Special Situation: Brain metastases

Matthias Preusser, MD
Associate Professor of Medicine
Department of Medicine I
Comprehensive Cancer Center Vienna
Medical University of Vienna

CNS Tumor Program
Disclosures

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Incidence of brain metastases

- Occur in 10-30% of all adult cancers
- Approx. 10 times more frequent than primary brain tumors
- Relative incidence increasing, due to
  - Effective systemic treatments → with longer survival
  - Improved imaging techniques and their increased availability
- Approx. half of all brain mets due to NSCLC, others:
  - Breast cancer
  - Melanoma
  - Unknown primary
  - Renal cell carcinoma

Barnholtz-Sloan... Sawaya RE. J Clin Oncol 22:2865-72, 2004
Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers

Anna S Berghoff,1,2 Sophie Schur,1,2 Lisa M Füreder,1,2 Brigitte Gatterbauer,2,3 Karin Dieckmann,2,4 Georg Widhalm,2,3 Johannes Hainfellner,2,5 Christoph C Zielinski,1,2 Peter Birner,2,6 Rupert Bartsch,1,2 Matthias Preusser1,2
Mutational heterogeneity in cancer

High brain met risk tumors!
Treatment approaches

- **Neurosurgery**
- **Radiotherapy**
  - Whole brain radiotherapy (WBRT)
  - Stereotactic radiosurgery/radiotherapy (SRS/SRT)
- **Systemic therapy**
  - Chemotherapy
  - Targeted therapies, e.g. tyrosine kinase inhibitors, antibodies
- **Supportive therapy**
  - Edema control
  - Anticonvulsants
  - Pain
Brain-metastatic cascade

Attachment and invasion at branchpoints: selectins, integrins, chemokines, VEGF, COX2, HBEGF, ST6GALNAC5, melanotransferrin, neurotrophins

Hematogenous dissemination

Pro-neoplastic astrocyte effects: heparanase/MMP upregulation, chemoprotection

Microglia recruitment via HIF1a and CXCR4, NO-mediated tumouricidity, potential pro-invasive effects

NSCLC: nodular growth and VEGF-dependent angiogenesis

Melanoma: vascular cooption via integrin beta 1 subunit

Perivascular dormancy

ECM degradation: heparanase, MMP

Preusser et al, Acta Neuropathol 2012
Growth patterns of brain metastases

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
<th>Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delineated</td>
<td>51%</td>
<td>Aa, Ab, Ac, Ad</td>
</tr>
<tr>
<td>Perivascular</td>
<td>18%</td>
<td>Ba, Bb, Bc, Bd</td>
</tr>
<tr>
<td>Diffuse</td>
<td>32%</td>
<td>Ca, Cb, Cc, Cd</td>
</tr>
</tbody>
</table>

Berghoff A (...) Preusser M. Neuro-Oncol 2013
The role of immune cells in the brain metastatic cascade

- Immune evasion is a hallmark of cancer
- Metastasis initiating cells have already performed immune evasion

Different characteristics of the inflammatory microenvironment between primary tumor and metastasis?

Van der Burg et al, Nat Rev 2016
Lymphatic Drainage of the CNS Redefined

LETTER

Structural and functional features of central nervous system lymphatic vessels

Lyve-1 DAPI
Inflammation in CNS diseases

Encephalitis

Multiple sclerosis

Gemistocytic astrocytoma
Tumor-infiltrating lymphocytes in brain tumors

Gehirnmetastase Lungenkarzinom

Glioblastom

Berghoff A (...) Preusser M. Onco-Immunol 2016
Microglia/macrophages in brain metastases

CD68
Prognostic role of TILs in brain metastases

A. Survival Functions

CD3+ TIL density
- Low
- High

$p = 0.015$

B. Survival Functions

CD8+ TIL density
- Low
- High

$p = 0.030$

C. Survival Functions

CD45RO+ TIL density
- Low
- High

$p = 0.006$

D. Survival Functions

Immuno Score
- Low
- Moderate
- High

$p = 0.026$

Berghoff, Onco-Immunol 2015
Immune cycle in brain tumors

1. Antigen release and antigen uptake
2. Antigen-presenting cell migration and lymph drainage
3. Antigen presentation and T-cell priming
4. T-cell traffic with migration through the blood–brain barrier and blood–tumour barrier
5. Interaction between T cell and tumour cell or antigen-presenting cell

Tumour cell
Antigen-presenting cell
Glioblastoma tumour
Microglia

Preusser et al, Nature Rev Neurol 2015
Blood brain barrier constituents

Pericyte
Astrocyte endfoot
Basement membrane
Tight junction
Endothelial cell
Transport routes across the intact blood brain barrier
Blood-brain barrier disruption

- Basement membrane discontinuation
- Disruption of tight junctions
- Fluid extravasation (edema)
- Tumor cell
Blood-brain barrier

Preusser et al. ESMO Open 2017

Cytotoxic activity

Chemoattraction

Adhesion

Transmigration

Lymphocyte

Lymphocyte extravasation
Immune checkpoint inhibitors for brain metastases?
Anti-CTLA4
Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi


<table>
<thead>
<tr>
<th></th>
<th>Cohort A (n=51)</th>
<th>Cohort B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mWHO</td>
<td>irRC</td>
</tr>
<tr>
<td>Global disease control</td>
<td>9 (18%, 8–31)</td>
<td>13 (25%, 14–40)</td>
</tr>
<tr>
<td>CNS disease control</td>
<td>12 (24%, 13–38)</td>
<td>13 (25%, 14–40)</td>
</tr>
<tr>
<td>Non-CNS disease control</td>
<td>14 (27%, 16–42)</td>
<td>17 (33%, 21–48)</td>
</tr>
<tr>
<td>Global objective response</td>
<td>5 (10%, 3–21)</td>
<td>5 (10%, 3–21)</td>
</tr>
<tr>
<td>CNS objective response</td>
<td>8 (16%, 7–29)</td>
<td>8 (16%, 7–29)</td>
</tr>
<tr>
<td>Non-CNS objective response</td>
<td>7 (14%, 6–26)</td>
<td>7 (14%, 6–26)</td>
</tr>
</tbody>
</table>

Data are n (%, 95% CI). mWHO=modified WHO criteria. irRC=immune-related response criteria.

*Table 3: Disease control and objective response after 12 weeks*

Cohort A: asymtomatic, no corticosteroids (n=51)
Cohort B: symptomatic, stable dose of corticosteroids (n=21)

4x Ipi 10 mg/kg every 3 weeks, then maintenance every 12 weeks
Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

Figure: Overall survival
Crosses indicate censored patients.
**Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial**

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi


<table>
<thead>
<tr>
<th>Immune-related events</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>22 (43%)</td>
<td>6 (12%)</td>
<td>0</td>
<td>8 (38%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>17 (33%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>6 (29%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16 (31%)</td>
<td>0</td>
<td>0</td>
<td>5 (24%)</td>
<td>0</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>3 (6%)</td>
<td>0</td>
<td>0</td>
<td>4 (19%)</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CNS-related events</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18 (35%)</td>
<td>2 (4%)</td>
<td>0</td>
<td>6 (29%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (22%)</td>
<td>0</td>
<td>0</td>
<td>2 (10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are n (%). Events occurring in at least 15% of patients in either cohort. *Grades 1–5 with National Cancer Institute’s Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0.

*Table 5: Adverse events*
Does anti-CTLA4 have a prophylactic effect for brain metastases?

Development of brain metastases in patients with metastatic melanoma while receiving ipilimumab

C. Frenard¹ · L. Peuvrel¹ · M. Saint Jean¹ · A. Brocard¹ · A. C. Knol¹ · J. M. Nguyen¹ · A. Khammari¹ · G. Quereux¹ · B. Dreno¹

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab (46 patients)</th>
<th>Vemurafenib (87 patients)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Cerebral metastases</td>
<td>21.7</td>
<td>29.9</td>
<td>0.4124</td>
</tr>
<tr>
<td>Sex ratio M/W</td>
<td>0.6</td>
<td>1.3</td>
<td>0.044</td>
</tr>
<tr>
<td>Mean age</td>
<td>58.07 years (±14.83)</td>
<td>59.6 years (±15.61)</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean breslow thickness</td>
<td>3.3 mm (±3.1)</td>
<td>4.5 mm (±3.9)</td>
<td>1.5</td>
</tr>
<tr>
<td>Histological subtype</td>
<td>NM: 14</td>
<td>NM: 28</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>SSM: 16</td>
<td>SSM: 40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALM: 5</td>
<td>ALM: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucosal: 5</td>
<td>Mucosal: 1</td>
<td></td>
</tr>
<tr>
<td>Unknown primary melanoma</td>
<td>6</td>
<td>16</td>
<td>0.43</td>
</tr>
</tbody>
</table>

NM nodular melanoma, SSM superficial spreading melanoma, ALM acral lentiginous melanoma
Anti-PD1
Response to nivolumab in two brothers with biallelic mismatch repair deficiency (bMMRD)

Bouffet, JCO 2016
PD-L1 expression in brain metastases

NSCLC brain metastasis

52.0% PD-L1 positive

Melanoma brain metastasis

45.7% PD-L1 positive

Berghoff et al, Histopathol 2014
Does the inflammatory microenvironment differ between primary tumor and brain metastasis?

PD-1 Inhibitor Pembrolizumab

NSCLC and melanoma brain metastases

18 melanoma, 18, NSCLC
Small, asymptomatic, no corticosteroids
Untreated or progressive after radiotherapy
10mg/kg pembrolizumab every two weeks
## PD-1 Inhibitor Pembrolizumab

**NSCLC and melanoma brain metastases**

<table>
<thead>
<tr>
<th></th>
<th>Melanoma (n=18)</th>
<th>NSCLC (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>0</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (17%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (17%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Treatment-related non-neurological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis or diarrhoea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (44%)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatological</td>
<td>6 (33%)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>2 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Haematological</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elevated aminotransferases</td>
<td>0</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

NSCLC = non-small-cell lung cancer. There were no treatment-related deaths. *Irrespective of attribution to study drug.

**Table 3:** Neurological adverse events and treatment-related non-neurological adverse events in all treated patients with melanoma or NSCLC

**Goldberg S.** *Lancet Oncol* 2016
What about anti-PD1 in symptomatic brain metastases?

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of IC metastases</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (10)</td>
</tr>
<tr>
<td>2–4</td>
<td>34 (52)</td>
</tr>
<tr>
<td>5–10</td>
<td>19 (29)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Median SoD of IC targets (mm; range)</td>
<td>23.5 (5–153)</td>
</tr>
<tr>
<td>Median number of EC metastatic sites (range)</td>
<td>3 (0–7)</td>
</tr>
<tr>
<td>Symptomatic BM</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>46 (70)</td>
</tr>
<tr>
<td>Yes</td>
<td>20 (30)</td>
</tr>
<tr>
<td>On steroids for symptomatic BM</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>51 (77)</td>
</tr>
<tr>
<td>Yes</td>
<td>15 (23)</td>
</tr>
</tbody>
</table>

Abbreviations: BM = brain metastases; EC = extracranial; IC = intracranial; SoD = sum of dimensions.
Response to anti-PD-1 in symptomatic melanoma brain metastases

Figure 2. Swimmer’s plot showing durable responses in patients who achieved an objective response to anti-PD1 therapy.
Impact of symptoms and baseline steroids

A. Intracranial progression free survival
   - No CNS symptoms
   - CNS symptoms

B. Overall survival
   - No CNS symptoms
   - CNS symptoms

C. Intracranial progression free survival
   - No steroids
   - Steroids (Independent of use for symptomatic BMs)

D. Overall survival
   - No steroids
   - Steroids (Independent of use for symptomatic BMs)

Parakh S. Br J Cancer 2017
Anti-PDL1
Atezolizumab in Advanced NSCLC Patients with Baseline Brain Metastases: a Pooled Cohort Safety Analysis

Rimas Lukas,1 Mayank Gandhi,2 Carol O’Hear,2 Sylvia Hu,2 Marcus Ballinger,2 Catherine Lai,2 Jyoti D. Patel3
1Department of Neurology, The University of Chicago Medicine, Chicago, IL, USA
2Genentech, Inc., South San Francisco, CA, USA
3Section of Hematology/Oncology, The University of Chicago Medicine, Chicago, IL, USA

Figure 2. Kaplan-Meier Curve of OS From OAK in Patients With Baseline Brain Metastases: Atezolizumab vs Docetaxel

No. at Risk
Atezolizumab 38 36 35 33 31 30 28 27 27 27 27 25 24 23 21 18 18 16 8 6 5 4 3
Docetaxel 47 40 38 37 33 30 29 27 24 21 20 19 18 16 14 12 11 9 8 7 6 5 1

HR 0.54
(95% CI 0.31, 0.94)
P = 0.0279

Median 11.9 mo
(95% CI 6.8, 14.4)
Median 20.1 mo
(95% CI 14.0, NE)
Combination of immune checkpoint inhibitors
Efficacy and safety of nivolumab plus ipilimumab in patients with melanoma metastatic to the brain: Results of the phase II study CheckMate 204

<table>
<thead>
<tr>
<th>Best overall response, n (%)</th>
<th>Global</th>
<th>Intracranial</th>
<th>Extracranial</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (3, 0–9)</td>
<td>14 (19, 11–29)</td>
<td>4 (5, 1–13)</td>
</tr>
<tr>
<td>PR</td>
<td>40 (53, 41–65)</td>
<td>28 (37, 26–49)</td>
<td>33 (44, 33–56)</td>
</tr>
<tr>
<td>SD &gt;6 months</td>
<td>5 (7, 2–15)</td>
<td>6 (8, 3–17)</td>
<td>2 (3, 0–9)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>42 (56, 44–68)</td>
<td>42 (56, 44–68)</td>
<td>37 (49, 38–61)</td>
</tr>
</tbody>
</table>

Brain met size max 3cm
No neurological symptoms or baseline steroids
NIVO 1 mg/kg + IPI 3 mg/kg Q3W x 4, then NIVO 3 mg/kg Q2W until progression or toxicity

Tawbi et al. ASCO 2017
A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients with melanoma brain metastases: The Anti-PD1 Brain Collaboration (ABC)

<table>
<thead>
<tr>
<th></th>
<th>A N = 25 nivo+ipi</th>
<th>B N = 25 nivo</th>
<th>C N = 16 nivo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICR % (95% CI)</td>
<td>44 (24, 65)</td>
<td>20 (7, 41)</td>
<td>6 (0, 30)</td>
</tr>
<tr>
<td>ICR Complete Response</td>
<td>16 (24, 65)</td>
<td>12 (7, 41)</td>
<td>0</td>
</tr>
<tr>
<td>ECR % (95% CI)</td>
<td>38 (18, 62)</td>
<td>26 (10, 48)</td>
<td>21 (5, 50)</td>
</tr>
<tr>
<td>6-mo PFS % (95% CI)</td>
<td>50 (33, 75)</td>
<td>29 (15, 56)</td>
<td>0</td>
</tr>
<tr>
<td>6-mo OS % (95% CI)</td>
<td>76 (59, 97)</td>
<td>59 (41, 86)</td>
<td>44 (25, 76)</td>
</tr>
</tbody>
</table>

Reduced activity in patients who progressed on BRAF inhibitors

Poor response in patients with neurological symptoms, leptomeningial disease or prior local therapy

Long et al. ASCO 2017
Combination of immune checkpoint inhibitors with radiotherapy
## Combination of immune checkpoint inhibitor and radiotherapy in brain metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary</th>
<th>n</th>
<th>RT</th>
<th>Drug</th>
<th>Brain control</th>
<th>Median survival</th>
<th>Toxicity</th>
<th>Median follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al. [85]</td>
<td>Melanoma</td>
<td>20</td>
<td>SRS</td>
<td>ipilimumab 1 during SRS 12 before SRS 7 after SRS</td>
<td>Not improved versus SRS alone (8 versus 9.1 mo)</td>
<td>Not improved versus SRS alone</td>
<td>No increased toxicity</td>
<td>7.3</td>
</tr>
<tr>
<td>Krisely et al. [83]</td>
<td>Melanoma</td>
<td>77</td>
<td>SRS</td>
<td>ipilimumab 27 + SRS 11 before SRS 15 after SRS</td>
<td>Brain local 37% NR</td>
<td>21.3 mo (versus 4.9 without ipi) No NR before/after</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Silk et al. [86]</td>
<td>Melanoma</td>
<td>72</td>
<td>WBRT 16 SRS 17</td>
<td>ipilimumab 33 + RT 12 before RT 21 after RT</td>
<td>Not significantly increased in 65% (OS 6 mo)</td>
<td>18.3 mo (versus 5.3 without ipi) 18.4 mo</td>
<td>No neuro-toxicity (ipi)</td>
<td>10</td>
</tr>
<tr>
<td>Mathew et al. [84]</td>
<td>Melanoma</td>
<td>58</td>
<td>SRS</td>
<td>ipilimumab 25 + SRS 4 before SRS 7 during SRS 12 after SRS</td>
<td>Brain 63%</td>
<td>69% (NS) (1-y OS) 66%</td>
<td>No increased toxicity</td>
<td>6</td>
</tr>
<tr>
<td>Kess et al. [82]</td>
<td>Melanoma</td>
<td>46</td>
<td>SRS</td>
<td>ipilimumab 33 without ipi 15 during SRS 19 before SRS 12 after SRS</td>
<td>Brain local 31% 100%</td>
<td>16.5 mo 3-y OS 50% 4 mo</td>
<td>during SRS: no relevant toxicity before SRS: ITH (13%0%), seizure (13%0%) after SRS: ITH (63%)</td>
<td>22</td>
</tr>
<tr>
<td>Tazi et al. [87]</td>
<td>Melanoma</td>
<td>10</td>
<td>SRS</td>
<td>ipilimumab During or after SRS</td>
<td>Brain local 8% 89%</td>
<td>16.5 mo</td>
<td>No increased toxicity</td>
<td>NR</td>
</tr>
<tr>
<td>Gerber et al. [88]</td>
<td>Melanoma</td>
<td>13</td>
<td>WBRT</td>
<td>ipilimumab 4 before WBRT 6 during WBRT 3 after WBRT</td>
<td>Brain 56%</td>
<td>64 mo</td>
<td>1 grade 3 cognitive change 100% new or worsening ITH</td>
<td>4</td>
</tr>
<tr>
<td>Cohen-Onbar et al. [89]</td>
<td>Melanoma</td>
<td>46</td>
<td>SRS</td>
<td>ipilimumab 14 before SRS 32 during/after SRS</td>
<td>Brain 33.6% 16.5%</td>
<td>6.4 mo</td>
<td>RN and post-SRS edema increased when ipi was administered during or after SRS pseudo clinical and radiological progression</td>
<td>7.9</td>
</tr>
<tr>
<td>Alomari et al. [90]</td>
<td>Melanoma NSCLC</td>
<td>2</td>
<td>SRS</td>
<td>Pembrolizumab 100%</td>
<td>Brain 50% 72.6%</td>
<td>13.8 mo</td>
<td>NA</td>
<td>NR</td>
</tr>
<tr>
<td>Ahmed et al. [91]</td>
<td>Melanoma</td>
<td>26</td>
<td>SRS</td>
<td>Nivolumab 6b before/after</td>
<td>Brain 53% 85%</td>
<td>(1-y) (1-y)</td>
<td>ITH: 9% Grade 3 oedema: 10%</td>
<td>9.4</td>
</tr>
</tbody>
</table>


ipilimumab = RT, radiation therapy; SRS, stereotactic radiosurgery; OS, overall survival; WBRT, whole-brain radiation therapy; NSCLC, non-small-cell lung cancer; NR, not reported; NS, non-significant; NA, not applicable; ITH, intra-tumor hemorrhage.
Summary

New treatment approaches for brain tumors are urgently needed.

Preclinical and clinical data support immunotherapy as a therapeutic opportunity in brain metastases.

Immunotherapies seem to be active in tumor types commonly causing brain metastases (lung cancer, melanoma).

Many open questions on biomarkers and combination/sequencing strategies.
Thank you!