IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-12

# Axitinib (renal cell carcinoma) –

## Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

## Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Axitinib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 29 June 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EQ-5D | European Quality of Life-5 Dimensions |
| FKSI-DRS | Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IFN-α | interferon-alpha |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| PFS | progression-free survival |
| PT | Preferred Term |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |
| VAS | visual analogue scale |

# 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 referred to as "the company"). The dossier was sent to IQWiG on 20 March 2017.

The company submitted a first dossier of the drug to be evaluated on 1 October 2012 for the early benefit assessment. In this procedure, by decision of 21 March 2013, the G-BA limited its decision until 21 March 2017. Reasons for the limitation of the decision were, on the one hand, the fact that data were missing for sunitinib-pretreated patients as well as for patients with locally advanced renal cell carcinoma without metastases or patients with non-clear cell renal cell carcinoma. On the other, there was uncertainty in the interpretation of the study results on side effects because these were not presented completely and differentiated by severity grade.

### Research question

The aim of the present report was to assess the added benefit of axitinib in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine.

The research questions shown in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of axitinib

| Research question | Subindication[a] | ACT[b] |
|---|---|---|
| 1 | Adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib | **Nivolumab** or everolimus |
| 2 | Adult patients with advanced renal cell carcinoma after failure of prior treatment with a cytokine | Sorafenib |

a: It is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the therapeutic decision and that treatment is palliative.
b: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT. For research question 1, the company chose nivolumab from the options presented.

The present assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

**Results**

***Research question 1: sunitinib-pretreated patients***

No data were available for the assessment of the added benefit of axitinib in patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib. Hence there was no hint of an added benefit of axitinib in comparison with the ACT. An added benefit for this research question is therefore not proven.

***Research question 2: cytokine-pretreated patients***

*Study characteristics*

For the present research question, the AXIS study, which was already included in the first assessment (commission A12-14), and study A4061051/2L were included in the benefit assessment. Both studies were randomized, open-label, active-controlled studies on the comparison of axitinib and sorafenib. The A4061051/2L study was almost only conducted in Asia.

The studies AXIS and A4061051/2L included adult patients with clear-cell metastatic renal cell carcinoma after failure of prior systemic treatment and an Eastern Cooperative Oncology Group Performance Status [ECOG PS] of $\leq 1$. For the present research question, only the subpopulation of cytokine-pretreated patients was relevant in each case. No patients with ECOG PS > 1, non-clear cell renal cell carcinoma or without metastases were included in the studies AXIS and A4061051/2L.

In the AXIS study, 723 patients were randomly allocated in a ratio of 1:1 to the 2 treatment arms. In the A4061051/2L study, 204 patients were randomly allocated in a ratio of 2:1 to the 2 treatment arms. The relevant subpopulation of the AXIS study comprised 126 patients in the axitinib arm and 125 patients in the sorafenib arm; the relevant subpopulation of the A4061051/2L study comprised 68 and 35 patients.

The specifications for the treatment of the patients, including possible dose adjustments, corresponded to the Summaries of Product Characteristics (SPCs) of axitinib and sorafenib in both studies.

Primary outcome of the studies was progression-free survival (PFS); relevant secondary outcomes were overall survival, morbidity and side effects.

*Risk of bias*

The risk of bias at study level for the studies AXIS and A4061051/2L was rated as low. In both studies, the risk of bias at outcome level was rated as low for overall survival, whereas the outcomes on morbidity and adverse events (AEs) in both studies had a high risk of bias.

*Results*

On the basis of the available data from the studies AXIS and A4061051/2L, at most proof, e.g. of an added benefit, can be derived for the outcome "overall survival". Due to the higher risk of bias, at most indications can be derived for the other outcomes if data from both studies are included in the assessment.

Mortality

There was no statistically significant difference between the treatment arms for the outcome "overall survival". As a result, there was no hint of an added benefit of axitinib versus sorafenib for this outcome; an added benefit is therefore not proven.

Morbidity

- Symptoms (FKSI-DRS)
- Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcomes "symptoms" (Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]) and "health status" (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]). As a result, there was no hint of an added benefit of axitinib versus sorafenib for these outcomes; an added benefit is therefore not proven.

Health-related quality of life

No patient-relevant outcomes that represent health-related quality of life in a suitable way were recorded in the studies AXIS and A4061051/2L. This resulted in no hint of an added benefit of axitinib in comparison with sorafenib; an added benefit is therefore not proven.

Side effects

- Serious adverse events
- Severe adverse events (CTCAE grade 3 or 4 adverse events)

No statistically significant difference between the treatment arms was shown for the outcomes "serious adverse events (SAEs)", "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4)". Hence there was no hint of greater or lesser harm from axitinib than from sorafenib for these outcomes; greater or lesser harm is therefore not proven.

- Treatment discontinuations due to adverse events

No interpretable data were available in any of the 2 studies for the outcome "treatment discontinuations due to AEs". Hence there was no hint of greater or lesser harm from axitinib than from sorafenib for this outcome; greater or lesser harm is therefore not proven.

- Specific adverse events
  - Alopecia
  - Hand-foot syndrome (CTCAE grade ≥ 3)

A statistically significant difference in favour of axitinib was shown for the outcomes "alopecia" and "hand-foot syndrome (CTCAE grade ≥ 3)". This resulted in an indication of lesser harm from axitinib than from sorafenib for each of these outcomes.

  - Rash

A statistically significant difference in favour of axitinib was shown for the outcome "rash". In addition, for this outcome, there was proof of an effect modification for the characteristic "region" (Asia, Europe, North America, other), which had no consequences for the present benefit assessment, however.

This resulted in an indication of lesser harm from axitinib than from sorafenib for the outcome "rash".

  - Dysphonia

A statistically significant difference to the disadvantage of axitinib was shown for the outcome "dysphonia". This resulted in an indication of greater harm from axitinib than from sorafenib for this outcome.

  - Fatigue (CTCAE grade ≥ 3)

For the outcome "fatigue (CTCAE grade ≥ 3)", an effect estimate was only calculable for the AXIS study. A statistically significant difference to the disadvantage of axitinib was shown in the AXIS study. This resulted in a hint of greater harm from axitinib than from sorafenib for this outcome.

  - Nausea

There was a statistically significant difference to the disadvantage of axitinib for the outcome "nausea". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. Hence there was no hint of greater or lesser harm from axitinib than from sorafenib for this outcome; greater or lesser harm is therefore not proven.

  - Thyroid hypofunction

Important heterogeneity between the studies was shown for the outcome "thyroid hypofunction". It was therefore not adequate to pool both studies for this outcome. Only the results of the AXIS study were used for the assessment because it was larger and also included patients from Europe. A statistically significant difference to the disadvantage of axitinib was shown in this study for the outcome "thyroid hypofunction". This resulted in a hint of greater harm from axitinib than from sorafenib for this outcome.

**Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]**

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.

***Research question 1: sunitinib-pretreated patients***

Since the company presented no data for the assessment of the added benefit of axitinib in patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib (research question 1), an added benefit of axitinib in comparison with the ACT for these patients is not proven.

***Research question 2: cytokine-pretreated patients***

Two relevant studies (AXIS and A4061051/2L) were available for research question 2 (cytokine-pretreated patients). In the overall assessment of the results, on the side of positive effects, there were 3 indications of lesser harm from axitinib: with the extent "major" in the category "serious/severe side effects" for the outcome "hand-foot syndrome (CTCAE grade ≥ 3)", and with the extent "considerable" in the category "non-serious/non-severe side effects" for each of the outcomes "alopecia" and "rash". No separate balancing was conducted for patients from Asia and Europe in comparison with patients from North America for the present benefit assessment.

On the side of negative effects, there was an indication of greater harm from axitinib in the category "non-serious/non-severe side effects" for the outcome "dysphonia" with the extent "considerable", and 2 hints of greater harm from axitinib, 1 in the category "serious/severe side effects" for the outcome "fatigue (CTCAE grade ≥ 3)" with the extent "minor" and 1 in the category "non-serious/non-severe side effects" for the outcome "thyroid hypofunction" with the extent "considerable". Overall, the positive effects were not completely outweighed by the negative effects, but the lesser harm of major extent was downgraded to lesser harm of considerable extent.

The company presented no complete overview of all AEs for the relevant subpopulation, but presented only results on selected events, which was only the case for CTCAE grade ≥ 3 AEs and for AEs of any severity grade. Information on frequencies of SAEs and discontinuations due to AEs was missing completely. Due to these uncertainties, the overall certainty of results was lowered to a hint.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of 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 to 3 cannot be drawn from the available data). 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). For further details see [1,2].

In summary, there is a hint of a considerable added benefit of axitinib in comparison with the ACT sorafenib for patients with advanced renal cell carcinoma after failure of prior treatment with a cytokine.

***Summary***

Table 3 presents a summary of the probability and extent of the added benefit of axitinib.

Table 3: Axitinib – probability and extent of added benefit

| **Research question** | **Subindication**[a] | **ACT**[b] | **Probability and extent of added benefit** |
|---|---|---|---|
| 1 | Adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib | **Nivolumab** or everolimus | Added benefit not proven |
| 2 | Adult patients with advanced renal cell carcinoma after failure of prior treatment with a cytokine[c] | Sorafenib | Hint of considerable added benefit |

a: It is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the therapeutic decision and that treatment is palliative.
b: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
c: Both relevant studies only included patients with clear-cell metastatic renal cell carcinoma with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2, non-clear cell renal cell carcinoma or without metastases.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

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

***Supplementary information on the implementation of the conditions of the limitation***

In the present dossier, the company only partly fulfilled the conditions of the limitation formulated by the G-BA in the first decision on axitinib. It still presented neither studies on sunitinib-pretreated patients nor on patients with locally advanced renal cell carcinoma without metastases or with non-clear cell renal cell carcinoma. Regarding the side effects of the studies AXIS and A4061051/2L, the company presented data on the AEs the G-BA had named as examples and also provided analyses for the specific AEs differentiated by severity grade (CTCAE grade ≥ 3) for the reassessment. However, since the present dossier contained no data on all AEs, differentiated by severity grade, that occurred in the relevant subpopulation, the choice of specific AEs was still not completely comprehensible.

## 2.2 Research question

The aim of the present report was to assess the added benefit of axitinib in comparison with the ACT in adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine.

The research questions shown in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of axitinib

| **Research question** | **Subindication**[a] | **ACT**[b] |
|---|---|---|
| 1 | Adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib | **Nivolumab** or everolimus |
| 2 | Adult patients with advanced renal cell carcinoma after failure of prior treatment with a cytokine | Sorafenib |

a: It is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the therapeutic decision and that treatment is palliative.
b: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT. For research question 1, the company chose nivolumab from the options presented.

The present assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

## 2.3 Research question 1: sunitinib-pretreated patients

### 2.3.1 Information retrieval and study pool (research question 1)

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

Sources of the company in the dossier:

- study list on axitinib (status: 1 February 2017)
- bibliographical literature search on axitinib (last search on 11 January 2017)
- search in trial registries for studies on axitinib (last search on 12 January 2017)
- bibliographical literature search on the ACT (last search on 11 January 2017)
- search in trial registries for studies on the ACT (last search on 11 January 2017)

To check the completeness of the study pool:

- search in trial registries for studies on axitinib (last search on 5 April 2017)

The company identified no study for a direct comparison of axitinib with sorafenib for this research question. The check of the completeness of the study pool also produced no studies of direct comparison of axitinib for sunitinib-pretreated patients.

For a possible indirect comparison, the company identified 2 studies comparing axitinib with sorafenib (AXIS and A4061051/2L, see Section 2.4) on the side of the drug to be assessed. On the side of the ACT, the company identified 1 study comparing nivolumab with everolimus (CheckMate 025 [3]).

The company did not conduct an indirect comparison because, according to the company, the results for sunitinib-pretreated patients were not reported separately in the nivolumab study and because, in addition, the available data were inadequate to guarantee sufficient similarity of the study populations of the 3 studies identified (see Section 2.6.2.3.2 of the full dossier assessment).

Hence, as in the first assessment on axitinib [4], no relevant studies were available for the present research question.

### 2.3.2 Results on added benefit (research question 1)

No data were available for the assessment of the added benefit of axitinib in patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib. Hence there was no hint of an added benefit of axitinib in comparison with the ACT. An added benefit is therefore not proven.

### 2.3.3 Probability and extent of added benefit (research question 1)

Since the company presented no data for the assessment of the added benefit of axitinib in patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib, an added benefit of axitinib in comparison with the ACT for these patients is not proven.

### 2.3.4 List of included studies (research question 1)

Not applicable as the company presented no relevant data for the benefit assessment.

## 2.4 Research question 2: cytokine-pretreated patients

### 2.4.1 Information retrieval and study pool (research question 2)

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

Sources of the company in the dossier:

- study list on axitinib (status: 1 February 2017)
- bibliographical literature search on axitinib (last search on 11 January 2017)
- search in trial registries for studies on axitinib (last search on 12 January 2017)

To check the completeness of the study pool:

- search in trial registries for studies on axitinib (last search on 5 April 2017)

No additional relevant study was identified from the check.

#### 2.4.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: axitinib vs. sorafenib

| Study | Study category | | |
|---|---|---|---|
| | Study for approval of the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) |
| A4061032 (AXIS[b]) | Yes | Yes | No |
| A4061051/2L | No | Yes | No |

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

The study pool concurred with the one of the company. For the present research question, the AXIS study, which was already included in the first assessment (commission A12-14 [4]), and study A4061051/2L were included in the benefit assessment. Both studies included, AXIS and A4061051/2L, compared axitinib with sorafenib.

Section 2.4.4 contains a reference list for the studies included.

#### 2.4.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: axitinib vs. sorafenib

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| AXIS | RCT, open-label, parallel | Adult patients with clear-cell metastatic renal cell carcinoma after failure of 1 prior systemic treatment with sunitinib, bevacizumab + IFN-α, temsirolimus or cytokines and with ECOG PS ≤ 1 | Axitinib (N = 361)<br>sorafenib (N = 362)<br><br>Relevant subpopulation thereof[b]<br>axitinib (n = 126)<br>sorafenib (n = 125) | Screening: 28 days<br><br>Treatment:<br>until death, progression, unacceptable side effects, discontinuation at the patient's request, withdrawal of consent<br><br>Follow-up:<br>outcome-specific, at most until death, withdrawal of consent or end of study (at least 3 years after randomization of the last patients) | 175 centres in 22 countries (Australia, Austria, Brazil, Canada, China, France, Germany, Greece, India, Ireland, Italy, Japan, Poland, Russia, Singapore, Slovak Republic, South Korea, Spain, Sweden, Taiwan, USA, United Kingdom)<br>9/2008–2/2016<br><br>Data cut-offs:<br>31 Aug 2010 (overall survival, morbidity, health-related quality of life, AEs)<br>1 Nov 2011 (overall survival, AEs)<br>Until the last visit (25 Feb 2016): follow-up of patients who were still under treatment (AEs) | Primary:<br>progression-free survival<br>Secondary:<br>overall survival, morbidity, AEs |

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: axitinib vs. sorafenib (continued)

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| A4061051/ 2L[c] | RCT, open-label, parallel | Adult patients with clear-cell metastatic renal cell carcinoma after failure of 1 prior systemic treatment with sunitinib, cytokines, or both, and with ECOG PS ≤ 1 | Axitinib (N = 135)<br>sorafenib (N = 69)<br><br>Relevant subpopulation thereof[b]<br>axitinib (n = 68)<br>sorafenib (n = 35) | Screening: 28 days<br><br>Treatment: until death, progression, unacceptable side effects, discontinuation at the patient's request, withdrawal of consent<br><br>Follow-up: outcome-specific, at most until death, withdrawal of consent or end of study (at least 3 years after randomization of the last patient) | 30 centres in 7 countries[d] (China, India, Malaysia, Philippines, Taiwan, Ukraine, USA)<br>8/2009–ongoing<br><br>Data cut-off 31 Oct 2011 | Primary: progression-free survival<br>Secondary: overall survival, health-related quality of life, morbidity, AEs |

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Cytokine-pretreated patients. The information provided in the following tables only refer to this subpopulation.
c: The A4061051 study consists of a study part that considers axitinib in first-line treatment and a second-line part (2L). Since only the second-line part is relevant for the present assessment, only this part is considered, hence the designation of the study as "A4061051/2L".
d: 99% of the patients were from Asia.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; INF: interferon; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: axitinib vs. sorafenib (cytokine population)

| Study | Intervention | Comparison |
|---|---|---|
| AXIS | Axitinib oral<br>starting dose: 2 x 5 mg/day<br>dose increase in case of good tolerability: up to 2 x 10 mg/day<br>dose reduction in case of intolerance: up to 2 x 2 mg/day<br>treatment interruption possible | Sorafenib oral<br>starting dose: 2 x 400 mg/day<br>dose increase not allowed<br>dose reduction in case of intolerance to 400 mg/day or every 2 days<br>treatment interruption possible |
| | **Pretreatment:**<br>▪ cytokine as first-line treatment<br>▪ no more than 1 prior systemic therapy<br>▪ no adjuvant or neoadjuvant systemic treatments<br><br>**Concomitant medication allowed:**<br>▪ palliative radiotherapy for pain control in bone metastases already present at the start of the study<br>▪ palliative and supportive care for disease-related symptoms, including pain medications<br><br>**Non-permitted concomitant medication:**<br>▪ strong CYP3A4 or CYP1A2 inducers<br>▪ strong CYP3A4 inhibitors<br>▪ chemotherapy or other experimental tumour therapies | |
| A4061051/ 2L | Axitinib oral<br>starting dose: 2 x 5 mg/day<br>dose increase in case of good tolerability: up to 2 x 10 mg/day<br>dose reduction in case of intolerance: up to 2 x 2 mg/day<br>treatment interruption possible | Sorafenib oral<br>starting dose: 2 x 400 mg/day<br>dose increase not allowed<br>dose reduction in case of intolerance to 400 mg/day or every 2 days<br>treatment interruption possible |
| | **Pretreatment:**<br>▪ cytokine as first-line treatment<br>▪ no more than 1 prior systemic therapy<br>▪ no adjuvant or neoadjuvant treatments < 6 months before study inclusion<br><br>**Concomitant medication allowed:**<br>▪ palliative radiotherapy for pain control in bone metastases already present at the start of the study<br>▪ palliative and supportive care for disease-related symptoms, including pain medications<br><br>**Non-permitted concomitant medication:**<br>▪ strong CYP3A4 or CYP1A2 inducers<br>▪ strong CYP3A4 inhibitors<br>▪ chemotherapy or other experimental tumour therapies | |
| CYP: cytochrome P450; RCT: randomized controlled trial; vs.: versus | | |

**Study design**

The studies AXIS and A4061051/2L were randomized, open-label, active-controlled studies on the comparison of axitinib and sorafenib. Both studies had a multicentre design.

The studies AXIS and A4061051/2L included adult patients with clear-cell metastatic renal cell carcinoma after failure of prior systemic treatment and with an ECOG PS of ≤ 1. The prior systemic therapy could consist of sunitinib, bevacizumab + interferon-alpha (IFN-α), temsirolimus or cytokines in the AXIS study, and of sunitinib, cytokines or both in the A4061051/2L study. For the present research question, only the subpopulation of cytokine-pretreated patients was relevant in each case.

The population with cytokine pretreatment investigated in the studies corresponded to the therapeutic indication of axitinib in the present research question. No patients with ECOG PS > 1, non-clear cell renal cell carcinoma or without metastases were included in the studies, however.

Randomization was stratified by ECOG PS and prior treatment in both studies. In the AXIS study, 723 patients were allocated in a ratio of 1:1 to treatment with axitinib (N = 361) or sorafenib (N = 362). In the A4061051/2L study, 204 patients were allocated in a ratio of 2:1 to treatment with axitinib (N = 135) or sorafenib (N = 69). The relevant subpopulation of the AXIS study comprised 126 patients in the axitinib arm and 125 patients in the sorafenib arm; the relevant subpopulation of the A4061051/2L study comprised 68 patients and 35 patients.

The AXIS study was conducted in 22 countries in Australia, North and South America, Asia and Europe. The A4061051/2L study was the second-line part of a study that investigated axitinib both in first-line treatment and in second-line treatment. This study was conducted in 7 countries, almost exclusively in Asia.

The specifications for the treatment of the patients, including possible dose adjustments, corresponded to the SPCs of axitinib and sorafenib [5,6] in both studies, except for the possibility to reduce the sorafenib dose to 400 mg every 2 days in case of intolerance. The corresponding SPC only recommends a reduction to 400 mg/day. It could be inferred from the study documents for both studies, however, that the average daily dose was at least 400 mg for all patients.

In both studies, treatment with axitinib or sorafenib was to be continued until disease progression (measured with the Response Evaluation Criteria in Solid Tumours [RECIST] version 1.0), death, unacceptable side effects, discontinuation at the patient's request, or withdrawal of consent. There were no restrictions regarding subsequent therapies. According to the study protocol, administration of axitinib or sorafenib was not mandated after completion of study treatment.

In the AXIS study, approximately 46% of the patients of the relevant subpopulation were receiving subsequent therapy at the second data cut-off (1 November 2011). The most common subsequent therapies were everolimus and sunitinib (about 16% to 23% of the patients). In the AXIS study, deviating from the study protocol, about 10% of the patients in the axitinib arm and about 9% of the patients in the sorafenib arm received sorafenib as subsequent therapy. No information on subsequent therapies in the relevant subpopulation was available for the A4061051/2L study. Of the total population, about 6% of the patients in the axitinib arm and about 13% of the patients in the sorafenib arm were receiving subsequent therapy at the time point of the data cut-off; this subsequent therapy consisted of sorafenib in 2 patients in the axitinib arm.

Primary outcome of the studies was PFS; relevant secondary outcomes were overall survival, morbidity and side effects.

**Analysis and data cut-offs**

For the AXIS study, analyses were conducted at 3 time points:

- first data cut-off (31 August 2010): final analysis of the primary outcome "PFS" (planned after 409 events)
- second data cut-off (1 November 2011): final analysis of the outcome "overall survival" (planned after 417 events)
- analysis at the end of the study (25 February 2016)

The first data cut-off was the primary basis for the first assessment of axitinib (commission A12-14 [4]). Analyses from the second data cut-off were only available for the outcome "overall survival"; these were included in the first assessment. In the present benefit assessment, the company supplemented the results from the second data cut-off of the AXIS study with analyses on AEs. Module 5 contains an analysis of side effects in patients who were still under treatment after the second data cut-off. This analysis was performed at the end of the study on 25 February 2016 and was only conducted for the total population. For the present benefit assessment, analogous to the first assessment, the analyses at the second data cut-off were used for the outcome "overall survival". In Module 4A, the company presented analyses for AEs for the relevant subpopulation at the first and second data cut-off. Due to the longer observation period and to ensure comparability with the all-cause mortality data, also the second data cut-off was used for this outcome for the benefit assessment. The majority of the patients of the relevant subpopulation (> 75%) had already completed their study treatment at this time point. Only results at the first data cut-off on 31 August 2010 were available for the questionnaires on morbidity. It can be inferred from the study documents that the questionnaires were no longer to be completed after the first data cut-off.

All analyses in the A4061051/2L study were based on a data cut-off on 31 October 2011. This data cut-off had not been prespecified by sample size planning. It was not clear from the study documents how the date of this data cut-off had been set.

**Planned duration of follow-up**

Table 8 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: axitinib vs. sorafenib

| Study<br>Outcome category<br>Outcome | Planned follow-up |
|---|---|
| **AXIS** | |
| Mortality | |
| Overall survival | Until death, withdrawal of consent or end of study (at least 3 years after randomization of the last patient) |
| Morbidity | |
| Symptoms (FKSI-DRS) | Until 28 days after the end of treatment |
| Health status (EQ-5D VAS) | Until 28 days after the end of treatment |
| Side effects | Until 28 days after the end of treatment |
| **A4061051/2L** | |
| Mortality | |
| Overall survival | Until death, withdrawal of consent or end of study (at least 3 years after randomization of the last patient) |
| Morbidity | |
| Symptoms (FKSI-DRS) | Until 28 days after the end of treatment |
| Health status (EQ-5D VAS) | Until 28 days after the end of treatment |
| Side effects | Until 28 days after the end of treatment |

EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The outcome "overall survival" was recorded until the end of study participation. The observation periods for the outcomes on morbidity and side effects were systematically shortened because they were only recorded for the time period of treatment (plus 28 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

**Characteristics of the study populations**

Table 9 shows the characteristics of the cytokine-pretreated patients in the included studies.

Table 9: Characteristics of the study populations – RCT, direct comparison: axitinib vs. sorafenib (cytokine population)

| **Study**<br>**Characteristics**<br>**Category** | **Axitinib** | **Sorafenib** |
|---|---|---|
| **AXIS** | N[a] = 126 | N[a] = 125 |
| Age [years], mean (SD) | 59 (11) | 60 (10) |
| Sex [F/M], % | 25/75 | 30/70 |
| Ethnicity, n (%) | | |
| White | 82 (65.1) | 81 (64.8) |
| Asian | 43 (34.1) | 42 (33.6) |
| Other | 1 (0.8) | 2 (1.6) |
| Geographical region, n (%) | | |
| Europe | 62 (49.2) | 60 (48.0) |
| Asia | 42 (33.3) | 41 (32.8) |
| North America | 19 (15.1) | 19 (15.2) |
| Other | 3 (2.4) | 5 (4.0) |
| ECOG PS, n (%) | | |
| 0 | 76 (60.3) | 76 (60.8) |
| 1 | 50 (39.7) | 49 (39.2) |
| Disease stage, n (%) | | |
| III | 8 (6.3) | 10 (8.0) |
| IV | 118 (93.7) | 115 (92.0) |
| Disease duration: time since histopathologic diagnosis [weeks], mean (SD) | 207.9 (254.5) | 191.9 (195.7) |
| Treatment discontinuation, n (%) | ND | ND |
| Study discontinuation, n (%) | ND | ND |
| **A4061051/2L** | N[a] = 68 | N[a] = 35 |
| Age [years], mean (SD) | 55 (14) | 59 (11) |
| Sex [F/M], % | 41/59 | 29/71 |
| Ethnicity, n (%) | | |
| White | 1 (1.5) | 0 (0) |
| Asian | 67 (98.5) | 35 (100) |
| ECOG PS, n (%) | | |
| 0 | 39 (57.4) | 20 (57.1) |
| 1 | 29 (42.6) | 15 (42.9) |
| Disease stage, n (%) | | |
| IV | 68 (100) | 35 (100) |
| Disease duration: time since histopathologic diagnosis [weeks], mean (SD) | ND | ND |
| Treatment discontinuation, n (%) | ND | ND |
| Study discontinuation, n (%) | ND | ND |

(continued)

Table 9: Characteristics of the study populations – RCT, direct comparison: axitinib vs. sorafenib (cytokine population) (continued)

a: Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The studies AXIS and A4061051/2L are largely comparable regarding the composition of the patient populations. The mean age of the patients in both studies was 56 years and 59 years; most patients were male (63% and 73%), and almost all patients had disease stage IV. There was a clear difference between the studies regarding the patients' ethnic origin. About 2 thirds of the patients in the AXIS study were white and 1 third Asian, whereas almost all patients in the A4061051/2L study were of Asian origin.

No data on treatment and study discontinuation for the relevant subpopulation were available for either of both studies.

**Course of the study**

The current dossier contained no information on the treatment duration of the patients and on observation periods for individual outcomes for either of both studies (see Table 10).

Table 10: Information on the course of the study – RCT, direct comparison: axitinib vs. sorafenib (cytokine population)

| **Study**<br>**Duration of the study phase**<br>**Outcome category** | **Axitinib** | **Sorafenib** |
|---|---|---|
| **AXIS** | N = 126 | N = 125 |
| First data cut-off 31 August 2010 | | |
| Treatment duration [months] | ND | ND |
| Observation period [months] | | |
| Overall survival, morbidity, health-related quality of life, side effects | ND | ND |
| Second data cut-off 1 November 2011 | | |
| Treatment duration [months] | ND | ND |
| Observation period [months] | | |
| Overall survival, morbidity, health-related quality of life, side effects | ND | ND |
| **A4061051/2L** | N = 68 | N = 35 |
| Treatment duration [months] | ND | ND |
| Observation period [months] | | |
| Overall survival, morbidity, health-related quality of life, side effects | ND | ND |

N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Disease progression was the main reason for discontinuation of the study medication in each of the total populations. The data on PFS were therefore used as an approximation to the treatment duration (in the absence of corresponding information). In both studies, a difference between the axitinib and the sorafenib arm in median PFS was shown in the relevant subpopulations (AXIS: 12.1 versus 6.5 months [first data cut-off, information on the second data cut-off not available]; A4061051/2L: 10.1 versus 6.5 months). Since all outcomes except overall survival were to be followed-up until 28 days after the end of treatment, a relevant difference between the observation periods can be assumed.

**Risk of bias at study level**

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: axitinib vs. sorafenib (cytokine population)

| 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 | | | |
| AXIS | Yes | Yes | No | No | Yes | Yes | Low |
| A4061051/2L | Yes | Yes | No | No | Yes | Yes | Low |
| RCT: randomized controlled trial; vs.: versus | | | | | | | |

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

Limitations resulting from the open-label study design are described in Section 2.3.2 with the outcome-specific risk of bias.

### 2.4.2 Results on added benefit (research question 2)

#### 2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - health status according to the EQ-5D VAS
  - symptoms according to the FKSI-DRS
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3 or 4)
  - treatment discontinuations due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4A) (see Section 2.6.2.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the studies included.

Table 12: Matrix of outcomes – RCT, direct comparison: axitinib vs. sorafenib (cytokine population)

| Study | Outcomes | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall survival | Symptoms (FKSI-DRS) | Health status (EQ-5D VAS) | Health-related quality of life | SAEs | Discontinuation due to AEs | Severe AEs (CTCAE grade 3–4) | Specific AEs[a] |
| AXIS | Yes | Yes | Yes | No[b] | Yes | No[c] | Yes | Yes |
| A4061051/2L | Yes | Yes | Yes | No[b] | No[c] | No[c] | Yes | Yes |

a: The following events are considered (MedDRA coding, PTs): "alopecia", "rash", "dysphonia", "fatigue (severe CTCAE grade ≥ 3 AE)", "hand-foot syndrome (severe CTCAE grade ≥ 3 AE)", "nausea" and "thyroid hypofunction".
b: No patient-relevant outcomes recorded in this category (see Section 2.6.2.4.3 of the full dossier assessment).
c: No usable data available (see Section 2.6.2.4.3 of the full dossier assessment).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

### 2.4.2.2 Risk of bias

Table 13 shows the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: axitinib vs. sorafenib (cytokine population)

| Study | Study level | Outcomes | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Overall survival | Symptoms (FKSI-DRS) | Health status (EQ-5D VAS) | Health-related quality of life | SAEs | Discontinuation due to AEs | Severe AEs (CTCAE grade 3–4) | Specific AEs[a] |
| AXIS | L | L | H[b, c] | H[b, c] | -[d] | H[b] | -[e] | H[b] | H[b, f] |
| A4061051/2L | L | L | H[b, c] | H[b, c] | -[d] | -[e] | -[e] | H[b] | H[b, f] |

a: The following events are considered (MedDRA coding): "alopecia", "rash", "dysphonia", "fatigue (severe CTCAE grade ≥ 3 AE)", "hand-foot syndrome (severe CTCAE grade ≥ 3 AE)", "nausea" and "thyroid hypofunction".
b: Different observation periods in potentially informative censoring.
c: Lack of blinding in subjective recording of outcomes.
d: No patient-relevant outcomes recorded in this category (see Section 2.6.2.4.3 of the full dossier assessment).
e: No usable data available (see Section 2.6.2.4.3 of the full dossier assessment).
f: In non-serious/severe AE outcomes: lack of blinding in subjective recording of outcomes (see Section 2.6.2.4.2 of the full dossier assessment).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "overall survival" was rated as low in both studies. This concurs with the company's assessment.

The outcomes on morbidity and on AEs had a high risk of bias in both studies. On the one hand, this was due to the different observation periods in potentially informative censoring and, on the other, (in the morbidity outcomes and non-severe/non-serious AEs) in the open-label study design. This assessment of the risk of bias at outcome level concurs with that of the company, which justified this only with the open-label study design, but not with the different observation periods, for all outcomes with high risk of bias.

There were no usable data on health-related quality of life. The FKSI-15 questionnaire was not included in the present benefit assessment because it was already considered to a large extent by inclusion of the FKSI-DRS subscale (category morbidity) in the present benefit assessment and could be allocated neither to health-related quality of life nor to symptoms (see Section 2.6.2.4.3 of the full dossier assessment).

There were also no usable data for the outcomes “SAEs” (in the A4061051/2L study) and “discontinuations due to AEs” (in both studies) because it cannot be excluded that a relevant proportion of the events was caused by progression of the underlying disease (see Section 2.6.2.4.3 of the full dossier assessment). This deviates from the assessment of the company, which used these outcomes for the assessment of the added benefit of axitinib.

#### 2.4.2.3 Results

Table 14 and Table 15 summarize the results of the comparison of axitinib with sorafenib in patients with advanced renal cell carcinoma after failure of prior treatment with a cytokine. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations. The available Kaplan-Meier curves on the survival time analyses of the outcomes included are presented in Appendix A of the full dossier assessment. The forest plots of all meta-analyses calculated by the Institute can be found in Appendix B of the full dossier assessment. The common AEs presented by the company in Module 4A are shown in Appendix C of the full dossier assessment.

Table 14: Results (overall survival, morbidity, side effects) – RCT, direct comparison: axitinib vs. sorafenib (cytokine population)

| Outcome category<br>Outcome<br>Study | Axitinib<br>N | Axitinib<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Sorafenib<br>N | Sorafenib<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Axitinib vs. sorafenib<br>HR [95% CI]; p-value |
|---|---|---|---|---|---|
| **Mortality** | | | | | |
| Overall survival | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | 29.4 [24.5; NC]<br>51 (40.5) | 125 | 27.8 [23.1; 34.5]<br>57 (45.6) | 0.81 [0.55; 1.19];<br>0.287[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | NA [15.9; NC]<br>26 (38.2) | 35 | NA [13.5; NC]<br>11 (31.4) | 1.10 [0.54; 2.24];<br>0.785[a] |
| Total | | | | | 0.87 [0.62; 1.22];<br>0.420[b] |
| **Morbidity** | | | | | |
| FKSI-DRS[c] | | | | | |
| AXIS<br>(first data cut-off 31 Aug 2010) | 126 | 10.2 [7.7; 16.5]<br>57 (45.2) | 125 | 7.6 [5.6; NC]<br>55 (44.0) | 0.89 [0.62; 1.30];<br>0.554[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | 12.9 [5.6; NC]<br>34 (50.0) | 35 | NA [5.6; NC]<br>13 (37.1) | 1.29 [0.68; 2.45];<br>0.434[a] |
| Total | | | | | 0.98 [0.71; 1.35];<br>0.904[b] |
| **Health-related quality of life** | | | | | |
| | | No patient-relevant outcomes recorded in this category | | | |
| **Side effects** | | | | | |
| AEs (supplementary information) | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | 0.4 [0.2; 0.5]<br>116 (92.1) | 123 | 0.2 [0.2; 0.3]<br>120 (97.6) | – |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | 0.3 [0.3; 0.5]<br>66 (97.1) | 35 | 0.2 [0.1; 0.4]<br>35 (100) | – |
| SAEs | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | 27.0 [18.6; NC]<br>41 (32.5) | 123 | NA [18.8; NC]<br>34 (27.6) | 1.01 [0.64; 1.59];<br>0.977[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | | | | No usable data[d] | |
| Severe AEs (CTCAE grade 3 or 4) | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | 4.6 [3.0; 7.5]<br>86 (68.3) | 123 | 2.8 [1.1; 6.0]<br>87 (70.7) | 0.84 [0.62; 1.13];<br>0.250[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | 6.5 [4.1; 9.3]<br>40 (58.8) | 35 | 6.5 [0.9; 13.8]<br>22 (62.9) | 0.87 [0.52; 1.46];<br>0.600[a] |
| Total | | | | | 0.85 [0.65; 1.10];<br>0.207[b] |

(continued)

Table 14: Results (overall survival, morbidity, side effects) – RCT, direct comparison: axitinib vs. sorafenib (cytokine population) (continued)

| Outcome category<br>Outcome<br>Study | Axitinib<br>N | Axitinib<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Sorafenib<br>N | Sorafenib<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Axitinib vs. sorafenib<br>HR [95% CI]; p-value |
|---|---|---|---|---|---|
| Discontinuation due to AEs | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | | | | No usable data[d] | |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | | | | No usable data[d] | |
| Alopecia | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | NA [NC; NC]<br>9 (7.1) | 123 | NA [NC; NC]<br>48 (39.0) | 0.14 [0.07; 0.28];<br>< 0.001[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | NA [NC; NC]<br>3 (4.4) | 35 | NA [NC; NC]<br>8 (22.9) | 0.17 [0.05; 0.66];<br>0.003[a] |
| Total | | | | | 0.14 [0.08; 0.27];<br>< 0.001[b] |
| Rash | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | NA [28.3; NC]<br>21 (16.7) | 123 | NA [NC; NC]<br>36 (29.3) | 0.47 [0.27; 0.81];<br>0.005[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | NA [NC; NC]<br>12 (17.6) | 35 | NA [NC; NC]<br>10 (28.6) | 0.51 [0.22; 1.18];<br>0.107[a] |
| Total | | | | | 0.48 [0.30; 0.76];<br>0.002[b] |
| Dysphonia | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | NA [NC; NC]<br>38 (30.2) | 123 | NA [NC; NC]<br>15 (12.2) | 2.76 [1.52; 5.03];<br>< 0.001[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | NA [NC; NC]<br>12 (17.6) | 35 | NA [NC; NC]<br>3 (8.6) | 2.01 [0.57; 7.14];<br>0.266[a] |
| Total | | | | | 2.61 [1.52; 4.48];<br>< 0.001[b] |
| Fatigue (CTCAE grade ≥ 3)[e] | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | NA [NC; NC]<br>18 (14.3) | 123 | NA [NC; NC]<br>6 (4.9) | 2.75 [1.09; 6.97];<br>0.026[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | NA [NC; NC]<br>2 (2.9) | 35 | NA [NC; NC]<br>0 (0) | NC |
| Total | | | | | NC |

(continued)

Table 14: Results (overall survival, morbidity, side effects) – RCT, direct comparison: axitinib vs. sorafenib (cytokine population) (continued)

| Outcome category<br>Outcome<br>Study | Axitinib<br>N | Axitinib<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Sorafenib<br>N | Sorafenib<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Axitinib vs. sorafenib<br>HR [95% CI]; p-value |
|---|---|---|---|---|---|
| Hand-foot syndrome (CTCAE grade ≥ 3)[f] | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | NA [NC; NC]<br>7 (5.6) | 123 | NA [NC; NC]<br>24 (19.5) | 0.26 [0.11; 0.59];<br>< 0.001[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | NA [NC; NC]<br>4 (5.9) | 35 | NA [NC; NC]<br>4 (11.4) | 0.46 [0.12; 1.85];<br>0.263[a] |
| Total | | | | | 0.30 [0.15; 0.62];<br>0.001[g] |
| Nausea | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | NA [NC; NC]<br>31 (24.6) | 123 | NA [NC; NC]<br>17 (13.8) | 1.77 [0.98; 3.20];<br>0.056[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | NA [NC; NC]<br>10 (14.7) | 35 | NA [NC; NC]<br>2 (5.7) | 2.50 [0.55; 11.41];<br>0.221[a] |
| Total | | | | | 1.85 [1.07; 3.22];<br>0.029[b] |
| Thyroid hypofunction | | | | | |
| AXIS<br>(second data cut-off 1 Nov 2011) | 126 | NA [NC; NC]<br>28 (22.2) | 123 | NA [NC; NC]<br>9 (7.3) | 3.28 [1.55; 6.96];<br>0.001[a] |
| A4061051/2L<br>(data cut-off 31 Oct 2011) | 68 | NA [15.5; NC]<br>20 (29.4) | 35 | NA [NC; NC]<br>7 (20.0) | 1.47 [0.62; 3.47];<br>0.384[a] |
| Total | Heterogeneity: $I^2$ = 47.7%; p = 0.167[h] | | | | |

a: Effect and 95% CI: Cox proportional hazards model; p-value: 2-sided log-rank test, stratified by ECOG PS 0 or 1.
b: Meta-analysis with fixed effect (homogeneous data situation, $I^2 = 0$).
c: Deterioration by ≥ 3 points during the study.
d: The analysis presented contained a very large number of events caused by progression of the underlying disease (see Section 2.6.2.4.3 of the full dossier assessment).
e: Results on the PT "fatigue" (all severity grades, HR [95% CI], p-value): 1.59 [1.03; 2.46], 0.034 (AXIS); 0.72 [0.33; 1.60], 0.419 (A4061051/2L); no meta-analysis due to heterogeneity ($I^2$ = 66.0%, p = 0.086).
f: Results on the PT "hand-foot syndrome" (all severity grades, HR [95% CI], p-value): 0.35 [0.24; 0.52], < 0.001 (AXIS); 0.52 [0.28; 0.96], 0.035 (A4061051/2L); 0.40 [0.28; 0.57], < 0.001 (meta-analysis).
g: Institute's calculation: meta-analysis with random effects according to DerSimonian and Laird.
h: Due to the heterogeneity, pooling both studies is not meaningful.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 15: Results (morbidity – health status) – RCT, direct comparison: axitinib vs. sorafenib (cytokine population)

| Outcome category<br>Outcome<br>Study | Axitinib | | | Sorafenib | | | Axitinib vs. sorafenib |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at start of study mean (SD) | Values at end of study mean (SD) | N[a] | Values at start of study mean (SD) | Values at end of study mean (SD) | MD [95% CI]; p-value[b] |
| **Morbidity** | | | | | | | |
| Health status (EQ-5D VAS)[c] | | | | | | | |
| AXIS (first data cut-off 31 Aug 2010) | 126 | 71.62 (17.84) | 63.57 (20.02) | 125 | 71.68 (16.55) | 63.66 (16.35) | -1.86 [-5.20; 1.49] 0.277 |
| A4061051/2L (data cut-off 31 Oct 2011) | 68 | 83.85 (13.85) | 76.38 (15.65) | 35 | 83.09 (11.72) | 69.46 (22.55) | 1.28 [-4.53; 7.09] 0.665 |
| Total | | | | | | | -1.08 [-3.98; 1.82]; 0.466[d] |

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Effect, 95% CI and p-value: MMRM with an intercept term, treatment, time, an interaction term treatment*time and baseline as covariables.
c: A positive change in comparison with the start of the study indicates improvement.
d: Institute's calculation: meta-analysis with random effects according to DerSimonian and Laird.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

On the basis of the available data from the studies AXIS and A4061051/2L, at most proof, e.g. of an added benefit, can be derived for the outcome "overall survival". Due to the higher risk of bias, at most indications can be derived for the other outcomes if data from both studies are included in the assessment. In other cases, only hints can be derived. This is the case for the outcomes "SAEs", "fatigue" and "thyroid hypofunction".

## Mortality

### *Overall survival*

There was no statistically significant difference between the treatment arms for the outcome "overall survival".

As a result, there was no hint of an added benefit of axitinib versus sorafenib for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

**Morbidity**

***Symptoms (FKSI-DRS)***

No statistically significant difference between the treatment arms was shown for the outcome "symptoms (FKSI-DRS)".

As a result, there was no hint of an added benefit of axitinib versus sorafenib for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

***Health status (EQ-5D VAS)***

There was no statistically significant difference between the treatment arms for the outcome "health status" (EQ-5D VAS).

As a result, there was no hint of an added benefit of axitinib versus sorafenib for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

**Health-related quality of life**

No patient-relevant outcomes that represent health-related quality of life in a suitable way were recorded in the studies AXIS and A4061051/2L.

This resulted in no hint of an added benefit of axitinib in comparison with sorafenib; an added benefit is therefore not proven.

This deviates from the assessment of the company, which allocated the FKSI-15 questionnaire to health-related quality of life and derived an indication of added benefit for this outcome.

**Side effects**

***Serious adverse events***

Interpretable data for the outcome "SAEs" were only available from the AXIS study (see Section 2.6.2.4.3 of the full dossier assessment). There was no statistically significant difference between the treatment arms in this study. Hence there was no hint of greater or lesser harm from axitinib than from sorafenib for this outcome; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company, which used the results of both studies for the assessment, however.

***Severe adverse events (CTCAE grade 3 or 4 adverse events)***

There was no statistically significant difference between the treatment arms for the outcome "severe AEs (CTCAE grade 3 or 4)".

Hence there was no hint of greater or lesser harm from axitinib than from sorafenib for this outcome; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

***Treatment discontinuations due to adverse events***

No interpretable data were available in any of the 2 studies for the outcome "treatment discontinuations due to AEs" (see Section 2.6.2.4.3 of the full dossier assessment). Hence there was no hint of greater or lesser harm from axitinib than from sorafenib for this outcome; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company, which used the results of both studies for the assessment, however.

***Specific adverse events***

*Alopecia*

A statistically significant difference in favour of axitinib was shown for the outcome "alopecia". This resulted in an indication of lesser harm from axitinib than from sorafenib for this outcome.

This concurs with the company's assessment.

*Rash*

A statistically significant difference in favour of axitinib was shown for the outcome "rash".

In addition, for this outcome, there was proof of an effect modification for the characteristic "region" (Asia, Europe, North America, other), which had no consequences for the present benefit assessment, however (see Section 2.4.2.4).

This resulted in an indication of lesser harm from axitinib than from sorafenib for the outcome "rash".

This principally concurs with the assessment of the company, which also derived an indication of an added benefit on the basis of the total population.

*Dysphonia*

A statistically significant difference to the disadvantage of axitinib was shown for the outcome "dysphonia". This resulted in an indication of greater harm from axitinib than from sorafenib for this outcome.

This concurs with the company's assessment.

*Fatigue (CTCAE grade ≥ 3)*

For the outcome "fatigue (CTCAE grade ≥ 3)", an effect estimate was only calculable for the AXIS study. A statistically significant difference to the disadvantage of axitinib was shown in the AXIS study. This resulted in a hint of greater harm from axitinib than from sorafenib for this outcome.

This deviates from the assessment of the company, which considered the outcome "fatigue" on the basis of all events irrespective of their severity grade and derived no hint of greater or lesser harm from axitinib than from sorafenib.

*Hand-foot syndrome (CTCAE grade ≥ 3)*

A statistically significant difference in favour of axitinib was shown for the outcome "hand-foot syndrome (CTCAE grade ≥ 3)". This resulted in an indication of lesser harm from axitinib than from sorafenib for this outcome.

The company also described an advantage of axitinib for the outcome "hand-foot syndrome" on the basis of all events irrespective of their severity grade and derived an indication of an added benefit.

*Nausea*

There was a statistically significant difference to the disadvantage of axitinib for the outcome "nausea". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however.

Hence there was no hint of greater or lesser harm from axitinib than from sorafenib for this outcome; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

*Thyroid hypofunction*

Important heterogeneity between the studies was shown for the outcome "thyroid hypofunction". It was therefore not adequate to pool both studies for this outcome. The AXIS study (251 patients) was notably larger than the A4061051/2L study (103 patients). In addition, the AXIS study also included patients from Europe, whereas the A4061051/2L study almost exclusively included patients from Asia. Hence in case of heterogeneity, the results of the AXIS study were used for the assessment. A statistically significant difference to the disadvantage of axitinib was shown in this study for the outcome "thyroid hypofunction".

This resulted in a hint of greater harm from axitinib than from sorafenib for this outcome.

This deviates from the assessment of the company, which used the meta-analysis of both studies for the assessment and derived an indication of lesser benefit of axitinib.

#### 2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment (see also Section 2.6.2.4.3 of the full dossier assessment):

- age (< 65 years, ≥ 65 years)
- sex (male, female)
- region (Asia, Europe, North America, other)

All subgroup characteristics and cut-off values mentioned were predefined. For all outcomes with high risk of bias due to different observation periods and potentially informative censoring, only the results with proof of an interaction between treatment and subgroup characteristic are presented (see Section 2.6.2.2 of the full dossier assessment). The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. Due to the high certainty of conclusions, subgroups are also considered for the outcome "overall survival" if there are indications of an effect modification (p-value < 0.2). In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least 1 subgroup.

Table 16 summarizes the subgroup results on the comparison of axitinib with sorafenib.

Table 16: Subgroups (side effects, event time analysis) – RCT, direct comparison: axitinib vs. sorafenib (cytokine population)

| Outcome<br>Characteristic<br>Study<br>Subgroup | Axitinib<br>N | Axitinib<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Sorafenib<br>N | Sorafenib<br>Median survival time in months [95% CI]<br>Patients with event n (%) | Axitinib vs. sorafenib<br>HR [95% CI][a] | Axitinib vs. sorafenib<br>p-value[b] |
|---|---|---|---|---|---|---|
| Rash | | | | | | |
| Region | | | | | | |
| AXIS | | | | | | |
| Asia | 42 | NA [NC; NC]<br>8 (19.0) | 40 | NA [0.6; NC]<br>16 (40.0) | 0.38 [0.16; 0.90] | 0.023 |
| Europe | 62 | NA [NC; NC]<br>3 (4.8) | 59 | NA [NC; NC]<br>14 (23.7) | 0.17 [0.05; 0.60] | 0.002 |
| North America | 19 | 11.7 [1.4; 28.3]<br>10 (52.6) | 19 | NA [4.5; NC]<br>6 (31.6) | 1.56 [0.55; 4.44] | 0.402 |
| Other | 3 | NA [NC; NC]<br>0 (0) | 5 | NA [NC; NC]<br>0 (0) | NC | NC |
| A4061051/2L | | | | | | |
| Asia | 67 | NA [NC; NC]<br>12 (17.9) | 35 | NA [NC; NC]<br>10 (28.6) | 0.52 [0.22; 1.20] | 0.116 |
| North America | 1 | NA [NC; NC]<br>0 (0) | 0 | NA [NC; NC]<br>0 (0) | NC | NC |
| Total | | | | | Interaction: | 0.022[c] |
| Asia + Europe[d] | | | | | 0.37 [0.21; 0.65][e] | < 0.001[e] |
| North America | | | | | 1.56 [0.55; 4.43][e] | 0.404[e] |

a: Unless designated otherwise: effect and 95% CI: Cox proportional hazards model.
b: Unless designated otherwise: p-value: 2-sided log-rank test, stratified by ECOG PS 0 or 1.
c: Institute's calculation, Q test for heterogeneity, subgroups Asia + Europe/North America.
d: Pooling of the subgroups Asia and Europe due to homogeneous effects (Q test for heterogeneity, Institute's calculation: p = 0.345). The subgroup "other" was not considered because of missing events.
e: Institute's calculation: meta-analysis with random effects according to DerSimonian and Laird.
CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

## Side effects

### *Rash*

There was proof of an effect modification by the characteristic "region" (Asia, Europe, North America, other) for the outcome "rash". Due to homogeneous effects (Q test for heterogeneity, Institute's calculation: p = 0.345), the subgroups of Asian and European patients could be pooled (see Table 16).

The meta-analysis showed a statistically significant effect in favour of axitinib for patients from Asia and Europe. For this subgroup, this resulted in an indication of lesser harm from axitinib than from sorafenib for this outcome. For patients from North America, the meta-analysis showed no statistically significant difference between the treatment arms. Regarding the German health care context, a separate balancing for patients from Asia and Europe versus patients from North America is not considered to be meaningful, however. The results for patients from Asia and Europe were therefore used for the present benefit assessment.

This principally concurs with the assessment of the company, which also derived an indication of an added benefit on the basis of the total population.

### 2.4.3 Probability and extent of added benefit (research question 2)

The derivation of probability and extent of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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 the added benefit.

#### 2.4.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.3.2 resulted in indications and hints of both lesser and greater harm from axitinib than from sorafenib. The extent of the respective added benefit at outcome level was estimated from these results (see Table 17).

Table 17: Extent of added benefit at outcome level: axitinib vs. sorafenib (cytokine population)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Axitinib vs. sorafenib**<br>**Median of time to event or MD**<br>**Effect estimate [95% CI]**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Mortality** | | |
| Overall survival | Median: 29.4 vs. 27.8 months[c]<br>HR: 0.87 [0.62; 1.22]<br>p = 0.420 | Lesser benefit/added benefit not proven |
| **Morbidity** | | |
| FKSI-DRS | Median (time to deterioration by ≥ 3 points): 10.2–12.9[d] vs. 7.6[c] months<br>HR: 0.98 [0.71; 1.35]<br>p = 0.904 | Lesser benefit/added benefit not proven |
| EQ-5D | Mean changes from the start of the study:<br>-4.50 – -5.41 vs. -8.05 – -14.77[d]<br>MD: -1.08 [-3.98; 1.82];<br>p = 0.466 | Lesser benefit/added benefit not proven |
| **Health-related quality of life** | | |
| No patient-relevant outcomes of this category recorded | | |
| **Side effects** | | |
| SAEs[e] | Median: 27.0 months vs. NA<br>HR: 1.01 [0.64; 1.59]<br>p = 0.977 | Greater/lesser harm not proven |
| Severe AEs<br>(CTCAE grade 3 or 4) | Median: 4.6–6.5 vs. 2.8–6.5 months[d]<br>HR: 0.85 [0.65; 1.10]<br>p = 0.207 | Greater/lesser harm not proven |
| Discontinuation due to AEs | No usable data | Greater/lesser harm not proven |
| Fatigue<br>(CTCAE grade ≥ 3 AEs) | Median: NA vs. NA<br>HR: 2.75 [1.09; 6.97][f]<br>HR: 0.36 [0.14; 0.92][g]<br>p = 0.026<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.90 \leq CI_u < 1.00$<br>greater harm, extent: "minor" |
| Hand-foot syndrome<br>(CTCAE grade ≥ 3 AEs) | Median: NA vs. NA<br>HR: 0.30 [0.15; 0.62]<br>p = 0.001<br>probability: "indication" | Outcome category: serious/severe side effects<br>$CI_u < 0.75$<br>lesser harm, extent: "major" |
| Alopecia | Median: NA vs. NA<br>HR: 0.14 [0.08; 0.27]<br>p < 0.001<br>probability: "indication" | Outcome category: non-serious/non-severe side effects<br>$CI_u < 0.80$<br>lesser harm, extent: "considerable" |

(continued)

Table 17: Extent of added benefit at outcome level: axitinib vs. sorafenib (cytokine population) (continued)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Axitinib vs. sorafenib**<br>**Median of time to event or MD**<br>**Effect estimate [95% CI]**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Rash | | |
| Region[h] | | |
| Asia + Europe | Median: NA vs. NA<br>HR: 0.37 [0.21; 0.65]<br>p < 0.001<br>probability: "indication" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>lesser harm, extent: "considerable" |
| North America | Median: 11.7 months[c] vs. NA<br>HR: 1.56 [0.55; 4.43]<br>p = 0.404 | Greater/lesser harm not proven |
| Dysphonia | Median: NA vs. NA<br>HR: 2.61 [1.52; 4.48]<br>HR: 0.38 [0.22; 0.66][g]<br>p < 0.001<br>probability: "indication" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: "considerable" |
| Nausea | Median: NA vs. NA<br>HR: 1.85 [1.07; 3.22]<br>HR: 0.54 [0.31; 0.93][g]<br>p = 0.029 | Outcome category: non-serious/non-severe side effects<br>0.90 ≤ $CI_u$ < 1.00<br>Greater/lesser harm not proven[i] |
| Thyroid hypofunction | Median: NA vs. NA<br>HR: 3.28 [1.55; 6.96][j]<br>HR: 0.30 [0.14; 0.65][g]<br>p = 0.001<br>probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: "considerable" |

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the $CI_u$.
c: Data from the AXIS study; the median time to event was not reached in the A4061051/2L study.
d: Minimum and maximum medians of the time to event or mean changes in each treatment arm in the studies included.
e: Usable data are only available from the AXIS study.
f: Data from the AXIS study, Study A4061051/2L: not calculable.
g: Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
h: No separate balancing conducted for patients from Asia and Europe in comparison with patients from North America for the present benefit assessment. Hereinafter, only the results for patients from Asia and Europe are therefore used.
i: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
j: Data from the AXIS study; no common effect estimate can be provided due to heterogeneous data situation.

AE: adverse event; CI: confidence interval; $CI_u$: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; MD: mean difference; NA: not achieved; SAE: serious adverse event; vs.: versus

#### 2.4.3.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of axitinib in comparison with sorafenib (cytokine population)

| **Positive effects** | **Negative effects** |
|---|---|
| Indication of lesser harm – extent: "major" (outcome category "serious/severe side effects": hand-foot syndrome [CTCAE grade ≥ 3]) | Hint of greater harm – extent: "minor" (outcome category "serious/severe side effects": fatigue [CTCAE grade ≥ 3]) |
| Indication of lesser harm – extent: "considerable" (outcome category "non-serious/non-severe side effects": alopecia) | Indication of greater harm – extent: "considerable" (outcome category "non-serious/non-severe side effects": dysphonia) |
| Indication of lesser harm – extent: "considerable" (outcome category "non-serious/non-severe side effects": rash) | Hint of greater harm – extent: "considerable" (outcome category "non-serious/non-severe side effects": thyroid hypofunction) |
| CTCAE: Common Terminology Criteria for Adverse Events | |

In the overall assessment of the results from both relevant studies, there are positive and negative effects with different certainty of results.

On the side of positive effects, there were 3 indications of lesser harm from axitinib: with the extent "major" in the category "serious/severe side effects" for the outcome "hand-foot syndrome (CTCAE grade ≥ 3)", and with the extent "considerable" in the category "non-serious/non-severe side effects" for each of the outcomes "alopecia" and "rash".

On the side of negative effects, there was an indication of greater harm from axitinib in the category "non-serious/non-severe side effects" for the outcome "dysphonia" with the extent "considerable", and 2 hints of greater harm from axitinib, 1 in the category "serious/severe side effects" for the outcome "fatigue (CTCAE grade ≥ 3)" with the extent "minor" and 1 in the category "non-serious/non-severe side effects" for the outcome "thyroid hypofunction" with the extent "considerable". Overall, the positive effects were not completely outweighed by the negative effects, but the lesser harm of major extent was downgraded to lesser harm of considerable extent.

In the present assessment, the derivation of the added benefit was solely based on a reduction of side effects. In this situation, it has to be checked whether the results on benefit outcomes exclude a disadvantage on the benefit side with sufficient certainty. The available data provided no indication of lesser benefit of axitinib in comparison with sorafenib.

The company presented no complete overview of all AEs at Preferred Term (PT) and System Organ Class (SOC) level for the relevant subpopulation, but presented only results on selected events, which was only the case for CTCAE grade ≥ 3 AEs and for AEs of any severity grade.

Information on frequencies of specific events in SAEs and discontinuations due to AEs was missing completely. Due to these uncertainties, the overall certainty of results was lowered to a hint.

In summary, there is a hint of a considerable added benefit of axitinib in comparison with the ACT sorafenib for patients with advanced renal cell carcinoma after failure of prior treatment with a cytokine.

### 2.4.4 List of included studies (research question 2)

**A4061051/2L**

Pfizer. Axitinib (AG-013736) for the treatment of metastatic renal cell cancer: full text view [online]. In: ClinicalTrials.gov. 06.01.2017 [Accessed: 12.04.2017]. URL: https://ClinicalTrials.gov/show/NCT00920816.

Pfizer. Axitinib (AG-013736) for the treatment of metastatic renal cell cancer: study results [online]. In: ClinicalTrials.gov. 06.01.2017 [Accessed: 12.04.2017]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00920816.

Pfizer. AG-013736 (axitinib) for the treatment of metastatic renal cell cancer (mRCC) [online]. In: EU Clinical Trials Register. [Accessed: 12.01.2017]. URL: http://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-018585-23.

Pfizer. Clinical study report for previously treated Asian patients on protocol A4061051: AG-013736 (axitinib) for the treatment of metastatic renal cell cancer; study A4061051; clinical study report [unpublished]. 2012.

Pfizer. Clinical study report for previously treated Asian patients on protocol A4061051: AG-013736 (axitinib) for the treatment of metastatic renal cell cancer; study A4061051; Zusatzanalysen [unpublished]. 2017.

Qin S, Bi F, Jin J, Cheng Y, Guo J, Ren X et al. Axitinib versus sorafenib as a second-line therapy in Asian patients with metastatic renal cell carcinoma: results from a randomized registrational study. Onco Targets Ther 2015; 8: 1363-1373.

**AXIS**

Cella D, Escudier B, Rini B, Chen C, Bhattacharyya H, Tarazi J et al. Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial. Br J Cancer 2013; 108(8): 1571-1578.

Chen Y, Rini BI, Motzer RJ, Dutcher JP, Rixe O, Wilding G et al. Effect of renal impairment on the pharmacokinetics and safety of axitinib. Target Oncol 2016; 11(2): 229-234.

Escudier B, Michaelson MD, Motzer RJ, Hutson TE, Clark JI, Lim HY et al. Axitinib versus sorafenib in advanced renal cell carcinoma: subanalyses by prior therapy from a randomised phase III trial. Br J Cancer 2014; 110(12): 2821-2828.

Escudier B, Rini BI, Motzer RJ, Tarazi J, Kim S, Huang X et al. Genotype correlations with blood pressure and efficacy from a randomized phase III trial of second-line axitinib versus sorafenib in metastatic renal cell carcinoma. Clin Genitourin Cancer 2015; 13(4): 328-337.e3.

Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013; 14(6): 552-562.

Pfizer. Axitinib (AG 013736) as second line therapy for metastatic renal cell cancer: full text view [online]. In: ClinicalTrials.gov. 21.02.2017 [Accessed: 12.04.2017]. URL: https://ClinicalTrials.gov/show/NCT00678392.

Pfizer. Axitinib (AG 013736) as second line therapy for metastatic renal cell cancer: study results [online]. In: ClinicalTrials.gov. 21.02.2017 [Accessed: 12.04.2017]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00678392.

Pfizer. Axitinib (AG-013736) as second line therapy for metastatic renal cell cancer: AXIS trial [online]. In: EU Clinical Trials Register. [Accessed: 12.01.2017]. URL: http://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-001451-21.

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

Pfizer. Axitinib (AG-013736) as second line therapy for metastatic renal cell cancer: AXIS trial; study A4061032; Zusatzanalysen [unpublished]. 2017.

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.

Rini BI, Quinn DI, Baum M, Wood LS, Tarazi J, Rosbrook B et al. Hypertension among patients with renal cell carcinoma receiving axitinib or sorafenib: analysis from the randomized phase III AXIS trial. Target Oncol 2015; 10(1): 45-53.

Ueda T, Uemura H, Tomita Y, Tsukamoto T, Kanayama H, Shinohara N et al. Efficacy and safety of axitinib versus sorafenib in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from the global randomized phase 3 AXIS trial. Jpn J Clin Oncol 2013; 43(6): 616-628.

## 2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of axitinib in comparison with the ACT is summarized in Table 19.

Table 19: Axitinib – probability and extent of added benefit

| Research question | Subindication[a] | ACT[b] | Probability and extent of added benefit |
|---|---|---|---|
| 1 | Adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib | **Nivolumab** or everolimus | Added benefit not proven |
| 2 | Adult patients with advanced renal cell carcinoma after failure of prior treatment with a cytokine[c] | Sorafenib | Hint of considerable added benefit |

a: It is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the therapeutic decision and that treatment is palliative.
b: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
c: Both relevant studies only included patients with clear-cell metastatic renal cell carcinoma with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2, non-clear cell renal cell carcinoma or without metastases.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

For cytokine-pretreated patients, this deviates from the approach of the company, which derived an indication of a minor added benefit for these patients.

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

**Supplementary information on the implementation of the conditions of the limitation**

The G-BA's justification on the first assessment of axitinib included the following statement [7]:

> *"For the group of sunitinib-pretreated patients (about 99% of the target population), suitable data for an assessment of axitinib in comparison with the ACT everolimus are currently lacking. […]*
>
> *In addition, axitinib was only investigated in patients with clear-cell metastatic renal cell carcinoma after failure of 1 prior systemic treatment. […] Data for patients with locally advanced renal cell carcinoma without metastases and for patients with non-clear cell renal cell carcinoma are therefore also desirable.*
>
> *In addition, there is uncertainty regarding the interpretation of the study results in the category "side effects" because complete results for the cytokine-pretreated patient*

*population on frequency, differentiated by severity grade of the events under axitinib in comparison with the ACT sorafenib were not available for all adverse events[8] relevant in the therapeutic indication and for the drug (such as bleeding, arterial/venous thromboembolic and embolic events, gastrointestinal perforation, posterior reversible encephalopathy syndrome).”*

In the present dossier, the company only partly fulfilled these conditions of the limitation. It still presented neither studies on sunitinib-pretreated patients nor on patients with locally advanced renal cell carcinoma without metastases or with non-clear cell renal cell carcinoma. Regarding the side effects of the studies AXIS and A4061051/2L, the company presented data on the AEs the G-BA had named as examples and also provided analyses for the specific AEs differentiated by severity grade (CTCAE grade ≥ 3) for the reassessment. However, since the present dossier contained no data on all AEs, differentiated by severity grade, that occurred in the relevant subpopulation, the choice of specific AEs was still not completely comprehensible (see also Section 2.4.3.2).

**References for English extract**

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373(19): 1803-1813.

4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Axitinib: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A12-14 [online]. 21.12.2012 [Accessed: 11.03.2013]. (IQWiG-Berichte; Volume 149). URL: https://www.iqwig.de/download/A12-14_Axitinib_Nutzenbewertung_35a_SGB_V.pdf.

5. Bayer Pharma. Nexavar: Fachinformation [online]. 11.2014 [Accessed: 30.01.2017]. URL: http://www.fachinfo.de.

6. Pfizer. Inlyta: Fachinformation [online]. 05.2016 [Accessed: 30.01.2017]. URL: http://www.fachinfo.de.

7. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Axitinib [online]. 21.03.2013. URL: http://www.g-ba.de/downloads/40-268-2240/2013-03-21_AM-RL-XII_Axitinib_TrG.pdf.

*The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-12-axitinib-renal-cell-carcinoma-benefit-assessment-according-to-35a-social-code-book-v-expiry-of-the-decision.7870.html.*