UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

THE "UPPROACH" APPROACH: A PHASE 2 STUDY OF UPFRONT INTENSITY MODULATED PROTON BEAM THERAPY (IMPT) AND CONCURRENT CHEMOTHERAPY FOR POST-OPERATIVE TREATMENT IN LOCO-REGIONALLY ADVANCED ENDOMETRIAL CANCER

Protocol Number: HP-00092397

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Date: 11/4/2020
Amended: 12/2/2021

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List of Abbreviations

3DCRT	Three-Dimensional Conformal Radiotherapy
AE	Adverse Event
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
BSA	Body Surface Area
CBCT	Cone-Beam Computed Tomography
ChT	Chemotherapy
CRF	Case Report Form
CRT	Chemoradiation
CTCAE	Common Terminology Criteria for Adverse Event
CTV	Clinical Tumor Volume
CTVn	Nodal CTV
CTVp	Primary CTV
D5W	5% Dextrose Injection
DEHP	Diethylhexlphthalate
DFS	Disease-Free Survival
DO	Density-Override
DSMQAC	Data Safety Monitoring / Quality Assurance
DVH	Dose-Volume Histogram
EPIC	The Expanded Prostate Cancer Index Composite
FFS	Failure-Free Survival
G-CSF	Granulocyte Colony-Stimulating Factor
GI	Gastrointestinal
GM-CSF	Granulocyte-Macrophage Colony-Stimulating
GTV	Gross Tumor Volume
GU	Genital and Urinary Systems
HDR	High Dose Rate
HIPAA	Health Insurance Portability and Accountability Act
IMPT	Intensity Modulated Proton Therapy
IMRT	Intensity Modulated Radiotherapy
IRB	Institutional Review Board
ITT	Intent-To-Treat Analysis Set
ITV	Internal Target Volume
ITVp	Internal Target Volume Primary
kV	Kilovoltage Imaging
LDR	Low Dose Rate
LN	Lymph Node
LRF	Locoreginal Failure
LVP	Large Volume Parenteral
LVSI	Lymph-Vascular Space Invasion
MFO	Multi-Field-Optimization
OAR	Organs at Risk
OS	Overall Survival
PA	Posteroanterior
PBT	Proton Beam Therapy
PFS	Progression-Free Survival
PHI	Protected Health Information
PO	Per Oral
PVC	Polyvinyl Chloride
QA CT	Quality Assurance Computed Tomography
RBE	Radiobiological Effective Dose
RT	Radiation Therapy
SAE	Serious Adverse Event
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SID	Study Identification Number
ULN	Upper Limit of Normal
WBC	White Blood Cells

1 Study Summary

Title	The "UPPROACH" Approach: A Phase 2 study of **Up**front Intensity Modulated **Pro**ton Beam Therapy (IMPT) **a**nd Concurrent **Ch**emotherapy for Post-Operative Treatment in Loco-Regionally Advanced Endometrial Cancer
Short Title	UPPROACH
Protocol Number	NCT04527900
Phase	Phase 2
Methodology	Open label, single arm
Study Duration	2.5-3 years
Study Center(s)	Maryland Proton Treatment Center University of Maryland Medical Center, Baltimore MD Upper Chesapeake Hospital, BelAir MD Baltimore Washington Medical Center, Glen Burnie MD Central Maryland Radiation Oncology, Columbia MD
Objectives	To determine if treatment compliance of upfront IMPT and concurrent chemotherapy for post-operative treatment in loco-regionally advanced endometrial cancer is non-inferior within a non-inferiority margin of Δ=10% to the historic compliance rate of CRT arm on GOG 258
Number of Subjects	21 subjects
Diagnosis and Main Inclusion Criteria	Patients with endometrial cancer who have undergone hysterectomy and require adjuvant radiation therapy and chemotherapy
Statistical Methodology	The primary endpoint is treatment compliance of upfront IMPT and concurrent chemotherapy. We will use a 1-sided exact binomial test for testing the primary hypothesis and descriptive analyses for secondary endpoints. A Pocock-style stopping boundary will be used for continual assessment of safety.

2 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

2.1 Background

Endometrial cancer is the fourth most commonly diagnosed cancer in women in the United States and the most common gynecologic malignancy. The American Cancer Society predicts 65,620 cases in the US for 2020 based on the National Cancer Institute's Surveillance, Epidemiology and End Results Database[1,2]. While patients who present with early stage disease maintain a favorable prognosis, patients with more advanced disease represent a more heterogenous group with 5-year overall survival ranging from 40-90%[3,4]. High-risk or advanced disease includes endometrioid endometrial cancer Stage I, grade 3 with extensive lymph-vascular space invasion (LVSI), Stage II, III, and IVA, or non-endometrioid histology (serous, clear cell, carcinosarcoma). Surgery remains first line treatment, with adjuvant treatment dependent upon surgical staging and prognostic factors.

*Rationale for Adjuvant Treatment**:***
Early studies such as GOG 99 and PORTEC-1 demonstrated the decrease in loco-regional recurrence with adjuvant radiation therapy, without an improvement in overall survival, however these patients were primarily early stage, with only some patients meeting criteria for high-intermediate risk[5,6]. Patients with high risk or advanced stage endometrial cancer have a higher risk of locoregional recurrence and therefore warrant pelvic radiotherapy.

GOG 122 established the role of adjuvant chemotherapy (ChT) in advanced endometrial cancer, as the combination of doxorubicin and cisplatin improved progression-free survival and overall-survival when compared to whole abdominal radiation therapy[7]. An Italian study similarly compared adjuvant ChT to radiation therapy (RT) in high risk endometrial cancer. While there was no statistical difference with respect to PFS or OS, there was a trend towards decreased locoregional recurrence with adjuvant RT and decreased distant metastases with adjuvant ChT[8].

Given the decrease in locoregional recurrence and distant metastases seen with RT and ChT respectively, multiple studies have investigated these as combined therapies. In RTOG 9708, a phase 2 study, patients with Stage IB grade 2-3, Stage II and Stage III received adjuvant pelvic RT combined with cisplatin, with outback cisplatin and paclitaxel.[9] This treatment was feasible as 98% of patients completed the protocol and there was 16% late grade 3 toxicity and 5% late grade 4 toxicity. At 4-year follow-up, there was 2% pelvic recurrence, 2% regional recurrence, and 19% distant recurrence.

More recently, PORTEC-3 randomized high risk patients (Stage IB grade 3 and/or LVSI, Stage II-III, or serous/clear cell histology any stage) to adjuvant RT or adjuvant chemoradiation (CRT).[10] The ChT consisted of two cycles of concurrent cisplatin followed by four cycles of carboplatin and paclitaxel. 92% of patients were able to complete concurrent cisplatin, while 71% of patients completed the 4 cycles of outback paclitaxel and 79% of patients completed the

outback carboplatin. There was no improvement in 5-year overall survival in the CRT group for the entire cohort, however there was a statistically significant improvement in failure-free survival (FFS), 75.5% versus 68.6%. On subset analysis however, in Stage III patients there was a 10% improvement in 5-yr OS and 12.55 improvement in FFS with CRT. Additionally, in patients with serous carcinoma, there was a 19% improvement in 5yr OS as well as a 12% improvement in FFS.[11]

While PORTEC-3 compared adjuvant CRT to adjuvant RT, another recently published study, GOG 258, compared adjuvant CRT to adjuvant ChT.[12] In GOG 258, patients with stage III and IV endometroid endometrial carcinoma or stage I and II clear cell/serous carcinoma with positive peritoneal washings were included. CRT regimen was similar to PORTEC-3 while adjuvant ChT alone involved 6 cycles of carboplatin/paclitaxel. 75% of patients completed the prescribed CRT within a median of 21 weeks, while 85% of patients completed the prescribed 6 cycles of ChT alone. The primary acute toxicities seen were gastrointestinal and hematologic, with 40% grade 3+ hematologic toxicity in the CRT group and 52% grade 3+ hematologic toxicity in the ChT group. At time of follow-up, there was decreased vaginal (2% vs 7%), pelvic and para-aortic recurrence (11% vs 20%) with CRT, however higher distance recurrence (27 vs 21%).

While there is a consensus that both adjuvant ChT and RT benefit patients with respect to locoregional and distant control, the sequencing of these therapies varies between institutions. Common approaches include sequential treatment, with 4-6 cycles of ChT followed by RT, sandwich therapy with RT sandwiched between 3 cycles of ChT, or concurrent CRT. Small retrospective studies have shown a benefit with respect to PFS and OS in the sandwich approach[13], however this has not been replicated in larger studies.

Rationale for Intensity-Modulated Proton therapy (IMPT):
While both RT and ChT improve oncologic outcomes in patients with high-risk and advanced endometrial cancer, toxicity is not minimal. The most common toxicities, as evidenced by multiple clinical trials above, include gastrointestinal and hematologic. The high proliferation rate of the mucosal barrier endothelium makes it particularly susceptible to RT-related toxicity and symptoms may present as cramping, diarrhea, anorexia, malaise and rectal discomfort[14]. Acutely, bone marrow toxicity may have a hematologic presentation as it is estimated that 25% of all bone marrow is located in the pelvis and hematopoietic stem cells are sensitive to radiation[15,16]. Bone toxicities are also more commonly observed as late toxicities and may take months to years to develop. The most common late side effect is a pelvic or sacral insufficiency fracture, thought to result from impaired osteoblast proliferation and resultant localized osteopenia.
Radiation techniques have evolved to improve upon the historical rates of bowel and bladder toxicity. Recently published RTOG 1203 randomized patients with endometrial or cervical cancer to adjuvant intensity modulated radiotherapy (IMRT) versus three-dimensional conformal radiotherapy (3DCRT).[17] There was no difference in 2-year LRF, DFS, or OS between the two arms. IMRT resulted in lower reduction in the mean Expanded Prostate Cancer Index Composite (EPIC) bowel score between baseline and end of RT (18.6 vs 23.6 points, $p = 0.048$). Similarly, lower decline in EPIC urinary score was noted (5.6 vs 10.4 points, $p = 0.03$). At the end of RT, frequent or almost constant diarrhea was less commonly reported with IMRT (33.7% vs 51.9%,

p = 0.01). Use of anti-diarrheal medications four or more times daily was also lower with IMRT (7.8% vs 20.4%, p =0.04). A more recent analysis of RTOG 1203 was published which found that clinician reported adverse events underrepresented those reported by patients. For example, the incidence of at least CTCAE grade 3 diarrhea was 4.7%, however 43.2% of patients reported diarrhea that occurred frequently or constantly.[18]

Even newer radiation techniques, such as intensity modulated proton therapy (IMPT) has been utilized more given the increased organ sparing and decreased toxicity. In more recent years, proton beam therapy (PBT) has become an increasingly common modality for the treatment of uterine malignancies and is capable of even more precise dose distributions than photon-based RT due to intrinsic properties of these much heavier particles.[19] Dosimetric/planning studies from other institutions confirm the significant reduction of dose to critical normal tissues like bladder, bowel, rectum, and bone marrow.[20-22]

Additionally, a single-institution study reported on their experience with pencil beam scanning for the postoperative treatment of gynecologic cancers and found low rates of grade 2 and grade 3 hematologic toxicity.[23] Preliminary data from the University of Maryland Medical Center has suggested that IMPT using pencil beam scanning is feasible in patients with endometrial cancer, with only 10% of patients developing grade 2 GI toxicity and no patients developing ≥ grade 3 GI or GU toxicities (abstract under review).

We would like to test the *hypothesis* that in the postoperative setting, patients with advanced endometrial cancer will be able to complete a course of full dose ChT – carboplatin and paclitaxel – concurrent with upfront pelvic IMPT. We propose a phase 2 study with the primary objective of testing treatment compliance in comparison to historical control of the CRT arm of GOG 258 study. Secondary objectives include evaluating both acute and delayed grade 3 toxicities.

3 Study Objectives

Primary Objective

1. To determine if treatment compliance of **Up**front Intensity Modulated **Pro**ton Beam Therapy (IMPT) **a**nd Concurrent **Ch**emotherapy (UPPROACH) for Post-operative Treatment in Loco-regionally Advanced Endometrial Cancer is non-inferior to the historic compliance rate of the chemoradiation arm of GOG 258 study

Secondary Objective

1. To estimate the incidence of ≥ Grade 3 acute gastrointestinal, urinary, and hematological toxicity (via CTCAE, PRO-CTCAE, and EPIC urinary and bowel domains) over the course of UPPROACH.
2. To estimate the incidence of ≥ Grade 3 delayed gastrointestinal and urinary toxicity (via CTCAE, PRO-CTCAE, and EPIC urinary and bowel domains) at 6 to 12 months post-completion of IMPT.
3. To prospectively collect biospecimens for translational research

4 Study Design

4.1 General Design

Surgery: hysterectomy +/- BSO +/- lymph node dissection/sampling	**REGISTER**	**Chemotherapy** Carboplatin AUC 5-6* + paclitaxel 175 mg/m2 q21 days for 6 cycles** AND **Intensity modulated proton therapy***** 45-50.4 Gy to pelvis (+/- lower para-aortic up to renal hilum) starting 2nd cycle chemotherapy	**ANALYSIS**

* Carboplatin AUC 5-6 left to the discretion of the treating physician

** Per physician discretion, patients may receive concurrent hormonal therapy or Trastuzumab (Herceptin) along with standard of care chemotherapy

*** Brachytherapy if clinically indicated

**** Patients whose insurance providers have denied proton therapy or patients who are unwilling to travel for their course of RT will be offered participation as a prospective cohort, treated per institutional standard of care, and will be followed for compliance and toxicity endpoints per study protocol (we would anticipate for an additional 40 patients, however this is not included in sample size below)

Required sample size: 21 patients

4.2 Primary Study Endpoints

1. Compliance rates of doublet ChT and concurrent IMPT. This will be measured as proportion of patients completing full 6 cycles of ChT.

4.3 Secondary Study Endpoints

1. Acute GI toxicity as measured by CTCAE, PRO-CTCAE, and EPIC bowel domain, during weekly radiation assessments
2. Acute urinary toxicity as measured by CTCAE, PRO-CTCAE, and EPIC urinary domain, during weekly radiation assessments
3. Acute hematologic toxicity as measured by CTCAE during pre-chemotherapy assessments
4. Late (6-month) GI toxicity as measured by CTCAE, PRO-CTCAE, and EPIC bowel domain during follow up assessment
5. Late (6-month) urinary toxicity as measured by CTCAE, PRO-CTCAE, and EPIC urinary domain during follow up assessment

5 Subject Selection and Withdrawal

5.1 Inclusion Criteria

4.1.1 Surgery must have included a hysterectomy. Bilateral salpingo-oophorectomy, pelvic lymph node sampling, para-aortic lymph node sampling, and omentectomy are optional
4.1.2 Patients will be staged according to FIGO 2009 staging system. Eligibility is defined based on clinical-pathologic features.
4.1.3 Patients with endometrioid endometrial cancer with the following:

- Stage IA grade 3 with extensive LVSI
- Stage IB grade 3
- Stage II
- Stage III (A, B, and C)
- Stage IVA who are recommended adjuvant whole pelvic RT (+/- lower para-aortic up to renal hilum) and systemic chemotherapy.

4.1.4 Patients with clear cell, serous papillary carcinoma, or carcinosarcoma with stages IA-III who are recommended adjuvant whole pelvic RT (+/- lower para-aortic up to renal hilum) and systemic chemotherapy.
4.1.5 Patients with a GOG Performance Status of 0, 1, or 2
4.1.6 Patients with adequate organ function, reflected by the following parameters:

- WBC ≥ 3000/mcl
- Absolute neutrophil count (ANC) ≥ 1000/mcl
- Platelet count ≥ 100,000/mcl
- SGOT, SGPT, and alkaline phosphatase ≤ 2.5 X upper limit of normal (ULN)
- Bilirubin ≤ 1.5 X ULN
- Creatinine ≤ institutional ULN (if serum creatinine > ULN, estimated GFR ≥ 45 ml/min)

4.1.7 Patients who have signed an approved informed consent and authorization permitting *release of personal health information*
4.1.8 Patients must be 18 years of age or older

5.2 Exclusion Criteria

4.2.1 Patients with leiomyosarcoma
4.2.2 Patients with clinically significant pelvic or para-aortic nodal disease, on post-surgery CT scan, that was not dissected and would require higher boost dose
4.2.3 Patients with recurrent endometrial cancer with gross nodal or vaginal disease requiring high dose radiotherapy, or history of prior chemotherapy
4.2.4 Patients with a history of prior pelvic/abdominal RT or with history of prior cancer treatment that contraindicates this protocol therapy including history of prior chemotherapy for any other malignancy.
4.2.5 Patients with a history of serious co-morbid illness or uncontrolled illnesses that would preclude protocol therapy
4.2.6 Patients with an estimated survival of less than three months
4.2.7 Patients with FIGO 2009 Stage IVB endometrial cancer

4.2.8 Patients with a history of myocardial infarction, unstable angina, or uncontrolled arrhythmia within 3 months from enrollment
4.2.9 Patients recommended to receive concurrent immunotherapy during radiation; though immunotherapy after completion of chemotherapy is allowed, if clinically indicated. Similarly, hormonal therapy or Trastuzumab can be added to chemotherapy and radiation (proton or photon) either concurrently or sequentially, if clinically indicated.

5.3 Subject Recruitment and Screening

Patients will be recruited from consults, UMGCCC websites, community colleagues, and the PI's or coinvestigators' (Co-Is') clinical practice. Research staff may also screen providers' clinical schedules to alert physicians of potentially eligible subjects. Once the PI or CO-I identify a potential candidate, they will provide a description of the study to determine if the patient is willing to consider enrollment. If the patient expresses interest in the study, a member of the research staff will be asked to continue the informed consent process in greater detail. Patients will not receive any compensation or incentive to participate in the study.

Patients will separately consent for participation in biospecimen collection, as this is an optional component of the trial protocol.

5.4 Dual Enrollment

Dual trial enrollment is permitted such that it does not interfere with receipt of this trial's protocol.

5.5 Early Withdrawal of Subjects

5.5.1 When and How to Withdraw Subjects

If a patient is found to have disease progression that would make them ineligible for radiation therapy, then they will be removed from the study. All data collected will still be used, however no data will be collected after withdrawal from the study.

6 Treatment Modalities

6.1 Chemotherapy

Carboplatin and paclitaxel

Agent	Dose/day	Route	Days
Carboplatin	AUC 5-6 (calculated AUC) *	IV in 1 hour	1, 22, 43, 64, 85, 106
Paclitaxel	175 mg/m^2	IV, in 3 hours	1, 22, 43, 64, 85, 106

* Carboplatin AUC 5-6 left to the discretion of the treating physician

Per physician discretion, patients may receive concurrent hormonal therapy or Trastuzumab (Herceptin) along with standard of care chemotherapy. Concurrent immunotherapy is not allowed during radiation but may be added after completing 6 cycles of chemotherapy, if clinically needed.

6.1.1 Carboplatin (Paraplatin®)

6.1.1.1 General Information

Formulation: Paraplatin is supplied as a sterile lyophilized powder available in single-dose vial 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.

Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, 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. When prepared as directed, Paraplatin solutions are stable for eight hours at room temperature, since no antibacterial preservation is contained in the formulation it is recommended that Paraplatin solutions be discarded eight hours after dilution.

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

Storage: Unopened vials of Paraplatin 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 imbalance, hypomagnesemia, hypocalcemia, and allergic reaction.

Supplier: Commercially available from Bristol-Myers Oncology.

Dose Calculations: See appendix for current instructions.

* Refer to package insert for additional information

6.1.2 Paclitaxel (Taxol®)

6.1.2.1 General Information

Formulation: Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water.

Supplier/How Supplied: Commercially available from Bristol-Myers Oncology. A sterile solution concentrate, 6 mg/ml available in 5 ml (30mg/vial), 16.7 ml (100mg/vial) and 50 ml (300mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use.

Solution Preparation: Paclitaxel, at the appropriate dose, will be diluted in 500 – 1000 ml of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D5W) (500 cc's is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate matter test for LVP's) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Storage: The intact vials should be stored between 20^0-25^0C (68^0-77^0F), in original package. Neither freezing nor refrigerator adversely affects the stability of the product.

Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3 – 1.2 mg/ml) are physically and chemically stable for 27 hours at ambient temperature (~25^0C) .

Administration of Paclitaxel:
Paclitaxel, at the appropriate dose and dilution, will be given as a continuous IV infusion. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and

connectors, such as the IV administration sets (polyethylene or polyolefin), which are used to infuse parenteral Nitroglycerin. Nothing else other than 0.9% sodium chloride is to be infused through the line where paclitaxel is being administered.

Adverse Effects:
Hematological: Myelosuppression
Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis
Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia
Pulmonary: Pneumonitis
Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication-Dexamethasone)
Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy
Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, radiation-recall reactions, erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
Liver: Increased SGOT, SGPT, bilirubin and alkaline phosphatase, hepatic failure, hepatic necrosis
Other: Alopecia, fatigue, arthralgias, myalgias, light-headedness, myopathy
Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata

*Refer to Package Insert for additional information

6.1.3 Chemotherapy Administration Protocol

The following protocol is suggested however may be adjusted per standard of care by the treating oncologist. Patients may receive chemotherapy under the care of a local oncologist outside of UMMC, with chemotherapy administration per institutional and provider policy/standard of care.

Paclitaxel will be administered in a three-hour infusion followed by carboplatin in a one-hour infusion. If used, docetaxel will be administered over 1 hour, also given prior to carboplatin.

In case of severe hypersensitivity to paclitaxel, where re-challenge is not medically indicated **or** if repeated severe reaction at challenge, paclitaxel should be substituted by docetaxel 60-75mg/m^2. Dose of docetaxel at the discretion of prescribing oncologist

Paclitaxel: 175mg/m^2, 3-hour infusion, Day 1, q21 days *or Docetaxel: 60-75mg/m^2, Day 1, q21 days*

followed by Carboplatin dosed to an AUC of 5-6, Day 1, q21 days for 6 cycles

6.1.4 Chemotherapy Premedications

The following protocols are suggested however may be adjusted per standard of care by the treating oncologist.

An antiemetic regimen is recommended. Such as: Famotidine 20mg IV, dexamethasone 20mg IV in 0.9% NS 50ml, diphenhydramine 25mg IV, ondansetron 16mg PO (if unable to take PO, give 8mg IV).

Additionally, it is recommended that a preparative regimen be employed to reduce the risk associated with hypersensitivity reactions. This regimen includes diphenhydramine 50mg IV q6h PRN for infusion reaction, hydrocortisone 100mg IV PRN for infusion reaction, famotidine 20mg IV x 1 dose PRN for infusion reaction, epinephrine 1:1000 (0.3mg) subcutaneous PRN for infusion reaction.

After recovery of symptoms, infusion may be re-challenged:

0-15 min: paclitaxel or carboplatin flow 15 ml/hour

15-30 min: NaCl 0.9% + 2mg clemastine

30-45 min: paclitaxel or carboplatin flow 84 ml/hour

45-90 min: if no reaction occurs, paclitaxel flow 170 ml/hour or carboplatin flow 500 ml/hour

Suggested pre-medication prior to docetaxel infusion include: Ondansetron 24mg PO x 1 dose on day 1, (if unable to take PO, give 16mg IV 50 mL 0.9% NS). Dexamethasone 20mg IV 0.9% D5W 50 mL x 1 dose on day 1.

Additional PRN medications per standard of care, that may include but are not limited to: lorazepam 1mg PO q6h PRN for nausea, vomiting, anxiety (if unable to take PO, give IV). Prochlorperazine 10mg PO q6h PRN for nausea or vomiting (if unable to take PO, give IV).

6.2 Proton Therapy

The whole pelvis will receive a total dose of 4500 cGy in 25 fractions to 5040 cGy in 28 fractions

6.2.1 Proton Treatment Planning

Technology requirements: Pencil beam scanning proton therapy is required for this protocol

RBE accounting and reporting:
For protons, the annotated dose refers to the RBE weighted dose. Dose will be reported in Gy (RBE), where 1Gy (RBE) = physical dose Gy x RBE (radiobiological effective dose), RBE = 1.1

Planning Margins:
The planning target for proton therapy is the CTV, consistent with standard practice. Setup and range uncertainties are accounted for using robust optimization, described below.

Robustness
Robust optimization is used to ensure adequate coverage in 13 scenarios (1 nominal plan, 6 cardinal directions, +/- 3.5% range uncertainty). Goal robustness should be to have 97% of the volume covered by 97% of the prescribed dose for each dose level, at minimum 95%/95%, in the

"worst case scenario" of robust evaluation. For all pelvic plans where beam entry and passage through bowel is anticipated, two special density-override (DO) scans will be derived to account for uncertainty in bowel filling. In one, loops of bowel will be considered to have the density of air, and in the other, the density of muscle. Robust optimization will be performed on these two DO scans in addition to the nominal, "un-processed" scan.

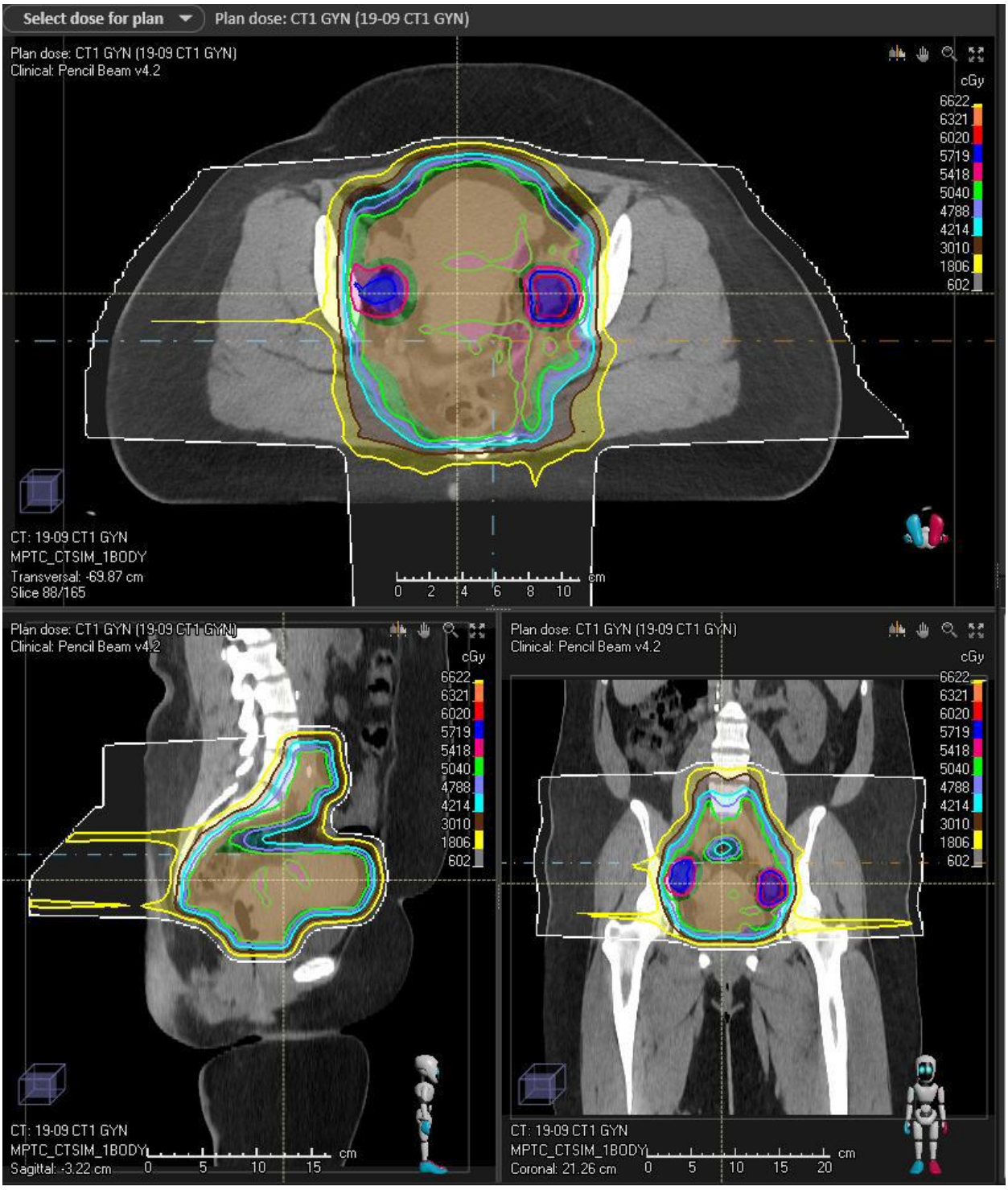
Beam Arrangement

Appropriate beam arrangements to be determined by the treating physician. As a general guideline, 2 laterals (with a midline block) and a PA (with rectal block) may be used. Other beam arrangements like posterior obliques can be used under some circumstances. A multi-field-optimization (MFO) method will likely be required if using the aforementioned beam angles.

If treating para-aortic nodes, 2 PO should be included to cover the para-aortics.

Example plan taken from MPTC Treatment Planning Guidelines:

Primary + pelvis



Proton delivery QA

A QA CT at some point during treatment course is required. It is recommended that this be performed every other week, however is left to the discretion of the treating physician.

Dose will be recalculated on the QA CT using a rigid registration with the planning CT by dosimetry, and subsequently evaluated by the treating physician. Deformable registration may be utilized to adapt OARs and targets to the QA CT position, with subsequent modification performed by the physician, if required. The physician should always evaluate the dose based on visualization of the dose distribution on the patient's anatomy rather than DVH review alone. QA CT should not be performed in the last 7 days of treatment as minimal alterations are possible at this late juncture.

6.2.2 Treatment Planning Simulation

Patient will be simulated supine, with arms above head (if treating para-aortics) or on the chest (if not treating the para-aortics).

Patient will be immobilized in the supine position with a Vac-Lok bag under upper thigh, with the addition of an upper Vac-Lok if treating para-aortics.

It is recommended that radiopaque marker seeds be inserted into the vaginal introitus for improved target delineation. This will be done for the empty bladder scan.

Oral and IV contrast may be used for better bowel and vessel delineation, however, is not required. If using contrast, a non-contrast scan must be performed first.

Patients should be scanned with both a full and empty bladder in order to create an ITV. The full bladder scan will be used for both planning and treatment. Patients should be instructed to drink 24-32 oz 30-60 minutes prior to simulation and treatment. Both full and empty bladder scans should be done non-contrast as well.

Axial images will be obtained every 3mm from the bottom of L1 to midthigh, except in cases of para-aortic involvement, where the superior border of the scan should end no sooner than the midsternum, but can be customized depending on patient specifics.

6.2.3 Image Guidance

kV every fraction aligning to bony structures. CBCT first three and then weekly, and as needed thereafter.

6.2.4 Definition of target volumes and margins

Please refer to RTOG Gynecological Atlas for volume specification. The atlas may be accessed on the RTOG website at: http://www.rtog.org/gynatlas/main.html

See also: http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx for contouring guidelines.

Gross tumor volume (GTV):
In most post-operative cases there will be no GTV, unless there is an identifiable area of residual disease

Clinical tumor volume (CTV):
CTV will be the combination of CTVp and CTVn as below.

Primary CTV (CTVp) - should encompass the vagina and paravaginal soft tissues. The inferior limit is usually around the level of the upper third of the pubic symphysis but can be individualized based on the inferior extent of tumor[24]; the lateral margin should be to the obturator muscle; at least 3cm of the vagina needs to be treated or at least 1 cm below the obturator foramen.

ITVp – generated by delineating CTV on full and empty bladder scans. If there is considerable rectal distention (gas or stool), then extend ITV into the rectum by 5 to 10 mm. The anterior extension of ITV into bladder.

Nodal CTV (CTVn) - should include the LNs that drain the involved site and adjacent perinodal soft tissue, including the internal, external, and common iliac LNs, presacral LN, and soft tissues to the level of S3. This will include the vessel, perinodal tissue on the pelvic wall side, and pertinent clips. The average margin will be 7 mm. Approximately 1–2 cm of tissue anterior to the S1–S3 sacral segments should be added for patients in order to include the presacral LN and uterosacral ligaments. The CTV of the nodes should end 7 mm from the L4/L5 interspace. If the paraaortic LNs are being treated because of a positive common iliac LN, the CTV should end at the top of L2; if a positive paraaortic node is present, then the CTV must end at the top of T12 so the CTV should be modified to accomplish this.

Patients with pathologically negative para-aortic lymph nodes will be treated with pelvic irradiation. If any para-aortic lymph node is positive on surgical sampling, with no clinically significant nodes seen on CT scan, the patient will receive extended field pelvic/para-aortic radiotherapy. Patients may receive para-aortic RT in the absence of para-aortic nodal staging information if the pelvic lymph nodes are positive.

For involvement of the distal 1/3 of the vagina, inguino-femoral nodes should also be covered in the treatment volume.

If the patient's tumor extends into the cervix, or invades deeply and extends into the lower uterine segment, of if there is lymph-vascular space invasion by tumor, or if the tumor has extended into the vagina, such a patient will receive intra-vaginal boost brachytherapy (HDR or LDR) at the discretion of the radiation oncologist.

6.2.5 Normal tissue dose volume constraints

OAR	Primary	Secondary
Kidneys	V18 < 50% (each)	
	Mean < 18Gy (each)	
If only one kidney present:	V18 < 15%	
	V6 < 30%	
Bone Marrow	V40 < 37	
	V20 < 80	
Femoral Head	V40 < 40%	

	V45 < 25%	
	50Gy ≤ 0.5cc	
Small Bowel	V40 < 30%	V20 ≤ 50%
	V55 < 10cc	V45 ≤ 15%
		V50 ≤ 10%
Rectum	V40 ≤ 80%	V40 ≤ 100%
	V30 ≤ 60%	
Bladder	V45 < 35%	V50 < 35%

6.3 Treatment Modifications

6.3.1 Dose Modifications of Carboplatin and Paclitaxel

Toxicity	**Adjustments/Remarks**
Hematologic toxicity	
ANC < 1.0 x 10^9/L	Treatment modifications will be made based on ANC rather than WBC count. Subsequent cycles of therapy will not begin until ANC ≥ 1.0 x 10^9/L If ANC < 500/mcl lasting > 7 days, dose reduce both carboplatin and paclitaxel of one level, without addition of G-CSF. If this occurs after prescribed dose reduction, then G-CSF may be utilized If patient is already at reduced dose level and the cycle is delayed > 7 days for reasons of hematologic toxicity, then G-CSF may be utilized
Platelets < 100 x 10^9/L	If platelets ≤ 25,000, dose reduce carboplatin only without change in paclitaxel dose Patients who require delay of > 7 days to allow for recovery of platelet count will receive a dose reduction of one level of both carboplatin and paclitaxel
Neurologic toxicity	
Neuropathy	Grade 2-4 peripheral neuropathy requires discontinuation of protocol therapy until symptoms resolve to ≤ Grade 1. When treatment resumes, paclitaxel dose should be reduced. Recurrent grade 2 requires delay of treatment until neuropathy resolves to grade 1. A delay exceeding 3 weeks of neurologic function recovery will require discontinuation of protocol. Discontinue the protocol regimen in patients with recurrent Grade 3 or any Grade 4 neurologic toxicity
Other toxicities	
Cardiac arrhythmias	Asymptomatic bradycardia associated with paclitaxel treatment is not indication to discontinue therapy. For symptomatic arrhythmia, paclitaxel infusion should be discontinued, and arrhythmia managed per standard practice. Patient will be removed from protocol treatment.
Nausea/vomiting	No dose adjustment is to be made for GI toxicity
Stomatitis or diarrhea	If any mucositis is present on day 21 of a cycle, treatment should be delayed until mucositis has returned to grade 0. Grade 3 or 4 mucositis or diarrhea requires a dose reduction of paclitaxel.
Other toxicities: Grade 3 or 4	Protocol treatment withheld until patients recover completely to Grade 1. The next dose of the agent believed responsible for the adverse event will be given at a one dose level reduction

6.3.2 Radiation Modifications

Radiation will be held for any Grade 4 toxicities until toxicity is ≤ Grade 2.

Radiation should continue to be delivered for ≤ Grade 3 non-hematologic toxicities in or outside the RT field.

6.3.3 Radiation Toxicities

Please see sections 6.1.1.1 and 6.1.2.1 for chemotherapy related toxicities.

Side effects expected from radiation therapy include: fatigue, diarrhea, rectal irritation, urinary frequency and dysuria, loss of pubic hair, darkening of skin in the treatment portal, and low blood counts.

Common long term-effects include: vaginal narrowing and shortening and dyspareunia

Uncommon long-term effects include: rectal bleeding, loose stool, rectal ulcer, dysuria, urinary frequency, hematuria, and vaginal vault necrosis.

Rare long-term effects include: bowel obstruction, urethral obstruction, and vesicovaginal or rectovaginal fistula

6.4 General concomitant medication and supportive care guidelines

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol.

Anti-emetic chemotherapy premedication as in section 6.1.4

Hypersensitivity reaction protocol as in section 6.1.4

Patients may receive antidiarrheals as needed. Imodium is recommended as needed. If diarrhea persists, Lomotil is recommended. Patients may receive antiemetics as needed. Patients may receive analgesics as needed.

Hematopoietic Growth Factors:

WBC growth factors (i.e. filgrastim [G-CSF], sargramostim [GM-CSF], pegfilgrastim [Neulasta], pegfilgrastim-cbqv [Udenyca]) may be used for neutropenia despite reduced dose, as in section 6.3.1. WBC growth factors may not be given prophylactically while a patient is receiving radiation, however it may be given prophylactically during chemotherapy only phase per ASCO practice guidelines.[25]

Patients will NOT receive prophylactic thrombopoietic agents. If they experience thrombocytopenia, treatment should be initiated following the judgment of the treating physician.

7 Study Procedures

7.1 Study Calendar

Tests & Observations	Prior to study	Weekly during RT	Week 3 & Week 5 of RT	Prior to each cycle of ChT	Follow-up after RT completion			
					3-6 wks	2-4 mos	5-7 mos	10-14 mos (optional)
Screening, informed consent, enrollment	X[1]							
History and Physical	X[1]	X		X	X	X	X	X[5]
CBC with diff	X[1]			X[2]				
CMP, Mag	X[1]			X[2]				
Plasma (green top)	X[3]		X[3]			X[3]	X[3]	
Abdomen and pelvis CT	X[4]						X[4]	X[4]
Chest X-ray or CT chest	X[6]							
CTCAE toxicity evaluation		X	X		X	X	X	X[5]
Bowel & Urinary Domain of EPIC	X		X		X	X	X	X[5]
PRO-CTCAE items for GI toxicity	X		X		X	X	X	X[5]

X[1] Must be obtained within 28 days of initiating protocol therapy
X[2] Must be obtained within 4 days prior to therapy
X[3] Optional
X[4] As clinically indicated. Consider for patients with high grade carcinoma (including poorly differentiated endometrioid, serous, clear cell, undifferentiated carcinoma, and carcinosarcoma)
X[5] As clinically indicated.
X[6] As clinically indicated. CT chest may be obtained if CXR is abnormal. Chest CT is acceptable in place of CXR for baseline screening.

7.2 The Expanded Prostate Cancer Index Composite (EPIC)

The EPIC is a comprehensive instrument that includes four domains (urinary, bowel, sexual and hormonal); each domain has been separately validated so they may be used independently from each other. Although EPIC was designed for prostate cancer patients, the items within the bowel and urinary domains do not mention the word "prostate." The items were designed to evaluate bowel and urinary function and both during and following radiation treatment of the pelvis. There is a total of 16 questions that cover both domains.
NOTE: EPIC is in the public domain and available for use free of charge. It is available and validated in Spanish and other languages.

7.3 PRO-CTCAE

The PRO-CTCAE instrument will be utilized as an additional assessment of GI and GU toxicity. Participants will be asked an additional 16 questions to assess these symptoms.

7.4 Biospecimen collection and sample banking

Patients will separately consent for participation in biospecimen collection. This will be optional and is not required for enrollment in the trial protocol. Given the time sensitivity of sample collection, this will be limited to patients who will be doing their follow up visits at the University of Maryland Medical Center or Maryland Proton Treatment Center.

Blood samples will be obtained from participants at up to four time points: before radiation treatment starts (required for participation in this aspect of the protocol), up to two times during treatment (one obtained during week 2-3 of treatment and one obtained during the last 1-1.5 weeks of treatment), and a last sample may be obtained at a follow-up appointment (at either the one, three, or six month follow up). Two 10 mL vials will be obtained at each time points in which blood is collected. If all four blood draws occur, a total of up to 80 mL will be collected.

Research serum samples will be labeled with the protocol number, participant's unique study identification number (SID), type of sample and the date of collection.

Samples will be stored indefinitely in the University of Maryland Biorepository or Department of Radiation Oncology. All specimens will be maintained in a secure freezer storage area in the school of medicine. Samples will be store indefinitely unless a participant requests removal of samples from the repository.

Investigators from within the University of Maryland may propose research projects using these samples and data. The requesting investigator will submit an IRB application for the proposed research.

8 Statistical Plan

8.1 Sample Size Determination

The proposal is using concurrent doublet ChT which increases toxicity risk while using IMPT which can reduce toxicity. The compliance rate for full 6 cycles of doublet Carboplatin-Paclitaxel (with or without dose-reductions) was 75% in after sequential CRT in the GOG 258 study. We expect the compliance rate to be 85% (H_A) for concurrent ChT/IMPT. We will test the hypothesis that concurrent ChT/IMPT yields a compliance rate that is non-inferior to the rate of sequential CRT within a non-inferiority margin of Δ=10%. A sample size of N=21 achieves 80.2% power to show non-inferiority using a 1-sided exact binomial test with a target significance level of 0.1. The actual achieved α is 0.092. We will be able to conclude non-inferiority within the chosen margin, if 17 or more of the 21 patients complete the 6 planned cycles of chemotherapy. Power and actual alpha were computed using binomial enumeration of all possible outcomes. As such, demonstrating non-inferiority with the combination allows the field to move forward.

8.2 Statistical Methods[26-29]

Analysis for primary endpoints:
The primary endpoint is completion of all the 6 planned cycles of chemotherapy. The proportion of patients completing all cycles will be calculated with an exact two-sided 80% confidence interval. If the lower limit of this interval excludes 65%. i.e. the 75% completion rate in GOG 258 minus the non-inferiority margin Δ=10%, we will conclude non-inferiority within a 10% margin.

Analysis for secondary endpoints:
GI, GU, and hematologic toxicity will be measured by the CTCAE and PRO-CTCAE weekly during IMPT and at 1, 3 and 6-months, and 12 months (last time point is optional) post-IMPT. EPIC bowel and urinary domain will be administered during week 3 and 5 of RT as well as at 1, 3, and 6-months post-IMPT. Toxicity will be reported through descriptive analyses. A significance level of 0.05 will be used for this comparison.

Stopping boundary for excess high-grade toxicity.

No. of pts., *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Boundary, b_n	-	2	3	3	3	3	4	4	4	4	4	5	5	5	5	5	5	6	6	6	6

As an added safety measure to prevent excess high-grade toxicity, we will define treatment dose-limiting acute toxicity (DLT) as any acute GI or GU adverse events greater than or equal to 4. Based on clinical significance and recognizing that the incidence of Grade 3-5 GI/GU toxicity in GOG 258 study was 15% and recognizing that overall Grade 4 or higher toxicity incidence was 14%, we will seek to consider a conservative estimate of 10% Grade 4 or higher GI/GU toxicity as our DLT boundary. Sequential boundaries will be used to monitor dose-limiting toxicity rate. The accrual will be halted if excessive numbers of dose-limiting toxicities are seen, that is, if the number of dose-limiting toxicities is equal to or exceeds b_n out of n patients with full follow-up (see table). When this happens, we can conclude that the incidence of DLTs statistically significantly exceeds the target Grade 4 or higher GI/GU toxicity of 10%. If the boundary is crossed at n=2, the DSMB will be tasked with reviewing all cases and decide whether the trial and study treatment should be halted/modified. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 5% when the rate of dose-limiting toxicity is equal to the acceptable rate, θ=0.10. All DLTs will be included in the safety analysis irrespective of whether the patient completed the planned course of therapy.

8.3 Subject Population(s) for Analysis

Intent-to-Treat Analysis Set (ITT): All subjects who are enrolled on the trial and receives at least 1 dose of the combined therapy. The ITT analysis set will be the default analysis set for all analysis of primary and secondary endpoints, unless otherwise specified.

Per-protocol analysis will also be performed.

9 Safety and Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) for adverse event (AE) reporting. CTCAE is located on the CTEP website at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

9.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study principal investigator of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The principal investigator should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management, e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9.3 Reporting of Serious Adverse Events

9.3.1 Study Principal investigator Notification by Investigator

A serious adverse event must be reported to the study principal investigator by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed or emailed to the study principal investigator within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone, email, and facsimile to:

Elizabeth Nichols, MD
enichols1@umm.edu
Phone: 410-328-6080
Fax: 410-328-2337

At the time of the initial report, the following information should be provided:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study principal investigator

9.3.2 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

9.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.4.1 Internal Data and Safety Monitoring Board

This study will be governed by the UMGCC Data Safety Monitoring / Quality Assurance Committee (DSMQAC). When the first six patients have completed the 56 days post-RT window for assessment of early toxicity, all cases will be reviewed by the DSMQAC with respect to grading of toxicities and their likely attribution to the study therapy. Any grade 5 toxicity and late unexpected severe adverse events will be reviewed by the DSMQAC. In addition, the study will be reviewed by the DSMQAC on an annual basis and a report will be uploaded in the continuing review submitted to the Institutional Review Board (IRB).

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.3 Data Collection

Endpoint data will be collected using source documents created by study personnel participant-specific binders and the Oncore database.

11 Study Monitoring, Auditing, and Inspecting

11.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the principal investigator, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will

be made in writing to the investigator and a copy of this decision will be provided to the principal investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.1 Gender and Minorities

Participating centers will not exclude potential subjects from participating in this or any study solely on the bases of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire endometrial cancer population by participating centers.

13 Study Finances

13.1 Funding Source

This study is being funded by the Radiation Oncology department and requires no outside source of funding.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study principal investigator prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, will be published, or passed on to any third party without the consent of the study principal investigator. Any investigator involved with this study is obligated to provide the principle investigator with complete test results and all data derived from the study.

15 References

1. Siegel, R.L., Miller, K.D. and Jemal, A. (2020), Cancer statistics, 2020. CA A Cancer J Clin, 70: 7-30. doi:10.3322/caac.21590
2. Klopp AH, Moughan J, Portelance L, et al. Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. Int J Radiat Oncol Biol Phys. 2013 May 1;86(1):83-90.

3. Randall, M. E., Filiaci, V. L., Muss, H., Spirtos, N. M., Mannel, R. S., Fowler, J., Thigpen, J. T., Benda, J. A., & Mackey, D. (2006). Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A gynecologic oncology group study. *Journal of Clinical Oncology*. https://doi.org/10.1200/JCO.2004.00.7617
4. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet*. 2010;375(9717):816-823. doi:10.1016/S0140-6736(09)62163-2
5. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study [published correction appears in Gynecol Oncol. 2004 Jul;94(1):241-2]. *Gynecol Oncol*. 2004;92(3):744-751. doi:10.1016/j.ygyno.2003.11.048
6. Creutzberg CL, Nout RA, Lybeert ML, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e631-e638. doi:10.1016/j.ijrobp.2011.04.013
7. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2006;24(1):36-44. doi:10.1200/JCO.2004.00.7617
8. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *Br J Cancer*. 2006;95(3):266-271. doi:10.1038/sj.bjc.6603279
9. Greven K, Winter K, Underhill K, Fontenesci J, Cooper J, Burke T. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. *Gynecol Oncol*. 2006;103(1):155-159. doi:10.1016/j.ygyno.2006.02.007
10. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial [published correction appears in Lancet Oncol. 2018 Apr;19(4):e184]. *Lancet Oncol*. 2018;19(3):295-309. doi:10.1016/S1470-2045(18)30079-2
11. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial [published correction appears in Lancet Oncol. 2019 Sep;20(9):e468]. *Lancet Oncol*. 2019;20(9):1273-1285. doi:10.1016/S1470-2045(19)30395-X
12. Matei D, Filiaci V, Randall ME, et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. *N Engl J Med*. 2019;380(24):2317-2326. doi:10.1056/NEJMoa1813181
13. Secord AA, Havrilesky LJ, O'Malley DM, et al. A multicenter evaluation of sequential multimodality therapy and clinical outcome for the treatment of advanced endometrial cancer. *Gynecol Oncol*. 2009;114(3):442-447. doi:10.1016/j.ygyno.2009.06.005

14. Carr KE. Effects of radiation damage on intestinal morphology. *Int Rev Cytol*. 2001;208:1–119. doi:10.1016/s0074-7696(01)08002-0
15. Oh, D., Huh, S. J., Nam, H., Park, W., Han, Y., Lim, D. H., Ahn, Y. C., Lee, J. W., Kim, B. G., Bae, D. S., & Lee, J. H. (2008). Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis of risk factors. *International journal of radiation oncology, biology, physics*, *70*(4), 1183–1188. https://doi.org/10.1016/j.ijrobp.2007.08.005
16. Bliss, P., Parsons, C. A., & Blake, P. R. (1996). Incidence and possible aetiological factors in the development of pelvic insufficiency fractures following radical radiotherapy. *The British journal of radiology*, *69*(822), 548–554. https://doi.org/10.1259/0007-1285-69-822-548
17. Klopp, A. H., Yeung, A. R., Deshmukh, S., Gil, K. M., Wenzel, L., Westin, S. N., Gifford, K., Gaffney, D. K., Small, W., Thompson, S., Doncals, D. E., Cantuaria, G. H. C., Yaremko, B. P., Chang, A., Kundapur, V., Mohan, D. S., Haas, M. L., Kim, Y. B., Ferguson, C. L., … Bruner, D. W. (2018). Patient-reported toxicity during pelvic intensity-modulated radiation therapy: NRG oncology-RTOG 1203. *Journal of Clinical Oncology*. https://doi.org/10.1200/JCO.2017.77.4273
18. Yeung AR, Pugh SL, Klopp AH, et al. Improvement in Patient-Reported Outcomes With Intensity-Modulated Radiotherapy (RT) Compared With Standard RT: A Report From the NRG Oncology RTOG 1203 Study. *J Clin Oncol*. 2020;38(15):1685-1692. doi:10.1200/JCO.19.02381
19. Delaney TF, Kooey HM. Protons and Charge Particle Radiotherapy, 1st, Lippincott Williams & Wilkins, Philadelphia 2008.
20. Song WY, Huh SN, Liang Y, et al. Dosimetric comparison study between intensity modulated radiation therapy and three-dimensional conformal proton therapy for pelvic bone marrow sparing in the treatment of cervical cancer. *J Appl Clin Med Phys*. 2010;11(4):3255. Published 2010 Aug 15. doi:10.1120/jacmp.v11i4.3255
21. van de Sande MA, Creutzberg CL, van de Water S, Sharfo AW, Hoogeman MS. Which cervical and endometrial cancer patients will benefit most from intensity-modulated proton therapy?. *Radiother Oncol*. 2016;120(3):397-403. doi:10.1016/j.radonc.2016.06.016
22. Dinges E, Felderman N, McGuire S, et al. Bone marrow sparing in intensity modulated proton therapy for cervical cancer: Efficacy and robustness under range and setup uncertainties. *Radiother Oncol*. 2015;115(3):373-378. doi:10.1016/j.radonc.2015.05.005
23. Lin et al. 2015 red journal initial report of pencil beam scanning proton therapy for posthysterectomy patients with gynecologic cancer
24. Lim K, Small W Jr, Portelance K, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. Int J Radiat Oncol Biol Phys. 2011;79:348–355.
25. 2006 Update of ASCO Practice Guideline Recommendations for the Use of White Blood Cell Growth Factors: Guideline Summary. J Oncol Pract. 2006;2(4):196-201. doi:10.1200/JOP.2006.2.4.196
26. Ivanova, A., Qaqish, B.F., and Schell, M.J. (2005). Continuous toxicity monitoring in phase II trials in oncology. Biometrics 61: 540-545.
27. Wu, Jianrong. 2015. 'Sample size calculation for the one-sample log-rank test', Pharmaceutical Statistics, Volume 14, pages 26-33.
28. Wu, Jianrong. 2014. 'A New One-Sample Log-Rank Test', J Biomet Biostat 5; 210.

29. Finkelstein D, Muzikansky A, Schoenfeld D. 2003. 'Comparing Survival of a Sample to That of a Standard Population', Journal of the National Cancer Institute, 95, pages 1434-1439.

16 Attachments

17 Appendix

17.1 CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

1. The Cockcroft-Gault formula will be used in GOG trials (not the Jelliffe formula).
2. Conversion of IDMS creatinine levels to “non-IDMS” values will not be permitted.
3. The carboplatin calculation tool on the GOG website has been updated. A legacy carboplatin calculator (using the Jelliffe formula and IDMS to “non-IDMS” conversion) is also available, if needed for dose modifications (see below).

Dosing of Carboplatin:
The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

Carboplatin doses will be based on the subject’s weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline.

In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a minimum value of 0.7 mg/dl. If a patient is currently being dosed using a creatinine value less than 0.7 mg/dl, adjust dose with next planned treatment. For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:

AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

Creatinine Clearance (mL/min) = [140-Age (years)] x Weight (kg) x 0.85

72 x serum creatinine (mg/dl)

Notes:

1) Weight in kilograms (kg):
   Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/

   Actual weight should be used for estimation of GFR for patients with BMI of less than 25.

   Adjusted weight should be used for estimation of GFR for patients with BMI of greater than or equal to 25.

   Adjusted weight calculation:
   Ideal weight (kg) = (Height (cm)/2.54) – 60) x 2.3) + 45.5

   Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

   If a patient with BMI of greater than or equal to 25 is currently being dosed using actual weight, adjust dose with next planned treatment.

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).
   At the time of a dose modification for toxicity:
   1) If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.
   2) If the dose of carboplatin (mg) at the time of dose modification, is higher than the previous dose due to the use of the Cockcroft-Gault formula [when the previous dose was calculated using the Jelliffe formula and IDMS to “non-IDMS” conversion (if applicable)], use the same method that was used to calculate the previous dose [Jelliffe formula and IDMS to “non-IDMS” conversion (if applicable)], to calculate the dose of carboplatin (mg) at the time of dose reduction. A legacy carboplatin calculator is available on the GOG website for this purpose. This will ensure that the patient is actually receiving a dose reduction.

General Chemotherapy Guidelines:

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21- or 28-day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for <10% weight changes. (04/28/2014)
- Maximum body surface area used for chemotherapy dose calculations will be 2.0 m2
- For chemotherapy dose calculations that use mg/kg, there will be no maximum kilogram amount used (doses will be calculated on actual weight in kg).

17.2 CARBOPLATIN + PACLITAXEL ORDER FORM (UMMC pts only)

UNIVERSITY OF MARYLAND
MEDICAL CENTER

ANTINEOPLASTIC AND BIOLOGICAL THERAPY
ORDER FORM
Orders are to be written for one complete cycle or for a maximum of 4 weeks of treatment

☐ INPATIENT ☐ OUTPATIENT ALLERGIES _____

DIAGNOSIS ❑ Cervical ❑ Endometrial ❑ Ovarian _____ TREATMENT CARBOplatin plus PACLitaxel CYCLE ___ of ___ (Every 3 weeks)

DEMOGRAPHIC INFORMATION (use CrCl parameters; re-calculate BSA for weight changes> 10%)

Age:_____	Ht: _____cm	Actual BW: _____kg AdjustedBW:_____kg	BSA:_____m^2 Use actual body weight	SCr: _____mg/dl minimum value 0.7mg/dL	CrCl: _____ml/min *See Comments* Use Cockcroft Gault Equation Use adjusted body weight if BMI ≥ 25kg/m2

☐ DISCONTINUE ALL PREVIOUS ANTINEOPLASTIC ORDERS

☐ **ADMINISTER ONLY IF LABS ARE AS FOLLOWS:**

❑ ANC ≥ 1,000 ❑ PLATELETS ≥100,000 ❑ Tbili ≤1.4 (see comments) ❑ Other _____

TREATMENT ORDERS	DOSE (IN MG) Round to nearest whole number	TREATMENT DATES
PACLitaxel IV in NS 0.9% x 1 dose on **day 1**. Administer over 3 hours.	175 mg / Dose/m^2 x _____ / BSA = _____ / Dose mg	
After completion of the Paclitaxel infusion give : CARBOplatin IV in D5W x 1 dose on **day 1**. Administer over 1 hour.	___ AUC (see comments) AUC 5 cervical/endometrial; AUC 5-7.5 ovarian	
PREMEDS-Prior to antineoplastic administration give: ❑ Famotidine 20mg IV. ❑ Dexamethasone 20 mg IV in 0.9% NS 50 mL. ❑ DiphenhydrAMINE 25 mg IV. ❑ Ondansetron 16mg PO. If unable to take PO, give 8 mg IV. **For hypersensitivity reactions: Stop infusion, notify MD. Have available at bedside and administer the following PRN according to hypersensitivity protocol:** ✓ DiphenhydrAMINE 50 mg IV Q6h PRN for infusion reaction. ✓ Hydrocortisone 100mg IV PRN for infusion reaction. ✓ Famotidine 20mg IV x 1 dose PRN for infusion reaction. ✓ EPINEPHrine 1: 1000 (0.3 mg) subcutaneous PRN for infusion reaction. **PRN-If needed, give:** ❑ Lorazepam 1 mg PO Q6h PRN nausea, vomiting, or anxiety. If unable to take PO, give IV. ❑ Prochlorperazine 10 mg PO Q6h PRN for nausea or vomiting. If unable to take PO, give IV.		

Comments:
Paclitaxel: Consider a dose reduction for Total bili > 1.4mg/dL.
Carboplatin mg dose to be calculated from AUC dose by pharmacy on each day of treatment with carboplatin calculator using most current height, weight, serum creatinine.
Monitor for infusion reaction symptoms of urticaria, hypotension, bronchospasm, stridor and hoarseness after administration. Notify MD immediately if symptoms occur.

NP/Fellow Name and Signature	RN Name and Signature	Attending Name and Signature
PRINT:	PRINT:	PRINT:
SIGNATURE:	SIGNATURE:	SIGNATURE:
DATE: TIME: PAGER#	DATE: TIME:	DATE: TIME: PAGER#

POCaC117 Reference: Parmar MK et al. Lancet 2003;361:2099-106. (cervical) Pectasides D et al. Gynecol Oncol 2008;109:250-4. (endometrial) Ozols RF et al. J Clin Oncol 2003;21:3194-200. (ovarian)
See Hypersensitivity Management Protocol for guidance. http://intra.umm.edu/ummc/cancer_orders/pdf/hypersensitivity_protocol.pdf.
Page 1 of 1 (rev. 08/14)

17.3 CARBOPLATIN + DOCETAXEL ORDER FORM: (UMMC pts only)

UNIVERSITY OF MARYLAND MEDICAL CENTER

ANTINEOPLASTIC AND BIOLOGICAL THERAPY ORDER FORM

Orders are to be written for one complete cycle or for a maximum of 4 weeks of treatment

❑ **INPATIENT** ❑ **OUTPATIENT** **ALLERGIES** _____

DIAGNOSIS_____ **TREATMENT** **DOCEtaxel plus CARBOplatin** **CYCLE** ____ **of** ____

(Indicated in cervical, endometrial, ovarian cancer) (Every 3 weeks)

DEMOGRAPHIC INFORMATION (Use C_1D_1 parameters; re-calculate BSA for weight changes >10%)

Age:_____	Ht: _____cm	Actual weight: _____kg Adjusted weight: _____kg	BSA:_____m^2 Use actual weight	SCr: _____mg/dl (minimum value 0.7mg/dL)	CrCl: _____ml/min *See Comments*

❑ **DISCONTINUE ALL PREVIOUS ANTINEOPLASTIC ORDERS**

ADMINISTER ONLY IF LABS ARE AS FOLLOWS (See comments):

❑ ANC ≥1,000 ❑ PLATELETS ≥100,000 ❑ Tbili ≤ 1.3 AST&ALT ≤ 2.5 x ULN ❑ Other _____

TREATMENT ORDERS	DOSE (IN MG) Round to nearest whole number	TREATMENT DATES
DOCEtaxel IV in NS 0.9% x 1 dose on **Day 1.** Administer over **1 hour**. Give First.	❑ 60 mg / $Dose/m^2$ x _____ / BSA = _____ / Dose mg **Dose modification (explain in comments) :** ❑ _____mg / $Dose/m^2$ x _____ / BSA = _____ / Dose mg **(Dose rounding applies if within 10%)** ❑ **Exclude from dose rounding**	
CARBOplatin IV in D5W x 1 dose on **Day 1.** Administer over **1 hour.** Give second.	6 AUC (see comments)	
PREMEDS-30 minutes prior to antineoplastic administration, give: ❑ Ondansetron 24 mg PO x 1 dose on **day 1.** If unable to take PO, give 16 mg IV 50 mL 0.9% NS. ❑ Dexamethasone 20 mg IV 0.9% D5W 50 mL x 1 dose on **day 1.** **PRN-If needed give:** ❑ Prochlorperazine 10 mg PO Q6h PRN nausea/vomiting. If unable to take PO, give IV.		
Comments: Patient needs a prescription for dexamethasone 8 mg PO Qday or 4 mg BID on days 2-4. Consider docetaxel dose reduction for Tbili > 1.3 or AST/ALT > 2.5 x ULN. Carboplatin mg dose to be calculated from AUC dose by pharmacy on each day of treatment with carboplatin calculator using most current height, weight, serum creatinine.		

NP/Fellow Name and Signature	RN Name and Signature	Attending Name and Signature
PRINT:	PRINT:	PRINT:
SIGNATURE:	SIGNATURE:	SIGNATURE:
DATE: TIME: PAGER#	DATE: TIME:	DATE: TIME: PAGER#

PO82 **Reference: Markman M et al. J Clin Oncol. 2001;19:1901-5**

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17.4 EPIC BOWEL DOMAIN

Page 1

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE LAST 4 WEEKS**.

1. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number)
About once a week..... 4
Rarely or never..... 5

2. How often have you had uncontrolled leakage of stool or feces?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number)
About once a week..... 4
Rarely or never..... 5

3. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number)
Usually..... 4
Always..... 5

4. How often have you had bloody stools **during the last 4 weeks**?

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number)
Usually..... 4
Always..... 5

5. How often have your bowel movements been painful **during the last 4 weeks**?

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number)
Usually..... 4
Always.....5

6. How many bowel movements have you had on a typical day **during the last 4 weeks**?

Two or less..... 1
Three to four.....2 (Circle one number)
Five or more.....3

7. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number)
About once a week.....4
Rarely or never..... 5

8. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Urgency to have a bowel movement	0	1	2	3	4
b. Increased frequency of bowel movements.....	0	1	2	3	4
c. Watery bowel movements.....	0	1	2	3	4
d. Losing control of your stools.....	0	1	2	3	4
e. Bloody stools	0	1	2	3	4
f. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4

9. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem.....3 (Circle one number)
Moderate problem..... 4
Big problem..... 5

17.5 EPIC URINARY DOMAIN

Page 1

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number)
   About once a week..... 4
   Rarely or never..... 5

2. Over the **past 4 weeks**, how often have you urinated blood?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number)
   About once a week..... 4
   Rarely or never..... 5

3. Over the **past 4 weeks**, how often have you had pain or burning with urination?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number)
   About once a week..... 4
   Rarely or never..... 5

4. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number)
   Occasional dribbling..... 3
   Total control..... 4

5. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

None	0	
1 pad per day	1	
2 pads per day	2	(Circle one number)
3 or more pads per day	3	

6. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

(Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a.	Dripping or leaking urine	0	1	2	3	4
b.	Pain or burning on urination	0	1	2	3	4
c.	Bleeding with urination	0	1	2	3	4
d.	Weak urine stream or incomplete emptying	0	1	2	3	4
e.	Waking up to urinate	0	1	2	3	4
f.	Need to urinate frequently during the day	0	1	2	3	4

7. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem	1	
Very small problem	2	
Small problem	3	(Circle one number)
Moderate problem	4	
Big problem	5	

THANK YOU VERY MUCH!!

17.6 PRO-CTCAE Questions

NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0
English
Form Created on 07 June 2020

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1.	a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very severe
	b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

2.	a. In the last 7 days, how OFTEN did you have NAUSEA?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
	b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very severe

3.	a. In the last 7 days, how OFTEN did you have VOMITING?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
	b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very severe

4.	a. In the last 7 days, how OFTEN did you have HEARTBURN?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
	b. In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very severe

5.	a. In the last 7 days, did you have any INCREASED PASSING OF GAS (FLATULENCE)?	
	O Yes	O No

6.	a. In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
	b. In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very severe

7.	a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very severe

8.	a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

9.	a. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
	b. In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very severe
	c. In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

10.	a. In the last 7 days, how OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
	b. In the last 7 days, how much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?				
	O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

11.	a. In the last 7 days, did you have any UNUSUAL VAGINAL DISCHARGE?				
	O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

12.	a. In the last 7 days, what was the SEVERITY of your PAIN OR BURNING WITH URINATION at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very severe

13.	a. In the last 7 days, how OFTEN did you feel an URGE TO URINATE ALL OF A SUDDEN?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
	b. In the last 7 days, how much did SUDDEN URGES TO URINATE INTERFERE with your usual or daily activities?				
	O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

14.	a. In the last 7 days, were there times when you had to URINATE FREQUENTLY?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
	b. In the last 7 days, how much did FREQUENT URINATION INTERFERE with your usual or daily activities?				
	O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

15.	a. In the last 7 days, did you have any URINE COLOR CHANGE?	
	O Yes	O No

16.	a. In the last 7 days, how OFTEN did you have LOSS OF CONTROL OF URINE (LEAKAGE)?				
	O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
	b. In the last 7 days, how much did LOSS OF CONTROL OF URINE (LEAKAGE) INTERFERE with your usual or daily activities?				
	O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

OTHER SYMPTOMS	
Do you have any other symptoms that you wish to report?	
O Yes	O No

Please list any other symptoms:	
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe