Cobimetinib in melanoma with BRAF V600 mutation: Indication of minor added benefit

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Cobimetinib (trade name: Cotellic) has been approved since November 2015 in combination with vemurafenib for the treatment of adults with advanced, i.e. metastatic or unresectable, melanoma with a BRAF V600 mutation. The Federal Joint Committee (G-BA) therefore commissioned the German Institute for Quality and Efficiency in Health Care (IQWiG) to examine whether cobimetinib in combination with vemurafenib has an added benefit over the appropriate comparator therapy vemurafenib alone.

IQWiG found positive and negative effects for several patient-relevant outcomes, which did not completely outweigh one another: An indication of a minor added benefit of the new drug combination compared with vemurafenib monotherapy remained.

Drugs inhibit enzymes of the MAP kinase signal pathway

In about half of all melanomas, the gene for the BRAF enzyme is mutated, which belongs to the MAP kinase signal pathway and which, in its changed form, contributes to increased cell proliferation. Drugs such as vemurafenib inhibit the activity of the mutated BRAF kinase. However, many melanomas develop resistance after some time; they bypass the blocked MAP kinase pathway. A second inhibitor targeting a different site is used to lower this risk: Cobimetinib inhibits the MEK enzyme, which follows BRAF in the signal pathway.

Assessment on the basis of the approval study

The drug manufacturer cited the study coBRIM, which was decisive for the approval, in its dossier. In this study, cobimetinib in combination with vemurafenib was directly compared with vemurafenib. The patient-relevant outcomes of this randomized, double-blind study were overall survival, symptoms, health status, health-related quality of life and adverse events. The risk of bias for the outcomes "morbidity", "health-related quality of life" and "adverse events" was rated as high.

Advantages in overall survival and further outcomes

Participants in the combination arm of the study survived significantly longer than in the vemurafenib arm: an indication of an added benefit of cobimetinib plus vemurafenib. Moreover, there were indications of lesser harm of the combination compared with vemurafenib monotherapy for three outcomes in the category of adverse events, namely neoplasms, alopecia and hyperkeratosis. In patients under 65 years of age, there was also a hint of an added benefit in the category "morbidity", i.e. less pain.

Also several disadvantages

This was offset by indications and hints of greater harm. For diarrhoea, nausea, vomiting and serous retinopathy/retinal detachment, this applied to the total population. In contrast, the hints of greater harm regarding severe adverse events and the adverse event "photosensitivity reaction" were limited to patients with certain metastasis stages.

The certainty of results was greater for the advantages, particularly overall survival, than for the disadvantages. Hence the considerable negative effects did not outweigh the considerable positive effects, but

only resulted in a downgrading of their extent. Overall, there is an indication of a minor added benefit of the combination cobimetinib plus vemurafenib compared with vemurafenib monotherapy.

G-BA decides on the extent of added benefit

This dossier assessment is part of the early benefit assessment according to the Act on the Reform of the Market for Medicinal Products (AMNOG) supervised by the G-BA. After publication of the dossier assessment, the G-BA conducts a commenting procedure and makes a final decision on the extent of the added benefit.

An overview of the results of IQWiG's benefit assessment is given by a German-language executive summary. In addition, the Website gesundheitsinformation.de, published by IQWiG, provides easily understandable German-language information.

More information: More English-language information will be available soon (Sections 2.1 to 2.6 of the dossier assessment as well as subsequently published health information on informedhealth.org). If you would like to be informed when these documents are available, please send an e-mail to " info@iqwig.de.

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