IQWiG Reports – Commission No. A22-65

Selpercatinib (RET fusion-positive NSCLC, first line) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Selpercatinib (RET-Fusions-positives NSCLC, Erstlinie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 September 2022). 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback of persons concerned or patient organizations was received within 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
ALK	anaplastic lymphoma kinase
CI	confidence interval
EGFR	Epidermal Growth Factor Receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GHD	Guardant Health Datenbank
GHD	Guardant Health Database
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
MTD	maximum tolerable dose
NSCLC	non-small cell lung cancer
PD-1	programmed cell death protein 1;
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
RCT	Randomized controlled Trial (randomisierte kontrollierte Studie)
RET	rearranged during transfection
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 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 30 June 2022.

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 have not previously been treated with a RET inhibitor. Subject of the present benefit assessment are adult patients in the first-line setting. The assessment of selpercatinib in adult patients with advanced RET fusion-positive NSCLC who require systemic therapy following prior platinum-based chemotherapy and/or treatment with immunotherapy, was already conducted (see dossier assessment A21-27 as well as decision and justification of the G-BA) and was not subject of the present benefit assessment.

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

Table 2: Research questions of the benefit assessment of selpercatinib

Research question	Therapeutic indication	ACT[a]
1	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in ≥ 50% of tumour cells; first-line therapy	Pembrolizumab as monotherapy
2	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in < 50% of tumour cells; first-line therapy	▪ Cisplatin[b] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[c]) or ▪ carboplatin[b] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[c]); see also Appendix VI to Section K of the pharmaceutical directive or ▪ carboplatin in combination with nab-paclitaxel or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel[e] or ▪ monotherapy with gemcitabine or vinorelbine[f]

a. Presented is the respective ACT specified by the G-BA. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against EGFR, ALK, BRAF or ROS1) is not an option for the patients at the time of treatment with selpercatinib. The patient group of adults with advanced RET fusion-positive NSCLC who have received a therapy other than a PD-1/PD-L1 antibody or platinum-containing chemotherapy is not considered relevant for the benefit assessment of selpercatinib in the present therapeutic indication due to an indication extension to first-line treatment.
b. In each case, the platinum component (carboplatin or cisplatin) was to be selected based on the two substances' differing toxicity profiles and on existing comorbidities; see Appendix VI of Section K of the German Pharmaceutical Directive.
c. Except in mainly squamous histology.
d. Only for patients without EGFR-positive or ALK-positive tumour mutations and with non-squamous histology.
e. Only in case of squamous histology.
f. Only for patients with ECOG PS 2 as an alternative to platinum-based combination therapy.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; 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

In the formulation of its research questions, the company followed the G-BA's specification. When naming the ACT, the company deviates from the G-BA's specification in so far as it adds an additional treatment option to the ACT for each research question:

- Research question 1: pembrolizumab in combination with pemetrexed and a platinum-based chemotherapy

- Research question 2: nivolumab in combination with ipilimumab and 2 cycles of a platinum-based chemotherapy

In this context, the company stated that these options could be considered as ACT in view of the currently valid treatment guidelines and due to their high therapeutic relevance. The specification of these options by the company has no consequences for the present assessment, as the company presented no evidence in comparison with the additional treatment options named by it.

The present assessment was conducted on the basis of the two research questions specified by the G-BA (populations and corresponding ACTs). The assessment is 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 RCTs on the direct comparison or on the adjusted indirect comparison using a common comparator of selpercatinib versus the ACT. For research question 2, the potentially relevant RCT LIBRETTO-431 was identified, which included adult patients with advanced or metastatic RET fusion-positive NSCLC receiving either selpercatinib or platinum-based chemotherapy + pemetrexed with or without pembrolizumab. However, results of this ongoing study are not yet available.

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.

Evidence presented by the company on the selpercatinib study LIBRETTO-001

LIBRETTO-001 is an ongoing, non-controlled, prospective basket 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 in several patient cohorts. Treatment with selpercatinib in phase 2 of the LIBRETTO-001 study was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). The two phases have already been described in detail in dossier assessment A21-27.

Patients with advanced RET fusion-positive NSCLC without prior systemic treatment are relevant for the present therapeutic indication (subpopulation NSCLC 1L of the company). 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 LIBRETTO-001 study and the regulatory analyses.

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. In addition, from the point of view of the company, high rates of overall survival and progression-free survival (PFS), as well as high rates of patients with an objective tumour response are shown.

Evidence presented by the company for the ACT

On the comparator side, the company identified the studies Gautschi 2017, Lee 2020, Shen 2020 (all 3 with intervention chemotherapy [different regimens]) and Bhandari 2021 (intervention: programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) antibodies in combination with platinum-based chemotherapy) 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. Moreover, the company identified 6 further studies on the ACT, which it did not use for its comparisons because, according to the company, no differentiated presentation of the comparator therapies or no differentiated presentation for patients with RET fusion took place in these studies or less than 10 patients with RET fusion-positive NSCLC in the first line were included.

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 of the fourth data cut-off (15 June 2021) for the outcomes "overall survival", "PFS" and "tumour response" for its subpopulation NSCLC 1L and compared them with those of the 4 studies in its study pool. For the outcome "tumour response", the company additionally calculated approximate relative risks with 95% confidence intervals (CIs) and p-values on the basis of the descriptive comparison.

Kaplan-Meier curves for the outcomes "overall survival" and "PFS", which are necessary for a comparison based on individual data, were available from the Shen 2020 study. The Kaplan-Meier curves were digitised by the company to extract the underlying patient-specific data and were used for event time analyses. The company presented both unweighted comparisons and matching-adjusted indirect comparison (MAIC) analyses based on these individual data.

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).

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 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. Moreover, the characteristic of PD-L1 expression was not recorded in the

LIBRETTO-001 study. Thus, it is not possible to differentiate the study population according to the research questions defined by the G-BA.

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

The data on the ACT presented by the company for the comparison of individual arms from different studies are not usable for the following reasons:

- In its specification of the ACT in the approved therapeutic indication, the G-BA differentiated between 2 research questions (PD-L1 expression ≥ 50% or < 50% of the tumour cells) for which the treatment options differ. None of the studies used by the company for its comparisons provides data on the PD-L1 expression (≥ 50% vs. < 50%) of the tumour cells. Therefore, it is not possible to say whether the patients in the studies on the comparator side received a therapy according to the specifications for the ACT. For example, for the Shen study (intervention: chemotherapy) it is unclear whether patients with a PD-L1 expression ≥ 50% of the tumour cells are included, for whom a therapy with pembrolizumab rather than chemotherapy would represent the adequate ACT.
- The comparisons presented by the company are comparisons of individual arms from different studies without adjustment regarding potentially relevant effect modifiers or prognostic factors. These are subject to inherent uncertainty due to the lack of randomization.
- MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment. In case of non-randomized comparisons without a common comparator, meaningful approaches towards confounder adjustment are usually only those that - unlike the MAIC analysis - involve the use of individual patient data. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data.

Irrespective of the implementation of the ACT in the comparator studies, the comparisons performed by the company are thus not suitable for the assessment of the added benefit of selpercatinib.

Conclusion

In summary, no suitable data are available for assessing the added benefit of selpercatinib in comparison with the ACT in adult patients with advanced RET fusion-positive NSCLC in the first line. 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. On the other hand, the comparison of individual arms from different studies presented by the company are not suitable for conclusions on the added benefit, as there is no subdivision according to PD-L1 expression and it is therefore not possible to verify whether the patients in the studies on the comparator side received a therapy according to the specifications for the ACT.

Probability and extent of added benefit

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

Table 3: Selpercatinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in ≥ 50% of tumour cells; first-line therapy	Pembrolizumab as monotherapy	Added benefit not proven
2	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in < 50% of tumour cells; first-line therapy	▪ Cisplatin[b] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[c]) or ▪ carboplatin[b] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[c]); see also Appendix VI to Section K of the pharmaceutical directive or ▪ carboplatin in combination with nab-paclitaxel or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel[e] or ▪ monotherapy with gemcitabine or vinorelbine[f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against EGFR, ALK, BRAF or ROS1) is not an option for the patients at the time of treatment with selpercatinib. The patient group of adults with advanced RET fusion-positive NSCLC who have received a therapy other than a PD-1/PD-L1 antibody or platinum-containing chemotherapy is not considered relevant for the benefit assessment of selpercatinib in the present therapeutic indication due to an indication extension to first-line treatment.
b. In each case, the platinum component (carboplatin or cisplatin) was to be selected based on the 2 substances' differing toxicity profiles and on existing comorbidities; see Appendix VI of Section K of the German Pharmaceutical Directive.
c. Except in mainly squamous histology.
d. Only for patients without EGFR-positive or ALK-positive tumour mutations and with non-squamous histology.
e. Only in case of squamous histology.
f. Only for patients with ECOG PS 2 as an alternative to platinum-based combination therapy.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1

The G-BA decides on the added benefit.

I 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 NSCLC who have not previously been treated with a RET inhibitor. Subject of the present benefit assessment are adult patients in the first-line setting. The assessment of selpercatinib in adult patients with advanced RET fusion-positive NSCLC who require systemic therapy following prior platinum-based chemotherapy and/or treatment with immunotherapy, was already conducted (see dossier assessment A21-27 [1] as well as decision [2] and justification [3] of the G-BA) and was not subject of the present benefit assessment.

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

Table 4: Research questions of the benefit assessment of selpercatinib

Research question	Therapeutic indication	ACT[a]
1	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in ≥ 50% of tumour cells; first-line therapy	Pembrolizumab as monotherapy
2	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in < 50% of tumour cells; first-line therapy	▪ Cisplatin[b] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[c]) or ▪ carboplatinb in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[c]); see also Appendix VI to Section K of the pharmaceutical directive or ▪ carboplatin in combination with nab-paclitaxel or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel[e] or ▪ monotherapy with gemcitabine or vinorelbine[f]

a. Presented is the respective ACT specified by the G-BA. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against EGFR, ALK, BRAF or ROS1) is not an option for the patients at the time of treatment with selpercatinib. The patient group of adults with advanced RET fusion-positive NSCLC who have received a therapy other than a PD-1/PD-L1 antibody or platinum-containing chemotherapy is not considered relevant for the benefit assessment of selpercatinib in the present therapeutic indication due to an indication extension to first-line treatment.
b. In each case, the platinum component (carboplatin or cisplatin) was to be selected based on the 2 substances' differing toxicity profiles and on existing comorbidities; see Appendix VI of Section K of the German Pharmaceutical Directive.
c. Except in mainly squamous histology.
d. Only for patients without EGFR-positive or ALK-positive tumour mutations and with non-squamous histology.
e. Only in case of squamous histology.
f. Only for patients with ECOG PS 2 as an alternative to platinum-based combination therapy.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1

In the formulation of its research questions, the company followed the G-BA's specification. When naming the ACT, the company deviates from the G-BA's specification in so far as it adds an additional treatment option to the ACT for each research question:

- Research question 1: pembrolizumab in combination with pemetrexed and a platinum-based chemotherapy
- Research question 2: nivolumab in combination with ipilimumab and 2 cycles of a platinum-based chemotherapy

In this context, the company stated that these options could be considered as ACT in view of the currently valid treatment guidelines [4,5] and due to their high therapeutic relevance. The specification of these options by the company has no consequences for the present assessment, as the company presented no evidence in comparison with the additional treatment options named by it.

The present assessment was conducted on the basis of the two research questions specified by the G-BA (populations and corresponding ACTs). The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Since no usable data are available for any of the research questions named by the G-BA, the 2 research questions are assessed together below (see Chapter I 3 to I 5).

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on selpercatinib (status: 13 April 2022)
- bibliographical literature search on selpercatinib (last search on 13 April 2022)
- search in trial registries/trial results databases for studies on selpercatinib (last search on 13 April 2022)
- search on the G-BA website for selpercatinib (last search on 13 April 2022)
- bibliographical literature search on the ACT (last search on 13 April 2022)
- search in trial registries/trial results databases for studies on the ACT (last search on 13 April 2022)
- search on the G-BA website for the ACT (last search on 13 April 2022)

To check the completeness of the study pool:

- search in trial registries for studies on selpercatinib (last search on 20 July 2022); for search strategies, see I Appendix A of the full dossier assessment

(Concurring with the company), the check of the completeness of the study pool identified no RCTs on the direct comparison or on the adjusted indirect comparison using a common comparator of selpercatinib versus the ACT.

For research question 2, the potentially relevant RCT LIBRETTO-431 [6,7] was identified, which included adult patients with advanced or metastatic RET fusion-positive NSCLC receiving either selpercatinib or platinum-based chemotherapy + pemetrexed with or without pembrolizumab. However, results of this ongoing study are not yet available.

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.

I 3.1 Evidence provided by the company

For selpercatinib, the company included the non-controlled basket study LIBRETTO-001 [8-12] and used the subpopulation of adult patients with advanced RET fusion-positive NSCLC without prior systemic therapy (first line, subpopulation NSCLC 1L of the company).

Moreover, the company used comparisons of individual arms from different studies. For these comparisons, the company identified 4 studies (Gautschi 2017 [13], Lee 2020 [14], Shen 2020 [15], Bhandari 2021 [16]).

I 3.1.1 Evidence on selpercatinib

Study LIBRETTO-001

LIBRETTO-001 is an ongoing, non-controlled, prospective basket study organized in 2 phases. The MTD was determined in the already completed phase 1. In the ongoing phase 2, the MTD was applied in several patient cohorts. Treatment with selpercatinib in phase 2 of the LIBRETTO-001 study was largely in compliance with the specifications of the SPC [17]. The two phases were already described in detail in dossier assessment A21-27 [1].

Data cut-offs and analysis populations

According to the company, 5 data cut-offs are available for the LIBRETTO-001 study:

- Data cut-off 1: 17 June 2019 with 531 patients (interim analysis)
- Data cut-off 2: 16 December 2019 with 702 patients (interim analysis, which provides the basis for the European approval)
- Data cut-off 3: 30 March 2020 with 746 patients (data cut-off requested by the Japanese regulatory authority; confirmatory data cut-off for the European approval)
- Data cut-off 4: 15 June 2021 with 796 patients (interim analysis, which is the basis for the European approval of the indication extension [first-line treatment of the advanced RET fusion-positive NSCLC])
- Data cut-off 5: 24 September 2021 with 45 patients (in consultation with the US regulatory authority; only includes data from cohorts of RET fusion-positive tumours except NSCLC and thyroid cancer)

Patients with advanced RET fusion-positive NSCLC without prior systemic treatment are relevant for the present therapeutic indication (subpopulation NSCLC 1L of the company). 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 LIBRETTO-001 study and the regulatory analyses. Of the 69 patients relevant to this therapeutic indication, 8 (11.6%) received a selpercatinib starting dose that deviated from the recommendations in the SPC.

Analogous to dossier assessment A21-27, the company distinguished between 2 analysis populations in the dossier, the safety analysis set and the efficacy analysis set. The analyses on

adverse events were based on the safety analysis set, which includes all patients who had received at least 1 dose of selpercatinib. The analyses of the benefit outcomes were based on the efficacy analysis set, which only included patients who had either received ≥ 6 months of treatment or whose treatment had been discontinued within 6 months after start of the therapy. At the time of the fourth data cut-off, on which the analyses presented by the company are based, these two analysis sets were identical.

Presented results

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 (particularly pain, fatigue and dyspnoea) and an improvement in quality of life. In addition, from the point of view of the company, high rates of overall survival and PFS, as well as high rates of patients with an objective tumour response are shown.

I 3.1.2 Evidence on the ACT

On the comparator side, the company identified the studies Gautschi 2017, Lee 2020, Shen 2020 and Bhandari 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 6 in Appendix B of the full dossier assessment). Moreover, the company identified 6 further studies on the ACT [18-23], which it did not use for its comparisons because, according to the company, no differentiated presentation of the comparator therapies or no differentiated presentation for patients with RET fusion took place in these studies or less than 10 patients with RET fusion-positive NSCLC in the first line were included.

Gautschi 2017 (chemotherapy)

The Gautschi 2017 study included 165 patients with RET fusion-positive NSCLC. The patients were identified in a total of 29 study centres in Europe, Asia and the United States between June 2015 and April 2016. Patients could have already received 1 or more prior therapy(ies). Therapies administered for NSCLC were a RET inhibitor or a systemic chemotherapy. 84 patients received platinum-based chemotherapy in the first line, predominantly in combination with pemetrexed (66 or 84 patients). The company considered these 84 patients for the comparison of overall survival and PFS. However, the publication provides no information on the treatment or observation periods or on the PD-L1 expression of the tumour cells. For 18 of these patients, it is also unclear which platinum-based chemotherapy they received. The aim of this study was to describe the clinical-pathological characteristics of patients with RET fusion-positive NSCLC and to document the clinical course under systemic therapy.

Lee 2020 (chemotherapy)

The Lee 2020 study included 59 patients with RET fusion-positive NSCLC who had been treated at the Samsung Medical Center in Seoul (South Korea) between January 2006 and

January 2018. The patients could have already received one or more prior therapies, but no further related information is available. Systemic chemotherapies, immunotherapies or kinase inhibitors were administered as treatment of the NSCLC. 36 patients received pemetrexed-based chemotherapy in the first line and were considered by the company for the comparison of tumour response. The publication provides no information on the treatment or observation periods or on the PD-L1 expression of the tumour cells. The aim of the study was to analyse the clinical characteristics and the tumour response of patients with RET fusion-positive NSCLC.

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 platinum-based chemotherapy with or without pemetrexed or pemetrexed as monotherapy in the first-line setting. For the comparison, the company used 38 patients for whom data on overall survival and PFS were available. The publication provides no information on the treatment or observation periods or on the PD-L1 expression of the tumour cells. Based on the available Kaplan-Meier curve, only assumptions can be made about the observation period. The aim of the study was to compare overall survival and PFS between patients who received pemetrexed-based chemotherapy and those who received another type of chemotherapy.

Bhandari 2021 (PD-1/PD-L1 antibodies in combination with platinum-based chemotherapy)

The Bhandari 2021 study is based on the Flatiron Health-Foundation Medicine Clinico-Genomic Database (CGDB) and the Guardant Health Database (GHD). The data of a total of 69 patients with advanced RET fusion-positive NSCLC who received immunotherapy with checkpoint inhibitors with or without other substances regardless of the line of treatment were analysed in this publication. 19 patients received a therapy regimen of carboplatin, pemetrexed and pembrolizumab in the first-line, with 7 patients coming from the GHD and 12 patients coming from the CGDB. For its comparisons, the company only considered 12 patients from the CGDB. It is not clear from the publication which epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutation status and which histology the tumours of these patients have. In addition, information on PD-L1 expression is lacking for 55% of the 69 patients. For the remaining 45%, PD-L1 expression is divided into ≥ 1% and < 1% of tumour cells. The aim of the study was to describe clinical outcomes such as overall survival, PFS or tumour response in patients with advanced RET fusion-positive NSCLC who received immunotherapy.

I 3.1.3 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 of the fourth data cut-off "(15 June 2021) for the outcomes "overall survival", "PFS" and "tumour response" for its subpopulation NSCLC 1L and compared them with those of the 4 studies in its study pool. For the outcome "tumour response", the company additionally calculated approximate relative risks with 95% CIs and p-values on the basis of the descriptive comparison.

Kaplan-Meier curves for the outcomes "overall survival" and "PFS", which are necessary for a comparison based on individual data, were available from the Shen 2020 study. The Kaplan-Meier curves were digitised by the company to extract the underlying patient-specific data and were used for event time analyses. The company presented both unweighted comparisons and MAIC analyses based on these individual data.

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).

I 3.2 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. 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. Moreover, the characteristic of PD-L1 expression was not recorded in the LIBRETTO-001 study. Thus, it is not possible to differentiate the study population according to the research questions defined by the G-BA (see also the following text and Table 4).

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

As described in Section I 3.1, 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 without prior systemic therapy (first-line). The data on the ACT presented by the company for the comparison of individual arms from different studies are not usable. This is justified below.

Implementation of the ACT

In its specification of the ACT in the approved therapeutic indication, the G-BA differentiated between 2 research questions.

- Patients with PD-L1 expression ≥ 50% of tumour cells
- Patients with PD-L1 expression < 50% of tumour cells

The observation options differed between these two research questions (see Table 4). None of the studies used by the company for its comparisons provides data on the PD-L1 expression (≥ 50% vs. < 50%) of the tumour cells. Therefore, it is not possible to say whether the patients in the studies on the comparator side received a correct therapy according to the specifications for the ACT. For example, for the Shen study (intervention chemotherapy) it is unclear whether patients with a PD-L1 expression ≥ 50% of the tumour cells were included, for whom a therapy with pembrolizumab rather than chemotherapy would represent the adequate ACT. For the Shen study, it is also unclear whether all patients used by the company for the comparison were in the first line.

Method of the comparison of individual arms of different studies

For the outcomes of overall survival, PFS and tumour response, the company presented comparisons of individual arms or MAIC analyses without common comparator. In the comparisons of individual arms presented by the company, results from different studies are compared without adjustment for potentially relevant effect modifiers or prognostic factors. These are subject to inherent uncertainty due to the lack of randomization.

The MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment [24]. In case of non-randomized comparisons without a common comparator, meaningful approaches towards confounder adjustment are usually only those that - unlike the MAIC analysis - involve the use of individual patient data [25]. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data. Moreover, for the only patient-relevant outcome of overall survival, there are no effects for which it can be safely ruled out in the present situation of a comparison of individual arms from different studies that they do not result solely from a systematic bias due to confounding variables.

Irrespective of the implementation of the ACT in the comparator studies, the comparisons performed by the company are thus not suitable for the assessment of the added benefit of selpercatinib.

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. On the other hand, the comparisons of individual arms from different studies presented by the company are not suitable for conclusions on the added benefit, as a subdivision according to PD-L1 expression is not possible and it is therefore not possible to verify whether the patients in the studies on the comparator side received a correct option of the ACT.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of selpercatinib in comparison with the ACT in adult patients with advanced RET fusion-positive NSCLC without prior systemic treatment (first line). This resulted in no hint of an added benefit of selpercatinib in comparison with the ACT for both research questions; in each case, an added benefit is therefore not proven.

I 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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in ≥ 50% of tumour cells; first-line therapy	Pembrolizumab as monotherapy	Added benefit not proven
2	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in < 50% of tumour cells; first-line therapy	▪ Cisplatin[b] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[c]) or ▪ carboplatin[b] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[c]); see also Appendix VI to Section K of the pharmaceutical directive or ▪ carboplatin in combination with nab-paclitaxel or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel[e] or ▪ monotherapy with gemcitabine or vinorelbine[f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against EGFR, ALK, BRAF or ROS1) is not an option for the patients at the time of treatment with selpercatinib. The patient group of adults with advanced RET fusion-positive NSCLC who have received a therapy other than a PD-1/PD-L1 antibody or platinum-containing chemotherapy is not considered relevant for the benefit assessment of selpercatinib in the present therapeutic indication due to an indication extension to first-line treatment.
b. In each case, the platinum component (carboplatin or cisplatin) was to be selected based on the 2 substances' differing toxicity profiles and on existing comorbidities; see Appendix VI of Section K of the German Pharmaceutical Directive.
c. Except in mainly squamous histology.
d. Only for patients without EGFR-positive or ALK-positive tumour mutations and with non-squamous histology.
e. Only in case of squamous histology.
f. Only for patients with ECOG PS 2 as an alternative to platinum-based combination therapy.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1

The assessment described above deviates from the company's assessment, which, on the basis of the fourth 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 its subpopulation NSCLC 1L.

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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