

In the case where a lesion that is present at baseline disappears and then reappears, if its reappearance occurs after the overall response is evaluated as CR, it will be considered “PD.” On the other hand, if there are other residual lesions, reappearance of the previous lesion will not itself be considered “a new lesion” or evaluated as “PD,” but the diameter of tumors will be added to the sum of diameters in the case of target lesions. For non-target lesions, it will be evaluated as “Non-CR/Non-PD” unless it falls under “unequivocal progression” in the definition of “PD.”

In cases where a lesion may be considered to be a new lesion, but where this has not been confirmed, it should not be concluded that it is a new lesion until repeat imaging testing, performed at appropriate intervals, confirms that it is a new lesion. It should then be considered to have appeared as a new lesion at the time of the imaging test on which it is confirmed as a new lesion.

If a positive FDG-PET scan lesion (which is FDG avid with an uptake greater than twice that of the surrounding tissue on an attenuation-corrected image) appears in a location with a negative FDG-PET at baseline, it will be considered to indicate the appearance of a new lesion. If a positive FDG-PET scan lesion appears after the start of protocol treatment without the use of FDG-PET scanning at baseline, it will be considered to indicate the appearance of a new lesion when a tumor lesion that is not identified by CT or MRI at baseline is confirmed in the location with a positive FDG-PET.

#### 9.2.3.5 Evaluation of overall (unconfirmed) response

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum recorded since baseline). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria in some circumstances.

**Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)**

Target Lesions	Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR	CR	Within normal limits	No	CR
CR	Non-CR/Non-PD	Any value	No	PR
CR	Not evaluated	Any value	No	PR
PR	Non-PD or NE	Any value	No	PR
SD	Non-PD or NE	Any value	No	SD
NE	Non-PD	Any value	No	NE
PD	Any	Any value	Yes or No	PD
Any	PD**	Any value	Yes or No	PD
Any	Any	PD	No	PD
Any	Any	Any value	Yes	PD

\*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

\*\* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

**Time Point Response for Patients with only Non-Measurable Disease at baseline  
(i.e., Non-Target Disease)**

Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR	Within normal limits	No	CR
CR	Above normal limits	No	Non-CR/non-PD*
Non-CR/non-PD	Any value	No	Non-CR/non-PD*
NE	Any value	No	NE
Unequivocal PD	Any value	Yes or No	PD
Any	PD	No	PD
Any	Any value	Yes	PD

\*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

\*\* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

**9.2.3.6 Progression is defined as any of the following:**

- 1) At least a 20% increase in the sum of the longest diameters of target lesions as compared with the smallest sum of the longest diameters.
- 2) The appearance of one or more new lesions.
- 3) Death due to disease without prior objective documentation of progression
- 4) Unequivocal progression of non-target lesions, excluding pleural effusion that has not been proven to be malignant by cytology.

### 9.2.3.7 Best overall confirmed response

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response	
CR	CR	CR	
CR	PR		SD, PD or PR*
CR	SD	SD	provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD	provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD	provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD	provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD	provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE	

\*If a CR is truly reached at the first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

Confirmation of CR or PR is needed to deem either one the "best overall response." Responses (CR and PR) require confirmation at least 4 weeks from initial documentation.

For this study, the minimum criterion for SD duration is 6 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or who die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment.

### **9.3 Progression-free survival (PFS)**

Progression-free survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first. Information on the date of last observation for PFS is also collected.

### **9.4 Survival**

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

### **9.5 Performance status (PS)**

PS will be evaluated using ECOG criteria [See Appendix 3-II].

### **9.6 Quality of life (QOL) assessment**

#### **9.6.1 Objectives of QOL survey**

As one of the secondary endpoints of this study, a QOL assessment and comparison based on patients' subjective views will be conducted.

- 1) To compare the differences in effects on QOL of paclitaxel weekly plus intravenous carboplatin versus intraperitoneal carboplatin as first-line therapy in women with epithelial ovarian, primary peritoneal or Fallopian tube cancer.
- 2) To compare QOL in overall survival between the two groups.
- 3) To conduct a subjective assessment of long-term effects (at one year and at two years) after IP reservoir port placement.
- 4) To conduct a QOL assessment for utility values to be used for an economic evaluation in health care as described in the following section 9.7.

#### **9.6.2 Methods of the QOL assessment**

In order to ensure the quality of the QOL assessment, cooperation with the Clinical Research Coordinator (CRC) or nurses is essential. It is recommended that QOL survey personnel be appointed at each site in advance, to provide the iPocc Trial Coordinating Center with the details.

At each assessment point, the QOL personnel will conduct a survey prior to the following treatment course. As a general rule, QOL questionnaires will be collected by QOL personnel, not by investigators, and will be forwarded to the iPocc Trial Coordination Center. In addition, in cases where patients themselves are unable to fill in the questionnaires due to exacerbation of their disease or for other reasons, QOL personnel may conduct a survey by reading out the questions on the questionnaires. In such case, the reasons why the patient was unable to fill in the survey themselves need to be provided.

#### **9.6.3 QOL scale**

In order to guarantee the comparativeness between this study and the phase III trial of intraperitoneal chemotherapy currently conducted by GOG, the following QOL items will be used for the scale of QOL assessment.

- 1) FACT-O: Functional assessment of cancer therapy-ovarian  
FACT-O is the scale that has been examined for reliability, validity and time-dependent

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<sup>32)</sup> 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 Cost-utility evaluation

### 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) For indirect costs, if the survey on direct non-medical costs along with the QOL survey on patients is conducted, these surveys will be conducted using the “Survey form for costs associated with treatment” [Appendix 2-⑦]. 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 during the following QOL survey period, and ③ survey forms including the EQ-5D questions to be used several times “during the QOL survey period after 84 weeks from the start of treatment.” For the “Survey on costs after 84 weeks from the start of treatment,” a strict timeline has not been established; however, the survey will be continued at least once a year concurrent with the follow-up.
- 5) The survey on costs is scheduled to be completed about 6 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 7 years after the start of study.

#### **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.

<http://kitasato-ctcc.mdsol.com>

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

eCRFs	Form Due		Remarks
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 - Pathology <sup>1)</sup> * <u>Histopathology Slides (Tumor tissue)</u> <sup>2)3)</sup> * <u>Histopathological Report prepared by institutions</u> <sup>4)</sup>	After surgery	No later than 4 weeks	See below 1) - 4) for the details.
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	

- 1) Histopathology slides are to be sent using the “Pathology” cover letter.
- 2) Three representative HE-stained slides (at least one slide) from different parts of the epithelial ovarian, Fallopian tube, or primary peritoneal cancer, are to be submitted to the iPocc Trial Coordinating Center, and to “Pathology”.

[Address and contact number to submit sample slides]

**iPocc Trial Coordinating Center**

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- 3) 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 also be provided.
- 4) 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. Write the Protocol-specific patient ID number in the report.

## 11 ADVERSE EVENT REPORTING

*\*International institutions outside Japan may need to refer to their country specific Appendix for ADVERSE EVENTS REPORTING.*

### 11.1 Adverse events to be reported

#### 11.1.1 Definition of serious adverse events (SAE)

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 completion/discontinuation of the protocol treatment. However, an adverse event which occurs 30 days or later after the completion/discontinuation 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 intensive 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 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 iPoc 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		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		
No causal relationship	Not required	Not required	Not required	Within 10 days	Not required	Within 10 days	Not required	Within 10 days	Within 10 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 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 international IDMC meeting will be held annually (or more frequently if the IDMC feels it appropriate) to review the study monitoring reports and an interim analysis report produced by the iPocc Trial Coordinating Center. 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 SAE reports to regulatory authorities**

#### **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 evaluation system of investigational medical care (ESIMeC and Section 3 advanced medicine)**

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 effect on the public and the research, according to the specifications in Table 2.

Table 2

Relevant regulations	Details to be reported	Reporting time frame	Reporting form*/Party receiving the report**	Reporter
<b>Ethical Guidelines</b>	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
<b>Section 3 Advanced Medicine</b>	<Safety reports> limited to adverse reactions (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 requires inpatient hospitalization or prolongation of existing hospitalization b) Cases that result or may result in a 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	“Form no. 4”/ (i) Head of the Regional Bureau of Health and Welfare, and (ii) Medical section of the Medical department, Bureau of Health, MHLW	Institution where the event has occurred*
	<Reports relating 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 advanced medical care being studied. Any health hazard information must be reported if obtained.	Report immediately	“Form no. 5”/ Head of Health Policy Bureau, Ministry of MHLW	Study chair who collected the relevant information
<b>ESIMeC</b>	<Safety reports> As per section 3 Advanced Medicine	(i) within 7 days (ii) within 15 days	“Form no. 5”/ (i) Head of Health Policy Bureau, Ministry of MHLW, and (ii) Minister of Health, Labour and Welfare via the Head of the Regional Bureau of Health and Welfare	Institution where the event has occurred
	<Reports relating to health hazard information> As per section 3 Advanced Medicine	Report immediately	“Form no. 6”/ Head of Health Policy Bureau, Ministry of MHLW	Study chair who collected the relevant information
<b>Health Labour Sciences Research by MHLW</b>	Information that has a major impact in public health	Report immediately	“Report on health hazard information”/Health Hazard Management Officer at MHLW	Study chair
<b>Article 77 of the Pharmaceutical Affairs Law</b>	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 Section 11.5.1.(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 (<http://www.kitasato-ctcc.jp/>). 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)

626 (Phase B)

746 (Phase A + Phase B)

Accrual period: May 2010 to April 2013

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 April 2016.

\*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 III part

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.<sup>10)</sup> 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.<sup>19)</sup>

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.

#### 13.1.2 Phase II part 1

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 Phase III part**

##### **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<sup>30)</sup> 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.

#### **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)<sup>18)</sup>. 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.