HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 JULY 2021
The legally binding text is the original French opinion version

entrectinib
ROZLYTREK 100 mg - 200 mg hard capsules

First assessment

Key points

Unfavourable opinion for reimbursement in adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options.

Role in the care pathway?

The treatment strategy for solid tumours is generally guided by their histological type. Consequently, patients with a tumour expressing NTRK gene fusion are treated in accordance with the guidelines based on tumour location or histological type, independently of their NTRK status.
The first-line treatments for early (localised) stages mostly consist of surgery and radiotherapy and, more specifically for thyroid cancers, radioactive iodine.
For certain types of tumours in which the therapeutic objective is curative surgical excision, preoperative systemic treatment may be recommended with the aim of making a tumour resectable and reducing the morbidity associated with surgery.

In advanced stages, management is mostly based on systemic treatment, the primary objective being to improve overall survival and the patient's quality of life. A number of criteria are involved in the therapeutic decision, including tumour histology, the patient's general condition and comorbidities. The treatment options differ depending on the type of cancer and the treatment line. Globally, several standard treatment lines can exist for locally advanced or metastatic stages. For example, in advanced breast cancer, there can be numerous treatment lines, including several lines of endocrine therapy and chemotherapy. In contrast, in infantile fibrosarcoma and salivary gland carcinoma, the number of treatment lines is more restricted.

Solid tumours with NTRK gene fusion represent a heterogeneous group of tumours, in both adults and children. At present, the frequency of fusion is not precisely known. Overall, this frequency is low (0.5% to 1%) in common cancers (e.g. lung, prostate, colon and breast cancers) and in CNS tumours, whereas it is high (> 80%) for certain rare cancers, for example in adults with salivary gland cancer of subtype MASC - Mammary Analogue Secretory Carcinoma, secretory breast cancer, and, in children, infantile fibrosarcoma.

Currently, the prognostic value of NTRK 1, 2 or 3 gene fusion in solid cancers is not known.

In addition to ROZYLTREK (entrectinib), another medicinal product (larotrectinib, VITRAKVI) has an MA specifically for the treatment of solid tumours with NTRK gene fusion. Its funding in France is currently limited to the subpopulation of paediatric patients with refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma or another soft tissue sarcoma, with NTRK (Neurotrophic Tyrosine Receptor Kinase) gene fusion (moderate conditional medical benefit and CAV V).

Role of the medicinal product in the care pathway

In a context in which the prognostic value of the presence of NTRK gene fusion is not known and considering:
- the very preliminary nature of the available efficacy data, based primarily on the results of a phase 2 non-comparative basket study (STARTRK-2) not meeting the Committee's minimum requirements to provide formal evidence of the clinical benefit of ROZLYTREK (entrectinib) irrespective of the tumour expressing NTRK fusion,
- the absence of clinical data supporting the efficacy and safety of ROZLYTREK (entrectinib) compared to supportive care for salvage situations,
- the lack of robust evidence of the absence of a therapeutic alternative for the patients included,
- the toxicity marked by an incidence of serious adverse events reported in almost one in two patients (48.7% of patients) and grade ≥3 adverse events in two in three patients (65.5% of patients), the Transparency Committee considers that ROZLYTREK (entrectinib) has no role in the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options.

The Committee considers that in a context in which no comparative data is available to guarantee the solidity of the conclusion with respect to the effect of treatment with ROZLYTREK (entrectinib), the introduction of this medicinal product into the care pathway is accompanied by a higher risk than for medicinal products for which the efficacy is based on a comparison conducted with control of the risk of wrongly concluding that the treatment is effective (two-tailed alpha risk conventionally accepted to be 5%).

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Advanced or metastatic solid tumours, all locations combined, are life-threatening, with a variability depending on location and histology. The natural course of solid cancers with NTRK gene fusion has not been characterised and the prognostic value of NTRK gene fusion in solid cancers is not known in clinical practice.

◗ This is a specific curative treatment for cancer (solid tumours).

◗ The efficacy/adverse effects ratio of ROZLYTREK (entrectinib) is low considering the limited clinical data derived from a cohort (n=71) which was one of six included in a phase 2, non-comparative basket study, which does not enable its clinical benefit to be determined given the uncertainties related to the following in particular (see Section 07.6 Summary and Discussion):

- the absence of a formalised comparison with current treatment,
- preliminary data supporting a heterogeneous indication in terms of tumour location, prognosis specific to each tumour and treatment lines;
- the prognostic value of NTRK gene fusion, which is not documented;
- the significant toxicity noted with time-limited follow-up of patients

and despite the seriousness of the clinical situations concerned.

◗ There is a medicinal alternative with funding in France with targeting of NTRK gene fusion in infantile fibrosarcoma and other soft tissue sarcomas (VITRAKVI, larotrectinib). In addition, depending on the context, several chemotherapy lines may be proposed or supportive care for situations in which the treatments options have been exhausted; consequently, there are therapeutic alternatives in these situations.

◗ As the dossier currently stands, given the low level of evidence of the data, in a context in which the prognostic value of the presence of NTRK gene fusion is not known, ROZLYTREK (entrectinib) has no role in the care pathway in adults (see Section 08 Role in the care pathway).

Public health impact

Despite:

- the seriousness of the diseases concerned,
- the low prevalence of solid tumours with NTRK gene fusion, with, in particular, a very high frequency of NTRK gene fusion in certain histological types, such as infantile fibrosarcoma,
- the medical need that is inadequately met or unmet depending on the situation,

but considering:

- the lack of response provided by ROZLYTREK (entrectinib) in view of the limited data available,
- the impact on the organisation of care, with the need to implement one or more diagnostic tests with an NTRK gene fusion detection strategy as part of routine clinical management,

ROZLYTREK (entrectinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ROZLYTREK (entrectinib) is INSUFFICIENT to justify public funding cover in the MA indication (adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options).

The Committee issues an unfavourable opinion for inclusion of ROZLYTREK (entrectinib) in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indication.