HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
Update
September 2017

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KEYTRUDA (pembrolizumab), anti-PD1 antibody

High clinical benefit and minor clinical added value for first-line treatment of advanced melanoma

Main points

- KEYTRUDA has been granted a marketing authorisation for monotherapy treatment of adults suffering from advanced melanoma.
- In B-RAF mutation-negative cases, similar to nivolumab (OPDIVO), it is recommended as a first-line treatment.
- In cases of B-RAF mutation, similar to nivolumab (OPDIVO), its role as an alternative to targeted therapies is currently the subject of debate, particularly in relation to the profile of patients suitable for receiving either of these two therapies as a first-line treatment.
- The new data, based on the follow-up from 2 previously assessed studies, do not shed new light on the assessment of the effective quantity of this medicinal product in the indication and at the marketing authorisation dosage.

Other indications*

KEYTRUDA has also been granted a marketing authorisation for the treatment of non-small cell lung cancer, classical Hodgkin's lymphoma and urothelial carcinoma (for more details, see marketing authorisation)

Therapeutic strategy

- The current treatment of advanced (non-resectable or metastatic) melanoma focuses, from the diagnosis stage, on patient selection based on the presence of B-RAF V600 tumour mutation or not.
- In B-RAF mutation-negative cases, pembrolizumab (KEYTRUDA) and nivolumab (OPDIVO) are recommended as first-line treatments.
  As a second-line treatment, ipilimumab (YERVOY) represents a therapeutic option, although no data are available on the efficacy of anti-CTL4 therapy (ipilimumab) after progression under anti-PD1 therapy.
- In cases of B-RAF mutation, the treatment firstly includes targeted bitherapy (B-RAF inhibitors + anti-MEK): dabrafenib (TAFINLAR) + trametinib (MEKINIST) or vemurafenib (ZELBORAF) + cobimetinib (COTTELIC). The role of nivolumab and pembrolizumab as an alternative to targeted therapies is currently the subject of debate, particularly in relation to the profile of patients suitable for receiving either of these two therapies as a first-line treatment.
  As a second-line treatment, pembrolizumab and nivolumab are recommended. The dabrafenib + trametinib combination is not recommended as a second-line treatment for relapsed patients having previously received B-RAF inhibitor monotherapy as a first-line treatment.
- **Role of the proprietary medicinal product in the therapeutic strategy**
  KEYTRUDA, administered as monotherapy, is most particularly a first-line treatment for patients not carrying a BRAF mutation and a second-line treatment for B-RAF mutation-positive patients in the case of relapsed patients treated with a B-RAF inhibitor.

* This summary does not concern these indications.

Clinical data

- The laboratory has furnished follow-up data from 2 studies: KEYNOTE 001 and 006 initially assessed by the HAS Board, with additional follow-up.
- KEYNOTE 001 is a phase I/II study, the primary endpoint of which was to assess the safety and anti-tumour activity of pembrolizumab with different dosage schedules, for advanced melanoma patients with or without B-RAF mutation. After 16 months of further follow-up with respect to the initial follow-up (total median follow-up of 31.8 months), the compiled data collection for all cohorts and all dosages combined (2 mg/kg or 10 mg/kg) suggests:
  - an overall response rate of 31.6%,
  - a median progression-free survival of 4.9 months,
  - a median overall survival of 24.4 months.

  Due to its preliminary nature, this study is not suitable for assessing the therapeutic contribution of KEYTRUDA in this indication.
- The study KEYNOTE 006 was conducted with an off-label dosage (10 mg/kg instead of 2 mg/kg) and, for this reason, the updated follow-up data cannot be applied to assess the therapeutic contribution of KEYTRUDA in the indication and at the marketing authorisation dosage.

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.
- The data available based on an update of the follow-up from two studies previously assessed by the HAS Board are not of a nature to modify the minor clinical added value** rating (CAV IV) assigned to KEYTRUDA by the Board in its opinion dated 16 March 2016.
- Approval for hospital treatment.

HAUTE AUTORITÉ DE SANTÉ
This document was drafted on the basis of the Transparency Committee opinion dated 3 May 2017 (CT-15825) 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".