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ONCOLOGY
New indication
July 2017

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

XALKORI (crizotinib), tyrosine kinase inhibitor

For the treatment of non-small cell lung cancer with ROS1 rearrangement, low clinical benefit for first-line treatment, moderate benefit for second-line and subsequent treatments, and no proven clinical added value for the management of this cancer

Main points

- XALKORI has been granted a marketing authorisation for adults with non-small cell lung cancer (NSCLC) carrying ROS1 rearrangement.
- The clinical data are limited for this indication with a low level of evidence and relating to an intermediate endpoint.
- There is no comparison to chemotherapy conventionally used in this context, or robust data on the prognostic value of the presence of ROS1.

Pre-existing indications*

XALKORI has also been granted a marketing authorisation for the treatment of advanced ALK+ NSCLC (for more details, see marketing authorisation).

Therapeutic strategy

- The therapeutic management of NSCLC differs according to the cancer stage. The conventional treatment for early stages is surgery. However, a large proportion of patients are diagnosed at an advanced stage of the disease (approximately 25 to 30% at the locally advanced stage and 40% at the metastatic stage) and early stages merely represent 25 to 30% of cases. The management of these cancers is based on systemic treatment. The therapeutic strategy is guided based on the presence of genetic alteration or not.
- Other criteria are also involved in the therapeutic decision: tumour histology, the patient's performance status and comorbidities. ROS1 rearrangements are exclusive of other oncogenic mutations detected in NSCLC (in particular EGFR mutations, KRAS mutations, ALK rearrangements). Cytotoxic chemotherapy regimens such as cisplatin or carboplatin in combination with one of the following medicinal products: pemetrexed, vinorelbine, gemcitabine, docetaxel or paclitaxel, are available for first-line treatment.
- Immunotherapy has enhanced the therapeutic arsenal with evidence of a gain in overall survival compared to chemotherapy, particularly for second-line treatment. However, these therapies have no specific action on ROS1 rearrangements.
  U.S. guidelines (2017) recommend crizotinib in cases of ROS1 rearrangements (ROS1+) from the first-line treatment stage.
- **Role of the proprietary medicinal product in the therapeutic strategy**
  XALKORI is a first- or second-line treatment for lung cancer patients with ROS1 rearrangement. Despite this recommendation, limitations exist, associated in particular with the lack of comparative data versus chemotherapy in this sub-population and the lack of data on the prognostic value of ROS 1 rearrangement.

Clinical data

* This summary does not concern this indication.

- A phase I study assessed the anti-tumour activity of crizotinib in the treatment of ROS1+ NSCLC in 53 patients, including 46 cases subject to failure of one or more treatment lines and 7 previously untreated. The median treatment duration was 101 weeks (approximately 2 years). Five complete responses and 32 partial responses were observed for an overall response rate of 70%. The median progression-free survival was 19.3 months (95% CI [14.8, not achieved]). The median overall survival had not been reached at the time of the analysis.
- The main adverse events associated with crizotinib treatment with a frequency ≥ 30% were in particular vision disorders (84.9%), oedema (45.3%), diarrhoea (41.5%) and transaminase elevation (30.2%).
- In a phase II study in which the assessment related to 36 patients, the objective response rate at 2 months (primary endpoint) was 54% and the median progression-free survival was 9.9 months. The median overall survival had not been reached at the time of the analysis.
- No comparative data to standard chemotherapy regimens conventionally administered to NSCLC patients regardless of ROS1 rearrangement status are available. Moreover, the European assessment report specifies that, due to limited data, in some cases with contradictory findings observed in the retrospective analyses, it is not possible to infer the prognostic value of ROS+. For this reason, a legitimate doubt remains on the probably greater performances expected from chemotherapy in this subgroup in the event of a good prognosis.
- Overall, this indication of XALKORI for ROS1+ NSCLC is based on very limited data (one phase I study and cohort data from one phase II study), with a low level of evidence and with no comparative data with respect to the chemotherapy regimens conventionally used (regardless of ROS 1 rearrangement status). The impact in terms of morbidity-mortality and quality of life therefore cannot be assessed in this population. Moreover, the prognostic value of a ROS1-positive status is not documented and the transferability of data from the phase I study is not guaranteed, in particular for first-line treatment due to the very restricted number of patients included (n=7).

Special prescription requirements

- Medicinal product subject to hospital prescription, reserved for medical oncology specialists or physicians with expertise in oncology.
- Medicinal product requiring monitoring during treatment.

Benefit of the medicinal product

- The actual clinical benefit* of XALKORI is low for first-line treatment, moderate for second-line and subsequent treatments, for the treatment of advanced-stage NSCLC with ROS1+ rearrangement.
- XALKORI does not provide any clinical added value** (CAV V) for the therapeutic strategy.
- Approval for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 17 May 2017 (CT-15941) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement".