Cooperative Group Update
- Japan; JCOG & WJOG -

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Chief, Division of Thoracic Surgery,
Respiratory Disease Center
Chair of Comprehensive Cancer Center,
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Cooperative Groups for Lung Cancer in Japan

**JCOG**, Tokyo, Multi-disease

*Japan Clinical Oncology Group*
- no legal entity
- only one fully MHLW-sponsored

**WJOG**, Osaka, Multi-disease

*West Japan Oncology Group*
- NPO
- donated from Industries/registration fee by investigators

**NEJ**, Sendai

*North East Japan TCOG*, Tokyo

*Tokyo Clinical Oncology G.*

**TCOG**, Tokyo

*Thoracic Oncology Research G.*

**LOGIK**, Fukuoka

*Lung Oncology G. in Kyusyu*

**SLCG/OLCSG**, Okayama

*Setouchi Lung Cancer G.*

**JMTO**, Kyoto

*The Japan Multinational Trial Organization*

**CJLSG**, Nagoya

*Central Japan Lung Study G.*
JCOG;
Japan Clinical Oncology Group
## JCOG/Lung Cancer Surgical Study Group

<table>
<thead>
<tr>
<th>Study No.</th>
<th>P.I.</th>
<th>Trial</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCOG0201</td>
<td>T. Koike</td>
<td>Diagnosis of Radiological Early Lung Cancer</td>
<td>Observation cohort</td>
</tr>
<tr>
<td>JCOG0707</td>
<td>M. Tsuboi</td>
<td>Adjuvant Chemotherapy for Stage IA(T1b)-IB NSCLC</td>
<td>Phase III</td>
</tr>
<tr>
<td>JCOG0804/</td>
<td>M. Tsuboi</td>
<td>Limited Resection (Wide wedge resection) for Possible Early Lung</td>
<td>Phase II</td>
</tr>
<tr>
<td>WJOG4507L</td>
<td></td>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>JCOG0802/</td>
<td>H. Asamura</td>
<td>Lobectomy and Limited Resection for NSCLC 2cm or less in size</td>
<td>Phase III</td>
</tr>
<tr>
<td>WJOG4607L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JCOG1205/</td>
<td>M. Tsuboi</td>
<td>Adjuvant chemotherapy for p-stage I-IIIA High Grade Neuroendocrine</td>
<td>Planning / phase III</td>
</tr>
<tr>
<td>1206</td>
<td></td>
<td>Lung Cancer (LCNEC, SCLC)</td>
<td></td>
</tr>
</tbody>
</table>
JCOG0707

Randomized phase III study

n=480

TS-1
(80mg/m2/day, day1-14, q3weeks, 1 year)
n=480

UFT
(250mg/m2/day, 2 years)

p-Stage IA (2cm<), IB Completely resected NSCLC
PS: 0-1
Age: 20 – 75 ys

Within 8 weeks after surgery

Stratified factors;
Institute, Gender, Size, Histology, Age

Primary endpoint: Overall survival,
Secondary endpoints: Disease-free survival and toxicity

P.I.; Tsuboi M.
JCOG0707 (UFT vs. TS-1 for p-stage I NSCLC )

Current enrollment: 692 cases at this June
JCOG0804/WJOG4507L; Phase II Trial of Limited Resection (Wide wedge resection) for Possible Early Adenocarcinomas (GGO – Part-solid GGO); (Single-arm study)

- Subject ---- Non-solid GGO or part-solid GGO
  Solid part < 25%
- Why one arm? ----- Very few event (cancer-related death) to perform comparative study
- Intervention ------ Wide Wedge resection
- Endpoint ------- Recurrence-free survival rate at any site
- Sample size-----330 patients
- Trial has started since June in 2009

PI; Tsuboi M (JCOG) & Yoshino I (WJOG)
Final enrollment: 334 cases in April, 2011
JCOG0802/WJOG4607L; Phase III Randomized Trial between Lobectomy and Limited Resection for Part-solid GGO – Solid T1a disease

Non-inferiority design

Randomize

Peripheral carcinoma, <=2 cm Negative hilar node

Since Aug. 2009

Lobectomy

Segmentectomy

Stratified factors; Institute, Gender, Histology (Ad vs, Non-ad), Solid or non-solid

Endpoints:
Primary: OS
Secondary: pulmonary function
Sample size: 1,100

PI: Asamura H. (JCOG) & Okada M (WJOG)
JCOG0802/WJOG4506L (small NSCLC LB vs. SG P3)

Current enrollment: 538 cases at this June
JCOG1205/1206; Randomized Phase III Study of Irinotecan+CDDP and ETP+CDDP for completely resected high neuroendocrine tumors (LCNEC, SCLC)

**p-Stage I-IIIA**
Completely resected HGNE-LC (LCENC, SCLC)
PS: 0-1
Age: 20 – 74 ys

**Within 8 weeks after surgery**

**Stratified factors:**
Institute, Gender, Stage, histology (SCLC/LCNEC, Age (70))

**Primary endpoint:** Overall survival,
**Secondary endpoints:** Disease-free survival and toxicity

P.I.; Tsuboi M.
<table>
<thead>
<tr>
<th>JCOG number</th>
<th>Phase</th>
<th>Target</th>
<th>Reference arm</th>
<th>Experimental arm</th>
<th>Primary endpoint</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCOG0202</td>
<td>III</td>
<td>LD (First line)</td>
<td>EP+RT→EP</td>
<td>EP+RT→IP</td>
<td>Overall survival</td>
<td>250</td>
</tr>
<tr>
<td>JCOG0509</td>
<td>III</td>
<td>ED (First line)</td>
<td>IP</td>
<td>AP</td>
<td>Overall survival</td>
<td>282</td>
</tr>
<tr>
<td>JCOG0605</td>
<td>III</td>
<td>Sensitive relapse</td>
<td>NGT</td>
<td>PEI</td>
<td>Overall survival</td>
<td>180</td>
</tr>
<tr>
<td>JCOG0901</td>
<td>II</td>
<td>Refractory relapse</td>
<td>-</td>
<td>Amrubicin</td>
<td>Response rate</td>
<td>80</td>
</tr>
<tr>
<td>JCOG1011</td>
<td>II</td>
<td>LD (First Line)</td>
<td>EP+RT→CODE</td>
<td>EP+RT→AP</td>
<td>Response rate</td>
<td>80</td>
</tr>
</tbody>
</table>

PC : Protocol concept developed


**Comparative Arms**

**Arm A:**
- Etoposide/Cisplatin
- 3 cycles

**Arm B:**
- Irinotecan/Cisplatin
- 3 cycles

**1st Induction Chemoradiotherapy**
- Etoposide/Cisplatin AHTRT 45Gy

**2nd Consolidation Chemotherapy**
- PCI for CR or good PR

**Selection Criteria**

*adjusted by PS [0 vs 1], response to induction chemoradiotherapy [CR+good PR vs PR+SD], and institutions
JCOG0202 Primary Analysis: OS after Randomization

MST
- EP: 3.2y 52.9% 35.8%
- IP: 2.8y 46.6% 33.7%

One sided p=0.703# HR=1.085
95%CI[0.805-1.464]

# Stratified log-rank test, with PS and Response to Induction Chemoradiotherapy as strata

Four cycles of EP plus AHTRT is still the standard treatment for LD-SCLC
A phase III study comparing amrubicin and cisplatin (AP) with irinotecan and cisplatin (IP) for the treatment of ED-SCLC: JCOG0509. Kotani et al.

**ED-SCLC**
- 20-70 yrs
- PS 0-1

**Stratification**
- PS
- institution
- sex

**Sample size**
- n = 282
- (n = 141 per Arm)

**Randomized**

**IP**
- irinotecan 60 mg/m² D1,8,15
- cisplatin 60 mg/m² D1
- Q4 weeks x 4 cycles

**AP**
- amrubicin 40 mg/m² D1-3
- cisplatin 60 mg/m² D1
- Q3 weeks x 4 cycles

PCI for CR cases
- 2.5Gy
- 10 Fr

**Stratification**
- PS
- institution
- sex

**Sample size**
- n = 282
- (n = 141 per Arm)

**Primary endpoint; Overall survival**
**Secondary endpoints; PFS, ORR, AE and QOL**

Accrual: May 2007 – December 2010
A phase III study comparing amrubicin and cisplatin (AP) with irinotecan and cisplatin (IP) for the treatment of ED-SCLC: JCOG0509. Kotani et al.

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Events</th>
<th>Median (m)</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP</td>
<td>142</td>
<td>103</td>
<td>18.0</td>
<td>[14.1-20.5]</td>
</tr>
<tr>
<td>AP</td>
<td>142</td>
<td>112</td>
<td>15.3</td>
<td>[13.7-18.0]</td>
</tr>
</tbody>
</table>

HR*: 1.33 95% CI 1.01-1.74,

*stratified Cox regression, with PS and sex as strata

Irinotecan plus cisplatin remains the standard treatment for ED-SCLC in Japan.
### JCOG/Lung Cancer Study Group for NSCLC

<table>
<thead>
<tr>
<th>Study number</th>
<th>phase</th>
<th>Target</th>
<th>Reference arm</th>
<th>Experimental arm</th>
<th>Primary endpoint</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0301</td>
<td>III</td>
<td>Elderly unresectable stage III</td>
<td>RT alone (60Gy)</td>
<td>RT (60Gy) + weekly CBDCA (30mg/m²) x 20 times</td>
<td>Overall survival</td>
<td>200</td>
</tr>
<tr>
<td>0803/ WJOG 4307L*</td>
<td>III</td>
<td>Elderly stage IIIB/IV</td>
<td>Doc.(60mg/m²) q3wks</td>
<td>Weekly Cis. (20mg/m²) + Doc (25mg/m²)</td>
<td>Overall survival</td>
<td>380</td>
</tr>
</tbody>
</table>

*; This trial was terminated after the planned interim analyses, because This study failed to demonstrate any advantage of the addition of weekly CDDP to single-agent DOC in first line chemotherapy for elderly advanced NSCLC patients.; ASCO2011
Updated Results of A Phase III Trial Comparing Standard Thoracic Radiotherapy with or without Concurrent Daily Low-dose Carboplatin in Elderly Patients with Locally Advanced NSCLC: JCOG0301. Okamoto et al.

N=200
Median age: 77 years old
PS0-2

RT arm: TRT 60Gy/30 fr

CRT arm: CBDCA 30mg/m²×20 times + TRT 60Gy/30 fr

Updated OS

Updated PFS

<table>
<thead>
<tr>
<th></th>
<th>MST (mo.)</th>
<th>3-yr (%)</th>
<th>HR (95%CI)</th>
<th>p</th>
<th>Med PFS (mo.)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT arm</td>
<td>16.5</td>
<td>14.3%</td>
<td>.64</td>
<td>.0033</td>
<td>6.9</td>
<td>.0030</td>
</tr>
<tr>
<td>CRT arm</td>
<td>22.4</td>
<td>34.6%</td>
<td>(.46-.89)</td>
<td>(one-sided)</td>
<td>8.9</td>
<td>(one-sided)</td>
</tr>
</tbody>
</table>

The CRT using daily carboplatin is considered to be the standard treatment for elderly pts with locally advanced NSCLC.
WJOG;
West Japan Oncology Group
## WJOG/Thoracic Oncology Study Group for NSCLC

<table>
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<tr>
<th>Study number</th>
<th>phase</th>
<th>Target</th>
<th>Reference arm</th>
<th>Experimental arm</th>
<th>Primary endpoint</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>5108L</td>
<td>III since Jun. 2009</td>
<td>Previous treated advanced adeno.</td>
<td>Gefitinib (250mg/day)</td>
<td>Erlotinib (150mg/day)</td>
<td>PFS (non-inferiority)</td>
<td>560</td>
</tr>
<tr>
<td>5208L</td>
<td>III since Jul. 2009</td>
<td>IIIB/IV, squamous</td>
<td>Cis. (80mg/m2) + Doc. (60mg/m2) x 4-6 cycles</td>
<td>Nedaplatin (100mg/m2)+ Doc. (60mg/m2) x 4-6 cycles</td>
<td>OS</td>
<td>350</td>
</tr>
<tr>
<td>5610L</td>
<td>III since Sep. 2010</td>
<td>Advanced non-sq. without harboring EGFR mutation</td>
<td>CBDCA+PEM+ Bev. followed by Bev. alone</td>
<td>CBDCA+PEM+ Bev. followed by Bev.+PEM</td>
<td>OS</td>
<td>620</td>
</tr>
</tbody>
</table>
**WJOG/Thoracic Oncology Study Group for NSCLC**

<table>
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<tr>
<th>Study number</th>
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<th>Experimental arm</th>
<th>Primary endpoint</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3605 (LETs study)*</td>
<td>III</td>
<td>IIIB/IV</td>
<td>Carbo. + Paclitaxel</td>
<td>Carbo. + TS-1</td>
<td>OS (non-inferiority)</td>
<td>560</td>
</tr>
<tr>
<td>6401L (IMPACT)</td>
<td>III</td>
<td>P-II-IIIA. EGFR-mut without T790M</td>
<td>Cis. + VNR</td>
<td>Gefitinib</td>
<td>DFS</td>
<td>230</td>
</tr>
</tbody>
</table>

*; JCO2010; 28: 5240-5246

*The translational research is ongoing.*
**IMPACT; WJOG6401L;** phase III trial of gefitinib as adjuvant therapy in NSCLC with EGFR mutation

**Primary endpoint:** DFS at 5 year

**Secondary endpoints:** OS and toxicity

**n=115**

- Stage II–IIIA
- EGFR mu-positive
- Without T790M
- Complete resection
- PS; 0-1
- 20-74 y.o.

**Randomize**

- Gefitinib 250mg/day for 2 yr.

**Since Sep. 2011**

**Current; 42+**

- Cis. (80mg/m2, day1) + VNR (25mg/m2, day1, 8) q3wks X 4 cycles

- **n=115**

**Stratified by:**

- Institute, Stage, Gender, 19 deletion vs. L858R

- P.I.; Tada H.
The SELECT study: A multicenter phase II trial of adjuvant erlotinib in resected epidermal growth factor receptor (EGFR) mutation-positive NSCLC. Neal et al.

N=63
Asian: 89%
Ex19/L858R: 61%/36%
I/II/IIIA: 53%/19%/28%

Disease Free Survival (DFS)
(from start of adjuvant erlotinib)

2-Year DFS
94% (95% CI 79.5-98.5%)
Median duration of follow-up
2.5 years

Overall Survival

Toxicities; tolerable
Primary endpoint;
2YS; 94%
**Progression Free Survival**

![Progression Free Survival Graph](image)

**Overall survival**

![Overall survival Graph](image)

**QOL**

Score changes of Global Health Status/QoL (items 29 & 30) in the EORTC QLQ-C30

![QOL Graph](image)

**Toxicity (Grade 3/4)**

![Toxicity Graph](image)

Patients responded to EORTC QLQ-C30 3 times: 1. before each treatment, 2. after the first dose of cisplatin, and 3. at the end of the second course. A high score for the Global Health Status/QoL represents a high QoL.

*S-1 plus cisplatin is a standard first-line chemotherapeutic regimen for advanced NSCLC in Japan.*
JIPANG; Randomized Phase III Study of PEM+CDDP and VNR+CDDP in adjuvant setting for completely resected Non-squamous LC

Within 8 weeks after surgery

p-Stage II-IIIA
Completely resected NSCLC
PS: 0-1
Age: 20 - 74 yrs

Stratified factors:
Institute, Gender, Stage, EGFR mut. status, Age (70)

Primary endpoint: Overall survival,
Secondary endpoints: Disease-free survival and toxicity

Cis. (75mg/m², day1) + PEM (500mg/m², day1)
q3wks x 4 cycles

Cis. (80mg/m², day1) + VNR (25mg/m², day1, 8)
q3wks x 4 cycles

n=400
Since Feb. 2012
Current; 20+

n=400

Primary endpoint: Overall survival,
Secondary endpoints: Disease-free survival and toxicity

P.I.; Tsuboi M.
NEJ009; Phase III study comparing gefitinib with gefitinib combined with carboplatin/pemetrexed for advanced non-small cell lung cancer with EGFR mutation

- NSCLC with sensitive EGFR mutations detected by PNA-LNA PCR clamp method
- Without T790M
- Stage IIIB/ IV
- Chemo-naïve
- ECOG PS 0-1
- 20-75 years old

Primary endpoint: Overall survival,
Secondary endpoints: PFS, ORR and toxicity

Carbo. (AUC=5, day1) + PEM (500mg/m2, day1) q3wks x 4 cycles + Gefitinib

Since Oct. 2011
Current; 50 cases +

Gefitinib (250mg/day)

Stratified factors; Institute, Gender, Stage

P.I.; Inoue A.
Summary

- JCOG/LCSSG-WJOG/SSG have several trials regarding surgical issues, especially the focus to sublobar resection for T1a disease.
- JCOG has trials regarding several SCLC and elderly NSCLC.
- WJOG have a lot of studies for NSCLC.
- Several phase III studies are performed by other groups