response in patients with ovarian cancer, and for response to symptomatic improvement in patients treated with platinum/taxane therapy. This is the QOL scale commonly used in clinical trials for ovarian cancer, which is composed of physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and additional concerns (12 items). In addition, FACT-GOG/abdominal discomfort (AD) will be used to evaluate abdominal discomfort symptoms in this study. This is composed of 4 items which includes two items from FACT-O.

2) FACT/GOG-NTX4:
   Of the eleven original scale items to be used to assess subjective symptoms of neurotoxicity, four items on which a validation study has been performed by GOG [35] as a scale to assess platinum/Paclitaxel-induced neurotoxicity will be used.
3) FACIT fatigue sub scale: Functional assessment of chronic illness therapy-fatigue scale:
   Fatigue evaluated by patients and its effects on daily life (13 items) will be assessed.
4) EQ-5D (EuroQol 5 Dimension): To be used to measure utility values for economic evaluation in health care (5 items)
5) ECOG Performance Status will be concurrently evaluated as QOL assessment by the treating physician/nurse.

9.6.4 Schedule of QOL assessment

In order to assess the differences between treatment arms (such as total QOL, abdominal pain, nausea, and malaise), the time-dependent differences in each treatment arm, and the delayed or long-term symptoms (such as neurotoxicity), QOL assessment will be conducted using QOL questionnaires【Appendix 2-⑥】in accordance with the following schedule.

1. After obtaining consent and before the start of protocol treatment
2. After 3 cycles of protocol treatment (9 weeks after the start of protocol treatment)
3. After 6 cycles of protocol treatment (18 weeks after the start of protocol treatment)
4. 36 weeks after the start of protocol treatment)
5. 60 weeks after the start of protocol treatment)
6. 84 weeks after the start of protocol treatment)

In addition, QOL questionnaires and assessment time points will remain the same even when there is a change in the method of treatment (including the discontinuation of protocol treatment). QOL assessment will remain even when the patient discontinues protocol treatment.

In this study, because there are some variations in the schedule of treatment such as delayed treatment, a maximum allowable time frame has been established for QOL assessment. For time points 2) and 3), an additional 3 weeks, and for time points 4) to 6), plus/minus 1 month will be considered an allowable time frame.

9.7.1 Objectives

To compare evaluations of cost associated with Paclitaxel weekly plus intravenous Carboplatin versus intraperitoneal Carboplatin as a first-line therapy in women with primary ovarian, peritoneal or Fallopian tube cancer.

9.7.2 Eligibility

Study sites : Study sites which are able to conduct surveys on QOL and receipt, and provide assistance in this trial. Conducting the clinical trial at study sites must be approved by IRB.

Sample size : Approximately 200 patients

9.7.3 Methods

QOL personnel who are appointed in advance at each site will assist with conducting QOL surveys in accordance with the manual 'Request for cooperation for QOL survey' 【Appendix 1-E】. QOL personnel will give patients the 'Survey form for costs associated with treatment' 【Appendix 2-⑦】 in each survey period and will assist them by providing an explanation. In addition, there is no restriction on patient support such as how to fill out the cost survey form or how to calculate the total costs.

Methods of analysis: cost-effectiveness analysis and cost-utility analysis will be performed.

- In the cost-effectiveness analysis, a comparison will be made by calculating the cost of one unit of outcome using cost per life year gained as a common outcome measure.
- In the cost-utility analysis, a comparison will be made by using cost per life year gained and utility-based QOL during that time. The QALY (Quality Adjusted Life Year) will be used as a unit in order to make comparisons between the two arms. As defined by the value "1" representing the best possible health state and the value "0" representing death, 1QALY means one year of life in the best possible health status.

9.7.4 Perspective on evaluation

Depending on the type of perspective to be taken for evaluation, the cost range concerned will differ. In this study, the evaluation will be conducted from a "societal perspective," including all the costs related to patients (co-payments, traveling expenses, and loss of work), medical institutions (labor cost to provide medical services, material costs, and expenditures), health insurance agencies (medical service fees to be paid to medical institutions), and the government (high-cost medical care, welfare payments).

9.7.5 Outcome measures

1) QALY (Quality-adjusted life year) will be used. "OS", one of secondary endpoints in the iPocc trial will be used for survival, and QOL will be calculated using the QOL questionnaires in this study.
2) QAPFY (Quality-adjusted progression-free year) will be used. "PFS", a primary endpoint in the iPocc trial, will be used for progression-free survival, and QOL will be calculated using QOL

questionnaires in this study.

9.7.6 Definitions of cost

In this study, both direct and indirect costs will be calculated.

1) Direct costs: direct medical costs (costs of treatment and procedures, costs to treat adverse drug reactions, costs of self-purchased drugs at pharmacies, fees for clinical examinations, medications, injections, procedures used for treatment, surgeries, tests, imaging, hospitalizations, special diets) and direct non-medical costs (traveling expenses, expenditure directly related to disease treatments such as wigs).
2) Indirect costs: loss of work due to treatment, caretakers' loss of work, housing renovation costs)
3) Coverage of expenses by personal medical insurance.

9.7.7 Discount rate

In order to convert the future expected streams of costs over time into a value amount at a certain time, a conversion will be used. Because it is a general practice to set the present value higher than the future value, future costs will be calculated using a "discount." Although there are several methods to calculate discount rates, a 3% annual discount rate will be used in this study. In addition, a 3% annual discount rate will be used for outcomes.

9.7.8 Methods of data collection

1) For PFS and OS, the data for patients who agreed to the cost evaluation in health care will be extracted from the data showing primary and secondary endpoints in the iPocc trial.
2) For QOL, "QOL questionnaires" in this trial will be used.
3) For direct costs, the data from receipts will be used. If the extramural pharmacy is used, its data will be collected as well. After removing all personal identifying information at each site, a copy of the receipts with the protocol patient ID number will be forwarded to the iPocc Trial Coordinating Center.
4) Indirect costs surveys will be conducted along with direct non-medical costs survey in accordance with the following schedule.*[1] Using the Survey Form for Costs Associated with Treatment①, ② and ③.【Appendix 2-⑦】

1. After obtaining consent and before the start of protocol treatment	Survey Form for Costs Associated with Treatment①*[2]
2. After 3 cycles of protocol treatment (9 weeks after the start of protocol treatment)	Survey Form for Costs Associated with Treatment②*[2]
3. After 6 cycles of protocol treatment (18 weeks after the start of protocol treatment)	
4. 36 weeks after the start of protocol treatment	
5. 60 weeks after the start of protocol treatment	
6. 84 weeks after the start of protocol treatment	
7. 84 weeks afterward the start of protocol treatment*[3]	Survey Form for Costs Associated with Treatment③*[2]

*[1] Cost survey will be discontinue when the patient started to receive a post-proctocol treatment

after discontinuation or compleation of the protocol treatment.

*2 The three types of survey forms for costs are to be used as follows: ① to be used once after obtaining informed consent and before the start of treatment, ② to be used 5 times when QOL survey is conducted, and ③ that includes the EQ-5D questions to be used several times afterwards 84 weeks from the start of treatment.

*3 After 84 weeks from the start of treatment," the strict timeline of cost survey is notdetermined. However, the survey will be continued at least once a year.

5) The survey on costs is scheduled to be completed about 8 years after the start of study.

9.7.9 Data collection period

The long-term data on the cost evaluation in health care is required to calculate QALY based on survival.

Accordingly, the collection of cost data will be continued as long as possible until such time when the main analysis results are published after completion of data fixation in the iPocc trial. The data collection period for the cost evaluation in health care is expected to continue for approximately 8

[Japan only]

9.7.10 Statistical analysis

The statistical analysis plan for the cost evaluation in health care will be established separately.

In the results, the following will be included. "Ratio of cost-effectiveness," that is, the cost to obtain 1QAPFY/1QALY in each arm will be calculated to determine the ratio of cost-effectiveness. In addition, the "Incremental cost-utility ratio" will be calculated to evaluate if the replacement therapy with Carboplatin IP is worth an additional cost implementation. This can be done by calculating the additional costs to obtain 1QALY (or 1QAPFY) in the IP arm.

10 DATA REPORTING SYSTEM

10.1 Informed consent form

A patient consent form must be signed and dated by the patient prior to tentative study registration. The consent form must be retained by the institution. 【See Appendix 2-①】

10.2 eCRF (electronic case report form)

eCRF must be submitted at the time points given in the following schedule. The eCRFs are to be accessed via the Rave system of the iPocc Trial Coordinating Center.

*The eCRFs are to be submitted for each cycle in the study regardless of dosage and schedule modification.

eCRFs	Form Due	
Background Information	Before final registration	N/A
Tentative Registration	At the time of tentative registration	N/A
Final Registration	At the time of final registration	N/A
Pre-Surgery	Within 28 days before the scheduled date of surgery	No later than 4 weeks
Surgical Report Histopathology Slides (HE-stained slides) Histopathological Report prepared by institutions	After surgery	No later than 4 weeks
Pre-Chemotherapy	Between the date after surgery and before administration of protocol treatment	No later than 4 weeks
CYCLE1-6	After completion of each cycle	No later than 4 weeks
End of Study	At the time of ending protocol treatment/completion	No later than 4 weeks
Follow Up	At the time of follow-up	No later than 4 weeks

10.3 Histopathology Slide, Histopathological Report

Three representative HE-stained slides (at least one slide) from different parts of the epithelial ovarian, fallopian tube, or primary peritoneal cancer, and histopathological reports by institutions are to be submitted to the iPocc Trial Coordinating Center within 4 weeks from the patient registration.

iPocc Trial Coordinationg Center stores all pathology slides which are sent from each institution.

1) Histopathology slides are to be sent using the eCRF, "Pathology" form as a cover letter.
2) The submitted slides will not generally be returned. However, in cases where the institution needs to have the slides returned, this needs to be requested when submitting the slides. The protocol-specific patient ID must be clearly labeled on the slides. It is recommended that patient initials are also provided.
3) A copy of the original histopathology report issued by each institution will be mailed to the iPocc Trial Coordinating Center after removal of personal information such as patient name, date of birth, and chart number. Label the Protocol-specific patient ID number in the report.

【Address and contact number to submit sample slides】

11 A

Inter ***lix for ADVE***

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11.1

11.1.1

A serious adverse event (SAE) is defined as any adverse event which meets one of the following criteria and occurs during protocol treatment or within 30 days after the final administration of the protocol treatment. However, an adverse event which occurs 30 days or later after the final administration of the protocol treatment shall be included in the definition only when a causal relationship to the study treatment cannot be ruled out.

1). results in death (Grade 5)
2). is life-threatening (Grade 4 non-hematotoxicity)
3). requires inpatient hospitalization or prolongation of existing hospitalization (Grade 3 or higher adverse events with hospitalization). However, "inpatient hospitalization" refers to hospitalization requiring treatment. Hospitalization for a purpose unrelated to an adverse event, planned hospitalization to reduce the inconvenience to patients caused by frequent hospital visits, or hospitalization for clinical examination or follow-up shall be excluded.
4). results in persistent or significant disability/incapacity
5). is a congenital anomaly/birth defect
6). any other medically important event as determined by the investigator (including unexpected Grade 2 or 3 adverse events)

11.1.2 Definition of unexpected serious adverse events

Unexpected serious adverse events are defined as those not listed in the latest version of the package insert for the relevant study drug or not be listed in the study protocol.

11.1.3 Definition of suspected unexpected serious adverse reaction (SUSAR)

An unexpected serious adverse event is classed as a suspected unexpected serious adverse reaction (SUSAR) only when its causal relationship to the study drug cannot be ruled out.

11.2 Reporting time frames

The investigator/sub-investigator must report the following events to the iPocc Trial Coordinating Center within the time frames shown in Table 1, REPORTING TIME FRAMES FOR SAFETY INFORMATION.

Table 1: Reporting time frames for safety information

	Grade 1	Grade 2		Grade 3				Grade 4 & 5	
				Unexpected		Expected			
	Unexpected / expected	Unexpected	Expected	*Requires hospitalization / Prolongation of existing hospitalization	*Requires no hospitalization / no prolongation of existing hospitalization	*Requires hospitalization / prolongation of existing hospitalization	*Requires no hospitalization / no prolongation of existing hospitalization	Unexpected	Expected
No causal relationship	Not required	Not required	Not required	Within 10 days	Not required	Within 10 days	Not required	**Within 24 hours Within 5 days	**Within 24 hours Within 5 days
A causal relationship cannot be ruled out	Not required	***Within 24 hours Within 10 days	Not required	**Within 24 hours Within 10 days	Within 10 days	Within 10 days	Not required	**Within 24 hours Within 5 days	**Within 24 hours Within 5 days

* Refer to Section 11.1.1 (3) for the definition of 'hospitalization.'

** The investigator is required to report to the iPocc Trial Coordinating Center within 24 hours after obtaining knowledge of the event by whatever means, and a written SAE report should be submitted within the designated period of time. However, when there is evidence that the progression of the primary disease is the cause of death, notification within 24 hours is not required; however, a written SAE report must be submitted.

*** For a Grade 2 unexpected events which meets Section 11.1.1 (6), the investigator must notify the iPocc Trial Coordinating Center of the event by whatever means no later than 24 hours after obtaining knowledge of the event by whatever means, and a written SAE report should be submitted within the designated period of time

- Even long after completion of the protocol treatment, the events which apply to (4) and (5) of 11.1.1 Definition of serious adverse events must be reported immediately upon discovery.

11.3 SAE reporting duration

The investigator should submit additional information until the events reported as serious adverse events result in one of the following outcomes: "improved", "recovered" or "death".

11.4 SAE reporting procedure

In the case of a serious adverse event, the following procedure should be followed. The details can be found in the "SAE Report and manual" 【Appendix 2-⑤】and "Flow chart of SAE reporting within Japan " 【Appendix 1-B】

11.4.1 Action to be taken by the investigator

11.4.1.1 Notifying institution

In case of a serious adverse event, the investigator shall notify the head of the institution according to the institutional SOP.

11.4.1.2 Notifying the study chair

1) Initial report

In case of a serious adverse event, the investigator shall report information available up to that point to the iPocc Trial Coordinating Center using the Rave system "SAE Report". The iPocc Trial

Coordinating Center shall confirm the information and request additional information from the investigator if necessary.

2) Additional reporting

If additional information is obtained or there are any questions from the study chair and the iPocc Trial Coordinating Center, the investigator shall provide an additional report. If an autopsy was performed, an "autopsy report" should be produced and attached.

11.4.1.3 Notifying relevant companies

After the occurrence of the serious adverse event, the investigator shall notify the relevant companies according to the institutional SOP.

11.4.2 Action to be taken by the iPocc Trial Coordinating Center

Upon obtaining the SAE report from the investigator, the iPocc Trial Coordinating Center shall take appropriate action depending upon whether the event falls under case (1) or (2) as described below.

(1) If it is determined that reporting to the regulatory authority is necessary and/or the participating investigators should be immediately notified, the iPocc Trial Coordinating Center shall immediately notify the study chair and the chairman of the JGOG Ovarian Committee. The chairman of JGOG/GOTIC of independent data-monitoring committees shall be notified if the study chair determines that discussion within IDMC is necessary.

(2) If case (1) is not applicable, the iPocc Trial Coordinating Center shall immediately notify the study chair, and the list of events shall be reported to the chairmen of the JGOG Ovarian Committee and JGOG/GOTIC IDMC upon submission of the monitoring reports.

11.4.3 Action to be taken by JGOG/GOTIC IDMC

After discussion with the chairmen of the JGOG/GOTIC Ovarian Committee, the study chair shall request deliberation by the JGOG/GOTIC IDMC. The IDMC shall discuss whether the study should be continued or discontinued, the need for protocol revision, the need for informed consent form revision, and the need for reporting to the participating institutions based on the report. The results of the discussion shall be delivered to the study chair by the chairman of JGOG/GOTIC IDMC. The study chair shall notify the chairman of the JGOG Ovarian Committee and the iPocc Trial Coordinating Center.

11.4.4 Review by the international IDMC

The international IDMC will be organized to assess the progress of the trial and the trial safety data with a view to recommending whether the trial should continue, be modified or be terminated. The international IDMC will review SAE data semi-annually from the study monitoring report.

The international IDMC will operate according to the following guidelines:

- The membership of the IDMC will include at least one statistician and at least one clinician experienced in clinical trials. Additional membership will reflect the specialties involved in the trial. All members of the international IDMC will be independent of the trial. If non-independent members are to be included, this will be justified and agreed by the participating GCIG groups.

- Deliberations of the international IDMC when considering outcome data by treatment arm are confidential. These data will not to be shared with anyone who is not a member of the international IDMC, unless agreed by the IDMC itself.
- The international IDMC will act in an advisory role and report its recommendations in writing to the study chair.
- A recognized formal statistical approach for the conduct of interim analyses will be employed, and in general the final recommendation from the international IDMC on the continuation of the study will be based on all available evidence. The formal statistical criteria for stopping on basis of efficacy in this study are described in the section 13.3.1.4.
- The international IDMC must formally approve any proposed publication of any trial data prior to the publication of the protocol-specified definitive analysis based on the primary endpoint.

The study monitoring reports and an interim analysis report produced by the iPocc Trial Coordinating Center will be reviewed by IDMC annually (or more frequently if the IDMC feels it appropriate). The IDMC meeting can be a teleconference after email discussions among the committee members, if necessary. For urgent communications deemed necessary due to emerging data, emails and teleconferences can be utilized. The international IDMC members are listed in Attachment 1.

11.4.5 Action to be taken by the study chair

Where an event occurs that necessitates reporting to the regulatory authorities or notification of the site investigators immediately as defined in section 11.4.2. (1), the study chair and the chairman of the JGOG Ovarian Committee shall provide the participating sites with the SAE report with the opinions of the study chair via JGOG/GOTIC Secretariats. In addition, when instructed to revise the protocol and/or the informed consent form by the JGOG/GOTIC IDMC, the study chair and the chairperson of the JGOG Ovarian Committee shall take action as soon as possible after consulting with the iPocc Trial Coordinating Center and shall report the changes to the participating sites via JGOG/GOTIC Secretariats. An event as defined in Section 11.4.2. (2) shall be reported to the participating sites, using a line listing in the semi-annual study monitoring report produced by the iPocc Trial Coordinating Center.

11.4.6 Action to be taken by the participating institutions

The investigator shall report information regarding serious adverse events to the head of the institution (or IRB) according to the institutional SOP. If revision of the protocol and/or changes to the informed consent form are involved, the decision of the IRB will be reported to the iPocc Trial coordination center.

11.4.7 Notifying the relevant companies

The JGOG/GOTIC Secretariats shall immediately report the discussion results of the IDMC and action taken or planned regarding the serious adverse event to the relevant companies involved in the study.

11.5.1 Specifications in ethical guidelines and ethical policies regarding clinical research

If unexpected serious adverse events occur, the heads of the individual participating institutions (all participating institutions) must report to the Minister of Health, Labour and Welfare (MHLW) using the specified form "Reports on unexpected serious adverse events" in compliance with the specifications in ethical guidelines related to clinical research. (Refer Table 2)

For reporting procedures to the MHLW, the following must be adhered to:

(1) Reporting directly from individual institutions to the MHLW

The event shall be reported from the institutions where events occur directly to the MHLW. The report should also be sent to the iPocc Trial Coordinating Center.

(2) Reporting from the iPocc Trial Coordinating Center reports on behalf of the institution to MHLW

The investigator shall forward the results of the review by the IRB/IEC to the iPocc Trial Coordinating Center. The iPocc Trial Coordinating Center will prepare a report and submit it to the MHLW, on behalf of the institution. After reporting to the MHLW, the iPocc Trial Coordinating Center will forward the final report to the site investigator.

11.5.2 Specifications in the Advanced Medical Service System B

In the event of SAEs that are specified for reporting in the evaluation system of investigational medical care (ESIMeC and the Section 3 advanced medicine), the iPocc Trial Coordinating Center must report immediately to the study chair and take action before the due date according to the specifications in Table 2.

11.5.3 Reports related to health hazard information

The study chair must immediately report relevant information obtained, if it is to have a major

[Japan only]

Table 2

Relevant regulations	Details to be reported	Reporting time frame	Reporting form*/Party receiving the report**	Reporter
Ethical Guidelines	Unexpected serious adverse events and faults related to the clinical trial a. Results in death b. Is life threatening c. Requires inpatient hospitalization or prolongation of existing hospitalization d. Results in persistent or significant disability/incapacity e. Is a congenital anomaly/birth defect	Report immediately	"Reports on unexpected serious adverse events"/ MHLW or delegated parties	Heads of all participating institutions
Advanced Medical Service System B	<< Serious Adverse Events related to the clinical trials under the Advanced Medical Service System B>> (i) Cases resulting in death or life-threatening cases (ii) The cases described below where the occurrence of the event, its incidence, and/or the conditions of onset were unexpected based on previously known results a) Cases that require inpatient hospitalization or prolongation of existing hospitalization b) Cases that result or may result in a permanent or obvious disability and functional disability that will impact daily activities c) Cases that threaten the patient other than a) and b), as well as serious cases where medical care is required to prevent conditions described in (i) and a) or b) of (ii) (e.g., cases requiring intensive treatment)	(i)within 7 days (ii)within 15 days	"Attachment7 Form no.1and no.2"/ The Minister of Health, Labour and Welfare through Head of the Regional Bureau of Health and Welfare,	Institution where the event has occurred*
	<Reports related to health hazard information> The parties are to commit to collecting the information on hazards that directly influence the safety and health of the public in regards to the relevant the Advanced Medical Service System B being studied. Any health hazard information must be reported if obtained.	Report immediately	"Attachment7 Form no.3"/ (i) Head of the Regional Bureau of Health and Welfare (ii) The minister of Health, Labour and Welfare	Study chair who collected the relevant information
Health Labour Sciences Research by MHLW	Information that has a major impact in public health	Report immediately	"Report on health hazard information"/Health Hazard Management Officer at MHLW	Study chair
Article 77 of the Pharmaceutical Affairs Law	Information that is needed to prevent the onset or spread of risk to public health and public hygiene	---	Minister of MHLW	Founder of the hospital, physicians, and/or other medical professionals.

* The latest version of the reporting form should be used. This can be found on the MHLW webpage.

** The submission to the regulatory authorities is to be carried out by the iPocc Trial Coordinating Center, except for those cases described in the Section11.5.1.(1).

11.6 Distribution of SAE information using the STUDY WEB-PAGE

The SAE reports for the study will be posted on the "Safety Reports" section of the secure STUDY WEB-PAGE (https://studyweb.kitasato-ctcc.jp/top.html). Additional information on SAE reporting will also be posted on this website.

All registered attending investigators and CRCs will receive an e-mail notification when a new SAE report is posted on the website.

Information related to drug safety may be separately provided to institutions of various countries from the manufacturer and distributors of the study drugs worldwide.

The principal investigator of each study institution will be responsible for access to SAE reports posted on the STUDY WEB-PAGE, as well as the reporting to regulatory authorities in each country and the individual IRB. The flow of events for reporting procedures of SAEs are provided in Flows of serious adverse event reporting.【See Appendix 1-B】

11.7 Compensation for trial-related injury

In consideration of characteristics of the targeted disease and treatment covered in this study, trial-related injury, including death, may occur. Medical costs generated by participating in this study will be assumed to be those associated with standard medical care. (In Japan, basic treatment costs are covered by national health insurance and ESIMeC.) If any trial-related injury occurs, JGOG/GOTIC, the relevant institution where the injury occurs, and the manufacturer are not obliged to provide compensations for such injuries. However, sufficient medical care should be provided by the relevant institution where trial-related injury occurs. Accordingly, compensation is considered to have been provided.

11.8 Clinical trials liability insurance

This study will be covered by "Clinical trials liability insurance" designed to provide monetary compensation only for negligence liability in case of protocol flaws.

12 STUDY DURATION

Target sample size and accrual period

Target sample size: 120 (phase A)
534 (Phase B)
654 (Phase A + Phase B)

Accrual period: May 2010 to November 2016

Follow-up period: Follow-up until 510 events are observed or until 3 years from the last patient is randomized to the study, whichever comes first. Consequently, follow-up is estimated to be completed in November 2019.

- Patients will receive the protocol treatment until disease progression, intolerable toxicity, or completion of 6-8 cycles of therapy.
- Patients are able to refuse the protocol treatment at any time for any reason.
- Patients will be followed for 3 years unless consent is withdrawn.

13 STATISTICAL ANALYSIS

13.1 Sample size

13.1.1 Phase B (Phase III trial)

The primary endpoint of this trial is progression-free survival (PFS). The results of the JGOG3016 trial showed that the median PFS in the dd-TC arm was approximately 28 months.[10] In addition, a meta-analysis conducted by the National Cancer Institute (NCI) and the Gynecologic Oncology Group (GOG) showed that the hazard ratio for PFS in the IP versus IV arms was 0.784, with a 21.6% decrease in the risk of progression in the IP arm.[19]

On the basis of the above evidence, the median PFS in the dd-TCiv arm of this trial is expected to be 28 months and a hazard ratio for PFS to be 0.78 in the dd-TCip arm versus the dd-TCiv arm. It would appear that a 22% decrease in the risk of progression is required to allow dd-TCip therapy to become a new standard treatment. Based on a registration period of 3 years and a follow-up period of 3 years, the required sample size and the number of events are 746 subjects (373 subjects per arm) and 510 events (239 events in the dd-TCip arm) in order to detect this hazard ratio with a two-sided 5% significance level and 80% power using a log-rank test. The final analysis will be performed after observing the required number of events described above or completing the planned follow-up period, whichever comes first. However, if a sufficient number of events have not been observed at the time of completion of the planned follow-up period, a prolongation of the follow-up period will be considered.

PS: As of Jaunary 20, 2013, the patient recruitment rate is lower than expected. Therefore, the required sample size, registration period and follow-up period are modified. Based on a registration period of 5 years and a follow-up period of 3 years, the required sample size and the number of events are 685 subjects and 510 events in order to detect the hazard ratio of 0.78 with a two-sided 5% significance level and 80% power using a log-rank test. <<1/20/2013>>

P.S: As of December 16, 2014, the patient recruitment rate is lower than expected. Therefore, the required sample size, registration period and follow-up period are modified. Based on a registration period of 6.5 years and a follow-up period of 3 years, the required sample size and the number of events are 654 subjects and 510 events in order to detect the hazard ratio of 0.78 with a two-sided 5% significance level and 80% power using a log-rank test. <<12/16/2014>>

13.1.2 Phase A (Phase II trial)

The results of JGOG 3016 conducted by JGOG and published in August 2009 showed that the treatment completion rate in the dd-TC arm was 47.0%; the occurrence rates of Grade 3 or higher (the worst Grade) adverse events were 91.7% for neutropenia, 80.4% for leukopenia, 68.6% for Hb decrease, and 43.6% for thrombocytopenia; and the response rate was 55.8%. On the basis of the above evidence, 46 subjects per arm will be needed as a required sample size in order to construct an exact 95% confidence interval with 15% accuracy using simulation. Because the dd-TCip arm may have a lower treatment completion rate and a higher rate of adverse events than the above results and there may be subjects without evaluable lesions that need to be considered for the response evaluation, the required sample size for the phase II part will be a total of 120 subjects (60 subjects

per arm).

13.2 Randomization and stratification factors

Subjects will be registered centrally and randomized using the minimization method. Stratification factors at the time of randomization will be as follows: registered institutions, FIGO stages (during surgery) (II vs. III vs. IV) and diameters of residual tumors (No gross tumor vs. less than 1 cm vs. greater than or equal to 1 cm and less than or equal to 2 cm vs. greater than 2 cm).

13.3 Statistical analysis

13.3.1 PhaseB (PhaseIII trial)

13.3.1.1 Analysis sets

The analysis of efficacy will be performed on all randomized subjects in accordance with the intention-to-treat (ITT) principle. In order to assess the robustness of the results, the same analyses will be done using all randomized subjects who satisfy the eligibility criteria. The analysis of safety will be performed on all subjects who have received at least one dose of study treatment.

13.3.1.2 The primary analysis of efficacy

The Kaplan-Meier method will be used to predict PFS. After calculating the median PFS and its non-parametric 95% confidence interval, the difference will be compared using the log rank test. The significance level of a test will be described separately in the section "interim analysis."

13.3.1.3 The secondary analyses of efficacy

The Kaplan-Meier method will be used to predict all survival curves, which will be compared using the log-rank test. Response rates in subjects with evaluable lesions will be predicted. In addition, the treatment completion rate in each arm will be predicted by defining subjects receiving a 6-cycle administration as subjects achieving treatment completion. The exact 95% confidence intervals for the response rates and the treatment completion rates in each arm will be calculated. The differences in tumor responses and treatment completion status between the arms will be compared using Fisher's exact test and a 95% confidence interval for the odds ratio based on normal approximation. Analyses of safety, quality of life (QOL) and cost effectiveness will be described separately in the following sections.

13.3.1.4 Interim analyses

Based on the assumption of proportional hazards, alternative hypotheses, and the uniformity of accrual rates, 255 events (half of the required number of events) are expected to be observed after approximately 3.2 years from the start of registration. Accordingly, the interim analysis of efficacy will be conducted once after 3.5 years from the start of registration or at the time when 255 events (half of the required number of events) are observed, whichever comes first. In order to maintain a significance level of 5% for the whole study, the significance levels at the first interim analysis and the last analysis will be expected to set at 0.3% and 4.7%, respectively, using the O'Brien-Fleming-type alpha spending function.

In addition, the conditional power [30)] will be calculated every year from the second year after the start of the study in order to help the IDMC decide whether to continue the study in case data

suggests that it is difficult to evaluate the treatment response. More specifically, using survey data and alternative hypotheses, the conditional probability that the null hypothesis is false at the last analysis will be predicted. When this conditional probability is less than 10%, early termination of the study for futility will be considered by the IDMC.

PS: As of Jaunary,20, 2013, the patient recruitment rate is lower than expected. Therefore, the required sample size, registration period and follow-up period are modified. Based on the assumption of proportional hazards, alternative hypotheses, and the uniformity of accrual rates, 255 events (half of the required number of events) are expected to be observed after approximately 4.5 years from the start of registration. Accordingly, the interim analysis of efficacy will be conducted once after 5 years from the start of registration or at the time when 255 events (half of the required number of events) are observed, whichever comes first. In addition, the conditional power will be calculated every year from the fourth year after the start of the study. <<1/20/2013>>

PS: As a result of the changes in enrollment period, total study period, and required number of cases, the period of interim analysis will be changed. As the total study period will become longer, the number of events required at the time of interim analysis will be changed from 255 to 230. By applying the O'Brien-Fleming α-spending function, the level of significance in the interim analysis will be 0.2%, and the level of significance of the final analysis will be 4.8%. While it is expected that 230 events will be observed in approximately 5.1 years after the commencement of enrollment, the number of monthly enrolled cases in the early stage of the study was smaller than other periods. On the assumption that the collection of number of events required will be behind schedule, the following changes will be made: The interim analysis will be conducted once after 5.5 years after the commencement of enrollment, or at the time when 230 events are confirmed, whichever comes first. For the same reason, the calculation of conditional power will be conducted at the time of interim analysis and annually thereafter. <<2014/12/16>>

13.3.1.5 Subgroup analysis

In order to examine the robustness of analysis results for the primary endpoint and the secondary endpoints, stratification analysis will be conducted for all estimates and comparison results using stratification factors and other patient background factors at the time of randomization.

13.3.1.6 Exploratory analysis

Exploratory analysis will be performed using an analysis model (Cox proportional hazards model and the logistic model).

13.3.1.7 Safety analysis

The number of adverse events in each arm will be calculated separately. In addition, the adverse events rate and the odds ratio will be calculated and compared using a 95% confidence interval based on normal approximation.

13.3.1.8 QOL and cost-effectiveness analyses

By comparing Quality of Life (QOL) of the dd-TCip therapy with that of the dd-TCiv therapy and

then comparing those results with ones from other relevant trials, the effects of the IP therapy on QOL and improvement in QOL with Carboplatin will be examined. Based on the assumption of a uniformity of accrual rates, because QOL data from more than 300 subjects are expected to be obtained up to 2 years from the start of study, QOL analysis will be performed 2 years after the start of the study. In addition, the medical costs for each treatment will be compiled around the same time. At the completion of the study or withdrawal, cost-effectiveness analysis considering efficacy endpoints, QOL and the medical costs will be performed together with a QOL analysis.

QOL data collected at baseline will be analyzed using the linear model adjusted for age and ECOG performance status (PS) determined prior to registration in accordance with the analysis published by Armstrong et al. (GOG 172 trial)[18]. QOL data collected at other times will be analyzed using the linear mixed model adjusted for age, PS determined prior to registration and QOL score at baseline. In order to examine the robustness of the results, the analysis will also be performed using adjustable factors that include institutions. The medical costs in each arm will be compiled and analyzed after 2 years from the start of study, and the incremental cost-effectiveness ratio (ICER) will be calculated, taking into consideration efficacy endpoints, QOL and the medical costs at the completion of study or at the time of patient withdrawal. The details of QOL and cost-effectiveness analysis will be recorded separately on a statistical analysis plan.

For the QOL assessment, the results from approximately 300 subjects accumulated during the first 2 years after the start of study will be published initially. All registered subjects from whom informed consents were obtained will be subject to cost-effectiveness analysis, and the publication of the results will be performed after the completion of primary endpoint analysis due to the requirements of data on PFS and OS.

PS: As of Jaunary,20, 2013, the patient recruitment rate is lower than expected. Therefore, the statistical analysis of QOL assessment will be performed after the completion of the study. <<1/20/2013>>

13.3.2 PhaseA (Phase II trial)

13.3.2.1 Analysis sets

A feasibility analysis of study treatment will be performed on subjects who have received at least one dose of study treatment.

13.3.2.2 Feasibility analysis

The number of subjects completing treatment, hematotoxicity, and non-hematotoxicity will be compiled in each arm and these occurrence rates will be predicted. In addition, adverse events rates and response rates in subjects with evaluable lesions will be compiled for each arm. An exact 95% confidence interval will be calculated for each rate. As backup materials for the decision whether to continue the study by the Independent Data Monitoring Committee, the odds ratio in each arm will be calculated, together with the p-values using Fisher's exact test and the 95% confidence interval for the odds ratio based on the normal approximation.

14 ETHICS

14.1 Ethical conduct of the clinical trial

All investigators associated with this clinical trial must conduct the study in accordance with the Declaration of Helsinki.【See Appendix 3-I】

This clinical trial must be conducted in accordance with the Ethical Guidelines for Clinical Studies (revised on July 31, 2008) and should follow "Good Clinical Practice (GCP) guidelines."

14.2 Protection of patients

All investigators related to this clinical trial must conduct the study in compliance with the ethical principles that have their origin in the Declaration of Helsinki.The rights, safety, and well-being of the trial participants are the most important considerations and should take precedence over the interests of science and society

14.3 Patient information and informed consent

Prior to registration, investigators will provide patients with the informed consent documents shown in Appendix2-① or other written documents approved by the Institutional Review Board (IRB) Independent Ethical Committee (IEC) and explain the following in detail:

1) Diagnosis and current condition;
2) This study is a clinical trial. The difference between a clinical trial and clinical practice;
3) The rationale, significance, necessity, and objectives of this study;
4) The content of protocol treatment;
5) The name of drugs, route of administration, dosage, treatment cycles, and duration of the overall protocol treatment;
6) The design of the clinical trial: This is a randomized phase II/III trial;
7) The reasonably expected benefits from protocol treatment;
8) The reasonably foreseeable toxicities (adverse events): in particular, expected adverse drug reactions induced by the IP therapy;
9) Possibilities of treatment-related death and other adverse sequelae;
10) The content of general practice (including palliative therapy) and standard treatment, and associated benefits and toxicities;
11) The benefits and disadvantages possibly arising from participation in the study;
12) The alternative treatments;
13) The benefits and disadvantages arising from alternative treatments;
14) That not giving consent for participation in the study will not cause any disadvantage to patients;
15) Patients may withdraw informed consent after giving it without being disadvantaged in any way;
16) The human rights of patients will be protected;
17) The confidentiality of the patient's name and personal information will be maintained;
18) The patient is free to ask questions regarding this trial of the investigators and the institutional principal investigator, as well as the iPocc Trial Coordinating Center by providing their contact information in writing.
19) The approximate planned number of patients to be involved in this clinical trial;
20) Patients will be informed in a timely manner if information becomes available that may be

relevant to the patient's willingness to continue participation in the clinical trial;

21) Costs for the treatment and compensation for health injury: an example on cost burden on patients in both arms, the content of compensation, and information on clinical trial insurance (liability insurance);
22) Agreement to the direct inspection and audit of the patient medical records
23) The conflicts of interest related to this clinical trial;
24) The clinical trial registration in the University hospital Medical Information Network-clinical registration (UMIN-CTR) and National Network of Libraries of Medicine (NLM).

14.4 Patient's consent

When an explanation of the study is provided to the patient (or the patient's legally authorized representative who is able to give consent on behalf of the patient) regarding his/her participation in the study, it is necessary to confirm that he/she fully understands the content of the study. In particular, for this study, sufficient explanation of the following must be given: 1) the possibility of adverse drug reactions induced by the IP therapy, 2) the difference in cost burden on patients between the arms, 3) that no monetary compensation will be provided for chemotherapy-related injury; however, prompt medical care will be provided, and this clinical trial is covered by clinical trial insurance; 4) conflicts of interest, and 5) that the clinical trial is registered at the UMIN in Japanese and at the NLM in English. When the patient agrees to participate in the trial, the patient and the Investigator who has provided an explanation of the trial must date and sign on the IRB approved consent form【See Appendix 2-①】. Informed consent must be obtained in writing.
A signed copy of the form must be given to the patient. The original consent must be retained in the clinical records of the institution.

14.5 Privacy protection and patient identification

The names of registered patients will not be revealed to the iPocc Trial Coordinating Center by the participating institutions. The identification of, and inquiries regarding, registered patients will be conducted using a protocol patient ID number assigned at the time of registration and the initials of patients.

14.6 Compliance with the protocol

Investigators participating in this clinical trial must conduct the study in compliance with the protocol to the extent that the patient's rights and safety are protected.

If noncompliance with the protocol is identified by monitoring or auditing processes, such noncompliance will be considered to be a "protocol deviation" or "protocol violation" based on the degree of noncompliance. When investigators determine that it is difficult to treat the patient in compliance with the protocol for any reason, they must contact the iPocc Trial Coordinating Center for further instructions.

If serious non-compliance with the ethical guidelines is discovered, the opinions of the IRB at the relevant institution must be sought, and the results should to be reported to the Minister of Health, Labour and Welfare (MHLW). The reporting procedures are as described in the section "Specifications in Ethical Guidelines" under 11.5.1. Serious non-compliance with ethical guidelines will be disclosed to other participating institutions, after review by the IDMC.

14.7 Approval by the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC)

Prior to participation in this clinical trial, the protocol and informed consent documents must be approved by the IRB/IEC. When IRB/IEC approval is granted, the investigator at each institution will fax a copy of the certificate of IRB/IEC approval to the iPocc Trial Coordinating Center.

faxed to the iPocc Trial Coordinating Center. The originals of the IRB/IEC approval certificate the notification of the Advanced Medical Service System B must be retained at each institution. The

[Japan Only]

14.8 Annual renewal of IRB/IEC Approval

In general, when any amendments are made to the protocol or informed consent documents during the course of the clinical trial, the amended protocol and informed consent documents must be approved by the IRB/IEC. The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, at least once per year. The copy of documents regarding IRB annual review should be submitted to Japanese Gynecologic Oncology Group office.

【Address and contact number to submit】

Japanese Gynecologic Oncology Group
Email: jgog-dc@insti.kitasato-u.ac.jp
FAX: 03-5206-1983

14.9 Changing the content of the protocol

Changes to the protocol made after approval by the IRB/IEC will be handled as two separate items: "Amendments" and "Revisions." In addition, any supplemental explanations without changes to the protocol will be regarded as "Memorandums." The definitions and the handling of these are as follows:

1) Amendment
   A partial change(s) to the protocol that may increase the risk to patients participating in the clinical trial or that affects the primary endpoint in the clinical trial.
   Requires approval by the Clinical Trial Review Committee in JGOG and GOTIC, and must be reported to each IRB in accordance with the policy established by each institution.
   The date of approval by the Clinical Trial Review Committee will be noted on the cover page of the protocol.
2) Revision
   A change(s) to the protocol that is not associated with any increased risk to patients participating in the clinical trial and that is not associated with the primary endpoint in the clinical trial.
   Does not require review by the Clinical Trial Review Committee, but should be reported.
   It is not necessary to record the date of approval by the Clinical Trial Review Committee on the