HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
May 2017

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

OPDIVO (nivolumab), anti-PD1 antibody

Clinical benefit of the OPDIVO + YERVOY combination:

- **high for the treatment of advanced melanoma only as a first-line treatment for patients with ECOG 0 - 1, with non-B-RAF-mutated tumour, not presenting with active brain metastasis and administered in centres equipped with an interdisciplinary medical resuscitation unit or equivalent but no clinical added value in patient care;**
- **insufficient in other cases for publicly funded care**

Main points

- OPDIVO in combination with ipilimumab has been granted a marketing authorisation for the treatment of adults with advanced (non-resectable or metastatic) melanoma.
- It is a first-line therapeutic option, which can only be offered in the context of a multidisciplinary review meeting to a selected population: advanced-stage melanoma, ECOG 0 or 1, with non-B-RAF-mutated tumour in the absence of active brain metastasis.

Pre-existing indications*

OPDIVO has also been granted a marketing authorisation for the treatment of kidney cancer and non-small cell lung cancer (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 BRAF 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 this anti-CTL4 therapy 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 (COTELLIC). The role of nivolumab and pembrolizumab as an alternative to targeted therapies is currently the subject of debate, along with the profile of the patients suitable for receiving either of these two therapies as a first-line treatment.
  As a second-line treatment, pembrolizumab or 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**

  The nivolumab + ipilimumab combination is a first-line therapeutic option, which can only be offered in the context of a multidisciplinary review meeting to a selected population suffering from advanced-stage melanoma: patients with ECOG 0 or 1, with non-B-RAF-mutated tumour in the absence of active brain metastasis.
  When choosing to prescribe this combination, it is necessary to account for the high frequency of treatment-related adverse events, particularly of grades ≥ 3 (55.0% versus 27.3% with ipilimumab alone). This information should be given to the patient prior to starting treatment.

* This summary does not concern this indication.

Clinical data

- A double-blind, randomised, phase III study (CA209067) compared the efficacy and safety, as a first-line treatment, of nivolumab alone versus ipilimumab alone (which is not the conventional treatment in this scenario) and the nivolumab + ipilimumab combination versus ipilimumab monotherapy, in non-resectable or metastatic melanoma patients with or without B-RAF mutation. In total, 945 patients were randomised (approximately 315 per group).
  In a final analysis, the median progression-free survival (co-primary endpoint) was longer in the nivolumab/ipilimumab combination group (11.5 months) than the ipilimumab monotherapy group (2.9 months), i.e. a gain of 8.6 months. The clinical relevance of this gain versus ipilimumab needs to be qualified insofar as the benefit comparison, with regard to the therapeutic strategy, would be that versus nivolumab monotherapy (median progression-free survival of 6.9 months). The overall survival data (co-primary endpoint) had not been finalised on the date of this analysis. The overall survival analysis conducted after 28 months of follow-up showed a median overall survival of 19.9 months in the ipilimumab group and survival not reached in any of the nivolumab groups.
- In a phase II study comparing nivolumab + ipilimumab versus ipilimumab alone in 142 treatment-naive patients, regardless of BRAF status, the objective response rate in the non-BRAF-mutated subgroup (primary endpoint) was 59.7% in the nivolumab + ipilimumab group versus 10.8% in the ipilimumab only group, p<0.0001. Due to a switch of over half of the ipilimumab group sample (55%) to the nivolumab / ipilimumab combination group, the overall survival data cannot be interpreted.
  In patients having discontinued the treatment due to toxicity (n=50), the objective response rate remained high in the nivolumab + ipilimumab group (67.4% in all randomised patients) including 16.8% of patients who obtained a complete response, thus suggesting durability of the response even after discontinuing treatment.
- The marketing authorisation dosage schedule is based on the nivolumab study protocols recommending continued administration until progression or intolerance; this observation of response retention in patients in remission after discontinuing nivolumab treatment raises the question of the legitimacy of continued treatment which would not provide any benefit in terms of efficacy but would expose patients to adverse effects.
- The effectiveness on progression-free survival and on overall survival should be considered against the increase in adverse events (AEs), particularly the increased frequency of treatment discontinuations. Indeed, approximately one out of every two patients treated with the nivolumab + ipilimumab combination discontinued the treatment due to adverse events (43.1% in the pivot study and 55.3% in the study CA209069) whereas this rate only applies to 13% of the nivolumab monotherapy group or 22% of the patients of the ipilimumab group. The main toxicities with this combination were colitis and diarrhoea and increased ASAL and ALAT levels.

Special prescription requirements

- Medicinal product for hospital use only.
- Prescription reserved for oncology specialists and physicians with oncology expertise.

Benefit of the medicinal product

- The actual clinical benefit* of OPDIVO is high only as a first-line treatment for patients with ECOG 0 or 1, with non-B-RAF-mutated tumours, not presenting with active brain metastasis and administered in centres equipped with an interdisciplinary medical resuscitation unit or equivalent. It is insufficient in other cases for publicly funded care.
- OPDIVO plus ipilimumab does not provide any clinical added value** (CAV V) for the treatment of adults with advanced melanoma in the population defined for the actual clinical benefit.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 3 May 2017 (CT-15561) 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".