Cooperative Group Update - Japan: JCOG & WJOG

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

Chair, Lung Cancer Surgical Study Group
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

NEJ, Sendai
North East Japan Clinical Oncology Group

TCOG, Tokyo
Tokyo Clinical Oncology Group

TORG, Yokohama
Thoracic Oncology Research Group

CJLSG, Nagoya
Central Japan Lung Study Group

JMTO, Kyoto
The Japan Multinational Trial Organization

SLCG/OLCSG, Okayama
Setouchi Lung Cancer Group

LOGIK, Fukuoka
Lung Oncology Group in Kyusyu

JCOG; Lung Cancer Committee

- Organizational Structure
  - Lung Cancer Study Group
    - Chair: Tomohide Tamura, M.D. Medical Oncology
  - Lung Cancer Surgical Study Group
    - Chair: Masahiro Tsuboi, M.D. Thoracic Surgery

- Mission
  - To establish the Standard of Care for Thoracic malignancies
  - Optimize treatment for patient subgroups or individual patients
  - Enhance therapeutic efficacy through translational research
    (near future issue, because of the JCOG tissue bank)
Slide 4

<table>
<thead>
<tr>
<th>Study No.</th>
<th>P.I.</th>
<th>Trial Description</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCOG0201</td>
<td>T. Koike</td>
<td>Diagnosis of Radiological Early Lung Cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>JCOG0707</td>
<td>H. Kato</td>
<td>Adjuvant Chemotherapy for Stage IA/IB-III</td>
<td>Phase III</td>
</tr>
<tr>
<td>WJOG4507L</td>
<td>M. Tsuboi</td>
<td>Limited Resection (Wide resection) for Possible Early Lung Cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>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>

Slide 5

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

Slide 6

**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 adenocarcinoma
- Pathological non-invasive adenocarcinoma: pN0, V(−), Ly(−)
- Statistical design:
  - Precision-based sample size: 450
  - Expected specificity: lower limit for 95% CI ≥ 97%

*Confidence interval*
**Slide 7**

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

Maximum tumor diameter (T)

Maximum consolidation diameter (C)

Consolidation = ground glass opacity

C/T ratio ≤ 0.5

Radiological non-invasive lung adenocarcinoma

*Exploratory analysis*

For cT1a

C/T ratio ≤ 0.25*

---

**Slide 8**

**Study population**

811 cT1N0M0 peripheral lung cancer

Adenocarcinoma: 671

Limited resection: 103

Lobectomy: 562

Adenocarcinoma: 545

Enrolled from 31 institutions from December 2002 through May 2004

Exploratory thoracotomy: 6

Others: 17

---

**Slide 9**

**JCOG0201: Patient characteristics**

**cT1a population (N = 289)**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (median)</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Gender</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>Maximum tumor size</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>C/T ratio</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>Lymph node</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*
**Slide 10**

### Results – Exploratory analysis

<table>
<thead>
<tr>
<th>Radiological diagnosis</th>
<th>Pathological diagnosis</th>
<th>cT1a (N = 289)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive (C/T ≤ 0.25)</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Invasive (C/T &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

**cT1a with C/T ratio > 0.25**

Radiological invasive lung adenocarcinoma

---

**Slide 11**

### JCOG0201; Overall survival

<table>
<thead>
<tr>
<th>Entire population (N = 545)</th>
<th>cT1a population (N = 289)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5yr-OS</td>
<td>5yr-OS</td>
</tr>
<tr>
<td>90.5%</td>
<td>93.0%</td>
</tr>
</tbody>
</table>

---

**Slide 12**

### 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%
  - 5yr-RFS: 97%
  - p = 0.058

- **Relapse free survival**
  - 5yr-RFS: 87.7%
  - p = 0.171

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 Relapse free survival

<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</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</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%*

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.
Slide 16

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 events (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 2009**

PI; Tsuboi M (JCOG) & Yoshino I (WJOG)

---

Slide 17

JCOG0804/WJOG4507L (early NSCLC LR P2)

Final enrollment: 334 cases at this April

Accrual number in month
Estimated accrual number
Accumulated accrual number

---

Slide 18

JCOG0802/WJOG4607L: Phase III Randomized Trial between Lobectomy and Limited Resection for Part-solid GGO – Solid T1a disease

- **Endpoints**:
  - Primary: OS
  - Secondary: pulmonary function

- **Sample size**: 1,100

- **Non-inferiority design**

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

Since Aug. 2009

PI: Asamura H. (JCOG) & Okada M (WJOG)
**Slide 19**

**JCOG0802/WJOG4607L**

- **Statistical Plan**
  - In order to have a 80% power to detected 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.

---

**Slide 20**

**JCOG0802/WJOG4506L**

(Jan NSCLC LB vs SG P3)

Current enrollment: 316 cases at this July

Accrual number in month

Estimated accrual number

Accumulated accrual number

---

**Slide 21**

**JCOG0707**

Randomized phase III study

n=480

p-Stage IA (2cm-), IB
Completely resected NSCLC 
P5, D-1
Age: 20 - 75 y
Within 8 weeks after surgery

Randomized by:

- Center
- Gender
- Size
- Histology
- Age

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

P.I.: Tsuboi M.
Slide 22

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

Current enrollment: 551 cases at this July

Slide 23

JCOG/Lung Cancer Study Group for SCLC

JCOG1011

Slide 24

JCOG/Lung Cancer Study Group for NSCLC

Study number, phase, target population, reference arm, experimental arm, primary endpoint, sample size, overall survival.
**Slide 25**

**Study Design**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Treatment</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Docetaxel alone (D)</td>
<td>1, 8, 15, 22, 29</td>
</tr>
<tr>
<td>D + C</td>
<td>Docetaxel 60 mg/m², Cisplatin 25 mg/m²</td>
<td>1, 8, 15, 22, 29</td>
</tr>
</tbody>
</table>

Both treatments were repeated until disease progression or unacceptable toxicity.

---

**Slide 26**

**Results of 1st Interim Analysis**

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

- 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

---

**Slide 27**

**Progression-Free Survival**

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>Median (m)</th>
<th>[95% C.I.]</th>
<th>6M-PFS (%)</th>
<th>[95% C.I.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>134</td>
<td>116</td>
<td>4.4</td>
<td>[3.4 - 5.1]</td>
<td>32.0</td>
<td>[24.0 - 40.2]</td>
</tr>
<tr>
<td>DP</td>
<td>138</td>
<td>117</td>
<td>4.7</td>
<td>[4.1 - 5.8]</td>
<td>40.7</td>
<td>[32.1 - 49.1]</td>
</tr>
</tbody>
</table>

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

* Months after randomization

---
**Overall Survival**

Median follow-up time for censored cases: 13.1 months

<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*

*stratified log-rank by age, one-sided

Data cut-off: Nov/2010

**Subset Analysis**

<table>
<thead>
<tr>
<th>Age &lt;75</th>
<th>≥75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>MST (m)</td>
</tr>
<tr>
<td>D</td>
<td>49</td>
</tr>
<tr>
<td>DP</td>
<td>53</td>
</tr>
<tr>
<td>HR</td>
<td>1.131</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age &lt;75</th>
<th>≥75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>MST (m)</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
</tr>
<tr>
<td>DP</td>
<td>12</td>
</tr>
<tr>
<td>HR</td>
<td>1.474</td>
</tr>
</tbody>
</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

p=0.496
**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.

**JCOG0803/WJOG4307L; 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
  - To optimize treatment for patient subgroups or individual patients
  - Enhance therapeutic efficacy through translational research
Slide 34

<table>
<thead>
<tr>
<th>Study number</th>
<th>phase</th>
<th>Target</th>
<th>Reference</th>
<th>Experimental</th>
<th>Primary endpoint</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0101</td>
<td>III</td>
<td>Postope. adjuvant, pT1N0M0 ; IIIb/IV</td>
<td>UFT (250mg/m², 3year)</td>
<td>GEM (100mg/m², 6 cycles)</td>
<td>OS</td>
<td>800</td>
</tr>
<tr>
<td>36ET (LETS study)</td>
<td>III</td>
<td>Cartes. + Paclitaxel</td>
<td>Cartes. + TS-1</td>
<td>OS (non-inferiority)</td>
<td>160</td>
<td></td>
</tr>
</tbody>
</table>

* The translational research is ongoing.

Slide 35

<table>
<thead>
<tr>
<th>Study number</th>
<th>phase</th>
<th>Target</th>
<th>Reference</th>
<th>Experimental</th>
<th>Primary endpoint</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>5108</td>
<td>III</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>5208</td>
<td>III</td>
<td>IIIB/IV, squamous</td>
<td>Cis (80mg/m²) + Doc. (60mg/m²) x 4-6 cycles</td>
<td>Nedaplatin (150mg/m²) + Doc. (60mg/m²) x 4-6 cycles</td>
<td>OS</td>
<td>330</td>
</tr>
<tr>
<td>5610</td>
<td>III</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>

Slide 36

Planning trials

Postoperative adjuvant studies
Slide 37

**WJOG6401L**: phase III trial of gefitinib as adjuvant therapy in NSCLC harboring activating mutation

- **Primary endpoint**: DFS at 5 years
- **Secondary endpoints**: OS and toxicity

Stratified by:
- Institute
- Stage
- Gender
- T790M vs. EGFR mutant status

**Randomization**
- gefitinib 250mg/day for 2 yrs.
- Cis. (80mg/m², day1) + VNR (25mg/m², day1, 8) q3wks x 4 cycles

**n=115**

Slide 38

**JIPANG**: Randomized Phase III Study of PEM+CDDP and VNR+CDDP for completely resected Non-squamous LC

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

Stratified factors:
- Institute
- Gender
- Stage
- EGFR mutant status
- Age

**Randomization**
- 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**

Slide 39

**JCOG-WJOG**: Randomized Phase III Study of Irinotecan+CDDP and ETP+CDDP for completely resected high neuroendocrine tumors (LCNEC, SCLC)

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

Stratified factors:
- Institute
- Gender
- Stage
- Histology (SCLC/LCNEC)
- Age

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

**n=320**
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 planning.