



TRANSPARENCY COMMITTEE SUMMARY 13 MAY 2020

The legally binding text is the original French opinion version

pembrolizumab
KEYTRUDA 50 mg powder for concentrate for solution for infusion
KEYTRUDA 25 mg/ml concentrate for solution for infusion

New indication

► Key points

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

► What therapeutic improvement?

Therapeutic improvement for KEYTRUDA (pembrolizumab) in combination with axitinib in the first-line treatment of advanced purely clear-cell renal cell carcinoma (RCC) or with a clear-cell component.

► Role in the care pathway?

The management of advanced renal cell carcinoma relies primarily on 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: favourable prognosis (0 criteria), intermediate prognosis (1 or 2 criteria) and poor prognosis (≥ 3 criteria).

Before the MA for Immunotherapies using the 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 was established in terms of overall survival versus an acceptable comparator (sunitinib) in patients with an intermediate or poor prognosis.

Role of KEYTRUDA (pembrolizumab) in combination with axitinib

KEYTRUDA (pembrolizumab) in combination with axitinib is a first-line treatment of advanced clear-cell renal cell carcinoma (RCC) or with a clear-cell component, all prognoses combined (favourable, intermediate unfavourable). Its superiority was established in the short term versus an acceptable comparator (sunitinib) in terms of progression-free survival and overall survival (in the ITT population) in patients predominantly in good general condition.

However, in the subpopulation with a favourable renal cell carcinoma prognosis, the Committee highlights the fact that, pending longer-term results, there are uncertainties with respect to the contribution in terms of progression-free survival and overall survival, whereas the toxicity of this combination is non-negligible compared to the available alternatives as monotherapy. In this respect, the Committee stresses that longer-term data were required by the EMA, in particular to characterise the contribution of this combination in this subpopulation and that it has asked to receive and analyse these data (see section on Other Committee recommendations).

In the subpopulation with an intermediate or unfavourable prognosis and given the concomitant development with the OPDIVO (nivolumab) / YERVOY (ipilimumab) combination, the role of KEYTRUDA (pembrolizumab) combined with axitinib compared to this other combination is not known. Consequently, the Committee proposes that the choice of treatment should be made in the context of the proposal made following a multidisciplinary review meeting, based on the safety profile of these medicinal products and patients' preferences.

Finally, given the concomitant development of BAVENCIO (avelumab) and KEYTRUDA (pembrolizumab), which have the same MA indication in combination with axitinib, the Committee considers that the choice between these two immunotherapies should take into consideration the lower level of evidence for BAVENCIO (avelumab) relative to overall survival to date, along with the safety profiles of these combinations.

COMMITTEE'S CONCLUSIONS

Clinical benefit

- ▶ Clear-cell kidney cancer is a serious, life-threatening disease.
- ▶ This is a specific curative treatment for clear-cell renal cell carcinoma (RCC) or with a clear-cell component.
- ▶ The short-term efficacy/adverse effects ratio of the KEYTRUDA (pembrolizumab)/axitinib combination is high in purely clear-cell renal cell carcinoma (RCC) or with a clear-cell component.
- ▶ There are therapeutic alternatives.
- ▶ It is a first-line treatment.

Public health impact

Considering:

- the seriousness of advanced clear-cell kidney cancer, irrespective of the prognosis,
 - its incidence estimated to be between 5,500 and 8,000 patients in France,
 - the partially met medical need,
 - the partial response to this medical need:
 - impact on short-term morbidity and mortality, with uncertainties, particularly in the subgroup with a favourable prognosis,
 - non-demonstrated impact on quality of life due to a lack of demonstrative data,
 - the absence of assessment of the impact of administration of KEYTRUDA (pembrolizumab) by injection combined with axitinib (orally) on the organisation of care,
- the KEYTRUDA (pembrolizumab)/axitinib combination is unlikely to have an impact on public health.

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

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

Clinical Added Value

Considering:

- demonstration of the superiority of the KEYTRUDA (avelumab) plus axitinib combination compared to sunitinib, considered to be an acceptable comparator, on the two primary endpoints in an interim analysis and with a short median follow-up of 12.8 months:
 - the progression-free survival assessed by an independent review committee (median of 15.1 months vs 11.1 months; HR=0.69; 95% CI [0.57; 0.84], p= 0.00014),
 - the overall survival: HR=0.53 CI_{95%} [0.38; 0.74]; p=0.00005, with, nonetheless, an uncertainty for the subgroup with a favourable prognosis,

despite:

- the additional toxicity of this combination compared to sunitinib with, in particular, a higher frequency of serious adverse events (40.3% vs 31.3%), grade ≥ 3 events (75.8% vs 70.6%) or events leading to discontinuation of treatment (30.5% vs 13.9%),
- the absence of any data on quality of life with a demonstrative value,
- uncertainties, particularly with respect to the respective contributions of each of the components of the pembrolizumab/axitinib combination,

the Committee considers that the KEYTRUDA (pembrolizumab)/axitinib combination provides a moderate clinical added value (CAV III) compared to sunitinib in the first-line treatment of advanced clear-cell renal cell carcinoma (RCC) or with a clear-cell component.