Dr Hofer has reported receiving congress travel support from Astellas in 2019, honorarium for Advisory Board role from MSD in 2019. Financial support paid directly to her institution by Roche for Advisory Board role in 2019.

Dr Kotecki has reported no conflicts of interest
BRAIN METASTASES (BM)

Key points

BM are increasing in incidence since systemic tumour therapies have improved, resulting in longer patient survival, better control of metastases in distant organs and also due to better diagnostic techniques.

The pathogenesis of BM has not been completely characterised to date.

Prognosis of patients with BM depends on patient characteristics (i.e. age, KPS), tumour entity and molecular profile. Years with good quality of life are attainable, especially in molecularly altered tumours, where targeted therapies are available (e.g. EGFRmut and ALK rearranged NSCLC, HER 2- amplified Breast Cancer).

Treatment of BM is primarily local with neurosurgery and/or stereotactic radiotherapy (depending on criteria such as immediate relief of brain pressure, need of a histology, number of metastases, performance status and systemic disease control). Whole-brain irradiation (WBRT), is largely abandoned, exceptions remain for prophylactic CNS irradiation (PCI) in SCLC, diffuse leptomeningeal disease and for palliative reasons (salvage radiotherapy).

Since patients with BM are no longer excluded from clinical trials, there is increasing evidence that newer generation TKIs and immuno-therapies (IO) are also effective in the brain. The brain is not immune-isolated.
AGENDA

1. Epidemiology
2. Pathogenesis of BM & Blood Brain Barrier
3. Prognostic scores
4. Therapeutic options for BM
5. Histologic entities
6. Summary
1. EPIDEMIOLOGY OF BM
For stage IV disease

- Melanoma
- Lung
- Breast HER2+
- Breast TN
- Breast all
- Esophagus adeno
- RCC
- CRC
- Stomach
- Ovary

SCLC 50-60%
RELATIVE FREQUENCIES OF TUMOUR TYPES

Brain metastases (%)

**Females**
- Ovary: 3%
- Gastrointestinal: 4%
- Lung: 8.3%
- Melanoma: 6.1%
- Kidney: 7.1%
- Others: 3%
- CUP: 8.4%
- Breast: 3%
- Uterus: 28.4%

**Males**
- Bladder: 11.4%
- Gastrointestinal: 14%
- Lung: 5.6%
- Melanoma: 6.9%
- Kidney: 10%
- Others: 50%
- CUP: 11.4%
- Prostate: 50%

BM: AN INCREASING ISSUE

Incidence of brain metastasis and MRI use from 1986 to 2006

Cumulative incidence of BM according to molecular subtype

1. Reprinted from Clin Neurol Neurosurg, 160:, Wang B-X, Impacts of EGFR mutation and EGFR-TKIs on incidence of brain metastases in advanced non-squamous NSCLC, P96–100, Copyright, with permission from Elsevier;
**BREAST**

Cumulative incidence of Stage IV disease

% BM at any time during their metastatic disease

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>ER+HER2−</th>
<th>ER+HER2+</th>
<th>ER−HER2+</th>
<th>Triple neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19</td>
<td>34</td>
<td>49</td>
<td>38</td>
</tr>
</tbody>
</table>

MELANOMA

20–25% of patients with BM at diagnosis
Cumulative incidence in Stage IV disease 40–60%
At autopsy, up to 80%
SCREENING FOR BM

Recommended for:

NSCLC stage II–IV
SCLC any stage
Melanoma stage IIIc–IV
Breast stage IV or recurrent disease¹,²
Germ-cell tumours with lung metastases
Alveolar soft part sarcoma (ASPS) any stage

¹ Cagney D, et al. JAMA Oncol 2018; 2. NCCN 01.2020, ESMO 2019
2. PATHOGENESIS OF BM AND BLOOD BRAIN BARRIER
The BBB is a selective barrier formed by endothelial cells, interconnected by tight junctions, pericytes, astrocytes, neuronal end-feet and other cells from the microglia forming the neurovascular unit, which separates the bloodstream circulation from the brain and the cerebrospinal fluid (CSF).
Transport across the BBB is highly regulated, however, less so in the presence of BM. It includes paracellular transport, passive and active transport and cell-mediated transcytosis thus limiting- at least partly- the passage of many drugs, some of which are dependent on P-glycoprotein (P-gp), an efflux transporter.
BLOOD BRAIN BARRIER AND DRUGS (3)

Tumour cells spread from the primary tumour or from metastatic lesions and colonise the brain parenchyma, involving several biological processes:

A. local invasion
B. intravasation into the bloodstream
C. circulating tumour cells
D. extravasation into the brain parenchyma through the blood brain barrier (BBB)
E. interaction with the CNS microenvironment
GROWTH PATTERNS OF BM

Glioma growth pattern

Brain metastases up to 50% show a glioma-like infiltrative pattern

1. Courtesy Dr S Hofer, University Hospital, Zurich; 2. Courtesy Prof. Dr. med. Tobias Pukrop, Universitaetsklinikum Regensburg.
TUMOUR ENTITIES WITH DIFFERENT TYPES OF INFILTRATION

BRAIN SPECIFIC MICROENVIRONMENT

Interactions between brain resident cells and tumour cells promote BM growth pathways (example)

PTEN loss induced by astrocyte-derived exosomal microRNA primes brain metastasis outgrowth via functional cross-talk between disseminated tumour cells and brain metastatic microenvironment

Paths of CSF drainage for macromolecules and immune cells

Immune cells can cross the BBB to gain access to the brain parenchyma and can leave the CNS during inflammation or tumour manifestation to reach the cervical lymph nodes.

Common ancestor cell of primary tumour and brain metastases

Common mutations of primary tumour and brain metastases

Primary tumour

Mutation only detected in the primary tumour

Mutations detected only in the brain metastases

Mutations detected only in the brain metastasis location 1

More actionable genetic alterations in BM than in the primary tumour

Brain metastasis – location 1

Brain metastasis – location 2

Common ancestor cell of brain metastases

CSF-DERIVED CIRCULATING TUMOUR DNA BETTER REPRESENTS THE GENOMIC ALTERATIONS OF BRAIN TUMOURS THAN PLASMA

N=12 patients (4 GBM, 6 BM from BC, 2 BM from LC)

Methodology:

- Targeted capture massively parallel sequencing DNA samples from CNS tumours, non-CNS metastases, CSF and plasma samples as well as germline DNA MSK-IMPACT – 341 genes
- Exome (germline and tumour DNA)
- Droplet Digital (dd)PCR on CSF ctDNA and plasma ctDNA designed to specifically detect point mutations selected by exome sequencing
CSF-DERIVED CIRCULATING TUMOUR DNA BETTER REPRESENTS THE GENOMIC ALTERATIONS OF BRAIN TUMOURS THAN PLASMA

1. ctDNA derived from CNS tumours is more abundantly present in the cerebrospinal fluid (CSF) than in plasma

2. CSF ctDNA levels longitudinally fluctuate in time and follow the changes in brain tumour burden providing biomarkers to monitor brain malignancies

Results build a proof-of-concept that opens the possibility to use CSF ctDNA to complement the diagnosis of LM

cDNA circulating tumour DNA
MAF mutant allelic frequencies, measured by ddPCR
BMBC Brain metastases from three breast cancer patients (1,2,4)
NA not assessed

3. PROGNOSTIC SCORES – DS-GPA (DISEASE SPECIFIC-GRADED PROGNOSTIC ASSESSMENT)

www.brainmetgpa.com

Guidance to estimate survival of patients with BM available for the following tumour entities:

- Lung cancer (including molecular marker)
- Melanoma (including molecular marker)
- Breast cancer (including molecular marker)
- Renal cell cancer
- Gastrointestinal cancer
- Sarcoma\(^1\)

\(^1\)Patrikidou A, et al. BMC Cancer 2020;20:117
DISEASE SPECIFIC-GRADED PROGNOSTIC ASSESSMENT (DS-GPA)

Summary of diagnosis-specific GPA indices, which estimates survival from brain metastases

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prognostic factors</th>
<th>GPA 0.0-1.0</th>
<th>GPA 1.5-2.0</th>
<th>GPA 2.5-3.0</th>
<th>GPA 3.5-4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>KPS</td>
<td>3.4</td>
<td>7.7</td>
<td>15.1</td>
<td>25.3</td>
</tr>
<tr>
<td></td>
<td>Subtype (triple negative, HR+, HER2+, HR/HER2+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI cancers</td>
<td>KPS</td>
<td>3.1</td>
<td>4.4</td>
<td>6.9</td>
<td>13.5</td>
</tr>
<tr>
<td>Melanoma</td>
<td>KPS</td>
<td>3.4</td>
<td>4.7</td>
<td>8.8</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td>Number of BM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC (adenocarcinoma)</td>
<td>Age (y)</td>
<td>6.9</td>
<td>13.7</td>
<td>26.5</td>
<td>46.8</td>
</tr>
<tr>
<td></td>
<td>KPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presence/absence of extracranial metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of BM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EGFR or ALK positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC (nonadenocarcinoma)</td>
<td>Age (y)</td>
<td>5.3</td>
<td>9.8</td>
<td>12.8</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>KPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presence/absence of extracranial metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of BM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>KPS</td>
<td>3.3</td>
<td>7.3</td>
<td>11.3</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td>Number of BM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC</td>
<td>Age (y)</td>
<td>3.0</td>
<td>5.5</td>
<td>9.4</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td>KPS</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Presence/absence of extracranial metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of BM</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
4. THERAPEUTIC OPTIONS FOR BM
THERAPEUTIC OPTIONS FOR BM

Depending on:

- Intracranial pressure
- Symptoms
- Number, size & site of metastases
- Extra-CNS disease control
- Performance status
- Sensitivity to systemic therapy
- Prognostic index: DS-GPA (disease specific-graded prognostic assessment)
LOCAL THERAPIES

Surgery and Stereotactic Radiotherapy (SRT)

Surgery is the most efficient method to immediately reduce mass effect and oedema from BM.

For effective local control, surgery followed by SRT plays an integral role for oligometastatic BM.

Repeat SRT may be offered for multiple BM.
## LOCAL THERAPEUTIC OPTIONS FOR BM

<table>
<thead>
<tr>
<th></th>
<th>SRS/SRT</th>
<th>Neursurgery</th>
<th>WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Small lesions (up to 3 cm) and a limited number (&lt;10)</td>
<td>Surgically accessible lesions</td>
<td>Multiple BM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controlled extra-CNS disease</td>
<td>Leptomeningeal metastases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good PS</td>
<td>Palliation (salvage RT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute decompensation due to a significant mass effect</td>
<td></td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Better preservation of NC function compared to WBRT, no OS advantage for either radiation modality¹</td>
<td>Tissue for histology</td>
<td>Significant risk for neurocognitive decline</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Will not treat microscopic tumour manifestation</td>
<td>Not always appropriate in the palliative setting</td>
<td>Side effects</td>
</tr>
<tr>
<td></td>
<td>No tumour tissue collection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LOCAL THERAPEUTIC OPTIONS FOR LEPTOMENINGEAL METASTASES (LM)

There are no randomised trials assessing efficacy and tolerance of RT in LM.

Focal RT is an option for symptomatic nodular disease, to resolve CSF flow obstruction or hydrocephalus.

WBRT may be considered for extensive nodular and symptomatic disease, coexistent BM and for palliation.

Cerebrospinal RT is rarely an option due to its toxicity.

Surgery is rarely an option, except for the insertion of a reservoir or ventriculo-peritoneal shunt.

There are no randomised trials assessing response to intra-CSF treatment for solid tumours versus best supportive care.

Drug used intrathecally: Methotrexate, thiotepa, liposomal cytarabine (no longer available!), gemcitabine, etoposide, topotecan and the monoclonal antibody trastuzumab. The chemotherapeutic drugs are usually not first choice for the most common tumours with LM.

Intra-CSF therapy has limited penetration (1-2 mm) in case of nodular disease, most drugs have a short half-life and are associated with considerable neurotoxicity, with the exception of trastuzumab. 


BM from highly chemotherapy-sensitive primary tumours (e.g. SCLC)

BM from primary tumours with identified molecular alteration, amenable to targeted therapy that cross the BBB (e.g. osimertinib for EGFRmut or alectinib for ALK altered NSCLC)

Asymptomatic BM found on screening MRI with planned systemic treatment

After exhaustion of other therapeutic options and availability of a drug (investigational or not)

Adapted from Lin, et al. J Clin Oncol 2015
## TARGETED TREATMENTS FOR BM

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Trial (setting)</th>
<th>n</th>
<th>Intracranial ORR</th>
<th>Extracranial ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSCLC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFRm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osimertinib</td>
<td>AURA3 (Stable asymptomatic CNSm)</td>
<td>116</td>
<td>70% MD, 40% NM/MD 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BLOOM (Confirmed LM)</td>
<td>32</td>
<td>91% MD, 66% NM/MD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FLAURA (Stable asymptomatic CNSm)</td>
<td>128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK/ROS1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceritinib</td>
<td>ASCEND-7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior Brain RT, prior Alki (Alk-Inhibitor)</td>
<td>42</td>
<td>39%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>Prior Alki only</td>
<td>40</td>
<td>27.6%</td>
<td>42.5%</td>
</tr>
<tr>
<td></td>
<td>Prior Brain RT only</td>
<td>12</td>
<td>28.5%</td>
<td>41.7%</td>
</tr>
<tr>
<td></td>
<td>Alki/RT naive</td>
<td>44</td>
<td>51.5%</td>
<td>61.4%</td>
</tr>
<tr>
<td></td>
<td>Alectinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALEX (Stable asymptomatic CNS/LMm)</td>
<td>122</td>
<td>85.7%</td>
<td>78.6%</td>
</tr>
<tr>
<td></td>
<td>(prior RT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HER2+ BC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib/capecitabine</td>
<td>LANDSCAPE (no prior WBRT)</td>
<td>45</td>
<td>65.9%</td>
<td></td>
</tr>
<tr>
<td>Neratinib/Capecitabine</td>
<td>TBRC 022 (prior RT allowed)</td>
<td>37</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Tucatinib/Trastuzumab/ Capecitabine</td>
<td>ONT 380 005 (including PD CNS)</td>
<td>23</td>
<td>42%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>HERCLIMB ONT-380-206 (including PD CNS)</td>
<td>(480)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipi/Nivo</td>
<td>Checkmate 204 (prior RT allowed)</td>
<td>94</td>
<td>57%</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>ABC trial (no prior RT)</td>
<td>25</td>
<td>44%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>BRAFm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabrafenib/Trametinib</td>
<td>COMBI-MB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>V600E no prior RT</td>
<td>76</td>
<td>58%</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>V600E prior RT</td>
<td>16</td>
<td>56%</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>V600K/D/R</td>
<td>16</td>
<td>44%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>V600 D/E/K/R</td>
<td>17</td>
<td>59%</td>
<td>41%</td>
</tr>
</tbody>
</table>
5. TUMOUR AND MOLECULAR ENTITIES
LUNG
Driver mutations in NSCLC adenocarcinomas


EGFR sensitizing 19.4%
EGFR 28%
KRAS 25.3%
No mutations 1.2%
UMD 12.0% (unknown mitogenic driver)
Other drivers 2.9%
PTEN loss 0.7%
CDKN2A loss 1.9%
BRAF non-V600E 1.3%
NF1 loss 1.9%
EGFR T790M 5.5%
EGFR exon20 2.1%
EGFR WT amp 1.0%
ALK fusion 3.8%
ROS1 fusion 2.6%
RET fusion 1.7%
BRAF V600E 2.1%
MET splice 3.0%
MET amp 1.4%
ERBB2 amp 1.4%
BRCA1/2 loss 1.3%
TSC1/2 loss 0.7%
MAP2K1 0.7%
PIK3CA 1.2%
NRAS 1.2%
ERBB2 mut 2.3%
Systemic treatment options

- Asymptomatic patients with BM can be considered for systemic therapy
- For EGFRmut BM, first line osimertinib is the treatment of choice. EGFR-dependent & independent mechanisms of osimertinib failure e.g. MET alterations (7%–24%), EGFR C797X (0%–29%), SCLC transformation (2%–15%), and oncogene fusions (1%–10%) are the most common mechanisms of resistance. Circulating tumour (ct)DNA in the CSF is currently evaluated for monitoring
- The timing of additional SRT is not precisely defined; however, RT seems to play an essential role despite good responses to targeted therapies
- Alectinib is first choice for ALK-altered BM. On target mutations are common, in this case next generation ALK inhibitors are recommended (e.g. lorlatinib)
- For RET-altered BM, selpercatinib seems promising with good brain penetrance
- Immunotherapies (IO) work in the brain as well as in the periphery, SRT may enhance the effect as might combination with chemotherapy (CT). Steroids required for BM, diminish effectiveness
- Patients with a good KPS and NSCLC without molecular alterations and those progressive on IO can be offered CT, which takes into account previous therapies and extra-CNS disease
Osimertinib in untreated $\text{EGFR}_{\text{mut}}$ advanced NSCLC

Progression-free survival in patients with CNS metastases

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
<th>$mo$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>53</td>
<td>15.2 (12.1–21.4)</td>
<td></td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>63</td>
<td>9.6 (7.0–12.4)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.30–0.74)

P<0.001

Median survival of NSCLC with and without ALK alterations

LUNG ALK-POSITIVE NSCLC

ALEX trial: Alectinib versus crizotinib first-line

CNS ORR

Measurable CNS lesions at baseline

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=22)</th>
<th>Alectinib (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS responders, n (%) (95% CI)</td>
<td>11 (50) (28, 72)</td>
<td>17 (81) (58, 95)</td>
</tr>
<tr>
<td>CNS complete response, n (%)</td>
<td>1 (5)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Median DOR in the CNS, months, (95% CI)</td>
<td>5.5 (2.1, 17.3)</td>
<td>17.3 (14.8, NR)</td>
</tr>
</tbody>
</table>

RR in the CNS of 81% with alectinib against 50% with crizotinib for measurable lesions

Cumulative incidence of BM

12% had an event of CNS progression with alectinib vs 68% with crizotinib

BREAST
Survival probability according to breast cancer subtype

ER+ HER2+ => med. 19 months
ER- HER2+ => med. 13 months
ER+ HER2- => med. 7 months
ER- HER2- => med. 4.4 months
Oestrogen-, Progesterone- and HER2- receptor discordance between primary tumour and BM

<table>
<thead>
<tr>
<th></th>
<th>1º tumour</th>
<th>BM</th>
<th>Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone-receptors</td>
<td>Negative</td>
<td>Positive</td>
<td>25%</td>
</tr>
<tr>
<td>HER-2</td>
<td>Negative</td>
<td>Positive</td>
<td>13%</td>
</tr>
</tbody>
</table>

Emerging systemic therapies in HER2 positive breast cancer BM

**Neratinib**: irreversible HER2/HER1 inhibitor

**Tucatinib**: highly selective HER2 inhibitor

While both drugs are working effectively against BM, in combination with chemotherapy (capecitabine), tucatinib has a much safer side-effect profile and reaches median PFS of 7.6 months.

BREAST HER-2 POSITIVE NERATINIB

Results of the Phase II TBRC 022 trial

Capecitabine/Neratinib cohort

- 39 patients with measurable BM from BC
- No prior lapatinib or capecitabine
- All but 3 had CNS PD after local CNS treatment

**Eligibility criteria**
- HER2+ metastatic breast cancer
- Stable or progressive brain metastases, or no evidence of CNS lesions
- Prior treatment with a taxane, trastuzumab, pertuzumab, or T-DM1 allowed
- ECOG performance status of 0 or 1

**Endpoints**
- Primary endpoint: PFS
- Secondary endpoints: ORR, DOR, CBR, safety and tolerability

**Therapies administered on 21-day cycle**
- Tucatinib at 300 mg twice daily
- Capecitabine at 1000 mg/m² twice a day on Days 1 through 14 of each cycle
- Trastuzumab as a loading dose of 8 mg/kg, followed by 6 mg/kg once every 21 days; can be given weekly if needed to compensate for treatment modifications
The HER2CLIMB trial met all primary and alpha-controlled secondary endpoints at the first interim analysis. Importantly, the secondary endpoint of PFS in patients with brain metastases was met.

### PFS by BICR

- **N=480***
  - Risk of progression or death was reduced by **46%**
  - 95% CI: 0.42 to 0.71, \( P<0.001 \)

### Overall survival

- **N=612**
  - Risk of death was reduced by **34%**
  - 95% CI: 0.50 to 0.88, \( P=0.005 \)

### PFS by BICR in patients with brain metastases

- **N=291**
  - Risk of death was reduced by **52%**
  - 95% CI: 0.34 to 0.69, \( P<0.001 \)

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PFS, progression-free survival; BICR, blinded independent central review.

Whether tucatinib might delay additional SRS or salvage WBRT will have to be evaluated.

PFS, defined as time from randomisation to documented disease progression (assessed by blinded independent central review) or death from any cause. Analysis does not include patients with dural lesions only.

N=16
No DLT of IT trastuzumab
Eleven patients had no toxicity attributed to IT trastuzumab.
Three patients achieved a clinical response, seven patients had stable disease and four patients had PD

Conclusions
The MTD and recommended Phase II weekly dose of IT trastuzumab in patients with HER2-BC and MC is 150 mg. Phase II using this dose regimen in MC from HER2-BC is ongoing.

Comments
IT trastuzumab in a 3-week schedule at a dose of 150 mg should be sufficient to treat HER2-positive non-bulky LM due to PK and outcome in a small series (n=3).
Intravenous trastuzumab may be omitted to control extra-CNS disease, since high systemic concentrations of trastuzumab could be measured by IT administration alone.

Abemaciclib is a selective CDK4/6 inhibitor

It crosses the BBB and reaches concentrations that are 10x higher than palbociclib

Effective against BM in xenograft models
Phase 2 trial for Hormone-Receptor positive (HR+) mBC

Cohort A: HR+, HER2- (n=58)
Cohort B: HR+, HER2+(n=27)
Cohort C: HR+, LM (n=10)

Primary endpoint: Intracranial ORR was not met. Intracranial clinical benefit rate of 24% in patients with heavily pretreated HR+, HER2– mBC
BREAST

Triple negative (TN)

Chemotherapy such as paclitaxel, eribulin, capecitabine, anthracyclins, vinorelbine platins may work

Trials with Immunotherapy, PARP inhibitors and antibody-drug conjugates are ongoing
MELANOMA
Immunotherapy (IO) and BM

Best results with IO doublets (Checkmate 204\textsuperscript{1}) nivolumab and ipilimumab

Patients not in need of steroids fare better\textsuperscript{1,2}

Sustainable remissions could be achieved (i.e. ORR up to 59\%\textsuperscript{3}), comparable to effects in the periphery\textsuperscript{1,2}

TKI-naive patients show better results (ABC trial\textsuperscript{3})

**MELANOMA**

*BRAF<sup>V600</sup> mutant*

High concordance of *BRAF<sup>V600</sup>* mutations in CNS and primary tumour

Dabrafenib plus trametinib are working fast and achieve response rates up to 60% (COMBI-MB<sup>1</sup>), the same holds true for newer TKI combinations

While ORRs in the CNS are similar to the periphery, duration of response in CNS is less sustained (median duration 6–8 mo vs 6– >10 mo)

Current trials are exploring triplets (TKI combinations plus IO) remission rates are expected to increase, as will grade 3 and 4 toxicities

---

Inoperable stage III/IV BRAF-mutated melanoma

IO first-line safe?

No

BRAFi/MEKi

Anti-PD-1
Anti-PD-1/Anti-CTLA-4
T-VEC

Clinical Trial
TKI rechallenge

Yes

Anti-PD-1
Anti-PD-1/Anti-CTLA-4
T-VEC

BRAFi/MEKi

Clinical Trial
IO rechallenge

## Melanoma Systemic Treatments for BM

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Trial (setting)</th>
<th>n</th>
<th>Intracranial ORR</th>
<th>Extracranial ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Ipi/Nivo</td>
<td>94</td>
<td>57%</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>¹Checkmate 204 (Prior RT allowed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>²ABC trial (No prior RT)</td>
<td>25</td>
<td>44%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>BRAF&lt;sub&gt;mut&lt;/sub&gt;</strong></td>
<td>Dabrafenib/Trametinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>³COMBI-MB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>V600E no prior RT</td>
<td>76</td>
<td>58%</td>
<td>55%</td>
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<tr>
<td></td>
<td>V600E prior RT</td>
<td>16</td>
<td>56%</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>V600K/D/R</td>
<td>16</td>
<td>44%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>V600 D/E/K/R</td>
<td>17</td>
<td>59%</td>
<td>41%</td>
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</tbody>
</table>

## IMMUNE CHECK-POINT(S) IN BM

<table>
<thead>
<tr>
<th>Authors</th>
<th>Phase</th>
<th>No. of pts</th>
<th>Tumour types</th>
<th>Characteristics</th>
<th>Treatment(s)</th>
<th>CNS ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg, et al. ASCO 2017</td>
<td>II</td>
<td>18</td>
<td>A. Melanoma</td>
<td>At least 1 untreated or progressive BM</td>
<td>Pembrolizumab</td>
<td>A: 22% B: 33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>B. NSCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Margolin, et al. Lancet Oncol 2012</td>
<td>II</td>
<td>72</td>
<td>Melanoma</td>
<td>Cohort A: neurologically asymptomatic Cohort B: neurologically symptomatic and on a stable dose of corticosteroids</td>
<td>Ipilimumab</td>
<td>A: 24% B: 10%</td>
</tr>
<tr>
<td>Tawbi, et al. Checkmate 204</td>
<td>II</td>
<td>75</td>
<td>Melanoma</td>
<td>Asymptomatic/non pretreated BM</td>
<td>Ipilimumab + nivolumab</td>
<td>56%</td>
</tr>
<tr>
<td>Long, et al. ASCO 2017 ABC trial</td>
<td>II</td>
<td>66</td>
<td>Melanoma</td>
<td>Cohort A/B: Asymptomatic/ non pretreated BM Cohort C: failed local therapy, neurologically symptomatic and/or with LM involvement</td>
<td>Ipilimumab + nivolumab (Cohort A/B)</td>
<td>A: 42% B: 20% C: 6%</td>
</tr>
<tr>
<td>Escudier, et al. ASCO 2017</td>
<td>II</td>
<td>44/58</td>
<td>mRCC</td>
<td>BM previously treated or not, but not requiring steroids</td>
<td>Nivolumab</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
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</tbody>
</table>
BEVACIZUMAB IN BM

Positive effects due to reduction of brain oedema, reduction of steroid use
Potential of synergy with Immunotherapy
Improvement of symptomatic radiation necrosis
INNOVATIVE TREATMENT STRATEGIES

Focus on prevention endpoints

Current failure rates of available treatments

Early detection strategies

Primary prevention
  - Predictive biomarkers for BM (ctDNA, CTC, homing signatures)

Use of effective screening tools: treat before symptoms and deterioration of QoL

Secondary prevention: avoid the next CNS event

Based on better knowledge of pathogenesis of brain metastasis (e.g. Brainstorm program – https://clinicaltrials.gov/ct2/show/NCT04109131)
Brain metastases (BM) are an increasing challenge confronting multiple disciplines.

Development of effective therapies to treat BM requires greater understanding of the means by which metastatic cells adapt to the distinct metabolic, chemical, and cellular composition of the brain microenvironment.

Likewise, greater insight is needed into the mechanisms blocking passage of therapeutic agents across the BBB, as well as into the immunologic proclivities of the brain microenvironment and the immune-evasive strategies implemented by BM.