14.7 Approval by the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC)

Prior to participation in this clinical trial, the protocol and informed consent documents must be approved by the IRB/IEC. When IRB/IEC approval is granted, the investigator at each institution will fax a copy of the certificate of IRB/IEC approval to the iPocc Trial Coordinating Center.

In addition, notification of acceptance of the Advanced Medical Service System B needs to be faxed to the iPocc Trial Coordinating Center. The originals of the IRB/IEC approval certificate the notification of the Advanced Medical Service System B must be retained at each institution. The faxed copies will be kept at the iPocc Trial Coordinating Center.

[Japan Only]

14.8 Annual renewal of IRB/IEC Approval

Annual renewal requirements for the protocol and informed consent documents to be reviewed and approved by the IRB/IEC will be in accordance with the applicable regulations at each institution. In general, when any amendments are made to the protocol or informed consent documents during the course of the clinical trial, the amended protocol and informed consent documents must be approved by the IRB/IEC. However, depending on the content of the amendments, the need for such approval can be determined by each institution.

14.9 Changing the content of the protocol

Changes to the protocol made after approval by the IRB/IEC will be handled as two separate items: "Amendments" and "Revisions." In addition, any supplemental explanations without changes to the protocol will be regarded as "Memorandums." The definitions and the handling of these are as follows:

1) Amendment
   A partial change(s) to the protocol that may increase the risk to patients participating in the clinical trial or that affects the primary endpoint in the clinical trial.
   Requires approval by the Clinical Trial Review Committee in JGOG and GOTIC, and must be reported to each IRB in accordance with the policy established by each institution.
   The date of approval by the Clinical Trial Review Committee will be noted on the cover page of the protocol.
2) Revision
   A change(s) to the protocol that is not associated with any increased risk to patients participating in the clinical trial and that is not associated with the primary endpoint in the clinical trial.
   Does not require review by the Clinical Trial Review Committee, but should be reported.
   It is not necessary to record the date of approval by the Clinical Trial Review Committee on the cover page of the protocol.
   The requirement of the IRB/IEC for review and approval will be in accordance with the decisions made by the institution in accordance with their policies.
3) Memorandum
   Not a change(s) to the protocol but a supplemental explanation(s) to be distributed from the

study chair to the trial-related personnel in order to reduce the differences in interpretation of the text or to promote awareness. It requires no review by the IRB.

14.10 Conflicts of interest (COI)

With regards to "the conflicts of interest in this clinical trial" of the study chair and investigators at each institution, the self-declaration forms submitted by investigators are reviewed and approved by the COI Review Committee or the IRB/IEC. Moreover, any conflicts of interest of the iPocc Trial Coordinating Center personnel and the statisticians will be reviewed and approved in compliance with the rules established by each organization.

When publishing the results of this clinical trial, the self-declaration forms for "the conflicts of interest in this clinical trial" of all investigators who will be listed as conference presenters and/or authors will be submitted to the COI Review Committee of GOTIC/JGOG for review. The publication of the clinical trial results will not be presented at domestic/international conferences or in medical journals until the conflicts of interest of all presenters/authors are approved by the COI Review Committee of the GOTIC/JGOG.

14.11 Financial support

This clinical trial is conducted with support by the Health Science and Labor Research Grants from the Ministry of Health, Labor and Welfare (MHLW). Some research funds from study groups also partially support this trial. The Gynecologic Oncology Trial and Investigation Consortium of North Kanto (GOTIC) are providing assistance in meeting the costs incurred in supporting the Clinical Research Coordinator (CRC) and the meeting organization. In addition, the cost for on-site monitoring and auditing are supported by the Japanese Gynecologic Oncology Group (JGOG).

Because part of the treatment to be used in this clinical trial involves a dosage and route of administration not covered by public health insurance, the drugs to be used for that portion will be provided by the pharmaceutical companies. Accordingly, treatment consisting of that covered by public health insurance and treatment provided at no cost will be conducted under the Advanced Medical Service System B established by the MHLW.

[Japan Only]

15 MONITORING AND AUDITING

International institutions outside Japan may need to refer to their country specific appendix for MONITORING AND AUDITING.

15.1 Monitoring of the study

Central monitoring will be performed by the iPocc Trial Coordinating Center in order to ensure that the clinical trial is conducted safely and in accordance with the protocol, and that the clinical trial data are accurately collected. On-site monitoring will be performed in accordance with the monitoring plan for the trial separately specified.

Routine monitoring reports, as a general rule, will be prepared twice a year on the basis of the reported data on eCRFs collected by the iPocc Trial Coordinating Center. The routine monitoring reports prepared by iPocc Trial Coordinating Center will be submitted to the Monitoring Committees and the Independent Data Monitoring Committees (IDMC) of both JGOG and GOTIC semi-annually, and international IDMC annually.

15.1.1 Routine monitoring

15.1.1.1 Monitoring procedures

The Committees of JGOG/GOTIC will review the routine monitoring reports.

15.1.1.2 Monitoring items

1) Patient accrual
2) Patient eligibility
3) Background information on patients
4) Status of protocol execution with reasons for discontinuation
5) Adverse events, especially SAE (serious adverse events) and the reporting status of such events
6) Protocol deviations (including cases of a possible deviation) and violations
7) Others, including the issues related to the progress and the safety of the clinical trial

15.1.1.3 Protocol deviations and violations

A protocol deviation occurs when drug administration, laboratory tests, or evaluation of toxicity and efficacy are not performed as specified in the protocol.

Deviations that exceed the scope of certain acceptable deviations previously determined by the iPocc Trial Coordinating Center and the study chair for each clinical trial will be listed on the monitoring reports as "a case with a possible deviation" and classified as one of the following after review by the monitoring committees.

1) Protocol violation

In principle, "a protocol violation" is a deviation from the protocol described below:

① That has an impact on the evaluation of the primary endpoint of the clinical trial
② That is caused by investigators or institutions without consultation with the study chair in advance.

③ That is intentional or systematic
④ That poses a risk or departs from the protocol significantly

Protocol violations will be disclosed upon publication of the study results.

(Examples of violations)

- Giving other types of chemotherapy or excluded concomitant medications during the protocol treatment
- Giving excess overdoses

2) Protocol deviations

A deviation that does not fall under either 1) Protocol violation or 3) Acceptable deviation.
A specific deviation observed in many cases may be stated when publishing the study results.

3) Acceptable deviation

A deviation within the scope of the acceptable deviations from the protocol previously or subsequently established by the iPocc Trial Coordinating Center and the study chair for each clinical trial.
They will not appear on the monitoring reports.

15.1.1.4 Review by the Independent Data Monitoring Committee (IDMC)

An IDMC will meet semi-annually to assess the progress of the clinical trial and the safety (and efficacy data for interim analysis) during the course of the clinical trial with the aim of recommending whether to continue, modify, or stop the clinical trial.

When the results from the phase A trial are available, the IDMC will review this data and decide whether to continue or discontinue the clinical trial. A decision to continue or discontinue the clinical trial will be made in a comprehensive manner that includes a review of the feasibility, together with possible efficacy, and on the basis of the result of the review, the IDMC will make a recommendation to the study chair regarding whether to continue or stop the clinical trial. If a decision is made to continue the clinical trial, the efficacy data in phase A will not be published. If it is decided to stop the clinical trial, all the data will be published.

An international IDMC will conduct the same review as described above on an annual basis. The international IDMC will operate in accordance with the following guidelines.

- The membership of the IDMC will include at least one inter-group statistician and at least one clinician experienced in clinical trials. Additional membership will reflect the specialties involved in the trial. All members of the IDMC will be independent of the trial. If non-independent members are to be included this will be justified and agreed to by the participating GCIG groups.
- The deliberations of the IDMC when considering outcome data by treatment arm are confidential. These data will not to be shared with anyone who is not a member of the IDMC, unless agreed by the IDMC itself.
- The IDMC will act in an advisory role and report its recommendations in writing to the study chair.
- A recognized formal statistical approach for the conduct of interim analyses will be employed and in general the final recommendation from the IDMC on the continuation of the study will

be based on all available evidence. The formal statistical criteria for stopping on basis of efficacy in this study are described in section 13. STATISTICAL ANALYSIS.

- The IDMC must formally approve any proposed publication of any trial data prior to the publication of the protocol-specified definitive analysis based on the primary endpoint.

15.2 Audit

For JGOG institutions, this study is the subject of an audit by the JGOG/GTOIC Audit Committees. Auditors appointed by the audit committee will visit the participating institutions, and verify the essential documents such as IRB/IEC approval and signed consent form. The auditors also verify the accuracy of the reported data in the eCRFs against original medical records as necessary in accordance with the procedures specified by the GOTIC/JGOG.

The audit results of each institution will be reported only to the investigator at the institution concerned and the GOTIC/JGOG audit committees. If published to any third party, the name of the institution will not be disclosed.

16 SPECIAL INSTRUCTIONS

16.1 Central evaluation of tumor response

In this study, central evaluation of tumor response will not be performed.

16.2 Central pathology review

A Central Pathology Review Committee will be convened once a year to review up to three representative slides per patient. These prepared slides will be reviewed to confirm if the pathological diagnosis is being properly conducted and to ensure that eligibility criteria are being met. The review may be performed using a web-based imaging system. The Central Pathology Review Committee for this trial will consist of the members of the GOTIC/JGOG Central Pathology Committee, as well as pathologists who belong to other study groups. As a general rule, prepared slides reviewed by the Central Pathology Committee will not be returned.

17 STUDY REGISTRATION AND PUBLICATION OF FINDINGS

This clinical trial will be registered through the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) in Japanese with the URL http://www.umin.ac.jp/ctr/index-j.htm, and Clinical Trials.gov in English with the URL http://clinicaltrials.gov/ to disclose information regarding the design, conduct, and publication of results of the clinical trial.

The study results will be presented at a medical meeting after the completion of the final analysis and published in an appropriate medical journal.

17.1 Publication of the results of the phase A trial

At the completion of the data analysis of the phase A trial, data other than the efficacy data will be presented at a medical meeting and the results will be published in an appropriate medical journal. However, if the clinical trial is discontinued, all results including the efficacy results will be published.

17.2 Guidelines on authorship of research papers

Authorship of research papers will be as follows: The first and second authors of the research paper will be either the study chair or the investigator/sub-investigator who belongs to the institution with the highest number of registered subjects. The selection of the first author at such an institution will be determined by the institution. However, the first author should be the person who most directly contributed to this clinical trial.

If the representative at such an institution with the highest number of registered subjects declines to be the first author, the study chair will be the first author and the representative at the institution with the highest number of registered subjects will be the second author.

The third and other authors will be determined through consultation among the participating investigators/ sub-investigators with high accrual. Other authors can include the international study co-chairs, a statistician, and/or appropriate representative from the iPocc Trial Coordinating Center. Since this is an international co-operative trial, the international study co-chairs who are actively involved will be included as authors.

18 RESEARCH ORGANIZATION

This is a Gynecologic Cancer Intergroup (GCIG) study.

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18.6 Research support organization【See Attachment1】

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プロトコル文書

日本語版

iPocc Trial

IntraPeritoneal therapy for Ovarian Cancer with Carboplatin

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婦人科悪性腫瘍研究機構

(GOTIC-001/JGOG3019)

上皮性卵巣癌・卵管癌・腹膜原発癌に対する

Paclitaxel毎週点滴静注＋Carboplatin 3週毎点滴静注投与対

Paclitaxel毎週点滴静注＋Carboplatin 3週毎腹腔内投与

のランダム化第II / III相試験

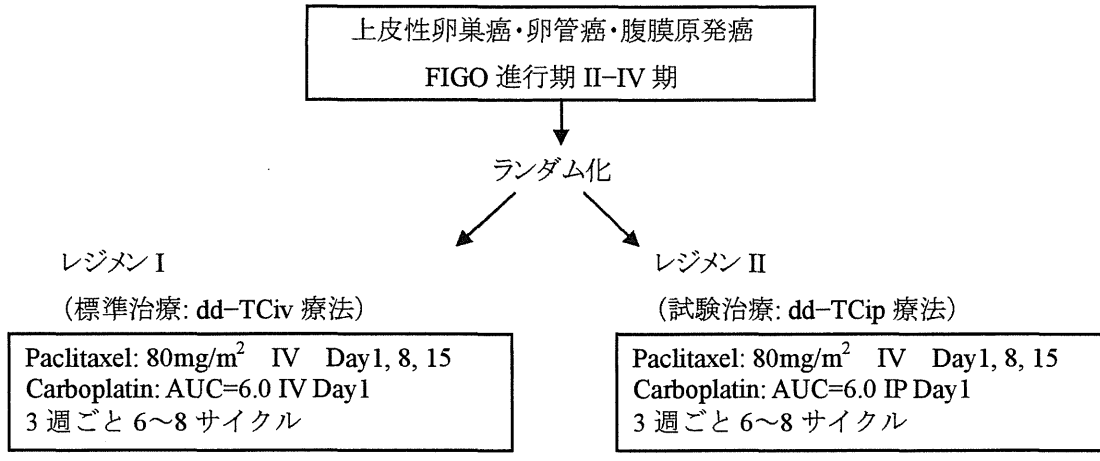
試験実施計画書

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

Version1.0 : 2010年4月26日
Version1.1 : 2010年5月26日
Version2.0 : 2011年8月25日 [English version1.0対応]
Version2.1 : 2011年9月12日 [English version1.1対応]
Version2.2 : 2012年4月01日 [English version1.2対応]
Version3.0 : 2013年1月20日 [English version2.0対応]

0　試験概要

0.1　治療シェーマ



0.2　目的

Phase A: Paclitaxel 毎週点滴静注(IV)投与および Carboplatin3 週毎腹腔内(IP)投与の併用療法(dd–TCip 療法)の Feasibility を確認する。

PhaseB: 上皮性卵巣癌・卵管癌・腹膜原発癌患者に対する first–line 化学療法としての Paclitaxel 毎週 IV 投与および Carboplatin 3 週毎 IV 投与の併用療法(dd–TCiv 療法)と Paclitaxel毎週 IV 投与および Carboplatin 3 週毎 IP 投与の併用療法(dd–TCip 療法)の有効性および安全性を比較し、Carboplatin IP 投与の意義を検討する。

<u>レジメン I(標準治療: dd–TCiv 療法)</u>

Paclitaxel 毎週 IV 投与および Carboplatin3 週毎 IV 投与の併用療法

<u>レジメン II(試験治療: dd–TCip 療法)</u>

Paclitaxel 毎週 IV 投与および Carboplatin3 週毎 IP 投与の併用療法

0.3　Phase、目標症例数、エンドポイント

0.3.1　PhaseA (第 II 相試験)　症例数:120 例

PhaseA から PhaseB への移行の判断は、両群の治療完遂率、血液毒性、非血液毒性、奏功率(測定可能病変を有するもの)などの feasibility について、International Independent Data Monitoring Committee (IIDMC)が総合的かつ第三者的に判断する。

IIDMC は、Phase A の全症例の eCRF 回収が終了した時点で開催審議され、試験継続の妥当性について研究代表者へ提言する。試験の継続可と判断された場合には、有効性のデータについては IIDMC のみが閲覧し、公表は行わない。試験の継続不可と判断された場合には、有効性・安全性データを含むすべてのデータをすみやかに公開する。

PhaseAからPhaseBへの移行には患者登録中断期間を設けないで、評価期間中も症例登録は続行する。

0.3.2 PhaseB(第III相試験) 症例数: 565例

合計症例数: 685 例 (PhaseA + PhaseB)

Primary Endpoint: 無増悪生存期間(PFS)

Secondary Endpoints: 全生存期間(OS)

腫瘍縮小効果(評価可能病変のある症例のみ)

有害事象の発現率

治療完遂率

Quality of Life(QOL)評価

費用効用分析

*PhaseAにおける120症例を最終解析に含む。

*必要イベント数は510例とする。

0.4 患者選択規準

0.4.1 適格規準

1) 術前にFIGO進行期II～IV期の上皮性卵巣癌、卵管癌または腹膜原発癌と推定される患者。
2) 開腹手術が予定されている患者(本登録には開腹術の施行が必須である)。
   ※初回腫瘍減量手術後の残存腫瘍の大きさは規定しない。すなわち試験開腹に終わった症例を含め、suboptimal症例も適格とする。
3) 一般状態(ECOG Performance Status)が0～2である患者。【Appendix 3-II参照】
4) 腹腔用リザーバーポートシステムの設置の同意が得られている患者。
5) 手術施行から8週間以内に抗癌剤投与の予定である患者。
6) 十分な主要臓器機能を有する患者。
   (臨床検査は手術予定日前28日以内に行われたものとする)

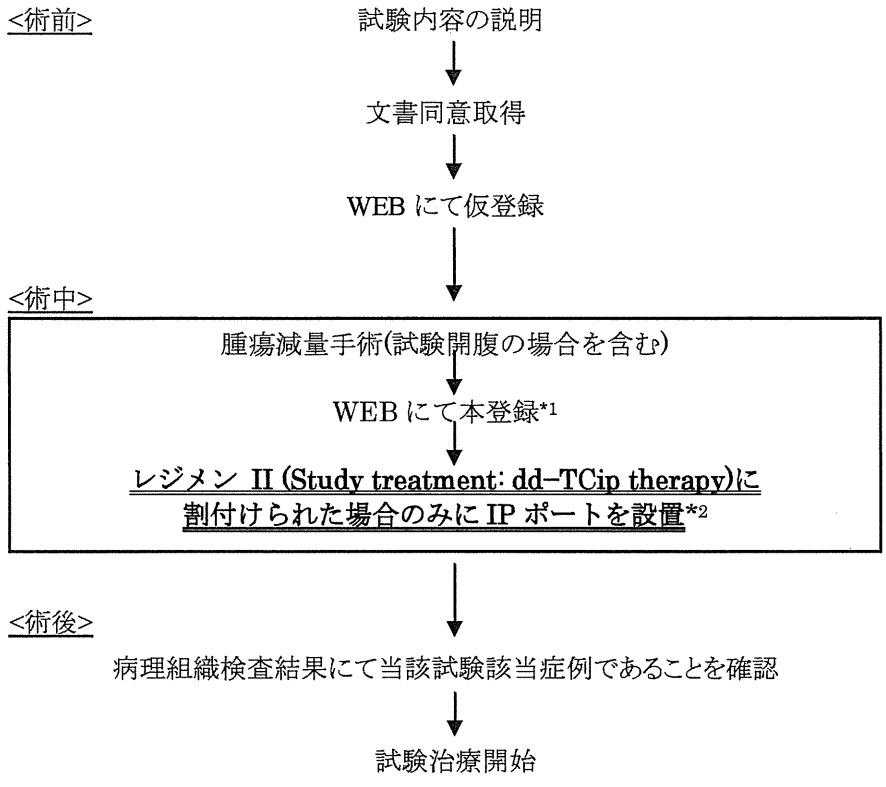
好中球数	1,500 /mm^{3}以上
血小板数	100,000 /mm^{3}以上
AST(GOT)、ALT(GPT)	100 IU/L以下
血清総ビリルビン	1.5 mg/dl未満
血清クレアチニン	1.5 mg/dl未満
心電図	正常範囲または 無症状でかつ治療を必要としない程度の異常(心疾患、重篤な不整脈のない症例)
末梢神経症状 (運動ニューロパチー、感覚ニューロパチー)	Grade1以下(CTCAEver4.0)

7) 治療開始後生存期間が3ヶ月以上期待できる患者。
8) 仮登録時の年齢が20歳以上の患者(上限は規定しない)。
9) 本試験参加について文書にて本人からの同意(不可能な場合はその法定代理人などの患者に代わって同意を成し得る者)が得られた患者。

0.4.2 除外規準

1) 組織型が卵巣境界悪性腫瘍であると予測される患者。
2) 当該疾患に対し、化学療法および放射線療法による前治療が行われている患者。
3) 全ての活動性の重複癌患者。(同時性重複がん及び無病期間が 5 年以内の異時性重複癌。ただし皮膚の基底細胞癌と扁平上皮癌、並びに局所治療により治癒と判断される上皮内癌もしくは粘膜内癌相当の病変は活動性の重複がんに含めない。)
4) 重篤な合併症を有する患者。
   例: 重篤な心疾患又は脳血管障害、コントロール困難な糖尿病又は高血圧症、肺線維症、間質性肺炎、出血、活動性の消化性潰瘍又、重篤な神経疾患を有するものは除外する。
5) ポリオキシエチレンヒマシ油(クレモホールELR)含有製剤(シクロスポリンなど)および、硬化ヒマシ油含有製剤(注射用ビタミン剤など)の投与歴に関連して過敏症が発現したことのある患者。
6) 持続的なドレナージを必要とする胸水貯留を認める患者。
7) 抗生剤を必要とする活動性の感染症患者。
8) 妊娠、授乳中及び妊娠している可能性のある患者。
9) 脳転移または脳腫瘍の身体所見がある患者。
10) 本試験の完遂やその後のフォローアップが困難であると予測される患者、または担当医が不適当と判断した患者。
11) 間質性肺炎の症状、その兆候を有する患者。

0.5 登録とランダム化の流れ



*1 本登録またはプロトコル治療を開始できなかった場合は、その理由および患者情報について Rave システムを用いて報告する。

*2 ただし、日常診療において初回腫瘍減量術ののちに IP ポート留置を行う国(日本以外)においては、患者がレジメン II (dd-TCip 療法)に割り当てられた後に、IP ポートの設置を行ってもよい。または、IP ポートの設置を初回手術時にすべての患者に対して行い、患者がレジメン I (dd-TCiv 療法)に割り当てられた場合に抜去してもよい。【6.3.3 参照】

0.6 試験期間

目標症例数および症例集積期間

目標症例数: PhaseA(120 例)
PhaseB(565 例)
合計症例数:685 例 (PhaseA + PhaseB)
※PhaseA における 120 症例を最終解析に含む。

症例集積期間: 2010 年 5 月 ～ 2015 年 5 月

追跡期間: 追跡調査は、上記の必要イベント数が観察されるか、最後の患者が登録後 3 年間観察されるまで全患者に対して継続される。従って、追跡調査はおおよそ 2018 年 5 月に完了する予定である。

※患者はいかなる時でも本試験による治療を拒否できる。

※同意が取り消されなければ追跡期間中は追跡調査が行われる。

0.7 問合せ先

【医学的判断を要するお問い合わせ】

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目 次

Appendix

別紙 1:研究組織

1. 本試験独自のマニュアル

A. IPS 挿入手順、腹腔内投与マニュアル

B. 重篤な有害事象報告の流れ

C-①. STUDY WEB-PAGE Procedure Manual

C-②. EDC System Procedure Manual

C-③. iPocc Trial Patient Registration Procedure Manual

D. 薬剤オーダー・配布・管理方法

E. QOL 調査担当者へのご協力のお願い

2. Form(見本)

①. 同意説明文書・同意書

②. FormA、FormC (REQUEST FORM for Rave USER ADMINISTRATION)

③. 症例登録票(緊急時のみ)

④. eCRF、 iPocc Trial eCRF Completion Manual

⑤. SAE REPORT、重篤な有害事象報告に関する手順

⑥. QOL 調査票

⑦. 患者さんの治療に関連する費用調査用紙

3. ガイドライン

I. ヘルシンキ宣言

II. ECOG の PS

III. CTCAE version4.0

IV. RECIST ガイドライン version1.1

V. 薬剤添付文書

VI. 過敏症反応時の処置方法

VII. G-CSF 使用に関する ASCO ガイドライン