HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
22 SEPTEMBER 2021

The legally binding text is the original French opinion version

Cabozantinib
CABOMETYX 40 and 20 mg film-coated tablets

New indication

Key points

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

Unfavourable opinion for reimbursement of CABOMETYX (cabozantinib) in combination with nivolumab in the first-line treatment of advanced renal cell carcinoma (RCC) with a histological type other than clear-cell in the absence of data.

What therapeutic improvement?

Therapeutic improvement, in the same way as the pembrolizumab/axitinib combination, for the cabozantinib/nivolumab combination compared to sunitinib only in the first-line treatment of advanced clear-cell renal cell carcinoma (RCC) or with a clear cell component.

Role in the care pathway?

Today, with the introduction of immunotherapy treatments, the European (EAU 2021, ESMO 2021) and American (NCCN 2021) guidelines recommend the following treatments as first-line therapy in patients with advanced clear-cell renal cell carcinoma, depending on the prognostic risk:

- in good prognosis situations:

The KEYTRUDA/INLYTA (pembrolizumab/axitinib) or CABOMETYX/OPDIVO (cabozantinib/nivolumab) combination including immunotherapy [1A/1B] (level of evidence 1 and recommendation grade A or B) is recommended.

The BAVENCIO/INLYTA (avelumab/axitinib) combination is not cited in these guidelines, given its lower level of evidence (moderate clinical benefit and CAV V, granted by the Transparency Committee in 2020).

- in intermediate or poor prognosis situations:

The same combinations including immunotherapy as those mentioned above - KEYTRUDA/INLYTA (pembrolizumab/axitinib) or CABOMETYX/OPDIVO (cabozantinib/ nivolumab) - as well as the OPDIVO/YERVOY (nivolumab/ipilimumab) combination are recommended as category [1A/1B] (level of evidence 1 and recommendation grade A or B). The superiority of the OPDIVO/YERVOY has been established versus SUTENT (sunitinib) in terms of overall survival only in intermediate or high-risk patients.

Tyrosine kinase inhibitors (TKIs) with SUTENT (sunitinib) and VOTRIENT (pazopanib) are also recommended, irrespective of prognosis, as therapeutic alternatives.

AVASTIN (bevacizumab) in combination with interferon, and the use of interleukin-2 (IL-2) can be used in certain clinical situations.

In the same way, in patients with a poor prognosis only, TORISEL (temsirolimus), is now considered to be a treatment option in patients with advanced renal cell carcinoma with at least 3 out of the 6 prognostic risk factors.

Role of the medicinal product in the care pathway

CABOMETYX (cabozantinib) in combination with nivolumab is a new treatment option in the first-line treatment of advanced clear-cell renal cell carcinoma (RCC) or with a clear cell component. The available data does not enable definition of the role of the CABOMETYX (cabozantinib) and OPDIVO (nivolumab) combination compared to the other available combinations:

- **KEYTRUDA/INLYTA (pembrolizumab/axitinib) irrespective of prognosis, and**
- **OPDIVO/YERVOY (nivolumab/ipilimumab) in the subpopulation of patients with an intermediate or poor prognosis.**

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.

In the absence of available data, the role of CABOMETYX (cabozantinib) in combination with nivolumab, like that of the other combinations including an immunotherapy currently available, has not been established in the first-line treatment of advanced renal cell carcinoma with a histological type other than clear-cell.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

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 CABOMETYX (cabozantinib)/OPDIVO (nivolumab) combination is high only in clear-cell renal cell carcinoma (RCC) or with a clear-cell component. In the treatment of non-clear-cell renal cell carcinoma, given the absence of available data, its efficacy/adverse effects ratio has not been established.

◗ 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 identified medical need provided by the CABOMETYX (cabozantinib)/OPDIVO (nivolumab) combination due to:
    - a demonstrated impact on morbidity and mortality in the short term compared to sunitinib, but without comparative data versus pembrolizumab + axitinib due to their concomitant development, and
    - a non-demonstrated impact on quality of life due to a lack of demonstrative data,
- the absence of assessment of the impact of administration of OPDIVO (nivolumab) by injection combined with CABOMETYX (cabozantinib) orally on the organisation of care,

the CABOMETYX (cabozantinib)/OPDIVO (nivolumab) combination is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of the CABOMETYX/OPDIVO (cabozantinib/nivolumab) combination is:
- substantial only in the first-line treatment of advanced clear-cell renal cell carcinoma (RCC) or with a clear cell component,
- insufficient to justify public funding cover in the first-line treatment of advanced renal cell carcinoma with a histological type other than clear-cell given the absence of data.

The Committee issues:
- **a favourable opinion for inclusion of both the CABOMETYX and OPDIVO medicinal products in the hospital formulary list and of the CABOMETYX medicinal product only in the retail formulary list of reimbursed proprietary medicinal products approved for use in: the first-line treatment of advanced clear-cell renal cell carcinoma (RCC) or with a clear cell component, and at the MA dosages.**

- **an <u>unfavourable opinion</u> for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the first-line treatment of advanced renal cell carcinoma with a histological type other than clear-cell, and at the MA dosages.**

Recommended reimbursement rate: 100%

Clinical Added Value

<u>In clear-cell renal cell carcinoma (RCC) or with a clear cell component</u>
Considering:
- **demonstration of the superiority of the CABOMETYX (cabozantinib) and nivolumab combination compared to sunitinib, considered to be an acceptable comparator at the time of implementation of the CHECKMATE 9ER study, with a median follow-up time of 15.70 months in the cabozantinib + nivolumab group and of 14.59 months in the sunitinib group relative to:**
  - **progression-free survival assessed by an independent review committee (primary efficacy endpoint): median of 16.59 months vs 8.31 months; HR = 0.51 CI95% [0.41; 0.64], p<0.0001,**
  - **overall survival (ranked secondary endpoint): the median was not reached in either of the two groups; HR=0.60 $CI_{98.89\%}$ [0.40; 0.89]; p=0.001,**

despite:
- **an additional toxicity of this combination compared to sunitinib, particularly in terms of serious adverse events (46.3% vs 39.7%), grade 3-4 events (70.3% vs 65.3%) or events leading to discontinuation of treatment (19.7% vs 16.9%),**
- **exploratory quality of life data,**

the Committee considers that combination of CABOMETYX (cabozantinib) with nivolumab, like the 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.

<u>In renal cell carcinoma with a histological type other than clear-cell</u>
Not applicable.