data, including efficacy and safety data, will be immediately made public.

In the transition from phase A to phase B, patient enrollment should be continued without interruption during the evaluation period.

1.2.2 Phase B (Phase III trial)

Primary Endpoint:	Progression-free survival (PFS)
Secondary Endpoints:	Overall survival (OS)
	Tumor response (only patients with evaluable disease)
	Incidence of adverse events
	Treatment completion rate
	Quality of Life (QOL) assessments
	Cost-utility analysis

2 BACKGROUND AND RATIONALE

2.1 Background and rationale for this study

2.1.1 Background

Approximately 8,000 women are estimated to receive a diagnosis of epithelial ovarian cancer each year in Japan. This disease has a very poor prognosis: 4,006 women died in 1996 and 4,467 women in 2005 [1]. To date, no effective screening regimen has been identified for ovarian cancer, so by the time patients see a doctor, 70% are diagnosed with stage III or IV cancer. The number of affected patients is currently on the increase. While the age-adjusted mortality rate in patients with ovarian cancer was 2.5 per 100,000 women in 1970, it was 4.7 in 1994, which is 1.9-fold increase in a period of 25 years. The rate is estimated to reach 7.4 in 2015, and the disease is likely to be the second leading cause of death due to gynecologic malignancies, after breast cancer [2].

Unlike many other solid tumors, it is well known that appropriate cytoreduction is associated with improved survival among women with epithelial ovarian cancer. The recommended treatment includes initial surgery, with the aim of removing as much tumor as possible, followed by chemotherapy [3), 4)]. Previously, platinum-based CAP therapy or CP therapy was the standard chemotherapy for epithelial ovarian cancer. Then, following the development of paclitaxel, a taxane drug, large scale comparative studies of a regimen that included paclitaxel were conducted (GOG-111 and OV-10) [5), 6)]. In a comparison between the combination of cisplatin and paclitaxel and cisplatin and cyclophosphamide in 410 stage III or IV ovarian cancer patients with residual tumor, it was found that combination therapy with paclitaxel was associated with significantly better results for both response rate (73% vs. 60%) and overall survival (38 months vs. 24 months). Based on these results, paclitaxel and cisplatin combination was considered a new standard chemotherapy for epithelial ovarian cancer. Subsequently, in order to reduce renal toxicity and gastrointestinal toxicity associated with cisplatin, clinical trials of combination therapy were conducted in which carboplatin was substituted for cisplatin (AGO and GOG-158). The results showed a reduction in toxicity even though the effectiveness of the paclitaxel and carboplatin was equivalent to that of the paclitaxel and cisplatin. Thus, partly because of the simplicity of its dosing regimen, the combination of paclitaxel and carboplatin has become recognized as a new standard therapy [7), 8)]. Consequently, in Japan, intravenous paclitaxel 175 to 180 mg/m^2 over 3 hours and intravenous carboplatin AUC=5 to 6 over

1 hour (TC therapy) has been commonly used as standard chemotherapy for epithelial ovarian cancer [1].

2.1.2 Validity of using weekly administration of paclitaxel as standard treatment

In patients with different types of solid tumors, an attempt has been made to increase the antitumor effect by decreasing the dosing interval of paclitaxel from 3 weeks to 1 week based on the concept of dose-dense therapy. Recently, researchers have reported that in a phase III trial of postoperative adjuvant therapy in patients with breast cancer, patients who received weekly paclitaxel have a significantly better prognosis than those with once-every-3-week administration [9]. In patients with epithelial ovarian cancer, the findings of a phase III randomized controlled trial of dose-dense therapy with paclitaxel (JGOG-3016) conducted by the Japan Gynecologic Oncology Group (JGOG) were presented at the 2008 annual meeting of the American Society of Clinical Oncology [10]. In the trial, the standard TC therapy with once-every-3-week administration was compared with the combination therapy, that is, once-every-3-week administration of carboplatin and weekly administration of 80 mg/m^2 of paclitaxel (dd–TC therapy). The results showed the progression-free survival was significantly longer in patients with the dd–TC therapy, 17.2 months vs. 28.0 months, and 3-year overall survival rate was significantly higher in those with the dose-dense therapy, 65.1% vs. 72.1%, (HR 0·75, 0·57–0·98; p=0·03). The study showed no difference in peripheral neurotoxicity; however, patients who received the dd–TC therapy had a significantly higher frequency of hematologic toxicity, and a lower treatment completion rate (63% vs. 48%). These findings provided by Japanese researchers have strongly impacted other researchers all over the world, and in the future, it is likely that weekly administration of paclitaxel will be substituted for the conventional dosing regimen in TC therapy. Therefore, the idea of using the dd–TC therapy as a standard treatment in a future of phase III trial is considered sufficiently valid.

2.1.3 History and current status of intraperitoneal chemotherapy in patients with ovarian cancer

Ovarian cancer often spreads to different sites within the peritoneal cavity via direct shedding or dissemination at an early stage. Because of this, several decades ago, intraperitoneal (IP) administration of anticancer drugs was proposed for patients with residual tumor after initial surgery or recurrent lesions confined to the peritoneal cavity [11]. When administered by intraperitoneal injection, certain drugs, including cisplatin and paclitaxel, have distinct pharmacokinetic advantages [12–14]. That is, these drugs remain longer in the peritoneal cavity at a higher concentration than with intravenous (IV) administration [16]. With IP administration of cisplatin, for example, a 10- to 20-fold greater exposure was reported in the peritoneal cavity compared with IV administration. Due to the fact that such highly concentrated drugs remain in the peritoneal cavity over a long period of time, IP administration of anticancer drugs theoretically shows greater promise for disease in the peritoneal cavity than IV administration. Conducting a randomized controlled study of IP cisplatin plus cyclophosphamide versus IV cisplatin plus cyclophosphamide for stage III ovarian cancer (GOG-104), Alberts et al. reported that patients in the IP group had a significantly better prognosis (median survival of 49 months vs. 41 months) and a reduction in adverse effects, compared with those in the IV group [14]. In subsequently-conducted GOG-114, a randomized controlled study of IP cisplatin plus IV paclitaxel versus IV cisplatin plus IV paclitaxel, survival was not significantly

different (median of 63.2 months vs. 52.2 months), but patients in the IP group had a significantly better recurrence-free survival (median of 27.9 months vs. 22.2 months) [17]. In the latest of the three American trials (GOG-172), patients receiving a regimen consisting of IV paclitaxel, IP cisplatin, and IP paclitaxel on Day 8 had a significantly better prognosis (median overall survival of 65.6 months vs. 49.7 months)[18].

Based on the results of these three randomized controlled studies, the National Cancer Institute (NCI) and Gynecologic Oncology Group (GOG) conducted a meta-analysis including other randomized controlled studies. The results showed that the IP therapy reduced the risk of death by 21.6%, compared with IV therapy. On January 5, 2006, NCI issued a clinical announcement stating, "For patients with ovarian cancer (FIGO stage III) who have undergone optimal surgical cytoreduction, consideration should be given to a regimen containing IP cisplatin and a taxane, whether given IV only or IV plus IP." [19] Following these results, much attention was focused on IP therapy for patients with epithelial ovarian cancer; however, because of toxicity concerns, including dosing regimen and catheter-related problems, this therapeutic approach has not been widely accepted. Furthermore, in GOG-172, the number of patients completing the planned 6 cycles of IP chemotherapy was only 42% due to toxicity; therefore, development of a regimen with lower toxicity is essential.

2.1.4 Rationale for substituting IP administration of carboplatin for that of cisplatin

It is well known that with IV administration, substitution of carboplatin for cisplatin achieves similar efficacy with less toxicity. With IP administration, on the other hand, based on animal studies and small scale, retrospective clinical reports showing that carboplatin is inferior to cisplatin in efficacy, cisplatin has primarily been used. Since these studies did not take into account effective doses of cisplatin and carboplatin, the necessity of reviewing the effectiveness of IP carboplatin with adequate dosing has been controversial. In recent years, researchers have been accumulating data demonstrating the superiority of IP administration of carboplatin over that of cisplatin. By retrospectively studying many cases, Fujiwara et al. reported that patients had a better prognosis when they received an adequate dose of IP carboplatin, $\geq$400 mg/m^2.[20] Miyagi et al. conducted a pharmacological analysis using a mathematical model. According to their report, there was no difference in platinum AUC in the serum between IP and IV administrations of carboplatin, but platinum AUC in the peritoneal cavity was approximately 17 times higher when IP carboplatin was administered. They also pointed out that IP administration of carboplatin is likely to be pharmacologically more effective than IV administration [21]. In light of these findings, carboplatin may achieve similar efficacy with reduced toxicity. Therefore, it is suggested that determining the efficacy of IP administration of carboplatin in phase III trials would provide a strong rationale for improving the QOL of patients receiving chemotherapy.

In GOG-172, both hematologic and non-hematologic toxicity were significantly higher in the IP arm than in the IV arm, and among patients in the IP arm, only 42 % completed 6 cycles of IP therapy. Because of the complex design of GOG-172, it is not clear whether this is due to IP administration of cisplatin, paclitaxel on Day 8, total dose of paclitaxel, or IP administration of paclitaxel. In addition, 34% of the patients who were unable to complete treatment had catheter-related problems.

In a phase II trial of IP carboplatin and IV paclitaxel, less than 10% of patients discontinued

treatment due to IP catheter-related issues, suggesting better tolerance. However, it is necessary to perform the study with careful attention to potential adverse events associated with silicon catheters (e.g. port infection, obstruction, bowel adhesion, and bowel perforation).[24)]

2.1.5 Rationale for including patients with suboptimal residual disease

When administered into the peritoneal cavity, anticancer drugs are thought to penetrate only several millimeters directly into the tumor. This has excluded IP administration in patients with large volume residual disease after initial surgery [22)]. A recent report on a retrospective study of TC therapy showed that a high response rate, 79%, was observed in patients with suboptimal residual disease after initial cytoreduction who were given IP carboplatin [23)]. In a phase II trial conducted by Miyagi of the Sankai Gynecology Study Group, an IV paclitaxel plus IP carboplatin combination yielded a superior response rate in patients with residual tumor [24)]. Furthermore, no difference was found in serum platinum AUC in the IP and IV groups. IP administration of carboplatin is considered to be a route of systemic administration that can be theoretically expected to be equally or even more effective in patients with suboptimal residual disease than IV administration. Thus, including patients with suboptimal residual disease is valid and very likely to increase the number of patients who could derive a benefit from IP administration.

2.1.6 Rationale for conducting a phase II/III trial

The efficacy and safety of dd-TCiv therapy has already been validated in JGOG-3016. In a preliminary toxicity analysis study [25)] and the above phase II trial by the Sankai Gynecology Study Group, the efficacy and safety of IP carboplatin plus IV paclitaxel once every 3 weeks has been tested. As a result, the recommended dose of IP carboplatin when IV paclitaxel 175 mg/m^2 was given concurrently was AUC 6 to 7 [25)], with a response rate when paclitaxel 175 mg/m^2 IV was given concurrently with carboplatin AUC 6 of 83%. Moreover, the completion rate for the planned 6 courses of treatment was very high at 85%, and toxicity was the same as that for IV administration [24)]. Toxicity associated with the IP port was observed in only 1 patient (4%) who had a port obstruction. These findings suggest that dd-TCip therapy is not inferior to dd-TCiv therapy in efficacy and may be a safe method of administration. However, efficacy and safety data are insufficient, and it is considered necessary to conduct a phase II trial prior to a phase III trial. In diseases such as ovarian cancer, however, the number of patients is limited, and now that chemotherapy is rapidly being developed, starting a phase III trial anew after completion of phase II trial creates a problem in terms of effective use of resources. Evaluating dd-TCip therapy using a phase II/III trial design, where patients for a phase II trial can also be candidates for phase III, allows the prompt implementation of a study, providing a strong rationale for conducting a phase II/III trial.

The purpose of this study is to verify the hypothesis that IP is superior to IV for carboplatin administration. At this time, prior to conducting the study, there is no evidence to indicate the superiority of IP administration of carboplatin. In addition, it is very unlikely that patients assigned to an IP arm will be exposed to any unacceptable risks associated with the IP administration of carboplatin. Therefore, the social benefits provided by this study are not considered not to undermine the well-being of the subjects.

Based on scientific evidence discussed above, we have planned a dd-TC therapy, that is, a randomized phase II/III trial of IV paclitaxel weekly plus concurrent IV carboplatin once every 3

weeks (dd-TCiv therapy), as a standard treatment, versus IV Paclitaxel weekly plus concurrent IP carboplatin once every 3 weeks (dd-TCip therapy), as study treatment.

2.2 Study design

Randomized phase II/III international multicenter clinical trial

3 CRITERIA/DEFINITIONS USED IN THIS STUDY

3.1 Staging

Staging will be defined by the International Federation of Gynecology and Obstetrics (FIGO, 1988).

3.2 Adverse events assessment

Adverse events will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0【See Appendix 3-III】.

3.3 Tumor response (Only patients with evaluable disease)

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be used 【See Appendix 3-IV】.

4 PATIENT SELECTION CRITERIA

4.1 Eligibility criteria

1) Patients assumed to have a stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer as a pre-surgery diagnosis
2) Patients scheduled to undergo laparotomy

   *Both optimal and suboptimal patients will be eligible to the study. (Suboptimal patients, as well as those who only undergo exploratory laparotomy, are eligible.)
3) ECOG Performance Status: 0-2
4) Patients who consent to placement of the IP port system, if randomized to Regimen II (study treatment: dd–TCip therapy)
5) Patients expected to receive the first protocol treatment within 8 weeks after the comprehensive staging surgery
6) Lab data and clinical examination

Data within 28 days before the scheduled date of surgery

Neutrophil count	$\geqq$ 1,500 /mm^3
Platelet count	$\geqq$ 100,000 /mm^3
AST (GOT)	$\leqq$ 100 IU/L
ALT (GPT)	$\leqq$ 100 IU/L
Total bilirubin	< 1.5 mg/dL
Serum Creatinine	< 1.5 mg/dL
Electrocardiogram (ECG)	Patients with normal ECG Asymptomatic patients with abnormal ECGs not requiring any medical intervention
Neuropathy (Both motor and sensory)	$\leqq$ Grade1 (CTCAE Version 4.0)

7) Patients expected to survive longer than 3 months from the starting date of the protocol therapy

8) Patients aged 20 years and older at the time of tentative-registration (with no upper age limit)
9) Patients who provide written informed consent for participation in this trial

4.2 Exclusion criteria

1) Patients assumed to have a borderline malignancy of the ovary, Fallopian tube, or primary peritoneal cancer
2) Patients who have received previous chemotherapy or radiation therapy to treat the current disease
3) Patients who have a synchronous malignancy or who have been progression-free less than 5 years for a metachronous malignancy (Patients with basal and squamous cell carcinoma of the skin, as well as carcinoma in situ, and intramucosal carcinoma cured by local treatment, are eligible for the study)
4) Patients with serious medical complications, such as serious heart disease, cerebrovascular accidents, uncontrolled diabetes mellitus, uncontrolled hypertension, pulmonary fibrosis, interstitial pneumonitis, active bleeding, an active gastrointestinal ulcer, or a serious neurological disorder
5) Patients who have had a hypersensitivity reaction to polyoxyethylated or hydrogenated castor oil
6) Patients with a pleural effusion requiring continuous drainage
7) Patients with an active infection requiring antibiotics
8) Patients who are pregnant, nursing or of child-bearing potential
9) Patients with clinical symptom(s) of brain metastasis
10) Patients for whom completion of this study and/or follow-up is deemed inappropriate for any reason
11) Patients with any signs/symptoms of interstitial pneumonia

5 DRUG INFORMATION

International institutions outside Japan may need to refer to their country specific Appendix for DRUG INFORMATION.

For full information on each drug, always refer to each package insert and obtain updated information.

The latest package insert at this time is provided in Appendix 【see Appendix 3-V】.
(For Japanese institutions, information on the current package insert in Japan can be found at:
Pharmaceuticals and Medical Devices Agency http://www.info.pmda.go.jp/index.html)

[Japan only]

5.1 Paclitaxel

5.1.1 Description

Acting as a precursor for microtubule assembly, paclitaxel has more affinity for the microtubules than for the subunit of tubulin dimers. By stabilizing microtubules, it inhibits the normal dynamic reorganization of the microtubule network and causes apoptosis. Major toxicities include myelosuppression (mainly neutropenia), peripheral neurotoxicity, arthralgia, myalgia, and hypersensitivity reactions. However, the use of adequate premedication can reduce the severity of hypersensitivity reactions. Paclitaxel is now being used worldwide as a standard agent indicated as first-line therapy for the treatment of epithelial ovarian cancer, as described in 2.1.1, and also as a therapeutic agent for recurrent epithelial ovarian cancer. Furthermore, it is commonly used in the treatment of cancer of the breast, corpus uteri, lung, and various other cancers.

* For additional information, see package insert.

* Drug ordering:
The study drug, i.e. paclitaxel on Day 1, Day 8 and Day 15, will be provided free of charge by a pharmaceutical company to research groups, and then distributed free of charge by research groups to participating institutions. **Note that insurance claims cannot be made.**
(For instructions for study drug ordering/distribution/management, 【see **Appendix 1-D**】.)

[Japan only]

* Dosing regimen: In this study, 80 mg/m^2 paclitaxel will be diluted in 5% dextrose or normal saline solution and administered IV over 1 hour. Premedications to prevent allergic reactions or other appropriate management, including a filter or an infusion tube/bag, will be necessary.
* The dose will be calculated using a body surface area no greater than 2.0 m^2.

5.1.2 Information extracted from the package insert

1) Product name: Paclitaxel Injection 30mg/5mL "NK", Paclitaxel Injection 100mg/16.7mL "NK"
Paclitaxel Injection 30mg "SAWAI", Paclitaxel Injection 100mg "SAWAI"

[Japan Only]

2) Formulation: The 5 mL vials and 16.7 mL vials contain 30 mg and 100 mg of paclitaxel, respectively.

3) Major adverse reactions

Hypersensitivity

Rash (5% to less than 20%), redness (less than 5%)

Cardiovascular

Hypotension (5% to less than 20%), arrhythmia, tachycardia, bradycardia, premature contractions, hypertension, palpitations, abnormal electrocardiogram, atrial fibrillation, ventricular fibrillation, cardiomegaly, angina (less than 5%)

Gastrointestinal

Nausea/vomiting (35.1%), diarrhea, anorexia, stomatitis, constipation (5% to less than 20%), dyspepsia, flatulence, gastritis, rectal pain, dysphagia, rectal disorder, gingivitis, bloating, cheilitis, tongue coating, gingival pain (less than 5%)

Liver

Elevated AST (GOT), elevated Al-P, elevated LDH, elevated ALT (GPT) (5% to less than 20%), elevated bilirubin (less than 5%)

Urinary

Abnormal electrolyte (5% to less than 20%), elevated BUN, elevated creatinine, proteinuria, dysuria, hematuria, urinary incontinence, urinary retention, hemorrhagic cystitis (less than 5%)

Skin

Hair loss (45.3%), maculopapular skin rash, pruritus, skin disease, skin ulcer, urticaria, nail disorder, epidermal peeling, hyperpigmentation, skin swelling, dermatitis, dry skin, nail discoloration (less than 5%)

Psycho-neurological

Dizziness, insomnia, anxiety, depression, somnolence, impaired thinking, tremor, syncope, agitation, neurological disorder, seizure ataxia, amnesia, hypotonicity, disturbance of consciousness, bradykinesia, speech impairment, hypertonicity, psychotic symptoms, delirium, nystagmus, movements involuntary, hoarseness, mood alteration (less than 5%)

Sensory

Scotoma, dysgeusia, visual disturbances, eye disorders, conjunctivitis, blurred vision, increased tearing, asthenopia, floaters, dry eye, keratitis, conjunctival bleeding, photopsia, ageusia, eye pain, ear pain, dysesthesia of the tongue (less than 5%)

Respiratory

Dyspnea (5% to less than 20%), hypoxia、increased cough, increased sputum, pharynx discomfort (less than 5%)

Generalized symptoms

Asthenia, abdominal pain, malaise, headache (5% to less than 20%), edema, pain, flu-like syndrome, swollen abdomen, chills, weight gain, weight loss (less than 5%)

Musculoskeletal

Arthralgia (32.3%), myalgia (28.8%), bone pain, back pain (5% to less than 20%), neck pain, low back pain (less than 5%)

Other

Fever, flushing (5% to less than 20%), chest pain, bleeding, injection site reaction,

peripheral edema, decreased total protein, decreased albumin, pelvic pain, sweating, hiccups, dry mouth, irregular bleeding, amenorrhea, injection site pain, feeling of drunkenness, hyperglycemia, hypoglycemia, dehydration (less than 5%)

4) Significant adverse effects

Shock, anaphylactic reaction

Shock (0.2%) or anaphylactic reactions (0.3%) may occur. Careful observation is required. If any of the following symptoms appear, discontinue the medication and take appropriate measures: dyspnea, chest pain, hypotension, tachycardia, bradycardia, flushing, angioedema, or sweating.

Myelosuppression leading to decreased white blood cells, etc.

Cytopenia (61.4%), neutropenia (55.5%), anemia [decreased hemoglobin (30.7%), decreased hematocrit (5.0%), decreased red blood cells (11.2%), etc.], thrombocytopenia (11.7%), and pancytopenia may occur. Careful checks of peripheral blood are required. If an abnormality is found, take appropriate measures, including dose reduction or temporary cessation. In association with prolonged myelosuppression, the following concurrent infections have been reported: urinary tract infection (2.3%), upper respiratory infection (4.8%), sepsis (0.9%), herpes zoster (1.0%), and pneumonia (1.1%). In a phase II trial of 3-hour intravenous infusion (paclitaxel alone) in Japan, the incidences of grade 3 or 4 decreased white blood cells and neutropenia were 43.7% (163/373) and 76.3% (284/372), respectively.

Peripheral neuropathy, paralysis

Peripheral neuropathy (43.8%) such as numbness, paralysis (0.1%), hemiplegia (less than 0.1%), or paresis may occur. If such symptoms appear, take appropriate measures including dose reduction or temporary cessation.

Interstitial pneumonia, pulmonary fibrosis

Interstitial pneumonia (0.5%) or pulmonary fibrosis (unknown frequency) may occur. Careful observation is required. If any of the following abnormalities are found, discontinue the medication and take appropriate measures such as the administration of an adrenal corticosteroid: fever, cough, dyspnea, abnormal findings on chest X-ray examination.

Acute respiratory distress syndrome

Acute respiratory distress syndrome (less than 0.1%) may occur. Careful observation is required. If any of the following abnormalities are found, discontinue the medication and take appropriate measures: rapidly progressive dyspnea, hypoxia, or abnormal findings on chest X-ray examination, such as bilateral diffuse pulmonary infiltration shadows.

Myocardial infarction, congestive heart failure, cardiac conduction disorder, pulmonary embolism, thrombophlebitis, stroke, pulmonary edema

Myocardial infarction (less than 0.1%), congestive heart failure (less than 0.1%), cardiac conduction disorder (unknown frequency), pulmonary embolism (0.1%), thrombophlebitis (0.4%), stroke (less than 0.1%), or pulmonary edema (less than 0.1%) may occur. Careful observation is required. If an abnormality is found, discontinue the medication.

Hearing loss, tinnitus

Hearing loss (0.2%) or tinnitus (0.5%) may occur. Careful observation is required. If an abnormality is found, discontinue the medication.

Gastrointestinal necrosis, bowel perforation, gastrointestinal bleeding, gastrointestinal ulcer

Gastrointestinal necrosis (unknown frequency), bowel perforation (less than 0.1%), gastrointestinal bleeding (less than 0.1%), or gastrointestinal ulcer (0.1%) may occur. Careful observation is required. If an abnormality is found, take appropriate measures including discontinuation of dosing.

Severe enteritis

Hemorrhagic colitis (less than 0.1%), pseudomembranous colitis (unknown frequency), or ischemic colitis (unknown frequency) may occur. Careful observation is required. If severe abdominal pain/diarrhea occurs, discontinue the medication and take appropriate measures.

Bowel obstruction, bowel paralysis

Bowel obstruction (1.6%) or bowel paralysis (0.1%) (anorexia, nausea/vomiting, severe constipation, abdominal pain, abdominal distension or abdominal relaxation, stasis of intestinal contents) may occur and lead to paralytic ileus. If bowel obstruction or bowel paralysis is found, discontinue the medication and take appropriate measures such as bowel decompression.

Hepatic dysfunction, jaundice

Hepatic dysfunction (4.0%) or jaundice (less than 0.1%) may occur. Careful observation is required. If an abnormality is found, discontinue the medication.

Pancreatitis

Pancreatitis (less than 0.1%) may occur. Careful observation is required. If an abnormality is found in serum amylase levels, take appropriate measures including discontinuation of dosing.

Acute renal failure

Acute renal failure (0.2%) may occur. Careful observation is required. If an abnormality is found in the values of BUN, serum creatinine, or creatinine/clearance, take appropriate measures including discontinuation of dosing.

Mucocutaneous ocular syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell's syndrome)

Mucocutaneous ocular syndrome (Stevens-Johnson syndrome) or toxic epidermal necrosis (Lyell's syndrome) may occur. Careful observation is required. If an abnormality is found, discontinue the medication and take appropriate measures.

Disseminated intravascular coagulation syndrome (DIC)

Disseminated intravascular coagulation syndrome (DIC) (0.1%) may occur. Careful observation is required. If an abnormality is found in the blood test results for platelet count, serum FDP, or plasma fibrinogen concentration, discontinue the medication and take appropriate measures.

5.2 Carboplatin

5.2.1 Description

Carboplatin, like cisplatin, is in a class of drugs known as platinum-containing compounds, and interacts with DNA like a bifunctional alkylating agent. Unlike cisplatin, it rarely produces gastrointestinal, renal or neurologic toxicity, and its dose-limiting toxicity is myelotoxicity (neutropenia and thrombocytopenia). No hydration is required, allowing simple administration, including easy outpatient administration. Since renal excretion is the major route of elimination for carboplatin, the severity of adverse effects will vary depending on renal function. Therefore, in most cases, the dose of carboplatin is determined using the Calvert formula, based on the renal glomerular filtration rate and target AUC. In this study, this formula is used with the intention of equalizing the amount of drug exposure among patients and improving the predictability of toxicity. An AUC of 4 to 7 appears to be a normal dose range.

* For additional information, see package insert.

* Drug ordering:

For the intravenous drug administration group (IV group), use a commercial drug (or a generic equivalent). (Insurance claims)

For the intraperitoneal administration group (IP group), use the study drug, i.e. carboplatin, which will be all provided free of charge by a pharmaceutical company to research groups, and then distributed free of charge by research groups to participating institutions. **Note that insurance claims cannot be made.**

(For instructions for study drug ordering/distribution/management, see **Appendix 1-D.**)

Caution must be exercised in making a clear distinction between the commercial drug and the study drug in drug use/management.

[Japan only]

Dosing regimen: Follow the instructions described in 7.3 and 7.4.

* The maximum dose will not exceed 1000 mg.

5.2.2 Information extracted from the package insert

1) Product name: Paraplatin Injection 50mg, Paraplatin Injection 150mg, Paraplatin Injection 450mg
Carboplatin Intravenous Infusion 50mg [SANDOZ], Carboplatin Intravenous Infusion 150mg[SANDOZ], Carboplatin Intravenous Infusion 450mg [SANDOZ]

[Japan Only]

2) Formulation: The 5 mL vials, 15 mL vials and 45 mL vials each contain 50 mg, 150 mg and 450mg of carboplatin, respectively.

3) Major adverse reactions

Digestive

Nausea/vomiting, anorexia (at least 10% or unknown frequency), diarrhea, stomatitis, abdominal pain, constipation (1% to less than 10%), dry mouth (less than 1%)

Renal

Hematuria, proteinuria (1% to less than 10%), oliguria (less than 1%)

Hypersensitivity

Urticaria (at least 10% or unknown frequency), rash (1% to less than 10%), pruritus (less than 1%)

Psycho-neurological

Peripheral neuropathy (numbness, etc.), headache (1% to less than 10%), tinnitus, decreased hearing, visual acuity loss, dizziness, seizure, dysesthesia, dysgeusia, nervousness, anxiety, insomnia (less than 1%)

Liver

Elevated ALT (GPT) (at least 10% or unknown frequency), elevated AST (GOT), elevated Al-P, elevated bilirubin, elevated LDH, elevated γ-GTP (1% to less than 10%)

Cardiovascular

Abnormal electrocardiogram (premature contraction), palpitation, hypertension, hypotension, arrhythmia (tachycardia, bradycardia, atrial fibrillation, atrial flutter, atrioventricular block) (less than 1%)

Electrolyte

Abnormal serum sodium, potassium, chloride, calcium, phosphorus, magnesium, etc. (1% to less than 10%), syndrome of inappropriate secretion of antidiuretic hormone (less than 1%)

Skin

Hair loss (at least 10% or unknown frequency), hyperpigmentation, nail discoloration, skin disease (less than 1%)

Other

General malaise, asthenia, elevated uric acid, chills, dehydration, weight loss, decreased albumin, dyspnea (at least 10% or unknown frequency), fever, edema (1% to less than 10%), pain, flushing, hot flashes, chest discomfort, hiccups, injection site reaction (redness, swelling, pain, etc.), hypoproteinemia (less than 1%)

4) Significant adverse effects

Myelosuppression leading to pancytopenia (less than 0.1%), etc.

Pancytopenia, anemia (decreased hemoglobin, decreased red blood cells, and decreased hematocrit), decreased white blood cells, neutropenia, thrombocytopenia, bleeding, etc. may occur. Careful checks of peripheral blood are required. If an abnormality is found, take appropriate measures including dose reduction, temporary cessation or discontinuation.

Shock, anaphylactic reaction (less than 0.1%)

Shock or anaphylactic reactions may occur. Careful observation is required. If any of the following symptoms appear, discontinue the medication and take appropriate measures: cyanosis, dyspnea, chest distress, hypotension, or bronchospasm. It appears that the frequency of shock or anaphylactic reactions tends to increase with an increase in the frequency of administration.

Interstitial pneumonia (0.1%)

Interstitial pneumonia may occur with fever, cough, dyspnea, or abnormal findings on chest X-ray examination. Careful observation is required. If an abnormality is found, discontinue the medication and take appropriate measures such as the administration of an adrenal corticosteroid.

Acute renal failure (less than 0.1%), Fanconi syndrome (unknown frequency)

Acute renal failure or Fanconi syndrome may occur. Careful observation is required. If an abnormality is found in the values of BUN, serum creatinine, or creatinine/clearance, discontinue the medication and take appropriate measures.

Hepatic failure, hepatic dysfunction, jaundice (each at an unknown frequency)

Hepatic failure, hepatic dysfunction, or jaundice may occur. Careful observation is required including periodic examination. If an abnormality is found, discontinue the medication and take appropriate measures.

Gastrointestinal necrosis, gastrointestinal perforation, gastrointestinal bleeding, gastrointestinal ulcer (each at an unknown frequency)

Gastrointestinal necrosis, gastrointestinal perforation, gastrointestinal bleeding, or gastrointestinal ulcer may occur. Careful observation is required. If an abnormality is found, discontinue the medication and take appropriate measures.

Hemorrhagic enteritis, pseudomembranous colitis (unknown frequency)

Hemorrhagic enteritis or pseudomembranous colitis may occur. Careful observation is required. If severe abdominal pain/diarrhea occur, discontinue the medication and take appropriate measures.

Paralytic ileus (less than 0.1%)

Bowel paralysis (anorexia, nausea/vomiting, severe constipation, abdominal pain, abdominal distension or relaxation, stasis of intestinal contents) may occur and lead to paralytic ileus. If bowel paralysis is found, discontinue the medication and take appropriate measures, such as bowel decompression.

Cerebral infarction (less than 0.1%), pulmonary infarction (unknown frequency)

Cerebral infarction or pulmonary infarction may occur. Careful observation is required. If an abnormality is found, discontinue the medication and take appropriate measures.

Thrombosis/embolism (unknown frequency)

Thrombosis/embolism (pulmonary embolism, cerebral thrombosis, arterial or venous thrombosis) may occur. Careful observation is required. If an abnormality is found, discontinue the medication and take appropriate measures.

Myocardial infarction, congestive heart failure (unknown frequency)

Myocardial infarction or congestive heart failure may occur. If an abnormality is found, discontinue the medication and take appropriate measures.

Hemolytic uremic syndrome (unknown frequency)

Hemolytic uremic syndrome mainly characterized by thrombocytopenia, hemolytic anemia or renal failure may occur. Careful observation is required including periodic blood tests (platelets, red blood cells) and renal function tests. If an abnormality is found, discontinue the medication and take appropriate measures.

Acute respiratory distress syndrome (unknown frequency)

Acute respiratory distress syndrome may occur. Careful observation is required. If any of

the following abnormalities are found, discontinue the medication and take appropriate measures: rapidly progressive dyspnea, hypoxia, or abnormal findings on chest X-ray examination such as bilateral diffuse pulmonary infiltration shadow.

Disseminated intravascular coagulation syndrome (DIC) (unknown frequency)

Disseminated intravascular coagulation syndrome (DIC) may occur. Careful observation is required. If an abnormality is found in the blood test results of platelet count, serum FDP, or plasma fibrinogen concentration, discontinue the medication and take appropriate measures.

Acute pancreatitis (unknown frequency)

Acute pancreatitis may occur. Careful observation is required. If an abnormality is found in serum amylase, serum lipase, etc., discontinue the medication.

Hearing (less than 0.1%)

Hearing loss or tinnitus may occur. Careful observation is required. If an abnormality is found, take appropriate measures including discontinuation of dosing.

5) Significant adverse effects (of a similar drug)

Papilloedema, retrobulbar neuritis, cortical blindness

In patients treated with cisplatin, visual disturbances such as papilloedema, retrobulbar neuritis and cortical blindness may occur infrequently. If any such abnormality is found, discontinue the medication.

Hemolytic anemia

In patients treated with cisplatin, Coombs-positive hemolytic anemia may occur. If an abnormality is found, discontinue the medication.

5.3 Major adverse reactions associated with IV administration of paclitaxel plus concurrent IP administration of carboplatin

Several reports have been published on major adverse reactions associated with IV administration of paclitaxel plus concurrent IP administration of carboplatin. The following tables show adverse reactions presented in three major reports.

Table 1 [31)]

	Grade 1	Grade 2	Grade 3	Grade 4
Malaise	48%	14%	2%	0%
Nausea	55%	21%	2%	0%
Vomiting	24%	19%	0%	0%
Constipation	24%	38%	5%	0%
Abdominal pain	33%	29%	0%	0%
Peripheral neuropathy (Sensory)	45%	12%	0%	0%
Peripheral neuropathy (Motor)	7%	2%	2%	0%
Myalgia/ Arthralgia	24%	29%	5%	0%
Neutropenia	Not recorded	Not recorded	29%	64%
Anemia	Not recorded	Not recorded	35%	35%
Thrombocytopenia	Not recorded	21%	36%	0%

Other serious adverse events

Catheter infection (2%), bowel perforation (2%)

Table 2 [24)]

	Grade 1	Grade 2	Grade 3	Grade 4
Hepatic dysfunction	Not recorded	12%	0%	0%
Renal dysfunction	Not recorded	0%	0%	0%
Peripheral neuropathy (Sensory)	Not recorded	0%	8%	0%
Peripheral neuropathy (Motor)	Not recorded	0%	0%	0%
Gastrointestinal toxicity	Not recorded	4%	0%	0%
Myalgia/ Arthralgia	Not recorded	4%	0%	0%
Neutropenia	Not recorded	Not recorded	25%	71%
Anemia	Not recorded	Not recorded	25%	4%
Thrombocytopenia	Not recorded	Not recorded	8%	8%

Other serious adverse events

Catheter obstruction (4%), Paclitaxel allergy (4%)

Table 3 [23)]

	Grade 1	Grade 2	Grade 3	Grade 4
Allergy	Not recorded	Not recorded	0%	2%
Malaise	Not recorded	Not recorded	2%	0%
Vomiting	Not recorded	Not recorded	2%	0%
Diarrhea	Not recorded	Not recorded	0%	0%
Constipation	Not recorded	Not recorded	0%	0%
Hepatic dysfunction	Not recorded	Not recorded	2%	0%
Peripheral neuropathy (Sensory)	Not recorded	Not recorded	5%	2%
Peripheral neuropathy (Motor)	Not recorded	Not recorded	2%	0%
Myalgia/ Arthralgia	Not recorded	Not recorded	0%	0%
Intestinal obstruction	Not recorded	Not recorded	0%	0%
Catheter infection	Not recorded	Not recorded	2%	-
Catheter obstruction	Not recorded	Not recorded	2%	-
Neutropenia	Not recorded	Not recorded	25%	68%
Anemia	Not recorded	Not recorded	34%	7%
Thrombocytopenia	Not recorded	Not recorded	23%	0%

6 PREPARATION PRIOR TO STUDY START

6.1 Preparation for surgical procedures

6.1.1 Mandatory requirement FOR ALL INVESTIGATORS

(i) Investigators participating in this study are required to contact the iPocc Trial Coordinating Center via email in advance, and receive a video on CD-ROM describing the surgical procedures required for IPS port placement. Investigators should watch and confirm their understanding of the IP port placement procedure.

(ii) Investigators are also required to read "Procedure for insertion of peritoneal reservoir port (Implantable Port System: IPS)【Appendix 1-A】".

6.1.2 Mandatory requirement ONLY FOR INVESTIGATORS WHO HAVE NO EXPERIENCE IN IP PORT PLACEMENT

Select one of the following and inform the iPocc Trial Coordinating Center of the option selected.

(i) Make a request to watch the surgery as an observer at Saitama Medical University International Medical Center.

(ii) Make a request for a telephone consultation regarding the IP port placement procedure.

(iii)Make a request for on-the-job training at your own institution.

[Japan only]

【Contact information】

iPocc Trial Coordinating Center
Kitasato University Research Center for Clinical Pharmacology,
Clinical Trial Coordinating Center
5-9-1 Shirokane, Minato-ku, Tokyo 108-8642 Japan
E-mail: iPocc@insti.kitasato-u.ac.jp
TEL: +81-3-5791-6419 or 6398
FAX: +81-3-5791-6399

6.2 Study entry procedures

This study utilizes the following electronic system for management of the study.

For distribution/receiving the study specific information:

the iPocc STUDY WEB-PAGE (http://www.kitasato-ctcc.jp/)

For patient registration/data entry:

the Rave system (http://kitasato-ctcc.mdsol.com)

Prior to patient registration in this study, these procedures should be followed.

1) Submit the following documents to the iPocc Trial Coordinating Center to complete institution registration on this study.
   (i) The IRB approval letter for this study

(ii) Form A*) and Form C (REQUEST FORM for Rave USER ADMINISTRATION)

【see Appendix 2-②】

*) If you already have a Rave user account from Kitasato for another study, please submit only Form C.

(iii) The letter of approval for the Evaluation System of Investigational Medical Care (ESIMeC)

[Japan only]

2) Activate the user account for the Rave system.【see Appendix 1-C-③】
Each investigator and clinical research coordinator (CRC) who submit Form A will receive an "Activation request email" for the Rave system. Please follow the steps described in the email to activate the user account.

3) Answer all the quizzes for this trial on the STUDY WEB-PAGE 【see Appendix 1-C-①】

*The participating site should keep Form A, Form C and the "Activation request email" for the Rave system containing a login username and an activation code.

*Web registration will be available only after completing procedures 1), 2) and 3) .

*The completion of these procedures would provide the iPocc Trial Coordinating Center the information for site selection.

【Contact information】

iPocc Trial Coordinating Center
Kitasato University Research Center for Clinical Pharmacology,
Clinical Trial Coordinating Center
5-9-1 Shirokane, Minato-ku, Tokyo 108-8642 Japan
E-mail :iPocc@insti.kitasato-u.ac.jp
TEL :+81-3-5791-6419 or 6398
FAX :+81-3-5791-6399

6.3 Patient registration

Patients will be registered according to the following steps:

1) Tentative-registration via the Rave system. (before surgery)
2) Final registration/randomization via the Rave system. (during surgery)

*In the event that the patient ends up not being registered after completion of tentative registration or the patient is determined to be ineligible based on the result of the histopathological examination, please enter the reason(s) why the patient cannot proceed to final registration on Form C via the Rave system.

6.3.1 Tentative registration

6.3.1.1 Tentative registration procedures 【see Appendix 1-C-②】

1) Prior to surgery, the investigator will need to determine whether the patient meets the criteria described in "4. PATIENT SELECTION CRITERIA" and obtain written informed consent from the patient undergoing surgery.

2) Eligibility criteria will be automatically checked when the patient data is entered. Only when all the data meet the criteria, will the tentative-registration be completed.

3) Tentative registration needs to be conducted via the Rave system at least 2 business days*) prior to surgery.

*) If tentative registration cannot be conducted within 2 business days prior to surgery, please notify the iPocc Trial Coordinating Center by email (iPocc@insti.kitasato-u.ac.jp).

The Rave system is available 24 hours a day, 365 days a year.

http://kitasato-ctcc.mdsol.com

See the tentative registration procedures in details in 【Appendix 1-C-③】

4) Fax registration (emergency only). **FAX: +81-3-5791-6399**

In the event that the web-based registration system is not available due to system failure, etc., tentative registration can be conducted via fax, as an emergency measure. Acceptance of tentative registration by emergency fax is limited to weekdays from 9:00 am to 5:00 pm, Japan time. (iPocc Trial Coordinating Center will be closed on Saturday, Sunday and holidays, so that emergency fax cannot be accepted.) The holiday schedule of the iPocc Trial Coordinating Center will be notified via email or on the STUDY WEB-PAGE, in advance.

The following steps should be followed for tentative registration via emergency fax.

① Notify the iPocc Trial Coordinating Center by email about the emergency fax.

② Send the "<Tentative>Patient Registration Form (WEB system down/Emergency use Only) 【See Appendix 2-③】" with all required data to the iPocc Trial Coordinating Center via fax.

③ The iPocc Trial Coordinating Center would complete the tentative registration process via the Rave system on behalf of the investigator.

[Standard Japanese holidays]

January 1-3,
The second Monday of January,
February 11,
March 20, 21,
April 29,
May 3-5,
The third Monday of July
The third Monday of September,
September 23
The Second Monday of October,
November 3,
November 23,
December 23,
December 29-31.

6.3.1.2 Notes for tentative registration

1) Tentative registration after initial cytoreduction will NOT be accepted.
   (Exceptions maybe granted for international sites. 【see section 6.3.3】)
2) Once the tentative registration is completed, it is not possible to cancel it from the database. In case of a duplicate registration, the initial tentative registration data and the tentative-ID (registration number) will be kept and used for the study analysis.
3) When a false registration or a duplicate registration is found, the investigator should promptly notify the iPocc Trial Coordinating Center.
4) If the expected date of surgery is changed after the tentative registration, notify the iPocc Trial Coordinating Center via email.
5) Each institution should keep the record of patient name, hospital chart No., tentative-registration date, tentative-ID, etc.

6.3.2 Final registration

6.3.2.1 Stratification factors

Patients are registered through the Rave system and randomized using the minimization method. The following three factors will be used as the randomization stratification factors:

(1) Residual tumor diameter
   (0 cm (No residual) vs. 0 cm＜residual＜1 cm vs. 1cm≦residual≦2 cm vs. >2 cm)
(2) FIGO stage (surgical staging) (stage II vs. III vs. IV)
(3) Institution

6.3.2.2 Surgery

1) Adequate specimens to determine histopathological diagnosis and FIGO stage must be obtained during initial surgical procedures.
2) It is desirable, but not mandatory, to confirm the diagnosis of epithelial ovarian, Fallopian tube or primary peritoneal cancer during surgery by intra-operative pathological diagnosis.
3) When all manipulations in the peritoneal cavity are completed, the final registration procedures should be followed, according to the section 6.3.2.3.
4) An IP port system is to be placed only when the patient is assigned to regimen II (dd-TCip therapy). The process of IP port placement is described in Appendix 1-A.
5) The IP port system for this study must be the Bard Titanium Implanted Port, 14.3Fr, (Reorder Number 0603006). Use of any other device is not allowed in this study.
6) After registration, no manipulations are allowed, with the exception of IP port placement.

6.3.2.3 Final registration/randomization procedures

(1) Web Entry

Patients must be registered for final registration via the Rave system. This Web-Entry system is available 24 hours a day, 7 days a week. The URL for the patient registration/randomization system is:

http://kitasato-ctcc.mdsol.com

See the final registration procedures in detail in 【Appendix 1-C-③】