Dabrafenib in melanoma: Added benefit not proven

January 7 2014

Dabrafenib (trade name: Tafinlar) has been approved in Germany since August 2013 for the treatment of advanced melanoma.In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) examined whether this new drug offers an added benefit over the appropriate comparator therapy.

According to the findings, an added benefit of dabrafenib is not proven: Regarding mortality, symptoms, health-related quality of life and treatment discontinuation due to side effects, no advantage can be derived from the dossier. Concerning other side effects, the data were too uncertain to allow drawing any conclusions.

G-BA specified dacarbazine as appropriate comparator therapy

Dabrafenib is an option for adult patients with melanoma that has a certain abnormal protein (BRAF V600 mutation) and that is unresectable or has already formed metastases.

The Federal Joint Committee (G-BA) has specified the drug dacarbazine as the appropriate comparator therapy.

Study allowed treatment switching

One study (BREAK-3), which directly compared dabrafenib and dacarbazine, was included in the assessment. It was envisaged from the beginning of the study that patients could switch from the dacarbazine to the dabrafenib group as soon as the x-ray showed progression of the disease (radiological progression).

Because of the treatment switching it remained unclear which treatment caused the results observed – this was the case for mortality as well as for symptoms, quality of life and side effects. Hence the reliability of the conclusions of the study results was very limited from the outset.

No survival advantage

The data on overall survival showed no statistically significant difference between the treatment groups. However, the manufacturer claimed an advantage for survival in its dossier, and particularly cited the measured time that patients survived without a progression of the disease becoming visible in the x-ray (PFS = progression-free survival).

This is a so-called surrogate outcome, however. It is only reasonable to use such a surrogate parameter if the effect of the treatment on the surrogate (PFS) predicts the effect the treatment has on the patient-relevant outcome (overall survival). However, since this relationship between PFS and overall survival was not shown in the dossier following the necessary scientific criteria, IQWiG could not use the data on PFS for the assessment.

Data on quality of life were partly not evaluable

Health-related quality of life was recorded in the study using two different questionnaires. In the case of the instrument particularly developed for cancer diseases (EORTC QLQ-C30), there were no

statistically significant differences between the two groups. In case of the questionnaire EQ-5D, a comprehensive instrument for various indications, no evaluable results were available.

There were also no relevant differences between the two treatment arms regarding symptoms.

Side effects: data uncertainty because of different treatment lengths

The available data hardly allow any conclusions on side effects. The main reason is that the length of treatment and observation was different for the patients in the two study arms – with an average length of 4.9 months for dabrafenib and of 2.8 months for dacarbazine. However, the longer a treatment lasts, the more likely it becomes that side effects occur. Hence the results are biased to the disadvantage of dabrafenib and not informative for most aspects concerning side effects.

The only exception is the outcome "treatment discontinuation due to side effects". However, there were no statistically significant group differences.

Because there were no positive effects regarding mortality, symptoms and quality of life, and the data on side effects were too uncertain, overall, IQWiG sees no proof of added benefit of dabrafenib compared with dacarbazine.

G-BA decides on the extent of added benefit

The dossier assessment is part of the overall procedure for early benefit assessments supervised by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a

commenting procedure, which may provide further information and result in a change to the benefit assessment. The G-BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

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 and brief German-language information on dabrafenib.

The G-BA website contains both general English-language information on benefit assessment pursuant to §35a Social Code Book (SGB) V and specific German-language information on the assessment of dabrafenib.

Provided by Institute for Quality and Efficiency in Health Care