HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
3 NOVEMBER 2021

The legally binding text is the original French opinion version

nivolumab/ipilimumab
OPDIVO 10 mg/ml concentrate for solution for infusion
YERVOY 5 mg/ml concentrate for solution for infusion

New indication

Key points

Favourable opinion for reimbursement in adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy, only in patients who have received no prior immunotherapy.

Unfavourable opinion for reimbursement in patients having received prior immunotherapy.

Role in the care pathway?

In metastatic colorectal cancer without the presence of mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H), in the event of failure of first-line fluoropyrimidine-based combination chemotherapy (+/- targeted therapy),a change of chemotherapy ± targeted therapy protocol is recommended. The medicinal products used as second-line therapy are 5-FU chemotherapies (FOLFOX, FOLFIRI), irinotecan/oxaliplatin, anti-VEGF therapy (bevacizumab, aflibercept, ramucirumab), anti-EGFR therapy (panitumumab, cetuximab), STIVARGA (regorafenib), LONSULF (trifluridine/tipiracil) and BRAFTOVI (encorafenib) in BRAF V600E mutation-positive patients.

In patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer, apart from first-line treatment with pembrolizumab (KEYTRUDA), the treatments used as second-line therapy are identical to those recommended in the absence of the MSI-H/dMMR genome abnormality.

Role of the medicinal product in the care pathway

The OPDIVO/YERVOY (nivolumab/ipilimumab) combination is a treatment alternative in adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy, only in patients who have received no prior immunotherapy.

Considering the absence of direct comparative data and the absence of an indirect comparison of good methodological quality, its role in the care pathway cannot be specified compared to the chemotherapy protocols used as second or later-line treatments.

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 OPDIVO/YERVOY (nivolumab/ipilimumab) combination is a curative treatment.

◗ Its efficacy/adverse effects ratio is moderate, given limited clinical data derived from a non-comparative study, and uncertainties related to the following in particular (see Section 07.6 Summary and Discussion):
- the absence of robust comparative data, even though there were clinically relevant comparators available,
- the preliminary supporting data in a heterogeneous population in terms of treatment lines (the second-line subgroup only concerned 27 patients),
- the methodological weaknesses of the indirect comparison provided,
- the toxicity marked by an incidence of serious adverse events (AEs) reported in more than half of patients (55%) and of grade ≥3 adverse events in almost two thirds of patients (62%).

◗ There are therapeutic alternatives (see section 05 Clinically relevant comparators).

◗ The OPDIVO/YERVOY (nivolumab/ipilimumab) combination is a treatment alternative in adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy, only in patients who have received no prior immunotherapy.

Public health impact

Considering:
- the seriousness of the disease and its prevalence,
- the identified partially met medical need,
- the potential partial response provided by the OPDIVO/YERVOY (nivolumab/ipilimumab) combination to the identified need,
- the absence of data enabling assessment of the additional impact on the organisation of care,
- the lack of demonstrated impact on quality of life,

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

Considering all these elements, the Committee deems that the clinical benefit of the OPDIVO/YERVOY (nivolumab/ipilimumab) combination is:
- **moderate in the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy, only in patients who have received no prior immunotherapy.**
- **insufficient to justify public funding cover in all other clinical situations (patients having received prior immunotherapy).**

The Committee issues a favourable opinion for inclusion of this combination in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy, only in patients who have received no prior immunotherapy, and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion of this combination in the hospital formulary list of reimbursed proprietary medicinal products approved for use in other clinical situations (patients having received prior immunotherapy).

Clinical Added Value

Within the reimbursement scope:

Considering:

- **efficacy data for the OPDIVO/YERVOY (nivolumab/ipilimumab) combination, derived from a phase 2 non-comparative study, suggesting an investigator-assessed objective response rate that is clinically relevant and complete response and survival rates that are not usually observed in these patients in the absence of treatment,**

and despite:

- **uncertainties with respect to the specific effect size of this combination, considering the absence of direct comparison and the methodological weakness of the indirect comparison provided, in a context in which a direct comparison with a treatment alternative with a robust methodology would have been possible,**
- **the safety profile, marked by an incidence of serious adverse events (AEs) reported in more than half of patients (55%) and of grade ≥3 adverse events in almost two thirds of patients (62%),**

the Transparency Committee considers, that as the dossier currently stands, the OPDIVO/YERVOY (nivolumab/ipilimumab) combination provides no clinical added value (CAV V) in the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy who have received no prior immunotherapy.