Targeted therapies and brain metastases in lung cancer patients

Benjamin Besse, MD, PhD
Medical Oncologist

19 septembre 2014
Targeted therapies and brain mets

- Brain mets in NSCLC

- Specific targeted therapies
  - EGFR mutations
  - ALK rearrangements
  - Strategy in patients with PD after TKI

- Unspecific targeted therapies
  - Bevacizumab and brain mets
  - WBRT and bevacizumab

- Conclusion
Targeted therapies and brain mets

- **Brain mets in NSCLC**
  - Specific targeted therapies
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    - ALK rearrangements
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Lung Cancer

✓ Incidence in France - 2012:
  - 2nd cancer in men (28 200 new cases)
  - 3rd cancer in women (11 300 new cases)

✓ Mortality in France - 2012:
  - 1st cancer in men (21 300 death)
  - 2nd cancer in women (8 700 death)

✓ Median OS advanced NSCLC = 13 months

✓ First cause of brain mets
  - 10 - 18% at the time of diagnosis, 40% in total

✓ Median OS advanced NSCLC + brain mets = 4 - 16 months
OS in brain mets patients

- Canadian cohort
- 3 RCT (BR.18, BR.21, BR.24)
- N=131(BM+)/1218(BM-)

BM Present (Median OS = 7.7 mo [95% CI=6.7,9.3])
BM Absent (Median OS = 8.6 mo [95% CI=7.9,9.5])

HR 1.05, 95%CI 0.85-1.28, stratified log-rank p=0.67

P.A. Bradbury et col. ASCO 2009 Abs 8075
M.J.Edelman et col. ASCO 2009 Abs 8076
## Chemotherapy – 1\textsuperscript{st} line

<table>
<thead>
<tr>
<th>Authors</th>
<th>Regimen</th>
<th>N</th>
<th>ORR (%) Cerebral</th>
<th>ORR (%) Extra-Cerebral</th>
<th>PFS (m)</th>
<th>OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotto et al, 1996</td>
<td>Cisplatine fotemustine</td>
<td>31</td>
<td>23</td>
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<td>4</td>
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<td>Minotti et al, 1998</td>
<td>Cisplatine Teniposide</td>
<td>23</td>
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<td>26</td>
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<td>Franciosi et al, 1999</td>
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<td>43</td>
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<td>Fujita et al, 2000</td>
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<td>30</td>
<td>50</td>
<td>62</td>
<td>4.6</td>
<td>12</td>
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<tr>
<td>Bernardo et al, 2002</td>
<td>Carboplatiné, navelbine, gemcitabine</td>
<td>22</td>
<td>45</td>
<td>NR</td>
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<td>8.2</td>
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<tr>
<td>Cortes et al, 2003</td>
<td>Cisplatine taxol</td>
<td>26</td>
<td>38</td>
<td>50</td>
<td>3.2</td>
<td>5.3</td>
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<tr>
<td>Galetta et al, 2011</td>
<td>Cisplatine fotemustine</td>
<td>25</td>
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<td>NR</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Barlesi et al, 2011</td>
<td>Cisplatine Pemetrexed</td>
<td>43</td>
<td>41.8</td>
<td>34.9</td>
<td>4.0</td>
<td>7.4</td>
</tr>
</tbody>
</table>
Results: biomarkers assessment (n=9911)

- **UKN/Other**: 53.8%
- **KRAS mut**: 27%
- **ALK rearrangement**: 3.7%
- **BRAF mut**: 1.7%
- **PI3K mut**: 2.6%
- **HER2 mut**: 0.9%
- **EGFR act mut**: 9.5%
- **EGFR res mut**: 0.8%

Results expressed in % on available analyses

Barlesi.F et al, ASCO 2013
Targeted therapies and brain mets

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- EGFR res mut: 0.8%
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Results expressed in % on available analyses

Barlesi.F et al, ASCO 2013
EGFR TKI in EGFRmut pts
Results of phase III studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>ORR (%)</th>
<th>PFS (m)</th>
<th>OS (m)</th>
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<tbody>
<tr>
<td>IPASS</td>
<td>gefitinib</td>
<td>132</td>
<td>71,2</td>
<td>9,8</td>
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<td>FIRST-SIGNAL</td>
<td>gefitinib</td>
<td>84,6</td>
<td>8,4</td>
<td>30,6</td>
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<td>WJTOG 3405</td>
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<td>NEJ 002</td>
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<td>114</td>
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<tr>
<td>OPTIMAL</td>
<td>erlotinib</td>
<td>82</td>
<td>83,0</td>
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<tr>
<td>EURTAC</td>
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<td>58</td>
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<td>LUX-LUNG 3</td>
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<td>230</td>
<td>56</td>
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<td>28,1</td>
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<td>ENSURE</td>
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<td>110</td>
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</table>
## EGFR TKI and Brain Mets

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>N</th>
<th>Selection</th>
<th>Prior treatment</th>
<th>Treatment</th>
<th>Brain RR (%)</th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porta et al. [65]</td>
<td>17 (subset)</td>
<td>EGFR mutated</td>
<td>No</td>
<td>Erlotinib</td>
<td>82</td>
<td>NR</td>
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<td>Park et al. [66]</td>
<td>28</td>
<td>EGFR mutated</td>
<td>No</td>
<td>Gefitinib or erlotinib</td>
<td>83</td>
<td>15.9</td>
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<tr>
<td>Li [68]</td>
<td>9</td>
<td>EGFR mutated</td>
<td>No</td>
<td>Gefitinib</td>
<td>89</td>
<td>NR</td>
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<tr>
<td>Kim et al. [67]</td>
<td>23</td>
<td>Asian never-smokers</td>
<td>No</td>
<td>Gefitinib or erlotinib</td>
<td>74</td>
<td>18.8</td>
</tr>
<tr>
<td>Welsh et al. [78]</td>
<td>40</td>
<td>Unselected</td>
<td>Yes</td>
<td>Erlotinib</td>
<td>86</td>
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<td>21.9</td>
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</tbody>
</table>

### Brain mets
- **ORR 74-89%**
- **OS 15.9-21.9 m**
## EGFR TKI and Brain Mets

### Summary
- **ORR**: 74-89%
- **OS**: 15.9-21.9 m
- **Phase III studies**
  - **ORR**: 56-84%
  - **OS**: 19.3 – 28.1 m

### Table: EGFR TKI and Brain Mets Studies

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<thead>
<tr>
<th>Author (Ref.)</th>
<th>N</th>
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</table>

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Zimmermann Cancer Treat Rev 14
TKI EGFR – largest cohort

- Never smokers, asymptomatic, synchrone
- Gefitinib 250mg or erlotinib 150mg
- No WBRT

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>N = 28</th>
<th>(%)</th>
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</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>23</td>
<td>(83)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>(11)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1</td>
<td>(3)</td>
</tr>
<tr>
<td>Not available</td>
<td>1</td>
<td>(3)</td>
</tr>
</tbody>
</table>

- Follow up 17.5 months
- PFS: 6.6 months - OS: 15.9 months
- Recurrence: Brain 13 pts, out of the brain 4 pts, both 4 pts
- WBRT in 14 patients at 12.6 months of diagnosis
WBRT and EGFR TKI?

- Phase II study
- 40 pts with brain mets
- Not selected on EGFRmut
- Erlotinib 1 wk then Erlotinib 100mg/d + WBRT (35Gy/14f) then erlotinib 150 mg/d
- Median age: 59, Median GPA: 1.5
- ORR 86%
- No unusual toxicity

OS

Brain PD

Welsh JCO 2013
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ALK inhibitors in clinical development

- Crizotinib (XALKORI, Pfizer) approved
- Ceritinib (ZYKADIA, Novartis) approved (US only) + EAP
- Alectinib (ALECENSA, Chugai/Roche) phase III (approved in Japan, only)
- AP26113 (Ariad) phase II
- ASP-3026 (Astellas) phase I
- PF-06463922 (Pfizer) phase I
- TSR-011 (Tesaro) phase I
- CEP-37440 (Teva) phase I
- X-396 (Xcovery) phase I
- RXDX (Ignyta) phase I

GUSTAVE ROUSSY
THÈME DU DIAPORAMA
## Crizotinib clinical trial efficacy data

<table>
<thead>
<tr>
<th>Profile</th>
<th>Line of Therapy</th>
<th>ORR</th>
<th>Median Duration of Response, Weeks</th>
<th>Median PFS, Months</th>
<th>OS Probability at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1001</td>
<td>Any line</td>
<td>60.8%</td>
<td>49.1</td>
<td>9.7</td>
<td>74.8%</td>
</tr>
<tr>
<td></td>
<td>Second-line and beyond</td>
<td>53%</td>
<td>42.9</td>
<td>8.5</td>
<td>61%</td>
</tr>
<tr>
<td>1014</td>
<td>First line</td>
<td>74%</td>
<td>49.0</td>
<td>10.9</td>
<td>84%</td>
</tr>
<tr>
<td>1005</td>
<td>Second-line only</td>
<td>65%</td>
<td>32.1</td>
<td>7.7</td>
<td>~70%</td>
</tr>
<tr>
<td></td>
<td>N=143</td>
<td></td>
<td>N=173</td>
<td>N=172</td>
<td></td>
</tr>
<tr>
<td>1007</td>
<td>N=261</td>
<td></td>
<td>N=173</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Crizotinib activity on brain mets

- Retrospective analysis of patients with (n=275) or without (n=613) brain mets from PROFILE 1005 and PROFILE 1007

- Intracranial DCR at 12 weeks ~ 60% in patients with brain metastases
  - 56% if untreated BM
  - 62% if previously treated BM

- Intracranial ORR ~ 25% in 40 patients with ≥1 brain metastasis identified as a target lesion at baseline
  - 18% if untreated BM
  - 33% if previously treated BM
Crizotinib and brain mets

- Crizotinib has real but decreased activity on brain mets
  - ORR of 25%
  - To compare to a systemic ORR of 49%

- CNS remains the dominant site of acquired resistance on therapy for ALK patients with or without brain metastasis
  - 71% of PD in patients with baseline brain metastasis
  - 27% of PD in patients without baseline brain metastasis

- Crizotinib has limited brain penetration (notably with an intact BBB) and may not be the best ALK inhibitor for brain metastasis
  - Crizotinib CSF-to-plasma ratio of 0.0026 (Costa et al JCO 2011)
  - Carcinomatous Leptomeningeal responses reported with alectinib
2\textsuperscript{nd} generation ALK TKI and Brain mets

**Alectinib**

- Duration on study (months):
  - On study: non-CR, non-PD
  - Discontinued: CR

**AP26113**

- Time on Treatment (Weeks):
  - On Study
  - Discontinued
Types of progression

Asymptomatic, indolent growth, multiple sites

Single site

Symptomatic, multiple sites
Approach to Management of Patients with TKI Acquired Resistance

- Asymptomatic, indolent growth, multiple sites → Continue TKI
- Symptomatic, multiple sites → Biopsy (EGFRmut) → Second line TKI or Chemotherapy
- Single site → (Biopsy) → Local therapy + resume TKI or 2nd line TKI

NCCN guidelines 2012 – present

Modified from Greg Reily
Targeted therapies and brain mets

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- Conclusion
Bevacizumab

- anti-VEGF monoclonal Ab
- half life 21 days (11-50)

Approved in 1\textsuperscript{st} line advanced NSCLC

<table>
<thead>
<tr>
<th>ECOG 4599\textsuperscript{1}</th>
<th>AVAiL\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS 12,3m vs 10,3m</td>
<td>13,1m vs 13,6m /13,4m</td>
</tr>
<tr>
<td>PFS 6,2m vs 4,5m</td>
<td>6,6m / 6,5m vs 6,1m</td>
</tr>
<tr>
<td>ORR 35% vs 15%</td>
<td>34,1% / 30,4% vs 20,1%</td>
</tr>
</tbody>
</table>


Meta-analysis of randomized trials
- 1 yr absolute benefit : 4%
- Median OS at 1yr: 55%
Bevacizumab toxicity
- frequent: HTA, proteinuria, epistaxis
- serious: hemorrhage, PE, wound healing issues

Bevacizumab and Brain Mets (approved 2009 in EU)

<table>
<thead>
<tr>
<th>Author</th>
<th>Phase</th>
<th>N</th>
<th>Cerebral Hemorrhage N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socinski et al.¹</td>
<td>II</td>
<td>115</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Besse et al.²</td>
<td>Métadanalyse</td>
<td>Groupe A: 187</td>
<td>3 (3,3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Groupe B: 321</td>
<td>3 (0,9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Groupe C: 131</td>
<td>1 (0,8%)</td>
</tr>
<tr>
<td>Crinò et al.</td>
<td>IV</td>
<td>2212</td>
<td>7 (2%)</td>
</tr>
</tbody>
</table>

Phase II study BRAIN

- Non squamous NSCLC
- Asymptomatic, non treated brain mets

Arm A
n=66
NSCLC Brain metastases 1\textsuperscript{st} line

Arm B
n=49
NSCLC Brain metastases 2\textsuperscript{nd} line

Screening D -28 to D0

$D_1 / C_1$

Treatment period

Post-therapeutic follow-up until death or end of study

Carboplatin + Paclitaxel (1 cycle = 3 weeks)

$C_1 - C_2 - C_3 - C_4 - C_5 - C_6$

- In the event of permanent discontinuation of chemotherapy due to toxicity, bevacizumab will be administered until disease progression, except in case of unacceptable toxicity or patient or investigator decision.

Bevacizumab until disease progression*

Erlotinib until disease progression*

Bevacizumab until disease progression*
## Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>B+CP (n=67)</th>
<th>B+E (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (68.7)</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (31.3)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>61.0 (40–79)</td>
<td>54.0 (34–70)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37 (55.2)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>1</td>
<td>30 (44.8)</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>59 (88.1)</td>
<td>23 (95.8)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>8 (11.9)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Recurrence of previous lung cancer, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>61 (91.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (9.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Metastatic sites, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>36 (53.7)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Liver</td>
<td>17 (25.4)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>14 (20.9)</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Pleura</td>
<td>4 (6.0)</td>
<td>–</td>
</tr>
<tr>
<td>Bone</td>
<td>34 (50.7)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (23.9)</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
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<td></td>
</tr>
<tr>
<td>Past smoker</td>
<td>33 (49.3)</td>
<td>17 (70.8)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20 (29.9)</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>14 (20.9)</td>
<td>3 (12.5)</td>
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</table>
## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>B+CP (n=67)</th>
<th>B+E (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month PFS rate, % (95% CI)</td>
<td>56.5 (43.8–67.4)</td>
<td>57.2 (37.0–76.3)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.7 (5.7–7.1)</td>
<td>6.3 (3.0–8.4)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>16.0 (12.0–21.0)</td>
<td>12.0 (8.9–20.2)</td>
</tr>
</tbody>
</table>

- The most frequent cause for bevacizumab withdrawal was progression:
  - intracranial progression in 20.9% (B+CP) and 16.0% (B+E) of patients
  - extracranial progression in 50.7% (B+CP) and 54.2% (B+E) of patients.
ORR – Paclitaxel carboplatinum bevacizumab

Cerebral Hemorrhage Rate: 1.5% (1pt, grade I)*

*all arms, n=91
Wt NSCLC vs oncogene addicted NSCLC
Conclusion

- **EGFRmut and ALK+ population**
  - TKI should be offered upfront if brain mets
  - TKI efficacy is not homogeneous (crizotinib less potent)
  - WBRT is safe with erlotinib low dose

- **Bevacizumab**
  - A ‘good partner’ for chemo in brain mets
  - WBRT + bevacizumab is feasible

- **Carcinomatous meningitis**
  - More frequent in EGFRmut/ALKmut population?
  - A definitive issue in long survivor

- **Trial requirements**
  - Specific trials and open the in phase I studies to these pts