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Trastuzumab Improves the Efficacy of Chemotherapy in Breast Cancer Treatment beyond Progression

The GBG 26 – TBP study of the German Breast Group addressed the question of whether the treatment of women with HER2-positive metastatic breast cancer with trastuzumab is effective beyond progression (Trastuzumab Beyond Progression TBP). In this study, women with metastatic HER2-positive breast cancer

who had progressed on prior trastuzumab treatment were treated either with a combination of trastuzumab (Herceptin®, Roche Pharma AG, Grenzach-Whylen, Germany) and capecitabine (Xeloda®, Roche Pharma AG) or capecitabine alone.

The primary objective of the study was to find out whether the continuation of trastuzumab treatment beyond progression could improve the efficacy of chemotherapy, in this case capecitabine, and hence progression of the disease would occur significantly later than with capecitabine therapy alone.

Further endpoints were response rate, duration of response, clinical benefit, side effects and overall survival of treatment with capecitabine with or without continuation of trastuzumab.

Between January 2004 and May 2007, 156 patients in total were included in the study, of whom 78 received the combination of trastuzumab and capecitabine and 78 received capecitabine monotherapy.

The results clearly demonstrate that the efficacy of capecitabine is significantly increased by continuing trastuzumab treatment:

- Median time to progression was increased from 5.6 to 8.2 months (hazard ratio 0.69; $P = 0.0338$) (fig. 1).
- Response rate was increased from 27% with capecitabine alone to 48.1% with capecitabine and trastuzumab (odds ratio = 2.50; $P = 0.0115$).
- Clinical benefit rate, which includes complete or partial responses and stable disease > 24 weeks was increased from 54.1 to 75.3% (odds ratio = 2.59; $P = 0.0068$).

Fig. 1. Time to disease progression. Product-limit survival estimates with number of subjects at risk. X = Capecitabine, XH = X + trastuzumab.

Fig. 2. Overall survival. Product-limit survival estimates with number of subjects at risk. X = Capecitabine, XH = X + trastuzumab.

- Duration of response was comparable between both treatment groups (3.4 and 3.9 months, respectively) (hazard ratio = 1.08; $P = 0.8159$).
- The follow-up period of 15.6 months is still too short to evaluate overall survival, however a positive trend for overall survival was observed, with an increase from 20.4 to 25.5 months in favour of the continuation of trastuzumab (hazard ratio 0.76; $P = 0.257$) (fig. 2).

The tolerability of capecitabine did not change by continuation of trastuzumab treatment. Only lower-grade, clinically non-relevant anemia was observed more often in the combination arm (64% vs. 41.6%, $P = 0.02$). Only 1 patient in the capecitabine plus trastuzumab arm experienced cardiac dysfunction. No therapy-related deaths occurred.

The GBG 26 study is the only randomized study worldwide that has prospectively demonstrated the efficacy of trastuzumab treatment beyond disease progression.

The first evidence for the effectiveness of trastuzumab treatment beyond disease progression was obtained from pre-clinical studies, which led to the frequent use of trastuzumab in this setting in clinical practice. Several non-randomized studies with women who had received prior trastuzumab treatment have already provided preliminary evidence for an increase in efficacy by continuing trastuzumab therapy. Due to the retrospective nature of these studies, however, the results might be biased by patient selection. Only the prospective, randomized GBG 26 – TBP study enables a definitive recommenda-

tion of continued treatment of trastuzumab beyond progression now.

The GBG 26 study was conducted by the German Breast Group in international collaboration with study groups and centers in Austria, The Netherlands, and Slovenia, Denmark and Great-Britain. The results of the study were presented by Prof. Dr. Gunter von Minckwitz on behalf of the study group at the European Society of Medical Oncology conference (ESMO) in Stockholm on September 14, 2008. For further information contact: tbp@germanbreastgroup.de

About GBG

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