Vismodegib in basal cell carcinoma: Added benefit not proven

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The drug vismodegib (trade name: Erivedge) is approved for the treatment of patients with two forms of basal cell carcinoma (BCC): symptomatic metastatic BCC and locally advanced BCC inappropriate for surgery or radiotherapy.

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 current standard therapy. However, no added benefit can be derived from the data presented in the company's dossier.

Currently hardly any chances of cure in advanced basal cell carcinoma

Basal cell carcinoma (also called "basalioma") is a malignant form of skin cancer, which mainly occurs on the head or neck. In most cases, timely surgery can prevent it from spreading. In an aggressive ("locally advanced") form and the occurrence of metastases, however, treatment options are limited. Often only symptoms can be relieved, but cure is no longer possible.

The manufacturer has now presented data from an approval study. According to this study, tumours shrank under vismodegib in some patients with symptomatic metastatic or locally advanced BCC.

G-BA distinguished different comparator therapies

The Federal Joint Committee (G-BA) specified several appropriate comparator therapies: In patients with symptomatic metastatic BCC for whom surgery was not an option, the drug was to be compared with radiotherapy. In patients with symptomatic metastatic BCC for whom radiotherapy was inappropriate, surgery was to be used as comparator therapy. In patients with symptomatic metastatic or locally advanced BCC for whom neither radiotherapy nor surgery was an option, the benefit of vismodegib was to be compared with the benefit of best supportive care. "Best supportive care" means palliative treatment tailored to the individual patient, i.e. a treatment that does not aim to cure, but to alleviate symptoms as good as possible (e.g. with adequate pain therapy) and improve quality of life.

Pharmaceutical company deviated from the G-BA's specification

In contrast to the G-BA's specifications, the pharmaceutical company exclusively compared its drug with best supportive care – claiming that surgery and radiotherapy in symptomatic metastatic BCC also had only a palliative effect. IQWiG did not accept this deviation from the specified appropriate comparator therapy: If it is assumed that different treatments are optimal for different patient groups, this differentiation also has to have an effect on the control groups.

Studies unsuitable for assessing the added benefit

However, the main problem was that the dossier was based solely on studies without control groups. An added benefit can only be derived from this kind of studies if "dramatic" patient-relevant effects occur in these studies. To estimate the effect size, other studies would have to be

used for comparison – in this case, studies known as "historical controls". If, for example, most patients died early in the historical controls, but many patients survived longer in the study with the new drug, this would be a "dramatic effect".

Based on the study data submitted, it was not possible to assess whether there were dramatic effects with regards to patient-relevant outcomes because tumour regression mainly measured with imaging techniques (the so-called "objective response rate") is a surrogate outcome and not necessarily patient-relevant. Moreover, the pharmaceutical company did not present any data on the appropriate comparator therapy so that no comparison could be made. Hence an added benefit versus the appropriate comparator therapy is not proven.

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 vismodegib.

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