A Phase II Trial Evaluating Quality of Life After HIPEC in Patients with Stage IIIC and IV Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma
Wake Forest Baptist Comprehensive Cancer Center (WFBCCC)
CCCWFU 83216

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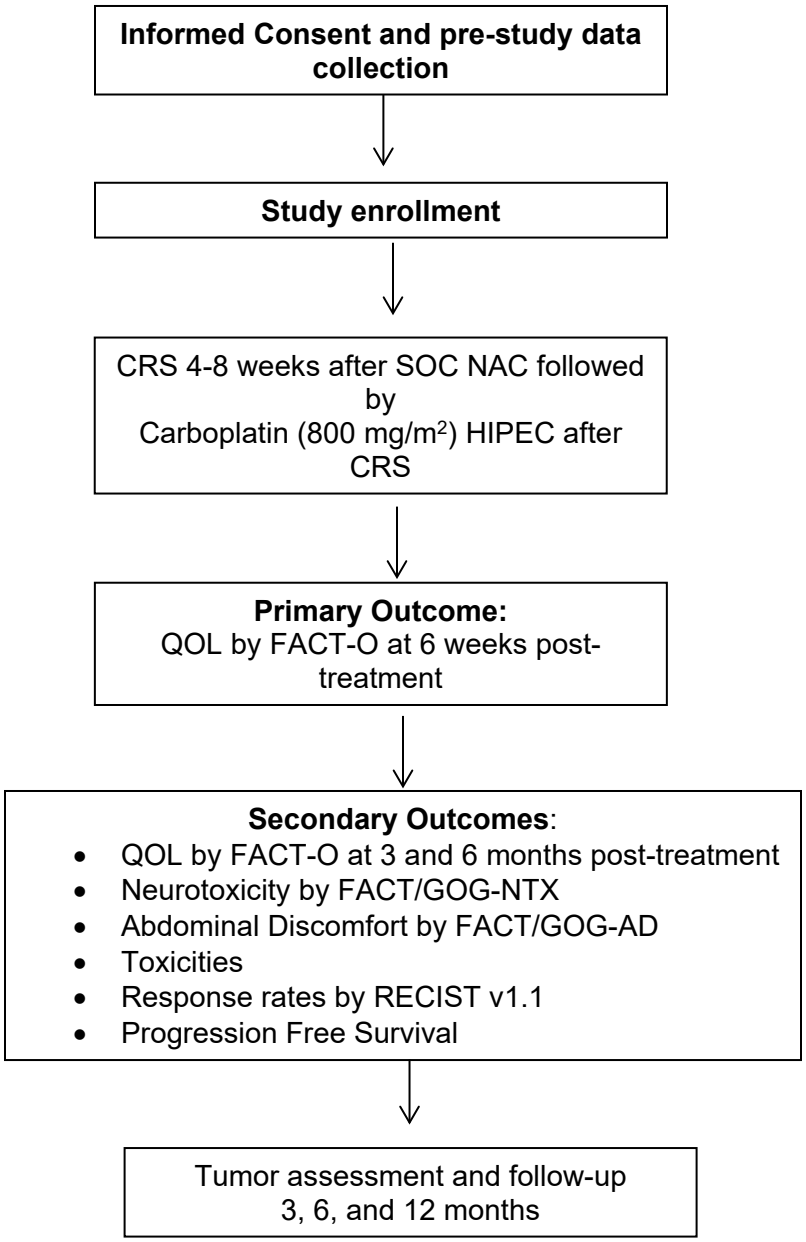
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1.0 Introduction and Background

1.1 Ovarian Cancer

Ovarian cancer is the twelfth leading cause of cancer death in the United States.[1] Less than 15% of patients are diagnosed at the local stage; for 61%, the cancer has metastasized.[1] For these patients, 5-year survival rates are a dismal 27%.[1]

1.2 Cytoreductive Surgery

The standard treatment for women presenting with advanced-stage ovarian cancer is surgical cytoreduction (CRS) and platinum-based chemotherapy agents.[2] CRS is either performed initially or after the administration of IV chemotherapy in the neoadjuvant (NAC) setting. Primary CRS and NAC followed by CRS have been associated with similar survival outcomes. There are fewer peri-operative complications and an improved quality of life (QOL) with the NAC approach. The standard first line chemotherapy agents, either after CRS or in the NAC setting, are platinum doublet regimens consisting of cisplatin and carboplatin with paclitaxel or docetaxel.[2] Intraperitoneal (IP) chemotherapy has been associated with improved survival in three randomized controlled trials compared to IV chemotherapy after primary CRS. However, IP chemotherapy has not been widely prescribed in the United States at least in part due to its increased toxicity and poorer QOL. Although the response rate for these first-line therapies is 70-80%, the majority of patients with advanced ovarian cancer will exhibit progression of their disease.[2]

1.3 HIPEC

Hyperthermic intraperitoneal chemotherapy (HIPEC) is based on the rationale that intraperitoneal chemotherapy has a substantial pharmacokinetic advantage over systemic chemotherapy. The hyperthermia effects cell membranes, cytoskeletons, synthesis of macromolecules and DNA repair mechanisms.[3] [4] Furthermore, mild hyperthermia has been shown to potentiate the anti-tumor effects of oxaliplatin, mitomycin C (MMC), and cisplatin.[5-9] While hyperthermia has some cytostatic properties, it is the synergetic effect on chemotherapeutic agents which has lead most centers to utilize hyperthermia with chemoperfusion. The primary objective of HIPEC is to maximize drug-tumor interaction while minimizing systemic toxicity. The HIPEC is delivered at the time of CRS and is a single treatment. This single dose treatment offers significant advantages over conventional IP chemotherapy in the decrease in the number of cycles/treatment time and recovery time after each IP dose are avoided.

The timing of peritoneal perfusion is critically important. Extensive evidence shows that the effect of postoperative versus intraoperative peritoneal perfusion is reduced by the rapid formation of intra-abdominal adhesions as well as complications related to intra-abdominal catheters.[9-11] Intraoperative peritoneal perfusion not only allows for the instillation of chemotherapeutic agents in an adhesion-free environment, it also minimizes the number of viable exfoliated tumor cells after resection.[12-14] Taken together, this represents the biologic foundation for the current use of HIPEC in the treatment of advanced ovarian malignancies.

1.4 Quality of Life

QOL in individuals receiving CRS plus IP chemotherapy tends to be low. Reports of QOL a year after HIPEC have been reported to return to near baseline levels. However, there is a lack of prospective studies adequately assessing QOL with CRS plus HIPEC in the area of ovarian cancer.

2.0 Objectives

2.1 Primary Objective(s)

2.1.1 To compare the QOL in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC at 6 weeks post-treatment vs. QOL in patients treated with intravenous-therapy (IV) chemotherapy presented in Armstrong et al. (2006).

2.2 Secondary Objective(s)

2.2.1 To describe the QOL in patients with advanced ovarian cancer treated with NAC followed by CRS with HIPEC at 3 and 6 months post-treatment.

2.2.2 To describe neurotoxicity in patients with advanced ovarian cancer treated with NAC followed by CRS with HIPEC.

2.2.3 To describe abdominal discomfort in patients with advanced ovarian cancer treated with NAC followed by CRS with HIPEC.

2.2.4 To describe toxicities in patients with advanced ovarian cancer treated with NAC followed by CRS with HIPEC.

2.2.5 To describe the response rate in patients with advanced ovarian cancer treated with NAC followed by CRS with HIPEC.

2.2.6 To estimate progression-free survival (PFS) in patients with advanced ovarian cancer treated with NAC followed by CRS with HIPEC.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed non-mucinous, epithelial stage 3 or 4 carcinoma of the ovary, fallopian tube or peritoneum.

3.1.2 Patients must not have received treatment for another malignancy within 3 years of enrollment.

3.1.3 Patients must have received at least 3 but not more than 6 cycles of carboplatin-doublet based IV neoadjuvant chemotherapy and achieved at least stable disease (radiographically confirmed) at the conclusion of this therapy.

3.1.4 Age ≥ 18 years.

3.1.5 ECOG performance status ≤ 2.

3.1.6 Patients must have adequate organ and marrow function as defined below (within 30 days of registration):

- absolute neutrophil count ≥1,500/mcL
- platelets ≥75,000/mcL
- total bilirubin ≤ 1.5 mg/dL
- creatinine clearance ≥ 50 mL/min
- AST(SGOT)/ALT(SGPT) ≤ 3 X institutional upper limit of normal
- alkaline phosphatase ≤ 3 X institutional upper limit of normal

3.1.7 The effects of HIPEC on the developing human fetus are unknown. For this reason, and because carboplatin doublet therapyconsists of pregnancy category D agents, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.8 Ability to understand and the willingness to sign an IRB-approved informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients may not be receiving any other investigational agents.

3.2.2 Patients with extra-abdominal metastatic disease.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to carboplatin doublet agents.

3.2.4 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.5 Pregnant women are excluded from this study because carboplatin doublet therapy consists of pregnancy category D agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with carboplatin doublet therapy, breastfeeding should be discontinued.

3.2.6 Men are excluded from participation due to the site-specific nature of the disease being studied.

3.3 Inclusion of Women and Minorities

Women of all races and ethnicity who meet the above-described eligibility criteria are eligible for this trial. Men are excluded from participation due to the site-specific nature of the disease being studied.

The study consent form will also be provided in Spanish for Spanish-speaking participants. We plan to enroll a total of 40 individuals. Based on these study participant numbers, we expect approximately 3.5% of study participants to be Hispanic/Latino (N = 1). We plan to enroll at least 15% Black or African American (N = 6), Due to population estimates and the population in the WFBCCC catchment area we expect no or low recruitment of American Indian/Alaska Native and Asian women. Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked with a protocol in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix B)
2. Complete the Protocol Registration Form (Appendix A)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:
   Protocol Registrar [redacted]
   Protocol Registrar FAX (336) 713-6772
   [redacted]

   [redacted]-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

   Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 QOL in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC as determined by the FACT-O questionnaire at 6 weeks post-treatment

5.2 Secondary Outcomes

5.2.1 QOL in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC as determined by the FACT-O questionnaire at 3 and 6 months post-treatment

5.2.2 Neurotoxicity in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC as determined by the FACT/GOG-NTX questionnaire

5.2.3 Abdominal discomfort in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC as determined by the FACT/GOG-AD questionnaire

5.2.4 Toxicities in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC (for one year post-op) as indicated by the number and severity of adverse events as defined by CTCAE v5.0

5.2.5 Response rates using RECIST v1.1 criteria in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC – at 3, 6, and 12 months post surgery.

5.2.6 PFS in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC

6.0 Treatment Plan

6.1 Study-Related Interventions

	Pre-Study[a]	O.R. Day (surgery)	Follow-up Post-Treatment Visits (+/- 2 weeks)			
			6 weeks	3 Mo	6 Mo	12 Mo
Informed consent	X					
Demographics	X					
Medical history	X		X	X	X	X
Concurrent meds	X	X	X	X	X	X
Height, Weight, BSA	X		X	X	X	X
Op Note, Path Report, Perfusion Flowsheet		X				
Adverse event evaluation		X[d]	X[d]			
Physical exam and ECOG PS	X		X	X	X	X
Vital signs	X	X	X	X	X	X
B-HCG[c]	X					
CBC w/diff, plts	X			X	X	X
CMP	X			X	X	X
CA-125	X			X	X	X
CT of Abdomen, pelvis[b]	X			X	X	X
FACT-O, FACT/GOG-NTX, and FACT/GOG-AD questionnaires	X		X	X	X	

a: Pre-Study visit will occur and pre-study procedures will be completed within 28 days prior to registration.
b: CT of abdomen/pelvis as per standard-of-care.
c: B-HCG is for women of child-bearing potential only.
d: Adverse event monitoring will begin at time of surgery and will continue for six (6) consecutive weeks. AEs will be recorded in WISER at the 6 week time point.

6.2 Treatment Administration

6.2.1 **Surgical Intervention and Subsequent Chemotherapy**

6.2.1.1 Preoperative Preparation

Patients will have a mechanical and antibiotic bowel preparation. Potential ostomy sites will be marked by the surgeon or the endostomal nurse prior to surgery.

6.2.1.2 HIPEC

Tumor Debulking and Establishment of Peritoneal Perfusion Circuit

The HIPEC will be preceded by a complete cytoreduction to maximize its therapeutic benefit. The goal of cytoreduction will be resection of all gross tumor. A generous midline incision will be utilized for all explorations. Resection of the peritoneum by stripping it off the abdominal wall combined with multi-visceral resections (such as splenectomy, large and small bowel resection, hysterectomy, etc.) will be utilized for maximal tumor debulking[19].

Patients will be cooled to a core temperature of about 34 to 35° C by passive measures (i.e., not warming airway gases or intravenous solutions) during cytoreduction. After the completion of cytoreductive surgery, peritoneal perfusion catheters will be placed percutaneously. Two inflow catheters (22Fr) will be directed beneath the left and right hemidiaphragms. One or two outflow catheters (32Fr) will be placed in the pelvis. Intraperitoneal catheters will be placed as per institutional standard practice. Temperature probes will then be placed on the inflow and outflow catheters. The abdominal skin incision will be temporarily closed with a running suture to prevent leakage of peritoneal perfusate. A perfusion circuit will be established with 3 L of crystalloid perfusate solution, such as sodium chloride, Lactated Ringers or Plasmalyte. If a perfusion circuit cannot be established with 3 liters a 4th liter is acceptable, but under no circumstances should the volume of perfusate be greater than 4 liters. Flow rates should be at least one liter per minute. The pelvic catheters will drain to a reservoir containing a coarse filter for debris and to reduce foaming. The heated chemotherapy solution will be added and circulated through the institution's standard perfusion equipment. The temperature of the fluid in the patient-return and patient-directed tubing will be monitored using stainless steel couplers with temperature probe connectors and needle probes at the tips of one inflow and one outflow cannula. The abdomen will be gently massaged throughout the perfusion to improve drug distribution to all peritoneal surfaces. Constant temperature monitoring will be done at all temperature probes. A perfusion record will be completed during HIPEC (see Appendix E). Following the perfusion, the peritoneum will be washed out with 3 liters of the crystalloid perfusate.

HIPEC Chemotherapy Administration

Carboplatin will be added to the perfusate once outflow temperatures exceed 39°C at a dose of 800 mg/m^2 [18]. A maximum inflow temperature of 42.5°C is tolerated during the perfusion. The target outflow temperature is 40°C. The total perfusion time after the initial addition of carboplatin will be 90 minutes. The carboplatin dose will be calculated based on the body surface area noted on admission (or as close to surgery day as possible). Following the perfusion, the peritoneum will be washed out with 3 liters of perfusate and passively drained. The skin will then be opened, and the cannulas removed under direct vision. If a bowel resection is performed, any anastomoses may be completed before or after HIPEC; ostomies will be completed at the end of the entire procedure. The abdomen will be inspected and the required anastomoses will be created. The fascia and skin will then be closed in a standard fashion and the requisite ostomies will be created if necessary.

6.2.1.3 Postoperative Care

The patient will be transferred to the post-anesthesia care unit for aftercare and then to the intensive care unit, if needed. Early and late complications of surgery will be recorded in the patient's research chart.

6.3 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, neupogen, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

6.4 Duration of Therapy

Therapy (HIPEC) will be administered for 90 minutes with carboplatin 800 mg/m2 during the surgery as described in Section 6.2.1.2 of this protocol.

6.5 Duration of Follow Up

Tumor assessment for all lesions will be performed while patients are in the protocol follow-up phase of this study at 3, 6, and 12 months. Patients who discontinue the trial without documented tumor progression should be evaluated for extent of disease at the time of trial discontinuation.

Patients will be followed for 30 days after the HIPEC intervention is administered for adverse events monitoring.

Patients will be followed for a minimum of 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.6 Criteria for Removal from Study

Patients may withdraw/be withdrawn from the trial at any time and for any reason. Patients will not be replaced. Some possible reasons for early withdrawal include the following:

- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial
- Unacceptable toxicity or any adverse event that precludes further participation in the trial
- Study completion or discontinuation
- Patient withdraws consent to continued participation in the trial

The reason and date of discontinuation are to be documented in the patient's medical record and in the CRF.

The investigator should complete all end of treatment procedures when a patient withdraws from treatment. All patients who discontinue the trial secondary to an adverse event should be followed until resolution, stabilization or return to a baseline condition. All patients who undergo HIPEC with study agents will be included in any safety analysis.

The Co-Principal Investigators may discontinue the trial at any time. Reasons for early trial discontinuation may include, but are not limited to, unacceptable toxicity of study treatment, a request to discontinue the trial from a regulatory authority or an IRB, or poor enrollment.

7.0 Treatment Delays/Treatment Modifications

In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation is planned for this study.

7.1 General Guidelines for Hematologic Toxicity

7.1.1 Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

7.1.2 Lower Limits for ANC and Platelet Count: ANC must be =>1500 and platelets =>75,000 to proceed with HIPEC with carboplatin 800 mg/m2.

7.1.3 Use of Hematopoietic Cytokines and Protective Agents

The use of hematopoietic cytokines and protective reagents are restricted as noted:

7.1.3.1 In general, patients will NOT receive prophylactic filgrastim (G-CSF), PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless they experience treatment delays or neutropenic delays or have missed or omitted doses, and should follow treatment modifications as specified for the following cycle (see Table A). However, patients may receive growth factors for management of neutropenic complications (e.g. neutropenic fever) in accordance with clinical treatment guidelines. G-CSF prophylactic treatment is recommended in subsequent cycles according to the tables A and B. Treating physicians are allowed some flexibility for treatment for severe neutropenia in the elderly for documented safety concerns.

7.1.3.2 Patients will NOT receive prophylactic thrombopoietic agents.

7.1.3.3 Patients may receive iron supplements and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They are not indicated in patients being treated with curative intent. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted. http://www.fda.gov/Medwatch/safety/2007/safety07.htm

7.2 **Unanticipated Major Surgical Procedures** – (Report all surgery on the Surgery Form Appendix D) For any unanticipated (emergent/urgent) major surgical procedure performed for reasons other than disease progression treatment should be held > 28 days postoperatively. Treatment delay is not required for minor procedures including a) the removal or insertion of a central venous catheter, nephrostomy tube, or ureteral stent or b) thoracentesis or paracentesis for symptom relief in the absence of disease progression.

7.3 Cardiac Toxicity
Symptomatic bradycardia is not an indication for routine monitoring or removal from study. Any arrhythmia or cardiac ischemia event should be discussed with Study Chair, and patient should be removed from study therapy if this is deemed necessary.

8.0 Measurement of Effect

8.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity after the first administration of chemotherapy.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received one cycle of therapy, and have had their disease re-evaluated will

be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Hematologic toxicities will be recorded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

8.3 Methods for Evaluation of Quality of Life

The principal parameters employed to assess the QOL and symptoms are the following self-administered questionnaires: FACT-O (FACT-G with 27 items plus 12 items specific to ovarian cancer). These questionnaires are to be completed at eight time points. The primary outcome will address FACT-O scores, but additional assessments of abdominal pain by FACT/GOG-AD and neurological symptoms by FACT/GOG-Ntx.

8.2 Quality of Life

Patient reported outcomes will be assessed at four time points:

1) Once at the pre-study visit.
2) At week 6 post-surgery
3) At months 3 and 6 in follow-up (post-op)

Patients' QOL, neurological symptoms and abdominal discomfort will be assessed with patient self-administered questionnaires.

QOL will be measured using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire. The FACT-O is a multidimensional QOL questionnaire developed and validated for use by ovarian cancer patients; it includes 4 subscales: Physical Well-Being (7 items), Social Well-being (7 items), Functional Well-Being (7 items), Emotional Well-Being (6 items) and Additional Ovarian Cancer Concerns (12-items). These subscales can be analyzed separately or aggregated to produce a total score. The FACT-O has demonstrated reliability, validity, and responsiveness to change over time 31 as well as sensitivity to improvements in QOL experienced by patients responding to platinum/taxane therapy. The 4-item FACT/GOG-NTX4 (neurotoxicity) subscale will be used to assess patient reported symptoms of neurotoxicity. The FACT-GOG/Abdominal Discomfort (AD) measure will be used to assess abdominal discomfort. The FACT/GOG-AD is a four item measure (two included in the FACT-O) which measures abdominal symptoms, with average inter-item correlations of 0.64, an internal consistency of 0.875, and responsiveness to change over time computed on study data prior to the 4th cycle of chemotherapy by Huang, et al 2007.[15]

8.5 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed within 90 days of registration prior to surgery.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., palpable abdominal masses). In the case of palpable lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and/or MRI: These techniques should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 2.5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology & Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is

mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.				

8.6 Methods for Evaluation of Survival

Disease-free Survival: Disease-free survival will be measured from the time of completion of treatment until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

9.0 Adverse Events List and Reporting Requirements

9.1 Adverse Event List

9.1.2 Carboplatin

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY				
		Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values†

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY				
		Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values†
Bone Marrow				
Thrombocytopenia	<100,000/mm3	59	35	< 0.001
	<50,000/mm3	22	11	0.006
Neutropenia	<2,000 cells/mm3	95	97	ns
	<1,000 cells/mm3	84	78	ns
Leukopenia	<4,000 cells/mm3	97	97	ns
	<2,000 cells/mm3	76	67	ns
Anemia	<11 g/dL	88	87	ns
	<8 g/dL	8	24	< 0.001
Infections		18	21	ns
Bleeding		6	4	ns
Transfusions		25	33	ns
Gastrointestinal				
Nausea and vomiting		94	96	ns
Vomiting		82	91	0.007
Other GI side effects		40	48	ns
Neurologic				
Peripheral neuropathies		13	28	0.001
Ototoxicity		12	30	< 0.001
Other sensory side effects		4	6	ns
Central neurotoxicity		23	29	ns
Renal				
Serum creatinine elevations		7	38	< 0.001
Blood urea elevations		-	-	-
Hepatic				
Bilirubin elevations		5	3	ns
SGOT elevations		23	16	ns
Alkaline phosphatase elevations		29	20	ns
Electrolytes loss				
Sodium		-	-	-
Potassium		-	-	-
Calcium		-	-	-
Magnesium		58	77	< 0.001
Other side effects				
Pain		54	52	ns
Asthenia		43	46	ns

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY				
		Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values†
Cardiovascular		23	30	ns
Respiratory		12	11	ns
Allergic		10	11	ns
Genitourinary		11	13	ns
Alopecia ‡		43	57	0.009
Mucositis		6	11	ns
*Values are in percent of evaluable patients †ns = not significant, p > 0.05 ‡May have been affected by cyclophosphamide dosage delivered				

9.2 Adverse Event Characteristics

- Adverse event monitoring will begin at the time of surgery and will continue for six (6) consecutive weeks post-op. AE's will be recorded in WISER at the six-week time point.
- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study treatment.
- Probable – The AE **is likely related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Unlikely – The AE **is doubtfully related** to the study treatment.
- Unrelated – The AE **is clearly NOT related** to the study treatment.

9.3 STRC SAE Reporting Requirements

The Safety and Toxicity Reporting Committee (STRC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix C. STRC currently requires that all unexpected grade 4 SAEs, all grade 5 SAEs, and any unplanned hospitalizations on these trials be reported to them for review. All WFBCCC Clinical Research Management (CRM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for STRC reporting are responsible for informing a clinical member of the STRC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

9.4 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

10.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 9.1.

10.1 Pharmaceutical Accountability

Drug accountability logs will be maintained for all agents used under this protocol. These logs shall record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication.

10.2 Carboplatin

Product description: PARAPLATIN® (carboplatin) for Injection, USP is supplied as a sterile, lyophilized white powder available in single-dose vials containing 50 mg, 150 mg, and 450 mg of

carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

Solution preparation: Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP, 5% Dextrose in Water (D5W), or 0.9% Sodium Chloride Injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

These dilutions all produce a carboplatin concentration of 10 mg/mL. PARAPLATIN can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP.

Storage requirements: Unopened vials of PARAPLATIN are stable for the life indicated on the package when stored at 25°C (77°F); excursions permitted from 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.

Stability: When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that PARAPLATIN solutions be discarded 8 hours after dilution.

Route of administration: PARAPLATIN is usually administered by an infusion lasting 15 minutes or longer. No pre- or post-treatment hydration or forced diuresis is required. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Disposal: Caution should be exercised in handling and preparing PARAPLATIN (carboplatin) for Injection, USP. Several guidelines on this subject have been published. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing PARAPLATIN (carboplatin) for Injection, USP. If PARAPLATIN (carboplatin) for Injection, USP or solutions containing PARAPLATIN (carboplatin) for Injection, USP contact the skin, immediately wash the skin thoroughly with soap and water. If PARAPLATIN (carboplatin) for Injection, USP or solutions containing PARAPLATIN (carboplatin) for Injection, USP contact mucous membranes, the membranes should be flushed immediately and thoroughly with water.

11.0 Correlative Studies

None

12.0 Data Management

The Appendices contain master copies of the case report forms (CRFs) to be used for this protocol.

Note: If the patient does not have protocol therapy at surgery, it is still necessary to submit Day 0 data and the No HIPEC Follow-Up form annually.

Informed consent document	EPIC

Protocol registration Form (Appendix B)	WISER
FACT-O, FACT-GOG-NTX4, FACT/GOG-AD (Appendices H, I, J)	WISER
Follow-up form (Appendix F)	WISER
RECIST measurement form (Appendix G)	WISER
Adverse Events Log (Appendix K)	WISER

The Protocol Registration Form and signed Informed Consent Form should be completed and faxed to the WFBCCC Registrar in order to enroll and randomize participants. All other CRFs & supporting documents should be faxed to the attention of the Study Coordinator according to the following schedule:

Form	**Submission Schedule**
Surgery Form	Form and reports within 30 days of surgery
Perfusion Record - HIPEC Form	Form within 30 days of surgery
Adverse Event Log	Form within 7 days of completion of time period.
Follow-Up / Measurement Form	Form and supporting documents within 7 days of mo. 3, 6, and 12
FACT-O, FACT/GOG-AD, FACT/GOG-NTX	Prestudy, , Week 6, months 3 and 6 post-treatment (follow-up)

13.0 Statistical Considerations

13.1 Analysis of Primary Objective

This is a descriptive study. The primary objective is to compare the QOL in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC vs. QOL in patients treated with IV chemotherapy at 6 weeks post-treatment presented in Armstrong et al. (2006). Only the patients treated with SOC NAC followed by CRS with HIPEC will be recruited in this study. The summary data of QOL for patients treated with IV chemotherapy collected in Armstrong et al. (2006) will be directly used. The same as Armstrong et al., QOL will be measured using the Fact-O questionnaire and treatment as a continuous outcome. The distribution of QOL at 6 weeks post-treatment will be examined. The descriptive statistics such as mean, standard deviation, median and interquartile range will be calculated. One sample t-test will be used to compare the mean QOL in the study sample to the mean QOL based on Armstrong et al.

13.2 Analysis of Secondary Objective

13.2.1 To describe QOL in patients with advanced ovarian cancer treated with SOC NAC followed by CRS with HIPEC as determined by the FACT-O questionnaire at 3 and 6 months post-treatment, the distribution of QOL at 3 and 6 months post-treatment will be examined. The descriptive statistics of QOL at 3 and 6 months post-treatment will be presented. In addition, the longitudinal data of QOL over time will be displayed graphically with individual trajectories.

13.2.2. To describe neurotoxicity at the end of study, the descriptive statistics will be presented. Since neurotoxicity is a 4-item measure from FACT/GOG-NTX4, counts and percentages will be calculated. Mean and standard deviation will be also calculated.

13.2.3. To describe abdominal discomfort at the end of study, the descriptive statistics will be presented. The abdominal discomfort is a 4-item score from FACT-GOG/AD. Counts and percentages will be calculated. Mean and standard deviation will be also calculated.

13.2.4. The toxicities will be measured by the number and severity of adverse events defined by CTCAE v5.0. Counts and percentages will be calculated for each adverse event. Mean, standard deviation, median, and interquartile range will be calculated for number of adverse events.

13.2.5. The response rate using RECIST criteria at each time point will be estimated. Counts and percentages will be calculated.

13.2.6. This secondary objective is to estimate progression free survival using survival analysis. Survival will be measured up to the time until progression, date of last contact, or death, whichever comes first. Kaplan-Meier survival curves will be used to estimate the survival probabilities. The survival probabilities for the whole sample and for the stratified groups (weekly or 3-weekly) will be calculated. The log-rank test will be used to compare the two stratified groups.

13.3 Power and Sample Size

The power calculation is performed to test the primary objective. It is calculated to compare the mean QOL between the study patients and the mean QOL from Armstrong et al. (2006). Based on Armstrong et al., the standard deviation of QOL at 6 weeks post treatment is 19.2. Fifty patients will be recruited. The dropout rate is anticipated to be very small, around 1 to 2% at 6 weeks post treatment. Assuming 80% power, a two-sided test and a significance level of 20%, the minimal detectable difference of QOL between the study sample and Armstrong et al. is 5.9. If assuming a higher dropout rate, say 10% at 6 weeks post treatment, the minimal detectable difference for QOL is 6.1. Based on Armstrong et al., the mean difference of QOL between the two standard treatments (IV vs. intraperitoneal) is 5.2. We assume that the mean difference between HIPEC and IV can be larger. However, we are also aware that we may not have enough power to detect the difference. This study is for the descriptive purpose. The data collected in this study can be very useful for future research.

13.4 Estimated Accrual Rate

Accrual is expected to be 40 patients in 18 months. Targeted accrual should be met within 1 ½ years. Under the current amendment (Protocol Version Date: 03/14/2023), an additional 10 patients will be recruited at an accrual rate of 1 patient per month.

13.5 Estimated Study Length

The total study length is approximately 3 years. The estimated study length for the current amendment (Protocol Version Date: 03/14/2023) is approximately 2 years.

13.6 Interim Analysis Plan

Interim reviews will be performed at 6 weeks, 3 and 6 months post-treatment to assess accrual, retention, the incidence of AEs and SAEs.

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Appendix A – Subject Eligibility Checklist

IRB Protocol No. 00044434	**CCCWFU Protocol No. 83216**
Study Title: A Phase II Trial Evaluating Quality of Life After HIPEC in Patients with Stage IIIC and IV Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma	
Principal Investigator: Michael Kelly, M.D.	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm ***
Patients must have histologically or cytologically confirmed non-mucinous, epithelial stage 3 or 4 carcinoma of the ovary, fallopian tube or peritoneum.	☐	☐	
Patients must not have received treatment for another malignancy within 3 years of enrollment	☐	☐	
Patients must have received at least 3 but not more than 6 cycles of carboplatin-doublet based IV chemotherapy AND achieved at least stable disease (radiographically confirmed) at the conclusion of this therapy.	☐	☐	
Age ≥18 years	☐	☐	
ECOG performance status ≤ 2.	☐	☐	
Patients must have adequate organ and marrow function as defined below (within 30 days of registration): -absolute neutrophil count ≥1,500/mcL -platelets ≥75,000/mcL -total bilirubin ≤ 1.5 mg/dL - creatinine clearance ≥ 50 mL/min -AST(SGOT)/ALT(SGPT) ≤ 3 X institutional upper limit of normal -alkaline phosphatase ≤ 3 X institutional upper limit of normal	☐	☐	
The effects of HIPEC on the developing human fetus are unknown. For this reason, and because carboplatin doublet therapy consists of pregnancy category D agents, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.	☐	☐	

Ability to understand and the willingness to sign an IRB-approved informed consent document	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm ***
Patients may not be receiving any other investigational agents.	☐	☐	
Patients with extra-abdominal metastatic disease	☐	☐	
History of allergic reactions attributed to compounds of similar chemical or biologic composition to carboplatin doublet agents.	☐	☐	
Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements	☐	☐	
Pregnant women are excluded from this study because carboplatin doublet therapy consists of pregnancy category D agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with carboplatin doublet therapy, breastfeeding should be discontinued	☐	☐	
Men are excluded from participation due to the site-specific nature of the disease being studied	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

WISER Assigned PID: _____

Signature of research professional confirming eligibility:_____ Date: __ __/__ __/__ __

Signature of Treating Physician: _____ Date: __ __/__ __/__ __

Signature of Principal Investigator**: _____ Date: __ __/__ __/__ __

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

Ethnicity (choose one): ☐ Hispanic

☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by WISER): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contacted by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at [redacted].

Appendix C – Mandatory STRC SAE Reporting Guidelines

Safety and Toxicity Review Committee (STRC) Serious Adverse Event (SAE) Notification SOP	Date: 07/10/2019

Mandatory STRC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Safety and Toxicity Review Committee (STRC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.
   There are three types of trials that are included in this category:
   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the STRC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization ≥ 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the STRC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the STRC by phone (or in-person) about the adverse event. The

nurse/coordinator should contact the treating physician prior to calling the STRC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire STRC committee will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the STRC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to STRC.

STRC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the STRC members will not be notified until a date is entered into the STRC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., study team members and STRC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the STRC has been contacted. Indicate the name of the STRC clinician that was contacted in the Event Narrative field in the SAE console of the particular subject.
1. Document whether or not the protocol should be suspended based on the discussion with the STRC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
2. Follow up/update the clinical member(s) of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date

5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the STRC clinician who was notified and Date/Time notified. In addition, state attribution by STRC clinician as either “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Definitely”. Always include the following here:
    i. STRC clinician name and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with STRC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification *This is required in order for the email notification to be sent*
13. Adverse Event Details – Enter all details for each AE associated with the SAE.

a. Course start date
b. Category
c. AE Detail
d. Comments
e. Grade/Severity
f. Unexpected Y/N
g. DLT Y/N
h. Attributions
i. Action
j. Therapy
k. Click ADD to attach the AE Detail to the SAE.

14. Enter Date Notified STRC -- *This is required for the email notification to be sent*

15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the “Date Notified STRC” and the “SAE Classification”. If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the STRC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the STRC members immediately so that their assessment can be obtained within the 24 hour time frame requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of STRC to Notify by Phone or Page:

[redacted]

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with a different STRC clinician. Allow up to 30 minutes for the new STRC clinician to respond to a phone call or page before contacting another member. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the STRC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of STRC.

STRC CLINICAN RESPONSIBILITY:

It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. STRC reserves the right to disagree with the Investigator's assessment. If STRC does not agree with the Investigator, STRC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the STRC report then an immediate suspension of enrollment should be considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the STRC and using that email “reply to all”. Entitle this new email “**Amendment** for (list date of event and patient ID)” this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click update. This will allow additional information to be added

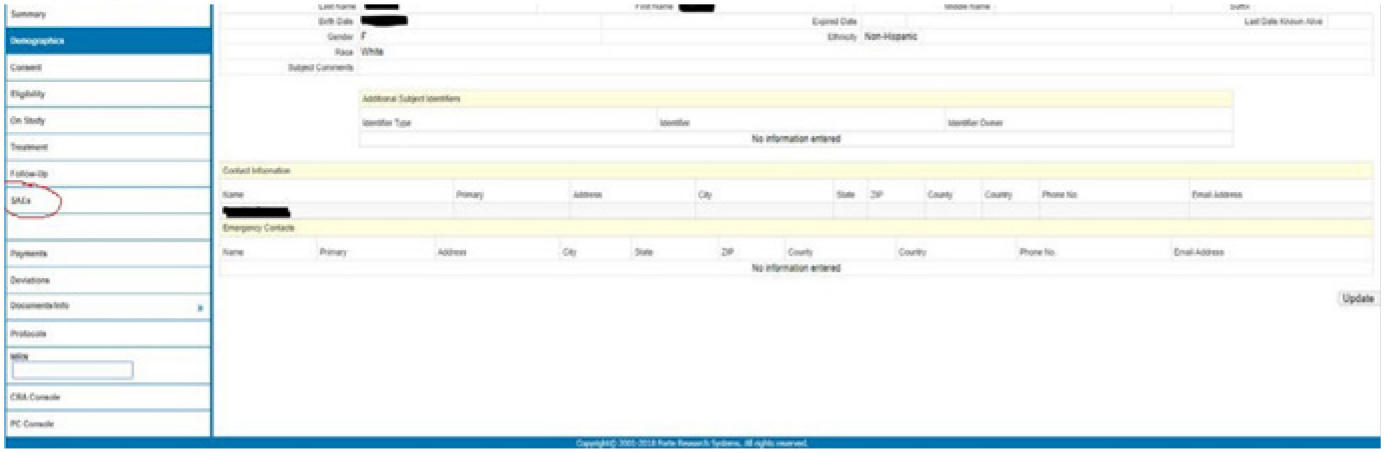
Acronyms

AE – Adverse Event
STRC-Safety and Toxicity Review Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

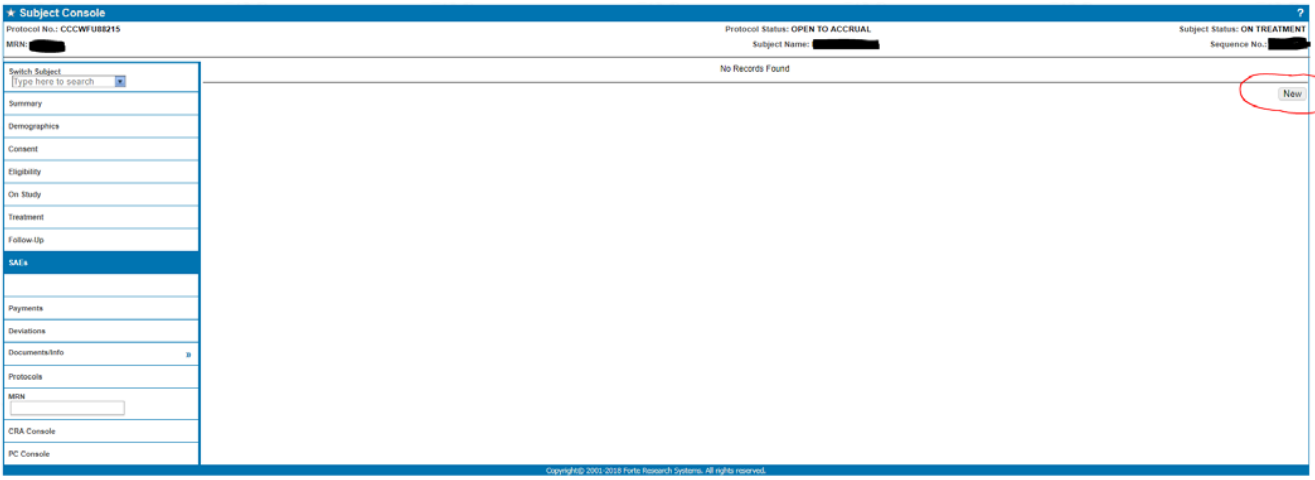
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

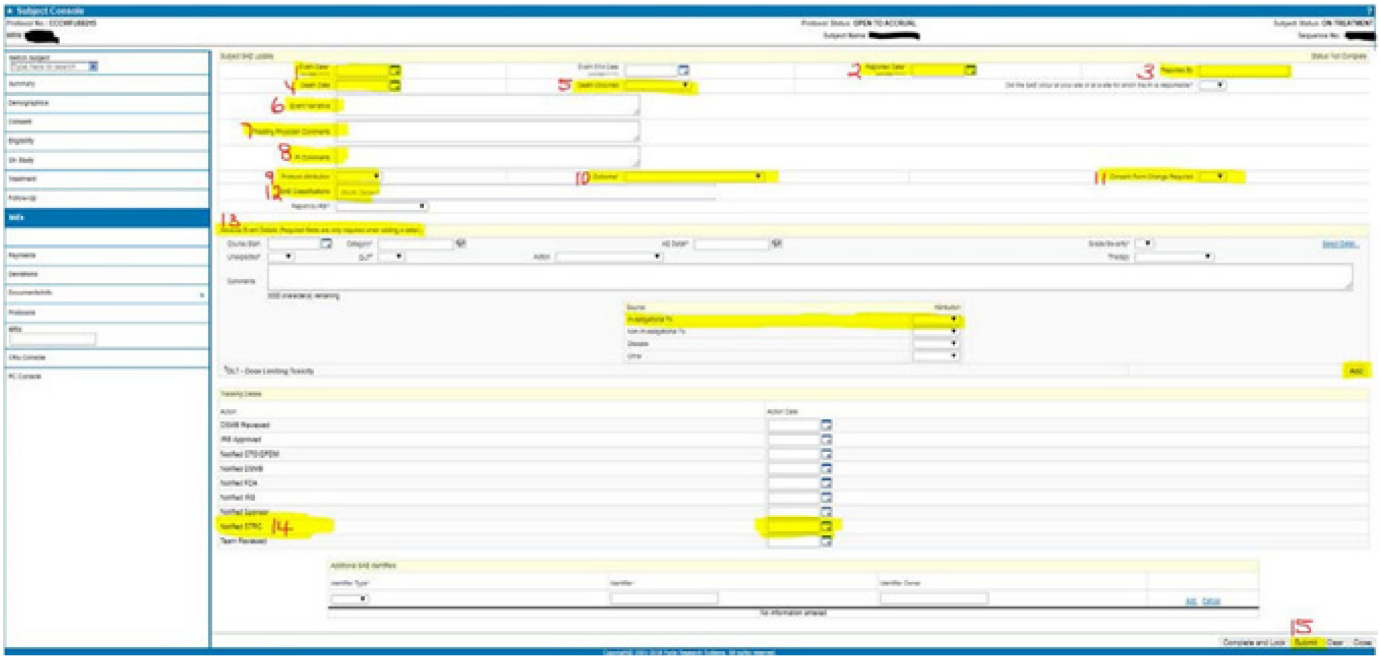
Screen Shot 1:



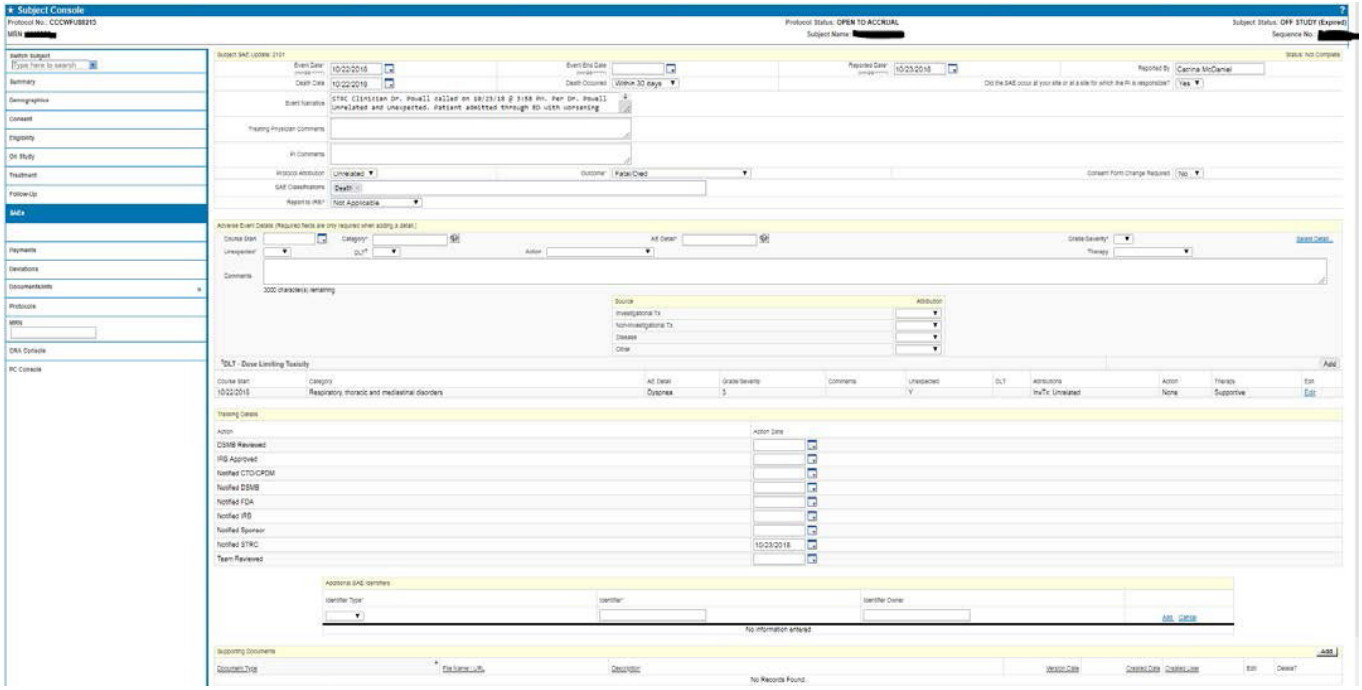
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



Appendix D - SURGERY FORM

FAX # 336-716-4334

Patient Initials;_____ **Study ID# 83216**
Institution:_____ **Surgeon _____**

DATE of SURGERY__ __/__ __/__ __

What was the BSA value that the dose was based on?: _____m^2 Weight____ Height____

- **What is the Resection Status after surgery? (circle) R0 R1 R2a R2b R2c**
- **What was the duration of HIPEC perfusion in minutes? _____min.**
- **What is the average Inflow / Outflow temperature (C^0)? I _____ / _____**
- **What was the length of surgical procedure from start to end? _____ hours**

Does the Operative Report accompany this form?____ YES _____NO

If not, note reason:
_____

_____

Does the Pathology report accompany this form?____ YES _____NO

If not, note reason:
_____

_____

Does the Perfusion Record – HIPEC flowsheet accompany this form?
____ YES ____NO

If not, note reason:
_____

_____
COMMENTS:

_____

_____

_____

Person Completing Form _____

DATE __ __/__ __/___ ___

Appendix E - PERFUSION RECORD - HIPEC Form

FAX # 336-716-4334

Patient Initials;_____ Study ID# 83216
DATE of SURGERY__ __/__ __/__ __

Institution:_____ Surgeon: _____Perfusate: _____
Perfusate Volume (L): _____

***Average Perfusate IN/OUT Temp: _____/_____ (*) Required fields**

*Time	Event Time	Flow	Temperatures			
			H2O	Perfusate In	Perfusate Out	Patient
	0 minutes *Carboplatin *Dose:_____					
	15 minutes					
	30 minutes					
	45 minutes					
	60 minutes Dose:_____					
	75 minutes					
	90 minutes					
	105 minutes					
	120 minutes					

Completed by:_____ Date: __ __/__ __/__ __

Appendix F - FOLLOW-UP FORM

FAX # 336-716-4334 Page 1of 1

Patient initials (Last, First): _____ Medical Record#: __ __ __ __ __ __ __ __

Institution: _____ Study number: **83216**

☐HIPEC

☐ 6 Week

☐ 3 month

☐ 6 month

☐ 12 month (PROs not filled out at this visit)

Please check visit and complete the rest of this form according to that protocol visit

Physical Exam/ vital signs DATE: __ __/__ __/__ __ (ECOG) Performance status_____

Was the FACT – O Questionnaire completed? Yes ____ No ____ N/A____

DATE: __ __/__ __/__ __

****Fax questionnaire along with this form.**

Was the CT/MRI or CXR of chest, abdomen, pelvis done? ____Yes ____No ____ N/A

DATE: __ __/__ __/__ __

****Fax CT/MRI report along with this form.**

Were LABS completed? _____ Yes_____ No

CBC with Diff.	**YES**	**NO**	**N/A**	**DATE __ __/__ __/__ __**
Serum Chemistry	**YES**	**NO**	**N/A**	**DATE __ __/__ __/__ __**
Tumor Markers	**YES**	**NO**	**N/A**	**DATE __ __/__ __/__ __**

****FAX LAB reports along with this form.**

CURRENT DISEASE STATUS

EVIDENCE OF PROTOCOL RELATED CANCER: ____ YES ____ NO

PROGRESSION: ____ YES _____NO (If first report of progression, complete the Measurement Form & attach: *No further report needs completed after the first report of progression.)

DEATH

DATE OF DEATH: _____

CAUSE OF DEATH: ____ CANCER ____ DRUG____SURGERY

COMPLICATIONS_____ OTHER (Specify):

_____

Person Completing Form _____Date completed __ __/__ __/__ __

Appendix G - MEASUREMENT FORM RECIST

	Target Lesions								
TARGET Lesions	**Lesion**	**Site**	**Imaging** *(ie,CT, MRI)*	**Baseline Date**: *(Se, Im)*	**Cycle_____ Date**: *(Se, Im)*	**Cycle_____ Date**: *(Se, Im)*	**Cycle_____ Date**: *(Se, Im)*	**Cycle_____ Date**: *(Se, Im)*	**Cycle_____ Date**: *(Se, Im)*
	01			mm	mm	mm	mm	mm	mm
	02			mm	mm	mm	mm	mm	mm
	03			mm	mm	mm	mm	mm	mm
	04			mm	mm	mm	mm	mm	mm
	05			mm	mm	mm	mm	mm	mm
	Sum of Diameters			mm	mm	mm	mm	mm	mm
	% Change (% Δ) from Baseline or Nadir* & absolute value (AbV)			NA / NA	% Δ / AbV				
	Target Lesion Response			**N/A**					

	Non-Target Lesions								
NON-TARGET Lesions	**Lesion**	**Site**	**Imaging**	**Baseline**	**Cycle_____**	**Cycle_____**	**Cycle_____**	**Cycle_____**	**Cycle_____**
	01								
	02								
	03								
	04								
	05								
	Non-Target Lesion Response			**N/A**					

	New Lesions									
New	1				**N/A**					
	2				**N/A**					
	3				**N/A**					

Overall Tumor Response	**Cycle___**	**Cycle___**	**Cycle___**	**Cycle___**	**Cycle___**
Radiologist Signature:					
Treating Physician Signature:					
PI Signature:					

Completed By:_____ **Signature of Principal Investigator*** _____

Date Completed: ___ ___/___ ___/___ ___ **Date Completed** ___ __/__ __/__ __

(*Signature needed for Assignment of Final Response at time of progression or End of Study)

Appendix H - FACT-O Form

Study Number: 83216 PID: __ __ __ __ __ __ __ __ __

Investigator: Michael Kelly, M.D. Date: __ __/__ __/__ __

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4

GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	<u>FUNCTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4

GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>ADDITIONAL CONCERNS</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
O1	I have swelling in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4

BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4

END OF FACT-O

Appendix I – FACT/GOG – AD (Abdominal Discomfort)

Study Number: 83216	PID: __ __ __ __ __ __ __ __ __
Investigator: Michael Kelly, M.D.	Date: __ __/__ __/__ __

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
AD1	I have pain	0	1	2	3	4
AD2	I have cramps in my stomach area	0	1	2	3	4
AD3	I have pain in my stomach area	0	1	2	3	4
AD4	Stomach pain interferes with my daily functioning	0	1	2	3	4

Appendix J – FACT/GOG - NTX

Study Number: 83216	PID: __ __ __ __ __ __ __ __ __
Investigator: Michael Kelly, M.D.	Date: __ __/__ __/__ __

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4

NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

Appendix K – Adverse Events Log

WFBCCC Adverse Event (AE) Log														
PI: **Subject PID:**							**MRN:**							
Cycle #: **Cycle Start Date:** **Cycle Start Time:**							**Cycle End Date:**			**Cycle End Time:**				
Adverse CTCAE Term	**Lab Value**	**Grade** (1-5) per CTC	**Start Date**	**End Date**	**Attribution** DEF= Definite PROB= Probable POSS= Possible UNLK= Unlikely UNRL= Unrelated	**Expected** N=No Y=Yes	**Serious Adverse Event Detail** NO=No LT=Life Threatening DTH=Death DIS=Disability HOS=Hospitalization CA=Caused congenital anomaly RI=Required intervention to prevent impairment	**Dose Limiting Toxitity (DLT)** N=No Y=Yes	**Action Taken** NO=None DR=Dose Reduced RI=Regimen Interrupted TD=Therapy discontinued INTR=Interrupted then reduced	**Therapy Given** NO=None SYM=Symptomatic SUP= Supportive VSUP=Vigorous supportive	**Reportable?** IRB- IRB STRC- STRC FDA- FDA SPON- Sponsor (Mark all that apply)	**Adverse Event Report (AER) Filed** N=No Y=Yes	**Outcome** R= Recovered TX=Still under treatment/ observation A=Alive with sequalae D=Died	**Treating MD Initials/Date**
Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.														
CTCAE Version 5 - https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf														
STRC- Safety and Toxicity Review Committee											Version 1/10/18			