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 (or laparoscopic exploratory surgery)
   *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【See Appendix3-II】
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)	≦ 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 evidence upon physical examination of brain tumor and any brain metastases
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.

(For Japanese institutions, information on the current package insert in Japan can be found at:

[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.

For both regimenI (Standard treatment: dd−TCiv therapy) and regimenII (Study treatment: dd−TCip therapy), use a commercial available drug (or a generic equivalent) then file a national

[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

[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.

For regimenI (Standard treatment: dd−TCiv therapy), use a commercial available drug (or a generic equivalent) then file a national heatith insuarane claims. For regimenII (Study treatment: dd−TCip therapy) , 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

[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

450mg

Carboplatin Intravenous Infusion 50mg [SANDOZ], Carboplatin Intravenous Infusion 150mg [SANDOZ] , Carboplatin Intravenous Infusion 450mg

[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 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 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%

Other adverse events

Vaginal anastomotic leak[32)33)34)]

Expression frequency of 'vaginal anastomotic leak' has a wide range from 0 to 18% according to the reports.[32)] The latest paper reported that 'vaginal anastomotic leak' is responsible for 6.7% of discontinuation of IP treatment. Accoridng to GOG-172[33)] trial which has a large sample size, the frequency of 'vaginal anastomotic leak' was 2.5% (5/205).

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.

[Japan only]

【Contact information】

iPocc Trial Coordinating Center
Kitasato Academic Research Organization, Kitasato University
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

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 (https://studyweb.kitasato-ctcc.jp/top.html)

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) FormA*) and FormC (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.

[Japan only]

2) Answer all the quizzes for this trial on the STUDY WEB-PAGE 【see Appendix 1-C-①】
3) 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.
4) Take e-learning program for the Rave system and get a certification.

- The participating site should keep FormA, 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), 3) and 4) .
- The completion of these procedures would provide the iPocc Trial Coordinating Center the information for site selection.

【Contact information】

iPocc Trial Coordinating Center
Kitasato Academic Research Organization, Kitasato University
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

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 obtain written informed consent from the patient and determine whether the patient meets the criteria described in "4. PATIENT SELECTION CRITERIA".
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*[1] at least 2 business days*[2] prior to surgery. See the tentative registration procedures in details in 【Appendix 1-C-③】

*[1] The Rave system is available 24 hours a day, 365 days a year.

*[2] 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).

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 Largest 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. *[1]
6) After registration, no manipulations are allowed, with the exception of IP port placement.

*[1] For institutions, if the Bard Titanium Implanted Port, 14.3Fr, (Reorder Number 0603006) is not available to obtain, other IP port may be allowed to use after consulting with the study chair. ***[Except Japan]***

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. See the final registration procedures in detail in【Appendix 1-C-③】. The URL for the patient registration/randomization system is:

http://kitasato-ctcc.mdsol.com

In the event that the web-based registration system is not available due to system failure or it is not possible to use the system during the surgery for any reason, the iPocc Trial Coordinating Center will complete the patient registration process on behalf of the investigator. Please follow the procedure below.

<Before the surgery date>

After tentative registration has been completed, inform the iPocc Trial Coordinating Center of the scheduled date and time of surgery via email 2 business days before surgery starts.

<During the surgery>

1) Upon completion of the comprehensive staging surgery, but immediately before the abdomen or abdominal wall is closed, the investigator or his/her designee will call the iPocc Trial Coordinating Center and notify the center of the institution name, the name of the investigator, the patient's birth date, the tentative registration number, and other stratification factors (the size of the residual tumor and the FIGO stage).
2) Emergency registration by phone will be available on weekdays from 9:00 am to 5:00 pm Japan time. Prior notification to the iPocc Trial Coordinating Center is necessary if final registration/randomization is likely to be after 5:00 pm.
3) The iPocc Trial Coordinating Center, on behalf of the investigator, will enter stratification factors and perform randomization via the Rave system. Randomization will take approximately 3-5 minutes.
4) The investigator or his/her designee will repeat the assigned regimen on the phone and confirm it with other attending medical staff at the site.
5) The IP port system will be placed only when the patient is assigned to regimen II (dd-TCip therapy).

iPocc Trial Coordinating Center

Kitasato Academic Research Organization, Kitasato UniversityClinical Trial Coordinating Center

TEL: +81-3-5791-6419 or 6398

Emergency final registration time:

9:00 am to 5:00 pm Japan time on weekdays, in general

No Emergency final registration will be accepted on Saturdays,

[Japan only as a general]

6.3.2.4 Notes for final registration/randomization

1) An email with the final registration/randomization result will be automatically sent to the investigator who had completed the final registration/randomization.
2) The investigator should confirm the "Protocol patient ID (final registration number)" and assigned regimen in the Rave system.
3) The assignment regimen should be recorded in the patient medical records.
4) Once the final registration is completed, it is impossible to cancel this from the database. In case of a duplicate registration, the initial final registration data and the Protocol patient ID (final registration number) will be kept and used for the study analysis.
5) When a false registration or a duplicate registration is found, the investigator should promptly notify the iPocc Trial Coordinating Center.

6.3.3 Notes for final registration (For institutions other than those in Japan)

For institutions that prefer to obtain randomization results after histopathological confirmation for epithelial ovarian cancer and staging, please follow the subsequent procedure. Tentative registration is exactly the same as those given in the Japanese guidelines. 【See section 6.3.1】

Final registration can be done after histopathological diagnosis has been made. In this case, the registration procedure is the same as that described in Section 6.3.2.2.

Placement of the IP port can be performed after the patient has been assigned to regimen II. IP port can be placed during surgery for all patients, and can be removed, when the patient is assigned to regimen II.

Please consult your institutional review committee regarding port insertion procedure that will be applied.

7 TREATMENT PLAN AND TREATMENT MODIFICATION CRITERIA

Protocol treatment and treatment modification will be implemented according to the protocol, as long as patient safety is not jeopardized. In the event that compliance with the protocol is not medically appropriate for the patient, the investigator may modify the protocol treatment using their medical judgment. This would be classed as a "protocol deviation" but may be considered to be a "clinically reasonable deviation."

7.1 Protocol treatment

Patients will be assigned to either of the following two regimens. The investigator should start the assigned protocol regimen within 8 weeks after the comprehensive staging surgery.

Regimen I (Standard treatment: dd−TCiv therapy)

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

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	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.

7.2 Dose calculation

A dose calculation tool is posted on the STUDY WEB-PAGE.

7.2.1 Calculation of body surface area (BSA)

1) The DuBois formula will be used to determine BSA, which will be used for dose calculation.
   DuBois Formula:
   BSA= Body Weight$^{0.425}$×Height$^{0.725}$×71.84/10000

where BSA is in m^2, Body Weight is in kg and Height is in cm.

2) In patients whose BSA is greater than 2.0 m^2, a BSA of 2.0 m^2 will be used.

7.2.2 Dose calculation for Paclitaxel

The dose of Paclitaxel will be calculated using the BSA determined by the DuBois formula.

7.2.3 Dose calculation for Carboplatin

1) The dose of Carboplatin will be calculated using the following Calvert formula [26].
   Calvert Formula:
   Carboplatin dose (mg/body) = target AUC × (GFR + 25)
2) In this study, the GFR is considered to be equivalent to the creatinine clearance (Ccr).
3) The Ccr is calculated using the following modified-Jelliffe formula [27].
   Modified-Jelliffe Formula:
   CCr = 〔98 - {0.8 × (age - 20)}〕 × BSA × 0.9 / (serum creatinine × 1.73)
   where Ccr is in mL/min, age is in years, BSA is in m^2, and serum creatinine is in mg/dl.

   When expressed in SI units, serum creatinine should be converted to mg/dL using the following equation: Serum creatinine (mg/dL)＝SI unit (μmol/L)/88.4
4) In patients whose serum creatinine is less than 0.6 mg/dL, a serum creatinine value of 0.6 mg/dL will be used for the calculation.
5) Dose recalculation for Carboplatin is not necessary unless the patient experiences a newly diagnosed urinary tract obstruction or CTCAE renal dysfunction of at least Grade 2 in severity (serum creatinine greater than 1.5 times the institution's upper limit of normal).
6) The maximum dose of Carboplatin will not exceed 1000 mg /person.

7.3 Regimen I (Standard treatment: dd−TCiv therapy)

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

7.3.1 Administration for Paclitaxel

1) After the introduction of premedication, the prescribed dose of Paclitaxel diluted in 250 mL of 5% dextrose or normal saline solution (NSS) and 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.

7.3.2 Dosing regimen for Carboplatin

1) Following the administration of Paclitaxel, the prescribed dose will be diluted in 250 mL of 5% dextrose or NSS and administered by IV over 1 hour.
2) Carboplatin will be given on Day 1 for each cycle.