

A Phase II Randomized Study: Outcomes after Secondary Cytoreductive Surgery with or without Carboplatin Hyperthermic Intraperitoneal Chemotherapy (HIPEC) followed by Systemic Combination Chemotherapy for Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

PROTOCOL FACE PAGE FOR
 MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Monmouth – All Protocol Activities
Westchester – All Protocol Activities
Bergen – All Protocol Activities
Nassau – All Protocol Activities

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a randomized phase II prospective study with the primary objective to determine the proportion of patients who are without evidence of disease progression at 24 months after secondary cytoreductive surgery (CRS) with or without carboplatin-based hyperthermic intraperitoneal chemotherapy (HIPEC) followed by systemic combination chemotherapy for recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer. Patients will be randomized intraoperatively to undergo CRS with HIPEC (arm A) or CRS only (arm B) in a manner 1:1. Both arms will receive a standard platinum-based systemic chemotherapy postoperatively (5 cycles in arm A and 6 cycles in arm B).

Patients eligible for this study are those with recurrent ovarian, primary peritoneal or fallopian tube carcinomas undergoing secondary CRS to a residual disease ≤ 0.5 cm for first platinum-sensitive recurrence. CRS will be performed in the usual fashion in both arms. After surgical cytoreduction, a single dose of carboplatin diluted in approximately 3-4 liters (not to exceed 8 liters) of normal saline will be administered via intraperitoneal (IP) perfusion for approximately 90 minutes in the hyperthermic phase (approximately 41°C-43°C) in arm A, as clinically indicated. After completion of the perfusion, the perfusate will be drained, and the abdomen and pelvis irrigated with normal saline to wash away any residual chemotherapeutic agent. The fascia and the skin will then be closed in the standard fashion. Arm B will undergo CRS only.

The primary endpoint for both arms is the proportion of patients who are without evidence of disease progression at 24 months after CRS with or without HIPEC. Progression-Free Survival (PFS) is defined as the duration of time from the day of CRS to time of progression or death, whichever occurs first. The proportion of patients who are without evidence of disease progression will be assessed at 6, 12, 18 and 24 months from the day of CRS using RECIST 1.1 guideline (version 1.1). After 24 months the study team will follow-up with patients periodically via chart review with regard to change in treatment, vital status, recurrence, disease status, and overall survival defined as the time period from the date of randomization to the date of the patient's death from any cause.

All patients will be followed for 4 weeks post CRS to assess toxicity and complications. Patients will then receive standard intravenous (IV) platinum-based chemotherapy for 5 cycles in arm A and for 6 cycles in arm B starting 4-6 weeks (Day 22 – Day 42 post surgery) from the day of surgery. The safety of HIPEC as well as the ability to complete at least 4 cycles of intravenous platinum-based chemotherapy will be assessed.

Collection of peritoneal and blood samples at MSKCC only: A complementary pharmacokinetic analysis will be nested into the ongoing randomized phase II trial. A total of 15 patients accrued at MSKCC will be included in the pharmacokinetic analysis. In patients randomized to HIPEC, sequential chronologic carboplatin concentrations will be measured in the peritoneal perfusate, the plasma and the ultrafiltrate. Peritoneal fluid and blood samples will be drawn before, during and after the HIPEC procedure. Peritoneal fluid sampling (5 ml) will occur before the addition of 800 mg/m² carboplatin into the hyperthermic isotonic normal saline perfusate (P0), then 15, 30, 45, 60, 75 and 90 minutes (P1-P6) after the administration of carboplatin. The last peritoneal fluid sample (P7) will be drawn after the peritoneal perfusate is irrigated with 3 L of isotonic normal saline. Simultaneously, blood samples (5 ml) will be drawn before the addition of carboplatin into the hyperthermic isotonic normal saline perfusate (B0), followed by 15, 30, 45, 60, 75 and 90 minutes (B1-B6) after the administration of IP carboplatin. All above mentioned specimens will be drawn in the operating room while the patient is under anesthesia. In addition to the intraoperative measurements during HIPEC, blood samples after

HIPEC is completed will be collected to analyze the systemic exposure of systemically absorbed carboplatin. Blood samples will be drawn at approximately 120, 150, 210, 330 and 1530 minutes (B7 – B11) after the intraperitoneal addition of carboplatin. These blood samples will be drawn either in the operating room or in PACU or on the floor. Every effort will be made to draw the blood samples as part of the routine postoperative blood work. As indicated on Appendix H, windows have been added to the time points of the peritoneal fluid and blood draws. In a select number of patients with minimal residual peritoneal disease after cytoreductive surgery and HIPEC we will be able to analyze tumor before and after HIPEC with carboplatin.

Processing of peritoneal fluid, blood samples and tumor samples at MSKCC only: All peritoneal fluid and blood samples will immediately be stored on ice before processing. The interval between acquisition of sample and processing should not exceed 120 minutes to avoid re-distribution and inactivation of carboplatin secondary to protein binding. The peritoneal samples will be purified from cellular particles and debris by centrifuging 5 ml of perfusate for 10 min at 4°C at 3200 x g. Plasma will be generated by centrifuging 5 ml of blood for 10 min at 4°C at 3200 x g. Carboplatin reacts with blood components and proteins (mostly albumin). This fraction carboplatin is inactive. In order to measure the free and unbound fraction of carboplatin in the blood an ultrafiltrate needs to be prepared. Ultrafiltrates are generated by centrifuging 1 mL of plasma in Amicon Centrifree YM-30 (MPS, Millipore Billerica, MA) for 20 min at 5 °C at 1500 x g. In a select number of patients with minimal residual peritoneal disease after cytoreductive surgery we will be able to analyse tumor before and after HIPEC with carboplatin. This will allow us to measure the concentration of carboplatin and to measure DNA-adduct formation within the tumor. All samples are stored at -80°C.

Bioanalysis for MSKCC patients only: The bioanalysis will be performed by Jan Beumler Pharm.D., Ph.D., at the University of Pittsburgh. Total carboplatin concentrations in plasma, ultrafiltrate, and perfusate, and potentially (if we have tissue before and after HIPEC) Platinum-DNA-adducts will be assessed with a Perkin-Elmer model 1100 flameless atomic absorption spectrometer (Perkin-Elmer, Norwalk, CT) as previously described by Kloft et al. [83]. DNA will be isolated from 1:3 (g/v) homogenates of tissue with ChargeSwitch gDNA Tissue Kits (Invitrogen). DNA content will be determined by UV absorption. Platinum concentrations will be determined by comparison with a standard curve performed in an appropriate matrix and on the same day as the assay.

Pharmacokinetic Analysis for MSKCC patients only: Descriptive statistics will be used to analyze the measured concentrations of carboplatin. Elimination half-life, area under the peritoneum and plasma concentration time curve, as well as peritoneal and systemic exposure and clearance of carboplatin administered as HIPEC will be analyzed. Concentration versus time data will be analyzed non-compartmentally with PK solutions (PKsummit), or, when appropriate, using the ADAPT 5 software for pharmacokinetic/pharmacodynamic systems analysis, using the maximum likelihood option.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- To determine the proportion of patients who are without evidence of disease progression at 24 months after CRS with or without HIPEC.

Secondary Objectives:

- To determine the toxicity and postoperative complications rate in both arms during the 4 week postoperative period.
- To determine the completion rate of four cycles of intravenous standard platinum-based chemotherapy in both arms.
- To assess the pharmacokinetics in a subset of patients randomized to receive HIPEC in the OR.

3.0 BACKGROUND AND RATIONALE

Ovarian cancer is the second most common gynecologic malignancy in the United States, with 21,880 estimated new cases in 2010, and the most lethal gynecologic malignancy, with 13,850 estimated deaths in the same year (1). While the stage-specific survival of patients with epithelial ovarian cancer (EOC) is similar to that of other gynecologic malignancies, the overall poor prognosis can be explained by the fact that the majority of patients (60-70%) present at an advanced stage (FIGO stage IIIC or IV) (2, 3).

The natural history of advanced (stage III/IV) EOC is one of clinical remission after primary CRS and postoperative chemotherapy followed by early or late recurrence in the majority (70-80%) of patients. Aggressive surgical cytoreduction and postoperative platinum/taxane-based chemotherapy have improved the median overall survival from 1 year in 1975 (stages II-III) (4) to approximately 5 years in 2005 (optimally debulked stage III) (5). However, the long-term cure rates languish between 20%-30% and relapse occurs in the majority of patients (5, 6).

Traditionally, we have categorized patients with a relapse at < 6 months as platinum “resistant” and selected non-platinum agents for treatment; and considered those at > 6 months as “sensitive” and selected platinum-based chemotherapy. There is no absolute interval that completely separates these patients. It is clear that response rates for re-treatment with platinum increase over a continuum as the interval from previous therapy lengthens: platinum-free interval of 5-12 months – 27%, 13-24 months – 33%, > 24 months 59%.

Combination platinum-based chemotherapy is preferred for first platinum-sensitive relapse. The ICON4/AGO-OVAR-2.2 study (7) compared single agent carboplatin with paclitaxel with carboplatin in a randomized fashion for patients with platinum-sensitive disease (defined generally as patients relapsing more than 6 months from prior platinum therapy). Both progression-free (HR 0.76, 0.66-0.80, $p = 0.0004$) and 1 year overall survival (50% vs. 40%) favored combination therapy. The more recent AGO study (8) similarly evaluated patients with platinum-sensitive disease treated with single agent carboplatin or carboplatin with gemcitabine. Patients receiving combination therapy had a progression-free interval of 8.6 months versus 5.8 months for the carboplatin monotherapy arm ($p = 0.0038$). This study was not powered to evaluate an overall survival endpoint. The third trial, CALYPSO trial (9), randomized 976 patients with platinum-sensitive disease to either pegylated liposomal doxorubicin plus carboplatin or paclitaxel with carboplatin. The pegylated liposomal doxorubicin doublet produced a superior progression-free survival (11.3 versus 9.4 months, HR = 0.82, $p < 0.001$) but there was no statistically significant difference in median overall survival (31.5 months, HR = 0.99, $p = .87$).

Therefore, based on the recent data showing that IV platinum-based combination chemotherapy is likely beneficial to patients with platinum-sensitive recurrent disease, it is important that any novel intervention in these patients allows for the administration of subsequent combination intravenous chemotherapy. HIPEC at the time of secondary cytoreduction for platinum-sensitive recurrence offers an opportunity to extend the potential benefits of the intraperitoneal route of chemotherapy delivery to secondary surgical cytoreduction, but it is still unclear, whether it will be superior to CRS alone and whether it will preserve the ability to complete standard postoperative IV chemotherapy.

Rationale for Intraperitoneal Drug Delivery

Currently, the standard adjuvant treatment in the primary setting consists of a platinum-taxane regimen. In 2006, the National Cancer Institute and the Gynecologic Oncology Group (GOG) recommended that IP/IV therapy be offered as the initial regimen for optimally cytoreduced stage III EOC patients (10). This was based on the analysis of three randomized trials that support the use of IP chemotherapy (5, 11, 12). In the most recent trial (GOG-172) (5), patients underwent optimal CRS and were randomized to a standard arm receiving IV cisplatin-paclitaxel or to an experimental arm receiving IV paclitaxel on day 1, IP cisplatin on day 2, and IP paclitaxel on day 8. At a median follow-up of 50 months, there was a statistically significant increase in the median progression-free and overall survival in the IP treatment group (a benefit of 5.5 and 15.9 months, respectively). In addition, a Cochrane database meta-analysis of randomized trials demonstrated a survival benefit with IP therapy (13). However, the role of IP chemotherapy in patients with a recurrent disease has not established yet.

The mechanism underpinning the superiority of IP therapy remains debatable. Both cisplatin and carboplatin administration achieve several fold higher concentration in the peritoneal cavity when given IP, with peritoneal/plasma ratios for the area under the concentration versus time curve (AUC) of 12 and 18, respectively (14). In addition, laboratory data suggest that platinum resistance, a major contributor to chemotherapy failure in this disease, is relative rather than absolute. Therefore, increasing platinum concentrations may overcome drug resistance (15). Alternatively, prolonged exposure with slow absorption times may contribute to the benefit. Other more innovative mechanisms including immune stimulation from peritoneal irritation have been implicated as well. Because peritoneal surface malignancies, including EOC, are relatively chemosensitive and remain confined within the peritoneal cavity for most of the disease natural history, they are an ideal target for evaluating regional intraperitoneal treatment particularly in the low volume platinum-sensitive setting (16).

Rationale for Adding Hyperthermia to Intraperitoneal Chemotherapy (HIPEC)

Hyperthermia, as a single modality, can cause selective lethal cell damage in malignant cells (17). This has been documented in ovarian carcinoma cells and in other cell lines (17-19). Temperatures of 42°C-45°C for 2-4 hours have been shown to be lethal for ovarian carcinoma cells but not for the non-neoplastic parental cell lines which were not significantly affected (17-19). The precise cytotoxic mechanisms associated with hyperthermia are unclear. These may include alterations in the cell membrane/nucleus, protein denaturation (20) and/or stasis in the tumor microcirculation (21). Although hyperthermia may affect the normal tissues, heat has been shown to disproportionately affect the hypoxic malignant cells. Hypoxic cells may also be more thermally sensitive due to the relatively acidotic setting and malnourished environment (22).

Moreover, hyperthermia appears to increase the sensitivity to the various chemotherapeutic agents, including platinum, both *in vitro* and *in vivo* (23-29). The increased platinum cytotoxicity with hyperthermia appears to be related to enhanced intracellular drug accumulation and adduct formation (25, 30). This has been demonstrated in both platinum-sensitive and platinum-resistant cell lines (22, 27, 31). In one study (31), the combination of hyperthermia and cisplatin enhanced cytotoxicity compared with either treatment alone, such that the platinum-resistant ovarian cancer

cell line became almost as sensitive as the parental cell line. In addition, increased cisplatin-DNA adducts were observed in the resistant cell line after the combined treatment compared with cisplatin alone. A good correlation was also found between the nuclear staining density and the fraction of surviving cells, indicating that the generated DNA adducts are an important determinant of toxicity and that it is a mechanism by which hyperthermia enhances cell kill (31). Besides cancer cells, platinum-DNA adduct formation can be measured in more readily available cells such as the leukocytes and the buccal cells and there appears to be a direct correlation between platinum-DNA adduct levels in leukocytes/buccal cells and disease response (32, 33).

When combined with IP treatment, hyperthermia increases intratumoral platinum concentrations in peritoneal tumor models and favorably influences cisplatin pharmacokinetics (31, 34). Besides examining the in vitro effects of hyperthermia when combined with platinum, the former study (31) evaluated ovarian cancer patients enrolled into a phase I study who underwent cisplatin HIPEC following CRS. In that study, the peritoneal perfusate to plasma drug concentration was approximately 15 indicating a favorable pharmacokinetic ratio. The platinum-DNA adduct formation in the tumor was inversely related to the distance from the surface of the nodules. However, at a distance of 3-5 mm, the nuclear staining density levels were still measurable and higher than in buccal cells (31). This pre-clinical/clinical data provide the rationale for evaluating HIPEC in patients with ovarian cancer; a disease in which standard IP chemotherapy has already been shown to be superior to IV chemotherapy.

Rationale for Combining Surgical Cytoreduction with HIPEC

Intraperitoneal cytotoxic agents penetrate directly to a depth of only several millimeters beneath the tumor surface (31, 35). Consequently, patients who are cytoreduced to small-volume or no residual disease are most logical to be considered for this approach. This has been demonstrated in several studies showing that the extent of residual disease prior to HIPEC is an important prognostic factor for outcome (36-42). In part, cytoreduction may improve response to HIPEC by eliminating poorly perfused, hypoxic and non-proliferating cancer cells that are relatively chemoresistant exposing the rapidly proliferating ones that are more chemosensitive (43). Furthermore, HIPEC administered at the time of debulking surgery permits the earliest and the most direct contact of the chemotherapeutic agent to the tumor bed and the surgical fields before adhesion formation.

HIPEC at the time of CRS was initially described by Spratt et al (44) in 1980 and continued to develop as a treatment modality for peritoneal carcinomatosis of multiple origins under Sugarbaker and colleagues at the Washington Cancer Institute (45). Today, there have been investigations from centers worldwide on HIPEC use in the different types of peritoneal surface malignancies including primary peritoneal cancer, pseudomyxoma peritonei, colorectal, gastric, and ovarian cancers. These studies have used a variety of chemotherapeutic agents, such as mitomycin C, cisplatin, doxorubicin, carboplatin, and pegylated doxorubicin (42, 45-49). The bulk of data is obtained mostly from observational clinical series and nonrandomized comparative studies. In the only randomized phase III study, patients with peritoneal carcinomatosis from advanced colorectal cancer were randomly assigned to standard systemic chemotherapy $\pm$ palliative surgery or to CRS with HIPEC (mitomycin C) plus standard systemic chemotherapy (50). A survival advantage was observed in the HIPEC arm (median disease-specific survival of 22 months versus 12 months) (50, 51). Noteworthy, the volume of residual disease following CRS was an important predictor of survival (50). The difficulty with interpreting this study is that it is impossible to separate the potential benefit of HIPEC from that of extensive surgical cytoreduction.

In ovarian cancer, previous studies have evaluated the use of HIPEC at the time of CRS in various settings and using different drugs (36-42, 52-66). In a recent review of the literature, Helm summarized the HIPEC experience in ovarian cancer at the significant time points along the disease natural history (front line, at the time of interval debulking, as consolidation therapy and in

the recurrent disease setting), reporting on a total of 21 studies (43). The most commonly used chemoperfusate was cisplatin. In the recurrent/persistent disease setting, median PFS following CRS and HIPEC ranged from 10-21.8 months (in those studies where PFS was reported) with one study reporting a mean PFS of 23.9 months. In 256 patients where perioperative morbidity data were reported, severe toxicities were mainly hematologic (4.3%) and increase in creatinine (3.9%), which was attributed mainly to cisplatin. Gastrointestinal anastomotic leaks were infrequent (1.6%) and the perforation rate was 2.3% (43). Importantly, the rate of severe morbidities following secondary CRS and HIPEC, overall, was not much different from that of secondary CRS alone (43, 67).

In the ovarian cancer literature, the largest HIPEC series to date comes from two centers in France (66). This study retrospectively (1991 – 2008) reviewed 268 procedures in 246 ovarian cancer patients, the majority of whom underwent their CRS and HIPEC after their first relapse. HIPEC was performed using a cisplatin-based regimen. Median overall survival was 49 months with a median disease-free survival of 13 months. The mortality rate was under 1% and the morbidity rate was about 10%. The degree of cytoreduction was again an independent prognostic factor for survival (66).

Rationale for Using Carboplatin, Instead of Cisplatin, During HIPEC

Carboplatin has been used in lieu of cisplatin for IV adjuvant therapy because of its better toxicity profile with less neurotoxicity and nephrotoxicity. In GOG-158 (6), the combination of IV carboplatin plus paclitaxel resulted in less toxicity, was easier to administer, and survival was not inferior to cisplatin plus paclitaxel (6).

The universal acceptance of the more recently studied IP/IV cisplatin (rather than carboplatin)-taxane regimen (5) has been limited by the frequent development of toxicities, mainly due to the IP cisplatin component. As is the case with systemic therapy, carboplatin may also be less toxic than cisplatin when delivered as HIPEC. This has been demonstrated in animal studies using intraperitoneal tumor rat models (25). The addition of hyperthermia (41.5°C for one hour) to IP cisplatin treatment at the maximum tolerated dose (MTD), resulted in a decrease in the MTD by 33% due to increased nephrotoxicity. The MTD of carboplatin, however, did not change following the addition of hyperthermia. Noteworthy, the combination of chemotherapy and hyperthermia (HIPEC) resulted in more cisplatin or carboplatin DNA adducts in the peritoneal tumors than after chemotherapy alone (25).

In humans, a large retrospective study using normothermic postoperative IP carboplatin, alone (13%) or in combination with either cyclophosphamide (70%) or paclitaxel (16%), as adjuvant treatment following primary cytoreduction demonstrated low toxicity (68). The median survival for the 37 stage III/IV patients who had disease of < 2cm was 51 months. Another study comparing IV to IP carboplatin, each in combination with IV paclitaxel, demonstrated no significant difference in hematological/non-hematological toxicities except for abdominal pain (69). Besides the acceptable toxicity profile of IP carboplatin, the relatively slower drug elimination and better confinement to the peritoneal cavity (14, 70) could, theoretically, provide an advantage over cisplatin when carboplatin is administered as HIPEC.

There are currently no estimates of efficacy for HIPEC with carboplatin in ovarian cancer. The existing studies on HIPEC had heterogeneous designs such as the inclusion of primary and recurrent disease combined, different chemotherapy drugs (cisplatin, mitomycin) and different criteria for the response assessment (54, 60, 64, 71, 72). Moreover, the majority of studies are retrospective in the nature. Recently, Helm et al (72) reported on the largest American experience with HIPEC in EOC to date using data from the HYPER-O registry; an internet-based registry collecting data from participating institutions. Data from eight institutions, cumulatively including a total of 141 patients, were analyzed. A subset of these patients was treated with carboplatin, with

the remainder receiving cisplatin, mitomycin or combination therapy. About 60% of all patients were treated in the recurrent disease setting with an equal percentage having bowel resection at the time of CRS. Median overall survival was 30.3 months (95% C.I.; 23.0-37.6) and median PFS 16.6 months (95% C.I. 12.1-21.1). Recognizing the limitations of a registry analysis, the median overall survival for those treated with carboplatin alone was more than twice that for those treated with cisplatin alone (71.5 month versus 28.6 months, respectively; $p=0.013$) and, in the group with a platinum-sensitive recurrence, the outcome was also significantly better with carboplatin than with cisplatin ($p=0.012$). Carboplatin therapy was one of few factors identified on multivariate analysis that were significantly associated with increased survival ($p<0.013$); the others being hospital stay ≤ 10 days, completeness of the cytoreduction and sensitivity to platinum (72).

Selection of Carboplatin Dose When Delivered as HIPEC at the Time of Cytoreductive Surgery

In addition to the studies discussed earlier demonstrating the safety and the feasibility of HIPEC in general (43, 66, 72), two phase I pilot studies have specifically evaluated carboplatin, delivered as HIPEC, in EOC patients following primary CRS (54, 71). Of note, there was no perioperative mortality with this technique in either study. The first study, from the NCI, examined the toxicity and the pharmacokinetics of carboplatin delivered via continuous hyperthermic peritoneal perfusion (i.e. HIPEC) in six patients at two doses (54). In that study, carboplatin was safely administered at 41°C-43°C for 90 minutes to three patients at a dose of 800 mg/m². Dose-limiting toxicities were observed at 1200 mg/m² and were exclusively hematological (54). None of the patients developed a bleeding diathesis, sepsis or wound complications as a consequence of HIPEC. Two patients had large bowel resection with anastomosis, performed prior to the delivery of HIPEC, without any adverse sequelae. The median time before tolerating any enteral feeding was 5 days (1-7 days). Importantly, the peak perfusate platinum concentrations were 8 to 15-fold higher than peak ultrafilterable plasma concentrations and the maximum patient core temperature was 40°C (54).

More recently, Lentz and colleagues reported on another phase I dose-escalating (400, 600, 800, 1000, and 1200 mg/m²) study administering carboplatin as HIPEC (90 minutes at an outflow temperature not exceeding 43°C) to 17 EOC patients mostly at primary surgery (71). They established the MTD at 1000 mg/m², with grade 4 myelosuppression developing in the first two patients treated at 1200 mg/m². These investigators reported no significant HIPEC-related non-hematologic toxicities, intraoperative complications or postoperative serious adverse events with this technique. No anastomotic complications were observed in the three patients who had bowel resection performed (one small bowel and two large bowels) as part of their initial CRS (including two patients treated at the MTD). One patient developed pulmonary embolism and a superficial wound dehiscence but subsequently underwent a second-look laparotomy with repeat HIPEC at the MTD (71).

Anesthetic considerations with HIPEC

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) is playing an increasing role in the therapeutic management of patients with peritoneal surface malignancies. It is a complex procedure that includes broad based abdominal and pelvic surgery to remove all visible tumors and HIPEC, a peritoneal perfusion utilizing approximately 3 liters of chemotherapeutic solution heated to approximately 42 degrees Celsius. Heated intraoperative chemotherapy achieves a high peritoneal concentration with limited systemic absorption (73).

Attention to electrolyte balance, coagulation status, hemoglobin values, and the potential renal toxicity of the chemotherapeutic agents with the subsequent requirements to maintain a steady urine output are also key components. The administration of large volume of any type of intravenous fluids will cause dilution of platelets and coagulation factors and may lead to

coagulopathy (74). During the heated chemotherapy, patients develop a hyperdynamic circulatory state that is characterized by steady increase in heart rate and cardiac output that reaches its maximum between 70-80 minutes of the 90 minute heated chemo. As the body temperature decreases after completion of the heated therapy, the hyperdynamic state begins to normalize, although studies have shown it will still be above baseline 10 minutes after the chemotherapeutic lavage is concluded (75). When the closed abdomen technique is used, its perioperative toxicity seems to be related to the hemodynamic and cardiac function changes associated with increased body temperature and increased intra-abdominal pressure (76). The anesthesiologist plays a major role in the management of these patients intraoperatively and a standardized approach to these patients has been developed to minimize potential morbidity and mortality. Appropriate hemodynamic monitoring and urinary monitoring is essential to properly identify and treat intravascular hypovolemia and oliguria. Standard monitors are applied along with a triple or quad lumen central venous catheter, an arterial line, and large bore peripherals. Heart rate is controlled with beta-blockers.

There are a few studies looking at the perioperative safety concerns for HIPEC patients. Studies by Kanakoudis et al encouraged extensive hemodynamic monitoring and found perioperative complications and changes in cardiac and hemodynamic functions were related to acute change in body temperature and increased abdominal pressure (76). The study by Esquivel et al suggests that the hemodynamic and cardiac function alterations observed during the heated intraoperative intraperitoneal chemotherapy seems to be determined by the thermal stress induced in the patient with its subsequent hyperdynamic circulatory state. The increase in the patients temperature causes increased cardiac output, decreased systemic vascular resistance, increased heart rate and increased end tidal CO₂ (75). To avoid perioperative complications from the hyperdynamic state, hemodynamic monitoring, liberal fluid administration and heart rate control should be done. The details of the anesthetic considerations can be found in the appendix E.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a randomized, phase II prospective study with the primary objective to determine the proportion of patients who are without evidence of disease progression at 24 months after CRS with or without HIPEC using the approach proposed by Simon (81). The target population for this study is patients with ovarian, primary peritoneal or fallopian tube cancers undergoing secondary CRS after the first platinum-sensitive recurrence. 'Platinum-sensitive' recurrence is defined as recurrence of the cancer 6 or more months after the completion of the primary platinum-based chemotherapy. After all eligibility criteria are met, patients will be randomized intraoperatively to undergo CRS with HIPEC (arm A) or CRS only (arm B) in a manner 1:1. CRS will be performed in the usual fashion in both arms. Carboplatin, delivered as HIPEC, will be administered at the time of surgery in arm A. Subjects will receive a single cycle of hyperthermic intraperitoneal chemotherapy. In some patients randomized to HIPEC at MSKCC only, peritoneal fluid and blood samples will be drawn before, during and after the HIPEC procedure. Patients will then go on to receive standard platinum-based combination doublet chemotherapy (carboplatin and paclitaxel, carboplatin and gemcitabine, or carboplatin and liposomal doxorubicin) for 5 cycles in arm A and for 6 cycles in arm B.

4.2 Intervention

Eligible patients consenting to this protocol will undergo their scheduled surgical procedure. An oncologist will evaluate all patients at time of study entry and will write all chemotherapy orders following standard institutional guidelines. After surgical cytoreduction to a residual disease ≤ 0.5 cm and intraoperative randomization, a single dose of carboplatin (800 mg/m²)

will be administered in approximately 3-4 liters normal saline (not to exceed 8 liters) via intraperitoneal hyperthermic perfusion using the closed-abdomen technique in arm A as clinically indicated (77). HIPEC will be continued for approximately 90 minutes in the hyperthermic phase (approximately 41°C-43°C). The current study will use an FDA-approved device that allows for standardization of treatment when delivering intraperitoneal hyperthermia.

At Memorial Sloan Kettering Cancer Center, the perfusion will be done by a perfusionist licensed in NYS provided by the company producing the HIPEC machine or by a faculty member experienced in HIPEC. The perfusionist will be approved to participate in the procedure by hospital and surgical administration prior to performance of any HIPEC procedures. Additionally, an inservice will be provided by the manufacturer of the HIPEC machine prior to the first procedure. At participating sites and MSK Alliance Clinical Trials Sites, the perfusion will be performed by a licensed perfusionist provided by the company producing the HIPEC machine. After the surgeons have gained experience, they can perform the perfusion without the assistance of the company.

At 4-6 weeks after CRS (Day 22-42 post surgery), patients will go on to receive 5 cycles of standard IV platinum-based chemotherapy in arm A and 6 cycles in arm B. The proportion of patients who are without evidence of recurrence in both arms will be assessed at 5, 12, 18 and 24 months after the day of surgery using RECIST 1.1 guideline (version 1.1).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Chemotherapy

Carboplatin

Will be prepared and administered as per standard institutional guidelines. For complete details, see the package insert for further information. Carboplatin will be infused over 30-minutes (standard institutional protocol) or by a 3-hour infusion (standard MSKCC desensitization protocol) (78).

Formulation: Carboplatin is available as a 10 mg/mL solution. When prepared as directed, carboplatin solutions are stable for 8 hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

Note: Aluminum reacts with carboplatin causing precipitation formation and loss of potency, therefore, needles or IV sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or the administration of carboplatin.

Storage: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

Adverse effects: Myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity, hepatic toxicity, electrolyte imbalances, hypomagnesemia, hypocalcemia, hyponatremia, fatigue, allergic reactions, alopecia, rare toxicities including ototoxicity, nephrotoxicity, edema, nervous system disorders (dizziness, blurred vision), hepatic toxicity, fever, weight loss, interstitial pneumonitis, hemolytic uremic syndrome and uremia.

Paclitaxel

Will be prepared and administered as per standard institutional guidelines. For complete details, see the package insert for further information.

Gemcitabine

Will be prepared and administered as per standard institutional guidelines. For complete details, see the package insert for further information.

Liposomal Doxorubicin

Will be prepared and administered as per standard institutional guidelines. For complete details, see the package insert for further information.

Concomitant Medications

Anticancer or Experimental Therapy: No other concurrent chemotherapy or anti-cancer therapy (other than those listed in Section 5) is permitted while the patient is on study.

Hematopoietic Growth Factors (G-CSF, pegylated G-CSF): Colony-stimulating factors may be used at the discretion of the treating physician but will not be used routinely.

Epoetin alfa (Procrit® or Aranesp®): Use of epoetin alfa is permitted at the discretion of the treating physician but not recommended.

Antiemetics and Premedications

Intravenous palonosetron (250 mcg), fosaprepitant (150mg) and dexamethasone (12 mg) will be administered per standard institutional guidelines for adults (high emetic potential chemotherapy) prior to the initiation of HIPEC. Patients not-randomized to HIPEC arm will receive antiemetics per standard institutional guidelines.

The dose, duration and time of administration of therapy may be modified as clinically indicated. This is only a suggested antiemetic regimen, modifications are permitted. If nausea and vomiting are not well controlled on this regimen or a patient has intolerance to one of these agents, substitutions and addition of alternate antiemetics may be used at the discretion of the clinical team.

Premedications and antiemetics for subsequent chemotherapy cycles will be administered per standard institutional guidelines.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

6.1.1 Inclusion Criteria for Eligibility prior to surgery

1. Age $\geq$ 21 years old.
2. Patients with histologic diagnosis of epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian tube carcinoma that has recurred >6 months since platinum-based chemotherapy (first recurrence) and who are scheduled for secondary surgical evaluation/cytoreduction.
3. Histologic epithelial cell types include serous, endometrioid, clear cell, or undifferentiated carcinomas, transitional cell carcinoma, mixed epithelial carcinoma, malignant Brenner's tumor, or adenocarcinoma N.O.S.

4. Karnofsky Performance Status (KPS) of $\geq 70\%$.
5. Disease-free interval ≤ 30 months.
6. No prior chemotherapy in the recurrent setting. Prior hormonal therapy is permitted. Concomitant anti-neoplastic anti-hormonal therapy (including tamoxifen, aromatase inhibitors etc.) is not allowed for patients participating in study treatment. Low-dose (physiologic) estrogen hormone-replacement therapy (HRT) may be given.
7. Patients receiving maintenance biologic therapy are eligible, provided their recurrence is documented more than 6 months from completion of primary cytotoxic chemotherapy (includes maintenance chemotherapy) and a minimum of 3 weeks has elapsed since their last infusion of biologic therapy at the start of protocol intervention, day 1.
8. Patients must be, after evaluation by the investigator, appropriate candidates for the administration of 5 to 6 cycles of standard platinum-based combination chemotherapy (carboplatin and paclitaxel, carboplatin and liposomal doxorubicin, or carboplatin and gemcitabine) following CRS with or without HIPEC.

Physical and Laboratory Test Findings

9. Bone marrow function:

Hemoglobin ≥ 8.5 g/dL.

Absolute neutrophil count (ANC) $\geq 1,000/\text{mm}^3$.

Platelets $\geq 100,000/\text{mm}^3$.

10. Renal function:

Creatinine $\leq 1.5\text{mg/dl}$

11. Hepatic function:

Bilirubin ≤ 1.5 times ULN.

ALT ≤ 3 times the ULN.

AST ≤ 3 times the ULN.

12. Neurologic function:

Peripheral neuropathy $\leq$ CTC AE grade 2.

13. Blood coagulation parameters:

PT with an INR of ≤ 1.5 and a PTT ≤ 1.5 times the ULN. For patients on full-dose oral anti-coagulation (such as warfarin or rivaroxaban), in-range INR (usually between 2 and 3) and a PTT <1.2 times the ULN.

14. Patients of childbearing potential must have a negative serum pregnancy test within 2 weeks prior to CRS and must be practicing an effective form of contraception during the study period.

6.1.2 Inclusion Criteria for Eligibility post-surgery

1. Patients will be consented prior to the surgical evaluation/cytoreductive surgery. Patients must have less than or equal to 0.5 cm residual disease at the completion of the secondary surgery to be eligible for the study.

6.2 Subject Exclusion Criteria

6.2.1 Exclusion Criteria for Eligibility prior to surgery

1. Tumors of low malignant potential (borderline carcinomas).
2. Subjects who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded.
3. Patients with a history of primary endometrial cancer are excluded unless the following conditions are met:
 - Stage not greater than IA.
 - Not a poorly differentiated subtype (including papillary serous, clear cell or other FIGO grade 3 lesions).
4. With the exception of non-melanoma skin cancer and other specific malignancies as noted above, subjects with other invasive malignancies, who had any evidence of the other cancer present within the last 1 year or whose previous cancer treatment contraindicates this protocol therapy, are excluded.
5. Subjects with known active acute hepatitis.
6. Subjects with active infection that requires parenteral antibiotics.
7. Active coronary artery disease (defined as unstable angina or a positive cardiac stress test).
8. Patients with a history of coronary artery disease may be included if they have had a normal stress test within 30 days of enrollment.
9. Uncontrolled hypertension defined as > 140/90 and not cleared for surgery at the time of consent.
10. New York Heart Association (NYHA) Class II or higher congestive heart failure.
11. History of cerebrovascular disease.
12. Immune deficiency: Clinically significant primary or acquired immune deficiency (i.e. AIDS or on immunosuppressive medication after organ transplant)
13. Patients with other concurrent severe medical problems unrelated to the malignancy that would significantly limit full compliance with the study or places them at an unacceptable risk for participation in the study.
14. Patients with known carboplatin or cisplatin allergy.
15. Life expectancy < 12 weeks.

6.2.2 Exclusion Criteria for Eligibility post-surgery

1. Evidence of extensive intraperitoneal adhesions at the time of surgery, as determined by the operating surgeon which prohibits intraperitoneal therapy.

7.0 RECRUITMENT PLAN

Patients will be recruited at Memorial Sloan Kettering Cancer Center (MSKCC) from the Gynecology Service, Department of Surgery and from the Gynecologic Medical Oncology Service, Department of Medicine, as well as the MSKCC Network Sites, MSKCC Alliance Clinical Trials Sites and participating sites. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at each institution. If the investigator is a member of the treatment team, she/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. The study aims to accrue a total of 100 patients (98 evaluable and randomized) participants. It is expected that each participating site will accrue 15-20 participants and the rest will be accrued at MSKCC (at least 50 participants at MSKCC).

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at each institution in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached.

This limited waiver will apply only to MSK.

8.0 PRETREATMENT EVALUATION

To be completed within 8 weeks of study day 1:

- Radiographic tumor measurement (IV and oral contrast enhanced CT of chest, abdomen, and pelvis is preferred, but MRI, PET-CT, and non-contrast CT are acceptable)

To be completed within 4 weeks of study day 1:

- Vital signs.
- History and physical examination (including height and weight).
- Anesthesia evaluation
- Karnofsky performance status.
- Toxicity assessment.
- Audiogram (for patients with a history of clinical hearing loss).
- ECG.

To be completed within 2 weeks of study day 1:

- CA-125.
- CBC (RBC, WBC, hemoglobin, hematocrit, platelet count) with ANC
- PT/PTT/INR.
- Comprehensive metabolic panel (BUN, creatinine, Na⁺, K⁺, Cl⁻, CO₂, Ca²⁺, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT).
- Magnesium.
- Serum pregnancy test (for women of childbearing potential only).

9.0 TREATMENT/INTERVENTION PLAN

Cytoreductive Procedure

1. Eligible patients will undergo standard surgical resection of recurrent ovarian, fallopian tube, or primary peritoneal cancer. The type of the incision and the use of minimally invasive surgery (robotic/laparoscopic), including hand-assisted laparoscopic procedures, will be left to the discretion of the surgeon. CRS will be performed in the usual fashion in both arms. After CRS is completed and the surgeon is ready to close the abdomen, the residual disease will be established by the surgeon.
2. To be eligible for the trial, CRS to a residual disease ≤ 0.5 cm needs to be accomplished in patients from both arms.
3. No specific interventions will be done for patients randomized to arm B (CRS only).
4. Following draping of the chest and legs, a large sterile adhesive drape will be placed over the entire field.
5. Surgical resections may include, but not limited to, total abdominal hysterectomy with bilateral salpingo-oophorectomy, infra-colic or total omentectomy, pelvic and para-aortic lymphadenectomy, splenectomy with or without distal pancreatectomy, partial liver resections, multiple peritonectomy procedures (pelvis, paracolic gutters, abdominal wall, diaphragmatic surfaces), full-thickness diaphragmatic resection, rectosigmoid colectomy, small bowel resection, tumor ablation and other cytoreductive procedures. Less extensive procedures, such as biopsies, may also be done.

Following completion of the CRS portion of the procedure, intraoperative hyperthermic perfusion will take place. HIPEC will be performed using the “closed” technique (See Appendices A-C for HIPEC Checklists) (77). Thirty minutes, approximately, prior to the completion of the cytoreduction, the perfusionist will prepare the FDA-approved device to deliver the Intraperitoneal Hyperthermia (IPH). The inflow/outflow catheters with temperature probes will be placed in the upper or lower abdomen and pelvis, as clinically indicated. The

temperature probe lines will then be handed off to the perfusionist and connected to the temperature cables on the Recirculator 8.0 or other FDA-approved device to ensure that the temperature probes are functional before closing the incision. At the surgeon's discretion, different styles of catheters may be employed to improve outflow and perfusion. This includes, but is not limited to the outflow lasso. After verifying that the inflow/outflow catheters are still in the proper position, the incision will then be closed in a running watertight fashion using a heavy suture. Care will be taken to ensure that the skin edges are not inverted and that the skin is tightly apposed around the tubing.

A perfusion circuit will be established with approximately 3-4 liters (not to exceed 8 liters, as clinically indicated) of normal saline from the Recirculator 8.0 or other FDA-approved device, which has been heated to approximately 41°C-44°C, into the abdomen at a rate of approximately 800 ml/min. Once the warmed perfusate has been pumped into the abdominal cavity and the temperature probes show a consistent inflow temperature of approximately 41°C-43°C and an outflow temperature of approximately 39°C-42°C, carboplatin (800 mg/m²) will be added to the perfusate and the timing of the approximately 90 minute treatment period will begin. The fluid will be circulated at a rate of approximately 300-2000ml/min, at physician's discretion. During the treatment period, continuous kneading of the patient's abdomen will be undertaken to ensure the even distribution of the chemotherapeutic agent to all the peritoneal surfaces. Care will be taken to watch for leakage of the perfusate and this will be addressed with additional suturing.

Once the circulating fluid has drained from the abdomen, approximately 3-4 liters of normal saline "rinse" will be added to the reservoir or pumped directly in the abdominal cavity. A new suction canister will be installed for 'open' irrigation. The surgical incision is then carefully opened, any residual fluid aspirated, and the inflow/outflow catheters and temperature probes are removed. A second irrigation with approximately 3-4 liters of normal saline will then be done. If bowel resection is done and anastomosis is planned, bowel anastomosis will be performed either before or after the HIPEC treatment at the discretion of the surgeon. The fascia and the skin are then closed in the usual fashion.

Postoperative Care

1. In general, patients from both arms will be maintained in the PACU/SACU and managed according to standard institutional criteria and procedures. However, the place for post-anesthesia recovery will be decided upon on an individual basis. An ICU attending consultation will be obtained for the first five patients. Because our PACU/SACU units are equipped to care for patients with multiple comorbidities who undergo extensive surgical procedures and because preliminary data suggest that carboplatin HIPEC is, generally, well tolerated, we expect that the majority of patients will not require ICU admission.
2. Thromboembolic prophylaxis will be maintained using standard institutional guidelines.
3. Adequate hydration will be maintained to sustain a urine output of approximately 30 ml/hr for the first 12-24 hours after surgery for patients in arm A. Target urine output may be increased as per standard institutional guidelines or as per physician's discretion.

Systemic Platinum-based Chemotherapy

Chemotherapy will begin 4-6 weeks following CRS (Day 22 – 42 post surgery) for 5 cycles in arm A and for 6 cycles in arm B. In the setting of platinum-sensitive recurrence, there is no clear best regimen except that the regimen should contain a platinum-based compound. The choice of concurrent chemotherapy agent administered with carboplatin will be at the physician and patient's discretion and based significantly on prior toxicity from past chemotherapies

used. These regimens (pegylated liposomal doxorubicin-carboplatin, gemcitabine-carboplatin and paclitaxel-carboplatin) result in similar efficacy and are the standard of care for platinum-sensitive recurrence.

Acceptable regimens and schedules are as follows:

- I. Carboplatin AUC 4-5 (q 3-4 weeks) with paclitaxel at 135-175 mg/m² q 3-4 weeks or 60-80 mg/m² weekly (days 1,8,15 of a 21 or 28 day cycle).
- II. Carboplatin AUC 4-5 (q 3-4 weeks) with gemcitabine at 675–800 mg/m² on days 1 and 8.
- III. Carboplatin AUC 4-5 (q 4 weeks) with liposomal doxorubicin at 30-40 mg/m² q 4 weeks.

The completion rate of four cycles of intravenous standard platinum-based chemotherapy will be assessed in both arms and this will address the cycle limitations. Dose modifications using standard procedures are allowed. Treatment delay of up to three weeks will be permitted.

Drug Administration

Carboplatin: Carboplatin will be administered intraoperatively as hyperthermic intraperitoneal infusion at a dose of 800 mg/m² diluted in normal saline approximately (125-250mL). The dose of carboplatin will be capped at the BSA 2.2 m². A single cycle of carboplatin HIPEC will be administered. Up to five cycles of standard platinum-based systemic chemotherapy will be administered postoperatively in patients who have met the pre-treatment guidelines after HIPEC.

Premedications: Intravenous palonosetron (250 mcg), fosaprepitant (150mg) and dexamethasone (12 mg) will be administered as antiemetics prior to the initiation of HIPEC. Patients not-randomized to HIPEC arm will receive antiemetics per standard institutional guidelines.

The dose, duration and time of administration of therapy may be modified as clinically indicated. This is only a suggested antiemetic regimen, modifications are permitted. If nausea and vomiting are not well controlled on this regimen or a patient has intolerance to one of these agents, substitutions and addition of alternate antiemetics may be used at the discretion of the clinical team.

Premedications and antiemetics for subsequent chemotherapy cycles will be administered per standard institutional guidelines.

Carboplatin Hypersensitivity Reactions

In routine clinical practice, acquired carboplatin hypersensitivity reactions are seen. Patients with a history of prior carboplatin hypersensitivity will not be eligible for this protocol. If a patient develops carboplatin hypersensitivity during subsequent systemic chemotherapy, the treatment will be stopped and may be continued later at the discretion of the attending medical oncologist. A prophylactic desensitization infusion may be used during the IV carboplatin portion of the study.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Part I (evaluation schedule)

	Baseline	Week 1 (POD 0-6)	Week 2 (POD 7-13)	Week 4 (POD 21-27)	Month 6	Month 12	Month 18	Month 24	Periodic Chart Review after 2
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									year follow- up completi on
CRS +/- HIPEC with PKs		X							
H&P, KPS	X ¹			X ⁷	X ^{5,7}	X ^{5,7}	X ^{5,7}	X ^{5,7}	
CA-125	X ²			X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	
CBC ¹¹ with ANC	X ²	X ³	X	X					
PT/INR/PTT	X ²	X							
CMP ¹⁰ , Mg ²⁺	X ²	X ³	X	X					
Pregnancy test (where applicable)	X ²								
Radiographic imaging ¹²	X ⁴			X ⁹	X ^{6,9}	X ⁹	X ⁹	X ⁹	
ECG	X ¹								
Audiogram (where applicable)	X ¹								
Survival Data									X

1: within 4 weeks before study treatment

2: within 2 weeks before study treatment

3: checked for the first week while hospitalized as clinically indicated per standard institutional guidelines

4: within 4-8 week before study treatment

5: within +/- 15 days from the scheduled follow up date

6: for patients who have not completed all cycles of chemotherapy within 6 months, imaging will be done after the completion of chemotherapy (maximum within 1 week after completion)

7: post day of surgery

9: +/- 15 days of H&P, KPS visit

10: CMP includes BUN, creatinine, Na⁺, K⁺, Cl⁻, CO₂, Ca²⁺, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT

11: CBC includes RBC, WBC, HGB, HCT, and platelet count

12: For pre-treatment imaging, IV and oral contrast enhanced CT of chest, abdomen, and pelvis is preferred, but MRI, PET-CT, and non-contrast CT are acceptable. For the post-operative baseline and subsequent follow up scans, IV and oral contrast enhanced CT of the chest, abdomen, and pelvis is also preferred. If a patient has a contraindication to CT contrast, a contrast enhanced MRI of the abdomen and pelvis and non-contrast CT of the chest should be pursued. If a patient has a contraindication to both CT and MRI contrast, a non-contrast CT of the chest, abdomen, and pelvis is acceptable. No other types of scans will be permissible for post-operative imaging unless extenuating circumstances necessitate their use.

Note: All followup appointments including week 1, week 2, week 4, 6 month, 12 month, 18 month, 24 months should be scheduled based on the date of surgery. Week 1, 2, and 4 assessments are to be completed within the specified post operative week. For example, Week 1 assessments are to be completed between post operative days (PODs) 0-6.

If a patient develops a contraindication to contrast after the post-operative baseline CT, the decision to perform subsequent non-contrast CT or MRI scans should be discussed with the radiologist and treating physician. This decision should take in to account tumor type and anatomic location and should be optimized to best allow for comparison with prior studies. If adequate comparison cannot be attained, then the patient will be considered inevaluable from that point forward.

All postoperative complications grade 3 or higher, as defined by Appendix J: MSKCC Surgical Secondary Events Grading System will be collected up to 4 weeks post surgery. For the purpose of the stopping rules for the HIPEC arm of this study IR-guided drainage of a non-infectious collection will not be considered as a grade 3 postoperative complication.

Patients in arm A will receive a single dose of heated intraperitoneal carboplatin, intraoperatively. Patients who meet the below specified pre-treatment guidelines will go on to receive additional systemic platinum-based chemotherapy postoperatively beginning 4-6 weeks after HIPEC. The systemic chemotherapy will be delayed for patients who do not meet these guidelines and will be initiated at the discretion of medical oncologist. The pre-treatment guidelines are monitored until recovery to $\leq$ grade 1 or to baseline (if baseline toxicity was > 1). Toxicities of HIPEC will be assessed using the CTCAE version 4.0 (79). For purposes of this study, the pre-treatment guidelines will be defined as follows:

- Neutropenia (ANC): systemic chemotherapy cannot be initiated with febrile neutropenia or prolonged grade 4 neutropenia ($ANC < 500/mm^3$) lasting more than 5 consecutive days. Interventional use of growth factors may be employed when indicated.
- Thrombocytopenia (PLT): system chemotherapy cannot be initiated with bleeding associated with grade 3 thrombocytopenia (platelets $< 50,000-25,000/mm^3$) or grade 4 thrombocytopenia (platelets $< 25,000/mm^3$)
- All non-hematologic toxicities as defined by CTCAE 4.0 grading for injury, poisoning and procedural complications (excluding post-operative hemorrhage, postoperative pain, deep venous thrombosis and pulmonary embolism) must be $\leq$ Grade 2. Pulmonary embolism (grade 4 toxicity) is excluded as it is a known complication of surgery and is more prevalent in patients with cancer.

Special note: Postoperative bowel recovery usually ranges from 3 to 10 days depending on the type of surgery and the individual patient. Therefore, attribution of postoperative nausea and vomiting will be carefully considered and will not be noted as related to HIPEC unless the recovery from the symptoms exceeds 10 days. All postoperative complications will be recorded as well as the time until the patient tolerates a regular diet.

Part II (during postoperative systemic chemotherapy)

Standard laboratory studies and procedures will be followed for patients receiving platinum-based chemotherapy.

11.0 TOXICITIES/SIDE EFFECTS

Carboplatin

Adverse effects: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, hepatic toxicity, ocular toxicity, and allergic reactions. Infrequent adverse effects: Cardiac abnormalities, anorexia, ototoxicity, rash, alopecia, ocular damage, and cancer-associated hemolytic uremic syndrome.

Bone marrow suppression is the dose-limiting toxicity. Thrombocytopenia with platelet counts below $50,000/mm^3$ occurs in 25% of patients and neutropenia with granulocyte counts below

1000/mm³ occurs in 16% of patients. The nadir usually occurs on day 21 in patients receiving single-agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm³; 74% have neutrophil counts above 2000/mm³ and 67% have leukocyte counts above 4000/mm³.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leukopenia and thrombocytopenia.

Vomiting occurs in 65% of patients (81% of previously treated ovarian cancer patients) and, in 33% of these, it is severe. Management of nausea and vomiting during treatment with carboplatin has been significantly improved with appropriate pre- and post-infusion antiemetics.

Mild or severe electrolyte abnormalities may occur (5%), especially hypokalemia/hypomagnesemia. Monitoring of electrolytes and electrolyte replacement will usually correct these abnormalities.

HIPEC

Side effects that have been possibly associated with HIPEC treatment include abdominal pain, ileus, wound infection, pleural effusion, spontaneous gastrointestinal perforations, peritonitis, intraabdominal abscesses, bowel anastomotic leaks and need for a repeat surgical procedure to manage a surgical complication. Because of the possibility of delayed return of bowel function, patients may require the use of total parenteral nutrition in the postoperative period.

Overall the addition of the HIPEC treatment to the CRS may increase the risk of complications versus surgery alone. However, it is likely that many of the complications reported with this technique are related to the extent of the surgical procedure and/or the extent of the disease rather than the HIPEC itself. In addition, when considering severe complications only, the reported rate of severe morbidities following secondary CRS and HIPEC, overall, is not much different from that of secondary CRS alone (43, 67).

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary endpoint of this study is to determine the proportion of patients who are without evidence of disease progression at 24 months after CRS with or without HIPEC. Progression-Free Survival (PFS) is defined as the duration of time from the day of CRS to time of progression or death, whichever occurs first. The proportion of patients who are without evidence of recurrence in both arms will be assessed 6, 12, 18 and 24 months after the day of surgery using RECIST 1.1 guidelines, which is a comprehensive radiologic approach to assess a disease progression and broadly used in the national and international clinical trials in ovarian, fallopian tube and primary peritoneal cancer (80). Patients with measurable disease on their 4 week post-operative scans will have formal RECIST reads with the study radiologist to record lesion measurements at the 6, 12, 18 and 24 month time points. Patients with no evidence of disease at 4 weeks post-op will also be followed at the 6, 12, 18, and 24 month time points using RECIST criteria, however since there will be no lesions to measure, the attending physician will review and confirm that the patient remains NED.

Toxicity will be determined using CTCAE version 4.0, complications will be determined using Appendix J: MSKCC Surgical Secondary Events grading system and will be monitored during the 4 week postoperative period (79). Based on our review of the literature, we expect

carboplatin HIPEC (800 mg/m²) to be minimally toxic with leucopenia, thrombocytopenia and electrolyte abnormalities being the most common side effects. Such events are generally self-limited and respond to supportive care. Preliminary data also suggest a low postoperative complication rate. Any such events will be treated appropriately as postoperative care requires, and meticulously tracked.

The secondary endpoint of this study is to determine the completion rate of IV standard platinum-based chemotherapy after CRS with or without HIPEC. Outcomes will be assessed according to the proportion of patients completing at least four cycles of postoperative systemic chemotherapy.

13.0 CRITERIA FOR REMOVAL FROM STUDY

In accordance with the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and the US FDA Regulations, a patient has the right to withdraw from the study at any time for any reason without prejudice to her future medical care by the physician or at the institution. The investigators also have the right to withdraw patients from the study (see below). Should a patient (or the patient's legally authorized representative) decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

A complete final evaluation will be made at the time of the patient's withdrawal, the physician will dictate the visit note with an explanation of why the patient is withdrawing, and an attempt will be made to perform a follow-up evaluation.

All patients who meet eligibility requirements and are randomized will be included in the analysis. Any patient found to be ineligible for the protocol, as designated in the section on Criteria for Subject Eligibility (i.e. a change in diagnosis), will be removed.

In addition, patients may be removed from the study if one or more of the following events occur:

- Significant non-compliance by the patient.
- Patient refusal to continue observations.
- Decision by the investigator that termination is in the patient's best medical interest.
- Unrelated medical illness or complication.
- Lost to follow-up.
- Patient has progression of disease

A patient who withdraws consent to participate in the study (i.e. patient choice) will be removed. Should they so desire, any patient withdrawing from the study will still have their surgical procedure performed as originally scheduled, without the inclusion of intraoperative hyperthermic chemotherapy.

14.0 BIOSTATISTICS

This is a randomized, phase II prospective study with the primary objective to determine the proportion of patients who are without evidence of disease progression at 24 months CRS with or without HIPEC using the approach proposed by Simon ("pick the winner" design) (81).

The design of a randomized study using a “pick the winner” approach has gained increased popularity recently especially within protocols from the Department of Medicine. The protocol was extensively worked upon and approved by the entire Department of Biostatistics here at MSKCC that felt that it is an acceptable approach in this setting. Furthermore, given the lack of data for this disease from randomized studies and the number of years it will take us to complete the current study (6 years for approximately 100 patients as compared to more than 200 patients for a superiority trial that would take 12 years), it is unethical and not feasible at this point to accrue a higher number of patients in order to compare the superiority of CRS+HIPEC over CRS alone in a direct arm-to-arm comparison. There are currently no estimates of efficacy for HIPEC with carboplatin in ovarian cancer. The existing studies on HIPEC had heterogeneous designs such as the inclusion of primary and recurrent disease combined, different chemotherapy drugs (cisplatin, mitomycin) and different criteria for the response assessment (54, 60, 64, 71, 72). We have explored the possibility to conduct this trial as a multicenter trial, however, the current study is the only available option that aims to establish efficacy estimates for HIPEC and it is powered to show an increase compared to the historical control estimate in this setting. These efficacy estimates obtained from this study can be the basis for a larger phase III study.

Arm A will undergo CRS and HIPEC and arm B will undergo CRS only. Patients in both arms will then go on to receive standard platinum-based combination chemotherapy (carboplatin and paclitaxel, carboplatin and gemcitabine, or carboplatin and liposomal doxorubicin) for 5 cycles in arm A and for 6 cycles in arm B. The design of “pick the winner” is often used to establish an efficacy estimate for a concurrent control. So it is acceptable that one arm involves the new drug intervention, while the other arm is a control arm. In this protocol, the arm B is the standard of care. While this design could be used to conduct two parallel Phase II studies, randomization ensures that there should not be baseline differences between the patients in the two arms and hence any observed differences in efficacy are due to the treatment. The primary endpoint for both arms is the proportion of patients who are without evidence of disease progression at 24 months. The survival estimates are obtained from a prospectively maintained database of patients who underwent CRS from 1/1991 to 10/2009 at our institution. PFS is defined as the duration of time from the day of CRS to time of progression or death, whichever occurs first.

Forty nine patients in each arm will be randomized and treated with the respective treatment as described above. Based on an exact binomial single stage design, each regimen is considered efficacious if in each arm there are at least 17 patients who are progression free at 24 months out of a total of 49 patients in each arm (with type I error of 10% and Type II error rate of 20% each; null hypothesis 25.5% and alternative hypothesis of 40%).

A proportion of patients $\geq 40\%$, who are without evidence of disease progression at 24 months, is considered acceptable, whereas a proportion of $\leq 25\%$ is considered not acceptable in this patient population. These proportions correspond to an increase in median PFS from 12.2 months to 18.2 months assuming exponential distribution.

If both regimens are efficacious then we plan to pick the arm with the higher rate of PFS at 24 months as follows based on the randomized phase II clinical trials approach proposed by Simon *et al* (81). If the number of patients who are progression free at 24 months in each arm is at least 17, and the difference in the number of progression free patients between the two arms exceeds at least 3 patients, then the arm with the highest number will be the treatment selected for further studies. If both arms have at least 17 patients who are progression free at 24 months, we will conclude that both arms are promising with PFS rate at 24 months that exceeds 25%. If both arms have at least 17 patients who are progression free at 24 months and they have equal number of patients who are progression free at 24 months, then the

“winning arm” will be the one with the least number of patients with grade 3 or higher postoperative complications as defined by Appendix J: MSKCC Surgical Secondary Events Grading System. If neither arm has at least 17 patients who are progression free at 24 months, the regimens in both arms would be considered as having a median PFS of approximately 12 months or less. The probability that no regimen is selected is approximately 17%, and the probability of selecting the treatment with the highest percent of progression free rate at 24 months is 78%, assuming one arm has a PFS rate of 40% or greater and the other arm has a PFS rate of 25.5 or less. No formal statistical comparison between the two arms is planned.

The safety endpoint of our trial is to determine toxicity and postoperative complication rates in both arms using NCI Common Terminology Criteria for Adverse Events version 4.0 and Appendix J: MSKCC Surgical Secondary Events Grading System (79). The frequencies of carboplatin based HIPEC toxicities and postoperative complications will be tabulated for each arm separately. Since this study involves patients undergoing CRS for recurrent ovarian, fallopian tube or primary peritoneal cancer, perioperative complications are expected. All complications will be carefully and prospectively monitored in patients for 4 weeks after the surgery. The incidence of major complications (grade 3 or higher) will be examined in details. In a retrospective review of our database of patients undergoing cytoreductive surgery for advanced ovarian cancer from January, 2001 to February 2004 at this institution, the rate of major complications was about 22% (82). There are inherent difficulties in getting accurate data from retrospective analyses and most do not consider postoperative interventional radiology drainage of a fluid collection a grade 3 complication; therefore, a complication rate of 25% seems reasonable. The study will be stopped early if the overall rate of major complications is more than twice the acceptable rate (>50%) following accrual of the first twenty patients and again after accrual of the first forty-nine patients. The stopping rule applies for the patients in arm A only, since the arm B is considered standard of care.

We will employ repeated significant testing to monitor complications and the corresponding stopping boundaries are provided in the table below:

Stopping criteria for Arm A (HIPEC)	Acceptable Rate (Unacceptable rate)	Stopping boundaries†	Probability of declaring the procedure unsafe under the unacceptable rate	Probability of declaring the procedure unsafe under the acceptable rate
Overall complications within 30 days of surgery as defined by Appendix J: MSKCC Surgical Secondary Events Grading System (≥ Grade 3)	25% (≥50%)	$\geq 9/20$ or $\geq 17/49$	0.99	0.10

Ineligible patients will go off the study and will no longer be followed up and will not be included in the analysis. Accrual will continue until 49 patients in each arm have will meet eligibility criteria at the time of CRS with or without HIPEC. All patients who meet eligibility requirements and are randomized will be included in the analysis. Patients who are lost to follow-up before 24 months will count as progressions for the primary endpoint in the respective arm.

Thus the study is expected to take approximately 5 years to accrue 100 patients (98 eligible and evaluable) patients assuming 20 patients per year will be enrolled. All patients without an event will be followed up for a minimum of 24 months so the study will be completed on average at 6 years.

A secondary analysis of estimating the completion rate will be conducted. The completion rate and a 95% confidence interval will be calculated for each arm separately. Completion is defined as patients being able to complete ≥ 4 out of 5 or 6 cycles of a standard systemic chemotherapy.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Patients will be randomized (1:1) to either arm A (CRS with HIPEC) or arm B (CRS only) intraoperatively after all eligibility criteria are established. Randomization will be accomplished by the method of random permuted block, and patients will be stratified by number of disease sites (single site: yes/no) and categorical preoperative disease-free interval (less or equal than 12 months: yes/no). The preoperative disease-free interval will be defined as a period from the day of completion of adjuvant postoperative platinum based chemotherapy to the day of recurrence. Sealed, opaque, non-resealable envelopes containing the assignment form will be used. The Clinical Research Coordinator at MSKCC will be responsible for executing the process for all sites. The MSKCC research staff will notify the enrolling site of their patient's randomization assignment via e-mail.

Although confirmation of Part II eligibility will be documented by the surgeon in the operative report, the Part II Eligibility Checklist may be signed by the surgeon within 5 business days post-surgery, as the surgeon will be scrubbed into the procedure and unable to sign in real time.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into CRDBi-Multicenter. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and the completeness of the registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. A log of all eligible patients will be maintained. Accrual rates and the extent and accuracy of the evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year, and more frequently if indicated.

16.2 Data and Safety Monitoring

The Data Safety and Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM plans at MSKCC were established and are monitored through the Clinical Research Administration Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf>

There are several different mechanisms by which clinical trials are monitored for data safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol is assessed for its level of risk and the degree of monitoring required. Each type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) is addressed and the monitoring procedures established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Benefits/Risks: The potential benefit for women who participate in this study is the potential for an increased progression free survival after secondary surgery by incorporating carboplatin HIPEC compared to standard surgery alone. The potential risk for women participating in this study would be an increased risk of toxicity, known or unknown, of this treatment regimen. The potential benefit to the society would be that a successful phase II study could lead to a larger randomized phase III trial which would improve our understanding of the treatment of these diseases and potentially extend survival for women with recurrent ovarian, peritoneal or fallopian tube cancers. Participation in this study may not provide any benefit to the individual participant and may or may not provide information which will ultimately benefit others.

Side Effects: Leukopenia, thrombocytopenia, nausea, vomiting, fatigue and electrolyte abnormalities are some of the most commonly reported adverse side effects. Such events are generally self-limited, and respond to supportive care. There is a possibility that this regimen may increase the risk of postoperative complications. Such events will be treated appropriately as postoperative care requires.

Alternatives/Options: The current standard treatment option for patients eligible for this study would be surgery, without the addition of HIPEC, followed by systemic combination chemotherapy. Whether or not a patient chooses to participate in this study will not affect the availability of standard, supportive, or other investigational treatment at MSKCC.

Financial Costs/Burdens: The drug used in this study is commercially available and standard. The patients will be responsible for the cost of the drug as well as the cost of the HIPEC infusion, and will be responsible for all treatment costs including the costs of the drug administration, physician's services, operating room costs, blood tests, and imaging studies. If hospitalization is necessary for a complication of treatment, the patient will be responsible for the bill.

Voluntary Nature of the Study: Participation in this study is entirely voluntary.

Inclusion of Children in Research: This protocol/project does not include children because the number of children with EOC is limited and because the majority is already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

The patients will be explained the extent of the risks, benefits, toxicities/side effects, alternatives/options for treatment, financial costs/burdens and the voluntary nature of the study.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
 - o An explanation of how the AE was handled
 - o A description of the participant's condition
 - o Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

Serious Adverse Events should be reported for 30 days postoperatively for all patients. Any event occurring after the 30 day postoperative period should be reported only if it is possibly, probably or definitely related to surgery or HIPEC.

Relationships and attributions for Serious Adverse Events will be given with respect to the surgery as the primary intervention. Any relationship or attribution with respect to HIPEC (if randomized) should be included in the Reaction Detail of the SAE report.

17.3 Sponsor Adverse Events Reporting Definitions

Not Applicable

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A: Surgeon's Checklist
 Appendix B: Anesthesiologist's Checklist
 Appendix C: Nurse's Checklist
 Appendix D: Further Details on HIPEC Technique
 Appendix E: Further Details on Anesthetic Considerations with HIPEC
 Appendix F: Perfusion data collection sheet (Intraperitoneal Hyperthermic Chemotherapy Perfusion Record)
 Appendix G: HIPEC Precaution Sign
 Appendix H: Pharmacokinetic Record
 Appendix J: Memorial Sloan Kettering Cancer Center's Surgical Secondary Events Grading System©
 Appendix K: Specimen Collection and Shipping Procedures