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Selpercatinib (RET fusion-positive 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 *Selbercatinib (RET-Fusions-positives NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 June 2021). Please note: This translation 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MTD	maximum tolerable dose
NSCLC	non-small cell lung cancer
PD-1	programmed cell death 1
PD-L1	programmed cell death-ligand -1
PFS	progression-free survival
RCT	randomized controlled trial
RET	rearranged during transfection
SGB	Sozialgesetzbuch (Social Code Book)
SOC	standard of care
SPC	Summary of Product Characteristics

1 Benefit assessment

1.1 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 selpercatinib. 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 12 March 2021.

Research question

The aim of the present report was to assess the added benefit of selpercatinib in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following platinum-based chemotherapy and/or treatment with immunotherapy.

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

Table 2: Research questions of the benefit assessment of selpercatinib

Research question	Therapeutic indication	ACT[b]
1	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a PD-1/PD-L1 antibody[a] as monotherapy	▪ Cisplatin[c] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[d]) or ▪ carboplatin[c] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[d]); see also Appendix VI to Section K of the Pharmaceutical Directive ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[e]
2	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a cytotoxic chemotherapy	▪ Docetaxel[f] or ▪ pemetrexed[g] or ▪ nivolumab or ▪ pembrolizumab[h] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[i]
3	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a PD-1/PD-L1 antibody[a] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[a] and platinum-containing chemotherapy	▪ Individual treatment under consideration of pretreatment and histology; choosing from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib and vinorelbine

a. Use of a PD-1/PD-L1 inhibitor within the pretreatment is not interpreted as a line of therapy to be considered with regard to the approval of pemetrexed, gemcitabine and nab-paclitaxel.
b. Presentation of the respective ACT specified by the G-BA. According to the G-BA, there are no standardized treatment recommendations for patients with RET fusion in the present therapeutic indication. Moreover, the G-BA assumes that the patients in the therapeutic indication had no indication for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF or ROS1) could be considered for the patients at the time of treatment with selpercatinib. It is also assumed that the patients were generally eligible for active antineoplastic therapy, which is why BSC was not considered as an ACT in the present case.
c. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the two substances and on the existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive.
d. Except in mainly squamous histology.
e. Only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment.
f. Only for patients with PD-L1-negative tumours.
g. Only for patients with PD-L1-negative tumours and except in mainly squamous histology.
h. Only for patients with PD-L1 expressing tumours (TPS ≥ 1 %).
i. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: Programmed Cell Death 1; PD-1: Programmed Cell Death 1; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TPS: Tumour Proportion Score

Deviating from the 3 research questions of the G-BA, the company investigated the following 2 research question in its dossier:

- Patients with advanced NSCLC and RET fusion with a prior systemic therapy (second line - patient group A1 of the company). The company summarizes the following patients under this heading:
  - after first-line treatment with a programmed cell death 1 (PD-1)/programmed cell death-ligand -1 (PD-L1) antibody
  - after first-line treatment with chemotherapy
  - after first-line therapy with a PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy
- patients with advanced NSCLC and RET fusion with at least 2 prior systemic therapies (third line and higher lines - patient group A2 of the company)

For its patient group A1 (second line), the company specified certain ACT options determined by the G-BA under consideration of the prior therapies. However, for patients after first-line therapy with chemotherapy, the company extended these options to include the combination docetaxel + ramucirumab. The specification of this option by the company has no consequences for the present assessment, as the company presented no evidence in comparison with docetaxel + ramucirumab as ACT.

For its patient group A2 (third line and higher lines), the company specified an individual therapy under consideration of response and tolerability of the prior therapy, histology and health status, choosing from afatinib, erlotinib, docetaxel, vinorelbine, docetaxel in combination with ramucirumab; docetaxel in combination with nintedanib; pembrolizumab, pemetrexed, nivolumab and atezolizumab. This deviates from the G-BAs ACT specified by the G-BA, which defined no separate ACT for patients with more than 1 prior lines of treatment. Research question 3 of the G-BA comprises both a part of the patients in the second line and those in higher lines of treatment.

The present assessment was conducted on the basis of the research questions specified by the G-BA (populations and corresponding ACTs).

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 completeness of the study pool identified no randomized controlled trials (RCTs) on the direct comparison or on the adjusted indirect comparison using a common comparator of selpercatinib versus the ACT.

The company additionally conducted an information retrieval and presented the non-controlled study LIBRETTO-001 on selpercatinib. Moreover, it conducted comparisons of individual arms from different studies.

Evidence on selpercatinib presented by the company

The basket study LIBRETTO-001 is an ongoing, non-controlled, prospective study organized in 2 phases. The maximum tolerable dose (MTD) was determined in the already completed phase 1. In the ongoing phase 2, the MTD was applied.

Phase 1 of the LIBRETTO-001 study

Phase 1 of the LIBRETTO-001 study included patients aged 12 years and older with locally advanced or metastatic solid tumours, regardless of RET status and pretreatment, who had progressed on or were intolerant to previous standard therapies, for whom no standard therapy was available, for whom standard therapy was not indicated from the investigator's point of view, or who refused standard therapy. The presence of an alteration of the RET gene was only an inclusion criterion after the minimum plasma concentration of selpercatinib specified in the study protocol had been reached. Pretreatment with certain drugs was permitted, but presented no inclusion criterion.

Phase 2 of the LIBRETTO-001 study

In phase 2 of the LIBRETTO-001 study, patients aged 12 years and older with locally advanced or metastatic solid tumours with RET alteration were enrolled into different cohorts. Cohort 1, which is relevant for the present indication, included patients with advanced or metastatic solid tumours with RET fusion and progression on or intolerance to standard therapy.

For all patients of phase 2, treatment started with 160 mg twice daily in 28-day cycles, irrespective of body weight; this does not correspond to the specifications of the Summary of Product Characteristics (SPC) for patients with a body weight of < 50 kg. Treatment was continued until occurrence of unacceptable toxicity, or occurrence of another event that led to treatment discontinuation (e.g. death, withdrawal of consent). In the event of progression, treatment could be continued in agreement with the company if tolerability and clinical benefit were given.

Primary outcome in phase 2 was the objective response rate. Patient-relevant secondary outcomes were "overall survival", "morbidity", "health-related quality of life" and "side effects".

Evidence presented by the company for the ACT

On the comparator side, the company identified Shen 2020, Drilon 2016, Mazieres 2019, Guisier 2020 and Hess 2021 for its envisaged comparisons of individual arms from different studies. These studies are retrospective data recordings. They also included a small number of patients with RET fusion-positive NSCLC and were identified by the company without restrictions regarding the prior therapies.

Presented results on outcome level

Study LIBRETTO-001

Relevant for the present therapeutic indication are patients with RET fusion-positive advanced NSCLC requiring systemic therapy after platinum-based chemotherapy and/or immunotherapy. The company presented the results of the subpopulation of the LIBRETTO-001 study who met these criteria. In doing so, the company differentiated the patients according to the number of previous therapies (A1: 85 patients in the second line, A2: 173 patients in the third line and in higher lines).

From the company's point of view, the intraindividual changes in the course of the LIBRETTO-001 study showed a reduction in symptom burden and an improvement in quality of life. Moreover, the company pointed out that the majority of patients achieved a better overall response under treatment with selpercatinib than under the treatment provided immediately before study inclusion.

Comparisons of individual arms from different studies

In order to compare selpercatinib with the ACT, the company at first provided a descriptive presentation of the results for the outcomes "overall survival", "progression-free survival (PFS)" and "tumour response" for its patient groups A1 (second-line) and A2 (third-line and higher lines) and compared them with those of the 5 studies in its study pool. In Module 4 A, it presented the second data cut-off (16 December 2019) and in the Appendix, it presented the third data cut-off (30 March 2020). For the outcome "overall survival", it only used the Mazieres 2019 study on the comparator side.

Assessment of the evidence presented by the company

The patient groups A1 and A2 of the LIBRETTO-101 study formed by the company are unsuitable to answer the research questions of the benefit assessment

In its dossier, the company divided the patients of the LIBRETTO-001 study with advanced RET fusion-positive NSCLC who received systemic therapy after platinum-based chemotherapy and/or treatment with immunotherapy only according to the number of prior therapies. Deviating from this, the G-BA differentiated the patients according to the type of their first-line therapy (PD-1/PD-L1 antibody as monotherapy vs. cytotoxic chemotherapy vs. PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy or sequential therapy with a PD-1/PD-L1 antibody and a platinum-containing chemotherapy).

The non-controlled study LIBRETTO-001 permits no conclusions on the added benefit

The results from the LIBRETTO-001 study are not suitable for the benefit assessment, as there are no data permitting a comparison with the ACT. The assessment of the added benefit requires comparative data.

Deviations from the specifications of the SPC in LIBRETTO-001.

Overall, for both patient groups A1 and A2, more than 20% of the considered patients included in the LIBRETTO-001 study were treated in a way that did not comply with the approval (different starting and maintenance doses of selpercatinib and treatment with selpercatinib beyond progression).

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

Due to the operationalization of the outcomes, only "overall survival" represents a patient-relevant outcome among the outcomes considered by the company. For this outcome, the company only used the Mazieres 2019 study, in which the patients received PD-1/PD-L1 antibodies in any line of treatment. The data of this study presented by the company are not usable for the comparison of individual arms from different studies:

on patient group A1 of the company:

- 100% of the patients of the LIBRETTO-001 study considered in patient group A1 were in the second line of treatment. However, it is unclear who of the relevant patients from the Mazieres 2019 study (n = 16 with RET fusion) are to be assigned to which line of treatment. The publication shows that about 40% of the patients in the total population (N = 551) are in the second line, but 53% of the patients are in higher lines of treatment. Even under the assumption of the company that these proportions in the overall population can also be transferred to the relevant patient population, the patients from LIBRETTO-001 and Mazieres 2019 are not comparable with regard to their lines of treatment.
- More than 40% of the patients in the LIBRETTO-001 study had already received a PD-1/PD-L1 antibody as prior therapy. A comparison with a PD-1/PD-L1 antibody therapy is not suitable for these patients, as re-treatment with a PD-1/PD-L1 antibody is not indicated for such patients according to the G-BA's ACT. However, the Mazieres 2019 study considered by the company represents precisely this comparison.

On patient group A2 of the company:

- All of the patients of the LIBRETTO-001 study considered in patient group A2 had at least 2 prior therapies, 65% of them already had PD-1/PD-L1 pretreatment. For patients in this line of treatment, a comparison versus a PD-1/PD-L1 antibody does not correspond to the ACT specified by the G-BA.

Irrespective of the previously mentioned points relating to the patient groups, the procedure of the company for presenting the results from the comparisons is overall selective and also calls the interpretability of the results from the comparison into question. This is justified below:

- The outcome "overall survival" was also recorded in the studies Guisier 2020 (9 patients with RET fusion-positive NSCLC, of which 6 patients were in the second line and 3

patients in higher lines of treatment) and Drilon 2016 (4 patients with RET fusion-positive NSCLC in the second line) identified by the company. However, the company did not use these studies, as the patient groups comprised less than 10 patients. This approach is not adequate given the small number of patients in all included studies, especially as the number of prior lines of treatment is similar in Guisier 2020 compared to Mazieres 2019.

- When comparing the results on overall survival after 12 months for patients with RET fusion-positive NSCLC from Mazieres 2019 with those from Guisier 2020, it can be seen that the 12-month survival rate is lower in Mazieres 2019 (53.9%) than in Guisier 2020 (88.9%). In the Drilon 2016 study identified by the company (chemotherapy; patients predominantly in the first line), patients also died significantly later than in Mazieres 2019. These aspects underline a suspected bias caused by patients with a higher line of treatment in Mazieres 2019.

Conclusion

The results presented by the company are unsuitable for the assessment of the added benefit of selpercatinib in comparison with the ACT. The results from the non-controlled study LIBRETTO-001 alone are not suitable for the benefit assessment, as data on the ACT are not available. Moreover, the comparisons of individual arms from different studies presented by the company are not suitable for conclusions on the added benefit, as the patients from LIBRETTO-001 and Mazieres 2019 are not comparable with regard to their lines of treatment. In addition, the comparisons used by the company do not reflect the research questions of the G-BA and the associated ACT options.

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

Based on the results presented, probability and extent of the added benefit of the drug selpercatinib in comparison with the ACT are assessed as follows:

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

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a PD-1/PD-L1 antibody[a] as monotherapy	▪ Cisplatin[c] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[d]) or ▪ carboplatin[c] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[d]); see also Appendix VI to Section K of the Pharmaceutical Directive ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[e]	Added benefit not proven
2	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a cytotoxic chemotherapy	▪ Docetaxel[f] or ▪ pemetrexed[g] or ▪ nivolumab or ▪ pembrolizumab[h] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[i]	Added benefit not proven
3	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a PD-1/PD-L1 antibody[a] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[a] and platinum-containing chemotherapy	▪ Individual treatment under consideration of pretreatment 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. Use of a PD-1/PD-L1 inhibitor within the pretreatment is not interpreted as a line of therapy to be considered with regard to the approval of pemetrexed, gemcitabine and nab-paclitaxel.
b. Presentation of the respective ACT specified by the G-BA. According to the G-BA, there are no standardized treatment recommendations for patients with RET fusion in the present therapeutic indication. Moreover, the G-BA assumes that the patients in the therapeutic indication had no indication for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF or ROS1) could be considered for the patients at the time of treatment with selpercatinib. It is also assumed that the patients were generally eligible for active antineoplastic therapy, which is why BSC was not considered as an ACT in the present case.
c. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the two substances and on the existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive.
d. Except in mainly squamous histology.
e. Only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment.
f. Only for patients with PD-L1-negative tumours.
g. Only for patients with PD-L1-negative tumours and except in mainly squamous histology.
h. Only for patients with PD-L1 expressing tumours (TPS ≥ 1 %).
i. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: Programmed Cell Death 1; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TPS: Tumour Proportion Score			

The G-BA decides on the added benefit.

1.2 Research question

The aim of the present report was to assess the added benefit of selpercatinib in comparison with the ACT in adult patients with advanced RET fusion-positive NSCLE who require systemic therapy following platinum-based chemotherapy and/or treatment with immunotherapy.

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

Table 4: Research questions of the benefit assessment of selpercatinib

Research question	Therapeutic indication	ACT[b]
1	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a PD-1/PD-L1 antibody[a] as monotherapy	▪ Cisplatin[c] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[d]) or ▪ carboplatin[c] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[d]); see also Appendix VI to Section K of the Pharmaceutical Directive ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[e]
2	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a cytotoxic chemotherapy	▪ Docetaxel[f] or ▪ pemetrexed[g] or ▪ nivolumab or ▪ pembrolizumab[h] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[i]
3	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a PD-1/PD-L1 antibody[a] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[a] and platinum-containing chemotherapy	▪ Individual treatment under consideration of pretreatment and histology; choosing from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib and vinorelbine

a. Use of a PD-1/PD-L1 inhibitor within the pretreatment is not interpreted as a line of therapy to be considered with regard to the approval of pemetrexed, gemcitabine and nab-paclitaxel.
b. Presentation of the respective ACT specified by the G-BA. According to the G-BA, there are no standardized treatment recommendations for patients with RET fusion in the present therapeutic indication. Moreover, the G-BA assumes that the patients in the therapeutic indication had no indication for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF or ROS1) could be considered for the patients at the time of treatment with selpercatinib. It is also assumed that the patients were generally eligible for active antineoplastic therapy, which is why BSC was not considered as an ACT in the present case.
c. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the two substances and on the existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive.
d. Except in mainly squamous histology.
e. Only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment.
f. Only for patients with PD-L1-negative tumours.
g. Only for patients with PD-L1-negative tumours and except in mainly squamous histology.
h. Only for patients with PD-L1 expressing tumours (TPS ≥ 1 %).
i. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: Programmed Cell Death 1; PD-1: Programmed Cell Death 1; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TPS: Tumour Proportion Score

Deviating from the 3 research questions of the G-BA, the company investigated the following 2 research question in its dossier:

- Patients with advanced NSCLC and RET fusion with a prior systemic therapy (second line - patient group A1 of the company). The company summarizes the following patients under this heading:
  - after first-line treatment with a PD-1/ PD-L1 antibody
  - after first-line treatment with chemotherapy
  - after first-line therapy with a PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy
- patients with advanced NSCLC and RET fusion with at least 2 prior systemic therapies (third line and higher lines - patient group A2 of the company)

For its patient group A1 (second line), the company specified certain ACT options determined by the G-BA under consideration of the prior therapies. However, for patients after first-line therapy with chemotherapy, the company extended these options to include the combination docetaxel + ramucirumab. The company states that, deviating from the assessment of the G-BA, it sees an added benefit for this therapy alternative versus docetaxel or pemetrexed in adult patients with locally advanced or metastatic NSCLC after tumour progression following platinum-containing chemotherapy. The specification of this option by the company has no consequences for the present assessment, as the company presented no evidence in comparison with docetaxel + ramucirumab as ACT.

For its patient group A2 (third line and higher lines), the company specified an individual therapy under consideration of response and tolerability of the prior therapy, histology and health status, choosing from afatinib, erlotinib, docetaxel, vinorelbine, docetaxel in combination with ramucirumab; docetaxel in combination with nintedanib; pembrolizumab, pemetrexed, nivolumab and atezolizumab. This deviates from the G-BAs ACT specified by the G-BA, which defined no separate ACT for patients with more than 1 prior lines of treatment. Research question 3 of the G-BA comprises both a part of the patients in the second line and those in higher lines of treatment.

The present assessment was conducted on the basis of the research questions specified by the G-BA (populations and corresponding ACTs.

Since usable data are not available for any of the research questions named by the G-BA, the assessment of all 3 research questions is performed below in joint sections of the report (see Section 1.3, 1.4 and Section 1.5).

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

1.3 Information retrieval and study pool

1.3.1 Information retrieval

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 niraparib (status: 23 February 2021)
- bibliographical literature search on tucatinib (last search on 23 February 2021)
- search in trial registries/trial results databases for studies on selpercatinib (last search on 23 February 2021)
- search on the G-BA website for selpercatinib (last search on 24 February 2021)
- bibliographical literature search on the ACT (last search on 23 February 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 23 February 2021)
- search on the G-BA website for the ACT (last search on 25 January 2021)

The completeness of the study pool was checked by:

- search in trial registries for studies on selpercatinib (last search on 23 March 2021); for search strategies, see Appendix C of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool for the 3 research questions of the G-BA identified no RCTs on the direct comparison or on the adjusted indirect comparison via a common comparator of selpercatinib versus the ACT.

Since the company identified no RCTs for direct comparisons or adjusted indirect comparisons, it additionally conducted an information retrieval for further studies and, in addition to a non-controlled study on the intervention side, presented a comparison of individual arms from different studies.

The check of the completeness of the company's study pool identified no additional potentially relevant studies on selpercatinib. The completeness of the study pool on the ACT was not checked.

The data presented by the company were unsuitable to draw conclusions on the added benefit of selpercatinib in comparison with the ACT. This is justified below.

1.3.2 Evidence provided by the company

For selpercatinib, the company included the non-controlled basket study LIBRETTO-001 [3-7] and used the subpopulation of adult patients with RET fusion-positive advanced NSCLC who

required systemic therapy after platinum-based chemotherapy and/or treatment with immunotherapy.

Moreover, the company used comparisons of individual arms from different studies. The company identified 5 studies for these comparisons, taking into account the ACT options named by it, irrespective of the patients' previous therapy (Shen 2020 [8], Drilon 2016 [9], Mazieres 2019 [10], Guisier 2020 [11] und Hess 2021 [12]).

1.3.2.1 Evidence on selpercatinib

Study LIBRETTO-001

LIBRETTO-001 is an ongoing, non-controlled, prospective study organized in 2 phases. The MTD was determined in the already terminated phase 1. In the ongoing phase 2, the MTD was applied in several patient cohorts. Both phases are described below. Table 9 and Table 10 in Appendix A of the full dossier assessment describe the study LIBRETTO-001.

Phase 1 of the LIBRETTO-001 study

Phase 1 of the LIBRETTO-001 study included patients aged 12 years and older with locally advanced or metastatic solid tumours, regardless of RET status and pretreatment, who had progressed on or were intolerant to previous standard therapies, for whom no standard therapy was available, for whom standard therapy was not indicated from the investigator's point of view, or who refused standard therapy. The presence of an alteration of the RET gene was only an inclusion criterion after the minimum plasma concentration of selpercatinib specified in the study protocol had been reached. Pretreatment with certain drugs was permitted, but presented no inclusion criterion.

MTD was determined according to a 3 + 3 algorithm based on the occurrence of dose-limiting toxicities (DLTs), with treatment to be discontinued if a DLT occurred. DLTs were pre-defined in the study protocol and included specific adverse events (AEs), e.g. febrile neutropenia of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3, occurring in cycle 1, i.e. within 28 days of the administration of the first dose. The dose steps to be administered (see Table 10 of the full dossier assessment) and the duration of the cycles per dose level (28 days) were also defined in the study protocol.

3 to 6 patients per dose level were treated to determine the MTD. MTD was achieved when at least 2 of the 3 to 6 patients had at least 1 DLT each. For each dose level, up to 15 additional patients could be included for further investigation of safety, pharmacokinetics and biological activity.

Following cycle 1, treatment was continued until occurrence of a discontinuation criterion (e.g. death, withdrawal of consent). The dose could be increased within the dose levels considered to be safe until the MTD was reached. In the event of progression, treatment was to be discontinued; however, it could be continued in consultation with the company if it was tolerated and the clinical benefit was assumed.

The MTD identified in phase 1 is 160 mg selpercatinib, orally, twice daily, in 28-day cycles. The dose corresponds to the dose for patients with a body weight of ≥ 50 kg recommended by the SPC. However, according to the SPC, patients with a body weight of < 50 kg should be administered 120 mg selpercatinib, orally, twice daily, in 28-day cycles [13].

In phase 1, 92 patients across all tumours were treated with a starting dose that did not correspond to the MTD. The proportion of patients who received a starting dose of 160 mg twice daily in phase 1 cannot be inferred from the information provided in Module 4 A. According to the study protocol, patients who received a starting dose of 160 mg twice daily and met the inclusion criteria for phase 2 could be considered for the analyses of the respective cohort of phase 2. It is also unclear to how many patients this applies.

Phase 2 of the LIBRETTO-001 study

In phase 2 of the LIBRETTO-001 study, patients aged 12 years and older with locally advanced or metastatic solid tumours with RET alteration were enrolled into the different cohorts presented in Table 9 of the full dossier assessment. Cohort 1, which is relevant for the present indication, included patients with advanced or metastatic solid tumours with RET fusion and progression on or intolerance to standard therapy.

For all patients of phase 2, treatment started with 160 mg twice daily in 28-day cycles, irrespective of body weight; this does not correspond to the specifications of the SPC for patients with a body weight of < 50 kg. Treatment was continued until occurrence of unacceptable toxicity, or occurrence of another event that led to treatment discontinuation (e.g. death, withdrawal of consent). If AEs occurred, the dose could be reduced twice in steps of 80 mg per day. In the event of progression, treatment was to be discontinued; however, it could be continued in consultation with the company if it was tolerated and the clinical benefit was assumed.

Primary outcome in phase 2 was the objective response rate. Patient-relevant secondary outcomes were “overall survival”, “morbidity”, “health-related quality of life” and “side effects”.

Recruitment for the LIBRETTO-001 study is still ongoing; 989 patients are to be recruited according to the registry entry as of 20 April 2021 [4].

Data cut-offs, analysis populations and presented results

According to the company, there are three data cut-offs for the LIBRETTO-001 study:

- First data cut-off: 17 June 2019 with 531 patients (interim analysis, based on the data provided by the company in the clinical study report [CSR])
- Second data cut-off: 16 December 2019 with 702 patients (interim analysis, which provides the basis for the European approval [14])
- Third data cut-off: 30 March 2020 with 746 patients (data cut-off requested by the Japanese regulatory authority; confirmatory data cut-off for the European approval [14]

Relevant for the present therapeutic indication are patients with RET fusion-positive advanced NSCLC requiring systemic therapy after platinum-based chemotherapy and/or immunotherapy. The data presented by the company comprise patients from both phase 1 and phase 2. The company explained having conducted the analyses in compliance with the line with the LIBRETTO-001 study and the regulatory analyses.

In the dossier, the company distinguished between 2 analysis populations, the safety analysis set and the efficacy analysis set. While the safety analysis set included all patients who had received at least 1 dose of selpercatinib, the efficacy analysis set only included patients who had either been treated for ≥ 6 months or whose treatment had been discontinued within 6 months of initiation. The definition of the efficacy analysis set according to Module 4 A is not found in the study protocol or in the statistical analysis plan; although there is a similar analysis population, which, however, is only used as the basis for the additional analyses on tumour response. The company considered the patients of the efficacy analysis set for the analyses of the benefit outcomes; this procedure had no consequence in the present data situation, as no suitable data were available for the assessment of the added benefit.

For the therapeutic indication to be assessed, the company presented the results of the second data cut-off (safety analysis set: 81 patients [A1: patients in the second line] and 169 patients [A2: patients in the third line and higher lines]) in Module 4 A and the results of the third data cut-off (safety analysis set: 85 patients [A1] and 173 patients [A2]) in the Appendix to Module 4 A of the full dossier assessment. The following considerations apply to the third data cut-off, because this includes more information than the second one.

Of the 85 patients from A1, at least 11 patients (13%) and of the 173 patients from A2, at least 31 patients (18%) were included in phase 1. A more detailed information was not possible based on the documents presented by the company.

In Module 4 A, the company presented results from the LIBRETTO-001 study. From the company's point of view, the intraindividual changes in the course of treatment with selpercatinib compared to the start of treatment show a reduction in symptom burden and an improvement in quality of life. Moreover, the company pointed out that the majority of patients achieved a better overall response under treatment with selpercatinib than under the treatment provided immediately before study inclusion.

1.3.2.2 Evidence on the ACT

On the comparator side, the company identified Shen 2020, Drilon 2016, Mazieres 2019, Guisier 2020 and Hess 2021 for its envisaged comparisons of individual arms from different studies. These studies are retrospective data recordings. The company takes the data presented in the dossier from the respective publications (see also Table 11 in Appendix B of the full dossier assessment).

Mazieres 2019 (IMMUNOTARGET; PD-1/PD-L1 antibodies)

The Mazieres 2019 study is based on the international patient register IMMUNOTARGET (24 centres in 10 countries). It comprises 551 patients with pathological diagnosis of lung cancer and various oncogenic driver mutations, including 16 patients with RET fusion. In one of the therapy lines, the patients received PD1/PD-L1 antibodies as monotherapy. Several therapy lines were allowed as pre-treatment. However, the publication provides no information on which therapies had been administered before. The primary outcome of the study was PFS depending on the driver mutation. The secondary outcome examined included overall survival. Inclusion in the registry took place between 05/2017 and 04/2018.

Shen 2020 (chemotherapy)

The Shen 2020 study included 62 adult patients with RET fusion-positive NSCLC, 50 of whom were in the advanced stage of disease. Patients were identified in 10 hospitals in China between 2011 and 2018 and could have received prior therapy; however, related information is not available. Therapies for NSCLC were pemetrexed-based chemotherapy or another type of chemotherapy. Of the 62 patients included, a total of 40 patients received first-line therapy and 28 patients received second-line therapy; patients could thus be included in the analyses (for PFS) with both lines of therapy. The aim of the study was to compare PFS and overall survival between patients who received pemetrexed-based chemotherapy and those who received another type of chemotherapy.

Hess 2021 (systemic anticancer therapies)

The Hess 2021 study is based on the Flatiron Foundation Medicine Clinico-Genomic database, which contains data of more than 2 million patients from 265 oncology clinics in the USA. The study included 5807 adult patients with metastatic NSCLC of whom 46 patients with RET fusion-positive tumour. To be included in the study, patients had to have started their initial systemic therapy within 180 days after the diagnosis of the metastatic stage and on 1 January 2011 or later. As the study was intended to reflect standard practice, all types of systemic therapies were possible. The 46 patients with RET fusion-positive tumour received various systemic therapies in their first-line treatment, including chemotherapy (partly with bevacizumab) and PD-1/PD-L1 antibodies as monotherapy or in combination with chemotherapy. 23 of the 46 patients with RET fusion-positive tumour subsequently received second-line treatment; the company considered this patient group (n = 23) for its comparisons. However, the publication provides no information on which systemic therapies these patients received in their second-line treatment and which pretreatment (= first-line therapy) was performed before. The aim of the study was to compare patient characteristics and clinical outcomes, such as overall survival, depending on the RET fusion status, but results for the second-line (n = 23) were only available for tumour response.

Moreover, the company used the Flatiron database to generate a control arm (referred to as "standard of care [SOC]" by the company), for which it selected patients from the database using defined criteria (e.g. criteria for pretreatment, see Section 1.3.2.3). The 11 patients

analysed in this SOC control arm were treated under consideration of the following therapies: bevacizumab or pembrolizumab + carboplatin with/without pemetrexed, pembrolizumab monotherapy, docetaxel + ramucirumab, alectinib, paclitaxel with/without carboplatin, vandetanib.

Drilon 2016 (chemotherapy)

The Drilon Study 2016 included 104 patients with advanced lung cancer and various tumour mutations of whom 18 patients had RET fusion-positive tumour. The patients were treated at the Memorial Sloan Kettering Cancer Center in New York (USA) between 2007 and 2014. The patients received pemetrexed monotherapy or combined chemotherapy as intervention and, if applicable, also as pretreatment; immune-based therapies, by contrast, were completely excluded. Of the 18 patients with RET fusion, 14 patients received first-line treatment and 4 patients received second-line treatment or a higher line of treatment. Primary outcome of the study was a comparison of PFS between patients with various tumour mutations.

Guisier 2020 (study IMAD 2, PD-1/PD-L1 antibodies)

The study IMAD 2 included 107 adult patients from centres of the French Lung Cancer Group with metastatic NSCLC and various tumour mutations of whom 9 patients had RED fusion. The 9 patients were treated with a PD-1/PD-L1 antibody in monotherapy in any line of treatment; 6 of them were in the second line. Chemotherapy or tyrosine kinase inhibitors were named as prior therapies of the patients. Patients who were already participating in a clinical study for an immunotherapy were excluded from the present study. Aim of the study was the recording of outcomes such as “PFS”, “tumour response” and “overall survival” depending on the tumour mutation.

1.3.2.3 Comparisons of individual arms from different studies

In order to compare selpercatinib with the ACT, the company at first provided a descriptive presentation of the results for the outcomes “overall survival”, “PFS” and “tumour response” for its patient groups A1 and A2 and compared them with those of the 5 studies in its study pool. In Module 4 A, it presented the second data cut-off (16 December 2019) and in the Appendix, it presented the third data cut-off (30 March 2021) For the derivation of the added benefit of selpercatinib, the company ultimately considered the following studies for comparison with the therapies used there for the outcomes mentioned above based on the second data cut-off:

Patient group A1 (second line):

- overall survival: Mazieres 2019 (PD-1/PD-L1 antibodies)
- PFS: Shen 2020 (chemotherapy), Mazieres 2019 (PD-1/PD-L1 antibodies)
- tumour response: Mazieres 2019 (PD-1/PD-L1 antibodies), Hess 2021 (systemic anticancer therapies)

Patient group A2 (third line and higher lines):

- overall survival: Mazieres 2019 (PD-1/PD-L1 antibodies)
- PFS: Mazieres 2019 (PD-1/PD-L1 antibodies)
- tumour response: Hess 2021 (systemic anticancer therapies)

For the comparisons presented, the company took Kaplan-Meier curves from available sources, where available, which are necessary for a comparison based on individual patient data. The Kaplan-Meier curves were digitised by the company to extract the underlying patient-specific data and were used for event time analyses.

Overall, the company did not consider the studies Drilon 2016 and Guisier 2020. It justified its approach by claiming that the relevant patient groups identified by it within the two studies were too small.

For the outcomes "overall survival" and "PFS", the company presented additional results from the Flatiron database as supplementary information, which it used to generate a control arm (under treatment with standard therapy; referred to as "SOC" by the company, see Section 1.3.2.2). For this purpose, the company analysed data from 11 patients who met the following criteria:

- presence of advanced/metastatic NSCLC
- presence of an (exclusive) RET fusion
- pretreatment with at least one systemic therapy, ([platinum-based] chemotherapy, PD-1/PD-L1 antibodies or PD-1/PD-L1 antibodies in combination with antibodies)
- start of systemic anti-cancer therapy in the subsequent line of therapy no earlier than 1 May 2017 (this is consistent with the start of inclusion in the LIBRETTO-001 study)
- no pretreatment with a selective RET inhibitor (e.g. cabozantinib or vandetanib)

Deviating from the presentation of the results from the other comparisons of individual arms, the company did not calculate the effect estimations separately for patient groups A1 and A2 when comparing the supplementary results from the Flatiron database.

Overall, the company claimed a hint of non-quantifiable added benefit for selpercatinib based on an overall consideration of the present evidence (comparisons of individual arms from different studies as well as the LIBRETTO-001 study).

1.3.3 Assessment of the evidence presented by the company

The data presented by the company in Module 4 A are unsuitable for the benefit assessment of selpercatinib versus the ACT. This is explained below.

The non-controlled study LIBRETTO-001 permits no conclusions on the added benefit

The company presented the results of the non-controlled LIBRETTO-001 study and performed descriptive considerations of the results. When describing the added benefit, the company also referred to intraindividual comparisons on best response according to imaging techniques under the last treatment before study inclusion and under treatment with selpercatinib.

The results from the LIBRETTO-001 study alone are not suitable for the assessment of the added benefit of selpercatinib compared to the ACT, as they do not allow a comparison with the ACT.

The patient groups A1 and A2 formed by the company are unsuitable to answer the research questions of the benefit assessment

In its dossier, the company divided the patients of the LIBRETTO-001 study with advanced RET fusion-positive NSCLC who received systemic therapy after platinum-based chemotherapy and/or treatment with immunotherapy only according to the number of prior therapies. In doing so, it distinguished between patients with 1 prior therapy (patient group A1 [second line]) and those who had received at least 2 prior therapies (patient group A2 [third line and higher lines]). Deviating from this, the G-BA differentiated the patients according to the type of their first-line therapy (PD-1/PD-L1 antibody as monotherapy vs. cytotoxic chemotherapy vs. PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy or sequential therapy with a PD-1/PD-L1 antibody and a platinum-containing chemotherapy).

The company stated that the G-BA determined corresponding patient groups when specifying the ACT. It explained having conducted subgroup analyses for LIBRETTO-001 to represent this classification. However, these were only performed for its patient group A1. According to the company, this results in the following subgroups for the efficacy analysis set:

- 9 patients (12%) with a monotherapy with a PD1 antibody as first-line treatment (subgroup 1)
- 34 patients (40%) with chemotherapy as first-line treatment (subgroup 2)
- 23 patients (29%) with a PD1 antibody and platinum-based chemotherapy as first-line treatment (subgroup 3)
- 12 patients (15%) with other prior therapies as first-line treatment (subgroup 4)

Subgroups 1 and 2 correspond to research questions 1 and 2 of the G-BA. The patients from subgroup 3, i.e., those pretreated with a PD-1 antibody and platinum-based chemotherapy as first-line treatment, however, had to be assigned to patient group 3 defined by the G-BA. These patients as well as those with more than 1 prior line of treatment (as in patient group A2 of the company: third line and higher) were considered by the G-BA in a joint research question. An individual therapy is specified as ACT for this total group. Based on the information provided

by the company on subgroup 4, it is unclear which therapies these patients received as pretreatment and whether the approval of selpercatinib includes these therapies as pretreatment.

The company did not consider its subgroup analyses on the intervention side for the submitted comparisons of individual arms from different studies. In Module 4 A, the company only described that the subgroup analyses from the LIBRETTO-001 study provided no hint of a possible modification of the therapeutic effect by the pretreatment.

Overall, the data from the LIBRETTO-001 study presented by the company are not usable for the benefit assessment. However, it can be assumed that basically relevant populations from the study can be delimited according to the G-BA's research questions.

Deviations from the specifications of the SPC in LIBRETTO-100.

Irrespective of the fact that no comparative data are available, the interpretability of the presented results of the LIBRETTO-001 study is limited, as the specifications of the SPC are not fulfilled in the subpopulations operationalized by the company for a relevant proportion of the patients in the third data cut-off:

Patient group A1 - safety analysis set:

- The starting dose deviated from the starting dose recommended in the SPC in 17 (20%) patients.
- Information on the proportion of patients who received an approval-compliant maintenance dose (160 mg twice daily or 120 mg twice daily). From the available information, it can be estimated that a maximum of 17 patients (20%) did not receive the correct maintenance dose.
- 19 (22%) patients were treated beyond progression, contrary to the specifications of the SPC.

Patient group A2 - safety analysis set:

- The starting dose deviated from the starting dose recommended in the SPC in 53 (31 %) patients.
- Information on the proportion of patients who received an approval-compliant maintenance dose (160 mg twice daily or 120 mg twice daily). From the available information, it can be estimated that a maximum of 38 patients (22 %) had not received the correct maintenance dose.
- 76 patients (44%) had received a multikinase inhibitor as prior therapy. Thus, at least 48 patients (28%) were treated in a way that was not compliant with the approval before being included in the LIBRETTO-001 study.
- 37 (21 %) patients were treated beyond progression, contrary to the specifications of the SPC.

Overall, for both patient groups A1 and A2, more than 20% of the considered patients included in the LIBRETTO-001 study were thus treated in a way that did not comply with the approval, which limits the interpretability of the results from the LIBRETTO-001 study presented by the company. Moreover, a large proportion of patients in patient group A2 had received drugs that were not approved in the therapeutic indication before being included in the study.

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

As described in Section 1.3.2, the company compared results on the outcomes "overall survival", "PFS" and "tumour response" from different studies for the comparison of selpercatinib with the options of the ACT for adult patients with advanced RET fusion-positive NSCLC who require systemic therapy after platinum-based chemotherapy and/or treatment with immunotherapy - divided into patient group A1 and A2. Irrespective of the described deviations in the formation of the subpopulations and the use of selpercatinib in the LIBRETTO-001 study, the data presented by the company on the ACT cannot be used for comparisons of individual arms from different studies (see also Table 11 in Appendix B of the full dossier assessment).

Due to the operationalization of the outcomes, only "overall survival" represents a patient-relevant outcome among the outcomes considered by the company. Therefore, only the comparisons on overall survival will be discussed in more detail below. For this outcome, the company only used the Mazieres 2019 study, in which the patients received PD-1/PD-L1 antibodies in any line of treatment. However, the results from this comparison are not interpretable for the following reasons:

on patient group A1 of the company:

- 100% of the patients of the LIBRETTO-001 study considered in patient group A1 were in the second line of treatment. However, it is unclear who of the relevant patients from the Mazieres 2019 study (n = 16) are to be assigned to which line of treatment. The publication shows that about 40% of the patients in the total population (N = 551) are in the second line, but 53% of the patients are in higher lines of treatment. Even under the assumption of the company that these proportions in the overall population can also be transferred to the relevant patient population, the patients from LIBRETTO-001 and Mazieres 2019 are not comparable with regard to their lines of treatment.
- More than 40% of the patients in the LIBRETTO-001 study had already received a PD-1/PD-L1 antibody as prior therapy. A comparison with a PD-1/PD-L1 antibody therapy is not suitable for these patients, as re-treatment with a PD-1/PD-L1 antibody is not indicated for such patients according to the G-BA's ACT. However, the Mazieres 2019 study considered by the company represents precisely this comparison.

on patient group A2 of the company:

- All of the patients of the LIBRETTO-001 study considered in patient group A2 had at least 2 prior therapies, 65% of them already had PD-1/PD-L1 pretreatment. For patients in this line of treatment, a comparison versus a PD-1/PD-L1 antibody does not correspond to the ACT specified by the G-BA,

Irrespective of the previously mentioned points relating to the patient groups, the procedure of the company for presenting the results from the comparisons is overall selective and also calls the interpretability of the results from the comparison into question. This is justified below:

On the comparator side, the company only considered the Mazieres 2019 study for its comparisons of the outcome "overall survival". This outcome was also recorded in the studies Guisier 2020 and Drilon 2016 identified by the company. However, the company did not include these studies because the patient groups comprise fewer than 10 patients (Drilon 2016: 4 patients with RET fusion-positive NSCLC in the second line; Guisier 2020: 9 patients with RET fusion-positive NSCLC, of whom 6 patients in the second line and 3 patients in higher therapy lines). This approach is not adequate given the small number of patients in all included studies, especially as the number of prior lines of treatment is similar in Guisier 2020 compared to Mazieres 2019.

When comparing the results on overall survival after 12 months for patients with RET fusion-positive NSCLC from Mazieres 2019 with those from Guisier 2020, it can be seen that the 12-month survival rate is lower in Mazieres 2019 (53.9%) than in Guisier 2020 (88.9%). The authors of Guisier 2020 (PD-1/PD-L1 antibodies) discussed the results deviating from Mazieres 2019 to the effect that the patients in their study are in an earlier line of treatment (approximately 70% in the second line and 30% in the third or a higher line for patients with RET fusion-positive NSCLC). In the Drilon 2016 study identified by the company (chemotherapy; patients predominantly in the first line), patients also died significantly later than in Mazieres 2019. These aspects underline a suspected bias caused by patients with a higher line of treatment in Mazieres 2019. The company itself did not comment these uncertainties.

Moreover, it remains unclear why the company did not use the additional analysis from the Flatiron database on overall survival (for the comparison with the SOC control arm), although this is based on more than 10 patients.

Irrespective of this, the comparisons presented by the company were comparisons of individual arms from different studies without adjustment for potentially relevant effect modifiers or prognostic factors. Due to the lack of randomization, these are subject to inherent uncertainty, so that an added benefit can only be derived if the effects are sufficiently large. In order to be able to interpret these at all, however, patient populations with similar characteristics are required. This does not apply to the comparisons presented by the company.

Completeness of the study pool on the comparator side questionable

Supplementary, it should be noted that the company's information retrieval on the ACT is not suitable for ensuring the completeness of the search results. The search strategies in the bibliographic databases MEDLINE and Embase, for instance, were not implemented with sufficient sensitivity. For example, the company severely restricted the searches with the search blocks for intervention and therapeutic indication, so that several publications on the studies submitted by the company were not identified (Guisier 2020, Hess 2021).

Conclusion

The results presented by the company are unsuitable for the assessment of the added benefit of selpercatinib in comparison with the ACT. The results from the non-controlled study LIBRETTO-001 alone are not suitable for the benefit assessment, as data on the ACT are not available. Moreover, the comparisons of individual arms from different studies presented by the company are not suitable for conclusions on the added benefit, as the patients from LIBRETTO-001 and Mazieres 2019 are not comparable with regard to their lines of treatment. In addition, the comparisons used by the company do not reflect the research questions of the G-BA and the associated ACT options.

1.4 Results on added benefit

There are not suitable data for the assessment of the added benefit of selpercatinib in comparison with the ACT in adult patients with advanced RET fusion-positive NSCLC who require systemic therapy following platinum-based chemotherapy and/or treatment with immunotherapy. This resulted in no hint of an added benefit of selpercatinib in comparison with the ACT for all 3 research questions.

1.5 Probability and extent of added benefit

The result of the assessment of the added benefit of selpercatinib in comparison with the ACT is summarized in Table 5.

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a PD-1/PD-L1 antibody[a] as monotherapy	▪ Cisplatin[c] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[d]) or ▪ carboplatin[c] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[d]); see also Appendix VI to Section K of the Pharmaceutical Directive ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[e]	Added benefit not proven
2	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a cytotoxic chemotherapy	▪ Docetaxel[f] or ▪ pemetrexed[g] or ▪ nivolumab or ▪ pembrolizumab[h] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[i]	Added benefit not proven
3	Adult patients with advanced RET fusion-positive NSCLC for whom systemic therapy is indicated; after first-line therapy with a PD-1/PD-L1 antibody[a] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[a] and platinum-containing chemotherapy	▪ Individual treatment under consideration of pretreatment 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. Use of a PD-1/PD-L1 inhibitor within the pretreatment is not interpreted as a line of therapy to be considered with regard to the approval of pemetrexed, gemcitabine and nab-paclitaxel.
b. Presentation of the respective ACT specified by the G-BA. According to the G-BA, there are no standardized treatment recommendations for patients with RET fusion in the present therapeutic indication. Moreover, the G-BA assumes that the patients in the therapeutic indication had no indication for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF or ROS1) could be considered for the patients at the time of treatment with selpercatinib. It is also assumed that the patients were generally eligible for active antineoplastic therapy, which is why BSC was not considered as an ACT in the present case.
c. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the two substances and on the existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive.
d. Except in mainly squamous histology.
e. Only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment.
f. Only for patients with PD-L1-negative tumours.
g. Only for patients with PD-L1-negative tumours and except in mainly squamous histology.
h. Only for patients with PD-L1 expressing tumours (TPS ≥ 1 %).
i. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: Programmed Cell Death 1; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TPS: Tumour Proportion Score			

The assessment described above deviates from the company's assessment, which, on the basis of the second data cut-off of the non-controlled study LIBRETTO-001 and the comparisons of individual arms from different studies, derived a hint of a non-quantifiable added benefit for each of its patient groups A1 and A2.

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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