Takei Y, Urabe M, Kume A, Machida S, Fujiwara H, Suzuki M, Ozawa K.: Suppression of lymph node and lung metastases of endometrial cancer by muscle-mediated expression of soluble vascular endothelial growth factor receptor-3. Cancer Sci 104:1107-1111,2013.

（研究分担者：青谷恵利子）

1. J.Westendorp L.Ness, A.Klimaszewski, K Willenberg, J Eggert, M.Bacon, J. Egger, M. Bacon, (Edited), Eriko Aotani, Yuko Saito, et al. The Manual for Clinical Trials Nursing, 3rd edition. Section XII International Clinical Trials Research – Chapter 60. Oncology Nursing Society: Pittsburgh: PA, 2014. In Press.
2. 谷岡哲也、上野修一、安原由子、真野元四朗、高橋みどり[監訳]【分担翻訳】青谷恵利子、上田伊佐子、大坂京子 他．Technological Competency As Caring in Nursing: A Model for Practice. 現代の看護におけるケアリングとしての技術力：実践のためのモデル 第２版. 第３章トロイの木馬の中にあるもの：テクノロジー、意識性、看護のメタパラダイム. ふくろう出版. 2013年10月18日.
3. 渡辺亨、大橋靖男、齋藤裕子、青谷恵利子【責任編集】【分担執筆】がん臨床試験テキストブック. [Principle and Practice of Clinical Trials in Oncology].医学書院. 2013年10月.
4. 秦友美、青谷恵利子、野中美和、川上温子、金津佳子、坪井沙絵、藤原恵一、紀川純三、落合和徳. がん領域における研究者主導臨床試験の安全性情報マネジメント. Jpn Pharmacol Ther 2013; 41 suppl 2 [Journal of Japan Society of Clinical Trials and Research] : S128-136. September 25, 2013.
5. Fujiwara K, Nagao S, Aotani E, Hasegawa K. Principle and evolving role of intraperitoneal chemotherapy in ovarian cancer. Expert Opin Pharmacother. 2013 Sep;14(13):1797-806.

（研究分担者：高野忠夫）

1. Takano T, Otsuki T, Tokunaga H, Toyoshima M, Utsunomiya H, Nagase S, Niikura H, Ito K, Yaegashi N, Yamada H, Tase T, Kagabu M, Shoji T, Sugiyama T, Sato N, Fujimoto T, Terada Y, Nakahara K, Kurachi H, Yokoyama Y, Mizunuma H, Soeda S, Nishiyama H, Matsumoto T, Sato S, Shimada M, Kigawa J.: Paclitaxel-carboplatin for advanced or recurrent carcinosarcoma of the uterus: the Japan Uterine Sarcoma Group and Tohoku Gynecologic Cancer Unit Study. Int J Clin Oncol. 2014 Jan 7.

2. Suzuki F, Nagase S, Suzuki K, Oba E, Hiroki E, Matsuda Y, Akahira J, Nishigori H, Sugiyama T, Otsuki T, Yoshinaga K, Takano T, Niikura H, Ito K, Sasano H, Yaegashi N.: Decreased expression of 14-3-3σ is predictive of poor prognosis for patients with human uterine papillary serous carcinoma. Tohoku J Exp Med. 2013;231(3):193-9.
3. Takano T, Niikura H, Ito K, Nagase S, Utsunomiya H, Otsuki T, Toyoshima M, Tokunaga H, Kaiho-Sakuma M, Shiga N, Nagai T, Tanaka S, Otsuki A, Kurosawa H, Shigeta S, Tsuji K, Yamaguchi T, Yaegashi N.: Feasibility study of gemcitabine plus docetaxel in advanced or recurrent uterine leiomyosarcoma and undifferentiated endometrial sarcoma in Japan. Int J Clin Oncol. 2013 Oct 24.
4. Niikura H, Kaiho-Sakuma M, Tokunaga H, Toyoshima M, Utsunomiya H, Nagase S, Takano T, Watanabe M, Ito K, Yaegashi N.: Tracer injection sites and combinations for sentinel lymph node detection in patients with endometrial cancer. Gynecol Oncol. 2013 Nov;131(2):299-303.
5. Kojimahara T, Nakahara K, Takano T, Yaegashi N, Nishiyama H, Fujimori K, Sato N, Terada Y, Tase T, Yokoyama Y, Mizunuma H, Shoji T, Sugiyama T, Kurachi H.: Yolk sac tumor of the ovary: a retrospective multicenter study of 33 Japanese women by Tohoku Gynecologic Cancer Unit (TGCU).Tohoku J Exp Med. 2013;230(4):211-7.

（研究分担者：榎本隆之）

1. Miyatake, T. Ueda, Y. Morimoto, A. Enomoto, T. Nishida, S. Shirakata, T. Oka, Y. Tsuboi, A. Oji, Y. Hosen, N. Nakatsuka, S. Morita, S. Skamoto, J. Sugiyama, H. Kimura, T., WT1 peptide immunotherapy for gynecologic malignancies resistant to conventional therapies: a phase II trial, J Cancer Res Clin, 139(3), 457-63, 2013
2. Hiramatsu, K. Ueda, Y. Yoshino, K. Fujita, M. Morii, E. Enomoto, T. Kimura, T., Conization using Shimodaira-Taniguchi procedure for adenocarcinoma in situ of the uterine cervix, Eur J Obstet Gyn R B, 168(2):218-21,DOI: 10.1016/j.ejogrb. [Epub ahead of print], 2013
3. Yokoyama, T. Yoshino, K. Ueda, Y. Enomoto, T., Association between Endometriosis and Ovarian Cancer: A Review of Epidemiologic, Pathologic, Genetic, and Clinical Data, Endometriosis: Risk Factors, Symptoms and Management, Pub.Date:2013-3rd Quarter, 2013,
4. Ueda, Y. Enomoto, T. Matsuzaki, S.

Kobayashi, E. Kimura, T. Yoshino, K. Fujita, M. Tsutsui, T. Kimura, T., Taxane-sensitivity of ovarian carcinomas previously treated with paclitaxel and carboplatin, Cancer Chemoth Pharm, 71(6):1411-6 ,2013

5. Ueda, Y. Miyatake, T. Nagamatsu, M. Yamasaki, M. Nishio, Y. Yoshino, K. Fujita, M. Tsutsui, T. Enomoto, T. Kimura, T., A phase II study of a combination chemotherapy using docetaxel and irinotecan for TC-refractory or TC-resistant ovarian carcinomas (GOGO-OV2 Study) and for primary clear or mucinous ovarian carcinomas (GOGO-OV3 Study), Eur J Obstet Gyn R B, 170(1),259-63,2013
6. Yoshino, K. Enomoto, T. Fujita, M. Ueda, Y. Kimura, T. Kobayashi, E. Tsutsui, T. Kimura, T., Salvage chemotherapy for recurrent or persistent clear cell carcinoma of the ovary: a single-institution experience for a series of 20 patients, Int J Clin Oncol, 18(1), 148-53, 2013
7. Yokoyama, T. Enomoto, T. Serada, S. Morimoto, A. Matsuzaki, S. Ueda, Y. Yoshino, K. Fujita, M. Kyo, S. Iwahori, K. Fujimoto, M. Kimura, T. Naka, T., Plasma membrane proteomics identifies bone marrow stromal antigen 2 as a potential therapeutic target in endometrial cancer, Int J Canc, 132(2), 472-84, 2013
8. Masatoshi,H.Tonsok,K.Hiromitsu,O. Izumi,I.Yuki,K.Takamichi,M.Atsushi,N.Takashi,U.Mitsuaki,T.Takayuki, E.Tadashi,K.Noriyuki,T.,Endometrial cancer:preoperative stagingUsing three-dimensional T2-weighted turbo spin-echo and diffusion-weighted MR imaging At 3.0 T:a prospective comparative study , Eur Radiol 23 ,2296-2305 2013
9. Matsuzaki S, Enomoto T, Serada S, Yoshino K, Nagamori S, Morimoto A, Yokoyama T, Kim A, Kimura T, Ueda Y, Fujita M, Fujimoto M, Kanai Y, Kimura T, Naka T.Annexin A4-conferred platinum resistance is mediated by the copper transporter ATP7A.Int J Cancer. 2013 Oct 8. doi: 10.1002/ijc.28526. [Epub ahead of print]
10. Hiromi,Ugaki.Yosiko,Komoto.Reisa ,Kakubari.Eriko,Tanaka.Hisashi,Konishi.Toshihiro Kitai.Saori,Nakajima.Miho,Muraji.Takayuki,Enomoto.masahiko,Takemura. Efficacy of Para-Aortic Lymphadenectomy in Ovarian Cancer:A Retrospective Study. J Canc Ther,4,28-32,2013

（研究分担者：岡本愛光）

1. 高橋 宏典(自治医科大学 産科婦人科), 弓削 主哉, 瀧澤 敬美, 松原 茂樹, 大口 昭英, 桑田 知

之, 薄井 里英, 松本 久宜, 佐藤幸保, 藤原 浩, 岡本 愛光, 鈴木光明, 瀧澤 俊広.絨毛外栄養膜細胞の内因性 miR-520c の発現抑制が CD44 を介した絨毛外栄養膜細胞の浸潤を促進している(MiR-520c down-regulation accelerates cell invasion through its target CD44 in extravillous trophoblast cells)(英語)(会議録) Reproductive Immunology and Biology(1881-607X)28 巻 1-2 Page97(2013.11)

2. 坂本 優(佐々木研究所附属杏雲堂病院), 嘉屋 隆介, 三宅 清彦, 小屋松 安子, 茂木 真, 室谷哲弥, 落合 和徳, 田中 忠夫, 岡本愛光. PDT の適応拡大 婦人科領域における PDT の適応拡大に向けて(会議録) 日本レーザー医学会誌 (0288-6200)34 巻 3 号 Page298(2013.10)
3. 坂本 優(佐々木研究所附属杏雲堂病院 婦人科), 嘉屋 隆介, 三宅清彦, 小屋松 安子, 茂木 真, 室谷哲弥, 落合 和徳,田中 忠夫, 岡本愛光. 管腔臓器の治療における適応拡大と普及を目指して 婦人科領域における PDT の適応拡大に向けて(会議録) 日本レーザー医学会誌 (0288-6200)34 巻 3 号 Page249(2013.10)
4. 鴨下 桂子(東京慈恵会医科大学附属病院 産婦人科), 杉本 公平, 大野田 晋, 山本 瑠伊, 飯倉絵理, 川口 里恵, 拝野 貴之, 林博, 遠藤 尚江, 岡本 愛光. 日本社会の妊孕能に対する認識と今後の課題(会議録) 日本生殖医学会雑誌 (1881-0098)58 巻 4 号 Page358(2013.10)
5. 福村 絢奈(東京慈恵会医科大学附属病院 病院病理部), 梅澤敬, 土屋 幸子, 芦川 智美, 梅森宮加, 高橋 潤, 鷹橋 浩幸, 池上雅博, 山田 恭輔, 岡本 愛光, 落合和徳, 沢辺 元司. LSIL 標本の review(会議録) 日本臨床細胞学会雑誌(0387-1193)52 巻 Suppl.2 Page576(2013.10)
6. 森本 恵爾(東京慈恵会医科大学附属柏病院 産婦人科), 佐々木寛, 黒田 高史, 松井 仁志, 宇田川治彦, 鈴木 二郎,小曽根 浩一, 飯田 泰志, 田部 宏, 高野 浩邦, 岡本 愛光, 金綱 友木子, 中野 雅貴, 森本 紀, 久保田 浩一. スポンジを用いた妊娠中 LBC の精度と採取時出血率の検討(会議録) 日本臨床細胞学会雑誌 (0387-1193)52 巻 Suppl.2 Page573(2013.10)
7. 宇田川 治彦(東京慈恵会医科大学附属柏病院 産婦人科), 岡本愛光, 佐々木 寛, 高野 浩邦, 田部宏, 飯田 泰志, 小曽根 浩一, 森本恵爾, 鈴木 二郎, 松井 仁志, 黒田高史, 金綱 友木子, 中野 雅貴, 片木 宏昭. 肺腺癌の子宮内膜への転移が示唆された一例(会議録) 日本臨床細胞学会雑誌 (0387-1193)52 巻 Suppl.2

Page537(2013.10)

8. 竹中 将貴(東京慈恵会医科大学附属第三病院 産婦人科), 田中 邦治, 津田 明奈, 山下 修位, 中島 恵子, 伊藤 ひとみ,飯倉 絵理, 鈴木 啓太郎, 柳田 聡, 礒西 成治, 福永 真治, 岡本 愛光. 子宮体部小細胞癌の一例(会議録) 日本臨床細胞学会雑誌(0387-1193)52巻 Suppl.2 Page526(2013.10)
9. 松野 香苗(東京慈恵会医科大学附属病院 産婦人科), 山田 恭輔, 高橋 一彰, 上田 和, 斎藤 元章, 高倉 聡, 鷹橋 浩幸,福永 貞治, 岡本 愛光. 膣に発生した Perivascular epithelioid cell tumor(PEComa)の 1 例(会議録) 日本臨床細胞学会雑誌(0387-1193)52 巻 Suppl.2 Page519(2013.10)
10. 梶原 一紘(東京慈恵会医科大学産婦人科), 和田 誠司, 堀谷 まどか, 土橋 麻美子, 田中 邦治, 種元智洋, 大浦 訓章, 岡本 愛光. 胎児死亡となった先天性 QT 延長症候群の 1 例(原著論文) 日本周産期・新生児医学会雑誌(1348-964X)49 巻 3 号 Page1115-1120(2013.09)
11. Shimizu A, Kobayashi N, Shimada K, Oura K, Tanaka T, Okamoto A, Kondo K. Novel gene therapy viral vector using non-oncogenic lymphotropic herpesvirus. PLoS One. 2013;8(2):e56027.
12. Koyama-Nasu R, Takahashi R, Yanagida S, Nasu-Nishimura Y, Oyama M, Kozuka-Hata H, Haruta R, Manabe E, Hoshino-Okubo A, Omi H, Yanaihara N, Okamoto A, Tanaka T, Akiyama T. The Cancer Stem Cell Marker CD133 Interacts with Plakoglobin and Controls Desmoglein-2 Protein Levels. PLoS One. 2013;8(1):e53710.
13. 舟木 哲(東京慈恵会医科大学 産婦人科講座), 梶原 一紘, 大浦 訓章, 佐藤 泰輔, 野口 幸子, 佐藤 陽一, 堀谷 まどか, 土橋 麻美子, 田中 邦治, 川口 里恵, 種元智洋, 恩田 威一, 岡本 愛光. 頸管妊娠に対し子宮動脈塞栓術施行後次回妊娠で分娩後大量出血をきたし再度子宮動脈塞栓術を施行した 1 例(原著論文/症例報告) 東京産科婦人科学会会誌(2186-0599)62 巻 3 号 Page450-455(2013.07)
14. 佐藤 安南(国立成育医療研究センター 周産期センター産科), 梅原 永能, 廣瀬 宗, 山村 倫啓, 上出 泰山, 和田 誠司, 渡辺 典芳, 塚原 優己, 久保 隆彦, 北川 道弘, 左合 治彦, 和田 誠司, 岡本 愛光. 帝王切開瘢痕部妊娠において異なる転帰をたどった 2 例(原著論文) 東京産科婦人科学会会誌 (2186-0599)62 巻 2 号 Page309-313(2013.04)
15. 石橋 由朗(東京慈恵会医科大学附属病院 手術部), 三澤 健之, 小村 伸朗, 大熊 誠尚, 芦塚 修

一, 尾高 真, 杉本 公平, 山田 祐紀, 柏木 秀幸, 森川 利昭, 矢永勝彦, 岡本 愛光, 顕川 晋, 森山寛. 【各科におけるトレーニングシステムの構築】 学内技術認定制度と連携した研修医からの内視鏡外科手術教育(解説/特集) 日本外科系連合学会誌 (0385-7883)38 巻 2 号 Page235-242(2013.04)学内技術認定制度

# Ⅱ．プロトコル

# プロトコル文書例

# 英語版

iPocc Trial

IntraPeritoneal therapy for Ovarian Cancer with Carboplatin

# GOTIC-001 / JGOG-3019

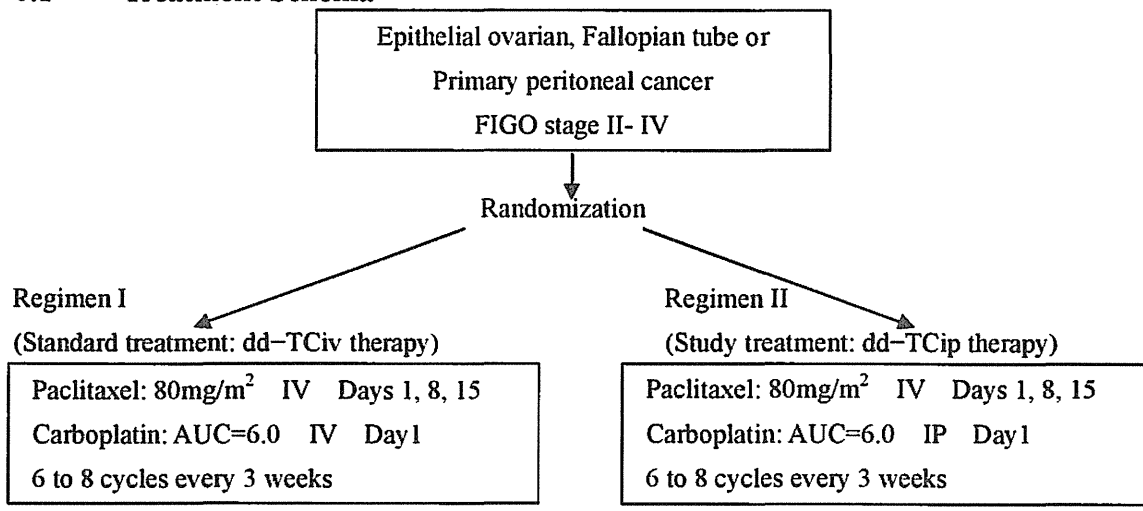
# A RANDOMIZED PHASE II/ III TRIAL OF INTRAVENOUS (IV) PACLITAXEL WEEKLY PLUS IV CARBOPLATIN ONCE EVERY 3 WEEKS VERSUS IV PACLITAXEL WEEKLY PLUS INTRAPERITONEAL (IP) CARBOPLATIN ONCE EVERY 3 WEEKS IN WOMEN WITH EPITHELIAL OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL CANCER

**UMIN Unique trial Number: UMIN000003670**
**Clinical Trials.gov ID: NCT01506856**

English version 1.0 (2011/08/25)
English version 1.1 (2011/09/12)
English version 1.2 (2012/04/01)
English version 2.0 (2013/01/20)

# 0 STUDY OVERVIEW

## 0.1 Treatment Schema




## 0.2 Objectives

Phase A: To confirm the feasibility of Paclitaxel administered by intravenous (IV) infusion weekly plus concurrent Carboplatin administered by intraperitoneal (IP) injection once every 3 weeks (dd-TCip therapy).

Phase B: To compare the efficacy and safety of the following two treatment regimens as first-line chemotherapy in women with epithelial ovarian, Fallopian tube or primary peritoneal cancer.

Regimen I (Standard treatment: dd-TCiv therapy)

Paclitaxel administered by IV infusion weekly plus concurrent Carboplatin administered by IV infusion once every 3 weeks

Regimen II (Study treatment: dd-TCip therapy)

Paclitaxel administered by IV infusion weekly plus concurrent Carboplatin administered by IP injection once every 3 weeks

## 0.3 Phase, Target Sample Size, and Endpoint

### 0.3.1 Phase A (Phase II Trial) Sample size: 120 (phase A)

A decision to move from phase A to phase B will be made independently and comprehensively by the Independent Data Monitoring Committee (IDMC), based on a review of feasibility, including treatment completion rate, hematologic toxicity, non-hematologic toxicity and response rate (in patients who have measurable disease) in both regimens.

When collection of eCRFs is complete for all patients in phase A, the IDMC will meet to review all data, including feasibility and safety data, and will make recommendations to the study chair regarding whether continuation of the study is acceptable. If a decision is made to continue the study, the efficacy data will be evaluated by, and accessible to, the IDMC, and the results will not be made

public. If a decision is made to discontinue the study, all data including efficacy and safety data will be immediately made public. In the transition from phase A to phase B, patient enrollment should be continued without interruption during the evaluation period.

**0.3.2 Phase B (Phase III Trial)** Sample size: 565 (Phase B)

| | |
|---|---|
| Total sample size: | 685 (Phase A + Phase B) |
| Primary Endpoint: | Progression-free survival (PFS) |
| Secondary Endpoints: | Overall survival (OS) |
| | Tumor response (only in patients with evaluable disease) |
| | Incidence of adverse events |
| | Treatment completion rate |
| | Quality of Life (QOL) assessments |
| | Cost-utility analysis |

- Data from the 120 patients in phase A will be included in the final analysis.
- 510 events are necessary for the final analysis.

## 0.4 Patient Selection Criteria

### 0.4.1 Eligibility criteria

1) Patients assumed to have a stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer as a pre-surgery diagnosis
2) Patients scheduled to undergo laparotomy
   Both optimal and suboptimal patients will be eligible for the study. (Suboptimal patients, as well as those who undergo only exploratory laparotomy, are eligible.)
3) ECOG Performance Status: 0-2
4) Patients who provide consent for placement of the IP port system, if randomized to Regimen II (Study treatment: dd-TCip therapy)
5) Patients expected to receive the first protocol treatment within 8 weeks after the comprehensive staging surgery
6) Lab data and clinical examination
   Data within 28 days before the scheduled date of surgery

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

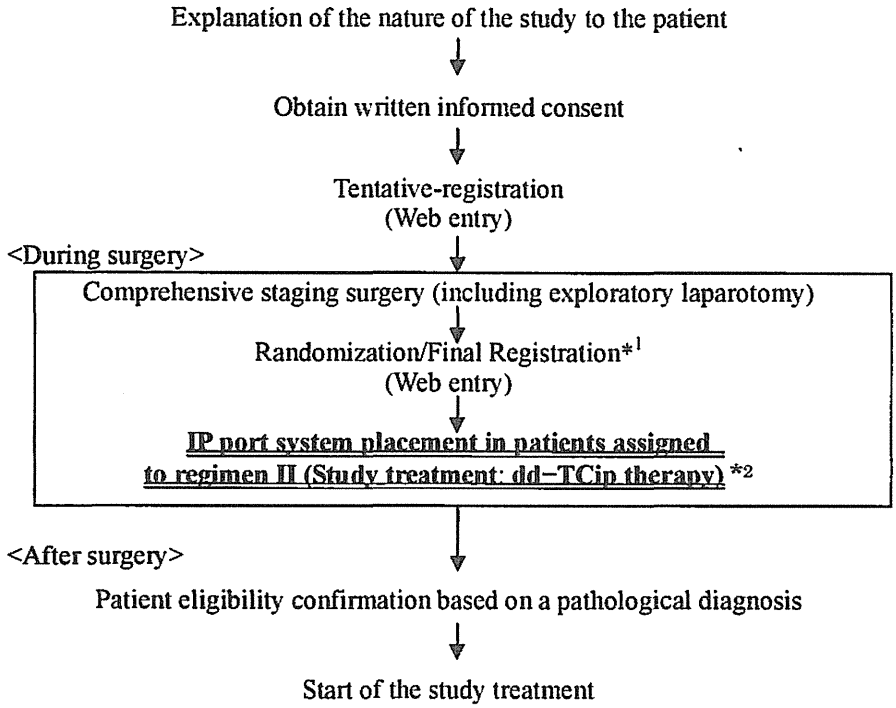
7) Patients expected to survive longer than 3 months from the start date of the protocol treatment
8) Patients aged 20 years and older at the time of tentative registration (with no upper age limit)
9) Patients who provide written informed consent for participation in this trial

### 0.4.2 Exclusion criteria

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

## 0.5 Registration and Randomization

<Before surgery>




*1 If the patient is not proceeding to the final registration or does not receive protocol treatment, please enter the patient data and reasons for not proceeding/not receiving protocol treatment into the Rave system.

*2 For institutions other than those in Japan where IP port placement is performed after comprehensive staging surgery as a regular practice, IP port placement can be done after the patient's randomization to regimenII. IP port can be placed during the surgery for all study patients, and then IP port can be removed, when the patient is assigned to regimenII. 【See 6.3.3】

## 0.6 Study Duration

Target sample size and Accrual period

Target sample size: Phase A (120 patients)
Phase B (565 patients)
Total sample size: 685 (Phase A + Phase B)

- Data from the 120 patients in phase A will be included in the final analysis.

Accrual period: May 2010 to May 2015

Follow-up period: Follow-up is until 510 events are observed or until 3 years from the last patient is randomized to the study, whichever comes first.
Consequently, follow-up is estimated to be completed in May 2018.

- Patients are able to refuse protocol treatment at any time for any reason.
- Follow-up observation will be continued unless the consent is withdrawn.

## 0.7 Contact Information

**【Queries which require a medical opinion】**

Study chair

Keiichi Fujiwara, MD, PhD

Saitama Medical University International Medical Center Comprehensive Cancer Center,

Department of Gynecologic Oncology

Address: 1397-1 Yamane Hidaka-shi, Saitama, 350-1298 Japan

Tel: +81-42-984-4531 or -4115 (after office hour: +81-42-984-4473)

Fax: +81-42-984-4741

E-mail: fujiwara@saitama-med.ac.jp

Physician coordinator

Shoji Nagao, MD, PhD

Saitama Medical University International Medical Center Comprehensive Cancer Center,

Department of Gynecologic Oncology

Address: 1397-1 Yamane Hidaka-shi, Saitama, 350-1298 Japan

Tel: +81-42-984-4531 or -4115 (after office hour: +81-42-984-4473)

Fax: +81-42-984-4741

E-mail: s_nagao@saitama-med.ac.jp

**【All other queries】**

iPocc Trial Coordinating Center

Kitasato University Research Center for Clinical Pharmacology,

Clinical Trials Coordinating Center

Address: 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642 Japan

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

Fax: +81-3-5791-6399

E-mail: iPocc@insti.kitasato-u.ac.jp

TABLE OF CONTENTS

## Appendix

### Attachment 1: Research Organization

**1. Study-specific manuals**

A. Manuals for IPS insertion procedures and intraperitoneal injection

B. Flow of serious adverse event reporting

C-①. STUDY WEB-PAGE Procedure Manual

C-②. EDC System Procedure Manual

C-③. iPocc Trial Patient Registration Procedure Manual

D. Drug ordering, distribution and management system

E. Request for cooperation for QOL survey

**2. Form (as samples)**

①. Informed consent documents

②. Form A / Form C (REQUEST FORM for Rave USER ADMINISTRATION)

③. Patient Registration Form: Emergency Use Only

④. eCRFs, iPocc Trial eCRF Completion Manual

⑤. SAE REPORT、iPocc SAE REPORT Completion Manual

⑥. QOL questionnaire

⑦. Survey form for costs associated with treatment for patients

**3. Guidelines**

I. Declaration of Helsinki

II. ECOG PS

III. CTCAE version 4.0

IV. RECIST Guidelines version 1.1

V. Drug Package Insert

VI. Procedures for hypersensitivity reactions

VII. ASCO guidelines for the use of G-CSF

# 1 OBJECTIVES AND ENDPOINTS

## 1.1 Objectives

Phase A: To confirm the feasibility of Paclitaxel administered by intravenous (IV) infusion weekly plus concurrent Carboplatin administered by intraperitoneal (IP) injection once every 3 weeks (dd-TCip therapy).

Phase B: To compare the efficacy and safety of the following two treatment regimens as first-line chemotherapy in women with epithelial ovarian, fallopian tube or primary peritoneal cancer.

Regimen I (Standard treatment: dd-TCiv therapy)

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

The 3-week period (21 days) is 1 cycle. A total of 6 to 8 cycles will be repeated.

Regimen II (Study treatment: dd-TCip therapy)

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

The 3-week period (21 days) is 1 cycle. A total of 6 to 8 cycles will be repeated.

## 1.2 Endpoints

### 1.2.1 Phase A (Phase II trial)

In phase A, feasibility, including treatment completion rate (in patients who have measurable disease), hematologic toxicity, non-hematologic toxicity and response rate in the two arms, will be determined independently by an Independent Data Monitoring Committee (IDMC).

When the collection of eCRFs is complete for all patients in phase A, the IDMC will meet to review all data including feasibility and safety data, and will make recommendations to the study chair regarding whether continuation of the study is acceptable.

For transition from the phase A trial to the phase B trial, the committee will make a decision based on the following criteria.

1) An unexpectedly high incidence of Grade 3 or greater hematologic and/or non-hematologic toxicities observed in dd-TCip therapy compared to dd−TCiv therapy.
2) An unexpectedly low response rate observed in dd-TCip therapy compared to dd−TCiv therapy.
3) An unexpectedly low treatment completion rate observed in dd-TCip therapy compared to dd−TCiv therapy.

Each criterion is evaluated on the basis of both statistical considerations, based on the odds ratio with a 95% confidence interval, and clinical considerations on whether or not to move to phase B. If all of the criteria (1), (2), and (3) are met, the transition to phase B will be abandoned after review by the IDMC. If any of the criteria are met, the IDMC will have a comprehensive discussion, and may refer to additional criteria, to determine whether or not to move to phase B. If none of the criteria is met, the transition to phase B will be decided after a review by the IDMC.

If a decision is made to continue the study, the efficacy data will be evaluated by and accessible to

the IDMC, and the results will not be made public. If a decision is made to discontinue the study, all data, including efficacy and safety data, will be immediately made public.

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

#### 1.2.2 Phase B (Phase III trial)

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

# 2 BACKGROUND AND RATIONALE

## 2.1 Background and rationale for this study

### 2.1.1 Background

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

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

Japan, intravenous Paclitaxel 175 to 180 mg/m$^2$ over 3 hours and intravenous Carboplatin AUC=5 to 6 over 1 hour (TC therapy) has been commonly used as standard chemotherapy for epithelial ovarian cancer [1].

### 2.1.2 Validity of using weekly administration of Paclitaxel as standard treatment

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

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

Ovarian cancer often spreads to different sites within the peritoneal cavity via direct shedding or dissemination at an early stage. Because of this, several decades ago, intraperitoneal (IP) administration of anticancer drugs was proposed for patients with residual tumor after initial surgery or recurrent lesions confined to the peritoneal cavity [11]. When administered by intraperitoneal injection, certain drugs, including cisplatin and Paclitaxel, have distinct pharmacokinetic advantages [12–14]. That is, these drugs remain longer in the peritoneal cavity at a higher concentration than with intravenous (IV) administration [16]. With IP administration of cisplatin, for example, a 10- to 20-fold greater exposure was reported in the peritoneal cavity compared with IV administration. Due to the fact that such highly concentrated drugs remain in the peritoneal cavity over a long period of time, IP administration of anticancer drugs theoretically shows greater promise for disease in the peritoneal cavity than IV administration. Conducting a randomized controlled study of IP cisplatin plus cyclophosphamide versus IV cisplatin plus cyclophosphamide for stage III ovarian cancer (GOG-104), Alberts et al. reported that patients in the IP group had a significantly better prognosis (median survival of 49 months vs. 41 months) and a reduction in adverse effects, compared with those in the IV group [14]. In subsequently-conducted GOG-114, a randomized controlled study of IP