IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Abiraterone acetate (new therapeutic indication) –

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

Extract

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[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group performance status
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IDMC	independent data monitoring committee
IDR	incidence density ratio
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
LH-RH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration resistant prostate cancer
OS	overall survival
PSA	prostate-specific antigen
RCT	randomized controlled trial
rPFS	radiographic progression-free survival
SAE	serious adverse event
SGB	*Sozialgesetzbuch* (Social Code Book)
SPC	Summary of Product Characteristics
TNM	tumour node metastasis

2 Benefit assessment

2.1 Extract of dossier assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of abiraterone acetate (hereinafter referred to as "abiraterone") in a therapeutic indication newly approved in December 2012. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to “the company”). The dossier was sent to IQWiG on 16.01.2013.

Research question

The aim of this report is to assess the added benefit of abiraterone compared with watchful waiting while maintaining conventional androgen deprivation therapy (ADT) according to approval for the following therapeutic indication: treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated.

The assessment was based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were included in the assessment.

Results

One direct comparative RCT (study COU-AA-302), the approval study of abiraterone for the therapeutic indication to be assessed, was included in the assessment.

The study COU-AA-302 was double-blind, randomized and placebo-controlled. Chemotherapy-naive adult men with mCRPC with asymptomatic or mildly symptomatic course of disease after failure of ADT were enrolled in the study. The patients were randomized to a treatment with abiraterone + prednisone or placebo + prednisone. In addition, 94% of the 1088 randomized patients in both treatment arms received a luteinizing hormone-releasing hormone (LH-RH) analogue as concomitant treatment. The study treatment according to the protocol was continued until progression occurred. When progression occurred, the patients discontinued the treatment phase with the study medication, and could receive treatment escalation chosen by the investigator (e.g. chemotherapy or radiotherapy, but also abiraterone). The patients were not told what their blinded study medication had been. Only the Eastern Cooperative Oncology Group performance status (ECOG-PS), use of opiate treatment, subsequent treatments (treatment escalation) and overall survival (OS) were recorded after the end-of-study visit at the end of the treatment phase with the study medication. Although this was a placebo-controlled study, it was suitable for deriving conclusions on the added benefit of abiraterone in comparison with watchful waiting while maintaining conventional ADT. Hereinafter, the treatment arms of the study will be referred to as "abiraterone" or "watchful waiting" in the text.

4 analyses – 3 interim analyses and one final analysis – were planned for the study. The company presented the results of 2 interim analyses for the study in Module 4 of the dossier. These analyses were based on the second and third data cut-off; the final analysis has not been conducted yet. Between the second and the third data cut-off, the independent data monitoring committee (IDMC) decided to end the double-blind treatment phase of the study ahead of schedule due to good efficacy, and to unblind the study. After the unblinding, the patients in the placebo arm could change to abiraterone treatment (crossover).

The results of the third data cut-off were used for the benefit assessment.

Risk of bias

The risk of bias at study level was rated as low for the study COU-AA-302. The influence the unblinding and the possibility of crossover from placebo to abiraterone after the second data cut-off had on the risk of bias was rated as low because this only concerned a small proportion of the patients and the effects regarding the relevant outcomes did not differ considerably between the second and the third data cut-off.

The risk of bias at outcome level was rated as low for OS and severe pain, which was measured on the basis of initiation of opiate treatment. The analyses of adverse events (AEs) included in the assessment were mainly rated as highly biased due to the uncertainty of the model assumptions.

Mortality

Abiraterone treatment resulted in a statistically significant prolongation of OS in comparison with watchful waiting. This led to an "indication" of an added benefit of abiraterone in comparison with watchful waiting while maintaining conventional ADT for this outcome.

Morbidity

Abiraterone treatment resulted in a statistically significant delay in the time to initiation of opiate treatment (as operationalization of the time until occurrence of severe pain) in comparison with watchful waiting. This led to an "indication" of an added benefit of abiraterone in comparison with watchful waiting while maintaining conventional ADT for this outcome.

Health-related quality of life

The company’s dossier contained no evaluable data on health-related quality of life. An added benefit of abiraterone in comparison with watchful waiting while maintaining conventional ADT is not proven for the outcome health-related quality of life.

Adverse events

There were no evaluable data for some of the outcomes on AEs. Hence the outcomes overall rate of AEs, rate of serious AEs (SAEs), fractures and fluid retention/oedema could not be considered in the benefit assessment.

The differences between abiraterone and watchful waiting were not statistically significant for severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 and 4), treatment discontinuations due to AEs, ischaemic heart disease and cardiac failure. Greater or lesser harm from abiraterone in comparison with watchful waiting while maintaining conventional ADT is not proven for these 4 outcomes.

Extent and probability of added benefit, patient groups with therapeutically important added benefit

On the basis of the results presented, the extent and probability of the added benefit of the drug abiraterone compared with the appropriate comparator therapy (ACT) is assessed as follows:

Overall, only positive effects remain at outcome level on the basis of the available and evaluable results. These are an "indication" of a minor added benefit in the outcome category mortality (OS) and an "indication" of a considerable added benefit for an outcome in the category serious/severe symptoms/late complications (severe pain measured on the basis of initiation of opiate treatment). An "indication" of a considerable added benefit of abiraterone in comparison with watchful waiting while maintaining conventional ADT was initially derived from the aggregation of these positive effects. For the most part, there were no adequate analyses available for the outcomes regarding harm. Hence no final conclusion can be drawn on these outcomes, and greater harm from abiraterone cannot be excluded with certainty, either. The available results, however, do not show signs of such a great harm that would justify downgrading the extent of the added benefit. The uncertainty regarding harm resulted in downgrading the probability of the added benefit of abiraterone to a "hint".

In summary, from the data presented, there is a "hint" of a considerable added benefit of abiraterone/prednisone or prednisolone versus the ACT (watchful waiting while maintaining conventional ADT) for the treatment of mCRPC in adult men with asymptomatic or mildly symptomatic course of disease after failure of ADT in whom chemotherapy is not yet clinically indicated.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on added benefit.

2.2 Research question

The benefit assessment of abiraterone was conducted according to the Summary of Product Characteristics (SPC) [3] for the following therapeutic indication: treatment of mCRPC in adult men with asymptomatic or mildly symptomatic course of disease after failure of ADT in whom chemotherapy is not yet clinically indicated.

The G-BA specified watchful waiting while maintaining conventional ADT or, if applicable, combined maximal androgen blockade with a non-steroidal anti-androgen (flutamide, bicalutamide) as ACT.

The company concurred with the G-BA's specification and chose watchful waiting while maintaining conventional ADT from the options mentioned. The company's approach regarding the choice of ACT seemed appropriate.

The assessment was conducted based on patient-relevant outcomes on the basis of direct comparative RCTs.

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 study pool of the assessment was compiled on the basis of the following information:

- Studies on abiraterone completed by the company up to 20.11.2012 (study list of the company).
- Results of a search in trial registries for studies on abiraterone (last search on 18.12.2012 in bibliographical databases, and on 19.11.2012 in trial registries, searches by the company).
- A search by the Institute in trial registries for studies on abiraterone to check the search results of the company up to 08.02.2013.

The resulting study pool for the comparison of abiraterone with the ACT corresponded to that of the company.

Further information on the inclusion criteria for studies in this 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

The study COU-AA-302 listed in Table 2 was included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison: abiraterone vs. watchful waiting

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
COU-AA-302	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a list of the data sources cited by the company for the studies included in the benefit assessment.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 and Table 4 describe the study used for the benefit assessment. The included study (COU-AA-302) was the approval study for the expansion of the therapeutic indication of abiraterone.

Table 3: Characteristics of the studies included – RCT, direct comparison: abiraterone vs. watchful waiting

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
COU-AA-302	RCT, double-blind, placebo-controlled, parallel	Chemotherapy-naive male adult mCRPC patients with asymptomatic or mildly symptomatic course of disease after failure of ADT	Abiraterone + prednisone + ADT (N = 546) Placebo + prednisone + ADT (N = 542)	14 days screening, treatment: until progression of disease, survival follow-up: every 3 months for up to 5 years	151 centres in Australia, Europe, Canada, and USA 4/2009 – 2/2014	Primary outcomes: OS, rPFS Secondary outcomes: time to initiation of opiate treatment, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.

ADT: androgen deprivation therapy; AE: adverse event; mCRPC: metastatic castration resistant prostate cancer; N: number of randomized patients; OS: overall survival; RCT: randomized controlled trial; rPFS: radiographic progression-free survival; USA: United States of America; vs.: versus

Table 4: Characteristics of the interventions – RCT, direct comparison: abiraterone vs. watchful waiting

Study	Intervention	Comparison	Concomitant medication
COU-AA-302	Abiraterone 250 mg, 4 tablets orally once daily, at least 1 hour before or 2 hours after a meal + prednisone 5 mg twice daily	Placebo, 4 tablets orally once daily, at least 1 hour before or 2 hours after a meal + prednisone 5 mg twice daily	**Concomitant medication permitted** Concomitant treatment with supportive drugs was allowed according to the hospital's guidelines. Patients without surgical castration had to be treated with an LH-RH analogue. Use of bisphosphonates was permitted, provided the treatment was ongoing at the start of the study treatment. **Concomitant medication prohibited** Concomitant use of other anticancer treatments including chemotherapy, hormone therapy (excluding LH-RH agonists) or immunotherapy. Initiation of bisphosphonate treatment.
The treatment with the study medication was continued until progression occurred. When progression occurred, the patients discontinued the treatment phase with the study medication, and could receive treatment escalation chosen by the investigator (e.g. chemotherapy or radiotherapy, but also abiraterone). The patients were not told what their blinded study medication had been.			
LH-RH: luteinizing hormone-releasing hormone; RCT: randomized controlled trial; vs.: versus			

The study COU-AA-302 is a randomized, double-blind and placebo-controlled study. It is a multicentre study exclusively conducted in Western industrial nations. Chemotherapy-naive adult men with mCRPC with asymptomatic or mildly symptomatic course of disease after failure of ADT were enrolled in the study.

A total of 1088 patients were randomly assigned in a ratio of 1:1, 546 patients to the abiraterone arm, and 542 patients to the placebo arm. Overall, the criteria of the approved therapeutic indication of abiraterone were regarded as being fulfilled for the patients enrolled in the study. The study as a whole is therefore relevant for the assessment. This concurs with the company's assessment.

Abiraterone was administered according to the current approval status. The patients in the abiraterone arm received 1000 mg of abiraterone + 10 mg of prednisone per day. The patients in the placebo arm received placebo + 10 mg of prednisone per day. The study treatment was administered according to a regimen described in the SPC [3]. The study treatment consisted of 28-day cycles and was continued until progression occurred. When progression occurred, the patients discontinued the treatment phase with the study medication, and could receive treatment escalation chosen by the investigator (e.g. chemotherapy or radiotherapy, but also abiraterone). The patients were not told what their blinded study medication had been. In the study protocol, the follow-up period was planned to last for up to 60 months. OS and radiographic progression-free survival (rPFS) were the primary outcomes. Patients without surgical castration had to receive an LH-RH analogue in addition to the study medication.

This treatment had to be started at least 4 weeks prior to the initiation of the treatment with the study medication. 94% of the 1088 randomized patients received this treatment after randomization. Use of bisphosphonates was permitted, provided the treatment was ongoing at the start of the study treatment.

4 analyses – 3 interim analyses and the final analysis – were planned for the study. The first interim analysis (first data cut-off: 20.12.2010) was planned based on the outcome rPFS. The 2 remaining interim analyses and the final analysis were planned based on OS. The second interim analysis (second data cut-off: 20.12.2011) was conducted after the number of 311 deaths specified in the protocol had been exceeded with 333 deaths that had occurred. The third interim analysis (third data cut-off: 22.05.2012) was conducted after the number of 425 deaths specified in the protocol had been exceeded with 434 deaths that had occurred. The final analysis has not been conducted yet and is to be performed when 773 patients will have died. Between the second and the third interim analysis, the IDMC decided to end the double-blind treatment phase of the study ahead of schedule due to good efficacy, and to unblind the study. After the unblinding, the patients in the placebo arm could change to abiraterone treatment (crossover). The third data cut-off from 22.05.2012 was still decisive for this benefit assessment because it covered the longest possible observation period, and also because its risk of bias was only marginally higher than that of the second data cut-off (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment). This concurred with the company's approach, which also used the third data cut-off for deriving the added benefit.

The median observation duration (including follow-up) up to the third data cut-off was 27.1 months. The median treatment time (minimum; maximum) was 13.8 (0.3; 34.9) months in the abiraterone arm, and 8.3 (0.1; 32.4) months in the placebo arm.

All outcomes were recorded until the end of the treatment phase with the study medication. The last documentation was performed during the end of study treatment visit. This visit took place between 14 and 28 days after the last dose of study medication. Deviating from this, AEs were recorded up to and including 30 days after the last dose of study medication. After that and until the end of the follow-up phase, only the ECOG-PS, use of opiate treatment, subsequent therapies and OS were recorded.

77% of the 546 randomized patients in the abiraterone arm, and 89% of the 542 randomized patients in the placebo arm had ended the treatment phase with the study medication because of progression or had discontinued for other reasons (e.g. withdrawal of informed consent or AEs), and 67% and 80%, respectively, of the randomized patients had received at least one subsequent treatment at the third data cut-off date. Chemotherapy (mainly docetaxel) was the most common subsequent therapy and was administered to 46% and 59% of the randomized patients.

Patients in the control arm of the study COU-AA-302 received placebo + prednisone while maintaining conventional ADT as concomitant medication. This treatment was accepted for

this benefit assessment as sufficient approximation to the ACT (watchful waiting while maintaining conventional ADT) because of the low dosage of prednisone. The study was therefore suitable for assessing the added benefit of abiraterone in comparison with the ACT. Hereinafter, the treatment in the placebo arm of the study will therefore be referred to as "watchful waiting".

Table 5 shows the characteristics of the patients in the study included.

Table 5: Characteristics of the study populations – RCT, direct comparison: abiraterone vs. watchful waiting

Study Treatment arm	N	Age [years] mean (SD)	Duration of disease [years] mean (SD)	BPI-SF pain score[a] n (%)[b]			ECOG-PS 0 / 1 n (%)
				0 – 1	2 – 3	≥ 4	
COU-AA-302							
Abiraterone/ prednisone/ADT	546	71 (9)	6.7 (4.9)	370 (68.6)	129 (23.9)	40 (7.4)	413 (75.6) / 133 (24.4)
Placebo/ prednisone/ADT[c]	542	70 (9)	6.5 (4.8)	346 (64.8)	147 (27.5)	41 (7.7)	409 (75.5) / 133 (24.5)

a: Worst pain within the last 24 hours
b: At the start of the study, the BPI-SF was only recorded for 539 patients in the abiraterone arm, and for 534 patients in the placebo arm.
c: Operationalization of watchful waiting
ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; ECOG-PS: Eastern Cooperative Oncology Group performance status; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Patient characteristics were largely comparable in both treatment arms. The mean age of the study population was between 70 and 71 years; about 76% of the patients had an ECOG-PS of 0. The mean duration of the disease was between 6.5 and 6.7 years. At the start of the study, about 66% of the patients had a Brief Pain Inventory-Short Form (BPI-SF) pain score of 0 or 1, about 25% of 2 or 3. In addition, about 7% of the patients had a BPI-SF pain score of ≥ 4, which contradicted the inclusion criteria of the study protocol. The company listed those 7% as missing in Table 4-11 of Module 4.

Although according to the inclusion criteria, in principle, also patients who exclusively had lymph node metastases could be enrolled in the study, only patients with distant metastases (tumour-node-metastasis [TNM stage M1) were enrolled. It is unclear to what extent the results of the study also apply to patients who exclusively have lymph node metastases.

Table 6 shows the risk of bias at study level.

Table 6: Risk of bias at study level – RCT, direct comparison: abiraterone vs. watchful waiting

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
COU-AA-302	yes	yes	(yes)[a]	(yes)[a]	yes	yes	low

A: Between the second and the third data cut-off, the IDMC decided to end the double-blind treatment phase of the study ahead of schedule and to unblind the study. However, no high risk of bias at study level was assumed due to the high proportion of patients who had already ended the study treatment because of progression or had discontinued for other reasons at the second data cut-off and due to the high proportion of subsequent therapies (see Section 2.7.2.4.2 of the full dossier assessment for more details).

IDMC: Independent Data Monitoring Committee, RCT: randomized controlled trial; vs.: versus

The risk of bias at the study level was rated as low for the study. This concurs with the company's assessment. The reason for this assessment is that, overall, the influence of the unblinding and the possibility of changing the therapy from placebo to abiraterone after the second data cut-off on the risk of bias was rated as low because this only concerned a small proportion of the patients and the effects regarding the relevant outcomes did not differ considerably between the second and the third data cut-off.

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, and Appendix 4-G of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

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

- Mortality:
  - OS
- Morbidity:
  - severe pain measured on the basis of initiation of opiate treatment
- health-related quality of life
- Adverse events:
  - overall rate of AEs
  - severe AEs (CTCAE Grade 3 and 4)
  - SAEs
  - treatment discontinuations due to AEs
  - specific AEs
    - fractures
    - fluid retention/oedema
    - ischaemic heart disease
    - cardiac failure

The choice of patient-relevant outcomes used for this benefit assessment deviated from that of the company, which used further outcomes in the dossier (Module 4). In particular, the outcomes rPFS and prostate-specific antigen (PSA) progression were not used because the company did neither prove the patient relevance it had postulated nor the validity as surrogate outcome sufficiently. However, additional outcomes were used for this assessment. Reasons for the choice of outcomes are given in Section 2.7.2.4.3 of the full dossier assessment.

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

Table 7: Matrix of outcomes – RCT, direct comparison: abiraterone vs. watchful waiting

Study	Outcomes										
	OS	Severe pain measured on the basis of initiation of opiate treatment	Health-related quality of life (FACT-P)	Overall rate of AEs	Severe AEs (CTCAE Grade 3 and 4)	SAEs	Treatment discontinuations due to AEs	Fractures	Fluid retention/oedema	Ischaemic heart disease	Cardiac failure
COU-AA-302	y	y	n[a]	y[b]	y[c]	y[b]	y	n	y[b]	y	y

a: No evaluable data were 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.
b: The data were presented in the dossier. The effect estimators could neither be taken from the dossier nor be calculated by the Institute due to the problems described in Section 2.7.2.4.3 of the full dossier assessment.
c: The analysis for determining the added benefit is limited to severe AEs (CTCAE Grade 3 and 4) that occurred within 3 months after the start of the study treatment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; n: no; OS: overall survival; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus; y: yes

Table 8: Risk of bias at study and outcome level – RCT, direct comparison: abiraterone vs. watchful waiting

Study	Study level	Outcomes										
		OS	Severe pain measured on the basis of initiation of opiate treatment	Health-related quality of life (FACT-P)	Overall rate of AEs	Severe AEs (CTCAE Grade 3 and 4)	SAEs	Treatment discontinuations due to AEs	Fractures	Fluid retention/oedema	Ischaemic heart disease	Cardiac failure
COU-AA-302	l	l	l	–[a]	–[a]	l	–[a]	h	–[a]	–[a]	h	h

a: No evaluable data available

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; h: high; l: low; OS: overall survival; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

There were no evaluable data on health-related quality of life, overall rate of AEs, SAEs, fractures or fluid retention/oedema available for the assessment. Therefore, no outcome-specific assessment of the risk of bias was conducted.

The risk of bias was rated as low for the outcomes OS and severe pain measured on the basis of initiation of opiate treatment. This concurs with the company's assessment (see Section 2.7.2.4.2 of the full dossier assessment).

There were no evaluable data for a large proportion of the outcomes on AEs. The company exclusively presented analyses on the basis of the naive proportion of the patients with at least one event in Module 4 of the dossier. These analyses could not be used for the benefit assessment because the observation duration in the 2 treatment arms differed considerably (median treatment duration of 13.8 months in the abiraterone arm, and of 8.3 months in the placebo arm). The analyses of the number of events per 100 patient years (based on the treatment duration) additionally partially presented by the company in the running text could not be considered because of unverifiable assumptions (see Section 2.7.2.4.2 of the full dossier assessment). In the case of rare events, the Institute performed its own calculations of the number of patients with event per 100 patient years (on the basis of the time to an event). For rare events, this analysis can serve as an approximation for the analysis of the time to an event. The risk of bias for these analyses was also rated as high, however. For severe AEs (CTCAE Grade 3 and 4), the dossier contained analyses on the proportion of patients who had at least one severe AE (CTCAE Grade 3 and 4) within 3 months after the start of the study treatment. The risk of bias was rated as low because the problem of different observation times did not exist for this analysis. The assessments deviate from those of the company, which rated the risk of bias as low for all outcomes included in the benefit assessment (see Section 2.7.2.4.2 of the full dossier assessment).

Table 9 and Table 10 summarize the results on the comparison of abiraterone and watchful waiting in patients in the therapeutic indication. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations. Table 11 contains additional information on the most frequent (≥ 1% in at least 1 treatment arm) severe AEs (CTCAE Grade 3 and 4) that occurred within 3 months after the start of the study treatment.

Only the results for the total population of the study COU-AA-302 were used for this benefit assessment. This deviated from the company's approach, which presented the results of the total population, but derived its conclusions on added benefit only separately for the group with favourable prognosis and for the group with unfavourable prognosis. These subgroups were not used because they were defined post hoc and no sufficient reasons were given for the validity of the cut-off values (see Section 2.7.2.2 of the full dossier assessment).

Table 9: Results on survival time, morbidity and quality of life – RCT, direct comparison: abiraterone vs. watchful waiting

Study Outcome category Outcome	Abiraterone/ prednisone/ADT		Placebo/ prednisone/ADT[a]		Abiraterone/ prednisone/ADT vs. placebo/prednisone/ADT[a]	
	N	Median survival time in months [95% CI]	N	Median survival time in months [95% CI]	HR [95% CI]	p-value
COU-AA-302[b]						
OS	546	35.3 [31.2; 35.3]	542	30.1 [27.3; 34.1]	0.79 [0.66; 0.96][c]	0.015[c]
	N	**25% quantile[d] time to event in months [95% CI]**	**N**	**25% quantile[d] time to event in months [95% CI]**	**HR [95% CI]**	**p-value**
Morbidity						
Time to initiation of opiate treatment (severe pain)						
	546	14.8 [13.0; 17.2][e]	542	12.0 [10.2; 13.0][e]	0.71 [0.59; 0.85][f]	< 0.001[f]
Health-related quality of life	No evaluable data					

a: Operationalization of watchful waiting
b: Third data cut-off (22.05.2012)
c: HR and p-value from log-rank test stratified according to ECOG-PS Grade (0 and 1).
d: Median time to event could not be estimated in at least one treatment arm because of the high proportion of censored data. The 25% quantile shows the time at which the Kaplan-Meier estimator of the survival function is below 75% for the first time.
e: The median event time was only reached in the placebo arm (23.7 [20.4; 30.3]).
f: Stratified according to ECOG-PS score (0 or 1)

ADT: androgen deprivation therapy; CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; N: number of analysed patients; OS: overall survival; RCT: randomized controlled trial; vs.: versus

Table 10: Results on adverse events – RCT, direct comparison: abiraterone vs. watchful waiting

Study Outcome	Abiraterone/ prednisone/ADT		Placebo/ prednisone/ADT[a]		Abiraterone/ prednisone/ADT vs. placebo/prednisone/ ADT[a]
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
COU-AA-302[b]					
Overall rate of AEs	No evaluable data				
Severe AEs (CTCAE Grade 3 and 4)[c]	542	98 (18.1)[d]	540	92 (17.0)[d]	1.06 [0.82; 1.37]; 0.652[e]
SAEs[f]	No evaluable data				
	N	**Patients with event n (n/100 patient years)[g]**	**N**	**Patients with event n (n/100 patient years)[h]**	**IDR [95% CI]; p-value**
Treatment discontinuations due to AEs[f]	542	58 (8.2)[d]	540	53 (10.7)[d]	0.77 [0.53; 1.11]; 0.160[e]
Fractures	No evaluable data				
Fluid retention/ oedema	No evaluable data				
Ischaemic heart disease	542	25 (3.5)[d]	540	20 (4.0)[d]	0.87 [0.49; 1.57]; 0.655[e]
Cardiac failure	542	12 (1.7)[d]	540	2 (0.4)[d]	4.20 [0.94; 18.76]; 0.060[e]

a: Operationalization of watchful waiting
b: Third data cut-off (22.05.2012)
c: Severe AEs (CTCAE Grade 3 and 4) within 3 months after the start of the study treatment for all patients
d: Institute's calculation of percentage or patients with event per 100 patient years
e: Institute's calculation of estimator, related confidence interval and p-value
f: CTCAE Grade 5 is not included.
g: Treatment time with study medication in the abiraterone arm: 707.5 years
h: Treatment time with study medication in the placebo arm: 495.0 years

ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; IDR: incidence density ratio; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 11: Most frequent (≥1% in at least 1 treatment arm) severe AEs (CTCAE Grade 3 and 4) within 3 months after the start of the study treatment – RCT, direct comparison: abiraterone vs. watchful waiting

Severe AEs (CTCAE Grade 3 and 4)[b,c]	**Abiraterone/ prednisone/ADT N = 542 Patients with event n (%)**	**Placebo/ prednisone/ADT[a] N = 540 Patients with event n (%)**
Alanine aminotransferase increased	23 (4.2%)	1 (0.2%)
Aspartate aminotransferase increased	11 (2.0%)	2 (0.4%)
Hyperglycaemia	7 (1.3%)	4 (0.7%)
Hyponatraemia	5 (0.9%)	6 (1.1%)
Hypertension	7 (1.3%)	10 (1.9%)

a: Operationalization of watchful waiting
b: Third data cut-off (22.05.2012)
c: Severe AEs (CTCAE Grade 3 and 4) within 3 months after the start of the study treatment for all patients
ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

Study COU-AA-302 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 derived from the data.

This assessment deviates from that of the company, which derived "proof" of added benefit both for the group with favourable prognosis and for the group with unfavourable prognosis from the study COU-AA-302.

Mortality

Overall survival

Abiraterone treatment resulted in a statistically significant prolongation of OS in comparison with watchful waiting. This led to an "indication" of an added benefit of abiraterone in comparison with watchful waiting while maintaining conventional ADT for the outcome OS. This assessment deviates from that of the company, which derived "proof" of added benefit for the patients in the group with favourable prognosis and no added benefit for the patients in the group with unfavourable prognosis.

Morbidity

Severe pain measured on the basis of initiation of opiate treatment

In this benefit assessment, the time to initiation of opiate treatment is used as operationalization for the occurrence of severe pain. Abiraterone treatment resulted in a statistically significant delay in the time to initiation of opiate treatment (severe pain) in

comparison with watchful waiting. This led to an "indication" of an added benefit of abiraterone in comparison with watchful waiting while maintaining conventional ADT regarding the occurrence of severe pain measured on the basis of initiation of opiate treatment. This assessment deviates from that of the company, which derived "proof" of added benefit both for the patients in the group with favourable prognosis and for the patients in the group with unfavourable prognosis.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life. An added benefit of abiraterone in comparison with watchful waiting while maintaining conventional ADT is therefore not proven for the outcome health-related quality of life. This assessment deviates from that of the company, which derived "proof" of added benefit both for the patients in the group with favourable prognosis and for the patients in the group with unfavourable prognosis.

Adverse events

Module 4 of the dossier did not contain any valid analyses for the assessment of AEs, which could be included in the benefit assessment. The data based on naive proportions (proportion of patients with at least one event) presented by the company did not constitute an adequate analysis due to the considerably different treatment durations with the study medication (and hence also observation durations) in both treatment arms (median treatment duration with the study medication: 13.8 months in the abiraterone arm, and 8.3 months in the placebo arm). The analyses of the number of events per 100 patient years (based on the treatment duration with the study medication) additionally partially presented by the company in the running text could not be considered either (see Section 2.7.2.4.2 of the full dossier assessment).

Therefore the analysis of the number of patients with events per 100 patient years was used for this benefit assessment, but only in the case of rare events (see Section 2.7.2.4.2 of the full dossier assessment). The incidence density ratio (IDR) was calculated as related effect measure. It was not possible to conduct a valid analysis for non-rare events on the basis of the data presented in the dossier.

No evaluable analyses were available for the overall rate of AEs, SAEs as well as the specific AEs fractures and fluid retention/oedema, due to the reasons described above. Greater or lesser harm from abiraterone in comparison with watchful waiting while maintaining conventional ADT is not proven for these outcomes. This assessment concurs with that of the company for the overall rate of AEs and the rate of SAEs. The company did not include the specific AEs fractures and fluid retention/oedema in the assessment.

There were also no evaluable data for severe AEs (CTCAE Grade 3 and 4) in Module 4 of the dossier. The approval documents contained an additional analysis of the proportion of patients with at least one severe AE (CTCAE Grade 3 and 4) within 3 months after the start of the study treatment, however. Since the differences in observation duration between the treatment

arms were not yet marked in this period, this analysis was used for the benefit assessment. There was no statistically significant difference between the treatment arms. Greater or lesser harm from abiraterone in comparison with watchful waiting while maintaining conventional ADT is therefore not proven for severe AEs (CTCAE Grade 3 and 4) that occurred within 3 months after the start of the study treatment.

The Institute's calculations of the proportion of patients with treatment discontinuations due to AEs per 100 patient years described above were conducted for the treatment discontinuations due to AEs. There was no statistically significant difference between the treatment arms. Greater or lesser harm from abiraterone in comparison with watchful waiting while maintaining conventional ADT is not proven for treatment discontinuations due to AEs.

The Institute also conducted its own calculation of the proportion of patients with at least one event per 100 patient years for the specific AEs ischaemic heart disease and cardiac failure. There was no statistically significant difference between the treatment arms for none of these outcomes. Greater or lesser harm from abiraterone in comparison with watchful waiting while maintaining conventional ADT is not proven for ischaemic heart disease and cardiac failure.

The assessments of the results on AEs mainly concur with those of the company. Only regarding treatment discontinuations due to AEs, the company's assessment deviates, which derived "proof" of greater harm from abiraterone for the patients in the group with unfavourable prognosis. It is to be noted that the company's assessment was only based on the results of the naive proportions. Moreover, the company derived conclusions on added benefit separately for the group with unfavourable prognosis and for the group with favourable prognosis. The company presented results on specific AEs in Module 4 of the dossier, but did not derive conclusions on added benefit of abiraterone.

Subgroup analyses

Subgroup analyses on the characteristics age (< 65 years versus > 65 years), ECOG-PS (0 versus 1), BPI-SF score (0 to 1 versus 2 to 3), patients with bone metastases (yes versus no) and geographical region were considered for this benefit assessment. Subgroup analyses on all these characteristics were only available for the outcome OS, partially not in Module 4, however. For the outcomes overall rate of AEs, SAEs, severe AEs, and treatment discontinuations due to AEs, subgroup analyses were only available for the characteristic age. These were not evaluable, however, as they were based on the raw proportions of patients with at least one event. The company did not present any subgroup analyses for the time until the initiation of opiate treatment (severe pain).

There is no "indication" ($0.05 \leq p < 0.2$) or "proof" ($p < 0.05$) for an effect modification regarding the outcome OS for any of the subgroup analyses considered.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and the effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

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

2.5.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 led to an "indication" of an added benefit of abiraterone versus the ACT (watchful waiting while maintaining conventional ADT) for the outcomes OS and severe pain measured on the basis of initiation of opiate treatment. The extent of the respective added benefit at outcome level was estimated from these results (see Table 12 and Table 13).

Table 12: Extent of added benefit at outcome level (beneficial outcomes): abiraterone vs. watchful waiting

Outcome	**Effect estimator [95% CI] p-value Time to event abiraterone/prednisone/ADT vs. placebo/ADT[a] (months) Probability[b]**	**Derivation of extent[c]**
Mortality[d]		
OS	HR: 0.79 [0.66; 0.96] p = 0.015 Median: 35.3 vs. 30.1 Probability: "indication"	Outcome category: survival time $0.95 \leq CI_o < 1$ Added benefit, extent: “minor”
Morbidity[d]		
Severe pain measured on the basis of initiation of opiate treatment	HR: 0.71 [0.59; 0.85] p < 0.001 25% quantile[e]: 14.8 vs. 12.0 Probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_o < 0.90$ Added benefit, extent: “considerable”
Health-related quality of life		
FACT-P	No evaluable data were available in the company’s dossier.	Lesser benefit/added benefit not proven

a: Operationalization of watchful waiting
b: Probability provided if statistically significant differences were present
c: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_o).
d: Third data cut-off (22.05.2012)
e: Median time to event could not be estimated in at least one treatment arm because of the high proportion of censored data. The 25% quantile shows the time at which the Kaplan-Meier estimator of the survival function is below 75% for the first time.
ADT: androgen deprivation therapy; CI: confidence interval; CI_o: upper limit of confidence interval; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; OS: overall survival; vs.: versus

Table 13: Extent of added benefit at outcome level (harmful outcomes): abiraterone vs. watchful waiting

Outcome	**RR [95% CI] p-value Number of patients with event (%) or IDR [95% CI] p-value Number of patients with event (n/100 patient years) Abiraterone/prednisone/ADT vs. placebo/prednisone/ADT[a] Probability[b]**	**Derivation of extent[c]**
Adverse events[d]		
Overall rate of AEs	No evaluable data available	Greater/lesser harm not proven
Severe AEs (CTCAE Grade 3 and 4)[e]	RR: 1.06 [0.82; 1.37] p = 0.652 98 (18.1%) vs. 92 (17.0%)	Greater/lesser harm not proven
SAEs	No evaluable data available	Greater/lesser harm not proven
Treatment discontinuations due to AEs	IDR: 0.77 [0.53; 1.11] p = 0.160 58 (8.2) vs. 53 (10.7)	Greater/lesser harm not proven
Fractures	No evaluable data available	Greater/lesser harm not proven
Fluid retention/oedema	No evaluable data available	Greater/lesser harm not proven
Ischaemic heart disease	IDR: 0.87 [0.49; 1.57] p = 0.655 25 (3.5) vs. 20 (4.0)	Greater/lesser harm not proven
Cardiac failure	IDR: 4.20 [0.94; 18.76] p = 0.060 12 (1.7) vs. 2 (0.4)	Greater/lesser harm not proven

a: Operationalization of watchful waiting
b: Probability provided if statistically significant differences were present
c: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval.
d: Third data cut-off (22.05.2012)
c: Severe AEs (CTCAE Grade 3 and 4) within 3 months after the start of the study treatment

ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; IDR: incidence density ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of abiraterone compared with watchful waiting

Positive effects	Negative effects
Indication of an added benefit – extent: "minor" (mortality: overall survival)	
Indication of an added benefit – extent: considerable (morbidity, serious/severe symptoms/late complications: severe pain measured on the basis of initiation of opiate treatment)	

Overall, only positive effects remain at outcome level on the basis of the available and evaluable results. These are an "indication" of a minor added benefit in the outcome category mortality (OS) and an "indication" of a considerable added benefit for an outcome in the category serious/severe symptoms/late complications (severe pain measured on the basis of initiation of opiate treatment). An "indication" of a considerable added benefit of abiraterone in comparison with watchful waiting while maintaining conventional ADT was initially derived from the aggregation of these positive effects. For the most part, there were no adequate analyses available for the outcomes regarding harm. Hence no final conclusion can be drawn on harm. Greater harm from abiraterone can also not be completely excluded. The available results, however, do not show signs of such a great harm that would justify downgrading the extent of the added benefit. However, the great uncertainty regarding harm resulted in downgrading the probability of the added benefit of abiraterone to a "hint".

In summary, there is a "hint" of a considerable added benefit of abiraterone versus the ACT (watchful waiting while maintaining conventional ADT) for the treatment of mCRPC in adult men with asymptomatic or mildly symptomatic course of disease after failure of ADT in whom chemotherapy is not yet clinically indicated.

2.6 List of included studies

Janssen Research & Development. Abiraterone acetate in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer: full text view [online]. In: Clinicaltrials.gov. 20.03.2013 [accessed 26.03.2013]. URL: http://clinicaltrials.gov/show/NCT00887198.

Janssen Research & Development. A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in asymptomatic or mildly symptomatic subjects with metastatic castration-resistant prostate cancer: study COU-AA-302; clinical study report [unpublished]. 2012.

Janssen Research & Development. A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in asymptomatic or mildly symptomatic subjects with metastatic castration-resistant prostate cancer: study COU-AA-302; report of updated data [unpublished]. 2012.

Janssen Research & Development. Messwiederholungsmodelle für BPI und FACT-P (Studie COU-AA-302, Interimsanalyse 2, ITT-Analyse) [unpublished]. 2012.

Janssen Research & Development. Rücklaufquote des FACT-P-Fragebogens in den jeweiligen Therapiezyklen (COU-AA-302; Interimsanalyse 2; ITT-Analyse) [unpublished]. 2012.

Janssen Research & Development. Rücklaufquote des FACT-P-Fragebogens in den jeweiligen Therapiezyklen (COU-AA-302; Interimsanalyse 3; ITT-Analyse) [unpublished]. 2012.

Janssen Research & Development. Kumulative Rücklaufquote des BPI-SF in den jeweiligen Therapiezyklen (COU-AA-302; Interimsanalyse 3; ITT-Analyse) [unpublished]. 2012.

Janssen-Cilag. Overall survival: treatment effects (HR), by subgroup (data cut 55) [unpublished]. 2012.

Janssen-Cilag. Radiographic PFS: treatment effects (HR), by subgroup (data cut 55) [unpublished]. 2012.

Janssen-Cilag. Treatment effects (HR), by subgroups (data cut 55%) [unpublished]. 2012.

Ryan CJ, Morris MJ, Molina A, Piulats JM, De Souza P, Li J et al. Association of radiographic progression-free survival (rPFS) adapted from Prostate Cancer Working Group 2 (PCWG2) consensus criteria with overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC): results from COU-AA-302 [Präsentationsfolien]. ESMO Congress 2012; 28.09.-02.10.2012; Wien, Österreich.

Ryan CJ, Smith MR, De Bono JS, Molina A, Logothetis CJ, De Souza P et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2012; 368(2): 138-148.

References for English extract

Please see full dossier assessment for full reference list.
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2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to § 35a Social Code Book V; extract; commission no. A11-02 [online]. 29.09.2011 [accessed 05.05.2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. European Medicines Agency. ZYTIGA 250 mg tablets: European public assessment report; product information [online]. 01.2013 [accessed 26.03.2013]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002321/WC500112858.pdf.

The full report (German version) is published under https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a13_06_abirateronacetat_neues_anwendungsgebiet_nutzenbewertung_gemass_35a_sgb_v_dossierbewertung.3351.html