HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
July 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

VARGATEF (nintedanib), tyrosine kinase inhibitor

Insufficient actual benefit in treatment of metastatic non-small-cell lung cancer

Main points

- VARGATEF has Marketing Authorisation in combination with docetaxel in the treatment of adults with locally advanced, metastatic or locally recurrent non-small-cell lung cancer, of adenocarcinoma histology type, after a first line of chemotherapy.
- VARGATEF in combination with docetaxel offers no gain in overall survival or quality of life compared with docetaxel alone.

Therapeutic use

- The management of non-small-cell lung cancer differs depending on the stage of the cancer.
  The reference treatment for early stages is surgery. The therapeutic strategy in inoperable patients should be guided from the 1st line of treatment according to the presence or absence of mutations. Other criteria also intervene in the treatment decision: tumour histology, the patient's performance score and comorbidities.
- In patients with a tumour harbouring anEGFR activating mutation, the recommended treatment is an anti-EGFR tyrosine kinase inhibitor. Three anti-EGFR tyrosine kinase inhibitors are currently indicated in 1st-line treatment: gefitinib (IRESSA), erlotinib (TARCEVA) and afatinib (GIOTRIF).
- In patients with a tumour non harbouring EGFR mutation, platinum-based chemotherapy is the reference (platinum salt combined with one of the following molecules: gemcitabine, taxanes (paclitaxel and docetaxel), vinorelbine or pemetrexed). In cases of non-squamous cell predominant tumours, bevacizumab can also be added to this dual therapy.
- As a second-line therapy, the reference treatment is monotherapy: pemetrexed only for non-squamous cell tumours or docetaxel or a targeted therapy (erlotinib or gefitinib) if this has not been administered in the first-line treatment.

Role of the medicinal product in the therapeutic strategy

- In the absence of additional data, VARGATEF has no role in the current therapeutic strategy for treatment of locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology type.

Clinical data

- A randomised, double-blind phase III trial compared the safety and efficacy of VARGATEF combined with docetaxel versus docetaxel/placebo in patients with locally advanced, metastatic or locally recurrent non-small-cell lung cancer, after a first line of chemotherapy.
  The study included 658 patients (50.1%) with an adenocarcinoma, 555 patients (42.2%) with a squamous cell carcinoma and 102 patients (7.7%) with other types of tumour histology. In the total study population, progression-free survival (primary endpoint) was 3.4 months in the VARGATEF combined with docetaxel group versus 2.7 months in the docetaxel/placebo group, or an absolute gain of 0.7 months (HR=0.79, 95% CI [0.68-0.92], p=0.0019).
  No difference was observed between the two groups in terms of overall survival: 10.1 months in the VARGATEF combined with docetaxel group versus 9.1 months in the docetaxel/placebo group (HR: 0.94, 95% CI [0.83-2.4]; p=0.2720).
  A predefined analysis was done on the population of patients with NSCLC of adenocarcinoma histology type (population covered by the Marketing Authorisation) and a median progression-free survival of 4.0 months was demonstrated in the VARGATEF group versus 2.8 months in the docetaxel/placebo group, meaning an absolute gain of 1.2 months (0.77; 95% CI [0.62-0.96]). In this subgroup covered by the Marketing Authorisation, the EGFR status was known for only 8 patients in the VARGATEF combined with docetaxel group and 12 patients in the comparator group.

In this subgroup, the median overall survival was 12.6 months in the VARGATEF combined with docetaxel group versus 10.3 months in the docetaxel/placebo group, or an absolute gain of 2.3 months (HR=0.83; 95% CI [0.70-0.99], p=0.0359).
The primary grade ≥ 3 adverse events of grades observed in the VARGATEF combined with docetaxel group were diarrhoea (4.3% vs 1.2%) and elevated transaminases (38.4% vs 9.6%).

- The Transparency Committee highlights the following points:
  - no patient in this study was treated in first line with a tyrosine kinase inhibitor and the EGFR status of the tumour was known in only 3% of patients in the subgroup covered by the Marketing Authorisation.
  - the national guidelines issued in 2010 guide the choice of the first line treatment according to the EGFR status in order to benefit from a targeted therapy. As a result, it is not certain that the results of this study could be transposed to clinical practice.
  - the Marketing Authorisation population comes from a subgroup of the pivotal study in which the results in the overall population showed a low gain of 0.7 months favouring VARGATEF versus the comparator, without improvement in the overall survival or quality of life of patients.

  Overall, taking account of all the above information, the confidence level in the results reported is unsatisfactory, and further trials are necessary in order to evaluate the quantity of effect of nintedanib (VARGATEF) and its place in the treatment of locally advanced, metastatic or locally recurrent non-small-cell lung cancer (NSCLC) of adenocarcinoma histology type.

Prescribing conditions

- Medicinal product for hospital use
- Medicine for prescription limited to certain healthcare professionals: oncologists or doctors competent in oncology.

Benefit of the medicinal product

- The actual benefit* of VARGATEF is insufficient to justify reimbursement by National Health Insurance.
- Does not recommend inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 01 July 2015 (CT-14048) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary 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 AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.