Clinical practice: approaching the reality of individual patients

António M. F. Araújo, MD, PhD
Head of the Service of Medical Oncology
Centro Hospitalar do Porto
Instituto de Ciências Biomédicas de Abel Salazar
Disclosure slide

I provided consultations or attended advisory boards for Astra-Zeneca, Eli Lilly Oncology, F. Hoffman-La Roche Ltd, Merck, Astellas and Pfizer, for which I received appropriate honoraria.
All different, yet all equal
Lung cancer – all different

Patient

Immunity

Microenvironment

Cancer
Lung cancer – all different
Cancer patient - all equal, yet all different

Age

Comorbidities and PS (driven by cancer or by comorbidities)

Patient preferences
Lung cancer – all different (stage)

Stage 1A
- Tumour up to 3cm in size
- Tumour up to 5cm in size

Stage 2A
- OR
  - Tumour is less than 5cm and there are cancer cells in lymph nodes nearby
  - Tumour is 5.7cm and in lymph nodes

Stage 2B
- OR
  - The cancer is growing into one of the following:
    - Chest wall
    - Nerve (phrenic)
    - The lining of the heart
    - Diaphragm
  - Tumour is 7cm or bigger
  - Tumour is in the main bronchus
  - There are 2 tumours in the same lobe

Stage 3A
- AND there are cancer cells in lymph nodes in mediastinum
- Tumour is up to 7cm

Stage 3B
- Tumour is any size and may be affecting nearby structures and is in the lymph nodes in either:
  - Neck nodes
  - Nodes near the collarbone
  - The mediastinum on opposite side
  - Hilar nodes
- AND it is in growing into one of these:
  - Voicebox nerve
  - Trachea
  - Oesophagus
  - Chest wall
  - Heart
  - In the other lobe
  - Diaphragm
  - Main blood vessel
  - Bone in spine

Stage 4
- OR
  - There is tumour in the fluid of the lining of lungs or heart
  - It has spread to another part of the body e.g., liver or bone, brain
NSCLC is a rapidly progressive disease

Stage I-IIIA
30%

Stage IIIB-IV
70%

Poor prognosis
1 year ≈ 33 %
2 years ≈ 11 %

Objectives of treatment
- Delay in disease progression
- Increase overall survival
- Delay deterioration of symptoms
- Maintaining or improving QoL

NSCLC is a rapidly progressive disease

Objectives of treatment
- Delay in disease progression
- Increase overall survival
- Delay deterioration of symptoms
- Maintaining or improving QoL

Survival Rate 1 year ≈ 33 %
Survival Rate 2 years ≈ 11 %

Poor prognosis

Stage I-IIIA
30%

Stage IIIB-IV
70%

Quantity of life
Quality of life

Lung cancer – all different

Patient

Immunity

Microenvironment

Cancer
Magnitude of genomic derangement

Drugable targets in smokers and never smokers

Molecular alterations in lung cancer – racial differences

Europe
All histology

US
Adenocarcinoma

East Asia
Adenocarcinoma, never smokers

(n=9,911)

(n=733)

(n=52)

Johnson, et al. ASCO 2013
Significantly mutated genes in squamous NSCLC

Nature 489:519-525, 2012
Evolution of NSCLC, from histology to molecular characteristics

Li T, et al. JCO, 2013
Individualized therapy of lung cancer

Factors are interrelated and are not independent

From therapy “one size fits all” to “tailored”

Algorithm for the treatment of advanced NSCLC in 2014

NSCLC advanced & PS 0-1

- **EGFR Mut+**: Erlotinib or gefitinib 1st line
- **ELM4-ALK Mut+**: Crizotinib 1st or 2nd line
- **EGFR and ALK negative and histology non-squamous**: Platin combined with pemetrexed (or other) Bevacizumab
- **EGFR and ALK negative and histology squamous**: Platin combined with gencitabine, paclitaxel or docetaxel

**Progression**

- Based on previous treatment

**Chemotherapy by algorithm**

Algorithm for the treatment of advanced NSCLC in 2014

NSCLC advanced & PS 0-1

EGFR Mut+

ELM4-ALK Mut+

EGFR and ALK negative and histology non-squamous

EGFR and ALK negative and histology squamous

Platin combined with pemetrexed (or other)
Bevacizumab

End of 1st line of CT

Pemetrexed or erlotinib or bevacizumab

Erlotinib

Based on previous treatment

Chemotherapy by algorithm

Erlotinib or gefitinib
1st line

Crizotinib
1st or 2nd line

# Use of TKI’s of EGFR

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref.</th>
<th>TKI</th>
<th>CTx</th>
<th>N #</th>
<th>PFS mos</th>
<th>HR</th>
<th>95% CI</th>
<th>OS mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS</td>
<td>Mok ¹</td>
<td>Gefitinib</td>
<td>Cb/Pac</td>
<td>261</td>
<td>9.5 vs 6.3</td>
<td>0.48</td>
<td>0.36-0.64</td>
<td>21.6 vs 21.9</td>
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<tr>
<td>First-SIGNAL</td>
<td>Han ²</td>
<td>Gefitinib</td>
<td>Cis/Gem</td>
<td>42</td>
<td>8.0 vs 6.3</td>
<td>0.54</td>
<td>0.26-1.10</td>
<td>27.2 vs 25.6</td>
</tr>
<tr>
<td>NEJ002</td>
<td>Maemondo ³</td>
<td>Gefitinib</td>
<td>Carb/Pac</td>
<td>230</td>
<td>10.8 vs 5.4</td>
<td>0.35</td>
<td>0.22-0.41</td>
<td>30.5 vs 23.6</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>Mitsudomi ⁴,⁵</td>
<td>Gefitinib</td>
<td>Cis/Doc</td>
<td>172</td>
<td>9.2 vs 6.3</td>
<td>0.49</td>
<td>0.33-0.71</td>
<td>36 vs 39</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Zhou ⁶, Zhang ⁷</td>
<td>Erlotinib</td>
<td>Carb/Gem</td>
<td>165</td>
<td>13.1 vs 4.6</td>
<td>0.16</td>
<td>0.10-0.26</td>
<td>22.7 vs 28.9</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Rosell ⁸</td>
<td>Erlotinib</td>
<td>P/Doc or Gem</td>
<td>174</td>
<td>9.7 vs 5.2</td>
<td>0.34</td>
<td>0.23-0.49</td>
<td>19.3 vs 19.5</td>
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<tr>
<td>LUX-Lung 3</td>
<td>Sequist ⁹</td>
<td>Afatinib</td>
<td>Cis/Pem</td>
<td>345</td>
<td>11.1 vs 6.9</td>
<td>0.47</td>
<td>0.34-0.65</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Gefitinib in 1st line of NSCLC

IPASS - PFS

Gefitinib in 1st line of NSCLC

IPASS - PFS

Gefitinib in 1st line of NSCLC

IPASS - PFS

Patients
- Chemonaive
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers
- Life expectancy ≥12 wks
- PS 0-2
- Measurable stage IIIb / IV disease

Endpoints
Primary
- Progression-free survival (non-inferiority)
Secondary
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

Exploratory
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

Gefitinib (250 mg / day)
1:1 randomisation
Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m²) 3 weekly

Overall
Hazard ratio, 0.74 (95% CI, 0.65 - 0.85)
P<0.001
Events: gefitinib, 453 (74.4%); carboplatin plus paclitaxel, 497 (81.7%)

EGFR-Mutation-Positive
Hazard ratio, 0.48 (95% CI, 0.36 - 0.64)
P<0.001
Events: gefitinib, 97 (73.5%); carboplatin plus paclitaxel, 111 (86.0%)

EGFR-Mutation-Negative
Hazard ratio, 2.85 (95% CI, 2.05 - 3.98)
P<0.001
Events: gefitinib, 88 (96.7%); carboplatin plus paclitaxel, 70 (82.4%)

Erlotinib in 1st line of NSCLC

EURTAC - PFS

**Patients**
- Chemonaïve
- Exon19 deletion or L858R Exon 21
- PS 0-2
- Measurable stage IIIb / IV disease

**Endpoints**
- Primary
  - Progression-free survival (non-inferiority)
- Secondary
  - Objective response rate
  - Overall survival

**1:1 randomisation**

**Cisplatin- or Carboplatin-based therapy**

## Gefitinib & Erlotinib in 1st line of NSCLC

### Adverse Events

#### IPASS

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Gefitinib (N = 607)</th>
<th>Carboplatin-Paclitaxel (N = 589)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adverse Events</td>
<td>CTC Grade 3, 4, or 5</td>
<td>CTC Grade 3, 4, or 5</td>
</tr>
<tr>
<td>Rash or acne†</td>
<td>402 (66.2)</td>
<td>132 (22.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>283 (46.6)</td>
<td>128 (21.7)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>145 (23.9)</td>
<td>17 (2.9)</td>
</tr>
<tr>
<td>Anorexia†</td>
<td>133 (21.9)</td>
<td>251 (42.6)</td>
</tr>
<tr>
<td>Pruritus†</td>
<td>118 (19.4)</td>
<td>74 (12.6)</td>
</tr>
<tr>
<td>Stomatitis†</td>
<td>103 (17.0)</td>
<td>51 (8.7)</td>
</tr>
<tr>
<td>Asthenic conditions†</td>
<td>102 (15.8)</td>
<td>259 (44.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>101 (16.6)</td>
<td>261 (44.3)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>82 (13.5)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>78 (12.9)</td>
<td>196 (33.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>73 (12.0)</td>
<td>173 (29.4)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>67 (11.0)</td>
<td>344 (58.4)</td>
</tr>
<tr>
<td>Neurotoxic effects†</td>
<td>66 (10.9)</td>
<td>412 (69.9)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>47 (7.7)</td>
<td>186 (31.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>39 (6.4)</td>
<td>113 (19.2)</td>
</tr>
</tbody>
</table>

#### EURTAC

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Erlotinib (n=84)</th>
<th>Standard chemotherapy (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>43 (51%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Rash</td>
<td>56 (67%)</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>44 (52%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>26 (31%)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>9 (11%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>12 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>7 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (10%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

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Use of TKI’s of EGFR

clinical practice guidelines

Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

First-line treatment with a TKI (erlotinib or gefitinib) should be prescribed to patients with tumors bearing an activating (sensitizing) EGFR mutation because of significantly higher RR, longer PFS, and better QoL when compared with first-line chemotherapy [32, 33] [I, A].

Level of evidence: I Strenght of recommendation: A
Algorithm for the treatment of advanced NSCLC in 2014

Crizotinib and NSCLC – phase 1 study

PROFILE 1005

Crizotinib in 2\textsuperscript{nd} line of NSCLC

PROFILE 1007

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

Randomize

N=318

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

Pemetrexed 500 mg/m\textsuperscript{2} or Docetaxel 75 mg/m\textsuperscript{2} IV, day 1, 21-day cycle (n=159)

CROSSOVER TO CRIZOTINIB ON PROFILE 1005

Adverse Event

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=172)</th>
<th>Chemotherapy (N=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Vision disorder\textsuperscript{†‡}</td>
<td>103 (60)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>103 (60)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea\textsuperscript{§}</td>
<td>94 (55)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Vomiting\textsuperscript{§}</td>
<td>80 (47)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>73 (42)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Elevated aminotransferase levels\textsuperscript{†}</td>
<td>66 (38)</td>
<td>27 (15)\textsuperscript{¶}</td>
</tr>
<tr>
<td>Edema\textsuperscript{†}</td>
<td>54 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46 (27)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Upper respiratory infection\textsuperscript{†}</td>
<td>44 (26)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>44 (26)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness\textsuperscript{†}</td>
<td>37 (22)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dyspnea\textsuperscript{†¶}</td>
<td>23 (13)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>14 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Algorithm for the treatment of advanced NSCLC in 2014

**NSCLC advanced & PS 0-1**

- **EGFR Mut+**
  - Erlotinib or gefitinib
    - 1st line

- **ELM4-ALK Mut+**
  - Crizotinib
    - 1st or 2nd line

- **EFGR and ALK negative and histology non-squamous**
  - Platin combined with pemetrexed (or other)
    - Bevacizumab
  - Chemotherapy by algorithm
  - Based on previous treatment

- **EFGR and ALK negative and histology squamous**
  - Platin combined with gencitabine, paclitaxel or docetaxel

**Progression Based on previous treatment**

End of 1st line of CT

Efficacy of Pemetrexed – Histology

1st Line of CT

Advanced-stage, previously untreated NSCLC patients (N = 1725)

Cisplatin 75 mg/m² on Day 1 +
Gemcitabine 1250 mg/m² on Days 1 and 8
Six 3-wk cycles

2nd Line of CT

Cisplatin 75 mg/m² on Day 1 +
Pemetrexed 500 mg/m² on Day 1
Six 3-wk cycles

Patients Randomized to Pemetrexed

Median; 95% CI

CP  11.8; 10.4, 13.2
CG  10.4; 9.6, 11.2

CP vs CG  Adjusted HR; 95% CI
0.81; 0.70, 0.94

Survival Probability

Survival Time (months) in Patients With Nonsquamous Histology

Percent Surviving

Overall Survival (months)

Non-squamous:
Median = 9.3

Squamous:
Median = 6.2

Peterson et al WCLC 2007 Abst P2 328

## Toxicity profile of Pemetrexed

### Grade 3 and 4 hematologic toxicities

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Cis/Pem N=839</th>
<th>Cis/Gem N=830</th>
<th>P</th>
<th>Pem N=265</th>
<th>Doc N=276</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>5.6%</td>
<td>9.9%</td>
<td>0.001</td>
<td>4.2%</td>
<td>4.3%</td>
<td>0.99</td>
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<tr>
<td>Neutropenia</td>
<td>15.1%</td>
<td>26.7%</td>
<td>&lt; 0.001</td>
<td>5.3%</td>
<td>40.2%</td>
<td>&lt; 0.001</td>
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<tr>
<td>Thrombocytopenia</td>
<td>4.1%</td>
<td>12.7%</td>
<td>&lt; 0.001</td>
<td>1.9%</td>
<td>0.4%</td>
<td>0.116</td>
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<tr>
<td>Febrile Neutropenia</td>
<td>1.3%</td>
<td>3.7%</td>
<td>0.002</td>
<td>1.9%</td>
<td>12.7%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Algorithm for the treatment of advanced NSCLC in 2014

NSCLC advanced & PS 0-1

- **EGFR Mut+**
  - Erlotinib or gefitinib
    - 1st line

- **ELM4-ALK Mut+**
  - Crizotinib
    - 1st or 2nd line

- **EFGR and ALK negative and histology non-squamous**
  - Platin combined with pemetrexed (or other)
  - Bevacizumab

- **EFGR and ALK negative and histology squamous**
  - Platin combined with gencitabine, paclitaxel or docetaxel

Progression Based on previous treatment

1st Line

- **1st Line**
  - End of 1st line of CT
  - Pemetrexed or erlotinib or bevacizumab
  - Erlotinib

2nd Line

- **Maintenance**
  - Chemotherapy by algorithm

Squamous NSCLC
ECOG 1594

Algorithm for the treatment of advanced NSCLC in 2014

NSCLC advanced & PS 0-1

- **EGFR Mut+**
  - Erlotinib or gefitinib 1st line

- **ELM4-ALK Mut+**
  - Crizotinib 1st or 2nd line

- **EGFR and ALK negative and histology non-squamous**
  - Platin combined with pemetrexed (or other)
  - Bevacizumab

- **EGFR and ALK negative and histology squamous**
  - Platin combined with gencitabine, paclitaxel or docetaxel

End of 1st line of CT

- Pemetrexed or erlotinib or bevacizumab
- Erlotinib

Based on previous treatment

Chemotherapy by algorithm

Progression

# Switch maintenance for NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Induction</th>
<th>Intervention</th>
<th>Primary endpoint</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Months</td>
<td>Months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>P</td>
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<tr>
<td>Fidias et al ¹</td>
<td>309</td>
<td>CarbG x 4 cycles</td>
<td>Immediate vs delayed docetaxel</td>
<td>OS</td>
<td>5.7 / 2.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ciuleanu et al ²</td>
<td>663</td>
<td>Platinum-based doublet x 4 cycles</td>
<td>Pemetrexed vs placebo</td>
<td>PFS</td>
<td>4.0 / 2.0</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Capuzzo et al ³</td>
<td>889</td>
<td>Platinum-based doublet x 4 cycles</td>
<td>Erlotinib vs placebo</td>
<td>PFS</td>
<td>2.83 / 2.55</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pérol et al ⁴</td>
<td>464</td>
<td>CisG x 4 cycles</td>
<td>Erlotinib vs gencitabine vs observation</td>
<td>PFS</td>
<td>2.9 / 3.8</td>
<td>&lt; 0.001</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>1.9</td>
<td>0.003</td>
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<tr>
<td>Miller et al ⁵</td>
<td>768</td>
<td>Platinum-based doublet + bevacizumab x 4 cycles</td>
<td>Erlotinib + Bevacizumab vs Placebo + Bevacizumab</td>
<td>PFS</td>
<td>4.76 / 3.75</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

Switch maintenance for NSCLC
Non-squamous population

CR, PR or SD after 4 cycles
of one of the following induction therapies:
- Gemcitabine + Platin
- Paclitaxel + Platin
- Docetaxel + Platin

RANDOMIZE

Pemetrexed 500 mg/m² EV, d1 + BSC
Until disease progression
n=441

Both arms received folic acid, vit. B12 and
dexametasone

Placebo EV, d1 + BSC
Until disease progression
n=222

2:1

Pemetrexed + BSC – 4.4 Months
Placebo + BSC – 1.8 Months
HR 0.44 (95% CI 0.36-0.55); p<0.0001

Pemetrexed + BSC – 15.5 Months
Placebo + BSC – 10.3 Months
HR 0.70 (95% CI 0.56-0.88); p=0.002

Switch maintenance for NSCLC

SATURN: PFS according EGFR mutation status

Chemonaive advanced NSCLC
n = 1,949

Mandatory tumor sampling

4 cycles of first-line platinum-based doublet

Non-PD
n = 889

1:1

Erlotinib 150mg/d
PD

Placebo
PD

EGFR Mutation +

HR = 0.10 (0.04–0.25)
Log-rank P < 0.0001

Erlotinib (n = 22)
Placebo (n = 27)

EGFR Wild-type

HR = 0.78 (0.63–0.96)
Log-rank P = 0.0185

Erlotinib (n = 199)
Placebo (n = 189)

Cappuzzo F et al, Lancet Oncol 11:521-529, 2010
## Continuation maintenance for NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Induction</th>
<th>Nº Cycles</th>
<th>Randomize</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Objective ↑ OS</th>
<th>Objective ↑ PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al 2001¹</td>
<td>Mitomicin + Vinblastine + Cisplatin</td>
<td>3</td>
<td>Induction</td>
<td>3 more cycles mais (n=153)</td>
<td>Observation (n=155)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Socinski et al 2002²</td>
<td>Carboplatin + Paclitaxel</td>
<td>4</td>
<td>Induction</td>
<td>Continuous treatment (n=116)</td>
<td>Observation (n=114)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Belani et al 2003³</td>
<td>Carboplatin + Paclitaxel</td>
<td>2-4</td>
<td>Induction</td>
<td>Paclitaxel (n=65)</td>
<td>Observation (n=65)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Westeel et al 2005⁴</td>
<td>Mitomicin + Ifosfamide + Cisplatin</td>
<td>2-4</td>
<td>Pos-Induction</td>
<td>Vinorelbina (n=91)</td>
<td>Observation (n=90)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Brodowicz et al 2006⁵</td>
<td>Gemcitabine + Cisplatin</td>
<td>4</td>
<td>Pos-Induction</td>
<td>Gemcitabine (n=138)</td>
<td>BSC (n=68)</td>
<td>No</td>
<td>TTP: Yes</td>
</tr>
<tr>
<td>Park et al 2007⁶</td>
<td>Paclitaxel, docetaxel or gemcitabine + Cisplatin</td>
<td>2</td>
<td>Pos-Induction</td>
<td>4 more cycles (n=158)</td>
<td>2 more cycles (n=156)</td>
<td>No</td>
<td>TTP: Yes</td>
</tr>
</tbody>
</table>

## Continuation maintenance for NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Induction</th>
<th>Intervention</th>
<th>Primary endpoint</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Months</td>
<td>Months</td>
</tr>
<tr>
<td>Sandler et al ¹</td>
<td>878</td>
<td>Carboplatin + Paclitaxel</td>
<td>Bevacizumab vs observation</td>
<td>OS</td>
<td>6.2 / 4.5</td>
<td>12.3 / 10.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+/- Bevacizumab x 6 cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirker et al ²</td>
<td>1125</td>
<td>Cisplatinum + Vinorelbin</td>
<td>Cetuximab vs observation</td>
<td>OS</td>
<td>4.8 / 4.0</td>
<td>11.3 / 10.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+/- Cetuximab X 6 cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paz-Ares et al ³</td>
<td>539</td>
<td>Cisplatinum + Pemetrexed</td>
<td>Pemetrexed vs placebo</td>
<td>PFS</td>
<td>6.9 / 5.6</td>
<td>16.9 / 14.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>x 4 cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Continuation maintenance for NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Induction</th>
<th>Intervention</th>
<th>Primary endpoint</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Months</td>
<td>Months</td>
</tr>
<tr>
<td>Sandler et al</td>
<td>878</td>
<td>Carboplatin + Paclitaxel +/- Bevacizumab x 6 cycles</td>
<td>Bevacizumab vs observation</td>
<td>OS</td>
<td>6.2 / 4.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pirker et al</td>
<td>1125</td>
<td>Cisplatinum + Vinorelbain +/- Cetuximab X 6 cycles</td>
<td>Cetuximab vs observation</td>
<td>OS</td>
<td>4.8 / 4.0</td>
<td>0.39</td>
</tr>
<tr>
<td>Paz-Ares et al</td>
<td>539</td>
<td>Cisplatinum + Pemetrexed x 4 cycles</td>
<td>Pemetrexed vs placebo</td>
<td>PFS</td>
<td>6.9 / 5.6</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Continuation maintenance for NSCLC

**Paramount trial**

**NSCLC**
- Non-squamous
- PS 0-1
- N = 1022

**Cisplatin + Pemetrexed**
- X 4 cycles
- N = 539

**PR / SD**

**BSC + Pemetrexed**
- 3/3 weeks until PD

**BSC + Placebo**
- 3/3 weeks until PD

---

### Continuation maintenance for NSCLC

#### Paramount trial

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1–2, n (%)</th>
<th>Grade 3–4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pemetrexed (N = 359)</td>
<td>Placebo (N = 180)</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>34 (10)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17 (5)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><strong>Nonlaboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td>44 (12)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>17 (5)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (11)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (6)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Edema</td>
<td>17 (5)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Neuropathy: sensory</td>
<td>9 (3)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Watery eye (epiphora, tearing)</td>
<td>9 (3)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Pain</td>
<td>11 (3)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

Lung cancer – all different

Patient

Immunity

Microenvironment

Cancer
Algorithm for the treatment of advanced NSCLC in 2014

NSCLC advanced & PS 0-1

- **EGFR Mut+**
  - Erlotinib or gefitinib (1st line)
- **ELM4-ALK Mut+**
  - Crizotinib (1st or 2nd line)
- **EGFR and ALK negative and histology non-squamous**
  - Platin combined with pemetrexed (or other)
  - Bevacizumab
  - End of 1st line of CT
  - Pemetrexed or erlotinib or bevacizumab
- **EGFR and ALK negative and histology squamous**
  - Platin combined with gencitabine, paclitaxel or docetaxel
  - Erlotinib

Based on previous treatment

Chemotherapy by algorithm

Bevacizumab plus CT for NSCLC

ECOG 4599

RR: 15% for Paclitaxel/Carboplatin vs 35% for Paclitaxel/Carboplatin + Bevacizumab

Bevacizumab plus CT for NSCLC

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CG + Placebo</th>
<th>CG + Bevacizumab (7.5 mg/kg)</th>
<th>CG + Bevacizumab (15 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, HR (95% CI; P value)</td>
<td>NA</td>
<td>0.75 (0.62-0.91; .0026)</td>
<td>0.82 (0.68-0.98; .0301)</td>
</tr>
<tr>
<td>RR, % (P value)</td>
<td>20</td>
<td>34 (&lt; .0001)</td>
<td>30 (&lt; .017)</td>
</tr>
<tr>
<td>Median survival, mos</td>
<td>13.1 ( -)</td>
<td>13.6 0.92 (.3664)</td>
<td>13.4 1.02 (.8420)</td>
</tr>
<tr>
<td>HR (P value)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bevacizumab plus CT for NSCLC

PointBreak

- Patients with advanced nonsquamous NSCLC
- No prior systemic treatment for lung cancer
- ECOG PS = 0/1
- N = 939

Primary End Point:
- OS (superiority study)

Lung cancer – all different

Patient

Cancer

Immunity

Microenvironment
Willam Coley (1862 – 1936)
Tumours use various mechanisms to escape the immune system

Immune escape mechanisms are complex and frequently overlapping

T-cell based immunomodulation

Differences in CTLA-4 and PD-1 blockade

CTLA-4 blockade (ipilimumab)

PD-1 blockade (nivolumab)

Tumour microenvironment

Activation (cytokines, lysis, proliferation, migration to tumour)

## Somme immune checkpoint inhibitors in NSCLC

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Target</th>
<th>Development Stage in NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Bristol-Myers Squibb</td>
<td>CTLA4</td>
<td>Phase III</td>
</tr>
<tr>
<td>Tremelimunab</td>
<td>MedImmune</td>
<td>CTLA4</td>
<td>Phase I</td>
</tr>
<tr>
<td>Nivolumab (BMS-936558)</td>
<td>Bristol-Myers Squibb</td>
<td>PD-1</td>
<td>Phase III</td>
</tr>
<tr>
<td>Lambrolizumab (MK-3475)</td>
<td>Merck</td>
<td>PD-1</td>
<td>Phase III</td>
</tr>
<tr>
<td>BMS-936559</td>
<td>Bristol-Myers Squibb</td>
<td>PD-L1</td>
<td>Phase I</td>
</tr>
<tr>
<td>Medi-4736</td>
<td>MedImmune</td>
<td>PD-L1</td>
<td>Phase I</td>
</tr>
<tr>
<td>MPDL-3280A</td>
<td>Genentech</td>
<td>PD-L1</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

Randomized phase II study of Ipilimumab and CT in advanced NSCLC

- Primary endpoint: irPFS
- Cx regimen: Pac 175 mg/m²/carbo AUC 6 prior to start of ipilimumab (10 mg/kg)

Randomized phase II study of Ipilimumab and CT in advanced NSCLC

Randomized phase II study of Ipilimumab and CT in advanced NSCLC

<table>
<thead>
<tr>
<th>Event</th>
<th>Control (n = 65)</th>
<th>Concurrent Ipilimumab (n = 71)</th>
<th>Phased Ipilimumab (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1 and 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Any adverse event, %</td>
<td>31</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>Any treatment-related adverse event, %</td>
<td>43</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>Treatment-related non-hematologic adverse events, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>22</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>46</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rash</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td>23</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy*</td>
<td>11</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic abnormalities, %†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>35</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>32</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>89</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Liver-function enzymes, %†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>35</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>32</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Nivolumab phase I trial in squamous/nonsquamous NSCLC

Open circles indicate censored events, denoting the time to the last known alive date before the date of data analysis, for patients without a death.

Duration of response and overall survival with nivolumab monotherapy in NSCLC

NSCLC responders\textsuperscript{a,b} by histology

All treated subjects with NSCLC

<table>
<thead>
<tr>
<th>Died/treated</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>94/129</td>
<td>9.90 (7.80,12.40)</td>
</tr>
</tbody>
</table>

Median OS: 9.9 months (7.8, 12.4)

1 year OS rate 42% (48 patients at risk)

2 year OS rate 24% (20 patients at risk)

Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

\textsuperscript{a}Responses were assessed by modified RECIST v1.0

\textsuperscript{b}All efficacy analyses based on data collected as of September 2013

### Nivolumab: activity across NSCLC histology

<table>
<thead>
<tr>
<th>NSCLC histology</th>
<th>Dose (mg/kg)</th>
<th>ORR % (n/N)</th>
<th>Stable disease rate ≥24 week, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>All doses</td>
<td>16.7 (9/54)</td>
<td>14.8 (8/54)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0 (0/18)</td>
<td>26.7 (4/15)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>22.2 (4/18)</td>
<td>5.6 (1/18)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>23.8 (5/21)</td>
<td>14.3 (3/21)</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>All doses</td>
<td>17.6 (13/74)</td>
<td>6.8 (5/74)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5.6 (1/18)</td>
<td>5.6 (1/18)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>26.3 (5/19)</td>
<td>10.5 (2/19)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>18.9 (7/37)</td>
<td>5.4 (2/37)</td>
</tr>
</tbody>
</table>

Selected adverse events (≥1%) in patients with NSCLC treated with nivolumab

- Select adverse event defined as an event with potential immunological aetiologies that require more frequent monitoring and/or unique intervention
- All patients have ≥1 year of follow-up
- Drug-related pneumonitis (any grade) occurred in 8 NSCLC patients (6%); 3 patients (2%) had grade 3-4 pneumonitis of which 2 cases were fatal

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Patients, n (%)</th>
<th>N=129</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related select adverse event</td>
<td>41 (53)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Skin</td>
<td>16 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>7 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>6 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

Nivolumab plus CT: change in tumour burden

Baseline tumour measurements are standardised to zero; tumour burden is measured as the sum of the longest diameters of target lesions. Horizontal lines denote 30% decrease for PR and 20% increase for PD per RECIST 1.1. Only patients with both baseline and on-study target lesion measurements are included.

Rizvi NA, et al. ASCO 2013. Abstract 8072
Nivolumab: change in tumour burden according to \textit{EGFR} and \textit{KRAS} mutation status

Dashed horizontal lines denote 30% decrease for PR (in the absence of new lesions) and 20% increase for PD per RECIST v1.0

Tumor heterogeneity

Tumors with identical histological type and biochemical parameters

Non small cell lung Cancer

The promise of pharmacogenomic testing

All patients with the same diagnosis

- No Benefit + Toxicity
- + Benefit + Toxicity
- + Benefit No Toxicity
- No Benefit No Toxicity

The personalized cancer care continuum

Conclusions

✓ Advanced NSCLC: A prevalent and deadly cancer

✓ First-line therapy: Several CT and targeted agents approved in recent years; choices driven specially by histology and/or mutational status (ie, EGFR and ALK and …)

✓ Second-line therapy: Choices depend on ECOG PS, prior treatment, current organ function, tumor histology, and molecular variables

✓ Special considerations: Important to consider patient age, initiating early palliative care, management of treatment-related adverse effects (eg, CINV, rash/cutaneous, cardiac)

✓ Future directions/ongoing needs: Many patients do not respond to or relapse on existing therapies; many promising agents under investigation