HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
16 DECEMBER 2020
The legally binding text is the original French opinion version

encorafenib
BRAFTOVI 75 mg hard capsules

New indication

Key points

Favourable opinion for reimbursement in the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy.

What therapeutic improvement?

Therapeutic improvement compared to treatment with irinotecan/cetuximab or FOLFIRI/cetuximab.

Role in the care pathway?

Currently, in the absence of a specific treatment for BRAF mutation in metastatic colorectal cancer (mCRC), patients with a BRAF V600E mutation are treated with the same drugs as other mCRC cases with wild RAS status. The second-line treatment of these patients with wild RAS mCRC depends on the first-line treatments received. It is primarily based on chemotherapy, usually combined with targeted anti-VEGF or anti-EGFR therapy. The anti-VEGF therapies indicated in this situation are AVASTIN (bevacizumab, indicated in combination with fluoropyrimidine-based chemotherapy), ZALTRAP (aflibercept, indicated in combination with FOLFIRI chemotherapy in the treatment of

resistant mCRC or that has progressed following oxaliplatin-based treatment) or CYRAMZA (ramucirumab) and the anti-EGFR therapies are ERBITUX (cetuximab) or VECTIBIX (panitumumab). In the event of non-eligibility for these medicinal products, the salvage therapies LONSURF (trifluridine/ tipiracil) or STIVARGA (regorafenib) may be considered.

According to the ESMO 2016 European guidelines and the SNFGE 2020 French guidelines, for second-line therapy it is recommended to switch to a different chemotherapy protocol to that used during first-line therapy. Combination with bevacizumab (or aflibercept if the FOLFOX protocol was used during first-line therapy) is recommended in most situations. In the event of use of an anti-EGFR or bevacizumab during first-line therapy, anti-EGFR treatments are not recommended as second-line therapy. In the event of first-line treatment with the FOLFOXIRI protocol + bevacizumab (recommended in the case of BRAF mutation), treatment with cetuximab or panitumumab combined with irinotecan is recommended. Patients not treated with bevacizumab in the context of its combination with chemotherapy during first-line treatment may receive this drug in the event of disease progression if they are eligible for this targeted therapy.

Role of the medicinal product in the care pathway

The Committee considers that the encorafenib-cetuximab combination is a second and later-line treatment for metastatic colorectal cancer with a BRAF V600E mutation.

In the absence of available data in patients with an ECOG score of 2 or more, the Committee recommends that the decision to initiate the treatment in these patients be discussed during a multidisciplinary team meeting.

Regular dermatological monitoring is necessary during treatment.

◗ Special recommendations

Given the important identified risk of the development of skin cancers under encorafenib-cetuximab treatment, the Committee recommends regular dermatological monitoring throughout treatment.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Metastatic colorectal cancer with BRAF V600E mutation is a serious, life-threatening disease.

◗ BRAFTOVI (encorafenib) in combination with cetuximab is a curative treatment.

◗ Its efficacy/adverse effects ratio is high.

◗ There are medicinal alternatives that are currently recommended but have no MA specifically in metastatic colorectal cancer with BRAF V600E mutation.

◗ The encorafenib-cetuximab combination is a second and later-line treatment for metastatic colorectal cancer with a BRAF V600E mutation.

Public health impact

Considering:

- the seriousness of metastatic colorectal cancer with a BRAF V600E mutation and its low prevalence,,
- the partially met medical need,
- the partial response to the identified need given the expected additional impact in terms of morbidity and mortality but the absence of a demonstrated impact in terms of quality of life and limitations in terms of the transposability of the study results,
- the absence of any demonstrated impact on the organisation of care (considering the combination of encorafenib (oral route) with cetuximab, administered as an IV infusion),

BRAFTOVI (encorafenib) in combination with cetuximab is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BRAFTOVI (encorafenib) in combination with cetuximab is substantial in the MA indication.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the new indication and at the MA dosages.

- **Recommended reimbursement rate: 100%**

Clinical Added Value

Considering:

- **demonstration, in an open-label phase 3 study, of the superiority of the encorafenib/cetuximab combination compared to irinotecan/cetuximab or FOLFIRI/cetuximab combinations in terms of overall survival and progression-free survival, with absolute improvements of 3 months and 2.7 months respectively (ranked secondary endpoints),**
- **the favourable general safety profile compared to the comparator group,**

but also:

- **the methodological limitations of the study, notably related to the population included and the comparator, considered to be non-optimal for all the study patients,**
- **the reported toxicity in terms of increased risk of skin cancers under encorafenib/cetuximab (3.2% versus 0%),**
- **the absence of robust quality of life data,**

the Committee considers that the encorafenib/cetuximab combination provides moderate clinical added value (CAV III) compared to treatment with irinotecan/cetuximab or FOLFIRI/cetuximab.