HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
February 2018

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KEYTRUDA (pembrolizumab), monoclonal antibody

High clinical benefit for urothelial cancer and minor clinical added value compared to chemotherapy in terms of overall survival.

Main points

- KEYTRUDA has been granted a marketing authorisation for the monotherapy treatment of adults with locally advanced or metastatic urothelial cancer having received prior platinum salt-based chemotherapy.
- Its superiority over chemotherapy has been established: absolute gain in median overall survival of 2.9 months in favour of pembrolizumab.
- It is the preferred therapeutic option over chemotherapy for second- and third-line treatments for these patients. However, KEYTRUDA increases the risk of death in the first two months of treatment compared to chemotherapy.

Other indications*

KEYTRUDA has also been granted a marketing authorisation for the treatment of metastatic melanoma, lung cancer, classical Hodgkin's lymphoma (for more details, see marketing authorisation).

Therapeutic strategy

- Until recently, only vinflunine (JAVLOR) had been granted a marketing authorisation for the second-line treatment of adult patients with non-resectable locally advanced or metastatic urothelial cancer after prior platinum salt-based chemotherapy failure.
- European guidelines (ESMO 2014) suggest, in cases of late-onset progression (>12 months), further platinum salt-based chemotherapy treatment or, in cases of early-onset progression (< 12 months): vinflunine, taxane, or inclusion in a clinical trial. Further European (EAU 2016) and French (CCAFU 2016) guidelines suggest treatment with vinflunine or inclusion in a clinical trial.
- **Role of the medicinal product in the therapeutic strategy**
  KEYTRUDA is the preferred therapeutic option over chemotherapy for patients with locally advanced or metastatic urothelial cancer having progressed during or after platinum salt based-chemotherapy (second- and third-line).
  However, the higher risk of early death (in the first two months of treatment) compared to chemotherapy must be taken into account when prescribing KEYTRUDA.
  The presence of liver metastases and rapid disease progression during a prior platinum salt-based treatment (interval since the latest chemotherapy of less than 90 days) are factors likely to be associated with a higher risk of early death.

Clinical data

* This summary does not concern these indications.

- A randomised, open-label phase III study compared pembrolizumab (n=270) to a chemotherapy regimen chosen by the investigator (paclitaxel, docetaxel or vinflunine, n=272) in 542 patients with locally advanced or metastatic urothelial cancer having received prior platinum salt-based chemotherapy.
- In the second intermediate analysis (median follow-up of 14.1 months), the median overall survival (primary endpoint) was 10.3 months in the pembrolizumab group and 7.4 months in the chemotherapy group, i.e. an absolute gain of 2.9 months in favour of pembrolizumab (HR=0.73 95% CI [0.59; 0.91], p= 0.002). The study did not demonstrate any statistically significant difference between the groups in respect of progression-free survival (co-primary endpoint).
- A review of the deaths occurring in the first months of follow-up shows a higher number of deaths in the pembrolizumab group (43 deaths) than in the chemotherapy group (24 deaths) in the first 2 months. The presence of liver metastases and rapid disease progression during a prior platinum salt-based treatment (interval since the latest chemotherapy of less than 90 days) have been identified to date as factors likely to be associated with a higher risk of early death.
- The safety profile appeared to be superior with pembrolizumab than with chemotherapy particularly in terms of incidence of adverse effects of grades ≥ 3 (52.3% in the pembrolizumab group and 62.7% in the chemotherapy group). The primary toxicities of pembrolizumab recorded in this study were particularly hypothyroidism (6.4% versus 1.2 % on chemotherapy), hyperthyroidism (3.8% versus 0.4% on chemotherapy) and inflammatory pneumopathy (3.8% versus 0.4% on chemotherapy).

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for oncology specialists or physicians with oncology expertise
- Medicinal product requiring special monitoring during treatment

Benefit of the medicinal product

- The actual clinical benefit* of KEYTRUDA is high
- KEYTRUDA provides a clinical added value** (CAV IV, minor) compared to chemotherapy in terms of overall survival
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 21 February 2018 (CT-16530) 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".