Ipilimumab in advanced melanoma: Added benefit for non-pretreated patients not proven

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In early 2014, the German Institute for Quality and Efficiency in Health Care (IQWiG) assessed the added benefit of ipilimumab in non-pretreated patients with advanced melanoma. The drug manufacturer claimed a noticeable increase in survival time and thus an added benefit versus dacarbazine, the appropriate comparator therapy specified by the Federal Joint Committee (G-BA). However, the indirect comparison conducted by the company was too uncertain, and the postulated effect was biased in favour of ipilimumab. Hence an added benefit was not proven.

In two addenda, the Institute now also examined updated and corrected analyses by the company as well as a possible added benefit versus a second comparator therapy. The result remained unchanged, however: An added benefit of ipilimumab is not proven for non-pretreated patients versus any of the two comparator therapies.

Advantage in pretreated patients

Ipilimumab is a monoclonal antibody used in melanoma if the disease is so advanced that the melanoma can no longer be surgically removed or has formed metastases. In 2012, the manufacturer presented informative data for pretreated patients from a randomized controlled trial. These data indicated a major advantage of ipilimumab in survival time in comparison with "best supportive care". This advantage was associated

with major risk of harm, however.

Effects in non-pretreated patients not interpretable

In October 2013, European approval was expanded to patients who have not been treated for their advanced melanoma. In a new dossier, the manufacturer subsequently also claimed an added benefit for this group versus the appropriate comparator therapy dacarbazine specified by the G-BA. IQWiG did not concur with this claim because the treatment effects presented by the manufacturer were not interpretable: The quality of the relevant indirect unadjusted comparison was too low, the results were biased in favour of ipilimumab, and not all relevant confounders were considered in the analysis.

Subsequent assessment in two addenda

In addition, the manufacturer had presented data on the comparison of ipilimumab with vemurafenib in its dossier. IQWiG did not examine these data in its dossier assessment because the G-BA had not specified vemurafenib as an appropriate comparator therapy at first. In March 2014, shortly before completion of the IQWiG dossier assessment, the G-BA commissioned the Institute to also assess the potential added benefit versus vemurafenib. Moreover, the manufacturer submitted corrected and updated data analyses in the commenting procedure on the dossier assessment in April 2014. Following the G-BA's commission, IQWiG now assessed these data in a second addendum.

Indirect comparison not interpretable

As so far there are no studies that directly compare ipilimumab with vemurafenib, the manufacturer used an indirect comparison, in which dacarbazine was used as a so-called common comparator. In this indirect comparison, on the one hand it used data from the BRIM-3 study, a

randomized phase 3 study comparing vemurafenib with dacarbazine.

For the second side of the indirect comparison, the manufacturer did not use a direct comparison between ipilimumab and dacarbazine. Instead, it used the unadjusted indirect comparison again, which it had already used for examining the added benefit in comparison with dacarbazine. Hence the indirect comparison between ipilimumab and vemurafenib is also subject to great uncertainties. No conclusions on added benefit can be derived from this.

General weakness of analysis not resolved

In the second addendum, the Institute examined the corrected analyses subsequently submitted by the manufacturer. This correction reduced the exclusion of patients, but, in the outcome "overall survival", the exclusion was still 20 percentage points higher on the ipilimumab side of the indirect comparison than on the dacarbazine side. Originally, the difference was almost 40 percentage points.

What is more important, however, is the fact that the documents subsequently submitted did not address the uncertainty resulting from the methods of the unadjusted indirect comparison. Overall, an added benefit of ipilimumab in non-pretreated patients with advanced melanoma versus dacarbazine or vemurafenib is still not proven.

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 the IQWiG dossier assessment, the G-BA conducted commenting procedures, in which the manufacturer submitted additional information. The G-BA subsequently commissioned IQWiG to assess the data subsequently submitted.

If, in the course of the discussions on a commission of the G-BA, a need for further revision arises, IQWiG presents its report in the form of an addendum. The Institute sent the two addenda on ipilimumab to the commissioning agency on 26 March and on 16 May 2014.

The G-BA then decides on the extent of the added benefit in each case, thus completing the early benefit assessment.

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