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Lenvatinib (thyroid carcinoma) –

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

Extract

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Ingo Schmidt-Wolf, Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment:

- Virginia Seiffart
- Ulrich Grouven
- Marco Knelangen
- Sabine Ostlender
- Min Ripoll
- Cornelia Rüdig
- Corinna ten Thoren
- Volker Vervölgyi

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
DTC	differentiated thyroid carcinoma
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
FACT-G	Functional Assessment of Cancer Therapy-General
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)
IU	international units
PFS	progression-free survival
RAI	radioactive iodine
RCT	randomized controlled trial
rhTSH	recombinant human TSH
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TSH	thyroid stimulating hormone
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
VEGFR	VEGF receptor

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. 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 15 February 2019.

Research question

The aim of the present report was to assess the added benefit of lenvatinib in comparison with sorafenib as appropriate comparator therapy (ACT) in patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

Table 2: Research question of the benefit assessment of lenvatinib

Research question	Therapeutic indication	ACT[a]
1	Progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)	Sorafenib
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company followed the G-BA's specification of 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 pool and study characteristics

No studies of direct comparison were identified for the assessment of the added benefit of lenvatinib in comparison with the ACT. The company presented an adjusted indirect comparison based on randomized controlled trials (RCTs) with placebo as common comparator and with one study on each side of the indirect comparison.

However, no suitable data from the 2 studies SELECT and DECISION were available for the adjusted indirect comparison between lenvatinib and the ACT sorafenib (see below).

SELECT (study with lenvatinib)

The SELECT study was a randomized, double-blind, multicentre, placebo-controlled study with lenvatinib. The study enrolled adult patients with histologically or cytologically confirmed diagnosis of a DTC (papillary, follicular or Hürthle cell). Patients had to have radiographically measurable disease and progression within 12 months prior to study inclusion. They had to have 131 iodine-refractory/resistant disease and were allowed prior treatment with at most 1 vascular endothelial growth factor (VEGF)- or VEGF receptor (VEGFR)-targeted therapy, e.g. sorafenib or sunitinib. Eastern Cooperative Oncology Group Performance Status (ECOG PS) had to be ≤ 2. Patients receiving thyroxine suppression therapy should not have elevated levels of thyroid stimulating hormone (TSH ≤ 5.50 µ international units [IU]/mL). If it was tolerable for the patients, the thyroxine dose was to be changed to achieve TSH suppression (TSH < 0.5 µIU/mL).

The study included 392 patients, who were randomized in a 2:1 ratio either to treatment with 24 mg day lenvatinib (N = 261) or corresponding placebo (N = 131).

Treatment was in compliance with the Summary of Product Characteristics (SPC). On occurrence of disease progression, patients could be unblinded and, if they were in the placebo arm, be switched to treatment with lenvatinib. At the time point of the primary analysis, 83% of the patients had already been switched from the placebo arm to treatment with lenvatinib.

Progression-free survival (PFS) was the primary outcome of the study. Patient-relevant secondary outcomes were overall survival and adverse events (AEs). Patient-relevant outcomes on morbidity and health-related quality of life were not recorded.

Relevant subpopulation for the indirect comparison

In contrast to the DECISION study (see below), the SELECT study could also enrol patients who had already received VEGF- or VEGFR-targeted therapy. This was the case in 23.7% of the patients (25.3% in the lenvatinib arm and 20.6% in the placebo arm). To improve the similarity of the studies for the indirect comparison of the studies SELECT and DECISION, the company therefore used the subpopulation of patients from the SELECT study who had not yet received VEGF/VEGFR-targeted therapy.

DECISION (study with sorafenib)

The DECISION study was a randomized, double-blind, multicentre, placebo-controlled study with sorafenib. The study enrolled adult patients with locally advanced or metastatic DTC (papillary, follicular, Hürthle cell or poorly differentiated). Patients had to have radiographically measurable disease and progression within 14 months prior to study inclusion. They had to have iodine-refractory disease; prior treatment with tyrosine kinase inhibitors, monoclonal anti-VEGF/VEGFR antibodies or other targeted therapies, cytotoxic chemotherapy or thalidomide and its derivatives were not allowed. ECOG PS had to be ≤ 2 and TSH levels < 0.5 mU/L.

The study included 417 patients, who were randomized in a 1:1 ratio either to treatment with sorafenib (N = 207) or corresponding placebo (N = 210).

Treatment was in compliance with the SPC. On occurrence of disease progression, patients could be unblinded and, at the physician's discretion, for as long as clinical benefit was observed, continue treatment with sorafenib or be switched from the placebo arm to treatment with sorafenib. Already at the time point of the primary analysis (31 August 2012; after 267 progression events), 71% of the patients had been switched from the placebo arm to treatment with sorafenib. At the final data cut-off on 30 August 2017, this was the case for 77% of the patients. In the sorafenib arm, 43% of the patients had progression and been unblinded at the primary data cut-off, with 27% of the patients continuing unblinded treatment with sorafenib. At the final data cut-off, 42% of the patients had continued unblinded treatment with sorafenib.

PFS was the primary outcome of the study. Patient-relevant secondary outcomes were overall survival, health status recorded with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS), health-related quality of life recorded with the Functional Assessment of Cancer Therapy-General (FACT-G), and AEs.

In consultation with the Food and Drug Administration (FDA), the study was ended at the time point of the final analysis of overall survival after 210 deaths.

Similarity of the studies for the indirect comparison

The studies SELECT and DECISION had a comparable design.

In both studies, patients in the placebo arm were allowed to switch from the placebo arm to treatment with lenvatinib or sorafenib, respectively, after disease progression. The proportions of patients from the placebo arms who switched to treatment with lenvatinib or sorafenib were similar in both studies already at the first available data cut-off.

In the DECISION study, patients in the intervention arm could continue treatment with sorafenib also after disease progression and subsequent unblinding at the physician's discretion if clinical benefit was observed. At the primary data cut-off, 27% of the patients had chosen this option, and 42% at the final data cut-off. The SELECT study did not envisage continued treatment with lenvatinib after disease progression for patients in the intervention arm, but subsequent therapies were not restricted. Nevertheless, only few patients in the SELECT study started subsequent therapy after ending the study medication (primary data cut-off on 15 November 2013: lenvatinib 16%, placebo 12% [without lenvatinib]). The different proportions of patients with subsequent therapy in the DECISION study compared with the SELECT study does not raise fundamental doubts about the similarity of the studies, but must be taken into account when interpreting the results of the indirect comparison.

The median treatment durations in the common comparator arms (placebo) were sufficiently comparable at the respective primary data cut-offs. Only incomplete information on treatment durations was available for the subsequent data cut-offs. However, in both studies, about 80% of the patients had been switched from the placebo arms to treatment with lenvatinib or sorafenib already at the primary data cut-off. It is therefore not assumed that the treatment durations in the placebo arms were decisively different.

The demographic and clinical characteristics of the patients were balanced between the study arms of the studies SELECT and DECISION and were sufficiently similar between these 2 studies.

Risk of bias

The risk of bias across outcomes was rated as low for both studies.

The outcome-specific risk of bias for the results of the outcome "overall survival" was rated as high both for the SELECT study and for the DECISION study. This was due to the high proportion of patients in the placebo arm who switched to treatment with lenvatinib or sorafenib after disease progression.

No usable data were available for the other outcomes included in the present benefit assessment (see below). The risk of bias for these outcomes was therefore not determined.

Results

The results of the included outcomes were not usable for the following reasons:

- The indirect comparison for the outcome "all-cause mortality" was based on only 1 study with outcome-specific high risk of bias for the underlying direct comparisons with the common comparator. Hence, the uncertainty in the available data was too high to be able to derive valid conclusions on added benefit or greater harm of lenvatinib in comparison with the ACT.
- No usable data for the indirect comparison were available for the outcomes on morbidity and health-related quality of life as only the DECISION study recorded patient-relevant outcomes in these categories.
- There were also no usable data for the outcomes on side effects (serious AEs [SAEs], discontinuation due to AEs, severe AEs [Common Terminology Criteria for Adverse Events, CTCAE ≥ 3]). In both studies, AEs were only observed until the end of the study medication (plus 30 days). However, there were no time-adjusted analyses, but only analyses based on the proportion of patients with events (effect measure: relative risk [RR]). These analyses were not adequate due to the clear difference in median treatment duration between intervention and placebo arm in both relevant studies (SELECT [total population]: 13.8 versus 3.9 months; proportion placebo arm 28%, DECISION: 10.6 versus 6.5 months; proportion placebo arm 61%).

Irrespective of this, none of the outcomes mentioned showed a statistically significant effect in the indirect comparison.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, probability and extent of the added benefit of the drug lenvatinib in comparison with the ACT are assessed as follows:

Since no usable data were available for the adjusted indirect comparison of lenvatinib with the ACT sorafenib, an added benefit of lenvatinib compared with the ACT is not proven.

The result of the assessment of the added benefit of lenvatinib in comparison with the ACT is summarized in Table 3.

Table 3: Lenvatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)	Sorafenib	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2015. In this assessment, the G-BA had determined a non-quantifiable added benefit of lenvatinib. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report was to assess the added benefit of lenvatinib in comparison with sorafenib as ACT in patients with progressive, locally advanced or metastatic, differentiated (papillary/ follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to RAI.

Table 4: Research question of the benefit assessment of lenvatinib

Research question	**Therapeutic indication**	**ACT[a]**
1	Progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)	Sorafenib
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company named sorafenib as ACT and thus followed the G-BA's specification.

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: 1 December 2018)
- bibliographical literature search on lenvatinib (last search on 27 November 2018)
- search in trial registries for studies on lenvatinib (last search on 28 November 2018)
- bibliographical literature search on the ACT (last search on 27 November 2018)
- search in trial registries for studies on the ACT (last search on 28 November 2018)

To check the completeness of the study pool:

- search in trial registries for studies on lenvatinib (last search on 11 March 2019)
- search in trial registries for studies on sorafenib (last search on 22 March 2019)

Concurring with the company, no relevant RCT on the direct comparison of lenvatinib versus the ACT was identified from the check. The company presented the results of the placebo-controlled SELECT study, however. It did not use the results for the derivation of an added benefit as this study contained no conclusions in comparison with the ACT specified by the G-BA.

The company identified 2 studies for an adjusted indirect comparison based on RCTs. The check of the completeness of the study pool produced no additional relevant studies for the indirect comparison presented by the company (see Section 2.3.1).

2.3.1 Studies included

The company presented an adjusted indirect comparison with placebo as common comparator and with one study on each side of the indirect comparison for the assessment of the added benefit of lenvatinib. Since there was only 1 RCT with lenvatinib in the relevant therapeutic indication and this RCT used placebo as comparison, in agreement with the company, placebo was the only possible common comparator for an adjusted indirect comparison.

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

Table 5: Study pool – RCT, indirect comparison: lenvatinib 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)
Study with lenvatinib			
E7080-G000-303 (SELECT[b])	Yes	Yes	No
Study with sorafenib			
DECISION	Yes	No	Yes

a: Study sponsored by the company.
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 concurred with that of the company. Figure 1 shows a schematic representation of the two indirect comparisons.

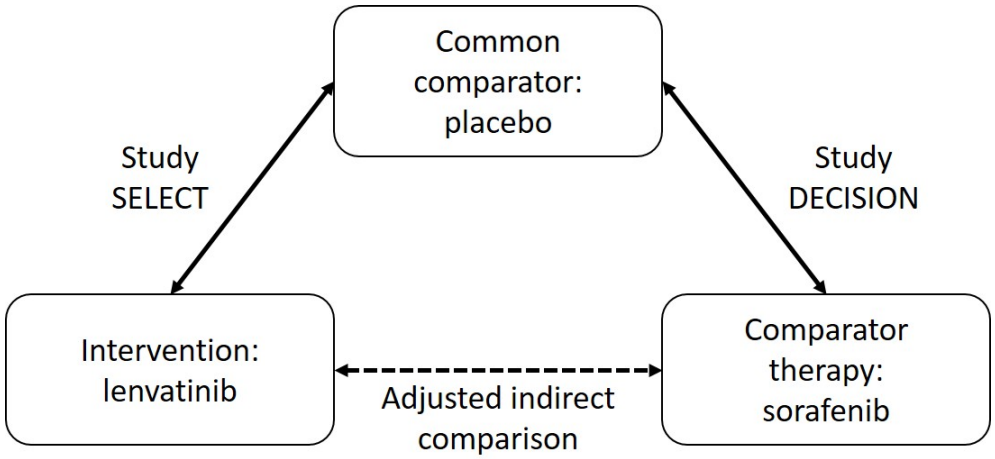

Figure 1: Study pool for the indirect comparison between lenvatinib and the ACT sorafenib

However, no suitable data from the 2 studies SELECT and DECISION were available for the adjusted indirect comparison between lenvatinib and the ACT sorafenib (see Sections 2.4.2 and 2.4.3 and Section 2.7.5.2 of the full dossier assessment for reasons).

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, indirect comparison: lenvatinib vs. sorafenib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with lenvatinib						
SELECT	RCT, double-blind, placebo-controlled; with optional treatment switching[b]	Adults with ▪ histologically or cytologically confirmed, locally advanced or metastatic, differentiated thyroid carcinoma[c], refractory to radioactive iodine ▪ confirmed disease progression[d] ▪ ≤ 1 prior VEGF/VEGFR-targeted therapy ▪ TSH ≤ 5.5 µIU/mL[e] ▪ ECOG PS ≤ 2	Lenvatinib (N = 261) placebo (N = 131) Subpopulation thereof used for the indirect comparison[f]: lenvatinib (n = 195) placebo (n = 104)	Screening: up to 28 days before start of treatment Treatment with study medication: until confirmed progression, unacceptable toxicity, withdrawal of consent or until primary analysis Follow-up: outcome-specific[g], until death or end of study	117 centres in Europe, North America, Asian-Pacific region, Japan and Latin America 7/2011–ongoing Data cut-offs: 1st data cut-off: 15 Nov 2013[h] 2nd data cut-off: 15 Mar 2014[i] 3rd data cut-off: 15 Jun 2014[j]	Primary: PFS Secondary: overall survival, AEs
Study with sorafenib						
DECISION	RCT, double-blind, placebo-controlled; with optional treatment switching[b]	Adults with ▪ locally advanced or metastatic thyroid carcinoma[c], refractory to radioactive iodine ▪ confirmed disease progression[d] ▪ no prior cancer therapy[k] ▪ TSH < 0.5 µIU/mL ▪ ECOG PS ≤ 2[l]	sorafenib (N = 207) placebo (N = 210)	Screening: ND Treatment with study medication: until confirmed progression, unacceptable toxicity, withdrawal of consent or until primary analysis Follow-up: outcome-specific[g], or until death or end of study	91 centres in Europe, North America and Asia 10/2009–8/2017 1st data cut-off: 31 Aug 2012[m] 2nd data cut-off: 31 May 2013 3rd data cut-off: 31 Jul 2015 4th data cut-off: 30 Aug 2017[n]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

(continued)

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

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: On confirmed disease progression, patients could switch from the placebo arm to unblinded treatment with lenvatinib (SELECT) or sorafenib (DECISION). In the DECISION study, patients with confirmed disease progression in the sorafenib arm could continue treatment with sorafenib at the physician's discretion for as long as clinical benefit was observed.
c: Contains the subtypes of papillary and follicular (including Hürthle cell) thyroid cancer in the SELECT study, and, additionally, poorly differentiated thyroid cancer in the DECISION study.
d: According to the RECIST criteria version 1.1 (SELECT) or 1.0 (DECISION) and confirmed with radiological assessment of CT and/or MRI scans within the last 12 (SELECT) or 14 (DECISION) months before informed consent for participation in the study.
e: The thyroxine dose was changed to achieve TSH suppression (TSH < 0.5 µIU/mL) if tolerated by the patients.
f: The SELECT study also enrolled patients with 1 prior VEGF/VEGFR-targeted therapy. To establish sufficient similarity of the patient populations for an indirect comparison, patients with prior VEGF/VEGFR-targeted therapy were excluded for the indirect comparison.
g: Outcome-specific information is provided in Table 8.
h: Primary analysis after 214 confirmed progression events or death before progression.
i: Additional safety analysis at the request of the FDA.
j: Additional analysis of overall survival at the request of EMA.
k: Including targeted therapy with tyrosine kinase inhibitors, VEGF/VEGFR-targeted therapies, cytotoxic chemotherapeutic agents and thalidomide.
l: Differing information in the publications: ECOG PS ≤ 2 in Brose et al. 2011, Worden et al. 2015, EMA 2014 [3-5], ECOG-PS 0–1 in Brose et al. 2014 [6].
m: Primary analysis after 267 confirmed progression events.
n: Final analysis after 210 deaths.

AE: adverse event; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; FDA: Food and Drug Administration; IU: international units; MRI: magnetic resonance imaging; n: relevant subpopulation; N: number of randomized (enrolled) patients; ND: no data; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; TSH: thyroid stimulating hormone; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor; vs.: versus

Table 7: Characteristics of the interventions – RCT, indirect comparison: lenvatinib vs. sorafenib

Study	Intervention/comparator therapy	Common comparator
Study with lenvatinib		
SELECT	Lenvatinib 24 mg (twice daily 10 mg + once 4 mg hard capsule), orally, once daily in the morning[a]	Placebo for lenvatinib (2 + 1 hard capsules), orally, once daily in the morning[a]
	▪ Dose adjustments, treatment interruptions or discontinuation of lenvatinib treatment due to intolerance were allowed[b]	
	Non-permitted pretreatment: ▪ > 1 VEGF/VEGFR-targeted therapy[c] ▪ lenvatinib, cancer treatment ≤ 21 days or treatment with an investigational agent ≤ 30 days before the first study medication (exception: treatment with TSH-suppressive thyroid hormones) ▪ anticoagulants (e.g. warfarin), except treatment with low molecular weight heparin **Permitted concomitant treatment:** ▪ all drugs that were required for the patients' health and did not interact with the study intervention ▪ treatment of complications and AEs as well as treatment for the alleviation of symptoms (e.g. blood products, blood transfusions, antibiotics, antidiarrhoeal drugs) at the investigator's discretion ▪ with caution: NSAIDs, low molecular weight heparin, drugs metabolized by CYP3A4 as well as CYP3A4 inhibitors or inducers (including herbal products or grapefruit) ▪ G-CSF and erythropoietin **Non-permitted concomitant treatment:** ▪ other anti-tumour therapies (exception: treatment with TSH-suppressive thyroid hormones)	
Study with sorafenib		
DECISION	Sorafenib twice 400 mg/day (twice 200 mg tablet) at 12-hour intervals, orally[a]	Placebo for sorafenib, twice 2 tablets/day at 12-hour intervals, orally[a]
	▪ Treatment interruptions, sequential dose reductions or discontinuation of sorafenib treatment due to intolerance were allowed[b]	
	Non-permitted pretreatment: ▪ targeted therapies (e.g. tyrosine kinase inhibitors, monoclonal antibodies against VEGF/VEGFR), thalidomide or cytotoxic chemotherapeutic agents[d] ▪ CYP3A4 inducers (e.g. St. John's Wort, dexamethasone > 16 mg/day, phenytoin, carbamazepine, phenobarbital) within 7 days before randomization **Concomitant treatment:** ▪ drugs with narrow therapeutic indices (e.g. warfarin) and drugs metabolized by the liver	

a: A treatment cycle was defined as 28 consecutive days.
b: Information complies with the specifications of the SPC.
c: To establish sufficient similarity of the patient populations for an indirect comparison, a subpopulation of the SELECT study without prior VEGF/VEGFR-targeted therapy was used for the indirect comparison.
d: Low-dose chemotherapy for radiosensitization was allowed.

AE: adverse event; CYP3A4: cytochrome P450 3A4; G-CSF: granulocyte colony-stimulating factor; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; TSH: thyroid stimulating hormone; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor; vs.: versus

Study design

SELECT (study with lenvatinib)

The SELECT study was a randomized, double-blind, multicentre, placebo-controlled study with lenvatinib. The study enrolled adult patients with histologically or cytologically confirmed diagnosis of a DTC (papillary, follicular or Hürthle cell). Patients had to have radiographically measurable disease and progression within 12 months prior to study inclusion. They had to have 131 iodine-refractory or resistant disease. Iodine refractoriness or resistance was defined by at least one of the following criteria:

1) One or several measurable lesions that do not show iodine uptake on any radioiodine scan.
2) One or several measurable lesions which, according to RECIST 1.1, show progression within 12 months of radioiodine therapy, despite radioiodine avidity being detected by pre- or post-treatment scans during treatment. These patients should not be candidates for possible curative surgery.
3) Cumulative radioiodine activity of > 600 mCi or 22 GBq, with administration of the last dose at least 6 months before enrolment.

The patients could be pretreated with at most 1 prior VEGF/VEGFR-targeted therapy such as sorafenib or sunitinib. ECOG PS had to be ≤ 2. Patients receiving thyroxine suppression therapy should not have elevated TSH levels (TSH ≤ 5.5 µIU/mL). If it was tolerable for the patients, the thyroxine dose was to be changed to achieve TSH suppression (TSH < 0.5 µIU/mL).

The study included 392 patients, who were randomized in a 2:1 ratio either to treatment with 24 mg day lenvatinib (N = 261) or corresponding placebo (N = 131). Stratification factors were geographical region (Europe/North America/other), prior VEGF/VEGFR-targeted therapy (0/1) and age (≤ 65/> 65).

Treatment was as shown in Table 7. Patients were treated until disease progression (according to the SPC, treatment should continue as long as clinical benefit is observed [7]), occurrence of unacceptable toxicity or withdrawal of the informed consent. There were no restrictions regarding subsequent therapies. On occurrence of disease progression, patients could be unblinded and, if they were in the placebo arm, be switched to treatment with lenvatinib. All patients were unblinded at the time point of the primary analysis (after 214 progression events). Patients in the placebo arm who had not previously had disease progression could then also switch to treatment with lenvatinib. At the time point of the primary analysis, 83% of the patients had already been switched from the placebo arm to treatment with lenvatinib.

PFS was the primary outcome of the study. Patient-relevant secondary outcomes were overall survival and AEs. Patient-relevant outcomes on morbidity and health-related quality of life were not recorded.

Relevant subpopulation for the indirect comparison

In contrast to the DECISION study (see below), the SELECT study could also enrol patients who had already received VEGF- or VEGFR-targeted therapy. This was the case in 23.7% of the patients (25.3% in the lenvatinib arm and 20.6% in the placebo arm). To improve the similarity of the studies for the indirect comparison of the studies SELECT and DECISION, the company therefore used the subpopulation of patients from the SELECT study who had not yet received VEGF/VEGFR-targeted therapy.

DECISION (study with sorafenib)

The DECISION study was a randomized, double-blind, multicentre, placebo-controlled study with sorafenib. The study enrolled adult patients with locally advanced or metastatic DTC (papillary, follicular, Hürthle cell or poorly differentiated). Patients had to have radiographically measurable disease and progression within 14 months prior to study inclusion. Their disease had to be refractory to iodine. Iodine refractoriness was defined as the presence of one or several detectable target lesions without iodine uptake shown on any radioiodine scan after RAI in a low-iodine diet and sufficient TSH elevation or recombinant human TSH (rhTSH) stimulation. Patients whose tumours had iodine uptake were only included in the study under certain circumstances:

1) if they had progressed despite treatment with only 1 RAI (≥ 3.7 GBq [≥ 100 mCi]) within the past 16 months,
2) if they had been treated with 2 RAIs within 16 months of each other with the last RAI administered more than 16 months ago and had progressed after each of both radioactive iodine treatments (each ≥ 3.7 GBq [≥ 100 mCi]), and
3) if they had received cumulative radioactive iodine therapy of ≥ 22.2 GBq (≥ 600 mCi).

Prior treatment with tyrosine kinase inhibitors, monoclonal anti-VEGF/VEGFR antibodies or other targeted therapies, cytotoxic chemotherapy or thalidomide and its derivatives were not allowed. ECOG PS had to be ≤ 2 and TSH levels < 0.5 mU/L.

The study included 417 patients, who were randomized in a 1:1 ratio either to treatment with 400 mg day sorafenib (N = 207) or corresponding placebo (N = 210). Stratification factors were age (≤ 60/> 60) and geographical region (Europe/North America/Asia).

Treatment was as shown in Table 7. The patients were treated until disease progression, occurrence of unacceptable toxicity or withdrawal of informed consent. There were no restrictions regarding subsequent therapies. On occurrence of disease progression, patients could be unblinded and, at the physician's discretion, for as long as clinical benefit was observed, continue treatment with sorafenib or be switched from the placebo arm to treatment with sorafenib. After the primary analysis (31 August 2012), Amendment 9 (26 February 2013) of the study protocol allowed patients in the placebo arm to be treated with sorafenib also before disease progression. Already at the time point of the primary analysis (31 August 2012; after

267 progression events), 71% of the patients had been switched from the placebo arm to treatment with sorafenib. At the final data cut-off on 30 August 2017, this was the case for 77% of the patients [8]. In the sorafenib arm, 43% of the patients had progression and been unblinded at the primary data cut-off, with 27% of the patients continuing unblinded treatment with sorafenib. At the final data cut-off, 42% of the patients had continued unblinded treatment with sorafenib.

PFS was the primary outcome of the study. Patient-relevant secondary outcomes were overall survival, health status recorded with the EQ-5D VAS, health-related quality of life recorded with the FACT-G, and AEs.

In consultation with the FDA, the study was ended at the time point of the final analysis of overall survival after 210 deaths.

Planned duration of follow-up observation

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
Study with lenvatinib	
SELECT	
Mortality	
Overall survival	Every 3 months until death or completion of the study by the sponsor
Morbidity	
Symptoms/health status	No usable data[a] or not recorded
Health-related quality of life	Not recorded
Side effects	
All outcomes in the category "side effects"	Until 30 days after the last dose of the study medication
Study with sorafenib	
DECISION	
Mortality	
Overall survival	Every 3 months
Morbidity	
Symptoms/health status (EQ-5D VAS)	No usable data[a] or ND
Health-related quality of life (FACT-G)	ND
Side effects	
All outcomes in the category "side effects"	Until 30 days after the last dose of the study medication

a: No patient-relevant morbidity outcomes recorded (see Section 2.7.5.3.2 of the full dossier assessment).

EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; ND: no data; PFS: progression-free survival; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes on side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (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. There were no data on follow-up observation for the outcomes "health status" and "health-related quality of life", which were only recorded in the DECISION study.

Available data cut-offs used for the indirect comparison

Three data cut-offs were conducted for the SELECT study and 4 for the DECISION study. The following Table 9 shows an overview of the data cut-offs and the reported outcomes.

Table 9: Overview of the data cut-offs and available outcomes – RCT, indirect comparison: lenvatinib vs. sorafenib

	SELECT			**DECISION**			
	15 Nov 2013[a]	**15 Mar 2014**[b]	**15 Jun 2014**[c]	**31 Aug 2012**[d]	31 May 2013[c]	31 Jul 2015	**30 Aug 2017**[e]
Overall survival	●	–	●[f, g]	●[f, g]	●[f, g]	●[f, g]	●[g]
Morbidity	●	–	–	●	–	–	–
Health-related quality of life	Outcome not recorded in the SELECT study			●	–	–	–
Side effects	●	●[h]	–	●[h]	–	–	–

a: Primary analysis after 214 confirmed progression events or death before progression.
b: Additional safety analysis at the request of the FDA.
c: Additional analysis of overall survival at the request of EMA.
d: Primary analysis after 267 confirmed progression events or death before progression.
e: Final analysis in consultation with the FDA after 210 deaths.
f: Main analysis of the company in the dossier on overall survival (adjusted using RPSFTM).
g: Sensitivity analysis of the company in the dossier on overall survival (unadjusted).
h: Main analysis of the company in the dossier on side effect outcomes.

EMA: European Medicines Agency; FDA: Food and Drug Administration; RCT: randomized controlled trial; RPSFTM: rank preserving structural failure time model; vs.: versus

The primary data cut-off of the SELECT study on 15 November 2013 had been planned a priori as primary analysis as soon as 214 events on the outcome "PFS" had occurred. Results on the outcomes "overall survival" and "side effects" were available for this data cut-off.

At the request of the regulatory authorities, 2 further data cut-offs were carried out: on 15 March 2014 for the analysis of safety (FDA) and on 15 June 2014 for the analysis of overall survival (European Medicines Agency [EMA]). Interim analyses had not been planned and were also not carried out.

In the DECISION study, the first data cut-off at 31 August 2012 had also been planned a priori as primary analysis. It was to be conducted as soon as about 267 PFS events had occurred. Results on the outcomes "overall survival", "health status", "health-related quality of life" and "side effects" were available for this data cut-off. A further data cut-off was conducted on 31 May 2013, probably at the request by EMA, for the analysis of overall survival. A third data cut-off was conducted in July 2013; data on overall survival were available for this data cut-off. The dossier contained no information on the reason for conducting this data cut-off. The final data cut-off was conducted on 30 August 2017 after 210 deaths in consultation with the FDA.

From the SELECT study, the data from the data cut-off on 15 June 2014 were used for the adjusted indirect comparison for overall survival, and the data from the data cut-off on 15 March 2014 for side effects. These 2 most recent data cut-offs had not been planned a priori, but were conducted at request of the regulatory authorities. An event-driven execution of the data cut-offs can therefore be excluded.

From the DECISION study, the data of the final data cut-off from 30 August 2017 were used for the adjusted indirect comparison for overall survival because this is the most recent data cut-off. No usable data for side effects were available from any of the data cut-offs carried out.

Study population

Table 10 shows the characteristics of the patients in the studies included.

Table 10: Characteristics of the study populations – RCT, indirect comparison: lenvatinib vs. sorafenib

Study Characteristics Category	SELECT		DECISION	
	Lenvatinib	Placebo	Sorafenib	Placebo
	N[a] = 195	N[a] = 104	N[b] = 207	N[b] = 210
Sex [F/M], %	50/50	45/55	50/50	55/45
Age [years], mean (SD)	62 (11)	62 (10)	62 (11)	62 (12)
Region, n (%)				
Europe	94 (48.2)	48 (46.2)	124 (59.9)	125 (59.5)
North America	53 (27.2)	29 (27.9)	36 (17.4)	36 (17.1)
Asia	39 (20.0)	20 (19.2)	47 (22.7)	49 (23.3)
Other	9 (4.6)	7 (6.7)	0	0
Ethnicity, n (%)				
White	148 (75.9)	80 (76.9)	123 (59.4)	128 (61.0)
Black	3 (1.5)	2 (1.9)	6 (2.9)	5 (2.4)
Asian	42 (21.5)	22 (21.2)	47 (22.7)	52 (24.8)
Hispanic	2 (1.0)	0	2 (1.0)	2 (1.0)
No data	0	0	29 (14.0)	23 (11.0)
ECOG PS, n (%)				
0	113 (57.9)	54 (51.9)	130 (62.8)	129 (61.4)
1	74 (37.9)	48 (46.2)	69 (33.3)	74 (35.2)
2	8 (4.1)	2 (1.9)	7 (3.4)	6 (2.9)
Metastases, n (%)				
Locally advanced	3 (1.5)	0	7 (3.4)	8 (3.8)
Metastatic	192 (98.5)	104 (100)	200 (96.6)	202 (96.2)
Site of metastases				
Liver metastases	37 (19.0)	22 (21.2)	28 (13.5)	30 (14.3)
Lung metastases	174 (89.2)	99 (95.2)	178 (86.0)	181 (86.2)
Bone metastases	73 (37.4)	35 (33.7)	57 (27.5)	56 (26.7)
Brain metastases	4 (2.1)	4 (3.8)	ND	ND
Musculoskeletal (non-bone) metastases/skin metastases	8 (4.1)	3 (2.9)	ND	ND
Lymph node metastasis	91 (46.7)	50 (48.1)	113 (54.6)	101 (48.1)
Pleural metastases	32 (16.4)	14 (13.5)	40 (19.3)	24 (11.4)
Metastases to pericardium/intra-abdominal mass	15 (7.7)	8 (7.7)	ND	ND
Head and neck	ND	ND	33 (15.9)	34 (16.2)
Time since diagnosis, months				
Mean (SD)	88.2 (86.8)	82.4 (66.9)	ND	ND
Median	59.3	66.2	66.2	66.9
Q1; Q3	32.3; 110.7	36.3; 106.6	ND	ND
Min; max	0.4; 573.6	6.0; 484.8	3.9; 362.4	6.6; 401.8

(continued)

Table 10: Characteristics of the study populations – RCT, indirect comparison: lenvatinib vs. sorafenib (continued)

Study Characteristics Category	SELECT		DECISION	
	Lenvatinib	Placebo	Sorafenib	Placebo
	N[a] = 195	N[a] = 104	N[b] = 207	N[b] = 210
Histology by central review, n (%)				
Papillary	123 (63.1)	72 (69.2)	118 (57.0)	119 (56.7)
Follicular[c]	72 (36.9)	32 (30.8)	50 (24.2)	56 (26.7)
Poorly differentiated	ND	ND	24 (11.6)	16 (7.6)
Well differentiated	ND	ND	2 (1.0)	1 (0.5)
Non-thyroid	ND	ND	0	1 (0.5)
Medullary	ND	ND	0	1 (0.5)
Oncocytic carcinoma	ND	ND	2 (1.0)	0
Carcinoma, NOS	ND	ND	0	3 (1.4)
Missing/nondiagnostic	ND	ND	13 (6.3)	14 (6.7)
Cumulative RAI (mCi)				
Mean (SD)	425.6 (327.1)	435.3 (332.6)	ND	ND
Median	301.0	319.1	400	376
Q1; Q3	200.0; 530.8	204.1; 509.3	ND	ND
Min; max	1.0; 1730.0	50.0; 1784.0	ND	ND
< 600, n (%)	140 (71.8)	80 (76.9)	ND	ND
≥ 600, n (%)	44 (22.6)	20 (19.2)	ND	ND
Previous systemic anticancer therapy, n (%)				
Yes	19 (9.7)	10 (9.6)	7 (3.4)	6 (2.9)
No	176 (90.3)	94 (90.4)	200 (96.6)	204 (97.1)
Previous radiotherapy, n (%)				
Yes	94 (48.2)	56 (53.8)	83 (40.1)	91 (43.3)
No	101 (51.8)	48 (46.2)	124 (59.9)	119 (56.7)
Treatment discontinuation[d], n (%)	ND[e]	ND[e]	75 (36.2)	22 (10.5)
Study discontinuation, n (%)	ND	ND	ND	ND

a: Relevant subpopulation (no prior VEGF/VEGFR-targeted therapy).
b: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c: Including the Hürthle cell variant of follicular thyroid carcinoma.
d: During blinding.
e: In the total population, 45 (17.2%) patients in the lenvatinib arm and 4 (3.1%) patients in the placebo arm discontinued treatment.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; mCi: mCurie; ND: no data; NOS: not otherwise specified; Q: quartile; RAI: radioactive iodine; RCT: randomized controlled trial; SD: standard deviation; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor; vs.: versus

The characteristics of the patients between the arms of the individual studies were sufficiently comparable.

In the SELECT study, the patients in the subpopulation without prior VEGF/VEGFR-targeted therapy had a mean age of 62 years; most of them were from Europe and white. Almost all of them had metastatic DTC, with lungs and lymph nodes as the most frequently affected sites of metastases. Most patients had not received prior systemic treatment; about half of the patients had received radiotherapy. About half of the patients were in good general condition (ECOG PS 0), only few patients had an ECOG PS of 2. Information on the number of patients who had discontinued therapy or the study was not available for the subpopulation.

The mean age of the patients in the DECISION study was also 62 years; about 60% of them were from Europe and white. Also in the DECISION study, almost all patients had metastatic DTC, the most frequently affected sites were the lungs and lymph nodes. Most patients had not received prior systemic treatment; about 40% of the patients had received radiotherapy. About 60% of the patients were in good general condition (ECOG PS 0), only few patients had an ECOG PS of 2. During the blinded treatment phase, about 1 third of the patients in the sorafenib arm had stopped treatment, whereas about 10% in the placebo arm had stopped treatment without unblinding. This does not include the patients who started open-label treatment with sorafenib after disease progression. There was no information on the number of patients who had discontinued the study.

The comparator arms of both studies are sufficiently comparable.

Treatment duration and observation period

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

Table 11: Information on the course of the study – RCT, indirect comparison: lenvatinib vs. sorafenib

Study **Duration of the study phase** **Outcome category**	**Lenvatinib or sorafenib**	**Placebo**
Study with lenvatinib		
SELECT	N = 261[a]	N = 131[a]
Treatment duration [months]		
Data cut-off 15 November 2013		
Median [Q1; Q3]	13.8 [5.9; 16.7]	3.9 [2.1; 8.1]
Mean (SD)	12.0 (6.75)	6.0 (4.97)
Data cut-off 15 March 2014		
Median [Q1; Q3]	16.1 [5.9; 19.6]	3.9 [2.1; 8.1]
Mean (SD)	13.7 (8.24)	6.1 (5.47)
Subpopulation without VEGF/VEGFR-targeted therapy:		
Median [Q1; Q3]	16.9 [ND]	4.2 [ND]
Data cut-off 15 June 2014	ND	ND
Observation period [months]		
Overall survival		
Data cut-off 15 November 2013		
Median [Q1; Q3]	17.1 [14.4; 20.4]	17.4 [14.8; 20.4]
Mean (SD)	ND	ND
Data cut-off 15 June 2014		
Median [Q1; Q3]	23.6 [ND]	24.1 [ND]
Mean (SD)	ND	ND
Morbidity, health-related quality of life	No patient-relevant outcomes recorded	
Side effects	ND	ND
Study with sorafenib		
DECISION	N = 207	N = 210
Treatment duration [months]		
Data cut-off 31 August 2012		
Median [Q1; Q3]	10.6 [5.3; 15.7]	6.5 [3.3; 12.9]
Data cut-off 30 August 2017	ND	ND
Observation period [months]		
Overall survival		
Data cut-off 31 August 2012		
Median [min; max]	ND[b]	ND[b]
Data cut-off 30 August 2017	ND	ND
Morbidity (health status), health-related quality of life	ND	ND
Side effects (data cut-off 31 August 2012)	ND	ND

(continued)

Table 11: Information on the course of the study – RCT, indirect comparison: lenvatinib vs. sorafenib (continued)

a: Information of the SELECT study refer to the total population.
b: Only information on the median observation period of all included patients from both study arms is available: 16.2 [0.03; 33.2].
max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: lower quartile; Q3: upper quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

For the SELECT study, the mean and median treatment durations differed between the treatment arms at the primary data cut-off (15 November 2013) and at the data cut-off from 15 March 2014. The median treatment duration of patients in the placebo arm was 28% and 25% of the treatment duration in the lenvatinib arm in the total population of the study and in the subpopulation of patients without prior VEGF/VEGFR-targeted therapy, respectively. Treatment after switching to lenvatinib was not taken into account for the placebo arm. The median observation period for overall survival, however, did not differ between the treatment arms. The dossier contained no information on the observation periods of the side effect outcomes.

For the DECISION study, the median treatment durations also differed between the treatment arms at the primary data cut-off (31 August 2012). The median treatment duration of patients in the placebo arm was 61% of the treatment duration in the sorafenib arm. Likewise, treatment after switching to sorafenib was not taken into account for the placebo arm. No information on treatment duration was available for the final data cut-off from 30 August 2017. No information for the individual treatment groups was available for the median observation period for overall survival. The dossier contained no information on the observation periods of other outcomes.

2.3.3 Similarity of the studies for the indirect comparison

The studies SELECT and DECISION had a comparable design.

In both studies, patients in the placebo arm were allowed to switch from the placebo arm to treatment with lenvatinib or sorafenib, respectively, after disease progression. The proportions of patients from the placebo arms who switched to treatment with lenvatinib or sorafenib were similar in both studies already at the first available data cut-off.

In the DECISION study, patients in the intervention arm could continue treatment with sorafenib also after disease progression and subsequent unblinding at the physician's discretion if clinical benefit was observed. At the primary data cut-off, 27% of the patients had chosen this option, and 42% at the final data cut-off. The SELECT study did not envisage continued treatment with lenvatinib after disease progression for patients in the intervention arm, but subsequent therapies were not restricted. Nevertheless, only few patients in the SELECT study started subsequent therapy after ending the study medication (primary data cut-off on 15 November 2013: lenvatinib 16%, placebo 12% [without lenvatinib]). The different proportions of patients with subsequent therapy in the DECISION study in comparison with the

SELECT study does not fundamentally question the similarity of the studies, but must be taken into account when interpreting the results of the indirect comparison.

With 3.9 months in the total population, and 4.2 months in the subpopulation in the SELECT study and 6.5 months in the DECISION study, the median treatment durations in the comparator arms were sufficiently comparable at the respective primary data cut-offs. Only incomplete information on treatment durations was available for the subsequent data cut-offs. However, in both studies, about 80% of the patients had been switched from the placebo arms to treatment with lenvatinib or sorafenib already at the primary data cut-off. It is therefore not assumed that the treatment durations in the placebo arms were decisively different.

The demographic and clinical characteristics of the patients were balanced between the study arms of the studies SELECT and DECISION and were sufficiently similar between these 2 studies. In the DECISION study, patients should have TSH levels of < 0.5 µIU/mL to be included in the study, whereas in the SELECT study, TSH levels were not allowed to be increased (≥ 5.5 µIU/mL). It can be inferred from the information on patient characteristics of the SELECT study, however, that about 90% of the included patients in the total population had TSH levels of ≤ 0,5 µIU/mL at baseline so that this difference in inclusion criteria was not relevant for the assessment. In addition, pretreatment with chemotherapy was only permitted in the SELECT study, but in relation to the total population per study arm, only about 10% of patients pretreated with chemotherapy were included in the study, so that this difference in inclusion criteria was also irrelevant for the assessment.

2.3.4 Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, indirect comparison: lenvatinib vs. sorafenib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Study with lenvatinib							
SELECT	Yes	Yes	Yes	Yes	Yes	Yes	Low
Study with sorafenib							
DECISION	Yes	Yes	Yes	Yes	Unclear	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

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 2.7.5.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
- Health-related quality of life
- 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 2.7.5.3.2 of the full dossier assessment).

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

Table 13: Matrix of outcomes – RCT, indirect comparison: lenvatinib vs. sorafenib

Study	Outcomes						
	Overall survival	Morbidity	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Further specific AEs
Study with lenvatinib							
SELECT	Yes	No[a]	No[b]	No[c]	No[c]	No[c]	No[c]
Study with sorafenib							
DECISION	Yes	Yes[d]	Yes[d]	No[c]	No[c]	No[c]	No[c]

a: No patient-relevant morbidity outcomes recorded (see Section 2.7.5.3.2 of the full dossier assessment).
b: Outcome not recorded.
c: For AEs, only analyses on relative risk with large differences in treatment durations between the arms are available. No usable data are available for an indirect comparison (see Sections 2.7.5.2 and 2.7.5.3.2 of the full dossier assessment).
d: Morbidity (health status) recorded with the EQ-5D VAS, health-related quality of life recorded with FACT-G. These outcomes were only recorded in the DECISION study. Hence, no usable data are available for the indirect comparison.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; PFS: progression-free survival; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: lenvatinib vs. sorafenib

Study	Study level	Outcomes						
		Overall survival	Morbidity	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Further specific AEs
Study with lenvatinib								
SELECT	L	H[a]	–[b]	-[c]	–[d]	–[d]	–[d]	–[d]
Study with sorafenib								
DECISION	L	H[a]	–[e]	–[e]	–[d]	–[d]	–[d]	–[d]

a: Large proportion of patients switching from the placebo arm to the intervention arm after progression (SELECT: no information for the relevant subpopulation; 88% in the total population, data cut-off from 15 June 2014; DECISION: 77%, data cut-off from 30 August 2017).
b: No patient-relevant morbidity outcomes recorded (see Section 2.7.5.3.2 of the full dossier assessment).
c: Outcome not recorded.
d: For AEs, only analyses on relative risk with large differences in treatment durations between the arms are available. No usable data are available for an indirect comparison (see Sections 2.7.5.2 and 2.7.5.3.2 of the full dossier assessment).
e: Morbidity (health status) recorded with the EQ-5D VAS, health-related quality of life recorded with FACT-G. These outcomes were only recorded in the DECISION study. Hence, no usable data are available for the indirect comparison.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The outcome-specific risk of bias for the results of the outcome "overall survival" was rated as high both for the SELECT study and for the DECISION study. This was due to the high proportion of patients in the placebo arm who switched to treatment with lenvatinib or sorafenib after disease progression. Already at the primary data cut-off, 83% of the patients in the placebo arm had switched to lenvatinib in the SELECT study; in the DECISION study, 71% had switched to sorafenib. At the used data cut-off from 15 June 2014 of the SELECT study, 88% of the patients in the placebo arm had switched to lenvatinib; at the final data cut-off from 30 August 2017 of the DECISION study, 77% had switched from the placebo arm to sorafenib. This deviates from the assessment of the company, which considered this outcome to have a low risk of bias in both studies due to the adjustment applied (see Section 2.7.5.3.1 of the full dossier assessment for further information on the adjustment).

No usable data for the indirect comparison were available for the outcomes on morbidity and health-related quality of life as only the DECISION study recorded patient-relevant outcomes in these categories.

No usable data for the indirect comparison were available for the outcomes "SAEs", "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs". In both studies, AEs were only observed until the end of the study medication (plus 30 days). However, there were no time-adjusted analyses, but only analyses based on the proportion of patients with events (effect measure: RR). These analyses were not adequate due to the clear difference in median treatment duration between intervention and placebo arm in both relevant studies (SELECT [total population]: 13.8 versus 3.9 months; proportion placebo arm 28%, DECISION: 10.6 versus 6.5 months; proportion placebo arm 61%). Deviating from this, the company considered the data on these outcomes as suitable for an indirect comparison. It rated the outcome-specific risk of bias for the results of the outcomes "SAEs", "discontinuation due to AEs" and "severe AEs" (CTCAE grade ≥ 3) as low.

2.4.3 Results

The results of the included outcomes were not usable for the following reasons:

- The indirect comparison for the outcome "all-cause mortality" was based on only 1 study with outcome-specific high risk of bias for the underlying direct comparisons with the common comparator. Hence, the uncertainty in the available data was too high to be able to derive valid conclusions on added benefit or greater harm of lenvatinib in comparison with the ACT (see Section 2.7.5.2 of the full dossier assessment).
- No usable data were available for the outcomes on side effects (SAEs, discontinuation due to AEs, severe AEs [CTCAE ≥ 3]) and on the outcomes "health status" and "health-related quality of life" (see Section 2.7.5.3 of the full dossier assessment).

Irrespective of this, none of the outcomes mentioned showed a statistically significant effect in the indirect comparison. The results of the included outcomes of the studies SELECT and DECISION are presented in Appendix B, Table 19, of the full dossier assessment; Kaplan-Meier curves on the event time analyses used for the present benefit assessment can be found in Appendix A of the full dossier assessment.

2.4.4 Subgroups and other effect modifiers

No subgroup analyses were available on the patient-relevant outcomes included in the benefit assessment. However, due to the high risk of bias of the results of the outcomes, a meaningful interpretation would also not be possible.

2.5 Probability and extent of added benefit

Since no usable data were available for the adjusted indirect comparison of lenvatinib with the ACT sorafenib, an added benefit of lenvatinib compared with the ACT is not proven.

The result of the assessment of the added benefit of lenvatinib in comparison with the ACT is summarized in Table 15.

Table 15: Lenvatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)	Sorafenib	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit on the basis of the adjusted indirect comparison of lenvatinib in comparison with the ACT sorafenib.

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

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2015. In this assessment, the G-BA had determined a non-quantifiable added benefit of lenvatinib. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

2.6 List of included studies

DECISION

Bayer. A double-blind, randomized phase III study evaluating the efficacy and safety of sorafenib compared to placebo in locally advanced/metastatic RAI-refractory differentiated thyroid cancer: clinical trial results [online]. In: EU Clinical Trials Register. 17.02.2019 [Accessed: 25.03.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-012007-25/results.

Bayer. A double-blind, randomized phase III study evaluating the efficacy and safety of sorafenib compared to placebo in locally advanced/metastatic RAI-refractory differentiated thyroid cancer [online]. In: EU Clinical Trials Register. [Accessed: 25.03.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012007-25.

Bayer. Nexavar versus placebo in locally advanced/metastatic RAI-refractory differentiated thyroid cancer: study results [online]. In: ClinicalTrials.gov. 13.09.2018 [Accessed: 25.03.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00984282.

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