Japanese Gynecologic Oncology Group

Endometrial Cancer Research

JGOG 2043

Study Protocol

Randomized phase III trial of AP (doxorubicin + cisplatin) therapy, DP (docetaxel + cisplatin) therapy, and TC (paclitaxel + carboplatin) therapy as adjuvant chemotherapy for endometrial cancer at a high risk of recurrence

Lead principal investigator: Daisuke Aoki, Department of Obstetrics & Gynecology, Keio University School of Medicine
Address: 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582
TEL: 03-3353-1211
FAX: 03-3353-0249

Japanese Gynecologic Oncology Group
Endometrial Cancer Committee

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1. Study Objective and Endpoints

1.1 Objective

The primary objective of this study is to evaluate AP therapy (doxorubicin [ADM] + cisplatin [CDDP]), DP therapy (docetaxel [DOC] + CDDP), and TC therapy (paclitaxel [PTX] + carboplatin [CBDCA]) as postoperative chemotherapy by performing comparisons using progression-free survival (PFS) in a high-risk group for endometrial cancer.

Group A: AP therapy, ADM	60 mg/m^2 + CDDP 50 mg/m^2 day 1	q3 weeks	six courses
Group B: DP therapy, DOC	70 mg/m^2 + CDDP 60 mg/m^2 day 1	q3 weeks	six courses
Group C: TC therapy, PTX	180 mg/m^2 + CBDCA AUC 6 day 1	q3 weeks	six courses

1.2 Endpoints

Primary endpoint:	Progression-free survival (PFS)
Secondary endpoints:	Overall survival (OS)
	Incidence of adverse events
	Administration state (tolerability)
	Status of lymph node dissection

2. Background and Rationale

2.1 Endometrial cancer

Gynecologic cancers can be broadly divided into ovarian/fallopian tube/peritoneal cancer and uterine cancer [3].

Uterine cancer is a malignancy that is generated in the uterus. The number of individuals affected by uterine cancer in 1996 was 17,433 individuals, and the age-adjusted incidence rate was 16.1 cases (per 100,000 person-years) in 1998. Uterine cancer can be further divided into cervical cancer, which occurs at the cervix and mainly consists of squamous cell carcinoma, and endometrial cancer, which occurs in the body of the uterus and mainly consists of adenocarcinoma. In Europe and the United States, the incidence of endometrial cancer is generally higher than that of cervical cancer (endometrial cancer accounts for 72.5% of uterine cancer in the United States) and is the highest among gynecologic cancers.

By contrast, the incidence of endometrial cancer in Japan is lower than that of cervical cancer, but no prevalence study has been conducted by separating cervical cancer from endometrial cancer. However, the number of patients with endometrial cancer is increasing year by year and was estimated to be approximately 5,000 patients in 2000. Given the increase in the number of patients with obesity, hypertension, and diabetes mellitus, which are the risk factors of endometrial cancer, the incidence of endometrial cancer in Japan may exceed that of cervical cancer in the near future, similar to that in Europe and the United States.

In these circumstances, the reevaluation of the previous treatment and the aggressive development of treatment, including the establishment of standard therapy for endometrial cancer, are important.

Most histologic types of endometrial cancer are endometrioid adenocarcinomas, which are further divided into histologic grades 1, 2, or 3. The other histologic types of endometrial cancer include serous and clear cell adenocarcinomas, which have been reported to exist rarely but have an extremely poor prognosis. The extremely rare histologic types of endometrial cancer include mucinous adenocarcinoma and squamous cell carcinoma.

In 2002, the percentages of cases for each histologic type were 86.5% for endometrioid adenocarcinoma, 3.0% for serous adenocarcinoma, 2.1% for clear cell adenocarcinoma, 0.6% for mucinous adenocarcinoma, and 0.2% for squamous cell carcinoma [4]. In 1990, the percentages of endometrioid adenocarcinoma cases that were treated were reported to be 60.8% for grade 1, 26.1% for grade 2, and 10.3 % for grade 3 [5].

For the staging of endometrial cancer, the surgical staging by the International Federation of Gynecology and Obstetrics (Fèdèration Internationale de Gynecologie et d'Obstetrique [FIGO]) is the adopted staging standard in the world. This shows that the initial treatment for endometrial cancer is basically surgical treatment and that the surgical stage is determined. Endometrial cancer is often associated with irregular vaginal bleeding at the early stage and is diagnosed as early stage cancer in most patients. In 2002, the proportion of patients for each stage was reported as follows, and 59.5% of patients had grade I cancer [6].

Ia	Ib	Ic	IIa	IIb	IIIa	IIIb	IIIc	IVa	IVb
18.4%	29.1%	11.8%	2.8%	4.7%	9.1%	0.6%	8.9%	0.5%	4.2%

In general, many patients with endometrial cancer are expected to be cured with surgery in combination with radiotherapy.

The 5-year survival rate by stage in patients with endometrial cancer who started treatment in 1990, where the staging was based on the pTNM classification, which is different from the current FIGO classification, can be estimated as follows, showing better results in patients with early endometrial cancer and apparently poor prognosis in patients with advanced endometrial cancer. The 5-year survival rate in overall patients with endometrial cancer was 70.8% at the time [5].

I	II	III	IV
83.6%	76.8%	51.8%	19.5%

Similar to these results in Japan, the 5-year survival rate by stage in patients with endometrial cancer, which was analyzed by FIGO between 1993 and 1995, is as follows[7]:

Ia	Ib	Ic	IIa	IIb	IIIa	IIIb	IIIc	IVa	IVb
88.9%	90.0%	80.7%	79.9%	72.3%	63.4%	38.8%	51.1%	19.9%	17.2%

Only surgical treatment as the initial treatment for endometrial cancer was reported to show better results in the 5-year survival rate for stage I or II of 85% or more [8]; however, it was also reported that the prognosis of stage III or IV was poor (as mentioned above) and that the 2- and 5-year survival rates for recurrent endometrial cancer were 19% [9] and 8% to 19.5% [9, 10], respectively.

Chemotherapy has been used for the treatment of such advanced or recurrent endometrial cancer. The progress in chemotherapeutic drugs has enabled a certain level of response to endometrial cancer; however, further improvements in the results of chemotherapy have been explored.

2.2 Chemotherapy against endometrial cancer

Active single agent

Agents such as CDDP, CBDCA, ADM, 5-fluorouracil (5-FU), and cyclophosphamide (CPA) is known to be effective in monotherapy against endometrial cancer; the response rate of each drug was reported to be 4% to 42% for CDDP, 27% to 33% for CBDCA, 19% to 37% for ADM, 21% to 23% for 5-FU, and 11% to 28% for CPA [11, 12]. Among these agents, CDDP, which is a platinum drug, and ADM, which is an anthracycline drug, seem to be key drugs showing a relatively higher response rate. CDDP binds to DNA chains via interstrand cross-link formation and inhibits DNA synthesis and subsequent cancer cell division, and ADM forms complexes with DNA and inhibits DNA and RNA polymerase reactions to suppress DNA and RNA biosynthesis.

Active combination therapy

To improve the response rate, combination chemotherapy with the abovementioned drugs, which have different mechanisms of action, was investigated. The results reported that the response rate was 31% to 56% for CAP (CPA + ADM + CDDP) [13, 14], 33% to 81% for ADM + CDDP [15, 16], and 31% to 46% for CPA + ADM[17]. On the basis of these results, combination therapy with CDDP and ADM has been adopted as a standard regimen in many countries. However, cases with improved response duration were infrequently reported in contrast to frequent reports that a >50% response rate was achieved. Therefore, many issues need to be considered in the future.

Combination chemotherapy with AP therapy

Study GOG107, which was a randomized phase III study that compared ADM 60mg/m^2 every 3 weeks and AP (ADM 60 mg/m^2 + CDDP 50 mg/m^2) therapy every 3 weeks in patients with advanced or recurrent endometrial cancer, showed significantly superior response rate and median PFS in AP therapy compared with ADM monotherapy: 42% versus 25% (P = 0.004) and 5.7 months versus 3.8 months (P = 0.014), respectively [18]. Furthermore, AP therapy also seemed to have an acceptable toxicity level; therefore, it has become accepted as a useful chemotherapy regimen for advanced or recurrent endometrial cancer and as a standard treatment against recurrent or advanced endometrial cancer in clinical research by GOG.

Study EORTC 55872, which was a randomized phase II/III study that compared ADM 60 mg/m^2 every 4 weeks and AP (ADM 60 mg/m^2 + CDDP 50 mg/m^2) therapy every 4 weeks in patients with advanced or recurrent endometrial cancer, showed that AP therapy had a significantly superior response rate to ADM monotherapy: 43% versus 17% (P < 0.001) [19]. Almost no difference was also observed in the toxicity results between Study EORTC 55872 and Study GOG107, and the efficacy and safety of the AP therapy in Study EORTC 55872 validated those in Study GOG107. Therefore, AP therapy has become accepted as a standard chemotherapy against advanced or recurrent endometrial cancer.

To investigate the superiority of chemotherapy to radiotherapy, Study GOG122, which was a randomized phase III study, was conducted to compare whole-abdominal irradiation (WAI: 30 Gy/20 fx plus 15 Gy boost to the pelvis/para-aortic area) and AP therapy in patients with postoperative stage III or IV endometrial cancer. The incidence of toxicity such as grade 3 or 4 white blood cell decreased, gastrointestinal symptoms, and treatment-related deaths was higher in AP therapy; however, the relative recurrent risk and mortality risk respectively decreased by 29% and 38% in the AP therapy group, thus showing significantly better results [1)]. On the basis of the above, despite its somewhat high toxicity, the availability of postoperative AP therapy against advanced endometrial cancer was established. Therefore, AP therapy is recommended as a standard treatment.

Combination chemotherapy with taxanes

Taxane-based agents have been clinically introduced, and their mechanisms of action include the promotion of tubulin polymerization, induction of excess microtubule formation, and stabilization of microtubules formed by the inhibition of depolymerization; the efficacy of PTX against advanced or recurrent endometrial cancer was also investigated, and the response rate of 24-hour PTX 250 mg/m^2 dosing was reported to be 35% [20)].

The response rate of PTX + CBDCA (TC therapy) was reported to be 62.5% to 72.7% [21, 22)].

An investigation on DOC, which is another taxane against advanced or recurrent endometrial cancer, reported a response rate of 33% [23)]. This report showed that DOC has a comparable response to PTX; therefore, DOC also seems to be effective against endometrial cancer.

For chemotherapy with PTX, Study GOG177, which was a randomized phase III study, was conducted to compare AP therapy and TAP therapy (PTX 160 mg/m^2 + ADM 45 mg/m^2 + CDDP 50 mg/m^2 + G-CSF every 3 weeks) [24)]. The results showed that the response rate, median PFS, and median OS were significantly superior in TAP therapy compared with AP therapy: 57% versus. 34% ($P < 0.01$), 8.3 months versus 5.3 months ($P < 0.01$), and 15.3 months versus 12.3 months ($P = 0.037$), respectively. However, TAP therapy had greater toxicity than AP therapy, including grade 2 peripheral neuropathy (27% versus 4%) and grade 3 peripheral neuropathy (12% versus 1%). Among the 131 patients in the TAP therapy group, 3 patients had symptomatic cardiac failure congestive, and 5 patients had treatment-related deaths. Therefore, TAP therapy was not concluded to be a standard treatment in terms of toxicity and tolerability.

Study GOG163, which was a randomized phase III study that compared AP therapy and AT therapy (ADM 50 mg/m^2 + PTX 150 mg/m^2 for 24 hours + G-CSF every 3 weeks) against advanced or recurrent endometrial cancer [25)]. This study showed no significant differences in the response rate, median PFS, or median OS between the AP and AT groups: 40% versus 43%, 7.2 months versus 6 months, and 12.6 months versus 13.6 months, respectively. Furthermore, no significant differences in hematotoxicity or upper gastrointestinal disorder were observed. The report did not show the availability of switching concomitant medication from CDDP to PTX in AT therapy requiring 24-hour PTX dosing and G-CSF support.

A randomized controlled phase II study was also conducted to compare AP therapy and TC therapy (3-hour PTX 175 mg/m^2 + CBDCA AUC 5 every 3 weeks) in patients with advanced or recurrent endometrial cancer [26)]. The results showed that the response rate, median PFS, and 15-month OS rate in 34 AP therapy patients and 36 TC therapy patients were 27.6% versus 35.3%, 3.9 months versus 5.1 months, and 31% versus 45%, respectively; toxicity such as infections, and nausea and vomiting were more likely to occur in the AP therapy group.

TAP therapy extended the survival time; however, it requires G-CSF administration and has significant potential toxicity such as a significant increase in peripheral neuropathy, cardiac failure, and treatment-related deaths. Furthermore, the results suggesting the availability of TC therapy from a phase II study should be validated in a phase III study in the future. On the basis of the above, AP therapy is considered the current standard chemotherapy against endometrial cancer.

2.3 High-risk group for postoperative recurrent endometrial cancer

Patients with endometrial cancer who underwent complete excision at the initial surgery may result in disease recurrence or death regardless if they have advanced or recurrent endometrial cancer. The

risk of recurrence has been evaluated on the basis of the surgical stage and histopathological prognostic factors such as histologic type and vascular invasion.

USGOG investigated the 5-year relapse free survival rate in 895 patients with stage I or II endometrioid adenocarcinoma of the uterus who underwent treatment between 1977 and 1983. The survival rates were 41% for patients with para-aortic lymph node metastasis or peritoneal dissemination, 58% for patients with metastasis to the pelvic lymph nodes or adnexa, 55% for patients with positive vascular invasion, 56% for patients with positive peritoneal cytology, 70% for patients with invasion in the lower body or the cervix of the uterus, and 93% for patients without any of these risk factors; the relative risk was reported to increase by 15 in patients with grade 3 endometrioid adenocarcinoma of the uterus [27].

A research investigating the relationship between the presence or absence of lymph node metastasis and histopathological prognostic factors reported that grade 2 histology with no myometrial invasion (stage Ia), grade 1 histology with depth of myometrial invasion up to 1/3, and no invasion in the cervix of the uterus or adnexa were included as factors that are unlikely to cause lymph node metastasis and that the presence of vascular invasion or grade 3 histology could cause lymph node metastasis regardless of the degree of myometrial invasion [28].

The histopathological prognostic factors that are likely to cause distant recurrence was also investigated [29]. A multivariate analysis in 599 patients who underwent initial surgery for 10 years before 1994 showed that distant recurrence was frequently observed in patients with stage I to III nonendometrioid carcinoma, positive peritoneal cytology, positive cervical stromal invasion, or positive lymph node metastasis, not in patients with stage IV.

On the basis of the abovementioned reports, the National Comprehensive Cancer Network recommended a postoperative adjuvant therapy depending on the conditions of the histologic grade, grade 3 histology, advanced age, vascular invasion, tumor size, degree of myometrial invasion, and involvement of outer third of uterus as factors that are highly likely to cause distant recurrence.

In Europe and the United States, radiotherapy that can be conducted on an outpatient basis and can be completed in a short amount of time has been accepted as a postoperative treatment for a high-risk group for postoperative recurrent endometrial cancer with a likelihood of hospitalization instead of chemotherapy [30].

By contrast, chemotherapy with anticancer drugs has been conducted at many medical institutions in Japan. Given that endometrial cancer may widely extend into the abdominal cavity, similar to ovarian cancer and in contrast to cervical cancer, whole-abdominal irradiation is needed when delivering radiotherapy. In Japan, radiotherapy has been conducted as a postoperative treatment in 9.4% of all endometrial cancer patients, most of whom seem to have received whole pelvis irradiation, whereas chemotherapy was reported to have been conducted in 33.7% of all endometrial cancer patients; Japan has a treatment strategy that differs from that of Europe and the United States [31].

The 5-year survival rate by postoperative treatment in Japan was 69.4% for radiotherapy and 67.7% for chemotherapy, thus showing that a comparable rate existed between the therapies [32]. On the basis of a comparison with historical control data, many medical institutions considered that chemotherapy is expected to have an equivalent or better effect than radiotherapy [33]. However, the efficacy of postoperative adjuvant chemotherapy has not been validated in a phase III study.

In the context of this treatment strategy in Japan, the Japanese Gynecologic Oncology Group (JGOG) conducted Study JGOG2033, which was a randomized phase III study, to compare postoperative radiotherapy (whole pelvic irradiation [WPI]) and postoperative chemotherapy (CPA 333 mg/m^2 + ADM 40 mg/m^2 + CDDP 50mg/m^2 [CAP]) in patients with a depth of myometrial invasion over 1/2 who underwent complete excision [2]. The results showed a better availability of postoperative adjuvant chemotherapy than that of radiotherapy in stages II and IIIa (positive cytology). This result was not the primary endpoint of Study JGOG2033 and was obtained from the subset analysis; therefore, further investigations are needed to provide the availability of postoperative chemotherapy for a high-risk group for postoperative recurrent endometrial cancer in comparison with standard chemotherapy.

2.4 Current chemotherapy for endometrial cancer in Japan

CPA is only covered in Japan by the National Health Insurance for endometrial cancer among drugs that have been used as effective drugs in Europe and the United States. Therefore, Japan has a wide experience in CAP therapy against ovarian cancer as a concomitant therapy that includes CPA. It was considered that this sufficient experience in using CAP therapy enabled the use of AP therapy as a treatment that omits CPA from CAP therapy, which is a standard treatment for advanced or recurrent endometrial cancer in foreign countries. On the basis of the above, AP therapy in which the CDDP dose was fixed to 50 mg/m^2, ADM dose was increased to 60 mg/m^2, and CPA as omitted was approved for coverage by the National Health Insurance in February 2005 [34].

However, given that there are few clinical experiences on AP therapy with increased ADM dose in Japan, a feasibility study has been conducted in a high-risk group for postoperative recurrent endometrial cancer [35]. In this study, AP (ADM 60 mg/m^2 + CDDP 50 mg/m^2) therapy was repeated every 3 weeks for three to six courses as the target. Twenty-two patients were enrolled in the study. The following course was started in approximately 1/3 patients because of persistent neutropenia; however, the treatment completion rate (proportion of patients who have completed treatment with the scheduled number of courses) was 86%, and no patient with treatment-related death or dose reduction was found. This result was better than the feasibility of Study GOG122, thus confirming that AP therapy can be satisfactorily conducted in Japan on the basis of the current situation of improved supportive care compared with the 1990s, when Study GOG122 was mainly conducted. Grade 3 or more major subjective and objective adverse events observed in 22 enrolled patients included infections such as periodontitis in 14% of the patients and febrile neutropenia and vomiting in 4.5% of the patients. Grade 3 or more abnormal changes in clinical laboratory values included neutrophil count decreased in 91% of patients and white blood cell count decreased in 64% of patients.

To investigate the efficacy of taxane monotherapy in patients with advanced or recurrent endometrial cancer, a sponsor-initiated phase II clinical study was conducted in Japan; PTX and DOC were approved for coverage by the National Health Insurance in May 2005 and August 2005, respectively. The response rates of PTX 210 mg/m^2 3 hours treatment given every 3 weeks were 30.4% (95% confidence interval: 13.2 to 52.9%) and 21.7% (95% confidence interval: 7.5 to 43.7%) according to assessments based on the Response Evaluation Criteria by the Chemotherapy for Gynecologic Malignancies and Response Evaluation Criteria in Solid Tumors (RECIST). Grade 3 or more subjective and objective adverse events observed in 23 enrolled patients included febrile neutropenia and constipation with 2 patients each and nausea, vomiting, fatigue, pain, urinary tract infection, oxygen saturation decreased, inappetence, arthralgia, myalgia, hypesthesia, dyspnea, packed red blood cell transfusion, and weight decreased with 1 patient each. Grade 3 or more abnormal changes in clinical laboratory values included neutrophil count decreased in 78.3% of patients (18 patients), white blood cell count decreased in 47.8% of patients (11 patients), hemoglobin decreased in 13.0% of patients (3 patients), potassium decreased in 8.7% of patients (2 patients), and sodium decreased in 4.3% of patients (1 patient) [36].

The response rate of DOC 70 mg/m^2/1–2 hours treatment given every 3 weeks was 31.3% (95% confidence interval: 16.1 to 50.0%) according to the assessment based on RECIST and 28.1% (95% confidence interval: 13.7 to 46.7%) according to the assessment based on the Response Evaluation Criteria in Solid Tumors by the Japan Society of Clinical Oncology. Grade 3 or more subjective and objective adverse events observed in 33 enrolled patients included inappetence in 6 patients; febrile neutropenia, vomiting, diarrhea, and fatigue with 3 patients each; nausea in 2 patients; and stomatitis/pharyngitis, edema, neuropathy/sensory disturbance, allergy, and rash/desquamation with 1 patient each. Grade 3 or more abnormal changes in clinical laboratory values included neutrophil count decreased in 93.9% of patients (31 patients), white blood cell count decreased in 78.8% of patients (26 patients), lymphopenia in 30.3% of patients (10 patients), and hemoglobin decreased in 3.0% of patients (1 patient) [37].

JGOG also conducted a randomized phase II study (Study JGOG2041) to explore the useful treatment regimens for advanced or recurrent endometrial cancer using a two-drug regimen of taxane, which has been widely used for the treatment of ovarian cancer and can become a key drug for endometrial cancer, and platinum. Platinum drugs that have been used for endometrial cancer includes CDDP in AP therapy and CBDCA in TC therapy. Given that the role of CBDCA in concomitant

therapy seems to remain unclear [38], three types of regimens among the four types of regimens to be tested, excluding TP therapy (PTX + CDDP), were investigated on the grounds that the regimen to be used for the treatment of ovarian cancer should be switched from TP therapy to TC therapy because neurotoxicity was frequently reported following treatment with TP therapy [39–41]; these three types of regimens include TC therapy (PTX 180 mg/m^2 + CBDCA AUC 6), DP therapy (DOC 70 mg/m^2 + CDDP 60 mg/m^2), and DC therapy (DOC 60 mg/m^2 + CBDCA AUC 6). Study JGOG2041 was designed to explore a regimen that is expected to provide better effects than the response rate of AP therapy (34%) in Study GOG177 described above and to develop a phase III study plan on the basis of the results obtained. The response rate to TC therapy was 60.0% (95% confidence interval: 40.6 to 77.3%). Grade 3 or more major subjective and objective adverse events observed in 30 evaluable patients included inappetence and nausea in 13.3% of patients, neuropathy (motor) (grade 2 or more) in 16.7% of patients, neuropathy (sensory) (grade 2 or more) in 20.0% of patients, and febrile neutropenia in 6.7% of patients. Grade 3 or more abnormal changes in clinical laboratory values included neutrophil decreased in 80.0% of patients, white blood cell decreased in 53.3% of patients, hemoglobin level decreased in 30.0% of patients, and platelets decrease in 26.7% of patients. The response rate to DP therapy was 51.7% (95% confidence interval: 32.5% to 70.6%). Grade 3 or more major subjective and objective adverse events observed in 30 evaluable patients included inappetence and diarrhea in 16.7% of patients, nausea in 13.3% of patients, and grade 3 to 4 infection accompanying neutrophil decreased in 16.7% of patients. Grade 3 or more abnormal changes in clinical laboratory values included neutrophil decreased in 86.7% of patients, white blood cell decreased in 76.7% of patients, and hemoglobin level decreased in 8.3% of patients. The response rate to DC therapy was 48.3% (95% confidence interval: 29.5% to 67.5%). Grade 3 or more major subjective and objective adverse events observed in 30 evaluable patients included inappetence in 10.0% of patients and nausea, febrile neutropenia, and infection in 6.7% of patients. Grade 3 or more abnormal changes in clinical laboratory values included neutrophil decreased in 90.0% of patients, white blood cell decreased in 86.7% of patients, hemoglobin level decreased in 33.3% of patients, platelets decreased in 13.3% of patients, and ALT increased in 6.7% of patients. The results above suggested the possibility of the better efficacy and tolerability of all three regimens compared with AP therapy. The proportion of patients with progressive disease (PD) was highest in the DC therapy group between three groups (TC:DP:DC = 13.3%:13.7%:27.6%).

PTX and DOC were requested to conduct an endometrial cancer treatment survey in Japan as instructions associated with the approval for coverage by the National Health Insurance; thus, JGOG conducted the survey by receiving a request from pharmaceutical companies. The results showed that the number of patients who underwent postoperative adjuvant chemotherapy between January and December in 2004 was 1,675 patients (192 sites), which account for 41.0% (1,675/4,090 patients) of patients who received surgery in 2004; the proportion of patients who underwent postoperative adjuvant radiotherapy, which has been commonly performed in Europe and the United States, was only 6.7% (273/4,090 patients). The current status of treatment is shown below. The groups in which at least 90% of patients underwent postoperative chemotherapy included all groups in stages III and IV, grade 3 positive vascular invasion group in stage IIb, grade 3 positive vascular invasion group in stage IIa, grade 2 positive vascular invasion group in stage Ic, and grade 3 positive vascular invasion group in stage Ic. The groups in which at least 50% of patients underwent postoperative chemotherapy included groups in stage Ic or higher, grade 2 positive vascular invasion group in stage Ib, and grade 3 positive vascular invasion group in stage Ib.

2.5 Reason for the preparation of the protocol

In general, many patients with endometrial cancer are expected to be cured with surgery in combination with radiotherapy; however, patients with advanced endometrial cancer have apparently poor prognosis. The 5-year survival rates by stage were 51.8% in stage III and 19.5% in stage IV, whereas the 5-year survival rate in all patients with endometrial cancer was 70.8% [5]. Chemotherapy has been used for the treatment of advanced or recurrent endometrial cancer. The progress in chemotherapeutic drugs has enabled a certain level of response to endometrial cancer. Among the combination chemotherapy programs that have been investigated previously, AP therapy provided better availability than ADM monotherapy and WAI and has been recommended as a standard

treatment [1, 18, 19]. As mentioned above, TAP therapy was reported to be better than AP therapy, but it was not accepted as a standard treatment because of its toxicity [24]. Therefore, the exploration of further improvements in the results of chemotherapy and regimen with better tolerability is required.

For chemotherapy using PTX, the results suggesting the availability of TC therapy reported from a comparison of AT therapy[25] and TC therapy[26] with AP therapy against advanced or recurrent endometrial cancer should be validated in a phase III study in the future.

Patients with endometrial cancer who have undergone complete excision at the initial surgery may result in disease recurrence or death regardless of advanced or recurrent endometrial cancer. Patients with stage IIb or higher, stage Ic endometrioid adenocarcinoma, any grade 3 endometrioid adenocarcinoma, significant vascular invasion, or nonendometrioid carcinoma are considered at high for postoperative recurrent endometrial cancer, for whom postoperative adjuvant therapy should be indicated [27, 28]. As a postoperative therapy for such a high-risk group for postoperative recurrent endometrial cancer, radiotherapy has been conducted in foreign countries [29]; by contrast, chemotherapy has mainly been conducted at many medical institutions in Japan [30–33]. However, the efficacy of postoperative adjuvant chemotherapy has not been validated in a phase III study. Study JGOG2033, which was conducted to compare WPI and CAP therapy in patients with depths of myometrial invasion over 1/2 who underwent complete excision showed that postoperative adjuvant chemotherapy has better availability than radiotherapy in stages II and IIIa (positive cytology) [2]; however, this result was obtained from the subset analysis, and further investigations are needed to provide the availability of standard chemotherapy, including AP therapy.

In Japan, AP therapy, taxane (PTX), and DOC were approved for coverage by the National Health Insurance in February 2005 [34], May 2005 [36], and August 2005, respectively [37]. For AP therapy, a feasibility study that was conducted in a high-risk group for postoperative recurrent endometrial cancer confirmed that AP therapy can be satisfactorily conducted in Japan [35]. For combination chemotherapy with platinum and taxane, Study JGOG2041, which was conducted in patients with advanced or recurrent endometrial cancer, suggested that TC, DP, and DC therapies may have better efficacy and tolerability than AP therapy.

On the basis of the above context and the results from Studies JGOG2033 and JGOG2041, JGOG planned to conduct a randomized phase III trial to compare AP therapy and combination chemotherapy with platinum and taxane in a high-risk group for postoperative recurrent endometrial cancer. The regimen to be investigated consists of the initial postoperative chemotherapy with AP therapy, TC therapy, or DP therapy on the following grounds: (1) the aggregated results of Study JGOG2041 showed that the incidence of PD was somewhat higher in the DC therapy group than in the other two groups; (2) the role of CBDCA in concomitant therapy remains unclear [38]. When using CDDP with substantial evidence of effectiveness, DOC as taxane has been selected as an option for combination therapy (PTX has been switched to being combined with CBDCA from being combined with CDDP to prevent the frequent occurrence of neurotoxicity [39–41]). The study patients included the following: (1) endometrial cancer patients with a residual tumor of 2 cm or less and are in the FIGO surgical stage III or IV (i.e., lesions are present in the abdominal cavity) because a comparison between radiotherapy and AP therapy have not been conducted yet in Japan even though postoperative adjuvant chemotherapy has been widely conducted in patients with stages Ic and II endometrial cancer; (2) stage I or II endometrial cancer patients with a depth of myometrial invasion > 1/2 as investigated in Study JGOG2033 and with histologic grade 2 or 3.

3. Patient Inclusion Criteria

Patients that are at high risk for postoperative recurrent endometrial cancer will be included in the study.

3.1 Eligibility criteria

1) Patients whose primary lesion has been histologically confirmed to be endometrial carcinoma (excluding sarcoma and carcinosarcoma)
2) Patients who underwent at least total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy and whose residual tumor diameter is 2 cm or less
3) Endometrial cancer patients who meet any of the following conditions identified by the histopathological examination of the resected specimen of the primary lesion:
   - Surgical stage I or II with depth of myometrial invasion > 1/2 and histologic grade 2 or 3*
     * Poor-prognosis histologic type (serous, clear cell, or anaplastic) should be handled as grade 3.

     For other histologic types, the grade should be determined on the basis of a feature of the adenocarcinoma component or cytologic atypia.
   - Surgical stage III
   - Surgical stage IV without distant metastasis outside the abdominal cavity*
     * E.g., metastasis to the thoracic cavity, mediastinum, or cervical lymph nodes
4) Patients who did not receive prior chemotherapy or radiotherapy for endometrial cancer
5) Patients beyond 14 days from the last day of hormonal therapy to enrollment into the study
6) Patients with an ECOG Performance Status (P.S.) of zero to two
7) Patients who are able to start the combination therapy within 8 weeks after surgery
8) Patients aged 20 years or older but less than 75 years old (at the time of enrollment)
9) Patients whose main organ functions (including bone marrow, heart, liver, and kidneys) have been maintained

   The following tests should be performed within 14 days prior to enrollment.

Neutrophil count	2,000/mm^3 or more
Platelet count	100,000/mm^3 or more
Hemoglobin level	9.0 g/dL or more
Both AST (GOT) and ALT (GPT)	100 U/L or less
Total serum bilirubin level	1.5 mg/dL or less
Serum creatinine level	1.2 mg/dL or less

   (Two instances of confirmation with the measurement are preferable.)

   The following tests should be performed within 21 days prior to enrollment or within 28 days prior to the planned date of the start of administration.

Creatinine clearance	60 mL/min or more
Electrocardiogram	Normal or asymptomatic and not requiring treatment
Left Ventricular Ejection Fraction (LVEF)	50% or more

10) Patients who have consented in writing to participate in this study

3.2 Exclusion criteria

1) Patients with cancer containing sarcoma components
2) Patients with apparent infection
3) Patients with serious complications (e.g., cardiac disorder, uncontrollable diabetes mellitus, malignant hypertension, and bleeding tendency)
4) Patients with a history of double cancer with disease-free interval of less than 5 years or patients with active double cancer
5) Patients with possible interstitial pneumonia or pulmonary fibrosis by plain chest X-rays and CT
6) Patients with pleural effusion and ascites requiring persistent drainage
7) Patients with peripheral neuropathy (motor and/or sensory) of grade 2 or greater

8) Patients with grade 2 or greater edema (extremity) (excluding disorders associated with the primary disease)
9) Patients with prior chemotherapy with doxorubicin (ADM)
10) Patients with a history of hypersensitivity to drug products containing polysorbate 80, polyoxyethylene castor oil (Cremophor EL®) (e.g., cyclosporine), or hydrogenated castor oil (e.g., vitamins for injections)
11) Patients who were determined inappropriate to enter into the clinical study by the principal investigator at each facility

4. Drug Information

4.1 Information on drugs used

The primary information for drugs used in this study shall be noted on the drug package insert of each drug (Appendix 8). When the drug package insert is revised, the new version should be used as a reference. Although the package inserts for each drug are attached to this study protocol, all personnel involved in this clinical study should make an effort to understand the latest information by using the latest versions of the package inserts on the Pharmaceuticals and Medical Devices Agency website (http://www.info.pmda.go.jp/).

4.2 Supply of drugs

Commercially available drugs shall be used.

4.2.1 Paclitaxel (PTX)

[1] Product name: Taxol® for injection 30 mg, Taxol® for injection 100 mg

[2] Ingredients/content: One vial of 5 and 16.7 mL contains 30 and 100 mg of paclitaxel, respectively.

[3] Serious adverse reactions

1) Shock, anaphylactoid symptoms
Subjects should be closely monitored for shock (0.2%) and anaphylactoid symptoms (0.3%). Study drug administration should be discontinued, and appropriate treatment should be given to subjects who had abnormalities such as dyspnea, chest pain, hypotension, tachycardia, bradycardia, flushing, angioedema, or sweating.

2) Bone marrow depression, including white blood cell decreased
Subjects should be closely monitored via peripheral blood tests for white blood cell decreased (59.7%), neutrophil decreased (53.5%), anemia (hemoglobin decreased [27.4%], hematocrit decreased [5.2%], erythrocytes decreased [6.4%], etc.), platelets decreased (10.6%), and pancytopenia. If an abnormality is observed, appropriate treatment such as dose reduction or washout period should be given. Simultaneous infections (urinary tract infection [2.2%], upper respiratory tract infection [4.4%], sepsis [0.9%], herpes zoster [1.1%], and pneumonia [1.0%], etc.) due to persistent bone marrow depression have also been reported. The incidence rates of white blood cell decreased and neutrophil decreased of grade 3 or greater were 43.7% (163/373) and 76.3% (284/372), respectively, in the phase II study of the 3-hour intravenous infusion (this study drug alone) conducted in Japan.

3) Peripheral neuropathy, paralysis
Peripheral neuropathy including numbness (41.2%), paralysis (0.1%), hemiplegia (less than 0.1%), or paresis may appear. Appropriate treatment such as dose reduction or washout period should be given if such symptoms appear.

4) Interstitial pneumonia, pulmonary fibrosis
Subjects should be closely monitored for interstitial pneumonia (0.5%) and pulmonary fibrosis (unknown frequency). Study drug administration should be discontinued if pyrexia, cough, dyspnea, or chest X-ray abnormal is observed, and appropriate treatment such as corticosteroid administration should be given.

5) Acute respiratory distress syndrome
Subjects should be closely monitored for acute respiratory distress syndrome (less than 0.1%). Study drug administration should be discontinued if dyspnea progressing rapidly, hypoxia, or chest X-ray abnormal findings (e.g., bilateral, diffuse, or pulmonary infiltrates) are observed, and appropriate treatment should be given.

6) Myocardial infarction, cardiac failure congestive, cardiac conduction disorder, pulmonary embolism, thrombophlebitis, stroke, and pulmonary edema
Subjects should be closely monitored for myocardial infarction (less than 0.1%), cardiac failure congestive (less than 0.1%), cardiac conduction disorder (unknown frequency), pulmonary embolism (0.1%), thrombophlebitis (0.4%), stroke (less than 0.1%), and pulmonary edema (less

than 0.1%). Study drug administration should be discontinued if an abnormality is observed.

7) Deafness, tinnitus
Subjects should be closely monitored for deafness (0.2%) and tinnitus (0.4%). Study drug administration should be discontinued if an abnormality is observed.

8) Gastrointestinal necrosis, intestinal perforation, gastrointestinal hemorrhage, and gastrointestinal ulcer
Subjects should be closely monitored for gastrointestinal necrosis (unknown frequency), intestinal perforation (less than 0.1%), gastrointestinal hemorrhage (less than 0.1%), and gastrointestinal ulcer (0.1%). Appropriate treatment such as study drug discontinuation should be given if an abnormality is observed.

9) Serious enterocolitis
Subjects should be closely monitored for enterocolitis such as colitis hemorrhagic, pseudomembranous colitis, and colitis ischemic. Study drug administration should be discontinued if conditions including severe abdominal pain or diarrhea appear, and appropriate treatment should be given.

10) Gastrointestinal obstruction, paralysis intestinal
Gastrointestinal obstruction (1.7%) or paralysis intestinal (0.1%) (including inappetence, nausea and vomiting, marked constipation, abdominal pain, abdominal distension, or abdominal flaccidity and intestinal stasis) can progress into ileus paralytic. Study drug administration should be discontinued if gastrointestinal obstruction or paralysis intestinal appears, and appropriate treatment (e.g., intestinal decompression) should be given.

11) Hepatic function disorder, jaundice
Subjects should be closely monitored for hepatic function disorder (4.4%) and jaundice. Study drug administration should be discontinued if an abnormality is observed.

12) Pancreatitis
Subjects should be closely monitored for pancreatitis (less than 0.1%). Appropriate treatment such as study drug discontinuation should be given if abnormalities in serum amylase or any other relevant levels are observed.

13) Acute kidney injury
Subjects should be closely monitored for acute kidney injury (0.2%). Appropriate treatment such as study drug discontinuation should be given if abnormal levels in BUN, serum creatinine, creatinine clearance, or any other relevant levels are observed.

14) Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome)
Subjects should be closely monitored for oculomucocutaneous syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome). Study drug administration should be discontinued if an abnormality is observed, and appropriate treatment should be given.

15) Disseminated intravascular coagulation
Subjects should be closely monitored for disseminated intravascular coagulation (DIC) (0.1%). Study drug administration should be discontinued if abnormal blood test results, including platelet count, serum FDP level, or plasma fibrinogen level, are observed, and appropriate treatment should be given.

[4] Other adverse reactions

Hypersensitivity	Rash (5% to less than 20%), redness (less than 5%)
Cardiovascular	Hypotension (5% to less than 20%), arrhythmia, tachycardia, bradycardia, extrasystoles, hypertension, palpitation, electrocardiogram abnormal, atrial fibrillation, ventricular fibrillation, cardiac hypertrophy, angina pectoris (less than 5%)
Gastrointestinal	Nausea and vomiting (33.8%), diarrhea, inappetence, stomatitis, constipation (5% to less than 20%), dyspepsia, meteorism/flatulence, gastritis, rectal pain, dysphagia, rectal disorder, gingivitis, bloating, tongue coated, gingival pain (less than 5%)
Hepatic	AST (GOT) increased, ALP increased, LDH increased, ALT (GPT) increased (5% to less than 20%), bilirubin increased (less than 5%)
Renal	Electrolyte abnormality (5% to less than 20%), BUN increased,

	creatinine increased, proteinuria (less than 5%)
Skin	Alopecia (42.3%); rash maculo-papular, nail discoloration (20% or greater, or unknown frequency), itching, skin disease, skin ulcer, urticaria, nail disorder, peeling, pigmentation, skin swelling (less than 5%)
Neuropsychiatric	Dizziness, sleeplessness, anxiety, depression, somnolence, thinking abnormal, tremor, syncope, agitation, neurological disorder, convulsion, ataxia, amnesia, feeling tense decreased, consciousness disturbed, bradykinesia, language disorder, feeling tense increased, psychiatric symptom, delirium, nystagmus, movements involuntary, hoarseness, mood variable (less than 5%)
Sensory	Scotoma, photopsia (20% or greater, or unknown frequency), taste perversion, abnormal vision, ageusia, eye pain, ear pain, tongue abnormal feeling (less than 5%)
Respiratory	Dyspnea (5% to less than 20%), hypoxia (less than 5%)
General symptoms	Asthenia, abdominal pain, malaise, headache (5% to less than 20%), edema, pain, flu-like syndrome, abdomen enlarged, chilliness, weight increased, weight decreased (less than 5%)
Musculoskeletal	Arthralgia (30.7%), myalgia (27.1%), bone pain, back pain (5% to less than 20%), neck pain, low back pain (less than 5%)
Other	Dehydration (20% or greater, or unknown frequency); pyrexia, flushing (5% to less than 20%); chest pain, cough increased, hemorrhage, injection site reaction, edema peripheral, protein total decreased, albumin decreased, pelvic pain, sweating, hiccups, dysuria, hematuria, eye disease, thirst, metrorrhagia, conjunctivitis, amenorrhea, injection site pain, feeling drunk, hyperglycemia, urinary incontinence, urinary retention, hypoglycemia, cystitis hemorrhagic, sputum increased, conjunctival hemorrhage, dry eye, keratitis (less than 5%)

4.2.2 Docetaxel

4.2.2.1

[1] Product name: TAXOTERE® for intravenous infusion

[2] Ingredients/content: One 80 mg vial of 2 mL contains 85.35 mg of DOC hydrate (80 mg as DOC).
One 20 mg vial of 0.5 mL contains 21.34 mg of DOC hydrate (20 mg as DOC).

[3] Serious adverse reactions

1) Bone marrow depression: Thorough blood tests should be performed to monitor the patient for bone marrow depression (white blood cell decreased [60 mg/m^2: 97.2%; 70 mg/m^2: 97.9%], neutropenia [60 mg/m^2: 95.2%; 70 mg/m^2: 98.4%], hemoglobin decreased [60 mg/m^2: 50.9%; 70 mg/m^2: 78.1%], and platelets decreased [60 mg/m^2: 11.7%; 70 mg/m^2: 13.0%]). Appropriate treatment such as lengthening dosage intervals, dose reduction, and washout should be given if an abnormality is observed. For the administration of this drug, the appropriate use of G-CSF products should be taken into account.
2) Shock symptoms (0.1%) and anaphylactoid symptoms (0.3%): Subjects should be closely monitored for shock and anaphylactoid symptoms including dyspnea, bronchospasm, blood pressure decreased, chest pressure sensation, and rash. Appropriate treatment such as study drug discontinuation should be given if a related symptom is observed.
3) Jaundice, hepatic failure, hepatic function disorder (unknown frequency): Liver function test values should be carefully checked to closely monitor for serious hepatic disorders including jaundice, hepatic failure, and marked increase of AST (GOT)/ALT (GPT)/ALP. Appropriate treatment such as study drug discontinuation should be given if an abnormality is observed.
4) Acute kidney injury (unknown frequency): Renal function test values should be carefully checked to closely monitor for serious renal disorders, including acute kidney injury. Appropriate treatment such as study drug discontinuation should be given if an abnormality is observed.

5) Interstitial pneumonia (0.2%), pulmonary fibrosis (unknown frequency): Interstitial pneumonia and/or pulmonary fibrosis may appear. A similar clinical symptom (radiation pneumonitis) may appear in patients who receive radiotherapy concomitantly. Subjects should be closely monitored, and appropriate treatment such as study drug discontinuation should be given if an abnormality is observed.
6) Cardiac failure (0.2%): Subjects should be closely monitored for cardiac failure. Appropriate treatment such as study drug discontinuation should be given if an abnormality is observed.
7) DIC (0.1%): Given the possibility of DIC, blood tests including platelet count, serum FDP level, and plasma fibrinogen concentration should be performed when necessary. If any symptoms appear, study drug administration should be discontinued, and appropriate treatment should be given.
8) Intestinal perforation (less than 0.1%), gastrointestinal hemorrhage (0.4%), ischemic enterocolitis (unknown frequency), colitis (0.1%): Given the possibility of intestinal perforation, gastrointestinal hemorrhage, ischemic enterocolitis, and colitis, appropriate treatment such as study drug discontinuation should be given if symptoms such as abdominal pain, hematemesis, melena, or diarrhea appear.
9) Ileus (unknown frequency): Subjects should be closely monitored for ileus. Appropriate treatment such as study drug discontinuation should be given if an abnormality is observed.
10) Acute respiratory distress syndrome (unknown frequency): Given the possibility of acute respiratory distress syndrome, subjects should be closely monitored if conditions including respiratory disorder appear, and appropriate treatment such as study drug discontinuation should be given.
11) Pancreatitis acute (unknown frequency): Subjects should be closely monitored for pancreatitis acute. Appropriate treatment such as study drug discontinuation should be given if abnormalities in serum amylase or any other relevant levels are observed.
12) Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), and erythema multiforme (unknown frequency): Subjects should be closely monitored for oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), and bullous and exudative eruption including erythema multiforme. Appropriate treatment such as study drug discontinuation should be given if an abnormality is observed.
13) Cardiac tamponade, pulmonary edema (unknown frequency), edema, and fluid retention (0.7%): Cardiac tamponade, pulmonary edema, serious edema, and fluid retention (e.g., pleural effusion and ascites requiring urgent drainage) have been reported.
14) Myocardial infarction, venous thromboembolism (unknown frequency): Myocardial infarction and venous thromboembolism have been reported.
15) Infection (1.4%): Infections including sepsis and pneumonia have been reported.
16) Syndrome of inappropriate antidiuretic hormone (SIADH) secretion (unknown frequency): Given the possibility of SIADH secretion, study drug administration should be discontinued if symptoms such as hyponatremia accompanied with blood hyposmosis, persistent urine sodium excretion, or consciousness disturbed appear, and appropriate treatment such as restriction of water intake should be given.
17) In addition to the above, mucositis including serious stomatitis, vasculitis, neuropathy peripheral, peripheral movement disorder including feelings of weakness of limbs, and radiation recall phenomenon have been reported.

[4] Other adverse reactions

Gastrointestinal	Inappetence (50% or greater); nausea and vomiting, diarrhea, stomatitis, occult blood (5% to less than 50%), abdominal pain, bloating, constipation, glossitis, dry mouth (less than 5%), gastroduodenal ulcer, esophagitis, hiccups (unknown frequency)
Hypersensitivity	Allergy, redness (5% to less than 50%); pruritus, flushing (less than 5%)
Skin	Alopecia (50% or greater), rash (5% to less than 50%), pigmentation, nail disorder (onycholysis, deformation, discoloration, subungual hemorrhage, subungual hematoma, subungual abscess) (less than 5%), peeling, hand and foot syndrome, cutaneous lupus erythematosus (unknown frequency)

Neuropsychiatric	Numbness (5% to less than 50%); headache, loss of consciousness, orientation disturbed, dizziness, stupor, deafness, tinnitus, dysgeusia, photophobia, abnormal vision, sleeplessness (less than 5%), somnolence, visual disturbance (visual flashes, flashing lights, scotoma) (unknown frequency)
Neuromuscular	Myalgia, arthralgia, muscular weakness, feelings of weakness, back pain, convulsion (less than 5%)
Hepatic	AST (GOT)/ALT (GPT)/γ-GTP/ALP/LDH increased (5% to less than 50%), bilirubin total increased (less than 5%)
Renal	Proteinuria, abnormal levels of K/Na/Cl/Ca, BUN increased (5% to less than 50%), creatinine increased, sugar urinary, hematuria, oliguria, pollakiuria (less than 5%)
Cardiovascular	Blood pressure decreased, blood pressure increased, arrhythmia, palpitation, tachycardia (less than 5%)
Respiratory	Dyspnea, pharyngitis, cough (less than 5%), sputum bloody (unknown frequency)
Other	General malaise (50% or greater), pyrexia, edema, protein total, albumin, A/G ratio, and CK (CPK) abnormal (5% to less than 50%), phlebitis, pain, chest pain, pantalgia, feeling hot, low back pain, epistaxis, hot flashes, lacrimation (less than 5%), lacrimal duct obstruction, dehydration (unknown frequency)

4.2.2.2 Reconstitution diluents for docetaxel

[1] Ingredients/content: One 80 mg vial of 6 mL contains 764.4 mg of 95% ethanol.
One 20 mg vial of 1.5 mL contains 191.1 mg of 95% ethanol.

4.2.3 Cisplatin (CDDP)

4.2.3.1

[1] Product name: BRIPLATIN®INJECTION, Randa® Injection

[2] Ingredients/content: One vial of 20, 50, and 100 mL contains 10, 25, and 50 mg of cisplatin, respectively.

[3] Serious adverse reactions

1) Acute kidney injury (less than 0.1%)
The patient's conditions should be closely monitored with frequent laboratory tests for serious renal disorders, including acute kidney injury. If abnormal levels in BUN, serum creatinine, creatinine clearance, or any other relevant levels are observed, study drug administration should be discontinued, and appropriate treatment should be given. Furthermore, hematuria, proteinuria, oliguria, or anuria may appear.
2) Bone marrow depression, including pancytopenia (less than 0.1%)
Subjects should be closely monitored via blood tests for pancytopenia, anemia, white blood cell decreased, neutrophil decreased, and platelets decreased. Appropriate treatment such as dose reduction, washout, or discontinuation should be given if an abnormality is observed.
3) Shock, anaphylactoid symptoms (less than 0.1%)
Subjects should be closely monitored for shock and anaphylactoid symptoms. Study drug administration should be discontinued if symptoms such as cyanosis, dyspnea, chest distressed feeling, or blood pressure decrease are observed, and appropriate treatment should be given.
4) Hypoacusis/deafness (1.4%), tinnitus (1.7%)
High-frequency hypoacusis, deafness, or tinnitus may appear. With dose increase, the incidence of acoustic organ disorder tends to increase. This trend is observed particularly with a daily dose of 80 mg/m^2 or more or a total dose of over 300 mg/m^2. Therefore, the administration should be made with careful monitoring.
5) Papilledema, optic neuritis retrobulbar, blindness cortical (less than 0.1% for all these conditions)
Visual disturbances such as papilledema, optic neuritis retrobulbar, and blindness cortical may appear. Study drug administration should be discontinued if an abnormality is observed.

6) Cerebral infarction (less than 0.1%), transient ischemic attack (less than 0.1%)
Cerebral infarction or transient ischemic attack may occur. Study drug administration should be discontinued if an abnormality is observed, and appropriate treatment should be given.

7) Hemolytic uremic syndrome (less than 0.1%)
Periodic blood tests (including platelet count and erythrocyte count) and renal function tests should be performed to closely monitor for hemolytic uremic syndrome, which is mainly characterized by platelets decreased, hemolytic anemia, and renal failure. Study drug administration should be discontinued if an abnormality is observed, and appropriate treatment should be given.

8) Myocardial infarction, angina pectoris, cardiac failure congestive, arrhythmia (less than 0.1% for all these conditions)
Subjects should be closely monitored for myocardial infarction, angina pectoris (including variant angina), cardiac failure congestive, and arrhythmia (ventricular fibrillation, cardiac arrest, atrial fibrillation, bradycardia, etc.). Study drug administration should be discontinued, and appropriate treatment should be given to subjects observed with chest pain, syncope, shortness of breath, palpitations, or electrocardiogram abnormal.

9) Hemolytic anemia (less than 0.1%)
Coombs positive hemolytic anemia may occur. Study drug administration should be discontinued if an abnormality is observed.

10) Interstitial pneumonia (less than 0.1%)
Subjects should be closely monitored for interstitial accompanied by pneumonia, cough, dyspnea, or chest X-ray abnormal. Study drug administration should be discontinued if an abnormality is observed, and appropriate treatment such as corticosteroid administration should be given.

11) Syndrome of inappropriate antidiuretic hormone secretion (less than 0.1%)
Given the possibility of SIADH secretion accompanied by hyponatremia, blood hyposmosis, increase in urine sodium excretion, hypersthenuria, convulsion, or consciousness disturbed, study drug administration should be discontinued if such symptoms appear, and appropriate treatment such as restriction of water intake should be given.

12) Hepatitis fulminant (less than 0.1%), hepatic function disorder (unknown frequency), jaundice (less than 0.1%)
Subjects should be closely monitored for hepatitis fulminant, hepatic function disorder, or jaundice. Appropriate treatment such as dose reduction, washout, or discontinuation should be given if an abnormality is observed.

13) Gastrointestinal hemorrhage, gastrointestinal ulcer, gastrointestinal perforation (less than 0.1% for all these conditions)
Subjects should be closely monitored for gastrointestinal hemorrhage, gastrointestinal ulcer, and gastrointestinal perforation. Appropriate treatment such as dose reduction, washout, or discontinuation should be given if an abnormality is observed.

14) Pancreatitis acute (less than 0.1%)
Subjects should be closely monitored for pancreatitis acute. Study drug administration should be discontinued if abnormal levels in serum amylase, serum lipase, or any other relevant levels are observed.

15) Hyperglycemia (less than 0.1%), aggravation of diabetes mellitus (less than 0.1%)
Hyperglycemia or aggravation of diabetes mellitus may occur, and serious cases with coma and ketoacidosis have been reported. Careful monitoring such as observation of blood sugar level or urine sugar should be made. Appropriate treatment such as study drug discontinuation should be given if an abnormality is observed.

16) Rhabdomyolysis (less than 0.1%)
Given the possibility of rhabdomyolysis, study drug administration should be discontinued if CPK increased, myoglobin blood increased, or urine myoglobin increased is observed, and appropriate treatment should be given.

[4] Other adverse reactions

Gastrointestinal	Nausea and vomiting, inappetence (10% or greater), diarrhea, stomatitis (1% to less than 10%), ileus, abdominal pain, constipation, bloating, and angular stomatitis (less than 1%)

Hypersensitivity	Rash, hot flush (less than 1%)
Neuropsychiatric	Peripheral neuropathy (e.g., numbness and paralysis) (1% to less than 10%)
	Language disorder, headache, dysgeusia, consciousness disturbed, orientation disturbed, convulsion, and Lhermitte's sign (less than 1%)
Hepatic	AST (GOT) increased, ALT (GPT) increased, ALP increased, and LDH increased (1% to less than 10%)
	Bilirubin increased, γ-GTP increased (less than 1%)
Cardiovascular	Palpitations, tachycardia, electrocardiogram abnormal, and Raynaud-like symptoms (less than 1%)
Electrolytes	Abnormal levels of serum sodium, potassium, chloride, calcium, phosphorus, magnesium, etc. (1% to less than 10%), tetany-like symptoms (less than 1%);
Skin	Alopecia (10% or greater), pruritus, pigmentation (less than 1%)
Other	General malaise (10% or greater), pyrexia (1% to less than 10%), dizziness, pain, anasarca, blood pressure decreased, hiccups, hyperuricemia, chest pain, and dehydration (less than 1%)

4.2.3.2

[1] Product name: Platosin® Injection, CISPLATIN for I.V. infusion "MARUKO"

[2] Ingredients/content: One vial of 20, 50, and 100 mL contains 10, 25, and 50 mg of CDDP, respectively.

[3] Significant adverse reactions and other adverse reactions

Materials: Refer to the drug package insert of Platosin® Injection and CISPLATIN for I.V. infusion "MARUKO."

4.2.4 Carboplatin (CBDCA)

4.2.4.1

[1] Product name: PARAPLATIN®FOR INJECTION 150 mg, PARAPLATIN®INJECTION

[2] Ingredients/content: One vial of 5, 15, and 45 mL contains 50, 150, and 450 mg of carboplatin, respectively.

[3] a) Serious adverse reactions

1) Bone marrow depression including pancytopenia (less than 0.1%)
Subjects should be closely monitored via peripheral blood tests for pancytopenia, anemia (hemoglobin decreased, erythrocytes decreased, and hematocrit decreased), white blood cell decreased, neutrophil decreased, platelets decreased, and hemorrhage. Appropriate treatment such as dose reduction, washout, or discontinuation should be given if an abnormality is observed.

2) Shock, anaphylactoid symptoms (less than 0.1%)
Subjects should be closely monitored for shock and anaphylactoid symptoms. Study drug administration should be discontinued if symptoms such as cyanosis, dyspnea, chest distressed feeling, blood pressure decreased, or bronchospasm appear, and appropriate treatment should be given. There is a trend of increasing frequency of shock and/or anaphylactoid symptoms as the number of times that the study drug is administered increases.

3) Interstitial pneumonia (0.1%)
Subjects should be closely monitored for interstitial pneumonia accompanied with a condition such as pyrexia, cough, dyspnea, and chest X-ray abnormalities. If an abnormality is observed, study drug administration should be discontinued, and appropriate treatment such as corticosteroid administration should be given.

4) Acute kidney injury (less than 0.1%), Fanconi syndrome (unknown frequency)
Subjects should be closely monitored for acute kidney injury or Fanconi syndrome. If abnormal levels in BUN, serum creatinine, creatinine clearance, or any other relevant levels are observed, appropriate treatment such as study drug discontinuation should be given.

5) Hepatic failure, hepatic function disorder, jaundice (unknown frequency for all these conditions)
Periodic tests and other measures should be taken to closely monitor subjects for hepatic failure,

hepatic function disorder, and jaundice. If an abnormality is observed, study drug administration should be discontinued, and appropriate treatment should be given.

6) Gastrointestinal necrosis, gastrointestinal perforation, gastrointestinal hemorrhage, gastrointestinal ulcer (unknown frequency for all these conditions)
   Subjects should be closely monitored for gastrointestinal necrosis, gastrointestinal perforation, gastrointestinal hemorrhage, and gastrointestinal ulcer. If an abnormality is observed, study drug administration should be discontinued, and appropriate treatment should be given.
7) Enterocolitis hemorrhagic, pseudomembranous colitis (unknown frequency)
   Subjects should be closely monitored for enterocolitis hemorrhagic and pseudomembranous colitis. If conditions including severe abdominal pain or diarrhea appear, study drug administration should be discontinued, and appropriate treatment should be given.
8) Ileus paralytic (less than 0.1%)
   Paralysis intestinal (including inappetence, nausea and vomiting, marked constipation, abdominal pain, abdominal distension or flaccidity, and intestinal stasis) can progress into ileus paralytic. Study drug administration should be discontinued if paralysis intestinal appears, and appropriate treatment such as intestinal decompression should be given.
9) Cerebral infarction (less than 0.1%), pulmonary infarction (unknown frequency)
   Subjects should be closely monitored for cerebral infarction and pulmonary infarction. Study drug administration should be discontinued if an abnormality is observed, and appropriate treatment should be given.
10) Embolism and thrombosis (unknown frequency)
    Subjects should be closely monitored for embolism and thrombosis (pulmonary embolism, cerebral thrombosis, or other arterial or venous thrombosis). Study drug administration should be discontinued if an abnormality is observed, and appropriate treatment should be given.
11) Myocardial infarction, cardiac failure congestive (unknown frequency)
    Given the possibility of myocardial infarction and cardiac failure congestive, study drug administration should be discontinued if an abnormality is observed, and appropriate treatment should be given.
12) Hemolytic uremic syndrome (unknown frequency)
    Periodic blood tests (including platelet count and erythrocyte count) and renal function tests should be performed to closely monitor for hemolytic uremic syndrome, which is mainly characterized by platelets decreased, hemolytic anemia, and renal failure. Study drug administration should be discontinued if an abnormality is observed, and appropriate treatment should be given.
13) Acute respiratory distress syndrome (unknown frequency)
    Subjects should be closely monitored for acute respiratory distress syndrome. Study drug administration should be discontinued if dyspnea progressing rapidly, hypoxia, or chest X-ray abnormal findings (e.g., bilateral, diffuse, or pulmonary infiltrates) are observed, and appropriate treatment should be given.
14) Disseminated intravascular coagulation (DIC) (unknown frequency)
    Subjects should be closely monitored for disseminated intravascular coagulation (DIC). Study drug administration should be discontinued if abnormal blood test results including platelet count, serum FDP level, or plasma fibrinogen level are observed, and appropriate treatment should be given.
15) Pancreatitis acute (unknown frequency)
    Subjects should be closely monitored for pancreatitis acute. Study drug administration should be discontinued if abnormal levels in serum amylase, serum lipase, or any other relevant levels are observed.

    b) Serious adverse reactions (similar drugs)

    1) Hypoacusis, deafness, tinnitus
       Cisplatin administration may result in high-frequency hypoacusis, deafness, or tinnitus. Therefore, the patient should be carefully monitored during and after administration.
    2) Papilledema, optic neuritis retrobulbar, and blindness cortical
       In rare cases, cisplatin administration may result in visual disturbances such as papilledema, optic neuritis retrobulbar, and blindness cortical. Study drug administration should be

discontinued if an abnormality is observed.

3) Hemolytic anemia
Cisplatin administration may result in Coombs positive hemolytic anemia. Study drug administration should be discontinued if an abnormality is observed.

[4] Other adverse reactions

Gastrointestinal	Nausea and vomiting, inappetence (10% or greater, or unknown frequency), diarrhea, stomatitis, abdominal pain, and constipation (1% to less than 10%), thirst (less than 1%)
Renal	Hematuria, proteinuria (1% to less than 10%); oliguria (less than 1%)
Hypersensitivity	Urticaria (10% or greater, or unknown frequency), rash (1% to less than 10%), pruritus (less than 1%)
Neuropsychiatric	Peripheral neuropathy (such as numbness), headache (1% to less than 10%), tinnitus, hypoacusis, visual impairment, dizziness, convulsion, dysesthesia, dysgeusia, nervousness, anxiety, and sleeplessness (less than 1%)
Hepatic	ALT (GPT) increased (10% or greater, or unknown frequency), AST (GOT) increased, ALP increased, bilirubin increased, LDH increased, and γ-GTP increased (1% to less than 10%)
Cardiovascular	Electrocardiogram abnormal (extrasystoles), palpitation, blood pressure increased, blood pressure decreased, arrhythmia (tachycardia, bradycardia, atrial fibrillation, atrial flutter, atrioventricular block) (less than 1%)
Electrolytes	Abnormal levels of serum sodium, potassium, chloride, calcium, phosphorus, magnesium, etc. (1% to less than 10%), syndrome of inappropriate antidiuretic hormone secretion (less than 1%)
Skin	Alopecia (10% or greater, or unknown frequency), pigmentation, nail discoloration, skin disease (less than 1%)
Other	General malaise, asthenia, uric acid level increased, chills, dehydration, weight decreased, albumin decreased, dyspnea (10% or greater, or unknown frequency), pyrexia, edema (1% to less than 10%), pain, flushing, hot flashes, abdominal discomfort, hiccups, injection site reaction (such as redness, swelling, and pain), and hypoproteinemia (less than 1%)

4.2.4.2

[1] Product name: Carbomerck for Injection 1%

[2] Ingredients/content: One vial of 5, 15, and 45 mL contains 50, 150, and 450 mg of carboplatin, respectively.

[3] Significant adverse reactions and other adverse reactions
Materials: Refer to the drug package insert of Carbomerck for Injection 1%.

4.2.5 Doxorubicin (ADM)

[1] Product name: ADRIACIN® Injection 10

[2] Ingredients/content: One vial contains doxorubicin hydrochloride 10 mg (potency) listed in the Japanese Pharmacopoeia.

[3] Significant adverse reactions

1) Subjects should be closely monitored for myocardial disorder and cardiac failure. Study drug administration should be discontinued if an abnormality is observed. Care should be taken for the administration of a total dose of over 500 mg/m^2 because this dose results in the frequent onset of serious myocardial disorder.
2) Periodic tests and other measures should be taken to closely monitor subjects for bone marrow depression including pancytopenia, anemia, white blood cell decreased, neutrophil decreased, and platelets decreased or hemorrhage. Appropriate treatment such as study drug discontinuation should be given if an abnormality is observed.
3) Subjects should be closely monitored for shock. Study drug administration should be

discontinued if an abnormality is observed, and appropriate treatment should be given.

4) Intravesical therapy may cause contracted bladder (0.9%). Study drug administration should be discontinued if an abnormality is observed, and appropriate treatment should be given.

[4] Other adverse reactions

Cardiac	Electrocardiogram abnormal, tachycardia (5% or greater), arrhythmia, chest pain (0.1% to less than 5%)
Hepatic	Liver disorder (0.1% to less than 5%)
Renal	Proteinuria (0.1% to less than 5%)
Gastrointestinal	Inappetence, nausea and vomiting, stomatitis, diarrhea (5% or greater)
Skin	Alopecia (5% or greater), pigmentation (0.1% to less than 5%)
Neuropsychiatric	Malaise, headache (0.1% to less than 5%)
Urinary (at the intravesical instillation)	Pollakiuria, micturition painful, cystitis, hematuria (5% or greater), feeling of residual urine (0.1% to less than 5%)
Respiratory	Pneumothorax and hemothorax (patients with pulmonary metastasis) (unknown frequency)
Hypersensitivity	Rash (0.1% to less than 5%)
Other	Pyrexia (5% or greater), epistaxis (0.1% to less than 5%)

5. Treatment Plan and Subject Enrollment and Assignment

5.1 Study method

5.1.1 Study design

Multicenter randomized phase III trial using the central registration system

5.1.2 Subject enrollment

[1]. Enrollment method

Central registration system by fax

[2]. Enrollment procedures

(1) The principal investigator or subinvestigator at each facility will obtain written consent from patients who meet the eligibility criteria and to whom no exclusion criteria apply.

(2) "Subject Enrollment Form" (Appendix 2) filled in necessary items will be faxed to the JGOG Enrollment Center.

(3) The JGOG Enrollment Center will review the eligibility of patients enrolled on the basis of the Enrollment Checklist. Thereafter, the JGOG Enrollment Center will randomize patients into groups A, B, or C by using the minimization method, enter the enrollment number, body surface area, and dose in the "Enrollment Result Checklist" (Appendix 2), and fax it back to the principal investigator or subinvestigator at each facility. The investigator at each facility is responsible for the calculation of body surface area and dose; therefore, the body surface area and dose should be calculated again and reviewed at the facility.

(4) The principal investigator or subinvestigator at each facility will start treatment as soon as possible, but not later than 7 days after the receipt of the "Enrollment Result Checklist" from the JGOG Enrollment Center.

[JGOG Enrollment Center]

Clinical Trials Coordinating Center, Research Center for Clinical Pharmacology, Kitasato University

5-9-1 Shirokane, Minato-ku, Tokyo 108-8642

TEL: 03-5791-6400

FAX: 0120-579-183 (Toll free)

Office hours: Monday–Friday 9:00 a.m. to 5:00 p.m.

(Closed: Saturdays, Sundays, legal public holidays, November 5, and December 28 to January 3)

(On legal public holidays, faxed documents could be received, but enrollment might be conducted on the next working day)

[Inquiries regarding subject enrollment and other matters]

Nobuyuki Susumu, Hiroyuki Nomura

Department of Obstetrics & Gynecology, Keio University School of Medicine

35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582

TEL: 03-3353-1211 (extension: 62386) FAX: 03-3353-0249

E-mail: jgog2043@jgog.gr.jp

[3]. Enrollment precautions

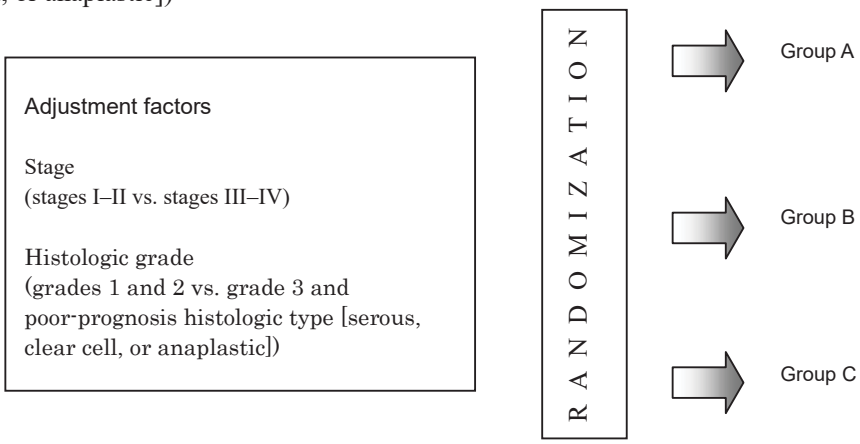
- The enrollment after the start of protocol study treatment is unacceptable without exception.
- The enrollment is accepted only when the "Subject Enrollment Form" is fully completed.
- The enrollment shall be made upon the receipt of the "Enrollment Result Checklist" that is issued after review of the eligibility by the JGOG Enrollment Center.
- Once a patient is enrolled, enrollment cannot be canceled (deletion from the database). If there are duplicate enrollments, information for the initial enrollment (enrollment number and assigned group) will be used.
- If any errors or duplicate enrollments are found, promptly contact the JGOG Enrollment Center.

[4]. Subject assignment

Treatment groups will be determined via dynamic random assignment.

Patients will be assigned in a 1:1:1 ratio to groups A, B, or C by using the minimization method based on the following adjustment factors.

1) Staging (stages I–II vs. stages III–IV)
2) Histologic grade (grades 1 and 2 vs. grade 3 and poor-prognosis histologic type [serous, clear cell, or anaplastic])



5.1.3 Treatment schedule

The following chemotherapy methods will be started as soon as possible but <u>not later than 7 days</u> after enrollment.

Group A:

AP therapy: doxorubicin + cisplatin			
Doxorubicin	60 mg/m^2	iv	Day 1
Cisplatin	50 mg/m^2	iv	Day 1
Every 3 weeks for six courses			

Group B:

DP therapy: ￥docetaxel + cisplatin			
Docetaxel	70 mg/m2	iv	Day 1
Cisplatin	60 mg/m2	iv	Day 1
Every 3 weeks for six courses			

Group C:

TC therapy: paclitaxel + carboplatin			
Paclitaxel	180 mg/m2	iv	Day 1
Carboplatin	AUC 6	iv	Day 1
Every 3 weeks for six courses			

[1]. Dose and dosing schedule

[1-1] Dose calculation method

The body surface area, which will be used to calculate the drug dose, will be determined using the DuBois formula (Appendix 10).

<u>However, the upper limit of the body surface area when calculating the drug dose is set as 2.0 m^2.</u>

1) Dose of ADM, CDDP, PTX, and DOC

The dose calculated per body surface area will be determined by truncating the figures after the decimal point.

2) Dose of CBDCA

The dose calculated using the Calvert formula will be determined by truncating the figures after the decimal point.

The dose calculated for CBDCA should not exceed 1,000 mg/body, and any dose calculated >1,000 mg/body should be considered as 1,000 mg/body.

Dose of CBDCA (mg/body) = Target AUC 6 × (GFR + 25)

For the GFR, the value calculated using the Jelliffe formula should be substituted.

$$\text{GFR} = \frac{98 - 0.8 \times (\text{Age} - 20)}{\text{Serum creatinine}} \times \frac{(\text{Body surface area}^{\#}) \times 0.9}{1.73}$$

#: Body surface area (m^2) = $71.84 \times H^{0.725} \times W^{0.425} \times 10^{-4}$
[W = Weight (kg); H = Height (cm)]
DuBois: Arch Intern Med 17:863, 1916
(Refer to the body surface area chart)

For the serum creatinine level, the use of the value obtained from multiple examinations is preferable.

No dose corrections should be made unless abnormal changes in the serum creatinine level over 1.5 mg/dL are observed after the start of protocol study treatment.

3) Dose corrections due to changes in body weight

No dose corrections should be made if the change in body weight after the start of treatment is within +/- 5 kg compared to the time of enrollment. However, if a change of over +/- 5 kg is observed, the dose shall be determined by recalculating the body surface area and GFR.

[1-2]. Group A: ADM + CDDP

ADM	60 mg/m^2	Intravenous administration within 10 minutes on Day 1
CDDP	50 mg/m^2	Intravenous administration over 120 minutes on Day 1

The above therapy is repeated as one course every 3 weeks for six courses.

a) Dosing method

1) Dissolve the required amount of ADM (60 mg/m^2) in water for injection or saline, and administer (infuse) the solution intravenously within 10 minutes.
2) Administer 1,000 mL of a starting electrolyte solution (equivalent to saline or half saline) for 240 minutes.
3) Remove the required stock solution of CDDP (50 mg/m^2), and mix it with 500 to 1,000 mL of saline or dextrose–saline solution. Infuse this mixed solution intravenously for a minimum of 120 minutes and a maximum of 180 minutes.
4) Administer 1,000 mL of a starting electrolyte solution (equivalent to saline or half saline) for 240 minutes after the dosing of CDDP.

b) Administration of infusion

The infusion will be given by using a method based on the usual CDDP dosing.

Infusion for CDDP (excerpted from the package insert)

1) Prior to CDDP dosing, 1,000 to 2,000 mL of appropriate fluids is given for at least 4 hours.

2) CDDP is mixed with 500 to 1,000 mL of saline or dextrose–saline solution depending on its dose at the time of CDDP dosing, and the mixed solution is infused intravenously for at least 2 hours. A prolonged infusion should be given under protection from light.
3) After CDDP dosing, 1,000 to 2,000 mL of appropriate fluids is given for at least 4 hours.
4) Attention should be paid to the maintenance of urine volume during CDDP dosing, and diuretics such as mannitol and furosemide should be administered as required.

Furthermore, it is necessary to maintain a certain level of renal blood flow and allow for diuresis on Day 2 to ensure the prevention of renal toxicity cause by CDDP. However, as described later, this therapy is likely to cause nausea and vomiting or inappetence, and it is highly likely that subjects will present with the signs and symptoms of dehydration and inadequate fluid intake on Day 2. Therefore, providing an adequate volume of infusion until at least Day 2 is preferable.

c) Measures for nausea and vomiting

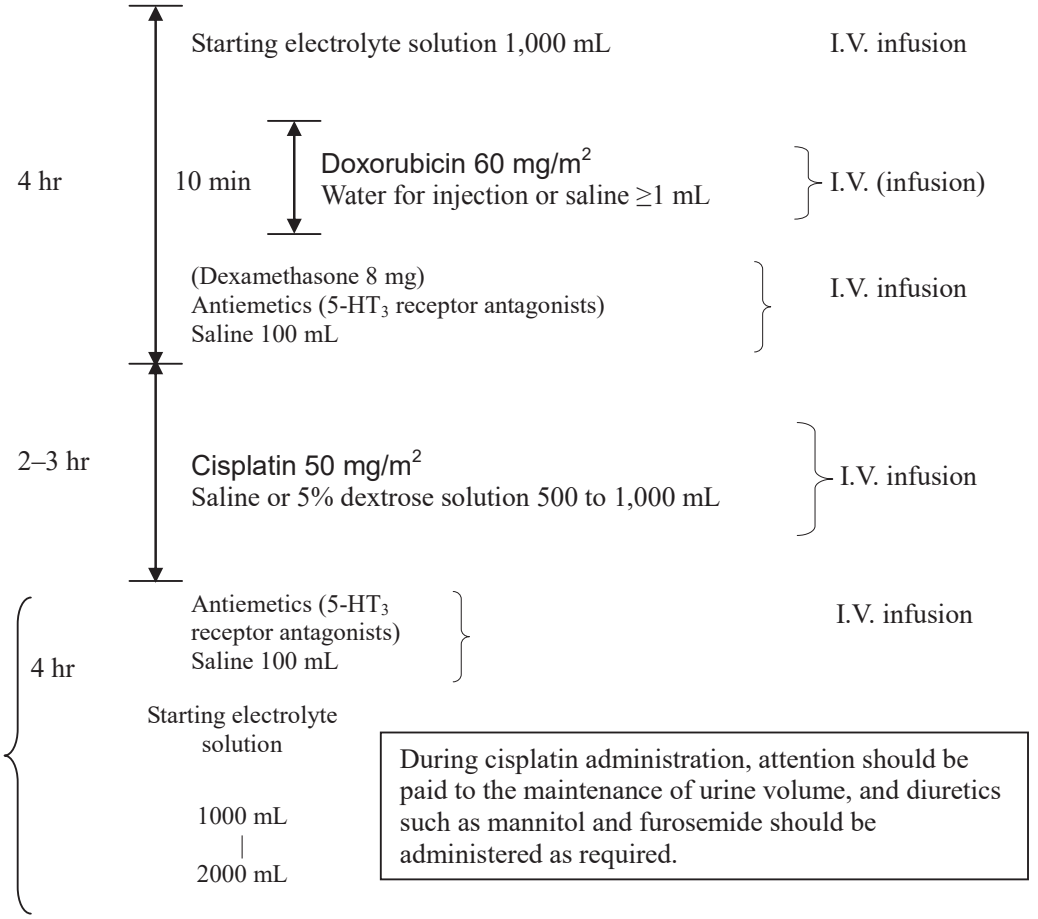
An aggressive prophylactic administration of a 5-HT_3 receptor antagonist (such as ondansetron and granisetron) and other kinds of antiemetics (such as steroids, metoclopramide, domperidone, and lorazepam) is recommended.

Specifically, the intravenous or oral administration of dexamethasone 8 to 20 mg with 5-HT_3 receptor antagonist on Day 1 is recommended to prevent acute vomiting (vomiting that occurred within 24 hours after the start of treatment). Twice-daily intravenous or oral administration of dexamethasone 4 to 8 mg on Days 2 to 4, together with twice- to four-times-daily intravenous or oral administration of metoclopramide 0.5 mg/kg, is recommended to prevent delayed vomiting (vomiting that occurred after 24 hours after the start of treatment). Furthermore, metoclopramide 0.5 mg/kg may cause extrapyramidal symptoms (drug-induced parkinsonism); therefore, a combination with promethazine hydrochloride (HIBERNA®) or biperiden (AKINETON®) is useful for the prevention of these symptoms.

«Reference» Dosing schedule

Group A: ADM + CDDP

Day 1



Combination with 5-HT_3 receptor antagonists, steroids, or metoclopramide will be aggressively conducted.

[1-3]. Group B: DOC + CDDP

DOC	70 mg/m^2	Intravenous administration over 60 minutes on Day 1.
CDDP	60 mg/m^2	Intravenous administration over 120 minutes on Day 1.

The above therapy is repeated as one course every 3 weeks for six courses.

a) Dosing method

1) First, administer DOC 70 mg/m^2. During the administration, dissolve the DOC in a total volume of reconstitution diluent to achieve a concentration of 10 mg/mL. (A total volume of reconstitution diluent is added to a vial of TAXOTERE and mixed slowly by inversion to avoid forming until a clear and homogeneous solution is obtained [for approximately 45 seconds]. After ensuring the homogeneity of the solution, it is allowed to stand for a few minutes until the form almost disappears. One mL of this solution [premixed solution] contains 10 mg of DOC.) Thereafter, remove the required amount of this premixed solution by using a syringe, and immediately mix it with 250 or 500 mL of saline or 5% dextrose solution. Infuse this mixed solution intravenously for a minimum of 60 minutes and a maximum of 120 minutes (if reconstitution diluent is used during preparation, the total volume must be used).
   The premixed solution should be adjusted using the following method if the reconstitution diluent containing ethanol is given to patients with hypersensitivity to alcohol.

   <Use of 5% dextrose solution or saline>
   Add 7 (1.8) mL of saline or 5% dextrose solution to 80 (20) mg TAXOTERE vial, shake vigorously, place the vial in an inverted position until the form almost disappears (for approximately 10 minutes), and ensure the homogeneity of the solution. If the solution is inhomogeneous, repeat mixing until the homogeneity is ensured. One mL of this clear and homogeneous solution contains 10 mg of DOC.
2) Administer a starting electrolyte solution of 750 to 1,000 mL (equivalent to saline or half saline) for 180 minutes immediately after the end of DOC dosing.
3) Remove the required stock solution of CDDP (60 mg/m^2) after the end of infusion, and mix it with 500 to 1,000 mL of saline or dextrose–saline solution. Infuse this mixed solution intravenously through the bypass connected to the saline line for a minimum of 120 minutes and a maximum of 180 minutes.
4) Administer 1,000 mL of a starting electrolyte solution (equivalent to saline or half saline) for 240 minutes after the dosing of CDDP.

b) Administration of infusion
   Infusion will be given with a method based on the usual CDDP dosing.

   Infusion for CDDP (excerpted from the package insert)
   1) Prior to CDDP dosing, 1,000 to 2,000 mL of appropriate fluids is given for at least 4 hours.
   2) At the time of CDDP dosing, CDDP is mixed with 500 to 1,000 mL of saline or dextrose–saline solution depending on its dose and is infused intravenously for at least 2 hours. A prolonged infusion should be given under protection from light.
   3) After CDDP dosing, 1,000 to 2,000 mL of appropriate fluids is given for at least 4 hours.
   4) During CDDP dosing, attention should be paid to the maintenance of urine volume, and diuretics such as mannitol and furosemide should be administered as required.

To ensure the prevention of renal toxicity cause by CDDP, it also seems to be necessary to maintain a certain level of renal blood flow and allow for diuresis on Day 2. However, as described later, this therapy is likely to cause nausea and vomiting or inappetence, and it is highly likely that subjects will present with the signs and symptoms of dehydration and inadequate fluid intake on Day 2. Therefore, it is preferable to give an adequate volume of infusion until at least Day 2.

c) Premedication

The administration of steroids for the prevention of allergy or edema during DOC dosing is optional at each facility but may be aggressively conducted. A specific example of administration is shown below as a reference.

<Reference example>

Oral administration of dexamethasone 8 mg/day (divided into twice) for a total of 3 days from the day before DOC dosing to the day after DOC dosing

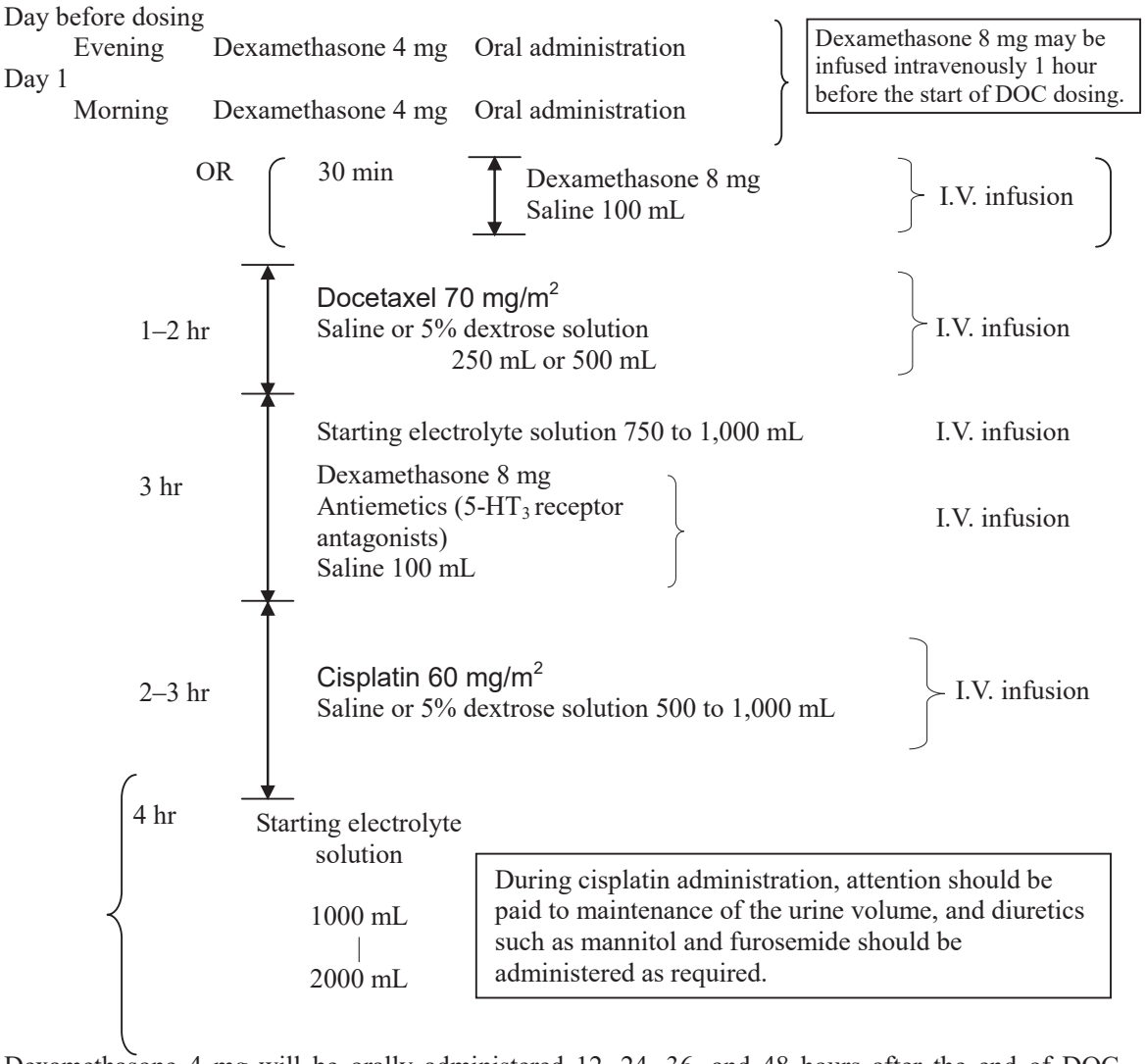
d) Measures for nausea and vomiting

The aggressive prophylactic administration of a 5-HT_3 receptor antagonist (such as ondansetron and granisetron) and other kinds of antiemetics (such as steroids, metoclopramide, domperidone, and lorazepam) are recommended.

Specifically, to prevent acute vomiting (vomiting that occurred within 24 hours after the start of treatment), dexamethasone 8 to 20 mg intravenous or oral administration with 5-HT_3 receptor antagonist on Day 1 is recommended. To prevent delayed vomiting (vomiting that occurred after 24 hours after the start of treatment), twice-daily intravenous or oral administration of dexamethasone 4 to 8 mg on Days 2 to 4, together with twice- to four-times-daily intravenous or oral administration of metoclopramide 0.5 mg/kg, is recommended. Furthermore, metoclopramide 0.5 mg/kg may cause extrapyramidal symptoms (drug-induced parkinsonism); therefore, combination with promethazine hydrochloride (HIBERNA®) or biperiden (AKINETON®) is useful for the prevention of these symptoms.

«Reference» Dosing schedule

Group B: DOC + CDDP



Dexamethasone 4 mg will be orally administered 12, 24, 36, and 48 hours after the end of DOC dosing.

Combination with 5-HT_3 receptor antagonists, steroids, or metoclopramide will be aggressively conducted.

[1-4]. Group C: PTX + CBDCA

PTX	180 mg/m^2	Intravenous administration for 3 hours on Day 1
CBDCA	AUC 6	Intravenous administration for 1 to 2 hours on Day 1

The above therapy is repeated as one course every 3 weeks for six courses.

a) Dosing method

1) After confirming that no occurrence of hypersensitivity reactions was observed with premedication, dissolve PTX 180 mg/m^2 in 250 to 500 mL of 5% dextrose solution or saline, and infuse the solution intravenously for 3 hours.
2) Mix the dose of CBDCA calculated using the Calvert formula with 250 or 500 mL of 5% dextrose solution or saline immediately after the end of PTX dosing, and infuse the mixed solution intravenously for 1 to 2 hours.

b) Short premedication

To prevent serious hypersensitivity associated with PTX dosing, the following premedication must be administered before PTX dosing: 30 minutes prior to PTX dosing, perform intravenous administration of dexamethasone sodium phosphate for injection (20 mg as dexamethasone), along with the oral administration of diphenhydramine hydrochloride tablet (50 mg as diphenhydramine hydrochloride) or chlorpheniramine maleate (2 mg as chlorpheniramine maleate), and intravenous administration of ranitidine hydrochloride for injection (50 mg as ranitidine) or famotidine for injection (20 mg as famotidine).

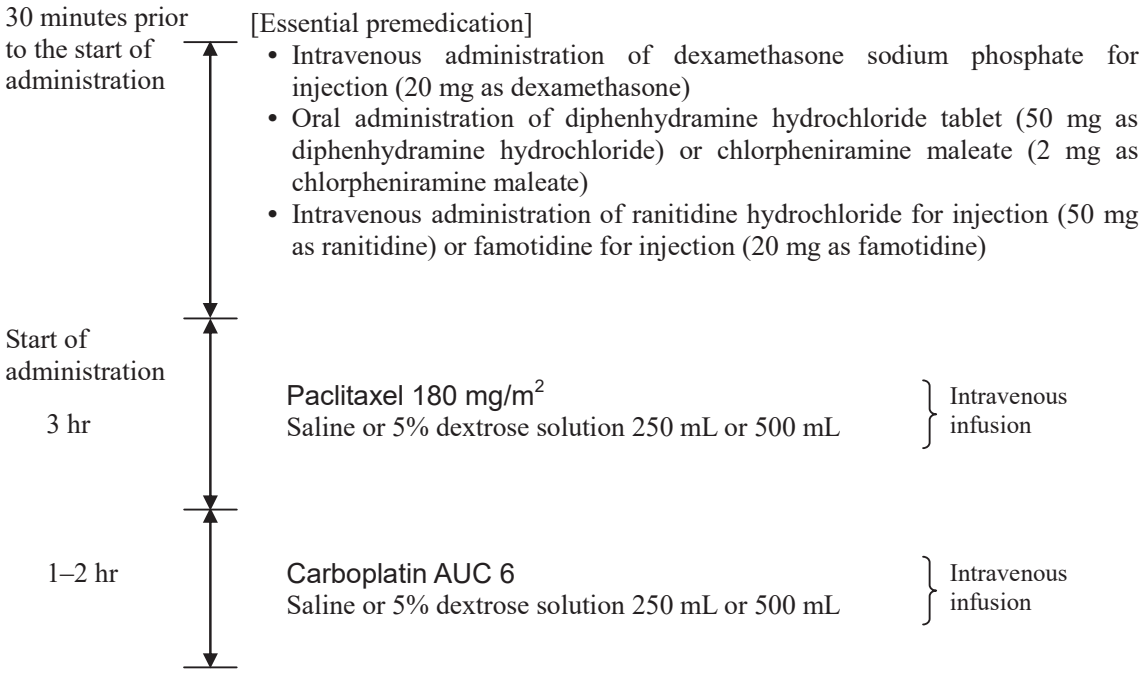
c) Device used for the administration of PTX

PTX should be administered through the in-line filter by using a membrane filter with a pore size of not more than 0.22 micron or less. Furthermore, a transfusion set that contains di-(2-ethylhexyl)phthalate (DEHP) as a plasticizer should not be used in areas touched by the PTX diluent.

«Reference» Dosing schedule

Group C: PTX + CBDCA

Day 1



5.2 Concomitant therapy during the treatment period

5.2.1 Prohibited concomitant therapies

[1] Treatment expecting antitumor effects

No treatments (including other antineoplastic drugs, hormone therapy, BRM, and radiotherapy) or any other investigational drugs that could affect the evaluation of this study will be permitted for concomitant use.

5.2.2 Permitted concomitant therapies and supportive care

Symptomatic treatment for treating an adverse reaction or adverse event is permitted as needed when concomitant use is determined to be clinically unavoidable.

The recommended concomitant therapies and supportive care are described below. These procedures shall not be deemed a protocol deviation even if they are not implemented.

[1] Antiemetics

To reduce nausea and vomiting, the prophylactic and therapeutic administration of a 5-HT_3 receptor antagonist (such as ondansetron and granisetron) and other kinds of antiemetics (such as steroids, metoclopramide, domperidone, and lorazepam) is allowed and actively recommended.

[2] Symptomatic treatment when white blood cells and neutrophil decrease

The administration of G-CSF products is allowed in accordance with the following insurance coverage. Prophylactic administration starting from the initial administration of the study drug should be avoided as much as possible (reference: ASCO guidelines regarding the use of G-CSF products [Appendix 11]). The use of G-CSF products should be recorded in the case report form (Appendix 9). Furthermore, the administration date, duration, and dose, as well as the time course of neutrophil and white blood cell counts, should be recorded and monitored.

Start timing	• When a neutrophil count of less than 1,000/mm^3 and pyrexia (38 °C or more in principle) are observed • When a neutrophil count of less than 500/mm^3 is observed • When a neutrophil count of less than 1,000/mm^3 with pyrexia (38 °C or more in principle) or a neutrophil count of less than 500/mm^3 is observed in the previous course, when a neutrophil count of 1,000/mm^3 is observed after the same chemotherapy treatment
Dosage Administration method	• Filgrastim 50 μg/m^2, lenograstim 2 μg/kg, or nartograstim 1 μg/kg Once daily, subcutaneous injection • Filgrastim 100 μg/m^2, lenograstim 5 μg/kg, or nartograstim 2 μg/kg Once daily, intravenous administration
Discontinuation timing	• Administration will be stopped when the neutrophil count exceeds 5,000/mm^3 or more after the lowest level is reached. • The discontinuation or dose reduction of this drug will be considered when the neutrophil count recovers to 2,000/mm^3 or more with no symptoms of infection and when the safety of the patient from reactions to this drug are determined to have been secured.

[3] Presence of pyrexia of 38 °C (axillary temperature) or more

Every effort should be made to identify the causal bacteria and appropriate antibiotics administered. The selection should take into account that some antibiotics require caution regarding concomitant use with study drugs.

[4] Symptomatic treatment for hypersensitivity (Appendix 3)

If hypersensitivity occurs, symptomatic treatment is allowed to be performed as necessary. If hypersensitivity occurred in the previous course(s), the prophylactic administration of steroids and antihistamines is allowed from the next course onward.

[5] Symptomatic treatment for edema (Appendix 4)

If edema occurs, Symptomatic treatment is allowed to be performed as necessary.If edema occurred in the previous course(s), the prophylactic administration of steroids is allowed from the next course onward.

[6] Symptomatic treatment for infection or pyrexia from suspected infection

If infection or pyrexia from suspected infection occurs, symptomatic treatment is allowed to be performed as necessary. If infection or pyrexia from suspected infection occurred in the previous course(s), the prophylactic administration of antihistamines is allowed from the next course onward.

[7] Symptomatic treatment for other conditions

If concomitant treatment, such as symptomatic treatment (including blood transfusion) when adverse reactions other than those above occur, is determined to be unavoidable for this treatment, the treatment shall be performed as appropriate, and the name of the concomitant drug, administration period, dose, and any other relevant information shall be recorded.

5.3 Interactions

Care should be taken in the concomitant use of the following therapies and drugs:

a) Aminoglycoside antibiotics, vancomycin hydrochloride, amphotericin B for injection, furosemide: administration of these drugs may potentiate renal disorder and acoustic organ disorder. These drugs should be administered with care when used as concomitant therapy. (CDDP/CBDCA)
b) Phenytoin: it has been reported that plasma phenytoin concentration was reduced by CDDP. This drug should be administered with care when used as concomitant therapy.
c) Azole antifungals (such as miconazole), erythromycin, clarithromycin, cyclosporine, midazolam, etc.: These drugs are thought to inhibit P450-CYP3A4 or inhibit the metabolism of DOC by competing with DOC, thus resulting in an increase in blood DOC concentration and potentiating adverse reactions.
d) Vitamin A, azole antifungals (such as miconazole), macrolide antibiotics (such as erythromycin), steroidal hormones (such as ethinyl estradiol), dihydropyridine calcium channel blockers (such as nifedipine), cyclosporine, verapamil, quinidine, midazolam, and phenacetin: These drugs inhibit enzymes such as P450-CYP2C8 and CYP3A4, thus resulting in the inhibition of PTX metabolism, which increases blood PTX concentration.

6. Changes/Modifications in Treatment Details

The administration period and dose can be changed as follows in accordance with the adverse drug reactions or recovery.

6.1 Changes in administration period from course 2 onward

Confirm that the subject satisfies the following criteria before the scheduled start of administration from course 2 onward. If the subject does not meet the following criteria, postpone the administration of the next course.

However, from course 2 onward, if the following criteria are not met after a maximum of 6 weeks after the start of administration, discontinue the study drug administration for this study.

1) Hematologic toxic effects
   Neutrophil count 1,500/mm^3 or more
   Platelet count 75,000/mm^3 or more

   If the neutrophil count is less than 1,500/mm^3 or the platelet count is less than 75,000/mm^3 in the blood test results before the scheduled administration, postpone the administration of all drug agents. If postponed, wait until the neutrophil count and platelet count respectively recovered to 1,500/mm^3 or more and 75,000/mm^3 or more before starting administration.
   In the case of G-CSF product administration, observe the subject for at least 3 days after administration, and confirm that the neutrophil count is 1,500/mm^3 or more.
2) Liver dysfunction/renal dysfunction
   AST(GOT) 100 U/L or less
   ALT(GPT) 100 U/L or less
   (However, if hepatic function abnormalities are clearly due to liver metastasis, AST and ALT may be allowed up to 150 U/L.)
   Total bilirubin 1.5 mg/dL or less
   Serum creatinine 1.5 mg/dL or less
   If serum creatinine is over 1.2 mg/dL in group A (ADM + CDDP concomitant treatment) and group B (DOC + CDDP concomitant treatment), measure the creatinine clearance level. This measurement for creatinine clearance level is 50 mL /min or more.
3) Pyrexia/performance status
   Pyrexia: less than 38°C (axillary temperature)
   P.S.: two or less
4) Neurological disorder
   Grade 1 or less: normal. Or disappearance of deep tendon reflex or dysesthesia (including aching). No functional disorder
5) Edema
   Grade 1 or less: no edema. Or no symptoms and does not require treatment
6) Diarrhea
   Grade 1 or less: no diarrhe. Or no increase in bowel movement count of four times or more
7) Other grade 2 or lower nonhematologic toxic effects that the investigator determines as requiring postponement of administration

6.2 Changes in dose from course 2 onward (reduction)

If any of the adverse events listed below are observed during the previous course, the dose for the next course shall be reduced one level in accordance with the table below regardless of whether there is a causal relationship with the study drug administration.

Once a dose is reduced, administration will be continued at that dose. However, if any adverse events that conflict with the dose reduction criteria occur despite a reduction to Level -2, the study drug administration shall be discontinued (Level -3).

Study drug administration may also be reduced by the investigator when necessary. In such cases, the reason for postponement will be reported on the case report form (Appendix 9).

The dose-limiting factor differs for each drug agent, and the reduction criteria for each drug agent is designated as follows.

1). Group A: ADM + CDDP

1-1). Dose reduction criteria for ADM

<Adverse events>

(1) If febrile neutropenia [neutrophil count of less than 1,000/$mm^3$and pyrexia of 38.5 °C or more: grade 3] is observed
(2) If grade 4 neutropenia (neutrophil count of less than 500/mm^3) persisting for at least 5 days is observed
(3) If grade 3 or more nonhematologic toxicity is observed
(excluding nausea/vomiting, inappetence, and fatigue)

However, if abnormalities in the general heart findings are observed and if LVEF is confirmed to be under 50%, 20%, or lower than the standard value, discontinue the drug administration for this study.

<Dose when there is a reduction>

Level	ADM dose (mg/m^2)
Level 0	60
Level -1	50
Level -2	40
Level -3	Discontinuation

1-2). Dose reduction criteria for CDDP

<Adverse events>

(1) If serum creatinine is over 1.2 mg/dL, measure the creatinine clearance level. This creatinine clearance level is less than 50 mL/min.
(2) If grade 3 or more nonhematologic toxicity is observed
(excluding nausea/vomiting, inappetence, and fatigue)

<Dose when there is a reduction>

Level	CDDP dose (mg/m^2)
Level 0	50
Level -1	40
Level -2	30
Level -3	Discontinuation

2). Group B: DOC + CDDP

2-1). Dose reduction criteria for DOC

<Adverse events>

(1) If febrile neutropenia [neutrophil count of less than 1,000/mm^{3}and pyrexia of 38.5 °C or more: grade 3] is observed
(2) If grade 4 neutropenia (neutrophil count of less than 500/mm^3) persisting for at least 5 days is observed
(3) If grade 3 or more nonhematologic toxicity is observed
(excluding nausea/vomiting, inappetence, and fatigue)

<Dose when there is a reduction>

Level	DOC dose (mg/m^2)
Level 0	70
Level -1	60
Level -2	50
Level -3	Discontinuation

2-2). Dose reduction criteria for CDDP
<Adverse events>
(1) If serum creatinine is over 1.2 mg/dL, measure the creatinine clearance level. This creatinine clearance level is less than 50 mL /min.
(2) If grade 3 or more nonhematologic toxicity is observed
(excluding nausea/vomiting, inappetence, and fatigue)

<Dose when there is a reduction>

Level	CDDP dose (mg/m^2)
Level 0	60
Level -1	50
Level -2	40
Level -3	Discontinuation

3). Group C ： PTX + CBDCA

3-1). Dose reduction criteria for PTX

<Adverse events>

(1) If febrile neutropenia [neutrophil count of less than 1,000/mm^{3}and pyrexia of 38.5 °C or more: grade 3] is observed
(2) If grade 4 neutropenia (neutrophil count of less than 500/mm^3) persisting for at least 5 days is observed
(3) If grade 2 or more peripheral neuropathy is observed
(4) If grade 3 or more nonhematologic toxicity is observed
(excluding nausea/vomiting, inappetence, and fatigue)

<Dose when there is a reduction>

Level	PTX dose (mg/m^2)
Level 0	180
Level -1	135
Level -2	110
Level -3	Discontinuation

3-2). Dose reduction criteria for CBDCA

<Adverse effects>

(1) If grade 3 or more platelets decreased (platelet count is less than $50,000/mm^3$) is observed
(2) If grade 3 or more nonhematologic toxicity is observed
(excluding nausea/vomiting, inappetence, and fatigue)

<Dose when there is a reduction>

Level	CBDCA dose
Level 0	AUC 6.0
Level -1	AUC 5.0
Level -2	AUC 4.0
Level -3	Discontinuation

6.3 Discontinuation criteria for protocol study treatment

If any of the following items are observed, the investigator will determine whether to discontinue the drug agent and observations, and tests and assessments at the discontinuation time point shall be conducted. The reason for discontinuation and the findings at the time of discontinuation shall be reported in the case report form (Appendix 9).

1) Occurrence of a serious adverse drug reaction (8.3.1 Adverse events requiring immediate reporting)
2) Apparent progression of a disease
3) When continuing the treatment is considered difficult because of a new accompanying disease or complication
4) Postponement of administration that exceeds the criteria in "6.1 Changes in administration period from course 2 onward" or changes that exceed the criteria in "6-2. Changes in dose from course 2 onward (reduction)"
   - When the subject does not satisfy the criteria for the next course even after a maximum of 6 weeks after the start of administration for the previous course
   - Occurrence of an adverse drug reaction in conflict with the dose reduction criteria in spite of a Level -2 reduction (Level -3)
   - When abnormality is observed in the general findings for the heart in group A (ADM + CDDP concomitant therapy) and when LVEF is confirmed and its value is <50% or >20% of the standard
5) When the patient requests to be discontinued
6) When protocol violation is found or ineligibility is found after the start of treatment
7) When the investigator determines that administration is difficult for reasons other than those stated above

7. Observation/Tests/Methods and Schedule

Observation/tests are conducted on the following items at the start of administration and for each course, and the results are entered into the case report form (Appendix 9).

If abnormal changes occur, record the degree and causal relationship with the study treatment drug in the case report form (Appendix 9).

7.1 Pre-enrollment evaluation items

The minimum pre-enrollment requisite evaluation items are listed below. The test date should be within 7 days from the scheduled start of the administration date.

7.1.1 Patient demographics

Subject initials, date of birth (age), medical record number (outpatient/hospitalization), enrollment date, date of consent form obtained, expected start date of treatment, primary tumor (primary tumor site, surgical staging, metastasis, and histological diagnosis), previous treatment (surgery, date of surgery, procedures, and content of hormonal treatment), surgical findings (status of lymph node dissection, degree of lesion infiltration, and histological differentiation), complications and treatment for complications, medical history, and history of hypersensitivity by allergic predisposition or a drug

7.1.2 Physical examination

General conditions (evaluation by five levels [0, 1, 2, 3, and 4] based on the grade [Appendix 5] of ECOG P.S.), body weight, body height

7.1.3 Subjective and objective symptoms

Evaluate the status before drug administration by using the NCI-Common Terminology Criteria for Adverse Events v3.0 (CTCAE) Japanese translation JCOG/JSCO version (Appendix 6).

7.1.4 Test items

The underlined items below are mandatory, but as many as possible of the other items should be conducted.

The test values should be obtained within 14 days before enrollment.

1) Hematology: red blood cell count, hemoglobin level, hematocrit level, white blood cell count, differential white blood count, neutrophil count, platelet count
2) Blood biochemistry test: total protein, albumin, total bilirubin, AST(GOT), ALT(GPT), Al-P, LDH, BUN, serum creatinine, electrolyte (Na, K, Cl, and Ca), etc.

The data for the following tests should be obtained within 21 days from the enrollment date (or 28 days from the scheduled start of the administration date).

1) Creatinine clearance
2) Twelve-lead ECG at rest
3) Calculation of LVEF level by cardioechography
4) Urine test: urine protein, urine sugar, urobilinogen

The data for the following tests should be obtained after surgery and within 21 days from the enrollment date.

1) Chest X-ray
2) Tumor marker (e.g., CA125)
3) CT or MRI

7.2 Tests and evaluations during the study period

The toxicity evaluation, clinical evaluation items required for efficacy evaluation, clinical tests, and imaging tests are described for each test interval.

7.2.1 Items to be evaluated once a week or more

The underlined items below are mandatory. The poorest values at each course should be noted.

1) Hematology: red blood cell count, hemoglobin level, hematocrit level, white blood cell count, differential white blood count, neutrophil count, platelet count
   (When the hematologic toxicity of grade 4 occurs, frequently conduct tests at intervals to confirm the persistence period of grade 4)

2) Blood biochemistry test: total protein, albumin, total bilirubin, AST(GOT), ALT(GPT), Al-P, LDH, BUN, serum creatinine, electrolyte (Na, K, Cl, and Ca), etc.

3) Urine test: urine protein, urine sugar, urobilinogen

7.2.2 Items to be evaluated at least once or more during each course

1) General condition: body weight, P.S.
2) Subjective and objective symptoms adverse event items in the NCI-CTCAE v3.0 Japanese translation JCOG/JSCO edition (Appendix 6). The poorest values at each course should be noted.
   (1) Allergy/immunity: allergic reaction
   (2) Gastrointestinal tract: inappetence, constipation, diarrhea, nausea, mucositis (stomatitis/pharyngitis), vomiting
   (3) Neurological: neuropathy (motor, sensory)
   (4) Pain: myalgia, arthralgia
   (5) Infection: febrile neutropenia, infection with neutropenia of grades 3 to 4, infection with normal neutrophil count or neutropenia of grades 1 to 2, and infection with unknown neutrophil count
   (6) General cardiology: left ventricular contractility dysfunction
   (7) Lymph nodes: edema
   (8) Dermatology/skin: alopecia, urticaria
   (9) Systemic symptoms: fatigue
   (10) Other

7.2.3 Tests to be appropriately performed as necessary

1) CT • MRI
2) Abdominal X-ray, chest X-ray, and chest CT
3) Creatinine clearance
4) Twelve-lead ECG at rest
5) Calculation of LVEF level by cardioechography
6) Tumor marker (e.g., CA125)
7) Other

7.3 Follow-up

Follow-ups will be performed for all subjects who received protocol study treatment, including the confirmation of the presence/absence of progression and the lesion findings (CT or MRI) regarding the confirmation of vital status at least every 6 months up to the fifth year counted from the day of enrollment. However, this will not apply to subjects who refuse to cooperate with follow-up.

7.4 Test observation items and implementation time

Perform the above observation/test/evaluation according to the implementation schedule shown below.

Items		Before enrollment	Course 1			Courses 2 to 6			Follow-up
			Week 1	Week 2	Week 3	Week 1	Week 2	Week 3	
Body height, body weight, P.S.		◎[4)]	◎[5)]	○	○	◎[5)]	○	○	(Perform appropriately as needed)
Adverse event		◎[4)]	◎[5)]	○[3)]	○[3)]	◎[5)]	○[3)]	○[3)]	
Clinical laboratory tests	General blood	◎[2)]	◎[5)]	○[3)] ---------		◎[5)]	○[3)] --------		
	Blood biochemistry	◎[2)]	◎[5)]	○----------		◎[5)]	○----------		
	Creatinine clearance	◎[2')]	----------(Perform appropriately as needed)----------						
ECG, cardioechography (LVEF)		◎[2')]	----------(Perform appropriately as needed)----------						
CT・MRI		○[1)]	-------(At least once every 6 months and perform appropriately as needed)-------						
Chest X-ray		○[1)]	---------- (Perform appropriately as needed)----------						
Tumor markers (e.g., CA125)		○[1)]	----------(Perform appropriately as needed)----------						
Abdominal X-ray, chest CT		----------(Perform appropriately as needed))----------							

◎: Mandatory ○: Perform as much as possible ----- : Perform as needed

1) Performed within 21 days before enrollment and after surgery
2) Performed within 14 days before enrollment
2') Performed within 21 days before enrollment or within 28 days before the scheduled start of administration
3) The poorest values at each course should be noted for adverse events.
4) Performed within 7 days of the scheduled start of administration
5) Performed before each administration (third week of the previous course) (However, data before enrollment is allowed for course 1.)

8. Adverse Events

8.1 Expected adverse drug reactions

Refer to "4-0. Drug information" for the details on the adverse reactions for antitumoral drugs used in this study. The expected adverse reactions and approximate frequency for each reaction in the groups of this study are shown below.

8.1.1 Adverse reactions expected for group A: ADM + CDDP (Feasibility test)

Expected adverse reactions	Occurrence of grade 3 or more
Neutropenia	91%
Leukopenia	64%
Infection	14%
Febrile neutropenia	5%
Vomiting	5%

8.1.2 Adverse reactions expected for group B: DOC + CDDP (JGOG2041 study)

Expected adverse reactions	Occurrence of grade 3 or more
Neutropenia	87%
Leukopenia	77%
Infection with grades 3–4 neutropenia	17%
Hemoglobin level decreased	10%
Inappetence	17%
Diarrhea	17%
Nausea	13%
Peripheral neuropathy (grade 2 or more)	0%

8.1.3 Adverse reactions expected for group C: PTX + CBDCA (JGOG2041 study)

Expected adverse reactions	Occurrence of grade 3 or more
Neutropenia	80%
Leukopenia	53%
Hemoglobin level decreased	30%
Platelets decreased	27%
Febrile neutropenia	7%
Peripheral neuropathy -motor- (grade 2 or more)	17%
Peripheral neuropathy -sensory- (grade 2 or more)	20%
Nausea	13%
Inappetence	13%

8.2 Compensation for health hazards

The medical expenses generated by participating in this study shall be covered by the health care insurance system. No compensation shall be provided if a health hazard occurs to a subject owing to participation in this study, and the subject shall be treated under normal medical treatment and under general medical practice.

8.3 Adverse events that must be reported

8.3.1 Adverse events that have emergency reporting obligation

The following adverse events are the target of emergency reporting:

1) All deaths within 30 days from the final protocol study treatment date or during protocol study treatment
   Regardless of causal relationship with protocol study treatment. When the subject has discontinued protocol study treatment, even if subsequent treatment has already started, it is the target of emergency reporting if it is within 30 days of the final protocol study treatment date ("30 days" is counted by designating the final protocol study treatment day as Day 0 and starting the count from the next day to 30 days).
2) Unexpected grade 4 nonhematologic toxicity (adverse events other than those in the blood/bone marrow classification of NCI-CTCAE v3.0)
   Adverse events that are not described as "serious adverse reactions" in "4-2. Supply of drugs" is a target for emergency reporting.

8.3.2 Adverse events that have normal reporting obligation

The following adverse events are the target of normal reporting.

1) All deaths after 31 days from the final protocol study treatment date wherein a causal relationship with the protocol study treatment cannot be ruled out
   This is applicable to deaths that are suspected as related to treatment but are not applicable to deaths that are clearly due to the primary disease.
2) Expected grade 4 nonhematologic toxicity (adverse events other than those in the blood/bone marrow classification of NCI-CTCAE v3.0)
   This is applicable to grade 4 nonhematologic toxicity among adverse events described as "serious adverse reactions" in Section 4-2. Note that even if they are expected, serious adverse events are the target of normal reporting.
3) Unexpected grade 2/grade 3 adverse events
   Applicable to grade 2/grade 3 adverse events that are not included in "4-2. Supply of drugs" or the package insert of the drug agent (Appendix 8).
4) Permanent or significant disability
   Aplastic anemia, myelosplastic syndrome, secondary cancer, etc.
5) Other serious medical events
   Those determined as important information that should be shared among the lead principal investigators and within the research groups that do not fall under 8-3-1. 2) and 8-3-2. 1) to 4).

8.4 Reporting obligation and reporting procedures to the principal investigator of the facility

8.4.1 Emergency reporting

When an adverse event that is the target of emergency reporting occurs, the doctor in charge notifies the principal investigator of the facility. If the principal investigator of the facility cannot be contacted, the doctor in charge or the facility coordinator must perform the responsibilities of the principal investigator of the facility as a substitute.

Primary report:
The principal investigator of the facility must enter the designated items in the report regarding adverse drug reactions (Appendix 7) within 72 hours of knowing about the occurrence of the adverse event, send a fax, and then call the research secretariat and JGOG Data Center.

Secondary report:
The principal investigator of the facility enters the designated items in the report regarding adverse drug reactions (Appendix 7), separately prepares a case report (A4: format is free) with more detailed information, and sends these two documents by mail or fax to the research secretariat and JGOG Data Center within 7 days. To prioritize the prompt notification of information, it is allowable to leave the undetermined sections blank.

Tertiary report:
The principal investigator of the facility enters all the blank items in the report regarding adverse drug reactions (Appendix 7) and sends the document by mail or fax to the research secretariat and JGOG Data Center within 15 days. If an autopsy was performed, attach the "autopsy report."

8.4.2 Ordinary report

The principal investigator of the facility enters the designated items in the report regarding adverse drug reactions (Appendix 7) and sends the document by mail or fax to the research secretariat and JGOG Data Center within 15 days of knowing about the occurrence of the adverse event.

8.5 Treatment group–specific treatment and study discontinuation

When a serious adverse event that may lead to the discontinuation of a treatment group–specific treatment (limited to group B or C) occurs during the study, the lead principal investigator or research secretariat will consult the Data Monitoring Safety Committee regarding the handling of the study including discontinuation upon discussion with the JGOG Uterine Cancer Committee and Protocol Committee (15-9).

If the Data Monitoring Safety Committee recommends discontinuation, the research secretariat will immediately report the discontinuation of the study and the reason for discontinuation to the principal investigators of the facilities.

9. Evaluation Method and Its Criteria

9.1 Evaluation of efficacy

9.1.1 Progression-free survival (PFS)

The period starting from the date of enrollment to count the days to the earliest event wherein an event is a day when confirmed as progression or day of death, regardless of cause.

- "Progression" includes both relapse or progression based on the imaging and progression of symptoms (clinical progression) that cannot be confirmed by diagnostic imaging. The determination of progression for cases with measurable lesions at enrollment will refer to the determination criteria in the RECIST (Response Evaluation Criteria in Solid Tumors) guidelines.
- In surviving cases wherein no progression is confirmed, the latest date confirmed as no progression (final progression-free survival date) will be the cutoff. The date of confirmation of no progression will be the latest date on which no progression is confirmed by the image or from the clinical standpoint.
- In cases discontinued owing to toxicity or refusal by the subject, handle these cases in the same manner for events and cutoff even in cases wherein other treatments are added as posttreatment. In other words, the study discontinuation date and start of posttreatment date are not the cutoff.
- If the progression diagnosis is performed by diagnostic imaging, the event is not the test date when "suspected relapse by imaging" but is the "test date" of the imaging test when "definite diagnosis" is obtained on a later date. If progression was confirmed clinically without depending on diagnostic imaging, the event is the date confirmed as progression.
- If a definite diagnosis of relapse is made by biopsy, it is considered an event on the clinical diagnosis date if a diagnosis of clinical relapse was obtained. If relapse was diagnosed on the basis of biopsy diagnosis because the diagnosis could not be made clinically, it is considered an event on the date of biopsy.
- An increase in tumor markers alone is not considered a progression.
- To perform an objective evaluation of the measurable lesions, measurements and evaluation are performed using the same method.
- Confirmation of lesion findings is also conducted as necessary during chemotherapy.
- The confirmation of events after the completion of chemotherapy is conducted at least every 6 months from the starting date for counting during the follow-up period.

9.1.2 Overall survival

Considering the date of enrollment as the date to start counting the days until the date of death from any cause as an event, the period is from the start of counting date until the event.

- In surviving cases, the cutoff will be the last date that the subject is confirmed to be alive.
- In cases lost to follow-up, the cutoff will be the last date that the subject is confirmed to be alive prior to being lost to follow-up.
- The confirmation of events after chemotherapy is conducted at least every 6 months from the starting date for counting during the follow-up period.

9.2 Other endpoints

9.2.1 Incidence rate of adverse events

The NCI-Common Terminology Criteria for Adverse Events v 3.0(CTCAE) Japanese edition JCOG/JSCO edition (Appendix 6) will be used for grading adverse events. The causal relationship with the protocol study treatment will be determined into the following two categories.

1. No reasonable possibility: The causal relationship between the relevant adverse event and study treatment is considered unlikely because of temporal relations, reasons related to the intervention of another drug/treatment, or reasons that adequately explain the absence of a causal relationship with the study treatment.

2. Reasonable possibility: The causal relationship between the relevant adverse event and study treatment is considered possible because of temporal relationship, reasons related to the intervention of another drug/treatment, or reasons that adequately explain the absence of a causal relationship with the study treatment.

9.2.2 Tolerability

Regarding administration status, the reasons for dose reduction, postponement, discontinuation and treatment refusal, dose per course, total dose, dose intensity[1)], relative dose intensity[2)], and cumulative dose intensity[3)] shall be tabulated (by group).

1) Dose intensity: dose per week per case
2) Relative dose intensity: ratio of the dose of the planned weekly dose and weekly dose actually administered for each case
3) Cumulative dose intensity: ratio of the planned total dose and actually administered total dose for each case

9.2.3 Lymph node dissection status

To investigate the implementation status of lymph node dissection in accordance with the handling rules for uterine cancer, the number of lymph node dissection by site per patient shall be tabulated, and the degree of lymph node dissection in each group will be compared and investigated.

9.2.4 Other

Within the range of results obtained via the case reports, other analyses may be conducted as necessary.

10. Statistical Considerations

10.1 Target number of subjects

780 subjects (260 subjects per group)

10.2 Rationale for target number of subjects

The GOG122 study reports that the 5-year PFS of AP therapy as postoperative chemotherapy for stages III–IV uterine cancer patients (residual tumor size under 2 cm) is approximately 42% [1]. The JGOG2033 study reported that the 5-year PFS of CAP therapy as postoperative chemotherapy for uterine cancer patients with over 1/2 of muscle layer infiltration was 82% [2]. These results cannot be used as the rationale for the target number of subjects in this study because the GOG122 study includes 20% serous adenocarcinoma and 50% histological differentiation at G3. The regimen used in the JGOG2033 study is CAP therapy, and it included 55% G1 cases.

In the NSGO EC-9501/EORTC-55991 study, the 5-year PFS of postoperative stages I, II, IIIa (positive for peritoneal cytodiagnosis only), and IIIc (positive for pelvic lymph node metastasis only) uterine cancer patients is reported as 72% for the postoperative radiotherapy group and 79% for the postoperative radiotherapy/chemotherapy (including AP therapy) combination group. The result of the uterine cancer treatment survey of JGOG participating facilities revealed the implementation of active postoperative chemotherapy for groups at high risk of relapse, which is the target of this study, by anticipating enrollment from a wide range of patients of stages III–IV complete implementation to stages I–II 1/2 of muscle layer infiltration at G2-3. The 5-year PFS for AP therapy in this study is predicted to be approximately 75%. If the hazard ratio of DP or TC therapy against AP therapy is approximately 63%, it is considered that the therapy of this study is a clinically significant therapy.

The enrollment period of this study will be designated as 4 years, the follow-up period after enrollment is completed as 5 years, and the two-sided significance level for the entire study is 5%. In this study, power is defined as the probability of detecting at least one pair with a difference in hazard (any-pair power), and this is designated as 80% or higher. An exponential distribution is assumed for the progression-free survival. Any-pair power was evaluated by Monte Carlo simulations (10,000 times) by using the above designated values and the closed testing procedures described in the "Statistical considerations" while changing the number of subjects. A similar Monte Carlo simulation (100 times) was performed while changing the seed value for random number generation, and 250 subjects was the number of subjects per group where the any-pair power stabilized and was over 80%. By taking into account that there may be several full analysis sets (FASs) and excluded cases, the target number of subjects per group was designated as 260 subjects. When the number of subjects was designated as 250, the all-pair power (probability of detecting all-pair differences) was stable and was over 80%; this approach was considered to guarantee sufficient power with this number of subjects.

10.3 Handling of patients

The Monitoring Committee will conduct the classification of patients into ineligible, discontinued/dropout, study protocol violation, noncompliance, etc.

In this study, the four types of analysis target populations, enrolled cases (ITT), FAS (full analysis set), PPS (per protocol set), and safety analysis target cases are defined below. In this study, the primary endpoints, progression-free survival (PFS) and overall survival are analyzed using the FAS as the main analysis target population. To discuss the stability of the efficacy results targeting the FAS, tabulation analysis will be performed on the ITT and PPS. The safety analysis target population will be the main analysis target group for adverse event incidence and tolerability.

1) ITT

Subjects who have been confirmed by the enrollment center as being within the eligibility criteria designated in the study protocol, do not violating the ineligibility criteria, and were allocated to a treatment group.

2) FAS

Among the ITT, subjects who have been administered the study drug agent at least once. Subjects who were discovered after allocation to violate the eligibility or ineligibility criteria are excluded from the FAS.

3) PPS

Among FAS, subjects who have not had a major deviation from the study protocol regarding dose and dosing schedule.

4) Safety analysis target cases

Among ITT, subjects who have been administered the study drug at least once.

10.4 Statistical discussion

10.4.1 Main analysis regarding efficacy and determination criteria

The primary objective of this study is to evaluate AP therapy, DP therapy, and TC therapy ,which is considered the standard therapy for postoperative chemotherapy, by performing comparisons using progression-free survival in a high-risk group for endometrial cancer. In other words, against the null hypothesis:

H_{0DP}: Hazard of AP therapy = hazard of DP therapy

H_{0TC}: Hazard of AP therapy = hazard of TC therapy

Test which of the hypotheses has different hazards. Furthermore, the difference in progression-free survival period between the study therapies, DP therapy and TC therapy, in other words, test the following:

H_{0DT}: Hazard of DP therapy = Hazard of TC therapy

When multiple study groups are compared each at a significance level of 5%, the problem of multiplicity arises when the significance level of the entire study increases over 5%. To avoid this problem, the following closed test procedures will be used. In other words, the new null hypothesis is as follows:

H_0: Hazard of AP therapy = hazard of DP therapy = hazard of TC therapy

This hypothesis is considered, and a hypothesis test is performed according to the following procedures:

Procedure 1) Perform log-rank test at a two-sided 5% significance level for null hypothesis H_0.

Procedure 2) If null hypothesis H_0 is rejected at a two-sided 5% significance level, perform the log-rank test at a two-sided 5% significance level for null hypotheses H_{0DP}, H_{0TC}, and H_{0DT}.

Procedure 3) If null hypothesis H_{0DP} is rejected at a two-sided 5% significance level, it is concluded that the hazard for AP therapy and DP therapy are statistically significantly different. If null hypothesis H_{0DT} is rejected at a two-sided 5% significance level, it is concluded that the hazard for DC therapy and TC therapy are statistically significantly different.

PFS function is estimated by the Kaplan–Meier method for each treatment group and drawn in a figure. To calculate the survival rate for each year, the Greenwood method is used with a two-sided 95% confidence interval.

10.4.2 Tabulation of secondary endpoints

In tabulation analysis of secondary endpoints, adjustment for multiplicity will not be performed.

10.4.2.1 Overall survival

Overall survival is estimated by the Kaplan–Meier method for each treatment group and drawn in a figure. To calculate the survival rate for each year, the Greenwood method is used with a two-sided 95% confidence interval. To investigate the difference among treatment groups, the log-rank test with a two-sided 5% significance level is performed.

10.4.2.2 Adverse event incidence

The number of cases of occurrences of adverse reactions/adverse events per treatment method, incidence, number of occurrences per grade, and incidence of over grade 3 shall be calculated. To compare the incidence of adverse reactions/adverse events and incidence of over grade 3 between treatment groups, the odds ratio will be calculated with a two-sided 95% confidence interval. To investigate whether there is a difference in grade distribution, a Mantel test with a two-sided 5% significance level will be performed.

10.4.2.3 Tolerability

The ratio of reduced/postpones or discontinued subjects per treatment method, ratio of courses reduced/postponed against number of actual courses administered, ratio of number of actual courses administered against the scheduled number of courses (six courses), median of dose intensity, and median of relative dose intensity shall be calculated. To compare the ratios, Fisher's exact test will be used with interval estimate as the exact 95% confidence interval for a binomial distribution.

10.4.2.4 Investigation of subpopulations and analysis using statistical models

To consider the stability of the results of PFS period and OS period targeting the FAS, an investigation on a subpopulation with allocation adjustment factor and patient characteristic factor as stratification factors will be performed. An analysis using statistical models will also be performed.

10.5 Final analysis

After the completion of the follow-up period, an analysis of all endpoints will be conducted at the JGOG Data Center after data lock.

11. Study Period

11.1 Study implementation period

Enrollment period: 4 years from October 2006

Follow-up period: 5 years after the completion of enrollment

(However, the period may be extended or shortened depending on the enrollment status of the subjects.)

12. Ethical Considerations

12.1 Protection of patients

This study shall comply with the ethical principles based on the Declaration of Helsinki and shall be conducted in accordance with the "Guidelines for Clinical Evaluation Methods for Anti-tumoral Agents." Furthermore, it shall comply with GCP.

12.2 Items regarding patient consent

The "Information Sheet/Consent Form" (Appendix 1) shall be given to all applicable patients for enrollment prior to the start of this study, and thorough explanations of the objective of this study, the anticipated effects, and the side effects will be provided. Consent must be voluntarily obtained in writing to participate in this study. The consent form should have the date of consent, the signature of the patient who received the explanation and provided consent, and signature of the physician(s) who conducted the explanation. Create copies of the consent form, and provide one copy to the subject. If necessary, keep one copy at the clinical study management room in the facility. The original shall be kept in the medical record/card.

12.2.1 Content to be explained

- Nature of the study
- Objective of the study
- Name, job, and contact details of the physician in charge
- Study methods
- Anticipated advantages and disadvantages of this study
- Items regarding other therapy methods
- Period of participation in the study
- Withdrawal from the study
- Lack of disadvantage to the patient by not participating in the study or canceling participation
- Confidentiality measures for personal information
- Necessary treatment in the event of health damage
- Items required related to the study

12.3 Privacy protection and patient identification

The names of enrolled patients are not conveyed to the JGOG Data Center from participating facilities. Identification and inquiries about patients are conducted using the case registration number issued upon enrollment, patient initials, date of birth, or medical card number. Information that may directly identify the patient that cannot be obtained without the illegal access of a third person to staff or database in the facility (e.g., the patient's name) will not be registered in the database of the JGOG Data Center. If the initials or medical card number cannot be disclosed, the following conditions must be satisfied to participate in this study.

- An organization is permanently designated within the participating facility (e.g., clinical study management room), and a patient identification code is issued. Furthermore, a table that matches the ID with the real medical card number is managed.
  (Ideally, the management should not be performed by individuals such as the lead principal investigator at the facility or facility coordinator at the departmental laboratory but by a permanent organization within the facility.)
- The storage period for the table to match the patient ID with the real medical card number should not be shorter than the storage period for the medical card at the facility.
- When the facility auditing of JGOG is conducted, the auditing of the management system of the table to match the patient ID and real medical card number must be allowed.
- If the patient's initials are masked, the initials must be indicated as "X.X." to distinguish it as a dummy with no exceptions.

12.4 Protocol compliance

All researchers who participate in this study shall comply with the study protocol so that the patient's safety and human rights will be protected.

12.5 Approval of the ethics review board (institutional review board) of the facility

To participate in this study, this clinical study protocol and informed consent form for patients must be approved by the ethics committee or institutional review board (IRB) at each facility.

When approval is obtained from the IRB, the principal investigator, subinvestigator, or coordinator at each facility is required to fax a copy of the IRB approval document to the JGOG Secretariat. The original copy of the IRB approval document is stored at each facility, and a copy is kept at the JGOG Secretariat and the JGOG Data Center.

Mailing address for IRB approval documents (JGOG Secretariat)
Administration Office
NPO Japanese Gynecologic Oncology Group
Komatsu Building 4F, 6-22 Kagurazaka, Shinjuku-ku, Tokyo 162-0825
FAX：03-5206-1983 TEL： 03-5206-1982

12.6 Annual renewal of IRB approval

Whether the annual renewal of the review of this clinical study protocol and informed consent form for patients must be approved by the ethics committee or IRB at each facility will be decided by the rules at each participating facility.

12.7 Handling of changes to the clinical study protocol

When any changes to the clinical study protocol are required because of the safety information or any other relevant reason after the protocol is approved by the Clinical Trial Review・Ethics Committee, the change shall be classified and handled separately as either an amendment or revision depending on the details. In the case of a supplementary explanation that is not considered a change in the protocol, this shall be separately prepared as a memorandum. The definitions and handling are as follows.

1) Amendment
(1) Definition
An amendment is defined as a partial change to the study protocol in relation to the primary endpoint of the study or a change that may increase the risk incurred by participating subjects.
(2) Procedures
- When the lead principal investigator/research secretariat determines that there is a need to amend the study protocol, they shall discuss this with the Uterine Cancer Committee and the JGOG Data Center to determine whether an amendment should be suggested. If an amendment is to be suggested, the lead principal investigator/research secretariat will prepare an amended clinical study protocol.
- The chairperson of the Uterine Cancer Committee will request a review of the amended clinical study protocol to the Steering Committee to obtain their approval.
- The lead principal investigator/research secretariat will request a review of the amended clinical study protocol to the Clinical Trial Review • Ethics Committee via the JGOG Secretariat to obtain their approval.
- If approval for the amended clinical study protocol is obtained, the JGOG Secretariat will report the result to the Uterine Cancer Committee for this study, and the chairperson of the Uterine Cancer Committee will report the result to the Steering Committee.

(3) Notice and delivery of the amended clinical study protocol to members

- The JGOG Secretariat will post information regarding the amendment of the clinical study protocol together with its details on the JGOG website and then send it to all JGOG members by e-mail.
- The JGOG Secretariat will send the amended clinical study protocol with the amendment date (the date of approval by the Clinical Trial Review・Ethics Committee) on the cover page to the relevant participating facilities.

(4) Approval by the IRB at the facility

The review and approval by the IRB at each facility is required

2) Revision

(1) Definition

A revision is defined as a partial change to the study protocol that does not relate to the primary endpoint of the study and does not involve the possibility of increasing the risk that may be incurred by participating patients.

(2) Procedure for revision

- When the lead principal investigator/research secretariat determines that there is a need to revise the study protocol, they shall discuss this with the Uterine Cancer Committee and the JGOG Data Center to determine whether a revision should be suggested. If a revision needs to be suggested, the lead principal investigator/research secretariat will prepare a revised clinical study protocol.
- The lead principal investigator/research secretariat will report the revised clinical study protocol to the Clinical Trial Review・Ethics Committee via the JGOG Secretariat.
- The chairperson of the Uterine Cancer Committee will report the revised clinical study protocol to the Steering Committee.

(3) Notice and delivery of the revised clinical study protocol to members

- The JGOG Secretariat will post information regarding the revision to the clinical study protocol together with its details on the JGOG website and then send it to all JGOG members by e-mail.
- The JGOG Secretariat will send the revised clinical study protocol with the revision date (the date on which it was reported to the Clinical Trial Review・Ethics Committee) on the cover page to the relevant participating facilities.

(4) Approval by the IRB at the facility

The review and approval by the IRB will be according to the rules established at each facility.

3) Memorandum

(1) Definition

A memorandum is a supplemental explanation to the clinical study protocol distributed to members involved in this study to reduce variations in the interpretation of the written content or draw particular attention to an item. A memorandum does not refer to a change to the clinical study protocol.

(2) Preparation procedures

- When the lead principal investigator/research secretariat determines that a memorandum is needed, they shall discuss this with the Uterine Cancer Committee and the JGOG Data Center to determine whether a memorandum should be prepared. If one is to be prepared, the lead principal/research secretariat will prepare the memorandum.
- The lead principal investigator/research secretariat will report to the JGOG Secretariat that a memorandum is being prepared.

(3) Notice and delivery of the memorandum to members

- The JGOG Secretariat will post information regarding the preparation of a memorandum together with its details on the JGOG website and then send it to all JGOG members by e-mail.
- The JGOG Secretariat will send the prepared memorandum to the relevant participating facilities.

(4) Approval by the facility IRB

Review and approval by the IRB will be according to the rules established at each facility.

12.8 Amendment to the study protocol/approval of the facility IRB at revision

When there is a change to the study protocol or explanation document for the patient after obtaining approval of the Clinical Trial Review Committee during the study, the amended study protocol and explanation document will require approval from the ethics review committee (or IRB) of each facility. If the content modification is not an amendment but a revision, the review and approval from the ethics review committee (or IRB) at each facility will be in accordance with the rules of each facility.

If approval is obtained, the principal investigator, subinvestigator, or coordinator at each facility will send a copy of the document that was approved by the IRB to the JGOG Secretariat by fax (FAX: 03-5206-1983). The original copy of the IRB-approved document will be kept by the doctor in charge or the facility coordinator. The copies are kept by the JGOG Secretariat and the JGOG Data Center.

12.9 Study protocol preparation record

March 31, 2006	Proposal of the study protocol
August 5, 2006	Preparation of the initial version of the protocol, Version 1.0
August 31, 2006	Approval by the JGOG Clinical Trial Review Committee, Version 1.1
October 1, 2007	JGOG Clinical Trial Review Committee, Version 2.0
January 28, 2010	JGOG Clinical Trial Review Committee, Version 3.0

13. Monitoring, Audit, and Reporting Methods

13.1 Periodic monitoring

Periodic monitoring shall be performed to check whether the study is being conducted safely and in accordance with the study protocol. Periodic monitoring shall be performed twice a year. A monitoring report shall be prepared by the JGOG Data Center on the basis of entered data, such as those on collected "case report forms" (Appendix 9), and this report shall be delivered to the relevant participating facilities after being fixed via necessary procedures and evaluations. These procedures are stipulated as follows.

13.1.1 Monitoring procedures

1) The JGOG Data Center shall prepare a periodic monitoring report on the basis of entered data, such as those on "case report forms" (Appendix 9) that are collected at a frequency stipulated in the relevant study protocol, and send this report to the Monitoring Committee.
2) The Monitoring Committee consists of members from the Uterine Cancer Committee and the lead principal investigator/research secretariat. The Monitoring Committee shall select a committee chairperson from among the members of the Uterine Cancer Committee other than the chairperson of the Uterine Cancer Committee.
3) The chairperson of the Monitoring Committee at the relevant study shall provide a further review of the periodic monitoring report and finalize its details at the meeting of the Uterine Cancer Committee.
   The chairperson of the Monitoring Committee at the relevant study shall submit the periodic monitoring report to the Data Monitoring Safety Committee via the JGOG Secretariat. If the Data Monitoring Safety Committee has any opinions or questions concerning the monitoring report, they should report this within 2 weeks to the JGOG Secretariat.
4) The JGOG Secretariat shall post the periodic monitoring report on the JGOG website after approval by the Data Monitoring Safety Committee.

13.1.2 Items

1) Subject recruitment achievement status: number of enrolled subjects - cumulative/by period, all facilities/by facility
2) Eligibility: ineligible subjects/possibly ineligible subjects: group/facility
3) Reason(s) for study treatment discontinuation/end during study treatment or end of study treatment: group/facility
4) Demographic factors at enrollment: group
5) Serious adverse events: group/facility
6) Adverse reactions/adverse events: group
7) Protocol deviation (including subjects with possibility of deviation): group/facility
8) Content of surgical resection: group/facility
9) Survival period: all enrolled subjects
10) Any other issues related to study progress or safety

13.2 Protocol deviations and violations

A protocol deviation is defined as any procedures, such as drug administration, laboratory tests, or evaluation of toxicity or efficacy, that are not performed in accordance with the clinical study protocol.

With respect to monitoring, patients who deviate from a certain acceptable range that has been set by the JGOG Data Center, and the lead principal investigator and/or research secretariat will be listed in the monitoring report as "patients with possibility of deviation." These patients will be classified into one of the following categories after review by the research secretariat and the research group.

1) Violation

A deviation from the study protocol is a deviation that meets multiple items below and is defined as a “violation” in principle.

(1) A deviation that affects the evaluation of the endpoints of the study
(2) A deviation that is caused by the principal investigator/subinvestigator/facility
(3) A deviation that is deliberate or systematic
(4) A significant deviation or a deviation that is significantly dangerous

“Violations” will be described by the patient at the time of publication in research papers.

<Examples of violations>

- Other anticancer drugs or prohibited concomitant drugs are used during the protocol study treatment (including drug products and radiotherapy)
- A particular drug or drugs in the treatment regimen was not continuously used in a number of patients
- Substantial overdose

2) Deviation

A deviation is defined as one to which neither 1) violation nor 3) acceptable deviation applies.

If a specific deviation is commonly observed, the deviation shall be described at the time of publication in research papers.

3) Acceptable deviation

Any deviations that stay within the acceptable range that is set in advance or later between the research group or lead principal investigator/research secretariat and the JGOG Data Center will not be described in the monitoring report.

13.3 Facility on-site audits

An auditor designated by the Auditing Committee will visit the participating facilities to check the IRB approval documents and informed consent forms and verify the case report form data (direct access to source documents) in accordance with the auditing manual designated by the Auditing Committee. The audit results of each facility will be reported only to the lead principal investigator of that facility and to the Auditing Committee. If the results are published to any other entity, the name of the facility will be masked.

14. Publication of Research Results

The lead principal investigator may report the progress status of the research and the research results at the Ministry of Health, Labour and Welfare Research Project Research Presentations and in reports.

After the final analysis of the research results and after obtaining approval from the Data Monitoring Safety Committee, the main academic papers and academic conferences will be submitted to specialized journals or in English journals.

14.1 Rules related to authorship upon publication of academic papers

The authorship related to the publication of academic papers is as follows, in principle.

The first author of the study results academic paper publication shall be the person in charge of duties or the representative person of the facility with the most enrolled subjects (the selection of the lead author from the relevant facility will be at the discretion of the facility. However, the lead author should in principle be the person who contributed most to the study). However, the relevant facility shall choose whether or not to take authorship. The second author shall be the lead principal investigator (the proposer of the protocol of this study: the study chair), and the third author shall be the statistician at the JGOG Data Center (one person in charge at the time of analysis for publication). The other persons shall be the coauthors and shall be listed in descending order of facility enrollment number in accordance with the limitations set forth in the submission rules for each academic paper. When the representative person from the facility with the most enrolled subjects declines the first author position, the first author shall be the lead principal investigator, and the second author shall be the representative person from the facility with the most enrolled subjects.

Protocol Committee members may be included as authors depending on their contribution to the preparation and implementation of the research, such as contributing to the process of completing the study protocol and analysis of research results. All coauthors shall be only those who review and agree with the publication contents before submission. Gratitude to the data manager at the JGOG Data Center will be expressed in the acknowledgments.

Given the possibility that there may be several academic conferences, the right to give presentations shall be given in the following order: 1. the representative person from the facility with the most enrolled subjects, 2. the lead principal investigator, and 3. the representative person from facilities.

15. Research Organization

This clinical study will be conducted as a clinical research of the Japanese Gynecologic Oncology Group (JGOG) (Director: Kazunori Ochiai) based on a study protocol proposed by the Ministry of Health and Labour research group (Principal researcher: Daisuke Aoki, Sub-researchers: Noriyuki Katsumata, Kazushige Kiguchi, Satoru Sagae, Noriaki Sakuragi, Nobuyuki Susumu, Masahiro Takeuchi, Hiroshi Hoshiai, Ichio Fukasawa, Nobuo Yaegashi) which is part of the Health Labour Sciences Research Grant for Clinical Cancer Research, A study to establish standard chemotherapy for uterine cancer.

15.1 Research organization

Japanese Gynecologic Oncology Group (JGOG)
Uterine Cancer Committee, Chairperson: Nobuo Yaegashi
Department of Gynecology and Obstetrics, Tohoku University Medical School
1-1 Seiryomachi, Aoba-ku, Sendai-shi, Miyagi, 980-8574, Japan
TEL: 022-717-7251 FAX: 022-717-7258

15.2 Lead principal investigator

Department of Obstetrics and Gynecology, Keio University School of Medicine
Daisuke Aoki
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
TEL: 03-3353-1211 FAX: 03-3226-1667

15.3 Research secretariat

Department of Obstetrics and Gynecology, Keio University School of Medicine
Nobuyuki Susumu, Hiroyuki Nomura
5 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
TEL: 03-3353-1211 (extension: 62386) FAX: 03-3353-0249
E-mail: jgog2043@jgog.gr.jp

15.4 JGOG administration office

NPO Japanese Gynecologic Oncology Group Yukio Takahashi
Komatsu Building 4F, 6-22 Kagurazaka, Shinjuku-ku, Tokyo 162-0825
TEL: 03-5206-1982 FAX: 03-5206-1983
E-mail: info@jgog.gr.jp

15.5 JGOG Enrollment Center/JGOG Data Center

Clinical Trials Coordinating Center, Kitasato Academic Research Organization, Kitasato University
5-9-1 Shirokane, Minato-ku, Tokyo 108-8642
TEL: 03-5791-6400 FAX: 03-5791-6407
E-mail: jgog-dc@kitasato-ctcc.jp

JGOG Enrollment Center / JGOG Data Center
Research Center for Clinical Pharmacology, Kitasato Institute
Director: Masahiro Takeuchi

15.6 Statistical analysis

Shirou Takahashi
Biostatistics unit, School of Pharmacy, Kitasato University
5-9-1 Shirokane, Minato-ku, Tokyo 108-8642
TEL: 03-5791-6322 FAX: 03-3444-2546
E-mail: takahashifu@pharm.kitasato-u.ac.jp

15.7 Monitoring committee (JGOG) (refer to Appendix 1)

15.8 Auditing committee (JGOG) (refer to Appendix 1)

15.9 Clinical trial review committee (JGOG) (refer to Appendix 1)

15.10 Data monitoring safety committee (JGOG) (refer to Appendix 1)

15.11 Protocol committee (refer to Appendix 1)

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Study JGOG2043

Randomized phase III trial of
AP (doxorubicin + cisplatin) therapy,
DP (docetaxel + cisplatin) therapy,
and TC (paclitaxel + carboplatin) therapy
as adjuvant chemotherapy
for endometrial cancer at a high risk of recurrence

Statistical Analysis Plan

May 31, 2017

Version 2.1

Hirofumi Michimae
Masahiro Takeuchi

Department of Clinical Medicine (Biostatistics),
Research and Education Center for Clinical Pharmacy,
School of Pharmacy, Kitasato University

Author (statistician)		Date of creation
Approver (statistical analysis manager)		Date of approval

Establishment/Revision History

Version	Date of establishment/ revision	Author	Contents
1.0	November 28, 2016	Hirofumi Michimae	First version
2.0	March 28, 2017	Hirofumi Michimae	In Section “7.6. Chemotherapy,” handling of decimal places was defined.
2.1	May 31, 2017	Hirofumi Michimae	In Section “7.8. Adverse Events,” statistical tests were added. In Section “7.5. Lymph Node Dissection,” the collection item was changed from the number of lymph nodes to the number of subjects.

Table of Contents

1. Study Overview

1.1. Study Title

A randomized phase III trial of AP (doxorubicin [ADM] + cisplatin [CDDP]) therapy, DP (docetaxel [DOC] + CDDP) therapy, and TC (paclitaxel [PTX] + carboplatin [CBDCA]) therapy as adjuvant chemotherapy for endometrial cancer at a high risk of recurrence.

1.2. Objective

The main objective of this study is to compare the progression-free survival (PFS) between AP therapy (ADM + CDDP), DP therapy (DOC + CDDP), and TC therapy (PTX + CBDCA) as adjuvant therapy in patients with endometrial cancer who are at a high risk for recurrence.

1.3. Subjects

Patients with endometrial cancer who have undergone surgery and are at a high risk for recurrence.

1.4. Study Treatment

Group A: AP therapy, ADM 60 mg/m^2 + CDDP 50 mg/m^2, day 1, q3 weeks, 6 courses

On day 1, ADM 60 mg/m^2 will be intravenously infused within 10 minutes and then 1000 mL of starting electrolyte solution (at a concentration equal to normal or half saline) will be administered over 240 minutes, followed by intravenous infusion of CDDP 50 mg/m^2 over ≥120 minutes. Subsequently, 1000 mL of starting electrolyte solution will again be administered over 240 minutes to achieve adequate diuresis. This course will be repeated every 3 weeks for 6 courses.

Group B: DP therapy, DOC 70 mg/m^2 + CDDP 60 mg/m^2, day 1, q3 weeks, 6 courses

On day 1, DOC 70 mg/m^2 will be intravenously infused over ≥60 minutes and within 120 minutes. Immediately after the end of DOC infusion, starting electrolyte solution (at a concentration equal to normal or half saline) will be administered over 180 minutes, followed by intravenous infusion of CDDP 60 mg/m^2 over ≥120 minutes. After CDDP infusion, 1000 mL of starting electrolyte solution will again be administered over 240 minutes to achieve adequate diuresis. This course will be repeated every 3 weeks for 6 courses.

Group C: TC therapy, PTX 180 mg/m^2 + CBDCA AUC 6, day 1, q3 weeks, 6 courses

On day 1, PTX 180 mg/m^2 will be intravenously infused over 3 hours. Immediately after the end of PTX infusion, CBDCA AUC 6 will be intravenously infused over ≥60 minutes. This course will be repeated every 3 weeks for 6 courses.

1.5. Planned Sample Size and Study Period

780 subjects (260 subjects in each group)

Study period

Enrollment period: 4 years from October 2006

Follow-up period: 5 years after the end of enrollment
(Note that the period may be prolonged or shortened depending on the patient enrollment rate.)

1.6. Others

As per the protocol.

2. Rationale for Sample Size

Study GOG122, which evaluated AP therapy as adjuvant chemotherapy for patients with stage III to IV endometrial cancer (with residual disease of ≤2 cm), reported that the 5-year PFS rate was approximately 42%. Study JGOG2033, which evaluated CAP (cyclophosphamide + AP) therapy as adjuvant

chemotherapy for patients with endometrial cancer with myometrial invasion >50%, reported that the 5-year PFS rate was 82%. Because Study GOG122 also included 20% patients with serous adenocarcinoma and 50% patients with a histological differentiation grade of 3 and Study JGOG2033 used the CAP therapy regimen and included 55% patients with a histological differentiation grade of 1, the results cannot be used for the rationale for sample size calculation.

Study NSGO EC-9501/EORTC-55991, which was conducted in patients with stage I, II, IIIa (only positive peritoneal cytology), or IIIc (only positive pelvic lymph node metastasis) endometrial cancer who had undergone surgery, reported that the 5-year PFS rate was 72% in the adjuvant radiotherapy group and 79% in the adjuvant radiotherapy plus chemotherapy (including AP therapy) group. The endometrial cancer survey results from JGOG participating sites indicated that adjuvant chemotherapy was actively used for patients at high risk for recurrence, a target population in this study, and we expect patients with stage III to IV endometrial cancer who have undergone complete resection and those with stage I to II endometrial cancer with myometrial invasion >50% and a histological differentiation grade of 2 to 3 to be extensively enrolled in this study. We therefore estimated the 5-year PFS rate of AP therapy to be approximately 75% in this study. If the hazard ratio of DP or TC therapy to AP therapy is 63%, the study therapy is considered clinically relevant.

The enrollment period of this study will be 4 years and the follow-up period after the end of enrollment will be 5 years, with an overall two-sided significance level of 5%. The power is defined as the probability of detecting at least one of the pairs that are different in hazards (any-pair power) and set at ≥80%. We assume that the PFS follows an exponential distribution. While changing the sample size, we evaluated any-pair power based on the setting above and the closed testing procedure specified in “Statistical Considerations” in 10000 Monte Carlo simulations. While changing the seed value for random number generation, we ran 100 similar Monte Carlo simulations and estimated that a sample of 250 patients in each group would provide the trial with an any-pair power of constantly >80%. Taking the possibility of some patients excluded from the full analysis set (FAS) into account, the sample size is selected at 260 in each group. At a sample size of 250, the probability of detecting all of the pairs

that are different (all-pair power) constantly exceeds 80%, and this sample size is considered to ensure adequate power.

3. Selection of Subjects to Be Included in Analyses

In this study, three types of analysis sets, enrolled subjects (intention-to-treat [ITT]), FAS, and safety analysis set, are defined as follows:

1) ITT analysis set

Patients assigned to any of the treatment groups who meet all the inclusion criteria specified in the protocol and do not meet any of the exclusion criteria, as confirmed by the enrollment center.

2) FAS

Enrolled patients who received at least one dose of the study drug, except for those who failed to meet the inclusion criteria or met any of the exclusion criteria after assignment.

3) Safety analysis set

Enrolled patients who received at least one dose of the study drug.

At the time of study planning, we selected FAS as the original main analysis set for the primary endpoint “PFS” and the secondary endpoint “overall survival.” We planned analyses in enrolled subjects and the per-protocol set (PPS) to discuss the stability of efficacy results from the FAS. However, the JGOG Uterine Cancer Committee reviewed the analysis sets, taking into consideration recent trends, before starting the final follow-up of this study. Because approximately 10 years had passed since this study had been planned, they determined it was better to follow the recent trends. They changed the main analysis set to the ITT analysis set and also planned the analysis in the FAS.

This change was notified to all participating sites. The safety analysis set is still the main analysis set for the incidence of adverse events and treatment status, as originally planned.

4. Primary and Secondary Endpoints

4.1. Primary Endpoint and Criteria for Difference

The main objective of this study is to compare the PFS of DP therapy or TC therapy with that of AP therapy considered as a standard adjuvant chemotherapy in patients with endometrial cancer who are at high risk for recurrence. Specifically, we will test whether the hazards are different in either of the following null hypotheses:

H_{0DP}: Hazard of AP therapy = Hazard of DP therapy

H_{0TC}: Hazard of AP therapy = Hazard of TC therapy

Furthermore, to compare the PFS between the study therapies, DP therapy and TC therapy, we will test the following hypothesis:

H_{0DT}: Hazard of DP therapy = Hazard of TC therapy

Such multiple comparisons between groups, each at a significance level of 5%, result in an overall significance level of >5%, a problem known as multiplicity. To avoid multiplicity, the following closed testing procedure will be used in this study. We will test a new null hypothesis:

H_0: Hazard of AP therapy = Hazard of DP therapy = Hazard of TC therapy

in the following steps:

Step 1) The null hypothesis H_0 will be tested using the log-rank test at a two-sided significance level of 5%.

Step 2) Only when the null hypothesis H_0 is rejected at a two-sided significance level of 5%, the null hypotheses H_{0DP}, H_{0TC}, and H_{0DT} will be tested using the log-rank test at a two-sided significance level of 5%.

Step 3) When the null hypothesis H_{0DP} is rejected at a two-sided significance level of 5%, the test will conclude that the hazard of AP therapy is statistically significantly different from that of DP therapy. When the null hypothesis H_{0TC} is rejected at a two-sided significance level of 5%, the test will conclude that the hazard of AP therapy is statistically significantly different from that of TC therapy. When the null hypothesis H_{0DT} is rejected at a two-sided significance level of 5%, the test will conclude that the hazard of DP therapy is statistically significantly different from that of TC therapy.

4.2. Secondary Endpoints

In the analysis of secondary endpoints, no multiplicity adjustment will be performed.

(1) Overall survival

(2) Incidence of adverse events

(3) Treatment status

(4) Lymph node dissection

4.3. Subpopulation Analysis and Statistical Model-Based Analysis

To take account of the stability of results on PFS and overall survival in the ITT analysis set, subpopulation analysis will be performed using assignment adjustment factors and patient demographics as stratification factors. Statistic model-based analyses will also be performed.

5. Analysis Procedure

5.1. Software to Be Used

All statistical analyses will be performed using SAS System Version 9.4 or later (SAS Institute).

5.2. Analysis Reporting

Analysis results will be summarized in the statistical analysis report and in figures and tables for reporting.

5.3. Handling of Missing Data

No imputation will be performed for missing data.

6. Handling of Significance Level, Display Digit, Form, and Unknown Date

The significance level is set at 5% (two-sided); the confidence interval is set at 95% (two-sided). In principle, display digits for each value will be defined below.

(1) Display digit for each variable

Month: Displayed to one decimal place after the number of days is divided by 365.2425/12.

To list values entered in case report forms, however, original values will be presented.

(2) Display digit for statistics

Frequency: Displayed as an integer (e.g., 54).

Proportion: Displayed to one decimal place (e.g., 23.4%).

Maximum and minimum: Displayed to the same decimal places as the variable.

Mean and median: Displayed to one more decimal places than the variable.

Standard deviation: Displayed to two more decimal places than the variable.

P value: Displayed to four decimal places.

Confidence interval: Displayed in the same manner as point estimates (mean and median).

(3) Handling of unknown dates

Unknown date: If the year and month are known but the day is not known, the day is handled as 1.

For example, the available date information is only December 2015 (day unknown), the date is handled as December 1, 2015.

7. Analysis Method

7.1. Subject Disposition

- The disposition of enrolled patients (treatment group, treated/untreated, exclusion from the FAS) will be presented.
- A list of untreated subjects and subjects excluded from the FAS will be created.

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7.2. Subject Demographics

Subject demographics will be collected by treatment group in the ITT analysis set. The following items will be collected: age, performance status, histologic type, histological differentiation grade, FIGO stage, surgery type, presence/absence of residual diseases, and ascites cytology result. For categorical data, the number and percentage of subjects will be presented; for continuous data, the number of subjects, mean, standard deviation, median, minimum, and maximum will be presented.

7.3. Progression-Free Survival

The between-group difference in PFS will be tested according to the procedures described in Section 4.1. Primary Endpoint and Criteria for Difference.

The PFS function will be estimated by the Kaplan–Meier method in each treatment group and the curve will be depicted. The median PFS, if available, and its 95% confidence interval will be calculated. In calculating the annual PFS, a two-sided 95% confidence interval will be constructed using the Greenwood formula.

The PFS will be calculated by subtracting the date of enrollment from the date of occurrence of the progression event, death, or last survival confirmation and then adding 1 day.

7.4. Overall Survival

The overall survival function will be estimated by the Kaplan–Meier method in each treatment group and the curve will be depicted. The median overall survival, if available, and its 95% confidence interval will be calculated. In calculating the annual overall survival, a two-sided 95% confidence interval will be constructed using the Greenwood formula. To evaluate the difference in overall survival between treatment groups, a log-rank test will be performed at a two-sided significance level of 5%.

The overall survival will be calculated by subtracting the date of enrollment from the date of death, or last survival confirmation and then adding 1 day.

7.5. Site of Recurrence

The site of recurrence will be presented by subject. In each treatment group, the site of recurrence and the number of subjects with recurrence will be presented.

7.6. Lymph Node Dissection

To evaluate the status of lymph node dissection according to the rules for handling endometrial cancer, the number of dissected lymph nodes will be presented by site and group and depicted in a histogram.

In addition, the number of subjects with positive dissected lymph nodes will be presented by treatment group.

7.7. Chemotherapy

The following values will be calculated by treatment group: the proportion of subjects with dose reduction/postponement or discontinuation, the proportion of courses with dose reduction/postponement to courses with actual treatment, the proportion of courses with actual treatment to the planned courses (6 courses), median dose intensity, and median relative dose intensity. In addition, these proportions will be compared using the Fisher exact test, and interval estimation will be performed using the exact 95% confidence interval based on binomial distribution.

To evaluate treatment status, the following will be presented by group: dose reduction, postponement, discontinuation, reason for treatment rejection, dose in each course, and total dose. Dose intensity (DI)[1)], relative dose intensity (RDI)[2)], and cumulative dose intensity (CDI)[3)] will be presented by group and drug.

1) DI: weekly dose by subject

DI = total dose (mg)/total duration of treatment (week)

Total duration of treatment = ((start date of the last course − start date of Course 1 + 1)/7) + 3

The total duration of treatment is rounded off to two decimal places.

2) RDI: ratio of the actually administered weekly dose to the planned weekly dose by subject

RDI = DI (mg/week)/planned weekly dose (mg/week)

3) CDI: ratio of the actually administered total dose to the planned total dose by subject

CDI = Actual total dose (mg)/planned total dose (mg)

7.8. Proportion of Subjects Who Completed Treatment

Treatment completion status will be presented by treatment group in the ITT analysis set. The frequency and proportion will be collected. Subjects with the number of treatment courses of 0 will also be included in the analysis and for proportion calculation; they will also be included in the denominator.

7.9. Adverse Events

The number of subjects with adverse events and the incidence of adverse events will be calculated by grade and treatment group, and the incidence of grade ≥3 adverse events will be calculated by treatment group. To compare the incidences of grade ≥3 adverse events between treatment groups, an odds ratio will be calculated and its two-sided 95% confidence interval will be constructed. To examine whether the distribution of grades differs between treatment groups, the Mantel test will be performed at a two-sided significance level of 5%.

For the adverse events “Neuropathy/Motor” and “Neuropathy/Sensory,” if the grade is ≥2, odds ratio calculation and the Mantel test will be performed.

7.10. Serious Adverse Events

Subjects with serious adverse events will be summarized for immediate reporting or regular reporting.

7.11. Subpopulation Analysis and Statistical Model-Based Analysis

To take account of the stability of results on PFS and overall survival, treatment effects will be evaluated using the proportional hazard model with assignment adjustment factors as covariates.

8. Revision History (Ver. 2.0 → Ver. 2.1)

Section	Before change	After change	Reason
7.8. Adverse Events	None	For the adverse events "Neuropathy/Motor" and "Neuropathy/Sensory," if the grade is ≥2, odds ratio calculation and the Mantel test will be performed.	Requested by researchers (April 17, 2017).
7.5. Lymph Node Dissection	In addition, the number of positive dissected lymph nodes will be presented by site and treatment group.	In addition, the number of subjects with positive dissected lymph nodes will be presented by treatment group.	For consistency to the output plan (Mock TLFs) prepared upon researcher's requests (May 31, 2017).

End of text