Trastuzumab treatment beyond progression in patients with HER2 positive metastatic breast cancer - interim report

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Background

Change of treatment in the situation of disease progression is considered as a general principle in oncology. It is so far unknown, if this holds true for targeted, non-cytotoxic treatments like the humanized antibody against HER2 trastuzumab. Preclinical data indicate that trastuzumab is effective against tumor cell proliferation as long as it is present, whereas trastuzumab withdrawal results in rapid tumor cell regrowth. [1] In an adjuvant study of patients with the trial protocol by Stavem et al. at 93 patients of the 230 pts in the trastuzumab arm received another therapy while continuing trastuzumab (18%) with chemotherapy, 24% as monotherapy. The duration of response was 6.7 months and 22% of the patients had a clinical benefit with acceptable toxicity [2]. Two retrospective analyses support the use of trastuzumab beyond progression. In a recent trial by Geyer et al. at the principle of continuing the AND HER-therapy with capcitabine in combination with capcitabine proved to be superior with the capcitabine. [3] The TBP trial is a prospectively randomized phase II study, designed to assess the time to progression in patients who are treated beyond progression with trastuzumab and capcitabine compared to capcitabine alone. Capcitabine was chosen because of its objective response rates of 20–25% with a median time to progression of 6 months in metastatic breast cancer patients. The combination of capcitabine and trastuzumab has been tested in a pilot study with promising efficacy results and a beneficial side-effect profile. [4]

Materials & Methods

Patients (pts) with pathologically confirmed, HER2 positive, locally advanced or metastatic breast cancer were stratified by type of previous therapy (taxane and trastuzumab) given to the patient. Treatment notice was confirmed by a written informed consent. Preclinical data with using 20–60% in the previously randomized patients. Patients were randomized to receive either capcitabine (2500 mg/m²) on days 1-14, q21 or the same capcitabine dose simultaneously to a continuation of study participation had to be less than 6 weeks. 2. 6 weeks was planned to recruit 214 pts per arm to show an improvement from 4 to 5.1 months (hazard ratio 0.8) by continuing treatment with trastuzumab (XH) 6 mg/kg body weight every 3 weeks. Trastuzumab-free interval before study participation had to be less than 6 months. Therefore, the trial protocol by Stavem et al. was chosen because of its objective response rates of 20–25% with a median time to progression of 6 months in metastatic breast cancer patients. The combination of capcitabine and trastuzumab has been tested in a pilot study with promising efficacy results and a beneficial side-effect profile. [4]

Primary objective: To compare the time to disease progression in patients with HER2 positive metastatic breast cancer beyond progression after previous treatment with trastuzumab randomized to capcitabine alone or in combination with trastuzumab.

Secondary objectives:

1. To compare the clinical benefit defined as CR, PR, or stable disease ≥ 24 weeks
2. To evaluate the safety of the capcitabine and trastuzumab combination
3. To compare overall survival between the two arms

Results

Between (2124 and 2591) pts (78 pts in arm X and 78 pts in XH) were randomized in the TBP trial. 111 pts had a pre-treatment with a taxane/trastuzumab combination as first-line treatment. 3. 3.4% of pts had other severe cardiac events (1x neutropenia, 1x severe anemia and 2x in arm XH). Hemorrhage toxicity was detected in 28.6% in arm X and in 32.8% in arm XH, no severe thrombocytopenia was documented. Also no fatal neuropathy occurred in both therapy arms. Relevant non-hematological toxicities (grade 3/4 in %) were vomiting 0.1/1.6%, diarrhoea 20.0/14.8%, mucositis 31.5/1.6%, hand-foot-syndrome (HFS) 23.9/31.1%, nail change 2.0/4.3%, myalgia 4.0/4.9% and allergy 3.0% /3.3% as shown in figure 2.

Conclusions

This interim report shows that:

1. Treatment with trastuzumab beyond progression in addition to capcitabine had numerically less events of tumor progressions (48 versus 53) and deaths (26 versus 31).
2. Combined treatment with trastuzumab and capcitabine reached a response rate of 43.8% and a median OS of 20.3 months in arm XH.

References


Table 1: Patients characteristics of treatment groups

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median age (in years)</th>
<th>Karnofsky Index</th>
<th>Menopausal Status</th>
<th>pT at 1st diagnosis</th>
<th>pN at 1st diagnosis</th>
<th>Grade at 1st diagnosis</th>
<th>Hormone receptor status</th>
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<tbody>
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<td>100</td>
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<td>gT1</td>
<td>gN1</td>
<td>G2/G3</td>
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</tr>
<tr>
<td>XH</td>
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<td>premenopausal</td>
<td>gT1</td>
<td>gN1</td>
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</tbody>
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Table 2: Overall survival (OS)

<table>
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<tr>
<th>Arm</th>
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<td>19.9</td>
</tr>
<tr>
<td>XH</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Figure 1: Study design

Figure 2: Severe toxicities (grade 3-4 in % pts)

Figure 3: Progression-free survival (PFS)

Figure 4: Overall survival (OS)