Capmatinib (NSCLC)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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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 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
AE	adverse event
ALK	anaplastic lymphoma kinase
BIRC	blinded independent review committee
CNS	central nervous system
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
METex14	mesenchymal-epithelial transition factor gene exon 14
nNGM	national Network Genomic Medicine
NSCLC	Non-small Cell Lung Cancer
PFS	progression-free survival
SAP	statistical analysis plan
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 capmatinib. 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 17 August 2022.

Research question

The aim of the present report is the assessment of the added benefit of capmatinib compared with the appropriate comparator therapy (ACT) in patients with advanced non-small cell lung cancer (NSCLC) requiring systemic therapy after immunotherapy and/or platinum-based chemotherapy. The NSCLC of the patients harbours alterations leading to mesenchymal-epithelial transition factor gene exon 14 skipping (METex14 skipping).

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 capmatinib (multipage table)

Research question	Therapeutic indication	ACT[a]
Adults with advanced[b] NSCLC harbouring METex14 skipping mutations		
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 and docetaxel in combination with nintedanib and vinorelbine

a. Presented is the respective ACT specified by the G-BA. It is assumed for the present therapeutic indication that patients were not indicated for definitive local therapy and, at the time of treatment with capmatinib, 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 and except in the case of predominantly squamous cell 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 protein1; PD-L1: programmed cell death-ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TPS: Tumour Proportion Score

On 06 September 2022, about 1 month after the company had submitted the dossier (12 August 2022), the G-BA modified the ACT as shown in Table 2. The original ACT communicated to the company with the G-BA letter of 21 September 2020, prior to the approval of capmatinib, comprised all lines of therapy of capmatinib in the treatment of adults with advanced NSCLC with METex14 skipping mutations, including first-line therapy. However, in June 2022, capmatinib was approved only for patients who require systemic therapy following treatment with immunotherapy and/or platinum-based chemotherapy. This corresponds to treatment with capmatinib in the second or higher therapy lines. 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 programmed cell death protein1 (PD-1) or programmed cell death-ligand 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 2). Research question 3 now comprises some of the patients in second-line therapy and 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 2020 for patients in the second or third line of therapy, rather than on the modified ACT. For research questions 1 and 2, there are 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 PD-1/PD-L1 antibody in combination with platinum-based chemotherapy separately from patients receiving third-line therapy. For these 2 patient populations, the company designated separate ACTs following the information from the consultation procedure. In each case, this is a patient-specific therapy, taking into account various criteria and drugs. In its dossier, the company presented comparative data only for patients in the second line of therapy, but not for the third line including higher lines

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 (for patients in the second therapy line) do not allow drawing a comparison of capmatinib with the ACT. This applies to both the original ACT and the modified ACT specified by the G-BA.

The present assessment was conducted in accordance with the modified ACT (comparison with the G-BA's ACT and separated by the 3 research questions). Since for the benefit assessment, no suitable data are available for any of the research questions specified in Table 2, all 3 research questions are assessed below in joint sections of the report.

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

Results

Evidence presented by the company – GEOMETRY mono-1 study

The ongoing GEOMETRY mono-1 study is an open-label, uncontrolled, prospective phase 2 cohort study whose recruitment has been completed. The study included a total of 373 adults with advanced (stage IIIB or IV) NSCLC with METex14 skipping mutation or MET amplification in the first line or higher lines of therapy. According to the present MET alteration and depending on whether they had received no or already 1 or 2 antitumour treatment(s) in the advanced stage of disease, the patients were assigned to a total of 7 cohorts, of which 2 were subdivided into subcohorts a and b (see also Table 6 of the full dossier assessment). 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 addition, tumours had to have wild-type epidermal growth factor receptor (EGFR) status (for exon 19 deletions and exon 21 L858R substitution mutations) and negative anaplastic lymphoma kinase (ALK) translocation status.

In all 7 cohorts, treatment with capmatinib was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). The primary outcome of the study is the objective response rate assessed by a blinded independent review committee (BIRC). Further patient-relevant outcomes were overall survival, morbidity, health-related quality of life, and adverse events (AEs) (see also Table 5).

In the dossier, the company presents results on patients with METex14 skipping mutation in the second or higher lines of therapy of the most recently updated 8th data cut-off from August 2021.

Evidence presented by the company – RECAP study

The RECAP study is a comparison of individual arms of different studies consisting of individual patient data on capmatinib from the prospective cohort study GEOMETRY mono-1 and individual patient data from the national Network Genomic Medicine (nNGM) database for representing the ACT. For this study, the company prepared a study protocol and a statistical analysis plan (SAP), but no entry exists in a study registry. The RECAP study included patients in the first or second-line therapy. Only the included patients in the second-line therapy are relevant for the present benefit assessment (subpopulations c, d and e of the company, see Table 6 of the full dossier assessment).

This comparison of individual arms from different studies records the following outcomes:

- Overall survival
- progression-free survival (PFS)
- Overall response rate

- time to progression in the central nervous system (CNS)
- Time to treatment discontinuation due to AEs
- Unplanned or prolonged hospitalization
- unplanned or prolonged hospitalization or death

From the perspective of the company, data on side effects in the RECAP study cannot be assessed due to the lack of available suitable registry data.

The studies and data sources used for the RECAP study by the company as well as the patient populations used from them are described below.

Comparisons of individual arms from different studies

In its dossier, the company presented comparisons of individual arms from different studies only for patients in the second line of therapy; it provided no comparative data for the third line including higher lines. The company subdivided the patient population in the second-line treatment according to the prior therapies specified by the G-BA (subpopulations c, d and e of the company, which can be assigned to research questions 1, 2 and 3 of the G-BA). Moreover, the company summarized all patients of the second-line therapy (pool population 1 of the company: n = 81 vs. n = 21). The company carried out a propensity score procedure exclusively for pool population 1 and presented comparisons of individual arms from different studies for the outcomes mentioned. According to the company, the combination of subpopulations c, d and e into pool population 1 leads to an increased certainty of results and informative value for the second line as a whole due to the higher number of patients.

Furthermore, the company presents comparisons of the individual arms from the two sources for the outcomes mentioned for the subpopulations without adjustment using the propensity score procedure. According to the company, it is not possible to calculate an interpretable propensity score due to the low number of patients in the respective subpopulations.

Assessment of the evidence presented by the company

The non-controlled study GEOMETRY mono-1 permits no conclusions on the added benefit

The company presented the results of the non-controlled GEOMETRY mono-1 study and performed descriptive considerations of the results. These descriptive results from the GEOMETRY mono-1 study alone are not suitable for the assessment of the added benefit of capmatinib compared to the ACT, as they do not allow a comparison with the ACT.

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

Regardless of the selection of the confounders named by the company and the propensity score procedure used, the comparisons based on pool population 1 are not suitable for

considering the study population according to the classification of the ACT (see Table 2). The sensitivity analyses comprise therapies that do not correspond to one of the options of the ACT specified by the G-BA taking into account the previous therapy, and are therefore also not suitable for a comparison of capmatinib with the ACT (54% of the patients included in the sensitivity analysis did not receive a treatment corresponding to the ACT).

Regardless of patient relevance, the results for the outcome of CNS progression are not interpretable

In the comparisons of two arms from different sources without a common comparator presented by the company, a statistically significant difference between the treatment arms is shown exclusively for the outcome "CNS progression" for patients who received cytotoxic chemotherapy as first-line treatment (subpopulation d of the company) (the comparisons based on pool population 1 also show a statistically significant difference between the treatment arms exclusively for the outcome "CNS progression"). Only patients without brain metastases at baseline were included in this analysis of the outcome "CNS progression". The outcome "CNS progression" was operationalized as time from start of treatment until first radiologically documented evidence of brain metastases. According to the study protocol, further brain scans in patients without brain metastases at baseline (confirmed by a brain scan at study entry) were only performed in the GEOMETRY mono-1 study (data for the intervention arm) in case of symptoms suggestive of brain metastases. This corresponds to the current recommendations for everyday health care in Germany. Therefore, it can be assumed that also in the patients from the nNGM centres (data for the comparator arm), a brain scan was only performed in the case of symptoms suggesting brain metastases. For this reason, the outcome "CNS progression" initially appeared patient-relevant in the operationalization presented by the company. However, only a subpopulation was analysed (for the outcome of CNS progression) for the intervention and the control arm, namely those patients who had no brain metastases at baseline. In principle, however, symptom-related progression, which takes into account symptoms perceived by patients, is also relevant for this outcome in patients with brain metastases at baseline.

In the GEOMETRY mono-1 study, the outcome of CNS progression was not prespecified and was especially reoperationalized for the RECAP study. After disease progression, patients underwent a safety follow-up for 30 days followed by survival follow-up. Thus, in the intervention arm of the GEOMETRY-mono-1 study, patients were only recorded for the outcome of CNS progression up to the point of disease progression confirmed by BIRC. In the comparator arm, based on the study protocol of the RECAP study and the Kaplan-Meier curves for PFS and CNS progression submitted by the company (see I Appendix B), it can be assumed that events for the outcome of CNS progression were recorded over the entire observation period - even after progression of the disease outside the CNS. Thus, on the one hand, under the assumption described above, this outcome was recorded for different lengths of time and,

on the other hand, in the intervention arm only over a systematically shortened observation period. Patients were censored after non-CNS progression. This is also reflected by the high number of patients censored for the outcome of CNS progression in the first months in the intervention arm. Hence, the analyses presented by the company in the dossier only recorded part of the CNS events in the intervention arm, i. e. those events that had occurred before non-CNS disease progression.

In addition, in the intervention arm, the requirements in the GEOMETRY mono-1 study, which stipulates a brain scan at study entry, ensure that no brain metastases are present in the patients. In the comparator arm, however, it cannot be ruled out that patients with asymptomatic brain metastases that were not detected before the start of treatment were also included in the analysis, since in everyday health care (and therefore also in the nNGM centres) a brain scan is not regularly performed at the start of treatment

Conclusion

The results presented by the company are unsuitable for the assessment of the added benefit of capmatinib in comparison with the ACT. On the one hand, the results from the non-controlled study GEOMETRY mono-1 alone are not suitable for the benefit assessment, as it does not permit a comparison with the ACT. On the other hand, the comparisons of individual arms from different studies presented by the company do not show any statistically significant effects in the individual outcomes except for the outcome “CNS progression” for subpopulation d of the company (research question 2). However, the results on the outcome “CNS progression” are not suitable for a comparison of individual arms, particularly due to the systematically shortened observation period in the intervention arm. Overall, the dossier provides no suitable data for any of the 3 research questions in order to be able to assess the added benefit of capmatinib compared to the ACT. For all research questions, this applies to both the original ACT and the modified ACT specified by the G-BA.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of capmatinib in comparison with the ACT for all 3 research questions; an added benefit is therefore not proven.

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

Table 3 summarizes the probability and extent of added benefit of capmatinib.

Table 3: Capmatinib – 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 and docetaxel in combination with nintedanib and vinorelbine	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: Capmatinib – 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 is assumed that patients are not indicated for definitive local therapy and that no molecularly stratified therapy (directed against EGFR, ALK, BRAF or ROS1) is being considered at the time of therapy with capmatinib. 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 protein1; PD-L1: programmed cell death-ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TPS: Tumour Proportion Score			

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is the assessment of the added benefit of capmatinib compared with the ACT in patients with advanced NSCLC requiring systemic therapy after immunotherapy and/or platinum-based chemotherapy. The NSCLC of the patients harbours alterations leading to METex14 skipping.

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 capmatinib (multipage table)

Research question	**Therapeutic indication**	**ACT[a]**
Adults with advanced[b] NSCLC harbouring METex14 skipping mutations		
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 antibodyc in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibodyc and platinum-containing chemotherapy	▪ Individualized treatment taking into account prior treatment and histology, selecting from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab and docetaxel in combination with nintedanib and vinorelbine

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

Research question	Therapeutic indication	ACT[a]
a. Presented is the respective ACT specified by the G-BA. It is assumed for the present therapeutic indication that patients were not indicated for definitive local therapy and, at the time of treatment with capmatinib, 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 and except in the case of predominantly squamous cell 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 protein1; PD-L1: programmed cell death-ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TPS: Tumour Proportion Score		

On 06 September 2022, about 1 month after the company had submitted the dossier (12 August 2022), the G-BA modified the ACT as shown in Table 4. The original ACT communicated to the company with the G-BA letter of 21 September 2020, prior to the approval of capmatinib, comprised all lines of therapy of capmatinib in the treatment of adults with advanced NSCLC with METex14 skipping mutations, including first-line therapy. However, in June 2022, capmatinib was approved only for patients who require systemic therapy following treatment with immunotherapy and/or platinum-based chemotherapy [3]. This corresponds to treatment with capmatinib in the second or higher therapy lines. 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 or 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 some of the patients in second-line therapy and 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 2020 for patients in the second or third line of therapy, rather than on the modified ACT. For research questions 1 and 2, there are no deviations from the modified ACT specified by the G-BA. In departure from research question 3 (see Table 4), however, the company analysed patients after first-line therapy with a PD-1/PD-L1 antibody in combination with platinum-based chemotherapy separately from patients receiving third-line therapy. For these 2 patient populations, the company designated separate ACTs following the information from the consultation procedure. In each case, this is a patient-specific therapy, taking into account various criteria and drugs. In its dossier, the company presented comparative data only for patients in the second line of therapy, but not for the third line including higher lines (see Section I 3.1).

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 (for patients in the second therapy line) do not allow drawing a comparison of capmatinib with the ACT (see Section I 3). This applies to both the original ACT and the modified ACT specified by the G-BA.

The present assessment was conducted in accordance with the modified ACT (comparison with the G-BA's ACT and separated by the 3 research questions). Since suitable data for the benefit assessment 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 I 3, I 4, and I 5).

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

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 capmatinib (status: 28 June 2022)
- bibliographical literature search on capmatinib (last search on 16 June 2022)
- search in trial registries/trial results databases for studies on capmatinib (last search on 16 June 2022)
- search on the G-BA website for capmatinib (last search on 05 July 2022)
- bibliographical literature search on the ACT (last search on 28 June 2022)
- search in trial registries/trial results databases for studies on the ACT (last search on 16 June 2022)
- search on the G-BA website for the ACT (last search on 05 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on capmatinib (last search on 13 September 2022); for search strategies, see I Appendix A of the full dossier assessment

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 capmatinib versus the ACT. This applies to all 3 research questions and corresponds to the company's assessment.

For questions 2 and 3, the potentially relevant RCT GeoMETry-III [4] was identified, which included adult patients with advanced NSCLC harbouring METex14 skipping mutation receiving either capmatinib or docetaxel. However, results of this ongoing study are not yet available.

Having identified no RCTs for direct comparisons or adjusted indirect comparisons, the company additionally conducted an information retrieval for further studies and presented the non-randomized retrospective RECAP study [5]. This study is a comparison of individual arms from different studies. The comparison was based on individual patient data on capmatinib from a prospective cohort study and individual patient data from the nNGM for representing the ACT.

The check of the completeness of the company's study pool identified no additional potentially relevant studies on capmatinib. 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 capmatinib in comparison with the ACT. This is justified below.

I 3.1 Evidence provided by the company

I 3.1.1 Evidence on capmatinib

GEOMETRY mono-1 study

The ongoing GEOMETRY mono-1 study is an open-label, uncontrolled, prospective phase 2 cohort study whose recruitment has been completed [6]. The study included a total of 373 adults with advanced (stage IIIB or IV) NSCLC with METex14 skipping mutation or MET amplification in the first line or higher lines of therapy. According to the present MET alteration and depending on whether they had received no or already 1 or 2 antitumour treatment(s) in the advanced stage of disease, the patients were assigned to a total of 7 cohorts, of which 2 were subdivided into subcohorts a and b (see also Table 6 of the full dossier assessment). Patients had to be in good general condition at baseline, corresponding to an ECOG Performance Status (ECOG PS) of 0 or 1. In addition, tumours had to have wild-type EGFR status (for exon 19 deletions and exon 21 L858R substitution mutations) and negative ALK translocation status. Patients with symptomatic CNS metastases who were neurologically unstable or who received an increasing dose of steroids for CNS symptoms in the 2 weeks prior to study entry were excluded.

In all 7 cohorts, treatment with capmatinib was largely in compliance with the specifications of the SPC [3]. The primary outcome of the study is the objective response rate assessed by a BIRC. Further patient-relevant outcomes were overall survival, morbidity, health-related quality of life, and AEs (see also Table 6 of the full dossier assessment).

Data cut-offs

According to the company, 8 data cut-offs are available for the GEOMETRY mono-1 study:

- Data cut-off 1: 20 May 2016 (interim analysis)
- Data cut-off 2: 15 August 2016 (interim analysis)
- Data cut-off 3: 09 August 2017 (interim analysis)
- Data cut-off 4: 15 April 2019 (interim analysis)
- Data cut-off 5: 28 October 2019 (data cut-off requested by the FDA)
- Data cut-off 6: 06 January 2020 (interim analysis)
- Data cut-off 7: 18 September 2020 (interim analysis, which provides the basis for the European approval)
- Data cut-off 8: 30 August 2021 (interim analysis)

In the dossier, the company presents results on patients with METex14 skipping mutation in the second or higher lines of therapy of the most recently updated 8th data cut-off from August 2021.

I 3.1.2 Study RECAP – comparison of individual arms from different studies

The RECAP study is a comparison of individual arms of different studies consisting of individual patient data on capmatinib from the prospective cohort study GEOMETRY mono-1 (see also Section I 3.1.1) and individual patient data from the nNGM database for representing the ACT. For this study, the company prepared a study protocol and an SAP, but no entry exists in a study registry. The RECAP study included patients in the first or second-line therapy. Only the included patients in the second-line therapy are relevant for the present benefit assessment (subpopulations c, d and e of the company).

This comparison of individual arms from different studies records the following outcomes:

- Overall survival
- PFS
- Overall response rate
- time to progression in the central nervous system (CNS)
- Time to treatment discontinuation due to AEs
- Unplanned or prolonged hospitalization
- unplanned or prolonged hospitalization or death

From the perspective of the company, data on side effects in the RECAP study cannot be assessed due to the lack of available suitable registry data.

The studies and data sources used for the RECAP study by the company as well as the patient populations used from them are described below.

Data sources for the RECAP study

Study GEOMETRY mono-1 (data source for the intervention arm of the RECAP study)

GEOMETRY mono-1 was described in Section I 3.1.1. For the intervention arm of the RECAP study, the company used cohorts 4, 5b, 6 and 7 with the data cut-off of 30 August 2021 of the GEOMETRY mono-1 study. For the present benefit assessment, the company considered 81 patients with METex14 skipping mutation in cohorts 4 and 6 who received capmatinib in second-line therapy.

nNGM Lung Cancer (data source for the comparator arm of the RECAP study)

For the comparative, non-randomized, prospectively planned RECAP study, data for adult patients (ECOG PS ≤ 1, EGFR wild-type and ALK-negative, no symptomatic CNS metastases) with locally advanced or metastatic NSCLC with METex14 skipping mutation were extracted from retrospective patient records from the nNGM database. Patients were diagnosed at one of the participating nNGM centres between 2018 and 2020, and data collection was until death or the end of recording (22 March 2022). All patients had already received 1 prior therapy with a PD-1 or PD-L1 antibody, cytotoxic chemotherapy or a PD-1 or PD-L1 antibody in combination with platinum-containing chemotherapy in an advanced stage of the disease. Third-line patients were not included in the study due to the very low number of patients expected in the nNGM centres.

The company states that it has implemented the ACT defined by the G-BA for the respective patient population in the main analysis according to the study protocol and SAP of the RECAP study. For this main analysis, the company considered 21 patients from the nNGM database with the criteria listed above (see also Table 6 of the full dossier assessment). In addition, it presents a prespecified sensitivity analysis "capmatinib vs. SoC" of the RECAP study, which according to the company, by including all therapies administered in the nNGM centres and taking into account the previous therapies defined by the G-BA, best reflects the German health care reality and enables the consideration of a larger number of patients (n = 46).

Comparisons of individual arms from different studies

In its dossier, the company presented comparisons of individual arms from different studies only for patients in the second line of therapy; it provided no comparative data for the third line including higher lines. The company subdivided the patient population in the second-line treatment according to the prior therapies specified by the G-BA (subpopulations c, d and e of the company, which can be assigned to research questions 1, 2 and 3 of the G-BA). Moreover, the company summarized all patients of the second-line therapy (pool population 1 of the company: n = 81 vs. n = 21). The company carried out a propensity score procedure exclusively for pool population 1 and presented comparisons of individual arms from different studies for the outcomes mentioned. According to the company, the combination of subpopulations c, d and e into pool population 1 leads to an increased certainty of results and informative value for the second line as a whole due to the higher number of patients.

Furthermore, the company presents comparisons of the individual arms from the two sources for the outcomes mentioned for the subpopulations without adjustment using the propensity score procedure. According to the company, it is not possible to calculate an interpretable propensity score due to the low number of patients in the respective subpopulations.

I 3.1.3 Assessment of the evidence presented by the company

Overall, when considering the entire available evidence (comparisons of individual arms from different studies as well as the GEOMETRY mono-1 study), the company claims a hint of a non-quantifiable added benefit for capmatinib compared to the ACT for the entire patient population, including the 3rd and higher lines of treatment. However, the data presented by the company are unsuitable for the benefit assessment of capmatinib in comparison with the ACT. This is explained below.

The non-controlled study GEOMETRY mono-1 permits no conclusions on the added benefit

The company presented the results of the non-controlled GEOMETRY mono-1 study and performed descriptive considerations of the results. These descriptive results from the GEOMETRY mono-1 study alone are not suitable for the assessment of the added benefit of capmatinib compared to the ACT, as they do not allow a comparison with the ACT.

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

Both comparisons based on pool population 1 and the sensitivity analysis are not suitable to consider the study population according to the classification of the ACT

Regardless of the choice of the confounders named by the company and the propensity score procedure used, the comparisons based on pool population 1 are not suitable for considering the study population according to the classification of the ACT (see Table 3). The sensitivity analyses comprise therapies that do not correspond to one of the options of the ACT specified by the G-BA taking into account the previous therapy, and are therefore also not suitable for a comparison of capmatinib with the ACT (54% of the patients included in the sensitivity analysis did not receive a treatment corresponding to the ACT).

Regardless of patient relevance, the results for the outcome of CNS progression are not interpretable

In the comparisons of two arms from different sources without a common comparator presented by the company, a statistically significant difference between the treatment arms is shown exclusively for the outcome of CNS progression for patients who received cytotoxic chemotherapy as first-line treatment (subpopulation d of the company) (the comparisons based on pool population 1 also show a statistically significant difference between the treatment arms exclusively for the outcome of CNS progression). Only patients without brain metastases at baseline were included in this analysis. The outcome “CNS progression” was operationalized as time from start of treatment until first radiologically documented evidence of brain metastases. According to the study protocol, further brain scans in patients without brain metastases at baseline (confirmed by a brain scan at study entry) were only performed in the GEOMETRY mono-1 study (data for the intervention arm) in case of symptoms

suggestive of brain metastases. This corresponds to the current recommendations for everyday health care in Germany [7,8]. Therefore, it can be assumed that also in the patients from the nNGM centres (data for the comparator arm), a brain scan was only performed in the case of symptoms suggesting brain metastases. For this reason, the outcome "CNS progression" initially appeared patient-relevant in the operationalization presented by the company. However, only a subpopulation was analysed (for the outcome of CNS progression) for the intervention and the control arm, namely those patients who had no brain metastases at baseline. In principle, however, symptom-related progression, which takes into account symptoms perceived by patients, is also relevant for this outcome in patients with brain metastases at baseline.

In the GEOMETRY mono-1 study, the outcome of CNS progression was not prespecified and was especially reoperationalized for the RECAP study. After disease progression, patients underwent a safety follow-up for 30 days followed by survival follow-up. Thus, in the intervention arm of the GEOMETRY-mono-1 study, patients were only recorded for the outcome of CNS progression up to the point of disease progression confirmed by BIRC. In the comparator arm, based on the study protocol of the RECAP study and the Kaplan-Meier curves for PFS and CNS progression submitted by the company (see I Appendix B), it can be assumed that events for the outcome of CNS progression were recorded over the entire observation period - even after progression of the disease outside the CNS. Thus, on the one hand, under the assumption described above, this outcome was recorded for different lengths of time and, on the other hand, in the intervention arm only over a systematically shortened observation period. Patients were censored after non-CNS progression. This is also reflected by the high number of patients censored for the outcome of CNS progression in the first months in the intervention arm. Hence, the analyses presented by the company in the dossier only recorded part of the CNS events in the intervention arm, i. e. those events that had occurred before non-CNS disease progression.

In addition, in the intervention arm, the requirements in the GEOMETRY mono-1 study, which stipulates a brain scan at study entry, ensure that no brain metastases are present in the patients. In the comparator arm, however, it cannot be ruled out that patients with asymptomatic brain metastases that were not detected before the start of treatment were also included in the analysis, since in everyday health care (and therefore also in the nNGM centres) a brain scan is not regularly performed at the start of treatment.

In the study report on the RECAP study, the company also presents a subgroup analysis for patients with known (asymptomatic) brain metastases at baseline. According to the study protocol, a brain scan was performed every 6 weeks in these patients in the intervention arm (data from the GEOMETRY mono-1 study). For the comparator arm (data of the nNGM) it must be assumed that, according to the current recommendations [7,8], brain scans were also

regularly performed in patients with known brain metastases. Thus, the assessment of a CNS progress was based exclusively on imaging techniques and did not consider any symptoms noticeable by the patients. Thus, this operationalization of the outcome (related to patients with known brain metastases) is not directly relevant to patients.

Conclusion

The results presented by the company are unsuitable for the assessment of the added benefit of capmatinib in comparison with the ACT. On the one hand, the results from the non-controlled study GEOMETRY mono-1 alone are not suitable for the benefit assessment, as it does not permit a comparison with the ACT. On the other hand, the comparisons of individual arms from different studies presented by the company do not show any statistically significant effects in the individual outcomes except for the outcome “CNS progression” for subpopulation d of the company (research question 2). However, the results on the outcome “CNS progression” are not suitable for a comparison of individual arms, particularly due to the systematically shortened observation period in the intervention arm. Overall, the dossier provides no suitable data for any of the 3 research questions in order to be able to assess the added benefit of capmatinib compared to the ACT. For all research questions, this applies to both the original ACT and the modified ACT specified by the G-BA.

I 4 Results on added benefit

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

I 5 Probability and extent of added benefit

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

Table 5: Capmatinib – 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	▪ Cisplatind in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexede) or ▪ carboplatin[d] in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexede); 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 antibodyc in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibodyc and platinum-containing chemotherapy	Individualized treatment taking into account prior treatment and histology, selecting from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab and docetaxel in combination with nintedanib and vinorelbine	Added benefit not proven

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

a. Presented is the respective ACT specified by the G-BA. For the present therapeutic indication, it is assumed that patients are not indicated for definitive local therapy and that no molecularly stratified therapy (directed against EGFR, ALK, BRAF or ROS1) is being considered at the time of therapy with capmatinib. 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 PS 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 protein1; PD-L1: programmed cell death-ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TPS: Tumour Proportion Score

The assessment described above deviates from the company's assessment, which 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.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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