HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
February 2018

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KISPLYX (lenvatinib), tyrosine kinase inhibitor

Insufficient clinical benefit to justify reimbursement for advanced kidney cancer in combination with everolimus.

Main points

- KISPLYX has been granted a marketing authorisation in combination with everolimus for the treatment of adults suffering from advanced kidney cancer having received prior anti-VEGF (vascular endothelial growth factor) therapy.
- Progression-free survival was improved compared to everolimus alone (absolute gain of 9.1 months), with a lack of benefit in terms of overall survival.
- The safety profile of the lenvatinib/everolimus combination is less favourable than that of everolimus alone.
- KISPLYX in combination with everolimus has no role in the therapeutic strategy for advanced kidney cancer, particularly given:
  - the recent presence in the therapeutic arsenal of medicinal alternatives (nivolumab and cabozantinib) that have demonstrated a benefit in terms of overall survival compared to everolimus as second-line and subsequent treatments in phase III studies,
  - the lack of data on the use of KISPLYX in combination with everolimus after failure of nivolumab and cabozantinib.

Therapeutic strategy

- The treatment of advanced kidney cancer depends on the disease prognosis. Three prognostic groups have been defined (favourable, intermediate or poor) based on clinical and pathological criteria.
- For patients with a good or intermediate prognostic status, the first-line treatments are:
  - SUTENT (sunitinib)
  - AVASTIN (bevacizumab)/interferon combination
  - VOTRIENT (pazopanib)

  Cytokine monotherapy remains a potential treatment option for the first-line treatment of metastatic clear cell renal adenocarcinoma.

  For patients with a poor prognostic status, the recommended treatment is the mTOR inhibitor TORISEL (temsirolimus), and tyrosine kinase inhibitors are an option.
- After the failure of tyrosine kinase inhibitors, OPDIVO (nivolumab) and CABOMETYX (cabozantinib) administered as monotherapy are preferential therapeutic options and can be used sequentially as second- and third-line treatments. Nivolumab and cabozantinib have demonstrated a benefit in terms of overall survival compared to everolimus after prior anti-VEGF therapy.

  INLYTA (axitinib) has been granted a marketing authorisation as a second-line treatment after the failure of prior cytokine or sunitinib therapy; however, after anti-VEGF therapy failure, nivolumab and cabozantinib should be preferred. NEXAVAR (sorafenib) has been granted a marketing authorisation solely for cases of cytokine (interferon or IL2) failure.
- **Role of the medicinal product in the therapeutic strategy**

  KISPLYX has no role in the therapeutic strategy for advanced kidney cancer.

Clinical data

- A randomised, open-label study compared the lenvatinib/everolimus combination to everolimus alone in 101 patients with advanced (non-resectable advanced or metastatic) predominantly clear cell renal carcinoma and having received prior anti-VEGF targeted therapy.
- The lenvatinib/everolimus combination demonstrated its superiority over everolimus alone on progression-free survival determined by the investigator (primary endpoint): median of 14.6 months in the lenvatinib 18 mg/everolimus 5 mg group versus median of 5.5 months in the everolimus 10 mg group, i.e. an absolute gain of 9.1 months in favour of the lenvatinib/everolimus combination: HR=0.40 95% CI = [0.24; 0.68] p= 0.0005. In the overall survival analysis (secondary endpoint without ranked sequential analysis), no difference between the two groups was detected: HR=0.55 95% CI = [0.30; 1.01].
- The number of grade 3 or 4 adverse events (72.5% versus 54%) and the number of treatment discontinuations due to adverse events (23.5% versus 12%) were higher in the lenvatinib/everolimus group than in the everolimus group. In the patients treated with the lenvatinib/everolimus combination, the lenvatinib dose was reduced for 70.6% of patients.
- Due to their concomitant development, no direct comparative study versus the clinically relevant comparators OPDIVO (nivolumab) and CABOMETYX (cabozantinib), which have demonstrated a gain in overall survival versus everolimus in phase III studies, are available.

Special prescription requirements

- Medicinal product subject to hospital prescription
- Prescription reserved for oncology specialists or physicians with oncology expertise
- Medicinal product requiring special monitoring during treatment

Benefit of the medicinal product

- The actual clinical benefit* of KISPLYX is insufficient.
- Not approved for non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 21 February 2018 (CT-15950) available at **www.has-sante.fr**

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