Optimal Adjuvant Treatment for Resected NSCLC

Yi-Long Wu
Guangdong Lung Cancer Institute
Guangdong General Hospital
Guangdong Academy of Medical Sciences
Guangzhou/P.R. China
Disclosure

• Conducting research sponsored by Roche, Boehringer-Ingelheim, AstraZeneca, Pfizer, Novartis, BMS;

• Received the honorarium from Roche, AstraZeneca, Eli Lilly, Sanofi.
Adjuvant Therapy Timeline

ANITA–CDDP-VNR vs OBS Stage IB-III A Douillard JY et al. Lancet Oncol 2006; 7: 719-27
IALT was first trial that confirmed ADJ in NSCLC, 2004

Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non–Small-Cell Lung Cancer

The International Adjuvant Lung Cancer Trial Collaborative Group*

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Events / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>569 / 1088</td>
<td></td>
<td>0.95</td>
<td>[0.81; 1.12]</td>
</tr>
<tr>
<td>ANITA</td>
<td>458 / 840</td>
<td></td>
<td>0.82</td>
<td>[0.68; 0.98]</td>
</tr>
<tr>
<td>BLT</td>
<td>152 / 307</td>
<td></td>
<td>1.00</td>
<td>[0.72; 1.38]</td>
</tr>
<tr>
<td>IALT</td>
<td>980 / 1867</td>
<td></td>
<td>0.91</td>
<td>[0.80; 1.03]</td>
</tr>
<tr>
<td>JBR10</td>
<td>197 / 482</td>
<td></td>
<td>0.71</td>
<td>[0.54; 0.94]</td>
</tr>
<tr>
<td>Total</td>
<td>2356 / 4584</td>
<td></td>
<td>0.89</td>
<td>[0.82; 0.96]</td>
</tr>
</tbody>
</table>

Chemotherapy better | Control better
Test for heterogeneity: p = 0.34
Chemotherapy effect: p = 0.004

LACE IPD SR: 4584 cases from 5 trials (JCO 2008, 26:3552)
Pts die within 5 years whether they receive chemotherapy or not

Pts live without receiving chemotherapy

Pts live because of chemotherapy

**Estimated absolute risk and benefit for 100 patients with NSCLC**

**Ⅱ、Ⅲ期**: To prevent one death at 5 years for every 15 patients treated.

**Ⅰ期**: To treat 43 patients to prevent one death
Neo-adjuvant: Overall survival
15 trials, 2385 patients, 1427 deaths

<table>
<thead>
<tr>
<th></th>
<th>Preoperative chemotherapy</th>
<th>Control</th>
<th>O-E</th>
<th>Variance</th>
<th>HR (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>France 1990</td>
<td>8/13</td>
<td>8/13</td>
<td>0.32</td>
<td>3.97</td>
<td></td>
</tr>
<tr>
<td>MD Anderson 1994</td>
<td>19/28</td>
<td>27/32</td>
<td>-6.40</td>
<td>11.19</td>
<td></td>
</tr>
<tr>
<td>Spain 1994</td>
<td>19/29</td>
<td>27/30</td>
<td>-8.88</td>
<td>9.65</td>
<td></td>
</tr>
<tr>
<td>MIP-91</td>
<td>137/179</td>
<td>146/176</td>
<td>-12.99</td>
<td>70.22</td>
<td></td>
</tr>
<tr>
<td>SWOG S9015</td>
<td>3/5</td>
<td>12/16</td>
<td>-1.04</td>
<td>2.94</td>
<td></td>
</tr>
<tr>
<td>JCOG 9209</td>
<td>28/31</td>
<td>25/31</td>
<td>2.25</td>
<td>12.97</td>
<td></td>
</tr>
<tr>
<td>Finland 2003</td>
<td>19/30</td>
<td>19/32</td>
<td>-0.50</td>
<td>9.48</td>
<td></td>
</tr>
<tr>
<td>MRC BLT</td>
<td>4/5</td>
<td>3/5</td>
<td>1.26</td>
<td>1.60</td>
<td></td>
</tr>
<tr>
<td>MRC LU22</td>
<td>151/258</td>
<td>158/261</td>
<td>-2.92</td>
<td>77.01</td>
<td></td>
</tr>
<tr>
<td>SWOG S9900</td>
<td>93/180</td>
<td>103/174</td>
<td>-9.31</td>
<td>48.84</td>
<td></td>
</tr>
<tr>
<td>China 2002</td>
<td>26/32</td>
<td>18/23</td>
<td>1.42</td>
<td>10.78</td>
<td></td>
</tr>
<tr>
<td>China 2005</td>
<td>8/19</td>
<td>14/21</td>
<td>-3.31</td>
<td>5.44</td>
<td></td>
</tr>
<tr>
<td>CheST</td>
<td>45/129</td>
<td>61/141</td>
<td>-10.27</td>
<td>26.39</td>
<td></td>
</tr>
<tr>
<td>NATCH</td>
<td>99/201</td>
<td>109/212</td>
<td>-4.11</td>
<td>51.95</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>682/1178</td>
<td>745/1207</td>
<td>-50.62</td>
<td>351.78</td>
<td></td>
</tr>
</tbody>
</table>

Overall effect

HR=0.87 (95% CI 0.78-0.96), p=0.007
5% survival improvement at 5 years
Heterogeneity: chi-square=18.75, df=14, p=0.175, I²=25.35

NSCLC Meta-analysis group Lancet 2014;383:1561
Preoperative Chemotherapy Plus Surgery Versus Surgery Plus Adjuvant Chemotherapy Versus Surgery Alone in Early-Stage Non–Small-Cell Lung Cancer

A

HR = 0.92 (95% CI, 0.81 to 1.04)  
P = .17
Events: Preoperative chemotherapy 117 (58.8%); Surgery 132 (62.9%)

B

HR = 0.96 (95% CI, 0.75 to 1.22)  
P = .74
Events: Adjuvant chemotherapy 125 (59.5%); Surgery 132 (62.9%)

OS

Preoperative chemotherapy vs Surgery alone:
HR = 0.96 (95% CI, 0.84 to 1.1); P = .56
Adjuvant chemotherapy vs Surgery alone:
HR = 0.99 (95% CI, 0.75 to 1.3); P = .93
Events: Preoperative chemotherapy 99 (49.7%); Adjuvant chemotherapy 102 (48.6%); Surgery 109 (51.9%)
CSLC 0501: Neo vs adj in resected NSCLC

Stratification:
Center
IB VS II VS IIIA

Eligible Stage IB-IIIA NSCLC
Randomize

Adjuvant Arm
- Surgery
- Docetaxel Carboplatin ×3 cycles
  101 cases

Neoadjuvant Arm
- Docetaxel Carboplatin ×3 cycles
- Surgery
  97 cases

multi-center
open label
phase 3 trial

Estimated Enrollment: 410
Start: Mar. 2006
Dec. 2010 (early closed)
Could we add a new drug in chemo double to improve survival?
E1505 not met its primary end point

OS hazard ratio (B:A): 0.99
95% CI: (0.81-1.21)
p = 0.93

DFS hazard ratio (B:A): 0.98
95% CI: (0.84-1.14)
p = 0.75

PLN04.03: Randomized phase III trial of adjuvant chemotherapy with or without bevacizumab in resected non-small cell lung cancer (NSCLC): Results of E1505 – Heather Wakelee, USA
MAGRIT, a double-blind, randomized, placebo-controlled phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC)

- **Study objective**
  - To determine if recMAGE-A3 + AS15 cancer immunotherapeutic (MAGE-A3 CI) as adjuvant therapy over 27 months improves DFS in patients with resected NSCLC

**Key patient inclusion criteria**
- Stages IB, II, IIIA NSCLC
- Completely resected tumour
- MAGE-A3-positive
- PS 0–2
  (n=2,272)

**Primary endpoint**
- DFS

**Secondary endpoints**
- OS, lung cancer specific survival, immunogenicity
- Safety, health-related QoL

**Stratification**
- Chemotherapy

**Randomization**
- 13 IM injections of MAGE-A3 CI (n=1,515) → PD
- 13 IM injections of placebo (n=757) → PD

MAGRIT trial: Adjuvant vaccine therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC)


*Likelihood ratio test from Cox regression model stratified by chemotherapy and adjusted for baseline variables used as minimisation factors

Summary: Current status of Adjuvant treatment

- Adjuvant and neo-adjuvant chemotherapy give 5% survival benefit for patients with resected stage 2-3A NSCLC
- Adjuvant chemo in stage 1b is controversy
- Adjuvant vaccine immunotherapy don’t work in resected NSCLC
- New adjuvant therapy paradigm is an option
## EGFR-TKI vs Chemotherapy in 1L EGFR-mu NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>TKI</th>
<th>Pts No.</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TKI</td>
<td>Chemo</td>
</tr>
<tr>
<td>IPASS</td>
<td>Asia, non-smoker</td>
<td>Gefitinib</td>
<td>261</td>
<td>9.5</td>
<td>6.3</td>
</tr>
<tr>
<td>First Signal</td>
<td>Korea, non-smoker</td>
<td>Gefitinib</td>
<td>42</td>
<td>8.4</td>
<td>6.7</td>
</tr>
<tr>
<td>NEJ002</td>
<td>Japan</td>
<td>Gefitinib</td>
<td>228</td>
<td>10.8</td>
<td>5.4</td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>Japan</td>
<td>Gefitinib</td>
<td>172</td>
<td>9.6</td>
<td>6.6</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>China</td>
<td>Erlotinib</td>
<td>154</td>
<td>13.1</td>
<td>4.6</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Caucasian</td>
<td>Erlotinib</td>
<td>174</td>
<td>9.7</td>
<td>5.2</td>
</tr>
<tr>
<td>LUX-Lung3</td>
<td>Asia, non-Asia</td>
<td>Afatinib</td>
<td>345</td>
<td>11.1</td>
<td>6.9</td>
</tr>
<tr>
<td>LUX-Lung6</td>
<td>Asia</td>
<td>Afatinib</td>
<td>364</td>
<td>11.0</td>
<td>5.6</td>
</tr>
<tr>
<td>ENSURE</td>
<td>China</td>
<td>Erlotinib</td>
<td>210</td>
<td>11.0</td>
<td>5.6</td>
</tr>
</tbody>
</table>

EGFR-TKI vs Chemotherapy in 1L EGFR-mu NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>TKI</th>
<th>Pts No.</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>TKI Chemo HR(95%CI)</th>
<th>TKI Chemo HR(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EGFR mutation+ subgroup analysis in phase III trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TKI Chemo HR(95%CI)</td>
<td>TKI Chemo HR(95%CI)</td>
</tr>
<tr>
<td>IPASS</td>
<td>Asia, non-smoker</td>
<td>Gefitinib</td>
<td>261</td>
<td>9.5</td>
<td>6.3</td>
<td>0.48 (0.36-0.64)</td>
<td>21.6</td>
</tr>
<tr>
<td>First Signal</td>
<td>Korea, non-smoker</td>
<td>Gefitinib</td>
<td>42</td>
<td>8.4</td>
<td>6.7</td>
<td>0.61 (0.31-1.22)</td>
<td>30.6</td>
</tr>
<tr>
<td>Phase III trials in EGFR mutation+ patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEJ002</td>
<td>Japan</td>
<td>Gefitinib</td>
<td>228</td>
<td>10.8</td>
<td>5.4</td>
<td>0.322 (0.236-0.438)</td>
<td>27.7</td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>Japan</td>
<td>Gefitinib</td>
<td>172</td>
<td>9.6</td>
<td>6.6</td>
<td>0.520 (0.378-0.715)</td>
<td>35.5</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>China</td>
<td>Erlotinib</td>
<td>154</td>
<td>13.1</td>
<td>4.6</td>
<td>0.16 (0.10-0.26)</td>
<td>32.1</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Caucasian</td>
<td>Erlotinib</td>
<td>174</td>
<td>9.7</td>
<td>5.2</td>
<td>0.37 (0.25-0.54)</td>
<td>22.9</td>
</tr>
<tr>
<td>LUX-Lung3</td>
<td>Asia, non-Asia</td>
<td>Afatinib</td>
<td>345</td>
<td>11.1</td>
<td>6.9</td>
<td>0.58 (0.43-0.78)</td>
<td>31.7</td>
</tr>
<tr>
<td>LUX-Lung6</td>
<td>Asia</td>
<td>Afatinib</td>
<td>364</td>
<td>11.0</td>
<td>5.6</td>
<td>0.28 (0.20-0.39)</td>
<td>26.3</td>
</tr>
<tr>
<td>ENSURE</td>
<td>China</td>
<td>Erlotinib</td>
<td>210</td>
<td>11.0</td>
<td>5.6</td>
<td>0.42 (0.27-0.66)</td>
<td>26.3</td>
</tr>
</tbody>
</table>

Target therapy has improved OS for advanced NSCLC with driver genes


3.5 : 2.4 : 2.1 year

ALK 4.3 year
EGFR 4.0 year
Knowledge Gaps

- Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?
  - Is EGFR mutation rate different between early stage and advanced NSCLC?
  - Heterogeneity in resected NSCLC
  - What novel treatment strategies are being pursued?
EGFR mutation between early and advanced NSCLC

2013 ASCO Early stage NSCLC
ICAN

2012 ASCO Advanced NSCLC
PIONEER

EGFR mutation (%)

Positive 55.2 50.2
Negative 44.8 49.8

**EGFR Mutation Rate by pStage**

![Bar graph showing EGFR mutation rates by pStage](Image)

**Stage 1 (N=291):** 59.5%

**Stage 2 (N=49):** 51%

**Stage 3 (N=138):** 47.1%

**Wu et al. ICAN study ESMO 2014**
Results: 3-yr DFS rate

3-yr DFS (Common Mut. vs. rare Mut. vs. wild type)

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>Disease-Free Survival Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>271 257 227 201 182 166 134</td>
</tr>
<tr>
<td>Rare</td>
<td>42   38  35  32   28  26  23</td>
</tr>
<tr>
<td>Wild type</td>
<td>255 234 197 166 149 136 106</td>
</tr>
</tbody>
</table>

Survival Probability

3-yr DFS (Exon19Del vs. Exon21 L858R)

<table>
<thead>
<tr>
<th>Mutation Types</th>
<th>Disease-Free Survival time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>exon19 deletion</td>
<td>139 128 133 120 117 106 94</td>
</tr>
<tr>
<td>Exon21 L858R</td>
<td>128 120 106 94 87 82 67</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>3-yr DFS rate(95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common mutation</td>
<td>66.0% (59.8%, 71.4%)</td>
<td>0.1021</td>
</tr>
<tr>
<td>Rare mutation</td>
<td>63.4% (46.7%, 76.1%)</td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>56.8% (50.2%, 62.8%)</td>
<td></td>
</tr>
</tbody>
</table>

*Log-Rank test;
^Common mutation (Sensitive mutation) include deletion, L858R deletion + L858R, rare mutation include unknown mutation and Other types, 4 patients with both L858R and deletion were excluded in Exon19Del VS. Exon21 L858R comparison.
Knowledge Gaps

- Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?
  - Is EGFR mutation rate different between early stage and advanced NSCLC?
  - Heterogeneity in resected NSCLC
- What novel treatment strategies are being pursued?
Retrospective study:
Adjuvant TKI for EGFR+ NSCLC

Difficult to distinguish the prognostic from the predictive impact of EGFR mutations in a retrospective study where EGFR TKI is preferably administered to higher stage diseases
Retrospective study: Adjuvant TKI for EGFR+ NSCLC

TABLE 3. Multivariate Disease-Free Survival Analysis

<table>
<thead>
<tr>
<th></th>
<th>n = 167</th>
<th>N (Event N)</th>
<th>2-yr Survival (95% CI)</th>
<th>Adjusted Hazard Ratio* (95% CI)</th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant erlotinib/gefitinib</td>
<td>56 (13)</td>
<td>89% (77-95)</td>
<td>0.53 (0.28-1.03)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>No adjuvant erlotinib/gefitinib</td>
<td>111 (43)</td>
<td>72% (61-80)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for sex, type of surgery, stage, and adjuvant cisplatin chemotherapy; hazard ratio less than 1.00 indicates improved survival.

TABLE 4. Multivariate Overall Survival Analysis

<table>
<thead>
<tr>
<th></th>
<th>n = 167</th>
<th>N (Event N)</th>
<th>2-yr Survival (95% CI)</th>
<th>Adjusted Hazard Ratio* (95% CI)</th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant erlotinib/gefitinib</td>
<td>56 (3)</td>
<td>96% (85-99)</td>
<td>0.62 (0.26-1.51)</td>
<td>0.296</td>
<td></td>
</tr>
<tr>
<td>No adjuvant erlotinib/gefitinib</td>
<td>111 (21)</td>
<td>90% (82-95)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for sex, type of surgery, stage, and adjuvant cisplatin chemotherapy; hazard ratio less than 1.00 indicates improved survival.
Adjuvant Gefitinib: JBR.19

- Path stage IB - III NSCLC
- Complete surgical resection
- PS 0-2
- Adjuvant chemo and/or XRT allowed

N = 503

Gefitinib 250 mg po qd x 2 years

Placebo PO qd x 2 years

All patients

EGFR Mutated

SELECT: Study Design

- Single arm, open-label Phase II study
- Adjuvant erlotinib following standard therapy

- Surgically resected Stage IA-IIIA NSCLC
- EGFR mut
- Surgically resected
- Completed routine adjuvant chemotherapy and/or XRT

Erlotinib 150 mg PO daily

Observation

CT surveillance q 6 mo x 3 years
q12 mo years 4 and 5

2 years duration

Primary Endpoint:
- 2-year Disease Free Survival >86%

Secondary Endpoints:
- Safety and Tolerability
- Median Disease Free Survival
- Overall Survival

Neal ASCO 2012; Abstr 7010.
SELECT: Disease-Free Survival

69% of patients completed >90% of therapy
39% of patients had 1+ dose reductions

Median follow-up time: 2.7 years

94% 2-Year DFS

69% of patients completed >90% of therapy
39% of patients had 1+ dose reductions

Patients at Updated 2yr DFS with N=100 is 89%

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

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

2:1
- 623 Erlotinib 150mg/day
- 350 Placebo

2-yr treatment period

- 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
Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non–Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial

![Graph A](image1)

**Graph A:**
- Disease-Free Survival (probability)
- Time (months)
- Placebo: Median = 48.2 months
- Erlotinib: Median = 50.5 months
- HR: 0.90 (95% CI, 0.74 to 1.10)

![Graph B](image2)

**Graph B:**
- Disease-Free Survival (probability)
- Time (months)
- Placebo: Median = 28.5 months
- Erlotinib: Median = 46.4 months
- HR: 0.61 (95% CI, 0.38 to 0.98)
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)

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
RADIANT Conclusions

• Erlotinib following resection and adjuvant chemotherapy did NOT prolong DFS in patients with EGFR expressing tumors

• In the subset of patients whose tumors had del19 and L858R mutations, DFS favored erlotinib.
  – Not statistically significant due to hierarchical testing.

• No Overall Survival benefit noted, even in EGFRmut
Knowledge Gaps

- Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?
  - Is EGFR mutation rate different between early stage and advanced NSCLC?
- Heterogeneity in resected NSCLC
- What novel treatment strategies are being pursued?
Resected NSCLC is heterogeneity: Major Changes in Stage 1B Classification

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1B</td>
<td>Stage 1B</td>
</tr>
<tr>
<td>T2 (&gt;3cm)</td>
<td>T2A (&gt;3-5cm)</td>
</tr>
<tr>
<td></td>
<td>T2B (&gt;5-7cm)</td>
</tr>
<tr>
<td>T3 (&gt;7cm)</td>
<td></td>
</tr>
</tbody>
</table>

13% stage 1B in IASLC database with 58% 5-y survival
CALGB 9633: Adjuvant chemo for stage 1B Survival by Tumor Size

Tumor ≥ 4 cm
- Chemotherapy (n = 99)
- Control (n = 97)

Survival Probability

HR: 0.69
90% CI: 0.48-0.99
P = .043

Tumor < 4 cm
- Chemotherapy (n = 63)
- Control (n = 71)

Survival Probability

HR: 1.12
90% CI: 0.75-1.07
P = .32

Including stage 2a and stage 2b

Resected NSCLC is heterogeneity

<table>
<thead>
<tr>
<th>Stage</th>
<th>MST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1A</td>
<td>119</td>
</tr>
<tr>
<td>Stage 1B</td>
<td>81</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>49</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>31</td>
</tr>
<tr>
<td>Stage 3A</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>Reference</th>
<th>Stage 1 (%)</th>
<th>Stage 2 (%)</th>
<th>Stage 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>Janjigian 2010</td>
<td>54</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>D’Angelo 2012</td>
<td>52</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Prospective</td>
<td>BR.19 2013</td>
<td>53</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Select 2014</td>
<td>44</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Radian 2014</td>
<td>51</td>
<td>33</td>
<td>16</td>
</tr>
</tbody>
</table>
What secret behind PFS from retrospective and prospective studies?

Radian ASCO 2014

Janjigian JTO 2010

D'Angelo JTO 2012

Survival time (Y)

Survival Probability

TKIs delay recurrence
not prolong overall survival

Stop drug in 2 years

(n=286)
Knowledge Gaps

- Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?
- Is EGFR mutation rate different between early stage and advanced NSCLC?
- Heterogeneity in resected NSCLC
- What novel treatment strategies are being pursued?
Phase II study of biomarker-guided neoadjuvant treatment strategy for IIIA-N2 non-small cell lung cancer based on epidermal growth factor receptor mutation status

- **Study objective**
  - To evaluate the role of biomarker-guided neoadjuvant treatment strategy in patients with IIIA-N2 NSCLC stratified by EGFR mutation status

- **Key patient inclusion criteria**
  - Resectable histologically documented stage IIIA-N2 NSCLC (n=24)

- **Primary endpoint**
  - RR

- **Secondary endpoints**
  - PFS and OS

**Flowchart**
- **EGFR mutation**
  - Neoadjuvant erlotinib for 42 days (n=12) → PD

- **Wild-type EGFR**
  - Neoadjuvant gemcitabine/carboplatin for 3 cycles (n=12) → PD
RR for erlotinib and GC regimen

58.3 % (7/12) for the erlotinib arm
25.0 % (3/12) for the GC arm

Fig. 1 Waterfall plot of response to neoadjuvant treatment. Abbreviations: GC, gemcitabine/carboplatin; E, erlotinib. Note: The response rate of one case in the GC arm was not available.
PFS and OS comparison

B: PFS comparison between the 2 arms

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>Median (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>12</td>
<td>12</td>
<td>6.9 (3.8 - 10.0)</td>
<td>0.071</td>
</tr>
<tr>
<td>GC</td>
<td>12</td>
<td>10</td>
<td>9.0 (3.1 - 15.0)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI) = 2.26 (0.91 - 5.61)

C: OS comparison between the 2 arms

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>Median (months)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>12</td>
<td>9</td>
<td>14.5 (0.0 - 33.4)</td>
<td>0.304</td>
</tr>
<tr>
<td>GC</td>
<td>12</td>
<td>7</td>
<td>29.3 (1.5 - 57.1)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI) = 1.71 (0.61 - 4.84)

Zhong & Wu JHO, 2015
CTONG 1103 (EMERGING) 2011-2018

- Treatment naive
- IIIA-N2 NSCLC
- N2 confirmed by mediastinoscopy / EBUS / PET-CT
- EGFR activating mutation
- ECOG 0~1
- Age ≥18 Y (n=90)

Primary endpoint
- ORR

Secondary endpoint
- Lymph node downgrade rate
- Complete resection rate
- pCR
- PFS
- OS
- QoL
- Safety

Exploratory research
- 24w & 48w DFS rate
- Biomarker profile
China: CTONG 1104 (ADJUVANT)  
Japan: WJOG 6401L

- Completely resected
- Pathological stage II-IIIA (N1-N2) NSCLC
- **EGFR** Act Mut+ (exon 19 deletion or exon 21 L858R mutation)
- PS 0–1, ≥18 yrs, < 75 yrs (n=220-230)

Primary endpoint
- Disease-free survival (PFS)

Secondary endpoints
- Overall survival (OS), 3 years DFS rate, 5 years DFS rate, 5 years OS rate, Safety, HRQoL (FACT-L, LCSS), exploratory biomarker analyses

Gefitinib 250mg/day  
24 months or disease progression or unacceptable toxicity.

- Vinorelbine (25 mg/m² d1,8)  
- Cisplatin 75mg/m² d1) q3w, up to 4 cycles

**Stratification factors**
- Mutation type
- N stage
- Smoking status

**Efficacy assessment**
- Every 3 months

---

Act Mut+ = activating mutations; ECOG = Eastern Cooperative Oncology Group; PS = performance status  
HRQoL = health-related quality of life; FACT-L = Functional Assessment of Cancer Therapy-Lung; LCSS = lung cancer symptom scale

**China:** 222 cases  
FPI: Sep. 15, 2011  
LPI: Apr. 24, 2014

**Japan:** 230 cases  
LPI: Dec 2015
ICOTINIB Phase III Adjuvant trials

- Completely resected stage II-IIIa NSCLC with EGFR mutations (Exon 19 or 21)
  - NCT01996098
    - AFTER 4 cycles adjuvant platinum chemotherapy
    - Randomized to Icotinib (125 mg po tid) x 6 or 12 mo vs Observation
    - DFS primary endpoint, N=477
    - PI: SY Wang – Sun Yat-sen University Cancer Center
  - Pending: NCT02125240
    - NO prior adjuvant therapy
    - Randomized to Icotinib (125 mg po tid) vs placebo
    - 2 yr DFS primary endpoint, N= 300
    - PI:YK Shi – Cancer Hospital, Chinese Academy of Medical Sciences
US ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial

Stage I-III NSCLC
<6 mo post-op
N=6000-8000
For ~300-400

EGFR mut (Sequencing)
- Erlotinib x 2 yrs
- Placebo x 2 yrs

ALK+ (FISH)
- Crizotinib x 2 yrs
- Placebo x 2 yrs
Adjuvant Therapy: Molecular Selection

EORTC 08115-REMANNANT: **NEO**adjuvant Afatinib (BIBW2992) in **EGFR** Mutant Operable NSCLC; a study of the EORTC Lung Cancer Group

Study coordinator: Dr Sanjay Popat, Royal Marsden Hospital

Stage I-III treatment naïve NSCLC (T1a-T3, N0-1, M0) UICC v7

R

Afatinib 40 mg qd; for 12 weeks followed by surgery with curative intent (anatomical lobectomy/pneumonectomy)

Immediate surgery with curative intent (anatomical lobectomy/pneumonectomy)

- There will be a minimum of 1 week between the last dose of afatinib and surgery.
- The first 5 patients will form a safety run-in to check that afatinib treatment doesn’t delay surgery
- Endpoints and statistical considerations under discussion

SINGAPORE 2015 18-21 DECEMBER SINGAPORE
Key Trials in Future

1. Stage 2-3
   - Completely resection
   - Driver genes alteration
   - Precise drug therapy
   - Chemotherapy
   - Precise drug therapy
   - Crossover

2. Stage 1b-2-3
   - Completely resection
   - Driver genes alteration
   - Precise drug therapy
   - 5 years
   - Chemotherapy
   - Or
   - Wait and Watch
3rd generation EGFR TKI in Neoadjuvant setting

Neoadjuvant Rocilitinib Trial: UCSF & UCD

EGFR-mutant Stage I-IIIA Biopsy-proven Surgically Resectable NSCLG (n=27) → 1 Cycle (~28 days) Rociletinib 500 mg BID → PET-CT ORR by RECIST 1.1, and metabolic response (Secondary Endpoint) → Optional 2nd Cycle of Rociletinib may be given → Surgical Resection → Primary Endpoint: Pathological Response

1° objective: pathologic response rate (<50% viable tumor cells)
2° objectives: ORR; complete pathologic response; 2 year PFS; 2 year OS; Tissue and blood biomarkers; Safety and tolerability

SOC Adjuvant Chemo and/or radiation Or Surveillance Follow for 2 year PFS/OS (secondary endpoint)

Investigator’s Discretion

Optional for Responders: Re-consent 1 year Adjuvant Rociletinib Follow for 2 year PFS/OS (secondary endpoint)
Checkpoint Inhibitor in Neoadjuvant Setting

**LCMC 3 Neoadjuvant Schema & Objectives**

1° **objective:** 15% PR; 2° **objectives:** Safety; OS and DFS; ORR by PD-L1 biomarker; Evaluate tumor and LN infiltrates.

If no progression is seen at D20 CT, an additional 2 cycles are given before surgery.
Conclusions

• Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?
  • Is EGFR mutation rate different between early stage and advanced NSCLC?
  • Heterogeneity in resected NSCLC
• What novel treatment strategies are being pursued?
  • Is There a Role for Adjuvant EGFR TKIs in Early NSCLC?
Conclusions

- Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?  
  Maybe

- Is EGFR mutation rate different between early stage and advanced NSCLC?  
  No

- Heterogeneity in resected NSCLC  
  Yes

- What novel treatment strategies are being pursued?  
  Waiting

- Is There a Role for Adjuvant EGFR TKIs in Early NSCLC?  
  Maybe
What is the optimal adjuvant treatment for resected NSCLC?

Adjuvant chemotherapy for Stage 2-3 NSCLC

2004

2015
Acknowledge my team!