Highlights ASCO 2011

Paul Germonpré
Highlights ASCO 2011

• Advanced NSCLC
  - EGFR-TKI in 1\textsuperscript{st} line treatment
  - Maintenance treatment with pemetrexed or EGFR-TKI
  - 2\textsuperscript{nd} line treatment options with EGFR-TKIs
• Local and locally advanced NSCLC
  - PET-CT for radiotherapy planning
  - Adjuvant cisplatin + pemetrexed
• SCLC
• Mesothelioma
1\textsuperscript{st} line EGFR-TKI vs chemotherapy in \textit{EGFR} mutation positive NSCLC

**Inclusion criteria:**
- Chemonaive pts with good PS
- EGFR mutation positive

**\textsuperscript{1}ary endpoint:** PFS

**EGFR-TKI**
- until PD

**Platinum-based chemotherapy**
- up to 4 or 6 cycles

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Ethnicity</th>
<th>EGFR-TKI</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>WJTOG3405</td>
<td>172</td>
<td>asian</td>
<td>Gefitinib</td>
<td>Cis + Doc (6x)</td>
</tr>
<tr>
<td>NEJ002</td>
<td>228</td>
<td>asian</td>
<td>Gefitinib</td>
<td>Carbo + Pacli (6x)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>165</td>
<td>asian</td>
<td>Erlotinib</td>
<td>Carbo + Gemci (4x)</td>
</tr>
<tr>
<td>EURTAC</td>
<td>174</td>
<td>caucasian</td>
<td>Erlotinib</td>
<td>Cis/Carbo + Doc/Gemci (4x)</td>
</tr>
</tbody>
</table>
EURTAC: baseline characteristics

<table>
<thead>
<tr>
<th>Updated analysis (Jan 26, 2011)</th>
<th>Erlotinib (n=86)</th>
<th>Chemotherapy (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>65 (24–82)</td>
<td>65 (29–82)</td>
</tr>
<tr>
<td>Gender, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>Female</td>
<td>67</td>
<td>78</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>1</td>
<td>55</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Former smoker</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>Never smoker</td>
<td>66</td>
<td>72</td>
</tr>
<tr>
<td>EGFR mutation type, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>L858R mutation</td>
<td>34</td>
<td>33</td>
</tr>
</tbody>
</table>

All patients were Caucasian and the majority (~90%) had stage IV disease and adenocarcinoma.

Rosell et al. J Clin Oncol 2011; vol 29 (suppl): 7503
Interim results of the European Erlotinib vs Chemotherapy (EURTAC) trial

**Mutant EGFR**

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>58% *</td>
<td>15%</td>
</tr>
<tr>
<td><strong>median PFS (m)</strong></td>
<td>9.7 *</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>HR for OS</strong>§</td>
<td>0.80 [0.47-1.37]</td>
<td></td>
</tr>
</tbody>
</table>

§ at time of analysis still >60% alive and 83% cross-over in chemo-arm
* P < 0.05
EURTAC: conclusions

- EURTAC is the first prospective study of an EGFR tyrosine-kinase inhibitor (TKI) versus chemotherapy for first-line treatment of *EGFR* mutation-positive NSCLC in Caucasian patients.
- The study results confirms significant benefit in PFS of erlotinib over standard chemotherapy:
  - 63% reduction in risk of progression (HR=0.37)
- OS data are immature, with high level of known crossover.
- No new safety findings (as expected):
  - Tolerability of erlotinib consistent with previous studies.
NEJ002: 1st line gefitinib vs carbo-paclitaxel in EGFR mutation + NSCLC (updated)

**Progression-free survival**

- Gefitinib (n=114)
- Carbo + Pacli (n=114)

**Overall survival**

- Gefitinib
- Carbo + Pacli

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>10.8 m***</td>
<td>5.4 m</td>
</tr>
<tr>
<td>Median OS</td>
<td>27.7 m</td>
<td>26.6 m</td>
</tr>
</tbody>
</table>

P<0.001***

Inoue et al. J Clin Oncol 2011; vol 29 (suppl): abstr 7519
NEJ002: 1st line gefitinib vs carbo-paclitaxel in EGFR mutation + NSCLC (updated)

Influence of EGFR TKI and subsequent therapies on OS

Inoue et al. J Clin Oncol 2011; vol 29 (suppl): abstr 7 519

Overall survival (%)

Days after randomization

Median OS
A: 27.7 months
B: 25.9 months
Log-rank test
A vs. B  p=0.482

Median OS
A: 35.8 months
B: 23.4 months
Log-rank test
A vs. B  p<0.001

EGFR-TKI + / Platinum + (n=186)
EGFR-TKI + / Platinum – (n=40)
EGFR-TKI – / Platinum + (n=2)

EGFR-TKI + / Platinum + with Pemetrexed or Docetaxel (n=81)
EGFR-TKI + / Platinum + without Pemetrexed and Docetaxel (n=105)
NEJ002: 1st line gefitinib vs carbo-pacli in EGFR mutation + NSCLC

- QoL evaluated using Care Notebook (= self-administered, cancer-specific questionnaire with multidimensional scales)

QoL was maintained for a significantly longer duration by gefitinib than carboplatin + paclitaxel.

→ QoL was maintained for a significantly longer duration by gefitinib than carboplatin + paclitaxel.

Yoshizawa et al. ESMO 2010.
NEJ002: conclusions

• The updated findings from this study show that gefitinib is associated with **superior benefits** over Carbo +Pacli in terms of **PFS and QoL**.

• There was no difference in OS between treatments, most likely due to the high level of patient crossover.

• These data suggest that for patients with a good PS and with **EGFR** mutations, triplet sequential therapy with EGFR TKI, platinum-based regimen and then pemetrexed or docetaxel may be preferable.
OPTIMAL: 1st line erlotinib vs carbo+gemci in asian pts with EGFR mutation

OPTIMAL: 1st line erlotinib vs carbo+gemci in asian pts with EGFR mutation

OPTIMAL: 1\textsuperscript{st} line erlotinib vs carbo+gemci in asian pts with \textit{EGFR} mutation

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total FACT-L</td>
<td>6.90 (3.07–15.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TOI</td>
<td>7.79 (3.44–17.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LCSS</td>
<td>6.77 (3.04–15.05)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Includes all patients with a baseline and ≥1 post-baseline QoL assessment.

Optimal: conclusions

• This updated analysis of the OPTIMAL study showed that erlotinib is associated with a significant PFS benefit vs standard chemotherapy as first-line treatment for patients with advanced NSCLC whose tumours harbour activating mutations.

• The PFS benefit with erlotinib was regardless of age, gender, PS, disease stage, tumour histology and smoking status.

• Patient QoL was also significantly improved with erlotinib compared with G/C.

• Erlotinib appears to be an important agent in the first-line treatment of EGFR Act Mut+ NSCLC.
# 1st line EGFR-TKI vs chemotherapy in EGFR mutation positive NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR</th>
<th>PFS</th>
<th>HR PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS (subgroup)</td>
<td>71% vs 47%</td>
<td>9.6 m vs 6.3 m</td>
<td>0.48</td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>62% vs 31%</td>
<td>9.2 m vs 6.3 m</td>
<td>0.49</td>
</tr>
<tr>
<td>NEJ002</td>
<td>74% vs 31%</td>
<td>10.8 m vs 5.4 m</td>
<td>0.30</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>83% vs 36%</td>
<td>14.7 m vs 4.6 m</td>
<td>0.16</td>
</tr>
<tr>
<td>EURTAC</td>
<td>58% vs 15%</td>
<td>9.7 m vs 5.2 m</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* all $P < 0.05$

Comparison of overall survival between pts who began 1st-line systemic therapy after gefitinib approval and pts who began treatment before gefitinib approval.

Patients with EGFR-mutations

→ EGFR mutations significantly predict a survival benefit from gefitinib in patients with advanced NSCLC.
# 1st line EGFR-TKI vs chemotherapy in EGFR wild-type NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>EGFR-TKI</th>
<th>Chemo</th>
<th>HR OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS (subgroup)</td>
<td>gefitinib</td>
<td>carbo + acli</td>
<td>1.18</td>
</tr>
<tr>
<td>First-SIGNAL</td>
<td>gefitinib</td>
<td>cis + gemci</td>
<td>1.19</td>
</tr>
<tr>
<td>TORCH</td>
<td>erlotinib</td>
<td>cis + gemci</td>
<td>1.36 *</td>
</tr>
</tbody>
</table>

* P<0.05

† Caucasian population with expected EGFR mutation rate ~10%

→ in the absence of an EGFR mutation (or of EGFR mutation results), chemotherapy remains the 1st-line treatment of choice

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Gefitinib as maintenance therapy in pts with advanced NSCLC: INFORM trial

**Study design**

**Inclusion criteria:**
- Stage IIIB/IV NSCLC
- PS 0-2
- Non-PD following 4 cycles of platinum-based chemotherapy

**Endpoints:**
- Primary: PFS
- Secondary: OS, ORR, DCR, QoL and safety
- Exploratory: biomarkers (EGFR mutations)

**Maintenance arm**
Gefitinib 250 mg/d until progression

**Control arm**
Placebo 1x/d until progression

The greatest magnitude of effect of PFS was observed in patients with EGFR mutation-positive tumours.
INFORM trial: ORR and OS

Treatment post discontinuation | Gefitinib | Placebo
--- | --- | ---
None | 49% | 33%
Targeted Rx | 8% | 32%
Chemotherapy | 40% | 53%
Other | 24% | 24%

Odds ratio (95% CI) = 54.1 (7.17, 408); p=0.0001

58% deaths at data cut-off

SATURN: PFS ~ EGFR mutation status

<table>
<thead>
<tr>
<th>Mutation Status</th>
<th>HR for PFS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EGFR wild type</td>
<td>0.78</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EGFR mut positive</td>
<td>0.10</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Saturn: overall survival

All patients

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib (N=438)</th>
<th>Placebo (N=451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All classes*</td>
<td>309 (71)</td>
<td>325 (72)</td>
</tr>
<tr>
<td>Taxanes (including docetaxel)</td>
<td>132 (30)</td>
<td>142 (31)</td>
</tr>
<tr>
<td>Antimetabolites (including pemetrexed)</td>
<td>105 (24)</td>
<td>103 (23)</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>72 (16)</td>
<td>80 (18)</td>
</tr>
<tr>
<td>EGFR TKIs</td>
<td>50 (11)</td>
<td>95 (21)</td>
</tr>
<tr>
<td>Platinum compounds</td>
<td>40 (9)</td>
<td>53 (12)</td>
</tr>
</tbody>
</table>

Data are n (%). *Number of cases with at least one treatment. TKI=tyrosine kinase inhibitor.

Table 3: Documented post-study treatments received

<table>
<thead>
<tr>
<th></th>
<th>HR for OS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.81</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EGFR wild type</td>
<td>0.77</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EGFR mut positive</td>
<td>0.83</td>
<td>NS</td>
</tr>
</tbody>
</table>

## Maintenance EGFR-TKI vs placebo in EGFR mutation positive NSCLC

<table>
<thead>
<tr>
<th>HR for PFS</th>
<th>Mutant <em>EGFR</em></th>
<th>Wild-type <em>EGFR</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>SATURN (^1)</td>
<td>0.10 *</td>
<td>0.78 *</td>
</tr>
<tr>
<td>INFORM (^2)</td>
<td>0.17 *</td>
<td>0.86</td>
</tr>
</tbody>
</table>

* \(P < 0.05\)

Paramount: Pemetrexed maintenance following Cisplatin + Pemetrexed

Primary endpoint: PFS
Paramount: Pemetrexed maintenance following Cisplatin + Pemetrexed

PFS during maintenance therapy (investigator assessment)

<table>
<thead>
<tr>
<th></th>
<th>Pem</th>
<th>Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression events</td>
<td>94%</td>
<td>96%</td>
</tr>
<tr>
<td>PFS (investigator)</td>
<td>4.1 vs 2.8 m</td>
<td>HR 0.59; p .00006</td>
</tr>
<tr>
<td>PFS (independent)</td>
<td>3.9 vs 2.6 m</td>
<td>HR 0.64; p .0002</td>
</tr>
<tr>
<td>ORR (independent)</td>
<td>2.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>QoL (EQ-5D)</td>
<td>no difference</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>6%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Significantly higher incidence of Grade 3/4 AEs with pemetrexed vs placebo (p≤0.05):
- Fatigue: 4.2% vs 0.6%
- Anaemia: 4.5% vs 0.6%
- Neutropenia: 3.6% vs 0%
PARAMOUNT: conclusions

- PARAMOUNT met its primary endpoint
- Pemetrexed as maintenance therapy significantly improved PFS versus placebo (HR 0.62)
  - Investigator-assessed PFS was confirmed by the independent assessment
- Pemetrexed was well tolerated, with a safety profile similar to that reported previously in a study of pemetrexed as maintenance therapy in NSCLC\(^1\)
- *These data suggest that pemetrexed is effective as maintenance therapy in patients with advanced nonsquamous NSCLC who have received pemetrexed + cisplatin induction therapy*


Single agent maintenance therapy for advanced stage NSCLC: a meta-analysis

• Study objective
  - To evaluate the effect of single agent maintenance therapy on survival in NSCLC

• Study type/design
  - Meta-analysis of randomized studies that evaluated the effect of single agent maintenance therapy on survival in NSCLC
  - Primary outcome: OS (secondary outcome: PFS)
  - 10 reports (3 abstracts, 7 publications) eligible for inclusion with a total of 3451 patients
  - were not included in this analysis
Single agent maintenance therapy for advanced stage NSCLC: a meta-analysis

• Key results
  - OS (HR 0.87, p=0.0003) and PFS (HR 0.84, p< 0.0001) were superior with maintenance therapy
  - ‘Switch’ maintenance therapy was associated with significant OS (HR 0.86, p= 0.00046) and PFS (HR 0.71, p<0.0001) improvement.
  - ‘Continuation’ maintenance therapy was not associated with survival benefit.
  - Similar improvements in OS and PFS were observed with EGFR-targeted agents (OS HR 0.86, p= 0.006; PFS HR 0.76, p<0.0001) and cytotoxic agents (OS HR 0.88, p=0.018; PFS HR 0.87, p<0.0001).
Single agent maintenance therapy for advanced stage NSCLC: a meta-analysis

• Key conclusions
  - Single agent maintenance therapy improves overall survival, though statistical significance was only noted with ‘switch’ maintenance
  - A survival benefit was observed with chemotherapy and EGFR-targeted therapy

NB: Results of PARAMOUNT and the gefitinib maintenance study from ASCO 2011 were not included in this analysis!
Negative TTF-1 status predicts for negative \textit{EGFR}-mutation in lung adenocarcinoma

- Prevalence \textit{EGFR} mutation in study population: 15-19%
- Retrospective study on 301 parafin-embedded tumors

<table>
<thead>
<tr>
<th>TTF-1</th>
<th>\textit{EGFR}-mutation</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>222</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>2</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

- Sensitivity: 99% ; \textbf{Negative predictive value: 93%}

\(\Rightarrow\) Patients with lung adenocarcinoma (~30%) that are TTF-1 negative have a high (99%) probability of being \textit{EGFR} WT. These patients could be initiated on chemotherapy while awaiting their results of \textit{EGFR} mutation testing.
Highlights ASCO 2011

• The presence of an *EGFR* mutation is the driving factor that determines outcome rather than the clinical characteristics (such as ethnicity, gender, smoking status or histology).

• The detection of *EGFR mutations* in patients with NSCLC is the first molecular predictive factor that offers patients a more effective and convenient targeted therapy than conventional chemotherapy regimens.
Highlights ASCO 2011

• The efficacy of the EGFR-TKI in *EGFR* mutation-positive NSCLC patients is independent from the line of therapy:
  → all patients with a known *EGFR* mutation should be treated with an EGFR-TKI.

• In the absence of an *EGFR* mutation (or of *EGFR* mutation results), chemotherapy remains the 1st-line treatment of choice.
### Highlights ASCO 2011

- **EGFR-TKI as 1\(^{st}\)-line treatment for NSCLC with activating *EGFR* mutations?**

<table>
<thead>
<tr>
<th>Pro</th>
<th>Contra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved progression free survival</td>
<td>Logistics of EGFR mutation analysis</td>
</tr>
<tr>
<td>Improved response rate</td>
<td>No improved overall survival</td>
</tr>
<tr>
<td>Improved QoL and symptom control</td>
<td></td>
</tr>
<tr>
<td>Favourable toxicity profile</td>
<td></td>
</tr>
</tbody>
</table>

**→** **EGFR-TKIs are the new standard of care for the 1\(^{st}\)-line treatment for NSCLC with known activating *EGFR* mutations!**
Pragmatic treatment algorithm for newly diagnosed non-squamous NSCLC

- TTF-1 +?
  - Ja
    - Wachten op EGFR-mutatie analyse.
  - Nee
    - Starten met platinum-doublet

- ORR?
  - Ja
    - 1st line EGFR-TKI
  - Nee
    - 1st line platinum-doublet

- EGFR mut+?
  - Ja
    - 2nd line upon PD
  - Nee
    - SD
      - "Switch maintainance"

- EGFR-TKI (maintenance or 2nd line)
Highlights ASCO 2011

• Advanced NSCLC
  - EGFR-TKI in 1\textsuperscript{st} line treatment
  - Maintenance treatment with pemetrexed or EGFR-TKI
  - 2\textsuperscript{nd} line treatment options with EGFR-TKIs

• Local and locally advanced NSCLC
  - PET-CT for radiotherapy planning
  - Adjuvant cisplatin + pemetrexed

• SCLC

• Mesothelioma
Phase III trial of gefitinib vs pemetrexed as second-line treatment in NSCLC

- Study performed in Korea (N 141)

- Primary endpoint: PFS

- The study closed early due to licensed indication changes for both pemetrexed (non-squamous) and gefitinib (EGFR mutation positive tumours) in South Korea

Phase III trial of gefitinib vs pemetrexed as second-line treatment in NSCLC

- Gefitinib was associated with superior efficacy to pemetrexed as second-line therapy in clinically selected Korean patients with NSCLC

- Gefitinib may be preferable to pemetrexed as second-line therapy in enriched NSCLC patients

Molecular predictors of outcome of gefitinib and docetaxel in previously treated NSCLC: INTEREST trial

Survival in pts with mutant *EGFR*

→ *EGFR* mutation-positive patients had longer progression-free survival and higher objective response rate (42.1% v 21.1%) with gefitinib *versus* docetaxel.
HORG: phase III study of erlotinib vs pemetrexed as 2\textsuperscript{nd} or 3\textsuperscript{rd} line treatment

- Stage IIIB/IV NSCLC
- 1–2 prior chemotherapy regimens
- ECOG PS 0–2

\( n=332 \)

Primary endpoint = time to progression (TTP)
Secondary endpoints = RR, OS, safety

Tarceva 150mg/day (\( n=166 \))

Pemetrexed (\( n=166 \))
Similar TTP and OS with erlotinib and pemetrexed in 2\textsuperscript{nd} or 3\textsuperscript{rd} line setting

**TTP**

- Tarceva (n=163)
- Pemetrexed (n=161)

**OS**

- Tarceva (n=166)
- Pemetrexed (n=166)

1-year survival rate (%)
- 35.7% Tarceva
- 38.5% Pemetrexed

\( p = 0.299 \)

\( p = 0.916 \)

Vamvakas et al. ASCO 2010
TTP with erlotinib and pemetrexed according to histology

- Squamous cell carcinoma (TTP):
  - Erlotinib: 4 months
  - Pemetrexed: 2.3 months
  - p = 0.016

- Non-Squamous cell carcinoma (TTP):
  - Erlotinib: 3.6 months
  - Pemetrexed: 3.4 months
  - p = 0.876

Vamvakas et al. ASCO 2010
Phase II: Erlotinib +/- MetMAb in 2nd/3rd-line NSCLC

**Study design**

**Key eligibility:**
- Stage IIIB/IV NSCLC
- 2nd/3rd-line NSCLC
- Tissue required
- PS 0–2

**Arm A**
- n=69
- MetMAb (15 mg/kg IV Q3W)
  + erlotinib (150 mg daily)

**Arm B**
- n=68
- Placebo (IV Q3W)
  + erlotinib (150 mg daily)

**R 1:1**

**Stratification factors:**
- Tobacco history
- PS
- Histology

**Co-primary objectives:**
- PFS in ‘Met Diagnostic Positive’ patients (est. 50%)
- PFS in overall ITT population

**PD**

**Add MetMAb**
- n=27
  - Must be eligible to be treated with MetMAb

Met IHC as a companion diagnostic

‘Met Diagnostic Positive’ was defined as majority (≥50%) of tumor cells with moderate or strong staining intensity.

- Met diagnostic status was assessed after randomization and prior to unblinding.
- 93% of patients had adequate tissue for evaluation of Met by IHC.
- 52% patients with evaluable tissue were “Met Diagnostic Positive”.

IHC: immunohistochemistry

MetMAb plus erlotinib in Met Dx+ pts

**PFS: HR=0.53**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (mo)</th>
<th>HR (95% CI)</th>
<th>Log-rank p-value</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + erlotinib</td>
<td>1.5</td>
<td>0.53 (0.28–0.99)</td>
<td>0.04</td>
<td>27</td>
</tr>
<tr>
<td>MetMAb + erlotinib</td>
<td>2.9</td>
<td></td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>

**OS: HR=0.37**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (mo)</th>
<th>HR (95% CI)</th>
<th>Log-rank p-value</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + erlotinib</td>
<td>3.8</td>
<td>0.37 (0.19–0.72)</td>
<td>0.002</td>
<td>26</td>
</tr>
<tr>
<td>MetMAb + erlotinib</td>
<td>12.6</td>
<td></td>
<td></td>
<td>16</td>
</tr>
</tbody>
</table>
MetMAb plus erlotinib in Met Dx- pts

**PFS: HR=1.82**
- Placebo + erlotinib: 2.7 (95% CI: 0.99–3.32) HR (0.05 Log-rank p-value)
- MetMAb + erlotinib: 1.62
- Median (mo): 14
- No. of events: 24

**OS: HR=1.78**
- Placebo + erlotinib: 15.8 (95% CI: 0.79–3.99) HR (0.16 Log-rank p-value)
- MetMAb + erlotinib: 8.1
- Median (mo): 15
- No. of events: 13
MetMAb + erlotinib in key subpopulations

- Benefit from MetMAb is not driven by EGFR mutation or FISH status.

MetMab + erlotinib: conclusions

• MetMab is a potent and selective inhibitor of the Met pathway
• MetMab + erlotinib improves PFS and OS in Met Dx+ patients
  - Not driven by key sub populations or imbalances in prognostic characteristics
• Differences in outcomes between different subpopulations highlight the importance of diagnostic development
• A Phase III study evaluating MetMab + erlotinib in Met Dx+ patients is expected to start accruing patients later this year
Afatinib and cetuximab in NSCLC pts with acquired resistance to erlotinib or gefitinib
Afatinib and cetuximab in NSCLC pts with acquired resistance to erlotinib or gefitinib

<table>
<thead>
<tr>
<th>Afatinib 40 mg</th>
<th>Cetuximab 250 mg/m²</th>
<th>Cetuximab 500 mg/m²</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>4 (8)</td>
<td>47 (92)</td>
<td>51</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>63 (49–76)</td>
<td>61 (41–82)</td>
<td>61 (41–82)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>1 (25)</td>
<td>35 (77)</td>
<td>37 (73)</td>
</tr>
<tr>
<td>Ethnicity: White/Black/Asian/American Indian, %</td>
<td>75/0/25/0</td>
<td>83/4/13/0</td>
<td>82/4/14/0</td>
</tr>
<tr>
<td>Baseline EGFR 0/1/2, %</td>
<td>25/75/0</td>
<td>21/75/4</td>
<td>22/75/4</td>
</tr>
<tr>
<td>Median time on erlotinib/gefitinib, months</td>
<td>10</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Prior chemotherapy, n (%)</td>
<td>3 (75)</td>
<td>36 (77)</td>
<td>39 (77)</td>
</tr>
<tr>
<td>T790M-positive*, n (%)</td>
<td>27 (57)</td>
<td>27 (53)</td>
<td></td>
</tr>
<tr>
<td>T790M-negative*, n (%)</td>
<td>2 (50)</td>
<td>15 (32)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>EGFR deletion 19, n (%)</td>
<td>2 (50)</td>
<td>27 (58)</td>
<td>29 (57)</td>
</tr>
<tr>
<td>EGFR L858R, n (%)</td>
<td>1 (25)</td>
<td>17 (36)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>Unknown/other, n (%)</td>
<td>2 (50)</td>
<td>5 (11)</td>
<td>7 (14)</td>
</tr>
</tbody>
</table>
Afatinib and cetuximab in NSCLC pts with acquired resistance to erlotinib or gefitinib

Response by mutation

<table>
<thead>
<tr>
<th></th>
<th>T790M+</th>
<th>T790M-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PR</td>
<td>50%</td>
<td>57%</td>
<td>51%</td>
</tr>
<tr>
<td>Confirmed PR</td>
<td>35%</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>SD</td>
<td>42%</td>
<td>36%</td>
<td>42%</td>
</tr>
<tr>
<td>DCR</td>
<td>92%</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td>PD</td>
<td>8%</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Afatinib and cetuximab in NSCLC pts with acquired resistance to erlotinib or gefitinib

- In this ongoing study, objective responses were observed in T790M-positive and T790M-negative tumours with:
  - a confirmed objective response rate of 40%
  - a disease control rate of 93%
- These data support that EGFR mutation-positive NSCLC, with acquired resistance to erlotinib and gefitinib, continues to depend on EGFR signaling

Highkights ASCO 2011

• Inhibition of the EGFR-pathway in 2\textsuperscript{nd} line setting?
  - in EGFR \textit{mut} + pts: EGFR-TKI are treatment of choice
  - in EGFR wild-type pts: EGFR-TKI (erlotinib) \(\approx\) chemo
  - in EGFR \textit{mut} + pts developing resistance to EGFR-TKI:
    the best is still to come (I hope) …
    but more phase 3 trials are needed (😉)
Highlights ASCO 2011

• Advanced NSCLC
  - EGFR-TKI in 1st line treatment
  - Maintenance treatment with pemetrexed or EGFR-TKI
  - 2nd line treatment options with EGFR-TKIs

• Local and locally advanced NSCLC
  - PET-CT for radiotherapy planning
  - Adjuvant cisplatin + pemetrexed

• SCLC

• Mesothelioma
Randomized trial of PET/CT vs CT for RT treatment planning in stage III NSCLC

- Planning of RT with PET-CT results in significant improvement of OS. This is most likely due to more accurate staging resulting in stage-appropriate treatment.
- SUV and clinical stage are strong predictors of OS.

<table>
<thead>
<tr>
<th></th>
<th>PET-CT</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>152</td>
<td>158</td>
</tr>
<tr>
<td>Median OS</td>
<td>20m</td>
<td>16m</td>
</tr>
<tr>
<td>2-yr OS</td>
<td>47%</td>
<td>39%</td>
</tr>
</tbody>
</table>
Cis+Pem vs Cis+VRB as adjuvant CT

Inclusion criteria:
- Completely resected stage IB, IIA, IIB and T3N1M0 NSCLC
- PS 0-1

Primary endpoint: “clinical feasibility” defined as
- no death AND
- no non-acceptance by patients leading to premature withdrawal
- no observation of DLT
  - neutropenia or thrombocytopenia grade 4 for >7d
  - Neutropenia grade 3/4 with fever/infection
  - thrombocytopenia with bleeding
  - non-hematological toxicity grade 3/4 related to chemotherapy

Cisplatin 50 mg/m² d1+8
Vinorelbine 25 mg/m² weekly every 4 weeks for 4 cycles

Cisplatin 75 mg/m² d1
Pemetrexed 500 mg/m² d1 every 3 weeks for 4 cycles

N=132
Cis+Pem vs Cis+VRB as adjuvant CT

Author’s conclusions:
• Cisplatin + Pememetrexed is safe and feasible
  - has less toxicity compared to Cis+Vrb
  - has superior dose delivery compared to Cis+Vrb
  - high dose density

Cis+Pem vs Cis+VRB as adjuvant CT

In the **FLEX**-trial:
- **Vb**: 25 mg/m² d1+8
- **Cis**: 80 mg/m² d1
  every 3 weeks

→ **Vb**: 200 & **C**: 320 !!

<table>
<thead>
<tr>
<th>Planned cumulative dose p.p. (mg/m²)</th>
<th>CVb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment interval / duration p.p. (weeks)</td>
<td></td>
</tr>
<tr>
<td>Application schedule Px / Vb p.p.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of patients receiving treatment p.p. (%)</th>
<th>CVb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>74.6</td>
</tr>
<tr>
<td>(95%-CI 62.5-84.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose delivery % planned</th>
<th>CVb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Px: 90</td>
<td></td>
</tr>
<tr>
<td>C: 90</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean doses (mg/m² [range])</th>
<th>CVb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Px: 1810 [500-2000]</td>
<td></td>
</tr>
<tr>
<td>C: 271 [75-300]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean dose density (mg/m²/week [range])</th>
<th>CVb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vb: 16 [2-25]</td>
<td></td>
</tr>
<tr>
<td>C: 16 [3-25]</td>
<td></td>
</tr>
</tbody>
</table>

Vb: 25 mg/m² d1+8
→ Vb planned dose density of 16.6 mg/m²/wk!!
Highlights ASCO 2011

• Advanced NSCLC
  - EGFR-TKI in 1\textsuperscript{st} line treatment
  - Maintenance treatment with pemetrexed or EGFR-TKI
  - 2\textsuperscript{nd} line treatment options with EGFR-TKIs

• Local and locally advanced NSCLC
  - PET-CT for radiotherapy planning
  - Adjuvant cisplatin + pemetrexed

• SCLC

• Mesothelioma
Phase III: amrubicin vs topotecan as second-line treatment for SCLC

- ORR: 31.1% vs 16.9% (p=0.001)
- OS in refractory patients: 6.2 vs 5.7 months (HR 0.77, p=0.047)
- Grade 3/4 AEs in amrubicin vs topo (all p<0.05)
  - Infection (16% vs 10%)
  - Febrile neutropenia (10% vs 4%)

<table>
<thead>
<tr>
<th></th>
<th>Amrubicin</th>
<th>Topotecan</th>
<th>HR</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/Events</td>
<td>424/336</td>
<td>213/175</td>
<td>0.880</td>
<td>0.1701</td>
</tr>
<tr>
<td>Median OS</td>
<td>7.5</td>
<td>7.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>6.8–8.5</td>
<td>6.6–8.5</td>
<td>0.733–1.057</td>
<td></td>
</tr>
</tbody>
</table>
COCIS individual patient data meta-analysis: Carbo vs Cis as 1st line treatment of SCLC

- Study objective
  - To compare the efficacy of cisplatin- vs carboplatin-based CT for the first-line treatment of SCLC

- Key results
  - Four eligible trials were included with a total of 663 patients
  - Median OS was 9.6 m with cisplatin and 9.4 m with carboplatin (HR 1.08; p = 0.69)
  - No evidence of treatment difference according to gender, stage, PS or age
  - Haematological toxicity was higher with carboplatin, and non-haematological toxicity was higher with cisplatin

- Key conclusions
  - COCIS is the first IPD meta-analysis in the treatment of poor prognosis and/or extensive stage SCLC
  - There appears to be no survival difference between cisplatin- and carboplatin-based CT in this setting
Phase III of thalidomide vs observation as maintenance in mesothelioma

- **Study objective**
  - To determine if thalidomide as maintenance therapy improves PFS in patients with MPM who have not progressed following initial therapy with pemetrexed/carboplatin or cisplatin

- **Results**
  - No difference in efficacy between study arms: TTP HR: 1.0 (0.7-1.2; p=0.71); OS HR 1.2 (0.9-1.6; p=0.30)
  - No obvious difference in post-study treatments between treatment arms

- **Conclusions**
  - Thalidomide as switch maintenance therapy in MPM is not effective
Highlights ASCO 2011

• It’s better to have an advanced (non-squamous) NSCLC than an advanced SCLC or a malignant mesothelioma