HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
May 2017

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KEYTRUDA (pembrolizumab), anti-PD1 antibody

High clinical benefit and moderate clinical added value compared to platinum salt-based bitherapy as first-line treatment for metastatic non-small cell lung cancer

Main points

- KEYTRUDA has been granted a marketing authorisation for the first-line monotherapy treatment of adults suffering from metastatic non-small cell lung cancer (NSCLC) with tumours expressing PDL1 at the threshold ≥ 50%, without EGFR or ALK tumour mutation.
- As a monotherapy, its superiority has been demonstrated over platinum salt-based bitherapy in terms of progression-free survival in the patient population with a PD-L1 tumour expression of ≥ 50%.
- Its safety profile is superior to that of platinum salt-based chemotherapy.
- It is a first-line treatment for this population.

Pre-existing indications*

KEYTRUDA has also been granted a marketing authorisation for the treatment of metastatic melanoma, conventional Hodgkin's lymphoma and urothelial carcinoma (for more details, see marketing authorisation)

Therapeutic strategy

- The therapeutic strategy for metastatic NSCLC must be defined in the context of multidisciplinary review meetings, based on the presence of molecular abnormalities (in particular, EGFR mutation, ALK translocation or ROS1 rearrangement), PD-L1 tumour expression, tumour histology (epidermoid or non-epidermoid), age, ECOG performance status, comorbidities and patient preferences
- In the absence of EGFR or ALK activating mutations or ROS1 rearrangement, in patients with no major comorbidities and with an ECOG performance status of 0 to 2:
  The conventional first-line treatment is a chemotherapy regimen (4 to 6 cycles) combining a platinum salt (cisplatin or carboplatin) with one of the following substances: gemcitabine, taxanes (docetaxel or paclitaxel), vinorelbine or pemetrexed (only for non-epidermoid carcinoma patients). The regimens are as follows:
  - patients aged < 70 years with epidermoid NSCLC and a performance status of 0 or 1: cisplatin-gemcitabine, cisplatin-docetaxel, cisplatin-vinorelbine, carboplatin-paclitaxel, carboplatin-nabpaclitaxel.
    For patients with epidermoid NSCLC and in whom the tumour expresses EGFR, the necitumumab-gemcitabine-cisplatin combination may also be envisaged as a first-line treatment.
  - patients aged < 70 years with non-epidermoid NSCLC and a performance status of 0 or 1: cisplatin-pemetrexed, cisplatin-gemcitabine, cisplatin-docetaxel, carboplatin-paclitaxel, carboplatin-nabpaclitaxel (+/- bevacizumab).
  - patients aged < 70 years with a performance status equal to 2 or aged ≥ 70 years and with a performance status of 0 to 2, regardless of tumour histology: carboplatin-based doublets or one of the following chemotherapy regimens in monotherapy form: gemcitabine, vinorelbine or docetaxel.

  For patients with non-epidermoid NSCLC, having a partial response or stable disease and a performance status of 0 to 1 after induction chemotherapy (4 to 6 cycles), it may be proposed to:
  - continue one of the first-line treatments used (pemetrexed; so-called "continuation maintenance" strategy;
  - use a different chemotherapy substance (pemetrexed) to those used for induction (so-called "switch maintenance" strategy).
- In the absence of EGFR or ALK activating mutations, for patients with an ECOG performance status of 3 to 4, recourse to superior supportive care is recommended.

* This summary does not concern these indications.

- In cases of EGFR or ALK mutation or ROS1 rearrangement, the recommended first-line treatment is:
  - EGFR tyrosine kinase inhibitor monotherapy (choice from: gefitinib, erlotinib or afatinib) regardless of ECOG performance status, for patients with an EGFR mutation;
  - crizotinib for patients with ALK gene translocation or in cases of ROS1 rearrangement.
- In cases of PD-L1 tumour expression, pembrolizumab is recommended as a first-line treatment for metastatic NSCLC patients with tumour cells not exhibiting molecular abnormalities and with strong PD-L1 ligand expression (TPS ≥ 50%).
- **Role of the proprietary medicinal product in the therapeutic strategy**
  KEYTRUDA is a first-line treatment for metastatic NSCLC patients with tumour cells not exhibiting EGFR or ALK mutations and with strong PD-L1 ligand expression (threshold ≥ 50%).

Clinical data

- A randomised open-label study assessed the efficacy and safety of pembrolizumab versus a standard platinum salt-based chemotherapy regimen (5 bitherapies including a platinum salt of the investigator's choice), in adults with metastatic NSCLC, with strong tumour PD-L1 ligand expression (TPS ≥ 50%), not exhibiting EGFR or ALK tumour mutations, and who were systemic metastatic NSCLC treatment-naive. In total, 305 patients were randomised: 154 to the pembrolizumab group and 151 to the standard treatment group.
- In the final analysis of progression-free survival PFS (median follow-up of 11.2 months), the median PFS (primary endpoint) was 10.3 months in the pembrolizumab group and 6.0 months in the standard treatment group, i.e. an absolute gain of 4.3 months in favour of the pembrolizumab group (HR = 0.50 95% CI [0.37; 0.68], p < 0.001).
  As permitted by the hierarchical structure of the endpoints envisaged in the protocol, it was possible to conduct the intermediate analysis of the overall survival; the median overall survival was not reached in either of the 2 groups.
- Given both the open nature of the study and the exploratory status of this endpoint, the data available do not permit a reliable conclusion on the quality-of-life assessment.
- The safety profile appeared to be superior with pembrolizumab compared to chemotherapy particularly in terms of incidence of adverse effects of grades ≥ 3 (53.2% in the pembrolizumab group and 72.7% in the chemotherapy group). The primary toxicities of pembrolizumab recorded in this study were particularly dysthyroidism (16.8% versus 2.6% on standard treatment) and inflammatory pneumopathy (5.8% versus 0.7% on standard treatment).

Special prescription requirements

- Medicinal product for hospital use only.
- Prescription reserved for oncology and medical oncology specialists and departments.
- Medicinal product requiring special monitoring during treatment.

Benefit of the medicinal product

- The actual clinical benefit* of KEYTRUDA is high.
- KEYTRUDA provides a moderate clinical added value** (CAV III) compared to platinum salt-based bitherapy for its indication.
- Approval 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".