

# 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

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## What is CCC and Why is Japan leading the Trial?

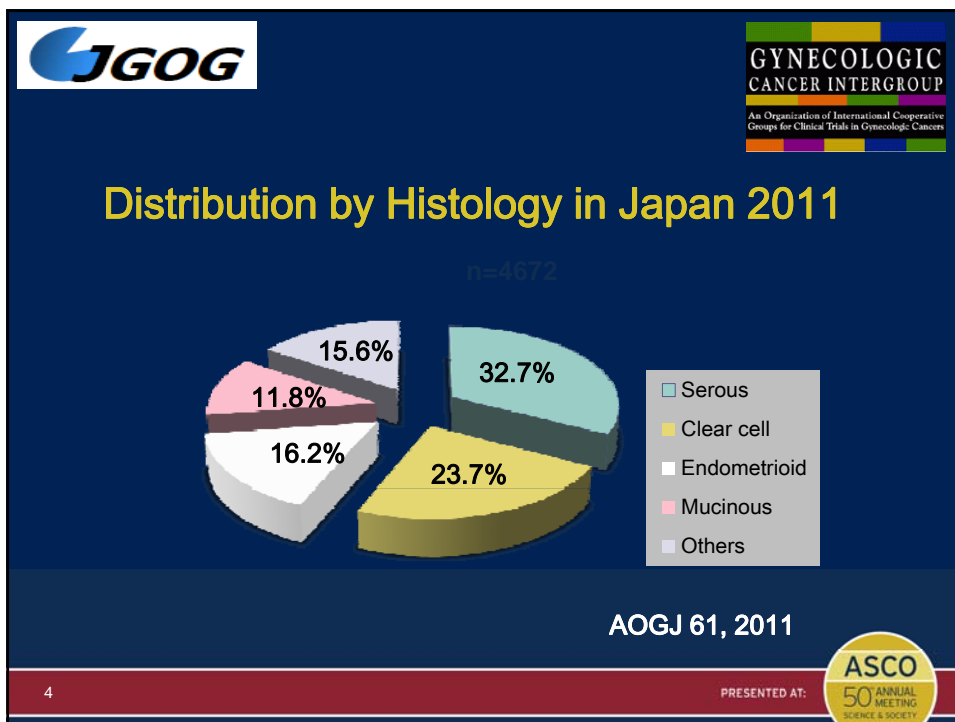
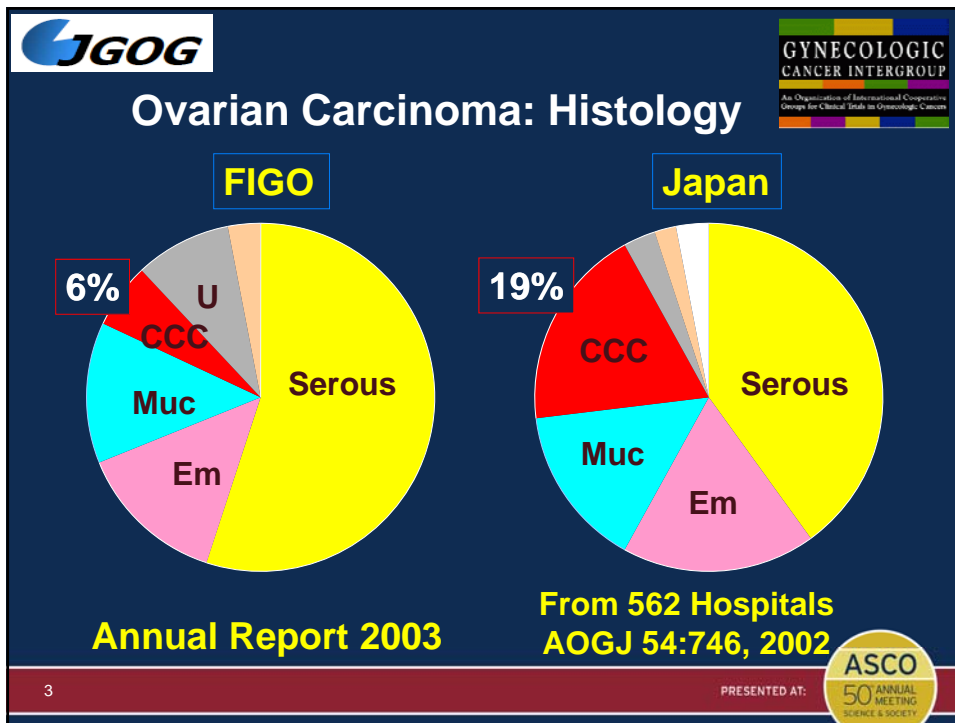
- Clear Cell Carcinoma of the Ovary (CCC) is one of the histological entities of epithelial ovarian cancer (1973, WHO classification)
- Incidence of CCC is rare in Western Countries (5%), but it is not rare in Japan (>20%)
- Retrospective studies conducted in Japan indicated that CCC is less sensitive 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.

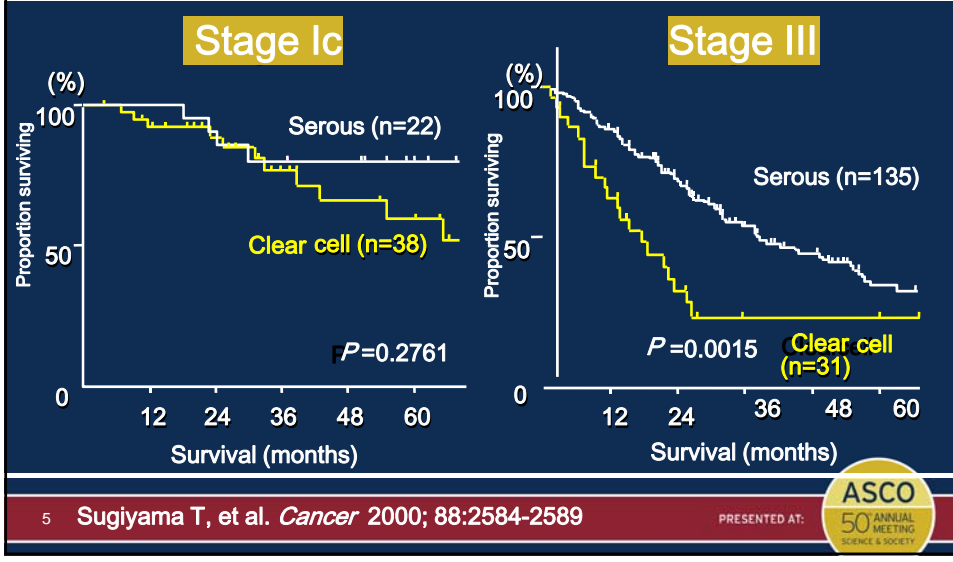
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Clear Cell Carcinoma vs Serous Adenocarcinoma :  
Overall Survival



Rational

Retrospective studies<sup>1, 2)</sup> and a randomized phase II trial<sup>3)</sup> 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.

## JGOG 3017/GCIG: Schema

-Clear Cell Ca  
-Stage I-IV

Web RANDOMIZATION

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

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

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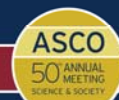


## JGOG 3017/GCIG: Objectives

- 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).

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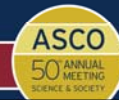
## JGOG 3017/GCIC: Statistical Considerations



- **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.

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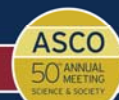
## JGOG 3017/GCIG: Statistical Considerations (cont.)



- **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.**

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## Eligibility

- Stage I to IV CCC

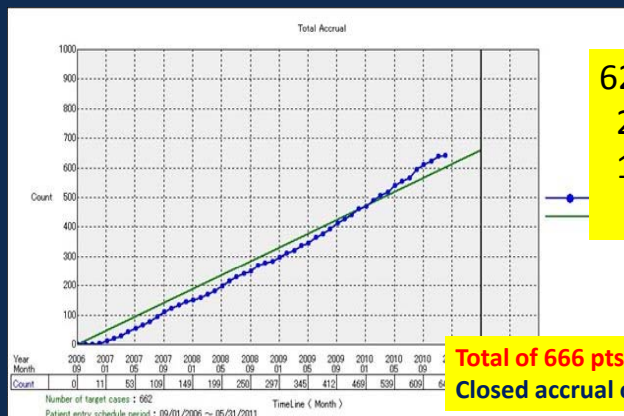
All patients must have had comprehensive staging surgery for ovarian carcinoma with appropriate tissue available for histological evaluation.

- 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.

## 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



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%)

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## 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	40(51.0%)	47(40.0%)
	Ic	55(47.0%)	103(52.4%)
	II-IV	39(41.0%)	103(52.4%)
Size of residual	Complete	267(46.4%)	277(50.0%)
	Optimal ( $\leq$ 1cm)	19(48.7%)	20(51.3%)
	Suboptimal (>1cm)	15(48.7%)	20(51.3%)

Stage I: 66.4%

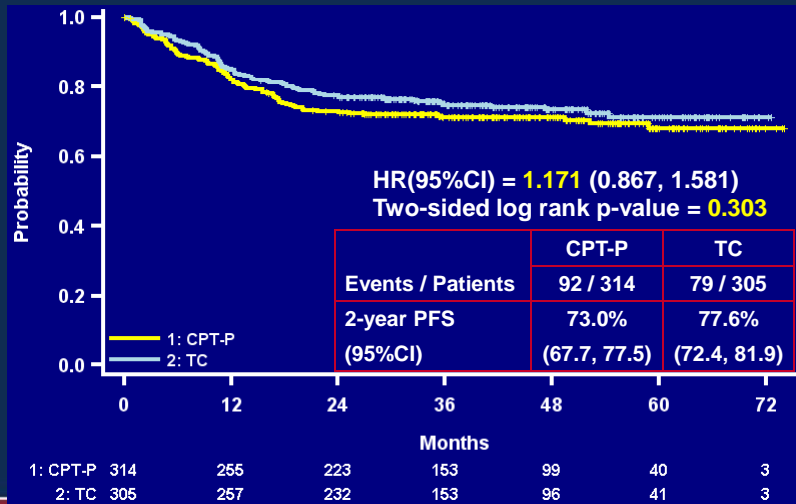
Complete: 87.9%

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

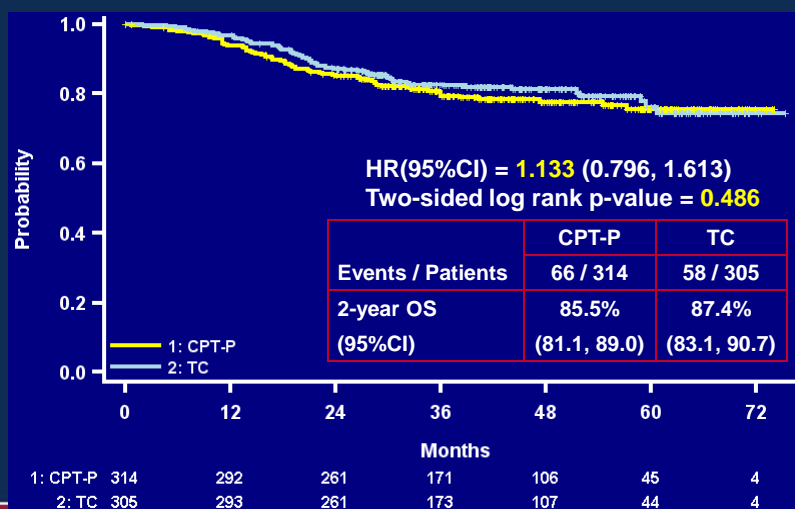


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### JGOG 3017: 2-year OS for TC vs CPT-P



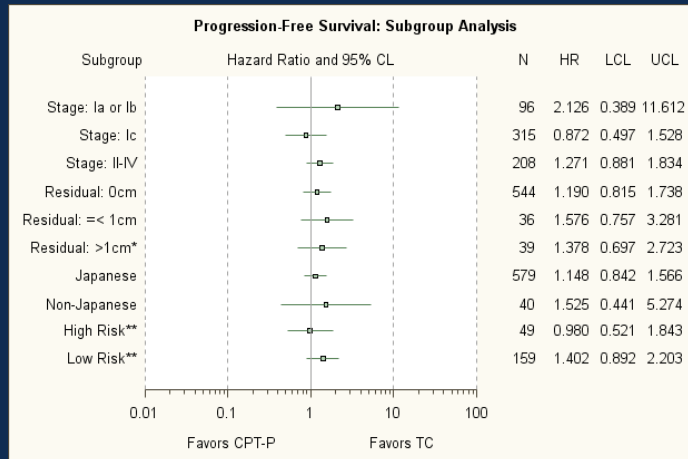
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# JGOG 3017: PFS Subgroup Analysis



\* Include stage IV patients

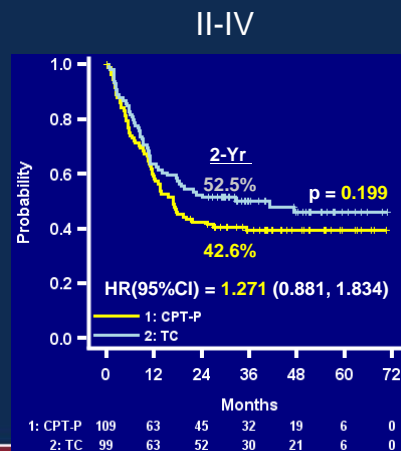
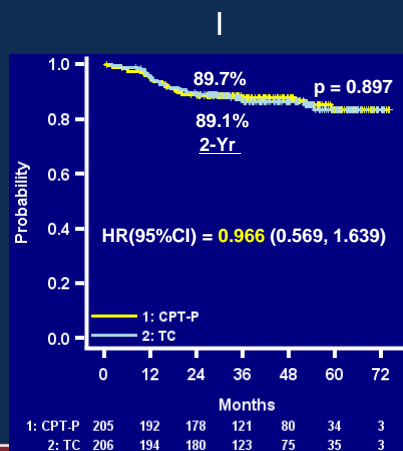
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\*\* High risk: suboptimal III + IV, Low risk: II + other III

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## PFS stage I vs stages II-IV

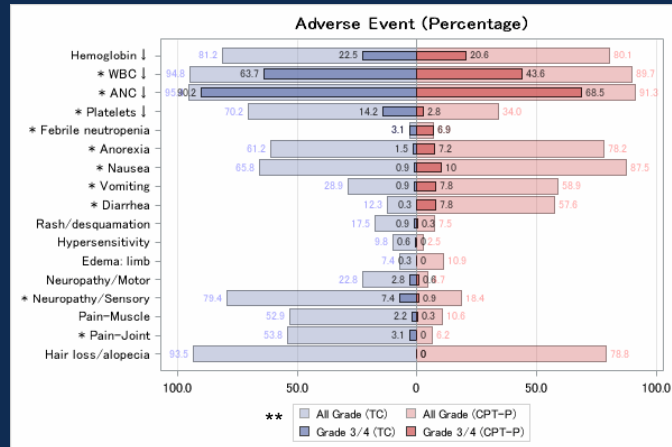


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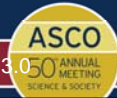


## JGOG 3017: Adverse Event (Percentage)



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

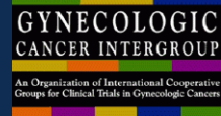
\*\* Classified according to Common Terminology Criteria for Adverse Events (CTCAE) 3.0



## 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 ( $p < 0.05$ ).



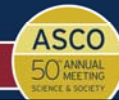


## JGOG 3017/GCIG: Conclusions

- 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.

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## Future perspective

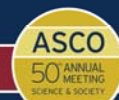


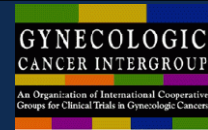
- New agent
  - mTOR inhibitor (Temsilimus GOG268, Eavelorims JGOG3021), Angiokinase inhibitor (BIBF1120, ENMD-2076) etc.,
- Stage I
  - Observation (JGOG3020: a Phase III randomized comparative study of surgery plus adjuvant chemotherapy and surgery alone in pts with surgical stage I epithelial ovarian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

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- Radiation

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# JGOG 3017: Acknowledgements

- The women who participated in the trial and their families
- The staff at JGOG3017 Coordinating Center at Kitasato University
- 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  
 Izuka 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  
 Koba 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



# 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 Medecial University Ibaraki Medical Center  
 Tokyo Medical University Hospital  
 Tokyo Metropolitan Komagome Hospital  
 Tokyo Women's Medical University Hospital  
 Tamishiro Chuo Hospital  
 Tosei General Hospital  
 Tattori Municipal Hospital  
 Tattori 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



# JGOG 3017: Acknowledgements



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Daegu Catholic University Medical Center  
Keimyung University Dongsan Medical Center  
Korea Institute of Radiological and Medical Science  
Samsung Medical Center  
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- The 8 GINECO institutions;  
Centre Catherine de Sienne  
Centre Etienne Dollet  
CHR Orleans  
CHU Morvan  
Hopital Hotel Dieu  
Hopital Jean Minjoz  
Hopital 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



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# JGOG3017: Study Team and Support



## Study Chair

– T Sugiyama (JGOG)

## Co-Study Chairs

- S Isonishi (JGOG)
- F Terauchi (JGOG)
- KT Kim (KOGOG)
- JW Kim (KOGOG)
- J Green (SGCTG)
- S Pignata (MITO)
- J Alexandre (GINECO)

## Study Statistician

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## Coordinating physician

– K Fujiwara (JGOG)

## IDMC

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- 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

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