Vandetanib in thyroid cancer: Added benefit not proven

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Vandetanib (trade name: Caprelsa) has been approved in Germany since February 2012 for the treatment of adult patients who have a particular form of aggressive thyroid cancer. In a new benefit assessment, the German Institute for Quality and Efficiency in Health Care (IQWiG) has now examined the added benefit of the drug pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG).

There is a hint that pain occurs later or gets worse later in a part of the patients, the ones aged under 65 years.But because of the overall poor data on side effects, no conclusion could be drawn about harm. Therefore it was not possible to balance positive and negative effects. Overall, an added benefit of vandetanib is therefore not proven.

Contents of the first dossier on vandetanib were incomplete

Vandetanib underwent a first " early benefit assessment procedure in 2012. In this procedure, the drug manufacturer did not present any data for the patients for whom the drug is approved. The added benefit was regarded as not proven because the contents of the dossier were incomplete. The pharmaceutical company could apply for a reassessment of vandetanib within a transition period and submit a new dossier to the Federal Joint Committee (G-BA).

"Best supportive care" as the appropriate comparator

therapy

In the newly submitted dossier, the company now presented an analysis of data for patients who were treated according to the approval status. As specified by the G-BA, vandetanib was compared with "best supportive care". This means the best possible supportive therapy, optimized for the individual patient for alleviation of symptoms and improvement in the quality of life.

The only study relevant for the benefit assessment, the approval study, compared the administration of vandetanib in combination with "best supportive care" with a treatment consisting of "best supportive care" in combination with a placebo.

Study population differed from approval population

Vandetanib is approved for patients with an "aggressive and symptomatic" medullary thyroid cancer (MTC) in whom surgery is not possible (anymore), the cancer is already very large or secondaries (metastases) have formed in other regions of the body. The European regulatory authority, the European Medicines Agency (EMA), had restricted the therapeutic indication in such a way in order to produce an overall positive benefit-risk balance. This is because treatment with vandetanib also involves major risks and can, for example, lead to severe heart rhythm disturbances.

However, in the study presented by the manufacturer, patients in whom the course of the disease was not "aggressive and symptomatic" were also enrolled. So the study population was much wider than the approval population. Only a subpopulation of the approval study was therefore relevant for the dossier assessment: the dossier provided analyses for patients with progressive and symptomatic course of disease, whose

characteristics IQWiG considered to be an adequate approximation to the approval population (with aggressive and symptomatic course of disease).

Risk of bias in the approval study

The risk of bias of the approval study is very high, particularly because the study participants could change the treatment as soon as the course of disease got worse (progression). About two thirds of the participants changed from the placebo group to the open treatment with vandetanib. At the same time, the median treatment duration in the study arm with vandetanib was considerably longer (88.6 weeks) than the one in the study arm with "best supportive care" alone (37.1 weeks).

With the exception of survival time, the analyses in the manufacturer's dossier for most outcomes were limited to observations made during the treatment the patients were originally allocated to. This means that data on courses of disease after the change of treatment were not considered anymore.

Pain progression in people aged under 65 years occurred later

There were no statistically significant differences between treatment with or without vandetanib regarding mortality (overall survival).

Regarding symptoms and complaints, there was a hint of a minor added benefit of vandetanib in people aged under 65 years: In the younger patients, the time to pain progression was almost eight months longer on average under vandetanib plus "best supportive care" than under "best supportive care" alone. IQWiG therefore initially considers there to be a hint of a minor added benefit of vandetanib. There was no advantage in

people aged over 65 years.

The manufacturer's dossier did not provide any usable data on health-related quality of life.

Greater harm cannot be excluded

The harm side remains completely unclear: The analysis did not consider the different treatment duration in both study arms adequately for most side effects (adverse events), so that no final conclusion on harm can be drawn. Greater harm from vandetanib can also not be excluded.

Since, due to the great uncertainty regarding harm, it can also not be excluded that negative effects outweigh the positive effects, an added benefit of vandetanib in comparison with "best supportive care" alone 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.

Provided by Institute for Quality and Efficiency in Health Care