Cooperative Group Update
- Japan; JCOG & WJOG -

Masahiro Tsuboi, M.D., Ph.D.

Group Chair,
Lung Cancer Surgical Study Group
in Japan Clinical Oncology Group (JCOG)
Chief, Division of Thoracic Surgery,
Kanagawa Cancer Center, Yokohama
Associate-Professor,
Department of Thoracic Surgery & Oncology,
Tokyo Medical University
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

**TCOG**, Tokyo
*Tokyo Clinical Oncology G.*

**NEJ**, Sendai
*North East Japan*

**TCOG**, Tokyo
*Thoracic Oncology Research G.*

**SLCG/OLCSG**, Okayama
*Setouchi Lung Cancer G.*

**JMTO**, Kyoto
*The Japan Multinational Trial Organization*

**LOGIK**, Fukuoka
*Lung Oncology G. in Kyusyu*

**TORG**, Yokohama
*Thoracic Oncology Research G.*

**CJLSG**, Nagoya
*Central Japan Lung Study G.*
JCOG; Lung Cancer Committee

• Organizational Structure
  ▫ Lung Cancer Study Group
    • Chair; Tomohide Tamura, MD  Medical Oncology
  ▫ Lung Cancer Surgical Study Group
    • Chair; Masahiro Tsuboi, MD  Thoracic Surgery

• Mission
  ▫ To establish the Standard of Care for Thoracic malignancies

• Goals
  ▫ Optimize treatment for patient subgroups or individual patients
  ▫ Enhance therapeutic efficacy through translational research (near future issue, because of the JCOG tissue bank)
## 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>H. Kato</td>
<td>Adjuvant Chemotherapy for Stage IA(T1b)-IB</td>
<td>Phase III</td>
</tr>
<tr>
<td>JCOG0804/WJOG4507L</td>
<td>M. Tsuboi</td>
<td>Limited Resection (Wide wedge resection) for Possible Early Lung Cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>JCOG0802/WJOG4607L</td>
<td>H. Asamura</td>
<td>Lobectomy and Limited Resection for NSCLC 2cm or less in size</td>
<td>Phase III</td>
</tr>
</tbody>
</table>
Five year-survival data of radiological non-invasive peripheral lung adenocarcinoma: Prospective cohort study for stage IA lung adenocarcinoma (JCOG0201)

Hishida T, et al. 14th WCLC
JCOG 0201: Objectives

● To validate radiological diagnosis of non-invasive lung adenocarcinoma by thin-section CT (TSCT)

● Inclusion: peripheral cT1N0M0

● Primary endpoint: specificity for radiological diagnosis of pathological non-invasive adeno

● Pathological non-invasive adeno: pN0, V(-), Ly(-)

● Statistical design:
  ➢ Precision-based sample size: 450
  ➢ Expected specificity: lower limit for 95% CI* ≥ 97%

*Confidence interval
Definition of radiological non-invasive lung adenocarcinoma by C/T ratio

Maximum consolidation diameter (C)

Maximum tumor diameter (T)

Consolidation

Ground glass opacity

$T = 17$

$C = 6$

$\frac{C}{T} \text{ ratio} = \frac{6}{17} = 0.35$

Radiological non-invasive lung adenocarcinoma

For cT1a

$\frac{C}{T} \text{ ratio} \leq 0.25^*$

*Exploratory analysis
Study population

811 cT1N0M0 peripheral lung cancer

Pre or intra-op pathology

Adenocarcinoma: 671

Limited resection: 103

Lobectomy: 562

Exploatory thoracotomy: 6

Enrolled from 31 institutions from December 2002 through May 2004

Adenocarcinoma: 545

Others: 17
### JCOG0201; Patient characteristics

**cT1a population (N = 289)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age years (median)</strong></td>
<td>61</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>129</td>
<td>45</td>
</tr>
<tr>
<td>Female</td>
<td>160</td>
<td>55</td>
</tr>
<tr>
<td><strong>Maximum tumor size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1 cm</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 1 cm</td>
<td>260</td>
<td>90</td>
</tr>
<tr>
<td><strong>C/T ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 0.25 (non-invasive on TSCT*)</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 0.25</td>
<td>254</td>
<td>88</td>
</tr>
<tr>
<td><strong>Lymph node</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>277</td>
<td>96</td>
</tr>
<tr>
<td>pN1</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>pN2</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Exploratory analysis*
## Results – Exploratory analysis

### cT1a (N = 289)

<table>
<thead>
<tr>
<th>Radiological diagnosis</th>
<th>Pathological diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-invasive</td>
<td>Invasive</td>
</tr>
<tr>
<td>Non-invasive (C/T ratio ≤ 0.25)</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Invasive (C/T ratio &gt; 0.25)</td>
<td>176</td>
<td>78</td>
</tr>
</tbody>
</table>

**cT1a with C/T ratio ≤ 0.25**

Radiological non-invasive lung adenocarcinoma
JCOG0201; Overall survival

Entire population (N = 545)

- 5 yr-OS: 90.5%

C T1a population (N = 289)

- 5 yr-OS: 93.0%

Median follow-up: 7.5 yrs
Survival of radiological non-invasive lung adenocarcinoma (cT1a with C/T ≤ 0.25; N = 35) vs. radiological invasive cT1a (C/T > 0.25; N = 254)

Overall survival

5yr-OS: 97%

92.4%

p = 0.171

Relapse free survival

5yr-RFS: 97%

87.7%

p = 0.058

Radiological non-invasive lung adenocarcinoma
One death due to unknown cause but no relapse
Survival of predefined radiological non-invasive lung adeno (cT1 with C/T ≤ 0.5; N = 121) vs. radiological invasive cT1 (C/T > 0.5; N = 424)

**Overall survival**
- 5yr-OS: 96.7%
- 88.8%

**Relapse free survival**
- 5yr-RFS: 95.8%
- 81.5%

<table>
<thead>
<tr>
<th>Pre-op size</th>
<th>C/T ratio</th>
<th>p-stage</th>
<th>Relapse</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5cm (cT1b)</td>
<td>0.44</td>
<td>pT1aN2</td>
<td>1.1Y (med LN, lung)</td>
<td>1.5Y (death)</td>
</tr>
<tr>
<td>2.1cm (cT1b)</td>
<td>0</td>
<td>pT1aN0</td>
<td>1.1Y (lung*)</td>
<td>6.1Y (alive)</td>
</tr>
</tbody>
</table>

*second primary?
Summary and future direction

cT1a with C/T ratio ≤ 25% on TSCT

Predicted non-invasive lung adenocarcinoma with a specificity of 98.7%*

*exploratory analysis

5-yr OS: 97%
No relapse

Cured by limited resection?

One arm (phase II) Wide wedge resection* trial (JCOG0804/WJOG4507L) is ongoing

*Segmentectomy without lymph node dissection allowed.
JCOG0201; Conclusions

- C/T ratio ≤ 0.5 failed to predict pathologic non-invasive lung adenocarcinoma.
- Exploratory definition (C/T ratio ≤ 0.25 in cT1a tumors) showed specificity of 98.7% to predict pathological non-invasive lung adeno.
- Survival for *cT1a with C/T ratio ≤ 0.25, "radiological non-invasive adeno"*, was extremely good (5yr-OS: 97.0%; no relapse).
- Favorable outcome of wide wedge resection trial for this population is expected.
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)
JCOG0804/WJOG4507L (early NSCLC LR P2)

Final enrollment: 334 cases at this April
JCOG0802/WJOG4607L; Phase III Randomized Trial between Lobectomy and Limited Resection for Part-solid GGO – Solid T1a disease

Non-inferiority design

Randomize

Periperal carcinoma, <=2 cm
Negative hilar node

Lobectomy
Since Aug. 2009

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)
**Statistical Plan**

- In order to have a 80% power to detect a hazard ratio of 1.54 (lobectomy v.s. segmentectomy), using a one-sided 5.0% level test, 1030 patients were required over 3 years with 5 years follow-up.

- The minimum number of events required for final analysis was 131 deaths.
JCOG0802/WJOG4506L
(small NSCLC LB vs. SG P3)

Current enrollment: 316 cases at this July
JCOG0707

Randomized phase III study

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

n=480

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

n=480

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

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

Current enrollment: 551 cases at this July

Accrual number in month
Estimated accrual number
Accumulated accrual number
# JCOG/Lung Cancer Study Group for SCLC

<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>
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</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>r 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
# 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>
JCOG0803/WJOG4307L; Study Design

<table>
<thead>
<tr>
<th>Stratification</th>
<th>Docetaxel alone (D)</th>
<th>Weekly Docetaxel + Cisplatin (DP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 70 yrs</td>
<td>Docetaxel 60 mg/m² on Day 1, 8, 15, 22, 29</td>
<td>Docetaxel 20 mg/m² on Day 1, 8, 15, 22, 29</td>
</tr>
<tr>
<td>PS 0,1</td>
<td></td>
<td>Cisplatin 25 mg/m² on Day 1, 8, 15, 22, 29</td>
</tr>
<tr>
<td>Advanced NSCLC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Both treatments were repeated until disease progression or unacceptable toxicity.
Results of 1\textsuperscript{st} Interim Analysis

- The 1\textsuperscript{st} planned interim analysis
  - Performed on 221 assessable patients on Sep 2010
  - D/DP: 108/113, <75/\geq75: 22/78\%, PS0/1: 35/65\%, III/IV: 32/68\%
  - Information time: 24\%
    (observed events 73/ planned events 304)

- MST (months)
  
<table>
<thead>
<tr>
<th></th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>17.3</td>
</tr>
<tr>
<td>DP</td>
<td>13.3</td>
</tr>
<tr>
<td>HR</td>
<td>1.557 [99.99% CI 0.624-3.884], p=0.969*</td>
</tr>
</tbody>
</table>

- The predictive probability that DP would be superior to D at the time of the final analysis was 0.996\%.
  → Recommendation for early termination of the study
### Progression-Free Survival

**Arm** | **N** | **Events** | **Median (m)** | **6M-PFS (%)**
--- | --- | --- | --- | ---
D | 134 | 116 | 4.4 [3.4-5.1] | 32.0 [24.0-40.2]
DP | 138 | 117 | 4.7 [4.1-5.8] | 40.7 [32.1-49.1]

HR: 0.924 [95% C.I. 0.714-1.197], p = 0.3036*

* Data cut-off: Nov/2010
* Log-rank test, one-sided
Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>Median (m) [95% C.I.]</th>
<th>1y-survival (%) [95% C.I.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>138</td>
<td>65</td>
<td>13.3 [10.8-19.4]</td>
<td>54.5 [44.8-63.3]</td>
</tr>
</tbody>
</table>

HR: 1.183 [95% C.I. 0.830-1.687], p = 0.824*

Median follow-up time for censored case: 13.1 months

Data cut-off: Nov/2010

*stratified log-rank by age, one-sided
Subset Analysis (Age <75 vs. ≥75)

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>MST (m)</th>
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</thead>
<tbody>
<tr>
<td>D (n=30)</td>
<td>10</td>
<td>24.1</td>
</tr>
<tr>
<td>DP (n=32)</td>
<td>12</td>
<td>17.3</td>
</tr>
<tr>
<td>**HR:**1.474</td>
<td>[95%CI 0.621-3.501]</td>
<td></td>
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<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>MST (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D (n=104)</td>
<td>49</td>
<td>14.5</td>
</tr>
<tr>
<td>DP (n=106)</td>
<td>53</td>
<td>13.3</td>
</tr>
<tr>
<td>**HR:**1.131</td>
<td>[95%CI 0.767-1.669]</td>
<td></td>
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</table>
Symptom Score (FACT-L)

Compliance:
- Baseline: 271 pts (98.2%)
- 6/8 weeks later: 258 pts (93.5%)
- 9/12 weeks later: 247 pts (89.5%)

Primary analysis: Proportion of pts with an improved symptom score at 9/12 weeks later.
- D arm: 53/135 (39.3%)
- DP arm: 50/136 (36.8%)

Secondary analysis: Averages of total scores and 95%C.I. at each point
Summary

◆ The MST of DP and D were 13.3 and 17.3 months, respectively, and the predictive probability that DP would be superior to D at the time of the final analysis was 0.996% in the 1st interim analysis.

◆ The updated MST of DP and D were 13.3 and 14.8 months, respectively.

◆ There were no significant differences between the two arms in PFS and response rate.

◆ The incidence of hematological toxicity was higher in D, and non-hematological toxicity was adversely higher in DP. These toxicities were well tolerable.

◆ Symptom score was more favorable in D than DP.

◆ There were no significant differences in EGFR mutation status and subsequent chemotherapies between the two arms in the additional analysis.
Conclusions

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.
WJOG; Lung Cancer Committee

- Organizational Structure
  - Thoracic Oncology Study Group
    - Chair; Kazuhiko Nakagawa, MD  Medical Oncology
  - Lung Cancer Surgical Study Group
    - Chair; Hirohito Tada, MD  Thoracic Surgery

- Mission
  - To establish the Standard of Care for Thoracic malignancies

- Goals
  - Optimize treatment for patient subgroups or individual patients
  - Enhance therapeutic efficacy through translational research
### WJOQ/Thoracic Oncology 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>0101</td>
<td>III</td>
<td>Postope. adjuvant, p-stage IB-IIIA</td>
<td>UFT (250mg/m2, 1year)</td>
<td>GEM (1000mg/m2, 6 cycles)</td>
<td>OS</td>
<td>600</td>
</tr>
<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>
</tbody>
</table>

*; The translational research is ongoing.
# WJOG/Thoracic Oncology 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>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>
Planning trials

*Postoperative adjuvant studies*
WJOG6401L; phase III trial of gefitinib as adjuvant therapy in NSCLC harboring activating mutation

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

Gefitinib 250mg/day for 2 yr.

n=115

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

n=115

Stratified by:
Institute, Stage, Gender, 19 deletion vs. L858R

Primary endpoint; DFS at 5 year
Secondary endpoints: OS and toxicity

P.I.; Tada H.
JIPANG; Randomized Phase III Study of PEM+CDDP and VNR+CDDP for completely resected Non-squamous LC

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

Within 8 weeks after surgery

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

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

n=400

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

n=400

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

P.I.; Tsuboi M.
JCOG-WJOG; Randomized Phase III Study of Irinotecan+CDDP and ETP+CDDP for completely resected high neuroendocrine tumors (LCNEC, SCLC)

p-Stage I-IIIA
Completely resected HR-LC
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

Cis. (60mg/m2, day1) + CPT-11 (60mg/m2, day1, 8, 15) q4wks x 4 cycles

Cis. (80mg/m2, day1) + ETP (100mg/m2, day1-3) q3wks x 4 cycles

n=320

P.I.; Tsuboi M.
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 adjuvant trials are being planned.