Should we test for EGFR and ALK in completely resected NSCLC

Yi-long Wu
Guangdong Lung Cancer Institute
Guangdong General Hospital
Guangzhou China
Treatment strategy based on TNM staging and molecular profile

<table>
<thead>
<tr>
<th>Stage</th>
<th>General treatment recommendations</th>
<th>5-year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>14% Surgical resection</td>
<td>50%</td>
</tr>
<tr>
<td>IB</td>
<td>10% Surgical resection, can consider adjuvant chemotherapy in selected cases (e.g. tumor size &gt; 4cm)</td>
<td>43%</td>
</tr>
<tr>
<td>IIA</td>
<td>6% Surgical resection followed by adjuvant chemotherapy</td>
<td>36%</td>
</tr>
<tr>
<td>IIB</td>
<td>5% Surgical resection followed by adjuvant chemotherapy</td>
<td>25%</td>
</tr>
<tr>
<td>IIIA</td>
<td>16% Multimodality treatment: chemotherapy, radiation, +/- surgery</td>
<td>19%</td>
</tr>
<tr>
<td>IIIB</td>
<td>8% Multimodality treatment: chemotherapy and radiation</td>
<td>7%</td>
</tr>
<tr>
<td>IV</td>
<td>41% Chemotherapy, consider targeted therapies according to driver mutations</td>
<td>2%</td>
</tr>
</tbody>
</table>

Mutation spectrum in Adenocarcinoma
- BRAF mutation
- NRAS mutation
- HER2 mutation
- RET translocation
- OTHER

Mutation spectrum in Squamous Cell Carcinoma
- FGFR1 amplification
- PTEN mutation
- PIK3CA mutation

Rebecca S. Heist and Jeffrey A. Engelman 2012 Cancer cell
# EGFR mutation vs. ALK rearrangement

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EGFR</th>
<th>EML4/ALK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Adeno TTF1+</td>
<td>Adeno TTF1+</td>
</tr>
<tr>
<td>Subtype</td>
<td>Non-musin</td>
<td>musin</td>
</tr>
<tr>
<td>Smoke</td>
<td>Non-smoker</td>
<td>Non-smoker</td>
</tr>
<tr>
<td>Race</td>
<td>East</td>
<td>All</td>
</tr>
<tr>
<td>Age-median</td>
<td>66y</td>
<td>52y</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male &gt; female</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Treatment</td>
<td>EGFR-TKI</td>
<td>ALK-inhibitor</td>
</tr>
</tbody>
</table>

Two class of disease
R0 resected NSCLC

TEST with the GOAL in Mind

EGFR
ALK

Molecular epidemiology study
Prognosis
Adjuvant TKI therapy
Tumor heterogeneity
Treatment after relapse
R0 resected NSCLC

TEST with the GOAL in Mind

EGFR

ALK

Molecular epidemiology study

Prognosis

Adjuvant TKI therapy

Tumor heterogeneity

Treatment after relapse
A non-interventional study on EGFR mutation status and clinical outcomes of Chinese patients with completely resected lung adenocarcinoma (ICAN study)

Yi-Long Wu1, Jun Wang2, Xiang-Yang Chu3, Zhi-Dong Liu4, Yi Shen5, Haitao Ma6, Xiang-Ning Fu7, Jian Hu8, Nai-K Zhou3, Yongyu Liu9, Xinming Zhou10, Jian-Jun Wang11, Kang Yang12, Jian Li13, Lin Xu14, Si-yu Wang15, Qun Wan16, Xu Liu17, Shun Xu18, Shaning Li19, Zhongyuan Chen20, Honghe Luo21, Ying Chen22, Changli Wang23

1, Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou/CHINA, 2, Peking University People’s Hospital, Beijing/CHINA, 3, 301Hospital, Beijing/CHINA, 4, Beijing Chest Hospital, Capital Medical University, Beijing/CHINA, 5, The Affiliated Hospital of Medical College Qingdao University, Qingdao/CHINA, 6, The First Affiliated Hospital of Soochow University, Suzhou/CHINA, 7, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan/CHINA, 8, The First Affiliated Hospital of Medical School of Zhejiang University, Hangzhou/CHINA, 9, Liaoning Cancer Hospital & Institute, Shenyang/CHINA, 10, Zhejiang Cancer Hospital, Hangzhou/CHINA, 11, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan/CHINA, 12, The First Affiliated Hospital of Third Military Medical University, Chongqing/CHINA, 13, Peing University First Hospital, Beijing/CHINA, 14, Jiangsu Cancer Hospital, Nanjing/CHINA, 15Thoracic surgery, Sun Yat-sen university cancer center, Guangzhou/CHINA, 16, Zhongshan Hospital Fudan University, Shanghai/CHINA, 17, West China Hospital, Sichuan University, Chengdu/CHINA, 18, The First Hospital of China Medical University, Shenyang/CHINA, 19, Peking Union Medical College Hospital, Beijing/CHINA, 20, Ruijin Hospital, Jiaotong University, Shanghai/CHINA, 21, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou/CHINA, 22, Jilin Cancer Hospital, Changchun/CHINA, 23, Tianjin Medical University Cancer Institute and Hospital, Tianjin/CHINA

§ Correspondence: syylwu@live.cn
**Methods**

**Study flow diagram**

- **Aaged ≥18 years**
- **With histological diagnosed lung adenocarcinoma**,
- **Received surgical complete resection**.
- **The tumor EGFR mutation testing was performed as routine clinical practice**

**Inform consent and eligibility**

**Collect EGFR mutation status and disease information**

**Follow clinical outcome till 3 years after the operation**

**Primary endpoint:**
- EGFR mutation status

**Secondary endpoints:**
- Adjuvant therapy setting
- Clinical outcomes (DFS)
- Risk factors of recurrence
Results

Primary endpoint
Overall EGFR mutation status

Total: 571 cases
Positive = 315 (55.17)
Negative = 256 (44.83)
Results

EGFR mutation frequency according to gender

- Male (n=291):
  - % of EGFR mutation positive patients: 44.33%
  - % of EGFR mutation negative patients: 55.67%

- Female (n=280):
  - % of EGFR mutation positive patients: 66.43%
  - % of EGFR mutation negative patients: 33.57%

P<0.0001
Results

EGFR mutation frequency by smoking status

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked (n=371)</td>
<td>61.73%</td>
</tr>
<tr>
<td>Ex-smoker (n=122)</td>
<td>44.26%</td>
</tr>
<tr>
<td>Current smoker (n=78)</td>
<td>41.03%</td>
</tr>
</tbody>
</table>

% of EGFR mutation positive patients
% of EGFR mutation negative patients

P<0.0001
The results of ALK IHC and FISH obtained from tissue microarray /biopsy specimens and whole sections after resection were concordant.

Simultaneous tests for ALK IHC and EGFR ,which has important implications for the storage and use of small biopsy or cytology samples for genetic analysis.
Clinicopathologic, histologic and cytologic features

ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: A comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features

Yunjian Pan, Yang Zhang, Yuan Li, Haichuan Hu, Lei Wang, Hang Li, Rui Wang, Ting Ye, Xiaoyang Luo, Yiliang Zhang, Bin Li, Deng Cai, Lei Shen, Yihua Sun, Haiquan Chen

a Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China
b Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China
c Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai 200032, China

Fig. 1. Spectrum of well-identified oncogenic driver mutations in 1139 lung adenocarcinoma. “Paneg” refers to EGFR, KRAS, HER2, BRAF, ALK, ROS1 and RET negative.

- solid-predominant adenocarcinoma
- extracellular mucin (P < 0.001)
- cribriform pattern (P < 0.001)
- signet ring cells (P < 0.001)
- hepatoid cytology (P < 0.001)

Prevalence and Clinical Outcomes for Patients With ALK-Positive Resected Stage I to III Adenocarcinoma: Results From the European Thoracic Oncology Platform Lungscape Project

Fiona H. Blackhall, Solange Peters, Lukas Bubendorf, Urania Dafni, Keith M. Kerr, Henrik Hager, Alex Soltermann, Kenneth J. O’Byrne, Christoph Dooms, Aleksandra Sejda, Javier Hernández-Losa, Antonio Marchetti, Spasenija Savic, Qiang Tan, Erik Thunnissen, Ernst-Jan M. Spee, Richard Cheney, Daisuke Nonaka, Jeroen de Jong, Miguel Martorell, Igor Letovancic, Rafael Rosell, and Rolf A. Stahel
**FISH and IHC in ALK+**

Fig 2. Agreement between fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC) results in anaplastic lymphoma kinase (ALK) status determination (n = 237). (*) Note: FISH was not feasible for three of 160 ALK IHC-negative samples.

Fig 3. Plot of H-score and fluorescent in situ hybridization (FISH) status for anaplastic lymphoma kinase (ALK) immunohistochemistry (IHC)-positive patients (n = 80).

R0 resected NSCLC

TEST with the GOAL in Mind

- Treatment after relapse
- EGFR
- ALK
- Molecular epidemiology study
- Prognosis
- Tumor heterogeneity
- Adjuvant TKI therapy
Patient desire

What is my genetic Profiles?

How long could I still live?
### ICAN Results

2nd endpoint

2-year DFS rate by EGFR mutation status

<table>
<thead>
<tr>
<th>Survival n (%)</th>
<th>EGFR mutation status</th>
<th>Statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Total</td>
</tr>
<tr>
<td>Survival with no evidence of recurrence</td>
<td>198(72.79)</td>
<td>170(63.67)</td>
<td>368(68.27)</td>
</tr>
<tr>
<td>Disease recurrence or death</td>
<td>74(27.21)</td>
<td>97(36.33)</td>
<td>171(31.73)</td>
</tr>
<tr>
<td>Total (missing)</td>
<td>272(12)</td>
<td>267(20)</td>
<td>539(32)</td>
</tr>
</tbody>
</table>

2-year DFS rate (95% CI)

- **Positive**: 72.89% (67.17%, 77.78%)
- **Negative**: 64.83% (58.85%, 70.16%)
- **Total**: 68.83% (64.75%, 72.54%)
NSCLC with *EGFR* mutations without TKI therapy had better survival than wild type?
Worse disease-free survival in never-smokers with ALK+ lung adenocarcinoma

IHC +++ vs. IHC 0/+  
FISH + vs. FISH -

Worse disease-free survival in ALK+ lung adenocarcinoma

**Figure A1 – Panel A:** Kaplan–Meier curves showing overall survival by ALK IHC status (N=1281)

- **ALK:** Anaplastic lymphoma kinase
- **IHC:** Immunohistochemistry

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**Figure A1 – Panel B:** Kaplan–Meier curves showing relapse–free survival by ALK IHC status (N=1281)

- **ALK:** Anaplastic lymphoma kinase
- **IHC:** Immunohistochemistry

**Figure A2 – Panel A: Forest plots for the multivariate overall survival Cox model (N=1281)**

ALK: Anaplastic lymphoma kinase; IHC: Immunohistochemistry; FISH: Fluorescence in situ hybridization; PS: Performance status;

HR: Hazard ratio; CI: Confidence interval

*"All Other" category includes: "Wedge Resection", "Segmentectomy", "Other" and "Missing".*
R0 resected NSCLC

TEST with the GOAL in Mind

EGFR

ALK

Molecular epidemiology study

Prognosis

Tumor heterogeneity

Treatment after relapse
R0 resected NSCLC

TEST with the GOAL in Mind

- Molecular epidemiology study
- Prognosis
- Adjuvant TKI therapy
- Tumor heterogeneity
- Treatment after relapse

EGFR ALK
Tailed therapy: Inter-tumor heterogeneity
MDT: intra-tumor heterogeneity

2012 NATURE REVIEWS
2012 NEJM
Heterogeneity of EGFR mutations within a mixed adenocarcinoma: Case report

Table 1  EGFR mutations within a single tumor by histological subtype

<table>
<thead>
<tr>
<th>Histological subtype (number of samples)</th>
<th>Homozygous deletion in exon 19</th>
<th>Heterozygous deletion in exon 19</th>
<th>No deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAH areas (n=4)</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>BAC areas (n=4)</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Papillary AD (n=4)</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acinar AD (n=4)</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>


Concomitant EGFR Mutations and ALK Rearrangements

![Image of immunohistochemistry results for EGFR, ALK, p-EGFR, and p-ALK]

**Legend:**
- **+++** indicates high expression
- **++** indicates moderate expression
- **+** indicates low expression
- **-/NA** indicates absence of expression or not available

**High p-EGFR and high p-ALK**
- P1: +++
- P2: +++
- P3: +++
- P6: ++
- P4: ++
- P8: ++
- P9: ++
- P7: +++
- P10: +++
- P13: ++

**High p-EGFR and low p-ALK**
- P1: +++
- P2: +++
- P3: +++
- P6: ++
- P4: ++
- P8: ++
- P9: ++
- P7: +
- P10: ++
- P13: +++

**Low p-EGFR and high p-ALK**
- P1: +++
- P2: +++
- P3: +++
- P6: +
- P4: +
- P8: +
- P9: +/
- P7: +++
- P10: +++
- P13: +++

References:
GGO vs solid lepidic vs invasive lepidic papillary
Surgery

Section*

* Select the maximum cross-section of the tumor lesion

HE staining

Pathologic diagnoses of each subtype in a slide

Lipidic  Acinar  Papillary  Squamous  Solid

DNA sequencing:
Ten microsections ×10-µm thickness

Detection of mutations/fusions for each pathological subtype in a slide
(DS for EGFR/KRAS, FISH for EML4-AKL)

Validation
(ARMS for EGFR, HRM for KRAS)

GLCI, unpublished data
Rare Discrepancies in a Driving Gene Alteration within Histologically Heterogeneous Primary Lung Cancers

GLCI, unpublished data
Mutation status between surgery and relapse samples

Heterogeneous Distribution of EGFR Mutations Is Extremely Rare in Lung Adenocarcinoma

Yasushi Yatabe, Keitaro Matsuo, and Tetsuya Mitsudomi

<table>
<thead>
<tr>
<th>Table 3. Mutation Patterns in Primary and Recurrent Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months After First Examination at Recurrent Tumor Sites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial Examination Site</th>
<th>Pleural Effusion</th>
<th>Lymph Node</th>
<th>Pericardiac Effusion</th>
<th>Lung Tumor</th>
<th>Central Spinal Fluid</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Average</td>
<td>Minimal-Maximal</td>
<td>No.</td>
<td>Average</td>
<td>Minimal-Maximal</td>
</tr>
<tr>
<td>Primary tumor</td>
<td>31</td>
<td>30</td>
<td>0-99</td>
<td>7</td>
<td>53</td>
<td>8-212</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>1</td>
<td>1</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td>2</td>
<td>17</td>
<td>7-28</td>
<td>3</td>
<td>11</td>
<td>3-20</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2</td>
<td>8</td>
<td>7-9</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>11</td>
<td></td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: All of the patients demonstrated identical mutation patterns in primary and recurrent tumors.
R0 resected NSCLC

TEST with the GOAL in Mind

- Treatment after relapse
- EGFR
- ALK
- Molecular epidemiology study
- Prognosis
- Tumor heterogeneity
- Adjuvant TKI therapy
Surgery + TKI in patients with Therapeutic target after relapse

TKI in R0 resected NSCLC

R0 resection → Integrated managements

relapse → EGFR-ALK inhibitor → progression → death

2-3 yr
Differential intrapulmonary metastasis from multifocal lung cancer

<table>
<thead>
<tr>
<th>Method</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martini and Melamed</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
<td>Metastasis</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
</tr>
<tr>
<td>ACCP criteria</td>
<td>Multiple primary</td>
<td>Not classified</td>
<td>Metastasis</td>
<td>Multiple primary</td>
<td>Metastasis</td>
<td>Metastasis</td>
<td>Multiple primary</td>
</tr>
<tr>
<td>Histologic subtyping</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
</tr>
<tr>
<td>Molecular analysis</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
<td>Different</td>
</tr>
<tr>
<td>Integrated analysis</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
<td>Multiple primary</td>
</tr>
</tbody>
</table>

BAC (50%)/acinar adenocarcinoma (50%)

RLL — 19 Months — LL

L858R

Wild-Type EGFR

2010 Chest 2010 CLC
## Summary

Should we test for EGFR and ALK in completely resected NSCLC???

<table>
<thead>
<tr>
<th>GOAL</th>
<th>Importance of TEST</th>
<th>Impact on Clinical Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular epidemiology study</td>
<td>High</td>
<td>Two class of disease</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Middle</td>
<td>Worse prognosis in NSCLC with ALK+</td>
</tr>
<tr>
<td>Adjuvant TKI therapy</td>
<td>High</td>
<td>No enough evidence but ongoing trials.</td>
</tr>
<tr>
<td>Tumor heterogeneity</td>
<td>Rare in driving gene</td>
<td>Offer rational for TKI treatment after relapse</td>
</tr>
<tr>
<td>Treatment after relapse</td>
<td>High</td>
<td>Local therapy and Integrated management should be considered</td>
</tr>
</tbody>
</table>
16TH WORLD CONFERENCE ON LUNG CANCER

IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

WWW.IASLC.ORG

Save the Date!

Abstract Submission Open: January 2015
Registration Open: January 2015
Abstract Submission Deadline: April 24, 2015
Abstract Notifications: June 22, 2015
Early Registration Deadline: June 26, 2015
Late Breaking Abstract Submission Deadline: July 10, 2015
Regular Registration Deadline: July 24, 2015

SEPTEMBER 6-9, 2015
DENVER, COLORADO, USA
FIGHTING LUNG CANCER