Nivolumab plus ipilimumab in melanoma: Added benefit in certain patients

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Nivolumab (trade name: Opdivo) in combination with ipilimumab (trade name: Yervoy) has been approved since May 2016 for adults with advanced melanoma. The German Institute for Quality and Efficiency in Health Care (IQWiG) examined in a dossier assessment whether this drug offers an added benefit.

According to the findings, treatment-naive patients with BRAF V600 mutation-negative tumour survive longer. This advantage differs by sex, however. At the same time, severe side effects are more common under nivolumab in combination with ipilimumab. Overall, IQWiG sees an indication of considerable added benefit in men, and a hint of a non-quantifiable added benefit in women.

The dossier contained no evaluable data for further patient groups.

G-BA defined three research questions

The Federal Joint Committee (G-BA) distinguished between three treatment situations in its commission: In treatment-naive patients whose tumour has BRAF V600 mutation (BRAF V600 mut tumour), the combination of nivolumab and ipilimumab was to be compared with vemurafenib. In treatment-naive patients whose tumour has no BRAF V600 mutation (BRAF V600 wt tumour), the G-BA specified ipilimumab as appropriate comparator therapy. In pretreated patients, the added benefit was to be assessed in comparison with treatment

adapted to the individual patient at the physician's discretion.

Proof of longer survival in men, indication in women

The dossier contained suitable data only for treatment-naive patients with BRAF V600 wt tumour; these were from two randomized controlled trials (RCTs), which compared the drug combination with ipilimumab.

The results on overall survival were from data cut-offs at which the patients had been observed for at least 18 or 24 months.

They showed that patients survive longer with the combination therapy, but that the effect depends on sex: The advantage is much more pronounced for men than for women. In men, proof of a major added benefit could be derived from the data. In women, there was an indication of an added benefit, the extent of which was non-quantifiable - it could therefore be minor, considerable, or major.

Results on other outcomes only for earlier data cut-offs

For the assessment of all other outcomes, the drug manufacturer used data recorded at earlier time points. This was not comprehensible because the patients were continued to be observed; therefore, as for overall survival, results at a later data cut-off would have been available at least for side effects.

In some outcomes, no differences between the treatment groups were shown. In others, there were differences, which were largely to the disadvantage of nivolumab plus ipilimumab, but often only concerned certain subgroups such as patients whose tumour has a high or low

metastasis stage.

Side effects: negative effects of major importance

The results on side effects were to the disadvantage of the drug combination. This particularly concerned severe side effects and discontinuation of treatment due to side effects. These effects were independent from sex.

Since only data on earlier data cut-offs were available for side effects, their true extent was unclear, however. It cannot be excluded that they developed further to the disadvantage of nivolumab plus ipilimumab up to the later data cut-offs, at which the data on survival were recorded.

Negative effects did not completely outweigh positive effects

Hence there were positive effects regarding longer survival time and negative effects in the form of more frequent (severe) side effects both in men and in women. Even though the side effects were severe, they did not completely outweigh the positive effects, but resulted in a downgrading of the extent of the added benefit. The uncertainty regarding side effects reduced the certainty of conclusions. Overall, an indication of considerable added benefit for treatment-naive men with BRAF V600 wt tumour could be derived from the data, and a hint of a non-quantifiable added benefit for women. This applied to the combination of nivolumab and ipilimumab in comparison with ipilimumab monotherapy.

No usable data available for two further treatment situations

The manufacturer presented no suitable data for treatment-naive patients with BRAF V600 mut tumour and for pretreated patients. An added benefit for these patients is therefore not proven.

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.

More information: www.iqwig.de/en/projects-resul … ode-book-v.7467.html

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