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Tepotinib (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 *Tepotinib (NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

Patient and family involvement

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

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MET	mesenchymal-epithelial transition factor
METex14	mesenchymal-epithelial transition factor gene exon 14
NSCLC	non-small cell lung cancer
PD-1	programmed cell death 1
PD-L1	programmed cell death-ligand 1
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
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 tepotinib. 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 28 February 2022.

Research question

The aim of the present report is to assess the added benefit of tepotinib in comparison with the appropriate comparator therapy (ACT) in adults with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

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

Table 2: Research questions of the benefit assessment of tepotinib

Research question	Therapeutic indication	ACT[a]
Adults with advanced[b] NSCLC harbouring METex14 skipping alterations		
1	Patients after first-line therapy with a PD-1/PD-L1 antibody[c] as monotherapy	▪ Cisplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]) or ▪ carboplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]); see also Appendix VI pertaining to Section K of the German Pharmaceutical Directive ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]
2	Patients after first-line therapy with platinum-containing chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[h] or ▪ nivolumab or ▪ pembrolizumab[i] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[j]
3	Patients after first-line therapy with a PD-1/PD-L1 antibody[c] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[c] and platinum-containing chemotherapy	▪ Individualized treatment taking into account prior treatment and histology, selecting from 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. Patients were presumably not indicated for definitive local therapy and, at the time of treatment with tepotinib, were not candidates for molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1). 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. Corresponds to the disease stage of locally advanced or metastatic NSCLC.
c. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be accounted for with regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel.
d. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities (see Appendix VI pertaining to Section K of the German Pharmaceutical Directive).
e. Except in mainly squamous histology.
f. Only for patients with an ECOG Performance Status of 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, TPS ≥ 1%.
j. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

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; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; PD-1: programmed cell death 1; PD-L1: programmed cell death-ligand 1; ROS1: c-ros oncogene 1; TPS: tumour proportion score

On 19 January 2022, about 1 month before the company submitted the dossier (22 February 2022), the G-BA modified the ACT as shown in Table 2. Research question 3 now comprises (a) some of the patients in second-line therapy and (b) the patients in higher lines of therapy.

While the company claims to have followed the ACT specified by the G-BA, the information provided in the company's dossier is based on the ACT discussed in the consultation procedure for patients in the second or higher lines of therapy, rather than on the modified ACT. For research questions 1 and 2, this results in no deviations from the modified ACT specified by the G-BA. In departure from research question 3 (see Table 2), however, the company analysed patients after first-line therapy with a programmed cell death 1 (PD-1) / programmed cell death-ligand 1 (PD-L1) antibody in combination with platinum-based chemotherapy separately from patients requiring third-line therapy. For these 2 patient populations, the company designated separate ACTs based on the discussion in the consultation procedure. Specifically, they each involve individualized therapy, but some of the criteria and drugs to be taken into account depart from the modified ACT.

The company's approach is of no consequence for the benefit assessment portion of this dossier assessment because the data submitted in the company's dossier do not allow drawing a comparison of tepotinib with the ACT. This applies both to the original ACT and the modified ACT specified by the G-BA.

The present assessment was conducted on the basis of the G-BA's modified ACT (populations and associated 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's assessment, the check for completeness of the study pool did not identify any relevant randomized controlled trials (RCTs) which allow a direct comparison of tepotinib with the ACT for any of the 3 research questions. As best available evidence, the company uses the single-arm approval study of tepotinib (VISION) for deriving added benefit. The VISION study is an ongoing, single-arm, 2-part study investigating the efficacy and tolerability of tepotinib in adults with advanced NSCLC harbouring a METex14 skipping alteration or a mesenchymal-epithelial transition factor (MET) amplification. By themselves, however, the results from the VISION study are unsuitable for assessing the added benefit of tepotinib compared to the ACT because they do not allow a comparison with the ACT.

To determine any added benefit of tepotinib, the company used a purely descriptive approach comparing the results of individual outcomes from the VISION study as well as from 2 non-interventional studies based on health and patient records (0015 and 0035). In this process, the company conducted neither information retrieval for the ACT nor a systematic analysis of its

presented 0015 and 0035 study cohorts. The data presented by the company for evaluating the results from its single-arm study are therefore unsuitable for assessing the added benefit of tepotinib in comparison with the ACT.

Hence, no relevant data are available for assessing the added benefit of tepotinib in comparison with the ACT in adults with advanced NSCLC harbouring alterations leading to METex14 skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy. Consequently, there is no hint of added benefit of tepotinib in comparison with the ACT for any of the 3 research questions; an added benefit is therefore not proven for any of them.

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

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

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with advanced[b] NSCLC harbouring alterations leading to METex14 skipping			
1	Patients after first-line therapy with a PD-1/PD-L1 antibody[c] as monotherapy	▪ Cisplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]) or ▪ carboplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]); see also Appendix VI pertaining to Section K of the German Pharmaceutical Directive or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]	Added benefit not proven
2	Patients after first-line therapy with platinum-containing chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[h] or ▪ nivolumab or ▪ pembrolizumab[i] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[j]	Added benefit not proven

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

3	Patients after first-line therapy with a PD-1/PD-L1 antibody[c] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[c] and platinum-containing chemotherapy	▪ Individualized treatment taking into account prior treatment and histology, selecting from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Patients were presumably not indicated for definitive local therapy and, at the time of treatment with tepotinib, were not candidates for molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1). 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. Corresponds to the disease stage of locally advanced or metastatic NSCLC.
c. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be accounted for with regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel.
d. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities (see Appendix VI pertaining to Section K of the German Pharmaceutical Directive).
e. Except in mainly squamous histology.
f. Only for patients with an ECOG Performance Status 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, TPS ≥ 1%.
j. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

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; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; PD-1: programmed cell death 1; PD-L1: programmed cell death-ligand 1; ROS1: c-ros oncogene 1; TPS: tumour proportion score

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of tepotinib in comparison with the ACT in adults with advanced NSCLC harbouring alterations leading to METex14 skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

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

Table 4: Research questions of the benefit assessment of tepotinib

Research question	Therapeutic indication	ACT[a]
Adults with advanced[b] NSCLC harbouring alterations leading to METex14 skipping		
1	Patients after first-line therapy with a PD-1/PD-L1 antibody[c] as monotherapy	▪ Cisplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]) or ▪ carboplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]); see Appendix VI pertaining to Section K of the German Pharmaceutical Directive or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]
2	Patients after first-line therapy with platinum-containing chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[h] or ▪ nivolumab or ▪ pembrolizumab[i] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[j]
3	Patients after first-line therapy with a PD-1/PD-L1 antibody[c] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[c] and platinum-containing chemotherapy	▪ Individualized treatment taking into account prior treatment and histology, selecting from 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. Patients were presumably not indicated for definitive local therapy and, at the time of treatment with tepotinib, were not candidates for molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1). 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. Corresponds to the disease stage of locally advanced or metastatic NSCLC.
c. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be accounted for with regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel.
d. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities (see Appendix VI pertaining to Section K of the German Pharmaceutical Directive).
e. Except in mainly squamous histology.
f. Only for patients with an ECOG Performance Status 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, TPS ≥ 1%.
j. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

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; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; PD-1: programmed cell death 1; PD-L1: programmed cell death-ligand 1; ROS1: c-ros oncogene 1; TPS: tumour proportion score

On 19 January 2022, about 1 month before the company submitted the dossier (22 February 2022), the company modified the ACT as shown in Table 4 [3]. The original ACT communicated during a consultation procedure in November 2020, prior to the approval of tepotinib, comprised all lines of therapy of tepotinib in the treatment of adults with advanced NSCLC with METex14 skipping alterations, including first-line therapy. Tepotinib was approved in February 2022, but only for patients who require systemic therapy after treatment with immunotherapy and/or platinum-based chemotherapy [4]. This corresponds to treatment with tepotinib in the second or higher therapy line. The G-BA's modified ACT therefore applies only to these patient populations. Furthermore, in the modified ACT, the G-BA combines, in a joint patient population, patients after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy as well as patients after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy (research question 3). For this patient population, the G-BA specified the joint ACT of individualized therapy (see Table 4). Research question 3 now comprises (a) some of the patients in second-line therapy and (b) the patients in higher lines of therapy.

While the company claims to have followed the ACT specified by the G-BA, the information provided in the company's dossier is based on the ACT communicated in the consultation procedure for patients in second-line or higher lines of therapy, rather than on the modified ACT. For research questions 1 and 2, this results in no deviations from the modified ACT specified by the G-BA. In departure from research question 3, however (see Table 4), the company analysed patients after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy separately from patients requiring treatment in third-line therapy. For these 2 patient populations, the company designated separate ACTs following the information from the consultation procedure. Specifically, they each involve individualized therapy, but some of the criteria and drugs to be taken into account depart from the modified ACT. In addition, the company presumes that the ACT specified for third-line therapy also applies to subsequent therapies. Irrespective of this assumption, the company's dossier contains data only for patients in second-line or third-line therapy. Due to low numbers of patients in the VISION study's individual populations, the company chose not to break down the population of patients into second-line therapy as per the categories specified for the ACT.

The company's approach is of no consequence for the benefit assessment part of this dossier assessment because the data submitted in the company's dossier do not allow a comparison of tepotinib with the ACT (see Section 2.3). This applies both to the original ACT and the modified ACT specified by the G-BA.

The present assessment was conducted in accordance with the ACT modified by the G-BA (populations and corresponding ACTs). Since usable data are not available for any of the research questions specified in Table 4, all 3 research questions are assessed below in joint sections of the report (see Sections 2.3, 2.4, and 2.5).

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on tepotinib (status: 3 January 2022)
- bibliographical literature search on tepotinib (last search on 3 January 2022)
- search in trial registries / trial results databases for studies on tepotinib (last search on 3 January 2022)
- search on the G-BA website for tepotinib (last search on 3 January 2022)

To check the completeness of the study pool:

- search in trial registries for studies on tepotinib (last search on 5 April 2022); for search strategies, see Appendix A of the full dossier assessment

The check for completeness of the study pool identified no relevant RCT allowing a direct comparison of tepotinib versus the ACT. This applies to all 3 research questions and corresponds to the company's assessment.

Having found no RCTs for direct comparisons or adjusted indirect comparisons, the company conducted an information retrieval for further investigations on tepotinib and submitted results from the single-arm approval study for tepotinib (VISION [5]). The company conducted no information retrieval for further investigations on the ACT.

The check of the completeness of the company's study pool identified no additional potentially relevant investigations on tepotinib.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of tepotinib in comparison with the ACT. This is justified below.

Evidence provided by the company

VISION study

The company does not identify any RCTs allowing a direct or adjusted indirect comparison of tepotinib with the ACT. As the best available evidence, the company used the approval study of tepotinib for deriving added benefit. The VISION study is an ongoing, single-arm, 2-part study investigating the efficacy and tolerability of tepotinib in adults with advanced NSCLC who harbour a METex14 skipping alteration or a MET amplification. The study included both patients without prior treatment as well as patients who already received up to 2 previous cancer therapies in the advanced stage of disease. Patients had to be in good general condition at

baseline, corresponding to an Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) of 0 or 1. In the first part of the study, patients were allocated based on their respective mutation in the MET gene, either to Cohort A (METex14 skipping alterations) or Cohort B (MET amplification). In the second part of the study, after completion of recruitment of Cohort A, patients with METex14 skipping alterations were included in Cohort C. Said cohort is the confirmatory cohort for Cohort A, and for the purposes of the benefit assessment, the company analysed it together with Cohort A (METex14 skipping cohort of the VISION study). The primary outcome of the study was objective tumour response in accordance with Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Patient-relevant secondary outcomes were outcomes concerning overall survival, morbidity, health-related quality of life, and adverse events. The study is expected to end in 2024.

The company based its benefit assessment mainly on the results from the single-arm VISION study. By themselves, however, the results from the VISION study are unsuitable for assessing the added benefit of tepotinib compared to the ACT because they do not allow a comparison with the ACT.

Based on results from routine care, company's approach for evaluating the results of the VISION study unsuitable for drawing conclusions on added benefit

In Section 4.4.2 of the dossier's Module 4 A, the company descriptively compares the results of isolated outcomes of the VISION study's METex14 skipping cohort (see above) versus the results from 2 retrospective, noninterventional studies (0015 study [6] and 0035 study [7]). According to the company, these results represent the routine care of patients in the therapeutic indication and serve to demonstrate their unfavourable prognosis. In this overall evaluation, the company concludes a relevant added benefit of tepotinib as the only treatment option approved in Germany for the therapeutic indication. Since a comparison with the ACT is impossible, the company derived a non-quantifiable added benefit of tepotinib for all evaluated patients, including those in a therapy line beyond third-line therapy.

The company's approach is not appropriate. The 0015 and 0035 studies are non-interventional studies conducted by the company which investigate the efficacy of therapies prior to the approval of tepotinib for patients with advanced NSCLC (stages IIIB to IV) using overall survival as well as tumour response. The studies are based on data obtained from electronic health records from oncology practices in the United States (study 0015) or patient files from 6 oncology centres in Israel, the Netherlands, Taiwan, and the United States (study 0035). For both studies, the inclusion criterion was the index diagnosis of advanced NSCLC with METex14 skipping alterations or MET amplification. No exclusion criteria were defined for either study. The analysis of the 0015 study (METex14 cohort) included 54 patients, of which only 5 met the VISION study's inclusion and exclusion criteria. The analysis of the 0035 study included 70 patients with METex14 skipping alterations (METex14 cohort). Of these patients, 44 met the VISION study's inclusion and exclusion criteria (VISION criteria cohort); however, the cohort also included patients other than those meeting these criteria, specifically patients

whose general health had not been rated on the basis of the ECOG-PS or Karnofsky index but was deemed by the treating physician to be “not reduced”.

To evaluate the added benefit of tepotinib, the company compared in a purely descriptive manner individual outcomes from the results of the VISION study as well as the above-described cohorts of studies 0015 and 0035, separately for patients in second-line therapy and third-line therapy. However, the company conducted neither an information retrieval for the ACT nor a systematic analysis of the cohorts of studies 0015 and 0035. The data presented by the company for evaluating the results from its single-arm study are therefore unsuitable for assessing the added benefit of tepotinib in comparison with the ACT.

Overall, the dossier therefore does not present any relevant data for assessing the added benefit of tepotinib. This applies to all research questions.

2.4 Results on added benefit

No relevant data are available for assessing the added benefit of tepotinib in comparison with the ACT in adults with advanced NSCLC harbouring alterations leading to METex14 skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy. Consequently, there is no hint of added benefit of tepotinib in comparison with the ACT for any of the 3 research questions; an added benefit is therefore not proven for any of them.

2.5 Probability and extent of added benefit

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

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with advanced[b] NSCLC harbouring alterations leading to METex14 skipping			
1	Patients after first-line therapy with a PD-1/PD-L1 antibody[c] as monotherapy	▪ Cisplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]) or ▪ carboplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]); see Appendix VI pertaining to Section K of the German Pharmaceutical Directive or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine[f]	Added benefit not proven
2	Patients after first-line therapy with platinum-containing chemotherapy	▪ Docetaxel[g] or ▪ pemetrexed[h] or ▪ nivolumab or ▪ pembrolizumab[i] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[j]	Added benefit not proven
3	Patients after first-line therapy with a PD-1/PD-L1 antibody[c] in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[c] and platinum-containing chemotherapy	▪ Individualized treatment taking into account prior treatment and histology, selecting from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Patients were presumably not indicated for definitive local therapy and, at the time of treatment with tepotinib, were not candidates for molecularly stratified therapy (against EGFR, ALK, BRAF, or ROS1). 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. Corresponds to the disease stage of locally advanced or metastatic NSCLC.
c. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be accounted for with regard to the approval of pemetrexed, gemcitabine, and nab-paclitaxel.
d. In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities (see Appendix VI pertaining to Section K of the German Pharmaceutical Directive).
e. Except in mainly squamous histology.
f. Only for patients with an ECOG Performance Status 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, TPS ≥ 1%.
j. Only for patients with PD-L1-negative tumours and adenocarcinoma histology.

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
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; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; PD-1: programmed cell death 1; PD-L1: programmed cell death-ligand 1; ROS1: c-ros oncogene 1; TPS: tumour proportion score			

The assessment described above deviates from the company's assessment, which derived non-quantifiable added benefit both for patients in second-line therapy and for those in third-line therapy and beyond.

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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