Sotorasib (NSCLC)

Benefit assessment according to §35a SGB V[1] (assessment after expiry of the decision)

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
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
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
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
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) 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 31 January 2023.

According to the justification paper on the decision dated 4 August 2022, a time limit was imposed for patient groups (b) and (c) because the European Medicines Agency required the company to submit the results and, among others, the study report for the primary analysis of the phase III CodeBreak 200 study by 31 March 2023 to confirm the efficacy and safety of sotorasib in the treatment of adult patients with Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C-positive advanced non-small cell lung cancer (NSCLC) compared to treatment with docetaxel. The decision was therefore time-limited for patient groups (b) and (c) in order to include more meaningful data on overall survival as well as on other patient-relevant outcomes in the benefit assessment in a timely manner.

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 advanced NSCLC with KRAS G12C mutation (as per G-BA, KRAS p.G12C mutation) who have progressed after at least 1 prior line of systemic therapy with cytotoxic chemotherapy or with a PD1/PD-L1 antibody in combination with platinum-containing chemotherapy or following sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy.

The G-BA's specification of the ACT results in the questions presented in Table 2 for the relevant patient groups of the present benefit assessment after expiry of the time limit.

Table 2: Research questions of the benefit assessment of sotorasib

Research question[a]	Therapeutic indication[b]	ACT[c]
2	Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[d] or ▪ Nemetrexed[d, e] or ▪ Nivolumab or ▪ Pembrolizumab[f] or ▪ Atezolizumab or ▪ Docetaxel in combination with nintedanib
3	Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with a PD-1/PD-L1 antibody[h] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[h] and platinum-containing chemotherapy	▪ Individualized treatment taking into account prior treatment and histology, choosing from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine

a. As per decision dated 4 August 2022, a time limit was imposed for patient groups (b) and (c) according to research questions 2 and 3 from assessment A22-28. Research question 1 from assessment A22-28 is therefore not subject of the present benefit assessment.
b. The G-BA assumes that patients were not therapeutically 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.
c. Presented is 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 of the company is printed in **bold**.
d. Only for patients with PD-L1-negative tumours.
e. Except with mainly squamous histology.
f. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
g. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.
h. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account with regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel.
i. 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 taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. In single-comparator studies, the extent to which conclusions can be drawn about a subpopulation is examined as part of the benefit assessment.

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

Research questions 2 and 3 of the present benefit assessment correspond to patient groups (b) and (c) in the G-BA's specification of the ACT. The company followed the G-BA's determination of the ACT for research questions 2 and 3 without making a choice for research question 2.

The company's dossier did not analyse research questions 2 and 3 separately. Instead, the wording of the company's research question already shows that the company did not break down the analysis into the 2 patient groups in accordance with the research questions specified by the G-BA . The company justifies this approach by arguing that the majority (96.8%) of the presented study's population (see Section I 4.1) fall under research question 3.

The present assessment was conducted separately for research questions 2 and 3 presented 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. Randomized controlled trials (RCTs) are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Research question 2: Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with cytotoxic chemotherapy

For adult patients with advanced NSCLC with KRAS G12C mutation after first-line therapy with cytotoxic chemotherapy, the company has not provided any data for assessing the added benefit of sotorasib in comparison with the ACT. This results in no hint of an added benefit of sotorasib in comparison with the ACT. An added benefit is therefore not proven.

Research question 3: Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

Results

Evidence presented by the company – CodeBreak 200 study

The CodeBreak 200 study is an ongoing 2-arm, randomized, active control, open-label, multicentre, phase III study. The study enrolled adult patients with locally advanced and inoperable or metastatic NSCLC with molecularly diagnosed KRAS G12C mutation. Patients had to exhibit disease progression during or after at least 1 prior systemic therapy for the advanced or inoperable disease stage. Prior therapy was to include platinum-containing combination chemotherapy with a PD-1/PD-L1 antibody or sequential therapy with platinum-containing combination chemotherapy and a PD-1/PD-L1 antibody unless they were contraindicated for 1 of the required therapies. To be enrolled in the study, patients had to exhibit an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1, no relevant renal or hepatic impairment, and no haematologic limitations.

A total of 345 patients were enrolled in the CodeBreak 200 study and were randomly allocated in a 1:1 ratio to treatment with either sotorasib (N = 171) or docetaxel (N = 174).

Sotorasib or docetaxel treatment was administered in accordance with the Summary of Product Characteristics (SPC). Treatment with the study drug was continued until disease progression, treatment intolerance, initiation of new anti-cancer therapy, withdrawal of consent, or death.

The study's primary outcome was progression-free survival based on blinded independent central review. Further patient-relevant outcomes comprised overall survival and carcinoma-specific symptoms. Outcomes from the health-related quality of life and side effects categories were also recorded.

The CodeBreak 200 study is still ongoing. Module 4 A of the company's dossier presents results from the 1st data cut-off of 2 August 2022 for the outcome categories of mortality, morbidity, health-related quality of life, and side effects.

CodeBreak 200 study unsuitable for the benefit assessment

Given the ACT specified by the G-BA for research question 3, afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine are options for individualized therapy, taking into account prior therapy and histology.

The presented CodeBreak 200 study is a single-comparator study in which all comparator arm participants received docetaxel monotherapy. The study did not offer individualized therapy, where a drug is selected by the investigator taking into account prior therapy and histology. The company has not justified this restriction of treatment options to docetaxel or the submission of a single-comparator study. Likewise, it has not provided any information on why docetaxel would represent the individually most suitable therapy for all patients enrolled in the comparator arm and therefore would correspond to individualized therapy according to the ACT specified by the G-BA.

The ACT specified by the G-BA has not been adequately implemented in the CodeBreak 200 study. The CodeBreak 200 study is therefore unsuitable for assessing the added benefit of sotorasib compared to the ACT specified by the G-BA.

Results on added benefit

Since no suitable data are available for the present research question, there is no hint of added benefit of sotorasib in comparison with the ACT; therefore, no added benefit is 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 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

Research question[a]	Therapeutic indication[b]	ACT[c]	Probability and extent of added benefit
2	Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[d] or ▪ Pemetrexed[d, e] or ▪ Nivolumab or ▪ Pembrolizumab[f] or ▪ Atezolizumab or ▪ Docetaxel in combination with nintedanib	Added benefit not proven
3	Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with a PD-1/PD-L1 antibody[h] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[h] and platinum-containing chemotherapy	▪ Individualized treatment taking into account prior treatment and histology, choosing from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine	Added benefit not proven

a. As per decision dated 4 August 2022, a time limit was imposed for patient groups (b) and (c) according to research questions 2 and 3 from assessment A22-28. Research question 1 from assessment A22-28 is therefore not subject of the present benefit assessment.
b. The G-BA assumes that patients were not therapeutically 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.
c. Presented is 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 of the company is printed in **bold**.
d. Only for patients with PD-L1-negative tumours.
e. Except with mainly squamous histology.
f. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
g. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.
h. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account with regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel.
i. 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 taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. In single-comparator studies, the extent to which conclusions can be drawn about a subpopulation is examined as part of the benefit assessment.

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.

I 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 advanced NSCLC with KRAS G12C mutation (as per G-BA, KRAS p.G12C mutation) who have progressed after at least 1 prior line of systemic therapy with cytotoxic chemotherapy or with a PD1/PD-L1 antibody in combination with platinum-containing chemotherapy or following sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy.

The G-BA's specification of the ACT results in the questions presented in Table 4 for the relevant patient groups of the present benefit assessment after expiry of the time limit.

Table 4: Research questions of the benefit assessment of sotorasib

Research question[a]	Therapeutic indication[b]	ACT[c]
2	Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[d] or ▪ Pemetrexed[d, e] or ▪ Nivolumab or ▪ Pembrolizumab[f] or ▪ Atezolizumab or ▪ Docetaxel in combination with nintedanib
3	Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with a PD-1/PD-L1 antibody[h] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[h] and platinum-containing chemotherapy	▪ Individualized treatment taking into account prior treatment and histology, choosing from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine

a. As per decision dated 4 August 2022, a time limit was imposed for patient groups (b) and (c) in accordance with questions 2 and 3 from assessment A22-28 [3]. Research question 1 from assessment A22-28 [4] is therefore not subject of the present benefit assessment.
b. The G-BA assumes that patients were not therapeutically 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.
c. Presented is 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 of the company is printed in **bold**.
d. Only for patients with PD-L1-negative tumours.
e. Except with mainly squamous histology.
f. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
g. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.
h. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account with regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel.
i. 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 taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. In single-comparator studies, the extent to which conclusions can be drawn about a subpopulation is examined as part of the benefit assessment.

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

Research questions 2 and 3 of the present benefit assessment correspond to patient groups (b) and (c) in the G-BA's specification of the ACT. The company followed the G-BA's determination of the ACT for research questions 2 and 3 without making a choice for research question 2.

The company's dossier did not analyse research questions 2 and 3 separately. Instead, the wording of the company's research question already shows that the company did not break down the analysis into the 2 patient groups in accordance with the research questions specified by the G-BA . The company justifies this approach by arguing that the majority (96.8%) of the study population from the presented study fit into research question 3.

The present assessment was conducted separately for research questions 2 and 3 presented 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. RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 2: Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with cytotoxic chemotherapy

I 3.1 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 sotorasib (status: 23 November 2022)
- bibliographical literature search on sotorasib (last search on 23 November 2022)
- search in trial registries / trial results databases for studies on sotorasib (last search on 23 November 2022)
- search on the G-BA website for sotorasib (last search on 23 November 2022)

To check the completeness of the study pool:

- search in trial registries for studies on sotorasib (last search on 14 February 2023); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check.

The company identifies the RCT CodeBreak 200 in its information procurement [5]. However, it does not divide the total study population into patient groups according to research questions 2 and 3 formulated by the G-BA. The company justifies this approach by arguing that the majority (96.8%) of the presented study's population (see Section I 4.1) fall under research question 3. This is plausible because 334 (96.8%) of the 345 patients in the study received prior treatment with PD-1 / PD-L1 inhibitor and platinum-containing chemotherapy (in combination or sequentially) and thus correspond to the patient group specified by the G-BA for research question 3. Overall no suitable data are therefore available for the assessment of research question 2.

I 3.2 Results on added benefit

For adult patients with advanced NSCLC with KRAS G12C mutation after first-line therapy with cytotoxic chemotherapy, the company has not provided any data for assessing the added benefit of sotorasib in comparison with the ACT. This results in no hint of an added benefit of sotorasib in comparison with the ACT. An added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

The company did not present any data for assessing the added benefit of sotorasib in adult patients with advanced NSCLC with KRAS G12C mutation after first-line therapy with cytotoxic

chemotherapy. An added benefit of sotorasib in comparison with the ACT is therefore not proven for these patients.

This assessment departs from that conducted by the company, which has derived an indication of considerable added benefit for all patients in the present therapeutic indication (adult patients with advanced NSCLC with KRAS G12C mutation who have progressed after a minimum of 1 prior systemic therapy) without differentiating the research questions.

I 4 Research question 3: Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

I 4.1 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 sotorasib (status: 23 November 2022)
- bibliographical literature search on sotorasib (last search on 23 November 2022)
- search in trial registries / trial results databases for studies on sotorasib (last search on 23 November 2022)
- search on the G-BA website for sotorasib (last search on 23 November 2022)

To check the completeness of the study pool:

- search in trial registries for studies on sotorasib (last search on 14 February 2023); for search strategies, see I Appendix A of the full dossier assessment

The check for completeness of the study pool revealed no relevant studies comparing sotorasib versus the ACT of individualized therapy.

The company, in contrast, identified the RCT CodeBreak 200 [5] and used it in its assessment. According to the time limit requirements imposed by the G-BA, the results from this study's clinical study report were to be submitted for a new benefit assessment after expiry of the time limit.

Evidence provided by the company

Design of the CodeBreak 200 study

The CodeBreak 200 study is an ongoing 2-arm, randomized, active control, open-label, multicentre, phase III study. The study enrolled adult patients with locally advanced and inoperable or metastatic NSCLC with molecularly diagnosed KRAS G12C mutation. Patients had to exhibit disease progression during or after at least 1 prior systemic therapy for the advanced or inoperable disease stage. Prior therapy was to include platinum-containing combination chemotherapy with a PD-1/PD-L1 antibody or sequential therapy with platinum-containing combination chemotherapy and a PD-1/PD-L1 antibody unless they were contraindicated for 1 of the required therapies. To be enrolled in the study, patients had to exhibit an ECOG-PS ≤ 1, no relevant renal or hepatic impairment, and no haematologic

limitations. In addition, the tumour cells were not to have any other oncogenic driver mutations (including gene mutations in epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK]).

A total of 345 patients were included in the CodeBreak 200 study and randomly allocated in a 1:1 ratio to treatment with either sotorasib (N = 171) or docetaxel (N = 174). The randomization was stratified by the number of prior therapies (1 versus 2 versus ≥ 2), ancestry (Asian versus not Asian), and prior history of central nervous system involvement (yes versus no).

Sotorasib or docetaxel treatment was administered in accordance with the SPC [6,7]. Treatment with the study drug continued until disease progression in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) criteria, treatment intolerance, initiation of new anti-cancer therapy, withdrawal of consent, or death. At the investigator's discretion, treatment continuation was possible under certain, predefined conditions.

The study's primary outcome was progression-free survival based on blinded independent central review. Further patient-relevant outcomes comprised overall survival and carcinoma-specific symptoms. Outcomes from the health-related quality of life and side effects categories were also recorded.

The CodeBreak 200 study is still ongoing. Module 4 A of the company's dossier presents results from the 1st data cut-off dated 2 August 2022 regarding the outcome categories of mortality, morbidity, health-related quality of life, and side effects.

Of the 345 patients, 334 (96.8%) received prior treatment with PD-1 / PD-L1 inhibitor and platinum-containing chemotherapy (in combination or sequentially) and thus correspond to the patient group defined by the G-BA for question 3. Prior treatment with platinum-containing chemotherapy alone was administered to 6 patients (3.5%) in the intervention arm and 3 patients (1.7%) in the comparator arm. One patient in the comparator arm received prior treatment with PD-1 / PD-L1 inhibitor therapy only. The company did not provide any information on contraindications to platinum-containing combination chemotherapy or treatment with a PD-1 / PD-L1 inhibitor. Almost all patients (96.8%) had non-squamous cell carcinoma. About one-third of the patients had an ECOG-PS of 0, and two-thirds were rated as an ECOG-PS of 1.

Individualized therapy not implemented in the CodeBreak 200 study

Given the ACT specified by the G-BA for research question 3, afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine may be taken into account as individualized therapy, taking into account prior therapy and histology.

The presented CodeBreak 200 study is a single-comparator study in which all comparator arm participants received docetaxel monotherapy. The study did not offer individualized therapy, where a drug is selected by the investigator taking into account prior therapy and histology. The company has not justified this restriction of treatment options to docetaxel or the submission of a single-comparator study. In Module 4 A, the company likewise provides no information showing that docetaxel represents the individually most suited therapy for all comparator arm participants and therefore corresponds to individualized therapy as specified as the ACT by the G-BA.

In the study protocol as well as in the publication on the study, the company discusses the selected study design, particularly why docetaxel monotherapy was used as the comparator therapy instead of a combination of docetaxel with ramucirumab or nintedanib [5,8]. In the present benefit assessment, the company's rationale is to be rejected for both drug combinations. Instead, it cannot be ruled out that comparator arm patients receive inadequate care, potentially impacting the observed effects. This is explained below.

With reference to the REVEL study [9], the company's study protocol states that the combination of docetaxel and ramucirumab offers an advantage over docetaxel monotherapy but is used less frequently in older patients > 65 years of age and is to be used in younger patients with better ECOG-PS. However, the CodeBreak 200 study population exclusively comprises patients with an ECOG-PS 0 to 1, i.e. with better health status, and over half of the patients were younger than 65 years. According to the SPC, ramucirumab in combination with docetaxel is indicated in the present therapeutic indication [10] and thus likely represents an adequate treatment option for a relevant proportion of enrolled patients.

Furthermore, the company points out in the study protocol and in the study publication that the combination of docetaxel and nintedanib offers an advantage over docetaxel monotherapy; it explains the choice of docetaxel as the comparator therapy with the fact that the combination is reportedly not available in all countries where the study is conducted. In the German health care system, nintedanib is available in combination with docetaxel and is indicated in the present therapeutic indication as per SPC [11]. Therefore, the combination of docetaxel and nintedanib may represent an adequate treatment option for a relevant percentage of enrolled patients.

Furthermore, neither the study's inclusion and exclusion criteria nor the patient characteristics clarify why docetaxel represents the best treatment option for each individual CodeBreak 200 participant and why the drug is to be preferred over the other individualized therapy options specified by the G-BA as the ACT (see Table 4). Most CodeBreak 200 participants do not exhibit any of the impairments described in the SPC for the various ACT options, e.g. renal (pemetrexed, erlotinib) or hepatic (erlotinib, vinorelbine) impairment or bone marrow impairment / haematological problems (pemetrexed, vinorelbine). Rather,

study participants all have an ECOG-PS ≤ 1 and as per the study's inclusion and exclusion criteria show no relevant renal or hepatic impairments and no haematologic limitations.

The above evaluation does not apply to the suitability of afatinib as a treatment option for enrolled patients. According to the SPC, afatinib is therapeutically indicated for the treatment of patients with locally advanced or metastatic NSCLC with squamous histology [12]. However, 96.8% of the CodeBreak 200 participants had non-squamous cell carcinoma.

In summary, the CodeBreak 200 study fails to adequately implement the ACT specified by the G-BA. The CodeBreak 200 study is not suitable for assessing the added benefit of sotorasib compared to the ACT specified by the G-BA.

I 4.2 Results on added benefit

The company has not supplied suitable data for assessing the added benefit of sotorasib compared to the ACT for adult patients with advanced NSCLC with KRAS G12C mutation after first-line therapy with a PD-1 / PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1 / PD-L1 antibody and platinum-containing chemotherapy. This results in no hint of an added benefit of sotorasib in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

The company has failed to provide suitable data for assessing the added benefit of sotorasib compared to the ACT for adult patients with advanced NSCLC with KRAS G12C mutation after first-line therapy with a PD-1 / PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1 / PD-L1 antibody and platinum-containing chemotherapy. An added benefit of sotorasib in comparison with the ACT is therefore not proven for these patients.

This assessment departs from that by the company, which has derived an indication of considerable added benefit for all patients in the present therapeutic indication (adult patients with advanced NSCLC with KRAS G12C mutation who have progressed after a minimum of 1 prior systemic therapy), without differentiating the research questions.

I 5 Probability and extent of added benefit – summary

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

Research question[a]	Therapeutic indication[b]	ACT[c]	Probability and extent of added benefit
2	Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[d] or ▪ Pemetrexed[d, e] or ▪ Nivolumab or ▪ Pembrolizumab[f] or ▪ Atezolizumab or ▪ Docetaxel in combination with nintedanib	Added benefit not proven
3	Adults with advanced NSCLC with KRAS G12C mutation after first-line therapy with a PD-1/PD-L1 antibody[h] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[h] and platinum-containing chemotherapy	▪ Individualized treatment taking into account prior treatment and histology, choosing from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine	Added benefit not proven

a. As per decision dated 4 August 2022, a time limit was imposed for patient groups (b) and (c) according to research questions 2 and 3 from assessment A22-28 [3]. Research question 1 from assessment A22-28 [4] is therefore not subject of the present benefit assessment.
b. The G-BA assumes that patients were not therapeutically 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.
c. Presented is 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 of the company is printed in **bold**.
d. Only for patients with PD-L1-negative tumours.
e. Except with mainly squamous histology.
f. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
g. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.
h. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account with regard to the approval of pemetrexed, gemcitabine and nab-paclitaxel.
i. 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 taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. In single-comparator studies, the extent to which conclusions can be drawn about a subpopulation is examined as part of the benefit assessment.

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.

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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