HER2 IHC Status of primary Breast Cancer Tumor and Brain Metastases in the BMBC Registry

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P 585

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Background

- Antibody-drug conjugates (ADCs) have reshaped the treatment of metastatic breast cancer (mBC). Trastuzumab Deruxtecan (T-DXd) is effective in HER2-positive mBC, including patients with CNS metastases (1, 2).
- New ADCs also showed efficacy in HER2 low and ultralow. For example, T-DXd (3, 4).
- CNS metastases are common in advanced BC. They develop in up to 71% of triple-negative and up to 37% of HER2(FISH)-negative, HR-positive mBC patients (5). Both subtypes include a relevant proportion of HER2-low/ultralow tumors.
- The HER2 IHC status of CNS metastases in HER2(FISH)-negative mBC remains largely unknown.
- The BMBC registry collects clinical data and biomaterial from patients with breast cancer and CNS metastases. This analysis evaluates the HER2 IHC status of CNS metastases. The goal is to provide insights into the potential role of T-DXd in HER2-low/ultralow brain metastases.

Patients and Methods

For this analysis, tissue samples from 263 BM and 74 primary breast cancer tumors were available, including 61 matched pairs.

Main objectives:

- To characterize the HER2 IHC status of brain metastases and primary BC tumors of BMBC patients
- To compare the clinical characteristics of patients with HER2 IHC 0/ ultralow/1-2+/3+/FISH pos, incl. the HR status
- Estimation and comparison of the overall survival (OS) after the diagnosis of BM and progression-free survival (PFS) after the diagnosis of BM

Results

Patient characteristics

- Patient characteristics were comparable across the HER IHC cohorts (N=263 patients with information of HER2 status in brain metastasis)
- Median age of BC diagnosis was 51.0 vs. 48.0 vs 51.5 vs. 51.0 years in the HER2 zero, ultralow, 1+/2+ and 3+ classes respectively
- Median age at time of BM diagnosis was 56.0 vs. 55.0 vs 56.5 vs. 54.0 years in the HER2 zero, ultralow, 1+/2+ and 3+ classes respectively
- Extracranial metastases at time of BM diagnosis were present in n=55 (59.1%), n=18 (66.7%), n=26 (65.0%), n=67 (65.0) in the HER2 zero, ultralow, 1+/2+ and 3+ classes respectively
- 141 pts (54.2%) had a positive ER and/or PR status, 119 pts (45.8%) had ER and PR negative tumor biology (n=3 missing)
- A significant difference was observed with respect to the following parameters:
  - The presence of leptomeningeal metastases was significantly more frequent in patients with HER2 1+/2+ biology (n=5, 12.5%), followed by HER2 0 (n=7, 7.5%) and HER2 3+ (n=2, 1.9%). No patient with a HER2 ultralow tumor biology had a leptomeningeal disease
  - Additionally, liver metastases as the first site of extracranial metastasis were significantly more common in patients with HER2 3+ (n=30, 29.1%), followed by HER2 0 (n=13, 14.0%), HER2 1+/2+ (n=5, 12.5%), and HER2 ultralow (n=3, 11.1%).

Results

HER2-IHC analysis of the entire cohort (N=263 patients with information of HER2 status in brain metastasis, N=74 patients with information of HER2 status in primary BC, Table 1)

- In primary breast cancer samples, the majority of patients — 33 cases (44.6%) — had an immunohistochemically (IHC) HER2 0 status. This was followed by IHC 3+ status in 31% of patients, IHC 1+ in 14.9%, and smaller proportions with IHC ultralow (8.1%) and IHC 2+ status (1.4%).
- In contrast, in the brain metastases, the majority of patients showed an IHC 3+ status — 103 cases (39.2%). This was followed by IHC 0 (35.4%), IHC 1+ (11.0%), IHC ultralow (10.3%), and IHC 2+ (4.2%) statuses in decreasing frequency.
- These findings suggest that, based on the tumor biology of the brain metastases, 60,8% (160 out of 263) of patients may potentially benefit from a targeted therapy with a Trastuzumab- Deruxtecan or other compounds targeting HER2 low tumors (39.2 % based on HER2 3+ status and additional 15.2% based on HER2 low as well as 6.5% based on ultralow (HR+) status)

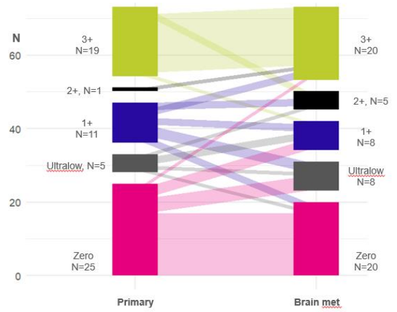
	IHC 3+ (n, %)	IHC 2+ (n, %)	IHC 1+ (n, %)	IHC ultralow (n, %)	IHC zero (n, %)
Primary tumor	23 (31.1%)	1 (1.4%)	11 (14.9%)	6 (8.1%)	33 (44.6%)
Brain metastasis	103 (39.2%)	11 (4.2%)	29 (11.0%)	27 (10.3%) (n=17 HR+, n=10 HR-)	93 (35.4%)

Table 2: HER2-IHC analysis of matched pairs

HER2-IHC analysis of matched pairs analysis (n=61)

- The most clinically relevant differences could be observed in the HER2 zero cohort resulting in a lower proportion of HER2 zero biology in BM (n=20, 32.8%, thereof n=17 (27.9%) with HER2 zero biology in the primary BC) vs. in the primary BC (n=25, 41.0%). (Table2)

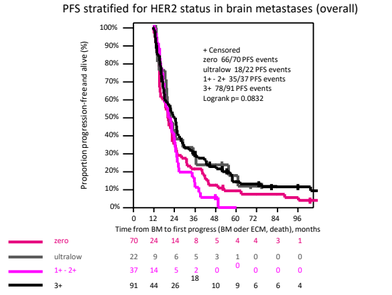
Table 1: Distribution of HER2-IHC classes among samples in the entire cohort



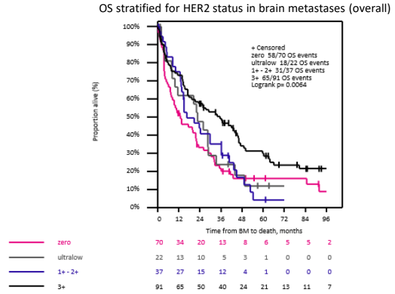
Survival analysis

- Median PFS was distributed as followed: the highest mPFS could be showed for pts with HER2 3+ BM (11.7 months, 95%CI 6.6-14.7), followed by HER2 ultralow (9.8 months, 95%CI 6.9-23.2) and HER2 1+/2+ (9.6 months, 95%CI 6.1-12.6). Patients with a HER2 zero status of BM showed the lowest PFS (8.6 months, 95% CI 4.1-11.1). Differences were not statistically significant.
- Median overall survival (mOS) was significantly different in the HER2-IHC cohorts (p=0.0064), showing the highest mOS for pts with HER2 3+ BM (35.4 months, 95%CI 17.7-46.0), followed by HER2 ultralow (22.7 months, 95%CI 8.0-28.6) and HER2 1+/2+ (16.5 months, 95%CI 13.2-36.2). Patients with a HER2 zero status of BM showed the lowest survival rate (13.1 months, 95% CI 7.5-21.7).

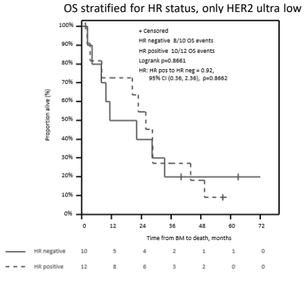
PFS stratified for HER2 status in brain metastases (overall)



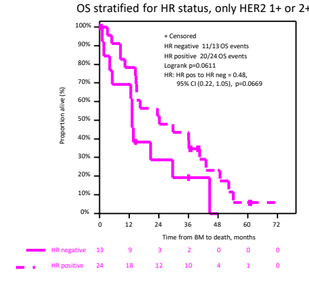
OS stratified for HER2 status in brain metastases (overall)



OS stratified for HR status, only HER2 ultra low



OS stratified for HR status, only HER2 1+ or 2+



Conclusions

- Our findings indicate that the HER2 IHC status of brain metastases is significantly associated with OS, suggesting it may serve as a prognostic biomarker.
- A substantial proportion of brain metastases exhibited HER2-ultralow, HER2-low, or HER2 3+ status, which may have therapeutic implications, particularly in the context of antibody–drug conjugate therapies targeting HER2.

References

1.DOI: 10.1056/NEJMoa2115022; 2.DOI https://doi.org/10.1038/s41591-024-03261-7; 3.DOI: 10.1056/NEJMoa2203690; 4.DOI: 10.1056/NEJMoa2407086; 5.DOIhttps://doi.org/10.1038/s41416-019-0619-y

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