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 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 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.

**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)]

**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.