Dabrafenib/trametinib in advanced BRAF V600 mutated melanoma: Indication of added benefit

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Dabrafenib (trade name: Tafinlar) has been approved since 2013 for the treatment of adults with advanced, i.e. metastatic or unresectable, melanoma with a BRAF V600 mutation. Since September 2015, dabrafenib has been approved for this therapeutic indication also in combination with trametinib (trade name: Mekinist), which was approved for use as monotherapy already in June 2014.

The German Institute for Quality and Efficiency in Health Care (IQWiG) therefore examined in two dossier assessments whether dabrafenib plus trametinib or trametinib alone offers an added benefit over the appropriate comparator therapy vemurafenib. According to the findings, no added benefit is proven for trametinib monotherapy because of a lack of suitable study data. For the combination therapy, however, there is an indication of a major added benefit for women and of a non-quantifiable added benefit for men.

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. New drugs such as dabrafenib or 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: Trametinib inhibits the MEK enzyme, which follows BRAF in the signal pathway.

Dabrafenib now also in combination with trametinib

According to an addendum on an IQWiG dossier assessment from March 2014, no added benefit is proven for dabrafenib alone in comparison with the appropriate comparator therapy vemurafenib: The results from the indirect comparison with the drug dacarbazine as so-called common comparator presented by the drug manufacturer allowed no reliable conclusions. It was unclear whether the patients investigated in the two studies were sufficiently similar regarding the prognosis of their disease.

New early benefit assessments of dabrafenib and trametinib became necessary because of the approval of the combination of dabrafenib and trametinib, for which the Federal Joint Committee (G-BA) again specified vemurafenib as appropriate comparator therapy. The manufacturer submitted data from the COMBI-v study, in which dabrafenib/trametinib was directly compared with vemurafenib, in both of its dossier.

Trametinib monotherapy: no suitable data

Additionally, the G-BA wanted to find out in a second research question whether this drug alone offers an added benefit in comparison with vemurafenib. For this purpose, the manufacturer cited an indirect comparison, but derived no added benefit of trametinib from it due to methodological concerns. IQWiG also concluded that no evaluable data were available for this research question. An added benefit of trametinib as monotherapy in comparison with the appropriate comparator therapy

is therefore not proven.

Combination therapy prolongs lifetime in women

The randomized, active-controlled COMBI-v study, however, was suitable for answering the question regarding the added benefit of the combination dabrafenib/trametinib in comparison with vemurafenib. Adults with unresectable or metastatic melanoma and confirmed BRAF V600 mutation who had not received prior systemic anti-cancer treatment were included.

Primary outcome of the study was overall survival, which was significantly longer in the dabrafenib/trametinib arm - with an effect modification by sex, however: There was an indication of an added benefit for women, whereas an added benefit in overall survival for men was not proven.

Advantages in further outcomes

There was a hint of an added benefit of the combination dabrafenib/trametinib for the time to deterioration for each of the following outcomes: pain, insomnia, appetite loss and diarrhoea. A hint of an added benefit was also found in health-related quality of life and in a number of specific adverse events. However, the dossier contained no suitable subgroup analyses on these outcomes, which show whether the results differ, e.g. by sex. It therefore remains unclear whether advantages exist only for women (or only for men) also for these outcomes.

The dossier contained further analyses on the influence of sex only for some side effects; these analyses were subject to high uncertainty, however. According to the findings, there is an indication of lesser harm

in comparison with the comparator therapy for men regarding serious side effects (adverse events CTCAE grade 3 or higher); i.e. of an advantage of the combination therapy. Due to the uncertainty of the analyses, the extent of this advantage is non-quantifiable.

Extent remains unclear in men

Overall, there is an indication of a major added benefit of dabrafenib/trametinib in comparison with vemurafenib for women with advanced melanoma with BRAF V600 mutation. For men with the same therapeutic indication, there is an indication of a non-quantifiable added benefit. This extent category is sometimes misunderstood to mean "added benefit less than minor", which can, in a manner of speaking, "only be seen with a magnifying glass". This is not the case, however: It only means that the extent of the added benefit cannot be clearly allocated to one of the categories ("minor", "considerable", "major").

G-BA decides on the extent of added benefit

These dossier assessments are 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 assessments, the G-BA conducts commenting procedures and makes a final decision on the extent of the added benefit.

More information: www.iqwig.de/download/A15-39_D … ertung-35a-SGB-V.pdf

www.iqwig.de/download/A15-40_T … ertung-35a-SGB-V.pdf