Thyroid cancer
Lung cancer
Sectors: Retail and hospital

HAUTE AUTORITÉ DE SANTÉ

# TRANSPARENCY COMMITTEE
## SUMMARY
## 2 JUNE 2021

*The legally binding text is the original French opinion version*

***selpercatinib***
**RETSEVMO 40 mg and 80 mg hard capsules**

**First assessment**

## Key points

Favourable opinion for reimbursement as monotherapy in:

- the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy;
- the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

Maintenance of this opinion is conditional on the re-evaluation of this medicinal product within a maximum period of 3 years on the basis of:

- the results of the phase 3 study in first-line treatment (LIBRETTO-431, results expected by October 2023 at the latest) in RET fusion-positive NSCLC, and
- comparative data for RETSEVMO (selpercatinib) versus the standard of care for patients receiving second or later-line therapy, as well as the results of the phase 3 study in first-line treatment (LIBRETTO-531, results expected by February 2025 at the latest), in RET-mutant MTC,
- and data from the registry of patients treated in France with RETSEVMO (selpercatinib) with RET-mutant MTC.

Unfavourable opinion for reimbursement as monotherapy in the treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

## What therapeutic improvement?

No clinical added value on the basis of currently available data in the care pathway for:
- adults with RET fusion-positive non-small cell lung cancer and
- adult and paediatric patients with RET-mutant medullary thyroid cancer.

## Role in the care pathway?

- Non-small cell lung cancer

In non-small cell lung cancer (NSCLC), rearranged during transfection (RET) fusions are observed in 1 to 2% of patients, primarily those with an adenocarcinoma.

Before the availability of selpercatinib, in the absence of a treatment specifically targeting the RET fusion, the treatments used as second and later-line therapy in the context of advanced or metastatic NSCLC with no targetable molecular alteration (EGFR, ALK, ROS1) and without specific data in patients with a RET rearrangement, were immunotherapy and/or chemotherapy.

Currently, in the event of RET rearrangement, French AURA guidelines (2021), propose inclusion in a clinical trial or named-patient ATU for pralsetinib or selpercatinib as options from the second line of therapy.

In patients with an EGFR, ALK, ROS1, BRAF-V600E alteration for whom targeted therapies are available, management is based on anti-EGFR, anti-ALK and anti-ROS1 TKIs from the first line of treatment and from the second line for BRAF-V600E.

**Role of the medicinal product in the care pathway**

Despite the low level of evidence of the data, taking into account the substantial medical need (supported by experts, in particular) and pending new efficacy and safety data, the Committee considers that RETSEVMO (selpercatinib), as monotherapy, is a treatment option for the management of advanced RET fusion-positive NSCLC, following prior treatment with immunotherapy and/or platinum-based chemotherapy (as second or later-line therapy).

It should be noted that in RET-positive patients, immunotherapy has not demonstrated efficacy in this context and that according to the NCCN guidelines (2021), the response rate is low.

It is necessary to highlight 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 RETSEVMO (selpercatinib), the introduction of this medicinal product into the treatment strategy 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%).

- Medullary thyroid cancer

In adults, in the event of aggressive and symptomatic/progressive, unresectable locally advanced or metastatic MTC, two tyrosine kinase inhibitors - vandetanib (CAPRELSA) and cabozantinib (COMETRIQ not marketed in France to date) - are currently recommended as systemic treatments as first-line therapy.

In paediatric patients, vandetanib (CAPRELSA) is currently the only systemic treatment available for medullary thyroid cancer in children aged 5 years or over at the unresectable locally advanced or metastatic stage, which must be limited to aggressive and symptomatic forms.

There are currently no validated alternatives in the event of failure of these treatments.

**Role of the medicinal product in the care pathway**

Despite the low level of evidence of the data, taking into account the substantial medical need (supported by patient associations and experts, in particular) and pending new efficacy and safety data, the Committee considers that RETSEVMO (selpercatinib), as monotherapy, is a treatment option for the management of advanced RET-mutant medullary thyroid cancer (MTC) following prior treatment with cabozantinib and/or vandetanib. The Committee highlights the fact that only one 17-year-old patient was treated in the study.

It is necessary to highlight 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 RETSEVMO (selpercatinib), the introduction of this medicinal product into the treatment strategy 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%).

- Advanced thyroid cancer (without medullary histology)

In patients with advanced RET fusion-positive thyroid cancer, in view of the limited data (19 assessable patients) available in this indication, the role of RETSEVMO as monotherapy has not been established.

In all the indications retained for reimbursement, it is necessary to take into account the risk of adverse events of particular interest, such as increased transaminase levels, QT prolongation, hypertension, hypersensitivity and haemorrhagic events, mentioned in the SPC.

## Special recommendations

As regards medullary thyroid cancer, due to the complexity of management of this rare cancer, the Committee recommends that the decision to initiate treatment with RETSEVMO (selpercatinib) be taken after a documented proposal resulting from a multidisciplinary team (MDT) meeting. Treatment should be initiated and monitored by an MTC reference or expert centre.

## COMMITTEE'S CONCLUSIONS

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

## Clinical benefit

### Non-small cell lung cancer (NSCLC)

◗ Non-small cell lung cancer (NSCLC) is a serious, life-threatening condition.

◗ RETSEVMO (selpercatinib) is a curative medicinal product.

◗ Its efficacy/adverse effects ratio has not been adequately established due to:
- the weakness of demonstration of its efficacy (preliminary data from a phase 1/2 non-comparative study, with little experience in terms of efficacy and safety) and the absence of comparative data, at least with external control scheduled in advance, and
- frequent and serious adverse effects (in particular increased transaminases with a risk of cytolysis, hypertension).

◗ There are therapeutic alternatives not specific to RET fusion in the management of NSCLC (see 05 Clinically relevant comparators). However, there are currently no other RET fusion-specific treatments with a marketing authorisation.

◗ It is a second or later-line therapy.

**Public health impact**

Considering:
- the seriousness of the disease,
- the low prevalence or incidence of solid tumours with RET gene fusion,
- the medical need partially met by non-specific treatments (without specific data in RET fusion-positive NSCLC),
- the partial response to the identified need that RETSEVMO (selpercatinib) may provide in view of the available preliminary data, and pending additional data.

RETSEVMO (selpercatinib) is unlikely to have an additional impact on public health.

**Considering all these elements, the Committee deems that, on the basis of current knowledge, the clinical benefit of RETSEVMO (selpercatinib) is low in the MA indication.**

**The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in this indication and at the MA dosages.**

**The Committee makes maintenance of the low clinical benefit conditional on the re-evaluation of RETSEVMO (selpercatinib) within a maximum period of 3 years based on the results of the phase 3 study in first-line treatment (LIBRETTO-431, the results of which are expected for October 2023 at the latest).**

**Recommended reimbursement rate: 100%**

### 1.1.1 Medullary thyroid cancer

◗ Medullary thyroid cancer (MTC) is a life-threatening disease.

◗ RETSEVMO (selpercatinib) is a curative medicinal product.

◗ Its efficacy/adverse effects ratio has not been adequately established due to:
- the weakness of demonstration of its efficacy (preliminary data from a phase 1/2 non-comparative study, with little experience in terms of efficacy and safety) and the absence of comparative data, at least with external control scheduled in advance, and
- frequent and serious adverse effects (in particular increased transaminases with a risk of cytolysis, hypertension).

◗ There are no alternatives with an MA at this stage of the disease.

◗ It is a second or later-line therapy.

**Public health impact**

Considering:
- the seriousness of the disease and its prevalence/incidence
- the unmet medical need following prior systemic treatment
- the partial response to the identified need in view of the preliminary data, the absence of demonstration with respect to quality of life (in particular with respect to the highly debilitating diarrhoea in this condition), and pending additional data,

RETSEVMO (selpercatinib) is unlikely to have an additional impact on public health.

**Considering all these elements, the Committee deems that the clinical benefit of RETSEVMO (selpercatinib) is low in the MA indication.**

**The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in this indication and at the MA dosages.**

**The Committee makes maintenance of the low clinical benefit conditional on the re-evaluation of RETSEVMO (selpercatinib) within a maximum period of 3 years, based on comparative data for RETSEVMO (selpercatinib) versus the standard of care for patients receiving second or later-line therapy, as well as the implementation of the phase 3 study in first-line treatment (LIBRETTO-531, results expected by February 2025 at the latest) and data from the registry of patients treated in France.**

◗ **Recommended reimbursement rate: 100%**

### 1.1.2 Thyroid cancer (non-medullary)

◗ Progressive, locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory to radioactive iodine is life-threatening.

◗ RETSEVMO (selpercatinib) is a curative medicinal product.

◗ Considering the limited data available in this indication, the efficacy/adverse effects ratio for this medicinal product has not been established.

◗ There are no alternatives with an MA at this stage of the disease.

◗ It is a second or later-line therapy.

**Public health impact**

Considering:
- the seriousness of the disease and its prevalence/incidence,
- the unmet medical need following prior systemic treatment,
- the lack of response to the medical need in view of the very limited data available, with 19 assessable patients (see section 07.5 Summary and discussion),

RETSEVMO (selpercatinib) is unlikely to have an additional impact on public health.

**Considering all these elements, the Committee deems that the clinical benefit of RETSEVMO (selpercatinib) is insufficient in the marketing authorisation indication to justify its funding by the French national health insurance system.**

**The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication and at the MA dosages.**

## Clinical Added Value

### In non-small cell lung cancer and medullary thyroid cancer

**Considering:**
- **the not very robust quality of research evidence for the efficacy of RETSEVMO (selpercatinib) based on data from a non-comparative phase 1/2 study (LIBRETTO-001), for which inclusions are ongoing;**
- **the absence of external comparison at least with a historic cohort;**
- **uncertainties with respect to maintenance of the efficacy of the objective response rates observed, with a short follow-up period;**
- **the prognostic value of RET alteration, inadequately determined in the absence of comparative data, particularly in non-small cell lung cancer;**
- **the very limited number of data in children in MTC;**
- **the substantial medical need (not met in the RETSEVMO indication for MTC and partially met in NSCLC) supported by patient associations and experts, in particular.**

**The Transparency Committee considers that RETSEVMO (selpercatinib), as monotherapy:**

- **provides no clinical added value (CAV V) in the care pathway for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy;**
- **provides no clinical added value (CAV V) in the care pathway for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.**