Non-Small-Cell Lung Cancer: Management of Brain Metastases

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Medical Oncology – Santa Maria della Misericordia Hospital, Perugia
New diagnosis of brain metastases in US estimated to be 21-43,000 per year

Global prevalence in cancer patients: 8.5-9.6%: only expected to increase!

Most common solid tumors metastasizing to brain:

- Lung: 19.9%
- Melanoma: 6.9%
- Renal Cell: 6.5%
- Breast: 5.1%

Tools for the Best Outcome in the Management of Brain Metastases:

- Radiation therapy
- Systemic therapies
- Symptoms Management
Tools for the Best Outcome in the Management of Brain Metastases:

- Radiation therapy
- Systemic therapies
- Symptoms Management
Brain Metastases: Systemic Therapy

- Local therapy: standard of care in 1° line
- Role of systemic therapy not well defined
- No FDA approved agents for this indication
## Factors Influencing Systemic Treatment Decisions:

<table>
<thead>
<tr>
<th>Patient Related</th>
<th>Disease Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Primary tumor type and chemosensitivity</td>
</tr>
<tr>
<td>Performance status</td>
<td>Systemic disease burden</td>
</tr>
<tr>
<td>Neurological findings</td>
<td>Single versus multiple brain metastases</td>
</tr>
<tr>
<td>Estimated prognosis</td>
<td>New versus recurrent brain metastases</td>
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<tr>
<td>Co-morbidities</td>
<td></td>
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<tr>
<td>Patient wishes</td>
<td></td>
</tr>
</tbody>
</table>
Systemic Therapy Options:

- **Systemic chemotherapy**
  - Blood brain barrier (BBB) penetration
  - Efficacy in the primary tumor

- **Targeted Therapy**
  - EGFR, ALK, ROS1

- **Immune Therapy**
  - CTL4

- **Clinical Trials**
<table>
<thead>
<tr>
<th>Publication</th>
<th>Chemotherapy</th>
<th>ORR CNS *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twelves CJ. 1990 (n=25, 19 evaluable)</td>
<td>Cyclophosphamide Vincristine Etoposide</td>
<td>53%</td>
</tr>
<tr>
<td>Kristjansen PE. 1993 (n=21, 13 evaluable)</td>
<td>Multidrug combination regimen</td>
<td>52%</td>
</tr>
<tr>
<td>Seute T. 2006 (n= 24, 22 evaluable)</td>
<td>Cyclophosphamide Doxorubicin Etoposide</td>
<td>27%</td>
</tr>
</tbody>
</table>

* Response Assessment in Neuro-Oncology (RANO)
Lin N. Lancet Oncology 2013
Non Small Cell Lung Cancer: First Line WBRT vs Chemo

![Graph showing survival rates for different treatments over time.]

- **PFS 3.6 vs 4.4 mo**
- **OS 9.1 vs 9.9 mo**
- WBRT-first arm, grade 3 of 4 neutropenia more frequent (79% vs 40%) during chemotherapy

**Conclusions:**
Primary chemotherapy is more feasible and can be an appropriate option for pts with synchronous brain metastasis with absent or controlled neurologic symptoms/signs.

Non Small Cell Lung Cancer: WBRT + SRS +/- Temozolomide or Erlotinib

- Median survival time 13.4, 6.3, and 6.1, not statistically significant.
- Time to CNS progression and PS at 6 months better in the WBRT + SRS arm.
- Grade 3 to 5 toxicity was 11%, 41%, and 49% (P<.001)

**Conclusions:**
The addition of TMZ or ETN to WBRT + SRS in NSCLC pts with 1 to 3 brain mets did not improve survival and possibly had a deleterious effect.

Sperduto PW. Int J Rad Onc Biol Phys 2013
Chemotherapy: Summary

- Few prospective phase II and III trials
- Consider chemotherapy with ability to cross BBB and efficacy in primary tumor
- SCLC: Consider 1 line chemotherapy if asymptomatic brain metastases and significant systemic disease
- No evidence to support use of systemic therapy with WBRT/SRS
Systemic Therapy Options:

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  - Blood brain barrier (BBB) penetration
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- **Clinical Trials**
Therapies for acquired resistance to EGFR TKIs in EGFR mutated NSCLC (awaiting evidence-based recommendations)

EGFR mutated NSCLC (TKI-sensitizing mutations)
- G719X
- exon 19 deletion
- exon 19 insertion
- L858R
- L861Q
- A763_Y764insFQEA

acquired resistance
a. pharmacokinetic (brain-CNS)
  (>50-60% EGFR-T790M)
  (<20% bypass tracks [MET, ERBB2, AXL, BRAF])
  (<5% neuroendocrine transformation/EMT)
  (>15% other mechanisms)
b. biologic

isolated brain-CNS progression
  local therapy + continue EGFR TKI

single site, oligoprogressive
  local therapy + continue EGFR TKI

asymptomatic, indolent growth, multiple sites
  continue EGFR TKI alone

symptomatic, multiple sites
  consider biopsy (research)
  (clinical trial) (transformation)
  cytotoxic chemotherapy +/- EGFR TKI; or clinical trial

gefitinib, erlotinib, afatinib and other EGFR TKIs
Second generation EGFR TKIs (Afatinib) show activity in brain metastases

80-years-old female with lung adenocarcinoma and BM at diagnosis

Nov 2013

Afatinib 40 mg a day

Jan 2014

*Chest CT scan:* dramatic reduction in lung nodules and pleural effusion. *BRAIN:* two lesions disappeared, one reduced.
Feb 2014 (baseline)

Apr 2014

Jul 2014

Never smoker 55-years old male, with left upper lobe adenocarcinoma bilateral lung nodules, mediastinal and supraclavicular nodes, brain metastases.

EGFR: del exon 19
Third generation EGFR TKIs (covalent pyrimidine EGFR-T790M TKIs) show activity in brain metastases

Presented By Lecia Sequist at 2014 ASCO Annual Meeting

**CO-1686**
- 3 previous treatment lines
- Erlotinib immediately before CO1686
- CNS lesion response

**AZD9291**
- 2 previous treatment lines
- Erlotinib immediately before AZD9291
- Rapid CNS lesion necrotic evolution

L. Crinò Medical Oncology Perugia, September 2014
ALK Inhibitors for ALK-Rearranged NSCLC

CNS: major site of progressive disease on CRIZOTINIB despite some CNS responses seen on therapy [Costa DB et al, World Conference on Lung Cancer, Sydney, AU October 2013]

ALECTINIB: 90% DCR in CNS

ALECTINIB, AP26113, CERITINIB, CRIZOTINIB: all have reported responses in the CNS
Intracranial/Brain metastases comprised the most common non-target lesion site of progressive disease in patients with or without baseline brain metastasis.

<table>
<thead>
<tr>
<th></th>
<th>Previously untreated for BM (n=109)</th>
<th>Previously treated for BM (n=166)</th>
<th>No BM detected (n=613)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Outcome</td>
<td>n</td>
</tr>
<tr>
<td>Target lesions only, n (%)</td>
<td>4</td>
<td>9%</td>
<td>8</td>
</tr>
<tr>
<td>Non-Target lesions or New lesions (n=43)</td>
<td>30</td>
<td>70%</td>
<td>39</td>
</tr>
<tr>
<td>Intracranial (IC)/Brain, n (%)</td>
<td>30</td>
<td>70%</td>
<td>39</td>
</tr>
<tr>
<td>Lung, n (%)</td>
<td>3</td>
<td>7%</td>
<td>6</td>
</tr>
<tr>
<td>Bone, n (%)</td>
<td>4</td>
<td>9%</td>
<td>8</td>
</tr>
<tr>
<td>Liver, n (%)</td>
<td>2</td>
<td>5%</td>
<td>3</td>
</tr>
</tbody>
</table>

Costa DB et al, World Conference on Lung Cancer, Sydney, AU October 2013
Efficacy of Ceritinib in Patients with Brain Metastases

Subset analysis of patients with clinically and neurologically stable brain metastases at baseline

ALK+ NSCLC
N=246

No Brain Metastases at Baseline
N=122

Brain Metastases at Baseline
N=124

ALKi treated
N=98

Measurable
N=10

ALKi naive
N=26

Measurable
N=4

Measurable brain metastases:
- Investigator identified, measured using RECIST 1.0; longest diameter 10 mm or more
- Either not previously radiated, or if previously radiated lesion has grown after irradiation

Presented by: Dong-Wan Kim

PRESENTED AT: ASCO 50th Annual Meeting, Science & Society
# Overall Response to Ceritinib in Patients with Brain Metastases at Baseline

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>ALK inhibitor treated</th>
<th>ALK inhibitor naïve</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Brain Metastases</td>
<td>N=98</td>
<td>N=26</td>
<td>N=124</td>
</tr>
<tr>
<td>ORR, n (%) (95% CI)</td>
<td>49 (50.0%) [39.7, 60.3]</td>
<td>18 (69.2%) [48.2, 85.7]</td>
<td>67 (54.0%) [44.9, 63.0]</td>
</tr>
<tr>
<td>DOR, median (months) (95% CI)</td>
<td>6.93 [4.80, 8.54]</td>
<td>NE [5.52, NE]</td>
<td>7.00 [5.45, 9.69]</td>
</tr>
<tr>
<td>6 month DOR (%) (95% CI)</td>
<td>53.1% [36.5, 67.1]</td>
<td>65.9% [35.4, 84.5]</td>
<td>56.3% [41.9, 68.4]</td>
</tr>
<tr>
<td>PFS, median (months) (95% CI)</td>
<td>6.70 [4.86, 8.38]</td>
<td>8.31 [4.63, NE]</td>
<td>6.90 [5.39, 8.38]</td>
</tr>
<tr>
<td>6 month PFS (%) (95% CI)</td>
<td>52.3% [40.9, 62.5]</td>
<td>65.6% [42.7, 81.2]</td>
<td>55.1% [45.0, 64.1]</td>
</tr>
</tbody>
</table>

CI, confidence interval; ORR, overall response rate; DOR, duration of response; PFS, progression-free survival; NE, non-estimable

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Presented by: Dong-Wan Kim

PRESENTED AT: ASCO 50th Annual Meeting 2023
# Overall Intracranial Response Rate for Patients with Measurable Brain Metastases at Baseline

<table>
<thead>
<tr>
<th>Best Overall Response n (%)</th>
<th>ALK inhibitor treated N=10</th>
<th>ALK inhibitor naïve N=4</th>
<th>All patients N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

| OIRR                        | 4 (40.0)                   | 3 (75.0)                | 7 (50.0)          |
| [95% CI]                    | [12.2, 73.8]               | [19.4, 99.4]            | [23.0, 77.0]      |

CI, confidence interval; OIRR, overall intracranial response rate

Presented by: Dong-Wan Kim
Conclusions:

- A high rate of durable responses and prolonged PFS were seen in both ALKi treated and ALKi naive pts.

- In all pts, the most common AEs were nausea, vomiting, and diarrhea. And most were grade 1 or 2.

- In the subset of pts with baseline brain metastases, Ceritinib also demonstrated a high rate of durable responses and prolonged PFS in both ALKi treated and ALKi naive pts.

- Ceritinib treatment showed activity in brain metastases.
CNS ACTIVITY OF ALECTINIB

- Evidence of preventing CNS metastasis in patients with negative baseline brain scan (26/47 enrolled patients)
  - 10 progressed systemically. No CNS metastasis occurred.
  - 16 active on the study. Median Duration 119+ days (range 9-266 days)
- 21/47 enrolled patients with baseline CNS lesions. RR as follows:

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>29%</td>
<td>24%</td>
<td>38%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- 9/21 patients with baseline CNS metastasis had measurable CNS lesions and no prior radiation within 4 weeks from first dose of alectinib. 5/9 achieved CNS PR (≥ 30% reduction in sum of largest dimension). 2/9 had CNS stable disease and 2/9 had CNS progression.

Ou, SH et al. World Conference on Lung Cancer Sydney, AU October 2013

Presented by: Leena Gandhi, MD PhD
CNS RESPONSES ON ALECTINIB

10602
760 mg BID cohort

January 8, 2013
March 8, 2013

10603 (started February 1, 2013)
CH5424802 760 mg bid

January 10, 2013
March 14, 2013

10604
900 mg BID

Day -12
Day +23

10605
900 mg BID

Day -4
Day +18

Ou, SH et al.
World Conference on Lung Cancer
Sydney, AU October 2013

Presented by: Leena Gandhi, MD PhD
CNS activity of Alectinib: Our experience

- 43-years-old man, lung adenocarcinoma stage IV (liver mets at diagnosis in 2012)
- Lung disease progression after a 1st line chemotherapy and brain progression after 1 year of Crizotinib therapy

Baseline (Dec 2013)

RC: 4 months of Alectinib (April 2014) [600 mg BID cohort]

RC: 8 months of Alectinib (Aug 2014)

L. Crinò Medical Oncology Perugia, September 2014
Systemic Therapy Options:

- **Systemic chemotherapy**
  - Blood brain barrier (BBB) penetration
  - Efficacy in the primary tumor

- **Targeted Therapy**
  - EGFR, ALK, ROS1

- **Immune Therapy**
  - CTL4, PDL1

- **Clinical Trials**
Effect in the CNS?

Phase II trial of MK-3475 untreated brain metastases melanoma and NSCLC

Phase I trial of nivolumab in asymptomatic untreated brain metastases NSCLC

www.clinicaltrials.gov, ¹NCT020850700, ²NCT01454102 accessed May 26, 2014
258 pts with advanced lung adenocarcinoma
Mostly female (58%) and never smokers
Median Age 60

Median Overall Incidence of BM at diagnosis 9.5% (25 pts), with median age 55

Overall Incidence of EGFR Mutation 33% (86 pts)
Overall Incidence of ALK Rearrangement 13% (35 pts)

Overall Incidence of BM in EGFR TKIs naive 14 (16%)
Overall Incidence of BM in EGFR TKIs treated 19 (22%)
Overall Incidence of BM in ALK TKIs naive 8 (22%)
Overall Incidence of BM in ALK TKIs treated 12 (34%)

Brain metastases represent the most common site of progressive disease in EGFR and ALK + patients
### Overall Intracranial Response Rate for ALK + patients

<table>
<thead>
<tr>
<th>Best Overall Response (n)</th>
<th>Alk-inhibitor treated (n = 12)</th>
<th>Alk-inhibitor naive (n = 8)</th>
<th>All patients (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Partial Response</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>OIRR (%)</td>
<td>10 (83%)</td>
<td>7 (87%)</td>
<td>17 (85%)</td>
</tr>
</tbody>
</table>

ALK inhibitors [Crizotinib, Ceritinib, Alectinib] show activity in Brain metastases (~ 90% in naïve)
### Overall Intracranial Response Rate for EGFR + patients

<table>
<thead>
<tr>
<th>Best Overall Response (n)</th>
<th>EGFR-inhibitor treated (n = 19)</th>
<th>EGFR-inhibitor naive (n = 14)</th>
<th>All patients (n = 33)</th>
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<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>OIRR (%)</td>
<td>16 (84%)</td>
<td>13 (92%)</td>
<td>29 (87%)</td>
</tr>
</tbody>
</table>

EGFR inhibitors [Erlotinib, Gefitinib, Afatinib] show activity in Brain metastases (> 90% in naïve)

**OIRR** Overall Intracranial Response Rate
## Median Overall Survival for Brain Metastases + patients

<table>
<thead>
<tr>
<th>EGFR/ALK Negative (mo)</th>
<th>EGFR Mutated (mo)</th>
<th>ALK Rearranged (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>
Conclusions:

- EGFR and ALK inhibitors show activity in brain metastases in our cohort, with a favourable control in both pre-treated and naive pts.

- TKIs demonstrated efficacy in prolonging the survival of this subset of patients, in line with previous literature data.

- Challenges and future directions for targeted therapies in brain metastases include both better characterization and drug design with respect to CNS distribution.

- Newer targeted therapies represent an additional therapeutic option for the treatment/prevention of brain metastases in pts with an appropriate molecular profile.
Thank you!