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

March 18 2014

The German Institute for Quality and Efficiency in Health Care (IQWiG) already assessed the added benefit of ipilimumab in advanced melanoma in 2012. A considerable added benefit was found for patients who had already received previous treatment. In the new dossier compiled by the drug manufacturer, the drug was now compared with the appropriate comparator therapy dacarbazine specified by the Federal Joint Committee (G-BA) also for non-pretreated patients.

Again, the manufacturer claimed a noticeable gain in survival time and thus an added benefit. This time, IQWiG did not concur with the interpretation: The effect was estimated on the basis of an indirect comparison of individual patient data. The data were very uncertain and, moreover, by unilaterally excluding patients with particularly unfavourable prognosis, the effect was biased in favour of ipilimumab. Hence an added benefit of ipilimumab in advanced melanoma for non-pretreated patients is not proven.

Approval expanded

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 from a randomized controlled trial for pretreated patients. These data indicated a major advantage of ipilimumab in survival time, which

was associated with major risk of harm, however.

After the European approval was expanded in 2013 to include patients who have not been treated for their advanced melanoma, the manufacturer now claimed an added benefit versus the appropriate comparator therapy dacarbazine specified by the G-BA also for this group.

Indirect comparison of low quality

However, the manufacturer neither presented a direct comparison nor a so-called adjusted indirect comparison between the study participants who received ipilimumab or the appropriate comparator therapy. Instead, it based its assessment on an indirect comparison of individual patient data from different studies on ipilimumab and on one single study on dacarbazine, from which it chose those patients who had not received previous treatment of advanced melanoma.

It can be assumed in these unadjusted indirect comparisons that patients on both sides of the comparison differ from each other with regards to important confounders, which can entail a systematic bias of the treatment effect. The manufacturer tried to account for these differences with a statistical method.

Results biased in favour of ipilimumab

However, the manufacturer only included those patients in its comparison for whom data on all confounders considered were available. Because of this, considerably more patients were excluded from the comparison on the ipilimumab side than on the dacarbazine side – e.g. 40% compared to not even 1% in the outcome "overall survival". In the outcome "side effects", the numbers were even further apart. Many

patients with particularly poor prognosis were apparently excluded from the analysis on the ipilimumab side. The effects were therefore highly biased in favour of ipilimumab.

Analysis did not consider all confounding variables

Furthermore, the manufacturer did not consider known confounders like the presence of visceral metastases, i.e. metastases in internal organs, or the time since the diagnosis of the melanoma in the analysis presented. The certainty of results, which was already low, was further downgraded because of this.

Since the treatment effects presented by the manufacturer were therefore not interpretable, an added benefit of ipilimumab in non-pretreated patients with advanced melanoma is 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 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.

Provided by Institute for Quality and Efficiency in Health Care