Binimetinib and encorafenib (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 was received in 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
BRAF	rapidly accelerated fibrosarcoma – isoform B
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PD-1	programmed cell death receptor 1
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

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 binimetinib (in combination with encorafenib) as well as of the drug encorafenib (in combination with binimetinib). 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 26 September 2024.

Research question

The aim of the present report is to assess the added benefit of binimetinib in combination with encorafenib and of encorafenib in combination with binimetinib (hereinafter referred to as "binimetinib + encorafenib") in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced non-small cell lung cancer (NSCLC) with a rapidly accelerated fibrosarcoma – isoform B (BRAF) V600E mutation.

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

Table 2: Research questions of the benefit assessment of binimetinib + encorafenib (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Adults with advanced NSCLC with PD-L1 expression ≥ 50% and a BRAF V600E mutation; first-line treatment[b, c]	▪ Dabrafenib in combination with trametinib or ▪ pembrolizumab as monotherapy or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy[d] or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin[d] or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin[d]

Table 2: Research questions of the benefit assessment of binimetinib + encorafenib (multipage table)

Research question	Therapeutic indication	ACT[a]
2	Adults with advanced NSCLC with PD-L1 expression < 50% and a BRAF V600E mutation; first-line treatment[b, c]	▪ Dabrafenib in combination with trametinib or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ atezolizumab as monotherapy[e] or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin[d] or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin[d] or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy[d]
3	Adults with advanced NSCLC with a BRAF V600E mutation; after first-line treatment[b, f]	▪ Dabrafenib in combination with trametinib

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed as per G-BA that there is no indication for definitive local therapy. In addition, it is assumed that another molecularly stratified therapy (directed against ALK, EGFR, exon 20, METex 14, NTRK, RET, or ROS1) is not an option for the patients at the time of treatment with binimetinib in combination with encorafenib.
c. Histologically, most tumours with BRAF V600 mutations are adenocarcinomas, which is why it is assumed that treatment options that are explicitly indicated for squamous tumour histology are not regularly used in this therapeutic indication.
d. Only for patients with ECOG PS 0–1.
e. Only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells.
f. It is assumed that treatment with binimetinib in combination with encorafenib is not an option for patients after first-line treatment with dabrafenib in combination with trametinib.

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; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1

The company followed the G-BA's ACT.

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, no randomized controlled trial (RCT) that would allow a direct comparison of binimetinib + encorafenib with the ACT was identified for the benefit assessment. As the company did not identify any RCT for the direct comparison of binimetinib + encorafenib in comparison with the ACT, it conducted an information retrieval for further investigations on binimetinib + encorafenib and identified the single-arm PHAROS study, which was the basis for the approval. As the PHAROS study does not allow a comparison with the ACT, it is unsuitable for assessing the added benefit of binimetinib + encorafenib. Overall, the company therefore presented no suitable data for deriving an added benefit in comparison with the ACT. This applies to all 3 research questions.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of binimetinib + encorafenib in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of binimetinib + encorafenib.

[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: Binimetinib + encorafenib – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with advanced NSCLC with PD-L1 expression ≥ 50% and a BRAF V600E mutation; first-line treatment[b, c]	▪ Dabrafenib in combination with trametinib or ▪ pembrolizumab as monotherapy or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy[d] or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin[d] or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin[d]	Added benefit not proven
2	Adults with advanced NSCLC with PD-L1 expression < 50% and a BRAF V600E mutation; first-line treatment[b, c]	▪ Dabrafenib in combination with trametinib or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ atezolizumab as monotherapy[e] or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin[d] or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin[d] or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy[d]	Added benefit not proven
3	Adults with advanced NSCLC with a BRAF V600E mutation; after first-line treatment[b, f]	▪ Dabrafenib in combination with trametinib	Added benefit not proven

Table 3: Binimetinib + encorafenib – 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. b. For the present therapeutic indication, it is assumed as per G-BA that there is no indication for definitive local therapy. In addition, it is assumed that another molecularly stratified therapy (directed against ALK, EGFR, exon 20, METex 14, NTRK, RET, or ROS1) is not an option for the patients at the time of treatment with binimetinib in combination with encorafenib. c. Histologically, most tumours with BRAF V600 mutations are adenocarcinomas, which is why it is assumed that treatment options that are explicitly indicated for squamous tumour histology are not regularly used in this therapeutic indication. d. Only for patients with ECOG PS 0–1. e. Only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells. f. It is assumed that treatment with binimetinib in combination with encorafenib is not an option for patients after first-line treatment with dabrafenib in combination with trametinib. 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; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1			

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of binimetinib in combination with encorafenib and of encorafenib in combination with binimetinib (hereinafter referred to as “binimetinib + encorafenib”) in comparison with the ACT in adult patients with advanced NSCLC with a BRAF V600E mutation.

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

Table 4: Research questions of the benefit assessment of binimetinib + encorafenib (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Adults with advanced NSCLC with PD-L1 expression ≥ 50% and a BRAF V600E mutation; first-line treatment[b, c]	▪ Dabrafenib in combination with trametinib or ▪ pembrolizumab as monotherapy or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy[d] or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin[d] or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin[d]
2	Adults with advanced NSCLC with PD-L1 expression < 50% and a BRAF V600E mutation; first-line treatment[b, c]	▪ Dabrafenib in combination with trametinib or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ atezolizumab as monotherapy[e] or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin[d] or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin[d] or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy[d]

Table 4: Research questions of the benefit assessment of binimetinib + encorafenib (multipage table)

Research question	Therapeutic indication	ACT[a]
3	Adults with advanced NSCLC with a BRAF V600E mutation; after first-line treatment[b, f]	▪ Dabrafenib in combination with trametinib

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed as per G-BA that there is no indication for definitive local therapy. In addition, it is assumed that another molecularly stratified therapy (directed against ALK, EGFR, exon 20, METex 14, NTRK, RET, or ROS1) is not an option for the patients at the time of treatment with binimetinib in combination with encorafenib.
c. Histologically, most tumours with BRAF V600 mutations are adenocarcinomas, which is why it is assumed that treatment options that are explicitly indicated for squamous tumour histology are not regularly used in this therapeutic indication.
d. Only for patients with ECOG PS 0–1.
e. Only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells.
f. It is assumed that treatment with binimetinib in combination with encorafenib is not an option for patients after first-line treatment with dabrafenib in combination with trametinib.

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; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1

The company followed the G-BA's ACT.

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 list on binimetinib + encorafenib (status: 23 September 2024)
- bibliographical literature search on binimetinib + encorafenib (last search on 27 July 2024)
- search in trial registries/trial results databases for studies on binimetinib + encorafenib (last search on 28 July 2024)
- search on the G-BA website for binimetinib + encorafenib (last search on 28 July 2024)

To check the completeness of the study pool:

search in trial registries for studies on binimetinib + encorafenib (last search on 10 October 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no RCT that would allow a direct comparison of binimetinib + encorafenib versus the ACT.

As the company did not identify any RCT for the direct comparison of binimetinib + encorafenib in comparison with the ACT, it conducted an information retrieval for further investigations on binimetinib + encorafenib, and identified the single-arm PHAROS study [3], which was the basis for the approval. The company neither conducted an information retrieval nor presented data on the ACT. A check for completeness of the study pool for further investigations was foregone because the data submitted by the company under further investigations are unsuitable for the benefit assessment due to the absence of a comparison with the ACT specified by the G-BA. This is justified below.

Evidence presented by the company – PHAROS study

PHAROS is an ongoing, single-arm study of binimetinib + encorafenib for the treatment of adult patients with metastatic NSCLC with a BRAF V600 mutation. The study included patients in first-line treatment, as well as pretreated patients who had received first-line treatment

- with platinum-based chemotherapy, or
- with an anti-PD-1 (programmed cell death receptor 1) inhibitor / anti-PD-L1 (programmed cell death ligand 1) inhibitor given alone or in combination with platinum-based chemotherapy, or

- with an anti-PD-1 inhibitor / anti-PD-L1 inhibitor given in combination with immunotherapy (e.g. ipilimumab) with or without platinum-based chemotherapy.

The study included 59 patients in the first line and 39 patients in the second line. For the benefit assessment, the company presented results for the total study population separated according to the number of prior therapies. The company did not present a separate analysis of patients in the first line according to PD-L1 expression ≥ 50% or < 50% in accordance with research question 1 and research question 2.

The PHAROS study is unsuitable for deriving an added benefit because it does not permit a comparison with the ACT. Hence, there are no suitable data for deriving an added benefit in comparison with the ACT. This applies to all 3 research questions.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of binimetinib + encorafenib in comparison with the ACT in adult patients with advanced NSCLC with a BRAF V600E mutation. There is no hint of an added benefit of binimetinib + encorafenib in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Table 5: Binimetinib + encorafenib – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with advanced NSCLC with PD-L1 expression ≥ 50% and a BRAF V600E mutation; first-line treatment[b, c]	▪ Dabrafenib in combination with trametinib or ▪ pembrolizumab as monotherapy or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy[d] or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin[d] or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin[d]	Added benefit not proven
2	Adults with advanced NSCLC with PD-L1 expression < 50% and a BRAF V600E mutation; first-line treatment[b, c]	▪ Dabrafenib in combination with trametinib or ▪ pembrolizumab in combination with pemetrexed and platinum-based chemotherapy[d] or ▪ atezolizumab as monotherapy[e] or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin[d] or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin[d] or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy[d]	Added benefit not proven

Table 5: Binimetinib + encorafenib – probability and extent of added benefit (multipage table)

3	Adults with advanced NSCLC with a BRAF V600E mutation; after first-line treatment[b, f]	▪ Dabrafenib in combination with trametinib	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed as per G-BA that there is no indication for definitive local therapy. In addition, it is assumed that another molecularly stratified therapy (directed against ALK, EGFR, exon 20, METex 14, NTRK, RET, or ROS1) is not an option for the patients at the time of treatment with binimetinib in combination with encorafenib.
c. Histologically, most tumours with BRAF V600 mutations are adenocarcinomas, which is why it is assumed that treatment options that are explicitly indicated for squamous tumour histology are not regularly used in this therapeutic indication.
d. Only for patients with ECOG PS 0–1.
e. Only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells.
f. It is assumed that treatment with binimetinib in combination with encorafenib is not an option for patients after first-line treatment with dabrafenib in combination with trametinib.

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; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1

The assessment described above deviates from the company's, which, based on the results of the PHAROS study, derived a hint of non-quantifiable added benefit for all patients in the therapeutic indication.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Riely GJ, Smit EF, Ahn MJ et al. Phase II, Open-Label Study of Encorafenib Plus Binimetinib in Patients With BRAF(V600)-Mutant Metastatic Non-Small-Cell Lung Cancer. J Clin Oncol 2023; 41(21): 3700-3711. https://doi.org/10.1200/JCO.23.00774.

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