Approaches to therapy of metastatic NSCLC: second-line and beyond

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Second-line: an evolving landscape

- Second-line chemotherapy improves disease-related symptoms and may improve survival in selected patients [III, C].
- Second-line chemotherapy (docetaxel, pemetrexate) improves disease-related symptoms and improves survival in selected patients [II, B].
- Second-line systemic treatment (docetaxel, erlotinib, or pemetrexed in patients with predominantly non-squamous histology) should be considered in appropriately selected patients [I, A].

Comparable options as the second-line therapy consist of pemetrexed—for a non-squamous histology only [42]—or docetaxel [43] [I, B]. Erlotinib was shown to improve the OS in second-line or in third-line NSCLC patients of all histologies not eligible for further chemotherapy, including patients with PS 3 [44].

Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as second-line therapy, if not received previously [I, A].

In the presence of an ALK rearrangement, second-third line treatment with crizotinib should be considered if not received as part of first-line therapy [10, 33].

ESMO Guidelines

11 years
In clinical practice, the % of pts receiving 2nd line therapy is far less
In the era of maintenance treatment, the % pts receiving 2nd line therapy may increase
Few data available on second-line after maintenance treatment

Prognostic factors for second-line treatment

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>Performance Status</td>
<td>0</td>
</tr>
<tr>
<td>Tumour stage</td>
<td>IIIb</td>
</tr>
<tr>
<td>Histologic type</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Type of first-line</td>
<td>Without platinum</td>
</tr>
<tr>
<td>Objective response to first-line</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Di Maio, et al. EJC 2010
Second-line: an integrated pathological/molecular approach

- Squamous cell cancer
  - Chemotherapy
  - Erlotinib
  - EGFR & ALK/ROS1 negative*
    - Chemotherapy
    - Erlotinib
    - EGFR-TKI beyond PD
    - EGFR-TKI beyond PD + Chemotherapy
    - EGFR ‘complete’ blockade
    - EGFR irreversible inhibition
  - ALK/ROS1 rearranged
    - Crizotinib
    - ALK-inhibitor

- Non squamous cancer
  - Chemotherapy
  - Erlotinib
  - EGFR
  - EGFR-TKI beyond PD
  - EGFR irreversible inhibition
  - ALK/ROS1 rearranged
    - Crizotinib
    - ALK-inhibitor

*Data indirectly extrapolated from trials dedicated to molecularly selected populations

Second-line: chemotherapy

- Squamous cell cancer
  - Chemotherapy
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*Data indirectly extrapolated from trials dedicated to molecularly selected populations
## Efficacy parameter

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Docetaxel 75 mg/m²</th>
<th>Pemetrexed 500 mg/m² (JMEI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAX 317 (n = 55)</td>
<td>(n = 283)</td>
</tr>
<tr>
<td>Response rate</td>
<td>5.5%</td>
<td>6.7%*</td>
</tr>
<tr>
<td>PFS</td>
<td>Not reported</td>
<td>2.9 mos.</td>
</tr>
<tr>
<td>Survival</td>
<td>7.5 mos.</td>
<td>7.9 mos.</td>
</tr>
<tr>
<td>1-yr survival</td>
<td>37%</td>
<td>29.7%</td>
</tr>
</tbody>
</table>

* Based on 120 evaluable patients

---

**Approved second-line cytotoxics: similar efficacy but...**

- **Docetaxel 75 mg/m²**
- **Pemetrexed 500 mg/m² (JMEI)**

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>TAX 317 (n = 55)</th>
<th>TAX 320 (n = 124)</th>
<th>JMEI (n = 288)</th>
<th>INTEREST (n = 733)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>5.5%</td>
<td>6.7%*</td>
<td>9.1%</td>
<td>7.6%</td>
</tr>
<tr>
<td>PFS</td>
<td>Not reported</td>
<td>1.9 mos.*</td>
<td>2.9 mos.</td>
<td>2.7 mos.</td>
</tr>
<tr>
<td>Survival</td>
<td>7.5 mos.</td>
<td>5.7 mos.</td>
<td>7.9 mos.</td>
<td>8.0 mos.</td>
</tr>
<tr>
<td>1-yr survival</td>
<td>37%</td>
<td>32%</td>
<td>29.7%</td>
<td>34%</td>
</tr>
</tbody>
</table>

* Based on 120 evaluable patients

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**Difference according to tolerability**

- **Survival without grade 3/4 toxicity**

  - **Docetaxel**
  - **Pemetrexed**


  *Pujol, et al. JTO 2007*
Difference according to histology

Non-squamous

- Median (95% CI): 9.3 (7.8–9.7)
- D: 8.0 (6.3–9.3)
- P vs D: Adjusted HR (95% CI): 0.78 (0.61–1.00)

Squamous

- Median (95% CI): 6.2 (4.9–8.0)
- D: 7.4 (5.0–9.5)
- P vs D: Adjusted HR (95% CI): 1.56 (1.08–2.26)

Scagliotti, et al. Oncologist 2009

No survival benefit from combination chemo over single-agent but...

Di Maio, et al. JCO 2009
...toxicity favors mono-chemotherapy

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. of patients with available data</th>
<th>Single agent</th>
<th>Combination</th>
<th>Exact OR</th>
<th>95% CI</th>
<th>P*</th>
<th>P for homogeneity∞</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>786</td>
<td>95% 24 136 35</td>
<td>2.04 1.38 to 3.04</td>
<td>.0002</td>
<td>.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>839</td>
<td>31% 7 31 7</td>
<td>1.00 0.57 to 1.76</td>
<td>.99</td>
<td>.032</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>839</td>
<td>9% 2 37 9</td>
<td>4.47 2.08 to 10.70</td>
<td>&lt; .0001</td>
<td>.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>839</td>
<td>7% 2 40 10</td>
<td>6.24 2.71 to 16.76</td>
<td>&lt; .0001</td>
<td>.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hematologic</td>
<td>839</td>
<td>106% 25 172 41</td>
<td>2.62 1.83 to 3.79</td>
<td>&lt; .0001</td>
<td>.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>839</td>
<td>12% 3 23 6</td>
<td>1.94 0.91 to 4.36</td>
<td>.081</td>
<td>.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>839</td>
<td>2% &lt; 1 1 &lt; 1</td>
<td>0.48 0.01 to 9.31</td>
<td>.62</td>
<td>.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>839</td>
<td>20% 5 42 10</td>
<td>2.28 1.25 to 4.28</td>
<td>.006</td>
<td>.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>839</td>
<td>7% 2 3 1</td>
<td>0.42 0.07 to 1.86</td>
<td>.22</td>
<td>.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>710</td>
<td>3% 5 1</td>
<td>1.85 0.35 to 12.04</td>
<td>.49</td>
<td>.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>700</td>
<td>9% 3 10 3</td>
<td>1.15 0.40 to 3.29</td>
<td>.82</td>
<td>.064</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>839</td>
<td>4% 1 5 1</td>
<td>1.28 0.27 to 6.50</td>
<td>.75</td>
<td>.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>839</td>
<td>6% 1 6 1</td>
<td>1.01 0.27 to 3.84</td>
<td>.99</td>
<td>.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>839</td>
<td>- 1 &lt; 1</td>
<td>- &lt; 1 -</td>
<td>-</td>
<td>.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any nonhematologic</td>
<td>839</td>
<td>92% 22 118 28</td>
<td>1.43 1.02 to 2.00</td>
<td>.034</td>
<td>.036</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Exact test stratified by trial
∞Exact test for homogeneity of ORs

CBDCA/PEM: a well tolerated second-line combination regimen

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Line of therapy</th>
<th>No. of pts</th>
<th>RR (%)</th>
<th>DCR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smit (2009)</td>
<td>Phase II*</td>
<td>2nd</td>
<td>119</td>
<td>16.8</td>
<td>71.4</td>
<td>4.2</td>
<td>8.0</td>
</tr>
<tr>
<td>Kim (2010)</td>
<td>Phase II</td>
<td>2nd/3rd</td>
<td>32</td>
<td>18.8</td>
<td>46.8</td>
<td>2.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Metro (2011)</td>
<td>Retrospective</td>
<td>2nd to 4th</td>
<td>80</td>
<td>42.5</td>
<td>77.5</td>
<td>5.8</td>
<td>17.4</td>
</tr>
<tr>
<td>Ardizzoni (2012)</td>
<td>Phase II*</td>
<td>2nd</td>
<td>119</td>
<td>12.6</td>
<td>67.0</td>
<td>3.5</td>
<td>9.2</td>
</tr>
</tbody>
</table>

*Ranomized
**Second-line: erlotinib**

Squamous cell cancer

- Chemotherapy
- Erlotinib

Non squamous cancer

- Chemotherapy
- Erlotinib

EGFR & ALK/ROS1 negative*

- Chemotherapy
- EGFR-TKI beyond PD
- EGFR-TKI beyond PD + Chemotherapy
- EGFR ‘complete’ blockade
- EGFR irreversible inhibition

EGFR mut +

ALK/ROS1 rearranged

- Crizotinib
- ALK-inhibitor

*Data indirectly extrapolated from trials dedicated to molecularly selected populations

---

**BR.21: Erlotinib vs. placebo**

Shepherd, et al. NEJM 2005
BR.21: men + smokers + squamous cancer

The hazard ratio for death is 0.66 (P = 0.010). Median survival times are 5.5 months and 3.4 months, respectively, for erlotinib and placebo.


BR.21: EGFR WT-only patients

Zhu, et al. JCO 2008
EGFR-TKI vs. chemotherapy in unselected pts: INTEREST & TITAN

No survival difference


TAILOR trial

- Stage IIIIB/IV
- Prior platinum-based doublet
- EGFR wild-type
- Known KRAS status
- ECOG PS 0-2

R 1:1

DOCETAXEL
75 mg/mq iv on day 1, 21
35 mg/mq iv on day 1, 8, 15

ERLOTINIB
150 mg po, daily

PRIMARY END POINT
OS

SECONDARY END POINTS
PFS
RR
QoL
Toxicity

STRATIFICATION
KRAS
Centre
Stage
Prior chemo
ECOG-PS (0-1 vs. 2)

Martelli, et al. AIOM 2012
702 registered

554 genotype assessed

222 randomized

219 ITT analysis

- 148 not eligible (21%)
  - Insufficient material 124
  - Not evaluable for EGFR and KRAS 24

- 332 non randomized
  - EGFR mut + 79
  - Non PD 116
  - Physician’s choice 33
  - Withdrawn of consent 23
  - Dead 64
  - Lost to follow up 14
  - Other 3

- 3 Major protocol violation

554 genotype assessed

- DOCETAXEL 110
- ERLOTINIB 109

Erlotinib 2.4 16.9%
Docetaxel 3.4 28.9%

Martelli, et al. AIOM 2012
EGFR-TKI: still some activity in *EGFR WT* pts

<table>
<thead>
<tr>
<th>N</th>
<th>EGFR</th>
<th>RR%</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>278</td>
<td>Mut. exon 19-21</td>
<td>74.1</td>
<td>8.5</td>
<td>19.6</td>
</tr>
<tr>
<td>272</td>
<td>Wild type</td>
<td>16.5</td>
<td>2</td>
<td>10.4</td>
</tr>
<tr>
<td>11</td>
<td>Mut. exon 20</td>
<td>0</td>
<td>1.4</td>
<td>4.8</td>
</tr>
<tr>
<td>15</td>
<td>G719</td>
<td>53.3</td>
<td>8.1</td>
<td>16.4</td>
</tr>
<tr>
<td>15</td>
<td>L861</td>
<td>60</td>
<td>6</td>
<td>15.2</td>
</tr>
<tr>
<td>15</td>
<td>Uncommon mutations</td>
<td>20</td>
<td>1.6</td>
<td>11.1</td>
</tr>
</tbody>
</table>


**EGFR WILD TYPE COMMENTS**

- Misleading concept: it likely consists of an array of important molecular subset of tumors
- Platinum based chemotherapy is superior to EGFR TKI in non mutated pts in first line, but current biomarkers cannot identify which patients should receive an EGFR TKI or chemotherapy after first line progression
- Potential biomarkers to investigate: new unknown mutations – phosphorylated EGFR
**KRAS WT status ‘drives’ the benefit from an EGFR-TKI in EGFR WT pts**

- **P = 0.04**
- **P = 0.08**

<table>
<thead>
<tr>
<th></th>
<th>PFS rate 6 months</th>
<th>PFS rate 12 months</th>
<th>PFS rate 24 months</th>
<th>OS rate 12 months</th>
<th>OS rate 24 months</th>
<th>OS rate 36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>50.7%</td>
<td>19.4%</td>
<td>2.9%</td>
<td>57%</td>
<td>38%</td>
<td>28%</td>
</tr>
<tr>
<td>KRAS WT</td>
<td>55.1%</td>
<td>24.4%</td>
<td>4.0%</td>
<td>94%</td>
<td>44%</td>
<td>31%</td>
</tr>
<tr>
<td>KRAS mut</td>
<td>38.8%</td>
<td>5.5%</td>
<td>0</td>
<td>35%</td>
<td>21%</td>
<td>21%</td>
</tr>
</tbody>
</table>


**Beyond erlotinib: irreversible pan-EGFR inhibition with dacomitinib**

Ramalingam, et al. JCO 2012
Second-line chemotherapy in *EGFR* mutant

Squamous cell cancer
- Chemotherapy
- Erlotinib

Non squamous cancer

- *EGFR & ALK/ROS1 negative*:
  - Chemotherapy
  - Erlotinib

- *EGFR mut +*:
  - Chemotherapy
  - *EGFR-TKI beyond PD*
  - *EGFR-TKI beyond PD + Chemotherapy*
  - *EGFR 'complete' blockade*
  - *EGFR irreversible inhibition*

- *ALK/ROS1 rearranged*:
  - Crizotinib
  - *ALK-inhibitor*

*Data indirectly extrapolated from trials dedicated to molecularly selected populations*

1st line *EGFR-TKI* may not influence sensitivity to chemotherapy

- Switch to platinum doublet recommended by NCCN guidelines 2013
- RR to chemotherapy following an *EGFR-TKI* similar to that observed with first-line chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carbo/Pac</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td>73.7% (n=114)</td>
<td>30.7% (n=114)</td>
</tr>
<tr>
<td>2nd line</td>
<td>28.8% (n=52)</td>
<td>58.5% (n=102)</td>
</tr>
</tbody>
</table>
Platinum-based chemotherapy may better EGFR-TKI beyond PD in EGFR-mutants

Wu, et al. IJC 2010

Chemotherapy +/- EGFR-TKI beyond PD for acquired resistance: IMPRESS

Activating EGFR mutation Progression on gefitinib No prior chemotherapy Sample size = 250

Primary endpoint: progression-free survival

Randomize

Cisplatin/Pemetrexed

Cisplatin/Pemetrexed + Ongoing gefitinib

NCT01544179
**Second-line chemotherapy in EGFR mutant**

**Squamous cell cancer**
- Chemotherapy
- Erlotinib

**Non squamous cancer**
- EGFR & ALK/ROS1 negative*
- Chemotherapy
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- Chemotherapy
- EGFR-TKI beyond PD
- EGFR-TKI beyond PD + Chemotherapy
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- EGFR irreversible inhibition

**ALK/ROS1 rearranged**
- Crizotinib
- ALK-inhibitor

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**PROFILE 1007 : Study Design**

**Key entry criteria**
- ALK+ by central FISH testing
- Stage IIIIB/IV NSCLC
- 1 prior chemotherapy (platinum-based)
- ECOG PS 0–2
- Measurable disease
- Treated brain metastases allowed

**Endpoints**
- Primary
  - PFS (RECIST 1.1, independent radiology review)
- Secondary
  - ORR, DCR, DR
  - OS
  - Safety
  - Patient reported outcomes (EORTC QLQ-C30, LC13)

**Randomize**

**N=318**

**Crizotinib 250 mg BID PO, 21-day cycle**
(n=159)

**Pemetrexed 500 mg/m²**, or
**Docetaxel 75 mg/m² IV, day 1, 21-day cycle**
(n=159)

**CROSSOVER TO CRIZOTINIB ON PROFILE 1005**

*Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

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*Shaw, et al. ESMO 2012*
<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Crizotinib (n=172(^a))</th>
<th>PEM (n=99(^b))</th>
<th>DOC (n=72(^b))</th>
</tr>
</thead>
<tbody>
<tr>
<td>median mo</td>
<td>7.7</td>
<td>4.2</td>
<td>2.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.59 (0.43 to 0.80)</td>
<td>0.30 (0.21 to 0.43)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Excludes 1 patient who did not receive study treatment; \(^b\)excludes 3 patients in chemotherapy arm who did not receive study treatment; \(^c\)vs crizotinib

**Second-line therapy: conclusions**

- In lung adenocarcinomas second-line treatment choices are mainly driven by patients’ molecular profile

- In the large majority of wild type patients single agent chemotherapy leaded by histology remains the standard therapy in good PS pts

- Chemotherapy choice is largely influenced by the regimen used in first-line and by response characteristics. Pemetrexed, Docetaxel and Gemcitabine represent current cytotoxic options