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# Regorafenib in metastatic colorectal cancer: Still hint of minor added benefit

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Regorafenib (trade name: Stivarga) has been approved since August 2013 for adults with metastatic colorectal cancer in whom previous treatments are no longer effective or for whom these alternatives are not an option. After a first early benefit assessment in January 2014, the German Institute for Quality and Efficiency in Health Care (IQWiG) now reexamined whether the drug offers an added benefit over the appropriate comparator therapy. This new assessment was conducted because a limitation of the corresponding decision by the Federal Joint Commission (G-BA) expired in July 2015.

According to the findings, IQWiG - as in 2014 - found a hint of a minor added benefit of regorafenib. Patients have a survival advantage, but certain severe side effects occur more frequently.

## "Best supportive care" was appropriate comparator therapy

The G-BA again specified "best supportive care" (BSC) as appropriate comparator therapy. BSC means a therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve quality of life.

In its second dossier, the drug manufacturer presented data from the two randomized controlled trials CORRECT and CONCUR. CORRECT was already included in the first dossier, but the manufacturer added new

analyses on symptoms, quality of life, and adverse events.

In both studies, one group was treated with regorafenib plus BSC, and the control group received a placebo plus BSC. However, it was not allowed to use other systemic anticancer treatments as part of the BSC.

## Reduced reliability of the conclusions: no more than a hint can be derived

The certainty of conclusions of the results of CORRECT and CONCUR is limited, which is why no more than a hint of an added benefit can be derived. On the one hand, it remained unclear whether the excluded anticancer treatments would have been able to relieve the symptoms and thus should have been part of the - palliative - BSC. On the other hand, only patients in better general condition (ECOG PS 0 or 1) could participate in the studies, although regorafenib is also approved for patients in poorer general condition (ECOG PS ? 2).

## Still no valid data on symptoms and quality of life

Presenting no data on patients in poorer general condition (ECOG PS ? 2), the manufacturer did not fulfil the G-BA's conditions. One of the reasons provided by the G-BA for limiting its 2014 decision was that data on such patients were missing.

Informative data on symptoms and complaints (morbidity) as well as on quality of life were another condition by the G-BA. In the first dossier, the data on these outcomes had not been evaluable because it remained unclear for a significant part of the patients why they had ended their treatment. The second dossier now contained additional analyses from the CORRECT study. These were not conducted adequately, however: The analyses did not comply with specifications provided in the manual

on the questionnaire used for recording the data - in contrast to the first dossier, where the analysis had been adequate in this respect.

## Advantage in survival, but disadvantage in severe side effects

Even under inclusion of the data from CONCUR the assessment results on the outcomes "overall survival" and "side effects" are still valid: There was a statistically significant difference in favour of regorafenib in overall survival, from which a hint of a considerable added benefit can be derived.

At the same time, severe side effects were more common under regorafenib. This applied particularly to certain types of skin rash (exanthemas), hand-foot syndrome, fatigue, and diarrhoea. Overall, IQWiG sees a hint of greater harm with the extent "major" for severe side effects.

This disadvantage does not completely outweigh the survival advantage, however. As in the first dossier assessment, IQWiG therefore overall sees a hint of a minor added benefit of regorafenib in comparison with the appropriate comparator therapy.

## G-BA decides on the extent of added benefit

This 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 dossier assessment, the G-BA conducts a commenting procedure and makes a final decision on the extent of the added benefit.

**More information:** www.iqwig.de/download/A15-43_R … ertung-35a-