HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
27 MAY 2020

The legally binding text is the original French opinion version

trastuzumab emtansine

KADCYLA 100 and 160 mg powder for concentrate for solution for infusion

New indication

Key points

Favourable opinion for reimbursement in the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

What therapeutic improvement?

Therapeutic improvement compared to trastuzumab in the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

Role in the care pathway?

The treatment of early breast cancer may be based on surgery, radiotherapy, chemotherapy (neoadjuvant and/or adjuvant) and hormone therapy, depending on the tumour type and grade, axillary lymph node involvement and the existence of hormone receptors.

When conservative surgery is impossible or if the patient is inoperable immediately, neoadjuvant systemic treatment (before surgery) aimed at reducing the tumour size and hence optimising the

chances of breast conservation may be initiated if the patient so desires. This treatment concerns the locally advanced stage (including inflammatory) or the early stage with a tumour measuring more than 2 cm in diameter.

After surgery, the over-expression of HER2 receptors warrants initiation of systematic adjuvant treatment, irrespective of the stage of the resected tumour. The adjuvant treatment of HER2-positive early breast cancer is generally based on anthracycline-based chemotherapy followed by taxane-based chemotherapy combined with targeted therapy with trastuzumab. At the end of the first chemotherapy cycle, treatment with trastuzumab should be maintained as single-agent maintenance therapy for 1 year.

ESMO 2019 and NCCN 2020 guidelines now differentiate between two clinical situations after the administration of neoadjuvant therapy:
- in the absence of residual disease (patients having obtained a pathological complete response or pCR) after neoadjuvant therapy or in the absence of neoadjuvant therapy: HER2-targeted therapy (trastuzumab ± pertuzumab) is continued for up to 1 year;
- in the event of residual disease (patients not having obtained a pathological complete response or non-pCR) after neoadjuvant therapy: monotherapy with trastuzumab emtansine.

Role of the medicinal product in the care pathway

In view of demonstration of the superiority of KADCYLA (trastuzumab emtansine) compared to trastuzumab with respect to a clinically relevant endpoint in an adjuvant therapy context: invasive disease-free survival, and despite increased toxicity, KADCYLA (trastuzumab emtansine) represents an alternative to trastuzumab only in the event of residual invasive disease (patients not having obtained a pathological complete response or non-pCR) after neoadjuvant taxane-based and HER2-targeted therapy, in accordance with the patient eligibility criteria in the pivotal study.

In the absence of specific clinical data in other situations, in particular the absence of residual invasive tumour or stage T1a/bN0 tumour before neoadjuvant chemotherapy, the benefit of KADCYLA (trastuzumab emtansine) has not been established and KADCYLA (trastuzumab emtansine) is not an alternative to trastuzumab in these specific situations.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ HER2-positive early breast cancer is a serious, life-threatening disease.
◗ This is a specific curative treatment for breast cancer with HER2 receptor amplification.
◗ The efficacy/adverse effects ratio is high.
◗ There is a medicinal alternative: trastuzumab.
◗ This medicinal product is a first-line drug in the adjuvant treatment of HER2-positive early breast cancer in the presence of residual invasive disease, in the breast and/or lymph nodes, and after neoadjuvant taxane-based and HER2-targeted therapy (see section 10 Role in the care pathway).

Public health impact

Considering:

- the seriousness of the disease and its incidence,
- the medical need, which is considered to be partially met,
- the partial response to the identified need given the superiority demonstrated compared to current treatment with trastuzumab in terms of invasive disease-free survival, but without any demonstrated impact to date on mortality or quality of life in the absence of data with a demonstrative value,
- the transposability that is not guaranteed insofar as the patient profile is not completely identical that of French patients (see section 09.5 Summary and Discussion),
- the increased toxicity:
    - grade ≥ 3 adverse events: 25.7% vs. 15.4%;
    - adverse events having led to treatment discontinuation: 18.0% vs. 2.1%,
    - with, in particular, the following important identified risks: interstitial lung disease / acute respiratory distress syndrome, hepatic toxicity, nodular regenerative hyperplasia (NRH) of the liver, infusion-related reaction / hypersensitivity, left ventricular dysfunction, thrombocytopenia and peripheral neuropathy
- the absence of assessment of the impact of administration of KADCYLA (trastuzumab emtansine) by the IV route on the organisation of care in a context in which trastuzumab is also available by the SC route,

KADCYLA (trastuzumab emtansine) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of KADCYLA (trastuzumab emtansine) by the IV route is substantial in the new MA indication, i.e., "as a single agent, in the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy".

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages.

Clinical Added Value

Considering:

- **demonstration of the superiority of KADCYLA (trastuzumab emtansine) compared to the standard treatment, trastuzumab, in terms of invasive disease-free survival with a significant improvement for this clinically relevant endpoint (HR = 0.50 $IC_{95\%}$ [0.39; 0.64]; p <0.0001) in a phase III open-label study,**

and despite:

- **the immaturity of overall survival data, preventing a conclusion being reached with respect to a benefit of KADCYLA (trastuzumab emtansine) compared to trastuzumab for this endpoint,**

- **the additional toxicity compared to trastuzumab with, in particular, more grade ≥ 3 adverse events (25.7% vs. 15.4%) or adverse events having led to treatment discontinuation (18.0% vs. 2.1%) and important identified risks (including hepatotoxicity, thrombocytopenia, bleeding events and peripheral neuropathy),**
- **the absence of any data on quality of life with a demonstrative value,**

the Committee considers that KADCYLA (trastuzumab emtansine) provides a moderate clinical added value (CAV III) compared to trastuzumab in the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.