JGOG

GYNECOLOGIC CANCER INTERGROUP

JGOG3017/GCIG Trial

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], Daisuke 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[*1], Fumitoshi Terauchi[*17], Keiichi Fujiwara[*18], Kazunori Ochiai[*1]

[*1]Jikei University, [*2]Iwate Medical University, [*3]H-STAT, [*4]Seoul National University, [*5]Sungkyunkwan University, [*6]Niigata University, [*7]Keio University, [*8]Juntendo University, [*9]St.Marianna University, [*10]Tokai University, [*11]Tohoku University, [*12]Kyushu University, [*13]University of Tsukuba, [*14]Istituto Nazionale Tumori di Napoli, [*15]Hopital Hotel Dieu, [*16]University of Liverpool, [*17]Tokyo Medical University, [*18]Saitama Medical University International Medical Center

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

JGOG

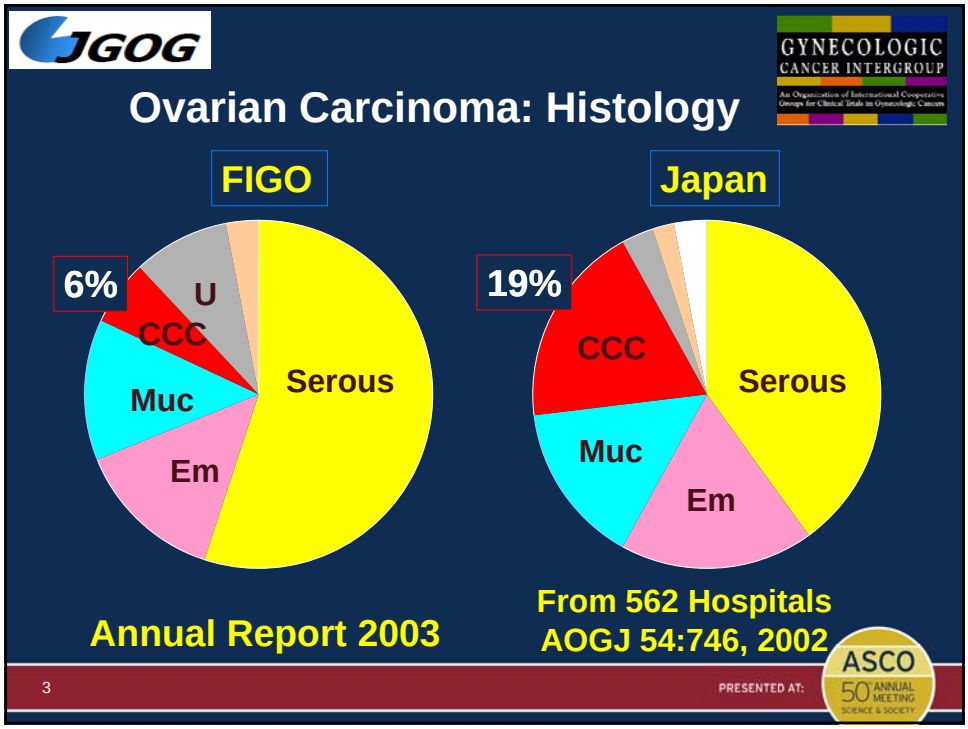
GYNECOLOGIC CANCER INTERGROUP

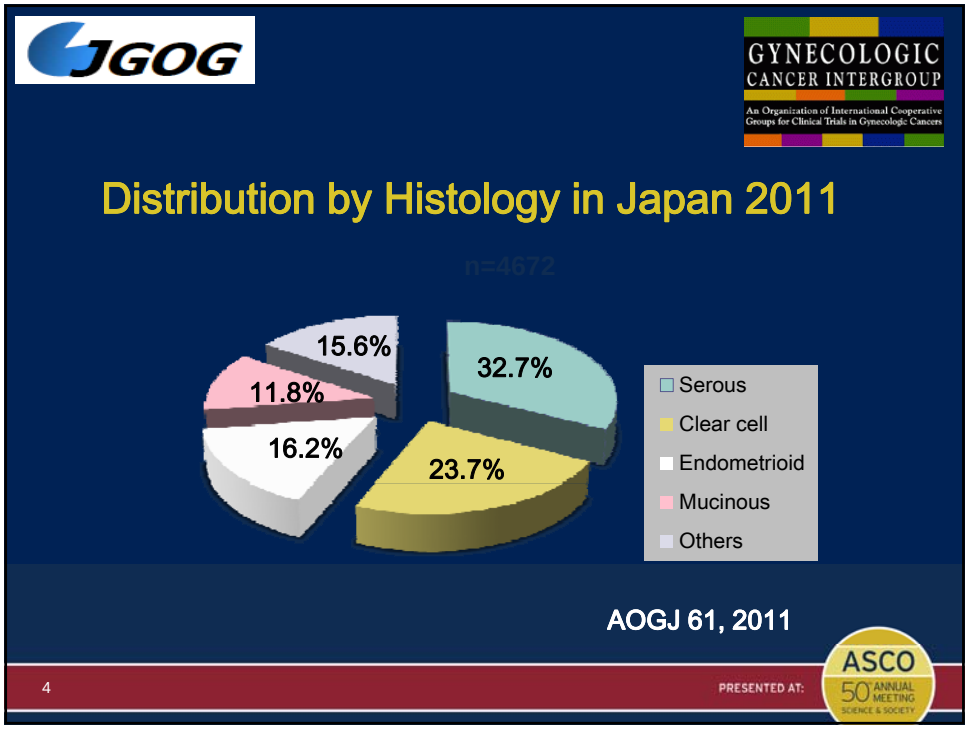
What is CCC and Why is Japan leading the Trial?

- 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.

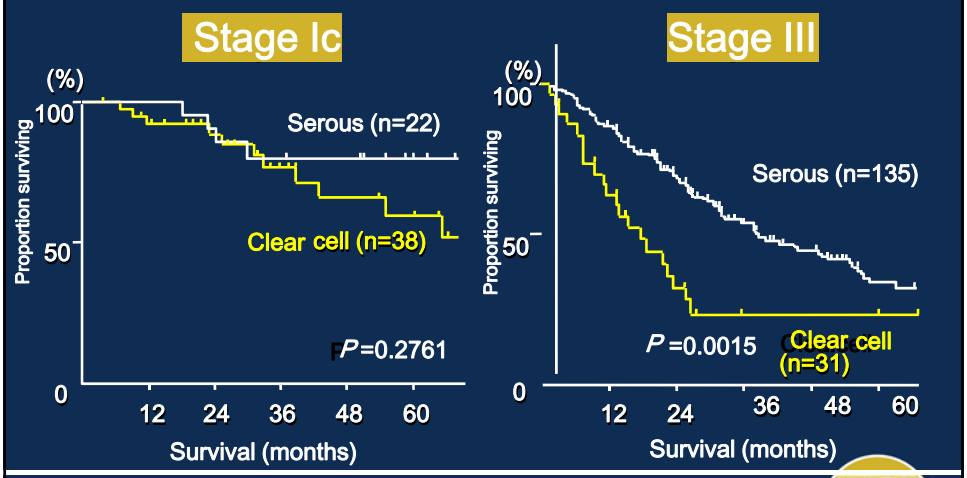
The critical question is whether paclitaxel/carboplatin (TC) therapy, the current standard for epithelial ovarian cancer (EOC) based upon the results of multiple RCTs, is an optimal regimen for CCC. Although the response rate of TC therapy for EOC is approximately 75%, this rate may not be applicable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

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY


JGOG
GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers
Ovarian Carcinoma: Histology
FIGO
Japan
6%
U
CCC
Muc
Em
Serous
19%
CCC
Muc
Em
Serous
Annual Report 2003
From 562 Hospitals
AOGJ 54:746, 2002
3
PRESENTED AT:
ASCO
50 ANNUAL MEETING
SCIENCE & SOCIETY


JGOG
GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers
Distribution by Histology in Japan 2011
n=4672
15.6%
11.8%
16.2%
32.7%
23.7%
Serous
Clear cell
Endometrioid
Mucinous
Others
AOGJ 61, 2011
4
PRESENTED AT:
ASCO
50 ANNUAL MEETING
SCIENCE & SOCIETY

Clear Cell Carcinoma vs Serous Adenocarcinoma : Overall Survival



5 Sugiyama T, et al. *Cancer* 2000; 88:2584-2589

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Rational

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

1. Takano et al. Oncol Rep. 2006;16(6):1301-6.
2. Takano et al. Int J Clin Oncol. 2007 12(4):256-60
3. Takakura et al. Int J Gynecol Cancer. 2010 ;20:240-7.

6

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

JGOG 3017/GCIG: Schema

-Clear Cell Ca
-Stage I~IV

Web RANDOMIZATION

TC
Paclitaxel 175 mg/m^2 (d1)
Carboplatin AUC 6 (d1)
Every 3 wk x 6

CPT-11/CDDP
CPT-11 60 mg/m^2 (d1, 8, 15)
Cisplatin 60 mg/m^2 (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)

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

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).

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

JGOG 3017/GCIC: Statistical Considerations

- **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.

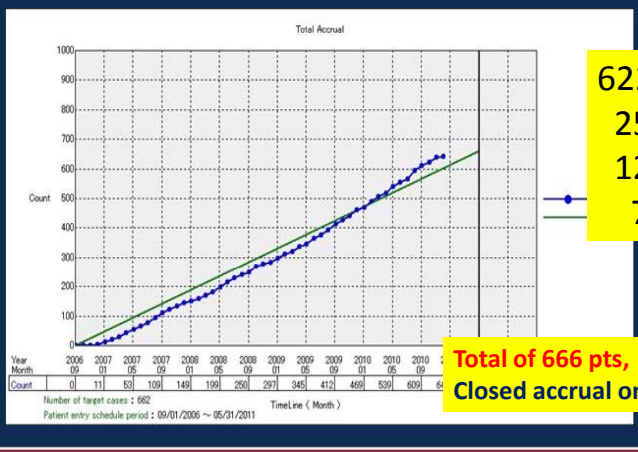
- Patients must be enrolled within 6 weeks after surgery.
- Clear cell histology must be dominant (> 50%).

  The histological diagnosis was confirmed by a international central pathology review (I-CPR) after registration.

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

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.

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

JGOG 3017/GCIG: Patient Enrollment

Patient Enrollment	TC	CPT-P
Patients enrolled	667	
Patients registered*	666	
Patient randomized**	332	332
Patients eligible**,***	305	314

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

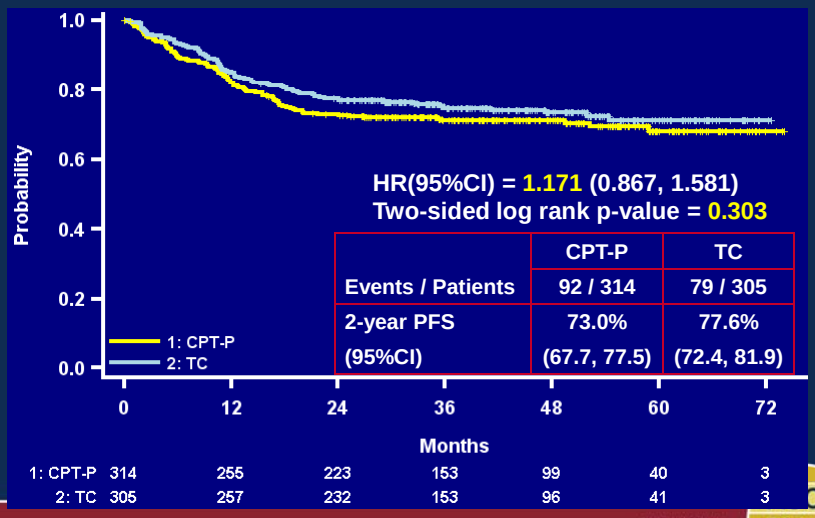
JGOG 3017/GCIG: Demographics & Baseline Characteristics

Demographics		TC(n=305)	CPT-P(n=314)
Age --- Median(Min-Max)		53y(30-81)	53y(30-75)
Race	**Japanese**	281(48.5%)	298(51.5%)
	Non-Japanese	24(60.0%)	16(40.0%)
Performance status (ECOG)	**0**	268(47.9%)	291(52.1%)
	1	37(61.7%)	23(38.3%)
Stage	**Ia-Ib**		
	Ic		
	II-IV		
Size of residual	**Complete**		
	Optimal (=<1cm)		
	Suboptimal (>1cm)		

Stage I: 66.4%

Complete: 87.9%

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



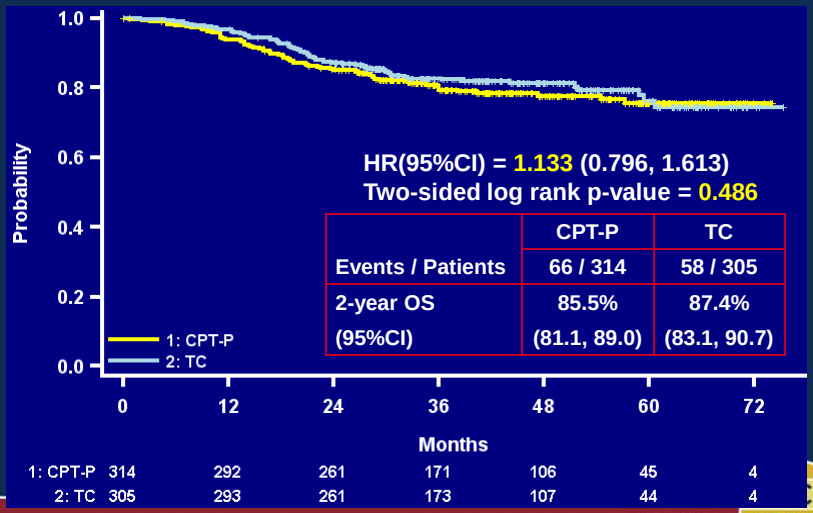
HR(95%CI) = 1.171 (0.867, 1.581)
Two-sided log rank p-value = 0.303

	CPT-P	TC
Events / Patients	92 / 314	79 / 305
2-year PFS (95%CI)	73.0% (67.7, 77.5)	77.6% (72.4, 81.9)

15

PRESENTED AT:

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



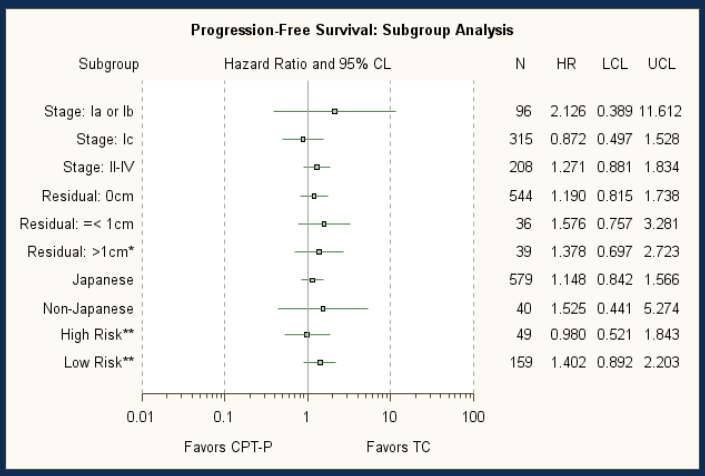
HR(95%CI) = 1.133 (0.796, 1.613)
Two-sided log rank p-value = 0.486

	CPT-P	TC
Events / Patients	66 / 314	58 / 305
2-year OS (95%CI)	85.5% (81.1, 89.0)	87.4% (83.1, 90.7)

16

PRESENTED AT:

JGOG 3017: PFS Subgroup Analysis



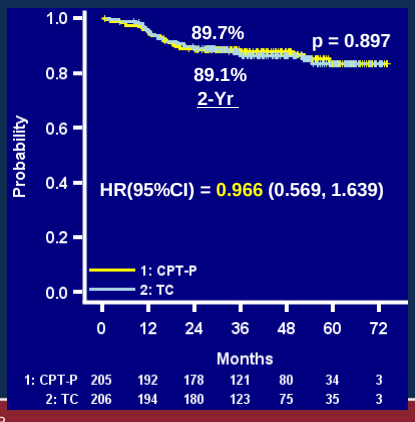
* Include stage IV patients

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

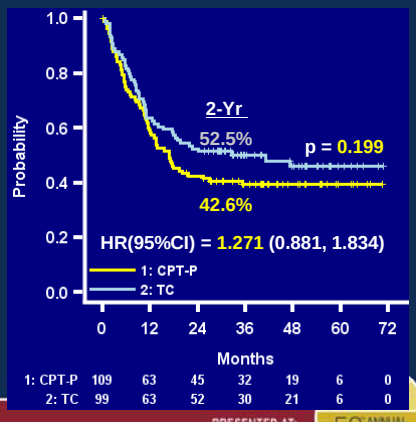
PRESENTED AT:

PFS stage I vs stages II-IV

I



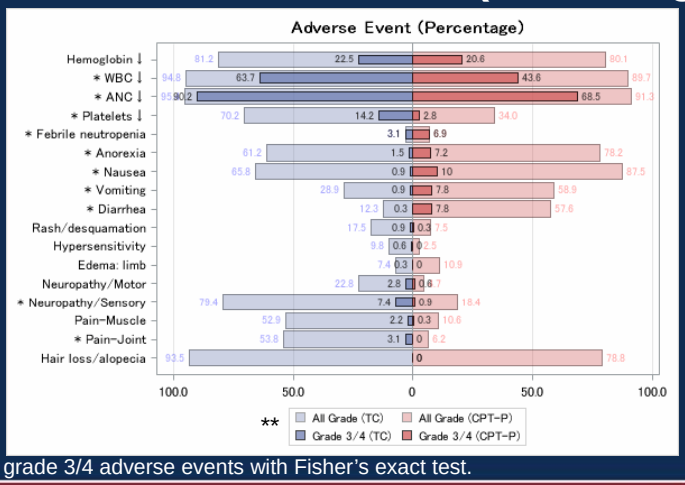
II-IV



18

PRESENTED AT:

JGOG 3017: Adverse Event (Percentage)



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

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

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 (Temsilorimus 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

JGOG 3017: Acknowledgements

- **The women who participated in the trial and their families**
- **The staff at JGOG3017 Coordinating Center at Kitasato Univer**sity
- The 111 JGOG institutions;

Aichi Cancer Center Hospital
Aichi Medical University Hospital
Asahikawa Kosei General Hospital
Ashikaga Red Cross Hospital
Cancer Institute Hospital
Dokkyo Medical University Hospital
Fukuoka University Hospital
Gunma University Hospital
Himeji Red Cross Hospital
Hirosaki University School of Medicine & Hospital
Hiroshima City Hospital
Hiroshima City, Asa Hospital
Hiroshima Prefectural Hospital
Hiroshima University Hospital
Hokkaido Medical Center
Hokkaido University Hospital
Hyogo Cancer Center
Iizuka Hospital
Iwate Medical University Hospital
Jikei University Aoto Hospital
Jikei University School of Medicine, Kashiwa Hospital
JR Sapporo Hospital
Juntendo University Hospital
Juntendo University Nerima Hospital
Juntendo Urayasu Hospital
Kagoshima City Hospital
Kaizuka City Hospital
Kanazawa University Hospital
Kansai Rosai Hospital
Kanto Medical Center NTT EC
Keio University Hospital
Kinki University School of Medicine
Kitasato University Hospital
KKR Sapporo Medical Center
Kobe City Medical Center General Hospital
Kochi Health Sciences Center
Kosei General Hospital
Kumamoto City Hospital
Kumamoto University Hospital
Kurume University Hospital
Kyoto Second Red Cross Hospital
Kyoto University Hospital
Kyoundo Hospital
Kyusyu University Hospital
Matsusaka General Hospital
Mie University Hospital
Misawa Municipal Hospital
Mitsui Memorial Hospital
Miyagi Cancer Center
Morioka Red Cross Hospital
Nagasaki Municipal Hospital
Nagasaki Prefectural Saiseikai Hospital
Nagasaki University Hospital
Nagoya City University Hospital
Nagoya University Hospital
Nara Medical University Hospital
Nara Prefectural Nara Hospital
National Cancer Center Hospital
National Defense Medical College Hospital
National Hospital Organization Kokura Medical Center
National Hospital Organization Kyusyu Medical Center
National Hospital Organization Saitama National Hospital
National Hospital Organization Shikoku Cancer Center
National Kyusyu Cancer Center
NHO Kure Medical Center And Chugoku Cancer Center
Niigata City General Hospital

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

JGOG 3017: Acknowledgements

- The 111 JGOG institutions; con't

Niigata University Medical & Dental Hospital
Oita Prefectural Hospital
Oita University Hospital
Okinawa Prefectural Chubu Hospital
Osaka City General Hospital
Osaka City University Hospital
Osaka Medical Center for cancer and Cardiovascular Diseases
Osaka Medical College Hospital
Osaka Rosai Hospital
Saga Medical School Hospital
Saga Prefectural Hospital KOSEIKAN
Saiseikai Sanjo Hospital
Saitama Medical Center, Saitama Medical University
Saitama Medical University Hospital
Saitama Medical University International Medical Center
Saitama Social Insurance Hospital
Sapporo Medical University Hospital
Shinsyu University Hospital
Shizuoka Cancer Center
Showa University Hospital
Showa University Northern Yokohama Hospital
St.Marianna University School of Medicine Hospital
The Jikei University Daisan Hospital
The Jikei University Hospital
Tochigi Cancer Center
Toho University Ohashi Medical Center
Tohoku University Hospital
Tokai University Hospital
Tokyo Medeical University Ibaraki Medical Center
Tokyo Medical University Hospital
Tokyo Metropolitan Komagome Hospital
Tokyo Women's Medical University Hospital
Tomishiro Chuo Hospital
Tosei General Hospital
Tottori Municipal Hospital
Tottori University Hospital
Toyama University Hospital
University Hospital, Kyoto Prefectural University of Medicine
University of Fukui Hospital
University of the Ryukyus Hospital
University of Tsukuba Hospital
Wakayama Medical University Hospital
Yamada Red Cross Hospital
Yamagata University Hospital
Yokohama City University Hospital

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

JGOG 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 Dollet
  - CHR 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

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

JGOG3017: 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)
– S Pignata (MITO)
– J Alexandre (GINECO)

Study Statistician
– T Hamano

Coordinating physician
– K Fujiwara (JGOG)

IDMC
– M Fukuoka
– WJ Hoskins
– YS Park
– S Pecorelli
– W Qian

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