Pembrolizumab in non-small cell lung cancer: Hint of considerable added benefit

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In non-small cell lung cancer (NSCLC) that has already formed metastases, the suitable treatment depends, among other factors, on the genes that are activated in the tumour cells and whether mutations have occurred that make certain treatments ineffective. Already since July 2016, the monoclonal antibody pembrolizumab (trade name: Keytruda) has been available for second-line treatment of locally advanced or metastatic NSCLC in adults whose tumours express the T-cell receptor ligand PD-L1 and who have received a prior chemotherapy regimen. Following extension of approval, the drug can also be used in first-line treatment if at least half of the tumour cells produce PD-L1 and, in addition, the tumours have no activating mutations of the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK).

The German Institute for Quality and Efficiency in Health Care (IQWiG) therefore examined in an early benefit assessment whether the drug offers an added benefit also for these patients. According to the findings, there is a hint of considerable added benefit in comparison with the appropriate comparator therapy - particularly due to the prolonged overall survival.

Comparison with platinum-based combination chemotherapies

The Federal Joint Committee (G-BA) specified several appropriate comparator therapies. Among others, patients in the comparator arm

could be treated with cisplatin or carboplatin in combination with a third-generation cytostatic agent. Carboplatin was reserved for patients with an increased risk of cisplatin-induced side effects.

The drug manufacturer chose these two comparator therapy options and submitted data from the KEYNOTE 024 study, which compared pembrolizumab with cisplatin- or carboplatin-based combination chemotherapy. In this study, not only participants with an increased risk of cisplatin-induced side effects received carboplatin-based combination chemotherapy. Due to the study design and the type of data presentation however, it was possible to restrict the data analyses to those patients who very probably fulfilled the prerequisite defined by the G-BA.

Reasons for comparator therapy decisions documented

Treatment with cisplatin can cause certain side effects such as hearing impairment, renal or cardiac insufficiency. According to the Pharmaceutical Directive, carboplatin should only be used in patients who have an increased risk of these side effects.

In the KEYNOTE 024 study, the investigator assessed the suitability of the individual participants for a specific platinum-based combination chemotherapy and the respective dose before randomization. Additionally, the manufacturer later asked the physicians for the reasons for the individual decisions for carboplatin-based treatment. Based on this information, the subpopulation that was most probably treated in compliance with the Pharmaceutical Directive could be determined. Some uncertainty remains because the manufacturer dossier contained no details on how the retrospective interview was conducted.

Advantages notably outweigh disadvantages

The data provided an indication of an added benefit of pembrolizumab in comparison with the comparator therapies for the patient-relevant outcome "overall survival". In the category "morbidity", there were hints of an added benefit for eight symptom outcomes, as well as for some aspects of health-related quality of life, such as the time to deterioration of physical or social functioning.

In the outcome category "side effects", there were no statistically significant differences in serious adverse events, but there was a hint of lesser harm of pembrolizumab for severe adverse events. In the total population, however, immune-related adverse events as well as some further specific adverse events were more common under the drug than in the comparator arm. (The company presented no data for this on the relevant subpopulation.) Other adverse events were more common in the comparator arm. Overall, there was a hint of lesser harm for side effects.

In the total population of the study, the effect was modified by the sex of the participants. Whether this also applied to the subpopulation considered here cannot be determined because the manufacturer did not present the data necessary for this. The possibility of an effect modification, as well as the remaining uncertainty regarding the choice of the relevant subpopulation, restricted the certainty of conclusions. In summary, there is a hint of considerable added benefit for the first-line treatment of patients with metastatic NSCLC and PD-L1-expressing tumours without activating EGFR and ALK mutations.

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.

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