HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
June 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

BRAFTOVI/MEKTOVI (encorafenib/binimetinib), BRAF and MEK inhibitor combination

Moderate clinical benefit in combination in the treatment of non-resectable or metastatic melanoma, for adults carrying a BRAF V600 mutation but no demonstrated clinical added value in the therapeutic strategy.

Main points

- BRAFTOVI/MEKTOVI has been granted a marketing authorisation for the treatment of non-resectable or metastatic melanoma, for adults carrying a BRAF V600 mutation.
- The encorafenib 450 mg / binimetinib 90 mg combination has demonstrated its superiority over vemurafenib on progression-free survival: 14.9 months versus 7.3 months corresponding to a gain of +7.6 months in absolute terms.
- It has not demonstrated any improvement in overall survival.

Therapeutic strategy

- The current treatment of advanced (non-resectable or metastatic) melanoma focuses, from the diagnosis stage, on patient selection based on the presence of BRAF V600 tumour mutation.
- The therapeutic strategy for the treatment of metastatic melanoma has incorporated immunotherapy (OPDIVO, KEYTRUDA) and BRAF and MEK inhibitor combinations into the therapeutic arsenal.
- In cases of BRAF V600 mutation, the treatment firstly includes a targeted dual therapy including the combination of a BRAF inhibitor and MEK inhibitor: dabrafenib + trametinib or vemurafenib + cobimetinib. The role of nivolumab and pembrolizumab as an alternative to these targeted therapies is currently the subject of debate, as is the profile of patients suitable for receiving either of these two therapies as a first-line treatment.
- **Role of the medicinal product in the therapeutic strategy**

  With evidence of a gain in progression-free survival in relation to vemurafenib, as for other BRAF/MEK inhibitor combinations, and despite the lack of evidence in terms of overall survival, unlike other BRAF/MEK inhibitor combinations in relation to vemurafenib or dabrafenib monotherapy, BRAFTOVI/MEKTOVI is a first-line therapeutic option for adult patients with non-resectable or metastatic melanoma carrying a BRAF V600 mutation.

Clinical data

- A multicentre, open-label, randomised phase III trial assessed the superiority of the encorarefenib (300 mg or 450 mg) and binimetinib combination in relation to vemurafenib or encorafenib monotherapy, in terms of progression-free survival (PFS) and overall survival (OS)
- The superiority of the encorafenib 450 mg / binimetinib 90 mg combination was demonstrated over vemurafenib monotherapy in terms of PFS (primary endpoint): 14.9 months (95%CI= [11.0-18.5]) versus 7.3 months (95%CI= [5.6-8.2]) with an HR = 0.54 (95%CI= [0.41-0.71]), p<0.001 equivalent to a gain of +7.6 months in absolute terms.
- It was not possible to compare overall survival for the encorafenib (450 mg) / binimetinib (90 mg) combination in view of the ranked test envisaging this analysis as the 4th ranked endpoint, while the 2nd ranked endpoint was non-significant.
- Almost all of the subjects reported an adverse event. The subjects' median exposure time was 51.2 weeks for the encorafenib 450 mg / binimetinib 90 mg combination, and 31.4 weeks for the encorafenib monotherapy group. Approximately half of the subjects receiving the encorafenib/binimetinib combination presented with grade 3 or 4

adverse events. The adverse events occurring in over 10% of the subjects in the encorafenib 450 mg / binimetinib 90 mg group but in under 10% of the subjects of the encorafenib monotherapy were: elevated plasma CPK, abdominal pain, blurred vision, anaemia, vertigo, elevated ALT, hypertension, rhinopharyngitis and peripheral oedema.

Specific prescribing conditions

- Medicinal product for hospital use only
- Medicinal product subject to prescription reserved for oncology specialists or physicians with oncology expertise

Benefit of the medicinal product

- The actual clinical benefit* of BRAFTOVI/MEKTOVI is moderate.
- BRAFTOVI/MEKTOVI provides no clinical added value** (CAV V) in the current therapeutic strategy.
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 12 June 2019 (CT-17431) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being 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) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement"