HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
23 MARCH 2022

The legally binding text is the original French opinion version

pralsetinib
GAVRETO 100 mg hard capsules

First assessment

Key points

Favourable opinion for reimbursement, in second and later-line therapy only, as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC).

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 (AcceleRET-Lung, primary analysis for December 2024) in RET fusion-positive NSCLC.

Unfavourable opinion for reimbursement, in first-line therapy, as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC).

What therapeutic improvement?

No clinical added value on the basis of currently available data.

Role in the care pathway?

At the advanced stage of the disease, patients are not eligible for surgery and their treatment is based on systemic therapy.

The first-line treatment of advanced NSCLC, in the absence of molecular abnormalities (EGFR mutations, or ALK or ROS-1 rearrangements) or in the presence of a molecular alteration for which no targeted therapy is currently available), is based on immunotherapy or immuno-chemotherapy, for eligible patients.

The second-line treatment of NSCLC is based on:
- the administration of a PD-1/ PD-L1 inhibitor if pembrolizumab has not been used as monotherapy or in combination (platinum and pemetrexed for non-squamous NSCLC; carboplatin and paclitaxel for squamous NSCLC) as metastatic first-line treatment in the event of PD-L1 ≥ 50%: OPDIVO (nivolumab), TECENTRIQ (atezolizumab) or KEYTRUDA (pembrolizumab) only in the event of tumours with PD-L1 over-expression ≥ 1%;
- chemotherapy with, in particular, pemetrexed-based protocols if this has not previously been used, or docetaxel-based protocols.

The 2021 French guidelines direct RET fusion-positive patients towards pralsetinib or selpercatinib from the second line of therapy, or towards a clinical trial.

In its December 2021 guidelines, the NCCN recommends the preferential use of selpercatinib or pralsetinib as first-line treatment when RET fusion has been detected before the initiation of treatment. When RET fusion is detected during the first systemic treatment line, it recommends completing the initially scheduled immuno-chemotherapy cycle or interrupting it and replacing it with selpercatinib or pralsetinib.
In the event of progression after the first line of treatment, and even if treatment has been continued with a RET inhibitor, subsequent treatment lines consist of immunotherapies and chemotherapies.

Role of the medicinal product in the care pathway

Considering:
- inclusion in the study of a heterogeneous patient population with a low representativity of treatment-naïve patients (75 patients out of the 233 assessable patients at the cut-off in November 2020);
- the impossibility of assessing the contribution of GAVRETO (pralsetinib) compared to chemotherapies in the absence of a direct comparison (single-arm trial) despite this comparison being possible;
- the existence of a phase 3 study, in first-line treatment, evaluating GAVRETO (pralsetinib) compared to chemotherapies ± immunotherapy, for which the primary analysis is expected in December 2024;
- the Committee considers that GAVRETO (pralsetinib) has no role in the first-line treatment strategy, in previously untreated patients.

In second and later-line treatment, the Committee takes into account the following points:
- the low level of evidence of the data: single-arm trial, for which the results are based on an objective response rate (68% in the overall study population);
- the medical need in second-line therapy, where the treatment options are more limited;
- and pending new efficacy and safety data;

the Committee considers that GAVRETO (pralsetinib), as monotherapy, is a treatment option.

It should be noted that in RET-positive patients, immunotherapy has not demonstrated efficacy in this context and that the response rate may be 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 GAVRETO (pralsetinib), 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%).

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

First-line treatment of RET-positive advanced NSCLC

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

◗ The proprietary medicinal product GAVRETO (pralsetinib) is a curative medicinal product.

◗ The 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, in which the primary endpoint - the objective response rate - is not the most appropriate for measuring a clinical benefit, with limited follow-up in terms of treatment exposure) and the absence of comparative data, at least with external control scheduled in advance, and
- the additional toxicity: occurrence of grade ≥ 3 adverse events in three quarters of the patients in the study; serious adverse events recorded in more than half of patients;
- the limited experience in terms of safety data, with a short exposure duration (median duration of around 8 months).

◗ There are therapeutic alternatives not specific to RET fusion in the management of NSCLC (see 05 Clinically relevant comparators) based on immuno-chemotherapies.

◗ On the basis of currently available data, the Committee considers that GAVRETO (pralsetinib) is a second and later-line treatment.

Public health impact
Considering:
- the seriousness of the disease,
- the low prevalence or incidence of RET fusion-positive NSCLC,
- the medical need partially met by non-specific treatments (without specific data in RET fusion-positive NSCLC),
- the lack of an additional response to the identified need in first-line therapy, in the absence of any demonstrated impact on morbidity and mortality, and on quality of life,
- the absence of any demonstrated impact on the organisation of care,

GAVRETO (pralsetinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of GAVRETO (pralsetinib) is insufficient to justify public funding cover, in first-line therapy, as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC).

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 this part of the indication.

Second and later-line treatment of RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor

- Non-small cell lung cancer (NSCLC) is a serious, life-threatening disease.
- The proprietary medicinal product GAVRETO (pralsetinib) is a curative medicinal product.

- The efficacy/adverse effects ratio has not been adequately established due to:
  - the low level of evidence of the data: single-arm trial, for which the results are based on an objective response rate (68% in the overall study population);
  - the medical need in second-line therapy, where the treatment options are more limited;
  - and pending new efficacy and safety data.

- There are therapeutic alternatives not specific to RET fusion in the management of NSCLC (see 05 Clinically relevant comparators), as well as the proprietary medicinal product RETSEVMO (selpercatinib), a RET inhibitor that was granted a marketing authorisation in February 2021.

- On the basis of currently available data, the Committee considers that GAVRETO (pralsetinib) is a second and later-line treatment.

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 lack of an additional response to the identified need in first-line therapy, in the absence of any demonstrated impact on morbidity and mortality, and on quality of life, pending additional data,
- the absence of any demonstrated impact on the organisation of care,

GAVRETO (pralsetinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of GAVRETO (pralsetinib) is low in second and later-line therapy, as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC), pending new efficacy and safety data.

The Committee makes maintenance of this opinion conditional on the re-evaluation of GAVRETO (pralsetinib) within a maximum period of 3 years based on the results of the phase 3 study in first-line treatment (AcceleRET-Lung, results of the primary analysis expected for December 2024).

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 part of the indication.

- **Recommended reimbursement rate: 100%**

Clinical Added Value

Second and later-line treatment of RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor

Considering:
- the not very robust quality of research evidence for the efficacy of GAVRETO (pralsetinib) based on data from a non-comparative phase 1/2 study (ARROW);
- the absence of data from an external comparison with an appropriate methodology;
- uncertainties with respect to maintenance of the efficacy of the objective response rates observed, with a short follow-up period. Results with a longer follow-up period are expected for December 2022;
- the prognostic value of RET fusion, inadequately determined, in particular in the absence of comparative data in NSCLC;
- the substantial medical need partially met in this treatment line;

the Transparency Committee considers that GAVRETO (pralsetinib) provides no clinical added value (CAV V) in the therapeutic strategy for the treatment of adult patients with RET fusion-positive advanced non-small cell lung cancer (NSCLC), in second and later-line treatment.