HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

IMFINZI (durvalumab), monoclonal antibody

High clinical benefit.
Moderate clinical added value in the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in patients in good condition whose tumours express PD-L1 ≥ 1% and whose disease has not progressed following concomitant chemoradiation therapy

Main points

- The MA for IMFINZI was granted with restricted use based on PD-L1 expression (≥ 1% of tumour cells) for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose disease has not progressed following platinum-based chemoradiation therapy.
- It has demonstrated superiority compared to placebo in terms of progression-free survival and overall survival, with an acceptable safety profile, observed in the short term (with a median follow-up of 25.2 months). However, the effect size cannot be robustly estimated on the basis of PD-L1 expression levels, due to the post hoc nature of the analyses.

Therapeutic strategy

- Surgical resection, the only curative treatment for NSCLC, is the reference treatment at localised stages (stages I and II) for operable patients.
- Around 25% of patients are diagnosed at a locally advanced stage corresponding to stage III of the disease (stages IIIA, IIIB and IIIC according to the TNM classification). The discussion relative to resectability only concerns stage IIIA tumours, on the basis of homolateral lymph node involvement (N2). Around two thirds of locally advanced NSCLC cases are diagnosed at an already unresectable stage.
- The reference treatment for locally advanced unresectable NSCLC is chemoradiation therapy if the patient's condition allows it. Chemotherapy should include 2 to 4 platinum salt-based courses combined with radiotherapy. Concomitant chemoradiation therapy is recommended in patients with a Performance Status (PS) 0 or 1, without comorbidities, aged under 70 years (between the ages of 70 and 75 years, it can be discussed) given its better results. Sequential chemoradiation therapy is recommended in patients with a PS ≥ 2 and/or elderly and/or weakened patients. Following chemoradiation therapy, treatment-free monitoring was recommended before the inclusion of durvalumab in the therapeutic strategy.
- **Role of the medicinal product in the therapeutic strategy**

  IMFINZI is a first-line treatment as IV monotherapy in its indication until disease progression or unacceptable toxicity, or for a maximum duration of 12 months.
- There are no data available concerning the efficacy and safety of durvalumab administered following sequential chemoradiation therapy (alternating chemotherapy and radiotherapy), corresponding to the administration regimen generally used in clinical practice in older patients and those in less good general health. In the absence of a study conducted specifically in patients with an EGFR mutated tumour, its role in the strategy is still to be determined.

Clinical data

- The evaluation of durvalumab is based on the results of a randomised, double-blind, phase III study comparing durvalumab with placebo in patients with locally advanced, unresectable NSCLC, included regardless of PD-L1 expression level and whose disease has not progressed following concomitant chemoradiation therapy.

- In total, 713 patients were randomised: 476 patients in the durvalumab group and 237 patients in the placebo group. The patients had a median age of 64 years and were in good condition (ECOG 0: 48.8%; ECOG 1: 50.8%). The majority of patients had locally advanced NSCLC of stage IIIA (53.0%) or IIIB (44.7%) and squamous (45.7%) or non-squamous histology (54.3%).
- In the total study population, on an ITT basis and with inclusion of patients regardless of PD-L1 expression level (N=713): this study was conclusive for the primary combined endpoints (progression-free survival and overall survival) during the interim analyses scheduled by the protocol (considered to be the primary analyses in accordance with the statistical analysis plan):
  - the median progression-free survival was 16.8 months in the durvalumab group versus 5.6 months in the placebo group, i.e. an absolute improvement of 11.2 months in favour of durvalumab, with median follow-up of 14.5 months, HR=0.52; $CI_{98.9\%}$ [0.39; 0.70], p<0.0001;
  - the median overall survival was not reached in the durvalumab group versus 28.7 months in the placebo group, with a median follow-up of 25.2 months, HR=0.68 $CI_{99.73\%}$ [0.469; 0.997]; p=0.00251.
- In the subpopulation retained by the MA, for which the PD-L1 expression level is ≥ 1%: (N=303/713), the analyses in this study subgroup were conducted post hoc, it is therefore necessary to consider the results obtained in the ITT population (see above) to best estimate the size effect in the PD-L1 ≥ 1% subgroup.
- Adverse events (AEs) having led to treatment discontinuation in the total study population (regardless of PD-L1 expression level) were more common in the durvalumab group (15.4%) than in the placebo group (9.8%). These primarily concerned pneumonitis (4.8% versus 2.6%), radiation pneumonitis (1.3% versus 1.3%) and pneumonia (1.1% versus 1.3%). The frequency of AEs of grade 3 or 4 was 32.0% in the durvalumab group and 27.8% in the placebo group. Twenty-one patients (4.4%) in the durvalumab group and 14 patients (6.0%) in the placebo group presented a grade 5 AE (death due to an adverse event). The important risks concern immune-mediated events: pneumonitis, hepatitis, colitis or diarrhoea, of endocrinological, dermatological or cardiac type (myocarditis)

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for oncology specialists or physicians with oncology expertise

Benefit of the medicinal product

- The actual clinical benefit* of IMFINZI is high in the MA indication.
- IMFINZI monotherapy provides clinical added value** (CAV III, moderate) compared to placebo in the treatment of locally advanced, unresectable NSCLC in patients in good condition whith tumour expression of PD-L1 ≥ 1% and whithout disease progression after concomitant chemoradiation therapy.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 06 February 2019 (CT-17432) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.
** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".