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Ibrutinib in CLL: Added benefit for treatment-naive patients not proven

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Ibrutinib was approved in 2014 for the treatment of certain adults with chronic lymphocytic leukaemia (CLL), particularly as second-line treatment. The therapeutic indication was expanded in 2016. The drug is now also approved for treatment-naive patients. The German Institute for Quality and Efficiency in Health Care (IQWiG) has now examined in a dossier assessment whether this drug offers an added benefit. This was not proven, however, because the drug manufacturer presented no suitable data for any of the total of three subgroups of patients.

G-BA defined three research questions

The Federal Joint Committee (G-BA) distinguished between three treatment situations in its commission and specified a different appropriate comparator therapy for each of them: In patients for whom chemo-immunotherapy is an option and for whom a combination therapy consisting of fludarabine, cyclophosphamide and rituximab (FCR) is also suitable, ibrutinib was to be compared with FCR. If chemo-immunotherapy is an option, but FCR is not, ibrutinib was to be tested against chemo-immunotherapy at the physician's choice.

The third research question concerned treatment-naive CLL patients for whom chemo-immunotherapy is not an option. In this patient group, ibrutinib was to be compared with best supportive care (BSC). BSC means the best possible supportive therapy, optimized for the individual patient for alleviation of symptoms and improvement in the quality of

life. Patients with specific mutations (17p deletion, TP53 mutation) were not subject of this assessment because ibrutinib has already been approved for them for a longer period of time.

Studies not sufficiently similar

For the first research question, the dossier contained no data at all. For the second patient group, for whom FCR is not an option, the manufacturer presented results from indirect comparisons because no studies of direct comparisons were available.

Sufficient similarity of the studies was not ensured in any of these indirect comparisons, however. In particular, the dosage of the drug differed in the respective comparator arms, and was partly too low. In addition, treatment did not comply with the approval in some of the patients. Furthermore, the participants differed regarding different aspects including age and accompanying diseases. It could therefore not be excluded that differences in the treatment results were solely caused by differences in dosage or the study populations.

Best supportive care not implemented

For the third research question, the manufacturer used a study of direct comparison. Its results were unsuitable for the assessment of the added benefit, however, because the study also included patients for whom an alternative chemo-immunotherapy would have been an option. In addition, all participants in the comparator arm received the identical drug. This means, however, that treatment was not optimized for the individual patient.

Hence the dossier contained no data that would be suitable for the assessment for any of the three research questions. An added benefit of

ibrutinib in comparison with the respective appropriate comparator therapy is therefore not proven in the expanded therapeutic indication either.

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

Provided by Institute for Quality and Efficiency in Health Care