KSR Ltd

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

This erratum was produced following an error identified by NICE.

In the quality assessment of the COU-AA-302 trial, the study was assessed as not using an ITT analysis. This is not correct. Therefore, we have produced a corrected page 36, deleting the following bullet point:

- Did the analysis include an intention-to-treat analysis: No. The ITT population did not include all patients randomised into the study, but those who received at least 1 dose of the allocated intervention.

And a corrected Table 4.3, in which the last cell now states: ‘Yes’.

and conference abstracts[1-7]. The only full journal publication for the trial was based on the second interim analysis.[8]

Table 4.2: Data sources for the pivotal RCT, COU-AA-302

COU-AA-302 analysis point	Cut-off date for the analysis	Data availability	Data source
First interim analysis	20.12.10	Unpublished	Clinical study report[9]
Second interim analysis	20.12.11	Published	Ryan et al. 2013[8] Review article[10] Patient-reported outcomes[11] Conference abstracts (ASCO, ESMO)[12, 13]
		Unpublished	Clinical study report[9]
Third interim analysis	22.05.12	Unpublished	Updated clinical study report[14]
		Published	Review article[10] Conference abstracts (ASCO, ASCO GU)[1-7]
Final analysis	N/A	N/A	N/A

Abbreviations: ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology.

4.1.4 Quality assessment

The quality assessments of the COU-AA-302 trial can be found in **A**ppendix 3, Section 10.3 of the MS, and in the table below.

The methods used to generate random allocation sequence and for concealment of allocation sequence were reported and were judged as adequate. Blinding status was clear and the study did not show any evidence of selective reporting. Overall, the COU-AA-302 trial was rated as being at a low risk of bias.

ERG Comment: The ERG agrees with the manufacturer's assessment on most items.

Disagreements with the manufacturer assessment of study quality were as follows:

- Imbalances in drop-outs between groups: No imbalances; but large numbers of drop-outs in both groups.
- Missing outcomes: No, all outcomes were reported. However, no data were reported for QoL scores by arm (baseline, follow-up and change scores).

Table 4.3: Quality assessment of COU-AA-302

Study question	Manufacturer's explanation: How is the question addressed in the study?	Manufacturer's assessment	ERG comment
Was randomisation carried out appropriately?	The randomisation schedule was generated by an independent statistician at Almac Clinical Technologies. Patients were	Yes	Low risk of bias

Study question	Manufacturer's explanation: How is the question addressed in the study?	Manufacturer's assessment	ERG comment
	assigned randomly in a 1:1 ratio to receive either abiraterone acetate plus prednisone or placebo plus prednisone. Patient eligibility was verified by the investigators, who then entered the stratification factor (i.e. baseline ECOG PS grade [0 versus 1]) into the Almac IWRS/IVRS system.		
Was the concealment of treatment allocation adequate?	All patients, family members, study personnel (at the study site, the sponsor, or participating Clinical Research Organization), and members of the IDMC were to remain blinded to treatment assignment until completion of the study with the exception of the circumstances described in the text below regarding blinding of treatment allocation. The matched placebo tablets given to patients in the placebo arm were also visually indistinguishable from the abiraterone acetate tablets.	Yes[a]	Low risk of bias
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	With a few exceptions, demographics and disease characteristics were balanced between the two treatment groups. The few differences in demographics and disease characteristics were not considered clinically relevant.	Yes	Low risk of bias
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	All patients, family members, study personnel (at the study site, the sponsor, or participating Clinical Research Organization), and members of the IDMC were to remain blinded to treatment assignment until completion of the study with the following exceptions: The Independent Biostatistician and Independent Statistical Programmer (employed by Novella) responsible for preparing interim tables, listings, and graphs for IDMC review who had no other responsibilities associated with the study. The IDMC, in order to evaluate whether the study should be stopped early for efficacy/futility or safety. Laboratory personnel performing	Yes[a]	Low risk of bias

Study question	Manufacturer's explanation: How is the question addressed in the study?	Manufacturer's assessment	ERG comment
	plasma concentration assays for pharmacokinetic analysis. The Independent Biostatistician provided laboratory personnel with patients' randomisation codes without sponsor involvement. This process was undertaken to avoid futile pharmacokinetic analysis of placebo specimens that did not contain abiraterone. Laboratory personnel received no other data associated with the patients, with the exception of deviation listings pertaining to the collection of the pharmacokinetic samples.		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No imbalances in dropouts between groups were observed	No imbalances in dropouts between groups were observed	No imbalances; but large numbers of drop-outs in both groups:
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The clinical study report and associated journal and conference publications for the COU-AA-302 study were available and were reviewed. There was no indication that the clinical study report did not include all the measured outcomes	No	No, all outcomes were reported. However, no data were reported for QoL scores by arm (baseline, follow-up and change scores)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population included all patients randomised into the study; patients were to be classified according to assigned treatment group, regardless of the actual treatment received. The ITT population was used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics.	Yes	Yes

Source: MS, Table 114, page 236[15]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IDMC, Independent Data Monitoring Committee; ITT, intent-to-treat; IVRS, Interactive Voice Response System; IWRS, Interactive Web Response System; N/A, not applicable; PS, performance status.

[a] It should be noted that an error resulted in the wrong AA study drug tablets being distributed by the sponsor. From 15.12.11 through 29.0312, these tablets were dispensed to 62 subjects assigned to the AAP group at 24 sites in the US and Canada. The affected tablets contained the proper dosage and formulation of AA, but were debossed with the text "AA250." The correct study tablets were not marked. This error resulted in the possibility that two subjects may have imputed their treatment assignment from the de-bossed tablets 5 days prior to the 20.12.11 cut-off date. The last bottle with de-bossed tablets was dispensed on 29.03.12. The issue was resolved.