CLINICAL STUDY PROTOCOL

Study Title:	SORAYA: A Phase 3, Single Arm Study of Mirvetuximab Soravtansine in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression
Study Number:	IMGN853-0417
Study Phase:	3
Product Name:	Mirvetuximab Soravtansine (IMGN853)
Indication:	Platinum resistant, advanced, high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression
Sponsor:	ImmunoGen, Inc. 830 Winter Street Waltham, MA 02451 USA
Sponsor Contact:	[redacted] Phone: [redacted] Email: [redacted]
Original Protocol Date (Version 1.0):	23 October 2019
Amendment No. and Date:	1 (18 December 2019) 1.1 (18 June 2020) Germany 1.2 (22 July 2020) Czech Republic, Germany, and United Kingdom 2.0 (28 August 2020)

SPONSOR SIGNATURE PAGE

[redacted]

[redacted]

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Date

ImmunoGen, Inc.

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigator Brochure for mirvetuximab soravtansine.

I have read the ImmunoGen Protocol IMGN853-0417 and agree to conduct the study as outlined and in conformance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) and applicable regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator Date

LIST OF ABBREVIATIONS

Table 1: List of Abbreviations and Definitions of Terms

Abbreviation	Term
ADA	anti-drug antibodies
ADC	antibody drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ADL	activities of daily living
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)
BICR	blinded independent central review
BIRC	blinded independent review committee
BRCA	breast cancer susceptibility gene
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CI	confidence interval
CNS	central nervous system
CR	complete response/remission
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DM4	N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine
S-methyl DM4	methylated N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Term
eCRF	electronic case report form
EOC	epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
EOT	End of Treatment
EPO	erythropoietin
ERB	Ethics Review Board
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FIH	first-in-human
FOLR1, FRα	folate receptor 1/folate receptor alpha
GI	gastrointestinal
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
IC_{50}	half maximal (50%) inhibitory concentration
IC	Investigators Choice
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IMGN	ImmunoGen
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MIRV	mirvetuximab soravtansine (IMGN853)
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nM	nanomolar
ORR	objective response rate
OS	overall survival
PD	progressive disease
PE	physical examination
PET	positron emission testing
PFS	progression-free survival
PFS2	time to second disease progression
PK	pharmacokinetics
PLT	platelets
PR	partial response/remission
PRN	as needed
PRO	patient-reported outcome
PROC	platinum-resistant ovarian cancer
PS	performance status
PT	prothrombin time
Q3W	every 3 weeks
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SC	Steering Committee

Abbreviation	Term
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SoD	sum of diameters
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TMT	thiol s-methyltransferase
TEAE	treatment-emergent adverse event
TPR	time point response
ULN	upper limit of normal
US	United States
Ventana FOLRI Assay	Ventana FOLR1 (FOLR1-2.1) CDx assay
WBC	white blood cell (count)
WCBP	woman of childbearing potential
WHO-DD	World Health Organization-Drug Dictionary

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ImmunoGen, Inc.

Name of Investigational Product: mirvetuximab soravtansine (MIRV; IMGN853)

Name of Active Ingredient: mirvetuximab soravtansine (MIRV; IMGN853)

Title of Study: SORAYA: A Phase 3, Single Arm Study of Mirvetuximab Soravtansine in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression

Number of Patients (planned): Approximately 110 patients

Study Center(s): Approximately 98 centers globally

Studied Period (months): Approximately 30 months, including follow-up.	**Phase of Development:** 3

Objectives:

Primary Objective

- To determine the efficacy of MIRV in patients with platinum-resistant ovarian cancer (PROC) and high folate receptor alpha (FRα) expression

Key Secondary Objective

- To determine the durability of response to MIRV in patients with PROC and high FRα expression

Additional Secondary Objectives

- To evaluate the safety and tolerability of MIRV
- To characterize the clinical activity of MIRV in patients with PROC and high FRα expression

Exploratory Objectives

[redacted]

Endpoints:

Primary Endpoint

- Objective response rate (ORR), which includes best response of complete response (CR) or partial response (PR) as assessed by the Investigator

Key Secondary Endpoint

- Duration of response (DOR), defined as the time from initial Investigator-assessed response (CR or PR) until progressive disease (PD) as assessed by the Investigator

Additional Secondary Endpoints

- Treatment-emergent adverse events (TEAEs) and laboratory test results, physical examination or vital signs

- CA-125 response determined using the GCIG criteria defined in Appendix C
- Progression-free survival (PFS), defined as the time from first dose of MIRV until Investigator-assessed radiological PD or death, whichever occurs first
- Overall survival (OS), defined as the time from first dose of MIRV until death

Study Design Overview:

This Phase 3 study is designed to evaluate the efficacy and safety of MIRV in patients with platinum-resistant high-grade serous epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer, whose tumors express a high-level of FRα, referred to throughout as PROC (platinum-resistant ovarian cancer). Patients will be, in the opinion of the Investigator, appropriate for single-agent therapy for their next line of therapy. FRα positivity will be defined by the Ventana FOLRI Assay.

Approximately 110 eligible patients will be enrolled to achieve a total of 105 efficacy evaluable patients. Efficacy evaluable patients include those who have measurable lesions (per RECIST v1.1) at baseline and received at least 1 dose of MIRV.

All patients will receive single-agent MIRV at 6 mg/kg adjusted ideal body weight (AIBW) administered on Day 1 of every 3-week cycle (Q3W).

Tumor response will be evaluated by the Investigator using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Computerized tomography (CT) or magnetic resonance imaging (MRI) scans will be collected for sensitivity analysis by blinded independent central review (BICR).

Patients will continue to receive MIRV until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the Sponsor terminates the study (whichever comes first).

Tumor assessments, including radiological assessments by CT/MRI scans will be performed at Screening and subsequently every 6 weeks (± 1 week) from Cycle 1 Day 1 (C1D1) for the first 36 weeks then every 12 weeks (± 3 weeks) until disease progression, death, the start of new anticancer therapy, or patient's withdrawal of consent (whichever occurs first).

Patients who discontinue MIRV for reasons other than progressive disease (PD) will continue with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks. After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of PD or the start of new anticancer therapy.

All patients who discontinue MIRV will be followed for survival every 3 months (± 1 month) until death, lost to follow-up, withdrawal of consent for survival follow-up, or end of study (EOS) (whichever comes first). Additional survival follow-up calls may occur periodically, if needed.

Study Eligibility

Inclusion Criteria

1. Female patients ≥ 18 years of age
2. Patients must have a confirmed diagnosis of high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer
3. Patients must have platinum-resistant disease:
   a. Patients who have only had 1 line of platinum based therapy must have received at least 4 cycles of platinum, must have had a response (CR or PR) and then progressed between > 3 months and ≤ 6 months after the date of the last dose of platinum

b. Patients who have received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum
Note: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression

Note: Patients who are platinum-refractory during front-line treatment are excluded (see exclusion criteria)

4. Patients must have progressed radiographically on or after their most recent line of anticancer therapy
5. Patients must be willing to provide an archival tumor tissue block or slides, or undergo procedure to obtain a new biopsy using a low-risk, medically routine procedure for immunohistochemistry (IHC) confirmation of FRα positivity
6. Patient's tumor must be positive for FRα expression as defined by the Ventana FOLRI Assay
7. Patients must have at least 1 lesion that meets the definition of measurable disease by RECIST v1.1 (radiologically measured by the Investigator)
8. Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, including at least 1 line of therapy containing bevacizumab, and for whom single-agent therapy is appropriate as the next line of treatment:
   a. Adjuvant ± neoadjuvant considered 1 line of therapy
   b. Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (ie, not counted independently)
   c. Therapy changed due to toxicity in the absence of progression will be considered part of the same line (ie, not counted independently)
   d. Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance
9. Patients must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
10. Patients must have completed prior therapy within the specified times below:
    a. Systemic antineoplastic therapy within 5 half-lives or 4 weeks (whichever is shorter) prior to first dose of MIRV
    b. Focal radiation completed at least 2 weeks prior to first dose of MIRV
11. Patients must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities (except alopecia)
12. Patients must have completed any major surgery at least 4 weeks prior to first dose of MIRV and have recovered or stabilized from the side effects of prior surgery
13. Patients must have adequate hematologic, liver and kidney functions defined as:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (1,500/μL) without G-CSF in the prior 10 days or long-acting WBC growth factors in the prior 20 days
    b. Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without platelet transfusion in the prior 10 days
    c. Hemoglobin ≥ 9.0 g/dL without packed red blood cell (PRBC) transfusion in the prior 21 days
    d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
    e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN

f. Serum bilirubin ≤ 1.5 x ULN (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin < 3.0 x ULN)
g. Serum albumin ≥ 2 g/dL

14. Patients or their legally authorized representative must be willing and able to sign the informed consent form (ICF) and to adhere to the protocol requirements
15. Women of childbearing potential (WCBP) must agree to use highly effective contraceptive method(s) (as defined in Section 5.8.6) while on MIRV and for at least 3 months after the last dose
16. WCBP must have a negative pregnancy test within the 4 days prior to the first dose of MIRV

Exclusion Criteria

1. Male patients
2. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade/borderline ovarian tumor
3. Patients with primary platinum-refractory disease, defined as disease that did not respond to (CR or PR) or has progressed within 3 months of the last dose of first-line platinum-containing chemotherapy
4. Patients with prior wide-field radiotherapy (RT) affecting at least 20% of the bone marrow
5. Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE)
6. Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring, such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and /or monocular vision
7. Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following:
   a. Active hepatitis B or C infection (whether or not on active antiviral therapy)
   b. Human immunodeficiency virus (HIV) infection
   c. Active cytomegalovirus infection
   d. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks prior to the first dose of MIRV

   Note: Testing at screening is not required for the above infections unless clinically indicated
8. Patients with a history of multiple sclerosis (MS) or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome)
9. Patients with clinically significant cardiac disease including, but not limited to, any of the following:
   a. Myocardial infarction ≤ 6 months prior to first dose
   b. Unstable angina pectoris
   c. Uncontrolled congestive heart failure (New York Heart Association > class II)
   d. Uncontrolled ≥ Grade 3 hypertension (per CTCAE)
   e. Uncontrolled cardiac arrhythmias
10. Patients with a history of hemorrhagic or ischemic stroke within 6 months prior to enrollment
11. Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)

12. Patients with a previous clinical diagnosis of noninfectious interstitial lung disease (ILD), including noninfectious pneumonitis
13. Patients requiring use of folate-containing supplements (eg, folate deficiency)
14. Patients with prior hypersensitivity to monoclonal antibodies (mAb)
15. Women who are pregnant or breastfeeding
16. Patients who received prior treatment with MIRV or other FRα-targeting agents
17. Patients with untreated or symptomatic central nervous system (CNS) metastases
18. Patients with a history of other malignancy within 3 years prior to enrollment

    Note: patients with tumors with a negligible risk for metastasis or death (eg, adequately controlled basal-cell carcinoma or squamous-cell carcinoma of the skin, or carcinoma in situ of the cervix or breast) are eligible
19. Prior known hypersensitivity reactions to study drugs and/or any of their excipients

Prohibited Concomitant Medications:

Any non-study anticancer agents, including but not limited to antineoplastic agents, biologics, mAbs, and hormonal therapy, or palliative RT during study treatment.

Investigational Product, Dosage and Mode of Administration:

Patients will receive MIRV 6 mg/kg AIBW Q3W.

Duration of Study Participation:

The duration of study participation for each patient extends from the signing of the ICF until the final follow-up study visit, termination from study, death, or withdrawal of consent.

Study Committees:

An Independent Data Monitoring Committee (IDMC) will not be utilized in this open-label, single-arm study of MIRV.

Table 2: Schedule of Assessments

Procedure	Pre-screening	Screening	Cycle 1 C=3 weeks		C2+	C3	EOT	30-Day Follow-up	Survival Follow-up
			D1	D8	D1	D8	≤ 7d from discon.	30 (+14) days from last dose	Every 3 months (±1 month) from EOT
Pre-screening Informed Consent	●								
Informed Consent		●[a]							
Eligibility		●[a]							
Demographics		●[a]							
Medical History		●[a]							
Confirm Disease Diagnosis/Current Stage		●[a]							
12-Lead ECG		●[b]	●[b]						
Coagulation (PT or INR/aPTT)		●[c]							
Urinalysis		●[c]							
FFPE archived tumor tissue and/or new biopsy[d]	●								
Physical Examination[e]		●[c]	●[f]		●		●	●	
Weight		●[c]	●		●		●	●	
Vital signs[g]		●[c]	●		●		●	●	
ECOG PS		●[c]	●[f]		●		●	●	
Hematology and Chemistry[h]		●[c]	●[f]		●		●	●	

Procedure	Pre-screening	Screening	Cycle 1 C=3 weeks		C2+	C3	EOT	30-Day Follow-up	Survival Follow-up
			D1	D8	D1	D8	≤ 7d from discon.	30 (+14) days from last dose	Every 3 months (±1 month) from EOT
Blood sample for Biomarkers	●	●							
Pregnancy Test[i]		●[i]	●[f]		●			●	
Ophthalmic Exam[j]		●[c]	Every other cycle from time treatment-emergent eye disorder first reported				●[j]	●[j]	
Ocular Symptom Assessment[k]		●[c]	●		●		●	●	
Radiologic Tumor Assessment[l]		●[a]	Every 6 (±1) weeks from C1D1 for first 36 weeks, then every 12 (±3) weeks				●[m]	●[m]	
CA-125[n]		●[c]	Collect at each radiologic tumor assessment (± 4 days)				●[m]	●[m]	
MIRV administration			●		●				
Record AE/SAEs and concomitant medications	●[o]	●	Collected continuously while patients are on study						
Blood sample for PK[p]			●	●	●[p]	●	●	●[p]	
Blood samples for immunogenicity[q]			●		●		●	●	
Survival Phone screen, including new anticancer therapy[r]									●

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; C = cycle; CA = cancer antigen; D = day; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EOT = End of Treatment; FFPE = formalin-fixed-paraffin-embedded; INR = international normalized ratio; PK = pharmacokinetics; PT = prothrombin time; SAE = serious adverse event.

Note: A patient's *BRCA* mutational status (germline or somatic mutation in tumor tissue) will be collected as part of her medical history if available. Patients without a known mutation will be classified as unknown.

[a] Must be within 28 days before C1D1 unless otherwise specified.

[b] ECG assessment may be performed predose at C1D1 if not performed previously up to 28 days prior to first dose of MIRV.

[c] Must be within 14 days before C1D1.

[d] Testing for FRα expression is required for all patients. Those who do not have archival tumor tissue to submit will be required to undergo procedures to obtain a new biopsy using a low-risk, medically routine procedure during the Pre-screening period to confirm eligibility. If the archival tumor tissue does not meet FRα criteria, a new biopsy tumor sample may be submitted and used to confirm this criterion.

[e] Complete physical examination (PE) is required at Screening and the 30-Day Follow-up visit. At all other study visits while on MIRV, patients will have symptom-directed PEs.

[f] ECOG, PE, pregnancy test for WCBP, and hematology and chemistry labs (if all parameters are within normal range) do not need to be repeated at C1D1 if performed within the previous 4 days during Screening.

[g] Vital signs (BP and body temperature) will be measured before start of infusion; post infusion vital signs should be collected as clinically indicated for potential infusion-related reaction.

[h] Hematology and chemistry labs may be performed up to 4 days prior to D1 of each cycle, and as clinically indicated while on treatment, with results reviewed before each MIRV administration. In the event of severe toxicity, laboratory tests must be repeated as clinically necessary until the toxicity resolves or stabilizes to baseline level.

[i] For women of childbearing potential (WCBP), a urine or serum pregnancy test must be performed within the 4 days prior to D1 of each cycle, and at the 30-Day Follow-up visit. It is recommended to perform monthly pregnancy tests for 3 months after the last dose of MIRV. Additional testing may be performed in accordance with institutional requirements or local regulation.

[j] Baseline ophthalmic exams will be performed by an ophthalmologist within 14 days before C1D1 and will include the following: visual acuity (with/without corrective lens; whichever best reflects the patient's usual functioning), slit lamp examination, intraocular pressure measurement, and indirect fundoscopy. All patients who have an ophthalmic exam on study treatment (post-baseline) due to emergence of visual signs or symptoms will have a complete ophthalmological examination performed at EOT visit or 30-Day Follow-up visit.

[k] Ocular symptoms assessment will be performed by the treating physician or other qualified individual before the start of each cycle. For patients reporting > CTCAE Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.

[l] Radiologic tumor assessment by CT/MRI scan. The same method of radiographic assessment used at Screening must be used at all subsequent radiographic assessments.

[m] If a patient discontinues before documentation of PD, a tumor assessment and CA-125 will be assessed at the EOT or 30-Day Follow-up visit, if not performed within the previous 6 weeks. Tumor assessments and CA-125 will continue to be performed every 12 (± 3) weeks until PD is documented per RECIST 1.1 or the patient starts new anticancer therapy. Patients who discontinue MIRV for reasons other than progressive disease (PD) will continue with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks. After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of PD, death, the start of new anticancer therapy, or patient's withdrawal of consent (whichever occurs first).

[n] CA-125 will be measured at the time of every tumor assessment (± 4 days) (responses will be confirmed according to GCIG criteria Appendix C).

[o] Only AEs/SAEs which are considered related to a study procedure (ie blood draw or fresh tumor biopsy) will be captured during the Pre-screening period, ie from the time of signing the Pre-screening consent (if one is utilized) until the signing of the main study informed consent, or until the patient is determined to be a screen failure.

[p] Blood samples for PK analysis will be taken within 1 hour after MIRV infusion on Day 1 of Cycles 1 and 3, and on Day 8 (±24 hours) of Cycles 1 and 3. Samples will also be collected prior to dosing on Day 1 of Cycles 2 and 4, and EOT and also at the 30-Day Follow-up, if feasible.

[q] Immunogenicity will be assessed in PK samples collected prior to dosing (predose) on C1D1, C2D1, C4D1, at EOT, and 30-Day Follow-up.

[r] Survival follow-up assessments will occur every 3 months (±1 month) until death, the patient is lost to follow-up or withdrawal of consent for survival follow-up, or EOS (whichever comes first). These assessments may be conducted by telephone. Information on the start of new anticancer therapy (including start date, therapy type/name, and response on treatment) should be collected. Additional survival follow-up calls may occur periodically if needed for regulatory requests or at time of database lock for either primary or final analysis.

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1. INTRODUCTION

1.1. Target Background

Folate receptor alpha (FRα) is a glycosylphosphatidylinositol-anchored cell surface protein encoded by the folate receptor 1 (*FOLR1*) gene. FRα internalizes folate, which is an essential cofactor 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, reduced folate carrier and proton-coupled folate transporter for folate uptake (Weitman 1992, Mantovani 1994, Elnakat 2004, Kelemen 2006, and Investigator Brochure).

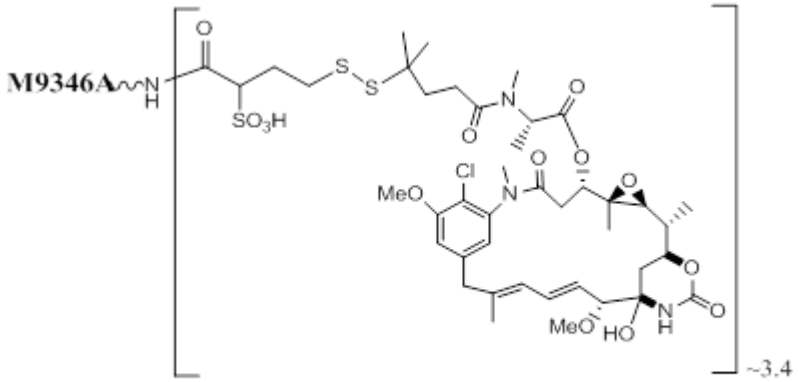
Published studies have demonstrated FRα overexpression by immunohistochemistry (IHC) in various epithelial tumors, particularly the serous and endometrioid histologic subtypes of ovarian and endometrial cancers (Scorer 2010, Garin-Chesa 1993, Kalli 2008, Crane 2012, Dainty 2007, Jones 2008, Ab 2015, and Allard 2007). IHC results obtained from patients screened or enrolled in the Phase 1 Study IMGN853-0401 and Phase 3 Study IMGN853-403 are generally consistent with the literature (Investigator Brochure). Assessment of the FRα distribution in the PROC expansion cohort of IMGN853-0401 demonstrated that approximately 40% of patients have high expression.

Several additional studies have further validated FRα as a target in serous epithelial ovarian cancer (EOC). First, quantitative polymerase chain reaction studies show ubiquitous FRα mRNA expression in serous EOC (Hanker 2012, Hoskins 1998, Hough 2001) and high levels of FRα mRNA correlate with poor response to chemotherapy and decreased disease-free survival (Chen 2012). Second, both Kalli et al and Crane et al have demonstrated that recurrent tumors retain FRα expression comparably to primary tumors as shown by serial biopsy sampling and IHC (Kalli 2008, Crane 2012). Third, studies with FRα-specific imaging agents have demonstrated real-time FRα expression at primary and metastatic tumor sites (Fisher 2008, Gaillard 2018, Garcia 2013, Garin-Chesa 1993, and van Dam 2011). Finally, a truncated form of FRα has been detected in ascites and blood of EOC patients (Basal 2009, Mantovani 1994), further confirming expression in this disease and suggesting that the receptor may serve as a circulating biomarker. Collectively, these data suggest that FRα is a promising target in solid tumors, particularly EOC.

1.2. Mirvetuximab Soravtansine

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 mAb to tumor antigens with the extraordinary cytotoxicity of maytansine derivatives, which are potent anti-microtubule agents that target proliferating cells. MIRV is an ADC designed to target FRα. It consists of the humanized anti-FRα mAb M9346A attached via a cleavable disulfide linker to the cytotoxic maytansinoid, DM4 (Figure 1).

Figure 1: Mirvetuximab Soravtansine Structure



DM4 is ~2% by weight relative to mAb.

Due to the nature of the conjugation process, the number of DM4 molecules attached to the mAb ranges from 1 to 7 molecules per Ab, with an average of 3 or 4 DM4 molecules per Ab. Conjugation of the maytansinoid to the tumor-targeting Ab ensures that the cytotoxic component remains inactive in the circulation. Release of the cytotoxic payload requires binding, internalization, and degradation of the Ab. 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, MIRV binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent (IC_{50} ≤ 1 nM) and selective cytotoxicity against tumor cells expressing FRα. Cytotoxic effects of MIRV in vitro is related to the level of cell-surface expression of FRα (Ab 2015). MIRV 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 MIRV.

1.3. Epithelial Ovarian Cancer

Ovarian cancer is a lethal disease with 22,530 new cases and 13,980 deaths expected in 2019 in the US (SEER Cancer Statistics Factsheet 2019). The estimated number of new EOC cases in the EU (EU27) in 2012 was 44,149 with 29,758 deaths (EUCAN Cancer Fact Sheet: Ovary 2019). The overall 5-year survival for EOC patients is only 44% (Cannistra 2004, Baldwin 2012).

Recent studies indicate that ovarian, peritoneal, and fallopian tube cancers are not distinct entities, but represent a spectrum of diagnoses that originate in the Mullerian tissue. Primary fallopian tube carcinoma and peritoneal cancers are now included in the ovarian cancer staging classification (Cobb 2015, Grant 2010, Naumann 2011, O'Shannessy 2013), and are considered to be part of EOC with the same treatment and outcomes.

Despite considerable improvements in primary therapy, 80% of the patients with advanced EOC are expected to relapse during or after treatment with platinum-containing regimens (Armstrong 2019). Disease recurring within 6 months of platinum-based chemotherapy is classified as *platinum resistant*, whereas, disease recurring longer than 6 months after therapy is termed *platinum sensitive.*

While PARP inhibitors (eg, olaparib and rucaparib) were initially approved as single-agent treatment for EOC patients with *BRCA* mutations (~15% of EOC) who received ≥ 2 prior regimens (Moore 2019), their greatest benefit appears to be as maintenance therapy, both in the recurrent platinum-sensitive (Mirza 2016) and front-line settings (Gonzalez-Martin 2019, Moore 2018), with the greatest treatment effect in patients with *BRCA* mutations or other mechanisms of homologous recombination deficiency.

Like PARP inhibitors, bevacizumab is also approved for EOC in combination with chemotherapy and as continued monotherapy in the maintenance setting. While bevacizumab is approved in combination with chemotherapy in the platinum-resistant setting, many patients receive it earlier in their disease course based on the approvals in the front-line and recurrent platinum-sensitive settings. For those who do receive it in the platinum-resistant setting, bevacizumab combinations are limited to patients who have received no more than 2 prior chemotherapy regimens and are not at risk for bowel perforations (recto-sigmoid involvement, bowel involvement and/or history of bowel obstruction) (Aghajanian 2012, Pujade-Lauraine 2014).

Those patients with PROC who have received prior bevacizumab, either in the platinum-resistant or in the platinum-sensitive setting, have few options. They typically receive subsequent single-agent chemotherapy. Unfortunately, response rates to single-agent chemotherapy are modest (~10 to 15%) and DOR is typically 4 to 8 months (Cannistra 2010, Matsuo 2010). Similarly, OS is poor (median ~11 to 14 months) (Naumann 2011, Pujade-Lauraine 2014). Because PROC remains a significant unmet medical need, the National Comprehensive Cancer Network (NCCN) guidelines recommend that platinum-resistant patients participate in clinical trials (NCCN Guidelines 2019).

The ORR with single-agent chemotherapy in this setting is ~12% in the AURELIA study and more recently in the CORAIL study, with additional studies reporting an ORR of 5% to 15% in similar populations of PROC (Gaillard 2018, Cannistra 2010, Pujade-Lauraine 2014, Pujade-Lauraine 2019).

1.4. Current Therapies

Patients with PROC who have either received bevacizumab or are ineligible for bevacizumab are generally treated with single-agent chemotherapy, leading to the poor outcomes described above (Section 1.3). The single-agent chemotherapies most commonly used include paclitaxel, pegylated liposomal doxorubicin, and topotecan.

1.5. Non-Clinical Studies of Mirvetuximab Soravtansine

1.5.1. Impact of FRα Expression

Studies assessing the potency and specificity of MIRV were conducted on a panel of FRα-positive cell lines with a wide range of FRα expression, as well as on FRα-negative cell lines. These studies revealed a positive correlation between the level of FRα expression on the cell surface, the amount of maytansinoid catabolites generated, and the degree of sensitivity of the cells to MIRV in vitro. MIRV is not active against low and negative FRα expressing cells.

1.5.2. Pharmacology

Results of nonclinical pharmacology studies demonstrate the following:

- FRα has limited normal tissue expression and marked expression in solid tumors, particularly cancers of the ovary and endometrium (Investigator Brochure). In vitro studies demonstrated that MIRV binds cell surface FRα with high apparent affinity (≤ 0.1 nM) and shows potent (IC_{50} ≤ 1 nM) and selective cytotoxicity against cells expressing FRα. MIRV-mediated cytotoxicity involves binding, internalization, and degradation of MIRV, which releases DM4. DM4 can be methylated to yield S-methyl-DM4. Both DM4 and S-methyl-DM4 can 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 MIRV express higher levels of FRα and release 10- to 100-fold more cytotoxic maytansinoid than cells resistant to MIRV.
- MIRV retains the inherent activities of its Ab 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 Ab-dependent cell-mediated cytotoxicity (ADCC) in vitro.
- MIRV demonstrates significant activity against FRα-positive xenografts. Partial and/or complete regressions in xenograft models of EOC were seen at doses of MIRV well below its maximum tolerated dose (MTD).

1.5.3. Pharmacokinetics

Nonclinical studies with MIRV 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 Ab clearance. An additional PK study with free DM4 was conducted in monkey. PK studies demonstrated the stability of MIRV in circulation after IV administration, with a distribution phase lasting about 24 hours followed by a slower terminal elimination phase. The data indicated that the PK of MIRV were approximately dose proportional within the ranges evaluated (1 to 10 mg/kg). These studies are further detailed in the Investigator Brochure.

1.5.4. Toxicology

MIRV was evaluated for toxicity after a single IV injection in cross-reactive (monkey) and non-cross-reactive (mouse) species. Results of these studies supported the first-in-human (FIH) study exploring the safety and tolerability of MIRV when administered once every 3 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 Investigator Brochure.

1.6. Clinical Studies of Mirvetuximab Soravtansine

1.6.1. First-in-Human Phase 1 Clinical Trial: Study IMGN853-0401

The first-in-human (FIH), Phase 1 study evaluated the safety, PK and pharmacodynamics of single-agent MIRV in patients with EOC and other FRα-positive tumors. The recommended Phase 2 dose (RP2D) for single-agent MIRV administered Q3W was determined to be 6.0 mg/kg AIBW. Data from this study are detailed in the Investigator Brochure.

The initial antitumor activity observed with MIRV monotherapy in Study IMGN853-0401, particularly in those patients with PROC, no more than 3 prior lines of therapy and FRα medium or high expression per the “PS2+” scoring method [defined by 2+ intensity staining of tumor cells with medium ≥50% to <75% of tumor cells and high ≥75% of tumor cells] suggested the potential for a significant improvement over single-agent chemotherapy. In the 36 patients with PROC who had received no more than 3 prior lines of therapy, and had FRα medium or high expression, MIRV was associated with a confirmed Investigator-assessed ORR of 47%, median DOR of 5.8 months, and median PFS of 6.7 months, comparing favorably with results seen with single-agent chemotherapy. Similarly, in the subset of 27 patients with FRα-high expression, the confirmed Investigator-assessed ORR was 44%, with median DOR of 7.8 months and median PFS of 6.7 months.

Safety data suggested that MIRV was well tolerated, with a safety profile primarily consisting of low-grade gastrointestinal (GI) AEs and blurred vision related to corneal keratopathy. The treatment-emergent adverse events (TEAEs) were manageable with standard medical care and/or dose modification, with a low rate (10%) of patients discontinuing MIRV due to a treatment-related TEAE.

1.6.2. Phase 3 Monotherapy Trial in Patients with Platinum-Resistant EOC, Peritoneal, and Fallopian Tube Cancer: Study IMGN853-0403

IMGN853-0403 was a Phase 3 study with the objective to evaluate the safety and efficacy of single-agent MIRV versus Investigators Choice (IC) chemotherapy in patients with PROC, primary peritoneal cancer, or fallopian tube cancer, and whose tumor was FRα-positive (medium or high expression) by the Ventana IHC assay using a "10x" scoring method (see Investigator Brochure). The study was designed to compare the efficacy of MIRV to that of approved single-agent selected standard of care chemotherapy (paclitaxel, PLD, or topotecan) in patients with

PROC who have received no more than 3 prior systemic treatment regimens and for whom single-agent chemotherapy is appropriate as the next line of therapy.

A total of 366 patients were randomized and assigned to MIRV or IC chemotherapy groups (248 and 118, respectively) and were included in the intent-to-treat (ITT) analysis. A total of 352 patients received at least 1 dose of MIRV or IC chemotherapy (243 and 109, respectively). All patients in the MIRV group received a dose of 6 mg/kg AIBW Q3W, while the patients in the IC chemotherapy groups received single-agent chemotherapy.

The primary endpoint was PFS by a blinded independent review committee (BIRC), which was assessed using the Hochberg procedure in the entire study population and in the FRα-high population. The Hochberg procedure enables the simultaneous testing of 2 overlapping populations. Under this statistical analysis plan, if the p-value of the primary endpoint in either population is greater than 0.05, the p-value in the other population needs to be less than or equal to 0.025 to achieve statistical significance. The primary endpoint, PFS, did not reach statistical significance in either the overall ITT population (p-value = 0.897; HR = 0.981) or in the pre-specified FRα-high population (p-value = 0.049; HR = 0.693).

This was the first study to evaluate available chemotherapy specifically in patients with high FRα expression. An examination of efficacy in the prespecified FRα-high population (by the 10x scoring method) showed clinically meaningful advantage for those patients randomized to MIRV versus IC chemotherapy across all endpoints. MIRV treatment in PROC patients with high FRα expression resulted in an ORR (by BIRC) of 24% (95% CI: 17.2, 31.5) compared with 10% (95% CI: 4.1, 19.3) for patients randomized to IC chemotherapy (p-value = 0.014), median PFS of 4.8 months (95% CI: 4.11, 5.68) versus 3.3 months (95% CI: 1.97, 5.59) for patients randomized to IC chemotherapy (p-value = 0.049; HR = 0.693), median OS in patients randomized to MIRV was not reached (95% CI: 12.58, not estimable) versus 11.8 months (95% CI: 9.20, not estimable) for patients randomized to IC chemotherapy (p-value = 0.033; HR = 0.618). OS results are not confounded by an imbalance in subsequent anti-cancer therapy. The median DOR using response evaluation criteria in solid tumors (RECIST) v1.1 per BIRC in the FRα-high population in patients randomized to MIRV was 5.7 months (95% CI: 4.17, -) versus 4.2 months (95% CI: 3.22, 8.71) for patients randomized to IC chemotherapy. Consistent with the observed tumor shrinkage, CA-125 responses per the Gynecologic Cancer InterGroup (GCIG) criteria occurred in 53% of FRα response-evaluable patients treated with MIRV versus 25% in the IC chemotherapy group. Analysis of time to second disease progression (PFS2) suggests that the clinical benefit observed with MIRV does not diminish the efficacy of subsequent therapy (patient randomized to MIRV median 10.1 months [95% CI: 9.03, 11.20] versus 8.4 months [95% CI: 7.10, 9.46] for patients randomized to IC chemotherapy [p-value < 0.001; HR = 0.557]).

Exploratory post-hoc analyses using the "PS2+" scoring method (see Section 1.1) demonstrated an even stronger treatment effect for MIRV in the high FRα subset defined by this method (Moore 2019).

The efficacy and safety of MIRV from this Phase 3 study were supported by patient-reported outcome (PRO) data, which showed a larger proportion of patients with a ≥ 15 point improvement in the European Organization for Research and Treatment of Cancer (EORTC)-

QLQ-OV28 Abdominal/GI symptom subscale from baseline to Week 8/9 compared to IC chemotherapy (32% vs 13.7% respectively, p=0.011).

The MIRV safety profile was predominantly characterized by low-grade nausea (51%), diarrhea (40%), and blurred vision (40%). These TEAEs are generally managed and mitigated with antiemetics, antidiarrheals, and lubricating/steroid eye drops. In the MIRV group, there were fewer ≥ Grade 3 TEAEs, and fewer TEAEs leading to dose reduction or delay and treatment discontinuation (46%, 37%, and 12%, respectively) compared with the IC chemotherapy group (61%, 45%, and 19%, respectively). While myelosuppression is an important safety issue with PLD and Topo, MIRV is associated with less myelosuppression compared to IC chemotherapy, with lower rates of neutropenia (7% vs. 39% all grade; 0% vs. 21% Grade 3+), thrombocytopenia (11% vs. 16% all grade; 0% vs. 4% Grade 3+) and anemia (14% vs. 29% all grade; 2% vs. 11% Grade 3+). Similarly, neurotoxicity is an important safety issue with Pac; MIRV, an ADC with the tubulin-directed payload DM4, is associated with less peripheral neuropathy than Pac (15% vs. 28% Grade 2+) and less alopecia (3% vs. 22% all grades). The safety profile of MIRV in the high FRα subset is consistent with that observed in the overall MIRV safety population.

For MIRV the mean half-life ($t_{½}$) was 115.1 hour (4.8 days), with little evidence of accumulation (mean accumulation ratio of 1.102).

There was no apparent relationship between patients testing positive for anti-drug antibodies (ADA) and MIRV exposure.

Please see the Investigator Brochure for information on Study IMGN853-0403.

1.6.3. Conclusion

The available safety and efficacy data from the 455 patients treated with single-agent mirvetuximab soravtansine in previous clinical studies are consistent with a positive risk benefit assessment. The potential benefit of the anti-tumor activity demonstrated by mirvetuximab soravtansine in patients with FRα high platinum resistant ovarian cancer, a population with high unmet need, outweighs the risks associated with the well tolerated safety profile, as summarized above.

1.7. Rationale for the Selection of Drug Dose Levels and Dosing Schedules

1.7.1. Mirvetuximab Soravtansine

The selection of the Phase 3 dose of 6 mg/kg AIBW IV Q3W was based on data obtained from Study IMGN853-0401, a FIH study designed to establish the MTD and determine the RP2D of MIRV when administered IV as a single-agent in adult patients with FRα-positive solid tumors who have relapsed or are refractory to standard therapies. The appropriateness of this dose and regimen in patients with PROC was further supported by the results of the Phase 3 study IMGN853-0403. For more information please see the Investigator Brochure.

1.8. Rationale for the Study Plan

The design of this study is based on data obtained from both the Phase 1 study (IMGN853-0401) and the Phase 3 study (IMGN853-0403), which showed a potential for a clinically meaningful ORR and DOR for MIRV when considering what would be expected with available single-agent therapies in this PROC population (eg, 12% ORR in the Aurelia and CORAIL studies [Pujade-Lauraine 2014, Gaillard 2018]). While the prior Phase 3 study did not reach statistical significance in the entire population (patients with medium and high FRα expression), those patients with high FRα expression showed promising results that, in conjunction with the Phase 1 study results, provide the rationale for conducting this trial.

This single arm Phase 3 study is designed to evaluate the efficacy and safety of MIRV administered at 6 mg/kg AIBW Q3W in patients with bevacizumab pretreated, platinum-resistant high-grade serous EOC, primary peritoneal, or fallopian tube cancer, whose tumors express a high level of FRα. Patients will be, in the opinion of the Investigator, appropriate for single-agent- therapy for their next line of therapy. FRα positivity (high FRα) will be defined by the Ventana FOLRI Assay. Please see the Investigator Brochure for details regarding scoring methodology used for patient selection.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To determine the efficacy of MIRV in patients with PROC and high FRα expression

2.1.2. Key Secondary Objective

- To determine the durability of response to MIRV in patients with PROC and high FRα expression

2.1.3. Additional Secondary Objectives

- To evaluate the safety and tolerability of MIRV
- To characterize the clinical activity of MIRV in patients with PROC and high FRα expression

2.1.4. Exploratory Objectives

[redacted]

2.2. Endpoints

2.2.1. Primary Endpoint

- ORR, which includes best response of CR or PR, as assessed by the Investigator

2.2.2. Key Secondary Endpoint

- DOR, defined as the time from initial Investigator-assessed response (CR or PR) until PD as assessed by the Investigator

2.2.3. Additional Secondary Endpoints

- Treatment-emergent adverse events (TEAEs) and laboratory test results, physical examination or vital signs
- CA-125 response determined using the GCIG criteria defined in Appendix C
- PFS, defined as the time from first dose of MIRV until Investigator-assessed radiological PD or death, whichever occurs first
- OS, defined as the time from first dose of MIRV until death

2.2.4. Exploratory Endpoints

[redacted]

3. STUDY POPULATION

3.1. Criteria for Selection of Patient Population

3.1.1. Inclusion Criteria

1. Female patients ≥ 18 years of age
2. Patients must have a confirmed diagnosis of high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer

3. Patients must have platinum-resistant disease:
   a. Patients who have only had 1 line of platinum based therapy must have received at least 4 cycles of platinum, must have had a response (CR or PR) and then progressed between > 3 months and ≤ 6 months after the date of the last dose of platinum
   b. Patients who have received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum
      Note: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression

   Note: Patients who are platinum-refractory during front-line treatment are excluded (see exclusion criteria)
4. Patients must have progressed radiographically on or after their most recent line of anticancer therapy
5. Patients must be willing to provide an archival tumor tissue block or slides, or undergo procedure to obtain a new biopsy using a low-risk, medically routine procedure for immunohistochemistry (IHC) confirmation of FRα positivity
6. Patient's tumor must be positive for FRα expression as defined by the Ventana FOLRI Assay
7. Patients must have at least 1 lesion that meets the definition of measurable disease by RECIST v1.1 (radiologically measured by the Investigator)
8. Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, including at least 1 line of therapy containing bevacizumab, and for whom single-agent therapy is appropriate as the next line of treatment:
   a. Adjuvant ± neoadjuvant considered 1 line of therapy
   b. Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (ie, not counted independently)
   c. Therapy changed due to toxicity in the absence of progression will be considered part of the same line (ie, not counted independently)
   d. Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance
9. Patients must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
10. Patients must have completed prior therapy within the specified times below:
    a. Systemic antineoplastic therapy within 5 half-lives or 4 weeks (whichever is shorter) prior to first dose of MIRV
    b. Focal radiation completed at least 2 weeks prior to first dose of MIRV
11. Patients must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities (except alopecia)
12. Patients must have completed any major surgery at least 4 weeks prior to first dose of MIRV and have recovered or stabilized from the side effects of prior surgery
13. Patients must have adequate hematologic, liver and kidney functions defined as:

a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1,500/µL) without G-CSF in the prior 10 days or long-acting WBC growth factors in the prior 20 days
b. Platelet count ≥ 100 x 10^9/L (100,000/µL) without platelet transfusion in the prior 10 days
c. Hemoglobin ≥ 9.0 g/dL without packed red blood cell (PRBC) transfusion in the prior 21 days
d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN
f. Serum bilirubin ≤ 1.5 x ULN (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin < 3.0 x ULN)
g. Serum albumin ≥ 2 g/dL

14. Patients or their legally authorized representative must be willing and able to sign the informed consent form (ICF) and to adhere to the protocol requirements
15. Women of childbearing potential (WCBP) must agree to use highly effective contraceptive method(s) (as defined in Section 5.8.6) while on MIRV and for at least 3 months after the last dose
16. WCBP must have a negative pregnancy test within the 4 days prior to the first dose of MIRV

3.1.2. Exclusion Criteria

1. Male patients
2. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade/borderline ovarian tumor
3. Patients with primary platinum-refractory disease, defined as disease that did not respond to (CR or PR) or has progressed within 3 months of the last dose of first-line platinum-containing chemotherapy
4. Patients with prior wide-field radiotherapy (RT) affecting at least 20% of the bone marrow
5. Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE)
6. Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring, such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and /or monocular vision
7. Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following:
   a. Active hepatitis B or C infection (whether or not on active antiviral therapy)
   b. Human immunodeficiency virus (HIV) infection

c. Active cytomegalovirus infection
d. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks prior to the first dose of MIRV

Note: Testing at screening is not required for the above infections unless clinically indicated

8. Patients with a history of multiple sclerosis (MS) or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome)
9. Patients with clinically significant cardiac disease including, but not limited to, any of the following:
   a. Myocardial infarction ≤ 6 months prior to first dose
   b. Unstable angina pectoris
   c. Uncontrolled congestive heart failure (New York Heart Association > class II)
   d. Uncontrolled ≥ Grade 3 hypertension (per CTCAE)
   e. Uncontrolled cardiac arrhythmias
10. Patients with a history of hemorrhagic or ischemic stroke within 6 months prior to enrollment
11. Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)
12. Patients with a previous clinical diagnosis of noninfectious interstitial lung disease (ILD), including noninfectious pneumonitis
13. Patients requiring use of folate-containing supplements (eg, folate deficiency)
14. Patients with prior hypersensitivity to monoclonal antibodies (mAb)
15. Women who are pregnant or breastfeeding
16. Patients who received prior treatment with MIRV or other FRα-targeting agents
17. Patients with untreated or symptomatic central nervous system (CNS) metastases
18. Patients with a history of other malignancy within 3 years prior to enrollment

    Note: patients with tumors with a negligible risk for metastasis or death (eg, adequately controlled basal-cell carcinoma or squamous-cell carcinoma of the skin, or carcinoma in situ of the cervix or breast) are eligible
19. Prior known hypersensitivity reactions to study drugs and/or any of their excipients

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4. INVESTIGATIONAL PLAN

4.1. Study Design

4.1.1. Overview and Schema

This Phase 3 study is designed to evaluate the efficacy and safety of MIRV in patients with platinum-resistant high-grade serous EOC, primary peritoneal, or fallopian tube cancer, whose

tumors express a high level of FRα. Patients will be, in the opinion of the Investigator, appropriate for single-agent- therapy. FRα expression will be defined by the Ventana FOLRI Assay.

Approximately 110 patients who have provided informed consent and meet study entry criteria will be enrolled to achieve a total of 105 efficacy evaluable patients. Efficacy evaluable patients include those who have measurable lesions (per RECIST v1.1) at baseline and received at least 1 dose of MIRV.

Enrolled patients will receive single-agent MIRV at 6 mg/kg AIBW administered Q3W.

Tumor response will be evaluated by the Investigator using RECIST v1.1. CT or MRI scans will be collected for sensitivity analysis by a BICR.

Patients will continue to receive MIRV until PD, unacceptable toxicity, withdrawal of consent, death, or until the Sponsor terminates the study (whichever comes first).

Tumor assessments, including radiological assessment by CT/MRI scan, will be performed at Screening and subsequently every 6 weeks (± 1 week) from C1D1 for the first 36 weeks then every 12 weeks (± 3 weeks) until PD, death, the start of new anticancer therapy, or patient's withdrawal of consent, whichever occurs first.

Patients who discontinue MIRV for reasons other than progressive disease (PD) will continue with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks. After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of PD or the start of new anticancer therapy.

All patients who discontinue study drug will be followed every 3 months (± 1 month) until death, lost to follow-up, withdrawal of consent for survival follow-up, or EOS, whichever comes first.

There will be no interim analysis.

4.1.2. Dose and Schedule for Mirvetuximab Soravtansine

MIRV will be administered at 6 mg/kg on Day 1 of every 3-week cycle (Q3W).

5. STUDY TREATMENT

5.1. Mirvetuximab Soravtansine

The investigational study drug, MIRV, will be provided by ImmunoGen, at a protein concentration of 5.0 mg/mL in an aqueous pH 5.0 buffered solution. See the Investigator Brochure for complete list of excipients.

5.1.1. Mirvetuximab Soravtansine Packaging

MIRV will be provided in a 20 mL glass, single-use Type I vial. The container closure for the Type I glass vials will consist of a 20 mm ETFE-coated serum stopper (Flurotec®) with a 20 mm aluminum TruEdge® seal with blue Flip-off® top.

Refer to the Pharmacy Manual for labeling information.

5.1.2. Mirvetuximab Soravtansine Accountability

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

Accountability and shipping documents for MIRV must be maintained by the Principal Investigator (PI) or designee (eg, the study pharmacist). The Investigator or designee must maintain an accurate record of all MIRV received, stored, dispensed, destroyed, and used in an Investigational Product Dispensing/Accountability Log or equivalent. These records must always be available for inspection, and a copy will be supplied to ImmunoGen on request. Information recorded on the Accountability Log will include dates and quantities of drug received, dates and quantities of drug dispensed, patient number and initials to whom drug is administered, lot number of drug administered, the recorder's initials, and dates and quantities of drug destroyed or returned. Upon receipt, vials should be visually inspected for vial integrity (ie, cracks or leaks) and a record of any damaged or suspect drug should be kept on the Accountability Log.

Upon completion of the study, all MIRV dispatched to a site must be accounted for and unused supplies destroyed according to the site's Standard Operating Procedures (SOPs) or returned to depot (refer to Pharmacy Manual). The original drug reconciliation records shall be maintained at the site and a copy collected and sent to ImmunoGen or designee once a representative of the company has confirmed the drug accountability.

Drug accountability will be monitored.

5.1.3. Mirvetuximab Soravtansine Study Treatment Compliance

MIRV supplied for the study may not be used for any purpose other than the study or administered other than as described in this protocol.

If necessary, MIRV from different drug lots may 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 equivalent) 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 PI (ie, hospital pharmacy, satellite pharmacy), it is the responsibility of the PI to ensure that all study drug is stored and administered as described (refer to Pharmacy Manual for instructions).

5.2. Assignment of Patient Number

Patient numbers are assigned in sequential order as patients sign the pre-screening informed consent to participate.

5.2.1. Enrolled Patient Definition

Patients who have consented to the study and have received at least 1 dose of study treatment, are considered enrolled. Patients who are issued a patient number, but who do not successfully complete the screening process and are not treated will be considered screen failures. Patient numbers for patients who screen fail will not be re-issued.

5.2.2. Patient Assignment to Dosing Regimens

All patients will receive MIRV 6 mg/kg AIBW Q3W.

5.3. Blinding Methods

Not applicable as this is an open-label, single-arm study.

5.4. Study Treatment Administration

5.4.1. Premedication for Study Treatment

All patients must receive 325 to 650 mg of acetaminophen/paracetamol (PO or IV), 10 mg IV dexamethasone, and 25 to 50 mg diphenhydramine (IV or PO) (equivalent drugs of similar drug classes is also acceptable) approximately 30 min before each infusion of MIRV. If individual patients require more intensive treatment to prevent infusion-related reactions (IRRs), investigators may modify the regimen accordingly. An antiemetic medication (eg, 5-HT_3 serotonin receptor antagonists such as palonosetron, granisetron or ondansetron or appropriate alternatives) is recommended before each MIRV dose and may be used any time at the discretion of the treating physician.

5.4.2. Prophylactic use of Eye Drops

5.4.2.1. Corticosteroid Eye Drops

All patients will be mandated to use corticosteroid eye drops as prescribed by the treating physician unless the risk outweighs the benefit as per the ophthalmologist/physician. All patients will be instructed to self-administer 1% prednisolone (Pred Forte® or generic equivalent) 6 times daily on Days -1 to 4 and QID on Days 5 to 8 of each cycle during the study. For individual patients who cannot tolerate the preservative contained in 1% prednisolone, other corticosteroid eye drops may be substituted (eg, difluprednate 0.05%; Durezol®) and administered on Days -1 to 8 of each cycle at a frequency prescribed by the ophthalmologist.

5.4.2.2. Lubricating Artificial Tears

Patients will be mandated to use preservative-free, lubricating artificial tears on a daily basis (as directed by the product label or the treating physician). Patients should be advised to wait at least 15 minutes after corticosteroid eye drop administration before instilling lubricating eye drops.

5.4.3. Preparation and Administration of Mirvetuximab Soravtansine

5.4.3.1. Calculation for Adjusted Ideal Body Weight

The total dose of MIRV is calculated based on each patient's AIBW using the following formula:

Adjusted Ideal Body Weight (AIBW)

AIBW = IBW[1] + 0.4 (Actual weight – IBW[1])

Where:

Ideal Body Weight (IBW)

IBW[1] (female) = 0.9H[1]-92

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

The weight used for calculation should be obtained before study drug administration on C1D1 (-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).

5.4.3.1.1. Preparation

MIRV 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. The desired amount of drug should be withdrawn from the vial(s) and diluted using 5% dextrose to a final concentration as outlined in the Pharmacy Manual.

Note: MIRV is incompatible with saline (0.9% sodium chloride). Therefore, dilutions should be made using 5% dextrose. Infusion bags must be labeled with the protocol number, patient number, storage temperature, dose, and volume of MIRV filtered into the bag, or labeled according to institutional protocol. Once the solution is prepared, the infusion bag should be stored at room temperature protected from direct sunlight, and the infusion must be completed within eight hours of preparation. Please refer to Pharmacy Manual for further details.

If necessary, MIRV from different drug lots may be mixed in a single-dose administration.

5.4.3.1.2. Administration

MIRV is administered at 6 mg/kg AIBW as an IV infusion following preparation as outlined in the Pharmacy Manual. Details on required and compatible infusion materials are also included in the Pharmacy Manual.

At C1D1 MIRV should be administered at a rate of 1 mg/min; after 30 min, the rate can be increased to 3 mg/min if well tolerated. If well tolerated after 30 min at 3 mg/min, the MIRV infusion rate may be increased to 5 mg/min. Subsequent infusions may be delivered at the tolerated rate. Therefore, the overall length of infusion will vary depending on dose and patient tolerability. After infusion, the IV line should be flushed with 5% dextrose as needed (PRN) to ensure delivery of the full dose.

Patients will be carefully observed during each infusion and vital signs are taken as outlined in the Schedule of Assessments (Table 2). Patients will remain in the clinic under observation for four hours after the first infusion, and for at least one hour after each subsequent infusion. While in the treatment area, patients are closely monitored for AEs.

5.5. Dose Modification Guidelines

Detailed MIRV dose modification guidelines are described below.

5.5.1. Treatment Criteria

In the absence of a TEAE that requires dose modification (as specified in the management guidance for a particular toxicity, see Section 5.5.1.1), a patient must meet the following criteria to receive MIRV at any cycle:

- ANC must be $\geq 1.5 \times 10^9$/L (1,500/μL)
- Platelet count must be $\geq 100 \times 10^9$/L (100,000/μL)
- All non-hematologic toxicities for which a causal association to study drug cannot be ruled out, must be ≤ Grade 2 or returned to baseline; the exceptions to this rule being:
  - Treatment-emergent ocular disorders, which must have recovered to ≤ Grade 1 or baseline
  - Treatment emergent pneumonitis which must have recovered to ≤ Grade 1

5.5.1.1. Mirvetuximab Soravtansine-Related Adverse Events

Dose modifications for MIRV-related AEs are described in Table 3.

Table 3: Dose Modifications for Mirvetuximab Soravtansine-Related Adverse Events

Severity Grade (CTCAE v5.0)	**Dose Modifications for MIRV [a]**
Hematological	
Neutropenia	
Grade 2 and Grade 3	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /µL) and resume at the same dose level
Grade 4	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /µL) and then resume at one 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 > 1 hour	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /µL) and then resume at one lower dose level
Thrombocytopenia	
Grade 2 and Grade 3	Hold drug until PLT count is ≥ 100 x 10^9/L (100,000/µL) and resume at same dose level
Grade 3 associated with clinically significant bleeding that requires transfusion therapy and Grade 4	Hold drug until PLT count is ≥ 100 x 10^9/L (100,000/µL) and then resume at one lower level
Non-hematological	
Nausea and Vomiting	
Grade 3 (despite use of optimal antiemetics)	Hold drug until resolved to ≤ Grade 1, then resume at one lower level
Grade 4	Permanently discontinue
Diarrhea	
Grade 3 (despite use of optimal anti-diarrheal treatment)	Hold drug until resolved to ≤ Grade 1, then resume at one lower level
Grade 4	Permanently discontinue
Ocular Disorders	Refer to Section 5.5.2
Noninfectious Pneumonitis	Refer to Section 5.5.3
Infusion-related Reactions	Refer to Section 5.5.5

Table 3: Dose Modifications for Mirvetuximab Soravtansine-Related Adverse Events (Continued)

Severity Grade (CTCAE v5.0)	Dose Modifications for MIRV [a]
All Other Non-hematological Toxicities (except AEs related to underlying disease, Grade 3 fatigue, isolated symptomatic Grade 3 biochemistry 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 one lower level 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 events (excluding Grade 3 hypertension)	Permanently discontinue
Grade 4 non-hematological toxicities	Permanently discontinue

Abbreviations: CTCAE = common terminology criteria for adverse events; ANC = absolute neutrophil count; PLT = platelets; CT = computed tomography; AE = adverse event.
[a] Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity will result in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity.

5.5.1.2. Mirvetuximab Soravtansine Dose Reduction Dose Levels

MIRV dose reduction will be as described in Table 4.

Table 4: Mirvetuximab Soravtansine Dose Reduction Dose Levels

If the patient was receiving MIRV at:	Dose should be reduced to:
6.0 mg/kg AIBW	5.0 mg/kg AIBW
5.0 mg/kg AIBW	4.0 mg/kg AIBW
4.0 mg/kg AIBW	Permanently discontinue
Reduction of MIRV below 4.0 mg/kg will not be permitted. Dose re-escalation is not permitted.	

Abbreviations: AIBW = adjusted ideal body weight; MIRV = mirvetuximab soravtansine.

5.5.1.3. Monitoring and Management of Nausea and Vomiting

Treatment-related nausea (46% all grade; 1% Grade 3+) and vomiting (16% all grade; 1% Grade 3+) have been reported in patients treated with MIRV, despite premedication with dexamethasone. Therefore, it is recommended that an antiemetic (eg, 5-HT_3 serotonin receptor antagonists such as palonosetron, granisetron or ondansetron) medication is provided before each MIRV dose (Section 5.8.1). Additional antiemetics may be used any time at the discretion of the treating physician, according to institutional or other practice guidelines American Society of

Clinical Oncology (ASCO), ESMO, and NCCN. Patients should be advised to contact their treating physician at the first sign of vomiting or worsening nausea.

5.5.1.4. Monitoring and Management of Diarrhea

Mild to moderate diarrhea has been reported in patients treated with MIRV. 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 loperamide 2 mg at the first sign of loose stool, with repeat dosing every two hours until symptoms resolve (Wadler 1998).

5.5.2. Ocular Disorders

Changes in visual acuity resulting from reversible keratopathy have been reported in other studies of DM4-containing immunoconjugates that use the SPDB linker (Younes 2012). Patients receiving MIRV in the Phase 1 and 3 trials (IMGN853-0401, IMGN853-0403) reported ocular AEs consistent with reversible keratopathy/corneal epitheliopathy.

5.5.2.1. Monitoring and Preventive Measures

In early dose escalation of Study 0401, a relationship was observed between MIRV plasma exposure and likelihood of an ocular event and response. Exposure-response modeling suggested that a dose of 6.0 mg/kg AIBW provided adequate exposure for response while also maintaining overall exposure within a range that decreased the potential for ocular AEs. Due to the observation of ocular disorders consistent with reversible keratopathy/corneal epitheliopathy in patients treated with MIRV, ocular function will be carefully monitored. Ocular symptom assessments will be performed at baseline and at Day 1 of every cycle thereafter (Table 2). Complete ophthalmologic exams will be performed in all patients at baseline and every other cycle thereafter if there is a TEAE reported.

Patients are advised to avoid using contact lenses while on MIRV. 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. Please refer to Section 5.4.2.1 and Section 5.4.2.2 for details on the prophylactic use of steroid eye drops and lubricating artificial tears. The use of UVA/UVB sunglasses is recommended in full daylight during the study. The use of temporary lower punctal plugs to increase lubrication of the eyes is optional if lubricating artificial tears and corticosteroid eye drops are not sufficient. 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.

5.5.2.2. Management and Dose Modification Guidelines

If a patient develops ocular symptoms of any grade, the patient is required to have a complete examination by an ophthalmologist. If a patient develops ≥ CTCAE Grade 2 ocular symptoms, treatment with MIRV must be interrupted. Treatment should not be interrupted solely for Grade 2 ocular signs (eg, Grade 2 keratopathy) unless they are also associated with Grade 2 ocular symptoms. Treatment with MIRV may resume if ocular symptoms improve to Grade 1 or baseline within 28 days of the next scheduled MIRV dose (refer to Table 5 for details). If ocular

symptoms last longer than 28 days, resumption of MIRV, with or without dose reduction, may be considered for those patients who have experienced clinical benefit if agreed upon between the Sponsor and the Investigator. Subsequent eye examinations will be scheduled to occur in every other cycle going forward, from the time that the AE was initially reported, and at either the EOT visit or 30-Day Follow-up Visit after treatment discontinuation, even if the results of the patient's ocular exam shows no obvious clinical findings. Management of treatment-emergent ocular AEs with inflammatory characteristics should include corticosteroid eye drops and/or other measures as indicated by an ophthalmologist.

Table 5: Management of Ocular Symptoms

Severity Grade (CTCAE v5.0)	**Management**	**Guidelines for MIRV Dose Modifications**
Grade 1	Complete eye exam as outlined in Schedule of Assessments (Table 2) Monitor for worsening symptoms	Continue MIRV dosing
Grade 2	Complete eye exam as outlined in Schedule of Assessments (Table 2) Repeat complete exam as clinically indicated Patients should have weekly symptomatic ocular assessments by the Investigator until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the Investigator	Hold MIRV dosing until AE has resolved to Grade 1 or better Patients with ocular symptoms lasting < 14 days may be allowed to resume MIRV at the same dose level Patients with ocular symptoms lasting ≥ 14 days but no more than 28 days may resume MIRV at one lower dose level Recurrence of Grade 2 toxicity on subsequent cycles despite best supportive care will require a MIRV dose reduction of one dose level
Grade 3	Complete eye exam as outlined in Schedule of Assessments (Table 2). Repeat complete exam as clinically indicated Patients should have weekly symptomatic ocular assessments by the Investigator until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the Investigator	Hold MIRV dosing Patients may be allowed to resume MIRV at a lower dose after AE has resolved to Grade 1 or better within 28 days Recurrence of Grade 3 toxicity on subsequent cycles despite best supportive care will require a MIRV dose reduction of one dose level
Grade 4	Complete eye exam as outlined in Schedule of Assessments (Table 2). Repeat complete exam as clinically indicated Patients should have weekly symptomatic ocular assessments by the Investigator until	Permanently discontinue MIRV

Severity Grade (CTCAE v5.0)	Management	Guidelines for MIRV Dose Modifications
	the symptoms resolve to Grade 1 or baseline or are deemed irreversible by the Investigator	

Abbreviations: AE = adverse event; CTCAE = common terminology criteria for adverse events; MIRV = mirvetuximab soravtansine.

5.5.3. Monitoring of Noninfectious Pneumonitis

Noninfectious pneumonitis has been observed after the administration of MIRV. Noninfectious pneumonitis 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 other clinically meaningful signs or symptoms of pulmonary toxicity, 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. Patients who are asymptomatic may continue dosing of MIRV with close monitoring.

The management and treatment guidelines outlined in Table 6 should be followed.

Table 6: Management of Noninfectious Pneumonitis

CTCAE v5.0 Grade	CTCAE v5.0 Definition	Medical Management of Pneumonitis	Guidelines for Dose Modifications[a]
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Monitor for pulmonary symptoms.	• Continue dosing in asymptomatic patients and monitor closely.
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL	• 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 may be indicated as recommended by a pulmonary specialist and/or institutional guidelines.	• Hold dosing until symptoms resolve to ≤ Grade 1. • MIRV may be resumed at same dose level or one dose level lower after discussion with the Sponsor.
Grade 3	Severe symptoms; limiting self-care ADL; oxygen indicated	• 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 MIRV.
Grade 4	Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)		

Abbreviations: ADL = activities of daily living; AE = adverse event; CT = computed tomography; MIRV = mirvetuximab soravtansine.

[a] Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity will result in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity.

5.5.4. Management of Electrolytes Imbalance

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

5.5.5. Potential Infusion-related Reactions

Some patients treated with IV infusions of therapeutic drugs have experienced concurrent infusion-related reactions (IRR) (see CTCAE Version 5.0). 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 (eg, 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 IRRs and for subsequent retreatment are provided in Table 7. Delayed IRRs may occur; therefore, patients should be advised to seek immediate medical treatment if symptoms newly develop and/or recur after discharge from clinic.

Patients who experience ≥ Grade 2 IRR during or immediately after administration of MIRV will have blood drawn for determination of drug concentration and ADAs to MIRV. The sample should be obtained within three hours of the onset of the reaction and one week later. Such patients should undergo all scheduled efficacy and safety evaluations.

Table 7: Management Guidelines for Potential Infusion-Related Reactions

Infusion Reaction CTCAE v5.0 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 (Q4h) PRN for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV PRN • Methylprednisolone (or equivalent) 125 mg IV PRN
Grade 2: Moderate	• Interrupt infusion and disconnect infusion tubing from patient • Promethazine (or equivalent) 150 mg PO per day (Q4h) PRN for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV PRN • Acetaminophen (or equivalent) 650 mg PO PRN • Methylprednisolone (or equivalent) 125 mg 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 Dex (or equivalent) 8 mg PO BID the day before drug administration and acetaminophen (or equivalent) 650 mg PO and diphenhydramine (or equivalent) 25-50 mg PO 30-60 min before dosing.
Grade 3: Severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae OR Grade 4: Life-threatening consequences, urgent intervention indicated	• Immediately stop infusion and disconnect infusion tubing from patient. • 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 IRR. • Advise patient to seek emergency treatment and notify Investigator/clinic if the infusion-related symptoms recur after discharge from clinic. • Report as an SAE (see Section 8.1.1.2). • Permanently discontinue study medication treatment

Abbreviations: BID = twice a day; CTCAE = common terminology criteria for adverse events; Dex = dexamethasone; IM = intramuscular; IRR = infusion-related reaction; IV = intravenously; PO = orally; PRN = as needed; SAE = serious adverse event; SQ = subcutaneous.

5.5.6. Discontinuation of Mirvetuximab Soravtansine Due to Toxicity

MIRV should be discontinued in the case of the following treatment-related events:

- Grade ≥ 3 cardiac event (excluding Grade 3 hypertension) (Section 5.5.1.1)
- Grade ≥ 3 pneumonitis event (Section 5.5.3)
- Non-hematologic events of Grade 4 severity (Section 5.5.1.1)
- Ocular events of Grade 4 severity (Section 5.5.2.2)
- Failure to meet re-treatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity unless otherwise specified in the management guidance for a particular toxicity. In such cases, continuation of MIRV may be considered for those patients who have experienced clinical benefit if agreed upon between the Sponsor and the Investigator.

5.6. Discontinuation of the Patients from the Study or Study Treatment

5.6.1. End of Treatment

Patients will continue to receive MIRV until they present with PD per RECIST 1.1, as assessed by study Investigator, unacceptable toxicity, withdraw consent, or death, whichever comes first, or until the Sponsor terminates the study. Study treatment and/or participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be reasons for the Investigator to remove a patient from the study drug:

- The patient suffers an intolerable AE
- Noncompliance, including failure to appear at one or more study visits
- The patient was erroneously included in the study

The reason for treatment discontinuation must be captured in the clinical trial database. Any AEs experienced up to the point of discontinuation and 30 days thereafter must be documented. 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. Patients will continue to be followed for OS, after discontinuing study drug (Section 9.3.3).

5.6.2. End of Study

Discontinuation from participation in the study will be documented in the clinical trial database. Reasons for EOS include withdrawal of consent, lost to follow-up, death, or study termination by Sponsor.

5.6.3. Withdrawal of Consent

The patient or legally authorized representative acting on behalf of the patient is free to withdraw consent to study treatment and/or participation in the study at any time irrespective of the reason. The Investigator must make every effort (eg, telephone, email, letter) to determine the primary

reason for this decision and record this information. Study treatment must be discontinued, and no further assessments conducted. Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up. If the patient or legally authorized representative withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before withdrawal of consent. All biological samples that have been already collected will be retained and analyzed at a later date. The patient or legally authorized representative may request destruction of any samples, and the Investigator must document this in the site study records. The SAP will specify how early withdrawals from treatment will be accounted for in the analyses of efficacy endpoints. Patients who have withdrawn from the study cannot be re-treated in the study and their inclusion and patient number must not be reused.

5.6.4. Lost to Follow-up

A study patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The Investigator should make all efforts to contact the patient and to determine the patient's health status, including at least her vital status (in accordance with applicable regulations related to privacy and confidentiality). A patient should not be considered lost to follow-up until due diligence has been completed and documented. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5.7. Period of Observation

For purposes of this study, the period of safety observation extends from the time of informed consent until the 30-Day Follow-up visit unless additional follow-up safety information is requested as described in Section 9.3. Short-term follow-up for patients who discontinue study drug without documented PD will be followed per RECIST 1.1 every 6 weeks (± 1 week) from C1D1 for the first 36 weeks then every 12 weeks (± 3 weeks) until PD, until the patient starts new anticancer treatment, the patient dies, or the patient withdraws consent, whichever comes first. All patients will be followed every 3 months (± 1 month) for survival until death, lost to follow-up, withdrawal of consent for survival or until EOS, whichever comes first.

5.8. Concomitant Medications and Procedures

All concomitant medications and supportive therapy taken within four weeks of Cycle 1, Day 1 and through 30 days after last study treatment must be recorded in the clinical database.

5.8.1. Antiemetic and Antidiarrheal Medications

An antiemetic (eg, 5-HT_3 serotonin receptor antagonists such as palonosetron, granisetron or ondansetron) medication is recommended before each MIRV dose; additional antiemetics and/or antidiarrheal (eg, loperamide) medications may be used any time at the discretion of the treating physician.

5.8.2. Folate-Containing Supplements

Folate-containing supplements should not be taken during the study.

5.8.3. Antineoplastic Therapy

All non-study related antineoplastic therapy, including but not limited to cytotoxic, immunotherapy, and VEGF-targeted therapy, is prohibited while on study drug.

5.8.4. Hematopoietic Growth Factors

Patients receiving recombinant erythropoietin (EPO) or darbepoetin-α before study start may continue to receive pretreatment doses.

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

5.8.5. Anticoagulants

The use of anticoagulant agents is allowed. Please see Section 5.8.8 if using apixaban and rivaroxaban due to CYP3A interaction potential.

5.8.6. Methods of Contraception

Women of childbearing potential must agree to use highly effective contraceptive method(s) while on study drug and for at least 3 months after the last dose of MIRV. A woman of childbearing potential is a woman who is considered fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

The following birth control methods may be considered highly effective (failure rate of less than 1% per year):

- Combined (estrogen and progesterone) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal

  - Transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

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 Institutional Review Board/Independent Ethics Committee (IECs /IRBs). Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods, etc) and withdrawal are not acceptable methods of contraception.

If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study WCBP must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days before the initiation of study medication for oral contraception) through the duration of study treatment and for at least 3 months after the last dose of MIRV. If there is any question that a WCBP will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.8.7. Other Concomitant Medications

Medications for the treatment of AEs or cancer symptoms (eg, packed red blood cells and pain medications), are allowed. Prophylactic use of steroids and/or antihistamines will be considered if needed. Additionally, medications (not addressed above) used to treat underlying medical conditions at study entry including antiemetics and antidiarrheals will be allowed to continue.

5.8.8. Medications that are CYP3A or MDR1 Substrates or CYP3A Substrates with Narrow Therapeutic Index

In vitro metabolism studies demonstrated that DM4 is predominantly metabolized by thiol s-methyltransferase (TMT) to form S-methyl DM4, which is further metabolized into sulfoxide-methyl-DM4. As S-methyl 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 one serving (250 mL) of grapefruit juice per day should be avoided.

Both DM4 and S-methyl DM4 are substrates for MDR1 efflux transporter. Their exposure could potentially increase in the presence of MDR1 efflux transporter. In vitro metabolism data also indicates that DM4 is a time-dependent inhibitor of CYP3A4.The risk of a significant in vivo drug-drug interaction caused by inhibition of CYP3A4 or MDR1 is unknown. Treatment of patients with concomitant medications that are inhibitors of MDR1, sensitive substrates of CYP3A or are CYP3A substrates with a narrow therapeutic index should be used with caution and carefully monitored (Appendix D).

5.9. Overdose and Medication Error

5.9.1. Overdose

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

5.9.2. Medication Error

The Sponsor must be notified within 24 hours of any error leading to the administration of either 10% more or 10% less than the intended dose; in such cases, the event must be reported in the clinical trial database. If an error resulted in a SAE, a Serious Adverse Event form must be submitted within 24 hours of the event (see Section 8.2.1).

6. PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER ASSESSMENTS

6.1. Pharmacokinetic Assessments – Mirvetuximab Soravtansine

The PK properties of MIRV and key metabolites will be evaluated following IV administration, as outlined in Table 2 and Table 8. Plasma samples will be collected to determine the concentration of MIRV (conjugate, total Ab, free DM4, S-methyl DM4 and possibly other metabolites).

Blood samples for PK analysis will be taken at the following timepoints:

Table 8: Pharmacokinetics Sampling Time Points

Visit	Time Point
C1D1	Predose (immunogenicity only); ≤ 1 hour after MIRV infusion
C1D8	Anytime during visit
C2D1	Before dosing
C3D1	≤ 1 hour after MIRV infusion
C3D8	Anytime during visit
C4D1	Before dosing
EOT	Anytime during visit
30-Day Follow-up	Anytime during visit

Abbreviations: C = cycle; D = day; EOT = End of Treatment.

Unscheduled visit: Any patient who experiences a ≥ Grade 2 IRR during or within 3 hours after the administration of MIRV will have blood drawn within 3 hours of the onset of the reaction and one week later for determination of drug concentration and ADAs to MIRV.

PK samples may also be obtained as feasible at any time during the treatment period for assessment of treatment-related SAEs if deemed appropriate by the Investigator and Sponsor.

Procedures for collection, storage and shipment of samples are provided in the applicable Laboratory Manual.

6.2. Immunogenicity Assessments – Mirvetuximab Soravtansine

The potential immunogenicity against MIRV will be assessed at C1D1, C2D1, C4D1, EOT, and 30-Day Follow-up, as outlined in Table 2. [redacted]

An ADA sample should be collected prior to dosing on C1D1. The sample for ADA analysis is taken from the PK tube predose on Day 1 of Cycles 2, and 4 and at the EOT and 30-Day Follow-up visits.

6.3. Evaluation of FRα Expression in Tumor Tissue

FRα expression varies with tumor histology, as reported in the literature and demonstrated in preclinical studies (Section 1.1 and Investigator Brochure). FRα expression in tumor samples will be analyzed using the Ventana FOLRI Assay, an immunohistochemical assay developed to detect FRα in cut slide specimens of formalin-fixed, paraffin embedded (FFPE) epithelial ovarian cancer tissue stained on the BenchMark ULTRA automated staining instrument using the Ventana OptiView DAB IHC Detection Kit. This assay will be conducted at a central laboratory. All patients must submit tumor tissue, or FFPE slides for analysis of FRα expression prior to enrollment.

PS2+ is the terminology used to reference a scoring method based on membrane stain intensity level of 2 or greater. The PS2+ scoring method requires the pathologist (at the central laboratory) to assess the percentage of tumor cells with moderate (2) and/or strong (3) membrane staining compared to the total number of viable tumor cells. To be considered positive for FRα expression and eligibility for the study, ≥ 75% of viable tumor cells must exhibit level 2 and/or 3 membrane staining intensity.

Only patients with the required FRα expression levels by Ventana FOLRI Assay are eligible to enroll in the study. If a patient wishes to enroll and does not have archival material available for analysis, she must undergo a biopsy to assess FRα expression. Patients for whom the only sites of disease would require biopsy procedures considered to be of significant risk must not be enrolled in the study. These procedures include (but are not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel.

Instructions regarding processing and shipment of all samples for FRα testing are detailed in the applicable Laboratory Manual.

6.4. Potential Predictive Markers of Drug Response

6.4.1. Blood Biomarkers

[redacted]

6.4.2. Tumor Biomarkers

Cancer is a disease driven by molecular level changes, which include mutations, DNA rearrangements and copy number changes, as well as changes in gene expression of key oncogenic pathways. Many of these changes determine or influence the aggressiveness of the disease, how the cancer responds to standard of care and/or novel therapeutic agents, and development of resistance to treatment. To evaluate how tumor molecular changes are associated with response to MIRV we will characterize the genomic profile (gene mutations, genomic translocations, etc) as well as gene expression levels of archival tumor samples using a fit for purpose technology such as next generation sequencing (NGS).

7. STUDY PROCEDURES

7.1. Informed Consent

Each patient or legally authorized representative will sign an IRB/IEC-approved ICF before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care (Table 2). Participants must be re-consented to the most current version of the ICF(s) per IRB/IEC guidelines during their participation in the study.

Patients will sign a pre-screening ICF to allow testing of fresh or archival tumor tissue by the assay required for study inclusion. If patients meet entry criteria for FRα positivity (high FRα)

they will sign the main study ICF and proceed with remaining screening procedures per the Schedule of Assessments. In some cases, the pre-screening ICF and main study ICF may be merged into a single ICF based on site-specific guidelines or preference.

7.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are assessed during Screening (within 28 days before the first dose of MIRV on Cycle 1, Day 1). All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the patient's routine clinical management and obtained before signing an ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the timeframe defined in the Schedule of Assessments (Table 2). A patient is considered enrolled when they have received their first dose of MIRV (Section 5.2.1).

7.3. Confirmation of Disease Diagnosis

At Screening, disease diagnosis, and current disease status are confirmed from information in the source record (Table 2).

7.4. *BRCA* Mutation Status

The *BRCA* mutation status from prior testing (information in the source record) will be recorded (Table 2). Patients with a *BRCA* mutation (germline mutation or somatic mutation in tumor tissue) are classified as positive and patients who were tested and shown to not have a *BRCA* mutation will be classified as negative. Patients without known *BRCA* mutation status in the source record are classified as unknown. If a patient with unknown status is tested and is found to have a *BRCA* mutation, this patient is considered *BRCA* mutation positive in analyses.

7.5. Demographic/Medical History

The age, sex, race and ethnicity of the patient are to be recorded during Screening for all patients who consent to the study (Table 2).

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.

7.6. Physical Examination, Weight, and Height

Physical examination (PE), height (Screening only) and weight must be performed as indicated in the Schedule of Assessments (Table 2). A complete PE, including assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system, will be completed at Screening and at the 30-Day Follow-up Visit. Directed PEs will be completed at additional time points as specified in the Schedule of Assessments.

7.7. Vital Signs

Vital signs include BP and body temperature. These signs are measured as outlined in Table 2.

7.8. Electrocardiogram (ECG)

A standard, single 12-lead ECG will be performed within 28 days prior to first dose.

7.9. Ocular Symptom Assessment and Ophthalmic Examination

7.9.1. Ocular Symptom Assessment

Ocular symptom assessment will be performed before the start of each cycle by the treating physician or other qualified individual. For patients reporting > CTCAE Grade 1 ocular symptoms, study drug will be held until the patient is evaluated by an ophthalmologist for a complete examination. The ocular symptom assessment will also be performed at EOT and the 30-Day Follow-up visit.

7.9.2. Ophthalmic Examination

An ophthalmic examination will be performed at Screening (within 14 days prior to first dose of study drug) by an ophthalmologist and will include the following: distant visual acuity, best corrected visual acuity, slit lamp examination, intraocular pressure measurement, and indirect fundoscopy. Patients who experience ocular TEAEs while on study will have a complete ophthalmologic exam performed at the emergence of the symptoms and at every other cycle thereafter. All patients who have an ophthalmic exam on study treatment (post-baseline) will have a complete ophthalmologic exam performed at the EOT visit or 30-Day Follow-up visit (Table 2).

7.10. Laboratory Assessments

Local laboratories will be used for the analysis of scheduled hematology, biochemistry, coagulation, and other tests collected as part of safety monitoring. Screening labs (Table 9) will be performed within 14 days of first dose. Repeat testing on Cycle 1, Day 1 is not required if tests were obtained within 4 days of dosing and are within acceptable ranges. Repeat testing will be performed as outlined in the Schedule of Assessments (Table 2) and as clinically indicated.

Note that before each administration of study drug, laboratory results must be reviewed to evaluate for potential toxicity.

7.10.1. Clinical Laboratory Panels

A list of clinical laboratory tests may be found in Table 9.

Table 9: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (Screening only)	Coagulation (Screening only)
• Hematocrit • Hemoglobin • WBC (with 5-part differential) • Platelet count	• Albumin • Alkaline phosphatase • ALT • AST • BUN or Urea • Calcium • Chloride • Creatinine • Glucose • Magnesium • Phosphorus • Potassium • Sodium • Total bilirubin	• pH • Ketones • Protein • Glucose • Occult blood • Leukocyte esterase • Nitrite	• PT or INR • aPTT

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; PT = prothrombin time; WBC = white blood cell count.

7.11. Pregnancy Screen

All WCBP will complete a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test within 4 days before the first dose of study drug and urine or serum pregnancy tests within 4 days of each study drug administration and at the 30-Day Follow-up visit. It is recommended to perform monthly pregnancy tests for 3 months after the last dose of MIRV. Additional testing may be performed in accordance with institutional requirements or local regulation. Pregnancy tests must be negative for the patient to be enrolled and to continue to receive the study drug (Table 2).

If a patient becomes pregnant or suspects pregnancy while participating in this study, the Investigator and Sponsor must be informed immediately (Section 8.2.2) and the patient will be withdrawn from study drug. See Section 8.2.2 for more details.

7.12. Eastern Cooperative Oncology Group Performance Status

ECOG PS (Appendix A) will be assessed during Screening and at other times specified in the Schedule of Assessments (Table 2). An assessment is not necessary on Day 1 of Cycle 1 if the

Screening assessment was obtained within the prior 4 days. ECOG is also assessed at EOT and 30 day follow up visit.

7.13. Tumor Response Assessment

7.13.1. Radiological Imaging

Radiologic tumor evaluation by CT or MRI of chest, abdomen, and pelvis will be performed within 28 days before first dose of study drug and every 6 weeks (±1 week) from C1D1 for the first 36 weeks on study and every 12 weeks (± 3 weeks) thereafter (Table 2). Patients who discontinue study treatment for reasons other than progressive disease (PD) will continue with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks. After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of PD or the start of new anticancer therapy. The same method of radiographic assessment used at Screening must be used at all subsequent radiographic evaluations. Copies of all imaging scans must be obtained and sent to a central imaging vendor designated by ImmunoGen as outlined in the Imaging Manual. The central imaging vendor will assess the quality of the images. The imaging vendor will be responsible for the formation and management of the blinded independent central review (BICR) which will be used as a sensitivity analysis of ORR and DOR by investigator.

Tumor response will be assessed by the Investigator using RECIST v1.1 (Eisenhauer 2009). Response as determined by the Investigator will be recorded in the clinical trial database.

The central imaging vendor will ensure that the central radiologists remain blinded to the local assessment from the Investigator and other unblinding information. This and all other imaging procedures will be documented in an independent review charter agreed upon between ImmunoGen and the imaging vendor before initiation of any BICR reviews.

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

7.13.2. CA-125

Serum CA-125 assessments will be performed within 14 days prior to the first dose of study drug, and at each radiologic tumor assessment (± 4 days) (Table 2). CA-125 should be assessed by the same laboratory throughout the study.

8. ASSESSMENT OF SAFETY

8.1. Recording Adverse Events and Serious Adverse Events

Adverse Events (AEs), including those attributed to study procedures, will be documented in the clinical trial database and monitored continuously throughout the study from the time of informed consent until 30 days after the patient's last study treatment.

Only AEs/SAEs which are considered related to a study procedure (ie blood draw or fresh tumor biopsy) will be captured during the pre-screening period, ie from the time of signing of the pre-screening informed consent (if one is utilized) until the time of signing of the main study informed consent, or until the patient is determined to be a screen failure. All AEs and SAEs, regardless of causality, will be captured after the main study ICF has been signed.

SAEs will continue to be followed by ImmunoGen Pharmacovigilance until resolution, stabilization or return to baseline. Beyond this defined reporting period, any unsolicited SAE assessed as related to the study drug by the Investigator and reported to ImmunoGen will be collected and processed. Additional information obtained after database lock, will reside solely in the safety database.

The Investigator should follow and provide updates for all AEs until clinical recovery is complete, laboratory values return to normal, the patient stabilizes, or death occurs, to ensure the safety of the patients. This may mean that observations continue beyond the last planned visit per protocol and that additional investigations may be requested by the Sponsor.

8.1.1. Definition of Adverse Events

8.1.1.1. Adverse Event

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 PE, vital signs, and weight

Note that PD 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 study informed consent until 30 days after last study treatment must be reported in the clinical database, regardless of the severity or relationship to study drug. Only AEs which are considered related to a study procedure (ie blood draw or fresh tumor biopsy) will be captured during the pre-screening period, ie from the time of signing the pre-screening consent (if one is utilized) until the signing of the main study informed consent, or until the patient is determined to be a screen failure. The Investigator should treat patients with AEs appropriately and observe them at

suitable intervals until the events stabilize, return to baseline or resolve. 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.

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 (eg, cause study drug discontinuation or constitutes in and of itself an SAE, or require therapy), and should be recorded in the clinical database 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 baseline or can be explained and the patient's safety is not at risk.

8.1.1.2. Serious Adverse Event

An SAE is any AE occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient 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

Note that hospitalization is defined as admission to treat a clinical AE. The following events would not be considered hospitalizations for SAE reporting purposes: 23-hour hold for observation, admission to a hospice facility or nursing home, respite care, outpatient surgery, social admission (eg, a homeless patient) or admission not associated with a precipitating clinical AE (eg, elective or pre-planned surgery, or in-patient administration of subsequent chemotherapy, etc).

8.1.1.3. Adverse Events of Special Interest

There are no AEs of special interest (serious or nonserious) associated with MIRV.

8.1.2. Classification of Adverse Events

All AEs will be evaluated according to the NCI CTCAE v5.0 (effective 27 November 2017). If the AE is not listed in the CTCAE v5.0, it should be graded based on the description given in Table 10.

Table 10: Adverse Event Severity

Severity	Definition
Grade 1 (Mild)	No limitation 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 in Table 11.

Table 11: Adverse Event Causal Relatedness

Relationship to 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 unambiguous evidence supporting another cause.
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 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 of study drug. 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 should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.

8.2. Adverse Events

8.2.1. Reporting Serious Adverse Events

Any SAE, regardless of relationship to study medication, which occurs in a patient from the time of study informed consent until 30 days after the last study treatment, must be recorded by the clinical site on an SAE report form. Only SAEs which are considered related to a study procedure (ie blood draw or fresh tumor biopsy) will be captured during the pre-screening period, ie from the time of signing the pre-screening consent (if one is utilized) until the signing of the main study informed consent, or until the patient is determined to be a screen failure. The SAE must also be recorded in the clinical trial database, including the Investigator's assessment regarding the relationship of the SAE to the study drug. The Investigator will promptly supply all information requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

The Investigator must submit the SAE Report Form to ImmunoGen Pharmacovigilance (or designee). This form must be completed and submitted within 24 hours of the Investigator's learning of the event using the contact information printed on the SAE form and contained within the SAE form completion instructions. Follow-up information must also be submitted using a new SAE Report Form.

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).
- An event term of "Death" should not be reported as an SAE, but rather be recorded as an outcome of a specific SAE term. Initially, the event term of "death" can be used until the actual cause of death is known. If an autopsy was performed, the autopsy report should be provided.

It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any suspected unexpected serious adverse reaction (SUSAR) report (CIOMS/MedWatch) regarding the study drug and that the report is submitted to the appropriate national regulatory agencies.

The Investigator (or Sponsor or contracted designee) must promptly report all SUSARs to the 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 Sponsor will also notify (through annual updates to the Investigator Brochure) the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication.

8.2.1.1. Reporting of Disease Progression

Disease progression is an anticipated occurrence in oncology drug development and is not an AE unto itself.

Progression of disease should not be reported as an SAE term; any serious medical event/condition that results from progression of underlying disease, if untoward, should be reported as the SAE.

Progression of disease with a fatal outcome does not need to be reported as an AE term. The applicable protocol CRF page(s) pertaining to death should be appropriately completed however, as disease progression.

8.2.2. Reporting a Pregnancy

Pregnancy and lactation are exclusion criteria. Women of child bearing potential, 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 (ie, who has had menses any time in the preceding 12 consecutive months) must agree to use highly effective contraceptive methods

(as defined in Section 5.8.6) while on study drug and for at least 3 months after the last dose of MIRV. In addition, it is recommended that patients undergo monthly pregnancy test for at least 3 months after the last dose of MIRV.

The Sponsor must be immediately notified in the event of a pregnancy occurring during the study and through 30 days after a patient's last dose of study drug. If a patient becomes pregnant the patient will be withdrawn from study drug. Pregnancy is not an AE unto itself and therefore should not be reported as an AE.

All pregnancies will be recorded on a Pregnancy Report and submitted according to the contact information on the form and in the completion guidelines.

Pregnancies, with the permission of the mother, will be followed to completion or termination using the designated sections of the Pregnancy report form.

Any SAE, occurring during the pregnancy to the mother or fetus, would require that a study SAE form also be completed/submitted.

9. STUDY ACTIVITIES

All study visits and assessments that must be performed during the study and follow-up are included in Table 2.

9.1. Screening Visit

The Investigator is responsible for keeping a record of all patients screened for entry into the study, including those who are subsequently excluded. The reason(s) for exclusion must be recorded.

9.1.1. Standard of Care Assessments

In some cases, clinical assessments performed before obtaining informed consent may be used to qualify the patient for the study if performed within the screening window. These include radiologic tumor assessment, PEs, laboratory results, urinalysis, or other assessments which may be considered part of standard of care. In these cases, repeat assessments may not be necessary before enrollment, unless individual parameters require further study or confirmation and are clinically appropriate.

Note that safety blood tests, and PE do not need to be repeated if normal and conducted within 4 days prior to C1D1.

9.2. End of Treatment Visit

Patients may voluntarily withdraw from the study drug 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 5.6. The clinical trial database will capture reasons for withdrawal.

Patients who withdraw or are removed from the study treatment will have an EOT visit within 7 days of the decision to discontinue study drug. Patients will undergo assessments as outlined in Table 2.

9.3. Follow-up Assessments

9.3.1. 30-Day Follow-up Visit

A 30-Day Follow-up visit will occur 30 days (+14 days) after last dose of MIRV and should occur prior to the start of new anticancer therapy.

In some cases, nonserious AE observations may continue beyond the safety visit. All ocular AEs will be followed until resolution, stabilization, or return to baseline. In these instances, additional information may be requested by ImmunoGen to adequately categorize the nature of the toxicity.

All SAEs will be followed until they resolve, stabilize or return to baseline, regardless of time from last dose or last visit.

9.3.2. Response Follow-up

Patients who discontinued MIRV for reasons other than PD will continue with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first. Prior to Week 36 (from Cycle 1, Day 1), assessments should occur every 6 weeks (± 1 week) as allowed by local requirements but must occur at an interval of no more than 12 weeks. After Week 36, assessment will occur every 12 weeks (± 3 weeks) until documentation of disease progression or the start of new anticancer therapy.

9.3.3. Survival Follow-up

All patients who discontinue MIRV for any reason will be followed for survival after disease progression as per Investigator, or after start of a new anticancer therapy. Survival status will be assessed every 3 months (± 1 month) until death, lost to follow-up, withdrawal of consent for survival follow-up or until EOS, whichever comes first. Additional survival follow-up calls may occur periodically if needed.

10. STATISTICAL METHODS

This is a Phase 3 study designed to evaluate the ORR of MIRV in patients with high FRα expressing, high-grade PROC.

All patients who have received at least 1 dose of MIRV will comprise the Safety Analysis Population.

The Efficacy Evaluable Population will include all patients who have received at least 1 dose of MIRV and have measurable lesions at baseline (per RECIST v1.1). The primary efficacy analysis of ORR and all other efficacy analyses will be based on the Efficacy Evaluable Population.

The safety analysis will be based on Safety Analysis Population.

All statistical analyses will be performed using SAS statistical software Version 9.4 or later, unless otherwise noted. For categorical variables, the number (n) and percent of each category within a parameter will be presented. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. There will be a detailed description of patient disposition, patient demographics, and baseline characteristics.

A SAP will fully describe the planned analyses for this trial and will be finalized prior to database lock.

10.1. Sample Size

Primary endpoint is confirmed ORR per Investigator assessment.

A sample size of 105 efficacy evaluable patients achieves 91% power to detect a difference in ORR of 12% (24% vs. 12%) using a 1-sided binomial test. The target significance level (1-sided α level) is 0.025. The actual significance level achieved by this test is 0.0242. These results assume that the ORR is 12% under the null hypothesis and 24-% under the alternative hypothesis.

Patients who have received at least 1 dose of MIRV but are not efficacy evaluable will be included in Safety Analysis Population. However, these patients will not be included in the Efficacy Evaluable Population and will be replaced for the purpose of sample size determination. A total of approximately 110 patients will be enrolled to achieve 105 efficacy evaluable patients.

10.2. Pharmacokinetic Analyses

PK parameters will not be calculated due to the sparse sampling scheme in this study. Summary statistics of the concentration at each time point (nominal time) will be presented. Graphical presentation of the data may also be completed using nominal time.

10.3. Safety Analyses

Safety analyses will be based on the Safety Analysis Population.

AEs and concomitant medication will be listed.

AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version and summarized per system organ class (SOC) and preferred term (PT).

Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD; 01 September 2019 or later version). A dictionary listing of all unique concomitant medications used in the study will be provided.

All hematology, blood chemistry, and vital signs will be listed per patient for each assessment and descriptive statistics will be tabulated for select criteria. Changes from baseline in hematology, blood chemistry, and vital signs will be summarized by treatment. Shifts in hematology and blood chemistry from Baseline values will be summarized. Plasma also will be evaluated for the presence of ADA.

10.4. Efficacy

Unless stated otherwise in the SAP, efficacy analyses will be performed on the Efficacy Evaluable Population.

10.4.1. Primary Efficacy Analysis

10.4.1.1. Objective Response Rate

The primary endpoint is ORR, which includes best response of CR or PR.

The primary endpoint of ORR (objective response = CR + PR) will be estimated along with a 95% CI by the Clopper-Pearson method based on the efficacy evaluable population.

The primary analysis of ORR will be conducted after all efficacy evaluable patients have:

- undergone at least 4 post-baseline tumor assessments, or
- experienced radiological disease progression, or
- died or had clinical progression within 105 days of first dose of study drug, or
- withdrawn from study for other reasons

10.4.2. Key Secondary Efficacy Endpoint

The key secondary endpoint of Investigator-assessed DOR will be estimated using Kaplan-Meier method for survival function estimate.

The initial analysis of DOR will be conducted at the time of primary analysis of ORR. An updated analysis of DOR will be conducted 12 months after the primary analysis of ORR, at the end of the study.

10.4.3. Additional Secondary Efficacy Endpoints

The additional secondary endpoints of Investigator-assessed PFS and OS will be estimated using Kaplan-Meier method for survival function estimate.

10.5. Interim Analysis

There are no planned interim analyses for this study. Efficacy data generated in the MIRV program in patients with FRα high expression (by the PS2+ scoring method), includes a 44% Investigator-assessed ORR in the 27 patients in IMGN853-0401 and a 38% Investigator-assessed ORR in the 116 patients in IMGN853-0403 (Moore 2019). In addition, an analysis of patients derived from both Study 0401 and Study 0403 who are eligible for this study (n=70), revealed an ORR by investigator of 31.4% with a DOR of 7.8 months. Thus, an interim analysis for futility in the current study in the same or a very similar population is not warranted.

11. QUALITY CONTROL AND ASSURANCE

11.1. Recording of Data and Data Quality Assurance

Data will be documented in various source documents (eg, the patient medical chart) and then manually entered into the clinical trial database. Clinical sites will be monitored by ImmunoGen or its designee to ensure the accuracy of data against source documents. If necessary, the study site will be contacted for corrections or clarifications.

Adverse events will be coded using the latest MedDRA version. Concomitant medications will be coded using the (WHO-DD; 01 September 2019 or later version. Training will occur at an Investigator meeting or at the site initiation visit or both. Remote web-based training may be provided. Instruction manuals (eg, laboratory manuals and pharmacy manuals) will be provided to aid consistency in data collection and reporting across sites.

This clinical study will be conducted according to ICH-GCP E6 (R2) guidelines. Quality oversight shall be maintained through proactive and continual risk assessment and mitigation at the operational level. GCP quality assurance audits will be conducted as needed as continued compliance oversight.

12. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

12.1. Ethical and Regulatory

This clinical study will be conducted by the Sponsor, the Investigator, delegated Investigator staff and sub-Investigator(s), in accordance with the protocol, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP, and all applicable local regulatory requirements.

This clinical study will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with ImmunoGen public disclosure commitments.

12.1.1. Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC approval of the protocol, the main study ICF and the pre-screening ICF (latter ICF is applicable for sites requesting permission to pre-screen for FRα positivity (high FRα) before performing any additional study related tests). 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, as given by the Sponsor on the cover page of the protocol.

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 FDA or other regulatory agencies (SUSARs), must be submitted promptly to the IRB/IEC.

12.1.2. Patient Information and Consent

An ICF that includes information about the study will be prepared and given to the patient, or the patient's legally authorized representative(s). The ICF will contain all FDA and ICH required elements and be approved by an IRB/IEC. The ICF must be in a language understandable to the patient or the patient's legally authorized representative(s). Before enrolling in the clinical study, the nature, scope, and possible consequences of the clinical study will be explained to the patient or the patient's legally authorized representative(s) in a form understandable to him or her. After the patient has been given ample time to read and ask questions regarding the ICF and has been informed that participation is voluntary, 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 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. The informed consent process must be recorded and dated in the patient's source document.

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 12.3.

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

A model of the pre-screening and the main study ICF will be provided to the sites separately for this protocol. The main study consent can be used to confirm a patient's consent to all study procedures and all study-specific screening tests. The pre-screening ICF can be used to pre-screen patients for FRα status before performing any additional study related tests. If a patient is eligible based on FRα expression level, the patient will be provided the main study consent and only after signing the main study ICF will additional study-specific screening tests be performed. Alternatively, the patient can be consented on both pre-screening and main study ICF at the same time; and FRα testing and study-specific screening assessments can be carried out in parallel.

Patients must be consented to the most current version of the ICF during their participation in the study.

12.2. Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572 or equivalent form. Study medications must be administered only under the supervision of the Investigators listed on this form. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572 or equivalent form.

The Investigator must 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.

12.3. Patient Confidentiality

Patient names will not be supplied to the Sponsor. If the patient name appears on any documents, it must be redacted before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Patient blood and tissue samples, and radiographic images sent to outside laboratories and/or CROs 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 patient. The patients will be told that representatives of the Sponsor, 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.

12.4. Study Monitoring

Sponsor or its designee will monitor the conduct of the trial on a regular basis throughout the duration of the study, according to the monitoring plan and in compliance with ICH-GCP E6 (R2). Monitoring of the study will serve to ensure: (a) The rights and well-being of human subjects are protected; (b) The reported trial data are accurate, complete, and verifiable from source documentation; and (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

The study monitor will train site personnel on the conduct of the trial. The monitor will assess the trial site’s compliance with the protocol and will periodically review and verify a sample of the patient data recorded on CRFs against source documentation. The study monitor will also review documents that provide evidence of the proper consent and eligibility of enrolled patients, the compliant conduct of study procedures, the administration and disposition of investigational product(s), the reporting of serious adverse events and adverse reactions, and the continued maintenance of trial records.

The Investigator will allocate adequate time to support such monitoring activities. The Investigator will also ensure that the monitor is given reasonable remote and/or on-site access to study-related documents, source documents (regardless of media) and study-related facilities (eg, investigational pharmacy, etc). Queries may be raised if any datum is unclear or contradictory. The Investigator and site personnel must address all queries in a timely manner.

12.5. Study Committees

12.5.1. Steering Committee

A Steering Committee (SC) will be comprised of lead Investigators from North America and Europe. The purpose of the SC is to provide overall guidance regarding design of the study, conduct and execution of the trial. This includes (but is not limited to) safety, efficacy, enrollment and contribution to scientific input for publications. Responsibilities of the SC and communication flow between ImmunoGen and the SC will be included in the SC charter document.

12.5.2. Independent Data Monitoring Committee

An IDMC will not be utilized in this study. Sponsor will monitor safety in accordance with ICH-GCP E6 (R2) guidelines.

12.6. Case Report Forms and Study Reports

Electronic case report forms (eCRFs) are provided for each patient. All forms must be filled out by authorized study personnel. The Investigator is required to sign/e-sign the eCRF 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 eCRF Critical Documents

Before ImmunoGen initiates the study at a given site, it is the responsibility of the Investigator to ensure that the following documents are made available to ImmunoGen or their designee:

- 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 Brochure, Patient Information/ICF, and any other written information to be provided regarding patient recruitment procedures
- Copy of IRB/IEC approved Patient Information/ICF/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 or equivalent form
- Completed Financial Disclosure Form

Additional documents such as laboratory reference ranges and certifications will be collected during the study. Ongoing regulatory approvals and notifications, as required, must also be made available to ImmunoGen.

12.7. Protocol Adherence

Each Investigator must adhere to the protocol as detailed in this document and agree that any changes to the protocol must be approved by ImmunoGen's authorized representative in writing before seeking approval, where necessary, from the IRB/IEC, Research Ethics Committee (REC), or Ethics Review Board (ERB). Each Investigator will be responsible for allowing only those patients who have met protocol eligibility criteria to be enrolled.

Modifications to the protocol should not be made without agreement of the Investigators and ImmunoGen. Changes to the protocol will require written IRB/IEC, REC, or ERB approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC/REC/ERB may provide expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC/REC/ERB. ImmunoGen will submit all protocol modifications to the appropriate regulatory authorities in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact ImmunoGen, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documentation.

Prospective waivers or exemptions are not permitted.

12.8. End of Study

EOS will occur 12 months after the primary analysis for ORR. If patients are still receiving clinical benefit from MIRV at EOS, either the study will be amended to allow those patients to continue to receive study treatment with limited data collection (eg SAEs, dosing information) until they are no longer benefiting or patients will be given the option to roll-over to a long-term extension study.

12.9. Study Termination

If the Sponsor, an Investigator, or Clinical Study 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 Investigators. In addition, a decision on the part of ImmunoGen to suspend or discontinue development of the study drug may be made at any time.

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

12.10. Site Termination

If ImmunoGen, an Investigator, or regulatory authorities discover conditions during the study that indicate that the study or related activities at a particular center should be terminated, this action may be taken after appropriate consultation between ImmunoGen and the Investigator. Conditions that may warrant study or center termination include but are not limited to:

- Discovery of an unexpected, serious, and/or unacceptable risk to patients enrolled in the study
- Decision on the part of ImmunoGen to suspend or discontinue testing, evaluation, or development of the clinical program
- Unacceptable benefit-risk relationship of the investigational product
- Recommendations of a regulatory body
- Investigator failure to comply with applicable regulatory authority requirements or protocol requirements
- Submission of knowingly false information from the center to ImmunoGen or regulatory authorities

Study or center termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR § 312 and in compliance with the principles set forth in International Conference on Harmonisation (ICH) Good Clinical Practices (GCP).

12.11. Access to Source Documentation

According to the ICH-GCP, the monitoring team must check the clinical trial database entries against the source documents. The ICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the IRB/IEC, and the regulatory authorities to have direct access to original medical records which support the data in the clinical trial database (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

12.12. Audits and Inspections

Regulatory authorities, the IEC/IRB, or the Sponsor 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 local regulations and current GCP guidelines will be followed. On-site review of the clinical trial database for completeness and clarity, crosschecking with source documents, and clarification of administrative matters will be performed.

12.13. Data Generation and Analysis

The clinical trial database will be developed and maintained by a CRO or other vendors as designated by ImmunoGen. ImmunoGen or its designee will be responsible for performing study data management activities and analyses.

12.14. Retention of Data

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

- a minimum of two years (or longer, if required by local/regional regulation) has elapsed after an approval of a marketing application which was supported by this study, or
- there are no pending or contemplated marketing applications, or
- at least two 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 Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

12.15. Financial Disclosure

The Investigator must disclose any financial interests in the Sponsor as described in 21 CFR Part 54 before beginning this study and for 12 months after the study has been completed. The appropriate form will be provided to the Investigator by the Sponsor, which will be signed and dated by the Investigator, before the start of the study. If financial interests change at any time during the study, an updated financial disclosure form is required.

All financial details relating to the Investigators' participation in this study are provided in the separate contract between the institution and ImmunoGen.

12.16. Insurance Compensation

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

12.17. 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 Sponsor, 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 Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. 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 Sponsor is obtained.

Information obtained during the conduct of this study will be used by ImmunoGen in connection with the development of the study drug. The study Investigator is obliged to provide ImmunoGen with complete test results and all data developed in this study. The Sponsor has full ownership of the original case report forms completed as part of the study. This information may be disclosed to other physicians who are conducting similar studies and to the global health authorities as deemed necessary by the Sponsor. Patient-specific information may be provided to other appropriate medical personnel related to the care of that patient only with patient's prior consent.

The Investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with ImmunoGen, provided ImmunoGen a copy of the draft document intended for publication, and obtained ImmunoGen's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential. ImmunoGen will use the information for registration purposes and for the general development of the drug.

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APPENDIX A. 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, eg, 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 B. RESPONSE DEFINITIONS (RECIST 1.1)

(Eisenhauer 2009)

DEFINITIONS

Baseline: Baseline is defined as the most recent assessment performed before 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/pneumonitis, 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 two lesions per organ and five 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 five 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, positron emission testing (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 locoregional 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 (eg, 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 assessments will be performed as indicated in Table 2. 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, 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

Radiologic tumor evaluation by CT or MRI of chest, abdomen, and pelvis will be performed within 28 days before first dose of study drug and every 6 weeks (±1 week) from C1D1 for the first 36 weeks on study and every 12 weeks (± 3 weeks) thereafter.

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 (eg, ‘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 (eg, 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 < 10mm.
Partial Response (PR)	At least 30% decrease in the sum of diameters (SoD of target lesions, taking as reference the baseline SoD
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesion, taken 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 (ie, 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 CA-125 above the normal limits if CA-125 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 (ie, 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 (ie, 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 C. GYNECOLOGIC CANCER INTERGROUP (GCIG) CRITERIA FOR EVALUATION OF CA-125

(Rustin 2004)

On the basis of the available data and extensive discussions among the cooperative groups within the GCIG, it is recommended that the following definition of response be used in ovarian cancer trials so that response can be measured by either RECIST or CA-125 criteria. If the response is evaluable by both criteria, then the date of response will be the date of the earlier of the two events.

Definition of response:

- ≥ 50% reduction in CA-125 levels from baseline
- the response must be confirmed and maintained for at least 28 days
- the pretreatment sample must be ≥ 2.0 times the ULN and within two weeks before starting treatment
- the date of response corresponds to the date when the CA-125 level is first reduced by 50%

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample
- Variations within the normal range of CA-125 levels will not interfere with the response definition.

Evaluation of Progression

Progression or Recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125, according to the following criteria:

a. Patients with elevated CA-125 pretreatment and normalisation of CA-125 must show evidence of CA-125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart, or
b. Patients with elevated CA-125 pretreatment, which never normalises must show evidence of CA-125 greater than, or equal to, two times the nadir value on two occasions at least one week apart, or
c. Patients with CA-125 in the normal range pretreatment must show evidence of CA125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart.

Elevated values must be confirmed by two separate measurements obtained at least one week apart. CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA [Taylor 2005 and Rustin 2005]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

A patient may be declared to have progressive disease on the basis of either the objective RECIST criteria or the CA-125 criteria. The date of progression will be the date of the earlier of the two events if both are documented.

Definition of progression after first-line therapy in ovarian cancer as proposed by the GCIG

GCIG subcategorized group	RECIST Measurable/non-measurable disease		CA-125
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of longest diameters (RECIST definition) or Any new lesions (measurable or non-measurable) *Date PD: date of documentation of increase or new lesions*	**AND / OR**	CA-125 ≥ 2 x ULN documented on two occasions # *Date of PD: first date of the CA-125 elevation to ≥ 2x nadir value*
B	As for A		CA-125 ≥ 2 x nadir value on two occasions # Date of PD: first date of the CA-125 elevation to ≥ 2x nadir value
B	As for A		As for A

GCIG groups A, B & C defined above.
Repeat CA-125 any time, but normally not less than 1 week after the first elevated CA-125 level. CA-125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA[a,b]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days, should not be taken into account.

[a] Taylor PT, Haverstick D. J Natl Cancer Inst 2005, 97:151, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer].

[b] Rustin GJS. J Natl Cancer Inst 2005, 97:152, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer].

Timing of CA-125 assessments:

The GCIG recommends that CA-125 measurements be taken at specific time intervals.

- The first sample would be collected within two weeks before treatment is started
- CA-125 assessments will be performed as indicated in Table 2.

- For each patient, the same assay method must be used and the assay must be tested in a quality-control scheme. Patients are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

This CA-125 response definition has been produced to evaluate relapse therapy. If assessing therapy that includes two treatment modalities for relapse (eg, surgery and chemotherapy), any CA-125 response results from both treatments. CA-125 cannot distinguish between the effects of each treatment. To calculate response rates in protocols, an ITT analysis should be used that includes all patients with an initial CA-125 level of at least twice the ULN as eligible and evaluable. In addition to calculating response rates in protocols, it is advisable to record those patients who have both a CA-125 response and whose CA-125 level falls to within the normal range.

APPENDIX D. LIST OF CONCOMITANT MEDICATIONS REQUIRING CAREFUL MONITORING

CYP Enzymes	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:
(http://www fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#classSub).

APPENDIX E. ADJUSTED IDEAL BODY WEIGHT (AIBW) CALCULATION

Adjusted Ideal Body Weight (AIBW)

$AIBW = IBW^1 + 0.4 (Actual\ weight - IBW^1)$

Ideal Body Weight (IBW)

$IBW^1\ (female) = 0.9H^1\text{-}92$

(^{1}H=height in cm; W=weight in kg)