2), it is important to consider that AAP both increases the time to docetaxel treatment (i.e. delaying chemotherapy) and increases survival. This AAP survival gain (see Table 2), is also incorporated in the benefits of delaying chemotherapy (i.e. QALY gain) discussed in the response to question 2 and question 3.

Table 3: Additional analysis based on Manufacturer's base case

Analaysis	**Pre-docetaxel QALY gain[a]**	**On-docetaxel QALY gain[a]**	**ICER**
1) Basecase[b]	0.71	-0.10	£46,756
2) Increasing Post-ADT baseline utility to [redacted]	[redacted]	-0.10	£38,851
3) Decreasing the on-docetaxel utility to 0.000	0.71	[redacted]	£44,466
4) Analyses 2 and 3 combined	[redacted]	[redacted]	£37,257

[a] QALY gain for AAP versus BSC (PP)

[b] Total QALY gain for AAP versus BSC (PP) is [redacted] in the base case (see MS Table 70)