CLINICAL STUDY PROTOCOL

Study Title:	MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression
Study Number:	IMGN853-0416
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]
Original Protocol Date (Version 1.0):	10 October 2019
Amendment No. and Date:	1 (09 December 2019) 1.1 (06 April 2020) (Belgium, Czech Republic, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom) 2 (04 December 2020)

SPONSOR SIGNATURE PAGE

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Date

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigator Brochure for mirvetuximab soravtansine. I have read the ImmunoGen Protocol IMGN853-0416 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
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
BRCA	breast cancer susceptibility gene
BSA	body surface area
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
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
ECHO	echocardiography

Abbreviation	Term
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
EOT	End of Treatment
EPO	erythropoietin
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FIH	first-in-human
FOLR1, FRα	folate receptor 1/folate receptor alpha
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HFS	hand-foot syndrome
HIV	human immunodeficiency virus
IA	interim analysis
IC	investigator's choice
IC_{50}	half maximal (50%) inhibitory concentration
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
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction

Abbreviation	Term
ITT	intent-to-treat
IV	intravenous
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MIRV	mirvetuximab soravtansine (IMGN853)
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA scan	multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nM	nanomolar
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PE	physical examination
PET	positron emission testing
PFS	progression-free survival
PFS2	time to second disease progression
PGIS	Patient global impression of severity
PK	pharmacokinetics
PLD	pegylated liposomal doxorubicin
PLT	platelets
PR	partial response/remission
PRO	patient-reported outcomes
PROC	platinum-resistant ovarian cancer
PS	performance status
PT	prothrombin time
Q3W	every 3 weeks
Q4W	every 4 weeks

Abbreviation	Term
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
RR	response rate
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SC	Steering Committee
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
TAb	total antibody
TEAE	treatment emergent adverse events
TPR	time point response
ULN	upper limit of normal
US	United States
WBC	white blood cell (count)
WCBP	woman of childbearing potential
WHO	World Health Organization
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: MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy 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 430 patients	
Study Center(s): Approximately 200 centers globally	
Studied Period (months): Approximately 30 months (including follow-up)	**Phase of Development:** 3

Objectives:

Primary Objective:

- To compare the progression-free survival (PFS) of patients randomized to mirvetuximab soravtansine (MIRV) vs. Investigator's choice of chemotherapy (IC Chemo)

Key Secondary Objectives:

- To compare the objective response rate (ORR) of patients randomized to MIRV vs. IC Chemo
- To compare overall survival (OS) of patients randomized to MIRV vs. IC Chemo
- To compare the primary patient-reported outcome (PRO) using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-OV28 (Abdominal/GI Symptom Scale) assessment from patients randomized to MIRV vs. IC Chemo

Additional Secondary Objectives:

- To compare the safety and tolerability of MIRV vs. IC Chemo
- To compare the duration of response (DOR) in patients randomized to MIRV vs. IC Chemo
- To compare the CA-125 response rate (RR) per Gynecologic Cancer Intergroup (GCIG) CA-125 criteria in patients randomized to MIRV vs. IC Chemo
- To compare the time to progression or death on the next line of treatment (PFS2) in patients randomized to MIRV vs. IC Chemo

Exploratory Objectives:

- To assess PRO using the EORTC QLQ-C30, EuroQol-5 Dimension 5-level (EQ-5D-5L), and Patient Global Impression of Severity (PGIS) questionnaires
- To evaluate concentrations of MIRV, total antibody (TAb), DM4 and S-methyl DM4, using sparse sampling
- To assess the immunogenicity of MIRV via anti-drug antibodies (ADAs)
- To evaluate potential biomarkers in blood and tumor tissue predictive of response to MIRV

Study Design Overview and Schema:

This Phase 3 study is designed to compare the efficacy and safety of MIRV vs. IC Chemo in patients with platinum-resistant high-grade epithelial ovarian cancer (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. Folate receptor alpha (FRα) positivity will be defined by the Ventana FOLR1 (FOLR1-2.1) CDx assay.

Eligible patients (N = 430), who have provided informed consent and meet study entry criteria will be randomized (1:1) to one of two arms:

- Arm 1 (n = 215): MIRV 6 mg/kg adjusted ideal body weight (AIBW) every 3 weeks (Q3W)
- Arm 2 (n = 215): IC Chemo, at one of the following regimens as determined by the Investigator prior to randomization:
  - Paclitaxel (Pac; 80 mg/m^2) administered QW within a 4-week cycle
  - Pegylated liposomal doxorubicin (PLD; 40 mg/m^2) administered Q4W
  - Topotecan (Topo; 4 mg/m^2) administered either on Days 1, 8, and 15 every 4 weeks or for 5 consecutive days (1.25 mg/m^2 Days 1–5) Q3W

Patients will be stratified by:

- Number of prior lines of therapy (1 vs. 2 vs. 3)
- IC Chemo (Pac vs. PLD vs. Topo) chosen prior to randomization

The table below shows the dose and schedule of the study drugs.

Group	Drug	Dose	Dosing Schedule
Arm 1	MIRV	6 mg/kg AIBW IV	Day 1 of a 3-week cycle
Arm 2	Pac	80 mg/m^2 IV	Days 1, 8, 15, and 22 of a 4-week cycle
	PLD	40 mg/m^2 IV	Day 1 of a 4-week cycle
	Topo	4 mg/m^2 IV	Days 1, 8, and 15 of a 4-week cycle
	Topo	1.25 mg/m^2 IV	Days 1 to 5 of a 3-week cycle

Disease progression will be evaluated by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1, Appendix B). Computerized tomography (CT) or magnetic resonance imaging (MRI) scans will be collected and held for sensitivity analysis by a blinded independent central review (BICR).

Patients will continue to receive study drug 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 all regimens) for the first 36 weeks then every 12 weeks (± 3 weeks) until disease progression, death, the initiation of subsequent anticancer therapy, or patient's withdrawal of consent, whichever occurs first.

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.

All patients who discontinue study drug 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. All patients will be followed for progression and survival.

Two interim analyses will be conducted, (1) an interim futility analysis (PFS only) when at least 110 PFS events have occurred, and (2) an interim analysis for OS at the time of final analysis of PFS when at least 330 PFS events have occurred. The final analysis for OS will be conducted when at least 300 deaths have occurred.

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 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 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 FOLR1 (FOLR-2.1) CDx assay
7. Patients must have at least one 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, and for whom single-agent therapy is appropriate as the next line of treatment:
    a. Adjuvant ± neoadjuvant considered one line of therapy
    b. Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered as 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 as 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. Patient must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
10. Time from prior therapy:
    a. Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter)

b. Focal radiation completed at least 2 weeks prior to first dose of study drug

11. Patients must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities
12. Major surgery must be completed at least 4 weeks prior to first dose 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 Section 5.9.6) in while on study drug and for at least 3 months after the last dose of MIRV or at least 6 months after the last dose of Pac, PLD, or Topo
16. WCBP must have a negative pregnancy test within 4 days prior to the first dose of study drug

Exclusion Criteria

1. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade or borderline ovarian tumor
2. 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
3. Patients with prior wide-field radiotherapy (RT) affecting at least 20% of the bone marrow
4. Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE)
5. 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
6. 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. HIV infection
    c. Active cytomegalovirus infection
    d. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug

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

7. Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome)
8. Patients with clinically significant cardiac disease including, but not limited to, any one 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
9. Patients assigned to PLD stratum only:
   - Left ventricular ejection fraction (LVEF) below the institutional limit of normal as measured by echocardiography (ECHO) or multigated acquisition (MUGA) scan
10. Patients with a history of hemorrhagic or ischemic stroke within six months prior to randomization
11. Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)
12. Patients with a previous clinical diagnosis of non-infectious interstitial lung disease (ILD), including noninfectious pneumonitis
13. Patients with required use of folate-containing supplements (eg, folate deficiency)
14. Patients with prior hypersensitivity to monoclonal antibodies
15. Women who are pregnant or lactating
16. Patients with 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 randomization

    Note: does not include 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)
19. Prior known hypersensitivity reactions to study drugs and/or any of their excipients
20. People who are detained through a court or administrative decision, receiving psychiatric care against their will, adults who are the subject of a legal protection order (under tutorship/curatorship), people who are unable to express their consent, and people who are subject to a legal guardianship order
21. Simultaneous participation in another research study, in countries or localities where this is the health authority guidance

Prohibited Concomitant Medications: Any non-study anticancer agents, including but not limited to antineoplastic agents, biologics, monoclonal antibodies (mAb), and hormonal therapy, or palliative radio therapy (RT) during study treatment.
Investigational Product, Dosage and Mode of Administration: Patients randomized to MIRV receive a dose of 6 mg/kg AIBW IV Q3W.
Reference Therapy, Dosage, and Mode of Administration: Pac will be administered at 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 of a 4-week cycle. PLD will be administered at 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 of a 4-week cycle. After Cycle 1, if tolerated, PLD may be delivered as a 1-hour infusion. Topo will be administered at 4 mg/m^2 as a 30 min IV infusion on Days 1, 8, and 15 of a 4-week cycle. Alternatively, Topo can be administered at 1.25 mg/m^2 over 30 min on Days 1 to 5 of a 3-week cycle. The dose of chemotherapeutic agents will be calculated using body surface area (BSA). Institutional conventions may be used to calculate BSA.
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 independently evaluate safety data of patients enrolled to the study, as well as the interim futility analysis. The structure of the committee, frequency of meetings and responsibilities are outlined in an IDMC charter.

Table 2: Schedule of Assessments for Arm 1 (Mirvetuximab Soravtansine): 3-Week Cycle

Procedure	Pre-screening	Screening	Cycle 1 C=3 weeks		C2+	EOT	30-day Follow-up	Response/ Survival Follow-up
			D1	D8	D1	≤ 7d from discon.	30 (+14) days from last dose	Every 3±1 month from EOT
Pre-screening Informed Consent	●							
Study Informed Consent		●[a]						
Eligibility		●[a]	●[b]					
Demographics		●[a]						
Medical History		●[a]						
Confirm Disease Diagnosis/Current Stage		●[a]						
12-Lead ECG		●[c, d]	●[d]					
Coagulation (PT or INR/aPTT)		●[c]						
Urinalysis		●[c]						
FFPE Archived Tumor Tissue and/or New Biopsy [e]	●							
Physical Examination [f]		●[c]	●[g]		●	●	●	
Weight		●[c]	●		●	●	●	
Height		●[c]						
Vital Signs [h]		●[c]	●		●	●	●	
ECOG PS		●[c]	●[g]		●	●	●	
Hematology and Chemistry [i]		●[c]	●[g]		●	●	●	
Blood Sample for Biomarkers	●							

Table 2: Schedule of Assessments for Arm 1 (Mirvetuximab Soravtansine): 3-Week Cycle (Continued)

Procedure	Pre-screening	Screening	Cycle 1 C=3 weeks		C2+	EOT	30-day Follow-up	Response/ Survival Follow-up
			D1	D8	D1	≤ 7d from discon.	30 (+14) days from last dose	Every 3±1 month from EOT
Pregnancy Test [j]		●[j]	●[g]		●		●	
Ophthalmic Exam [k]		●[c]	Every other cycle from time treatment-emergent eye disorder first reported			●	●	
Ocular Symptom Assessment [l]		●[c]	●		●	●	●	
Radiologic Tumor Assessment [m]		●[a]	Every 6 (±1) weeks from C1D1 for first 36 weeks, then every 12 (±3) weeks			●[n]	●[n]	
CA-125 [o]		●[c]	Collect at each radiologic tumor assessment (±4 days)			●[n]	●[n]	
PRO Assessment [p]		●[c,d]	Day 1 of every cycle through Week 24, then every 12 weeks until documentation of PD or start of a new anticancer therapy [p]			●		●[p]
Mirvetuximab Soravtansine (MIRV) Administration			●		●			
Record AE/SAEs and Con-meds	●[q]	●	Collected continuously while patients are on study					●[r]
Blood Sample for PK [s]			●	●	●[s]	●	●[s]	
Blood Samples for Immunogenicity [t]			●		●[t]	●	●[t]	
Survival Phone Screen, Including New Anticancer Therapy [u]								●

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; PRO = patient-reported outcome; PT = prothrombin time; SAE = serious adverse event.

[a] Must be within 28 days before C1D1.

[b] Confirm before first dose.

[c] Must be within 14 days before C1D1.

[d] ECG and PRO assessment may be performed predose at C1D1 if not performed previously during screening.

[e] 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 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 meet this criterion.

[f] Full physical examination (PE) is required at Screening and the 30-day Follow-up visit. Symptom-directed PEs while on study drug.

[g] ECOG, PE, pregnancy, 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.

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

[i] Hematology and chemistry labs may be performed up to 4 days prior Day 1 of each cycle, and as clinically indicated while on treatment, with results reviewed before each drug administration. In the event of severe toxicity, laboratory tests must be repeated as clinically necessary until the toxicity resolves or stabilizes to baseline level.

[j] For women of childbearing potential (WCBP), a urine or serum pregnancy test will be performed within 4 days prior to Day 1 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.

[k] 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 had an ophthalmic exam on study treatment (post-baseline) will have a complete ophthalmological examination performed at EOT visit or 30 day follow-up visit.

[l] 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.

[m] Radiologic tumor assessment by CT/MRI scan.

[n] If a patient discontinues before documentation of progressive disease (PD), a tumor assessment and CA-125 will be assessed at the EOT visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Tumor assessments and CA-125 will continue to be performed. Patients who discontinue study treatment for reasons other than progressive disease (PD) will continue 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 comes first).

[o] CA-125 responses will be confirmed according to GCIG criteria.

[p] Includes the EQ5D-5L, QLQ-C30, QLQ-OV28, and PGIS assessments. At visits where administered, the PROs should be completed before other procedures at the beginning of clinic visit. PRO assessments will occur Day 1 of every cycle up to Week 24 and then approximately every 12 weeks (± 3 weeks), at the time of tumor assessment, until documentation of PD or the start of new anticancer therapy.

[q] 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.

[r] All ocular AEs will be followed until resolution, stabilization, or return to baseline.

[s] 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 on the day of MIRV infusion prior to dosing on Day 1 of Cycles 2 and 4, EOT, and also at the 30-Day Follow-up if feasible.

[t] Immunogenicity will be assessed in PK samples collected prior to dosing (predose) on C2D1, C4D1, and anytime at EOT, and 30-day Follow-up. There will be an ADA only collection prior to dosing on Day 1 of Cycle 1.

[u] Survival follow-up assessments will occur every 3 months (±1 month) until death, the patient is lost to follow-up or withdraws of consent for survival follow-up, or EOS, whichever comes first. These assessments may be conducted by telephone. Information on initiation of other 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.

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. Testing may be performed to support exploratory endpoints at the end of the trial; however, results will not be communicated to treating physicians or patients.

Table 3: Schedule of Assessments for Arm 2 (Topotecan): 3-Week Cycle

Procedure	Pre-screening	Screening	Cycle 1+ Cycle = 3 weeks	EOT	30-day Follow-up	Response /Survival Follow-up
			D1	≤ 7d from discon.	30 (+14) days from last dose	Every 3±1 month from EOT
Pre-screening Informed Consent	●					
Study Informed Consent		●[a]				
Eligibility		●[a]	●[b]			
Demographics		●[a]				
Medical History		●[a]				
Confirm Disease Diagnosis/Current Stage		●[a]				
12-Lead ECG		●[c,d]	●[d]			
Coagulation (PT or INR/aPTT)		●[c]				
Urinalysis		●[c]				
FFPE Archived Tumor Tissue and/or New Biopsy [e]	●					
Physical Examination [f]		●[c]	●[g]	●	●	
Weight		●[c]	●	●	●	
Height		●[c]				
Vital Signs [h]		●[c]	●	●	●	
ECOG PS		●[c]	●[i]	●	●	
Hematology and Chemistry [j]		●[c]	●[g]	●	●	
Blood Sample for Biomarkers	●					
Pregnancy Test [k]		●[k]	●[g]		●	

Table 3: Schedule of Assessments for Arm 2 (Topotecan): 3-Week Cycle (Continued)

Procedure	Pre-screening	Screening	Cycle 1+ Cycle = 3 weeks	EOT	30-day Follow-up	Response/ Survival Follow-up
			D1	≤ 7d from discon.	30 (+14) days from last dose	Every 3±1 month from EOT
Ophthalmic Exam [l]		●[c]	Every other cycle from time treatment-emergent eye disorder first reported	●	●	
Ocular Symptom Assessment [m]		●[c]				
Radiologic Tumor Assessment [n]		●[a]	Every 6 (±1) weeks from C1D1 for first 36 weeks, then every 12 (±3) weeks	●[o]	●[o]	
CA-125 [p]		●[c]	Collect at each radiologic tumor assessment (±4 days)	●[o]	●[o]	
PRO Assessment [q]		●[c,d]	Day 1 of every cycle through Week 24, then every 12 weeks until documentation of PD or start of a new anticancer therapy [q]	●		●[q]
Topotecan (Topo) Administration [r]			●			
Record AE/SAEs and Con-meds	●[s]	●	Collected continuously while patients are on study			
Survival Phone Screen, Including New Anticancer Therapy [t]						●

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; PRO = patient-reported outcome; PT = prothrombin time; SAE = serious adverse event.

[a] Must be within 28 days before C1D1.
[b] Confirm before first dose.
[c] Must be within 14 days before C1D1.

[d] ECG and PRO assessment may be performed predose at C1D1 if not performed previously during screening.
[e] 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 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 meet this criterion.
[f] Full examination (PE) is required at Screening and the 30-day Follow-up visit. Symptom-directed PEs while on study drug.
[g] PE, pregnancy, 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.
[h] Vital signs (BP and temperature) will be measured before start of infusion; post infusion vital signs should be collected as clinically indicated for potential infusion related reaction.
[i] ECOG does not need to be repeated at C1D1 if performed within the previous 4 days during Screening.
[j] Hematology and chemistry labs may be performed up to 4 days prior Day 1 of each cycle, and as clinically indicated while on treatment, with results reviewed prior to each drug administration. In the event of severe toxicity, laboratory tests must be repeated as clinically necessary until the toxicity resolves or stabilizes to baseline level.
[k] For WCBP, a urine or serum pregnancy test will be performed within 4 days prior to Day 1 of each cycle and at the 30-day Follow-Up visit. It is recommended to perform monthly pregnancy tests for 6 months after the last dose of chemotherapy. Additional testing may be performed in accordance with institutional requirements or local regulation.
[l] 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 had 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.
[m] Ocular symptoms assessment will be performed by the treating physician or other qualified individual at screening and as clinically indicated if symptoms appear on study. For patients reporting > CTCAE Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.
[n] Radiologic tumor assessment by CT/MRI scan.
[o] If a patient discontinues before documentation of PD, a tumor assessment and CA-125 will be assessed at the EOT visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Tumor assessments and CA-125 will continue to be performed. Patients who discontinue study treatment for reasons other than progressive disease (PD) will continue 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 comes first).
[p] CA-125 responses will be confirmed according to GCIG criteria.
[q] Includes the EQ5D-5L, QLQ-C30, QLQ-OV28, and PGIS assessments. At visits where administered, the PROs should be completed before other procedures at the beginning of clinic visit. PRO assessments will occur Day 1 of every cycle up to Week 24 and then approximately every 12 weeks (± 3 weeks), at the time of tumor assessment, until documentation of PD or the start of new anticancer therapy.
[r] Topo administered daily on Days 1-5; no assessments are required on Days 2-5 unless clinically indicated.
[s] 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.
[t] Survival follow-up assessments will occur every 3 months (±1 month) until death, the patient is lost to follow-up or withdraws of consent for survival follow-up, or EOS, whichever comes first. These assessments may be conducted by telephone. Information on initiation of other 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.

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. Testing may be performed to support exploratory endpoints at the end of the trial; however, results will not be communicated to treating physicians or patients.

Table 4: Schedule of Assessments for Arm 2 (Pegylated Liposomal Doxorubicin; Weekly Paclitaxel; Weekly Topotecan): 4-Week Cycle

Procedure	Pre-screening	Screening	Cycle 1 (C1)			C2			C3+			EOT	30-day Follow-up	Response/ Survival Follow-up
		Day	1	8/15*	22*	1	8/15*	22*	1	8/15*	22*	≤ 7d from discon.	30 (+14) days from last dose	Every 3±1 month from EOT
Pre-screening Informed Consent	●													
Study Informed Consent		●[a]												
Eligibility		●[a]	●[b]											
Demographics		●[a]												
Medical History		●[a]												
Confirm Disease Diagnosis/Current Stage		●[a]												
12-Lead ECG		●[c,d]	●[d]											
ECHO/MUGA scan [e] (PLD only)		●[a]												
Coagulation (PT or INR/aPTT)		●[c]												
Urinalysis		●[c]												
FFPE Archived Tumor Tissue and/or New Biopsy [f]	●													
Physical Examination [g]		●[c]	●[h]			●			●			●	●	
Weight		●[c]	●			●			●			●	●	

Table 4: Schedule of Assessments for Arm 2 (Pegylated Liposomal Doxorubicin; Weekly Paclitaxel; Weekly Topotecan): 4-Week Cycle (Continued)

Procedure	Pre-screening	Screening	Cycle 1 (C1)			C2			C3+			EOT	30-day Follow-up	Response/ Survival Follow-up
		Day	1	8/15*	22*	1	8/15*	22*	1	8/15*	22*	≤ 7d from discon.	30 (+14) days from last dose	Every 3±1 month from EOT
Height		●[c]												
Vital Signs [i]		●[c]	●	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●	●	
ECOG PS		●[c]	●[j]			●			●			●	●	
Hematology and Chemistry [k]		●[c]	●[h]			●			●			●	●	
Blood Sample for Biomarkers	●													
Pregnancy Test [l]		●[l]	●[h]			●			●				●	
Ophthalmic Exam [m]		●[c]	Every other cycle from time treatment-emergent eye disorder first reported									●	●	
Ocular Symptom Assessment [n]		●[c]												
Radiologic Tumor Assessment [o]		●[a]	Every 6 (±1) weeks from C1D1 for first 36 weeks, then every 12 (±3) weeks									●[p]	●[p]	
CA-125[q]		●[c]	Collect at each radiologic tumor assessment (±4 days)									●[p]	●[p]	
PRO Assessment [r]		●[c,d]	Day 1 of every cycle through Week 24, then every 12 weeks until documentation of PD or start of a new anticancer therapy[r]									●		●[r]
PLD Administration			●			●			●					

Table 4: Schedule of Assessments for Arm 2 (Pegylated Liposomal Doxorubicin; Weekly Paclitaxel; Weekly Topotecan): 4-Week Cycle (Continued)

Procedure	Pre-screening	Screening	Cycle 1 (C1)			C2			C3+			EOT	30-day Follow-up	Response/ Survival Follow-up
		Day	1	8/15*	22*	1	8/15*	22*	1	8/15*	22*	≤ 7d from discon.	30 (+14) days from last dose	Every 3±1 month from EOT
Topotecan (Topo) Administration			●	●		●	●		●	●				
Paclitaxel (Pac) Administration			●	●	●	●	●	●	●	●	●			
Record AE/SAEs and Con-meds	●[s]	●	Collected continuously while patients are on study											
Survival Phone Screen, Including New Anticancer Therapy[t]														●

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; PRO = patient-reported outcome; PT = prothrombin time; SAE = serious adverse event.

*** Study visits on D8, D15, and D22 or only required for patients receiving infusions on those days. For example, a patient randomized to PLD would only be required to have clinic visits on D1 of each cycle.**

[a] Must be within 28 days before C1D1.

[b] Confirm before first dose.

[c] Must be within 14 days before C1D1.

[d] ECG and PRO assessment may be performed predose at C1D1 if not performed previously during screening.

[e] Only for patients assigned to the PLD stratum prior to randomization. The same method of assessment technique should be used throughout the study. To be performed at Screening and as clinically indicated for patients receiving PLD. If the patient's LVEF drops below normal or by at least 15% from the baseline value, study drug should be interrupted. Discuss event with Sponsor before resuming treatment.

[f] 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 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 meet this criterion.

[g] Full examination is required at Screening and the 30-day Follow-up visit. Symptom-directed physical examinations while on study drug.

[h] PE, pregnancy, 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.

[i] Vital signs (BP and temperature) will be measured before start of infusion; post infusion vital signs to be collected as clinically indicated for potential infusion related reactions. Vital signs should only be collected on dosing days, thus for patients randomized to PLD, this would only be on D1 of each cycle, and for patients on Topo, this would be on D1, D8, and D15.

[j] ECOG does not need to be repeated at C1D1 if performed within the previous 4 days during Screening.

[k] Hematology and chemistry labs may be performed up to 4 days prior Day 1 of each cycle, and as clinically indicated while on treatment, with results reviewed before each drug administration. In the event of severe toxicity, laboratory tests must be repeated as clinically necessary until the toxicity resolves or stabilizes to baseline level.

[l] For WCBP, a urine or serum pregnancy test will be performed within 4 days prior to Day 1 of each cycle and at the 30-day Follow-Up visit. It is recommended to perform monthly pregnancy tests for 6 months after the last dose of chemotherapy. Additional testing may be performed in accordance with institutional requirements or local regulation.

[m] Baseline ophthalmic exams will be performed by an ophthalmologist within 14 days prior to 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 had 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.

[n] Ocular symptoms assessment will be performed by the treating physician or other qualified individual at screening and as clinically indicated if symptoms appear on study. For patients reporting > CTCAE Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.

[o] Radiologic tumor assessment by CT/MRI scan.

[p] If a patient discontinues before documentation of PD, a tumor assessment and CA-125 will be assessed at the EOT visit or 30-day Follow-up visit, if not performed within the previous 6 weeks. Tumor assessments and CA-125 will continue to be performed. Patients who discontinue study treatment for reasons other than progressive disease (PD) will continue 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 comes first).

[q] CA-125 responses will be confirmed according to GCIG criteria.

[r] Includes the EQ5D-5L, QLQ-C30, QLQ-OV28, and PGIS assessments. At visits where administered, the PROs should be completed before other procedures at the beginning of clinic visit. PRO assessments will occur Day 1 of every cycle up to Week 24 and then approximately every 12 weeks (± 3 weeks), at the time of tumor assessment, until documentation of PD or the start of new anticancer therapy.

[s] 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.

[t] Survival follow-up assessments will occur every 3 months (±1 month) until death, the patient is lost to follow-up or withdraws of consent for survival follow-up, or EOS, whichever comes first. These assessments may be conducted by telephone. Information on initiation of other 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.

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. Testing may be performed to support exploratory endpoints at the end of the trial; however, results will not be communicated to treating physicians or patients.

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1. INTRODUCTION

1.1. Target Background

Folate receptor α (FRα) is a glycosylphosphatidylinositol-anchored cell surface protein encoded by the folate receptor 1 (*FOLR1*) gene. FRα internalizes folate, which is an essential co-factor for one-carbon transfer reactions that are required for DNA and RNA synthesis, cell growth and proliferation. Marked upregulation of FRα occurs during neonatal development and in cancer, suggesting that the receptor functions primarily under conditions of high folate demand. In contrast, normal adult tissues generally lack FRα expression and employ alternative transporters such as folate receptor β, reduced folate carrier and proton-coupled folate transporter for folate uptake (Weitman 1992, Mantovani 1994, Elnakat 2004, Kelemen 2006, Investigator Brochure).

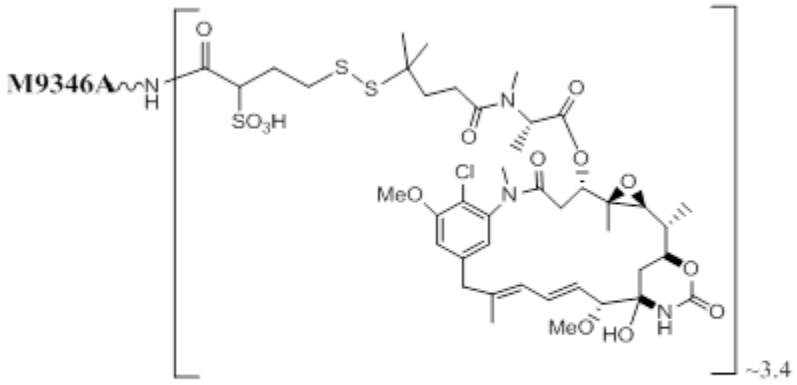
Published studies have demonstrated FRα overexpression by immunohistochemistry (IHC) in various epithelial tumors, particularly serous and endometrioid ovarian cancers and serous and endometrioid endometrial cancers (Scorer 2010, Garin-Chesa 1993, Kalli 2008, Crane 2012, Dainty 2007, Jones 2008, Ab 2015, 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). While assessing the FRα distribution in the PROC (platinum-resistant ovarian cancer) expansion cohort, approximately 40% of patients had 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, 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 one to seven molecules per Ab, with an average of three or four 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 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 13,930 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 48% (SEER Cancer Statistics Factsheet 2019).

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.* Patients with platinum-resistant disease typically receive single-agent chemotherapy (eg, PLD, topotecan [Topo], gemcitabine, paclitaxel [Pac], or other) at relapse. Unfortunately, response rates (RR) are modest (~15%) and duration of response (DOR) is typically 4 to 8 months (Cannistra 2010, Matsuo 2010). Similarly, overall survival (OS) is poor (median OS ~11 months). Bevacizumab was approved for use in combination with chemotherapy for recurrent EOC in the platinum-resistant setting (Pujade-Lauraine 2014). Because platinum-resistant EOC (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).

Commonly used agents for PROC are Pac, Topo and PLD, all of which have modest levels of activity, which underscores the need for improved therapies.

In addition to single-agent cytotoxic chemotherapy, bevacizumab combinations and poly-ADP ribose polymerase (PARP) inhibitors (eg, olaparib, niraparib, and rucaparib) are approved for treatment of previously treated EOC. These agents, however, are subject to treatment limitations. In particular, 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 receive bevacizumab + chemotherapy typically receive subsequent single-agent chemotherapy if they remain eligible for further treatment.

PARP inhibitors (eg, olaparib and rucaparib) are approved as single-agent treatment for patients with breast cancer susceptibility gene (*BRCA*) mutated EOC (~15% of EOC) and have received ≥ 2 prior regimens (Moore 2019) based on the durable responses seen in this subset of EOC. The activity of PARP inhibitors in *BRCA* wild-type patients with PROC is negligible, with response rates of approximately 5% (Gelmon 2011, Moore 2019, Sandhu 2013).

1.4. Current Therapies

Current management of advanced stage disease includes surgical tumor debulking, followed by adjuvant platinum- and taxane-based chemotherapy. However, the majority of the patients will recur (Garcia 2013). Patients with relapsed platinum sensitive disease are often treated with carboplatin alone or as part of a combination regimen (Pfisterer 2006), whereas those with platinum-resistant disease may be treated with a variety of agents, including Pac, Topo and PLD.

See Section 1.7.2 for more information on the background and doses/regimens of Pac, Topo, and PLD selected for this study.

1.5. Non-Clinical Studies of Mirvetuximab Soravtansine

1.5.1. Correlation of FRα Expression with MIRV Activity

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 mg/kg – 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 FIH (FIH) study exploring the safety and tolerability of MIRV when administered once every three weeks to patients with advanced solid tumors. Potential risks suggested by these studies as well as clinical experience with other maytansinoid ADCs include hematologic abnormalities, electrolyte alterations, injection site reactions, infusion reactions, immunogenicity, hepatic abnormalities, and peripheral neuropathy. Toxicology studies are further detailed in the 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 for single agent MIRV administered once every three weeks was determined to be 6.0 mg/kg adjusted ideal body weight (AIBW). Data from this study, including PK and treatment-emergent adverse events (TEAEs) reported by patients enrolled in the dose escalation cohorts 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 original "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, as detailed in the Investigator Brochure) suggested the potential for a significant improvement over single-agent chemotherapy (Pac, PLD, or Topo). Specifically, 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 progression-free survival (PFS) of 6.7 months, which compared favorably with what would be expected 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.

The initial safety profile of MIRV suggested that it was well tolerated, with a safety profile primarily consisting of low grade gastrointestinal (GI) adverse events (AEs) and blurred vision related to corneal keratopathy. The 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.

Safety data are further detailed in the MIRV Investigator Brochure.

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 vs. Investigator's choice of chemotherapy (IC Chemo) in patients with platinum-resistant EOC, primary peritoneal cancer, or fallopian tube cancer, and whose tumor

was FRα-positive (medium or high expression) by the Ventana IHC assay. The study was designed to compare the efficacy of MIRV to that of approved single-agent selected standard of care chemotherapy (Pac, PLD, or Topo) 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 the MIRV group or the IC Chemo groups (248 and 118, respectively) and were included in the ITT analysis. A total of 352 patients received at least 1 dose of MIRV or IC Chemo (243 and 109, respectively), and were included in the Safety population analysis. All patients in the MIRV group of the Safety population received a dose of 6 mg/kg AIBW every 3 weeks (Q3W). The patients in the IC Chemo group received a dose of single-agent chemotherapy.

The primary endpoint was PFS by a blinded independent review committee, 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 is the first study to evaluate available chemotherapy specifically in patients with high FRα expression. An examination of efficacy in the FRα-high population showed clinically meaningful advantage for those patients randomized to MIRV vs. IC Chemo across all endpoints. MIRV treatment in PROC patients with high FRα expression resulted in an ORR of 24% (95% CI: 17.2, 31.5) compared with 10% (95% CI: 4.1, 19.3) for patients randomized to IC Chemo (p-value = 0.014), median PFS of 4.8 months (95% CI: 4.11, 5.68) vs. 3.3 months (95% CI: 1.97, 5.59) for patients randomized to IC Chemo (p-value = 0.049; HR = 0.693), median OS in patients randomized to MIRV was not reached (95% CI: 12.58, not estimable) vs. 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, -) vs. 4.2 months (95% CI: 3.22, 8.71) for patients randomized to IC Chemo. 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 (compared with 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] vs. 8.4 months [95% CI: 7.10, 9.46] for patients randomized to IC Chemo [p-value < 0.001; HR = 0.557]).

The efficacy and safety of MIRV from this Phase 3 study were supported by 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 Chemo (32% vs 13.7% respectively, p=0.011).

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 ADA and MIRV exposure.

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 Chemo 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 Chemo, 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.

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 MIRV in previous clinical studies are consistent with a positive risk benefit assessment. The potential benefit of the anti-tumor activity demonstrated by MIRV 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 recommended phase 2 dose (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.

1.7.2. Chemotherapeutic Agents in the Investigator's Choice Arm

The three drugs most commonly used in the setting of platinum resistance are PLD, Pac and Topo (Ledermann 2013 [ESMO Guidelines], NCCN Guidelines 2019 and Luvero 2014). The ability of patients to tolerate the bone marrow suppressive effects of cytotoxic chemotherapy is

less than that of patients receiving initial therapy. Modified doses and administration schedules (outside of the label for first line or second-line EOC) are therefore, typically used to treat EOC in such settings.

1.7.2.1. Paclitaxel

Pac is a taxane that can stabilize microtubules to inhibit cell division. The drug was approved for treatment of recurrent EOC when response rates (RR) of 25% to 37% were observed in multiple Phase 2 trials testing the 3-weekly schedule (McGuire 1989, Thigpen 1994, Rowinsky 1995). In the study by Thigpen et al, a median PFS of 4.2 months and an OS of 16 months were observed. A Phase 2 trial showed that weekly dosing could lead to a 20.9% ORR in platinum- and Pac-resistant EOC patients (Gynecologic Oncology Group 2006). This alternative weekly dosing schedule for Pac was studied in many trials in refractory, persistent, or recurrent EOC patients, as reviewed by Baird et al (Baird 2010). A randomized Phase 3 study comparing weekly vs. 3-weekly Pac in recurrent EOC patients (of whom half were platinum-resistant) showed no difference in RR, PFS, or OS. However, the weekly schedule had a better safety profile than the 3-weekly schedule, as considerably less neutropenia, neuropathy, and myalgia were observed (Rustin 2004). Of note, the occurrence of neutropenia was also reduced when Pac was infused over 3 hours instead of 24 hours (Eisenhauer 1994). A recent randomized Phase 2 clinical trial (CARTAXHY) tested the efficacy of weekly Pac as a single agent, or in combination with carboplatin, or weekly Topo in patients with PROC. The results showed that the combination treatments increased hypersensitivity reactions, febrile neutropenia, and anemia, and did not improve ORR or median PFS when compared to single agent weekly Pac (Lortholary 2012).

The approved schedule of Pac Q3W for second-line treatment of EOC is associated with a high rate of myelosuppression, particularly neutropenia, and peripheral neuropathy. Investigators therefore developed interest in evaluating the antitumor activity and tolerability of Pac administered on a weekly schedule, exploring it in several Phase 2 studies (Rustin 2004, Markman 2002). The weekly schedule is associated with similar efficacy and an improved toxicity profile, with less bone marrow suppression and neuropathy, as summarized by Baird et al (Baird 2010). Toxicities are managed with dose reductions and/or holding the D22 dosing on the weekly schedule. In the Phase 3 AURELIA study, the weekly Pac regimen resulted in an ORR of 30.2% in patients with PROC with 1 to 2 prior lines of therapy (Poveda 2015).

1.7.2.2. Topotecan

Topo's mechanism of action is different from that of Pac, as it does not directly block cell division, but instead induces irreversible DNA damage. Topo inhibits topoisomerase 1, leading to both single and double stranded DNA breaks that eventually promote apoptosis. Topo (administered QD the first 5 days of 21-day cycles) was approved for treatment of EOC after failure of initial or subsequent chemotherapy. This approval was based on a Phase 3 trial that showed it to be at least as effective as Pac, with ORR of 21% vs. 13%, and median PFS of 23 weeks vs. 14 weeks, respectively (ten Bokkel Huinink 1997). Unfortunately, Topo treatment led to severe bone marrow suppression with 80% Grade 4 neutropenia, 25% Grade 4 thrombocytopenia, and 41% Grade 3 or 4 anemia (ten Bokkel Huinink 1997).

As such toxicities are often dose limiting, multiple clinical trials have studied alternative dosing schedules to improve the tolerability of Topo treatment (Armstrong 2019, Armstrong 2004, Hoskins 1998, Markman 2000). For example, one Phase 2 trial tested the effect of the "standard" dosing of Topo (1.5 mg/m^2, daily the first 5 days of 21-day cycles) compared with an alternative dosing regimen (1.75 mg/m^2, QW for 4 weeks, repeated every six weeks) in patients with recurrent EOC. The alternative dosing regimen led to a lower ORR (9.6% compared with 22.6% in the standard dosing arm), but also decreased myelotoxicity (52% of patients had Grade 3 or 4 granulocytopenia in comparison with 94% in the standard dosing arm) (Hoskins 1998). A subsequent Phase 2 trial tested the effect of yet another dosing schedule (1.5 mg/m^2, daily the first three days of 21-day cycles) (Markman 2000). Compared to historical controls, this alternative dosing regimen seemed to decrease the toxicity of Topo (Armstrong 2004). In a meta-analysis of various clinical trials, it was concluded that modification of the Topo dose, and potentially the dosing schedule, can indeed reduce hematologic toxicity without decreasing the efficacy of the drug (Armstrong 2019).

The approved Topo dosing for relapsed EOC is 1.5 mg/ m^2/d, administered on days 1 to 5 of a 3-week schedule. However, reduced doses (ie, 1.25 mg/m^2/d) are associated with decreased toxicity and similar outcome, thereby being widely used in routine clinical practice (Sehouli 2009). Results from several studies suggest that women with relapsed EOC may benefit from similar effectiveness but significantly lower hematologic toxicity if Topo is administered in a weekly schedule. A Phase 2 trial of the North-Eastern German Society of Gynaecology Oncology Ovarian Cancer Study Group, has compared weekly schedule vs. the conventional 5-day schedule, reporting comparable OS rates and a favorable toxicity profile for weekly 4.0 mg/m^2/week Topo, making it another viable option in PROC (Sehouli 2011). Based on this evidence from the literature, a conventional (1.25 mg/m^2/d, on days 1 to 5 of a 3-week schedule) and an alternative (4.0 mg/m^2/week, days 1, 8, and 15 of a 4 week cycle) schedules of Topo were selected for the study.

1.7.2.3. Pegylated Liposomal Doxorubicin

PLD is approved as monotherapy in recurrent PROC. The approved dose and schedule of 50 mg/m^2 every 28-days of PLD results in a substantial incidence (approximately 20%–30%) of Grade 3 "hand-foot-syndrome" (Markman 2011). Considerable clinical experience generated since the initial regulatory approval of PLD has revealed equivalent clinical activity with substantially less severe adverse events when this agent is administered at a dose of 40 mg/m^2 (rather than 50 mg/m^2) on a 4-week schedule (Markman 2011). Results of two randomized Phase 2 trials (Markman 2000, Wilailak 2004) provide strong support for the conclusion that the 40 mg/m^2 dose level of PLD is therapeutically equivalent to the higher (and more toxic) dose approved for standard use in the second-line management of EOC. Recently a study was conducted to show equivalence in efficacy of PLD 40 mg/m^2 and PLD 50 mg/m^2 (Yoshizawa 2015). This randomized controlled study also supports the use of an initial dose of 40 mg/m^2 PLD.

PLD is another standard chemotherapy regimen used for treating PROC. The active component of this drug (doxorubicin) is an anthracycline that intercalates DNA, leading to inhibition of replication and, subsequently, the inhibition of proper cell division. Efficacy of PLD in PROC

EOC has been confirmed in several Phase 2 trials. In detail, the trial by Muggia et al reported a 26% RR, median PFS of 5.7 months, and OS of 11 months (Muggia 1997). A subsequent trial showed a 17% ORR and median PFS of 4.5 months (Gelmon 2011). Of note, a Phase 3 trial testing Topo treatment vs. PLD treatment showed a trend toward a higher ORR in the PROC patients subset treated with PLD, although there was no improvement of PFS or OS (Gordon 2001, Gordon 2004).

1.8. Rationale for the Study Plan

The design of this study is based on data obtained from Phase 3 study (IMGN853-0403), which showed a potential for a clinically meaningful advantage for MIRV over IC Chemo (the same therapies selected for this study) in patients with high FRα expression. While that prior study did not reach statistical significance in the entire population (patients with medium and high FRα), those patients with high FRα expression showed promising results.

This Phase 3, open-label, randomized study is designed to compare the efficacy of MIRV to selected standard IC Chemo in patients with platinum-resistant high-grade EOC, primary peritoneal, or fallopian tube cancer, whose tumors express a high level of FRα.

This study will compare the safety and efficacy of MIRV administered at 6 mg/kg AIBW Q3W with IC Chemo (Pac, PLD or Topo). Patients will be enrolled 1:1 into one of two arms as follows:

- ***Arm 1:*** MIRV 6 mg/kg AIBW Q3W
- ***Arm 2:*** IC Chemo

1.9. Rationale for the Study Population

The study population included in this study was initially based on clinical observations from a Phase 1 study of MIRV (Study IMGN853-0401), which showed promising clinical activity in patients with PROC. Results from that study suggested that higher FRα levels correlated with response to treatment (Martin 2015). Based on those results, a large, randomized Phase 3 study in patients with platinum-resistant advanced high-grade EOC, primary peritoneal, or fallopian tube cancers was initiated. Eligible patients were required to have tumors expressing what was considered a medium or high level FRα expression per the Ventana IHC assay using a newly implemented "10x" scoring method. Results from this study showed that while the study did not meet the primary endpoint per Hochberg procedure, MIRV showed consistently favorable efficacy when compared to IC Chemo in measures of PFS, ORR, OS, DOR, PFS2, CA-125, and PRO endpoints in patients high FRα expression. Subsequent review demonstrated that the "10x" scoring method for the FOLR1 IHC assay misclassified a significant percentage of patients, and thus further impacted the study results. Ad hoc analyses of the PS2+ high FRα patients revealed enhanced benefit from MIRV for ORR, PFS and OS compared to IC Chemo controls. These findings warranted a follow-up study focusing solely on patients with high FRα expression using the original "PS2+" scoring method. Thus, the present study will enroll a similar PROC population to the prior Phase 3 study, with the exception that patients are required to have high FRα expression by PS2+ scoring as determined by the Ventana FOLR1 (FOLR-2.1) CDx assay.

Please refer to the Investigator Brochure for more details on the Ventana FOLR1 assay and the FRα expression threshold selected for this study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To compare the PFS of patients randomized to MIRV vs. IC Chemo

2.1.2. Key Secondary Objectives

- To compare the ORR of patients randomized to MIRV vs. IC Chemo
- To compare OS of patients randomized to MIRV vs. IC Chemo
- To compare the primary patient-reported outcome (PRO) using the EORTC QLQ-OV28 (abdominal/GI symptom scale) assessment from patients randomized to MIRV vs. IC Chemo

2.1.3. Additional Secondary Objectives

- To compare the safety and tolerability of MIRV vs. IC Chemo
- To compare the DOR in patients randomized to MIRV vs. IC Chemo
- To compare the CA-125 RR per GCIG CA-125 criteria in patients randomized to MIRV vs. IC Chemo
- To compare the time to progression or death on the next line of treatment (PFS2) in patients randomized to MIRV vs. IC Chemo

2.1.4. Exploratory Objectives

- To assess PRO using the EORTC QLQ-C30, EQ-5D-5L, and Patient Global Impression of Severity (PGIS) questionnaires
- To evaluate concentrations of MIRV, TAb, DM4 and S-methyl DM4, using sparse sampling
- To assess the immunogenicity of MIRV via anti-drug antibodies (ADAs)
- To evaluate potential biomarkers in blood and tumor tissue predictive of response to MIRV

2.2. Endpoints

2.2.1. Primary Endpoint

- PFS, defined as the time from date of randomization until Investigator-assessed progressive disease (PD) or death, whichever occurs first. Results will be summarized by arm
  - Kaplan-Meier method for survival function estimate
  - Stratified Cox proportional hazard regression for hazard ratio (HR) estimate
  - Stratified log-rank test for hypothesis testing

2.2.2. Key Secondary Endpoints

- Objective response includes best response of complete response (CR) or partial response (PR) as assessed by the Investigator
  - Stratified Cochran-Mantel-Haenszel (CMH) test for treatment comparison
  - Clopper-Pearson method for 95% CI estimation
- OS defined as the time from date of randomization until the date of death. Patients alive at the time of analysis will be censored at the last known date known to be alive
  - Kaplan-Meier method for survival function estimate
  - Stratified Cox proportional hazard regression for HR estimate
  - Stratified log-rank test for hypothesis testing
- Primary PRO assessment, defined as the number of patients achieving at least 15 point absolute improvement at Week 8 or Week 9 in the abdominal/GI scale of EORTC QLQ-OV28

2.2.3. Other Secondary Endpoints

- DOR defined as the time from initial response until Investigator-assessed PD for all patients who achieve a confirmed objective response (PR or CR)
  - Kaplan-Meier method for survival function estimate
  - Unstratified Cox proportional hazard regression for HR estimate
  - Unstratified log-rank test for hypothesis testing
- CA-125 response determined using the GCIG criteria defined in Section 8.14.2. CA-125 response per GCIG criteria will be determined programmatically
- PFS2 defined as the time from date of randomization until second disease progression or death whichever occurs first. Results will be summarized by arm
- TEAEs, laboratory test results, physical examination findings, and vital signs

2.2.4. Exploratory Endpoints

Exploratory endpoints are provided below. The analysis and subsequent results of these assessments may be reported in separate documents and not included in the Statistical Analysis Plan or Clinical Study Report, respectively.

- EORTC QLQ-C30/OV-28, EQ5D-5L, and PGIS
- PK parameters will not be calculated due to the use of a sparse sampling schedule. Summary statistics of intact ADC, total Ab, DM4 and S-methyl DM4 concentration data by time will be presented
- Immunogenicity is defined as the presence of ADA to MIRV. Based on seroconversion status, the impact of ADA on both efficacy and safety will be evaluated
- Identification of soluble FRα levels and other biomarkers, such as protein, genetic, and/or gene expression changes, related to solid malignancies and/or MIRV or IC Chemo mechanism of action. Patient samples will only be used for exploratory research related to this trial and the development of MIRV

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 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 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 FOLR1 (FOLR-2.1) CDx assay
7. Patients must have at least one 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, and for whom single-agent therapy is appropriate as the next line of treatment:
    a. Adjuvant ± neoadjuvant considered one line of therapy
    b. Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered as 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 as 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. Patient must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
10. Time from prior therapy:
    a. Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter)
    b. Focal radiation completed at least 2 weeks prior to first dose of study drug
11. Patients must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities
12. Major surgery must be completed at least 4 weeks prior to first dose 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. AST and 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 5.9.6) while on study drug and for at least 3 months after the last dose of MIRV or at least 6 months after the last dose of Pac, PLD, or Topo
16. WCBP must have a negative pregnancy test within 4 days prior to the first dose of study drug

3.1.2. Exclusion Criteria

1. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade or borderline ovarian tumor
2. 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
3. Patients with prior wide-field radiotherapy (RT) affecting at least 20% of the bone marrow
4. Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE) v5.0
5. 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
6. 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. HIV infection
    c. Active cytomegalovirus infection
    d. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug

    Note: Testing at screening is not required for the above infections unless clinically indicated
7. Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome)
8. Patients with clinically significant cardiac disease including, but not limited to, any one 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

9. Patients assigned to PLD stratum only:
    - Left ventricular ejection fraction (LVEF) below the institutional limit of normal as measured by echocardiography (ECHO) or multigated acquisition (MUGA) scan
10. Patients with a history of hemorrhagic or ischemic stroke within six months prior to randomization
11. Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)
12. Patients with a previous clinical diagnosis of non-infectious interstitial lung disease (ILD), including noninfectious pneumonitis
13. Patients with required use of folate-containing supplements (eg, folate deficiency)
14. Patients with prior hypersensitivity to monoclonal antibodies
15. Women who are pregnant or lactating
16. Patients with 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 randomization

    Note: does not include 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
19. Prior known hypersensitivity reactions to study drugs and/or any of their excipients
20. People who are detained through a court or administrative decision, receiving psychiatric care against their will, adults who are the subject of a legal protection order (under tutorship/curatorship), people who are unable to express their consent, and people who are subject to a legal guardianship order
21. Simultaneous participation in another research study, in countries or localities where this is the health authority guidance

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 compare the efficacy and safety of MIRV vs. IC Chemo in patients with platinum-resistant high-grade 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 FOLR1 (FOLR1-2.1) CDx assay.

This study will be opened/active at approximately 200 sites globally. Eligible patients (N = 430), who have provided informed consent and meet study entry criteria will be randomized (1:1) to one of two arms:

- Arm 1 (n = 215): MIRV 6 mg/kg AIBW Q3W
- Arm 2 (n = 215): IC Chemo, at one of the following regimens as determined by the Investigator prior to randomization:
  - Paclitaxel (Pac; 80 mg/m^2) administered QW
  - Pegylated liposomal doxorubicin (PLD; 40 mg/m^2) administered Q4W
  - Topotecan (Topo; 4 mg/m^2) administered either on Days 1, 8, and 15 every 4 weeks (Q4W) or for 5 consecutive days (1.25 mg/m^2 Days 1–5) Q3W

Patients will be stratified by the following variable at baseline:

- Number of prior lines of therapy (1 vs. 2 vs. 3)
- IC Chemo (Pac vs. PLD vs. Topo) chosen prior to randomization

Disease progression will be evaluated by the Investigator using RECIST v 1.1 (Appendix B). CT or magnetic resonance imaging (MRI) scans will be collected and held for sensitivity analysis by a BICR.

Patients will continue to receive study drug 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 C1D1 (for all regimens) for the first 36 weeks then every 12 weeks (± 3 weeks) until disease progression, death, the initiation of subsequent anticancer therapy, or patient's withdrawal of consent, whichever occurs first.

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, death, the start of new anticancer therapy or patient's withdrawal of consent (whichever comes first).

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 end of study (EOS), whichever comes first. All patients will be followed for PFS2 and survival until 300 deaths have occurred.

Two interim analyses will be conducted, (1) an interim futility analysis (PFS only) when at least 110 PFS events have occurred, and (2) an interim analysis for OS at the time of final analysis of PFS when at least 330 PFS events have occurred. The final analysis for OS will be conducted when at least 300 deaths have occurred.

4.1.2. Dosing and Dosing Schedules for Mirvetuximab Soravtansine and Chemotherapeutic Agents

The dose and schedule of study treatment are outlined in Table 5.

The dose of chemotherapeutic agents will be calculated using body surface area (BSA). Institutional conventions may be used to calculate BSA.

Table 5: Study Drug Doses and Schedules of Administration

Group	Drug	Dose	Dosing Schedule
Arm 1	MIRV	6 mg/kg AIBW IV	Day 1 of a 3-week cycle
Arm 2	Pac	80 mg/m^2 IV	Days 1, 8, 15, and 22 of a 4-week cycle
	PLD	40 mg/m^2 IV	Day 1 of a 4-week cycle
	Topo	4 mg/m^2 IV	Days 1, 8, and 15 of a 4-week cycle
	Topo	1.25 mg/m^2 IV	Days 1 to 5 of a 3-week cycle

Abbreviations: MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; Topo = topotecan; AIBW = adjusted ideal body weight.

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®) on the top and product contact surface with a 20 mm aluminum TruEdge® seal with blue Flip-off® top. Refer to the Pharmacy Manual for labeling information.

5.1.2. 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, contract research organization representative, or auditor). 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. The clinical trial database shall also record details of MIRV administration such as date and time of administration.

Drug accountability will be monitored.

5.1.3. MIRV Study Treatment Compliance

The 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 form, or to administer these supplies to a patient not enrolled in this study. If investigational supplies are to be dispensed from any facility other than that supervised directly by the 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. Investigator's Choice Chemotherapeutic Agents

Since the type of IC Chemo received is one of the stratification factors, it is required that the choice of the chemotherapy agent, Pac or PLD or Topo, be made prior to randomization. Pac, PLD and Topo are supplied as commercially available formulations. Refer to the prescribing information or SmPC for complete information.

A separate Investigational Product Dispensing/Accountability Log or equivalent must be maintained for Pac, PLD, and Topo. 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 Investigational Product Dispensing/Accountability Log or equivalent.

5.3. Assignment of Patient Number

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

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

5.3.1. Enrolled Patient Definition

Patients who have consented to the study and randomized, are considered enrolled. Patients who are issued a patient number, but who do not successfully complete the screening process and are

not randomized will be considered screen failures. Patient numbers for patients who screen fail will not be re-issued.

5.3.2. Patient Assignment to Dosing Regimens

Eligible patients will be randomly assigned 1:1 to MIRV 6 mg/kg AIBW Q3W (Arm 1) or IC Chemo (Arm 2; Pac, PLD or Topo).

Cycle 1 Day 1 must occur within seven calendar days from randomization.

Patients will be stratified as follows:

- Number of prior therapies (1 vs. 2 vs. 3)
- IC of chemotherapy (Pac, PLD, or Topo)

5.4. Blinding Methods

Not applicable as this is an open-label study. A Data Access Plan will describe procedures to restrict access to efficacy data for certain team members.

5.5. Study Treatment Administration

5.5.1. Premedication for Study Treatment

5.5.1.1. Mirvetuximab Soravtansine

All patients receiving MIRV must receive 325-650 mg of acetaminophen/paracetamol (PO or IV), 10 mg IV dexamethasone, and 25-50 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.

5.5.2. Prophylactic use of Corticosteroid Eye Drops

Patients receiving MIRV 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 receiving MIRV 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. Given the lack of availability in some regions, if prednisolone eye drops cannot be obtained, alternate steroid eye drops are acceptable.

5.5.2.1.1. Lubricating Artificial Tears

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

5.5.2.2. IC Chemotherapy

Patients receiving Pac, PLD or Topo may receive premedication at the discretion of the Investigator or according to institutional guidelines.

5.5.3. Preparation and Administration of Mirvetuximab Soravtansine

5.5.3.1. Calculation for Adjusted Ideal Body Weight

The total dose of drug is calculated based on each patient's AIBW using the following formula (Appendix E):

Adjusted Ideal Body Weight (AIBW)

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

Where:

Ideal Body Weight (IBW)

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

(^1H=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).

5.5.3.1.1. 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 **s**tudy drug from different drug lots may be mixed in a single-dose administration.

5.5.3.1.2. Administration

MIRV is administered at 6 mg/kg 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 study drug 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 prn to ensure delivery of the full dose.

Patients are carefully observed during each infusion and vital signs are taken as outlined in the Schedule of Assessments (Table 2, Table 3, and Table 4). 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.

5.5.3.2. Preparation and Administration of IC Chemotherapy

Precautions should be taken when handling Pac, PLD, and Topo. Refer to the Pharmacy Manual and package inserts for more information.

5.5.3.3. Preparation and Administration of Paclitaxel

Pac will be administered at 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 of a 4-week cycle. Pac will be prepared as described in the prescribing information and administered IV at 80 mg/m^2. Body weight at C1D1 (-14 days) is to be used to calculate BSA to determine the required dose. No dose modifications are foreseen unless the patient's body weight changes by ±10% from baseline.

5.5.3.4. Preparation and Administration of Pegylated Liposomal Doxorubicin

PLD will be prepared as described in the prescribing information and administered at 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 of a 4-week cycle. After Cycle 1, if tolerated, PLD can be delivered as a 1-hour IV infusion. Body weight at C1D1 (-14 days) is to be used to calculate BSA to determine the required dose. No dose modifications are foreseen unless the patient's body weight changes by ± 10% from baseline.

5.5.3.5. Preparation and Administration of Topotecan

Topo will be prepared as described in the prescribing information and administered at 4 mg/m^2 as a 30-min IV infusion on Days 1, 8 and 15 of a 4-week cycle. Alternatively, Topo may also be administered at 1.25 mg/m^2 as a 30-min IV infusion on Days 1 to 5 of a 3-week cycle. Body weight at C1D1 (-14 days) is to be used to calculate BSA to determine the required dose. No dose modifications are foreseen unless the patient's body weight changes by ± 10% from baseline.

5.6. Dose Modification Guidelines

Detailed MIRV and chemotherapy-specific dose modification guidelines are described below.

5.6.1. Mirvetuximab Soravtansine

5.6.1.1. Treatment Criteria

In the absence of a TEAE that requires dose modification (as specified in the management guidance for a particular toxicity, see Section 5.6.1.2), a patient must meet the following criteria to receive study drug at any cycle:

- ANC must be ≥ 1.5 x 10^9/L (1,500/μL)
- Platelet count must be ≥ 100 x 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

5.6.1.2. Mirvetuximab Soravtansine-related Adverse Events

Dose modifications for MIRV-related adverse events are described in Table 6.

Table 6: Dose Modifications for Mirvetuximab Soravtansine-related Adverse Events

Severity Grade (CTCAE)	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 > one h)	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 5.6.1.6
Noninfectious Pneumonitis	Refer to Section 5.6.1.7
Infusion-related Reactions	Refer to Section 5.6.1.9
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 results in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity.

5.6.1.3. Mirvetuximab Soravtansine Dose Reduction Dose Levels

MIRV dose reduction will be as described in Table 7.

Table 7: 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.

5.6.1.4. 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 5.9.1). 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.

5.6.1.5. 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 2 mg loperamide at the first sign of loose stool, with repeat dosing every two hours until symptoms resolve (Wadler 1998).

5.6.1.6. 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. At the 6 mg/kg AIBW Q3W dose level Grade 3 TEAEs of dry eye, keratopathy, vision blurred, eye pain, and photophobia were reported in Phase 3 Study IMGN853-403.

5.6.1.6.1. Monitoring and Preventive Measures

In early dose escalation, there was a relationship between MIRV plasma exposure with increased likelihood of an ocular event as well as with 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 adverse events. 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,

Table 3, and Table 4). 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 5.5.2 and Section 5.5.2.1.1 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 8 should be followed.

5.6.1.6.2. 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 8 for details). If ocular symptoms last longer than 28 days, resumption of MIRV 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 8: Management of Ocular Symptoms

Severity Grade (CTCAE v5.0 Grade)	Management	Guidelines for MIRV Dose Modifications
Grade 1	Complete eye exam as outlined in Schedule of Assessments (Table 2, Table 3, Table 4) Monitor for worsening symptoms	Continue MIRV dosing
Grade 2	Complete eye exam as outlined in Schedule of Assessments (Table 2, Table 3, Table 4) 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 [a] 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, Table 3, Table 4). 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 [a] 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, Table 3, Table 4). 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 irreversible by the Investigator	Permanently discontinue MIRV

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

[a] If ocular symptoms last longer than 28 days, resumption of MIRV may be considered for those patients who have experienced clinical benefit if agreed upon between the Sponsor and the Investigator.

5.6.1.7. Monitoring of Non-infectious Pneumonitis

Non-infectious pneumonitis has been observed after the administration of MIRV. Non-infectious 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 9 should be followed.

Table 9: Management of Non-infectious 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 Grade 4	Severe symptoms; limiting self-care ADL; oxygen indicated Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)	• 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.

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 results in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity.

5.6.1.8. Management of Electrolytes Imbalance

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

5.6.1.9. 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 10. 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 antibodies to MIRV (ADA). 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 10: 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 9.1.1.2). • 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.

5.6.1.10. 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 5.6.1.2)
- Grade ≥ 3 pneumonitis event (Section 5.6.1.7)
- Non-hematologic events of Grade 4 severity (Section 5.6.1.2)
- Ocular events of Grade 4 severity (Section 5.6.1.6)
- 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.

5.6.2. Paclitaxel

Label warnings, manufacturer's recommendations and standard clinical practice should be followed. Guidelines for dose interruptions and dose modifications are described in Table 11.

Table 11: Paclitaxel Dose Modification Guidelines

Severity Grade (CTCAE v5.0 Grade)	Dose Modification
Hematological Toxicities	
Grade 1	No action
Grade 2 & 3	Hold Pac until ANC and PLT levels meet the following criteria: Day 1: ANC ≥ 1.5 x 10^9/L (1,500/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) Day 8, 15 & 22: ANC ≥ 1.0 x 10^9/L (1,000/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) Resume treatment at same dose level
Grade 4	Hold Pac until ANC and PLT levels meet the following criteria: Day 1: ANC ≥ 1.5 x 10^9/L (1,500/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) Day 8, 15 & 22: ANC ≥ 1.0 x 10^9/L (1,000/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) Dose reduce by 1 level and/or omit D22 dose
For febrile neutropenia and/or severe bleeding, permanently discontinue Pac	
Non-hematological Toxicities	
Grade 1	No action
Grade 2	No action; for patients experiencing neurotoxicity, dose reduce by 1 level and/or omit D22 dose.
Grade 3	Dose reduce by 1 level and/or omit D22 dose.
Grades 3 and 4	Hold Pac until the event resolves or improves to Grade 1. Dose reduce by 1 level and/or omit D22 dose.

Abbreviations: ANC = absolute neutrophil count; CTCAE = common terminology criteria for adverse events; D = day; Pac = paclitaxel; PLT = platelet.

Administration of granulocyte colony stimulating factor (G-CSF) or erythropoietin (EPO) is permitted as per institutional guidelines.

5.6.2.1. Dose Reduction Dose Levels

Pac dose reduction will be as described in Table 12.

Table 12: Paclitaxel Dose Reductions

If the patient was receiving Pac at:	Dose should be reduced to:
80 mg/m^2	70 mg/m^2
70 mg/m^2	60 mg/m^2

* Reduction of the Pac below 60 mg/m^2 will not be permitted. Instead of a second dose reduction, 70 mg/m^2 can be maintained if one weekly dose is omitted within 1 cycle. Dose re-escalation is not permitted.

5.6.2.2. Criteria for Permanent Discontinuation of Paclitaxel

Pac will be permanently discontinued for febrile neutropenia and/or severe bleeding.

5.6.3. Topotecan

Label warnings, manufacturer's recommendations and standard clinical practice should be followed. Guidelines for dose interruptions and dose modifications are described in Table 13.

Table 13: Topotecan Dose Modification Guidelines

Severity Grade (CTCAE V5.0 Grade)	Dose Modification
Hematological Toxicities	
Grade 1	No action required.
Grades 2 or 3	Hold Topo until ANC and PLT levels meet the following criteria: Day 1: ANC ≥ 1.5 x 10^9/L (1,500/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) Day 8, & 15: ANC ≥ 1.0 x 10^9/L (1,000/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) Re-treat at same dose level.
Grade 4 or any grade neutropenia complications (fever, infection)	Hold Topo until ANC and PLT levels meet the following criteria: Day 1: ANC ≥ 1.5 x 10^9/L (1,500/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) Day 8, & 15: ANC ≥ 1.0 x 10^9/L (1,000/µL) and platelets ≥ 100 x 10^9/L (100,000/µL) Dose reduce by one level.
Non-hematological Toxicities	
Grade 1	No action required.
Grade 2	No action required.
Grades 3 or 4	Hold Topo until the event improves to Grade 1 or resolves. Dose reduce by one level.

Abbreviations: CTCAE = common terminology criteria for adverse events; ANC = absolute neutrophil count; PLT = platelets.

Administration of G-CSF or EPO is permitted according to approved institutional guidelines.

Patients who receive Topo and develop a TEAE requiring an interruption of Topo may resume treatment at a reduced dose level as shown in Table 14.

5.6.3.1. Dose Reduction Dose Levels

Topo dose reduction will be as described in Table 14 and Table 15.

Table 14: Topotecan Dose Reductions (Weekly Schedule)

If the patient was receiving Topo at:	Dose should be reduced to:
4 mg/m^2	3.5 mg/m^2
3.5 mg/m^2	3 mg/m^2

* Reduction of the Topo below 3mg/m ^{2}will not be permitted. Dose re-escalation is not permitted.

Table 15: Topotecan Dose Reductions (Five Days Schedule)

If the patient was receiving Topo at:	Dose should be reduced to:
1.25 mg/m^2	1.0 mg/m^2
1.0 mg/m^2	0.75 mg/m^2

* Reduction of the Topo below 0.75mg/m^2 will not be permitted. Dose re-escalation is not permitted.

5.6.3.2. Criteria for Permanent Discontinuation of Topotecan

Treatment should be permanently discontinued according to the guidelines shown in Table 16, in case the observed TEAE is unmanageable despite dose reductions.

Table 16: Adverse Events Requiring Permanent Discontinuation of Topotecan

Severity Grade (CTCAE v5.0 Grade)	Adverse Event
Hematological Toxicities	
Grade 4	ANC < 0.5 x 10^9/L for more than two weeks
Grade 4	Thrombocytopenia for more than 2 weeks
Non-hematological Toxicities	
Grade 3 or 4	Mucositis
Grade 3 or 4	Neurotoxicity
Grade 3 or 4	Toxicities (except nausea, vomiting, and alopecia) lasting for more than three weeks

5.6.4. Pegylated Liposomal Doxorubicin

Label warnings, manufacturer's recommendations and standard clinical practice should be followed.

5.6.4.1. Hematological Toxicities

Patients receiving PLD are at risk of bone marrow suppression. Leukopenia is usually transient; hematological AEs may require dose delays or reductions as indicated in Table 17.

Table 17: Pegylated Liposomal Doxorubicin Dose Modification Guidelines for Hematological Adverse Events

Severity Grade	ANC	Platelets	Modification
Grade 1	< LLN to 1.5 x 10^9/L (< LLN to 1,500/µL)	< LLN to 75.0 x 10^9/L (< LLN to 75,000/µL)	Resume treatment; no dose reduction
Grade 2	< 1.5 to1.0 x 10^9/L (< 1,500 to 1,000/µL)	< 75.0 to 50.0 x 10^9/L (< 75,000 to 50,000/ µL)	Delay until ANC 1.5 x 10^9/L (≥ 1,500/µL) and platelets ≥75.0 x 10^9/L (75,000/µL); re-dose with no dose reduction
Grade 3	< 1.0 to 0.5 x 10^9/L (< 1,000 to 500/µL)	< 50.0 to 25.0 x 10^9/L (50,000 to 25,000/ µL)	Delay until ANC 1.5 x 10^9/L (≥ 1,500/µL) and platelets ≥75.0 x 10^9/L (75,000/µL); re-dose with no dose reduction
Grade 4	< 0.5 x 10^9/L (< 500/µL)	< 25.0 x 10^9/L (< 25,000/ µL)	Delay until ANC 1.5 x 10^9/L (≥ 1,500/µL) and platelets ≥75.0 x 10^9/L (75,000/µL); re-dose at 25% dose reduction or continue previous dose with cytokine support

5.6.4.2. Non-hematological Toxicities

5.6.4.2.1. Hand-foot Syndrome

Hand-foot syndrome (HFS) is a disease characterized by palmar-plantar skin eruptions with swelling, pain, erythema and, for some patients, desquamation of the skin of the hands and feet. HFS has been observed in patients receiving PLD at doses of 50 mg/m^2 and, with less frequency, in those receiving PLD at 30 mg/m^2. If patients present with symptoms/signs consistent with HFS, the dose of PLD should be modified as indicated in Table 18.

Table 18: Pegylated Liposomal Doxorubicin Dose Modification Guidelines for Hand-foot Syndrome and Mucositis

Severity Grade (CTCAE v5.0 Grade)	HFS Symptoms	Mucositis Symptoms	Dose Reduction/Discontinuation
Grade 1	Mild erythema, swelling, or desquamation not interfering with daily activities	Painless ulcers, erythema, or mild soreness	Continue PLD, unless previous Grade 3 or 4 HFS. In case of previous Grade 3/4 HFS, delay up to 2 weeks and decrease dose by 25%.
Grade 2	Erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter	Painful erythema, edema, or ulcers, but can eat	Hold PLD until resolved to Grade 1 or baseline. If after 2 weeks there is no resolution, PLD should be discontinued. If no prior Grade 3-4 HFS, resume at the dose preceding the event. If previous HFS Grade 3-4 toxicity, decrease dose by 25%.
Grade 3	Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing.	Painful erythema, edema, or ulcers; cannot eat	Hold PLD until resolved to Grade 1 or baseline. Decrease dose by 25%. If after 2 weeks there is no resolution, PLD should be discontinued.
Grade 4	Diffuse or local process causing infectious complications, a bed ridden state, or hospitalization.	Requires parenteral or enteral support	

Abbreviations: PLD = pegylated liposomal doxorubicin; HFS = hand-foot syndrome.

If patients receiving PLD experience a TEAE, their PLD dose should be reduced as indicated in Table 19. Patients who require dose reductions below 20 mg/m^2 should discontinue their PLD treatment.

5.6.4.2.2. Cardiac Toxicity

Patients receiving PLD are at risk for cardiac toxicity. Cardiac function should be carefully monitored in these patients. If the patient's LVEF drops below normal or by at least 15% from the baseline value, study drug should be interrupted and event should be discussed with Sponsor before resuming treatment.

5.6.4.3. Criteria for Permanent Discontinuation of PLD

Patients who require dose reductions below 20 mg/m^2 should permanently discontinue their PLD treatment.

5.6.4.4. Dose Reduction Dose Levels

PLD dose reduction will be as described in Table 19.

Table 19: Pegylated Liposomal Doxorubicin Dose Reductions

If the patient was receiving PLD at:	Dose should be reduced to:
40 mg/m^2	30 mg/m^2
30 mg/m^2	20 mg/m^2*

* Reduction of the PLD dose below 20 mg/ m^2 will not be permitted. Patients who require dose reductions below 20 mg/m^2 should discontinue their PLD treatment. Dose re-escalation is not permitted.

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

5.7.1. End of Treatment

Patients will continue to receive study drug 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 EOT electronic case report form (eCRF). Any AEs experienced up to the point of discontinuation and 30 days thereafter must be documented on the AE eCRF. All serious adverse events (SAEs), and those AEs assessed by the Investigator as at least possibly related to study drug should continue to be followed until they resolve or stabilize, whichever comes first. Patients will continue to be followed for PFS2 and OS, after discontinuing study drug (Section 10.3.3).

5.7.2. End of Study

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

5.7.3. 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 Statistical Analysis Plan (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.

5.7.4. 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.

5.8. Period of Observation

For purposes of this study, the period of safety observation extends from the time of pre-screening informed consent until the 30-day follow-up safety visit unless additional follow-up safety information is requested as described in Section 9.1 and Section 10.3.1. 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 begins subsequent 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.

5.9. 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 on the appropriate electronic case report form (eCRF). The identity of all medications, dosage, and route of administration, frequency, duration of administration, and indication for use will be recorded in the appropriate sections of the eCRF.

5.9.1. 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.

5.9.2. Folate-Containing Supplements

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

5.9.3. 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.

5.9.4. Hematopoietic Growth Factors

Patients receiving recombinant 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.

5.9.5. Anticoagulants

The use of anticoagulant agents is allowed. Please see Section 5.9.8 if using apixaban and rivaroxaban due to CYP3A interaction potential.

5.9.6. 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 or at least 6 months after the last dose of Pac, PLD, or Topo. 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 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. Contraception requirements must be adhered to for at least 3 months after the last dose of MIRV and at least six months after the last dose of Pac, Topo and PLD. 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.

5.9.7. 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 to alleviate mild-moderate infusion reactions. Additionally, medications (not addressed

above) used to treat underlying medical conditions at study entry including antiemetics and antidiarrheals will be allowed to continue.

5.9.8. 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 carefully monitored (Appendix D).

5.10. Overdose and Medication Error

5.10.1. Overdose

There is no known treatment/antidote available for MIRV. For IC Chemo agents, please follow management guidelines for overdose as described in the prescribing information and/or institutional guidelines. Supportive measures should be instituted if an instance arises in which a patient suffers an overdose of any study drug.

5.10.2. 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 on the eCRF. If an error resulted in a SAE, a Serious Adverse Event form must be submitted within 24 hours of the event (see Section 9.2.1).

6. PHARMACOKINETIC AND IMMUNOGENICITY 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 20. 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 time points:

Table 20: Pharmacokinetics Sampling Time Points

Visit	Time Point
C1D1	≤ 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 three hours of the onset of the reaction and one week later for determination of drug concentration and antibodies to MIRV (ADA).

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. The potential impact of immunogenicity on PK, safety, and efficacy of MIRV and total Ab will be explored.

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. There will be an ADA only collection prior to dosing on Day 1 of Cycle 1.

7. BIOMARKER RESEARCH STUDIES

7.1. 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 FOLR1 (FOLR1-2.1) CDx 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 FOLR1 (FOLR1-2.1) CDx assay are eligible to enroll in the study (see the Investigator Brochure Section 5 for details on the assay and the FRα expression threshold selected for this 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.

7.2. Exploratory Biomarker Studies

Studies in tumor tissue and blood will be performed to explore potential biomarkers of MIRV sensitivity and resistance. The sections below describe activities that are planned, but other additional biomarkers/biological pathways may be investigated based on emerging data.

7.2.1. Soluble FRα

An exploratory endpoint of the study is to assess if Soluble FRα levels in blood at pre-screening are predictive or prognostic of response to MIRV or IC Chemo. The blood sample collected during pre-screening will only be used for the measurement of Soluble FRα.

7.2.2. Potential Predictive Markers of Drug Response

The molecular characterization of enrolled patient's tumor tissue may be conducted to determine the relationship between molecular alterations and clinical response, which may help identify patients who are most likely to benefit from treatment with MIRV or IC Chemo. Next-generation sequencing techniques may be used to evaluate somatic mutations, copy number variations, rearrangements, and expression patterns of multiple genes and/or proteins commonly altered in solid tumors.

New assays for candidate biomarkers associated with sensitivity or resistance to MIRV or IC Chemo, identified in the current study or earlier studies, may also be developed and tested on patient samples.

7.2.3. Future Use of Biomarker Samples

For patients who consent to it, unused tumor tissue after biomarker testing may be used for other research purposes. These other research analyses will help to understand either disease subtypes or drug responses, to develop and/or validate a bioassay method, or to identify new drug targets

or biomarkers. These samples will remain labeled with the same identifiers used during the study, ie, patient ID. They will be transferred to the Sponsor (or a subcontractor site), which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (Section 13.3).

8. STUDY PROCEDURES

8.1. 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, Table 3, and Table 4). Patient 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 and collection of a blood sample for the measurement of Soluble FRα. 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.

8.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are assessed during Screening (within 28 days before the first dose of any study drug on Cycle 1, Day 1). All screening evaluations must be completed and reviewed prior to first dose to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients 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. A patient is considered enrolled when randomized to a study treatment (Table 2, Table 3, and Table 4).

8.3. Confirmation of Disease Diagnosis

At Screening, disease diagnosis, and current disease status are confirmed from information in the source record (Table 2, Table 3, and Table 4).

8.4. *BRCA* Mutation Status

The *BRCA* mutation status from prior testing (information in the source record) will be recorded (Table 2, Table 3, and Table 4). 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.

8.5. Demographic/Medical History

The age, race, and gender of the patient are to be recorded during Screening for all patients who consent to the study (Table 2, Table 3, and Table 4).

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.

8.6. 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, Table 3, and Table 4). 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.

8.7. Vital Signs

Vital signs include BP and body temperature. These signs are measured as outlined in Table 2, Table 3, and Table 4.

8.8. Electrocardiogram (ECG)

A standard, single 12-lead ECG will be performed within 14 days prior to first dose to determine study eligibility.

8.9. Ocular Symptom Assessment and Ophthalmic Examination

8.9.1. Ocular Symptom Assessment

Ocular symptom assessment will be performed at screening for all treatment arms. Ocular symptom assessment will be performed before the start of each cycle for patients in Arm 1 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 (Table 2, Table 3, and Table 4).

8.9.2. 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 had 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, Table 3, and Table 4).

8.10. 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 21) 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, Table 3, and Table 4) and as clinically indicated.

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

8.10.1. Clinical Laboratory Panels

A list of clinical laboratory tests may be found in Table 21.

Table 21: 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.

8.11. 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 prior to Day 1 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 and for 6 months after the last dose of chemotherapy. 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, Table 3, and Table 4).

If a patient becomes pregnant or suspects pregnancy while participating in this study, the Investigator and Sponsor must be informed immediately (Section 9.2.2) and the patient will be withdrawn from study drug. See Section 9.2.2 for more details.

8.12. 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, Table 3, and Table 4). An assessment is not necessary on Day 1 of Cycle 1 if the Screening assessment was obtained within the prior 4 days.

8.13. ECHO/MUGA Scan

ECHO or MUGA scans will be performed only in patients receiving PLD (Table 4). ECHO or MUGA scans will be performed at Screening and as clinically indicated. The same test should be performed throughout the trial.

8.14. Tumor Response Assessment

8.14.1. 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, Table 3, and Table 4). 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).

Tumor response will be assessed by the Investigator using RECIST 1.1 (Eisenhauer 2009). Response as determined by the Investigator will be recorded in the clinical trial database. If the

primary endpoint (PFS by Investigator) is statistically significant at the final analysis, the BICR assessment will be used for a sensitivity analysis of PFS and objective response rate (ORR).

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.

8.14.2. CA-125

Serum CA-125 assessments (Appendix C) will be performed within 14 days prior to the first dose of study drug, and at each radiologic tumor assessment (± 4 days) (Table 2, Table 3, and Table 4). CA-125 should be assessed by the same laboratory throughout the study.

8.15. Quality of Life Questionnaires

Quality of life (QOL) questionnaires EORTC QLQ-C30, EORTC QLQ-OV28, EQ-5D-5L, and PGIS (Greimel 2003, Osoba 1994) will be used in this trial. The questionnaires should be given to the patient and completed during their Screening visit and at other times specified in the Schedule of Assessments (Table 2, Table 3, and Table 4). At visits where administered, the questionnaires should be completed before other procedures at the beginning of clinic visit. The patient should not be sent home with the questionnaires to complete and return at their next visit.

QOL questionnaires assessments are to continue to be administered for patients in response follow-up. Assessment will occur at the time of tumor assessments approximately every 12 weeks (± 3 weeks) until documentation of PD or the start of new anticancer therapy.

The EORTC QLQ-OV28 abdominal/GI subscale at week 8/9 is a key secondary endpoint, and thus this time point is the most critical, in addition to screening.

All questionnaires should be provided in the patient's local language at the beginning of the study visit before any interaction with the study Investigator, including procedures and treatments, and receipt of results from any tests to avoid bias to patient's response to the study questionnaire. Patients should be given sufficient space and time to complete all study questionnaires at each visit and should be encouraged to complete any missing responses.

8.16. Health-care Resource Utilization

Resource Utilization Data will be collected on the following healthcare resources: hospitalizations, unscheduled office visits, and admission to hospice care or nursing home facility.

9. ASSESSMENT OF SAFETY

9.1. Recording Adverse Events and Serious Adverse Events

Adverse events (AEs), including those attributed to study procedures, will be documented on the AE eCRF 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.

In patients receiving MIRV, all ocular AEs will be followed until resolution, stabilization, or return to baseline.

SAEs will be followed up 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.

9.1.1. Definition of Adverse Events

9.1.1.1. Adverse Event (AE)

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

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

9.1.1.2. Serious Adverse Event (SAE)

A 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).

9.1.1.3. Adverse Events of Special Interest

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

9.1.2. 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 22.

Table 22: 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 23.

Table 23: 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.

9.2. Adverse Events

9.2.1. 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 on the patient's AE eCRF, including the Investigator's assessment regarding the relationship of the SAE to the study drug (MIRV, Pac, PLD, or Topo). 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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) for review in accordance with national regulations. IRB/IEC notification of the SUSAR may take the form of a submission of a copy of the CIOMS/MedWatch report or other format accepted by the IRB/IEC. A copy of the CIOMS/MedWatch report and notification to IRB/IEC should be retained in the site's study files.

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

9.2.1.1. 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.

9.2.2. Reporting a Pregnancy

Pregnancy and lactation are exclusion criteria. Women of child bearing potential (WCBP), defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (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 5.9.6) while on study drug and for at least 3 months after the last dose of MIRV and for at least 6 months after the last dose of IC Chemo (Pac, PLD, and Topo). In addition, it is recommended that patients undergo monthly pregnancy tests 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. 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.

10. STUDY ACTIVITIES

All study visits and assessments that must be performed during the study and follow-up are included in Table 2, Table 3, and Table 4.

10.1. 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.

10.1.1. 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, hematology results, serum chemistry results, coagulation 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.

10.2. 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 5.6.2.2, Section 5.6.3.2, and Section 5.6.4.3.

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.

Additionally, these patients will undergo a 30-day follow-up safety visit. The eCRF will capture reasons for withdrawal.

10.3. Follow-up Assessments

10.3.1. Safety Follow-up

A safety follow-up visit will occur 30 days (+14 days) after last dose of study drug.

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

10.3.2. Response Follow-up

Patients who discontinued study treatment 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 PD or the start of new anticancer therapy. Additional survival follow-up calls may occur periodically if needed.

10.3.3. PFS2 and Survival Follow-up

All patients who discontinue study treatment for any reason will be followed for survival after disease progression as per Investigator, or after start of anticancer therapy. All patients will be followed for survival 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.

For the purposes of evaluating PFS2, information related to subsequent anticancer therapies and disease progression during survival follow-up will be collected.

11. STATISTICAL METHODS

This is a Phase 3 study designed to evaluate the efficacy of MIRV compared with that of standard of care IC Chemo in patients with in high FRα expressing, platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers.

All randomized patients will comprise the intent-to-treat (ITT) population. Efficacy will be evaluated using the ITT population. Safety will be evaluated in the population of randomized patients who have received at least one dose of study drug.

All statistical analyses will be performed using the most recently released SAS statistical software, 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. The safety analyses will be based on patients who receive at least one dose of MIRV or IC Chemo.

11.1. Sample Size

Primary endpoint is PFS per Investigator assessment. The study is designed to test the null hypothesis that the survival function for PFS is the same between the MIRV arm and the IC Chemo arm vs. the alternative hypothesis that the survival function of PFS is different between MIRV and IC Chemo arm. Approximately 430 patients will be randomized 1:1 (approximately 215 patients each in the MIRV and IC Chemo arms, respectively) over a period of approximately 18 months. The final analysis of PFS will be conducted when at least 330 events have occurred. The study will have 90% power to detect a PFS HR of 0.7. An interim futility analysis for PFS will be conducted when at least 110 events have occurred. The study may stop if the observed HR for PFS at the futility interim analysis is > 1. No alpha-spending is needed for this futility only analysis.

The final analysis of OS will be conducted when at least 300 events have occurred. There will be one interim analysis (IA) for OS at the time of final analysis of PFS, at which time approximately 200 (60%) deaths will have been observed. A Lan-DeMets alpha-spending function using an O'Brien-Fleming stopping boundary will be used to control overall type I error for OS at 2-sided alpha level of 0.05. The study will have 90% power to detect an OS HR of 0.6857.

Only if the primary endpoint of PFS is statistically significant, a hierarchical testing procedure will be used to control the study-wise error rate (SWER) for key secondary endpoints of ORR, OS, and the primary PRO, in that order.

Sample size and power was determined using R gsDesign and gsSurv packages with the following assumptions:

- Median PFS for the IC Chemo arm is 3.5 months
- Median PFS for the MIRV arm is 5 months
- Overall attrition rate for PFS event is 13%
- Median OS for the IC Chemo arm is 12 months
- Median OS for the MIRV arm is 17.5 months

11.2. Stratification

Randomization will be stratified by:

- Number of prior lines of therapy (1 vs. 2 vs. 3)
- IC Chemo (Pac vs. PLD vs. Topo)

Since the type of IC Chemo received is one of the stratification factors, it is required that the choice of the chemotherapy agent (Pac, PLD, or Topo) be made prior to randomization.

11.3. 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.

11.4. Safety Analyses

Safety analyses will be based on patients who receive at least one dose of MIRV or IC Chemo.

Adverse events and concomitant medication will be listed.

Adverse events 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.

11.5. Efficacy

Unless stated otherwise in the SAP, efficacy analyses will be performed on the ITT population. The ITT population is defined as all randomized patients.

11.5.1. Primary Efficacy Analysis

11.5.1.1. Progression-Free Survival

Primary endpoint is PFS per Investigator assessment. The study is designed to test the null hypothesis that the survival function for PFS is the same between the MIRV arm and the IC Chemo arm vs. the alternative hypothesis that the survival function of PFS is different between MIRV and the IC Chemo arm.

The final analysis of PFS will be conducted when at least 330 events have occurred. The study will have 90% power to detect a PFS HR of 0.7. An interim futility analysis for PFS will be

conducted when at least 110 events have occurred. The study may stop if the observed HR for PFS at the futility IA is > 1. No alpha-spending is needed for this futility only analysis.

The primary endpoint of Investigator-assessed PFS, will be estimated using Kaplan-Meier method. Comparison between treatment arms will be conducted using Cox proportional hazard regression and log rank test.

The null hypothesis is:

- H_0: the survival function for PFS is the same between MIRV arm and IC Chemo arm

And the alternative hypothesis is:

- H_a: the survival function for PFS is different between MIRV arm and IC Chemo arm

The primary endpoint of PFS will be tested using stratified log-rank test (stratified by the stratification factors used in randomization).

11.5.2. Secondary Efficacy Endpoints

11.5.2.1. Objective Response Rate

Objective response includes best response of CR or PR.

The secondary endpoint of ORR (objective response = CR + PR) will be estimated along with a 95% CI. The ORR of the MIRV arm and that of the IC Chemo arm will be compared using the Stratified Cochran-Mantel-Haenszel (CMH) test for treatment comparison and Clopper-Pearson method for 95% CI estimation.

11.5.2.2. Overall Survival

The secondary endpoints of OS, DOR, and PFS (as assessed by the Investigator) will be estimated using Kaplan-Meier method for survival function estimate. Comparison between treatment arms will be conducted using Cox proportional hazard regression and log rank test and a stratified log-rank test for hypothesis testing.

The final analysis of OS will be conducted when at least 300 events have occurred. There will be one IA for OS at the time of final analysis of PFS, at which time approximately 200 (60%) deaths will have been observed. A Lan-DeMets alpha-spending function using an O'Brien-Fleming stopping boundary will be used to control overall type I error for OS at 2-sided alpha level of 0.05. The study will have 90% power to detect an OS HR of 0.6857.

11.5.2.3. Patient Reported Outcomes

The abdominal/GI scale of EORTC QLQ-OV28 PRO will be a key secondary endpoint and will include the number of patients achieving at least a 15 point absolute improvement at Week 8/9 assessment.

11.6. Interim Analysis

Two IAs will be conducted during the study.

The first interim analysis is futility only and will be conducted when at least 110 PFS events have occurred. The study may stop for futility if the observed PFS HR is > 1. This IA applies to PFS only.

The second IA will be conducted at the final analysis of PFS when at least 330 PFS events have occurred. This IA applies to OS only and will be the first interim look of OS. A Lan-DeMets alpha-spending function using an O'Brien-Fleming stopping boundary is used to control overall type I error for OS at 2-sided alpha level of 0.05. It is projected that approximately 200 deaths will have occurred at this IA.

The final analysis of OS will be conducted when at least 300 deaths have occurred. It is projected that the final analysis for OS will be approximately 1 year after the final analysis of PFS.

If the primary endpoint of PFS is statistically significant and preliminary data suggest that 300 deaths will not occur within 1 year after the final analysis of PFS, another IA of OS may be conducted 1 year after the final analysis of PFS and the stopping boundary will be adjusted according to the prespecified alpha-spending method.

11.7. Patient-reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-OV28, EQ-5D-5L, and PGIS questionnaires will be used to collect data on the patient's functioning, health-related QOL, disease symptoms and health status.

The primary PRO endpoint is the number of patients achieving at least a 15% (≥ 15-point) absolute improvement on the QLQ-OV28 abdominal/GI symptom subscale (items 31-36) at the Week 8/9 assessment (Stockler 2014). Patients with missing week 8/9 questionnaires will be excluded from analysis unless they have PD or death prior to week 8/9 assessment in which case they will be included as unimproved.

Results will be summarized and presented by each treatment arm. Comparison between the two treatment arms will be carried out using appropriate statistical tests. Details of the analysis methods for PRO endpoints will be described in a PRO Statistical Analysis Plan.

11.8. Multiple Comparisons

11.8.1. Multiple Comparisons for Primary Efficacy Endpoint

No multiple comparisons are needed for a single primary efficacy endpoint.

11.8.2. Multiple Comparisons for Key Secondary Efficacy Endpoints

If the primary endpoint of PFS is statistically significant at 2-sided alpha level of 0.05, the hierarchical testing procedure will be used to test the key secondary endpoints in the following order at 2-sided alpha level of 0.05 to control the study-wise type I error.

- ORR per RECIST 1.1 criteria as assessed by the Investigator
- OS (time from randomization to death from any cause)
- Primary PRO endpoint of abdominal/GI Symptom Scale of EORTC QLQ-OV28

12. QUALITY CONTROL AND ASSURANCE

12.1. 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 by study site personnel. 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 (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.

13. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

13.1. 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 Good Clinical Practice (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.

13.1.1. 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.

13.1.2. 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 or the patient's legally authorized representative(s) 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 13.3.

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, as well as collect a blood sample for Soluble FRα. 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.

13.2. Investigators and Study Administrative Structure

Before initiation of the study, the Investigators at US sites 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.

13.3. 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.

13.4. 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.

13.5. Study Committees

13.5.1. 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 the Independent Data Monitoring Committee (IDMC), SC and ImmunoGen will be included in the SC charter document.

13.5.2. Independent Data Monitoring Committee

An IDMC has been established for this study and specific guidelines on the operation and purpose of the IDMC is documented in a Charter. The committee includes at least 3 members, including a statistician and medical oncologists experienced in the treatment of EOC. Safety review meetings will be held as per the IDMC charter and as needed if any unexpected safety signals emerge during the study. The IDMC will be responsible for independently evaluating safety data of patients enrolled to the study. Decisions on study termination, amendment of the protocol, or cessation of patient recruitment will be made after recommendations from the IDMC have been assessed by the Sponsor.

13.6. 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.

13.7. 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.

13.8. 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.

13.9. End of Study

EOS will occur after the final analysis of OS, which will be conducted when at least 300 deaths have occurred. It is projected that the final analysis for OS will be approximately 1 year after the final analysis of PFS. After the final analysis of OS, the last survival follow-up visit for the last patient will be performed and the study will close. At the time of the final analysis for OS, if patients are still receiving clinical benefit from study treatment at EOS, either the study will be amended to allow those patients to continue to receive 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.

13.10. 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.

13.11. 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 the IDMC or 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 Section 312 and in compliance with the principles set forth in International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

13.12. Access to Source Documentation

According to the ICH E6 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).

13.13. 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 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.

13.14. Data Generation and Analysis

The clinical database will be developed and maintained by a CRO or an EDC technology provider as designated by ImmunoGen. ImmunoGen or its designee will be responsible for performing study data management activities and analyses.

13.15. 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.

13.16. 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.

13.17. 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.

13.18. 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

(Oken 1982)

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 Lesions: 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, 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 measurements will be performed as indicated in Table 2, Table 3, and Table 4. 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

Patients will have tumor measurements 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 measurements will be performed as indicated in Table 2, Table 3, and Table 4.

- 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)