IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Abiraterone acetate –

Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Abirateronacetat – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 29.12.2011). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

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[2] Due to legal data protection regulations, employees have the right not to be named.

List of abbreviations

Abbreviation	Meaning
AE	adverse event
ACT	appropriate comparator therapy
BPI-SF	Brief Pain Inventory – Short Form
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mCRPC	metastatic castration-resistant prostate cancer
PSA	prostate-specific antigen
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SAE	serious adverse event
WHO	World Health Organization

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 05.10.2011, in accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) wrote to IQWiG to commission the benefit assessment of the drug abiraterone acetate. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company").

Research question

The present benefit assessment relates to the treatment of metastatic castration-resistant prostate cancer (mCRPC) of adult men and was carried out separately for 2 patient populations.

Best supportive care population

The "best supportive care" population comprises patients who are not eligible for further treatment with docetaxel.

The appropriate comparator therapy (ACT) for this patient population is palliative treatment with dexamethasone, prednisone, prednisolone or methylprednisolone as well as best supportive care (BSC) (e.g. adequate pain therapy). BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.

The first objective of the present report is therefore to assess the added benefit of abiraterone acetate in combination with prednisone or prednisolone compared with dexamethasone, prednisone, prednisolone or methylprednisolone as well as BSC in patients with mCRPC who are not eligible for further treatment with docetaxel.

This benefit assessment considered studies that investigated the comparison of abiraterone acetate together with prednisone/prednisolone in combination with BSC or without BSC versus treatment with the ACT. One study was included in the assessment. The assessment was carried out by means of the comparison performed in the included study, i.e. abiraterone acetate in combination with prednisone and BSC (abiraterone/prednisone/BSC) versus prednisone and BSC (placebo/prednisone/BSC). The assessment was undertaken in respect of patient-relevant outcomes and the study included was a direct comparative randomized controlled trial.

Docetaxel retreatment population

The "docetaxel retreatment population" comprises patients for whom further treatment with docetaxel is still an option.

The ACT for this patient population is docetaxel in combination with prednisone or prednisolone.

A further objective of the present report is therefore to assess the added benefit of abiraterone acetate in combination with prednisone or prednisolone compared with docetaxel in combination with prednisone or prednisolone in patients with mCRPC who are not eligible for further treatment with docetaxel.

Results

One relevant study was included in the benefit assessment (Study COU-AA-301), which was the pivotal study for the approval of abiraterone acetate. This study was double-blind, randomized and placebo-controlled. The study medication consisted of abiraterone acetate + prednisone in one treatment arm and of placebo + prednisone in the other treatment arm. In addition, patients in both treatment arms also received BSC as co-medication, i.e. the study compared abiraterone/prednisone/BSC with placebo/prednisone/BSC. Data for the best supportive care population were available on the basis of this study. No adequate data were submitted for the docetaxel retreatment population (see below).

Best supportive care population

The risk of bias of the study included in the benefit assessment was low, both at the study level and also for the individual outcomes. On the basis of the evidence from this study, indications, e.g. of an added benefit, could be derived from the data.

Mortality

Over the entire observation period, treatment with abiraterone acetate/prednisone/BSC produced a statistically significant prolongation in overall survival compared with treatment with placebo/prednisone/BSC. There is an indication of an added benefit of abiraterone acetate/prednisone/BSC over prednisone/BSC for this outcome.

Morbidity

Treatment with abiraterone acetate/prednisone/BSC produced a statistically significant prolongation in the time to the first skeletal-related event and the time to pain progression compared with treatment with placebo/prednisone/BSC. There is an indication of an added benefit of abiraterone acetate/prednisone/BSC over prednisone/BSC for both outcomes.

Health-related quality of life

The company’s dossier contained no evaluable data on health-related quality of life. An added benefit of abiraterone acetate/prednisone/BSC is not proven for this outcome.

Adverse events

None of the differences in the proportion of patients with adverse events (AEs), AEs of the Common Terminology Criteria for Adverse Events (CTCAE) Grades 3 and 4, serious AEs (SAEs) and AEs that led to discontinuation or to death were statistically significant under

abiraterone/prednisone/BSC compared with placebo/prednisone/BSC. For these 5 outcomes, greater/lesser harm from abiraterone acetate/prednisone/BSC than from prednisone/BSC is not proven.

Docetaxel retreatment population

The company submitted studies for indirect comparisons and further investigations for the assessment of the added benefit for the docetaxel retreatment population. In order to ensure the completeness of the study pool for the indirect comparisons and further investigations, the company's dossier is required to include a search in trial registries. Since this search was not presented in the dossier, it is unclear whether the study pool for the indirect comparisons and the further investigations is complete. The studies on indirect comparisons and further investigations were therefore not used for the benefit assessment. Regardless of this, the presented documents would not have been usable for the benefit assessment because of methodological deficiencies and inadequate interventions. An added benefit for the docetaxel retreatment population is not proven.

Probability and extent of the added benefit, patient groups with therapeutically important added benefit

On the basis of the results presented and taking outcome categories and effect sizes into account, the extent and probability of the added benefit of the drug abiraterone acetate is assessed as follows:

For the best supportive care population, there is an indication of a considerable added benefit of abiraterone acetate/prednisone/BSC over prednisone/BSC. This overall conclusion concerning the extent of added benefit is based on the aggregation of the extents of added benefit derived at the outcome level.

For the docetaxel retreatment population, an added benefit of abiraterone acetate in combination with prednisone or prednisolone over docetaxel in combination with prednisone or prednisolone is not proven.

The procedure for deriving the overall conclusion on the added benefit is a proposal from IQWiG. The G-BA decides on the added benefit.

2.2 Research question

For the therapeutic indication "treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy" [1], the company adhered to the ACTs specified by the G-BA, i.e. separate ACTs were used for the patient population who are not eligible for further docetaxel treatment (hereinafter: "best supportive care population") and for the patient population for whom further docetaxel treatment is still an option (hereinafter: "docetaxel retreatment population"). The respective

ACTs are shown in Table 1. The Institute concurs with the designation of the ACT by the company in the 2 patient populations.

Table 1: Patient populations and appropriate comparator therapy

Patient population	Appropriate comparator therapy	Comparison
Best supportive care population[a]	"Palliative treatment with dexamethasone, prednisone, prednisolone or methylprednisolone as well as best supportive care (BSC) (e.g. adequate pain therapy). BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life".	Abiraterone acetate in combination with prednisone or prednisolone vs. dexamethasone, prednisone, prednisolone or methylprednisolone as well as BSC
Docetaxel retreatment population[b]	"Docetaxel in combination with prednisone or prednisolone".	Abiraterone acetate in combination with prednisone or prednisolone vs. docetaxel in combination with prednisone or prednisolone
a: In the dossier, the company calls this population "Population A" or "Patient population A". b: In the dossier, the company calls this population "Population B" or "Patient population B". BSC: best supportive care.		

The objective of this report is therefore to assess the added benefit of:

- Abiraterone acetate in combination with prednisone or prednisolone versus dexamethasone, prednisone, prednisolone or methylprednisolone as well as BSC (as defined in Table 1) in patients of the best supportive care population and
- Abiraterone acetate in combination with prednisone or prednisolone versus docetaxel in combination with prednisone or prednisolone in patients of the docetaxel retreatment population.

The benefit assessment in the best supportive care population considered studies that investigated the comparison of abiraterone acetate in combination with prednisone/prednisolone with or without BSC versus treatment with the ACT.

In the placebo-controlled study included in the assessment, patients in the abiraterone acetate + prednisone treatment arm as well as those in the placebo + prednisone treatment arm received a concomitant treatment rated as BSC. Thus, the study compared the administration of abiraterone acetate in combination with prednisone and BSC with a combination of prednisone and BSC. To take account of this fact and to clearly designate the comparison in the report, the treatment arms of this study are named as follows in this assessment report: "abiraterone/prednisone/BSC" and "placebo/prednisone/BSC".

The assessment was carried out in respect of patient-relevant outcomes. Only direct comparative randomized controlled trials were included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The Institute compiled the study pool of the benefit assessment on the basis of the following information:

- Studies on abiraterone acetate completed by the company up to 19.08.2011
- Results of a bibliographical literature search and a search in trial registries for studies on abiraterone acetate (last search in bibliographical databases on 30.08.2011, in trial registries on 12.09.2011 [searches by the company])
- The Institute's own search in trial registries for studies on abiraterone acetate (search date: 17.10.2011) to check the company's search results. This check produced no deviations from the study pool presented in the company's dossier.

The resulting study pool for the direct comparison corresponded to that of the company.

The company also undertook searches to identify relevant studies for indirect comparisons and further investigations in bibliographical databases to draw conclusions about the added benefit of abiraterone acetate in the docetaxel retreatment population and the added benefit of abiraterone acetate compared with cabazitaxel. In order to ensure the completeness of the study pool for the indirect comparisons and further investigations, the company's dossier is required to include a search in trial registries. Since this search was not presented in the dossier, it is unclear whether the study pool for the indirect comparisons and the further investigations is complete (see Section 2.7.2.3.1 in the full dossier assessment). The indirect comparisons and further investigations were therefore not used for the benefit assessment. Regardless of this, the presented documents would not have been usable for the benefit assessment because of methodological deficiencies and inadequate interventions (see Sections 2.7.2.1 and 2.7.2.3.2 of the full dossier assessment).

Further information about the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included in the assessment

The Institute's study pool deviated substantially from that of the company, because - as explained in Section 2.3 - the studies for the indirect comparisons and the further investigations were not used for the benefit assessment.

The study listed in Table 2 was included in the benefit assessment.

Table 2: Study pool – studies per patient population

Patient population Study	Study category		
	Pivotal study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
***Best supportive care* population**			
COU-AA-301	yes	yes	no
Docetaxel retreatment population			
–	The studies submitted could not be used for the benefit assessment because the completeness of the study pool is unclear due to deficiencies in the search.		
a: Study for which the company was sponsor, or in which the company was otherwise financially involved.			

Section 2.6 contains a list of data sources that the company named for the included study, as well as the reference to the "Statistical Update Report" [2] in Module 5, which is also a source for the benefit assessment.

Further information about the results of information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1, 4.3.2.1.1 and 4.3.2.3.1 of the dossier and in Section 2.7.2.3 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 and Table 4 describe the study used for the benefit assessment. This study (COU-AA-301) was the pivotal study for approval of abiraterone acetate. Despite some uncertainties, the Institute concurs with the company's assessment that the study population of COU-AA-301 can be used to draw conclusions about the best supportive care population (see Section 2.7.2.4.1 of the full dossier assessment for explanation).

In summary, the study is suitable for the benefit assessment concerning the best supportive care population; however, it is not suitable for drawing conclusions about the docetaxel retreatment population.

Table 3: Characteristics of the study included in the assessment – RCT for the direct comparison of abiraterone/prednisone/BSC vs. placebo/prednisone/BSC (best supportive care population)

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
COU-AA-301	RCT, double-blind, placebo-controlled	Adult men (≥ 18 years) with metastatic, castration-resistant prostate cancer with at least one but not more than 2 failed chemotherapies, of which at least one contained docetaxel	Abiraterone/ prednisone/BSC (n = 797) Placebo/prednisone/ BSC (n = 398)	Treatment: Start cycle 1 until treatment discontinuation (due to progression or toxicity), 28-day cycles Follow-up: Up to 60 months (5 years)	Australia, Austria, Belgium, Canada, France, Germany, Hungary, Italy, The Netherlands, Ireland, Spain, United Kingdom, United States of America 08.05.2008 to 28.07.2009 (recruitment).	Primary: Overall survival Secondary: Time to pain progression (BPI-SF), time to first skeletal-related event, health-related quality of life, adverse events

a: Extracted primary outcome criteria contain information without consideration of relevance for this benefit assessment. Extracted secondary outcome criteria contain exclusively information on the relevant available outcomes for this benefit assessment.
BPI-SF: Brief Pain Inventory – Short Form, BSC: best supportive care, RCT: randomized controlled trial.

Table 4: Characteristics of the interventions – RCT for the direct comparison of abiraterone acetate/prednisone/BSC vs. placebo/prednisone/BSC (best supportive care population)

Study	Abiraterone acetate/prednisone/BSC	Placebo/prednisone/BSC
COU-AA-301	Test medication: Abiraterone acetate 250 mg, 4 tablets orally once daily at least 1 hour before or 2 hours after a meal + prednisone 5 mg twice daily	Test medication: Placebo, 4 tablets orally once daily at least 1 hour or 2 hours after a meal + prednisone 5 mg twice daily
	Concomitant medication (in both treatment arms): According to the study protocol, supportive medication could be used as per guidelines. Use of luteinizing hormone-releasing hormones, analgesics and corticosteroids was not restricted. Use of bisphosphonates was permitted, provided the treatment had existed at the start of the study treatment. Palliative radiation and a change in the dose of corticosteroids and bisphosphonates were permitted, provided a patient met at least 1 but not all 3 criteria[a] for discontinuation of the study treatment.	
a: These criteria were: – PSA progression (defined as an increase of ≥ 25% over the last pretreatment value and an increase in the absolute-value PSA level by at least 5 ng/mL), – radiographical evidence of progression, – symptomatic or clinical progression. BSC: best supportive care, PSA: prostate-specific antigen, RCT: randomized controlled trial.		

Study COU-AA-301 was a randomized, double-blind, placebo-controlled study and enrolled adult men with mCRPC who had undergone 1 or 2 failed chemotherapy regimens, of which at least one had contained docetaxel. A total of 1195 patients were randomly assigned in a ratio of 2:1, 797 patients to the abiraterone acetate + prednisone treatment arm and 398 patients to the placebo + prednisone treatment arm (Table 3). Patients in the former arm received 1000 mg abiraterone acetate + 10 mg prednisone daily, whereas those in the latter arm were given placebo + 10 mg prednisone daily. The study treatment was administered according to a regimen described in the Summary of Product Characteristics (Table 4 and [1]). Study treatment consisted of 28-day cycles and was continued until it had to be discontinued due to progression of the study indication or toxicity (Table 3). In addition to the study treatment, patients in both treatment arms were treated with BSC, without any substantial restrictions (Table 4). In the study protocol, the follow-up period was planned to last for up to 60 months (Table 3). The primary outcome was overall survival.

Table 5 shows the characteristics of the patients in the study included for the best supportive care population.

Table 5: Characteristics of the study population – RCT for the direct comparison of abiraterone acetate/prednisone/BSC vs. placebo/prednisone/BSC (best supportive care population)

Study treatment arm	**N[a]**	**Age [years] median (range)**	**Previous prostate cancer therapies[b] n (%)**	**Evidence of disease progression PSA only / radiographical progression with or without PSA progression n (%)**	**ECOG Performance Status n (%)**
COU-AA-301					
Abiraterone acetate / prednisone / BSC	797	69 (42-95)	1 cytotoxic chemotherapy: 558 (70) 2 cytotoxic chemotherapies: 239 (30) Docetaxel: 793 (99)	238 (30) / 559 (70)	Score: 0 or 1: 715 (90) 2: 82 (10)
Placebo / prednisone / BSC	398	69 (39-90)	1 cytotoxic chemotherapy: 275 (69) 2 cytotoxic chemotherapies 123 (31) Docetaxel: 397 (100)	125 (31) / 273 (69)	Score: 0 or 1: 353 (89) 2: 45 (11)

a: Number of randomized patients.

b: Only cytotoxic chemotherapies were shown. Information about other previous prostate cancer therapies can be found in Module 4.

BSC: best supportive care, ECOG: Eastern Cooperative Oncology Group, N: number of all patients, n: number of patients in a category, PSA: prostate-specific antigen.

Patient characteristics were largely comparable in both treatment arms. The median age of the study population was 69 years; approx. 90% of patients had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. In about 30% of patients the progression of prostate cancer was only demonstrated by the concentration of prostate-specific antigen (PSA). In agreement with the therapeutic indication, virtually all patients had received at least one docetaxel-based regimen before enrolment in the study (Table 5).

The risk of bias at the study level is shown in Table 6.

Table 6: Risk of bias at the study level – RCT for the direct comparison of abiraterone acetate/prednisone/BSC vs. placebo/prednisone/BSC (best supportive care population)

Study	Random sequence generation	Allocation concealment	Blinding		Selective reporting	Other sources of bias	Risk of bias at the study level
			Participants	Personnel			
COU-AA-301	yes	yes	yes	yes	no	no	low
BSC: best supportive care, RCT: randomized controlled trial.							

The risk of bias at the study level was rated as low for the study. This concurs with the company's assessment.

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4 Sections 4.3.1.2.1, 4.3.1.2.2, 4.3.2.1.2 and 4.3.2.3.2 of the dossier and in Sections 2.7.2.2, 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results concerning added benefit

This assessment considered the following patient-relevant outcomes (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality:
  - overall survival
- Morbidity:
  - skeletal-related events
  - pain progression (Brief Pain Inventory – Short Form [BPI-SF], World Health Organization [WHO] Analgesic Ladder)
- Health-related quality of life
  - No evaluable data available in the company's dossier
- Adverse events
  - Overall rate of AEs
  - AEs of CTCAE Grades 3 and 4
  - SAEs
  - Discontinuation due to AE
  - AEs that resulted in death

The patient-relevant outcomes chosen by the Institute deviate from those chosen by the company, which used additional outcomes in the dossier (Module 4) (for reasons for the Institute's choice of outcomes, see Section 2.7.2.4.3 of the full dossier assessment).

Table 7 shows for which outcomes data were available in the study included. The risk of bias for these outcomes is shown in Table 8.

Table 7: Matrix of outcomes – RCT for the direct comparison of abiraterone acetate/prednisone/BSC vs. placebo/prednisone/BSC (best supportive care population)

Study	Overall survival	Skeletal-related events	Pain progression	Health-related quality of life	Overall rate of AEs	CTCAE Grade 3 and 4 AEs	Serious AEs	Discontinuation due to AE	AEs that resulted in death
COU-AA-301	yes	yes	yes	–[a]	yes	yes	yes	yes	yes

a: No evaluable data available in the company's dossier, for reasons, see Sections 2.7.2.2 and 2.7.2.4.3 of the full dossier assessment.

AE: adverse event, BSC: best supportive care, CTCAE: Common Terminology Criteria for Adverse Events, RCT: randomized controlled trial.

Table 8: Risk of bias at the study and outcome level – RCT for the direct comparison of abiraterone acetate/prednisone/BSC vs. placebo/prednisone/BSC (best supportive care population)

Study \ Outcome	Study level	Overall survival	Skeletal-related events	Pain progression	Health-related quality of life	Overall rate of AEs	CTCAE Grade 3 and 4 AEs	Serious AEs	Discontinuation due to AE	AEs that resulted in death
COU-AA-301	low	low	low	low	–[a]	low	low	low	low	low

a: No evaluable data available in the company's dossier, for reasons, see Sections 2.7.2.2 and 2.7.2.4.3 of the full dossier assessment.

AE: adverse event, BSC: best supportive care, CTCAE: Common Terminology Criteria for Adverse Events, RCT: randomized controlled trial.

Except for the non-evaluable data on health-related quality of life, the availability of data for the study can be presumed to be good.

The risk of bias at the outcome level was rated as low for all outcomes included for which evaluable data were available in the company's dossier. This concurs with the company's assessment.

Further information about the choice of outcome and risk of bias at the outcome level can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3.1 of the dossier and in Sections 2.7.2.2, 2.7.2.4.2, 2.7.2.4.3, 2.7.2.8 and 2.7.2.9.4 of the full dossier assessment.

2.4.1 Results for the best supportive care population

Table 9 and Table 10 summarize the results of the benefit assessment for the comparison of abiraterone acetate/prednisone/BSC versus placebo/prednisone/BSC in patients in the best supportive care population. Table 11 gives additional information about individual AEs. The data correspond to those submitted by the company and were, in part, supplemented by the Institute's own calculations where these were not reported in the dossier. In addition, information was supplemented using data from Module 5 of the dossier.

In the dossier, the company presented 2 analyses for the study included. Analysis 1 was an interim analysis, which was undertaken when the number of 534 deaths specified in the

study protocol for this purpose had been exceeded. Analysis 2 was undertaken once the number specified in the study protocol for the final analysis of 797 deaths had reached 97% (775 deaths). Analysis 2 was used for the benefit assessment (a detailed commentary on the submitted analyses can be found in Section 2.7.2.4.3 of the full dossier assessment).

Table 9: Mortality, morbidity and health-related quality of life – RCT for the direct comparison of abiraterone acetate/prednisone/BSC vs. placebo/prednisone/BSC (best supportive care population)

	Abiraterone acetate / prednisone/BSC		**Placebo / prednisone/BSC**		**Abiraterone acetate / prednisone/BSC vs. placebo / prednisone/BSC[a]**	
Mortality						
Overall survival	**Total N**	**Median [95% CI] days**	**Total N**	**Median [95% CI] days**	**Hazard ratio [95% CI]**	**p-value**
	797	482 [451; 518]	398	341 [317; 400]	0.74 [0.64; 0.86]	< 0.001
Morbidity						
Skeletal-related events	**Total N**	**25% quantile[b] [95% CI] days**	**Total N**	**25% quantile[b] [95% CI] days**	**Hazard ratio [95% CI]**	**p-value**
	797	301 [225; 366]	398	150 [120; 198]	0.62 [0.48; 0.79]	< 0.001
Pain progression (BPI, WHO Analgesic Ladder)	**Total N**	**25% quantile[b] [95% CI] days**	**Total N**	**25% quantile[b] [95% CI] days**	**Hazard ratio [95% CI]**	**p-value**
	785	225 [171; 311]	389	142 [91; 253]	0.69 [0.53; 0.88]	0.003
Health-related quality of life						
	No evaluable data available in the company's dossier.					

The results come from Study COU-AA-301, Analysis 2.

a: Cox regression, stratified according to ECOG score (0 or 1 vs. 2), pain score (present vs. absent), number of previous chemotherapy regimens (1 vs. 2), nature of progression (only PSA vs. radiographic).

b: Median time to event and the related confidence interval could not be estimated because of the high proportion of censored data. The 25% quantile shows the time at which the probability of occurrence of an event is 25%.

BPI: Brief Pain Inventory, BSC: best supportive care, CI: confidence interval, ECOG: Eastern Cooperative Oncology Group, N: number of all patients, PSA: prostate-specific antigen, RCT: randomized controlled trial, WHO: World Health Organization.

Table 10: Adverse events – RCT for the direct comparison of abiraterone acetate/prednisone/BSC vs. placebo/prednisone/BSC (best supportive care population)

Adverse events	Abiraterone acetate / prednisone/BSC		Placebo / prednisone/BSC		Abiraterone acetate / prednisone/BSC vs. placebo / prednisone/BSC	
Proportion of patients with	**Total N**	**n (%)**	**Total N**	**n (%)**	**Relative risk [95% CI][a]**	**p-value[b]**
AE	791	784 (99.1)	394	390 (99.0)	1.00 [0.99; 1.01]	0.760
AEs of CTCAE Grade 3 and 4	791	478 (60.4)	394	240 (60.9)	0.99 [0.90; 1.09]	0.900
SAE[c]	791	335 (42.4)	394	172 (43.7)	0.97 [0.85; 1.11]	0.709
Discontinuation due to AE	791	162 (20.5)	394	93 (23.6)	0.87 [0.69; 1.09]	0.230
AEs that resulted in death	791	105 (13.3)	394	61 (15.5)	0.86 [0.64; 1.15]	0.329

The results come from Study COU-AA-301, Analysis 2.

According to the information in the dossier, the numbers for AEs and SAEs do not include any AEs of CTCAE Grade 5. It is not clear from the dossier whether the number for discontinuation due to AEs includes AEs of CTCAE Grade 5.

a: Institute's calculation, proportion of events.

b: Institute's calculation, Fisher's exact test.

c: Termed as "severe" (schwere) AEs in Module 4 of the dossier.

AE: adverse event, BSC: best supportive care, CTCAE: Common Terminology Criteria for Adverse Events, N: number of all patients, n: number of patients with events, RCT: randomized controlled trial, SAE: serious adverse event.

Table 11: Number (%) of patients with AEs of CTCAE Grades 3 and 4 with a relative frequency of ≥ 5% in any treatment arm – RCT for the direct comparison of abiraterone acetate/prednisone/BSC vs. placebo/prednisone/BSC (best supportive care population)

AEs of CTCAE Grade 3 and 4[a]	Abiraterone acetate / prednisone/BSC N = 791 n (%)	Placebo / prednisone/BSC N = 394 n (%)
Back pain	56 (7.1)	40 (10.2)
Bone pain	51 (6.4)	30 (7.6)
Arthralgia	40 (5.1)	17 (4.3)
Pain in extremity	24 (3.0)	20 (5.1)
Fatigue	72 (9.1)	41 (10.4)
Anaemia	62 (7.8)	32 (8.1)
Spinal cord compression	23 (2.9)	20 (5.1)

The results come from Study COU-AA-301, Analysis 2.

a: Coding according to Medical Dictionary for Regulatory Activities.

AE: adverse event, BSC: best supportive care, CTCAE: Common Terminology Criteria for Adverse Events, N: number of all patients, n: number of patients with events, RCT: randomized controlled trial.

In the Institute's view, Study COU-AA-301 does not meet the particular requirements placed on the derivation of proof from a single study (see Section 2.7.2.8.1 of the full dossier assessment). Hence, at most indications – e.g. of an added benefit – could be inferred from the data.

This assessment deviates from that of the company, which derived proof of added benefit in the best supportive care population from Study COU-AA-301.

Mortality

Over the entire observation period, treatment with abiraterone acetate/prednisone/BSC produced a statistically significant prolongation of overall survival compared with treatment with placebo/prednisone/BSC. There is an indication of an added benefit of abiraterone acetate/prednisone/BSC over prednisone/BSC for the outcome "overall survival". For interpretation of the survival curve, see Section 2.7.2.4.3 of the full dossier assessment.

Morbidity

Treatment with abiraterone acetate/prednisone/BSC produced a statistically significant prolongation of the time to the first skeletal-related event and time to pain progression compared with treatment with placebo/prednisone/BSC. There is an indication of an added benefit of abiraterone acetate/prednisone/BSC over prednisone/BSC for both outcomes.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life. An added benefit of abiraterone acetate/prednisone/BSC is not proven for this outcome.

Adverse events

The proportions of patients with AEs, AEs of CTCAE Grades 3 and 4, SAEs and AEs that resulted in discontinuation or death, did not differ substantially between abiraterone acetate/prednisone/BSC and placebo/prednisone/BSC. The respective comparisons were not statistically significant and for these 5 outcomes, greater/lesser harm from abiraterone acetate/prednisone/BSC than from prednisone/BSC is not proven.

Appraisal of the assessment of added benefit by the company

The above assessments of the Institute on added benefit in terms of mortality, morbidity and health-related quality of life deviate from those of the company, which derived a proof of an added benefit (not explicitly at the outcome level, but overall). Furthermore, for the Institute greater/lesser harm in terms of adverse events is not proven, whereas the company justifies the "clear proof of the presence of an added benefit of abiraterone acetate" with the "good tolerability" of abiraterone acetate. The company also did not derive added benefit regarding adverse events at the outcome level.

Further information about outcome results of the direct comparison in the best supportive care population can be found in Module 4, Section 4.3.1.3.1 of the dossier and in Section 2.7.2.4.3 of the full dossier assessment.

2.4.2 Results for the docetaxel retreatment population

To investigate the added benefit for the docetaxel retreatment population, the company presented studies for indirect comparisons and further investigations. As already explained in Section 2.3.1 the corresponding studies were not used for the benefit assessment because of the lack of searches in trial registries (see also Section 2.7.2.3.1 in the full dossier assessment). Regardless of this, these studies would not have been usable for the benefit assessment because of methodological deficiencies and inadequate interventions (see Sections 2.7.2.1 and 2.7.2.3.2 in the full dossier assessment).

An added benefit for the docetaxel retreatment population is not proven. This assessment deviates substantially from that of the company, which derived an added benefit for this population.

Further information about outcome results of the indirect comparisons and the further investigations in the docetaxel retreatment population can be found in Module 4, Sections 4.3.2.1.3 and 4.3.2.3.3 of the dossier and in Sections 2.7.2.5 and 2.7.2.7 of the full dossier assessment.

2.5 Extent and probability of the added benefit

Derivation of the extent and probability of added benefit is presented below for each patient population at the outcome level, taking into account outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [3].

The assessment of added benefit was carried out separately for the best supportive care population and the docetaxel retreatment population.

The procedure for deriving the overall conclusion on added benefit based on the aggregation of the conclusions derived at the outcome level is a proposal from IQWiG. The G-BA decides on added benefit.

2.5.1 Best supportive care population

2.5.1.1 Evaluation of added benefit at the outcome level

The data presented in Section 2.4.1 for the best supportive care population resulted in an indication of added benefit of abiraterone acetate/prednisone/BSC over prednisone/BSC. An assessment of the extent of the respective added benefit at the outcome level was then carried out and is shown in Table 12.

Table 12: Extent of added benefit at the outcome level: abiraterone acetate/prednisone/BSC vs. prednisone/BSC (best supportive care population)

	Effect estimator [95% CI] / quantile of time to event abiraterone acetate/prednisone/BSC vs. placebo/prednisone/BSC / p-value / probability[a]	**Derivation of extent[b]**
Mortality		
Overall survival	HR 0.74 [0.64; 0.86] median: 482 days (15.8 months) vs. 341 days (11.2 months) p < 0.001 probability: "indication"	Outcome category: survival time $0.85 \leq CI_0 < 0.95$ Added benefit, extent: "considerable"
Morbidity		
Time to first skeletal-related event	HR 0.62 [0,48; 0,79] 25% quantile[c]: 301 days (9.9 months) vs. 150 days (4.9 months) p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_0 < 0.90$ Added benefit, extent: "considerable"
Time to pain progression	HR 0.69 [0.53; 0.88] 25% quantile[c]: 225 days (7.4 months) vs. 142 days (4.7 months) P = 0.003 probability: "indication"	Outcome category: non-serious /non-severe symptoms /late complications[d] $0.80 \leq CI_0 < 0.90$ Added benefit, extent: "minor"
Health-related quality of life		
	No evaluable data available in the company's dossier.	Lesser benefit/added benefit not proven.
Adverse events		
AE	RR[e] 1.00 [0.99; 1.01] 99.1% vs. 99.0% p = 0.760	Greater/lesser harm not proven.
AEs of CTCAE Grades 3 and 4	RR[e] 0.99 [0.90; 1.09] 60.4% vs. 60.9% p = 0.900	Greater/lesser harm not proven.
SAE	RR[e] 0.97 [0.85; 1.11] 42.4% vs. 43.7% p = 0.709	Greater/lesser harm not proven.
Discontinuation due to AE	RR[e] 0.87 [0,69; 1,09] 20.5% vs. 23.6% p = 0.230	Greater/lesser harm not proven.
AEs that resulted in death	RR[e] 0.86 [0.64; 1.15] 13.3% vs. 15.5% p = 0.329	Greater/lesser harm not proven.

(continued)

Table 12: Extent of added benefit at the outcome level: abiraterone acetate/prednisone/BSC vs. prednisone/BSC (best supportive care population) (continued)

a: Probability is provided, if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_0).
c: The 25% quantile shows the time at which the probability of occurrence of an event is 25%.
d: The classification into these (non-serious/non-severe) outcome categories was made from inspection of the pain data at the start of study treatment (and/or start of the study) and the deterioration during the course of the study.
e: Institute's calculation, proportion of event.
AE: adverse event, BSC: best supportive care, CI: confidence interval, CI_o: upper confidence interval, CTCAE: Common Terminology Criteria for Adverse Events, HR: hazard ratio, RR: relative risk, SAE: serious adverse event.

2.5.1.2 Overall conclusion on added benefit

The summary of results that determine the overall conclusion on added benefit is shown in Table 13.

Table 13: Results contributing to the overall conclusion on added benefit: abiraterone acetate/prednisone/BSC vs. prednisone/BSC (best supportive care population)

Positive effects	**Negative effects**
Indication of an added benefit – extent "considerable" (survival time: overall survival)	—
Indication of an added benefit – extent "considerable" (serious/severe symptoms/late complications: time to first skeletal-related event)	
Indication of an added benefit – extent "minor" (non-serious /non-severe symptoms/late complications: time to pain progression)	
BSC: best supportive care.	

In summary, for the best supportive care population, i.e. for patients who are not eligible for further treatment with docetaxel, there is an indication of a considerable added benefit of abiraterone acetate/prednisone/BSC over the ACT prednisone/BSC.

2.5.2 Docetaxel retreatment population

As described in Section 2.4.2 the studies for the docetaxel retreatment population could not be used for the benefit assessment because of the uncertainty regarding the completeness of the study pool.

The added benefit of abiraterone acetate in combination with prednisone or prednisolone over the ACT (docetaxel in combination with prednisone or prednisolone) is not proven for the docetaxel retreatment population.

2.5.3 Extent and probability of the added benefit - summary

For the 2 patient populations relevant to the benefit assessment, the resulting extent and probability of the added benefit of abiraterone acetate compared with the relevant ACTs is shown in the overview in Table 14.

Table 14: Abiraterone acetate: extent and probability of added benefit

Patient population	**Appropriate comparator therapy**	**Comparison**	**Extent and probability of the added benefit**
Best supportive care population	"Palliative treatment with dexamethasone, prednisone, prednisolone or methylprednisolone as well as best supportive care (BSC) (e.g. adequate pain therapy). BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life".	Abiraterone acetate / prednisone/BSC vs. prednisone/BSC	Indication of a "considerable" added benefit of abiraterone acetate/prednisone/BSC.
Docetaxel retreatment population	"Docetaxel in combination with prednisone or prednisolone".	Abiraterone acetate in combination with prednisone or prednisolone vs. docetaxel in combination with prednisone or prednisolone	Added benefit not proven.
BSC: best supportive care.			

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment

2.6 List of included studies

COU-AA-301

Cougar Biotechnology. A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy; study COU-AA-301; clinical study report [unpublished]. 2010.

Cougar Biotechnology. A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in patients with metastatic castration resistant prostate cancer who have failed docetaxel-based chemotherapy: study COU-AA-301; clinical study report [online]. In: EU Clinical Trials Register. [Accessed on: 29.09.2011]. URL: https://www.clinicaltrialsregister.eu/ctr-search/components/view.xhtml.

Cougar Biotechnology. Abiraterone acetate with prednisone or prednisolone for the treatment of patients with metastatic advanced prostate cancer (castration-resistant prostate cancer) who have received prior chemotherapy containing a Taxane: study COU-AA-301; clinical overview [unpublished]. 2011.

De Bono JS, Logothetis CJ, Fizazi K, North S, Chu L, Chi KN et al. Abiraterone acetate (AA) plus low dose prednisone (P) improves overall survival (OS) in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) who have progressed after docetaxel-based chemotherapy (chemo): results of COU-AA-301, a randomized double-blind placebo-controlled phase III study. Ann Oncol 2010; 21(Suppl 8): 3.

De Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364(21): 1995-2005.

De Bono JS, Scher HI. A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in patients with metastatic castration resistant prostate cancer who have failed docetaxel-based chemotherapy [online]. In: International Clinical Trials Registry Platform. 23.08.2011 [Accessed on: 29.09.2011]. URL: http://apps.who.int/trialsearch/trial.aspx?trialid=NCT00638690.

Fizazi K, De Bono JS, Haqq C, Logothetis CC, Jones RJ, Chi K et al. Abiraterone acetate plus low-dose prednisone has a favorable safety profile in metastatic castration-resistant prostate cancer progressing after docetaxel-based chemotherapy: results from COU-AA-301, a randomized, double-blind, placebo-controlled, phase III study. European Urology Supplements 2011; 10(2): 338.

Harland S, De Bono JS, Haqq C, Staffurth J, Hao Y, Gangnon D et al. Abiraterone acetate improves functional status in patients with metastatic castration-resistant prostate cancer (mCRPC) post-docetaxel: results from the COU-AA-301 phase 3 study. Eur J Cancer 2011; 47(Suppl 1): S484.

Janssen Research & Development. Statistical report of updated data from study COU-AA-301: protocol COU-AA-301; phase 3; JNJ-212082 (abiraterone acetate) [unpublished]. 2011.

Janssen-Cilag. To what extent data from the ECOG 0-1 status can be extrapolated with ECOG 2? [unpublished]. 2011.

Janssen-Cilag. Patients receiving ZYTIGA reported consistently superior outcomes on patient-reported measures of pain, functional status, and pain: Post-hoc-Analyse [unpublished]. 2011.

Logothetis C, De Bono JS, Molina A, Basch EM, Fizazi K, North SAW et al. Effect of abiraterone acetate (AA) on pain control and skeletal-related events (SRE) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) post docetaxel (D): results from the COU-AA-301 phase III study. J Clin Oncol 2011; 29(Suppl): Abstract 4520.

Scher HI, De Bono JS. Abiraterone acetate in castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy [online]. In: ClinicalTrials.gov. 19.08.2011 [Accessed on: 29.09.2011]. URL: http://clinicaltrials.gov/show/NCT00638690.

Scher HI, Logothetis C, Molina A, Goodman OB, Sternberg CN, Chi KN et al. Improved survival outcomes in clinically relevant patient subgroups from COU-AA-301, a phase III study of abiraterone acetate (AA) plus prednisone (P) in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel-based chemotherapy. J Clin Oncol 2011; 29(Suppl 7): Abstract 4.

Sternberg CN, Scher H, Molina A, North S, Mainwaring P, Hao Y et al. Fatigue improvement/reduction with abiraterone acetate in patients with metastatic castration-resistant prostate cancer (mCRPC) post-docetaxel: results from the COU-AA-301 phase 3 study. Eur J Cancer 2011; 47(Suppl 1): S488-S489.

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