



Treatment for HER2-Positive Brain Metastases

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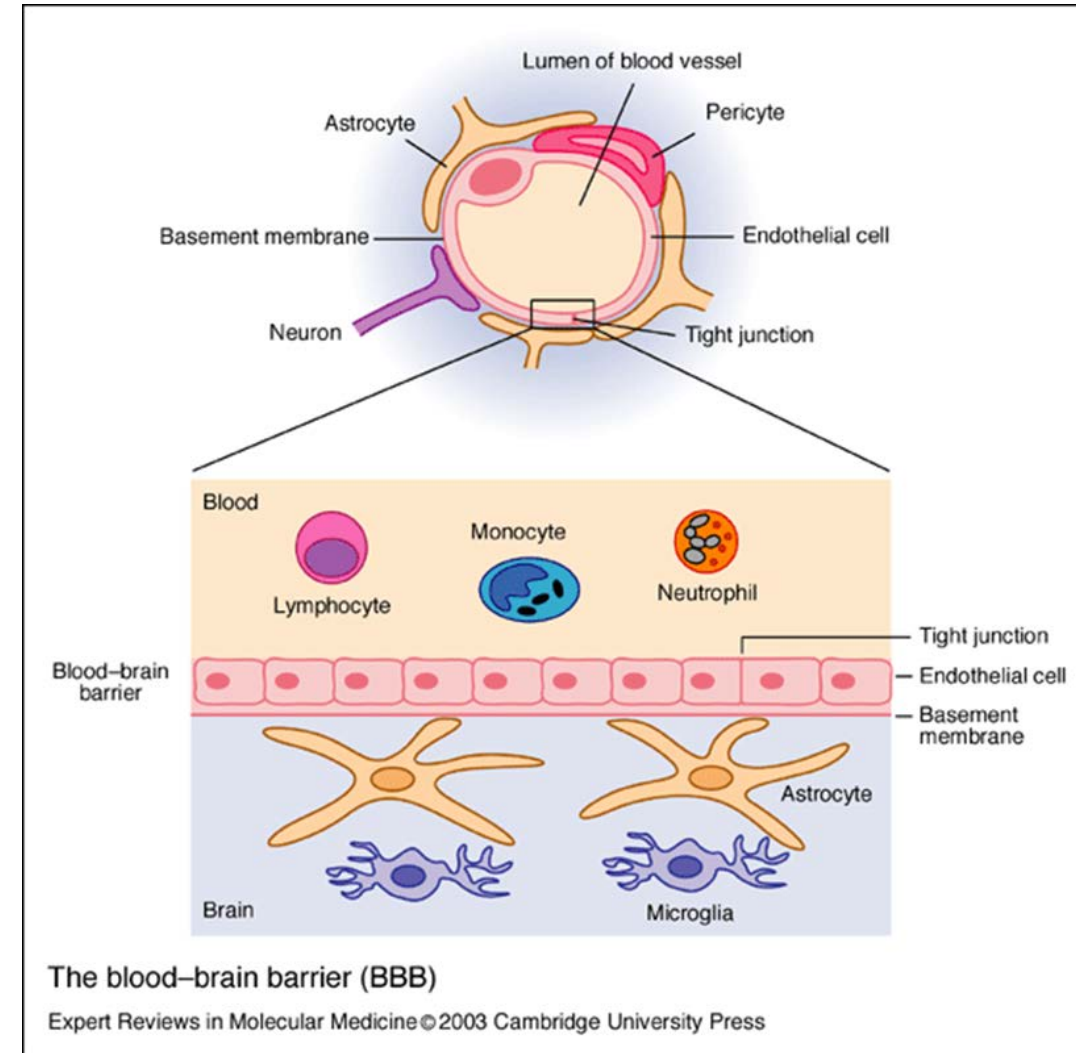


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Breast cancer Brain Metastases: Challenges faced...

- Increasingly common consequence of advanced breast cancer
 - Incidence 30% HER2+¹, 50% triple negative² advanced BC
- Blood brain barrier, efflux pumps in brain endothelium limit exposure to cytotoxics
- Clinical trials frequently excluded patients with CNS disease
 - Previous trials specifically targeting patients with brain metastases few

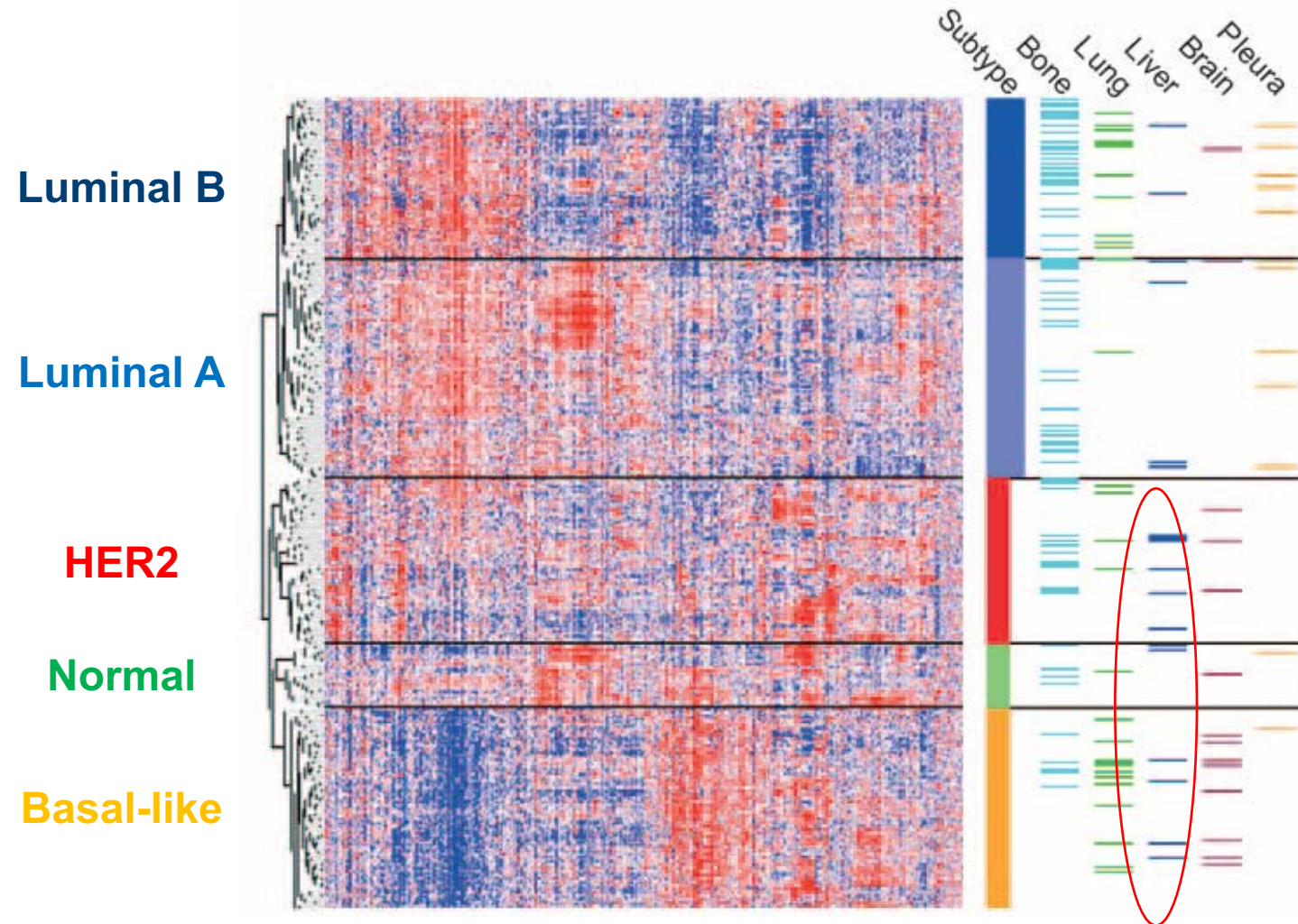


¹ Bendell et al. Cancer 2003

² Lin et al. Cancer 2008



The brain is a common site of HER2+ Breast Cancer Metastases



Smid et al. CCR 2008



NCCN: Systemic Therapy Options expanded in 2021



NCCN Guidelines Version 1.2021 Central Nervous System Cancers

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY BRAIN METASTASES

- Tumor Agnostic^W
 - ▶ *NTRK* gene fusion tumors
 - ◊ Larotrectinib¹⁸
 - ◊ Entrectinib¹⁹
 - ▶ TMZ 5/28 schedule

- Breast Cancer^X
 - ▶ HER2 positive
 - ◊ Ado-trastuzumab emtansine (T-DM1)¹¹³
 - ◊ Capecitabine + lapatinib^{114,115}
 - ◊ Capecitabine + neratinib^{116,117}
 - ◊ Paclitaxel + neratinib (category 2B)¹¹⁸
 - ◊ Tucatinib + trastuzumab^Y + capecitabine (category 1) (if previously treated with 1 or more anti-HER2-based regimens)¹¹⁹
 - ▶ HER2 Non-specific
 - ◊ Capecitabine¹²⁰⁻¹²⁴
 - ◊ Cisplatin (category 2B)^{125,126}
 - ◊ Etoposide (category 2B)^{125,126}
 - ◊ Cisplatin + etoposide (category 2B)^{126,127}
 - ◊ High-dose methotrexate (category 2B)^{o,128}

- Melanoma^X
 - ▶ BRAF V600E positive
 - ◊ Dabrafenib¹²⁹⁻¹³¹/trametinib¹³²
 - ◊ Vemurafenib^{133,134}/cobimetinib^Z (category 2B)
 - ▶ BRAF non-specific
 - ◊ Ipilimumab + nivolumab (preferred)¹³⁵⁻¹³⁷
 - ◊ Ipilimumab¹³⁸
 - ◊ Nivolumab¹³⁶
 - ◊ Pembrolizumab¹³⁹

***Tucatinib and TDM1 added to list 2020**

- Non-Small Cell Lung Cancer^X
 - ▶ EGFR-sensitizing mutation positive
 - ◊ Osimertinib¹⁴⁰⁻¹⁴²
 - ◊ Pulsatile erlotinib¹⁴³⁻¹⁴⁵
 - ◊ Afatinib (category 2B)¹⁴⁶
 - ◊ Gefitinib (category 2B)^{147,148}
 - ▶ *MET* exon 14 mutated
 - ◊ Capmatinib¹⁴⁹
 - ▶ *ALK* rearrangement positive
 - ◊ Brigatinib^{150,151}
 - ◊ Lorlatinib¹⁵²
 - ◊ Alectinib^{153,154}
 - ◊ Ceritinib¹⁵⁵
 - ▶ *ALK* rearrangement positive or *ROS1* positive
 - ◊ Crizotinib (category 2B)¹⁵⁶
 - ▶ PD-L1 positive
 - ◊ Pembrolizumab^{139,157}
 - ◊ Nivolumab¹⁵⁸⁻¹⁶⁰
- Small Cell Lung Cancer^X
 - ◊ Topotecan (category 2B)
- Lymphoma^X
 - ◊ High-dose methotrexate¹⁶¹

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Strategies with additional data in 2020 - 2021:

HER2 TKIs:
Tucatinib in LMDz
Neratinib
Pyrotinib

Her2 targeting ADCs:
TDM1
Trastuzumab Deruxtecan