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 over-expressing 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 original 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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**trastuzumab emtansine**

| 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.

**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 emtansine** 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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**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. 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.

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**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.