HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
13 MAY 2020

The legally binding text is the original French opinion version

crizotinib
XALKORI 200 and 250 mg hard capsules

Reevaluation

Key points

Favourable opinion for reimbursement only for the second and later-line treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC). In this indication, the clinical benefit is now low (previously it was moderate).

Now unfavourable opinion for reimbursement for the first-line treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC).

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

Surgical treatment is recommended at the early stage of the disease, whereas systemic therapy is necessary at locally advanced or metastatic stages. This treatment is guided by the presence or otherwise of molecular abnormalities, the PD-L1 expression status of the tumour and the patient's ECOG status.

ROS1 rearrangements, found in 1 to 2% of NSCLC cases, are exclusive of the other oncogenic mutations found in NSCLC (EGFR mutations, KRAS mutations, ALK fusions, etc.) and were discovered recently.

Crizotinib (XALKORI) is the first treatment to have an MA in ROS1-positive NSCLC. Before the arrival of crizotinib, the treatment of ROS1-positive NSCLC was based on platinum-based chemotherapy. Some recommendations also propose the off-label use of ceritinib (ZYKADIA).

As second or later-line therapy, the use of crizotinib (XALKORI), if it was not used as first-line therapy, or chemotherapy (platinum or pemetrexed-based) is recommended. Only the American guidelines recommend the use of immunotherapy (pembrolizumab or atezolizumab) in combination with chemotherapy, in the event of positive PDL-1 expression (≥ 1%), and the absence of contraindications and for patients in good general condition (ECOG 0-1).

Role of the medicinal product in the care pathway:

Considering:

- the absence of solid data concerning the prognostic value of positive ROS1 expression,
- the absence of robust comparative data for XALKORI (crizotinib) versus the chemotherapy conventionally used in ROS1-positive NSCLC patients, despite the Committee's initial request, in a context in which the comparative data from the ESME observational study are exploratory, making it possible to assess the additional contribution of XALKORI (crizotinib) in the therapeutic strategy,
- uncertainties concerning the transposability of the results to clinical practice in patients receiving first-line therapy, given their low proportion in the studies (15% of study population),
- and its preferential use as second and later-line therapy in clinical practice in accordance with the data provided in real-life conditions,

the Committee considers that the role of XALKORI (crizotinib) is as second and later-line therapy only in previously-treated ROS1-positive NSCLC patients. XALKORI (crizotinib) no longer has a role to play in first-line therapy in chemotherapy-naive patients.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Non-small cell lung cancer (NSCLC) is a serious, life-threatening condition
◗ This is a curative treatment specific to ROS1-positive NSCLC.
◗ The efficacy/adverse effects ratio has not been adequately established given the limited data and the absence of a comparison with the chemotherapy conventionally used in this context, particularly as first-line treatment (see paragraph 08.5 of the present opinion).
◗ There are medicinal alternatives, represented by standard chemotherapy not targeting the ROS1 rearrangement, and ceritinib (ZYKADIA), used off-label and recommended.
◗ This is a second and later-line treatment only in previously-treated ROS1-positive NSCLC patients. This treatment no longer has a role as first-line treatment (see paragraph 09 of the present opinion).

Public health impact

Considering:
- the seriousness of the disease, with a 5-year survival rate of 18%,
- its low incidence,
- the medical need, which is considered to be partially met by the chemotherapies conventionally used in this context, without differentiation of ROS1 rearrangement status,
- the absence of a demonstrated impact on morbidity and mortality and on quality of life compared to the chemotherapy conventionally used in this context, without differentiation of ROS1 rearrangement status,
- the lack of any demonstrated impact on the organisation of care (hospitalisation, AE, etc.),

XALKORI (crizotinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of XALKORI (crizotinib) is:
- **insufficient to justify its funding by the French national health insurance system as first-line treatment,**
- **low in second and later-line treatment,**

in the treatment of advanced non-small cell lung cancer (NSCLC) with ROS1 (Proto-Oncogene 1, Receptor Tyrosine Kinase) rearrangement.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only in the second and later-line treatment of ROS1-positive advanced non-small cell lung cancer (NSCLC).

Clinical Added Value

Considering:
- **the limited clinical data for crizotinib (XALKORI), with a low level of evidence (non-comparative cohorts from phase I and II studies concerning an interim endpoint),**
- **the absence of direct or indirect robust comparative data versus the chemotherapy conventionally used in ROS1-positive NSCLC patients, whereas a comparison had been requested by the Committee,**
- **the absence of solid data concerning the prognostic value of positive ROS1 expression,**

the Committee considers that XALKORI (crizotinib) provides no clinical added value (CAV V) in the therapeutic strategy.