Afatinib: Added benefit depends on mutation status

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Afatinib (trade name: GIOTRIF) has been approved in Germany since September 2013 for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGF receptor mutations who have not been treated with an EGF receptor tyrosine-kinase inhibitor (EGFR TKI). In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) examined whether this new drug offers an added benefit over the appropriate comparator therapy.

Evaluable data were only available for non-pretreated patients in relatively good general condition (ECOG PS 0 or 1). According to the findings, there is an indication of a major added benefit in patients with the EGFR mutation Del19, and a hint of a minor added benefit of afatinib in patients under the age of 65 with L858R mutation. In contrast, the Institute found an indication of lesser benefit versus the comparator therapy in patients with other EGFR mutations. The pharmaceutical company presented no relevant data for pretreated patients.

Only indicated in activating receptor mutations

When a so-called non-small cell lung cancer is locally advanced or has already formed metastases, it might not be possible anymore to remove the tumour surgically. New drugs like tyrosine-kinase inhibitors are used

to block specific growth signals that receptors on the surface of tumour cells receive and send to the inside of the cells.

How well patients respond to such substances depends on several factors, including the occurrence of certain mutations in the tumour cells which activate the receptors. The tyrosine-kinase inhibitor afatinib is only approved for the treatment of patients in whose tissue samples activating mutations in the EGFR gene were detected.

Several patient groups and comparator therapies

Depending on the pretreatment of the patients and their general condition (categorized according to the Eastern Cooperative Oncology Group Performance Status, ECOG PS for short), the Federal Joint Committee (G-BA) specified several appropriate comparator therapies: In non-pretreated patients, afatinib was to be compared either with another tyrosine-kinase inhibitor (gefitinib or erlotinib), or – if they had an ECOG PS of 0 or 1 – with a combination chemotherapy with cisplatin and a third-generation cytostatic agent. In non-pretreated patients with ECOG PS 2, i.e. worse general condition, the new drug was to be compared with the third-generation cytostatic agent gemcitabine.

For patients with at least 1 previous chemotherapy, gefitinib or erlotinib were also stipulated as comparator therapy.

Only data for non-pretreated patients

The pharmaceutical company submitted data from a single randomized controlled trial (LUX-Lung 3) in its dossier. The non-pretreated participants in this study had an ECOG PS of 0 or 1 at the start of the study, and were either treated with afatinib or with a combination of cisplatin and the third-generation cytostatic agent pemetrexed.

IQWiG does not accept the manufacturer's opinion that the results of the LUX-Lung 3 study can also be transferred to non-pretreated patients with ECOG PS 2. For pretreated patients, the manufacturer presented data from a single-arm study, which are unsuitable for the assessment of an added benefit because there is no comparison with the appropriate comparator therapy.

Hence the added benefit of afatinib versus the respective appropriate comparator therapy is not proven for non-pretreated patients with ECOG PS 2 and for patients with previous chemotherapy.

Different treatment durations impair interpretation

In the LUX-Lung 3 study, afatinib was administered once daily until the disease progressed, treatment was no longer tolerated, or the doctor or the patient demanded treatment discontinuation. The comparator therapy "cisplatin with pemetrexed" could also be discontinued prematurely; however, it was not used for more than 6 cycles of 21 days each.

This led to considerable differences in the median treatment durations between the afatinib arm (336 days) and the comparator arm (105 days). This limited the reliability of the conclusions of the results on symptoms and quality of life. The data on side effects were so uncertain that only qualitative conclusions could be drawn.

It depends on the EGFR mutation status

The effect of afatinib in non-pretreated patients with ECOG PS 0 or 1 depends on the EGFR mutation present in the patients' tumours.

For patients with Del19 mutation, there is overall an indication of a major added benefit because afatinib had better results in overall

survival than the combination chemotherapy, and positive effects – some of them age-dependent – predominated with regards to symptoms and health-related quality of life.

In L858R mutation, there was no statistically significant effect in overall survival. However, in patients younger than 65 years, overall, advantages of afatinib predominate in symptoms and quality of life, resulting in a hint of a minor added benefit for these patients.

In contrast, for patients with a different EGFR mutation than Del19 or L858R, the study data indicate that they have lesser benefit from afatinib than from the combination of cisplatin and pemetrexed.

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

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