Implications for clinical practice

Martin Reck
Department of Thoracic Oncology
LungClinic Grosshansdorf
Germany
Disclosures

• Member of the advisory board: Roche, Lilly, Daichi-Sankyo, BMS, AstraZeneca

• Honoraria for lectures: Roche, Lilly, Daichi-Sankyo, AstraZeneca
Chemotherapy has changed...

Meta-Analysis of 52 randomised trials

- 9387 patients
- 778 patients in randomised trials with platinum based chemotherapy
- **10% Increase in 1 year survival**
- Increase in median survival by 1.5 months (6 vs. 8 months)
- **Significant reduction of tumor associated symptoms**

![Graph showing percent survival over time for Supportive care and Supportive care plus Chemotherapy]
Proposed Treatment Algorithm – Advanced Stage NSCLC

- **EGFR-mutation-Analysis**
  - Non Squamous NSCLC
  - **EGFR-Mut+**
  - Tarceva
  - Platinum-Doublt + Bevacizumab
  - Bevacizumab eligible
  - Klinisch
    - Bevacizumab
    - Platinum-Doublt
  - Progression

- **EGFR-wildtyp/unknown**
  - Good PS
    - Non-squamous
      - Bevacizumab eligible
      - Bevacizumab ineligible
      - Clinical (PS)
    - Squamous
      - Platinum-Doublt
      - Bevacizumab eligible
      - Bevacizumab ineligible

- **Progression**
  - Tarceva
  - Erlotinib or Pemetrexed
  - Based on prior therapy

**Chemotherapy by Algorithm**
- Tarceva or Pemetrexed or Docetaxel, based on prior therapy


- PS = Performance status; 1L-E = 1st-Line-maintenance-therapy
which indeed induces a couple of implications....
Implications

- Correct pathological diagnosis
1. Step: Conventional Criteria

Squamous Cell Carcinoma
SCLC

Adenocarcinoma
NSCLC

2. Step: Immunohistochemistry

Limited number of marker Subtyping

3. Step: EGFR Mutation test

In appropriate settings

Reduction of NOS < 10%!
Implications

- Correct pathological diagnosis
- Assessment of EGFR mutation status
Clinical efficacy of EGFR-TKIs as first-line therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pop.</th>
<th>Drug</th>
<th>EGFR Mut + (N)</th>
<th>ORR % TKI vs CT</th>
<th>PFS (HR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS¹</td>
<td>Asia</td>
<td>Gefitinib</td>
<td>261</td>
<td>71.2 vs 47.3</td>
<td>0.48 (0.36, 0.64)</td>
</tr>
<tr>
<td>First-SIGNAL²</td>
<td>Asia</td>
<td>Gefinitb</td>
<td>42</td>
<td>84.6 vs 37.5</td>
<td>0.61 (0.31, 1.22)</td>
</tr>
<tr>
<td>WJTOG 3405³</td>
<td>Asia</td>
<td>Gefitinib</td>
<td>172*</td>
<td>62.1 vs 32.2</td>
<td>0.49 (0.34, 0.71)</td>
</tr>
<tr>
<td>NEJGSG002⁴</td>
<td>Asia</td>
<td>Gefitinib</td>
<td>224**</td>
<td>73.7 vs 30.7</td>
<td>0.30 (0.22, 0.41)</td>
</tr>
<tr>
<td>OPTIMAL⁵</td>
<td>Asia</td>
<td>Erlotinib</td>
<td>154***</td>
<td>83 vs 36</td>
<td>0.16 (0.10, 0.26)</td>
</tr>
<tr>
<td>EURTAC⁶,⁷</td>
<td>Europe/Asia</td>
<td>Erlotinib</td>
<td>174#</td>
<td>58.1 vs 14.9</td>
<td>0.37 (0.25, 0.54)</td>
</tr>
<tr>
<td>Lux Lung 38</td>
<td>European/Asian</td>
<td>Afatinib</td>
<td>345</td>
<td>56 vs 23</td>
<td>0.58 (0.34, 0.65)</td>
</tr>
</tbody>
</table>

Clinical Consequence? (The question of four A)

• Availability (where can the test be done?)
• Affordability (who has to pay how much?)
• Acurateness (which test is used?)
• Acceleration (how many days to get the result?)

• Interaction with pathologist / molecular pathologist will be crucial!
Implications

- Correct pathological diagnosis
- Assessment of EGFR mutation status
- New algorithms for tumor sampling?
EGFR resistance mediating mechanisms

Sequist et al, Sci Transl Med 2011
EGFR resistance mediating mechanisms

Sequist et al, Sci Transl Med 2011

Combination chemotherapy + EGFR-TKI
Chemotherapy
IGF-Inhibitors
PIK3 TKI
HGF AB
cMet TKI
Met Mab

Change of EGFR-TKI
Second Generation EGFR-TKIs
Combination EGFR-TKI + EGFR AB
Treatment of EGFR Resistance

Tumor Sample

EGFR-Mutation Exon 19/21

Progression

Second Tumor sample?

Second Generation TKI

Chemotherapy

C Met Inhibitor
Clinical consequence

• **Implementation** of sequential biopsies in diagnostic algorithm of molecular characterized patients

• **Balanced use** of tumor material for morphological (transition to SCLC?) and molecular diagnosis (appearance of new driving mutation?)
Implications

- Correct pathological diagnosis
- Assessment of EGFR mutation status
- New algorithms for tumor sampling?
- New algorithms for molecular diagnosis?
Oncogenic mutations

Squamous Cell NSCLC

- Unknown 37%
- FGFR1 amplification 25%
- PTEN mutation 17%
- PIK3CA mutation 8%
- PTEN loss, complete 11%
- DDR2 mutation 0%
- KRAS mutation 2%

Adenocarcinoma

- EGFR 17%
- KRAS 22%
- EML4-ALK 7%
- AKT1, NRAS, MEK1, MET AMP, HER2, PIK3CA, BRAF 2%
- DOUBLE MUTANTS 3%

Mutation found in 54% (280/516) of tumors completely tested (CI 50-59%)

Paik et al., ASCO 2012; abstr 7505; Kris MG et al., ASCO 2011, abstr 7506
Clinical Consequences

- A lot of oncogenic mutations appear at a frequency of \( \leq 5\% \).
- Comprehensive testing is not feasible for all non academical sides – establishment of cooperation network structures **and** databases will be necessary.
- Should we enrich populations for testing? – we got another lesson from the EGFR story
- Besides sophisticated molecular screening – still intelligent clinical validation will be gold standard.
Implications

• Correct pathological diagnosis
• Assessment of EGFR mutation status
• New algorithms for tumor sampling?
• New algorithms for molecular diagnosis?
• New algorithms for treatment schedules?
# The Switch Maintenance Registration Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS HR (p)</th>
<th>OS HR (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JMEN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pem</td>
<td>0.5 (&lt;0.0001)</td>
<td>0.79 (0.012)</td>
</tr>
<tr>
<td>Placebo</td>
<td>(&lt;0.0001)</td>
<td>(0.012)</td>
</tr>
<tr>
<td>SATURN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>0.71 (&lt;0.0001)</td>
<td>0.81 (0.009)</td>
</tr>
<tr>
<td>Placebo</td>
<td>(&lt;0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

Switch maintenance: TKI and pemetrexed show improved PFS and OS

## Continuation Maintenance Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS HR</th>
<th>OS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>Paramount</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pem</td>
<td>0.64</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>0.0002</td>
<td>0.019</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avaperl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemetrexed + Bevacizumab</td>
<td>0.48</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continuation maintenance: Pemetrexed and Pemetrexed/Bevacizumab show improved PFS and OS

Clinical consequences and challenges

- Length of the induction therapy – how long can we give cisplatin?
- New treatment paradigm: no fixed number of treatment cycles
- New treatment to explain: Treatment as long as benefit is seen
- Different emphasis on adverse reactions: not every adverse reaction is included in the CTC – even CTC grade 2 fatigue can considerably influence quality of life.
- Principles of tumour measurement: How often? What should be done when progression is slow?
Implications

• Correct pathological diagnosis
• Assessment of EGFR mutation status
• New algorithms for tumor sampling?
• New algorithms for molecular diagnosis?
• New algorithms for treatment schedules?
• New algorithms for management of side effects?
## New agents – now toxicities

<table>
<thead>
<tr>
<th>Agent</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR-TKI</td>
<td>Rash, Diarrhea, Paronychia</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Hand-Foot Syndrome, Rash, Fatigue</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Myalgia, Pain, Mucositis</td>
</tr>
<tr>
<td>Anti-VEGF Agents</td>
<td>Bleeding, Hypertension, Proteinuria, thrombembolic events</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Liver toxicity, Eye toxicity</td>
</tr>
<tr>
<td>Ganetespib</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Colitis, Skin toxicity, liver toxicity</td>
</tr>
</tbody>
</table>
Clinical consequences

• Adequate information
• Adequate Management and Dose modification guidelines
• Adequate Grading system
Implications

• Correct pathological diagnosis
• Assessment of EGFR mutation status
• New algorithms for tumor sampling?
• New algorithms for molecular diagnosis?
• New algorithms for treatment schedules?
• New algorithms for management of side effects?
• The forgotten patients?
New data in PS2?

Overall survival

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>1.0</td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pemetrexed/carboplatin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

OS at 6 months, %
Pemetrexed: 50%
Pemetrexed/carboplatin: 65%

OS at 12 months, %
Pemetrexed: 18%
Pemetrexed/carboplatin: 43%

HR=0.57 (0.41–0.79); p=0.001

Lilenbaum et al. J Clin Oncol 30: 2012 (suppl; abstr 7506)

PS 2 = PS 2?
Clinical Consequences

• Clear definition of PS2 / Frail patients
• Further studies in this population are needed to get a true picture of lung cancer!
Studies in first-line NSCLC treatment
