Handout Slides Metastasiertes Nicht-Kleinzeliges Bronchialkarzinom

25. DESO Kurs 19.-21.2.2015

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Kantonsspital St. Gallen
Klinische Relevanz der Histologie

- Plattenepithelkarzinom
  - Kein Bevacizumab
  - Kein Pemetrexed
  - Keine molekularen Untersuchungen

→ Wichtig:
  Plattenepithel- vs. Nicht-Plattenepithelkarzinom
8008^: A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC) – Thatcher N et al

• Key results

**OS**

**Time since randomisation (months)**

**Overall survival (%)**

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI), months:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine/cisplatin+necitumumab</td>
<td>11.5 (10.4, 12.6)</td>
</tr>
<tr>
<td>Gemcitabine/cisplatin</td>
<td>9.9 (8.9, 11.1)</td>
</tr>
</tbody>
</table>

**HR (95% CI) 0.84 (0.74, 0.96); p=0.012***

*Log-rank test (stratified)

Follow-up time (median): Gemcitabine/cisplatin+necitumumab: 25.2 months; gemcitabine/cisplatin: 24.8 months

Thatcher et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8008^)
LBA8006\(^\ast\): REVEL: A randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy – Perol M et al

- **Key results**
  - Ramucirumab+docetaxel significantly improved survival over placebo+docetaxel

### OS

<table>
<thead>
<tr>
<th>使用</th>
<th>Median (95% CI)</th>
<th>Censoring rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAM+DOC</td>
<td>10.5 (8.5, 11.2)</td>
<td>31.8%</td>
</tr>
<tr>
<td>PL+DOC</td>
<td>9.1 (8.4, 10.0)</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

**RAM+DOC vs PL+DOC:**
- Stratified HR (95% CI) 0.857 (0.751, 0.979)
- Stratified log-rank p=0.0235

### PFS

<table>
<thead>
<tr>
<th>使用</th>
<th>Median (95% CI)</th>
<th>Censoring rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAM+DOC</td>
<td>4.5 (4.2, 5.4)</td>
<td>11.1%</td>
</tr>
<tr>
<td>PL+DOC</td>
<td>3.0 (2.8, 3.9)</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

**RAM+DOC vs PL+DOC:**
- Stratified HR (95% CI) 0.762 (0.677, 0.859)
- Stratified log-rank p<0.0001

RAM, ramucirumab; DOC, docetaxel

Garon Lancet 2014
Prädiktiver Wert des PDL-1 Rezeptors?
(Programmed cell death ligand 1)

- **Inhibition T Zell Antwort**
  - T-cell Co Rezeptor CTLA-4 mAK
    - Ipilimumab (iPFS 5.7 m, OS 12.2 m) \(^{1}\)
    - Tremelimumab
  - **Anti PD-1 mAK**
    - Nivolumab (ORR 17%, n=128) \(^{2-5}\)
    - Lambrolizumab
  - **Anti PD-L1 mAK**
    - BMS-936559 (ORR 10%, n=75) \(^{6}\)
    - MPDL-3280A (ORR 22%, n=41, PDL -1 positive: 4/5 responders) \(^{7}\)
      - Update (ORR 23%, n=53, **46% in PD-L1 IHC 2 und 3**) \(^{8}\)

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Anti-PD1 in vorbehandelten Patienten (Nivolumab)

Laufende Phase III Studie: Nivolumab vs docetaxel

Press release 2015: positiv!

Brahmer WCLC 2013
LBA43: Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC) – Garon E et al

• Study objective
  – To evaluate the efficacy and safety of pembrolizumab among a number of cohorts of patients with EGFR+ or ALK+ advanced NSCLC

Nonrandomised (n=33)
  • PD-L1+ tumours\(^a\)
  • ≥2 previous therapies
  
  Pembro
  10 mg/kg Q3W

Nonrandomised (n=40)
  • PD-L1+ tumours\(^a\)
  • ≥2 previous therapies\(^b\)
  
  Pembro
  10 mg/kg Q2W

Randomised (n=144)
  • PD-L1+ tumours\(^a\)
  • ≥1 previous therapy\(^b\)
  
  Pembro
  10 mg/kg Q3W
  Pembro
  10 mg/kg Q2W

Randomised (n=45)
  • PD-L1+ tumours\(^a\)
  • Treatment naïve
  
  Pembro
  10 mg/kg Q2W
  Pembro
  10 mg/kg Q3W

Nonrandomised (n=45)
  • PD-L1+ tumours\(^a\)
  • ≥1 previous therapy\(^b\)
  
  Pembro
  2 mg/kg Q3W
  Pembro
  10 mg/kg Q2W

Primary endpoint
• ORR

Secondary endpoints
• Immune-related response criteria

\(^a\)Tumour PD-L1 expression was determined by a prototype assay to inform enrolment. Samples were independently reanalysed using a clinical trial IHC assay

\(^b\)Including ≥1 therapy platinum-containing doublet. \(^c\)First 11 patients randomised to 2 mg/kg q3w and 10 mg/kg q3w. The remaining 34 patients were randomised to 10 mg/kg q2w and 10 mg/kg q3w.

Analysis cut-off date is September 11, 2014 for the nonrandomised cohort of 45 patients treated at 2 mg/kg q3w

Garon et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA43
LBA43: Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC) – Garon E et al

- Key results
  - Robust antitumour activity was observed in both treatment-naïve and previously treated advanced NSCLC observed for all doses and schedules assessed

**PFS (RECIST v1.1, Central Review)**

- Treatment naïve: Median PFS: 27 weeks (95% CI 14, 45)
  - 24-week PFS: 51%

- Previously treated: Median PFS: 10 weeks (95% CI 9.1, 15.3)
  - 24-week PFS: 26%

**OS**

- Treatment naïve: Median OS: NR (95% CI NE, NE)
  - 6-month OS: 86%

- Previously treated: Median OS: 8.2 months (95% CI 7.3, NR)
  - 6-month OS: 59%

Analysis cutoff date: March 3, 2014
**LBA43: Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC) – Garon E et al**

**Key results (cont.)**
- Strong PD-L1 tumour expression correlated with improved response, PFS and OS

**Conclusions**
- Pembrolizumab was effective in patients with treatment-naïve or previously treated advanced NSCLC
- In particular, patients with strong PD-L1 tumour expression may benefit from this treatment

Strong PD-L1 positivity defined as staining in ≥50% of tumour cells, and weak PD-L1 positivity as staining in 1–49% of tumour cells. Negative staining is no PD-L1 staining in tumour cells. Data cutoff: March 3, 2014.

Garon et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA43
# Clinical Development of Inhibitors of PD-1 Immune Checkpoint

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Molecule</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab (BMS-936558)</td>
<td>Fully human IgG4 mAb</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab (CT-011)</td>
<td>Humanized IgG1 mAb</td>
<td>CureTech</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (MK-3475)</td>
<td>Humanized engineered IgG4 mAb</td>
<td>MSD</td>
</tr>
<tr>
<td></td>
<td>AMP-224</td>
<td>Rec. PD-L2-Fc fusion protein</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-936559</td>
<td>Fully human IgG4 mAb</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td></td>
<td>Medi-4736</td>
<td>Engineered human IgG1 mAb</td>
<td>MedImmune/As trazeneca</td>
</tr>
<tr>
<td></td>
<td>MPDL-3280A</td>
<td>Engineered human IgG1 mAb</td>
<td>Genentech</td>
</tr>
<tr>
<td></td>
<td>MSB0010718C</td>
<td>Engineered human IgG1 mAb</td>
<td>EMD Serona</td>
</tr>
</tbody>
</table>

Courtesy of Prof. Zippelius
Molekulare Tests am Kantonsspital St. Gallen

- EGFR Mutation (PCR)
- KRAS Mutation (PCR)
- HER2 Mutation (PCR)
- BRAF Mutation (PCR)
- ALK Rearrangement (FISH)
- ROS1 Rearrangement (FISH)
- RET Rearrangement (FISH)
- MET Amplifikation (FISH)
- FGFR1 Amplifikation (FISH)
- PTEN (PCR, FISH)
- HER2 Amplifikation (FISH)
EGFR- Mutation

~10%

Adenokarzinom
Wenig-/ Nieraucher
Asiaten
Frauen
Objective response rate in EGFR mutation positive and negative patients

Overall response rate (%)

- **Mutation positive patients**:
  - Gefitinib: 71.2% (n=132)
  - Carboplatin / paclitaxel: 47.3% (n=129)

- **Mutation negative patients**:
  - Gefitinib: 1.1% (n=91)
  - Carboplatin / paclitaxel: 23.5% (n=85)

Odds ratio >1 implies greater chance of response on gefitinib

EGFR M+ odds ratio (95% CI) = 2.75 (1.65, 4.60), p=0.0001

EGFR M- odds ratio (95% CI) = 0.04 (0.01, 0.27), p=0.0013

Mok, NEJM 2009
## Randomisierte Studien mit EGFR Erstlinien-TKIs bei EGFR- Mutation

<table>
<thead>
<tr>
<th>Studie</th>
<th>Studienarm</th>
<th>N</th>
<th>Ansprechrate</th>
<th>Progressionsfreies Überleben (Monate)</th>
<th>Gesamtüberleben (Monate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEJ002 1</td>
<td>Gefitinib Chemotherapy</td>
<td>114</td>
<td>74%* 31%</td>
<td>10.8 * 5.4</td>
<td>27.7 26.6</td>
</tr>
<tr>
<td>WJTOG 2</td>
<td>Gefitinib Chemotherapy</td>
<td>86</td>
<td>62%* 32%</td>
<td>9.2 * 6.3</td>
<td>36 39</td>
</tr>
<tr>
<td>OPTIMAL 3</td>
<td>Erlotinib Chemotherapy</td>
<td>82</td>
<td>83%* 36%</td>
<td>13.7 * 4.6</td>
<td>NS NS</td>
</tr>
<tr>
<td>EURTAC 4</td>
<td>Erlotinib Chemotherapy</td>
<td>77</td>
<td>58%* 15%</td>
<td>9.7 * 5.2</td>
<td>23 19</td>
</tr>
<tr>
<td>LUX 3 5</td>
<td>Afatinib Chemotherapy</td>
<td>230</td>
<td>60.8%* 22.1%</td>
<td>13.6 * 6.9</td>
<td>NR</td>
</tr>
<tr>
<td>LUX 6 6</td>
<td>Afatinib Chemotherapy</td>
<td>242</td>
<td>66.9% 23%</td>
<td>11 * 5.6</td>
<td>NR</td>
</tr>
<tr>
<td>Wu et al 7</td>
<td>Erlotinib Chemotherapy</td>
<td>110</td>
<td>68.2% 39.3%</td>
<td>11.1* 5.7</td>
<td>NR</td>
</tr>
</tbody>
</table>

*: p<0.001

NR: nicht rapportiert NS: nicht signifikant

Zusammenfassung TKI 1L bei EGFR Mut+

- PFS und QL/Symptomkontrolle besser als mit Chemotherapie
- Kein Gesamtüberlebensvorteil
- ABER: ALLE Patienten entwickeln Resistenz
Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation-positive nonsquamous non-small cell lung cancer (NSCLC): An open-label randomized trial

PFS

(n=150)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Number at risk</th>
<th>Erlotinib + bevacizumab</th>
<th>Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>EB 75</td>
<td>E 77</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>EB 72</td>
<td>E 66</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>EB 69</td>
<td>E 57</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>EB 64</td>
<td>E 44</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>EB 60</td>
<td>E 39</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>EB 53</td>
<td>E 29</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>EB 49</td>
<td>E 24</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>EB 38</td>
<td>E 21</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>EB 30</td>
<td>E 18</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>EB 20</td>
<td>E 13</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>EB 13</td>
<td>E 8</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>EB 8</td>
<td>E 4</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>EB 4</td>
<td>E 1</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>EB 4</td>
<td>E 0</td>
<td></td>
</tr>
</tbody>
</table>

Median (months) 16.0 9.7
HR (95% CI) 0.54 (0.36, 0.79)
p-value* 0.0015

*log-rank test, two-sided

Seto Lancet 2014
Welches ist der beste EGFR TKI?

- **LUX Lung 7:**
  - afatinib vs. gefitinib (N=316), completed

- **ARCHER 1050:**
  - dacomitinib vs gefitinib (n= 440)

- **TIGER1:**
  - CO 1686 (rociletinib) vs. erlotinib (N=200)

- **FL AURA:**
  - AZD9291 vs. erlotinib oder gefitinib (N=650)
Erlotinib über Progression hinaus

Aspiration single arm phase 2

Investigator choice: EGFR TKI continuation beyond progression

Park, ESMO 2014

**PFS1**

- Median PFS1: 10.8 months (95% CI 9.2–11.1)

**PFS2**

- Median PFS2 (n=93; 79 PD events): 14.1 months (95% CI 12.2–15.9)
- 3.1 months
1223O: ASPIRATION: first-line erlotinib (E) until and beyond RECIST progression (PD) in Asian patients (pts) with EGFR mutation-positive (mut+) NSCLC – Park K et al

• Key results (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Post-PD erlotinib (n=93)</th>
<th>No post-PD erlotinib (n=78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS1, months (95% CI)</td>
<td>11.0 (9.1, 11.0)</td>
<td>7.4 (5.6, 9.2)</td>
<td>0.0096</td>
</tr>
<tr>
<td>Median depth of response, %</td>
<td>-48.7\textsuperscript{a}</td>
<td>-42.2\textsuperscript{b}</td>
<td>0.0389</td>
</tr>
<tr>
<td>Median time from baseline to best overall response, days</td>
<td>56</td>
<td>59</td>
<td>0.8840</td>
</tr>
<tr>
<td>Median time from best overall response to PFS1, days</td>
<td>169</td>
<td>113</td>
<td>0.0047</td>
</tr>
<tr>
<td>ECOG PS 0/1 at PFS1, %</td>
<td>95.7</td>
<td>78.2</td>
<td>0.0005</td>
</tr>
<tr>
<td>Grade ≥3 AEs at PFS1, %</td>
<td>19.4</td>
<td>19.2</td>
<td>0.9837</td>
</tr>
</tbody>
</table>

\textsuperscript{a}n=90, \textsuperscript{b}n=70

• Conclusions
  – Continuing erlotinib beyond RECIST PD is feasible in patients with EGFR M+ NSCLC
  – The optimal patient subset that will benefit from post-PD erlotinib remains to be validated

**Study objective**

- To compare continuation treatment with gefitinib + chemotherapy versus chemotherapy alone in patients with advanced NSCLC and acquired resistance to first-line gefitinib

**Key patient inclusion criteria**

- Stage IIIB/IV NSCLC
- EGFR mutation positive
- WHO PS 0–1
- Achieved response* with first-line gefitinib
- PD <4 weeks prior to study (n=265)

**Primary endpoint**

- PFS

*CR/PR ≥4 months or SD >6 months

**Secondary endpoints**

- OS, ORR, DCR
- Safety and tolerability, health-related QoL

Mok et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA2_PR
Erlotinib continuation beyond progression with cisplatin-pemetrexed: IMPRESS

- **Gefitinib (n=133)**
  - Median PFS, months: 5.4
  - Number of events, n (%): 98 (73.7)
  - HR (95% CI) = 0.86 (0.65, 1.13); p=0.273

- **Placebo (n=132)**
  - Median PFS, months: 5.4
  - Number of events, n (%): 107 (81.1)

**Patients at risk:**
- Gefitinib: 133 → 110 → 88 → 40 → 25 → 12 → 6 → 0
- Placebo: 132 → 100 → 85 → 39 → 17 → 5 → 4 → 0

Mok, ESMO 14
OS (at 33% of events)

Additional ad-hoc OS analysis included brain metastases vs no brain metastases at baseline (33% gefitinib vs 23% placebo at baseline) as a covariate: HR (95% CI) = 1.55 (1.00, 2.41); p=0.05
1. Clinically relevant
   - Small cell transformation
   - Acquired T790M
2. Uncommon but targetable
   - MET amplification
   - HER2 amplification
   - BRAF mutation
3. Of biological Interest
   - AXL, CRKL, FGFR 1/2/3 overexpression, anti-apoptosis...
3rd generation TKI

Best percentage change from baseline in target lesion:
T790M+ evaluable patients, expansion cohorts only (N=107)

- ORR = 64% (69/107; 95% CI 55%, 73%) in patients with EGFR T790M+ NSCLC
- Overall disease control rate (CR+PR+SD) = 94% (101/107; 95% CI 88%, 98%)

AZD 9291

Modified from Thomas Lynch, 2014 ASCO Annual Meeting; Janne ASCO 2014; Sequist ASCO 2014; Klm ASCO 2014
Cetuximab and afatinib

N=119
ORR =29%

Figure 2. Waterfall plot showing maximum percentage change from baseline in size of tumors in patients who received the concurrent regimen of afatinib and cetuximab. Data available for 119 patients. Tumor tissue from 2 patients was uninformative as to T790M status. SLD, sum of the longest diameter.

Janjiagian Cancer Discovery 2014
BRAF in stage I-IIIA versus IIIB/IV

Litvak, JTO 2014
LBA38_PR: Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): A multicenter, open-label, phase II trial (BRF113928) – Planchard B et al

- **Study objective**
  - To investigate efficacy of dabrafenib in patients with BRAF V600E-mutant advanced NSCLC

**Key patient inclusion criteria**
- Stage IV NSCLC
- BRAF V600E mutation
- Progression on systemic chemotherapy
- ECOG PS 0–2

**Primary endpoint**
- ORR

**Secondary endpoints**
- PFS, duration of response, OS
- Safety, tolerability
- Population pharmacokinetics

**Key results**

- Dabrafenib was associated with ORR of 32% and DCR of 56%

<table>
<thead>
<tr>
<th></th>
<th>≥ 2nd line (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR, n (%)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>SD*, n (%)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>23 (29)</td>
</tr>
<tr>
<td>Not evaluable, n (%)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Response rate, i.e. confirmed CR + PR (95% CI), %</td>
<td>32 (21.9, 43.6)</td>
</tr>
<tr>
<td>Disease control rate, i.e. confirmed CR + PR + SD (95% CI), %</td>
<td>56 (44.7, 67.6)</td>
</tr>
</tbody>
</table>

*SD is defined as meeting SD ≥12 weeks (planned time for the second post-baseline disease assessment)*

GSK phase I trial of dabrafenib for BRAF V600E

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**Responders in ≥ 2nd Line**  
N = 25  

| Progressed, n (%) | 12 (48) |  
| Ongoing, n (%)    | 13 (52) |

**Duration of Response**  

| Median, months (95% CI) | 11.8 (5.4 – NR) |  
| < 6 months, n (%)       | 11 (44), 4 ongoing |  
| > 6 months, n (%)       | 14 (56), 9 ongoing |  
| > 9 months, n (%)       | 10 (40), 8 ongoing |  
| > 12 months, n (%)      | 6 (24), 4 ongoing |  

| Median PFS*, months (95% CI) | 5.5 (2.8 – 7.3) |

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*a 62% of patients progressed or died.

ORR 32% (n=78)