Added benefit of eribulin in breast cancer is not proven

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Eribulin (trade name: Halaven) was approved in March 2011 for women with locally advanced or metastasizing breast cancer in whom the disease has progressed despite prior drug therapy.

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 eribulin offers an added benefit compared with the present standard therapy.

According to the results of the assessment, the currently available evidence provides "hints" that eribulin may increase survival time in patients for whom taxanes or anthracyclines are no longer an option. However, it is unclear how many more weeks or months patients can survive. No survival advantage was shown in patients who can still be treated with taxanes or anthracyclines. At the same time, due to a lack of suitable data it cannot be excluded with sufficient certainty that eribulin causes greater harm in the form of side effects. Overall, IQWiG therefore concludes that an added benefit of eribulin is not proven.

G-BA specifies appropriate comparator therapy

According to the legal ordinance, benefit assessments must follow the approval status. This refers both to the new drug to be evaluated and to the therapies used in the comparator groups.

Eribulin is approved for patients in whom the disease has progressed further, despite having received at least two cycles of a taxane and anthracycline containing chemotherapy (unless these treatments were considered unsuitable). As appropriate comparator therapies, the Federal Joint Committee (G-BA) has specified either monotherapy with capecitabine, 5-fluorouracil, or vinorelbine or renewed therapy with taxanes or anthracyclines, insofar as this is an option for patients.

The pharmaceutical company followed this specification of the appropriate comparator therapy. However, by the wording of the research question and the inclusion criteria of the dossier, the company also allowed other treatments as a comparator therapy for eribulin.

One study included in the assessment

One relevant study was available for the early benefit assessment, an approval study on eribulin (EMBRACE). However, drugs that were not a component of the appropriate comparator therapy were also used in this study. 18% of patients even received treatment that is not approved in Germany for the indication investigated (gemcitabine monotherapy).

Overall, only 69% of patients in the comparator group were treated according to the specifications of the G-BA. Nevertheless, in the dossier the manufacturer uses the results of all patients (overall population). This is an approach that IQWiG cannot accept.

No survival advantage in patients who can still be treated with taxanes or anthracyclines

Data on overall survival and side effects (adverse events), but not on quality of life, were analysed in the study, so that per se no conclusions about the latter outcome are possible.

For the outcome "overall survival", separate data were available for the sub-population treated with the appropriate comparator therapy. As the analysis showed, patients in the eribulin group for whom treatment with taxanes or anthracyclines could still be an option did not survive longer than patients who received these treatment alternatives. An added benefit is therefore not proven.

"Hint" of an increase in survival in patients for whom taxanes or anthracyclines are no longer an option

The situation is different in patients for whom taxanes or anthracyclines are no longer an option. The data show a survival advantage here, at least for the first time point of analysis. In contrast, statistically significant differences were no longer observed between treatment groups at a second, later time point of analysis. It cannot be calculated exactly how many weeks or months longer patients receiving eribulin survived. However, the difference in the study was not more than a few months.

From the data analysed, IQWiG initially infers a "hint" of an added benefit in patients for whom treatment with taxanes or anthracyclines is no longer an option; the extent of this added benefit is unquantifiable but can at best be classified as "considerable".

No separate data on adverse events in the sub-population

In contrast to the outcome "overall survival", data on side effects (adverse events) were only available for the overall population; no separate data were provided for the sub-population treated with one of the appropriate comparator therapies specified. In its assessment, IQWiG additionally investigated the data for the overall population in

order to obtain an impression of potential harm caused by the interventions.

According to the results, both the overall rate of adverse events and the rate of severe adverse events were statistically significantly higher in the eribulin group than in the comparator group. IQWiG infers from these results that greater harm from eribulin cannot be excluded with sufficient certainty for the sub-population investigated in the dossier assessment.

Negative effects may outweigh positive ones

Overall IQWiG cannot infer an added benefit of eribulin from the data available. This also applies to the sub-group of patients for whom taxanes or anthracyclines are no longer an option. This is because it cannot be excluded that the negative effects (severe adverse events) outweigh the positive effects (survival). It cannot be excluded that eribulin may even be more harmful than beneficial in patients who could still be treated with taxanes or anthracyclines.

G-BA decides on the extent of added benefit

The procedure for inferring the overall conclusion on the extent of added benefit is a proposal from IQWiG. The G-BA, which has opened a formal commenting procedure, decides on the extent of added benefit.

The following extract (PDF, 186 kB) provides an overview of the results of IQWiG's benefit assessment. The website gesundheitsinformation.de, which is issued by IQWiG, provides easily understandable brief information (German version).

The G-BA website contains both general information on benefit

assessments pursuant to §35a Social Code Book V and specific information on the assessment of eribulin (German version).

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