HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
16 JUNE 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 combination with 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

What therapeutic improvement?

Therapeutic improvement compared to chemotherapy.

Role in the care pathway?

The current management for metastatic non-small cell lung cancer (NSCLC) in first line-treatment, in the absence of molecular abnormalities (EGFR mutations, or ALK or ROS-1 rearrangements), is based on immunotherapy, for eligible patients.

Pembrolizumab (anti-PDL1 immunotherapy) is a first-line treatment:

- as monotherapy, in PD-L1 ≥ 50% patients, and
- in combination with chemotherapy, irrespective of PD-L1 expression:
  - in combination with pemetrexed and platinum chemotherapy, in non-squamous NSCLC,
  - in combination with carboplatin and paclitaxel (or nab-paclitaxel) chemotherapy, in squamous NSCLC.

In the event of contraindication to immunotherapy, or to one of the chemotherapy drugs combined with pembrolizumab, chemotherapy is indicated. This involves dual therapy combining a platinum (cisplatin or carboplatin) with one of the following substances: vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed (only in non-squamous NSCLC for the latter). In non-squamous NSCLC, in the absence of contraindications, bevacizumab can be added to the dual chemotherapy regimen; and atezolizumab can be combined with bevacizumab + paclitaxel + carboplatin.

Role of the medicinal product in the care pathway

Combination of OPDIVO/YERVOY (nivolumab/ipilimumab) and 2 cycles of platinum-based chemotherapy is an alternative in the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

However, the Committee regrets the absence of data enabling the role of the OPDIVO/YERVOY (nivolumab/ipilimumab) combination to be positioned compared to current standard of care therapies: pembrolizumab as monotherapy, only if PD-L1 ≥ 50%, as well as the pembrolizumab + chemotherapy combination, irrespective of PD-L1 expression.

Considering these elements, the role of the nivolumab/ipilimumab combination plus 2 cycles chemotherapy compared to these different protocols is not known therefore. The Committee considers that the therapeutic decision should be taken after a documented proposal resulting from a multidisciplinary team meeting. This choice should take into account the efficacy and safety results of each protocol, along with the patient's general condition and preferences. The Committee highlights the fact that patients with an ECOG score > 1 were not included in the study.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Metastatic non-small cell lung cancer (NSCLC) is a serious, life-threatening condition.

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

◗ Its efficacy/adverse effects ratio is moderate, given:
- a higher toxicity compared to chemotherapy, with 47% of patients having grade 3-4 adverse events, the need to permanently discontinue treatment for 28% of patients, and the occurrence of immunological adverse events, with an increased frequency compared to single-agent immunotherapy with nivolumab alone,
- the impossibility of assessing the efficacy and safety of this dual immunotherapy compared to single-agent immunotherapy in the absence of data assessing the relative contribution of the components of the combination,

◗ There are therapeutic alternatives, in particular pembrolizumab (as monotherapy or in combination with chemotherapy), which has demonstrated a superiority over chemotherapy alone in terms of overall survival, with an acceptable safety profile.

◗ Combination of OPDIVO/YERVOY (nivolumab/ipilimumab) and 2 cycles of platinum-based chemotherapy can be a first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation. The role of the combination compared to pembrolizumab cannot be specified as the dossier currently stands, in the absence of direct comparative data.

Public health impact

Considering:
- the seriousness of NSCLC, particularly at the metastatic stage,
- the incidence of the disease,
- the partially met medical need,
- the partial response to the identified need provided by nivolumab/ipilimumab in combination with 2 chemotherapy cycles,
- the lack of demonstrated impact on quality of life,
- the absence of data enabling assessment of the additional impact on the organisation of care,

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

Given all of these elements, the Committee considers that the clinical benefit of the OPDIVO/YERVOY (nivolumab/ipilimumab) combination is moderate in the MA indication.

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

Clinical Added Value

Considering:

- **demonstration of the superiority of nivolumab/ipilimumab in combination with 2 chemotherapy cycles, compared to chemotherapy, in terms of overall survival (HR=0.69 [CI95%: 0.56-0.86], with an individual estimate of an absolute improvement of 3.4 months, deemed clinically relevant), in an open-label, randomised phase 3 study;**

and despite:

- **a comparator that is not optimal on the date of the assessment;**
- **the absence of data making it possible to differentiate between the proportion attributable (efficacy and toxicity) to each immunotherapy (nivolumab/ipilimumab), and hence the specific value of the combination of these two drugs compared to monotherapy (nivolumab or ipilimumab);**
- **a higher toxicity, with the occurrence of grade ≥ 3 adverse events in 47% of patients, in particular immunological (with an increased frequency compared to single-agent immunotherapy), and permanent discontinuation of treatment due to an adverse event in 28% of patients;**
- **the lack of demonstrated impact on quality of life;**

the Transparency Committee considers that combination of OPDIVO/YERVOY (nivolumab/ipilimumab) and 2 cycles of platinum-based chemotherapy provides a minor clinical added value (CAV IV) compared to chemotherapy in the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.