Brain metastasis: future developments

Matthias Preusser
Medical University of Vienna
Disclosures

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Blood-brain barrier

64Cu-DOTA-trastuzumab PET

Branched evolution: moving targets

Common ancestor cell of primary tumor and brain metastases

Common mutations of primary tumor and brain metastases

Branched evolution of brain metastases

Primary tumor

Common ancestor cell of all brain metastases

Mutations detected only in the brain metastases

Mutations detected only in brain metastasis location 1

Common ancestor cell of primary tumor and brain metastases

Common mutations of primary tumor and brain metastases

Primary tumor

Mutations detected only in the primary tumor

D

Lung adenocarcinoma (098)

1st BM recurrence

2nd BM recurrence

Time (2 years)

50 mutations

Chr 2p H.amp (ALK)

APC p.S673G

MECOM H.amp

IL7R/SLC1A3 H.amp

YAP1/BIRC3/BIRC2/
TMEM123/MMP7/MMP20 H.amp

SMAD4 Del

BM

MAP2K4 p.D149

ZNF217 H.amp

NOTCH2 p.P6fs

TP53 p.G279fs

MYC H.amp

KIT Amp

Berghoff et al; Semin Neurol. 2018
# Predictive biomarkers in brain metastases

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Biomarker</th>
<th>Test method</th>
<th>Discordance rate between primary tumor and brain metastasis</th>
<th>Approved targeted drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>EGFR mutation</td>
<td>Gene sequencing</td>
<td>0–32 %</td>
<td>Gefitinib, Erolitinib</td>
</tr>
<tr>
<td></td>
<td>ALK rearrangement</td>
<td>FISH</td>
<td>0–12.5 %</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>HER2 amplification</td>
<td>IHC, FISH</td>
<td>0–14 %</td>
<td>Lapatinib, Trastuzumab, Pertuzumab, T-DM1</td>
</tr>
<tr>
<td></td>
<td>ER and PR expression</td>
<td>IHC</td>
<td>30–50 %</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF mutations</td>
<td>Gene sequencing, IHC, COBAS V600 test</td>
<td>0 %</td>
<td>Vemurafenib, Dabrafenib, Trametinib</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>RAS mutations</td>
<td>Gene sequencing</td>
<td>Unknown</td>
<td>Cetuximab, Panitumumab</td>
</tr>
<tr>
<td>Gastroesophageal cancer</td>
<td>HER2 amplification</td>
<td>IHC, FISH</td>
<td>0 %</td>
<td>Trastuzumab</td>
</tr>
</tbody>
</table>


HER2 over-expression

- Breast cancer: 10-20%
- Gastric cancer: 7-34%
- IHC -> CISH
- Disconcordance rate: 14%
- HER2 targeting therapies
  - Antibodies: trastuzumab, pertuzumab, T-DM1
  - TKI: Lapatinib, Afatinib
Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study

Thomas Bachelot, Gilles Romieu, Marie Campone, Véronique Diéras, Claire Croset, Florence Dalenc, Marta Jimenez, Emilie Le Rhun, Jean-Yves Pierga, Anthony Gonzales, Marianne Leheurette, Julien Gomont, Maya Gutierrez, Hervé Core, Jean-Marc Ferrero, Catherine Laible-Dreux

Table 3: Objective CNS response in assessable patients

<table>
<thead>
<tr>
<th>Reduction</th>
<th>Patients (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥80% reduction</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>50–&lt;80% reduction</td>
<td>20 (45%)</td>
</tr>
<tr>
<td>20–&lt;50% reduction</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>0–&lt;20% reduction</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Progression*</td>
<td>7 (16%)</td>
</tr>
</tbody>
</table>

*Two patients had progression outside of the CNS.

Time to WBRT 8.3 months
Activity of T-DM1 in Her2-positive breast cancer brain metastases

Rupert Bartsch\textsuperscript{1,2}, Anna S. Berghoff\textsuperscript{1,2}, Ursula Vogl\textsuperscript{3}, Margaretha Rudas\textsuperscript{1,4}, Elisabeth Bergen\textsuperscript{1,2}, Peter Dubsky\textsuperscript{1,5}, Karin Dieckmann\textsuperscript{1,6}, Katja Pinker\textsuperscript{1,7}, Zsuzsanna Bago-Horvath\textsuperscript{1,4}, Arik Galid\textsuperscript{8}, Leopold Oehler\textsuperscript{3}, Christoph C. Zielinski\textsuperscript{1,2}, Michael Gnant\textsuperscript{1,5}, Guenther G. Steger\textsuperscript{1,2}, Matthias Preusser\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Best intracranial response</th>
<th>0</th>
<th>3</th>
<th>4</th>
<th>3</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0.0</td>
<td>30.0</td>
<td>40.0</td>
<td>30.0</td>
<td>50.0</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial Clinical Benefit Rate (CBR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key words: T-DM1, Her2-positive breast cancer, brain metastases, ADC, intracranial response, OS, PFS, BM.
EGFR mutations

• Sequencing
  • Exon 19 Deletion
  • L858R (Exon 21)
  • T790M Exon 20)

• 10-15% of adeno-carcinomas NSCLC
  • Never smokers, women, Asian heritage

• Risk for brain metastases?

• Diskordance rate: 0-32%

Grommes et al, Neuro-Oncology (2011)
EGFR TKI

• 1. generation: Erlotinib, Gefitinib
• 2. generation: Afatinib
• 3. generation (T790M): Osimertinib
• Liquid Biopsy
• Kombination with SRS/WBRT
• Pulsatile regimen?

“Pulsatile” high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer

Christian Grommes, Geoffrey R. Oxnard, Mark G. Kris, Vincent A. Miller, William Pao, Andrei I. Holodny, Jennifer L. Clarke, and Andrew B. Lassman

Department of Neurology (C.G., I.L.C., A.B.L.); Neuro-radiology Service (A.I.H.); and Thoracic Oncology Service (G.R.O., M.G.K., V.A.M., W.P.), and the Brain Tumor Center (C.G., A.I.H., A.B.L.), Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York, NY (M.G.K., V.A.M., A.I.H., A.B.L.)
Osimertinib or Platinum–Pemetrexed in EGFR T790M–Positive Lung Cancer


B Patients with CNS Metastases

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Median Progression-free Survival</th>
<th>Hazard ratio for disease progression or death, 0.32 (95% CI, 0.21–0.49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>93</td>
<td>8.5 (6.8–12.3)</td>
<td></td>
</tr>
<tr>
<td>Platinum–pemetrexed</td>
<td>51</td>
<td>4.2 (4.1–5.4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>93 80 46 27 14 4 0</td>
</tr>
<tr>
<td>Platinum–pemetrexed</td>
<td>51 32 9 4 2 0 0</td>
</tr>
</tbody>
</table>
ALK and ROS1

- ALK-EML4 translocation
  - 5-10% NSCLC (adenocarcinoma)
- ROS1 rearrangements
  - 1-2% of NSCLC (adenocarcinoma)
- IHC -> FISH
- Disconcordance rate: 0-10%

- ALK TKI
  - Crizotinib, Alectinib, Ceritinib

ALK gene translocations and amplifications in brain metastases of non-small cell lung cancer

Matthias Preussner1,2, Anna S. Berghoff1,2, Ayseguel Ilhan-Mutlu4,2, Manuel Magerle2, Carina Dimboe4,2, Georg Wiedmann1,2, Karin Deichmann2, Christine Marosi1,2, Adelheid Wibber1,2, Monika Hackl1, Sabine Zochbauer-Müller1, Andreas von Deimling3, Sebastian F. Schoppmann1, Christoph C. Zehnder4,2, Berthold Streubel1, Peter Birrer1,2
Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study


100
80
60
40
20
0

Progression-free survival

Day 1 3 6 9 12 15 18 21 24 27 30

100
80
60
40
20
0

Progression-free survival

Day 1 3 6 9 12 15 18 21 24 27 30

HR 0.40 (95% CI: 0.25–0.64)
P < 0.0001

Crizotinib (n=58)
Alectinib (n=64)

7.4 mo (6.6 to 9.6)
NR (9.2 to NR)

Number at risk
Crizotinib 58 48 66 22 17 9 6 3 1
Alectinib 64 54 41 39 36 31 24 10 4 1

MEDIZINISCHE UNIVERSITÄT WIEN
BRAF mutation

- Melanoma: 50%
- NSCLC: 2-3%
- Colon-carcinoma: 10%
- IHC (V600E) or sequencing
- Disconcordance: 0%
- TKI
  - Dabrafenib, Vemurafenib
  - Combination with MEK inhibitors
Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial


A

Best confirmed intracranial response
- Complete response
- Progressive response
- Partial response
- Stable disease

Maximum change from baseline measurement (%)

B

Progression-free survival (%)

Number at risk (number censored)

Median 5.6 months (95% CI 3.3–7.4)

C

Overall survival (%)

Time since first dose (months)

Number at risk (number censored)

Median 10.8 months (95% CI 8.7–19.6)
Immune check-point inhibition

Preusser et al, Nature Rev Neurol 2015
T cells in brain metastases

More dense T cell infiltrates in secondary than in primary brain tumors

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>66.7%</td>
<td>NSCLC Brain metastasis</td>
</tr>
<tr>
<td>LGG</td>
<td>43.4%</td>
<td></td>
</tr>
</tbody>
</table>

*CD3+ lymphocytes Tumor cells*

References:
- Berghoff A et al. Neurooncol 2014
- Berghoff A et al. Neurooncol 2017(2)
PD-L1 expression in primary and secondary brain tumors

Glioblastoma

Brain metastases

88%

Melanom: 46%

Lungenkarzinom: 52%

Berghoff A et al. Neurooncol 2014
Berghoff A et al. Neurooncol 2017 (2)
Berghoff AS et al. Histopathol 2015
Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial


<table>
<thead>
<tr>
<th>ECOG performance status</th>
<th>Melanoma (n=18)</th>
<th>NSCLC (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6 (33%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>1</td>
<td>12 (67%)</td>
<td>15 (83%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mutation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>6 (33%)</td>
<td>NA</td>
</tr>
<tr>
<td>NRAS*</td>
<td>3 (19%)</td>
<td>NA</td>
</tr>
<tr>
<td>KRAS</td>
<td>NA</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>EGFR</td>
<td>NA</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>ALK</td>
<td>NA</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1 positive</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>18 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of previous systemic therapy regimens</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4 (22%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>1</td>
<td>7 (39%)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (17%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>4 (22%)</td>
<td>4 (22%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous ipilimumab</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6 (33%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Surgical resection</td>
<td>8 (44%)</td>
<td>2 (21%)</td>
</tr>
<tr>
<td>Whole brain radiotherapy</td>
<td>3 (17%)</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Stereotactic radiosurgery</td>
<td>9 (50%)</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of total brain lesions per patient</th>
<th>Melanoma (n=18)</th>
<th>NSCLC (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 (4-12)</td>
<td>6 (3-18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of target brain lesions per patient</th>
<th>Melanoma (n=18)</th>
<th>NSCLC (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 (1-4)</td>
<td>2 (1-5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size of all target lesions (mm)</th>
<th>Melanoma (n=18)</th>
<th>NSCLC (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated (mm)</td>
<td>11 (8-14)</td>
<td>8 (7-10)</td>
</tr>
<tr>
<td>Progression after previous SRS or WBRT (mm)</td>
<td>10 (7-13)</td>
<td>8 (7-10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total number of target brain lesions in all patients</th>
<th>Melanoma (n=18)</th>
<th>NSCLC (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total previously untreated</td>
<td>32 (13 patients)</td>
<td>43 (16 patients)</td>
</tr>
<tr>
<td>Total progressing after previous SRS or WBRT</td>
<td>13 (5 patients)</td>
<td>3 (2 patients)</td>
</tr>
<tr>
<td>Progression after previous SRS</td>
<td>7 (3 patients)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are median (IQR), unless otherwise stated. NSCLC = non-small-cell lung cancer. SRS = stereotactic radiosurgery. WBRT = whole brain radiotherapy.

Table 2: Number and size of total and target brain metastases in patients with melanoma or NSCLC
### Table 3: Neurological adverse events and treatment-related non-neurological adverse events in all treated patients with melanoma or NSCLC

<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.
Efficacy and Safety of the Combination of Nivolumab Plus Ipilimumab in Patients With Melanoma and Asymptomatic or Symptomatic Brain Metastases (CheckMate 204)

Hussein Tawbi,1 Peter Forsyth,2 F. Stephen Hodi,3 Christopher Lao,4 Stergios Moschos,5 Omid Hamid,6 Michael B. Atkins,7 Karl Lewis,8 Reena P. Thomas,9 John A. Glaspy,10 Sekwon Jang,11 Alain Algazi,12 Nikhil I. Khushalani,2 Michael A. Postow,13 Anna C. Pavlick,14 Marc Ernstoß,15 David A. Reardon,3 Agnes Balogh,16 Jasmine Rizzo,16 Kim Margolin17

1University of Texas, MD Anderson Cancer Center, Houston, TX; 2Moffitt Cancer Center and Research Institute, Tampa, FL; 3Dana-Farber Cancer Institute, Boston, MA; 4University of Michigan, Ann Arbor, MI; 5University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; 6The Angeles Clinic and Research Institute, Los Angeles, CA; 7Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; 8University of Colorado Comprehensive Cancer Center, Aurora, CO; 9Stanford University Hospital, Palo Alto, CA; 10Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA; 11Inova Schar Cancer Institute, Virginia Commonwealth University, Fairfax, VA; 12University of California, San Francisco, San Francisco, CA; 13Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; 14New York University Langone Medical Center, New York, NY; 15Roswell Park Cancer Institute, Buffalo, NY; 16Bristol-Myers Squibb, Princeton, NJ; 17City of Hope, Duarte, CA

Abstract Number 9501
## Response to Treatment – Asymptomatic Patients

### Patients (n = 101)

<table>
<thead>
<tr>
<th>Best overall response, n (%)</th>
<th>Intracranial</th>
<th>Extracranial</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>29 (29)</td>
<td>11 (11)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Partial response</td>
<td>26 (26)</td>
<td>38 (38)</td>
<td>40 (40)</td>
</tr>
<tr>
<td>Stable disease ≥ 6 months</td>
<td>4 (4)</td>
<td>6 (6)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>27 (27)</td>
<td>16 (16)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>15 (15)</td>
<td>30 (30)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18 (18)</td>
</tr>
</tbody>
</table>

- **Death prior to first on-study assessment**: 3 (3) Intracranial, 3 (3) Extracranial, 2 (2) Global
- **Early discontinuation due to toxicity**: 0 (0) Intracranial, 1 (1) Extracranial, 1 (1) Global
- **Stable disease < 6 months**: 8 (8) Intracranial, 15 (15) Extracranial, 10 (10) Global
- **Other**: 4 (4) Intracranial, 11 (11) Extracranial, 5 (5) Global

### ORR, n/N (%)

- **(95% CI)**
  - Intracranial: 55/101 (54%) (44–64%)
  - Extracranial: 49/101 (49%) (38–59%)
  - Global: 51/101 (51%) (40–61%)

### CBR<sup>b</sup>, n/N %

- **(95% CI)**
  - Intracranial: 59/101 (58%) (48–68%)
  - Extracranial: 55/101 (54%) (44–64%)
  - Global: 55/101 (54%) (44–64%)

<sup>a</sup>Seven of these patients did not have extracranial disease at baseline; <sup>b</sup>Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months.
Intracranial Tumor Burden Change and Characteristics of Intracranial Response – Asymptomatic Patients

<table>
<thead>
<tr>
<th>N = 101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to response, months, (range)</td>
</tr>
<tr>
<td>Median duration of response, months (95% CI)</td>
</tr>
<tr>
<td>Ongoing response among responders</td>
</tr>
</tbody>
</table>

Median change: −57.1%
High efficacy in a- to oligosymptomatic patients

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

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Table 2. Response to Treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intracranial (N=94)</th>
<th>Extracranial (N=94)</th>
<th>Global (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response — no. (%)*</td>
<td>24 (26)</td>
<td>7 (7)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Partial response</td>
<td>28 (30)</td>
<td>40 (43)</td>
<td>40 (43)</td>
</tr>
<tr>
<td>Stable disease for ≥6 mo</td>
<td>2 (2)</td>
<td>6 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>31 (33)</td>
<td>28 (30)</td>
<td>33 (35)</td>
</tr>
<tr>
<td>Could not be evaluated†</td>
<td>9 (10)</td>
<td>13 (14)</td>
<td>8 (9)</td>
</tr>
</tbody>
</table>

Objective response‡

| No. of patients                        | 52                  | 47                  | 48            |
| Percent of patients (95% CI)           | 55 (45–66)          | 50 (40–60)          | 51 (40–62)    |

Clinical benefit§

| No. of patients                        | 54                  | 53                  | 53            |
| Percent of patients (95% CI)           | 57 (47–68)          | 56 (46–67)          | 56 (46–67)    |

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Progression-Free Survival – Symptomatic Patients

Number of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>Intracranial</th>
<th>Extracranial</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients at risk:</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>PFS (%) at Months</td>
<td>100</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Median follow-up = 5.2 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CheckMate 204

Events/ Median (95% CI)
patients

- Intracranial: 13/18, 1.2 (0.7–1.3)
- Extracranial: 10/18, 2.2 (0.8–NR)
- Global: 11/18, 1.2 (0.8–NR)
Concordance of intra- & extracranial responses with ipilimumab?

Includes patients with evaluable radiological assessments ≥ 12 weeks

* Intracranial metastases only
Safety and Efficacy of Nivolumab Plus Ipilimumab in Patients With Advanced Renal Cell Carcinoma With Brain Metastases: Interim Analysis of CheckMate 920

Hamid Emamekhoo,1 Mark Olsen,2 Bradley Carthon,3 Alexandra Drakaki,4 Ivor Percent,5 Ana M. Molina,6 Daniel Cho,7 Johanna Bendell,8 Lucio Gordan,9 Arash Rezazadeh-Kalebasty,10 Daniel J. George,11 Thomas Hutson,12 Edward Arrowsmith,13 Richard Lee,14 Tina C. Young,14 Jennifer L. Johansen,14 David Leung,14 Scott S. Tykodi15

Abstract Number 4517
Objective response rate and best overall response in patients with aRCC and brain metastases

<table>
<thead>
<tr>
<th>Response</th>
<th>Cohort 3 (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate, %</strong></td>
<td>29</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>13–49</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>8 (29)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (32)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>5 (18)</td>
</tr>
</tbody>
</table>

Events | Median PFS, months (95% CI) |
-------|-----------------------------|
11/28   | 9.0 (2.9–NE)               |

Progression-free survival (probability) 62.3%

No. at risk: 28 16 12 8 2 2 0
Prevention of brain metastases

Table S6. Incidence of New Lesions in the Intention-to-Treat Population (BICR).*

<table>
<thead>
<tr>
<th>New lesion site†</th>
<th>Durvalumab (N=476)</th>
<th>Placebo (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
</tr>
<tr>
<td>Any new lesion</td>
<td>97 (20.4)</td>
<td>76 (20.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>56 (11.8)</td>
<td>41 (17.3)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>27 (5.7)</td>
<td>27 (11.4)</td>
</tr>
<tr>
<td>Brain</td>
<td>26 (5.5)</td>
<td>26 (11.0)</td>
</tr>
<tr>
<td>Liver</td>
<td>9 (1.9)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>Bone</td>
<td>8 (1.7)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>3 (0.6)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (1.9)</td>
<td>5 (2.1)</td>
</tr>
</tbody>
</table>

*According to RECIST v1.1.
†A patient may have had more than one new lesion site.
BICR, Blinded Independent Central Review; RECIST, Response Evaluation Criteria In Solid Tumors.
Summary

- Systemic therapies for brain metastasis patients rapidly evolving
  - Target treatments
  - Immunotherapies

- Combination and sequencing with other therapies to be established

- Prevention of brain metastases an emerging clinically relevant paradigm
Thank you for your attention!
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