Novel Therapies and Therapeutic Targets in Non-Small Cell Lung Cancer

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Non-Small Cell Lung Cancer (NSCLC): Background

- Lung cancer continues to be a leading cause of cancer-related mortality worldwide, 1.4 million deaths annually.¹
- Lung cancer is the leading cause of cancer-related deaths in the U.S.²
- In the U.S., the annual number of lung cancer deaths equals the deaths due to breast, prostate, colorectal, and pancreas cancer combined (159,810).²
- Poor prognosis. Overall 5-year survival = 15%. Distant metastatic disease, 5-year survival < 5%
- Most patients present with advanced disease
  - 55% of patients present with stage IIIB or IV³

Lung Cancer Histologic Types

- Adenocarcinoma 40%
- SCLC 10-15%
- NOS 1–15%
- Large Cell 10-15%
- Squamous Cell 25-30%
- SCLC 10-15%
- Adenocarcinoma 40%

NON-SMALL CELL LUNG CANCER STAGING (seventh edition)

M (Distant Metastasis)

M0  None
M1a: Separate tumor nodule(s) in contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
M1b: Distant metastasis

Systemic Therapy for Metastatic NSCLC

- Goal
  - Tumor reduction, palliation of symptoms, QoL
  - Improve survival
- Meta-analyses demonstrate 27% reduction in risk of death with cisplatin-based chemotherapy (worse with alkylating agents)
- Carboplatin easier to administer and less toxic than cisplatin; may have slightly lower RR
Systemic for Metastatic NSCLC (cont’d)

- Platinum doublet standard.
- Non-platinum options
- 4 – 6 cycles
- Performance status, weight loss, smoking status associated with degree of toxicity
- For a minority of patients, molecular targeted therapies have become new treatment options
ECOG trial 1594: Randomised four-arm Study in Advanced NSCLC

Stratification
- PS 0 or 1, 2
- Wt loss
- Stage IIIb, IV
- Brain mets

Randomise

Paclitaxel 135 mg/m² over 24 hours, day 1
CDDP 75 mg/m², day 2
Cycle = 3 weeks

Gemcitabine 1000 mg/m² days 1, 8, and 15
CDDP 100 mg/m² day 1
Cycle = 4 weeks

Docetaxel 75 mg/m² day 1
CDDP 75 mg/m² day 1
Cycle = 3 weeks

Paclitaxel 225 mg/m² over 3 hours, day 1
Carboplatin (AUC=6) day 1
Cycle = 3 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PC</th>
<th>GC</th>
<th>DC</th>
<th>PCb</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>21</td>
<td>22</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Median TTP (months)</td>
<td>3.4</td>
<td>4.2*</td>
<td>3.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>31</td>
<td>36</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>2-year survival (%)</td>
<td>10</td>
<td>13</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

*p = 0.001 vs PC arm; CDDP = cisplatin
Carboplatin/paclitaxel became the ECOG reference standard for its future studies on the basis of the safety results observed in this study.

Systemic Therapy for Metastatic NSCLC: Non-Squamous vs Squamous Carcinoma

• Until 2006, NSCLC histologic subtype did not impact choice of chemotherapy
• Bevacizumab approved in 2006 in combination with carboplatin, paclitaxel for non-squamous NSCLC
• Pemetrexed approved 2008 in combination with cisplatin for non-squamous.
Which of the following statements are true for molecular testing of NSCLC tumors?

A. Molecular testing is considered research
B. EGFR mutation and ALK gene rearrangement testing is standard of care for adenocarcinomas
C. Heavy smokers are more likely to have targetable molecular abnormalities
D. P53 and K-RAS mutation testing is standard of care for all NSCLC subtypes
Targeted Therapy: Driver Mutations in Lung Adenocarcinomas

A driver mutation was found in 54% (280/516) of tumors completely tested (CI 50-59%)

Johnson et al on behalf of LCMC investigators, WLCC July 2011 Abstract #O16.01
Kris et al. on behalf of LCMC investigators, ASCO June 2011 Abstract #CRA7506
EGFR mutations

- Found in 10% - 15% of all lung cancer patients and 85% who clinically respond to EGFR TKIs (gefitinib, erlotinib, afatinib)
- Found more commonly in never-smokers, adenocarcinomas, BAC, women, Asians
- Predominantly located in EGFR exons 19 - 21
- EGFR mutations may be associated with sensitivity or resistance (T790M) to EGFR TKIs.
- 85-90% of EGFR TKI sensitive mutations are either exon 19 deletions or exon 21 L858R mutation.

Patient with L858 EGFR mutation

Newly diagnosed
3-16-07

3 months of erlotinib
6-18-07
# EGFR Tyrosine Kinase Inhibitors: Phase III First-line Trials in EGFR Mutation-positive NSCLC

<table>
<thead>
<tr>
<th>Agents</th>
<th>N</th>
<th>PFS (mo)</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib vs carboplatin, paclitaxel (NEJ002)¹</td>
<td>230</td>
<td>10.8 vs 5.4 (HR 0.30, P&lt;0.001)</td>
<td>74 vs. 31% (P&lt;0.001)</td>
</tr>
<tr>
<td>Gefitinib vs cisplatin, docetaxel (WJTOG3405)²</td>
<td>172</td>
<td>9.2 vs 6.3 (HR 0.49, P&lt;0.0001)</td>
<td>62 vs 32% (P&lt;0.0001)</td>
</tr>
<tr>
<td>Erlotinib vs carboplatin, gemcitabine (OPTIMAL, CTONG-0802)³</td>
<td>165</td>
<td>13.1 vs 4.6 (HR 0.16, P&lt;0.0001)</td>
<td>83 vs 36% (P&lt;0.0001)</td>
</tr>
<tr>
<td>Erlotinib vs cisplatin/carboplatin, gemcitabine or docetaxel (EURTAC)⁴</td>
<td>173</td>
<td>9.7 vs 5.2 (HR 0.37, P&lt;0.0001)</td>
<td>63 vs 18% (P&lt;0.0001)</td>
</tr>
<tr>
<td>Afatanib vs cisplatin, pemetrexed (LUX-Lung 3)⁵</td>
<td>345</td>
<td>11.1 vs 6.9 (HR 0.58, P=0.001)</td>
<td>56 vs 23% (P=0.001)</td>
</tr>
<tr>
<td>Afatanib vs cisplatin, gemcitabine (LUX-Lung 6)⁶</td>
<td>364</td>
<td>11 vs 5.6 (HR 0.28, P&lt;0.0001)</td>
<td>67 vs 23% (P&lt;0.0001)</td>
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OPTIMAL, CTONG-0802 Study: PFS

OPTIMAL, CTONG-0802: QoL and Symptoms

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Total FACT-L</th>
<th>TOI</th>
<th>LCS</th>
</tr>
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<tbody>
<tr>
<td>PS, smoking history and gender</td>
<td>6.73 (3.01–15.04), P &lt; 0.0001</td>
<td>7.46 (3.33–16.72), P &lt; 0.0001</td>
<td>7.22 (3.23–16.13), P &lt; 0.0001</td>
</tr>
<tr>
<td>EGFR mutation type, smoking history and histological type</td>
<td>6.69 (3.01–14.85), P &lt; 0.0001</td>
<td>8.07 (3.57–18.26), P &lt; 0.0001</td>
<td>7.54 (3.38–16.85), P &lt; 0.0001</td>
</tr>
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</table>

Includes all patients with a baseline and ≥1 post-baseline QoL assessment.


ALK Gene Rearrangement-Positive NSCLC

- ALK gene-rearrangement in NSCLC first reported in 2007. Most common fusion gene EML4-ALK. Estimated prevalence 3-5%.
- Associated with adenocarcinoma histology, never- or light smoking history, EGFR and KRAS WT, younger age
- EML 4 ALK is not a favorable prognostic factor (unlike EGFR mutations)
- Crizotinib, an oral TKI targeting ALK, c-Met, ROS1
  - US FDA-approved 2011 crizotinib, based on Phase II trial ORR 61%, low toxicity
  - Recent Phase III trial vs 2nd-line chemotherapy positive.
  - 3/2014: Phase III trial vs 1st-line chemotherapy positive.

Primary Endpoint: Progression-free Survival

Median PFS 7.7 vs 3.0 mo (HR 0.49, P<0.0001)

ORR 65% vs 20% (P<0.001)

ROS1 Rearrangement-Positive NSCLC

- ROS1 – a tyrosine kinase of the insulin receptor family.
- ROS1 gene-rearrangement reported in 1.7% - 2.6% NSCLC.
- Associated with adenocarcinoma histology, never- or light smoking history, younger age, higher grade
- Crizotinib Phase I trial expansion cohort included 33 ROS1-positive NSCLC patients.
  - Median age 51 yr, 79% never-smokers, 97% adenoca
  - RR 56%

Bergeron et al. JCO 2012, 30:863; Ou et al JCO 2013 (suppl; abstract 8032).
Clinical tumor responses in ROS1+ NSCLC treated with crizotinib

**Fig 3.** Two hundred ninety-three cells were transfected with cDNAs encoding EML4-ALK E13;A20 or CD74-ROS1. At approximately 45 hours after transfection, cells were treated with increasing amounts of crizotinib for 2 hours. Lysates were subjected to immunoblotting with antibodies specific for the indicated proteins.

**Fig 4.** Response of an ROS1-positive patient with advanced non–small-cell lung cancer to crizotinib. Computed tomography scans of the chest were obtained (A and C) at baseline and (B and D) after 12 weeks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.

Bergethon et al. JCO 2012
Davies et al. AACR 2012
Doebele IASLC Targeted Therapy 2012
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EGFR TKI Mechanisms of Acquired Resistance.

CO-1686 Targets EGFR T790M: Preliminary Efficacy Data in T790M+ NSCLC

- 6 of 9 patients with PR

<table>
<thead>
<tr>
<th>Number of Previous EGFR TKI lines</th>
<th>1</th>
<th>2</th>
<th>2</th>
<th>2</th>
<th>4</th>
<th>2</th>
<th>2</th>
<th>1</th>
<th>1</th>
</tr>
</thead>
</table>

Change from Baseline (%)

* EGFRi immediately before CO-1686

Remains on treatment, not progressed

Progressed (one patient remains on treatment post-progression)

Weeks on treatment

Soria WCLC 2013
Ceritinib (ZYKADIA): Clinical Activity

- Phase 1 studies examined doses of 50 to 750 mg daily.
- Multicenter trial, dose 750 mg daily
- N = 163, ALK-positive, previously treated with crizotinib
- Median age 52 years. Adenoca (93%), female (54%), never/former smoker (97%)
- RR 44%
- FDA accelerated approval 4/29/14.
**ras/raf/MAPK Pathway**

- **RAS** mutations seen in 20-30% of NSCLC\(^1\)
- **RAS** mutations associated with a worse prognosis\(^2\)
- Tumors harboring **RAS** mutations do not respond to EGFR inhibition\(^3\)
- Encouraging data combining MEK inhibitors with chemotherapy

Role of PD-1 in Suppressing Antitumor Immunity


Brahmer J et al, ASCO 2012 Abst 7509
Role of PD-1 in Suppressing Antitumor Immunity

Activation
(cytokines, lysis, prolif., migration)

Inhibition
(dergy, exhaustion, death)

Brahmer J et al, ASCO 2012 Abst 7509
Role of PD-1 in Suppressing Antitumor Immunity

**APC**

- **B7.1**
- **CD28**

**MHC-Ag**

**T cell**

- **TCR Signal 1**
- **(+ Signal 2**

**Inhibition**

- (anergy, exhaustion, death)

**Activation**

- (cytokines, lysis, prolif., migration)

**PD-1**

**PD-L1**

**Anti-PD-1**

**Tumor**

Pardoll DM, Nat Rev Cancer 2012
Response of Metastatic NSCLC (Nivolumab, 10mg/kg)

- Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression
- Dx ‘04, EGFR mutation +; Rx Gem/carbo, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and lastly pemetrexed

Brahmer J et al, ASCO 2012 Abst 7509
Conclusions

• For the majority of advanced NSCLC patients, platinum-based chemotherapy remains the standard of care. Treatment goals are prolongation of survival and improvement in tumor-related symptoms and quality of life.

• Molecular testing is now a standard of care for adenocarcinomas. For patients with targetable mutations, oral cancer drugs (erlotinib, gefitinib, afatinib, crizotinib) are more effective than chemotherapy.

• Clinical trials will help to define appropriate treatment options for patients who develop resistance to targeted therapies.

• Therapies targeting RAS-mutant NSCLC and anti-tumor immunity pathways represent exciting areas of clinical research.