MANAGEMENT OF EGFR-TKI RESISTANCE
BY LOCAL THERAPY, CHEMOTHERAPY AND ANTIANGIOGENESIS

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Germany
DISCLOSURES

Member of the advisory board: Roche, Lilly, Daichi-Sankyo, BMS, AstraZeneca, Pfizer, Boehringer-Ingelheim

Honoraria for lectures: Roche, Lilly, Daichi-Sankyo, AstraZeneca, BMS, Boehringer-Ingelheim
EGFR-MUTATION
A FASCINATING DEVELOPMENT

- Meaningful clinical and radiologic response from 04/13 to 12/14
- Maintenance of quality of life (full time working)

- ... However most patients progress after 12-14 months
EGFR-RESISTANCE
THE MOLECULAR PERSPECTIVE

Mechanisms of Resistance:
• Acquired resistance mutation (T790M)
• Activation of bypass pathway:
  • MET Amplification
  • KRAS Activation
  • HER2 Upregulation
  • BRAF, CRKL, DAPK, FGF, HER3, IGF, JAK2, MED12, NF-κB, PTEN, PUMA, ROR1, VEGF...
• Impairment of EGFR TKI mediated Apoptosis (BIM modification)
• Histologic transformation (SCLC, EMT)
EGFR-RESISTANCE
THE CLINICAL PERSPECTIVE

- Slow, asymptomatic progression
- Local progression
- Symptomatic progression
EGFR-RESISTANCE
THE CLINICAL PERSPECTIVE

• Slow, asymptomatic progression
• Continuation of EGFR TKI?
ASPIRATION: STUDY DESIGN

- Inclusion criteria: patients ≥18 years with confirmed stage IV or recurrent NSCLC with exon 18–21 mutations (except T790M) with measurable disease and ECOG PS 0–2

- Exclusion criteria: T790M mutations, prior chemotherapy, prior treatment with anti-HER agents, uncontrolled systemic conditions, pre-existing lung conditions, warfarin use

- Primary endpoint: PFS1 (time to RECIST PD or death)

- Secondary endpoints:
  - PFS2 (time to off-erlotinib PD if erlotinib was extended beyond RECIST PD)
  - PFS1 in exon 19 deletion/L858R subsets
  - OS
  - ORR/DCR/BOR
  - safety
ASPIRATION: POST PROGRESSION PFS

In patients receiving post-PD erlotinib (n=93)

- PFS1 was 11.0 months
- the difference between PFS1 and PFS2 was an additional 3.1 months

Survival probability

Progression-free survival time (months)

EGFR-RESISTANCE
THE CLINICAL PERSPECTIVE

• Slow asymptomatic progression ➔ Continuation of TKI
• Local Progression ➔ Local Treatment?
OLIGOPROGRESSIVE DISEASE
CLINICAL EXPERIENCE

• Screening of 204 patients
  • Activating EGFR-mutations
  • Benefit after treatment with EGFR-TKI
• 35 patients (17%): PD in CNS
• 17 patients received radiotherapy of CNS Mets and continuation of EGFR-TKI
• 18 patients were not eligible due to prior radiotherapy, comorbidities, size of CNS mets, poor PS and other reasons.

Shukuya T et al, Lung Cancer 2011
OLIGOPROGRESSIVE DISEASE
CLINICAL EXPERIENCE

Response rate: 41%
DCR: 76%

Median OS: 13.4 m
Median PFS: 2.6 m

Similar data for patients with bone metastasis: PFS 3 m, OS 11m
OLIGOPROGRESSIVE DISEASE
CLINICAL EXPERIENCE

- 65 patients with oligoprogression
  - PD in 38 patients with ALK translocation following crizotinib
  - PD in 27 patients with EGFR mutations following treatment with erlotinib
- Primary PFS (PFS 1):
  - 9.0 months (ALK +)
  - 13.8 months (EGFR +)
- CNS relapse rate
  - 46% (ALK +)
  - 22% (EGFR +)
- Local treatment: Local ablative therapy, standard radiation therapy, stereotactic radiosurgery, whole brain radiotherapy

Weickhart A et al, J Thorac Oncol 2012
OLIGOPROGRESSIVE DISEASE
CLINICAL EXPERIENCE

Weickhart A et al, J Thorac Oncol 2012
MANAGEMENT OF PROGRESSION

• Local Progression ➔ Local Treatment
• Slow asymptomatic progression ➔ Continuation of TKI
• Symptomatic progression?
SYMPTOMATIC PROGRESSION CONCEPTS

- **Switch / Modification of TKI**
- Combination with chemotherapy
- Combination with EGFR Antibody
- Combination with VEGF Antibody
- Combination with immunotherapy?
Patients with:
- Adenocarcinoma of the lung
- Progressed after one or two lines of chemotherapy (incl. one platinum-based regimen) and ≥12 weeks of treatment with erlotinib or gefitinib

Randomization 2:1 (Double Blind)

Oral afatinib 50 mg once daily plus BSC

Oral placebo once daily plus BSC

No significant difference in OS (HR 1.08; p=0.74)
**LUX-LUNG 5**

**Key patient inclusion criteria**
- Stage IIIIB/IV NSCLC
- Failed ≥1 line of chemotherapy and erlotinib/gefitinib
- ECOG PS 0–2 (n=1302)

**Primary endpoint**
- PFS

*Those progressing who had received ≥12 weeks of benefit from afatinib

**Secondary endpoints**
- ORR, OS and safety

**Afatinib 40 mg/day + paclitaxel 80 mg/m²/week (n=134)**

**Afatinib 50 mg/day (n=1154)**

**Single agent investigator’s choice chemotherapy (n=68)**

**Stratification**
- Gender
- Prior duration of EGFR TKI

Schuler et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8019^)
**LUX-LUNG 5**

<table>
<thead>
<tr>
<th>Key results</th>
<th>Afatinib + paclitaxel (n=134)</th>
<th>Investigator choice (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS event, n (%)</td>
<td>105 (78.4)</td>
<td>54 (79.4)</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>5.6</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.60 (0.43, 0.85)</td>
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</table>

**OS**

<table>
<thead>
<tr>
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<th>Investigator choice (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS event, n (%)</td>
<td>100 (74.6)</td>
<td>46 (67.6)</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>12.2</td>
<td>12.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00 (0.70, 1.43)</td>
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</table>

**Conclusion**

PFS (and ORR) were significantly improved with continued afatinib combined with paclitaxel vs CT alone in heavily pretreated patients with acquired resistance to erlotinib/gefinib and progression after afatinib monotherapy.

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Schuler et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8019^)
MAINTAINING ERBB BLOCKADE IN EGFR-MUTATED LUNG CANCER (MARBLE) - AIO-TRK-0114

- NSCLC stage IV (UICC 7)
- *EGFR* mutated
- Progression after 1st line afatinib (≥ 6 months)

Cis-/Carboplatin + Pemetrexed (3-4 cycles) → CR/PR/SD

Trial submitted to German Central Ethic Committee
FPI planned Q2 2015
210 patients required from 30 sides (multinational)

Afatinib 40 mg/d

Pemetrexed 500 mg/m² q21d

PI: Martin Schuler, Essen
SYMPTOMATIC PROGRESSION CONCEPTS

• Switch / Modification of TKI
• **Combination with chemotherapy**
• Combination with EGFR Antibody
• Combination with VEGF Antibody
• Combination with immunotherapy?
THE PHASE III, RANDOMISED IMPRESS STUDY

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

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

*CR/PR ≥4 months or SD >6 months
IMPRESS Trial: Key results

- **Key results**
  - No statistically significant improvement in PFS with continuation of gefitinib; OS in favour of placebo arm but analysis was immature

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib (n=133)</th>
<th>Placebo (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>14.8</td>
<td>17.2</td>
</tr>
<tr>
<td>Number of events, n (%)</td>
<td>50 (37.6)</td>
<td>37 (28.0)</td>
</tr>
<tr>
<td>HR(^a) (95% CI)</td>
<td>1.62 (1.05, 2.52); p=0.029</td>
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<th>Gefitinib (n=133)</th>
<th>Placebo (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Number of events, n (%)</td>
<td>98 (73.7)</td>
<td>107 (81.1)</td>
</tr>
<tr>
<td>HR(^a) (95% CI)</td>
<td>0.86 (0.65, 1.13); p=0.273</td>
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</tr>
</tbody>
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\(^a\)Primary Cox analysis with covariates

Mok et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA2_PR
FASTACT-2 (MO22201; CTONG0902) STUDY DESIGN

<table>
<thead>
<tr>
<th>Screening</th>
<th>Study treatment</th>
<th>Maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated stage IIIB/IV NSCLC, PS 0/1 (n=451)</td>
<td>Gemcitabine 1,250mg/m² (d1, 8) + carboplatin AUC=5 or cisplatin 75mg/m² (d1) + erlotinib 150mg/day (d15–28); q4wks x 6 cycles GC-erlotinib (n=226)</td>
<td>Erlotinib 150mg/day</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine 1,250mg/m² (d1, 8) + carboplatin AUC=5 or cisplatin 75mg/m² (d1) + placebo (d15–28); q4wks x 6 cycles GC-placebo (n=225)</td>
<td>Placebo</td>
</tr>
</tbody>
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1:1; stratified by stage, histology, smoking status and chemo regimen

Primary endpoint: PFS with IRC confirmation

Secondary endpoints: subgroup analyses, OS in all patients and subgroups, ORR, duration of response, TTP, NPR at 16 weeks, safety, QoL

NSCLC = non-small cell lung cancer; PS = performance status; PD = disease progression; AUC = area under the curve; q4wks = every 4 weeks; IRC = independent review committee; OS = overall survival; ORR = objective response rate; TTP = time to progression; NPR = non-progression rate; QoL = quality of life

Wu Y, Lancet Oncology 2013
FASTACT-2
RESULTS

Kaplan-Meier curve of progression-free survival (A) and overall survival (B) in the intention-to-treat population

Med PFS: 7.6 vs 6.0 m (HR 0.57, p < 0.0001)

Med OS: 18.3 vs 15.2 m (HR 0.79, p: 0.042)
FASTACT-2
RESULTS

Median PFS 6.7 vs 5.9 m (HR 0.97, p: 0.85)

Median OS: 14.9 vs 12.2 m (HR 0.77, p: 0.16)

PFS and OS in Patients with EGFR wild-type disease

Wu Y, Lancet Oncology 2013
FASTACT-2
RESULTS

PFS and OS in patients with activating EGFR mutations

Median PFS 16.8 vs 6.9 m (HR 0.25, p<0.0001)
Median OS 31.4 vs 20.6 m (HR 0.48, p: 0.009)

Wu Y, Lancet Oncology 2013
SYMPTOMATIC PROGRESSION CONCEPTS

- Switch / Modification of TKI
- Combination with chemotherapy
- Combination with EGFR Antibody
- Combination with VEGF Antibody
- Combination with immunotherapy?
ANOTHER BENEFIT: COMBINATION OF IRREVERSIBLE EGFR-TKI AND EGFR-ANTIBODY?

Cetuximab resistant T24PR3

Cetuximab Sensitive T24

Quesnelle KM, ClinCancer Res 2011; 17: 5935-44
AFATINIB AND CETUXIMAB: RESULTS

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>Med PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>29%</td>
<td>4.7 m</td>
</tr>
<tr>
<td>T790M+</td>
<td>32%</td>
<td>4.8 m</td>
</tr>
<tr>
<td>T790M-</td>
<td>25%</td>
<td>4.6 m</td>
</tr>
</tbody>
</table>

Janjigian YY, Cancer Discovery 2014
SYMPTOMATIC PROGRESSION CONCEPTS

• Switch / Modification of TKI
• Combination with chemotherapy
• Combination with EGFR Antibody
• Combination with VEGF Antibody
• Combination with immunotherapy?
DUAL BLOCKADE OF KEY SIGNALING PATHWAYS PROVIDES COMPLEMENTARY ANTITUMOR EFFECTS

Anti-EGFR agents inhibit tumor cell growth and block synthesis of angiogenic proteins (e.g., bFGF, VEGF, TGF-α) by tumor cells.

Anti-VEGF agents inhibit the key angiogenic mediator VEGF binding to receptors on the surface of endothelial cells.
ERLOTINIB + BEVACIZUMAB VS ERLOTINIB
STUDY DESIGN

Chemotherapy-naive
Stage IIIIB/IV or postoperative recurrence
Non-squamous NSCLC
Activating EGFR mutations*
   Exon 19 deletion
   Exon 21 L858R
Age ≥20 years
PS 0–1
No brain metastasis

* T790M excluded

Stratification factors:
sex, smoking status, clinical stage, EGFR mutation type

EB combination
Erlotinib 150mg qd + bevacizumab 15mg/kg q3w (n = 75)

E monotherapy
Erlotinib 150mg qd (n = 75)

Primary endpoint:
PFS (RECIST v1.1, independent review)

Secondary endpoints:
OS, tumor response, QoL, safety

Exploratory endpoint:
biomarker assessment

Kato et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8005)
# Objective Tumor Response

<table>
<thead>
<tr>
<th></th>
<th>EB (n = 75)</th>
<th>E (n = 77)</th>
<th>*P value</th>
</tr>
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<tbody>
<tr>
<td>CR</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td>-</td>
</tr>
<tr>
<td>PR</td>
<td>49 (65%)</td>
<td>48 (62%)</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>22 (29%)</td>
<td>19 (25%)</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>0 (0%)</td>
<td>6 (8%)</td>
<td>-</td>
</tr>
<tr>
<td>NE</td>
<td>1 (1%)</td>
<td>3 (4%)</td>
<td>-</td>
</tr>
</tbody>
</table>

### EB Combination

- **Responder (CR or PR)**
- **Non-responder (SD, PD or NE)**

### E Monotherapy

- **Tumor volume change from baseline (%)**

Median duration of response: 13.3 months with EB vs 9.3 months with E

*Fisher’s exact test

ORR: 69% vs 64%, *P* = 0.4951

DCR: 99% vs 88%, *P* = 0.0177
PROGRESSION FREE SURVIVAL
PRIMARY ENDPOINT: PFS BY INDEPENDENT REVIEW

Kato et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8005)
OTHER PHASE II STUDIES OF AN EGFR TKI + BEVACIZUMAB

**RC1126**
- ACCRU [USA]
  - Stage IV NSCLC
  - Non-squamous histology
  - ECOG PS 0–1
    - (n=150)
- Primary endpoint: PFS
- Erlotinib 150mg/day + bevacizumab 15mg/kg i.v. q3w

**BELIEF**
- ETOP [EU]
  - Stage IIIB/IV NSCLC
  - Non-squamous histology
  - ECOG PS 0–2
    - (n=102)
- Primary endpoint: PFS
- Erlotinib 150mg/day + bevacizumab 15mg/kg i.v. q3w
  - Sub-study 1: T790M+ (n=35)
  - Sub-study 2: T790M– (n=67)

**OLCSG 1001**
- OLCSG [JAPAN]
  - Stage IV NSCLC
  - Non-squamous histology
  - ECOG PS 0–2
    - (n=42)
- Primary endpoint: 1-yr PFS rate
- Gefitinib 250mg/day + bevacizumab 15mg/kg i.v. q3w

SYMPTOMATIC PROGRESSION CONCEPTS

- Switch / Modification of TKI
- Combination with chemotherapy
- Combination with EGFR Antibody
- Combination with VEGF Antibody
- Combination with immunotherapy?
PD-1 INHIBITION + EGFR-TKI IN EGFR MUTANT PATIENTS?

- 21 Patients (20 patients refractory after previous EGFR TKI)
- 7 Patients T790M mutation
- RR 19%
- PFS-Rate 24w: 51%, med PFS: 29.4 w
- 1-year OS: 73%
- Option for patients without T790M mutation?

Chemotherapy-naïve patients with stage IIIb or IV NSCLC (non-squamous; EGFR MT) \( ^a \) → Nivolumab 3 mg/kg IV Q2W + erlotinib 150 mg/day PO until disease progression or unacceptable toxicity → Primary objective: safety and tolerability
Secondary objectives: ORR and 24-wk PFS rate

Rizvi NA, J Clin Oncol 2014; 32 (suppl 5, Poster 36), Gettinger S, ESMO 2014: abstr 1054PD
CONCLUSION

• Relevant Factors for management of EGFR-TKI resistance:
  • Molecular Background (T790M?)
  • Localization (systemic vs localized progression) (Local therapies)
  • Kinetics (slow vs rapid) (Maintenance of TKI)
• Combination of CT and TKI after PD not superior to CT
• Combination of CT and intercalated TKI in first-line setting of interest
• Further concepts under investigation