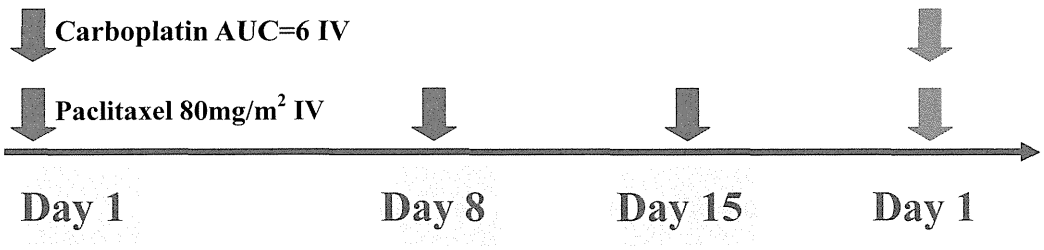
7.3.3 Example of Regimen I (Standard treatment: dd−TCiv therapy)

Day 1	
9:00 AM	Premedication【See section 7.8.4】
9:30 AM	NSS (250 mL) + Paclitaxel (80 mg/m^2) IV infusion (approximately 60 minutes)
10:30 AM	NSS (250 mL) + Carboplatin (AUC=6) IV infusion (over 30 minutes)
Day 8	
9:00 AM	Premedication
9:30 AM	NSS (250 mL) + Paclitaxel (80 mg/m^2) IV infusion (approximately 60 minutes)
Day 15	
9:00 AM	Premedication
9:30 AM	NSS (250 mL) + Paclitaxel (80 mg/m^2) IV infusion (approximately 60 minutes)



7.4 Regimen II (Study treatment: dd−TCip therapy)

Paclitaxel:	80 mg/m^2	1 hour IV infusion	Days 1, 8, and 15
Carboplatin:	AUC = 6.0	single IP injection	Day 1

- The 3-week period (21 days) is 1 cycle. A total of 6 to 8 cycles will be repeated.
- Protocol treatment comprises 6 cycles. However, if interval debulking surgery (IDS) is performed after 3, 4 or 5 cycles, the patients can receive up to 3 additional cycles of the protocol treatment. If the investigator considers that the patient may recieve deriving benbefit from continuing protocol treatment, additional protocol treatment may be allowed up to 8 cycles after consulting with the Study Chair.

7.4.1 Administration of Paclitaxel

1) After the introduction of premedication, the prescribed dose of Paclitaxel diluted in 250 mL of 5% dextrose or normal saline solution (NSS) will be administered by intravenous infusion over 1 hour through an exclusive line.
2) Paclitaxel will be given on Days 1, 8 and 15 for each cycle.

7.4.2 Administration of Carboplatin

1) During IV administration of Paclitaxel, the IP port will be punctured using the Huber needle*[1], and 1000 mL to 1500 mL of normal saline solution will be intraperitoneally injected.
2) After completion of Paclitaxel IV administration, the prescribed dose of Carboplatin prepared in a syringe will be given as a single injection through the Huber needle.

3) Following injection of the total dose of Carboplatin, 10 mL of heparinized normal saline solution will be injected, and the Huber needle will be removed.
4) Carboplatin will be given on Day 1 for each cycle.

*[1] The Huber needle used in this study must be the following three types of needles (use different length of needles based on adipose thickness). Use of any other device is not allowed in this study.

- NIPRO Specially Processed Needle for Elimination of Dangerous Coring at Puncture Coreless Needle Set (1.5cm); #24-270
- NIPRO Specially Processed Needle for Elimination of Dangerous Coring at Puncture Coreless Needle Set (2.5cm); #24-257
- NIPRO Specially Processed Needle for Elimination of Dangerous Coring at Puncture Coreless Needle Set (3.5cm); #24-258

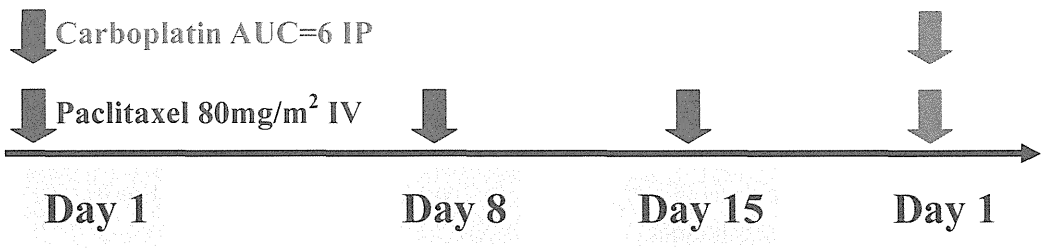
For institutions, if the Huber needle is not available to obtain, other needles may be allowed to use after consulting with the study chair. ***[Except Japan]***

7.4.3 Notes for IP administration (For details, 【see Appendix1-A】)

1) Pay careful attention to prevent infection. IP-related infection may possibly cause peritonitis.
2) Port puncture should be performed aseptically using surgical gloves.
3) Completely sterilize the skin at the puncture site with Isodine solution.
4) When Carboplatin is given as a single injection, it is recommended to inject approximately 10 mL first, and inject the rest after observation to check for any allergic reactions.
5) Remove the IP port immediately if peritoneal infection is suspected.
6) Discontinue IP administration if catheter obstruction is suspected.
7) In patients with massive ascites, it is not always necessary to intraperitoneally administer 1000 mL to 1500 mL of normal saline solution. Based on the medical judgment of the investigator, an adequate amount of normal saline solution should be administered. The investigator should confirm that there is no difficulty associated with injection of Carboplatin.
8) If there is a problem in IP administration of normal saline solution, catheter obstruction or bowel adhesion to the area surrounding the catheter may be suspected. In such a case, the investigator should discontinue IP administration and notify the iPocc Trial Coordinating Center.
9) If any allergic reaction to Carboplatin is observed, stop Carboplatin injection, and please inform the iPocc Trial Coordinating Center. 【See Appendix3-V】 Switching Carboplatin (IP) to cisplatin (IP) is not generally allowed for this study.
10) If any severe abdominal pain is observed, conduct next IP administration very slowly under careful observation, taking into consideration bowel adhesion to the area surrounding the catheter. If severe abdominal pain occurred again, despite slow IP administration, please notify the iPocc Trial Coordinating Center via email to seek advice from the study chair.
11) In case of changing in the route of administration from IP administration to IV administration, please notify the iPocc Trial Coordinating Center via email.

7.4.4 Example of Regimen II (Study treatment: dd−TCip therapy)

Day 1	
9:00 AM	Premedication
9:30 AM	NSS (250 mL) + Paclitaxel (80 mg/m^2) IV infusion (60 minutes)
	IP Port puncture, and injection NSS(1000mL to 1500mL) IP injection(full open)
10:30 AM	Completion of Paclitaxel infusion
	Carboplatin (AUC = 6) Single IP injection
	Heparinized NSS (10 mL) IP injection,
	Removal of the Huber needle
Day 8	
9:00 AM	Premedication
9:30 AM	NSS (250mL) + Paclitaxel (80mg/m^2) IV infusion (60 minutes)
Day 15	
9:00 AM	Premedication
9:30 AM	NSS (250mL) + Paclitaxel (80mg/m^2) IV infusion (60 minutes)



7.5 Criteria for starting protocol treatment [For both Regimen I and II]

7.5.1 Criteria for starting protocol treatment on Cycle 1

7.5.1.1 Criteria for starting Day 1of Cycle1

After surgery, the investigator needs to confirm that the patient meets all clinical laboratory data criteria. 【See the section 4.1.】 The laboratory data referred to for each patient should be that obtained within 2 weeks before the first date of protocol treatment.

7.5.1.2 Criteria for starting Day 8 and Day 15 of Cycle 1

1) Within 2 days before starting administration of protocol treatment, the patient meets all criteria described in Table 1.
2) If the patient fails to meet all criteria in Table 1, treatment can be delayed by up to 3 weeks.
3) In case of failure to meet the criteria even after a 3-week delay, the protocol treatment should be discontinued. (However, if the same treatment as the protocol-directed treatment is to be given after more than 3 week delay, we request the treatment to be continued as close as possible to the protocol-directed treatment. Ssubmission of eCRFs is also necessary for such a case., see the section 7.7.2.)

Table 1. Criteria for starting Paclitaxel administration on Day 8 and Day 15

Item	Criteria for starting
Absolute neutrophil count	≥ 500 /mm^3
Platelet count	$\geq 50{,}000$ /mm^3

7.5.2 Criteria for starting successive cycles

7.5.2.1 Criteria for starting administration on Day 1 of successive cycles

1) Within 2 days before starting administration of the protocol treatment, the patient meets all criteria described in Table2.
2) If the patient fails to meet all the criteria in Table 2, treatment can be delayed by up to 3 weeks.
3) In case of failure to meet the criteria even after a 3-week delay, the protocol treatment should be discontinued. (However, if the same treatment as the protocol-directed treatment is to be given after more than 3 week delay, we request the treatment to be continued as close as possible to the protocol-directed treatment. Ssubmission of eCRFs is also necessary for such a case., see the section 7.7.2.)

Table 2. Criteria for starting administration on Day 1 after cycle 2

Item	Criteria for starting
Absolute neutrophil count	$\geq 1{,}000$ /mm^3
Platelet count	$\geq 75{,}000$ /mm^3
Peripheral neuropathy	Grade 1 or 0
Other non-hematologic toxicities (except hair loss, fatigue, nausea, constipation, weight change)	Grade 1 or 0

7.5.2.2 Criteria for starting administration on Day 8 and Day 15 of successive cycles

Same as section 7.5.1.2. criteria for starting administration Day 8 and Day 15 of cycle 1

7.6 Dose reduction criteria [For both Regimen I and II]

7.6.1 Dose reduction process

1) If patients meet any one of the reduction criteria shown in Table 3 during the previous cycle, the dose will be reduced by one level in subsequent cycles according to the dose reduction levels shown in Table 4.
2) Even if patients meet two or more of the reduction criteria, the dose will be reduced by only one level in the subsequent cycle. (Do not reduce the dose by two levels at once.)
3) If patients meet the criteria again after reducing the dose, the dose will be reduced again by a further one level in the subsequent cycle according to the dose reduction levels shown in Table4.
4) Up to two dose reductions are allowed. Protocol treatment in subsequent cycles will be discontinued if patients meet the criteria after the second reduction. (In the event that the same treatment as in the protocol treatment is continued after discontinuation of the protocol

treatment, see section 7.7.2.)

5) Once the dose has been reduced, it should not be increased for subsequent cycles.

6) If the investigator determines that it is appropriate to modify the treatment for other reasons, notification should be provided to the iPocc Trial Coordinating Center.

Table 3. Dose reduction criteria

Reduction criteria	Drug to be reduced
Cycle delayed more than 2 weeks (15days≦) but for no more than 3 weeks (≦21days) because the patient did not meet the criteria for starting treatment described in Table 2	The doses of both Paclitaxel and Carboplatin are reduced by -1 level .
Dose-limiting neutropenia (DLT-ANC)[*1] or Dose-limiting thrombocytopenia (DLT-PLT)[*2] during the previous cycle	
Grade3 non-hematological toxicities (Except for alopecia, fatigue, nausea, constipation, peripheral neuropathy, or peritoneal irritation sign [abdominal pain]vaginal anastomotic leak at the time of IP administration or weight change)	
Grade 2 or greater peripheral neuropathy observed in the previous cycle.	The dose of Paclitaxel alone is reduced by -1 level.

*1 Neutropenia (DLT−ANC):

① Febrile neutropenia: neutrophil count decreased associated with fever as specified in CTCAEv4.0.

② Prolonged Grade 4 neutropenia (absolute neutrophil count less than 500/mm3) for at least7 days despite the use of G-CSFs. Neutropenia without complication lasting for less than 7 days is not DLT-ANC.

*2 Thrombocytopenia (DLT−PLT):

① Grade 4 thrombocytopenia (<25,000/mm^3).

② Thrombocytopenia with a bleeding tendency (25,000/mm^3 to <50,000/mm^3) is observed, and/or platelet transfusion is required.

Table4. Dose modification for toxicity

Level	Paclitaxel (mg/m^2)	Carboplatin (AUC)
0	80	6.0
-1	70	5.0
-2	60	4.0
-3	Discontinued	Discontinued

7.6.2 Management of hypersensitivity reactions to Paclitaxel 【see Appendix 3-VI】

1). Hypersensitivity reactions to Paclitaxel are NOT considered to be a dose-limiting toxicity.

2). It may be possible to administer the total dose of Paclitaxel after treating hypersensitivity reactions.

3). When a patient is re-challenged after the occurrence of hypersensitivity reactions to Paclitaxel, slower administration of Paclitaxel should be performed for subsequent doses.

7.6.3 Recalculation of dose

7.6.3.1 Dose recalculation for renal dysfunction

Considering the dosage and regimen in this protocol, renal dysfunction is usually not directly associated with chemotherapy-induced adverse effects. However, if serum creatinine is greater than 1.5 times the institution's upper limit of normal, the dose of Carboplatin should be recalculated for each cycle.

7.6.3.2 Dose recalculation for weight gain/loss

If patient weight change is less than 10% compared with the weight at the start of protocol treatment, recalculation of the dose for the subsequent cycle will not be required. In the event of weight gain/loss of more than or equal to 10%, the dose will be recalculated. If patient weight changes more than or equal to 10% compared with the weight at recalculation, the dose need to be recalculated again.

7.7 Criteria for protocol treatment completion/discontinuation

[For both Regimen I and II]

7.7.1 Criteria for protocol treatment completion

1) Protocol treatment should be completed at 6 cycles.*[1]
2) If interval debulking surgery (IDS) is performed, the patient can receive up to 3 additional cycles of the protocol treatment after IDS.

*[1] If the investigator considers that the patient may recieve deriving benbefit from continuing protocol treatment, additional protocol treatment may be allowed up to 8 cycles after consulting with the Study Chair. This need to be written in the patient medical records.

7.7.2 Criteria for protocol treatment discontinuation

1) Discontinuation of protocol treatment due to adverse events.
   ① Greater than 3-week delay*[1]
   ② Grade 4 non-hematologic toxicity
   ③ The third dose reduction (level -3)*[1]
2) Discontinuation of protocol treatment due to a patient request.
3) Patient death during protocol treatment.
4) Development of disease progression after the starting the protocol treatment.
5) When the investigator determines that the protocol treatment is no longer appropriate for the patient. (including cases where treatment is switched from dd-TCip therapy to dd-TCiv therapy). In such a case, notification should be provided to the iPocc Trial Coordinating Center.

*[1] In cases where the same treatment as the protocol treatment is continued, even after more than a 3-week delay and/or at a smaller dosage than the protocol-directed treatment, patients may, in some cases, not be excluded from the study. Therefore, it is necessary to continue the treatment

according to the test/observation schedule specified in the protocol, and submit the case report form likewise.

7.8 Concurrent/supportive therapy [For both Regimen I and II]

7.8.1 G-CSF

1) No prophylactic administration of G-CSF, such as filgrastim or lenograstim, PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) is allowed.
2) The ASCO Guidelines indicate the following【see Appendix 3-VII】

(1) Conditions for G-CSF use
   ① ANC is less than 1000/mm^3 (Grade3) and a fever (38℃/100.4℉ or higher) is observed.
   ② ANC is less than 500/mm^3 (Grade4).
   ③ Either of the above conditions ① or ② were observed in the previous cycle with an ANC of less than 1000/mm^3 in current cycle.

(2) Dosage and administration
   A dose of 50 μg/m^2 will be administered daily by subcutaneous injection.

(3) Conditions for G-CSF discontinuation
   ① When patients have an ANC of greater than or equal to 5000 /mm^3 after daily injection of G-CSF.
   ② When patients have an ANC of greater than or equal to 2000/mm^3 without any symptoms suggestive of infection and with no anticipated additional risk to the patients due to good response to previous G-CSF administration, at the discretion of the investigator.

7.8.2 Treatment for anemia

Patients may receive erythropoietin (EPO), iron supplements, and/or blood transfusions as clinically indicated for management of anemia.

7.8.3 Antiemetic drugs

Prophylactic administration of a 5-HT3 antagonist or other antiemetic drugs for reducing nausea and vomiting is recommended.

7.8.4 Antiallergic drugs

Prophylactic administration of a steroid or antihistamine agent for preventing allergic reaction to Paclitaxel is recommended.

7.8.5 Premedications: an example

For all cycles when Paclitaxel is administered, an appropriate premedication regimen should be employed.

1) 30 minutes prior to Paclitaxel administration, patients will receive the following short premedication to reduce the risk of hypersensitivity reactions. This regimen should include dexamethasone 20 mg intravenously or orally, anti-histamine H1 (such as diphenhydramine 50 mg orally), anti-histamine H1 (such as ranitidine hydrochloride 50 mg intravenously [28]).
2) If patients have no allergic reactions during cycle 1, the dose of dexamethasone may be

gradually decreased to 20 mg, 8 mg, 4 mg, 2 mg and 1 mg for subsequent cycles.

7.8.6 Acceptable concurrent/supportive therapy and surgery

1) If concurrent use of drugs (antimicrobial agents, analgesic, blood transfusion, etc.) for treating complications or adverse events is necessary, such drugs can be used at the discretion of the investigator.
2) Various symptomatic therapies for treating peripheral neuropathy caused by Paclitaxel can be used at the discretion of the investigator.
3) IDS is allowed to be performed after 3, 4 or 5 cycles of the protocol treatment. In such cases, the protocol treatment must be restarted within 8 weeks after IDS. If IDS is performed, patients can receive up to 3 additional cycles of the protocol treatment after IDS.

7.8.7 Unacceptable concurrent/supportive therapy and surgery

1) All anticancer treatments other than the protocol treatment with Paclitaxel and Carboplatin will not be accepted. Those include all cancer drugs except Paclitaxel and Carboplatin, immunotherapy, radiation therapy, etc.
2) Administration of any drugs undergoing clinical trials will not be accepted. (An exception may be granted after a diagnosis of progressive disease. For such a case, the iPocc Trial Coordinating Center should be notified in advance to discuss this with the study chair.)
3) Second-look surgery must not be carried out.

7.8.8 Post-protocol treatment after completion/discontinuation of the protocol treatment

No further anticancer therapy should be given after completion of 6-8 cycles of the protocol treatment until disease progression is documented.[*1]

Once the patient discontinued without completing protocol-directed therapy, post-protocol treatment is not specified.

When post-treatment is given, the regimen, administration method, given dose, duration of administration, etc. must be reported on the follow-up form.

[*1] If the investigator considers that the patient may recieve deriving benbefit from continuing protocol treatment, additional protocol treatment may be allowed up to 8 cycles after consulting with the Study Chair.

8 OBSERVATIONS AND TEST SCHEDULE

8.1 The following surveys and examinations must be conducted in accordance with the specified schedule, and the evaluation forms must be filled out.

Parameters	Prior to tentative-registration	After surgery - prior to the start of therapy	During protocol therapy				At completion of therapy or withdrawal	After therapy - during follow-up period
			Every week	Prior to each cycle	Every 2 cycles	Every 3 cycles		
Explanation of the study	●							
Signed informed consent	●							
Background data	●							
Surgery and pathological findings		●						
Medical history (Past, Current)	●							
Physical examination and PS (ECOG)	●	●[2)]		●			●[10)]	●[13)]
CBC, Differential, Platelets	●[1)]	●[2)]	●[4)5)]	●[5)]			●[10)]	
Electrolytes (Na, K, Cl, Ca), BUN, serum creatinine, CA125 and other tumor markers (creatinine clearance, if necessary)	●[1)]	●[2)]		●[5)]			●[10)]	
Total bilirubin, ALT(GPT), AST(GOT), ALP, LDH	●[1]	●[2)]		●[5)]			●[10)]	
Chest X-ray (or Chest CT scan)	●[1]	●[2)]			●[7)]		●[11)]	
Electrocardiogram (ECG)	●[1]	●[2)]					●[11)]	
Radiographic Tumor measurements		●[3)]			●[8)]		●[12)]	●[13)]
Adverse events		●[2)]		●			●[9)]	●[9)]
Serious adverse event reporting			●[6)] →	→	→	→	→	→
QOL assessment		●[14)]				●[14)]	●[14)]	●[14)]
Cost assessment		●[15)] →	→	→	→	→	●[15)] →	●[15)]

Notes:

1. To be conducted within 28 days prior to scheduled surgery.
2. To be conducted within 14 days prior to the start of protocol treatment after comprehensive staging surgery.
3. In the event that residual tumor(s) are found at the time of surgery, abdominal/pelvic CT or MRI must be performed within 28 days prior to the start of protocol therapy after surgery. If the use of contrast agents is contraindicated, plain CT or MRI must be performed. When IDS is conducted, abdominal/pelvic CT or MRI must be performed again within 28 days prior to the start of protocol treatment after the IDS.
4. To be conducted at least once a week.
5. To be conducted within 2 days prior to the next cycle of protocol treatment except for CA125 and other biomarkers. CA125 and other biomarkers are allowed to be tested within 28 days prior to Day1 of the cycle but after Day15 of the previous cycle.

6. In the event that adverse events to be reported occur, prompt reporting is required. 【See Appendix 2-⑤】
7. If an abnormal condition is detected at the time of tentative registration, or if it is necessary to determine the effect of therapy, plain chest X-P must be performed repeatedly. It is not mandatory in other cases.
8. With or without measurable lesions, CT or MRI must be performed every 2 cycles (after 2 cycles, after 4 cycles, after 6 cycles, (after 8 cycles), and at the time of discontinuation of the protocol treatment). If the use of contrast agents is contraindicated, plain CT or MRI must be performed. In order to evaluate the effect of therapy, the same test method must be used for every evaluation, and RECIST (version 1.1) will be used for evaluation.
9. The final evaluation of adverse events must be conducted 3 weeks after the final administration of the protocol treatment. Unless the protocol treatment-related adverse reactions more than Grade 2 are observed at the time of this evaluation, follow-up observations of adverse events are not required. If adverse reactions more than Grade 2 are reported, evaluations must be conducted at each follow-up until such events resolve. However, a Severe Adverse Event (SAE) which occurs within 30 days after the last administration of the protocol treatment is required to submit SAE report. 【See 11.1 for a detail】
10. To be conducted approximately 7 days after the final administration at the time of compleation/discontinuation of the protocol treatment. If adverse reactions more than Grade2 are observed, evaluations must be conducted at the time of 3 weeks after the final administration of protocol treatment.
11. To be conducted if necessary.
12. CT or MRI must be performed within 28 days after the final administration at the time of compleation/discontinuation of the protocol treatment. However, this is not required when the discontinuation of protocol treatment is due to tumor progression.
13. Follow-ups must be conducted after the discontinuation or completion of protocol treatment as follows: 3-month intervals for the first 2 years, 6-month intervals for the following 2 years, and once a year thereafter. Follow-ups must include the evaluation of general clinical condition and CA-125 test as a minimum standard. Additionally, CT or MRI must be performed at times of suspected progression of the disease. Investigators may shorten the intervals of follow-ups and of CT or MRI if necessary.
14. The QOL survey【See Appendix 2-⑥】must be conducted as follows: after obtaining informed consent and prior to the start of protocol treatment, after 3 cycles of protocol treatment (or after 9 weeks from the start of treatment), after 6 cycles of protocol treatment (or after 18 weeks from the start of treatment), after 36 weeks from the start of protocol treatment, after 60 weeks from the start of protocol treatment, and after 84 weeks from the start of protocol treatment.
15. Survey forms in relation to the patient's expenses 【See Appendix 2-⑦】if possible with copies of receipts are to be mailed to the iPocc Trial Coordinating Center. The evaluation must be conducted by using the following three types of survey forms: ① to be used once "after the obtaining of informed consent and prior to the start of protocol treatment," ② to be used 5 times simultaneously with the QOL evaluations, and ③ to be used "during the follow-up period after 84 weeks from the start of protocol treatment" after the completion of QOL evaluations.

9 EVALUATION CRITERIA

9.1 Adverse events

9.1.1 Definitions of adverse events (AE), adverse reactions (AR), and unexpected adverse reactions (UAR)

An adverse event (AE) is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient receiving an investigational drug, whether or not it is considered related to this investigational drug. An adverse reaction (AR) is any unfavorable and unintended reaction that occurs at any dose level. An unexpected adverse reaction (UAR) is an adverse reaction (AR) that is of a nature or severity not consistent with the applicable product information.

9.1.2 Evaluation of AE and AR

AE and AR are to be evaluated using the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

AE and AR that occur or worsen during this study are to be recorded on case report forms with the details of the AE, date of occurrence, Grade and relationship between the event and the investigational drug.

The investigator will assess the causal relationship of the event to the study drug in accordance with the following classification: "Reasonable possibility of a relationship to the study drug" is either Yes or No. If there is SOME evidence to suggest a causal relationship, it will be recorded as "Yes" on the CRF. When there is LITTLE evidence of any causal relationship and there may have been other factors that contributed to the AE, it will be recorded as "No" on the CRF. "A reasonable possibility of the relationship to the study drug" will include any AE that is deemed definitely, probably, possibly or unlikely. "No reasonable possibility of a relationship to the study drug" will include any AE that is deemed unrelated.

"Relationship to the protocol treatment" is categorized as the follows: 'Definite', 'Probable', 'Possible', 'Unlikely' or 'Unrelated'. 'Unlikely' and 'Unrelated' are categorized as "not related to the to the protocol treatment".

All AEs will be documented in the patient medical records and eCRFs. All AEs must be followed until resolution, or for at least 30 days after discontinuation of study treatment, whichever comes first or until toxicity has resolved to baseline, or until the toxicity is considered to be irreversible. Progressive disease (PD) or symptoms caused by the PD are not necessary to report as AE, except the events of 'Patient Died' or 'Life threatening'. 【See 11.1 for a detail】

An exacerbation of a pre-existing condition is an AE. Abnormal laboratory test results that are deemed clinically significant by the investigator and that lead to a change in the dosage of the study treatment or temporary or permanent
discontinuation of the study treatment in the CRF.

9.1.3 Expected AEs, and actions to be taken

Please refer to the latest version of the Package Insert of each drug for expected adverse events related the study drugs used in this trial. Some of the expected AEs and the actions to be taken are listed below.

9.1.3.1 Hematotoxicity

Leukopenia, neutropenia, erythropenia, and thrombocytopenia may occur during the study treatment period. In severe cases, G-CSF and blood component transfusion (erythrocytes and thrombocytes) are to be administered. The necessity of blood component transfusion will be determined by the investigator. The frequency of administration and dose per administration shall be reported on case report forms. 【See the section 7.8】

9.1.3.2 Non-hematotoxicity

1 Anaphylactic reaction

Because the occurrence of anaphylactic reactions has been reported, sufficient medical history of the patient should be taken and the instructions for premedication described in section7.8 should be followed. If an anaphylactic reaction occurs, the proper treatment should be promptly offered. If a Paclitaxel-induced anaphylactic reaction occurs, it is recommended that extended premedication be provided for the following courses. If repeated anaphylactic reactions occur, discontinuation of the protocol therapy should be considered. If a Carboplatin-induced anaphylactic reaction occurs, the discontinuation of protocol treatment should be considered.

2 Peripheral neuropathy

Peripheral neuropathy such as numbness in the extremities has been reported. If Grade 2 or greater peripheral neuropathy observed in the previous cycle, reduce the dose of Paclitaxel alone by -1 level.

3 Myalgia and arthralgia

The symptoms of myalgia and arthralgia usually appear within 2 to 3 days after the administration of Paclitaxel followed by a remission in a few days. In case of strong pain, the use of analgesic agents may be considered. In severe cases, dose reduction or discontinuation of the investigational drug for the following cycles is to be considered.

4 Abdominal pain

Abdominal pain while receiving an intraperitoneal injection of Carboplatin has been reported. If any severe abdominal pain is observed, conduct next IP administration very slowly under careful observation, taking into consideration bowel adhesion to the area surrounding the catheter. If severe abdominal pain occurred again, despite slow IP administration, please notify the iPocc Trial Coordinating Center via email to seek advice from the study chair. Even though it is not mandatory, it is recommended to warm normal saline solution at a temperature of 37℃ in case of peritoneal irritation sign of abdominal pain occurred.

5 Cardiovascular symptoms

Arrhythmia or asymptomatic bradycardia may occur. ECG monitoring should be performed before initial administration of the protocol treatment.

6 Gastrointestinal symptoms

Nausea, vomiting, and stomatitis may occur. A decision regarding the use of antiemetic agents will be made by the attending investigator 【See section 7.8.2.】. Dose reduction or discontinuation of the study drug shall not be undertaken due to nausea and constipation.

7 Skin

Alopecia, skin rash, and skin flushing may occur. If any of these symptoms occur, the appropriate treatment is to be given by the investigator.

8 Fever

If fever occurs, a prompt investigation of the cause and the proper treatment should be given. Particularly where febrile neutropenia is suspected, strict management according to guidelines is required.【See section 7.6 and 7.8】

9 Infections

If infection is suspected, the appropriate administration of drugs, such as antibiotics and antimycotics are to be given promptly. The patient's general status should be closely observed.

9.2 Tumor response evaluation

Patients participating in this trial include those who clinically have no residual tumors and those who have residual tumors to be measured by physical examinations and/or radiographic imaging.

Assessment of residual tumors must be performed within 28 days before the start of protocol treatment after surgery.

Responses in patients with measurable lesions identified by radiographic imaging performed right before starting tumor of the protocol treatment will be evaluated as below. The RECIST criteria (version 1.1) are to be used for response evaluation【See Appendix 3-IV】. Patients having only non-target lesions are also to be reported on case report forms.

9.2.1 Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Sites of disease selecsted, method of assessment, examination date, longest for non-nodal lesions, short axis for nodal lesions and a sum of the diameters should be reported on eCRF.

9.2.2 Disease Parameters

Measurable disease:

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10 mm by CT scan, as >20 mm by chest x-ray, or >10 mm with calipers on clinical examination. All tumor measurements must be recorded in decimal fractions of centimeters.

Malignant lymph nodes:

To be considered pathologically enlarged and measurable, a lymph node must be >15 mm on the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Bone lesions:

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can

be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions:

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible, repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be reproducibly measured should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions:

All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

If multiple non-target lesions are identified in the same organ or location, it is possible to record them as a single item. (e.g., multiple enlarged pelvic lymph nodes or multiple liver metastases).

In addition, lymph nodes with the smallest short axis of less than 10 mm will be considered normal, and not included in non-target lesions.

9.2.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as close as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions:

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≧10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray:

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI:

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans), but NOT for the lungs.

As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and, the lesions should be measured/assessed on the same pulse sequence.

PET-CT:

At present, the low-dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. For these reasons, this study will not allow PET-CT use for RECIST 1.1 response criteria.

Ultrasound:

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy:

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

CA-125 (Ovarian, Fallopian tube and primary peritoneal cancer trials):

CA-125 alone cannot be used to assess response in this protocol.

9.2.4 Response Criteria

The first response evaluation will be conducted after the second cycle, followed by once every 2 cycles (after the fourth cycle, after the sixth cycle (after the eighth cycle), and when discontinuing the protocol treatment).

Determination of response should take into consideration for all target and non-target lesions and, if appropriate, biomarkers.

9.2.4.1 Evaluation of Target Lesions

Complete Response (CR):

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR):

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD):

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered to be progression).

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters.

Not evaluable (NE):

When at least one target lesion is not evaluated at a particular time point.

$$\text{The percentage decrease in the sum of diameters} = \frac{\text{The sum of diameters measured prior to treatment} - \text{The sum of diameters measured at evaluation}}{\text{The sum of diameters measured prior to treatment}} \times 100\ \%$$

$$\text{The percentage increase in the sum of diameters} = \frac{\text{The sum of diameters measured at evaluation} - \text{The smallest sum diameters}}{\text{The smallest sum diameters}} \times 100\ \%$$

9.2.4.2 Evaluation of Non-Target Lesions

Complete Response (CR):

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered to be in complete clinical response.

Non-CR/Non-PD:

Persistence of one or more non-target lesion(s).

Progressive Disease (PD):

Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally take precedence over target lesion status. It must be representative of overall disease status change, not an increase in size of a single lesion.

Not evaluable (NE):

When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions is exceptional, the opinion of the investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the principal Investigator.

9.2.4.3 Evaluation of biomarkers

Biomarker-based progression or recurrence involves assessing the patient's longitudinal CA-125 values. However, CA125 alone cannot be used to assess response in this protocol. If [an elevated?] CA125 value is observed, radiographic imaging should be obtained.

9.2.4.4 Evaluation of new lesions

New lesions are those that appear for the first time during the protocol treatment, and this category does not include any tumor lesions recorded prior to the start of treatment.

However, to be designated as "new lesions," it is necessary to ensure that there is no change in images due to differences in scanning technique or imaging modality from the methods used for baseline evaluations, and that there is no change in images due to the presence of something other than a tumor. For example, a cystic lesion that appeared in the focal area due to a necrotic liver metastasis shall not be considered a new lesion. Newly identified lesions during follow-up in a location that was not examined at baseline (before registration) will be considered as new lesions.

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.

9.2.4.5 Evaluation of overall (unconfirmed) response

Table1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

In this study, all evaluations of overall respose after IDS should be NE, except the case that a patient condition becames PD.

Table1. 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	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.

Table2. 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	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

9.2.4.6 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.

9.2.4.7 Best overall confirmed 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.

Table3. Best overall response based on confirmed CR and PR.

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	provided minimum criteria for SDduration met, otherwise, PD
CR	PD	provided minimum criteria for SD duration met, otherwise, PD
CR	NE	provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	provided minimum criteria for SD duration met, otherwise, PD
PR	NE	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.

In this study, best overall response should be PR when IDS is performed after PR. (When IDS is performed, PR confirmation of 4 weeks from initial documentation is not necessary.)

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