HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
OPINION
13 MAY 2020

avelumab
BAVENCIO 20 mg/ml concentrate for solution for infusion

New indication

Key points

Favourable opinion for reimbursement of BAVENCIO (avelumab) in combination with axitinib in the first-line treatment of advanced clear-cell renal carcinoma (RCC) or with a clear-cell component.

What therapeutic improvement?

No clinical added value in the therapeutic strategy for BAVENCIO (avelumab) in combination with axitinib in the first-line treatment of advanced clear-cell renal carcinoma (RCC) or with a clear-cell component.

Role in the care pathway?

The management of advanced renal cell carcinoma mostly relies on the identification of disease prognostic factors. According to International Metastatic RCC Database Consortium classification criteria (time between diagnosis and initiation of systemic therapy, haemoglobin level, corrected calcium level, Karnofsky performance score, neutrophils and platelets), patients are divided into 3 categories: good prognosis (0 criteria), intermediate prognosis (1 or 2 criteria) and poor prognosis (≥ 3 criteria).

Before the MA of Immunotherapies like OPDIVO (nivolumab) / YERVOY (ipilimumab) combination then KEYTRUDA (pembrolizumab) and BAVENCIO (avelumab), each one in combination with axitinib (INLYTA), the recommended first-line treatments were as follows:

- sunitinib (SUTENT), pazopanib (VOTRIENT) or the bevacizumab (AVASTIN)/interferon combination in patients with a good or intermediate prognosis.
- temsirolimus (TORISEL) in patients with a poor prognosis.

Furthermore, in its opinion of 10 July 2019, the Transparency Committee considered that the superiority of the nivolumab (OPDIVO) + ipilimumab (YERVOY) combination has been established in terms of overall survival versus an acceptable comparator (sunitinib) in patients with an intermediate or poor prognosis.

Role of BAVENCIO (avelumab) in combination with axitinib

BAVENCIO (avelumab) in combination with axitinib is indicated in the first-line treatment of advanced clear-cell renal carcinoma (RCC) or with a clear-cell component, all prognoses combined (favourable, intermediate unfavourable). Its superiority has been established in the short term versus an acceptable comparator (sunitinib) in terms of progression-free survival in patients in good general condition, including patients whose tumours have a PD-L1 expression level ≥ 1%, but with no impact to date on overall survival, unlike other immunotherapies.

Given the concomitant development of BAVENCIO (avelumab) and KEYTRUDA (pembrolizumab), that have the same MA indication in combination with axitinib, and pending the results of the final analysis on overall survival for BAVENCIO (avelumab) / axitinib (see section on Other Committee recommendations), the Committee considers that the best level of evidence of KEYTRUDA (pembrolizumab) on overall survival should be favoured, while also taking into consideration the safety profiles of these combinations.

Similarly, for the choice between BAVENCIO (avelumab) / axitinib and OPDIVO (nivolumab) / YERVOY (ipilimumab) in their shared indication, i.e., in patients with an intermediate or unfavourable prognosis, pending the results of the final analysis on overall survival for BAVENCIO (avelumab) / axitinib, the Committee considers that the best level of evidence of OPDIVO (nivolumab) / YERVOY (ipilimumab) on overall survival should be favoured, while also taking into consideration the safety profiles of these combinations and patients' preferences.

01 COMMITTEE'S CONCLUSIONS

01.1 Clinical benefit

◗ Clear-cell renal carcinoma is a serious, life-threatening disease.
◗ This is a curative treatment of clear cell renal carcinoma (RCC) or with a clear-cell component.
◗ The short-term efficacy/adverse events ratio of the BAVENCIO (avelumab)/axitinib combination is moderate in the treatment of advanced clear-cell renal carcinoma (RCC) or with a clear-cell component.
◗ There are therapeutic alternatives.
◗ It is a first-line treatment.

Public health impact

Considering:

- the severity of advanced clear-cell renal carcinoma, regardless of the prognosis,
- its incidence estimated to be between 5,500 and 8,000 patients in France,
- the partially met medical need,
- the lack of response to this medical need (impact on morbidity but no demonstrated impact on mortality pending the final analysis relative to OS and in a context where alternatives have demonstrated it, and no demonstrated impact on quality of life),
- the impact on the organisation of care of BAVENCIO (avelumab) administration by injection combined with axitinib (orally) has not been assessed;

the BAVENCIO (avelumab) + axitinib combination is unlikely to have an impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BAVENCIO (avelumab) in combination with axitinib is moderate in the first-line treatment of advanced clear-cell renal carcinoma (RCC) or with a clear-cell component.

The Committee issues a favourable opinion for inclusion of BAVENCIO (avelumab) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the first-line treatment of advanced clear-cell renal carcinoma (RCC) or with a clear-cell component, in combination with axitinib and at the MA dosages.

01.2 Clinical Added Value

Considering:

- **the demonstration of the superiority of the BAVENCIO (avelumab) + axitinib combination compared to sunitinib, considered to be an acceptable comparator, only on progression-free survival assessed by an independent review committee (primary endpoint) in an interim analysis and with a short median follow-up (< 1 year):**
  - **in the PD- L1 ≥ 1% subpopulation: median of 13.8 months vs 7.2 months, HR = 0.6 $CI_{95\%}$ [0.475; 0.790]; p<0.0001,**
  - **in the ITT population: median of 13.8 months vs 8.4 months; HR = 0.69 $CI_{95\%}$ [0.563; 0.840], p<0.0001) but,**
- **the lack of demonstrated superiority on overall survival (other primary endpoint) on the first 2 interim analyses and pending the results of the final analysis, in a context in which comparators have demonstrated it,**
- **the additional toxicity of this combination compared to sunitinib with, in particular, a higher frequency of serious adverse events (34.6% vs 28.7%), or events leading to discontinuation of at least one treatment (22.8% vs 13.4%),**
- **the lack of quality-of-life data with a demonstrative value,**

The Committee considers that, as the dossier currently stands, the BAVENCIO (avelumab) / axitinib combination provides no clinical added value (CAV V) in the first-line treatment of advanced clear-cell renal carcinoma (RCC) or with a clear-cell component.