Translated from ***Rev Prescrire*** **September 2014; 34 (371): 656**

trastuzumab emtansine

An inadequately assessed combination of two cytotoxic drugs

Abstract

● There is no consensus on second-line treatment for women with metastatic or locally advanced breast cancer overexpressing HER-2 protein in whom treatment with a taxane + *trastuzumab* has failed. *Capecitabine* is one option. Adding *lapatinib* does not prolong survival.

● *Trastuzumab emtansine* (Kadcyla°, Roche) has received EU marketing authorisation for use in this setting. It consists of two covalently bound drugs: *trastuzumab*, a monoclonal antibody that binds to HER-2 receptors, and *DM1*, a cytotoxic microtubule inhibitor. *DM1* is derived from *maytansine*, a cytotoxic drug abandoned in the 1980s because it proved to be too toxic after systemic administration.

● Clinical evaluation of *trastuzumab emtansine* is based on an unblinded trial versus *capecitabine* + *lapatinib* in 991 patients. The use of *lapatinib* in all patients in the control group is questionable. An interim analysis suggested that overall survival was about 6 months longer with *trastuzumab emtansine* (30.9 versus 25.1 months).

● In addition to the adverse effects of *trastuzumab* (thrombocytopenia, heart failure, etc.), *trastuzumab emtansine* causes frequent and potentially life-threatening hepatic toxicity, peripheral neuropathy, and urinary tract infections. *Trastuzumab emtansine* appears to be less toxic to the skin and mucous membranes than the *capecitabine* + *lapatinib* combination.

● *DM1* is metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP3A5 and is also a P-glycoprotein substrate, creating a potential risk of multiple pharmacokinetic interactions.

● *Trastuzumab emtansine* appears to be teratogenic and embryotoxic.

● The international nonproprietary name of this drug is easily confused with *trastuzumab*.

● In practice, it is best to at least wait for the full results of the only available comparative trial of *trastuzumab emtansine* before drawing conclusions about its harm-benefit balance and its possible use if it represents a real therapeutic advance.

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JUDGEMENT RESERVED

In women with metastatic or locally advanced breast cancer overexpressing HER-2 protein in whom a first line of treatment including a taxane and *trastuzumab* has failed, the full results of a trial comparing *trastuzumab emtansine* versus the *capecitabine* + *lapatinib* combination are not yet available. It would be advisable to await these results, as an interim analysis showing a survival advantage of about 6 months provides weak evidence. In addition, more information is needed on the risk of thrombocytopenia and hepatic toxicity. Meanwhile, treatment with *capecitabine* or another better-known cytotoxic drug is a less risky option.

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trastuzumab emtansine

powder to be diluted for IV infusion

KADCYLA°

- **100** or **160 mg** of *trastuzumab emtansine* per vial

cytotoxic drug; anti-HER-2 antibody

■ **Indication:** *"(…) as a single agent (…) for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:*
– received prior therapy for locally advanced or metastatic disease, or
– developed disease recurrence during or within six months of completing adjuvant therapy".
[EU marketing authorisation, centralised procedure]

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

PRESCRIRE'S RATINGS

Our judgement is based on the therapeutic advance of the new product.
It considers not only the inherent value of each product in terms of its risk-benefit balance, but also its advantages and disadvantages relative to existing products available in France. Note that the relative value of new products can vary from one country to another.

BRAVO: The product is a major therapeutic advance in an area where previously no treatment was available.

A REAL ADVANCE: The product is an important therapeutic innovation but has certain limitations.

OFFERS AN ADVANTAGE: The product has some value but does not fundamentally change the present therapeutic practice.

POSSIBLY HELPFUL: The product has minimal additional value, and should not change prescribing habits except in rare circumstances.

NOTHING NEW: The product may be a new substance but is superfluous because it does not add to the clinical possibilities offered by previous products available. In most cases it concerns a me-too product.

JUDGEMENT RESERVED: The editors postpone their rating until better data and a more thorough evaluation of the drug are available.

NOT ACCEPTABLE: Product without evident benefit but with potential or real disadvantages.

Quality of information from pharmaceutical companies

In response to our systematic requests

Company provided detailed information including unpublished data and packaging items.

Company provided information limited to administrative and published data.

Company provided minimal information, mainly administrative data.

Company provided no information.

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