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Lenvatinib (renal cell carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Lenvatinib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 December 2016). 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSKCC	Memorial Sloan Kettering Cancer Center
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
VEGF	vascular endothelial growth factor

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 lenvatinib in combination with everolimus (hereinafter referred to as "lenvatinib + everolimus"). 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 29 September 2016.

Research question

The aim of this report was to assess the added benefit of lenvatinib + everolimus in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced renal cell carcinoma following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of lenvatinib + everolimus

Therapeutic indication	**ACT**[a]
Adult patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy	Everolimus
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor	

The company concurred with the G-BA's specification on the ACT.

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

Results

Study characteristics

Study E7080-G000-205 (hereinafter referred to as "study 205") was included in the benefit assessment.

Adult patients with unresectable advanced or metastatic, mainly clear-cell, renal cell carcinoma were included in the phase 2 study. The patients' disease must have progressed on their previous treatment or within 9 months of stopping that treatment. In addition, the patients had disease progression after one prior VEGF-targeted therapy of the unresectable

advanced or metastatic disease. Patients had to be in good general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1).

Patients were randomly allocated in a ratio of 1:1:1 to treatment with lenvatinib + everolimus, lenvatinib monotherapy or everolimus monotherapy. A total of 153 patients were randomized (51 patients to the lenvatinib + everolimus arm, 52 patients to the lenvatinib arm and 50 patients to the everolimus arm).

The patients in the lenvatinib + everolimus arm received a daily dosage of 18 mg lenvatinib and 5 mg everolimus orally. The patients in the everolimus arm received a daily dosage of 10 mg everolimus orally. Dose modifications were allowed in both relevant treatment arms and corresponded to the requirements of the respective Summaries of Product Characteristics (SPCs).

Treatment with lenvatinib + everolimus or everolimus was to be continued in both study arms at most until disease progression or occurrence of unacceptable toxicity. Following discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could be treated with subsequent therapies.

The planned duration of study 205 depended on reaching a predefined number of progression events. Primary analysis of progression-free survival (PFS) was planned for this time point. The study was continued after the primary analysis. Patients who were still under treatment at the time point of the primary analysis continued treatment according to randomization.

There were 3 data cut-offs for study 205. The third data cut-off on 31 July 2015 was relevant for the benefit assessment. This was conducted post hoc following a recommendation by the regulatory authorities to obtain more mature data with greater informative value.

Risk of bias

The risk of bias at study level was rated as low. The risk of bias at outcome level was rated as high for all outcomes except overall survival.

Results

Mortality

For the decisive third data cut-off on 31 July 2015, treatment with lenvatinib + everolimus resulted in a statistically significant advantage for lenvatinib + everolimus. This resulted in an indication of an added benefit of lenvatinib + everolimus in comparison with everolimus.

Morbidity

No patient-relevant outcomes of the category “morbidity” were recorded in study 205. This resulted in no hint of an added benefit of lenvatinib + everolimus in comparison with everolimus for morbidity; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was not investigated in study 205. This resulted in no hint of an added benefit of lenvatinib + everolimus in comparison with everolimus for health-related quality of life; an added benefit is therefore not proven.

Side effects

- Serious adverse events, discontinuation due to adverse events, severe adverse events (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was shown for the outcomes "serious adverse events (SAEs)", "discontinuation due to adverse events (AEs)" and "severe AEs" (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). Hence there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with everolimus; greater or lesser harm is therefore not proven.

- Specific adverse events

There was no statistically significant difference between the treatment arms for the outcomes "anaemia" and "hypertension" (CTCAE grade 3 or 4). Hence there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with everolimus; greater or lesser harm is therefore not proven.

A statistically significant difference to the disadvantage of lenvatinib + everolimus was shown for the outcome "diarrhoea" (CTCAE grade 3 or 4). Under consideration of the risk of bias, this resulted in a hint of greater harm from lenvatinib + everolimus in comparison with everolimus.

No usable data were available for the further selected specific AEs "infections", "pneumonitis" and "haemorrhages". Hence there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with everolimus for these outcomes; greater or lesser harm is therefore not proven.

Extent and probability 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 lenvatinib + everolimus compared with the ACT is assessed as follows:

[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 the overall assessment, there is a positive and a negative effect of different certainty of results.

On the positive side, there is an indication of an added benefit with the extent “minor” in the category “mortality”. On the side of negative effects, this is accompanied by a hint of greater harm with the extent “considerable” in the category “serious/severe side effects” for the outcome “diarrhoea” (CTCAE grade 3 or 4).

It should be noted that both the positive and the negative effects can be underestimated or overestimated due to the low number of patients in the study and the resulting lack of power to identify statistically significant effects. This makes the balancing of the effects difficult. In addition, data on health-related quality of life are lacking. Due to the uncertainties described, the overall certainty of results was lowered to a hint.

Due to the mortality advantage, a minor added benefit remains overall despite the hint of greater harm of considerable extent and the lacking data on health-related quality of life. This is explained by the course of the Kaplan-Meier plot on overall survival in conjunction with the absolute proportion of patients with severe diarrhoea.

In summary, there is a hint of a minor added benefit of lenvatinib + everolimus versus the ACT everolimus for patients with advanced renal cell carcinoma.

Table 3 presents a summary of the extent and probability of the added benefit of lenvatinib + everolimus.

Table 3: Lenvatinib + everolimus – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adult patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy	Everolimus	Hint of minor added benefit
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor		

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

2.2 Research question

The aim of this report was to assess the added benefit of lenvatinib + everolimus in comparison with the ACT in adult patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of lenvatinib + everolimus

Therapeutic indication	**ACT[a]**
Adult patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy	Everolimus
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor	

It was assumed that treatment with curative intent is not (or no longer) an option for the patients in the present therapeutic indication at the time point of the therapeutic decision and that treatment is therefore palliative.

The company used the ACT specified by the G-BA.

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

2.3 Information retrieval and study pool

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 lenvatinib (status: 15 August 2016)
- bibliographical literature search on lenvatinib (last search on 1 August 2016)
- search in trial registries for studies on lenvatinib (last search on 1 August 2016)

To check the completeness of the study pool:

- search in trial registries for studies on lenvatinib (last search on 12 October 2016)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool of the company – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study E7080-G000-205 (205[b])	Yes	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 for the benefit assessment of lenvatinib + everolimus in comparison with everolimus consisted of study 205 and concurred with that of the company.

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included by the company – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study 205	RCT, open-label, parallel	▪ Adult patients with unresectable advanced or metastatic, mainly clear-cell, renal cell carcinoma ▪ disease progression after one prior VEGF-targeted therapy ▪ disease progression during or after the last pretreatment within 9 months before study enrolment ▪ ECOG PS 0, 1	Lenvatinib + everolimus (N = 51) lenvatinib (N = 52)[b] everolimus (N = 50)	Screening: within 21 days before randomization Treatment: at most until progression, unacceptable toxicity or withdrawal of consent. Patients who were under treatment at the time point of the primary analysis continued treatment according to randomization. Follow-up: outcome-specific, at most until death or withdrawal of consent	37 centres in Czech Republic, Poland, Spain, United Kingdom, United States 3/2012–ongoing First data cut-off[c]: 13 June 2014 Second data cut-off[d]: 10 December 2014 Third data cut-off[e]: 31 July 2015	Primary: PFS Secondary: overall survival, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment/from the information provided by the company in Module 4 of the dossier.
b: The arm is not relevant for the assessment and is not shown in the next tables.
c: Predefined primary analysis after at least 90 progression events across all study arms and at least 60 events for each of the prespecified comparisons between the study arms.
d: Data cut-off conducted post hoc.
e: Data cut-off conducted post hoc following a recommendation by the regulatory authorities.
AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; ND: no data; PFS: progression-free survival; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study	Intervention	Comparison
Study 205	Lenvatinib 18 mg + everolimus 5 mg/day orally	Everolimus 10 mg/day orally
	Dose reduction according to the SPC or dose interruption in case of grade 2 or 3 toxicity allowed	
	Prior therapy: ▪ VEGF-targeted treatment of unresectable, advanced or metastatic renal cell carcinoma: e.g. sunitinib, sorafenib, pazopanib, bevacizumab, axitinib, vatalanib ▪ no mTOR inhibitors including everolimus, temsirolimus ▪ no anticancer treatment within 21 days or any investigational agent within 30 days prior to the start of the study ▪ no major surgery within 3 weeks prior to study inclusion	
	Concomitant treatment: ▪ supportive treatment of disease-related symptoms (including transfusions, antibiotics, antidiarrhoeal drugs, etc.) ▪ corticosteroids for short-term treatment of acute symptoms ▪ G-CSF, erythropoietin ▪ bisphosphonates **Restricted concomitant treatment:** ▪ acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, low molecular weight heparin ▪ CYP3A4 and/or P-gp inhibitors, inducers and substrates **Non-permitted concomitant treatment:** ▪ any other anticancer treatment except the study medication ▪ corticosteroids for the palliative treatment of symptoms	

CYP3A4: cytochrome P450 3A4; G-CSF: granulocyte colony-stimulating factor; mTOR: mammalian target of rapamycin; ND: no data; P-gp: P-glycoprotein; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; VEGF: vascular endothelial growth factor; vs.: versus

Study 205 was a randomized, open-label, active-controlled phase 1b/2 study for the approval of lenvatinib in combination with everolimus. In the first part of the study (approval phase 1b), the dose for the lenvatinib + everolimus combination was determined. This part of the study was not used for the present benefit assessment. The patients in this phase 1b were not included in the second part of the study. In the second part of the study (approval phase 2), the patients were treated in 3 study arms: lenvatinib in combination with everolimus, everolimus monotherapy, and lenvatinib monotherapy. This part of the study was used for the present benefit assessment.

Adult patients with unresectable advanced or metastatic, mainly clear-cell, renal cell carcinoma were included in the phase 2 study. The patients' disease must have progressed on their previous treatment or within 9 months of stopping that treatment. In addition, the patients had disease progression after one prior VEGF-targeted therapy of the unresectable advanced or metastatic disease. Patients had to be in good general condition ECOG PS of 0 or 1. Since no patients with an ECOG PS of > 1 were included, it remains unclear whether the

results of the study are valid for these patients. Patients with brain metastases were also not included in the study.

The population investigated in the study largely corresponded to the therapeutic indication of lenvatinib + everolimus.

Randomisation was stratified by haemoglobin levels (≤ 13 g/dL versus > 13 g/dL for men and ≤ 11.5 g/dL versus > 11.5 g/dL for women) and corrected serum calcium levels (≥ 10 mg/dL versus < 10 mg/dL). The patients were randomly allocated in a ratio of 1:1:1 to treatment with lenvatinib + everolimus, lenvatinib or everolimus. A total of 153 patients were randomized: 51 patients to the lenvatinib + everolimus arm, 52 patients to the lenvatinib arm and 50 patients to the everolimus arm. The study arm with the lenvatinib + everolimus combination and the study arm with everolimus monotherapy were relevant for the present benefit assessment.

The patients in the lenvatinib + everolimus arm received a daily dosage of 18 mg lenvatinib and 5 mg everolimus orally. The patients in the everolimus arm received a daily dosage of 10 mg everolimus orally. Dose modifications were allowed in both relevant treatment arms and corresponded to the requirements of the respective SPCs [3,4].

Previous medication that was considered necessary for the patients' health could be continued. In addition, all patients could receive concomitant supportive treatment of disease-related symptoms. All medications which were not expected to influence the analysis or to interact with the drugs of the study were allowed for the medication used before and for the concomitant medication. No other anticancer treatments such as chemotherapy, endocrine therapy, radiotherapy or immunotherapy were allowed.

Treatment with lenvatinib + everolimus or everolimus was to be continued in both study arms at most until disease progression or occurrence of unacceptable toxicity. Following discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could be treated with subsequent therapies. There was no information regarding limitation of the subsequent therapy. Switching from the comparator to the intervention group was not mandated. At the first data cut-off, the proportion of patients with subsequent therapy was 25.5% in the lenvatinib + everolimus arm and 32.0% in the everolimus arm.

Primary outcome of the study was PFS; relevant secondary outcomes were overall survival and side effects. Health-related quality of life was not recorded in study 205.

Analysis and data cut-offs

For study 205, only one time point of analysis was preplanned for the primary outcome "PFS". This primary analysis of PFS was to be conducted on reaching at least 90 progression events across all 3 study arms and at least 60 progression events for each of the prespecified

comparisons between the study arms. The data cut-off for the primary analysis of PFS was conducted on 13 June 2014. At this time point, analyses on overall survival and on side effects were additionally conducted. Patients who were still under treatment at the time point of the primary analysis continued treatment according to randomization. One further data cut-off, which had not been preplanned, was conducted on 10 December 2014 to update the data on overall survival. This data cut-off was not used for the present benefit assessment because it was conducted post hoc without justification. The third data cut-off on 31 July 2015 was conducted following a recommendation by the Food and Drug Administration (FDA) to obtain more recent data with greater informative value. The European Medicines Agency (EMA) also used this data cut-off for the approval of lenvatinib. The company presented results on overall survival and side effects for this data cut-off. The third data cut-off was considered decisive for the present benefit assessment because the data were more recent and it can be assumed that the time point of the data cut-off was not data-driven.

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: lenvatinib + everolimus vs. everolimus

Study **Outcome category** **Outcome**	**Planned follow-up**
Study 205	
Mortality	
Overall survival	Every 8 weeks until the primary analysis, then[a] every 12 weeks until death, end of study or withdrawal of consent to be contacted
Morbidity	No patient-relevant outcomes recorded in this category
Health-related quality of life	Not investigated in the study
Side effects	
All outcomes in the category "side effects"	Until 30 days after the last dose of the study medication

a: Patients who were under treatment at the time point of the primary analysis continued treatment according to randomization.
RCT: randomized controlled trial; vs.: versus

Of the outcomes included, only overall survival was recorded until death. Side effects were recorded up to 30 days after the last dose of the study medication.

The observation periods for the outcomes on side effects were systematically shortened because they were only recorded for the time period of treatment (plus 30 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.

Table 9 and Table 10 show the characteristics of the patients in the studies included.

Table 9: Patient characteristics (demography) – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study Characteristics Category	**Lenvatinib + everolimus**	**Everolimus**
Study 205	N[a] = 51	N[a] = 50
Age [years], mean (SD)	62 (8)	59 (9)
BMI (kg/m^2)		
Mean (SD)	27.3 (3.7)	27.9 (4.8)
Sex [F/M], %	31/69	24/76
Ethnicity, n (%)		
White	50 (98)	47 (94)
Asian	1 (2)	2 (4)
Other	0 (0)	1 (2)
Data cut-off 13 June 2014:		
Treatment discontinuation, n (%)	38 (74.5)	47 (94.0)
Study discontinuation, n (%)	1 (2)	1 (2)
Data cut-off 31 July 2015:		
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients.

AE: adverse event; BMI: body mass index; 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

Table 10: Patient characteristics (disease characteristics) – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study **Characteristics** **Category**	**Lenvatinib + everolimus**	**Everolimus**
Study 205	N[a] = 51	N[a] = 50
ECOG PS, n (%)		
0	27 (52.9)	28 (56.0)
1	24 (47.1)	22 (44.0)
Time from diagnosis (RCC) to randomization (months)		
Median [min; max]	31.8 [5.1; 215.9]	26.0 [2.0; 147.2]
Extent of RCC at study entry, n (%)		
Unresectable advanced	4 (7.8)	1 (2.0)
Metastatic RCC	47 (92.2)	49 (98.0)
MSKCC risk score, n (%)		
Favourable	12 (23.5)	12 (24.0)
Intermediate	19 (37.3)	19 (38.0)
Poor	20 (39.2)	19 (38.0)
Heng criteria		
Favourable	8 (16.0)	9 (18.0)
Intermediate	32 (64.0)	29 (58.0)
Poor	10 (20.0)	12 (24.0)
Number of prior treatment regimens, n (%)		
1	44 (86.3)	41 (82.0)
2	6 (11.8)	9 (18.0)
3	1 (2.0)	0
Prior VEGF-targeted treatment, n (%)		
Yes	51 (100.0)	50 (100.0)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

ECOG PS: Eastern Cooperative Oncology Group Performance Status, max: maximum; min: minimum; MSKCC: Memorial Sloan Kettering Cancer Center; n: number of patients in the category; N: number of randomized patients; RCC: renal cell carcinoma; RCT: randomized controlled trial; SD: standard deviation; VEGF: vascular endothelial growth factor; vs.: versus

The demographic and disease-specific patient characteristics were sufficiently comparable between the 2 study arms. The mean age of the patients in study 205 was about 60 years. The majority of the patients were male and white. The mean body mass index (BMI) was about 28 kg/m^2 in both study arms.

Only patients with ECOG PS 0 or 1 were included in the study; more than half of the patients had an ECOG PS of 0. The median time since diagnosis was slightly higher in the combination arm than in the everolimus arm. Most patients in both arms had metastases. In

addition, most patients had an intermediate or poor risk profile according to the Memorial Sloan Kettering Cancer Center (MSKCC) score or the Heng criteria.

The proportion of treatment discontinuations at the first data cut-off on 13 June 2014 was lower in the lenvatinib + everolimus arm than in the everolimus arm and in both arms was mostly caused by radiological progression of the disease or AEs. The proportion of patients with radiological progression was 37.3% in the combination arm versus 70.0% in the everolimus arm. The proportion of patients who discontinued the study was 2% in each arm. No information on study or treatment discontinuation was available for the decisive data cut-off on 31 July 2015.

Although treatment with lenvatinib + everolimus is principally not limited to clear-cell renal cell carcinoma according to the approval [3], only patients with clear-cell renal cell carcinoma were included in study 205 except for one patient in the lenvatinib + everolimus arm. With up to 90%, this histological subtype constitutes the largest group of renal cell carcinomas, however [5,6].

Table 11 shows the mean/median treatment duration of the patients and the observation period for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study **Data cut-off** **Duration of the study phase** **Outcome category**	**Lenvatinib + everolimus**	**Everolimus**
Study 205	N = 51	N = 50
Data cut-off 13 June 2014		
Treatment duration [months]		
Median [min; max][a]	7.59 [0.66; 22.60]	4.06 [0.26; 20.07]
Mean (SD)[a]	9.37 (6.64)	6.15 (5.18)
Observation period	ND	
Data cut-off 31 July 2015		
Treatment duration	ND	
Observation period [months]		
Mortality	ND	
Morbidity	No patient-relevant outcomes recorded in this category	
Health-related quality of life	Not investigated in the study	
Side effects		
Median [min; max][a]	8.77 [0.49; 32.43]	5.26 [0.92; 33.58]
Mean (SD)[a]	11.89 (9.16)	7.34 (6.79)

a: Institute's calculation from days.

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

At the time point of the first data cut-off on 13 June 2014, the median treatment duration was notably longer in the lenvatinib + everolimus arm (7.59 months) than in the everolimus arm (4.06 months). No information on treatment duration was available for the decisive data cut-off on 31 July 2015.

Information on the observation period for side effects was available for the decisive data cut-off on 31 July 2015. The median observation period for side effect was notably longer in the combination arm: 8.77 months in the lenvatinib + everolimus arm and 5.26 months in the everolimus arm. Follow-up was conducted up to 30 days after the last dose of the study medication.

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at study level – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

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			
Study 205	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for study 205 was rated as low. This concurs with the company's assessment.

Restrictions resulting from the different observation periods between the treatment arms are described in Section 2.4.2 and in Section 2.7.2.4.2 of the full dossier assessment under the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - no patient-relevant outcomes recorded in this category

- Health-related quality of life
  - not recorded in the study included
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs CTCAE grade ≥ 3
  - 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 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 13 shows for which outcomes data were available in the studies included.

Table 13: Matrix of outcomes – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study	Outcomes											
	Overall survival	**Morbidity**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Anaemia (PT, CTCAE grade 3 or 4)**	**Diarrhoea (PT, CTCAE grade 3 or 4)**	**Hypertension (PT, CTCAE grade 3 or 4)**	**Haemorrhages (SMQ)**	**Infections (SOC)**	**Pneumonitis (PT)**
Study 205	Yes	No[a]	No[b]	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	No[c]	No[c]

a: No patient-relevant outcomes recorded in this category.
b: Not investigated in the study.
c: No usable data available; for reasons, see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; vs.: versus

2.4.2 Risk of bias

Table 14 shows the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study	Study level	Outcomes											
		Overall survival	Morbidity	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Anaemia (PT, CTCAE grade 3 or 4)	Diarrhoea (PT, CTCAE grade 3 or 4)	Hypertension (PT, CTCAE grade 3 or 4)	Haemorrhages (SMQ)	Infections (SOC)	Pneumonitis (PT)
Study 205	L	L	-[a]	-[a]	H[b, c]	H[b, c]	H[b, c]	H[b, c]	H[b, c]	H[b, c]	-[d]	-[d]	-[d]

a: Outcome not recorded.
b: Potential informative censoring.
c: Within the Cox proportional hazards model, deviating stratification of the primarily planned analysis of the outcome "overall survival" (see Section 2.7.2.4.2 of the full dossier assessment).
d: No usable data available.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; vs.: versus

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

The risk of bias due to potential informative censoring was rated as high for all outcomes of the category "side effects". This deviates from the assessment of the company, which assessed the risk of bias for the outcomes on side effects as low.

No patient-relevant outcomes were recorded in the category "morbidity"; health-related quality of life was not investigated in study 205.

2.4.3 Results

Table 15 and Table 16 summarize the results of the comparison of lenvatinib + everolimus in patients with advanced renal cell carcinoma.

Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. If available, Kaplan-Meier plots on the outcomes included are presented in Appendix A of the full dossier assessment.

Table 15: Results (mortality, morbidity) – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study **Outcome category**	**Lenvatinib + everolimus**		**Everolimus**		**Lenvatinib + everolimus vs. everolimus**
Outcome	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value**
Study 205 (data cut-off 31 July 2015)					
Mortality					
Overall survival	51	25.5 [16.4; 32.1][b] 32 (62.7)	50	15.4 [11.8; 20.6][b] 37 (74.0)	0.59 [0.36; 0.97] 0.035[c]
Morbidity	No patient-relevant outcomes recorded in this category				
Health-related quality of life	Not investigated in the study included				

a: HR and 95% CI from Cox proportional hazards model stratified by haemoglobin and corrected serum calcium.
b: Median calculated using point estimates based on the Kaplan-Meier method and the 95% CI based on the Greenwood formula.
c: Institute's calculation from data on the 95% CI.
CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 16: Results (side effects) – RCT, direct comparison: lenvatinib + everolimus vs. everolimus

Study Outcome category Outcome	Lenvatinib + everolimus N	Lenvatinib + everolimus Median time to first event in days [95% CI] Patients with event n (%)[a]	Everolimus N	Everolimus Median time to first event in days [95% CI] Patients with event n (%)[a]	Lenvatinib + everolimus vs. everolimus HR [95% CI][b]; p-value
Study 205 (data cut-off 31 July 2015)					
Side effects					
AEs (supplementary information)	51	4 [ND] 51 (100.0)	50	8 [ND] 50 (100.0)	-
SAEs	51	361 [ND] 30 (58.8)	50	232 [ND] 21 (42.0)	1.18 [0.66; 2.10] ND
Discontinuation due to AEs	51	NA [ND] 13 (25.5)	50	NA [ND] 6 (12.0)	1.64 [0.62; 4.37] ND
Severe AEs (CTCAE grade ≥ 3)	51	48 [ND] 39 (76.5)	50	177 [ND] 27 (54.0)	1.59 [0.96; 2.62] ND
Anaemia (CTCAE grade 3 or 4)	51	NA [ND] 4 (7.8)	50	NA [ND] 6 (12.0)	0.50 [0.14; 1.83] ND
Diarrhoea (CTCAE grade 3 or 4)	51	NA [ND] 10 (19.6)	50	NA [ND] 1 (2.0)	9.22 [1.18; 72.19] ND
Hypertension (CTCAE grade 3 or 4)	51	NA [ND] 7 (13.7)	50	NA [ND] 1 (2.0)	6.02 [0.74; 49.34] ND
Haemorrhages[c]	51	ND	50	ND	ND
Infections[d]	51	ND	50	ND	ND
Pneumonitis[e]	51	ND	50	ND	ND

a: Median calculated using point estimates based on the Kaplan-Meier method and the 95% CI based on the Greenwood formula.
b: HR and 95% CI from unstratified Cox proportional hazards model.
c: The CSR contained the following event numbers for the SMQ "haemorrhage terms (excl laboratory terms)" for the data cut-off on 13 June 2014: lenvatinib + everolimus 15 (29.4%), of which 4 (7.8%) with CTCAE grade ≥ 3; everolimus 13 (26.0%), of which 1 (2.0%) with CTCAE grade ≥ 3.
d: The CSR provided the following event numbers for the MedDRA SOC "infections and infestations" with CTCAE grade ≥ 3 for the data cut-off on 13 June 2014: lenvatinib + everolimus 5 (9.8%); everolimus 4 (8.0%) (see Table 25 in Appendix B of the full dossier assessment).
e: The CSR provided the following event numbers for the MedDRA PT "pneumonitis" with CTCAE grade ≥ 3 for the data cut-off on 13 June 2014: lenvatinib + everolimus 0 (0.0%); everolimus 3 (6.0%) (see Table 25 in Appendix B of the full dossier assessment).

AE: adverse event; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; vs.: versus

Mortality

Overall survival

For the decisive third data cut-off on 31 July 2015, treatment with lenvatinib + everolimus resulted in a statistically significant advantage for lenvatinib + everolimus. This resulted in an indication of an added benefit of lenvatinib + everolimus in comparison with everolimus.

This concurs with the company's assessment.

Morbidity

No patient-relevant outcomes of the category "morbidity" were recorded in study 205. This resulted in no hint of an added benefit of lenvatinib + everolimus in comparison with everolimus for morbidity; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of added benefit for the outcome "PFS" in the category "morbidity".

Health-related quality of life

Health-related quality of life was not investigated in study 205. This resulted in no hint of an added benefit of lenvatinib + everolimus in comparison with everolimus for health-related quality of life; an added benefit is therefore not proven.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment arms for the outcome "SAEs". Hence there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with everolimus; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs". Hence there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with everolimus; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Severe adverse events (CTCAE grade ≥ 3)

There was no statistically significant difference between the treatment arms for the outcome "severe AEs" (CTCAE grade ≥ 3). Hence there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with everolimus; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific adverse events

The specific AEs presented in Table 16 were identified during the investigation of the topic. The dossier contained survival time analyses on severe AEs CTCAE grade 3 or 4 for the outcomes of the most common Preferred Terms (PTs) "anaemia", "hypertension" and "diarrhoea". The dossier only contained analyses on the basis of the frequency of events for the outcomes "haemorrhages" (Standardized Medical Dictionary for Regulatory Activities Query [SMQ]), "infections" (System Organ Class [SOC]) and "pneumonitis" (PT). The relative risks based on this constitute no adequate analysis because of the differences in observation periods in both treatment arms, however (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment).

Anaemia and hypertension (CTCAE grade 3 or 4)

There was no statistically significant difference between the treatment arms for the outcomes "anaemia" and "hypertension" (CTCAE grade 3 or 4). Hence there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with everolimus; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which did not use these outcomes for the derivation of the added benefit.

Diarrhoea (CTCAE grade 3 or 4)

A statistically significant difference to the disadvantage of lenvatinib + everolimus was shown for the outcome "diarrhoea" (CTCAE grade 3 or 4). Under consideration of the risk of bias, this resulted in a hint of greater harm from lenvatinib + everolimus in comparison with everolimus.

This deviates from the assessment of the company, which did not use this outcome for the derivation of the added benefit.

Haemorrhages, infections and pneumonitis

There were no usable data for the outcomes "haemorrhages", "infections" and "pneumonitis". Hence there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with everolimus for these outcomes; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which did not use these outcomes for the derivation of the added benefit.

2.4.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the present assessment:

- age (< 65 years, ≥ 65 years)
- sex (men, women)
- region (Europe, USA)

The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. For the outcome "overall survival", results were to be presented if there was at least an indication of an interaction between treatment effect and subgroup characteristic. For all other outcomes, only results for which there was proof of an interaction are presented due to the different treatment durations and resulting different observation periods and the potentially informative censoring (see Section 2.7.2.2 of the full dossier assessment). In addition, subgroup results are only considered if there is a statistically significant and relevant effect in at least one subgroup.

Module 4 A contains usable data on the included outcomes "overall survival", "SAEs", "discontinuation due to AEs" and "severe AEs" (CTCAE grade ≥ 3) for all subgroup characteristics mentioned. The company presented survival time analyses on the subgroup results for the decisive data cut-off on 31 July 2015.

The results of study 205 showed no indication or proof of an effect modification by the characteristics considered for the outcome "overall survival". The outcomes of the category "side effects" showed no proof of an effect modification in the subgroup analyses. The subgroup results are therefore not presented in the benefit assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and 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.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in the following assessment of lenvatinib + everolimus in comparison with everolimus:

- an indication of an added benefit for overall survival
- a hint of greater harm for the outcome "diarrhoea" (CTCAE grade 3 or 4)

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: lenvatinib + everolimus vs. everolimus

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Lenvatinib + everolimus vs. everolimus** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 25.5 vs. 15.4 months HR: 0.59 [0.36; 0.97] p = 0.035[c] probability: "indication"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
No patient-relevant outcomes recorded in this category		
Health-related quality of life		
Not investigated in the study included		
Side effects		
SAEs	Median: 361 vs. 232 days HR: 1.18 [0.66; 2.10] p = ND	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NA vs. NA HR: 1.64 [0.62; 4.37] p = ND	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 48 vs. 177 days HR: 1.59 [0.96; 2.62] p = ND	Greater/lesser harm not proven
Anaemia (CTCAE grade 3 or 4)	Median: NA vs. NA HR: 0.50 [0.14; 1.83] p = ND	Greater/lesser harm not proven
Diarrhoea (CTCAE grade 3 or 4)	Median: NA vs. NA HR: 9.22 [1.18; 72.19] HR[d]: 0.11 [0.01; 0.85] p = ND probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Hypertension (CTCAE grade 3 or 4)	Median: NA vs. NA HR: 6.02 [0.74; 49.34] p = ND	Greater/lesser harm not proven
Haemorrhages	No usable data	Greater/lesser harm not proven
Infections and infestations	No usable data	Greater/lesser harm not proven
Pneumonitis	No usable data	Greater/lesser harm not proven

(continued)

Table 17: Extent of added benefit at outcome level: lenvatinib + everolimus vs. everolimus (continued)

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: Institute's calculation from data on the 95% CI.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
AE: adverse event; CI: confidence interval, CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; NA: not achieved; ND: no data; SAE: serious adverse event; vs.: versus

2.5.2 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 lenvatinib + everolimus in comparison with everolimus

Positive effects	**Negative effects**
Mortality ▪ overall survival indication of an added benefit – extent: "minor"	Serious/severe side effects ▪ diarrhoea (CTCAE grade 3 or 4): hint of greater harm – extent: "considerable"
Health-related quality of life was not investigated in the study included	
CTCAE: Common Terminology Criteria for Adverse Events	

In the overall assessment, there is a positive and a negative effect of different certainty of results.

On the positive side, there is an indication of an added benefit with the extent "minor" in the category "mortality". On the side of negative effects, this is accompanied by a hint of greater harm with the extent "considerable" in the category "serious/severe side effects" for the outcome "diarrhoea" (CTCAE grade 3 or 4).

It should be noted that both the positive and the negative effects can be underestimated or overestimated due to the low number of patients in the study and the resulting lack of power to identify statistically significant effects. This makes the balancing of the effects difficult. In addition, data on health-related quality of life are lacking. Due to the uncertainties described, the overall certainty of results was lowered to a hint.

Due to the mortality advantage, a minor added benefit remains overall despite the hint of greater harm of considerable extent and the lacking data on health-related quality of life. This is due to the course of the Kaplan-Meier plot on overall survival in conjunction with the absolute proportion of patients with severe diarrhoea.

In summary, there is a hint of a minor added benefit of lenvatinib + everolimus versus the ACT everolimus for patients with advanced renal cell carcinoma.

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

Table 19: Lenvatinib + everolimus – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Extent and probability of added benefit**
Adult patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy	Everolimus	Hint of minor added benefit
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor		

This deviates from the approach of the company, which derived an indication of major added benefit for the population of adult patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy.

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

2.6 List of included studies

Eisai. An open-label, multicenter Phase Ib/2 study of E7080 alone, and in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma following one prior VEGF-targeted treatment [online]. In: EU Clinical Trials Register. [Accessed: 16.11.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-019484-10.

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Eisai. An open-label, multicenter phase 1b/2 study of E7080 alone, and in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma Following one prior VEGF targeted treatment; study E7080-G000-205; final statistical analysis plan [unpublished]. 2014.

Eisai. An open-label, multicenter phase 1b/2 study of E7080 alone, and in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma following one prior VEGF-targeted treatment; study E7080-G000-205; clinical study protocol; amendment 05 [unpublished]. 2014.

Eisai. An open-label, multicenter phase Ib/2 study of E7080 alone, and in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma following one prior VEGF-targeted treatment: study E7080-G000-205; clinical study report [unpublished]. 2015.

Eisai. A study of E7080 alone, and in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma following one prior vascular endothelial growth factor (VEGF)-targeted treatment: study E7080-G000-205; Zusatzanalysen [unpublished]. 2016.

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Please see full dossier assessment for full reference list.

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