Immuno- and Molecular-Profiling of Breast Cancer Metastasis in the CNS

N. Abele[1], M. Berner[1], R. Stöhr[1], A. Hartmann[1], C. Mawrin[2], R. Erber[3,1]

[1]Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Comprehensive Cancer Center Erlangen-EMN (CCC ER-EMN), Erlangen, Germany, [2]Institute of Neuropathology OvGU Magdeburg, Magdeburg, Germany, [3]Institute of Pathology University Regensburg, Regensburg, Germany

Friedrich-Alexander-Universität
Faculty of Medicine

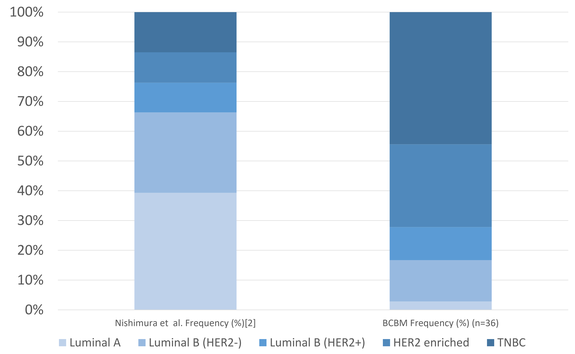
Correspondence:
University Hospital Erlangen, Institute of Pathology, Krankenhausstraße 8-10, 91054 Erlangen GER
Niklas Abele, niklas.abele@uk-erlangen.de

Uniklinikum Erlangen
Institute of Pathology
Direktor: Prof. A.Hartmann

Breast cancer brain metastasis (BCBM) represents a significant challenge with poor prognosis. Certain breast cancer subtypes, notably HER2-positive and triple-negative breast cancer (TNBC), are associated with a higher risk of brain metastasis[1]. Understanding these unique properties, distinct from primary tumors, is crucial for therapeutic strategies.

Methods:

We evaluated intracranial **BCBM from 36 patients** for hormone receptor (ER/PR), HER2-status (incl. HER2 low and HER2 ultra-low), Ki-67 status, PD-L1 expression, tumor-infiltrating lymphocytes (TILs) as well as PIK3CA mutations. Biomarker frequencies were compared against published data from breast cancer cohorts.



Molecular-like Subtype	BCBM Frequency (n)	SEER Frequency[3]	Nishimura et al. Frequency[2]
HER2 enriched	**27.8 % (10)**	4.6 %	10.2 %
TNBC	**44.4 % (16)**	12.2 %	13.5 %
Luminal B (HER2+)	**11.1 % (4)**	10.3 %	10.0 %
Luminal B (HER2-)	**13.9 % (5)**	72.7 % (all HR+/HER2-)	27.0 %
Luminal A	**2.8 % (1)**		39.3 %

Results:

Primary breast cancer is predominantly HR+/HER2- (**Luminal A/B** HER2-) (63 - 73 %), this subtype comprised only 16.7 % (6/36) of our BCBM cases. Conversely, **TNBC** (44.4 %, 16/36) and **HER2-positive** subtypes (38.9 %, 14/36) were significantly overrepresented in our cohort compared to their prevalence in primary breast cancer (12 – 14 % and 15 - 20 %, respectively)[2,3].

Overall median **Ki-67** was 30.0 % (mean 42.6 %) and most cases, 88.9 % (32/36) showed high proliferation (Ki-67 ≥20 %), with 33.3 % (12/36) demonstrating very high proliferation (Ki-67 ≥50 %) [2].

Among the HER2-negative cases (n = 22), most (87 %) were **HER2 low** (64 %, 14/22) or at least **HER2 ultra-low** (23 %, 5/22).

PD-L1 expression (SP263 CPS ≥10) was very low, found in only 2.8 % (1/36) of cases. A slightly larger subset (8.3 %, 3/36) met the IC positivity criterion (IC ≥1 %) with SP142. This low prevalence of actionable PD-L1 expression contrasts significantly with rates observed in primary TNBC (38 % for CPS ≥10 in KEYNOTE-355 and 34 % for IC ≥1 % in CheckMate 7FL)[4,5].

TILs were significantly lower compared to primary breast cancer and across all subtypes; only 5.9 % cases had high TILs (≥60 %) compared to the 19 % found in literature[6].

PIK3CA analysis revealed 20 % (6/30) of cases with mutations and no significant deviation from the expected frequencies in respect of the molecular subtype[7].

Conclusion:

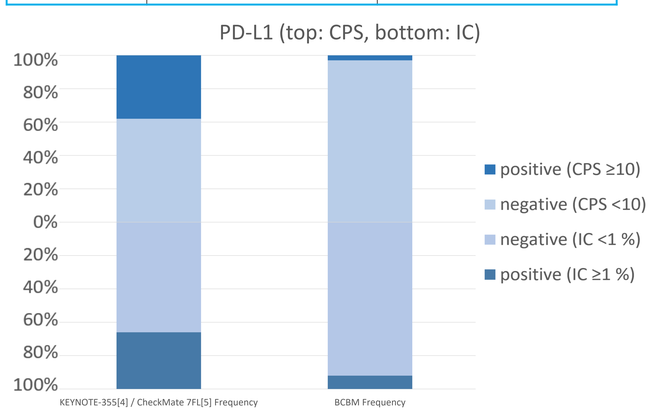
Our findings indicate BCBMs exhibit a distinct molecular landscape characterized by an enrichment of TNBC and HER2-positive subtypes with high proliferation.

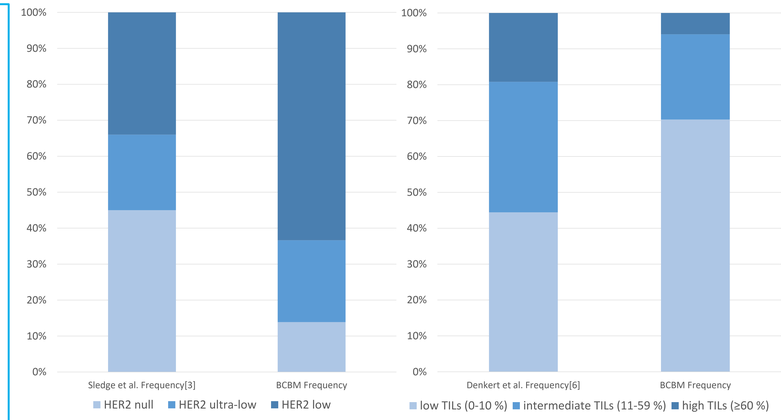
The frequency of HER2 low and ultra-low among traditionally HER2 negative cases, furthermore, give way for additional treatment paths, e.g. with Trastuzumab-deruxtecan[8].

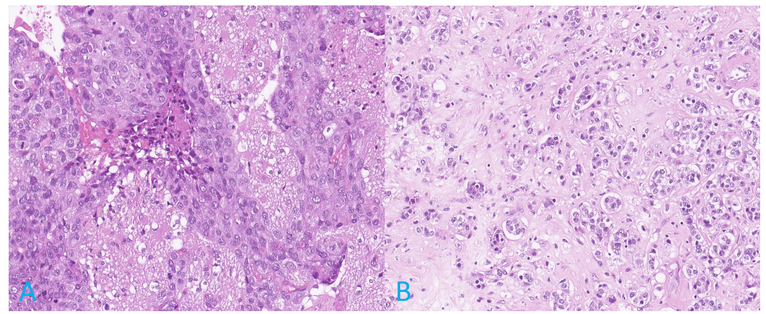
PD-L1 expression and TILs appear to be markedly lower than in primary breast cancer. This suggests a very different tumor microenvironment for metastasis to the CNS, with implications for immunotherapy efficacy.

These insights highlight the unique biology of BCBM, emphasizing the need for biomarker analysis on metastatic tissue to guide personalized therapeutic strategies.

Ki-67 index	BCBM Frequency (n)	Nishimura et al. Frequency[2]
<20 %	**11.1 % (4)**	45.1 %
≥20 % and <50 %	**55.6 % (20)**	40.6 %
≥50 %	**33.3 % (12)**	14.2 %
median	**30.0 %**	22.0 %







Infiltrative growth could be catagorized into two histomorpohological growth-patterns:
A) clustered / cohorts (81 %, 29/36); B) diffuse (19 %, 7/36)

References:

[1] Witzel, I., Oliveira-Ferrer, L., Pantel, K., Müller, V. & Wikman, H. *Breast cancer brain metastases: biology and new clinical perspectives*. Breast Cancer Res 18, 8 (2016).

[2] Nishimura, R., et al. *Ki-67 as a prognostic marker according to breast cancer subtype and a predictor of recurrence time in primary breast cancer*. Exp Ther Med 1, 747-754 (2010).

[3] Howlader, N., et al. *US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status*. J Natl Cancer Inst 106(2014).

[4] Cortes, J., et al. *Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer*. N Engl J Med 387, 217-226 (2022).

[5] Loi, S., et al. *Neoadjuvant nivolumab and chemotherapy in early estrogen receptor-positive breast cancer: a randomized phase 3 trial*. Nature Medicine 31, 433-441 (2025).

[6] Denkert, C., et al. *Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy*. Lancet Oncol 19, 40-50 (2018).

[7] Network, T.C.G.A. *Comprehensive molecular portraits of human breast tumours*. Nature 490, 61-70 (2012).

[8] Bardia, A., et al. *Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer*. N Engl J Med 391, 2110-2122 (2024)

Disclosure statement:

N.A. has received honoraria from Mindpeak and Siemens Healthineers. M.B. has received honoraria from Mindpeak. A.H. has received honoraria from BMS, MSD, Roche, Cepheid, Qiagen, Agilent, Diaceutics, Lilly, AstraZeneca, Boehringer Ingelheim, Abbvie, Janssen-Cilag, Pfizer, and Ipsen. R.E. has received honoraria from Roche, Eisai, Pfizer, BioNTech, Lilly, Veracyte, Diaceutics, Mindpeak, AstraZeneca, MEDAC, Menarini Stemline, and Novartis.