HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
February 2016

BRIEF SUMMARY OF THE HAS BOARD OPINION

OPDIVO (nivolumab), anti-PD-1 antibody

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

Main points

- OPDIVO has marketing authorisation as monotherapy in the treatment of adults with advanced (unresectable or metastatic) melanoma.
- In the absence of BRAF mutation, like pembrolizumab (KEYTRUDA), it is recommended as first-line treatment.
- If there is BRAF mutation, like pembrolizumab (KEYTRUDA), 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, nivolumab (OPDIVO) and pembrolizumab (KEYTRUDA) 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 as is the profile of patients who could receive one of these two treatments as first-line therapy.
- Nivolumab and pembrolizumab 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**
  OPDIVO, in monotherapy, is a 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 randomised, double-blind study conducted in 418 non-BRAF mutated patients as a first-line treatment versus dacarbazine, overall survival (% of deceased subjects, primary endpoint) was 24% (50/210 patients) in the nivolumab group and 46% (96/208) in the dacarbazine group: HR = 0.42; 99.79% CI = [0.25-0.73]; p<0.0001.
- In another randomised, double-blind study conducted in 945 patients, regardless of BRAF mutation, in first-line treatment versus ipilimumab, the median progression-free survival (co-primary endpoint) was 6.9 months in the nivolumab group versus 2.9 months in the ipilimumab group. On the interim analysis date, for a median patient follow-up of 12.5 months, the percentage of events (disease progression or death) was 55% (174/316) in the nivolumab group and 74% (234/315) in the ipilimumab group: HR = 0.57; 95% CI = [0.43-0.76]; p<0.0001.
- In another randomised, open-label study conducted in 405 patients regardless of BRAF mutation as a second or third-line treatment versus chemotherapy, at the discretion of the investigator (dacarbazine or carboplatin+paclitaxel):
  - The objective response rate (co-primary endpoint) was 32% (38/120 patients) in the nivolumab group versus 11% (5/47 patients) in the chemotherapy group.

- During the interim analysis planned after 169 patients died, the percentage of deaths from all causes (co-primary endpoint) was 44.5% (121/272 patients) in the nivolumab group versus 45.9% (61/133) in the chemotherapy group: HR = 0.93; 95% CI [0.68 -1.26]; not significant.

- Nivolumab appears to have a better safety profile than standard chemotherapy or ipilimumab. Serious adverse events (grade 3 or greater) were reported in 34 to 44% of patients depending on the study, the most commonly observed are of immunological origin: thyroid dysfunction, diarrhoea, elevated ASAT/ALAT/gamma-GT, renal insufficiency/elevated serum creatinine, pruritus, rash, vitiligo, erythema.
- 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 OPDIVO is substantial.
- OPDIVO provides moderate clinical added value** (CAV III) 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 13 January 2016 (CT-14578) 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 Transparency Committee 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 Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".