Women's Triple-Negative First-Line Study: A Phase II Trial of Mirvetuximab Soravtansine is Patients with Localized Triple-Negative Breast Cancer (TNBC) with Tumors Predicted Insensitive to Standard Neoadjuvant Chemotherapy (NACT) Including a Lead-in Cohort to Establish Activity in Patients with Metastatic TNBC.

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AIBW	Adjusted ideal body weight
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the time-concentration curve
BUN	Blood urea nitrogen
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response/remission
CRC	Cohort Review Committee
CRF	Case report form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DM4	N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine
DM4-Me	Methylated-N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine
DOR	Duration of response
DTR	Deep tendon reflex
EC	Endometrial Cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOC	Epithelial ovarian cancer

Abbreviation or Specialist Term	Explanation
FRα	Folate receptor α
GCIG	Gynecologic cancer intergroup
GCP	Good clinical practice
GI	Gastrointestinal
GOG	Gynecologic oncology group
HFS	Hand-foot syndrome
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
IBW	Ideal body weight
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IHC	Immunohistochemistry
IMGN	ImmunoGen
IMGN853	Mirvetuximab soravtansine
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
LBW	Lean body weight
LDH	Lactic acid dehydrogenase
LFT	Liver function test
Mab	Monoclonal antibody
MAD	Maximum administered dose
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate

Abbreviation or Specialist Term	Explanation
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PET	Positron emission testing
PFS	Progression-free survival
PFT	Pulmonary function tests
PGP	p-glycoprotein
PK	Pharmacokinetics
PLD	Pegylated liposomal doxorubicin
PO	Per orem (by mouth)
PR	Partial response/remission
PRES	Posterior reversible encephalopathy syndrome
PS	Performance status
PT	Prothrombin time
RBC	Red blood cell (count)
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SoD	Sum of diameters
SOC	Standard of care
SOP	Standard operating procedure
STD	Severely toxic dose
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
T_{max}	Maximum time
TBW	Total body weight
TTP	Time to progression
ULN	Upper limit of normal

Abbreviation or Specialist Term	Explanation
UPC	Urine protein creatinine ratio
US	United States
VHL	Von Hippel Lindau
V_{SS}	Volume of distribution at steady state
WBC	White blood cell (count)
WCBP	Woman of child bearing potential
WHO	World Health Organization
WHO-DD	World Health Organization –Drug Dictionary

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1. INTRODUCTION

1.1. Target Background

Folate receptor α (FRα) is a glycosyl phosphatidylinositol-anchored cell surface protein encoded by the FOLR1A gene. FRα binds and internalizes folate, which is an essential co-factor for one carbon transfer reactions that are required for DNA and RNA synthesis, cell growth and proliferation. Marked upregulation of FRα occurs during neonatal development and in cancer, suggesting that the receptor functions primarily under conditions of high folate demand. In contrast, normal adult tissues generally lack FRα expression and employ alternative transporters such as folate receptor β (FRβ), reduced folate carrier and proton-coupled folate transporter for folate uptake (Weitman 1992, Markman 2000, Mantovani 1994, Elnakat 2004, Kelemen 2006, and Investigator's Brochure).

TNBC accounts for 15-20% of all breast cancers and has been associated with younger age at diagnosis as well as a higher incidence in minority populations. Treatment of TNBC relies exclusively on chemotherapy and this approach is associated with limitations including poor bioavailability and off target effects in healthy cells. Nanotechnology has resulted in more precise drug delivery systems and several therapeutic nanocarriers have been FDA approved for the delivery of potent cytotoxic agents in a number of tumor types, including breast cancer. Targeting tumors with nanotechnology requires both the rational design of nanocarriers as well as an understanding of underlying tumor biology, including surface antigen expression. Clinical and preclinical data have suggested evidence of activity for using nanocarriers to target folate receptors for treatment of TNBC. FRα is a membrane bound protein with a high affinity for binding and transporting folate into cells. Not surprisingly, overexpression of FRα confers a growth advantage by increasing uptake of folate and activating alternate cell signaling pathways. FRα expression is also notably higher in epithelial malignancies compared to normal cells, including ovarian, lung and breast cancers. FRα expression is common in TNBC with 67% of these tumors demonstrating tumor cell membrane staining and nearly 40% expressing high levels of FRα. [9]

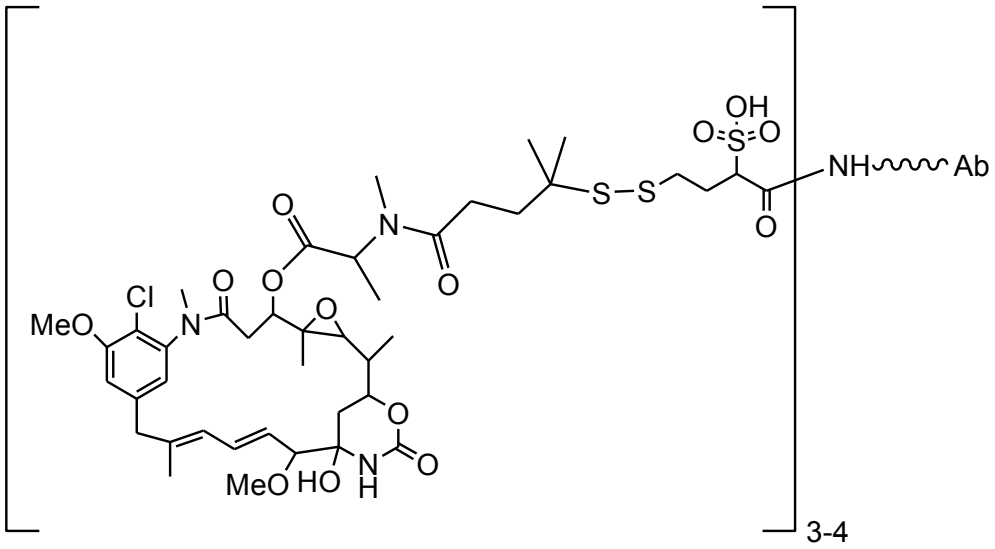
Importantly, nanoparticle delivery of potent maytansinoids using antibody conjugates has also demonstrated feasibility with diminished toxicity in breast cancers that express high levels of surface HER2. In HER2+ early stage breast cancer, the ADAPT trial reported a pCR rate of ~29% for single agent T-DM1 (Gluz, et al. J Clin Oncol 33, 2015; suppl; abstr 506) and pCR rates of 57% have also been reported when combined with docetaxel, though toxicity rates were much higher with doublet therapy (Martin, et al. SABCS, 2013). It is anticipated that mirvetuximab soravtansine will have similar rates of excellent pathologic response given the similar maytansinoid conjugate and high expression of surface FRα in nearly 40% of TNBCs.

1.2. IMGN853

Because of its tumor specific expression and capacity to internalize small and large molecule ligands, FRα has emerged as a promising target for antibody drug conjugate (ADC) therapy. ADCs combine the specificity of monoclonal antibodies to tumor antigens with the extraordinary cytotoxicity of maytansine derivatives, which are potent anti-microtubule agents that target

proliferating cells. IMGN853 is an ADC designed to target FRα. It consists of the humanized anti- FRα monoclonal antibody M9346A attached via a cleavable disulfide linker to the cytotoxic maytansinoid, DM4 (Figure 1).

Figure 1: IMGN853 Structure



DM4 is ~2% by weight relative to monoclonal antibody.

Due to the nature of the conjugation process, the number of DM4 molecules attached to the monoclonal antibody ranges from 1 to 7 molecules per antibody, with an average of 3 or 4 DM4 molecules per antibody. Conjugation of the maytansinoid to the tumor-targeting antibody ensures that the cytotoxic component remains inactive in the circulation. Release of the cytotoxic payload requires binding, internalization, and degradation of the antibody. The released payload then kills the cell by inducing G2-M arrest and cell death. Cellular processing of maytansinoid conjugates can also generate lipophilic catabolites that cross cell membranes and kill neighboring cells (Erickson 2006).

In vitro, IMGN853 binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent ($IC_{50} \leq 1$ nM) and selective cytotoxicity against tumor cells expressing FRα. Cytotoxic effects of IMGN853 *in vitro* is correlated to level of cell-surface expression of FRα. IMGN853 additionally demonstrates significant activity against FRα -positive xenografts, with partial and complete remissions observed in ovarian models (Ab 2015). Together with the selective upregulation of FRα in solid tumors, these results provide the rationale for exploring the clinical utility of IMGN853.

1.3. Triple Negative Breast Cancer (TNBC)

The study will enroll patients with advanced/metastatic TNBC and chemotherapy insensitive non-metastatic TNBC undergoing neoadjuvant therapy while enrolled in the ARTEMIS trial (MDA protocol 2014-0185).

1.3.1. Neoadjuvant Treatment of TNBC

Patients with localized TNBC are preferably treated with systemic chemotherapy (usually sequential anthracycline→taxane) in the neoadjuvant setting (NACT). Pathologic response to NACT can be determined by measuring the amount of residual cancer remaining in the breast and draining lymph nodes and is such a powerful indicator of prognosis that the Food and Drug Administration (FDA) has recognized significant improvement in complete response to neoadjuvant therapy as a pathway to drug approval. Investigators at MD Anderson have developed and validated a scoring system known as the Residual Cancer Burden (RCB) to quantify the extent of disease remaining after NACT.[1] Approximately 50% of TNBC patients treated with standard NACT will have either pathologic compete response (pCR/RCB-0) or minimal residual disease (RCB-I) at the time of surgical resection and those patients have identical and exceptionally good long-term prognosis (less than 10% risk of developing distant metastatic disease within 5 years). Unfortunately, those with more extensive disease (RCB-II or RCB-III) have a much worse prognosis, with 50%-80% of patients developing distant metastatic disease within 3 years of initial diagnosis.[2] Clinical trials of NACT in breast cancer have also demonstrated that patients without response to their first chemotherapeutic regimen have very low chance (5%) of achieving pCR after their second neoadjuvant course of chemotherapy.[3] However, this has not been the case with targeted regimens such as trastuzumab in HER2+ tumors, suggesting that intrinsic resistance to chemotherapy can be overcome with appropriate targeted therapy.[4] Though several targeted agents have been tested for treatment in TNBC, so far none have been successful. The underlying causes of this failure are commonly attributed to the molecular heterogeneity of tumors classified within the 'catch all' category of TNBC as well as the dilution effects of chemotherapy sensitive disease. Recent advances in molecular characterization have identified subgroups of TNBC with distinct molecular features that, if appropriately selected, may be more responsive to targeted therapy, leading to rapid improvement of outcomes in this high-risk breast cancer population. [5-9]

Our platform consists of a clinical trial to identify and characterize chemotherapy insensitive TNBC (**ARTEMIS**: **A Robust TNBC Evaluation FraMework to Improve Survival.** (PI: Moulder, Figure 2) as well as a diverse portfolio of phase II therapeutic trials to treat chemoinsensitive TNBC. In the ARTEMIS trial,

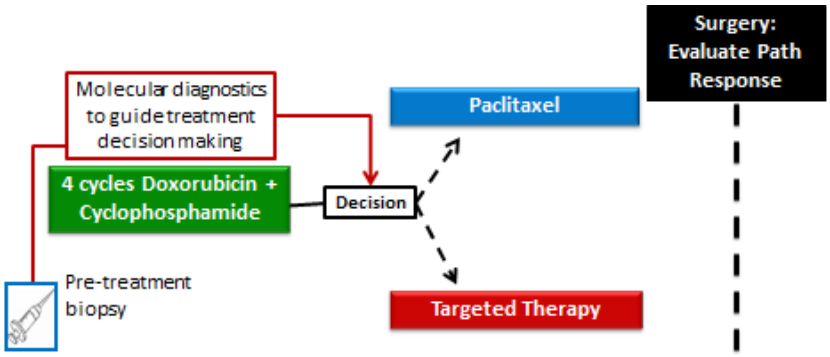


Figure 2: M.D. Anderson Neoadjuvant Research Platform for TNBC

treatment naïve patients (n=360) with newly diagnosed, localized TNBC undergo a pretreatment biopsy and then immediately start their initial phase of anthracycline-based chemotherapy. As such, the results of the molecular characterization are used in combination with response assessment after initial chemotherapy (clinical exam/diagnostic imaging) to identify chemotherapy insensitive disease and inform the second phase of neoadjuvant therapy based upon the patient's tumor characteristics, thus using a 'second hit' strategy in the middle of neoadjuvant chemotherapy to overcome drug resistance. Patients enrolled onto ARTEMIS will use imaging assessment of response to predict chemosensitivity. All patients are treated the same (Figure 3).

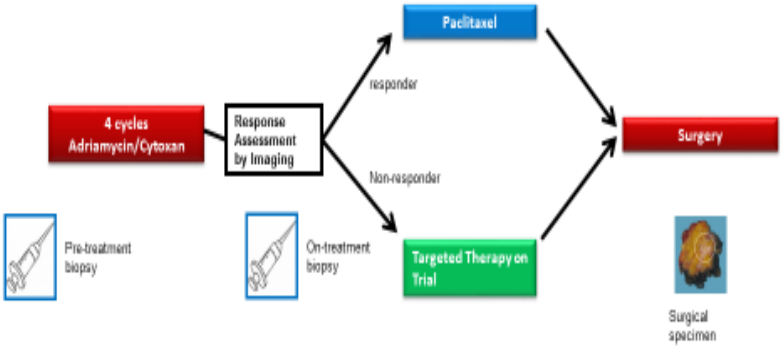


Figure 3: ARTEMIS uses imaging assessment of response to predict chemosensitivity. Notably, molecular profiling using IHC is an integral biomarker in the study design as it is used to select a therapeutic trial from the BMO research portfolio.

1.3.2. Folate receptor α expression in TNBC

Moderate to high expression of folate receptor alpha (FRα) has been associated with a worse prognosis in women with breast cancer independent of tumor size, nodal status or receptor status. Though an independent prognostic factor, FRα expression most often occurs in TNBC with 67% of these tumors demonstrating tumor cell membrane staining and nearly 40% expressing high levels of FRα (3+ in greater than 50% of cells).[9]

Preclinical data also suggest that using nanocarriers to target FRα for the treatment of TNBC is also feasible. For example, vintafolide, a small molecule drug conjugate consisting of folate linked to a potent vinca alkaloid demonstrated 80% complete response rates in mice bearing MDA-MB-231 xenografts (SABCS, 2013). Also, folic acid conjugation of micellar nanoparticles were able to successfully deliver the fatty acid synthase inhibitor orlistat which resulted in improved intracellular drug delivery and cytotoxicity compared to free orlistat in TNBC cell lines. Our group has also led vaccine trials targeting folate receptors as adjuvant therapy for patients with high risk breast cancer, many of who had residual disease after NACT.

1.4. Non-Clinical Studies of IMGN853

1.4.1. Pharmacology

Results of nonclinical pharmacology studies demonstrate the following:

- FRα (gene name FOLR1) has limited normal tissue expression and marked expression in epithelial tumors, particularly serous and endometrioid ovarian cancers and serous endometrial cancers, as assessed by IHC (Investigator's Brochure).
- In vitro studies demonstrated that IMGN853 binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent (IC50 ≤ 1 nM) and selective cytotoxicity against cells expressing FRα. IMGN853-mediated cytotoxicity involves binding, internalization, and degradation of IMGN853, which releases DM4. DM4 and a second catabolite, S-methyl-DM4, then inhibit tubulin polymerization and microtubule assembly, causing cell death. The lipophilic molecules S-methyl DM4 and DM4 can also diffuse to neighboring cells and induce bystander killing.
- *In vitro* cytotoxicity studies suggest that cells sensitive to IMGN853 express higher levels of FRα and release 10- to 100-fold more cytotoxic maytansinoid than cells resistant to IMGN853.
- IMGN853 retains the inherent activities of its antibody moiety, M9346A, including binding affinity (apparent affinity ≤ 0.1 nM) and selectivity for FRα, capacity for uptake, internalization and degradation by FRα-positive target cells, and ability to induce antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro*.
- IMGN853 demonstrates significant activity against FRα-positive xenografts. Partial and/or complete regressions in xenograft models of epithelial ovarian cancer were seen at doses of IMGN853 well below its maximum tolerated dose (MTD).
- IMGN853 shows significant *in vivo* efficacy against ovarian (IGROV-1, OVCAR-3 and OV-90 models) and NSCLC (NCI-H2110 model) tumor xenografts.
    - Combination IMGN853 + BEV is more efficacious than either agent administered as a monotherapy in ovarian (OV90 and IGROV-1) tumor xenografts as well as in an ovarian cancer patient derived xenograft model (ST088). In the patient derived xenograft model, the IMGN853 + BEV combination is more efficacious than combination therapy consisting of paclitaxel + BEV.
    - Combination IMGN853 + carboplatin is more efficacious than either agent administered as a monotherapy in the OV90 ovarian tumor xenograft model. Combination IMGN853 + carboplatin is more efficacious than carboplatin + paclitaxel in the model.
    - Combination IMGN853 + PLD is more efficacious than either agent administered as a monotherapy in the ST088 ovarian cancer patient derived xenograft model.

Pharmacology studies are further detailed in the IMGN853 Investigator's Brochure.

1.4.2. Pharmacokinetics

Nonclinical studies with IMGN853-cross reactive (monkey) and non-cross reactive (mouse) species were conducted to define pharmacokinetics (PK) parameters and to determine the stability of the linker and impact of conjugation on antibody clearance. An additional PK study

with free DM4 was conducted in monkey. PK studies demonstrated the stability of IMGN853 in circulation, showed clearance via a distribution phase lasting about 24 hours followed by a slower terminal elimination phase after intravenous administration, and suggested linear PK. These studies are further detailed in the IMGN853 Investigator's Brochure.

1.4.3. Toxicology

IMGN853 was evaluated for toxicity after a single intravenous injection in cross reactive (monkey) and non-cross reactive (mouse) species. Results of these studies supported the first-in-human (FIH) trial exploring the safety and tolerability of IMGN853 when administered once every three weeks to patients with advanced solid tumors. Potential risks suggested by these studies as well as clinical experience with other maytansinoid ADCs include hematologic abnormalities, electrolyte alterations, injection site reactions, infusion reactions, immunogenicity, hepatic abnormalities, and peripheral neuropathy. Toxicology studies are further detailed in the IMGN853 Investigator's Brochure.

1.5. Clinical Studies of IMGN853

1.5.1. First-in-Human Phase 1 Study: Study 0401

Study 0401 is a Phase 1, FIH, study designed to establish the maximum tolerated dose (MTD) and determine the recommended Phase 2 dose (RP2D) of IMGN853 when administered intravenously as a single agent in adult patients with FRα-positive solid tumors who have relapsed or are refractory to standard therapies. The study is comprised of two stages, dose escalation and dose expansion, and two dosing schedules, Schedule A (IMGN853 on Day 1 every 21 days) and Schedule B (IMGN853 on Days 1, 8, and 15, every 28 days).

The primary aim of the dose-escalation phase is to evaluate the safety and tolerability of IMGN853, to identify the MTD, and to characterize the PK profile of IMGN853 for each of the two dosing schedules. NCI CTCAE version 4.03 is used to grade the severity of treatment-emergent adverse events. Dose escalation is complete for both schedules.

For Schedule B, the starting dose of IMGN853 was 1.1 mg/kg, which was 1/3 the 3.3 mg/kg dose level, which was deemed clinically safe in nine patients on a Q3W schedule. IMGN853 was administered on Days 1, 8, and 15, with cycles repeating every 28 days. All doses were calculated according to adjusted ideal body weight (AIBW). Patients were enrolled in cohorts of 3 to 6 patients. The starting dose of IMGN853 for Schedule B was 1.1 mg/kg, which is 1/3 of the 3.3 mg/kg dose level, a dose level which was well tolerated in the nine patients dosed on the Q3W schedule. Twenty-five patients were enrolled to the following dose levels: 1.1, 1.8, 2.0 and 2.5 mg/kg (AIBW). The MTD was determined to be 2.0 mg/kg (AIBW). The cohort review committee (CRC) convened to review safety, PK and efficacy data from the dose escalation cohorts, as well as available data from patients dosed on Schedule A. These findings were presented at the ASCO annual meeting (Borghaei, 2015).

The modified weekly schedule did not provide any apparent safety or efficacy advantage. Based on safety and overall response data collected through May 2015, the CRC determined that all

new patients will receive IMGN853 treatment according to Schedule A (Q3W) only. Patients currently enrolling in the trial are receiving IMGN853 at the MTD of 6 mg/kg once every three weeks. Of note, the safety data available to date indicate that the MTD is equal to the RP2D.

As of January 31, 2016, 176 patients have been dosed. At least one treatment-emergent adverse event (TEAE) was reported by 171 patients (97%). Treatment-emergent adverse events of Grade 1 or 2 were most common (100 patients, 57%), 58 patients (33%) reported Grade 3 TEAEs, eight patients (5%) reported Grade 4 and five patients (3%) experienced a Grade 5 TEAE.

The most common TEAEs, reported in ≥ 20% of patients included diarrhea (75 patients, 43%); nausea (68 patients, 39%); fatigue (65 patients, 37%); vision blurred (49 patients, 28%); headache (44 patients, 25%); vomiting (43 patients, 24%); neuropathy peripheral (42 patients, 24%); aspartate aminotransferase (AST) increased (40 patients, 23%); and abdominal pain (38 patients, 22%). Please refer to the Investigators' Brochure for detailed safety information.

1.6. Rationale for the starting dose

1.6.1. IMGN853

Mirvetuximab soravtansine has demonstrated activity (objective response rate of 53%) as a single agent in heavily pretreated, FRα expressing tumors such as epithelial ovarian carcinoma (Borghaei, et al. J Clin Oncol 33, 2015-suppl; abstr 5558) with acceptable toxicities of diarrhea, fatigue, punctate keratitis, blurred vision and nausea. The maximum tolerated dose (MTD) of 6 mg/kg IV has been established for a q 3 week schedule. No patients with TNBC were enrolled on this initial phase I trial, but it is anticipated that mirvetuximab soravtansine will have similar efficacy in metastatic TNBC and may overcome chemotherapy insensitive disease in the neoadjuvant setting in select TNBCs that express high levels of FRα.

1.7. Rationale for the Study Plan

Given the challenges of neoadjuvant trials for drug development in TNBC, the multi-disciplinary program at MD Anderson has designed an innovative drug development strategy that identifies and molecularly characterizes chemotherapy insensitive TNBC and determines the effect of a subtype-specific targeted agent (either alone or in combination with chemotherapy) to induce excellent pathologic response (pCR/RCB-0 or I). This strategy uses a minimal number of patients (n=37) to give a go/no go signal for further development of a targeted agent in the neoadjuvant setting and provides the preliminary data needed to inform the design of larger, randomized trials. Because chemoinsensitive disease is associated with such a dismal prognosis in TNBC, exploring novel agents that show preliminary evidence of activity in the metastatic setting is a viable strategy as potentially curative chemotherapy is not compromised in this high risk patient population. Taken together, the activity of mirvetuximab soravtansine in advanced, heavily pretreated ovarian cancer and the common expression of high levels of FRα in TNBCs support the rationale to determine the activity of mirvetuximab soravtansine for the neoadjuvant treatment of high risk, chemotherapy insensitive TNBC. As such, we propose using a lead-in cohort of 20 patients with metastatic TNBC who have received no more than 2 prior therapies for metastatic disease to determine the response rate of mirvetuximab soravtansine in TNBC. If 2

patients develop response to therapy, the neoadjuvant portion of the trial will be activated to determine the pathologic response rate in chemotherapy insensitive, localized TNBC.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives

- Determine if mirvetuximab soravtansine as a single agent is likely to induce response in at least 20% of patients with metastatic FRα+ TNBC.
- Determine if mirvetuximab soravtansine, as a single agent, in the neoadjuvant setting will improve rates of excellent pathologic response (pCR/RCB-0 or RCB-I) from 5% to 20% in patients with high risk, chemotherapy insensitive, FRα+ TNBC.

2.2. Primary Endpoints

- Response rate as measured by RECIST
- Pathologic response as measured by RCB after completion of neoadjuvant therapy

2.3. Secondary Objectives

- Determine the radiographic response rate as measured by ultrasound and/or MRI (partial response + complete clinical response) for mirvetuximab soravtansine in chemotherapy insensitive, FRα+ localized TNBC or using RECIST criteria in patients with FRα+ advanced TNBC.
- Determine toxicity of 4 cycles of mirvetuximab soravtansine given in the neoadjuvant setting following anthracycline based therapy (cohort B) and unrestricted cycles in patients receiving therapy in the advanced/metastatic setting (cohort A).
- Determine disease free survival (DFS) at 3 years for patients treated with mirvetuximab soravtansine given in the neoadjuvant setting; progression free survival (PFS), duration of response (DOR) and overall survival at 3 years (OS at 3 years) in patients receiving therapy for advanced/metastatic TNBC.
- Compare disease response (as measured by pCR/RCB-I) in patients with FRα+ chemotherapy resistant disease treated on clinical trial with mirvetuximab soravtansine in the neoadjuvant setting to those with similar molecular features who receive standard taxane-based chemotherapy as the second phase of their NACT.

2.4. Secondary Endpoints

- Volumetric change of the primary tumor as measured by ultrasound and/or MRI
- Treatment-emergent adverse events and clinically significant ≥ Grade 3 changes in laboratory test results, physical examination or vital signs
- DFS, PFS, DOR, OS
- Pathologic response as measured by RCB after completion of neoadjuvant therapy in patients with chemotherapy insensitive FRα+ TNBC treated with mirvetuximab soravtansine compared to those treated with standard taxane based therapy

2.5. Exploratory Objectives (Cohort B only)

- Correlate response to mirvetuximab soravtansine with expression of FRα/FOLR1 in primary tumors.
- Determine if treatment with the antibody drug conjugate mirvetuximab soravtansine alters the tumor microenvironment of TNBC making the tumors more susceptible to treatment with antibodies targeting the T cell inhibitory molecule PD-1 or its ligand PD-L1.

2.6. Exploratory Endpoints

- RCB status will be correlated with FRα as measured by immunohistochemistry and expression of FOLR1 using RNAseq.
- Changes in microenvironment will be studied using multiplex immunofluorescence for T cell and NK cell markers performed on pre- and post-treatment specimens.

3. STUDY POPULATION

3.1. Criteria for Selection of Patient Population

Patients with advanced breast cancer or localized, chemotherapy insensitive TNBC that express low levels of FRα will be enrolled onto this study. For purposes of study entry, low FRα expression on the cell surface will be defined as ≥25% of cells with ≥ 1+ expression. TNBC will be defined as estrogen receptor (ER) <10%, progesterone receptor (PR) <10% and HER2 0-2+ using standard immunohistochemistry (IHC). Tumors that are HER2 2+ by IHC must demonstrate non-amplification (ratio <2) by standard in situ hybridization techniques (CISH or FISH).

3.1.1. Diagnosis, allowable prior therapy and disease measurability:

This study will accrue two cohorts of patients those with advanced/metastatic TNBC (cohort A) and those with Patients with localized, chemotherapy insensitive TNBC (cohort B). Patients in cohort A will have no limit on prior treatment regimens for metastatic disease and patients in cohort B will have received no more than 4 cycles of Adriamycin-based neoadjuvant therapy as per the ARTEMIS trial. Patients enrolled in cohort A must have disease measurable using RECIST criteria and those enrolled in cohort B must have tumors ≥1.0 cm in size post Adriamycin-based neoadjuvant therapy. Patients receiving neoadjuvant paclitaxel in the control arm of 2014-0185 who meet the following criteria will be chosen for this analysis:

Tumor expression of vimentin is ≥50% and

- Develops clinical or radiographic progression on AC chemotherapy
- Has less than 10% reduction in the volumetric size of the primary tumor
- Predicted chemotherapy insensitive and has a <80% reduction in the size of the primary tumor

3.1.2. Inclusion Criteria

3.1.2.1. Inclusion Criteria for Patients Enrolled into Cohort A:

1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1
3. Confirmed invasive triple-negative breast cancer defined as ER<10%; PR<10% by IHC and HER2 0-1+ by IHC or 2+, FISH < 2, gene copy number < 4.
4. Archived tissue available pre-screening to confirm FRα+ breast cancer.
5. Confirmed FRα+ breast cancer pre-screening defined as low FRα expression: ≥25% of cells having ≥1+ expression.
6. Measureable disease by RECIST.

7. No limit to prior therapies for metastatic disease. Relapse of disease within 6 months of adjuvant or neoadjuvant chemotherapy is considered 1 line of therapy for metastatic disease.
8. Adequate bone marrow function as shown by:
   - ANC $\geq 1.5 \times 10^9$ /L,
   - Platelets $\geq 100 \times 10^9$ /L,
   - Hb >9 G/dL.
9. Adequate organ function as shown by:
   - Total serum bilirubin $\leq$2.0 mg/dL,
   - ALT and AST $\leq$2.5x ULN ($\leq$5x ULN in patients with liver metastases),
   - INR$\leq$ 2;
   - Serum creatinine $\leq$1.5x ULN;
   - Serum albumin >2.
10. Signed informed consent obtained prior to any screening procedures.
11. Time from prior therapy:
    a. Systemic anti-neoplastic therapy: five half-lives or four weeks, whichever is shorter. Hormonal therapy is not considered anti-neoplastic therapy.
    b. Radiotherapy: wide-field radiotherapy (e.g. > 30% of marrow-bearing bones) completed at least four weeks, or focal radiation completed at least two weeks, prior to starting study treatment
12. Patients must have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia).
13. WCBP must have a negative pregnancy test within 3 days prior to the first dose of study treatment.

3.1.2.2. Inclusion Criterial for Patients Enrolled into Cohort B:

14. Age $\geq$ 18 years.
15. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1
16. Confirmed invasive triple-negative breast cancer defined as ER<10%; PR<10% by IHC and HER2 0-1+ by IHC or 2+, FISH < 2, gene copy number < 4.
17. Confirmed FRα+ breast cancer defined as low FRα expression: $\geq$25% of cells having $\geq$1+ expression.

18. Clinical or radiologic primary tumor size of at least 1.5cm prior to enrollment onto protocol 2014-0185 (ARTEMIS). Primary tumor size of at least 1.0 cm or evidence of continued lymph node involvement by imaging (ultrasound or MRI) after Adriamycin-based neoadjuvant therapy.
19. Primary tumor sample collected before NACT started (on ARTEMIS) and underwent molecular testing for integral biomarkers including immunohistochemical assessment of FRα.
20. Received at least one dose of an anthracycline-based NACT. Patients are eligible if therapy was discontinued due to disease progression or therapy intolerance. Patients with disease progression on anthracycline-based therapy should be evaluated by the surgical team. If the patient is deemed inoperable at the time of evaluation, the patient may continue to undergo protocol therapy with a goal of reduction in tumor size to become operable. If the patient is deemed at high risk of becoming inoperable by the surgical team based upon tumor size or location, the patient will be considered ineligible for study and will be recommended to go to surgery.
21. Primary tumor size of at least 1.0 cm by imaging (ultrasound or MRI) or evidence of continued lymph node involvement by imaging (ultrasound or MRI) after Adriamycin-based neoadjuvant therapy.
22. Baseline MUGA or echocardiogram showing LVEF ≥ 50% within 6 weeks prior to initiation of NACT.
23. Adequate bone marrow function as shown by:
    - ANC $\geq 1.5 \times 10^9$ /L,
    - Platelets $\geq 100 \times 10^9$ /L,
    - Hb >9 G/dL.
24. Adequate organ function as shown by:
    - Total serum bilirubin ≤2.0 mg/dL,
    - ALT and AST ≤2.5x ULN (≤5x ULN in patients with liver metastases),
    - INR≤ 2;
    - Serum creatinine ≤1.5x ULN;
    - Serum albumin >2.
25. Signed informed consent obtained prior to any screening procedures.
26. Patients must have at least 3 and no more than 5 weeks between anthracycline-based therapy and start of treatment with mirvetuximab soravtansine.
27. Patients must have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia).

28. WCBP must have a negative pregnancy test within 3 days prior to the first dose of study treatment.

3.1.3. Exclusion Criteria

3.1.3.1. Exclusion Criteria for Patients in Cohort A:

1. Pregnant or lactating women.
2. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study
3. Women of childbearing potential (WCBP), defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during the study and 12 weeks after. Highly effective contraception methods include a combination of any two of the following:
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS);
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository;
    - Total abstinence or;
    - Male/ female sterilization.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

4. Male patients whose sexual partner(s) are WCBP who are not willing to use adequate contraception, during the study and for 12 weeks after the end of treatment.
5. Patients with > Grade 1 peripheral neuropathy
6. Active or chronic corneal disorder, including but not limited to the following: Sjögren's syndrome, Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, and also active ocular conditions requiring on-going treatment/monitoring such as wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, presence of papilledema, and acquired monocular vision.
7. Serious concurrent illness or clinically-relevant active infection, including, but not limited to the following:
    - Known active hepatitis B or C

- Known Human Immunodeficiency Virus (HIV) infection
- Varicella-zoster virus (shingles)
- Cytomegalovirus infection
- Any other known concurrent infectious disease, requiring IV antibiotics within 2 weeks of study enrollment

8. Clinically- significant cardiac disease:
   - Recent myocardial infarction (≤6 months prior to day 1),
   - Unstable angina pectoris,
   - Uncontrolled congestive heart failure (New York Heart Association > class II),
   - Uncontrolled hypertension (≥ CTCAE v4.03 Grade 3),
   - Prior history of hypertensive crisis or hypertensive encephalopathy,
   - Uncontrolled cardiac arrhythmias,
   - Clinically-significant vascular disease (e.g. aortic aneurysm, or dissecting aneurysm),
   - Severe aortic stenosis,
   - Clinically significant peripheral vascular disease,
   - ≥ Grade 3 cardiac toxicity following prior chemotherapy
   - QTc >470 for females and >450 for males
9. History of neurological conditions that would confound assessment of treatment-emergent neuropathy.
10. History of hemorrhagic or ischemic stroke within the last 6 months
11. History of cirrhotic liver disease
12. Previous clinical diagnosis of non-infectious pneumonitis or non-infectious interstitial lung disease.
13. Prior hypersensitivity to monoclonal antibodies
14. Patients who have a history of another primary malignancy, with the exceptions of: non-melanoma skin cancer, and carcinoma in situ of the cervix, uteri, or breast from which the patient has been disease free for ≥3 years
15. Carcinomatous meningitis, untreated central nervous system (CNS) disease or symptomatic CNS metastasis. Patients with previously treated CNS metastasis (excluding carcinomatous meningitis) may participate if they are stable (without evidence of progression by imaging, using identical imaging modality at each assessment, for at least 4 weeks prior to first dose of study treatment), have no evidence of new or emerging CNS metastasis, and are not using steroids for at least 7 days prior to first dose of study treatment.

16. History or evidence of thrombotic or hemorrhagic disorders within 6 months before first study treatment
17. Required used of folate-containing supplements (e.g. folate deficiency)

3.1.3.2. Exclusion Criteria for Patients in Cohort B:

18. Pregnant or lactating women.
19. Presence of metastatic disease or prior radiation therapy of the primary breast carcinoma or axillary lymph nodes.
20. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study
21. Women of childbearing potential (WCBP), defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during the study and 12 weeks after. Highly effective contraception methods include a combination of any two of the following:
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS);
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository;
    - Total abstinence or;
    - Male/ female sterilization.

    Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.
22. Male patients whose sexual partner(s) are WCBP who are not willing to use adequate contraception, during the study and for 12 weeks after the end of treatment.
23. Patients with > Grade 1 peripheral neuropathy
24. Active or chronic corneal disorder, including but not limited to the following: Sjögren's syndrome, Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, and also active ocular conditions requiring on-going treatment/monitoring such as wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, presence of papilledema, and acquired monocular vision.

25. Serious concurrent illness or clinically-relevant active infection, including, but not limited to the following:
    - Known active hepatitis B or C
    - Known Human Immunodeficiency Virus (HIV) infection
    - Varicella-zoster virus (shingles)
    - Cytomegalovirus infection
    - Any other known concurrent infectious disease, requiring IV antibiotics within 2 weeks of study enrollment
26. Clinically- significant cardiac disease:
    - Recent myocardial infarction (≤6 months prior to day 1),
    - Unstable angina pectoris,
    - Uncontrolled congestive heart failure (New York Heart Association > class II),
    - Uncontrolled hypertension (≥ CTCAE v4.03 Grade 3),
    - Prior history of hypertensive crisis or hypertensive encephalopathy,
    - Uncontrolled cardiac arrhythmias,
    - Clinically-significant vascular disease (e.g. aortic aneurysm, or dissecting aneurysm),
    - Severe aortic stenosis,
    - Clinically significant peripheral vascular disease,
    - ≥ Grade 3 cardiac toxicity following prior chemotherapy
    - QTc >470 for females and >450 for males
27. History of neurological conditions that would confound assessment of treatment-emergent neuropathy.
28. History of hemorrhagic or ischemic stroke within the last 6 months
29. History of cirrhotic liver disease
30. Previous clinical diagnosis of non-infectious pneumonitis or non-infectious interstitial lung disease.
31. Prior hypersensitivity to monoclonal antibodies
32. Patients who have a history of another primary malignancy, with the exceptions of: non-melanoma skin cancer, and carcinoma in situ of the cervix, uteri, or breast from which the patient has been disease free for ≥3 years
33. History or evidence of thrombotic or hemorrhagic disorders within 6 months before first study treatment
34. Required used of folate-containing supplements (e.g. folate deficiency)

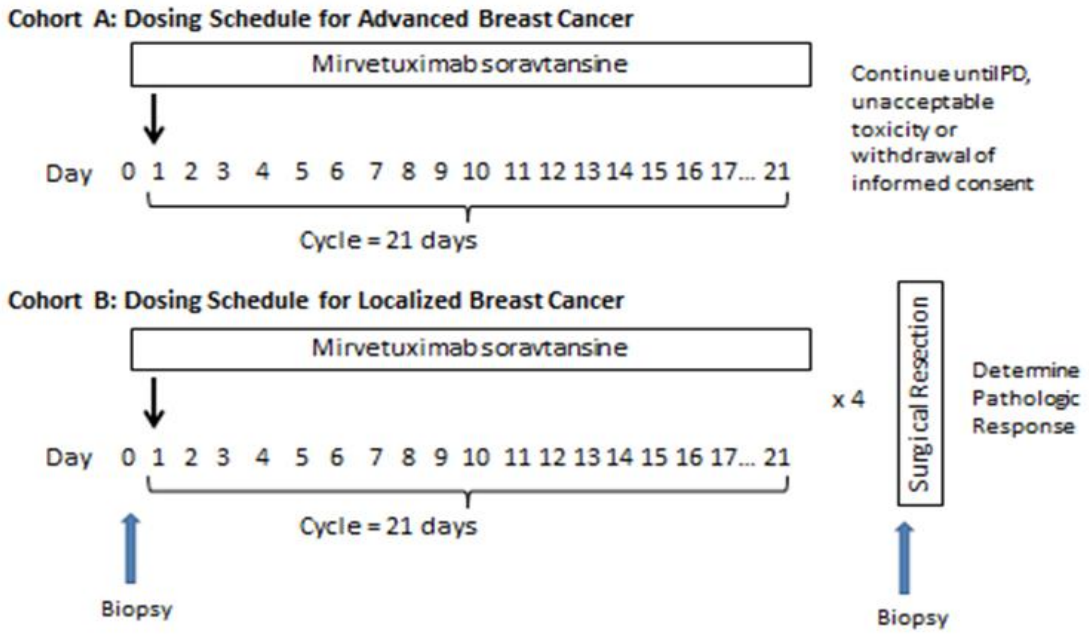
4. INVESTIGATIONAL PLAN

4.1. Study Design

4.1.1. Overview and Schema

This study will accrue two cohorts of patients. All patients will receive mirvetuximab soravtansine IV on day 1 of a 21-day cycle. Patients with advanced/metastatic TNBC (Cohort A) will receive therapy until disease progression, unacceptable toxicity or withdrawal of informed consent. Patients with localized, chemotherapy insensitive TNBC (Cohort B) will receive a maximum number of 4 cycles prior to undergoing surgical resection of their disease. Patients with clinical disease progression at any point during neoadjuvant therapy will be allowed to proceed with surgical resection. Surgery will occur no sooner than 4 weeks after day 1 of the last cycle of therapy administered.

Figure 4: Study Design Schema



4.1.1.1. Dose

The starting dose of IMGN853 will be 6 mg/kg for all patients treated, with the dose calculated using AIBW. All IMGN853 doses will be calculated according to AIBW.

Patients who experience toxicity requiring dose reduction as described in section 4.1.2 will be dosed at level -1 or -2 for subsequent cycles as per guidelines in section 5.10.4.1. Patients who continue to have toxicity that meets requirements for dose reduction past dose levels -2 will

discontinue protocol therapy. Those treated in the neoadjuvant cohort (cohort B) will proceed with surgical resection once toxicity has returned to ≤grade 1 or baseline.

Table 1: Dose Modification Levels

Dose Level	IMGN853[1] (mg/kg, IVq3W)
Cohort A	
1	**6**
-1	5
-2	4
No further treatment; patient will discontinue protocol therapy.	
Cohort B	
1	**6**
-1	**5**
-2	4
No further treatment. Patient will be recommended to go to surgery.	

[1]*IMGN853 dose calculated using adjusted ideal body weight (AIBW). Maximum allowable dose is 6 mg/kg AIBW. All patients begin at Dose Level 1 for Day 1, Cycle 1.*

4.1.2. Definition: Toxicity Requiring Dose Reduction

Toxicity requiring dose reduction will be defined as a TEAE or abnormal laboratory value related to IMGN853 (i.e., assessed as unrelated to disease, intercurrent illness, or concomitant medications), including those TEAEs and abnormal laboratory values that result in a failure to meet the criteria for re-treatment (Section 5.10.1.1.). Toxicity will be considered related to the study treatment unless there is clear evidence of an alternative explanation.

If a patient experiences a toxicity requiring dose reduction any point during study treatment as outlined in (Table 2), the study treatment must be stopped and the toxicity(ies) in question must be followed until resolution or stabilization. If treatment is to be resumed, then re-treatment criteria must be met (Section 5.10.3.) and administration of IMGN853 must be resumed at a lower dose per dose modification guidelines (Section 5.10.4.1.).

Table 2: Toxicity Requiring Dose Reduction

TOXICITY	CRITERIA REQUIRING DOSE REDUCTION
Dose delays	Failure to meet re-treatment criteria within the specified timeframe (Section 5.10.1.1)
Severity Grade (CTCAE v4.03)	**Dose Modifications for IMGN853**
Hematological	
Neutropenia	
Grade 2 and Grade 3	Hold drug until ANC is $\geq 1.0 \times 10^9$/L (1000/μL) then resume at the same dose level.
Grade 4	Hold drug until ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and then resume at a lower dose level
Febrile neutropenia Grade 3 or 4 (with a single temperature reading ≥38.3°C or a sustained temperature of >38°C for > one hour)	Hold drug until ANC is $\geq 1.0 \times 10^9$/L (1000/μL) and then resume at a lower dose level.
Thrombocytopenia	
Grade 2 and Grade 3	Hold drug until platelet count is $\geq 75 \times 10^9$/L (75,000/μL) and resume at same dose level
Grade 3 associated with clinically significant bleeding that requires transfusion therapy and Grade 4	Hold drug until platelet count is $\geq 75 \times 10^9$/L (75,000/μL) and then resume at a lower dose level
Non-hematological	
Nausea and Vomiting	
Grade 3 (that persists for 72 hours despite use of optimal anti-emetics)	Hold drug until resolved to ≤ Grade 1, then resume at lower level
Grade 4 (that persists for 24 hours despite use of optimal anti-emetics)	Permanently discontinue
Diarrhea	
Grade 3 (that persists for 72 hours despite use of optimal anti-diarrheal treatment)	Hold drug until resolved to ≤ Grade 1, then resume at a lower dose level

Grade 4 (that persists for 24 hours despite use of optimal anti-diarrheal treatment)	Permanently discontinue
Ocular Disorders	Refer to Section 5.9.2
Non-infectious Pneumonitis	Refer to Section 5.9.3
Infusion Related Reactions	Refer to Section 5.9.1
All Other Non-hematological Toxicities (except AEs related to underlying disease, Grade 3 fatigue, isolated symptomatic Grade 3 biochemical laboratory abnormalities that last for <7 days including electrolyte abnormalities that respond to medical intervention)	
Grade 3	Hold drug until resolved to ≤ Grade 1, then resume at lower dose. For any Grade 3 hepatic toxicity that does not resolve to baseline within seven days, an abdominal CT scan must be performed to assess whether it is related to disease progression.
≥ Grade 3 Cardiac Event	Permanently discontinue
Grade 4 non-hematological toxicities	Permanently discontinue
Abbreviation: Common Terminology Criteria for Adverse Events (CTCAE) For any dose limiting hepatic toxicity, evaluations should be performed to determine the underlying etiology and rule out drug-induced liver injury (Hy's Law)	

5. STUDY TREATMENT

5.1. Description of Study Treatment

The investigational study drug, IMGN853, will be provided by ImmunoGen, Inc. at a protein concentration of 5.0 mg/mL in an aqueous pH 5.0 buffered solution. IMGN853 will be available in a 20 mL glass vial with 20 mL deliverable volume. IMGN853 should be stored upright at 2-8°C. Refer to the Pharmacy Manual for more information.

5.2. IMGN853 Packaging

IMGN853 will be provided in a 20 mL Type I glass vial. The container closure for the Type I glass vials will consist of a 20 mm ETFE-coated serum stopper (Flurotec®) on the top and product contact surface with a 20 mm aluminum TruEdge® seal with blue Flip-off® top. Refer to the Pharmacy Manual for labeling information.

5.3. Storage, Handling and Compatibility

Specific details regarding storage and handling can be found in the Pharmacy Manual.

Accountability and shipping documents for all drugs supplied by the Grantor must be maintained by the Principal Investigator or designee (e.g., the study pharmacist). The Investigator or designee must maintain an accurate record of the receipt and dispensing of IMGN853 study drugs in a drug accountability log or equivalent. These records must always be available for inspection, and a copy will be supplied to ImmunoGen, Inc., on request. Information recorded on these accountability and shipping documents will include quantities received, dates and amount dispensed, the recorder's initials, patient number and initials to whom administered, lot number of drug administered, and drug lost, damaged or destroyed.

Upon completion of the study, all study drug dispatched to a site must be accounted for and unused supplies returned to ImmunoGen Inc., or destroyed according to the site's Standard Operating Procedures (SOPs). The original drug reconciliation records shall be maintained at the site and a copy collected and sent to ImmunoGen once a representative of the company has confirmed the drug accountability. The pharmacy shall maintain accurate records of all study drugs that have been received, stored, dispensed, destroyed, and used. The electronic case report form (eCRF) should also record details of IMGN853 study drug administration such as date and time of administration.

Drug accountability should be monitored regularly.

5.4 Study Treatment Compliance

The IMGN853 and combination drugs supplied for the study (if any) may not be used for any purpose other than the study or administered other than as described in this protocol.

IMGN853 from two different drug lots cannot be mixed in a single dose administration.

Under no circumstances is the Investigator allowed to release study drug supplies to any physician not named in the Food and Drug Administration (FDA) Form 1572 or to administer these supplies to a patient not enrolled in this study. If investigational supplies are to be dispensed from any facility other than that supervised directly by the Principal Investigator (i.e., hospital pharmacy, satellite pharmacy), it is the responsibility of the Principal Investigator to ensure that all study drug is maintained in the manner described.

5.5 Assignment of Patient Number

Patient numbers are assigned in sequential order as patients sign informed consent to participate.

The Investigator will certify that the patient satisfies all eligibility criteria at screening and continues to satisfy all inclusion and exclusion criteria on Cycle 1, Day 1 prior to dosing.

5.5.1 Enrolled Patient Definition

Patients who have consented to the study and who have received at least one dose of study treatment will be considered enrolled. Patients who are issued a patient number, but who do not

successfully complete the screening process and who do not receive a dose of IMGN853 will be considered a screen failure. Patient numbers for patients who screen fail will not be re-issued.

5.5.2. Patient Assignment to Dosing Regimens

5.6. Blinding

Not applicable as this is an open-label study.

5.7. Study Treatment Administration

5.7.1. Study Treatment Overview and Schedule

IMGN853 is an experimental anticancer drug, and, as with other potentially toxic compounds, caution should be exercised when handling this compound. It is recommended that gloves and protective garments be worn during preparation. Refer to the Pharmacy Manual and package inserts for more information.

For logistical reasons such as holidays, delays in the scheduled study treatment for up to 3 days will be permitted in Cycles 1 and 2. Additionally, shifts in the start of a new cycle by -1 or +3 days will be permitted in Cycles ≥ 3.

5.8. Drug Preparation and Administration

5.8.1. Premedication for Study Treatment

All patients must receive 325-650 mg of acetaminophen/paracetamol (PO or IV), 10 mg IV dexamethasone, and 25-50 mg diphenhydramine (PO or IV) (equivalent drugs of similar drug classes is also acceptable) approximately 30 minutes prior to each infusion of IMGN853. If individual patients require more intensive treatment to prevent infusion-related reactions, investigators may modify the regimen accordingly.

5.8.2. Preparation and Administration of IMGN853

5.8.2.1. Calculation for Adjusted Ideal Body Weight (AIBW)

In the on-going phase 1 study with IMGN853, the use of AIBW to calculate the dose of IMGN853 reduced the intra-cohort variability in Cmax and AUC_0-∞ values, thereby improving the safety profile of IMGN853.

The total dose of drug will be calculated based on each patient's adjusted body weight using the following formula:

Adjusted Ideal Body Weight (AIBW)

1. $IBW^1 + 0.4$ (Actual weight – IBW^1)

Where:

Ideal Body Weight (IBW)

1. IBW[1] (male) = 0.9H[1]-88
2. IBW[1] (female) = 0.9H[1]-92

([1]H=height in cm; W=weight in kg)

The weight used for calculation should be obtained prior to study drug administration on Cycle 1 Day 1 (+/- 14 days) and thereafter should only be modified for significant (≥ 10%) changes in body weight (not influenced by weight gain or loss attributed to fluid retention).

5.8.2.2. Preparation

The desired amount should be withdrawn from the vial(s) and diluted using 5% dextrose to a final concentration as outlined in the Pharmacy Manual. Note: IMGN853 is incompatible with saline (0.9% sodium chloride). Therefore, dilutions must be made using 5% dextrose. Infusion bags must be labeled with the protocol number, patient number, storage temperature, dose, and volume of IMGN853 filtered into the bag, or according to institutional protocol. Once the solution is prepared, the infusion bag must not be left in direct sunlight, and the infusion must be completed within 8 hours of preparation.

Study drug from two different drug lots cannot be mixed in a single dose administration.

5.8.2.3. Administration

The starting dose level of IMGN853 will be 6 mg/kg using AIBW for IMGN853 will be administered as an IV infusion following preparation as outlined in the Pharmacy Manual. An IV tubing administration set with a 0.22 micron in-line filter must be used for infusion. For patients who have not been administered IMGN853 as a prior anti-cancer therapy, IMGN853 should be administered at a rate of 1 mg/min; after 30 minutes, the rate can be increased to 3 mg/min if well tolerated. If well tolerated after 30 minutes at 3 mg/min, the IMGN853 infusion rate may be increased to 5mg/min. Subsequent infusions may be delivered at the tolerated rate. Therefore, the overall length of infusion will vary depending on dose and patient tolerability. Following infusion, the IV line should be flushed with 5% dextrose as needed to ensure delivery of the full dose.

Patients will be carefully observed during each infusion and vital signs taken as outlined in the Schedule of Clinical Assessments (Appendix A and Table 9). They will remain in the clinic under observation for 4 hours after the completion of the first infusion of IMGN853, and for at least 1 hour after each subsequent infusion.

5.9 Monitoring and Management of Adverse Events

5.9.1. Potential Infusion-related Reactions

Some patients treated with IV infusions of therapeutic drugs have experienced concurrent infusion-related reactions (see CTCAE Version 4.03). The signs and symptoms may vary and include for example, headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion. Before any infusion is started, appropriate medical personnel, medication (e.g. epinephrine, inhaled beta agonists, antihistamines, and corticosteroids), and other required resources to treat anaphylaxis must be readily available. In general, Investigators should manage acute allergic or hypersensitivity reactions according to Institutional practices. General guidelines for the management of acute infusion-related reactions and for subsequent retreatment are provided in Table 3. Delayed infusion-related reactions may occur; therefore patients should be advised to seek immediate medical treatment if symptoms newly develop and/or recur after discharge from clinic.

Table 3: Management Guidelines for Potential Infusion-related Reaction

Infusion Reaction CTCAE v4.03 Severity Grade	Management
Grade 1: Mild, transient reaction	• Maintain infusion rate unless progression of symptoms to ≥ Grade 2; if symptoms worsen, refer to guidelines below • Promethazine (or equivalent) 150 mg PO **per day** for nausea (or equivalent) • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn • Methylprednisolone 125 mg (or equivalent) IV prn

Infusion Reaction CTCAE v4.03 Severity Grade	Management
Grade 2: Moderate	• Interrupt infusion and disconnect infusion tubing from patient • Promethazine (or equivalent) 150 mg PO **per day** for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn • Acetaminophen (or equivalent) 650 mg PO prn • Methylprednisolone 125 mg (or equivalent) IV prn • After recovery from symptoms, resume the infusion at 50% of the previous rate and if no further symptoms appear, gradually increase rate until infusion is completed. • For subsequent dosing in future cycles, patients should be pre-medicated with dexamethasone (or equivalent) 8 mg PO BID the day prior to drug administration and acetaminophen (or equivalent) 650 mg PO and diphenhydramine (or equivalent) 25-50 mg PO 30-60 minutes prior to dosing.
Grade 3: Severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae OR Grade 4: Life-threatening consequences, urgent intervention indicated	• Immediately stop infusion and disconnect infusion tubing from subject • Administer diphenhydramine (25-50 mg) IV (or equivalent) • Administer IV steroids (methylprednisolone (or equivalent) up to 0.5mg/kg Q 6h) to treat ongoing reaction and prevent recurrence • Administer bronchodilators (nebulized albuterol/salbutamol, 2.5-5 mg in 3 mL of saline or equivalent) as medically indicated • Administer normal saline as medically indicated • Administer epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) SQ or IM) as medically indicated. Epinephrine should only be used if all other treatment methods fail to manage the infusion-related reaction. • Advise patient to seek emergency treatment and notify investigator/clinic if the infusion-related symptoms recur after discharge from clinic. • Report as a serious adverse event (see Section 7.14.1) • Permanently discontinue study medication treatment

5.9.2. Monitoring and Management of Treatment-emergent Ocular Disorders

5.9.2.1. Monitoring - Potential Ocular Disorders

Changes in visual acuity resulting from corneal epithelium disorders have been reported in other studies of DM4-containing immunoconjugates that use the SPDB linker (Younes, 2012). Due to the observation of ocular disorders in patients treated with IMGN853 Q3W at dose levels > 3.3 mg/kg, patients will be carefully monitored for ocular symptoms. Complete ophthalmologic exams and ocular symptom assessments will be performed in all symptomatic patients as described in the following schedule:

Table 4: Schedule for Ophthalmic Assessments

Assessment[1]	Screening	Day 1 (All Cycles)	Prior to Day 1 Dose (Every other Cycle)[2]	End of Study Visit	30-Day Follow Up Safety Visit
Ophthalmologic history – patients will be asked about ocular symptoms such as history of dry eye, and contact lens use	X				
Complete Exam: - Visual acuity - Indirect fundoscopy - Slit lamp examination under dilatation - Intraocular pressure measurement - Corneal photography (optional)			Patients who report treatment-emergent changes in vision	X	X
Schirmer's test[3]			Patients who report treatment-emergent changes in vision		
Ocular symptom assessment (blurred vision, ocular discomfort, etc.)	X	X		X	X

[1] Performed by a board-certified ophthalmologist

[2] Within 1 week prior to Day 1 dose of every other cycle, required for patients who have experienced signs or symptoms of ocular toxicity and for those with blurred vision but normal eye exams.

[3] For patients experiencing ocular symptoms, the Schirmer's test will be repeated at the first ophthalmology exam and subsequent ophthalmologic exams if clinically indicated.

If a Patient develops ocular symptoms of any grade, the patient is required to have a complete examination by an ophthalmologist. If the patient develops > CTCAE grade 1 ocular symptoms (Appendix C) treatment with IMGN853 will be interrupted. Therapy may resume if ocular

disorders improve to Grade 1 or baseline within one cycle; a complete ocular examination will be required in every other cycle going forward, and at either the end of treatment or 30-day follow-up safety visit.

5.9.2.2. Management Guidelines for Ocular Disorders

In order to prevent dry eye, which may predispose a patient to corneal irritation, patients will be required to regularly use preservative-free, lubricating artificial tears on a daily basis (as directed by the product label or the treating physician) for the duration of their IMGN853 treatment. Patients should also be firmly advised to avoid using contact lenses while on study. Baby shampoo and a soft cloth should be used to clean the eyes, and a warm compress at bedtime may be used to decrease any possible inflammation on the eyelid's surface. The use of UVA/UVB sunglasses is recommended for use outside in full daylight during the course of the study. The use of punctal plugs to increase lubrication of the eyes is also recommended. If patients report signs or symptoms of ocular disorders, including, but not limited to, blurred vision or eye irritation, the management and dose modification guidelines outlined in Table 5 should be followed.

Patients who have experienced study drug-related changes in vision, such as blurred vision, will have a complete ophthalmic examination performed prior to the start of every other cycle and at the end of study or 30-day follow up visit following end of treatment, even if the results of the patient's ocular exam is normal. Management of treatment emergent ocular disorders with inflammatory characteristics should include corticosteroid eye drops and/or other measures as indicated by an ophthalmologist.

Table 5: Management of Ocular Disorders

Severity Grade (CTCAE v4.03 Grade)[1]	Management	Guidelines for IMGN853 Dose Modifications
Grade 1	• Complete eye exam as outlined in Table 4. • Monitor for worsening symptoms • Patient may use steroid eye drops to treat corneal keratopathy per ophthalmologist recommendation	• Continue IMGN853 dosing
Grade 2	• Complete eye exam by an ophthalmologist as outlined in Table 4. Repeat complete exam as clinically indicated. • Patients may use steroid eye drops to treat corneal keratopathy per ophthalmologist recommendation • Patients should have weekly symptomatic ocular assessments until the symptoms resolve to grade 1 or baseline (Section 5.10.3) or are deemed to be irreversible by the investigator	• Hold IMGN853 dosing. • Patients with ocular disorders less than 14 days may be allowed to resume therapy at the same dose level. • Patients with ocular disorders who experience dosing delays>14 days, may resume treatment at a reduced dose level (see Table 8)

Grade 3	• Complete eye exam as outlined in Table 4. Repeat complete exam as clinically indicated. • Patients may use steroid eye drops to treat corneal keratopathy per ophthalmologist recommendation • Patients should have weekly symptomatic ocular assessments until the symptoms resolve to grade 1 or baseline (Section 5.10.3) or are deemed to be irreversible by the investigator.	• Hold IMGN853 dosing • Patients may be allowed to resume therapy at a lower dose than the one they were receiving when the symptoms began (see Table 8).
Grade 4	• Complete eye exam as outlines in Table 4. Repeat complete exam as clinically indicated. • Patients may use steroid eye drops to treat corneal keratopathy per ophthalmologist recommendation • Patients should have weekly symptomatic ocular assessment until the symptoms resolve to grade 1 or baseline (Section 5.10.3) or are deemed to be irreversible by the investigator.	• Permanently discontinue IMGN853 dosing.
[1]Appendix D includes CTCAE version 4.03 Grade definitions for select ocular disorders.		

5.9.3. Monitoring of Non-Infectious Pneumonitis Following the Administration of Study Treatment

Non-infectious pneumonitis has been observed following the administration of IMGN853 and may result in fatigue, shortness of breath, cough or respiratory distress. Drug-induced pneumonitis may be immediately life-threatening. If a patient presents with signs or symptoms consistent with pneumonitis and/or a clinically meaningful change in pulse oximetry value, the patient should be immediately evaluated. Patients are advised to notify their treating physician immediately if they experience new or worsening shortness of breath, cough or respiratory distress.

For patients diagnosed with pneumonitis without an infectious etiology, the management and treatment guidelines outlined in Table 6 should be followed.

Table 6: Management of Non-Infectious Pneumonitis

Severity Grade (CTCAE v4.03 Grade)	Medical Management of Pneumonitis	Guidelines for Dose Modifications
Grade 1	• Radiologic assessment (CT scan and/or chest x-ray) should be performed as clinically indicated. • Monitor for pulmonary symptoms	• Continue dosing after discussion with Grantor.

Grade 2	• Radiologic assessment (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids may be indicated as recommended by a pulmonary specialist and/or institutional guidelines.	• Hold dosing until symptoms improve. • IMGN853 may be resumed at same dose level after discussion with the Grantor.
Grade 3	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines. • Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed. • The pneumonitis event must be followed until resolution	• Hold IMGN853 dosing until symptoms resolve. • IMGN853 may be resumed at a lower dose level after discussion with the Grantor.
Grade 4	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines. • Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed. • The pneumonitis event must be followed until resolution.	• Permanently discontinue IMGN853 dosing.

5.9.4. Monitoring and Management of Diarrhea Following the Administration of Study Treatment

Mild to moderate diarrhea has been frequently reported in patients treated with IMGN853. Patients should be advised to contact their treating physician at the first sign of diarrhea. Patients may then be treated according to standard institutional practice. One suggested regimen would be the administration of 2 mg loperamide at the first sign of loose stool, with repeat dosing every 2 hours until symptoms resolve (Wadler, 1998).

5.9.5. Monitoring and Management of Nausea and Vomiting Following the Administration of Study Treatment

Nausea and vomiting have been reported in patients treated with IMGN853. Patients should be advised to contact their treating physician at the first sign of vomiting or worsening nausea. Patients should be treated according to the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines for the use of antiemetics (Basch, 2011) outlined in Table 7.

Table 7: Management of Nausea and Vomiting

Severity Grade (CTCAE v4.03 Grade)	Management
Grade 1	• No additional therapy required
Grade 2	• Administer a 5-HT_3 receptor antagonist on day 1 (e.g. palonosetron, granisetron, or ondansetron) in combination with dexamethasone on days 1-3 or treat as per institutional guidelines. Aprepitant may be added to the combination.
Grades 3 and 4	• Administer a neurokinin 1 receptor antagonist (e.g. aprepitant on days 1-3 or fosaprepitant on day1), in combination with 5-HT_3 receptor antagonist on day 1 only, and dexamethasone on days 1-3 or 1-4 or treat per institutional guidelines.

5.9.5.1. Management of Electrolytes Imbalance

Prompt attention should be given to the correction of potential electrolytes imbalance, especially hypokalemia and hypomagnesemia.

5.10. Treatment Guidelines

5.10.1. Re-treatment Criteria

5.10.1.1. To Begin a New Cycle of Treatment or continue treatment within a cycle

In the absence of a toxicity requiring dose reduction or dose delay, for a patient to begin a new cycle or continue a cycle of therapy, the following criteria must be met.

- ANC must be $\geq 1.5 \times 10^9$/L (1,500/μL) (Cycle 1 Day 1 only)
- ANC must be $\geq 1.0 \times 10^9$/L (1,000/μL)
- Platelet count must be $\geq 75 \times 10^9$/L (75,000/μL)

- All non-hematologic toxicities for which a causal association to study treatment cannot be ruled out, must be ≤ Grade 2 (except alopecia) or returned to baseline; the exceptions to this rule are:
  - Treatment-emergent ocular disorders, which must have recovered to ≤ Grade 1 or baseline
  - Treatment-emergent pneumonitis which must have recovered to ≤ Grade 1

If the patient does not meet these criteria, dosing will be delayed and the patient should be re-evaluated within 48-72 hours. Dosing with study drug may resume if these criteria have been met. If the adverse event can be attributed to study drug, drug will be held or discontinued as per the Dose Modification Guidelines described in (Section 5.10.4.). However, if the next cycle is delayed by greater than 14 days because of insufficient recovery from a treatment-related toxicity, this will be viewed as a toxicity requiring dose reduction or dose delay (Section 4.1.2.). If the next cycle is delayed due to treatment-related toxicity longer than 3 weeks then the patient should be removed from study treatment. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon between the Grantor and the Investigator.

The use of granulocyte growth factors in accordance with ASCO guidelines may be implemented at the discretion of the treating physician after Cycle 1.

5.10.2. Follow-up for AEs Leading to Discontinuation

Patients who experience a non-laboratory AE requiring dose reduction or dose delay must be evaluated weekly, at a minimum, until resolution to ≤ Grade 1 or baseline and then at least monthly until return to baseline or stabilization of the event, whichever comes first. For abnormal laboratory values that qualify as a toxicity requiring dose reduction or dose delay, patients will be followed twice weekly until values return to < Grade 1 or baseline, whichever comes first.

Patients who discontinue study treatment for an AE or an abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals until resolution or stabilization of the adverse event or laboratory abnormality, whichever occurs first.

5.10.3. Criteria for Re-Initiation of Study Treatment Following Occurrence of a Toxicity Requiring Dose Modification

Study treatment will be stopped if a patient experiences a toxicity requiring dose modification at any time during the study. It may resume, with applicable dose adjustments (Section 5.10.4.1) if the following criteria are met:

- ANC must be ≥ 1.0 x10^9/L (1,000 /μL)
- Platelet count must be ≥ 75 x 10^9/L (75,000/μL)
- All clinically-significant non-hematologic toxicities for which a causal association to study treatment cannot be ruled out must be ≤ Grade 1 (except alopecia) or returned to baseline

If the patient does not meet these criteria, dosing will be delayed and the patient should be re-evaluated within 48-72 hours. Dosing may resume if these criteria have been met. If the next cycle is delayed due to treatment-related toxicity longer than 3 weeks then the patient should be removed from study treatment. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon between the Grantor and the Investigator.

5.10.4. Dose Modification Guidelines

5.10.4.1. IMGN853 Dose Reduction Following a Toxicity Requiring Dose Modification

Patients with toxicity requiring dose modifications of IMGN853 should be dose reduced according to Table 8. Patients who develop toxicity requiring dose modifications or adverse events requiring an interruption of IMGN853 for >1 week may resume treatment at a reduced dose level as shown in Table 8 provided the criteria outlined in Section 5.10.3.are met. Patients experiencing an initial event requiring dose reduction should receive subsequent therapy using dose level -1. If a second event requiring dose reduction occurs, subsequent therapy should be administered using dose level -2. If a third event occurs, the patient will discontinue protocol therapy.

Table 8: IMGN853 Dose Modification Guidelines

Dose Level	**IMGN853[1] (mg/kg, IVq3W)**
Cohort A	
1	**6**
-1	5
-2	4
No further treatment; patient will discontinue protocol therapy.	
Cohort B	
1	**6**
-1	5
-2	4
No further treatment. Patient will be recommended to go to surgery.	

[1]IMGN853 dose calculated using adjusted ideal body weight (AIBW). Maximum allowable dose is 6 mg/kg AIBW. All patients begin at Dose Level 1 for Day 1, Cycle 1.

5.10.5. Discontinuation of Study Treatment Due to Adverse Events

If IMGN853 is discontinued, the patient will enter follow up for survival endpoints.

Study treatment should not be resumed in the case of the following treatment-related events.

- ≥ Grade 3 cardiac event
- Other non-hematologic events of Grade 4 severity that do not respond to appropriate medical management within 48 hours.
- Failure to meet re-treatment criteria within 3 weeks due to insufficient recovery from a treatment-related toxicity. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon between the Grantor and the Investigator.

5.11. Removal of the Patient from the Study or from Study Drug Administration

The patient or legal guardian acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. For this protocol, patients withdrawn for reasons other than toxicity or disease progression during Cycle 1 may be replaced.

Patients will be removed from the study treatment when their disease worsens, and there is no clinical benefit. Additionally, a patient's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a patient from the study:

- The patient suffers an intolerable adverse event
- Non-compliance, including failure to appear at one or more study visits
- The patient was erroneously included in the study
- The study is terminated by the Grantor

If a patient or the patient's legal guardian(s), acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the Investigator, the reason for discontinuation must be captured in the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. All serious adverse events (SAEs), and those AEs assessed by the Investigator as at least possibly related to study drug should continue to be followed until they resolve or stabilize, whichever comes first.

5.11.1. Replacement of Patients who are Withdrawn Prior to the End of Cycle 1

Only patients who sign the informed consent form and receive at least one dose of IMGN853 will be considered enrolled. If an enrolled patient is discontinued from study treatment for reasons other than safety (e.g., withdrawal of consent, non-compliance, death due to disease

progression) prior to the end of Cycle 1, he or she will be replaced (i.e., an additional patient will be added to the cohort). Patients who do not complete Cycle 1 due to an AE will not be replaced. Patients who are replaced will be followed for safety and other assessments according to the protocol.

5.12. Period of Observation

For purposes of this study, the period of safety observation extends from the time of informed consent until the final evaluation during the study, including the 30-day follow-up safety visit. Short-term follow-up for patients who discontinue study therapy without documented progressive disease will continue every 3 months until the patient's disease worsens, until the patient begins subsequent anti-cancer treatment, or until the patient dies, whichever comes first.

5.13. Concomitant Medications and Procedures

All concomitant medications and supportive therapy taken within 4 weeks of Cycle 1, day 1 and through 30 days after last study treatment must be recorded on the appropriate eCRF. The identity of all medications, dosage, and route of administration, frequency, duration of administration, and indication for use will be recorded in the appropriate sections of the eCRF.

5.13.1. Lubricating Artificial Tears

Patients will be required to regularly use preservative-free, lubricating artificial tears on a daily basis (as directed by the product label or treating physician).

5.13.2. Antiemetic and antidiarrheal medications

Antiemetic (e.g. 5-HT3 serotonin receptor antagonists such as palonosetron, granisetron or ondansetron) and antidiarrheal (e.g. loperamide) medications may be used at the discretion of the treating physician.

5.13.3. Folate-Containing Vitamins

Folate-containing vitamins are not to be taken during the course of the study.

5.13.4. Antineoplastic Therapy

Other chemotherapy, investigational agents, immunotherapy, or biologic therapy will not be permitted during the study.

Palliative radiotherapy during study treatment should be discussed with the Grantor prior to implementation. If the Investigator and Grantor agree it is in the best interest of the patient, palliative radiotherapy may be performed however the patient will be censored in the PFS analysis from the time radiotherapy was performed if treatment was performed on a target or non-target lesion.

5.13.5. Hematopoietic Growth Factors

Patients receiving recombinant erythropoietin or darbepoietin-α prior to study start may continue to receive pre-treatment doses.

The use of erythropoietic and granulocyte growth factors in accordance with ASCO guidelines may be implemented at the discretion of the treating physician after Cycle 1.

5.13.6. Other Concomitant Medications

Medications for the treatment of adverse events or cancer symptoms (e.g. packed red blood cells and pain medications), are allowed. Prophylactic use of steroids and/or antihistamines will be considered if needed to alleviate mild-moderate infusion-related reactions. Additionally medications (not addressed above) used to treat underlying medical conditions at study entry including anti-emetics and anti-diarrheal will be allowed to continue.

5.13.7. Medication Metabolized Through Cytochrome P450 (CYP3A)

In vitro metabolism studies demonstrated that DM4 is predominantly metabolized by thiol s-methyltransferase (TMT) to form Me-DM4, which is further metabolized into sulfoxide-methyl-DM4. As Me-DM4 has been shown to be primarily metabolized by CYP3A, its exposure could potentially be increased in the presence of strong CYP3A inhibitors. Drinking greater than 1 serving (250 mL) of grapefruit juice per day should be avoided.

Available in vitro metabolism data suggest DM4 has a potential to inhibit CYP3A activity in vivo. The risk of a significant in vivo drug-drug interaction caused by DM4 inhibition of CYP3A is not currently known, therefore, treatment of patients with concomitant medications that are sensitive substrates of CYP3A or are CYP3A substrates with a narrow therapeutic index (Appendix E) should be carefully monitored.

5.14. Overdose and Medication Error

Overdose – There is no known treatment/antidote available for IMGN853. Supportive measures should be instituted if an instance arises in which a patient suffers an overdose of any study drug.

Medication Error – The Grantor must be immediately notified in the event of error in prescribing, dispensing, administering and/or use of IMGN853 or of any study drug, and the event must be reported on the eCRF. If an error resulted in a serious adverse event, a Serious Adverse Event Report Form must be submitted within 24 hours of the event (see Section 7.14.1).

6. TRANSLATIONAL RESEARCH STUDIES (COHORT B ONLY)

Several biomarkers, including FRα, will be evaluated as potential biomarkers of clinical response to IMGN853. These will help guide further clinical development of IMGN853. It is anticipated that expression of the gene that encodes FRα (FOLR1) as measured by RNAseq may predict response to therapy and response will be correlated in tumors categorized as FOLR1+ using level of expression. Similarly, it is anticipated that FRα+ staining will also be correlated with response.

Additionally, preclinical data have shown that antibody drug conjugates that include microtubule-targeted agents such as the maytansinoid DM4 that is incorporated in mirvetuximab soravtansine, enhance the maturation and activation of dendritic cells. This in turn leads to stimulation of an anti-tumor T cell response that can be augmented with antibodies targeting the T cell inhibitory molecules PD-1 (and its ligand PD-L1) and CTLA-4. Based on these data, a study combining mirvetuximab soravtansine with the anti-PD-1 antibody pembrolizumab has been initiated for patients with FRα-positive ovarian cancer.

There is also significant interest in using agents targeting T cell inhibitory molecules in TNBC. The Keynote 012 trial (Nanda et al SABCS, 2014) enrolled patients with locally advanced or metastatic TNBC with some degree of PD-L1 expression. Patients received the anti-PD-1 antibody pembrolizumab dosed at 10mg/kg every two weeks. The overall response rate was 18.5%. For those who responded, those responses appears to be durable. At a median follow-up of 9.9 months, the median duration of response had not been reached. At the 2015 annual meeting of the AACR, Emens et al. reported that the anti-PD-L1 antibody atezolizumab was safe with evidence of clinical activity. The 24-week progression-free survival rate was 27% with an objective response rate of 19%. At the 2015 SABCS, Dirix and colleagues presented data from the Javelin trial that investigated the anti-PD-L1 antibody avelumab. In patients with TNBC, the objective response rate was approximately 10%. Correlative studies in this trial showed that patients with tumors with an immune cell infiltrate expressing PD-L1 were more likely to respond to treatment. In order to provide the necessary preclinical data to support a trial combining mirvetuximab soravtansine with immune checkpoint blockade agents, to include those targeting PD-1 or PD-L1, we will characterize the immunophenotype of the tumor and microenvironment in specimens obtained pre- and post-treatment from patients treated with mirvetuximab soravtansine.

Enrollment onto ARTEMIS mandates that patients undergo biopsies at the following time points: pretreatment, after 4 cycles of anthracycline-based chemotherapy, and at the time of surgical resection (upon completion of all neoadjuvant therapy). Tissue from these biopsies will be used to generate molecular profiles by RNAseq, comprehensive gene sequencing and immunohistochemistry as part of the MD Anderson TNBC Cancer Moon Shot. Slides will be made available to perform the IHC studies proposed and to evaluate FOLR1 by RNAseq.

6.1. Correlation between FRα Expression and IMGN853 anti-tumor activity

FRα expression varies with tumor histology, as reported in the literature and demonstrated in our pre-clinical studies (Sections 1.1 and Investigators' Brochure). Based on the hypothesis that tumors expressing higher levels of FRα are more likely to be susceptible to anti-tumor activity of IMGN853, a threshold for FRα expression was determined for enrollment in this study. This was done based on molecular epidemiology data generated in a number of patient samples representative of different tumor types, as well as clinical anti-tumor activity data from the FIH study 0401.

6.1.1. Evaluation of FRα Expression in Tumor Tissue

FRα expression in tumors will be analyzed via IHC. All patients must submit archived tumor tissue, or formalin-fixed, paraffin embedded slides for analysis of FRα expression by IHC prior to enrollment.

Only patients with the required FRα expression levels by IHC ($\geq$25% of tumor at $\geq$1+ intensity) will be eligible to enroll in the study.

The tumor samples will be analyzed for FRα expression in the Companion Diagnostics Pharma Services CAP-accredited or CLIA-certified laboratory and Pathology Services at Ventana Medical Systems, Inc. or local lab using Ventana Class I IVD.

To determine FRα expression in patient tumor specimens and support patient selection, ImmunoGen engaged the services of Ventana Medical Systems, Inc. (VMSI) to develop an IHC-based clinical trial assay. The assay utilizes FOLR1-2.1, a murine monoclonal antibody recognizing the receptor in FFPE samples and discovered at ImmunoGen, and the Ventana OptiView DAB Detection Kit on a Ventana BenchMark XT fully automated slide stainer. The assay has been optimized and analytically validated with respect to specificity, sensitivity, and precision using normal and tumor tissue controls, and is suitable for the semi-quantitative determination of FRα protein expression in formalin-fixed paraffin embedded tissue samples.

Assay Interpretation

Board certified pathologists evaluate FRα expression in tumor cells. Membrane and cytoplasmic staining (the latter for information only) are scored separately for the percentage of cells stained at 1+ (weak), 2+ (moderate), and 3+ (strong) staining intensity. Zero (0) indicates the absence of FRα expression. H score is calculated as 1*(% cells stained at intensity 1+) + 2*(% cells stained at intensity 2+) + 3*(% cells stained at intensity 3+) and has a range of 0-300.

VENTANA has developed the VENTANA FOLR1 (FOLR1-2.1) CDx Assay to aid in the selection of patients who may benefit from mirvetuximab soravtansine treatment. VENTANA

FOLR1 (FOLR1-2.1) CDx Assay encompasses a combination of the anti- FRα (FOLR1-2.1) mouse monoclonal primary antibody for use with the BenchMark ULTRA automated staining platform and the OptiView DAB IHC Detection kit. This assay has been optimized and

analytically validated with respect to specificity, sensitivity, and reproducibility per FDA guidance for Investigational Use Only (IUO) assays, and is suitable for determining eligibility.

Patient sample screening using this assay will be done in the Ventana Translational Diagnostics (TDx) CAP/CLIA Laboratory.

IHC data will be used to further define associations between FRα expression and clinical response.

6.2. Exploratory Biomarker Studies (Cohort B Only)

In order to provide the necessary preclinical data to support a trial combining mirvetuximab soravtansine with immune checkpoint blockade agents, to include those targeting PD-1 or PD-L1, we propose to characterize the immunophenotype of the tumor and microenvironment in specimens obtained pre- and post-treatment from patients enrolled on this proposed neoadjuvant trial. Multiplex immunofluorescence will be performed on pre- and post-treatment specimens using the Opal™ multiplex staining kit and imaged using the Vectra™ microscope. We will use 2 panels that have been optimized in collaboration with the Immunotherapy Platform at MD Anderson. Panel 1 includes the following antibodies: AE1/AE3 (pan-cytokeratins), CD3 (pan T cell marker), CD4 (helper T cell marker), CD8 (cytotoxic T cell marker), PD-L1 and CD68 (macrophage marker). Panel 2 include: AE1/AE3, PD1, and FOXP3 (regulatory T cells), CD45 Ro (memory T cell response), CD57 (NK cell marker) and granzyme B.

7. STUDY PROCEDURES

7.1. Informed Consent (Pre-screening and Study)

Each patient or legally authorized representative must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.1.1 Pre-screening informed consent – identifies triple-negative breast cancer patients that appear to be eligible candidates. The pre-screening ICD allows for either archived tissue (cohort A) or fresh tumor biopsy (cohort B) to be tested for FRα. Only patients found to be FRα positive, per protocol criteria, will be enrolled into the clinical trial.

7.1.2 Study informed consent – once patients have been determined FRα positive, per protocol criteria, they may sign the study informed consent. The patients will then begin screening tests required for the clinical trial. Patients not found to be FRα positive will not sign the study informed consent.

7.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be assessed during screening (within 28 days prior to the first dose of any study drug on Cycle 1, day 1). A patient is considered enrolled when administered the first dose of drug.

7.3. Confirmation of Disease Diagnosis

At screening, disease diagnosis and current disease status will be confirmed from information in the source record.

7.4. Demographic/Medical History

The age, race, and gender of the patient are to be recorded during screening.

During the Screening period, a complete medical history will be compiled for each patient. The history will include the background and progress of the patient's primary malignancy and include a description of all prior therapies for the primary malignancy.

7.5. Physical Examination, Weight and Height

Physical examination, height (screening only) and weight must be performed as indicated in the Schedule of Clinical Assessments (Appendix A.). A complete physical examination will be completed at screening and end of treatment. Directed physical examinations will be completed at additional time points as specified in the Schedule of Events.

Weight will be measured at screening and at other times specified in the Schedule of Clinical Assessments (Appendix A).

7.6. Vital Signs

Vital signs will be measured as outlined below and in Appendix A.

Table 9: Vital Sign Measurements

	Screening	Day 1 of All Cycles [a] (Predose)	Every 30 Minutes During IMGN853 Infusion [b]	Immediately Following Completion of IMGN853 Infusion [c]	4-Hous Post End of IMGN853 Infusion [d]	End of Treatment and Follow Up Visits
Blood Pressure	●	●	●	●	●	●
Pulse	●	●	●	●	●	●
Respiratory Rate	●	●	●	●	●	●
Temperature	●	●	●	●	●	●

[a] Within 10 minutes prior to start of infusion of IMGN853
[b] ± 10 minutes
[c] Within 10 minutes following completion of infusion of IMGN853
[d] **Cycle 1 only**. If the patient's infusion was well-tolerated, the 4-hour post IMGN853 infusion assessment will not be required in Cycles ≥2.

7.7. Laboratory Assessments

Patients should be in a seated or supine position during blood collection. Screening labs (hematology, clinical chemistry, and urinalysis) may be performed within 28 days of first dose prior to the start of Cycle 1, Day 1. Laboratory assessments may be performed up to 48 hours prior to day 1 of subsequent cycles but must be evaluated by the treating practitioner prior to administration of therapy. Repeat testing will be performed as outlined in the Schedule of Clinical Assessments (Appendix A) and as clinically indicated.

Note that prior to each administration of IMGN853, laboratory results must be reviewed to evaluate for potential toxicity.

7.7.1. Clinical Laboratory Panels

A list of clinical laboratory tests are found in Table 10.

Table 10: Clinical Laboratory Tests

Hematology	Serum Chemistry	Coagulation Tests
• Hematocrit • Hemoglobin • WBC (with 5-part differential) • RBC • Platelet count	• Albumin • Alkaline phosphatase • ALT • AST • BUN • Calcium • Carbon dioxide • Chloride • Creatinine • Glucose • LDH • Magnesium • Phosphorus • Potassium • Sodium • Total Bilirubin	• PT • aPTT (APTT) • INR

WBC, white blood cell count; RBC, red blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; LDH, lactic acid dehydrogenase; GFR, glomerular filtration rate; INR, International Normalized Ratio; PT, Prothrombin time; aPTT, Activated partial thromboplastin time

7.8. Pregnancy Screen and Prevention

Women of child bearing potential (WCBP), defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months) must agree to use effective contraceptive methods. Acceptable single methods include: intrauterine device, vasectomy of a female patient's male partner, and contraceptive rod implanted into the skin. Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception. Acceptable combination methods (requiring use of two of the following) are acceptable: diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide), cervical cap with spermicide (nulliparous women only), contraceptive sponge (nulliparous women only), male condom or female condom (cannot be used together), or hormonal contraceptive such as oral contraceptive pill, estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection. Acceptable methods of contraception must be used while on study treatment and for at least twelve weeks after the last dose of IMGN853.

All female patients of child-bearing potential will complete a serum beta-human chorionic gonadotropin (β-HCG) or urine pregnancy test (not more than 3 days before the first dose of IMGN853); this test must be negative for the patient to be enrolled and to receive the study drug. If a female patient becomes pregnant or suspects pregnancy while participating in this study, the Investigator and Grantor must be informed immediately and the patient will be withdrawn from study treatment.

7.9. Eastern Cooperative Oncology Group Performance Status

ECOG performance status (Appendix B) will be assessed during screening and at other times specified in the Schedule of Clinical Assessments (Appendix A). An assessment is not necessary on day 1 of Cycle 1 if the screening assessment was obtained within 3 days prior to day 1.

7.10. Radiologic Imaging

Radiographic tumor evaluation by computed tomography (CT) or MRI of chest, abdomen, and pelvis will be performed within 28 days prior to first dose and at every 6 weeks thereafter (±1 week) (Appendix A). The same radiographic assessment used at screening must be used at all subsequent radiographic evaluations.

7.11. Tumor Response Assessment

7.11.1. RECIST

Tumor response for patients with measurable lesions should be assessed using RECIST 1.1 (Eisenhauer 2009, 0). Patients with measurable lesions should be assessed using CT or MRI scan approximately every second cycle, from the date of first dose until the 30-day Follow-up visit. Although progression may be determined by the investigator based upon clinical deterioration, every effort should be made to document progression using radiographic methods. The basis for determination of progression per clinical deterioration should be documented.

The site is expected to maintain a copy of digital data for the retention period applicable to the protocol, Good Clinical Practice (GCP), and federal, international, and/or state legal and medical requirements.

Note: It is very important that the same method of radiologic assessment be used throughout the study and that the same lesions are followed.

7.12. Eligibility Based on FRα Expression

Instructions regarding processing and shipment of biopsy samples and archival tissues are detailed in the Laboratory Manual. The assay used to assess FRα is an investigational IHC assay developed by Ventana.

All patients must have documented expression of FRα by IHC (≥25% of tumor staining at ≥1+ intensity) prior to enrollment. IHC may be performed on archival tissue to determine eligibility. If archival tissue is not available, then a fresh tumor biopsy must be obtained. Assessment of Safety

7.13. Recording Adverse Events and Serious Adverse Events

AEs (including SAEs) will be documented in an AE eCRF, Research Electronic Data Capture (REDCap), and monitored continuously throughout the study from the time of informed consent until 30 days after the patient's last study treatment or until the event has resolved or stabilized or becomes chronic, whichever comes first. AEs attributed to study procedures should also be documented in REDCap.

For patients who discontinue study treatment due to a study-related AE, the reporting time-period may be extended. These patients must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals until resolution, stabilization or chronic state of the adverse event or laboratory abnormality, whichever comes first (see Section 5.10.2.).

If the Investigator considers it necessary to report an AE considered study drug related in a study patient occurring after the end of study, he or she should contact the Grantor to determine how the AE should be documented and reported.

7.13.1. Definition of Adverse Events

7.13.1.1. Adverse Event (AE)

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. AEs include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

Note that progressive disease should not be reported as an AE unless it is considered to be drug-related by the investigator.

All AEs, including AEs attributed to study procedures, occurring from the time of informed consent until 30 days after last study treatment must be reported in REDCap, regardless of the severity or relationship to study drug. The Investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize, resolve or are considered chronic. AEs may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

Table 11: Adverse Event Recording Guidelines

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

In addition, AEs may also include laboratory values that become significantly out of range. Such abnormal laboratory values or test results constitute AEs if they induce clinical signs or symptoms, are considered clinically significant (e.g., the reason for study discontinuation or constitutes in and of itself a Serious Adverse Event, or require therapy, e.g., any hematologic abnormality that requires transfusion or growth factor treatment); and should be recorded in REDCap under the signs, symptoms or diagnosis associated with them. In the event of an out-of-range value, the laboratory test should be repeated until it returns to normal or can be explained and the patient's safety is not at risk.

7.13.1.2. Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of informed consent, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.13.1.3. Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the Grantor's product for which ongoing monitoring and rapid communication by the investigator to the Grantor could be appropriate. These are reportable to the Grantor using an SAE form and in the same timeframe as SAEs

7.13.1.3.1. IMGN853

IMGN853 has one AESI: pneumonitis

7.13.2. Classification of Adverse Events

All AEs will be evaluated according to the NCI CTCAE version 4.03 (effective 14 June 2010). If the AE is not listed in the CTCAE version 4.03, it should be graded based on the description given in Table 12.

Table 12: Adverse Event Severity

Severity	Definition
Grade 1 (Mild)	No limitations of usual activities
Grade 2 (Moderate)	Some limitation of usual activities
Grade 3 (Severe)	Inability to carry out usual activities
Grade 4 (Life-threatening)	Immediate risk of death
Grade 5 (Fatal)	Resulting in death

Relationship of an AE or SAE to study medication is to be determined by the Investigator based on the definitions listed in Table 13. Relationship should be attributed not only to the combination regimen, but also to each drug within the combination regimen.

Table 13: Adverse Event Causal Relatedness

Relationship to the Product(s)	Definition
Not Related	No relationship between the event, including laboratory test abnormality, and the administration of study drug. There is no

	temporal relationship and there is ambiguous evidence supporting another case.
Relationship to the Product(s)	**Definition**
Unlikely Related	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Possibly Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of study drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the study drug withdrawal may be lacking or unclear.
Probably Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. The association of the clinical event, including laboratory test abnormality, must also have some biologic plausibility, at least on theoretical grounds.
Definitely Related	A clinical event, including laboratory test abnormality occurring in a plausible time relationship to study drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

7.14. Adverse Events

7.14.1. Reporting Serious Adverse Events

Any SAE, regardless of relationship to study medications, which occurs in a patient from the time of informed consent until 30 days after the last study treatment of IMGN853 should be recorded by the clinical site on an SAE report form. The SAE must also be recorded in the patient's eCRF, including the causality assessment of the Investigator as to the relationship of the SAE to the study treatment [IMGN853]. The Investigator will promptly supply all information identified and requested by the Grantor (or contract research organization [CRO]) regarding the SAE.

The Investigator must report the SAE to ImmunoGen Pharmacovigilance (or designee) on an SAE Report Form. This form must be completed and submitted within 24 hours of the Investigator's learning of the event, to the contact persons listed in the Safety Management Plan

provided to each site and maintained in the Investigator study files. Any follow-up information must also be completed on a follow-up an SAE Report Form, and submitted to the same contacts.

When reporting SAEs, the following additional points should be noted:

- The underlying diagnosis or syndrome should be reported as the primary SAE term, rather than the signs or symptoms (signs and symptoms may be described in the narrative).
- Progression of disease should not be reported as an SAE unless it is considered to be drug-related by the investigator; any serious medical event/condition that results from progression of underlying disease should be reported as the SAE.
- Death should not be reported as an SAE, but rather as an outcome of a specific SAE, unless the event preceding the death is unknown. In these exceptional cases, death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.

It is the responsibility of the Grantor to ensure that each Investigator receives a copy of any CIOMS/MedWatch report that has been submitted to the appropriate national regulatory agencies as notification of a suspected unexpected serious adverse reaction (SUSAR). The Investigator (or Grantor or Grantor's representative if so designated) must promptly report all SUSARs to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for review in accordance with national regulations. IRB/IEC notification of the SUSAR may take the form of a submission of a copy of the CIOMS/MedWatch report or other format accepted by the IRB/IEC. A copy of the CIOMS/MedWatch report and notification to IRB/IEC should be retained in the site's study files.

In addition to CIOMS/MedWatch reports, the Grantor will also notify the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication through annual updates to the IB.

Disease progression and/or progression of the disease under study are anticipated occurrences in oncology drug development, and as such, are considered expected as per the current investigator's brochure for the compound. If a patient expires from progression of disease and/or from the disease under study during the period of obligation to report serious adverse events, disease progression and/or progression of the disease under study with a fatal outcome do not need to be reported as serious adverse events. The applicable protocol CRF page(s) pertaining to death should be appropriately completed however, as disease progression.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Grantor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Grantor.

All patients with serious adverse events must be followed up until the event returns to baseline, stabilizes or becomes chronic.

SAE Reporting to ImmunoGen and NCCN

SAEs, including those that are expedited (MedWatch/CIOMS preferred. Listing acceptable) should be sent to ImmunoGen at: IMGNPVGSAFETY@immunogen.com; **AND** to NCCN at ORPreports@nccn.org OR 215-358-7699

IND SAFETY REPORTS (final MedWatch only) must be sent, upon submission to FDA, to: 8
IND SAFETY REPORTS (final 53IST_SUSAR@immunogen.com

7.14.2. Reporting Adverse Events of Special Interest

Any AESI, regardless of relationship to study medications, which occurs in a patient from the time of informed consent until 30 days after the last study treatment, should be recorded by the clinical site on an SAE report form. The reporting procedures outlined in Section 7.14.1.will be followed for reporting any AESI, including AESIs are reportable to the Grantor in the same timeframe as SAEs.

7.14.3. Reporting a Pregnancy

Pregnancy and lactation are exclusion criteria. The Grantor must be immediately notified in the event of a pregnancy occurring during the course of the study and through 30 days after a patient's last dose of IMGN853 and through 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier. Pregnancy is not to be reported as an AE; the pregnancy report form should be used to report a pregnancy. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). The reporting procedures in Section 7.14.1, will be followed, including pregnancies and pregnancy outcomes listed above are reportable to the Grantor in the same timeframe as SAEs. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8. STUDY ACTIVITIES

All study visits and assessments that must be performed during the study and follow-up are included in Appendix A.

8.1. Screening Visit

The Investigator is responsible for keeping a record of all patients screened for entry into the study and subsequently excluded. The reason(s) for exclusion must also be recorded. The following screening procedures must be performed within 28 days prior to day 1, unless otherwise specified.

8.1.1. Standard of Care Assessments

In some cases, clinical assessments performed prior to obtaining informed consent may be used to qualify the patient for the study. These include radiological tumor assessment, physical examinations, hematology, serum chemistry results, coagulation studies, urinalysis, or other assessments which may be considered part of normal standard of care. In these cases, repeat assessments may not be necessary prior to enrollment, unless individual parameters require further study or confirmation and are clinically appropriate.

8.2. End of Treatment Visit

Patients may voluntarily withdraw from the study treatment at any time for any reason, and without prejudice to further treatment. In addition, patients may be withdrawn by the Investigator if they do not feel the patient is deriving clinical benefit or because the patient is experiencing unacceptable toxicity. The reasons for which a patient may be prematurely discontinued are listed in Section 5.11.

Patients who withdraw or are removed from the study treatment will have an end of treatment visit within 7 days of the decision to discontinue study treatment. Additionally, these patients will undergo a 30-day follow-up safety visit. The eCRF will capture reasons for withdrawal.

8.3. Follow-up Assessments

8.3.1. Safety Follow-up

A safety follow-up visit will occur 30 days (+ 14 days) after the last treatment.

All serious adverse events, and those adverse events assessed by the Investigator as at least possibly related to study drug should continue to be followed until they resolve or stabilize, whichever comes first. Reporting of SAEs are detailed in Section 7.14.1.

8.3.2. Response Follow-up

Patients who have discontinued study treatment for reasons other than PD will be followed per Revised Response Criteria (RECIST 1.1, see 0) every 12 weeks (+/- 3 weeks) until documentation of PD, or until the patient starts subsequent anti-cancer therapy, whichever comes first.

9. STATISTICAL METHODS

Advanced/Metastatic Disease (Cohort A): A 20% response rate in metastatic TNBC is considered clinically meaningful and would be the threshold to activate the proposed neoadjuvant cohort. Using a standard inference-based Simon-type design, p0 is specified as the response rate threshold below which a treatment would be clearly unacceptable and p1 is specified as the response rate above which the treatment would be clearly acceptable. For this cohort, p0 will be defined as 2.5% and p1 will be 20%. Response (defined as confirmed CR or PR by RECIST) will be assessed after 10 patients with measurable metastatic disease have undergone response assessment. If at least 1 patient develops response to therapy, the cohort will continue to accrue until a total of 20 patients with measurable disease have undergone response assessment. If at any point, 2 patients develop response to therapy, the 20% activity threshold will have been met and accrual can begin to the neoadjuvant cohort while accrual to the metastatic cohort continues to a total of 20 patients. If no patient develops confirmed response in the initial 10 patients, accrual to the single agent regimen will be stopped. This two-phase design has the following properties where p=true response rate, PET=probability of early termination (after the first stage, n=10) and PDS=probability of declaring success (i.e. that the treatment is worthy of further study) after the second stage:

Table 14: Probability of Protocol Success

P	PET	PDS
0.010	0.90	0.02
0.025	0.78	0.07
0.050	0.60	0.21
0.100	0.35	0.51
0.150	0.20	0.73
0.200	0.11	0.86
0.250	0.06	0.93
0.300	0.03	0.97

PDS at p0 is equal to alpha (probability of false positive conclusion) and PDS at p1 is equal to the power (1- beta = probability of true positive conclusion). So, for the proposed design, alpha = 7% and we have 86% power. The probability of early termination at p0 = 78%.

Following this design, for subsequent patient safety, enrollment will be halted while waiting for one of the first 10 patients to respond to therapy. If there are no responses within the first six months of starting treatment in the first 10 patients or <2 responses in the 20 patients treated using single agent therapy, then accrual will be held and a discussion for amending the trial will be held with NCCN and ImmunoGen to either: 1) include a doublet of mirvetuximab soravtansine in combination with carboplatin, or 2) to expand accrual as a single agent in the metastatic setting and forgo the neoadjuvant cohort of patients.

Neoadjuvant (Cohort B): This will be a non-randomized open label phase II study. Counting pCR (RCB-0) or RCB-I as response, a two-stage Gehan-type design will be employed with 14 patients in the first stage. If at least one patient responds, 23 more patients will be added for a total of 37 patients. This design has a 49% chance of terminating after the first stage if the true response rate is 0.05, 23% chance if the true rate is 0.10, 10% if the true rate is 0.15 and 4% if the true rate is 0.20. If accrual continues to the second stage and a total of 37 patients are enrolled, the 95% confidence interval for a 0.20 response rate will extend from 0.10 to 0.35. For patients who complete 4 cycles of mirvetuximab soravtansine, the proportion of patients with pCR (RCB-0) or RCB-I as the response rate along with a Wilson (score) 95% confidence interval (CI) will be estimated.

Secondary Objectives:

Radiographic response rate (partial response + complete clinical response) will be estimated, and reported with a 95% CI.

Toxicity will be measured according to CTCAE v4.0. Adverse events and serious adverse events will be summarized in order of prevalence, with the highest grade experienced by each patient reported for each adverse event.

DFS, PFS, and OS will be estimated using the Kaplan-Meier method from the date of enrollment onto this study until the date of progression or death without evidence of progression (for DFS), date of disease progression (for PFS) or death (for OS). Patients alive and disease-free at the latest clinical evaluation will be censored for DFS and OS at the date of that evaluation. DFS, PFS and OS will be reported with a 95% CI. Duration of response will be measured from the date of confirmed response to the date of disease progression (as measured by RECIST) or discontinuation of study drug due to toxicity.

In the neoadjuvant setting (Cohort B), disease response (as measured by pCR/RCB-I) in patients with chemotherapy resistant disease treated with mirvetuximab soravtansine will be compared to those with similar molecular features who receive standard taxane-based chemotherapy while enrolled in the ARTEMIS trial. Though this comparison will not be a randomized comparison, it will provide evidence as to whether patients treated with mirvetuximab soravtansine derive additional clinical benefit and the comparison can be used to provide preliminary data for confirmatory phase III clinical trial design. A one-sided Fisher's exact test will be used to compare the pCR rate (RCB=0 or I) between the standard therapy patients and the mirvetuximab soravtansine treated patients. Assuming 13 standard therapy patients with a true pCR rate of 5% and 37 mirvetuximab soravtansine patients with a pCR rate of 40%; we will have 76.9% power to detect a significant increase in the pCR rate at the 0.05 significance level. As an exploratory analysis, the distribution of RCB scores measured on a continuous scale will be compared between these two groups using a Wilcoxon rank-sum test. Assuming that there is a 0.72 probability that the RCB is less for the mirvetuximab soravtansine treated group, the Wilcoxon rank-sum test will have approximately 81% power to detect a difference in the distribution of RCB scores.

Exploratory Objectives:

Potential biomarkers of response will be correlated with pathologic response to mirvetuximab soravtansine versus paclitaxel (patients who receive standard of care on ARTEMIS) using

appropriate statistical analyses for the biomarker of interest. It is anticipated that expression of the gene that encodes FRα (FOLR1) as measured by RNAseq may predict response to therapy and response will be correlated in tumors categorized as FOLR1+ using level of expression. Similarly, it is anticipated that FRα+ staining will also be correlated with response. Protein expression will be graded 0, 1+, 2+ or 3+ by IHC by a single collaborating pathologist. Degree of expression will then be correlated with presence of FOLR1 as measured by RNAseq as well as response to therapy. Presence of mutations will also be correlated with response. Further, multivariate logistic regression models will be fitted to the data that include three explanatory variables; namely dichotomous variables for treatment (targeted therapy vs paclitaxel), FOLR1 expression, and the interaction. The interaction will be examined to investigate if the relationship between FOLR1 expression status and pathologic response (RCB-0 or I) is different for the two treatments.

The Investigator is responsible for completing the cohort summary report and submitting it to the IND office Medical Monitor for review and approval.

Cohort A (Metastatic TNBC Cohort):

A Response/Toxicity Summary will be submitted after the first ten evaluable patients complete the fourth cycle of study, prior to continue enrollment, and after all 20 evaluable patients complete the fourth cycle of study therapy

Cohort B (Neoadjuvant Cohort):

A Response/Toxicity Summary will be submitted to IND Office Medical Monitor after the first fourteen evaluable patients, and after all 37 patients complete the fourth cycle of study therapy.

9.1. Quality control and assurance

Data will be captured using validated systems. Adverse events will be coded using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03; National Cancer Institute; June 14, 2010; NIH Publication No 09-5410.

All required data will be entered into the clinical or safety database in accordance with Code of Federal Regulations (CFR) 21 Part 11 compliance. The database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be given restricted access based on their role in the study through a password protected environment. All missing data will be explained.

Data should be entered in the system must be verifiable against source documents.

10. ADMINISTRATIVE CONSIDERATIONS, STUDY MONITORING AND DATA MANAGEMENT

10.1. Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must complete a Form FDA 1572. Study medications may be administered only under the supervision of the Investigators listed on this form. Curriculum vitae must be kept on file for the Investigators and sub-investigators listed on Form FDA 1572.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

10.2. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

Before initiation of the study, the Investigator must provide the Grantor with a copy of the written IRB/IEC approval of the protocol and the study ICF. This approval must refer to the ICF(s) and to the study title, study number, and version and date of issue of the study protocol. Grantor Status reports must be submitted to the IRB/IEC at least once per year or as per institutional guidelines. The IRB/IEC must be notified of completion of the study and a final report must be provided to the IRB/IEC. A copy of these reports will be sent to the study clinical monitor or designee. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs which are subject to expedited reporting to the US Food and Drug Administration (FDA) or other regulatory agencies (SUSARs) must be submitted promptly to the IRB/IEC.

10.3. Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Grantor and Investigators abide by Good Clinical Practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

10.4. Patient Information and Consent

Before enrolling in the clinical study, the patient or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An ICF that includes information about the study will be prepared and given to the patient, or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements. The ICF must be in a language understandable to the patient or the patient's legally

authorized representative(s) and must specify who informed the patient or the patient's legally authorized representative.

After reading the informed consent document, the patient or the patient's legally authorized representative(s) must give consent in writing. If the patient or the patient's legally authorized representative(s) is unable to read, oral presentation and explanation of the written ICF and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient or by the patient's legally authorized representative(s). The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the patient or the patient's legally authorized representative(s). The original signed and dated consent document will be retained by the Investigator. Patient confidentiality will be maintained as outlined in Section 10.5.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

10.5. Patient Confidentiality

Patient names will not be supplied to the Grantor. If the patient name appears on any documents, it must be redacted before a copy of the document is supplied to the Grantor. Study findings stored on a computer will be stored in accordance with local data protection laws. Patient blood and tissue samples sent to outside laboratories and/or CROs (e.g. IHC laboratory) are identified by study patient number only to ensure maintenance of confidentiality. The patient consent form will state publications resulting from this study will not refer to patient name or include any other information that might disclose the identity of the subject. The patients will be told that representatives of the Grantor, a designated CRO, the IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

10.6. Study Monitoring

Monitoring procedures that comply with current GCP guidelines will be followed. On-site review of the case report forms (CRFs) for completeness and clarity, cross-checking with source documents, and clarification of administrative matters should be performed.

10.7. Grantor Case Report Forms and Study Reports

Case report forms (paper or electronic) are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original CRF entry must indicate the reason for change. The Investigator is required to sign/e-sign the CRF after all data have been captured for each patient. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by re-signing the CRF.

10.8. Critical Documents

Before the trial initiates (i.e., obtains informed consent from the first patient), it is the responsibility of the Investigator to ensure that the following documents are available:

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the document and document revision reviewed, including but not limited to: the protocol, any protocol amendments, Investigator's Brochure, Patient Information/Informed Consent Form, and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form/any other written information/advertisement
- List of IRB/IEC Committee members/constitution or equivalent compliance statement
- Study and Financial agreement(s)
- Completed Form FDA 1572
- Completed Financial Disclosure Form

10.9. Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will be made in consultation with NCCN and Grantor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Grantor-investigator will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

A record of patients screened, but not entered into the study, is also to be maintained.

When immediate deviation from the protocol is required to eliminate an immediate hazard to patients, the Investigator will contact the Grantor or its designee if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the Medical Monitor and may be required to be submitted to the IRB/IEC as per institutional guidelines.

Protocol modifications will only be initiated by the Grantor-investigator and must be approved by the IRB/IEC and submitted to the FDA or other applicable international regulatory authority before initiation.

10.10. End of Study

End of study is defined as the date when the last patient on study has withdrawn or been discontinued from the study and all necessary follow up visits have been completed in order to complete safety and anti-tumor activity assessments.

10.11. Study termination

10.11.1. Study Termination

If the Grantor, an Investigator, or Study Clinical Monitor discovers conditions arising during the study that indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study must be terminated after appropriate consultation between ImmunoGen and the Investigator. In addition, a decision on the part of ImmunoGen to suspend or discontinue development of the test material may be made at any time.

Within 15 days of premature closure, ImmunoGen must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

10.11.2. Site Termination

A study may be terminated for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site
- Failure of the Investigator to enter patients at an acceptable rate
- Insufficient adherence by the Investigator to protocol requirements
- Insufficient, incomplete, and/or unevaluable data

10.12. Access to Source Documentation

Regulatory authorities, the IEC/IRB, or the Grantor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

10.13. Data Generation and Analysis

The clinical database will be developed and maintained by the investigator or designee and will be responsible for performing study data management activities and analyses.

10.14. Retention of Data

Essential documents should be retained until the following requirements are met:

- A minimum of 2 years has elapsed following the last approval of a marketing application and,
- there are no pending or contemplated marketing applications, or
- at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, or
- the record retention policies and guidelines for countries in which the study is being conducted are followed (whichever is longer)

It is the responsibility of the Grantor to inform the Investigator or institution as to when these documents no longer need to be retained.

10.15. Financial Disclosure

The Investigator should disclose any financial interests in the Grantor as described in 21 CFR Part 54 prior to beginning this study and 12 months after the study has completed. The appropriate form will Grantor be signed and dated by the Investigator, prior to the start of the study.

10.16. Publication and Disclosure Policy

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. All information concerning the product as well as any matter concerning the operation of the Grantor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Grantor and are unpublished, are confidential and must remain the sole property of the Grantor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Grantor is obtained.

Information obtained during the conduct of this study may be used by ImmunoGen in connection with the development of the study drug. This information may be disclosed to other physicians who are conducting similar studies and to the FDA as deemed necessary by the Grantor.

SUPPORTER MAY PUBLISH THE RESULTS OF OR SUBMIT ABSTRACTS OF THE STUDIES AFTER REVIEW BY NCCN AND GRANTOR. SHOULD THE RESULTS OF A STUDY OR STUDIES BE DERIVED FROM A MULTICENTER STUDY, NEITHER NCCN, NOR ANY MEMBER INSTITUTION(S) SHALL PUBLISH ITS OWN INDIVIDUAL RESULTS, BUT RATHER, ALL SHALL PARTICIPATE IN A JOINT, MULTICENTER PUBLICATION OF THE STUDY RESULTS. NCCN SHALL CONTRACTUALLY REQUIRE EACH MEMBER INSTITUTION TO AGREE TO (A) PROVIDE GRANTOR A COPY OF ANY MANUSCRIPT OR ABSTRACT RELATING TO A STUDY, (B) NOT PUBLISH ANY MANUSCRIPT OR ABSTRACT RELATING TO A STUDY UNTIL GRANTOR HAS HAD AN OPPORTUNITY TO REVIEW IT, (C), UPON THE WRITTEN REQUEST OF GRANTOR, DELAY THE PUBLICATION AND DISCLOSURE OF SUCH MANUSCRIPT OR ABSTRACT TO ANY THIRD PARTY FOR UP TO AN ADDITIONAL SIXTY (60) DAYS SO THAT GRANTOR MAY SEEK PATENT PROTECTION OF INTELLECTUAL PROPERTY RIGHTS, (D) DELETE FROM ANY MANUSCRIPT OR ABSTRACT ANY INFORMATION THAT GRANTOR REQUESTS AND BELIEVES IS ITS CONFIDENTIAL INFORMATION, (E) ACKNOWLEDGE GRANTOR AS THE SUPPLIER OF THE STUDY DRUG AND (F) NOT ISSUE A PRESS RELEASE THAT REFERENCES THE STUDIES OR RESULTS WITH GRANTOR'S NAME OR TRADEMARKS WITHOUT THE PRIOR WRITTEN CONSENT OF GRANTOR. NCCN SHALL CONTRACTUALLY REQUIRE EACH MEMBER INSTITUTION TO PROVIDE A FINAL REPORT OR MANUSCRIPT FOR PUBLICATION FOR REVIEW WITHIN NINE (9) MONTHS OF THE CONCLUSION OF THE APPLICABLE STUDY

11. LIST OF REFERENCES:

Ab O, Whiteman KR, Bartle LM, et al. IMGN853, a folate receptor-α (FRα)-targeting antibody-drug conjugate, exhibits potent targeted antitumor activity against FRα-expressing tumors. *Molecular Cancer Therapeutics* 14(7): 1605-1613, 2015.

Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: A Gynecologic Oncology Group Study. *Journal of Clinical Oncology* 29:2259-2265, 2011.

Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase II trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent eithlial ovarian, primary peritoneal or Fallopian tube cancer. *Journal of Clinical Oncology* 30 (17): 2039-2045, 2012.

Akram T, Masseelall P, Fanning J, Carboplatin and paclitaxel for the treatment of advanced or recurrent endometrial cancer. *American Journal of Obstetrics and Gynecology* 192: 1365-7, 2004.

Allard JE, Risinger JI, Morrison C, et al. Overexpression of folate binding protein is associated with shortened progression-free survival in uterine adenocarcinomas. *Gynecologic Oncology* 107: 52-57, 2007.

Basal E, Eghbali-Fatourechi GZ, Kalli KR, et al. Functional folate receptor alpha is elevated in the blood of ovarian cancer patients. PLOS ONE 4: e6292, 2009.

Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology* 29: 4189-4196, 2011.

Burger R, Brady M, Bookman M, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *New England Jornal of Medicine* 365: 2473–2483, 2011.

Cannistra SA. Cancer of the Ovary. *New England Journal of Medicine* 351:2519-2529, 2004.

Chen YL, Chang MC, Huang CY et al. Serous ovarian carcinoma patients with high alpha-folate receptor had reducing survival and cytotoxic chemo-response *Molecular Oncology* 6: 360-369, 2012.

Crane LMA, Arts JG, van Oosten M, et al. The effect of chemotherapy on expression of folate receptor-alpha in ovarian cancer. *Cellular Oncology* 35(1): 9-18, 2012.

Dainty LA, Risinger JI, Morrison C, et al. Overexpression of folate binding protein and mesothelin are associated with uterine serous carcinoma. *Gynecologic Oncology* 105: 563-570, 2007.

Eisenhauer E, Therasse P, Bogaerts J, et al. New response criteria in solid tumors: Revised RECIST Guideline (version 1.1). *European Journal of Cancer* 45: 228-247, 2009.

Elnakat H, Ratnam M. Distribution, functionality and gene regulation of folate receptor isoforms: implications for targeted therapy. *Advanced Drug Delivery Reviews* 56: 1067-1084, 2004.

Erickson HK, Park PU, Widdison WC, et al. Antibody-Maytansinoid conjugates Are Activated in Target Cancer Cells by Lysosomal Degradation and Linker-Dependent Intracellular Processing. *Cancer Research* 66:4426-4433, 2006.

Fisher RE, Siegel BA, Edell SL, et al., Exploratory study of 99mTc-EC20 imaging for identifying patients with folate-receptor positive solid tumors. *Journal of Nuclear Medicine* 49:899-906, 2008.

Garcia A, Singh H. Bevacizumab and ovarian cancer. *Therapeutic Advances in Medical Oncology* 5 (2): 133-141, 2013.

Garin-Chesa P, Campbell I, Saigo PE, et al. Trophoblast and ovarian cancer antigen LK26, sensitivity and specificity in immunopathology and molecular identification as a folate binding protein. *American Journal of Pathology* 142: 557-567, 1993.

Gordon AN, Granai CO, Rose PG et al. Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer, *Journal of Clinical Oncology* 18: 3093–3100, 2000.

Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. Journal of Clinical Oncology 19:4048–4052, 2001,

Hough CD, Cho KR, Zonderman AB, et al. Coordinately up-regulated genes in ovarian cancer. *Cancer Research*. 61: 3869-3876, 2001.

Humber CE, Tierney JF, Symonds RP, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. *Annals of Oncology* 18: 409-20, 2007.

Jones MB, Neuper C, Clayton A, et al., Rationale for folate receptor alpha targeted therapy in "high risk" endometrial carcinomas. *International Journal of Cancer* 123: 1699-1703, 2008.

Kalli KR, Oberg AL, Keeney GL, et al. Folate receptor alpha as a tumor target in epithelial ovarian cancer. *Gynecologic Oncology* 108: 619-629, 2008.

Kelemen LE. The role of folate receptor α in cancer development, progression and treatment: cause, consequence or innocent bystander? *International Journal of Cancer* 119: 243-250, 2006.

Markman M, Kennedy A, Webster K, et al, Phase 2 trial of liposomal doxorubicin (40mg/m^2) in platinum/paclitaxel-refractory ovarian and fallopian tube cancers and primary carcinoma of the peritoneum, *Gynecologic Oncology* 78: 369–372, 2000.

Mantovani LT, Miotti S, Menard S, et al. Folate binding protein distribution in normal tissues and biological fluids from ovarian carcinoma patients as detected by the monoclonal antibodies MOv18 and MOv19. *International Journal of Cancer* 30A: 363-369, 1994.

Muggia FM, Hainsworth JD, Jeffers S, et al. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. *Journal of Clinical Oncology* 15: 987-993, 1997.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* 5(6):649-655, 1982.

Rustin GJS, Quinn M, Thigpen T, et al. New guidelines to evaluate the Response to Treatment in Solid Tumors (Ovarian Cancer). *Journal of Clinical Oncology* 96(6): 487-88, 2004.

Scorer P, Lawson N and Quinn A. A full immunohistochemical evaluation of a novel monoclonal antibody to folate receptor-alpha (FR-α). *Novacastra Journal of Histopathology* 3: 8-12, 2010.

Surveillance, Epidemiology, and End Results (SEER) Cancer Stat Fact Sheets. *htpp://seer.cancer.gov/statfacts/html/corp/html* Accessed August 10, 2015

van Dam GM, Themelis G, Crane LM, et al. Intraoperative tumor-specific fluorescence imaging in ovarian cancer by folate receptor-α targeting: first in-human results. *Nature Medicine* 17: 1315-1319, 2011.

Wadler S, Benson A, Engelking C, et al. Recommended Guidelines for the Treatment of Chemotherapy-Induced Diarrhea. *Journal of Clinical Oncology* 16: 3169-3178, 1998.

Weitman SD, Lark RH, Coney LR et al. Distribution of the folate receptor GP38 in normal and malignant cell lines and tissues. *Cancer Research* 52: 3396-3401, 1992.

Younes A, Kim S, Romaguera J, et al. Phase I multidose-escalation study of the anti-CD19 maytansinoid immunoconjugate SAR3419 administered by intravenous infusion every 3 weeks to patients with relapsed/refractory B-cell lymphoma. *Journal of Clinical Oncology* 30:2776-2782, 2012.

APPENDIX A. SCHEDULE OF CLINICAL ASSESSMENTS COHORT A –

Activity	Screening	Cycle 1			Cycle2			Cycle 3			Cycle ≥4	End of Treatment	30-Day Follow-up (+14 Days)
		Day 1	Day 2	Day 8& 15	Day 1	Day 8& 15	Day 15 to 21	Day 1	Day 2	Day 8 & 15	Day 1		
Informed Consent	•[a]												
Demography	•[a]												
Medical History	•[a]												
Confirm Disease Diagnosis/Current Stage and Prognostic Index Evaluation	•[a]												
Record Baseline Signs and Symptoms	•	•											
Review and document IC/EC	•												
Confirm patient continues to satisfy I/E Criteria including expression of FRα		•											
Confirm patient meets retreatment criteria					•			•			•		
Height	•[a]												
Physical Examination[b]	•[c]	•		•	•	•		•			•	•	•
Weight	•[c]	•			•			•			•	•	•
Vital Signs[d]	•[c]	•	•		•	•		•	•		•	•	•
Pulse Oximetry	•	•	•	•	•	•		•	•	•	•	•	•
ECOG PS	•[c]	•[m]			•			•			•	•	•
Hematology and Chemistry [f]	•[c]	•		•	•	•		•		•	•	•	•
Coagulation (PT/INR/ aPTT) [f]	•[c]	•			•			•			•		•
Pregnancy Test (urine or serum) [e]	•[c, g]	•[g]			•[g]			•[g]			•[g]		•[g]
Ophthalmic examinations [h]		Every other cycle (from point at which toxicity first reported)[k]										•	•
Schirmer's Test [h]		For patients who experience treatment-emergent eye disorders, the Schirmer's Test will be repeated at the first on-study ophthalmic examination and at subsequently if clinically indicated											

Activity	Screening	Cycle 1			Cycle2			Cycle 3			Cycle ≥4	End of Treatment	30-Day Follow-up (+14 Days)
		Day 1	Day 2	Day 8& 15	Day 1	Day 8& 15	Day 15 to 21	Day 1	Day 2	Day 8 & 15	Day 1		
Ocular Symptom Assessment [h]		●			●			●			●	●	●
Biopsy [n]	●											●	
Radiologic tumor assessment [i]	●[a]						Every 2 cycles[i]					●[j]	●[j]
IMGN853 Administration		●			●			●			●		
AE and SAE assessments	●[l]	●	●	●	●	●	●	●	●	●	●	●	●
Record concomitant medication	●[a]	●	●	●	●	●	●	●	●	●	●	●	●

a. Within 28 days prior to the start of Cycle 1, Day 1
b. Directed physical examination is acceptable while on study treatment. Full examination is required at screening and the EOT visit.
c. Within 14 days prior to the start of Cycle 1, Day 1
d. Vital Signs (blood pressure, pulse, respiration rate, and temperature) will be measured as outlined in the full protocol (Section 8.6)
e. Only for WCBP
f. Day 1 laboratory assessments may be performed up to 4 days prior to study agent administration. Laboratory results must be reviewed prior to each scheduled administration of IMGN853. In the event of severe toxicity, laboratory tests must be repeated as necessary until toxicity resolves or stabilizes.
g. A urine or serum pregnancy test will be performed at screening, prior to dosing on Day 1 of every cycle (it can be performed up to 3 days prior to Day 1) and at the 30-Day Follow-up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.
h. Baseline ophthalmic exams will be performed in symptomatic patients by a board-certified ophthalmologist and will include the following: visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, and optional corneal photography. A Schirmer's test will be performed at baseline for all patients, and for patients who experience ocular symptoms, it will be repeated at the first on-study ophthalmic examination and at subsequently if clinically indicated. May be performed within 14 days of Cycle 1, Day 1. Ocular symptom assessment will be performed prior to the start of each cycle by the treating physician or other qualified individual. If the subject reports ocular symptoms then IMGN853 will be stopped and the subject will then be referred to an ophthalmologist for a complete examination (detailed in full protocol). Patients who experience ocular toxicity will have a complete ophthalmologic exam performed every other cycle, including patients with blurred vision but normal eye exams. All patients will have complete ophthalmologic exam performed at the End of Treatment visit or 30-Day Follow-up.
i. Radiographic tumor assessment by CT or MRI scan is to be performed every 2 cycles (± 1 week)
j. If a patient discontinues prior to documentation of PD, a tumor assessment is to be performed at the End of Study visit or 30-Day Follow up visit, if not performed within the previous 6 weeks. Tumor assessments will be performed every 12 weeks until progression is documented or the patient begins a new treatment regimen. Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST 1.1 every 12 weeks (±3 weeks) until documentation of PD, starting a subsequent anti-cancer therapy or for up to one year from Cycle 1, Day 1, whichever comes first.
k. As clinically indicated.
l. All AEs and SAEs from the time of informed consent are recorded.

m. ECOG assessment is not necessary on Cycle 1 Day 1 if screening assessment was performed within 3 days prior to Day 1.
n. For Cohort A collection of archival tissue/biopsy for FRα screening only.

SCHEDULE OF CLINICAL ASSESSMENTS COHORT B

Activity	Screening	Cycle 1			Cycle2			Cycle 3			Cycle ≥4	End of Treatment	30-Day Follow-up (+14 Days)
		Day 1	Day 2	Day 8& 15	Day 1	Day 8& 15	Day 15 to 21	Day 1	Day 2	Day 8 & 15	Day 1		
Informed Consent	•[a]												
Demography	•[a]												
Medical History	•[a]												
Confirm Disease Diagnosis/Current Stage and Prognostic Index Evaluation	•[a]												
Record Baseline Signs and Symptoms	•	•											
Review and document IC/EC	•												
Confirm patient continues to satisfy I/E Criteria including expression of FRα		•											
Confirm patient meets retreatment criteria					•			•			•		
Height	•[a]												
Physical Examination[b]	•[c]	•		•	•	•		•			•	•	•
Weight	•[c]	•			•			•			•	•	•
Vital Signs[d]	•[c]	•	•		•	•		•	•		•	•	•
Pulse Oximetry	•	•	•	•	•	•		•	•	•	•	•	•
ECOG PS	•[c]	•[m]			•			•			•	•	•
Hematology and Chemistry [f]	•[c]	•		•	•	•		•		•	•	•	•
Coagulation (PT/INR/ aPTT) [f]	•[c]	•			•			•			•		•
Pregnancy Test (urine or serum) [e]	•[c, g]	•[g]			•[g]			•[g]			•[g]		•[g]
Ophthalmic examinations [h]		Every other cycle (from point at which toxicity first reported)[k]										•	•
Schirmer's Test [h]		For patients who experience treatment-emergent eye disorders, the Schirmer's Test will be repeated at the first on-study ophthalmic examination and at subsequently if clinically indicated											

Activity	Screening	Cycle 1			Cycle2			Cycle 3			Cycle ≥4	End of Treatment	30-Day Follow-up (+14 Days)
		Day 1	Day 2	Day 8& 15	Day 1	Day 8& 15	Day 15 to 21	Day 1	Day 2	Day 8 & 15	Day 1		
Ocular Symptom Assessment [h]		●			●			●			●	●	●
Biopsy [n]												●	
Radiologic tumor assessment [i, j]	●[a]						Every 6 weeks (±1 week)[i, j]					●[j]	
IMGN853 Administration		●			●			●			●		
AE and SAE assessments	●[l]	●	●	●	●	●	●	●	●	●	●	●	●
Record concomitant medication	●[a]	●	●	●	●	●	●	●	●	●	●	●	●

a. Within 28 days prior to the start of Cycle 1, Day 1
b. Directed physical examination is acceptable while on study treatment. Full examination is required at screening and the EOT visit.
c. Within 14 days prior to the start of Cycle 1, Day 1
d. Vital Signs (blood pressure, pulse, respiration rate, and temperature) will be measured as outlined in the full protocol (Section 8.6)
e. Only for WCBP
f. Day 1 laboratory assessments may be performed up to 4 days prior to study agent administration. Laboratory results must be reviewed prior to each scheduled administration of IMGN853. In the event of severe toxicity, laboratory tests must be repeated as necessary until toxicity resolves or stabilizes.
g. A urine or serum pregnancy test will be performed at screening, prior to dosing on Day 1 of every cycle (it can be performed up to 3 days prior to Day 1) and at the 30-Day Follow-up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.
h. Baseline ophthalmic exams will be performed in symptomatic patients by a board-certified ophthalmologist and will include the following: visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, and optional corneal photography. A Schirmer's test will be performed at baseline for all patients, and for patients who experience ocular symptoms, it will be repeated at the first on-study ophthalmic examination and at subsequently if clinically indicated. May be performed within 14 days of Cycle 1, Day 1. Ocular symptom assessment will be performed prior to the start of each cycle by the treating physician or other qualified individual. If the subject reports ocular symptoms then IMGN853 will be stopped and the subject will then be referred to an ophthalmologist for a complete examination (detailed in full protocol). Patients who experience ocular toxicity will have a complete ophthalmologic exam performed every other cycle, including patients with blurred vision but normal eye exams. All patients will have complete ophthalmologic exam performed at the End of Treatment visit or 30-Day Follow-up.
i. Radiographic tumor assessment of breast and/or involved lymph nodes by ultrasound or MRI is to be performed every 6 weeks (± 1 week)
j. If a patient has evidence of progression on exam or by symptoms report, a tumor imaging is to be performed.
k. As clinically indicated.
l. All AEs and SAEs from the time of informed consent are recorded.
m. ECOG assessment is not necessary on Cycle 1 Day 1 if screening assessment was performed within 3 days prior to Day 1.
n. At EOT if primary tumor size > 1cm.

APPENDIX B. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

APPENDIX C. RESPONSE DEFINITION (RECIST 1.1)

(Eisenhauer 2009)

DEFINITIONS

Baseline: Baseline is defined as the most recent assessment performed prior to the first dose of study treatment. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable Lesions: Except for lymph nodes (described below), measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion is twice the slice thickness).

- To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Non-measurable lesion: all other lesions (or sites of disease) including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable.

- Lymph nodes that have a short axis < 10mm are considered non-pathological and are not to be recorded or followed.
- Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as target lesions and measured and recorded at baseline.

- Target lesions are to be selected on the basis of their size (lesions with the longest diameter) to represent all involved organs, and to be those that lend themselves to reproducible repeated measurements.
- It may be the case that on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- Target lesions will be measured at each assessment (longest axis for non-nodal lesions, shortest axis for measurable malignant nodal lesions).

Non-target lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥ 10 to < 15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as non-target lesions and recorded at baseline.

- Measurements of these lesions are not required, but the presence, absence, unequivocal progression of each is to be recorded throughout follow-up.
- Lymph nodes that have a short axis < 10 mm are considered non-pathological and are not to be recorded or followed.

Special Considerations

Clinical Examination of Lesions: Superficial or visible lesions that cannot be assessed by CT scan or MRI will only be considered for response assessment if these lesions are biopsy-proven metastatic lesions and ≥ 10 mm in diameter. These lesions will be considered non-measurable and thus non-target for response assessment.

Cystic lesions: Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesion.

Bone lesions: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Lesions with prior local treatment: Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable; however, if they meet the following criteria, they may be considered for study:

- there has been prior documented progression in the lesion by at least 2 sequential CT or MRI scans performed after the completion of radiation, or
- histopathological evidence of progression

Additionally, if such lesions meet the criteria for measurability, they may be considered target lesions.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesion at baseline should be used during each follow-up assessment. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam (referring to biopsy-proven visible lesions(s) at the vaginal apex).

Chest X-ray: Lesions that are identified on chest X-ray must be confirmed and followed by CT scan. If there is/are pre-existing chest lesion(s) before the baseline tumor assessment, a chest X-ray is not necessary to assess those lesions. The pre-existing chest lesion(s) must be assessed at baseline and followed by CT scans.

Conventional CT or MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion is twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scan) except for lung.

CA 125: Tumor marker CA 125 alone cannot be used to assess response or determine progression; however, it will be followed. CA 125 measurements should be scheduled to approximately coincide with radiological assessment (every 6 weeks±1 week). Patients whose CA 125 is above the upper normal limit at baseline will need to have their values normalize to ≤ upper normal limit, in addition to complete disappearance of measurable or evaluable disease, in order to be considered in complete response.

Other methods of assessment, PET-CT, ultrasound and FDG-PET should not be used for response assessment in this study.

Time Point Assessments

Patients will have tumor measurements performed within 28 days prior to baseline and every 6 weeks thereafter (±1 week).

At baseline, tumors and lymph nodes are classified and documented as target or non-target per the definitions provided above. It is possible to record multiple non-target lesions involving the same organ as a single item (e.g., 'multiple liver metastases').

At all post-baseline evaluations, the baseline classification (target, non-target) is to be maintained and lesions are to be documented and described in a consistent fashion over time (e.g., recorded in the same order on source documents and CRFs).

For target lesions, measurements should be taken and recorded in metric notation. All tumor measurements must be recorded in millimeters.

At each assessment, a sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported. The baseline sum of the longest diameters (SLD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SLD (nadir) since, and including, the baseline value will be used as reference for evaluating progression.

After baseline, the actual size of the target lesion should be documented, if possible, even if the lesions become very small. If in the opinion of the radiologist, the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator of "too small to measure" will be provided on the CRF (a default value of 5 mm will be imputed during analysis).

Non-target lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesion, if any, are to be documented separately.

At each evaluation, a time point response is to be determined for target lesions, non-target lesions, new lesions and overall.

Time Point Response Criteria

	Target Lesion Time Point Response (TPR)
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least 30% decrease in the SoD of target lesions, taking as reference the baseline SoD
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesions, taking as reference the smallest (nadir) SoD since and including baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not Applicable (N/A)	No target lesions identified at baseline
Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criteria for PD

If the target lesion for a patient meets the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir SoD is 0 (i.e., the patient had a prior target lesion CR), the re-appearance of any prior target lesions to any degree constitutes PD.

	Non-Target Lesion TPR
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level if tumor marker at baseline is above the upper normal limit. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of CA125 above the normal limits if CA125 at baseline is above the upper normal limit
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not Applicable (N/A)	No non-target lesions identified at baseline
Unable to Evaluate (UE)	One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criteria for PD

If the target lesion for a patient meets the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir SoD is 0 (i.e., the patient had a prior target lesion CR), the re-appearance of any prior target lesions to any degree constitutes PD.

New Lesion TPR	
Yes	Lesion present at follow-up visit either for the very first time or re-appearing (i.e., lesion was present at baseline, disappeared at a follow-up visit and re-appeared later).
No	No new lesions present at follow up
Unable to Evaluate (UE)	Patient non assessed or incompletely assessed for new lesion

Determining Overall TPR

Target Lesion TPR	Non-Target TPR	New Lesions TPR	Overall TPR
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE	No	PR*
PR	Non-PD or NA or UE	No	PR*
SD	Non-PD or NA or UE	No	SD
UE	Non-PD	No	UE
PD	Any	No or Yes or UE	PD
Any	PD	No or Yes or UE	PD
Any	Any	Yes	PD
NA	CR	No	CR*
NA	Non-CR/non-PD	No	Non-CR/non-PD
Non-PD	Non-PD	UE	UE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior time point.

*Patients with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met

Confirmation - The main goal of confirmation of objective response is to avoid overestimating the observed response rate. For patients with an overall response of PR or CR a given time point, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response.

Best Overall Response - Best overall response, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at any time point.

APPENDIX D. CTCAE Version 4.03 Grading for selected Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03; National Cancer Institute; June 14, 2010; NIH Publication No 09-5410

Adverse Event	Grade				
	1	2	3	4	5
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise	Death
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self-care ADL		-
Dry Eye	Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self-care ADL		-
Keratitis		Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Decline in vision (worse than 20/40 but better than 20/200); limiting self-care ADL	Perforation or blindness (20/200) or worse) in the affected eye	-
Eye disorders – Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-
Abbreviations: Activities of Daily Living (ADL)					

APPENDIX E. EXAMPLES OF SENSITIVE IN VIVO CYP SUBSTRATES AND CYP SUBSTRATES WITH NARROW THERAPEUTIC RANGE (7/28/2011)

CYP Enzyme	Sensitive Substrates	Substrates with Narrow Therapeutic Range
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

Ref: FDA drug development resources (Accessed on June 9, 2016) (http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionlabeling/ucm093664.htm#classSub)