Mayo Clinic Cancer Center

MC1463: Avatar-Directed Chemotherapy in Platinum-Resistant Ovarian, Primary Peritoneal and Fallopian Tube Cancers

Principal Investigator: [redacted]

Co-Investigators: [redacted]

Statistician: [redacted]

Investigational Device
IDE Exempt (NSR status per FDA determination): Mouse Avatar model

Drug Availability
Commercial Agents**:** topotecan (Hycamtin®); paclitaxel (Taxol®); liposomal doxorubicin (Doxil®); Gemcitabine (Gemzar®); bevacizumab (Avastin®)

***** Investigator having responsibility for this protocol
√ Study contributor(s) not responsible for patient care.

Document History	Effective Date
Activation	July 21, 2015
Mayo Addendum 1	July 21, 2015
Mayo Addendum 2	July 21, 2015
Mayo Addendum 3	June 8, 2016
Mayo Addendum 4	April 13, 2018

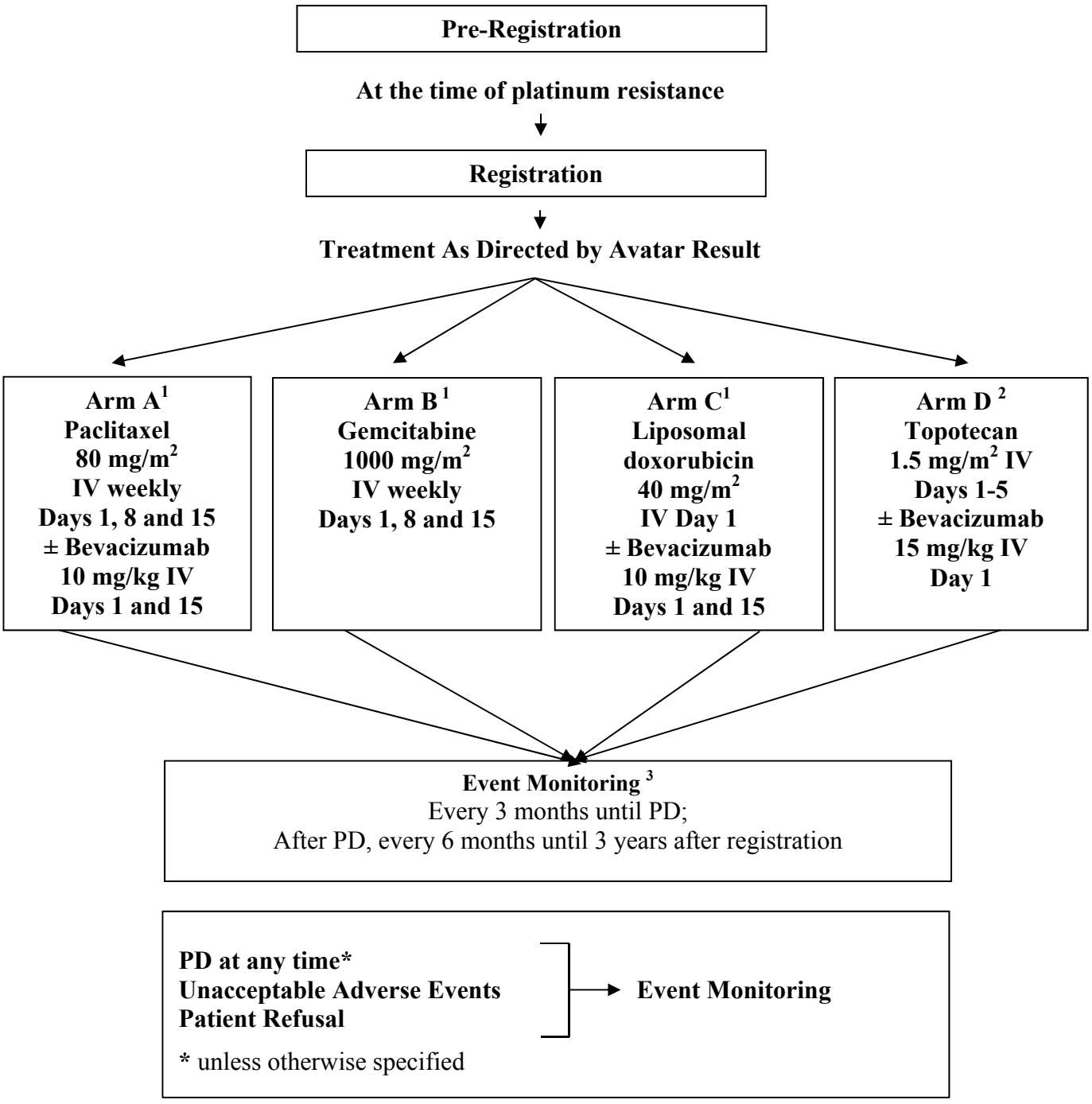
Protocol Resources

Questions:	Contact Name:
Patient eligibility*; test schedule; treatment delays, interruption or adjustments; dose modifications; adverse events; forms completion and submission	[redacted]
Forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Serious Adverse Events	[redacted]

*No waivers of eligibility per NCI

Table of Contents

Schema


Pre-Registration
At the time of platinum resistance
Registration
Treatment As Directed by Avatar Result
Arm A[1]
Paclitaxel
80 mg/m2
IV weekly
Days 1, 8 and 15
± Bevacizumab
10 mg/kg IV
Days 1 and 15
Arm B[1]
Gemcitabine
1000 mg/m2
IV weekly
Days 1, 8 and 15
Arm C[1]
Liposomal
doxorubicin
40 mg/m2
IV Day 1
± Bevacizumab
10 mg/kg IV
Days 1 and 15
Arm D[2]
Topotecan
1.5 mg/m2 IV
Days 1-5
± Bevacizumab
15 mg/kg IV
Day 1
Event Monitoring[3]
Every 3 months until PD;
After PD, every 6 months until 3 years after registration
PD at any time*
Unacceptable Adverse Events
Patient Refusal
Event Monitoring
* unless otherwise specified

If a patient is deemed ineligible or a cancel, please refer to Section 18.1 for follow-up information.

[1] Cycle length = 28 days. Note that after Cycle 1, treating physicians may adjust 28-day cycles to 21-day cycles at their discretion. See Section 7.0 for details.

[2] Cycle length = 21 days. Note that topotecan may be administered at 4 mg/m^2 weekly Day 1, 8 and 15 ± bevacizumab 10 mg/kg IV Days 1 and 15 on a 28 day schedule at treating physicians discretion. See Section 7.0 for details

[3] Event monitoring will take place by means of a patient phone call or chart review to assess vital status and progression status only.

Generic name: Topotecan Brand name(s): Hycamtin® Mayo Abbreviation: TOPA Availability: Commercial	Generic name: Paclitaxel Brand name(s): Taxol® Mayo Abbreviation: TAXOL Availability: Commercial
Generic name: Liposomal Doxorubicin Brand name(s): Doxil® Mayo Abbreviation: DOXIL Availability: Commercial	Generic name: Gemcitabine Brand name(s): Gemzar® Mayo Abbreviation: GEMZAR Availability: Commercial
Generic name: Bevacizumab Brand name (s): Avastin® Mayo Abbreviation: AVASTN Availability: Commercial	

1.0 Background

Ovarian cancer affects an estimated 22,280 women in the US annually. While it is the second most common gynecological malignancy, it is the most lethal gynecological malignancy (Siegel *et al.*, 2012). The lethality of OC is due to the high frequency of cases diagnosed at a late stage (Horner *et al.*, 2009)). In addition, most patients who initially respond to treatment will eventually relapse and respond only modestly to salvage chemotherapy, contributing to lethality of OC. When compared to other cancers in women, the death-to-incidence ratio of epithelial OC (EOC; 70 per 100) is more than four times that of breast cancer (17 per 100) and similar to that of lung cancer (Siegel *et al.*, 2012). Despite incremental improvements in disease-free survival over the last three decades, cure rates are essentially unchanged (Barnholtz-Sloan *et al.*, 2003). Barriers to better outcomes include a lack of individualized therapy and limitations of the preclinical models used to evaluate novel anticancer agents in EOC.

Multiple agents have activity for the treatment of platinum resistant ovarian cancer (PR-OC), but the optimal agent is not known. As a result, one of several agents are chosen based on adverse event profiles, schedule and patient/physician preference without selection based on which would be most active. Pegylated liposomal doxorubicin (PLD) has response rates in the range of 11 to 19.7%, with progression free survival (PFS) ranging from 12-22 weeks (Gordon *et al.,* 2001; Mutch *et al.,* 2007). The response rates of gemcitabine (Gem) range from 9 to 22% with 8-16 weeks PFS (Mutch *et al.,* 2007; Lund *et al.*, 1994; Ojeda Gonzalez *et al*., 2008; von Minckwitz *et al.*, 1999). Topotecan (TPT) has a response rate between 9 and 19%, depending on study and schedule, with a PFS ranging from 16-20 weeks (Gordon *et al.,* 2001; Sehouli *et al*., 2011). Weekly paclitaxel (PTX) has response rates of 21 to 25% and PFS of 14- 24 weeks, though some smaller studies have demonstrated higher response rates (Markman *et al.,* 2006; Markman *et al.,* 2002). Recently, a randomized phase III clinical trial (AURELIA) was reported, which incorporated these agents as 'physicians' choice' in the control arm in the treatment of PR-OC. The response rates were 12.6% (95% CI 8.0-18.4%), with a median PFS of 3.4 months (95% CI 2.2-3.7 months). Given these poor outcomes from salvage chemotherapy, we believe Avatar-directed chemotherapy can change these outcomes by assigning patients to the most effective regimen in their own, personal Avatar. We believe by identifying the correct chemotherapy, we can increase the response rates to 40% or greater, with an inherent increase of median PFS greater than 6 months. In addition, the significance of having a reliable model of testing sensitivity to individual therapies is substantial, as it could be applied to novel therapies and produce tissue that would be useful to performing correlative studies, including identification of signature profiles, without biopsies.

1.1 Avatar Project Overview

Beginning in March 2010, viable tumor from consenting ovarian cancer patients undergoing primary debulking surgery has been collected and heterotransplanted directly into severe combined immunodeficiency (SCID) mice to establish primary tumor grafts. Tumors harvested from patients under sterile conditions are

mechanically disrupted and injected into the intraperitoneal cavities of the mice using methods developed by Beth Karlan and colleagues (2002). Engrafted tumor is then surgically resected, minced and re-injected into additional mice to generate aliquots of tumor for future use, including pathological evaluation, molecular characterization and drug treatment studies. Alternatively, minced tumor aliquots are frozen in viable fashion for re-engraftment at a later date. The molecular and histologic characteristics of the patient's source tumor can then be compared to those of the tumor graft. Clinical outcomes from the source patients are correlated in a de-identified fashion to these parameters, with the help of the Mayo Ovarian SPORE Biospecimens Repositories at Mayo Clinic Rochester, Mayo Clinic Florida and Mayo Clinic Arizona. (**Figure 3)**. In addition, two Avatar co-clinical trials involving biopsy specimens collected at the time of tumor recurrence (MC1464 and MC1561) have helped to define the standard operating procedures to demonstrate the feasibility of engrafting Avatar tumors from biopsy specimens obtained from patients with ovarian.

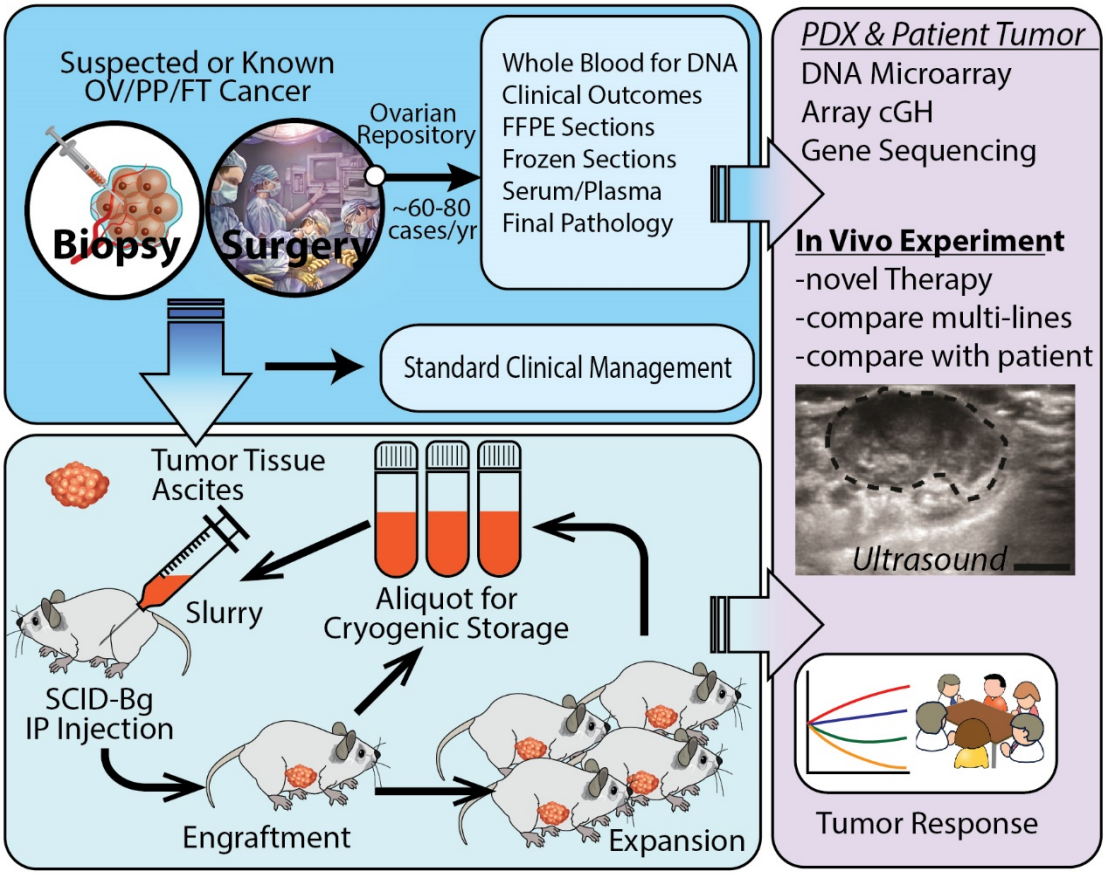


Figure 3. Model establishment and characterization. Patient derived xenograft (PDX) models are generated from ovarian (OV), primary peritoneal (PP), and fallopian tube (FT) cancer patients and propagated in severe combined immunodeficient biege-mutated (SCID-bg) mice. PDX models are also referred to as Avatars.

1.2 Avatar Engraftment Success

To date, this effort has resulted in a high percentage of engrafted carcinomas (failure rate [> 1 year w/o engraftment] is only 13.2%) with an engraftment rate of approximately 74% (Haluksa *et al.*, 2012). The gap between these two values represents models that may have engrafted, but have not been verified as epithelial tumors (see Preliminary Studies section on 'Troubleshooting Lymphoma Development in Model System'). As of April 2013, models from over 270 individual patients have been injected and over 160 have engrafted and are available for further assessment. Primary tumor procurement and injection in mice continues. The engrafted models represent the gamut of ovarian, primary peritoneal and fallopian tube histologic subtypes that are seen in the clinic (**Figure 4, A**), and are unique in the number, range of histologies, volume of clinical annotation, and array-based data available. Since the availability of our model to direct therapy in patients in time sensitive, we have been closely monitoring time to engraftment (**Figure 4, B)**. Over the course of our experience developing Avatar models, our time to engraftment has improved from a median of 153 days to 105 days. Thus, while this models system could not be used to generate response data for directing initial adjuvant therapy, it would be feasible for directing recurrent therapy, given the median time to progression of 18-24 months in OC (Armstrong *et al.*, 2006; McGuire *et al.,* 1996).

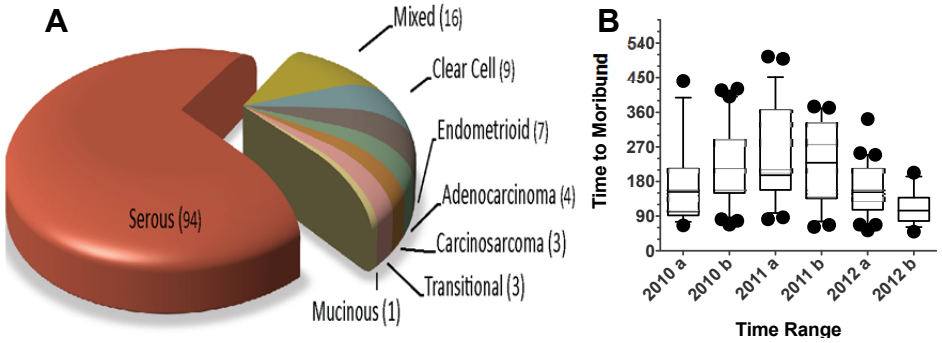


Figure 4. Histologic and engraftment characteristics of Avatar models. A) Graphical representation of the histologic distribution of 137 engrafted Avatar tumor graft models as of July 2012. B) Box and Whisker plots (10-90 percentile) of time-to-moribund state as surrogate for Avatar engraftment. Filled circles represent outliers.

One of the advantages of this approach is that the carcinomas are engrafted *in vivo* without growth on plastic. Thus, these carcinomas develop and interact with stroma in an environment more similar to that of the patient. Importantly, as has been demonstrated with other patient-derived tumor models, tumor engraftment was prognostic (Garrido-Laguna *et al.,* 2011; Nemati *et al.*, 2010; Weroha *et al.*, 2013). Patients with successfully engrafted Avatars have poor outcomes compared to patients whose Avatars do not engraft (**Figure 5)**. As a result, development of Avatar-directed therapies will be used for patients in greatest need.

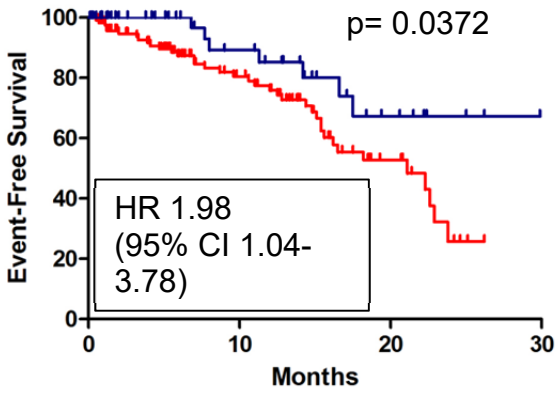


Figure 5. Avatar Engraftment Predicts Poor Survival- Events (recurrence, progression or death) in patients from successfully engrafted Avatars (red) or unsuccessfully engrafted (blue) are plotted by Kaplan-Meier survival analysis. Groups are compared using Log-Rank test.

1.3 Use of M-Mode Ultrasonography for Tumor Monitoring

Accurate assessment of tumor growth and response to therapy is vital to tumor graft-based experiments. As our orthotopic model necessitates intraperitoneal growth in an immunocompromised model, tumor monitoring poses a challenge. For instance, small animal CT, PET, or MRI scanners are not located in the animal barrier area, thus are not practical for frequent or non-terminal measurements. To overcome these barriers, we have employed transabdominal portable ultrasound since it also avoids the need for general anesthesia while providing accurate pre- and post-treatment tumor measurements, thereby allowing each animal to function as its own reference. While ultrasound is not typically used for monitoring tumor responses in OC patients, due to the large area surface area, operator dependence and inferior reproducibility in human patients (van Persijn *et al.*, 2010), mice have a much smaller intra-abdominal/pelvic surface area and are amenable to repeated ultrasound measurements, which others have demonstrated to be accurate and feasible (Dreys *et al.*, 2000; Rooks *et al.*, 2001). To assess this on our own model system, tumor diameter in 35 mice bearing tumor grafts were assessed using an L-25x 13-6 MHz linear transducer with a SonoSite S-Series ultrasound device and plotted to caliper-derived diameter measurements at necropsy. An excellent correlation between tumor diameter by ultrasounds and caliper measurements was observed (**Figure 6**). To improve reproducibility, the image representing the largest tumor diameter is captured and cross-sectional area is calculated using ImageJ 1.46 platform independent software (Schneider *et al.*, 2012)). Although serial CA125 measurements have been proposed for ovarian tumor grafts (Baknert *et al.*, 2011), the assay in our series did not prove sensitive enough to be useful (Data not shown).

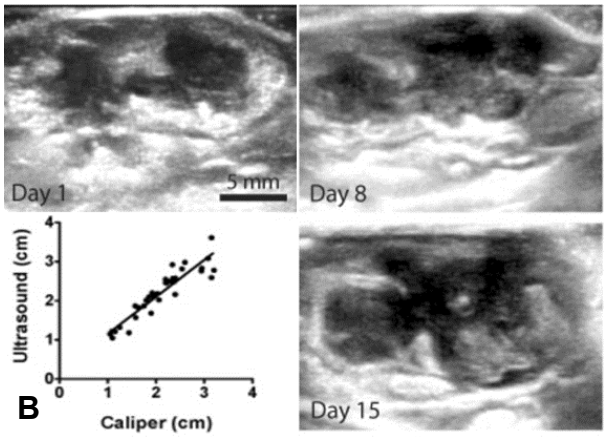


Figure 6. Transabdominal ultrasound assessment of tumor change in untreated controls. (a) Representative serial ultrasound images from a saline-treated PH015 tumor graft showing growth over 15 days. Scale bar = 5 mm. Tumors are hypoechoic relative to the surrounding bowel. (b) Tumor diameter in 35 mice bearing tumor grafts were assessed by ultrasound and plotted to caliper-derived diameter measurements at necropsy. The Spearman correlation was r = 0.941.

1.4 Characterization of Avatar Models

The underlying hypothesis is that the tumor grafts are more likely to share characteristics of the patient's neoplasm compared to *in vitro* selecting for clonal populations of cells capable of growing in culture. Reassuringly, the histologies (including extent of stromal component), was similar in the Avatar tumor graft compared to the source patient tumor. This was assessed by H&E staining for a general evaluation of tissue substructures. Pan-cytokeratin staining was done, to ensure the presence of a human epithelial tumor and Ki-67 confirmed that the proliferative index of the patient and tumor graft were similar. An example of this shown is **Figure 7a**. In regards to the stromal component of our tumors, we have demonstrated (Appendix 1, submitted manuscript) that this is murine in origin, but recapitulates the degree of stromal involvement (low, intermediate, high) that is observed in the source patients. These data support our speculation that the epithelial tumor component may be programmed to develop a supportive stromal component as individual as each patients' epithelial component. As many ovarian cancers are characterized by their deficiencies in DNA repair and genomic instability, we have also evaluated tumors by array CGH to ensure the fidelity of any DNA amplifications/deletions presents. These evaluations were also aided by our collaboration with the Mayo Clinic Ovarian Cancer Repository, who were able to provide individual patient match germ line DNA for controls. These demonstrated a striking similarity between Avatar tumor graft and source patient aberrations in DNA, with the understanding that some differences may be due to the presence of murine DNA. An example is shown in **Figure 7b**. In addition, the most commonly gained/lost genes in ovarian cancer, as determined

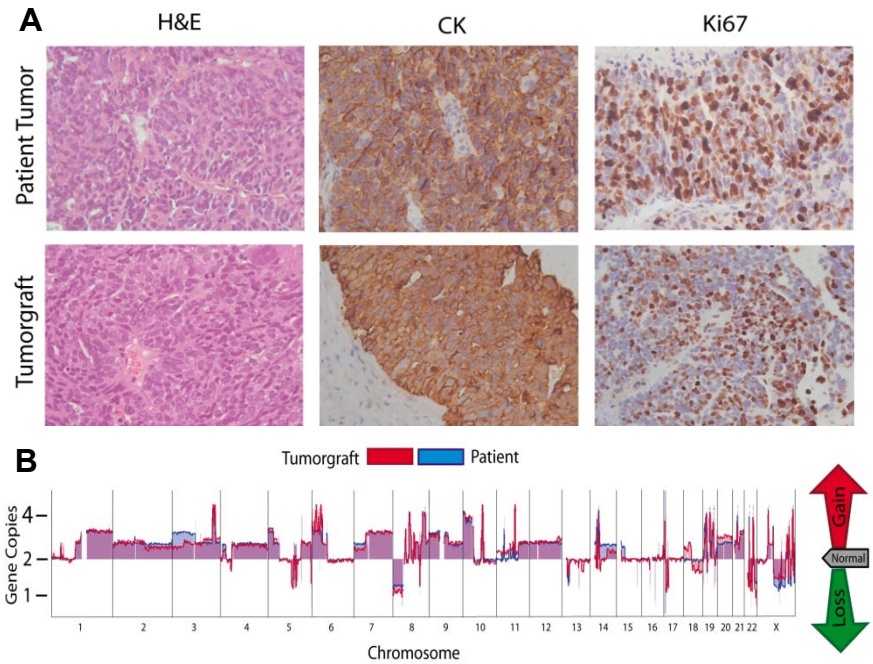


Figure 7. Xenograft models closely replicate source neoplasms. Carcinomas from the patient and tumor graft were compared pathologically (A) by H&E, cytokeratin (CK) and Ki-67 staining. Array cGH (B) demonstrates similar deletions and amplifications in tumor graft and the source patient tumor.

by gene copy number analysis and DNA sequencing of 489 ovarian serous carcinomas from The Cancer Genome Atlas (TCGA) Research Network, *Nature,* 474:2011) including RB1, NF1, PTEN, TACC3, MYC, KRAS, CCNE1 and others have been demonstrated in our Avatar models.

To further evaluate the molecular characteristic, we have performed gene expression arrays using the Affymetrix U133 Plus 2.0 Whole Genome array platform. Using DNA microarray profiling on 27 early-passage serous ovarian tumor grafts, we performed an unsupervised clustering profile on these tumor grafts with the raw data set from the 489 serous ovarian tumors evaluated in TCGA data set (*Nature*, 474:2011). Most models (Weroha *et al.,* 2013)) cluster with the proliferative subtype while the remaining cluster with either dedifferentiated (Mutch *et al.*, 2007) or immunoreactive (Gordon *et al*., 2001). No samples cluster with mesenchymal subtypes, likely the result of human stroma being replaced with murine stroma in our models. Upon analyzing the genes most upregulated in our clustered subtypes, the genes most upregulated in the differentiated (SLPI, MUC1, MUC16), proliferative (SOX11, HMGA2) and immunoreactive (CXCL10, CXCL11) Avatar sets are also upregulated in the TCGA data set(24). Additional characterization has been performed to determine the mutational status of homologous recombination (HR) genes, including BRCA1 and 2, which are deficient in many OC(25-28). This has been performed on 50 models to date by a massively parallel sequencing strategy and verified

with Sanger sequencing and copy number variant determination in collaboration with Dr. Elizabeth Swisher (University of Washington)(Walsh *et al*., 2011; Walsh *et al*., 2010). Mutations in BRCA1, BRCA2, CHEK2, ATM, ATR, XRCC2 and others have been identified. These data are currently being used to select models for the development of PARP inhibitors, but are beyond the scope of discussion here.

1.5 Concordance of Avatars with Patient Response to Chemotherapy

Despite the supportive data that demonstrate the similarity between Avatar tumors and their source patients on a histological and molecular basis, the clinical relevance of the models would be best realized by determining their similarity in responsiveness to treatment. Given the importance of platinum-based chemotherapy in the front-line treatment of ovarian cancer, we evaluated the responsiveness of Avatar models to paclitaxel/carboplatin. Models were selected from patients who had differential outcomes (platinum-resistant and platinum-sensitive) following front line therapy with paclitaxel/carboplatin. Once tumors were established, treatment was administered in a blinded fashion, with an investigator performing the ultrasound measurements that was unaware of the outcome. We demonstrated that response to chemotherapy was concordant in Avatar models from four patients with platinum-resistant ovarian cancer (tumors did not regress with platinum chemotherapy) and five patients with platinum-sensitive ovarian cancer (tumors regressed; Weroha *et al*., 2013, **see Figure 8**).

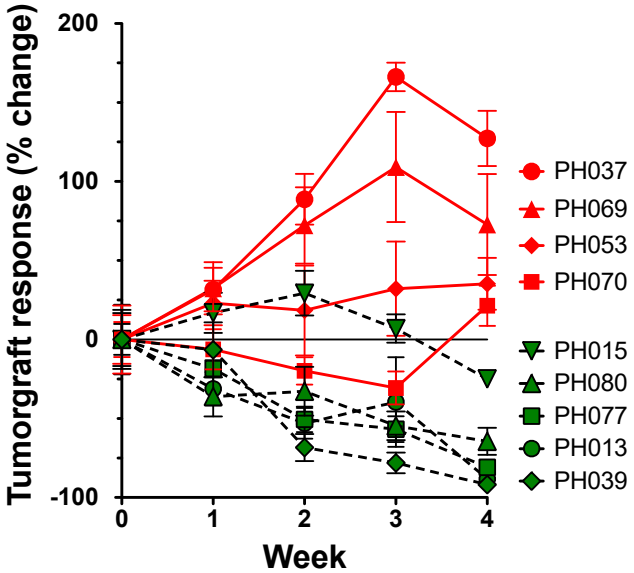


Figure 8. Tumor graft response concordant with patient response- Tumor grafts procured from patients with platinum-sensitive (green) and platinum-resistant (red) ovarian cancer were established in SCID mice. Upon formation of tumors measurable by ultrasound, tumors were then treated with weekly paclitaxel (15 mg/kg) and carboplatin (50 mg/kg).

1.6 Directing Chemotherapy in Patients with Platinum Resistant Ovarian Cancer with Results from their Own Avatar

Given these data, the goals of our proposed research is to use each individual patient's Avatar to determine what salvage chemotherapy their tumors are sensitive to and direct the selection of their chemotherapy at the time of developing PR-OC. We believe we are in position to challenge the existing paradigm of treating OC patients as a ***group***. We now have the methodology to treat patients as ***individuals***. For example, the response rates of salvage chemotherapy, such as topotecan, are in the 10-20% range when PR-OC patients are treated as a group. However, the response rates with topotecan are surely much higher in the patients that have tumors responsive to topotecan. Our data suggests that our Avatars generated for each individual patient can determine which chemotherapy agent in patients with PR-OC will be most effective. By directing therapy in PR-OC patients with results from their own Avatar, we believe we can increase the **effective response rate** and clinical benefit of salvage chemotherapy agents in patients with PR-OC. We believe these results will be practice changing, in that we will be able to make informed therapy decisions in PR-OC, instead of our standard practice of physicians' choice.

For this trial, eligible patients would have had tumors procured at the time of their surgery or at the time of a platinum-sensitive recurrence, had an Avatar established and now have recurrence of their ovarian, primary peritoneal or fallopian tube cancer that was resistant to platinum. As we have archived and 'live' tissue on patients at the time of initial surgical debulking, there will be no correlative tissue or other specimens collected for such patients. However, for patients with recurrent platinum sensitive cancer who are planning to undergo a biopsy or surgical resection for clinical indications, the procured tumor would be used to attempt Avatar engraftment. Examples include but are not limited to (1) patients with suspected recurrent cancer needing a biopsy to confirm recurrence, (2) patients needing fresh tissue for molecular profiling (e.g. FoundationOne, Caris, TEMPUS, etc.), (3) patients undergoing tumor debulking for palliation or curative intent, (4) patients consenting to undergo a procedure for research specimens.

Patients will receive standard chemotherapy treatments for this patient population - but the delivery will be directed by an investigational methodology. We will test the response rate of Avatar-directed salvage chemotherapy in patients with PR-OC.

1.7 Addition of bevacizumab to chemotherapy regimens

The addition of bevacizumab was based on the results of the AURELIA study, which compared salvage chemotherapy combinations with salvage chemotherapy regimens for platinum-resistant ovarian cancer (Product information, Genentech; Pujade-Lauraine *et al*., 2014). Investigators in this study chose between pegylated liposomal doxorubicin, weekly paclitaxel or topotecan. Patients were then randomized to receive the single agent chemotherapy or in combination with bevacizumab. The PFS hazard ratio was found to be 0.48 (95% CI, 0.38 to 0.60; unstratified log-rank P < .001), favoring the combination arm. Median PFS was 3.4 months with chemotherapy alone versus 6.7 months with bevacizumab-containing therapy. RECIST ORR was 11.8% versus 27.3%, respectively (P = .001). The OS HR was 0.85 (95% CI, 0.66 to 1.08; P < .174; median OS, 13.3 v 16.6 months, respectively). Grade ≥ 2 hypertension and proteinuria were more common with bevacizumab. GI perforation occurred in 2.2% of bevacizumab-treated patients.

As bevacizumab does not recognize the murine epitope of murine VEGF, bevacizumab will not be investigated as part of therapy development as described in section 1.6. Rather, it will be added to the standard chemotherapy backbone at the discretion of the treating physician/investigator.

2.0 Goals

2.1 Primary Goal

To determine the response rate of Avatar-directed salvage chemotherapy in patients with platinum-resistant ovarian, primary peritoneal and fallopian tube cancers.

2.2 Secondary Goals

2.21 To determine the progression-free survival of patients with platinum-resistant ovarian, primary peritoneal and fallopian tube cancers receiving Avatar-directed salvage chemotherapy.

2.22 To determine the overall survival of patients with platinum-resistant ovarian, primary peritoneal and fallopian tube cancers receiving Avatar-directed salvage chemotherapy.

2.23 To determine the adverse events for patients with platinum-resistant ovarian, primary peritoneal and fallopian tube cancers receiving Avatar-directed salvage chemotherapy.

2.24 To determine the correlation between patient response and response in their Avatar.

2.25 To enrich the Avatar response signature in response to Avatar-directed therapy using patient outcomes.

2.26 To compare the response rates between patients who did or did not receive bevacizumab treatment.

3.0 Patient Eligibility

3.1 Pre-Registration Inclusion Criteria

3.11 Females of age ≥ 18 years at pre-registration.

3.12 Histologic confirmation of ovarian, primary peritoneal or fallopian tube cancer of any subtype.

3.13 Prior consent to have tumors used for unspecified future research.

3.14 Ability to provide written informed consent.

3.15 Willing to agree to periodic contact with a member of the study team during the period that the cancer has not recurred and/or has not become platinum resistant.

3.16 Willing to agree that the local medical oncologist may be informed that patient has agreed to participate in the study.

3.2 Registration Inclusion Criteria

3.21 Platinum resistant or refractory ovarian, primary peritoneal or fallopian tube cancer of any subtype. Platinum resistance is defined as cancer recurrence < 6 months following completion of platinum-based chemotherapy. Platinum refractory cancers progress while on chemotherapy. **Note:** Platinum-sensitive disease is allowed in cases where there is a contraindication to platinum-based therapy (i.e., allergy to platinum). This must be reviewed and approved by the Principal Investigator.

3.22 Successful Avatar engraftment from initial surgery or surgery/biopsy of recurrent cancer with successful expansion and treatment outcome of Avatar therapy.

3.23 ECOG Performance Status (ECOG PS) of 0, 1 or 2. See Appendix I

3.24 Measurable disease or non-measurable disease as defined in Section 11.0. For patients with non-measureable disease, they must also have a CA-125

measurement of > 35 U/mL or 2 X their documented nadir on 2 separate measurements 1 week apart.

3.25 The following laboratory values obtained ≤ 21 days prior to registration. CBC, sodium, potassium, AST, bilirubin and creatinine are to be obtained pre-study. **Note:** Treatment initiation and dosing modification should be performed at the individual investigators discretion and be consistent with the product label and their medical practice.

3.26 Negative urine or serum pregnancy test performed ≤ 7 days prior to registration, for women of child bearing potential only

3.27 Willing to return to enrolling institution for follow-up or have a local physician willing to submit response and outcome data.
Note: Any and all therapy, potentially in its entirety, may be conducted outside of the Mayo Clinic.

3.3 Registration Exclusion Criteria

3.31 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women

3.32 Prior treatment with Doxil, Topotecan, Gemzar or Taxol chemotherapy for platinum-resistant cancer. **Note**: Allowed prior therapy with Doxil or Gemzar if given for platinum sensitive disease in combination with a platinum drug **AND** the Avatar data indicates a drug other than Doxil or Gemzar would be effective. **Note:** Allowed prior therapies for patients following confirmation of platinum-resistant cancer include:

Therapeutic antibodies, such as bevacizumab
Small molecule kinase inhibitors, such as pazopanib
Vaccines and immunotherapy
Poly (ADP-ribose) polymerase (PARP) inhibitors
Endocrine therapies, such as letrozole
Metronomic oral Cytoxan

All of these exceptions should be confirmed with the PI prior to registration

3.33 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.34 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy. **Note*:*** Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.35 Uncontrolled intercurrent illness judged by the treating investigator to preclude treatment with chemotherapy.

3.36 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.37 Other active malignancy ≤ 3 years prior to registration. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. **Note**: If there is a history of prior malignancy, they must not be receiving treatment for their cancer.

4.0 Test Schedule (At the time of registration only)

	Active Monitoring Phase		
Tests and procedures	**≤ 21 days prior to registration**	**Prior to subsequent treatment cycle**	**At the end of treatment**
History and exam, weight, ECOG Performance Status (PS)	X		X
Adverse event assessment	X	X	X
Hematology group: WBC (including ANC), hemoglobin, platelets	X	X	X
Chemistry group: Sodium, Potassium, AST, Bilirubin, Creatinine	X	X	X
CA125 [2]	X	X	X
Urine or serum pregnancy test [1]	X		
CT imaging – abdomen/pelvis [3]	X	X[4]	X

Footnotes for Section 4.0:

1. For women of childbearing potential only. Must be performed ≤ 7 days prior to registration.
2. CA125 is to be performed every other cycle.
3. Use same imaging throughout the study. Patients must return to Mayo for imaging prior to every other cycle. Copies of any images performed at LMD are required. **Note:** After discussion with PI, provisions may be made for changing the timing of pre-reg scan or use of different imaging modalities. Copies of any images performed at LMD are required.
4. Prior to every other cycle only.

Note: Cycle length is 28days for paclitaxel, gemcitabine and liposomal doxorubicin. After Cycle 1, treating physicians may adjust 28 day cycles to 21 day cycles at their discretion. See Section 7.0 for details. Patients receive topotecan by standard labeled schedule, which is Day 1-5, every 21 days. At the discretion of the investigator, topotecan may be delivered weekly days 1, 8 and 15, every 28 days.

5.0 Grouping Factor

Avatar Recommended Treatment (as provided by PI at the time of recurrence): Paclitaxel alone vs. paclitaxel plus bevacizumab vs. gemcitabine vs. liposomal doxorubicin alone vs. liposomal doxorubicin plus bevacizumab vs. topotecan alone vs. topotecan plus bevacizumab

6.0 Registration Procedures

Patient pre-registration and registrations will be performed by Mayo CRA using the Mayo Clinic Cancer Center Remote Registration Application. All patients must be registered using Mayo Clinic Rochester, Mayo Clinic Arizona or Mayo Clinic Florida as the location and under the supervision of a Mayo Medical Oncologist.

6.1 Pre-Registration

6.11 To pre-register a patient, access the Mayo Clinic Cancer Center (MCCC) webpage and enter the registration application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration application are available on the MCCC webpage [redacted]) and detail the process for completing and confirming patient registration. **Users should refer to the section titled "Pre-Registration Components" for details on how to pre-register a patient to a study.** It is the responsibility of the individual pre-registering the patient to confirm the process has been successfully completed. Patient pre-registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office at [redacted] If the patient was pre-registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the pre-registration.

- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about a Registered Subject."

6.12 Documentation of the initial IRB approval must be on file in the Registration Office before an investigator may pre-register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation (no less than annually) will be maintained by the

Regulatory Office and stored in the protocol file. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

6.13 At the time of pre-registration, the Registration Application will verify the following:

- IRB approval
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.2 Registration

6.21 To register a patient, access the Mayo Clinic Cancer Center (MCCC) webpage and enter the registration application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration application are available on the MCCC webpage ([redacted] and detail the process for completing and confirming patient registration. **Users should refer to the section titled "Pre-Registration Components" for details on how to register a pre-registered patient to a study.** Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office at [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.

- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.22 At the time of registration, the Registration Application will verify the following:

- Patient eligibility

6.23 Treatment cannot begin prior to registration and must begin ≤ 21 days after registration.

6.24 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.25 Treatment on this protocol must be given under the care of a medical oncologist or gynecology surgical oncologist. This may include physicians outside of the Mayo Clinic.

7.0 Protocol Treatment

7.1 Treatment Schedule

7.11 Pre-Treatment Medications

Pre-treatment medications are to be given as per institutional/investigator standards.

7.12 Protocol Treatment

Protocol treatment is assigned as per Avatar response.

The Avatar Tumor Review Board is responsible for reviewing Avatar mouse response results and relevant clinical details for each patient to determine the study treatment.

The Avatar Tumor Review Board is composed of the principal investigator and representatives from oncology, the Avatar lab, biostatistics and patient advocates. The Avatar Tumor Review Board meets on an as-needed basis and records official minutes to document the study treatment.

Protocol Specified Dosing of Standard Chemotherapies

Arm	Agent	Dose	Route	Days	Retreatment
A	Paclitaxel[2]	80 mg/m^2	IV	1, 8, 15	Every 28 days
	Bevacizumab[3]	10 mg/kg	IV[4]	1, 15	
B	Gemcitabine	1000 mg/m^2	IV	1, 8, 15	Every 28 days
C	Liposomal Doxorubicin	40 mg/m^2	IV	1	Every 28 days
	Bevacizumab[3]	10 mg/kg	IV[4]	1, 15	
D [1]	Topotecan	1.5 mg/m^2	IV	1 through 5	Every

	Bevacizumab[3]	15 mg/kg	IV[4]	1	21 days

1 At the discretion of the investigator, topotecan may be delivered on a weekly schedule of 4 mg/m^2 IV weekly on Days 1, 8 and 15 every 28 days + optional bevacizumab 10 mg/kg IV days 1 and 15 every 28 days.

2 Patients should be premedicated with corticosteroids, an antihistamine and H2 blockers prior to each paclitaxel dose as per institutional standard.

3 Bevacizumab is optional and may or may not be administered at physician's discretion

4 The initial bevacizumab infusion will be over 90 minutes with subsequent infusions over 60 minutes and then 30 minutes as tolerated.

Acceptable Alternative Dosing of Standard Chemotherapies After Cycle 1

Arm	Agent	Dose	Route	Days	Retreatment
A	Paclitaxel[1]	80 mg/m^2	IV	1, 8, 15	Every 21 days
	Bevacizumab[2]	15 mg/kg	IV[3]	1	
B	Gemcitabine	1000 mg/m^2	IV	1 and 8	Every 21 days
C	Liposomal Doxorubicin	40 mg/m^2	IV	1	Every 21 days
	Bevacizumab[2]	15 mg/kg	IV[3]	1	
D	Topotecan	4 mg/m^2	IV	1 and 8	Every 21 days
	Bevacizumab[2]	15 mg/kg	IV[3]	1	

1 Patients should be premedicated with corticosteroids, an antihistamine and H2 blockers prior to each paclitaxel dose as per institutional standard.

2 Bevacizumab is optional and may or may not be administered at physician's discretion

3 The initial bevacizumab infusion will be over 90 minutes with subsequent infusions over 60 minutes and then 30 minutes as tolerated.

7.2 Treatment by a Local Medical Oncologist

Treatment may be administered by the local medical oncologist. Local medical oncologist must agree to provide required data for study completion. Treatment will be administered by the treating physician's standard procedures.

8.0 Dosage Modification Based on Adverse Events

Dose modifications should be made per the product labeling, investigators decision and clinical judgment. The principal investigator may be contacted for counsel regarding any dose modification questions.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics
Antiemetics may be used at the discretion of the treating physician.

9.2 Blood Products and Growth Factors
Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2005 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. *J Clin Oncol* **24**: 3187-3205, 2006.

9.3 Full Supportive Care
Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, anti-emetics received from the first administration of study drugs until 30 days after the final dose are to be recorded in the medical record.

9.4 Diarrhea
This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting [redacted]	Mayo Sites – attach to MCCC Electronic SAE Reporting Form
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted]	Will automatically be sent to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form [redacted] AND attach MedWatch 3500A: [redacted]	Will automatically be sent to [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website: [redacted]

a. Identify the grade and severity of the event using the CTCAE version 4.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to Agent(s) or Procedure

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

System Organ Class (SOC)	**Adverse Event/ Symptoms**	CTCAE Grade at which the event **will not** be expeditedly reported[1]
General disorders and administrations site conditions	Fatigue	Grade 3
	Malaise	Grade 3
	Alopecia	Any grade

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.
Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Imaging Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.31 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.42 General Reporting Instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] or investigational agents or commercial/investigational agents on the same arm.

For commercial agents:

Submit form MedWatch 3500A to the FDA, [redacted] r online at [redacted]

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"

under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:

    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

    - Myelodysplastic syndrome (MDS)

    - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.55 Pregnancy, Fetal Death and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection

can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form: [redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and

not specified in Section 10.6:

10.611 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.612 Grade 5 AEs (Deaths)

10.6121 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6122 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

11.1 Response Criteria for Ovarian Cancer Patients

Treatment Evaluation in Patients with Measurable or Evaluable (Non-Measurable) Disease.

Note: Patients may have CA 125 elevation alone to be eligible for this trial. However, if they do have radiographic or other evidence of measureable/evaluable disease, that disease should continue to be followed to assess tumor status.

11.11 Evaluable Disease
Patients with evaluable disease must have an increase in serum CA 125 level, as defined as follows:

1) Normalization of the CA 125 during first-line chemotherapy followed by an increase of ≥ 35 units/mL;
or
2) Normalization of the CA 125 during first-line chemotherapy followed by a doubling of the CA 125 beyond the upper limit of normal with a confirmatory measurement within a period of 4

weeks or less that shows the same or higher CA 125 level.

11.12 Disease Progression

Disease progression in evaluable patients will be defined as one or more of the following:

1) Any new disease and/or clear progression of evaluable disease;
2) 2 fold elevation in CA125 from its lowest level (either initial level or nadir, whichever is lowest, since study enrollment) combined with CA125 elevation confirmed by re-assay at any time.

11.13 Complete Response

A complete response (CR) in evaluable patients will be defined as:

1) Disappearance of any sign of (evaluable) disease, and
2) Normalization of CA125; if CA 125 normalizes, it should be confirmed at any time.

11.14 Partial Response

A partial response (PR) in evaluable patients will be defined as:

1) Decrement in CA125 by > 50%, and
2) Improvement in any additional evaluable disease (if present) as assessed by the enrolling physician

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1; Eisenhauer *et al.*, 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.2 Schedule of Evaluations

For the purposes of this study, patients should be evaluated at baseline and every other cycle (just before cycle 3, 5, 7, etc.) using CT imaging.

11.3 Definitions of Measurable and Non-Measurable (Evaluable) Disease

11.31 Measurable Disease

11.311 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥ 2.0 cm with chest x-ray, or as ≥ 1.0 cm with CT scan, CT component of a PET/CT or MRI.

11.312 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.313 A malignant lymph node is considered measurable if its short axis is > 1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Note: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.32 Non-Measurable Disease

11.321 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.4 Guidelines for Evaluation of Measurable Disease

11.41 Measurement Methods

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.42 Acceptable Imaging Modalities for Measurable Disease

- Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT
  If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

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

- Physical Examination
  For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- FDG-PET or PET/CT
  FDG-PET or PET/CT scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET or PET/CT scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET or PET/CT scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET or PET/CT imaging can be identified according to the following algorithm:

    a. Negative FDG-PET or PET/CT at baseline with a positive FDG-PET or PET/CT at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET or PET/CT at baseline and a positive FDG-PET or PET/CT at follow-up:

i. If the positive FDG-PET or PET/CT at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

ii. If the positive FDG-PET or PET/CT at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET or PET/CT scan.

iii If the positive FDG-PET or PET/CT at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.43 Measurement at Follow-up Evaluation

- A subsequent scan must be obtained at least 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of at least 4 weeks (see Section 11.54).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.5 Measurement of Effect

11.51 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.31) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.31), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurement in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD)
  A sum of the longest diameters for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD)
  A sum of the longest diameters for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.52 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.32) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.533.

11.53 Response Criteria

11.531 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.2. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.532 Evaluation of Target Lesions

- Complete Response (CR)
  All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to < 1.0 cm.

- Partial Response (PR)
  At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.51).

- Progression (PD)
  At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (see Section

11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 11.42 for details in regards to the requirements for PD via FDG-PET or PET/CT imaging.

- Stable Disease (SD)
  Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.533 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR)
  All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have reduction in short axis to < 1.0 cm.

- Non-CR/Non-PD
  Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD)
  At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

  c. See Section 11.42 for details in regards to the requirements for PD via FDG-PET or PET/CT imaging.

11.54 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions and Target Lymph Nodes	Non-Target Lesions and Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated[1]	No	PR[2]
SD	CR Non-CR/Non-PD Not All Evaluated[1]	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated[1]	No	Not Evaluated (NE)[3]
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated[1]	Yes or No	PD
CR/PR/SD/PD/ Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/ Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated[1]	Yes	PD

1. See Section 11.531
2. Note: This study uses the modified protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.
3. Note: 'Not Evaluated (NE)' in the table is equivalent to 'Not Assessed (NA)' in the Theradex dictionary (CA form), while 'NE' in the Theradex dictionary stands for 'Not Evaluable'.

For Patients with Non-Measurable Disease Only:

Non-Target Lesions and Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated[1]	No	Not Evaluated (NE)[2]
Unequivocal PD	Yes or No	PD
Any	Yes	PD

1. See Section 11.431

2. NOTE: 'Not Evaluated (NE)' in the table is equivalent to 'Not Assessed (NA)' in the Theradex dictionary (CA form), while 'NE' in the Theradex dictionary stands for 'Not Evaluable'.

11.55 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss > 10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of > 1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Initial Stage

I vs. II vs. III vs. IV

12.2 Tumor Histology Type

Ovarian (Serous) vs. Fallopian tube (Serous) vs. Primary Peritoneal (Serous) vs. Ovarian (Endometrioid) vs. Ovarian (Other) vs. Fallopian tube (Other) vs. Primary peritoneal (Other)

12.3 Prior Chemotherapy Regimens

Dose dense paclitaxel/carboplatin IV vs. weekly paclitaxel/carboplatin IV vs. Q3W paclitaxel/carboplatin IV vs. NOS paclitaxel/carboplatin IV vs.

paclitaxel/cisplatin IV vs. paclitaxel/cisplatin IP vs. paclitaxel/carboplatin/ bevacizumab IV vs. paclitaxel/cisplatin/bevacizumab IV vs. docetaxel/carboplatin IV vs. gemcitabine/carboplatin IV vs. liposomal doxorubicin/carboplatin IV vs. other cisplatin-containing regimen NOS vs. other carboplatin-containing regimen NOS

12.4 Platinum Allergy
Yes vs. No

12.5 Avatar Results
First: Paclitaxel vs. gemcitabine vs. liposomal doxorubicin vs. topotecan vs. other, specify
Second, Third or Fourth: Paclitaxel vs. gemcitabine vs. liposomal doxorubicin vs. topotecan vs. other, specify vs. failure

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Treatment
Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Disease Progression
Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Off Treatment for Other Reasons than PD
Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

13.4 Ineligible
A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the follow up phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until patient comes off protocol treatment must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted

13.4 Major Violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the follow-up phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.5 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

None.

15.0 Drug Information

15.1 Paclitaxel (Taxol®)

15.11 Background

Antineoplastic Agent, Antimicrotubular, Taxane derivative. Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G_2 mitotic phase, and inhibiting cell replication. In addition, the drug can distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

15.12 Formulation

Commercially available for injection 6 mg/mL (5 mL, 16.7 mL, 25 mL, and 50 mL) [contains alcohol and purified Cremophor EL (polyoxyethylated castor oil)].

15.13 Preparation, Storage, and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature and protect from light. Dilute in 250-1000 mL D_5W or 0.9% NaCl to a concentration of 0.3 – 1.2 mg/mL. Solutions in D_5W and 0.9% NaCl are stable for up to 3 days at room temperature. Chemotherapy dispensing devices

(e.g., Chemo Dispensing Pin) should not be used to withdraw paclitaxel from the vial.

Paclitaxel should be dispensed in either glass or non-PVC containers (e.g., Excel/PAB). Use no polyvinyl (non-PVC) tubing (e.g., polyethylene) to minimize leaching.

15.14 Administration
Infuse IV over 1-96 hours. When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives (cisplatin, carboplatin) to limit myelosuppression and to enhance efficacy. Infuse through a 0.22 micron in-line filter and non-absorbing administration set.

15.15 Pharmacokinetic Information
Distribution:
$V_{d:}$ Widely distributed into body fluids and tissues; affected by dose and duration of infusion
V_{dss}: 1- to 6-hour infusion: 67.1 L/m^2
V_{dss}: 24-hour infusion: 227-688 L/m^2

Metabolism:
Hepatic via CYP2C8 and 3A4; forms metabolites (primarily 6α-hydroxypaclitaxel).

Half-life elimination 1- to 6-hour infusion:
Mean (beta): 6.4 hours,
3-hour infusion: Mean (terminal): 13.1-20.2 hours
24-hour infusion: Mean (terminal): 15.7-52.7 hours

Excretion:
Feces (~70%, 5% as unchanged drug); Urine (14%)

Clearance:
Mean: Total body: After 1- and 6-hour infusions: 5.8-16.3 L/hour/m^2; after 24-hour infusions: 14.2-17.2 L/hour/m^2

15.16 Potential Drug Interactions
Cytochrome P450 Effect:
Substrate (major) of CYP2C8, CYP3A4; Induces CYP3A4 (weak).

Increased Effect/Toxicity:
CYP2C8 inhibitors may increase the levels/effects of paclitaxel. Refer to the package insert or LexiComp[1] for example inhibitors.

Decreased Effect:

CYP2C8 inducers may decrease the levels/effects of paclitaxel. Refer to the package insert or LexiComp[1] for example inducers.

Herb/Nutraceutical Interactions:
Avoid black cohosh, dong quai in estrogen-dependent tumors.
Avoid valerian, St John's wort (may decrease paclitaxel levels), kava kava, gotu kola (may increase CNS depression).

15.17 Known Potential Adverse Events
Consult the package insert for the most current and complete information. Percentages reported with single-agent therapy.

U.S. Boxed Warning: Bone marrow suppression is the dose-limiting toxicity; do not administer if baseline absolute neutrophil count (ANC) is <1500 cells/mm^3 (1000 cells/mm^3 for patients with AIDS-related KS); reduce future doses by 20% for severe neutropenia.
U.S. Boxed Warning: Severe hypersensitivity reactions have been reported.

Common known potential toxicities, > 10%:
Cardiovascular: Flushing, ECG abnormal, edema, hypotension.
Dermatologic: Alopecia, rash.
Gastrointestinal: Nausea/vomiting, diarrhea, mucositis, stomatitis, abdominal pain (with intraperitoneal paclitaxel)
Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, bleeding.
Hepatic: Alkaline phosphatase increased, AST increased.
Local: Injection site reaction (Erythema, tenderness, skin discoloration, swelling).
Neuromuscular & skeletal: Peripheral neuropathy, arthralgia, myalgia, weakness.
Renal: Creatinine increased.
Miscellaneous: Hypersensitivity reaction, infection.

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Bradycardia, tachycardia, hypertension, rhythm abnormalities, syncope, venous thrombosis.
Dermatologic: Nail changes.
Hematologic: Febrile neutropenia.
Hepatic: Bilirubin increased.
Respiratory: Dyspnea.

Rare known potential toxicities, < 1% (Limited to important or life-threatening):

Anaphylaxis, ataxia, atrial fibrillation, AV block, back pain, cardiac conduction abnormalities, cellulitis, CHF, chills, conjunctivitis, dehydration, enterocolitis, extravasation recall, hepatic encephalopathy, hepatic necrosis, induration, intestinal obstruction, intestinal perforation, interstitial pneumonia, ischemic colitis, lacrimation increased, maculopapular rash, malaise, MI, necrotic changes and ulceration following extravasation, neuroencephalopathy, neutropenic enterocolitis, ototoxicity, pancreatitis, paralytic ileus, phlebitis, pruritus, pulmonary embolism, pulmonary fibrosis, radiation recall, radiation pneumonitis, pruritus, renal insufficiency, seizure, skin exfoliation, skin fibrosis, skin necrosis, Stevens-Johnson syndrome, supraventricular tachycardia, toxic epidermal necrolysis, ventricular tachycardia (asymptomatic), visual disturbances.

15.18 Drug Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.19 Nursing Guidelines

15.191 Premedicate with steroids, antihistamines, and H2 blockers as per institutional guidelines.

15.192 Mix the infusion bag well. Thorough admixture of this drug often prevents a hypersensitivity reaction. An inline filter of < 0.22 micron must be used distal to the infusion pump. Filter may need to be changed if infusion is to be prolonged >12 hours. Inspect solution for excessive particulate matter, if present do not use.

15.193 Caution patients that the alcohol contained in the infusion may cause impairment in operating heavy equipment or in driving a vehicle and to assess their ability before trying either. Advise avoidance of any alcohol or depressants such as sedatives and opiates if not necessary.

15.194 Assess the patient frequently for the first 30 minutes. Taxol® hypersensitivity reactions, which may include chest pain, back pain, flushing, diaphoresis, dyspnea, pruritus, hypotension, hypertension, bronchospasm and/or urticaria, usually occur early in the infusion. Have the anaphylaxis tray available.

15.195 If a reaction occurs, stop the infusion immediately. Epinephrine, IV fluids, diphenhydramine, and methylprednisolone may be used as per MD's order.

15.196 Approximately 60% of patients experience peripheral sensory neuropathy (numbness, tingling, burning pain, fine motor skills impairment, paresthesias, distal sensory loss). Patients receiving higher doses at shorter infusion times are at greater risk. Most cases have been reported at doses > 170 mg/m^2/day and with cumulative doses over multiple courses of therapy. The nerve damage may take months to resolve. Nonsteroidal anti-inflammatory agents and opiates have not been effective in treating neuropathic pain. Consult MD about trying tricyclic antidepressants or possibly Neurontin.

15.197 Increased risk of cardiotoxicity when given in combination with doxorubicin, with a sharp increase in risk of CHF once cumulative dose of doxorubicin is > 380 mg/m^2. At this point Taxol should be continued as a single agent only. Monitor for sign/symptoms of CHF. Instruct patient to report any swelling in the hands, arms, feet, or legs, and any chest pain.

15.198 Mucositis can usually be managed with a salt and soda mouthwash (1 tsp. Salt, 1 tsp. Soda and 1 quart boiled water) or try OTC oral Lysine or Vitamin E.

15.199a Narcotics and nonsteroidal anti-inflammatory drugs may be used to manage the myalgias.

15.199b Monitor CBC closely. Neutropenia is most severe in patients who have had previous chemotherapy. Instruct patient to report signs or symptoms of infection, unusual bruising or bleeding to the health care team.

15.199c There is an increased risk of neutropenia and stomatitis when given prior to doxorubicin. Therefore Taxol should always be given after doxorubicin administration.

15.199d Monitor IV site closely and establish patency before administration. Paclitaxel is an irritant, however rarely rash, radiation recall, and ulceration have occurred with infiltration of drug.

15.199e Monitor liver function tests

15.199f Inform patient about total alopecia.

15.199g If given on the same day as a platinum agent, paclitaxel should be administered first to limit myelosuppression and enhance efficacy of agent.

15.2 Gemcitabine (Gemzar®)

15.21 Background

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase, specific for the S-phase of the cell cycle. Gemcitabine is phosphorylated intracellularly by deoxcytidine kinase to gemcitabine monophosphate, which is further phosphorylated to active metabolites gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine diphosphate inhibits DNA synthesis by inhibiting ribonucleotide reductase; gemcitabine triphosphate incorporates into DNA and inhibits DNA polymerase.

15.22 Formulation

Commercially available for injection:
Powder for reconstitution: 200 mg and 1 gram vials.
Solution for injection: 38 mg/mL 200 mg, 1 gm, and 2 gm vials.
MUST BE DILUTED BEFORE USE.

15.23 Preparation, Storage and Stability

Powder for Reconstitution:

Store intact vials at room temperature. Reconstitute the 200 mg vial with preservative free 0.9% NaCl 5 mL or the 1000 mg vial with preservative free 0.9% NaCl 25 mL. Resulting solution is 38 mg/mL. Dilute with 50-500 mL 0.9% NaCl or D_5W to concentrations as low as 0.1 mg/mL. Reconstituted vials are stable for up to 35 days and infusion solutions diluted in 0.9% NaCl are stable up to 7 days at 23ºC when protected from light; however, the manufacturer recommends use with 24 hours for both reconstituted vials and infusion solutions. Do not refrigerate.

Solution for Injection:

Store intact vials at refrigeration temperature between 2º to 8ºC (36º to 46ºF). Do not freeze. Each vial contains a gemcitabine concentration of 38 mg/mL. The appropriate amount of drug should be further diluted with 50-500 mL 0.9% NaCl or D_5W to concentrations as low as 0.1 mg/mL. When prepared as directed, diluted gemcitabine solutions are stable for 24 hours at controlled room temperature.

15.24 Administration
Refer to the drug treatment section of the protocol for specific administration directions and infusion rates. Gemcitabine is normally infused IV over 30 minutes. Note: Prolongation of the infusion time > 60 minutes has been shown to increase toxicity. Gemcitabine is being investigated in clinical trials for fixed dose rate infusion administration at doses from 1000 mg/m^2 to 2200 mg/m^2 at a rate of 10 mg/m^2/minute. Prolonged infusion times increase the accumulation of the active metabolite, gemcitabine triphosphate. Patients who receive gemcitabine fixed dose rate infusions experience more grade three and four hematologic toxicities.

15.25 Pharmacokinetic Information
Distribution:
Infusions < 70 minutes: 50 L/m^2; Long infusion times: 370 L/m^2
Protein binding: Low

Metabolism:
Metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleoside metabolites

Half-life elimination:
Gemcitabine: Infusion time ≤ hour: 32-94 minutes; infusion time 3-4 hours: 4-10.5 hours
Metabolite (gemcitabine triphosphate), terminal phase: 1.7-19.4 hours
Time to peak, plasma: 30 minutes after completion of infusion

Excretion:
Urine (92% to 98%; primarily as inactive uridine metabolite); feces (< 1%)

15.26 Potential Drug Interactions
Increased Effect/Toxicity: Gemcitabine may increase the levels/effects of fluorouracil. Gemcitabine may enhance the adverse pulmonary effects of bleomycin.
Ethanol/Nutrition/Herb Interactions Ethanol: Avoid ethanol (due to GI irritation).

15.27 Known Potential Adverse Events
Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema, edema

Central nervous system: Pain, fever, somnolence
Dermatologic: Rash, alopecia, pruritus
Gastrointestinal: Nausea/vomiting, constipation, diarrhea, stomatitis
Hematologic: Anemia, leukopenia, thrombocytopenia, neutropenia, hemorrhage and myelosuppression is the dose-limiting toxicity
Hepatic: Transaminases increased, alkaline phosphatase increased, bilirubin increased
Renal: Proteinuria, hematuria, BUN increased
Respiratory: Dyspnea
Miscellaneous: Flu-like syndrome, infection

Less common known potential toxicities, 1% - 10%:
Local: Injection site reactions
Neuromuscular & skeletal: Paresthesia
Renal: Creatinine increased
Respiratory: Bronchospasm

Rare known potential toxicities, < 1% (Limited to important or life-threatening):
Adult respiratory distress syndrome, anaphylactoid reaction, anorexia, arrhythmias, bullous skin eruptions, cellulitis, cerebrovascular accident, CHF, chills, cough, desquamation, diaphoresis, gangrene, GGT increased, headache, hemolytic uremic syndrome (HUS), hepatotoxic reaction, hypertension, insomnia, interstitial pneumonitis, liver failure, malaise, MI, peripheral vasculitis, Petechiae, pulmonary edema, pulmonary fibrosis, radiation recall, renal failure, respiratory failure, rhinitis, sepsis, supraventricular arrhythmia, weakness

15.28 Drug Procurement
Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 Nursing Guidelines

15.291 Monitor CBC, differential, PLTs prior to each dose. Myelosuppression is the principal dose-limiting factor. Modification may be considered by physician when bone marrow suppression is suspected.

15.292 Evaluate hepatic and renal function prior to initiation of therapy and periodically thereafter. Closely observe those patients with a history of preexisting mild renal impairment or hepatic insufficiency. Encourage hydration.

15.293 Gemzar clearance is affected by age and gender. Grade 3/4

thrombocytopenia has been more common in elderly women.

15.294 Antiemetics may be required for probable mild to moderate nausea and vomiting. Assess for their effectiveness.

15.295 Instruct patient in management of possible mild diarrhea and stomatitis.

15.296 Gemzar may cause fever in the absence of clinical infection. Fever can be accompanied by other flu-like symptoms. Instruct patient to report fever or flu-like symptoms to healthcare team. Treat symptoms as they occur.

15.297 Macular or finely granular maculopapular eruptions were experienced by 30% of patients tested. Instruct patients to report any skin changes.

15.298 Instruct patient to report any respiratory changes.

15.299 Burning may occur at the injection site. May apply heat during infusion to minimize pain.

15.3 Doxorubicin Liposomal (Doxil®)

15.31 Background
Doxorubicin Liposomal inhibits DNA and RNA synthesis by intercalating between DNA base pairs causing steric obstruction and inhibits topoisomerase-II at the point of DNA cleavage. Doxorubicin Liposomal is also a powerful iron chelator. The iron-doxorubicin complex can bind DNA and cell membranes, producing fee hydroxyl (OH) radicals that cleave DNA and cell membranes. Doxorubicin is active throughout entire cell cycle. Doxorubicin Liposomal is a pegylated formulation which protects the liposomes, and thereby increases blood circulation time.

15.32 Formulation
Commercially available for injection, solution: 2 mg/mL (10 mL, 30 mL)

15.33 Preparation, Storage, and Stability
Store intact vials of solution under refrigeration at 2ºC to 8ºC (36ºF to 46ºF); avoid freezing. Prolonged freezing may adversely affect liposomal drug products, however, short-term freezing (< 1 month) does not appear to have a deleterious effect. See the treatment section of the protocol for specific dilution instructions. Generally, dose of doxorubicin liposomal less than or equal to 90 mg should be diluted in 250 mL of D5W prior to administration. Doses greater than 90 mg should be diluted in 500 mL D5W. Diluted doxorubicin

liposomal may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF); administer within 24 hours. Do not infuse with in-line filters.

15.34 Administration
Refer to the treatment section of the protocol for specific administration instructions. Doxorubicin Liposomal is usually administered IVPB over 60 minutes; manufacturer recommends administering at initial rate of 1 mg/minute to minimize risk of infusion reactions until the absence of a reaction has been established, then increase the infusion rate for completion over 1 hour. Do not administer I..M. or S.C. Do not infuse with in-line filters. Avoid extravasation (irritant), monitor site; extravasation may occur without stinging or burning. Flush with 5-10 mL of D5W solution before and after drug administration, incompatible with heparin flushes. Monitor for local erythematous streaking along vein and/or facial flushing (may indicate rapid infusion rate).

15.35 Pharmacokinetic Information
Distribution: V_{dss}: 2.7-2.8 L/m^2
Protein binding, plasma: Unknown; non-liposomal (conventional) doxorubicin: 70%
Metabolism: Hepatic and in plasma to doxorubicinol and the sulfate and glucuronide conjugates of 4-demethyl,7-deoxyaglycones
Half-life elimination: Terminal: Distribution: 4.7-5.2 hours, Elimination: 44-5 hours
Excretion: Urine (5% as doxorubicin or doxorubicinol)

15.36 Potential Drug Interactions
Cytochrome P450 Effect: Substrate (major) of CYP2D6; 3A4; Inhibits CYP2B6 (moderate), 2D6 (weak), 3A4 (weak)

Increased Effect/Toxicity: Bevacizumab and trastuzumab may enhance the cardiotoxic effect of anthracycline antineoplastics. Cyclosporine may increase the levels/effects of doxorubicin; may increase neurotoxicity and/or enhance hematologic toxicity. Doxorubicin may potentiate the toxicity of cyclophosphamide (hemorrhagic cystitis) and mercaptopurine (hepatotoxicity). CYP2D6 inhibitors may increase the levels/effects of doxorubicin. CYP3A4 inhibitors may increase the levels/effects of doxorubicin. Sorafenib may increase the levels/effects of doxorubicin. Paclitaxel may reduce doxorubicin clearance and increase toxicity, including cardiotoxicity of doxorubicin.

Decreased Effect: Doxorubicin Liposomal may decrease the absorption of cardiac glycosides. CYP3A4 inducers may decrease the levels/effects of doxorubicin. Doxorubicin may diminish the therapeutic effect of stavudine and zidovudine.

Ethanol/Nutrition/Herb Interactions
Ethanol: Avoid ethanol (due to GI irritation).
Herb/Nutraceutical: St John's wort may decrease doxorubicin levels.

15.37 Known Potential Adverse Events
Consult the package insert for the most current and complete information.

U.S. Boxed Warnings:
Doxorubicin may cause cumulative, dose-related myocardial toxicity (concurrent or delayed).
Acute infusion reactions may occur, some may be serious/life-threatening.
Use with caution in patients with hepatic impairment.
Severe myelosuppression may occur.
Liposomal formulations of doxorubicin should NOT be substituted for conventional doxorubicin hydrochloride on a mg-per-mg basis.

Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema
Central nervous system: Fever, headache, pain
Dermatologic: Alopecia, palmar-plantar erythrodysesthesia/hand-foot syndrome, rash
Gastrointestinal: Stomatitis, vomiting, nausea, mucositis, constipation, anorexia, diarrhea, dyspepsia, intestinal obstruction
Hematologic: Myelosuppression, neutropenia, leukopenia, thrombocytopenia, anemia
Neuromuscular & skeletal: Weakness, back pain
Respiratory: Pharyngitis, dyspnea
Miscellaneous: Infection

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Cardiac arrest, chest pain, edema, hypotension, pallor tachycardia, vasodilation
Central nervous system: Agitation, anxiety, chills, confusion, depression, dizziness, emotional lability, insomnia, somnolence, vertigo
Dermatologic: Acne, bruising, dry skin, dermatitis, furunculosis, maculopapular rash, pruritus, skin discoloration, vesiculobullous rash
Endocrine & metabolic: Dehydration, hyperbilirubinemia, Hypercalcemia, hyperglycemia, hypokalemia, hyponatremia
Gastrointestinal: Abdomen enlarged, anorexia, ascites, cachexia, dyspepsia, dysphagia, esophagitis, flatulence, gingivitis, glossitis,

ileus, mouth ulceration, oral moniliasis, rectal bleeding, taste perversion, weight loss, xerostomia
Genitourinary: Cystitis, Dysuria, leucorrhea, pelvic pain, Polyuria, urinary urgency, vaginal bleeding, vaginal moniliasis
Hematologic: Hemolysis, prothrombin time increased
Hepatic: ALT increased
Local: Thrombophlebitis
Neuromuscular & skeletal: Arthralgia, hypertonia, myalgia, neuralgia, neuritis (peripheral), neuropathy, paresthesia, pathological fracture
Ocular: Conjunctivitis, dry eyes, retinitis
Otic: Ear pain
Renal: Albuminuria, hematuria
Respiratory: Apnea, cough, epistaxis, pleural effusion, pneumonia, rhinitis, sinusitis
Miscellaneous: Allergic reaction; infusion-related reactions; moniliasis, diaphoresis

Rare known potential toxicities, < 1% (Limited to important or life-threatening):
Abscess, acute brain syndrome, abnormal vision, acute myeloid leukemia (secondary), alkaline phosphatase increased, anaphylactic or anaphylactoid reaction, asthma, balanitis, blindness, bone pain, bronchitis, BUN increased, bundle branch block, cardiomegaly, cardiomyopathy, cellulitis, CHF, colitis, creatinine increased, cryptococcosis, diabetes mellitus, erythema multiforme, erythema nodosum, eosinophilia, fecal impaction, flu-like syndrome, gastritis, glucosuria, hemiplegia, hemorrhage, hepatic failure, hepatitis, hepatosplenomegaly, hyperkalemia, hypernatremia, hyperuricemia, hyperventilation, hypoglycemia, hypolipidemia, hypomagnesemia, hypophosphatemia, hypoproteinemia, hypothermia, injection site hemorrhage, injection site pain, jaundice, ketosis, lactic dehydrogenase increased, kidney failure, lymphadenopathy, lymphangitis, migraine, myositis, optic neuritis, palpitation, pancreatitis, pericardial effusion, petechia, pneumothorax, pulmonary embolism, radiation injury, sclerosing cholangitis, seizure, sepsis, skin necrosis, skin ulcer, syncope, tenesmus, thromboplastin decreased, thrombosis, tinnitus, urticaria, visual field defect, ventricular arrhythmia

15.38 Drug Procurement
Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 Nursing Guidelines

15.391 Check CBC and platelet counts. Instruct patient to watch for signs of infection, bleeding, and anemia.

15.392 Advise patient that their urine may turn pink in color for approximately 24 hours after administration of the drug.

15.393 Adriamycin is a vesicant. Check IV patency before and frequently during administration. If extravasation occurs, refer to institutional extravasation policy.

15.395 Hair loss occurs 2-4 weeks after initial injection and can be complete. Regrowth begins 2-3 months after discontinuation.

15.396 Beware of Adria "flare" that can occur during administration. The reaction consists of an erythematous streak up the vein receiving the infusion. Adjacent veins may also demonstrate red streaks. Urticaria and pruritus can be associated with the reaction. The use of corticosteroids and/or antihistamines has been helpful.

15.397 Administer antiemetics to minimize nausea and vomiting.

15.398 Assess for alterations in mucous membranes. Stomatitis occurs within 7-10 days after injection. It begins with burning sensation and can progress to ulceration, which can last 3 days. Carafate slurry may be useful. Adequate nutritional counseling is important. Topical anesthetics such as viscous Xylocaine can be used symptomatically.

15.399a Advise patient that there is often significant malaise and fatigue 1-2 weeks after injection.

15.399b Adriamycin may potentiate toxicity of other antineoplastic therapies. It has reportedly exacerbated Cyclophosphamide (Cytoxan, CTX) induced hemorrhagic cystitis.

15.399c Assess heart and lung sounds. Monitor vital signs (resting pulse). Be alerts to early signs of cardiotoxicity, i.e., dyspnea, steady weight gain, nonproductive cough, arrhythmias, tachycardia, and pulmonary rales. Instruct patients to report any of these signs or symptoms to their health care provider.

15.399d Document cumulative dose, which should not exceed maximum cumulative dose.

15.399e Advise patient of probable facial flushing for several hours after drug administration, especially if given quickly.

15.4 Topotecan (Hycamtin®)

15.41 Background

Topotecan binds to topoisomerase I and stabilizes the cleavable complex so that relegation of the cleaved DNA strand cannot occur. This results in the accumulation of cleavable complexes and single-strand DNA breaks. Topotecan acts in S phase of the cell cycle.

15.42 Formulation

Commercially available Injection, powder for reconstitution, as hydrochloride: 4 mg [base]

15.43 Preparation, Storage, and Stability

Store intact vials at room temperature and protect from light. Reconstitute with 4 mL Sterile Water for Injection. This solution is stable for up to 28 days at room temperature. Topotecan should be further diluted in 50-100 mL of D5W or 0.9% Sodium Chloride. Refer to the treatment section for final dilution volume. This solution is stable for 24 hours at room temperature or up to 7 days under refrigeration.

15.44 Administration

Administer IV piggyback over 30 minutes or by 24-hour continuous infusion. See specific administration instructions in the treatment section of the protocol.

15.45 Pharmacokinetic Information

Distribution:
V_{dss} of the lactone is high (mean: 87.3 L/mm^2; range: 25.6-186 L/mm^2), suggesting wide distribution and/or tissue sequestering

Protein binding: ~35%

Metabolism: Undergoes a rapid, pH-dependent hydrolysis of the lactone ring to yield a relatively inactive hydroxyl acid in plasma; metabolized in the liver to N-demethylated metabolite

Half-life elimination: I.V.: 2-3 hours; renal impairment: 5 hours

Excretion: I.V.: Urine (51%; 3% as N-desmethyl topotecan); feces (18%; 2% as N-desmethyl topotecan)

15.46 Potential Drug Interactions
Increased Effect/Toxicity:
Filgrastim may cause prolonged and sever neutropenia and thrombocytopenia if administered concurrently with topotecan; initiate filgrastim at least 24 hours after topotecan. Platinum derivatives (carboplatin, cisplatin, oxaliplatin) may enhance the adverse/toxic effects of topotecan; monitor for hematologic toxicity, especially if the platinum derivative is administered prior to topotecan.

15.47 Known Potential Adverse Events
Consult the package insert for the most current and complete information including U.S. Boxed Warnings pertaining to severe diarrhea and severe myelosuppression.

Common known potential toxicities, > 10%:
Central nervous system: Fatigue, fever, pain, headache
Dermatologic: Alopecia, rash
Gastrointestinal: Nausea, vomiting, diarrhea, constipation, abdominal pain, anorexia, stomatitis
Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, neutropenic fever/sepsis
Neuromuscular & skeletal: Weakness
Respiratory: Dyspnea, cough

Less common known potential toxicities, 1% - 10%:
Hepatic: Transient increase in liver enzymes
Neuromuscular & skeletal: Paresthesia
Miscellaneous: Sepsis

Rare known potential toxicities, < 1% (Limited to important or life-threatening):
Abdominal pain, allergic reactions, anaphylactoid reactions, angioedema, bleeding (severe, associated with thrombocytopenia), dermatitis (severe), injection site reactions (mild erythema, bruising), neutropenic colitis, pancytopenia, pruritus (severe)

15.48 Drug Procurement
Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.49 Nursing Guidelines

15.491 Monitor CBC. The dose-limiting toxicity is leukopenia. WBC count decreases with increasing doses. When drug is

administered at 1.5 mg/m^2/day for 5 days, an80-90% decrease in WBC count at nadir is typically seen after the first cycle.

15.492 Neutropenia is not cumulative. Grade 4 neutropenia (<500 cells/mm^3) is most common during the first cycle (60% of the patients) and occurs in approximately 39% of all cycles, with a median duration of 7 days. Nadir occurs at approximately the median of 12 days. Sepsis is possible. Watch for profound neutropenia and instruct patient in low count precautions and to report signs of infection to health care team immediately.

15.493 Monitor PLT count. Grade 4 thrombocytopenia (< 25,000/mm^3) occurs in approximately 27% of patients and in 9% of cycles, with a median duration of 5 days and platelet nadir at a median of 15 days. Platelet transfusion may be needed. Instruct patient to report any unusual bleeding or bruising.

15.494 Monitor HGB. Grade 3 or 4 anemia occurs in approximately 37% of patients and in 14% of cycles. Median nadir is seen at day 15. Transfusions have been needed in approximately 50% of patients.

15.495 Myelosuppression can be more severe when drug is given with cisplatin.

15.496 Nausea is experience by approximately 65% of patients. Vomiting is experienced by approximately 45%. Diarrhea by approximately 30%. Premedicate with anti-emetics and monitor for their effectiveness. Administer anti-diarrheals as indicated. Assess status.

15.497 Encourage paced activities and frequent rest periods to deal with the fatigue which is experienced by approximately 30% of patients.

15.498 Approximately 28% of patients experience stomatitis. Advise patient in cryotherapy preventive measures, try treating with vitamin E oil if stomatitis occurs.

15.499a Monitor LFT's and renal function. Dose reductions may be necessary in those with hepatic and renal dysfunction.

15.499b Advise patients of possible reversible alopecia which has been seen in 49% of patients.

15.5 Bevacizumab (Avastin®)

15.51 Background

Bevacizumab is classified as an Anti-VEGF Monoclonal Antibody and a Vascular Endothelial Growth Factor (VEGF) Inhibitor. Bevacizumab is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).

15.52 Formulation

Commercially available for injection 25 mg/mL (4 mL, 16 mL).

15.53 Preparation, storage, and stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at refrigeration temperature (2ºC to 8ºC), protect from light, do not freeze or shake. Prior to infusion, dilute prescribed dose of bevacizumab in 100 mL 0.9% NaCl. Do not mix with dextrose-containing solutions. Diluted solutions are stable for up to 8 hours under refrigeration.

15.54 Administration

IV infusion, usually after the other antineoplastic agents. Refer to treatment section for specific order of administration. Infuse the initial dose over 90 minutes. Infusion may be shortened to 60 minutes if the initial infusion is well tolerated. The third and subsequent infusions may be shortened to 30 minutes if the 60-minute infusion is well tolerated. Monitor closely during the infusion for signs/symptoms of an infusion reaction. Some institutions use a 10-minute infusion (0.5 mg/kg/minute) for bevacizumab dosed at 5 mg/kg.

15.55 Pharmacokinetic information

Distribution: $V_{d:}$ 46 mL/kg (limited extravascular distribution)
Half-life elimination: ~20 days (range: 11-50 days)
Clearance: 2.75-5 mL/kg/day. A low serum albumin and high tumor burden increase clearance by 30% and 7% respectively. Clearance increases with increasing body weight, and is 15% slower in women than men.
Time to steady state: 100 days

15.56 Potential Drug Interactions

Increased Effect/Toxicity: Bevacizumab may increase the levels/effects of anthracyclines, Irinotecan, Sorafenib, and Sunitinib. Serum concentrations of irinotecan's active metabolite may be increased by bevacizumab; an approximate 33% increase has been observed.

15.57 Known potential adverse events

Consult the package insert for the most current and complete information. U.S. Boxed Warnings include severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous system hemorrhage, epistaxis, and vaginal bleeding. Avoid use in patients with serious

hemorrhage or recent hemoptysis. Percentages reported as Monotherapy and as part of combination chemotherapy regimens.
Common known potential toxicities, > 10%:
Cardiovascular: Hypertension, thromboembolic events, hypotension.
Central nervous system: Pain, headache, dizziness, fatigue, sensory neuropathy.
Dermatologic: Alopecia, dry skin, exfoliative dermatitis, skin discoloration.
Endocrine & metabolic: Hypokalemia.
Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, stomatitis, gastrointestinal hemorrhage, dyspepsia, taste disorder, flatulence, nausea, vomiting, weight loss.
Hematologic: Hemorrhage, neutropenia, leukopenia.
Neuromuscular & skeletal: Weakness, myalgia, back pain.
Ocular: Tearing increased.
Renal: Proteinuria.
Reproductive system and breast disorders: Ovarian failure, vaginal hemorrhage. As an IgG1, bevacizumab may be secreted in human milk. Women should avoid breast feeding.
Respiratory: Upper respiratory infection, epistaxis, dyspnea, rhinitis
Miscellaneous: Infection, pneumonia, catheter infection, wound infections.

Less common known potential toxicities, 1% - 10%:
Cardiovascular: DVT, venous thrombus/embolus, arterial thrombosis, syncope, intra-abdominal venous thrombosis, cardio-/cerebrovascular arterial thrombotic event, CHF, left ventricular dysfunction, supraventricular tachycardia.
Central Nervous System: Confusion, abnormal gait, CNS hemorrhage, reversible posterior leukoencephalopathy syndrome (RPLS), syncope
Dermatologic: Acne, nail disorder, pruritus, rash desquamation, skin ulcer, urticaria, and wound dehiscence.
Ear and labyrinth disorders: Vertigo
Endocrine& metabolic: Dehydration, hyperglycemia, hyponatremia.
Gastrointestinal: Xerostomia, colitis, ileus, gingivitis, fistula, gastroesophageal reflux, gastrointestinal perforation, intra-abdominal abscess, mouth ulceration, tooth abscess, gastritis, gingival pain, ileus, gastrointestinal ulcer
Genitourinary: Polyuria/urgency, vaginal hemorrhage.
Hematologic: Anemia, febrile neutropenia/infection, thrombocytopenia, decreased hemoglobin, increased prothrombin time
Hepatic: Bilirubinemia.
Nervous system disorders: Peripheral sensory neuropathy
Neuromuscular & skeletal: Bone pain
Renal: Acute kidney injury, hematuria
Respiratory: Voice alteration (hoarseness), cough, pneumonitis/pulmonary infiltrates, hemoptysis, pulmonary embolism
Miscellaneous: Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Anaphylactic and anaphylactoid-type reactions.

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Anastomotic ulceration, angina, cerebral infarction, gall bladder perforation, hemorrhagic stroke, hypertensive crises, hypertensive encephalopathy, intestinal necrosis, intestinal obstruction, mesenteric venous occlusion, microangiopathic hemolytic anemia (when used in combination with Sunitinib), acute coronary syndrome, heart failure, myocardial infarction, ventricular arrhythmia, ventricular fibrillation, nasal septum perforation, nephrotic syndrome, renal failure, pancytopenia, polyserositis, pulmonary hemorrhage, pulmonary hypertension, renal failure, renal thrombotic microangiopathy, subarachnoid hemorrhage, toxic anterior segment syndrome, transient ischemic attack, ureteral stricture, wound healing complications

15.58 Drug procurement
Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.59 Nursing Guidelines

15.591 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that bevacizumab is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur stop the infusion immediately and contact MD. Have emergency equipment nearby and be prepared to administer emergency treatment as ordered by MD.

15.592 Monitor urine dipstick or UPC as required by the test schedule

15.593 Evaluate IV site regularly for signs of infiltration.

15.594 Bleeding in the absence of thrombocytopenia is a dose limiting toxicity. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.

15.595 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially closely.

15.596 Patient may experience Grade 1-2 nausea, however vomiting is uncommon. Medicate as ordered and monitor for effectiveness.

15.597 Monitor for skin rash, instruct patient to report to MD.

15.598 Monitor blood pressure. Administer antihypertensives as ordered by MD.

15.599a Monitor for signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), or myocardial infarction (MI) including

new or worsening angina. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or shortness of breath to MD immediately.

15.599b Asthenia and headache were reported commonly during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.

15.599c Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the MD.

15.599d Patients receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained. For patients on warfarin for venous access prophylaxis, routine monitoring is satisfactory.

15.599e A rare but serious complication of bevacizumab is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.

15.599f Gastrointestinal perforation with or without abdominal abscess is rare but possible. This may present itself as vague abdominal pain associated with constipation and vomiting. Instruct patient to report abdominal pain to the MD.

15.599g Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

15.599h Warn female patients of the possibility of ovarian failure and subsequent infertility. Vaginal hemorrhage is also possible. Instruct patients to report any heavy or unusual vaginal bleeding to health care team.

16.0 Statistical Considerations and Methodology

16.1 Overview

This study will be a single-stage phase II study to determine the initial clinical benefit of Avatar directed chemotherapy. Patients will receive any one of 4 treatment arms (A-D) based on the result of their Avatar. The primary endpoint will be the percentage of patients with a confirmed tumor response, pooled across all 4 treatment arms. The null hypothesis will be set at a 20% for a confirmed

response, which is the typical response rate observed with standard treatment (see section 1 for details). The Avatar directed chemotherapy approach will be deemed worthy of further investigation if 40% or more of patients have a confirmed response. Secondary endpoints will consist of progression-free survival (PFS), overall survival (OS), and adverse events. In addition, this study will also assess a couple translational endpoints as well.

16.11 Primary Endpoint

The primary endpoint of this trial is the proportion of patients with a confirmed tumor response, where we will pool across all patients. The confirmed response rate will be estimated using RECIST 1.1 criteria. A confirmed tumor response is defined to be either a CR or PR noted as the objective status on 2 consecutive evaluations at least 4 weeks apart. Confirmed tumor response will be evaluated using the first 6 cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for tumor response. Eligible patients who go off treatment early, prior to being evaluated for response, will be considered as failures.

16.12 Sample Size

The one-stage study design is fully described in Section 16.2. Fifty-three evaluable patients will be accrued onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 7 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is expected to be 60 patients. We anticipate pre-registering 240 patients in order to register a total of 60 patients per the study design.

16.13 Accrual Time and Study Duration

The anticipated accrual rate is approximately 2 patients per month. Therefore, the accrual period for this phase II study is expected to be approximately 30 months. The final analysis can begin approximately 40 months after the trial begins, i.e. as soon as the last patient has been followed for around 6 months plus time for data entry and clean-up.

16.2 Statistical Design

16.21 Decision Rule

The largest confirmed response rate where the proposed Avatar directed chemotherapy approach would be considered ineffective in this population is 20%, and the smallest confirmed response rate that would warrant subsequent studies with this approach in this patient population is 40%. The following one-stage design uses 53 evaluable patients to test the null hypothesis that the true confirmed response rate in this patient population is at most 20%.

16.211 Final Analysis Decision Rule

Enter 53 evaluable patients into the study. If 15 or fewer patients have a confirmed tumor response, we will consider this Avatar directed chemotherapy approach to be ineffective in this patient population. If 16 or more patients have a confirmed tumor response (30%), we may recommend further testing of this approach in subsequent studies in this patient population.

16.212 Over Accrual

If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients is discussed in Section 16.35.

16.213 Data and Safety Monitoring

The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The trial is monitored continually by the study team who are notified of every grade 4 and 5 event in real time. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office. Any safety issues requiring protocol changes are communicated through protocol amendments.

Adverse Event Stopping Rule: Based on previous experience with this disease, we expect approximately 30% of patients to experience Grade 4+ adverse events. If at any time, 8 of the initial 20 patients or 40% of all patients (i.e., when accrual is greater than 20 patients), have experienced any Grade 4 or 5 adverse event (at least possibly related to the study treatment), accrual to the study will be suspended to allow for a full review of the data. Each grade 5 event will be reviewed on a case by case basis in a real time fashion to determine whether study accrual should be suspended. After consideration by the study team [ie, Study Chair(s), Statistician, Operations Office, etc] and consultation with representatives at the primary Internal Review Board (IRB) affiliated with the Operations Office, a decision will be made as to whether and how the study will proceed.

16.22 Power and Significance Level

Assuming that the number of confirmed responses is binomially distributed, the significance level is 5% when the true confirmed response

rate is 20% and the power is 95% when the true confirmed response rate is 40%.

16.23 Other Considerations
Toxicity, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

16.31 Primary Endpoint
The proportion of confirmed responses (i.e. successes) will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true success proportion will be calculated according to the exact Binomial method. The primary analysis will pool across all patients, but we will also look at the tumor reponse rate by treatment arm as well in an exploratory fashion.

16.32 Definitions and Analyses of Secondary Endpoints
Note: All of these secondary analyses will be conducted across all patients and by treatment arm).

16.321 Progression-Free Survival (PFS)
PFS is defined as the time from registration to the first of either disease progression or death from any cause. Patients who receive the study drug, but then never return for an evaluation will be censored on their last follow-up date. PFS will be estimated using the method of Kaplan-Meier.

16.322 Overall survival (OS) is defined as the time from registration to death from any cause. OS will be estimated using the method of Kaplan-Meier.

16.323 As a descriptive analysis, we will also compare the response rates between patients who did or did not receive bevacizumab treatment. For this analysis, we will use the Chi-square or Fisher's Exact test. We will also report the response rates by treatment type as well (bevacizumab or no bevacizumab).

16.33 Adverse Events
All patients that have intitiated treatment will be considered evaluable for adverse event (AE) analyses. The maximum grade for each type of AE will be recorded for each patient, and frequency tables will be reviewed to determine AE patterns.

16.34 Translational Endpoints

- To determine the correlation between patient response and response in their Avatar. This analysis will be highly exploratory and will focus on the frequency (%) of patients who had an Avatar response and a clinical tumor response for the same treatment. We will report the overall concordance rate and confidence interval as well.

- To enrich the Avatar response signature in response to Avatar-directed therapy using patient outcomes. This will be an exploratory analysis that will use the outcome data from this trial to inform future work using Avatar directed therapy.

16.35 Over Accrual
If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals as though they were accrued for the final analysis.

16.4 Inclusion of Women and Minorities

16.41 This study will be available to all eligible women, regardless of race or ethnic origin.

16.42 There is no information currently available regarding differential effects of this regimen in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.43 Based on prior studies involving similar disease sites, we expect about 10% of patients will be classified as minorities by race and all will be women. Expected sizes (per study design) of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	3	0	3
Not Hispanic or Latino	57	0	57
Ethnic Category: Total of all subjects	60	0	60
Racial Category			
American Indian or Alaskan Native	0	0	0

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Asian	3	0	3
Black or African American	3	0	3
Native Hawaiian or other Pacific Islander	0	0	0
White	54	0	54
Racial Category: Total of all subjects	60	0	60

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

None.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Pre-Registration Material(s)

Case Report Form (CRF)	Pre-Screen Phase (No active testing)
Pre-Registration Screening Failure	Complete only if patient is NOT registered after he/she is pre-registered

Initial Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤ 14 days after registration
RECIST Measurement - Baseline	
End of Active Treatment/Cancel Notification	Submit ≤ 14 days after registration if withdrawal/refusal occurs prior to beginning protocol therapy

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Evaluation/Treatment	X	X
Adverse Event	X	X
RECIST Measurement	X	X
End of Active Treatment/Cancel Notification		X
ADR/AER	At each occurrence (See Section 10.0)	

Follow-up Material(s)

CRF	Event Monitoring Phase [1]				
	Every 3 months Until PD [2]	At PD [2]	Every 6 Months After PD	Death	New Primary
Event Monitoring	X [2]	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.
2. Submit relevant radiographic images as a digital image with a viewing tool free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s) of tumor response at baseline, tumor response and/or progression. Submit copy of documentation of response or progression to the MC1463 Principal Investigator, [redacted]

19.0 Budget

19.1 Costs Charged to Patient
Routine Clinical Care

19.2 Tests to be Research Funded
None.

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Appendix I: ECOG Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix II: Local Medical Oncologist Contact Letter (Avatar in Production)

Date

Re: (Patient Name),
(Mayo Clinic Patient Registration Number)

Dear Dr. (Name),

When your patient (name) had surgery at the Mayo Clinic, she agreed to participate in a study that allowed use of her tumor specimen for research purposes. We would like to share with you information about a research study that used her tumor specimen. We are attempting to develop a patient-derived xenograft, also known as an Avatar, which may be able to guide treatment should the patient have a platinum-resistant recurrence of her disease. We have implanted tumor specimens in research mice and are propagating them in hopes that we can grow the tumors and then treat the mice with the most common second-line chemotherapy agents such as paclitaxel, doxil, topotecan or gemcitabine. Should the Avatar be successfully established and your patient experience a platinum resistant recurrence of her disease, we would ask (Name) to return to Mayo Clinic to discuss participating in Avatar directed chemotherapy, with the most successful agent being disclosed to you or her treating medical oncologist.

Key points about the study:

- Platinum resistance will be defined as recurrence of disease <6 months from the completion of platinum-based chemotherapy. If you are unsure whether the patient is platinum-sensitive or platinum-resistant, please contact us prior to initiating treatment, as treatment for platinum-resistant disease prior to learning of the Avatar data would make her ineligible for the study.

- The patient may receive her chemotherapy in your office – we would simply ask that you stay in contact with us as to her treatment status

- If the patient has treatment in your office, we would ask that she comes to Mayo for evaluation and then for scans every other cycle as required by the study. We will share these scans with you.

- The patient can receive bevacizumab (Avastin) as an AURELIA-eligible regimen.

- There is no cost to the patient for the Avatar generation. Treatment and evaluation by CT or MRI imaging is a standard of care treatment. There are no further biopsies or research blood draws needed.

If you have any questions or concerns, please feel free to contact me. I have included citations for some recent publications on the Avatars.

Sincerely,
(Mayo Site PI)
(Telephone number)

Citations:

1. Clin Cancer Res. 2014 Mar 1;20(5):1288-97. doi: 10.1158/1078-0432.CCR-13-2611. Epub 2014 Jan 7

2. Biochim Biophys Acta. 2015 Mar 14;1855(2):223-234. doi: 10.1016/j.bbcan.2015.03.002

3. Front Oncol. 2013 Dec 4;3:295. doi: 10.3389/fonc.2013.00295

Appendix III: Local Medical Oncologist Contact Letter (Existing Avatar)

Date

Re: (Patient Name),
(Mayo Clinic Patient Registration Number)

Dear Dr. (Name),

When your patient (name) had surgery or a biopsy at the Mayo Clinic, she agreed to participate in a study that allowed use of her tumor specimen for research purposes. We would like to share with you information about a research study that used her tumor specimen. We have developed a patient-derived xenograft, also known as an Avatar, which may be able to guide treatment should the patient have a platinum-resistant recurrence of her disease. We have implanted tumor specimens in research mice and grown the tumors. We are treating the mice with the most common second-line chemotherapy agents such as paclitaxel, doxil, topotecan or gemcitabine. Should your patient experience a platinum resistant recurrence of her disease, we would ask (Name) to return to Mayo Clinic to discuss participating in Avatar directed chemotherapy, with the most successful agent being disclosed to you or her treating medical oncologist.

Key points about the study:

- Platinum resistance will be defined as recurrence of disease <6 months from the completion of platinum-based chemotherapy. If you are unsure whether the patient is platinum-sensitive or platinum-resistant, please contact us prior to initiating treatment, as treatment for platinum-resistant disease prior to learning of the Avatar data would make her ineligible for the study.

- The patient may receive her chemotherapy in your office – we would simply ask that you stay in contact with us as to her treatment status

- If the patient has treatment in your office, we would ask that she comes to Mayo for evaluation and then for scans every other cycle as required by the study. We will share these scans with you.

- The patient can receive bevacizumab (Avastin) as an AURELIA-eligible regimen.

- There is no cost to the patient for the Avatar generation. Treatment and evaluation by CT or MRI imaging is a standard of care treatment. There are no further biopsies or research blood draws needed.

If you have any questions or concerns, please feel free to contact me. I have included citations for some recent publications on the Avatars.

Sincerely,
(Mayo Site PI)
(Telephone number)

Citations:

1. Clin Cancer Res. 2014 Mar 1;20(5):1288-97. doi: 10.1158/1078-0432.CCR-13-2611. Epub 2014 Jan 7

2. Biochim Biophys Acta. 2015 Mar 14;1855(2):223-234. doi: 10.1016/j.bbcan.2015.03.002

3. Front Oncol. 2013 Dec 4;3:295. doi: 10.3389/fonc.2013.00295

Appendix IV: Patient Contact Letter (Avatar in Production)

Date

(Patient Name)
(Mayo Clinic Patient Registration Number)
(Patient Home Address)

Dear (Title) (Name),

Previously, you granted permission for tumor tissue removed during your surgery or biopsy at Mayo Clinic to be used for future research. As part of this future research, we have transferred tumor tissue to a mouse in an attempt to successfully produce an 'Avatar', a tumor model that reproduces the original tumor.

We have previously shown that patients respond to chemotherapy very much like their Avatars. We are hoping now to be able to produce and use the Avatar to help identify the best chemotherapy for the patient in a clinical research study.

This research study would be conducted only if the cancer recurs and becomes resistant to treatment with platinum-based chemotherapy (such as carboplatin). We would ask patients to return to Mayo Clinic at this time to sign consent and register for the study. All chemotherapy treatments are FDA-approved and may be given by your local medical doctor at home; however, please note that you would be asked to return to Mayo Clinic every 8 weeks to have a CT or MRI scan to determine if your cancer is responding well to the treatment.

There is no cost to participate in this study beyond the normal clinical costs of treating the cancer (such as chemotherapy drugs and CT or MRI scans, etc.).

If you are interested in possibly taking part in this study, or if you would like more information, please contact (study coordinator) at (telephone).

Sincerely,
(Mayo Clinic Site PI)

Appendix V: Patient Contact Letter (Existing Avatar)

Date

(Patient Name)
(Mayo Clinic Patient Registration Number)
(Patient Home Address)

Dear (Title) (Name),

Previously, you granted permission for tumor tissue removed during your surgery at Mayo Clinic to be used for future research. As part of this future research, we have transferred tumor tissue to a mouse and successfully produced an 'Avatar', a tumor model that reproduces the original tumor.

We have previously shown that patients respond to chemotherapy very much like their Avatars. We are hoping now to use the Avatar to help identify the best chemotherapy for the patient in a clinical research study.

This research study would be conducted only if the cancer recurs and becomes resistant to treatment with platinum-based chemotherapy (such as carboplatin). We would ask patients to return to Mayo Clinic at this time to sign consent and register for the study. All chemotherapy treatments are FDA-approved and may be given by your local medical doctor at home; however, please note that you would be asked to return to Mayo Clinic every 8 weeks to have a CT or MRI scan to determine if your cancer is responding well to the treatment.

There is no cost to participate in this study beyond the normal clinical costs of treating the cancer (such as chemotherapy drugs and CT or MRI scans, etc.).

If you are interested in possibly taking part in this study, or if you would like more information, please contact (study coordinator) at (telephone).

Sincerely,
(Mayo Clinic Site PI)