IQWiG Reports – Commission No. A18-62

Binimetinib (melanoma) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Binimetinib (Melanom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 21 December 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Binimetinib (melanoma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
27 September 2018

Internal Commission No.:
A18-62

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

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

Medical and scientific advice:

- Ingo Schmidt-Wolf, University Hospital Bonn, Department of Integrated Oncology, Bonn, Germany

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

IQWiG employees involved in the dossier assessment:

- Katharina Wölke
- Florina Kerekes
- Christopher Kunigkeit
- Ulrike Lampert
- Min Ripoll
- Cornelia Rüdig
- Anke Schulz
- Volker Vervölgyi

Keywords: binimetinib, encorafenib, melanoma, benefit assessment, NCT01909453, NCT01689519

Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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. 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 27 September 2018.

Research question

The aim of this report is to assess the added benefit of binimetinib in combination with encorafenib (hereinafter binimetinib + encorafenib) in comparison with the appropriate comparator therapy (ACT) in adults with unresectable or metastatic melanoma with rapidly accelerated fibrosarcoma isoform B (BRAF) V600 mutation.

Table 2 shows the 2 research questions for this assessment and the ACTs specified by the G-BA.

Table 2[2]: Research questions of the benefit assessment of binimetinib + encorafenib

Research question	Indication	ACT[a]
1	Treatment-naïve adults with unresectable or metastatic melanoma with BRAF V600 mutation.	**Vemurafenib + cobimetinib** or dabrafenib + trametinib
2	Pre-treated adults with unresectable or metastatic melanoma with BRAF V600 mutation.	Individualized therapy upon the treating physician's discretion depending on the respective prior therapy and in consideration of the approval status[b]
a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**. b: Except dacarbazine and lomustine. ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma isoform B; G-BA: Federal Joint Committee		

In deviation from the G-BA's specifications, the company chose vemurafenib + cobimetinib as the appropriate comparator therapy (ACT) for all patients in the therapeutic indication (adults with unresectable or metastatic melanoma with BRAF V600 mutation), regardless of prior treatment status. The company's methodology was not plausible.

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

Using the ACTs specified by the G-BA for the two research questions, this assessment was conducted using patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results on research question 1: treatment-naïve patients

Study pool and study characteristics

For research question 1, no directly comparative RCTs were found to assess the added benefit of binimetinib + encorafenib in comparison with the ACT. The company presented an adjusted indirect comparison using the common comparator of vemurafenib, with one study each on either side of the indirect comparison.

COLUMBUS (study with binimetinib + encorafenib)

The part of the COLUMBUS study which is relevant for this benefit assessment is a randomized, open-label, multicentre, actively controlled, 3-arm parallel group study. For this assessment, the study's binimetinib + encorafenib arm and vemurafenib arm are relevant. The study included adult patients with histologically confirmed, unresectable or metastatic melanoma (stage IIIB, IIIC, or IV according to the 7th edition of the American Joint Committee on Cancer [AJCC] classification) and confirmed BRAF V600 mutation. To be included, patients with metastases to the central nervous system had to have been treated for them and be in good general condition (as measured by an Eastern Cooperative Oncology Performance Status [ECOG-PS] of 0 or 1).

The inclusion criteria allowed patients to have received first-line immunotherapy for unresectable or metastatic melanoma with BRAF V600 mutation. For research question 1, however, only the subpopulation of treatment-naïve patients is relevant. Nevertheless, the total population of the COLUMBUS study can be used to answer research question 1 since only about 4% of all included patients received prior treatment with first-line immunotherapy.

A total of 192 patients were randomly allocated to the study's binimetinib + encorafenib arm and 191 to the vemurafenib arm. Randomization was stratified by the factors of metastatic classification (IIIB + IIIC + M1a + M1b/M1c), ECOG-PS (0/1), and first-line immunotherapy (yes/no).

For the most part, treatment was in accordance with the Summaries of Product Characteristics (SPCs). Patients were treated until disease progression, unacceptable toxicities, the investigator's decision to stop treatment, patient withdrawal of consent, loss to follow-up, premature termination of the study, or death. Under certain conditions, continued treatment of the patient after disease progression was allowed upon the investigator's discretion. The dose modifications for toxicity provided for in the COLUMBUS study did not fully conform with the SPCs.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, disease symptoms, health status, health-related quality of life, and adverse events (AEs).

coBRIM (study with vemurafenib + cobimetinib)

The coBRIM study is a randomized, double-blind, multicentre, actively controlled study comparing vemurafenib in combination with cobimetinib with vemurafenib + placebo.

The study included adult patients with histologically confirmed, unresectable or metastatic melanoma (stage IIIC, or IV according to the 7th edition of the AJCC classification) and confirmed BRAF V600 mutation. To be included, patients with metastases to the central nervous system had to have been treated for them and be in good general condition (ECOG-PS of 0 or 1).

Patients who received prior systemic cancer therapy for treating advanced melanoma (stage IIIC or stage IV) were excluded.

The study randomized 495 patients in a 1:1 ratio, 247 to the vemurafenib + cobimetinib arm and 248 to the vemurafenib arm. Stratification factors were geographic region (North America/Europe/Australia, New Zealand, and elsewhere) and metastatic classification (IIIC + M1a + M1b/M1c) at the start of the study.

For the most part, treatment was in accordance with the SPCs. Patients were treated until disease progression, unacceptable toxicities, withdrawal of consent, or death. The dose reductions due to adverse events which were provided for in the study did not fully conform with the SPCs.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, disease symptoms, health status, health-related quality of life, and AEs.

Similarity of studies for the indirect comparison

Similarity of study conduct

Duration of treatment and follow-up

For the data cut-offs used, the median duration of treatment and follow-up in the common comparator arm was sufficiently comparable in the COLUMBUS and coBRIM studies.

Deviations in vemurafenib treatment

In the common comparator arm of the COLUMBUS study, re-escalation of the vemurafenib dose was allowed under certain conditions, in deviation from the SPC. The study documents do not support an estimate of the number of patients affected. This vemurafenib re-escalation option did not exist in the coBRIM study. Also in deviation from the SPC, 17.8% of patients in the COLUMBUS study continued to be treated with vemurafenib after disease progression. In the coBRIM study, treatment continued until disease progression, in accordance with the SPC. However, the median treatment duration in the vemurafenib arms was comparable between the

COLUMBUS and coBRIM studies. Since the coBRIM study was blinded, patients in the common comparator arm were treated with vemurafenib + placebo, instead of vemurafenib monotherapy in the COLUMBUS study.

Follow-up therapies

The percentage of patients who received antineoplastic follow-up therapy after disease progression was slightly higher in the common comparator arm of the COLUMBUS study, at 62.3%, than in the common comparator arm of the coBRIM study, at 50.4%. However, since the studies were, at least in part, conducted simultaneously, patients in both studies had similar follow-up therapy options, and the type of administered follow-up therapies was largely comparable in the two studies.

Similarity of patient populations

The demographic and disease-specific characteristics of the included patients were largely comparable in the common comparator arms of the studies. However, there was a difference in the lactate dehydrogenase (LDH) value at the start of the study, which was discussed as a prognostic factor for overall survival in stage IV. In the common comparator arm of the coBRIM study, elevated LDH values at the start of the study were seen in about 15% more patients than in the common comparator arm of the COLUMBUS study.

Differences between the common comparator arms were also found in terms of prior treatment under the adjuvant scenario, which was allowed in both studies. In the common comparator arm of the COLUMBUS study, about 15% more patients received adjuvant prior therapy than in the common comparator arm of the coBRIM study. Prior therapy with a BRAF/MEK inhibitor (MEK: mitogen-activated extracellular signal-regulated kinase), which would affect subsequent treatment of the advanced stage with a BRAF/MEK inhibitor, was excluded in both studies. No data are currently available on whether other prior adjuvant therapies influence subsequent therapy in the advanced stage.

Summary

The examination of the two studies for similarity revealed differences in the included patients as well as in study conduct, but these differences do not necessarily lead to a rejection of the assumption of similarity. Due to differences between the studies in terms of their surveying and follow-up strategies, however, no usable data are available on the outcome level for the outcome categories of morbidity, health-related quality of life, and adverse events.

Risk of bias

The risk of bias at study level is assessed as low for both studies. The risk of bias at outcome level is considered low for the results on overall survival. For the outcomes of symptoms, health status, health-related quality of life, and outcomes of the category of adverse events, no usable data are available for the indirect comparison.

Given that only one study each was available for either side of the indirect comparison, and that neither homogeneity nor consistency was assessable (no direct comparative study), the adjusted indirect comparisons support no more than a low certainty of results. Therefore, in this situation, at most hints, for instance of an added benefit, can be derived.

Mortality

Overall survival

For the outcome of overall survival, the adjusted indirect comparison shows no statistically significant difference between binimetinib + encorafenib and vemurafenib + cobimetinib. Consequently, there is no hint of added benefit of binimetinib + encorafenib in comparison with vemurafenib + cobimetinib; an added benefit is therefore not proven.

Morbidity

Symptoms (measured by the symptoms scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 [EORTC QLQ-C30]) and health status (measured by the visual analogue scale [VAS] of the European Quality of Life Questionnaire 5 Dimensions [EQ-5D VAS])

For the outcomes of symptoms and health status, no usable data were available. This is due to differences in the way outcomes in the studies were surveyed, leaving the effect on results unclear. Therefore, the results on these outcomes are not inherently comparable and not usable for an indirect comparison.

Consequently, there is no hint of added benefit of binimetinib + encorafenib in comparison with vemurafenib + cobimetinib; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life (as measured by the EORTC QLQ-C30 functional scales)

For the outcome of health-related quality of life, no usable data were available. This is due to differences in the way the outcome was surveyed in the studies, leaving the effect on results unclear. Therefore, the results on this outcome are not inherently comparable and not usable for an indirect comparison.

Consequently, there is no hint of added benefit of binimetinib + encorafenib in comparison with vemurafenib + cobimetinib; an added benefit is therefore not proven.

Adverse events

SAEs, discontinuation due to AEs, and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

For the results on the outcomes on adverse events, no usable data were available. This is due to differences in follow-up as well in study design, leaving the effect on results unclear. Therefore, the results on these outcomes are not usable for an indirect comparison.

Consequently, there is no hint of greater or lesser harm of binimetinib + encorafenib in comparison with vemurafenib + cobimetinib; greater or lesser harm is therefore not proven.

Results on research question 2: pre-treated patients

For research question 2 (pre-treated patients), no directly comparative studies were found. The studies used by the company for an adjusted indirect comparison are not suitable for deriving an added benefit of binimetinib + encorafenib.

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

On the basis of the presented results, the probability and extent of added benefit of the drugs binimetinib + encorafenib in comparison with the ACT is assessed as follows:

As to research question 1, for the outcome of overall survival, there is no hint of added benefit of binimetinib + encorafenib. For the outcome categories of morbidity, health-related quality of life, and adverse events, no data usable for an indirect comparison are available. Hence, for treatment-naïve adult patients with unresectable or metastatic melanoma with BRAF-V600 mutation, there is no hint of added benefit of binimetinib + encorafenib in comparison with vemurafenib + cobimetinib; an added benefit is therefore not proven.

No relevant data are available for research question 2. For pre-treated adult patients with unresectable or metastatic melanoma with BRAF V600 mutation, an added benefit of binimetinib + encorafenib in comparison with the ACT is not proven.

Table 3 presents a summary of the 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

Indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment-naïve adults with unresectable or metastatic melanoma with BRAF V600 mutation[b]	**Vemurafenib + cobimetinib** or dabrafenib + trametinib	Added benefit not proven
Pre-treated adults with unresectable or metastatic melanoma with BRAF V600 mutation.	Individualized therapy upon the discretion of the treating physician depending on the respective prior therapy and taking into account the approval status[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b: The studies on which the benefit assessment is based included patients with an ECOG-PS of 0 or 1. It is unclear whether the observed effects translate to patients with ECOG-PS ≥ 2.
c: Except dacarbazine and lomustine.
ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma isoform B; G-BA: Federal Joint Committee

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

Note:

An addendum (A19-18) to dossier assessment A18-62 has been published.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-62-binimetinib-melanoma-benefit-assessment-according-to-35a-social-code-book-v.10623.html.