Treatment Options for Patients with EGFRm NSCLC

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Discussion

• Abstract 130O – Efficacy and safety of BI 1482694 (HM61713), an EGFR mutant-specific inhibitor, in T790M-positive NSCLC at the recommended phase II dose – Keunchil Park et al

• 131O - Combination of chemotherapy and gefitinib as first-line treatment of patients with advanced lung adenocarcinoma and sensitive EGFR mutations: A randomised controlled trial - Baohui Han et al
How the *EGFR* Story Has Unfolded in NSCLC

- **1993**: Gefitinib becomes first FDA-approved EGFR TKI for the treatment of NSCLC.
- **2003**: Several studies find *EGFR* mutations in NSCLC patients.
- **2004**: FDA approval of erlotinib in 2nd-line setting.
- **2005**: IPASS trial demonstrates efficacy of gefitinib in patients with *EGFR* mutations.
- **2009**: Gefitinib approved in Europe as 1st-line therapy for *EGFR*-mutant patients.
- **2010**: Gefitinib withdrawn from US market after failure to provide survival benefit in confirmatory trials.
- **2013**: Molecular mechanisms of acquired resistance to EGFR TKIs begin to be unraveled.
- **2014**: FDA approval of osimertinib in 2nd-line setting for *EGFR* T790M-positive patients.
- **2015**: Afatinib FDA-approved for 1st-line treatment of *EGFR*-mutant patients.
- **2015**: FDA approval of gefitinib as 1st-line therapy for *EGFR*-mutant patients.
- **Breakthrough therapy status given to *EGFR* resistance-targeting TKIs rociletinib (CO-1686) and osimertinib (AZD9291).**

Identification of *EGFR* overexpression in lung cancer tissue sparks development of *EGFR*-targeted therapies.
Discussion

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Acquired Resistance to 1st and 2nd generation EGFR TKIs

Multiple Generations of EGFR TKIs

<table>
<thead>
<tr>
<th>Generation</th>
<th>Drug Name</th>
<th>Target(s)</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st generation</td>
<td>Erlotinib</td>
<td>EGFR</td>
<td>reversible</td>
</tr>
<tr>
<td>1st generation</td>
<td>Gefitinib</td>
<td>EGFR</td>
<td>reversible</td>
</tr>
<tr>
<td>2nd generation</td>
<td>Afatinib</td>
<td>EGFR/HER2</td>
<td>irreversible</td>
</tr>
<tr>
<td>2nd generation</td>
<td>Dacomitinib</td>
<td>panHER</td>
<td>irreversible</td>
</tr>
<tr>
<td>3rd generation</td>
<td>Rolecitinib</td>
<td>mutEGFR</td>
<td>irreversible</td>
</tr>
<tr>
<td>3rd generation</td>
<td>AZD9291</td>
<td>mutEGFR</td>
<td>irreversible</td>
</tr>
</tbody>
</table>

Adapted from: Gibbons and Byers et al, Cancer Discov, 2014
AZD9291 mono-anilino-pyrimidine compound, irreversible mutant selective EGFR-TKI

Rociletinib (CO-1686) a 2,4-disubstituted pyrimididine molecule, irreversible mutant-selective EGFR-TKI

HM61713 selective inhibitor for activating EGFR and T790M mutations

EGF816: Covalent, irreversible, EGFR-TKI for EGFR and T790M mutations

ASP8273 Mutant selective irreversible of EGFR and T790M mutations
**BI 1482694 (HM61713) - *In vitro* cell growth inhibition in NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>Inhibition concentration (IC\textsubscript{50}, nM)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>H358</td>
</tr>
<tr>
<td>EGFR WT</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>449</td>
</tr>
<tr>
<td>Afatinib</td>
<td>31</td>
</tr>
<tr>
<td>BI1482694</td>
<td>2,225</td>
</tr>
<tr>
<td>EGFR\textsuperscript{Del19}</td>
<td></td>
</tr>
<tr>
<td>EGFR\textsuperscript{L858R/T790M}</td>
<td></td>
</tr>
</tbody>
</table>

- Oral EGFR mutant-specific TKI
  - Potent and irreversible inhibition of sensitizing (Del19, L858R) and resistance (T790M) EGFR mutations
  - More than 200-fold selectivity over wild-type EGFR
In vitro inhibitory concentrations of EGFR-TKIs

Costa DB et al. TLR 2015;4:809-15

First generation
EGFR TKIs
- gefitinib
- erlotinib

Second generation
EGFR TKIs
- afatinib

Third generation
EGFR TKIs
- AZD9291
- rociletinib

Inhibitory concentration of EGFR TKI
### ORR and tumor shrinkage in T790M+ patients (independent review)

- **Evaluable patients (n=69)**

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Number (Percentage)</th>
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</thead>
<tbody>
<tr>
<td>OR (confirmed and unconfirmed), n (%)</td>
<td>43 (62)</td>
</tr>
<tr>
<td>Disease control, n (%)</td>
<td>63 (91)</td>
</tr>
<tr>
<td>Confirmed OR, n (%)</td>
<td>32 (46)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>31 (45)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>NE, n (%)</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

- **DoR** is immature; in patients with confirmed OR, response duration ranged between 6 and 31 weeks at data cut-off
# Third-generation EGFR TKIs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>DLT</th>
<th>Recommended dose</th>
<th>RR</th>
<th>Toxicity</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>AZD9291</td>
<td>-</td>
<td>80 mg QD</td>
<td>61%</td>
<td>Diarrhea, rash, nausea, ILD, QTc prolongation, decreased appetite</td>
<td>Phase III</td>
</tr>
<tr>
<td>CO-1686</td>
<td>hyperglycemia</td>
<td>500 mg BID</td>
<td>53%</td>
<td>Hyperglycemia, nausea, diarrhea, QTc prolongation, fatigue</td>
<td>Phase III</td>
</tr>
<tr>
<td>EGF816</td>
<td>Rash, acute kidney injury</td>
<td>320 mg once per day (than 240 within trial)</td>
<td>60%</td>
<td>Rash, diarrhea, stomatitis, pruritus</td>
<td>Phase II</td>
</tr>
<tr>
<td>BI1482694/HM 61713</td>
<td>Abdominal pain, diarrhea</td>
<td>800 mg QD</td>
<td>62%</td>
<td>Diarrhea, nausea, dry skin, rash, pruritus</td>
<td>Phase II</td>
</tr>
<tr>
<td>ASP 8273</td>
<td>Diarrhea, nausea, malaise, colitis, biliary tract infection</td>
<td>300 mg QD (MTD 400 mg QD)</td>
<td>67%</td>
<td>Diarrhea, nausea, vomiting, rash (few), ILD, hyponatremia, QTc prolongation</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
**Acquired resistance to rocletinib**

- 12 patients with T790M+ tumors at start of rocletinib
- 13 biopsy samples
- 7 tumors retained T790M at the time of rocletinib resistance
  - 3 tumors gained EGFR amplification
- 6 had loss of T790M at the time of rocletinib resistance
  - Tumors became T790 wild type
  - 2 T790 wild-type tumors has conversion to SCLC histology

**Acquired resistance to AZD9291**

- Study of cell free plasma DNA (cfDNA) from 15 patients with acquired resistance to AZD9291 (all had T790M at the start of AZD9291).
- 6/15 cases: acquired C797S mutation
  - genotype: EGFR exon19 del, T790M, C797S
- 5/15 cases: maintained T790M; no C797S
  - genotype: EGFR exon19 del, T790M
- 4/15 cases: lost T790M mutation
  - genotype: EGFR exon19 del
Sensitivity of different combinations of primary, secondary and tertiary combinations of EGFR mutations

- **T790M⁻**
  - **L718Q⁺**
    - Resistant to third-generation EGFR TKIs
    - Sensitive to AZD9291 (exon 19 deletion only)
    - Sensitive to gefitinib (exon 19 deletion only, not the L858R mutant) and afatinib
  - **L844V⁺**
    - Resistant to WZ4002 and CO-1686
    - Sensitive to gefitinib, afatinib, and AZD9291
  - **C797S⁺**
    - Resistant to third-generation EGFR TKIs
    - Sensitive to gefitinib and afatinib (reduced sensitivity observed for the L858R mutant)

- **T790M⁺**
  - **L718Q⁺**
    - Resistant to all tested EGFR TKIs
    - Partially sensitive to AZD9291 (exon 19 deletion only)
  - **L844V⁺**
    - Sensitive to AZD9291 only
  - **C797S⁺**
    - Resistant to all EGFR TKIs when in cis with T790M
    - Sensitive to first- plus third-generation TKIs when in trans with T790M
    - Partially sensitive to cetuximab

Acquired resistance to *EGFR T790M* specific TKIs
The next issue...New treatment algoorythms?

Ex 19 del

**First gen TKI**

**Second gen TKI**

**Third gen TKI**

First gen TKI

Third gen TKI

Ex 19 del

C797S

First + Third gen TKI

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**EGFR allele**

* Exon 19 deletion

* T790M

* C797S

Multiple third-generation EGFR inhibitors being developed.

- High response rates across the board in first/second generation resistant tumors with T790m.

Optimal sequence of these EGFR inhibitors is currently unknown.

- The presence of specific EGFR resistance mutations to 3rd generation EGFR TKIs will also matter in selecting therapy.
- AEs may dictate use of specific agents in specific clinical contexts.

Will first generation EGFR TKIs be replaced as the first-line treatment in EGFR mutated tumors?

Will these agents be effective in the adjuvant setting?

How will immune therapy play a role in combination with these agents?

What is the prognostic role of these tertiary mutations?
Discussion

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Key features of the study

- **Hypothesis**: Lower TS expression in EGFR mutants and gefitinib down-regulate TS. **Activity of AC in front line when combined with Gefitinib**
- Small phase II randomized East-Asian study (≈ 40 per arm) with some (expected unbalances in demographics)
- DCR inferior for AC
- Data indicate a PFS benefit for AC+G versus G versus AC. OS data not available
- PFS data for del19 indicate a not significant difference between G and G+AC
- Toxicity profile of G versus G+AC pretty similar. No ILD
Down-regulation of TS by Gefitinib in NSCLC

A

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Time (h)</th>
<th>DPD</th>
<th>OPRT</th>
<th>TS</th>
<th>E2F-1</th>
<th>Actin</th>
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<tbody>
<tr>
<td>Mia</td>
<td>0</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Paca-2</td>
<td>0</td>
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<td></td>
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<tr>
<td>H460</td>
<td>0</td>
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<td></td>
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</tr>
<tr>
<td>Ma-53</td>
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<tr>
<td>Ma-1</td>
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</table>

B

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Time (h)</th>
<th>DPD</th>
<th>OPRT</th>
<th>TS</th>
<th>E2F-1</th>
<th>Actin</th>
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<tbody>
<tr>
<td>H460</td>
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<tr>
<td>Ma-1</td>
<td>0</td>
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</tr>
</tbody>
</table>

Graphs showing relative TS mRNA levels over time in H460, Ma-53, and Ma-1 cells treated with Gefitinib (5μM).
Synergistic activity of gefitinib with S-1 through TS down-regulation

A
H460

B
Ma-53

C
Ma-1

- Control
- S-1
- Gefitinib
- S-1 + Gefitinib
How to investigate Pem plus Gefitinib in the clinical setting

- Concurrent Gefitinib and Pemetrexed (as previously done in INTACT and TRIBUTE)
- Intercalating Gefitinib and Pemetrexed (as in the FASTACT trial)
- Pemetrexed followed by Gefitinib (similarly to INFORM trial)
- Adding Pemetrexed at progression
- Confounding Factors: EGFR mutation vs. clinically enriched vs. general population and line of therapy
Docetaxel induces M-phase arrest and apoptosis, enhanced by the anti-cell survival effect of erlotinib.

Erlotinib induces G₁ arrest, which can block the M-phase activity of docetaxel.

## Chemotherapy added to EGFR-TKI

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>N</th>
<th>Primary Endpoint</th>
<th>Patients</th>
<th>Treatment arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP</strong></td>
<td>II</td>
<td>60</td>
<td>PFS</td>
<td>Acquired resistance to Gefitinib</td>
<td>Gefitinib + S-1</td>
</tr>
<tr>
<td>(UMIN000006433)</td>
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<tr>
<td><strong>LOGiK1102</strong></td>
<td>II</td>
<td>80</td>
<td>PFS</td>
<td>Acquired resistance to $2^{nd}$ line~ EGFR-TKI</td>
<td>EGFR-TKI + Singlet chemo</td>
</tr>
<tr>
<td>(UMIN000006976)</td>
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<td></td>
<td>Singlet chemo</td>
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<tr>
<td><strong>JMTO LC12-01</strong></td>
<td>II</td>
<td>60</td>
<td>PFS</td>
<td>$\geq$75 years, Acquired resistance to $1^{st}$ line Gefitinib</td>
<td>Gefitinib + DTX</td>
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<td>(UMIN000007765)</td>
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<td></td>
<td>DTX</td>
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<tr>
<td><strong>LOGiK1105</strong></td>
<td>II</td>
<td>70</td>
<td>PFS</td>
<td>$\geq$70 years, Acquired resistance to $1^{st}$ line Gefitinib</td>
<td>Gefitinib + Singlet chemo</td>
</tr>
<tr>
<td>(UMIN000008027)</td>
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<td>Singlet chemo</td>
</tr>
<tr>
<td><strong>NEJ017</strong></td>
<td>II</td>
<td>100</td>
<td>PFS</td>
<td>$\geq$75 years or PS2, Acquired resistance to $1^{st}$ line EGFR-TKI</td>
<td>EGFR-TKI + DTX or PEM</td>
</tr>
<tr>
<td>(UMIN000008364)</td>
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<td></td>
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<td></td>
<td>DTX or PEM</td>
</tr>
<tr>
<td><strong>IMPRESS</strong></td>
<td>III</td>
<td>250</td>
<td>PFS</td>
<td>Acquired resistance to $1^{st}$ line Gefitinib</td>
<td>Gefitinib + CDDP/PEM</td>
</tr>
<tr>
<td>(NCT01544179)</td>
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<td></td>
<td></td>
<td></td>
<td>CDDP/ PEM</td>
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</table>
### IMPRESS - PFS (primary endpoint; ITT)

#### Graphical Representation

- **Probability of PFS**
- **Time of randomisation (months)**

#### Clinical Findings

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib (n=133)</th>
<th>Placebo (n=132)</th>
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</thead>
<tbody>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td><strong>Number of events, n (%)</strong></td>
<td>98 (73.7)</td>
<td>107 (81.1)</td>
</tr>
<tr>
<td><strong>HR$^a$ (95% CI)</strong></td>
<td>0.86 (0.65, 1.13)</td>
<td></td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.273</td>
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</tr>
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#### Patients at Risk

<table>
<thead>
<tr>
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<th>Gefitinib</th>
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<tr>
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</tr>
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<td>2</td>
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<td>4</td>
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<td>6</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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*Soria JC et al. Lancet Oncol. 2015; 16: 990-98*
Inclusion Criteria:
- Adult patients ≥18 years (≥20 years in Japan and Taiwan)
- Confirmed advanced (Stage IV) or recurrent NS NSCLC
- Activating EGFR mutations
- ECOG PS ≤1
- No prior systemic chemotherapy, immunotherapy, or biological therapy

- **Enrollment period:** February 2012 – August 2013
- **Data cut-off date:** 22 April 2015

- Planned enrollment of 188 patients for 145 PFS events with 70% power to detect an HR=0.79 with a one-sided $\alpha$ level of 0.2
- Tumor samples were collected for biomarker analyses
- Patients were followed up approximately every 90 days (±14 days) after study treatment discontinuation for survival

**Cheng Y. et al. Proc. IASLC 2015 –oral 17.2**
Primary Endpoint: PFS – ITT Population

Subgroup analysis: G+P more active in female, never smokers and Korean vs. others patients

Randomised phase II study of gefitinib + pem/platinum vs. pem/platinum in NS-NSCLC

Gefitinib intercalated on days to 16 of a 3 week cycle
Enrolled and randomized n=117 – PC-G n=58 – PC n=59
Primary end point: non progression rate at 12-weeks (84.5% versus 83.1%, p=0.87)
ORR 50% versus 47.4%
Toxicity: Higher incidence of skin rush in PC-Gefitinib

Phase III study of Pemetrexed /Cisplatin followed by Gefitinib versus Gefitinib Alone in Never Smoker Asians with advanced NS-NSCLC

- NSCLC: Non-squamous histology
- Stage IIIb/IV
- Chemo-naïve (1st line)
- PS: 0-1
- Never smoker or light ex-smoker**
- Unknown, untested, inconclusive EGFR mutation status

N=226

Pemetrexed 500mg/m² + Cisplatin 75mg/m², IV x 6 cycles, Q3W

Gefitinib 250mg/day PO

Primary Endpoint: Superiority in PFS
Assuming HR: 0.68

Phase III study of Pemetrexed /Cisplatin followed by Gefitinib versus Gefitinib Alone in Never Smoker Asians with advanced NS-NSCLC

Second line post-discontinuation therapy in the Gefitinib arm

F

HR (Pem vs Non-Pem): 0.57, 95% CI: 0.29–1.14; p=0.108

Patients at Risk
Pem  33  31  29  25  22  17  13  10  2
Non-Pem 23  20  16  11  9  7  5

Overall Survival (months)

Future Directions & Ongoing Questions

- Although chemo is more effective in EGFR mutants the level of activity is definitively inferior to dedicated targeted therapies
- Is the combination of pemetrexed and gefitinib (or any EGFR TKI) a research priority? No
- A role for chemo (concurrent or intercalated to EGFR TKI) may theoretically exist for Exon21 mutations
- Are the data today presented worth of a phase III study? Not sure