Abstract # PO 141

SUCCESSFUL USE OF HER2-TARGETED AGENTS IN PATIENTS WITH HEAVILY PRETREATED HER2-NEGATIVE METASTATIC BREAST CANCER PRESENTING WITH ELEVATED SERUM LEVELS OF THE HER2 EXTRACELLULAR DOMAIN AND/OR HER2 OVEREXPRESSING CIRCULATING TUMOR CELLS

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INTRODUCTION

- Approximately 20% of breast cancer (BC) patients (pts) are considered to have HER2-positive (HER2+) disease.
- Recently HER2-positivity is defined as overexpression of the HER2 protein by immunohistochemistry (IHC; DAKO score 3+) or amplification of the HER2 gene of chromosome 17 by in-situ hybridization (ISH; HER2 : CEP17 > 2.0) [Wolff et al. 2013].
- A considerable of proportion of HER2-negative (HER2-) pts with metastatic BC (MBC) may present with elevated serum levels of the HER2 extracellular domain (sHER2) and/or HER2 overexpressing circulating tumor cells (CTCs) during their further clinical course [Lipton et al., 2005].
- These “occult” HER2+ pts may be candidates for anti-HER2 targeted therapy (Tx) albeit normally not subjected to such treatment [Ardavanis et al., 2008].
- Results of large-scaled clinical trials such as DETECT-III which have been set up to address this issue are still lacking.
- This observational study was initiated to gain more insights into the feasibility of HER2-directed Tx in pts with tissue HER2- MBC with elevated sHER2 levels and/or HER2+ CTCs in the clinical routine.

METHODS

- 30 pts with heavily pretreated HER2- MBC (ER+, n=26) were included. The majority had visceral or mixed visceral disease. Pts had failed a median of 7 prior systemic treatments (range 1-16). Patients characteristics are summarized in Table 1.
- sHER2 was measured by a commercial chemiluminescence immunoassay (Siemens Healthcare Diagnostics, Eschborn, Germany). sHER2-positivity (sHER+) was defined as two consecutive sHER2 levels > 15 ng/mL determined within 4 weeks (wks)
- CTCs were determined by using the CellSearch™ technology (Veridex, Raritan, NJ, USA) which allows for simultaneously measuring HER2 overexpression by immuno-fluorescence. HER2-positivity was defined as the presence of at least one HER2+ CTC in 7,5 mL blood tested in duplicates.
- 8 pts were sHER2+ only, 7 had HER2+ CTCs and 15 pts were positive for both sHER and HER2 overexpressing CTCs.
- All pts received anti-HER2 Tx with trastuzumab (H; n=18), lapatinib (L; n=4), H+L (n=2), or H+pertuzumab (H+P; n=6). HER2-targeted Tx was given alone (n=5), or in combination with endocrine agents (n=5), cytotoxics (n=17), or other targeted drugs (n=3).
- Responses were scored according to RECIST 1.1.
- Treatment duration was defined as the time between start of Tx and the cessation of the particular anti-HER2 regimen, death or loss to follow-up.
- Overall survival (OS) was calculated from the start of anti-HER2 Tx and death from any reason or loss to follow-up by using Kaplan-Meier statistics.

RESULTS

- Anti-HER2 Tx was generally well tolerated. In two pts with L and one pt with H+L, anti-HER Tx was prematurely stopped due to toxicity (diarrhea, fatigue).
- Median treatment duration was 16.1 wks, range: 1-72.9 wks (Figure 1A).
- Whereas 6 pts (20%) had PD, 12 pts (40%) achieved PR and another 12 pts (40%) showed SD accounting for an objective response rate of 40% and a clinical benefit rate (CBR) of 80% (Table 2).
- Median OS was 76.1 wks , range: 1-187.9 wks (Figure 1B).
- In 25 pts, 9 with PR, 12 with SD, and 4 with PD, results of serial sHER measurements at baseline and after 3 wks of Tx were available. Percent sHER changes are illustrated in Figure 2.
- The majority of pts with PD showed increasing sHER levels.
- In the majority of pts with PR or SD, sHER decreased by more than 20% from baseline.
- 2 pts with PR, however, showed increasing sHER values. Interestingly, both these pts were treated with L.
- In 19 pts, 8 with PR, 7 with SD, and 4 with PD, repeated CTC counts at 6 from baseline were available (Figure 3).
- All pts with PD showed increasing CTCs counts.
- All pts with SD and PR presented with decreasing CTC values, most of them normalizing within 6 wks.

CONCLUSIONS

- Study limitation: small sample size.
- Strength: represents a real-world population of patients treated for “occult“ HER2-positive MBC.
- Confirms results of a previous study of trastuzumab-based therapy in HER2- MBC with elevated sHER2 levels.
- Anti-HER2 Tx may be valid option for heavily pretreated HER2- MBC with pathological sHER values and/or HER2+ CTCs.
- Most patients with PR and SD showed declining sHER2 levels. However two individuals responding to lapatinib presented with an sHER2 increase with may be due to a facilitated HER2 cleavage mediated by lapatinib.
- Serial CTC measurements may be the more accurate predictor of response to anti-HER2 treatment.
- Results of randomized phase III trials in “occult“ HER2+ MBC such as DETECT-III are eagerly awaited.

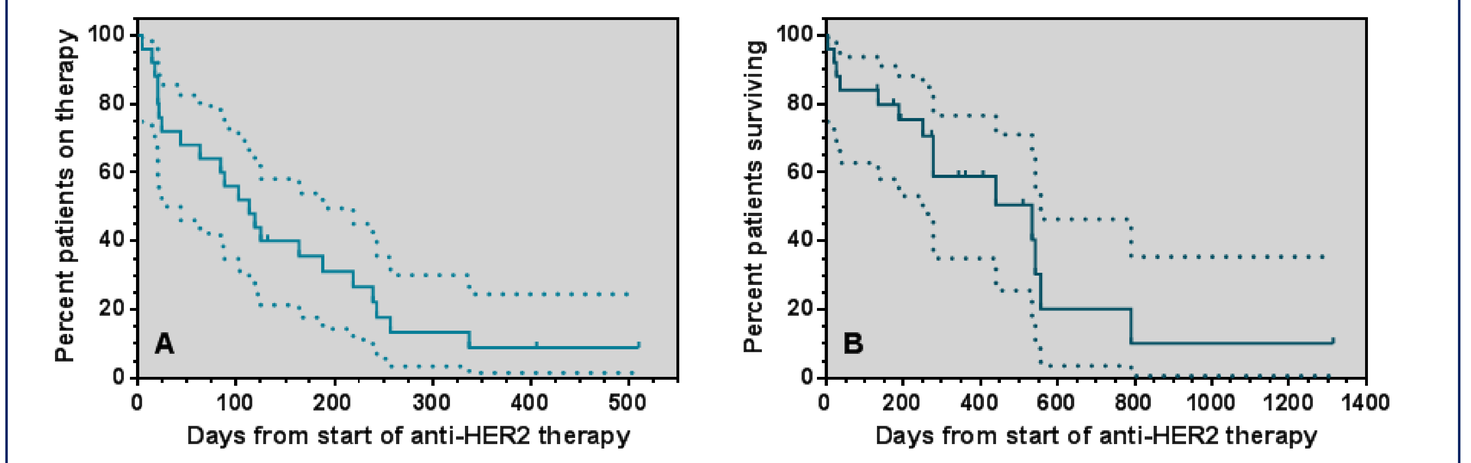

Figure 1: Kaplan-Meier plots showing (A) duration of and (B) overall survival after anti-HER2 therapy for pts with “occult“ HER2+ MBC. Dashed lines represent the 95% CI.

Table 1: Patients´ characteristics

Age	
Median	52.5
Range	35-84
Menopausal status	**n (%)**
Pre-/perimenopausal	8 (27)
postmenopausal	22 (73)
Estrogen receptor status	**n (%)**
positive	26 (87)
negative	4 (13)
Type of metastases	**n (%)**
Bone/soft tissue	8 (27)
Visceral	3 (10)
Mixed	19 (63)
No. of prior systemic treatments	
Median	7
Range	1-16
Type of anti-HER2 treatment	**n (%)**
Trastuzumab	18 (60)
Lapatinib	4 (13)
Trastuzumab + lapatinib	2 (7)
Trastuzumab + pertuzumab	6 (20)
Concomittant drugs	**n (%)**
None	5 (17)
Endocrine agents	5 (17)
Cytostatics	17 (57)
Anti-angiogenic agents	3 (10)

Table 2: Efficacy of anti-HER2 therapy

Response according to RECIST 1.1	**n (%)**
Complete remission (CR)	-
Partial remission (PR)	12 (40)
Stable disease (SD)	12 (40)
Progressive disease (PD)	6 (20)
Objective response rate (ORR)	12 (40)
Clinical benefit rate (CBR)	24 (80)
Duration of treatment	**Weeks**
Median	17.0
Range	1.0-72.9
Overall survival	**weeks**
Median	76.1
Range	1.0-187.9

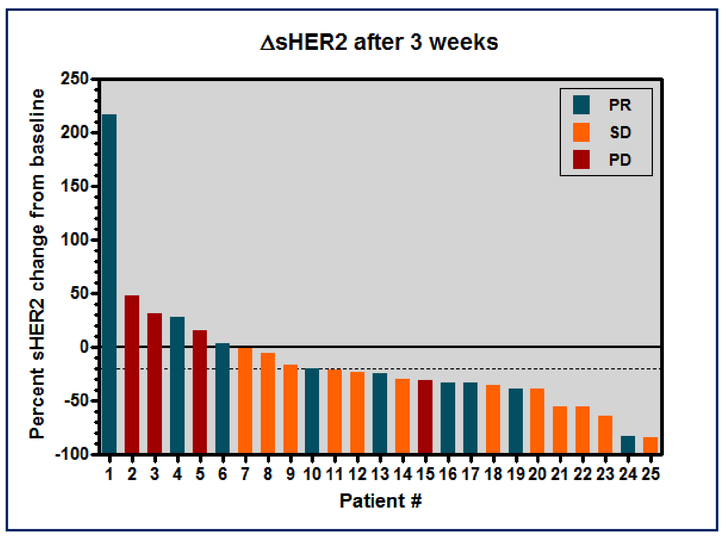

Figure 2: Waterfall plot demonstrating the relative sHER2 changes from baseline (ΔsHER2) after 3 weeks from start of treatment

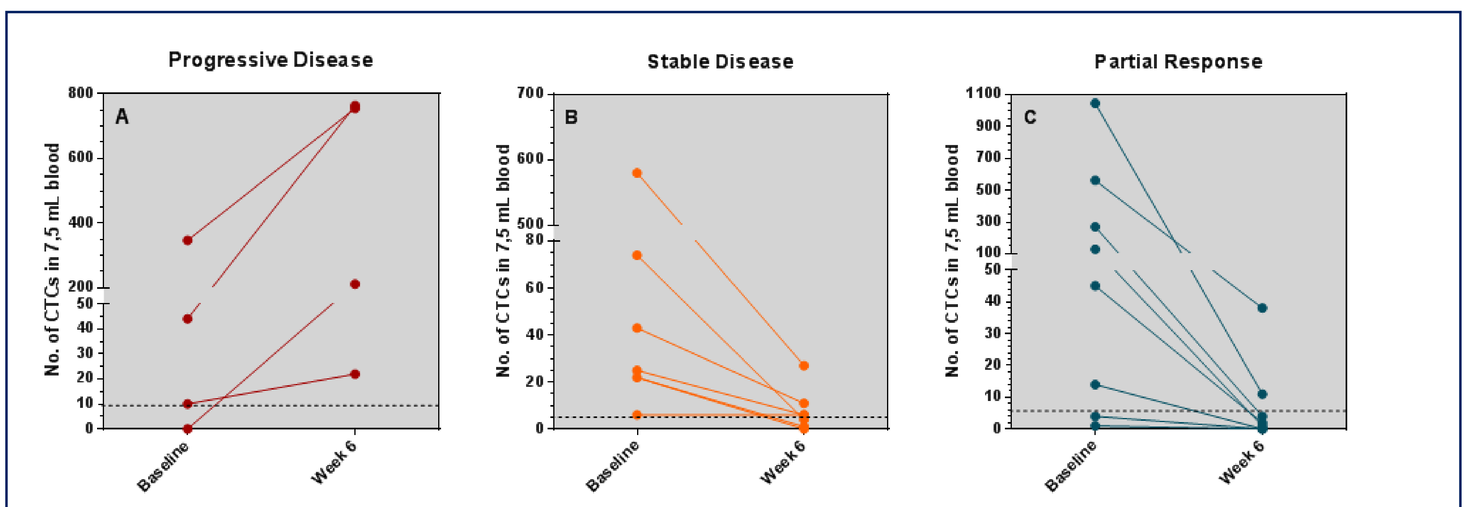

Figure 3: Absolute changes in CTC counts within 6 weeks from start of therapy; (A) patients with progressive disease, (B) patients with stable disease; (C) patients with partial response. It should be noted that all patients with PD had increasing CTC counts whereas all patients with SD or PR had decreasing and often normalized CTC counts

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