Mayo Clinic Cancer Center

MC1365, A Randomized Phase II Trial of a Genetically Engineered NIS-Expressing Strain of Measles Virus Versus Investigator's Choice Chemotherapy for Patients with Platinum-Resistant Ovarian, Fallopian, or Peritoneal Cancer

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†Study contributor(s) not responsible for patient care

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Protocol Resources

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*No waivers of eligibility per NCI

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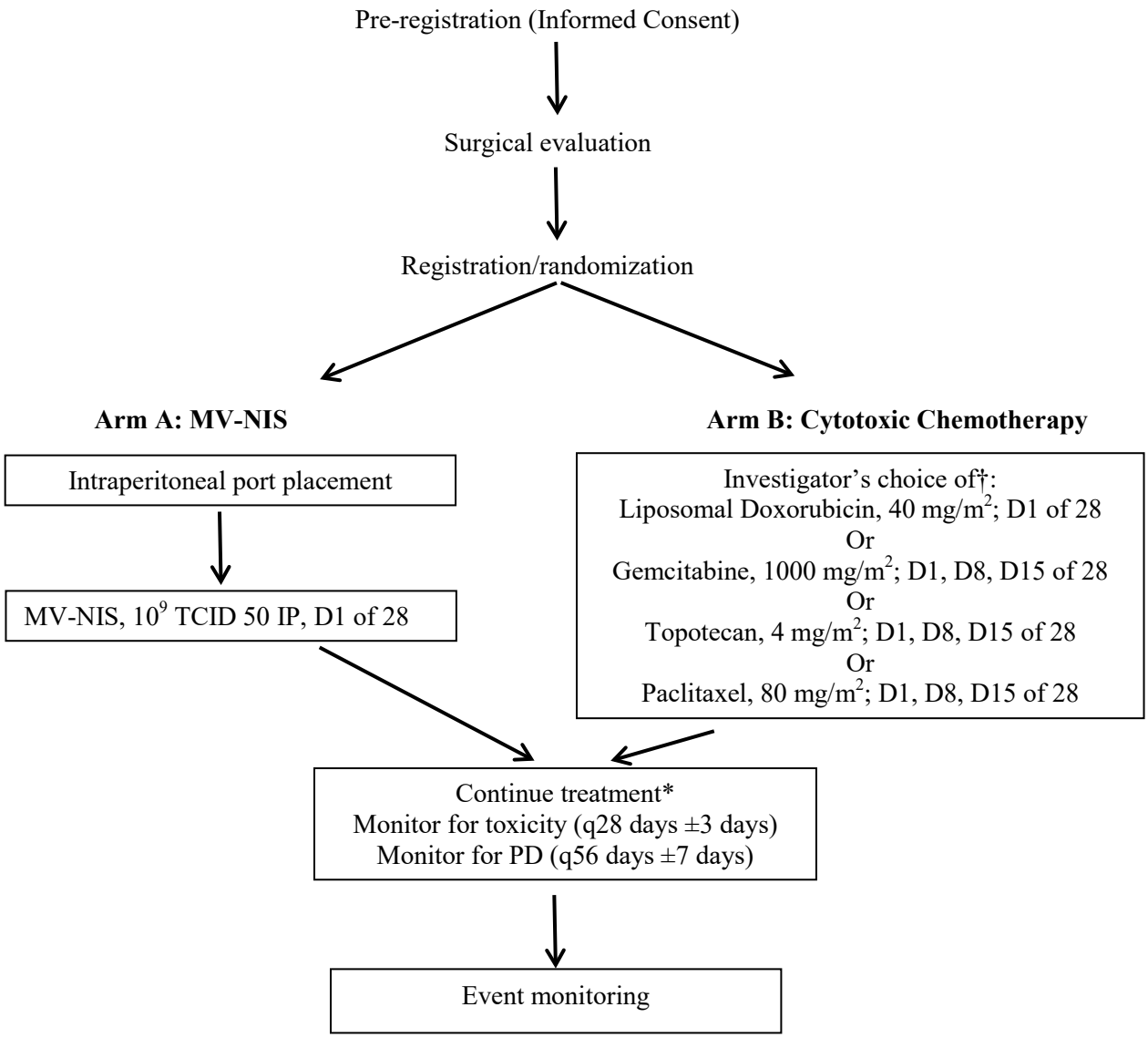
Schema (non-bulky disease ≤5 cm)



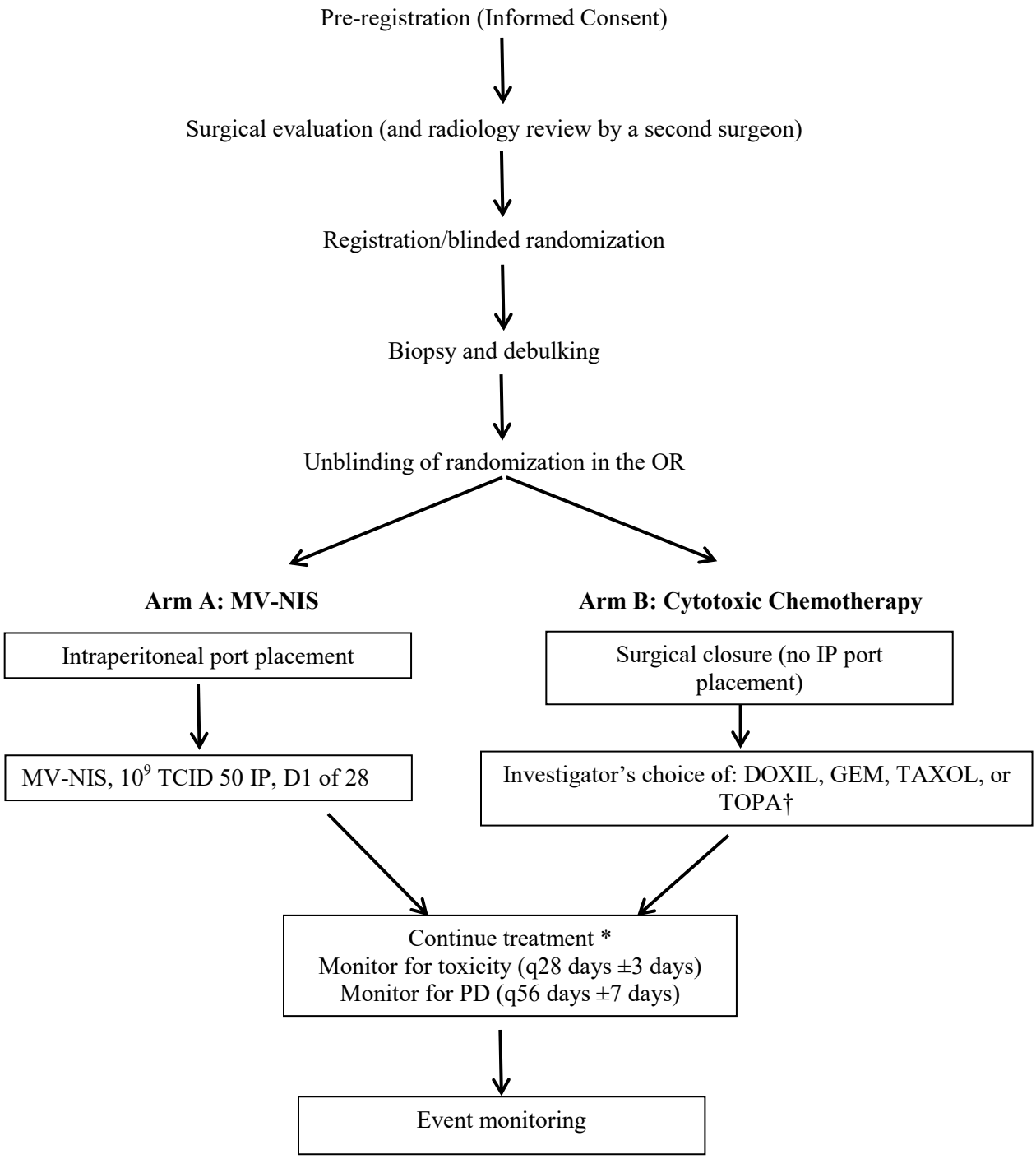
Cycle length = 28 days

*Patients who develop PD but do not have progressive cancer-associated symptoms and are tolerating treatment well may continue therapy (either Arm) at the discretion of the treating investigator until additional progression is documented.

†Bevacizumab may be added to liposomal doxorubicin, topotecan, or paclitaxel regimens as part of standard care

Generic name or synonym	Liposomal Doxorubicin	Gemcitabine	Topotecan	Paclitaxel	Bevacizumab	NIS-Measles Virus (Edmonston Strain)
Brand name	Doxil	Gemzar	Hycamtin	Taxol	Avastin	-----
Mayo abbreviation	PLD	GEM	TOPA	TAXOL	AVAST	MV-NIS
Availability	Commercial	Commercial	Commercial	Commercial	Commercial	Mayo Pharmacy

Schema (bulky disease >5 cm)



Cycle length = 28 days

*Patients who develop PD but do not have progressive cancer-associated symptoms and are tolerating treatment well may continue therapy (either arm) at the discretion of the treating investigator until additional progression is documented.

†Bevacizumab may be added to liposomal doxorubicin, topotecan, or paclitaxel regimens as part of standard care

1.0 Background

1.1 Ovarian, fallopian, and peritoneal cancer

Ovarian cancer (along with fallopian and peritoneal cancer, collectively referred to as OC) is the second most common malignancy of the female genital tract in the United States. According to the American Cancer Society, there were an estimated 16,000 deaths in the United States in 2007 (1). Because there is no effective screening method for ovarian cancer, more than 70% of cases are diagnosed after the tumor has already spread beyond the ovaries. Although initial surgery and chemotherapy are often effective in inducing remission of OC, most patients will experience disease relapse despite initial treatment; 5-year survival with distant spread of OC is only 26.9% (2).

Because most histologies of OC are initially sensitive to chemotherapy, patients with recurrent OC are frequently treated with cytotoxic therapy; however, OC ultimately becomes resistant or refractory to this form of treatment. Platinum-resistance, defined as an incomplete response to platinum-containing chemotherapy or OC progression within six months of receipt of platinum-containing chemotherapy, portends a poor prognosis and often is associated with a limited response to non-platinum-containing chemotherapy. Overall survival in platinum-resistant OC is often less than one year. New therapies for platinum-resistant OC are badly needed.

1.2 Measles virus as cancer therapy

The idea of using measles virus strains as anticancer therapy has emerged from the observation that natural measles infection can result in an antitumor effect. For example, natural infection with measles virus has been shown to lead to regression in patients with Hodgkin's disease and non-Hodgkin's lymphoma (3, 4).

Measles virus is a negative strand, RNA virus, whose genome includes six protein products (5). Three of these proteins participate in the formation of the viral envelope; the H-protein is the surface glycoprotein which mediates measles virus attachment to its receptors, the CD46 molecule (6), the SLAM receptor (the latter being predominantly present on activated B and T cells) and the epithelial receptor nectin-4 (7). The F-protein is responsible for cell after viral attachment has taken place. During natural infection with the measles virus, the virus replicates in susceptible tissues causing a very characteristic cytopathic effect, with development of multinucleated giant cells (syncytia). Cells infected by measles virus express F and H-proteins on their membranes and therefore become highly fusogenic. These cells can cause fusion not only with other infected cells but also with uninfected neighboring cells. Although wild type measles virus can lead to a potentially serious infectious disease, attenuated strains (vaccine strains) of measles virus have an excellent safety record and have resulted in significant decreases in measles incidence and mortality worldwide (8).

In preclinical studies we showed that intratumoral or intravenous injection of a measles virus strain, deriving from the Edmonston vaccine lineage, can cause growth inhibition or total regression for a variety of established tumors and xenografts (9).

Systemic use of an attenuated strain of measles virus as an anticancer agent can be potentially hampered by high levels of protecting anti-measles virus antibodies, which are present in more than 90% of the Western population as a result of immunization or natural infection (10). Ovarian cancer, however, provides us with a unique opportunity to exploit the antitumor potential of the vaccine strain of measles virus. In 85% of patients, ovarian cancer remains confined within the peritoneal cavity, providing an optimal

setting for viral delivery and direct virus-tumor interaction.

MV strains have demonstrated potent antitumor activity against human epithelial ovarian cancer cells *in vitro* and *in vivo*. Most importantly, the virus was selectively oncolytic for ovarian tumor cells but caused minimal cytopathic damage on normal ovarian surface epithelium and normal mesothelium. This selectivity was in part mediated through overexpression of the measles virus receptor CD46 in ovarian cancer cells in contrast to low levels of expression in mesothelial cells and normal ovarian surface epithelial cells. When an MV derivative producing the human carcinoembryonic antigen (MV-CEA) was injected directly into established subcutaneous SKOV3ip.1 human epithelial ovarian xenografts in athymic mice, the virus induced complete regression of 80% of the tumors. Survival of mice bearing intraperitoneal tumors was significantly enhanced by virus therapy. The median survival of mice in the treated group was more than 80 days compared to 30 days for the control group. By day 48 post-implantation of cells, all mice in the control group had developed ascites and had to be euthanized. Similar data were subsequently obtained with MV-NIS (11, 12). Toxicology and biodistribution studies in measles virus infection susceptible Infar^{ko} CD46 Ge mice have demonstrated the safety of the approach (13).

1.3 Clinical experience with MV-NIS in ovarian cancer

A phase I trial of intraperineal administration of MV-CEA has been completed (14). 21 patients were treated with MV-CEA i.p. every four weeks for up to six cycles at ten different dose levels from 10^3 to 10^9 TCID50. We observed no dose-limiting toxicity, treatment induced immunosuppression, development of anti-CEA antibodies, increase in anti-CEA antibody titers or viral shedding in urine or saliva. Dose dependent CEA elevation in peritoneal fluid and serum was observed. Immunohistochemical analysis of patient tumor specimens revealed overexpression of measles virus receptor CD46 in 13/15 patients. Best objective response was dose-dependent disease stabilization in 14/21 patients with a median duration of 92.5 days (range 54 to 277 days). Five patients had significant decrease in CA-125 levels. Median survival of patients on study was 12.5 months, (range 1.3 to 38.4 months) comparing favorably to an expected median survival of 6 months in this patient population. MV-NIS is an MV-Edmonston derivative, identical to MV-CEA except that it encodes the sodium iodine symporter (NIS) gene instead of the CEA gene (15). MV-NIS is at least as efficacious as MV-CEA in orthotopic ovarian cancer models (12)and it allows use of radioactive iodine isotopes for imaging (12) and treatment purposes.

Six patients have been treated in 2 dose levels of MV-NIS (10^8 -10^9 TCID50), and an additional 10 patients at a 10^9 TCID50 dose expansion cohort for a total of 16 patients. No dose-limiting toxicity was observed. Most common cycle 1 toxicities included mild (grade 1-2) abdominal pain (8 patients); grade 1-2 fatigue (7 patients); and grade 1-2 fever (3 patients). There was no treatment-induced immunosuppression as assessed by DTH, CD4, CD8, IgG and complement levels, no significant increase in the titers of MV antibodies in response to treatment and no viral shedding in urine or mouth gargle specimens. NIS expression in patient tumors following treatment was demonstrated in 3 patients by ^{123}I uptake on SPECT CTs and was associated with long progression-free survival. Study patients were heavily pretreated with a mean of 4.3 chemotherapy regimens at study entry (range 1-8). Median time to progression was 2.13 months (range 0.8-32.5 + mo), and median overall survival 26.6 months (range 1.8-33.9 + mo); the latter compares favorably with outcomes in other contemporary series of novel therapeutics in recurrent platinum-resistant OC (6-12 months). In a pilot study to investigate the mechanism of these favorable outcomes, the development of antitumor immune response

in study patients was tested by performing pre- and post-treatment IFN-gamma and IL-4 ELISPOT assays against insulin-like growth factor binding protein 2 (IGFBP2) and folate receptor alpha. In 3/4 patients, there was significant increase of anti-tumor specific T-cells ($p<0.05$) suggesting that MV treatment of recurrent ovarian cancer patients can elicit cellular immune response against the patients' tumor (16).

1.4 Liposomal doxorubicin in platinum-resistant ovarian cancer

There are several chemotherapy regimens that demonstrated clinical efficacy in patients with platinum-resistant OC. Among these are liposomal doxorubicin (DOXIL), gemcitabine (GEM), topotecan (TOPA), and weekly paclitaxel (TAXOL). Each of these regimens is, therefore, a reasonable comparator for MV-NIS as therapy for platinum-resistant OC.

DOXIL has been approved by the FDA for use in OC patients whose cancer has progressed or recurred after platinum-based chemotherapy. Single-agent DOXIL was initially studied as a single-agent therapy for OC patients at 50 mg/m^2 (17), but due to toxicity at this dose, DOXIL is generally given at 40 mg/m^2 in clinical practice and as a standard in clinical trials (18). Common toxicities from DOXIL include hematologic toxicity (neutropenia and thrombocytopenia), palmar-plantar erythrodysesthesia (hand-foot syndrome), and stomatitis. Median time to progression (TTP) and OS for patients treated with DOXIL in a phase III clinical trial were 16 weeks and 56 weeks, respectively (18).

1.5 Gemcitabine in platinum-resistant ovarian cancer

GEM is an alternative to DOXIL that is also commonly used as a single agent therapy for platinum-resistant OC. GEM is also FDA-approved in combination with carboplatin for patients with platinum-sensitive OC. When used as a single agent in platinum-resistant OC in the context of a randomized phase III clinical trial, GEM was associated with neutropenia, anemia, and thrombocytopenia. Median time to progression (TTP) and OS for patients treated with DOXIL in a phase III clinical trial were 20 weeks and 51 weeks, respectively (18).

1.6 Topotecan in platinum-resistant ovarian cancer

TOPA gained approval as a treatment for relapsed ovarian cancer based on a study comparing topotecan administered at 1.5 mg/m^2 daily for 5 days. In this study, TOPA showed superiority to paclitaxel 175 mg/m^2 in TTP (23 vs 14 weeks, P=0.002) (19). Because of the high rate of myelosuppression seen with the daily TOPA schedule in patients with relapsed ovarian cancer, investigators have studied alternative dosing schedules for single-agent topotecan. A prospective study evaluating patients receiving TOPA given weekly at 4 mg/m^2 on Days 1, 8, and 15 of a 28 day cycle demonstrated good tolerability (20). A randomized phase II study compared daily TOPA with weekly TOPA, and this study showed that while clinical benefit rate and PFS slightly favored daily TOPA, OS was similar between daily and weekly TOPA (21). As a result, weekly TOPA is commonly used in patients with platinum-resistant OC. Hematologic toxicity is the most common dose-limiting side effect for TOPA.

1.7 Weekly paclitaxel in platinum-resistant ovarian cancer

Because most patients with OC are initially treated with TAXOL and either carboplatin or cisplatin, many patients with platinum-resistant OC are also resistant to TAXOL. However, several studies have demonstrated objective tumor responses to weekly TAXOL even in TAXOL-resistant patients (22). This has led to the formal investigation

of weekly TAXOL in a multicenter phase II clinical trial (23). This study demonstrated a favorable toxicity profile, with peripheral neuropathy as the most common grade 3/4 toxicity. PFS and OS with weekly TAXOL 80 mg/m^2 are 6.1 and 10.43 months, respectively (22).

1.8 Bevacizumab in combination with chemotherapy for platinum-resistant ovarian cancer

Multiple studies have demonstrated the clinical activity of bevacizumab in various clinical contexts of OC. In the AURELIA open-label randomized phase III trial, patients with platinum-resistant OC were assigned to treatment with chemotherapy alone (liposomal doxorubicin, topotecan, or weekly paclitaxel) or chemotherapy plus bevacizumab. The addition of bevacizumab led to an improvement in PFS from a median of 3.4 to 6.7 months, although the difference in OS was not deemed statistically significant (Ref PMID: 24637997). Based on this trial, bevacizumab is approved by the FDA for platinum-resistant OC at a dose of 10 mg/kg every 2 weeks in combination with liposomal doxorubicin, topotecan, or weekly paclitaxel.

1.9a Surgery for recurrent ovarian cancer

Secondary cytoreductive surgery is sometimes employed as a means of cancer control for patients with recurrent OC. While secondary cytoreduction is most commonly used in patients with platinum-sensitive recurrent OC, prospective randomized studies have not definitively identified which patients with recurrent OC benefit from secondary cytoreduction. For patients with platinum-resistant OC, secondary cytoreduction is infrequently offered, most often in a scenario in which the surgeon believes that a gross total cytoreduction is feasible without a high risk for major perioperative morbidity.

1.9b Rationale for the study design

Viral therapy with MV-NIS has demonstrated promising clinical activity in patients with platinum-resistant OC, with especially favorable survival demonstrated in patients with non-bulky disease. DOXIL, GEM, TOPA, and TAXOL are conventional chemotherapy options that are acceptable therapies commonly used in the setting of platinum-resistant OC, and selection of which of these regimens to use is often individualized based on prior chemotherapy exposure and toxicity. Given that the maximal benefit from MV-NIS therapy was in those patients with non-bulky disease, and given that secondary cytoreduction is an acceptable practice in a limited number of platinum-resistant OC patients in whom gross total cytoreduction can be achieved without high risk of major perioperative morbidity, it is reasonable to include patients with non-bulky (≤5 cm) disease, as well as patients with bulky disease for whom gross total cytoreduction is deemed achievable. Therefore, we will compare efficacy of MV-NIS therapy with conventional chemotherapy chosen from the above four regimens by the treating investigator. To ensure similar patient characteristics among patients treated with MV-NIS versus conventional chemotherapy, we will randomize patients adjudged to be candidates for intraperitoneal port placement (and cytoreductive surgery, for those patients with >5 cm disease) to either MV-NIS or “dealer’s choice” chemotherapy, in a 2:1 ratio, stratifying patients by the number of prior therapies to which the patient is resistant, as well as by disease extent (non-bulky versus bulky). In this way, we will compare the safety, tolerability, and clinical efficacy of MV-NIS and chemotherapy. We will also compare anti-tumor immune responses elicited by MV-NIS therapy with those elicited by chemotherapy.

2.0 Goals

2.1 Primary objective:

2.11 Compare clinical efficacy of Arm A (MV-NIS therapy) and Arm B (standard cytotoxic chemotherapy), as measured by overall survival (OS).

2.2 Secondary clinical objectives:

2.21 Compare progression-free survival (PFS), overall survival at 12 months (OS12), progression-free survival at six months (PFS6), and objective response rate (ORR) between MV-NIS therapy and standard chemotherapy.

2.22 Assess safety and tolerability of MV-NIS, and compare with standard chemotherapy.

2.23 Compare quality of life as assessed by FACT-O between MV-NIS and standard chemotherapy.

2.3 Translational objectives:

2.31 Assess the time course of viral gene expression and virus elimination and biodistribution of virally infected cells at various time points after infection with MV-NIS using SPECT/CT imaging within the NV-NIS treatment arm.

2.32 Assess viremia, viral replication, and viral shedding/persistence following intraperitoneal administration within the NV-NIS treatment arm.

2.33 Measure humoral and cellular immune responses to MV-NIS within the NV-NIS treatment arm.

2.34 Measure changes in anti-OC immune responses in both treatment arms.

2.35 Perform transcriptomic analysis on tumor biopsy specimens to determine a gene expression profile predictive of therapeutic response to MV-NIS.

3.0 Patient Eligibility

3.1 Pre-Registration -Inclusion Criteria

3.11 Ability to understand and the willingness to sign a written informed consent document.

3.12 The effects of the candidate chemoprevention agents on the developing human fetus remain incompletely defined. However, study participants will be women who have gone through a bi-lateral oophorectomy procedure(see Section 3.22).

3.13 Willingness to be evaluated for surgical placement of an intraperitoneal port and undergo biopsy if feasible for a research sample.

3.2 Registration/Randomization - Inclusion Criteria

3.21 Age ≥18 years.

3.22 Recurrent, persistent, or progressive epithelial ovarian, fallopian tube, or primary peritoneal cancer after treatment with bilateral oophorectomy and either cisplatin or carboplatin and either paclitaxel, albumin-bound paclitaxel, or docetaxel. Histologic confirmation of the primary tumor is required. Eligible histologies include serous, endometrioid, clear cell, mucinous, transitional cell, undifferentiated, or mixed carcinoma.

3.23 Platinum-resistant or platinum-refractory disease, defined as either
1) less than a complete response to the most recent carboplatin- or cisplatin-containing chemotherapy regimen,
2) serum CA-125 ≥2 x ULN within 180 days of last dose of carboplatin- or cisplatin-containing chemotherapy, confirmed by a second CA-125 (the second CA-125 does not have to be within 180 days of chemotherapy), or
3) CT or PET/CT evidence of cancer recurrence within 180 days of last dose of carboplatin- or cisplatin-containing chemotherapy.

3.24 The following laboratory values obtained ≤7 days prior to registration:

- ANC ≥1500/µL
- PLT ≥100,000/µL
- Total bilirubin ≤ ULN
- AST ≤2 x ULN
- Creatinine ≤1.5 x ULN
- Hgb ≥9.0 g/dL

3.25 Willingness to return to Mayo Clinic Rochester or another participating institution for follow-up. Patients who are randomized to Arm B (cytotoxic chemotherapy) may receive chemotherapy at any oncology clinic able to provide the protocol-directed therapy and willing to send laboratory data to the participating institution; however, patients must be willing to return to the participating institution every two months for evaluation. Patients who are randomized to Arm A must be willing to receive all treatment and follow-up at a participating institution.

3.26 Life expectancy ≥12 weeks.

3.27 Willingness to provide all biologic specimens as required by the protocol.

3.28 Measurable disease by RECIST criteria (see Section 11.0), or evaluable disease by CA-125. (NOTE: CA-125-evaluable disease is defined as serum CA-125 ≥2 x ULN that is determined by the treating clinician to be due to recurrent ovarian, fallopian tube, or primary peritoneal cancer.)

3.29a Normal cardiac function, as determined by LVEF ≥ institutional lower limit of normal on echocardiogram or MUGA ≤1 month prior to registration.

3.29b If DOXIL is selected as the investigator's choice chemotherapy:

- Lifetime exposure to doxorubicin ≤240 mg/m^2 (or equivalent biologic dose if prior exposure to a different anthracycline).

3.29c Candidate for surgical placement of an intraperitoneal port, as determined by a gynecologic oncology surgeon.

3.29d Must have anti-measles immunity as demonstrated by serum IgG anti-measles antibody levels of ≥1.1 EU/ml as determined by BioPlex Measles IgG multiplex flow immunoassay

3.3 Registration/Randomization - Exclusion criteria

3.31 Epithelial tumors of low malignant potential, stromal tumors, and germ cell tumors of the ovary.

3.32 Evidence of measurable disease (per RECIST 1.1) outside of the peritoneal cavity (ex: mediastinal lymphadenopathy, parenchymal liver metastasis, or symptomatic pleural effusion proven or suspected to be due to cancer).
Note: Asymptomatic pleural effusion with or without minimal pleural involvement as long as there is no measurable disease outside the peritoneum/retroperitoneum is allowed.

3.33 Bulky metastases, defined as any tumor nodule or lymph nodes >5 cm in greatest dimension on axial images on pre-treatment CT, PET/CT, or MRI.
Note: Patients with bulky (>5 cm) disease for whom gross total cytoreduction is deemed feasible by a surgeon (with confirmation by a second surgeon after radiologic review) are eligible for participation in the context of cytoreductive surgery.

3.34 Resistant to <u>all</u> of the following: DOXIL, GEM, TOPA, and weekly TAXOL.
(NOTE: Resistance is defined as either
1) less than a complete response to any chemotherapy regimen containing the agent in question (consider weekly TAXOL as a separate agent from every-three-week TAXOL),
2) serum CA-125 ≥2 x ULN within 180 days of last dose of chemotherapy containing the agent in question, confirmed by a second CA-125 (the second CA-125 does not have to be within 180 days of chemotherapy), or
3) CT or PET/CT evidence of cancer recurrence/progression within 180 days of last dose of chemotherapy containing the agent in question. (For example, if a patient previously received carboplatin and GEM, had a complete response, and had initial evidence of relapse >180 days after the last dose of GEM, that patient would not be considered resistant to GEM.))

3.35 ECOG performance status (PS) of 3 or 4.

3.36 History of other malignancy ≤5 years prior to registration except for non-melanoma skin cancer, carcinoma *in situ* of the cervix, and DCIS.

3.37 Active infection ≤7 days prior to study entry.

3.38 Any of the following prior therapies:
- Chemotherapy ≤3 weeks prior to study entry
- Immunotherapy ≤4 weeks prior to study entry
- Biologic therapy ≤4 weeks prior to study entry
- Extensive abdominal surgery if it includes enterotomy(ies) ≤3 weeks prior to study entry. (NOTE: This criterion does not apply to placement of the peritoneal Port-A-Cath or lysis of adhesions at the time of study entry.)
- Any viral or gene therapy prior to study entry

3.39a Failure to recover to ≤Grade 1 from acute, reversible effects of prior chemotherapy, excluding alopecia regardless of interval since last treatment. (NOTE: Patients with residual peripheral neuropathy are allowed.)

3.39b New York Heart Association classification III or IV congestive heart failure, known symptomatic coronary artery disease, symptoms of coronary artery disease on systems review, or known cardiac arrhythmias (atrial fibrillation or SVT).

3.39c Other cardiac or pulmonary disease that, at the investigator's discretion, can impair treatment safety.

3.39d CNS metastases or seizure disorder.

3.39e HIV-positive test result, or history of other immunodeficiency.

3.39f History of organ transplantation.

3.39g History of chronic hepatitis B or C.

3.39h Other concurrent chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered investigational (utilized for a non-FDA-approved indication and in the context of a research investigation).

3.39i Any concurrent medications which could interfere with the trial.

3.39j History of tuberculosis or history of PPD positivity.

3.39k Treatment with oral/systemic corticosteroids, with the exception of topical or inhaled steroids or steroids given for the purpose of adrenal replacement given at physiologic doses.

3.39l Exposure to household contacts ≤15 months old or household contact with known immunodeficiency.

3.39m Allergy to measles vaccine or history of severe reaction to prior measles vaccination.

3.39n Allergy to iodine. (NOTE: This does not include reactions to intravenous contrast materials.)

3.39o Any other pathology or condition which the principal investigator may deem to negatively impact treatment safety.

3.39p On anticoagulation and unable to discontinue temporarily for up to 7 days.

4.0 Test Schedule

4.1 Arm A: MV-NIS

Tests and procedures	Pre-treatment phase				Treatment phase					
	≤28 days prior to regis-tration	≤7 days prior to regis-tration	Surgery (after randomization prior to Cycle 1, Day 1)	After randomization *after* port placement, prior to Cycle 1, Day 1	Cycle 1, Day 3 (±1 day)	Cycle 1, Day 8 (±1 day)	Cycle 1, Day 15 (±1 day)	≤5 days prior to Day 1 of Cycle 2 and every cycle thereafter	≤5 days prior to Day 1 of Cycle 3 and every *other* cycle thereafter	End of treat-ment
History, exam, vital signs, PS, weight				X[9]				X		
Assessment of AEs	X			X[9]				X		
Surgical evaluation[1]	X									
Intraperitoneal port placement and excisional biopsy (+ cytoreduction in patients with bulky disease)			X[10]							
Hematology group[2]: Hb, WBC, ANC, ALC, Plt		X						X		
Chemistry group[3]: Cr, AST, AP, Tbili		X		X[9]				X		
Coagulation panel[4]: PT, apTT, INR	X									
Anti-Measles IgG testing[R]	X									
Chest X-ray	X									
Tumor imaging CT abdomen/pelvis or PET/CT abdomen/pelvis or MRI abdomen/pelvis				X[5,9]					X[5]	
CA-125	X			X[9]				X		
Echocardiogram/MUGA[R]	X									
HIV blood test[R]	X									
Mouth gargle specimen[7,R]				X[9]	X	X		X[11]		
Peritoneal aspirate[7,R]			X		X	X				
Urine sample[7,R]				X[9]	X	X		X[11]		
Research blood tests[7,R]	X			X[9]	X	X	X	X		X
SPECT/CT imaging[8,R]				X[9]	X	X	X[8]	X[8]		
FACT-O questionnaire[6]				X[9]				X		

1. Pre-registration procedure: To determine if peritoneal port placement is feasible.

[FOOTNOTES CONTINUE ON NEXT PAGE]

2. Hb = hemoglobin, WBC = white blood cell count, ANC = absolute neutrophil count, ALC = absolute lymphocyte count, Plt = platelet count
3. Cr = creatinine, AST = aspartate aminotransferase, AP = alkaline phosphatase, Tbili = total bilirubin
4. PT = prothrombin time (including international normalized ratio—INR), aPTT = activated partial thromboplastin time
5. Measurement of indicator lesions. For surveillance during treatment, patients will undergo CT or PET/CT or MRI before every odd cycle (prior to Cycle 3, Cycle 5, etc) until PD. If a patient develops asymptomatic PD and wishes to continue study treatment, another CT or PET/CT or MRI will be performed after one additional cycle. If no further progression is noted, CT or PET/CT or MRI will be performed every other cycle.
6. QOL booklets must be used.
7. For a complete list of research tests, see Section 14. NOTE: Some testing is only done in Rochester.
8. SPECT/CT scans on Cycle 1, Days 15 and 28 will be elective, based on whether there is continued uptake on prior imaging studies. SPECT/CT will only be performed in Cycle 2 if positive imaging is obtained in Cycle 1. In this case, SPECT/CT imaging in Cycle 2 will be timed to correspond to the most positive SPECT/CT in Cycle 1.
9. These evaluations should take place after peritoneal Port placement and ≤7 days prior to initiation of MV treatment (≤14 days for CT/MRI).
10. To be completed per treatment Section 7.11; 4 weeks (±2 week) prior to administration of Cytomel®. A biopsy should be attempted in all patients, if tissue is not found, patient remains eligible. For patients with bulky disease, cytoreduction to no gross residual disease should be attempted; however, if this is not feasible, the patient is still eligible for IP port placement and protocol treatment.
11. Prior to Cycle 2 only.

R. Research-funded

4.2 Arm B: Cytotoxic chemotherapy (non-bulky disease ≤5 cm)

	Pre-treatment phase			Treatment phase				
Tests and procedures	≤28 days prior to regis-tration	≤7 days prior to regis-tration	After randomization, prior to Cycle 1, Day 1[9]	Day 8 of each cycle (±3 days)	Day 15 of each cycle (±3 days)	≤7 days prior to Day 1 of Cycle 2 and every cycle thereafter[12]	≤7 days prior to Day 1 of Cycle 3 and every other cycle thereafter[12]	End of treatment
History, exam, vital signs, PS, weight			X				X	
Assessment of AEs	X		X				X	
Surgical evaluation[1]	X							
Hematology group[2]: Hb, WBC, ANC, ALC, Plt		X	X	X[8]	X[8]	X		
Chemistry group[3]: Cr, AST, AP, Tbili		X	X			X		
Coagulation panel[4]: PT, apTT, INR	X							
Anti-Measles IgG testing[R]	X							
Chest X-ray	X							
CT abdomen/pelvis or PET/CT abdomen/pelvis or MRI abdomen/pelvis[5]			X				X[5]	
CA-125[11]	X		X			X		
Echocardiogram/MUGA	X[R]						X[6]	

	Pre-treatment phase			Treatment phase				
Tests and procedures	≤28 days prior to regis-tration	≤7 days prior to regis-tration	After randomization, prior to Cycle 1, Day 1[9]	Day 8 of each cycle (±3 days)	Day 15 of each cycle (±3 days)	≤7 days prior to Day 1 of Cycle 2 and every cycle thereafter[12]	≤7 days prior to Day 1 of Cycle 3 and every other cycle thereafter[12]	End of treatment
HIV blood test[R]	X							
Research blood tests[7,R]	X		X			X[10]	X[10]	X
FACT-O questionnaire[13]			X				X	

1. Pre-registration procedure: To determine if peritoneal port placement is feasible.
2. Hb = hemoglobin, WBC = white blood cell count, ANC = absolute neutrophil count, ALC = absolute lymphocyte count, Plt = platelet count
3. Cr = creatinine, AST = aspartate aminotransferase, AP = alkaline phosphatase, Tbili = total bilirubin
4. PT = prothrombin time (including international normalized ratio—INR), aPTT = activated partial thromboplastin time
5. Measurement of indicator lesions. For surveillance during treatment, patients will undergo CT or PET/CT or MRI before every odd cycle (Cycle 3, Cycle 5, etc) until PD. If a patient develops asymptomatic PD and wishes to continue study treatment, another CT or PET/CT or MRI will be performed after one additional cycle. If no further progression is noted, CT or PET/CT, or MRI will be performed every other cycle.
6. For patients receiving DOXIL, an echocardiogram or MUGA is required once the patient has received 480 mg/m^2 DOXIL or equivalent and every other cycle thereafter while receiving DOXIL therapy.
7. For a complete list of research tests, see Section 14. NOTE: No research tests are required for Arm B patients in Florida and Arizona.
8. Day 8 and Day 15 Hematology group testing is required only for patients receiving GEM, TAXOL, or TOPA.
9. ≤7 days prior to initiation of treatment.
10. ONLY for patients receiving chemotherapy at Mayo Clinic in Rochester, MN. Prior to Cycle 2, Day 1; After Cycle 2, research blood tests will be performed at the same times as the patient undergoes CT or PET/CT or MRI abdomen pelvis (i.e., before every odd cycle starting with Cycle 3).
11. Not required at non-Mayo visits, but if obtained, CA-125 results are to be submitted even if the test is completed more often.
12. Data may be submitted more often if there are clinic visits where tests and procedures are conducted.
13. QOL booklets must be used. They are completed prior to each cycle of treatment. If an Arm B patient will be receiving treatment without a monthly clinic visit, send extra booklets and stamped return envelopes home with the patient so the patient may complete the questionnaires at the appropriate times and return them to the clinic.

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4.3 Arm B: Cytotoxic chemotherapy (bulky disease >5 cm)

	Pre-treatment phase				Treatment phase				
Tests and procedures	≤28 days prior to regis-tration	≤7 days prior to regis-tration	Surgery (after randomization prior to Cycle 1, Day 1)	After randomization, *after* port placement, prior to Cycle 1, Day 1[9]	Day 8 of each cycle (±3 days)	Day 15 of each cycle (±3 days)	≤7 days prior to Day 1 of Cycle 2 and every cycle thereafter[12]	≤7 days prior to Day 1 of Cycle 3 and every *other* cycle thereafter[12]	End of treatment
History, exam, vital signs, PS, weight				X				X	
Assessment of AEs	X			X				X	
Surgical evaluation[1]	X								
Cytoreductive surgery and excisional biopsy			X[10]						
Hematology group[2]: Hb, WBC, ANC, ALC, Plt		X			X[11]	X[11]	X		
Chemistry group[3]: Cr, AST, AP, Tbili		X		X			X		
Coagulation panel[4]: PT, apTT, INR	X								
Anti-Measles IgG testing[R]	X								
Chest X-ray	X								
CT abdomen/pelvis or PET/CT abdomen/pelvis or MRI abdomen/pelvis				X[5]				X[5]	
CA-125	X			X			X		
Echocardiogram/MUGA[R]	X							X[8]	
HIV blood test[R]	X								
Research blood tests[7,R]	X			X			X[14]	X[14]	X
FACT-O questionnaire[6]				X			X		

1. Pre-registration procedure: To determine if peritoneal port placement is feasible.
2. Hb = hemoglobin, WBC = white blood cell count, ANC = absolute neutrophil count, ALC = absolute lymphocyte count, Plt = platelet count
3. Cr = creatinine, AST = aspartate aminotransferase, AP = alkaline phosphatase, Tbili = total bilirubin
4. PT = prothrombin time (including international normalized ratio—INR), aPTT = activated partial thromboplastin time
5. Measurement of indicator lesions. For surveillance during treatment, patients will undergo CT or PET/CT or MRI before every odd cycle (prior to Cycle 3, Cycle 5, etc) until PD. If a patient develops asymptomatic PD and wishes to continue study treatment, another CT or PET/CT or MRI will be performed after one additional cycle. If no further progression is noted, CT or PET/CT or MRI will be performed every other cycle.
6. QOL booklets must be used. They are completed prior to each cycle of treatment. If an Arm B patient will be receiving treatment without a monthly clinic visit, send extra booklets and stamped return envelopes home with the patient so the patient may complete the questionnaires at the appropriate times and return them to the clinic.

7. For a complete list of research tests, see Section 14. NOTE: No research tests are required for Arm B patients in Florida and Arizona.
8. For patients receiving DOXIL, an echocardiogram or MUGA is required once the patient has received 480 mg/m^2 DOXIL or equivalent and every other cycle thereafter while receiving DOXIL therapy.
9. ≤7 days prior to initiation of treatment.
10. To be completed per treatment Section 7.11; 4 weeks (±2 week) prior to Cycle 1, Day 1. Cytoreduction and biopsy should be attempted in all patients, if tissue is not found or removed, patient remains eligible.
11. Day 8 and Day 15 Hematology group testing is required only for patients receiving GEM, TAXOL, or TOPA.
12. Not required at non-Mayo visits, but if obtained, CA-125 results are to be submitted even if the test is completed more often.
13. Data may be submitted more often if there are clinic visits where tests and procedures are conducted.
14. ONLY for patients receiving chemotherapy at Mayo Clinic in Rochester, MN: Prior to Cycle 2, Day 1; After Cycle 2, research blood tests will be performed at the same times as the patient undergoes CT or PET/CT or MRI abdomen pelvis (i.e., before every odd cycle starting with Cycle 3).

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5.0 Stratification Factors

5.1 Number of control arm regimens to which the patient is resistant (see definition of resistance under Section 3.34): 0 vs. 1 vs. 2 vs. 3.

5.2 ECOG performance status: 0 vs. 1vs. 2.

5.3 Extent of disease at enrollment: ≤2 cm vs. greater than 2 cm but less than or equal to 5 cm vs. >5 cm.

6.0 Registration/Randomization Procedures

6.1 Pre-Registration (Step 1)

6.11 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization 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 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution 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 [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."

6.12 Prior to accepting the pre-registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient pre-registration eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information.

6.13 Pre-registration tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.2 Registration Requirement:

NOTE: Patient case must be evaluated by a gynecologic oncologist prior to registration.

6.21 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization 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/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an 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 [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 A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.27, 14.1 and 17.1).

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

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] 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.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

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

- IRB approval
- patient eligibility

6.25 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.26 Consent and treatment on this protocol must commence at Mayo Clinic Rochester or a participating site under the supervision of a gynecologic oncologist.

6.27 Treatment cannot begin prior to registration. For patients in Arm A, surgery must occur ≤14 days after registration. For patients in Arm B, chemotherapy must

begin ≤14 days after registration in non-Bulky Disease patients, 14-42 days after surgery in Bulky Disease patients.

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

6.29a All required baseline symptoms (see Section 10.5) must be documented and graded**.**

6.29b Blood draw kits will be available on site for patients being treated at Mayo Clinic and will be given or sent to patients being treated at local institutions (Arm B only), as needed.

6.29c Patient questionnaire booklets must be utilized; copies are not acceptable for this submission.

6.3 Randomization Procedures

6.31 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.32 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned in a 2:1 fashion to one of the following treatment groups using the Pocock-Simon dynamic allocation procedure which assigns patients to the arm that minimizes the stratification factor imbalance with 75% probability (28). The procedure has been shown to be able to accommodate a large number of factors (10-20) without difficulty (29). We use the range method and the stratification factors are all assumed to have equal weights.

- Arm A: MV-NIS
- Arm B: Cytotoxic Chemotherapy

6.33 For patients with bulky disease (>5 cm), the study coordinator will assure the surgeon is aware of the arm assignment AFTER debulking so the surgeon knows whether to place the intraperitoneal port or whether to proceed with surgical closure. See Appendix V.

7.0 Protocol Treatment

There are different surgical procedures post-registration depending on bulky vs non-bulky disease, thus patients with bulky disease will be unblinded post biopsy and debulking. Upon surgeon notification of arm assignment, those on Arm A will undergo port placement prior to surgical closure (see Section 7.122) and those on Arm B will undergo surgical closure (see Section 7.222).

7.1 Treatment schedule – Arm A (MV-NIS)

7.11 Pre-Registration

7.111 Patients with non-bulky disease will be evaluated for intraperitoneal port placement by a gynecologic oncologist.

7.112 Patients with bulky disease will be evaluated for cytoreductive surgery and intraperitoneal port placement by a gynecologic oncologist. If deemed a candidate for surgery, a second gynecologic oncologist must review imaging studies and concur that surgery is appropriate.

7.12 Post-Registration

7.121 Patients with non-bulky disease will have surgery for biopsy and intraperitoneal port placement. A waiting period of 4 weeks (±2 weeks) will commence prior to receipt of Cytomel®.

7.122 Patients with bulky disease will undergo surgery for biopsy and debulking. Patients will undergo intraperitoneal port placement prior to surgical closure. A waiting period of 4 weeks (±2 weeks) will commence prior to receipt of Cytomel®.

Pre-medication Prior to Administration of MV-NIS			
Agent	**Dose**	**Route**	**Day**
Cytomel®*	0.025 mg	1 tablet three times a day	Day -7 through day of last SPECT/CT scan

*For a patient who is receiving thyroid replacement (e.g., levothyroxine), discuss the case with Endocrinology prior to administering Cytomel®. It may be appropriate to reduce or omit Cytomel® for patients receiving thyroid replacement to avoid thyrotoxicosis.

MV-NIS Administration				
Agent	**Dose**	**Route**	**Day**	**Re RX**
MV-NIS	10^9 TCID50	IP	1	q 4 wks
After MV-NIS Administration				
^{123}I	5 mCi (±10%)	Oral	Day 3 and 8 of study (2 additional doses may be given for imaging based on imaging results)	

7.123 Patients will receive Cytomel® to prevent thyroid uptake when repeated imaging doses of ^{123}I are administered.

7.124 The *in vivo* distribution of MV-NIS infected cells and the kinetics of virus spread and elimination will be monitored by SPECT/CT imaging of the abdomen and pelvis after oral ^{123}I administration (2 hours after a range of –5 mCi, ±10%).

SPECT/CT imaging (i.e. abdomen and pelvis) will be performed on Days3 and 8 after MV-NIS administration. In addition patients may be imaged on Days 15 and 28. These scans will be elective, based on whether there is continued uptake on prior imaging studies. Imaging by SPECT/CT is to be performed in Cycle 2 only if positive imaging is obtained in Cycle 1. In this case, SPECT/CT imaging in Cycle 2 will be timed to correspond to SPECT/CT in Cycle 1.

7.125 The virus will be administered through intraperitoneal port that will be surgically placed at the time of study entry. If ascites is present, it will be drained through the intraperitoneal port prior to administration of MV-NIS. The patient will receive an infusion of the assigned dose of MV-NIS diluted in 500 ml of NS over 30 minutes. Treatment will be administered at the Clinical Research and Trials Unit (CRTU).

7.126 In Rochester, patients will be admitted the evening prior to administration and dismissed 24 hours after administration of the agent. For the first cycle, patients should be observed for at least 8 hours after administration. Patients who are not local will need to stay in town overnight to ensure no subacute issues arise.
For subsequent cycles, the agent will be administered in the outpatient setting and the patients will be observed in the facility for at least one hour and up to three hours after administration of the agent.
A saline lock for IV access, if necessary, will be placed prior to viral administration.

7.2 Treatment schedule – Arm B

7.21 Pre-Registration

7.211 Patients with non-bulky disease will be evaluated for intraperitoneal port placement by a gynecologic oncologist.

7.112 Patients with bulky disease will be evaluated for cytoreductive surgery and intraperitoneal port placement by a gynecologic oncologist. If deemed a candidate for surgery, a second gynecologic oncologist must review imaging studies and concur that surgery is appropriate.

7.22 Post-Registration

7.221 Patients with non-bulky disease will not be subject to a waiting period and may start treatment within 7 days post-registration/randomization but no later than 14 days.

7.222 Patients with bulky disease will undergo surgery for biopsy and debulking. After completion of debulking, patients will NOT undergo intraperitoneal port placement and will simply have surgical closure. A waiting period of 4 weeks (±2 weeks) will commence prior to receipt of chemotherapy.

7.223 Treatment is with one of the following agents: liposomal doxorubicin, gemcitabine, topotecan, or paclitaxel, as selected by the treating

investigator. Premedications may be adjusted after Cycle 1, Day 1 at the discretion of the treating investigator. The treating investigator may select any of the four treatment options to which a patient is not already resistant based on clinical judgment or based on chemotherapy sensitivity assays, including participation in a clinical trial using tumor xenografts to predict chemotherapy sensitivity.

7.224 A patient may not begin study on one treatment and switch to a different treatment. If the clinician determined the selected treatment is not beneficial to the patient, the patient will go off treatment for the purposes of this study and will be followed per protocol (see Section 13.61).

7.23 Information per Treatment Agent

7.231 Liposomal Doxorubicin

7.2311 Pretreatment

Agent	Dose	Route	Day
Dexamethasone*	10-20 mg	PO (preferred) or IV	1

*Dexamethasone is optional at the discretion of the treating investigator. Default is to omit.

7.2312 Protocol treatment

Agent	Dose	Route	Day	Retreatment
Liposomal Doxorubicin (DOXIL)	40 mg/m^2	IV*	1	Every 28 days.

*In 250 ml D5W over one hour. Initial rate is 1 mg/min and increased after the first 30 minutes of uneventful observation to be completed over 1 hour.

7.232 Gemcitabine

7.2321 Pretreatment

Agent	Dose	Route	Day
Dexamethasone*	Per institutional standard of care	PO (preferred) or IV	1, 8, 15

*Dexamethasone is optional at the discretion of the treating investigator. Default is to omit.

7.2322 Protocol treatment

Agent	Dose	Route	Day	Retreatment
Gemcitabine (GEM)	1000 mg/m^2	IV*	1, 8, 15	Every 28 days.

*Round to nearest 100 mg. Give in 250 mL 0.9 Normal Saline IV infusion over 30 minutes.

7.233 Topotecan

7.2331 Pretreatment

Agent	Dose	Route	Day
Dexamethasone*	Per institutional standard of care	PO (preferred) or IV	1, 8, 15

*Dexamethasone is optional at the discretion of the treating investigator. Default is to omit.

7.2332 Protocol treatment

Agent	Dose	Route	Day	Retreatment
Topotecan (TOPA)	4 mg/m^2	IV*	1, 8, 15	Every 28 days.

*In 100 ml D5W or 0.9 Normal Saline IV infusion over 30 minutes.

7.234 Paclitaxel

7.2341 Pretreatment

Agent	Dose	Route	Day
Dexamethasone	20 mg	IV*	1
Dexamethasone	10 mg	IV*	8, 15
Famotidine	20 mg	IV*	1, 8, 15
Diphenhydramine	50 mg	IV*	1
Diphenhydramine	25 mg	IV*	8, 15

*Give 15 minutes before paclitaxel.

7.2342 Protocol treatment

Agent	Dose	Route	Day	Retreatment
Paclitaxel (TAXOL)	80 mg/m^2	IV*	1, 8, 15	Every 28 days.

*In 250 ml 0.9% Normal Saline IV infusion over 1 hour.

7.235 Bevacizumab

Bevacizumab may be added to liposomal doxorubicin, topotecan, or paclitaxel, NOT gemcitabine

7.2351 Pretretment - None

7.2352 Protocol treatment

Agent	Dose	Route	Day	Retreatment
Bevacizumab (BEV)	10 mg/kg	IV	1, 15	Every 28 days.

8.0 Dosage Modification Based on Adverse Events

For Arm A, strictly follow the modifications in this table until individual treatment tolerance can be ascertained. For Arm B (all FDA-approved therapies), the dose modifications are suggestions, and actual dose modification will be performed at the discretion of the treating provider. (The treating provider does not need to be from the consenting site for patients randomized to Arm B.) If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Dose modifications apply to the treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

8.1 Criteria for dose delays, dose modifications, and treatment discontinuation

ALERT: *ADR reporting may be <u>required</u> for some adverse events. See Section 10.0*

→ Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified ←

CTCAE CATEGORY	ADVERSE EVENT	AGENT(S)	DOSE MODIFICATIONS
BASED ON INTERVAL ADVERSE EVENT (Day 8 or Day 15)			
Investigations	Platelet count decreased Grade 2+: <75,000 Neutrophil count decreased Grade 3+: <1,000	GEM, TOPA, or TAXOL	Omit treatment until ≤Grade 1, then ↓ by one dose level. If no recovery to ≤Grade 1 after 21 days, then discontinue treatment and follow up per Section 18.
*All other non-hematologic categories**	Nonhematologic Grade 3		Omit treatment until ≤Grade 1, then ↓ by one dose level. If no recovery to ≤Grade 1 after 14 days, then discontinue treatment and follow up per Section 18.
	Grade 4		Discontinue treatment and follow up per Section 18.
AT SCHEDULED RETREATMENT (e.g. Day 1 of subsequent cycle)			
Investigations	Platelet count decreased 75,000-100,000 Neutrophil count decreased Grade 2: 1,000-1,500	DOXIL, GEM, TOPA, TAXOL, or MV-NIS	Hold treatment until ≤Grade 1 and platelet count >100,000. If this is the first treatment delay for a patient at this dose level, then it is acceptable to continue this dose level *or* ↓ by one dose level (at the discretion of the treating investigator). If this the second treatment delay, then ↓ by one dose level. If no recovery to ≤Grade 1 after 14 days, then discontinue treatment and follow up per Section 18.
	Platelet count decreased Grade 2+: <75,000 Neutrophil count decreased Grade 3+: <1,000		Hold treatment until ≤Grade 1, then ↓ by one dose level. If no recovery to ≤Grade 1 after 14 days, then discontinue treatment and follow up per Section 18.
*All other non-hematologic categories**	Nonhematologic Grade 3		Hold treatment until ≤Grade 1, then ↓ by one dose level. If no recovery to ≤Grade 1 after 14 days, then discontinue treatment and follow up per Section 18.
	Grade 4		Discontinue treatment and follow up per Section 18

CTCAE CATEGORY	ADVERSE EVENT	AGENT(S)	DOSE MODIFICATIONS
Viremia	Any	MV-NIS	Hold treatment until viral titer undetectable and recheck weekly, then ↓ by one dose level. If no recovery to undetectable after 14 days, then discontinue treatment and follow up per Section 18.

*Dose modification for nausea and vomiting will be implemented only if they persist despite optimal antiemetic treatment.

8.2 Dose levels

Agent	Initial treatment (dose level 0)	First dose reduction (dose level -1)	Second dose reduction (dose level -2)	Third dose reduction (dose level -3)
DOXIL*	40 mg/m^2	30 mg/m^2	20 mg/m^2	Discontinue treatment
GEM*	1000 mg/m^2	750 mg/m^2	500 mg/m^2	Discontinue treatment
TOPA*	4 mg/m^2	3 mg/m^2	2 mg/m^2	Discontinue treatment
TAXOL*	80 mg/m^2	60 mg/m^2	40 mg/m^2	Discontinue treatment
MV-NIS	10^9 TCID50	10^8 TCID50	10^7 TCID50	Discontinue treatment

*For Arm B patients, the above dose levels are suggestions. Dose modifications will be initiated by the treating provider.

9.0 Ancillary Treatment

9.1 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.

9.2 Antiemetics and Antidiarrheals

Prophylactic administration of antiemetics or antidiarrheals prior to Cycle 1 Day 1 of treatment will not be allowedfor patients on Arm A. However, antiemetics and/or antidiarrheals may be given prior to all other treatments should a patient develop nausea/vomiting/diarrhea associated with treatment.

Acceptable treatment options for nausea/vomiting include:

- ondansetron 4-8 mg po q 8 hours prn or 4 mg IV q 8 hours prn
- granisetron 1 mg po q 12 hours prn or 10 mcg/kg q 12 hours prn
- prochlorperazine 5-10 mg po q 6-8 hours prn, 25 mg rectally bid prn, or 2.5-5 mg IV by slow infusion (5 mg/min) q 6 hours prn
- lorazepam 0.5-2 mg po q 4-6 hours prn
- **Dexamethasone as an antiemetic is not allowed for patients on Arm A.**

Acceptable treatment options for diarrhea include:

Loperamide 4 mg after first diarrheal bowel movement and 2 mg after each subsequent one up to 16 mg a day and atropine sulfate/diphenoxylate hydrochloride (Lomotil) 2 tab q 6 hours prn or 10 ml q 6 hours prn.

Acceptable treatment options for fever include acetaminophen 500 mg 1-2 tabs q 4-6 hours prn up to 4 grs a day and NSAIDs, such as ibuprofen 400 mg q 4-6 hours prn or naproxen 250-500 mg bid.

9.3 Bevacizumab infusion reactions

If a patient develops an infusion reaction to bevacizumab, the patient may be treated with acetaminophen 650 mg by mouth every 4 hours as needed for fever, diphenhydramine 25 mg by mouth every 4 hours as needed for infusion reactions (may repeat after 15 minutes if first dose ineffective), and meperidine 25 mg IV every 15 minutes as needed for rigors (maximum dose 50 mg).

9.4 Measles - diagnosis

Diagnosis of measles in this trial is based on the CDC definition of clinical measles and includes:

- a generalized rash lasting ≥3 days, and
- temperature ≥38.3°C (≥101°F), and
- cough, coryza, and conjunctivitis.

9.5 Measles - treatment

Should a patient develop measles, treatment with immune globulin will be administered 400 mg/kg/d for 3-5 days. Aerosolized ribavirin (6 gr/d) can also be considered at the discretion of the treating physician for patients not responding to immune globulin. Patients who develop measles will be removed from the trial and followed up to 15 years for evidence of persistent toxicity.

9.6 Co-enrollment in other trials

Patients randomized to Arm A are not to be considered for enrollment in any other study involving a pharmacologic agent (drugs, biologics, immunotherapy approaches, gene therapy) during enrollment on MC1365, whether for symptom control or therapeutic intent. Patients randomized to Arm B may be considered for concurrent enrollment in other studies of pharmacologic agents for symptom control, but not in studies of pharmacologic agents for therapeutic intent.

9.7 Echocardiogram/MUGA for DOXIL Treatment

Patients receiving DOXIL must undergo an echocardiogram or MUGA upon reaching a lifetime doxorubicin dose of 480 mg/m^2 (or equivalent amount when added with other anthracyclines), and every other cycle thereafter. Left ventricular ejection fraction (LVEF) must be within normal limits to continue DOXIL.

10.0 Adverse Event (AE) Reporting and Monitoring

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 web site:

[redacted]

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (refer to Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.5). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

NOTE: "Unexpected adverse experiences" means any adverse experience that is not identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

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.

10.4 Expedited Reporting Requirements for IND/IDE Agents

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [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.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported 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 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[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

Additional instructions:

1. Use Mayo Clinic Cancer Center Electronic *Serious Adverse Event Reporting Form* [redacted]
2. Provide copies to [redacted] by email
3. The MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

10.5 Required Routine Reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

Category	Adverse events/Symptoms	Baseline	Each evaluation
General Disorders and Administrative Site Conditions	Fever	X	X
	Chills	X	X
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X
	Palmar-plantar erythrocysesthesia syndrome	X	X
Gastrointestinal disorders	Diarrhea		X
	# of stools	X	
	Flatulence	X	X
	Nausea	X	X
	Vomiting	X	X
	Enterocolitis infectious	X	X
Respiratory, thoracic and mediastinal disorders	Dyspnea	X	X
Neurologic disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X
Cardiovascular disorders	Left ventricular systolic dysfunction	X	(once the patient reaches a lifetime cumulative dose of DOXIL of 480 mg/m^2, then every other cycle thereafter)

10.51 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 10.5:

10.511 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

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

10.513 Grade 5 AEs (Deaths)

10.5131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5132 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.

11.0 Treatment Evaluation

For the purposes of this study, patients should be re-evaluated every 8 weeks. Modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria will be used.

11.1 Definitions

11.11 Measurable disease: the presence of at least one measurable lesion.

11.12 Measurable lesions: lesions that can be accurately measured in at least one dimension with longest diameter >20 mm. With spiral CT scan, lesion must be >10 mm in at least one dimension.

11.13 Non-measurable lesions: all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT) and other non-measurable lesions. These include: ascites; abdominal masses that are not confirmed and followed by imaging techniques; and cystic lesions.

11.2 Response Criteria

11.21 Evaluation of target lesions

A maximum of 4 (two per organ) measurable lesions should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Complete Response (CR):	Disappearance of all target lesions and normalization of CA125 if elevated at baseline.
Partial Response (PR):	At least 30% decrease in the sum of the longest diameter (LD) of target lesion taking as reference the baseline sum LD
Progression (PD):	As least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD

11.22 Evaluation of non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as “present” or “absent.”

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor maker level
Non-Complete Response: (non-CR):	Persistence of one or more non-target lesions or/and maintenance of tumor marker level above the normal limits

Progression (PD):	Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Notes:

- If tumor markers are measured and are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- Cytology and histology

  If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

  The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.23 Evaluation of response by CA-125

11.231 CA-125 should ***not*** be used in evaluating response to therapy unless there is no measurable or evaluable disease by imaging criteria as defined above.

11.232 If a patient has no measurable or evaluable disease by imaging criteria, responses are defined as follows:

Complete Response (CR):	Normalization of CA-125
Partial Response (PR):	At least 50% decrease in CA-125
Progression (PD):	As least a 50% increase in CA-125
Stable Disease (SD):	Neither sufficient decrease in CA-125 to qualify for PR nor sufficient increase to qualify for PD

11.24 Evaluation of best overall response

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

Target Lesions	Non-Target Lesions	New Lesions	**Overall Response**
CR	CR	No	**CR**
CR	Non-CR/Non-PD	No	**PR**
PR	Non-PD	No	**PR**
SD	Non-PD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

Notes:
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

11.3 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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

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

- Conventional **CT and MRI** should be performed with cuts of 10mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis.

11.4 Duration of response

11.41 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

11.42 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

12.0 Descriptive factors

12.1 Serous histology: Yes vs. No.

12.2 Prior bevacizumab: Yes vs. No.

12.3 Measurable disease: Yes vs. No.

13.0 Treatment/ Follow-up Decision at Evaluation of Patient

13.1 Patients will be treated until PD.

13.2 Patients who have not had PD at time of their reassessment and have not experienced intolerable toxicity will be allowed to continue protocol treatment at the same dose level until PD.

13.3 Those patients who have not had PD but have experienced unacceptable toxicity may be eligible for retreatment at a lower dose (see Section 8.0).

13.4 Patients with PD but no progression of cancer-related symptoms may continue study treatment (either Arm) for one additional cycle at the discretion of the treating investigator followed by restaging studies. If the new imaging and/or CA-125 do not demonstrate additional PD, then patients may continue protocol treatment and will revert to the disease evaluation plan detailed in Section 4.0. (The imaging and/or CA-125 that initially demonstrated PD will serve as a new baseline going forward.) If the new imaging and/or CA-125 demonstrate additional PD, then patients will go off treatment and will be followed as described in Section 18.1.

13.5 Those patients who have had PD with progression of cancer-related symptoms will go off treatment and will be followed as described in Section 18.1.

13.6 Off-Study Criteria

13.61 Those patients who refuse further treatment, or are on Arm B and will be changing treatment regimens, will go off treatment and will be followed for the purpose of this study as described in Section 18.1.

13.62 A *screen failure* is a consented subject that has not been registered/randomized and fails to satisfy eligibility criteria or has decided not to continue treatment (either on their own behalf or under the direction of their physician).

- All materials required for pre-randomization and a Screen Failure CRF will be submitted.

13.63 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 event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility 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. Event monitoring will be required per Section 18.0 of the protocol.

13.64 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 event-monitoring 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.

13.65 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. The patient will go directly to the event-monitoring phase of the study, and event monitoring will be required per Section 18.0 of the protocol.

14.0 Pharmacologic/Correlative Studies

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

14.11 **Arm A: MV-NIS**

Assessment	Mandatory or optional	Blood or body fluid being collected	Volume to collect per tube	Prior to registration	≤7 days prior to Cycle 1, Day 1	Cycle 1, Days 3 and 8	Cycle 1, Day 15	≤5 days prior to Day 1 each subsequent cycle	End of treatment	Storage
Immunologic[1]	Mandatory	Blood	Variable	5 mL (1x5 mL red top tube)	20 mL (2x10 mL red top tubes)			5 mL (1x5 mL red top tube)	5 mL (1x5 mL red top tube)	Ambient
Immunologic[1]	Mandatory	Blood	Variable	60 mL (6x10 mL green top tubes or 1x60 mL heparin syringe)	180 mL (18x10 mL green top tubes or 3x60 mL heparin syringes)	10 mL (1 x 10 mL green top tube)	10 mL (1 x 10 mL green top tube)	60 mL (6x10 mL green top tubes or 1x60 mL heparin syringe)	60 mL (6x10 mL green top tubes or 1x60 mL heparin syringe)	Ambient
Viral	Mandatory	Blood	5 mL		5 mL (2 x 2.5mL PAXgene tubes)	5 mL (2 x 2.5mL PAXgene tubes)	5 mL (2 x 2.5mL PAXgene tubes)	5 mL (2 x 2.5mL PAXgene tubes)[4]	5 mL (2 x 2.5mL PAXgene tubes)	Ambient
Viral[1]	Mandatory	Urine	50 mL		X	X		X[4]		Frozen -80°C after processing and adding Trizol at CRTU
Viral[1]	Mandatory	Mouth gargle	50 mL		X	X		X[4]		Frozen -80°C after processing and adding Trizol at CRTU
Viral[1]	Mandatory	Peritoneal fluid[2]	500 mL		X[3]	X				On ice after draw

1. Rochester only: This testing will *only* be done for patients seen in Rochester MN.
2. *Before* administering MV-NIS, attempt to aspirate 500 ml of peritoneal fluid. If less than 100 ml of fluid can be aspirated, add 1000 ml of 0.9 normal saline intraperitoneally and re-attempt to aspirate up to 500 ml of peritoneal fluid. NOTE: If aspiration was attempted and no aspirate was obtained, it is not a deviation.
3. Use peritoneal fluid obtained at the time of port placement for this instance (≤7 days prior to Cycle 1, Day 1) only.
4. Prior to Cycle 2 only.

14.12 **Arm B: Cytotoxic Chemotherapy – Rochester only**

Assessment	Mandatory or optional	Blood or body fluid being collected	Volume to collect per tube	Prior to registration	≤7 days prior to Cycle 1	Prior to Cycle 2 (Only for Pts treated at Mayo Clinic)	≤7 days prior to Day 1 of Cycle 3 and every ***other*** cycle thereafter[2]	End of treatment	Storage
Immunologic[1]	Mandatory	Blood	Variable	5 mL (1x5 mL red top tube)	20 mL (2x10 mL red top tubes)	5 mL (1x5 mL red top tube)	5 mL (1x5 mL red top tube)	5 mL (1x5 mL red top tube)	Ambient
Immunologic[1]	Mandatory	Blood	Variable	60 mL (6x10 mL green top tubes or 1x60 mL heparin syringe)	180 mL (18x10 mL green top tubes or 3x60 mL heparin syringes)	60 mL (6x10 mL green top tubes or 1x60 mL heparin syringe)	60 mL (6x10 mL green top tubes or 1x60 mL heparin syringe)	60 mL (6x10 mL green top tubes or 1x60 mL heparin syringe)	Ambient

1. Rochester only: This testing will *only* be done for patients seen in Rochester, MN.
2. After Cycle 2, research blood tests will be performed at the same times as the patient undergoes imaging for their cancer (i.e., before every odd cycle starting with Cycle 3)

14.2 Shipping and Handling

14.21 **Samples collected in CRTU (Rochester) will be processed and held perTables 14.11and 14.12** until picked up by

[redacted]

14.22 Samples collected at Mayo Clinic in Florida or Arizona will be shipped overnight:

- PAXgene blood tubes – room temperature overnight shipping

[redacted]

14.3 Background and Methodology

(Protocols for assays conducted by Mayo Clinic Department of Laboratory Medicine not included).

The goals of the immunologic studies is to determine whether an immune measurement or tissue marker can predict increased clinical benefit from MV-NIS treatment relative to cytotoxic chemotherapy, and to determine how MV-NIS impacts the endogenous immune response to OC.

14.31 Interferon gamma (IFN-γ) ELISpot Assay

ELISpot Assays measure the frequency of responding antigen-specific T cells per unit of peripheral blood mononuclear cells (PBMCs). On Day 1, 2.5 x105 PBMCs/well will be plated into 96-well plates in 3-well replicates in 200 mcl of RPMI-1640 containing 10% human AB serum (T-cell medium) in the presence or absence of 10 mcg/ml peptide antigen. The cells will be incubated at 37°C. For the 10 day assay, IL-2 (Zeptometric, Inc. Buffalo, NY) will be added to 10 U/ml on day 5. On Day 8, 2.5 x 105/well irradiated autologous PBMCs and 10 mcg/ml antigens (folate receptor alpha—FRα, HER-2, IGFBP2, p53, NY-ESO-1, mesothelin, and MV) will be added. On day 9, the cells are then transferred to an anti-IFN-γ−coated nitrocellulose (NC)-plate (Millipore Corporation, Bedford, MA). The NC-plate will be incubated (37°C) for a further 20–24 hours followed by washing three times using PBS containing 0.05% Tween-20. Alternatively, for the 3 day assay, antigens will be added on day 1. For both assays, once incubation with antigen is complete, the plate will be incubated for 2.5 hours at RT in PBS with 5 mcg/ml biotinylated anti–IFN-γ Ab, washed in PBS, and further incubated with 100 mcl/well avidin-horseradish peroxidase (HRP, Vector Laboratories, Burlingame, CA)) for 2 hours at room temperature. The anti-IFN-γ and biotinylated anti-IFN-γ antibody pair will be obtained from Mabtech (Sweden). After 3 washes in PBS, the plate will be incubated with 100 mcl/well HRP-colorimetric substrate (BD Biosciences) for 20 minutes, rinsed with cool tap water, and allowed to dry completely. The nitrocellulose plates will be read on an AID ELISpot reader (Cell Technology, Inc., Columbia MD, reader software v.3.1.1.). A positive response is defined as a frequency that is significantly ($p<0.05$, two-tailed t test) greater than the mean of control no-antigen wells and detectable (i.e., >1:100,000). We will test responses to media (negative control), phorbol 12-myristate 13-acetate (PMA) and ionomycin (positive control), Candida, Influenza vaccine, folate receptor alpha (FRα), and insulin-like growth factor receptor binding protein two (IGFBP2).

14.32 Multiplexed Cytokine Analysis

Antigen-specific cytokine profiles will also be examined to determine the skewing of the T cell response. PBMCs (4×10^5) will be cultured in 200 mcl medium (RPMI 1640 medium plus 10% FBS plus 1% penicillin/streptomycin/ glutamine) containing the immune stimulus of interest (or media alone) in duplicate wells of a microtiter plate. The PBMCs will be incubated at 37°C in 5% CO_2 for 48 h; the supernatants subsequently harvested, transferred to a storage plate, and frozen at –80°C for later analysis. A panel of 17 cytokines and chemokines will be analyzed using a multiplexed approach with commercially available human 17-plex kits. The following cytokines will be assessed: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, CXCL8 (IL-8), IL-10, IL-12, IL-13, IL-17A, IFN-γ,

TNF-α, CCL2 (MCP-1), CCL4 (MIP-1β), G-CSF, and GM-CSF. A customized platform obtained from Meso Scale Discovery (Gaithersburg, MD) will be used to determine the cytokine concentrations using the Sector 2400 instrument (Meso Scale Discovery). Cytokine concentrations will be determined based on a standard curve generated on each plate using the manufacturer-supplied reagents.

14.33 Enzyme-linked immunosorbent assay (ELISA)

Antibodies are a key aspect of immune responses to tumors. Antigen (10 mcg/well) will be prepared in 0.06 M carbonate buffer and added to ELISA microtiter plates for 24 hours. Antigens will include media (negative control), Candida, Influenza vaccine, FRα, IGFBP2, tetanus, keyhole limpet hemocyanin (KLH), and p53. Antigens to be tested include Plates will be washed with PBS and blocked with 3% BSA-PBS. One hundred microliters of diluted sera (1:100 for peptide and 1:40 for tetanus toxoid in 1%BSA-PBS) will be added and the plates further incubated for 24 hr followed by washing with PBS/0.1% Tween-20. A 1:2000 dilution of anti-IgG-HRP is then added to wells for 1 hour followed by washing and color development after adding 100 mcl TMB (3,3',5,5' tetramethylbenzidine) substrate to the wells. Color development is stopped with 50 mcl of a 0.1N HCl solution. For the standard curve, serial dilutions of human IgG will be added to separate wells. Optical densities will be read on a Softmax Pro multiplate reader. A treatment-induced increase in OC antigen-specific antibody responses will be defined as (1) a 2-fold or greater increase in OC antigen-specific antibody at any point during treatment if there were detectable pre-treatment levels of OC antigen-specific T cells or (2) OC antigen-specific antibodies at any point during treatment if pre-treatment levels of OC antigen-specific antibodies are non-detectable.

14.34 Detection and quantitation of MV nucleoprotein mRNA from blood, urine, and mouth gargle specimens

Assessment of viremia and viral shedding.

Patient's peripheral blood mononuclear cells will be monitored for evidence of measles virus viremia. This will be performed by collecting 2.5 ml of blood in PAXgene Blood RNA tubes (2 tubes per each time point draw) according to the manufacturer's recommendations (Qiagen). The PAXgene Blood RNA tube, is part of a system used to collect blood for RNA extraction ona proprietary reagent that immediately stabilizes intracellular RNA for three days at room temperature (18 to 25C) and five days when kept in a regular fridge (2 to 8C).

Viral shedding will be assessed by quantitative RT-PCR of throat gargle specimens(s) and urine samples, both being processed under sterile conditions at CRU. Testing will be performed [redacted]

Sample processing in CRTU for viremia and viral shedding will be done using sterile techniques and laminar flow hood. Mouth wash (gargle) samples consist of 2 x 15 ml of commercial Scope® mouth rinsing fluid (or equivalent) that are gargled in the back of the throat (not swished in the mouth) and then are collected in 50 ml sterile conical tubes (a total of 15 ml needs to returned for further processing), spun down at 3000rpm and the supernatant discarded. The remaining pellet is suspended in 1 ml Trizol® reagent (Invitrogen Cat #15596026-100ml, or Cat# 10296028-200ml), mixed well and transferred to

sterile 2 ml cryovials. The samples are kept in a negative 80 freezer until picked up by [redacted] will be notified to pick up the samples.

Urine will be collected by clean catch method in a container set up by nursing, then transferred to sterile 50ml tubes (a maximum of eight tubes will be processed for each time point). The tubes are spun down at 3000 rpm, the supernatant discarded and 1 ml Trizol reagent added to each pellet, mixed well and each pellet transferred to a 2 ml cryovial. The samples processed will be kept in a negative 80 freezer. [redacted] will be notified to pick up the samples.

Quantitative RT-PCR will be performed as previously described (24). Briefly, the quantitative RT-PCR assay was optimized for primers, probe, and magnesium concentration with TaqMan RNA to CT 1-step kit.. A 50-µL quantitative RT-PCR reaction volume will be used to amplify the MV-N genomic RNA target, in the presence of 0.3 mmol/L each of forward (5′-GGG TGT GCC GGT TGG A-3') and reverse (5′-AGA AGC CAG GGA GAG CTA CAG A-3') -primers, 0.2 mmol/L Black Hole Quencher–labeled probe (5′-/56-FAM/TGG GCA GCT CTC GCA TCA CTT GC/ 3BHQ_1/-3′), 4 mmol/L MgCl, and 1 mcg or a maximum total volume of 5 mcl of the RNA isolate. One cycle of reverse transcriptase reaction (15 min at 48°C) will be applied, followed by a denaturation step (10 min at 95°C) and 40 cycles of amplification (15 s 95°C and 1 min 60°C), with fluorescence measured during the extension. A standard curve of 10-fold dilutions containing 10^7 to 10 MV-N gene copies/mL will be generated using a manufactured RNA oligo (IDT) () and having the following sequence: 5′-rGrGrG rUrGrU rGrCrC rGrGrU rUrGrG rArArG rArUrG rGrGrU rArGrC rUrCrU rCrGrC rArUrC rArCrU rUrGrC rUrCrU rGrCrU rGrGrG rCrCrC rGrGrU rUrUrC rUrCrU rGrUrA rGrCrU rCrUrC rCrCrU rGrGrC rGrGrC rUrUrC rU-3′-3′. Quantification and subsequent calculation of copy number will be done using the standard curve and the ROCHE480 Quantitative PCR System software.

14.35 Isolation of cells from peritoneal aspirates and detection of viral replication by Vero cell overlay assay.
After peritoneal fluid is received in the laboratory, cells will be separated from the supernatant by centrifugation. Subsequently, the different cell populations will be separated using a Percoll gradient as previously described (25). The identity of epithelial ovarian carcinoma cells will be confirmed by immunostaining for cytokeratin E1/E3(26, 27). Vero cells will be (American Type Culture Collection) plated at a concentration of 2 × 105 per well and incubated overnight at 37°C. The next day, 103 patient cells isolated from the peritoneal fluid will be added to duplicate wells. SKOV.IP3 or SKOV3 cells infected with MV-NIS at a multiplicity of infection of 1.0, and MV-NIS will be used as positive controls. Plates will be incubated for 5 d and will be examined daily for syncytia formation.

14.36 Transcriptomic analysis of peripheral blood immune cell subsets

Participating patients will be asked to give at least 1, preferably 2 samples of blood - no less than 1 day apart and no more than 4 weeks apart – both draws to be prior to receiving the first dose of treatment.

Peripheral blood (up to 40 ml) will be drawn into heparinized tubes. Procedures will be put into place to ensure immediate pick-up of blood samples: a special studies card will be printed to direct person drawing blood to page the research lab prior to drawing the blood. Lab personnel will retrieve the samples from the blood draw area and hand-carry to the research laboratory in Guggenheim. Samples will be coded and de-identified once they are received in the lab. Blood will be processed immediately: immune cell subsets will be isolated, select subsets will be stimulated ex vivo, and RNA will be purified from these cell subsets. ONLY the final RNA preparations will be stored prior to batch analysis (library construction and sequencing). Library construction, NextGen RNA sequencing, and Bioinformatics processing will be conducted by the Mayo Genomics Facility.

15.0 Drug Information

15.1 **MV-NIS** (NIS-Measles Virus – Edmonston Strain)

MV-NIS is a live, tissue culture adapted measles virus engineered to express the human thyroidal sodium iodide symporter (NIS). The virus was constructed by inserting the NIS gene (cDNA) into a full-length infectious molecular clone of an attenuated Edmonston lineage measles virus (MV-tag). This virus is not a vaccine. MV-NIS propagates on Vero cells with kinetics equivalent to the parental strain of virus. It propagates selectively in human cancer cells that it infects by binding preferentially to CD46, a membrane protein that is overexpressed in tumor cell lines including myeloma. The virus is directly cytopathic to tumor cells leading to the formation of multinucleated syncytia that die by apoptosis. MV-NIS infected tumor cells express NIS, a membrane ion channel that actively transports iodide into cells. Radioiodine uptake by cells expressing NIS provides the basis for in vivo radioiodine imaging that can reveal the profile of MV-NIS gene expression and the location of MV-NIS infected cells during virus spread and elimination.

15.11 Preparation and storage: MV-NIS will be prepared at the Virus and Vector Production Laboratory (VVPL) of the Molecular Medicine Program at Mayo Clinic and stored at -80°C. The virus will be thawed and mixed with normal saline prior to administration. (See Appendix IV)

15.12 Administration: MV-NIS will be administered intraperitoneally (30 minutes) in 500 ml of normal saline under close observation in the Clinical Research Unit.

15.13 Known potential adverse events:

15.131 The most common adverse effect noted is burning and stinging at the site of injection; however, this is not applicable in this study given intraperitoneal administration. Occasionally, moderate fever 38.3°-39.4°C has been noted in the month after vaccination, usually within 5-12 days after injection. Rash, which is usually minimal, has been noted. Less commonly, high fever over 39.4°C or mild lymphadenopathy have been reported.

15.132 Occasional reactions:

- Moderate to high fever lasting 1-2 days, starting within a week or two of the vaccination
- A rash, lasting 1-2 days
- Cough and rhinitis
- Erythema multiforme (skin rash)

15.133 Unexpected and rare reactions associated with measles vaccines:

- Allergic reactions to the vaccine including anaphylaxis
- Reactions at the injection site such as wheal, flare or urticaria
- Thrombocytopenia
- Diarrhea

15.14 Nursing guidelines: Due to the very early investigational nature of this drug, no nursing guidelines are known. Please monitor patients closely and follow Section 10.0. More than 90% of the U. S. population has measles virus immunity as a

result of natural infection or immunization. Immune status for measles virus is mandatory for Mayo Medical Center personnel. Therefore administration of the agent is not expected to result in any risk for nursing or ancillary staff.

15.2 Doxorubicin Liposomal (Doxil®)

15.21 **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.

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

15.23 **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.

15.24 **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 SubQ. 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).

15.25 **Pharmacokinetic information**:
Distribution: V_{dss}: 2.7-2.8 L/m^2
Protein binding, plasma: Unknown; nonliposomal (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)

15.26 **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.

15.27 **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

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

15.29 **Nursing Guidelines:**

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

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

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

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

15.295 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.

15.296 Administer antiemetics to minimize nausea and vomiting.

15.297 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.

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

15.299a Adriamycin may potentiate toxicity of other antineoplastic therapies. It has reportedly exacerbated Cyclophosphamide (Cytoxan, CTX) induced hemorrhagic cystitis.

15.299b 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.

15.299c Document cumulative dose, which should not exceed maximum cumulative dose.

15.299d Advise patient of probable facial flushing for several hours after drug administration, especially if given quickly.

15.3 **Gemcitabine** (Gemzar®)

15.31 **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.

15.32 **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.

15.33 **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.

15.34 **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.

15.35 **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%)

15.36 **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).

15.37 **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, 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

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

15.39 **Nursing Guidelines:**

15.391 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.

15.392 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.

15.393 GEMZAR clearance is affected by age and gender. Grade 3/4 thrombocytopenia has been more common in elderly women.

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

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

15.396 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.

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

15.398 Instruct patient to report any respiratory changes.

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

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, an 80-90% 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 3-4 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% and 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 LFTs 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 **Paclitaxel** (Taxol®)

15.51 **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.

15.52 **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)].

15.53 **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 nonpolyvinyl (non-PVC) tubing (e.g., polyethylene) to minimize leaching.

15.54 **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 nonsorbing administration set.

15.55 **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

15.56 **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).

15.57 **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.

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

15.59 **Nursing Guidelines:**

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

15.592 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.

15.593 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.

15.594 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.

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

15.596 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.

15.597 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.

15.598 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.

15.599a Narcotics and nonsteroidal anti-inflammatory drugs may be used to manage the myalgias.

15.599b 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.

15.599c There is an increased risk of neutropenia and stomatitis when given prior to doxorubicin. Therefore Taxol should always be given after doxorubicin administration.

15.599d 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.

15.599e Monitor liver function tests.

15.599f Inform patient about total alopecia.

15.599g If given on the same day as a platinum agent, paclitaxel should be administered first to limit myelosuppression and enhance efficacy of agent.

15.6 Bevacizumab

15.61 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).

15.62 Formulation

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

15.63 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.

15.64 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.

15.65 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

15.66 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.

15.67 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 adverse events, >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 adverse events, 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 adverse events, <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

15.68 Drug procurement

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

15.69 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.

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

15.693 Evaluate IV site regularly for signs of infiltration.

15.694 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.

15.695 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.

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

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

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

15.699a 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.

15.699b 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.

15.699c Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the MD.

15.699d 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.

15.699e 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.

15.699f 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.

15.699g 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.

15.699h 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 Study Overview

This randomized Phase II trial will compare the OS in patients with ovarian cancer who received MV-NIS to patients who received investigator's choice chemotherapy (liposomal doxorubicin, gemcitabine, topotecan, or paclitaxel). This trial implements one interim futility analysis.

16.2 Primary Endpoint

16.21 The proposed immune response mechanism of action for MV-NIS may result in a long-term survival benefit after disease progression. The primary endpoint is OS as defined as the time from registration/randomization to death due to all causes. OS is measured from randomization rather than start of study therapy as the surgery for port placement is considered a necessary prerequisite to the MV-NIS treatment.

16.22 All patients who meet the eligibility criteria, sign the consent form, and are randomized will be considered evaluable for estimation of OS.

16.3 Primary Analysis

The primary goal is to compare MV-NIS versus investigator's choice chemotherapy, where the alternative hypothesis is that the MV-NIS has improved OS compared to investigator's choice. We will enter 60 evaluable patients to the study using a 2:1 randomization scheme (40 MV-NIS and 20 cytotoxic chemotherapy), unless the study is stopped early at the time of the interim futility analysis (see below).

With 60 evaluable patients per arm, we have 80% power to detect an improvement for MV-NIS in the median OS from 14 to 26.5 months (hazard ratio (HR)=0.53), assuming a 1-sided significance level of 0.15 (30) and an accrual rate of 3 patients per month. The primary analysis will be a comparison the MV-NIS versus investigator's choice chemotherapy using a one-sided log-rank test, where a HR<0.715 in favor of MV-NIS is needed to reject the null hypothesis. This final analysis will take place after 44 total events have occurred across both arms combined (which should happen after about 30 months of follow-up in all evaluable patients).

The primary efficacy model will be stratified by all the stratification factors for this study.

16.4 Interim Futility Analysis

16.41 The interim futility analysis will happen after 22 events are observed across both arms combined. The interim futility boundary was selected using EAST software. We selected a Rho family "Beta" spending function with rho parameter "equal" 1.3. To reject the alternative hypothesis at the interim analysis (i.e. reject the measles virus as promising), the HR will need to be ≥1 for the MV-NIS versus investigator's choice chemotherapy, which corresponds to a 1-sided (30) p-value ≥0.50. If the HR is less than 1 (1-sided p <0.50), the study will continue to full accrual and the final analysis will be conducted as discussed above.

16.42 The study will not stop accrual at the time of the interim analysis, unless undue toxicity or a higher than expected accrual rate is observed.

16.5 Secondary Analysis Plans

16.51 (Goal 2.21):

16.511 PFS is defined as the time from start of study therapy to the date of first observation of disease progression or death due to any cause (whichever comes first). The distribution of PFS for both arms of the study will be estimated using the Kaplan-Meier method, and be compared using a one-sided logrank test.

16.512 OS at 12 months (OS12) and PFS at 6 months (PFS6) distributions both arms of the study will be estimated using the Kaplan-Meier method, and be compared using a one-sided logrank test.

16.513 A confirmed tumor response is defined to be a CR or PR noted as the objective status on 2 consecutive evaluations at least 4 weeks apart. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response. Objective response rates (ORR) will be compared between treatment arms using chi-square or fisher exact methodology as appropriate.

16.52 (Goal 2.22): Safety and tolerability of MV-NIS as compared to standard therapy will be evaluated using all patients who have received any study treatment as well as summarizing those who have been included in the efficacy analyses. The overall adverse event rates for grade 3 or higher adverse events will be compared between arms using Chi-Square tests.

16.53 (Goal 2.23): Quality of life as measured by the FACT-Ov will be compared between treatment arms. The assessment will be scored according to the assessment scoring algorithm at each collection time. Scores at end of each cycle will be compared using Wilcoxon procedures. Generalized linear mixed models that incorporate main effects of treatment arm, time and interaction of arm and time will be applied to analyze the longitudinal data of QOL. Patient demographics, baseline prognostic factors and other confounding variables may be considered as covariates for further exploration. Population-level and subject-level longitudinal plots will be plotted to display the trend of patient reported QOL.

16.6 Translational Endpoints

16.61 (Goals 2.31-2.35): Translational endpoints are numerous. All analyses with respect to the translational endpoints of this study are intended to be hypothesis-generating and descriptive in nature. Data will be gathered for a number of laboratory correlative variables as described in the goals for each patient. Descriptive statistics and simple scatterplots will form the basis of presentation of these data. Correlations between these laboratory values and other outcome measures will be carried out by standard parametric and nonparametric correlation procedures (Pearson's and Spearman's coefficients).

16.62 Supplementary analysis of select endpoints may include subset analyses according to descriptive and stratification factors.

16.7 Sample Size, Accrual Time and Study Duration

16.71 Patients who are Pre-Registered but fail to meet criteria for successful surgical placement of an interperitoneal port, will not be registered or randomized to this trial and will not count towards the accrual.

16.72 A maximum of 60 evaluable patients will be accrued onto this randomized phase II study unless the study is closed early for excessive toxicity or lack of efficacy. We anticipate accruing an additional 10% of patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is about 66 patients. The expected accrual rate is about 3 patients per month. With this accrual rate, we expect to finish accrual within about 22 months. We anticipate that the study will take approximately 60 months to complete. This allows a 30-month follow-up for the final patient enrolled, along with data entry and analysis.

16.73 For purpose of Clinicaltrails.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least 26 months.

16.8 Adverse Events Stopping Rule

Within arm A, a specific interim toxicity analysis will be performed once at least 20 evaluable patients have been followed for 3 months (accrual will not stop during this three-month time period). Accrual will be temporarily suspended if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy either of the following:

If 3 or more patients in the first 20 treated patients (or 15% or more after 20 patients have been accrued) experience a grade 4 or higher nonhematologic adverse event.

16.9a Accrual Monitoring Stopping Rule

Given the expected accrual rate is around 3 patients per month, it is expected that the study will take around 3.5 years to fully accrue. We plan to monitor the accrual continually and if we only end up accruing 15 patients or less in the first year (after study activation), we will consider stopping the trial for slow accrual.

16.9b Study Monitoring

16.9b1 This study will be monitored by the Mayo Clinic Data Safety Monitoring Board (DSMB). Reports containing patient characteristics, toxicity and administrative information will be provided to the DSMB every three months, with the first report due at the first reporting period after study initiation. Reports will be due January 31 and July 31 or April 30 and October 31, unless otherwise specified by the DSMB.

16.9b2 This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. A full report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

16.9c Minorities Distributions (sex, race, ethnicity)

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	0	2
Not Hispanic or Latino	64	0	64
Ethnic Category: Total of all subjects	66	0	66
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	65	0	65
Racial Category: Total of all subjects	66	0	66

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

For Arm A patients, baseline tumor specimens obtained either at study entry (when feasible) or from previous surgery (when biopsy attempt is unsuccessful) will be examined for cellular immune infiltration, HLA-B7 expression, and have transcriptomic analysis performed (Next Gen) to characterize measles permissive signatures and immune signatures.

17.1 Summary Table of Research Tissue Specimens to be collected for this Protocol (Arm A and bulky disease patients only)

Correlative Study (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Process at site? (Yes or No)	Temperature & Conditions for Storage /Shipping
Tumor biopsy (at time of debulking surgery and/or port placement)	Mandatory	Formalin Fixed (use archived sample if biopsy not obtained)	FFPE Block or 10 unstained FFPE slides (5 micron), 2 unstained FFPE slides (10 micron), 1 FFPE slide stained with hematoxylin and eosin	Yes	Ambient

17.2 Storage of pathology specimens

Slides/blocks will be shipped to and stored in [redacted] laboratory:

[redacted]

18.0 Data Collection Procedures

18.1 Submission Timetable

18.11 Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Preregistration Screening Failure	At Pre-registration
On-Study	≤2 weeks after registration
Baseline Adverse Event	
Laboratory Form Arm A Baseline	
Laboratory Form Arm B Baseline	
RECIST Measurement Form (Baseline)	
Research Submission Form Arm A Baseline	
Research Submission Form Arm B Baseline	
Concomitant Medication Form (Baseline)	
CA125 Form Baseline	
Booklet Compliance[1]	
Patient Questionnaire Booklet[1]	
Research Tissue Submission Arm A (Bulky and non-Bulky) and Arm B (Bulky) (Prior to Cycle 1)	At peritoneal catheter implantation
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Complete only when patient does not complete the Patient Reported Outcome Booklet containing the FACT-O.
2. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.

18.12 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 Arm A – Cycle 1	X	X
Evaluation/Treatment Arm A – Cycles 2 and All Subsequent Cycles	X	X
Evaluation/Treatment Arm B	X	X
CA125 Form	X	X
RECIST Measurement	X	X
Nadir/Adverse Event Arm A	X	X
Nadir/Adverse Event Arm B	X	X
Laboratory Form Arm A	X	X
Laboratory Form Arm B	X	X
Concomitant Medication	X	X
Research Submission Form Arm A	X (see Section 14.0)	

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Research Submission Form Arm B	X (see Section 14.0)	
End of Active Treatment/Cancel Notification		X
ADR/AER	At each occurrence (see Section 10.0)	
Booklet Compliance[1]	X	X
Patient Questionnaire Booklet[2]	X	X

1. Complete only when patient does not complete the Patient Reported Outcome Booklet containing the FACT-O.
2. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.

18.13 Follow-up Material(s)

CRF	Event Monitoring Phase[1]			
	Q 3 months until PD	At PD	After PD q.6 months	Death
Event Monitoring	X	X	X	X

1. If a patient is still alive 5 years after registration, no further follow-up is required, but one event monitoring form must be completed for all patients to record progression status.
2. **Note: Submit documentation of progression to the MCCC Operations Office, Attention QAS for MC1365 via** [redacted]

19.0 Budget Considerations

19.1 Costs charged to patient

Routine clinical care.
For patients randomized to Arm A, MV-NIS will be provided free of charge by Mayo.
For patients randomized to Arm B (cytotoxic chemotherapy), DOXIL, GEM, TOPA, TAXOL, or bevacizumab, along with costs associated with infusion and monitoring, will be billed to the participant as conventional care.

Rochester only: Participants randomized to Arm A will not be billed for room and board or nursing charges while at the Clinical Research and Trials Unit (CRTU). However, the participant may be billed for ancillary expenses such as any oral medications prescribed at the time of discharge.

19.2 Tests to be research funded

Insertion of the intraperitoneal port, all pharmacological/correlative studies (covered by the Ovarian SPORE, the Schulze Foundation Study Budget, and the Minnesota Ovarian Cancer Alliance).
Cytomel® (liothyronine sodium) or equivalent generic will be provided free of charge.

20.0 References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007;57(1):43-66.
2. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al. Cancer Statistics Review. National Cancer Institute, Bethesda, MD; 1975-2010 [updated 1975-2010; cited 2011]; Available from: http://seer.cancer.gov/csr/1975_2010.
3. Bluming AZ, Ziegler JL. Regression of Burkitt's lymphoma in association with measles infection. Lancet. 1971;2(7715):105-6.
4. Taqi AM, Abdurrahman MB, Yakubu AM, Fleming AF. Regression of Hodgkin's disease after measles. Lancet. 1981;1(8229):1112.
5. Griffin D, Bellini W. Measles Virus in Fields Virology. Fields B, Knipe D, Howley P, editors: Lippincott-Raven Publishers; 1996.
6. Dorig RE, Marcil A, Chopra A, Richardson CD. The human CD46 molecule is a receptor for measles virus (Edmonston strain). Cell. 1993;75(2):295-305.
7. Muhlebach MD, Mateo M, Sinn PL, Prufer S, Uhlig KM, Leonard VH, et al. Adherens junction protein nectin-4 is the epithelial receptor for measles virus. Nature. 2011;480(7378):530-3. PMCID: 3245798.
8. Cutts FT, Markowitz LE. Successes and failures in measles control. J Infect Dis. 1994;170 Suppl 1:S32-41.
9. Galanis E. Therapeutic potential of oncolytic measles virus: promises and challenges. Clin Pharmacol Ther. 2010;88(5):620-5.
10. Fine PE. Herd immunity: history, theory, practice. Epidemiol Rev. 1993;15(2):265-302.
11. Peng KW, TenEyck CJ, Galanis E, Kalli KR, Hartmann LC, Russell SJ. Intraperitoneal therapy of ovarian cancer using an engineered measles virus. Cancer Res. 2002;62(16):4656-62.
12. Hasegawa K, Nakamura T, Harvey M, Ikeda Y, Oberg A, Figini M, et al. The use of a tropism-modified measles virus in folate receptor-targeted virotherapy of ovarian cancer. Clin Cancer Res. 2006;12(20 Pt 1):6170-8.
13. Peng KW, Frenzke M, Myers R, Soeffker D, Harvey M, Greiner S, et al. Biodistribution of oncolytic measles virus after intraperitoneal administration into Ifnar-CD46Ge transgenic mice. Hum Gene Ther. 2003;14(16):1565-77.
14. Galanis E, Hartmann LC, Cliby WA, Long HJ, Peethambaram PP, Barrette BA, et al. Phase I trial of intraperitoneal administration of an oncolytic measles virus strain engineered to express carcinoembryonic antigen for recurrent ovarian cancer. Cancer Res. 2010;70(3):875-82. PMCID: 2890216.
15. Dingli D, Peng KW, Harvey ME, Greipp PR, O'Connor MK, Cattaneo R, et al. Image-guided radiovirotherapy for multiple myeloma using a recombinant measles virus expressing the thyroidal sodium iodide symporter. Blood. 2004;103(5):1641-6.
16. Galanis E, Atherton PJ, Dowdy SC, Cliby WA, Haluska PJ, Jr., Long HJ. Intraperitoneal (IP) administration of an oncolytic measels virus (MV) strain expressing the sodium iodine symporter gene in patients (pts) with advanced ovarian cancer (OvCa). Mol Ther. 2013;21(S1):S6.
17. Muggia FM, Hainsworth JD, Jeffers S, Miller P, Groshen S, Tan M, et al. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. J Clin Oncol. 1997;15(3):987-93.
18. Ferrandina G, Ludovisi M, Lorusso D, Pignata S, Breda E, Savarese A, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol. 2008;26(6):890-6.
19. ten Bokkel Huinink W, Lane SR, Ross GA. Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. Ann Oncol. 2004;15(1):100-3.

20. Le T, Hopkins L, Baines KA, Rambout L, Fung-Kee-Fung M. Prospective evaluation of weekly topotecan in recurrent platinum-resistant epithelial ovarian cancer. Int J Gynecol Cancer. 2008;18(3):428-31.
21. Sehouli J, Stengel D, Harter P, Kurzeder C, Belau A, Bogenrieder T, et al. Topotecan Weekly Versus Conventional 5-Day Schedule in Patients With Platinum-Resistant Ovarian Cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. J Clin Oncol. 2011;29(2):242-8.
22. Le T, Hopkins L, Baines KA, Rambout L, Al Hayki M, Kee Fung MF. Prospective evaluations of continuous weekly paclitaxel regimen in recurrent platinum-resistant epithelial ovarian cancer. Gynecol Oncol. 2006;102(1):49-53.
23. Markman M, Blessing J, Rubin SC, Connor J, Hanjani P, Waggoner S. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol. 2006;101(3):436-40.
24. Myers R, Harvey M, Kaufmann TJ, Greiner SM, Krempski JW, Raffel C, et al. Toxicology study of repeat intracerebral administration of a measles virus derivative producing carcinoembryonic antigen in rhesus macaques in support of a phase I/II clinical trial for patients with recurrent gliomas. Hum Gene Ther. 2008;19(7):690-8. PMCID: 2748764.
25. Hamburger AW, Dunn FE, White CP. Percoll density gradient separation of cells from human malignant effusions. Br J Cancer. 1985;51(2):253-8. PMCID: 1977035.
26. Kruk PA, Maines-Bandiera SL, Auersperg N. A simplified method to culture human ovarian surface epithelium. Lab Invest. 1990;63(1):132-6.
27. Wu S, Boyer CM, Whitaker RS, Berchuck A, Wiener JR, Weinberg JB, et al. Tumor necrosis factor alpha as an autocrine and paracrine growth factor for ovarian cancer: monokine induction of tumor cell proliferation and tumor necrosis factor alpha expression. Cancer Res. 1993;53(8):1939-44.
28. Pocock SJ, Simon R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics 31(1):103-115, 1975 Mar.
29. Therneau TM. How many stratification factors are “too many” to use in a randomization plan? Controlled Clin Trials. 1993;14: 98-108.
30. Rubinstein LV, Kron EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposeal for phase II screening trials. J Clin Oncol. 2005; 23(28):7199-206.
31. J Clin Oncol. 2014 May 1;32(13):1302-8. doi: 10.1200/JCO.2013.51.4489. Epub 2014 Mar 17.
32. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial.
33. Pujade-Lauraine E1, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag D, Ray-Coquard I.

Appendix I: ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From [redacted]

Appendix II: Patient Information Sheet

PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains 1 set of questions:
    a. Functional Assessment of Cancer Therapy – Ovarian (FACT-O)

2. Directions on how to complete the set of questions are written on the top of the FACT-O.

3. During your clinic visit:
    a. Please complete the booklet PRIOR TO RECEIVING your next cycle of treatment and return it to your nurse or your physician.

4. You will be given your provider's name and telephone number. You can call anytime if you have any concerns or questions regarding this assessment.

Thank you for taking the time to help us.

Appendix III: FACT-O

FACT-O (Version 4)

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

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

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends…….…...……	0	1	2	3	4
GS2	I get emotional support from my family…...…...	0	1	2	3	4
GS3	I get support from my friends……..	0	1	2	3	4
GS4	My family has accepted my illness…….….	0	1	2	3	4
GS5	I am satisfied with family communication about my illness……...	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support) …….……..…..	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section*	0	1	2	3	4
GS7	I am satisfied with my sex life …….……...….	0	1	2	3	4

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

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

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home) ……..…	0	1	2	3	4
GF2	My work (include work at home) is fulfilling ……	0	1	2	3	4
GF3	I am able to enjoy life ……..…….....	0	1	2	3	4
GF4	I have accepted my illness…….....	0	1	2	3	4
GF5	I am sleeping well ……..……..…..	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun ..……	0	1	2	3	4
GF7	I am content with the quality of my life right now…..	0	1	2	3	4

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
O1	I have swelling in my stomach area…….	0	1	2	3	4
C2	I am losing weight……	0	1	2	3	4
C3	I have control of my bowels ……	0	1	2	3	4
O2	I have been vomiting……...……	0	1	2	3	4
B5	I am bothered by hair loss ……..……	0	1	2	3	4
C6	I have a good appetite ……..……	0	1	2	3	4
C7	I like the appearance of my body ……	0	1	2	3	4
BMT5	I am able to get around by myself……...……	0	1	2	3	4
B9	I am able to feel like a woman……..……	0	1	2	3	4
O3	I have cramps in my stomach area……..….	0	1	2	3	4
BL4	I am interested in sex ..……..……..……	0	1	2	3	4
BMT7	I have concerns about my ability to have children….	0	1	2	3	4

Appendix IV: Prep and Storage of MV-NIS

Standard Operating Procedure for the Preparation of MV-NIS (NIS-Measles Virus-Edmonston Strain) dilutions for patient administration

MV-NIS will be manufactured at the Mayo Clinic Viral Vector Production Laboratory of the Department of Molecular Medicine. The product will be labeled appropriately and provided to the designated pharmacy in single-dose vials with batch-dependant infectious titer expressed in$TCID_{50}$ units/mL.

MV-NIS containing vials will be transported on dry ice and stored at ≤-65° C.

The appropriate number of vials will be thawed and diluted in a timely manner to provide product ready for patient administration.

The appropriate amount of MV-NIS will be withdrawn from the vial(s). Several dilution steps may be necessary to accurately compound the doses per clinical protocol. This will be accomplished by diluting MV-NIS in preservative-free normal saline to a total volume of 500 mL in an infusion bag for intraperitoneal administration. MAYO ONLY: Any remaining thawed virus or intermediate dilutions will be refrigerated and transported on ice to Mayo Clinic Viral Vector Production Laboratory for determination of TCID 50/mL as indicated.

All reconstitution and preparation will be performed by the Pharmacy in a Biological Safety Cabinet using aseptic technique.

The expiration of the diluted virus is **2.5 hours** at room temperature after preparation of the infusion bag is complete.

The final product for administration will be labeled appropriately for dispensing within the institution.

Appendix V: Arm Assignment Script for Bulky Disease

Arm A: Bulky Disease The patient is randomized to Arm A. Please place an intraperitoneal port prior to surgical closure.

Arm B: Bulky Disease The patient is randomized to Arm B. Please DO NOT place an intraperitoneal port; rather proceed with surgical closure.