HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
Update
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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

YERVOY (ipilimumab), monoclonal antibody

Substantial clinical benefit in monotherapy in the treatment of advanced melanoma in second-line and beyond in the absence of BRAF mutation and in third-line and beyond in the presence of BRAF mutation, but no clinical benefit demonstrated compared with usual management (chemotherapy and supportive care)

Insufficient clinical benefit to justify its inclusion on the list of reimbursable products in monotherapy in the treatment of advanced melanoma in other cases

Main points

- YERVOY has Marketing Authorisation in the treatment of adult patients with advanced (unresectable or metastatic) melanoma.
- Since the arrival of anti-PD-1 immunotherapy and so-called targeted therapies, monotherapy with YERVOY no longer has a role in the first-line treatment of advanced-stage melanoma, regardless of the BRAF status of the tumour, or in second-line treatment in the presence of a BRAF mutation.
- No methodologically admissible data document the efficacy and safety of YERVOY in the situations where it is now used (second-line and beyond in the absence of BRAF mutation and third-line and beyond in the presence of BRAF mutation).

Therapeutic use

- The current management of advanced (unresectable or metastatic) melanoma involves screening patients for a BRAF mutation in the tumour as soon as they are diagnosed:
  - In the absence of BRAF mutation (wild-type BRAF), nivolumab (OPDIVO) or pembrolizumab (KEYTRUDA) are recommended as first-line treatment. The combination of ipilimumab with nivolumab is an option in a limited sub-group. 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. In the event of failure, chemotherapy (including dacarbazine) is discussed as third-line treatment. Depending on the patient's characteristics and the apparent toxicities on immunotherapy, the use of dacarbazine may also be considered from the second line as an alternative to ipilimumab.
  - If there is BRAF mutation, the first-line treatment consists of a targeted dual therapy (combination of a BRAF inhibitor and an anti-MEK agent): dabrafenib (TAFINLAR) combined with trametinib (MEKINIST) or vemurafenib (ZELBORAF) combined with cobimetinib (COTELLIC). In some cases, the use of anti-PD1 immunotherapy may be proposed. After failure of targeted dual therapy, use of an anti-PD1, nivolumab (OPDIVO) or pembrolizumab (KEYTRUDA) are recommended as second-line treatment. Ipilimumab may be proposed as third-line treatment. Chemotherapy, including dacarbazine, is discussed as a fourth-line treatment. Depending on the patient's characteristics and the apparent toxicities on immunotherapy, the use of dacarbazine may also be discussed as a third-line treatment as an alternative to ipilimumab.
- **Role of the proprietary medicinal product in the therapeutic strategy**

  YERVOY monotherapy is a treatment for:
  - second-line and beyond in absence of BRAF mutation;
  - third-line and beyond in presence of BRAF mutation.

  Depending on the patient's profile (general condition, comorbidities, LDH level, toxicities related to prior lines of treatment, etc.), alternatives to monotherapy with YERVOY are chemotherapy and supportive care.

Clinical data

- Since the last assessments of YERVOY (2013 and 2014), YERVOY has been used as a comparator treatment in studies evaluating OPDIVO (nivolumab) and KEYTRUDA (pembrolizumab). In both studies, the efficacy of ipilimumab in terms of overall survival and progression-free survival was inferior to those of nivolumab or pembrolizumab in treatment-naïve patients. Therefore, monotherapy with ipilimumab is no longer recommended in first-line treatment of patients without BRAF mutation or in second-line treatment of patients with BRAF mutation.
- New descriptive data of 57 patients from the extension phase of a study evaluating OPDIVO (nivolumab) document the efficacy of ipilimumab as second-line treatment after failure of monotherapy with anti-PD1. The median survival of these 57 patients was 16.62 months (95% CI = [12.68; not evaluable]). The methodological limitations of these data did not allow for quantification of the effect of treatment by ipilimumab after failure of an anti-PD1.
- The main risks involve gastrointestinal toxicity and immunological toxicity.

Special prescribing conditions

- Medicinal product reserved for hospital use
- Prescription reserved for cancer treatment or clinical oncology specialists
- Medicinal product requiring special monitoring during treatment

Benefit of the medicinal product

- The actual benefit* of YERVOY as a monotherapy is:
  - insufficient to justify inclusion on the list of medicines reimbursed by National Health Insurance in treatment-naïve patients (regardless of the BRAF status of the tumour) and in second-line in the presence of a BRAF mutation,
  - substantial in second-line and beyond in the absence of BRAF mutation and in third-line and beyond in the presence of BRAF mutation.
- In the situations where it is now used, YERVOY does not provide clinical added value** (CAV V) in the management strategy of these patients, which includes chemotherapy and supportive care
- Recommends inclusion on the list of reimbursable products for hospital use only in monotherapy for the treatment of advanced melanoma in second-line and beyond in the absence of BRAF mutation and in third-line and beyond in the presence of BRAF mutation.
- Does not recommend inclusion on the list of reimbursable products for hospital use in monotherapy for the treatment of advanced melanoma:
  - in treatment-naïve patients (regardless of the BRAF status of the tumour),
  - and in second-line for advanced melanoma in the presence of a BRAF mutation.

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This document was created on the basis of the Transparency Committee Opinion of 07 June 2017 (CT-15132 and CT-15764) and is 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”.