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Title: RANDOMIZED PHASE II EVALUATION OF CARBOPLATIN/PACLITAXEL WITH AND WITHOUT TRASTUZUMAB (HERCEPTIN®) IN HER2/neu+ PATIENTS WITH ADVANCED/RECURRENT UTERINE SEROUS PAPILLARY CARCINOMA

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RANDOMIZED PHASE II EVALUATION OF CARBOPLATIN/PACLITAXEL WITH AND WITHOUT TRASTUZUMAB (HERCEPTIN®) IN HER2/*neu*+ PATIENTS WITH ADVANCED/RECURRENT UTERINE SEROUS PAPILLARY CARCINOMA

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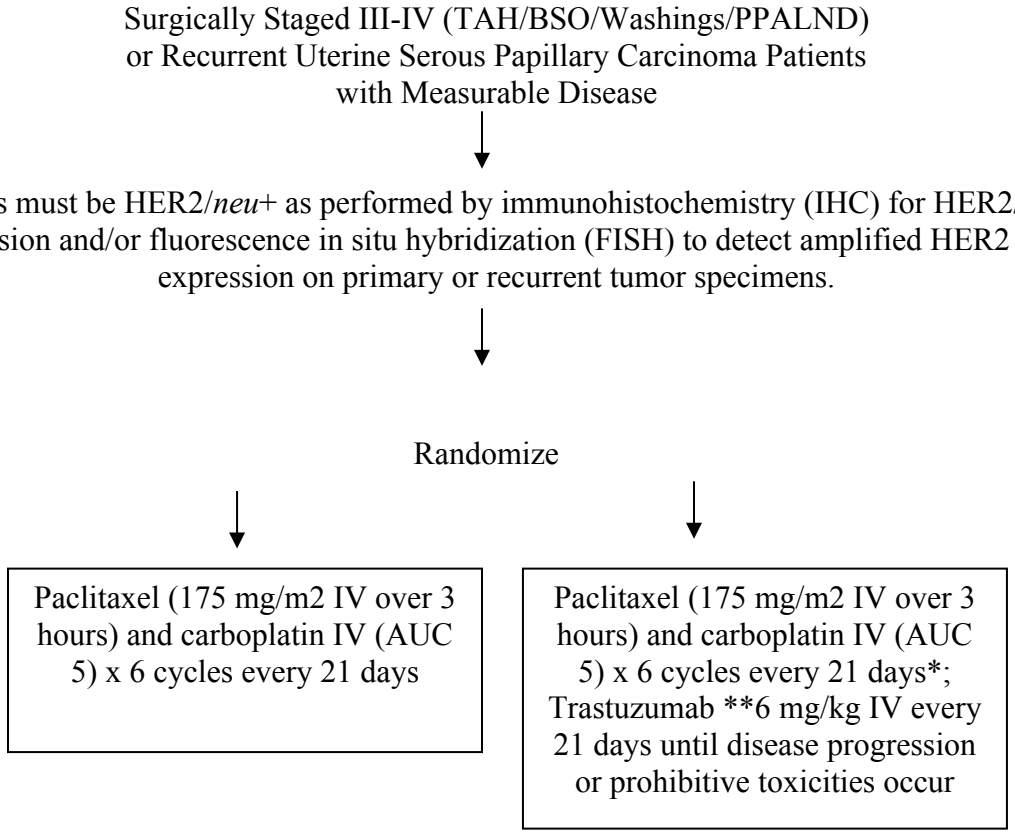
RANDOMIZED II SCHEMA



*Additional cycles may be administered if the investigator feels that the subject would receive clinical benefit from continued chemotherapy treatment

**first dose of Trastuzumab will be at 8mg/kg, in subsequent cycles the dose will be decreased to 6 mg/kg as described in section 6.124.6.

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1.0 OBJECTIVES

1.1 Primary objective

1.1.1 To estimate whether the addition of trastuzumab to paclitaxel and carboplatin chemotherapy improves progression free survival (PFS) when compared to paclitaxel and carboplatin alone in USPC patients overexpressing HER2/*neu* at 3+ level by IHC or positive by FISH

1.2 Secondary objectives

1.2.1 To assess objective response rate (ORR)

1.2.2 To assess overall survival (OS)

1.2.3 To assess the safety profile of trastuzumab in USPC patients

1.3 Exploratory/correlative objectives

1.3.1 To determine peripheral blood natural killer (NK) cell numbers and activity in HER2/*neu*+ USPC patients to provide a basis for assessing the possible therapeutic contributions of immune mechanisms of action of trastuzumab

1.3.2 To study HER2/*neu* extracellular domain (ECD) circulating levels in the plasma of USPC patients overexpressing HER2/*neu* before, during and after treatment to elucidate whether changes in HER2/*neu* ECD would predict response to trastuzumab

1.3.3 To determine whether CA-125 levels correlate with disease activity in advanced and/or recurrent disease.

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2.0 BACKGROUND AND RATIONALE

Cancer of the uterine corpus is the most prevalent gynecologic tumor in women, with an estimated 43,470 cases and 7,950 deaths in the United States in 2010 (1). Uterine serous papillary carcinoma (USPC) is an aggressive variant of endometrial cancer (2). Although it accounts for less than 10% of all endometrial tumors, it accounts for a disproportionate number of relapses and endometrial cancer-related deaths (2). USPC, referred to as a Type II endometrial cancer, is characterized by a high-grade, complex histology and is biologically more aggressive than its type I counterpart, endometrioid adenocarcinoma (2). Type I and II endometrial cancers appear to have a different pattern of molecular alterations that underlie pathogenesis and progression. While endometrioid carcinomas tend to have alterations in the tumor suppressor gene, PTEN, these are uncommon in USPC, with p53 mutations and HER2/*neu* expression occurring more commonly in this tumor subtype (3). Both early-stage (Stage I/II with disease confined to the uterus) and advanced disease states (Stage III/IV with metastases present outside of the uterus) behave aggressively. USPC has a tendency to invade the lymphatic and vascular spaces and lymph nodes and to microscopically or macroscopically involve other intraperitoneal structures, despite minimal or no invasion present within the uterus. These tumor characteristics lead to high recurrence rates and a poor prognosis for patients (2-5).

Because of poor results with surgery alone, both radiation therapy and chemotherapy have been added postoperatively in an effort to improve outcomes (5). However, the benefit of these modalities as well as the optimal treatment for each disease stage remains unclear. Our research group recently reported on the largest series of Stage I/II USPC patients in the literature and demonstrated a significant improvement in recurrence rates, progression free and overall survival in patients treated with carboplatin/paclitaxel-based regimens (6). Specifically, all carboplatin/paclitaxel +/-RT-treated patients had a lower risk of recurrence (9.2%) compared to radiation-only-treated (24.2%, p=0.04) and observed patients after surgery (30.2%, p=0.004). On multiple logistic regression analyses, adjuvant treatment strategy (p=0.036) and sub-stage (p=0.003) were significantly associated with recurrence. Five-year progression-free (p=0.009) and overall survival (p=0.012) were again highest in chemotherapy treated patients when compared to RT-treated and OBS patients.

Recurrence rates in women diagnosed with advanced stage disease are much higher than for early-stage disease, with rates of 50-90% reported in published studies (7-11). These recurrences are often extra-pelvic and largely unsalvageable and highlight the need for effective systemic therapy in the treatment of this disease. Goff and colleagues reported that 72% of surgically staged USPC patients will have advanced-stage disease (extra-uterine, Stage III-IV) at the time of initial laparotomy (10). GOG #33 demonstrated that para-aortic nodal disease was more common in patients with USPC tumors, and GOG #94 demonstrated that in Stage III/IV UPSC patients treated with whole abdominal radiation, the majority of failures were multisite and extrapelvic (with distant failures not being uncommon) (9). These findings indicate that radiation therapy alone has a limited role in the management of USPC. It has been suggested that USPC tumors more closely resemble ovarian cancers than endometrial cancers. The high rates of intra-abdominal disease spread and intra-abdominal failures reported support this concept, and have led to the use of ovarian cancer-based chemotherapy regimens as treatment. As more effective chemotherapeutic agents have been identified in endometrial cancer, combination regimens have demonstrated improved responses, and

at least in populations with advanced disease, chemotherapy (doxorubicin and cisplatin) has shown superiority to radiation alone (GOG #122) (11).

Chemotherapy, either alone or in combination with radiotherapy, has been evaluated in the management of advanced-staged endometrial cancer. As USPC is a rare tumor subtype, it is often grouped with more common endometrial tumor subtypes (ie, endometrioid adenocarcinoma) in prospective treatment studies. However, studies suggest that USPC patients tend to fare worse and may exhibit more heterogeneity of response to chemotherapy than their counterparts with less aggressive subtypes (2-5). Therefore, there is potential benefit in studying UPSC as its own clinical entity.

In terms of the relevant studies on advanced-stage endometrial cancer—many of which included USPC patients—there are several reports that help guide management. Burke reported on 62 patients with high-risk endometrial cancer (21% with USPC or CC histologies) treated with cisplatin, adriamycin, and cyclophosphamide following surgical staging (12). Three-year survival was 82% in patients without extra-uterine disease. Levenback described 20 patients with all stages of USPC treated with the same regimen and reported a 5-year survival of 23% (13). Paclitaxel has demonstrated significant activity in endometrial cancer patients with advanced or recurrent disease in two GOG phase II studies (GOG 86-O, 129-C) (14-15). The combination of cisplatin and adriamycin versus cisplatin, adriamycin and paclitaxel (TAP) was then studied in GOG #177, a Phase III trial of primary, advanced-stage endometrial cancer patients with superior progression-free and overall survival outcomes noted in the TAP cohort (16). TAP is currently being evaluated sequentially with radiation in GOG-184, and is also being compared to paclitaxel/carboplatin in GOG-209, a Phase III equivalence study, in the same cohort of patients.

Paclitaxel has also demonstrated activity specifically in USPC tumors as reported by Ramondetta and colleagues from M.D. Anderson Cancer Center (17). They reported a 77% objective response rate in a small series of patients with advanced disease. Hoskins reported experience using paclitaxel and carboplatin with and without radiation in 63 patients with advanced and recurrent endometrial cancer. In a subgroup of 15 patients with advanced USPC tumors, the response rate was 60%, and 2 out of 4 patients with recurrent disease responded to the regimen (18). Carboplatin has demonstrated comparable activity to cisplatin in most gynecologic malignancies, including endometrial cancer (19-20). Substituting carboplatin for cisplatin appears to reduce toxicity and increase ease of administration (21-25).

A recent Phase II pilot study of pelvic radiation therapy "sandwiched" between platinum/taxane-based therapy in Stage I-IV USPC patients demonstrated that this regimen had excellent antitumor activity, but the majority of patients with advanced disease recurred during the three year study period (21). Phase III GOG data on advanced/recurrent endometrial cancers of all subtypes have demonstrated median progression-free survival (PFS) rates of 7-8 months and median overall survival (OS) rates of 15 months, despite treatment with platinum/taxane-based chemotherapy (16). Finally, two recent Phase III studies from the Japanese Gynecologic Oncology Group (GOG) and NSGO/EORTC, respectively demonstrated that patients with high-risk, early-stage endometrial cancers treated with chemoradiation had improved progression-free and overall survival when compared to patients treated with radiation therapy alone. Patients with USPC were included in these trials (26-27).

In addition to platinum/taxane-based chemotherapy, another reasonable approach to the treatment of USPC may lie in targeted therapy. Several studies have demonstrated that the human epidermal

growth factor receptor 2 gene (HER2, also known as c-*erb*B2 and HER2/*neu*), is over-expressed in 18 to 80% of USPC and may contribute to USPC transformation and tumorigenesis (28-35). In some of these studies, HER-2/*neu* overexpression has been identified as an independent variable associated with poor outcome in USPC patients, and one that occurs more frequently in African-American women than in Caucasian women (32,33). In a single institution study of 26 USPC samples evaluated by Santin et al, 62% exhibited HER2/*neu* overexpression (34). Protein overexpression and gene amplification were found to correlate in 100% (9/9) of the 3+ positive tumors but in only 2/7 (29%) of the 2+ positive tumors (34). Consistent with these results, in a recent exploratory immunohistochemical analysis of HER-2/*neu* expression in advanced endometrial carcinoma performed by the GOG, HER-2/*neu* overexpression [either 2+ (moderate) or 3+ (strong)] was detected in 23 of 38 (61%) of the USPC tested in a centralized core lab facility (35). High HER-2/*neu* expression levels in USPC have also been reported by Diane-Montez et al. (36), with 12 of the 25 (48%) USPC cases in the John Hopkins' series demonstrating HER-2/*neu* overexpression. Of interest, in this study, a significant association of HER-2/*neu* overexpression with surgical staging was detected, with 81.8% advanced stage disease vs. 28.6% early stage disease showing HER-2/*neu* overexpression (36). Taken all together, these results raise the possibility of therapeutic strategies that target HER2, such as using the anti-HER2 monoclonal antibody trastuzumab (Herceptin) may have significant therapeutic potential in USPC patients harboring advanced and/or recurrent disease.

Results from large randomized clinical trials for patients with HER-2 positive invasive breast cancer have shown that patients who received trastuzumab in combination with chemotherapy had a significant decrease in risk for breast cancer recurrence when compared with patients who received the same chemotherapy without trastuzumab (37). Importantly, clinical responses to trastuzumab used as single agent in breast cancer patients are reported on the order of 10-15%, while the overall response rate to trastuzumab in combination with chemotherapeutic agents may increase in the same patient populations to > 50% (37). On the basis of these results, a significantly higher clinical activity of trastuzumab when used in combination with chemotherapy may be expected in USPC patients harboring advanced and/or recurrent disease over expressing HER2/*neu*. While previous studies in HER2/*neu* positive breast cancer have demonstrated improved efficacy of trastuzumab and paclitaxel with the addition of carboplatin, there are no studies in the literature evaluating combination platinum/taxane chemotherapy with trastuzumab in USPC patients.

A Phase II study of single agent trastuzumab in advanced/recurrent endometrial cancer patients of any histology has recently been reported from the GOG (38). This study was not able to demonstrate single agent activity of trastuzumab against endometrial carcinoma patients harboring tumors with HER2/*neu* overexpression. Such results, however, have been recently challenged due to the many shortcomings in the design of the GOG181b study (39). Moreover, evidence of trastuzumab clinical activity in a handful of heavily pretreated endometrial carcinoma patients has been recently reported as case reports in the medical literature (40-42).

Clinical efficacy of trastuzumab has been postulated to depend on multiple direct or indirect action mechanisms that may produce cytostatic and/or cytotoxic antitumor cell effects. CD16 and natural killer (NK) cells appear to play a central role in mediating the anti-tumor effects of trastuzumab therapy, and an inherent resistance to trastuzumab has been noted in some HER2/neu positive breast cancer patients with specific polymorphisms of CD16 (43-44). To date, trastuzumab therapy and the immunologic basis for its putative activity (or inactivity) have not been studied in UPSC.

Clearly, there is a critical need to determine the optimal chemotherapy regimens and whether targeted therapy may be beneficial in women with USPC over expressing HER2/neu. Therefore, the purpose of this study is to perform a randomized Phase II evaluation of Carboplatin/Paclitaxel with or without Trastuzumab (Herceptin®) in patients with HER2/*neu*+ advanced stage/recurrent disease with an emphasis on determining the progression free survival in USPC patients and assessing immunologic markers predictive of trastuzumab response.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.1.1 Patients must have advanced (stage III-IV) or recurrent histologically confirmed USPC.

3.1.2 Patients must harbor a tumor HER2/*neu*+ based upon IHC staining score of "3+" or 2+ with confirmed gene amplification by FISH to be included.

3.1.3 All patients diagnosed with recurrence must have measurable disease. In recurrent patients, paraffin embedded USPC tumor tissue must be available from either primary surgery, tumor purified from ascites or from CT-guided biopsy of recurrent disease. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation or plain x-ray, or ≥ 10 mm when measured by spiral CT and/or MRI.

3.1.4 Patients with recurrence must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST v1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.1.5 Patients may be optimally or suboptimally debulked after surgery.

3.1.6 Patients with measurable recurrent disease of any previous substage (I-IV) are eligible to enrollment.

3.1.7 The diagnosis must be histologically confirmed by a gynecologic pathologist as containing ≥10% uterine papillary serous (UPSC) adenocarcinoma in the specimen.

3.1.8 Patients must have adequate bone marrow function: WBC greater than or equal to 3,000/ul, Platelets greater than or equal to 75,000/ul, Granulocytes greater than or equal to 1500/ul. Renal function: creatinine less than or equal to 2.0 mg/dL Hepatic function: Bilirubin ≤ 1.5 X laboratory normal. SGOT ≤ 3 X laboratory normal.

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3.1.9 Patients must be enrolled within 8 weeks of primary surgery or within 8 weeks after diagnosis of recurrent disease.

3.1.10 Patients must have an ECOG performance status of 0, 1 or 2.

3.1.11 Patients must have signed an approved informed consent

3.1.12 Patients with recurrent disease may have received prior treatment with carboplatin /paclitaxel but must have had a treatment free interval of > 6 months

3.1.13 Patients with recurrent disease may not have received more than three prior chemotherapies for treatment of their uterine cancer

3.1.14 Patients must have recovered from effects of recent surgery, radiotherapy or chemotherapy

3.1.15 Patients who have received prior doxorubicin may not have had more than 320 mg/m^2 total dose and must have a normal LVEF (≥ 45%). (This includes Doxil or other liposomally encapsulated doxorubicin preparations.)

3.1.16 Patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to the study entry and be practicing an effective form of contraception.

3.1.17 Patients must be at least 18 years of age. The safety and efficacy of trastuzumab in pediatric patients has not been established

3.2 Ineligible Patients:

3.2.1 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancers are excluded if there is any evidence of other malignancy being present within the last five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy

3.2.2 Patients who have a significant history of cardiac disease, i.e., uncontrolled hypertension, unstable angina, uncontrolled congestive heart failure, or uncontrolled arrhythmias within 6 months of registration (NYHA classification III-IV).

3.2.3 Patients with any unstable medical issue (including cardiac issues as above, active treatment for pulmonary embolism, CVA, renal or hepatic insufficiency, active infection/sepsis requiring IV antibiotics).

3.2.4 Known brain/leptomengial involvement of the disease, active neurological disease, dementia.

3.2.5 Patients who have received prior therapy with trastuzumab or any other anti-epidermal growth factor type II receptor antibody.

3.2.6 Patients who have an uncontrolled seizure disorder, or active neurological disease.

3.2.7 Patients known to be seropositive for HIV and active hepatitis, even if liver function studies are in the eligible range.

3.2.8 Known hemorrhagic diathesis or active bleeding disorder.

3.2.9 Patients requiring supplemental oxygen.

3.3 Inclusion of Minorities:

3.3.1 As men do not have uteri, only women will be enrolled in this trial. Participating institutions will not exclude potential subjects from participating in this or any study solely on the basis 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 USPC population treated by participating institutions.

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4.0 STUDY MODALITIES

4.1 Chemotherapy

4.11 Paclitaxel (NSC #673089) 175 mg/m^2 will be administered intravenously every 21 days for 6 cycles. Additional cycles may be administered if the investigator feels that the subject would receive clinical benefit from continued chemotherapy treatment.

4.12 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.

4.131 Supplier/How Supplied: Commercially available. A sterile solution concentrate, 6 mg/ml, in 5 ml vials (30 mg/vial) or 17 ml vials (100 mg/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.

4.132 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 mls 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 polyvinylchloride (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 LVPs) 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.

4.133 Storage: The intact vials should be stored between 2-25°C (36-77°F).

4.134 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 48 hours.

4.135 Intravenous Administration of Paclitaxel: Paclitaxel, at the appropriate dose and dilution, will be given as a 3-hour 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.

4.136 Adverse Effects:

4.136.1 Hematologic: Myelosuppression

4.136.2 Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis

4.136.3 Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia

4.136.4 Pulmonary: Pneumonitis

4.136.5 Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication--Dexamethasone)

4.136.6 Neurologic: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy

4.136.7 Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, radiation-recall reactions, erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)

4.136.8 Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus

4.136.9 Liver: Increased SGOT, SGPT, bilirubin and alkaline phosphatase, hepatic failure, hepatic necrosis

4.136.10 Other: Alopecia, fatigue, arthralgia, myalgia, lightheadedness, myopathy

4.136.11 Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata

4.136.12 *Refer to Package insert for additional information

4.2 Carboplatin (Paraplatin® - NSC #241240) AUC 5 will be administered intravenously every 21 days for 6 cycles. Additional cycles may be administered if the investigator feels that the subject would receive clinical benefit from continued chemotherapy treatment.

4.21 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.

4.22 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 8 hours at room temperature, since no antibacterial preservative is contained in the formulation it is recommended that Paraplatin® solutions be discarded 8 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®.

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

4.24 Adverse effects:
Hematologic: Myelosuppression
Gastrointestinal: Nausea and vomiting, diarrhea,
Neurologic: Peripheral neuropathy, central neurotoxicity
Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
Liver: Increased SGOT, SGPT, bilirubin and alkaline phosphatase
Other: Fatigue, electrolyte imbalance, hypomagnesemia, hypocalcemia

4.25 Supplier: Commercially available. Bristol-Myers Squibb Oncology

4.26 Administration: Carboplatin AUC 5 IV Day 1 with a 30 minutes infusion time

4.27 * Refer to Package insert for additional information

4.3 Targeted Therapy

4.3.1 Trastuzumab (Herceptin®)

4.3.1.1 On day 1, an 8 mg/kg loading dose of trastuzumab will be administered over a 90-minutes period. Beginning on Day 21, patients will receive 6 mg/kg of trastuzumab,

administered intravenously every 21 days and continued indefinitely every 21 days after 6 cycles of cytotoxic therapy are completed and until progression of disease or prohibitive toxicities occur. Additional cycles may be administered if the investigator feels that the subject would receive clinical benefit from continued chemotherapy treatment.

4.3.1.2 How supplied: Trastuzumab, manufactured by Genentech and available commercially, is supplied as a freeze-dried preparation at a nominal content of 440 mg per vial for parenteral administration. This agent is formulated in histidine, trehalose, and polysorbate 20. Each vial of trastuzumab is packaged with one 30 ml vial of bacteriostatic water for injection, USP, 1.1% benzyl alcohol.

4.3.1.3 Preparation: Reconstitution with 20 ml of the supplied diluent provides a solution containing 21 mg/ml trastuzumab. The reconstituted solution is designed for multiple uses and must be stored under refrigeration. Reconstituted trastuzumab should be clear to slightly opalescent and colorless to pale yellow. The vial must be used within 28 days after reconstitution. If a patient has a known allergy to benzyl alcohol, Sterile Water for injection without a preservative may be used. However, the reconstituted solution should be used immediately and the unused portion discarded. Provided below are directions for reconstituting each vial of trastuzumab:

Using a sterile syringe, slowly inject 20 ml of the supplied diluent (or sterile water, if appropriate) into the vial. The stream of diluent should be directed into the lyophilized cake. Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. DO NOT SHAKE. Vigorous handling of solutions of trastuzumab may result in aggregation of the protein and create cloudy solutions. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The solution should be essentially free of visible particles, clear to slightly opalescent and colorless to pale yellow. Reconstituted trastuzumab should be further diluted in 250 ml of 0.9% Sodium Chloride for Injection, USP, prior to administration. Solutions for infusion prepared in polyvinylchloride (PVC) or polyethylene bags may be stored at 2-8°C (36-46°F) for up to 24 hours prior to use. Dextrose 5% solution should not be used.

4.3.1.4 Administration: Trastuzumab is given by slow intravenous infusion only. A typical dosing schedule is 6 mg/kg administered every 21 days. The initial dose of 8 mg/kg is infused over 90 minutes. If this is well tolerated, subsequent infusions may be given over 30 minutes.

4.3.2 Storage and Stability: Trastuzumab is shipped from the Genentech Clinical Repository at ambient temperature via overnight courier but must be placed in a refrigerator at 2-8°C (36-46°F) immediately upon receipt to ensure optimal retention of physical and biochemical integrity. DO NOT FREEZE. When

stored appropriately, trastuzumab is stable through the date stamped on the vial label. Vials reconstituted with the provided diluent (Bacteriostatic Water for Injection) are stable for up to 28 days when stored refrigerated at 2-8°C (36-46°F).

4.3.3 Supplier: Genentech, Inc. Commercially available for subjects enrolled at Yale under the standard of care.

4.3.4 Toxicities of trastuzumab: Hematologic toxicity is infrequent. Mild to moderate diarrhea has been observed. Pulmonary fibrosis has been reported. **(**During the first infusion with trastuzumab, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of trastuzumab infusion). Trastuzumab discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headaches, dizziness, dyspnea, hypotension, rash, and asthenia. The symptoms occurred infrequently with subsequent trastuzumab infusions.

4.3.4.1 Cardiac Toxicities: Seven percent of patients receiving trastuzumab as single agent have been noted to develop any cardiac dysfunction; 5% of patients developed class III/IV heart failure. 94% of the patients had received prior anthracyclines.

4.3.5 Product Complaint: A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Product Complaints **with** an AE (adverse event) should be reported via email/fax to:
usds_aereporting-d@gene.com OR 650-238-6067

Product Complaints **without** an AE (adverse event) should be reported via email to:
kaiseraugst.global_impcomplaint_management@roche.com

All complaints must be filed within 15 calendar days for approved products. Complaints can be reported using a Medwatch, CIOMS or any Genentech-approved reporting form (same as SAEs, AESI etc.).

5.0 CORRELATIVE STUDIES

5.1 Immunohistochemistry (IHC): Uterine or metastatic tumor sites will be collected at the time of primary staging surgery. The tumor will be processed and paraffin-embedded by a research technician in the surgical pathology department. Archival tumoral tissue or tumor cells isolated from ascites will be studied in patients with recurrent disease that do not go to surgery. The Dako Hercep test will be performed as initial evaluation for HER2/*neu* protein over-expression in USPC samples. Membranous staining for HER2/*neu* will be scored according to the Dako Hercep test criteria and scored as 0, 1+, 2+, 3+ (45-48). Uterine serous tumors showing a 3 + positive screening test are eligible for enrollment. USPC samples showing 2+ positivity by IHC for HER2/*neu* by Hercep test must also show gene amplification by fluorescent in situ hybridization (FISH) to be eligible for study enrollment. All IHC and FISH assays will be centrally reviewed in the Pathology Department at Yale University where confirmatory IHC and/or FISH review and/or testing will be performed. Patients will be allowed to initiate therapy prior to confirmation.

5.2 Fluorescence in-situ hybridization (FISH): Only the cases with 2+ membranous staining on IHC will be submitted to confirmatory FISH analysis based on a known correlation established in breast cancer and recent reports in USPC (34,46-48). Fluorescence in situ hybridization (FISH) is regarded as the best diagnostic test for detecting HER-2/*neu* amplification: it has high sensitivity (96.5%) and specificity (100%) for detecting amplification of HER-2/*neu* (45-48). Fluorescence in situ hybridization (FISH) analysis will be performed on sections of paraffin-embedded tissue using dual-color DNA FISH probes. For the detection of HER2/*neu* amplification a Pathvysion LSI, Her-2 (17q11-12) probe labeled with Spectrum Orange will be used in combination with a CEP 17 centromeric probe labeled with Spectrum Green (Abbott) as previously reported by Santin et al., (34).

Of note: as concordance between HER2/neu protein expression by IHC and gene amplification by FISH has not definitely been demonstrated in cases where IHC may be positive (3+) but gene amplification is negative, we shall use IHC as the gold standard test to determine patient eligibility to trastuzumab therapy.

5.3 Exploratory Objectives

5.3.1.1 Isolation of peripheral blood mononuclear cells and plasma to determine peripheral blood natural killer (NK) cell numbers, cytotoxic activity and circulating HER2/neu levels by ELISA.

5.3.1.2 Anticoagulated vials of peripheral blood (i.e., 15 mL total in sodium heparin) will be collected from each patient prior to the first treatment with trastuzumab, after 3 and 6 cycles of therapy and after 3 months after the end of chemotherapy. Peripheral blood mononuclear cells (PBMCs) will be used in flow cytometry studies to identify CD56+CD3- NK cells, CD56+CD3+ NK-T cells and CD56+/CD16+ NK cells numbers and in cytotoxicity assays

against HER2/*neu* positive targets as previously described (44). Plasma levels of HER2/*neu* will be quantified by ELISA.

6.0 TREATMENT PLAN AND ENTRY PROCEDURE/REGISTRATION PROCEDURE

6.1 Study Entry

6.11 Patients will be screened and consented by the P.I. or a member of the study staff at each respective institution. Patient Randomization Form to be faxed and approved by Lead Institution PI prior to entry into trial. NOTE: Do not perform MUGA/ECHO unless patient is randomized to Trastuzumab arm of study.

6.12 Treatment Plan

This is a two arm, randomized Phase II design with HER2/*neu*+ advanced/recurrent USPC disease. Patients with USPC meeting eligibility criteria will undergo immunohistochemistry for HER2/*neu* expression and/or fluorescence in situ hybridization (FISH) to detect amplified HER2/*neu* gene expression.

6.121 HER2/*neu*+: Patients who have HER2/*neu* positive disease (i.e., 3+ USPC) by IHC and/or FISH + results will be randomized to receive six cycles of chemotherapy with carboplatin and paclitaxel with or without concurrent trastuzumab. They will also have peripheral blood drawn to perform in vitro studies to provide a basis for assessing the possible therapeutic contributions of immune mechanisms of action of trastuzumab.
The trastuzumab shall be continued indefinitely in these patients until disease progression of prohibitive toxicities occur.

6.122 CA-125 Exploratory Analysis: Of note, retrospective studies suggest that CA-125 may be a marker of active disease in women with USPC (49) Therefore, in an exploratory analysis, CA-125 will be drawn on each patient with other labs prior to treatment, after each cycle and then at 3 month intervals if remission is achieved.

6.123 Chemotherapy: Carboplatin AUC 5 and Paclitaxel 175 mg/m^2 (3 hours) every 21 days x 6 cycles will be given to all patients. Three weeks of therapy will be considered one cycle. Additional cycles may be administered if the investigator feels that the subject would receive clinical benefit from continued chemotherapy treatment.

6.124.1 Methods of Chemotherapy Administration
Maximum body surface area used for dose calculations will be 2.0 m^2 as per GOG Chemotherapy Procedures Manual.

6.124.2 Sequence and timing of drug administration: Carboplatin will be administered as a 30 minute infusion. Carboplatin will be infused after Paclitaxel.

6.124.3 Paclitaxel will be administered as a 3-hour infusion on this study. For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed to reduce the risk with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), anti- histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

6.124.4 Antiemetic Regimens: It is anticipated that nausea and vomiting may be a significant side effect of chemotherapy. The following representative antiemetic regimens are suggested: Ondansetron 8-32 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV 30 minutes prior to drug administration, or Granisetron 10 mcg/kg IV (or 2 mg PO) 30 minutes prior to chemotherapy, with or without lorazepam 0.5-2.0 mg IV 30 minutes prior to chemotherapy or aloxi 0.25 mg IV 30 minutes prior to chemotherapy.

6.124.5 Dosing of Carboplatin
The dose will be calculated to reach a target area under the curve (AUC) of concentration x time 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. Institutional guidelines should be followed when calculating carboplatin dose.

In patients with an abnormally low serum creatinine (less than or equal to 0.7 mg/dl), due to reduced protein intake and/or low muscle mass, the creatinine clearance should be determined using a minimum of 0.7 mg/dL.

Calvert Formula: Carboplatin dose (mg) = target AUC × (GFR +25)
For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance. The creatinine clearance (Ccr) is estimated by the method of Cockcroft-Gault using the following formula:
Ccr= [140-age(years)] x Weight (kg)x 0.85/(72 x Scr)
Where: Ccr = estimated creatinine clearance in ml/min
Age = patient's age in years (from 20-80)
Scr = serum creatinine in mg/dl

In the absence of new renal obstruction or elevation of serum creatinine above 1.5 x ULN (CTC grade2), the dose of carboplatin will not be recalculated for subsequent cycles, but will be subject to dose modification for hematologic criteria and other events as noted.

The Maximum GRF according to the new NCI recommendations to be used in the Calvert Formula should not exceed 125 ml/min. Therefore, the maximum allowed dose of carboplatin is 750 mg (AUC 5).

6.124.6 Dosing of Trastuzumab Therapy: 8 mg/kg of trastuzumab will be administered IV over a 90-minute period and on the same day as chemotherapy (but after the patient has received paclitaxel and carboplatin). The drug will be administered every 21 days thereafter at a dose of 6 mg/kg and if the patient tolerates the initial 90 minute infusion, a 30 minute infusion will be used for subsequent doses. Therapy will be continued on an every 21 day basis until disease progression or adverse effects prohibit further treatment. Antiemetic pre-treatment is not required.

Trastuzumab will usually be administered in an outpatient setting. When study medication is administered to a patient, emergency resuscitation equipment must be available in the clinic. Patients must remain under medical supervision for 1 hour following completion of the first dose of trastuzumab administration.

If a Grade 3 or 4 toxicity occurs during an infusion of trastuzumab or during the post-infusion observation period, the infusion must be immediately stopped and the patient must be monitored for a minimum of 1 additional hour. If the toxicity does not resolve to ≤ grade 1 within an hour, the patient must be admitted to the hospital for additional monitoring. In most cases patients experiencing a reaction such as fever, rigors, or dyspnea with the initial trastuzumab infusion will not experience a recurrence, and may receive further treatment as scheduled. If the reaction was mild, the infusion may be restarted the same day. If the reaction was severe, pretreatment with diphenhydramine or prolongation of infusion duration may be employed at the discretion of the treating physician. Patients with underlying pulmonary pathology are at increased risk of severe or life-threatening pulmonary reactions and should be closely monitored. Such patients and their caregivers should be instructed to contact their nurse or physician or go to the nearest urgent care facility immediately if they develop clear discomfort after a treatment with trastuzumab.

6.124.7 Stage III-IV patients should receive systemic chemotherapy (i.e., carboplatin and paclitaxel with or without trastuzumab) followed by radiation therapy. Depending on pathologic findings, in addition to pelvic radiation, para-aortic

radiation and/or vaginal brachytherapy are allowed at the discretion of the treating oncologist.

6.124.8 Surgical Procedures: There will be no surgical modifications. Pelvic and para-aortic node dissection is required for the purpose of this protocol unless gross extra-uterine disease is present at time of initial surgery.

7.0 TREATMENT MODIFICATIONS

7.1 Dose reduction levels:

Drug	Initial dose (A)	Reduced dose (B)	Units
Paclitaxel	175	135	mg/m2
Carboplatin	5.0	4.0	AUC

7.2 **Hematologic toxicity**

7.21 Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below. The use of hematopoietic cytokines and protective reagents are restricted as noted:

7.21.1 Patients will NOT receive prophylactic growth factors [filgrastim (GCSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications after treatment modifications specified below.

7.21.2 Patients will NOT receive prophylactic thrombopoietic agents.

7.21.3 Patients may receive erythropoietin for management of anemia AFTER documentation of hemoglobin less than 10 g/dl (CTCAE v4.0 grade 2).

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

7.21.5 Subsequent cycles of therapy will not begin until the ANC is ≥ 1500 cells/microliter (CTCAE v4.0 grade 1) and the platelet count is ≥ 100,000/microliter. Therapy will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a two week delay will be removed from study therapy.

7.21.6 For first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥7 days, reduce carboplatin and paclitaxel chemotherapy by one dose level on subsequent cycles.

7.21.7 For recurrent febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥7 days (after initial dose reduction), add prophylactic growth factors. In this circumstance, it is recommended that G-CSF at a dose of 5 microgram/kg/day* (or equivalent dosing of pegfilgrastim or sargramostim) will be administered subcutaneously starting the day after the last dose of chemotherapy (normally day 2-4) and continuing through hematopoietic recovery. Growth factors should not be used within 72 hours of a subsequent dose of chemotherapy.

7.21.8 Patients with grade 4 thrombocytopenia will have a 1 level dose reduction in the carboplatin only.

7.21.9 There will be no dose modifications on the basis of uncomplicated granulocyte nadirs lasting less than 7 days.

7.3 Non**-hematologic toxicity**

7.31Neurotoxicity: Neurologic Toxicity Grade 2 (at the discretion of the investigator) or Grade 3 or greater peripheral neuropathy requires discontinuation of protocol therapy until symptoms resolve to Grade 1. When treatment is resumed the carboplatin dose should be reduced to an AUC of 4 and paclitaxel should be reduced to level B. The protocol regimen will be discontinued in patients with recurrent Grade 3 or any Grade 4 neurologic toxicity.

7.32 Gastrointestinal Adverse Effects: Grade 1-2 nausea/vomiting with chemotherapy or radiation therapy, and grade 1-2 diarrhea after radiation therapy may be expected. Patients may receive the investigator's choice of drugs for the control of nausea and vomiting. Grade 4 gastrointestinal toxicity will require hospital admission for IV hydration. Stomatitis or diarrhea: If any mucositis is present on day 21 of a cycle, treatment should be withheld until the mucositis has returned to Grade 1. Grade 3 or 4 mucositis or diarrhea; require a dose reduction of paclitaxel.

7.33 Genitourinary Adverse Effects: Increased frequency with dysuria may occur in some patients. This may be treated symptomatically with antispasmodics and increased fluid intake. Urinary tract infection should be ruled out if the symptoms persist.

7.34 Adjustments for Cardiac Toxicity: Asymptomatic bradycardia is not an indication for discontinuation of therapy. However, the Paclitaxel infusion should be discontinued for chest pain, clinically significant arrhythmia, hypotension, or serious allergic reaction. Any arrhythmia that is felt to necessitate discontinuation of Paclitaxel should be discussed with the Study Chair as soon as possible.

7.35 Dose Adjustments for > Grade 3 Non-Hematologic Toxicity: Decrease Paclitaxel and Carboplatin combination one dose level, and resume treatments after recovery to ≤ grade 1 toxicity.

7.36 Paclitaxel hypersensitivity reaction: If hypersensitivity reactions to paclitaxel or its vehicle (Cremaphor) occur, it will usually be during the first few minutes of infusion. Appropriate symptomatic therapy should be given. Continued treatment may be considered if the reaction is not life-threatening; however, patients must be cautioned about potential recurrences of the reaction. Should the patient decide to continue with treatment it is preferable that this be done on the same day of the occurrence. Patients will follow the institutional protocol for paclitaxel desensitation. A suggested procedure would be to administer the drug first with 1 ml of the original IV solution diluted in 100 ml over one hour, then 5 ml in 100 ml over one hour, then 10 ml in 100 ml over one hour, and finally, the original solution at the original speed.

7.37 Myalgias in the several days following paclitaxel treatment may be severe, and should receive aggressive symptomatic treatment, including narcotics or steroids as required. They are not, however, an indication for dose reduction.

7.38 Hepatic toxicity: Bilirubin must return to within normal limits prior to further therapy.

7.4 Trastuzumab: Although patients will undergo routine monitoring during therapy, organ-specific toxicities that require dose modification are not anticipated with trastuzumab, and there are no provisions for dose reduction. As noted above, infusion duration may be lengthened at the discretion of the treating physician.

7.41 Therapy with trastuzumab should be discontinued in patients with any new cardiac symptoms or findings of cardiac dysfunction. Therapy should also be discontinued if the LVEF is documented to fall to a value ≤ 40% or decrease ≥ 15 absolute percentage points, from baseline (for example, from a value of 60% to 45%).

7.42 **Criteria for removal from trastuzumab treatment**:

7.43 Inability to tolerate trastuzumab because of toxicity.

7.44 The patient may withdraw from the study at any time.

7.45 Patients with evidence of disease progression or significant side effects will be removed from study treatment.

7.46 New cardiac toxicity as specified in exclusion criteria.

8.0 STUDY PARAMETERS

8.1 Observations and Tests

The following observations and tests are to be performed and recorded before, during, and after treatment:

Parameter	Pre-Treatment (28 Days)	During Chemotherapy +/-Trastuzumab	During Trastuzumab Therapy	After Therapy (every 3 mo. X 2 yrs, then every 6 mo. X 3 yrs, then yearly)
History, PE (including pelvic), Performance Status, Toxicity Evaluaton,weight	X	1	1	X
CBC /Diff/Platelets	5	1,7	1,7	2
Chemistries:Serum Cr,BUN,K,Mg,Bili	5	1,7	1,7	2
CA 125	5	3	3	X
Urinalysis	5	2	2	2
SGOT,SGPT,Alk Phos	5	1,7	2	2
Vital signs	X	1	1	2
EKG	X	2	2	2
Toxicity	X	1	1	2
*Radiographic tumor evaluation and measurement (Chest/Abd/Pelvis)	6	6	6	X
LVEF	X	4	4	2
**PMBC collection for Translational Studies	X	After the 3rd and 6th cycle		3 months after the end of carboplatin/taxol(both study arms)

1 Patients should be seen/examined before each cycle of chemotherapy. A physical exam only needs to be completed every 3 months while on trastuzumab maintenance.
2 Repeat only as clinically indicated.
3 Retrospective studies suggest that CA-125 may be a marker of active disease in women with USPC. Therefore, CA-125 will be drawn prior to treatment, after each cycle of chemotherapy and then per protocol
4 LVEF can be determined by gated cardiac scan (such as MUGA) or echo. Repeat measurements should be obtained using the same technique after cycle 3, after cycle 6 and every 3 months while on Trastuzumab.
5 Must be obtained within 14 days prior to initiating protocol therapy.
6 Must be obtained within 28 days prior to initiating protocol therapy, after cycle 3 and after cycle 6. To be obtained at the end of treatment and every 3 months x 2 years, then every 6 months x 3 years, then yearly until disease progression.
7 CBC/Differential/Platelets and chemistries must be obtained within 4 days of re-treatment with protocol therapy or per institutional guidelines.
* Repeat CT scan or MRI should use similar equipment and techniques to ensure consistent measurements
** See Appendix D for collection and shipping information.

8.2 To be completed within 28 days prior to initiation of therapy

- Documentation of tumoral HER2/*neu* by IHC and /or FISH
- Medical history including list of current medications and dosing schedules.
- History of previous therapies for current disease; any residual toxicity from prior therapies should be recorded by using the grading schema in NCI Common Toxicity Criteria v4.0.
- A physical examination will be performed. A pelvic examination is required only if this method is used to evaluate measurable disease. All measurable disease will be documented with uni-dimensional tumor measurements if clinically possible.
- ECOG performance status
- CT of the chest, abdomen and pelvis or MRI
- Baseline measurements of tumor size
- PBMC to be used in flow cytometry (i.e., analysis of NK cells) and cytotoxic assays of NK activity against K-562 cells and HER2/neu + USPC-ARK2 and USPC-ARK3 cell lines (i.e., 15 mL in heparinized tubes of patient's peripheral blood-see Appendix D).
- Vital Signs (blood pressure, pulse, respiratory rate, temperature)
- Baseline EKG
- LVEF measurement by MUGA or Echo if randomized to receive Trastuzumab

8.3 To be completed within 14 days of initiation of therapy

- Complete blood count with leukocyte differential and platelet count
- Serum chemistries to include magnesium, SGPT, SGOT, alkaline phosphatase, total bilirubin, BUN, serum creatinine and potassium.
- Serum CA-125
- Urinalysis

8.4 To be obtained 1 week prior to each chemotherapy cycle (approximately every 3 weeks) +/-7 days to allow for holidays/patient schedule issues:

- Weight
- Vital Signs (blood pressure, pulse, respiratory rate, temperature)
- A physical examination will be performed. A pelvic examination is required only if this method is used to evaluate measurable disease. All measurable disease will be documented with uni-dimensional tumor measurements if clinically possible. A physical exam only needs to be completed every 3 months while on trastuzumab maintenance.
- ECOG performance status
- Serum CA-125
- Assessment of treatment related toxicities

8.4.1 To be obtained within 4 days of retreatment with protocol therapy or per institutional guidelines:

- Complete blood count and leukocyte differential and platelet count
- Serum chemistries (magnesium, SGPT, SGOT, total bilirubin, BUN, serum creatinine), electrolytes. These tests may be done up to 2 days prior to MD visit

8.5 To be obtained after 3 cycles, after 6 cycles and every 3 months for patients randomized to receive Trastuzumab:

- LVEF by MUGA or Echo performed every 3 months while on trastuzumab. Must use same method as baseline assessment.

8.5.1 To be obtained after 3 cycles, after 6 cycles and 3 months after completion of carboplatin/taxol chemotherapy:

- PBMC to be used in flow cytometry (i.e., analysis of NK cells) and cytotoxic assays of NK activity against K-562 cells and HER2/neu + USPC-ARK2 and USPC-ARK3 cell lines (i.e., 15 mL in heparinized tubes of patient's peripheral blood-**see Appendix D**)

8.6 To be obtained at the end of treatment and every 3 months x 2 years, then every 6 months x 3 years, then yearly until disease progression*:

- Adverse events/toxicities-if study-related and ongoing
- Serum CA-125
- A physical examination will be performed. A pelvic examination is required only if this method is used to evaluate measurable disease.
- CT of the chest abdomen and pelvis or MRI
- Evaluation of tumor measurement

***Note:** In order to more precisely determine time of progression, the investigator is encouraged to obtain radiologic assessments earlier than 3 months if there is a strong clinical suspicion of progression of disease to either confirm or refute the clinical impression.

8.7 Patients will be followed every 3 months for survival only after confirmed disease progression.

9.0 EVALUATION CRITERIA

9.1 Objective Response

The major parameters of response to be assessed include Progression-Free Survival, Overall Survival, documentation of Sites of Recurrence, and Treatment Related Toxicity. Treatment response will be based on RECIST v1.1 Guidelines for Measurable Lesions.

9.11 Measurable Lesions- Only recurrent patients with measurable lesions will be enrolled in the study. All target lesions must be assessed using the same technique as baseline. Included in the evaluations are the following standard response criteria for target lesions:

- Complete Response (CR): Disappearance of all target lesions. No new lesions. Lymph nodes must be <10mm short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameters. No new lesions.
- Progressive Disease (PD): The appearance of a new lesion, or at least a 20% increase in the sum of the longest diameters of the target lesions, taking as the reference the smallest sum of the longest diameters recorded since treatment started, and at least 5mm increase.
- Stable Disease (SD): Target lesions do not qualify for CR, PR, or progression. No new lesions.

All non-target lesions must be assessed using the same technique as baseline. Included in the evaluations are the following standard response criteria for non-target lesions:

- Complete Response: The disappearance of all non-target lesions.
- Incomplete Response/Stable Disease: The persistence of one or more non-target lesion(s).
- Progression Disease: The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. provides cycle responses for all combinations of tumor responses in target and non-target lesions with or without new lesions.

9.12 Progression-Free Survival will be defined as date from entry to a particular protocol to date of reappearance or increasing parameters of disease on imaging (CT scan or MRI) or by clinical exam or death from any cause, or is censored at date of last disease assessment.

9.13 Survival will be defined as observed length of life from entry to a particular protocol to death or, for living patients, date of last contact.

9.14 Sites of Recurrence will be assessed. Any clinical or radiological evidence for new tumor, preferably confirmed by pathology, will be considered as a recurrence. Pattern of relapse to be noted:

9.14.1 Pelvic (peritoneal, nodal)
9.14.2 Abdominal (peritoneal, nodal, visceral, ascites)
9.14.3 Diaphragmatic
9.14.4 Distant (nodal, parenchymal, liver, lungs, others)
9.14.5 Omental
9.14.6 Effusions (pleural, ascites)

9.15 Treatment Toxicity: The grade level of the various toxicities will be classified using the Common Toxicity Criteria, version 4 (CTC, v.4) guidelines. Acute toxicities will be scored if occurring </= 30 days from treatment completion, and chronic if > 30 days. Frequency and duration of treatment interruptions due to the treatment toxicity will be assessed.

10.0 DURATION OF STUDY

10.1 This study will continue as long as treatment protocols remain activated.

10.2 The patient must be followed quarterly for two years and every six months for three additional years, and thereafter annually or at time of recurrence until death.

11.0 STUDY MONITORING AND REPORTING PROCEDURES

11.1 Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator with the help of the Remote Monitoring Coordinator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or the Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

11.2 The risks associated with the current study are deemed moderate for the following reasons:

1. We do not view the risks associated with the Trastuzumab as minimal.
2. We do not view the risks associated with the combined use of Carboplatin, Paclitaxel and Trastuzumab as minimal.
3. Given the now established safety and validity of studies performed using Trastuzumab (FDA approved since September, 1998), we do not view the proposed study as high risk.
4. Given our experience with the combined co-administration of Carboplatin, Paclitaxel and Trastuzumab, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

11.3 Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator Dr. Alessandro Santin , according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

11.4 Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

11.5 Plan for Determining Seriousness of Adverse Events:

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

Refer to Section 12.0 of the protocol for guidelines

11.6 Plan for reporting Reportable Adverse Events and other unanticipated problems involving risks to subjects or others to the IRB

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the drug/device/intervention; and b)other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. **This information is discussed in Section 12.0 of the protocol.**

11.7 Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol.

X Yale Cancer Center Data and Safety Monitoring Committee (DSMC)

X Genentech, Inc.

The principal investigator Alessandro Santin will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

11.8 ADVERSE EVENT REPORTING FOR COMMERCIAL DRUG STUDIES

Genentech Requirement for reporting:

This study will utilize the CTC version 4.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 4.0 can be downloaded from the CTEP home page.

Toxicity Grade	Type[a]	Local IRB	Study Coordinators Via email/fax/phone
4,5	Unknown	Yes	Yes
5	Known	No	Yes*
2,3	Unknown	No	No
4 (non-myelo)	Known	No	No
4 (myelo[b])	Known	No	No

* If clearly related to the commercial agent(s)

[a] Type (Known or unknown) is based on toxicities included in the package insert or literature of known toxicities associated with the study drug(s).

[b] Myelosuppression, which includes neutropenia, anemia, thrombocytopenia

11.9 ASSESSMENT OF SAFETY

11.9.1 SPECIFICATION OF SAFETY VARIABLES

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to **Trastuzumab**, all events of death, and any study specific issue of concern.

11.9.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated

with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with advanced recurrent uterine serous papillary carcinoma that were not present prior to the AE reporting period. See Section **11.10.**
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

11.9.2 Serious Adverse Events

Refer to Section 12.0 of the study protocol.

11.9.3 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in Section 11.10 and 12.0 respectively, are collected and reported to the appropriate IRB(s), and Genentech, Inc. in accordance with FDA regulations at 21CFR 312.32 (a)(IND Safety Reports).

11.9.4 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

11.9.5 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel

during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately.

Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the **Trastuzumab** (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

> There is a plausible temporal relationship between the onset of the AE and administration of the **Trastuzumab** and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the **Trastuzumab** and/or the AE abates or resolves upon discontinuation of the **Trastuzumab** or dose reduction and, if applicable, reappears upon re-challenge.

No

> Evidence exists that the AE has an etiology other than the **Trastuzumab** (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to **Trastuzumab** administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are **listed** or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those **not listed** in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis. **Refer to Section 12.0 for further guidelines**.

11.10 PROCEDURES FOR ELICITING AND RECORDING ADVERSE EVENTS

11.10.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinical visit?

"Have you had any new or changed health problems since you were last here?"

11.10.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations. All information will be recording using Oncore Clinical Trials Management System.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the conduct of the research must be reported to the Yale Principal Investigator and the Remote Monitoring Coordinator immediately (if possible) to ensure that all over site committees are properly informed. All information will be entered into Oncore Clinical Trials Management System and updated appropriately. Further determination regarding the need to submit to the subjects local IRB, Yale University HHRP following IRB Policy 710 for reporting Unanticipated Problems Involving Risk to Subjects and Genentech Drug Safety Committee will be reviewed. Specific information is outlined in section 12.0 of the protocol.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history.

A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE.

If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions

Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or

Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 30 days of awareness after the last dose of study drug, a report should be completed and

expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the **Trastuzumab** should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior **Trastuzumab** exposure.

If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct reconciliationfor the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

11.11 STUDY CLOSE-OUT REPORTS

Any Clinical Study Report (final study report), abstracts or literary articles that are a result of the study should be sent to Genentech for review.

Copies of such reports should be mailed to the assigned Medical Science Liaison (MSL) to the study: Christine Ryan, MSN, NP at cryan@gene.com

12.0 PROCEDURES FOR REPORTING UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS, INCLUDING ADVERSE EVENTS (UPIRSOs)

12.1 Expedited Reporting of UPISROs Occuring at Yale

AEs classified as "serious" and "unexpected" that are possibly, probably, or definitely attributed to drug administration, or SAEs whose frequency exceeds expectations, require expeditious handling and reporting.

Serious Adverse Event (SAE)
Any adverse event that results in any of the following outcomes:

- death,
- a life-threatening experience,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity,
- a congenital anomaly/birth defect, or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

The PI will promptly investigate all safety information related to an adverse experience. If the results of the PI's investigation show an adverse drug experience not initially determined to be reportable (based on whether the event is serious, unexpected, and associated with drug administration) is so reportable, the PI will report such experience. Follow-up information to a safety report shall be submitted as soon as the relevant information is available.

Reporting to the Yale Human Investigation Committee

Timeframe for Reporting

1. Events that may require a temporary or permanent interruption of study activities by the Principal Investigator or sponsor to avoid potential harm to subjects should be reported to the IRB **immediately** (if possible), followed by a written report to the IRB using the UPIRSO Reporting Form (710 FR 4) **no more than 5 calendar days** after the Yale Principal Investigator becomes aware of the event**.**

2. Internal Events (defined above) should be reported to the IRB using the UPIRSO Reporting Form (710 FR 4) **within 5 calendar days** of the Principal Investigator becoming aware of the event.

3. External Events (defined above) should be reported to the IRB using the UPIRSO Reporting Form (710 FR 4) **within 15 calendar days** of the Yale University Principal Investigator (PI) becoming aware of the event ONLY IF either of the following are true:

(a) The Yale PI has concluded that an immediate change to the protocol is necessary to address the risks raised by the event, OR

(b) A monitoring entity (e.g., an external IRB at the site where the problem or event occurred, the sponsor, or the Data Safety Monitoring Board) has required modifications/amendments to the research protocol or consent documents as a result of the event.

For all reports of external events, the UPIRSO Reporting Form (710 FR 4) must include the following information:

(a) a clear explanation of why the event or series of events has been determined to meet criteria for reporting;

(b) a description of the proposed protocol changes and any corrective actions to be taken by the PI in response to the external event; and

(c) any aggregated data and an analysis or summary from the sponsor or DSMB, when applicable and available, sufficient to explain the significance of the event or series of events in order to ensure the information is interpretable and relevant to the IRB's task of protecting the rights and welfare of human participants.

Reporting to Investigators at Collaborating Sites

The Yale PI will notify all participating investigators in a written safety report of any adverse experience **associated with the use of the drug** that is both **serious** and **unexpected** as soon as possible and in no event later than 15 calendar days after the sponsor's (PI's) initial receipt of the information. [21CFR312.32(c)]

12.2 SUB SITE INVESTIGATOR SAE REPORTING REQUIREMENTS

The collaborating investigator (Sub Site PI) in a multi-center trial will report **serious**, **unexpected** adverse events occurring at their site to the Yale Principal Investigator **regardless of attribution** immediately (if possible) of knowledge of the event. Full written reports should be submitted to the Yale PI within 5 calendar days of initial knowledge of the report. A Medwatch 3500A shall be used for reporting this event following the instructions outlined in section 12.3. This information will also need to be recorded in Oncore Clinical Trials Management System in the SAE section. Information entered into Oncore will directly reflect the Medwatch 3500A submission.

Send SAEs to the Yale Principal Investigator:

Name: Alessandro Santin,MD
Phone: 203-737-4450
Email: alessandro.santin@yale.edu
Fax:203-737-4339

12.3 SAE Reporting to Genentech

Investigators must report all SAEs to Genentech within the timelines described below to:

The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682

or

(650) 225-5288

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

- Serious AE reports that are related to the Product will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the Product will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

Additional Reporting Requirements to Genentech include the following.

- Any reports of pregnancy following the start of administration with the Product will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

Note: Investigators should also report events to their IRB as required.

MedWatch 3500A Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known

- Supportive laboratory results and diagnostics

Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/medwatch/getforms.html

At all times, the Remote Monitoring Coordinator is available to facilitate submissions and answer any questions regarding the process for all sub site staff.

13.0 MULTI-SITE MANAGEMENT AND COORDINATION

13.1 Overview

This is a multi-site trial where **Dr. Alessandro D. Santin** is the lead Principal Investigator for Yale University and for all non-Yale sites. The Gynecological Oncology research team at Yale University consisting of a Multi-site Research Coordinator, Remote Monitoring Coordinator, Multi-site Data Manager, Clinical Research Nursing Coordinator, Specimen Procurement Coordinator and a Multi-site Administrative Assistant will provide multicenter research support for all sites involved in this project. The YCCI clinical trials management support staff will provide clinical database systems support and training through the use of Oncore Clinical Trials Management System.

13.2 Initiation of Study

Once sub-site IRB approval has been obtained and all required start up documents have been submitted, Dr. Alessandro D. Santin will perform a Site Initiation Visit (SIV) prior to enrollment of study subjects. This will be either on-site or via teleconference with each participating site PI and staff available. Members of the Gynecologic Oncology research team will be available to answer all protocol questions. Once this has taken place with the participating site they may enroll subjects into the protocol. All pre and post SIV documents will be collected and stored in accordance with the Gynecologic Oncology Research SOP for collection of regulatory documents.

13.2.1 Investigational Site Training

Dr. Alessandro D. Santin or an appointed designee will provide investigational staff training prior to study initiation. Training topics will include but are not limited to: Good Clinical Practice (GCP), AE reporting, study details and procedure, study documentation, specimen procurement and shipping, informed consent, and enrollment. Sub sites are supplied with telephone and e-mail contact for all personnel and encouraged to contact with any questions regarding the conduct of the protocol.

13.2.2 Data Collection

Sites will use Oncore Clinical Trials Management System for all data associated with the protocol. Data managers at participating centers will receive Oncore access once they are designated by the site PI, complete an Oncore access request and submit HIPAA training certification. Individuals will receive Oncore training by a member of the YCCI clinical trials management support staff. Subjects entered into the system will be identified by a subject number assigned after randomization. The confidentiality of records that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The database will be monitored by the Multi-site Data manager and the Remote-site Monitoring Coordinator to ensure that data is entered in a timely manner.

13.3 Monitoring

Dr. Alessandro D. Santin or an appointed designee must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On-site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain compliant.

In addition, remote monitoring of data may be performed periodically requiring the site to submit de-identified patient data for comparison to the Remote-site Monitoring Coordinator. The study may be audited by the Yale University DSMB internal auditors. Yale University DSMB audit reports will be kept confidential.

13.4 Study Enrollment Procedures

Any modification of the original consent document provided to participating sites by the Coordinating Center must be approved in advance by the Coordinating Center. Rationale will be provided with any request for a change. A copy of each site's IRB and Coordinating Center approved informed consent document must be on file at the Gynecological Oncology Regulatory office before subjects may be enrolled.

To register eligible patients on this study, each site will contact the Multi-site Coordinator; Lisa Baker, RN (203-785-6398) or Martha Luther, RN (203-737-2781) and provide the signed and dated eligibility checklist, completed signature page of the consent form and additional source documents if requested by the Principal Investigator or Multi-site Coordinator. Once the Principal Investigator or Multi-site Coordinator verifies eligibility, the patient will be randomized and a unique subject study number will be issued. The subject will not be identified by name.

13.5 Responsibilities of the Lead Investigator Dr. Alessandro D. Santin:

The lead investigator is responsible for the overall conduct of the study at all participating sites and for monitoring the safety and quality of the data as well as compliance to the protocol and with applicable federal regulations and Good Clinical Practice (GCP).

The lead investigator will monitor accrual rates at all sites for adequate progress, ensure appropriate coordination, submission of documents and approval of the protocol as well as consent documents and any subsequent amendments at all sites. There will be only one version of these documents that will be used by all participating institutions and the lead investigator is responsible for assuring that the correct versions are used by all participating institutions.

No additional sites will be added to the study without a proposed amendment and review and approval by the Yale Cancer Center Protocol Review Committee and the Yale IRB (HIC).

The lead investigator has the authority to suspend accrual at any site not complying with this protocol, including not submitting data in a timely manner. Any suspension of accrual will be reported to the Yale University Data Safety Monitoring Committee (DSMC) as well as to the Yale University HHRP. Site principal investigators must report the suspension to their IRB.

13.6 Responsibilities of the Coordinating Center

The coordinating center, under the direction of the lead investigator Dr. Alessandro D. Santin, MD, is responsible to ensure that each participating site has the appropriate assurance on file with the Office for Human Research Protection (OHRP) or their local/central Institutional Review Board (IRB). The coordinating center is responsible for obtaining copies of OHRP/IRB assurance for each site prior to enrollment of subjects at the site.

13.7 IRB Approvals

The Coordinating Center is responsible to ensure that no patients are entered on study without full IRB approval and that IRB re-approval is appropriately maintained. A copy of the IRB approval document from each participating institution will be obtained by the Coordinating Center prior to activation of the study at any site. Documentation of reapproval must be provided to the Coordinating Center in a timely manner or registration will be halted at any site in which a current continuing approval is not on file at the Coordinating Center.

13.8 Amendments and Consents

The Coordinating Center will maintain a copy of all amendments, consent forms, and approvals from each site. Consent forms will be reviewed and approved by the Coordinating Center to ensure consistency with the Yale IRB approved consent. Should changes to the protocol or consent become necessary, protocol amendments will be issued by the Coordinating Center to all sites for local site approval prior to implementation, unless there is an apparent immediate hazard to a subject or the subject's best interest is endangered. Any such deviation from the approved protocol will be promptly reported to the lead investigator.

13.9 Responsibilities of Participating Sites:

The principal investigator at each site is responsible for the overall conduct of the study at their site and for monitoring the safety and quality of the data as well as compliance to the protocol and with applicable federal regulations and (GCP).

The principal investigator at each site is responsible for assuring that all the required data is collected and entered onto the e-CRFs using Oncore Clinical Trials Management Systems in accordance with study-specific requirements and that the data submission and reporting timelines are met. The coordinating center will perform onsite monitoring periodically to ensure adherence to the protocol as well as regulatory compliance.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study design: This will be a randomized, open-label Phase II multicenter study of advanced/recurrent UPSC patients, with an emphasis on identifying and treating women having HER2/*neu*+ disease. The incidence of HER2/*neu*+ USPC patients in the retrospective literature ranges from 18-80%. However, the percentage is known to increase with advancing stage, and most of these studies are small and are confounded by patients of various disease stages. In a recent GOG study of patients with largely advanced-stage USPC, HER2/*neu* expression rates (i.e., 2+ and 3+) were >60% (35).

With regard to sample-size planning, almost 100% of recurrences in women with advanced-stage disease will happen within the first two years after diagnosis. Based upon historical Phase III data of outcomes in advanced or recurrent endometrial cancer patients treated with platinum/taxane-based therapy (median PFS=~7.0-8.0 months) and retrospective data on advanced stage USPC patients (median PFS ~6 months), we would anticipate a 6-month median PFS in patients treated with chemotherapy alone.

14.2 Primary objective

To estimate whether the addition of trastuzumab to paclitaxel and carboplatin chemotherapy improves progression free survival (PFS) when compared to paclitaxel and carboplatin alone in USPC patients over expressing HER2/*neu*

14.3 Secondary objectives

To assess objective response rate (ORR)
To assess overall survival (OS)
To assess the safety profile of Trastuzumab in USPC patients

14.4 Exploratory/correlative objectives

To determine peripheral blood natural killer (NK) cell numbers and activity in HER2/*neu*+ USPC patients to provide a basis for assessing the possible therapeutic contributions of immune mechanisms of action of trastuzumab.
To study HER2/*neu* extracellular domain (ECD) circulating levels in the plasma of USPC patients over expressing HER2/*neu* before, during and after treatment to elucidate whether changes in HER2/*neu* ECD would predict response to trastuzumab.
To determine whether CA-125 levels correlate with disease activity in persistent and/or recurrent disease.

14.5 Subjects will be stratified by (a) Study Site and (b) Disease Stage (i.e. Stage III or Stage IV or Recurrent Disease). Subjects will be assigned at a 1:1 allocation ratio to Arm A (Carboplatin+Paclitaxel) or Arm B (Carboplatin+Paclitaxel plus Trastuzumab) by randomization.

14.6 Primary endpoint. Progression-free survival (PFS), defined as the length of time from randomization to disease recurrence, disease progression, or death for any reason. Subjects who are

alive and who did not experience disease recurrence or progression by the end of the study will be censored for the primary endpoint at the date of their last contact.

14.7 Statistical analysis plan for primary endpoint. Arm B (Carboplatin+Paclitaxel plus Trastuzumab) will be compared to Arm A (Carboplatin+Paclitaxel) for an increase in PFS by means of the log rank test, conducted using a one-sided alpha=0.10. A single interim analysis for futility will be conducted when the observed number of recurrence/progression/death events reaches 26 or ≥30% of the required total of 85.

14.8 Statistical power requirement. Under the analysis plan for the primary endpoint, the proposed study will be required to have 90% power to detect a 43% decrease in hazard of a recurrence/progression/death event in Arm B compared to Arm A (hazard ratio = 0.57). This 43% decrease in hazard is equivalent to an increase in median PFS from 6 months in the control arm to 10.5 months in the trastuzumab arm. For the sample-size calculation, we will assume a median PFS of 6 months in the control arm. For the interim-analysis adjustment, we will use the Lan-DeMets (O'Brien-Fleming) spending function to allocate Type II error.

14.9 Study design, sample size, and study duration. The following study design meets the statistical power requirement:

- A total of 100 subjects will be accrued to the study, at a rate of five subjects per month for a total of 20 months.
- The interim analysis for futility will take place when 26 recurrence/progression/death events have occurred. If the log-rank z-score has a value more negative than –1.328 (equivalent to a 1-sided *P* value greater than 0.908, and to an apparent 69% increase in hazard for trastuzumab compared to control), then the result will be taken as evidence of treatment futility, and the study will be terminated early, before reaching full accrual. Based on an accrual rate of 5 subjects per month and a 6-month median PFS in the control arm, we expect to observe 26 events at 12.9 months into the study, when cumulative accrual should be 65 subjects or fewer (≤65% of 100).
    - This early stopping rule has probability=0.0030 of Type II error (inappropriately causing early termination) when the true trastuzumab effect is a 43% decrease in hazard compared to control.
    - The interim-analysis trigger point of 26 events was chosen to be early enough to allow a data monitoring board sufficient time to review the results and make a decision before final accrual of 100 subjects is reached.
- The final analysis for efficacy will take place when 85 recurrence/ progression/death events have occurred. Based on an accrual rate of 5 subjects per month and a 6-month median PFS in the control arm, we expect to observe 85 events at 33.6 months of study duration.

- The study is thus expected to last slightly more than 2.75 years under current assumptions of 100 subjects accrued at 5 per month and median PFS of 6 months in the control arm.
- Early drop-outs and ineligible subjects. If an enrolled subject drops out of the study *before* receiving treatment, or is found to have been ineligible, she will be replaced. Up to ten such early drop-outs and ineligibles will be replaced in this manner; thus, the study may enroll up to 110 subjects in order to assure the required sample size of 100. If an enrolled subject drops out of the study *after* receiving treatment, she will not be replaced, and her time on study will be censored at the date of her study withdrawal.

14.10 Correlative studies in HER2/*neu*+ cohort

Association of IHC, FISH, plasma HER2/*neu* levels and NK cell number and activity with PFS using Cox proportional hazards regression will be performed.

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APPROVED BY THE YALE UNIVERSITY IRB 5/6/2020

Appendix A:

FIGO Surgical Stages for Endometrial Cancer

IA Tumor confined to the uterus, no or < 50% myometrial invasion

IB Tumor confined to the uterus, > 50% myometrial invasion

II Cervical stromal invasion, but not beyond uterus

IIIA Tumor invades serosa or adnexa

IIIB Vaginal and/or parametrial involvement

IIIC1 Pelvic node involvement

IIIC2 Para-aortic involvement

IVA Tumor invasion bladder and/or bowel mucosa

IVB Distant metastases including abdominal metastases and/or inguinal lymph nodes

Appendix B:
Performance Status Criteria
HIC# 1012007786
Protocol version 12.0
Version date: 03 April 2020

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix C:
Adverse Events to Study Agents

HIC# 1012007786
Protocol version 12.0
Version date: 03 April 2020

Adverse Event List(s) for Commercial Agent(s)

Paclitaxel:

- Hematologic: 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)
- Neurologic: 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, arthralgia, myalgia, lightheadedness, myopathy
- Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata
- (Please refer to package insert for the comprehensive list of adverse events.)

Carboplatin:

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting, diarrhea,
- Neurologic: Peripheral neuropathy, central neurotoxicity
- Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
- Liver: Increased SGOT, SGPT, bilirubin and alkaline phosphatase
- Other: Fatigue, electrolyte imbalance, hypomagnesemia, hypocalcemia
- Please refer to package insert for a comprehensive list of adverse events.

Trastuzumab:

ALLERGY/IMMUNOLOGY

Allergic reaction/hypersensitivity, (including drug fever)
Allergic rhinitis (including sneezing, nasal
stuffiness, postnasal drip)
Allergy/Immunology - Other
(Angioedema)

BLOOD/BONE MARROW

Hemoglobin
Leukocytes (total WBC)
Neutrophils/granulocytes (ANC/AGC)

CARDIAC ARRHYTHMIA
Sinus tachycardia
Supraventricular arrhythmia -
nodal/junctional

CARDIAC GENERAL
Cardiac General - Other (Cardiac arrest)
Cardiac General - Other
(Cardiomyopathy)
Cardiac troponin I (cTnI)
ɜHypertension
Hypotension
Left ventricular systolic dysfunction
Pericardial effusion (non-malignant)
Pericarditis

CONSTITUTIONAL SYMPTOMS
Fatigue (asthenia, lethargy, malaise)
Fever (in the absence of neutropenia,
where neutropenia is defined as ANC <1.0x 10e9/L)
Rigors/chills

DERMATOLOGY/SKIN
Rash/desquamation
Rash: acne/acneiform
Ulceration
Urticaria (hives, welts, wheals)

GASTROINTESTINAL
Anorexia
Diarrhea
Mucositis/stomatitis
(functional/symptomatic)
Nausea
Vomiting
INFECTION
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C)
Infection - Other (Herpes simplex)
Infection with unknown ANC

METABOLIC/LABORATORY
Alkaline phosphatase

AST, SGOT (serum glutamic oxaloacetictransaminase)
GGT (gamma-glutamyl transpeptidase)

PAIN
Pain - abdomen NOS Pain – back
Pain – bone, joint, muscle
Pain - chest/thorax NOS Pain – head/headache
Pain - neuralgia/peripheral nerve
Pain - tumor pain
Pain NOS

PULMONARY/UPPER RESPIRATORY
Adult respiratory distress syndrome
(ARDS)
Bronchospasm, wheezing
Cough
Dyspnea (shortness of breath)
Hypoxia
Pleural effusion (non-malignant)
Pneumonitis/pulmonary infiltrates
Pulmonary - Other (Non-cardiogenic pulmonary edema)
Pulmonary fibrosis
Voice changes

SYNDROMES
Cytokine release syndrome/acute infusion reaction
Flu-like syndrome

APPENDIX D
STUDY PI and Shipping address*:
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E-mail: alessandro.santin@yale.edu

I. Summary of Specimen Requirements

1) **A)** IHC stained slide(s) showing HER2/neu 3+, FISH + slides or 2+ expression along with an H&E stained slide of the primary/recurrent USC for Yale Pathology confirmatory assessment, **B)** Formalin-Fixed, Paraffin-Embedded Tumor Tissue Block or unstained slides

2) Whole Blood Specimens (10 cc in Lithium Heparin and/or Sodium Heparin) **and** 5-7 cc EDTA (purple top tubes)

II. Time Points Deadlines and Recommendations

1) IHC stained slides showing HER2/neu 3+, FISH + slides or 2+ expression along with an H&E stained slide of the primary/recurrent USC for Yale Pathology confirmatory assessment and formalin-fixed, paraffin-embedded primary or recurrent tumor (1st choice: block, 2nd choice: 20 unstained sections), should be shipped to the Yale Department of Obstetrics & Gynecology at the time of patient enrollment in a FED-EX envelope for overnight delivery. A preprinted FED-EX label will be provided. In order to produce the label, a date of shipment is necessary. Please e-mail michele.montagna@yale.edu and martha.luther@yale.edu with the date of shipment and a pre-printed label will be e-mailed back to you. **Please send all FISH slides in a light-protected case**.

2) Whole blood (minimum 10 mL) drawn into dark green top (Lithium Heparin or Sodium Heparin) tubes **and** 5-7 cc EDTA (purple top tubes) for translational research studies will be collected before the first treatment (i.e., within 28 days of initiation of therapy), after the 3rd and 6th cycle of chemotherapy (at least 20 days from the chemotherapy infusion) and at 3 months after the end of carboplatin/paclitaxel chemotherapy. Blood samples should be shipped at room temperature to the Yale Department of Obstetrics & Gynecology the day the specimen is collected in a FED-EX envelope for overnight delivery. A preprinted FED-EX label will be provided. In order to produce the label, a date of shipment is necessary. Please e-mail michele.montagna@yale.edu and martha.luther@yale.edu with the date of shipment and a pre-printed label will be e-mailed back to you.

NO BLOOD DRAWS OR SHIPMENTS ON FRIDAYS