Pembrolizumab in advanced melanoma: Added benefit for certain patients

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Pembrolizumab (trade name: Keytruda) has been approved since July 2015 for adults with advanced melanoma that can no longer be surgically removed or has already formed metastases. The German Institute for Quality and Efficiency in Health Care (IQWiG) examined in a dossier assessment whether this drug offers an added benefit over the appropriate comparator therapy.

According to the findings, an added benefit can be derived for different patient groups: In pretreated patients for whom ipilimumab is a suitable next treatment, severe and serious side effects as well as discontinuations due to side effects occur later under pembrolizumab. Overall, this results in an indication of a considerable added benefit.

Treatment-naive adults whose tumour has no BRAF V600 mutation survive longer with the new drug and have advantages in one subdomain of quality of life. These advantages result in a hint of a minor added benefit.

Appropriate comparator therapy depends on pretreatment and tumour mutation

Pembrolizumab is a monoclonal antibody used in advanced melanoma if the melanoma can no longer be surgically removed or has already formed metastases. The drug has been designed to enhance the body's immune reaction to the tumour.

The Federal Joint Committee (G-BA) distinguished between three patient groups in its specification of the appropriate comparator therapy: In pretreated adults, pembrolizumab is to be compared with individual treatment. In treatment-naive adults whose tumour has no BRAF V600 mutation, dacarbazine or ipilimumab are possible appropriate comparator therapies; and in treatment-naive adults whose tumour cells have mutated (BRAF V600 mut), vemurafenib is an option.

No evaluable data for relevant subpopulation

The drug manufacturer presented two randomized controlled trials (RCTs) for pretreated patients. A subpopulation of the study KEYNOTE 002 was relevant for the assessment, namely pretreated adults for whom dacarbazine was specified as chemotherapy in the comparator arm before randomization. However, the manufacturer dossier only provided analyses for the total study population so that no evaluable data were available for the relevant subpopulation.

Increased uncertainty because dosage was not in compliance with the approval

The second study, KEYNOTE 006, was a multicentre and open-label RCT with three treatment arms: One patient group received pembrolizumab in a dosage of 10 mg/kg body weight (BW) every three weeks, and another patient group received the same dosage, but every two weeks. Study participants in the comparator arm were treated with ipilimumab (3 mg/kg BW every three weeks for four treatment cycles).

With 10 mg/kg BW, the dosage of pembrolizumab was higher in two arms of the study than recommended by the approval (2 mg/kg BW). The analyses conducted by IQWiG concur with the assessment of the European Medicines Agency (EMA), however: It can be assumed that

there are no relevant differences in efficacy and harm outcomes between the dosage of 10 mg/kg BW every three weeks and the dosage according to the approval and that the results from this study arm is transferable to the treatment regimen of the approval. Despite the dosage that was not in compliance with the approval, KEYNOTE 006 was therefore used for the assessment. However, the interpretation of the study results was subject to uncertainty for this reason.

Considerable added benefit for certain patients with pretreatment

Advantages of pembrolizumab were shown in adults with malignant melanoma for whom ipilimumab constitutes a suitable individual treatment because of their prior therapy: Severe and serious side effects as well as study discontinuations due to severe side effects occurred later than under ipilimumab. In conclusion, there is an indication of considerable added benefit of pembrolizumab in comparison with ipilimumab for this patient group.

Since no suitable data were available for pretreated patients for whom ipilimumab is not a treatment option, there is no hint of an added benefit for this patient group.

Minor added benefit in treatment-naive patients without tumour mutation

Treatment-naive patients whose tumour has no BRAF V600 mutation survived longer under pembrolizumab than under ipilimumab. In addition, pembrolizumab delayed the time point at which social participation decreases.

A hint of a minor added benefit of pembrolizumab in comparison with

ipilimumab can be derived for this patient group in each case from the advantages in overall survival and in social participation as aspect of health-related quality of life.

No added benefit in treatment-naive patients with BRAF V600 mutation

The manufacturer presented no data for treatment-naive patients with mutated tumour (BRAF V600 mut). Hence no hint of an added benefit can be derived for this patient group.

More information: www.iqwig.de/download/A15-33_P … ertung-35a-SGB-V.pdf

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