Targeted Therapies for Advanced NSCLC

Current Clinical Developments

Friday, June 3, 2016

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Learning Objectives

1. Review the molecular pathology of lung cancer and examine its relevance for clinical practice.

2. Outline the safety and efficacy of first-line therapies for advanced NSCLC, including first generation EGFR and ALK inhibitors.

3. Evaluate treatment approaches used to overcome EGFR and ALK resistance in advanced NSCLC, including the safety and efficacy of second- and third-line therapies and recommended molecular testing.

4. Appraise emerging concepts with EGFR TKIs and ALK inhibitors, including their role in adjuvant therapy, combination therapies, and other evolving data.
Looking to the Future with Targeted Therapies in NSCLC
Tony Mok, MD
Li Shu Fan Medical Foundation
Professor of Clinical Oncology
Department of Clinical Oncology
The Chinese University of Hong Kong
Hong Kong, China
Disclosures

• I consult for ACA Biosciences, AstraZeneca, AVEO Oncology/Biodesix, BioMarin, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis Oncology, geneDecode, GlaxoSmithKline, Janssen, Lilly, Merck Serono, MSD, Novartis, Pfizer, Roche/Genentech, SFJ Pharmaceuticals Group, and Vertex

• I am a member of the speakers’ bureaus for Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis Oncology, GlaxoSmithKline, Janssen, Lilly, MSD, Novartis, Pfizer, and Roche/Genentech

• I am a major stock holder in Sanomics Ltd

• I am not on any scientific advisory boards
Looking into the Future
"Those that fail to learn from history, are doomed to repeat it."

Winston Churchill
Looking to Next Five Years Based on History of The Past Five

2011 to 2015  2016  2017 to 2021
### 2011 to 2015

<table>
<thead>
<tr>
<th>MADE IT</th>
<th>DIDN’T MAKE IT</th>
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<tbody>
<tr>
<td>• Crizotinib for ALK positive lung cancer</td>
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</tbody>
</table>
Why didn’t we make it?
Why didn’t we make it?

Overall Survival (Months)

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Placebo (13 events)
Median: not reached
Log-rank test: p=0.8153
HR: 1.09 (95% CI: 0.545, 2.161)

Erlotinib (22 events)
Median: not reached

Number at Risk
Placebo 59 57 56 55 53 51 50 49 48 47 46 44 43 42 41 40 39 38 37 36 35 34 33 32 31 30 29 28 27 26 25 24 23 22 21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
Erlotinib 102 100 94 91 88 85 82 79 76 73 70 67 64 61 58 55 52 49 46 43 40 37 34 31 28 25 22 19 16 13 10 7 4 1 0

RADIANT

EGFR by IHC or FISH

ECOG1505

Overall Survival Probability

START

None

MAGE-A3 expression by IHC

MARGRIT

Primary endpoint: Overall survival

Median OS

L-BLP25 (N=829) 25.6 mo
Placebo (N=410) 22.3 mo
Adjusted HR 0.88 (95% CI 0.75–1.03) p=0.123*

None
Biomarker-Based Adjuvant Studies
RADIANT EGFRm Subgroup Disease-Free Survival

-placebo (32 events)
Median: 28.5 m

-Erlotinib (39 events)
Median: 46.4 m

Log-rank test: p=0.0391

HR: 0.61 (95% CI: 0.384, 0.981)

The difference is not statistically significant

Number at Risk
Placebo: 59 49 43 35 30 23 15 12 10 5 0 0
Erlotinib: 102 94 80 76 68 56 35 22 10 3 0 0

RADIANT EGFRm Subgroup

Overall Survival

Overall Survival (Months)

Overall Survival Probability

Placebo (13 events)
Median: not reached

Erlotinib (22 events)
Median: not reached

Log-rank test: p=0.8153

HR: 1.09 (95% CI: 0.545, 2.161)

Number at Risk
Placebo 59  57  56  53  51  50  41  30  24  14  5  0
Erlotinib 102 100 94 91 88 86 75 43 26 15 7 0

CTONG1104 Phase III Trial
Adjuvant Gefitinib vs Chemotherapy

Stage II-IIIA (N1-N2) NSCLC with EGFR activating mutation (ADJUVANT)

- EGFR M+ Post-surgical Stage II and Stage III A NSCLC
- 1:1 randomization
- Adjuvant gefitinib (24 months)
- Adjuvant vinorelbine plus platinum chemotherapy (4 cycles)

FPI: Sept 15, 2011

- Sample size was estimated to be 220 when HR of DFS; the primary endpoint was estimated to be 0.6; the enrollment period was to be 2 years; the period of follow-up after the final enrollment was to be 5 years; statistically significant level (α) was to be 0.05; the statistical power was to be 80%; the estimated total events is 122 from 208 analysed patients.

24 sites, 41 patients randomized (2012/9)
Gefitinib for Mutation+ Lung Cancer as Adjuvant Chemotherapy

(A randomized phase III trial of adjuvant gefitinib versus cisplatin and vinorelbine in completely resected (stage II-III) NSCLC patients with mutated EGFR)

Assumptions:
- DFS for chemo 28 months
- HR=0.65
- Alpha=0.0025(one sided), beta=0.2
- Necessary DFS events=169
- Registration 3y, f/u 5y
- Sample size=217

Patients
- Completely resected, stage II-III NSCLC
- EGFR mutation (exon 19 del or L858R)
- NO T790M

CDDP/VNR
- Median PFS=28 months
- Median DFS=43 months
- HR=0.65

Endpoints
- 1° Disease free survival
- 2° OS Safety
- Recurrence Pattern

Potential problems with both studies:
1. DFS as primary endpoint
2. Not powered for overall survival
3. Duration of exposure to TKI at 2 years

Gefitinib
- 250 mg/day for 2 years
- N=115

Vinorelbine
- 25 mg/m² d1, 8
- q3 weeks X 4 courses
- N=115

Off study
- No mutation

PI: Hitohito Tada, MD
ALCHEMIST-Screening Study

**Trial Schema**

Trials conducted at sites in the NCI Clinical Trials Networks: NCTN & NCORP

Non-squamous NSCLC (n=6000 to 8000 pts)

Clinical/Pathologic Stage IB (≥4cm), II, IIIA

Post-Op cohort with negative surgical margins

**Pre-op cohort**

**Post-op cohort**

Complete resection + standard adj therapy per treating physician

Central EGFR & ALK genotyping

**FFPE tissue & blood specimen**

EGFR-mutation:
Phase III trial of erlotinib vs placebo x 2 years (n=410) after any adj tx

ALK-rearranged:
Phase III trial of crizotinib vs placebo x 2 years (n=360) after any adj tx

Without Molecular Alterations: Followed q6 months x 5 years after any adj tx

FFPE tissue from biopsy done at recurrence

Advanced genomics at the NCI
Resected NSCLC tissue tested on ALCHEMIST Screening Trial

Patients with tumors with an EGFR mutation

RANDOMIZE

Erlotinib
150 mg po BID x 2 years

Placebo
po BID x 2 years

1 cycle = 21 days

Long Term Follow-up

Long Term Follow-up

Primary endpoint is overall survival
Resected NSCLC tissue tested on ALCHEMIST Screening Trial

 Patients with tumors with an ALK re-arrangement

Randomize

1 cycle = 21 days

Crizotinib 250 mg po BID x 2 years

Placebo po BID x 2 years

Accrual has been slow!!

Primary endpoint is overall survival
ADAURA Phase III Trial

Osimertinib vs Placebo

- Stage IB-IIIA
- Primary NSCLC
- EGFR mutation positive including the atypical mutations
- WHO PS0,1
- Completed resection and adjuvant chemotherapy

- Primary endpoint: disease-free survival (DFS)
- Secondary endpoints: OS, DFS and OS in patients with del19/L858R

ClinicalTrials.gov Identifier: NCT02511106.
# 2011 to 2015

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<tr>
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<tr>
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</table>
What is the reason(s) for success?

- Specific biomarker selection
- Expanded phase I program

Should we combine EGFR/ALK TKI with other agent(s)?
Potential Combination(s)

- EGFR/ALK TKI
- Antiangiogenesis
- Chemotherapy
- Immunotherapy
Potential Combination(s)

- EGFR/ALK TKI
- Antiangiogenesis
- Chemotherapy
- Immunotherapy
JO25567 Phase II Trial
Erlotinib +/- Bevacizumab

Assessed for eligibility

Randomized ($N=154$)

EB combination ($N=77$)
Withdrawn before treatment started:
Thrombosis: 1
Pleural effusion: 1

Received EB and eligible for analysis ($N=75$)

E monotherapy ($N=77$)

Received E and eligible for analysis ($N=77$)

JO25567 Phase II Trial
PFS by Independent Review

Median (months)

<table>
<thead>
<tr>
<th></th>
<th>EB</th>
<th>E</th>
</tr>
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<tbody>
<tr>
<td>HR</td>
<td>0.54 (95% CI, 0.36–0.79)</td>
<td></td>
</tr>
<tr>
<td>P value*</td>
<td>.0015</td>
<td></td>
</tr>
</tbody>
</table>

*log-rank test, two-sided

NEJ026 Phase III Trial
Erlotinib +/- Bevacizumab

Non-sq NSCLC
Previously untreated
Age 20 or above
EGFR M+ N=214

Erlotinib + Bevacizumab

Primary endpoint: PFS
Secondary endpoint: OS, RR, Safety

Erlotinib

Recommend Pem/Platinum

Recommend Pem/Platinum + Bevacizumab
RELAY Phase III Trial
Erlotinib +/- Ramucirumab

- Age >18
- Stage IV NSCLC
- EGFR exon 19/21 +ive
- T790m -ive
- Measurable disease

N=462

Started in May 2015

Ramucirumab 10 mg/kg every 2 wks + Erlotinib 150 mg daily
Placebo + Erlotinib 150 mg daily

Primary endpoint: PFS
Potential Combination(s)

- EGFR/ALK TKI
- Antiangiogenesis
- Chemotherapy
- Immunotherapy
FASTACT-2 Phase III Trial
*Intercalated Chemotherapy and Erlotinib*

Stage IIIIB/IV untreated NSCLC

**EGFR Mutation**

**EGFR Wild Type**

JMIT 05 Phase II East-Asian Trial
Gefitinib +/- Pemetrexed

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 α 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

JMIT 05 Phase II East-Asian Trial

**PFS (Primary End Point)**

Significantly prolonged median PFS in the gefitinib + pemetrexed arm (15.8 months) vs the gefitinib arm (10.9 months)

- **Median PFS, months (95% CI)**
  - Gefitinib + Pemetrexed: 15.8 (12.6, 18.3)
  - Gefitinib: 10.9 (9.7, 13.9)

- **Adjusted HR**: 0.68 (0.48, 0.96)
- **Adjusted P-value**: 1-sided=0.01; 2-sided=0.03

**Patients at Risk**
- Gefitinib + Pemetrexed: 126
- Gefitinib: 65

---

Gefitinib +/- Pemetrexed/Carboplatin Randomized Phase II Study

Advanced NSCLC
- Adenocarcinoma
- EGFR exon 19/21 mut+
- First-line treatment
- PS 0-1

N=121 patients

Primary endpoint in PFS

Pem/carbo + Gefitinib day 5 to 21 x 6 cycles
- PFS 18.8 month
- RR 83%

Pem/carbo x 6 cycles
- PFS 5.8 months
- RR 33%

Gefitinib
- PFS 12 months
- RR 66%

Is Pemetrexed + Gefitinib better?

Pem/carbo + Gefitinib: Median PFS 16 months

Gefitinib: Median PFS 10 months

Pem/carbo: PFS 6 months
Potential Combination(s)

- Antiangiogenesis
- Chemotherapy
- Immunotherapy
- EGFR/ALK TKI
What can we expect from anti-PD-1/PD-L1 therapy in patients with EGFR/ALK driver oncogenes?
# PD-1/PD-L1 Inhibitors

**MGH Retrospective Analysis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EGFR-Mutant or ALK-Positive (N=26)</th>
<th>EGFR WT or ALK-Negative (N=28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>54.5</td>
<td>64.5</td>
<td>.004</td>
</tr>
<tr>
<td>Range</td>
<td>36-75</td>
<td>52-77</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking History – no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>14 (54)</td>
<td>1 (4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Light (≤10 pack-years)</td>
<td>6 (23)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Heavy (&gt;10 pack-years)</td>
<td>6 (23)</td>
<td>26 (93)</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
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<tr>
<td>Adenocarcinoma</td>
<td>25 (96)</td>
<td>20 (71)</td>
<td>.036</td>
</tr>
<tr>
<td>Squamous</td>
<td>1 (4)</td>
<td>7 (25)</td>
<td></td>
</tr>
<tr>
<td><strong>Molecular Genotype – no. (%)</strong></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EGFR Mutation</td>
<td>20 (77)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ALK Rearrangement</td>
<td>6 (23)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>KRAS Mutation</td>
<td>0 (0)</td>
<td>10 (36)</td>
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</tr>
<tr>
<td>Other/Unknown</td>
<td>0 (0)</td>
<td>18 (64)</td>
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<tr>
<td><strong>Prior Lines of Therapy</strong></td>
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<td>.006</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Range</td>
<td>0-8</td>
<td>0-4</td>
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<tr>
<td><strong>Prior TKIs – no. (%)</strong></td>
<td></td>
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<td>&lt;.001</td>
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<tr>
<td></td>
<td>22 (85)</td>
<td>5 (18)</td>
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<tr>
<td><strong>PD-1 vs. PD-L1 Inhibitors</strong></td>
<td></td>
<td></td>
<td>.358</td>
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<tr>
<td>PD-1 Inhibitors</td>
<td>21 (81)</td>
<td>19 (68)</td>
<td></td>
</tr>
<tr>
<td>PD-L1 Inhibitors</td>
<td>5 (19)</td>
<td>9 (32)</td>
<td></td>
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</tbody>
</table>
PD-1/PD-L1 Inhibitors
Response by Mutation or Smoking Status

Objective Response Rate by Mutation Status

- EGFR-mutant or ALK-positive: 3.8%
- EGFR WT/ALK negative: 25%

$P = 0.052$

Objective Response Rate by Smoking Status

- Never/Light Smokers: 4.5%
- Heavy Smokers: 21.9%

$P = 0.122$
PD-1/PD-L1 Inhibitors

**PFS by Mutation Status**

**Progression-Free Survival**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Median</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>EGFR Mut or ALK+</td>
<td>1.93 months</td>
<td>1.87-2.30 months</td>
</tr>
<tr>
<td>EGFR WT or ALK-</td>
<td>2.20 months</td>
<td>1.93-5.80 months</td>
</tr>
</tbody>
</table>

**Hazard Ratio 0.577**

*P=0.041*

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 26</td>
<td>3 1 1 1 1 1 0</td>
<td></td>
</tr>
<tr>
<td>Group 2 28</td>
<td>10 6 3 3 2 0</td>
<td></td>
</tr>
</tbody>
</table>
**ALK TKI with Immunotherapy**

- **Cohorts**
  - [-1 dose cohort] ceritinib 300 mg daily + nivolumab (3 mg/kg every 2 weeks)
  - [1st dose cohort] ceritinib 450 mg daily + nivolumab (3 mg/kg every 2 weeks) [starting dose level]
  - [2nd dose cohort] ceritinib 600 mg daily + nivolumab (3 mg/kg every 2 weeks)

**Dose-escalation phase**

- **Starting Dose**
  - N=3-6 Ceritinib 300 mg + Nivolumab 3mg/kg

**2nd Dose Level**

- N=3-6 Ceritinib 450 mg + Nivolumab 3mg/kg

**Dose expansion phase**

- N=30 Nivolumab + Ceritinib (at MTD or RDE) ALK inhibitor-treated (ALK inhibitor as last therapy excluding ceritinib)
- N=30 Nivolumab + Ceritinib (at MTD or RDE) ALK inhibitor naïve
TATTON
Multi-Arm Osimertinib Phase IB Trial

Part A – dose escalation
Patient with progression on any EGFR TKI

- Osimertinib + durvalumab (anti-PD-L1 mAb)
- Osimertinib + selumetinib (MEK1/2 inhibitor)
- Osimertinib + savolitinib (MET inhibitor)

Part B – dose expansion

First-line: osimertinib + durvalumab

- T790M-directed EGFR-TKI progressors, cMET negative: osimertinib + selumetinib
- Second-line, cMET negative: osimertinib + selumetinib
- T790M-directed EGFR-TKI progressors, cMET positive: osimertinib + savolitinib
- Second-line, cMET positive: osimertinib + savolitinib

## TATTON Phase IB Trial
### Osimertinib + Durvalumab

<table>
<thead>
<tr>
<th>Characteristic, n</th>
<th>Part A</th>
<th>Part B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Osimertinib 80 mg daily/durvalumab 3 mg/kg every 2 weeks (N=10)</td>
<td>Osimertinib 80 mg daily/durvalumab 10 mg/kg every 2 weeks (N=13)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>3/7</td>
<td>6/7</td>
</tr>
<tr>
<td><strong>Age, median (range), years</strong></td>
<td>67 (46-78)</td>
<td>58 (44-73)</td>
</tr>
<tr>
<td><strong>Treatment location and ethnicity</strong></td>
<td>Asia/USA</td>
<td>Japanese/Asian</td>
</tr>
<tr>
<td></td>
<td>6/4</td>
<td>3/5/1/1</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td>Current/Former/Never/Unknown</td>
<td>0/3/7/0</td>
</tr>
<tr>
<td><strong>Therapy line, median (range)</strong></td>
<td>3.5 (2-10)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td><strong>Immediate prior therapy</strong></td>
<td>Gefitinib/Erlotinib/Afatinib/Other</td>
<td>4/1/3/2</td>
</tr>
<tr>
<td><strong>EGFRm</strong></td>
<td>Ex19 del/L858R/Unknown</td>
<td>6/4/0</td>
</tr>
<tr>
<td><strong>T790M status</strong></td>
<td>Negative/Positive</td>
<td>7/3</td>
</tr>
</tbody>
</table>

## TATTON Phase IB Trial

**Osimertinib + Durvalumab: Toxicity**

<table>
<thead>
<tr>
<th>AE by preferred term, occurring in &gt;3 patients at any dose, n</th>
<th>Part A</th>
<th></th>
<th>Part B</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Osimertinib 80 mg daily/durvalumab 3mg/kg every 2 weeks (N=10)</td>
<td>Osimertinib 80 mg daily/durvalumab 10mg/kg every 2 weeks (N=13)</td>
<td>Osimertinib 80 mg daily/durvalumab 10mg/kg every 2 weeks (N=11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Rash (grouped terms)</td>
<td></td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>ILD (grouped terms)</td>
<td></td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
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<td>3</td>
<td>0</td>
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<tr>
<td>Pyrexia</td>
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<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>7</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Investigator-assessed ORR was 67% (6/9) and 21% (3/14) in patient with T790M positive and T790M negative NSCLC, respectively, and 70% (7/10) in EGFRm treatment-naïve patients.
Long List of Early Trials

- Durvalumab + Gefitinib in EGFR mut+ NSCLC
- Durvalumab + Osimertinib in EGFR mut+ NSCLC [part of TATTON]
- Nivolumab + Erlotinib in EGFR mut+ Erlotinib failure [part of Checkmate 012]
- Nivolumab + Ceritinib in ALK translocated Crizotinib failure
- Atezolizumab + Erlotinib in EGFR mut+ NSCLC
- Atezolizumab + Alectinib in ALK translocated Crizotinib failure
- Pembrolizumab + Rociletinib in EGFR mut+ Erlotinib failure
- Pembrolizumab + Afatinib in EGFR mut+ Pembrolizumab failure
- Pembrolizumab + Crizotinib in ALK translocated NSCLC
- Pembrolizumab + Dabrafenib/Trametinib in KRAS mut+ NSCLC
Looking into the Future
ARCHER 1050 Phase III Study

Dacomitinib vs Gefitinib

Advanced NSCLC
- Adenocarcinoma
- EGFR exon 19/21 mut+
- First-line treatment
- PS 0-1

N=440 patients

Randomize

Dacomitinib
45 mg daily

Gefitinib
250 mg daily

Primary endpoint in
PFS
14.8 vs 9.5 months

Stratification
- Race
- Exon 19 v 21

Completed accrual in March 2015
FLAURA Phase III Study

**Osimertinib vs Gefitinib or Erlotinib**

- **Enrollment** by local* or central# EGFR mutation testing of biopsy sample
- **Stratified by:**
  - Asian/non-Asian
  - Ex19del/L858R

**Randomize patients 1:1**

- Osimertinib (80 mg po daily)
- EGFR-TKI standard of care##:
  - gefitinib (250 mg po daily)
  - erlotinib (150 mg po daily)

**RECIST 1.1 assessment every 6 weeks until objective progressive disease**

- Patients randomized to standard of care may receive AZD9291 after progression §

**Primary objective:** efficacy by PFS

---

*With central laboratory assessment performed for sensitivity
#cobasTM EGFR Mutation Test (Roche Molecular Systems)
##Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation
§Patients randomized to the standard of care treatment arm may receive open-label treatment with AZD9291 on central confirmation
Targeting *EGFR* Mutations

**Future**

Advanced stage NSCLC

*EGFRm* (by tissue or blood)

Gefitinib
Erlotinib+/-Bev
Afatinib
Dacomitinib
Osimertinib

Continue TKI beyond RECIST PD

T790m+
Osimertinib
Rociletinib
HMI 61713

T790m-
Chemo +/- Bev

PD

Anti-C797S Tx

Rebiopsy

? role of ICI
ASCEND-4 Phase III Study
*Ceritinib vs Chemotherapy*

Eligibility criteria:
- 
  - *ALK*-positive locally advanced/metastatic non-squamous NSCLC
  - No prior treatment for advanced disease

Primary endpoint = PFS

- **Ceritinib 750 mg**
  - (N=174)

- **Pemetrexed/cisplatin OR Pemetrexed/carboplatin**
  - every 3 weeks
  - (N=174)

- Pemetrexed every 3 weeks
ALEX Phase III Study
Alectinib vs Crizotinib

Eligibility criteria:
• ALK-positive locally advanced/metastatic NSCLC
• No prior treatment for advanced disease

Primary endpoint = PFS by IRR*

J-ALEX
ASCO 2016

*Closed by IDMC at preplanned interim analysis after primary end-point of PFS met.
Targeting \textit{ALK} Translocations

\textit{Future}

\textbf{Crizotinib/ceritinib/alectinib} 

\textbf{CNS met} 

\textbf{Alectinib/ceritinib if prior crizotinib} 

\textbf{Re-biopsy} 

\textbf{Y} 

\textbf{N} 

\textbf{Others} 

\textbf{G1202R} 

\textbf{Gate-keeper mut} 

\textbf{2nd generation according to sensitivity}

\textbf{Chemo} 

\textbf{Loratinib}
Summary

• Biomarker driven adjuvant studies
  – EGFR: Two Asian studies on DFS, ALCHEMIST study on OS
  – ALK: ALCHEMIST study on OS (slow)

• Combination strategies
  – With anti-angiogenesis: NEJ26
  – With chemotherapy: FASTACTII, pemetrexed/carboplatin
  – With immunotherapy: uncertain efficacy/toxicity

• Second/third generation TKI as first line therapy
  – EGFR: dacomitinib, osimertinib
  – ALK: ceritinib, alectinib
Thank you!

Please visit us at: www.ceconcepts.com