Targeted agents in lung cancer: EGFR TKI and beyond

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The Changing Paradigm

Advanced Stage IIIB/IV

Suitable for standard chemotherapy?

Yes

PT-based doublet

PT-based doublet + bevacizumab

Consider TKI as first line

No

First-line

Second/third-line

EGFR TKI: erlotinib, gefitinib
Chemotherapy: docetaxel, pemetrexed, other single agent
Cancer Biomarkers: Clinical application

Indicators of underlying biological process/pathogenesis

Diagnosis
- Detection of early lesions
- Diagnostic markers

Treatment
- Selection of therapy – Personalized medicine

Prognostication
- Progress monitoring
Driver Genes of Lung Adenocarcinoma-2011

東西方人肺癌不同

Caucasians

- Others: 40%
- K-ras: 30%
- EGFR: 10%
- MET: 3-5%
- HER2: 3%
- ALK: 3-5%
- B-raf: 3%

East Asia

- Others: 25%
- EGFR: 50%
- K-ras: 10%
- MET: 4%
- HER2: 3%
- ALK: 5%
- B-raf: 1%

Courtesy of Prof PC Yang, National Taiwan Univ.
## Targeted therapies in NSCLC

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Corresponding drugs</th>
<th>Clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR-TKI</td>
<td>EGFR Mutation at exons 18 - 21</td>
<td>Gefitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erlotinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Afatinib</td>
</tr>
<tr>
<td>Monoclonal-antibody against EGFR</td>
<td>EGFR gene copy number</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>Monoclonal antibody against VEGFR</td>
<td>?</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>EML4-ALK inhibitor</td>
<td>EML4-ALK gene rearrangement</td>
<td>Crizotinib, Ceritinib</td>
</tr>
</tbody>
</table>
Molecular analyses

**EGFR protein expression**
- Immunohistochemistry (IHC)
  - Dako pharmDx kit

**EGFR gene copy number**
- Fluorescent in-situ hybridization (FISH)
  - Abbott/Vysis EGFR/CEP7 probes

**KRAS and EGFR mutations**
- DNA extraction, PCR and sequencing

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**EGFR**
- Length of CA repeat region in intron 1 of *EGFR* gene is inversely proportional to level of EGFR protein expression
  - generally longer in Asians versus non-Asians

**CA-SSR1 polymorphism**
- Sequencing of *EGFR* intron 1 in genomic DNA extracted from whole blood samples

SSR1 = simple sequence repeat 1

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Treatment selection factors

In the past:
- Disease staging (TNM)
- Performance status (PS)

Now and in addition:
- Histology
- Bevacizuman eligibility
- Molecular profiling
## Histological subtypes

<table>
<thead>
<tr>
<th></th>
<th>Adenocarcinoma</th>
<th>Squamous cell carcinoma</th>
<th>Small cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR-TKI</strong></td>
<td>Effective in mutant</td>
<td>Effective in mutant but much less than adenocarcinoma</td>
<td>Ineffective</td>
</tr>
<tr>
<td>e.g. Gefitinib, Erlotinib, Afatinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALK inhibitor</strong></td>
<td>Effective in ALK rearranged tumor</td>
<td>Not enough data</td>
<td>Ineffective</td>
</tr>
<tr>
<td>e.g. Crizotinib, Ceritinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pemetrexed</strong></td>
<td>Effective</td>
<td>Ineffective</td>
<td>Ineffective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gemcitabine</strong></td>
<td>Effective</td>
<td>Effective</td>
<td>Effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VEGF-inhibitor</strong></td>
<td>Effective</td>
<td>Unsafe to use</td>
<td>No data</td>
</tr>
<tr>
<td>e.g. Bevacizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EGFR-TKI as first line treatment
## Summary of first line trial of EGFR-TKI with EGFR mutation

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>N (EGFR mut +)</th>
<th>RR</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mok et al</td>
<td>IPASS</td>
<td>266</td>
<td>71.2% vs 47.3%</td>
<td>9.8 vs 6.4 months</td>
<td>21.6 vs 21.9 months</td>
</tr>
<tr>
<td>Lee et al</td>
<td>First-SIGNAL</td>
<td>42</td>
<td>84.6% vs 37.5%</td>
<td>8.4 vs 6.7 months</td>
<td>30.6 vs 26.5 months</td>
</tr>
<tr>
<td>Mitsudomi et al</td>
<td>WJTOG 3405</td>
<td>86</td>
<td>62.1% vs 32.2%</td>
<td>9.2 vs 6.3 months</td>
<td>Pending</td>
</tr>
<tr>
<td>Maemondo et al</td>
<td>NEJGSG002</td>
<td>114</td>
<td>73.7% vs 30.7%</td>
<td>10.8 vs 5.4 months</td>
<td>30.5 vs 23.6 months</td>
</tr>
<tr>
<td>Zhou et al</td>
<td>OPTIMAL</td>
<td>154</td>
<td>83% vs 36%</td>
<td>13.1 vs 4.6 months</td>
<td>NA</td>
</tr>
<tr>
<td>Rosell et al</td>
<td>EURTAC</td>
<td>135</td>
<td>58% vs 15%</td>
<td>9.7 vs 5.2 months</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Clinical trials with Afatinib in different phases

<table>
<thead>
<tr>
<th></th>
<th>LUX-Lung 1</th>
<th>LUX-Lung 2</th>
<th>LUX-Lung 3</th>
<th>LUX-Lung 4</th>
<th>LUX-Lung 5</th>
<th>LUX-Lung 6</th>
<th>LUX-Lung 7</th>
<th>LUX-Lung 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>Phase IIB/III</td>
<td>Phase II</td>
<td>Phase III</td>
<td>Phase I/II</td>
<td>Phase III</td>
<td>Phase III</td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
<tr>
<td><strong>EGFR status</strong></td>
<td>All</td>
<td>EGFR M+</td>
<td>EGFR M+</td>
<td>All</td>
<td>All</td>
<td>EGFR M+</td>
<td>EGFR M+</td>
<td>Squamous</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>EGFR TKI failures</td>
<td>First/second-line</td>
<td>First-line</td>
<td>EGFR TKI failures</td>
<td>EGFR TKI failures</td>
<td>First-line</td>
<td>First-line H2H</td>
<td>Second-line H2H</td>
</tr>
<tr>
<td><strong>Countries</strong></td>
<td>Global</td>
<td>USA/Taiwan</td>
<td>Global</td>
<td>Japan</td>
<td>Global</td>
<td>Asia</td>
<td>Global</td>
<td>Europe/Korea</td>
</tr>
<tr>
<td><strong># patients (planned)</strong></td>
<td>585</td>
<td>129</td>
<td>330</td>
<td>90</td>
<td>900</td>
<td>364</td>
<td>264</td>
<td>800</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>OS</td>
<td>ORR</td>
<td>PFS</td>
<td>Safety/ORR</td>
<td>OS</td>
<td>PFS</td>
<td>PFS/DCR</td>
<td>PFS</td>
</tr>
<tr>
<td><strong>Timing/status</strong></td>
<td>Complete</td>
<td>Ongoing</td>
<td>Mar 2011</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Further issues to resolve

- How to choose which one in the first line setting?
  Gefitinib, Erlotinib, Afatinib
- Combination with other anti-cancer treatment?
- Treatment beyond progression?
- How to overcome resistance?
Maintenance treatment with EGFR-TKI
FASTACT-2 Study Design

**Screening**

- Previously untreated stage IIIB/IV NSCLC, PS 0/1 (n = 451)

**Study treatment**

- 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)

**Maintenance phase**

- Erlotinib 150mg/day → PD
- Placebo → PD
  - Erlotinib 150mg/day

1:1; stratified by stage, histology, smoking status and chemo regimen

IRC = independent review committee

**EGFR Mutation Status in FASTACT-2**

- **All patients**: 451
- **Tested for EGFR mutation**: 241

**EGFR mutation status**

- **EGFR mutation-positive**: 97
- **EGFR wild type**: 136
- **Single resistance mutation**: *n = 8: one with T790M (received placebo); one with S768I (received placebo); six with exon 20 mutations (two received erlotinib, four received placebo)

210 patients in the study had unknown EGFR mutation status.

Improved Overall Survival Outcomes

OS Benefit Confined to Patients With EGFR Mutations

What to do on disease progression?
Cessation of EGFR TKI upon Progression

<table>
<thead>
<tr>
<th>Changes in tumor on CT and FDG-PET</th>
<th>After stopping gefitinib or erlotinib</th>
<th>After restarting gefitinib or erlotinib</th>
<th>3 wks after adding everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median change in tumor diameter</td>
<td>+9%</td>
<td>-1%</td>
<td>-8%</td>
</tr>
<tr>
<td>Mean change in tumor diameter</td>
<td>+9%</td>
<td>1%</td>
<td>-9%</td>
</tr>
<tr>
<td>Range in change in tumor diameter</td>
<td>-13% to +29%</td>
<td>-14% to +23%</td>
<td>-34% to +15%</td>
</tr>
<tr>
<td>Median change in tumor volume</td>
<td>+50%</td>
<td>-1%</td>
<td>-11%</td>
</tr>
<tr>
<td>Mean change in tumor volume</td>
<td>+61%</td>
<td>-4%</td>
<td>-10%</td>
</tr>
<tr>
<td>Range in change in tumor volume</td>
<td>-4% to +260%</td>
<td>-27% to +15%</td>
<td>-40% to +26%</td>
</tr>
<tr>
<td>Median change in SUV_{max}</td>
<td>+18%</td>
<td>-4%</td>
<td>-18%</td>
</tr>
<tr>
<td>Mean change in SUV_{max}</td>
<td>+23%</td>
<td>-11%</td>
<td>-11%</td>
</tr>
<tr>
<td>Range in change in SUV_{max}</td>
<td>-17% to +87%</td>
<td>-45% to +62%</td>
<td>-39% to +82%</td>
</tr>
</tbody>
</table>
IMPRESS: Chemo or Chemo With Gefitinib at Progression

Advance stage NSCLC with EGFR mutation → Gefitinib → PD by RECIST → Gefitinib + Pem/Platinum, Pem/Platinum

Primary endpoint: PFS

Co-PI: Soria J; Mok T

On disease progression:

- If systemic disease progression involving primary tumor or multiple different sites:
  
  Try to switch to alternative agents, EGFR-TKI or chemotherapy, if options available

- If oligo-metastasis, e.g. solitary brain or bone metastasis:
  
  Try to treat local metastasis and continue with target agents until further PD and alternative agents available
Acquired resistance to EGFR-TKI

1. Previously treated with a single-agent EGFR-TKI
2. Either of the following:
   A. A tumor that harbors a sensitive EGFR mutation (i.e, G719X, exon 19 deletion, L858R, L861Q)
   B. Objective clinical benefit from treatment with an EGFR TKI as defined by either:
      i. Documented PR or CR (RECIST or WHO), or
      ii. Significant and durable (≥ 6 months) clinical benefit (SD) after initiation of EGFR-TKI
3. Systemic PD while on continuous EGFR-TKI within the last 30 days
4. No intervening systemic therapy between cessation of EGFR-TKI and initiation of new therapy

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors

Jackman et al. JCO 2010; Mok JCO 2010
Possible mechanisms of acquired resistance

- EGFR Exon 20 T790M mutation
- c-Met amplification
- Unknown mechanisms

Or

Could they be primary T790M originally present but did not get detected?
## Incidence of primary T790M

<table>
<thead>
<tr>
<th>Study</th>
<th>Technique</th>
<th># cases/# EGFRm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inukai, CR 2006</td>
<td>Sequencing Enriched PCR</td>
<td>1/98 (1%) 4/98 (4%)</td>
</tr>
<tr>
<td>Sequist, JCO 2008</td>
<td>Sequencing</td>
<td>2/34 (6%)</td>
</tr>
<tr>
<td>IPASS, NEJM 2009</td>
<td>SARMS</td>
<td>7/261 (3%)</td>
</tr>
<tr>
<td>Maheswaran, NEJM 2009</td>
<td>SARMS</td>
<td>10/36 (28%)</td>
</tr>
<tr>
<td>Rossell ASCO 2010</td>
<td>Taqman + PNA probe</td>
<td>45/129 (35%)</td>
</tr>
<tr>
<td>Hata, JTO, 2010</td>
<td>PNA-LNA clamp</td>
<td>3/318 (1%)</td>
</tr>
</tbody>
</table>
Difference in PFS Is Partly Attributed to the Pre-existing T790M Mutation

- SLCG: 129 erlotinib treated patients with activated EGFR mutation subjected to Taqman sequencing for exon 20 T790M
- 35% found to have pre-treatment co-existence of T790M mutation
- PFS in T790M +ive: HR 4.35; 1.85-10.17 ($p = 0.001$)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median</th>
<th>95% CI</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T790M positive</td>
<td>45</td>
<td>12</td>
<td>7.6–16.4</td>
<td>0.05(*)</td>
</tr>
<tr>
<td>T790M negative</td>
<td>84</td>
<td>18</td>
<td>14.1–21.9</td>
<td></td>
</tr>
</tbody>
</table>

Rosell R et al. *Proc ASCO* 2010;Abstract 7514.
Study Design

Phase I, open-label, multicentre study of AZD9291 in Asian and Western patients with advanced NSCLC who have documented radiological progression while on prior therapy with an EGFR-TKI

Objectives
1° safety and tolerability in EGFR-TKI-refractory patients
2° Include: Define MTD, safety and tolerability as first-line therapy,* PK, preliminary efficacy

Escalation
Not preselected by T790M status (rolling six design)

Expansion
Preselected by T790M status, n = up to 30, approximately

*Dose escalation based on safety and PK

Cohort 1 20 mg → Cohort 2 40 mg → Cohort 3 80 mg → Cohort 4 160 mg → Cohort 5 240 mg ...

Cohort MTD

T790M+
T790M-
T790M+
T790M-
T790M+
T790M-
T790M+
T790M-
T790M+
T790M-
T790M+
T790M-

*Prior therapy not permissible in this cohort
†Paired biopsy cohort patients with T790M+ tumors, n = up to 12
MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics
NCT01802632, www.clinicaltrials.gov
**In Vitro and In Vivo Activity of AZD9291**

- **AZD9291** is a potent oral, irreversible inhibitor of EGFR that contains EGFR-TKI-sensitising (EGFR+) and resistance mutations (T790M)

- Good potency and high selectivity demonstrated in enzymatic and cellular *in vitro* assays¹

<table>
<thead>
<tr>
<th>Model</th>
<th>WT LoVo cells</th>
<th>EGFR+ PC9 cells</th>
<th>EGFR+/T790M H1975 cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD9291 phospo-EGFR</td>
<td>480</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>IC₅₀ nM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Profound regression in EGFR-mutant tumour models, showing sustainable complete macroscopic tumour response out to at least 200 days

Irreversible EGFR inhibitors
Irreversible pan-HER TKI PF 299804

Patients clinically selected:

* Never-* or former light-smoker†; Asian or KRAS WT non-Asian

OR

Known EGFR mutation

Additional inclusion criteria:

• Adenocarcinoma histology
• Chemotherapy-naïve
• ECOG PS 0/1

Endpoints:

Primary
• PFS rate at 4 months

Secondary:
• PFS
• OS
• ORR
• Safety

Exploratory:
• Serial tissue- and blood-based biomarkers (T790M)

Data cut-off: 28 July 2010

* Never-smoker: <100 cigarettes, cigars, or pipes over lifetime, and none in 12 months
† Former light-smoker: ≤15 years since last cigarette, and less than 10 pack-years of prior cigarette smoking

Mok, et al. ESMO 2010
Activity and Tolerability of Afatinib (BIBW 2992) and Cetuximab in NSCLC Patients with Acquired Resistance to Erlotinib or Gefitinib

Janjigian YY et al.
Proc ASCO 2011;Abstract 7525.
Third Generation EGFR TKI

Erlotinib
Gefitinib

CO1686
WZ4002
Phase I Study on CO1686

Best Response for Target Lesions
T790M Positive Patients: 900 mg BID FB and HBr by Dose

ORR = 64%, to date

ASCO 2014 – Abs #8010: ORR=58% in pts with T790M+ (n=40)

**ALK Pathway**

Translocation

Or

Inversion

**ALK**

**ALK fusion protein**

\[\text{PI3K} \rightarrow \text{STAT3/5} \rightarrow \text{mTOR} \rightarrow \text{S6K} \rightarrow \text{BAD} \rightarrow \text{Cell survival} \]

\[\text{RAS} \rightarrow \text{MEK} \rightarrow \text{ErK} \rightarrow \text{IP3} \rightarrow \text{Tumor cell proliferation} \]

\[\text{PLC-Y} \rightarrow \text{PI2P} \]

*Subcellular localization of the ALK fusion gene, while likely to occur in the cytoplasm, is not confirmed.\(^1,2\)

ALK-Positive NSCLC

ALK translocation in NSCLC \impliesoncogenic activation

- Adenocarcinomas
- Never or light smokers
- Median age 50 years
- No sex differences

ALK rearrangement detection

- FISH dual specific break apart probe
- Immunohistochemistry
- RT-PCR detection
EML4-ALK rearrangement

EML4-ALK rearrangement +  EML4-ALK rearrangement -
EML4-ALK gene rearrangement

ALK IHC -ve  ALK IHC +
Patients with *ALK*-Positive NSCLC Do Not Appear to Respond to EGFR TKIs

<table>
<thead>
<tr>
<th>Platinum-based chemotherapy</th>
<th>ALK (N = 12)</th>
<th>EGFR (N = 8)</th>
<th>WT/WT* (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, %</td>
<td>25</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>TTP, months</td>
<td>9</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EGFR TKI</th>
<th>ALK (N = 10)</th>
<th>EGFR (N = 23)</th>
<th>WT/WT* (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, %</td>
<td>0</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>TTP, months</td>
<td>5</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>

*WT/WT = wild type: no ALK fusion or EGFR mutation*
Tumor Responses to Crizotinib for Patients with ALK-positive NSCLC

Maximum change in tumor size (%)

- Progressive disease
- Stable disease
- Confirmed partial response
- Confirmed complete response

-30%

*Partial response patients with 100% change have non-target disease present

# Crizotinib Studies in ALK-Positive NSCLC

<table>
<thead>
<tr>
<th></th>
<th>PROFILE 1001(^1) (N = 143)</th>
<th>PROFILE 1005(^2) (N = 259)</th>
<th>PROFILE 1007(^3) (N = 172)</th>
<th>PROFILE 1014(^4) (N = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Line of therapy</td>
<td>Any line</td>
<td>2(^\text{nd}) line and beyond</td>
<td>2(^\text{nd}) line</td>
<td>1(^\text{st}) line</td>
</tr>
<tr>
<td>ORR</td>
<td>61%</td>
<td>60%</td>
<td>65%</td>
<td>74%</td>
</tr>
<tr>
<td>PFS, median (months)</td>
<td>9.7</td>
<td>8.1</td>
<td>7.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Survival probability at 12 months</td>
<td>75%</td>
<td>NA</td>
<td>70%</td>
<td>NA</td>
</tr>
</tbody>
</table>

To look for ALK rearrangement

- In EGFR-wildtype NSCLC (Adenocarcinoma or NSCLC-NOS)
- If screened ALK rearranged (preferred) or ALK IHC positive, consider upfront use of Crizotinib
- On disease progression, consider re-biopsy and Ceritinib if available
# Next Generation ALK Inhibitors in Crizotinib Resistance

<table>
<thead>
<tr>
<th>Company</th>
<th>Status</th>
<th>ORR</th>
<th>DR</th>
<th>CNS Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceritinib (LDK378)</td>
<td>Novartis Approved</td>
<td>55%</td>
<td>7.4 months</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(N = 163)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alectinib (CH5424802)</td>
<td>Roche Breakthrough therapy designation</td>
<td>55%</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(N = 44)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Side Effects of Ceritinib

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>50-300 (n = 10)</th>
<th>400 (n = 14)</th>
<th>500 (n = 10)</th>
<th>600 (n = 10)</th>
<th>700 (n = 5)</th>
<th>750 (n = 81)</th>
<th>All patients (N = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5 (50)</td>
<td>10 (71)</td>
<td>9 (90)</td>
<td>10 (100)</td>
<td>5 (100)</td>
<td>67 (83)</td>
<td>106 (82)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (30)</td>
<td>9 (64)</td>
<td>7 (70)</td>
<td>8 (80)</td>
<td>4 (80)</td>
<td>67 (83)</td>
<td>98 (75)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (50)</td>
<td>8 (57)</td>
<td>6 (60)</td>
<td>8 (80)</td>
<td>4 (80)</td>
<td>53 (65)</td>
<td>84 (65)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (30)</td>
<td>5 (36)</td>
<td>4 (40)</td>
<td>8 (80)</td>
<td>0</td>
<td>41 (51)</td>
<td>61 (47)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1 (10)</td>
<td>2 (14)</td>
<td>3 (30)</td>
<td>2 (20)</td>
<td>4 (80)</td>
<td>33 (41)</td>
<td>45 (35)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (10)</td>
<td>3 (21)</td>
<td>3 (30)</td>
<td>4 (40)</td>
<td>2 (40)</td>
<td>29 (36)</td>
<td>42 (32)</td>
</tr>
<tr>
<td>Abdominal pain</td>
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<td>1 (7)</td>
<td>2 (20)</td>
<td>2 (20)</td>
<td>1 (20)</td>
<td>31 (28)</td>
<td>39 (30)</td>
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<tr>
<td>Appetite</td>
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<td>0</td>
<td>3 (30)</td>
<td>4 (40)</td>
<td>3 (60)</td>
<td>26 (32)</td>
<td>38 (29)</td>
</tr>
<tr>
<td>AST increased</td>
<td>1 (10)</td>
<td>3 (21)</td>
<td>2 (20)</td>
<td>2 (20)</td>
<td>3 (60)</td>
<td>22 (27)</td>
<td>33 (25)</td>
</tr>
</tbody>
</table>

Clinical Activity of Alectinib in Crizotinib-Resistant ALK-positive NSCLC

Overall RR 54.5% across all cohorts for all patients

Waterfall plot

% tumor shrinkage

Days on study

Response rate 54.5% all cohorts

<table>
<thead>
<tr>
<th>Dose (mg BID)</th>
<th>300</th>
<th>460</th>
<th>600</th>
<th>760</th>
<th>900</th>
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</thead>
<tbody>
<tr>
<td>RR %</td>
<td>2/7</td>
<td>5/7</td>
<td>7/10</td>
<td>2/7</td>
<td>8/13</td>
</tr>
<tr>
<td></td>
<td>29%</td>
<td>71%</td>
<td>70%</td>
<td>29%</td>
<td>62%</td>
</tr>
</tbody>
</table>

(*) : off study, data cut-off Sept. 12, 2013

Treatment for lung cancer

Non-small cell lung cancer

Early stage → Resection

Locally Advanced → Tests for targets

Chemo±RT ± resection

Advanced

Relapse → Tests for targets

Chemo±RT ± resection

Small cell lung cancer

Limited Stage

Tests for targets

Chemo

Extensive Stage

Chemo±RT

Chemo or targeted therapy
Lung Cancer in Asians

**EGFR mutant**
- TKI responsive
- TKI resistance
- Re-biopsy on progression
- **EGFR, KRAS, EML4-ALK, ROS1**
- Feedback for clinical management +/- prognostication

**EGFR wildtype**
- Activation/addiction to other driving molecular targets or pathways
Future: Immunotherapy
New Hope for Advanced NSCLC

- Several Immune checkpoint blockade inhibitors in clinical trials

- PD-1 inhibitors
  - Nivolumab
  - MK-3475

- PD-L1 inhibitors
  - MPDL3280A
  - MEDI4736

- Anti CTLA-4
  - Ipilimumab

Summary

- Importance of histological tumor typing and molecular profiling
- Upfront EGFR-TKI for EGFR mutant lung tumor, especially in adenocarinosas and NSCLC-NOS
- Systemic chemotherapy +/- bevacizumab is effective for EGFR wildtype tumor
- Evidence for treatment beyond progression till alternative treatment available
- Re-biopsy is always advisable to check for change in tumor histological subtype and repeat molecular profiling
- Look for alternative targets, ALK or ROS1, with which targeted agents are available
Thank you