IQWiG Reports – Commission No. A18-37

Cabozantinib (renal cell carcinoma) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Cabozantinib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 September 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Cabozantinib (renal cell carcinoma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
6 June 2018

Internal Commission No.:
A18-37

Address of publisher:
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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.

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Keywords: cabozantinib, carcinoma – renal cell, benefit assessment, NCT01835158

Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 cabozantinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 6 June 2018.

Research question

The aim of this report is to assess the added benefit of cabozantinib in comparison with the appropriate comparator therapy (ACT) in the treatment of advanced renal cell carcinoma in treatment-naïve adults at intermediate to poor risk.

For the assessment, 2 research questions were derived from the ACT specified by the G-BA. They are presented in Table 2.

Table 2[2]: Research questions of the benefit assessment of cabozantinib

Research question	Indication	ACT[a]
1	Treatment-naïve adults with advanced renal cell carcinoma at intermediate risk (1–2 risk factors from the IMDC criteria)[b]	Bevacizumab + interferon alpha-2a or pazopanib or **sunitinib**
2	Treatment-naïve adults with advanced renal cell carcinoma at poor risk (≥ 3 risk factors from the IMDC criteria)[c]	Temsirolimus

a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b: In the assessment referred to as: "Patients at intermediate risk"
c: In the assessment referred to as: "Patients at poor risk"
G-BA: Federal Joint Committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

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

Research question 1: Patients at intermediate risk

Study pool and study characteristics

For research question 1, the company presented the randomized controlled trial (RCT) CABOSUN, which compares cabozantinib with sunitinib. It included 157 treatment-naïve adult patients with locally advanced or metastatic clear cell renal cell carcinoma at intermediate risk

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

(81% of patients in each arm) or poor risk (19% of patients in each arm) in accordance with the criteria of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).

The primary outcome of the CABOSUN study was progression-free survival (PFS); patient-relevant secondary outcomes were overall survival and outcomes from the adverse events category. Outcomes from the category of health-related quality of life were not surveyed in the study.

The CABOSUN study was initially not planned as a pivotal study. Due to the subsequent application for marketing authorization, there were special aspects, particularly in methods and results documentation as well as in the analysis of results, which lead to limited interpretability of study data.

Risk of bias

The risk of bias on the study level was rated as high for the CARBOSUN study. Therefore, the risk of bias for the outcomes overall survival, severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥ 3) and discontinuation due to AEs was rated as high as well. For SAEs and specific AEs, no relevant data were available. No patient-relevant outcomes from the morbidity category and no outcomes from the health-related quality of life category were surveyed.

Results

Mortality

For the outcome overall survival, no statistically significant difference was found between cabozantinib and sunitinib. However, for this outcome, an effect modification by the attribute immunohistochemical hepatocyte growth factor receptor (MET-IHC) status was found. For patients with positive MET-IHC status, this results in a hint of added benefit. For patients with negative MET-IHC status, this does not result in a hint of an added benefit; therefore, there is no proof of added benefit.

The CABOSUN study was missing data on the MET-IHC status of a relatively high percentage of patients (17%). In addition, the percentage differs between the two treatment arms (cabozantinib: 10%; sunitinib: 23%). Particularly in consideration of the CABOSUN study's open design, this imbalance may potentially have resulted from the allocated treatment group. While the effect for patients with positive MET-IHC status is not put into question, this uncertainty leads to the extent of added benefit of cabozantinib being rated as not quantifiable for patients with positive MET-IHC status.

Morbidity

In the CABOSUN study, no patient-relevant outcomes of the morbidity category were surveyed. Consequently, there is no hint of an added benefit of cabozantinib in comparison with sunitinib; an added benefit is therefore not proven.

Health-related quality of life

The CABOSUN study did not survey health-related quality of life. Consequently, there is no hint of an added benefit of cabozantinib in comparison with sunitinib; an added benefit is therefore not proven.

Adverse events

- SAEs

For the outcome SAEs, no usable data were available. Consequently, there was no hint of greater or lesser harm of cabozantinib in comparison with sunitinib; greater or lesser harm is therefore not proven.

- Severe AEs (CTCAE Grade ≥ 3)

For the outcome severe AEs (CTCAE Grade ≥ 3), no statistically significant difference was found between cabozantinib and sunitinib. However, an effect modification by the attribute sex was found for this outcome. In women, this results in a hint of lesser harm of cabozantinib in comparison with sunitinib. In men, there is no hint of greater or lesser harm of cabozantinib; greater or lesser harm is therefore not proven.

- Discontinuation due to AEs

For the outcome discontinuation due to AEs, no statistically significant difference was found between cabozantinib and sunitinib. Consequently, there was no hint of greater or lesser harm of cabozantinib in comparison with sunitinib; greater or lesser harm is therefore not proven.

- Specific AEs

Due to the peculiarities regarding the surveying of AEs, it would have been possible to select specific AEs only on the basis of common AEs from the category of severe AEs (CTCAE Grade ≥ 3). However, no usable data were available for this purpose. Although the company presents survival analyses for select specific AEs, which it chose on the basis of striking differences between treatment arms and under consideration of patient relevance, no complete listing of all AEs including survival analyses is available. In consideration of the different observation times, it is therefore not possible to select specific AEs. Consequently, there is no hint of greater or lesser harm of cabozantinib in comparison with sunitinib; greater or lesser harm is therefore not proven.

Research question 2: Patients at poor risk

For research question 2, the company did not present any data for assessing the added benefit of cabozantinib in comparison with the ACT. Consequently, there is no hint of added benefit in comparison with the ACT. An added benefit is therefore not proven.

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

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

Research question 1: Patients at intermediate risk

When considering all usable data, the effects are exclusively positive for cabozantinib in comparison with sunitinib. They are found for the outcome overall survival in patients with a positive MET-IHC status and for the outcome severe AEs (CTCAE Grade ≥ 3) in women. No meaningful summary interpretation of results, taking into account both effect modifications for the 2 outcomes, can be derived. Due to the fatal course of disease, the outcome overall survival is attributed greater relevance in this situation; therefore, this outcome is considered a priority. Consequently, for the overall conclusion on added benefit, only the attribute MET-IHC status is used due to the effect modification for the outcome overall survival.

In summary, for treatment-naïve patients with advanced renal cell carcinoma at intermediate risk and with a positive MET-IHC status, this results in a hint of a non-quantifiable added benefit in comparison with the ACT. The facts that no patient-relevant outcomes or no outcomes of the categories morbidity and health-related quality of life were surveyed and that the SAEs were not usable also contributed to the added benefit being assessed as non-quantifiable. For other patients of the target population (patients with negative MET-IHC status), added benefit is not proven.

Research question 2: Patients at poor risk

For patients at poor risk, the company did not present any data for assessing the added benefit of cabozantinib in comparison with the ACT. Consequently, there is no hint of added benefit in comparison with the ACT. An added benefit is therefore not proven.

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

[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].

Table 3: Cabozantinib – probability and extent of added benefit

Research question	Indication	ACT[a]	Probability and extent of added benefit
1	Treatment-naïve adults with advanced renal cell carcinoma at intermediate risk (1–2 risk factors of the IMDC criteria)[b]	Bevacizumab + interferon alfa-2a or pazopanib or **sunitinib**	Patients with positive MET-IHC status: ▪ Hint of non-quantifiable added benefit Patients with negative MET-IHC status: ▪ Added benefit not proven
2	Treatment-naïve adults with advanced renal cell carcinoma at poor risk (≥ 3 risk factors from the IMDC criteria)[c]	Temsirolimus	Added benefit not proven

a: Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b: In the assessment, referred to as: "Patients at intermediate risk"
c: In the assessment, referred to as: "Patients at poor risk"
G-BA: Federal Joint Committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; MET-IHC status: Immunohistochemical hepatocyte growth factor receptor status

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

Note:

An addendum (A18-70) to dossier assessment A18-37 has been published.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 04 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

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

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-37-cabozantinib-renal-cell-carcinoma-benefit-assessment-according-to-35a-social-code-book-v.10100.html.