Bronchial carcinoma: Added benefit of crizotinib not proven

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Since August 2016 crizotinib (trade name: Xalkori) has also been available for adults with advanced non-small cell lung cancer (NSCLC) in whom the structure of the enzyme "proto-oncogene tyrosine-protein kinase" (ROS1) is altered in the tumour tissue. In an early benefit assessment the German Institute for Quality and Efficiency in Health Care (IQWiG) investigated whether this drug offers advantages for patients over the appropriate comparator therapies. According to the findings, such an added benefit is not proven: for one patient group, the dossier does not contain any data at all; for two further groups, the data are unsuitable for assessment.

G-BA distinguishes between three treatment situations

The disease in question is not considered to be "rare", nor does crizotinib have orphan drug status. However, the number of affected patients is small: according to estimates, in Germany not more than about 1300 patients have ROS1-positive tumours.

For the current assessment the Federal Joint Committee (G-BA) distinguished between three treatment situations. The relevant criterion is on the one hand, whether patients have already been pretreated or not, and on the other, whether pretreated patients are eligible for further chemotherapy or not.

For already pretreated patients no longer eligible for chemotherapy, crizotinib was to be compared with best supportive care (BSC). For eligible patients, depending on the type of pretreatment the G-BA specified different combinations of cytostatic drugs as the appropriate comparator therapy.

Drug manufacturer presented one-arm studies

The dossier does not contain data for the BSC population. In contrast, it does for the chemotherapy population; however, the data presented are unsuitable for assessing benefit or harm.

The drug manufacturer initially presented a number of one-arm studies, partly including small, retrospective case series. The studies enrolled a total of 281 participants, including only 32 without pretreatment. Crizotinib was approved on the basis of these studies; however, they are unsuitable for the comparative assessment of added benefit.

Studies on ALK-positive tumours used

In addition, the drug manufacturer used two randomized controlled trials (RCTs) in which, however, the tumours of the participants were not ROS1-positive but anaplastic lymphoma kinase (ALK)-positive, that is, showed a different type of mutation.

On the basis of these RCTs, crizotinib was approved for advanced NSCLC with ALK-positive tumours, initially for pretreated patients in 2012 and then also for non pretreated patients in 2015. The subsequent benefit assessment showed a hint of a considerable added benefit for certain patients.

Similarity hypothesis not supported

The drug manufacturer also claimed an added benefit for patients with a ROS1 mutation, stating that the data were applicable to these patients. Among other things, the manufacturer justified this claim by stating that not only the ALK and ROS1 receptors, but also the patient characteristics and the "natural" course of disease were similar; however, solely a claim unsupported by scientific evidence was made.

Therefore IQWiG itself conducted a first explorative search for studies that could provide information on patient characteristics and the course of treatment. But the few studies available provide an incomplete and inconsistent picture; in any case they do not support the similarity hypothesis.

As these studies are also unsuitable for the assessment, an added benefit of crizotinib is not proven for any of the three research questions.

Early approval on the basis of fewer data

Beate Wieseler, Head of IQWiG's Drug Assessment Department, notes: "I am surprised that the drug manufacturer has invested little effort in justifying why the study results are supposed to be applicable between the two types of mutations. The current dossier assessment also shows what problems can arise for early benefit assessments if drugs are approved early on the basis of relatively few data - we often see this, particularly in rarer diseases. If the European Medicines Agency (EMA) were to implement their 'adaptive pathways' plan and in future were to approve even more drugs with even fewer data, then this problem could be further aggravated."

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