HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

TAFINLAR (dabrafenib), protein kinase inhibitor (anti-BRAF)
MEKINIST (trametinib), protein kinase inhibitor (anti-MEK)

High clinical benefit in the adjuvant treatment of stage III melanoma with BRAF V600 mutation after complete resection, and moderate clinical improvement in the therapeutic strategy.

Main points

- The TAFINLAR/MEKINIST has been granted a marketing authorisation in the adjuvant treatment of adults suffering from stage III melanoma carrying a BRAF V600 mutation, after complete resection.
- This combination has demonstrated its superiority over the placebo in terms of improvement of disease-free survival after complete resection of a stage III skin melanoma carrying a BRAF V600E/K mutation, though without having demonstrated to date any gain in terms of overall survival.
- It is a first-line treatment in its indication. Failing any direct comparison data, its role relative to nivolumab immunotherapy in the event of BRAF V600 mutation not known.

Therapeutic strategy

- In the context of the adjuvant treatment of melanoma with high risk of recurrence, the following points were recommended:
  - Assess patients with resected stage III melanoma to administer interferon as adjuvant treatment.
  - Patients with regional microscopic lymph node involvement and/or ulcerated primary lesion constitute those subjects most likely to benefit from this treatment.
  - Encourage the participation of patients with stage IIIB or later melanoma in clinical trials.
- According to the guidelines of the French society for dermatology, updated in November 2018, patients suffering from stage III melanoma expressing a BRAF V600 mutation are eligible for adjuvant treatment, both by the dabrafenib/trametinib combination and by anti-PD-1 immunotherapy. Failing any comparative studies of these two strategies, there are no arguments for recommending one treatment over the other.
  In the event of wild-type BRAF tumour, patients are eligible for anti-PD-1 immunotherapy. There are no arguments for preferring one anti-PD-1 over another.
- **Role of the medicinal product in the therapeutic strategy**

  The TAFINLAR/MEKINIST combination is a first-line treatment in its indication.

  In all patients, the LVEF must be assessed prior to initiation of treatment, one month after initiation of treatment, then approximately once every 3 months throughout the treatment.

Clinical data

- One phase III randomised, double-blind study versus placebo assessed the efficacy and safety of dabrafenib + trametinib versus placebo in adults suffering from stage III skin melanoma carrying a BRAF V600E/K mutation, after complete resection. In total, 870 patients were randomised: 438 in the dabrafenib + trametinib group and 432 in the placebo group. The median age was of 51 years (18% were over the age of 65 years).
- After a median follow-up period of 34 months in the dabrafenib + trametinib group and of 33 months in the placebo group, median disease-free survival time (DFS, primary endpoint) was of 16.6 months in the placebo group and was not reached in the dabrafenib + trametinib group (HR = 0.47; CI95% [0.39; 0.58]).

Overall survival was a ranked secondary endpoint. During the primary analysis of the primary endpoint (DFS), the intermediate analysis of overall survival failed to show any difference between the two treatment groups: only 153 deaths were reported, 60 (14%) in the dabrafenib + trametinib group and 93 (22%) in the placebo group, of the 597 expected for the final analysis of overall survival (NS).

- The choice of comparator (placebo) is acceptable insofar as the active historical comparator (interferon) displays a low level of efficacy and an unfavourable safety profile.
  The incidence of treatment discontinuations due to adverse events (AEs) was 26% in the dabrafenib and trametinib group and 3% in the placebo group. Serious adverse events (SAEs) were reported in 36% of patients in the dabrafenib and trametinib group, versus 10% in the placebo group. The only SAEs considered to be treatment-related and reported in ≥1% of patients in the dabrafenib + trametinib group were fever (15%), chills (3%) and reduced left ventricular ejection fraction (3%). In the placebo group, cases of reduced left ventricular ejection fraction deemed to be treatment-related were reported in 1% of patients.

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 TAFINLAR/MEKINIST is high in the marketing authorisation indication.
- TAFINLAR/MEKINIST provides moderate clinical added value** (CAV III) in the therapeutic strategy.
- Approved for non-hospital and hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 06 February 2019 (CT-17406) 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".