# Long-term survival of HER2-positive breast cancer patients with brain metastases: final analysis of the Brain Metastases in Breast Cancer Registry (BMBC)

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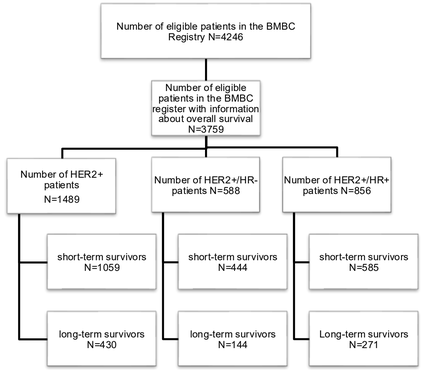
## Background

- The incidence of central nervous system (CNS) metastases in patients with breast cancer (BC) has increased over the past years[1]
- Survival of the patients with CNS metastases is still unsatisfactory
- Up to 50% of patients with a metastatic HER2-positive BC develop CNS metastases
- Several studies have identified patient's characteristics associated with long-term survival in BC with CNS metastases
- Factors associated with a long-term survival in patients with a HER2-positive BC and CNS metastases have not been analyzed until now

## Patients and Methods

The clinical data of patients diagnosed with CNS metastases of BC from the year 2000 onwards has been prospectively and retrospectively collected in the registry. Patients registered before July 1st 2024 were included. A total of 4246 patients were included in the analysis. 1,489 patients had a HER2-positive BC. Long-term survival was defined as overall survival (OS) from time of diagnosis of CNS to death in the upper third of the survival curve, resulting in a cut-off for patients with a short-term vs. long-term survival of < vs. >= 25.92 months and a median OS of 50.9 months for the long-term survivors. Consequently, 430 patients were categorized as long-term survivors. Treatment modalities were compared between short-term and long-term survivors using the Fisher's exact or Pearson chi-squared ($X^2$) tests. Univariate and multivariate logistic regression analyses were conducted to exploratively characterize the prognostic factors associated with long-term survival. All reported p-values were two-sided, and the significance level was set at 0.05. Confidence intervals (CIs) symmetrically covered 95%.




## Results

- Among short-term survivors, the median age at BC diagnosis was 53.0 (range: 20.0-92.0) years, and the median age of diagnosis of CNS metastases was 58.0 years (range: 22.0-93.0). In contrast, long-term survivors had a median age at diagnosis of BC of 48.0 years (range: 24.0-78.0) and a median age of 52.0 years (range: 25.0-85.0) at time of diagnosis of the CNS metastases.
- Long-term survivors had significantly more frequently ER and/or PR positive tumor biology (ER+ and/or PR+ 65.3 vs. 56.9%, p=0.003), a better performance status (ECOG) at time of CNS metastases diagnosis (EGOG 0-1 81.0 vs. 56.3%, p<0.001), and a lower number of CNS metastases comparing to patients in the short-term survival group (n=1 BM 40.0% vs. 25.3%, p<0.001).
- Leptomeningeal metastases were significantly less common in long-term survivors (7.7 vs. 12.7%, p=0.005). Furthermore, long-term survivors had significantly less often extracranial metastases (ECM) at diagnosis of CNS metastases (72.6% vs. 82.5%, p<0.001)
- Among long-term survivors, a significantly higher rate of patients who had asymptomatic CNS metastases (27.0 vs. 20.9%, p=0.012) could be observed.
- The number of therapy lines in the metastatic setting as well as application of HER2 targeted therapies were significantly associated with a higher probability for long-term survival

### Survival Analysis

- The median OS in HER2+/HR- long-term survivors was 49.2 months (95% CI 46.2-59.7) and was comparable with HER2+/HR+ long-term survivors (49.1 months, 95% CI 45.1-58.1) (Figure 1)
- In the multivariate analysis, younger age, HR+ status, better performance status, lower BM number as well as application of HER2-targeted treatment after BM diagnosis were significantly associated with long-term survival in a multivariate analysis (Table 1)

Figure 1: Overall survival in patients with HER2-positive BC and BM, according to HR status

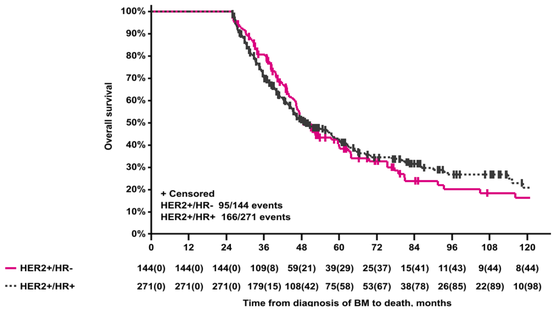



Table 1: Multivariate logistic regression in long-term vs. short-term survivors

| Parameter | Category | Odds Ratio | 95%-CI | p-value |
|---|---|---|---|---|
| AntiHER2 treatment after CNS metastases diagnosis | no | | | . |
| | yes | 2.32 | (1.58, 3.42) | <.001 |
| Age at CNS metastases diagnosis | <60 | | | . |
| | >=60 | .513 | (.342, .768) | .001 |
| HR status at BC diagnosis | both ER and PgR negative | | | . |
| | ER and/or PgR positive | 1.72 | (1.16, 2.56) | .007 |
| ECOG a CNS metastases diagnosis | ECOG 0-1 | | | . |
| | ECOG 2-4 | .495 | (.321, .764) | .001 |
| Number of CNS metastases | 1 | | | .003 |
| | 2-3 | .763 | (.471, 1.24) | .271 |
| | >=4 | .536 | (.336, .856) | .009 |
| CNS metastases Location: Meninges | no | | | . |
| | yes | .629 | (.312, 1.27) | .195 |
| >= 2nd-line metastatic treatment before CNS metastases diagnosis | no | | | . |
| | yes | .487 | (.305, .777) | .003 |
| ECM at CNS metastases diagnosis | no | | | . |
| | yes | .826 | (.513, 1.33) | .429 |
| Chemotherapy after CNS metastases diagnosis | no | | | . |
| | yes | 1.42 | (.930, 2.17) | .104 |

**Treatment modalities among patients with long-term survival vs short-term survival**

| Parameter | Category | Short-term survivors N=1059 N (%) | Long-term survivors N=430 N (%) | Overall N=1489 N (%) | p-value |
|---|---|---|---|---|---|
| AntiHER2 treatment before CNS metastases | no | 397 (37.5) | 162 (37.7) | 559 (37.5) | 0.953 |
| | yes | 662 (62.5) | 268 (62.3) | 930 (62.5) | |
| | missing | 0 | 0 | 0 | |
| Trastuzumab after CNS metastases | no | 887 (83.8) | 240 (55.8) | 1127 (75.7) | <.001 |
| | yes | 172 (16.2) | 190 (44.2) | 362 (24.3) | |
| | missing | 0 | 0 | 0 | |
| Trastuzumab + Pertuzumab after CNS metastases | no | 1052 (99.3) | 413 (96.0) | 1465 (98.4) | <.001 |
| | yes | 7 (0.7) | 17 (4.0) | 24 (1.6) | |
| | missing | 0 | 0 | 0 | |
| Lapatinib after CNS metastases | no | 900 (85.0) | 303 (70.5) | 1203 (80.8) | <.001 |
| | yes | 159 (15.0) | 127 (29.5) | 286 (19.2) | |
| | missing | 0 | 0 | 0 | |
| T-DM1 after CNS metastases | no | 944 (89.1) | 260 (60.5) | 1204 (80.9) | <.001 |
| | yes | 115 (10.9) | 170 (39.5) | 285 (19.1) | |
| | missing | 0 | 0 | 0 | |
| Tucatinib after CNS metastases | no | 1036 (97.8) | 405 (94.2) | 1441 (96.8) | <.001 |
| | yes | 23 (2.2) | 25 (5.8) | 48 (3.2) | |
| | missing | 0 | 0 | 0 | |
| Trastuzumab Deruxtecan after CNS metastases | no | 1044 (98.6) | 392 (91.2) | 1436 (96.4) | <.001 |
| | yes | 15 (1.4) | 38 (8.8) | 53 (3.6) | |
| | Missing | 0 | 0 | 0 | |
| Local treatment of CNS Metastases | Surgery only | 52 ( 5.8) | 22 ( 5.3) | 74 ( 5.7) | <.001 |
| | Radiotherapy (RTH) only | 647 (72.6) | 228 (55.3) | 875 (67.2) | |
| | Surgery and RTH | 192 (21.5) | 162 (39.3) | 354 (27.2) | |
| | Missing | 168 | 18 | 186 | |

## Conclusions

- Our analysis of the large BMBC registry identified factors associated with long-term survival in patients with a HER2-positive BC and CNS metastases.
- The application of HER2-targeted therapies, age, HR status, ECOG performance status, and number of CNS metastases were significantly associated with long-term survival.
- Our analysis provides a substantiation for designing future (de)- escalation trials in order to optimize treatment regimens and integrate new therapeutic options in the management of patients with BC and CNS metastases.

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Presenting author Patricia von Kroge declares no conflict of interest in regard of the presented analysis