HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
March 2018

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

TAFINLAR (dabrafenib), **in combination with MEKINIST** (trametinib), protein kinase inhibitors

Insufficient clinical benefit to justify public funding of the TAFINLAR / MEKINIST combination for advanced non-small cell lung cancer carrying a BRAF V600 mutation.

Main points

- TAFINLAR and MEKINIST have been granted a marketing authorisation in combination for the treatment of advanced non-small cell lung cancer (NSCLC) carrying a BRAF V600 mutation.
- It is not possible to assess the clinical added value of the combination due to the lack of comparative data with respect to clinically relevant comparators, particularly in respect of overall survival compared to chemotherapy, even though this comparison was possible.
- This combination has no role in the treatment strategy for advanced NSCLC carrying a BRAF V600 mutation.

Pre-existing indications*

TAFINLAR monotherapy or in combination with trametinib and MEKINIST monotherapy or in combination with dabrafenib have been granted a marketing authorisation for the treatment of adults with non-resectable or metastatic melanoma carrying a BRAF V600 mutation.

Therapeutic strategy

- The therapeutic treatment strategy for advanced NSCLC must be defined in the context of a multidisciplinary review meeting, based on the presence of molecular abnormalities (in particular, EGFR mutation or ALK translocation), PD-L1 tumour expression, tumour histology (epidermoid or non-epidermoid), age, ECOG performance status, comorbidities and patient preferences.
- In the presence of a molecular abnormality, particularly EGFR mutation or ALK translocation, the recommended treatment is:
  - EGFR tyrosine kinase inhibitor (TKI) monotherapy as a first-line treatment (choice from: gefitinib, erlotinib or afatinib, treatments having demonstrated their benefit compared to chemotherapy, essentially in terms of progress-free survival) regardless of ECOG performance status, for patients with an EGFR mutation and bitherapy based on platinum salts or osimertinib for patients carrying the EGFR T790M mutation having progressed during or after EGFR TKI therapy;
  - treatment with crizotinib followed by ceritinib or alectinib (treatments having demonstrated their benefit compared to chemotherapy, essentially in terms of progression-free survival) for patients with ALK translocation.
- In the absence of EGFR or ALK activating mutations, for patients with no major comorbidities and with an ECOG performance status of 0 to 2:
  - The conventional first-line treatment is a chemotherapy regimen (4 to 6 cycles) combining a platinum salt (cisplatin or carboplatin) with one of the following substances: gemcitabine, taxanes (docetaxel or paclitaxel), vinorelbine or pemetrexed (only for non-epidermoid carcinoma patients).
  - For patients with non-epidermoid NSCLC, having a partial response or stable disease and a performance status of 0 to 1 after induction chemotherapy (4 to 6 cycles), it may be proposed to continue one of the first-

* This summary does not concern these indications.

line treatments used (pemetrexed; so-called "continuation maintenance" strategy) or use a different chemotherapy substance (pemetrexed) to those used for induction (so-called "switch maintenance" strategy).

- In cases of PD-L1 tumour expression ≥ 50%, pembrolizumab is recommended as a first-line treatment.
- As a second-line treatment, regardless of the histological type (epidermoid or non-epidermoid), nivolumab (regardless of the PD-L1 tumour expression level) and pembrolizumab (in cases of PD-L1 tumour expression ≥ 1%) immunotherapies are the preferential treatments over chemotherapy (docetaxel or pemetrexed monotherapy).

- **Role of the medicinal product in the therapeutic strategy**

  The combination of TAFINLAR plus MEKINIST has no role in the treatment strategy for advanced NSCLC carrying a BRAF V600 mutation, given the lack of comparative data versus clinically relevant comparators (chemotherapy, anti-PD1 immunotherapies).

Clinical data

- The efficacy data for the dabrafenib/trametinib combination are based on a non-comparative phase II study on 93 patients with advanced NSCLC carrying a BRAF V600 mutation. As a second-line and subsequent treatment (57 patients), the overall response rate was 63.2% (36/57 patients) (95% CI [49.3; 75.6]), with a large majority of partial responses (34/57 patients). As a first-line treatment (36 patients), the overall response rate was 61% (22/36 patients) (95% CI [43.5; 76.9]), with a partial response in 20/36 patients.
- The safety profile of the combination for NSCLC was similar to that observed for melanoma treatment. Adverse events resulted in definitive treatment discontinuation in 14% (8/57) of the patients who received the dabrafenib / trametinib combination as a second-line and subsequent treatment and in 19% (7/36) of the patients who received the dabrafenib / trametinib combination as a first-line treatment. Grade 3 or 4 adverse events were reported in 49% (28/57) of second-line and subsequent treatment patients and in 56% (20/36) of first-line treatment patients. The most frequently reported adverse events were: fever, nausea, diarrhoea, peripheral oedema, dry skin, fatigue, loss of appetite, skin rash and neutropoenia.

Special prescription requirements

- Medicinal products subject to hospital prescription.
- Prescription reserved for oncology specialists or physicians with oncology expertise.

Benefit of the medicinal product

- The actual clinical benefit* of the TAFINLAR/MEKINIST combination is insufficient to justify public funding cover.
- Not approved for non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 07 March 2018 (CT-16334)
available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) consists of its benefit particularly on the basis of its clinical performances and the severity of the disease 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) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement".