Treatment of EGFR-Mutation+ NSCLC in 1st- and 2nd-Line

Martin Reck
David F. Heigener
Department of Thoracic Oncology
Hospital Grosshansdorf
Germany

Identification of driver mutation in tumor specimens from 1000 patients with lung adenocarcinoma: The Lung Cancer Mutation Consortium (LCMC)

Kris MG et al., ASCO 2011, #CRA7506
Importance of EGFR mutations

- Tumours with these mutations have been shown to be highly responsive to EGFR TKIs.
- In the case of EGFR, exon 19 deletions for example, lead to the expression of an EGFR protein that is permanently addicted to signal transduction, even in the absence of stimulating ligands.

Somatic mutations in EGFR

Located in TK domain, exon 19 and 21 most common

- 46% Exon 19 deletions
- 40% L858R substitution
- 9% Codon 719 variants
- 2% Other variants
- 9% Exon 20 variants
- 3% Exon 20 variants
- 3% Other variants

TKIs = tyrosine-kinase inhibitors

2. Faber, et al. PNAS 2009

Paez et al 2004; Sequist et al 2007
Clinical characteristics do not completely predict EGFR mutation status

Spanish Lung Cancer Group trial in advanced NSCLC patients with EGFR mutations (n=350)\(^1\)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Smoking status</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Never smoker</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>30</td>
<td>26</td>
<td>9</td>
</tr>
</tbody>
</table>

Significant segment of EGFR M+ population fall outside typical subgroups

BAC, bronchioloalveolar carcinoma

\(^1\)Rosell et al 2009

IPASS

Patients
- Chemo-naive
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIIB / IV disease

Endpoints
- Primary
  - PFS (non-inferiority)
- Secondary
  - Objective response rate (ORR)
  - Overall survival (OS)
  - Quality of life (QoL)
  - 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/m\(^2\))

3 weekly\(^\dagger\)

End of cycle 6

\(^*\)Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; \(^\dagger\)limited to a maximum of 6 cycles

Carboplatin / paclitaxel was offered to gefitinib patients upon progression

PS, performance status; PFS, progression-free survival

Mok et al 2009
PFS survival in EGFR M+ and M- patients

EGFR M+

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carboplatin / paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>132</td>
<td>129</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.48 (0.36, 0.64)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Median (m)</td>
<td>9.5</td>
<td>6.3</td>
</tr>
</tbody>
</table>

EGFR M-

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carboplatin / paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>91</td>
<td>85</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>2.85 (2.05, 3.68)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Median (m)</td>
<td>1.5</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Probability of PFS

Mok et al 2009

Primary Cox analysis with covariates, intent-to-treat (ITT) population

Hazard ratio (HR) <1 implies a lower risk of progression on gefitinib

PFS and ORR with first-line gefitinib versus doublet chemotherapy in EGFR mutation-positive Asian patients across three Phase III studies

<table>
<thead>
<tr>
<th>Study</th>
<th>ORR %</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS</td>
<td>Gefitinib (n=132)</td>
<td>71.2</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>C / P (n=129)</td>
<td>47.3</td>
<td></td>
</tr>
<tr>
<td>First-SIGNAL</td>
<td>Gefitinib (n=26)</td>
<td>84.6</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>C / C (n=16)</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>NEJ002</td>
<td>Gefitinib (n=98)</td>
<td>74.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>C / P (n=100)</td>
<td>29.0</td>
<td></td>
</tr>
</tbody>
</table>

Mok et al 2009; Lee et al 2009; Kobayashi et al 2009
Randomized trials with erlotinib in EGFR mutant patients

- PFS probability
- Erlotinib (n=86)
- Chemotherapy (n=87)

HR=0.37 (0.25–0.54)
Log-rank p<0.0001

Tolerability
IPASS and EURTAC

<table>
<thead>
<tr>
<th>Adverse Event (CTC 3,4)</th>
<th>IPASS</th>
<th>EURTAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>Carbo/Pac</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Rash</td>
<td>3.1%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.8%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3.7%</td>
<td>67.1%</td>
</tr>
<tr>
<td>Febr. Neutrop.</td>
<td>0.2%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.2%</td>
<td>10.6%</td>
</tr>
<tr>
<td>ILD</td>
<td>2.6%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>


Rosell R, ASCO 2011: abstract 7503; Mok T, NEJM 2009
Tolerability
IPASS and EURTAC

<table>
<thead>
<tr>
<th></th>
<th>IPASS</th>
<th>EURTAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gefitinib</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>AEs all grades</td>
<td>95.6%</td>
<td>96%</td>
</tr>
<tr>
<td>Treatment related AEs</td>
<td>88.6%</td>
<td>92%</td>
</tr>
<tr>
<td>Grade 3,4 AEs</td>
<td>17%</td>
<td>45%</td>
</tr>
<tr>
<td>SAE</td>
<td>3.5%</td>
<td>7%</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>4%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Treatment related AEs 88.6% 96.6% 92% 95%
Grade 3,4 AEs 17% 56.7% 45% 81%
SAE 3.5% 9.0% 7% 16%
AE leading to discontinuation 4% 11.4% 5% 14%

Rosell R, ASCO 2011: abstract 7503; Mok T, NEJM 2009

IPASS: HRQoL and symptom improvement by EGFR mutation status

**EGFR mutation positive**
- OR (95% CI) = 2.01 (1.79, 2.07) p<0.001
- OR (95% CI) = 2.91 (2.32, 3.67) p=0.001
- OR (95% CI) = 2.50 (1.55, 6.02) p=0.001

**EGFR mutation negative**
- OR (95% CI) = 0.21 (0.16, 0.61) p=0.002
- OR (95% CI) = 0.33 (0.16, 0.79) p=0.001
- OR (95% CI) = 0.28 (0.14, 0.55) p=0.001

Post hoc analyses, evaluable for quality of life population
p-values are derived from logistic regression analysis with covariates WHO PS, smoking history and gender
HRQoL = health-related quality of life, EQ-5D evaluable for quality of life, FACT-L = functional assessment of cancer therapy - lung, TOI = trial outcome index, LCS = lung cancer subscale

Thongprasert et al 2011
IPASS: time to improvement in HRQoL and symptoms in patients with EGFR mutation positive tumours treated with gefitinib

<table>
<thead>
<tr>
<th></th>
<th>Total FACT-L</th>
<th>TOI</th>
<th>Symptoms by LCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=131</td>
<td>n=131</td>
<td>n=131</td>
</tr>
<tr>
<td>Improved, n (%)</td>
<td>92 (70.2)</td>
<td>92 (70.2)</td>
<td>99 (75.6)</td>
</tr>
<tr>
<td>Median time to</td>
<td>8</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>improvement, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min–max time to</td>
<td>6–209</td>
<td>6–85</td>
<td>6–255</td>
</tr>
<tr>
<td>improvement, days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post hoc calculations performed on patients who improved
Evaluable for quality-of-life population
Thongprasert et al 2011

OPTIMAL Quality-of-life-Analysis: Patients’ QoL was significantly improved

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

Zhou C et al., ASCO 2011, #7520
EGFR-TKI in EGFR-mutant patient
Case report

- 10/07 – 02/08 Chemotherapy + VEGF-Inhibitor
- 02/08 – 10/08 Maintenance
- 10/08 Progression (no symptoms)
- 10/08 – 09/11 Erlotinib
- Skin Rash (Grade 1 – 3, Alopecia, Paronychia)
- Working full time (teacher), active sports
- 47 months (4 years) in good Qul
- Since 03/11 slow progression without symptomatic deterioration

T790M

MET amplification

Source: Engelman JA, Janne PA. Clin Cancer Res.2008;14:2895-9
**BIBW 2992:**  
**Efficacy in EGFR-TKI resistant Cell Lines**

Anchorage-independent growth

<table>
<thead>
<tr>
<th></th>
<th>wild type</th>
<th>H1666</th>
<th>L858R</th>
<th>L858R+T790M</th>
<th>NCI-1975</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC50 [nM]</td>
<td>gefitinib</td>
<td>157</td>
<td>5</td>
<td>&gt;800</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>BIBW 2992</td>
<td>60</td>
<td>0.7</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

Tumor response by BIBW 2992

Resistant NSCLC (Model)  
(EGFR L858R/T790M expression in lung)

![Tumor Volume Comparison](image)

Collaboration with Dr. Kwok Kin Wong (DFCI)

**LUX Lung 1: Design**

**Preselection of Patients**

Patients with:
- Adenocarcinoma of the lung
- Stage IIIB/IV
- Progressed after one or two lines of chemotherapy (incl. one platinum-based regimen) and 312 weeks of treatment with erlotinib or gefitinib
- ECOG 0–2

N=585

Randomization 2:1 (Double Blind)

Oral afatinib 50 mg once daily plus BSC  
Oral placebo once daily plus BSC

Primary endpoint: Overall survival (OS)

Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

- East Asian patients  
  - 58%/56%
- Never smoker  
  - 63%/62%
- Median treatment TKI  
  - 10.2/9.7 m

*Miller V et al, ESMO 2010*
Afatinib + Cetuximab

Phase Ib, open-label, multicenter trial in the US and The Netherlands

NSCLC with EGFR mutation

OR
SD ≥6 months with erlotinib/gefitinib

OR
Partial or complete response to erlotinib/gefitinib

Disease progression

Stop erlotinib/gefitinib for ≥72 hours

Dose escalation schema 3–6 patients per cohort

Afatinib p.o. daily + escalating doses of i.v. cetuximab q 2 weeks

Dose levels starting at:
afatinib 40 mg + cetuximab 250 mg/m²

Predefined maximum dose:
afatinib 40 mg + cetuximab 500 mg/m²

MTD cohort expanded up to 80 EGFR mutation-positive patients:
40 T790M+ and 40 T790M–

1EGFR G719X, exon 19 deletion, L858R, L861Q; 2Progression of disease (Response Evaluation Criteria in Solid Tumors v1.1) on continuous treatment with erlotinib or gefitinib within the last 30 days; 3Amended from original 14-day interval; 4Acquisition of tumor tissue after the emergence of acquired resistance was mandated.
i.v.=intravenous; MTD=maximum tolerated dose; NSCLC=non-small cell lung cancer; SD=stable disease.

Horn L, WCLC 2011

PFS by independent review

• No significant difference in OS (HR 1.08; p=0.74)
• High number of poststudy treatments (68%/79%)

Miller V et al, ESMO 2010
Tumor Regression by T790M Mutation Status at Recommended Dose

Confirmed Response Rate: 35%
Disease Control Rate: 95%

Most Frequent Adverse Events at Recommended Dose

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade ≥3 n (%)</th>
<th>All Grades n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>5 (8)</td>
<td>53 (87)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (5)</td>
<td>40 (66)</td>
</tr>
<tr>
<td>Xerosis</td>
<td>1 (2)</td>
<td>34 (56)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (3)</td>
<td>31 (51)</td>
</tr>
<tr>
<td>Skin fissures</td>
<td></td>
<td>29 (48)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>27 (44)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3)</td>
<td>25 (41)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>1 (2)</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2)</td>
<td>18 (30)</td>
</tr>
</tbody>
</table>
c-MET pathway and c-MET signaling inhibition strategies


Tivantinib (ARQ 197): Phase II study design

Randomized, placebo-controlled, double-blind study

NSCLC
- Inoperable locally adv/metastatic disease
- ≥1 prior chemo (no prior EGFR TKI)

Endpoints
- 1° PFS
- 2° ORR, OS
- Subset analyses
- Crossover: ORR

Erlotinib 150 mg PO QD +
Tivantinib 360 mg PO BID 28-day cycle

Erlotinib 150 mg PO QD +
Placebo PO BID 28-day cycle

BID, twice daily; EGFR, endothelial growth factor receptor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; QD, once daily; TKI, tyrosine kinase inhibitor

Full data will be presented by Dr. Spigel (Session IV)

**Tivantinib (ARQ 197): PFS according to patient sub-group**

Cox proportional hazard ratio analysis of median PFS by patient subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median PFS (95% CI), months</th>
<th>Unadjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>Tivantinib/Erlotinib</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>26/24</td>
<td>3.2 (1.9–4.2)</td>
</tr>
<tr>
<td>Non-squamous cell</td>
<td>58/59</td>
<td>4.4 (3.5–7.3)</td>
</tr>
<tr>
<td>c-MET FISH &gt;4</td>
<td>19/18</td>
<td>3.6 (1.9–5.7)</td>
</tr>
<tr>
<td>c-MET FISH &gt;5</td>
<td>8/11</td>
<td>5.6 (3.8–NE)</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>8/11</td>
<td>5.6 (1.9–7.5)</td>
</tr>
<tr>
<td>EGFR wt</td>
<td>51/48</td>
<td>3.2 (1.9–4.2)</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>10/5</td>
<td>2.3 (1.8–NE)</td>
</tr>
<tr>
<td>KRAS wt</td>
<td>49/45</td>
<td>3.6 (1.9–4.2)</td>
</tr>
</tbody>
</table>

• A PFS benefit associated with tivantinib + erlotinib was observed in patients with tumours harboring amplified c-MET, wild-type EGFR or mutant KRAS

Schiller et al. J Clin Oncol 2010;28:18s (suppl; abstr LBA7002)
**Tivantinib (ARQ 197): Phase III MARQUEE study**

Multicentre, randomized, double-blind, placebo-controlled study

- NSCLC
- Inoperable locally adv/metastatic disease
- Non-squamous histology
- 1–2 prior chemo regimens (no prior EGFR TKI)
- Prior adjuvant/ maintenance therapy allowed

**Randomize**

<table>
<thead>
<tr>
<th>Erlotinib 150 mg PO QD + Tivantinib 360 mg PO BID 28-day cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib 150 mg PO QD + Placebo 28-day cycle</td>
</tr>
</tbody>
</table>

- 1° Endpoint OS (ITT population)
- 2°/Exploratory endpoints:
  - PFS (ITT population)
  - OS and PFS in EGFR WT patients
  - Safety and toxicity
  - QOL/FACT-L
  - Biologic sub-groups

- 988 patients
- Stratify by EGFR and KRAS mutation status
- c-MET status will be assessed by both IHC and FISH
- Interim analysis performed at 50% of events

---

**MetMAb: anti-c-MET antibody**

- **MetMAb**: Unique one-armed monovalent monoclonal antibody designed to prevent HGF-mediated stimulation of pathway
- Preclinical activity across multiple tumor models

---

HGF, hepatocyte growth factor

Phase II: Erlotinib +/- MetMAb in 2\textsuperscript{nd}/3\textsuperscript{rd} line NSCLC

**Key eligibility:**
- Stage IIIb/IV NSCLC
- 2\textsuperscript{nd}/3\textsuperscript{rd}-line NSCLC
- Tissue required
- PS 0–2

\*N=137

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

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

**Stratification factors:**
- Tobacco history
- Performance status
- Histology

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

**Other key objectives:**
- OS in ‘c-MET Diagnostic Positive’ patients
- OS in overall ITT patients
- Overall response rate
- Safety/tolerability

\*128 NSCLC patients enrolled from 3/2009 to 3/2010 plus 9 SCC patients enrolled through 8/2010; Data presented includes >5 additional months of follow-up

Spigel et al. J Clin Oncol 29: 2011 (suppl); Abstract 7505

ITT, intent-to-treat; IV, intravenous; OS, overall survival; PFS, progression-free survival; PS, performance status; SCC, small cell carcinoma

Full data will be presented by Dr. Spigel (Session IV)
MetMAb + erlotinib leads to improved outcomes in both PFS and OS in Met Diagnostic Positive patients

Met DX+

Met DX-

Spigel DR et al., ASCO 2011, #7505

---

c-MET inhibitors under investigation in NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>MoA</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tivantinib</td>
<td>Daiichi Sankyo/</td>
<td>Selective c-MET TKI</td>
<td>III</td>
</tr>
<tr>
<td>(ARQ 197)</td>
<td>ArQule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Exelxis/BMS</td>
<td>Non-selective c-MET,</td>
<td>II</td>
</tr>
<tr>
<td>(XL184)</td>
<td></td>
<td>VEGFR2, RET TKI</td>
<td></td>
</tr>
<tr>
<td>MetMAb</td>
<td>Genentech</td>
<td>Anti-c-MET Ab</td>
<td>II</td>
</tr>
<tr>
<td>AMG102*</td>
<td>Amgen</td>
<td>Anti-HGF Ab</td>
<td>II (RCC, GBM, prostate, others)</td>
</tr>
</tbody>
</table>

*Of potential interest in NSCLC but has yet to be investigated in lung cancer tumour types

Ab, antibody; GBM, glioblastoma multiforme; HGF, hepatocyte growth factor; MoA, mechanism of action; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGFR2, vascular endothelial growth factor receptor 2
Conclusion

• EGFR-Mutation important oncogenic alteration in NSCLC
• Mutation status has to be confirmed
• Improved objective and symptomatic efficacy of EGFR-TKI compared to standard chemotherapy in EGFR mutant tumors
• C-MET Overexpression/Amplification and T790 Mutation potential mechanisms for EGFR-TKI resistance