HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
3 MARCH 2021

The legally binding text is the original French opinion version

pembrolizumab

KEYTRUDA 25 mg/ml concentrate for solution for infusion

KEYTRUDA 50 mg powder for concentrate for solution for infusion

Re-evaluation

Key points

Favourable opinion for maintenance of reimbursement only in the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR-positive (EGFR+) tumour mutations should also have received targeted therapy before receiving KEYTRUDA (pembrolizumab).

Unfavourable opinion for reimbursement in patients with ALK-positive (ALK+) tumour mutations, who should also have received targeted therapy before receiving KEYTRUDA (pembrolizumab).

What therapeutic improvement?

Therapeutic improvement compared to docetaxel in patients whose tumours express PD-L1 with a ≥ 1% TPS

In ALK + patients: not applicable.

Role in the care pathway?

Before the advent of PD-1 inhibitors, the care pathway for the treatment of non-small cell lung cancer (NSCLC) after failure of chemotherapy was as follows: in the absence of an activating EGFR mutation and ALK gene rearrangement, in eligible patients, it was recommended to propose second-line monotherapy, the nature of which depended on the drugs used previously: docetaxel or pemetrexed (only for non-squamous lung cancers).

Today, the second-line treatment of metastatic NSCLC is based on the administration of a PD-1 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) or,
- TECENTRIQ (atezolizumab) or,
- KEYTRUDA (pembrolizumab) only in the event of tumours with PD-L1 over-expression ≥ 1%.

Chemotherapy retains a second-line role in patients in whom first-line immunotherapy has failed.

In the event of activating EGF (EGFR) mutation, present in approximately 10% of cases of NSCLC, after the failure of tyrosine kinase inhibitor (TKI) monotherapy targeting the EGFR or the erlotinib – ramucirumab combination (CYRAMZA), it is recommended to test for the presence of a T790M+ mutation. Osimertinib (TAGRISSO) is the reference treatment in the event of a positive result for the mutation and if it has not been used as first-line therapy. If the result for the mutation is negative, the recommended treatment is platinum salt-based chemotherapy combined with one of the following drugs: gemcitabine, vinorelbine, taxanes (docetaxel and paclitaxel) or pemetrexed. Bevacizumab may be added depending on the case to some of these combinations for non-squamous NSCLC.

In patients with ALK+ NSCLC (3.5%), the therapeutic arsenal has been expanded with the addition of specific treatments targeting this genome abnormality: crizotinib (XALKORI), ceritinib (ZYKADIA), alectinib (ALECENSA).

Role of the medicinal product in the care pathway

After the failure of prior platinum-based chemotherapy, KEYTRUDA (pembrolizumab) as monotherapy is a second or later-line alternative, only in the event of tumours with PD-L1 over-expression ≥ 1%, to OPDIVO (nivolumab) or TECENTRIQ (atezolizumab) in patients with squamous or non-squamous, locally advanced or metastatic NSCLC.

In the absence of any comparative data, the role of KEYTRUDA (pembrolizumab) versus TECENTRIQ (atezolizumab) or OPDIVO (nivolumab) is not known.

In patients with an EGFR mutation, the role of KEYTRUDA (pembrolizumab) remain to be studied, with an optimal level of evidence.

In patients with an ALK gene rearrangement (ALK+), KEYTRUDA (pembrolizumab) has no role in the care pathway in the absence of clinical data.

COMMITTEE'S CONCLUSIONS

Clinical benefit

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

◗ The proprietary medicinal product KEYTRUDA (pembrolizumab) is a curative medicinal product.

◗ The efficacy/adverse effects ratio is high in the MA indication, with the exception of advanced NSCLC with ALK gene rearrangement, for which the efficacy/adverse effects ratio has not been established in the absence of clinical data.

◗ There are medicinal alternatives (see 05 Clinically relevant comparators).

◗ This is a second or later-line treatment, following the failure of prior chemotherapy in the event of tumours with PD-L1 over-expression ≥ 1%.
As the dossier currently stands, and in the absence of available clinical data, KEYTRUDA (pembrolizumab) has no role in the event of ALK gene rearrangement.

Public health impact:

Considering:

- the seriousness of NSCLC, particularly at the locally advanced or metastatic stage with failure of prior platinum-based chemotherapy,
- the incidence of the disease,
- the partial response (due to the lack of demonstrated impact on quality of life) to the identified medical need, in the population evaluated in the KEYNOTE-010 study, with the exception of the subpopulation with ALK gene rearrangement (in the absence of data, n=8 patients in the KEYNOTE-010 study),
- the lack of an expected impact on the organisation of care,

KEYTRUDA (pembrolizumab) is unlikely to have an additional impact on public health in this indication.

Considering all these elements, the Committee deems that the clinical benefit of KEYTRUDA (pembrolizumab) in the indication: "KEYTRUDA (pembrolizumab) as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA (pembrolizumab)":

- **remains substantial in the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS, with patients with activating EGFR mutation also having to have received a prior targeted therapy;**
- **is insufficient to justify public funding cover in the treatment of adult patients with locally advanced or metastatic NSCLC with ALK gene rearrangement, after prior chemotherapy.**

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use only in the following part of the indication "KEYTRUDA (pembrolizumab) as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with-EGFR tumour mutations should also have received targeted therapy before receiving KEYTRUDA (pembrolizumab)" and at the MA dosage.

Clinical Added Value

- **Within the reimbursement scope, i.e. in the MA indication with the exception of advanced NSCLC with ALK gene rearrangement (ALK+):**

The available data is not of a nature to modify the Committee's assessment; KEYTRUDA (pembrolizumab) provides a minor clinical added value (CAV IV) compared to docetaxel in the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS following the failure of at least one prior chemotherapy regimen. Patients with EGFR positive mutations should also have received targeted therapy before receiving KEYTRUDA (pembrolizumab).

- **Within the scope included in the MA but not retained for reimbursement, i.e. advanced NSCLC with ALK gene rearrangement (ALK+):**

Not applicable