Overcoming Resistance to 1\textsuperscript{st}/2\textsuperscript{nd} Generation EGFR-TKIs and ALK Inhibitors in oncogene-addicted advanced NSCLC

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Disclosure

Honoraria and consultancy fees from AstraZeneca, Boeringher Ingelheim, Roche and Pfizer
Outline

Overcoming Resistance to EGFR-TKIs

Overcoming Resistance to Crizotinib

Conclusion
Overcoming Resistance to EGFR-TKis
## Phase 3 Trials of EGFR-TKIs in M+

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median PFS (mos)</th>
<th>Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TKI</td>
<td>CT</td>
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<tr>
<td>IPASS</td>
<td>261</td>
<td>9.5</td>
<td>6.3</td>
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<tr>
<td>First Signal</td>
<td>42</td>
<td>8.0</td>
<td>6.3</td>
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<tr>
<td>NEJ002</td>
<td>194</td>
<td>10.8</td>
<td>5.4</td>
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<tr>
<td>WJTOG</td>
<td>172</td>
<td>9.2</td>
<td>6.3</td>
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<tr>
<td>OPTIMAL</td>
<td>154</td>
<td>13.1</td>
<td>4.6</td>
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<tr>
<td>EURTAC</td>
<td>174</td>
<td>10.4</td>
<td>5.1</td>
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<tr>
<td>LUX-LUNG 3</td>
<td>345</td>
<td>11.1</td>
<td>6.9</td>
</tr>
<tr>
<td>LUX-LUNG 6</td>
<td>364</td>
<td>11.1</td>
<td>5.6</td>
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</table>
Mechanisms of Resistance

Sequist et al, Sci Transl Med 2011
Repeat Biopsy at progression

GFPC 12-01 study
100 pts - 18 centres
82/100 fit for biopsy - 25% insufficient
Results influenced Rx in 30% of pts

MSKCC study
155 Adeno with acquired resistance
92% re-biopsied - 20% insufficient
T790M (63%), Her 2 Amp (13%), Met Amp (5%),
SCLC (3%)

Tackling T790M mutation
AZD9291

Oral, selective and irreversible inhibitor of EGFR activating mutations and T790M

**Wild Type EGFR**

**EGFRm**

**T790M+**

AZD9291

**Wild Type EGFR**

**EGFRm**

**T790M+**

Early generation EGFR-TKIs preferentially bind the activated EGFR mutant kinase and the wild type EGFR kinase

Planchard et al, TAT 2015. Presentation 010.4
AZD9291 Phase I study (AURA)

Rolling six design

Cohort 1
20 mg
T790M+
T790M-

Cohort 2
40 mg
T790M+
T790M-

Cohort 3
80 mg
T790M+
T790M-

Cohort 4
160 mg
T790M+
T790M-

Cohort 5
240 mg
T790M+

Total N=253

Planchard et al, TAT 2015. Presentation 010.4
AZD9291 Phase I study (AURA)

NO DLTs. NO MTD. RP2D: 80 mg OD

AEs: Mostly G1/2. Commonly Diarrhea/rash
6 cases of pneumonitis-like AEs

<table>
<thead>
<tr>
<th>Anti-tumor Efficacy</th>
<th>T790M pos</th>
<th>T790M neg</th>
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<tbody>
<tr>
<td>ORR (%)</td>
<td>61</td>
<td>21</td>
</tr>
<tr>
<td>DCR (%)</td>
<td>95</td>
<td>61</td>
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<tr>
<td>PFS (mos)</td>
<td>9.6</td>
<td>2.8</td>
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</tbody>
</table>

Median duration of response (80mg): 8.2 mos

Planchard et al, TAT 2015. Presentation 010.4
AZD9291 - Clinical Development

AURA (NCT01802632)
• Phase II extension – further assessment of efficacy and tolerability of AZD9291 80 mg QD in patients with T790M+ NSCLC

AURA 2 (NCT02094261)
• Confirmatory global Phase II – assessment of efficacy and tolerability of AZD9291 80 mg QD in patients with T790M+ NSCLC

AURA 3 (NCT02151981; recruiting)
• Phase III – AZD9291 vs platinum-based doublet chemotherapy in second-line patients with T790M+, advanced/metastatic NSCLC who have progressed following prior therapy with an EGFR-TKI
Rociletinib (CO-1686)

Irreversible (covalent) inhibitor of EGFR activating mutations and T790M

Spares WT EGFR signalling

Potent activity and EGFR pathway blockade in cell lines with activating and T790M EGFR mutations
Rociletinib - TIGER-X Phase I study

Phase 1/2 study, examined 2 formulations and multiple doses/schedules

Therapeutic doses: 900 mg BD (original formulation) or ≥500 mg BD HBr salt tablet (PK optimized formulation). RP2D 650 mg BD.

Early efficacy also in EGFR T790M+
TIGER-X Expansion Phase in T790M+

N=56. 500 mg BD and 625 mg BD dose

RR: 67%, DCR 89%, PFS: 10.4 months

AEs: Hyperglycemia, Nausea, Vomiting, Appetite loss and Fatigue. G3/4 Hyperglycemia: 14%

Hyperglycemia is due to metabolite M502 (reversible inhibitor of IGF1R and IR)

Soria et al, TAT 2015. Presentation 010.3
Anti-tumor activity in T790M-

- RECIST ORR = 42% overall
- RECIST ORR = 50% in patients treated with 625mg BID immediately off prior TKI
- mPFS = 7.5mo
Rociletinib - Clinical Development

**TIGER-X (Ph 2)**
- Single arm – expansion cohorts
- ≥2nd-line mutant EGFR NSCLC, T790M+

**TIGER-1 (Ph 2/3)**
- Randomized rociletinib vs erlotinib
- 1st-line, treatment-naïve

**TIGER-2 (Ph 2)**
- Single-arm
- 2nd-line mutant EGFR NSCLC, T790M+
- Patients progressing on 1st-line EGFR TKI
- Now adding T790M– cohort

**TIGER-3 (Ph 3)**
- Randomized rociletinib vs chemotherapy
- >2nd-line mutant EGFR NSCLC, T790M+ and T790M– (sequential analysis)

Soria et al, TAT 2015. Presentation 010.3
HM61713 - Phase I/II study

Open-label study conducted at 16 centers in Korea

Expansion part 2*
T790M patients who had progression on prior EGFR TKI therapy

Dose escalation part
Progression on at least 2 prior regimens, including EGFR TKI

* Currently ongoing

3+3 design, cohort 1-11 (N=50)
Treatment with HM61713
75-1200 mg/day

Arm A (N=42)
failure of prior TKI within 4 weeks

Arm B (N=41)
failure of prior TKI before 4 weeks or more

Kim et al, TAT 2015. Presentation 010.2
HM61713 - Phase I/II study

Expansion cohort: 83 pts

AEs: Mostly G1/2. Nausea, Skin toxicity, headaches, appetite loss and diarrhea.

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<tr>
<th>Anti-tumor Efficacy</th>
<th>T790M pos</th>
<th>T790M neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>29.2</td>
<td>11.8</td>
</tr>
<tr>
<td>DCR (%)</td>
<td>75</td>
<td>55.9</td>
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<tr>
<td>PFS (wks)</td>
<td>18.9</td>
<td>10</td>
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</table>

Phase 2 part ongoing (800 mg OD)
Overcoming Resistance to Crizotinib
Crizotinib in ALK+ advanced NSCLC

Profile 1014

Profile 1007

Solomon et al. NEJM 2014; Shaw et al NEJM 2013.
Mechanisms of Acquired Resistance

Pharmacological mechanisms → Inadequate drug exposure → Biological mechanisms

Inadequate drug exposure → Alteration of Drug Target
Inadequate drug exposure → Activation of Bypass Tracks
Alteration of Drug Targets (‘ALK-Dominant’ mechanism)

Mutations of ALK Kinase Domain
L1196M - ‘Gatekeeper’

Confer resistance to different ALK-inhibitors:
G1202R, F1174C: Ceritinib
V118L and I1171T: Alectinib

ALK gene amplification
Activation of Bypass Tracks

- EGFR mutation
- Activation of EGFR WT/KIT/HER2 receptors
- KRAS mutation
- Activation of PI3K/AKT/mTOR pathway
- Activation of HSP90 pathway
Next Generation ALK-TKIs
Ceritinib Phase I/II study

Crizotinib-naive (n=83) and pretreated (n=163)

Dose reduction/discontinuation rate: 52.2%/9.4%

FDA Approval in April 2014
EMA conditional approval February 2015
Crizotinib-pretreated pts

<table>
<thead>
<tr>
<th></th>
<th>m DoR (mos)</th>
<th>NE</th>
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<tbody>
<tr>
<td>ORR (%)</td>
<td>55.4</td>
<td>NE</td>
</tr>
<tr>
<td>m DoR (mos)</td>
<td>7.4</td>
<td>NE</td>
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<tr>
<td>PFS (mos)</td>
<td>6.9</td>
<td>NE</td>
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Alectinib Japanese Phase I/II study

Active against L1196M and other ALK Muts
Crizotinib-naive pts (N=70)

No DLTs. RP2D: 300 mg BD.

<table>
<thead>
<tr>
<th>Phase 2 portion (N=46)</th>
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<tbody>
<tr>
<td>ORR (%)</td>
<td>93.5</td>
</tr>
<tr>
<td>m DoT (mos)</td>
<td>14.8</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>NR</td>
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</table>

Mostly mild AEs. G3 AEs:26%

Alectinib US Phase I/II study

Crizotinib-pretreated/intolerant pts (N=47)

RP2D: 600 mg BD.

<table>
<thead>
<tr>
<th>Phase 1 portion (N=44)</th>
<th>ORR (%)</th>
<th>55</th>
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<tbody>
<tr>
<td>CNS mets (n=21)</td>
<td>ORR (%)</td>
<td>52</td>
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</tbody>
</table>

FDA breakthrough-therapy designation

Brigatinib (AP26113) Phase I/II study

Active against ALK Muts, EGFR Mut and T790M
5-arm Phase II. ALK+ NSCLC (N=79)

<table>
<thead>
<tr>
<th></th>
<th>ALKi pre-treated (N=65)</th>
<th>ALKi-naive (N=7)</th>
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<tbody>
<tr>
<td>ORR (%)</td>
<td>69.2</td>
<td>100</td>
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<tr>
<td>m DoR (wks)</td>
<td>48.6</td>
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<tr>
<td>PFS (wks)</td>
<td>56.1</td>
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Brain Metastases: RR 71% (N=10)
AEs: Nausea, fatigue, diarrhea and dyspnea (early onset)

Gettinger et al. ESMO 2014. Abs 5146
Conclusions

Exciting agents in clinical development

Re-biopsy and tumour genotyping is crucial

Rationally designed clinical trials are needed to optimize treatment strategies