HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
Update
March 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

IBRANCE (palbociclib), protein kinase inhibitor

High clinical benefit in combination with letrozole, for menopausal women, with advanced HR+/HER2- breast cancer, in the absence of short-term life-threatening symptomatic visceral involvement, not pre-treated for the advanced stage of their disease and not having received a non-steroidal aromatase inhibitor as part of an adjuvant treatment in the previous 12 months and minor clinical improvement compared to letrozole alone.

Insufficient clinical benefit to justify reimbursement in combination with exemestane or anastrozole and for non-menopausal women and/or those with short-term life-threatening symptomatic visceral involvement

Main points

- IBRANCE has been granted a marketing authorisation for the treatment of locally advanced or metastatic hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer in combination with an aromatase inhibitor.
- In combination with letrozole, its superiority has been demonstrated over letrozole alone in terms of progression-free survival (HR = 0.576 95%CI [0.463; 0.718], with an absolute gain of 10.3 months. The overall survival data are not yet mature; the final analysis is expected in 2020.
- No data are available documenting its efficacy and safety in combination with anastrozole or exemestane. The data in respect of IBRANCE in combination with letrozole are restricted to menopausal women.

Pre-existing indication*

- IBRANCE has also been granted a marketing authorisation for the treatment of locally advanced or metastatic HR+ and HER2- breast cancer in combination with fulvestrant in women who have received prior endocrine therapyy.

Therapeutic strategy

- The objective of the treatment of locally advanced or metastatic breast cancer is to enable stabilisation with an improvement of quality of life, or even remission of variable duration for up to several years. The choice of systemic treatment is dependent on the histological characteristics of the tumour, predictive factors for response to treatments (hormone receptor and/or HER2 receptor expression), previously administered treatments and their safety, metastatic disease presentation and the time to recurrence.
- If the tumour is HR+/HER2- and in the absence of short-term life-threatening symptomatic visceral involvement, the therapeutic strategy is based on hormone therapy. In menopausal women, treatment with non-steroidal aromatase inhibitors (letrozole or anastrozole) is recommended as a first-line treatment, unless they were previously administered as part of adjuvant therapy discontinued less than 12 months previously. It is recommended to add a CDK4/6 inhibitor (IBRANCE[palbociclib], KISQALI [ribociclib] or VERZENIOS

* This summary does not cover this indication.

[abemaciclib]), despite a lack of evidence to date of a benefit in terms of overall survival compared to a non-steroidal aromatase inhibitor alone. Tamoxifen remains a first-line option.

- In the presence of short-term life-threatening symptomatic visceral involvement, chemotherapy remains the conventional treatment.

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

For the treatment of locally advanced or metastatic HR+ / HER2- breast cancer, in the absence of short-term life-threatening symptomatic visceral involvement, for menopausal women, IBRANCE is a therapeutic option, in combination with letrozole as a first-line treatment for cases diagnosed at an advanced stage or late-onset progression (more than 12 months after the end of adjuvant treatment). However, the combinations with anastrozole or exemestane have no role in the therapeutic strategy in the absence of clinical data documenting their efficacy and safety.
The Committee raises the question of the clinical benefit of systematically adding a CDK 4/6 inhibitor to hormone therapy, from the first-line of treatment for metastatic cases, given the lack of evidence of a gain in overall survival or in quality of life and considering the increased adverse events, particularly haematological toxicity, with IBRANCE. No data suitable for establishing the optimal therapeutic sequence are available.

Clinical data

- The updated findings of a randomised, double-blind phase III trial, comparing the palbociclib/letrozole combination versus letrozole alone are available. Previously, only the primary analysis had been assessed.
- In this trial, evidence was obtained of the superiority of palbociclib vs letrozole in terms of progression-free survival evaluated by the investigator (primary endpoint): 24.8 months versus 14.5 months, or an absolute gain of 10.3 months: HR = 0.576 95%CI [0.463; 0.718] p< the envisaged threshold of. The follow-up analyses with a longer follow-up period but not envisaged in the protocol provided by the pharmaceutical company are consistent with the primary analysis. The overall survival data are not available to date.
- No data for non-menopausal women in this indication and no data in combination with exemestane or anastrozole are available.
- The safety profile of palbociclib remains marked by a high risk of myelosuppression and in particular neutropenia. In clinical trials, 77% of patients treated with palbociclib experienced a grade 3 or 4 adverse event (especially severe neutropenia) versus 24% of patients treated with letrozole or fulvestrant alone. A pharmacovigilance investigation has been in place since October 2018 for palbociclib.

Specific prescribing conditions

- Hospital prescription and reserved for oncology and medical oncology specialists and departments.

Benefit of the medicinal product

- The actual clinical benefit* of IBRANCE for menopausal women with no short-term life-threatening symptomatic visceral involvement is:
  - <u>high</u> in combination with letrozole for women not pre-treated for the advanced stage of the disease and not having received a non-steroidal aromatase inhibitor (letrozole or anastrazole) as in the context of adjuvant treatment within the previous 12 months
  - <u>insufficient</u> in combination with anastrozole or exemestane to justify public funding coverage.
- The actual clinical benefit* of IBRANCE for non-menopausal women and/or those with short-term life-threatening symptomatic visceral involvement is insufficient to justify public funding cover.

- IBRANCE provides minor clinical added value** (CAV IV) compared to letrozole alone.
- Approval for maintaining reimbursement for non-hospital and hospital treatment within a restricted indication.

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This document was drafted on the basis of the Transparency Committee opinion dated 20 March 2019 (CT-17010)
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"