

IQWiG Reports – Commission No. A12-14

Axitinib –

**Benefit assessment according
to § 35a Social Code Book V¹**

Extract

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EQ-5D (=EuroQuol-5D)	European Quality Of Life-5 Dimensions
FKSI	Functional Assessment of Cancer Therapy – Kidney Symptom Index
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms
G-BA	<i>Gemeinsamer Bundesausschuss</i> (Federal Joint Committee)
HR	hazard ratio
ICTRP	International Clinical Trial Registry Platform Search Portal
IQWiG	<i>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen</i> (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
PH model	proportional hazards model
PRES	posterior reversible encephalopathy syndrome
RCC	renal cell carcinoma
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SGB	<i>Sozialgesetzbuch</i> (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit 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 the drug axitinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to “the company”). The dossier was sent to IQWiG on 01.10.2012.

Research question

The aim of this report is to assess the added benefit of axitinib compared with sorafenib as appropriate comparator therapy (ACT) in patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with a cytokine (cytokine population) and everolimus as ACT after failure of prior treatment with sunitinib (sunitinib population).

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

Results

A total of one relevant study (AXIS study) was available for the direct comparison of axitinib with the ACT sorafenib. This was the approval study of axitinib, an ongoing, open-label, and parallel-group RCT. Adult patients with metastatic RCC after failure of a prior systemic treatment (including cytokine, sunitinib) were enrolled. Patients were randomized to axitinib or sorafenib in a ratio of 1:1. The cytokine population from this study was thus relevant to answer the research question. No direct comparative studies were available for the comparison of axitinib with everolimus for the sunitinib population. An indirect comparison was planned, but could not be conducted because there was no study for the intermediate comparator sorafenib in which patients had been given prior treatment with sunitinib. Following a check of the methodology, results from other investigations by the company were not usable. Therefore, the results described below relate solely to the cytokine population.

The risk of bias at study level of the AXIS study was low, so that in principle indications, e.g. of an added benefit, could be derived, provided outcome-specific aspects did not weaken the informative value. The risk of bias for the outcome “overall survival” at outcome level was rated as low. For the outcomes “quality of life”, “symptoms” as well as “adverse events (AEs)”, the risk of bias was high. In each case, the high risk of bias arose because the requirement of non-informative censorings for an unbiased estimation of the hazard ratio (HR) in the Cox proportional hazards (PH) model was not met. The high risk of bias for the outcome “health-related quality of life” and “symptoms” was also due to the open-label study design.

Mortality (outcome: “overall survival”)

There was no statistically significant difference between axitinib and sorafenib for the outcome “overall survival”. An added benefit of axitinib for this outcome is not proven.

Morbidity (outcome: “symptoms”)

Symptoms were assessed using the results recorded with the instrument Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS). This is a disease-specific instrument with 9 questions about symptoms. There was no statistically significant difference between axitinib and sorafenib. An added benefit of axitinib for this outcome is not proven.

Health-related quality of life

Health-related quality of life was assessed on the basis of the results recorded with the instrument FKSI-15. This is a disease-specific instrument with 15 questions. There was no statistically significant difference between axitinib and sorafenib.

In the AXIS study, the generic instrument “European Quality Of Life-5 Dimensions” (EuroQol [EQ]-5D) was also used. Data for the cytokine population were not provided.

In summary, an added benefit of axitinib for health-related quality of life is not proven.

Adverse events

The analysis of the overall rate of AEs showed that an AE was observed in almost all patients during the course of the study. The time to first occurrence of an AE was longer under axitinib than under sorafenib. However, this difference cannot be interpreted because there was no information on the nature of the events and relevance of the delay. The relevance of a delay is questionable, especially for non-serious and transient AEs. Greater or lesser harm from axitinib than from sorafenib for the overall rate of AEs is therefore not proven.

There were no statistically significant differences in the time to first occurrence of a severe AE (CTCAE Grade ≥ 3), a serious AE (SAE) or treatment discontinuation due to an AE. Greater or lesser harm from axitinib than from sorafenib in relation to these aspects is not proven.

Analyses of individual severe AEs (CTCAE Grade ≥ 3) or SAEs were not provided for the cytokine population. The present assessment was also to consider the results of outcomes relevant in the indication (venous/arterial thromboembolic events, bleeding events, posterior reversible encephalopathy syndrome [PRES] and gastrointestinal perforation). Once again, there were no results on these events for the population relevant to the assessment. Greater or lesser harm from axitinib than from sorafenib in relation to these outcomes is not proven.

Analyses were provided of the most common AEs in the total study population (frequency $> 20\%$). It remains unclear whether these AEs were also the most common AEs in the

cytokine population. It is therefore possible that relevant differences between the treatment groups in respect of other AEs were not identified. This uncertainty could not be resolved on the basis of the available data.

The results on the AEs “alopecia”, “rash” and “hand-foot syndrome” showed a statistically significant difference in favour of axitinib for each of them. On the other hand, for the AEs “dysphonia”, “fatigue” and “nausea” there was in each case a statistically significant difference in favour of sorafenib. Overall, it remains unclear whether the observed effects for the cytokine population also applied to severe events, because the dossier contained no results on this point. An analysis of AEs in the cytokine population according to the severity grades of the Common Terminology Criteria for Adverse Events (CTCAE) is not only generally worthwhile on medical grounds, but is also relevant when assessing the extent of added benefit. The assessment of events potentially very troublesome for patients (e.g. hand-foot syndrome) underlines the importance of the generally relevant information on severity grades in the respective population considered. Since, overall, it remains unclear whether the observed effects for the cytokine population also applied to severe events, the results on the basis of the available information were included as non-severe events in the assessment of the extent of added benefit.

The risk of bias at outcome level was taken into account when deriving conclusions on the probability of added benefit based on AE results. The direction of the risk of bias was considered. The risk of bias was rated as high. It is assumed that the on-average longer treatment time of the axitinib group put axitinib at a disadvantage, since more AEs could be documented when the observation period was longer. If axitinib had an advantage, the estimator would tend to underestimate the true effect. In the case of an observed advantage of sorafenib, then the estimator would, on the other hand, tend to overestimate the true effect. Against this background, an indication of lesser harm from axitinib than from sorafenib would have to be derived for each of the events “alopecia”, “rash” and “hand-foot syndrome”.

However, the remaining uncertainty about the fact that the severity of the described events and the identification of the most common AEs in the cytokine population relevant to this assessment remain unclear must be taken into account in the reliability of the conclusions concerning the results on AEs. Therefore the “indication” was downgraded to a “hint”. There is thus a hint of lesser harm from axitinib than from sorafenib for the events “alopecia”, “rash” and “hand-foot syndrome”. For the event “dysphonia”, there is a hint of greater harm from axitinib than from sorafenib. Because of the marginal effect size for the events “fatigue” and “nausea”, there is no proof of greater harm from sorafenib.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

The overall conclusion on the extent of added benefit for the relevant subpopulations after prior treatment with a cytokine or sunitinib compared with the ACT is shown separately for each subpopulation.

On the basis of the results presented, the extent and probability of the added benefit of the drug axitinib compared with the ACT is assessed as follows:

For patients with advanced metastatic RCC after failure of a **prior treatment with a cytokine**, overall, positive and negative effects remain compared with the ACT. On the positive side, for 3 of the outcomes of the category “non-severe/non-serious AEs” there is in each case lesser harm with the probability “hint“ and the extent “considerable“. On the negative side, for one outcome of the category “non-severe/non-serious AEs” there is greater harm with the probability “hint“ and the extent “considerable”.

No evaluable data were available for the comparison of axitinib with the ACT everolimus in patients with advanced metastatic RCC after failure of a **prior treatment with sunitinib**. The added benefit of axitinib over everolimus in patients previously treated with sunitinib is not proven.

Table 2 summarizes the extent and probability of added benefit for the relevant subpopulations of this benefit assessment.

⁴ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm from an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

Table 2: Axitinib: extent and probability of added benefit

Therapeutic situation^a	ACT	Extent and probability of added benefit
Treatment of advanced metastatic RCC in adult patients after failure of prior treatment with sunitinib ("sunitinib population")	Everolimus	Added benefit not proven.
Treatment of advanced metastatic RCC in adult patients after failure of prior treatment with cytokines ("cytokine population")	Sorafenib	Hint of a considerable added benefit of axitinib
<p>a: The AXIS study specified that patients with metastatic RCC were to be enrolled. According to the SPC [3] axitinib is approved for patients with advanced RCC. In addition to patients with metastatic RCC, the therapeutic indication thus also covers patients with locally advanced RCC without metastases. It is unclear whether the observed effects are also applicable to these patients. For this reason, the results of the AXIS study are not applied to the patients with locally advanced RCC without metastases.</p> <p>ACT: appropriate comparator therapy, RCC: renal cell carcinoma, SPC: Summary of Product Characteristics.</p>		

In summary, there is a hint of a considerable added benefit of axitinib over the ACT sorafenib for patients with advanced metastatic RCC after failure of prior treatment with a cytokine. An added benefit of axitinib over the ACT everolimus after failure of a prior treatment with sunitinib is not proven.

The overall conclusion regarding added benefit was based on the aggregation of the extent of added benefit derived at outcome level.

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

2.2 Research question

Axitinib is a drug for the treatment of advanced RCC. The benefit assessment was conducted according to the Summary of Product Characteristics (SPC) [3] for adult patients after failure of prior treatment with sunitinib or a cytokine.

The company named the following therapies as ACT for the treatment of advanced RCC in adult patients:

- After failure of prior treatment with sunitinib, the ACT everolimus or sorafenib.
- After failure of prior treatment with a cytokine, the ACT sorafenib.
- After failure of prior treatment with sunitinib or a cytokine, the ACT sorafenib.

Table 3 shows the ACT specified by the G-BA.

Table 3: Therapeutic situation and ACT specified by the G-BA

Therapeutic situation	ACT
Treatment of advanced metastatic RCC in adult patients after failure of prior treatment with sunitinib (hereinafter referred to as “sunitinib population”)	Everolimus
Treatment of advanced metastatic RCC in adult patients after failure of prior treatment with cytokines (hereinafter referred to as “cytokine population”)	Sorafenib
ACT: appropriate comparator therapy, RCC: renal cell carcinoma	

The company deviated from the ACT of the G-BA in that, in addition to the ACT specified by the G-BA, it designated sorafenib as ACT after failure of prior treatment with sunitinib, as well as after prior treatment with sunitinib *or* a cytokine. However, these prior treatments are not part of the approved therapeutic indication of sorafenib (see Section 2.7.1 of the full dossier assessment).

For this assessment of added benefit, the ACT specified by the G-BA is therefore followed.

The assessment was conducted based on patient-relevant outcomes. Only direct comparative RCTs were included in the assessment.

Further information on the research question can be found in Module 3, Section 3.1 and in 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 axitinib completed by the company up to 03.08.2012 (study list of the company).
- Results of a search in bibliographical databases and trial registries for studies on axitinib (last search 29.08.2012 in bibliographical databases and 03.08.2012 in trial registries, searches by the company)
- Results of a search in bibliographical databases and trial registries for studies on the ACT everolimus (last search 01.08.2012 in bibliographical databases and 05.08.2012 in trial registries, searches by the company).
- Results of a search in bibliographical databases and trial registries for studies on the ACT sorafenib (last search 21.08.2012 in bibliographical databases and 05.08.2012 in trial registries, searches by the company).
- A search by the Institute in trial registries for studies on axitinib to check the search results of the company up to 15.10.2012. The check produced no deviations from the study pool presented in the company’s dossier.
- A search by the Institute in a trial registry for studies on everolimus to check the search results of the company up to 25.10.2012.
- A search by the Institute in a trial registry for studies on sorafenib to check the search results of the company was not necessary.

The resulting study pool for the direct and indirect comparison of axitinib with everolimus or sorafenib 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 listed in the following tables was included in the benefit assessment.

Table 4: Study pool – RCT, direct comparison – AXIS study – axitinib versus sorafenib, cytokine population

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)
AXIS (A4061032)	yes	yes	no

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
RCT: randomized controlled trial

The AXIS study specified that patients with metastatic RCC were to be enrolled. According to the SPC [3] axitinib is approved for patients with advanced RCC. In addition to patients with metastatic RCC, the therapeutic indication thus also covers patients with locally advanced RCC without metastases. It is unclear whether the effects observed in the study are also applicable to patients with locally advanced RCC. For this reason, the results of the AXIS study are not applied to the patients with locally advanced RCC without metastases.

The company's statement that no valid adjusted indirect comparison of axitinib with everolimus is possible for the sunitinib population is accepted (see Section 2.7.2.2 of the full dossier assessment). At the same time, the company's method for a simulated treatment comparison described in Section 4.3.2.3 in Module 4, performed as part of further investigations, is not accepted (see Section 2.7.2.7 of the full dossier assessment). As a result of these two decisions, studies identified with the aim of conducting an adjusted indirect comparison and/or conducting further investigations, were excluded. This applied to the TARGET [4-6] and RECORD-1 [7-15] studies included by the company for the indirect comparison and the further investigations.

No studies for the direct comparison of axitinib with everolimus could be identified (see also Section 2.7.2.3.1 of the full dossier assessment). One RCT on the direct comparison of axitinib with sorafenib was included. The study pool for the benefit assessment of axitinib concurs with the company's study pool for the direct comparison of axitinib with the ACT sorafenib.

Section 2.6 contains a list of the data sources cited by the company for the studies included in the benefit assessment. The company cited the entry in the registry ClinicalTrials.gov both from the original registry as well as via the meta registry International Clinical Trials Registry Platform (ICTRP). In Section 2.6 only the entry in the original registry is named.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 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 5 and Table 6 describe the study used for the benefit assessment. This is the approval study for axitinib.

The AXIS study is an ongoing open-label, parallel-group RCT. It is a multicentre study and is being conducted in western industrialized nations as well as countries in Asia and Latin America. Axitinib is compared with sorafenib. The patients were stratified according to previous treatment and severity (Eastern Cooperative Oncology Group, ECOG) and randomized in a ratio of 1:1 to receive axitinib or sorafenib. The subpopulation previously treated with a cytokine is relevant for this assessment because the study comparator is the ACT only for this subpopulation. Adult patients with metastatic RCC after failure of prior systemic treatment were enrolled.

A total of 723 patients were randomized, of whom 251 had been previously treated with a cytokine and were therefore relevant for the benefit assessment. This means a deviation from the approach of the company which, in its dossier, considered the sunitinib population as well as the cytokine population from the AXIS study as relevant to the assessment.

At the time of this benefit assessment, observation of the patients in the study was not yet complete. The planned final analysis of the primary outcome “progression-free survival” (PFS) was planned for the time at which 409 patients had shown progression of the disease or had died. The data cut-off date for the analysis was 31.08.2010. The mean treatment duration of the treatment groups of the cytokine population at the data cut-off of 31.08.2010 for axitinib was 265.6 days (standard deviation [SD] 154.8) and for sorafenib 242.5 days (SD: 147.8). Data relating to the outcomes “health-related quality of life”, “symptoms” and “AEs” were recorded 28 days after the end of treatment. Among the patient-relevant outcomes, analyses for the time point 01.11.2011, which had been carried out as part of the approval process, were only available for “overall survival”. Data for the outcome “overall survival” are being recorded after a longer follow-up observation of up to 3 years after randomization, so that in this document, the term “treatment period“ is not used for the outcome “overall survival”, but “observation period“ instead.

Both axitinib as well as sorafenib were administered according to their current approval status. This meant for axitinib a starting dose of 2 x 5 mg daily that could be increased, if the drug was well tolerated, to a maximum of 2 x 10 mg daily. The starting dose for sorafenib was 2 x 400 mg daily. Dose reductions or even treatment interruptions were possible for both interventions according to defined criteria. Apart from palliative radiotherapy under certain conditions, concomitant therapies were not allowed. No specifications were made regarding subsequent therapy for the follow-up phase (still ongoing) after the end of study treatment.

Table 5: Characteristics of the study included – RCT, direct comparison – AXIS study – axitinib versus sorafenib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
AXIS (A4061032)	RCT, open-label, parallel	Adult patients with metastatic RCC with clear-cell component after failure of prior systemic treatment with either sunitinib, bevacizumab (+ interferon alpha), temsirolimus or cytokines	Axitinib (N = 361) Sorafenib (N = 362) Of which approval population after first-line therapy with a cytokine: axitinib (n = 126) sorafenib (n = 125)	<i>Treatment:</i> Until first occurrence of progression, death, unacceptable toxicity or withdrawal of patient <i>Follow-up visit:</i> 28 days after the end of treatment <i>Follow-up survival and subsequent treatments:</i> At least 3 years after start of treatment (randomization) or until death	Western industrialized nations as well as countries in Asia and Latin America Ongoing study Recruitment September 2008-July 2010 Analysis at planned data cut-off: 31.08.2010 (further analyses at later data cut-offs available)	<i>Primary:</i> Progression-free survival <i>Secondary:</i> Overall survival, health-related quality of life, adverse events
b: 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.						
N: Number of randomized patients, n: relevant subpopulation, RCC: renal cell carcinoma, RCT: randomized controlled trial						

Table 6: Characteristics of interventions – RCT, direct comparison – AXIS study – axitinib versus sorafenib

Study	Axitinib	Sorafenib	Concomitant medication	Subsequent treatment and follow-up observation
AXIS (A4061032)	Starting dose: 2 x 5 mg/day, possible dose increase if well-tolerated: 2 x 7 mg/day or 2x 10 mg/day Dose reductions with defined criteria: 2 x 3 mg/day or 2 x 1 mg/day or treatment pause/discontinuation	Starting dose: sorafenib 2 x 400 mg/day Dose reductions if ADR suspected: 1 x 400 mg/day or 400 mg every 2nd day or treatment pause/discontinuation	Palliative radiotherapy: for pain control and only at bone sites that were already affected by metastases at the start of the study	After end of study treatment: no further specifications regarding subsequent therapy Documentation of subsequent therapy during the follow-up observation period
ADR: adverse drug reactions, RCT: randomized controlled trial				

Table 7 shows the characteristics of the patients in the study included. For the sake of completeness, data on the total study population are also shown in this table. The cytokine population accounted for 34.7% of the total population, which consisted of many more men than women. The mean age of the study population of 60 years was rather young for this indication. All patients were assigned an ECOG performance status 0 or 1, i.e. they were still physically active or restricted to some degree but were able to carry out light activities themselves. Since – as already described above – a stratified randomization after first-line therapy and severity (ECOG) was performed, the characteristics were, as expected, in each case equally distributed over the two study arms.

Table 7: Characteristics of the study population – RCT, direct comparison – AXIS study – axitinib versus sorafenib

Group	N (%)	Age [years] mean (SD)	Sex f/m %	Tumour stage III/IV n (%)	Ethnic origin White/non-white n (%)	ECOG status [0/1] n (%)	MSKCC risk group Version 2004^a favourable/intermediate/poor n (%)
<i>Study population:</i>							
Axitinib	361 (100)	60 (10.5)	26.6/73.4	39 (10.8)/322 (89.2)	278 (77.0)/83 (23.0)	195 (54.0)/162 (44.9)	100 (27.7)/134 (37.1)/118 (32.7)
Sorafenib	362 (100)	60 (10.1)	28.7/71.3	40 (11.0)/322 (89.0)	269 (74.3)/93 (25.7)	200 (55.2)/160 (44.2)	101 (27.9)/130 (35.9)/120 (33.1)
<i>Cytokine population</i>							
Axitinib	126 (34.9)	59 (10.9)	24.6/75.4	8 (6.3)/118 (93.7)	82 (65.1)/44 (34.9)	75 (59.5)/51 (40.5)	52 (41.3)/38 (30.2)/35 (27.8)
Sorafenib	125 (34.5)	60 (9.5)	30.4/69.6	10 (8.0)/115 (92.0)	81 (64.8)/44 (35.2)	74 (59.2)/51 (40.8)	50 (40.0)/37 (29.6)/31 (24.8)
<p>a: In its dossier, the company used the 1999 and 2004 versions of the MSKCC risk group classification to show the risk groups. Since the 2004 version was used to record data for the efficacy analyses, the corresponding data for the 2004 version for the MSKCC group are shown. (Version: 2004: consideration of the following risk factors: haemoglobin below the lower normal range, corrected serum calcium > 10 mg/dl, an ECOG status of 1; favourable = no risk factor present, intermediate = 1 risk factor present, poor = more than 1 risk factor present)</p> <p>ECOG: Eastern Cooperative Oncology Group, f: female, MSKCC: Memorial Sloan-Kettering Cancer Centre, m: male, n: number of patients, N: number of randomized patients, RCT: randomized controlled trial, SD: standard deviation</p>							

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, direct comparison – AXIS study – axitinib versus sorafenib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Potential selective reporting	Other factors influencing risk of bias	Risk of bias at study level
			Patient	Treating staff			
AXIS (A4061032)	yes	yes	no	no	no	no	low
RCT: randomized controlled trial							

The risk of bias at study level for the AXIS study was rated as low. This concurs with the company's assessment. The lack of blinding in the AXIS study did not lead to a different assessment of the risk of bias at study level, but was taken into account when the risk of bias at outcome level was considered.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and also in Appendix 4-G of the dossier and in Sections 2.7.2.2 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
 - Overall survival
- Morbidity
 - Symptoms (FKSI-DRS)
- Health-related quality of life
 - FKSI-15
 - EQ-5D
- Adverse events
 - Overall rate of AEs
 - Most common AEs (> 20%)
 - Severe AEs (CTCAE Grade \geq 3)
 - Serious AEs (SAEs)

- Treatment discontinuations due to AEs
- Venous thromboembolic events
- Arterial thromboembolic events
- Bleeding events
- PRES
- Gastrointestinal perforation

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4). In particular, the outcome “progression-free survival” was not used for this assessment since neither the patient relevance postulated in the dossier (in this study, PFS was exclusively recorded using imaging methods) nor the validity of a surrogate characteristic was presented. However, additional outcomes were used for this assessment (see Section 2.7.2.4.3 of the full dossier assessment for reasons for the choice of outcomes).

Table 9 shows for which outcomes data on the relevant cytokine population were available in the study included. Table 10 describes the risk of bias for these outcomes.

Table 9: Matrix of outcomes – RCT, direct comparison – AXIS study – axitinib vs. sorafenib, cytokine population

Study	Outcomes													
	Overall survival	Symptoms (FKSI-DRS)	Health-related quality of life (FKSI-15)	Health-related quality of life (EQ-5D)	Overall rate of AEs	Severe AEs (CTCAE Grade ≥ 3)	SAEs	Treatment discontinuations due to AEs	Venous thromboembolic events	Arterial thromboembolic events	Bleeding events	PRES	Gastrointestinal perforation	
AXIS (A4061032)	y	y	y	n	y	y	y	y	n	n	n	n	n	
AE: adverse event, CTCAE: Common Terminology Criteria for Adverse Events, FKSI: Functional Assessment of Cancer Therapy – Kidney Symptom Index, FKSI-DRS: Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms, n: no, PRES: posterior reversible encephalopathy syndrome, RCT: randomized controlled trial, SAE: serious adverse event, y: yes														

Table 10: Risk of bias at study and outcome level – RCT, direct comparison – AXIS study – axitinib versus sorafenib, cytokine population

Study	Outcomes													
	Study level	Overall survival	Health-related quality of life (FKSI-15)	Health-related quality of life (EQ-5D)	Symptoms (FKSI-DRS)	Overall rate of AEs	Severe AEs (CTCAE Grade ≥ 3)	SAEs	Treatment discontinuations due to AEs	Venous thromboembolic events	Arterial thromboembolic events	Bleeding events	PRES	Gastrointestinal perforation
AXIS (A4061032)	l	l	h	- ^a	h	h	h	h	h	- ^a	- ^a	- ^a	- ^a	- ^a
<p>a: No estimation of the risk of bias possible, because no data for the cytokine population available. AE: adverse event, CTCAE: Common Terminology Criteria for Adverse Events, FKSI: Functional Assessment of Cancer Therapy Kidney Symptom Index, FKSI-DRS: Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms, h: high l: low, PRES: posterior reversible encephalopathy syndrome, RCT: randomized controlled trial, SAE: serious adverse event</p>														

No analyses were available of EQ-5D, venous/arterial thromboembolic events, bleeding events, PRES or gastrointestinal perforation. Therefore no outcome-specific assessment of the risk of bias was conducted.

The risk of bias for the outcome “overall survival” was rated as low. This corresponds with the company’s assessment. The open-label study design, coupled with the continued treatment after the end of axitinib or sorafenib treatment, did not lead to a high risk of bias because the continued treatments in the two groups took place to a similar extent (see Section 2.7.2.4.2 of the full dossier assessment).

The risk of bias for the outcomes “health-related quality of life” (recorded using FKSI-15), “symptoms” (recorded using FKSI-DRS), and the outcomes relating to AEs is rated as high. This is because in both cases an unbiased estimation of the HR in the Cox-PH model assumes non-informative censorings in both groups. Due to the stopping rules defined in the study, the axitinib group showed an approximately 23 days longer treatment time than the sorafenib group. The mean treatment time in the cytokine population [data cut-off 31.08.2010] was 265.6 (SD: 154.8) days for axitinib and 242.5 (SD: 147.8) days for sorafenib. As a result of the different treatment periods between the treatment groups, the assumption of non-informative censorings is not met. For AEs, this means that because of the longer treatment time, more AEs, SAEs and discontinuations due to an AE could occur in the axitinib group than in the sorafenib group. For the outcomes “health-related quality of life” and “symptoms”,

the high risk of bias – in agreement with the company’s assessment – is also due to the open-label study design. The only deviation is that, unlike the company’s approach, this benefit assessment assigns the measuring instrument FKSI-DRS to the outcome “symptoms” (see Section 2.7.2.4.3 of the full dossier assessment). For AEs the assessment of a high risk of bias – apart from the time to first occurrence of a treatment discontinuation due to an AE – deviates from that of the company (see Section 2.7.2.4.3 of the full dossier assessment).

A further uncertainty in the assessment of AEs arose from the fact that information on how many patients in the cytokine population completed the study treatment and how high the proportion of patients was who received a subsequent therapy, was available exclusively for the data cut-off date of 01.11.2011. The analyses of AEs were, however, based on the data cut-off of 31.08.2010. Information from the data cut-off of 01.11.2011 cannot be simply applied to the earlier time. This is because the proportion of patients in the treatment groups who had completed study treatment or subsequent therapy at the earlier data cut-off could have been different to that at the later cut-off. The remaining uncertainty was of no consequence because the risk of bias was already rated as high for other reasons (see Section 2.7.2.4.2 of the full dossier assessment).

Table 11 and Table 12 summarize the results of the comparison of axitinib with sorafenib in patients with metastatic RCC for the cytokine population. The data from the company’s dossier were supplemented, where necessary, by the Institute’s own calculations. In addition, data from Module 5 of the dossier were added.

Table 11: Results – RCT, direct comparison, AXIS study – axitinib versus sorafenib, cytokine population

Outcome category Outcome	Axitinib		Sorafenib		Axitinib vs. sorafenib
	N	25% quantile survival time in months [95% CI] ^a	N	25% quantile survival time in months [95% CI] ^a	HR [95% CI] p-value
Mortality					
Overall survival ^b					
<i>Data cut-off date 31.08.2010</i>	126	15.9 [11.6; n.e.]	125	12.2 [10.7; n.e.]	0.744 [0.423; 1.307] 0.304 ^c
<i>Data cut-off date 01.11.2011</i>	126	15.9 [13.1; 22.5]	125	13.8 [11.7; 18.0]	0.813 [0.555; 1.191] 0.288 ^c
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI]; p-value
Morbidity^d					
Symptoms (FKSI-DRS) ^e , response	126	58 (46.0)	125	55 (44.0)	0.933 [0.645; 1.351]; 0.713 ^c
Health-related quality of life^d					
FKSI-15 ^f , response	126	56 (44.4)	125	57 (45.6)	0.858 [0.593; 1.241]; 0.416 ^c
EQ-5D	No analyses available for the cytokine population				
<p>a: The median time to the event and the associated confidence interval could not be estimated because at the time of analysis, not 50%, but 40.5% (axitinib) and 45.6% (sorafenib) of the patients had died. The 25% quantile is the time at which 25% of patients had an event (Kaplan-Meier estimator).</p> <p>b: FAS analysis of the intention-to-treat population.</p> <p>c: Institute's calculation, p-value for Cox regression using the Wald statistic.</p> <p>d: Data cut-off date 31.08.2010.</p> <p>e: Time to deterioration defined as a fall of at least 3 points compared with the condition at the start of the study.</p> <p>f: Time to deterioration defined as a fall of at least 5 points compared with the condition at the start of the study.</p> <p>CI: confidence interval, EQ-5D: European Quality Of Life-5 Dimensions, FAS: full analysis set, FKSI: Functional Assessment of Cancer Therapy – Kidney Symptom Index, FKSI-DRS: Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms, HR: hazard ratio, , n.e.: no estimator, N: number of analysed patients, n: number of patients with event, vs.: versus</p>					

Table 12: Results on adverse events^a – RCT, direct comparison, AXIS study – axitinib versus sorafenib, cytokine population

Outcome Operation- alization	Axitinib		Sorafenib		Axitinib vs. sorafenib
	N	Time to first occurrence median [95% CI] [days]/ Patients with events n (%)	N	Time to first occurrence median [95% CI] [days]/ Patients with events n (%)	HR [95% CI]; p-value ^b
Adverse events					
Total	126	11 [8; 15]/ 116 (92.1)	123	7 [5; 8]/ 120 (97.6)	Not interpretable ^c
Most common AEs (> 20%) ^d					
Alopecia	126	n.e./ 6 (4.8)	123	n.e./ 44 (35.8)	0.102 [0.043; 0.240]; < 0.001
Decreased appetite	126	n.e./ 30 (23.8)	123	n.e./ 23 (18.7)	1.310 [0.760; 2.255]; 0.330
Rash	126	n.e./ 17 (13.5)	123	n.e./ 36 (29.3)	0.396 [0.223; 0.706]; 0.002
Diarrhoea	126	227 [141; 469] / 62 (49.2)	123	328 [134; n.e.] / 56 (45.5)	0.954 [0.664; 1.369]; 0.799
Dysphonia	126	n.e./ 38 (30.2)	123	n.e./ 15 (12.2)	2.643 [1.454; 4.807]; 0.001
Fatigue	126	n.e./ 46 (36.5)	123	n.e./ 30 (24.4)	1.624 [1.024; 2.573]; 0.039
Hand-foot syndrome	126	n.e./ 37 (29.4)	123	45.0 [21; 361] / 71 (57.7)	0.350 [0.235; 0.522]; < 0.001
Hypertension	126	371 [59; n.e.] / 60 (47.6)	123	n.e./ 52 (42.3)	1.171 [0.808; 1.698]; 0.405
Nausea	126	n.e./ 27 (21.4)	123	n.e./ 14 (11.4)	1.963 [1.029; 3.743]; 0.041
Severe adverse events (CTCAE Grade ≥ 3)					
Total	126	166 [96; 254] / 74 (58.7)	123	84 [32; 155] / 83 (67.5)	0.750 [0.548; 1.026]; 0.072
Serious adverse events					
Total	126	n.e./ 27 (21.4)	123	n.e./ 31 (25.2)	0.790 [0.472; 1.324] 0.370
Treatment discontinuations due to AEs					
Total	126	n.e./ 7 (5.6)	123	n.e./ 9 (7.3)	0.715 [0.266; 1.922] 0.506
Venous thromboembolic events					
No results available					

(continued on next page)

Table 12: Results on adverse events^a – RCT, direct comparison, AXIS study – axitinib versus sorafenib, cytokine population (continued)

Outcome	Axitinib		Sorafenib		Axitinib vs. sorafenib
	N	Time to first occurrence median [95% CI] [days]/ Patients with events n (%)	N	Time to first occurrence median [95% CI] [days]/ Patients with events n (%)	HR [95% CI]; p-value ^b
Arterial thromboembolic events					No results available
Bleeding events					No results available
PRES					No results available
Gastrointestinal perforation					No results available
<p>a: Data cut-off date 31.08.2010 b: Institute's calculation, p-value for Cox regression using the Wald statistic c: For example, this could include a large number of transient AEs. No information was available about this, so it is unclear what an effect would mean. d: The choice of the most common AEs was made by the company on the basis of the total study population. It remains unclear whether this choice also applies to the most common AEs in the cytokine population. AE: adverse event, CI: confidence interval, CTCAE: Common Terminology Criteria for Adverse Events, HR: hazard ratio, n.e.: no estimator, n: number of patients with events, N: number of analysed patients, PRES: posterior reversible encephalopathy syndrome, RCT: randomized controlled trial</p>					

The company used a one-tailed log-rank test with the significance level of 0.025 for the comparison between the treatments for results of the operationalization “Time to first occurrence”. Since, in the context of this assessment, a two-tailed research question was posed, a two-tailed test with the probability level of 0.05 should be used. This was implemented for the benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment).

Since only one study was available, no more than “indications”, for example of an added benefit, could be derived, provided outcome-specific aspects did not weaken the informative value.

As regards AEs, despite the above-mentioned high risk of bias, the informative value was not downgraded in this dossier assessment if there was an advantage of axitinib over sorafenib. Due to the stopping rules defined in the study, the axitinib group showed a longer treatment time of approximately 23 days than the sorafenib group. This means that in relation to AEs, more AEs, SAEs and discontinuations due to an AE could have occurred in the axitinib than in the sorafenib group because of the longer treatment time. If in this situation fewer AEs occurred in the axitinib than in the sorafenib group, the difference between axitinib and sorafenib could actually have been even greater. It can therefore be assumed that if there was

an advantage for axitinib, this would be a conservative estimator, i.e. the estimator would possibly underestimate the true effect. In the case of an advantage for sorafenib, i.e. if fewer AEs were observed in the sorafenib group than in the axitinib group, the difference between axitinib and sorafenib might actually have been smaller, if the sorafenib group had been observed for as long as the axitinib group. In other words, an effect would then tend to be overestimated. In the case of an advantage for sorafenib, the high risk of bias therefore led to a downgrading of the probability (see Section 2.7.2.4.2 of the full dossier assessment).

The results described below refer exclusively to the cytokine population.

Mortality

Overall survival

Because of the longer observation period, the analysis at the 2nd data cut-off date (01.11.2011) was primarily used to assess the outcome “overall survival”. There was no statistically significant difference between axitinib and sorafenib in this outcome for the cytokine population. The results of the analysis at the 1st data cut-off date (31.08.2010) do not contradict this result. An added benefit of axitinib for this outcome is not proven. This assessment deviates from that of the company, which did not limit the conclusion to the cytokine population, but applied it to the total study population.

In the subsequent course of the assessment of subgroup characteristics, there was an indication of an effect modification by the characteristic “sex”. As a result, conclusions on added benefit regarding the outcome “overall survival” were based on the subgroups. The subgroup analyses, the interpretation of their results and overview of the evidence can be found in detail at the end of this section. In summary, neither for men nor for women is an added benefit of axitinib proven in terms of overall survival.

Morbidity

Symptoms (FKSI-DRS)

There was no statistically significant difference in the proportion of patients with a deterioration of at least 3 points on the FKSI-DRS between axitinib and sorafenib (data cut-off date 31.08.2010). An added benefit of axitinib for this outcome is not proven. This conclusion deviates from the company’s assessment, which did not consider the FKSI-DRS for the outcome “symptoms”.

Health-related quality of life

FKSI-15

There was no statistically significant difference in the proportion of patients with a deterioration of at least 5 points on the FKSI-15 between axitinib and sorafenib (data cut-off date 31.08.2010). An added benefit of axitinib for this outcome is not proven. This assessment deviates from that of the company, which did not limit the conclusion to the cytokine population.

EQ-5D

There were no results for “health-related quality of life” measured with the EQ-5D for the cytokine population. An added benefit of axitinib for this outcome is not proven. This assessment deviates from that of the company, which did not consider EQ-5D in the dossier (see also Section 2.7.2.4.3 of the full dossier assessment).

Overall, an added benefit of axitinib is not proven for health-related quality of life. This assessment does not deviate from that of the company.

Adverse events

The analyses of AEs were performed for the data cut-off date of 31.08.2010.

The analysis of the overall rate of AEs showed that an AE was observed in almost all patients in the course of the study. The time to first occurrence of an AE under axitinib was longer than under sorafenib. However, this difference cannot be interpreted because no information on the nature of the event and the relevance of the delay was available. The relevance of a delay is questionable, especially for non-serious and transient AEs. Greater or lesser harm from axitinib than from sorafenib for the overall rate of AEs is therefore not proven. The assessment regarding the operationalization of the time to first occurrence of an AE deviates from that of the company, which in this case derived a statistically significant effect and hence lesser harm from axitinib.

There were no statistically significant differences for the time to first occurrence of a severe AE (CTCAE Grade ≥ 3), an SAE or a treatment discontinuation due to an AE. Greater or lesser harm from axitinib than from sorafenib in this respect is not proven. These assessments for SAEs and treatment discontinuations due to an AE deviate from those of the company, because it did not consider these events for the cytokine population in Module 4.

There are no results for the cytokine population for the following relevant outcomes: venous thromboembolic events, arterial thromboembolic events, bleeding events, PRES and gastrointestinal perforation. Therefore in each case, greater or lesser harm from axitinib than from sorafenib is not proven for these outcomes.

No consideration of frequent severe AEs (CTCAE Grade ≥ 3) was possible, because the dossier did not contain a corresponding analysis for the cytokine population. Also absent were the most common events of all AEs in the cytokine population. Only a selection of the most common AEs in the total population was available for the further description of the nature of the AEs that had occurred (in more than 20% of patients). However, the analysis of AEs in the cytokine population was available for these AEs. These data are shown in Table 12. This situation regarding data leads to an increased uncertainty regarding the AEs. It is unclear whether the most common events in the total population of the study were also the most common in the cytokine population. Moreover, due to the missing analysis of the common severe AEs in the cytokine population, the severity of the relevant AEs could not be

estimated. An analysis of AEs according to CTCAE grades of severity in the cytokine population is not only generally worthwhile for medical reasons, because information on the severity grades is also used to assess the extent of added benefit.

The results from the Cox PH model for individual AEs show a statistically significant difference in favour of axitinib for the events “alopecia”, “rash” and the “hand-foot syndrome” in each case and a statistically significant difference in favour of sorafenib for “dysphonia”, “fatigue” and “nausea”. The hand-foot syndrome in particular can be a potentially very troublesome event for patients. Hence, a severity classification for the cytokine population according to CTCAE (see above) would be especially relevant. From the data for the total study population, it appears that the majority of individual events were of CTCAE Grades 1 and 2. At the same time, the difference between the treatment groups especially for the Grade 3 events was particularly large (5% versus 16%). It is not clear whether this can be applied to the cytokine population.

Overall, it remains unclear whether the observed effects for the cytokine population also apply to severe events. Therefore, on the basis of the available information, the results are included as non-severe events in the assessment of the extent of added benefit.

Overall, the results on AEs are subject to several uncertainties (see also Section 2.7.2.4.3 of the full dossier assessment):

- No analyses of individual severe AEs (CTCAE-Grad ≥ 3) were provided for the cytokine population, but solely for the total study population.
- The analysis of frequently occurring AEs for the cytokine population relates solely to those events that often occurred in the total study population ($> 20\%$). It remains unclear whether these AEs were also the most common AEs in the cytokine population. It is therefore possible that relevant differences between the groups in other AEs were not identified. This uncertainty cannot be resolved on the basis of the available data. In addition, the severity classification of the results shown in Table 12 in the cytokine population is unknown. (It should be pointed out that for the cytokine population, data on venous and arterial thromboembolic events, bleeding events, PRES and gastrointestinal perforation, as well as severe AEs [CTCAE Grade ≥ 3] would have been preferred for use as individual events for the benefit assessment.)
- The mean treatment time in the cytokine population (data cut-off date 31.08.2010) was approximately 23 days longer for the axitinib group than for the sorafenib group. Kaplan-Meier curves would have been desirable for the (important) AEs in order to better interpret the effects. It is assumed that the on-average longer treatment time of the axitinib group was to the disadvantage of axitinib. The longer treatment time in the axitinib group meant that more AEs, SAEs and discontinuations due to AEs could occur than in the sorafenib group. If in this situation fewer AEs occurred in the axitinib than in the sorafenib group, the difference between axitinib and sorafenib could actually be even

greater. It can therefore be assumed that if there was an advantage for axitinib, this would be a conservative estimator, i.e. the estimator would possibly underestimate the true effect. In the case of an advantage for sorafenib, i.e. if fewer AEs were observed in the sorafenib group than in the axitinib group, the difference between axitinib and sorafenib might actually have been smaller if the sorafenib group had been observed for as long as the axitinib group. That means that the estimator would possibly overestimate the true effect.

The high risk of bias at outcome level would have led to a downgrading from an “indication” to a “hint” of lesser harm from axitinib versus sorafenib for the events “alopecia”, “rash” and “hand-foot syndrome”. Because of the above-mentioned direction of a possible bias within the analysis of the individual outcomes, the high risk of bias would, however, in the first instance, not lead to a downgrading of the informative value and therefore to an indication of lesser harm from axitinib versus sorafenib for the events “alopecia”, “rash” and “hand-foot syndrome”. However, the remaining uncertainty about the fact that the severity of the described events and the identification of the most common AEs in the cytokine population relevant to the assessment remain unclear must be taken into account in the reliability of the conclusions concerning the results on AEs. Due to this uncertainty, the “indication” is finally indeed downgraded to a “hint”. There is thus a hint of lesser harm from axitinib than from sorafenib for the events “alopecia”, “rash” and “hand-foot syndrome”. Due to the high risk of bias at outcome level for the event “dysphonia”, the assessment is that the effect tends to be overestimated and the uncertainty in the submitted analyses also leads to a hint of greater harm from axitinib than from sorafenib. Because of the marginal effect size for the events “fatigue” and “nausea”, there is no proof of greater harm from sorafenib (see also Appendix A of Benefit Assessment A11-02 [2]).

Relevant subgroups

The results of the AXIS study concerning the outcome “overall survival” were investigated for a possible effect modification by the characteristics “age” ($</\geq$ 65 years, prospectively specified) and “sex”, in order to reveal any effect differences between patient groups. The prerequisite for proof of differing effects was a statistically significant homogeneity or interaction test ($p \leq 0.05$). A p-value between 0.05 and 0.2 provided an indication of different effects. As the dossier contained no interaction tests, these were conducted by the Institute for this benefit assessment.

There was no proof of an effect modification for the characteristic “age” ($p \geq 0.2$). Conversely, for “sex” there was an indication of an effect modification (interaction test: $p = 0.087$) that necessitated a separate consideration of the results for women and men. Table 13 and Figure 1 show the results of the subgroup analysis for the characteristic “sex”.

Table 13: Subgroups: Outcome “overall survival”^a – AXIS study – axitinib versus sorafenib, cytokine population

Characteristic Subgroup	Axitinib		Sorafenib		Axitinib vs. sorafenib	
	N	25% quantile survival time [95% CI] ^b [months]	N	25% quantile survival time [95% CI] ^b [months]	HR [95% CI] p-value ^c	Interaction test p-value ^d
Sex						
Women	31	21 [14.1; 29.4]	38	12.7 [4.1; 20.5]	0.481 [0.227; 1.017] 0.056	
Men	95	13.8 [9.2; 22.5]	87	14.2 [11.7; 20.1]	1.032 [0.658; 1.619] 0.891	0.087

a: Data cut-off date 01.11.2011
b: The median time to the event and its associated confidence interval could not be estimated because at the time of the analysis not 50%, but 40.5% (axitinib) or 45.6% (sorafenib) of the patients had died. The 25% quantile shows the time at which the probability of occurrence of an event is 25%.
c: Institute’s calculation, p-value for Cox regression using the Wald statistic
d: Institute’s calculation, Cochran’s Q test.
CI: confidence interval, HR: hazard ratio, N: number of analysed patients, RCT: randomized controlled trial, vs.: versus

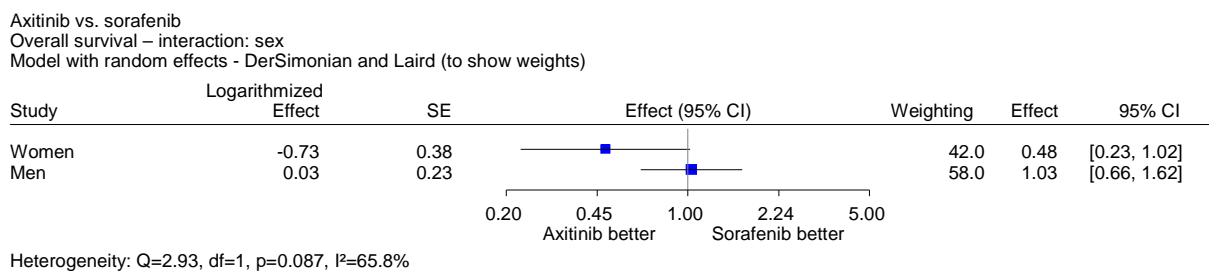


Figure 1: Overall survival, subgroups according to sex, axitinib versus sorafenib

Both for men and for women, the difference between axitinib and sorafenib was not statistically significant. Neither for men nor for women was there therefore an added benefit of axitinib in terms of overall survival. The company did not consider the subgroups separately (see also Section 2.7.2.4.3 of the full dossier assessment).

When men and women were considered separately, it is noticeable that, despite the lack of statistical significance, the HR in women suggested a numerical advantage of axitinib over sorafenib. On other hand, the HR in men did not suggest such an advantage of one of the two interventions.

Subgroup analyses for the characteristics “age” and “sex” for other patient-relevant outcomes as well as the characteristics “severity” and “ethnicity” for all patient-relevant outcomes

would have been relevant for the benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment).

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.5 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit at outcome level for patients previously treated with a cytokine is presented below, taking into account the various 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 decision on added benefit is made by the G-BA.

2.5.1 Assessment of added benefit at outcome level

In patients with advanced metastatic RCC after prior treatment with a cytokine, for axitinib, the data presented in Section 2.4 showed a hint of lesser harm regarding the events “alopecia”, “rash” and “hand-foot syndrome” and a hint of greater harm regarding “dysphonia” compared with sorafenib. The extent of the respective added benefit at outcome level was estimated from these results (see Table 14).

Table 14: Axitinib versus sorafenib – extent of added benefit at outcome level, cytokine population

Outcome	Effect estimator [95% CI]^a/ proportion of events axitinib vs. sorafenib^b/p-value/ probability^c	Derivation of extent^d
Mortality		
Overall survival	<i>Data cut-off 31.08.2010</i> HR 0.744 [0.423; 1.307] 25% quantile survival time [95% CI] (months) 15.9 [11.6; n.e.] vs. 12.2 [10.7; n.e.] p = 0.304 ^e <i>Data cut-off 01.11.2011</i> HR 0.813 [0.555; 1.191] 25% quantile survival time [95% CI] (months) 15.9 [13.1; 22.5] vs. 13.8 [11.7; 18.0] p = 0.288 ^e	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (FKSI-DRS), Response	HR 0.933 [0.645; 1.351] 46.0% vs. 44.0% p = 0.713 ^e	Lesser benefit/added benefit not proven
Health-related quality of life		
FKSI-15. Response	HR 0.858 [0.593; 1.241] 44.4% vs. 45.6% p = 0.416 ^e	Lesser benefit/added benefit not proven
EQ-5D	No analyses available for the cytokine population	Lesser benefit/added benefit not proven
Adverse events		
Time to first occurrence of an AE	Not interpretable Median: 11 [8; 15] vs. 7 [5; 8] days	Lesser/greater harm not proven
Time to first occurrence of alopecia	HR 0.102 [0.043; 0.240] No estimator 4.8% vs. 35.8% p < 0.001 ^e Probability: "indication"	Outcome category: non-serious/non-severe AEs CI ₀ ≤ 0.80 Lesser harm from axitinib, extent: considerable
Time to first occurrence of decreased appetite	HR 1.310 [0.760; 2.255] No estimator 23.8% vs. 18.7% p = 0.330 ^e	Lesser/greater risk of harm not proven

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Table 14: Axitinib versus sorafenib – extent of added benefit at outcome level, cytokine population (continued)

Outcome	Effect estimator [95% CI] ^a / proportion of events axitinib vs. sorafenib ^b /p-value/ probability ^c	Derivation of extent ^d
Time to first occurrence of rash	HR 0.396 [0.223; 0.706] No estimator 13.5% vs. 29.3% p = 0.002 ^e Probability: “indication”	Outcome category: non-serious/non-severe AEs CI _o ≤ 0.80 Lesser harm from axitinib, extent: “considerable”
Time to first occurrence of diarrhoea	HR 0.954 [0.664; 1.369] Median: 227 [141; 469] vs. 328 [134; n.e.] days 49.2% vs. 45.5% p = 0.799 ^e	Lesser/greater risk of harm not proven
Time to first occurrence of dysphonia	HR 2.643 [1.454; 4.807] HR 0.378 [0.208; 0.688] ^f No estimator 30.2% vs. 12.2% p = 0.001 ^e Probability: “hint”	Outcome category: non-serious/non-severe AEs CI _o ≤ 0.80 Greater harm from axitinib, extent: “considerable”
Time to first occurrence of fatigue	HR 1.624 [1.024; 2.573] HR 0.616 [0.389; 0.977] ^f No estimator 36.5% vs. 24.4% p = 0.039 ^e	Outcome category: non-serious/non-severe AEs CI _o > 0.90 Lesser harm not proven ^g
Time to first occurrence of hand-foot syndrome	HR 0.350 [0.235; 0.522] Median: n.e. vs. 45.0 [21; 361] days 29.4% vs. 57.7% p < 0.001 ^e Probability: “indication”	Outcome category: non-serious/non-severe AEs CI _o ≤ 0.80 Lesser harm from axitinib, extent: “considerable”
Time to first occurrence of hypertension	HR 1.171 [0.808; 1.698] Median: 371 [59; n.e.] days vs. n.e. 47.6% vs. 42.3% p = 0.405 ^e	Lesser/greater risk of harm not proven
Time to first occurrence of nausea	HR 1.963 [1.029; 3.743] HR 0.509 [0.267; 0.972] ^f No estimator 21.4% vs. 11.4% p = 0.041 ^e	Outcome category: non-serious/non-severe AEs CI _o > 0.90 Lesser harm not proven ^g

(continued on next page)

Table 14: Axitinib versus sorafenib – extent of added benefit at outcome level, cytokine population (continued)

Outcome	Effect estimator [95% CI] ^a / proportion of events axitinib vs. sorafenib ^b /p-value/ probability ^c	Derivation of extent ^d
Time to first occurrence of a severe AE (CTCAE-Grade ≥ 3)	HR 0.750 [0.548; 1.026] Median: 166 [96; 254] vs. 84 [32; 155] days 58.7% vs. 67.5% p = 0.072 ^e	Lesser/greater risk of harm not proven
Time to first occurrence of an SAE	HR 0.790 [0.472; 1.324] No estimator 21.4% vs. 25.2% p = 0.370 ^e	Lesser/greater risk of harm not proven
Time to first occurrence of treatment discontinuation due to AEs	HR 0.715 [0.266; 1.922] No estimator 5.6% vs. 7.3% p = 0.506 ^e	Lesser/greater risk of harm not proven
Venous thromboembolic events	No results available	Lesser benefit/added benefit not proven.
Arterial thromboembolic events	No results available	Lesser benefit/added benefit not proven.
Bleeding events	No results available	Lesser benefit/added benefit not proven.
PRES	No results available	Lesser benefit/added benefit not proven.
Gastrointestinal perforation	No results available	Lesser benefit/added benefit not proven.
<p>a: The AXIS study specified that patients with metastatic RCC were to be enrolled. According to the SPC [3] axitinib is approved for patients with advanced RCC. In addition to patients with metastatic RCC, the therapeutic indication thus also covers patients with locally advanced RCC without metastases. It is unclear whether the observed effects are also applicable to these patients. For this reason, the results of the AXIS study are not applied to the patients with locally advanced RCC without metastases.</p> <p>b: Unless otherwise noted</p> <p>c: Probability provided, if statistically significant differences were present.</p> <p>d: Estimations of effect size made depending on outcome category with different limits based on the upper limit of the confidence interval (CI₀).</p> <p>e: Institute's calculation, p-value for Cox regression using the Wald statistic.</p> <p>f: Proportion of events sorafenib versus axitinib (reversed direction of effect to enable direct use of limits to derive extent of added benefit).</p> <p>g: Because upper limit of confidence interval is above the named threshold of 0.90.</p> <p>AE: adverse event, CI: confidence interval, CI₀: upper limit of confidence interval, EQ-5D: European Quality Of Life-5 Dimensions, FKSI: Functional Assessment of Cancer Therapy – Kidney Symptom Index, FKSI-DRS: Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms, HR: hazard ratio, n.e.: no estimator, PRES: posterior reversible encephalopathy syndrome, RCC: renal cell carcinoma, SAE: serious adverse event, SPC: Summary of Product Characteristics.</p>		

2.5.2 Overall conclusion on added benefit

The overall conclusion on the extent of added benefit of axitinib versus the ACT is shown separately for the relevant subpopulations after prior treatment with a cytokine or sunitinib.

Table 15 summarizes the results that were considered in the overall conclusion on the extent of added benefit of axitinib versus the ACT sorafenib for patients with advanced metastatic RCC after failure of **a prior treatment with a cytokine**.

Table 15: Positive and negative effects from the assessment of axitinib compared with sorafenib, cytokine population

Positive effects	Negative effects
Hint of lesser harm – extent: “considerable” (non-serious/non-severe AEs ^a : alopecia)	Hint of greater harm – extent: “considerable” (non-serious/non-severe AEs ^a : dysphonia)
Hint of lesser harm – extent: “considerable” (non-serious/non-severe AEs: rash)	
Hint of lesser harm – extent: “considerable” (non-serious/non-severe AEs ^a : hand-foot syndrome ^a)	
<p>a: No analyses of the classification of severity grades of the individual events in the cytokine population were available. Since the severity grades of the events in the cytokine population remain unclear, the individual AEs were assigned to the outcome category non-serious/non-severe AEs. The hand-foot syndrome in particular can be a potentially very troublesome event for patients. Therefore the analysis of the severity grades is relevant for an adequate description of the AEs and the determination of the extent of added benefit.</p> <p>AE: adverse event</p>	

Overall, positive and negative effects remain. On the positive side, there is lesser harm with the probability “hint” and extent “considerable” for each of 3 outcomes of the category “non-serious/non-severe AEs”. On the negative side, there is a greater harm, also with the probability “hint” and extent “considerable”, for one outcome of the category “non-serious/non-severe AEs”.

In this situation, an added benefit should be derived from the reduction in AEs alone. In the process, the results of the benefit parameters should always also be considered and it should be possible to exclude, with adequate certainty, that the intervention being assessed has an unfavourable influence on the benefit parameters in comparison with the ACT. From this assessment, there are no signs that in the cytokine population axitinib achieves considerably worse results for the outcomes “overall survival”, “health-related quality of life” and “symptoms” than sorafenib.

In summary, for patients with advanced metastatic RCC who have received first-line therapy with a cytokine, there is a hint of a considerable added benefit of axitinib over the ACT sorafenib.

As described in Section 2.3, there are no evaluable data for the comparison of axitinib with the ACT everolimus for the subpopulation of patients with advanced metastatic RCC after

failure of a **prior treatment with sunitinib**. The added benefit of axitinib versus everolimus in patients previously treated with sunitinib is not proven.

2.5.3 Extent and probability of added benefit - summary

An overview of the extent and probability of added benefit (Table 16) for the various therapeutic situations of axitinib compared with the ACT is given below:

Table 16: Axitinib: extent and probability of added benefit

Therapeutic situation ^a	ACT	Extent and probability of added benefit
Treatment of advanced metastatic RCC in adult patients after failure of prior treatment with sunitinib ("sunitinib population")	Everolimus	Added benefit not proven.
Treatment of advanced metastatic RCC in adult patients after failure of prior treatment with cytokines ("cytokine population")	Sorafenib	Hint of a considerable added benefit of axitinib
<p>a: The AXIS study specified that patients with metastatic RCC were to be enrolled. According to the SPC [3] axitinib is approved for patients with advanced RCC. In addition to patients with metastatic RCC, the therapeutic indication thus also covers patients with locally advanced RCC without metastases. It is unclear whether the observed effects are also applicable to these patients. For this reason, the results of the AXIS study are not applied to the patients with locally advanced RCC without metastases.</p> <p>ACT: appropriate comparator therapy, RCC: renal cell carcinoma, SPC: Summary of Product Characteristics.</p>		

The overall assessment deviates substantially from that of the company, which claimed the following added benefit for the populations corresponding to the approval status (see also Section 2.7.2.8.2 of the full dossier assessment):

- For the sunitinib population the company claimed a hint of a considerable added benefit.
- For the cytokine population the company claimed an indication of a major added benefit.

Further information on 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

AXIS

Pfizer. Axitinib (AG-013736) as second line therapy for metastatic renal cell cancer: AXIS trial [online]. In: EU Clinical Trials Register [accessed 20.11.2012]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number%3A2008-001451-21.

Pfizer. Axitinib (AG-013736) as second line therapy for metastatic renal cell cancer: AXIS trial; study A4061032; final statistical analysis plan (SAP); version 1.2 [unpublished]. 2009.

Pfizer. Axitinib (AG-013736) as second line therapy for metastatic renal cell cancer: AXIS trial; study A4061032; final full clinical study report [unpublished]. 2011.

Pfizer. Axitinib (AG-013736) as second line therapy for metastatic renal cell cancer: AXIS trial; study A4061032; clinical study report erratum [unpublished]. 2011.

Pfizer. Axitinib (AG-013736) for the treatment of advanced renal cell carcinoma: summary of clinical safety [unpublished]. 2011.

Pfizer. Axitinib (AG 013736) as second line therapy for metastatic renal cell cancer: full text view [online]. In: Clinicaltrials.gov. 16.07.2012 [accessed 08.09.2012]. URL: <http://clinicaltrials.gov/show/NCT00678392>.

Pfizer Pharma. Axitinib (Inlyta): Additional analyses to the Benefit Assessment Dossier according to §35a SGB V [unpublished, in German]. 2012.

Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011; 378(9807): 1931-1939.

UBC Axitinib Modeling Team. Simulated treatment comparison: axitinib vs. everolimus and best supportive care; project number M2-9442 [unpublished]. 2012.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23.09.2011 [accessed 05.05.2012]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.
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. Inlyta: European public assessment report; product information [online]. 13.09.2012 [accessed 21.01.2013]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002406/WC500132188.pdf.
4. Escudier B. New perspectives: an oral multikinase inhibitor in patients with advanced RCC. *Eur Urol Supplements* 2007; 6(7): 499-504.
5. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; 356(2): 125-134.
6. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009; 27(20): 3312-3318.

7. Beaumont JL, Butt Z, Baladi J, Motzer RJ, Haas T, Hollaender N et al. Patient-reported outcomes in a phase III study of everolimus versus placebo in patients with metastatic carcinoma of the kidney that has progressed on vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. *Oncologist* 2011; 16(5): 632-640.
8. Bracarda S, Hutson TE, Porta C, Figlin RA, Calvo E, Grünwald V et al. Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: a RECORD-1 subgroup analysis. *Br J Cancer* 2012; 106(9): 1475-1480.
9. Calvo E, Escudier B, Motzer RJ, Oudard S, Hutson TE, Porta C et al. Everolimus in metastatic renal cell carcinoma: subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. *Eur J Cancer* 2012; 48(3): 333-339.
10. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer* 2010; 116(18): 4256-4265.
11. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; 372(9637): 449-456.
12. Oudard S, Thiam R, Fournier LS, Medioni J, Lamuraglia M, Scotte F et al. Optimisation of the tumour response threshold in patients treated with everolimus for metastatic renal cell carcinoma: analysis of response and progression-free survival in the RECORD-1 study. *Eur J Cancer* 2012; 48(10): 1512-1518.
11. Porta C, Calvo E, Climent MA, Vaishampayan U, Osanto S, Ravaud A et al. Efficacy and safety of everolimus in elderly patients with metastatic renal cell carcinoma: an exploratory analysis of the outcomes of elderly patients in the RECORD-1 Trial. *Eur Urol* 2012; 61(4): 826-833.
12. Tsukamoto T, Shinohara N, Tsuchiya N, Hamamoto Y, Maruoka M, Fujimoto H et al. Phase III trial of everolimus in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from RECORD-1. *Jpn J Clin Oncol* 2011; 41(1): 17-24.
13. White DA, Camus P, Endo M, Escudier B, Calvo E, Akaza H et al. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. *Am J Respir Crit Care Med* 2010; 182(3): 396-403

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