HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 JULY 2021
The legally binding text is the original French opinion version

nivolumab
OPDIVO 10 mg/ml concentrate for solution for infusion

Indication extension

Key points

Unfavourable opinion for reimbursement, as monotherapy, in the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Role in the care pathway?

Therapeutic strategies for oesophageal squamous cell carcinoma are defined based on the histological type (squamous cell/adenocarcinoma) and stage of the cancer. In patients with unresectable advanced, metastatic oesophageal squamous cell carcinoma, use of systemic treatment alone (palliative chemotherapy) is the standard treatment.

The main medicinal products used in combination are cisplatin and 5- fluorouracil. Other regimens, such as the FOLFOX regimen combining fluorouracil-oxaliplatin-folinic acid, are sometimes used as a treatment option.

In certain metastatic gastro-oesophageal junction (GEJC) adenocarcinomas over-expressing HER 2, treatment with a targeted therapy (trastuzumab) may also be proposed in combination with chemotherapy.

Apart from nivolumab (the subject of the present assessment), no other medicinal products currently have an MA specifically as second-line therapy in unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after a first line of chemotherapy. However, in this situation ESMO (2016) European guidelines and NCCN (2021) American guidelines recommend, in particular, taxanes (docetaxel or paclitaxel) as monotherapy in eligible patients. Patients in poor general condition are managed by supportive care.

Role of the medicinal product in the care pathway

Considering, on the one hand:
- **the demonstrated superiority of nivolumab versus monotherapy with taxanes (docetaxel or paclitaxel) on overall survival (primary endpoint) in a phase 3, randomised, open-label study (ATTRACTION-III) with a modest absolute improvement of 2.5 months and survival curves that cross (additional effect size difficult to interpret - see 07.4 Summary and discussion);**
- **the more favourable safety profile of nivolumab compared to taxanes (AE grades 3-4: 38.3% vs 70.7%; serious AEs: 32.5% vs 63.2%; AE having led to treatment discontinuation: 13.9% vs 15.9%) with, however, more frequent grade 5 AEs with nivolumab: 3.3% versus 2.4%);**

But taking into account, on the other hand:
- **concerns related to the excess mortality observed with nivolumab compared to chemotherapy in the 5 months following randomisation in a context in which no specific factor associated with these early deaths could be identified;**
- **the non-guaranteed transposability of the results to French patients (patients predominantly native to Asia [95.7%]) and the exclusion of patients with a poor general condition (ECOG score ≥ 2), who are nonetheless the most representative in routine practice at this stage of the disease;**
- **the absence of any possible conclusion with respect to progression-free survival given the early interruption of the ranked analysis sequence;**
- **the absence of a formal conclusion on quality of life (exploratory endpoint and open-label study);**

the Transparency Committee considers that, on the basis of currently available data, OPDIVO (nivolumab), as monotherapy, has no role in the care pathway for oesophageal squamous cell carcinoma (OSCC) in the treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

- Oesophageal cancer is a serious, life-threatening disease.

- The medicinal product OPDIVO (nivolumab) is a curative medicinal product.

- Its efficacy/adverse effects ratio has not been adequately established in this indication extension despite a modest improvement in overall survival (absolute improvement of 2.5 months) given uncertainties related to the study results, in particular:
  - the unexplained early excess mortality reported at the start of the treatment (no predictive factor for these early deaths could be identified),
  - non-compliance with good clinical practices for a subgroup of patients (n=31),
  - problems related to the transposability of the results to the French population and related to exclusion of patients with an initial performance score ≥ 2),
  - the absence of demonstration relative to progression-free survival and quality-of-life.

- Alternatives are available as second-line therapy that are limited and do not currently have an MA in Europe (taxanes), as well as supportive care for patients in poor general condition.

- On the basis of currently available data, OPDIVO (nivolumab), as monotherapy, has no role in the care pathway for oesophageal squamous cell carcinoma (OSCC) in the treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy (see section 08 of this opinion).

Public health impact

Considering:
- the seriousness of the disease, which is life-threatening in the short term, and its prevalence,
- the partially met medical need,
- the lack of additional response to the identified partially met need (absence of expected impact on morbidity and mortality given the numerous uncertainties identified (see discussion chapter). No impact on quality of life compared to taxanes as monotherapy has been demonstrated to date),
- the lack of expected impact of nivolumab on the organisation of care,

OPDIVO (nivolumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of OPDIVO (nivolumab) is insufficient to justify its public funding cover in the new MA indication.

The Committee issues an unfavourable 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.