HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
2 JUNE 2021

The legally binding text is the original French opinion version

pembrolizumab
KEYTRUDA 25 mg/ml concentrate for solution for infusion

New indication

Key points

Favourable opinion of KEYTRUDA (pembrolizumab) for reimbursement as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults, only in patients unresectable from the outset.

Unfavourable opinion for reimbursement in patients initially resectable.

What therapeutic improvement?

Therapeutic improvement compared to chemotherapy ± targeted therapy.

Role in the care pathway?

In patients initially resectable, curative metastatic surgery is recommended, accompanied by perioperative chemotherapy (pre and postoperative). In patients initially unresectable, the use of targeted therapies, in combination with chemotherapy, is recommended as first-line treatment (except in the event of contraindications: organ failure, poor ECOG score, heart failure).

The recommended chemotherapy protocols (ESMO) are:
1) in combination with bevacizumab:
- double chemotherapies: FOLFOX/CAPOX/FOLFIRI
- FOLFOXIRI6 triple chemotherapy, in selected patients (considered to be “fit” and for whom cytoreduction is targeted)
- single-agent chemotherapy with 5-FU, in patients unable to tolerate a more aggressive treatment
2) in combination with panitumumab or cetuximab: FOLFOX/FOLFIRI chemotherapies double.

Some tumours may be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). However, apart from KEYTRUDA (pembrolizumab), there is currently no specific treatment for these patients. Their management remains identical to that for patients without MSI-H/dMMR disease.

Role of the medicinal product in the care pathway

KEYTRUDA (pembrolizumab) is a first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults initially unresectable.

Given the initially increased risk of progression (first 2-3 months) in patients having received pembrolizumab, compared to those having received chemotherapy ± targeted therapy, the Committee recommends caution when treating patients at a high risk of progression/early death. The Committee considers that the therapeutic decision should be taken after a documented proposal resulting from a multidisciplinary team meeting.

For second-line treatment (outside the scope of the current indication for KEYTRUDA (pembrolizumab)) in BRAF V600E mutation-positive patients, the Committee highlights that the encorafenib-cetuximab combination has only been assessed in patients having received a first line of chemotherapy +/- targeted therapy. The role of the encorafenib-cetuximab combination, as second-line therapy, in patients having received a first line of treatment with KEYTRUDA (pembrolizumab) is not currently known. In the absence of available data enabling assessment of the best strategy in BRAF V600E mutation-positive patients, the Committee recommends that this strategy be discussed during a multidisciplinary team meeting.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Metastatic colorectal cancer is a serious, life-threatening disease.

◗ The proprietary medicinal product KEYTRUDA (pembrolizumab) is a curative medicinal product.

◗ The efficacy/adverse effects ratio is high in patients initially unresectable.

◗ There are therapeutic alternatives.

◗ KEYTRUDA (pembrolizumab) is a first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults initially unresectable.

Public health impact

Considering:

- the seriousness of the disease and its prevalence,
- the partially met medical need,
- the lack of response to the identified need considering the available data (improvement in progression-free survival, absence of impact on overall survival and quality of life),
- the absence of data enabling assessment of the additional impact on the organisation of care,

KEYTRUDA (pembrolizumab) is not liable to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of KEYTRUDA (pembrolizumab) is:

- **substantial in the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults initially unresectable;**
- **insufficient to justify public funding cover in all other clinical situations (patients initially resectable).**

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use only in the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults initially unresectable and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in other clinical situations (patients initially resectable).

Clinical Added Value

◗ Within the reimbursement scope:

Considering:

- **demonstration of the superiority of KEYTRUDA (pembrolizumab) as monotherapy compared to standard chemotherapy ± targeted therapy, in terms of progression-free survival: mean increase of 2.9 months [CI95%: 0.7-5.1] over the first 24 months of follow-up, in a randomised, open-label phase 3 study, and**
- **the safety profile marked by a lower frequency of grade 3-5 adverse events and serious adverse events, and a higher frequency of adverse events of particular interest (identified as important risks in the RMP);**

and despite:

- **the absence of demonstration of an increase in overall survival in an interim analysis scheduled by the protocol;**
- **the absence of any formal conclusion that can be drawn based on the quality-of-life results;**

the Transparency Committee considers that KEYTRUDA (pembrolizumab) as monotherapy provides a minor clinical added value (CAV IV) compared to chemotherapy ± targeted therapy in the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults initially unresectable.