HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
April 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

KEYTRUDA (pembrolizumab), anti-PD1 antibody

High clinical benefit in relapsed or refractory classical Hodgkin's lymphoma after failure of autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV) treatment, or in the event of transplantation ineligibility after BV treatment failure, though no demonstrated clinical added value in the therapeutic strategy.

Main points

- KEYTRUDA has been granted marketing authorisation for the treatment of adults with relapsed or refractory classical Hodgkin's lymphoma (HLc) in 2 situations: after failure of autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV) failure, or in patients ineligible for transplantation and after BV treatment failure.
- Its efficacy was established by a non-comparative, multi-cohort study demonstrating that a high objective response rate (between 66.7 and 75.4%) was obtained over a median follow-up period of 15.9 months.
- Acute graft-versus-host disease, along with ASCT-related deaths, were observed, more frequently than expected, in patients receiving an allograft following pembrolizumab treatment. This excess risk justifies the need for a multidisciplinary review meeting, including haematologists specialising in stem cell transplantation, before initiation of pembrolizumab treatment.

Pre-existing indications*

KEYTRUDA has also been granted marketing authorisation for the treatment of melanoma, non-small cell lung cancer and urothelial carcinoma at the time of the opinion summary.

Therapeutic strategy

- The first-line treatment of choice for cHL involves intensive ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) chemotherapy, possibly followed by radiotherapy of the initially impacted lymph nodes. The choice of protocol and number of cycles is determined by disease prognostic factors and potential long-term treatment complications.
- In the event of relapse during second-line treatment, salvage chemotherapy (DHAP [dexamethasone, cisplatin, cytarabine], MINE [mitoguazone, ifosfamide, vinorelbine, etoposide], ICE [ifosfamide, carboplatin, etoposide] or IVA [ifosfamide, etoposide, doxorubicin]) followed by autologous haematopoietic stem cell transplantation, gives a complete response rate in approximately 50% of patients.
- If disease progression or recurrence is observed after autologous transplantation, brentuximab vedotin treatment is recommended. Recently, ADCETRIS (brentuximab vedotin) was granted marketing authorisation for prophylaxis, as post-HSC transplantation consolidation treatment in adults with increased risk of recurrence or progression.
- In the event of multiple relapses or refractory cHL, options for subsequent treatment include:
  - bendamustine, lenalidomide and everolimus (off-label), with overall response rates below 50% and median progression-free survival times of circa 4 to 6 months, observed in studies with low level of evidence;
  - anti-PD-L1 antibodies with marketing authorisation (nivolumab and pembrolizumab).
- In the event of a good response to remedial therapy, HSC allograft is discussed.

Role of the medicinal product in the therapeutic strategy

* This summary does not cover these indications.

KEYTRUDA is an alternative treatment in these new indications.
In the absence of comparative data with the other anti-PD1 antibody, OPDIVO, for their common indication (failure of transplantation and brentuximab vedotin), the role of KEYTRUDA relative to OPDIVO remains unknown.
As for OPDIVO, if the therapeutic strategy suggests allogenous transplantation, the decision to prescribe an anti-PD1 antibody should be made in light of the observed number of graft-versus-host reactions, which is higher in all patients having received an anti-PD1.

Clinical data

- The clinical data for recurrent or resistant cHL are derived from a single, on-going phase II non-comparative, multi-cohort study. Of the 3 cohorts created, two included patients concerned by the MA:
  o cohort 1 (n=69): resistant or relapsed patients after autologous stem cell transplantation (ASCT) and in the event of failure or recurrence after post-ASCT brentuximab-vedotin;
  o cohort 2 (n=81): patients not eligible for ASCT (mainly due to the absence of complete or partial response after salvage chemotherapy) and in the event of failure or recurrence after BV;
  In cohort 1, the overall response rate (primary endpoint) was 72.5% after median follow-up of 7.1 months, and 75.4% following an updated analysis (after median follow-up of 15.9 months).
  In cohort 2, the overall response rate (primary endpoint) was 65.4% after median follow-up of 7.1 months, and 66.7% following an updated analysis (after median follow-up of 15.9 months).
- Among the 23 patients with cHL who underwent autologous HSC transplantation after treatment with pembrolizumab, and after median follow-up of 5.1 months, 6/23 (26%) suffered an acute graft-versus-host reaction, one of which had a fatal outcome. Two/23 (9%) suffered severe hepatic veno-occlusive disease after using a reduced intensity conditioning, one of which had a fatal outcome.

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 KEYTRUDA is high.
- KEYTRUDA does not provide any clinical added value** (CAV V) in the management strategy for relapsed or refractory cHL after failure of autologous stem cell transplantation and brentuximab vedotin (BV) treatment, like OPDIVO, or in the event of ineligibility for transplantation and after BV treatment failure.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 04 April 2018 (CT-16458) available at **www.has-sante.fr**

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