HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
Focus
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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

AFINITOR (everolimus), tyrosine kinase inhibitor

Minor improvement, in combination with exemestane, in the treatment of hormone receptor-positive, HER2-negative advanced breast cancer

Main points

- AFINITOR has Marketing Authorisation, in combination with exemestane, in the treatment of hormone receptor-positive, HER2/neu-negative advanced breast cancer in postmenopausal women without symptomatic visceral disease after recurrence or progression of the disease following treatment with a non-steroidal aromatase inhibitor.
- The combination AFINITOR + AROMASINE (everolimus + exemestane) provides a minor clinical benefit in the treatment of this type of cancer.
- This combination is integrated into the treatment strategy as adjuvant treatment prior to cytotoxic chemotherapy.

Pre-existing indications

AFINITOR already has Marketing Authorisation in breast cancer and neuroendocrine tumours of pancreatic origin.
This summary does not cover these indications.

Therapeutic use

- The presence of hormone receptors (for oestrogens and/or progesterone) is a predictive marker for the response to treatment.

If the breast cancer is hormone-dependent, its treatment in postmenopausal women is:

- Early stage: Adjuvant hormone therapy based on tamoxifen or aromatase inhibitors: ARIMIDEX (anastrozole), FEMARA (letrozole) or AROMASINE (exemestane).
- Advanced stage:

The first-line treatment in the absence of any factor pointing to a poor prognosis is a non-steroidal aromatase inhibitor (anastrozole or letrozole) in patients who have not undergone adjuvant treatment or who have stopped this more than 12 months previously. Tamoxifen is also still a first-line option.
The second-line treatment is hormone therapy, for which the optimal sequence is not established. In particular, after progression following first-line treatment with an aromatase inhibitor: tamoxifen, aromatase inhibitor in patients who have not yet been treated with one (non-steroidal: anastrozole, letrozole; or steroidal: exemestane), fulvestrant, megestrol or an androgen.
Chemotherapy is normally reserved for cancers that are progressing aggressively or with symptomatic visceral disease.

Role of the medicinal product in the therapeutic strategy

In the treatment of hormone receptor-positive, HER2/neunegative advanced breast cancer, the orally administered combination AFINITOR + AROMASINE is an adjuvant therapy given prior to (intravenous) cytotoxic chemotherapy; it may be proposed only in postmenopausal patients without symptomatic visceral disease after failure of a non-steroidal aromatase inhibitor (letrozole or anastrozole).

Clinical data

- The everolimus+exemestane combination has been compared with exemestane on its own in a randomised double-blind study in 724 postmenopausal women with locally advanced or metastatic hormone receptor-positive, HER2-negative breast cancer that is recurring or progressing during or after treatment with a non-steroidal aromatase inhibitor (letrozole or or anastrozole). Since the previous assessment, the final analysis of global survival is now available.
  Compared with exemestane on its own, the addition of everolimus (10 mg/day) to exemestane (25 mg/day) showed:
  - a longer median progression-free survival (primary endpoint): 7.82 versus 3.19 months, i.e. an increase of 4.63 months (HR = 0.45; $CI_{95\%}$ [0.38; 0.54]);
  - no change in global survival (secondary endpoint) in the final analysis: 31 versus 26.6 months (HR = 0.89; $CI_{95\%}$ [0.73; 1.1]; not significant);
  - comparable quality of life.

- The post-hoc subgroup analyses as a function of the presence or absence of visceral metastases and line of treatment did not provide information of a level of evidence sufficient to draw any conclusions about the efficacy and safety of this combination specifically in these populations, given the methodological shortcomings.

- The current safety data have shown that the combination everolimus 10 mg/day + exemestane 25 mg/day versus exemestane on its own (25 mg/day) resulted in an increase in the incidence of treatment stoppages owing to adverse events (29% versus 5%), in serious adverse events (33% versus 16%) and in grade 3 or 4 adverse events (55% versus 29%).
  The moun special warnings concern non-infectious pneumonitis, infections and oral ulceration.

Benefit of the medicinal product

- The actual benefit* of AFINITOR is moderate.
- In the treatment of patients with hormone receptor-positive, HER2/neunegative locally advanced or metastatic breast cancer, AFINITOR in combination with exemestane provides minor clinical added value (CAV IV) in postmenopausal women without symptomatic visceral disease after recurrence or progression of the disease following treatment with a non-steroidal aromatase inhibitor.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 01 April 2015 (CT-13838) 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.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".