ASCO 2014: Promise and Progress in the Treatment of Lung Cancer

Fadlo Raja Khuri, MD
Professor and Chair
Department of Hematology & Medical Oncology, Deputy Director
Winship Cancer Institute of Emory University
Roberto C. Goizueta Chair in Cancer Research

September 6, 2014
Educational Objectives

- New roles for targeted therapies for early stage disease?
- Consolidation chemotherapy’s last stand in Stage III NSCC?
- Current treatment algorithms for patients with NSCLC with known and unknown driver mutations
- Selecting treatment in patients without an actionable mutation
- Defining the role of prophylactic cranial radiation in small cell lung cancer
The Best Way to Fight Advanced NSCLC Is to Prevent it...Stop Smoking!

*Age-adjusted to 2000 US standard population.
How Much Does Chemotherapy Contribute to Cure in Early Stage NSCLC?

- Stage IB-3%
- Stage II- 10%
- Stage III- 13%

LACE Meta-analysis, Pignon et al, JCO.
RADIANT Trial Design

Tumor samples EGFR IHC+ and/or EGFR FISH+

Stage IB–IIIA NSCLC
Complete surgical resection

No adjuvant chemotherapy
Up to 4 cycles of platinum-based doublet

≤90 d
≤180 d

(N=973) Randomization stratified by: histology, stage, prior adjuvant chemo, EGFR FISH status, smoking status, country

2:1
2-yr treatment period

(n=623) Erlotinib 150mg/day

(n=350) Placebo

Radiology assessment: every 3 months on treatment and yearly during long-term follow up

Primary endpoint: DFS
Secondary endpoints: Overall survival (OS); DFS and OS in patients with del19/L858R (EGFR M+)

Presented by: Dr. Karen Kelly
ASCO 2014
Disease-free Survival KM Plot

Placebo (156 events)
Median: 48.2 m

Erlotinib (254 events)
Median: 50.5 m

Log-rank test: p = 0.3235

HR: 0.90 (95% CI: 0.741, 1.104)
Overall Survival KM Plot

- **Placebo (95 events)**: Median: not reached
- **Erlotinib (182 events)**: Median: not reached

**Log-rank test**: $p=0.3350$

**HR**: 1.13 (95% CI: 0.881, 1.448)

<table>
<thead>
<tr>
<th>Overall Survival (Months)</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>623</td>
</tr>
<tr>
<td>6</td>
<td>586</td>
</tr>
<tr>
<td>12</td>
<td>549</td>
</tr>
<tr>
<td>18</td>
<td>519</td>
</tr>
<tr>
<td>24</td>
<td>489</td>
</tr>
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<td>30</td>
<td>467</td>
</tr>
<tr>
<td>36</td>
<td>412</td>
</tr>
<tr>
<td>42</td>
<td>288</td>
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<td>48</td>
<td>193</td>
</tr>
<tr>
<td>54</td>
<td>118</td>
</tr>
<tr>
<td>60</td>
<td>51</td>
</tr>
<tr>
<td>66</td>
<td>0</td>
</tr>
</tbody>
</table>

Median follow-up duration = 47 months.

**ASCO 2014**

Presented by: Dr. Karen Kelly
Disease-free Survival: *EGFR M+*

- **Placebo** (32 events)
  - Median: 28.5 months
- **Erlotinib** (39 events)
  - Median: 46.4 months

**Log-rank test:** $p = 0.0391$ (not statistically significant due to hierarchical testing)

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

<table>
<thead>
<tr>
<th>Disease-free Survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Placebo (32 events)</td>
</tr>
<tr>
<td>Number at Risk</td>
</tr>
<tr>
<td>Placebo 59 49 43 35 30 23 15 12 10 5 0 0 0</td>
</tr>
<tr>
<td>Erlotinib 102 94 80 76 68 56 35 22 10 3 0 0 0</td>
</tr>
</tbody>
</table>
Overall Survival: EGFR M+

- 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)

<table>
<thead>
<tr>
<th>Overall Survival (Months)</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
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<tr>
<td>18</td>
<td>53</td>
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<tr>
<td>24</td>
<td>51</td>
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<tr>
<td>30</td>
<td>50</td>
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<tr>
<td>36</td>
<td>41</td>
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<tr>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>54</td>
<td>14</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>66</td>
<td>0</td>
</tr>
</tbody>
</table>
SELECT phase II study
Penell et al, ASCO 2014, abstract 7514

- Adjuvant Erlotinib in EGFR mutation +
- 76% 2 yr DFS historical control
- 45% stage I, 27% stage II, 28% stage III
- 2/3 received nearly 2 years of therapy
SELECT results

• 2 year DFS was 89%!
  – Stage I: 96%
  – Stage II: 78%
  – Stage III: 91%

• 29 recurred: only 4 during erlotinib
  – Most who recurred off erlotinib, responded when re-challenged
Questions to consider

- What is the meaning of improved DFS in the absence of OS in the adjuvant setting?

- What level of evidence is required?
  - Is this sufficient?
  - Phase III trials?
## ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification And Sequencing Trial)

Umbrella Protocol Will Screen Patients

<table>
<thead>
<tr>
<th>Trial Category</th>
<th>A151216 ALCHEMIST</th>
<th>E5412</th>
<th>A081105</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Registry/Intervention with biopsy at recurrence</td>
<td>ALK+</td>
<td>EGFR mut</td>
</tr>
<tr>
<td>Prevalence</td>
<td>all comers</td>
<td>~5%</td>
<td>~10%</td>
</tr>
<tr>
<td>Total Sample Size</td>
<td>6000 – 8000</td>
<td>378 (5% inflation)</td>
<td>430 (5% ineligible)</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>N/A</td>
<td>Overall Survival</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>Power</td>
<td>N/A</td>
<td>80%</td>
<td>85%</td>
</tr>
<tr>
<td>One-sided $\alpha$</td>
<td>N/A</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>N/A</td>
<td>0.67</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Decision Tree for Adjuvant Therapy for NSCLC: Utilization of Data to positively impact outcomes

- Personalization of care by histology (pemetrexed and possible bevacizumab) for nonsquamous
- Molecular markers
  - ERCC1, etc, not helpful
  - EGFR and ALK testing critical at the time of surgery
- Support ALCHEMIST by referring and enrolling patients with EGFR and ALK mutation carrying tumors
Locally Advanced NSCLC: Definition

- Stage IIIA
  - Bulky N2 disease
  - Multi-station N2 disease
- Stage IIIB
  - T4 (not including patients with additional nodules in other lobes)
  - N3 disease
  - Supraclavicular lymph node involvement

Approximately 15-20% of NSCLC will fit into the above categories - 150,000 to 200,000 cases each year globally
RTOG 9410: Concurrent vs. Sequential

P-value (log-rank): 0.038

ChemoRT

Cisplatin 50 mg/m² IV d 1, 8, 29, 36
Etoposide 50 mg/m² IV d 1-5 & 29-33
Concurrent RT 59.4 Gy (1.8 Gy/fr)

Stratification Variables:
PS 0-1 vs 2
IIIA vs IIIB
CR vs. non-CR

Randomize

Docetaxel 75 mg/m² q 3 wk × 3
Observation

Hanna et al, J Clin Oncol, 2008
Overall Survival (ITT) Randomized Patients (n=147)

Observation: Median: 24.1 months (18.0-34.2)
3 year survival rate: 27.6%
Docetaxel: Median: 21.5 months (17.0-34.8)
3 year survival rate: 27.2%
P-value: 0.940
Study Design

Multinational, phase III randomized trial

Locally Advanced, Inoperable Stage III NSCLC

Stratified by center, performance

Randomization

CRRT

PD → Off protocol

Consolidation Chemotherapy

4-8 weeks

Observation

Week

Conc Chemoradiotherapy

Consolidation (Weekly DP)

1 2 3 4 5 6 7 8 9

Week 1-4:

Docetaxel

CDDP

TRT

66 Gy/6.5 weeks

Week 5-9:

↑ 20mg/m²

↑ 35mg/m²

Presented by: Keunchil Park, M.D., Ph.D.

Presented By Keunchil Park at 2014 ASCO Annual Meeting
## Compliance of Consolidation Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>CCRT + Consolidation (n=209)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td><strong>Cycle 3</strong></td>
<td></td>
</tr>
<tr>
<td>Day 8</td>
<td>88</td>
</tr>
<tr>
<td>Day 1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cycle 2</strong></td>
<td></td>
</tr>
<tr>
<td>Day 8</td>
<td>21</td>
</tr>
<tr>
<td>Day 1</td>
<td>5</td>
</tr>
<tr>
<td><strong>Cycle 1</strong></td>
<td></td>
</tr>
<tr>
<td>Day 8</td>
<td>15</td>
</tr>
<tr>
<td>Day 1</td>
<td>10</td>
</tr>
<tr>
<td><strong>No consolidation</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>66</td>
</tr>
</tbody>
</table>

Presented by: Keunchil Park, M.D., Ph.D.
Overall Survival

Median follow-up: 50.7 months

Hazard ratio = 0.911
(95% CI, 0.720-1.253)
P = 0.438

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Events</th>
<th>mOS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT alone</td>
<td>209</td>
<td>145</td>
<td>20.63 (17.58, 26.28)</td>
</tr>
<tr>
<td>CCRT + consolidation</td>
<td>211</td>
<td>134</td>
<td>21.78 (17.71, 24.74)</td>
</tr>
</tbody>
</table>
Progression-free Survival

Median follow-up: 50.7 months

Hazard ratio = 0.906
(95% CI, 0.734-1.119)
P = 0.410

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Events</th>
<th>mPFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT alone</td>
<td>209</td>
<td>180</td>
<td>8.05 (7.56, 8.90)</td>
</tr>
<tr>
<td>CCRT + consolidation</td>
<td>211</td>
<td>169</td>
<td>9.10 (7.92, 10.94)</td>
</tr>
</tbody>
</table>
Key Chemotherapy Questions in Stage III NSCLC

• Is there an optimal drug regimen and cycle number?
• How do we best integrate molecular therapies or immunological approaches?
• How should we advance therapy for marginally resectable stage III disease?
• Can we develop better preclinical models?
VEGF Inhibition

Ferrara N, Nature 2005; 438: 967-974
REVEL: Ramucirumab-Human VEGFR-2 ab

Positive per Press Release, 2014
Primary endpoint = OS
REVEL: Overall Survival

ITT Population

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI)</th>
<th>Censoring Rate</th>
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</thead>
<tbody>
<tr>
<td>RAM+DOC</td>
<td>10.5 (9.5-11.2)</td>
<td>31.8%</td>
</tr>
<tr>
<td>PL+DOC</td>
<td>9.1 (8.4-10.0)</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

RAM+DOC vs PL+DOC:
Stratified HR (95% CI) = 0.857 (0.759-0.979)
Stratified log-rank $P = .0235$

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Survival Time (months)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>RAM+DOC 628</td>
<td>527</td>
<td>415</td>
</tr>
<tr>
<td>PL+DOC 625</td>
<td>501</td>
<td>386</td>
</tr>
</tbody>
</table>

ORR | Median PFS
---|-------------
RAM + DOC 22.9% | 4.5 mo
PL + DOC 13.6% (p<0.001) | 3.0 mo (HR 0.76 p<0.0001)
FIRST LINE THERAPY COMBINING CHEMOTHERAPY WITH AN EGFR ANTIBODY – NECITUMUMAB IN SQUAMOUS NSCLC

Haven’t we been down this road before? i.e. the FLEX trial?

Study Design

Presented by Nick Thatcher at 2014 ASCO Annual Meeting

**Screening**
Entry criteria:
Stage IV squamous NSCLC¹,²
ECOG PS 0-2

**Gem-Cis + Neci q3w (N = 545)**
- Necitumumab (800 mg D1, D8)
- Gemcitabine (1250 mg/m², D1, D8)
- Cisplatin (75 mg/m², D1)

**Gem-Cis q3w (N = 548)**
- Gemcitabine (1250 mg/m², D1, D8)
- Cisplatin (75 mg/m², D1)

Randomization (R) stratified by: ECOG PS (0-1 vs. 2) and geographic region (North America, Europe and Australia; vs. South America, South Africa and India; vs. Eastern Asia)

Patient selection not based on EGFR protein expression

Radiographic tumor assessment (investigator read): at baseline and every 6 weeks until PD
Mandatory tissue collection

¹ AJCC TNM Classification, 7th edition, 2009; ² UICC TNM Classification of Malignant Tumors, 7th edition, 2009

Presented By Nick Thatcher at 2014 ASCO Annual Meeting
Primary Outcome: Overall Survival (ITT)

HR (95%CI): 0.84 (0.74, 0.96); p=0.012*

*Log rank test (stratified)

Presented by Nick Thatcher at 2014 ASCO Annual Meeting
Progression-Free Survival (ITT)

HR (95% CI): 0.85 (0.74, 0.98); p = 0.020*

Median PFS (95% CI), months:
- Gem-Cis + Noci: 5.7 (5.6, 6.0)
- Gem-Cis: 5.5 (4.8, 5.6)

*Log rank test (stratified)

Hazard ratio

- 0.85 ITT population (N = 1093)
- 0.82 <70 yrs (N = 888)
- 1.07 ≥70 yrs (N = 205)
- Female (N = 185)
- 0.63 Male (N = 908)
- 0.90
- Caucasian (N = 913)
- 0.88 Non-caucasian (N = 180)
- 0.70
- Ex-light & non-smoker (N = 97)
- 0.88 Smoker (N = 995)
- 0.85
- PS 0 (N = 344)
- 0.84 PS 1 (N = 652)
- 0.86 PS 2 (N = 96)
- 0.79

Progression-free survival as assessed by investigators

Presented by: Nick Thatcher
Is The Glass Half Full or Half Empty?

HALF FULL

- Met its endpoint
- Improvement in multiple subgroups
- Easier dosing compared to cetuximab

HALF EMPTY

- Modest survival benefit
- Lack of biomarker – does put H
- Score to rest

Is wild type EGFR really a target in NSCLC????

Presented by: Julie R. Brahmer, M.D., M.Sc.
## Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Patient Population</th>
<th>Current Baseline Median OS (months)</th>
<th>Improvement Over Current OS That Would Be Clinically Meaningful (months)</th>
<th>Target HRs</th>
<th>Improvement in Improvement 1-Year Survival Rate (%)*</th>
<th>Improvement in Improvement in PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic cancer FOLFIROX-eligible patients</td>
<td>10 to 11&lt;sup&gt;19&lt;/sup&gt;</td>
<td>4 to 5</td>
<td>0.67 to 0.69</td>
<td>48 → 63</td>
<td>4 to 5</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer Gemcitabine or gemcitabine/ nab-paclitaxel-eligible patients</td>
<td>8 to 9&lt;sup&gt;20,21&lt;/sup&gt;</td>
<td>3 to 4</td>
<td>0.6 to 0.75</td>
<td>35 → 50</td>
<td>3 to 4</td>
<td></td>
</tr>
<tr>
<td><strong>Lung cancer</strong> Nonsquamous cell carcinoma</td>
<td>13&lt;sup&gt;22&lt;/sup&gt;</td>
<td>3.25 to 4</td>
<td>0.76 to 0.8</td>
<td>53 → 61</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lung cancer Squamous cell carcinoma</td>
<td>10&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2.5 to 3</td>
<td>0.77 to 0.8</td>
<td>44 → 53</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer Metastatic triple-negative, previously untreated for metastatic disease</td>
<td>18&lt;sup&gt;24,26&lt;/sup&gt;</td>
<td>4.5 to 6</td>
<td>0.75 to 0.8</td>
<td>63 → 71</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Colon cancer Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)</td>
<td>4 to 6&lt;sup&gt;28&lt;/sup&gt;</td>
<td>3 to 5</td>
<td>0.67 to 0.67</td>
<td>25 → 35</td>
<td>3 to 5</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FOLFIROX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Current → target.

These two phase III trials don’t meet these criteria.

Ellis LM et al JCO 2012
NSCLC Landscape Change - 2014

Traditional

- Adenocarcinoma
- Squamous
- Large Cell

Adenocarcinoma
- AKT
- BRAF
- VEGFR
- HER2
- EPHA/B
- PDGFR
- FGFR
- INSR
- PI3K
- MAPK
- KRAS
- EGFR
- ALK
- Unknown

Squamous Cell Carcinoma
- FGFR1 Amp
- EGFRvIII
- PI3KCA
- DDR2TK
- Unknown
Erlotinib +/- Bevacizumab as Second-Line Therapy (BeTa): Subgroup Analysis

Herbst, Lancet 2011
Study design

Chemotherapy-naïve
Stage IIIB/IV or postoperative recurrence
Non-squamous NSCLC
Activating EGFR mutations*
  Exon 19 deletion
  Exon 21 L858R
Age ≥20 years
PS 0–1
No brain metastasis

* T790M excluded

Stratification factors:
sex, smoking status, clinical stage, EGFR mutation type

EB combination
Erlotinib 150mg qd + bevacizumab 15mg/kg q3w (n = 75)

E monotherapy
Erlotinib 150mg qd (n = 75)

Primary endpoint:
PFS (RECIST v1.1, independent review)

Secondary endpoints:
OS, tumor response, QoL, safety

Exploratory endpoint:
biomarker assessment

Presented by Terufumi Kato at 2014 ASCO Annual Meeting
Acquired exon 20 mutation found in >50% of patients with acquired resistance to EGFR TKI

- Increases relative affinity of mutant EGFR for ATP, may also cause steric hindrance to erlotinib
- More likely to show progression in lungs/pleura
- Less commonly detected in CNS
- Patients with T790M mutation may have better prognosis than patients without T790M

**T790M in Acquired Resistance**

Best response in Phase 1 and early Phase 2 expansion cohort patients

Centrally confirmed T790M+ patients within therapeutic dose range (N=40)

ORR to date: 58%
AZD9291: Response rate* in central T790M+

- ORR* = 64% (69/107; 95% CI 55%, 73%) in patients with EGFR T790M+ NSCLC
- Overall disease control rate (CR+PR+SD) = 94% (101/107; 95% CI 88%, 98%)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>N (107)</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>10</td>
<td>50%</td>
</tr>
<tr>
<td>40</td>
<td>29</td>
<td>62%</td>
</tr>
<tr>
<td>80</td>
<td>34</td>
<td>68%</td>
</tr>
<tr>
<td>160</td>
<td>28</td>
<td>64%</td>
</tr>
<tr>
<td>240</td>
<td>6</td>
<td>83%</td>
</tr>
</tbody>
</table>

*Includes confirmed responses and responses awaiting confirmation; # represents imputed values.
Population: all dosed central T790M+ patients with a baseline RECIST assessment and an evaluable response (CR/PR, SD or PD), N=107 (from 120 T790M+ patients, 13 patients with a current non-evaluable response are not included).
QD, once daily; central T790M+, T790M positive by central laboratory testing

Presented by: Pasi A. Jänne
ALK Fusion Gene

- Potent oncogenic activity
- Present in approximately 4% to 5% of NSCLC
- More common in
  - Never smokers
  - Adenocarcinoma
  - Signet-ring morphology

### Objective Response Details

<table>
<thead>
<tr>
<th></th>
<th>N = 116†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>61% (52-70)</td>
</tr>
<tr>
<td>Median response duration</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Median time to response</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Disease control rate at 8 weeks and 16 weeks</td>
<td>79%, 67%</td>
</tr>
</tbody>
</table>

*Excludes patients with early death and indeterminate response (n = 106).
†Includes patients with early death and indeterminate response (n = 116).
PROFILE 1014 Study Design

Key entry criteria
- ALK-positive by central FISH testing
- Locally advanced, recurrent, or metastatic non-squamous NSCLC
- No prior systemic treatment for advanced disease
- ECOG PS 0–2
- Measurable disease
- Stable treated brain metastases allowed

Endpoints
- Primary
  - PFS (RECIST 1.1, independent radiologic review [IRR])
- Secondary
  - ORR
  - OS
  - Safety
  - Patient-reported outcomes (EORTC QLQ-C30, LC13)

Randomization
N=343

Crossover to Crizotinib permitted after progression

Crizotinib
250 mg BID PO, continuous dosing (n=172)

Pemetrexed
500 mg/m² + cisplatin 75 mg/m² or carboplatin AUC 5–6 q3w for ≤6 cycles (n=171)

Notes:
- ALK status determined using standard ALK break-apart FISH assay
- Stratification factors: ECOG PS (0/1 vs. 2), Asian vs. non-Asian race, and brain metastases (present vs. absent)
- Assessed by IRR
Primary Endpoint Met: Crizotinib Superior to Pemetrexed-based Chemotherapy in Prolonging PFS$^a$

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=172)</th>
<th>Chemotherapy (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>137 (80)</td>
</tr>
<tr>
<td>Median, months</td>
<td>10.9</td>
<td>7.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.45 (0.35–0.60)</td>
<td></td>
</tr>
<tr>
<td>P$^b$</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk
Crizotinib       172  120  65  38  19  7  1  0
Chemotherapy      171  105  36  12  2  1  0  0

Data cutoff: November 30, 2013

$^a$Assessed by IRR

$^b$1-sided stratified log-rank test
Ceritinib in Advanced Anaplastic Lymphoma Kinase Rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC) – Results of the ASCEND-1 Trial (#8003)

Dong-Wan Kim,1 Ranee Mehra,2 Daniel SW Tan,3 Enriqueta Felip,4 Laura QM Chow,5 D Ross Camidge,6 Johan Vansteenkiste,7 Sunil Sharma,8 Tommaso De Pas,9 Gregory J Riely,10 Benjamin J Solomon,11 Juergen Wolf,12 Michael Thomas,13 Martin Schuler,14 Geoffrey Liu,15 Armando Santoro,16 Margarida Geraldes,17 Anthony L Boral,18 Alejandro Yovine,19 Alice T Shaw20

1Seoul National University Hospital, Seoul, Korea; 2Fox Chase Cancer Center, Philadelphia, PA; 3National Cancer Center, Singapore; 4Vall d’Hebron University, Barcelona, Spain; 5University of Washington, Seattle, WA; 6University of Colorado, Denver, CO; 7University Hospital KU Leuven, Leuven, Belgium; 8Huntsman Cancer Institute, Salt Lake City, UT; 9Instituto Europeo di Oncologia, Milan, Italy; 10Memorial Sloan-Kettering Cancer Center, New York, NY; 11Peter MacCallum Cancer Center, Melbourne, VIC, Australia; 12University Hospital Cologne, Cologne, Germany; 13Thoraxklinik, University of Heidelberg, Translational Lung Research Center Heidelberg, Member of the German Center for Lung Research, Heidelberg, Germany; 14University Hospital Essen, University Duisburg-Essen, Essen, Germany and German Cancer Consortium, Heidelberg, Germany; 15Princess Margaret Cancer Center, Toronto, Canada; 16IRCCS Institute Clinico Humanitas, Milan, Italy; 17Novartis Pharma, East Hanover, NJ; 18Novartis Institutes for BioMedical Research, Cambridge, MA; 19Novartis Pharma AG, Basel, Switzerland; 20Massachusetts General Hospital, Boston MA

Presented By Dong-Wan Kim at 2014 ASCO Annual Meeting
LDK 378: A Potent and Selective ALK Inhibitor

Any advanced ALK-positive cancer progression on standard therapy (dose escalation starting at 50 mg/day)

Completed N = 59

Additional enrolled N = 71

ALK-positive lung cancer
Prior ALKi therapy

≤2 months after prior ALK TKI

>2 months after prior ALK TKI

ALK-positive lung cancer
naive to ALKi

Non-lung ALK-positive tumors

NCT01283516

Continuous oral dosing
21/d cycles

Primary objective: Determination of MTD

Secondary objectives: Safety, pharmacokinetics, and preliminary antitumor activity

ALKi = ALK inhibitor; MTD = maximum tolerated dose.

Best Percentage Change from Baseline (NSCLC)

- ALK inhibitor treated
- ALK inhibitor naïve

N = 228*

* Patients with measurable disease at baseline and at least 1 post baseline assessment without unknown response for target lesion or overall response

Presented by: Dong-Wan Kim

Presented By Dong-Wan Kim at 2014 ASCO Annual Meeting
Progression-Free Survival in Patients with ALK+ NSCLC

Presented by Dong-Wan Kim at 2014 ASCO Annual Meeting

Median: non-estimable (95% CI 8.31, non-estimable)
PFS rate at 12 months: 61.3%

Median: 8.21 months (95% CI 6.70, 10.12)
PFS rate at 12 months: 39.1%

Median: 6.90 months (95% CI 5.39, 8.41)
PFS rate at 12 months: 28.4%
Ceritinib Treatment Showed Anti-tumor Activity in the Brain

- 36 year old male patient with lymph node, brain, adrenal, and liver metastases
- Previously treated with radiation therapy, chemotherapy, and progressed on crizotinib

Patient remains on ceritinib 750 mg after 17 months

Figure courtesy of Dr. Daniel Tan

Presented by: Dong-Wan Kim
Toxicity Challenges with Ceritinib

- Greater than with crizotinib
- Dose reduction – 59% (!)
  - Increased ALT/AST, nausea, diarrhea, vomiting
- Discontinuation due to adverse effects – 10%
  - Pneumonia, ILD/pneumonitis, decreased appetite

- Oncologists need to know to dose-reduce early
  - 750 mg daily may be more than needed

Kim, A#8003
AP26113: Preliminary Anti-Tumor Activity in ALK-Positive Patients

Recommended Phase 2 dose: 180 mg/day
Common AE: Fatigue, nausea, and diarrhea

AE = adverse event

Data as of 17 April 2013. *ALK-TKI naive. †Received prior crizotinib and prior LDK378. Non-NSCLC diagnoses: ‡neuroendocrine carcinoma; §inflammatory myofibroblastic tumor; ‡‡ACUP; ¶Patient was PD by RECIST 1.1 due to second primary tumor of melanoma. Camidge DR et al. ASCO 2013 Annual Meeting. Abstract 8031.
Alectinib in Crizotinib-Resistant ALK-Positive NSCLC

- N = 47 patients
- 70% received ≥2 prior regimens

Objective response rate 60%
Adverse events: Myalgia, fatigue, peripheral edema, elevated CPK, nausea, and photosensitivity (grades 1/2)

Mutations detected in 60% of tumors tested

MET = membrane receptor essential for embryonic development and would healing; HER2 = human epidermal growth factor receptor 2; BRAF = human gene that makes a protein called “B-raf”; KRAS = a protein that stimulates signaling pathways downstream from EGFR

Kris MG et al. JAMA May, 2014
Lung Cancer Mutation Consortium: Survival by Group

Kris MG et al  JAMA May 2014
Crizotinib: selective inhibitor of ALK, MET and ROS

Presented By D. Camidge at 2014 ASCO Annual Meeting

13 ‘hits’ <100X selective for Met

Cellular selectivity on 10 of 13 relevant hits

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC50 (nM) mean*</th>
<th>Selectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>ALK</td>
<td>40–60</td>
<td>5–8X</td>
</tr>
<tr>
<td>ROS</td>
<td>55</td>
<td>7X</td>
</tr>
<tr>
<td>RON</td>
<td>80</td>
<td>10X</td>
</tr>
<tr>
<td>Axl</td>
<td>294</td>
<td>34X</td>
</tr>
<tr>
<td>Tie2</td>
<td>448</td>
<td>52X</td>
</tr>
<tr>
<td>Abl</td>
<td>1,159</td>
<td>166X</td>
</tr>
<tr>
<td>IRK</td>
<td>2,887</td>
<td>334X</td>
</tr>
<tr>
<td>Lck</td>
<td>2,741</td>
<td>283X</td>
</tr>
<tr>
<td>Sky</td>
<td>&gt;10,000</td>
<td>&gt;1000X</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>&gt;10,000</td>
<td>&gt;1000X</td>
</tr>
<tr>
<td>PDGFRβ</td>
<td>&gt;10,000</td>
<td>&gt;1000X</td>
</tr>
</tbody>
</table>

High probability of ALK, MET and ROS inhibition at clinically relevant doses

*Measured using ELISA capture method

http://meetinglibrary.asco.org/content/41375?media=vm
Patient eligibility:
NSCLC MET amplification cohort

- Patients (≥ 18 years) had histologically confirmed advanced NSCLC, and
  - measurable disease per RECIST v1.0
  - adequate organ function
  - resolution of acute toxic effects of prior therapies or surgical procedures (CTCAE Grade ≤ 1)
  - received no prior MET- or HGF-targeted therapies

In archival tumor tissue, MET amplification was determined by FISH

- MET not amplified (not eligible)
  - MET/CEP7 ratio < 1.8

- MET amplified (low MET level)
  - MET/CEP7 ratio ≥ 1.8 – ≤ 2.2

- MET amplified (intermediate MET level)
  - MET/CEP7 ratio > 2.2 – ≤ 5.0

- MET amplified (high MET level)
  - MET/CEP7 ratio ≥ 5

CEP7, chromosome 7 centromere signal; CTCAE, Common Toxicity Criteria for Adverse Events; FISH, fluorescence in-situ hybridization; RECIST, Response Evaluation Criteria In Solid Tumors

Presented By D. Camidge at 2014 ASCO Annual Meeting
# Objective response rate

<table>
<thead>
<tr>
<th>MET Level</th>
<th>n</th>
<th>ORR, % (95% CI)</th>
<th>Best Response, n (%)</th>
<th>Median Duration of Response, weeks (range)</th>
<th>Duration of Stable Disease, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>0 (0–84)</td>
<td>0</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Low MET</td>
<td>6</td>
<td>17 (0–64)</td>
<td>1 (17)</td>
<td>16 (24.1–128.0)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Intermediate MET</td>
<td>6</td>
<td>67 (22–96)</td>
<td>3 (50)</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>High MET</td>
<td>6</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td></td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

- **ORR, objective response rate.**
- **MET**, metabolic tumor burden.
- **RECIST v1.0**, based on investigator assessment.
- **Complete response + partial response**; CI based on exact F distribution.
- Descriptive statistics are presented based on all responders.
- Among patients with stable disease as best overall response.

Presented By D. Camidge at 2014 ASCO Annual Meeting
# Clinical Development of PD-1 Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Molecule</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab-BMS-936558</td>
<td>Fully human IgG4</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab CT-011</td>
<td>Humanized IgG1</td>
<td>Phase II multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab MK-3475</td>
<td>Humanized IgG4</td>
<td>Phase III</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-936559 (no longer in development in NSCLC)</td>
<td>Fully human IgG4</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Medl-4736</td>
<td>Engineered human IgG1</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>MPDL-3280A</td>
<td>Engineered human IgG1</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>MSB0010718C</td>
<td>Human IgG1</td>
<td>Phase I</td>
</tr>
</tbody>
</table>
MK-3475 in First Line Treatment of NSCLC: Initial Signal of Activity from Phase I Trial

- MK-3475: humanized, high affinity, monoclonal IgG4 antibody that exerts dual ligand blockade of the PD-1 pathway
- KEYNOTE-001: ongoing phase I study including patients with advanced NSCLC
- Key First Line Eligibility Criteria
  - EGFR Wild Type and Negative for ALK rearrangement (first 11 could have had)
  - 1% Tumor PD-L1 expression determined centrally from fresh biopsy using prototype IHC assay (22C3 antibody)
- Randomized to 10 mg/kg IV q 2 wks or q 3 wks
- Assessment q 9 weeks using RECIST 1.1 and irRC

Antitumor Activity by MK-3475 Dose

<table>
<thead>
<tr>
<th>MK-3475 Dose</th>
<th>RECIST v1.1, Central Review&lt;sup&gt;a&lt;/sup&gt;</th>
<th>irRC, Investigator Review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>DCR&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>n</td>
<td>n (%) [95% CI]</td>
<td>n (%) [95% CI]</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>11 (26%) [14%-42%]</td>
</tr>
</tbody>
</table>

- Interim median PFS:<br>  27.0 weeks (95% CI, 13.6-45.0) by RECIST v1.1 per central review – 6.75 mo<br>  37.0 weeks (95% CI, 27.0-NR) by irRC per investigator review - 9.25 mo

- Comparing to classic chemotherapy in the first line setting
- Phase 3 studies
  - Gemcitabine + Cisplatin RR= 22-32%, Median PFS – 5.1 mo
  - Taxol + Carboplatin RR=15-25%, Median PFS – 4.5 mo.
  - Pemetrexed + Cisplatin RR=30%, Median PFS – 4.8 mo. (5.3 mo Nonsquam)


Presented by: Julie R Brahmer, M.D., M.Sc.
**ASCO Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes**

### Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Patient Population</th>
<th>Current Baseline Median OS (months)</th>
<th>Improvement Over Current OS That Would Be Clinically Meaningful (months)</th>
<th>Target HRs</th>
<th>Improvement in 1-Year Survival Rate (%)*</th>
<th>Improvement in PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic cancer</td>
<td>FOLFIRINOX-eligible patients</td>
<td>10 to 11[19]</td>
<td>4 to 5</td>
<td>0.67 to 0.69</td>
<td>48 to 63</td>
<td>4 to 5</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Gemcitabine or gemcitabine/nab-paclitaxel-eligible patients</td>
<td>8 to 9[20,21]</td>
<td>3 to 4</td>
<td>0.6 to 0.75</td>
<td>35 to 50</td>
<td>3 to 4</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Nonsquamous cell carcinoma</td>
<td>13[22]</td>
<td>3.25 to 4</td>
<td>0.76 to 0.8</td>
<td>53 to 61</td>
<td>4</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Squamous cell carcinoma</td>
<td>10[23]</td>
<td>2.5 to 3</td>
<td>0.77 to 0.8</td>
<td>44 to 53</td>
<td>3</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>Metastatic triple negative, previously untreated for metastatic disease</td>
<td>18[24-26]</td>
<td>4.5 to 6</td>
<td>0.75 to 0.8</td>
<td>63 to 71</td>
<td>4</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)</td>
<td>4 to 6[26]</td>
<td>3 to 5</td>
<td>0.67 to 0.67</td>
<td>25 to 35</td>
<td>3 to 5</td>
</tr>
</tbody>
</table>

*Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

*Current → target.

---

Ellis LM et al JCO 2012

Presented by: Julie R. Brahmer, M.D., M.Sc.
S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy

Multiple Phase II-III Arms with “rolling” Opening & Closure

- **Biomarker Profiling (NGS/CLIA)**
  - FGFR ampl, Mut, Fusion
  - CDK4/6i ampl
  - CCND1, CCND2, CCND3, cdk4 ampl

- **Non-Match**
- **CT**
- **PD-L1i**

- **Biomarker**

- **Biomarker Profiling (NGS/CLIA)**

- **CT**

- **CDK 4/6i**

- **PFS/OS**

- **FGF Ri**

- **PFS/OS**

- **C-MET Expr**

- **PFS/OS**

- **HGFi+E**

- **PFS/OS**

CT = chemotherapy (docetaxel or gemcitabine), E = erlotinib

PI: V. Papadimitrakopoulou (SWOG); Steering Committee Chair: R. Herbst (YALE, SWOG); Lung Committee Chair: D. Gandara; Translational Chair: F. Hirsch; Statistical Chair: M. Redman
Decision Tree for the Management of Advanced NSCLC - Utilization of Contemporary Tools

- Personalization of Care by histology (pemetrexed and bevacizumab) for non-squamous
- Molecular markers
  - ERCC1 etc. not helpful
  - 1st line EGFR and ALK testing critical
- Maintenance therapy
  - Switch or continuation pem or erlotinib
- EGFR and ALK 1st, 2nd, 3rd generation drugs on the market or in development
But Will These Criteria Take into Account Raising the Tail of the Curve which is where the Power of Immunotherapy Theoretically Lies?

Ellis LM et al JCO 2012
PCI for SCLC: Current Role

• Well Established Role in LD-SCLC Pts with Response

• EORTC Trial (NEJM 2007) Established PCI as Alternative for ED-SCLC Patients: Survival Benefit!

• New Toxicity-Mitigating Approaches Under Study

• How do these two trials compare?
Seto et al: Phase III PCI Trial

**1\textsuperscript{st} line chemo**
Platinum-based doublet

- Any response
- No BM by MRI assessment

PCI: 25 Gy
10 fractions

- No response
- Any response
- No BM by MRI assessment

Follow-up by MR imaging

Stratification by Age (70\(\leq\) / <70), PS (0-1 / 2), Response (CR / PR+MR), Institutions

Primary endpoint: Overall Survival

Secondary endpoints: Time to BM (evaluated every 3 months)
- Progression-Free Survival (PFS)
- Safety
- Mini Mental State Examination (MMSE)
Time to Brain Metastasis (Seto)

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td>BM at 12 months</td>
<td>32.4%</td>
<td>58.0%</td>
</tr>
</tbody>
</table>

Gray's test: $P < 0.001$ (2-sided)
Progression-Free Survival (Seto)

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of PFS Events</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.12 (0.82-1.54)</td>
<td></td>
</tr>
<tr>
<td>Median PFS (95%CI), mo</td>
<td>2.2 (2.0-2.6)</td>
<td>2.4 (2.1-2.9)</td>
</tr>
</tbody>
</table>

Arm A: PCI

Arm B: No PCI

months
Overall Survival (Seto)

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI n=84</th>
<th>Arm B: no PCI n=79</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of OS Events</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.38 (0.95-2.02)</td>
<td></td>
</tr>
<tr>
<td>Median OS (95%CI), mo</td>
<td>10.1 (8.5-13.2)</td>
<td>15.1 (10.2-18.7)</td>
</tr>
</tbody>
</table>

Stratified log-rank test: $P=0.091$ (2-sided)
# EORTC vs Japanese PCI Trials

<table>
<thead>
<tr>
<th></th>
<th>EORTC (Slotman)</th>
<th>Japan (Seto)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Patients</strong></td>
<td>286 Enrolled</td>
<td>224 of 330 Enrolled</td>
</tr>
<tr>
<td><strong>PCI Dose/Fx</strong></td>
<td>Variable</td>
<td>25 Gy/10 Fractions</td>
</tr>
<tr>
<td><strong>Pre-Enrollment Neuro-Imaging</strong></td>
<td>Not Required</td>
<td>MR Brain Required</td>
</tr>
<tr>
<td><strong>Follow-up Imaging</strong></td>
<td>Not Required</td>
<td>MR Brain Required</td>
</tr>
<tr>
<td><strong>Neuro Function Data</strong></td>
<td>Limited</td>
<td>Limited</td>
</tr>
</tbody>
</table>
Educational Objectives

• New roles for targeted therapies for early stage disease?
• Consolidation chemotherapy’s last stand in Stage III NSCC?
• Current treatment algorithms for patients with NSCLC with known and unknown driver mutations
• Selecting treatment in patients without an actionable mutation
• Defining the role of prophylactic cranial radiation in small cell lung cancer