Aflibercept in colorectal cancer: Indication of minor added benefit

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The drug aflibercept (trade name: Zaltrap) has been approved in Germany since February 2013 in combination with a certain chemotherapy for adults with metastatic colorectal cancer in whom chemotherapy with oxaliplatin could not stop the disease from progressing. 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. According to this, considerable advantages in respect of overall survival are accompanied by major potential harm in the form of side effects. Overall, there is therefore an indication of a minor added benefit of aflibercept.

Aflibercept complements chemotherapy

Aflibercept in combination with a chemotherapy consisting of irinotecan /5-fluorouracil/folinic acid (FOLFIRI) was compared with FOLFIRI alone. The approval study (VELOUR), which compared the treatment "aflibercept plus FOLFIRI" with the treatment "placebo plus FOLFIRI", was available for the benefit assessment. This was a randomized and double-blind study, i.e. the patients were assigned randomly to one of the two treatment groups, and neither the patients nor the doctors knew whether aflibercept with FOLFIRI or FOLFIRI alone was used.

A total of 178 centres in Europe, America, Australia, New Zealand,

South Africa and Korea took part in this multinational study: The participants were 1226 adults with adenocarcinoma of the colon or rectum who had recurrence after failure of a chemotherapy containing the drug oxaliplatin.

Overall survival: indication of considerable added benefit

Half of the patients who received FOLFIRI chemotherapy alone had died after 12 months. Half of the patients who received aflibercept in combination with FOLFIRI chemotherapy had died after 13 to 14 months. This means that life expectancy increased by 1 to 2 months on average (median). For overall survival, this led to an indication of an added benefit with the extent "considerable" for the combination of aflibercept with FOLFIRI in comparison with FOLFIRI alone.

The manufacturer's dossier did not provide any results, or any results that could be used, on symptoms and complaints (morbidity) and health-related quality of life. Hence an added benefit of aflibercept in comparison with the appropriate comparator therapy for these outcome categories is not proven.

Side effects: indications of greater harm

Serious events and severe adverse events (e.g. infection, diseases of organs, metabolism, blood and lymph system) as well as treatment discontinuations due to severe adverse events were more frequent during the treatment with aflibercept than during the treatment with FOLFIRI alone in all age groups.

In summary, there is an indication of greater harm with major extent from the treatment with aflibercept plus FOLFIRI in comparison with

FOLFIRI alone for several outcomes of the category side effects.

Overall, indication of minor added benefit

Overall, positive effects of aflibercept are accompanied by negative effects with the same certainty of results: the indication of a considerable added benefit in mortality (overall survival) has to be weighed up against the indications of greater harm with major extent regarding side effects. IQWiG therefore downgrades the extent of the added benefit of aflibercept in comparison with the appropriate comparator therapy from "considerable" to "minor".

IQWiG published a first assessment of aflibercept (trade name: Eylea) on 15th March 2013. This dealt with a different therapeutic indication, however, namely the "treatment of wet age-related macular degeneration (AMD)".

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.

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