Randomized phase III trial of adjuvant chemotherapy with gemcitabine vs. S-1 for resected pancreatic cancer patients (JASPAC 01 study)

Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC)

Presented at the Gastrointestinal Cancers Symposium
Presented data is the property of the author.
JASPAC 01  Disclosure

- **Sponsor**: Pharma Valley Center, Shizuoka Industrial Foundation

- **Funder**: TAIHO Pharmaceutical Co. Ltd., Japan.
CONKO-001 trial (JAMA 2007)
Post-op adjuvant chemotherapy (gemcitabine: GEM) prolonged DFS of resected pancreatic cancer (PC) pts.

GEM is a standard treatment for resected PC pts.

GEST trial (ASCO 2011)
Monotherapy with S-1, oral fluoropyrimidine, showed non-inferiority to GEM for unresectable PC pts.

S-1 is an option of standard care for advanced PC pts in Japan.
S-1 (tegafur, gimeracil, oteracil potassium) is an oral “DPD inhibitory fluoropyrimidine (DIF)” widely used to treat various solid tumors in East Asia.

Biochemical action of S-1

- **DPD**, dihydropyrimidine dehydrogenase
- **OPRT**, orotate phosphoribosyltransferase
- **5-FU**
- **FUMP**
- **F-β-Ala**
- **Gimeracil**
- **Oteracil potassium**
- **Bone marrow**
- **Liver and Tumor (CYP 2A6)**
- **Tumor**
- **GI tract**
- **Neurotoxicity**
- **Degradation**
- **Phosphorylation**

**Antitumor activity**
**GI toxicity**
**Myelotoxicity**
JASPAC 01 Objective

Objective
To assess non-inferiority of S-1 to GEM on overall survival (OS) as adjuvant chemotherapy for resected PC

Endpoints
- Primary endpoint: OS
- Secondary endpoints: Relapse-free survival, Adverse events, Health-related QOL
JASPAC 01 Study Design

- Randomized, phase III, open-label, multicenter study

**Curative resection for PC**

Within 10 weeks after surgery

**Randomization**

- **Stratification factors**
  - Institution
  - Residual tumor status (R0/R1)
  - Nodal status (N0/N1)

- **GEM 1000mg/m²**
  Div on days 1, 8, and 15, repeated every 4 wks, for 6 courses

- **S-1 40-60mg**, twice a day
  4 wks oral administration, repeated every 6 wks, for 4 courses
JASPAC 01 Major Eligibility Criteria

- Histologically proven invasive ductal adenocarcinoma of the pancreas
- UICC (ver. 6) stage II or lower, or stage III with combined resection of the celiac artery
- Histologically confirmed R0 or R1 residual disease
- Peritoneal lavage cytology showing negativity for cancer cells
- ECOG performance status of 0 or 1
- No previous chemo- or radiotherapy within 3 years
- Enrollment within 10 weeks after pancreatectomy
- Adequate renal, hepatic and bone marrow function
- Written informed consent
JASPAC 01 Statistics

- Assessment of non-inferiority of S-1 to GEM

- Hypothesis
  - 3-year survival of GEM: 36%
  - Expected hazard ratio (HR) of S-1: 0.87
  - Non-inferiority margin of HR: 1.25

- Required sample size
  - n=360 (randomized 1:1)
    - power = 80%    two sided alpha = 0.05
**JASPAC 01 Recruitment and Analysis**

- **Planned analysis**
  - Interim analysis: 180 deaths, \( \alpha \) (one sided) = 0.001
  - Final analysis: 240 deaths

- **Enrollment**
  - 385 pts, Apr. 2007 – Jun. 2010 (3 years 3 months)
  - From 33 institutions in Japan

- **Interim analysis**
  - Aug. 2012, based on the follow-up data up to Jul. 2012
JASPAC 01 Recommendation from IDMC after the Interim Analysis

Independent data monitoring committee statement

The IDMC recommended the investigators to publish the results of the interim analysis, on survival data up to Jul. 2012, immediately.
JASPAC 01  Patient Disposition

385 patients enrolled
Apr. 2007 – Jun 2010

193 pts for GEM
1 pt: recurrence on the enrolled day
192 eligible pts for GEM
1 pt: no treatment
191 pts for GEM (99%)

192 pts for S-1
1 pt: paraaortic node mets at surgery
191 eligible pts for S-1
4 pts: no treatment
187 pts for S-1 (97%)

Full analysis set: 378 pts
## JASPAC 01  Patient Demographics (1)

### Patient characteristics, Baseline data

<table>
<thead>
<tr>
<th></th>
<th>GEM (n=191)</th>
<th>S-1 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> yrs</td>
<td>65.7 [8.6]</td>
<td>65.9 [9.5]</td>
</tr>
<tr>
<td><strong>Gender</strong> male / female</td>
<td>104 (54%) / 87 (46%)</td>
<td>106 (57%) / 81 (43%)</td>
</tr>
<tr>
<td><strong>ECOG PS</strong> 0 / 1</td>
<td>128 (67%) / 63 (33%)</td>
<td>131 (70%) / 56 (30%)</td>
</tr>
<tr>
<td><strong>White blood cell</strong> /mm³</td>
<td>5599 [1496]</td>
<td>5646 [1677]</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong> g/dL</td>
<td>11.7 [1.2]</td>
<td>11.9 [1.1]</td>
</tr>
<tr>
<td><strong>Platelet</strong> × 10⁴/mm³</td>
<td>26.6 [8.4]</td>
<td>28.0 [10.4]</td>
</tr>
<tr>
<td><strong>ALT</strong> IU/L</td>
<td>29.9 [19.2]</td>
<td>32.1 [19.6]</td>
</tr>
<tr>
<td><strong>AST</strong> IU/L</td>
<td>29.8 [15.9]</td>
<td>29.4 [14.5]</td>
</tr>
<tr>
<td><strong>Total Bilirubin</strong> mg/dL</td>
<td>0.6 [0.2]</td>
<td>0.6 [0.2]</td>
</tr>
<tr>
<td><strong>Creatinine</strong> mg/dL</td>
<td>0.6 [0.2]</td>
<td>0.6 [0.2]</td>
</tr>
</tbody>
</table>

* Mean [SD]
## JASPAC 01 Patient Demographics (2)

### Tumor characteristics

<table>
<thead>
<tr>
<th></th>
<th>GEM (n=191)</th>
<th>S-1 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong></td>
<td>1,2 / 3,4</td>
<td>1,2 / 3,4</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>0 / 1</td>
<td>0 / 1</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>I / II, III</td>
<td>I / II, III</td>
</tr>
<tr>
<td><strong>R</strong></td>
<td>0 / 1</td>
<td>0 / 1</td>
</tr>
<tr>
<td><strong>CA19-9</strong></td>
<td>≤37 / &gt;37</td>
<td>≤37 / &gt;37</td>
</tr>
<tr>
<td><strong>Operative procedure</strong></td>
<td>PD# / DP##</td>
<td>PD# / DP##</td>
</tr>
</tbody>
</table>

- **PD**: pancreaticoduodenectomy
- **DP**: distal pancreatectomy

*Not measured in 1 pt of the S-1 group, **excluding 5 pts undergoing total pancreatectomy*
JASPAC 01 Overall Survival

- S-1  82 pts (44%) dead
- GEM 123 pts (64%) dead
Total deaths: 205 pts

2-year OS
- S-1 70% [95% CI, 63-76]
- GEM 64% dead

HR of S-1 = 0.56
[99.8% CI, 0.36-0.87]
P<0.0001 for non-inferiority
P<0.001 for superiority (log-rank test)

2-year OS
- S-1 53% [95% CI, 46-60]
- GEM 50% [95% CI, 42-58]

median OS: 25.5 months

No. at risk
- S-1 187 172 127 68 28 1
- GEM 191 151 95 51 16 3

P<0.0001 for non-inferiority
P<0.0001 for superiority (log-rank test)

Presented at the Gastrointestinal Cancers Symposium #145 2013 ASCO GI
JASPAC 01  Relapse-Free Survival

- S-1 median: 23.2 months [95% CI, 17.5-32]
- GEM median: 11.2 months [95% CI, 9.7-13.5]

HR of S-1 = 0.56 [95% CI, 0.43-0.71]

2-year RFS
49% [95% CI, 42-57]
29% [95% CI, 22-35]

log-rank: p<0.0001

No. at risk
S-1 187 126 89 45 26 1
GEM 191 90 53 30 10 1

Presented at the Gastrointestinal Cancers Symposium #145 2013 ASCO GI
## JASPAC 01  Compliance for Protocol Treatment

<table>
<thead>
<tr>
<th></th>
<th>GEM (n=191)</th>
<th>S-1 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completed</strong></td>
<td>110 pts (58%)</td>
<td>135 pts (72%)</td>
</tr>
<tr>
<td><strong>Discontinued</strong></td>
<td>81 pts (42%)</td>
<td>52 pts (28%)</td>
</tr>
</tbody>
</table>

(Reasons for discontinuation)

<table>
<thead>
<tr>
<th>Reason</th>
<th>GEM</th>
<th>S-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>26 (14%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>48 (25%)</td>
<td>40 (21%)</td>
</tr>
<tr>
<td>Pt’s refusal</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
### Laboratory data

<table>
<thead>
<tr>
<th></th>
<th>GEM (n=191)</th>
<th>S-1 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>32%</td>
<td>7%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Platelets</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>AST</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>ALT</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

(CTCAE Ver. 3.0)
## JASPAC 01  Adverse Events (2)

### Symptoms

<table>
<thead>
<tr>
<th></th>
<th>GEM (n=191)</th>
<th>S-1 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Fever</td>
<td>0.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

(CTCAE Ver. 3.0)
JASPAC 01 Summary

The interim analysis of JASPAC 01 study showed:

- OS of the GEM group was very similar to CONKO-001
  median: JASPAC 01 25.5 months, CONKO-001 22.1 months

- non-inferiority of S-1 to GEM on OS

- even superiority of S-1 to GEM on OS

- improved RFS in the S-1 group compared with the GEM group

- both S-1 and GEM were well tolerated in adjuvant setting
JASPAC 01  Conclusions

- Adjuvant chemotherapy with S-1 for resected PC pts is shown superior to GEM

- S-1 may be considered as the new standard treatment for resected PC pts
Acknowledgement

We thank the patients, their families, clinicians, and support staffs who participated in this study.

Participating Institutions

- Shizuoka Cancer Center Hospital
- National Cancer Center Hospital East
- Kobe University Graduate School of Medicine
- Ogaki Municipal Hospital
- Aichi Cancer Center Hospital
- Osaka National Hospital
- Saitama Cancer Center
- Kanagawa Cancer Center
- Chiba Cancer Center
- Asahikawa Medical University
- Jichi Medical University
- Tochigi Cancer Center
- Gunma Prefectural Cancer Center
- Kasugai Municipal Hospital
- Hokkaido University Graduate School of Medicine
- National Hospital Organization Kure Medical Center
- Toyohashi Municipal Hospital
- Shikoku Cancer Center
- Shizuoka General Hospital
- University of Tsukuba
- Nagoya University
- Fujita Health University
- Yamagata University
- Yokohama City University
- National Hospital Organization Kyushu Cancer Center
- Hyogo Prefectural Nishinomiya Hospital
- Seirei Mikatahara General Hospital
- Toyama Prefectural Central Hospital
- Tokyo Women's Medical University
- Tokyo Women's Medical University Medical Center East
- Tokyo Women's Medical University Yachiyo Medical Center
- Kushiro City General Hospital
- Hirosaki University

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