HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
April 2016

BRIEF SUMMARY OF THE HAS BOARD OPINION

KEYTRUDA (pembrolizumab), anti-PD1 antibody

Minor clinical added value in first-line treatment of advanced melanoma.

Main points

- KEYTRUDA has marketing authorisation as monotherapy in the treatment of adults with advanced (unresectable or metastatic) melanoma.
- In the absence of BRAF mutation, like nivolumab (OPDIVO), it is recommended as a first-line treatment.
- If there is BRAF mutation, like nivolumab (OPDIVO), its role as an alternative to targeted therapies is currently debated, especially the patient profile that could receive one of these two treatments as a first line.

Therapeutic use

The current management of advanced (unresectable or metastatic) melanoma involves screening patients as soon as they are diagnosed for a BRAF mutation in the tumour:

- In the absence of BRAF mutation, pembrolizumab (KEYTRUDA) and nivolumab (OPDIVO) are recommended as first-line treatment.
  In second-line treatment ipilimumab (YERVOY) is a therapeutic option although there are no data on the efficacy of anti-CTL4 agents (ipilimumab) after progression on anti-PD1 agents.
- If there is BRAF mutation, the initial treatment consists of a targeted dual therapy (BRAF inhibitors + anti-MEK agents): dabrafenib (TAFINLAR) + trametinib (MEKINIST) or vemurafenib (ZELBORAF) + cobimetinib (COTTELIC). The role of nivolumab and pembrolizumab as alternatives to these targeted therapies is currently debated, and particularly the profile of patients that could receive one of these two treatments as first-line therapy.
  Pembrolizumab and nivolumab are recommended as second-line treatment. The dabrafenib + trametinib combination is not recommended as second-line therapy in patients who have already received a BRAF inhibitor as monotherapy in first-line treatment.
- **Role of the medicinal product in the therapeutic strategy**
  KEYTRUDA, in monotherapy, is first-line treatment in patients who do not have a BRAF mutation and a second-line treatment in BRAF mutated patients.

Clinical data

- In a phase I/II study, whose objective was to evaluate the anti-tumour activity and safety of pembrolizumab with different dosage regimens, in patients with advanced melanoma with or without BRAF mutation, naïve or in second-line treatment, no difference was shown between the pembrolizumab 2 versus 10 mg/kg every 3 week groups, in terms of objective response (primary endpoint).
- In another phase III, randomised, open-label study conducted in 834 patients, regardless of BRAF mutation, in first-line treatment versus ipilimumab, the median progression-free survival (co-primary endpoint) was 4.1 months in the pembrolizumab 10 mg/kg/3 week group versus 2.8 months in the ipilimumab group. On the interim analysis date, for a median patient follow-up of 14 months, the percentage of events (disease progression or death) was 61% (170/277) in the pembrolizumab 10 mg/kg/3 week group and 71% (198/278) in the ipilimumab group: HR = 0.59; 95% CI = [0.48-0.73]; p<0.00001.
  In terms of overall survival, the percentage of death was 33% (92/277) in the pembrolizumab 10 mg/kg/3 week group and 40% (112/278) in the ipilimumab group: HR = 0.69; 95% CI=[0.52-0.90]; p=0.00358 (<nominal p=0.005 predefined in the protocol).
- Another phase II, randomised, open-label study conducted in 540 patients regardless of BRAF mutation, in second-line or third-line treatment versus chemotherapy, at the discretion of the investigator (dacarbazine or

temozolomide or carboplatin+paclitaxel): during the interim analysis planned after 169 patients died, the percentage of events occurring (disease progression or death) was 72% (129/180) in the pembrolizumab 2 mg/kg/3 week group and 87% (155/179) in the ipilimumab group: HR = 0.57; 95% CI = [0.45-0.73]; p<0.0001.

- Pembrolizumab appears to have a better safety profile than standard chemotherapy or ipilimumab. Serious adverse events (grade 3 or greater) were reported in 37 to 47% of patients depending on the study for the pembrolizumab 2 mg/kg dosage regimen (marketing authorisation dosage), the most commonly observed are of immunological origin: thyroid dysfunction, diarrhoea, colitis, pneumonia, pruritus, rash.
- No PD-L1 expression threshold value is standardised and validated, this varies from one study to another depending on the compound evaluated. This biomarker, in the current state of knowledge, cannot be used for prognosis purposes to assess any difference according to PD-L1 expression.

Special prescribing conditions

- Medicinal product reserved for hospital use.
- Prescription restricted to cancer treatment and oncology specialists and departments.
- Medicinal product requiring special monitoring during treatment.

Benefit of the medicinal product

- The actual benefit* of KEYTRUDA is substantial.
- Due to the level of proof of the demonstration of efficacy (open-label study, different interim analyses, dose finding in late stage development), KEYTRUDA provides a minor clinical added value** (CAV IV) in this indication.
- Recommends inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the HAS Board Opinion of 16 March 2016 (CT-14660) available at **www.has-sante.fr**

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Board assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Board assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".