

## Trastuzumab in combination with metronomic cyclophosphamide and methotrexate in patients with HER-2 positive metastatic breast cancer

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Received June 12, 2006; Accepted September 15, 2006.

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### ABSTRACT

#### Background

HER2/*neu* overexpression is linked to promotion of angiogenesis in breast cancer. We therefore tested the activity of the combination of Trastuzumab with metronomic, low dose chemotherapy with cyclophosphamide (CTX) and methotrexate (MTX) in metastatic breast cancer (MBC).

#### Methods

Between April 2002 and June 2005, twenty-two patients with metastatic breast cancer with the presence of overexpression or amplification of HER2-*neu*, all pre-treated with trastuzumab plus other cytotoxics, were treated with trastuzumab (6 mg/kg every three weeks) in combination with metronomic chemotherapy (MTX 2.5 mg, bid on Day 1 and Day 4 every week) and CTX (50 mg daily) (CM).

#### Results

The 22 enrolled patients are evaluable: most had an ECOG performance status of 0 (17 pts), and all were pre-treated with chemotherapy for metastatic disease; 14 had progressive disease at study entry, and 11 had progressive disease during the last trastuzumab therapy. Metastatic sites included: lung (5 pts), liver (14 pts), bone (12 pts), lymph nodes (8 pts), central nervous system (CNS) (9 pts). We observed 4 partial remission (PR) (18%, 95% CI 5–40%), 10 stable disease (SD) (46%, 95% CI 24–68%), and 8 PD (36%, CI 17–59%). The clinical benefit (RP plus RC plus SD for  $\geq 24$  weeks) in all pts and in pts with disease resistant to previous trastuzumab therapy were 46% (95% CI, 24–68%) and 27% (95% CI, 6–61%), respectively. Median time to progression was 6 months and median duration of treatment was 5 months (range, 0.7 to 18.4 months and range, 1 to 18 months, respectively). Overall clinical toxicity was generally mild. Grade  $\geq 2$  reversible liver toxicity and leukopenia were reported in 5 and 3 pts, respectively.

#### Conclusion

The combination of trastuzumab and metronomic chemotherapy is effective and minimally toxic in advanced breast cancer patients. The efficacy observed in patients with disease resistant to trastuzumab supports the need of larger trial to confirm a role of this combination to delay acquired trastuzumab resistance.