Mayo Clinic Cancer Center

MC1266 Phase I/II Trial of Intraperitoneal Administration of adipose tissue derived mesenchymal stem cells infected with a NIS-Expressing Derivative Manufactured from a Genetically Engineered Strain of Measles Virus in Patients with Recurrent Ovarian Cancer

Study Chair: [redacted]

Study Co-Chairs: [redacted]

Statisticians: [redacted]

† Study contributor(s) not responsible for patient care

Drug Availability

Supplied Investigational Agent(s): MV-NIS (NIS-Measles Virus – Edmonston Strain (IND #15317), MV-NIS/MSC (Mesenchymal Stem Cell (MSC) infected with NIS-Measles Virus – Edmonston Strain)

Purchased with study funds: Liothyronine (Cytomel®, T3)

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Protocol Resources

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

*No waivers of eligibility per NCI

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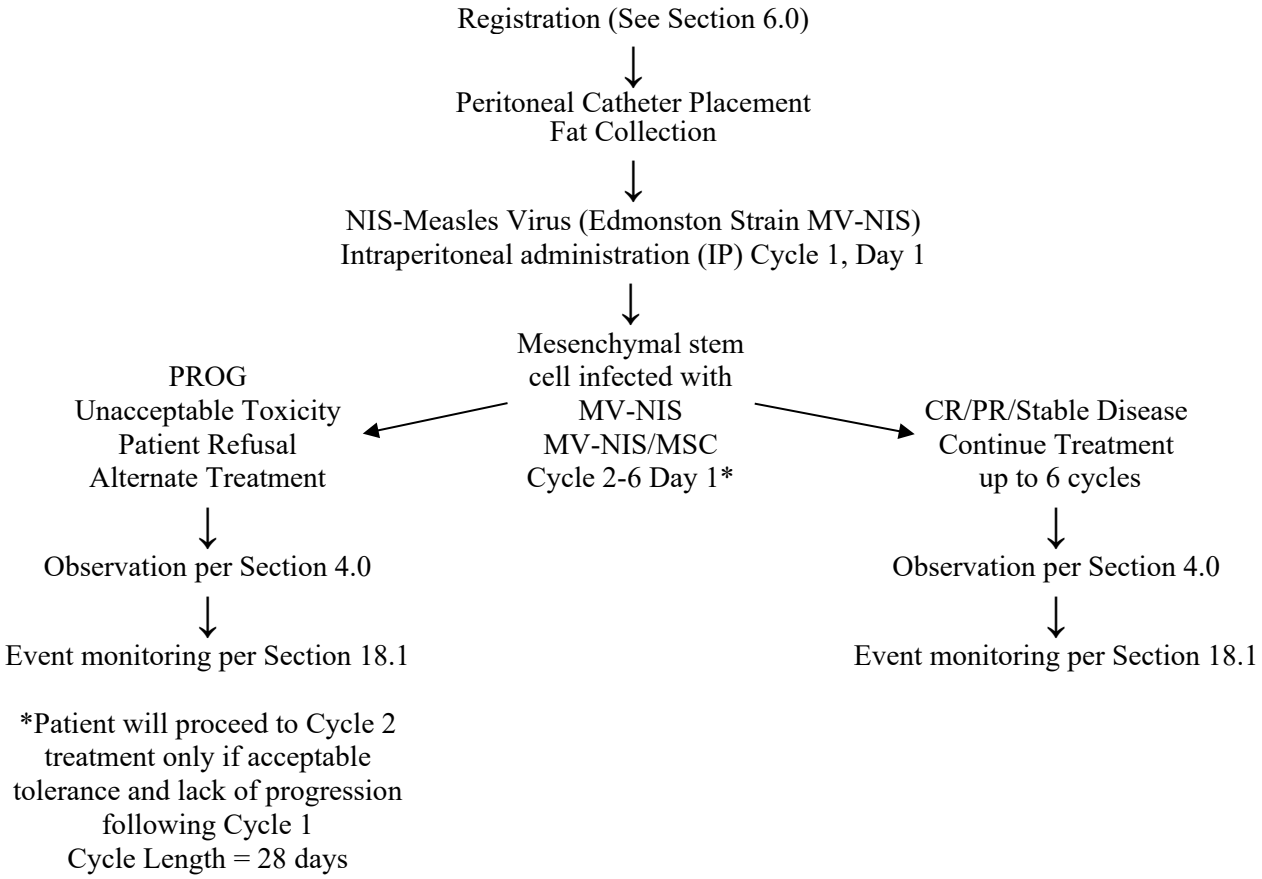
Schema MV-NIS



Mayo Drug Names/Abbreviations

Generic name: Synonym: Brand Name(s): Mayo abbreviation:	None - NIS-Measles Virus (Edmonston Strain) MV-NIS
Generic name: Synonym: Brand Name(s): Mayo abbreviation:	None-Mesenchymal stem cell infected with NIS-Measles Virus (Edmonston Strain) MV-NIS/MSC
Generic name: Synonym: Brand Name(s): Mayo abbreviation:	Liothyronine sodium Cytomel® T3

1.0 Background

1.1 Ovarian cancer

Ovarian cancer is the second most common malignancy of the female genital tract in the United States, with an estimated 14,000 deaths in 2013[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. Seventy to 80% of patients continue to present with advanced disease, and despite the high response rate that can be obtained with a platinum/taxane based regimen, the majority of these patients will relapse. The available salvage therapy for relapsed disease consists mostly of chemotherapy or biologic agents such as bevacizumab and it is not curative. It can lead to responses in the minority of patients and most patients will subsequently progress in a few to several months. There is an urgent need for innovative approaches for the treatment of advanced disease.

1.2 Measles virus as a 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 [2,3].

Measles virus is a negative strand, RNA virus, whose genome includes six protein products [4]. 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 [5], the SLAM receptor (the latter being predominantly present on activated B and T cells) and the epithelial receptor nectin-4 [6]. 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 [7].

In preclinical studies, we showed that intratumoral or intravenous injection of a measles virus strain, derived from the Edmonston vaccine lineage, can cause growth inhibition or total regression for a variety of established tumors and xenografts [8].

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 [9]. 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 [10]. Toxicology and biodistribution studies in measles virus infection susceptible Infar^{ko} CD46 Ge mice have demonstrated the safety of the approach [11].

1.3 Clinical experience with MV derivatives in ovarian cancer treatment:

A phase I trial of intraperineal administration of MV-CEA has been completed. 21 patients were treated with MV-CEA IP 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 [12]. MV-NIS is at least as efficacious as MV-CEA in orthotopic ovarian cancer models [10] and it allows use of radioactive iodine isotopes for imaging [10] and treatment purposes [12]. A phase I trial with phase II dose expansion of MV-NIS in patients with recurrent ovarian cancer has been completed. Six patients have been treated at the dose expansion part of the study and 10 patients at the dose expansion cohort. No dose-limiting toxicity has been observed. Median overall survival was a very promising 26.6 months (range 1.8-33.9+ months) despite the fact that patients were heavily pretreated. MV-NIS has the advantage that can be easily produced in higher titer and an FDA-approved protocol has been developed for this purpose and employed in subsequent studies.

1.4 Rationale for use of cells as viral delivery vehicles:

One of the potential limitations following intraperitoneal administration of the measles virus pertains to the presence of neutralizing antibodies in the peritoneal cavity [13]. Furthermore, when the virus is diluted in normal saline, which is its current delivery vehicle, it is expected that within 4 to 6 hours the viral containing solution will have been absorbed systemically; the latter suggests that viral delivery through an approach allowing longer contact with the target tumor sites, could increase infectivity and further improve antitumor efficacy.

1.5 Adipose tissue derived mesenchymal stem cells (MSC) can be successfully infected by MV and allow the virus to resist immune serum neutralization [13].

To determine the susceptibility of MSC to MV infection, MSC were infected with MV-RFP at MOI (0.01, 0.1, 1.0 or 4.0). There was a corresponding increase in the numbers of

infected cells with increase in MOI. To enable quantitation of the percentage of infected cells by flow cytometry, MSC were maintained in media containing a fusion inhibitory peptide (+FIP) that prevents intercellular fusion (syncytia formation). At MOI of 1.0 and 4.0, 20% and 60% of cells were expressing RFP by 48h post infection, respectively.

Viability of MSC post infection by MV-GFP (MOI 1.0) was determined by trypan blue exclusion assay. In the presence of FIP, there was no significant difference in numbers of viable cells in the infected culture over time. The numbers of viable cells decreased by 96h if the infected MSC were allowed to fuse with neighboring cells in the absence of FIP. The amount of viral progeny produced by infected MSC (cell-associated virus) or conditioned media (released virus) was determined by $TCID_{50}$ titrations. Infected MSC were able to propagate the virus, but to a smaller extent, compared to Vero producer cells. The majority of measles virus progeny was cell-associated, requiring freeze/thaw cycles to release the viruses.

Intercellular fusion is more resistant to neutralizing anti-MV antibodies than cell-free virus: the anti-MV IgG titers in different lots of human AB pooled sera were determined using an enzyme immunoassay. An individual with a titer of more than 20 EU/mL is measles immune. Full plaque reduction neutralization (PRN) assays using 250 $TCID_{50}$ MV-GFP were also performed to determine the corresponding virus neutralization titers of the sera. Pooled AB serum lot K61552 (277 EU/mL, PRN=256) and lot C80553 (300 EU/ml, PRN=256) were used in all subsequent experiments.

Vero cells were infected with MV-GFP (10^3 $TCID_{50}$) in the absence or presence of increasing concentrations of measles immune serum. The numbers of infectious centers (syncytia) in the Vero monolayer were counted at 48h post infection and represented as a percentage of syncytia count in the absence of anti-MV antibodies. `Naked' MV-GFP was neutralized by measles immune sera; no syncytium was detected at the highest concentration of human serum used (1:4 dilution, 69 EU/mL). It was not until at 1:128 serum dilution (2 EU/mL) that 40% of infectious centers was recovered in the Vero monolayer.

To determine if MSC could deliver MV to target cells in the presence of anti-MV antibodies, MSC were preinfected with MV-GFP at MOI 1.0 and the next day, MSC were overlaid on Vero cells (1 MSC: 100 Vero cells) in the presence of increasing concentrations of measles immune serum. MSC associated viruses were more resistant to the neutralizing effects of anti-MV antibodies. At 1:4 serum dilution (69 EU/mL), 40% of infectious centers was present and at 1:16 dilution, the numbers of infectious centers were comparable to the control in which no serum was added. Hence, infected MSC were able to fuse with Vero cells and delivered MV infection to the target cells in an environment with a high amount of anti-MV antibodies.

1.6 Infected MSC localize to ovarian cancer metastases after intraperitoneal administration and result in significant antitumor efficacy [13].

Athymic mice were implanted intraperitoneally with SKOV3ip.1 human ovarian cancer cells and 7 days later, mice were injected IP with MV-Luc infected MSC and imaged non-invasively for Fluc gene expression. Firefly luciferase signals were seen both in tumor-free and tumor-bearing mice given MV-Luc infected MSC at day 1 post MSC delivery. In the non-tumor bearing mice the MV-Luc infected cells were seen at the injection site and at the omental region by Day 3, the luciferase signals had decreased significantly and were undetectable by day 7 after death of the virus infected MSC cells. In contrast, bioluminescent signals remained high and continued to increase over time in tumor-bearing mice given MV-Luc infected MSC. It is evident that in tumor-bearing

mice, the infected MSC were able to transfer MV-Luc infection to the peritoneal tumors. The infected tumors continued to propagate the virus, resulting in increase of Fluc bioluminescent signal even after death of the infected MSC. As expected, naked MV-Luc was highly efficient at infecting tumors in these measles naïve mice.

To determine if MSCs co-localized with the tumor nodules, another cohort of mice bearing intraperitoneal SKOV3ip.1, OVCAR5 or A2780 human ovarian tumors were injected IP with CellTracker Red CMTPX dye labeled MSC (MV infected or uninfected). Tumors were harvested and examined directly under a fluorescence microscope 24h later. Abundant red fluorescent MSC were found at the omental tumor nodules and on smaller peritoneal tumor nodules that have seeded on the mesenteric linings or intestines. There was no apparent difference in the biodistribution of uninfected and infected MSC; both types of MSC were able to traffick to and localize on the tumors. Gross examination of the peritoneal cavity indicated that peritoneal tumor nodules in all 3 models of ovarian cancer were covered with red fluorescent MSC. In the OVCAR5 model in which there was significant coverage of the peritoneum wall by a cake of tumor cells, abundant MSC were found on the tumor cake. In contrast, the tumor free peritoneal wall next to this tumor cake had minimal numbers of MSC. When given IP into control athymic mice with no tumor, MSC accumulated predominantly on the omentum. Cryosections of the peritoneal tumors were examined using confocal microscopy to determine the extent of MSC infiltration into the tumor parenchyma. At 4h and 24h post cell infusion, red fluorescent MSC were seen lining the surface of the tumor nodules and in the tumor parenchyma.

Antitumor efficacy in the presence of neutralizing antibodies
Athymic mice were implanted with SKOV3ip.1-Gluc tumor cells and 8 days later, mice received saline or equal numbers (1×10^6) of `naked' cell free MV-Luc or MV-Luc infected MSC. Mice were imaged non-invasively using bioluminescent imaging for Gluc expression with colenterazine substrate (tumor burden) and the next day, for Fluc expression using D-luciferin substrate (viral gene expression). Imaging was performed one day apart to ensure that all Gluc bioluminescent signals had disappeared prior to Fluc imaging. We observed a good correlation between the location and intensity of Gluc and Fluc signals indicating robust infection of the tumors by cell-free and MSC-associated virus in measles naïve animals. In measles immune animals, the MV-Luc infected MSC were able to transfer the infection to ovarian tumors, resulting in increase in Fluc signal. In contrast, `naked' MV-Luc was neutralized by the anti-measles antibodies and the peritoneal tumors were not infected. Hence, delivery of MV is superior when MSC are used as virus carriers in measles immune animals. The increase in Fluc signal in the tumors at day 7 was not due to presence of infected MSC. A significant portion of virus infected MSC died by day 3 post IP delivery into mice resulting in complete loss of bioluminescent signals.

To investigate the antitumor activity of the various treatments, athymic mice were implanted IP with 2×10^6 SKOV3ip.1-Gluc tumor cells and 8 days later, mice were passively immunized by IP administration of measles immune human serum (50 EU) or given saline. Three hours later, mice were given equal numbers (1×10^5) of cell-free MV-NIS or MV-infected MSC IP. The MV/MSC had been loaded with MV-NIS by incubation with virus at MOI 4.0 for 2 hours (approximately 60% infection) and washed once in PBS. In the measles immune groups, MV-NIS and MV/MSC were subsequently incubated in vitro with measles immune serum (50 EU) for 30 min at 37°C prior to injection into the animals to ensure neutralization of any surface bound virus. Thus, each measles immune mouse received a total of 100 EU of anti-MV IgG Ab.

The Kaplan Meier survival curves of the mice were plotted. The median survival for saline control was 31 days (n=5 mice), uninfected MSC was 31 days (n=5 mice), MV (−Ab) was 64 days (n=12 mice), MV (+Ab) was 31 days (n=12 mice), MV/MSC (−Ab) was 62 days (n=10 mice) and MV/MSC (+Ab) was 66 days (n=11 mice). All mice in the saline, uninfected MSC, and MV (+Ab) groups (22 out of 22) were euthanized because they developed bloody ascites (3–4.5 mL), with extensive dissemination of ovarian tumors in the peritoneal cavity, perigastric area and on the peritoneal side of the diaphragm. In contrast, only a few of the mice in the MV (−Ab) or MV/MSC groups (+ Ab and – Ab) developed ascites (6 out of 33). Several of the mice appeared jaundiced and were euthanized (12 out of 33). Examination at necropsy indicated tumor obstruction/constriction around the gall bladder or bile duct. The rest of the animals were euthanized due to weight loss of more than 20%, or development of an ulcerated subcutaneous tumor at the injection site towards the end of the study.

The survival curves of the respective treatment groups were compared against the saline control and the p values were determined. Uninfected MSC did not have any antitumor activity against human ovarian cancer, survival of these mice was not significantly different from the saline treated group ($p=0.92$). As expected, MV-NIS (−Ab) significantly extended the survival of mice compared to saline control ($p<0.0001$). However, the antitumor activity of MV-NIS was negated in passively immunized mice. Thus, there was a significant difference in survival outcome using `naked' MV-NIS in measles naïve mice versus measles immune mice ($p<0.0001$). In contrast to therapy using cell-free virus, treatment of passively immunized mice with MV-infected MSC significantly extended the survival of mice ($p<0.0001$), doubling the median survival from 31 days (MV-NIS +Ab) to 66 days for MV/MSC +Ab. Furthermore, there was no significant difference in therapy using MV/MSC in measles naïve or measles immune animals ($p=0.93$). The presence of pre-existing antimeasles antibodies did not diminish the delivery and transfer of MV from infected MSC. We did not observe a significant difference in survival of measles naïve mice treated with MSC-associated MV compared to cell-free virus ($p=0.67$).

Cryosections of omental tumors harvested at necropsy were immunostained with an antibody specific for the measles nucleocapsid (MV-N) protein and CD68, a macrophage marker. MV-N positive areas were found in MV-NIS (−Ab), MV/MSC (−Ab) and MV/MSC (+Ab) tumors but not in MV-NIS (+Ab) tumors. Staining for CD68+ macrophages indicated abundant infiltration of phagocytic macrophages into the MV infected tumors, either surrounding or in necrotic areas or co-localizing with the MV-N positive areas. It is likely that the macrophages are phagocytic in nature, as suggested by the abundance of CD68 staining in the necrotic areas of the tumors. There were also areas of MV-N staining with no corresponding CD68 staining.

The study was subsequently extended to include evaluation of the ability of infected MSC to seek other human ovarian cancer cell lines, specifically A2780 and OVCAR5. Intraperitoneally implanted MSC successfully demonstrated their ability to home to and localize to these tumors and subsequently transfer the virus to the tumor cells [Mader and Peng, unpublished data].

1.7 Successful MSC generation from the adipose tissue of ovarian cancer patients:

Following IRB approval, adipose tissue was obtained in the form of fat biopsies from three recurrent ovarian cancer patients and six newly diagnosed patients. MSCs were successfully isolated and expanded. Importantly, all lots of patient-derived MSCs could be infected with MV with a range of 6-90% infectivity. These patient-derived infected

MSCs were administered to mice with peritoneal involvement by ovarian cancer. The MSC successfully homed to undelivered virus to this human ovarian cancer tumors as demonstrated via fluorescent xenogene imaging.

1.8 Pilot assessment of MSC tumorigenicity

Three groups of athymic mice were administered (1) SKOV3ip.1 human ovarian cancer cells, (2) SKOV3ip.1 cells in conjunction with MSC (1:1 ratio). MSC did not enhance or suppress tumor growth.

Our data collectively demonstrate that MSC can be successfully isolated from ovarian cancer of the adipose tissue cancer patients expanded in vitro and infected with MV strains with a high infectivity. Infected MSC can home into peritoneal ovarian tumors, thus supporting the concept of improving viral delivery in patients with recurrent ovarian cancer in whom the virus is administered intraperitoneally.

These data collectively support that adipose tissue derived MSCs can effectively deliver MV to ovarian cancer metastasis and increase treatment efficacy at the presence of neutralizing antibodies.

2.0 Goals

2.1 Phase I

To determine the maximally tolerated dose (MTD) of intraperitoneal administration of an Edmonston's strain measles virus genetically engineered to produce NIS (MV-NIS) in patients with recurrent ovarian cancer, delivered by adipose tissue derived mesenchymal stem cells (MSC).

2.2 Phase II:

2.21 Primary:

To assess the 12-month overall survival of patients treated with this regimen

2.22 Secondary:

2.221 To assess the tolerability of this regimen

2.222 To assess the 4-month progression free survival of patients treated with this regimen

2.223 To assess the response rate, progression-free survival, and overall survival of patients treated with this regimen

2.23 Translational:

2.231 To 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 versus MSC delivered MV-NIS using SPECT/CT imaging.

2.232 To assess viremia, viral replication, and measles virus shedding/persistence following intraperitoneal administration.

2.233 To assess humoral and cellular immune response to the injected virus.

2.234 To assess in a preliminary fashion the development of antitumor immune response.

3.0 Patient Eligibility

3.1 Inclusion criteria

3.11 Age ≥18 years.

3.12 Must have:
- Recurrent or progressive ovarian cancer, primary peritoneal cancer or fallopian tube cancer after prior treatment with platinum and taxanes
- Histologic confirmation of the original primary tumor
- Prior bilateral oophorectomy

3.13 The following histologic epithelial cell types are eligible:
Serous adenocarcinoma, endometroid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma NOS.

3.14 ECOG performance status (PS) of 0, 1, or 2.

3.15 The following laboratory values obtained ≤7 days prior to registration:
- ANC ≥1500/μL
- PLT ≥100,000/μL
- Total bilirubin ≤ upper normal limit
- AST ≤2 x ULN
- Creatinine ≤1.5 x ULN
- Hgb ≥9.0 g/dL

3.16 Normal cardiac function as defined by a normal ejection fraction by MUGA or echocardiogram.

3.17 Provide informed written consent.

3.18 Willing to return to Mayo Clinic Rochester for follow-up.

3.19a Life expectancy ≥12 weeks.

3.19b Willing to provide all biologic specimens as required by the protocol.

3.19c Measurable disease by exam or CT scan, or for patients with CA-125 elevation or with microscopic residual but without measurable disease on imaging, willingness to undergo laparoscopy for evaluation of treatment effect if no radiographic progression after 6 treatment cycles.

3.19d CD4 count ≥200/μL or ≥15% of peripheral blood lymphocytes

3.2 Exclusion criteria

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

3.22 Known standard therapy for the patient's disease that is potentially curative or definitely capable of extending life expectancy. Subjects will be excluded if this is their first relapse and they have recurred >6 months from completion of primary (adjuvant) chemotherapy.

3.23 Active infection ≤5 days prior to registration.

3.24 History of tuberculosis or history of PPD positivity.

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

3.26 Any of the following prior therapies:
- Chemotherapy ≤3 weeks prior to registration
- Immunotherapy ≤4 weeks prior to registration
- Biologic therapy ≤4 weeks prior to registration
- Extensive abdominal surgery if it includes enterotomy(ies) ≤3 weeks prior to registration. This criterion does not apply to placement of the peritoneal port-a-cath or lysis of adhesions at the time of registration.
- Any viral or gene therapy prior to registration.
- Radiation therapy to the abdomen or pelvis.

3.27 New York Heart Association Classification III or IV, known symptomatic coronary artery disease, or symptoms of coronary artery disease on systems review, or known cardiac arrhythmias (atrial fibrillation or SVT).

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

3.29a Requiring blood product support.

3.29b CNS metastases or seizure disorder.

3.29c HIV-positive test result or history of other immunodeficiency.

3.29d History of organ transplantation.

3.29e History of chronic hepatitis B or C.

3.29f 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).

3.29g Intra-abdominal disease >8 cm in diameter at the time of registration, intrahepatic disease, or disease beyond the abdominal cavity. Patients with intra-abdominal lymph node involvement are eligible based on biodistribution data indicating viral dissemination to lymph nodes following intraperitoneal administration [14].

3.29h Treatment with oral/systemic corticosteroids, with the exception of topical or inhaled steroids.

3.29i Exposure to household contacts ≤15 months old or household contact with known immunodeficiency.

3.29j Allergy to measles vaccine or history of severe reaction to prior measles vaccination.

3.29k Allergy to iodine. This does not include reactions to intravenous contrast materials.

3.29l Any other pathology or condition where the principal investigator may deem to negatively impact treatment safety.

4.0 Test Schedule

4.1 Schedule of assessments

Tests and Procedures	Pre-Treatment			Active Treatment							Observation[1]	
	≤7 days prior to registration	At peritoneal catheter placement*	Post catheter placement visit*[2,3]	Cycle 1 Day 1 prior to treatment*	Cycles 1-6, Day 1	Cycle 1 and 2, Day 3	Cycle 1 and 2, Day 8	Cycle 1 and 2, Day 15	Cycles 3-6, Day 3; Cycles 1-6, Day 23	Cycles 2-6, Day 1 prior to treatment; and End of treatment	q 3 months until progression or alternate treatment	3 months, 6 months, and 12 months after progression or alternate treatment
window						±1 day	±1 day	±1 day	±72 hours	±3 days		
History and exam, wt, height[4], PS, vital signs, assessment of toxicity[5]	X		X		X[6]					X	X	X
Gyn Consult for Port Placement	X											
Adverse event assessment			X[7]							X	X	
Hematology group (WBC, ANC, Lymphocyte count, Hgb, PLT)	X		X				X	X		X	X	X
INR, APTT	X						X			X		
Chemistry group (AST, AP, Na, K, Creat, bili)	X		X				X			X	X	X
Urine analysis including sediment	X		X									
Chest x-ray	X		X									
Echo/ or MUGA	X[8]											
HIV blood test	X											
Tumor Measurement / Evaluation of indicator lesion (CT, MRI, etc.)[9]	X		X[10]							X	X	X
ECG	X		X							X	X	X
SPECT CT[R,11]			X			X	X	X[12]		X[13]		
CA125			X							X	X	X

[1] Follow instructions in Section 13 for Observation; then Section 18 for Event Monitoring
[2] Laboratory evaluation and imaging do not need to be repeated if the patient has a peritoneal port PRIOR to enrollment/registration if done ≤14 days before C1D1
[3] ≤7 days prior to treatment unless otherwise noted
[4] Height only needed at baseline
[5] Additional assessment of toxicity will be performed as described in Section 8.0.
[6] Weight and PS only
[7] ≤2 weeks prior to treatment
[8] To be performed ≤42 days prior to registration
[9] For patients with measurable disease. Must be ≤21 days so we have enough time for scans (CT to be performed with contrast) and prior to all subsequent cycles (without contrast if SPECT is to be performed; otherwise with contrast). Pre-registration and post-port placement CTs to be reviewed and compared with subsequent CTs. **Post-port placement CT will be used as the baseline scan for response purposes**. See Section 11.0 for Response Evaluation Criteria in Solid Tumors (RECIST). NOTE: Same modality CT or MRI should be used throughout the trial.
[10] **Post-port placement CT will be used as the baseline scan for response purposes**.
[11] See Table 4.1.
[12] See Table 4.1. Scans at Cycle 1, Day 15, Day 28, and Cycle 2, Day 15 are optional.
[13] See Table 4.1. Scans on Cycles 3-6 are optional only needed if prior scans are positive.

Tests and Procedures	Pre-Treatment			Active Treatment							Observation[1]	
	≤7 days prior to registration	At peritoneal catheter placement*	Post catheter placement visit*[2,3]	Cycle 1 Day 1 prior to treatment*	Cycles 1-6, Day 1	Cycle 1 and 2, Day 3	Cycle 1 and 2, Day 8	Cycle 1 and 2, Day 15	Cycles 3-6, Day 3; Cycles 1-6, Day 23	Cycles 2-6, Day 1 prior to treatment; and End of treatment	q 3 months until progression or alternate treatment	3 months, 6 months, and 12 months after progression or alternate treatment
window						±1 day	±1 day	±1 day	±72 hours	±3 days		
Assessment of immune competence[R], Immunoglobulins, CD4 & CD8 counts, complement levels (clinical test)	X[14]									X[15]		
Measles virus immunity[R] Serum anti-measles IgG (clinical test)	X									X[16]		
Ascites anti-measles IgG[R]**				X*			X[17]			X[18]		
IFN-γ· IL-10 measles ELISPOT[R]**				X*						X[19]		
Assessment of viral shedding[R]**				X*		X	X		X			
Assessment of Viremia (PMBC)[R]**				X*		X	X	X	X			
Peritoneal aspirates[R]**		X*				X	X			X[20]		
Tumor biopsy, Tumor and benign tissue[R,21]		X*										
Fat aspirate [R]		X*										
Assessment of immune response against tumor				X*						X[22]		
Cytokine multiplex assays				X*						X[23]		
Study Drug Administration					X[24]							
Concomitant Medications[25]		X*		X	X					X		

* To be performed after registration but prior to study agent being given on Cycle 1, Day 1.
** See Section 14.0 for details.
R Research funded

[14] To be performed ≤42 days prior to registration
[15] Prior to Cycle 2 and Cycle 3
[16] Not done at end of treatment
[17] **Day 8 of Cycle 1 only**
[18] Cycle 3 Day 1 only
[19] Not done at end of treatment
[20] Not done Cycle 2 Day 1; Not done at end of treatment
[21] Can be done anytime up to one month prior to registration. Not necessary if adequate prior biopsy material exists. Only fat grossly free of tumor will be collected. See Section 17.0 for details.
[22] Not done at end of treatment
[23] Not done at end of treatment
[24] Cycle 1 is MV-NIS and Cycle 2-6 are MV-NIS/MSC
[25] To be completed per tables in Section 18.0

4.2 Nuclear imaging Tables

Table 4.21 Cycle 1[a,c]

TIMEPOINT		SPECT/CT
Pre-treatment		X
Day 3		X
Day 8		X
Day 15 (optional-see footnote)		X[b]
Day 28 (optional-see footnote)		X[b]

Table 4.22 Cycle 2 and *optional* Cycle 3[a,c]

TIMEPOINT		SPECT/CT
Pre-treatment		
Day 3		X
Day 8		X
Day 15 (optional-see footnote)		X[b]
Day 28 (optional-see footnote)		X[b]

a. The scheduling of the nuclear imaging will be as close to the stated time points as possible. Flexibility of ±1 day will be allowed.
b. These scans will be elective, based on whether there is continued uptake on prior imaging studies.
c. Imaging with SPECT CT will be performed in cycles 1 (MV-NIS alone) and 2 (MSC delivered MV-NIS). Imaging to be performed in Cycle 3, only if positive imaging is obtained in Cycle 2- these tests in Cycle 3 will continue as long as the prior scan is positive up to a maximum of 15 total. In this case, SPECT/CT imaging in Cycle 3 will be timed to correspond to SPECT/CT in Cycles 1and 2.

5.0 Grouping Factors:

5.1 Phase I vs Phase II

5.2 Dose level: -1 vs 0 vs 1 ***(Phase I only)***

5.3 Disease: Measurable vs non-measurable

6.0 Registration/Randomization Procedures

6.1 Phase I

6.11 Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] for dose level and to ensure that a place on the protocol is open to the patient.

6.12 To register a patient, fax [redacted] a completed eligibility checklist to the Mayo Clinic Cancer (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time, Monday through Friday.

6.2 Phase II

6.12 Registration Procedures

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, 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 a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration 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."

6.3 Phase I and II

6.31 A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19d, 14.0, and 17.0).

6.32 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.

6.33 At the time of registration, Registration Office personnel will verify the following:

- IRB approval
- patient eligibility
- existence of a signed consent form
- existence of a signed authorization for use and disclosure of protected health information.

In addition, the following will be recorded:

- Patient has/has not given permission to store samples for future research of cancer
- Patient has/has not given permission to store samples for future research to learn about, prevent or treat other health problems
- Patient has/has not has given Mayo permission to give their samples to outside researchers

6.34 Treatment on this protocol must be administered at Mayo Clinic Rochester under the supervision of a medical or gynecologic oncologist.

6.35 Treatment cannot begin prior to registration and must begin ≤42 days after registration.

6.36 Pretreatment tests must be completed within the guidelines specified on the test schedule.

6.37 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.38 Following patient registration, the clinical research associate (CRA) will notify [redacted] for coordination of collection and delivery of specimens for laboratory correlative studies.

6.39 Patients will be admitted to the CRTU (Clinical Research and Trials Unit) on the evening prior to each cycle of therapy. The clinical research associate (CRA) should inquire with the CRTU on bed availability prior to registering the patient.

7.0 Protocol Treatment

Note: For patients who have surgery for intraperitoneal port placement, a waiting period of 4 weeks (±2 weeks) will commence prior to receipt of Cytomel®.

7.1 Treatment schedule – Phase I

Agent	**Dose**	**Route**	**Day**
Pre-medication prior to administration of MV-NIS Cycles 1 & 2. Given prior to Cycle 3 if the Cycle 2 SPECT/CT is positive.			
Liothyronine sodium (Cytomel®)	0.025 mg	1 tablet three times a day	Day –7 through day of last SPECT/CT scan

Cycle 1			
Agent	**Dose**	**Route**	**Day**
MV-NIS[1]	10^9 TCID50	IP	Day 1

[1]MV-NIS will be diluted in 500 mL of 0.9% Sodium Chloride and administered over 30 minutes

Cycles 2-6[1]				
Agent	**Dose**	**Route**	**Day**	**Re-Rx**
MV-NIS infected MSC(MV-NIS/MSC)[2]	Assigned by the Registration Office	IP	Day 1	Every 28 days for up to 5 cycles

[1]Patient will proceed to Cycle 2 treatment, only if acceptable tolerance and lack of progression following Cycle 1
[2]MV-NIS/MSC will be diluted in 500 mL of Lactated Ringers and administered over 30 minutes

After MV-NIS Administration			
Agent	**Dose**	**Route**	**Day**
^{123}I	5 mCi	Oral	Day 3 and 8 of study (2 additional doses may be given for imaging based on imaging results)

7.11 Upon consent and prior to Cycle 1, patients will undergo fat aspiration at the time of catheter placement. The surgeon placing the catheter will be performing the procedure. Once it is collected, it will be placed in Sterile Buffered Saline and transported to the Human Cellular Therapy Laboratory for manufacturing and freezing. If patients have already had catheter placement, fat aspiration can be conducted in the Clinical Research Trials Unit (CRTU).

7.12 Patients will receive liothyronine sodium (Cytomel®) to prevent thyroid uptake when repeated imaging doses of ^{123}I are administered.

7.13 The virus will be administered through intraperitoneal port-a-cath that will be surgically placed at the time of study entry. If ascites is present, it will be drained through the port-a-cath prior to administration of MV-NIS. The patient will receive infusion of the assigned dose of MV-NIS diluted in 500 mL of 0.9% Sodium Chloride over 30 minutes in Cycle 1. The assigned dose of MV-NIS infected MSC will be diluted in 500 mL of Lactated Ringer's and administered over 30 minutes (Cycles 2-6). Treatment will be administered at the Clinical Research and Trials Unit (CRTU).

7.14 The *in vivo* distribution of MV-NIS infected cells and the kinetics of virus spread and elimination will be monitored by SPECT/CT imaging after oral ^{123}I administration (2 hours after 5 mCi).

SPECT/CT imaging will be performed on Days 3 and 8 after MV-NIS administration. In addition patients may be imaged on Days 15 and 28 if previous imaging is positive for continued uptake.

These scans will be elective, based on whether there is continued uptake on prior imaging studies. Imaging at the same schedule will be performed in Cycle 2. Imaging by SPECT/CT to be performed in Cycle 3, only if positive imaging is obtained in Cycle 2. In this case, SPECT/CT imaging in Cycle 3 will be timed to correspond to SPECT/CT in Cycle 2.

7.15 The first and second cycle will be administered in the inpatient setting. Patients will be admitted the evening prior to administration and dismissed 24 hours after administration of the agent. For subsequent cycles, the agent will be administered in the outpatient CRU and the patients will be observed in the facility for three hours after administration of the agent. A saline lock for IV access, if necessary, will be placed prior to viral administration.

7.2 Phase I Dose Escalation:

Level	**Dose infected cells** (MV-NIS/MSC)
-1	10^6
0*	10^7
1	10^8

*Starting dose.

7.21 Patients will be observed for a minimum of 4 weeks after the third patient at each cohort has received treatment on Cycle 2, before new patients are treated. The study will temporarily close. Resolution of viremia is required prior to dose escalation being allowed. Doses will not be escalated in any individual patient.

7.22 For this protocol, dose-limiting toxicity (DLT) will be defined as an adverse event attributed (definitely, probably, or possibly) to the MV-NIS infected MSC study treatment and meeting the following criteria:

Toxicity	**Definition**
Hematologic	≥Grade 3 per NCI Common Terminology Criteria for Adverse Events v4.0 except grade 3 ANC lasting <72 hours.
Investigations	Creatinine increased ≥2 times baseline
Other nonhematologic	≥Grade 3 per NCI Common Terminology Criteria for Adverse Events v4.0*
Viremia**	Lasting for ≥6 weeks from last viral administration
Allergic reaction	The Grade 2 allergic reactions: asymptomatic bronchospasm and/or urticaria; and ≥Grade 3 allergic reactions

* Grade 3 nausea, vomiting, or diarrhea, while receiving the maximum supportive care regimen described in the protocol, will be considered dose-limiting. Alopecia will not be considered dose limiting.

** Viremia is defined as detection of any titer of virus by RT-PCR in patient's PBMCs. Detection limit for this assay is 1000 genome copies/mcg RNA.

7.23 Accrual for this study will cease permanently if:
a) 2 or more patients experience DLT at a particular dose level during the phase I component or
b) any patient experiences a Grade 5 treatment-related toxicity.

7.24 Dose de-escalation:
Dose de-escalation MV-NIS: If dose-limiting toxicity is seen at dose level 0, patients will be entered at a dose level of 10^6 infected MSC.

7.25 If a patient on the phase I component fails to complete the initial course of MSC therapy (defined as drug administration on Cycle 2 plus four weeks of observation) for reasons other than toxicity, the patient will be regarded as treatment intolerant and an additional patient will be treated at the current dose level; however, all toxicity information will be utilized in the analysis. For these instances, a specific notation will be made for review by the Scientific Progress Review Committee (SPRC).

7.26 The MTD of the phase I component of the trial will be used as the dose for the phase II component of the trial (See Section 16.0).

7.3 Treatment schedule – Phase II

7.31 Premedication

Agent	Dose	Route	Day
Pre-medication Prior to Administration of MV-NIS cycles 1 & 2. Given prior to cycle 3 if the cycle 2 SPECT/CT is positive.			
Liothyronine sodium (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 (ex. 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.

7.32 Cycle 1

Cycle 1			
Agent	**Dose**	**Route**	**Day**
MV-NIS	10^9 TCID50	IP	Day 1

7.33 Cycles 2-6

Cycles 2[1]-6				
Agent[2]	**Dose**	**Route**	**Day**	**Re-Rx**
MV-NIS /MSC	10^8 MV-NIS/MSC	IP	Day 1	Every 28 days for up to 5 cycles

[1]Patient will proceed to Cycle 2 treatment, only if acceptable tolerance(i.e. not meeting criteria for treatment discontinuation as per section 8.0) and lack of progression following Cycle 1. Given the difference between MV-infected MSC (cycle 2) versus naked MV treatment (cycle 1), if progressive disease at the end of cycle 1, patient may still proceed with cycle 2 treatment at the discretion of the treating physician, if the progression is asymptomatic.

[2]If MSC not available (e.g., due to manufacturing issues) patient may receive MV-NIS alone at same dose as Cycle 1.

7.34 Prior to Scans

After MV-NIS Administration			
Agent	**Dose**	**Route**	**Day**
^{123}I	5 mCi	Oral	Day 3 and 8 of study (2 additional doses may be given for imaging based on imaging results)

7.35 Liothyronine sodium (Cytomel®)

Patients will receive Liothyronine sodium (Cytomel®) to prevent thyroid uptake when repeated imaging doses of ^{123}I are administered.
NOTE; For a patient who is receiving thyroid replacement (ex. 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.

7.36 Virus administration

The virus will be administered through intraperitoneal port-a-cath that will be surgically placed at the time of study entry. If ascites is present, it will be drained through the port-a-cath prior to administration of MV-NIS. The patient will receive infusion of the assigned dose of MV-NIS diluted in 500 ml of NS over 30 minutes. The assigned dose of MV-NIS /MSC will be diluted in 500 ml of Lactated Ringer's and administered over 30 minutes (Cycles 2-6). Treatment will be administered at the Clinical Research Unit (CRU).

7.37 Monitoring by SPECT/CT

The *in vivo* distribution of MV-NIS infected cells and the kinetics of virus spread and elimination will be monitored by SPECT/CT imaging after oral ^{123}I administration (2 hour after 5 mCi).

SPECT/CT imaging will be performed on Days 3 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 at the same schedule will be performed in Cycle 2. Imaging by SPECT/CT to be performed in Cycle 3, only if positive imaging is obtained in Cycle 2. In this case, SPECT/CT imaging in Cycle 3 will be timed to correspond to SPECT/CT in Cycle 2.

7.38 Administration Setting

The first and second cycle will be administered in the inpatient setting. Patients will be admitted the evening prior to administration and dismissed 24 hours after administration of the agent. For subsequent cycles, the agent will be administered in the outpatient CRU and the patients will be observed in the facility for three hours after administration of the agent. A saline lock for IV access, if necessary, will be placed prior to viral administration.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table until individual treatment tolerance can be ascertained. 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.

ALERT: *ADR reporting may be <u>required</u> for some adverse events. See Section 10.*
→→ 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			
Investigations	Grade 3 Platelet count decreased	MV-NIS/	↓ by one dose level.**
	Grade 3 Neutrophil count decreased		
	Grade 4 Platelet count decreased		Discontinue treatment and follow up per Section 18
	Grade 4 Neutrophil count decreased		
All other non-hematologic categories*	Grade 3 Nonhematologic		↓ by one dose level.**
	Grade 4 Nonhematologic		Discontinue treatment and follow up per Section 18.
AT SCHEDULED RETREATMENT (e.g. Day 1 of subsequent cycle)			
Investigations	Grade 3 Platelet count decreased	MV-NIS/ MSC	↓ by one dose level.**
	Grade 3 Neutrophil count decreased		
	Grade 4 Platelet count decreased		Discontinue treatment and follow up per Section 18.
	Grade 4 Neutrophil count decreased		
All other non-hematologic categories*	Grade 3 Nonhematologic		Wait until ≤Grade 1 then retreat per interim toxicity**.** If no resolution within 2 weeks (Week 6), discontinue treatment and follow-up per Section 18.0
	Grade 4 Nonhematologic		Discontinue treatment and follow-up per Section 18.0

CTCAE CATEGORY	ADVERSE EVENT	AGENT(S)	DOSE MODIFICATIONS
Other specific event	Viremia		If no resolution within 2 weeks (Week 6), discontinue treatment and follow-up per Section 18.0

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

** If patient is at lowest level, discontinue therapy and proceed to observation

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 the first cycle of treatment will not be allowed; however, prophylaxis is allowed prior to subsequent cycles should a patient develop nausea/vomiting associated with the first treatment cycle.

- Dexamethasone as antiemetic is not allowed.

Acceptable treatment options for nausea include ondansetron 4 mg PO every 8 hours as needed, if still nauseated in one hour may give an additional 4 mg.

Acceptable treatment options for vomiting include: First prochlorperazine 10 mg every 6 hours as needed (if unable to take orally) give 10 mg IV every 6 hours as needed. Second (if still vomiting 30 to 60 minutes status post prochlorperazine) lorazepam 0.5 mg PO every 4 hours as needed. If unable to take oral medications, may administer IV.

Acceptable treatment options for diarrhea include: First suggest loperamide 4 mg after first diarrheal bowel movement and 2 mg after each subsequent one up to 16 mg a day. If diarrhea is not controlled with loperamide, may try atropine sulfate/diphenoxylate hydrochloride (Lomotil®) 2 tablets every 6 hours as needed or 10 mL every 6 hours as needed.

Acceptable treatment options for fever include acetaminophen 500-1000 mg every 6 hours as needed up to 4 grams a day. If fever is not controlled with acetaminophen or the patient has a contraindication to acetaminophen, may give ibuprofen 400 mg every 6 hours as needed (first) or naproxen 250-500 mg twice daily (second).

9.3 Diagnosis of measles

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.

9.4 Support if patient is diagnosed with measles

Should a patient develop measles, treatment with immune globulin will be administered at a dose of 400 mg/kg/day for 3-5 days. Aerosolized ribavirin (6 g/day) 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.

9.5 Coenrollment in other trials or studies

Patients participating in Mayo Clinic Cancer Center Phase I Program clinical trials are not to be considered for enrollment in any other study involving a pharmacologic agent (drugs, biologics, immunotherapy approaches, gene therapy) whether for symptom control or therapeutic intent.

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 (see 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 the event must 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 10.6 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 neither 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

10.41 **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

10.42 General reporting instructions

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

Use Mayo Expedited Event Report form:

[redacted] or investigational agents or commercial/investigational agents on the same arm.

10.43 Reporting of re-occurring SAEs

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

10.5 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:

System Organ Class (SOC)	Adverse events/Symptoms	Baseline	Each evaluation
General disorders and administration site conditions	Fever	X	X
	Chills	X	X
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X
Gastrointestinal disorders	Diarrhea		X
	# of stools	X	
	Flatulence	X	X
	Nausea	X	X
	Vomiting	X	X
	Abdominal pain	X	X
Respiratory, thoracic and mediastinal disorders	Dyspnea (shortness of breath)	X	X

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 10.6:

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 4 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response. Modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria will be used. NOTE: Per Section 7.3, if progressive disease at the end of Cycle 1, patient may still proceed with Cycle 2 treatment at the discretion of the treating physician, if the progression is asymptomatic.

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 3 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)

Note:

- 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 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 Confirmatory measurement/Duration of response

11.41 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

11.42 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.

11.43 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.

11.5 Evaluation criteria for patients enrolled in the study based on a positive second look or after secondary debulking but without measurable disease

Patients will be monitored radiographically for reappearance or increasing parameters of disease. Use of only the CA-125 tumor marker will not be taken as an indicator of progression. Patients who have not progressed after 6 cycles of treatment will have a laparoscopy performed for evaluation of treatment efficacy.

12.0 Descriptive Factors

12.1 Ascites present: Yes vs. no.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 No PD and no intolerable toxicity

Patients who have not had PD at time of their reassessment and have not experienced intolerable toxicity will be allowed to continue protocol treatment until PD or for a maximum of 6 cycles.

13.2 Stable disease

Patients who experience regression or stable disease will be allowed to continue treatment for up to 6 cycles.

13.3 No PD and intolerable toxicity

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 Observation/Completion of 6 cycles without PD

Those patients who have

- completed 6 cycles of treatment without PD or
- have documentation of PD prior to completion of 6 cycles or
- who refuse further treatment or
- start alternate treatment or
- have unacceptable toxicities necessitating the stopping of treatment

will go off treatment and will be followed for observation per the test schedule. Patients will stay on observation until 1 year post-PD/alternate treatment per Section 4.0**,** then go to event monitoring. NOTE: Patients who refuse to return for observation will go to event monitoring.

13.5 Event Monitoring

Those patients completing observation or refusing to participate in observation will go to event monitoring per Section 18.13. If a patient does not have progressive disease at any

time during the study (treatment/observation/event monitoring), at least one (1) Event Monitoring form is required to be completed preferably at the end of event monitoring.

13.6 Replacement

If a patient enrolled in the phase I component fails to complete the initial course of therapy (defined as MSC drug administration on Cycle 2 and four weeks observation) for reasons other than toxicity, the patient will be regarded as treatment intolerant and an additional patient will be treated at the current dose level; however, all toxicity information will be utilized in the analysis. For these instances, a specific notation will be made for review by the Scientific Progress Review Committee (SPRC).

13.7 Ineligible

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

13.8 Major Violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the 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.

13.9 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. 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

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

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect (# of tubes to be collected)	Pre-Treatment-At peritoneal catheter placement	Cycle 1, Day 1 (prior to treatment as base-line)	Cycles 1 & 2 Day 3	Cycles 1 & 2 Day 8	Cycles 1 & 2 Day 15 and 23 (±72 hrs)	Cycles 2-6, Day 1 (prior to treatment)	Cycles 3-6, Day 3, 23 (±72 hrs)	Process at CRU site? (Yes or No)	Temperature Conditions for Storage Shipping
Peritoneal aspirate collection (See Section 14.21)	Mandatory	Peritoneal aspirates	300 mL Sterile	All available	X[3]		X	X		X[2]		NO draw only	On ice
Viremia	Mandatory	Whole Blood	PAXgene Blood RNA tubes	2.5 mL		X	X	X	X		X	NO draw only	Ambient (whole blood)
Viral shedding	Mandatory	Urine	50 mL sterile tubes-falcon	200 mL -4 50mL tubes		X	X	X	X[1]		X	Yes	On ice, then freeze after processing
Viral shedding	Mandatory	Mouth gargle	50 mL sterile tubes-Falcon	2 X 15mL		X	X	X	X[1]		X	Yes	On ice, then freeze after processing
Immune response to viral administration	Mandatory	Whole Blood	7 green top tubes	7 x 10 ml		X				X		NO draw only	Ambient (whole blood)
Immune response against the tumor	Mandatory	Whole Blood	1 red top tube	1 x 10 ml		X				X		NO draw only	Ambient (whole blood)

1. Day 23 only
2. Cycles 3-6 only
3. Only for patients who have peritoneal catheter placement as part of the trial

14.2 Collection and Processing

14.21 Evaluation of peritoneal aspirate (ascitic fluid or lavage at the absence of ascites). Previous studies of intraperitoneal chemotherapy have shown the feasibility of retrieval of carcinoma cells for pathologic evaluation [15,16]. Harvested cellular material will be tested prior to treatment and on Days 3 and 8 Cycles 1 and 2, and again prior to treatment for Cycles 3-6 for: a) viral replication (RT-PCR and co-culture with Vero cells); b) *in situ* hybridization for measles virus N-specific mRNA. Supernatant from the peritoneal aspirate will be tested for: a) viral replication (co-culture with Vero cells); b) anti-measles virus antibodies at baseline, Days 3 and 8 of Cycle 1, Day 1 of Cycle 2 prior to treatment, Day 3 and 8 of Cycle 2 and prior to treatment Cycles 3-6. If in addition to peritoneal aspirate, a biopsy is obtained post treatment, tumor and adjacent peritoneum will be examined for cytopathic effect and tested for viral replication and in situ hybridization. Testing will be performed in [redacted] laboratory. All attempts to obtain peritoneal fluid will be made per Section 14.0, but it will not be a protocol deviation if no peritoneal fluid is collected on patients whose port is not easily accessed.

14.22 Assessment of viremia and viral shedding. Patient's peripheral blood mononuclear cells will be monitored for evidence of measles virus viremia. This monitoring 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). Tubes will be kept at room temperature and [redacted] notified to pick up the samples. Quantitative RT-PCR to be performed prior to treatment, on Day 1, then on Day 3, 8, 15 and 23 of Cycles 1 and 2, and on Day 1, 3, and 23 for Cycles 3-6. Viral shedding will be assessed by quantitative RT-PCR of throat gargle specimens(s) and urine samples, both being processed under sterile conditions on Days 1, 3 8, of Cycles 1 and 2, prior to treatment on Day 1 Cycle 3-6 . Testing will be performed in [redacted] laboratory.

Sample processing in GCRC 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] laboratory personnel. [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 degree Celsius freezer. [redacted] will be notified to pick up the samples.

If a patient is found to be shedding the virus in urine or throat gargle specimens(s), family members who don't have documentation of immunity, will be offered testing to assess anti-measles virus immunity by Enzyme Immunoassay (Diamedix, see section 3.18) and testing of throat gargle specimens(s) for the presence of MV-NIS. Measles vaccination will be offered to seronegative individuals, per standard clinical practice.

14.23 Assessment of peripheral immune response to viral administration: measles virus specific immunity will be measured by means of (a) measuring anti-measles virus specific antibodies (IgG) at baseline, and day 1 of cycle 2-6 prior to treatment and (b) IFN-γ and IL-10 measles ELISPOT [17] to be performed at baseline, and day 1 of cycle 2 prior to treatment and day 1 prior to treatment cycle 3 -to 6. This testing will be performed in [redacted] laboratory. Cells received from [redacted] from [redacted]

14.24 Assessment of immune response against the tumor. This will be assessed by evaluating the immune response against insulin-like growth factor binding protein 2 and the folate receptor alpha [18], using IFN-gamma and IL-4 ELISPOT assays and cytokine multiplex analysis (17-plex) to be performed at baseline, and prior to treatment day 1 of cycles 2-6. These assays will be performed at the laboratory of [redacted] as previously described [18]. IFN-gamma and IL-4 ELISPOT assays will determine the frequencies of Th1 and Th2 tumor antigen specific T cells, respectively. Cytokine multiplex assays will evaluate the levels proinflammatory cytokines in both the cellular supernatants and the serum, to identify the breadth (i.e. polyfunctionality) of the immune responses. 10 ml of blood will be drawn into 7 green-top heparin tubes and 1 red top sera clot tube and kept at room temperature. [redacted] will be notified to pick-up the samples and transfer to [redacted] lab.

15.0 Drug Information

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

15.11 **Background**: 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.

15.12 **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.

15.13 **Administration**: The virus will be administered intraperitoneally over 30 minutes in 500mL of 0.9% Sodium Chloride under close observation in the Clinical Research Unit.

15.14 Known potential toxicities

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.

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)

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 pruritus
- Thrombocytopenia
- Diarrhea

15.15 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 MV-NIS/MSC (Mesenchymal Stem Cell (MSC) infected with NIS-Measles Virus – Edmonston Strain)

15.21 **Background**: Mesenchymal Stem cells will be processed in Human Cellular Therapy Lab (HCTL) in Rochester, MN. The MV-NIS/MSC combination facilitates the delivery of the MV-NIS to the tumor cells, by allowing the MSC to protect the MV-NIS from immune destruction before arriving at the tumor sites.

15.22 **Preparation and storage**: Upon consent and enrollment and prior to Cycle 1, patients will undergo fat aspiration at the time of catheter placement. Tissue will be transported to the Human Cellular Therapy Lab (HCTL) in Rochester, MN for manufacturing and freezing. Manufacturing will start with enzymatic digestion of the fat tissue followed by expansion of plastic-adherent cells. Cells will be cultured until a sufficient number are obtained for the treatment protocol. At the final passage, cells will be harvested/pooled and pre-freeze characterization samples will be removed. Testing prior to frozen storage will include aerobic and anaerobic culture, endotoxin, mycoplasma PCR, karyotype, and flow cytometry for markers characteristic of MSC. After release and on the day of infusion, i.e. Cycles 2-6, the appropriate number of cryovials/cells will be removed from the freezer, thawed, washed (to remove DMSO), infected with MV-NIS for 2 hours and combined into a single, final product (500 mL bag of Lactated Ringer's). Final product assessment will include viability, gram stain, aerobic and anaerobic cultures, and endotoxin. Product will be labeled and made available for infusion if all release criteria are met (See Certificate of Analysis for specific release criteria). Standard operating procedures (SOPs) have been developed solely for production of h-MSC and have been used under previous INDs (BB IND 14788, and BB IND 15176) and for production of MV-NIS (IND10895)

15.23 **Administration:** MV-NIS/MSC will be administered intraperitoneally over 30 minutes in 500 mL Lactated Ringer's at the Clinical Reseach Unit.

15.24 **Potential Drug Interactions**: No drug interactions are known at this time.

15.25 Known potential toxicities

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.

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)

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 pruritus
- Thrombocytopenia
- Diarrhea

15.26 **Drug procurement:** MV-NIS is manufactured by the Virus and Vector Production Laboratory (VVPL) of the Molecular Medicine Program at Mayo Clinic and stored at -80°C. When administered as a single agent, the virus will be thawed and mixed with normal saline prior to administration. The MV-NIS/MSC mixture will be prepared in the Human Cellular Therapy Laboratory. Product ready for administration will be delivered by HCTL staff to the patient bedside or clinical ward for administration.

15.27 **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.

15.3 Liothyronine for Oral Administration (Cytomel®, T3)

15.31 **Background**: Liothyronine (T3) is a thyroid product. The principal pharmacologic effect of exogenous thyroid hormones is to increase the metabolic rate of body tissues. Thyroid hormones are also involved in the regulation of cell growth and differentiation. Although the precise mechanism of action by which thyroid hormones affect metabolism and cellular growth and differentiation is not clearly established, it is known that these physiologic effects are mediated at the cellular level, principally via triiodothyronine; a major portion of triiodothyronine is derived from thyroxine by deiodination in peripheral tissues. Sound-alike/look-alike issues: Do not confuse with levothyroxine. T3 is an error-prone abbreviation (mistaken as acetaminophen and codeine [i.e., Tylenol #3].

15.32 **Formulation**: Commercially available for oral administration as:
Tablets: 5 mcg, 25 mcg, 50 mcg

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature preferably below 25ºC (77ºF).

15.34 **Administration:** Refer to the treatment section for specific administration instructions. Sound-alike/look-alike issues: Do not confuse with levothyroxine. T3 is an error-prone abbreviation (mistaken as acetaminophen and codeine [i.e., Tylenol #3].

15.35 **Pharmacokinetic information**:
Protein binding: low
Bioavailability: >95%

15.36 **Potential Drug Interactions**:
Oral Anticoagulants: Thyroid agents may potentiate the hypoprothrombinemic effect of warfarin and other oral anticoagulants, apparently by increasing catabolism of vitamin K-dependent clotting

factors. When thyroid agents are administered to patients receiving oral anticoagulants, the prothrombin time should be determined frequently and anticoagulant dosage adjusted accordingly, and patients should be observed closely for adverse effects. It has been suggested that the dosage of the oral anticoagulant be reduced by one-third when thyroid therapy is started. No special precautions appear to be necessary when oral anticoagulant therapy is initiated in patients already stabilized on maintenance thyroid replacement therapy.

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Because the treatment is short term only for cancer clinical trials only mild and transient side effects are expected. These include:
Cardiac: tachycardia, transient atrial fibrillation, cardiac arrhythmia
CNS: feeling of warmth, anxiety, insomnia
Neurologic: tremor

Less common known potential toxicities, 1% - 10%:
See below

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

Liothyronine shares the toxic potentials of other thyroid agents, and the usual precautions of thyroid agent therapy should be observed. Adverse reactions to Liothyronine result from over dosage and are manifested principally as signs and symptoms of hyperthyroidism including fatigue, weight loss, increased appetite, palpitations, nervousness, hyperactivity, anxiety, irritability, emotional lability, diarrhea, abdominal cramps, vomiting, elevated liver transaminase concentrations, sweating, tachycardia, increased pulse and blood pressures, angina pectoris, cardiac arrhythmias, tremors, muscle weakness, headache, insomnia, intolerant to heat, fever, hair loss, flushing, decreased bone mineral density, impaired fertility, and menstrual irregularities. Complications of severe over dosage may include cardiac decomposition, cardiac failure, myocardial infarction, cardiac arrest, and possibly death secondary to cardiac arrhythmia or failure. Seizures have been reported rarely with levothyroxine therapy. The effects of Liothyronine may appear within 24 to 72 hours after initiation of therapy or an increase in dosage.

Hypersensitivity reactions to excipients in formulations of thyroid agents have been reported rarely. Manifestations include urticaria, pruitus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting, and diarrhea), fever, arthralgia, serum sickness, and wheezing. Thyroid also may rarely cause GI intolerance in patients highly sensitive to pork.

15.38 **Drug procurement:** Provided free of charge to study participants. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 **Nursing Guidelines**

15.391 Patients who are on concomitant oral anticoagulants should have their PT/INR monitored frequently and adjust doses accordingly.

15.392 Patients may experience tachycardia, transient A-fib or other cardiac arrhythmia. Instruct patient to report any palpitations, or chest pain to study team immediately.

15.393 Patients may experience mild flushing. Warn patient of side effect

15.394 Insomnia may be seen. Instruct patient in good sleep hygiene methods, medicinal sleeping aids may be needed. Monitor for effectiveness.

15.395 Patients may experience tremor.

15.396 Monitor for signs/symptoms of overdose (as listed above). Usually these symptoms will present themselves within 24-72 hours of initiating of therapy or increase in dosage.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a Phase I/II study designed to (a) determine the MTD and toxicity of attenuated MV-NIS virus with MSC delivery in the treatment of ovarian tumors in the phase I component, and to (b) assess 12-month overall survival of ovarian cancer patients receiving this regimen, (c) assess 4-month progression free survival of ovarian cancer patients receiving the regimen, (d) assess toxicities associated with this regimen, (e) assess progression free and overall survival of ovarian cancer patients treated with this regimen, and (f) assess translational research endpoints in the phase II component.

16.2 Phase I Component

16.21 Study Design

The single arm phase I component is using the standard 3+3 design for phase I clinical trials [15, 16].

16.22 MTD Definition and Determination.

The MTD Definition: MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% (1-(1-0.25)6).

The MTD Determination:

16.221 The first cohort of 3 patients will be treated at the starting dose level 0.

16.222 Three patients will be treated at a given dose level and observed for at least 4 weeks from start of cycle 2 of treatment to assess toxicity.

16.223 If DLT is not seen in any of the 3 patients at a given dose level, then 3 additional patients will be treated at the next dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.

16.224 If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded, and further accrual will cease to this cohort. If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

16.225 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

16.23 Accrual and study duration.

Patients will be accrued in cohorts of 3. The phase I component may require as many as 18 patients (6 each for the 3 dose levels) but is more likely to require 9

patients (3 at dose level 0 and 6 at dose level 1). It is expected to take approximately 5 months to assess each cohort of 3 (2 months to accrue 3 patients, 2 months for evaluation of cycle 2, and 1 month for data collection and analysis); thus the expected study duration of the phase I component is 15 months.

16.24 Phase I Analyses

The number and severity of all adverse events (overall, and by dose-level) will be tabulated and summarized. The grade 3+ adverse events will also be described and summarized in a similar fashion. Overall toxicity incidence as well as toxicity profiles by dose level and patient will be explored. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

Although correlative samples will be collected for all patients (Phase I and II), only the phase I patients treated at the MTD will stay on-study for the Phase II portion and be included in the efficacy and translational analyses.

16.3 Phase II Component

16.31 Overview

The phase II component is a single arm, two stage Simon design to determine efficacy of the MV-NIS regimen.

16.32 Primary Endpoint

The primary endpoint of this trial is the proportion of patients alive at 12 months (i.e., 365 days) after study registration (OS12). An eligible patient who signs the consent form, begins study therapy, and are not lost to follow-up before 12 months will be considered evaluable for assessment of treatment efficacy. To be classified as a "success", a patient must be evaluable and be alive at least 12 months (i.e., 365 days or more) after registering to the study. If the patient is lost to follow-up prior to being on-study for 12 months, they will be considered unevaluable and will be replaced for these analyses.

Note: To obtain estimates of the proportion of patients achieving OS12 under the null hypothesis, we reviewed recent literature of clinical trials for recurrent platinum resistant ovarian cancer. A recent phase III trial [22] of PLD +/- patupilone patients in 829 patients with platinum resistant OVCA (progressed within 6 months of most recent platinum regimen) had OS12 of 53% across both arms; however, most patients (74%) had received only a single prior regimen. Another recent randomized phase II trial [23] of weekly versus 5-day topotecan assessed 194 patients with platinum resistant (progressed within 6 months following a platinum regimen) or platinum refractory (stable or progressive disease while being given platinum) OVCA and found a median survival of 9.3 and 9.6 months in the two arms, corresponding to an OS12 of approximately 40%; most patients (74%) had received a single prior regimen. An older [24] randomized phase III study of PLD vs. topotecan showed 1 year survival of 41.5% and 43.2% for platinum refractory patients (n=255) in the two arms. In addition, a recent characterization [25] of survival in 2nd through 6th line therapy in relapsed ovarian cancer indicated a median OS of 17.6 months at first relapse, 11.3 months at second relapse, and 8.9 months at third relapse. Thus, given the median number of prior therapies in the previous MV-CEA and MV-NIS trials was 3 and 4, respectively, using the same eligibility criteria as the currently trial, we conservatively estimate an OS12 rate of 40% under the null hypothesis.

16.33 Analysis Plans

The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-five percent binomial confidence intervals for the true success proportion will be calculated.

16.34 Design, Power, and Significance Level

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 40%, and the smallest that would warrant further subsequent studies is 62.5%. This design uses 24 evaluable patients to test the null hypothesis that the true complete response rate is at most 40%. Based on the design above, the decision rule has 90% power to detect a true success proportion of 62.5% with an alpha of 0.10.

First Stage: Enter 12 evaluable patients to the study. The 6 patients treated at the MTD in the phase I portion of the study will be included in this 12-patient total. If at most 5 successes in the first 12 evaluable patients, this regimen will be considered ineffective in this patient population and the study will be terminated. Otherwise, if the number of successes is at least 6, accrual will continue.

Final Decision rule: If 12 or fewer successes are observed in the first 24 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of successes is at least 13, this will be considered evidence of promising activity, and the treatment may be recommended for further testing in subsequent studies.

16.35 Over Accrual

If more than the target number of patients is accrued, the additional patients will not be used to evaluate the final decision rule. However, they will be included in the final analyses, which are described in section 16.33.

16.36 Adverse Event Stopping Rule:

If 4 out of the first 12, or 8 out of the first 24 or if at any time after the first 24 patients enrolled, 33% or more experience an adverse event that follows the DLT definition as listed in Section 7.22 on any cycle of treatment, accrual to the trial will be temporarily suspended. All AE data will be reviewed by the study team and the FDA before a decision can be made regarding whether the trial can re-open with the same dosing, amended dosing, or permanently closed.

16.37 Other Considerations:

Overall survival, time to progression, toxicity, and correlative measurements observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.38 Secondary/Tertiary Analyses:

16.381 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.

16.382 Progression-free survival at 4 months (PFS4). To compare the progression-free survival of MV-NIS/MSC in reference to outcomes previously observed on patients treated with MV-NIS and MV-CEA, as another indicator of improved efficacy we will assess the rate of patients

achieving PFS4. Patients who are alive and progression free 4 months (121 days) after study registration will be considered a success for PFS4. The rate of PFS4 on the prior MV-CEA and MV-NIS trial was approximately 24%.

16.3821 Test of improved PFS4 on MV-NIS/MSC compared to MV-NIS and MV-CEA. This decision rule uses a single stage design with a maximum of 24 patients to test the secondary null hypothesis that the true success proportion in the given patient population is at most 25%. If 2 or fewer successes are observed in the first 24 evaluable patients, we will consider the PFS4 in the MV-NIS/MSC regimen to be no greater than the PFS4 observed in the MV-NIS and MV-CEA trial. If 3 or more successes are observed in the first 24 evaluable patients, we will conclude that this treatment regimen has adequate evidence of improved efficacy on MV-NIS/MSC as measured by PFS4 compared to MV-NIS and MV-CEA.

With 24 patients, the study has 90% power at an alpha of 0.10 to conclude the current regimen has improved PFS4 if the true PFS4 rate is at least 45%

16.383 Overall survival is defined to be the length of time from study registration to a date of death due to any cause or last follow-up. The distribution of survival time will be estimated using the method of Kaplan-Meier.

16.384 Progression-free survival is defined to be the length of time from study registration to the first of either death due to any cause or progression. Patients that have not died or progressed will be censored on their last follow-up date. If a patient dies without documentation of disease progression, the patient will be considered to have had tumor progression at the time of death unless there is sufficient documented evidence to conclude no progression occurred prior to death. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.

16.385 Kaplan-Meier survival curves and logrank tests will be used to estimate the survival and progression-free time distributions of (a) the study patients and (b) study patient subsets defined by disease and/or correlative characteristics. These analyses are intended to be hypothesis generating and descriptive in manner. In addition, comparisons of overall PFS and OS in patients treated with MV-NIS/MSC will be made to patients enrolled on the prior MV-CEA and MV-NIS trial in an exploratory manner.

16.386 Toxicity:

All eligible patients that have initiated treatment will be considered evaluable for toxicity analyses. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

16.387 Translational Research Endpoints:

All analyses with respect to the translational component 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 above (i.e. anti-measles virus antibody and the presence of replicating virus, see 2.23) 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 using Spearman's coefficients, chi-squared tests, Wilcoxon rank-sum tests, Kaplan-Meier curves, and Cox proportional hazards models, where appropriate.

16.4 Routine Monitoring

This study will be monitored by the Mayo Clinic Cancer Center Data Safety Monitoring Board. In addition, efficacy, toxicity, and administrative information for this trial will be reviewed by the study team twice per year in conjunction with the DSMB review. The study team will monitor the trial for evidence of severe adverse effects and feasibility problems.

16.5 Inclusion of Women and Minorities

16.51 This study will be available to all eligible patients regardless of race or ethnic group.

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

16.53 Based on Mayo Clinic Cancer Center studies involving similar disease sites, we expect about 5% patients will be classified as minorities by race and 100% of patients will be women.

The expected accrual by gender and racial/ethnic group is summarized in the following table (based on goal of 5% minority accrual and 100% accrual of women):

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	2	0	0	2
Not Hispanic or Latino	34	0	0	34
Ethnic Category: Total of all subjects	**36**	**0**	**0**	**36**
Racial Category				
American Indian or Alaskan Native	1	0	0	1
Asian	0	0	0	0
Black or African American	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
White	35	0	0	35
Racial Category: Total of all subjects	**36**	**0**	**0**	**36**

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. **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:

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	At peritoneal catheter implantation	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Tumor biopsy	Mandatory	Formalin Fixed and Frozen	Biopsy	X[1]	Yes	Ambient Formalin Fixed and (-80º C) snap frozen
Benign sample	Mandatory	Formalin Fixed and Snap Frozen Benign tissue	Tissue piece	X[1]	Yes	Ambient Formalin Fixed and (-80º C) snap frozen
Fat Aspirate	Mandatory	Fat Aspirate	Tissue	X	Yes	Placed in Sterile Buffered Saline, then freeze after processing

1. If patient already has a port at the time of study enrollment, archived tumor tissue, one H&E slide and 5 unstained slides should be requested.

17.2 Collection and Processing

17.21 At the time of the catheter implantation, two samples will be obtained. Approximately one teaspoon of fat will be collected through the incision (only fat grossly free of tumor will be collected) and a tumor Biopsy is to be performed if medically feasible when surgeon is placing the port. When possible, tumor and benign tissue will be collected in the OR, processed by the frozen section lab (specify one snap frozen and one FFPE, and sent to PRC), with the request to call and page [redacted]

17.22 At the time of catheter implantation, fat aspirate will be collected. The surgeon placing the catheter will be performing the procedure. Once it is collected, it will be placed in Sterile Buffered Saline and transported to the Human Cellular Therapy Laboratory at Hilton 2-68 for manufacturing and freezing. Manufacturing will start with enzymatic digestion of the fat tissue followed by expansion of plastic-adherent cells. Cells will be cultured until a sufficient number are obtained for the treatment protocol. At the final passage, cells will be harvested/pooled and pre-freeze characterization samples will be removed. Testing prior to frozen storage will include aerobic and anaerobic culture, endotoxin, mycoplasma PCR, karyotype, and flow cytometry for markers characteristic of MSC. After release and on the day of infusion, i.e. Cycles 2-6, the appropriate number of cryovials/cells will be removed from the freezer, thawed, washed (to remove DMSO), infected with MV-NIS for 2 hours and combined into a single, final product (500 mL bag of Lactated Ringer's). Final product assessment will include viability, gram stain, aerobic and anaerobic cultures, and endotoxin.

Alternatively, the fat aspirate can be obtained by Human Cellular Therapy Laboratory (IMPACT) personnel using the IMPACT standard SOP at the CRTU/Charlton 7.

18.0 Records and Data Collection Procedures

18.1 Submission Timetables

18.11 Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study Form	≤2 weeks after registration
Baseline Adverse Event Form	
Laboratory Form Baseline	
Pretreatment RECIST Measurement Form[1]	
Research Submission Form	
Concomitant Medication (Baseline – Prior to Catheter Placement)	
Concomitant Medication (Baseline – Prior to Cycle 1)	
Research Tissue Submission Form (Baseline)	At peritoneal catheter implantation
End of Active Treatment/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Post-catheter scan

18.12 Test Schedule Material(s)

	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
CRF	At each evaluation during treatment	At end of treatment (end of Cycle 6)	Observation
Evaluation/Treatment Form Cycle 1	X[2]	X	
Evaluation/Treatment Form Cycles 2-6	X[2]	X	
Evaluation/Observation Form			X[1]
Active Monitoring RECIST Measurement Form	X	X	X[1]
Nadir/Adverse Event Form	X	X	X[1]
Laboratory Form(see section 4.0)	X	X	X[1]
Concomitant Medication Form	X	X	
Research Submission Form	X (see Section 14.0)		
End of Active Treatment/Cancel Notification Form		X	
ADR/AER	At each occurrence (see Section 10.0)		

1. Complete at each evaluation during Observation (see Section 4.0).
2. Complete at each evaluation during Active Treatment (see Section 4.0).

18.13 Follow-up Material(s)

	Event Monitoring Phase[1]	
CRF	q. 6 mos.	Death
Event Monitoring Form[2]	X	X

1. If a patient is still alive 5 years after registration, no further follow-up is required, but at least one (1) event monitoring form must be completed for all patients to record progression status.
2. **Note: Submit documentation of progression via attachment in Medidata Rave .**

19.0 Budget Considerations

MV-NIS

19.1 Costs charged to patient

Routine clinical care
Participants will not be billed for room and board or nursing charges while at the Clinical Research 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

The MV-NIS and adipose tissue derived mesenchymal stem cells will be provided free-of-charge by Mayo Clinic. Insertion of the port-a-cath, cost of liothyronine sodium (Cytomel®), all pharmacological/correlative studies, and procedures done solely for study purposes, such as SPECT/CT scans (covered by the Ovarian SPORE and the FAMSEA Study Budget).

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