FUTURE DEVELOPMENTS IN LEPTOMENINGEAL METASTASES

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DISCLOSURE OF INTEREST

Emilie Le Rhun

- Personal financial interests: Tocagen, Abbvie, Daiichy Sankyo, Mundipharma and Novartis
- Institutional financial interests: Mundipharma and Amgen
- Non-financial interests: Abbvie
Diagnosis
- CSF analysis
- MRI response assessment

Management
- intrathecal treatment
- systemic pharmacotherapy
Diagnosis
- CSF analysis
- MRI response assessment

Management
- intrathecal treatment
- systemic pharmacotherapy
Cerebrospinal fluid cell-free tumour DNA as a liquid biopsy for primary brain tumours and central nervous system metastases

J. Secane¹,²,³,⁴, L. De Mattos-Arruda¹, E. Le Rhun¹,⁵,⁶, A. Bardelli⁷,⁸ & M. Weller¹⁰

Neuro-Oncology

Liquid biopsy in central nervous system metastases: a RANO review and proposals for clinical applications

Adrienne Boire¹, Dieta Branduma, Priscilla K. Brastianos, Emilie Le Rhun, Mammeet Ahluwalia, Larry Junck, Michael Glantz, Morris D. Groves, Eudocia G. Lee, Nancy Lin, Jeffrey Reizer, Roberta Rudá, Michael Weller¹, Martin J. van den Bent¹, Michael A. Vogelbaum, Susan Chang, Patrick Y. Wen, and Riccardo Soffietti
Table 3  Potential clinical applications of liquid biopsy in the management of CNS metastases

- Diagnosis of LM when CSF cytology is negative or inconclusive
- Diagnosis of brain metastasis from unknown primary tumor or multiple lesions
- Quantification of residual tumor following surgical resection
- Differential diagnosis between pseudoprogression/radionecrosis and tumor progression
- Early indication of tumor response following cytotoxic or targeted agents
- Early diagnosis of tumor relapse
- Prediction of resistance to targeted agents
- Monitoring of treatment of resistance mutations with specific targeted agents
- Evaluation of prognosis (based on number of cells and molecular features)
- Screening in patients at high risk for brain or leptomeningeal metastases.

**Neuro-Oncology**

Liquid biopsy in central nervous system metastases: a RANO review and proposals for clinical applications

Achim T. Reiter, Dieter Brabant, Patrick H. Strohmeyer, Erich Le Rider, Maxime El-Ammari, Larry Jacob, Michael Ganslo, Markus E. Groen, Enrico C. Lee, Nancy Nix, Jeffrey Reiter, Roberto Pata, Michael Kalter, Martin J. van den Bremer, Michael A. Angelopoulos, Susan Zhang, Patrick F. Wee, and Maximilian Ruffetti
Diagnosis

- CSF analysis
- MRI response assessment

Management

- intrathecal treatment
- systemic pharmacotherapy
### Table 1: Intraclass Correlation Coefficients (ICC) for Change Scores

<table>
<thead>
<tr>
<th>Item</th>
<th>NO + NR (n=19)</th>
<th>NO (n=10)</th>
<th>NR (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change score 1</td>
<td>ICC</td>
<td>LCL</td>
<td>UCL</td>
</tr>
<tr>
<td></td>
<td>0.48</td>
<td>0.32</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>0.35</td>
<td>0.18</td>
<td>0.59</td>
</tr>
</tbody>
</table>

An intraclass coefficient of correlation (ICC) > 0.8 indicates good agreement.

- 22 cases: score at baseline and at first follow-up MRI
- 10 neuro-oncologists and 9 neuroradiologists

**Score 1:** as provided by the rater
**Score 2:** 7-items score as proposed by the LANO group
**Score 3:** 6-items score omitting epidural lesions because these should not be part of LM assessment
<table>
<thead>
<tr>
<th>Patient Identification</th>
<th>Reference Scan</th>
<th>Follow-Up</th>
<th>Response Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name or number:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of birth:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dates of MRI**

<table>
<thead>
<tr>
<th>Relevant history</th>
<th>n.a.</th>
<th>Treatment since reference scan:</th>
<th>Change from previous MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI findings</td>
<td>Present (1) or absent (0) or non-evaluable [NE]</td>
<td>Individual dimensions (N1, N2, N3: X x Y mm) of 3 largest measurable nodules (measurable defined as &gt; 5 x 5 mm (orthogonal diameters in 2 planes))</td>
<td></td>
</tr>
</tbody>
</table>

**Items related to assessment to leptomeningeal metastasis**

**Brain**

<table>
<thead>
<tr>
<th>Nodules (subarachnoid or ventricular)</th>
<th>n.a.</th>
<th>n.a.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptomeningeal linear enhancement</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

**Spine**

| Nodules (subarachnoid) | n.a. | n.a. | |

**Spine**

| Parenchymal (intramedullary) metastases | CR | PR | SD | PD |

**Brain**

| Parenchymal (brain) metastases | CR | PR | SD | PD |
Diagnosis
- CSF analysis
- MRI response assessment

Management
- intrathecal treatment
- systemic pharmacotherapy
INTRATHECAL TREATMENT
trastuzumab in HER2 + breast cancer LM
Table 1 Summary of studies describing IT administration of trastuzumab

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>IT treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preusser et al., 2013 [14]</td>
<td>IT trastuzumab dose escalation 5–100 mg + PLD i.v. + trastuzumab i.v.</td>
</tr>
<tr>
<td>Hofer et al., 2012 [24]</td>
<td>IT trastuzumab (dose escalation 100–150 mg) q2- q3 weeks + trastuzumab i.v</td>
</tr>
<tr>
<td>Mego et al., 2011 [15]</td>
<td>IT MTX 15 mg + IT cytarabine 24 + IT hydrocortisone 24 mg + IT trastuzumab (20–40 mg escalating dose) weekly + trastuzumab i.v</td>
</tr>
<tr>
<td>Mego et al., 2011 [15]</td>
<td>IT MTX 15 mg + IT cytarabine 24 + IT hydrocortisone 24 mg + IT trastuzumab (20–100 mg escalating dose) weekly</td>
</tr>
<tr>
<td>Oliveira et al., 2011 [16]</td>
<td>IT trastuzumab 25 mg weekly + IT prednisone 25 mg → IT trastuzumab 25 mg weekly + IT prednisone 25 mg + trastuzumab i.v. + capecitabine</td>
</tr>
<tr>
<td>Ferrario et al., 2009 [17]</td>
<td>IT trastuzumab (dose escalation 20–30 mg) weekly + 2 dose of MTX (10 mg weekly) → 40 mg IT trastuzumab q3 weeks + trastuzumab i.v. + PLD i.v.</td>
</tr>
<tr>
<td>Colozza et al., 2009 [18]</td>
<td>IT trastuzumab 12.5 mg q3 weeks + trastuzumab i.v.</td>
</tr>
<tr>
<td>Allison et al., 2009 [26]</td>
<td>IT trastuzumab 20–60 mg weekly or every other week</td>
</tr>
<tr>
<td>Allison et al., 2009 [26]</td>
<td>IT trastuzumab 20–60 mg weekly or every other week</td>
</tr>
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</tr>
<tr>
<td>Allison et al., 2009 [26]</td>
<td>IT trastuzumab 20–60 mg weekly or every other week</td>
</tr>
<tr>
<td>Stemmler et al., 2008 [20]</td>
<td>IT trastuzumab 20 mg + IT MTX 12 mg</td>
</tr>
<tr>
<td>Mir et al., 2008 [19]</td>
<td>IT trastuzumab (dose escalation 20–100 mg) weekly</td>
</tr>
<tr>
<td>Shojima et al., 2008 [25]</td>
<td>IT trastuzumab 25 mg/kg weekly</td>
</tr>
<tr>
<td>Platini et al., 2006 [21]</td>
<td>IT trastuzumab 20–25 mg weekly + paclitaxel i.v. + trastuzumab i.v</td>
</tr>
<tr>
<td>Stemmler et al., 2006 [22]</td>
<td>IT trastuzumab dose escalation 4–20 mg + trastuzumab i.v. + capecitabine per.os</td>
</tr>
<tr>
<td>Laufman and Forshoefel, 2001 [23]</td>
<td>IT trastuzumab dose escalation 5–20 mg + IT MTX 15 mg + IT Thiotepa 15 mg + paclitaxel i.v. + trastuzumab i.v.</td>
</tr>
</tbody>
</table>
## RETROSPECTIVE COHORTS OF HER2+ BREAST CANCER LM TREATED WITH INTRATHECAL TRASTUZUMAB

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Schedule of T administration</th>
<th>Concomittant systemic therapy</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>20-50 mg X2/w for 1 month then 20-50 mg /14d for 1 month then 80 mg/14 or 28 d</td>
<td>14 pts (78%)</td>
<td>5.4</td>
<td>7.2</td>
<td>Figura 2019</td>
</tr>
</tbody>
</table>
IT administration of trastuzumab (30 mg, 60 mg, 100 mg or 150 mg dose levels) once a week

Table 2

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>IT dose level administered (mg)</th>
<th>Major toxicity attributed to intrathecal trastuzumab* or toxicity that forced postponement of the treatment for more than 2 weeks</th>
<th>Minor toxicity attributed to intrathecal trastuzumab (total duration of symptoms in weeks)</th>
<th>Immediate toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 and 7*</td>
<td>30</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4–6 and 8</td>
<td>60</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>9–12</td>
<td>100</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>13–16</td>
<td>150</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

* Major toxicities attributed to intrathecal trastuzumab were grade 3 or 4 toxicities attributed to intrathecal administration.

Patient No. 7 was assigned a 60 mg dose of trastuzumab but accidentally received a 30 mg dose of trastuzumab at each injection.

median OS after enrolment was 7.3 months (range 12 days-27.9 months)
AT-47. PHASE I TRIAL OF INTRATHECAL TRASTUZUMAB IN HER2 POSITIVE LEPTOMENINGEAL METASTASES
Jeffrey Raizer1, Elena Pentsova2, Antonio Omuro3, Nancy Lin3, Lakshmi Nayak3, Eudocia Quante3, and Priya Kumthekar1; 1Northwestern University, Chicago, IL, USA; 2Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3Dana Farber Cancer Institute, Boston, MA, USA

INTRODUCTION: Trastuzumab is a humanized monoclonal antibody against Her2 whose limitation is central nervous system penetration that often leads to brain and leptomeningeal metastases (LM) in the setting to controlled systemic HER2 positive breast cancer. We performed a phase I clinical trial of intrathecal (IT) trastuzumab in patients with HER2 positive breast cancer and LM. METHODS: IRB consented patients were treated at defined dose levels; protocol was modified to accelerate dose escalation and increase IT dosage. Dose levels of IT treatment 10 mg, 20 mg, 40 mg, 60 mg and 80 mg were examined. Treatment was given twice a week x4 weeks, then once a week x4 weeks then every other week until progressive disease. MRI was done at 4 week intervals x2 then every 8 weeks. CSF was assessed every other week x2 then every 4 weeks. RESULTS: 13 women with HER2 positive breast cancer, 1 man with a glioblastoma, and one woman with anaplastic ependymoma were enrolled with a median age of 55 (42-67) and median KPS of 80 (60-90). Three patients were treated at the 10mg dose level, three at 20mg, one at 40mg, one at 60mg and 7 at 80mg. At the 80 mg dose level a patient was added as one patient was removed before complete evaluation and another patient had a grade 4 DLT of arachnoiditis. One patient had the Ommaya reservoir removed for infection unrelated to treatment. Data on CSF levels shows therapeutic levels in the patients treated with 10 mg, 20 mg and 40 mg; data analysis on CSF at 60 and 80 mg is pending. CONCLUSION: IT Trastuzumab is well tolerated up to 80 mg IT. Complete CSF PK data will be presented. A phase II study is underway at the 80 mg dose.
INTRATHECAL TREATMENT
pemetrexed in NSCLC LM
patients diagnosed with recurrent or progressive LM from NSCLC

IP twice per week for 2 weeks in induction therapy, followed by once per week for 4 weeks in consolidation therapy.

**Figure 1**: Study schema.

**Figure 2**: Study profile. IP: intrathecal pemetrexed; DLT, dose-limiting toxicity; AEs, adverse events; MTD, maximally tolerated dose.
10 patients EGFR +, 1 ALK +

SAE: 31% (4/13) of the cases, including myelosuppression, radiculitis, and elevation of hepatic aminotransferases (EHA). Study protocol was revised due to lethal myelosuppression (vitamin B12 and folic acid supplementation).

DLT: myelosuppression, radiculitis, and EHA. Two patients (2/2) developed dose-limiting myelosuppression at 15mg level. One patient (1/6) experienced dose-limiting radiculitis and EHA at 10mg level. MTD was 10mg.

Response rate: 31% (4/13); disease control rate: 54% (7/13)

Pemetrexed was appropriate for intrathecal administration. IP at 10mg dose in combination with vitamin supplementation on the schedule of 1–2 times per week showed controllable toxicity and good efficacy. This regimen paves the way for subsequent clinical trial.
INTRATHECAL TREATMENT

nivolumab in melanoma LM
single center Phase I/Ib trial (NCT03025256)
- Melanoma LMD pts with concurrent IT (via Ommaya) and IV nivo.
- The initial dose escalation phase (up to 18 pts) will determine the safety and recommended dose (primary objective) followed by an expansion cohort (12 pts) at the recommended dose to assess overall survival (secondary objective).
- Cycle 1 will consist of IT nivo only at a starting flat dose of 5mg. In subsequent cycles, IT nivo will be followed the next day by IV nivo 240mg Q2W.
- Pts will be hospitalized overnight for the IT dosing and monitored for neurotoxicity, including signs of elevated intracranial pressure.
- Recommended dose of combined intrathecal (IT) and intravenous (IV) nivolumab defined as the highest dose for which the posterior probability of toxicity is closest to 30% (dose escalation part) [Time Frame: Up to 28 days]
- The Bayesian modified toxicity probability interval method will be used to find the recommended dose.
- Pts must have radiographic and/or CSF cytopathologic (CSF) confirmed LMD.
- Prior therapy with systemic CPI and steroid use (≤ 4 mg / 24 hrs of dexamethasone or equivalent) to control CNS symptoms is allowed.
Diagnosis
- CSF analysis
- MRI response assessment

Management
- intrathecal treatment
- systemic pharmacotherapy
Study design: ANG1005-CLN-04 for Recurrent BCBBM

- **Primary Endpoints**
  - Intracranial objective response rate (iORR)

- **Secondary Endpoints**
  - Extracranial objective response rate (eORR) and duration of response
  - PFS, OS
  - Safety and tolerability
  - Pharmacokinetics

**Response Assessments:**
- Intracranial tumor responses by modified CNS RECIST v1.1
- Extracranial tumor responses by RECIST v1.1

**Breast cancer brain mets with or without LC**
- n=72 (safety) & n=58 (efficacy)

**Treatment Schedule:**
- ANG1005 600 mg/m²
- IV Q3 weekly
- MRI/CT after every 2 cycles
- Until disease progression, unacceptable toxicity
ANG1005-CLN-04; Best iORR in LC Patients

<table>
<thead>
<tr>
<th>Sample size, n^a</th>
<th>All LC Patients</th>
<th>HER2+</th>
<th>HER2-</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR, n (%)</td>
<td>23</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Confirmed PR, n (%)^b</td>
<td>2 (9%)</td>
<td>2 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>12 (52%)^c</td>
<td>8 (55%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>6 (26%)</td>
<td>3 (20%)</td>
<td>3 (37%)</td>
</tr>
<tr>
<td>Clinical benefit (SD+PR), %</td>
<td>74%</td>
<td>80%</td>
<td>63%</td>
</tr>
</tbody>
</table>

^a Based on evaluable patients with clinical or radiological evaluation ≥ 4 weeks from C1D1
^b A PR with a ≥25% decrease in the index lesion
^c One patient with SD was pathologically determined to be a complete response (pCR) in an index lesion

Data as of February 29, 2016 as measured by investigators

ANG1005-CLN-04 Kaplan-Meier Estimates in LC Patients

All LC Patients

**Product-Limit Survival Estimate**

- Estimated Median Survival (95% CI): 34.6 weeks/8.0 months (24.1-40.9wks)
- OS at 6 months (95% CI): 63.6% (42.9, 78.5)

LC Patients per HER2 Status

**Product-Limit Survival Estimates**

- HER2+ Median Survival (95% CI): 38.9 weeks/9.0 months (23.3wks-NE)
- HER2+ OS at 6 months (95% CI): 63.3% (35.8, 81.6)
- HER2- Median Survival (95% CI): 31.9 weeks/7.4 months (5.9-37.7wks)
- HER2- OS at 6 months (95% CI): 63.6% (29.7, 84.5)

Data as of April 27, 2016
OSIMERTINIB AND LUNG CANCER LM

**BLOOM study design overview**

Phase I study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of AZD3759 or osimertinib in patients with EGFRm advanced NSCLC

**Dose escalation**

- **AZD3759**
  - Cohort 1: 50 mg BID
  - Cohort 2: 100 mg BID
  - Cohort 3: 200 mg BID
  - Cohort 4: 300 mg BID
  - Cohort 5: 500 mg BID

- **Osimertinib 160 mg QD**
  - EGFR-TKI pre-treated patients with NSCLC and LM

**Dose expansion cohorts**

- Leptomeningeal metastasis
  - EGFR-TKI naïve or pre-treated
- Brain metastasis
  - EGFR-TKI naïve

- Cohort 1: EGFRm NSCLC and LM
  - Stable extracranial disease, N=21 (current report)
- Cohort 2: T790M positive NSCLC and LM
  - No restriction on stable extracranial disease, N=20 (accrual ongoing)

*Both AZD3759 200 mg and 300 mg BID were explored to evaluate long-term tolerability and efficacy.

†Requires stable extracranial disease if EGFR TKI pre-treated.

‡T790M status is based on testing of an extracranial tumor or plasma sample, BID, twice daily; QD, once daily.

Presented by: James Chih-Hsin Yang

NCT02223869
BLOOM study design: osimertinib LM cohort 1

Study cohort objectives – cohort 1: EGFRm NSCLC and LM
To assess the safety and tolerability of osimertinib in patients with LM

First patient dosed: April 14, 2015

**Osimertinib LM cohort 1**
- Advanced or metastatic EGFRm NSCLC and confirmed diagnosis of LM by positive CSF cytology
- Key inclusion criteria:
  - Primary tumor with EGFR L858R or exon 19 deletion
  - Prior EGFR-TKI treatment
  - ECOG PS 0–2
  - Stable extracranial disease
  - At least one LM lesion by MRI scan

**Assessments**
- Adverse events
- Efficacy assessment:
  - OS
  - Brain MRI and extracranial MRI or CT scan††
  - CSF cytology
  - Neurological exam
  - CNS symptoms
- PK in CSF
- Quantification of EGFRm DNA in CSF

Data cut-off: March 10, 2016

Presented by: James Chih-Hsin Yang

NCT02228369

*As assessed by study investigator; †modified RECIST for CNS disease; RECIST 1.1 for extracranial disease.
CT/MRI: CSF cytology and neurological exam frequency every 8 weeks. 1 cycle = 21 days of continuous dosing.
CSF, cerebrospinal fluid; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group Performance Status.
MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria In Solid Tumors.
Patient demographics: osimertinib LM cohort 1

- All 21 patients were Asian with adenocarcinoma histology
- Two patients had T790M detected in CSF at study entry; 6 patients had T790M detected in plasma
- Duration of treatment: 1–49 weeks ongoing
- Twenty-one patients dosed; 15 patients are ongoing treatment
  - Safety analysis: n=21
  - Efficacy analysis n=21*

<table>
<thead>
<tr>
<th>Characteristic, n</th>
<th>N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: male / female</td>
<td>6 / 15</td>
</tr>
<tr>
<td>Age: median (range), years</td>
<td>50.0 (44-75)</td>
</tr>
<tr>
<td>Smoking status: current / former / never</td>
<td>1 / 5 / 15</td>
</tr>
<tr>
<td>ECOG PS: 0 / 1 / 2</td>
<td>1 / 11 / 9</td>
</tr>
<tr>
<td>Neurological assessment at baseline: normal / abnormal</td>
<td>11 / 10</td>
</tr>
<tr>
<td>Prior lines of systemic therapy: median (range)</td>
<td>3.0 (1-8)</td>
</tr>
<tr>
<td>Prior whole brain radiotherapy</td>
<td>11</td>
</tr>
<tr>
<td>Prior EGFR-TKIs*: gefitinib / erlotinib / docetaxel / HM11713 (B1 1420594)</td>
<td>16 / 3 / 1 / 1</td>
</tr>
<tr>
<td>Prior systemic response to EGFR-TKI: partial response / stable disease / progressive disease</td>
<td>14 / 9 / 1</td>
</tr>
<tr>
<td>Tumor tissue EGFR mutation status (local test): Ex19Del / L858R</td>
<td>9 / 13</td>
</tr>
</tbody>
</table>

Summary of adverse events

- Twenty patients experienced ≥1 AE
- Grade ≥3 AEs were observed in 9 (43%) patients
  - Drug-related Grade ≥3 AEs were observed in 3 (14%) patients
- Serious AEs occurred in 3 (14%) patients, none of which were drug-related
- AEs leading to dose interruption and dose reduction were observed in 2 (10%) patients due to skin pruritus and neutropenia, respectively
  - No drug-related AEs led to dose discontinuation
- One patient died due to aspiration pneumonia not related to drug

<table>
<thead>
<tr>
<th>Drug-related AEs by preferred term, n (%)</th>
<th>CTCAE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Rash (grouped terms)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Dermatitis acniform</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

*Only AEs with frequency ≥10% were listed.
One drug-related Grade 3 neutropenia not listed in the Table.
Osimertinib activity across LM assessments

Efficacy assessments were conducted on 21 patients

- Seven patients had confirmed radiological improvement
- Two patients had confirmed CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed improved neurological function

<table>
<thead>
<tr>
<th>Best MRI imaging intracranial response, n (%)</th>
<th>N=21</th>
<th>Confirmed</th>
<th>Unconfirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responding</td>
<td>10</td>
<td>7 (33)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11</td>
<td>9 (43)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Early withdrawal</td>
<td>2</td>
<td>2 (10)</td>
<td></td>
</tr>
</tbody>
</table>

Population efficacy, N=21. *Response confirmation was done at week 4 weeks after the initial response. *Response assessed by neurological examination.

**Time on treatment**

Fifteen patients are ongoing treatment at time of data cut-off (March 10, 2016). 7 of whom have been on treatment for >9 months.

*Patient discontinued due to patient preference. Assessment of patients at time of data cut-off.

Two patients experienced AEs leading to dose reduction; one patient had solid tumors and one patient had metastatic disease.
Survival of patients with non-small cell lung cancer having leptomeningeal metastases treated with immune checkpoint inhibitors

Fig. 1. Swimmer plot of patients with NSCLC having leptomeningeal metastases treated with immune checkpoint inhibitors. Abbreviations: PD-L1: programmed death-ligand 1; NCCN: National Comprehensive Cancer Network; LM: leptomeningeal metastases; SCC: squamous cell carcinoma; unk: unknown; AC: adenocarcinoma; KRAS: Kirsten rat sarcoma viral antigen mutation; beva: bevacizumab; carbo: carboplatin; TKI: tyrosine kinase inhibitor; ALK: anaplastic lymphoma kinase translocation; nav: navelbin; m: months; EGFR: epidermal growth factor receptor mutation; WT: wild type; BRAF: v-raf murine sarcoma viral oncogene homologue B; amp: amplification; ICE: immune checkpoint inhibitor; tx: therapy; BSC: best supportive care; PD: progressive disease; NE: not evaluable.
CONCLUSION

- Developments in the diagnosis and response assessment tools
- Developments of new therapeutic approaches
- Need for phase I trials followed by randomized trials