HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
December 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

OPDIVO (nivolumab), monoclonal antibody

High clinical benefit in the adjuvant treatment of melanoma with lymph node involvement or metastatic disease having had a complete resection, and moderate clinical added value in the therapeutic strategy.

Main points

- OPDIVO has been granted a marketing authorisation for the monotherapy adjuvant treatment of adults suffering from melanoma with lymph node involvement or metastatic disease having had a complete resection.
- It has demonstrated its superiority over ipilimumab in terms of reduction of recurrence, in the context of adjuvant treatment of melanoma with high risk of recurrence with an acceptable safety profile.
- The available data do not allow any conclusions concerning improved overall survival to be drawn.
- This treatment should be preferred over the historical treatment, interferon.

Therapeutic strategy

- In the context of the adjuvant treatment of melanoma with high risk of recurrence, the following points were recommended:
  - assess patients with resected stage III melanoma to administer interferon as adjuvant treatment.
  - patients with regional microscopic lymph node involvement and/or ulcerated primary lesion constitute those subjects most likely to benefit from this treatment.
  - encourage the participation of patients with stage IIIB or later melanoma in clinical trials.
- According to the guidelines of the French society for dermatology, updated in November 2018, patients suffering from stage III melanoma expressing a BRAF V600 mutation are eligible for adjuvant treatment, both by the dabrafenib/trametinib combination and by anti-PD-1 immunotherapy. In the absence of comparative studies of these two strategies, there are no arguments for recommending one treatment over the other.
  In the event of wild-type BRAF tumour, patients are eligible for anti-PD-1 immunotherapy. There are no arguments for preferring one anti-PD-1 over another.
- **Role of the medicinal product in the therapeutic strategy**
  In light of the demonstrated superiority of nivolumab over ipilimumab (active medicinal product with a marketing authorisation as an adjuvant in the United States) in terms of recurrence reduction in a context of adjuvant treatment of melanoma with high risk of recurrence and with an acceptable safety profile, OPDIVO should be preferred over the historical treatment, interferon.
  In the absence of direct comparison data, its role relative to new therapeutic alternatives, (pembrozilumab, dabrafenib/trametinib in the event of BRAF V600 mutation) is not known.

Clinical data

- One phase III randomised double-blind study compared the efficacy and safety of nivolumab monotherapy at a dose of 3 mg/kg, once every two weeks for a year, versus ipilimumab in the adjuvant treatment of melanoma with lymph node involvement or metastatic disease, having had a complete resection. At inclusion, patients presented primarily skin melanomas (84.5%) of stage IIIB (34.3%), IIIC (46.6%) and IV (18.7%), with ulceration for 31.8% of patients. In 50.3% of cases, the melanoma was primary, whereas in 48.9% of cases it was a recurrence. PD-L1 expression was negative (<5%) for most patients (61.9%) and the melanoma had BRAF mutation in 42.1% of cases (consistent with the known frequency of BRAF mutation).
- The available results are those of an intermediate analysis, considered as the primary analysis of this study (analysis of all patients with follow-up of at least 18-months).
- Nivolumab demonstrated to be superior to ipilimumab in terms of recurrence-free survival (RFS) (primary endpoint), with an HR = 0.65; CI97%: 56% [0.51; 0.83], p<0.0001. In all, 360 recurrence events were observed, of which 34% (n=154) in the nivolumab group and 45.5% (n=206) in the ipilimumab group, i.e. an absolute difference of approximately 10% in favour of nivolumab.
  The median RFS was not reached in either group.
- Overall survival analyses (secondary endpoint with hierarchical procedure) as stipulated by the protocol, are not available to date as the minimum required follow-up period has not been reached.
- The frequency of adverse events (AEs) requiring treatment discontinuation was 9.7% in the nivolumab group and 42.6% in the ipilimumab group. The proportion of patients who presented with a grade 3 or 4 AE was of 25.4% in the nivolumab group and 55.2% in the ipilimumab group. The incidence of serious AEs grade was of 17.5% in the nivolumab group and 40.4% in the ipilimumab group.

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for oncology or haematology specialists or physicians with expertise in oncology or blood disorders.

Benefit of the medicinal product

- The actual clinical benefit* of OPDIVO is high in the marketing authorisation indication.
- OPDIVO provides moderate clinical added value** (CAV III) in the therapeutic strategy, including only the historical interferon treatment.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 05 December 2018 (CT-17226) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a 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 ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".