HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
June 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

YERVOY (ipilimumab), monoclonal antibody

Insufficient clinical benefit to justify reimbursement in the treatment of adolescents (12 to 17 years) with advanced melanoma due to the absence of role in the therapeutic strategy

Main points

- YERVOY monotherapy has MA in the treatment of adolescent patients age 12 years and over with advanced (non-resectable or metastatic melanoma).
- Its clinical benefit is insufficient in treatment-naive or pretreated adolescents (age 12 to 17 inclusive), in light of, in particular, efficacy and safety data especially limited in adolescents, the superiority of anti-PD1 (nivolumab, pembrolizumab) demonstrated compared to ipilimumab in treatment-naive adults and the absence of efficacy or safety data in adults after failure of standard treatments (anti-PD1 or anti-B-RAF/anti-MEK).
- YERVOY has no role in the current therapeutic strategy for advanced melanoma in adolescents.

Pre-existing indication*

YERVOY already has similar MA in adults.

Therapeutic strategy

- Available recommendations for management focus on the treatment of adults with advanced melanoma, which is based on patient screening at the time of diagnosis, according to whether the tumour exhibits B-RAF mutation or not:
  - in the absence of B-RAF mutation (B-RAF, wild-type), nivolumab (OPDIVO) or pembrolizumab (KEYTRUDA) are recommended as first-line treatments. The ipilimumab and nivolumab combination is an option in a small sub-group. As a second-line treatment, ipilimumab (YERVOY) represents a therapeutic option, although no data are available on the efficacy of anti-CTL4 therapy (ipilimumab) after progression under anti-PD1 therapy. In the event of escape, chemotherapy, including dacarbazine, is discussed in third-line. According to the patient's characteristics and toxicity occurring with immunotherapy, the dacarbazine option can also be discussed from the second-line as alternative to ipilimumab.
  - in the event of B-RAF mutation, first-line treatment is based on a B-RAF inhibitor and an anti-MEK combination: dabrafenib (TAFINLAR) combined with trametinib (MEKINIST) or vemurafenib (ZELBORAF) combined with cobimetinib (COTELLIC). In some cases, anti-PD1 immunotherapy can be offered. In second-line treatment, after failure of the targeted bitherapy, the use of an anti PD1, nivolumab (OPDIVO) or pembrolizumab (KEYTRUDA) are recommended. Ipilimumab can be offered in third-line. Chemotherapy, including dacarbazine, is discussed in fourth-line. According to the patient's characteristics and toxicity occurring with immunotherapy, the dacarbazine option can also be discussed in the third-line as alternative to ipilimumab.
- In adults, since the advent of immunotherapy and so-called targeted therapies, YERVOY monotherapy no longer has a role in the first-line treatment of advanced melanoma, regardless of the B-RAF status of the tumour or in second-line in patients with mutated B-RAF. YERVOY monotherapy remains however a second-line treatment and further in adults in the absence of B-RAF mutation or third-line and further in the presence of B-RAF mutation.
- According to the adult patient's profile (general condition, comorbidities, LDH levels, toxicity related to previous treatment lines, etc.) the alternatives to YERVOY monotherapy are chemotherapy and supportive care.
- **Role of the medicinal product in the therapeutic strategy**

* This summary does not concern these indications.

The management of adolescents with advanced (non-resectable or metastatic) melanoma is generally similar to that of adults. Compared to YERVOY, immunotherapy treatments (nivolumab or pembrolizumab) have demonstrated superior efficacy in adults and exhibit a better safety profile. Ipilimumab (YERVOY) monotherapy therefore has no role in the current therapeutic strategy for advanced melanoma in adolescents (age 12 to 17 inclusive).

Clinical data

- Efficacy and safety data in the treatment of adolescents with advanced melanoma with ipilimumab monotherapy at the MA dosage (3 mg/kg) are highly limited. They are taken from the data of 4 adolescents treated with ipilimumab at the dose confirmed by the MA (3 mg/kg) in a phase 2, non-comparative study. Given the recruitment difficulties, especially concomitant recruitment in clinical studies evaluating other treatments (e.g.: anti-PD1), this study was terminated early.
  Among the 4 adolescents, overall survival after 1 year (primary endpoint) was 75% (CI95% [12.8; 96.1]) and median survival 18.2 months (CI95% [8.9; 18,2]). None of the 4 patients showed a response (complete or partial): one had stable disease and the 3 others progressed. Median progression-free survival was 2.6 months (CI 95% [2.3; 8.5]).
  Among the 4 adolescents treated at the dose of 3 mg/kg (3 patients received the 4 injections), one adolescent completed the study and 3 left early due to a treatment-related serious adverse event (hepatitis) for 1 patient, and disease progression for the other 2.
- The data available suggest that ipilimumab is less well-tolerated in adolescents than in adults.
- The impact of YERVOY on morbidity and mortality was not demonstrated in adolescents, regardless of the treatment line at the advanced stage.

Special prescription requirements

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

Benefit of the medicinal product

- The clinical benefit* of YERVOY is insufficient to justify public funding cover.
- Not approved for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 27 June 2018 (CT-16832) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product 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.