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 OVEREXPRESSION CIRCULATING TUMOR CELLS

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INTRODUCTION

• Approximately 20% of breast cancer (BC) patients (pts) are considered to have HER2-positive (HER2+)-positive disease.
• Recently HER2-positive 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 hybridisation (ISH; HER2 / CEP17 > 2.0) ( van'T Veer et al. 2013).
• A considerable 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).
• Those “occult” HER2+ pts may be candidates for anti-HER2 targeted therapy (Tx) albeit normally not subjected to such treatment (Aradvani et al., 2008).

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 summarised 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=3), or H+pertuzumab (H+P; n=4). HER2 targeted Tx was given alone (n=5), or in combination with endocrine agents (n=5), tyrosine kinases (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-HER2 Tx was prematurely stopped due to toxicity (diarrhea, fatigue).
• Median treatment duration was 16.1 wks, range: 1.7-29.9 wks (Figure 1A).
• 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.
• In all pts with PD 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 a valid option for heavily pretreated HER2- MBC with pathological sHER values and/or HER2+ CTCs.
• Most patients with PR and SD showed declining sHER levels. However two individuals responding to lapatinib presented with an sHER2 increase which 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.