Randomized Phase III Trial of Paclitaxel plus Carboplatin (TC) Therapy versus Irinotecan plus Cisplatin (CPT-P) Therapy as First Line Chemotherapy for Clear Cell Carcinoma of the Ovary

Aikou Okamoto*1, Toru Sugiyama*2, Tetsutaro Hamano*3, Jae-Weon Kim*4, Byoung-Gie Kim*5, Takayuki Enomoto*6, Daishuke Aoki*7, Yasuhisa Terao*8, Nao Suzuki*9, Mikio Mikami*10, Nobuo Yaegashi*11, Kiyoko Kato*12, Hiroyuki Yoshikawa*13, Sandro Pignata*14, Jerome Alexandre*15, John Green*16, Seiji Isonishi*17, Fumitoshi Terauchi*17, Keiichi Fujiwara*18, Kazunori Ochiai*1

What is CCC and Why is Japan leading the Trial?

- Clear Cell Carcinoma of the Ovary (CCC) is one of the histological entities of epithelial ovarian cancer (1973, WHO classification)
- Incidence of CCC is rare in Western Countries (5%), but it is not rare in Japan (>20%)
- Retrospective studies conducted in Japan indicated that CCC is less sensitive to chemotherapy and prognosis is poorer than in cases of serous/endometrioid adenocarcinoma of the ovary.

   The critical question is whether paclitaxel/carboplatin (TC) therapy, the current standard for epithelial ovarian cancer (EOC) based upon the results of multiple RCTs, is an optimal regimen for CCC. Although the response rate of TC therapy for EOC is approximately 75%, this rate may not be applicable to CCC.
Ovarian Carcinoma: Histology

Annual Report 2003
From 562 Hospitals
AOGJ 54:746, 2002

Distribution by Histology in Japan 2011
n=4672

AOGJ 61, 2011
### Clear Cell Carcinoma vs Serous Adenocarcinoma: Overall Survival

#### Stage Ic

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Stage Ic (%)</th>
<th>Stage III (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous (n=22)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Clear cell (n=38)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Proportion surviving**

- Survival (months): 0, 12, 24, 36, 48, 60
- **P** = 0.2761

#### Stage III

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Stage Ic (%)</th>
<th>Stage III (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous (n=135)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Clear cell (n=31)</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

**Proportion surviving**

- Survival (months): 0, 12, 24, 36, 48, 60
- **P** = 0.0015

---

### Rational

Retrospective studies\(^1, \ 2\) and a randomized phase II trial \(^3\) showed that irinotecan is a promising candidate for the treatment of CCC.

---

JGOG 3017/GCIG: Schema

- Clear Cell Ca
- Stage I–IV

**Randomization**

**TC**
- Paclitaxel 175 mg/m² (d1)
- Carboplatin AUC 6 (d1)
  - Every 3 wk x 6

**CPT-11/CDDP**
- CPT-11 60 mg/m² (d1, 8, 15)
- Cisplatin 60 mg/m² (d1)
  - Every 4 wk x 6

326 patients in each arm, 652 total for 4.25 years

**Study Chair** Toru Sugiyama, MD (Iwate Medical University)
**Study Co-Chair** Seiji Isonishi, MD (Jikei University School of Medicine)
Fumitoshi Terauchi, MD (Toho University)

JGOG 3017/GCIG: Objectives

- Primary endpoint was progression-free survival (PFS).
- Secondary endpoints were overall survival (OS), response rate (in cases with measurable disease only), and adverse event (frequency and grade).
• **Sample size calculation**
  - Assuming that the 5 year PFS of TC arm and CPT-P arm are 40% and 50%, respectively, with an accrual period of 4.25 years and total duration of 6.5 years, 652 patients and 323 events are required with a one-sided type I error of 0.05 and a power of 80% using log-rank test.
  - After protocol modification due to an unexpectedly large proportion of patients with non-clear cell carcinoma, with an accrual period of 4.75 years and total duration of 6.75 years, 662 patients are required.

---

**JGOG 3017/GCIG: Statistical Considerations (cont.)**

• **Primary analysis set**
  - All randomized patients whose histological diagnosis are confirmed by a central pathology review.

• **Interim analyses**
  - Single formal interim analysis for efficacy and annual informal interim analyses for futility planned and carried out.
  - At the time of interim analysis, IDMC recommended continuing study.

• **All p-values reported in this slide are two-sided.**
Eligibility

- Stage I to IV CCC
  All patients must have had comprehensive staging surgery for ovarian carcinoma with appropriate tissue available for histological evaluation.
- Patients must be enrolled within 6 weeks after surgery.
- Clear cell histology must be dominant (> 50%).
  The histological diagnosis was confirmed by an international central pathology review (I-CPR) after registration.

GCIG/JGOG 3017: Accrual

- Last Patient Follow up: March 2013
- Final Data Analysis: September 2013

622 pts --Japan
25 pts --Korea
12 pts --France
7 pts --UK

Total of 666 pts,
Closed accrual on March 1, 2011.
**JGOG 3017/GCIG: Patient Enrollment**

<table>
<thead>
<tr>
<th>Patient Enrollment</th>
<th>TC</th>
<th>CPT-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled</td>
<td>667</td>
<td></td>
</tr>
<tr>
<td>Patients registered*</td>
<td>666</td>
<td></td>
</tr>
<tr>
<td>Patient randomized**</td>
<td>332</td>
<td>332</td>
</tr>
<tr>
<td>Patients eligible** ** ***</td>
<td>305</td>
<td>314</td>
</tr>
</tbody>
</table>

* Reason: Duplicated patient registration: 1
** Reason: Patient consent withdrawal: 4
*** Reason: Excluded by International Central Pathological Review Committee: 43 (6.5%)

**JGOG 3017/GCIG: Demographics & Baseline Characteristics**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>TC(n=305)</th>
<th>CPT-P(n=314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age --- Median(Min-Max)</td>
<td>53y(30-81)</td>
<td>53y(30-75)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>281(48.5%)</td>
<td>298(51.5%)</td>
</tr>
<tr>
<td>Non-Japanese</td>
<td>24(40.0%)</td>
<td>16(40.0%)</td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>268(47.9%)</td>
<td>291(52.1%)</td>
</tr>
<tr>
<td>1</td>
<td>37(61.7%)</td>
<td>23(38.3%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia-Ib</td>
<td>145(47.8%)</td>
<td>152(48.2%)</td>
</tr>
<tr>
<td>II-IV</td>
<td>160(54.1%)</td>
<td>162(52.0%)</td>
</tr>
<tr>
<td>Size of residual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>267(49.1%)</td>
<td>277(50.9%)</td>
</tr>
<tr>
<td>Optimal (&lt;1cm)</td>
<td>19(52.8%)</td>
<td>17(47.2%)</td>
</tr>
<tr>
<td>Suboptimal (&gt;1cm)</td>
<td>19(48.7%)</td>
<td>20(51.3%)</td>
</tr>
</tbody>
</table>

Stage I: 66.4%
Complete: 87.9%
JGOG 3017: 2-year PFS for TC vs CPT-P

HR(95%CI) = 1.171 (0.867, 1.581)
Two-sided log rank p-value = 0.303

<table>
<thead>
<tr>
<th>Events / Patients</th>
<th>CPT-P</th>
<th>TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year PFS</td>
<td>92 / 314</td>
<td>79 / 305</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(67.7, 77.5)</td>
<td>(72.4, 81.9)</td>
</tr>
</tbody>
</table>

JGOG 3017: 2-year OS for TC vs CPT-P

HR(95%CI) = 1.133 (0.796, 1.613)
Two-sided log rank p-value = 0.486

<table>
<thead>
<tr>
<th>Events / Patients</th>
<th>CPT-P</th>
<th>TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year OS</td>
<td>66 / 314</td>
<td>58 / 305</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(81.1, 89.0)</td>
<td>(83.1, 90.7)</td>
</tr>
</tbody>
</table>
JGOG 3017: PFS Subgroup Analysis

** Progression-Free Survival: Subgroup Analysis **

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage Ia or Ib</td>
<td>96</td>
<td>2.126</td>
<td>0.899 to 11.612</td>
</tr>
<tr>
<td>Stage Ic</td>
<td>315</td>
<td>0.487</td>
<td>0.347 to 1.528</td>
</tr>
<tr>
<td>Stage II/IV</td>
<td>208</td>
<td>1.271</td>
<td>0.881 to 1.834</td>
</tr>
<tr>
<td>Residual 0cm</td>
<td>544</td>
<td>1.190</td>
<td>0.815 to 1.738</td>
</tr>
<tr>
<td>Residual ≤ 1cm</td>
<td>36</td>
<td>1.576</td>
<td>0.757 to 3.281</td>
</tr>
<tr>
<td>Residual &gt; 1cm*</td>
<td>39</td>
<td>1.378</td>
<td>0.697 to 2.723</td>
</tr>
<tr>
<td>Japanese</td>
<td>579</td>
<td>1.148</td>
<td>0.842 to 1.566</td>
</tr>
<tr>
<td>Non-Japanese</td>
<td>48</td>
<td>1.525</td>
<td>0.441 to 5.274</td>
</tr>
<tr>
<td>High Risk**</td>
<td>43</td>
<td>0.989</td>
<td>0.621 to 1.543</td>
</tr>
<tr>
<td>Low Risk**</td>
<td>159</td>
<td>1.402</td>
<td>0.892 to 2.203</td>
</tr>
</tbody>
</table>

* Include stage IV patients

** High risk: suboptimal III + IV, Low risk: II + other III

PFS stage I vs stages II-IV

- Stage I: 89.7% vs 89.1%, p = 0.897

- Stage II-IV: 52.5% vs 42.6%, p = 0.199

18-Yr HR(95%CI) = 0.966 (0.569, 1.639)

2-Yr HR(95%CI) = 1.271 (0.881, 1.834)
**JGOG 3017: Adverse Event (Percentage)**

* Classified according to Common Terminology Criteria for Adverse Events (CTCAE) 3.0

** p<0.05 for grade 3/4 adverse events with Fisher’s exact test.

** JGOG 3017/GCIG: Summary

- With 44.3 months median follow-up, the 2-year PFS: 73.0% (95% CI: 67.7-77.5) in the CPT-P arm vs. 77.6% (95% CI: 72.4-81.9) in the TC arm were not significantly different (HR: 1.171, 95% CI: 0.867-1.581, p=0.303).

- Two-year OS was 85.5% in CPT-P arm (95% CI: 81.1-89.0) and 87.4% in TC arm (95% CI: 83.1-90.7), respectively (HR: 1.133, 95% CI: 0.796-1.613, p=0.486).

- Grade 3/4 leukopenia, neutropenia, thrombocytopenia, peripheral sensory neuropathy and joint pain occurred more frequently in the TC arm (p<0.05), whilst grade 3/4 anorexia, diarrhea, nausea, vomiting and febrile neutropenia occurred more frequently in the CPT-P arm (p<0.05).
JGOG 3017/GCIG: Conclusions

- In this first CCC-specific international clinical trial, a survival benefit was not observed by CPT-P.
- Paclitaxel with carboplatin remain to be a standard chemotherapy for CCC. However, since the toxicity profile is different, CPT-P can be an alternative choice of chemotherapy for CCC.

Future perspective

- New agent
  - mTOR inhibitor (Temsirolimus GOG268, Evelorims JGOG3021), Angiokinase inhibitor (BIBF1120, ENMD-2076) etc.,
- Stage I
  - Observation (JGOG3020: a Phase III randomized comparative study of surgery plus adjuvant chemotherapy and surgery alone in pts with surgical stage I epithelial ovarian cancer)
- Radiation
JOGG 3017: Acknowledgements

- The women who participated in the trial and their families
- The staff at JOGG3017 Coordinating Center at Kitasato University
- The 111 JGOG institutions:

Aichi Cancer Center Hospital
Aichi Medical University Hospital
Awaikawa Kosai General Hospital
Asahi Red Cross Hospital
Cancer Institute Hospital
Dokkyo Medical University Hospital
Fukuoka University Hospital
Gifu University Hospital
Himaj Red Cross Hospital
Hiroaki University School of Medicine & Hospital
Hiroshimo City Hospital
Hiroshima City, Aka Hospital
Hiroshima Prefectural Hospital
Hiroshima University Hospital
Hokkaido Medical Center
Hokkaido University Hospital
Hyoqo City Hospital
Iwate Medical University Hospital
Juntendo University Hospital
Juntendo University Hospital
Kagoshima City Hospital
Kamakura University Hospital
Kansai Rosai Hospital
Kanto Medical Center NTT EC
Kato University Hospital
KAWA University School of Medicine
Kawasaki City Hospital
Kawasaki City Hospital
Kawasaki Jikei Hospital
Kawasaki Medical Center
Kawasaki Rosai Medical Center
Kohei University Hospital
Kosei General Hospital
Kumamoto City Hospital
Kumamoto University Hospital
Kure City Hospital
Kyoto Prefectural University Hospital
Kyoto University Hospital
Kyushu University Hospital
Lambert University Hospital
Matsusaka General Hospital
Mie University Hospital
Miyazaki University Hospital
Miyagi Cancer Center
Miyawaki Red Cross Hospital
Nagasaki Municipal Hospital
Nagasaki Prefectural Beppu Hospital
Nagasaki University Hospital
Nagoya City, Edogawa Hospital
Nagoya University Hospital
Nagoya Medical University Hospital
Nara Prefectural Nara Hospital
National Cancer Center Hospital
National Defense Medical College Hospital
National Hospital Organization Tokyo Medical Center
National Hospital Organization Kyushu Medical Center
National Hospital Organization Saitama National Hospital
National Hospital Organization Shikoku Cancer Center
National Hospital Organization Shikoku Medical Center
Nagoya University Hospital
NHO Kure Medical Center And Chugoku Cancer Center
Nigata City Central Hospital
Nigata City General Hospital
Nihon University Medical Center
Oita Prefectural Hospital
Oita University Hospital
Okinawa Prefectural Chubu Hospital
Osaka City General Hospital
Osaka City University Hospital
Osaka Medical College Hospital
Osaka Rosai Hospital
Saga Medical School Hospital
Saga Prefectural Hospital KOSEIKAN
Saitama Medical Center
Saitama Medical University Hospital
Saitama Medical University International Medical Center
Saitama Medical University Hospital, National Hospital Organization
Saitama Social Insurance Hospital
Sapporo Medical University Hospital
Shiga University Hospital
Shiga University of Medicine, Kashiwa Hospital
Shizuoka Cancer Center
Shizuoka City Hospital
Shizuoka University Hospital
Shizuoka University Hospital
Shizuoka University Northern Yokohama Hospital
Soka University School of Medicine
St. Mary's University Hospital
The Jikei University Hospital
The Jikei University Hospital
The Jikei University Hospital
The Jikei University Hospital
The Jikei University Hospital
Tohoku Cancer Center
Tohoku University Otsuchi Medical Center
Tohoku University Hospital
Tokai University Hospital
Tokyo Medical University Hospital
Tokyo Medical University Saitama Medical Center
Tokyo Medical University Hospital
Tokyo Metropolitan Komagome Hospital
Tokyo Women's Medical University Hospital
Tottori University Hospital
Tottori Medical Center
Toyama University Hospital
Tosa University Hospital
Toyama University Hospital
University Hospital
University Hospital
University of Fukui Hospital
University of the Ryukyu Hospital
University of Tsukuba Hospital
Wakayama Medical University Hospital
Yamada Red Cross Hospital
Yamagata University Hospital
Yokohama City University Hospital

23
PRESENTED AT:

ASCO GYN

JOGG 3017: Acknowledgements

- The 111 JGOG institutions; con't

Nigeria University Medical & Dental Hospital
Old Prefectural Hospital
Old University Hospital
Osaka Prefectural Chubu Hospital
Osaka City General Hospital
Osaka City Hospital
Osaka Medical Center for cancer and Cardiovascular Diseases
Osaka Medical College Hospital
Osaka Rosai Hospital
Saitama Medical School Hospital
Saitama Prefectural Hospital KOSEIKAN
Saitama Medical Center
Saitama Medical University Hospital
Saitama Medical University International Medical Center
Saitama Social Insurance Hospital
Sapporo Medical University Hospital
Shiga University Hospital
Shiga University of Medicine, Kashiwa Hospital
Shizuoka Cancer Center
Shizuoka City Hospital
Shizuoka University Hospital
Shizuoka University Hospital
Shizuoka University Northern Yokohama Hospital
St. Mary's University Hospital
The Jikei University Daisan Hospital

24
PRESENTED AT:

ASCO GYN

12
JOGG 3017: Acknowledgements

- The 6 KGOG institutions:
  - Asan Medical Center
  - Daegu Catholic University Medical Center
  - Keimyung University Dongsan Medical Center
  - Korea Institute of Radiological and Medical Science
  - Samsung Medical Center
  - Seoul National University Hospital

- The 8 GINECO institutions:
  - Centre Catherine de Sienne
  - Centre Etienne Dolbe
  - CHU Orleans
  - CHU Morvan
  - Hopital Hotel Dieu
  - Hopital Jean Minjoz
  - Hospital Americain
  - Institut Bergonie

- The 4 SGCTG/UK institutions:
  - Beatson West of Scotland Cancer Centre
  - Clatterbridge Centre for Oncology
  - Hammersmith Hospital
  - Royal Marsden Hospital

- The 1 MITO institution:
  - Istituto Nazionale dei Tumori

JOGG3017: Study Team and Support

**Study Chair**
- T Sugiyama (JGOG)

**Co-Study Chairs**
- S Isonishi (JGOG)
- F Terauchi (JGOG)
- KT Kim (KGOG)
- JW Kim (KGOG)
- J Green (SGCTG)
- J Pignata (MITO)
- J Alexandre (GINECO)

**Study Statistician**
- T Hamano

**Coordinating physician**
- K Fujiwara (JGOG)

**IDMC**
- M Fukuoka
- WJ Hoskins
- YS Park
- S Pecorelli
- W Giani

**International CPR**
- SG Silverberg
- T Kaku
- M Fukunaga
- N Kato
- T Kiyokawa
- Y Mikami
- S Moritani
- T Moriya
- T Motoyama
- T Nagasaka
- Y Ohishi
- H Yanai
- M Yasuda
- Y Sasajima
- S Tejima
- N Teramoto
- H Tsuda
- IS Kim
- S Losito
- D Millan
- MC Vacher-Lavenu