HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
September 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

BAVENCIO (avelumab), anti-PDL1 antibody

High clinical benefit as monotherapy, in adults previously treated with chemotherapy, for the treatment of metastatic Merkel cell carcinoma and minor clinical added value for management.

Insufficient clinical benefit to justify reimbursement in chemotherapy-naive adults

Main points

- BAVENCIO has been granted a conditional marketing authorisation as monotherapy for the treatment of patients with metastatic Merkel cell carcinoma (MCC).
- Following chemotherapy failure, due to comorbidities and contraindications to non-first-line chemotherapies, there is no medicinal alternative to BAVENCIO, except for supportive care.
- In the absence of comparative studies versus first-line metastatic chemotherapy and/or, at least, versus supportive care in patients previously treated by chemotherapy, the level of evidence of the results, observed in a single phase II non-comparative study, is insufficient to demonstrate that BAVENCIO has an impact on mortality of quality of life.

Therapeutic strategy

- At the metastatic stage of MCC, patients are usually treated with conventional chemotherapy. Two chemotherapy protocols are recommended: carboplatin-etoposide, or cyclophosphamide-doxorubicin-vincristine.
  The cardiac toxicity of doxorubicin, or the renal and neurological toxicity of platinum, significantly reduces the use of these chemotherapies in previously treated elderly patients. Indeed, after failure of chemotherapy at the metastatic stage, in the presence of contraindications to non-first-line chemotherapeutic protocols in the population concerned, with a median age of approximately 75 years at the time of diagnosis, and with comorbidities, supportive care is considered.

- **Role of the medicinal product in the therapeutic strategy**
- **Chemotherapy-naive patients**
  In the absence of clinical data compared to the chemotherapy conventionally used in first line metastatic disease, whereas this comparison was feasible, the therapeutic benefit of BAVENCIO is not established. It thus has no place as monotherapy in first-line treatment of metastatic MCC.

- **Patients previously treated by chemotherapy**
  Despite the available data concerning a single-arm study, whereas comparison to usual treatments was feasible, with a small population of patients pre-treated by chemotherapy, and despite the limited long-term clinical data available, BAVENCIO monotherapy can be used after failure of chemotherapy.
  No data are available in patients with active central nervous system metastases and in immunocompromised patients, even though immunosuppression represents one of the main risk factors for MCC.

Clinical data

The available data are derived from a single phase II non-comparative study involving two cohorts:

- In the cohort of 88 patients previously treated with at least one line of chemotherapy (including 57 with one prior line and 27 with two prior lines), with a median age of 72.5 years and in good general condition (ECOG 0: 55.7%

or 1: 44.3%) in the main analysis, with a median follow-up of 10.4 months, the confirmed overall response rate (primary endpoint) was of 31.8% (28/88), of which 9% complete responses and 22.7% partial responses. The median response time was not reached and the median overall survival time was of 11.3 months. With additional perspective (median follow-up of 16.4 and 21.9 months), the overall response rate was of 33% (29/88).
Treatment-related adverse events led to permanent discontinuation of treatment in 6 patients (6.8%). At least one adverse event of grade ≥ 3 was reported in 68.2% of patients; the most common were: anaemia (10.2%), lymphopenia (6.8%), disease progression (6.8%) and hypertension (6.8%). A total of 14 patients (15.9%) presented at least one immunological event, four of which were of grade ≥ 3. Drip-related reactions, reported in 19 patients (21.6%), were of grade 1 (5 patients) or 2 (14 patients). Given the non-comparative nature of the study, the data available do not permit a reliable conclusion on the quality-of-life assessment.

- In the cohort of 112 chemotherapy-naive patients, the primary endpoint results (sustained response rate) are not yet available. The MA will be granted subject to the submission of these results in 2020.

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for oncology and medical oncology specialists.

Benefit of the medicinal product

- The actual clinical benefit* of BAVENCIO monotherapy in the MA indication is:
  - insufficient as first-line treatment of metastatic MCC, in chemotherapy-naive patients, pending a demonstrative comparative study versus chemotherapy;
  - susbtantial in adults previously treated with chemotherapy.
- BAVENCIO monotherapy provides a minor improvement in actual clinical benefit** (IACB IV) in the management of patients with metastatic MCC previously treated by chemotherapy.
- Not approved for hospital treatment in the chemotherapy-naive population.
- Approved for reimbursement for hospital treatment. exclusively in adults previously treated by chemotherapy in the MA indication and at the MA dosages. Continuing favourable opinion is subject to submission, with a maximum period of one year, of data comparing BAVENCIO to usual patient management. BAVENCIO will then be reassessed at this point.

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This document was drafted on the basis of the Transparency Committee opinion dated 19 September 2018 (CT-16584) 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 besubstantial, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"