IQWiG Reports – Commission No. A18-59

Dabrafenib (melanoma) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Dabrafenib (Melanom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 20 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.

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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:

- Deborah Ingenhag
- Lars Beckmann
- Michaela Florina Kerekes
- Christopher Kunigkeit
- Inga Overesch
- Min Ripoll
- Cornelia Rüdig
- Volker Vervölgyi

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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 dabrafenib. 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 24 September 2018.

Research question

The aim of this report is to assess the added benefit of dabrafenib in combination with trametinib (hereinafter dabrafenib + trametinib) in comparison with watchful waiting as the appropriate comparator therapy (ACT) in the adjuvant treatment of adults with stage III melanoma with rapidly accelerated fibrosarcoma isoform B (BRAF) V600 mutation, following complete resection.

Table 2[2]: Research questions of the benefit assessment of dabrafenib + trametinib

Indication	ACT[a]
Adjuvant treatment of adults with stage III[b] melanoma with BRAF V600 mutation following complete resection	Watchful waiting[c]
a: Presentation of the ACT specified by the G-BA. b: According to AJCC classification. c: The G-BA did not further specify the ACT of watchful waiting. See Section 2.3.2 of the full report for the definition of the ACT in this assessment. ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; BRAF: rapidly accelerated fibrosarcoma isoform B (serine/threonine protein kinase B-Raf); G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

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

Results

Study design

One relevant study (COMBI-AD) is available for the benefit assessment. The COMBI-AD study is a randomized, double-blind, placebo controlled, multicentre study. The study included adult patients with completely resected, histologically confirmed, cutaneous stage III melanoma (according to version 7 of the classification of the American Joint Committee on Cancer) with BRAF V600E/K mutation. It excluded patients in stage IIIA with lymph node metastases ≤ 1 mm. Hence, the study population does not fully coincide with the therapeutic indication, which is not limited to a specific BRAF V600 mutation or in terms of the size of lymph node

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

metastases. In addition, only patients in good general health as measured by Eastern Cooperative Oncology Performance Status 0 or 1 were included.

The study included a total of 870 patients and randomized them in a 1:1 ratio either to treatment with dabrafenib + trametinib (N=438) or placebo (N = 432).

Except for dose adjustments, patient treatment was in accordance with the Summary of Product Characteristics (SPC). In deviation from the SPC, no 3rd dose reduction stage to 50 mg twice daily was specified for dabrafenib. However, this is not believed to have any relevant effect on the study results.

The primary outcome of the study was relapse-free survival. Patient-relevant secondary outcomes were overall survival, health status, and adverse events.

Following a relapse, it was possible for patients and the treating physician to be unblinded. There were no restrictions as to the choice of follow-up therapies; they were to be conducted in accordance with local practice. A treatment switch from the placebo arm to treatment with dabrafenib + trametinib was not provided for in the protocol. The type of follow-up therapy as well as response to the follow-up therapy were to be documented.

Data cut-offs

The COMBI-AD study is still ongoing. For the outcome of relapse, the results at the 1st data cut-off (30 June 2017) and the 2nd data cut-off (30 April 2018) are pooled in this benefit assessment. For all other outcomes examined in this benefit assessment, results are available only for the 1st data cut-off (30 June 2017).

Implementation of the ACT of watchful waiting

The examinations performed in the COMBI-AD study do not fully reflect the recommendations of the S3 guideline. There are differences in terms of diagnostic procedures (which do include neither sonography of lymph nodes nor laboratory diagnostics of the tumour marker S100B) and examination intervals. Nevertheless, patients in the COMBI-AD study were examined closely and for the specific purpose of detecting a relapse; therefore, the examination regimen used in the COMBI-AD study is seen as a sufficient approximation of the ACT of watchful waiting.

Risk of bias

The risk of bias at study level and the risk of bias at outcome level for all outcomes examined in the benefit assessment, except health status, is rated as low. For the outcome of health status, operationalized by the Visual Analogue Scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D), a high risk of bias was found. For all outcomes other than health status, at most indications, for example of an added benefit, can be derived. Due to the high risk of bias, at most a hint of added benefit can be derived for the outcome of health status, operationalized by the EQ-5D VAS.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found between treatment groups in favour of dabrafenib + trametinib in comparison with placebo. For the outcome of overall survival, this results in an indication of added benefit of dabrafenib + trametinib in comparison with the ACT of watchful waiting.

Morbidity

Relapse

For the outcome of relapse, this benefit assessment pooled the results from the 1st and 2nd data cut-offs. At both the 1st data cut-off and the 2nd data cut-off, a statistically significant difference between treatment groups was found in favour of dabrafenib + trametinib in comparison with placebo. For the outcome of relapse, this results in an indication of added benefit of dabrafenib + trametinib in comparison with the ACT of watchful waiting.

The results on the outcome of relapse-free survival, which were presented as supplementary information, also exhibit a statistically significant difference for each of the two cut-offs between treatment groups in favour of dabrafenib + trametinib in comparison with the placebo.

Health status (EQ-5D VAS)

For the outcome of health status, as measured by EQ-5D VAS, no statistically significant difference between treatment groups was found at Month 12. This does not result in a hint of added benefit of dabrafenib + trametinib in comparison with the ACT of watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

The COMBI-AD study did not survey any outcomes in this category.

Adverse events

SAEs

For SAEs, a statistically significant difference was found between treatment groups to the disadvantage of dabrafenib + trametinib in comparison with placebo. For the outcome of SAEs, there was, however, an effect modification by the attribute of age. Patients < 65 years of age as well as those ≥ 65 years of age both exhibit a statistically significant difference to the disadvantage of dabrafenib + trametinib in comparison with placebo. For both subgroups, this results in an indication of greater harm of dabrafenib + trametinib in comparison with the ACT of watchful waiting, but the extent differs between subgroups.

Severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

For each of the outcomes of severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, there is a statistically significant difference between treatment groups to the disadvantage of dabrafenib + trametinib in comparison with placebo. For both outcomes, this results in an

indication of greater harm of dabrafenib + trametinib in comparison with the ACT of watchful waiting.

Specific AEs

Serious eye disorders, serious fever, gastrointestinal disorders

Serious eye disorders, serious fever, and severe gastrointestinal disorders (CTCAE grade ≥ 3) each exhibit a statistically significant difference between treatment groups to the disadvantage of dabrafenib + trametinib in comparison with placebo. For each of these outcomes, this results in an indication of greater harm of dabrafenib + trametinib in comparison with the ACT of watchful waiting.

Neoplasms

According to the study protocol, de novo cancer was to be recorded until the end of the study. However, the company presented only analyses for the general follow-up period for AEs (until 30 days after the end or discontinuation of therapy). For neoplasms, no statistically significant difference between treatment groups was found in these analyses. Consequently, there is no hint of greater or lesser harm of dabrafenib + trametinib in comparison with the ACT of watchful waiting; greater or lesser harm is therefore not proven.

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

On the basis of the results presented, the probability and extent of added benefit of the drug dabrafenib in combination with trametinib in comparison with the ACT are assessed as follows:

Overall, both positive and negative effects were found for dabrafenib + trametinib in comparison with watchful waiting.

Positive effects of major extent were found for overall survival and of considerable extent for relapse (both data cut-offs). In contrast, negative effects were found for serious/severe adverse events, in part in subgroups, with extents ranging up to major. No data are available on the outcome category of health-related quality of life. The negative effects and missing data on health-related quality of life do not fully negate the advantage regarding overall survival, but they do lead to a downgrading of the added benefit.

[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].

In summary, for patients with stage III melanoma with BRAF V600 mutation following complete resection, there is an indication of considerable added benefit of dabrafenib + trametinib as adjuvant therapy in comparison with the ACT of watchful waiting.

Table 3 presents a summary of the results of the benefit assessment of dabrafenib + trametinib in comparison with the ACT.

Table 3: Dabrafenib + trametinib – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of adult melanoma patients in stage III[b] with a BRAF V600 mutation following complete resection[c]	Watchful waiting	Indication of considerable added benefit

a: Presentation of the ACT specified by the G-BA.
b: According to AJCC classification.
c: According to the marketing authorization, the therapeutic indication being assessed here comprises patients in stage III with BRAF V600 mutation, following complete resection. However, patients in stage IIIA were not included in the COMBI-AD study unless they exhibited lymph node metastases > 1 mm. The mutation of the BRAF gene was restricted to V600E and V600K substitution. The study population therefore does not fully cover the therapeutic indication. It remains unclear whether the observed effects would also be seen in patients in stage IIIA according to the AJCC7 classification who have lymph node metastases ≤ 1 mm; according to the AJCC8 classification, these patients do not necessarily have to be in stage IIIA. In addition, it remains unclear whether the observed effects translate to patients with another BRAF V600 mutation.

ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; BRAF: rapidly accelerated fibrosarcoma isoform B (serine/threonine protein kinase B-Raf); 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 (G19-05) to dossier assessment A18-59 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/a18-59-dabrafenib-melanoma-benefit-assessment-according-to-35a-social-code-book-v.10619.html.