IQWiG Reports – Commission No. A21-168

Pralsetinib (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 *Pralsetinib (RET-Fusions-positives NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 March 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Pralsetinib (RET fusion-positive NSCLC) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
14 December 2021

Internal Commission No.
A21-168

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Jörg Trojan, Frankfurt University Hospital, Frankfurt am Main, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

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

IQWiG employees involved in the dossier assessment

- Erika Baumbach
- Moritz Felsch
- Petra Kohlepp
- Ulrike Lampert
- Dominik Schierbaum
- Sonja Schiller
- Ulrike Seay
- Volker Vervölgyi

Keywords: Pralsetinib, Carcinoma – Non-Small-Cell Lung, Benefit Assessment

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MTC	medullary thyroid cancer
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
RET	rearranged during transfection
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pralsetinib. 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 14 December 2021.

Research question

The aim of the present report was to assess the added benefit of pralsetinib in comparison with the appropriate comparator therapy (ACT) in patients with rearranged during transfection (RET) fusion positive, advanced non-small cell lung cancer (NSCLC) who were previously untreated with a RET inhibitor.

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

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

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 monotherapy
2	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in < 50% of tumour cells; first-line therapy	▪ Cisplatin or carboplatin[b] in combination with a third-generation cytostatic[c] 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]
3	Adults with advanced RET fusion-positive NSCLC after first-line therapy with PD-1/PD-L1 antibody monotherapy	▪ Cisplatin or carboplatin in combination with a third-generation cytostatic[c] or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]
4	Adults with advanced RET fusion-positive NSCLC after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[h] or ▪ nivolumab or ▪ pembrolizumab[i] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[j]
5	Adults with advanced RET fusion-positive NSCLC after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-based chemotherapy	Individualized treatment, taking into account prior treatment and histology, with a choice of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine

a. Presented is the respective ACT specified by the G-BA. For the present therapeutic indication, it was assumed that patients were not indicated for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1) was an option for the patients at the time of treatment with pralsetinib. Patients were further assumed to be generally eligible for active antineoplastic therapy, and therefore, best supportive care was not an ACT option in the present case.
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. Vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in mainly squamous histology).
d. Only for patients without EGFR-positive or ALK-positive tumour mutations and with nonsquamous histology.
e. Only in case of squamous histology.
f. Only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment.
g. Only for patients with PD-L1-negative tumours.
h. Only for patients with PD-L1-negative tumours who do not have mainly squamous histology.
i. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
j. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

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

Research question	Therapeutic indication	ACT[a]
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; 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 wording of its research questions and the specification of the ACT, the company followed the G-BA only to some extent:

For research question 1 (adults with advanced RET fusion-positive NSCLC with programmed cell death ligand 1 [PD-L1] expression in ≥ 50% of tumour cells; first-line therapy), the company followed the G-BA, specifying pembrolizumab as the ACT (company's research question 1a).

For research question 2 (adults with advanced RET fusion-positive NSCLC with PD-L1 expression in < 50% of tumour cells; first-line therapy), the company partially followed the G-BA, listing only some of the G-BA's ACT options (company's research question 1b).

The company did not separately examine the G-BA's research questions 3 to 5, but analysed treatment-experienced patients jointly, in departure from the G-BA's specifications (company's research question 2). For all treatment-experienced patients, regardless of the type of prior therapy, the company listed some of the G-BA's ACT options for research question 4.

The company's deviations remain without consequence for the present assessment because the company did not submit any suitable evidence for pralsetinib in comparison with the ACT.

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's findings, the check of completeness of the study pool did not identify any relevant study for a direct or adjusted indirect comparison of pralsetinib with the ACT. However, the ongoing randomized controlled trial (RCT) AcceleRET Lung was found to be potentially relevant for research question 2. Said RCT enrolled treatment-naive patients with locally advanced or metastatic RET-fusion-positive NSCLC and treated them with either pralsetinib or platinum-based chemotherapy with or without pembrolizumab. Study results are not yet available.

Evidence provided by the company

Having found no RCTs for use in direct comparisons or adjusted indirect comparisons, the company additionally conducted an information retrieval for further studies on pralsetinib and

submitted results from the 1-arm ARROW study. The company conducted no information retrieval for further investigations on the ACT. Instead, it used data from the IMpower132 RCT for comparing individual arms from different studies. The check for completeness of the company's study pool identified no additional potentially relevant studies on pralsetinib. The completeness of the study pool on the ACT was not checked.

ARROW is a 1-arm study enrolling patients with RET-fusion-positive NSCLC, medullary thyroid cancer (MTC), or other RET-altered solid tumours. Patients are treated with pralsetinib once daily in 4-week cycles.

Lack of suitability of the data presented by the company for assessing benefit

The data presented by the company are unsuitable for drawing conclusions on the added benefit of pralsetinib versus the ACT for the following reasons:

- Due to its 1-arm design, the ARROW study is unsuitable for deriving any added benefit of pralsetinib in comparison with the ACT.
- The company did not conduct an information retrieval for further studies on the comparator therapy. For its intended comparison by means of propensity score analyses, the company used the IMpower132 study on the comparator side. However, the company's study pool for further investigations is potentially incomplete because the company failed to conduct an information retrieval on the ACT side.
- The company has conducted the propensity score analyses only for the outcomes of overall survival and progression-free survival and presented the results only as supplementary information. It presented results for outcomes on symptoms, health-related quality of life, and side effects only from the ARROW study. This renders the results submitted for the comparison of the ARROW and IMpower132 studies incomplete.
- Irrespective of these shortcomings, in the present scenario of indirect comparison without a common comparator, the identified effects are not sufficiently large to rule out with certainty that they result solely from systematic bias due to confounders.

In summary, no suitable data are available for assessing the added benefit of pralsetinib versus the ACT in adult patients with RET fusion-positive advanced NSCLC who had received no prior treatment with RET inhibitors. Hence, there is no hint of an added benefit of pralsetinib in comparison with the ACT; an added benefit is therefore not proven.

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

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

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

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

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 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 or carboplatin[b] in combination with a third-generation cytostatic[c] 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
3	Adults with advanced RET fusion-positive NSCLC after first-line therapy with PD-1/PD-L1 antibody monotherapy	▪ Cisplatin or carboplatin[b] in combination with a third-generation cytostatic[c] or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[e]	Added benefit not proven
4	Adults with advanced RET fusion-positive NSCLC after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[h] or ▪ nivolumab or ▪ pembrolizumab[i] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[j]	Added benefit not proven
5	Adults with advanced RET fusion-positive NSCLC after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-based chemotherapy	Individualized treatment, taking into account prior treatment and histology, with a choice of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine	Added benefit not proven

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. For the present therapeutic indication, it was assumed that patients were not indicated for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1) was an option for the patients at the time of treatment with pralsetinib. Patients were further assumed to be generally eligible for active antineoplastic therapy, and therefore, best supportive care was not an ACT option in the present case. 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. Vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in mainly squamous histology). d. Only for patients without EGFR-positive or ALK-positive tumour mutations and with nonsquamous histology. e. Only in case of squamous histology. f. Only for patients with ECOG-PS 2 as an alternative to platinum-based combination treatment. g. Only for patients with PD-L1-negative tumours. h. Only for patients with PD-L1-negative tumours who do not have mainly squamous histology. i. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells). j. 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; 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-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1			

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of pralsetinib in comparison with the ACT in patients with advanced RET fusion-positive NSCLC who have not previously been treated with a RET inhibitor.

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

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

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 monotherapy
2	Adults with advanced RET fusion-positive NSCLC with PD-L1 expression in < 50% of tumour cells; first-line therapy	▪ Cisplatin or carboplatin[b] in combination with a third-generation cytostatic[c] 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]
3	Adults with advanced RET fusion-positive NSCLC after first-line therapy with PD-1/PD-L1 antibody monotherapy	▪ Cisplatin or carboplatin[b] in combination with a third-generation cytostatic[c] or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]
4	Adults with advanced RET fusion-positive NSCLC after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[h] or ▪ nivolumab or ▪ pembrolizumab[i] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[j]
5	Adults with advanced RET fusion-positive NSCLC after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-based chemotherapy	Individualized treatment, taking into account prior treatment and histology, with a choice of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine

a. Presented is the respective ACT specified by the G-BA. For the present therapeutic indication, it was assumed that patients were not indicated for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1) was an option for the patients at the time of treatment with pralsetinib. Patients were further assumed to be generally eligible for active antineoplastic therapy, and therefore, best supportive care was not an ACT option in the present case.
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. Vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in mainly squamous histology).
d. Only for patients without EGFR-positive or ALK-positive tumour mutations and with nonsquamous histology.
e. Only in case of squamous histology.
f. Only for patients with ECOG-PS 2 as an alternative to platinum-based combination treatment.
g. Only for patients with PD-L1-negative tumours.
h. Only for patients with PD-L1-negative tumours who do not have mainly squamous histology.
i. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells).
j. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

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

Research question	Therapeutic indication	ACT[a]
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; 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 wording of its research questions and the specification of the ACT, the company followed the G-BA only to some extent:

For research question 1 (adults with advanced RET fusion-positive NSCLC with PD-L1 expression in ≥ 50% of tumour cells; first-line therapy), the company followed the G-BA, specifying pembrolizumab as the ACT (company's research question 1a).

For research question 2 (adults with advanced RET-fusion positive NSCLC with PD-L1 expression in < 50% of tumour cells; first-line therapy), the company partially followed the G-BA, listing only some of the G-BA's ACT options (company's research question 1b).

The company did not separately examine the G-BA's research questions 3 to 5, but analysed treatment-experienced patients jointly, in departure from the G-BA's specifications (company's research question 2). For all treatment-experienced patients, regardless of the type of prior therapy, the company listed some of the G-BA's ACT options for research question 4.

The company's deviations remain without consequence for the present assessment because the company did not submit any suitable evidence for pralsetinib in comparison with the ACT.

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

Since usable data are not available for any of the research questions named by the G-BA, all 5 research questions are assessed in joint sections of the below report (see Sections 2.3, 2.4, and 2.5).

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on pralsetinib (status: 4 October 2021)
- bibliographical literature search on pralsetinib (last search on 4 October 2021)

- search in trial registries / trial results databases for studies on pralsetinib (last search on 4 October 2021)
- search on the G-BA website for pralsetinib (last search on 4 October 2021)

To check the completeness of the study pool:

- Bibliographic literature search on pralsetinib (most recent search on 28 December 2021); see Appendix A of the full dossier assessment for search strategies

Direct comparison

In its information retrieval, the company identified no RCTs directly comparing pralsetinib versus the ACT for the present benefit assessment. The check for completeness likewise produced no directly comparative RCT.

However, the ongoing RCT AcceleRET Lung [3], which enrolled treatment-naive patients with locally advanced or metastatic RET-fusion-positive NSCLC and treated them with either pralsetinib or platinum-based chemotherapy with or without pembrolizumab, was found to be potentially relevant for research question 2. Study results are not yet available.

Further investigations

Having found no RCTs for direct comparisons or adjusted indirect comparisons, the company additionally conducted an information retrieval for further investigations on pralsetinib and submitted results from the 1-arm ARROW study [4]. The company conducted no information retrieval for further investigations on the ACT. To compare individual arms from different studies, the company instead used data from an RCT for which it had access to individual patient data.

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

The data presented by the company are unsuitable for drawing conclusions on the added benefit of pralsetinib in comparison with the ACT. The reasons are explained below.

Evidence provided by the company

ARROW study

The ARROW study is a 1-arm study enrolling patients with RET fusion-positive NSCLC, MTC, or other RET-altered solid tumours. In study phase I, the pralsetinib dose was escalated; in phase II, patients receive 400 mg pralsetinib once daily in 4-week cycles. Patients are treated until disease progression, unacceptable toxicity, or treatment discontinuation. Based on the type of prior treatment (no prior treatment, platinum-based prior treatment, or specific prior treatment), patient origin (China or rest of the world), and type of tumour (NSCLC, MTC, other), the study consists of 9 cohorts, 3 of which comprise patients with NSCLC:

- patients with platinum-based prior treatment
- patients without platinum-based prior treatment
- patients from China with platinum-based prior treatment

Coprimary outcomes in study phase II are the objective response rate and the assessment of safety and tolerability. Patient-relevant secondary outcomes are overall survival and outcomes on symptoms and health-related quality of life. The ARROW study is still ongoing.

The company based its benefit assessment mainly on the results of the ARROW study. However, due to its 1-arm design, it is not possible to derive any added benefit of pralsetinib in comparison with the ACT on the basis of the ARROW study.

Potentially incomplete evidence presented by the company for the ACT

The company did not conduct a search for further investigations on the comparator therapy. The company has access to individual patient data from the studies IMpower132 [5] and Impower110 [6]. These studies enrolled treatment-naive patients with NSCLC who had, however, not been tested for RET fusion and were each treated with a combination of platinum and pemetrexed. The company aims to compare these patients with ARROW participants using propensity score analyses. However, it used only the IMpower132 study for the comparison. The company justified its approach with the fact it deems this study's population to be better comparable with ARROW participants because unlike in the IMpower110 study, these patients were not selected according to PD-L1 status. The company has conducted the propensity score analyses only for the outcomes of overall survival and progression-free survival and presented the results only as supplementary information. It presented results for outcomes on symptoms, health-related quality of life, and side effects only from the ARROW study. In addition, the company did not indicate for which research question the results of these analyses allow drawing conclusions. The company likewise failed to present any information on the patients' PD-L1 status which might provide insight as to the relevant research question.

The company's approach was not appropriate. The company's failure to conduct an information retrieval on the ACT side leaves the company's study pool potentially incomplete for the additional investigations. In addition, the company carried out the comparison only for individual outcomes. Irrespective of these shortcomings, in the present scenario of indirect comparison without a common comparator, the identified effects are not large enough to rule out with certainty that they result solely from systematic bias due to confounders.

Unsuitable propensity score analysis

Irrespective of the completeness of the study pool, the propensity score analyses presented by the company as supplementary information are unsuitable for the benefit assessment. This is due, firstly, to the analysis methods being insufficiently documented. For instance, the company's dossier does not describe the approach used to identify and select confounders. While further stating that, even according to its own weighting, the confounders of sex and

CNS metastases were imbalanced, the company does not draw any consequences from this finding. Since IMpower132 participants had not been tested for RET fusion, the company's propensity score analysis additionally rests on the assumption that RET fusion is not a major prognostic factor. However, the publications cited by the company fail to adequately support this assumption [7-13]. For this reason, the company presented the results of the propensity score analyses only as supplementary information. The company provided no information on positivity or overlapping of the patient groups which were compared by means of propensity score analysis. Overall, the company's approach was not appropriate.

Conclusion

The results presented by the company are unsuitable for assessing the added benefit of pralsetinib in comparison with the ACT. Taken alone, the results from the 1-arm ARROW study are unsuitable for the benefit assessment because no data are available in comparison with the ACT. Additionally, the indirect comparison presented by the company is unsuitable for drawing conclusions on added benefit because the company did not carry out an information retrieval for studies for the comparator therapy, rendering the study pool potentially incomplete. Overall, no suitable data were therefore available for assessing the added benefit of pralsetinib in comparison with the ACT.

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of pralsetinib versus the ACT in adult patients with advanced RET fusion-positive NSCLC who were previously untreated with RET inhibitors. Hence, there is no hint of an added benefit of pralsetinib in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

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

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

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 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 or carboplatin[b] in combination with a third-generation cytostatic[c] 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
3	Adults with advanced RET fusion-positive NSCLC after first-line therapy with a PD-1/PD-L1 antibody as monotherapy	▪ Cisplatin or carboplatin[b] in combination with a third-generation cytostatic[c] or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[e]	Added benefit not proven
4	Adults with advanced RET fusion-positive NSCLC after first-line therapy with cytotoxic chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[h] or ▪ nivolumab or ▪ pembrolizumab[i] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[j]	Added benefit not proven
5	Adults with advanced RET fusion-positive NSCLC after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and a platinum-based chemotherapy	Individualized treatment, taking into account prior treatment and histology, with a choice of afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine	Added benefit not proven

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. For the present therapeutic indication, it was assumed that patients were not indicated for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1) was an option for the patients at the time of treatment with pralsetinib. Patients were further assumed to be generally eligible for active antineoplastic therapy, and therefore, best supportive care was not an ACT option in the present case. 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. Vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in mainly squamous histology). d. Only for patients without EGFR-positive or ALK-positive tumour mutations and with nonsquamous histology. e. Only in case of squamous histology. f. Only for patients with ECOG-PS 2 as an alternative to platinum-based combination treatment. g. Only for patients with PD-L1-negative tumours. h. Only for patients with PD-L1-negative tumours who do not have mainly squamous histology. i. Only for patients with PD-L1-expressing tumours (PD-L1 expression in ≥ 1% of tumour cells). j. 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; 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-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1			

The assessment described above departs from that by the company, which derived a hint of non-quantifiable added benefit for the entire therapeutic indication.

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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