GOLF 2016

Métastases cérébrales
Quelle stratégie?

Benjamin Besse
Oncologue médical

21 septembre 2016
Disclosures

- No personal financial disclosures
- Institutional grants for clinical and translational research
  - AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis, GSK, Servier, EOS, Onxeo, OncoMed, Inivata, OSE Pharma
Brain metastases management

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Specific targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion
GUSTAVE ROUSSY

THÈME DU DIAPORAMA
Brain metastases management

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Specific targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion

And a special focus on pokemons
Brain metastases management

- **Brain mets in NSCLC**
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Specific targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion
Brain mets in lung Cancer

- 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

---

**Median OS from trials investigating WBRT, chemotherapy regimens and molecularly targeted treatments.**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Median OS range, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT regimens</td>
<td></td>
</tr>
<tr>
<td>WBRT alone</td>
<td>5.2-7.2</td>
</tr>
<tr>
<td>WBRT + SRS</td>
<td>10.3-13.4</td>
</tr>
<tr>
<td>WBRT + chemotherapy</td>
<td>3.7-12.6</td>
</tr>
<tr>
<td>Chemotherapy regimens</td>
<td>7.6-8.2</td>
</tr>
<tr>
<td>Targeted therapies</td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>5-15</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>9.1-19.1</td>
</tr>
<tr>
<td>Erlotinib in EGFR positive</td>
<td>18.9-19.1</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

---

Brain mets in lung Cancer

- 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

Quality of Life

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])
BMAbsent (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
Brain metastases management

- Brain mets in NSCLC
- **Blood Brain Barrier**
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Specific targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion
Why is it difficult to treat brain metastases?

*The Blood-Brain Barrier: Bottleneck in Brain Drug Development*

- >98% of small molecule drugs do not cross the BBB
- ~100% of large molecule drugs do not cross the BBB
- <1% of drug companies have a BBB drug targeting program
- <1% of academic neuroscience programs emphasize BBB transport biology

*FIG. 1.* Whole body autoradiogram of an adult mouse sacrificed 30 min after intravenous injection of radiolabeled histamine, a small molecule that readily enters all organs of the body, except for the brain and spinal cord.

Pardridge WM et al, NeuroRX 2005: 2, 3
# Blood Brain Barrier

The art of illusion

## Table 4: Metastatic brain tumor tissue concentration of agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>MW</th>
<th>Lipophilicity&lt;sup&gt;a&lt;/sup&gt;</th>
<th>N</th>
<th>O</th>
<th>TBR</th>
<th>n</th>
<th>Primary cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin [30]</td>
<td>298</td>
<td>-2.1939</td>
<td>2</td>
<td>0</td>
<td>0.78</td>
<td>18</td>
<td>Lung</td>
</tr>
<tr>
<td>Liposomal Daunorubicin [31, 32]</td>
<td>564</td>
<td>0.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
<td>10</td>
<td>8.36</td>
<td>1</td>
<td>Adenocarcinoma NOS</td>
</tr>
<tr>
<td>Etramustine [34]</td>
<td>440</td>
<td>5.7</td>
<td>1</td>
<td>3</td>
<td>17.8</td>
<td>2</td>
<td>Melanoma, Thyroid</td>
</tr>
<tr>
<td>Etoposide [35-37]</td>
<td>589</td>
<td>1</td>
<td>0</td>
<td>13</td>
<td>0.116</td>
<td>1</td>
<td>Adenocarcinoma NOS</td>
</tr>
<tr>
<td>Idarubicin [39]</td>
<td>497</td>
<td>0.2</td>
<td>1</td>
<td>9</td>
<td>5.6</td>
<td>1</td>
<td>Breast</td>
</tr>
<tr>
<td>Mitoxantrone [42]</td>
<td>444</td>
<td>-3.1</td>
<td>4</td>
<td>6</td>
<td>32.02</td>
<td>5</td>
<td>Multiple&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paclitaxel [43, 44]</td>
<td>854</td>
<td>3</td>
<td>1</td>
<td>14</td>
<td>0.77</td>
<td>8</td>
<td>Lung, Melanoma</td>
</tr>
<tr>
<td>Teniposide [33, 45, 46]</td>
<td>657</td>
<td>1.5</td>
<td>0</td>
<td>13</td>
<td>1.03</td>
<td>8</td>
<td>Lung, melanoma, colon</td>
</tr>
<tr>
<td>Temozolomide [25]</td>
<td>194</td>
<td>-2.8</td>
<td>6</td>
<td>2</td>
<td>0.118</td>
<td>5</td>
<td>NSCLC</td>
</tr>
</tbody>
</table>

*Studies sorted alphabetically by agent name. TBR tissue to blood ratio, MW molecular weight rounded to nearest g mol⁻¹, N number of nitrogen atoms, O number of oxygen atoms, n sample size. MW, N, O, log(p) data from [pubchem.ncbi.nlm.nih.gov](http://pubchem.ncbi.nlm.nih.gov) unless otherwise referenced.*

<sup>a</sup> Lipophilicity measured as log(p)

<sup>b</sup> Cisplatin administered intra-arterially

<sup>c</sup> Chemical data shown is for daunorubicin hydrochloride

<sup>d</sup> Breast, lung, paraganglioma, teratocarcinoma

---

Adapted from E. Le Rhun

DU DIAPORAMA

Pitz et al. 2011

635
Brain CT Scan

There is no more BBB when a brain met is there!!

<table>
<thead>
<tr>
<th>Agent</th>
<th>Moleculat Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visipaque™</td>
<td>1550</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>854</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>298</td>
</tr>
</tbody>
</table>
Brain metastases management

- Brain mets in NSCLC
- Blood Brain Barrier
- **Radiotherapy**
  - WBRT
  - SABR
- Chemotherapy and antiangiogenic drugs
- Specific targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion
NSCLC & BM unsuitable for Surgery or SABR

Stratification:
- Centre
- PS
- Gender
- status of BM
- status of primary lung cancer

The primary outcome measure was quality-adjusted life-years (QALYs).
QALYs = OS + EQ-5D questionnaire.

Dexamethasone plus WBRT (20 Gy, 5 fractions)

Optimal supportive care (OSC)

N=538

Mulvena, The Lancet 2016
Non-inferiority trial
1-week non-inferiority boundary
Delta QALYs = 4.7 days

OS = 9.2 wks (WBRT) vs 8.5 wks (OSC)
HR 1.06

(95% CI 0.90–1.26, p=0.084)

Need 6 weeks for full benefit of RT after completion of RT?
Here OS 9 weeks!!
### QUARTZ

<table>
<thead>
<tr>
<th></th>
<th>WBRT (n/N)</th>
<th>OSC (n/N)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>157/157</td>
<td>157/157</td>
<td>1.17 (0.93-1.46)</td>
</tr>
<tr>
<td>Female</td>
<td>110/112</td>
<td>112/112</td>
<td>1.04 (0.80-1.36)</td>
</tr>
<tr>
<td><strong>Age group (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>66/67</td>
<td>48/48</td>
<td>1.48 (1.01-2.16)</td>
</tr>
<tr>
<td>60-69 years</td>
<td>110/110</td>
<td>123/123</td>
<td>1.22 (0.94-1.58)</td>
</tr>
<tr>
<td>≥70 years</td>
<td>91/92</td>
<td>98/98</td>
<td>0.75 (0.56-1.00)</td>
</tr>
<tr>
<td><strong>KPS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>101/101</td>
<td>102/102</td>
<td>0.94 (0.71-1.25)</td>
</tr>
<tr>
<td>≥70</td>
<td>166/168</td>
<td>167/167</td>
<td>1.21 (0.97-1.50)</td>
</tr>
<tr>
<td><strong>Extra-cranial metastases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>123/122</td>
<td>124/124</td>
<td>1.24 (0.96-1.59)</td>
</tr>
<tr>
<td>Yes</td>
<td>146/147</td>
<td>145/145</td>
<td>0.96 (0.77-1.22)</td>
</tr>
<tr>
<td><strong>Primary NSCLC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>96/98</td>
<td>94/94</td>
<td>1.31 (0.98-1.74)</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>169/169</td>
<td>172/172</td>
<td>0.97 (0.78-1.20)</td>
</tr>
<tr>
<td><strong>Number of Brain metastases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>79/80</td>
<td>82/82</td>
<td>1.00 (0.73-1.36)</td>
</tr>
<tr>
<td>2</td>
<td>56/56</td>
<td>56/56</td>
<td>1.11 (0.76-1.62)</td>
</tr>
<tr>
<td>3</td>
<td>28/28</td>
<td>22/22</td>
<td>1.11 (0.63-1.95)</td>
</tr>
<tr>
<td>4</td>
<td>15/15</td>
<td>20/20</td>
<td>0.70 (0.35-1.40)</td>
</tr>
<tr>
<td>5</td>
<td>84/85</td>
<td>89/89</td>
<td>1.37 (1.01-1.86)</td>
</tr>
<tr>
<td><strong>RPA class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22/22</td>
<td>8/8</td>
<td>1.81 (0.78-4.19)</td>
</tr>
<tr>
<td>2</td>
<td>143/145</td>
<td>156/156</td>
<td>1.06 (0.85-1.33)</td>
</tr>
<tr>
<td>3</td>
<td>100/100</td>
<td>102/102</td>
<td>0.95 (0.72-1.26)</td>
</tr>
<tr>
<td><strong>GPA class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5-4.0</td>
<td>5/5</td>
<td>2/2</td>
<td>1.08 (0.19-6.12)</td>
</tr>
<tr>
<td>2.5-3.0</td>
<td>38/39</td>
<td>40/40</td>
<td>1.65 (1.04-2.60)</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>108/109</td>
<td>104/104</td>
<td>1.11 (0.85-1.46)</td>
</tr>
<tr>
<td>0.0-1.0</td>
<td>111/111</td>
<td>123/123</td>
<td>0.95 (0.72-1.23)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>267/269</td>
<td>269/269</td>
<td>1.10 (0.93-1.32)</td>
</tr>
</tbody>
</table>

Mulvena, The Lancet 2016
WBRT toxicity

Table 4. Testing of Deterioration Status From Baseline in Hopkins Verbal Learning Test During Follow-up Using Reliable Change Index

- Phase III PCI vs observation in locally advanced NSCLC
- First prospective ‘Neurocognitive’ trial focused on NSCLC
- Significant # favors Observation, mostly at 12 mths
- Main differences in Short & Delayed Memory

Courtesy of F.Dhermain Sun, JCO 2011
WHOLE-BRAIN RADIOTHERAPY WITH SIMULTANEOUS INTEGRATED BOOST TO MULTIPLE BRAIN METASTASES USING VOLUMETRIC MODULATED ARC THERAPY


Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands
ATTENTION!

LE BULBIZARRE
A 2 CERVEAUX
ATTENTION!
LE BULBIZARRE
A 2 CERVEAUX
ATTENTION!
LE BULBIZARRE
A 2 CERVEAUX
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

Welsh JCO 2013
Bevacizumab and WBRT?

- Retrospective, multicenter study
- NSCLC patients with inoperable brain metastasis
- Bevacizumab followed by WBRT ≤ 6 months
- N=41

- 10 neurologic events (22%)
  - 5 cerebral hemorrhages (11%)
  - 2 deaths
  - no link with time between infusion of bevacizumab and toxicity
Bevacizumab and WBRT?

Diagnostic CBNPC
Diagnostic métastases cérébrales
Traitement par bevacizumab
Radiothérapie encéphalique in toto
Décès

Survives Médians:
3,5 mois
5,7 mois
12 mois
13,4 mois
22,3 mois

Arrondeau et al. ESMO 2013
Contestation Invasive

- Contention invasive = 1 séance de 15 – 20 Gy

"Radiochirurgie": RS
- Précision < mm

Contestation non-invasive
- = 1 seule ou 3 à 5 séances RT

STARI

Précision ~ 1 mm
Gamma-Knife

The patient can communicate via video camera and an intercom at all times. The treatment time varies between 20 minutes and several hours depending on the complexity of the treatment.

Perfexion is designed to treat patients with different types of brain disorders, for example benign and malignant tumors.

Gamma Knife Perfexion is fully automated. The radiation unit is part of the machine itself. The radiation beams are shaped exactly for the tumor. Several tumors can be treated in one session.
Couch with 6 degrees of freedom

Collimator Multilames de 2.5 mm + IMRT & Arc therapy

 Courtesy of F. Dhermain
SRS +/- WBRT : meta-analysis of 3 RCT

69 studies identified based on search of key words:

- 57 were not RCT
- 2 RCT excluded as WBRT vs. SRS plus WBRT
- 3 RCT excluded as WBRT plus surgery vs. WBRT
- 1 RCT excluded as WBRT plus surgery vs. surgery
- 1 RCT excluded at WBRT plus surgery vs. SRS
- 1 RCT excluded as WBRT plus SRS vs. WBRT plus surgery
- 1 RCT excluded as WBRT plus SRS vs. SRS plus systemic therapy

5 BM < 3.5 cm

Favors SRS alone, in particular if less than 50 y/o

Courtesy of F.Dhermain

Sahgal, IJROBP 2015
Don't routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.

Randomized studies have demonstrated no overall survival benefit from the addition of adjuvant whole brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) in the management of selected patients with good performance status and brain metastases from solid tumors. The addition of WBRT to SRS is associated with diminished cognitive function and worse patient-reported fatigue and quality of life. These results are consistent with the worsened, self-reported cognitive function and diminished verbal skills observed in randomized studies of prophylactic cranial irradiation for small cell or non-small cell lung cancer. Patients treated with radiosurgery for brain metastases can develop metastases elsewhere in the brain. Careful surveillance and the judicious use of salvage therapy at the time of brain relapse allow appropriate patients to enjoy the highest quality of life without a detriment in overall survival.

Courtesy of F.Dhermain, an radiation oncologist.
Radionecrosis

160 pts, 271 BM, median FU 17 months

% radionecrosis
17% at 1 yr, 34% at 2 yrs

SYMPTO: 12% at 1 yr

FU < 6 months : patients excluded

Fig. 1 Actuarial incidence of radionecrosis

Courtesy of F. Dhermain
Kohutec, J Neurooncol 2015
Délai médian à la Nécrose: **11 mois**

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Characteristics of radionecrosis diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrosis characteristics</td>
<td>Number (%) of lesions</td>
</tr>
<tr>
<td>Time to necrosis (months), median (range)</td>
<td>10.8 (2.7–47.7)</td>
</tr>
<tr>
<td>Presence of symptoms</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47 (67.1 %)</td>
</tr>
<tr>
<td>No</td>
<td>23 (32.9 %)</td>
</tr>
<tr>
<td>Method of diagnosis</td>
<td></td>
</tr>
<tr>
<td>Pathologic</td>
<td>22 (31.4 %)</td>
</tr>
<tr>
<td>Radiographic</td>
<td>48 (68.6 %)</td>
</tr>
<tr>
<td>MRI alone</td>
<td>27 (38.6 %)</td>
</tr>
<tr>
<td>MRI with PET</td>
<td>21 (30.0 %)</td>
</tr>
</tbody>
</table>
Brain metastases management

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- **Chemotherapy and antiangiogenic drugs**
  - Chemo first? or RT first?
  - Bevacizumab and brain mets
- Specific targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion
GFPC1 95-01

NSCLC & BM
>50% symptomatic

Arm A

N = 171

Arm B

Robinet, Ann Oncol 2001
Overall Survival

Log-rank $P = .836$

G1: 24 weeks
G2: 21 weeks
SRS vs. Observation

- 105 patients with 1 to 4 brain metastases, never-S
- SRS → CT vs. CT upfront End-point: OS

OS (mo): 14.6 vs. 15.3

~30% of EGFRmut in both arms
## Chemotherapy – 1st 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>
<td>Nr</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Minotti et al, 1998</td>
<td>Cisplatine Teniposide</td>
<td>23</td>
<td>35</td>
<td>26</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Franciosi et al, 1999</td>
<td>cisplatine etoposide</td>
<td>43</td>
<td>30</td>
<td>Nr</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Fujita et al, 2000</td>
<td>Cisplatine ifosfamide CPT11</td>
<td>30</td>
<td>50</td>
<td>62</td>
<td>4.6</td>
<td>12</td>
</tr>
<tr>
<td>Bernardo et al, 2002</td>
<td>Carboplatine, navelbine, gemcitabine</td>
<td>22</td>
<td>45</td>
<td>NR</td>
<td>6.2</td>
<td>8.2</td>
</tr>
<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>
</tr>
<tr>
<td>Galetta et al, 2011</td>
<td>Cisplatine fotemustine</td>
<td>25</td>
<td>NR</td>
<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>
<tr>
<td>Bailon et al, 2012</td>
<td>Carboplatine Pemetrexed</td>
<td>26</td>
<td>40</td>
<td>40</td>
<td>7.7</td>
<td>9.7</td>
</tr>
</tbody>
</table>
GFPC 02-2013 METAL 2

non squamous, asymptomatic BM
CT = pemetrexed/cisplatin

RT if symptoms

RT= radiothérapie
C= chimiothérapie d’induction
m= chimiothérapie de maintenance
Phase II study BRAIN

- Non squamous NSCLC
- Asymptomatic, non treated brain mets
- Mandatory RMI

Arm A: n=66

<table>
<thead>
<tr>
<th>NSCLC BM</th>
<th>1\textsuperscript{st} line</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carboplatin + Paclitaxel Q3W, 6 cycles</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab until disease progression*</td>
</tr>
</tbody>
</table>

Arm B: n=49

<table>
<thead>
<tr>
<th>NSCLC BM</th>
<th>2\textsuperscript{nd} line</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erlotinib until disease progression*</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab until disease progression*</td>
</tr>
</tbody>
</table>

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

Besse et al. CCR 2016
ORR – Paclitaxel carboplatine bevacizumab

*all arms, n=91

Besse et al. CCR 2016
## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>B+CP (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month PFS rate, % (95% CI)</td>
<td>56.5 (43.8–67.4)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.7 (5.7–7.1)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>16.0 (12.0–21.0)</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.
## 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.

Cerebral Hemorrhage Rate : 1,5% (1pt, grade I)*

Besse et al. CCR 2016
Brain metastases management

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Targeted therapies
  - EGFR
  - ALK
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion
## 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.</td>
<td>17 (subset)</td>
<td><em>EGFR</em> mutated</td>
<td>No</td>
<td>Erlotinib</td>
<td>82</td>
<td>NR</td>
</tr>
<tr>
<td>Park et al.</td>
<td>28</td>
<td><em>EGFR</em> mutated</td>
<td>No</td>
<td>Gefitinib or erlotinib</td>
<td>83</td>
<td>15.9</td>
</tr>
<tr>
<td>Li</td>
<td>9</td>
<td><em>EGFR</em> mutated</td>
<td>No</td>
<td>Gefitinib</td>
<td>89</td>
<td>NR</td>
</tr>
<tr>
<td>Kim et al.</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.</td>
<td>40</td>
<td>Unselected</td>
<td>Yes</td>
<td>Erlotinib</td>
<td>86</td>
<td>11.8</td>
</tr>
<tr>
<td>Luchi et al.</td>
<td>41</td>
<td><em>EGFR</em> mutated</td>
<td>No</td>
<td>Gefitinib</td>
<td>87.8</td>
<td>21.9</td>
</tr>
</tbody>
</table>

### Brain mets
- **ORR 74-89%**
- **OS 15.9-21.9 m**
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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Li [68]</td>
<td>9</td>
<td>EGFR mutated</td>
<td>No</td>
<td>Gefitinib</td>
<td>89</td>
<td>NR</td>
</tr>
<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>
<td>11.8</td>
</tr>
<tr>
<td>Luchi et al. [80]</td>
<td>41</td>
<td>EGFR mutated</td>
<td>No</td>
<td>Gefitinib</td>
<td>87.8</td>
<td>21.9</td>
</tr>
</tbody>
</table>

Brain mets
- ORR 74-89%
- OS 15.9-21.9 m

Phase III studies – all comers
- ORR 56-84%
- OS 19.3 – 28.1 m
Afatinib (LUX-Lung 3&6): brain metastases

**With Brain Metastases**

- **Ataxinib**: 3.98, 11.14, 19.12
- **Pemetrexed + Cisplatin**: 3.06, 5.39, 9.69

**Hazard ratio (95% CI)**: 0.54 (0.29-1.25)

**Log-rank test p value**: 0.1378

**HR=0.54**

**Without Brain Metastases**

- **Ataxinib**: 8.15, 13.77, 22.00
- **Pemetrexed + Cisplatin**: 2.76, 8.11, 12.29

**Hazard ratio (95% CI)**: 0.48 (0.34-0.66)

**Log-rank test p value**: <0.0001

**HR=0.48**

The magnitude of PFS improvement similar to pts without BM
Afatinib (LUX-Lung 3&6): brain metastases

**A LUX-Lung 3**

With Brain Metastases

- Afatinib: 25th, Median, 75th
  - 8.15, 13.77, 22.05
- Pemetrexed + Capstatin: 3.06, 5.39, 9.69

Hazard ratio (95% CI): 0.54 (0.29–1.25)

Log-rank test p value: 0.1375

Number at risk
- Afatinib: 26, 17, 12
- Pemetrexed + Capstatin: 33, 21, 13

**Without Brain Metastases**

- Afatinib: 25th, Median, 75th
  - 8.15, 13.77, 22.05
- Pemetrexed + Capstatin: 2.76, 6.11, 12.29

Hazard ratio (95% CI): 0.45 (0.34–0.69)

Log-rank test p value: <0.0001

Number at risk
- Afatinib: 15, 6, 3
- Pemetrexed + Capstatin: 15, 6, 3

**B LUX-Lung 6**

With Brain Metastases

- Afatinib: 25th, Median, 75th
  - 7.00, 11.07, 19.35
- Gemcitabine + NE: 4.78, 8.21, 19.35

Hazard ratio (95% CI): 0.47 (0.15–1.21)

Log-rank test p value: 0.1000

Number at risk
- Afatinib: 22, 12, 11
- Gemcitabine + NE: 18, 7, 2

**Without Brain Metastases**

- Afatinib: 25th, Median, 75th
  - 13.92, 19.35, 25.41
- Gemcitabine + NE: 18, 7, 2

Hazard ratio (95% CI): 0.22 (0.15–0.33)

Log-rank test p value: <0.0001

Number at risk
- Afatinib: 118, 162, 134
- Gemcitabine + NE: 18, 7, 2

Pooled analysis AURA trials

- PFS by medical history of brain metastases

Median PFS, months (95% CI)
- Full analysis set: 9.7 (9.7, NC)
- With brain metastases: 8.0 (6.9, 8.5)
- Without brain metastases: 9.7 (9.7, NC)

Maturity of PFS data in the full analysis set is 39%; median follow-up for PFS was 6.8 months.
Brain metastases management

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- **Targeted therapies**
  - EGFR
  - ALK
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion
30% of ALK+ patients had brain metastasis at baseline and 35-50% develop brain metastases.

Shaw AT et al, Lancet Oncol 2011: 12, 1004

Figure 1. The actuarial incidence of isolated central nervous system failure, measured by the Kaplan-Meier method, in patients with clinical benefit from epidermal growth factor tyrosine kinase inhibitors.
Crizotinib and efficacy in brain

- Crizotinib has a poor CNS penetration with a CSF-to-plasma ratios of 0.026
- Retrospective study of PROFILE 1005, 1007

**PFS:** 8.8 / 6 / 5.9

**Intracranial DCR:** ~60%

*N=275 (Treated /Untreated: 109/166)*
# ALK inhibitors and RR to brain

<table>
<thead>
<tr>
<th>Author</th>
<th>Medicament</th>
<th>N</th>
<th>Réponse intracrânienne</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALK réarrangé</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Ceritinib* (phase I)</td>
<td>75</td>
<td>65% (disease control rate)</td>
</tr>
<tr>
<td>Ou et al.</td>
<td>Alectinib* (phase II)</td>
<td>35</td>
<td>57%</td>
</tr>
<tr>
<td>Shaw et al.</td>
<td>Alectinib* (phase II)</td>
<td>16</td>
<td>75%</td>
</tr>
<tr>
<td>Gadgeel et al</td>
<td>Alectinib* (phase I/II)</td>
<td>21</td>
<td>52%</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Brigatinib* (phase II)</td>
<td>21</td>
<td>67%</td>
</tr>
</tbody>
</table>

*Patients crizotinb-resistant
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
### J-ALEX phase III study in ALK+

**Key Entry Criteria**
- Stage IIIb/IV or recurrent ALK-positive NSCLC
- ALK centralized testing (IHC and FISH or RT-PCR)
- ECOG PS 0-2
- ≥1 measurable lesion assessed by investigator
- Treated/asymptomatic brain metastases allowed
- ≤1 prior chemotherapy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Alectinib</th>
<th>Crizotinib</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (independent)</td>
<td>91.6%</td>
<td>78.9%</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>NR</td>
<td>10.2</td>
<td>HR:0.34, p&lt;0.001</td>
</tr>
</tbody>
</table>

*IRF Independent Review Facility*
ASCEND 7 trial ongoing

ALK+ NSCLC with BMs: CERITINIB 750 mg/d orally

Prior ALK-TKI, prior RT
Prior ALK-TKI, no prior RT
ALK-TKI-naïve, prior RT
ALK-TKI-naïve, no prior RT
Leptomeningeal carcinomatosis

- Primary outcome: overall response rate
- Secondary outcomes: intra-cranial / extra-cranial response rates, overall survival
### Lorlatinib (PF06463922)

<table>
<thead>
<tr>
<th>Mutation Status</th>
<th>Cell Line</th>
<th>Lorlatinib PF06463922</th>
<th>Crizotinib (LDK-378)</th>
<th>Alectinib (CH5424802)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML4-ALK v1</td>
<td>NH3T3</td>
<td>1.3</td>
<td>80</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BaF3</td>
<td>3.6</td>
<td>90</td>
<td>41</td>
</tr>
<tr>
<td>EML4-ALK L1986M</td>
<td>NH3T3</td>
<td>21</td>
<td>843</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BaF3</td>
<td>43</td>
<td>1164</td>
<td>70</td>
</tr>
<tr>
<td>EML4-ALK G1269A</td>
<td>NH3T3</td>
<td>15</td>
<td>605</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BaF3</td>
<td>80</td>
<td>689</td>
<td>134</td>
</tr>
<tr>
<td>EML4-ALK G1202R</td>
<td>NH3T3</td>
<td>77</td>
<td>1000</td>
<td>&gt;10000</td>
</tr>
<tr>
<td></td>
<td>BaF3</td>
<td>113</td>
<td>562</td>
<td>549</td>
</tr>
<tr>
<td>EML4-ALK N1151Tins</td>
<td>NH3T3</td>
<td>38</td>
<td>1268</td>
<td>1066</td>
</tr>
<tr>
<td></td>
<td>BaF3</td>
<td>50</td>
<td>902</td>
<td>296</td>
</tr>
<tr>
<td>EML4-ALK S1206Y</td>
<td>NH3T3</td>
<td>4.2</td>
<td>626</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BaF3</td>
<td>1.2</td>
<td>152</td>
<td>60</td>
</tr>
<tr>
<td>EML4-ALK C1156Y</td>
<td>NH3T3</td>
<td>1.6</td>
<td>478</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BaF3</td>
<td>1.5</td>
<td>406</td>
<td>177</td>
</tr>
<tr>
<td>EML4-ALK F1174L</td>
<td>NH3T3</td>
<td>0.2</td>
<td>165</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BaF3</td>
<td>4.0</td>
<td>150</td>
<td>181</td>
</tr>
</tbody>
</table>

**Clinical Activity: Maximum Percentage Change in Target Lesion Size**

- N=50 (88% pre-treated)
- 60% Brain Metastases

No prior TKI  | 1 Prior TKI  | >1 Prior TKI

PD occurred in 14 patients: new lesions (n=8), non-target lesions (n=2), both new and non-target lesions (n=4).
Brain metastases management

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion
Immunotherapy: Pembrolizumab

- N=36 (18 melanoma, 18 PD-L1+* NSCLC patients)
- 1 untreated or progressive brain metastasis (5 and 20 mm in diameter) without associated neurological symptoms or the need for corticosteroids.

Brain response in NSCLC patients: 33%
Median DoR: 3.2-7 months
Brain metastases management

- Brain mets in NSCLC
- Blood Brain Barrier
- Radiotherapy
- Chemotherapy and antiangiogenic drugs
- Targeted therapies
- Immunotherapy
- Leptomeningeal carcinomatosis
- Conclusion
Leptomeningeal metastasis

- Incidence 3.8% in NSCLC. Liao – JTO 2015
- Median OS 3.6-11 months. Umemura – Lung Cancer 2012
- Performance status is the best prognosis factor
- ITC improve OS: 7.5 vs. 3.6 mo. Wu – Oncol Letter 2016
- Incidence in EGFR-mutant pt: 9%. Kuiper – Lung Cancer 2015
Osimertinib LM metastases: BLOOM study

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

Osimertinib 160 mg QD

Data cut-off: March 10, 2016

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

Best MRI imaging intracranial response, n (%)

<table>
<thead>
<tr>
<th>Response</th>
<th>Confirmed</th>
<th>Unconfirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responding</td>
<td>7 (33)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (43)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Early withdrawal</td>
<td>2 (10)</td>
<td></td>
</tr>
</tbody>
</table>
Low CSF penetration with current EGFR TKI

Median $K_{puu,\text{brain}} = 0.86$

AZD3759 is not a substrate
- of PGP
- and BCRP efflux transporters

Rat model

Significantly prolonged animal survival in
PC-9 BM model, compared with gefitinib, erlotinib, icotinib
New EGFR TKI: AZD3759 (not T790M)

- Long lasting activity
- Drug-related adverse events: rash and diarrhea
- ADZ3759 achieved concentrations above IC50 for target inhibition in CSF in all patients ≥ 200 mg BID
Carcinomatous meningitis (French experience)

40 pts - EGFRmut

Symptoms

95%

90%

45%

28%

Carcinomatous meningitis (French experience)

RMN cerebrale diagnostica

22

14

citologia rachicentesi positiva

90%

45%

28%

Sintomi neurologici

GUSTAVE ROUSSY

THÈME DU DIAPORAMA

Biondani et al.
ORR to EGFR TKI

ORR

RP: 55%

DCR

RP + SD: 78%

- If RP or SD: improvement of symptoms
- OS 6 mois
Increase TKI dose?

- **N=14 (36%)**

1) Erlotinib increase (n=8)
   - 150mg to 300mg (n=7)
   - Weekly high dose (n=1)

2) Switch from gefitinib to erlotinib (n=6)
   - ORR=29%
   - DCR=64%
Conclusion

- BLOOD BRAIN BARRIER DOES NOT EXIST IN BRAIN METS
- SABR and surgery are key players
- WBRT can be delayed
- ORR to chemotherapy: same as extra-cranial disease
- Bevacizumab, a good partner for brain mets?
- EGFRmut and ALK+ population: TKI should be offered upfront if brain mets
- Carcinomatous meningitis: increase TKI dose is an option