ESMO Clinical Practice Guidelines

Solange Peters
MD-PhD
Oncology Department
Lausanne University Hospitals
Switzerland

ADVANCED NON SMALL CELL LUNG CANCER
Disclosures

I have provided consultation, attended advisory boards and/or provided lectures for:

F. Hoffmann–La Roche, Ltd; Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Morphotek, Merrimack, Merck Serono, MSD, Amgen, Clovis, Astellas and Tesaro, for which I received honoraria.

I declare no conflict of interest.
Lung adenocarcinoma, mild aphasia
Radiotherapy for multiple lung carcinoma brain metastases

Brain metastases treatment depends on the prognosis based on recursive partitioning analysis (RPA) class

Class I:
- <65 years old
- good performance status (Karnofsky Index (KI) ≥70%)
- no other extra-cranial metastases
- controlled primary tumour

Class II: in between

Class III:
- KI<70%

Standard treatment of class I/II patients with >3 brain metastases is whole brain radiotherapy (WBRT). The most frequent schedules are 20 Gy in 5 fractions or 30 Gy in 10 fractions, with no difference in outcome [I, A]

In class III patients, only best supportive care (BSC) is recommended, with a median survival of <2 months.

Timing for radiotherapy for multiple brain metastases in lung carcinoma

• *In patients with asymptomatic brain metastases who have not received prior systemic therapy (e.g. chemotherapy, TKIs), systemic treatment and deferred WBRT should be considered [II, B]*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Brain RR (%)</th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/paclitaxel/vinorelbine or gemcitabine</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>Cisplatin/ifosfamide/irinotecan</td>
<td>50</td>
<td>12.7</td>
</tr>
<tr>
<td>Cisplatin/fotemustine</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Cisplatin/teniposide</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Carboplatin/vinorelbine/gemcitabine</td>
<td>45</td>
<td>7</td>
</tr>
<tr>
<td>Cisplatin/etoposide</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Cisplatin/vinorelbine</td>
<td>27</td>
<td>NA</td>
</tr>
<tr>
<td>Cisplatin/pemetrexed</td>
<td>41.9</td>
<td>7.4</td>
</tr>
<tr>
<td>Carboplatin/pemetrexed</td>
<td>30</td>
<td>9.1</td>
</tr>
</tbody>
</table>

ESMO guidelines, Reck M. et al., Ann Oncol 2014
Radiotherapy for brain metastases in EGFR M+ lung carcinoma

- Efficacy of EGFR TKI therapy in brain metastases is accurately paralleled by its efficacy in the lung primary lesions and other metastatic sites
- Whether WBRT can be postponed even in neurologically symptomatic patients is a matter of debate with no prospective data available

<table>
<thead>
<tr>
<th>N</th>
<th>Selection</th>
<th>Prior treatment</th>
<th>Treatment</th>
<th>Brain RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 (subset)</td>
<td>EGFR mutated</td>
<td>No</td>
<td>Erlotinib</td>
<td>82</td>
</tr>
<tr>
<td>28</td>
<td>EGFR mutated</td>
<td>No</td>
<td>Gefitinib or erlotinib</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>EGFR mutated</td>
<td>No</td>
<td>Gefitinib</td>
<td>89</td>
</tr>
<tr>
<td>23</td>
<td>Asian never-smokers</td>
<td>No</td>
<td>Gefitinib or erlotinib</td>
<td>74</td>
</tr>
<tr>
<td>40</td>
<td>Unselected</td>
<td>Yes</td>
<td>Erlotinib</td>
<td>86</td>
</tr>
<tr>
<td>41</td>
<td>EGFR mutated</td>
<td>No</td>
<td>Gefitinib</td>
<td>87.8</td>
</tr>
</tbody>
</table>

Zimmermann, Cancer Treat Rev 2014
ESMO guidelines, Reck M. et al., Ann Oncol 2014
Molecular testing in NSCLC

• Genetic alterations which are key oncogenic events have been identified in numerous small subsets of NSCLC. Two of these alterations have been validated as reliable targets for selective pathway directed systemic therapy.

• EGFR mutation testing is recommended in all patients with advanced NSCLC of a non-squamous subtype [I, A]. Testing is not recommended in patients with a confident diagnosis of squamous cell carcinoma, except in never/former light smokers (<15 packs per year) [IV, A]
Molecular testing in NSCLC

The opportunity of applying systemic molecular-based targeted approaches for other driver alterations (such as ROS1, BRAF, HER2, and RET) is currently under evaluation.

Tissue should be prioritized for EGFR and ALK testing. EGFR and ALK results should be available within 2 weeks (10 working days).

Lindenman, JTO 2013,
ESMO guidelines, Reck M. et al., Ann Oncol 2014
First-line therapy for EGFR M+NSCLC

- Activating (sensitising) EGFR mutations are predictive for response to EGFR TKIs resulting in an improved RR, PFS, and QoL as well as a better tolerability when compared with first-line chemotherapy

- EGFR TKI therapy statistically significantly delays disease progression and should be considered as front-line therapy [I, A]

ESMO guidelines, Reck M. et al., Ann Oncol 2014
## PFS: EGFR TKIs versus Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>EGFR TKI</th>
<th>n</th>
<th>Median PFS in TKI arm (months)</th>
<th>P value</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib</td>
<td>154</td>
<td>13.1</td>
<td>&lt;0.0001</td>
<td>0.16</td>
</tr>
<tr>
<td>First Signal</td>
<td>Gefitinib</td>
<td>42</td>
<td>8.4</td>
<td>&lt;0.084</td>
<td>0.61</td>
</tr>
<tr>
<td>IPASS</td>
<td>Gefitinib</td>
<td>261</td>
<td>9.5</td>
<td>&lt;0.0001</td>
<td>0.48</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>Gefitinib</td>
<td>177</td>
<td>9.2</td>
<td>&lt;0.001</td>
<td>0.48</td>
</tr>
<tr>
<td>NEJSG 002</td>
<td>Gefitinib</td>
<td>200</td>
<td>10.8</td>
<td>&lt;0.001</td>
<td>0.36</td>
</tr>
<tr>
<td>Ensure</td>
<td>Erlotinib</td>
<td>217</td>
<td>11</td>
<td>&lt;0.0001</td>
<td>0.34</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib</td>
<td>174</td>
<td>9.4</td>
<td>&lt;0.0001</td>
<td>0.42</td>
</tr>
<tr>
<td>LUX-3</td>
<td>Afatinib</td>
<td>308</td>
<td>13.6</td>
<td>&lt;0.0001</td>
<td>0.47</td>
</tr>
<tr>
<td>LUX-6</td>
<td>Afatinib</td>
<td>364</td>
<td>11.0</td>
<td>&lt;0.0001</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Treatment of EGFR-addicted NSCLC at resistance, harboring T790M

1) Chemotherapy
2) Gefitinib beyond RECIST progression
3) Chemotherapy + EGFR TKI
4) Afatinib
5) Afatinib + cetuximab
6) 3rd generation EGFR TKI (AZD9291, CO-1686, HM61713, through a clinical trial)
Treatment of EGFR M+ NSCLC at resistance

Camidge, Nat Rev Clin Oncol 2014
Evidence of clinical benefit related to continuation of EGFR TKI beyond progression in selected patients is accumulating, but formally remains an issue to be prospectively studied before firm conclusions can be drawn.
Treatment of EGFR-addicted NSCLC at resistance

Camidge, Nat Rev Clin Oncol 2014
ESMO guidelines, Reck M. et al., Ann Oncol 2014
TKI after progression on TKI

modified from Thomas Lynch, ASCO 2014; Kim, ASCO 2014; Janne ASCO 2014; Sequist ASCO 2014
First line chemotherapy after EGFR TKI failure

1) Cisplatin / pemetrexed
2) Cisplatin / pemetrexed / bevacizumab
3) Carboplatin / pemetrexed
4) Carboplatin / pemetrexed / bevacizumab
5) Docetaxel
6) Pemetrexed
7) Carboplatin / paclitaxel / bevacizumab
Chemo after TKI, any evidence?

Little prospective data on chemo after TKI in mEGFR disease

### ESMO Presidential session: IMPRESS TRIAL

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>N</th>
<th>RR</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gridelli, JCO 2012</td>
<td>Cis/gem</td>
<td>13</td>
<td>15%</td>
<td>Prospective</td>
</tr>
<tr>
<td>Wu, IJC 2010</td>
<td>Various</td>
<td>41</td>
<td>15%</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Goldberg, ASCO 2012</td>
<td>Various</td>
<td>28</td>
<td>18%</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Yoshimura, JTO 2012</td>
<td>Pem/TKI</td>
<td>27</td>
<td>26%</td>
<td>Prospective</td>
</tr>
</tbody>
</table>

Modified from Oxnard, ASCO 2013
First line chemotherapy
General statements

• Several regimens have shown comparable efficacy

• The expected toxicity profile should contribute to the selection of the chemotherapy regimen

• Meta-analyses have shown higher RRs for cisplatin combinations when compared with carboplatin combinations

ESMO guidelines, Reck M. et al., Ann Oncol 2014
First line chemotherapy PS 0-1

Schiller, NEJM 2002
Cisplatin as the European standard

mOS 9.1 vs 8.4 mos (p=NS), absolute benefit 3% at 1yr

-> Statistically significant in patients with non-squamous tumors or treated with third-generation chemotherapy

Ardizzoni, J Natl Cancer Inst 2007
A recent meta-analysis showed a slight but significant survival benefit with pemetrexed-based combination chemotherapy compared with gemcitabine- or docetaxel-based combinations and of a pre-planned subgroup analysis of a large randomised phase III trial.

Pemetrexed use should be restricted to nonsquamous NSCLC in any line [I, A].

Bevacizumab with platinum based chemotherapy

- Two meta-analyses showed a significant improvement of RR, PFS, and OS for the combination of bevacizumab and platinum-based chemotherapy compared with platinum-based chemotherapy.

Therefore, the combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients [I, A]

ESMO guidelines, Reck M. et al., Ann Oncol 2014
Thanks for your attention!