Resistance to EGFR TKIs: Irreversible Inhibitors

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EURTAC: Erlotinib significantly improves PFS as first-line treatment for EGFR mutant NSCLC

- Erlotinib provided significant benefit over chemotherapy
  - 63% reduction in risk of progression or death; HR=0.37
  - Median OS for erlotinib vs chemotherapy: 22.9 months vs 18.8 months; P=0.8702
  - OS data are immature and confounded by second-line treatment

Erlotinib (n=86)
Chemotherapy (n=87)
Median PFS
Erlotinib: 9.7 months
Chemotherapy: 5.2 months
HR=0.37 (0.25–0.54); log-rank P<0.0001

ORR= overall response rate; OS= overall survival
Rosell R et al. ASCO 2011; Abstr. 7503
Acquired resistance mechanisms to EGFR-TKIs

- Secondary EGFR mutations: T790M.
- MET amplification.
- HGF high levels.
- Downstream effectors: PTEN loss, PI3K mut.
- Small cell lung cancer (SCLC) transformation.
- Epithelial to Mesenchimal Transition (EMT).
- DRG: BRCA1 mRNA levels.
- FAS and NFKB signalling.
- VEGF/VEGFR.
- IGFR1, IGFBP.
Neratinib (HKI272)

- NSCLC patients with ≥12 weeks of prior TKI therapy were placed in:
  - Arm A, if EGFR mutation positive (91p)
  - Arm B, if EGFR wild-type (48p)
- All patients received daily oral neratinib, initially at 320 mg but subsequently reduced to 240 mg because of excessive diarrhea (50% Grade 3)
- Low activity (PR 3%) in EGFR mut patients with prior benefit from TKIs.
- No responses in EGFRwt and T790M.
- Striking activity in exon 18 G719X +:
  - 3/4 patients with PR.
  - Median PFS 52.7 weeks

Sequist L, J Clin Oncol 2010

Study BR.26: Phase 3 Study in Advanced NSCLC After Failure of Prior Chemotherapy and Prior EGFR-targeted Therapy

**Trial design**
- Randomized, Phase 3, double-blind, placebo-controlled
- Interim (OS)

**Endpoints**
- Primary: OS
- HR: 1.33
- Secondary: PFS, OR, and PROs

**Study sites**
- Global (Canada, Latin America, Australia, Asia, Italy)

**Key entry criteria**
- Prior chemo (1/2) and EGFR
- PS 0–3
- All histologies
- Available tissue (KRAS)

**Randomize**
- Dacomitinib (PF-00299804) 45 mg QD + BSC
- Placebo + BSC

N=720

Interim analysis (N=360 patients, 200 events)
Study 1028: Dacomitinib vs. Erlotinib
Phase 2, Second/Third-Line Post-Chemotherapy

Trial design
Open-label, Phase 2, randomized

Endpoints
Primary: PFS
Secondary: OS, best overall response (RECIST), safety, PRO

Study sites
Global
47 sites
12 countries

Accrual
Nov 08–Oct 09

188 patients
117 KRAS WT
Advanced NSCLC
1/2 prior chemotherapies
ECOG PS 0–2
Tissue available

Stratification:
• Non-smokers vs. smokers
• Adenocarcinoma vs. nonadenocarcinoma
• East Asian vs. non-East Asian

Dacomitinib
45 mg QD

Erlotinib
150 mg QD

1:1

PRO = patient-reported outcomes; ECOG PS = Eastern Cooperative Oncology Group performance status;
RECIST = Response Evaluation Criteria in Solid Tumours

Boyер M, et al. Presented at WCLC 2011; Abstract 745

Study 1028: Dacomitinib vs. Erlotinib
Progression Free Survival – All and KRAS WT

All patients

• Median PFS was 12.4 vs 8.3 weeks
• *HR=0.66 with 2-sided P=0.012

KRAS WT

• Median was 16.1 vs 8.3 weeks
• *HR=0.50 with 2-sided P=0.002

*Based on the stratified log-rank test with EGFR, KRAS and baseline ECOG PS as the stratification factors

ORR² favored dacomitinib vs. erlotinib: 17.0% vs 6.4%, two-sided P=0.04
Clinical benefit (CR + PR + SD ≥ 24 weeks) dacomitinib vs. erlotinib: 29.8% vs 14.9%, two-sided P=0.02

ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease

Study 1028: Dacomitinib vs. Erlotinib
Treatment-Related Adverse Events in ≥10% of Patients

<table>
<thead>
<tr>
<th>Adverse event, (%)</th>
<th>Dacomitinib 45 mg QD (n=93)</th>
<th>Erlotinib 150 mg QD (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3*</td>
<td>Total</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>73</td>
</tr>
<tr>
<td>Dermatitis acneform</td>
<td>11</td>
<td>65</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Paronychia</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Exfoliative rash</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Acne</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>

*Four grade 4 AEs considered to be related to dacomitinib were reported (increased alanine aminotransferase, n=1; increased aspartate aminotransferase, n=1; anemia, n=1; increased blood creatinine, n=1). One grade 4 adverse event (pneumonia) considered to be related to erlotinib was reported. Four grade 5 events occurred during the study: due to pneumonia and pneumonitis (one patient each) on dacomitinib, and pneumonia and pulmonary embolism (one patient each) on erlotinib.

9 patients discontinued due to TRAEs: 7 receiving dacomitinib and 2 receiving erlotinib.

Boyer M, et al. Presented at WCLC 2011; Abstract 745

A Phase 3 Study Of Dacomitinib vs. Erlotinib for the Treatment of Advanced Non-Small Cell Lung Cancer

Trial design: Double blind, randomized, Phase 3, global
Endpoints: Primary: PFS
Secondary: OS*, best overall response (RECIST), safety, PROs
Co-primary patient populations:
- In patients who have previously had at least one (and no more than two) chemotherapy regimen for advanced disease within the two co-primary populations:
  - All patients with advanced NSCLC
  - Patients with NSCLC that is confirmed KRAS WT

*The study is appropriately powered to show difference in OS.
Study 1017: Clinical Activity of Dacomitinib in 1st-Line Advanced NSCLC with an EGFR-Activating Mutation

![Graph showing clinical activity of Dacomitinib](image)

- Exon 19 deletion
- L858R
- Exon 18 and/or 20

n=33/34 evaluable

- All patients with typical EGFR mutations had some degree of tumor shrinkage
- PFS data still maturing; expect 1Q2012 (current 95% CI: 11-19 months)

Mok T, et al. Presented at ESMO 2010; Abstract LBA18

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Dacomitinib (PF-00299804) + Crizotinib (PF-2341066) in EGFR mu Combined MET and EGFR Inhibition

![Graph showing combined MET and EGFR inhibition](image)

Combined MET and EGFR inhibition blocks PI3K/AKT and ERK signaling, and restores sensitivity in vitro and in vivo in dacomitinib-resistant tumors

Phase 1b Study A8081006: Crizotinib + Dacomitinib (PF-00299804) in NSCLC with Resistance to Erlotinib or Gefitinib

NCT01121575

Advanced NSCLC
Escalation cohort
Crizotinib: escalating dose starting at 200 mg BID until MTD + Dacomitinib: escalating dose starting at 30 mg QD until MTD

Expansion cohort 1
Crizotinib BID + Dacomitinib QD at MTD until PD

Expansion cohort 2
Dacomitinib 45 mg QD
Crizotinib BID + Dacomitinib QD at MTD until PD

Advanced NSCLC with acquired resistance* to TKIs

No biopsy
Mandatory entrance tumor biopsy

*Acquired resistance is defined as progression following either an initial response or SD (for at least 6 months) while taking erlotinib or gefitinib. Hypothesis: T790M and/or c-Met are drivers in this population

Trial design
Open-label
Cohort 1: MTD of combination
Cohort 2: Dacomitinib until PD then MTD combination

Endpoints
Primary: Safety, dose-limiting toxicity
Secondary: PK, OR, DR, PFS, biomarkers

Afatinib*: In vitro profile

Afatinib is an irreversible ErbB receptor family blocker

<table>
<thead>
<tr>
<th>Molecular potency</th>
<th>Molecular selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ErbB1 [nM] 0.5</td>
<td>Kinase panel 10 µM 0/50</td>
</tr>
<tr>
<td>ErbB2 [nM] 14</td>
<td>PanLab 10 µM 3/62</td>
</tr>
<tr>
<td>ErbB4 [nM] 1</td>
<td>CYP3A4 50 µM 0/6</td>
</tr>
<tr>
<td>VEGFR2 [nM] &gt;10000</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cellular activity</th>
<th>afatinib</th>
<th>erlotinib</th>
<th>gefitinib</th>
<th>lapatinib</th>
<th>neratinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR - PO4 (A431)</td>
<td>13</td>
<td>5</td>
<td>35</td>
<td>105</td>
<td>22</td>
</tr>
<tr>
<td>H3555 caspase proliferation</td>
<td>0.7</td>
<td>40</td>
<td>5</td>
<td>63</td>
<td>7</td>
</tr>
<tr>
<td>HER2 - PO4 (BT474)</td>
<td>35</td>
<td>930</td>
<td>370</td>
<td>99</td>
<td>77</td>
</tr>
<tr>
<td>BT474 HER2 proliferation</td>
<td>12</td>
<td>829</td>
<td>1070</td>
<td>52</td>
<td>24</td>
</tr>
<tr>
<td>EGFR - PO4 (NCI-H1975)</td>
<td>93</td>
<td>&gt;4000</td>
<td>&gt;4000</td>
<td>&gt;4000</td>
<td>579</td>
</tr>
<tr>
<td>NCI-H1975 caspase proliferation</td>
<td>99</td>
<td>&gt;4000</td>
<td>&gt;4000</td>
<td>&gt;4000</td>
<td>172</td>
</tr>
</tbody>
</table>

**Afatinib (BIBW2992)**

**PRECLINICAL**

Anti-tumor activity of BIBW 2992 in NSCLC H1975 xenografts carrying EGFR L858R/T790M

- NSCLC patients with ≥12 weeks of prior TKI therapy and ≥1 chemo.
- n = 585 patients enrolled.
- Randomized 2:1 to afatinib or placebo.
- RR 7.4% with afatinib.
- PFS 3.3 vs 1.1 months (HR 0.38)

Yang C ASCO 2008
Miller VA ESMO 2010

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**LUX LUNG 1: STUDY DESIGN**

A multicentre, randomized, double-blind Phase II/III trial of afatinib* plus best supportive care (BSC) versus BSC in patients with NSCLC who have progressed after chemotherapy and erlotinib or gefitinib

**Study Population**

- Adenocarcinoma of the lung
- Stage III/IV
- Progressed after one or two lines of chemotherapy (including one platinum-based regimen) and ≥12 weeks of treatment with erlotinib or gefitinib
- ECOG 0–2

N=585

**Randomization**

2:1

- Oral Afatinib* 50 mg once-daily plus BSC
- Oral placebo once-daily plus BSC

Primary endpoint: overall survival
Secondary endpoint: PFS

* BIBW 2992 or Afatinib is an investigational agent, its efficacy and safety have not been established. V Miller, et al. Ann Oncol 2008;21(suppl 8):Abstract LBA1 and presentation
LUX-Lung 1 – PFS by independent review

Hazard ratio (95% CI) = 0.38 (0.306, 0.475)
Log-rank test p-value <0.0001

LUX-Lung 1 – Updated overall survival (primary analysis)

Confounded by an imbalance of subsequent lines of chemotherapy

Placebo: Median 11.7 months
Afatinib: Median 11.0 months
HR=1.001
p=0.502
LUX-Lung 2: Trial design

LUX-Lung 2
A multicentre Phase II, open-label, single-arm trial of afatinib* in patients with NSCLC and EGFR mutation

Patients with:
• Adenocarcinoma of the lung
• Stage IIIb/IV
• EGFR mutation
• Chemo-naïve or progressive disease following first-line chemotherapy
• ECOG PS 0–2

N=120 (planned)

Oral afatinib once-daily
until disease progression or undue toxicity

Response assessment at 4, 8 and 12 weeks; every 8 weeks thereafter

Primary endpoint: Objective response rate (ORR)
Secondary Endpoint: Progression-free survival (PFS), disease control rate (DCR), overall survival (OS)


*This is an investigational agent. Its efficacy and safety have not been established.

LUX-Lung 2 –
Maximum decrease in target lesion size


**LUX-Lung 2 – Progression-free survival**

- Del15: PFS events = 28/52, median PFS = 14.6 months (95% CI: 11.9, NA)
- L858R: PFS events = 29/54, median PFS = 16.6 months (95% CI: 10.1, NA)
- Other: PFS events = 19/23, median PFS = 9.8 months (95% CI: 3.0, 13.1)

**LUX-Lung 2 – Adverse events**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Afatinib* 40 mg (n=30)</th>
<th>Afatinib 50 mg (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3†</td>
<td>All grades</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2 (6.7%)</td>
<td>29 (96.7%)</td>
</tr>
<tr>
<td>Rash/acne</td>
<td>2 (6.7%)</td>
<td>27 (90.0%)</td>
</tr>
<tr>
<td>Nail effect</td>
<td>2 (6.7%)</td>
<td>24 (80.0%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>–</td>
<td>15 (50.0%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>–</td>
<td>14 (46.7%)</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>–</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>–</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (6.7%)</td>
<td>9 (30.0%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>–</td>
<td>8 (26.7%)</td>
</tr>
<tr>
<td>Ocular effect</td>
<td>–</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (3.3%)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>–</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>–</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Lip effects</td>
<td>–</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3.3%)</td>
<td>4 (13.3%)</td>
</tr>
</tbody>
</table>

†This is an investigational agent. Its efficacy and safety have not been established.

‡No Grade 4 or 5 occurred for these events.

*Based on maximum tolerated dose of 90 mg.
A randomized, open-label, Phase III study of Afatinib* compared with chemotherapy as first-line treatment for patients adenocarcinoma of the lung harbouring an EGFR-activating mutation.

Patients with:
- Adenocarcinoma of the lung
- Presence of EGFR mutation in the tumour tissue
- Stage III/IV
- No prior treatment with chemotherapy for advanced/metastatic disease
- No prior treatment with EGFR inhibitors
- ECOG 0 or 1

Randomization

Afatinib* 40 mg orally once daily

Cisplatin+gemcitabine

N=330

Primary endpoint: PFS

Secondary endpoint: ORR

* BIBW 2992 or Afatinib is an investigational agent, its efficacy and safety have not been established.


A randomized, open-label, Phase III Study of afatinib* compared with chemotherapy as first-line treatment for patients with adenocarcinoma of the lung harbouring an EGFR-activating mutation.

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Randomization

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N=330

Primary endpoint: PFS

Secondary endpoint: ORR

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1. LUX-Lung 6: Study Design
NSCLC patients with clinically defined AR (Jackman JCO 2010) received oral afatinib 40 mg daily with escalating dose cohorts of biweekly cetuximab at 250 and 500 mg/m2.

- 47 of 80 patients have been enrolled and received the predefined maximum dose (RP2D):
  - afatinib 40 mg +
  - cetuximab 500 mg/m2)

- Confirmed PRs were observed in 18/45 evaluable patients (40%), including 9/26 PRs in patients with documented T790M mutations.
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>

Overcoming T790M: novel mutant-selective TKI

WZ4002 inhibits EGFR phosphorylation and induces significant tumour regression in murine models of EGFR T790M.

Zhou W et al., Nature 2009
**MET amplification**

- Present in 5-11% of clinical specimens from patients with acquired EGFR-TKI resistance.
- Leads to gefitinib resistance by driving ERBB3-dependent activation of PI3K (Engelman J, Science 2007).
- Inhibition of EGFR signaling induces HGF-mediated clonal selection of pretreatment MET amplification (Turke, Ca Cell 2010).
- MET inhibitors may be able to overcome MET-mediated resistance to EGFR kinase inhibitors, even in cells harboring T790M mutation (Bean J, PNAS 2007).

**HGF mediated-resistance**

- Recently, high-level HGF expression was detected both in tumors with intrinsic (29%) and acquired resistance (61%) (Yano JTO 2011).
- HGF induces gefitinib-resistance by restoring the PI3K/Akt pathway through Gab1, but not EGFR or ErbB3 (Yano, Cancer Res 2008; Turke, Ca Cell 2010).
- Inhibition of EGFR signaling induces HGF-mediated clonal selection of pretreatment MET amplification (Turke, Ca Cell 2010).
- A humanized MAb to HGF, TAK-701, combined with gefitinib, overcome gefitinib resistance induced by HGF in a preclinical model (Okamoto, Mol Ca Cell 2010).
- PI3K/Akt pathway inhibition could overcome HGF-mediated resistance to EGFR-TKIs (Donev IS, CCR 2011).
Treatment for patients resistant to EGFR-TKIs

Conclusions

- There is not a standard treatment for patients resistant to EGFR-TKIs.
- At least one third of the mechanisms of EGFR resistance remain to be defined → we need to re-biopsy patients.
- Irreversible EGFR inhibitors block the growth of NSCLC cell lines harboring T790M mutations, but have failed to demonstrate relevant activity in the clinical setting.
- Irreversible EGFR TKIs may play a role on NSCLC patients w/wo EGFR mutation not previously exposed to reversible TKIs.
- Promising data come from dual EGFR targeting, but must be confirmed in larger, well-defined sets of TKI resistant patients.
- New class of EGFR inhibitors and combination therapies targeting both EGFR signaling and related pathways have shown promising preclinical activity that have to be confirmed in the clinical setting.

Gracias

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