

pertuzumab (PERJETA°) after surgery for some breast cancers at high risk of recurrence

NOT ACCEPTABLE

Pertuzumab compared to placebo: survival rate the same and risk of invasive disease almost unchanged, but a higher risk of adverse effects, in particular heart failure.

PERJETA° - _pertuzumab_ concentrate for solution for intravenous infusion

- **420 mg** of *pertuzumab* (30mg/ml) per 14 ml vial

antineoplastic; anti-HER2 monoclonal antibody

New indication: *"in combination with trastuzumab and chemotherapy in (...) the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence".* [EU centralised procedure]

In women with non-metastatic breast cancer, surgical excision is the standard treatment. Adjuvant chemotherapy, i.e. after surgery, is often proposed, in order to prolong survival or reduce the risk of local recurrence and metastasis. When the tumour over-expresses the HER2 protein, addition of *trastuzumab* (a monoclonal antibody with anti-HER2 activity) to adjuvant chemotherapy prolongs survival (1,2).

Pertuzumab (Perjeta°, Roche) is another monoclonal antibody with anti-HER2 activity. In the neoadjuvant setting, i.e. before surgery, it has an unfavourable harm-benefit balance (2). *Pertuzumab* has also been authorised for use in the adjuvant setting, in addition to *trastuzumab* and chemotherapy, in women with non-metastatic breast cancer overexpressing HER2 protein and at high risk of recurrence (3).

In this setting, a randomised, double-blind trial (Aphinity) evaluated *pertuzumab* versus placebo as an addition to the combination of *trastuzumab* + chemotherapy in 4805 patients (almost exclusively women). The risk of recurrence was considered to be high, mainly because of lymph node involvement or absence of hormone receptors on the tumour cells (3-5). In about 80% of patients, adjuvant chemotherapy mainly comprised an anthracycline (3). After a median follow-up of at least 45 months, mortality was about 3.5% in both groups (3,4). The proportion of patients alive without invasive disease (the primary endpoint) after 3 years was 94% in the *pertuzumab* group versus 93% in the placebo group (p=0.0446) (3-5).

The adverse effect profile of *pertuzumab* mainly includes heart failure, diarrhoea, skin and mucous membrane disorders (including mucositis and skin rashes), and hypersensitivity reactions, which were reported in the Aphinity trial (2,6). As had been observed in the neoadjuvant setting, combining *pertuzumab* with *trastuzumab* increased the incidence of symptomatic heart failure, which was reported in 0.6% of patients versus 0.2% of those not receiving *pertuzumab*. Cardiac disorders disappeared in about 46% of patients in the *pertuzumab* group versus 66% in the placebo group, after a median period of 27 weeks and 16 weeks respectively (2,3). Since *pertuzumab* has been marketed, rare cases of tumour lysis syndrome have been reported (7).

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Literature search up to 11 July 2019

In response to our request for information, Roche provided us with published articles, administrative documents and packaging items.

1- Prescrire Editorial Staff "Adjuvant trastuzumab for breast cancer. Longer follow-up confirms improved overall survival" *Prescrire Int* 2012; **21** (133): 285-287.

2- Prescrire Editorial Staff "Pertuzumab before breast cancer surgery. Co-administered with trastuzumab: no benefit but more adverse effects" *Prescrire Int* 2017; **26** (184): 176-177.

3- EMA - CHMP "Public assessment report for Perjeta. EMEA/H/C/002547/II/0034" 26 April 2018: 120 pages.

4- von Minckwitz G et al. "Adjuvant pertuzumab and trastuzumab in Early HER2-positive breast cancer" *N Engl J Med* 2017; **377** (2): 122-131.

5- HAS - Commission de la transparence "Avis-Perjeta" 5 June 2019: 22 pages.

6- Prescrire Rédaction "pertuzumab" Interactions Médicamenteuses Prescrire 2019.

7- EMA "Perjeta. Procedural steps taken and scientific information after the authorisation" 15 April 2019: 13 pages.

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