HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
November 2014

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

YERVOY (ipilimumab), monoclonal antibody

No clinical added value demonstrated as a first-line treatment of advanced melanoma in adults when compared with existing therapeutic strategies

Main points

- YERVOY now has Marketing Authorisation as first-line treatment for advanced (unresectable or metastatic) melanoma in adult patients.
- In view of the low level of evidence of the submitted studies, YERVOY provided no demonstrable clinical benefit compared with the existing first-line therapeutic strategy for the treatment of advanced melanoma in adults.

Pre-existing indication

YERVOY already has Marketing Authorisation in the treatment of advanced (unresectable or metastatic) melanoma in adult patients who have received prior therapy. This summary does not cover this indication

Therapeutic use

Current first-line treatment for advanced melanoma (unresectable or metastatic) is directed from diagnosis towards selecting patients based on whether or not they have a BRAF mutation.
In cases of mutation, the choice of treatment involves targeted therapy, currently represented by vemurafenib (ZELBORAF) or dabrafenib (TAFINLAR) as monotherapy.

Role of the medicinal product in the therapeutic strategy

In the absence of BRAF mutation, ipilimumab (YERVOY) is considered to be an acceptable first-line option. In the specific case of non-mutated BRAF tumours associated exclusively with brain metastasis, treatment is based on the use of ipilimumab (YERVOY) or fotemustine. The role of adjuvant radiotherapy should be discussed.

Clinical data

- An a posteriori pooled analysis was performed on the data from chemotherapy-naïve patients taken from four randomised studies (three phase II study and one phase III) and treated with ipilimumab at a dose of 3 mg/kg (n = 78 patients). The estimated overall survival rate at 1 year (primary endpoint) was 54.1%. This analysis presents several statistical and methodological weaknesses that need to be underlined: firstly, there is the potential bias associated with a post-hoc pooled analysis on subgroups of patients from different studies that does not follow the hypothetical-deductive approach; and secondly, the lack of a comparative analysis with the existing therapeutic strategy.

- An interim analysis was performed on two retrospective observational cohort studies of patients followed-up in the United States:
  - In one of the studies (n = 90 patients), the overall survival rate observed at 1 year was 49.4% and the observed median survival was 11.5 months.
  - In the other study (n = 160 patients), the overall survival rate observed at 1 year was 60.8% and the observed median survival was 15.5 months.
  The level of evidence of these results remains low (memory bias and non-comparative studies).

- An indirect comparison included 16 randomised studies; the results suggest that the overall survival in the long term (≥ 24 months) with ipilimumab seems to be better than the other treatment regimens assessed as monotherapy (dacarbazine, temozolomide, vemurafenib). A hazard ratio in favour of ipilimumab was observed in month 24 in comparison with dacarbazine: HR = 0.46, with temozolomide: HR = 0.40, and finally with vemurafenib: HR = 0.47. The analysis including vemurafenib presupposes that ipilimumab has equivalent efficacy, depending on whether patients are BRAF mutation carriers or not.

- Treatment-related serious adverse events (grades ≥ 3) were reported in 13 to 14% of patients; those most commonly observed are of immunological origin. The safety data provided in this new indication are comparable to the safety profile known to date for this proprietary medicinal product.

Prescribing conditions

Medicine for hospital prescription, restricted to oncologists or doctors with cancer training and requiring special supervision during treatment.

Benefit of the medicinal product

- The actual benefit* of YERVOY is moderate in the first-line extension of indication for the treatment of adult patients with advanced melanoma (unresectable or metastatic), without BRAF mutation and in slow progression patients in a good general state of health and a life expectancy of more than 3 months.

- In the absence of any demonstrably superior efficacy or safety over the existing first-line therapeutic strategy for the treatment of advanced melanoma in adults, YERVOY does not provide a clinical added value ** (CAV V, nonexistent).

- Recommends inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 19 November 2014 (CT-13608) 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”.