X 1000 mg/m^2 bid (750 if greater than or equal to 65 years) days 1−14; H 4 mg/kg day 1 as a loading dose then 2 mg/kg i.v. weekly starting on day 8. Treatment was continued until progression or unacceptable toxicity.

Results: Fifty patients (pts) have been treated. At baseline median age was 53.5 years (18% greater than or equal to 65); 54% had received chemotherapy for early breast cancer, including anthracycline + taxane in 16%, anthracycline without taxane in 30%, and taxane without anthracycline in 2%. The majority of pts (82%) had visceral involvement. Median number of cycles given was 9. The median relative dose intensities were: H 96%, NVBo 75%, X 77%. NVBo dose was escalated to 80 mg/m^2 in 87% of pts. The objective response rate (RR) in 46 evaluable pts was 74%, including complete response in 13%. Disease was stabilised in a further 20%. Subpopulation analysis showed an 85% RR in 20 chemonaive pts, a 68% RR in 38 pts with visceral metastases, and a 65% RR in 26 pts with liver metastases. After median follow-up of 17.6 months, median progression-free and overall survival have not been reached. Treatment is ongoing in 12 pts. The regimen was well tolerated. NCI CTC v2 G3/4 adverse events were: neutropenia 69% of pts, hand-foot syndrome (G3 only) 18%, diarrhoea 16%, vomiting 12%, febrile neutropenia 8%, fatigue 8%, infection with G3/4 neutropenia 4%, LVEF decline 4%, stomatitis 4%.

Conclusion: The combination of NVBo + X + H is a very effective and well-tolerated first-line treatment for HER2-positive MBC.

579 Poster

Inhibition of angiogenesis and breast cancer progression in vivo by an N-terminal 80 kDa recombinant fragment of human thrombospondin-2

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Background: Thrombospondin-2 (TSP-2) is an endogenous angiogenesis inhibitor. During multistage carcinogenesis tumor development and angiogenesis is enhanced in TSP-2 deficient mice. In addition, stable overexpression of the TSP-2 gene inhibited the tumor growth and angiogenesis of human squamous cell carcinoma xenotransplants. Here we investigated the potential antitumoral efficacy of systemic TSP-2 therapy in breast cancer.

Method: We expressed a recombinant 80 kDa fragment of human TSP-2 (NTF-TSP-2), encompassing the N-terminal globular region through the three type 1 repeats, in human kidney 293 EBNA cells, using a modified pCEP4 expression vector. Breast cancer growth was investigated using an established xenotransplantation model of MDA-MB-453 breast cancer cells. Lymph node and lung metastasis were analyzed by quantification of human Alu sequences by real-time PCR.

Results: Daily intraperitoneal injections of NTF-TSP-2 resulted in a significant inhibition of the growth of human MDA-MB-435 breast carcinoma cells in vivo and tumor angiogenesis was significantly reduced. In mice systemically treated with NTF-TSP-2 both lymph node as well as lung metastasis were significantly reduced. NTF-TSP-2 inhibited vascular endothelial growth factor induced tube formation of human dermal microvascular endothelial cells on Matrigel in vitro. Moreover, NTF-TSP-2 potently induced human dermal microvascular endothelial cell apoptosis in vitro.

Conclusions: These data identify NTF-TSP-2 as a potent systemic inhibitor of tumor growth and metastasis, acting by inhibition of angiogenesis.

580 Poster

Continued trastuzumab therapy for patients with HER2-positive breast cancer

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Background: Patients (pts) with HER2-positive breast cancer (BC) are at increased risk of brain metastases (BM). This may be a biological characteristic of HER2-positive BC and/or may result from significantly longer survival in these pts as use of trastuzumab (H) has become more widespread. To explore the possible benefits of continued H in pts with BM, we reviewed cases from our clinic.

Patients and Methods: We identified 12 pts with HER2-positive BC with BM who received H for early or metastatic BC.

Results: Median age was 49 yrs (range 33−65). All had HER2 overexpression (IHC 3+ or FISH positive). Tumor stage was 2 in 9 pts and 4 in 3 pts at first diagnosis of BC. All received H + taxane (paclitaxel n = 11); H was also given with vinorelbine (n = 2), carboplatin (n = 3), capecitabine (n = 4), liposomal doxorubicin (n = 4) and letrozole (n = 1) and as monotherapy in 6 pts. First administration of H was for early BC in 3 pts (neoadjuvant 2, adjuvant 1) and for metastatic BC in 9 (1st-line 6, 3rd-line 1, 5th-line 1, 6th-line 1). All pts showed complete or partial response to H-containing therapy. Whole brain radiotherapy (WBRT) was given in 11 pts after development of BM. H is ongoing in 4 pts. Median overall survival (OS) from diagnosis of MBC is 32.5 months. Median OS from diagnosis of BM is 11.5 months.

	OS from diagnosis of BM, median (range)
No. of H-containing regimens	
2 (n = 6)	9.5+ (3–13)
3 (n = 3)	19+ (2–22)
⩾5 (n = 3)	31+ (6–48+)
Setting of first H-containing regimen	
Neoadjuvant (n = 2)	(6+–31+)
Adjuvant (n = 1)	48+
Metastatic (n = 9	11 (2–22)
Treatment after diagnosis of BM	
H alone (n = 3)	8+ (5–12)
H and a single line of chemo (n = 5)	11 (2–19+)
H and multiple lines of chemo (n = 4)	26.5 (6+–48+)

Conclusions: Pts with HER2-positive BC with BM are a heterogeneous population and analysis of such pts is difficult. However, this series suggests that it is appropriate to continue H therapy in pts with evidence of BM. Our data are consistent with those of Bartsch et al. (J Neurooncol 2007), who reported improved OS if H was continued after WBRT for BM compared with historical controls, and Nam et al. (SABCS 2007, #4061), who reported prolonged OS in pts receiving H after the onset of BM.

581 Poster

Continuation of trastuzumab-based therapy beyond disease progression in metastatic breast cancer patients – a retrospective one center analysis

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Background: Clinical value of the continuation of trastuzumab-based (TZB) therapy beyond disease progression in HER-2-overexpressing metastatic breast cancer (MBC) patients (pts) still remains uncertain.

Methods: A retrospective analysis was performed to assess the effectiveness of TZB therapy for MBC pts treated in our institution from 2002 to 2007 outside clinical trials.

Results: A total of 46 pts were evaluated. Median age: 48.5 years (range, 33−62). 16 pts (34.7%) were premenopausal. Hormonal receptors status: 18 pts ER(+), 2 pts PgR(+), 2 unknown. HER-2 overexpression was determined by IHC staining (3+ score) in all pts. Metastases location: 31 pts soft tissues/bones, 31 pts visceral disease. Median number of metastatic sites: 2 (range: 1−4). 29 pts (63%) had metastases in ⩾2 locations. 27 pts (58.7%) received neo/adjuvant chemotherapy: 19 pts doxorubicin (FAC or AC), 11 pts CMF, 3 pts docetaxel (AT), 7 pts other protocol. Median previous chemotherapy lines for advanced disease: 1 (range: 0−6). 25 pts received doxorubicin/epirubicin, 19 pts docetaxel, 12 pts vinorelbine as a part of advanced disease chemotherapy. Trastuzumab was administered at standard doses and combined with docetaxel, vinorelbine, cisplatin, capecitabine, etoposide, gemcitabine or administered as monotherapy. Response for the first-line TZB therapy was as follows: CR 7/46 pts (15.2%); PR 20/46 pts (43.5%). Median TTP was 7.0 months (range: 0−46). 33/46 pts (72%) received a second-line TZB therapy beyond disease progression. Response for the second-line therapy: CR 2/33 pts (6%); PR 15/33 pts (45.5%). Median TTP was 4.6 months (range: 0−44). 6/33 pts received a third-line and subsequent lines (up to six lines) of TZB therapy. PR for subsequent lines of therapy was observed in 4 pts. Median survival has not been reached. Pts who received ⩾2 of TZB regimens survived significantly longer than pts who had received only 1 regimen (P = 0.004 logrank). Pts with metastases in 1 location survived significantly longer than pts with metastases in ⩾2 sites (P = 0.02 logrank).

Conclusions: Continuation of trastuzumab-based therapy beyond disease progression seems to be effective in a large proportion of HER-2-overexpressing metastatic breast cancer patients, producing long-lasting responses in some of them.