Futibatinib (cholangiocarcinoma)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
FGFR2	fibroblast growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug futibatinib. 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 30 May 2024.

Research question

The aim of the present report is the assessment of the added benefit of futibatinib as monotherapy in comparison with pemigatinib as appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after at least one prior line of systemic therapy.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of futibatinib

Therapeutic indication	**ACT**[a]
Adult patients with locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after at least one prior line of systemic therapy	Pemigatinib
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; FGFR2: fibroblast growth factor receptor 2; G-BA: Federal Joint Committee	

The company designated pemigatinib as the ACT, thus following the G-BA's specification.

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

Results

The check of the completeness of the study pool produced no relevant randomized controlled trial (RCT) on the direct comparison of futibatinib versus the ACT. As the company did not identify any RCTs for direct comparisons, it conducted an information retrieval for RCTs on the intervention and the ACT for indirect comparisons as well as an information retrieval for non-randomized comparative studies, for which, however, it did not identify any studies either. Therefore, the company also conducted an information retrieval for further investigations on the intervention and the ACT. In doing so, it identified the single-arm study TAS-120-101,

hereinafter referred to as FOENIX-CCA2, for the intervention. For the ACT, it identified the single-arm study FIGHT-202.

Evidence provided by the company

For its assessment, the company used the results of the single-arm FOENIX-CCA2 study and, for overall survival, a comparison of individual arms based on the FOENIX-CCA2 and FIGHT-202 studies, presenting both a naive comparison and matching-adjusted indirect comparison (MAIC) analyses without a common comparator for the indirect comparison of treatment with futibatinib versus pemigatinib. Overall, based on an aggregated analysis of the available evidence, the company assessed the added benefit of futibatinib in comparison with the ACT as not proven.

Data presented by the company are unsuitable for the benefit assessment

The consideration of single-arm data on treatment with futibatinib from the FOENIX-CCA2 study allows no comparison with the ACT and is therefore not suitable for the derivation of an added benefit.

The MAIC analyses presented by the company for the comparison of results on the outcome "overall survival" from the FOENIX-CCA2 study with the results from the FIGHT-202 study are also not usable for the benefit assessment. MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment. In case of non-randomized comparisons without a common comparator, meaningful confounder adjustment is generally only possible for those comparisons that – unlike the MAIC analysis – involve the use of individual patient data. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data. Hence, the results presented by the company on the basis of MAIC analyses are unsuitable for assessing the added benefit of futibatinib. Furthermore, the company’s approach of carrying out the MAIC analyses only for the outcome "overall survival" is not appropriate.

Regardless of the company's approach, there is no statistically significant difference between the treatments for the outcome "overall survival", neither in the naïve comparison of the two study arms nor in the MAIC analyses.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of futibatinib 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]

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

Table 3: Futibatinib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after at least one prior line of systemic therapy	Pemigatinib	Added benefit not proven

a. Presented is the ACT specified by the G-BA.

ACT: appropriate comparator therapy; FGFR2: fibroblast growth factor receptor 2; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of the present report is the assessment of the added benefit of futibatinib as monotherapy in comparison with pemigatinib as appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after at least one prior line of systemic therapy.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of futibatinib

Therapeutic indication	**ACT[a]**
Adult patients with locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after at least one prior line of systemic therapy	Pemigatinib
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; FGFR2: fibroblast growth factor receptor 2; G-BA: Federal Joint Committee	

The company designated pemigatinib as the ACT, thus following the G-BA's specification.

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

I 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 lists on futibatinib (status: 15 March 2024)
- bibliographical literature search on futibatinib (last search on 15 March 2024)
- searches in trial registries/trial results databases for studies on futibatinib (last search on 15 March 2024)
- searches on the G-BA website for futibatinib (last search on 15 March 2024)
- bibliographical literature search on the ACT (last search on 15 March 2024)
- search in trial registries/trial results databases for studies on the ACT (last search on 15 March 2024)
- searches on the G-BA website for the ACT (last search on 15 March 2024)

To check the completeness of the study pool:

- search in trial registries for studies on futibatinib (last search on 18 June 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check for the completeness of the study pool produced no RCT on the direct comparison of futibatinib versus the ACT.

As the company did not identify any RCTs for direct comparisons, it conducted an information retrieval for RCTs on the intervention and the ACT for indirect comparisons as well as an information retrieval for non-randomized comparative studies, for which, however, it did not identify any studies either. Therefore, the company also conducted an information retrieval for further investigations on the intervention and the ACT. In addition, it identified the single-arm study TAS-120-101 [3], hereinafter referred to as FOENIX-CCA2, for the intervention, which was instrumental in the authorization of futibatinib in the present therapeutic indication. For the ACT, it identified the single-arm study FIGHT-202 [4].

For its assessment, the company used the results of the single-arm FOENIX-CCA2 study and, for overall survival, a comparison of individual arms based on the FOENIX-CCA2 and FIGHT-202 studies. In considering the data presented by the company as a whole, the company concluded in its assessment that an added benefit of futibatinib over pemigatinib for the present research question is not proven.

The completeness of the study pool for further investigations was not checked. However, the information presented by the company in Module 5 of the dossier already indicated that study NCT04256980 [5] is another relevant study on the ACT pemigatinib. In Module 5 of the dossier, the company described this study in a report that includes a systematic literature search and an indirect comparison to support the use of futibatinib in patients with advanced cholangiocarcinoma and FGFR aberrations [6]. The study NCT04256980 was included in this report on the basis of a conference abstract [7]. Since then, a publication on this study has become available, Shi 2023 [8], which the company identified through its bibliographic literature search but then excluded at the title-abstract screening level. However, excluding the publication at the title-abstract level is inappropriate based on the information available in the abstract of the publication Shi 2023. The company also identified the study during its search in trial registries, but excluded it on the grounds of missing full publications, study reports, detailed results reports from a trial register, or results on the study.

However, in view of the information available in the publication Shi 2023 [8] , the study is considered relevant for the present research question, contrary to the assessment of the company. Hence, the company's study pool for further investigations is incomplete on the ACT side.

Irrespective of the incompleteness of the company's study pool with regard to further investigations on the ACT, the data submitted by the company are unsuitable for deriving any conclusions on the added benefit of futibatinib in comparison with the ACT for patients in the present therapeutic indication. This is explained in the following sections.

Evidence provided by the company

FOENIX-CCA2 study

The FOENIX-CCA2 study is a single-arm, open-label, multicentre phase 1 and phase 2 study of futibatinib treatment in adult patients with advanced solid tumours, which was conducted in different parts (hereafter referred to as phase 1 and phase 2 parts). The phase 1 part of the study was subdivided into a dose escalation phase [9], in which the futibatinib dose for the phase 2 part was determined, and an expansion phase [10], in which patients with various advanced solid tumours and fibroblast growth factor (FGF)/FGFR aberrations were examined, advanced solid tumours and fibroblast growth factor (FGF)/FGFR aberrations, including patients with intrahepatic cholangiocarcinoma and FGFR2 fusion or FGFR2 rearrangement. The phase 2 part of the study [11] included only adult patients with locally advanced, metastatic, unresectable intrahepatic cholangiocarcinoma and FGFR2 fusion or FGFR2 rearrangement. Patients also had to have received at least one prior systemic therapy with gemcitabine and platinum-based chemotherapy for the phase 2 part. In addition, disease progression had to have been documented during the most recent prior therapy.

In the phase 2 part of the study, 103 patients were treated continuously with a starting dose of 20 mg futibatinib daily in accordance with the Summary of Product Characteristics (SPC) [12]. In case of toxicities, dose reductions were planned. In the expansion phase of the phase 1 part, a total of 197 patients with different advanced solid tumours and FGF/FGFR aberrations were treated with 16 mg or 20 mg futibatinib daily, including 19 patients whose tumour localisation, genotype, prior treatment and futibatinib dosage match the research question at hand.

The primary outcome of the expansion phase of the phase 1 part and of the phase 2 part of the FOENIX-CCA2 study was the objective response rate according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. Further outcomes included overall survival, outcomes in the categories of morbidity and health-related quality of life, as well as adverse drug reactions.

The company used results from the phase 2 part of the study for its benefit assessment. In addition, for individual outcomes , it presented supportive results from a subpopulation of 19 patients covered by the present research question from the phase 1 expansion phase of the study.

FIGHT-202 study

The FIGHT-202 study is a single-arm, open-label, multicentre phase 2 study investigating the treatment of pemigatinib in adult patients with advanced/metastatic or unresectable cholangiocarcinoma. Patients were included in the study according to the results of a genetic test for FGF/FGFR status and allocated to cohorts A, B, and C. Cohort A included patients with FGFR2 fusion or FGFR2 rearrangement, while cohort B included patients with other FGF/FGFR alterations, and cohort C included patients without FGF/FGFR alterations [13]. The prerequisite for inclusion in the study was documented disease progression after at least one prior line of systemic therapy.

In cohort A of the study, 108 patients with FGFR2 fusion or FGFR2 rearrangement were treated with a starting dose of 13.5 mg pemigatinib daily in 21-day cycles with 2 weeks of treatment and 1 week of pause in treatment in accordance with the SPC [14]. In case of toxicities, dose reductions were planned.

The primary outcome of the study was the objective response rate according to RECIST version 1.1. Other outcomes included overall survival, outcomes in the categories of morbidity and health-related quality of life, as well as side effects.

For its assessment, the company used results for patients with FGFR2 fusion or FGFR2 rearrangement from cohort A of the study.

Analyses presented by the company

For its assessment, the company used results on treatment with futibatinib from the phase 2 part of the single-arm study FOENIX-CCA2. In addition, for individual outcomes , it supportive presented results from a subpopulation from the phase 1 expansion phase of the study.

For the outcome "overall survival", the company also presented a comparison of individual arms based on the results of the FOENIX-CCA2 and FIGHT-202 studies. In doing so, it presented both a naive comparison and a MAIC analysis without a common comparator for the indirect comparison of treatment with futibatinib versus pemigatinib. The MAIC analyses for futibatinib are based on results from individual patient data, while for the study on pemigatinib, data were generated from the Kaplan-Meier curve using the Guyot (2012) method [15].

Overall, based on an aggregated analysis of the available evidence (comparison of individual arms based on the FOENIX-CCA2 and FIGHT-202 studies for the outcome "overall survival", as well as results for other outcome categories from the FOENIX-CCA2 study) the company assessed the added benefit of futibatinib in comparison with the ACT as not proven.

Assessment of the evidence presented by the company

The analyses presented by the company are unsuitable for the benefit assessment of futibatinib in comparison with the ACT. This is explained below.

The consideration of single-arm data on treatment with futibatinib from the FOENIX-CCA2 study allows no comparison with the ACT and is therefore not suitable for the derivation of an added benefit.

Comparisons of individual arms of different studies are not suitable for the benefit assessment

The MAIC analyses presented by the company for the comparison of results on the outcome "overall survival" from the FOENIX-CCA2 study with the results from the FIGHT-202 study are also not usable for the benefit assessment.

MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment [16]. In case of non-randomized comparisons without a common comparator, meaningful confounder adjustment is generally only possible for those comparisons that – unlike the MAIC analysis – involve the use of individual patient data [17]. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data. Hence, the results presented by the company on the basis of MAIC analyses are unsuitable for

assessing the added benefit of futibatinib. Furthermore, the company's approach of carrying out the MAIC analyses only for the outcome "overall survival" is not appropriate.

Regardless of the company's approach, there is no statistically significant difference between the treatments for the outcome "overall survival", neither in the naïve comparison of the two study arms nor in the MAIC analyses.

Irrespective of the fact that the data presented by the company are not suitable for the present benefit assessment for the reasons described above, there is also uncertainty as to whether he results from the FOENIX-CCA2 and FIGHT-202 studies are transferable to the current health care context. According to the current guideline on the diagnosis and treatment of hepatocellular carcinoma and biliary carcinomas [18], all patients with inoperable locally advanced or metastatic cholangiocarcinoma are to be offered a combination therapy of cisplatin, gemcitabine and durvalumab as a first-line palliative systemic therapy, assuming that their general condition is adequate. For both studies, it is not clear from the available information on prior treatment that durvalumab was administered to the included patients as prior therapy. The prior therapy essentially comprised the drugs that were the standard of care in first-line therapy prior to the authorization of the combination therapy of cisplatin, gemcitabine and durvalumab, meaning the combination chemotherapy of gemcitabine and cisplatin without durvalumab. The patients included in the FOENIX-CCA2 and FIGHT-202studies therefore differ from the patient population eligible for treatment with futibatinib or pemigatinib in the current German health care context, the majority of whom are expected to have undergone prior treatment with durvalumab.

The change in the therapy standard due to the authorization of durvalumab as an addition to the previous combination chemotherapy has also had an impact on the authorization procedure of futibatinib (conditional approval in the present therapeutic indication). Consequently, the RCT comparing futibatinib with a combination therapy of gemcitabine and platinum-based chemotherapy in the first-line treatment of advanced cholangiocarcinoma, TAS-120-301, FOENIX-CCA3 [19], which the company had originally planned as a requirement for the conditional approval, was terminated prematurely by the company. Instead, the company was required to present the results of the RCT TAS-120-205, FOENIX-CCA4 [20], comparing two futibatinib dosages without a control group [21]. The company justified the switch to a study without a control group on the grounds of recruitment problems, among other things due to the authorization of durvalumab in combination with chemotherapy for first-line therapy as a new, alternative, non-experimental treatment option. In addition, 2 competitive phase 3 studies [22,23] on other FGFR inhibitors in the same planned therapeutic indication, each investigating the new drug in comparison with gemcitabine in combination with cisplatin, would have limited the pool of potential study participants [24].

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of futibatinib in comparison with the ACT in patients with locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or FGFR2 rearrangement that has progressed after at least one previous line of systemic therapy. There is no hint of an added benefit of futibatinib in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for futibatinib in comparison with the ACT.

Table 5: Futibatinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after at least one prior line of systemic therapy	Pemigatinib	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; FGFR2: fibroblast growth factor receptor 2; G-BA: Federal Joint Committee		

The assessment described above concurs with that of the company, which also derived no added benefit in the overall view.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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