Addendum on regorafenib in metastatic colorectal cancer: Added benefit no longer proven

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Regorafenib (trade name: Stivarga) has been approved since 2013 for adults with metastatic colorectal cancer in whom previous treatments are no longer effective or for whom these alternatives are not an option. In two previous benefit assessments conducted in early 2014 and in early 2016, the German Institute for Quality and Efficiency in Health Care (IQWiG) found a hint of a minor added benefit of the drug over the appropriate comparator therapy: A survival advantage was accompanied by more frequent severe side events. However, IQWiG had also criticised in these assessments that the manufacturer had not adequately analysed the data on patient-reported outcomes (symptoms and quality of life).

In the commenting procedure after the second dossier assessment, the manufacturer presented changed analyses on health-related quality of life and symptoms. The Federal Joint Committee (G-BA) then commissioned IQWiG to conduct a supplementary assessment, a so-called addendum. According to the findings, an added benefit of the drug in comparison with the appropriate comparator therapy "best supportive care" (BSC) is no longer proven.

Manufacturer presented new analyses with its comment

IQWiG had assessed the data on quality of life and symptoms on

regorafenib already three times before: The manufacturer had presented inadequate analyses on these outcomes in the dossier from 2013, in the comments on the assessment from 2014 and in the current dossier from 2015. In the 2015 dossier, for example, the manufacturer had not complied with specifications provided in the manual on the questionnaire used for recording the data, although it had considered these in the previous procedure.

The manufacturer now provided a new analysis in the current commenting procedure. This analysis also has deficiencies, but allowed IQWiG to assess the data.

Additional negative effects revealed

The new analyses showed additional negative effects of regorafenib regarding quality of life. In addition, there was a disadvantage in the symptom "diarrhoea", which was already apparent in the assessment of severe side effects. In the overall consideration, the negative effects now outweighed the advantage in all-cause mortality. An added benefit of regorafenib in comparison with BSC is therefore not proven for patients with metastatic colorectal cancer.

"Had we not been persistent in our inquiries and insisting on the adherence to the standards, we would not have been able to include these data in our assessment", says Thomas Kaiser, Head of the Drug Assessment Department. "Data that reveal disadvantages of the drug - and that otherwise would not have become public."

G-BA decides on the extent of added benefit

The 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 manufacturer's dossier and the IQWiG dossier assessment, the manufacturer submitted additional information in the commenting procedure. The G-BA subsequently commissioned IQWiG to assess the data subsequently submitted. IQWiG now presents this assessment in the form of an addendum. The G-BA makes a final decision on the extent of added benefit.