

## Background

- The incidence of brain metastases (BM) in breast cancer (BC) patients is rising
- The development of BM is associated with a limited prognosis and a decreased quality of life
- Survival of patients with BM of BC has not improved over the last decades<sup>1</sup>
- Up to 40% of patients with a human epidermal growth receptor 2 (HER2)-positive metastatic BC develop BM
- Identification of factors associated with long-term survival is important for the improvement of treatment modalities

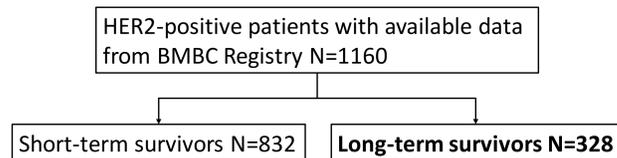
## Patients and Methods

A total of 1160 HER2-positive patients out of 3234 patients of the Brain Metastases in Breast Cancer Registry (BMBC) was available for the analysis. The clinical data of patients diagnosed with BMs of BC from the year 2000 onward has been prospectively and retrospectively collected in the registry. Patients registered before 5<sup>th</sup> of December 2020, were included in this analysis

Long-term survival was defined as overall survival (OS) in the upper third of the survival curve resulting in a cut-off of 23 months. 328 patients were categorized as long-term survivors (Figure 1).

Baseline characteristics were compared by Wilcoxon test, Fisher's exact test resp. Pearson  $\chi^2$  test between short-term vs. long-term survivors. Uni- and multivariate logistic regression analyses were performed to characterize exploratively the prognostic behavior of several factors to the assignment in the group of long-term survivors. All reported p-values were two sided, and the significance level was set to 0.05. CIs symmetrically cover 95%.

Figure 1: Patient cohort including in the analysis



## Clinical characteristics of HER2-positive long-term survivors compared to other patients:

- Long-term survivors compared to other patients:
  - were younger at BC and BM diagnosis (median 48 vs 53 and 52 vs 57 years, p<0.001)
  - had more often hormone receptor positive tumor biology (ER+ and/or PR+ 65 vs 56%, p=0.009)
  - had lower tumor grading (G3 53% vs.62%, p=0.04)
  - had better ECOG performance status at time of BM diagnosis (ECOG 0-1: 80 vs 56%, p<0.001)
  - had lower BM number (n=1 BM 38 vs 25%, p<0.001)
  - had lower rate of extracranial metastases at BM diagnosis (69 vs 82%, p<0.001)
  - had lower rate of leptomeningeal metastases (6 vs 11%, p=0.018)
  - were more often neurologically asymptomatic at BM diagnosis (28 vs 20%, p=0.005)

Table 1: Treatment modalities of HER2-positive long-term survivors

Local treatment	Short term survivors N(%)	Long-term survivors N(%)	P-Value
Surgery only	39 (5.6)	15 (4.9)	<.001
Radiotherapy only	505 (72.3)	174 (56.3)	
Surgery and radiotherapy*	154 (22.1)	120 (38.8)	
missing	134	19	

\*no significant differences dependent on the type of the radiotherapy ( data not shown)

Table 2: HER2-targeted treatment (after BM diagnosis)

HER2-targeted treatment after BM	Short-term-survivors N(%)	Long-term-survivors N(%)
Trastuzumab	90 (34.9)	76 (41.1)
Trastuzumab+Pertuzumab	28 (10.9)	24 (13.0)
Lapatinib-containing regimes	89 (34.5)	59 (31.9)
TDM1	52 (20.2)	30 (16.2)

- Long-term survivors were significantly more often treated with a combination of brain surgery and radiotherapy (39 vs 22%, p<0.001).
- 443 patients were treated with anti-HER2-targeted therapies after the diagnosis of BM (in overall 764 therapy lines, for 1 patient in one therapy line the setting was not specified), in average 1.4 lines (range: 1-8) lines in short-term and 2.2 lines (range: 1-10) lines in long-term survivors.

## Results

- Median OS in long-term survivors was 45.2 months (95%CI 40.4-47.7).
- Median time from diagnosis of BM to progress (BM, extracranial metastases or death) was 21.9 months (95%CI 18.9-23.6).
- Age, ECOG, number of BM, extracranial metastases and anti-HER2 therapy were significantly associated with a categorization of long-term survivors in multivariate analysis (Table 3).

Figure 2: Overall survival in HER2-positive long-term survivors

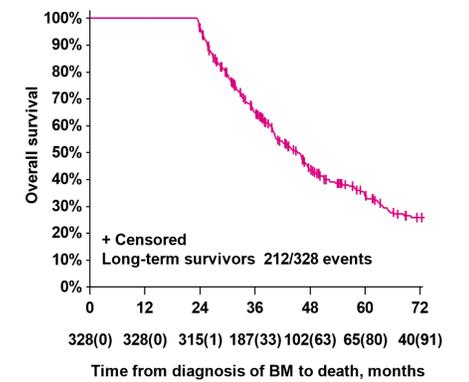


Table 3: Univariate and multivariate logistic regression in long-term survivors vs. short-term survivors

Parameter at diagnosis	Category	Univariate analysis		Multivariate analysis	
		Odds Ratio* (95% CI)	p-value	Odds Ratio* 95% CI	p-value
Age, years**	≥60 vs < 60	0.45 (0.34-0.60)	<0.001	0.59 (0.38-0.91)	<b>0.018</b>
Hormone receptor	positive vs negative	1.43(1.1-1.88)	0.008	1.47 (0.96-2.25)	0.078
ECOG**	2-4 vs 0-1	0.33(0.21-0.5)	<0.001	0.51 (0.32-0.82)	<b>0.006</b>
Number of BM	2-3 vs 1	0.62(0.44-0.88)	0.006	0.66 (0.39-1.13)	0.127
	≥4 vs 1	0.49(0.36-0.67)	<0.001	0.53 (0.32-0.88)	<b>0.015</b>
Leptomeningeal metastases	Yes vs no	0.55(0.33-0.91)	0.02	0.70 (0.30-1.66)	0.421
Clinical symptoms**	Yes vs no	0.64(0.48-0.87)	0.004	0.68 (0.41-1.14)	0.147
Extracranial Metastases**	Yes vs no	0.49(0.36-0.65)	<0.001	0.58 (0.36-0.94)	<b>0.028</b>
Chemotherapy***	Yes vs no	2.36(1.82-3.07)	<0.001	1.40 (0.86, 2.28)	0.174
Anti-HER2 therapy***	Yes vs no	2.88(2.21-3.74)	<0.001	1.98 (1.23-3.19)	<b>0.005</b>

\*An odds ratio ≥1 means to have a higher probability to be assigned to the group of long-term survivors; \*\*at diagnosis of BM; \*\*\*after diagnosis of BM

## Conclusions

- Our analysis identified factors associated with long-term survival of HER2-positive BC patients with BM and characterized clinical features of this patient cohort
- Anti-HER2 targeted therapy after BM diagnosis is an important factor associated with long-term survival of HER2-positive patients with BM
- Hormone receptor status was not significantly associated with long-term survival in HER2-positive patients, although significantly better survival could be shown in triple-positive patients with BC and BM in the previous BMBC subanalysis<sup>2</sup>
- Further HER2-targeted agents are urgently needed to improve survival of HER2-positive BC patients with BM
- The role of a multimodal approach (an optimal combination of local brain therapy and systemic treatment options) in the treatment of BM of HER2-positive BC patients should be further evaluated in prospective trials

## References

- Witzel et al. Treatment and outcomes of patients in the Brain Metastases in Breast Cancer Network Registry. Eur J Cancer. 2018;102:1-9.
- Laakmann et al. Characteristics of patients with brain metastases from human epidermal growth factor receptor 2-positive breast cancer: subanalysis of Brain Metastases in Breast Cancer Registry. ESMO Open. 2022;7:100495. doi: 10.1016/j.esmoop.2022.100495.

Corresponding author: Dr.med. Elena Laakmann | Email: e.laakmann@uke.de

