IQWiG Reports – Commission No. A22-28

Sotorasib (NSCLC) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Sotorasib (NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2022). 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.

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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.

Patient and family involvement

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

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ALK	anaplastic lymphoma kinase
CRISP	Clinical Research platform Into molecular testing, treatment and outcome of (non-)Small cell lung carcinoma Patients
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KRAS	Kirsten rat sarcoma viral oncogene homologue
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
ROS1	c-ros oncogene 1
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 sotorasib. 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 15 February 2022.

Research question

The aim of the present report is to assess the added benefit of sotorasib monotherapy in comparison with the appropriate comparator therapy (ACT) in adult patients with Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C-mutated (as per G-BA, KRAS p.G12C-mutated) advanced non-small cell lung cancer (NSCLC) who have progressed after at least 1 prior line of systemic therapy.

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

Table 2: Research questions of the benefit assessment of sotorasib (multipage table)

Research question	Subindication[a]	ACT[b]
1	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line monotherapy with a PD-1/PD-L1 antibody	▪ Cisplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]) or ▪ carboplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]); see also Appendix VI of Section K of the German Pharmaceutical Directive ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]
2	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[e,g] or ▪ nivolumab or ▪ pembrolizumab[h] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[i]
3	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with a PD-1/PD-L1 antibody[c] in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[c] and platinum-based chemotherapy	▪ Individualized treatment[j] consistent with prior treatment and histology, with the available options of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib and vinorelbine

a. The G-BA assumes that patients were not indicated for definitive local therapy and that, at the time of treatment with sotorasib, patients were not candidates for molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1). The G-BA further assumes patients to be generally eligible for active antineoplastic therapy; therefore, best supportive care was not an ACT option in the present case.
b. Presented is the respective ACT specified by the G-A.
c. With regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel, the use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account.
d. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities; see Appendix VI to Section K of the German Pharmaceutical Directive.
e. Except in mainly squamous histology.
f. Only for patients with ECOG-PS 2 as an alternative to platinum-based combination treatment.
g. Only for patients with PD-L1-negative tumours.
h. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
i. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.
j. For the implementation of individualized therapy in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1

The company followed the G-BA's determination of the ACT for research questions 2 and 3 without making a choice. In departure from the G-BA's specification, the company added the treatment option of docetaxel to the ACT for research question 1. This departure by the company remains without consequence for the present benefit assessment because the company did not present any evidence for sotorasib in comparison with docetaxel for research question 1.

The company's dossier did not analyse research questions 1 through 3 separately. Instead, the wording of the company's research question already shows that the company did not break down the analysis into the 3 subpopulations specified by the G-BA on the basis of prior therapies. The company justifies this approach by arguing that, on the intervention side, > 80% of the available patient population from its approval study fit into research question 3. On the ACT side, the company used data from a registry but, once again, did not analyse any subpopulations, justifying this approach by low patient numbers. The company did not specify the research question into which it categorized the patient population on the ACT side. Despite the fact that, on the intervention side, the vast majority of data apply to research question 3 and, on the ACT side, it remains unclear into which research question the company categorized the patient population, the company used said data to eventually derive added benefit for the entire target population.

The justification provided for departing from the 3 research questions specified by the G-BA is not sound, and the company's approach is not appropriate. As per the commission, this benefit assessment and the derivation of the added benefit have been done separately for the 3 research questions defined by the G-BA.

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

Results

Concurring with the company, the check of the study pool revealed no randomized controlled trial (RCT) enabling either a direct comparison with the ACT or an adjusted indirect comparison via a common comparator for the 3 research questions. Having identified no data for direct comparisons or adjusted indirect comparisons, the company additionally conducted an information retrieval for further studies and has presented results from an uncontrolled study on the intervention side. Furthermore, the company compared individual arms from different studies and, for this purpose, used this uncontrolled study on the intervention side as well as results from a registry study on the ACT side.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of sotorasib in comparison with the ACT. Below, the evidence presented by the company is described, and the reasons for its unsuitability for the benefit assessment are provided.

Evidence provided by the company

On the intervention side, the company included the uncontrolled study CodeBreak 100 for a comparison of individual arms from different studies and, for this purpose, used the results from adult patients with KRAS G12C-mutated advanced NSCLC who presented with disease progression after prior treatment with programmed cell death protein 1 (PD-1) / programmed cell death ligand 1 (PD-L-1) antibody and/or platinum-based combination chemotherapy. Among the 126 patients, 102 (81%) conform to the patient population for research question 3 as defined by the G-BA. Sotorasib treatment was in accordance with the Summary of Product Characteristics (SPC). The primary outcome of the study was the objective response rate. Further outcomes comprised overall survival and carcinoma-specific symptoms. Outcomes from the categories "health-related quality of life" and "side effects" were also recorded.

On the ACT side, the company used the CRISP KRAS G12C registry study, which is based on the "Clinical Research platform Into molecular testing, treatment and outcome of (non-)Small cell lung carcinoma Patients" (CRISP) patient registry, for its intended comparison of individual arms from different studies. The CRISP KRAS G12C registry study included patients with KRAS G12C-mutated locally advanced or metastatic NSCLC who were under second-line therapy. The company does not specify the research question to which this patient population is to be allocated. For the descriptive comparison with the CodeBreak 100 study, the company has presented results on the outcomes of overall survival and progression-free survival.

Evidence presented by the company unsuitable for the benefit assessment

Incomplete study pool on the comparator side

On the comparator side, the company's final study pool consists only of the above-described CRISP KRAS G12C registry study. The company does not cite any reasons for the submitted dossier using data only from the CRISP registry for the comparison of individual arms from different studies on the ACT side despite the fact that further potentially relevant patient registries exist which included patients with various mutations (including KRAS G12C mutation). For instance, the company itself mentioned the Flatiron Health database as a potential further data source in its consultation with the G-BA (9 April 2021). In addition, the company submitted data from the Flatiron Health database in the sotorasib assessment procedure by the National Institute for Health and Care Excellence (NICE). Hence, the company's study pool for further investigations is incomplete on the ACT side.

Comparisons presented by the company unsuitable for drawing conclusions on added benefit

The presented analyses represent descriptive comparisons of individual arms from different studies without adjustment for potentially relevant effect modifiers or prognostic factors. However, analyses are available only for the patient-relevant outcome of overall survival, thus precluding the weighing of benefit versus harm in this benefit assessment. Furthermore, the effects found for the outcome of overall survival are small enough to be potentially attributable exclusively to systematic bias.

No analysis of the 3 research questions specified by the G-BA

On both sides of the comparison, the company has foregone a breakdown into the 3 patient populations specified by the G-BA. Overall, it is unclear which research questions are addressed by the company's descriptive comparison. On the basis of the administered prior therapies, the patient population from the CRISP KRAS G12C registry study covers all 3 research questions specified by the G-BA. Irrespective of the general unsuitability of the comparison presented herein, this population is unsuitable as a control group for the CodeBreak 100 study because > 80% of CodeBreak 100 participants are to be allocated to the G-BA's research question 3. All things considered, it is neither plausible nor appropriate for the company to use this data constellation to derive added benefit for the entire target population.

Conclusion

Overall, the company's approach is not appropriate. Firstly, the data presented by the company for the benefit assessment are unsuitable because they constitute a descriptive comparison of individual arms from different studies, and the observed effects are not large enough. Secondly, the study pool on the ACT side is incomplete. In addition, the data from the CodeBreak 100 study have been incompletely analysed, with some data cut-offs not being presented. Furthermore, the company did not analyse the data based on the 3 research questions specified by the G-BA. Overall, the data presented by the company are unsuitable for assessing any added benefit of sotorasib in comparison with the ACT specified by the G-BA.

Results on added benefit

No suitable data are available for any of the 3 research questions in the assessment of added benefit of sotorasib in comparison with the ACT specified by the G-BA in adult patients with KRAS G12C-mutated advanced NSCLC who have progressed after a minimum of 1 prior line of systemic therapy. This results in no hint of added benefit of sotorasib in comparison with the ACT for any of the 3 research questions; hence, no added benefit is proven for any of them.

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 added benefit of the drug sotorasib in comparison with the ACT is assessed as follows:

Table 3 shows a summary of the probability and extent of added benefit of sotorasib.

[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: Sotorasib – probability and extent of added benefit (multipage table)

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit
1	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with a PD-1/PD-L1 antibody[c] as monotherapy	▪ Cisplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]) or ▪ carboplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]); see also Appendix VI of Section K of the German Pharmaceutical Directive ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]	Added benefit not proven
2	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[e,g] or ▪ nivolumab or ▪ pembrolizumab[h] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[i]	Added benefit not proven
3	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with a PD-1/PD-L1 antibody[c] in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[c] and platinum-based chemotherapy	Individualized treatment[j] consistent with prior treatment and histology, with the available options of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib and vinorelbine	Added benefit not proven

a. The G-BA assumes that patients were not indicated for definitive local therapy and that, at the time of treatment with sotorasib, patients were not candidates for molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1). The G-BA further assumes patients to be generally eligible for active antineoplastic therapy; therefore, best supportive care was not an ACT option in the present case.
b. Presented is the respective ACT specified by the G-BA.
c. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be considered with regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel.
d. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities; see Appendix VI to Section K of the German Pharmaceutical Directive.
e. Except in mainly squamous histology.
f. Only for patients with ECOG-PS 2 as an alternative to platinum-based combination treatment.
g. Only for patients with PD-L1-negative tumours.
h. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
i. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.
j. For the implementation of individualized therapy in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.

Table 3: Sotorasib – probability and extent of added benefit (multipage table)

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1			

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of sotorasib monotherapy in comparison with the ACT in adult patients with KRAS G12C-mutated (as per G-BA, KRAS p.G12C-mutated) advanced NSCLC who have progressed after at least 1 prior line of systemic therapy.

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

Table 4: Research questions of the benefit assessment of sotorasib (multipage table)

Research question	Subindication[a]	ACT[b]
1	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line monotherapy with a PD-1/PD-L1 antibody	▪ Cisplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]) or ▪ carboplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]); see also Appendix VI of Section K of the German Pharmaceutical Directive ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]
2	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[e,g] or ▪ nivolumab or ▪ pembrolizumab[h] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[i]
3	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with a PD-1/PD-L1 antibody[c] in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[c] and platinum-based chemotherapy	▪ Individualized treatment[j] consistent with prior treatment and histology, with the available options of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine

a. The G-BA assumes that patients were not indicated for definitive local therapy and that, at the time of treatment with sotorasib, patients were not candidates for molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1). The G-BA further assumes patients to be generally eligible for active antineoplastic therapy; therefore, best supportive care was not an ACT option in the present case.
b. Presented is the respective ACT specified by the G-BA.
c. With regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel, the use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account.
d. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities; see Appendix VI to Section K of the German Pharmaceutical Directive.
e. Except in mainly squamous histology.
f. Only for patients with ECOG-PS 2 as an alternative to platinum-based combination treatment.
g. Only for patients with PD-L1-negative tumours.
h. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
i. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.
j. For the implementation of individualized therapy in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1

The company followed the G-BA's determination of the ACT for research questions 2 and 3 without making a choice. In departure from the G-BA's specification, the company added the treatment option of docetaxel to the ACT for research question 1. This departure by the company remains without consequence for the present benefit assessment because the company did not present any evidence for sotorasib in comparison with docetaxel for research question 1.

The company's dossier did not analyse research questions 1 through 3 separately. Instead, the wording of the company's research question already shows that the company did not break down the analysis into the 3 subpopulations specified by the G-BA on the basis of prior therapies. It justifies this approach by reasoning that on the intervention side, 80% of the available patient population from its approval study (see Section 2.3) was to be allocated to research question 3. On the ACT side, the company used data from a registry (see Section 2.3), without also grouping the data into subpopulations, justifying this approach by low patient numbers. The company did not specify the research question into which it categorized the patient population on the ACT side. The company used these data to eventually derive added benefit for the entire target population despite the fact that on the intervention side, the vast majority of data apply only to research question 3, and on the ACT side, it remains unclear to which research question the company allocated the patient population.

The justification provided for departing from the 3 research questions specified by the G-BA is not sound, and the company's approach is not appropriate. As per the commission, this benefit assessment and the derivation of the added benefit have been done separately for the 3 research questions defined by the G-BA. Section 2.3 describes the company's approach in detail.

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 lists on sotorasib (status: 15 November 2021)
- bibliographical literature search on sotorasib (last search on 15 November 2021)
- search in trial registries / trial results databases for studies on sotorasib (last search on 15 November 2021)
- search on the G-BA website for sotorasib (last search on 15 November 2021)
- bibliographical literature search on the ACT (last search on 15 November 2021)
- search in trial registries / trial results databases for studies on the ACT (last search on 15 November 2021)
- search on the G-BA website for the ACT (last search on 15 November 2021)

To check the completeness of the study pool:

- search in trial registries for studies on sotorasib (last search on 4 March 2022); for search strategies, see Appendix A of the full dossier assessment
- scoping search for further relevant data sources on the ACT

In concurrence with the company, the check of the study pool revealed no RCT enabling a direct comparison with the ACT nor an adjusted indirect comparison via a common comparator for the 3 research questions.

No results are available yet for the potentially relevant ongoing RCT CodeBreak 200 [3], which enrolled treatment-experienced patients with KRAS G12C-mutated advanced NSCLC.

Having identified no data for direct comparisons or adjusted indirect comparisons, the company additionally conducted an information retrieval for further studies and has presented results from an uncontrolled study on the intervention side. Furthermore, it compared individual arms from different studies and, for this purpose, used this uncontrolled study on the intervention side as well as results from a registry study on the ACT side.

The check for completeness of the company's study pool identified no additional potentially relevant studies on sotorasib. The completeness of the study pool on the ACT was not systematically checked, but a scoping search showed that further relevant data sources do exist (the completeness of the study pool on the comparator side is discussed below).

The data presented by the company are unsuitable for drawing conclusions on the added benefit of sotorasib in comparison with the ACT. Below, the evidence presented by the company is described, and the reasons for its unsuitability for the benefit assessment are provided.

Evidence provided by the company

On the intervention side, the company included the uncontrolled CodeBreak 100 study for a comparison of individual arms from different studies, and, to this end, using the results from adult patients with KRAS G12C-mutated advanced NSCLC [4-7]. On the ACT side, the company used the CRISP KRAS G12C registry study for its intended comparison of individual arms from different studies [8-11].

CodeBreak 100 study

The ongoing CodeBreak 100 study is an open-label, uncontrolled, multicentre phase I and phase II study investigating sotorasib. Phase I of the study determined, among other things, the recommended sotorasib dosage. The study's phase II investigated sotorasib monotherapy. The study enrolled adult patients with locally advanced or metastatic solid tumours (NSCLC, colorectal carcinoma, etc.) with molecularly diagnosed KRAS G12C mutation. For the present benefit assessment, the company analysed only patients with NSCLC in the CodeBreak 100 study's phase II. It is unclear whether patients treated in accordance with approval in phase I

would have been relevant for the analysis. The CodeBreak 100 study's phase II is described below. Phase I as well as the other tumour entities are not discussed further.

To qualify for the study's phase II, patients with KRAS G12-mutated NSCLC had to have disease progression after treatment with a PD-1/PD-L1 antibody and/or platinum-based combination chemotherapy as well as targeted therapy of oncogenic driver mutations such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or c-ros oncogene 1 (ROS1) mutation (where these therapies were indicated). To be included in the study's phase II, patients additionally had to have received a maximum of 3 prior lines of therapy and be in a general condition corresponding to Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1.

Sotorasib treatment was administered in accordance with the SPC [12]. Treatment with the study medication was continued until progression of disease in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1 or until disease progression not meeting RECIST criteria but accompanied by deterioration of symptoms or the patient's general health. Under certain conditions, continuing therapy was permissible even after disease progression. Treatment discontinuation was also possible for other reasons, including the patient's wishes, adverse events, or need for an alternative therapy.

The primary outcome of the study was the objective response rate. Further outcomes comprised overall survival and carcinoma-specific symptoms. Outcomes from the categories "health-related quality of life" and "side effects" were also collected.

According to Module 4 A of the company's dossier, 2 data cut-offs are available for the CodeBreak 100 study:

- First data cut-off: 1 September 2020 (prespecified primary analysis)
- Second data cut-off: 1 December 2020 (data cut-off requested by the United States regulatory authority)

The publication by Skoulidis [4] as well as the European Public Assessment Report [13] show that additional, more recent data cut-offs are available (15 March 2021 and 20June 2021). These data cut-offs are not presented in the company's dossier. The study documents do not show whether these data cut-offs were prespecified. The company's approach is not appropriate because the G-BA's dossier template requires a full listing of all data cut-offs.

Module 4 A of the company's dossier presents results from the 1st data cut-off (126 patients) regarding the outcome categories of mortality, morbidity, health-related quality of life, and side effects. As supplementary information, the company presents the results from the 2nd data cut-off for the outcomes of overall survival, progression-free survival, and response. Among the 126 patients, 102 (81%) fit the patient population for research question 3 as defined by the G-BA.

CRISP KRAS G12C registry study

The CRISP KRAS G12C registry study is based on the CRISP ongoing, open-label, non-interventional, prospective clinical patient registry, which includes over 150 centres, all of which are located in Germany. The registry comprises adult patients, most with a pathological diagnosis of NSCLC in stage IV or IIIB (where no curative surgery or chemoradiotherapy is possible), but also patients in other NSCLC stages and patients with small-cell lung cancer. To be included in the registry, patients must be enrolled no later than 4 weeks after the start of first-line therapy. Registry enrolment started in December 2015. Investigated outcomes are, e.g. overall survival, progression-free survival, response as well as patient-reported data on health-related quality of life, depression, and physical and mental health.

According to the company's Module 4 A, the CRISP KRAS G12C registry study enrolled patients with locally advanced or metastatic NSCLC who had been followed up for at least 1 year by the 30 June 2021 data cut-off (N = 6490), exhibited a KRAS G12C mutation and ECOG-PS 0 or 1, and were on second-line therapy (N = 62). It remains unclear why the company requires a follow-up duration of 1 year. Furthermore, the company did not state whether individual patient follow-up begins with the start of ACT, as was the case in the CodeBreak 100 study. The company does not specify the research question to which this patient population is to be allocated. For the descriptive comparison with the CodeBreak 100 study, the company's Module 4 A presents results on the outcomes of overall survival and progression-free survival.

Evidence presented by the company unsuitable for the benefit assessment

Incomplete study pool on the comparator side

On the comparator side, the company's final study pool consists only of the above-described CRISP KRAS G12C registry study. However, in its consultation with the G-BA (9 April 2021) [14], the company itself already mentioned the Flatiron Health database as a potential further data source [15,16]. In addition, the company submitted data from the Flatiron Health database for the sotorasib assessment procedure by NICE [17,18]. Furthermore, a scoping search showed that, in the present therapeutic indication, further potentially relevant patient registries exist which include patients with various mutations (including KRAS G12C mutation) (e.g. Netzwerk Genomische Medizin [19,20]). The company does not cite any reasons why, for the comparison of individual arms from different studies, the submitted Module 4 A of the dossier used only data from the CRISP registry on the ACT side. Hence, the company's study pool for further investigations is incomplete on the ACT side.

Comparisons presented by the company unsuitable for drawing conclusions on added benefit

Irrespective of the incompleteness of the study pool, the analyses presented by the company constituted descriptive comparisons of individual arms from different studies without adjustment for potentially relevant effect modifiers or prognostic factors. However, analyses are available only for the patient-relevant outcome of overall survival, thus precluding the

weighing of benefit versus harm in this benefit assessment. Furthermore, the effects found for the outcome of overall survival are small enough to be potentially attributable exclusively to systematic bias.

No analysis of the 3 research questions specified by the G-BA

As already described in Section 2.2, the company has foregone a breakdown into the 3 patient populations defined by the G-BA because > 80% of the patients included on the intervention side were reportedly to be allocated research question 3 (80% rule). The company further explained that, due to the small number of patients (N = 62), it likewise did not form subpopulations on the ACT side. The company derived added benefit for the entire target population, disregarding the 3 research questions specified by the G-BA.

The company's approach is not appropriate. While it is plausible for the company to apply the 80% rule and assign the patient population of the CodeBreak 100 study to research question 3 on the intervention side, the company did not state to which research question it allocated the patient population form the CRISP KRAS G12C registry study on the ACT side. Overall, it therefore remains unclear which research question is addressed by the company's descriptive comparison. On the basis of the administered prior therapies, only 14 patients (23%) in the CRISP KRAS G12C registry study had received prior therapy as defined for the patient population of the G-BA's research question 3, while the remaining patients were to be allocated to the populations for research question 1 or 2. Unlike the intervention side, this patient population therefore cannot be allocated to research question 3. Irrespective of the general unsuitability of the comparison presented here, the CRISP KRAS G12C registry study's population is therefore an unsuitable control group for the CodeBreak 100 study because it reflects a different patient population which comprises all 3 research questions specified by the G-BA. All things considered, it is neither plausible nor appropriate for the company to use this data constellation to derive added benefit for the entire target population.

Conclusion

Overall, the company's approach is not appropriate. Firstly, the data presented by the company for the benefit assessment are unsuitable because they constitute a descriptive comparison of individual arms from different studies, and the observed effects are not large enough. Secondly, the study pool on the ACT side is incomplete. In addition, the data from the CodeBreak 100 study have been incompletely analysed because some data cut-offs are not presented. Furthermore, the company did not analyse the data based on the 3 research questions specified by the G-BA. Overall, the data presented by the company are unsuitable for assessing any added benefit of sotorasib in comparison with the ACT specified by the G-BA.

2.4 Results on added benefit

No suitable data are available for any of the 3 research questions in the assessment of added benefit of sotorasib in comparison with the ACT specified by the G-BA in adult patients with KRAS G12C-mutated advanced NSCLC who have progressed after a minimum of 1 prior line

of systemic therapy. This results in no hint of added benefit of sotorasib in comparison with the ACT for any of the 3 research questions; hence, no added benefit is proven for any of them.

2.5 Probability and extent of added benefit

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

Table 5: Sotorasib – probability and extent of added benefit (multipage table)

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit
1	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with a PD-1/PD-L1 antibody[c] as monotherapy	▪ Cisplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]) or ▪ carboplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]); see also Appendix VI of Section K of the German Pharmaceutical Directive ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]	Added benefit not proven
2	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[e,g] or ▪ nivolumab or ▪ pembrolizumab[h] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[i]	Added benefit not proven
3	Adults with KRAS p.G12C-mutated advanced NSCLC after first-line therapy with a PD-1/PD-L1 antibody[c] in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[c] and platinum-based chemotherapy	Individualized treatment[j] consistent with prior treatment and histology, with the available options of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine	Added benefit not proven

a. The G-BA assumes that patients were not indicated for definitive local therapy and that, at the time of treatment with sotorasib, patients were not candidates for molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1). The G-BA further assumes patients to be generally eligible for active antineoplastic therapy; therefore, best supportive care was not an ACT option in the present case.
b. Presented is the respective ACT specified by the G-BA.
c. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be considered with regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel.
d. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities; see Appendix VI to Section K of the German Pharmaceutical Directive.
e. Except in mainly squamous histology.
f. Only for patients with ECOG-PS 2 as an alternative to platinum-based combination treatment.
g. Only for patients with PD-L1-negative tumours.
h. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
i. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.
j. For the implementation of individualized therapy in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.

Table 5: Sotorasib – probability and extent of added benefit (multipage table)

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1			

The assessment described above deviates from the assessment by the company, which has derived non-quantifiable added benefit for all patients in the present therapeutic indication (adult patients with KRAS G12C-mutated advanced NSCLC who have progression after a minimum of 1 prior systemic therapy).

The G-BA decides on the added benefit.

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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