HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
January 2018

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KISQALI (ribociclib), protein kinase inhibitor (CDK 4/6)

High clinical benefit but no proven clinical added value with respect to the first-line therapeutic strategy for advanced metastatic HR+/HER2- breast cancer, in menopausal women, in the absence of short-term life-threatening symptomatic visceral involvement.

Insufficient clinical benefit to justify reimbursement in combination with anastrozole or exemestane and/or in the presence of short-term life-threatening symptomatic visceral involvement.

Main points

- KISQALI has been granted a marketing authorisation in combination with an aromatase inhibitor for the initial hormone therapy-based treatment of menopausal women with advanced hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer.
- In exchange for a higher toxicity in terms of neutropoenia, hepatobiliary and cardiac disorders, adding ribociclib to letrozole prolongs the median progression-free survival by 9.3 months (25.3 months in the letrozole + ribociclib group versus 16 months in the letrozole + placebo group) in menopausal female patients previously untreated for advanced-stage breast cancer and not having received aromatase inhibitor as part of adjuvant therapy in the previous 12 months. No gain in overall survival or in quality of life has been demonstrated to date.
- It is not possible to determine the benefit and clinical added value of ribociclib in the context of a combination other than with letrozole and/or in cases of short-term life-threatening symptomatic visceral involvement failing efficacy and safety data.

Therapeutic strategy

- The choice of systemic treatment for locally advanced or metastatic breast cancer 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 tolerance, metastatic disease presentation and the time to onset of 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 for metastatic cases unless they were previously administered as part of adjuvant therapy discontinued less than 12 months previously. Recently, the CDK 4/6 inhibitor, palbocicib, notably confirmed its benefit as a first-line treatment for metastatic cases (in combination with letrozole) or as a second-line treatment (in combination with fulvestrant). No data suitable for establishing the optimal therapeutic sequence are available.
- In the presence of short-term life-threatening symptomatic visceral involvement, the therapeutic strategy is based on chemotherapy.

Role of the medicinal product in the therapeutic strategy

- KISQALI is a treatment option for the first-line treatment of metastatic cases of HR+ and HER2- breast cancer, following diagnosis at such an advanced stage or in cases of late-onset recurrence. Systematically adding a CDK4/6 inhibitor to letrozole, from the first-line treatment of metastatic cases, raises questions.
- If the combination of a CDK4/6 inhibitor with letrozole is envisaged, on a case-by-case basis, the choice between palbociclib and ribociclib should take into account the hepatic and cardiac safety profile of KISQALI involving precautions for use (see SPC of KISQALI).

KISQALI has no role in the treatment of HR+/HER2- breast cancer, in menopausal women, in combination with anastrozole or exemestane and/or in cases of short-term life-threatening symptomatic visceral involvement, failing clinical data.

Clinical data

- The assessment of ribociclib is based on a double-blind phase III study comparing ribociclib (administered per os at a dose of 600 mg per day for 21 consecutive days followed by a 7-day interval) in addition to letrozole (at a dose of 2.5 mg once daily for 28 days) versus letrozole alone in 668 menopausal female patients previously untreated for advanced-stage breast cancer and not having received an aromatase inhibitor as part of adjuvant therapy in the 12 months prior to randomisation. Over one third (34%) were newly diagnosed at the metastatic stage and the other two thirds (66%) were diagnosed with late-onset recurrence post-adjuvant therapy (441/668).
- The superiority of adding ribociclib to letrozole over letrozole alone was demonstrated on the median progression-free survival determined by the investigator (primary endpoint) during an intermediate analysis. With an additional 11.1 months of follow-up, the median progression-free survival was 25.3 months in the letrozole + ribociclib group and 16 months in the letrozole + placebo group, HR=0.57 $CI_{95\%}$ [0.46; 0.70]; $p=9.63x10^{-8}$ (below the envisaged threshold of $1.29x10^{-5}$ for the final analysis). No difference was demonstrated in terms of overall survival (ranked secondary endpoint) between the two groups in the first two intermediate analyses. The exploratory quality-of-life analysis suggests a lack of difference between the two groups.
- Adverse events were more frequent in the letrozole + ribociclib group than in the letrozole alone group, particularly:
  - adverse events resulting in treatment discontinuation: 15% versus 3%,
  - adverse events of grades ≥ 3: 81.2% versus 32.7%; essentially: neutropoenia (48.2% versus 0.6%), hypertension (9.9% versus 9.9%), increased ALAT and/or ASAT (15% versus 2.4%),
  - adverse events requiring dose interruption (71.3% versus 14.8%) or dose reduction (44.6% versus 3%). The high risks identified in the Risk Management Plan (RMP) are myelosuppression, hepatobiliary toxicity and cardiac toxicity with QT prolongation.

Special prescription requirements

- Hospital prescription reserved for oncology and medical oncology specialists.
- Medicinal product requiring special monitoring during treatment.

Benefit of the medicinal product

- The actual clinical benefit* of KISQALI for its indication is:
  - <u>in combination with letrozole</u>:
    - high in the absence of short-term life-threatening symptomatic visceral involvement;
    - insufficient in the presence of short-term life-threatening symptomatic visceral involvement;
  - <u>in combination with anastrozole or exemestane</u>: insufficient.
- Adding KISQALI to letrozole does not provide any clinical added value** (CAV V) for the first-line therapeutic strategy of metastatic cases of HR+/HER2- breast cancer in menopausal women, not having received a non-steroidal aromatase inhibitor (letrozole or anastrazole) as part of adjuvant therapy in the previous 12 months, in the absence of short-term life-threatening symptomatic visceral involvement.
- Approval for non-hospital pharmacy reimbursement and for hospital treatment within a restricted scope.

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This document was drafted on the basis of the Transparency Committee opinion dated 31 January 2018 (CT-16471)
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".